Neuron: Electrolytic Theory & Framework for Understanding its operation

Abstract: The Electrolytic Theory of the Neuron replaces the chemical theory of the 20th Century. In doing so, it provides a framework for understanding the entire Neural System to a comprehensive and contiguous level not available previously. The Theory exposes the internal workings of the individual neurons to an unprecedented level of detail; including describing the amplifier internal to every neuron, the Activa, as a liquid-crystalline semiconductor device. The Activa exhibits a differential input and a single ended output, the axon, that may bifurcate to satisfy its ultimate purpose. The fundamental neuron is recognized as a three-terminal electrolytic signaling device. The fundamental neuron is an analog signaling device that may be easily arranged to process pulse signals. When arranged to process pulse signals, its axon is typically myelinated. When multiple myelinated axons are grouped together, the group are labeled "white matter" because of their translucent which scatters light. In the absence of myelination, groups of neurons and their extensions are labeled "dark matter." The dark matter of the Central Nervous System, CNS, are readily divided into explicit "engines" with explicit functional duties. The duties of the engines of the Neural System are readily divided into "stages" to achieve larger characteristic and functional duties.

Keywords: Activa, liquid-crystalline, semiconductors, PNP, analog circuitry, pulse circuitry, IRIG code,

Excerpts from

The NEURONS and NEURAL SYSTEM

This material is excerpted from the full β-version of the text. The final printed version will be more concise due to further editing and economical constraints.

A Table of Contents and an index are located at the end of this paper.

A few cross-refs. have yet to be defined and are indicated by "xxx."

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Neural Concepts

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A useful rule in studies of neural circuits is never to accept randomness as an organizing principle because it discourages doing experiments to test for specificity.

G. M. Shepherd, 2005

He who loves practice without theory is like a seafarer who boards ship without wheel or compass and knows not whither he travels

Leonardo Da Vinci

I heartily beg that what I have here done may be read with forbearance; and that my labors in a subject so difficult may be examined, not so much with the view of censure, as to remedy their defects.

Sir Isaac Newton, *Principia*

There is a unifying force behind all manifestations of nature, which we cannot fully comprehend, but we can try to explain it with the means at our disposal.

Eulogy to John von Neumann, 1957

1. Introduction, Prior Art & Fundamentals of Science[1]

Drawing is the Education of the Eye. It is more interesting than words. The language of the tongue is often used to disguise our thoughts, whereas the language of the pencil is clear and explicit.

James Nasmyth, 1808-1890.

"An era can be said to end when its basic illusions are exhausted"

-Arthur Miller

The primary tasks of the neural system are to collect information, make decisions based on that information, and implement those decisions through commands to the non-neural tissue of the organism. The fundamental goal of neuroscience is to understand how these tasks are accomplished. This volume is dedicated to that goal, to providing a detailed description of the neural system of animals. It employs a new electrolytic paradigm that provides a more sophisticated framework than the chemical concept employed under the old paradigm.

The focus of this work is on the circuits and mechanisms causing a phenomenon, rather than on reporting the phenomenon.

The new paradigm describes the neuron as containing a three-terminal active electrolytic device formed by the junction of real semiconducting bilayer membranes (lemma), as the foundation of **The Electrolytic Theory of the Neuron**. This theory replaces the previous paradigm based on a two-terminal active device (the axolemma membrane alone) formed of a putative permeable membrane subject to the Nernst Equation and supporting the flow of alkali ions through the membrane.

The old paradigm of the neural system based primarily on chemical mechanisms is no longer tenable. While it was the dominant paradigm during the last half of the 20th Century, neuroscience has been held back through reliance on this concept. The primary signaling functions within the neural system are based on its electrolytic character (Electrolytic = involving the transfer of electrical charge in a liquid or liquid crystalline environment.). The flow of electrons through an active electrolytic semiconducting device is the fundamental mechanism in the new paradigm. It is only the secondary functions, providing electrical

[1]Released: January 5, 2019

power to the electrolytic circuits, that are fundamentally chemical in nature.

This 21st Century electrolytic paradigm has proven extremely successful; its success, particularly in describing the visual, auditory, olfactory/gustatory and visceral systems of humans, overshadows any criticism generated within the context of the old paradigm. Several recent medical breakthroughs could not have been achieved in the absence of this new paradigm. Many of the paradoxes reported in the recent academic literature are also explained by this paradigm. The current understanding of the operation of the central nervous system, in the visual, auditory and smell contexts, would not be available without this new paradigm.

[xxx expand the following]

> ***The correlation of the data of Washburn & Moises and The Electrolytic Theory of the Neuron summarily expressed in Section 9.7.2 is startling. There can be no doubt that The Electrolytic Theory of the Neuron has replaced the archaic chemical theory of the neuron developed in spasms during the 20th Century.***

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The primary task of this book is to provide The Electrolytic Theory of the Neuron based on a new a 21st Century paradigm. Summarizing Meyer's ideas[2], "Throughout the history of science 'paradigm shifting' ideas and theories have typically been presented in books." **First**, books allow scientists to make sustained and comprehensive arguments for new ideas. **Second**, new scientific theories often synthesize a broad range of evidence from many related disciplines or sub-disciplines of science. As such, they are often inherently interdisciplinary in scope. **Third**, by creating a larger audience, a book can avoid constraint by an entrenched establishment and cause a broader reevaluation of an established theory among a wider audience. A book is the appropriate forum for a new paradigm. The scope of this paradigm fits the above context. It is so broad it cannot be addressed in a small group of journal articles of 4 to 20 text pages. Furthermore, the new paradigm provides such visibility into the neural system that many detailed diagrams are required to explore the subject matter in detail. This book makes one long argument for the Electrolytic Theory of the Neuron and the resulting neural system of the biological organism. Schopenhauer made an important observation[3], "All truth passes through three stages. **First**, it is ridiculed. **Second**, it is violently opposed. **third**, it is accepted as being self-evident." This work is designed to aid the passage of the Electrolytic Theory of the Neuron through these stages as quickly as possible. With the advent of the Internet, it is hoped the process described by Schopenhauer can be sped up considerably.

> Sanchez described the "7 Biology Myths No Electrical Engineer Would Ever Tolerate" in a recent paper[4]. This work provides a much more detailed interpretation and rationalization of these myths and answers to all of them at the very detailed level.

The winds of change are finally appearing in the neurosciences. These winds should speed acceptance of the Electrolytic Theory of the Neuron. Shreenivasaiah et al. have described a "System" approach to the development of more sophisticated quantitative models of the neural system with a focus on the cardiac system[5]. They suggest a holistic approach "unlike the traditional biology with a reductionist viewpoint which focuses' on examining

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[2]Meyer, S. (2009) Signature in the Cell. NY: Harper Collins page 6

[3]Schopenhauer, Arthur (1788-1860)

[4]Sanchez, E. (2010) 7 Biology Myths No Electrical Engineer Would Ever Tolerate *On-line Blog* http://cosmicfingerprints.com/ee/comment-page-3/#comment-28914

[5]Shreenivasaiah, P. Rho, S-H. Kim, T. Kim, D. (2008) An overview of cardiac systems biology *J Mol Cell Cardiol* vol 44, pp 460-469

characteristics of isolated components in the biological system." In reviewing the state of the art, they conclude, "All biological systems are inherently complex." However, although the systems are complex, the complexity is overstated when reductionists fail to model components of the system adequately (or properly). Inadequate modeling at the component level adds to the difficulty associated with "poor cohesion between the datasets." They discuss the features of abstract models that are qualitative in nature with few details versus lower abstraction models that are mechanistic, quantitative, and offer details related to operation and connectivity of individual components. They discuss the necessity for powerful computational tools for comprehensive model development. This work will show that sophisticated computational tools are not required to the degree they suggest when appropriate closed-form descriptions of individual components are employed. The goal of this work is to provide closed-form descriptions of all neural system elements.

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A major goal of this work is to overcome the reliance of the neuroscience community on metaphors and conceptual sketches in the discussions of neural functions. As Meyer has noted (page 21), "Metaphors reign where mystery resides. The use of metaphors in science derive from the lack of adequate knowledge. Much of current neuroscience relies upon the language of purpose, upon teleological (philosophical) metaphor, instead of the language of process. This has become particularly true in the field of molecular biology, the most reductionist of sub-discipline of modern biology. The use of the term function is the perfect example.

The term, function, is used in a wide variety of meanings in the neurosciences (and philosophical discussions of the neural system). Teleologically (philosophically), a function attributes a purpose to a structure or a trait. Hardcastle has devoted many pages to wide variations on this theme[6]. At a more substantive level, functions relate inputs to outputs, and a functional analysis decomposes a system into contributing sub-processes. Function will be used in its philosophical context only in the first chapter of this work. Subsequently, function will be used to describe the relationship between an input and an output. This usage stresses the reductionist approach of this work. The neural system is dependent on the performance of individual neurons (modified generic cells), and specifically on the operation of the electrolytic circuits within those neurons. All neural operations and phenomena are ultimately traceable to the operation of a handful of individual neuron types. Ultimately a reductionist approach to the neural system should lead to a theory and various supporting models satisfying Chalmers' definition of a neural correlate of consciousness[7]. No work can achieve that goal based only on the currently available empirical data.

This work will not cross the chasm between philosophy and neuroscience. Its goal is to solidify a rational, empirically supported, model of the neural system that remains firmly on the neuroscience side of the chasm. To this end, the definition of terms is a critical matter and an extensive glossary of these definitions is provided as an integral part of this work. Different usage of these terms in philosophical writings only define the chasm between neuroscience and philosophy.

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Within neuroscience, two major approaches have evolved, the holistic and the reductionist.

The holistic, or top-down, approach has provided only limited knowledge about the operation of the neural system. Its primary product has been what the cryptology community calls traffic analysis; it provides a description of the sources and end points of typically large groups of individual neural circuits. It has not provided more detailed information concerning the methods of signal encoding or information carried over the

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[6]Hardcastle, V. ed. (1999) Where Biology Meets Psychology. Cambridge, MA: MIT Press

[7]Chalmers, D. (2000) What is a neural correlate of consciousness? *In* Metzinger, T. *ed.* Neural Correlates of Consciousness. Cambridge, MA: MIT Press

circuits. Recent advances in neural imaging have greatly expanded our knowledge in the traffic analysis area but the resolution remains coarse (involving millions o f circuits as a minimum).

The reductionist, or bottom-up, approach has provided detailed knowledge about the operation of the individual neurons, including most aspects of the coding used to transmit information over the circuits.

The marriage of the reductionist and holistic approaches is about to provide a significant increase in our knowledge of the neural system. It is about to reveal the character of the information carried over individual circuits and circuit groups.

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The goal of this work is to combine a reductionist view (ground up) with a holistic view (top down) of a very complex biological system to obtain an overall understanding of the neural system. To organize the resulting data, and database, the system will be subdivided into a contiguous set of functional stages. A contiguous description of the functional elements within each stage will then be presented, avoiding caricatures in favor of explicit relationships (down to the molecular level in most cases). To this end, the neural system will be subdivided into eight stages (**Sec. 1.1.2**) , the eighth being unique to the cardiac system (**Chapter 20**).

Following this plan, the chapters after the first few will generally focus on these stages. The first few chapters will focus on defining the fundamental neural circuits, including the Activa, the core active electrolytic device found within every neuron.

> The discovery and description of the Activa, an electrolytic semiconducting liquid crystalline electrical device formed by the multiple lemma of a neuron (US Patent # 5,946,185), is key to this work. It has been described extensively in the earlier work of the author. It will be described in greater detail in **Chapter 2** of this work.

Chapters on consciousness and memory will appear following the development of stage 5.

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It is useful to differentiate between communications and surveillance in physiology. Communications is generally defined as the transfer of information between entities. The entities need not be of the same species (or class of cells). Surveillance is generally defined as obtaining an understanding of an entities external environment. For an animal, the external environment is generally the surrounding ecological environment. For a cell, it may be the physical, chemical and stereographic configuration of adjacent cells.

It will be important in this work to differentiate between external communications and surveillance related to a biological entity versus internal communications and surveillance. External surveillance may involve volatile chemicals reaching the external chemical sensory modalities. Internal surveillance may involve the sensing of the concentration of a totally non-volatile chemical in the blood stream.

Signaling is generally defined as a method used to communicate. Thus, a telephone number can be communicated by signaling methods involving writing, recitation, posting on a signboard, tapping on a drum, etc. Signaling per se does not propagate communications. The propagation of information requires the sender and receiver to employ the same code while signaling. Voicing a telephone number to your dog will result at best in a quizzical look from the dog. It will evoke much the same response from another human who does not understand your spoken language.

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Physiologists often note vision and hearing involve ***relatively linear and generally monotonic translations*** from the light and audio environments into the neural signaling environment.

They also note the lack of such a "relatively linear and generally monotonic translation" in the case of many forms of chemical communications. The code used in signaling may or may not involve a linear transformation. There is no requirement that a translation code be monotonic. It is only necessary that the sender and the receiver understand the code.

It will be shown in this work that both vision and hearing employ nonlinear and non-monotonic translations, specifically Riemann Transforms, in the extraction of information from the signals received by the stage 4 thalamic reticular nucleus of the diencephalon.]

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Within an organism, it has long been the custom to concentrate on chemical communications between elements of the organism. This has been fostered by the early importance of pharmacology in human medicine and physiology. Many of these concepts of chemical communications have been fostered by the presence of specific chemicals at specific locations within the organism. The parallel concepts associated with electrolytic chemistry and physical chemistry have been largely ignored until recent times.

This work will demonstrate that the concept of the neural system as an electrolytic system leads to levels of understanding far beyond what has been achieved based on chemical concepts alone. It will present the Electrolytic Theory of the Neuron as a replacement for earlier concepts. This work is in considerable conflict with, and provides entirely new perspectives on Basic Neurochemistry as propounded by Siegel et al. over many years[8],[9]. Siegel has been assembling this compendium since 1972 and the organization of the volume and contributing authors have necessarily changed over the years. The 7th Edition appears significantly smaller than the 6th Edition but this may be due to a change in publisher. Siegel et al. is directed to and prepared by those in the medical profession. Much of the chemistry discussed is highly relevant, however, it must be interpreted from a different perspective. Introduction of the Electrolytic Theory of the Neuron provides a great deal more continuity and quantitative precision to the study of the neural system.

Within the Electrolytic Theory of the Neuron, the text by Marchlewska-Koj, Lepri & Muller-Schwarze entitled "Chemical Signals in Vertebrates[10]" should be more precisely labeled "Chemical Signals between Vertebrates." Most of the work involves the signaling between vertebrates using pheremones. At this time, humans do not understand the code used in signaling by pheromones although the purpose appears to be largely communications of a sexual nature.

The Electrolytic Theory of the Neuron establishes a different role for most of the chemicals previously labeled neurotransmitters, based largely on their physical location near neurons. The primary neurotransmitter will be shown to be the electron in a fluid environment. Neurotransmitters other than the electron (and hole) will be labeled neuromodulators in this work. Many chemicals previously labeled neurotransmitters, such as acetylcholine and nitric oxide, will be shown to be neuroaffecters (a subcategory under neuromodulators) exhibiting a familial relationship to the hormones of the glandular system. Others such as glutamic acid and GABA (gamma amino butyric acid) will be critical to providing the electrical power used in the electrolytic neural system.

This work will only consider chemical communications related to the external environment of an organism (except when discussing stage 7 neural activity, the generation of neuro-affectors for purposes of controlling muscular activity and introducing hormones into the

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[8]Siegel, G. Agranoff, B. Albers, R. Fisher, S. & Uhler, M. (1999) Basic Neurochemistry, molecular, cellular and medical aspects, 6th Ed. NY: Lippincott-Raven

[9]Siegel, G. Albers, R. Brady, S. & Price, D. (2006) Basic Neurochemistry, molecular, cellular and medical aspects, 7th Ed. NY: Elsevier

[10]Marchlewska-Koj, A. Lepri, J. & Muller-Schwarze, D. *eds.* (2001) Chemical Signals in Vertebrates 9. NY: Kluwer Academic

bloodstream).

1.1 Introduction to & context of this work

This work is designed to provide the first comprehensive theory of the neural system of biology, including from the physiological (or operating) perspective as opposed to the anatomical perspective. Knowledge in the field of the neuron has been expanding rapidly in the last few decades but no new comprehensive work has appeared. The recent release of Yost is the fifth edition of an introductory text dating from 1985[11]. The volume by Levitan & Kaczmarek provides extensive material on the histological character of the neuron and a review of the concepts of neural operation developed during the mid-fifty years of the 20th Century[12]. However, it does little to explain how the neuron operates at the detailed level (such as how the action potential is generated). Zagoren & Fedoroff have provided a valuable text focused on the histology of the Node of Ranvier with only limited conceptual information on its physiology[13]. The imagery is limited mostly to light microscopy which is not able to show the crucial functional elements within the Node of Ranvier. It does not address the complex electrophysiology within the pre-nodal and post-nodal regions of the node.

Using the terminology adopted by Maxwell in the title of his 1873, this work covers the last 25 years of my studies and is a "Treatise on the Neuron and Neural System," really more of an explorer's report, written for those who want not only to follow but to venture further in the subject matter. In that regard, it can be described, like the science historian Thomas Kuhn described Maxwell's work, as a paradigm shift–a fundamental change in the set of shared beliefs and method that guide scientists' thought and work. Like other similar shifts, this one didn't properly take hold until several decades later, when a new generation of scientist with young and open minds had succeeded to old guard (Forbes & Mahon, pg 212).

Squire et al. have addressed the terminology used in the neurosciences[14]. They describe it as "hierarchal, distributed, descriptive and historically based." In fact, up until recently, it has been fundamentally based on visible observation using light microscopy. As a result, it is heavily weighted toward the fields of anatomy, morphology and limited histology. They continue, "With a necessarily gracious view to the past, this confusing terminology could be viewed as the intellectual cost of focused discourse with predecessors in the enterprise." "In vertebrates, the components of the nervous system were named for both their appearance and their location." However, not for their function. They further note, ". . . the names of the major parts of the brain were based on creative interpretations of early dissectors of the brain, attributing names to brain segments based on their appearance in the freshly dissected state; hippocampus (shaped like the sea horse) or amygdala (shaped like the almond), cerebrum (the main brain), and cerebellum (a small brain)." Many of the resulting morphological demarcations do not conform to the functional demarcations of the system.

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[11]Yost, W. (2007) Fundamentals of Hearing: An Introduction. 5th Ed. NY: Academic Press

[12]Levitan, I. & Kaczmarek, L. (1991) The Neuron: Cell and Molecular Biology. NY: Oxford Press

[13]Zagoren, J. & Fedoroff, S. (1984) The Node of Ranvier. NY: Academic Press

[14]Squire, L. Bloom, F. McConnell, S. et al. *eds*. (2003) Fundamental Neuroscience, 2nd Ed. NY: Academic Press

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Ito has tried to describe the levels of understanding involved in the neural system specifically but applicable to any scientific undertaking. His figure on page 3 of his 1984 book is indicative of the challenge[15]. He uses a broad set of terms that seem to lack any consistency from the viewpoint of lexical semantics. **Figure 1.1.1-1** extends his concept into the realm of the neuron.

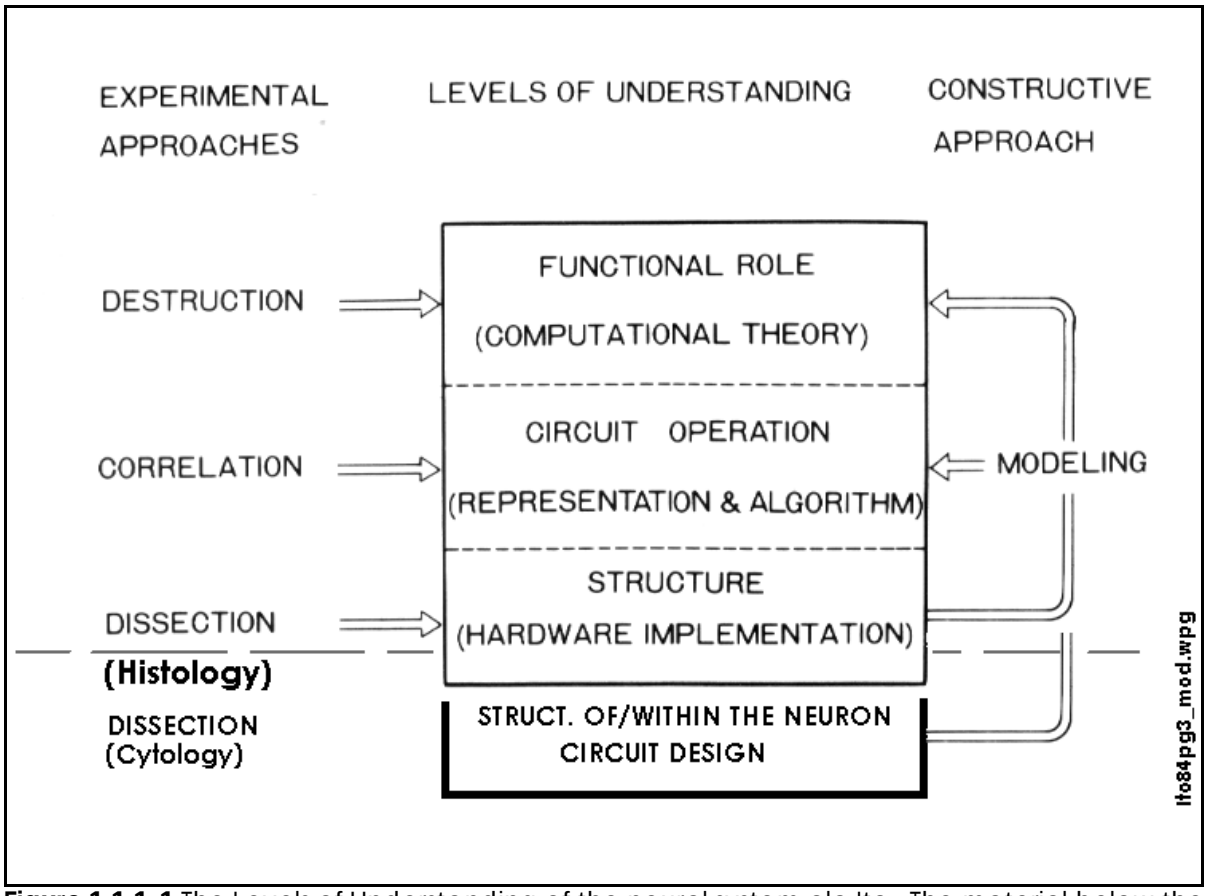

Figure 1.1.1-1 The Levels of Understanding of the neural system ala Ito. The material below the dashed line has been added. This material is absolutely necessary to move from a conceptual to a deterministic understanding of the neural system. Extended from Ito, 1984.

Without detailed knowledge of the operation of the neurons, the results of all histological, correlation and destruction-based observations remain in the arena of concepts. Modeling activities without such detailed knowledge remain without firm foundations; they constitute pedagogical exercises.

Ito spent several pages discussing how he was using the words in the figure before moving on the scope of his monograph. As part of the discussion, he noted, "The question, 'What does the brain do?' is the most intriguing question of neuroscience." His answers relating to the cerebellum appear naive based on more recent knowledge. His overview of his text on page 7 does not indicate that he will discuss the operation of individual neurons or neural circuits, only broad concepts based primarily on his three aspects on the left side of the

[15]Ito, M. (1984) The Cerebellum and Neural Control. NY: Raven Books

figure.

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This work will deviate from the conventional morphological demarcations in many areas as required to understand the actual operation and function of the neural system. It will also add considerable new terminology to which the reader is probably not accustomed.

When discussing the cognitive functions of the brain related to the terms "mind" and "consciousness," the transition between the realm of neuroscience and philosophy is a significant one. It is important to note whether a given citation is to a philosophical discussion, that does not rely upon detailed anatomy or on physiology, or to a neuroscience-based discussion.

This work is one of neuroscience rather than philosophy; and it recognizes the movable nature of the chasm separating the two. To this end, a conventional definition of a theory from the behavioral sciences is used here[16], leaving the definition of a theory from a philosophical perspective to the philosophers[17]. Kerlinger defined a theory as "a set of interrelated constructs, definitions, and propositions that present a systematic view of phenomena by specifying relations among variables, with the purpose of explaining and predicting the phenomena." This definition can stand if the constructs and propositions are expressed using closed form mathematics rather than words.

In neuroscience, the phenomena have been the focus, with only localized theories presented to suggest causes of the individual phenomenon. This approach has been supported by the journal editors who oppose presentations of theories, particularly comprehensive theories, separate from laboratory investigation.

Like the term theory, the term model has been used in a wide variety of contexts in science. These range from the animal model representing an animal exhibiting similar physiological characteristics to a human in a specific area, to the symbolic model describing a biological function from a mathematical perspective. As this work progresses, it becomes important to recognize ultimately that there is no animal model globally equivalent to the human. This is particularly true in its cognitive powers, and some sensory powers. Even among the higher primates, different species are claimed to best model different aspects of the human system.

Although immense amounts of useful data have been collected from "animal models," this work is focused on the general theory of the mammalian neural system irrespective of the biological source. In a majority of this work, a model is defined as a representation or depiction supporting the conceptual understanding of one or more aspects of a theory (**Section 1.1.2.1**).

It has been the practice in mathematical modeling of the neural system to attack small parts of the overall problem and employ simplistic equations to describe isolated phenomena; frequently the equations are algebraic in form or employ unsolved differential equations. The latter have become popular because of the availability of high speed computers. These machines can provide numerical solutions to such differential equations, based on whatever initial and final conditions the investigator specifies (regardless of the physical realizability of these conditions).

The goal of this work is reductionist in concept and practice, to describe the individual detailed mechanisms required to understand the total neural system. Because of this goal, the "field theories" (Uttal, pp 114-145) involving the description of the global patterns of

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[16]Kerlinger, F (1986) Foundations of behavioral research. New York : Holt, Rinehart and Winston page 9

[17]Uttal, W. (2005) Neural Theories of Mind. Mahwah, NJ: Lawrence Erlbaum Assoc. Chap. 1

electroneural activity, as the result of the activity of millions to billions of neurons (the holistic approach), are only used sparingly. The results of these field theories are generally labeled event related potentials (ERP) or evoked brain potentials (EVBP) and include the common EEG, EKG etc. After discussing the frequent use of transcendental calculation to interpret field theory data, Uttal settles on the greatest problem with field theories, "This brings us to the great conceptual flaw of all field theories–the fact that these mathematical tools may not represent reality (page 144)." Following a discussion of Fourier Transform functions, he goes on using italics, "*This is so because it works (mathematically) to reduce a function to a set of basis functions regardless of whether or not the underlying processes or neural machinery represented by the basis functions actually exist!*" This work will show the neural system does not compute mathematical transcendental functions of the type Uttal describes. It can only accomplish limited transcendental calculations using a technique called computational anatomy (as used in Stages 2 and 4 of most of the sensory modalities. As a result, field theories involving transcendental functions can not be plausibly associated with neural signaling.

At some point in the later chapters of this work, the chasm between neuroscience and philosophy, between the brain and the mind, must be approached if not addressed. The historical term mind is being replaced by consciousness in major portions of the recent literature. An important goal is to achieve a "Neural Correlate of Consciousness" (NCC). After cogitating on the meaning of the word correlate, Uttal settles on his definition of a neuroscientific theory of mind (consciousness):

1. The primary attribute of a neural theory of mind is the ontological assumption that the mind si a function of brain activity.
2. A corollary of 1. is that a true neuroscientific theory of mind must assume that some particular aspect of brain activity is the equivalent of mind, not just any correlated activity."
3. Another general attribute of a neuroscientific theory of mind is that of accepted complexity. With rare exceptions, all current cognitive neuroscientists working in this field accept the Neuron Doctrine–the idea that the nervous system is made up of contiguous, but not continuous, discrete neurons. See further discussion of this point in **Sections 1.1.5 & 18.7**.

1.1.1 "Signaling" as a term of art within biology

Alluding briefly to the United States Patent Office, they have created a long list that is continually being expanded and updated as "Terms of Art." This is a very large hierarchal tree that helps them find a home for "everything" that has been invented or claimed to have been invented. They structure their entire organization around these terms of art, populating administrative sections dealing with these various terms of art.

Within biology, there appears to be a similar blossoming of signaling concepts that need to be interpreted to avoid confusion among investigators. It has been pointed out to me that since 2008, the AAAS has published a journal called "Science Signaling" (SS). While SS focuses primarily on chemical signaling, other related fields (network properties, systems analysis, etc.) are also included. The AAAS definitions rely heavily on, and generally support the chemical theory of the neuron. This work discounts the chemical theory of the neuron in favor of the much more successful Electrolytic Theory of the Neuron, where the principle neurotransmitter throughout the neural system (except at the neuron/muscle and neuron/glandular interface) is the electron. Even the neuron/glandular interface is subject to additional clarification as to the mechanisms involved. In some cases, the initial glandular cell can be considered a modified neuron.

1.1.1.1 Signal transduction in the broadest AAAS context

According to the AAAS[18];

"Signal transduction refers to the *biochemical* processes by which cells respond to cues in their internal or external environment. Because signal transduction mechanisms are the

[18] http://stke.sciencemag.org/about/

natural control circuits that regulate biological systems, they provide potent targets for development of therapeutic agents to combat disease or otherwise alter the behavior of biological systems. Signal transduction research is an intensely active field of biomedical research and is of interest to a broad array of scientists. Science Signaling should be useful to scientists who specialize in signal transduction, as well as the many scientists who need to follow and apply the current findings of this field even though their primary interest may not be the signal transduction mechanisms themselves."

To avoid undue confusion, this work will define signaling as;

- A communications process across the general environment involving two or more living organisms
    - Exocrine communications involving the release of a specific element of communications.
        - Chemical signaling
        - Optical signaling
        - Acoustic signaling
        - Mechanical (contact) signaling

- A communications process between two or more elements within a living organism
    - Pericrine communications within a distance of less than one micron
    - Paracrine communications within the CNS or similar major structure
    - Endocrine communications within the bounds of an identifiable organism

Even this framework requires expansion within various terms of art. As an example, signaling within the pericrine environment of the CNS is frequently divided into;

- Neural signaling
- Glial signaling
- Hormonal signaling
    - instigated by neural signaling and involving neuro–modulators in this work

In very special cases, some authors have also described autocrine signaling

- Autocrine communications, the release of a neurotransmitter by a presynaptic tissue of a synapse that impacts the operation of that same presynaptic tissue.

1.1.1.2 Signaling within the neural system and its interfaces

The AAAS definition of transduction (written by chemically trained authors) is heavily biased toward chemical phenomenon. Visual cues and acoustic cues, as examples do not involve any chemical phenomenon in their initial transduction unless Physical and quantum-mechanical phenomena are included in the definition of chemistry. Similarly, the AAAS definition does not appear to accommodate totally electronic (more specifically electrolytic) communications between cells. ***It is proposed here that electrolytic communications is the principle means of communications between neurons***.

To avoid confusion, this work is focused exclusively on neural signaling in the following contexts;

- neuron-to-neuron signaling (involving neurotransmitters–the electron and the hole) and
- neuron-to-non neurons signaling (involving neuro-modulators–generally simple but very specific chemicals).

The simplest signaling by neuro–modulators involves signaling at very short distance, pericrine signaling (involving primarily nitric oxide (NO) and acetylcholine (ACh). More complex neuro–modulators are called hormones and typically affect their targets over longer distances, paracrine, endocrine and exocrine distances.

In many animals, the exocrine system takes on a specific form in combination with specialized olfactory receptors, and the neuro–modulators are described as pheromones.

Bassler has spoken considerably on the subject of signaling between bacteria[19]. She has even identified "receptors" on the surface of the bacterium contributing to this communications. With organism the size of bacteria, the definitions of paracrine, pericrine, and exocrine may require further specialization. This delineation will be left to those working in that field.

1.1.2 Overall purpose of this book

This book is designed to provide the reader a broad understanding of the neural system based on a single coherent theory and a set of consistent models supporting that theory. It was initially designed to rationalize the content of a myriad of freestanding papers and texts around the apparent cornerstones of the field. This turned out to be impossible. The cornerstones were found to lack the necessary strength and to contain arbitrary constraints. It became necessary to define an entirely new framework for understanding the neuron and the neural system. As a result, this book is based on a theory that will be unfamiliar to many readers until it is shown to be the actual underpinning of much of the conventional wisdom. It represents a significant departure from the chemically-based perspective of the neuron presented in undergraduate biology programs at this time. Although the old chemical theory is frequently proclaimed from the bully-pulpit, **signaling within the neural system is not based on chemical processes, signaling between neurons is entirely electrolytic. Only the interface of the neural system with other cell types is chemical in character.**

The goal of this work is to provide the complete theory and supporting empirical data in accordance with the methods of neuroscience while meeting the stated philosophical requirements of a good theory according to Uttal (pages 3-6, 13-15 & 248). While showing concern about the dangers of a good theory to empirical research, Uttal notes the following. "Regardless of these 'dangers,' theory still represents the pinnacle of scientific thinking." The theory presented here is analytical, a higher form than a probabilistic or logical theory according to the philosophers.

This is the first publication of the complete electrolytic theory of the neuron, and the operation of the Activa based thereon, in text form. Because of the difficulty of presenting the cognitive and assimilative process used during the preparation of this work to discover the electronic nature of the neuron, an alternate pedagogical approach will be followed below. A fundamental neuron will be synthesized on paper to highlight its most important electrical properties. This pedagogical presentation will familiarize all readers with the many interdisciplinary features found within the neuron. The work will then proceed to discuss the functional performance of various specialized neurons and the unique techniques used by some of them.

The author has reviewed an immense amount of the literature over the last 20 years in order to present this work and its two companions. No single source has been found that provides an end to end theory (with descriptive models) of the neural system applicable to any animal. While a variety of recent texts have appeared, they are generally designed for the pedagogical market; and do not offer an adequate overall description of the neural system, an adequate detailed descriptions of the elements of the neural system, or a cohesive combination of these two descriptions. They employ vastly varying symbology. **Section 1.1.4** addresses this situation.

An impressive example of an academic work aimed at pedagogy is Dayan & Abbott (2001[20]). The book offers virtually no biochemistry, biophysics or bioelectronics directly related to the mechanism of the neural system. Therefore, it develops a series of "straw-men" models of the neural system in a totally pedagogical framework. As an example, it continues to discuss the potential methods of encoding information onto an action potential stream, but does not recognize that the actual code used is well known and was used extensively in

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[19]Bassler, B. (2006) Cell-to-cell communication in bacteria: a chemical discourse. *Harvey Lect.* 2004-2005 100: 123-142.

[20]Dayan, P. & Abbott, L. (2001) Theoretical Neuroscience. Cambridge, MA: MIT Press

man-made telemetry systems (including those developed at MIT) up through the 1980's (**Chapter 9**). In their chapter 5, they continue to show allegiance to the archaic and never demonstrated Huxley-Hodgkin model of a neuron and to the totally inadequate Rall model of an axon as an RC cable (**Section 9.1.1.3**) instead of its depiction as an optimal coaxial RLC cable. While incorporating the most sophisticated mathematics, their integrate and fire model of a neuron fails to incorporate the two thresholds employed in every stage 3 encoding neuron (a forward current threshold and the actual relaxation oscillator threshold). Their text tends to statistical descriptions of mechanisms demonstrably deterministic at the individual circuit level.

> It is not obvious that Dayan & Abbott ever address the analog neuron (over 95% of all neurons) in contrast to their focus on pulse generating neurons.
>
> The title of their text might be more appropriately "Conceptual Modeling in Neuroscience in the absence of a Biological (physiological) Model."

The fundamental approach in this work is an academic investigation leading to a defendable theory based on the empirical data of others but avoiding the largely extraneous conceptual descriptions of the neural system that lack either foundation or multiple points of support. The process has followed the procedure described by Stewart[21] for solving a difficult mathematical problem and attributed to Poincare; preparation followed by incubation followed by illumination. The investigator must absorb a great deal of information associated with the problem and then let the subconscious mind ponder the information for a (frequently extended) period of time before the mind informs the conscious mind that a solution has been found. While this approach may sound nebulous, it is very near the procedure I have used for the more difficult portions of the problem. I keep a notepad on my bed table and frequently awake in the morning with the feeling I must immediately unload my mind, via the wordprocessor, of important findings.

1.1.2.1 The new handbook on multisensory integration & other material

The recent release of the New Handbook of Multisensory Processes[22] continues the predominance of material attempting to build a qualitative understanding of the neural system based on a predominantly conceptual base. It is an excellent source of references to laboratory investigations but offers no practical description of sensory operation or their actual commonality or convergence. The editor admits to little effort to rationalize the terminology between the authors os individual chapters and a paucity of models within the text. The 1000 letter size pages of the volume are dominated by textual discussions, including extensive "Commentary" preceding each group of chapters, with only a few caricatures for figures. The text generally discusses convergence as occurring on individual neurons (figure I-1 and page 5) rather than on groups of neurons within a larger engine of millions of neurons. Most of the chapter authors appear to be academics with names not found widely in the histological laboratory or physiology literature.

Chapter 3 on the thalamus, by Hackett, is one of the most comprehensive of its kind as noted by Meredity in the Commentary preceding that chapter. Although it does not appreciate the extended role of the thalamic reticular nucleus (TRN), his description of the ventral LGN (lateral geniculate nuclei) corresponds to the visual PGN (perigeniculate nucleus) of this work. Figure 3.1, 3.2 and 3.3 of Hackett show a familial relationship to some of the more detailed figures of this work by suggesting the two way signaling between the thalamus and cortical areas. He does recognize features along the brachia of the superior and inferior colliculi corresponding to the visual and auditory PGN's of this work. Some of his anatomical breakdowns are quite detailed but their operatioal roles are based primarily on traffic analysis rather than signaling. Hackett's overall conclusions are two;

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[21]Stewart, I. (2013) Visions of Infinity. NY: Basic Books page 12

[22]Stein, B. ed. (2012) The New Handbook of Multisensory Processes. Cambridge, MA: MIT Press

> "At present, the full complement of multisensory inputs into the thalamus and cortex has not been determined, and it is likely that significant interactions are present but have not yet been identified."
>
> "Thus examination of the rodent literature leaves an impression vastly different from that drawn from the carnivore and primate literature.'

The very simple figure 5-4 of chapter 5 by Meredith et al. does illustrate the fact that the central foveola of the visual modality is processed differently from the remainder of the retina (developed in detail in **Section 8.2** of this work and the author's other work on vision).

Figure 15.1 is repeated from Rolls (1999) and offers a very cursory (and unidirectional) mapping of convergence of the sensory modalities. Chapter 17 by Ward offers some useful insights into synesthesia, including some statistics but only caricatures as figures. Chapter 25 supports the Ward material while also providing some experience related to the features and limitations of cochlear implants.

Chapter 32 is one of the few providing usable data. It focuses on the adaptability of the brain of the barn owl in merging visual and acoustic information.

Shipp has recognized the major importance of the thalamus[23]. Unfortunately, his global view did not recognize the shell covering the pulvinar as the critical TRN. Shipp proposed that the pulvinar itself acted as a "remote hub for coordinating spatial activity within multiple cortical visual maps." Chalfin et al. give additional citations supporting this view and suggest, "At a minimum the lateral posterior pulvinar complex thus serves the brain to identify and focus attention on a particular object or task[24]."

The importance of the pulvinar and the thalamus will become more obvious now that these elements have been successfully imaged using fMRI techniques[25,26].

1.1.2.2 Initial description of the architecture of the neural system

Many authors have attempted to define the neural system. Bullock & Horridge provides an early definition appropriate to the 1965 time period and now obsolete[27].

> "An organized constellation of cells (neurons) specialized for the repeated conduction of an excited state from receptor cells or from other neurons to effectors or to other neurons."

The following is suggested as a more focused definition of the neural system.

> The neural system consists of an organized constellation of neurons specialized for; sensing the environment in and around the animal, evaluating the options available relative to that environment (frequently with respect to earlier perceptions of the

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[23]Shipp, S. (2004) The brain circuitry of attention *Trends Cogn Sci* vol 8, pp 223-230

[24]Chalfin, B. Cheung, D. Muniz, Jose. et al. (2007) Scaling of neuron number and volume of the pulvinar complex in new world primates: comparisons with humans, other primates, and mammals *J Comp Neurol* vol 504(3), pp 265-274

[25]Fischer, J. & Whitney, D. (2012) Attention gates visual coding in the human pulvinar *Nature Commun* vol 3 (1051)

[26]Komura, Y. Nikkuni, A. Hirashima, N. Uetake, T. & Miyamoto, A. (2013) Responses of pulvinar neurons reflect a subject's confidence in visual categorization *Nature Neurosci* vol 16, pp 749–755 doi:10.1038/nn.3393

[27]Bullock, T. & Horridge, G. (1965) Structure and Function in the Nervous System of Invertebrates. NY: Freeman

environment stored in memory), and controlling the potential responses designed to modify the position of the animal with respect to that environment.

The scope and complexity of the neural system is proportional to the complexity of the species; the later complexity is matched to the complexity of the ecological environment of the species.

Discussion of the neural system is aided greatly by a top level architecture. This work will subdivide the overall neural system into a number of major functional stages (many of which are replicated within the system) with the last stage used to introduce a series of functionally complete mini-neural systems within the overall system.

The descriptive names of the functional stages are:

0. The Physiological Stage prior to transduction,
   Examples are the outer, middle and inner ear (prior to transduction) as acousto-mechanical elements. Similarly, the eyelids, lens and vitreous humor of the eye.
1. The Signal Generation Stage including transduction,
2. The Peripheral Signal Processing Stage,
3. The Signal Propagation Stage,
4. The afferent Signal Manipulation Stage within the CNS,
5. The Signal Cognition Stage, with its associated memory
6. The efferent Signal Manipulation Stage within the CNS and
7. The Response Stage required to maintain the health of and provide locomotion for the animal.
   7A. The Response Stage associated with the musculo-skeletal system.
   7B. The Response Stage associated with the glandular system.
8. The hybrid neurons of the hypophysis (pituitary gland) that accept chemical inputs, provide chemical outputs and process internal signals electrolytically
9. The mini-neural systems of the visceral system, subject to further subdivision.

Stage 1. Signal generation by sensory neurons
Stage 2. Signal processing within the peripheral nervous system
Stage 3. Signal projection between major processing centers of the system (distances exceeding two millimeters).
Stage 4. Signal manipulation (merging & information extraction) at the entrance to the central nervous system
Stage 5. Cognition (information manipulation & correlation leading to instruction development)
Stage 6. Instruction interpretation and command generation
Stage 7. Command implementation (by affecting non-neural tissue via multiple avenues)
Stage 8. Hybrid neurons of the hypophysis (pituitary gland)
Stage 9. Cardiocytes capable of command relaying as well as muscular response to stimulation

It is noted that Stage 3 neural circuits may appear throughout the mammalian system when signal projection is required over significant distances. Stage 3 circuit utilization in non-mammals is yet to be definitized.

Only stages 4, 5 & 6 will be associated with the central nervous system (CNS). The other stages, even if located within the cranium, are external to the blood-brain barrier (BBB) of the brain and will be considered portions of the peripheral nervous system (PNS). The location of the hypophysis, and possibly the hypothalamus straddles the BBB.

Stage 7 can be further subdivided into stage 7A associated with stimulating muscle tissue directly and stage 7B associated with the neural/endocrine glandular system interface.

The definition of Stage 9 neurons will be replaced with a more detailed set of definitions in **Chapter 20**.

After describing all of the functional stages (except the mini-systems) in detail, the work will introduce six operational modes as overlays to the functional architecture.

These modes have been given descriptive operational names to aid understanding. They are;

1. The Alarm mode–a largely reflexive operating mode designed to protect the subject against external threats, even before its cognitive capabilities become aware of the threat.

2. The Awareness mode–a mode designed to support a general familiarity with the external environment surrounding the subject.

3. The Analytical mode–a mode designed to determine the unique characteristics of specific acoustic signals or events associated with the surrounding environment.

4. The Cognitive mode–the mode developed to consider the meaning of signals received from the Awareness and Analytical modes (and frequently after the fact from the Alarm mode).

5. The Volition mode–the high level mode used by the cognitive elements of the CNS to instruct the lower level element of the efferent neural system to take action.

6. The Command mode–the low level mode used to prepare and implement instructions (via the musculo-skeletal system) received from the cognitive elements of the CNS, and to carry out preprogrammed responses upon instruction from the Alarm mode circuitry.

Some of these modes are subdivided into sub-modes because of the significantly different tasks they support. These sub-modes will be defined as the need arises.

The definition of these stages and operational modes greatly simplifies describing the neurological system. Their detailed definition will occur in the chapters to follow. [The list is slightly expanded from the shorter list used in earlier sensory-oriented books by the author.]

In conformance with conventional usage, the term modality will be associated with a specific sensory or response capability and used to describe all of the functional and operational aspects of that individual capability. Generally, each sensory modality has a complete set of the first four stages and each response modality has a complete set of stages 6 & 7. The cognition stage sits at the top of the neural system and is common to all signaling paths, except where it has delegated authority to a variety of shorter "reflex arc" paths following a learning experience.

1.1.2.3 An outline of this volume

This initial chapter is designed to orient the reader relative to;
- several archaic concepts still prevalent in the literature,
- to introduce the Theory of the Electrolytic Neuron, and
- provide a summary discussion of the biological membrane critical to all biological cells, and particularly the neurons.

Chapters 1 through **3** form the foundation of this work. They introduce the Activa, the active electrolytic semiconductor device found at the very core of every neuron. When assembled with a group of additional electrolytic elements, each Activa forms the core of an amplifier known as a conexus, a building block found in all neurons. The Activa exhibits "transistor action," the same quantum-mechanical mechanism found in man-made transistors.

Following the introductory and background material in this chapter, **Chapters 1** & **2** will be devoted to the description of various types of neurons based on the Activa, the critical active electrolytic device found within every neuron and between most neurons. After discussing the features of a variety of neurons, **Chapter 2** will discuss another remarkable configuration. It will be shown that a synapse also exhibits "transistor action" when it is

configured appropriately (**Section 2.4**). This finding forces the inescapable conclusion that the morphological neuron is not the fundamental physiological unit of the neural system. *Activas are found outside of morphological neurons.* It can be shown that the neuron is the fundamental morphological and genetic unit but not the fundamental physiological unit. As will be developed in later chapters, a question arises whether the neuron can be considered the fundamental metabolic unit. It appears the projection neuron often relies upon nearby glia to provide critical chemical reaction products for use in the remote portions of its axon.

Chapter 2 will continue the pedagogical presentation by developing the topology of the more complex forms of neurons found in the neural system. Each major functional type of neuron will be discussed in detail. It will also review the morphology of neurons based on a better understanding of the nature of the functional elements found within and associated with neurons. By comparing the morphology and the topology of each type of neuron, it will become obvious that "Form follows Function" *and available real estates* in biological neurons. Additional discussion of the topology of the synapse will also be presented. Like man-made transistors, biological Activas exhibit a range of parameters depending on their application.

Chapter 3 will describe the means by which the neurons are provided electrical power. It discusses the predominant form of electrostenolytics providing the negative potentials found within cells. It will also address the recently uncovered positive electrostenolytic source that appears peculiar to the cardiocytes of the heart.

Chapter 4 develops the architectures of (primarily mammalian) neural systems in order to provide a means of annotating major engines of neural activity. Individual large scale engines are typically composed of a few million to a billion individual neurons. Smaller individual engines are usually estimated at one to four million neurons.

Chapter 5 will review a great many aspects of the morphology of neurons and the neural system.

Chapters 6 through **9** will change perspective and focus on the operational parameters of each type of neuron. They will be discussed in the context of the peripheral nervous system (PNS). **Chapters 10** & **11** will address the Central Nervous System at two distinct levels. First at a gross level to aid later interpretation and then at the level of individual feature extraction engines within the Central Nervous System (CNS).

Chapters 10 through **12** will focus on the organizational aspects of the neural system.

Chapter 13 will address the electrical performance of the neurons as individual circuits.

Chapter 14 is undefined at this time. [xxx]

Chapter 15 will discuss the higher level performance of the complete afferent neural system.

Chapter 16 will address the neuroaffectors of the efferent neural system, including the role of the neural system as the controlling interface with the skeletal muscle system.

Chapters 17 and **18** address the still poorly understood aspects of memory and consciousness. The discussion is more superficial than that in earlier chapters.

Chapter 19 provides a brief summary of the overall functional performance of the neural system in the context of the complete sensory, cognition, and skeletal operations aspects of the organism.

Chapter 20 explores the unique character of the mini-neural systems associated with the visceral elements of the animal. The enteric and cardiac systems exhibit fascinating features not common to the primary neural system focused on sensory, intellectual and skeletal operations. The unique character of the cardiocytes (myocytes) of the heart are explored.

Chapter 21 will briefly address the emotional performance of the organism as controlled by the neural system.

Chapter 22 will also briefly address the response of the neural system related to pain.

Chapter 23 is a recent addition and addresses the glandular-affectors and the Crine modality (an expansion of the field presently labeled endocrinology). The Crine modallity is found to be poorly explored with very little known concerning the operation of the stage 7B neuroaffectors interfacing with the Crine modality.

The book concludes with an extensive Glossary and comprehensive Index. Some additional material will be found on the website in the form of appendices.

1.1.2.4 Providing a firm framework for any science

Science employs a variety of models to aid in visualizing the operations of mechanisms of all complexities. In the biological sciences, descriptive, mechanistic and interpretive models have been widely used. Dayan & Abbott have defined these terms in their text related more to their subtitle than their title[28].

Descriptive models–summarize large amounts of experimental data compactly yet accurately, thereby characterizing what neurons and neural circuits do. These models may be based loosely on biophysical, anatomical, and physiological findings, but their primary purpose is to describe phenomena, not to explain them.

Mechanisitc models– address the question of how nervous systems operate on the the basis of known anatomy, physiology and circuitry.

Interpretive models– use computational and information-theoretic principles to explore the behavioral and cognitive significance of various aspects of nervous system function, addressing the question of why nervous systems operates as they do.

In addition, the experimental field makes extensive use of animal models.

Animal models– animals with specific biological sub-systems similar to those of man that allow the results of experiments to be associated with the equivalent human sub-system by analogy. As the level of detail expands, the relevance of the analogy tends to decrease.

A more serious problem is the frequent use of only limited, partial and frequently floating models.

Floating models– models that are only extensive enough to incorporate the investigators immediate results and not able to show the relevance of the results within a larger context.

[28]Dayan, P. & Abbott, L. (2001) Theoretical Neuroscience. Cambridge, MA: MIT Press

As will be shown below, the floating model and the animal model can lead to significant problems. As an example, the squid of Hodgkin & Huxley is an invertebrate. Like the axons of other invertebrates, the giant axon of the squid does not generate action potentials. Their *in-vitro* experiments involved draining the axoplasm from the axon, and inserting a conducting wire the length of the axon. They also took great pains to emasculate the other neuritic structures from the soma and axon of the cell. It will be shown the pulse responses recorded by those investigators were artifacts of their test protocol. This response has been taken by much more sophisticated later investigators as typical of mammalian action potentials (without demonstration of this proposition.). Thus, their conclusions that have been transferred to the mammalian model were based on an *in-vitro*, floating, and highly modified animal model.

The use of floating models and limited protocols introduce a second major shortcoming into many investigations, the development of overly simple laws only applying to a limited dynamic range of a sensory environment. Weber's Law, Fechner's Law and many other laws of neuroscience only apply to a limited dynamic range. Extending them beyond the range in which they were validated often leads to unrealistic results. These two laws are based on the concept that the "just noticeable" difference, Δs, is proportional to the magnitude of the stimulus, s, such that $\Delta s/s$ is a constant. When the above two laws are applied in vision, they only apply to the photopic regime of vision. It is shown in a companion work they specifically do not apply to the hypertopic, mesotopic or scotopic regimes. Similarly in hearing, they only apply to the phonotopic regime.

1.1.3 Overall purpose of this chapter

The purpose of this chapter is two-fold. The first fold is to provide a very brief overview of the fundamental technology and organization of the neural system and make the reader aware of the very extensive glossary provided by this work (**Appendix A**). The second fold is to review a variety of fundamental concepts (replacing archaic concepts with more serviceable processes) and principles involved in understanding the neural system.

This initial chapter devotes considerable time to the underlying technologies that are used in the neural system. This focus on the basics is required to help those readers who lack the necessary academic preparation in areas of physics and electronics.

As noted earlier, this work does not build on past conceptual theories of the neuron. In fact, it will take exception to many long held concepts that have become part of the common wisdom of the biological community. To deviate so far from the common wisdom requires some introductory remarks justifying the path taken. These remarks will be found in **Sections 1.2**.

> A major goal of this chapter is achieved in **Section 1.2.6** where a *new and expanded* **Neuron Doctrine** is presented in axiomatic form. This doctrine is distinctly separate from that attributed to the philosophy arena in **Section 1.2.7**.

Sections 1.3 & 1.4 will present a set of fundamental principles appropriate to the understanding of the new paradigm. **Section 1.3** will address the field of Electrolytics, as a branch of Electrochemistry, required to understand the operation of the neural system. It will be followed by **Section 1.4** which will review the physical chemistry of the neurolemma, frequently described as the biological bilayer membrane (BLM). **Section 1.5** will then address the electrolytic aspects of a real BLM. This work will differentiate the BLM into four unique electronic configurations depending on its underlying physical chemistry. These individual configurations play a major role in understanding the operation of the neuron and the neural system. The type 2 BLM will be shown to be the most important to the operation of the neural system. It is the type most intimately involved in the electrolytic mechanisms associated with signaling.

> During the remainder of this work, the expression BLM will be limited to defining a natural biological bilayer membrane. Where appropriate or necessary for clarity, the

expression BLM will be preceded by one or more descriptive adjectives.

Performance data from the cited literature will be introduced throughout this work to support the theoretical model. An excellent source of much *performance* data is Moller[29]. While the subtitle stresses "anatomy and physiology," the text is very light on the underlying circuits and mechanisms employed in the neural system. This work fills that void.

1.1.4 Models used in this work

This work strives to use the most detailed neurological and electrophysiological models possible. To the greatest extent possible, it seeks to support these models with mechanisms described using a firm mathematical foundation.

> At a very gross level, this work will recognize the lower animals as lacking a neocortex, with the paleocortex terminating at the hypothalamus of the brain stem. The higher animals will exhibit a neocortex of various levels of complexity but generally lacking a significant prefrontal cortex, PFC. The hominoids, or possibly just *Homo*, will be characterized by their well differentiated prefrontal cortex.
>
> It appears the morphologically defined hypothalamus, and its nearby tissue contain many sensory elements (Noback, chapter 11) involved in maintaining homeostasis in animals (Pennartz, page 29).
>
> The suprachiasmatic nucleus or nuclei (SCN) is a tiny region of the brain in the hypothalamus, situated directly above the optic chiasm. It is responsible for controlling circadian rhythms. The SCN receives input from specialized photosensitive ganglion cells in the retina via the retinohypothalamic tract.

A majority of the work applies to all mammals, particularly with respect to elements of the peripheral nervous system (PNS). It becomes more specialized when discussing the central nervous system (CNS). Emphasis is placed on the human exclusively when discussing the operations of stages 4 and 5 of the CNS.

Erwin has acted as Series Editor on a massive library entitled "Comparative Primate Biology." Volumes 1 (edited by Swindler & Erwin[30]) and 4 (edited by Steklis & Erwin[31]) are particularly relevant to this work. While dated at the detail level, it is not likely to be replaced in the near future (See later paragraphs in this subsection relative to Nieuwenhuys et al. of 1998). Volume 1 is particularly complete in discussing the evolution of the primates and great apes, including detailed measurements at the anatomical level leading to a variety of different cladograms based on the criteria invoked. It lists several hundred systemic parameters on which a cladogram can be based, and discusses the weighting used by different investigators as of 1986. The volume also includes a broad discussion of the evolution of blood types among the primates. Volume 4 provides a great deal of information related to the neural system of the primates at the anatomical and histological level. This includes information concerning the "subcortical" level (i.e., the diencephalon), including data on the perigeniculate nucleus (PGN) as differentiated from the perigeniculate nucleus. It also provides a clear delineation between the pretectum (a series of individual nuclei, page 368) and other elements of the diencephalon. It also details many of the histological and cytoarchitectural features of the cortical association areas (particularly in the context of vision and visual attention). It notes specifically the frontal eye field (FEF) is located within Brodmann's Area #8. Page 421 begins a large section on the somatosensory modality. The volume concludes with a comprehensive review of the motor cortex in the context of

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[29]Moller, A. (2003) Sensory Systems. NY: Academic Press

[30]Swindler, D. & Erwin, J. (1986) systematics, Evolution and Anatomy, vol 1 *of series by* Erwin, J. *ed.* Comparative Primate Biology, NY: Liss

[31]Steklis, H. & Erwin, J. (1988) Neurosciences, vol 4 *of series by* Erwin, J. *ed.* Comparative Primate Biology, NY: Liss

voluntary movements.

The use of animal models to approximate the performance of the human begins to break down in stages 4 and 5. Elements of the diencephalon (mid-brain) in particular, along with the expansion of the cerebral hemispheres and limbic system, begin to evolve beyond that of the other primates. The following material will demonstrate how the use of the monkey and other species below the super-family, *Hominidae*, becomes inappropriate when stages 4 and 5 are of interest. Even the chimpanzee and gorilla are no match for the performance of the human in these areas. The only logical animal model approaching *Homo Sapiens* appears to be the orangutan (genus *Pongo*). There has been precious little research on this genus for a variety of reasons. However, Swindler & Erwin do review the available data as of 1986.

Nieuwenhuys et al. have provided a massive work in three volumes (2200 pages) under the title, "The Central Nervous System of Vertebrates[32]." While published in 1998, the Preface stresses its very long gestation period, dating from the 1960's. The work is devoted to the comparative biology of the nervous systems of vertebrates from the strictly classical (and chemical theory) perspective. The text is the result of a near lifetime of work by the principle author. Despite the title, ***the text totally ignores the functional and operational aspects of the central nervous system***. In addition, it almost totally lacks any graphic imagery other than hand drawn sketches. Some of these may qualify as camera lucida images but they are not so marked. While commendable work, it contributes nothing to the understanding of the functions of the neural system. It does provide some excellent interpretations of how words are used in comparative morphology, etc. in Chapter 6, section 6.2.5.2;

> "The central nervous systems of all vertebrates are topologically equivalent. Topology is the geometry of distortion, the branch of mathematics, which investigates the properties that remain unchanged when geometric configurations are subjected to one-to-one continuous transformations. In these transformations it is allowed to change distances, to bend, stretch or twist the configurations. However, it is forbidden to 'cut' or to 'tear'."
>
> "Comparative neuroanatomy derives all of its principles and basic concepts from its mother science: morphology.
>
> It was recognized from the very beginning of morphology that the position of parts with respect to each other forms the prime and principal criterion for the establishment of homologies. These relationships are mainly, if not wholly, determined by the relative position and connection of parts ... From the beginning, similarity in function was excluded as a criterion for the establishment of homologies.
>
> The concept of homology expresses the existence of typical and specific correspondences between the parts of members of natural groups of living beings. The recognition and the systematic search for homologies marks the beginning of morphology as a separate scientific discipline.
>
> The terms 'analogy' and 'analogue' are used to denote similarity in function. Thus, Owen (1843) defined analogue as " ... a part or organ in one animal which has the same function as another part or organ in a different animal." It should be noted that, according to Owen's definitions, structures can be both homologous and analogous."

Unfortunately, many of the definitions are too narrow to be useful when it is recognized that morphological features may be homologous and analogous at the histographic and cellular level but may be significantly different at the functional level because of differences in the software (commands or instructions applied to other terminals of a neuron) or firmware (a difference in bouton level connectivity among adjacent neurons). It must also be pointed

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[32]Nieuwenhuys, R. Donkelaar, J. Nicholson, C. et al. *in 3 volumes* (1998) The Central Nervous System of Vertebrates. Berlin: Springer-Verlag

out that beyond the narrow field of comparative neuroanatomy, the term homology is used quite differently. Kosower[33] in particular uses the term "functional homology" when discussing the similarities between his putative chromophores of vision.

Nieuwenhuys et al. provides considerable data, in sketch form, in Chapter 22 related to mammals.

Nieuwenhuys, Voogd & Huijzen[34] published a follow-on text in 2008 under a similar name but internally different. "The present edition of The Human Central Nervous System differs considerably from its predecessors. In previous editions, the text was essentially confined to a section dealing with the various functional systems of the brain. This section, which has been rewritten and updated, is now preceded by 15 newly written chapters, which introduce the pictorial material of the gross anatomy, the blood vessels and meninges and the microstructure of its various parts and deal with the development, topography and functional anatomy of the spinal cord, the brain stem and the cerebellum, the diencephalon and the telencephalon." Unfortunately, the term function is used in its traditional usage in anatomy, related to connectivity and physical movement, and not to its usage with respect to the neural signaling function.

Recently, genetics has moved forward in surpassing anatomy and cladograms as methods of differentiating between species. In 2017, Susan Milius prepared an article[35] for a popular audience noting a conversation, apparently with Richard Richards–a philosopher of biology at the University of Alabama (Tuscaloosa), concerning how to define species. He noted the wide variety of ways to tabulate species. Some of these were listed in greatly simplified form,

Species concept	**A species is**
Morphological	the smallest group with a persistent difference in form
Ecological	a lineage with its own distinct ecological niche
Genetic groups	a group of natural interbreeders genetically separated from other
Bioeconomic	a unit in the natural economy that competes reproductively with other units

The morphological differentiation of primates has recently become questioned by the recognition of the fact that the human genetic structure (23 genes rather than the 24 present in all other primates studied to date). It appears gene #2 & #3 of the other primates have become fused in *Homo Sapien*, leading to major differences in the conformation and neural capabilities of *Homo Sapien* relative to the other primates (as a minimum) . See **Section 1.2.8** for recent terminology and findings in genetics.

1.1.4.1 Order Primate focused on the human

The Order Primate is characterized by a distinctive cerebral cortex overlaying the "old brain" found in lower chordates. The Order Primate includes 12 families, 52 genera and 181 species

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[33]Kosower, E. (1988) Assignment of groups responsible for the "opsin shift" and light absorptions of rhodopsin and red, green, and blue iodopsins (cone pigments) *PNAS USA* vol 85, pp 1076-1080 http://www.pnas.org/content/85/4/1076.full.pdf

[34]Nieuwenhuys, R. Voogd, R. Huijzen, J. et al. (2008) The Human Central Nervous System. NY: Springer

[35]Milius, S. (2017) The fuzzy art of defining species *Science News*, Nov 11 edition, vol 192(8), pp 22-24

according to a recent source, Peters & Rockland[36]. While they explicitly use the above hierarchy under the tabular heading Primates, they do not use it within the same hierarchy. They switch to suborders, families and species. Hickman has used the sequence Orders, suborders, super families, families and species. Szalay & Delson has given an even more extensive phylogeny of the primates including super families, sub families and 27 families[37]. This background is indicative of how disorganized the field of taxonomy remains to this day. Because of this confusion, the following paragraphs can only be considered illustrative–but based on Hickman as stated earlier.

Anthropoidea is the suborder of the apes, monkeys and humans. The suborder is frequently divided into both species and a description of their origin. Of the families in this sub-order, there are two super families. The first consists of the monkeys and lesser apes and the second, *Hominoidea*, contains the great apes and humans. The designation of humans gets awkward since man is the only species, *Homo Sapiens*, within the family, *Homo*. Some authors have labeled humans more generically as Old World Anthropoids (sometimes labeled Old World Primates). The Old World refers to Asia in this context with the New World including Africa. These labels should be differentiated from the Old World Monkeys and may still be inappropriate. The terms Old and New are not used in taxonomy as many would guess.

The eyes of *Anthropoidea* exhibit several unique features and limitations on their performance. These eyes have evolved to provide a simultaneous field of view of slightly more than 180 degrees in azimuth and a maximum of less than 90 degrees in elevation. They do this while maintaining a significant area of stereoscopic vision that includes a fovea of about 6.26 degrees diameter. The fovea and the accommodation provided by the optical system are critical to the visual performance of these animals.

Preuss[38] has noted in Gazzaniga (2009) that the fundamental phylograms of mammals have been rearranged about every 30 years, particularly in 1924 (Grafton, Elliot & Smith), 1959 W. Clark) and 1999 (Fleagle). This work will suggest it is time for another review that incorporates the orangutan more completely and relies more heavily on DNA data.

There has been a recent proposal to move the chimpanzees, *Pan troglodytes* and *Pan paniscus* from the family *Pongidae* into the family *Homo* based on their degree of similarity in DNA (claimed to be 99.4%)[39,40]. This work focused on genes that did not code for proteins. While one of the most capable of the great apes, the chimpanzee, *Pan troglodytes*, still appears inadequate compared to *Homo Sapiens* in these areas. It should also be noted that 99.4% is not a particularly close match being that about 96% is shared by all members of *Mammalia*.

Figure 1.1.4-1 describes the primates from the perspective of vision, ca. 2008 and before. It is a hybrid of the terminology of Hickman and that proposed by M. Goodman of Wayne State University Medical School. The precise reasoning is based not only on the eyes but also the signal processing within the central nervous system. The particulars of these systems will be

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[36]Peters, A. & Rockland, K. (1994) Cerebral Cortex, Vol. 10, Primary Visual Cortex in Primates. NY: Plenum, pp xix-xx

[37]Szalay, F. & Delson, E. (1979) Evolutionary History of the Primates. NY: Academic Press

[38]Preuss, xxx (2009) The cognitive neuroscience of human uniqueness *In* Gazzaniga, M. *ed. in chief,* The Cognitive Neurosciences. Cambridge, MA: MIT Press Chap xxx

[39]Goodman, M. (2003) Natural Selection's Role in Shaping 99.4% Nonsynonymous DNA Identity Between Congeneric Humans and Chimpanzees, *Proc Natl Acad Sci*. May 19, article #2172

[40] Wildman, D. Uddin, M. Liu, G. Grossman, L. & Goodman, M. (2003) Implications of natural selection in shaping 99.4% nonsynonymous DNA identity between humans and chimpanzees: Enlarging genus Homo *PNAS* vol 100(12), pp 7181–7188

addressed in **Chapters 15, 16** & **17**. Goodman estimates *Hominidae* and *Pongidae* diverged about 6–7 million years ago. Similarly, *Homo* and *Pan* diverged about 5-6 million years ago. It has been particularly difficult for the community to define the internal nodes (ancestors) along the medial line. This has led to many investigators to use classification names for nodes along this line rather than specific animal names. The node labeled *Hominidae* is an example. Contemporary thought suggests a common ancestor must link *Homo* and *Pan.* This ancestor is totally conceptual at this time. The terminal nodes are easy to identify. Those shown contain currently existing species. Many studies in the literature essentially ignore the orangutan (*Simia or Pongo*).

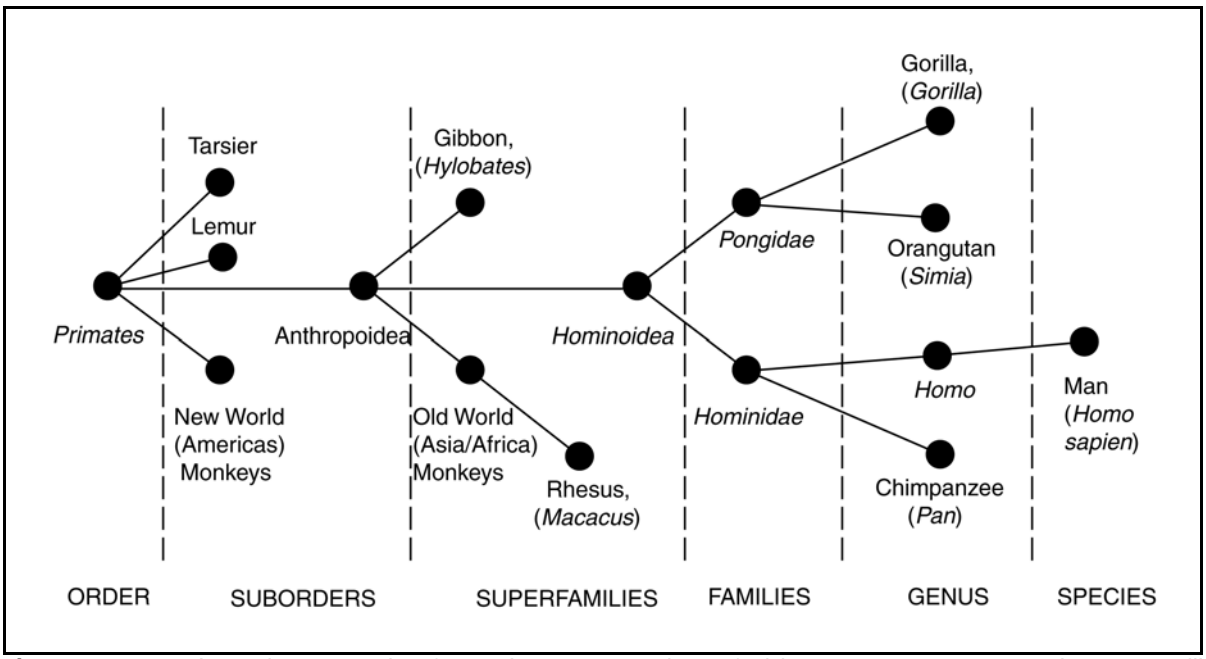

Figure 1.1.4-1 The primate order from the perspective of vision ca. 2008. Later chapters will support this particular phylogenic arrangement up through the family level. The New World Monkeys have prehensile tails and non-opposable thumbs. The Old World Monkeys have four opposable thumbs and non-prehensile tails. The position of the Gibbon (*Hylobates*) in this figure is particularly ambiguous. *Hylobates* and *Hominoidea* lack tails. *Pan* is reported to have a thalamus (critical to visual performance) most closely approximating that of *Homo sapiens*. However, this report did not include the orangutan in the comparison. See text.

Steiper et al. have provided an analysis that describes many of the tradeoffs involved in setting dates within the phylogenic tree[41]. They tend to put the divergence of *Anthropoidea* back to 30 million years (as adopted in the next figure) compared to the 21 million of Goodman and of Wildman. They note the lack of skeletal fossils from the rain forest areas, and particularly of chimpanzee.

Ruse and Travis have recently provided a variety of comparisons between members of *Anthropoidea*[42] related to the nervous system, particularly the size of the cranium over time, and many developmental aspects of the human. On page 261, they say the latest findings put the human with gorilla and Pan (chimpanzee) instead of with orangutan. However, their

[41]Steiper, M. Young, N. & Sukarna, T. (2004) Genomic data support the hominoid slowdown and an Early Oligocene estimate for the hominoid–cercopithecoid divergence *PNAS* vol 101(49), pp 17021–17026

[42]Ruse, M. & Travis, J. *eds*. (2009) Evolution Cambridge, MA: Harvard Univ. Press

evidence appears to be largely a repeat of that of Goodman. Unfortunately, they do not compare the genomic codes of the members of *Anthropoidea* (see **Section 1.1.4.2** below).

Marx has recently provided a broad ranging popular review of the Phylogenic Tree similar to that above[43].

Humans have an additional specialized area within the fovea. This foveola, of 1.18 degrees mean diameter, is critical to the ability of the human to interpret even finer detail than most members of *Anthropoidea* and to read. The foveola is a major component of the Precision Optical System, POS, parts of which were previously labeled the auxiliary optical system of the brain. The POS is a high performance, two-stage, sampled-data servo system that includes the oculomotor system. This system plus the angular acuity and the agility of the human eyes separates them from all other *Hominidae* (with the possible exception of *Pan* (chimpanzee) and *Pongo* (orangutan). Detailed retinal studies could help resolve the evolutionary relationship (based on their visual capabilities. between these primates.

1.1.4.2 *Hominidae* as a distinct variant within the great apes of *Anthropoidea*

There are significant differences in the brains of the great apes and man, compared to the brains of the lesser apes and monkeys. The functional difference is primarily in the midbrain and limbic systems. Prior to the development of magnetic resonance imaging (MRI), these two regions were the least studied and most difficult to study. **Chapter 15** will show that the pulvinar of the midbrain is far more developed in man than in any other species, family, super-family, etc. studied to date It is a key element in the ability of man to read and analyze fine spatial detail in object space. Only a few of the great apes can approach the human in these areas. When investigating reading and the analysis of fine detail, the lesser apes and monkeys are not homologous with humans.

The British Broadcasting Company has prepared a set of videos on the orangutan that are very informative. A recent one has shown the orangutan in a remarkable light that humans like to associate with themselves[44]. A fully grown orangutan comes across a coon chick that is in a confining pool of water with expected dire consequences. The orangutan shows a great deal of interspecies compassion for the chick and spontaneously improvises a tool (a leaf it offers as a ramp for the chick, or as a scoop) before settling on delicately lifting the chick out of the water with its hand and then studying the chick intensely. Another clip shows an orangutan spontaneously whistling chords that are clearly not genetic or familial in character. In December of 2011, the National Geographic magazine commented on the observations of Anne Russon of York University. She observed orangutans being reintroduced to the wild. She noted they were capable of sawing wood, open locked doors, drink from cups and now catch fish by hand (or by stealing trap lines laid by humans when they see or assume there are fish present).

Even more recent evidence (2011) is key to confirming the close link between humans and orangutans. The decoding of the complete genome of the orangutan has introduced additional consternation. Alice Park of Time magazine has reported, "while humans, apes and chimps share a common ancestor, *Homo sapiens* and orangutans retain genetic traits that have been lost by primates species more closely related to us[45]." Two researchers from Denmark highlighted this situation, "In the process (of evolution), chimps for mysterious reasons lost some orangutan DNA that humans retained[46]." Gaining relevant code only

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[43]Marx, V. (2003) All in the family *Genomics Proteomics* Nov/Dec pp 18-23

[44]http://www.bbc.co.uk/news/world-europe-13814508

[45]Park, Alice (2011) Humans' closest genetic kin, Time Magazine, February, 14, 2011. NY: Time-Warner

[46]Mailund, T. & Schierup, M. (2011) as interviewed by Park of previous citation.

requires a few mutations. Losing code is much more difficult. No record has been found in the literature showing such a loss has occurred in the real world to date. The statements by Park and by Mailund & Schierup reflect old school thinking. An alternate wording of their material is suggested; While humans, apes and chimps share a common ancestor, the group consisting of humans (*Homo sapiens*) and orangutans (*Pongo*) show maximum commonality based on their genomic code. Their more extensive DNA suggests they have evolved beyond the other members of the group.

The report by Parks was based on the release of a major study by Locke and 101 co-authors (including two with the surname, Fulton but not related to this author) published in Nature on 27 January 2011[47]1. This major study of the orangutan is at the cutting edge of science. However, the conclusions are derived from the complete genome of only one female specimen. The Locke et al. paper and its citations 26 & 29, among others, discuss some of the underlying assumptions concerning their overall results. The results are presented with a strong homocentric aspect with a major suggestion that the orangutan and human parted ways 14-15 million years ago which is consistent with the above figure (but much earlier than the dates of Goodman and Wildman et al.). However, they conclude that the chimpanzee and gorilla remained part of the human branch of the phylogenic tree until much later (4-5 million years ago for the chimpanzee) when they separated through *degeneration*, the loss of segments of genetic code that remained in the human genome.

Figure 1.1.4-2 shows the phylogenic tree of Anthropoidea proposed for 2010 forward. Placing *Homo* and *Pongo* in the same family (*Hominidae*) on the phylogenic tree as in the above figure obviously causes problems in the names beginning at the family level. Transposing *Pongo* and *Pan* at the genus level while maintaining the family names is the obvious solution. This transposition has been proposed many times previously based on lesser evidence. The transposition leaves *Hominidae* with only two families. As seen, the designation of sub-species in the case of the orangutan is little different than racial, or even ethnic, designations in humans.

The Locke et al. analysis would have *Panidae* separating from the family *Hominidae* (rather than the super-family, *Hominoidea*) as little as 4.5 million years ago, during the time of Lucy and other pre-humanoids. This would conflict with the generally accepted age six million years for one early humanoid. Efforts to clarify this situation involves ongoing efforts to complete the genome of *Gorilla*. See **Section 8.1.1.1**.

[47]Locke, D. Hillier, L. et al. *more than 100 names* (2011) Comparative and demographic analysis of orang-utan genomes *Nature* vol 469, pp 529–533

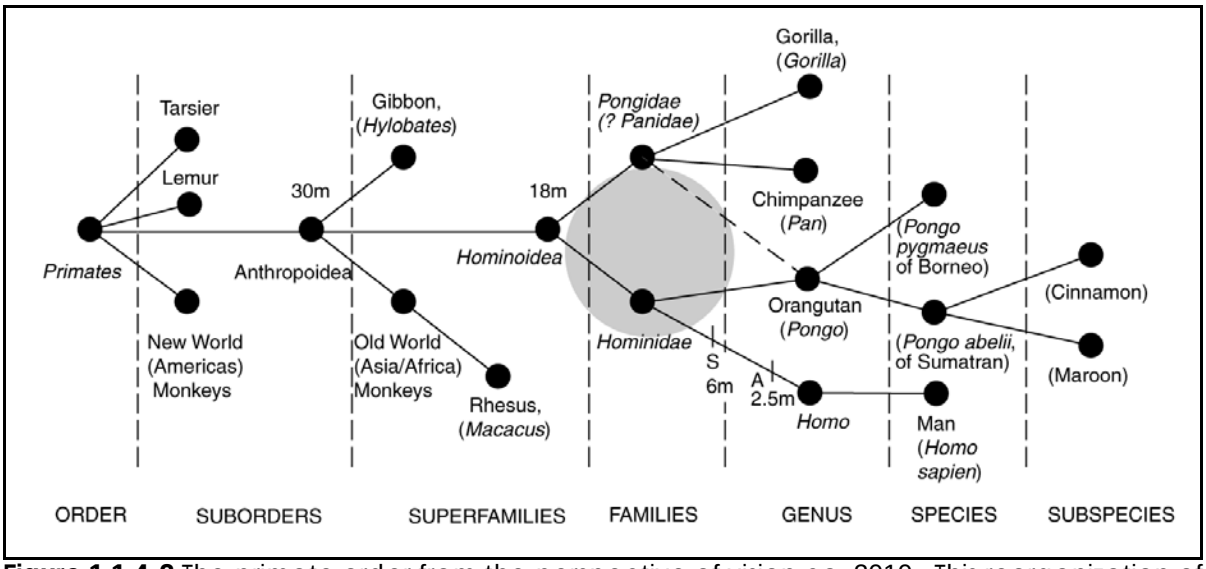

Figure 1.1.4-2 The primate order from the perspective of vision ca. 2010. This reorganization of the phylogenic tree of Primates follows the latest genomic code revelations. It now employs the percentage similarity in the genomic code as a primary factor. The family name *Pongidae* is replaced by *Panidae* and the dashed line is no longer functional. *Pong* is shown with two species, who developed over time (probably less than 2 million years) on opposite sides of a prominent body of water. A and S are defined in the next figure.

Schwartz has described the evolution of these species using an expansion of a region of the above diagram[48]. **Figure 1.1.4-3** shows his interpretation using a slightly different nomenclature and based on detailed dentition. He notes, "Few morphological features emerge as uniting humans and one or both of the African apes, and, contrary to popular opinion, the nonmorphological data do not support a human-African-ape theory of relatedness to the exclusion of other hypotheses. Most phylogenetically significant characters are shared by humans and the orangutan." He shows *Sivapithicus* (S) separating from *Pongo* six million years ago and *Australopithicus* (A) separating from *Homo* only 2.5 million years ago.

[48]Schwartz, J. Eckhardt, R. Friday, A. et al. (1984)Hominoid Evolution: A Review and a Reassessment *Cur Anthropol* vol. 25(5), pp 655-672

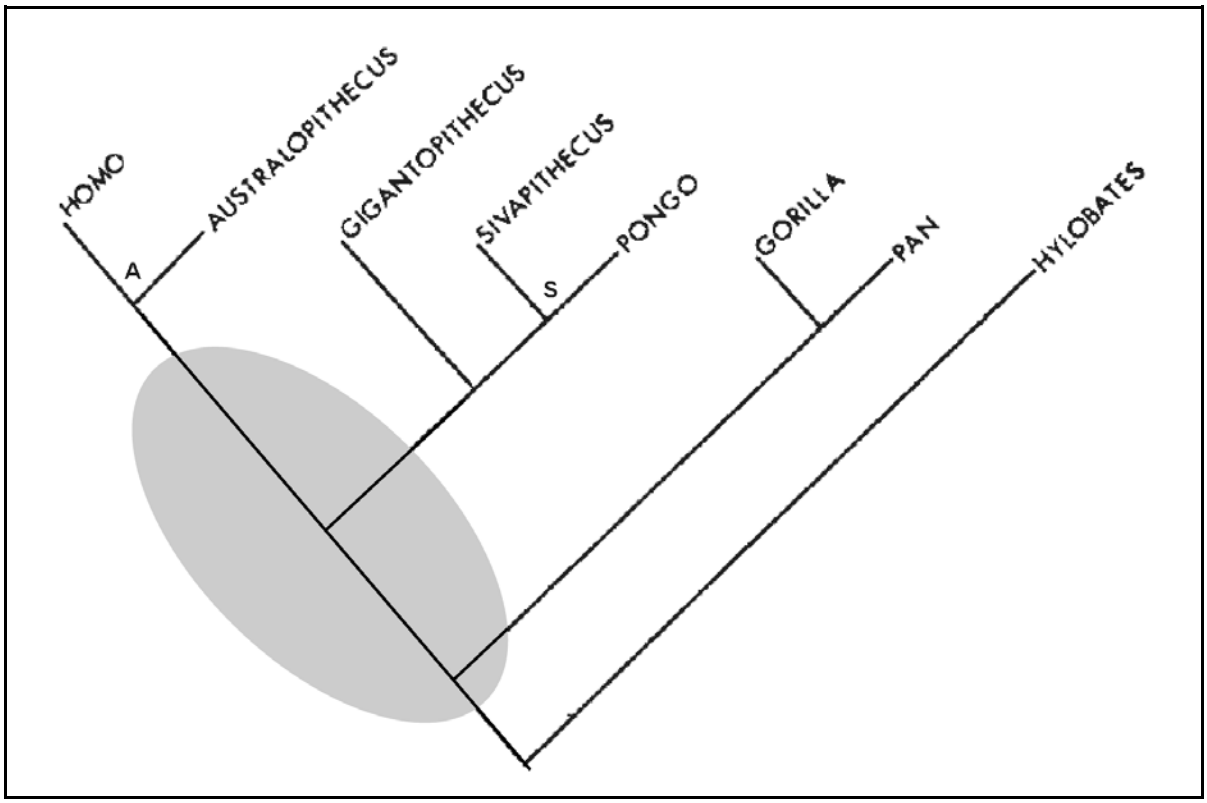

Figure 1.1.4-3 Proposed recent evolution among the primates. S and A are represented slightly differently from the above figure. From Schwartz, 1984.

These phylogenic trees are compatible with that of Manly & Koppl in 1998[49].

In 2014, Venn et al. provided new data using more recent and defendable estimates of genetic mutation rates among the primates[50]. Using their new data, they assert, "Our results indicate a mutation rate of 1.2×10^{-8} per base pair per generation, but a male contribution seven to eight times that of females and a paternal age effect of three mutations per year of father's age. Thus, mutation rates and patterns differ between closely related species." Their results show the bifurcation between chimpanzees and humans occurred much earlier than the estimates based on Goodman (2003) and Preuss (2009), and in very good agreement with the estimates presented here in the above figure. Their calculations provide new slower mutation rates based on a more sophisticated framework "implying an average time to the most common ancestor of 13 million years, . ." They thereby support the hypothesis that the last major bifurcation between homo and another primate probably involves the orangutan (Pongo) about 10-14 million years ago.

In 2015, Paabo[51], repeated the conventional view based on a 2002 paper that Pongo separated from the other primates in the 12-14 Myr time period but included the following in

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[49]Manley, G. & Koppl, C. (1998) Phylogenetic development of the cochlea and its innervation *Cur Opin Neurobiol* vol 8(4), pp 468-474

[50]Venn, O. Turner, I. Mathieson, I. et al. (2014) Strong male bias drives germline mutation in chimpanzees *Science* vol 344(6189), pp 1272-1275

[51]Paabo, S. (2015) Neanderthal Man: In search of Lost Genomes. NY:Basic Books page 93

his caption, "(although these dates are very uncertain)"

Figure 1.1.4-4 shows an evolutionary depiction of Homo over the last seven million years by DeSalle & Tattersall. They also provide a more inclusive time line at the end of their book. Walter has provided a similar time line without the caricatures of the skulls in a popular book[52].

Mai & Ashwell noted (page 13 of Paxinos & Mai, 2004), "Analysis of the hominid fossil record indicates that relative brain size increased rather late in hominid evolution (approximately 2–3 million years ago) and that this increase was not due to a phylogenetic reduction of body size, which actually increased considerably during hominid evolution."

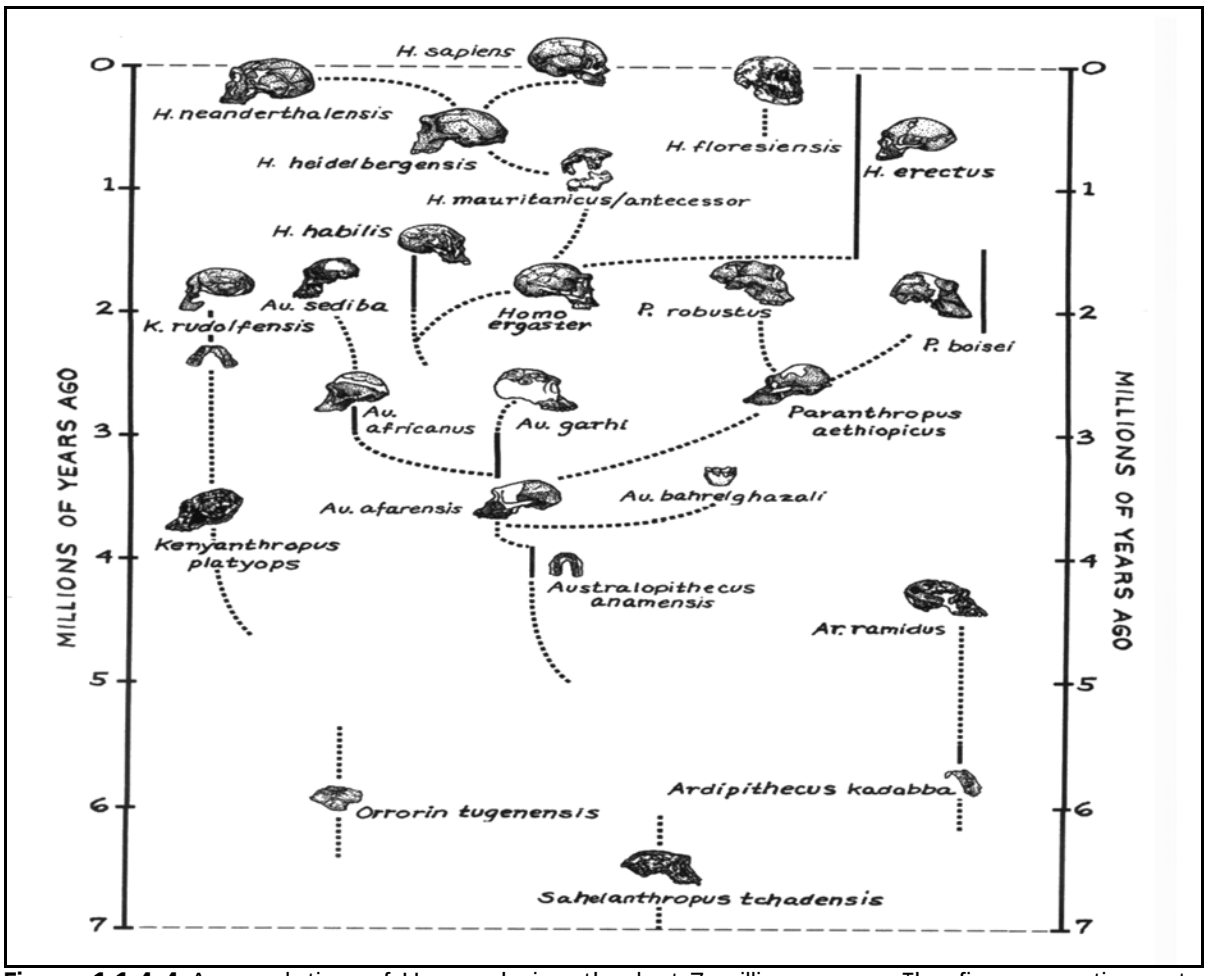

Figure 1.1.4-4 An evolution of Homo during the last 7 million years. The figure continues to include many dashed and broken links as appropriate to such a figure. From Desalle & Tattersall, 2012

1.1.4.2.1 Recent appraisals of the orangutan (*Pongo*)

Beginning in 1993, a series of reports on the capabilities of the Orangutan began appearing

[52]Walter, C. (2013) Last Ape Standing. NY: Walker & Co.

in the academic literature and popular videos. Recently, long term behavioral studies of the orangutan in the wild (multiple specimens), as well as one case of an orangutan raised in a human household until entering its adolescent years, has been reported (most vividly in a NOVA program on public television in the USA[53]). The principle orangutan living in a human environment was named Chantek. He was raised at the University of Tennessee at Chattanooga during the 1970's while on loan from the Yerkes Primate Project in Atlanta, GA. The intelligence of this animal was documented to be as intelligent as any chimpanzee (*Pan*). His sign language capabilities were quite sophisticated and included a long list of individual signs. He describes himself as a "orangutan person" and mastered the concept of money as a medium of exchange to purchase commodities in exchange for work. He also invented new symbolic expressions when he encountered new situations.

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Chapter 10 will discuss additional information suggesting the close relationship between *Pongo* and *Homo Sapiens*.

1.1.4.2.2 Did Homo sapien branch from within the family *Hominidae*?–Genetics

Although there have been endless studies of the chimpanzee and to a lessor extent the gorilla as analogous species to the human and the chimpanzee has frequently served as a model for the human species, it is not clear how long the investigators have known of the difference in chromosomes between the DNA of human and these other species. It would seem this difference would be an important flag in discussing the similarities or differences between these species.

Recently, genetic investigators have asserted(Mukherjee, 2016, page 322) that the human genetic code "is divided into *twenty-three pairs* of chromosomes—forty-six in all—in most cells in the body. All other apes, including gorillas, chimpanzees and orangutans, have *twenty-four pairs*. At some point in hominid evolution, two medium-size chromosomes in some ancestral primate fused to form one. The human genome departed cordially from the ape genome several to over ten million years ago, acquiring new mutations and variations over time. **We lost a chromosome, but gained a thumb**" [emphasis added]. This assertion is essentially gratuitous as all primates have thumbs; the old word monkeys have opposable thumbs. It is compatible with **Figure 1.1.4-2** above but raises the question of whether the departure occurred from the family *Hominidae* or might have occurred earlier from the super family *Hominoidea*. As Schwartz noted, that figure shows, *Sivapithicus* (S) separating from *Pongo* six million years ago and *Australopithicus* (A) separating from *Homo* only 2.5 million years ago. These dates are compatible with the comments by Mukherjee. See **Section 8.1.1.1**. A DNA sample from *Sivapithicus* and/or *Australopithicus* would shed considerable light on this situation.

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[53]Miles, L. (2014) The Ape Who Went to College Washington, DC: Corporation for Public Broadcasting www.youtube.com/watch?v=9mKsDHXwvCE *Also,* http://www.chantek.org/

The large metacentric Chromosome 2 of Homo appears to be the result of a fusion between two smaller telocentric chromosomes found in the other Great Apes[54]. The citation is to a continuing blog of considerable breadth. **Figure 1.1.4-5** shows the most recent graphic evidence for the genetic mutation leading to *Homo*. Genetic evidence of this type largely replaces any discussion of evolution based on cladograms. The arguments between creationists and evolutionists continues with each largely ignoring the evidence presented from the other side. Robert Williams, University of Tennessee Health Science Center, continues to be a principal on the evolutionist side. He has asserted, "only a miniscule 0.15% of the 480,000 biologists and geologists accept creationism." The numbers are obviously his estimates.

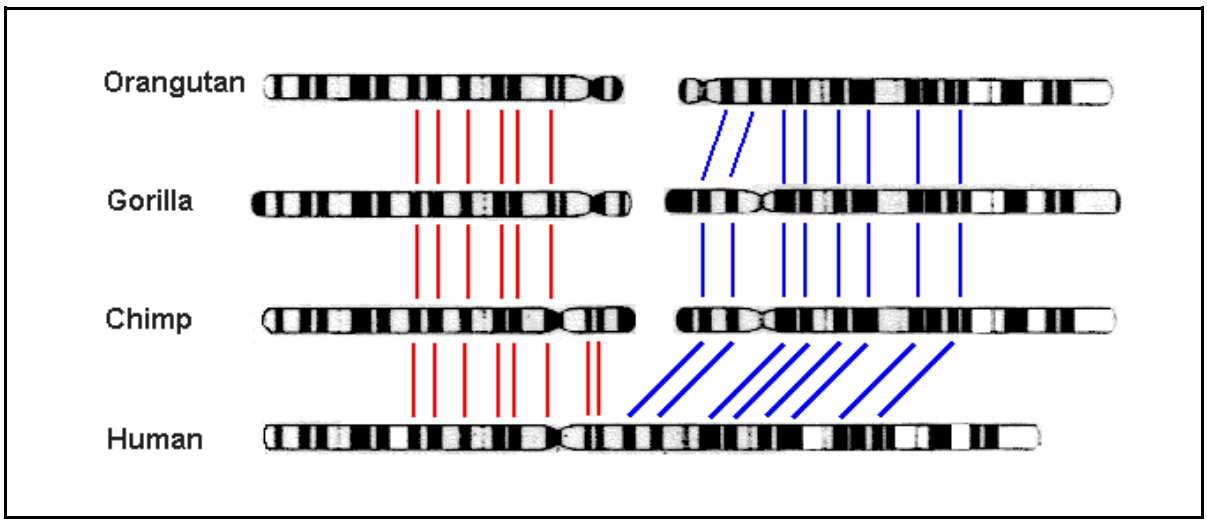

Figure 1.1.4-5 Chromosomal differences between *Homo* and the great apes. See text. From Williams, ca. 1999.

Quoting Williams, "Humans have a characteristic diploid chromosome number of 2N=46 whereas the other Great Apes (orangutans, gorillas, and chimps) are all 2N=48. The large metacentric Chromosome 2 of Homo appears to be the result of a fusion between two smaller telocentric chromosomes found in the other Great Apes. In the figure above, Q-banding patterns in the chimp acrocentrics are homologous to those of the 2p (short) and 2q (long) arms of human Chromosome 2: the alignments are indicated. As well, ape telomeres (the ends of chromosomes) characteristically consist of tandem repeats of the motif 5'-TTAGGG-3'. Such sequences are also present In the human centromere (the middle of the chromosome), but at one point the order changes abruptly to 5'-CCCTAA-3', the reverse complement of the standard pattern, as predicted by a telomere to telomere fusion of ancestral ape-like chromosomes."

This subject is currently of great interest in the genetic literature (search: 24 chromosome ape). Ventura et al. have presented a paper in 2012[55]. The subject matter and nomenclature is highly specialized. Their Sequence Analyses section closes with, "The phylogenetic analyses generally support independent expansions of the duplicated sequences in chimpanzee and gorilla. Using an estimated orangutan divergence of 14 million years ago (mya) from the human lineage, we can approximate these expansions to

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[54]Williams, R. (1999) Comparison of the Human and Great Ape Chromosomes as Evidence for Common Ancestry *In* Stear, J. *ed*. The Evolutions Education Site Ring. http://www.gate.net/~rwms/EvoEvidence.html

[55] Ventura, M. Catacchio, C. Sajjadian, S. et al. (2012) The evolution of African great ape subtelomeric heterochromatin and the fusion of human chromosome 2 *Genome Res* vol 22, pp 1036-1049

have initiated between 5 and 7 mya." Their Discussion section begins with, "In this study, we characterize the genomic organization and evolution of the chromosomal caps of gorilla and chimpanzee chromosomes. We operationally distinguish two genomic architectures—cap regions, consisting of hyperexpanded arrays of human chromosome 2 and 10 segmental duplications (chimpanzee and gorilla, respectively) interspersed with StSat (Fig. 2), and subcap regions composed of lower-copy segmental duplications admixed with occasional tracts of StSat. This subterminal heterochromatin and the corresponding transition regions are absent from the genomes of both human and orangutan." They support the proposition of **Figure 1.1.4-2** that Orangutan and Human are more closely related than humans and either chimpanzee or gorilla. However, many of their experiments did not include the relevant orangutan material. They also note in their figure 7A divergence of species at the 7.18 mya and 4.73 mya points in agreement with Schwartz.

Weiss et al. presented a slightly earlier (2007) paper of narrower scope[56]. It noted, "The human
chromosomes are used as a basis for describing the comparative results and do not necessarily reflect the evolutionary trait that is discussed elsewhere (reviewed in Weinberg[57] of 2005). Weiss et al. noted, "The surprisingly high number of 28 new or refined breakpoints in the orangutan may be due to the fact that these great ape species are not in the focus of science as are the chimpanzees. Therefore, they have not been extensively studied in detail and have not yet been sequenced."

1.1.4.2.3 Relative size and interconnectivity of mammalian brains

Figure 1.1.4-6 shows a recent study among many species of mammals[58]. It shows a significant separation between the human brain and that of other members of *Hominoidea*. This separation might be relevant to the above discussion of the precise phylogeny of the primates. The human brains are all shown with the same volume based on the common calculation by Hanggi et al. The ratio between the corpus callosum and total brain size reflects the individual investigators estimates from the corpus callosum as documented by Hanggi et al.

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[56]Weise, A. Gross, M. Schmidt, S. et al. (2007) New aspects of chromosomal evolution in the gorilla and the orangutan *Int J Mol Med* vol 19, pp 437-443

[57]Wienberg J (2005) Fluorescence in situ hybridization to chromosomes as a tool to understand human and primate genome evolution *Cytogenet Genome Res* vol 108, pp 139-160,

[58]Hanggi, J. Fovenyi, L. Liem, F. Meyer, M. & Jancke, L. (2014) The hypothesis of neuronal interconnectivity as a function of brain size—a general organization principle of the human connectome *Front Human Neurosci* vol 8, article 915

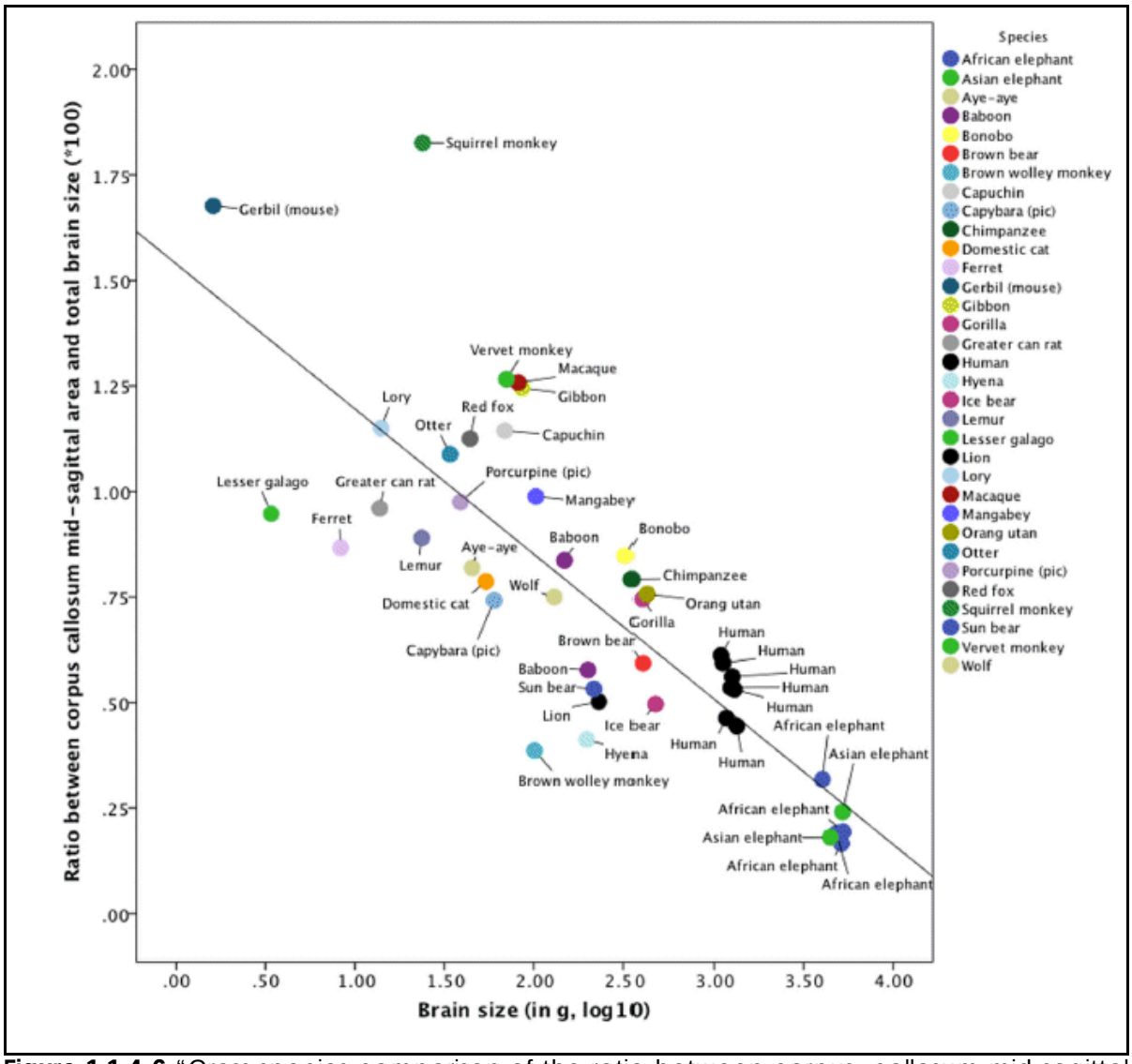

Figure 1.1.4-6 "Cross-species comparison of the ratio between corpus callosum mid-sagittal area and brain size. The values used to construct this scatterplot as well as the references of the publications, from which these values were derived, can be found in Supplementary Table4 of the original paper. .Note that for humans, brain size was measured in cm^3. The explained variance of this linear regression is $R^2 = 0.644$." See text. From Hanggi et al., 2014.

1.1.4.3 A comparison of the physiological model of vision and hearing

The author has recently published two volumes on the operation of the vision and hearing modalities on the internet. These earlier volumes, "Processes in Biological Vision[59]" [PBV] and Hearing: A 21st Century Paradigm" (also available online in expanded form as Processes in

[59]Fulton, J. (2004 & updated through 2018) Processes in Biological Vision http://neuronresearch.net/vision/

Biological Hearing[60] [PBH]) provide earlier descriptions of the discovery of the Activa and the development of the Electrolytic Theory of the Neuron. These works provided a rare opportunity to compare the operation of the visual and auditory systems from a functional perspective. The citations for the paper back versions of these works (not updated) are provided in **Section 1.2.3**. **Figure 1.1.4-7** shows the close parallel between these two systems in chordates. The upper half, representing vision, and the lower half, representing hearing, are virtually identical even when using the conventional morphological names. Only the physiological energy collecting mechanism, the transduction mechanism associated with the sensory neurons, and the information extraction routines, the software, are changed.

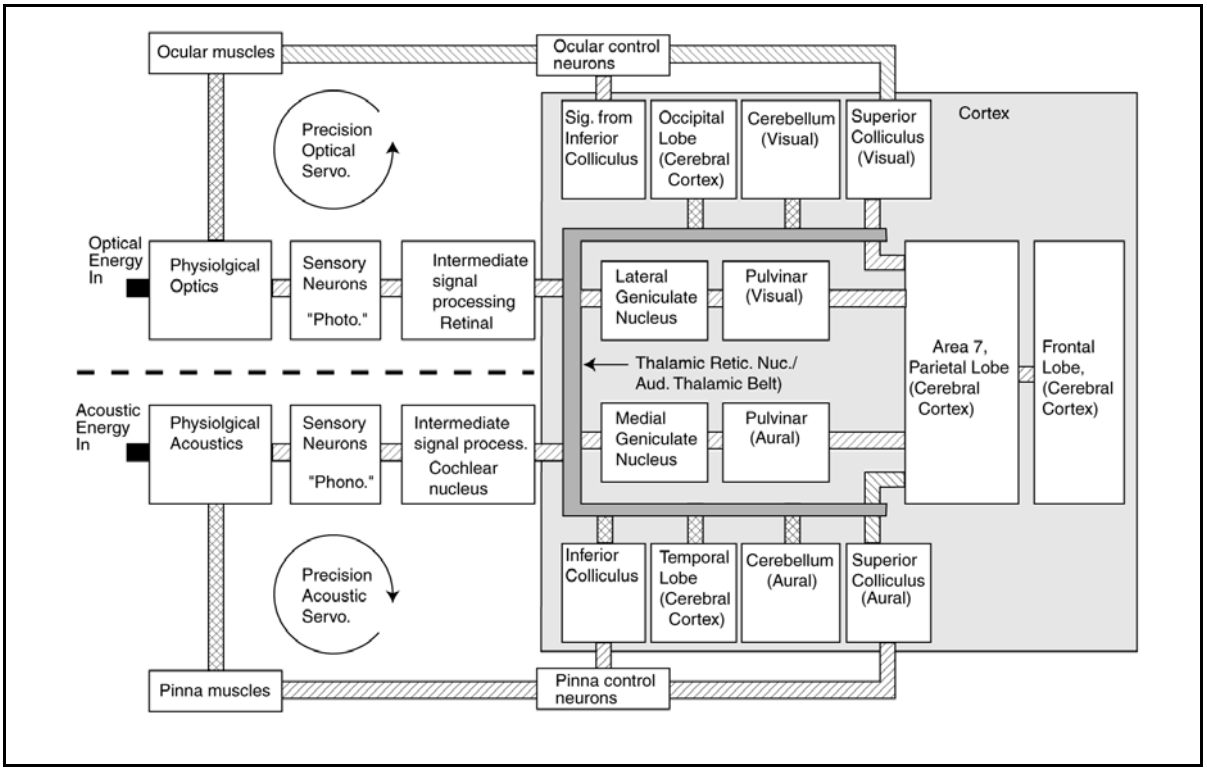

Figure 1.1.4-7 A comparison of the visual and auditory system block diagrams based on the Electrolytic Theory of the Neuron. The figure is generic to many families of the phylum,*Chordata,* but even more specifically to the amniotes. While the ability to move the ears has largely atrophied in humans, it remains a major capability among other members of the phylum.

The figure is generic to all chordates BUT it is proposed that the elements shown *within* the thalamic reticular nucleus (TRN) are developed to a uniquely high degree in humans. The orangutan may exhibit the same elements developed to a lesser degree. A key to understanding how close they are in this relationship may be a function of whether the orangutan exhibits a foveola and can achieve the high visual acuity of human vision.

1.1.5 Top level block diagrams of the neural system

It is useful to be familiar with the modular nature of the neural system and how these modules are coordinated. These functional block diagrams can be compared to the morphology and cytoarchitecture of the system.

[60]Fulton, J. (2008 and updated through 2018) Processes in Biological Hearing http://neuronresearch.net/hearing/

34 Neurons & the Nervous System

Donders has generally been credited with the earliest attempt to organize the functional areas of the neural system[61]. He was seriously limited by the technology of the 1860's. Sternberg reviewed the history of block diagrams over the next 100 years during a centennial celebration of Donders' work[62]. The Sternberg discussion notes that Donders had used the term stages to separate major functional blocks [63]. However, as in Donder's case, Sternberg discussed the block diagram using the basic assumption that the overall system was linear rather than logarithmic in character and involved many alternate paths. He then discusses the intervening history.

> "The work of Donders (1868) that we have been commemorating was based on the idea that the time between stimulus and response is occupied by a train of successive processes, or stages: each component process begins only when the preceding one has ended. Donders developed the subtraction method to measure the durations of some of these stages, and thereby study their properties; mean reaction-times (RTs) from two different tasks are compared, where one task is thought to require all the stages of the first, plus an additional stage. The difference between mean RTs is taken to be an estimate al the mean duration of the interpolated stage. The method was popular for several decades (see Jastrow, 1890) and then came into disfavor (see Kulpe,1895)."
>
> "Although it has seen something of a revival in the last few years (five citations)), little is known about how to test the validity of any particular application of the subtraction method. The underlying conception of the RT as a sum of durations of a series of stages is now a popular one, but there is remarkably little strong supporting evidence. And there is even less evidence that stage durations are stochastically independent, an assumption often incorporated with the idea of additivity (three citations)."

The problems these sources raised was clearly related to the ability of the neural system to learn and subsequently take short cuts based on subsequent activities employing this learning.

Sternberg did introduce "A new method is proposed for using reaction-time (RT) measurements to study stages of information processing. It overcomes the limitations of Donders' and more recent methods, and permits the discovery of stages, assessment of their properties, and separate testing of the additivity and stochastic independence of stage durations. The main feature of the additive-factor method is the search for non-interacting effects of experimental factors on mean RT." A major problem with Sternberg's work is that it does not recognize the multitude of alternate signal paths leading to a specific reaction-time. This work will provide progressively more fine-grained block diagrams leading to a better understanding of the overall system and the resulting performance of the neural system.

The Sternberg paper is well worth reviewing in order to understand the path taken by more recent researchers within the psychology community. His concluding remarks are succinct but do not rely upon any electrophysiological experiments.

- "The additive-factor method cannot distinguish processes, but only processing stages. This distinction bears on the interpretation for example, of the interaction of time uncertainty and relative signal-frequency found by Bertelson and Barzeele (1965) and correctly felt by them to be important in the understanding of preparation."
- "A second proviso about the additive-factor method is related to techniques of data

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[61]Donders, F. (1868/1969). On the speed of mental processing. In W.G. Koster (Trans. & ED.) Attention and performance II: *Acta Psychologica* vol 30, pp 412-431

[62] Centennial Edition honoring Donders (1969) *Acta Psychologica* vol 30

[63]Sternberg, S. (1969). The discovery of processing stages: Extensions of Donders' method *Acta psychologica* vol 30, pp 276-315

analysis. The usual significance tests performed in conjunction with analysis of variance are asymmetric: one is forced to assume that effects are additive (null hypothesis) unless the contrary can be proved. Given the strong implications of additivity, this asymmetry seems particularly inappropriate."
- "The icka of a processing stage that I have presented should be thought of as tentative and subject to refinement by future research."

- - - -

Figure 1.1.5-1 is a block diagram of the complete neural system as found in the higher chordates, including humans (expanded from a similar figure by Randall[64] and subject to further annotation in **Section 1.2.7**). A schematic based on a different perspective appears in Lambert & Kinsley[65].

A little recognized feature of the neural system is the fact the visceral nerve leading to the cardiac and enteric neural systems, is not included in the spinal cord below the vertebra labeled **cervical nerves** (Lambert & Kinsley, page 89). As in the injury to Steve Reeves (an actor playing Superman during the 1990's) cutting of the spinal cord at the base of the cranium leaves the visceral neural system intact. It will also be developed here that the cardiac and enteric systems can be considered total neural systems in their own right. They exhibit both afferent and efferent neural paths and primarily accept high level commands and report only summary sensory information to the CNS (See **Chapter 20**). They do remain subject to the glandular system as they are major participants in the cardio-vascular system.

[64]Randall, xxx (1997)

[65]Lambert,K. & Kinsley, C. (2011) Clinical Neuroscience: Psychopathology and the Brain, 2nd Ed. NY: Oxford Univ. Press pg 65

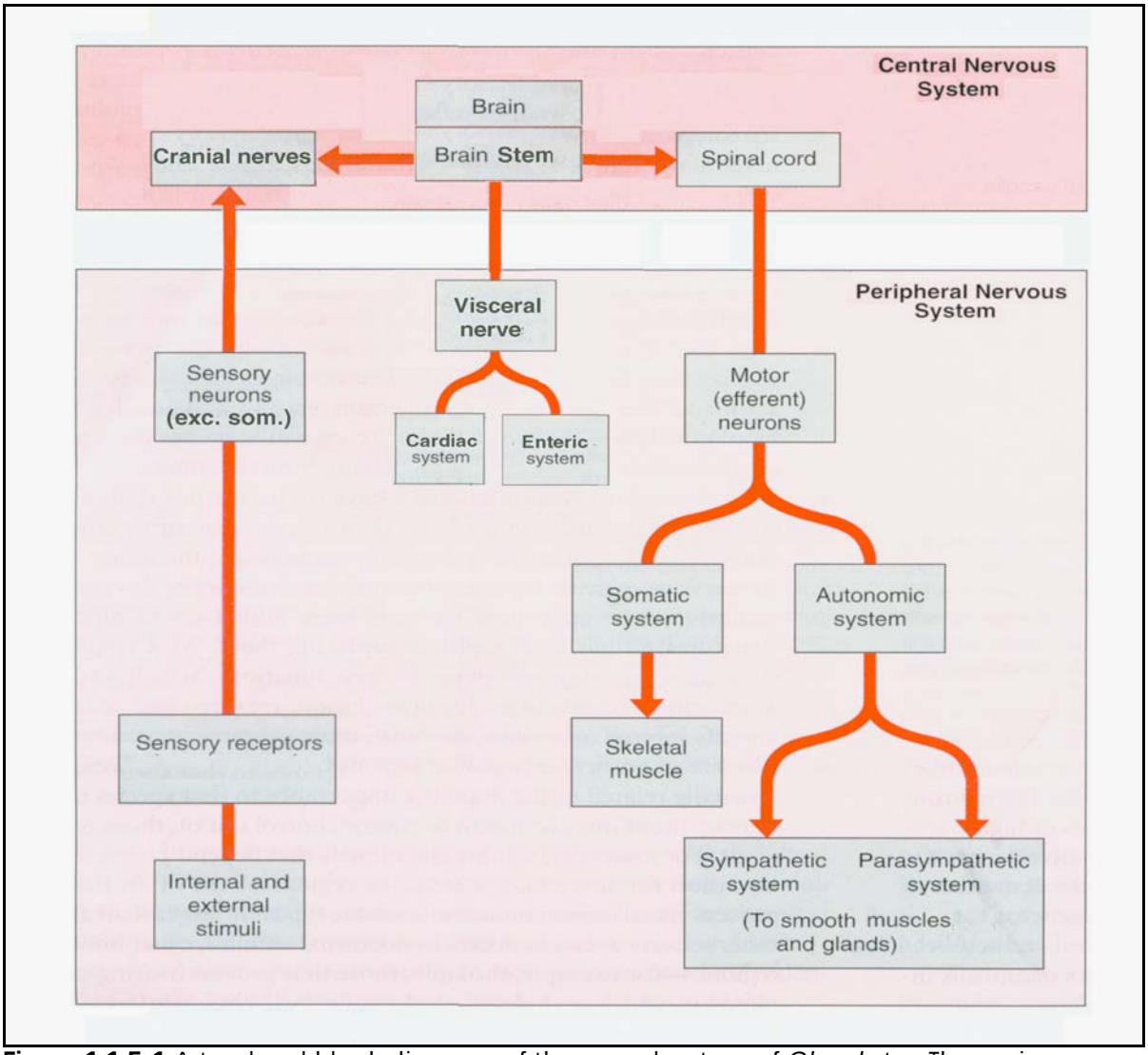

Figure 1.1.5-1 A top level block diagram of the neural system of *Chordata*. The major sensory modalities (except the somatosensory modalities) exit the brainstem within the cranium. The distinctly separate path of the Visceral nerve is also shown exiting the brain stem and leading to the cardiac and enteric systems (that can be considered complete neural systems in their own right). See text. Compare to Randall, 1997.

It is also important to note the major external sensory modalities (other than the somatosensory neurons) are services by cranial nerves that also operate entirely separate from the spinal cord.

Additional details of the somatosensory neuron paths appear in **Section 8.8**.

Figure 1.1.5-2 is expanded over the previous figure to show the general interface between the sensory modalities and the CNS based on the literature and the details developed in the author's other works. Further expansion of the afferent system, including additional couples, will be found in **Chapter 8** and an expansion of the efferent system will be found in **Chapters 10 & 16**.

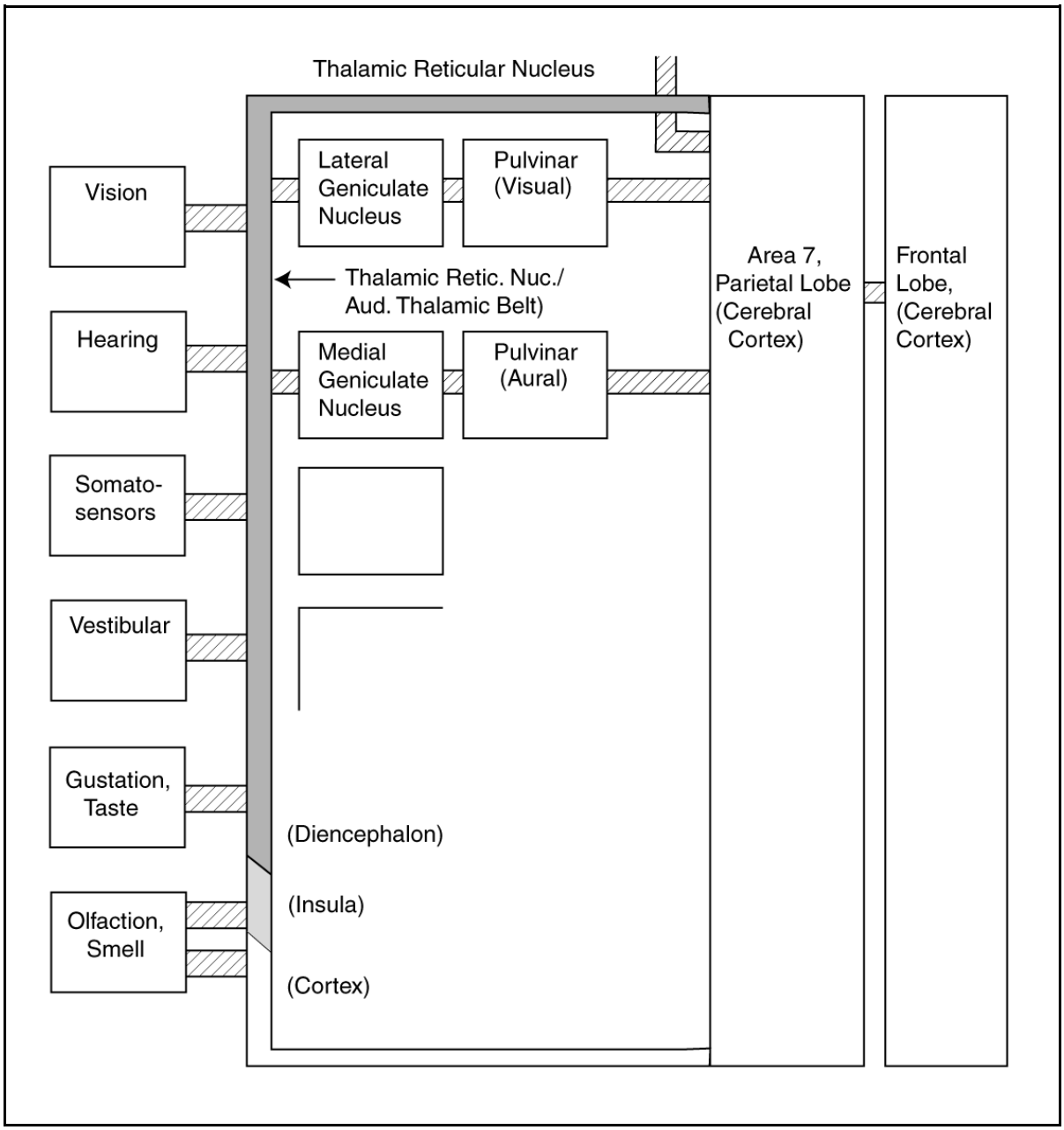

Figure 1.1.5-2 Top level block diagram of the sensory modalities of the afferent neural system. Below hearing, the internal organization of stage 4 of the CNS has yet to be detailed. While there is a recognized path to it, the role of the TRN in olfaction remains to be resolved. See text.

The lower left of the figure highlights the difficulty of comparing the functional and morphological descriptions of the system. The figure is drawn to indicate how all of the sensory modalities interconnect functionally to the cerebral cortex via the thalamic reticular nucleus, even though the morphologist frequently indicate the olfactory nerve interfaces with a transverse gyri, the insula or the cerebral cortex directly (shown in parentheses).. On an inflated or flatmap of the brain (see **Chapter 10**), the mapping between functional areas and morphological areas is not one-to-one.

Figure 1.1.5-3 provides an alternate top level block diagram detailing the many stages of the neural system that will be expanded further in later chapters of this work. *This diagram will be used as the foundation for this work*. This diagram employs a minimum of eight recognizable stages to accommodate understanding of the neural system. Stage 0 is reserved for the non-neural portions of the system that are highly physiologically tailored to the requirements of a given sensory modality but do not involve neural signaling *per se.* The neural based stages are generally numbered orthodromically from the sensory neurons of the specific sensory modality of interest. It is important to note that stage 3 was originally defined as it related to the visual modality outside of the CNS. It soon became apparent that the circuits of stage 3 are used as a fundamental method of signal transmission throughout the CNS, wherever signals must be transmitted over distances exceeding two millimeters. Chapter 9 of this work has been devoted to describing the circuits of stage 3.

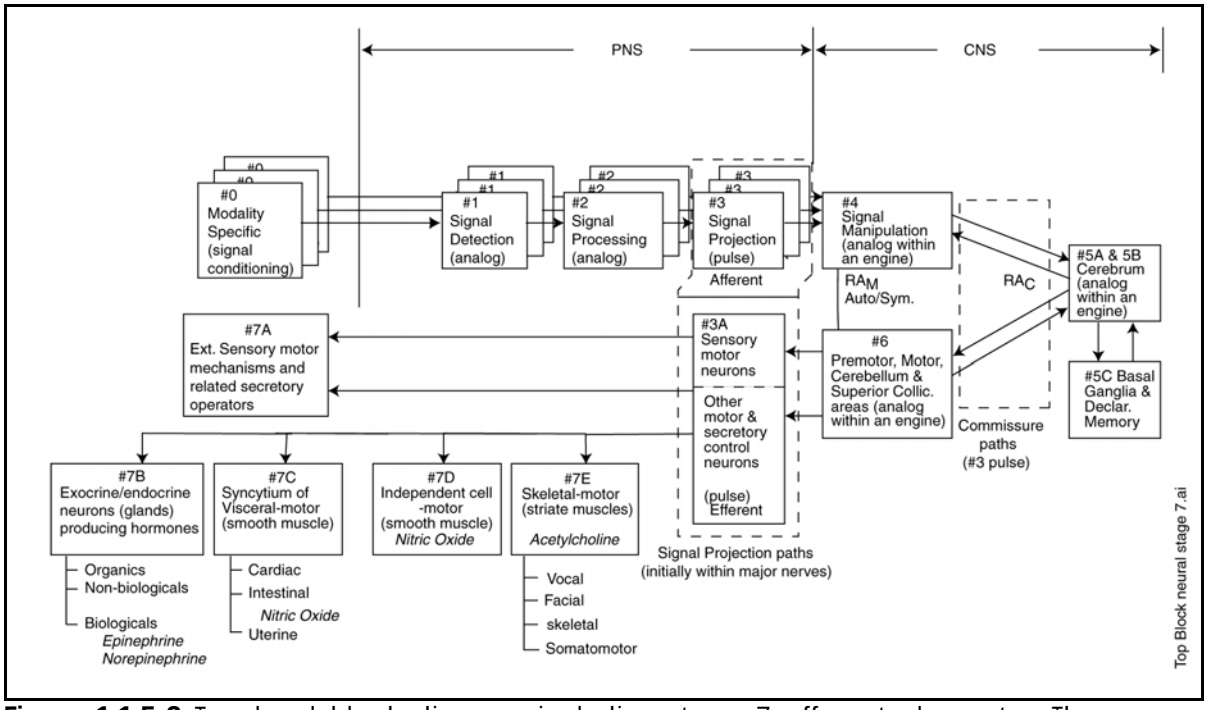

Figure 1.1.5-3 Top level block diagram including stage 7 efferent elements. The sensory modalities of the afferent neural system are shown stacked but without specific identification. The response modalities of stage 7 are shown individually but at a superficial level. The stage 3 engines are shown only in their most important roles. The complexity of the stage 4 information extraction and stage 5 cognitive engines can not be represented adequately in this figure. These stages make considerable use of "star network" interconnections and multiple forms of large capacity memory.

Several variants of this figure have been used in discussions of individual sensory modalities. The details of this figure will be addressed in later chapters of this work. The emanations from the stage 7 neurons typically relate to type 4 conexi (**Section 5.1.2.4**). The major emanations targeting muscles are developed in **Chapter 16**. The major emanations from stage 7 supporting the crine modality (the glandular system) are developed in **Chapter 23**. The most studied part of the crine modality concerns the endocrine subsystem of **Section 23.4**. The lesser known exocrine emanations are developed in **Section 23-6**. The formulation of the stage 7 functional activity is subject to modification as additional inter-relations related to the phenomena involved are developed in the electrolytic context.

Section 16.5.3 develops, and makes it eminently clear, that stage 7 neurons are the only neurons with a prominent pedicle at the end of their axons. These pedicles contain the machinery for generating secretions that affect non neural cells, including the cardiocytes.

Chapters 12 through 17 will develop additional nomenclature to address stage 5 cognition. It will be subdivided into three distinct portions, stage 5A logical cognition, stage 5B emotional cognition and stage 5C cognition support (memory).

1.1.5.1 The advent of comparative physiology at the engine level

Beginning with the 21st Century, investigations have been undertaken to compare the functional physiology of different species rather than behavioral differences. Significant studies have been undertaken among the primates in particular. These studies are beginning to explain why the chimpanzee (Pan) for example can not perform intellectual and hand dexterity tasks beyond that of a 3-4 year old child. These comparative analyses will be addressed in detail in **Chapter 19** xxx on the performance, and variations in performance, of the neural system. The results presented there are based on very small numbers of subjects from a given species. As a result, the conclusions must be considered more as potential differences until larger statistical data bases are developed.

1.1.6 Problems associated with symbology below the level of block diagrams

In any study involving multiple technologies and multiple academic disciplines, symbology becomes a major problem. The symbology of one discipline may appear totally incomprehensible to those of a different discipline. To alleviate this problem in this work, a relatively verbose language will be used along with many citations to papers discussing the symbology used in the appropriate field. **Section 1.2.5.3.3** will develop the problem further and later chapters will address the problem of symbology as required.

Section 1.2.5.3.3 develops a more detailed symbology for use by the bioscience community, particularly by interdisciplinary workers in the computational biology community.

1.1.7 Major discoveries incorporated into this text

The Electrolytic Theory has surfaced many features of the neuron and neural system that have not previously been documented. These discoveries are the primary justification for the Theory. Questions are answered that have not even been asked within the context of the dual alkali-ion or chemical theories. Some of these findings will be summarized here to provide credibility for the overall work. They will be addressed in detail subsequently.

The fundamental principles underlying the Paradigm Shift of this work are five.

A. All neural (and in fact all biological) tissue exists in the liquid-crystalline state of matter *in-vivo*.
Treating neural or biological tissue as in the solid or liquid state of matter leads to erroneous results.

B. All mechanisms operating within the neural system are deterministic.
Variations measured empirically are due to thermodynamic variation or test set limitations (noise).

C. The fundamental neurolemma is a phospholipid bilayer where each bilayer is amphiphilic
The resulting fundamental neurolemma is a barrier to both hydrophilic and lipophilic materials.

The fundamental neurolemma is impervious to the hydrophilic alkali and alkali-earth ions, such as sodium and potassium

D. The fundamental neurolemma (type 1) is a barrier to all electrical charges and forms a near perfect capacitor.
A modified (type 2) neurolemma forms a near perfect semiconducting electrical diode while remaining a barrier to all ionic and molecular transport.

A modified (type 3) neurolemma supports the transfer of electrically neutral molecules through the lemma.

A further modified (type 3( ) or type 5) has been identified recently in **Section 16.5.2.4.1**. The parentheses generally contain a specific amino acid or amino acid derivative.

Section 8.1.2.1 will provide the most definitive discussion of the lemma.

E. The Laws of Semiconductor Physics apply to liquid-crystalline semiconducting (type 2) neurolemma.

Specific juxtaposition of two type 2 neurolemma lead to an "Active Electrolytic Device."

Application of the appropriate electrical potentials to an Active Electrolytic Device results in “transistor-action" and electrical signal amplification.

1.1.7.1 Axioms & Corollaries based on the Major Discoveries

The Neuron is Electrolytic	The Neuron is Semiconducting	The Neuron is a 3-terminal device	Gap Junction is an active device
Neural System is modular & plastic	Neural System is 95% analog	Neural system is exponential NOT linear	2 neural syst. executives
4 chromophores of vision	Tectorial memb. of hearing is passive	Taste has 4 receptors	Smell has 15-25 receptors
Cardiac Muscle is special	Amino acids power neural syst.		

Figure 1.1.7-1 Major discoveries encountered in developing this paradigm shift in the theory of the neuron and neural system. See text.

Each entry in the above table is addressed below in order.

1. The neural system is based fundamentally on the electrolytic chemistry of the liquid-crystalline state of matter (rather than the ionic or electrodic chemistry of dilute solutions.).

The fundamental neurolemma is not porous and the conventional rules of osmotic chemistry do not apply.

The equations of Nernst, Donnan & Goldman, applicable to dilute solutions and porous membranes, play a negligible role in the operation of the neural system.

2. The discovery of the Activa, the active biological liquid-crystalline semiconductor device that is the equivalent of the solid-state semiconductor device, the transistor.

This device, the Activa, is the key to the operation of the animal nervous system. It is the mechanism underlying the apparent excitability of

biological membranes. With the Activa, and a recognition of the passive role the cell membrane plays, the first foundation is established for the Hodgkin-Huxley equations.

3. The discovery that a neuron is a three-terminal device.
   The nominal neuron exhibits three electrolytic structures, the dendritic input structure, the poditic input structure (most easily recognized as the second of the "bi-stratified" dendritic trees in many neurons) and the axonal output structure.

4. The discovery that the "gap junction" is itself an Activa.
   The gap junction is found to be the principal interface between neurons of the animal nervous system. With this discovery, it possible to explain the nearly perfect coupling for the signal current provided by the gap junction. It is also possible to explain the function of the various metabolites in the vicinity of the junction. The "soup or sparks" debate is rationalized.

5. The discovery that the neural system can be described as an orderly system of modules, and that it employs common neural circuits across a wide range of sensory and operating modalities.
   The neural system of the human is highly plastic during the first few years of life. Modules can be reassigned new roles under control of the thalamic reticular nucleus (TRN)

6. The discovery that more than 95% of the neurons in the neural system operate as analog circuit elements.
   All neural circuits employed in sensing, cognition and neuro-affectation operate in the analog mode.

   Less than 5% of the neurons of a mammal employ pulse signaling techniques.

7. The discovery that the neural system is fundamentally nonlinear.
   It employs the diode (an exponential electrolytic device) as its primary electrical element.

   The diodes are used in a large signal mode that employs their exponential current-voltage characteristic.

8. The discovery that the neural system employs two distinct "executives."
   The first is the conscious (or high level) executive of sensation and volition found in the prefrontal cortex.

   The second is the aconscious (or low level) executive operating as the unseen and unperceived coordinator of all physiological functions found in the thalamic reticular nucleus (TRN).

   In many cases, the aconscious executive can control the information presented to the conscious executive

9. The discovery of a new family of retinoids, the Rhodonines, that are the four actual chromophores (sensory receptors) of animal vision.
   The existence of this family solves the longstanding problem of the exact nature of the chromophores and eliminates the protein Opsin from the equation. With their elucidation, it is now possible to establish closed form equations for nearly every phenomena in animal vision. Many of these equations eliminate previously held assumptions from further consideration.

10. The discovery that the tectorial membrane is a passive element in the operation of the cochlea of hearing, supporting the critical role of Hensen's stripe.

This discovery has led to the application of the Marcatili Effect to explain the frequency selection process employed in hearing, and to the elimination of any need for mechanical force amplification and feedback within the cochlea.

11. The discovery of the four gustaphores of taste and the encoding of all taste stimuli into a three-dimensional sensation space.
This has led to the coordination of the myriad behavioral studies on taste sensations, and the rational explanation for the putative role of a fifth gustaphore related to the label, "umami."

12. The discovery that the olfaction modality relies upon coordinate chemistry and the dipole potential of specific stimulants to create an overall sensation in a multi-dimensional olfaction space (estimated 15-25 dimensions).
This finding has rationalized the very limited, and largely speculative, concepts related to the olfactory modality in the literature. It has also led to a fundamental framework explaining the potential for multiple olfactophores in a single molecular stimulant.

13. The discovery of the fundamentally unique form of neuro-mylo-cyte employed in the heart of animals.
The cardiac myocyte includes the functions of a neuron and is more properly labeled a cardiocyte.
While not resulting in any great change in the direction of neural research, it does rationalize the understanding of cardiac operation.

14. The neural system is powered by a unique set of amino acids
The two acidic amino acids, glutamate & aspartate, provide the (principle) negative potential powering each neuron of the neural system.

No other rational for the existence of only these two acidic amino acids has been discovered.

The conversion of glutamic acid (glutamate) to gamma-amino butyric acid (GABA) and carbon dioxide with the release of an electron is the fundamental mechanism powering the neural system.

One of three basic amino acids, lysine, provides the positive potential required to bias some specific neurons, particularly the cardiocytes (cardiac myocytes).

In-vitro experiments without the amino acids in the bathing solution will fail after a short interval.

•The most important of these discoveries was the nature of the basic mechanism that facilitates the neural system. It is the same mechanism that created the recent explosive growth in electronics and communication, “transistor action.”

These axioms and corollaries will be expressed within the semantics of the historical neuroscience community in **Section 1.2.6**.

The metabolic functions of the neuron associated with genesis, growth and homeostasis will be largely ignored in the following discussions. The signaling functions of the neuron are of paramount importance. Failure to differentiate between these roles can lead to considerable confusion.

The neurosecretory functions of neurons is critically important in two distinct situations. First, the sensory neurons create protein material that is utilized internally in piezoelectric sensing and through excretion in the case of epidermal sensory hairs and in the opsin disks acting as substrates in photon sensing. Second, they also release a variety of chemicals as

neuroaffectors of the hormonal system. These functions are distinctly separate from the signaling function. The functions related to sensing are explored in depth in the companion volumes enumerated in **Section 1.1.4**. The neuroaffector role is developed in **Chapter 16**. Smith has also discussed the neurosecretory neurons from a more general perspective[66].

1.1.7.2 Other significant findings

This work has uncovered a variety of unique operating elements and operating mechanisms that relate to the neuron. Some of these are foreign to the historical literature. However, they are critical to an understanding of the neural system of a biological system. This makes them critical to the operation of the visual system.

As discussed in detail below and in other sections, this work accepts the following facts as fundamental:

+ The individual Activas found within the neural system, even within a single neuron, vary considerably in performance. This performance is tailored to the specific function required.

+ ***Internal*** feedback, both positive and negative, plays a major role in the operation of the neurons. Internal feedback has not been discussed previously in the neurological literature. Many types of neurons contain an Activa employed in a feedback loop that is ***internal*** to the neuron.

+ the electrical signaling system in the animal uses the diode as the fundamental resistive impedance--not the resistor. This fact, combined with the active characteristics of the Activa, make the use of Ohm's law unsatisfactory in evaluating the operation of most neurons.

+ the diode associated with each individual lemma of a neuron has a resistive component that has unusual properties of its own.

+ the electrical properties of a membrane vary with the immediate environment on each side of it. They also vary with the temperature and other internal characteristics of the membrane itself. Isolation of the membrane, or significantly changing its electrical environment, will significantly change its performance.

+ the fluid environment surrounding a neuron is an integral part of the functional neuron--disturbing this environment (as by careful washing) significantly affects the performance of the neuron. A neuron should never be washed with distilled water or any detergent.

+ regions of the lemma of a neuron can be subdivided into four distinct subtypes based on their electrical characteristics.

+ ions of the alkali and alkali-earth atoms are unable to penetrate any type of lemma of a neuron.

+ terminal neuron are the source of, and control the release of most hormones.

+ the neurons act in place of putative enzymes in many situations. They provide a substrate and affect a wide range of chemical reactions in place of or augmenting enzymes.

+ the transient overshoot frequently encountered when discussing the

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[66]Smith, C. (1989) The Neuron as a secretory cell, Chapter 14 of Elements of Molecular Neurobiology. NY: John Wiley & Sons

action potential of a neuron at a conceptual level needs to be discussed more completely. The intrinsic feature is frequently a normal result of the active circuitry employed internal to the neuron and does not involve any external feedback mechanism. It is more appropriately labeled the after-depolarization or the after-hyperpolarization as appropriate[67]. On the other hand, the recorded overshoot is frequently caused or emphasized by the parameters of an inadequately designed test set.

+ the cardiocytes (myocytes that are actually neuro-myo-cytes) of the heart exhibit a host of specialized features including several alternate after-depolarization waveforms.

+ a single lemma of a neuron, and particularly the axolemma, does not satisfy the definition of an active electronic device. **All types of individual biological membrane are electrically un-excitable**. They are passive electrical circuits that can generally be represented as the insulator in a capacitor or by a battery and a diode in series. More complex representations may be required if significant capacitance is present or if unusual large signal conditions are forced upon the membrane.

Based on these premises, the reader can clearly see why this work and the discussions and conclusions appearing in the previous literature are not compatible in most respects. On the other hand, most of the data in the literature is completely compatible with the theory developed here.

1.2 Developing the context of this work

As a result of this work, and the author's earlier work in vision, hearing, taste and smell, it can now be said unequivocally that, **The neural system of animals is an electronics-based, not a chemical-based system**. As noted in Section 1.2.5, failure to recognize this fact has caused a significant slowing of the development in this field for the last half century. Until investigators and teachers with broader backgrounds in the relevant engineering and mathematical disciplines appear in the field, progress will continue to be curtailed significantly. It is anticipated that this will require at least a decade. However, one decade is considerably faster than the two decades or more required before the wide adoption of the work of Faraday in the first half and of Maxwell in the second half of the 19th Century[68].

The situation among current professors remains that encountered by Maxwell when he encountered the celebrated Cambridge tutor, Isaac Todhunter during the 1880's. Maxwell bumped into Todhunter outside of his laboratory and invited Todhunter in to see a demonstration of conical refraction, a hot research topic of the day. Todhunter replied, "**No thank you. I've been teaching it all my life and I don't want my ideas upset by seeing it now**." (Forbes & Mahon, pg230)

The neural system exhibits a complexity equal or exceeding that of any system created by man to date. It is necessary to develop a structure to support an orderly discussion of its operation, components and underlying mechanisms. The task is not an easy one. Rose has presented a graphic for use in discussions of the neural system. **Figure 1.2.1-1** reproduces his figure with two substantial changes. First, the label chemical has been moved into the box shared with physical to make way for the previously unappreciated electrolytic regime of the neural system. Without an appreciation of the electrolytic character of the neural system, understanding the system is impossible. The electrolytic operation of the individual neurons and synapses is key to the overall operation of the neural system. Second, an additional state of matter has been introduced above the descriptors, anatomical-biochemical.

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[67]Ganong, (1975) Medical Physiology, 7th Ed. Los Altos, CA: Lange Publishing pg 22

[68]Forbes, N. & Mahon, B. (2014) Faraday, Maxwell, and the Electromagnetic Field. Amherst, NY: Promethius Books

Without an appreciation of the liquid-crystalline state of matter, the anatomical-cytological, biochemical–and more important physiological character of the neural system cannot be appreciated.

The labels are largely arbitrary and he stresses the boundaries between activities are quite fluid. His arrows on the right are very much conceptual. It does not appear he means them to terminate when they meet. This work is focused on addressing the physical fundamentals of the neural system and progressing up through the regimes shown to as close to the top of this hierarchy as the state of the art will allow. Upon reaching the psychological level, the theory of this work introduces a new level of detail that needs to be implemented in many clinical protocols to obtain data at a more detailed and trackable level than previously required. This work does not address the social psychological or purely sociological levels.

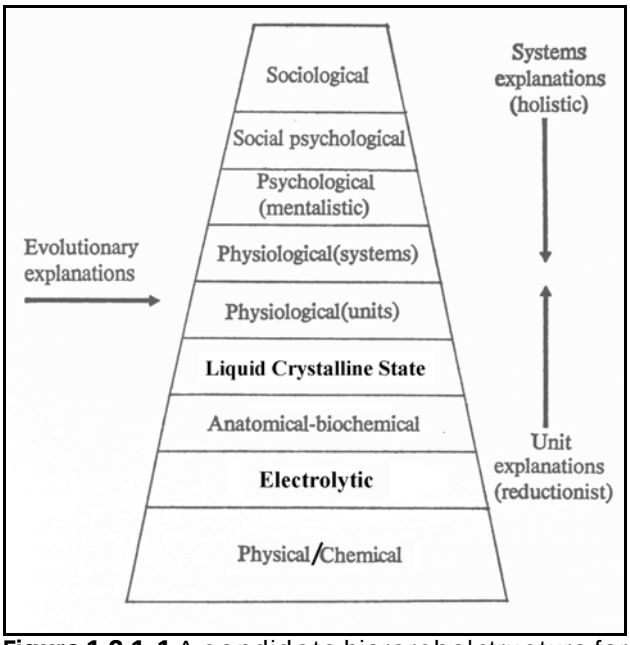

Figure 1.2.1-1 A candidate hierarchal structure for neural research. Modified from Rose, 1976

Shepherd developed a first order linear description of the levels of brain activity shown in **Figure 1.2.1-2**. In his description (on the left), the genes define the roles of ions and molecules within the neural system. The physical size of these elements is irrelevant in this listing.

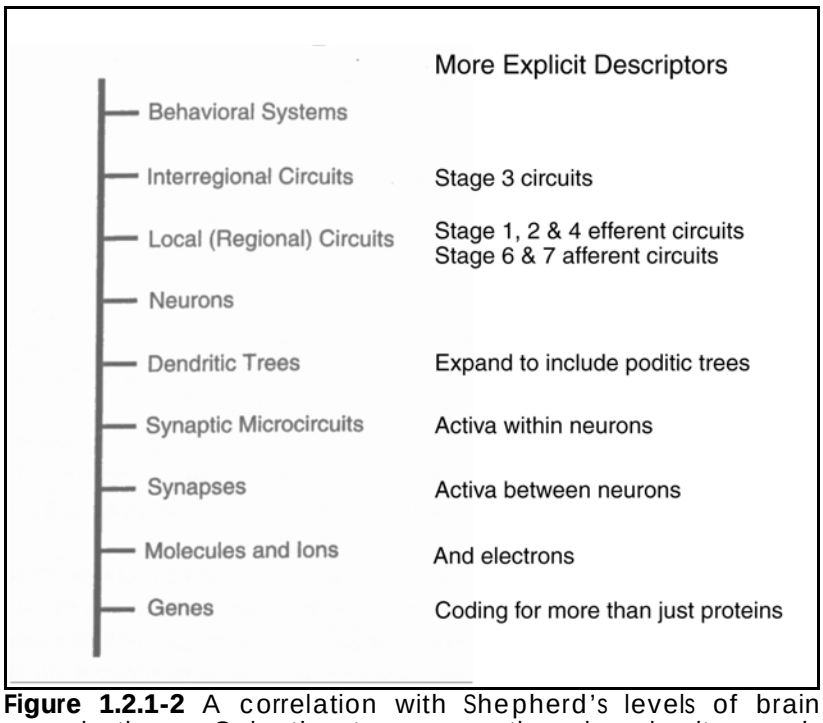

Figure 1.2.1-2 A correlation with Shepherd's levels of brain organization. Only the term synaptic microcircuits needs modification. See text. Expanded from Shepherd, 2004.

He provided a single sentence description of each of these elements. The result is only a superficial description of the architectural, functional and morphological organization of the brain. Recent work in genetics has shown how the genes perform many other functions, including controlling the time of implementation and the rate of implementation of many mechanisms. The figure above the level of molecules and ions can be effectively divided into efferent and afferent pathways.

The right column shows a set of more explicit descriptors based on this work. Except for the ambiguity concerning the label neuron and synaptic

microcircuits, the match is quite good. It is suggested the term synaptic be dropped in front of microcircuits and the functional portion of a neuron be considered a microcircuit formed by the Activa and its associated electrolytic components

Shepherd also compared his interpretation of the organization of the brain to that of the digital computer, and found the digital computer wanting. A better comparison would have been with a large corporate information system with a corporate headquarters, remote sales offices, and remote manufacturing locations; each location having many interconnected computational centers with their own tailored peripheral computers, and all tied together by a private internet.

> The truly unique capability of the brain and neural system is its ability to process *asynchronous analog* signals. Humans have yet to discover how to use this mode of computation successfully in the industrial environment.

Marcus has presented an essay on his conceptual understanding of the brain as a computer. He makes many significant assertions but does not provide any references or citations[69]. In personal communications, he insists the biological brain can perform transcendental calculations, such as correlation functions and integral calculus, based entirely on behavioral data rather than any description of the neural circuit architectures available. He concludes, "The sooner we can figure out what kind of computer the brain is, the better."

This work is designed to address all facets of the neural system, and at least superficially address all aspects of the architecture, function and operation of that system. To achieve this, a more complex set of organizational charts will be presented below. **Figure 1.2.1-3**. summarizes the overall signaling plan associated with the afferent sensory cognitive and response generation modalities of the mammals to be developed in this work. It omits the efferent neural activity which is explored separately below because of its complexity.

[69]Marcus, G. (2015) Face it, your brain is a computer. *NYTimes*, 28 June, Sunday Review, page 12

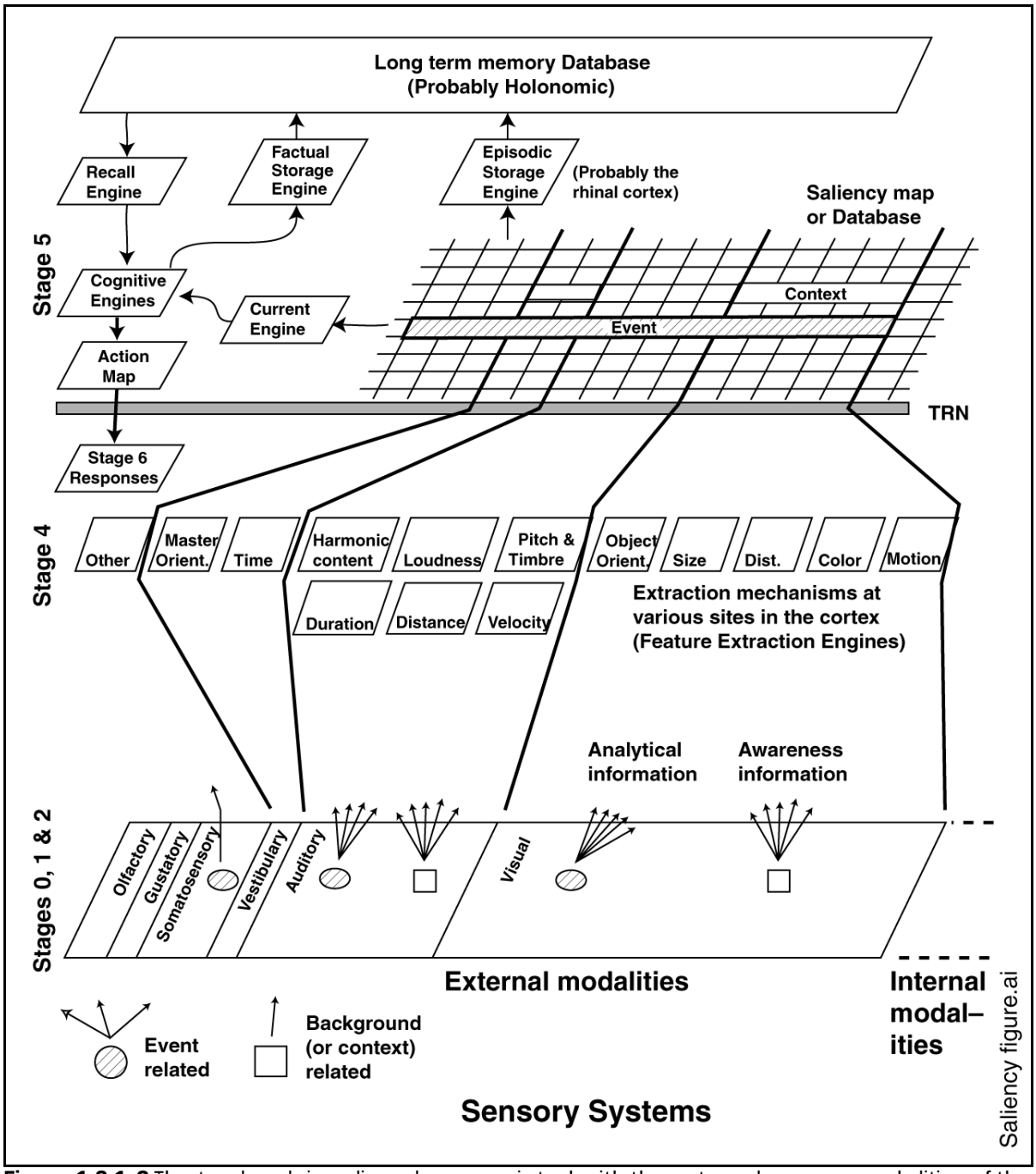

Figure 1.2.1-3 The top level signaling plan associated with the external sensory modalities of the mammal focused on the saliency map as the interface between the stage 4 (information extraction) and stage 5 (cognitive) engines. The bridge labeled TRN represents the thalamic reticular nucleus; the TRN is the main switchboard between the sensory modalities and the central nervous system. It also has a significant role to play in directing signals from stage 2 to various stage 4 engines (not shown).

This figure will be addressed in detail beginning in **Chapter 15**. However, the merged signals from the five historical senses, when combined in the saliency map and presented to the cognitive stage, constitute the "common sense" described originally by Aristotle. Separately,

the discussion of memory in Chapter 17 will identify the instantaneous and/or current version of the saliency map will be described as the working memory portion of declaratory memory; the long term memory database forms the majority of the declaratory memory.

Stage 5, cognition, includes much of the limbic system at this level of discussion. The limbic system both accepts a variety of stage 4 signals and impacts the steps in cognition that develop the instructions forwarded to the stage 6 neurons for command generation. The cerebellum (not shown) is intimately involved with both stages 4 and 6 where it can operate within a variety of very sophisticated reflex arcs. It includes a significant amount of specialized memory not shared with other elements of the neural system. The cerebellum will be discussed in detail in **Chapter 15**.

Figure 1.2.1-4. shows a similar top level block diagram for the efferent neural system and the neuroaffectors of stage 7. The major paths controlling the skeletal muscle system (stage 7A) and the neural source of the hormonal system (stage 7B) are shown explicitly. The individual major and minor glands of the neuro–hormonal interface are not shown. The figure shows the explicit location of electrolytic synapses within the neural system (between all neural stages) and the explicit location of chemical synapses at the neural/non-neural interfaces. The details related to this figure will be found in **Chapter 16**.

As noted in Section

1.2.1 Placing the electrolytic versus chemical theories in context

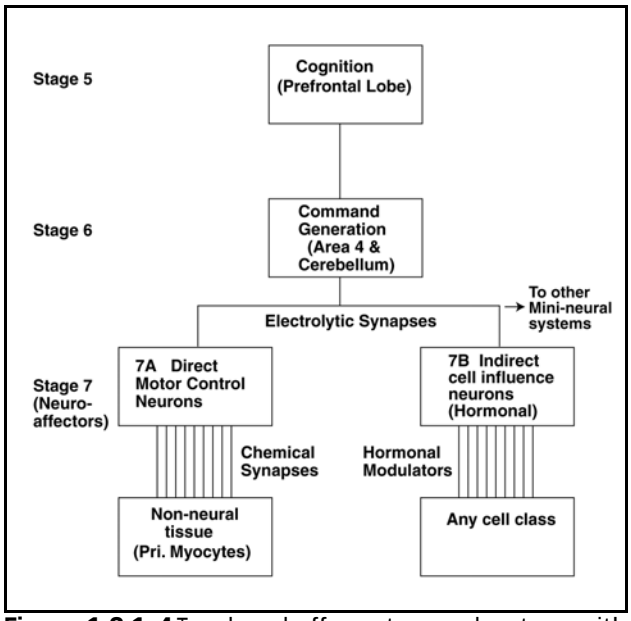

Figure 1.2.1-4 Top level efferent neural system with neuroaffectors. This figure expands on the earlier figure focused on the afferent neural system. See text.

The long-standing argument between supporters of the electrical and chemical theories of neural operation has lacked an adequate foundation. Karczmar et al. have provided an extensive and well referenced description of the arguments made by both sides[70]. All of the arguments are based on experimental evidence at the morphological and pharmacological levels. They lack significant support from the histological and cytological levels. The equivocation of John Eccles under pressure of his colleagues is good evidence of this, discussed on page 10 of Karczmar et al. Interestingly, the most often presented evidence for chemical transmission at a synapse is conceptual in character and always supported using electrical measurements (usually involving stage 7A neurons). Many of these were based on measurements preceding the invention of the vacuum tube amplifier, as well as the transistor amplifier. The critically important electron microscope only appeared in the late 1950's. Even recent measurements have generally been made by researchers with limited background in electrical engineering. Specifically, they lack knowledge of both electrolytic and semiconductor theory and application. Karczmar et al. concluded a portion of their discussion by noting, "The extension of this proof to other spinal sites and to transmitters other than ACh is technically difficult, and the pertinent research is continuing."

Examples of the superficiality of the resultant discussions are common in the literature. Even

[70]Karczmar, A. Koketsu, K. & Nishi, S. (1986) Autonomic and Enteric Ganglia: Transmission and its Pharmacology. NY: Plenum Press pp 9-12

in 1991, page 54 of Brown[71] discusses "two main types of excitatory electrical synapses." He then discusses their features with out a single circuit diagram, or suggestion concerning the impedance levels of the various circuit elements. Nor does he provide citations to the actual research, including the critical test protocol used.

Taylor and Low have discussed the inadequacy of the commonly applied passive diffusion laws to satisfy the measured transfer of amino acids across simple biological membranes[72]. They note most amino acids are hydrophilic molecules with Kp values much lower than 1.0 and invoke specialized (and the politically correct term) "pores" for this purpose. They immediately define pores as actually "Transporters," saying, "Metabolically important amino acid movement across cell membranes involve transporter (or "carriers") rather than channels (aqueous pores)."

The properties of semiconductors will play a primary role in the following discussions. A semiconductor is a material exhibiting an organized lattice structure at the molecular level, typically a solid crystal or a liquid crystal, with a forbidden zone of quantum physics, the distance between the upper energy level of its valence band and the lower level of its conduction band, that is less than one electron-volt. When two such materials are brought into intimate contact, important quantum-physical processes occur. One of these is the so-called transistor effect.

> A metal does not exhibit a forbidden zone by definition, It only conducts current in the conduction band by means of charges (electrons) of only one polarity (negative). Semiconductors are capable of conducting current via two charge-carrying "particles: of opposite sign. The conventional particle is the electron moving within the conduction band from regions of negative potential to regions of positive potential. The second particle is the "hole," the absence of an electron from an expected location within the lattice of a solid crystal or liquid crystal. The hole moves within the valence band from a positive potential region to a negative potential region. The mobility (average speed divided by the electrical field gradient) of the electron and the hole need not be the same in a given lattice. Nor need there be equal numbers of electrons and holes per unit volume of a semiconductor. If there are more negative (electron) charge carriers, the material is defined as *n*-type. If there are more positive (hole) charge carriers, the material is defined as *p*-type.
>
> With a hole actually being an absence of an expected electron at a location in the lattice. The hole is filled by an electron jumping from a previously filled location, thereby creating a new hole. The action is repeated in order to fill the new hole. This saltatory action results in an apparent motion of a positive charge in the opposite direction to the actual electron(s) movement.
>
> In solid state semiconductor devices, it is common to have a positive (*p*-type) semiconductor on one side of a physical junction and a negative (*n*-type) semiconductor on the other. This results in a unique situation called a pn junction. Such a junction is electrically unidirectional and it is defined as an electrical diode. This junction is characterized by a *potential barrier* that will be introduced later. It plays a major role in the permeability of biological lemma to electrons, ions and neutral (but polar) molecules.

Prior to the discovery of the Transistor Effect in the late 1940's, mankind did not possess the knowledge required to understand how the neural system (including specifically the synapse) operated. Lacking such knowledge led to a "Bayesian trap," discussion of the likelihood (probability) that various possibilities contributed to an outcome, when the candidate list of possibilities was incomplete. Only in the time of John Eccles daughter, Rosamond Eccles, could discussions about the possibility of electrical transmission within the neural system be

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[71]Brown, A. (1991) Nerve Cells and Nervous Systems: An Introduction to Neuroscience. NY: Springer-Verlag

[72]Taylor, P. & Low, S. (1999) Investigaton of amino acid transfer across tissue membranes In El-Khoury, A. ed. Methods of Investigation of Amino Acid and Protein metabolism. NY: CRC Press Chap 1

rationally considered. She was the first researcher to actually record neural signals intra-cellularly (Karczmar et al., page 80).

A critical shortcoming in the recent neuroscience discussions (1980 to the present) has been the lack of adequate definition of what is being discussed, i.e., clarity as to whether the investigator is discussing neuron-to-neuron signal projection, neuron to glandular affectation or neuron to muscle affectation. It will be shown the former is entirely electrolytic in character while the latter involve a variety of secretions by terminal neurons. It will be shown the major neuro-affectors (terminal neurons secreting chemical agents) supporting the muscular system can be described as a paracrine (local) form of the neuro-affectors supporting the glandular system. Karczmar et al. (page 38) describe the neuro-affectors of the paracrine (stage 7A) and endocrine type (stage 7B) using his "concept of the paraneurons."

The chemical theory of the neuron that has evolved in the academic community has achieved a level of chemical complexity that is out of proportion to the complexity of the equivalent neural circuits, elements and modalities. As an example, Shepherd has described a single synapse graphically (page 4) along with a description of 12 individual chemical processes/events occurring within that one element. Each of these processes/elements is described using multiple sentences and considerable chemical equation shorthand. His twelfth process/event is labeled "other effects." Karczmar et al. (page 68) have noted that many of Shepherd's listed substances "are intrinsic to the ganglia and their elements and/or are present in the blood." If correct, this ubiquitous presence raises questions about their specific role in neurotransmission.

On the other hand, the synapse can be defined within the Electrolytic Theory of the Neuron as a very high quality "active electrolytic diode" formed from the asymmetrical biasing of a symmetrical three-terminal electrolytic device called an Activa.

Shepherd proceeds to define inhibitory and excitatory synapses without any functional description of their difference. He only notes a minor cytological difference suggesting the presynaptic vesicles in the inhibitory synapse are not round (page 6). The Electrolytic Theory of the Neuron shows that inhibition and excitation are features of the neuritic structure of neurons. The dendrites provide non inverting (in some applications labeled excitatory) inputs and the podites provide inverting (sometimes described as inhibitory) input terminals leading to the three-terminal Activa inside every neuron. The third terminal of the Activa is connected to the output terminal of the neuron typically labeled the axon in its simplest form.

In some contexts, the bi-stratified dendritic tree of the neuron is actually formed of two distinctly different functional parts. The apical dendritic tree (or primary tree) is the true dendritic tree and represents the non-inverting input to the neural amplifier. The one or more basal dendritic trees (or secondary dendrite trees) are actually the poditic trees that provide the inverting input to the neural amplifier. In this expanded notation, the dendrites and podites together can be described as neurites.

Another important feature of the Electrolytic Theory of the Neuron is it presents an entirely deterministic explanation of the neural system, and specifically the operation of all of the examined sensory modalities. The largely conceptual chemical theory has never been able to offer more than probability-based conceptual relationships.

The Electrolytic Theory differs fundamentally from the Dual Alkali-ion Theory proposed in the 1950's and prevalent in the literature to date. It also differs fundamentally from the chemical theory of the synapse.

In the Electrolytic Theory of the Neuron, the neuron contains at least three electrically isolated chambers. Electrons are introduced initially into the interior of the axon chamber through an electrostenolytic mechanism. This action polarizes the interior. Electrons are then removed from the interior of the conduit through an Activa as part of the signal generation function, thereby depolarizing it (**Section 1.2.3)**. It is worth noting that individual electrons pass readily and directly through the type 2 lemma of the neuron and the associated

synapse.

Neuroscience texts oscillate between those that assert a continuous hydraulic path across synapses and Nodes of Ranvier, and those that assert a hydraulic barrier due to these structures and the lemma of the adjacent neural segments. There is no change from electrons within the axolemma to chemical neurotransmitters within the "synaptic gap" and then back to electrons as part of the signaling function.

Finally, considerable data on the intracellular potentials of neurons have been presented in the literature. However, the great bulk of the data lacks two specific characteristics. First, it fails to recognize that neurons contain multiple internal compartments (a minimum of three) related to their neural functions (**Section 1.2.3**). Second, it fails to recognize that neurons are biased to perform a variety of unique tasks. Some of these tasks involve analog signaling and some involve pulse signaling. The quiescent and active potentials of the individual compartments within a neuron (forming the Activa) vary significantly based on their application. Thus, Nishi has noted a range of –40 mV to –110 mV for the "resting potential" of ganglion cells. "This large range is probably due to technical artifacts, such as neuronal injuries or tip potentials of micro-electrodes." In fact, the resting potential of the axoplasm (the collector potential of the Activa) of neurons designed to produce action potentials is typically between –130 mV and –154 mV. However, the resting potential of the axoplasm of sensory neurons is typically –70 mV when biphase signals are processed, as in the visual system particularly. See **Section 8.2**.

Attempting to relate the quiescent potential of an undifferentiated compartment of a neuron to the electrolytic equilibrium constants of ions in solution (particularly Na^+ and K^+) is a total waste of time. Such activities and the determination of relative permeabilities of membrane based on these values is another example of the Bayesian Trap. The neurons employ active electrolytic devices operating at impedance levels far below that of metallic ions and putative semipermeable membranes. Because of their impedance level, and the actual impermeability of the lemma of cells to metallic ions, they are totally independent of any potential related to inorganic ion concentrations. **Chapter 3** will demonstrate these potentials ultimately relate to the electrical energy generated by the electrostenolytic mechanism. This mechanism most prominently transforms glutamic acid into gamma amino-butyric acid (GABA) and carbon dioxide while generating a maximum potential of –154 mV.

> The above facts are clearly shown by a quote from Karczmar et al. (page 81). **"One would then expect that the replacement of Na^+ by an impermeant cation will hyperpolarize the membrane. It is puzzling, however, that only a small depolarization occurs when Na^+ is replaced with impermeant foreign cations." This statement by Karczmar et al. should be *prima facia* evidence for falsifying the chemical theory of the neuron (and as a minimum the dual alkali-ion theory of the neuron). If Na^+ need not be present in the extra-neural environment, its passage through the lemma of the neuron cannot be a critical factor in the operation of the neuron.**
>
> It will be shown in **Section 1.2.5.8** that, the terms sodium current, potassium current, etc. are euphemisms for actual electrical currents flowing in more complex (three-terminal) circuits than envisioned by the (two-terminal) chemical theory of the neuron.

On page 85, Karczmar et al. establishes the semiconductor relationship of the electrical elements of the neuron. On page 87, they present the measured intracellular voltage-current relationship of such a diode (presumably the axolemma of a rabbit neuron). His subsequent pages document the logarithmic characteristic of such diodes and the exponential time constant characteristics of the axoplasm associated with this axolemma. The figure on page 378 of Karczmar et al. clearly demonstrates (to the experienced eye) how the signal projection neurons generating action potentials are in fact analog amplitude driven relaxation oscillators of a well-known semiconductor type. His waveforms relate to the axoplasm of his neurons. Furness & Costa[73], writing in the same time period, have shown similar waveforms. Their analysis is brief and incomplete. Some of their waveforms relate to

[73]Furness, J. & Costa, M. (1987) The Enteric Nervous System. Edinburgh: Churchill Livingstone

the axoplasm and some relate to the dendroplasm and podaplasm of their test neuron. Their data is collected from parametric excitation (excitation introduced into a circuit (compartment) by the investigator while measuring the potential of that same circuit (compartment). The waveforms do not represent *in-vivo* operation of these circuits. Their figure 5.5 (credited to Wood & Mayer, 1978) shows the operation of the axoplasm when excited parametrically by a rectangular current waveform that is passed through a probe forming a lead-lag network (specifically a high-pass network). The waveform of the actual current entering the axoplasm is not shown. The waveform shown is that of their current generator. The time-constant of their high-pass filter is easily determined from these waveforms.

There are electrical engineering textbooks and laboratory experiments illustrating the same *exact* performance as measured by the above investigators. It is only necessary to scale the operating potentials from those associated with a silicon-type transistor to those of a biological-type Activa (**Chapter 1**). Parametric excitation is seldom used in man-made circuits because normal-mode excitation is so easily introduced. It is occasionally used to demonstrate circuit stability under adverse operating conditions. In the context of biology, pharmaceutical intervention, along with exocrine hormone intervention, will be shown to be forms of parametric stimulation (**See Glossary**).

The chemical theory of the neuron as it currently stands is a Bayesian trap created by men unfamiliar (at the time) with electrolytic chemistry, the physical chemistry of the phospholipids and the neurolemma, the existence of liquid crystalline state of matter, quantum and semiconductor physics, and transistor action. This is a result envisioned by Schopenhauer, "Everyone takes the limits of his own vision for the limits of the world."

> ***The two facts; that the cell lemma is fundamentally not subject to the theories of Nernst, Donnan & Goldman, and that the neuron can operate in the total absence of sodium ions, effectively falsifies (refutes) the chemical theory of the neuron.***

These facts are explored in detail in **Section 1.4.2** below.

1.2.1.1 Initial origins of the chemical theory

Since the days of Giovanni Galvani until the 1930's, it had been assumed that the neural system was electrically based. The origins of the chemical theory of the neuron are largely lost in history and little documentation of its development exists in the literature after the mid 1950's, particularly in any comprehensive form. A recent Wikipedia assertion, lacking any attribution is that,

> "A neuron is an electrically excitable cell that processes and transmits information by electrical and chemical signaling."

Brooks has provided a brief overview of a major milestone in the chemical theory in the popular press[74]. He attributes the theory to a dream and subsequent experiment by the German pharmacologist, Loewi, in 1921[75]. It is remarkably difficult to find an English translation of this paper. However, Loewi did synopsize his work twenty-four years later[76]. The naivete of Loewi with regard to electronics expressed in that paper is either appalling, or indicative of the limited knowledge of semiconductor physics and the physiology of the nervous system at that time. The discovery of the vacuum tube was nearly concurrent with his original 1921 "dream" and subsequent experiment, and the discovery of the transistor

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[74]Brooks, M. (2011) Free Radicals. Overlook Press pages 24-26

[75]Loewi, O. (1922) Über humorale Übertragbarkeit der Herznervenwirkung II. Mitteilung *Archiv Euro J Physiol* vol 193(1), pp 201-213

[76]Loewi, O. (1945) Chemical transmission of nerve impulses *Amer Sci* vol. 33(3),pp 159–

occurred virtually concurrently with that 1945 paper. A modern oscilloscope did not appear until the 1950's.

1.2.1.1.1 Overview of the Loewi experiment

Loewi's experiments are described in some detail, but inadequately from an experimental rigor perspective, in his 1945 lecture. In the simplified form used in introductory biophysics classes today, the experiments are described in Chapter 5 entitled Synaptic Activity of Albany.edu class notes[77]. The terminology used is quite different from that of Loewi.

"Introduction

> Otto Loewi studied the heart of the frog, which-like our own hearts- is supplied by two different peripheral nerves. One, the sympathetic nerve, excites the heart and makes it beat more rapidly; the other , the vagus, shows the heart. The problem was to discover the mechanism by which the effects of nerve impulses in either of these nerves are communicated to the heart muscle. Many believed that the electrical nerve impulse spread from the nerve to the muscle as an electrical wave; Loewi thought otherwise.
>
> Loewi tested two isolated frog hearts, one with the sympathetic and vagus nerves intact, the other with the nerves removed. A small tube containing salt water was placed in the heart with the nerves attached. When he stimulated the vagus nerve, the heartbeat slowed, as expected. Then he took salt solution that had been in the stimulated heart and placed it inside the heart without nerves. It too immediately slowed- exactly as if its own (missing) vagus nerve had been stimulated.
>
> He repeated the same procedure, stimulating the sympathetic nerve instead. The effect was again as if the nerve of the denervated heart itself were stimulated: the denervated heart began beating faster. These results could not be explained electrically; the nerves must have secreted chemicals into the salt solution that directly affect the muscles of the denervated heart.
>
> In one simple experiment, Loewi had demonstrated three important findings: (1) that communication at the gap between nerve and heart muscle was chemical, (2) that each nerve released a different transmitter substance, and (3) that it was the characteristics of the different transmitter substances that caused the increase or decrease in heart rate. This was the first direct experimental evidence of the action of chemical neurotransmitters."

Such global level experiments are totally inadequate in today's scientific environment to describe cytological level processes. They only serve to confuse the student in the pedagogical environment. The last paragraph is totally unfounded based on more in-depth knowledge of biophysics of the neural and cardiac systems.

1.2.1.1.2 Refutation of the assertions of Loewi

The fundamental disparaging of the proposals, that the neurons were electrically-based, in the 1945 Loewi paper are easily refuted (falsified). They are so weak, they could only have been shared with sycophants, acolytes and unknowing readers (such as Brooks). Loewi asserted in his opening paragraph;

> "This (electrical) theory, however, encountered two difficulties. In the first place, there is no tissue continuity between the nerve and the effector organ which would permit the electrical wave to pass from one to the other; they are merely contiguous, that is, the end of a nerve fiber makes only a synaptic contact with the effector organ. Secondly–and this was the greater difficulty– how is it possible for electrical waves propagated over certain fibers to increase the activity of the effector organs, whereas impulses from other so-called inhibitory nerves decrease of even stop effector activity?

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[77]Frye, C.(1999) Chapter 5 of class notes, Psy 314. 601 Albany.edu

The theory of electrical transmission was obviously not the answer to the problem."

In fact, based on our knowledge gained in the second half of the 20th Century, the prepositional portions of the above arguments are the very heart of the modern electrolytic theory of the neuron while the conclusion portions are not supported by the facts associated with the prepositional portion. The contiguous but none-continuous character of the synapse at the tissue level is the very essence of the electrolytic synapse as it forms an "active diode" using electrical terminology (**Section 2.4**). The ability of two signals to have the opposite effect on the activity of an effector, or an orthodromic neuron, is totally obvious when the amplifier within every neuron is recognized to be a three terminal device exhibiting a pair of differential inputs. One input to such a device is non-inverting and the other is inverting relative to the output (**Chapter 2**, specifically **Section 2.5.2**).

It must be noted that Loewi's use of a reptile (frog) with a one-chamber heart introduces additional questions about the applicability of Loewi's claims to mammals. No effort was made at that time to show the cells of the reptilian heart exhibited the complexity of the cardiocytes of the mammalian heart (Chapter 20, Section 20.3). The fact that mammalian cardiocytes are hybrids exhibiting the features of both muscle and neuron make the comment by Loewi that he removed the neurons of the reptilian heart either irrelevant or in error. from a functional perspective. He gave no indication of the size of the smallest neurons he removed from his samples and the limited optical resolution of the microscopes of his day could not see the smaller neurons.

1.2.1.1.3 Subsequent reinforcement of the chemical theory

Loewi rose rapidly within the early pharmacology community, achieving the Chair in Pharmacology at the University of Graz in 1909 at 34 years of age. His charisma served him very well after that, but his long time association with Sir Henry Dale was even more important. They shared a Nobel Prize in 1936 based primarily on the simple Loewi experiment and its effective exploitation within a narrow community. Loewi's Nobel lecture on the experiments fifteen years after the fact is readily available[78].

Writing later, Dale who was both an associate and greatest promoter of Loewi's hypotheses said, the discovery "opened a new vista" in biology. He expanded the work and then made the astounding but unsupported claim that "all communications between neurons is chemical."

Due to World War II, Loewi emigrated to the USA in 1940 to join New York University. While Loewi's presence in the modern bioscience community is negligible, his glorification (near deification with a collection of reminiscences published 45 years after his death) continues within the pharmacology community[79]. He was a prolific author within that narrow community.

Loewi did not know, but it is now known, that the functional cells of the heart are not typical of the neural system. **Chapter 20** of this work addresses the heart as well as other visceral organs, of the mammals in particular. The cells of the heart are labeled cardiocytes because they combine the functional elements of muscle cells (myocytes) and neurons (neurocytes). As summarized in **Section 20.3**, it is not possible to remove the neural elements of the heart by histological methods without disassembling every cell of the heart. Alternately, the cardiocytes of the heart at the electrical nodes generate excitatory neural signals *de novo*. While the rate of signal generation by these cardiocytes is affected by their chemical environment of these cells, their immunity to nominal changes in this environment is a major feature.

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[78]: "Otto Loewi - Nobel Lecture: The Chemical Transmission of Nerve Action". Nobelprize.org. 23 Aug 2012 http://www.nobelprize.org/nobel_prizes/medicine/laureates/1936/loewi-lecture.html

[79]Donnerer, J. & Lembeck, F. (2006) The Chemical Languages of the Nervous System: History of Scientists and Substances. NY: Karger

Addressing the oversimplification of his claims, ***Loewi's selection of heart tissue of a reptile as a nominal example of neural tissue of all animals ranks among the great overreaches of exploratory science along with the selection of a locomotion neuron of a mollusc by Huxley and Hodgkin to represent a propagation neuron of a mammal*** (See the next section).

1.2.1.2 Initial comments on the dual alkali-ion theory

The Dual Alkali-ion Theory (involving sodium and potassium as charge carriers) was proposed by Hodgkin & Huxley in their series of papers culminating in 1952. As noted by Hodgkin in an introductory paper[80], their approach did not involve the use of the optimal "scientific method." It was highly constrained. They defined the scope of their work.

"In order to restrict the field, the review has been confined to the problem of conduction in single fibres, and any consideration of *junctional-tissue* or the central nervous system has been omitted. Wherever possible, experiments will be discussed in terms of a general hypothesis, which may be regarded as the modern counterpart of the membrane theory of Bernstein (1912) and Lillie (1923). Briefly, the hypothesis is that the action potential depends on a rapid sequence of changes in the permeability to the sodium and potassium ions. It makes use of the observation that potassium is concentrated inside most excitable cells, whereas sodium and chloride are relatively dilute."

Their constrained analysis was a derivative of an earlier conceptual analysis (based on only the potassium ion) dating from 1912. Although not explicitly stated in the above quotation, their analysis contained other implicit and explicit constraints. The Alkali-ion Theory only applies to the neurons that generate "action potentials." However, they did not explicitly define their action potential. The tone of their discussion suggests they were speaking about the pulse waveforms usually associated with projection neurons in mammals. Less than 5% of the neurons in a given organism generate action potentials (operate in the phasic domain). Most of this 5% consists of *transition* circuits that accept electrotonic (analog) signals and generate phasic signals at their output. The remainder of this 5% consists of circuits that reproduce phasic signals following stimulation by preceding phasic signals. It is this latter small group that was the subject of Hodgkin & Huxley's attention. Thus, their analyses applied to much less than 5% of the neurons in a typical organism. The rest of the neurons operate exclusively in, or form a bridge to, the electrotonic (analog) domain. The Alkali-ion Diffusion Theory has never attempted to explain the operation of the *transition* neurons (typically stage 3 ganglion cells) or the totally electrotonic cells (typically neurons of stages 1, 2, 4, 5 & 6).

The Hodgkin & Huxley exposition contained another major constraint. In their laboratory investigations they denuded their neuron (and axon) significantly to focus on the axolemma of that neuron. This action changed the operational mode of the *in-vitro* giant axon compared with its *in-vivo* operation.

By concentrating on the axolemma of a neuron, as compared to the complete axon compartment, they necessarily constrained their concept to a two-terminal device. A more general exploration in the area, to include "junctional-tissue" would have allowed them to consider a more general situation involving a three-terminal device. The three-terminal device of the Electrolytic Theory overcomes many problems remaining in the Dual Alkali-ion Theory.

The Dual Alkali-ion Theory is based on an explanation of neural operation derived from an understanding of the conventional chemistry of the first half of the 20th Century. It did not consider the quantum-mechanical mechanisms revolutionizing the world of science outside biology at that time. By analogy, the constrained analysis of Hodgkin & Huxley left them attempting to explain the heat source of the stars before the discovery of atomic energy.

Because of these shortcomings, the Dual Alkali-ion Theory has not led to a significant increase in knowledge regarding the detailed operation of the neuron. The expanded understanding

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[80]Hodgkin, A. (1951) The ionic basis of electrical activity in nerve and muscle *Biol Rev*. Vol. 26, pp 339-409

of the amphipathic nature of the axolemma has caused serious problems with that theory. Many investigators have noted the slow progress in understanding the neuron while relying upon the Dual Alkali-ion Diffusion Theory. They have claimed future progress will require a paradigm shift in the basic concept of a neuron. One approach to overcoming these shortcomings has been the conceptual introduction of pores and gates into the membrane forming the lemma. This approach is clearly a crutch designed to support an inadequate model.

1.2.1.3 Initial comments on the chemical theory of the synapse

The physical dimensions of the synapse are extremely small, the diameter of their active cross section area is measured in nanometers, not microns or millimeters. This size has constrained many investigations into their physical structure and the detailed content of the space between the adjacent pre- and post synaptic lemma..

The chemical theory of the synapse has long been conceptualized based primarily on the identification of receptor sites on post-synaptic neurites sensitive to a variety of pharmaceuticals. The assumption has been that, since these sites are receptive to these pharmaceuticals, there must be a matching secretion site associated with the nearby axon releasing these chemicals. Many papers have been written proposing an alternate electronic theory of the synapse. It appears the Dons of physiology determined that only the chemical theory was correct during the 1950's and 1960's. Little peer reviewed material has appeared since relating to the electronic theory of the synapse. In the last two decades, the atmosphere has softened and a few tentative proposals have been made that call for or recognize electronic synapses in specialized (but statistically dominant) situations.

Efforts have been under way for many years to demonstrate that chemical secretion is the crucial step in the operation of a synapse. No laboratory has successfully demonstrated the manufacture of such materials within the axon, the secretion of these materials by the axon, or the transport of such materials from the axon to the neurite within the very confined space of the synapse. Alternately, the Electrolytic Theory shows that the pharmaceutically identified sites on the neurites are actually associated with either of two electrostenolytic processes. The first type of site creates the electrical power that drives the neural system. The second type of site accepts neuromodulators that influence operation of the neuron.

This work presents an alternate theory defining a neuron and synapse that are entirely electrolytically based. It provides a paradigm shift in approach that explains the operation of both phasic and electrotonic neurons. Furthermore, it provides a consistent analytical framework and explanation of the detailed operation of all types of neurons. The level of detail goes beyond even the level of questions that can be posed under the above chemical diffusion-based theory.

1.2.1.4 Initial comparison of the Electrolytic and Dual-Alkali theories

> **No legitimate method of comparing the Electrolytic Theory of the Neuron (and neural system) with the Dual Alkali-ion Diffusion Theory** exists due to the artificial constraints introduced into the latter. The Electrolytic Theory focuses on the “junctional-tissue” occurring within and between neurons. This “junctional-tissue” was dismissed as irrelevant in the Dual Alkali approach. **The Electrolytic Theory also addresses quantum-mechanical mechanisms largely unknown at the time of the Dual Alkali approach.**

Three papers by the Moises team[81],[82],[83] are key to showing how individual elements of the chemical theory of the neuron can be incorporated into the more general electrolytic theory of the neuron. The last paper is a comprehensive review that contains new material but calls on the earlier two papers. These papers will be discussed in detail in **Chapter 16**.

Experimentally evaluating the neuron has been difficult in the past because of the extremely high impedance levels involved. The equivalent resistance associated with a square micron of biological membrane frequently falls in the region between 500 megohms and 5000 megohms. Shepherd said that "The generation of ionic currents useful for the propagation of action potentials requires the movement of significant numbers of ions across the membrane in a relatively short period of time.[84]" The statement is correct from a physiological perspective if the word ionic is deleted and the word ions is replaced with charges. However, it is misleading from an instrumentation perspective. The currents associated with the typical neuron at operational voltages are quite small compared with the capability of normal chemical instrumentation. A saturation current of 25 pA current (which is relatively large) calculates to only 16×10^7 charges per second passing a given surface plane. For a more common 2.5 pA current lasting only one millisecond, only 16,000 charges need pass through a given surface. When compared with Avogadro's Number, this is an extremely small value. This number of charges remains far below the measurement threshold of current techniques of physical chemistry. Therefore, confirmation of many proposed ionic currents in neuroscience by chemical means remains elusive. 16,000 charges is less than one micro-micro-micro-mole.

On a related subject, Puil has given estimates of the amount of glutamate needed to excite a functional spinal neuron[85]. "Using several assumptions, the threshold amount of S-glutamate which is sufficient to excite a cerebral cortical neuron is believed to be about 10^{-14} mole and this may serve as a first approximation of the amount of S-glutamate require to excite a spinal neuron." 10^{-14} mole is 10,000 micro-micro-micro moles.

Considerable care is required if such small currents are to be measured at such high impedance levels using electrical instrumentation. The capacitance of the test probes frequently affects the measurements severely. In at least one paper published from a prestigious institution, a figure reproduces the transient response of the test probe rather than the target element of a neuron.

Ignoring the individual concepts involved in the Alkali-ion Diffusion Theory will frequently be necessary in the development of this work. This may be difficult for some readers to accept.

1.2.1.5 Null, alternate and proposed hypotheses

In Science, a null hypotheses is offered with the intent that it be struck down and result in an improved hypotheses. Frequently a comparison is made between the stated null hypothesis and an attractive alternate hypothesis, on the assumption the alternate will survive where attacks on the null hypothesis refute it (falsify it in Popper's lexicon). A proposed hypothesis is generally the surviving hypothesis of the above process.

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[81]Washburn, M. & Moises, H. (1992) Muscarinic responses of rat basolateral amygdaloid neurons recorded *in vitro*. *J Physiol* vol 449, pp 121-154

[82]Womble, M. & Moises, H. (1992) Muscarinic inhibition of M-current and a potassium leak conductance in neurons of the rat basolateral amygdala *J Physiol* vol 457, pp 93-114

[83]Moises, H. & Womble, M. (1995) Acetylcholine-operated ionic conductances in central neurons *In* Stone, T. *ed*. CNS Neurotransmitters and Neuromodulators: Acetylcholine. Boca Raton, FL: CRC Press pp 129-148

[84]Shepherd, G. (1998) Synaptic Organization of the Brain, 4th ed. NY: Oxford University Press pg 45

[85]Puil, E. (1981) S-glutamate: its interactions with spinal neurons *Brain Res Rev* vol. 3, pp 229-332

The hypothesis provided by this work has passed many tests and even demonstrated its predictive capability (for instance, it explains why the organic inositol ligand is perceived as salty even though it contains no sodium, lithium or for that matter chlorine). The reason is simple *muco*-inositol is the ligand used as the receptor of the sensory receptor neuron supporting the sodium sensitive gustatory channel. Thus inositol as a stimulant forms a dimer with the *muco*-inositol used as the sodium channel receptor, thereby stimulating the perception of inorganic sodium.

The hypothesis and its corrollaries presented here is very robust, has passed many tests, is the only comprehensive hypothesis available and is therefore offered as a proposed hypothesis with elements of a theory. Other investigators are encouraged to treat it as a null hypothesis and attempt to refute any and all parts of it. However, totally semantic arguments cannot be considered a serious refutation. Data is the necessary ingredient in any refutation. In optimum form, the data should be statistically precise (a standard deviation significantly less than 1/3 of the mean value).

1.2.1.6 Tabula Rasa hypothesis and John Locke

Tabula rasa is the epistemological theory that individuals are born without built-in mental content and that their knowledge comes from experience and perception. John Locke (1632-1704) stated the concept even more specifically according to Wikipedia, " tabula rasa was the theory that at birth the mind is a ``blank slate'' without rules for processing data, and that data is added and rules for processing are formed solely by one's sensory experiences."

While very influential in a wide variety of fields in 17th Century British philosophy, his position relative to the operation of the neural system on reflection seems primitive and simplistic. While it can be argued the mind is not fully developed at birth, it is also true that a wide variety of animals are able to walk and even run within moments of birth. Human babies are generally credited with being able to respond to sounds prior to birth and to recognize a variety of simple objects very shortly after birth. There seems little doubt that the autonomous neural system is sufficiently developed prior to birth that it supports respiration, cardiac circulation, digestion, excretion and a wide variety of other functions at birth. These activities are not compatible with tabula rasa. The fundamental framework, the majority of the interconnections of the neural system, and many algorithms required for survival are in place prior to birth.

Subsequent to birth, a wide variety of neural capabilities are further optimized through learning and implementation of a very high capacity memory.

1.2.1.7 The value of a definition over an empiricism

Yockey (page 45) has provided a useful evaluation of a definition! "We are always allowed to make definitions, provided we also prove theorems that show that the new concept is not merely a convenient empiricism. Definitions are useful if, and only if, such theorems exist, otherwise they are empty." As is obvious from reading the biological literature, most so–called definitions are in fact "convenient empiricisms!"

1.2.2 Preview--initial description of an Activa & top level glossary

This work will define and redefine many terms in order to achieve greater clarity and specificity. This will be awkward with respect to some terms used previously in a conceptual manner; often these terms have been given different meanings during different time periods. "Neurotransmitter" and "action potential" are two specific examples.

> This work will subdivide the conceptual term neurotransmitter into multiple more precise terms, and then assign the term neurotransmitter to the only actual element flowing between neurons for signaling purposes, the *electron*!
>
> Historically, "action potential" has been used to define virtually any electrical

waveform recorded from a neuron. Both analog and pulse waveforms have been given this designation indiscriminately. This work will separate these waveforms into an analog group (generator potentials, signal processing potentials and neuro-affector potentials) and a pulse group (true action potentials used in stage 3 signal projection). As noted, true action potentials have been documented primarily in mammals. However, their presence in reptiles and other advanced families is likely. They have not been documented in *mollusca*.

The analog waveforms are clearly not limited to the on or off condition. Comments asserting unequivocally that the neural system is limited to on-off signal propagation must be avoided[86], especially when they are refuted on another page in the same volume (Katz et al, pg 37) by a different author. At the detailed level, the action potentials of the stage 3 signal projection neurons do not have an "on" state, the criteria is the presence or absence of a transient pulse within a given time frame.

At this point, the discussion is beginning to use a large number of specialized terms. Although some of the following terms have not yet been introduced, it is useful to provide an initial glossary related to this text. The figures needed to understand these terms fully will appear in the following sections. This brief glossary is placed here to remind the reader that all terms used in this text are precisely defined. This precision reduces the amount of wiggle room and encourages greater precision in discussions related to this text. A comprehensive glossary appears in **Appendix A**.

Communications– The general concept used in biology describing communications between organisms is not employed here. Such communication is typically associated with a first messenger, the carrier of the "message." Investigators have attempted to continue the analogy by defining a second messenger as a conceptual material within the second organism (**Section 1.1.5.5**).

In this work, communications is much more specific. It consists of the signals within the neural system used to pass information to the CNS and the signals within the neural system used to execute the instructions of the CNS. In brief, communications is the transfer of sensory information, instructions, and skeleto-muscular commands within the biological organism.

Conductance–The ratio of total net charge transported through a two-terminal substance per unit time divided by the potential applied to that substance. The conductance must frequently be further specified with respect to steady state versus dynamic conditions. It frequently shows variation when operating under small-signal versus large-signal conditions. Within the substance, it is frequently useful to differentiate between the various types of charge transport found. This differentiation can lead to the description of (specific) ion conductance, electron conductance and hole conductance.

Electrostenolysis– The generation of an electrical potential across a type 2 or 4 lemma (bi-layer membrane or BLM) as part of a chemical reaction. The reaction occurs on one surface of the membrane acting as a catalytic substrate. The potential is a response to the movement of fundamental electrical charges through the membrane.

Fundamental charges–The electron and the proton (and the emulation of a proton known as a hole–literally the absence of an electron).

Hole–The idea of a location in an otherwise neutral crystalline molecular lattice where an electron is missing.

Hole transport–The apparent motion of positive charges through the valance band of a liquid or metallic crystalline material by electrons jumping from one electronic void in the lattice to another. The average velocity of this motion of electrons described the apparent mobility of the holes. See **Section 1.2.1.3**.

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[86]Katz, et al. xxx (1999) page 16

Interneural matrix (INM)–The electrolyte surrounding one or more neurons.

Intra-axon–A segments of axon connecting two Nodes of Ranvier.

Intrinsic battery– A representation of a quantum-mechanical junction in a crystalline material where the charge distribution is not uniform. This "intrinsic battery" is not capable of supporting an external current in the performance of thermodynamic work (the generation of heat).

Ion-pump– A conceptual mechanism for causing the transfer of ions from one side of a cell membrane to the other. Such a conceptual mechanism is redefined in this work based on the underlying mechanisms. It is considered a type of charge-pump. See also electrostenolysis and electron-pump.

Neuron–A specialized organic cell used to communicate information from one portion of the animal to another. The definition of the neuron is frequently extended to neuro-secretory cell. This is because of the propensity of the terminal cells in a signal path to exhibit a distinct secretory function. The elementary neuron is characterized by three signal carrying electrical structures converging on an active electrolytic device within the cell, the Activa. The neuron contains internal electrically-insulating partitions. It is also characterized by a group of specialized regions of the plasma membrane associated each of these partitions.

Permeability–A term synonymous with conductivity but usually restricted to the bulk conduction of ions, uncharged particles and other molecules through a permeable bulk material. The term has been subject to reinterpretation to satisfy various theories of the BLM (Troshin, 1966, pg 3)

Resistivity-- A measure of the bulk electrical properties of a material. It is typically proportional to the thickness of the material and inversely proportional to the cross sectional area that a current passes through traversing the material. Thus, it has the units of Ohm-cm in the CGS system. See also thin-film resistivity.

Signal transduction–

1. (with respect to the hormonal system) An intracellular cascade of biochemical events that follow the interaction between extracellular growth factors and their membrane receptors, ending in the switch of nuclear mechanisms controlling the proper biological responses. (Battistini, et. al. 1993 in Papa & Tager)

2. (with respect to the sensory mechanisms of the neural system) The transfer of acoustic energy, electromagnetic energy or tactile motion by quantum-mechanical sensors into free electrons that can be further processed by the neural system.

Signaling–The transfer of sensory information, and skeleto-muscular instructions and commands over the neural system of the biological organism. Does not include the communications carried out by the hormonal system.

Thin-film resistivity– A measure of the electrical properties of a material having a characteristic (largely invariant) thickness such as a bilayer membrane. Defined as the resistivity of the "bulk" material multiplied by the nominal thickness of the film. Units are Ohms-cm^2. See also resistivity.

1.2.2.1 Types of neurons

Seven functionally distinct classes of neurons are known. These are the signal detection neurons, the signal manipulation neurons, the hybrid neurons, the signal projection neurons and the affector neurons. Those of importance here include;

Projection neurons--Neurons optimized to transmit information over long distances within the animal. The distances are longer than one mm. Frequently described as principal

neurons or relay neurons. They accept action potentials at their input and produce action potentials at their output. They are found in the stage 3 circuits of this work.

Sensory neurons– Significantly modified neurons where their input structure has been adapted to accept energy from the environment of the organism.

Interneurons– Neurons optimized to process information within a local area (one mm.) prior to transmission. Frequently described as intrinsic neurons. Exhibit electrotonic (analog) waveforms at both their input and output. Bipolar and lateral neurons are members of this group. These neurons are found in the stage 2 and stage 4 circuits of this work.

Lateral neurons–Neurons recognized morphologically as connecting parallel neural signaling paths generally within the 1st and 2nd lateral processing matrices of the retina. This group includes the horizontal neurons and the amercine neurons of stage 2 circuits.

> **Amercine neurons**--A special type of interneuron in which the axon and one neurite are next to each other and are surrounded by a common section of plasma membrane. The structure of this type cannot be discovered by morphological techniques except using electron microscopy. An electron-micrograph can image the interior membrane wall between the two structures. Alternately, careful electrophysiological measurements can identify the different electrical potentials between the axon and the neurite. This type of neuron is found in stage 2 circuits.

Encoding neurons--Also known as ganglion cells in vision. Hybrid neuron cells that generate "action potentials" at their output in response to electrotonic input signals. Used in stage 3 circuits.

Decoding neurons–Hybrid neurons used to receive "action potentials" and to generate electrotonic waveforms in support of further signal processing within the brain or to control muscle tissue. The stellate cells of the cortex are typical examples. Used in stage 3 circuits.

Affector neurons– Neurons developed to exude, or otherwise release, a variety of chemicals for purposes of influencing non-neural, and also modulate neural, cells of the organism.

1.2.2.2 Cytological parts of a neuron

Figure 1.2.2-1 is a preview of a complete neuron as developed in **Section 1.2.2**. It is shown without further elaboration except for the definitions following in this section. It highlights the internal complexity of the neuron and the variety of fuels required for its ontogeny and homeostasis. The internal activa shown at center-left is the key active functional element in a neuron.

Discussed more fully in **Section 8.1.1.2** is the fact that proteins and peptides play only a limited functional role in the neural system. Individual neurons, and knots of neurons, frequently described as engines in this work, depend on other elements of the neural system for physical support. The role of proteins is primarily within the nucleus, the ribosomes and other organelles involved in creating the many types of non-protein molecules used in the cell (such as the basically non-protein lemma and the reticular membrane). While many protein-based enzymes have been identified within the neuron, these enzymes primarily mediate the action of other non-protein molecules and more complex molecular structures (such as films of liquid crystals). **Section 1.2.8** and **Section 8.1.1.1** review the 21st Century understanding of the genetic code as it has evolved radically from its 20th Century interpretation.

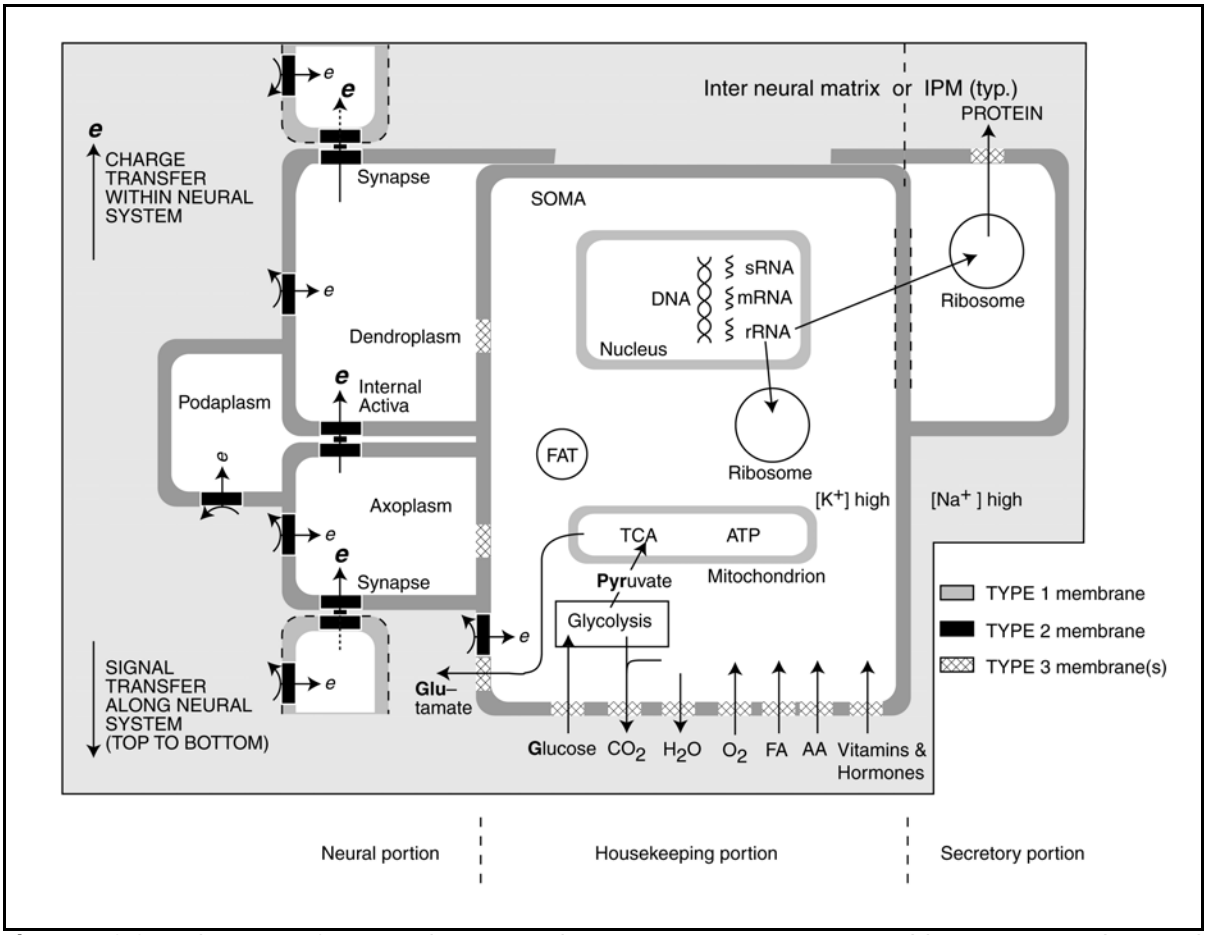

Figure 1.2.2-1 Diagram of a complete generic neurosecretory neuron. This neuron can be used in a wide variety of neural applications with a minimum number of optimizations. The role of proteinaceous material in the neuron is primarily for the purpose of creating other non-proteinaceous molecules and structures. Within the neuron, this proteinaceous material is focused on the various ribosomes and their initial sources within the nucleus. See text.

Figure 1.2.2-2 presents the electrical circuit diagram and the histological configuration of a basic neuron. As above, the detailed description of this figure will be found in **Chapter 1**. It is shown here to provide a preview of the level of detail found in this work. Functionally, the nucleus plays no role in the signaling operations of the neuron. The nucleus is outside of frames A and B of this figure. The Activa is labeled A (the transistor symbol) in frame A. It is enclosed by the dashed box in frame B where its fundamental histological structure is shown as a sandwich of two lemma with a region of liquid crystalline water between them. Each chamber of the neuron exhibits a separate and distinct operation potential, V_D, V_P & V_A.. Frame A also indicates the fundamental relationship between the supply potentials serving these chambers.

Nucleus--That portion of a neuron concerned with the control of growth and maintenance of the neuron. It is responsible for producing the various versions of DNA and RNA distributed within the cell. The nucleus does not participate in neural signaling.

Activa--The functional portion of the neuron, an active three-terminal electrolytic semiconductor device found (1) within the cell body and (2) at the junction of the neuritic (dendritic and poditic) and axonal structures. It is recognizable by electro-physiological

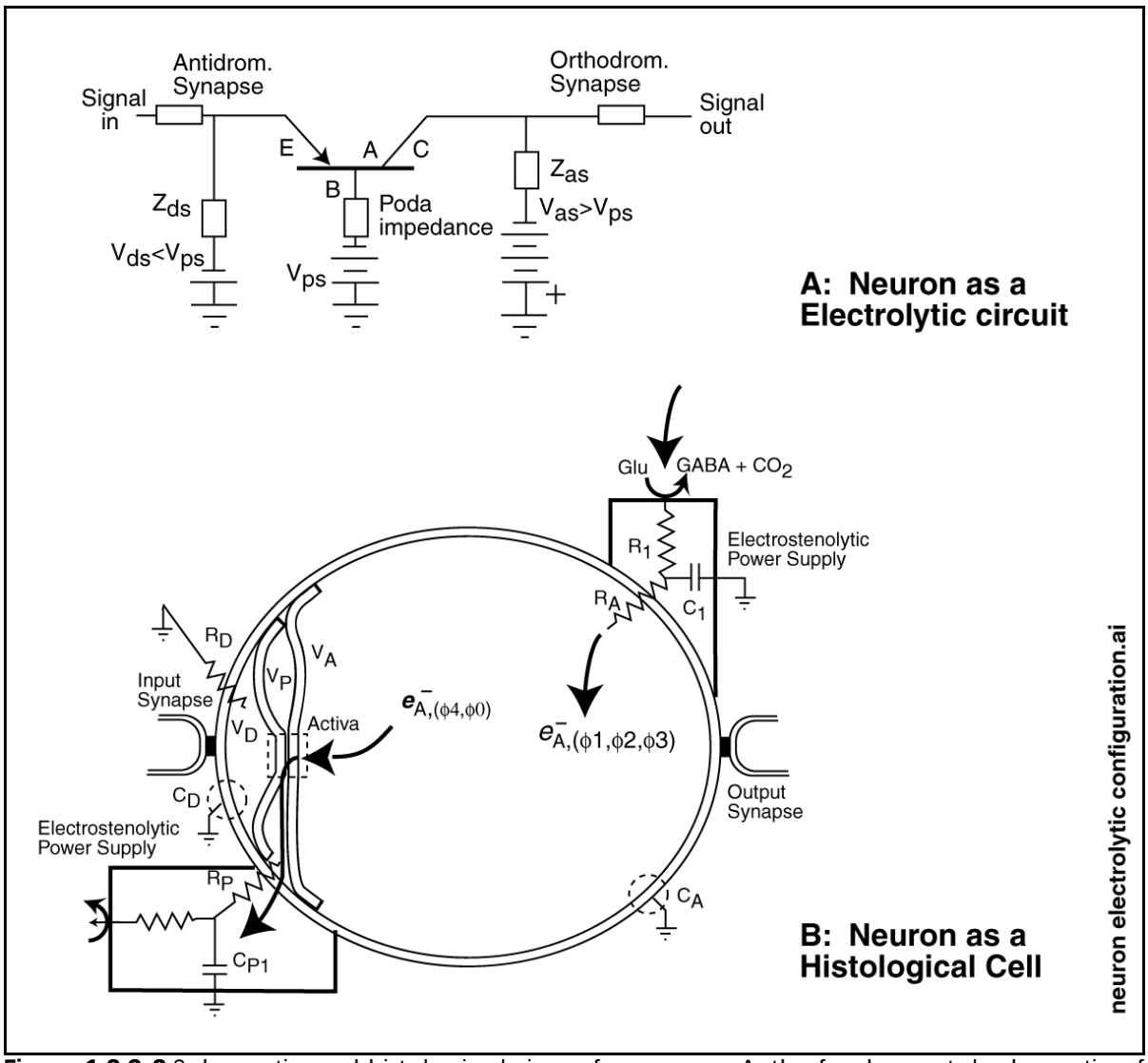

Figure 1.2.2-2 Schematic and histological view of a neuron. A; the fundamental schematic of any stage 2 through stage 7A neuron. B; the histological configuration of any stage 2 through stage 7 neuron. Electrons are supplied to the axon chamber by the electrostenolytic power supply at upper right. Electrons leave the axon chamber via the Activa and the poditic circuit at lower left. The net electron charge on the axolemma capacitance, C_A, determines the potential of the axoplasm. C_A is part of the impedance Z_{as} in frame A.

probing or high magnification electron microscopy.

Cell body--That region of a cell surrounding the Nucleus, and portions of the conduits of the signaling mechanism in neurons. It supports the manufacture of many chemicals used to support the signaling function. Also called the Soma.

Plasma membrane--The outer membrane completely surrounding a cell and consisting of a double wall membrane of two leaves. Each leaf usually consists of a liquid crystalline film of biological phospho-triglycerides. The membrane is usually divided by internal membranes into at There are at least three distinct functional sections of lemma in neurons. These sections are associated with the morphologically defined axons, dendrites and podites. These sections of the membrane may show further specialization. The character of the membrane is also divided into four functional types.

Type 1 lemma consists of a continuous molecularly symmetrical liquid crystalline bilayer of phospholipid material that is impervious to virtually all molecular material and is an excellent electrical insulator. This type forms the bulk of the lemma of any cell, particularly where it is myelinated (**Section 1.2.3.5.1**).

Type 2 lemma consists of a molecularly *asymmetrical* continuous liquid crystalline bilayer where the individual molecular layers are homogeneous but consist of different phospholipid materials. It is impervious to transverse molecular flow but acts as an electrical diode with respect to electron flow. This is the region of primary interest in this work. It is the backbone of the neurological system and supports both neural signaling and electrostenolysis. It will be discussed in many following sections.

Type 3 lemma consists of a liquid crystalline bilayer that is largely impervious to all materials but contains islands of protein or sterol material that are presumed to penetrate both layers of the bilayer membrane. The penetrations are thought to support the transport of selected, electrically neutral, materials through the membrane.

Type 4 lemma consists of a lemma in contact with the external neural environment that has the phospholipid of its outer bilayer incorporating an additional moiety forming a stereochemical receptor. It is found as a region of an overall membrane supporting the electrostenolytic mechanism or, as acting as a sensory receptor in the olfactory or gustatory modalities. Its functional properties are clear and its bilayer-receptor combination is typically a phospholipid with an amino acid as the receptor. The precise molecular structure of some applications of type 4 lemma will be described in **Sections 8.4** through **8.6**.

As noted by Cole in 1966, "Several experiments suggest strongly that ion permeability at least does not involve more than a few per cent of the membrane volume, so most of the molecular structure is passive and quiet if not completely inert[87]." While using different semantics than defined above and in **Section1.4**, his comment is certainly relevant. He is describing type 1 lemma as defined here. The limited area of the type 3 membrane is different from the type 1, 2 and 4 regions that are inert to molecular transport. The type 3 membrane is of little interest to neural signaling. Its primary purpose is to maintain homeostasis. It will be discussed briefly in the paragraphs of **Section 1.2.2.**

Plasmas–The high concentration, high viscosity, heterogeneous, hydrophilic materials found within the water based solute of cells. The material is frequently present as a gel or a liquid crystal. Typically of four distinct types; cytoplasm, dendroplasm, podaplasm & axoplasm. The last three of these are functional with respect to signaling.

Nuclear membrane--The membrane separating the nucleus from the cell body of a neuron.

Soma--See cell body.

1.2.2.3 Functional parts of a neuron

Activa–The fundamental active device providing "transistor action" within the body of a neuron. Most easily identified by electrical probing as within the "hillock" of a projection (stage 3) neuron.

Conexus– A cytologically/morphologically recognizable electrical circuit complex within a neuron. The combination of an Activa combined with a few other electrolytic components defines the conexus within the neuron.

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[87]Cole, K. (1966) The melding of membrane models Ann NY Acad Sci pp 405-408

Neurite–A global name for the functional input structures of a neuron. It includes the dendrites and the podites. Each neurite contains at least one reticulum filled with a conducting plasma that terminates at the Activa within the neuron.

Dendrite–The input to the non-inverting terminal of the Activa within a neuron. It is frequently a highly complex tree-like structure. Contains at least one reticulum filled with a conducting plasma. This reticulum contacts the emitter of the Activa of the neuron.

Podite–The third signaling structure of a neuron. Occurs in two applications.

(1) Frequently the connection between the surrounding plasma and the base terminal of the Activa within a neuron. Frequently represented by a specialized region of the plasma membrane in contact with the surrounding plasma.

(2) The input to the inverting terminal of the Activa within a neuron. It is frequently a highly complex tree-like structure similar to a dendritic tree.

(3) Culminates in at least one reticulum filled with a conducting plasma. This reticulum contacts the base of the Activa of the neuron.

Axon–The output conduit of a neuron. It usually lacking the extensive arborization associated with the neurites. Contains an inner core, labeled the reticulum. It is filled with a conducting plasma, the axoplasm, connecting the Activa collector to the electrostenolytic supply and the pedicle of the neuron. In stage 3 neurons, it is frequently replicated in electrically and chemically isolated axon segments.

Node of Ranvier– Functionally, a point of signal regeneration between the axoplasm of axon segment #n and axon segment #n+1 of a stage 3 signal projection neuron.

(1) Cytologically, the location of a three terminal Activa with terminals contacting the above two axon segments and the surrounding plasma.

(2) Morphologically, a discontinuity in the myelin coating of an axon that allows (a) electrical access between the base of the signal regenerating Activa and the surrounding interneural plasma and (b) electrical access between the surrounding interneural plasma and the regions of both axon segment #1 and axon segment #2 involved in power generation. May also provide chemical access between the axons and the nearby glia.

Specialized regions of the plasma membrane are used to create power sources in the neuron. By employing various bio-energetic materials coating the outer and/or inner surface of these regions, obtaining the appropriate amplitude and polarity of bias voltage within each plasma of a neuron is possible. The mechanism involved is known as electrostenolysis. It is believed that all of the materials are amino acids participating in a metabolic process known as the glutamate cycle. These bio-energetic materials are replaced upon consumption via diffusion. Two distinct diffusion rates have been defined for the material found within the reticulum of an axon. *Slow transport* at rates of about one mm. per day and *fast* (rapid) *transport* at rates of several hundred mm. per day. Neither of these rates is compatible with signaling.

Power sources--Unnamed specialized regions on the surface of the plasma membrane where electrostenolytic processes employ bio-energetic materials to establish electrical potentials supporting the signal handling properties of the neuron. These sources can be represented by an electrical current source in parallel with an electrical diode or as electrical voltage sources in series with a diode.

Autoradiography has been successfully used to image the above structures within a neuron.

1.2.2.4 Functional parts between neurons

Signaling Synapses–

(1) Functionally, a point of low loss signal transmission between the axoplasm of an axon, or axon segment, and a neurite of a following neuron.

(2) Cytologically, the location of a three terminal Activa with terminals contacting the preceding axoplasm, the postsynaptic neurite and the surrounding INM matrix.

(3) Morphologically, a discontinuity in the neural signaling chain caused by the architecture of the neural system. Generally described as the space between two serial neurons. Typically less than 100 Angstrom long within the active gap region.

The **Node of Ranvier** can be considered a quasi-internal synapse between axon segments of a stage 3 neuron where the axon segments are electrically separate but are supported chemically by a common cell nucleus.

1.2.2.5 Functional parts of an Activa

To avoid new terminology in electrolytics, the names used for analogous solid state structures will be used. The Activa is a "pnp" type of sandwich (or junction) structure at the molecular level. All biological Activa are believed to be of the "pnp" type. Holes are the majority electrical carrier in "pnp" type active devices. When properly biased electrically, the Activa exhibits "transistor action." By exhibiting this capability, it becomes an active three-terminal device characterized by power amplification. This amplification may be exemplified by either current or voltage amplification.

Emitter--The input structure of the Activa (marked E in frame A above). The emitter function may involve several independent emitter substructures.

Collector--The output structure of the Activa (marked C in frame A above).

Base--The middle structure of the Activa, represented by "n" in the designation "pnp." The critical area of the Activa in which "transistor action" is achieved. It is marked B in frame A above.

The input structure of an Activa consists of a semiconducting type 2 lemma which allows current to pass through it when biased positively between the dendritic terminal and the base. The output structure of the Activa is an identical semiconducting type 2 lemma which also allows current to pass through it when biased positively between the axon terminal and the base. *However, it is not used with this bias arrangement*.

The base structure is formed by a thin layer of water confined between the two lemma. The confinement is quantum-mechanical in nature and the water assumes a liquid crystalline character at room temperature known as "semi-metallic water." Chaplin has discussed this form of water using the label metallic water[88]. This water is different from the "metallic water that astronomers are attributing to that on or at the core of various planets and moons. It is a bulk form of the "ice" that Finkelstein & Ptitsyn associate with the water immediately adjacent to a hydrophobic molecule(s) such as those of a membrane[89]. Water associated with hydrophobic molecules in this form are known as clathrates. Where the hydrophobic material is molecularly simpler, the water forms a cage around the material as in the clathrates of the deep sea. Chaplin notes, "Whilst the molecular movements within liquid water require the constant breaking and reorganization of individual hydrogen bonds on a picosecond timescale, it is thought by some that the instantaneous degree of hydrogen-bonding is very high (>95%, at about 0˚C to about 85% at 100˚C and gives rise to extensive networks, aided by bonding cooperativity." This is specifically the temperature range of most biological activity.

The presence of this thin layer of water is well known to biophysicist employing the

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[88]Chaplin, M. (2011) Water Structure and Science. http://www.lsbu.ac.uk/water/index.html

[89]Finkelstein, A. & Ptitsyn, O. (2002) Protein Physics. NY: Academic Press pp 50-51 &

"freeze-fracture" technique to study the molecular structure of membranes under high magnification electron microscopy. After they fracture their membranes and place the sample into the vacuum chamber of the microscope, the gradual evaporation of the thin layer of water constitutes a "virtual leak" in their vacuum system that effectively diminishes the capability of their microscope.

To achieve transistor action in an active biological, electrolytic semiconductor device of the "pnp" type, it is necessary that the emitter be biased positively with respect to the base. Similarly, the collector must be biased negatively with respect to the base.

Biological junction--(1)At the molecular level, the nominal location of the interface between the emitter and the base or the base and the collector of an Activa. Useful in establishing the location of the space charge layer in an Activa.

(2) At the molecular level, the nominal location of the interface between the "p" and the "n" type material found in the plasma membrane, or any "three layer" membrane (using the morphological expression), of a cell. Useful in establishing the location of the space charge layer in the diode associated with a power source in the membrane wall.

(3) At the morphological level, the common name for the structure at the signaling interface between two neurons.

There has been occasional discussion in the literature attempting to conceptually associate "gates" in biological membranes with the properties of a field effect transistor[90]. These discussions have not led to the detailed description of the mechanisms involved. Using a term from patent law, these concepts have not been reduced to practice. The Activa is a junction type and not a field effect type electrolytic transistor.

1.2.3 Preview--Fundamental framework of the neural system

Neuroscience has traditionally defined the neural system from a morphological perspective. The tendency under this perspective has been to think "function follows form." Such a portrayal has provided little insight into the operation of the neural system. This work adopts a functional perspective and adopts the contrary motto, "form follows function."

Function is used here as a noun, in the context of the underlying *process* of a given neural structure; it is not used as a verb, to describe the *purpose* or resulting action of the structure, as frequently found in neuroscience texts.

The primary roles of the neural system are three. The first responsibility is to convert representations of the external environment into signals compatible with the neural system. The second responsibility is to transport information from one location in the organism to another. The third responsibility is to evaluate and generate responses based on that information. The complexity of the neural system used to meet these goals is awesome in the human. The human brain was estimated as containing a minimum of 10 billion (10^{10})neurons and about 100 trillion synapses in 2000[91]. The current phasic transistor count for a single chip was about 0.5 billion in 2003 (Itanium by Intel[92]) with a fan-out (number of output connections to transistor of less than 10. Thus the circuit counts are comparable but the topology and mode of operation are entirely different.

More recently, the count has risen dramatically to about 100 billion with 10 billion found in each of the pulvinar and the cerebellum alone. Zillmer & Spiers cited Kalat (1998) in 2001 when they asserted the Cerebral cortex and associated areas included 12-15 billion neurons

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[90]Sigworth, F. (2003) Life's transistors *Nature* vol. 423, pp 21-22

[91]Carter, R. (2000) Mapping the Mind. London: Orion Books page 288

[92]Kurzweil, R. (2006) Moore's Law. NewScientist 13 May edition, page 37

with an additional 70 billion neurons in the cerebellum and one billion in the spinal cord. Based on Stern in 2013[93], the estimated number of neurons in the human brain was 86 billion. In 2015, Pennartz raised the ante again[94]. He asserts the cerebellum contains ~100 billion neurons with the neocortex containing ~20 billion and a total count of around 150 billion neurons in the complete human brain.

> Estimates of the number of neurons in the CNS, or total neural system, are generally not supported by any evidence, not even the resolving power of the microscope used to count the neurons in a sample area. Therefore, these estimates should be considered anecdotal. All of these estimates depend on the resolution of the instrumentation used. The number of neurons appears to rise exponentially as smaller sizes, below one micron diameter axons, are included in the analysis.
>
> Historically, total neuron counts have been arrived at by measuring the number of neurons in a small area of the cerebral cortex and then extrapolated that count to the total area of the CNS on the assumption that the total area is known. In general, several areas of the CNS appear to be much richer in neurons per unit area than the cerebral cortex, specifically the thalamus and the cerebellum. Currently, the unfolded surface area of the thalamus and the cerebellum are unknown.

A companion to this work, **Biological Vision: A 21st Century Tutorial** has addressed the neural systems of a myriad of animals in all three major phyla, Arthropoda, Mollusca and Chordata[95]. While their uses of the neural system may vary considerably, the characteristics of the individual neural elements do not. A neural system consisting of the same functional building blocks is found in all of these animals. This has been demonstrated in a second companion work, **Biological Hearing: A 21st Century Paradigm**[96]. The dominant factor impacting the operation of these systems is temperature. The electrolytic and quantum-mechanical mechanisms used in the neural system depend on the viability of the tissue and fluids forming their substrate. Because of this dependence, they are temperature sensitive and are subject to irreversible damage outside the conventional biological temperature range. This range extends from about the freezing point of saline solution to approximately forty-five degrees Centigrade.

1.2.3.1 Differentiation of neurons from a stem-cell

Progress is being made in understanding the fundamental cells simpler than neurons. This work includes not only various stem cell efforts but also studies of prokaryote and early eukaryote cell lines. The work in prokaryote cells has even differentiated between those able to manufacture their own constituents via ribosomes and those that cannot. The recent series of articles in Science indicate the status of these efforts[97,98]. The title of the first paper should not be a surprise. However, these investigators do tabulate the complete protein inventory, a proteome, of their bacterium along with a complete RNA inventory, a transcriptome and all of its metabolic reactions, a metabolome. They did not report on the detailed character of the cell membrane which is predominantly an assortment of

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[93]Stern, P. (2013) Connections, connections, connections *Science* vol 342 pg 577

[94]Pennartz, C. (2015) The brain's representational power: On consciousness and the integration of modalities. Cambridge, MA: MIT Press ISBN 9780262029315

[95]Fulton, J. (2004) Biological Vision: A 21st Century Tutorial. Victoria, BC, Canada: Trafford

[96]Fulton, J. (2008) Biological Hearing: A 21st Century Paradigm. Victoria, BC, Canada: Trafford

[97]Kuhner et al. (2009) Proteome organization in a minimal bacterium *Science* vol 326(5957), pp 1235-1240

[98]Guell, M. et al. (2009) Transcriptome complexity in a genome-reduced bacterium *Science* vol 326(5957), pp 1268-1271

phosphoglycerides. The prokaryotes incorporate little or no internal compartmentation. The eukaryotes employ extensive compartmentation into what are generally called organelles based on their biological function. In the case of neurons, there are additional compartments associated with their neural functions, the dendrite, podite and axon compartments or chambers.

Figure 1.2.3-1 provides a roadmap for the differentiation of a proto-cell (stem-cell) into one of a variety of neurons. A stem cell can differentiate into one of at least four different cell families. The family of most interest here is the neuro-secretory family, B. This family is responsible for interpreting the external environment via the sensory neurons, performing the complex signal manipulations related to cognition, and affecting the operation of a broad range of other cell types. To identify the types of neurons employed in these functions, a series of stages have been defined previously.

Stages 2 through 6 of the neural system employ a wide variety of specialized techniques to collate neural signals and extract information that can be used to coordinate a wide variety of actions. A major finding of this work is that the neuroaffector type neurons are the source of the hormones within the animal system.

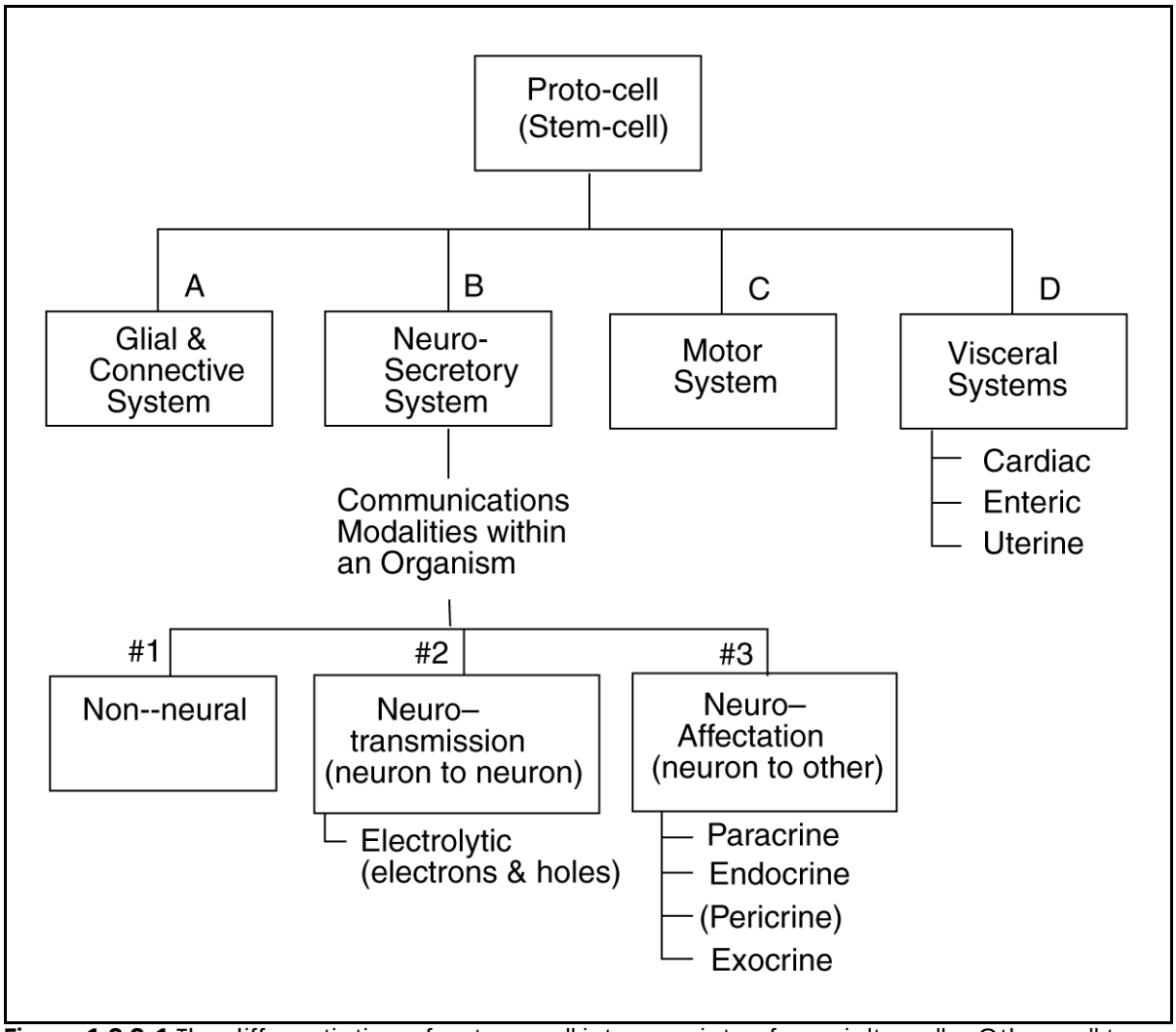

Figure 1.2.3-1 The differentiation of a stem-cell into a variety of specialty cells. Other cell types are shown for orientation and discussion purposes. Neural sensing neurons are found in stage 1. The neural signaling neurons are found in stages 2 through 6. Neuroaffector neurons are found in stage 7 and perform a variety of roles. See text.

1.2.3.2 The conventional view of communications and signaling

The biological community has defined communications within the organism very broadly. It is critically important that this term be clearly defined in this work. Signaling in the broad biological sense will be addressed first. Some of the signaling tasks relate to long time frames and are easily accomplished using the endocrine (hormonal) system, via stage 7 in conjunction with the vascular system. The Paracrine and autocrine modalities operate over short ranges that rely more upon diffusion within the local region rather than rely upon the vascular system. The majority of the neural system, Stages 1–6, are implemented specifically to support the more time sensitive signaling requirements. This type of signaling will be addressed in the majority of this work, except in **Chapter 16**.

Spaargaren, et. al. explored the subject of biological communications recently from the

conventional perspective[99]. Their interpretation is not supported here, because of the availability of the much more powerful Electrolytic Theory of the Neuron. Communications within the neural system is by signaling recognizable by any communications engineer. It involves the passage of electrical currents (based on the flow of electrons) long conduits interrupted periodically by amplifiers. Some of these amplifiers are for signal processing purposes. Other amplifiers are primarily for signal regeneration purposes.

1.2.3.3 Reintroduction of electronic signaling in neuroscience

While accepting the concept of electronic (in place of chemical) signaling is difficult for many chemically trained biological researchers, it is inescapable. After more than 50 years, the chemical-based ideology has been unable to explain even the most basic properties of the system at the detailed level. Many examples of the failure of the chemical-based ideology are available. Most involve situations not even addressed by that ideology. The operation of the ganglion cell is a good example. No chemically based explanation has been presented as to how an action potential is generated in response to an electrotonic signal within a ganglion cell. Similarly, no theoretical explanation has been presented explaining how a Node of Ranvier regenerates the action potential applied to its input terminal. There is no explanation based on the chemical theory of how a horizontal or amercine cell of the retina forms an output signal that is the algebraic difference between two electrotonic input signals.

The evidence in the literature is overwhelming that the neural system is electronically based. Theoretical explanations of each of the above examples are readily available under the Electrolytic Theory of the Neuron. While communications between non-neural cells is clearly dominated by chemical processes, neurons are highly specialized to convey information by a different mechanism. The information conveyed within an organism by chemical means is primarily associated with homeostasis and growth. The response time related to these operations is typically long (several seconds to weeks). The information conveyed within the neural system of an organism by electronic means is primarily related to interaction with, and response to, the environment surrounding the organism. The response time of these operations is typically limited by the mechanical properties of the skeletal motor system. Within specific systems, the response may be very rapid. Within the visual system, responses to changes in the environment occur typically within tens of milliseconds (following extensive internal computation). To support these response times, the actual communications bandwidths associated with these fast responses is generally above 100 Hertz.

1.2.4 Preview--fundamental neural signaling mode of neural systems

The following preview is not designed to convince the skeptical reader. It is designed only as a preview of the following material to provide the reader a contextual framework.

Noback has provided the conventional definition of a neuron shared by many authors and dating from Cajol. "The neuron is the keystone; it is the *morphologic unit*, the *functional* unit, and the *ontogenetic* unit of the nervous system[100]." While this is a satisfactory introductory definition for pedagogy, it is not scientifically adequate for two reasons. First, it will be shown that there is a functional unit that is frequently replicated within a single neuron, and between neurons. Second, the stage 3 neuron absent its myelination (provided by a separate cell) is not a complete functional unit. Shepherd & Koch have recently taken a big step forward by describing the synapse as the basic functional unit of neural circuits[101]. However, their discussion is based entirely on the conventional chemical view of the synapse that is not supported here. They also remain unaware of the Activa within each neuron.

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[99]Spaargaren, M. Delaat, S. & Boonstra, J. (1993) General mechanistic patterns of signal transduction across membranes, *Chapter 1 in* Shinitzky, M. *ed*. Biomembranes: Signal Transduction Across Membranes. NY: Balaban Publishers

[100]Noback, C. (1967 The Human Nervous System. NY: McGraw-Hill pg 28

[101]Shepherd, G. (1998) The Synaptic Organization of the Brain, 4th ed. NY: Oxford University Press pg 3

The Activa plus its necessary electrical biasing components (together labeled the conexus) is properly defined as the *functional* unit of the neural system, whether located within a neuron or between two neurons.

The signal projection role supporting the collection of sensory information and distribution of commands can be described functionally by **Figure 1.2.4-1(A)**. A signal (I_{in}) is delivered to a series of electrolytic conduits as shown. A message related to that signal is projected along the neural system until it emerges at the output as a signal, I_{out}. This figure highlights the fundamental functional unit enclosed by the small dashed box. This unit includes a junction plus a pre-junction electrolytic conduit and a post junction electrolytic conduit. The following material will show that this fundamental unit can be described as in frame (B). In this frame, the junction between the two electrolytic conduits may be connected to an additional source of electrical bias. Under the appropriate conditions, the circuit of (B) can be portrayed as in (C). In (C), the junction is portrayed as an electrolytic transistor, known as an Activa, that operates exactly like a man-made transistor.

As readily seen from frame A, the definition of the fundamental (repeating) unit of signaling is largely arbitrary, it can be defined as,
1. extending from the center of one conduit section to the center of the next conduit section and including one active junction,
2. beginning at the entrance to one conduit section and extending through it and one active junction to the entrance to the next conduit section, or
3. beginning with the entrance to one active junction and extending through one conduit section to the entrance to the next active junction.

The most useful description is #3. It can accommodate a differential input at the entrance to the active junction, as well as multiple branch conduits feeding connecting to the entrance, as developed below. This will be described as the active junction-conduit pair beginning in **Section 1.2.5**.

The configuration of the fundamental functional unit of the neural system in (C) exhibits great flexibility. By varying the associated components and biases, the circuit can be made to operate in a variety of electrically functional modes as suggested by (D). **Chapters 1** & **2** will develop these capabilities in detail.

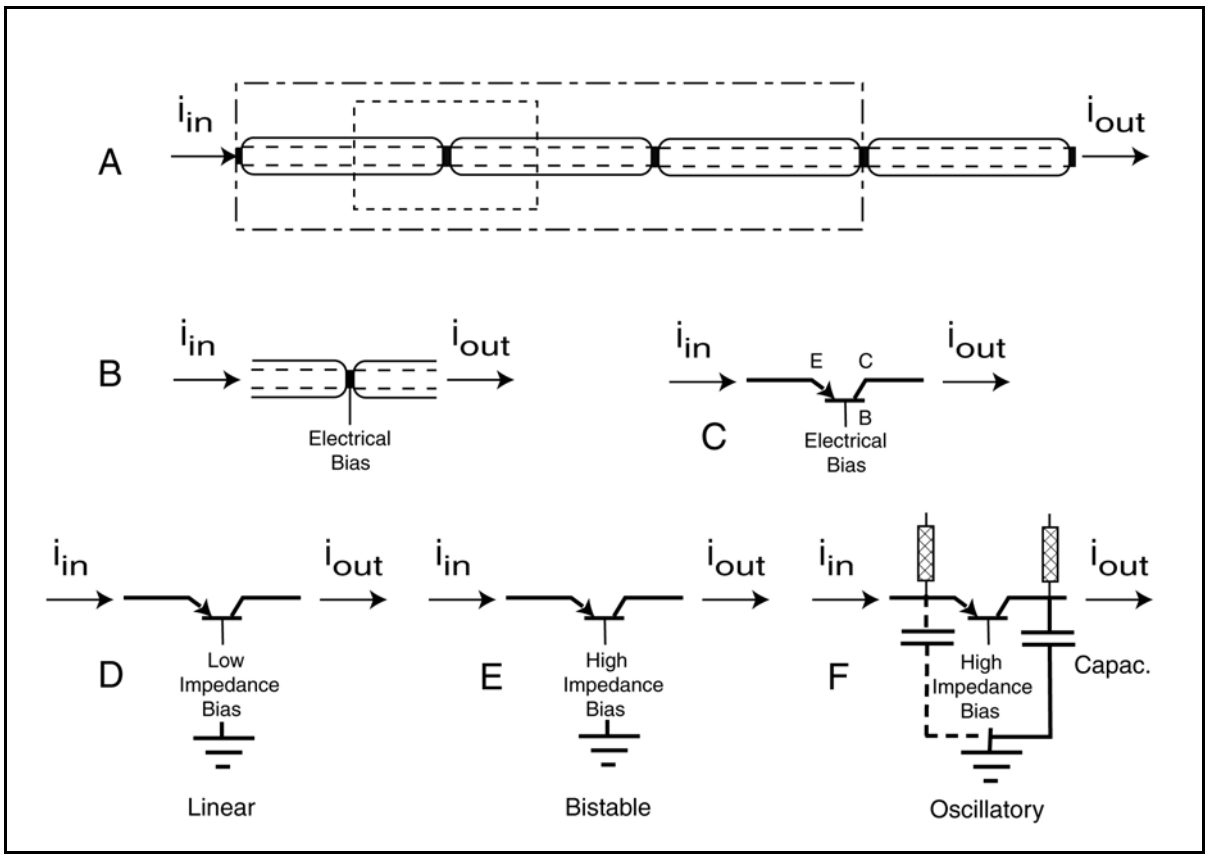

Figure 1.2.4-1 The fundamental functional form of the neuron and its electrical variations. A; the fundamental signaling path within the neural system. B; one active device-conduit representation of the fundamental signaling unit. C; the active device, conduit representation using standard semiconductor device terminology. D; more complex electrolytic configurations of the active device-conduit pair hinting at the functional performance achievable at the output of the circuit relative to the input.

Chapter 2 will review the details of the electrolytic model of the neuron and neural system in both morphological and electrophysiological contexts. **Figure 1.2.4-2** previews how the fundamental functional unit can be packaged within the traditional morphological envelopes of the literature. The shaded parts of each figure are associated with the metabolic and homeostatic aspects of the neuron. The other features are associated with the primary task of neural signaling. These caricatures highlight a variety of important facts.

First, the original morphological designation, monopolar neuron is seen to be unfortunate. Both the morphologically described monopolar and bipolar neurons are functionally identical.

Second, every fundamental functional unit within a neuron consists of a three-terminal circuit consisting of a dendrite, an axon, and a third terminal known as a podite. The podite need not be visible using light microscopy. It may only exist as a specialized area of plasmalemma of the cell. This configuration accounts for the frequent description of axo-soma junctions in the literature. When the podite terminal is more highly developed, it can exhibit a tree-like structure not unlike a conventional dendrite. The references in the literature to a bi-stratified dendritic tree frequently refers to a combination of a single dendritic tree and a poditic tree. These structures can be distinguished by their geometrical arrangement where they merge with the soma.

Third, a single soma can support many fundamental functional units as shown in (E). Each

conduit receives metabolic and homeostatic support from the single nucleus and soma. The functional units can be difficult to recognize under light microscopy. The junction completely enclosed within the soma can only be identified by electron microscopy. It is generally found within the "hillock" of the soma leading to the axon. The junctions along the axon between the Activa and the terminal junction (known as a synapse) are known as Nodes of Ranvier. These nodes are also difficult to study when they are largely enclosed by the soma. The form shown in (E) is labeled bipolar for consistency with the literature. In fact, this form is the only form shown that is exclusively associated with stage 3 action potentials. Forms (A) through (D) are typically associated with tonic signals unless they are transition type circuits. Using the circuit modifications suggested in (D) of the previous figure, transition type circuits can be adapted to other functions. When configured as a tonic-to-phasic converter, the neuron is known as a ganglion neuron. When configured as a phasic-to-tonic converter, the neuron is known as a stellite neuron.

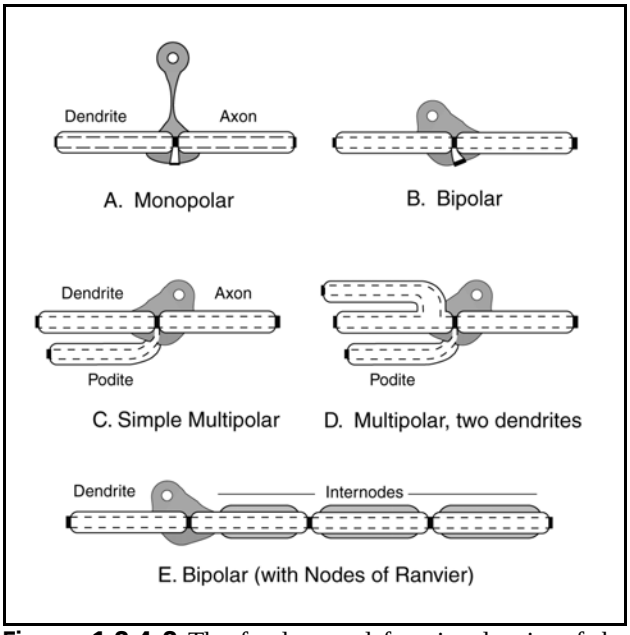

Figure 1.2.4-2 The fundamental functional units of the neuron within a morphological context. The nucleus of each neuron is shown by the white disk within each soma. The nucleus does not participate in the neural operation of the cell.

The term stell*i*te neuron is used to provide a functional description of a particular type of neuron, as opposed to the term stell*a*te which is frequently used to describe the star-like morphological shape of many neurons when viewed from the pedicle of the (straightened) axon..

1.2.5 Problems with the analytical tools and the conceptual phenomena of neuroscience

Before proceeding, it is important to point out the virtually continuous changing of chemical notation describing organic chemicals within the biological community over the last 120 years. Elias has produced a two-volume set trying to follow and rationalize this terminology[102]. ***The volumes are indispensable when reviewing the past literature.***

The neural system of animals is an electronics-based, not a chemical-based system. This has surfaced a significant problem in pedagogy and applied research. No known professors, lecturers or introductory text authors have been identified who possess an adequate preparation in the engineering and mathematics subject matter required to properly teach the physiology and/or functional operation of the neural system (or its components).

A fascinating read illustrating this point was offered by an experienced (dare I say philosopher as opposed to scientist) investigator in 1993[103]. It was very difficult to determine when the ideas of this very experienced thinker went beyond science fiction into theological

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[102]Elias, H-G. (2005) Macromolecules. NY: Wiley-VCH

[103] Berkovich, S. (1993) On the Information Processing Capabilities of the Brain: Shifting the Paradigm *Nanobiology* vol 2(2), pp 99-107

concepts. The text contained no graphics, formulas or tables. From another perspective, he demonstrated by analogy that the bumble-bee cannot possibly fly based on the engineering principles known to him, even though it in fact does.

After ruling out a variety of technologies that he was basically uneducated in (Maxwell's Laws, the functional character of the myelinated axon, and semiconductor physics), he determines that a unfathomably high capacity system outside of the individual brain must be shared among all animate objects in order to achieve the specific performance of the individual human brain. He was unable to define where in the Cosmos this intelligence existed and did not propose in any realistic way the communications mechanism used to communicate between it and an individual, except to define an individual address code for each animate creature above a certain undefined biological complexity.

Because of the lack of experienced teachers and investigators, and in the resulting absence of adequate data, or adequate analysis of the available data, the neural literature has remained largely on the philosophical side of the chasm described in the introduction. This has resulted in a particular problem in a variety of areas highlighted in the following sections.

Paxinos & Mai have produced a 2nd massive edition[104] of their "The Human Nervous System." It appears to focus on the medical aspects of physiology and histology of value to the surgeon. While it is a reference work in morphology and top level histology, it includes little material on cytology and virtually nothing on the detailed functionality of the human system. While the term, system, is used freely when discussing many of the sensory modalities, only caricatures of the engines of each modality are presented along with detailed morphological figures for that modality. Virtually no performance data or mechanisms of operation are introduced. A few MRI images are presented to confirm general concepts They are of limited resolution and do not stress the long integration time required to acquired to acquire the imagery. There is no chapter addressing the internal structure of the neuron or sensory neurons. No discussion is presented addressing the analog versus pulse operation of the neurons. No material appears showing how the correlation of various signaling streams are combined or introduced into a saliency map useful to the stage 5 cognition engines of the CNS.

> Paxinos & Mai summarized a variety of competing terms for the same feature as time has progressed and attempted to rationalize the current usage in these areas. It is careful to note the very limited information available concerning the stage 4 operations of the PGN and pulvinar of the diencephalon.
>
> Percheron prepared chapter 20 on the Thalamus in the Paxinos & Mai text. He occasionally encounters semantic difficulties when translating his thoughts from French to English. On page 612, he notes the absence of a pulvinar in a majority of the primates. The absence of this critically important element in precision sensory information extraction and association makes analogies with the the sensory performance of other primates difficult.
>
> He also notes "The later phylogenetic development of the pulvinar is almost explosive, the number of neurons being said to exceed the total number of neurons al all other nuclei." He goes on, "There are no true 'nuclei' or even parts within the pulvinar. The inner organization is made up of more or less coincident basins to and territories from the cortex. The main pulvinar and nucleus medialis have common connections, in continuous stripes. They constitute together a large isothalamic superregio medio-posterior, which represents some sort of an 'associative' thalamus ('association region,' Dewulf et al., 1973), involving more tha one half of the whole thalamic volume in man. His term regio = "classic nuclei." Like the medial nucleus, the pulvinar essentially receives from and sends axons to the cortex." He may be speaking more of the pulvinar covering, the thalamic reticular nucleus, TRN, than the pulvinar alone.

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[104]Paxinos, G. & Mai, J. *eds*. (2004) The Human Nervous System, 2nd Ed. San Diego, CA: Elsevier Academic Press

Percheron used **Figure 1.2.5-1** to organize his presentation related to the thalamus. He begins a section with the heading, Diencephalon" with "There remains confusion concerning which cerebral elements really belong to the thalamus." He then describes an isothalamus and an allothalamus based on a nomenclature that Percheron et al. developed in an extensive 1996 paper[105]. While offering added clarity in nomenclature , It is not apparent that this terminology has gained wide acceptance in subsequent academic literature. The wording in both the 1996 paper and chapter 20 is sometimes awkward do to translation problems. Percheron appears to say the isothalamus constitutes non-myelinated neurons forming various engines within the pulvinar with allothalamus [probably] consisting of the myelinated interconnecting neurons. He provides several accompanying clarifications.

> "As will be seen later, the classical subdivision of the thalamus was done using reference to myelinic lamellae. Arnold's (1838), the first, described a 'stratum reticulatum (reticulate not 'reticular'), lateral to the thalamic mass. It was separated from it by the lamella perithalamica or 'lamina medullaris externa'. . ." The stratum reticulatum appears to be the thalamic reticular nucleus, TRN, of this work. Alternately, he defines a peripeduncular nucleus that combined with the lateral geniculate body in fact forms a continuous sheet, wrapping the external face of the thalamus of the thalamus (including that of the lateral geniculate body" that could constitute the TRN. He defines the pulvinar as the regio posterior. He notes the close association of the pulvinar with the rest of the thalamus but notes a variety of unusual features. "The pulvinar constitutes the posterior pole of the thalamus. . . As noted, in the preceding paragraph, the pulvinar has no complete border with the nucleus medialis. . .The problem of the subdivision of this large neuronal mass remains difficult and is not yet fixed. . .The great variety of tracings [available] exemplifies the difficulty of delineating a border between the 'medial pulvinar' and the lateral. For Van Buren and Borke (1972), these pulvinar divisions are largely areal designations of convenience.
>
> He closes his discussion of the pulvinar with two statements. "The problem of the subdivision of this large neuronal mass remains difficult and is not yet fixed. . . Chemoarchitectonics, except for the particular parts analyzed below, do not lead to precise borders."

[105]Percheron, G. Francois, C. Talbi, B. Yelnik, J. & Fenelon, G. (1996) The primate motor thalamus *Brain Res Rev* vol 22, pp 93-181

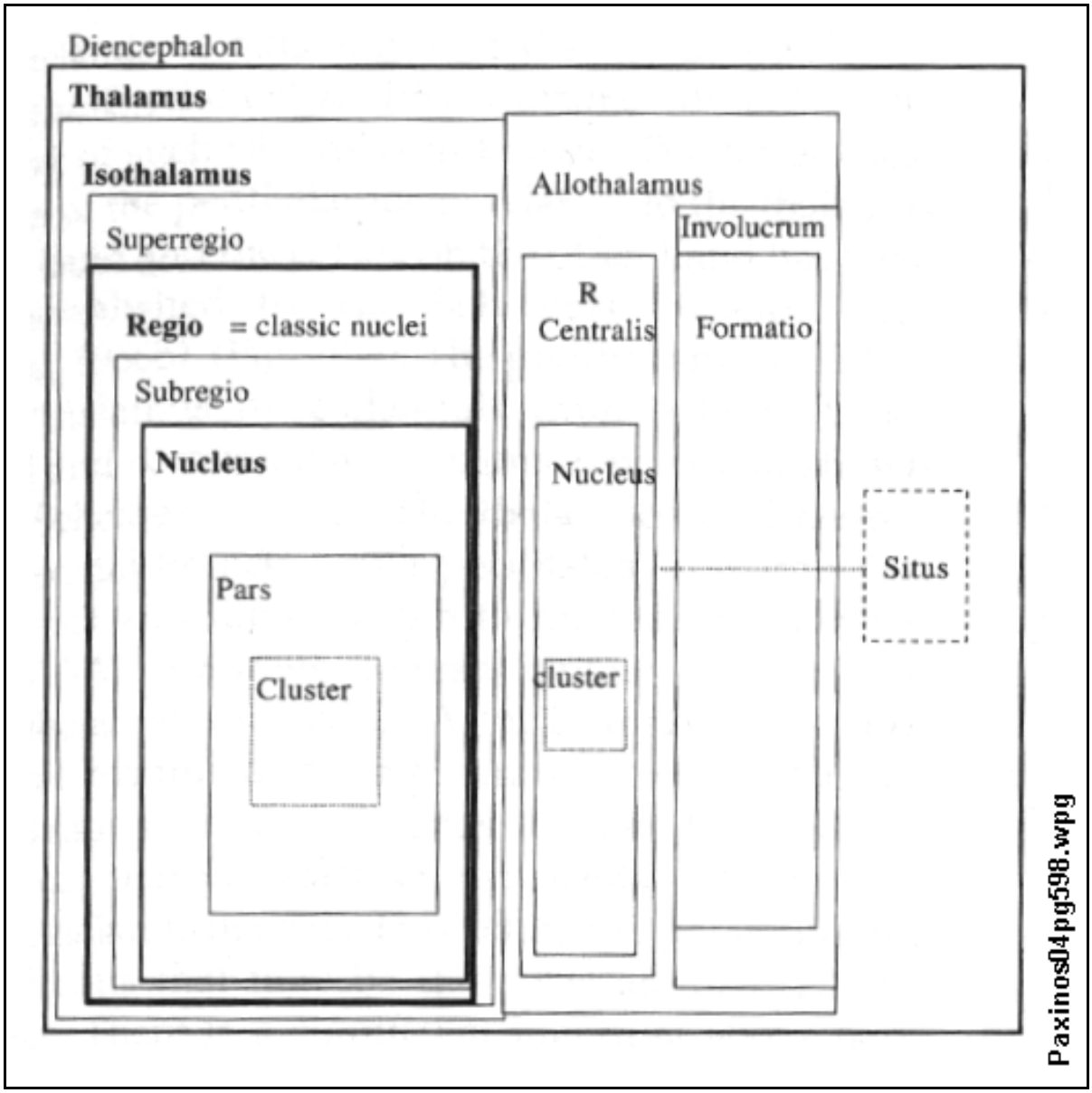

Figure 1.2.5-1 "Diagram of the hierarchical subdivision of the thalamus. As for zoological taxonomy, all levels are not filled. A site is not a formal subdivision and simply a distinctive topographic indication." See text. From Percheron, 2004.

IN the 1996 paper, the assertion is made (page 111), " 'Regio posterior' or 'Pulvinar'. This corresponds to a huge part of the volume of the thalamus of primates, particularly in man. One subdivision, usually included in the pulvinar, must be removed from it as it receives a sizeable input from the superior colliculus [Bender, 1981]." The paper is describing the PGN–pulvinar couple of this work. It consists of the functionally critical perigeniculate nucleus,PGN, of the visual modality and the cited section of the pulvinar. While the PGN is located morphologically in the *Brachia* of the superior colliculus, it is not a functional portion of the superior colliculus. The foveola-PGN-pulvinar couple is the critical information extraction pathway for human precision vision within the 1.2 degree diameter field centered on the point of fixation.

The Bender citation should be replaced by the recent paper focused on the human

pulvinar[106]. The Arcaro et al. paper is extensive and valuable. After discussing the generic field maps of a few lower primates, it notes, "However, the organization of these visual field maps appears to differ across primate species (Li et al., 2013). In humans, neuro-imaging studies have demonstrated contralateral biases (Cotton and Smith, 2007) and some systematic representation of visual space within the ventral pulvinar (Schneider, 2011; DeSimone et al., 2015). However, the exact organization of these representations in the human has yet to be resolved. Further, the relation of visual field maps to cortical connectivity in humans is unknown.

The Arcaro et al. study, focused on fMRI at T = 3 Tesla, involving 19 subjects and using a variety of visual test stimuli. While exploratory in concept and protocol, it collected vast amounts of data that is reviewed in **Section 4.6.4.3**.

Pfaff & Volkov have edited a massive five volume source book released in 2016 with an intriguing title[107]. It is an update of a 2013 edition with only Pfaff's name as editor. A more appropriate title might be Neuroscience in transition at the start of the 21st Century. The material is a large series of articles in essay form rather than academic reports. The articles contain a minimal number of citations and are dominated by caricatures rather than block diagrams, schematics and more definitive material. As noted in the Frontmatter, the authors are experts in their narrow field and not necessarily experienced authors with a broad view. Each article reviews the past 20th Century superficially and provides an "Outlook" contemplating future activity in that specialty. Much of the material depends on archaic concepts based strictly on chemistry rather than electorlytics.

The most up to date portion of Pfaff & Volkov deals with neuroimaging, three articles in Part XIV, but even in this area it lacks recent results related to the most effective functional Magnetic Resonance Imaging, fMRI, such as diffusion tensor fMRI or dfMRI. No information is provided concerning the details of the transduction mechanism or of the related Excitation/De-excitation equations , E/D, for any sensory receptor neurons of any sensory modality.

This work, "The neurons and neural system," will expand the neuroscience side of the art in each area, and move the chasm between philosophy and neuroscience significantly in the direction of science. In doing so, it shows the previous dogmatic concepts are archaic. It will develop the true character of the above mechanisms/phenomena. The goal is to replace dogma/doctrine based on philosophy and concepts by laws based on neuroscience and detailed mechanisms.

The recent introduction of computer-aided non-invasive imaging techniques have provided a boon to understanding the physiology of the biological system. **Section 7.1.2.2** in Chapter 7 on the modeling of biological systems provides an overview of the spatial and temporal resolution of the techniques now available to the investigator.

1.2.5.1 Brief critiques of other recent relevant works

Two recent clinical texts illustrate the state of the neuroscience literature, "the recent paradigm." The 950 page "Textbook of Medical Physiology, 8th Ed.," with over 100 pages dedicated to neurological subjects and the operation of smooth muscle, does not address

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[106]Arcaro, M. Pinsk, M. & Kastner, S. (2015) The Anatomical and Functional Organization of the Human Visual Pulvinar *J Neurosci* vol 35(27), pp 9848 –9871

[107]Pfaff, D. & Volkov, N. (2016) Neuroscience in the 21st Century. NY: Springer *available on-line through most large university libraries*

the role of or index nitrogen oxide[108]. The 1500 page "Fundamentals of Neuroscience" of 1999 by Zigmond et al. initially defines a framework for the conventional types of neurotransmitters and then spends several pages describing the shortcomings of this framework[109]. The description of the mammalian action potential in that volume relies on signals recorded from the giant axon of the squid, a non-mammalian species that does not generate action potentials of the type described, *in-vivo*.

Neither of these texts recognized the three-terminal character of the neuron or discussed the internal electrochemical nature of the neuron. Zigmond et al. did recognize the electrical synapse but treated it as a linear bilateral passive network with resistive coupling..

Wilson, H. (1999) "Spikes, Decisions & Actions: Dynamical Foundations of Neuroscience" is out of print but available on the internet http://cvr.yorku.ca/webpages/wilson.htm#book The book employs several simplifications in order to solve differential equations that obscure the underlying fundamental mechanisms. The "cascade of equations" approach limits the system analyzed to only one time constant. His use of simple linear matrices also limits the applicability of the approach. His conformal transformation between the retina and the primary visual cortex is presented without scales and is less precise than that presented here. His discussion of the action potential is based on the analysis of the giant axon of the squid by Hodgkin & Huxley.

Gazzaniga has recently edited the third edition of a major volume on the human neural system from a largely clinical and behavioral perspective. It is a comprehensive presentation and includes a wealth of information, including on memory, consciousness and perception. However, it lacks a physiological framework with which to place the material in operational perspective[110].

Rakic et al. follow Preuss with a description of the genesis of the primate cerebral cortex with an emphasis on cognition[111]. The material provides a perspective not found in most texts. It stresses the orderly migration of neural cells from an initial point on the ventral surface of the cerebral tissue to their ultimate location in various layers of the tissue and the interconnection of those neurons.

Basbaum has edited a major compendium on the senses[112]. While providing a series of very broad overviews by leaders in a variety of speciality fields, it does not provide a contiguous discussion of the sensory portion of the neural system. The work involves six individual massive volumes. As a result, some (major) libraries are choosing to include it in their collection only in electronic form. Interestingly, the volumes on vision do not explain how the human neural system supports reading and the volume on hearing still does not explain in detail how the individual tonal frequencies of sound are separated in the cochlea.

Preuss has provided an interesting comparison of the human and (a very select group of) primate brains as of 2004[113]. While very interesting and evocative reading, he draws very few conclusions. The fact there are on the order of 350 species of primates (that vary greatly in

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[108]Guyton, A. (1991) Textbook of Medical Physiology, 8th Ed. NY: Saunders

[109]Zigmond, M. Bloom, F. Landis, S. Roberts, J. & Squire, L. (1999) Fundamentals of Neuroscience. NY: Academic Press pp 196-225 & 226-227

[110]Gazzaniga, M. *ed.-in chief* (2004), The Cognitive Neurosciences, 3rd Ed. Cambridge, MA: MIT Press

[111]Rakic, P. Ang, E. & Breunig, J. (2004) Setting the stage for cognition: genesis of the primate cerebral cortex *In* Gazzaniga, M. *ed.-in chief*, The Cognitive Neurosciences, 3rd Ed. Cambridge, MA: MIT Press Chapter 3.

[112]Basbaum, A. et al. (2008) The Senses. NY: Elsevier

[113]Preuss, T. (2004) What is it like to be a human *In* Gazzaniga, M. *ed.-in chief*, The Cognitive Neurosciences, 3rd Ed. Cambridge, MA: MIT Press Chapter 1.

brain size and complexity) is not apparent in the writing. Like other recent authors, Preuss overlooks the fact that birds are animals that share bipedalism with humans. Preuss does note the enlarged diencephalon in humans compared to other primates. While noting the limited geometric similarity between the human brain and other primates, he does not address the remarkable similarity between the human brain and that of the primate orangutan and that of the dolphin. The dolphin brain is actually about 20% larger in linear dimension than the human brain and very similarly folded[114]. It exhibits a significantly larger cerebellum than in the human[115]. While the orangutan brain is smaller, it exhibits similar folding. Preuss also notes the lack of any up to date maps of the brain of humans and apes. He notes Brodmann's human map of 1909 is still the reference for human brain discussions, even while Brodmann's other maps of primates have been updated repeatedly. It is not obvious that Preuss examined any data related to the Orangutan (Man of the Forest), or that he included this genus under his label, "apes." His discussion of the morphological descriptions of neurons is cursory. His material on genetics is up to date A OD 2000, but suggests how far this field has yet to advance (**Section 1.2.5.1.1**).

Eisenberg, a very prominent figure in the academic world of human microbiology and physiology, has recently presented a call to the mathematical community[116]. He calls on them to do a better job of interpreting the neurological system, but admits that the physiological community has failed almost totally to provide them a contiguous model of how the neurological system operates. At the same time he laments his limited understanding of the electrolytic chemistry of the neuron, without introducing any discussion of the role of the bilayer membrane in its operation.

> Eisenberg submitted a patent application in 2003 for a "Liquid based electronic device" that was withdrawn after the first office action by the patent examiner. The examiner did cite my 1999 US Patent. His application appears to be a catch all of ideas related to controlling ionic currents in an insulating tube.

It is a premise of this work that humans, dolphins and orangutans are the most advanced animals with respect to their nervous systems, and the only animals with a highly evolved diencephalon. The evolved diencephalon has a major impact on the ability of the animal to process complex sensory input information, such as symbolic logic. The orangutan is the preferred subject, versus the chimpanzee, for invasive neurological research designed to provide state of the art information on the human neural system and its performance.

1.2.5.1.1 Genetics and the neural system

Shortly after discovering how the genes of DNA could specify the expression of a specific protein and before the limitations and variation on the process were elucidated, and with the arrival of large scale computer aided data mining techniques, genetics enjoyed a period of "excessive exuberance." The result was a great abundance of papers during the 1990's of less than precise information and value. Rose & Rose have discussed this situation in a recent popular book[117]. Pages 258-263 and page 282 notes, "Over the decades, as neuropharmacologists and neurophysiologist discovered more and more neurotransmitters, each in turn became the molecule of the moment as a target for pharmaceutical intervention." As an example, "Like chlorpromazine in the 1950's, the specific serotonin reuptake inhibitors (SSRIs) became the new wonder-drugs." and, "When the evidence began

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[114]Bailliere (1857); Frontpiece *In* Swanson, L. (2003) Brain Architecture. NY: Oxford Press

[115]Lambert, K. & Kinsley, C. (2011) Clinical Neuroscience, 2nd Ed. NY: Oxford Univ Press page 78

[116]Eisenberg, R. (2012) Life's Solutions are Complex Fluids: A Mathematical Challenge. Self-published through Rush University, Chicago, Ill.

[117]Rose, H. & Rose, S. (2012) Genes, Cells and Brains. NY: Verso Chapter 8 The irresistible rise of the neurotechnosciences

to pile up that the drugs aimed at single transmitter targets were not very effective, the theory changed–perhaps the problem lay in the balance between different transmitters?" This is typically the conventional approach of today with regard to synapses between neurons. An unbelievable variety of neurotransmitters are presumed to flow from a pedicle of an axon to a bouton of a dendrite (Section xxx).

The well known researcher, Svante Paabo[118], has made a profound statement in 2015,

> ***"The dirty little secret of genomics is that we still know next to nothing about how a genome translates into the particularities of a living and breathing individual."***

An interesting situation has arisen where a gene is found to cause the expression of a protein among various tissue types throughout the body, but the role of that protein within a given cell is not defined. The role of the protein is left entirely to conjecture within a given specialty community. A given specialist typically ignores the expression of the protein in tissue outside his field and describes a specific conceptual role for that protein within a specific cell of interest.

Kolata has provided a very useful report on the effect of genetic mutations on the organism in general[119]. The article is based on that of Roberts et al. who investigated the genome of 53,666 identical twins in registries from the United States, Sweden, Finland, Denmark and Norway[120]. The study showed the genome was probabilistic and not deterministic with respect to diseases as currently defined.

Even more recently, Macosko and McCarroll[121] used the title, "Our Fallen Genomes" to introduce a paper by McConnell et al[122]. on the considerable variation in genetic signatures within the neurons of even monozygotic twins. These findings soften many of the previous assertions relating to the neurons and other bodily tissue.

Marshall has provided a popular book, by an electrical engineer of considerable breadth, describing recent advancements in genetics[123]. The book highlights the difficulties encountered by those anticipating that simple mutations can result in major changes among species and within the phylogeny as a whole. He stresses the similarity between the genetic code of DNA and the organization of the code structures associated with man-made computer code (**Section 1.2.8.2**).

1.2.5.1.2 The psychologists view of the neural system

This work is not clinically oriented but does reflect pertinent facts drawn from the clinical literature. These facts are found mostly in **Chapter 18** of the companion work, "Biological Vision: A 21st Century Tutorial" that relates to abnormalities of the neural system.

Zillmer, et al. have provided the current text neuropsychology[124]. Part One provides a

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[118]Paabo, S. (2015) Neanderthal Man: In search of Lost Genomes. NY:Basic Books page 208

[119]Kolata, G. (2012) Study Says DNA's Power to Predict Illness Is Limited NY: *NY Times* 2 April 2012

[120]Roberts, N. Vogelstein, J. Parmigiani, G. Kinzler, K. Vogelstein, B. & Velculescu, V. (2012) The Predictive Capacity of Personal Genome Sequencing *Sci Translational Med* published on line 2 April

[121]Macosko, E. & McCarroll, S. (2013) Our Fallen Genomes *Science* vol 342, nol 6158, pp 564-565

[122]McConnell, M. Lindberg, M. Brennand, K. et al. (2013) Mosaic Copy Number Variation in Human Neurons *Science* vol342, pp 632-637

[123]Marshall, P. (2015) Evolution 2.0: Breaking the Deadlock between Darwin & Design. NY: Perseus Books

[124]Zillmer, E. Spiers, M. & Culbertson, W. (2008) Principles of Neuropsychology, 2nd Ed. NY: Barnes & Noble

historical review of early surgeries involving the neural system. Part Two provides an overview of the neural system and the principle sensory modalities from the psychologists perspective. Part Three discusses disorders of the brain, again from a psychologists perspective. The work includes many interesting figures. They are not particularly relevant to the study of the neural system at the functional, or specific features and performance, levels.

Lambert & Kinsley have also provided a text on clinical neuroscience that can be quite useful[125]. It appears to cover a broader range of conditions than Zillmer et al. and provide more definitions of terms.

With the advent of the internet, more and more lectures and seminars occurring at remote locations are becoming available to anyone. A recent seminar of 1:28:47 duration sponsored by the World Science Festival is well worth attending. However, the content of the program shows how little the typical bio-psychologist researcher really understands about the physiology of the animal system[126]. As an example, one eminent researcher (at around the 50:00 point) analogized the neural system as containing no wires, only bags of sea water and operating like a series of interconnected squirt guns. The lack of understanding that the sea water acts as a conductor encased (in the case of stage 3 signal projection neurons) an insulator (myelin) forming a quite functional coaxial cable (**Section 9.xxx**) seems to have escaped the speaker completely.

Eagleman[127] has provided a much broader review of the performance of the brain from a psychologist's (neuroscientist's) perspective via a series of six 30 minute programs prepared for PBS, the Public Broadcasting Service in the USA. The programs are for a general audience but the material is consistent with the behavioral aspects of the human neural system as presented in this work. He reflects the commonly held viewpoint of the neuron as a chemical, rather than an electrolytic entity and discusses the morphology and anatomy of the brain without serious consideration of how it operates at the fundamental level. The implication is that all neurons produce "action potentials."

1.2.5.2 Problems with mathematics in current bio-science research

[

Until recently, most of the research in the bio-sciences was dominated by those trained in psychology and other soft sciences, frequently before going on to medical school or entering an academic doctoral program. These candidates frequently had very limited training in statistical analysis, such as computer crutches like the Statistical Package for the Social Sciences (SPSS) currently distributed by IBM and were seldom exposed to more advanced fields such as multi-dimensional scaling (MDS) techniques.

1.2.5.2.1 Shortcomings of the SPSS software in fundamental research

In a widely available introduction to the SPSS program, the authors go out of their way to point out the students using SPSS need not understand what they are doing, the program will perform all of the number crunching for them[128]. This leaves the average bio-science practitioner poorly equipped to address the material in this work, from both an understanding and an analytical capability perspectives.

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[125]Lambert, K. & Kinsley, C. (2011) Clinical Neuroscience, 2nd Ed. NY: Oxford Univ. Press

[126]World Science Festival (2014) Architecture of the mind: A blueprint for the Human Brain. http://www.worldsciencefestival.com/2014/01/full_program_architects_of_the_mind_a_blueprint_for_the_human_brain/

[127]Eagleman, D. (2017) The Brain with David Eagleman. Washington, DC: Public Broadcasting Service Library at PBS.org *Available for purchase as a book or DVD*

[128]Hanna, D. & Dempster, M. (2012) Psychology Statistics for Dummies. NY: Wiley

SPSS offers a spreadsheet quite similar to a common Excel spreadsheet but with some special tools to annotate missing values in a set and the generation of a series of specialized graphs. Hanna & Dempster provided a series of very brief definitions of many terms in a hierarchal form. They also offered **Figure 1.2.5-2** clarifying the "box and whisker" terminology (sometimes called boxplots) used in Psychology. Note the elimination of an obvious outlier from the data set and the fact the whiskers are based on the range of the data. The top and bottom of the box represent quartile values rather than ± one standard deviations. The horizontal line represents the median rather than the mean. They note some confusion on these points as many researchers prefer to use the mean and standard deviation. In SPSS, these two interpretations are only a click away from each other.

Hanna & Dempster do give a good summary of the different tests used in inferential analysis (Pearson's, Spearman's correlation & Kendalls'tau-b co-efficient) and their applicability. They also describe the ANOVA, the ANalysis Of VAariance tests in some detail. They conclude their text with a series of critical points related to presenting the results of a research project.

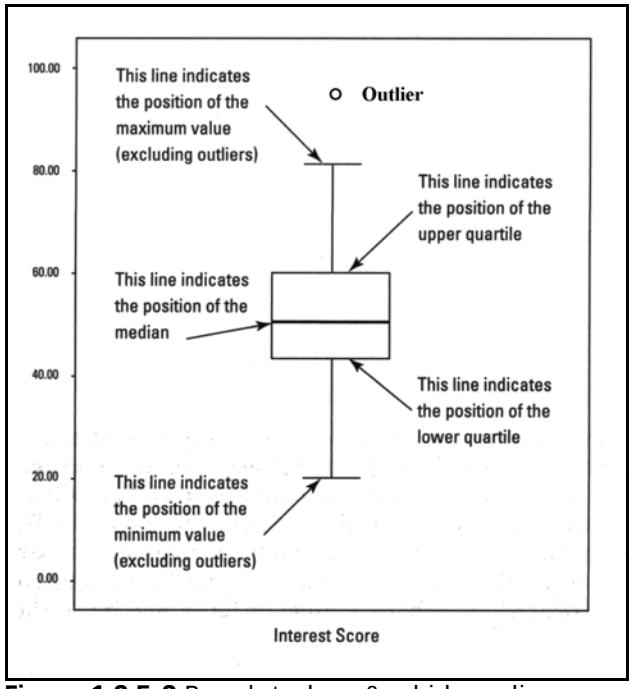

Figure 1.2.5-2 Boxplots, box & whiskers diagrams, frequently used in psychology studies. From Hanna & Dempster, 1976.

1.2.5.2.2 Clarifying the "linear" Regression Analysis protocol

Hansch has described the methodology underlying a "linear" regression analysis in an appendix to his paper[129]. **Figure 1.2.5-3** illustrates the computational concept for a first order linear equation. It involves a straight line through a set of data points. "By best straight line we mean a line that is set so that the sum of squares of distances from the point to the line (indicated by the dashed lines) is a minimum." Hansch describes an equation as linear with respect to its coefficients even if it is a second or higher order equation. For data points associated with a higher order "linear" equation, the procedure gives an extraneous fit of a straight line to the underlying function. Such a linear regression analysis may be quite useful in first order chemical reactions of pharmacology, but it is not useful in higher order analyses, unless the underlying equation applicable to the data points can be reduced to a first order equation, such as the logarithm of an original exponential function, and the data points replotted appropriately.

If a transform is used to create a pseudo-linear representation of the data, it is necessary to overlay the transform plot by a linear grid and interpret the data points relative to that grid in order to use the equations of regression analysis defined by Hansch.

Notice, for a higher order equation, a more appropriate representation of the points to the underlying equation would be better fit if the distance of the points from the line was taken as the minimum (perpendicular) distance from the line to the point. Unfortunately, this involves a much more difficult mathematical situation than that addressed by Hansch.

Investigators frequently use a software package labeled "regression analysis" improperly to evaluate a data set based on other than a first order equation.

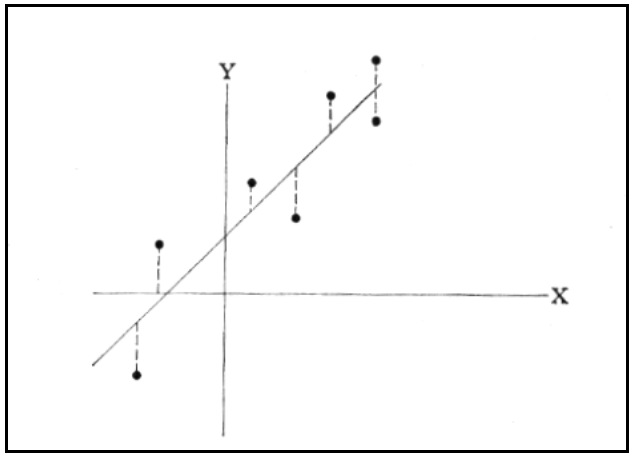

Figure 1.2.5-3 The regression analysis concept. It only applies to a first order equation with linear coefficients. From Hansch,1973.

1.2.5.2.3 Absence of the Heaviside unit step function from Bioscience

While the Heaviside unit step function is widely employed in representations of stimuli in bio-science research, its absence from calculations related to the results of those stimuli prevent the use of more demanding mathematical manipulations in order to increase accuracy and uncover many important features of the bio-science process being examined. The Excitation/De-excitation, E/D, Equation (a.k.a. Photoexcitation/De-excitation,P/D Equation) requires an understanding of the Heaviside unit function.

The Wolfram Organization has provided an excellent introduction to the Heaviside unit step function[130].

The Heaviside step function is a mathematical function denoted *H(x)*, or sometimes *theta(x)* or *u(x)* (Abramowitz and Stegun 1972, p. 1020), and also known as the "unit step function." The term "Heaviside step function" and its symbol can represent either a piecewise constant

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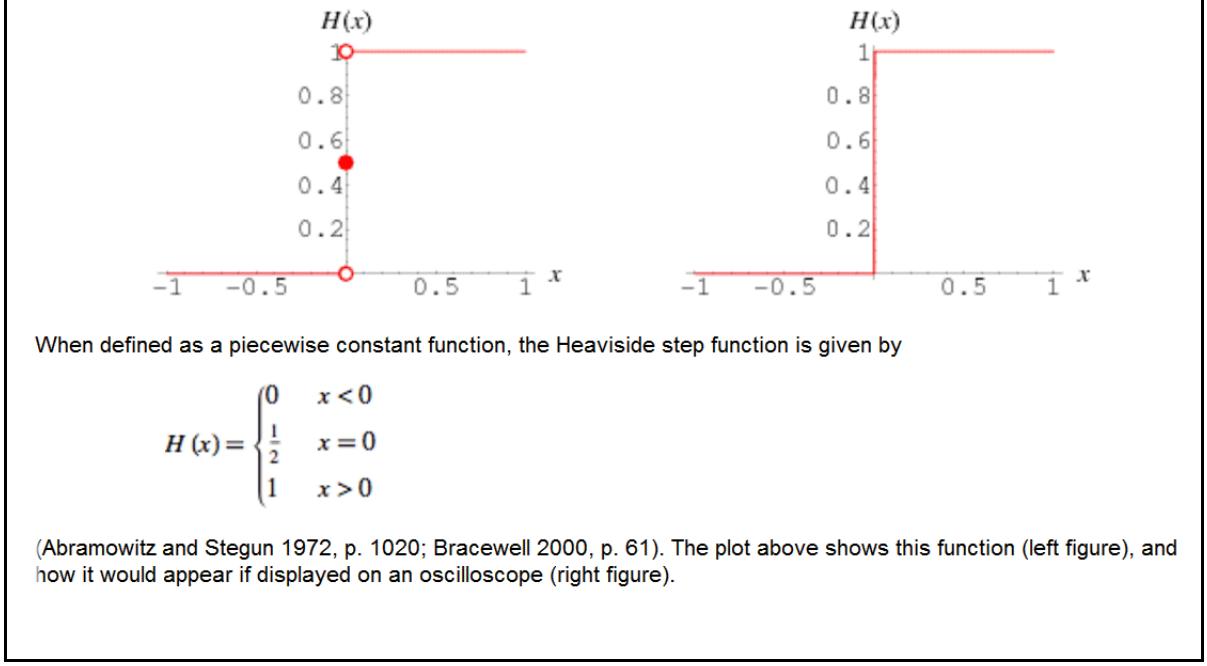
[129]Hansch, C. (1973) Quantitative approaches to pharmacological structure–activity relationships *In* Cavallito, C. *ed.* Structure–Activity Relationships. NY: Pergamon Press pg 150

[130]- - - (2018) Heaviside unit step function http://mathworld.wolfram.com/HeavisideStepFunction.html

function or a generalized function. **Figure 1.2.5-4** illustrates this unit step function.



When defined as a piecewise constant function, the Heaviside step function is given by

$$H(x) = \begin{cases} 0 & x < 0 \\ \frac{1}{2} & x = 0 \\ 1 & x > 0 \end{cases}$$

(Abramowitz and Stegun 1972, p. 1020; Bracewell 2000, p. 61). The plot above shows this function (left figure), and how it would appear if displayed on an oscilloscope (right figure).

Figure 1.2.5-4 The Heaviside unit step function. From Wolfram on Internet.

The Heaviside unit step function is a key to the use of the Calculus in bio-science. It is most often used in conjunction with the rectangular function where the rectangular function[131] (also known as the rectangle function, rect function, Pi function, gate function, unit pulse, or the normalized boxcar function) is defined as shown in **Figure 1.2.5-5**.

$$\text{rect}(t) \quad \text{or} \quad \Pi(t) = \begin{cases} 0 & \text{if } |t| > \frac{1}{2}, \\ \frac{1}{2} & \text{if } |t| = \frac{1}{2}, \\ 1 & \text{if } |t| < \frac{1}{2}. \end{cases}$$

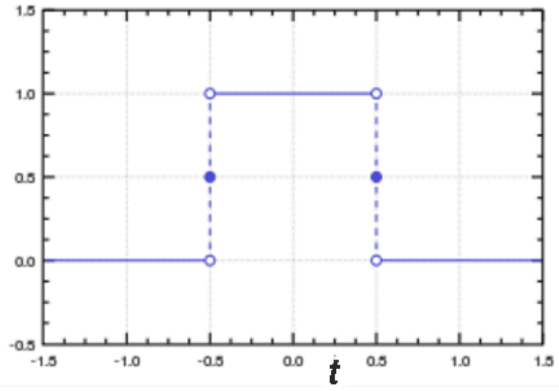


Figure 1.2.5-5 The rectangular, Pi function, unit pulse or normalized boxcar function. From Wikipedia, 2018.

[131] - - - (2018) The Rectangular Function https://en.wikipedia.org/wiki/Rectangular_function

These two functions can be expressed in many alternate mathematical forms, including differential and integral forms.

1.2.5.3 Problems with using inadequate engineering tools

Understanding of the neural system remains hampered by the breadth of many investigators background. The remarks of Whittaker appear to be due to this condition[132]. He comments that "electrical neurotransmission, though speedy, is also unselective. It is an all-or-nothing affair, incapable of being quantitatively modified or integrated with other afferent impulses." His position appears to be based strictly on his familiarity with individual action potentials, and not on the coding used in strings of action potentials to convey information, nor the analog signals found so widely in the neural system and retina.

Similarly in 1992, Hille uses the interesting bold headline, "Ohm's law is central" and presents an entire book on excitable membranes that relies heavily on kinetic models and never introduces the integral calculus or differential equations[133]. This work shows that his headline is frivolous. Ohm's Law is not only not central, but it is largely inappropriate. Ohm's Law, usually introduced to non-electrical engineering students in a brief overview course, applies only to linear (and passive) impedances. In its conventional form, it cannot be used to evaluate circuits containing nonlinear circuit elements and/or sources of electricity. It must be replaced by Kirchoff's Laws in the analysis of neural systems. Virtually the only mention of Kirchoff's Laws found in the neurological literature was a passing one by Eckert & Randall[134].

1.2.5.3.1 Misapplication of Ohm's Law

A recurring problem has been the repeated attempts to use the most elementary possible electrical engineering and mathematical tools to explain complex bio-electro-chemical processes. As a few examples;

+ Ohm's Law is frequently invoked to quantify impedances which are clearly not independent of the current passing through them--a linearity requirement fundamental to Ohm's Law. See above and Starzak[135]. In some cases a variant of Ohm's Law can be used to determine the dynamic or "local resistance" given by Δvoltage/Δcurrent.

+ Ohm's Law is frequently invoked to quantify impedances in networks containing current and/or voltage sources. These sources must be eliminated from the computations if correct impedance values are to be obtained. Otherwise only effective (not real) impedances are measured. These effective parameters become functions of the test set and protocol used.

+ Attempts are still being made in the community to measure resistances and conductances in the neuron not only in the presence of voltage/current sources and active devices, but also in the presence of internal feedback mechanisms (See **Sections 9.3.1 & 20.3**).

+ No discussion of internal feedback within a neuron has been found in the neural literature.

By looking closely at Ohm's Law, and recognizing it is only a part of Kirchoff's Laws, the

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[132]Whittaker, V. (1975) Membranes in synaptic function. *In* Weissmann,G. & Claiborne, R. *ed*. Cell Membranes: Biochemistry, Cell Biology & Pathology. NY: HP Publishing Co. Chap 9, pg 167

[133]Hille, B. (1992) Ionic channels of excitable membranes. Sunderland, MA: Sinauer Associates.

[134]Eckert, R. & Randall, D. (1978) Animal Physiology. San Francisco, CA: W. H. Freeman, pg 118

[135]Starzak, M. (1984) The Physical Chemistry of Membranes. NY: Academic Press pg. 309

situation can be put in better perspective.

> **Ohm's Law** is defined in the ISO Definition of Electrical Terms. "The voltage across any part of a circuit is equal to the product of the current in amperes and the resistance in ohms, *provided that the current is steady and that there are no sources of emf (power sources) within this part of the circuit*."

If the current is not steady, and particularly if the resistance is a function of the current, the more general Kirchoff's Laws must be used to evaluate the circuit. Kirchoff''s Laws remove each of the restrictions noted in the above definition of Ohm's Law.

Figure 1.2.5-6 illustrates the significant difference between the value of a static resistance given by Ohm's Law, $R_s = V/I$ and the dynamic or local resistance given by $R_d = \Delta V/\Delta I$ = the slope of the waveform at the data point. The figure is from Mueller & Rudin who worked in area units. Therefore, their numerical values are quite low. The impedance would rise significantly as the area of measurement approached a single area of type 2 lemma (although not necessarily proportionately). A true resistance is represented by a straight line passing through 0,0 in this graph (such as the lines labeled A and B. Any other set of data points on this graph do not represent a resistance. The curved line is clearly that of a diode, including its reverse breakdown voltage occurring in the –150 to –170 mV range. Two resistance values can be calculated at each point where the lines intersect the diode characteristic. At point A, the ratio between the two types of resistance is 9:1, at point B, the ratio is 11:1. Only the dynamic resistance, based on the slope of the diode characteristic and not given by Ohm's Law, has any meaning.

A review of the graphics of Eliasof reproduced later in this chapter will show the difference between static and dynamic resistance remains 3:1 or greater for low membrane potentials. Their work also surfaces the frequent situation where an impedance is formed by a combination of a diode and a resistance. The curve in quadrants 2 and 3 of the figure, including the region of electrical breakdown, involve totally different mechanisms not involving simple resistors.

Discussion of the electrical regionalization of the interior of a cell is largely absent from the literature. Discussion of the electrical properties of the resulting individual membrane enclosed plasmas of a neuron is also largely absent from the literature. Failure to cross these intellectual bridges has restricted understanding of the neuron.

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In a circuit containing a voltage or current source, attempting to measure the resistance of one element of the circuit will give erroneous results. The measuring apparatus becomes another element of the overall circuit and shares current flow with the other circuit elements. The correct method of measuring an impedance is to isolate it from all other circuit elements in accordance with Kirchoff's Laws. This requires short circuiting all voltage sources and opening all paths to current sources. These conditions are clearly difficult if not impossible for most *in-vivo* and *in-vitro* electrophysiology. Outside of this work,

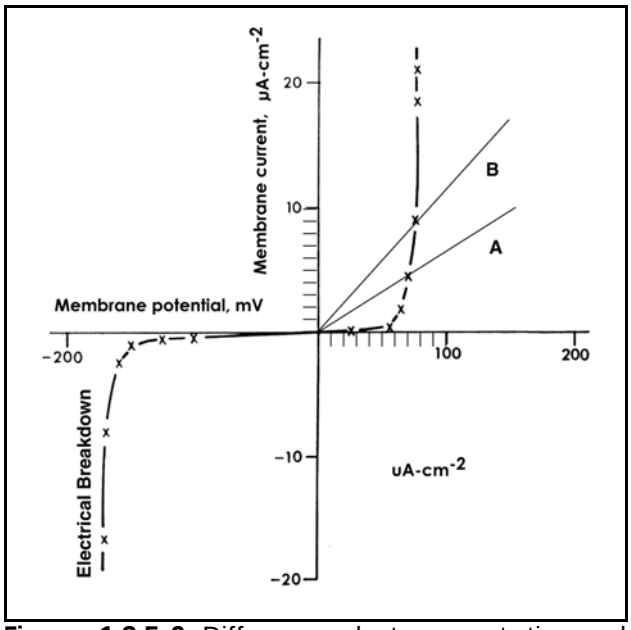

Figure 1.2.5-6 Difference between static and dynamic resistance of a lemma acting as an electrical diode. At the data point, A, the static resistance is 16,000 and the dynamic resistance is 1700 ohms–cm^2. At the data point B, the static resistance is 8,600 and the dynamic resistance is 800 ohms–cm^2. See text. Modified from data and graphic by Mueller & Rudin, 1968.

there is no reported knowledge about the details of the voltage and current sources in a neuron. As a result, the measurement of individual resistive impedances is quite difficult. Fortunately, it is possible to measure capacitances more directly. Subsequent to measuring the capacitance, it is frequently possible to employ transient measurements to determine the relaxation time constant of a circuit and thus measure the effective resistance of the circuit indirectly.

The technique of pulsing the axoplasm during patch clamp experiments is an example of using the transient approach to measuring both the total capacitance of the axolemma as well as the effective dynamic resistance between the axoplasm and the surrounding neural matrix. The latter measurement is generally distorted by the Activa within the neuron acting as a current source.

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The 2007 text by van Drongelen presents a particularly complex situation[136]. While suggesting the reader need have only a reasonable but modest mathematical background, he describes this background as including "complex algebra, basic calculus and introductory knowledge of differential equations." These are not the only skills required of a neuroscientist. Furthermore, these are skills foreign to a majority of practicing neuroscientists and only hopefully being acquired by recent bioengineering graduates. The book is written by one largely outside of the neuroscientific community. He presents a very concentrated (cram) course in higher mathematics that involves primarily transcendental mathematical functions, a class of functions foreign to the internal operation of the neural system. Hence, his title would be more appropriate if it were "Non-neural signal processing for neuroscientists." His presentation has wide applicability to data reduction related to signals recorded from the neural system but not to the origin of those signals.

> A transcendental function is a function which "transcends" algebra in the sense that it cannot be expressed in terms of a finite sequence of the algebraic operations of addition, subtraction, multiplication, and root extraction.
>
> Examples of transcendental functions include the exponential function, the logarithm, and the trigonometric functions. More complex examples involve the integration and differentiation of such transcendental functions, including the Fourier Transform, the correlation functions, the complicated probability functions and their relatives.

The neural system relies upon data comparators and lookup tables to avoid entirely the need for transcendental calculations beyond the simple logarithmic conversion achieved using a simple resistor-capacitor (RC) circuit.

A second problem with the van Drongelen text is his emphasis on the linear- time-invariant (LTI) character of the assumed neural system. The problem has two aspects. First, the very concept of adaptation associated with all of the sensory modalities of the neural system is the antithesis of time invariance. The neural system is fundamentally time-variant. Second, the application of linearity to the concept of the neural system fails at the very first stage of every sensory modality. Each sensory neuron displays a logarithmic conversion of the sensed energy to the voltage signal at its axon. Thus, the neuroscientist is routinely confronted with a non-linear-time-varying (NLTV) system.

His attempt to discuss the neural system using an LTI assumption leads to the fundamental problem raised by earlier neuroscientists, the choice of considering the system probabilistic or of introducing non-linear processes. These neuroscientists have invariably chosen very simple statistical mechanisms rather than address the demonstrably deterministic character of the neural system. Introduction of the NLTV assumption leads to a tractable explanation of the neural processes without an actual simplification in the mathematical complexity of the task.

The use of the LTI assumption also suggests the system is passive in order to insure linearity.

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[136]van Drongelen, W. (2007) Signal Processing for Neuroscientists. NY: Academic Press

This is a major fault with this approach. The neural system is fundamentally active, with amplifiers (Activa) at every node of the neural system. Note the output amplitude of every signal propagation neuron is approximately 110 mV based on an input amplitude of less than 20 mV. Thus a better description of the neural system is an ***active*** non-linear time-variant NLTV system

For reasons not addressed in his book, van Drongelen did not address the subject of modulation theory in his text, particularly the easily implemented form of time delay modulation forming the core of the neural signal propagation function, and the subject of diode circuit decoding used to recover the information transmitted within the system. He avoided the subject of the inductor-capacitor (LC) circuit that is key to the understanding of the action potential of the neural system. He also avoided any discussion of active circuits within the neural system in keeping with the strict concept of linear circuits.

As the neuroscientist explores the operation of the neural system going forward, it is critically important that he be familiar with the concepts of filter theory and control theory developed in Electrical Engineering or consults with a bioscientist with cross training in this field at the graduate degree level. There are introductory level texts discussing these concepts, and providing many examples, but the algebra becomes fairly intense for those with limited background[137].
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A particular problem in the neuroscience literature occurs in the introduction to many papers. The authors casually recapitulate the conclusions drawn by others. These conclusions are frequently based on conventional wisdom, and intuitive conclusions following an analysis of limited empirical evidence. This leads to an ever-expanding database of limited theoretical consequence. The literature applicable to the putative neurotransmitters is an excellent example.

As noted by Swanson page (223 and 229), terminology is a major problem in the neurosciences. Workers in different disciplines have adopted a variety of terms for identical or similar morphological features and functional notions. Minimizing the introduction of new terminology is important in a field where so much interdisciplinary science is needed. This work will rely heavily on the nomenclature used by Shepherd[138] in the neurobiological area and the definitions and symbols standardized by the IEEE in the electronics area. However, recognition of the three-terminal nature of the Activa will necessarily affect and require expansion of Shepherd's contribution. As will be seen below, his definition of a dendrite has been assigned to the more general term neurite. It will also require expansion of the four chief functional compartments defined most recently by Kandel, Schwartz & Jessell[139], to an expanded list. Added to the list of the cell body, dendrites, axons and terminals are an internal Activa and several other elements. These include a proliferation of external Activas, a second class of neurite defined as a podite, and multiple electrostenolytic sites critical to the operation of the neuron.

Swanson has defined a hierarchal taxonomy of the central nervous system in concept[140]. Unfortunately, his taxonomy is already six levels deep (with tab stops spilling off the page) by the time he describes the major lobes of the cortical plate of the cerebral cortex.

The large (1414 pages) text edited by Kandel, Schwartz & Jessell is in its fourth edition and is destined to play a major pedagogical role for many years. Like any work prepared by many individual authors, it contains many conflicting presentations, particularly among the large collection of caricatures instead of photographic records. Many of these will be highlighted

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[137]Maddock, R. (1982) Poles and Zeroes in electrical and control engineering. NY: Holt, Rinehart & Winston

[138]Shepherd, G. (1988) Neurobiology. NY: Oxford Univ. Press, pg 63- 71

[139]Kandel, E. Schwartz, J. & Jessell, T. (2000) Principles of Neural Science, 4th Ed. NY: McGraw-Hill, Pg. 67

[140]Swanson, L. (1998) Brain Maps: Structure of the Rat Brain, 2nd Ed. NY: Elsevier Science page 194

in Chapters 8 and 9 of this work. The fourth edition contains several major chapter rewrites from earlier editions. However, it contains very little material on the actual functional and cytological elements of the neuron. Much of the data involves individual clinic-based psychophysical evaluations.

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Because of these procedural difficulties, integrating most of the relevant discussions in the literature into this work is very difficult. The models and concepts proposed in the literature are not adequately founded. On the other hand, some data reported in the literature can be used effectively if care is taken to learn what the specific, and important, conditions and parameters of measurement were.

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1.2.5.3.2 Sensory code, neural code & other superficial concepts

The use of the terms sensory code and neural code have been used throughout the neural literature without specific definition. Leaving these terms superficially defined has led to great confusion. It has led Halpern to recommend the clearly reactionary course of eliminating these "Unnecessary and troublesome constructs" in favor of a single more global term such as transformation[141]. His purview from a Department of Psychology and of Neurobiology and Behavior is obviously a parochial one. This is exemplified by his cursory discussion of the fields of biological optics and hearing in general. He fails to recognize how many different "transforms" occur within the neural system (extended to include the neuro-musular and neuro-glandular systems).

The neural system employs dozens if not hundreds of different transforms. These transforms are concatenated endlessly through a system that is highly parallel in its peripheral portion and "transforms" into a highly complex mesh organization in its central portion. The engineering and mathematical fields have necessarily used additional semantic terms to augment discussion of these transforms. Two of the goals of bioengineering education have been to bring the language of these fields into biology and to identify biological mechanisms employing common mechanisms, processes and protocols.

While Halpern claims the term sensory code is never used for pre-neural processes such as the optics of the eye, describing these by merely using his preferred term transform is inadequate. The optics employs many different transforms, most importantly the anamorphic transform giving the eye its unusually wide field of view while maintaining high resolution over only a small field of view. However, these transforms have been given individual and specific names, such as the Fresnel Transform. The relationship between these specific names and the term transform may not always be recognized by those in the soft sciences. As an example, he recommends abandoning the term sensory coding in favor of the term sensory transformation when there is the term sensory transduction already in wide use for this function. Transduction is specifically applied to the transformation of an energy profile in one domain into an energy profile in a second domain.

The neural system employs linear, nonlinear, logarithmic, exponential, discontinuous (Riemann) and many other transforms within various spatial, auditory, temporal and other domains. It also employs many additional transforms between domains, such as the specific encoding and decoding by stage 3 neurons (See **Chapter 9**) of analog domain information into a phasic domain to facilitate economical propagation of neural systems. Without this type of coding mammals would not have evolved as efficiently. Halpern's suggestion, that the term untransformation can be avoided by merely using transformation again in a different sense, is not nearly as useful as using additional specific terms, such as decode. Decode has a much more subtle and specific meaning than merely to transform (defined in

[141]Halpern, B. (2000) Sensory coding, decoding, and representations: unnecessary and troublesome constructs *Physiol Behav* vol 69, pp 115-118

his abridged dictionary as *to change the nature, function, or condition of; convert*.") Decode is *to recover the underlying information within a signaling format*.

The key point is there are many euphemistic terms used in the literature when discussing sensory codes (generally meaning transductions) and many neural codes (generally meaning transformations) used within the neural system. They need to be clearly identified semantically. The goal of neuroscience is to expand the lexicon of the neural system using precise expressions.

1.2.5.3.3 Limited use of standardized symbology in flow diagrams

The complexity of neurophysiological processes is far beyond that found in most chemical processing streams. Attempts to describe neurophysiological processes using the terminology from chemistry has led to bizarre schematics and flow diagrams exhibiting the free spirit of the creative mind at work. Unfortunately, this freedom has led to virtually irreconcilable differences between diagrams attempting to explain the same process. Little effort has been made within the neurophysiological community to acquire a standard nomenclature for neural processes and events. Recently, Novere et al. noted this situation in their figure 1 and their Table 1[142].

After reviewing the current situation, Novere et al. have made an attempt to overcome this problem by adopting the principles being used to develop the array of markup languages of current computer science. However, their effort still appears focused on one small corner of neuroscience. The effort can not describe the electrical portion of the neuron. However, the language, known as Systems Biology Graphical Notation (SBGN) is layered and it can be expanded. It currently consists of three modules. "Together they enable scientists to represent networks of biochemical interactions in a standard, unambiguous way." Unfortunately they do not incorporate any elements of electrical engineering and cannot represent the operation of a neuron in a meaningful way.

Their effort is large scale, involving many schools, and is admirable, but the results will take a long time to be widely accepted. The language is supported by a secretariat at (http://sbgn.org/). Appendix B of the Process Description Language, http://dx.doi.org/10.1038/npre.2009.3721.1 , provides a template of symbols currently supported by the language. Appendix C of the Process Description Language lists the challenges of the language left for future resolution. It currently can not handle a voltage controlling a rate of reaction or secretion.

1.2.5.3.4 Inadequacy in available software tools

Many software tools found in the field of neuroscience have been developed on the fly without adequate attention or skill in software development of the investigator. Similarly, a discussion between a software developer and the laboratory investigator seldom exhibits sufficient depth of information transfer and is frequently inadequate.

List et al[143]. have made a significant effort to define rules that a software developer should use in attempting to support wet laboratory investigators. The scope is necessarily global in character. Their Rule 5 is the most subject to clarification. They suggest not exposing the investigator to all of the parameters used in the software. This is extremely dangerous, particularly when the software developer adopts a Bayesian approach and assumes only a specific set of parameters are all that might be involved in solving a new research task. *The failure of software programs to recognize the ultra-violet signaling channel in chordate vision has been a detriment to science for decades.* An investigator frequently needs to recognize

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[142]Novere, N. Hucka, M. Mi, H. et al. (2009) The Systems Biology Graphical Notation *Nature Biotech* vol 27, pp 735-741

[143]List, M. Ebert, P. & Albrecht, F. (2017) Ten Simple Rules for Developing Usable Software in Computational Biology *PLoS Comput Biol* vol 13(1): e1005265. doi:10.1371/journal.pcbi.1005265

the limitations of the software by reviewing all of the pertinent "buried parameters." A superior approach is to provide an off-line description of all of the parameters used and their scope in a separate section.

Rule 1 & 2 of List et al. do not appear to address adequately the question of how the software developer becomes familiar with the subtleties of the demands on the software inherent in research problems. Having initial discussions with potential users is generally not adequate. The conversations need to be in depth.

Novere et al., discussed in the previous sub-section, have attempted to develop a comprehensive symbology that can be implemented in software packages with less chance of misunderstanding.

1.2.5.4 Problems with the biological membrane literature

To understand the operation of the neuron, the characteristics of the plasma membrane enclosing the neuron must be well understood. Unfortunately, the theoretical, and even conceptual, activity in this field has lagged behind the empirical effort. This has led to many conceptual models of membranes based on inadequate floating models.

The literature before 1950 is sparse and was based almost exclusively on a very simple concept; lacking the investigative power of the electron microscope, the biological membrane was considered a symmetrical semipermeable membrane separating two aqueous (low concentration) solutions. The semipermeability was initially based only on particle size. Later investigators also suggested the permeability could vary with the electrical charge on the particles.

Following the publication of the work of Hodgkin, Huxley and Katz in the 1950's, there was a massive renewal of interest in biological membranes. Many books were published on the subject in the 1960's. However, these remained based on the above conceptual model of the semipermeable membrane separating two dilute solutions. These materials were not consistent. Troshin published a book in 1966 highlighting the problems with the various conceptual treatments and the theories (largely notions) extant at that time[144]. His comments highlight the condition of the literature then.

> "The problem has been studied for more than seventy years. . . . To date, however, research workers have sharply divergent opinions about the fundamental questions of cell permeability."
>
> The conception ruling at the present time is the membrane theory; as is well known; the basis of this is the idea that any animal and plant cell behaves like an osmometer. Advocates of the old (classical) membrane theory assert that almost all the water in the protoplasm does not differ in its physico-chemical characteristics from the water of the surrounding medium and is an ordinary solvent and that all the fundamental mineral substances forming part of the composition of the protoplasm in it are in the dissolved state and are completely ionized.
>
> After the formulation of the fundamental proposition of the membrane theory, it quickly grew into a conception of wide application in general biology.
>
> Weissmann & Claiborne edited a comprehensive volume in 1975[145]. While quite wide ranging, the chapters are quite dated. The book remains a compendium of information and data, but almost every concept must be reviewed in the light of

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[144]Troshin, A (1966) Problems of Cell Permeability. NY: Pergamon Press. Translated by Hell, M. & Widdas, W.

[145]Weissmann, G. & Claiborne, R. (1975) Cell Menbranes: Biochemistry, Cell Biology & Pathology. NY: HP Publishing

current knowledge.

Soon however, the membrane theory encountered difficulties which it was unable to overcome. Already at the beginning of this century (early 1900's), several distinguished physiologists came out against this theory, pointing out that its fundamental propositions were erroneous.

Comparison of the facts relating to cell permeability with the material characterizing other facets of the activity of cells demonstrates convincingly that the present need is not for the improvement of some or other link in the membrane theory, but for its complete revision." [Emphasis added]

The reader should note the use of such theological terms as Dogma and Doctrine in some of the following material. The appearance of these terms in the scientific literature outside Neuroscience is rare. They are a sign of the deviation from the scientific method found in this field. The need for a completely new theory, not a revision, will continue to emerge within this section. The new theory is addressed initially in **Section 1.3.**

1.2.5.4.1 The use of excessive shorthand in important research

A problem in pedagogy reporting the results of applied research is the use of shorthand by investigators or textbook authors that they fail to define clearly. An extremely common situation involves describing energy transfers involving enzymes. Madigan et al represent the exception[146]. After discussing the transition from NAD^+ to $NADP^+$ in a paragraph labeled "Electron Carriers," they write in a footnote, "Strictly speaking NAD^+ or $NADP^+$ carries two electrons and one proton, the second H^+ being released to solution. Therefore, $NAD^+ + 2e^- + 2H^+$ actually yields $NADH + H^+$. However, for simplicity, we write $NADH + H^+$ as NADH. This subtlety is lost on the majority of students entering post-graduate programs.

1.2.5.5 Problems with Applied Mathematics texts addressing biology

There are a number of applied mathematics texts that address the mathematics of the neural system without acquiring any detailed knowledge of, or adopting any fundamental models of, the system. Wilson is a specific example[147]. Wilson begins with the assumption that the neural system employs a bistable signaling environment as found in digital computers. This is not the case. The phasic portion of the neural system is obviously monostable. The monopulse character of the action potentials does not support a second stable state. As is common in these books when they attempt to simplify the differential equations describing the neural system, they employ a cascade of first order differential equations all exhibiting a common time constant (see earlier Wilson citation). While, an interesting pedagogical case, such a cascade is essentially useless in an actual system. A careful examination of any action potential will show the attack time constant of the waveform is significantly different from the decay time constant. This is the typical situation for a switching-type relaxation oscillator as used in the neural system (**Chapter 2**). **Section 7.3.2.2** of "Hearing: A 21st Century Paradigm" discusses the temperature sensitivity of the time constants that are not addressed in Wilson).

Norwich[148] has recently presented a paper employing the ultimate in "reduced models" to show that all that is required is an understanding of thermodynamic principles (from Boltzman, and more recently Shannon) to understand the operation of the sensory system (including his concept of adaptation. His presentation, while correct at that level of reduction, does not lead to any of the realizations presented in this work. The paper might be of use in the obfuscation of entry level students by a professor in a lecture hall.

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[146]Madigan, M. Martinko, J. & Parker, J. (1997) Biology of Microorganisms, 8th Ed of Brock. NY: Prentise-Hall page 123

[147]Wilson, H. (1999) Spikes, decisions, and actions. NY: Oxford Univ Press

[148]Norwich, K. (2014) A physical basis for sensory perception *Physica A* vol 414, pp 61-75

In analyzing the foundation under the work of Hodgkin & Huxley, he defines the foundation of their differential equations. He notes their dependence on Ohm's Law, which requires linearity within the system, instead of the more general Kirchoff's laws applicable to a nonlinear situation. He also assumes continuity in the underlying, but unspecified, operating mechanism over the duration of the action potential. This assumption is questionable based on the change in time constants, and is in fact false. Finally, he also notes the hypothesis never stated or explicitly supported by Hodgkin over his entire lifetime, that there are physical currents of heavy ions flowing in and out of the neural cell in quantities and rates supporting neural signaling. He goes on to require the currents in the Hodgkin & Huxley equations to be statistically independent and therefore summable. This was an assumption of Hodgkin & Huxley's method of analysis, not a proposition.

More recently, Pullan et al. have presented a book stressing the "continuum approach" to analyzing the components of complex neural waveforms[149] that are clearly not continuous. Several approaches in the book incorporate the h, i & j parameters, ala Hodgkin & Huxley. The continuum-based approach is in a sense fallacious. The variables h, i, & j are "dimensionless gating variable" used to switch the value of these multipliers between zero and one at arbitrary times, sometimes more than once (Pullan et al., page 93).

1.2.5.6 Scarcity of the concept of impedance in physical chemistry

The operation of complete neurons are critically dependent on the transfer of electrical signals between components of the neuron. The mode of transfer and the efficiency of transfer are dependent on the characteristic electrical impedance of these components. Physical chemistry in general and the Chemical Theory of the Neuron in particular do not include a well developed construct of impedance.
While physical chemistry recognizes a one-way reaction and even a series of one-way reactions, it does not recognize a series-parallel group of such one-way reactions. Such networks are key to an understanding of the summation networks of synapses found throughout the neural system. These networks depend on the forward and backward impedance of each of the synapses to provide the "or" function of Boolean Algebra without losing sensitivity to small input signals..

The concept of impedance is found primarily in engineering, as opposed to science. It plays a crucial role in many aspects of signal transmission. The International Dictionary of Physics and Electronics devotes nearly six pages just to defining subsidiary relationships related to impedance[150].

In the absence of a concept of impedance, the description of the neuron using chemical principles is fundamentally constrained. This fact will become obvious in **Chapter 10**.

1.2.5.7 Inappropriate generalization of the stage 7 chemical synapse

The dogma of the chemical synapse arose based on the studies of the termination of neurons at the muscles (stage 7A). The chemical synapse is infrequently found in the neural system. They occur at the axon pedicles of orders of magnitude less than one percent of all neurons. Neurons releasing chemicals at the pedicles are defined below as neuroaffector neurons of stage 7. *All other neurons passing signal information employ electrons as the neurotransmitter.* These include the neuron-to-neuron synapses, and the internal axon segment to axon segment synapses (known as Nodes of Ranvier). See **Section 4.2.3**.

While the release of chemicals at the pedicles of axons is statistically infrequent, such release

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[149]Pullan, A. Buist, M. & Cheng, L. (2005) Mathematically Modeling the Electrical Activity of the Heart. London: World Scientific

[150]Michels, W. et. al. (1961) International Dictionary of Physics and Electronics, 2nd ed. NY: Van Nostrand, Inc. pp 586-591

plays a major part in the physiology of the organism. These chemicals act as both neuroaffectors of non-neural tissue and neuromodulators of virtually all cells (**Chapter 16**).

1.2.5.8 "Sodium current" was & is a euphemism

The concept of in-rushing and out-rushing ionic currents, as used in neuroscience, will forever be associated with the names Hodgkin and Huxley[151]. However, it is important to appreciate three situations. First, they rejected the "classical form of the membrane theory" of their time. Second, how they arrived at the media implementing their "currents" is interesting and third, what alternate implementations are available. Hodgkin & Huxley recorded electrical current moving into and out of their axoplasm (using electrical instrumentation). They presumed this current was passing directly through the axolemma. Using the common wisdom that current flowed from positive terminal to negative terminal as positive charges, they looked for a potential source of such current. They surmised that the inward current was probably due to the flow of sodium ions from the extracellular matrix, through the axolemma and into the axoplasm. They used the euphemistic term "sodium current" to describe this putative inward current and related it to the rising edge of the positive going "action potential" of their squid. Similarly, they surmised that the outward current was probably due to the flow of potassium ions in the opposite direction and related to the trailing edge of their "action potential." They did not contemplate any other current path within the external lemma of their neuron. These assumptions were based primarily on the relative concentration of these two types of ions in the axoplasm and surrounding medium. They did not demonstrate the accuracy of their premise. Attempts to verify their assumptions and corroborate their measurements in the last 50 years have been spectacularly unsuccessful.

> A quote from Karczmar et al. (page 81) is most convincing. **"One would then expect that the replacement of Na^+ by an impermeant cation will hyperpolarize the membrane. It is puzzling, however, that only a small depolarization occurs when Na^+ is replaced with impermeant foreign cations." This statement by Karczmar et al. should be *prima facia* evidence for falsifying the chemical theory of the neuron (and as a minimum the dual alkali-ion theory of the neuron). If Na^+ need not be present in the extra-neural environment, its passage through the lemma of the neuron cannot be a critical factor in the operation of the neuron.**

Hodgkin & Huxley also stated a fundamental fact in their summary paper related to their studies. "At present the thickness and composition of the excitable membrane are unknown." There have been a few experiments designed to show the permeability of biological membranes to radioactive sodium ions. Hille summarized this activity in 1977[152]. His references should be reviewed to obtain important experimental details. More recently, Hille has provided an important discussion of how ionic channels have come to be named[153]. He pointed out, "The naming of ionic channels has not been systematic. . . . Finally, it is tacitly assumed that each component of the model corresponds to a type of channel, and the putative channels are given the same names as the permeability components in the original analysis."

It is now known that the membranes of neural conduits are impervious to ions and their thickness is so thin that quantum-mechanical effects must be considered in describing their electronic characteristics. Recent efforts have been made to redefine the underlying mechanism as depending on pores or channels within the membrane. Attempts to verify the presence of such structures in the laboratory have also been unsuccessful, *particularly in the case of myelinated axons.*

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[151]Hodgkin, A. & Katz, B. (1949) The effect of sodium ions on the electrical activity of the giant axon of the squid *J Physiol* vol 108, pp 37-77

[152]Hille, B. (1977) Ionic basis of resting and action potentials, Chapter 4 *In* Handbook of Physiology, Section 1, Vol. I, Kandel, E. *ed*. pg. 111

[153]Hille, B. (1984) Op. Cit. pp. 5-6

As developed in **Figure 1.2.2-2**, there is an alternate explanation for these currents as they relate to an axon. This explanation is based on the transfer of charge by electrons instead of ions. Since electrons have negative charges, their motion is in the opposite direction than presumed for positive ions. A putative inward flow of positive charges ("sodium") through the exterior axolemma is actually caused by the flow of electrons out of the axoplasm by a different path. This flow depolarizes the axoplasm. Alternately, an outward flow of positive charges ("Potassium") is actually caused by electrons flowing into the axoplasm from the extracellular medium, thereby polarizing the axoplasm. This explanation negates the need for the so-called "independence principle" proposed by Hodgkin & Huxley but never confirmed.

Hodgkin & Huxley did not address the flow of current into or out of the dendroplasm or other neurite plasmas. These currents have generally been ignored in the experimental literature.

1.2.5.8.1 The putative role of Ca^{2+} and K^{+} in neural operation

Besides the flow of sodium through a plasma membrane, a similar flow of Ca^{2+} and K^{+} have also been postulated.

As noted in Chapter xxx, the flow of Ca^{2+} through a membrane has never been demonstrated directly. Its original description as a current through the neural plasma was proposed by Huxley & Hodgkin to explain the creation of the waveforms they recorded during early tests preceding the patch clamp technique. Such a current has been discussed as a fait accompli ever since. Bird & Putney have provided a discussion of the difficulties in measuring the putative Ca^{2+} current in the neural context[154]. The difficulties are obvious from their remarks and the title of their paper.

Bird & Putney also discuss the putative flow of K^{+} ions through the plasma membrane.

The role of Ca^{2+} in muscle (sarcomere contraction and recovery) appears well established. However, its release and transport is frequently related to its complexing with complicated negative ions.

1.2.6. Archaic Dogma found in current neuroscience literature

The term dogma has routinely been used to describe the hypotheses, based primarily on philosophy, concerning the form and operation of the neurons. The difference between dogma and doctrine in the neuroscience and philosophy areas is difficult to discern. They are typically taken as synonymous.

Many archaic concepts continue to appear in the neuroscience literature designed for pedagogy. They are generally presented based on floating models and cannot be justified based on more comprehensive model. They are products of an earlier time.

It is not recognized, even among many researchers in the field that the neural system is primarily an analog system, supported by a phasic signal propagation subsystem employing action potentials (described as stage 3 in this work). However, ample evidence exists that this is true. Consider for a moment whether the neural circuits of the retina are part of the central nervous system. If they are, consider whether they can be considered typical of the CNS neural circuits. The neural circuitry of the retina is well understood and documented. All neurons of the retina (over 95%), except the ganglion cells of stage 3 (about 5%), operate in the analog domain. Similarly, visually-evoked potentials (VEP) recorded from the cortex are analog in character. Tootell et al. have recently provided an example of these

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[154]Bird, G. & Putney, J.(2006) Fluorescent indicators–facts and artifacts. *In* Putney, J. *ed*. Calcium Signaling, 2nd Ed. NY: Taylor & Francis

waveforms[155].

As noted in Section 1.0, Sanchez has documented "7 Biology Myths No Electrical Engineer Would Ever Tolerate." They are listed here to highlight the many objections to the archaic concepts discussed below.

1.2.6.1 The archaic chemical theory of the Neuron

The neuron has been studied intensely since medieval times. Its electrochemical aspects have been studied in parallel with electricity itself beginning in the 18th century. Yet, no clear and concise (preferably axiomatic) description of the operation of the neuron based on chemical principles has been presented to date. Major attempts to define the neuron based on the chemical theory have occurred periodically. The following brief synopses and quotations are needlessly wordy because that is the only way the chemical theory of the neuron has been expressed.

••The earlier studies have consistently suffered from one aspect that is excessively common in the biological fields. The empirical investigators of a given time have sought to solve problems with inadequate theoretical and/or mathematical tools. Tasaki[156] stated the situation succinctly: "We see repeatedly that physiologists prefer mathematically formulated theories of excitation, even when the quantities which are treated in their theories are of dubious physicochemical significance." These comments are obviously the words of investigators looking back in time. They are intended to provide a current evaluation but may lack adequate reverence for the work of others outside Tasaki's narrow field. Workers from outside look upon the work Tasaki is discussing with similar lack of reverence, particularly when chemical kinetics is used to support broad physiological hypotheses by physicochemists. Tasaki has provided an excellent synopsis of the history of the electrochemistry of the neuron up through 1982. No significant change has occurred at the foundation level since then (except for the greater recognition of the salutatory aspect of action potential propagation along the axon).

••In 1987, McGeer, Eccles & McGeer presented an entire textbook on molecular neurobiology that hardly addressed the electrolytic nature of the neural system. It dismissed the idea of an electrolytic (electronic) synapse within the neural system out of hand on page 14 of 770 pages[157]. It is worth quoting the opening and closing sentences of their paragraph. They open with "Only brief reference need be made to electrical synapses, where transmission is by electric currents flowing from the presynaptic to the postsynaptic component." After discussing a variety of alternatives, and later devoting whole chapters to chemical synapses, they close with a clear statement. "It is well to keep in mind, therefore, that the classical descriptions presented here fall far short of telling the complete story of how neurons communicate by chemical messengers." The natural conclusion is that they were unable to confirm their ideological position.

One of the classic descriptions that fall short is given in their Chapter 5, Principles of Synaptic Chemistry. The opening sentence of this chapter says "Unfortunately, the (chemical) transmitters are not known for the vast majority of the neurons in the central nervous system (CNS)." It then provides a series of criteria for determining if a compound is a neurotransmitter based on anatomical, chemical, physiological and

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[155]Tootell, R. Nelissen, K. Vanduffel, W. & Orban, G. (2004) Search for color 'center(s) in macaque visual cortex *J Opt Soc Am A* vol 14, pp 353-363

[156]Tasaki, I. (1982) Physiology and electrochemistry of nerve fibers. NY: Academic Press

[157]McGeer, P. Eccles, J. & McGeer, E. (1987) Molecular Neurobiology of the Mammalian Brain. NY: Plenum Press. pg 14.

pharmacological grounds only. No mention is made of the impact of such a compound on signaling or cognitive functions, or the possibility that the neurotransmitter is an electronic charge..

••Burn (a noted pharmacologist of his day) has provided a running history of the development of the chemical theory of the neural system, that was in its fifth edition in 1975[158]. His reportage stresses the gross level of the experiments used to develop and confirm the chemical theory. In general whole organs, or major parts of organs, were perfused with a variety of biological organics and the results noted. To obtain more decipherable results, the same perfusions were repeated using sets of two biological chemicals in sequence. The results remained inconclusive, especially when the process was performed on similar tissue of different species, or even different types of muscle tissue. The criteria used to identify a "neurotransmitter" was whether the material in question appeared after some specific neural or muscular activity OR whether it was involved in some type of neural or muscular response. The question was never whether the material emanated from a specific neuron and impinged upon a second neuron, thereby conveying information. While interesting, the conflicting actions related to the presence of acetylcholine on the surface of striated, smooth and cardiac muscle (page 47) shouts for the more detailed understanding of what is going on at the cellular level. The demonstrations of chemical transmission by Loewi (1921) and by Dale et al. in the 1920's (including the inconsistencies they reported between similar situations) appear quaint in the light of more modern information concerning the complex nature of the individual neuron.

••The 1980's saw more experimentation at the histological level, with some early work at the cytological (ultrastructural) level. However, interpretation of the results remained highly unsatisfactory, as typified by the discussions at the 1987 Tokyo conference on Neurotransmitters and neuroreceptors[159].

••The 1990's saw the extension of the cytological work, largely from the morphological perspective, using the light and electron microscopes and also saw the beginning of electrophysiological investigations (some employing voltage clamp techniques) involving external iontophoretic intervention[160]. Most of the cytological work remained focused on defining where acetylcholine (ACh) appeared in the neural system. Martinez-Murillo & Rodrigo summarized the situation[161]. "In summary, ACh histochemistry can be considered a rather limited procedure for labeling CNS neurons that use ACh as a neurotransmitter at their synapses. Therefore, alternative methods have been sought." They presented a considerable bibliography. In essence, they found neurons they identified as cholinergic nearly everywhere but could not describe the associated neural architecture or function. Pirch, writing in chapter 6 of the same volume, noted the following. "Acetylcholine influences neuronal activity via nicotonic or muscarinic receptors and the result can be (1) enhancement of excitability to other transmitters, (2) depolarization and initiation of action potentials, or (3) inhibition." Thus, the role of acetylcholine has not been defined explicitly. His discussion centered on iontophoretic studies. He stated the following. "Iontophoretic application of acetylcholine to medial and/or lateral geniculate neurons *in vivo* can result in either increases or decreases in firing rate. . . Both nicotinic and muscarinic receptors are involved in these responses." Thus the role of acetylcholine alone was ambiguous but its role in connection with another material may be definable. He introduces another section saying the following. "*In-vitro* studies have revealed that there are both

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[158]Burn, J. (1975) The Autonomic Nervous System, 5th Ed. Oxford: Blackwell Scientific Publications

[159]Kuriyama, K. (1987) Neurotransmitters & Neuroreceptors. Excerpta Medica pg 24

[160]Stone, T. ed. (1995) CNS Neurotransmitters and Neuromodulators. Boca Raton, FL: CRC Press

[161]Martinez-Murillo, R. & Rodrigo, J. (1995) The localization of cholinergic neurons and markers in the CNS In Stone, T. *ed*. Op. Cit. Chapter 1

depolarizing and hyperpolarizing influences of acetylcholine on thalamic neurons." He provided references to other studies where "responses of some cat auditory cortex neurons were facilitated and others were inhibited by ACh."

••Zillmer provided an essay on "The Neuron Hypothesis" from the psychological perspective in 2011[162]. It does not address the physiological aspects of the neuron except to refer to "other scientists know. . ."

••Stone provided a 40th anniversary retrospective for the Society for Neuroscience in 2009 that reviewed the state of the art of neuroscience, from the conventional chemical perspective[163]. While giving a competent review, he notes there have been incremental advances but no major breakthroughs since the 1960's.

The chemical theory of the neuron has gone nowhere during the last 100 years (excluding pedagogical circles where it has been expressed repeatedly *ad infinitum*). Fortunately, other later investigators still accept at least the possibility that electrolytic synapses occur[164].

1.2.6.2 The archaic Neuron Doctrine

A variety of versions of a neuron doctrine have evolved within the philosophy of the neural system. Only recently has it become possible to describe a neuron doctrine based on neuroscience. This more refined version will be addressed in axiomatic form based on the Electrolytic Theory of the Neuron after the following summary of the historical record based on the chemical theory.

••Shepherd presented a largely philosophical and historical review of the Neuron Doctrine as of 1991[165]. Shepherd reiterated the position of the virtually forgotten Waldeyer from the 1890's that the nerve cell is the anatomical unit, physiological unit, metabolic unit, and developmental unit of the nervous system. While shepherd uses the term genetic in place of developmental on page 4, he equates the two terms on page 285. Uttal has attempted to briefly summarize and update shepherds position (pages 91-97) using the term genetic instead of developmental. Barlow also quotes Waldeyer "more precisely" using the term, developmental[166]. While the choice of terms may be a problem of translation from the German, it is significant. While all cells of an individual contain a single DNA, the expression of that DNA varies widely even among neurons. Thus, there is no genetically identifiable unit neuron. Alternately, the term developmental is closely related to the ontogeny and homeostasis common to all neurons.

••Waldeyer's neuron doctrine came to a high level of controversy at the Nobel Lectures of 1906. Cajal originally promulgated what became the reductionist version of the Neuron Doctrine in his lecture at that ceremony while Golgi argued for the holistic version of the same doctrine. The Golgi approach eventually became the *Neural System* Doctrine defined below. Both of these doctrines were based entirely on morphology and have been revered by morphologists ever since. The Cajal approach is described today as a bottom-up or reductionist approach. The Golgi approach is

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[162]Zillmer, E. (2001) The Neuron Hypothesis *In* Zillmer, E. & Spiers, M.(2001) Principles of Neuropsychology. NY: Wadsworth page 53

[163]Snyder, S. (2009) Neurotransmitters, receptors, and second messengers galore in 40 years. *J Neurosci* vol 29(41), pp 12717-12721

[164]Brown, A. (1991) Nerve Cells and Nervous Systems. NY: Springer Verlag Chapter 5

[165]Shepherd, G. (1991) Foundations of the Neuron Doctrine. NY: Oxford university Press

[166]Barlow, H. (1995) The neuron doctrine in perception *In* Gazzaniga, M. *ed.-in chief* (2004), The Cognitive Neurosciences, 2rd Ed. Cambridge, MA: MIT Press pp 415-435, pg 416 *dropped from subsequent editions*

> described today as a top-down, a field, a holistic, a reticularist or a mesh network approach. Beginning in the last quarter of the 1900's, the underlying concepts separating these approaches began to erode as the physiology of the neural system became better understood. The formal marriage of these two approaches has been hindered by the enormous complexity of the brain. This matter was reviewed by Bennett in 1997[167]. The competition between Cajal and Golgi in this arena is also reviewed by Uttal (pages 92-94).

Finding an explicit and updated statement of the Neuron Doctrine in Shepherd's book is difficult. His chapter and section titles include (in the following order), The Neuron Doctrine, Modern Revisions of the Neuron Doctrine, and Revising the Neuron Doctrine. However, these headings do not lead to an explicit statement. The summary of Shepherd's views given by Uttal in 2005 (pages 94-95) shows shepherd's position is archaic. Shepherd drew a revealing conclusion after 292 pages reviewing the historical record. "Despite the 50 years of work that led to the classical neuron doctrine, the progress over the past 100 years, and the accelerated pace of recent research, our understanding of the neuron is still at an early stage." On the same page, he proposes adding a fifth basic unit, the minimum information processing unit. This appears to be unnecessary because information processing occurs in a psychological dimension that relies upon the underlying signals extracted by stage 4 signal manipulation neurons in the signaling dimension.

> Although largely philosophical, there is a question of whether the term information or signal should be used to describe one of the minimum features of the neuron. Information is a largely abstract term describing the content or capacity of a channel, whereas signals are easily identified and recorded in the laboratory. Neurons process signals, whether those signals contain any identifiable useful information or not. The term "minimum signal processing unit" appears more appropriate in this discussion.

Reviewing the current knowledge of the neural system, conclusions different from, and more precise than, those repeated by Shepherd are appropriate. From a reductionist perspective, the physiological unit of the nervous system consists of a three-terminal active device followed at its output by an electrolytic conduit leading to the next active device. *This configuration is below the level of the cell*. In order to support the necessary ontogeny and homeostasis, one or more of these device-conduit pairs are enveloped by the lemma of an otherwise non-neural cell to form the basic anatomical unit. Metabolically, significant but inconclusive evidence suggests it is the neuron cell defined here combined with at least one glial cell that forms the fundamental metabolic unit of the neural system. Although a clearer definition of "minimum information processing unit" is needed, it is clear that a single three-terminal device-conduit pair is capable of significant signal (alternately, information) processing.

From a holistic perspective, the neural system consists of a nearly endless concatenation of device-conduit pairs in a generalized multidimensional mesh network. The recognition of the mesh character of the neural system is the foundation of the old reticular theory of the neural system. Understanding any aspect of consciousness requires understanding the interconnections of at least a significant part of this network.

> The top-down holistic approach involves histology and the emerging technology of magnetic resonance imaging (MRI), to perform what the cryptology community calls traffic analysis. These techniques lead to a definition of the source, routing and destination of large groups of neurons forming nerves and commissure but little else. Electrophysiology allows the recording of the specific coded signals carried by a neuron. However, the coarseness of the above techniques do not provide data about the signal encoding methods used or the information content of the nerves or the individual neurons.
>
> The traffic analysis maps of the brain look remarkably similar to the maps of traffic over

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[167]Bennett, M. (1997) Gap junctions as electrical synapses. J. Neurocytol. vol 26, pp 349-366

undersea cables linking various islands and continents plotted on a globe.

The bottom-up reductionist approach, coupled with the Electrolytic Theory of the Neuron, provides detailed information about the development and physiology of both the individual neurons and the nerves. It has revealed the various methods of signal encoding used within the neural system but has not yet revealed the underlying signals used, or the specific information carried, by individual neurons. The imminent merging of the holistic and reductionist material in this work promises to reveal both the actual un-encoded signal and the information content of individual neural circuits for the first time.

Shepherd's review shows that the initial Doctrine was based entirely on morphology. As time progressed, a set of putative chemical processes was defined that supported the morphological conclusions. Only in the 1950's were the electrical potentials associated with the neuron confirmed. Simultaneously, the ability of an electrical current to transfer across a "gap junction" was demonstrated. These findings caused two unresolved problems. The operation of the synapse conflicted with the idea that the neuron (as a cell) was the basic physiological unit. The ability of a current to spread across a gap junction, and the ability of that flow to be reversed under revised electrical biasing, caused a problem with the notion of a chemical "neurotransmitter" mediating signaling across the gap. These problems have not been explained within the ideology that has arisen around the historical Neuron Doctrine.

1.2.6.3 The archaic Central Dogma of Neuroscience

An alternate set of authors have promulgated a "Central Dogman of Neuroscience." It is as difficult to quantify as the Neuron Doctrine.

••Dowling, writing in 1992, developed what he described as the Central Dogma of Neuroscience[168]. He described the Dogma by use of a highly conceptual sketch that was not supported by any morphological or electrophysiological model. Furthermore, it invoked the concept of a synaptic potential generated by mechanisms at the post synaptic terminal. The Dogma does not differentiate clearly between electrotonic and pulse signals. The sketch also introduces external feedback, at the individual neuron level, without any demonstration of its actual occurrence within the neural system. It further confuses the concepts of encoding and modulation by associating electrotonic signals with the RF signals of an AM band radio. As will be shown in Chapter 9, the electrotonic signals are encoded by stage 3 neurons into a signal more closely related to an FM band radio.

••Meanwhile, in a more philosophical context, Barlow was continuing to expound his theories and dogma of neuroscience[169]. The focal point of his 1972 writing was a "single neuron theory," that a complete percept of a scene could be correlated with the "firing" of one neuron. The writings of Barlow are not supported by any extensive functional analysis of neurophysiology but are primarily his interpretation of a series of behavioral observations. The five philosophical dogma of Barlow (1972) recited by Uttal appear superficial based on current neuroscientific knowledge. They represent a prior philosophical position before the neuroscience/philosophy chasm moved by the expansion of the neuroscience domain.

••In 2005, Uttal addressed the current confusion concerning neuron dogma in considerable depth (pp 91-98 & 154-194). As his title to his section 5.1.1 indicates, he struggled to achieve clarity concerning what he called "The classic and currently fully accepted Neuron Doctrine is a very specific statement about the anatomy and physiology of neurons."

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[168]Dowling, J. (1992) Neurons and Networks. Cambridge, MA: Harvard University Press, pp 56-57

[169]Barlow, H. (1995) The neuron doctrine in perception. The cognitive neurosciences. *In* Gazzaniga, M.*ed*. The cognitive neurosciences.. Cambridge, MA: MIT Press. pp 415-435

> Uttal addressed Barlow's five dogma of 1972, Barlow's apparent softening of his writings from dogmatic to more eclectic in 1995, and then presented his counter arguments to the dogma in three similarly numbered "questionable dogma." Barlow continued to soften his views relative to a single neuron theory in 2001[170].

The march of neuroscience has exposed the lack of precision in the philosophical assertions of these authors. Neither Barlow's dogma or the contrary "questionable dogma" of Uttal appear particularly relevant to the highly mesh oriented central nervous system we now recognize (particularly through fMRI imaging if nothing else). These philosophical discussions contribute little to the growing knowledge of the known physiology of the neural system and will not be continued or expanded here. As Uttal noted (page194), "The very empirical foundations of single neuron theory are evaporating just as some of the logical problems are becoming more evident." And. "What the single neuron theory and the field theories share in common is their dependence upon concepts and ideas that themselves are at best imaginative inventions rather than compelling empirical proofs or sound logical arguments."

As noted earlier, the neuropsychology community has pursued a substantially different concept of the "Neuron Hypothesis" as discussed by Zillmer[171].

1.2.6.4 The Archaic Notion of the Standalone Axon

Hodgkin & Huxley performed an extensive laboratory investigation on the large neuron of the squid, *Loligo* during the 1940's culminating in an extensive series of papers in 1952. Their published results relating to the non-myelinated neuron of a member of *Mollusca* have been widely interpreted as applying to the myelinated projection neurons of *Chordata*. This has come true in spite of the extensive work of Tasaki and others, both before and after that of Hodgkin & Huxley, showing quite contrary results.

It is important to distinguish carefully, when reviewing a body of work, between the experimental findings and the conceptual picture on which the study is based, or which emerges from the given study. As noted in the introduction, the analyses of Hodgkin & Huxley were highly constrained and did not address many other physical mechanism available to explain their measured data. They did not investigate, eliminate or accept the possibility that the putative action potential of *Loligo* originated in junctional tissue. Their final set of equations contains an exceedingly high number of arbitrary constants and independent variables that can be used to match virtually any set of initial conditions. The equations defining *m, h, n* & *p* used by Hodgkin & Huxley, and reproduced in Frankenhaueser & Huxley, also suffer from inconsistency in the units associated with the variables. These labels actually apply to unit-less "switching functions," that turn on the associated terms at a given time or for a given interval. The mechanism controlling this switching is not described.

The merging of the so-called cable equation (for a lossy cable) with the wave equation (that only applies to a loss-free cable) appears undefendable. Their assumption of a real number (as opposed to a complex number) for their "conduction velocity" is completely incompatible with their assumed lossy cable. Such a cable always exhibits a complex "conduction velocity" where the phase shift component, β, is always a function of frequency (wavelength).

They were unable to solve their differential equations describing the putative action potential of *Loligo*. As a result, they were unable to define the transient and steady state components of the predicted waveform and confirm that their assumed initial condition were correct.

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[170]Barlow, H. (2001) Redundancy reduction revisited *Network Comp Neur Sys* vol 12(3), pp 241-253

[171]Zillmer, E. (2001) The Neuron Hypothesis *In* Zillmer, E. & Spiers, M.(2001) Principles of Neuropsychology. NY: Wadsworth page 53

They proceeded by using an arduous series of mathematical tabulations based only on the proposed set of differential equations. No one is known to have reproduced their mathematical procedures *ab initio*.

As Cole noted on page 476, "As to curve-fitting, the procedure and the results of Hodgkin & Huxley (1952b) are entirely unorthodox and are looked at with both amazement and admiration by trained mathematicians." An alternate expression might be "courteous consternation" or simple "courteous disbelief." The orthodox goal of a mathematician is to derive a set of mathematically consistent equations that provide incite into the underlying mechanism being studied. It is difficult to comprehend the goals of Hodgkin & Huxley when all they have prepared is a very complex mathematical procedure for creating a template approximating a poorly characterized response intimately related to their test configuration. As noted in statement (15) of Frankenhaueser & Huxley, the resulting template does not describe any specific fibre but only an undocumented ensemble of fibers.

Other problems related to their mathematical manipulations are summarized in Appendix C xxx.

The reader is cautioned that exception is not taken to any of the data presented by Hodgkin & Huxley, or Cole. It is the interpretation and the calculated waveforms (as a function of time), that fail to satisfy the operational requirements of a valid theory/model, that are questioned. Most readers are not aware that their widely reproduced figure 17 (page 530) does not represent the ionic currents flowing through a membrane but only the variations in conductance proposed by them *ad hoc*. Figure 18 (page 531) showing their predicted currents is seldom reproduced because it is so difficult to justify.

Further consideration of the sodium ion-based Dual Alkali-ion Diffusion Theory of the axon or neuron will be postponed until after an alternate theory is presented. The alternative provides a theoretical framework with which to evaluate the propositions developed by Hodgkin & Huxley (which were based entirely on curve-fitting to empirical data).

1.2.6.5 Redefining the poorly defined concept of a second messenger

Micro-ecologists and biologists have frequently asserted a mechanism of communications between separate organisms (presumably of the same species). Such communication is typically associated with a first messenger, the carrier of the "message." Investigators have attempted to continue the analogy through a logical extension, by defining a second messenger as a conceptual material found within the second organism. At least in higher organisms, it has been assumed the second messenger is a chemical released within a sensory neuron of the neural system. However, the detailed description of this second messenger has remained undefined.

At least since the definition of the double helix by Watson & Crick, there has been a tendency to define the second messenger as a protein. However, more recently, other options have resurfaced. The Handbook of Lipid Research (1996) discusses (admittedly in a protected forum) the potential for a lipid to be the second messenger[172]. However, the literature remains deficient in describing how, the first messenger causes the generation of the second messenger, and how said second messenger (whether a protein or a lipid) causes a change in electrical potential at the pedicle of an axon.

This work replaces these putative descriptions of the second messenger with a more realistic messenger within the sensory neurons of the second organism. The second messenger is the electron; at a more precise quantum-physical level, it is the electrons solid state partner, the "hole"). The detailed properties and involvement of these entities is developed in **Section 1.2.1.3**.

1.2.7 The Neuron Doctrine and other Dogma in the Electrolytic paradigm

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[172]Bell, R. Exton, J. & Prescott, S. (1996) Handbook of Lipid Research, Vol 8, Lipid Second Messengers. NY: Plenum Press Preface & Chapters 3, 5 & 6

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Integration of the new technologies, first introduced in **Section 1.1.4** and discussed in detail in **Chapters 1** & **2**, into the study of the neuron leads to a new and more detailed Neuron Doctrine and Neuron System Doctrine.

> The following discussions are meant to exclude the recent discussions in the philosophy domain relating to an arbitrarily named Neural Doctrine in that arena[173,174].

This section will restate the earlier dogma of philosophy in the context of neuroscience using the more precise terminology introduced in **Section 1.1.4.**

Cajal originally promulgated what came to be called the Neuron Doctrine at the end of the 1800's. It was based entirely on morphology and has been revered by morphologists ever since. However, beginning in the last quarter of the 1900's, the concept began to wear thin due to the work of electrophysiologists as reviewed by Bennett[175]. Cajal also promulgated a Law of Dynamic Polarization[176]

> Contrary to the Neuron Doctrine originally promulgated by Cajal which proposed that the neuron was the fundamental unit of the neural system, it will be shown that **the smaller box shown in Figure 1.2.3-2(A) encloses the actual fundamental unit of the neural system.** Due to the three-terminal configuration of the Activa, **it is also necessary to reformulate and subdivide the Law of Dynamic Polarization**.

Based on the currently available knowledge, the guiding principles drafted by Cajol, Dowling and others should be reformulated into the following statements.

> The following Doctrine and Laws apply to all neurons of the biological nervous system. They describe the **analog** operation of all signal processing neurons. These are found in the retina, the central nervous system and at nodes and terminals of the peripheral nervous system.
>
> Every neuron contains at least one active electrolytic semiconducting device capable of amplification. The Node of Ranvier and the synapse are morphological labels for active electrolytic circuits containing at least one semiconducting device–an Activa.
>
> If supported by electrolytic components of appropriate value, the **analog Activa within a neuron can be made to oscillate and generate phasic waveforms** (known as action potentials). Such circuits are used in the signal projection neurons of the nervous system. These are found in the optic nerve, the long neurons of the peripheral nervous system and in the commissure of the brain.
>
> The vast majority of the neurons of any neural system (over 95% in humans) operate in the analog mode (process electrotonic signals).
>
> Although employing *internal* negative feedback widely, *external* negative feedback is rarely if ever used in the neural system.

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[173]Gold, I. & Stoljar, D. (1999) A neuron doctrine in the philosophy of neuroscience *Behav Brain Sci* vol 22, 809–830 *with extensive discussion on* pp 831-869

[174]Byrne, A. & Hilbert, D. (1999) Two Radical Neuron Doctrines Behav Brain Sci vol 22(5), pg 833

[175]Bennett, M. (1997) Gap junctions as electrical synapses. J. Neurocytol. vol 26, pp 349-366

[176]Brown, A (1991) Nerve Cells and Nervous Systems. NY: Springer-Verlag, Intro to Chap. 10

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1.2.7.1 A revised and expanded neuron doctrine *in axiomatic form*

The following work will demonstrate a considerably different neuron doctrine than reviewed above. It is based on the current scientific record in neuroscience rather than the earlier philosophical discussions.

To help organize the material and insure it is semantically straightforward and editorially clear, it will be offered as a set of axioms and sub-axioms or corollaries, reverting to the approach championed by Cajal. In fact, the set will be offered in two sets of axioms and corollaries. The first will relate to the neural system, following the reticular approach championed by Golgi in his 1906 Nobel address. The second will relate to the neuron as a component, following the approach professed by Cajal in his 1906 Nobel address. No figures will be used in this section to illustrate the concepts listed. Earlier material has addressed all of the elements appearing in the doctrine. Each of these axioms will be discussed in the appropriate context using appropriate representations in subsequent sections of the work.

The Electrolytic Theory of the Neuron provides a comprehensive neuron doctrine and framework that incorporates the critical aspects of the single neuron theory originally attributed to Cajal and the critical aspects of the mesh (reticular) theory originally attributed to Golgi.

The first set of axioms and corollaries are offered to describe the neuron doctrine at the overall neural system level. The second set will address the doctrine from the perspective of individual neurons.

These listings can be used as a reference list for referral during later discussions. Proceeding down each list leads to an ever more detailed description of the neural system.

1.2.7.1.1 The Neural System Doctrine

• The neural system consists of an active three-terminal electrolytic device associated with an electrolytic conduit, the pair being concatenated with similar pairs endlessly in a generalized multidimensional mesh network.

•• Electrolytic–an electronic element formed of one or more electronically (as opposed to ionically) conducting fluid filled elements.

•• Active–an electrolytic device capable of providing power gain (amplification or impedance transformation) with respect to an identifiable signal,

•• The active three-terminal electrolytic device is the analog of a PNP type solid state transistor.

•• The active three-terminal electrolytic device is defined in a biological context as an Activa.

• The number of device-conduit pairs found in the lowest animals approaches one and in higher mammals consists of more than 10^{13} individual device-conduit pairs.

•• The maximum number of device-conduit pairs is currently unknowable and the proposed number typically increases one order of magnitude (10x) every decade for humans.

•• It is expedient to associate large numbers (4-100 million) of individual device-conduit pairs into “engines” based on their functional association, which tends to exhibit morphological compactness.

•• Groups of functional engines frequently perform related roles within units defined as stages 1 through 7 of the neural system. 1) sensory signal generation, 2) signal processing, 3) signal projection, 4) signal manipulation (analysis), 5) cognition, 6) command generation, 7) neuro affectation. **Figure 1.2.7-1** shows the relationships between these stages and the parallelism among the afferent (sensory) and efferent (action or response) modalities.

• The neural system consists of multiple subsystems formed of groups of the stages defined above and associated with afferent, efferent, cognitive and memory modalities.
•• The afferent subsystems consist of the sensory modalities.

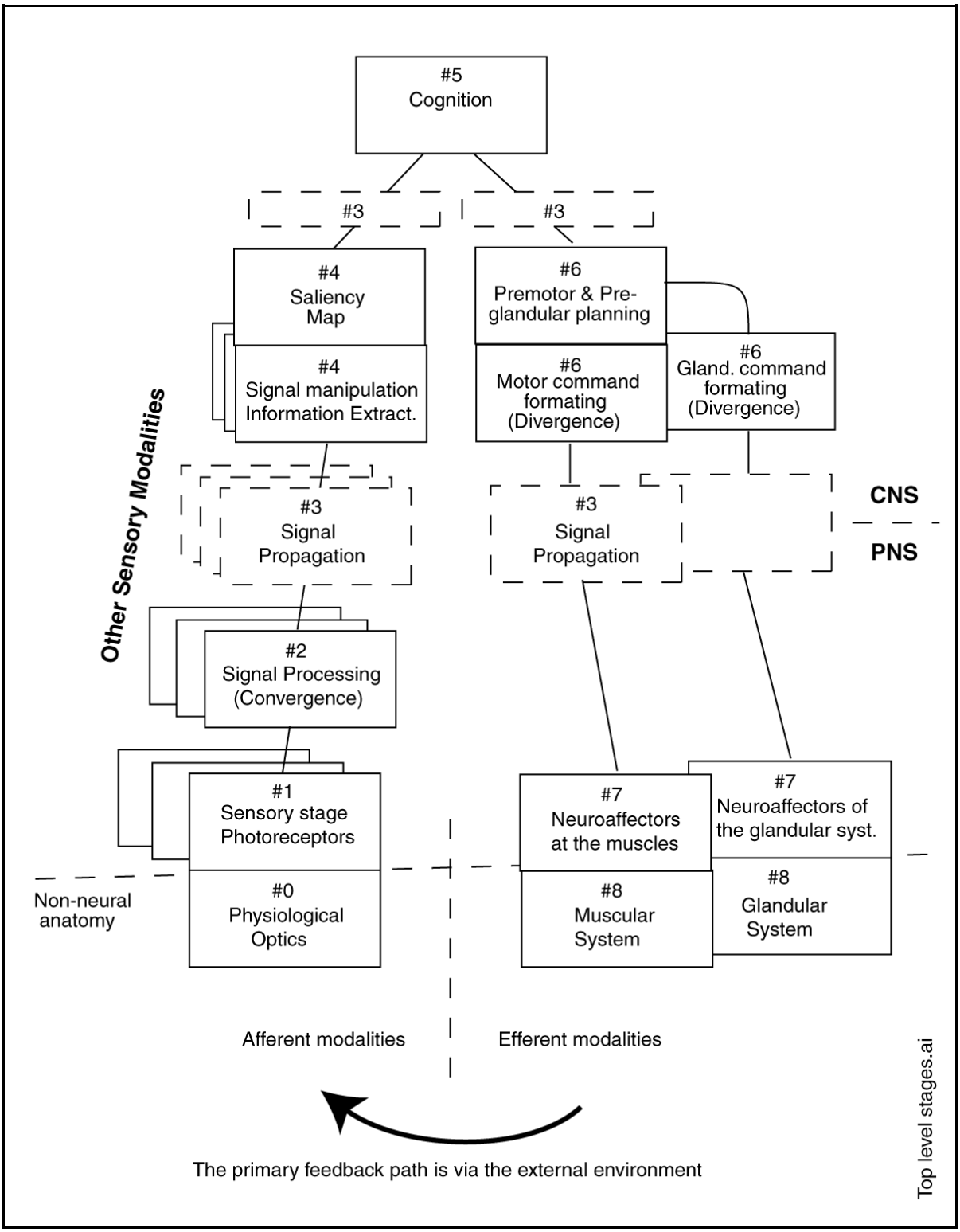

Figure 1.2.7-1 The generic stages of the top level block diagram of the neural system. Note the reoccurrence of stage 3, the signal projection stage, connecting major engines and stages more than a few millimeters apart. Note also the importance of external feedback via the external environment. See text.

•• The efferent subsystems consist of the neuro-motor and neuro-glandular modalities.
•• The cognitive modality is unitary and centered on the prefrontal cortex in humans.
•• The memory modalities include declaratory (recallable) and non-declaratory (procedural) memory.

• The neural system is bi-symmetrical in organization and morphology in accordance with the bi-symmetric organization of the animal kingdom.
•• The bi-symmetrical organization is followed only partially in the stage 5 cognitive centers within the prefrontal cortex of the central nervous system.

• The neural system employs multiple signaling overlays of the stages defined above associated with the sensory signal, awareness, alarm, analytical, volitional and command modes.
•• These modes operate in a hierarchal manner under executive control.

• The executive control of the neural system in higher animals is divided between conscious control and nonconscious control.
•• Conscious control of the neural system in mammals is centered in the prefrontal cortex and declaratory memory.
•• Nonconscious control of the neural system in mammals is centered in the thalamic reticular nucleus of the mid brain (diencephalon) and procedural (non-declaratory) memory.

• The concept of consciousness has come to replace the earlier terms mind and (non-theological) soul.
•• Consciousness is defined in terms of the subjects awareness and command of the surrounding environment via volitional activity based on cognition.
•• Unconsciousness implies a complete lack of awareness, control and cognition.
•• Subconsciousness implies the inability to readily recall certain declaratory events.
•• Sleep is associated with limited but finite awareness and control but nearly normal (and in some cases augmented) cognition.

1.2.7.1.2 The Updated Neuron Doctrine

The Neuron Doctrine of this work reformulates the philosophical concepts, reviewed by Shepherd and dating from Waldeyer, Cajal and Golgi,.in the framework of modern neuroscience. This Neuron Doctrine begins with the three-terminal Activa device-conduit pair as the minimal functional (or physiological) unit. The neuron is not a minimal physiological unit since it frequently contains two of the minimal functional units.

• The sub-cellular three-terminal device-conduit pair and its associated electrical biasing elements are the *minimum physiological unit* of the neural system.
•• This sub-cellular configuration requires the support of a biological cell for ontogeny and homeostasis.
•• Sensory and signal projection neurons typically contain more than one minimum physiological units.
•• The synapse used between neurons of stages 1 through 7 also contain this sub-cellular configuration.

• The neuron is the *minimum anatomical* unit and *minimum developmental unit* of the neural system.
•• The neuron is derivable from a stem cell of cytology via genetic coding.
•• The neuron is a discrete biological cell augmented with an electrolytic signaling capability
•• The neuron is more cytologically complex than a stem cell.
•• The basic neuron has evolved into a large family of specialized neurons under genetic control.

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• The neuron is the *minimum metabolic unit*.
  •• The primary source of metabolic energy for the developmental portion of the neuron is the oxidation of glycogen, a derivative of glucose.
  •• The primary source of energy for the neural portion of the neuron is the conversion of glutamate (glutamic acid) to GABA with the release of CO_2.

• A functional neuron contains at least one three-terminal electrolytic Activa, one electrolytic output conduit (axon segment) and the necessary additional electrolytic elements to bias the Activa into its active operating region plus the cellular elements required for homeostasis.
  •• The Activa and at least three electrolytic conduits (axon plus two neurites) are enveloped by the external lemma of the associated biological cell.
  •• The individual electrolytic conduits are electrically isolated from each other by internal lemma.
  •• The three individual terminals of the Activa are connected to at least three discreet areas of type 2 lemma on the surface of the neural cell.
  •• Each discreet area of the lemma that is associated with an electrostenolytic process provides electrical bias to a specific terminal of the Activa.
  •• The electrical biases are specified so the axon acts as the output conduit of the neuron.
  •• Additional electrolytic contacts can be made to the neurite conduits in order to introduce signals from previous neurons in a concatenated chain.

• The neurons are powered by an electrostenolytic process utilizing glutamate and the backup aspartate (aspartic acid).
  •• Glutamate and aspartate are the only *acidic* amino acids; as such, they are negatively charged and are the only possible source of a negative potential to the fluids within the neuron.
  •• The breakdown of glutamate in the electrostenolytic process generates GABA, gamma amino butyric acid and carbon dioxide (which are both electrically neutral following release of an electron to the neural electrolyte).
  •• The maximum potential supplied to the axon of a neuron is nominally –154 mV relative to the surrounding external neural matrix.
  •• The neural portion of the cardiocytes of the heart employ a second electrostenolytic process employing a positively charged (basic) amino acid, believed to be lysine.

• A neuron is fundamentally an analog amplifying device.
  •• An analog signal input to the first type of neurite, the dendrite, appears at the output terminal axon as an amplified signal of the same polarity.
  •• An analog signal input to the second type of neurite, the podite, appears at the output terminal axon as an amplified signal of opposite polarity.
  •• Amplification involves increasing the power at the output relative to the power at the input terminal(s); it may not involve voltage or current gain but a reduction in the impedance of the output signal.
  •• **95%** of the neurons in the typical neural system (all stages except stage 3) operate in the analog mode.
  •• The axon segments (conduits) of neurons operating in the analog mode are not myelinated.
  •• Signal projection within analog neurons is by electrolytic charge movement, as opposed to ionic movement, within the liquid-crystalline plasma.
  •• Action potentials are not generated by analog amplifying neurons (except under parametric stimulation in the laboratory).

• A neuron can be configured to operate in the phasic mode and generate action potentials.
  •• The phasic mode has a unitary stable point and does not exhibit two stable states.
  •• Only **5%** of the neurons in the typical neural system (stage 3 neurons) operate in the phasic mode.
  •• Long stage 3 phasic neurons incorporate additional three-terminal Activa-conduit pairs within the lemma of the neuron at intervals of about two millimeters.

•• The additional three terminal Activa and their supporting biasing elements are known morphologically as Nodes of Ranvier.
•• The axon segments (conduits) of phasic neurons are myelinated
•• Signal projection within the axon conduit(s) of phasic neurons is by Maxwellian wave propagation, note diffusion (conduction).

• The output electrolytic conduit of a neuron connects to the input conduit (neurite) of the subsequent concatenated neuron via a three-terminal active electrolytic device named a synapse.

•• the synapse is formed from a specialized portion of the lemma of the presynaptic neuron and a specialized portion of the lemma of the post synaptic neuron sandwiching an extremely thin layer of semi-metallic water.
•• The synapse is typically biased as a diode; as such, it exhibits a highly efficient one-way transfer function without polarity inversion.
•• The synapse is an electrically reversible circuit element; *this feature refutes the previous dogma that a synapse must be chemical because of its unitary transmission direction and relatively long delay*[177].

The following paragraph encapsulates the *new* Neuron Doctrine;

The neuron is the <u>fundamental biologically sustainable unit</u> of the nervous system. It is the minimum viable cellular structure. However, it is not the fundamental functional unit. <u>Each neuron contains one or more fundamental functional (signaling) units</u> internally and is associated with one or more external fundamental units (synapses) connecting it to an anti- or orthodromic structure. <u>Each fundamental functional unit consists of an active electrolytic three-terminal semiconductor device, an Activa</u>, supported by its peripheral electrolytic components, and associated with one orthodromic conduit. It may be found within or between neurons.

1.2.7.2 Subsidiary laws of neuron operation

For completeness, a set of subsidiary laws, patterned after earlier versions by Cajal and others (Shepherd, pages 195-205) are offered in this section. The offerings are not compatible with the simpler, morphology based, versions of the earlier era. In concert with the earlier assertion of Cajal (Shepherd, page 208), these laws show the soma of the cell plays no role in the signaling function of the neuron.

1.2.7.2.1 The Law of the Activa–The Activa is a three-terminal <u>analog</u> electrolytic semiconductor device forming the core of each fundamental signaling unit of the nervous system. It is a PNP type junction device. When appropriately biased electrically, the Activa is capable of signal (power) amplification. This signal (power) amplification can be expressed as an increase in voltage or current or as a change in impedance level associated with the voltage or current.

Like their metallic semiconductor brethren, the electrolytic Activa is bilateral. If the bias potentials are reversed, signal amplification can be observed at the emitter (dendritic terminal) due to a stimulus applied to the collector (axon terminal).

1.2.7.2.2 The Law of Internal Dynamic Polarization– All neurons are actively polarized internally such that all of the associated Activa are capable of amplification. This polarization involves multiple electrolytic chambers (conduits) within each neuron. When a dynamic electrical signal is impressed between two of the three appropriately polarized terminals of the Activa, an amplified signal appears between the third terminal and either of the first two. The external connections of the neuron to the two terminals of the Activa upon which the signal is impressed are considered neurites (dendrites and podites). The third external connection to the Activa is considered the axon.

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[177]Uttal, W. (2005) Neural Theories of Mind. Mahwah, NJ: Lawrence Erlbaum Assoc. page 94

1.2.7.2.3 The Law of External Dynamic Polarization– The axon of a neuron and the neurites of all orthodromic neurons are actively polarized relative to the immediately surrounding environment such that the Activa of each synapse is capable of signal amplification. All dynamic signals passing between neurons emanate from an axon and are impressed upon one of two types of neurites, a dendrite or podite.

1.2.7.2.4 The Law of Signal Polarity–A signal impressed upon the dendrite of a neuron will be amplified and the signal delivered to its axon will be of the same polarity. A signal impressed upon the podite of a neuron will be amplified and the signal delivered to its axon will be of the opposite polarity.

1.2.7.3 Alternate wording of the Neuron Doctrine *in axiomatic form*

An alternate wording of the Neuron Doctrine elucidated above is available on the Neural Research website. Http://neuronresearch.net/neuron/files/doctrine.htm

1.2.8 Genetics & epigenetics at the start of the 21st Century

> **BULLETIN (5 Sept 2012)–** ***The genetics community, specifically the heavily NIH funded "Encode Project," announced today that at least 80% of the 98% of the human genetic code previously defined as noncoding or "junk" is actually viable functional code. However, only the previously identified 2% of the complete genome is known to code for proteins. See below.***

Van Speybroeck et al. have edited an important symposium record describing the state of genetics at the beginning of the 21st Century[178]. They demonstrate DNA can no longer be considered a continuous series of genetic codes that are transcribed in a linear unidirectional manner. About 2-3% of the DNA actually codes for proteins. They also note the emergence of noncoding DNA or "junk" code as critically important to the functioning of the organism. The complexity of DNA encoding is much more sophisticated than represented in the genetic literature prior to 1995. This additional complexity is encompassed in the definition of the expanded field of epigenetics, "The study of changes in gene function that are mitotically and/or meiotically heritable and that do not entail a change in DNA sequence." Morange provided a comprehensive review of the field of genetics and epigenetics in the Van Speybroeck et al. volume. McGill & Zoghbi, writing in Charney et al, have noted the changes in the definition of epigenetics during the last two decades. They also described some of the recent changes in the concept such as those related to Skinner & to Blackburn described below. The major limitation on the field of genetics to date has been its narrow focus on the specification of proteins (including enzymes) by the genetic code. It has not yet shown how the specification for, and generation of, any of the sugars, lipids and other classes of molecules found within the biological system is accomplished via the genetic code.

At the turn of the Century, human DNA is estimated to contain 3,000 million base-pairs. Only about 150 million of these are in genes. It is estimated that 95% or more of this DNA is shared with the other primates. Recall the DNA must support the formation and operation of a whole suite of common biological elements (hearts to lungs to fingernails) Only about 3 million of these (0.1%) vary between individual humans. Ryan has written a book for the popular audience describing some of the questions gaining importance at that time, particularly regarding the importance of mitochondria[179]. He noted the consternation of the genetics community when the number of defined genes was only 40,000 compared to an expected 100,000. He notes the expanding view that the interaction between genes (and other DNA material) may be the controlling factor in many biological activities.

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[178]Van Speybroeck, L. Van de Vijer, G. & De Waele, D. (2002) From Epigenesis to Epigenetics: The Genome in Context. NY: New York Academy of Sciences

[179]Ryan, F. (2002) Darwin's Blind Spot: Evolution beyond natural selection. NY: Houghton Mifflin

Section 8.1.1.1 is the temporary home for additional detailed characteristics of the genetic code.

In 2011, a raging argument was under way to account for the large amount of genetic code not coding for proteins, currently estimated at 50-60%. Nowiccki suggested in 2004 that the amount not coding for proteins is about 85%[180]. The label junk has now been replaced by dark matter of the genome, ala dark matter in cosmology[181].

Merin, writing in 2005, has discussed the current role of DNA[182]. He notes, "the human genome contains ~3.2 billion nucleotides arranged in 22 pairs of autosomal chromosomes (chromosomes 1–22) and two sex chromosomes (X and Y). The chromosomes differ in sequence, gene content, size, and structure." Most importantly, he notes that "Most of the DNA, however is not arranged in functional units, and only 3% of the human genome encodes proteins." and "there is accumulative evidence indicating that it has many important functions including various regulatory roles." Some authors in 2011 have placed the percentage at only 2%.

2012 has brought real progress with relation to the coding of non protein material by the genome.

Linhardt and colleagues have succeeded in constructing *de novo* a complex carbohydrate, a proteoglycan called heparin[183,184]. They have also uncovered the sequence of the first carbohydrate biopolymer–a molecule called bikunin. While admittedly the simplest of biopolymers, the work demonstrates the presence of codes within DNA dark matter for materials other than proteins.

When the DNA is transcribed to RNA, much of the nucleotides are removed as not coding for proteins. The pieces of RNA that are cut out and thrown away are called *introns (Intervening sequence*), while the remaining pieces that are spliced together are called *exons* at one level and genes at another. Each exon codes for a specific protein.

Long non-coding RNAs (LncRNAs) are not translated into proteins and were initially considered to be part of the 'dark matter' of the genome. Recently, it has been shown that LncRNAs play a role in the recruitment of chromatin modifying complexes and can influence gene expression[185]

Merin (page 14) also noted the evolving recognition of greatest importance; that "Most human traits and inherited diseases are controlled by more than one gene;"

During the week of September 5, 2012, the results of the heavily funded Encode Project were released and multiple papers published in several journals simultaneously. The project announced that at least 80% of the 98% of the genome previously described as junk code was biologically active, i.e., at nearly 80% of the total genome is now known to consist of active material. Most of this material does not code for proteins but consists of "switches,

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[180]Nowicki, S. (2004) Biology: The Science of Life. *On DVD's* The Teaching Company

[181]Jarvis, K. & Robertson, M. (2011) The noncoding universe BMC Biology vol 9, pp52-53

[182]Merin, S. (2005) Introduction to human molecular genetics *In* Inherited Eye Diseases. NY: Taylor & Francis Chapter 3

[183]Linhardt, R. (2012) Copy Cats *Rensselaer* Winter publication, pp 18-23

[184]Ly, M. Leach, F. Laremore, T. Toida, T. Amster, I. Linhardt, R..(2011) The proteoglycan bikunin has a defined sequence *Nat Chem Biol* vol 7(11), pp xxx

[185]Fan, J. Xing, Y. Wen, X. Jia, R. et al. (2015) Long non-coding RNA ROR decoys gene-specific histone methylation to promote tumorigenesis *Genome Biol* vol 16, page 139 doi:10.1186/s13059-015-0705-2

regulators or enhancers."

> "Encode succeeded the Human Genome Project, which identified the 20,000 genes that underpin the blueprint of human biology. But scientists discovered that those 20,000 genes constituted less than 2% of the human genome. The task of Encode was to explore the remaining 98%—the so-called junk DNA—that lies between those genes and was thought to be a biological desert."
>
> The discovery "is like a huge set of floodlights being switched on" to illuminate the darkest reaches of the genetic code, said Ewan Birney of the European Bioinformatics Institute in the U.K., lead analysis coordinator for the Encode results.

Within the last 2-3 years, it has become clear that there is no single "human genome." Individuals differ significantly from the first claimed complete genome.

Crick among others has noted the variation in the epigenetics among individuals of the same species and the resultant difference in drug efficacy. This difference has been demonstrated in drugs such as Plavix and the family of PDE-5 inhibitor drugs, including Viagra.

The recent explosion in DNA testing for genealogical purposes has highlighted the presence of multiple copies of individual stretches of DNA. The number of copies of each stretch is significant. No change is required in the genomic code of a stretch is required. A change in the number of copies of a given stretch constitutes a mutation.

The comments above further support the assertion of Paabo quoted in **Section 1.2.5.1.1.**

Skinner has prepared an article for the popular press on the trans-generational epigenetics of DNA, suggesting how the methylation of the individual genes can introduce differences over spans of 4-5 generations[186].

Blackburn at the University of California, San Francisco was awarded the Nobel Prize in 2009 for her work defining the large variation in the number of repeats of individual stop codes (telomeres) of the chromosomes in DNA and their documented changes in the phenotypes associated with those individual variations (over only a few generations).

The complementary role of mitochondrial DNA (which follows the female line) is also gaining understanding.

It is becoming clear that an individual is more unique than previously suggested with mutations in their DNA, variances in the methylation of their DNA and contributions from their mitochondrial DNA.

In September of 2015, a major article written for the quasi-popular press appeared providing a significantly different base-line understanding of the genome than previously presented. It must be read before any 21st Century scientist prepares to opine on the genome[187].

A second, important book by Marshall, highlighting some of the same problems associated with 20th Century genetics and providing new insights also appeared in 2015. It is discussed in Sections 1.2.8.2 & 1.2.8.4. It stressed the importance of "transposition" and "Horizontal Gene Transfer" at the expense of mutation in explaining the modifications of a species or within the broader phylogeny.

A third important book by Mukherjee, focused on the more detailed level of the gene,

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[186]Interlandi, J. (2013) Michael Skinner:Code breaker *Smithsonian* 78-84

[187]Schwartz, S. (2015) The shifting nuclear terrain Science News Washington, DC: *Soc Science & Public* pp 18-21

provides both a history of gene research and a summary of a great many facets of the genes and heredity otherwise scattered throughout a very large literature[188]. It is written in a format suitable for a popular audience but with 500 footnotes. The features of the genes are discussed in **Section 1.2.8.7.**

Also in 2015, Field & Davies published a very comprehensive overview of what is currently known about the biocode associated with DNA[189]. It is also a must read for any astute student of the genome, genomics and epigenomics. Epigenomics describes the additional decoration of the DNA not anticipated before the turn of the 21st Century. It highlights a significant paradigm shift and expansion with regard to our understanding of the genomic code. They define DNA as a fourth class of biological matter associated with cellular molecules, after proteins, fats and sugars. They also describe a popular high school experiment to isolate long liquid crystals of DNA from plants or animals. They also highlight the very considerable problems associated with "de-extincting" a species based on the results of experiments involving cloning (as in the example of the sheep, "Dolly"). They also highlight the fact the estimated number of genes in a given species is growing with time almost as fast as estimates of the total number of neurons in the human brain. They implore researchers to never use the term "junk DNA" again and note, the term non-coding DNA or "ncDNA is turning out to be a misnomer of the highest order." They also note, "In fact, when coding for RNA is allowed as a definition of gene as well as coding for proteins directly, the the human genome might have over 160k genes." They also note the lack of a species specific genome, as originally envisioned and pursued by the NIH in competition with Craig Venture's independent commercial venture. They note a typical human genome may vary by 20 per cent from the nominal template developed and advertised at the conclusion of the above competition.

Their figure 4, reproduced here as **Figure 1.2.8-1** provides an estimate of how much of the human genome has been introduced in past eons as bacterial evolved into primates. If additional resolution were possible, the progression from the primates to humans would involve only about 1% or less of the total pie.

[188]Mukherjee, S. (2016) The Gene: An Intimate History. NY: Scribner

[189]Field, D. & Cavies, N. (2015) Biocode: The new age of genomics. NY: Oxford Press

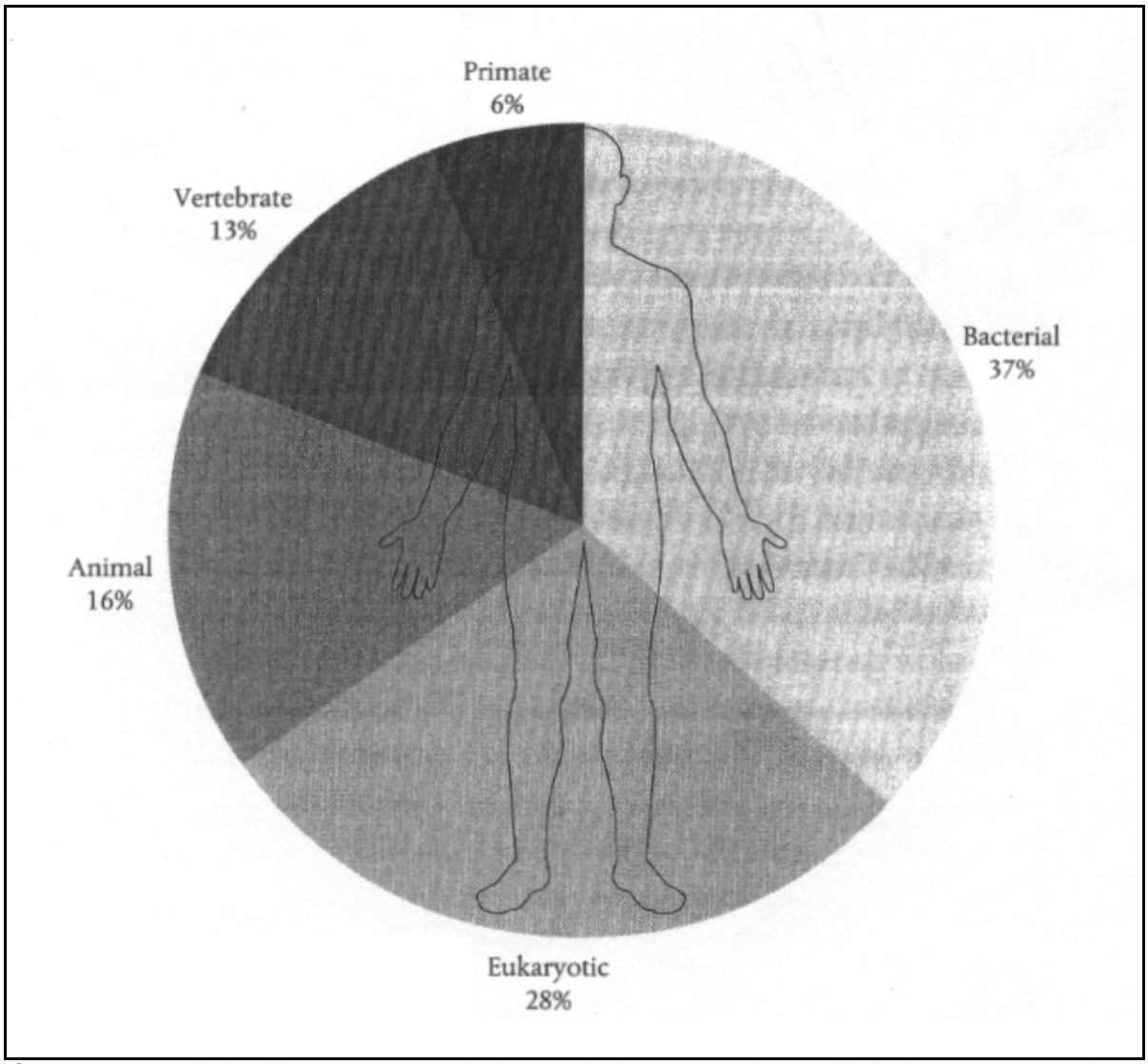

Figure 1.2.8-1 Origin of human genes during evolution. More than a third of our genes evolved in our bacterial ancestors and only 6 per cent in our time as primates (even less during our time as humans). From Field & Davies, 2015.

1.2.8.1 Terminology of DNA, RNA and the genes

Shapiro provided a paper with "The objective of explaining why and how evolution must be viewed afresh at the end of the 20th Century[190]." While consisting almost entirely of text, it does address a wide range of emerging concepts. He notes, "Most of the basic concepts in conventional evolutionary theory predate 1953 when virtually nothing was known about DNA." Following the elucidation of the double helix form of DNA at the molecular level, he

[190]Shapiro, J. (1999) Genome system architecture and natural genetic engineering in evolution *Ann NY Acad Sci* vol 870, pp 23-35

asserts, "The conceptual universe of molecular genetics is as different from classical genetics and evolutionary theory as quantum physics is from classical mechanics." His focus is on "episodic, multiple, nonrandom DNA rearrangements needed to account for the evolution of novel genomic system architectures. . ."

Marshall provided a more recent (2015) and different perspective to that of Shapiro. Marshall further confirmed Shapiro's assertion that the genetic framework in the literature prior to 1999 needs to be largely abandoned based on new discoveries in genetics.

Figure 1.2.8-2 summarizes the types of mutations currently recognized relating to the DNA Code. The figure also appears in **Section 8.1.1.1.4** with additional discussion.

Marshall categorized the mutations under;
- Random noise (potentially fatal to the creation of desirable proteins and possibly to the phenotype,
- Substitution (no significant effect on the generation of the target protein or the phenotype)
- Adaptive noise other than substitution (potentially leading to new species, and
- Epigenetic modifications (leading to minor modifications to a phenotype, even among identical twins and clones).

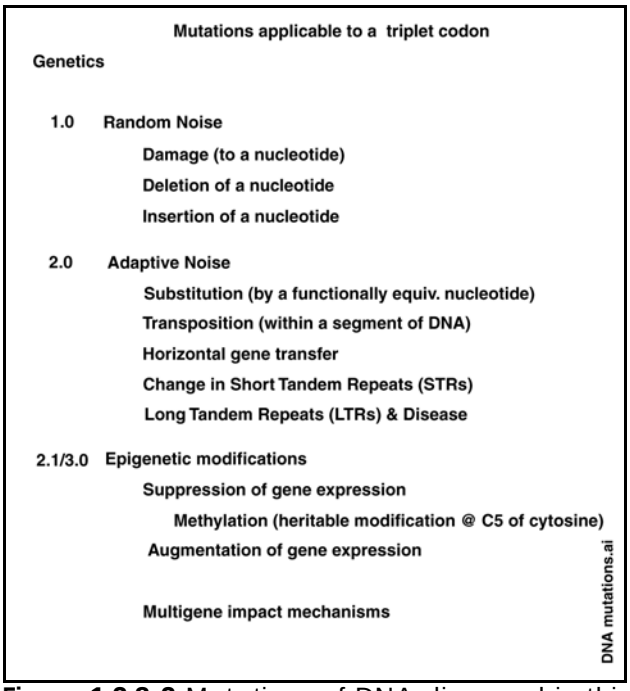

Figure 1.2.8-2 Mutations of DNA discussed in this work. The list is liable to grow as applied research investigations (largely empirical) continue. The Evolution labels shown in the left generally follow Marshall. See text.

The label random noise corresponds roughly to Yockey's "Noise" and the adaptive noise of Marshall corresponds roughly to Yockey's "Genetic noise." The Epigenetic modifications are basically a 21st Century addition to the literature of the field. Marshall has described the random noise category as Evolution 1.0 and generally of little research interest. He places the Adaptive Noise category as Evolution 2.0 and the category of considerable research interest.

A change in short tandem repeats (STR) is of considerable interest in current genealogical testing and ancestral tracking. The purpose of these STRs along the genetic code of DNA (and the changes encountered infrequently in the DNA of a family) is not yet well understood. The impact on the traits between a father and son are not yet documented adequately because of the infrequency of these changes among a population.

Marshall also describes epigenetic modification and similar developments at the cutting edge of genetic research. Mukherjee presents additional information related to epigenetic modifications. Three potential classes of epigenetic modifications are described in the figure under this new category. This category could be labeled Evolution 2.1 or the broader category of Evolution 3.0 depending on how important it becomes. The potential for both augmentation and/or suppression of gene expression is addressed briefly on pages 400–401 of Marshall, is defined herein in **Section 8.1.1.1.2** and addressed in **Section 8.1.1.1.4**.

Tandem repeats are an interesting artifact of the genetic code. Short tandem repeats, STR's, are a ubiquitous feature of the typical genome. These repeats are generally in the range of a few to 30-50 repeats at a given location. Their functional role is not well understood. They may be useful in error correction mechanisms associated with the ribosomes. They may be indicative of minor changes in the expression of various traits in the phenotype. Long tandem repeats, LTR's, are significantly longer than the STR sequences (typically longer than

50 and infrequently reaching 1000 repeats. LTR's generally lead to much more serious situations (diseases). STR's generally can be included within the open reading frame (ORF) of the ribosomes. The longer LTR's frequently can not be included within the ORF.

The multigene impact mechanisms relate to multiple genes within a common chromosome.

1.2.8.2 Linguistic analogy between genetic code and human language

Marshall has noted the work of Ji[191] in comparing human language and the genetic code. Ji's report appeared in a special issue of the Annals of the New York Academy of Science devoted to "Molecular Strategies in Biological Evolution." It constitutes a fitting marker to the field of genetics at the end of the 20th Century. **Figure 1.2.8-3** provides a compromise between the complete table of Ji and a simplified version as it appears in Marshall. Marshall re-titled the figure and he also changed the first line under DNA Equivalent from "4 nucleotides (or 24 amino acids)" to "4 nucleotides and 20 amino acids." The latter appears to be the more technically correct since the nucleotides of genetics are formed from nucleic acids rather than amino acids. Marshall made other condensations in the name of simplicity.

Linguistics	Human Language	Cell Language (DNA Equivalent)
Alphabet (L)	Letters	4 nucleotides and 20 amino acids
Lexicon (W)	Words	Structural genes
Sentences (S)	Strings of Words	Groups of genes coordinated by spatial temporal genes
Grammar (G)	Rules of sentence formation	Folding patterns of DNA according to nucleotide sequences
Phonetics (P)	Phonation, audition, etc.	Gene expression through protein binding and Epigenetics
Semantics (M)	Meaning of words & sentences	Cell processes driven by conformons and intracellular dissipative structures
First Articulation	Forming Sentences from Words	Sequences of gene expression in space and time
Second Articulation	Forming Words from Letters	Organization of nucleotides into genes

Figure 1.2.8-3 The linguistic elements of DNA and human language. Conformons are defined in **Section 8.1.1.1.2**. See text. Modified from Ji, 1999 as influenced by Marshall, 2015.

Ji has written extensively on the isomorphism between cell and human languages[192], introducing the term "cellese" as a contraction of cell language. He conceptualizes a variety of codes as subdivisions of the genetic code, found primarily in the non-protein coding portion (by far the major portion), of DNA. In alignment with the above table, he defines a "syntactic genetic code, a semantic genetic code—"in regions that were previously called spatiotemporal genes." He makes the interesting comment relative to the "wedding cake" analogy suggested in this work, "It is thought that semantic genetic information is a subset of syntactic genetic information just as semantically meaningful sentences constitute but a small subset of grammatically correct sentences in human language." As a result, both semantic genetic code and the rules for first and second articulation may vary with application within the broader genetic code. This interpretation avoids the awkward description by Ji of the DNA mass involved in his Table 2 (1999). Rather than "the sum of all the genetic information encoded in DNA is 200%," the syntactic code (100%) consists of lexical genetic code (3% in humans) plus the semantic code (97%).

As of the Predictions section of his 1999 paper, Ji did not consider the role of epigenetics and methylation in the operation of his spatio-temporal genes.

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[191]Ji, S. (1999) The linguistics of DNA: words, sentences, grammar, phonetics, and semantics. *Annals New York Acad Sci* vol 870, pp 411-417

[192]Ji, S. (1997) Isomorphism between cell and human languages: molecular biological, bioinformatic and linguistic implications *Biosystems* vol 44, pp 17-39

Trifonov was an early investigator of codes in DNA not related to protein formation[193].

> "Nucleotide sequences carry genetic information of many different kinds, not just instructions for protein synthesis (triplet code). Several codes of nucleotide sequences are discussed including: (1) the translation framing code, responsible for correct triplet counting by the ribosome during protein synthesis; (2) the chromatin code, which provides instructions on appropriate placement of nucleosomes along the DNA molecules and their spatial arrangement; (3) a putative loop code for single-stranded RNA-protein interactions. The codes are degenerate and corresponding messages are not only interspersed but actually overlap, so that some nucleotides belong to several messages simultaneously."

Trifonov was also an early investigator into repeat codes in DNA,

> "Tandemly repeated sequences frequently considered as functionless "junk" are found to be grouped into certain classes of repeat unit lengths. This indicates some functional involvement of these sequences. A hypothesis is formulated according to which the tandem repeats are given the role of weak enhancer-silencers that modulate, in a copy number-dependent way, the expression of proximal genes."

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[193]Trifonov, E. (1989) The multiple codes of nucleotide sequences *Bull Math Biol* vol 51(4), pp 417-432 doi:10.1007/BF02460081

1.2.8.3 A common misconception about cloning

lambert & Kingsley recently made a point by reproducing **Figure 1.2.8-4** and attributing it to Texas A&M College of Veterinary Medicine. It clearly shows that a clone need not be an identical copy only displaced in developmental time from its source. The DNA alone as it is currently understood does not carry all of the relevant information to create a true copy. Alternately the DNA may include epigenetic features, such as methylation of at least one gene, not associated with the parent.

1.2.8.3.1 Results of gene-editing research ca. Jan 2019

The field of gene splicing to achieve specific changes in clones to ostensibly improve farm stocks by improving the breed have resulted in many failed attempts. A recent attempt to reconfigure the DNA of animals to give all white furred animals failed badly. On15 December, 2018, the Wall Street Journal[194] prepared a major report on "Deformities shadow gene-editing research."

The results indicate that by modifying a gene at a location known to contribute to an individual parameter, dependable results can not be expected. As the WSJ noted, ". . scientists have only begun to understand what the tens of thousands of individual genes do. Moreover, they are far from unraveling how those genes interact with each other."

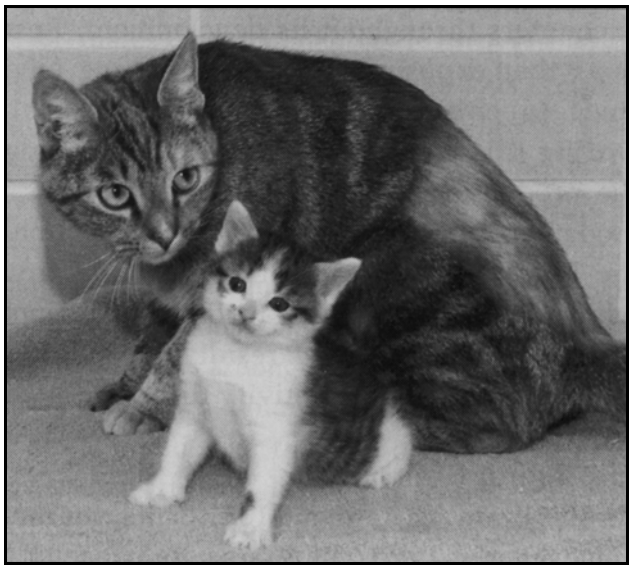

Figure 1.2.8-4 The kitten is a clone of the cat, but, as evident genetic clones do not always develop identical phenotypes. From Lambert & Kinsley, 2011.

Not only is the genetic code a position sensitive code but it also incorporates overlay encoding. Thus some of the many stop codes defined to date may be a stop code for an identified gene but not for the overlay gene. The result is any modification to the code that changes the distance between specific genes or peptide pairs can result in multiple changes in the phenotype. The phenotype may exhibit many unexpected characteristics.

The definitions of the words genotype and phenotype are rapidly evolving. It is clear that humans have no idea of how to describe a genotype at the detailed level, and therefore gene-splicing becomes a gamble as to how the phenotype will vary from the genotype providing the initial DNA.

> A conceptual result might be the attempt to change the color of a species of spider by gene splicing with the result that the new phenotype could not build a web.

1.2.8.4 Relationships within the DNA code

Marshall developed the concept of the DNA code as an analog to the code(s) used to deliver a message over the Internet. This work will attempt to expand that concept. He

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[194]Rana, P. & Craymer, L. (2018) Deformities shadow gene-editing research Wall Street Journal, 15-16 December, page C-3

compared the framework of a DNA molecule to the 7-layer OSI (Open Systems Interconnect) model used in communications engineering. The model is a product of the Open Systems Interconnection project at the International Organization for Standardization (ISO), maintained by the identification ISO/IEC 7498-1. The 7-layer OSI model incorporates a physical layer (the lowest layer consisting of discrete electrical circuit elements) as well as functional groups[195] such as the application and network layers. Wikipedia provides a good overview of the OSI model[196]. The 7-layer model includes multiple sublayers (labeled subnets) to accommodate encryption etc.

Marshall's electrical engineering education provided him with a background for understanding information theory as developed by Claude Shannon during the 1940's and early 1950's. However, some of his comments concerning random noise and random noise like pulse messages suggest he has not reviewed the more recent work in pseudo-random codes so widely used today in encryption[197] of even simple cell phone messages but also most importantly in banking and the Global Positioning System (GPS).

> ***Unfortunately, the framework of Marshal has not resulted in an analogy between information theory and the current understanding of genetic coding.*** The problem is largely in our understanding of the genetic code!! (See later in this Section) As yet, there is no algorithm between the "universal genetic code" and the actual proteins, and non proteins, described in words in the literature. Knight & Landweber provided their Table 1 listing five different renditions of the genetic code pointing to arginine in 1998.

In the 1940's and 1950's, Shannon only addressed what might be called quantized messages. The message had to consist of alphabetic characters and could not consist of analog sound. He addressed analog messaging in greater detail during the late 1950's. That background will be expanded here to include both quantized and analog messages relating to the neural system.

> It is not generally known in the engineering community that Shannon's initial work prior to World War II was in genetic theory[198]. With the War, his attention was diverted to code breaking and led to his fundamental advances in Information Theory. He is not known to have returned to genetics after the war.

Marshall has presented a framework for interpreting the very complex relationships associated with the DNA code. The framework itself is multidimensional. To achieve his goal, Marshall employs a variety of simple block diagrams, the concept of the nested Russian dolls known as matryoshka, and the multiple "blades" of a Swiss Army Knife. He also carries a running list of reasons that the Darwinian version of evolutions, as expanded far beyond Darwin's original description, cannot work. This leads him to develop his more intricate but plausible description of Evolution 2.0 (summarized on his page 148).

Marshall likens DNA to a true code that is dependent on an associated set of grammatical rules for its interpretation, just as any true code does. He decries the use of the term code-like to describe DNA.

Marshall's initial focus is on describing DNA as a long code that incorporates a variety of major and minor elements that can be read using a variety of templates or filters based on an extensive grammar defining the language used by the DNA.

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[195]Microsoft (updated to 2014) The OSI Model's Seven Layers Defined and Functions Explained https://support.microsoft.com/en-us/kb/103884

[196]Wickepedia, *no author* (2016) OSI model https://en.wikipedia.org/wiki/OSI_model

[197]https://en.wikipedia.org/wiki/Pseudorandom_noise

[198]Shannon, C. (1940) An Algebra for Theoretical Genetics. MIT PhD Thesis http://dspace.mit.edu/bitstream/handle/1721.1/11174/34541447-MIT.pdf

> Marshall uses an unusual way of organizing his citations to reflect their principle target based on the assigned citation number (e.g., 400–499, Linguistic Models of DNA).

Marshall addresses the label "junk DNA" directly. "There is no such thing as junk in the trunk when it comes to DNA. At least 80 percent of our DNA is active and necessary. If you deleted it, our bodies would fail. Or our children or grandchildren would be missing something critical that they need to survive."

A critical part of Marshall's hypothesis is that there is a fertile ground to be mined between probabilistic and deterministic concepts. He describes this area using the term Shannon introduced long ago, "ergodic." Marshall struggles with the definition of this term by using cursory examples. The available dictionaries are also less than adequate. Wikipedia has a definition described using items 1 & 2 below[199].

1. (mathematics, physics) Of or relating to certain systems that, given enough time, will eventually return to previously experienced state.
2. (statistics, engineering) Of or relating to a process in which every sequence or sample of sufficient size is equally representative of the whole.

3. In 1 & 2, the process being observed may appear probabilistic or deterministic in the short term. In the medium term, the process may appear to be chaotic in the mathematical sense.

Many investigators have labeled neurological processes as probabilistic because they do not have adequate background to recognize the ergodic or even deterministic character of the processes they are exploring. Within the neural system of biology, the vast majority of processes are in fact deterministic.

Marshall developed his analog between DNA and the Internet using the Russian *matryoshka* (the doll enclosing another doll, enclosing another doll, ad infinitum). He used this doll to develop his concept of DNA as a nesting of multiple messages but did not pursue his concept as far as needed in this work. **Figure 1.2.8-5(A)** expands on his concept marginally. The label "Word document" can be replaced by the more general "Office document" as it can contain a variety of types of program files (e.g., Excel, PowerPoint, etc.). Although less well known, there are matryoshka where one doll encloses multiple small dolls, such as a group of children. Similarly, a text file can be expanded to include multiple data files etc., and there is no limit on the number of text segments or pictures incorporated into a single Word document.

Frame (**B**) shows a typical representation of a segment of DNA found in the current literature analogous to frame (**A**). The empirical representation has yet to subdivide the introns into sub-elements prior to the start instruction and does not appear to have identified the call instruction developed in conjunction with frame (**C**).

> A cross-section of a tiered wedding cake (as shown in frame (**C**) is frequently taken as a better analogy than a matryoshka (or the simple label, "a 7-layer model") because it emphasizes the fact each layer continues to operate under the upper layers (with a distinct opening element on the left, a distinct closing element on the right, and continuity between these elements while the higher layers open, operate and close).
>
> As shown in frame (C), The opening intron consists of a set up portion, a start instruction for that layer and one or more call instructions to another program. This other program may be found within the DNA strand or be present in a ribosome used to decode the mRNA derived from the DNA strand.

Regardless of the analogy, but referring to the matryoshka and random mutations, Marshall noted (page 47), "DNA is also a stack of Russian dolls. You corrupt one tiny bit of data and it

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[199] https://en.wiktionary.org/wiki/ergodic

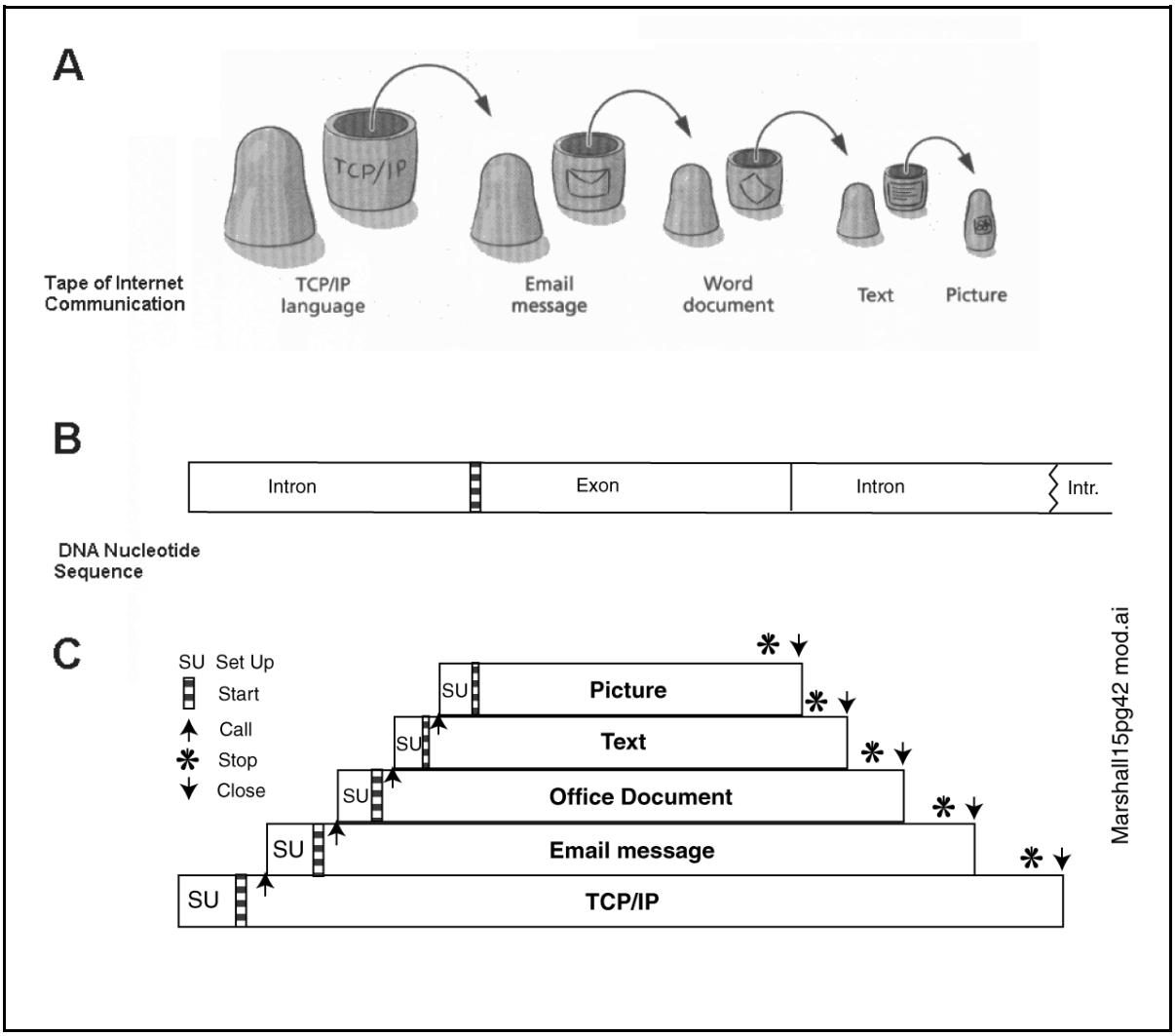

Figure 1.2.8-5 Analog between DNA strand and a message received over the Internet. A; Illustrating the matryoshka doll concept. B; Inadequately defined DNA sequence. C; Wedding cake analogy to DNA nucleotide sequence. These analogies assume each Internet message is transmitted sequentially without subdivision into packets. See text. Frame (A)from Marshall, 2015.

grinds the whole doll into splinters; even a tiny corruption in DNA can cause major birth defects." While this corruption appears minor, the wedding cake analogy illustrates how it could effect all of the individual layers if it occurs in the setup for the TCP/IP layer prior to the call to another program. If it occurs within the code of a higher layer, it may prevent the higher layers from executing properly or it may corrupt the message.

In analogy to a tape copy of an Internet message (without its division into packets), the DNA sequence is derived from a genotype (original source) and results in a complete phenotype (an offspring, after mitosis). The DNA sequence is not limited to a sequential nesting leading to a specific feature of a phenotype. The nesting within the DNA sequence can incorporate a wide variety of chromosomes which in turn incorporate a nearly endless variety of genes.

Chapter 6 of Marshall explains many of these additional features in text form. He notes,

"The simple act of sending me a Word doc with pictures in it involves at least seven

> Russian dolls—seven layers of 'message inside a message.' Really, there are dozens of layers—I skipped a few just to keep things simple." Obviously, the encryption layer and multiple verification layers have been omitted from these simple descriptions.
>
> "When you press send, your computer stacks all those Russian dolls at lightning speed. Your message speeds through an Ethernet (or other cable) out of your house, onto the internet, and comes to me.
>
> When I open your email, the Russian dolls come apart in the exact reverse order. When I open your document, the last Russian doll pops open. Now I can read your document and look at your pictures."

Page 7 of Marshall lists critically important ideas to keep in mind related to the above quotation.

> "• A language is a sophisticated code. Every doll represents a different language. Microsoft Word '.doc' format is a special language used by the Word program, email format is a language, and TCP/IP (Transmission Control Protocol (TCP) and Internet Protocol (IP)) is a language. Your email to me is multiple languages inside of languages.
>
> • As your email comes to me, if any part of the message gets corrupted, it won't just hurt one layer—it will usually destroy *all* the layers. Its like chopping your entire stack of Russian dolls in half with an axe. If you're exceptionally lucky, you only splinter the outer two and leave the inner ones intact. But even one tiny data corruption as the (complete message) speeds across the internet will wreck large amounts of information and possibly everything. Ask anyone who's tried to recover a crashed hard drive!
>
> • The dolls have to be unpacked in the reverse order they were packed in. You can never, ever violate this rule! Each doll has to be unpacked by the program that understands its particular language. No other program will work. You edit Word docs in a Word word processor. You edit emails with an email program. You need to edit pictures in a photo editor. You can't edit pictures in Microsoft Excel. I cannot overstate this point, because in a multilayered system, *any change (mutation) to the code has to obey the rules of that particular layer, while leaving the other layers perfectly intact*. Otherwise, your delicate Russian doll shatters.
>
> • Every layer has mechanisms to check for errors and correct them. When you save a Word document, the Microsoft Word program triple-checks that every single bit has been stored correctly. Software programs, hardware, and networks employ special built-in systems to do this job, called *checksums* and *cyclic redundancy checks*. When you save or send your email, the email message with the Word doc inside passes through another set of checks.
>
> • At the end of the day, every single one of those Russian dolls is a single string of 1's and 0's—the alphabet of computer languages. A message inside a message inside a message. The program interprets the message. Without it, the message's meaning can't be understood."

The TCP/IP is frequently considered a "suite" because of the number of subnets within these layers of the OSI. A comprehensive guide to the details of the suite is available[200].

Marshall correctly asserts, "Information Organization in DNA is the Same as in Digital Data" processed via the Internet or via many other man-made systems. A current problem is that man has yet to interpret many of the internal elements of the DNA code. Some of these elements may include thousands to millions of individual nucleotides.

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[200]Kozierok, C. (2015) The TCP/IP Guide http://www.tcpipguide.com/

> At one point referring to an intron, Marshall asserts that the opening sequence to one layer (associated with one doll) is 59 characters long. Recall a few years ago, the National Security Agency fought desperately to prevent 128 character encryption from being used because they had difficulty breaking into such methods.
>
> An intron sequence of 59 characters can contain an immense amount of information. It is quite likely such a long sequence may represent multiple opening sequences as in frame (C), or very complex information about the subnets (multiple documents) included in that layer.

Marshall began a more detailed discussion of the DNA code by comparing the internal elements of a typical DNA element with the internal elements of a typical computer file in **Figure 1.2.8-6**.

> The more complex fundamental code of DNA (for protein instructions, triplet groups using 4 bits, A, C, G, T) compared to man-made computers (2 bits, 1's and 0's) will be explored below.

His words relating to the nested computer file are a bit too simple compared to the actual case. As an example, the Header of a typical email message conforms to the TCP/IP Standard promulgated by the World Wide Web (WWW) Organization. Rather than just say, "Hello, I've got something to say", it typically contains ten to 100's of lines of code describing what language it is written in, how the content is organized, who was the author and his organization, the routing the message took to reach you and a variety of verification subroutines, etc. Similarly, the footer contains a variety of lines of code used to clear registers, reset pointers and remove a variety of subroutines opened by the header rather than just "I'm all done now, goodbye." The actual text within the email frequently incorporates another header, typically conforming to the HTML5 standard also promulgated by the WWW Organization, and another footer that says more than just "I'm all done now, goodbye." The actual data appears in one of at least 30 different versions of the old ASCII code, which has been replaced by a more standardized set of codes (ISO 8859) supporting the symbols used by an extensive set of different human languages.

A similar situation occurs in the individual nested DNA element, except all of the content of the various "Start codes" and "Stop codes" are not presently identified to the extent they are known and documented in the computer files. In fact, the names of the equivalent start and stop codes are not actually known or standardized for the elements of the DNA code. Clearly, the header known as the "promoter" preceding a gene is capable of providing considerable more information than just "Hello, I've got something to say." The "terminator" following the gene is also capable of causing a variety of actions beyond saying only "This is the end of the gene." Learning more about the character of the individual nested DNA element is currently being intensely studied throughout the bio-genetic community.

In the case of the individual gene, the terminator not only indicates the end of the gene but indicates this termination should be identified in the RNA code transcribed from this section of DNA code so it can be used to create a protein.

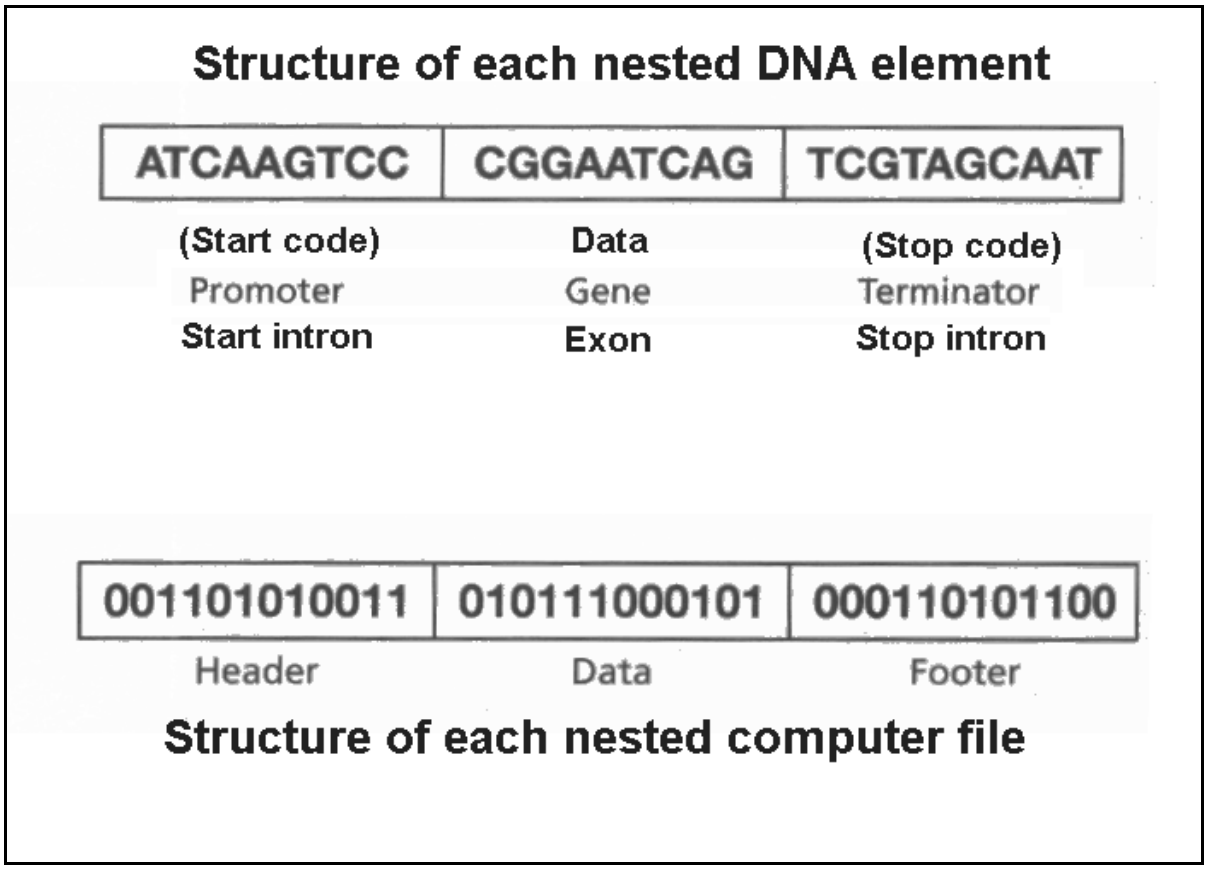

Figure 1.2.8-6 Elements of the nested DNA and computer codes. The labels used for the various nested DNA elements vary greatly within the literature. An assortment of labels are shown below Marshall's labels. The letters within the data structure of DNA encoding for proteins occur in triplet groups without any delineation. See text. Modified from Marshall, 2015.

As noted above, the start codes (promoters and/or introns before an exon of interest) reported in the literature may be up to 59 characters long. This length suggests such long sequences may contain considerable information and may consist of more than a single start code.

Figure 1.2.8-7 provides a table of the RNA codes leading to various nucleic acids. The DNA codes are the same except U is replaced by T. Each triplet (codon) is read from the 5'—>3' direction (**Section 8.1.1.1.3**). Perez describes this table and its DNA equivalent as the Universal Genetic Code table[201]. Knight & Landweber offered a more color-coordinated version in 1998 while focusing on arginine. "The various sites that have been suggested as the primitive binding sites are shown in Figure 2." Knight & Laandweber concentrated on 2D stick models of their molecules in the paper.

The one letter codes for the nucleic acids are entirely different from the one letter codes for the amino acids. The nucleic acids are all derived from the multiple

[201]Perez, J-C. (2010) Codon populations in single-stranded whole human genome DNA Are fractal and fine-tuned by the Golden Ratio 1.618 *Interdiscip Sci Comp life Sci* vol 2(3), pp 228-240 doi:10.1007/s12539-010-0022-0 *There is a followup Errata.*

nitrogen heterocyclic ring structure of pyrimidine. They are labeled bases, but are not exclusively basic.

An example for the RNA code for glutamic acid would read 5'-GAA-3' or 5'-GAG-3' using the one-letter nucleic acid codes. Actual peptides and proteins would be represented by longer sequences of nucleic acids.

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Information Theory would suggest the lack of delimiters (in the absence of extensive error detection and associated error correction capabilities) between signaling blocks associated with DNA would be catastrophic for the organism. An insertion or deletion of a single codon early in the DNA sequence would make essentially all of the subsequent code unreadable by the ribosomes tasked with creating mRNA. This situation is so serious that an extensive search for delimiters, error detection capabilities and error correction capabilities should be a primary activity within the genetic research community.

Knight et al. (1999) provided a clearer understanding of their color-coordination and then developed the quandary of that time concerning the code[202]. "The pattern of chemical interactions between the 64 codons and 20 amino acids remains largely unknown. Only when these interactions are known will we be able to understand the relative importance of selection, history and chemistry in code evolution."

First base (5' end)	Second base: U	Second base: C	Second base: A	Second base: G	Third base (3' end)
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U
	UUC Phe	UCC Ser	UAC Tyr	UGC Cys	C
	UUA Leu	UCA Ser	UAA Stop	UGA Stop	A
	UUG Leu	UCG Ser	UAG Stop	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC Leu	CCC Pro	CAC His	CGC Arg	C
	CUA Leu	CCA Pro	CAA Gln	CGA Arg	A
	CUG Leu	CCG Pro	CAG Gln	CGG Arg	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC Ile	ACC Thr	AAC Asn	AGC Ser	C
	AUA Ile	ACA Thr	AAA Lys	AGA Arg	A
	AUG Met or start	ACG Thr	AAG Lys	AGG Arg	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC Val	GCC Ala	GAC Asp	GGC Gly	C
	GUA Val	GCA Ala	GAA Glu	GGA Gly	A
	GUG Val	GCG Ala	GAG Glu	GGG Gly	G

Figure 1.2.8-7 The genetic code of RNA (based on nucleic acids) for the amino acids common to most species. See text. The most important amino acid of the neural system is glutamic acid, Glu, with aspartic acid, Asp, as its backup. They are the source of electrical power to each of the individual neurons.

Work since the turn of the 21 Century has made considerable progress in understanding how the non-protein-coding, or "junk code" plays a major role in the overall process of reading the code and implementing the code. However, the quotation of Paabo (2015) in **Section 1.2.5.1.1** remains relevant:

> ***"The dirty little secret of genomics is that we still know next to nothing about how a genome translates into the particularities of a living and breathing individual."***

How an individual physical structure (example, the head of the T4 bacteriophage) is formed from the genetic code remains a mystery.

- - - -

The empirical literature is ambivalent about start and stop codes. The ODBMB speaks of the minimal "start codon is AUG that codes for the first amino acid residue in the synthesis of all prokaryotic and mitochondrial proteins." Alternately it describes a "start point" as "the base pair in DNA at which the first nucleotide is incorporated into an RNA transcript. It is usually a

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[202]Knight, R. Freelander, S. & Landweber, L. (1999) Selection, history and chemistry: the three faces of the genetic code TIBS vol 24, pp 241-247

purine, and often is the central base of the sequence CAT." Marshall indicates a minimal stop code consists of the sequence, TAG. The ODBMB indicates there are three options, UGA, UAG & UAA that signal the termination of translation of a messenger RNA molecule and the release of the nascent polypeptide chain." These ambiguities are explained in "Biology Exams 4 U[203]" where differences in the DNA between species are described. Exams 4 U is not a well curated site and is not recommended for general reading.

As typically illustrated in the literature, a single intron separates two exons. This intron is better shown as containing two parts, a "stop intron" following the first exon and a "start intron" before the start of the second exon. Because of the potential for nesting, either of these intron types may actually consist of multiple introns of either the stop or start variant. The multiple introns would belong to different levels of nested codes.

Marshall asserts (page 19), quoting Kawaguchi O'Huigin & Klein[204], "There are small bits of data (pseudogenes) that are shared only by humans and primates, and found nowhere else in the animal kingdom."

Marshall relies upon a book published by Yockey in 2005. It is written at a quite fundamental level, is a pleasure to contemplate and is available online[205]. In that book (page 13), Yockey asserts, "Computer programers call a code a system of symbols and rules used to represent instructions to a computer."

1.2.8.4.1 The genetic code as a true code based on information theory

Yockey developed his Theory of Information starting from a historical perspective and then incorporated Shannon's early work in a context suitable for "Synthetic Biology." He noted,

> "The primary or source alphabet used in computers and electronic communication is the binary alphabet [0, 1). Shannon (1948) understood before anyone else that a binary source alphabet could be extended by forming ordered pairs, ordered triplets, ordered quadruplets, and so forth to form receiving alphabets larger than two. In computer technology, the information in the binary source alphabet is called a bit; these extensions are called a byte. In molecular biology these extensions are called codons. Accordingly, because of the structure of DNA and mRNA, the natural choice for the source genetic alphabet is four letters that correspond to the four nucleotides typical of DNA or mRNA. Nature had extended the primary four-letter alphabet to the six-bit, sixty-four-member alphabet of the genetic code (*his* Section 2.1.2). Each amino acid except Trytophan and Methionine has more than one codon. Thus, the genetic code is redundant (not degenerate). The sloppy terminology designating the genetic code as degenerate is responsible for most of the misunderstanding of the genetic information processing system."

Yockey proceeds to develop essentially all of the fine points associated with Communications Theory and notes many areas requiring caution. As an example, when discussing unassigned code letters in a message he notes,

> "The other code letters are called non-sense because they have been given no sense or meaning assignment in the receiving alphabet. (Remember that non-sense does not mean nonsense or foolishness.) Unfortunately, the use of the word "nonsense" persists in many current publications."

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[203] http://www.biologyexams4u.com/2013/03/genetic-code-definition-characteristics.html

[204] Kawaguchi, H. O'Huigin, C. & Klein, J. (1992) Evolutionary origin of mutations in the primate Cytochrome P450c21-gene *Amer J Human gen* vol 50, pp 766-780

[205] Yockey, H. (2005) Information Theory, Evolution, and the Origin of Life. Cambridge: Cambridge Univ Press. http://www.krusch.com/books/evolution/Information_Theory_Evolution_Origin_Life_Yockey.pdf

Yockey (page 30) also supports a common contention of this work,

> "The road we have taken, the one less traveled, has led us to the Shannon–McMillan-Breiman Theorem. It is, almost without exception, unknown to authors in molecular biology, and without it they have been led to many false conclusions."

Yockey (page 35) developed his isomorphism (analogy) between Shannon's communications model and the DNA communication channel in **Figure 1.2.8-8** . The extent of the label "channel code" has been adjusted to include one-half of each of the coding and decoding elements on conceptual grounds.

In the upper frame, the word code on the left refers to the plain text of the message as it might appear on a piece of paper. The word code on the right refers to the reconstructed (recovered) plain text as it might be printed on a piece of paper.

The boxes below the label translation on the right of the lower frame represent the translation table required to recover the plain text message, the protein alphabet, that can be used to create a specific protein.

Yockey did not describe his figure in detail. However, he did describe the difference between his "noise" and his "genetic noise." He described his noise as a mutation that either 1) modifies one of the nucleic acids in the triplet code (codon), 2) makes an insertion of at least one nucleic acid at a specific location in a triplet code, or 3) deleted at least one nucleic acid at a specific location in a triplet code. Any of these effects of noise will have a major impact on the ability of the DNA or mRNA code to mediate creation of a correct protein. On the other hand, his genetic noise involves the substitution of one nucleic acid by another that is functionally equivalent (see the above figure) or by the modification of one nucleic acid (in place) into a functionally equivalent form. While the first situation is possible, it is not likely to occur in practice. The second modification is virtually impossible due to the magnitude of the chemical change involved. He did note that his decoding box on the right, also labeled translation, represented a ribosome. He also noted the insertion of multiple copies of the same code fragment, now known to be quite common in DNA was an effective method of suppressing decoding failures due to a simple noise perturbation in one of the copies. The variation in the number of copies of a given DNA code fragment is now a fundamental tool in genealogy. Yockey did not discuss how a ribosome compared these copies. As Yockey noted, the ability of the DNA code to be corrected via the multiple copies of various code fragments has ensured "the genetic message can indeed survive for 3 . 8 5 billion years from the origin of life."

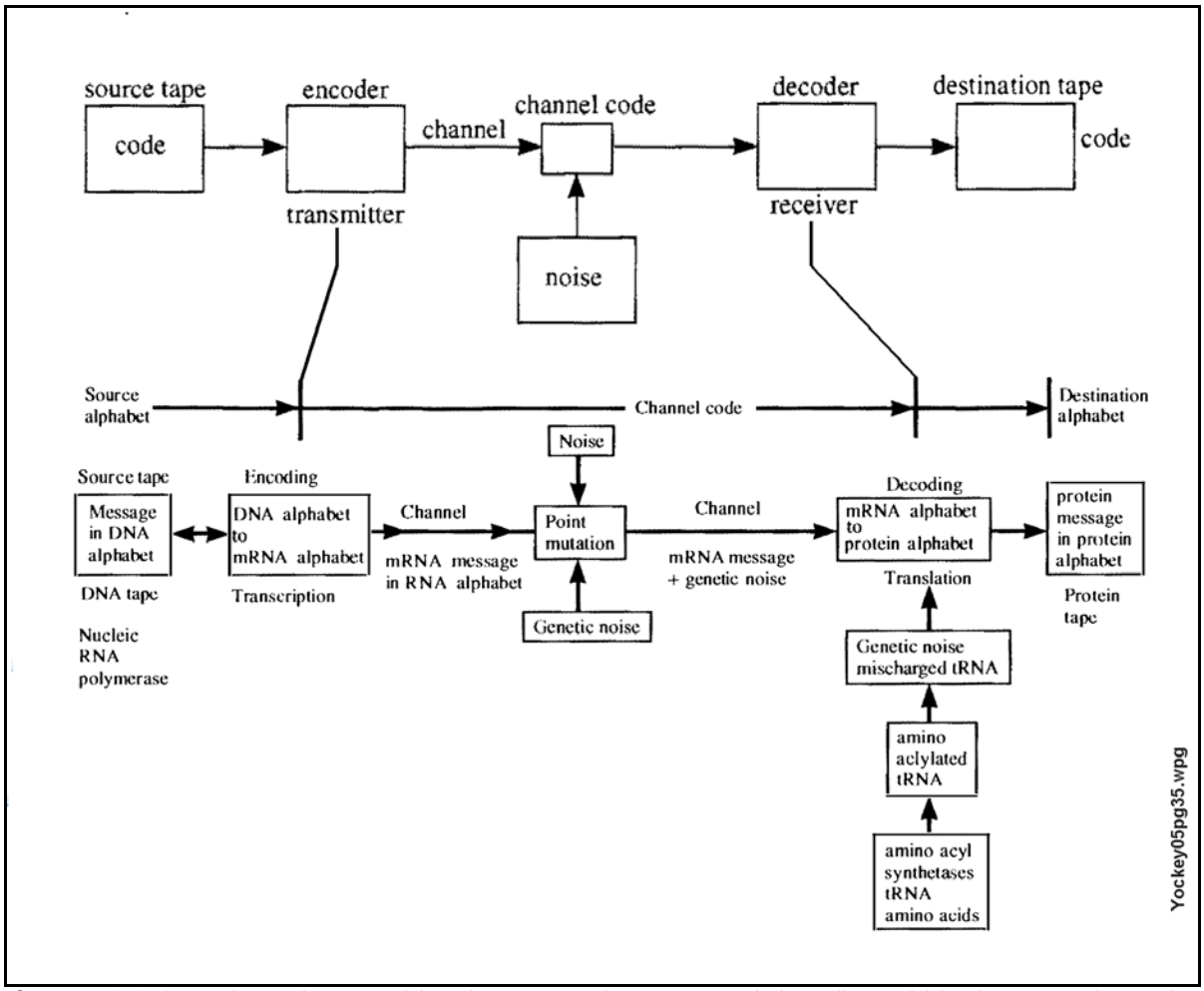

Figure 1.2.8-8 Yockey's isomorphism between Shannon and signaling within the genetic code. Yockey decorated the lower portion of the figure with a variety of terms in use in his time. They are not always adequately defined adjacent to his figure in his text. The sources of noise are negligible within the DNA transcription process. See text. Modified from Yockey, 2005.

As noted by Marshall (page 105), the accumulated noise from both the genetic processes of replication and external perturbations does not interfere with the DNA replication process. The destination message is usually identical to the originating message to within 99.9999999% (nine 9's in the language of the semiconductor industry which struggles to achieve six 9's in the purity of silicon crystalline wafers).

1.2.8.4.2 Other, some archaic, writings on the genetic code

Charrel undertook a major study in 1995[206] to correlate the elements of DNA with the equivalent elements within a man-made computer system existing in a "cloud" and accessed via the Internet. This involved comparing the elements of a DNA sample to the equivalent elements of a computer system beyond the pedagogy of a typical bio-engineer

[206]Charrel, A. (1995) Tierra: Network Version. ATR Technical Report TR-H-145 http://life.ou.edu/pubs/charrel/charrel.pdf

without significant industrial experience.

Two major areas of the 1995 Charrel paper involved **Reproduction** (involving two parents in analogy to the terms use in conventional biology). Reproduction involved **recombination** or **mutation** leading to a new strand of DNA. Recombination requires at least two parents. Children are created by combining parts of the "genome" of each parent to form a new DNA code that is used to generate an individual different from either parent.

Charrel defined mutation as;

"A mechanism which modifies part of the genome of a parent to create a child. The modification is controlled by a probabilistic function, which can be as simple as flipping a bit in the genome with a (low) fixed probability, or as complicated as a set of different and possibly quite complex functions for each part of the genome."

Marshall spends considerable time disparaging the idea that flipping a single bit has ever achieved a new sustainable genotype. Only more complex modifications involving transposition and/or horizontal gene transfer has ever been shown to lead to a viable new species.

> It is a major part of Marshall's hypothesis, supported by this work that damage to the nucleic acid incorporated into a nucleotide represented by one of the four letter codes, insertion of an extra nucleotide into a sequence, or deletion of a nucleotide from a sequence in a non-delineated (the normal mode of coding) portion of a DNA strand will make the code no longer transcribable into mRNA and/or translatable from mRNA into the correct protein.

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Andrianantoandro et al[207]. provided a paper in 2006 discussing additional details related to the analogy between the DNA code and the code(s) used in man-made computers. "Synthetic biologists engineer complex artificial biological systems to investigate natural biological phenomena and for a variety of applications." They went on, "We outline the basic features of synthetic biology as a new engineering discipline, covering examples from the latest literature and reflecting on the features that make it unique among all other existing engineering fields." Their analysis was not as fundamental as that introduced by Marshall and expanded upon by Charrel.

Their perspective was closer to a conventional biologist and asserted, "The classical engineering strategies of standardization, decoupling, and abstraction will have to be extended to take into account the inherent characteristics of biological devices and modules. To achieve predictability and reliability, strategies for engineering biology must include the notion of cellular context in the functional definition of devices and modules, use rational redesign and directed evolution for system optimization, and focus on accomplishing tasks using cell populations rather than individual cells." **This paragraph can and should be rewritten to recognize the need to standardize biological terminology to a level approaching that of engineering before attempting to provide meaningful analogies.** See **Section 8.1.1.1**. Engineering biology is more than capable of handling the limited definition of cells and cell populations found in the current literature. The conclusion of their Abstract is noted, "The discussion brings to light issues at the heart of designing complex living systems and provides a trajectory for future development." Their figure 1 is primitive in the context of this work and the analogies introduced by Marshall, Charrel, etc. Their discussion of biological devices is very well structured but at a very high level. They do not describe the specific elements of a neural cell that supports signaling or how that signaling is accomplished. Their biological modules are at the block diagram level rather than the schematic level and there is not discussion of the mechanisms involved in signaling at the

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[207] Andrianantoandro, E. Basu, S. Karig, D. & Weiss, R. (2006) Synthetic biology: new engineering rules for an emerging discipline *Mol Syst Biol* www.molecularsystemsbiology.com Article number: 2006.0028 doi:10.1038/msb4100073

circuit level within a cell. Their Box 1 includes and illustrates a variety of "throw-away statements" such as "Biological systems are inherently noisy, and must either minimize or take advantage of stochastic fluctuations to maintain function." **Such statements are intrinsically false and indicate the limited level to which the investigators have addressed the paradoxes they encountered or their attempts to resolve these paradoxes**. Marshal (page 302) describes the more appropriate situation as "ergodic;" an appropriate mixture of probabilistic and deterministic mechanisms (until the appropriate fundamental mechanism is discovered relating to each circuit). The term ergodic can be expanded to incorporate chaotic mechanisms as well until the underlying rules of the apparently chaotic mechanism are determined.

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Andrianantoandro et al. addressed the analogy between DNA and the OSI 7-layer model in 2006. However, they did it within the context of the chemical theory of the neuron. The analogy can be improved upon by recognizing the Activa and other electronic components within the cells to describe the module layer and the physical layer of the neurological system. Their concepts expressed in figure 1 assume a totally different character under the Electrolytic Theory of the Neuron.

> "The goal of synthetic biology is to extend or modify the behavior of organisms and engineer them to perform new tasks. One useful analogy to conceptualize both the goal and methods of synthetic biology is the computer engineering hierarchy (Figure 1). Within the hierarchy, every constituent part is embedded in a more complex system that provides its context. Design of new behavior occurs with the top of the hierarchy in mind but is implemented bottom-up. At the bottom of the hierarchy are DNA, RNA, proteins, and metabolites (including lipids and carbohydrates, amino acids, and nucleotides), analogous to the physical layer of transistors, capacitors, and resistors in computer engineering. The next layer, the device layer, comprises biochemical reactions that regulate the flow of information and manipulate physical processes, equivalent to engineered logic gates that perform computations in a computer. At the module layer, the synthetic biologist uses a diverse library of biological devices to assemble complex pathways that function like integrated circuits. The connection of these modules to each other and their integration into host cells allows the synthetic biologist to extend or modify the behavior of cells in a programmatic fashion. Although independently operating engineered cells can perform tasks of varying complexity, more sophisticated coordinated tasks are possible with populations of communicating cells, much like the case with computer networks."

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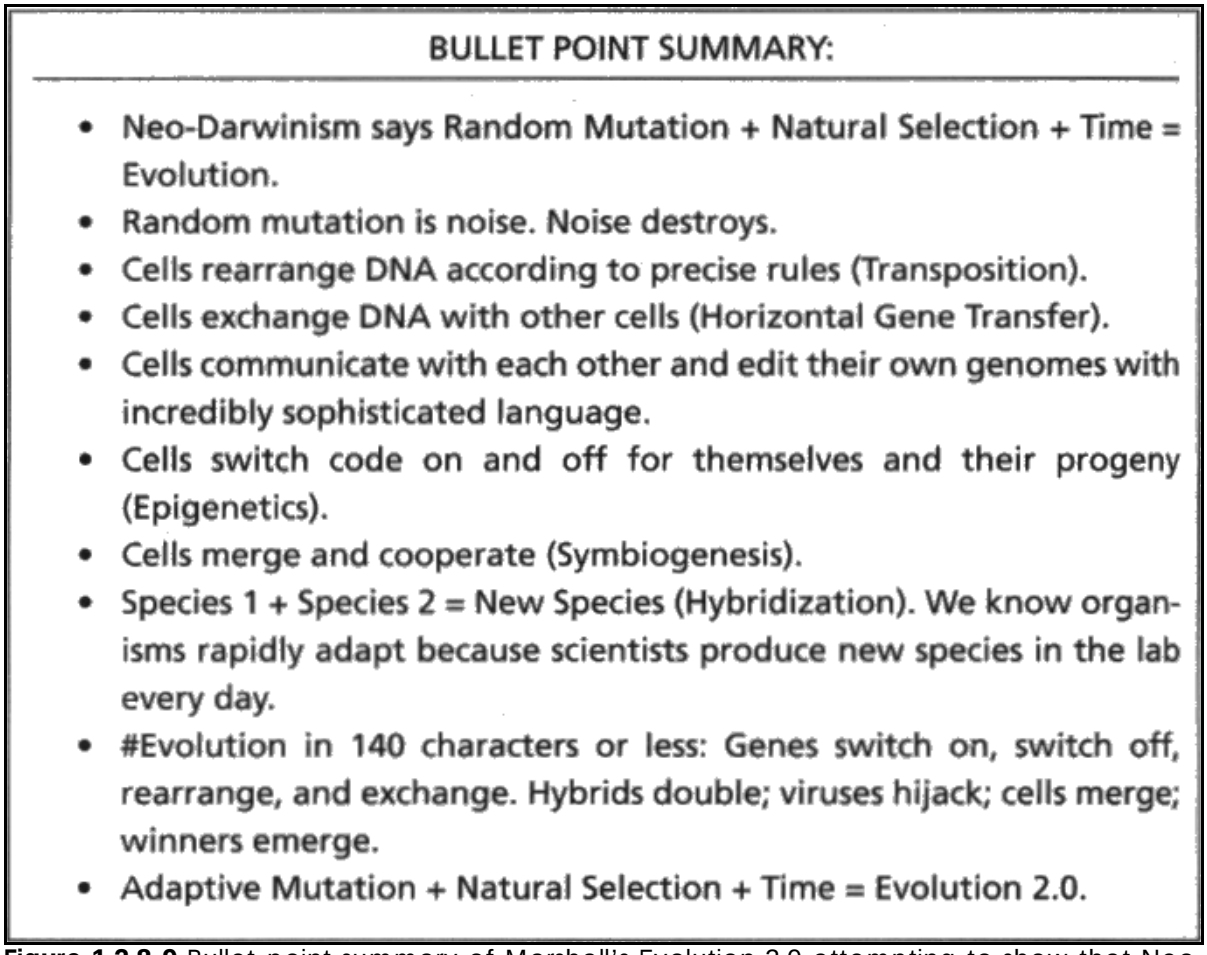
1.2.8.4.3 The importance of transposition and horizontal gene transfer within genetics

Marshall, as an outsider and fresh thinker has developed an entirely new concept of evolutionary genetics. He labels his concept Evolution 2.0. It is based on his compilation of the latest research reported in the literature but not summarized adequately because of the inertia of the genetics community to new ideas. He labels this the Semmelweis Reflex, "New knowledge being rejected by a community because it overturns entrenched norms, popular beliefs, and accepted paradigms." This author has considerable sympathy for Marshall's situation for obviously similar reasons. See Marshall, pages 80-85.

Marshall's key hypothesis is that random mutation at a single point in a strand of mRNA has never been shown to result in a useful new species. Random mutations essentially introduce noise into the genome that is necessarily destructive. Said more clearly, single point mutations by their very character are destructive of the very sophisticated and highly optimized genetic code. Many of the error sensing capabilities of the genetic code are designed to uncover single point mutations and stop the process of biogenesis associated with that damaged code.

Marshall summarizes his development of Evolution 2.0 in **Figure 1.2.8-9** In the last line, adaptive mutation is a term he uses to describe the more sophisticated mutations of genetics. It does not include random single point mutations of Evolution 1.0 (summarized in the first two lines of the figure).



BULLET POINT SUMMARY:

- Neo-Darwinism says Random Mutation + Natural Selection + Time = Evolution.
- Random mutation is noise. Noise destroys.
- Cells rearrange DNA according to precise rules (Transposition).
- Cells exchange DNA with other cells (Horizontal Gene Transfer).
- Cells communicate with each other and edit their own genomes with incredibly sophisticated language.
- Cells switch code on and off for themselves and their progeny (Epigenetics).
- Cells merge and cooperate (Symbiogenesis).
- Species 1 + Species 2 = New Species (Hybridization). We know organisms rapidly adapt because scientists produce new species in the lab every day.
- #Evolution in 140 characters or less: Genes switch on, switch off, rearrange, and exchange. Hybrids double; viruses hijack; cells merge; winners emerge.
- Adaptive Mutation + Natural Selection + Time = Evolution 2.0.

Figure 1.2.8-9 Bullet point summary of Marshall's Evolution 2.0 attempting to show that Neo-Darwinian Evolution (based on random mutation) is faulty and must default to Evolution 2.0 based on more sophisticated mutation techniques. See text. From Marshall, 2015.

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In chapter 17, Marshall discusses why neither the neo-Darwinists or the intelligent design communities have told the whole story in their writings.

- - --

Marshall and Mukherjee (both writing in the 21st Century) have addressed both long term evolution and short term (a few generations) heredity. Mukherjee notes that Dobzhansky introduced two words in the 1940's that help describe the processes involved succinctly. A genotype is an organism's genetic composition. It can refer to one gene, a configuration fo genes, ore even an entire genome. A phenotype, in contrast, refers to an organism's physical or biological attributes and characteristics. Dobzhansky asserted what is now known to be inadequate, according to Mukherjee, "a genotype *determines* a phenotype."

Dobzhansky noted, first, genotypes were not the sole determinants of phenotypes. And second, that some genes are activated by external triggers or by random chance. Dobzhansky is also credited with asserting, the relentless matching of an organism to its environment *is the engine* that drives evolution. This position was followed by recognition that a phenotype was not determined by one gene in a one-to-one manner.

After developing the character of transposition and horizontal gene transfer as they relate to the DNA code, Marshall noted the change from the conventional assertion of Neo-Darwinism related to evolution;

~~Random mutation + natural selection + time = evolution~~

to his key assertion;

Adaptive mutation + natural selection + time = Evolution 2.0

where adaptive mutation involves either transposition and/or horizontal gene transfer at specific locations within the DNA strand but does not include simple one-character mutation at random locations within the DNA code.

A fuller discussion of Marshall's thesis is found in **Section 8.1.1.1.4**.

Mukherjee reviewed the literature of the gene from the perspective of heredity. Mukherjee has offered an interesting assertion that replaces earlier discussions related to heredity(**Section 8.1.1.1.7**) that he describes as;

~~a genotype determines a phenotype~~

He offers the alternative;

a genotype + environment + triggers + chance = phenotype

The importance of the chance element was not discussed in detail. Chance is always available as a catchall in biological research for a lack of sufficiently detailed knowledge by the investigator. It is suggested that this element may have negligible impact once the processes are understood in more detail.

Mukherjee's triggers may include, supplement or complement processes that suppress specific genes like methylation.

The similarity (parallelism) between the evolutionary concept of Marshall and the hereditary concept of Mukherjee should be obvious.

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Mukherjee provides a brief review (pages 146-149) of the initial vision of Watson on the character of DNA and the subsequent discussions of Watson & Crick leading to their discovery of the specific arrangement of the DNA molecule.

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Marshall describes transposition as "blade #1" of his Swiss Army Knife of Evolution 2.0. He describes horizontal gene transfer as "blade #2" of his Swiss Army Knife.

Marshall also describes "epigenetics" as "blade #3 of the Evolution 2.0 Swiss Army Knife. It's a switch that 'grays out' genes, altering DNA's function without changing the DNA sequence itself. It produces differenet cell types in fetal development; it alters tissues based on the external environment, and passes learned traits to offspring. Coding sequences stay the same but their expression is altered through a combination of mechanisms."

Blade #4 was associated with symbiogenesis in his chapter 15.

Blade #5 was associated with genome duplication in chapter 16. He explores genome duplication via hybridization (page 136) as the principle means for creating entirely new species. He noted that most hybridizations result in sterile offspring (male donkey + female horse = sterile mule), but not always. He noted the hybridization of two invertebrate sea squirt species appear to have created a vertebrate hagfish; "a dramatic change in a short period of time."

1.2.8.4.4 Methylation as an important modification of a genetic code

Marshall defines methylation from an engineering perspective as;

• "Methylation as the mechanism defining how diffeent cell types get built from the exact same strand of DNA. One methylation pattern activates the genes for building neurons; another pattern builds muscle tissue; another builds skin cells.

• Methylation is an ingenious form of data compression, because multiple epigenetic templates can generate completely different messages from the same sentence.

• Not only that, the organism can shuffle around methylated codon snippets to work out further adaptations. During this time, the silent section of DNA are like (occupy) random access memory in a computer—extra space where secondary jobs get done without interfering with the current business of the organism.

• And of course, in order for this (the above) to work, the epigenetic mechanism must observe the grammatical rules of the DNA language."

Methylation is playing an ever expanding role in understanding diseases such as the cancers[208].

1.2.8.4.5 The RNA code as it relates to arginine

Knight & Landweber published a paper addressing the genetic code involved in arginine to citruline conversion[209]. It also reviewed the basics of RNA coding as of that time. They began with,

> "The selection of RNA molecules (aptamers) that bind amino-acid ligands has made theories about the origin of the genetic code at last testable. The genetic code assigns similar amino acids to similar codons. This could be a result of selection to minimize the effect of mutations or translation error, or of codon concession by metabolic precursors to related derivatives."

They conclude their paper with,

> "The pattern of chemical interactions between the 64 codons and 20 amino acids remains largely unknown. Only when these interactions are known will we be able to understand the relative importance of selection, history and chemistry in code evolution."

The state of understanding and reading the DNA & RNA codes leading to a specific protein, or non-protein via sections of the "junk" portions of these codes, remains very limited. No one claims to be able to predict the result of a translation of these codes into specific molecules

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[208]Phillips, T. (2008) The role of methylation in gene expression *Nature Education* 1(1):116 http://www.nature.com/scitable/topicpage/the-role-of-methylation-in-gene-expression-1070

[209]Knight, R. & Landweber, L. (1998) Rhyme or reason: RNA-arginine interactions and the genetic code Chem Biol vol 5, pp R215-R220 http://biomednet.com/elecref/10745521005R0215
0

can be done as of 2018.

1.2.8.4.6 A brief list of the simplest proteins/peptides

Appendix 4 of Marshall has provided a short list of the simplest of over one million cataloged proteins/peptides, **Figure 1.2.8-10**. In a sense, Marshall mislead his audience by suggesting his first protein consisted of only five amino acids. His brief text does not differentiate and there is no official delineation between peptide and proteins. Most who discuss this difference suggest at least six amino acids are required to identify a functional protein. The amino acid sequences use the single letter code for each amino acid. Thus Met-enkephalin, the first peptide, consists of tyrosine, glycine, glycine, phenylalanine, methionine. As Marshall notes, this brief sequence is an immature form of Met-enkephalin. On his website, he provides a URL to more complete data related to this protein[210]. This immature sequence appears four times in this form, and two additional times in an expanded form (that appear once each) in the protein, Proenkephalin-A. The complete protein is labeled HGNC:8831 or PENK in the human organism databases. This protein is described as formed of 8 identifiable peptide chains. In mature form, PENK involves 267 base-pairs with a total weight of 30,787. The initial signal peptide is 24 amino acids long (from 1 to 24 in the sequence). The second entry in his table is a recognized protein, Microcin C7, associated with Escherichia coli and consisting of 7 amino acids.

> The www.uniprot.org website exemplifies the lack of a strong central authority establishing and controlling the nomenclature in biology. While the empiricist will insist such control would tie his hands, the lack of it at the appropriate stage contributes to the chaotic nature of the database(s). The UniProt consortium is performing a powerful function by trying to collate a vast amount of information from dozens of individual databases.

[210] http://www.uniprot.org/uniprot/P01210

Amino Acid Sequence (encoded message)*	Output Peptide/Protein† (organism name)	# of Amino Acids
YGGFM	Met-enkephalin (HS)	5
MRTGNAN	Microcin C7 (EC)	7
DRVYIHPF	Angiotensin 2 (HS)	8
CYIQNCPLG	Oxytocin (HS)	9
CYFQNCPRG	Vasopressin (HS)	9
QHWSYGLRPG	Gonadoliberin-1 (HS)	10
RPKPQQFFGLM	Substance P (HS)	11
DVPKSDQFVGLM	Kassinin (KS)	12
GGAGHVPEYFVGIGTPISFYG	Microcin J25 (EC)	21
RSCCPCYWGGCPWGQNCYPEGCSGPKV	Neurotoxin 3 (AS)	27
HSQGTFTSDYSKYLDSRRAQDFVQWLMNT	Glucagon (HS)	29
APLEPVYPGDNATPEQMAQYAADLRRYINML-TRPRY	Pancreatic hormone (HS)	36
KCNTATCATQRLANFLVHSSNNFGAILSSTN-VGSNTY	Islet amyloid polypeptide (HS)	37
CTPGSRKYDGCNWCTCSSGGA-WICTLKYCPPSSGGGLTFA	Serine protease inhibitor 3 (SG)	40
DDGLCYEGTNCGKVGKYCCSPIGKYCVCYD-SKAICNKNCT	Pollen allergen Amb t 5 (AT)	40
VGIGGGGGGGGGGSCGGQGGGCGGC-SNGCSGGNGGSGGSGSHI	Microcin B17 (EC)	43
TTCCPSIVARSNFNVCRLPGTPEALCATYTG-CIIIPGATCPGDYAN	Crambin (CA)	46
ATYNGKCYKKDNICKYKAQSGKTAICKCYVK-KCPRDGAKCEFDSYKGKCYC	Antifungal protein (AG)	51
GIVEQCCTSICSLYQLENYCNFVNQHLC-GSHLVEALYLVCGERGFFYTPKT	Insulin A-B chains (HS)	51

Figure 1.2.8-10 A list of the simplest proteins, up to 51 amino acids in the RNA sequence. Marshall did not provide a key to the organism name in this figure. From Marshall, 2015.

1.2.8.5 Investigations relating to the methylation of DNA base-pairs

Schubeler has provided a recent review and extensive bibliography discussing the epigenetic process of methylation of the base-pairs of DNA during cell division[211]. A number of caricatures are provided to introduce the subject matter.

In 2007, Reik[212] noted, "Development is, by definition, epigenetic. Differences in the programmes of gene expression that result in the development of different organs and tissues occur without changes to the sequence of our DNA (with one or two exceptions). There is nothing mysterious in this concept; subsets of the ~30,000 genes in our genome are active in different tissues and organs, depending on their regulation by different sets or combinations of transcription factors. This implies that if we were to take all of the transcription factors that activate genes in a liver cell and transfer them to a brain cell (while inactivating all brain-specific transcription factors), then the brain cell would turn into a liver cell."

Reik & Kelsey (2014) discussed the methylation of DNA and subsequent de-methylation during human embryo development in considerable detail[213]. Caricatures are also provided to aid the reader. Lacking such caricatures, the semantics and terminology of the subject matter is quite difficult.

1.2.8.6 The flow of genetic information

Figure 1.2.8-11, modified from Marshall, delineates the flow of genetic information based on his "Evolution 2.0" extended to include the evolution 2.1/3.0 concept of **Section 1.2.8.1**. The state of the genes appearing at the top of this figure are not defined in detail on page 410 of Marshall.

A vertical line running through the label "Genes" offers alternate interpretations of this figure.

First; the vertical line can separate considerations related to evolution 2.0 on the right from evolution 2.1/3.0 on the left as discussed above.

Second; since the genetic material following fertilization of the egg is generally passed through to the genes of the reproductive organs unchanged, the vertical line can be considered a short cut path from the genes of the parents to the reproductive mechanisms of the Organism. The potential to modify the genes in the sperm or eggs of the organism would appear to focus

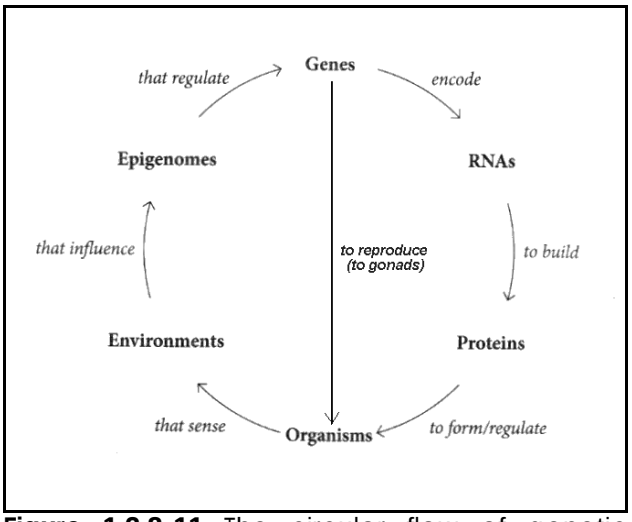

Figure 1.2.8-11 The circular flow of genetic information as of 2016. A vertical line through "Genes" and "Organisms" separates evolution 2.0 on the right from evolutions 2.1/3.0 on the left. See text. From Marshall, 2016.

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[211]Schübeler, D. (2015) Function and information content of DNA methylation *Nature* vol 517, pp 321- 3 2 6 doi:10.1038/nature14192

[212]Reik, W. (2007) Stability and flexibility of epigenetic gene regulation in mammalian development *Nature* vol 447, pp 425-432 DOI: 10.1146/annurev.ge.20.120186.001345

[213]Reik, W. & Kelsey, G. (2014) Cellular memory erased in human embryos *Nature* vol 511, pp 540-541

physiologically on the gonads of the organism. However, the genes cannot be modified epigenetically until after the organism has sensed the environmental challenge.

1.2.8.7 More detailed relationships involving the genes

Cite Section 8.1.2.xxx or 8.1.1.1.7

The formation of a single neuron type may involve thousands to millions of genes. Examples of a single genetic mutation causing significant disease is probably a major fallacy.

1.2.8.7.1 Structure of the virus, E. coli T4 bacteriophage

Wood & Edgar described the physical building of the very simple virus known as "*E. coli* T4 bacteriophage" in 1967[214]. It is reproduced in **Figure 1.2.8-12**. The process was illustrated in chapter 33 of Lehninger (1972). It involved over 100 separate genes. Lehninger included a genetic map and a flow diagram showing what genes contributed to each structure in the assembly of the bacteriophage. Lehninger also described when a mutation might cause a fatal (conditional or major) condition. Tropp[215] expanded our knowledge relating to T4 in2008. Tropp provides a different number of facets for the head of the T4 bacteriophace. He also pointed out the name bacteriophage is an archaic name. Such viruses do not eat the target bacteria but, instead, use it as a reproduction factory. Tropp provided a new volume addressing and updating many phases in molecular biology. The advances in understanding the form and function of viruses has been extensive.

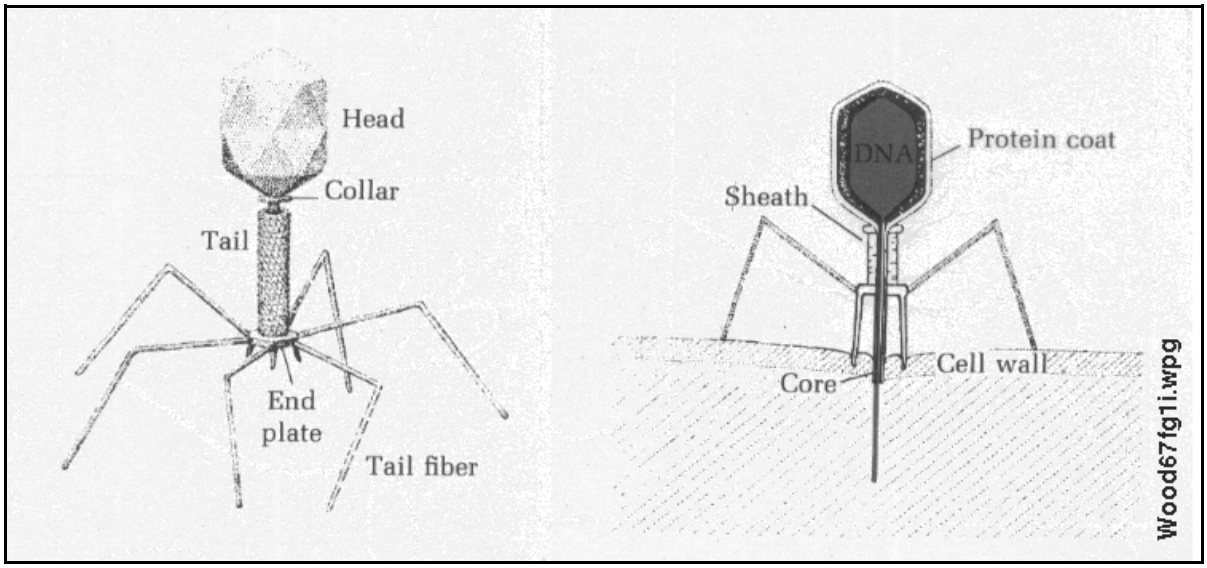

Figure 1.2.8-12 Structure of the virus, *E, coli* T4 Bacteriophage. The head consists of 30 facets. Creation of this single active, and infectious, virus involves over 100 genes. The head contains primarily its own DNA. See text. From Wood & Edgar, 1967.

1.2.8.7.1 Matrixing of genetic information ala a PLA

It is appropriate to pause and consider a thought experiment. What if the genetic material

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[214]Wood, W. & Edgar, R. (1967) Building a Bacterial Virus. NY: Scientific American

[215]Tropp (2008) Molecular Biology: Genes to Proteins. Boston, MA: Jones & Partlett Chapter 8

of a given individual could be arranged into an array similar to a cross-word puzzle or a programmable logic array, PLA, of current electronics engineering?

Figure 1.2.8-13 illustrates the cross-word puzzle concept courtesy of the NY Times. This example provides a variety of means to establish a specific set of genes related to a specific medical symptom as well as a means to establish all of the genes related to a specific syndrome. The "Across" notation corresponds to the rows in an array; the "down" notation corresponds to a column. Diagonals of the array can also be important in coding. Note that an error at one character location can affect the information associated with a column and row and diagonal simultaneously.

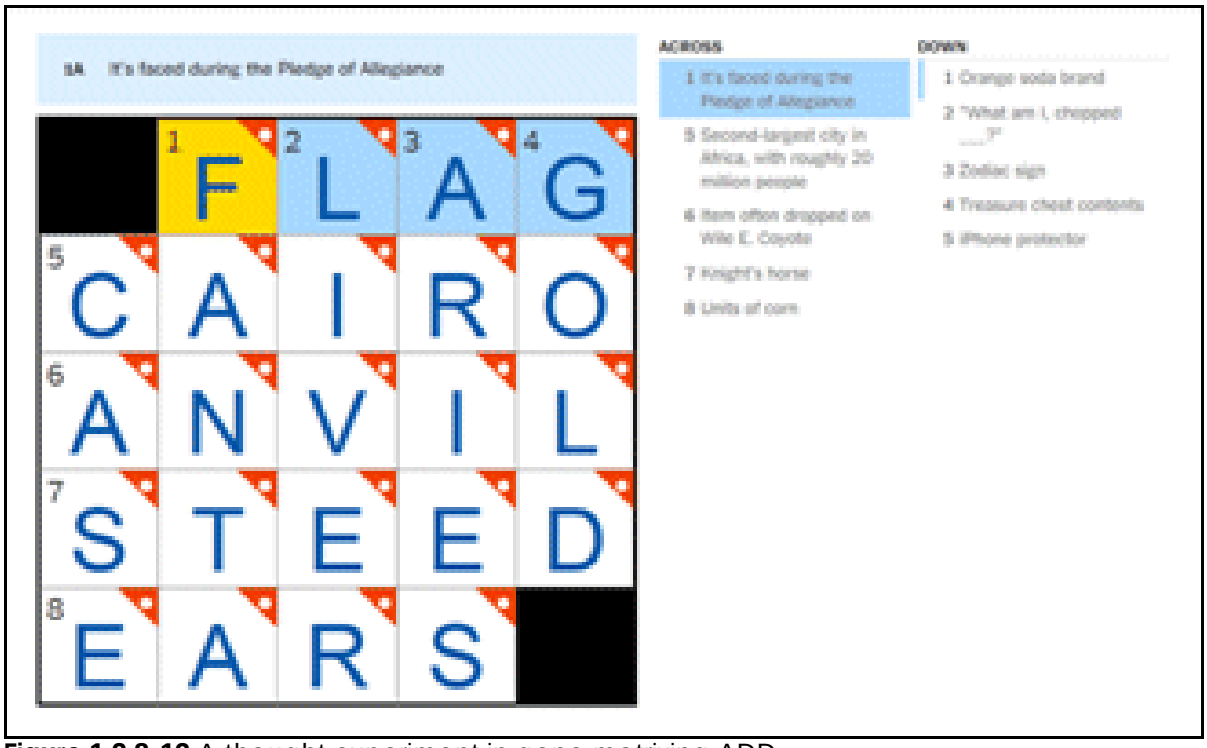

Figure 1.2.8-13 A thought experiment in gene matrixing ADD.

For purposes of discussion, assume the genes are laid down in horizontal rows stacked vertically. In this case, any gene insertion, deletion or extension would result in a significant rearrangement in any sequence of genes accessed by a horizontal, vertical or diagonal sampling.

The stacking arrangement, a Riemann transform, is similar to the arrangement asserted to be used in hearing to convert a continuous frequency range into a repetitive octave scale (**Section xxx of PBH**). In pure mathematics, it is described as a Riemann transform.

The above thought experiment employed a 2- dimensional, or 2-ary space. For an n-ary space, the potential and complexity of the accesses becomes much larger. If a gene is either eliminated, added or changed in length within the RNA strand, additional complexity is introduced. If there is a line start or stop marker at intervals along the RNA strand, the distortion in the overall gene arrangement provided by the Riemann transform could be mitigated.

The peptide sequences in the start and/or stop codes identified in many genes are much

longer than necessary from an information theory perspective. Their length could be used to provide redundancy in order to achieve a better signal-to-noise ratio. Alternately the codes may represent both a gene starting point and a Riemann transform marker.

If the arrangement of the genes is determined by the folding of the RNA strand, the problem can also become more complex. If some part of a gene or pseudogene is varied in length, the folding of the RNA may also be changed.

Lin et al. have provided **Figure 1.2.8-14** summarizing the results of recent research in a diagram compatible with the above example[216]. Their abstract describes the scope of their paper,

> In this review, we discuss the current understanding of those autism risk genes that affect the structural connectivity of neurons. We sub-categorize them into
> (1) cytoskeletal regulators, e.g., motors and small RhoGTPase regulators;
> (2) adhesion molecules, e.g., cadherins, NCAM, and neurexin superfamily;
> (3) cell surface receptors, e.g., glutamatergic receptors and receptor tyrosine kinases;
> (4) signaling molecules, e.g., protein kinases and phosphatases; and
> (5) synaptic proteins, e.g., vesicle and scaffolding proteins.
> Although the roles of some of these genes in maintaining neuronal structural stability are well studied, how mutations contribute to the autism phenotype is still largely unknown."

Although all of these five factors may play a role, the presumption of this work is that the immediate problem has to do with forming permanent synapses as a result of dendritic and axonal spines pairing. Other more remote factors are presumed to play a less focused role and may contribute more importantly to other diseases. Even with these presumptions, the figure shows six molecules (shown in black type, at the intersection of the three sets of possibilities.

Lin et al. note, "Autism spectrum disorder (ASD) is a neurodevelopmental clinical condition currently diagnosed based on the DSM-5 criteria reflecting symptoms, possibly of varying severity, in social interaction, communication and behavior. See **Section 10.9.4.3 of PBH**.

> This figure should not be taken as authoritative. The source article was labeled a "Review." It contained seventeen pages of citations and is clearly the result of the amalgamation of information representing a shotgun view of the available information. The figure specifically omits a leading contender for a cause of autism, Fragile X mental retardation protein or FMRP, a recognized genetic mediation in the fragile X syndrome, FXS, closely related if not a dominant feature of autism (**Section 10.5.1.4 of PBH**). FMRP should appear in dark type in the shared areas of this figure.

[216]Lin, Y-C. Frei, J. Kilander, M. et al. (2016) A Subset of Autism-Associated Genes Regulate the Structural Stability of Neurons *Front Cell Neurosci* vol 10, article 263 https://doi.org/10.3389/fncel.2016.00263

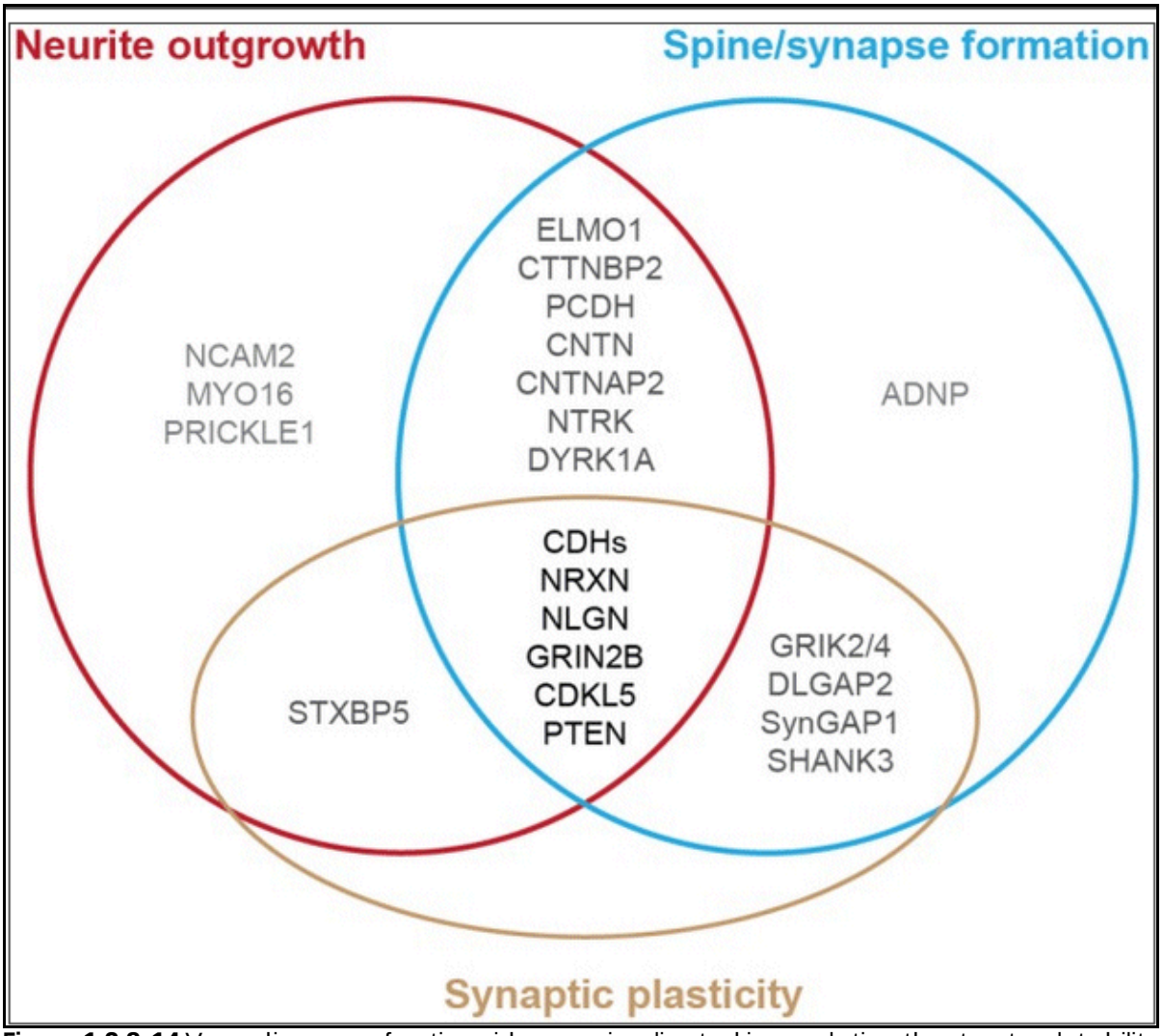

Figure 1.2.8-14 Venn diagram of autism-risk genes implicated in regulating the structural stability of neurons. This example is for illustration, it is not authoritative. See text. Each circle represents a cellular pathway to regulate the structural stability of neurons, including neurite outgrowth (red), dendritic spine or synapse formation (blue), and synaptic plasticity (gold). Experimental evidence shows that many autism-risk genes regulate at least one cellular pathway to maintain the integrity of neuronal structures. Genes that regulate only one pathway are labeled in light gray. Genes that regulate two pathways are labeled in dark gray. Genes that regulate three pathways are labeled in black. See text. From Lin et al., 2016.

Waltes et al. has assembled a useful list of abbreviations relating to the genetics of autism and related diseases[217]. The paper is quite difficult reading for someone outside of the specialty. They note, "Autism spectrum disorders (ASD) are heterogeneous disorders with a high heritability and complex genetic architecture. Due to the central role of the fragile X mental retardation gene 1 protein (FMRP) pathway in ASD we investigated common

[217]Waltes, R. Duketis, E. Knapp, M. et al.(2014) Common variants in genes of the postsynaptic FMRP signalling pathway are risk factors for autism spectrum disorders *Hum Genet* vol 133(6), pp 781–792 doi:10.1007/s00439-013-1416-y

functional variants of ASD risk genes regulating FMRP. We genotyped ten SNPs in two German patient sets (N = 192 and N = 254 families, respectively)." They go on to conclude, "These findings underpin the role of ASD candidate genes in postsynaptic FMRP regulation suggesting that an imbalance of specific isoforms of CYFIP1, an FMRP interaction partner, and CAMK4, a transcriptional regulator of the FMRP gene, modulates ASD risk."

1.2.8.8 Genetics of the phospholipids of a cell lemma

There are few academic papers discussing the creation of phospholipids, much less phospholipid bilayer membranes forming the cell lemma, in the literature. Raetz provided an early paper in 1986 that is listed on the PubMed.gov website. The Raetz paper (42 pages) suggested many problems related to this subject, particularly with the small amount of data related to E. coli[218]. The paper is the most recent on this subject cited by PubMed. In 1994, the Raetz team proposed a relationship between a specific gene and the formation of a phospholipid prototype[219]. In 1997, Dowhan discussed the molecular basis of phospholipid membranes but only casually mentions their genetic code relationship[220].

In their "Discussion" section, Mohan et al. noted, "The *fab*A-encoded dehydrase has been extensively studied and is a pivotal enzyme in the biosynthesis of *cis*-unsaturated fatty acids (Kass and Rloch, 1967) in *E. coli*. "The significant homology between *orf*17 and *fob*A strongly suggests that *orf*17 encodes another dehydrase, presumably one that is involved in saturated fatty acid biosynthesis." In short, they were unable to establish any genetic code sequence leading to the synthesis of any phospholipid. The upper path in their figure 1 is suggestive but very incomplete as to how these genes result in a protein capable of assembling a phosphoglyceride as complex as phosphatidylethanolamine or phosphatidylcholine, that is the outer bilayer of the lemma, (much less the variants of these molecules used to form sensory receptors of taste and smell). See **section 8.5** and **section 8.6** regarding the form of these sensory receptors.

Lu et al. have provided a large amount of fundamental data concerning the possible synthesis of phospholipids on the inner membrane of E. coli that may eventually lead to an understanding of the genotype leading to the lemma of eukaryotic cells[221].

There have been no other, more recent (2016), citations in Google Scholar related to a sequence in the DNA genetic code leading to a phospholipid found in cell lemma.

1.2.8.7.1 Information needed by a cell to form a sensory receptor EXPAND

It is useful to consider the information that must be available from the DNA regarding a specific type of sensory receptor.

1. Somehow the DNA must be able to specify where a given sensory neuron will be formed on the anatomy of the organism.

    - For taste, the sensory receptors of a given type are grouped in different topographical areas of the tongue and inside of the aural cavity (**Section 8.5**).

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[218]Raetz, C. (1986) *Annu Rev Genet* vol 20, pp 253-295.

[219]Mohan, S. Kelly, T. Eveland, S. et al. (1994) An Escherichia coli Gene (FabZ) Encoding (3R)-Hydroxymyristoyl Acyl Carrier Protein Dehydrase *J Bio Chem* vol 269(52), pp 32896-32903

[220]Dowhan, W. (1997) Molecular Basis for Membrane Phospholipid Diversity:Why Are There So Many Lipids? *Annu Rev Biochem* vol 66, pp 199-232 DOI: 10.1146/annurev.biochem.66.1.199

[221]Lu, Y-H. Guan, Z Zhao, J. & Raetz, C. (2011) Three Phosphatidylglycerol-phosphate Phosphatases in the Inner Membrane of Escherichia coli *J Bio Chem* vol 286(7), pp 5506–551

- For olfaction, the sensory receptors of different types are inter mixed on the surface of the olfactory epithelium of the nose (**Section 8.6**).

- For oskonation, the sensory receptors of different types are inter mixed on the surface of the vomeronasal epithelium of the nose (**Section 8.6.15**).

2. Somehow the DNA must be able to specify the particular sensory receptor location on the outer lemma of the sensory neuron.

    This location is on the surface of the dendrite(s).

3. Somehow the DNA must be able to specify the chemical composition of the sensory receptor on the outer lemma of that sensory neuron.

4. Somehow the DNA must be able to specify the internal reticulum of the sensory neuron will approach the outer lemma at the location of item 2 in order to form the 1st Activa.

5. Somehow the DNA must include the instruction for creating the tailored phospholipid of the outer lemma at the location of item 2.

6. Somehow the DNA must include the instruction for the tailored phospholipid of item 5 to condense with a specified amino acid to create a specifically configured sensory receptor molecule at the location of item 2.

7. Somehow the DNA must assure that selected individual amino acids are available in the external matrix adjacent to the phospholipids of item 5

7. [xxx sketch the above listing to show the sequence is complete.]

Figure 1.2.8-15 illustrates only the chemical synthesis of the “Lewis Acid” sensory receptor molecule of **Section 8.6**. It is based on a sketch in Mohan et al. (1994, figure 1) that is shown between the two vertical bars.

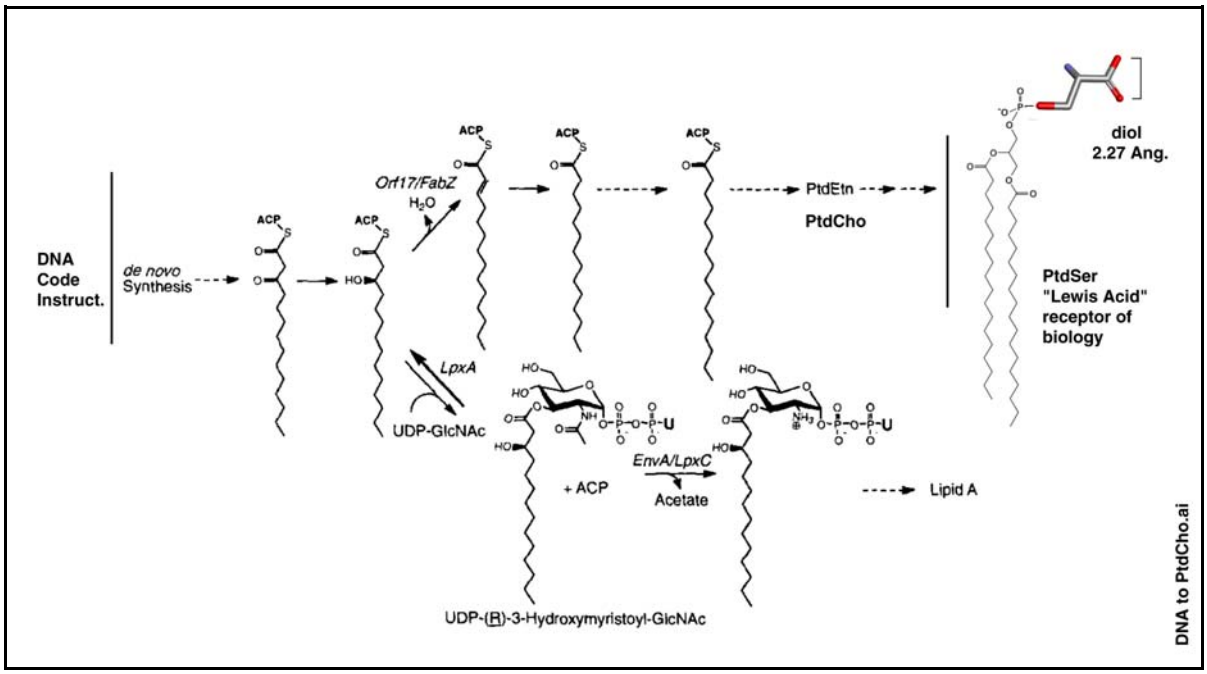

Figure 1.2.8-15 DNA code instructions to Lewis Acid receptor. No detailed instructions from within the "junk" portion of the DNA have been discovered as of 2016. The theoretical "Lewis Acid" receptor found in both the aural cavity and the nasal cavity predicted by this work is shown on the right. See text. Annotated from Mohan et al., 1994.

Mohan et al. originally described a potential *de novo* synthesis leading to the synthesis of phosphatidyl ethanolamine (PtdEtn) which is the inner phospholipid of most external lemma for mammals. It is not likely the correct phospholipid. Phosphatidyl Choline (PtdCho) is the normal external bilayer. Even with this change, as indicated, there are many remaining steps leading to the ultimate synthesis of PtdSer, the theoretical "Lewis Acid" receptor of this work. PtdSer is one of nine phospholipid receptors employed in the olfactory modality (**Section 8.6.2**). The critical portion of PtdSer is the diol with a nominal spacing of 2.27 Angstrom. This diol is able to form a dimer with any molecule with a diol ligand on its outer surface. The dimer is a temporary structure easily formed via two hydrogen bonds. It can be disassembled during any washout process used to explore the operation of the olfactory modality (leaving no residue of the sensory mechanism).

Mohan et al. asserted with regard to this figure, "(3R)-Hydroxymyristoyl-ACP is an intermediate in *de novo* saturated fatty acid biosynthesis in E. coli. However, it is not obvious that this is the appropriate intermediate leading to the receptors of chemical sensing in mammals. The transition path from an ACP (Acyl Carrier Protein) based sulfur head group to a phoshate-based head group is not obvious.

The literature would suggest the generation of the lemma of mammal cells is different from that of E. coli. (see Leninger (1982, page516). Leninger develops an alternative used by mitochondria and ribosomes (page 519). He describes (page 523) the formation of PtdSer in mammals. He also notes, malonyl-S-ACP cannot replace acetyl CoA in the elongation of mammalian fatty acids. On page 525, he discusses other routes to phosphatidyl ethanolamine and phosphatidyl choline specifically that do not involve ACP-S compounds. These routes would not use the genes suggested in Mohan et al.

As recognized from the structure of PtdSer, the sensory neuron receptors of animal chemical sensing involve one of nine amino acid ligands. ***The chemical sensory neuron receptors do not contain or rely upon any peptide or protein moiety for the sensing function whatsoever.***

1.2.9 Absence of a sensory role for G-proteins (GPCR)

During the last quarter of the 20th Century, it became *de rigeur* to define a conceptual role for what were called G-proteins (also known as guanine nucleotide-binding proteins) for virtually every sensory receptor in the neural system. This was primarily because a seven segment protein was found on the sensory neurons in may situations. However, it was never determined what their specific operating mechanism was.

Bockaert & Pin provided a review of the situation in 1999[222]. Their paper is enlightening. Their abstract reads in part;

> "Among membrane-bound receptors, the G protein coupled receptors (GPCRs) are certainly the most diverse. They have been very successful during evolution, being capable of transducing messages as different as photons, organic odorants, nucleotides, nucleosides, peptides, lipids and proteins. Indirect studies, as well as two-dimensional crystallization of rhodopsin, have led to a useful model of a common 'central core', composed of seven transmembrane helical domains, and its structural modifications during activation. There are at least six families of GPCRs showing no sequence similarity. They use an amazing number of different domains both to bind their ligands and to activate G proteins."

While appropriate to an abstract, the paper does little to demonstrate their "being capable of transducing messages as different as photons, organic odorants, nucleotides, nucleosides, peptides, lipids and proteins." It also highlights "There are at least six families of GPCRs showing no sequence similarity." Their only common characteristic, based on modeling, appears to be, "a common 'central core', composed of seven transmembrane helical domains." In the introduction, they also note,

> "GPCRs are certainly among the oldest devices devoted to signal transduction being present in plants, yeast and slime mold, as well as in protozoa and the earliest diploblastic metazoa."

The remainder of the paper is focused on the gross structure of the G-proteins and their potential genome relationships. No mention of their method of sensing is included in the paper. The open questions were summarized in their conclusions;

> "The GPCR saga started with one very simple question addressed over 25 years ago: how do hormones, such as glucagon and noradrenaline, activate adenylyl cyclase? Although we now know the basic principles of cell–cell communication, there is no doubt that very important chapters and many questions remain to be addressed, including: how are GPCRs targeted within the cell? What is the physiological significance of their homo- and heterodimerization? What is the biological importance of their interactions with proteins other than G proteins? And finally, the crucial question, how will we succeed in resolving the GPCR structure?"

Wikipedia, poor on mechanisms but pretty good on tabulations, indicates;

> "There are three main G-protein-mediated signaling pathways, mediated by four sub-classes of G-proteins distinguished from each other by sequence homology (Gas, Gai/o, Gaq/11, and Ga12/13). Each sub-class of G-protein consists of multiple proteins, each the product of multiple genes and/or splice variations that may imbue them with differences ranging from subtle to distinct with regard to signaling properties, but in general they appear to be reasonably grouped into four classes."

None of these classes are particularly optimized for sensory receptor applications. In both of the above citations, the term signaling is used in the very generic sense used in the chemical

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[222]Bockaert, J. & Pin, J. (1999) Molecular tinkering of G protein-coupled receptors: an evolutionary success *EMBO J* vol 18(7), pp 1723–1729

theory of the neuron. There is no discussion of how a photon excites a G-protein.

Charney et al. have provided a discussion[223] of the very large number of G-proteins associated with sensory receptors (Table 3.2) and an even larger list of "Estimated number of genes coding for proteins in signal transduction" (Table 4.1). The supporting material is entirely conceptual, aimed at a clinical audience and lacks any definitive mechanism(s) associated with actual transduction.

All of the discussions in the literature are dominated by cartoons of how the G-proteins "could" be used. But specific details are sorely lacking.

> ***No detailed information has been found showing a unique role for a GPCR in performing the sensory transduction associated with any sensory modality of the neural system.*** **Chapter 8** will provide details of sensory transduction in each of the sensory modalities based on the Electrolytic Theory of the Neuron.

The volume of literature related to GPCR's appears to have diminished during the 21st Century.

1.2.9.1 Example of recent investigations assuming a GPCR

As recently as 2008, Kleene has discussed the olfactory modality on the assumption that a GPCR is a primary transducer[224]. While starting off with the statement, "Most vertebrate olfactory receptor neurons share a common G-protein–coupled pathway for transducing the binding of odorant into depolarization." no definitive graphic is presented supporting this statement.

The complexity of the putative GPCR mechanism is described in words as;

> "The depolarization (of the putative GPCR) involves 2 currents." And, "At least 10 mechanisms may contribute to termination of the response; several of these result from an increase in intraciliary Ca2+. It is not known to what extent regulation of ionic concentrations in the cilium depends on the dendrite and soma."

The paper fails to show any specific mechanism of olfactory transduction. It ends with the paragraph;

> "We are far from having a quantitative understanding of the transduction process. Computational frameworks are being developed, but many key parameters have no experimental support. Even the resting state of the cilium is not well understood. Is diffusion within the cilium limited by the axoneme, which may occlude much of the ciliary volume? Does the basal body hinder diffusion between the cilium and the dendritic knob, and does this influence ionic homeostasis? The thermodynamic basis of ciliary ionic homeostasis is mysterious. It is not clear whether the cilium's resting ionic gradients are controlled at the cilium or in the dendrite and soma. Undiscovered factors in the cytoplasm or the mucus may influence the dynamic range. This might explain why, in all species examined, the dose–response relation is much shallower if the neuronal membrane is intact."

Section 8.6 of this work will provide details of the olfaction transduction process applicable to more than 20 specific classes of odorophores based on the Electrolytic Theory of the Neuron. No GPCR's are involved in this working hypothesis.

1.2.10 A summary list of the Top Level Diagrams used in this work

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[223]Charney, D. Nestler, E. et al. (2009) Neurobiology of Mental Illness, 3rd Ed. NY: Oxford Univ Press Chapters 3 & 4

[224]Kleene, S. (2008) The Electrochemical Basis of Odor Transduction in Vertebrate Olfactory Cilia *Chem. Senses* vol 33, pp 839–859

146 Neurons & the Nervous System

This work attempts to document the operation of the neural system from a graphical perspective in order to support more precise textual discussions than usually found in neuroscience works. Locating these diagrams within the overall body of this work becomes difficult. Therefore, this section will act as a guide to these diagrams.

Top Block Diagram–Section 4.2.3
- Top level block diagram of the neural system–Section 7.1.7
- Top Block Diagram with an expanded stage 7– Section xxx
- Top Block Diagram with an expanded secretory section– Section xxx
- Top Block Diagram of the afferent signal manipulation paths–Section 4.2.4 & 7.2.1
- Top Block Diagram of vision based on stage 3 neuron count–Section 4.7.1
- Top Block Diagram of vision, ***emerging***, ca 2002–Section 15.6.4
  - Block Diagram of the overall visual system of humans–4.2.4
  - Block Diagram of the oculomotor servomechanism–7.2.1
- Top Block Diagram with circuit details, Usrey–Section xxx
- Top level architecture of the visual mesencephalon–4.6.2
- Top Block Diagram of prefrontal cortex–Section 4.6.3
- Top level architecture of the gustatory modality–Section 8.4.3
- Top Block Diagram of the gustatory modality of the rodent–Section 8.4.3
- Top Block Diagram of mammalian olfactory modality–Section 8.4.3

- Top Block Diagram of prefrontal cortex with cytoarchitecture overlay–12.2.1
  - Block Diagram & "action map" of the motor portion of the cerebral cortex–12.5.4
- Top Block Diagram of cortical vision from the signaling and servomechanism perspective–15.6.6
- Top Block Diagram for discussing memory– 17.1.1
- Top Block Diagram (a taxonomy) of mammalian memory systems–17.2.1
- Top Block Diagram of the animal neural system, multiple sensory modalities–18.1.1
- "*Global neuronal workspace*" with nonconscious executive–18.1.1

Top Level Schematic– Section xxx
- Top level schematic of the sensory modalities–Section 4.2.3
- Top Level Schematic of the autonomous system– Section 4.2.3
- Top level signaling plan associated with the external sensory modalities–4.6.2 & 7.2.1
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- Top level signaling diagram of mammalian sensory and cognition systems– 15.1.1
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- Top Level Circuit Diagram, stage 3–
- Top Level Circuit Diagram, stage 4–
- Top Level Circuit Diagram, stage 6–

Topology of neuron elements
- Topology of the bipolar cell–Section 4.4.1
- Topology and circuit diagram of the lateral cell– Section 4.4.2

Topology of the stage 3 signal propagation circuit–Section 9.1.1
Topology of the retina as an exemplar–Section 9.2.1
Topology, operation and waveforms of the ganglion encoding neuron–9.2.3
Topology of flattened human cerebral cortex with Brodmann's regionalization–10.2.2**
Topology, top level, of the visual system – Sections 10.11.4 & 15.2.4
Topology of a dual interval voltage patch-clamp experiment–Section 13.1
Topology of the optic lobe of *Octopus vulgaris*–15.2.1
Topological map of the cortical portion of the visual system of man–15.5.2
Topology within the CNS leading to latency calculations–15.6.7

**Felten & Shetty provide the most complete annotation of the cytoarchitecture of the human CNS in their chapter three[225]. The figures drawn by Netter are excellent.

1.3 A new formal foundation for studies in bioelectrochemistry

The broad field of electrochemistry applicable to solutions (including electro-osmotic chemistry when a barrier was present) evolved very rapidly during the 20th Century. Early in that time period, the field began with coarse studies of the electrical properties of ionizable materials in solvents. This led to extensive studies of the osmotic properties of these materials in the presence of externally applied electrical potentials. This led to the recognition that the nature of the interface between the metallic electrodes used to introduce the potential, and the electrolytes was complex. At that point, the field of electrochemistry evolved into the study of electrolysis (of solutions) and the study of electrodics (of metal-solution interfaces). This was the state of the art in the late 1930's to early 1950's.

In the mid 1950's (after the principal work of Hodgkin & Huxley and their school had been completed) the field of semiconductor physics came to the fore with the discovery of the transistor. This discovery opened a new field of electronic processes within semiconductors. Although these materials were conceptually located between insulators and metals, they exhibited entirely different properties than either of these states of matter. These materials were found to employ the laws of osmosis in a new and different way, particularly with regard to the unusual field potentials found within the materials at sub-molecular scales. These fields were a result of the laws of quantum-mechanics. Soon thereafter, in the 1960's, a new state of matter was documented for the first time as the liquid crystalline state. This state of matter was positioned between liquids and crystals in much the same way that solid-state semiconductors were positioned between (normally non-crystalline) metals and (typically insulating) crystals. The laws of osmosis also helped understand this state of matter when the unique quantum-mechanical aspects of the material were recognized.

Much of the currently available textbook literature has yet to recognize the significance of the liquid crystalline phase of water in the bioelectrochemistry of the neural system. Most of the relevant literature focuses on the properties of water in the liquid state[226,227,228,229,] but answers concerning its nature in the liquid crystalline state are still elusive, particularly when constrained between two lemma. Dowben has addressed the structured state of water and also provided considerable material on the free energy of formation of many organic

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[225]Felten, D. & Shetty, A. (2003) Netter's Atlas of Neuroscience. NY: Elsevier

[226]Adamson, A. (1973) A text book of Physical Chemistry NY: Academic Press pp. 321-322 & 507-509

[227]Conway, B. (1964) Modern aspects of electrochemistry. (Bockris & Conway editors) NY: Butterworths Chapter 2

[228]Eyring, H. (1970) Physical Chemistry: an advanced treatise. NY: Academic Press pp. 150-155

[229]Rattee, I. & Breuer, M. (1974) The physical chemistry of dye adsorption. NY: John Wiley & Sons. pg. 20

materials, etc[230]. Chaplin has provided information that is largely conceptual related to water in this confined state[231].

Revel and Karnovsky have documented the porosity of the material in the 20–40 Angstrom gap of a gap junction to lanthanum hydroxide[232]. This porosity to the proposed semi-metallic water crystal filling this gap is probably due to the substitution of lanthanum ions for hydrogen ions in the lattice.

In spite of the above activity, Fry noted the following in 1972. "Let us state the odious truth at the outset: electrochemical techniques are generally ignored at present in synthetic organic chemistry, even in comprehensive textbooks and review series devoted to synthesis[233]." The situation has changed little since then and applies equally to the even broader biological field. The field is complex with a great many variables which are themselves variables. Establishing a strong foundation to use in addressing this problem is difficult. Clear definitions of terms is a critical factor.

A disproportionate amount of the biology literature is founded on a limited understanding of the kinetics of chemical reactions. The kinetics of such reactions have often been simplified to the point that they do not relate to such reactions carried out in a complex biological environment instead of an isolated beaker. In more complex environments, the kinetic principles employed must be compatible with the more general thermodynamic situation. Unfortunately while necessary, applying such thermodynamic principles is more complicated. Walz has recently presented a comprehensive discussion of the ground rules, and the application procedures related to thermodynamics as they apply to biological systems[234].

Of particular concern here is the common practice of examining a neuron *in-vitro* where *in-vitro* means in a totally different environment not compatible with the operation or the survival of the neuron. In many cases, some of considerable historical importance, operating elements of the neuron have been mutilated prior to testing in the laboratory.

In accordance with the Walz paper, the subject of non-biological electrochemical cells as taught in most physical chemistry texts does not include a cell in complete contact with its environment. The types of cells usually addressed are only two:

1. The chemical cell, based on an emf being generated within the cell (a conventional battery) due to a chemical reaction.

2. The concentration cell, in which the emf is due to the free energy decrease attending the transfer of matter from one part of the cell to another through a semi-porous membrane (such as recent "lithium ion batteries').

These are both two terminal cells and their basic features are well described in the literature[235]. Their more subtle features related to bioelectrochemistry will be addressed in **Section 1.3.3.1**.

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[230]Dowben, R. (1969) General physiology: a molecular approach. NY: Harper & Row pp. 96-112

[231]Chaplin,

[232]Revel, J. & Karnovsky, M. (1967) *J Cell Biol* vol. 33, pp C7-C12

[233]Fry, A. (1972) Synthetic Organic Electrochemistry. NY: Harper & Row pg 1

[234]Walz, D. (1995) Thermodynamics of irreversible processes applied to biological systems: a survey *In* Melandri, B. Milazzo, G. & Blank, M. *eds*. Bioelectochemistry IV NY: Plenum Press pp 329-348

[235]Maron, S. & Lando, J. (1974) Fundamentals of Physical Chemistry. NY: Macmillan, Chapter 14

A key point developed by Walz is the subtleties between reversibility and equilibrium. He makes a very quotable statement. "Firstly, thermodynamics dealing with equilibrium states only (i. e. *classical* thermodynamics or *thermostatics*) is inappropriate for the assessment of living systems. By the same token *reversible processes*, i. e. processes which proceed through a sequence of states all at or very close to equilibrium, can be assumed at most for some processes in a living system only under certain conditions. As long as the system is alive there are processes which proceed irreversibly. Hence, thermodynamics of irreversible process (or *non-equilibrium thermodynamics*) is the appropriate tool. Secondly, a biological system or any part of it cannot be treated as if it would *not* exchange energy and/or matter with surroundings (i.e. as an isolated system in the thermodynamic sense)." To understand these admonitions, the reader is encouraged to review the Walz paper.

The other problem, often supported by the elder members of the community is the tendency to avoid baseline models and precise definition of terms in the interest of broader exploration. This approach has led to great confusion and needless exploration outside the guidelines of the scientific method. The only productive approach is to concentrate harder on following the specific steps in the scientific method while being aware of the work of others in parallel, although possibly remote appearing, fields.

1.3.1 A paradigm shift in bioelectrochemistry

Piccolino made an interesting observation in 1998[236]. "The voltage-dependence of the ion permeability changes involved in the discharge of the nervous impulse links electricity in a fundamental way to this event (the activation of the phasic neuron), and makes unlikely any hypothesis that considers the electrical phenomenon only as one of the many possible functional expressions of nerve excitation." While discussing his thesis in a broader discussion of the work of Hodgkin and Huxley, he did not discuss the ground rules of his thesis. Piccolino's thesis is heavily dependent on the constraints introduced by Hodgkin & Huxley. He does not even discuss the role of the dendritic and other neuritic structures in the generation of the action potential and fails to review the operation of the 95% of all chordate neurons that do not involve the generation of action potentials **at all**. Piccolino did note; "The questions left largely unresolved by the Hodgkin-Huxley studies concerned the mechanism of ion permeation through the membrane." **Section 1.4.2** will show that this question has been largely resolve and it is no longer relevant to neuroscience.

> The fundamental (type 1) lemma of the neuron is impervious to ions, in fact the type 1 lemma includes an energy barrier sufficient to prevent any charged or uncharged, hydrophilic or lipophilic biologically relevant particle from traversing the lemma in either direction. See Anderson & Fuchs cited below.

It is proposed that the theory developed here involves a paradigm shift that was outside of the purview of Piccolino and circumvents his assertion.

It would have been far outside the purview of Hodgkin & Huxley. The Electrolytic Theory of the Neuron dismisses the concept of ions passing through individual biological membranes for purposes of signaling in favor of a junctional tissue concept. In this concept, an entirely different mechanism is proposed that relies upon quantum-mechanics occurring in the junctional tissue between axonal and neuritic tissue to explain the operation of the neuron. **The charge carrier in the Electrolytic Theory is the electron, not an ion**. The junctional tissue model is a three-terminal model as opposed to the two-terminal model of Hodgkin & Huxley. This model does not require the putative, and un-demonstrated, Independence Principle of Hodgkin & Huxley, or the unexplained variation in the permeability of the plasmalemma (controlled by an unknown hand?) to ions of sodium or potassium for purposes of signaling.

To develop the Electrolytic Theory, a major review of the literature was performed. The conflicts found within that literature led to special attention being placed on the fundamentals underlying the empirically observed and intuitively explained material. Of

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[236]Piccolino, M. (1998) Animal electricity and the birth of electrophysiology: the legacy of Luigi Galvani *Brain Res Bull* vol. 46, no. 5, pp 394-396, pg 400

particular importance was a review of the protocols and test sets used by Hodgkin & Huxley in their seminal experiments of the early 1950's. A careful analysis of this material, based on modern electrical engineering principles surfaced two important facts. First, many waveforms they observed and reported did not have the characteristics of action potentials. Second, the waveforms they observed and reported did not relate to an active mechanism associated with a free-standing plasma membrane of an axon. **Appendix C** xxx will review their program.

Simultaneously, a large amount of data was reviewed concerning the electrical and physical characteristics of the Node of Ranvier. The examination of physical parameters exposed the presence of a crystalline form of semi-metallic water within the narrowest region of the structure formed by the pre and post nodal membranes. The low physical permeability of this material is not compatible with the movement of various heavy ions across this gap. However, its high electrical permeability is compatible with the movement of electrons across such a gap. The examination of the electrical characteristics of this Node showed it to be capable of generating an action potential. This action potential exhibited much more power than the excitation required to initiate it. *This characteristic is the hallmark of an underlying active mechanism*. The challenge was to find this mechanism.

1.3.2 Clarification of the states of matter and discipline of electrolytic chemistry

To understand the operation of the neural system, it is important to put the requisite technology and tools in proper perspective. The field of electrochemistry has been described by Bockris and Reddy[237]. Their figure has been expanded in **Figure 1.3.2-1** to include the additional technologies needed (shown shaded). The key change is to include the liquid-crystalline state of matter, an absolute requirement for understanding biological materials and processes. The liquid crystalline state is critical to the formation of the Activa and the achievement of transistor action within and between neurons. The broad field of Electrical Engineering contributes to understanding the stimulation of neurons. Electrical Engineering is also critical to the understanding of the variety of mechanisms that are created within the organism based on Physical Chemistry. Finally, too many investigators have ignored the subtleties of physics and electrical engineering when designing their instrumentation..

[237]Bockris, J. & Reddy, A. (1970) Modern Bioelectrochemistry, vol. 1. NY: Plenum Press pg 26

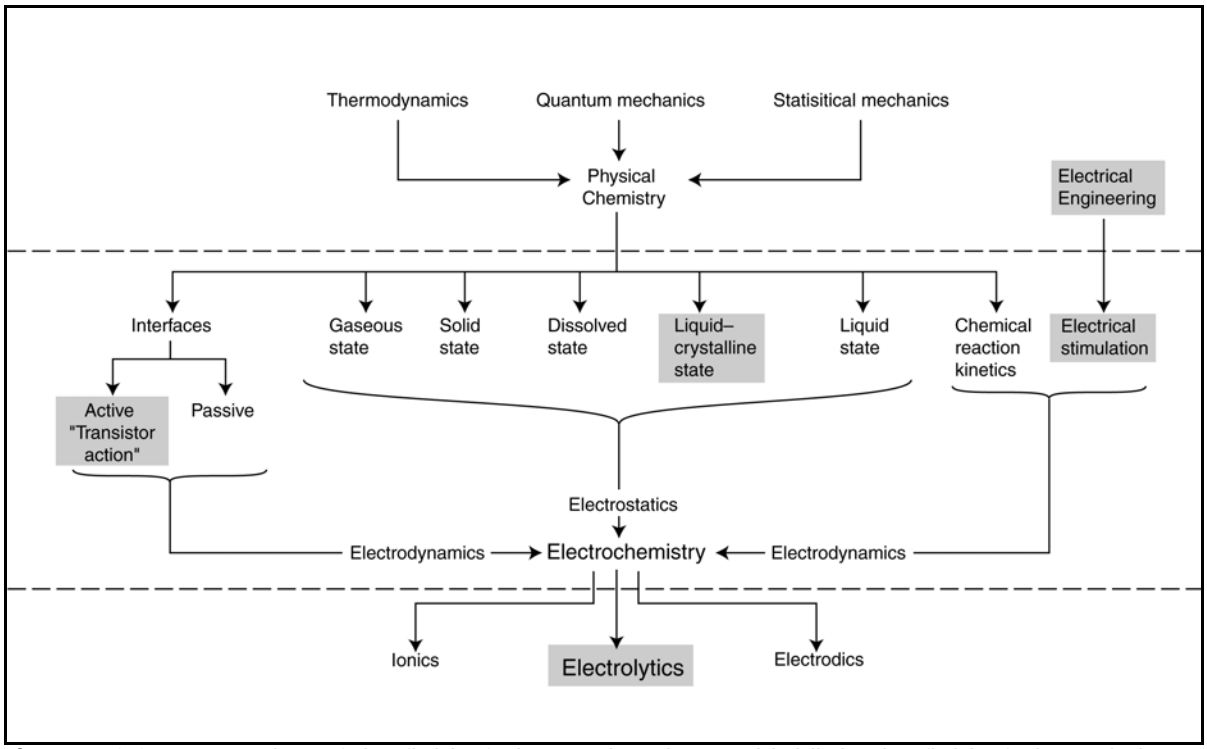

Figure 1.3.2-1 Expansion of the field of electrochemistry to highlight the field of electrolytics or electrolytic chemistry. Expansions include the shaded boxes. Ionics is the field of electrochemistry for solutes below 0.1M concentration. Electrolytics is the field of electrochemistry involving solutes above 0.1M concentration and particularly in the liquid crystalline state. See text. Compare to Bockris & Reddy, 1970

In this work, the field of bioelectrochemistry will be divided into four main areas:

1. electrodics – the electrical interactions between metals and electrolytes at an interface
2. electrolytics–
    2a. (unnamed) – the interactions between semiconducting lemma and high molar concentration electrolytes (typically liquid crystalline in form).
    2b. (unnamed) – the interaction between insulating lemma and high molar concentration electrolytes
3. ionics – the interaction of low molar concentration solutes and solvents with electrical fields
4. electrostenolytics – the reaction of solutes carried to and involving stereochemically the surface of a biological substrate (generally a type 2 lemma).

The specific definition of electrodics from Bockris & Reddy is quite adequate if the term electronic is replaced with metallic. Electrodics is the study of processes that occur at the surface of a metallic conductor in contact with a liquid phase electrolyte. With that change, the fields of electrolytics and ionics can be addressed more precisely.

The distinction between electrolytics and ionics is a critical one because of the nature of the dominant ionic element, water. Water has many unique properties. Water has a tendency to assume the liquid-crystalline state even at temperatures above four degrees when in contact with other materials or when forced into a very narrow space (measured in tens to hundreds of molecules in thickness). Under these conditions, water is frequently described as a liquid-crystalline material called semi-metallic water. Water in the liquid crystalline form is of extreme interest in the study of the neurological system. This structure shares many properties with conventional (very low ionic mobility) ice but involves less cross-bonding between lattice structures (**Section 1.3.2.2**).

This tendency leaves a critical distinction to be made between water present in dilute solutions and water as found in neural tissue. In "dilute solutions," taken here as a molarity of less than 0.1M, the parameters associated with water suggest it is a major constituent in the field of ionics. At dilute concentrations, water also plays a major role in the field of electrodics. However, at higher concentrations, especially those describable using the terms gel and liquid crystal, the parameters of water play a primary role in the field defined here as electrolytics.

As suggested earlier, viable biological membranes are generally considered to exist in the liquid-crystalline phase. The unique electrical properties of these membranes is largely associated with their liquid-crystalline phase. The field of electrolytics is defined as the study of the interaction of water-based solutions and biological membranes, when both are present in the liquid-crystalline phase. This definition generally limits electrolytics to water-based solutions with a molarity greater than 0.1M. Bockris & Reddy suggest this nonaqueous arena as a new frontier in ionics. This field has been named electrolytics here. In this new context, ionics is defined as the study of solutions at concentrations below 0.1M.

The discussion of electrostenolytic reactions will be differed until **Chapter 3**.

1.3.2.1 Charge transport in technologies/states of matter

> It was unfortunate that in the time of Benjamin Franklin (circa 1800), electricity was arbitrarily defined as employing the flow of positive charges (a current) from a positive terminal to the negative terminal of a battery. It was not until 1897 that JJ Thomson discovered the truth. The carrier in electronic circuits was the negative charge (the electron) flowing from the negative terminal to the positive terminal of a battery. The fact that **the primary charge carrier is the electron** in most states of matter is not widely recognized in the biological literature.

Each of the states of matter, and each of the technologies related to these states, described in the above figure rely upon specific charge carriers and specific charge transport mechanisms. **TABLE 1.3.2** describes these situations. Ionics occupies a unique role in this table. Ionics, the electrochemistry of aqueous solutions at less than 0.1M, is the only technology that actually involves a positive charge carrier, the positive ion along with a negative charge carrier. All of the other transport mechanisms and states of matter rely upon the electron as the charge carrier. In the case of electrodics, positive ions may accept an electron as they are neutralized and negative ions may give up an electron as they are neutralized. No fundamental positive charge carrier is involved in these redox reactions. In the case of semiconductors, whether metal-based or liquid crystalline-based, the electron plays two distinct roles. When excited into the conduction band of quantum-mechanics theory from a previously neutral lattice, an electron moves freely in response to the local electric field gradient. On the other hand, when an electron is excited into the conduction band, it leaves behind "a lack of an electron"in the previously neutral valance band of the lattice. This vacancy is described as a "hole" in both electronics. and semiconductor physics. Since such a lack of an electron represents an unstable condition within the lattice, an electron from another center within the lattice will jump to the hole location and thereby neutralize that part of the lattice, leaving a hole behind. In the absence of an electric field, the direction of the above jump is random. However, if there is an electric field gradient present, an electron closer to the negative region of the field will jump preferentially in the direction of the positive source of the field. As a result of this jump, the hole will appear to have moved in the direction of the positive field gradient, i. e., toward the negative region of the field. This saltatory mode of charge motion within the valance band of a semiconductor has seldom appeared in the biological literature. The saltatory motion of holes is a major player in semiconductor physics. It will be shown that hole current is the dominant form of charge transport in the liquid crystalline material forming most tissue in the animal body and all cell lemma. Such saltatory hole motion (due to electrons in the valance band) is easily demonstrate by performing Hall Effect measurements on lemma and other semiconducting tissue.

TABLE 1.3.2

Charge Carriers in various States of Matter

Technology	State of Matter	Positive Carrier	Negative Carrier
Electronics	Metallic conductor	----	electrons
Electronics	Metal semiconductor	saltatory electrons*	electrons
Electrodics	Metal/Liquid interface	----	electrons
Electrolytics	Liquid crystal semicond.	saltatory electrons*	electrons
Ionics	Liquid conductor	+ ions	– ions
Electrostenolytics	Solid/Liq. Crystal Interface	saltatory electrons*	electrons

* Saltatory electrons are known by the synonym, holes. They move within the valence band of the material. All other electrons move within the conduction band. There is a third band associated with traps in semiconducting materials that does not appear to be important here.

The Hodgkin & Huxley school attempted to explain the operation of the axon of a neuron based on a very limited model of the complete neuron, "any consideration of *junctional-tissue* or the central nervous system has been omitted." Based on the state of the art of that day, they assumed the remainder of the neuron was essentially passive and only the axon played an active role. They also decided to treat the lemma of the axon as a symmetrical semipermeable membrane based on the osmotic chemistry of that day. By ignoring the electrical properties of the termini of the axon, they found it necessary to account for the potential of the axoplasm because of currents flowing through the largely uncharacterized lemma of the axon. At that point, they incorporated their knowledge of the field of electrochemistry as it stood at that time. They based their work on the known electro-osmotic properties of common (physically and electrically symmetrical) materials separating electrolytes. They were unable to address the actual physics of the virtually unknown molecular structure and size of the lemma. From this point forward, their analyses depended upon the application of the laws of ionic chemistry to an actual problem in semiconductor physics and electrolytic chemistry. This application was inappropriate.

In the 1951 Hodgkin paper, and the more expansive Hodgkin & Huxley papers of 1952, their proposed in-rushing (conventional) current was related to the rising phase of the action potential. Subsequently, the in-rushing current was *euphemistically* labeled the sodium current on the basis of the high concentration of sodium in the extra-neural environment and the assumption that electrical currents consisted of positive charges. The out-rushing current was associated with the falling phase of the action potential. It was subsequently labeled *euphemistically* the potassium current based on similar logic. The ionic component of the labels were not based on any experimental evidence other than the relative concentration of the species on each side of the lemma. No role was assigned to the potential flow of electrons or holes through the membrane. Their ionic labels became more directly associated with the flow of actual charge through the axolemma of a neuron as the years passed and the terms entered the vernacular. A major problem involved the flow of two positive ions in opposite directions under the influence of a single electrical field gradient during the same time interval. The implausibility of this phenomenon was explained through their adoption of an "independence principle" *that has yet to obtain a theoretical foundation* after more than 50 years.

There is no current evidence for an alternate (beyond the conceptual) to electrons and holes as the only charge carriers found in type 1, 2 & 4 lemma.

1.3.2.2 The special properties of water

Neither the biological or neurological literature have addressed the role of water in the neurological systems of animals in detail. The above partition of electrochemistry into ionics and electrolytics solves a long standing dilemma. Investigators studying ionics have traditionally relied upon parameters measured at the asymptotes associated with infinite dilution. The appropriate parametric values when studying electrolytics are the asymptotes when the concentration approaches the solid state.

1.3.2.2.1 Solutions, solvation and liquid crystalline water

In general, fluids associated with the neural system have a molarity of greater than 0.5M. At these concentrations, the mobility (and other parameters) of the solutes are not the textbook values. Further, many ions and molecules of interest in biology aggregate with multiple molecules of water to form solvated molecular structures exhibiting their own unique properties. The migration of these larger aggregations, while in the electrically neutral state, within a given solution are more restricted than for the simple molecule. When ionized, the mobility of these materials are also reduced. For the remainder of this work, all solutions will be assumed to have a molarity exceeding 0.5M and will generally exhibit the properties of a gel or a liquid crystal.

Water itself exhibits drastically different properties as a function of temperature and state of confinement. The properties of water change significantly in the temperature range below four degrees centigrade as it becomes liquid crystalline in character prior to freezing into a true crystal. Water can also transition to the liquid crystalline phase at higher temperatures under other conditions. In both the liquid-crystalline and crystalline state, as well as in the liquid state, water exhibits the properties of a semiconductor. In fact the definition of pH is based on the semiconducting properties of water. One molecule in 10^7 becomes ionized at 25 C, even under conditions of perfect purity. This is an ionization rate per unit volume orders of magnitude higher than that of other common semiconductors.

1.3.2.2.2 The liquid-crystalline and crystalline form of water

Figure 1.3.2-2 illustrates the electronic configuration of the water molecule. It is a highly asymmetric molecule containing two pairs of non-bonded electrons (each pair shown as 2*e*) associated with the oxygen atom. This asymmetry makes the molecule highly polar electrically. This dipole moment is one of the highest found in chemistry and suggests the materials ability to dissolve other polar materials. The asymmetry also allows the molecule to support four, not three, linkages to other molecules, as shown in the next figure. In the dilute state, the bond angle and spacing between the atoms are shown on the right. Bockris & Reddy give the mean O–O distance for water as 2.92 Angstrom (without specifying the temperature) and 2.76 Angstrom for ice.
The tetrahedral form of the molecule is critical to the following discussion.

As noted above, water, in the liquid crystalline and crystalline states, exhibits electrical properties that differ significantly from those taught in lower university courses. Bockris & Reddy have struggled to describe and explain these

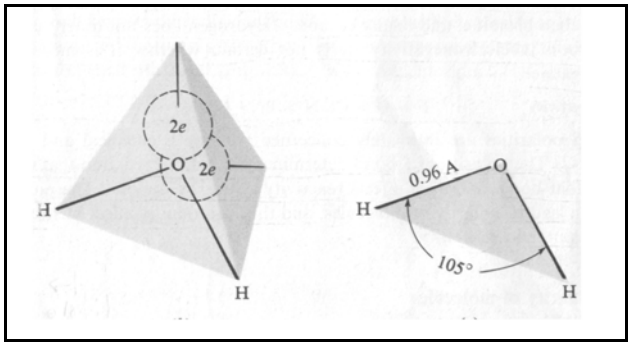

Figure 1.3.2-2 The stereographic form of the water molecule. Note the significant polar character of the molecule due to the two pairs of non-bonding electrons arranged asymmetrically with respect to the hydrogen atoms.

properties[238]. They include an interesting footnote below their Table 2.11 related to the limited knowledge available as late as 1970. A fundamental problem is their choosing to treat the water molecule as planar instead of tetrahedral as shown in their own figure. As a result, the lattice model of water in their figure 5-11 is that of $(H_1O)_n$ instead of $(H_2O)_n$. As a result, they describe a planar crystal with square lattice faces instead of the correct model with hexagonal lattice faces (and significant out of plane structures).

Figure 1.3.2-3 represents the lattice as drawn using Molecules–3D *Pro* as distributed by Molecular Arts.

The upper part of this figure shows three layers of the planar hexagonal lattice formed by water when in the form of semi-metallic water or ice. Note the first order asymmetry within each hexagonal ring. The oxygen atoms shown at position 1 are bound to their neighboring hydrogens within the hexagon by ionic bonds (two-tone solid links). However, the oxygen atoms at position 4 are bound to the adjacent hydrogens within the ring by hydrogen bonds (dotted link) associated with the unpaired electrons of the oxygen atom. Those at positions 2, 3, 5 & 6 are bound to the adjacent hydrogens by a mixture of bond types. As noted above, each oxygen atom acts as if it supports four valence linkages with adjacent hydrogen atoms, through a pair of ionic and a pair of hydrogen bond-like linkages associate with its non-bonded electrons. This is most easily seen in the lower row of oxygen atoms in the lower frame of the figure.

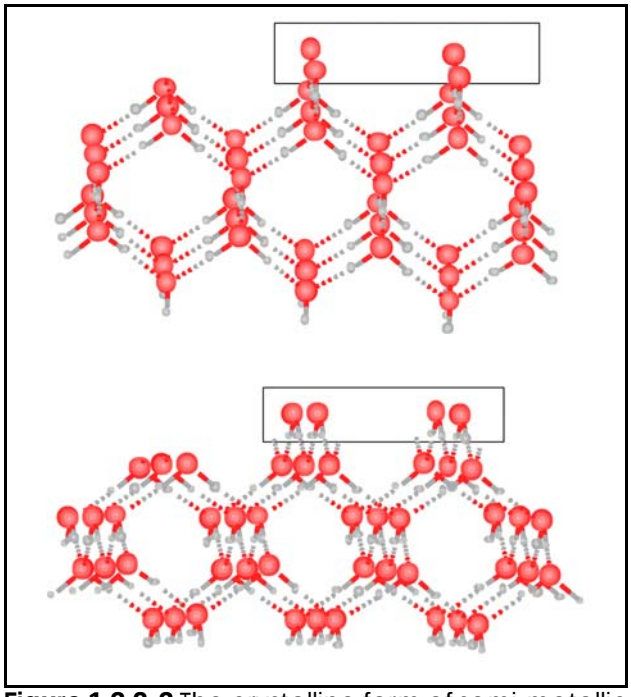

Figure 1.3.2-3 The crystalline form of semi-metallic water and ice. Three layers of the lattice are shown from two slightly different perspectives. The atoms in the boxes belong to adjacent lattices. Note, all of the oxygen atoms exhibit unpaired electrons with which they can form hydrogen bonds (dotted lines) with nearby hydrogen atoms. The two-tone solid lines represent ionic bonds between hydrogen and oxygen of the same molecular group. The dotted lines show hydrogen bonds between a hydrogen and an oxygen belonging to separate molecules. See text.

Individual sheets of liquid crystalline and crystalline water connect to adjacent sheets in a complex arrangement (not shown in the figure). The bonds to a sheet above tend to occur at every other oxygen. The bonds to a sheet below occur at the interdigitated oxygen atoms. This arrangement preserves the tetrahedral structure of the individual molecule. The bonds to adjacent sheets is even more complicated as shown within the box along the top of the bottom frame of the figure. Note each of the two oxygen atoms in each pair along the top of the bottom frame bond to two lattice rings in separate layers. As a result, *two* layers in one "row" of the crystal bond to *three* layers in the adjacent "row." This complex assortment of bonding techniques and locations provide a variety of unique properties to the overall liquid crystalline or crystalline forms of water.

Chaplin has suggested there are many electrons free to move about in the π-bond space of semi-metallic water of this type, suggesting far different properties for this material compared to simple water.

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[238]Bockris, J. & Reddy, A. (1970) Modern Bioelectrochemistry. NY: Plenum Press Chapter 5, pp 461-488

1.3.2.2.3 Hole forming and mobility in liquid-crystalline water

Bockris & Reddy review the potential mechanisms of charge transport within liquid crystalline and crystalline water based on the conventional practice of starting with parameters drawn from the electrochemistry of dilute solutions. They found the situation perplexing. They note what they call the abnormal mobility of the proton and show the use of Stokes Law to describe such mobility does not give reasonable results. They then describe several other putative mechanisms that they also find unsatisfactory. All of these involve the actual physical motion of a proton through a lattice. No discussion of the alternate approach found so satisfactory and used in all other sciences involving semiconducting materials.

The approach described here involves the motion of electrons within the valance band of the lattice in a way that superficially mimics the motion of a putative proton. The motion of charge is described symbolically as that of a "hole." In the case of water, the hole arises from the excitation of one of the non-bonding electrons associated with oxygen into the conduction band. The ionic group consisting of one oxygen and two hydrogens left behind now exhibits a net positive charge. However, **the group does not contain three hydrogen atoms** and **cannot** be described as a hydronium ion, H_3O^+. It is properly described as H_2O^* to designate the excited state of the oxygen atom. This polar group is now subject to any electric field applied to the crystal. However, it is a member of a crystalline structure and its physical movement is greatly constrained. Instead of moving, the group accepts an un-bonded electron from an adjacent neutral group. This previously excited oxygen is now neutral and the previously neutral oxygen is now excited. The effect is the same as if the "hole" on the first group had been transferred to the second group. The apparent motion of a hole in the direction of the electric field is actually due to the motion of individual electrons moving saltatorially in the opposite direction.

The net current through the crystal due to an applied field is found to consist of the mobility of free electrons within the conduction band and to holes within the valence band. The proportion of the total current due to each of these components is determined by the relative mobility of each component.

The weak bonds described above account for the tendency of liquid crystals of semi-metallic water and ice to exhibit significant ionization. They are associated with many of the oxygen atoms of the lattice and exhibit properties related to both hydrogen and covalent-like bonds. These weak bonds have a length of about 1.8 Angstrom in the crystalline form.

The minimum excitation energy required to generate an electron-hole pair in liquid crystalline (semi-metallic) water is difficult to determine from the literature. Sliney has provided data that bounds the value at endothermic body temperatures to less than 2.34 electron-volts based on measurements of the photoelectric effect[239]. From an analysis of the performance of the adaptation amplifier within the photoreceptor cells of vision (**Section 8.2**), the value is more likely less than 2.2 electron-volts.

The conduction band electrons and valence band holes exhibit different mobilities that can be measured individually using the Hall Effect. However, no independent values for these parameters have been located in the literature for liquid-crystalline water. As will be shown in **Section 6.3.5**, the mobility of the holes in the valence band (calculated based on the net current within an electrochemical cell, appears to be significantly higher than the mobility of the electrons in the conduction band at biological temperatures. As a result, the effective mobility of the holes can be estimated. Bockris & Ready gives the mobility of several species (using their early terminology in Table 5.2) as:

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[239]Sliney, D. Wangemann, R. Franks, J. & Wolbarsht, M. (1976) Visual sensitivity of the eye to infrared laser radiation. J. Opt. Soc. Am. vol. 66, no. 4

holes (their protons) in water	$3x10^{-3}$
ions (e.g., K^+) in water	$\sim 5x10^{-4}$
holes (their protons) in ice	10^{-1} to 1
ions (e.g., Li^+) in ice	$<<10^{-8}$

with units of $cm^2sec^{-1}V^{-1}$.

These values illustrate the difficulty with the Bockris & Reddy assumption that protons are the source of charge flow in water and ice. While the mobility of the dominant charges in water (presumed to be protons) are similar to that of potassium ions, the case is drastically different in ice (and liquid crystalline water). The holes have a mobility seven to eight orders of magnitude higher than lithium, the next larger ion to hydrogen. This mobility is about two orders of magnitude higher than ionic charge transport in liquid water. Their calculations using Stokes Law and other thermodynamic calculations do not support this high mobility. Such high mobility would not be expected of any ion in a crystalline material. On the other hand, the movement of holes (a euphemism for the saltatory motion of electrons from ionic center to ionic center) is not limited by the diffusion of actual ions. In fact, the mobility of holes is marginally increased by the shorter distance between ionic centers.

> **Bockris & Reddy close their discussion on page 474 with, "One fundamental conclusion can be drawn from this anomalous behaviour of migrating protons. Protons must conduct by a mechanism which is radically different from that used by other ions." The simple fact, well known from semiconductor physics, is that the apparent motion of positive charges is actually due to what are called minority carriers, holes in the electronic matrix that are saltatory in location due to the action of electrons moving through the matrix by jumping from one hole and creating another hole. Their underlying assumption that protons migrate is facetious. Protons do not move through the matrix like other ions.** Their definition of "a passing-the-proton game" is not supportable on technical grounds. Their figures 5.10 and 5.11 are archaic. Figure 5.11 can be represented by an electron leaving the matrix to neutralize the hydrogen ion on the left and simultaneously create a minority carrier, a "hole," near the left edge of the matrix. Subsequent saltatory electron motion from right to left can be interpreted (incorrectly) as an equivalent proton motion from left to right. Ions heavier than protons typically move (very slowly) through the interstatial spaces within a lattice. Bockris & Reddy present a section 5.3.3 (pages 476-487) attempting to define a different proton jumps based on "difficult" calculations. The best they claim is their calculations have "the right order of magnitude in comparison with experiment." They go on, "Thus, after the initial encouragement at finding a model which gives the correct order of magnitude, from the anomalous proton mobility, one begins to have doubts and hence second thoughts." They then proceed to consider additional potential models of proton migration that turn out poorly.
>
> Caution should be observed when discussing hydrogen bonding (or London bonding) in the following discussion. Proton migration is not the proper interpretation of the underlying fundamental mechanism.

In physics, chemistry, and electronic engineering, an electron hole (often simply called a hole) is the lack of an electron at a position where one could exist in an atom or atomic lattice. In most semiconductors, the effective mass of a hole is much larger than that of an electron. This results in lower mobility for holes under the influence of an electric field and this may slow down the speed of the electronic device made of that semiconductor. There are many sources describing the operation of holes in semiconductors[240],[241]. The book of record on the subject remains that of Shockley[242]. Both of these sources are focused on solid state

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[240]Hu, C. (2010) Modern Semiconductor Devices for Integrated Circuits. Chapter 1

[241]https://people.eecs.berkeley.edu/~hu/Chenming-Hu_ch1.pdf

[242]Shockley, W. (1950) Electrons and Holes in Semiconductors. Princeton, NJ: Van Nostrand

semiconductors rather than the liquid crystalline and coordinate bonded states of matter of interest here. Semiconductors distinguish themselves from metals and insulators by the fact that they contain an "almost-empty" conduction band and an "almost-full" valence band. This also means that we will have to deal with the transport of carriers in both bands. While not often addressed as a semiconductor, water is the most prevalent of semiconductors. The whole field of solution chemistry is dependent on the level of holes and electrons in water. The pH value of a water -based solution is a direct measure of the degree to which the solvent is conducting. **Figure 1.3.2-4** shows a conventional semiconductor physics view of hole (or minority carrier) conduction in any lattice. The effective mass and effective mobility of holes in liquid crystalline water is a matter of interest in this work (Section xxx). Table 1–3 of Hu (page 13) would suggest the effective mass of the positive hole would be in the range of 0.3 times the mass of the free electron mass (m_0 = 9.11 x 10-31 kg). Ratee & Breuer may provide more information. However, their work was very early, 1974. [xxx not in UCI or Google Scholar]

Dowben described the motion of "holes" in water conceptually, using the language of chemistry, in 1969[243] as did Lehninger in 1970. Dowben showed how the lattice unit ($H_9O_4^+$) supported the motion of an electrical charge without requiring the motion of any physical particle in **Figure 1.3.2-5**. This is accomplished by a hydrogen atom changing its bond allegiances. At top, the hydrogen to the right of the + sign exhibits a conventional bond with the oxygen on its left and a coordinate (or hydrogen, or London) bond with the oxygen on its right. In the middle frame, these bonds have reversed and the + charge is now found on the middle oxygen. The bottom frame shows the process repeated by the hydrogen to right of center. In these two steps, the charge has moved along a zig-zag path (angle of 104 degrees) equal to 5.36 Angstrom While he used the expression, "a series of sequential reactions involving proton jumps," it is clear no proton actually moved. What moved was the + charge, known in quantum and semiconductor physics as a "hole." This charge is actually associated with a pair of non-bonding electrons associated with the respective oxygen atoms.

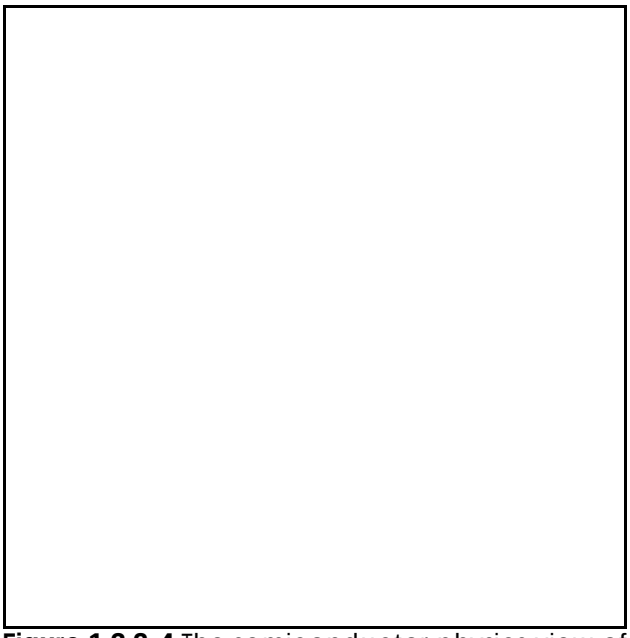

Figure 1.3.2-4 The semiconductor physics view of hole conduction STILL LOOKING.

Dowben notes this charge mobility is higher in ice than in liquid water.

[243]Dowben, R.(1969) General Physiology: a molecular approach. NY: Harper & Row

Lehninger[244] noted the mobility of the charge associated with the water lattice (semi-metallic water) is stable up to 100 centigrade and six times the mobility of either sodium or potassium ions in solution at 25 centigrade..

The very high mobility of holes in semi-metallic water is largely responsible for the temporal frequency response of the typical neuron. Holes are known to move through lattices of semi-metallic water in times smaller than 10^{-13} seconds per step. Hole mobility is a basic parameter of the electrolytic liquid crystalline semiconductor known as the Activa (Defined in Chapter 2).

1.3.2.2.4 Hole formation and mobility in water–Grotthuss mechanism

The Grotthuss mechanism is now a general name used within the physical chemistry community for the proton-hopping mechanism within aqueous solution. In liquid water the solvation of the excess proton is idealized by two forms: the H_9O_4+ (Eigen cation) or H_5O_2+ (Zundel cation). While the transport mechanism is believed to involve the inter-conversion between these two solvation structures, the details of the hopping and transport mechanism is still debated. Currently there are two plausible mechanisms:

1.Eigen to Zundel to Eigen (E–Z–E), on the basis of experimental NMR data[245],
2.Zundel to Zundel (Z–Z), on the basis of molecular dynamics simulation.
The calculated energetics of the hydronium solvation shells were reported in 2007 and it was suggested that the activation energies of the two proposed mechanisms do not agree with their calculated hydrogen bond strengths, but mechanism 1 might be the better

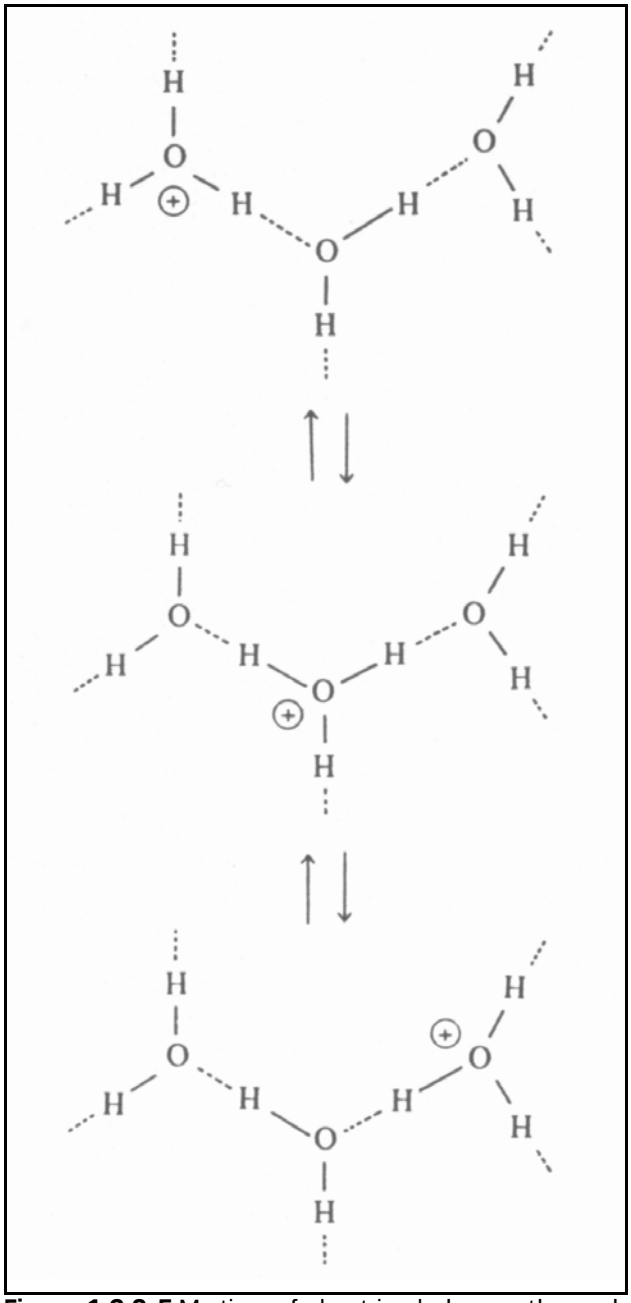

Figure 1.3.2-5 Motion of electrical charge through semi-metallic water. The three frames are of the same molecules. The frames have changed only through the Hydrogen atoms changing their allegiances. No motion of atoms has occurred. See text. From Dowben, 1975.

[244]Lehninger, A. (1970) Biochemistry. NY: Worth Publishing pp 39-44

[245]Agmon, Noam (1995). "The Grotthuss mechanism". *Chem. Phys. Lett.* 244 (5–6): 456–462

candidate of the two[246].[4]

Addition: By use of conditional and time-dependent radial distribution functions (RDF), it was shown that the hydronium RDF can be decomposed into contributions from two distinct structures, Eigen and Zundel. The first peak in g(r)[clarification needed] of the Eigen structure is similar to the equilibrium, standard RDF, only slightly more ordered, while the first peak of the Zundel structure is actually split into two peaks. The actual proton transfer event was then traced (after synchronizing all PT events so that t=0 is the actual event time), revealing that the hydronium indeed starts from an Eigen state, and quickly transforms into the Zundel state as the proton is being transferred, with the first peak of g(r) splitting into two[247].

1.3.2.2.5 Hole formation and mobility in nucleic acids

Based on the above paragraphs, it appears the theoreticians of physical chemistry and of quantum mechanics do not speak or share ideas with each other. The concept of a hole as found in semiconductor physics is beginning to appear in the biological sciences.

Holes were reported in relation to DNA research beginning in the 1990's. Bixon, Giese et al. presented a group of papers under both names as lead beginning in 1998[248]. They identified the motion of charges along the nucleic acid chains and sought to evaluate the frequency and distance involved in these motions. Based on their chemical training, the describe "hole hopping" in the context of holes as "positive ions (H^+)." They describe the rate of hole hopping as 10^9 hops/sec over distances of at least 300 ± 70 Angstrom. They did not report a mean velocity for their holes. By 2005, Conwell was providing more information concerning hole hopping[249]. She noted that the Bixon & Giese team had considered the holes as localized whereas she found them to be delocalized and the hopping was associated with a "polaron," a term encountered frequently during an earlier day in semiconductor physics. The polaron first appeared in 1933. Today, a polaron is a quasi-particle composed of a charge and its accompanying polarization field within a polarizable medium (typically a semiconductor lattice). Conwell noted, "An important set of experiments carried out recently by Barton and colleagues showed that, contrary to the assumptions of Giese, Bixon, and Jortner and many others, the wavefunction of a hole is delocalized over a number of bases, which may include cytosines (Cs) and presumably thymines (Ts) as well as Gs and As. The finding of delocalization is significant because a hole on C or T has much higher energy than a hole on G or A."

Grozema et al. noted the intense interest in charge migration in DNA and developed ideas related to hole conduction along DNA molecules in 2002[250]. They developed a variety of values depending on the analytical technique and assumptions made. The spread is large.

Stewart has shown an interesting hydrogen bonding relationship between the nucleic pairs in

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[246]Markovitch, Omer; Agmon, Noam (2007). Structure and energetics of the hydronium hydration shells. *J Phys Chem* A 111 (12): 2253–6

[247]Markovitch, Omer; et al. (2008). Special Pair Dance and Partner Selection: Elementary Steps in Proton Transport in Liquid Water. *J. Phys. Chem*. B 112 (31): 9456–9466

[248]Bixon, M.Giese, B.Wessely, S. Langenbacher, T. et al. (1998) Long-range charge hopping in DNA *PNAS* vol. 96(21), pp 11713–11716

[249]Conwell, E. (2005) Charge transport in DNA in solution: The role of polarons *Proc Nat Acad Sci USA* vol 102(25), pp 8795-8799

[250] Grozema, F. Siebbeles, L. Berlin, Y. & Ratner, M. (2002) Hole Mobility in DNA: Effects ofStatic and Dynamic Structural Fluctuations *Chemphyschem* vol 6, pp 536

DNA[251]. It stresses the multiple hydrogen-bond nature of the relationship between both thymine and adenine and between cytosine and guanine. As a result, these base pairs have almost identical stereographic shapes..

The quasi-particle is frequently described using the ball on a rubber sheet model also used by Einstein to describe a mass warping a space-time continuum. If the number of electrons or holes is relatively high, as it is in most electronic semiconductor devices, the distortion (polarization) of the lattice is averaged out and only the presence of the charges need be considered.

Conwell described two types of polaron. The second type was evaluated in an electrical field of 5.8×10^3 V/cm. This value is slightly above a typical value for semiconductor mobility experiments because the mobility in n-type silicon is a function of the field for $\xi > 10^3$ V/cm. At 5.8×10^3 V/cm, the charge was found to move seven bases or 2.4 nm in 138 picoseconds for a mean drift velocity of 2×10^3 cm/s. The mobility of the charge is given by the drift velocity divided by the field strength or $\mu = 0.344$ cm^2/V-s. This is a very low value compared to that of silicon (500-1300 cm^2/V-s) or germanium (1800-3800 cm^2/V-s). The low value may be associated with the fact the DNA molecule does not constitute a regular three-dimensional lattice.

1.3.3 Electrostatics and the Principle of Electrical Neutrality

The principle of electrical neutrality plays a major role in the study of both chemistry and electricity. **Unfortunately, the name is used for two distinctly different concepts**.

In chemistry, the Principle of Electrical Neutrality is used to describe the electrical potential established between two solutes that are allowed to equilibrate on opposite sides of a semipermeable membrane. It is based on the equilibrium potential or Nernst Potential[252]. The solutes may contain only one ionizable species or many ionizable species. However, Matthews makes the important caveat. "The Nernst equation only applies to one ion at a time and only to ions *that can cross the barrier*." A problem exists when discussing neurons based on this caveat. The area of any biological bilayer membrane involved in neural signaling is not semipermeable to ions. This diffusion based version of the Principle of Electrical Neutrality does not apply to impermeable lemma separating two solutes regardless of the electrolytes present.

In electricity, the Principle of Electrical Neutrality is used entirely differently. The electromagnetics based version of the Principle of Electrical Neutrality applies in all cases regardless of the nature of any individual material within the region being examined. It also applies when part(s) of the region is filled with an ionized plasma(s) (whether a gas or a liquid). Two concepts are involved.

Gauss's Law for Electric Fields plays an important role in describing any electrical field. It is most easily applied to static electrical fields. The subject is treated thoroughly in Kraus[253]. The proper application of this principle to the neural conduit requires careful analysis. The formulation stated by Matthews, and noted above, is needlessly narrow. The situation under discussion involves a conductive electrolyte within an insulating or quasi-insulating membrane. By definition, a boundary layer separates these materials. There are two separate principles that must be applied to this situation. The first concept is based on one of Maxwell's Equations of Electromagnetics. These laws are usually presented in differential form. When presented in integral form, the first law is known as Gauss's Law for Electric Fields; *the surface integral of the normal component of the electric flux density vector, **D**, over any closed surface equals the charge enclosed, Q* (using the rationalized mks system of units). The second concept is based on another interpretation of one of Maxwell's Laws. *The total*

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[251]Stewart, I. (2011) Mathematics of Life: Unlocking the Secrets of Existence. London: Profile Books pp94-98

[252]Matthews, G. (1991) Op. Cit. pp 27-29

[253]Kraus, J. (1953) Electromagnetics. NY: McGraw-Hill. Chapters 1 & 2.

*net charge **within** any complete conductive or semi-conductive system must be zero*[254].

> Note that the first concept applies to any closed surface, whether it contains conductive material or not. The second only applies to a conductive volume.

Based on the above two concepts, the potential between the inside of the membrane and the outside of the membrane is given by the total net charge enclosed by the membrane. The first concept does not concern itself with how the charge is distributed within the membrane. The second concept calls for the total net charge within the conducting electrolyte to be equal to zero. This concept does not concern itself with the total charge within the membrane, only that within the bulk electrolyte. Any excess electronic charges within the boundary of the electrolyte cannot exist there in the steady state. The individual electrons will repel each other. The result is that these electrons will form a shell at the boundary layer between the electrolyte and the insulating membrane. Thus, the charge within a membrane surrounding a conductive electrolyte need not be zero. Excess free electrons can be present, and potentially move, along the surface of the boundary layer between the membrane and the electrolyte. However, they cannot move through the electrolyte without an exchange of charge between the constituents of the solution.

In the configuration at hand, it is Gauss's Law of Electric Fields that is important.

> **No requirement exists for the net charge within a conduit membrane to equal zero.**

On the other hand,

> **A requirement does exist for the net charge within any equilibrated electrolyte to equal zero**.

The net charge within a conduit can be changed by mechanisms independent of the ionic particles present in the plasma.

Finally, the specific types of charges within the electrolyte are of no importance in this situation. It is imperative that the experimentalist recognize the possibility of charge within a closed fundamental membrane that is not related to the level of ionization within the electrolyte. This charge is found in the boundary layer between the dielectric membrane and the electrolyte.

The Principal of Neutrality in electronics is more fundamental, but does not conflict with the Principal of Neutrality in chemistry.

1.3.4 The ion-channel work of Eisenberg

Eisenberg, of Rush University, has been attempting to unravel the operation of the neurons for a long time based on the concept of ionic flow along a channel. He is widely published and widely known within the physical chemistry community, but much less so within the broader neuroscience community. His work is beginning to converge on some of the work in this material. However, his work is based on the perspective of a physical chemist entering the realm of more complex organic structures than usually encountered in man-made plants based on the principles of physical chemistry.

Eisenberg's writings are extensive, but those of the 1990's through the present are of the most interest here. His paper on "crowded charges" is very useful, particularly section XIII describing the remaining unsolved problems associated with his primary hypothesis[255]. There is an interesting introduction to this material. Some quotations follow:

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[254]Kraus, J. (1953) Op. Cit. pp 68-70

[255]Eisenberg, B. (2009) Crowded charges in ion channels *In* Rice, S. & Dinner, A. *eds*. Advances in Chemical Physics, Vol 148, 1st Ed. NY: Wiley & Sons *also at* http://arxiv.org as arXiv 1009.1786v1

> Page 181 "Indeed, solving unsolved problems in a mature science like physical chemistry may be important for its future, as Stuart Rice hinted. Technological advances are crucial for an infant science like computational biology, and an adolescent science like molecular biology. They may be somewhat less important for an adult science like physical chemistry. Scientists understandably can easily overlook—thereby denying—the unsolved problems of past generations. Scientists, like all people, have enormously strong mechanisms of denial necessary for their collective survival."

As usual, definitions are critical in inter-disciplinary work. He frequently speaks of concentrations of charge in solution under conditions that suggest non-equilibrium electrostatic conditions, i.e., electrolytic plasmas. He also speaks of small channels. Channels with the molecular size diameters are frequently described as pores in other literature to distinguish them from the very small but immensely larger (tubes of 0.1 to 1 micron diameter.) associated with cytological structures. Table I of his paper (page 114) summarizes some of the complexities of discussing ionic channels in biological systems. ***Eisenberg's focus is on ionic channels defined as pores in the more general biophysics and neuroscience literature.***

Eisenberg regularly attributes more difficulty to solving the problems of non-equilibrium concentrations of ions than sending a man to the Moon (attributed to Kunz), and similar aphorisms.

> "From my outsider's point of view, the unsolved problems in physical chemistry start with some of the oldest. The unfortunate fact is that Werner Kunz' remark previously cited (p. 10 of Ref. [654]) is an understatement."

These aphorisms can appear naive to someone actively working on the detailed description of the flow of gases (and ions) in a rocket motor exhaust, or in the immediate aftermath of the explosion of an atomic bomb. The largest computers in the World have long been focused on these most difficult problems, and achieved considerable success relative to the work of the channels and pores community..

Another aphorism that is difficult to defend in this work, but widely repeated in the pedagogical literature, is;

> "III. ACTION POTENTIAL IS A COOPERATIVE PHENOMENON
> One of the most important interactions of channels is the cooperative behavior that produces the main signal of the nervous system, the action potential." [Page 98]

It has been shown by a variety of broadly experienced and well published investigators that less than 5% of the neurons in any individual chordate neural system produce action potentials. The other 95% generate analog signals that are passed within individual engines of the system. As an example, each human ocular contains not less than 15 million neurons, only about one million of which are ganglion cells that generate action potentials.

1.3.4.1 The deductive approach of Eisenberg

Eisenberg frequently focuses on "reduced models." These are by definition simplified models and frequently are considered isolated or "floating models" in this work. His central theme in the crowded charges paper appears to be that variational methods of analysis[256] will provide the ultimate solution to the problems of charge flow within biology.

> "The first unsolved problem then is to use a variational method to (try to) compute the properties of mixtures of electrolytes, starting with the simplest colligative properties, moving to equilibrium properties in general and then to nonequilibrium properties of diffusion and conductance in mixed solutions." [Page 182]

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[256]Eisenberg, R Hyon, Y. & Liu, C. (2010) Energetic Variational Analysis EnVarA of Ions in Calcium and Sodium Channels *Biophysical J* vol. 98(3), suppl 1, pp 515+

> "A variational approach attacks all these issues all at once, but it is in its infancy, only a few years past conception, and so its success it not yet known." [Page 188]

The Eisenberg philosophy is in sharp contrast to the much simpler deterministic features of the biological system exploited in this work. It is not clear whether the gels (liquid crystalline materials) found in most neural cells are included in the above quotation when one speaks of "diffusion and conductance." These gels (>10M) are clearly not low concentration solutions.

Eisenberg's philosophy appears to continue to focus on the deductive approach to the Scientific Method, ostensibly that of Popper, but without the falsification aspect. Page 117 asserts,

> "H. The Scientific Method and Channels
> Guess a model; check it; fix it, and add more if needed."

He uses the expression "guess and check" repeatedly in the development of a null hypothesis. In his philosophy, falsify is replaced by the more proactive term "check it." This variant reflects the anticipation that the hypothesis can be built upon without rejection.

In retrospect, this work has focused on (or relied upon) an expanded philosophy involving both the inductive and the deductive portions of the Scientific Method ala Marmarelis (**Section 7.1.1**). Following the data is more important than trying to guess a model based primarily on laboratory experience or intuition.

1.3.4.2 A carefully worded and very important caveat

Eisenberg is careful to point out an important facet of exploratory research;

> "The reader should be warned that most of the current–voltage or current–voltage time recordings in the literature are not directly relevant to the theories described here. The theories described here are for currents through a single channel protein molecule of a single type with controlled voltage and concentration across it. Such measurements are hard to make. Most recordings in the literature are from ensembles of channels, measured in what is often called the "whole cell recording" using the patch clamp method [133, 136] to measure current from whole cells, not from single channels. These measurements are of current through the "conductances" of many channels, perhaps through many chemically different types of channels that have different structures, functions, and genes." [Page 152]

It should be noted that all (or nearly all) of the data included in his crowded charges paper are from laboratory experiments at the scale of the patch clamp method.

1.3.4.3 Attempts to define an active electronic device within an ion channel (pore)

Eisenberg has prepared a series of papers focused on defining the requirements for and the potential development of an active device within the neural system based on ionic flow within a channel. Interestingly, several of the figures in his papers, on crowded charges and the papers enumerated below, involve data also cited in this work as fundamental to understanding the neuron.
Eisenberg appears to describe the diameter of single charged ions when in solution using their diameters when in the gaseous state. This work has found that ionic sodium, as an example, cannot exist as a simple ion in solution. It immediately coordinate bonds with typically six, but at least four, water molecules. The result is a much larger minimum structure than the two Angstrom diameter used in his figures 8 & 9 in the crowded charges paper (and presented many other places in the literature). As shown in the material on gustation in this work, the coordinate chemical complex of the sodium ion in solution is typically ten Angstrom in diameter (**Section 8.5.4** xxx), unless forces or conditions are present that can overcome these coordinate bonding forces. Eisenberg was careful to point out his calculations

assumed a "non-hydrated sodium ion." It was not obvious from the text how this condition was obtained in a highly concentrated aqueous solution.

In the crowded charge paper, copyright 2012, Eisenberg noted;

> "B. Gating Processes
> This chapter does not deal further with the gating process that opens channels because simulations of gating are not quite in our grasp and the physical basis of gating has not yet been described by reduced models. (Historical note: despite their numbers, models based on arrows [9, 257, 258] instead of physics have not proven useful and make little connection to the physical properties of channel properties or ions. A British physiologist, who in fact had written a number of arrow models, once told me "You can tell how much is known by how few papers are written on a subject. When it is understood, little more needs to be said." [Page 106]

Two recent papers appear to summarize his concept of the active devices within a neuron[257,258]. Based on a patent application filed in 2003, his ideas remained broad as to the actual structure of any biological transistor, whether it could be a field-effect device, a junction device or a combination of both.

The "Living transistor: . . ." paper (2005) defines Eisenberg's view of an ion channel;

> "Ion channels are proteins with a hole down the middle embedded in cell membranes. Membranes form insulating structures and the channels through them allow and control the movement of charged particles, spherical ions, mostly Na+, K+, Ca++, and Cl-."

Eisenberg proceeds with a discussion of the widespread use of man-made transistors and then makes a bold statement;

> "While physicists and engineers were creating transistors in germanium and silicon, biophysicists—that I call channologists—were discovering life's transistors in biological cells. These analogs of transistors are specialized proteins that control electricity (and much else) in the biological tissues and cells of our wrist or ear. Life's transistors are ion channels."

Eisenberg offer's little beyond the claim in the last line of the quotation. The paper ranges over a variety of properties of solutions, of proteins and potential densities of ions in different situations. However, it never describes a physical device that qualifies as a biological transistor. He asserts his analogy between transistors and ion channels only holds if the ion channel is open (a clearly trivial case). The paper does little to define a biological transistor. It contains no equations and only two figures, a reconstruction of a protein based on X-ray crystalography and a very simple cartoon of a "cell."

The "Living Devices: . . ." paper (2012) is primarily a discussion of his philosophy of what should be done to describe an active neural device, not how to define one, or his hypothetical for such a device. The paper contains no hard data or any figures.

1.3.5 Electrostenolytics

As its name implies, electrostenolytics is the study of an electronic process occurring on a surface in an electrolytic environment. The field is relatively narrow in its application to man-made systems and its literature is therefore immature. Fuel cells are the dominant man-made application at this time. The process involves a redox reaction and can involve the transfer of fundamental charges to or from the substrate. Electrostenolytics also has a commercial application in the technique of electrodeless electroplating.

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[257]Eisenberg, B. (2005) Living transistors: A physicist's view of ionic channels

[258]Eisenberg, B. (2012) Living Devices: The Physiological Point of View *published via* http://www.arXiv.org.

Electrostenolytics offers an alternate mechanism to that of an enzymatic reaction in biology.

Whereas caricatures of the process frequently show external electrodes contacting two electrolytes separated by a substrate[259], this is not the simplest form of electrostenolysis. In its simplest form, no external electrical circuit is required and only one electrolyte is involved. The process frequently involves only a local electrolytic current loop similar to that employed in the rusting of metal in sea water. The "classical form" of electrostenolytics defined by Tien, Karvaly & Shieh is based on descriptions dating from the 1860's and represents a much more complex set of reactions[260]. These reactions involve both currents through the electrochemical cell and redox reactions at the membrane surfaces. Habib & Bockris provide a more comprehensive discussion of the process, including the static condition where no current flows through an external circuit[261]. They also make comparisons to the field of electrochemistry involving fuel cells. Their discussion and figure 5 also show that only one redox process needs to be present at a time. Siddiqi & Tien readdressed the subject of electrostenolysis in 1983 and provide references[262].

When the electrostenolytic process involves a stereo-specific chemical reaction, it may more properly be described as an electro-chemico-stenolytic process. This is the case in the process used to provide electrical power to the neurons and the neural system. It appears to be the case in a great many mechanisms of bio-organic chemistry (including pharmacology).

When the process produces free atoms at one surface of the substrate, these materials may be deposited on the surface depending on their solubility in the electrolyte. Discolored or mirrored surfaces may be formed depending on the surface texture of the substrate. The result of the process is also of interest in diagnosis of pathological conditions of the retina (See **Chapter 18** of **Processes in Biological Vision**).

The electrostenolytic process is critical to the operation of each conduit and Activa of the neural signaling system. The typical chemical reaction involves the conversion of glutamic acid (glutamate) into GABA with the release of CO_2 and an electron. This electron appears on the inner surface of the neurolemma. There, it generates a potential in conjunction with the capacitance of the lemma. The electrostenolytic process is detailed in **Chapter 3**.

1.3.5.1 The reverse electron transport phenomenon

The concept of a reverse electron transport phenomenon of biology is not supported here. This section is provided to explain why. The concept is similar to the never proven and unneeded concept of the Independence Principle introduced by Hodgkin & Huxley.

Elbehti et al. have provided what they call "first evidence of an uphill electron transfer through a bacteria membrane[263]. They only provide a caricature showing iron oxidation

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[259]Tien, H. (1974) Bilayer lipid membranes. (*also in* Marino, A. (1988) Modern bioelectricity. NY: Marcel Dekker, Chap 7 written by Zon & Tien, pg 191)

[260]Tien, H. Karvaly, B. & Shieh, P. (1977) Electrostenolytics in bilayer lipid membranes. J. Coll. Inter. Sci. vol. 62, no. 1, pp. 185-188

[261]Gutmann, F. & Keyzer, H. (1986) Modern bioelectochemistry. NY: Plenum Press. pp. 73-89

[262]Siddiqi, F. & Tien, H. (1983) Electrochemistry of bilayer lipid membranes in Milazzo, G. ed, Topics in Bioelectrochemistry and Bioenergetics, vol. 5 NY: John Wiley & Sons pp 157-221

[263]Elbehti, A. Brasseur, G. & Lemesle-Meunier, D. (2000) First Evidence for Existence of an Uphill Electron Transfer through the bc1 and NADH-Q Oxidoreductase Complexes of the Acidophilic Obligate Chemolithotrophic Ferrous Ion-Oxidizing Bacterium *Thiobacillus ferrooxidans. J Bacteriol* vol 182(12) pp 3602–3606

providing a soluble electron carrier that is then able to interact with various ligands or enzymes embedded in the plasma membrane. They measured the relative absorbances of selected products of the reactions to support their lengthy discussion.

Madigan et al. have defined a purported phenomenon in the biology of microorganisms[264]. They define a "reverse electron transport–the energy-dependent movement of electrons against the thermodynamic gradient to form a strong reductant from a weaker electron donor." This definition was presented without accompanying graphics (except for caricatures).

Solomon & Bard have presented a different description in their introduction[265], "We use the term 'reverse electron transfer' to describe a redox reaction in which an electron is transferred in an apparently "uphill" direction from the reduced form (R_1) of a couple with a more positive standard reduction potential to the oxidized form (O_2) of one with a lower reduction potential. Such thermodynamically unfavorable reactions are common in living systems and have been known for over 35 years." O_2 in this case refers to an oxygen in the second reaction and not the molecule. While their title is liquid/liquid interface, their example is two liquids separated by a biological membrane (which is not defined in detail).

These definitions can apparently be applied to a variety of situations. They can be read as more phenomenological than mechanistic. The case illustrated by Solomon appears more complex than that involved in many cross membrane transfers. When applied to a biological membrane, they appear to be based on the assumption that the electrical potential across a cell membrane is somehow intrinsic to the membrane or due to a negative source associated with the interior of the cell. **Figure 1.2.2-2** showed the basic functional arrangement of a cell functioning as a neuron. Looking only at the axolemma compartment is of interest here. A later section in this chapter will show how the type 2 lemma of a cell is a reverse biased diode. Looking more closely at the nominal cell membrane consisting of both type 1 and type 2 membrane in **Figure 1.3.3-1** provides considerable insight.

The left frame of the figure shows a type 1 biological membrane biased by an unknown source. The upper surface contacts the external fluid matrix. The lower surface contacts the plasma of the cell. The membrane acts as a totally passive, high quality capacitor. The second frame shows a type 2 membrane similarly placed and also biased by an unknown source. The type 2 membrane is represented by its electrical equivalent, a diode oriented as shown. With the inside of the membrane at a negative potential, the diode is reverse biased and no current flows through the diode.

The third frame shows a type 2 membrane, oriented as above, and its electrical equivalent but with an electrostenolytic source between the surface of the membrane and the fluid

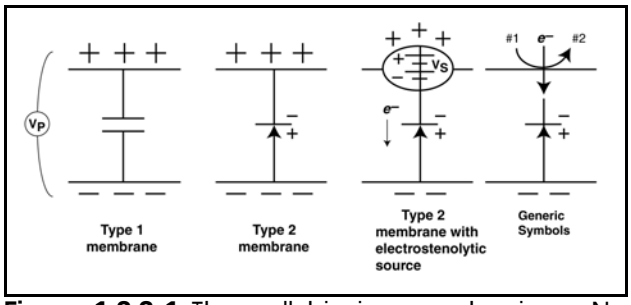

Figure 1.3.3-1 The cell biasing mechanism. No current flows in the left or middle frames, the diode is reverse biased. The electron current in the type 2 membrane on the right is a forward electron current because the potential V_S is larger than V_P. The net electrical field within the membrane causes the diode to be forward biased and electron current to flow in the direction shown (in consonance with the thermodynamic gradient). See text.

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[264]Madigan, M. Martinko, J. & Parker, J. (1997) Biology of Microorganisms, 8th Ed of Brock. NY: Prentise-Hall page 474

[265]Solomon, T. & Bard, A. (1995) Reverse (Uphill) Electron Transfer at the Liquid/Liquid Interface *J Phys Chem* vol 99, pp17487-17489

surround. The electrostenolytic source is oriented to place a negative potential on the negative terminal of the diode. If the electrical potential of the plasma is less than the potential of the electrostenolytic source, current will flow through the diode as shown and increase the negative potential of the plasma to that of the source. The circuit is completed by the charge accumulating on the capacitor formed by the adjacent membrane. This is the actual mechanism of biasing the plasma of a cell. While Madigan et al. and Solomon might describe this current as a reverse electron current (flowing toward the negative potential of the plasma), it is clearly seen that it is a forward electron current through a forward biased diode formed by the type 2 membrane because the electrical field due to V_S (the source of energy) exceeds the electric field due to the plasma potential, V_P, within the membrane. The net electric (thermodynamic) field is opposite to the electric (thermodynamic) field assumed by the above authors.

Both Madigan et al. and Solomon used a mixed analogy. They speak of energy (in kilo-Joules if quantified) and fields conceptually as volts/membrane (or volts/cm if quantified). By using only one set of terminology, the source energy can be expressed in electron-volts, the source potential in volts and the field in volts/cm as done in the figure.

The fourth frame shows the symbology that will be used here. The arc represents the oxidation of any agent of interest with the injection of an electron into and through the membrane via the diode which is forward biased if the potential representing the energy released by the oxidation exceeds the plasma potential. In the CGS system, the numerical value of the potential in volts is equal to the numerical value of the energy in electron-volts.

The above figure can also be used to explain photosynthesis and industrial extraction of ores by microbial leaching without invoking the conceptual "reverse electron transport" phenomenon. The electrical source is associated with the photon absorber complexed with the hydrophilic head of the phospholipid on the outer surface of the membrane. The energy of the absorbed photon should be expressed in electron-volts. The cutoff wavelength for photosynthesis is then given by the wavelength at which the source potential, V_S, no longer exceeds the plasma potential, V_P. This is known as the Einstein Effect in semiconductor physics, for which he won his only Nobel Prize.

The above figure can also be used to describe the long wavelength photosensitivity of the animal eye but in a slightly different context. See **Section 17.2.2.5.2** in "Processes in Biological Vision."

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The electrostenolytic process is well recognized in the studies of metabolism. However, it is normally described using a different terminology specific to that field. Berry, honoring the 80th birthday of the patriarch of that field, Sir Hans Krebs, has provided an extensive article that includes most of the elements of electrostenolytics found associated with the neural system[266]. In that context, they describe the redox reactions on a membrane surface as causing the transfer of electrons across the membrane. The transfer occurs in opposition to a previously present electrostatic potential. They describe this process as "reverse electron transfer" and treat it as a unique situation instead of recognizing that it is the normal situation in any electromotive source. The fact is that the metabolites are acting as the electrolyte in a battery in generating the electrostatic potential from the flow of electrons. They also note the reversibility of the reaction by discussing redox cycles. The reversibility in the case of neurons is limited by the tendency of the GABA and CO_2 to diffuse away from the site.

When all is said, Berry offers an important statement: "It is concluded that energy-dependent reverse(d) electron transfer is a fundamental feature of the living state. It provides a mechanism for the reversal of thermodynamically unfavorable redox reactions by energy

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[266]Berry, M. (1980) The function of energy-dependent redox reactions in cell metabolism. FEBS Letters, vol. 117, supplement, pp. K106-K119

coupled steps, distinct from the forward reactions." Paraphrasing, he continues, these redox reactions maintain the cell in a state removed from chemical equilibrium and helps support a balance between degradative and synthetic processes. Finally, "It would appear that living systems can conserve energy derived from degradation of foodstuffs, not only by synthesizing new chemical bonds, but also by storing separated charge. The energy conserved in the electric field so created can be used to drive . . . reversed electron transfer . . . This interaction of chemical and electrical energy within the cell makes living systems highly efficient units operating close to equilibrium."

Ohki has said; "Until recently the possibility of electron conduction in living systems was not seriously considered, with perhaps a few notable exceptions to be mentioned below. Traditionally, the origin of electrical potentials observed in living systems has been attributed almost exclusively to ionic permeability." He goes on to discuss the electron transfer now assumed in photosynthesis[267].

Beginning in the 1990's, the study of reverse electron transfer has blossomed into its own specialty within the family of electron transfer processes. It has been intensively studied within the mitochondria of animal cells. It has been studied most intensively in the plasma membrane of light sensitive bacteria. These studies have developed the "electron hole" as a significant feature of DNA processes. It has also described the transport distance as at least 25 Angstrom and suggested it may occur by "tunneling" or by hydrogen bonding. .

1.4 The physical chemistry of biological membranes

Developing the physical chemistry of the BLM without recognizing the quantum-mechanical conditions that are involved is impossible. These will be addressed below in detail.

Stein noted a problem in 1967 when discussing biological membranes[268]. "The very definition of the term 'cell membrane' is a matter of contention. In fact, we cell biologists use the term 'cell membrane' or 'plasma membrane'—we shall use these terms interchangeably— in at least three quite different senses. In the anatomical sense, the cell membrane is the external limiting region of the cell. . . ." "In the biochemical sense, the cell membrane is a 'fraction' of the cell prepared by the now classical techniques of selective disintegration of the whole cell, followed by differential centrifugation." "Finally, in the physiological sense, the 'cell membrane' is a hypothetical structure invented to explain certain data on the 'permeability of cells' and to explain other data on the distribution of metabolites and other molecules between the cell and the fluid in which the cell is immersed." *It is time to prohibit such license among investigators.* Only real plasma membranes are of interest in this work. Any "hypothetical structure" must conform entirely with reproducible experimental facts.

Weissmann & Claiborne edited a comprehensive volume in 1975[269]. While quite wide ranging, the chapters are quite dated. The book remains a compendium of information and data, but almost every concept must be reviewed in the light of current knowledge. [xxx review this volume in my library in the light of the Electrolytic Theory of the Neuron.]

The focus of this section will be on the properties of a simple (type 1) BLM in an electrolytic environment. Such a membrane is associated with the fundamental lemma of a cell. It is differentiated from a "mosaic membrane" that may contain inclusions, and a "skin" that consists of multiple cells and/or other structures. The mosaic membrane is defined as a type 3 membrane in this work.

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[267]Ohki, S. (1985) The origin of electrical potential in biological systems *in* Srinivasan, S. et. al. Comprehensive Treatise of Electrochemistry, vol. 10, Bioelectrochemistry. NY: Plenum Press pg 83+

[268]Stein, W. (1967) Op. Cit. pp1-2

[269]Weissmann, G. & Claiborne, R. (1975) Cell Menbranes: Biochemistry, Cell Biology & Pathology. NY: HP Publishing

Mueller & Rudin addressed the natural evolution of cellular membranes in considerable technical detail[270]. They show why the conventional wisdom of their time (based on protein walled cells) was most probably wrong. The protein wall of a plant cell is actually an extra-cellular feature with the lemma inside of it. There is no protein wall in an animal cell. Both Mueller & Rudin, and Ehrenstein, note the appearance of the liquid crystalline molecular bilayer membrane under the electron microscope. Mueller & Rudin describe it as palisade like. Ehrenstein in Adelman describes the appearance as railroad tracks. Both of these analogies are supportive of the liquid crystalline form of the lemma.

The initial requirements on a biological membrane are several;

1. To provide chemical and electrical isolation of the interior of the cell from the external environment.
2. To support homeostasis.
3. To provide an excess electrostatic charge within the cell plasma membrane in order to support the nominal shape of the cell.
4. To support electrical signaling when required as part of a neuron.

The first requirement is met by forming the lemma as a back-to-back pair of amphiphilic molecular layers, the commonly encountered phospholipid bilayer membrane. Such a structure is hydrophilic at its exterior surfaces but highly lipophilic internally. Such a structure is impervious to virtually all polar and nonpolar molecules and any electrical charges.

The second requirement is met by specialized regions of the fundamental membrane probably consisting of proteins, embedded in and spanning the membrane, capable of transporting neutral molecules through the membrane probably via a complexing of the protein and the molecule to be transported.

The third requirement is strictly a structural one. The mutual electrostatic repulsion of the excess electrical charges forces the membrane into a nominally spherical shape.

The fourth requirement is associated with the neural function. A mechanism must be provided for varying the potential between the inside and outside of the membrane in a controllable manner.

Three principal theories of the biological membrane have been used during the last century:

A. A chemically undefined membrane with an internally homogeneous structure. The structure is semipermeable to the flow of various ions and molecules. Little or no consideration is given to its permeability to the elementary electron. This is the membrane of Nernst, Donnan & Goldman. This type membrane dominated biological discussions, including those of Hodgkin & Huxley, from its initial description in the third quarter of the 19th Century until the membrane was shown to be impermeable to ions during the second half of the 20th Century.

B. A phospholipid based bilayer membrane as an internally asymmetrical structure. The structure is semipermeable to the flow of electrons but impermeable to ions and other molecules. This is the simplest membrane of current biology and neuroscience. It became popular during the second half of the 20th Century and is of greatest interest in this chapter.

C. A lipid membrane of poorly defined structure with protein inclusions. The inclusions provide an array of putative pores or channels. These devices support the passage of various ions or molecules through the membrane. This type of membrane was defined conceptually during the second half of the 20th Century as it became clear alkali metal ions could not pass through the simple symmetrical bilayer membrane.

Shepherd drew a conclusion related to the last theory without considering the second. "The

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[270]Mueller, P. & Rudin, D. (1969) Op. Cit. pp 237-240

rapid rate of ionic flow occurring during the generation of an action potential is far too high to be achieved by an active transport mechanism, but rather results from the opening of ion channels[271]." This statement was speculative and based on limited visibility. While many caricatures of this type of membrane exist, little or no data from the electron microscope exists to support the association of this type of membrane with the neural signaling process.

Goldman, writing in Adelman, presented a good discussion of a scientific model of a biological lemma[272]. He couches his material within his view of a model. However, his perspective might be considered too narrow. His assumption is that substantial size particles must move through the membrane but does not recognize a difference between the signaling and other metabolic functions. He does provide a series of lists describing (or questioning) the characteristics of an axon membrane from that perspective.

The generally accepted position now is that these ionic materials can only move through a type 3 BLM when in the "undissociated state" or when complexed with another material. Armstrong addressed this change in ideology beginning in 1971[273]. However, Armstrong was not aware of the complex quantum-mechanical nature of the BLM when he discusses its electrical characteristics.

The neuron, as a cell, has evolved from the initial cell described above to include additional internal partitions beyond those associated with the nucleus and other chemical processing areas. In the following discussions, the membrane region supporting the metabolic health and growth of the cell are of little interest. This region will be discussed in **Section 1.4.2.9** along with discussions concerning ion-pumps. The regions of primary interest to neuroscience are the symmetrical lipid bilayer (type 1) regions and the asymmetrical lipid bilayer regions. The symmetrical regions make up most of the walls of dendrites, podites and axons. These regions are passive in nature and provide very high quality electrical isolation. The asymmetrical lipid bilayer regions are small areas that perform a variety of critically important tasks as defined below.

Although, the following analysis does not concentrate on the detailed molecular, and sub-molecular properties, of the BLM, it does depend on those fundamental properties. Yeagle has provided a comprehensive work assembling material on both the theoretical molecular chemistry of these membranes and their measured properties[274]. That work differentiates between many meso-states of matter and explores the family relationships between the fatty-acids. Subtle differences are discussed between liquid crystals and gels. Yeagle's work is limited primarily to the study of symmetrical bilayers (pages 54 & 141) except where he reports on natural lemma. Yeagle does describe six motifs (functional properties) he associates with a membrane (page 3). He describes most of these in relation to the organelles within a typical cell. However, he does not include any motif related to signaling. He also provides considerable dimensional data concerning primarily synthetic membranes.

Houslay & Stanley have provided a discussion of modeling BLMs[275]. It is mostly conceptual but includes many properties of membranes.

The tentative nature of the present state of the putative pores and channels is reflected in the summary by Unwin. This review paper will be examined more closely in **Section 1.4.2.10**.

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[271]Shepherd, G. (1998) Synaptic Organization of the Brain, 4th ed. NY: Oxford University Press pg 45

[272]Goldman, D. (1971) Excitability models, *in* Adelman, W. *ed.* Biophysics and Physiology of Excitable Membranes NY: Van Nostrand Reinhold pp 337-356

[273]Armstrong, W. (1971) The cell membrane and biological transport *in* Selkurt, E. *Ed*. Physiology, 3rd ed. Boston, MA: Little Brown pp 1-3

[274]Yeagle, P. (1992) The structure of biological membranes. Boca Raton, FL: CRC Press.

[275]Houslay, M. & Stanley, K. (1982) Dynamics of Biological Membranes. NY: John Wiley & Sons

The above alphabetical categories are not totally independent and fail to provide a distinct framework for discussing BLMs. An alternate set of numeric categories will be used henceforth. They are all based on two liquid-crystalline molecular films of amphiphilic organic material formed into a bilayer. The definitions of the three principle lemma types by composition were presented in **Section 1.4** and are repeated here.

Type 1–A continuous liquid-crystalline bilayer structure where each layer is homogeneous and the two layers consist of the same amphiphilic phospholipid material. The structure is largely impervious to all biological materials and is an insulator relative to electrical charges.

Type 2–A continuous liquid-crystalline bilayer structure where the individual amphiphilic molecular layers are homogeneous but consist of different phospholipid materials. It is electrically asymmetrical and forms a diode. The structure is largely impervious to all materials other than electrons and/or holes.

Type 3–A liquid-crystalline bilayer structure that is largely impervious to all materials but contains islands of protein or sterol material penetrating both layers of the bilayer membrane. The penetrations are thought to support the transport of selected neutral materials through the membrane.

Using a caricature that will be described more fully later, these membrane types can be illustrated in **Figure 1.4.1-1**. The left cylinder describes the dendritic input to the cell. The right cylinder represents the axon output of the cell. The white disk defines the nucleus of the cell within the soma or body of the cell. The role of the dashed lines will be discussed later. In this caricature, large portions of the external lemma are shown as type 1 membrane. These areas are impervious to the diffusion of materials or electrons. The axon is frequently enclosed in a multilayer lipid wrapping (myelination) that further impedes the flow of material (and electrons) from the surrounding matrix through the membrane. The areas shown in heavy black along the periphery of the membrane represent regions of type 2 material that remain impervious to materials other than electrons. Under the appropriate electrical conditions, these areas act as electrical diodes. The remaining periphery is shown shaded and includes areas of type 3 membrane. These areas are permeable to a variety of materials required by the cell to maintain homeostasis and growth.

1.4.1 The environment of the neuron

Although it is well established that the neurons employ a variety of electrical signals, their classification for purposes of this work must be much more precise. Electrical signaling can be accomplished in a variety of environments:

+ the electromagnetic environment of free space,

+ the electro-metallic environment of vacuum tube electronics,

+ the electro-semi-metallic or solid-state environment of semiconductor electronics,

+ the electro-liquid (electrolytic) environment of aqueous electronics, such as batteries,

and as shown below,

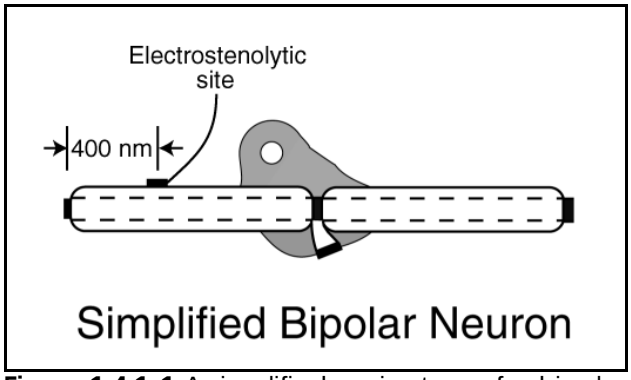

Figure 1.4.1-1 A simplified caricature of a bipolar neuron. The bulk of the plasmalemma consists of type 1 bilayer membrane. The solid black areas along the periphery of the cell are proposed regions of type 2 membrane material. The shaded area can accommodate type 3 membrane material. Type 3 membrane is optimized for transporting material through the membrane to the nucleus (white disk).

+ the electro-semi-liquid or **liquid crystalline environment of the neuron**.

The neuron exists in and is controlled by the laws of electrolytic electrochemistry defined in **Section 1.3**. Although various aspects of these fields have been studied and documented extensively, no work could be found that focused on the aspects of the science needed to support a clear understanding of the functional characteristics of the neuron. A brief summary of the necessary technology will be given in this section and below.

The characteristics of the neuron are developed in detail in **Chapter 1**. Briefly, the neuron is an electrolytic system involving multiple high molarity electrolytes associated with specialized regions of one or more liquid crystalline membranes. By creating structures within this electrolytic environment, the animal can create a signaling system that we call the nervous system. The system typically consists of a variety of neural types that are all electrolytically based. It will be shown, however, that a very simple underlying type of neuron can be easily expanded topologically to satisfy a wide range of requirements. In this work, this proto-neuron will be described initially as a fundamental cell leading to a fundamental neuron.

1.4.1.1 The nature of the electrolytes of the neuron

The general literature of cytology defines the material within the external cell wall of a neuron as (1) the *ground substance* or *cytoplasmic matrix*, and (2) the organelles and other inclusions suspended in it. This definition fits the cytoplasm within the soma of the simple cell. However, it is not sufficiently explicit to support additional internal membrane structures as found in a neuron. The presence of the word ground will also cause problems where it conflicts with conventional electronic terminology. For purposes of this work, a more detailed and specific set of definitions is needed. The cytoplasmic matrix will be redefined as including all of the plasmas, organelles, *internal cell membranes* and other inclusion within the plasma (or outer) cell membrane. The cytoplasmic matrix will be further divided into least four separate matrices;

+ the dendroplasm found within the dendrite(s), or input structure of the neuron, and separated from most of the soma by an internal membrane

+ the axoplasm found within the axon(s), or output structure of the neuron, and separated from most of the soma by an internal membrane. Several areas may be defined within the axon. These areas are isolated by their own lemma and contain their own axoplasm; i. e., the regions between the Nodes of Ranvier known as intra-axons or axon segments.

+ the podaplasm found within the poda or third terminal area of the neuron. This podaplasm may be separated from most of the soma by an internal membrane.

+ the common cytoplasm found associated with the nucleus and other housekeeping structures of the neuron and restricted to the area of the soma not defined above.

Although the electron microscope has provided new details and allowed considerable discussion of the inclusions in the above plasmas, it has only provided limited information about the plasmas themselves. The literature in this area is based mainly on physical contact and chemical analysis with some tests involving optical techniques. The only area large enough to support most of these observations is the cytoplasm as defined above. The other plasmas are quite limited in volume and difficult to aggregate without contamination. It will be assumed that all these plasmas have the same bulk electrical properties and largely the same hydraulic properties.

Because of its importance in the overall function of a neuron, the interneuron matrix (INM) surrounding the neuron must also be referenced here. This material can also be considered a plasma based on its content. It is crucial to the operation of the neuron. It is also

significantly different in composition from the other plasmas. Loewy & Siekevitz[276] provide some numbers in this area.

TABLE 1.4.1
Ionic concentrations in the Squid axon and the surrounding body fluid

	Concentration in milliequivalents per liter				
	K^+	Na^+	Cl^-	Organic anions	
Squid axon (axoplasm)		400	50	40-100	345
Body fluid (interneuron plasma)	10	460	540	----	
Sea water[277]	19.4	415	486		

The difference in concentration of sodium and potassium ions led Hodgkin and Huxley to assume (incorrectly) these materials must play a role in neural signaling. The differences between these ionic concentrations may play an important part in the homeostasis of the neuron but no part in the signaling function.

1.4.1.2 The liquid crystalline materials of the neuron

Loewy & Siekevitz also provide a brief but readable summary of the nature of these plasmas. "The ground substance has the unusual property of being capable of both viscous flow like a liquid and of elastic deformation like a solid . . . Generally, the cytoplasmic matrix near the outer membrane, often referred to as the ectoplasm, tends to be more like a solid whereas the interior of the cell, or endoplasm, is generally in a more fluid state . . . Most workers agreed that although the ground substance appeared optically homogeneous in the light microscope, it must nevertheless contain a submicroscopic skeleton responsible for its elastic properties." These observations relate to the properties of what is now called a liquid crystal. These comments serve to focus attention in two areas:

+ the electrolytes of the neuron are not dilute solutions, they are highly concentrated solutions

+ the electronic state of the solvent, water, is quite complex--more so when combined in a matrix exhibiting liquid crystalline properties.

Usually, the electrolytes of the neuron are nematic liquid crystals while the plasma membrane is a smectic liquid crystal. This arrangement agrees with Wolken's model of a fundamental cell[278]. The endoplasm will be associated with the reticulum. The reticulum is a central region within a neurite or axon that is frequently identified using electron microscopy. Determining whether it is a separate membrane is difficult unless very high magnification techniques are used.

1.4.1.3 The complex internal membrane structures of the neuron

The membranes of a neuron are closely related to the membranes of any other type of cell. However, they do possess many specialized regions that are specific to neurons. It appears the most complex neurons incorporate both neural and secretory functions. Those of the heart share neural and muscular functions.

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[276]Loewy, A. & Siekevitz, P. (1969) Cell structure and function. NY: Holt, Rinehart & Winston pp. 54-62

[277]interpolated values from Lehninger, A. (1970) Biochemistry. Worth Publishers, Inc. pp. 608-609

[278]Wolken, J. (1986) Light and life processes, photoreceptors and evolution. NY: Van Nostrand Reinhold. pg. 54

Many authors have presented simple definitions of a model membrane. As Houslay & Stanley have pointed out: "No single published model of membrane structure embodies all the features of a biological membrane[279]." These authors also discuss the state of experiments to reconstitute the "defined membrane ***functions***" using material mined from previously vital biological membranes. Their work was at an early stage in the 1980's.

With the availability of high resolution electron microscopy, the intricate internal structure of cells has become evident. This intricacy extends to the membranes forming the boundaries, both internal and external, of a cell. There are many types of physical junctions occurring between cell membranes. Many appear to be lap joints between two bilayer membranes.

More recently the separation of the internal plasmas of a neuron into at least three distinct volumes has occurred. This has resulted in the identification of three distinct conduits formed by the axolemma, the dendrolemma and the podalemma. These structures will be discussed in detail below.

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[279]Houslay, M. & Stanley, K. (1982) Dynamics of biological membranes. NY: John Wiley & Sons, pg. 9-26 & Chapter 5

1.4.2 Characterizing the electrolytic environment of a biological membrane

A more precise understanding of the mechanisms at work at a neural membrane-electrolyte interface is needed. No significant experimental activity related to a BLM separating two electrolytes has occurred since the efforts of Goodman in the 1950's. Stein prepared a book in 1967 that provides some excellent data on synthetic biological membranes[280]. Adelman edited an extensive review in 1971 designed for pedagogy[281]. Finkelstein, writing for a general audience within his discipline, oversimplified the mechanisms involved[282]. His assertion that by squeezing a hydrocarbon film down to a thickness of 50 Angstrom, the permeability properties of a lipid bilayer would be emulated appears simplistic. It overlooks the quantum-mechanical facts related to such a thin lipid bilayer. He noted a reluctance by the community to accept his assertion. This is particularly true with respect to his assertion that "ordinary" olive oil has the same permeability characteristics as a plasma membrane. It does not! To circumvent this fact, he then fell back on the idea that significant proteinaceous intrusions into the integrity of the bilayer lipid accounted for its actual properties. Finkelstein & Cass, writing in the above volume, showed that their reconstituted bilayer membranes did not contain pores suitable for transporting water molecules.

The boundary conditions related to the types of BLMs defined above must be addressed. The boundary conditions applicable to a putative homogeneous membrane are irrelevant to the neuron. The more complex problem related to "skins" of animals need not be addressed here. Skins contain a variety of individual zones performing a myriad of functions beyond neurological signaling

A matter of growing importance is defining when and where the rules of ionic chemistry versus the rules of electrolytic chemistry must be used in the neural system. Electrolytic chemistry is variously known as colloidal chemistry or gel chemistry. These alternate names suggest the lack of mobility of the ions in electrolytic chemistry compared to their performance in ionic chemistry.

This section will review the electrolytic environment related to BLMs from three perspectives. The first will review the new knowledge available concerning the molecular nature of these membranes. The second will examine the quantum-mechanical conditions associated with the structure of the membranes. The third will examine the boundary layers associated with the interface between a membrane and electrolytes of significantly different molecular structure. These are frequently called Helmholtz layers or the double layer in electrochemistry (see **Section 10.1.3**).

This discussion will be limited to simple BLMs as opposed to complex structures such as skins. Skins, such as those of humans and the experimentally popular frogs, contain a variety of macromolecular structural features not found in neural membranes and not relevant to this work. In this section, the primary interest is in BLMs that consist of two bilayers that are semipermeable to electrons and holes due to their asymmetry at the molecular level.

From this time forward, a neural membrane cannot be considered from a global perspective. It must be recognized that it consists of multiple specialized regions. The properties of these regions must be addressed individually.

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[280]Stein, W. (1976) Op. Cit. Chapter 1

[281]Adelman, W. (1971) Biophysics and Physiology of Excitabel Membranes. NY: Van Nostrand Reinhold

[282]Finkelstein, A. (1987) Water movement through lipid bilayers, pores, and plasma membranes. NY: John Wiley & Sons. pg 94.

Before proceeding, it is important to review the comprehensive texts of Starzak[283] and of Eckert[284] in the light of the previous material in **Section 1.4.** Unfortunately, Starzak frequently falls into one of the situations described in **Section 1.1.5.** His work must be read *in-toto* because he frequently changes position as the subject is presented in more detail (compare his figures 5.19 and 8.1). These problems are undoubtedly related to his focus on pedagogy. The details of his work will be discussed in more detail in **Chapter 9**. He presents many figures which relate to the phenomenon of "transistor action." However he, like many others, did not have the background to recognize the presence of an Activa. Eckert discusses many aspects of permeability and transport. However, it is not always easy for the reader to decide what material applies to simple membranes and what applies to more complex multiple cell structures such as skins. His comments on pages 67-71 are particularly relevant to the following discussion of simple bilayer membranes. Subsequently, he discusses more complex membranes that he labels fluid mosaic models and finally multiple cellular membranes (labeled here as skins). The potential methods of ion transport through these more complex structures are addressed on his page 80.

When discussing neural signaling, it is important to begin with the discussion of fundamental BLMs. Fluid mosaic models and skins are irrelevant to the signaling function and their introduction into the discussion should be avoided. For purposes of this work, the fluid mosaic model is a type 3 membrane. It will only be associated with the genesis and metastasis of individual cells. These are long term processes and do not involve time scales related to neural signaling.

Limiting the discussion to fundamental BLMs still leaves a large arena to cover. As earlier, morphology can help up to a point. Beyond that point, biochemistry and molecular topology become important disciplines. These are followed by the very important discipline of electrolytic chemistry. The morphologist is generally limited to structures larger than one micron by light microscopy. In neurobiology, the more important characteristics are at the molecular level.

1.4.2.1 The gross molecular structure and electrical character of a membrane

All neural cells employ an external cell wall (not to be confused with the cellulose-based outer "cell wall" of plants) that can be described as a typical biological membrane. Such a typical membrane consists of two films of molecules separated by an extremely small space. It is frequently described as a three-layer structure because of its appearance when using the light microscope.

The fundamental BLM consists of two liquid crystalline layers of phospholipid material arranged with their hydrophobic (non-polar) surfaces next to each other. The two physical layers are known as leaflets. The hydrophilic ends of these molecules form the outer surface of each leaflet. The resulting membrane is hydrophilic but impervious to water. The precise liquid crystalline geometry of these leaflets is described by the smectic phase[285]. The resulting sandwich is less than 100 Angstrom thick. The precise definition of the boundaries of the individual layers becomes difficult in this quantum-mechanical size range. The chemical constituents of the membrane are typically multiple regions formed by different members of the phosphatidyl ethanolamine (PE) family in one bilayer and a member of the phosphatidyl choline (PC) family in the other layer.

Historically, PE was known as Cephalin and PC was known as Lecithin. However, as suggested above, and stressed by Chapman, PE and PC are not complete chemical names, they are

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[283]Starzak, M. (1984) The physical chemistry of membranes. NY: Academic Press

[284]Eckert, R. (1988) Animal Physiology. 3rd ed. NY: W. H. Freeman Chapter 4.

[285]Blumstein, A. (1978) Liquid crystalline order in polymers. NY: Academic Press, pgs. 7 & 265

family names[286].

Although the two layers may appear identical under the electron microscope, a critical difference frequently exists between the phosphatidyl groups as well as the so-called head groups. The difference may involve only one atom, one ligand or one polymeric segment, in either group.

Chapman has also presented a figure reproducing a small region of myelin membrane (30 Angstrom by 30 Angstrom) which appears to contain a wide variety of fatty acid molecules in a nearly random organization. **Figure 1.4.2-1** reproduces his figure with annotation.

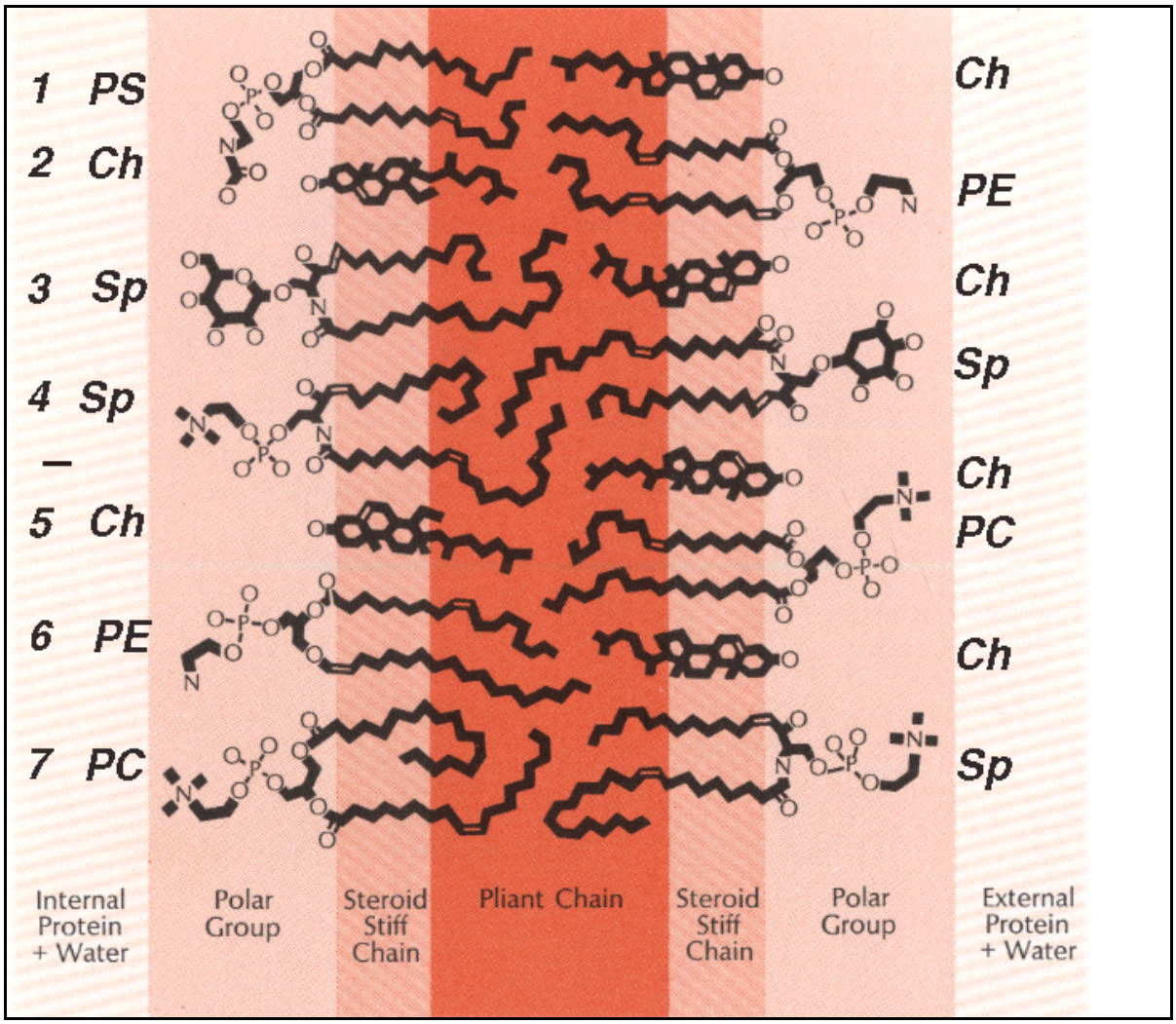

Figure 1.4.2-1 A detailed drawing of a mixed region of lemma ADD. "Actual complexity of membrane structures, as opposed to the highly schematized diagams hitherto depicted, is suggested by this drawing–itself considerable simplified–showing a portion of myelin membrane. This tiny section, only about 30 x 30 Angstrom, contains six cholesterol molecules, five phospholipid molecules of three different types, and four sphingolipid molecule of two different types." See text. Annotated (italics) from Chapman, 1975.

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[286]Chapman, D. (1975) The bilayer hypothesis of membrane structure. *In* Weissmann, G. & Claiborne, R. *ed.* Cell Membranes; Biochemistry, Cell Biology & Pathology. NY: HP Publishing Co. pg 15

The molecules he described in his text have been labeled in this figure. He lists four sphingolipids, SP, The phospholipids, (PE, PC & PS), were identified. Two molecules containing derivatives of inositol (one containing a heterocyclic ring) at the surfaces of the membrane are combined with sphingolipids (row 3,left and row 4,right). Even if this is myelin and not neural tissue, it raises the question of whether sphingolipids can exhibit electrical characteristics similar to the phospholipids. The sphingolipids contain a nitrogen atom in the bridge between the two fatty acid chains. The presence of this nitrogen atom might even suggest more interesting electrical characteristics.

If the sphinatidylamino acids phosphatidylamino acids are electrically similar, row 7 would represent a nominally perfect insulator and be labeled a type 1 lemma in this work. Similarly, row 4 could represent a type 2 lemma, since it would represent a dissimilar pair of nominally similar lipid moieties joined to different amino acids. To make progress considerably more figures like this are needed to determine a statistical base and many of those figures need to relate to specific areas of neuron lemma (and be recorded separately from other tissue types. Pearson & Pascher (1979) have provided specific micrographs of neural tissue that show much more orderly lipid chains.

Chapman also provides stylized data on the transition between liquid crystal membrane and gel-membrane when in a water solution as a function of temperature (page 20).

Goodsell has presented a beautiful stereographic caricature of a lipid bilayer at a scale of 10,000,000:1[287]. It models each atom of each molecule of the liquid crystal lipid making up each of the two bilayers. The two layers appear to be symmetrical. The result is a model exhibiting a well defined hydrophobic region between the layers but no effort was made to model the content of this region. Unfortunately, it is difficult to describe the variability in the structure of membranes in a single figure. The potential variety of phospholipids used in membranes makes precise definition in the hydrophobic region difficult.

The key feature of the natural lemma is related to its hydrophilic and lipophilic regions. The outer surfaces of the lemma are hydrophilic and will not allow lipophilic materials to contact them. The inner surfaces of the bilayers of the lemma are both lipophilic and will not allow hydrophilic materials to approach them. Thus unmodified natural lemma form an impermeable barrier to both hydrophilic and lipophilic materials. *Such a barrier is not compatible with the equations of Nernst, Donnan and Goldman.*

The preparation of artificial bilayers of lipid material has been studied intensely by Mueller, et. al. Their methods allow the fabrication of asymmetric bilayers[288]. The data they collected on membranes formed in the absence of a hydrocarbon solvent is excellent. Unfortunately, they did not use PC or PE to form their bilayer membranes and produced thinner membranes than generally found in biological membranes. Siddiqi & Tien also discuss asymmetrical bilayers and provide a more explicit variant of the Montal & Mueller fabrication cell[289].

An asymmetrical biological membrane separating two different solutions forms an electrical diode. By proper selection of the phosphoglycerides involved, diodes of different intrinsic impedances can be obtained. By proper adjustment of the area of the membrane formed from a specific phosphoglyceride(s), the power handling capabilities of this area can be determined. If external test equipment is attached to the two solutions, the impedance of the configuration will be seen to be highly asymmetrical and therefore nonlinear. The static

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[287]Goodsell, D. (1993) in Rodieck 1998, pg 91

[288]Montal, M. & Mueller, P. (1972) Formation of bimolecular membranes from lipid monolayers and a study of their electrical properties *Proc Nat Acad Sci USA* vol. 69, pg 3561

[289]Siddiqi, F. & Tien, H. (1983) Electrochemistry of bilayer lipid membranes in Milazzo, G. ed, Topics in Bioelectrochemistry and Bioenergetics, vol. 5 NY: John Wiley & Sons pp 157-221

electrochemistry of such configurations acting as diodes is well understood[290]. However, little emphasis has been placed on the dynamic characteristics of these configurations.

The more detailed semiconductor properties of BLM configurations are less well understood. **Figure 1.4.2-2** illustrates the fundamental situation. (a) shows the conventional electrochemical description of a single BLM immersed between two different solutions. (b) shows the same situation but with the BLM described at the molecular level.

(a) shows that no ions actually pass through the membrane. Instead, all reduction and oxidation occur at the respective surfaces with only charge actually passing through the BLM (shown by the horizontal lines). This charge is composed of two components, electrons and "+" charges or holes. The net charge transfer is the algebraic sum of these two components. The ratio between these two components is an important characteristic of a semiconductor. In BLM's of interest to neuroscience, the hole current dominates in one leaflet of the membrane cross section and that material is described as "p" (positive) type material. The dominant current in the other leaflet is dominated by electrons. It is described as "n" type material. The overall material is described as a "pn" junction and exhibits a perfect diode impedance characteristic under low charge flow conditions.

(b) shows how this "pn" type material operates at the molecular level. The BLM consists of two phosphoglycerides arranged in two liquid crystalline films and a region of liquid crystal water associated with the hydrophilic (outer) surfaces of each film. Oxidation or reduction occurs at the respective exterior surfaces. The charge generated within the BLM is then transported within the BLM in the valence band of the liquid crystals by holes. These are empty electron sites in the crystalline lattice that are continually filled by electrons jumping from a filled site to the empty site. It is tempting to think of the holes moving along the fatty acid chain of each molecule. However, this is a poor analogy. Each molecule occupies a lattice site in the liquid crystal. The charge appears to move from site to site, not from atom to atom.

The electrical properties of the asymmetrical bilayer membrane are becoming clearer. Gruner, writing in

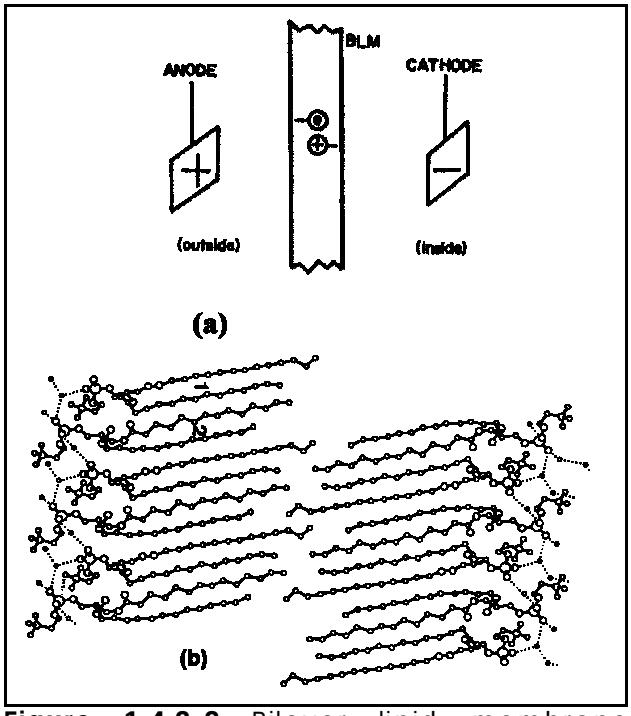

Figure 1.4.2-2 Bilayer lipid membrane configurations. (a) Conventional electrochemical model of a BLM separating two solutions. Only electrons and/or holes can penetrate the BLM when it is forward biased. When reverse biased, no charges can penetrate it. (b) Molecular level model of same BLM showing liquid crystalline structures. The two leaflets are identical and are composed of two alternating phosopholipids, #1 & #2.

[290]Tien, H. (1974) Bilayer lipid membranes. NY: Dekker

Yeagle[291], has discussed the interface between the hydrophobic components of the two molecular films in detail. He defines two major physical states. In the first, the two phospholipid films exhibit a clear bilayer midplane. In the second, the fatty acid chains of the phospholipids are of unequal length and interdigitation occurs between the two films. Three levels of interdigitation are defined. These levels of interdigitation probably account for the diode properties of the resultant membrane (See **Sections 1.4.3** & **1.5**). Further discussion of the chemical properties of these interdigitated membranes is found in Slater & Huang[292].

The electrical characteristic of this configuration is that of a perfect diode in series with a battery. The operating characteristics of the diode and of the battery are determined by the area of the ***active portion*** of the BLM. Although cell walls may appear uniform under the electron microscope, detailed study would show they have a very spotted appearance at the functional level--different regions providing different capabilities.

The BLM making up an exterior cell wall is oriented in such a way that the interior of the cell can sustain a negative potential, i.e., the diode associated with the BLM is reverse biased. This condition is obtained by having the "n " type material of the junction in contact with the fluid surrounding the cell.

1.4.2.2 The molecular constituents of a biological membranes

Both PE and PC exist in a variety of species depending on the exact fatty acids incorporated at each of the two positions in the nonpolar tail[293]. **Figure 1.4.2-3** shows their basic polar structure. A similar figure tailored for spectroscopic studies appears on page 310 of Yeagle. A figure by Finean in Stein highlights the problem in displaying these materials[294]. Every author's version is stereo-metrically different.

> **As pointed out by Lehninger**[295] and illustrated by Stryer[296], these molecules are so complex that they are usually shown in a standardized form in which all the fatty acids are shown as palmitic acid for convenience. This obscures several points of significance here:
> + PE and PC are large families containing many species,
> + The two fatty acid components need not be the same,
> + The fatty acid in the 2-position is usually unsaturated,
> + The fatty acids may be in isomeric forms other than all-*trans*.
> + As many as 100 different members of the PE and PC family may be present in a single membrane, probably congregating in different regions.

These materials can have different physical lengths (affecting their dielectric properties), different geometric spacings (affecting their permeabilities) and possibly different stereochemistry. The length is typically equal to 1.25 Angstroms per CH_2 group in the chain. The cross-sectional area of each chain is between 20 and 26 sq. Angstrom[297].

Chapman has provided a broader discussion of the structure of the triglycerides and

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[291]Gruner, S. (1992) Nonlamellar lipid phases *In* Yeagle, P. The Structure of Biological Membranes. Boca Raton, FL: CRC Press pp 175-180 QH601 .S777 1992

[292]Slater, J. & Huang, C. (1988) Interdigitated bilayer membranes. *Prog Lipid Res* vol. 27, pp 328+

[293]Yeagle, P. (1992) The Structure of Biological Membranes. Boca Raton FL: CRC Press pg. 17

[294]Stein, W. (1967) Op. Cit. pg 10

[295]Lehninger A. (1970) Biochemistry. Worth Publishers, Inc. pg 196.

[296]Stryer, L. (1981) Biochemistry. 2nd. ed. NY: W. H. Freeman Chapter 12, pp 283-312

[297]Barrow, Gordon (1961) Physical Chemistry. NY: McGraw-Hill pp 755-757

phospholipids.

The term phosphotriglyceride will frequently be replaced with the more general term phospholipid below for convenience.

The two layers can also be symmetrical or asymmetrical with respect to each other. The asymmetrical type is quite common[298].

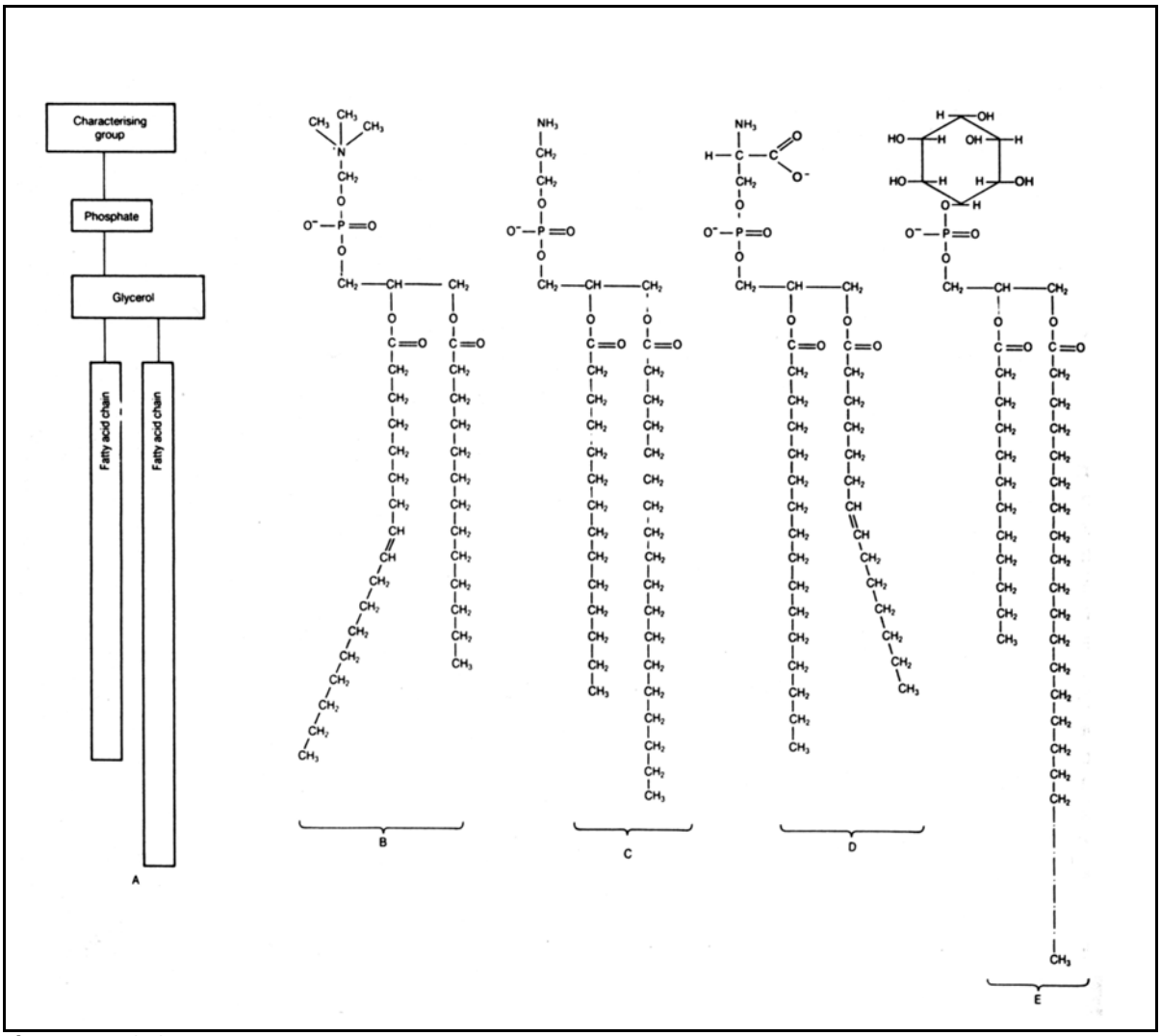

Figure 1.4.2-3 CR Principal phosphotriglycerides in animal neural membranes. Their dual fatty acid character and polar nature are shown. A; schematic diagram. B; phosphatidyl choline (lecithin). C; phosphatidyl ethanolamine (cephalin). D; phosphatidyl serine. E; phosphatidyl inositol. From Smith, 1989.

Sphingomyelin is another phospholipid material quite closely related to PC (while it contains phosphocholine as its "head," it differs stereochemically from PC). This material is found primarily in brain and nerve tissue. It is a primary candidate for one of the asymmetrical

[298]Miljanich, G. et. al. (1979) Disaturated and dipolyunsaturated phospholipids in the bovine retinal outer segment disk membrane. *Biochim. Biophysic. Acta*. vol. 552, pp 294-306

bilayers forming the diode regions of neurolemma.

As will be discussed below, the biological bilayer membrane when immersed in electrolytes has been shown experimentally to be the equivalent of a diode and battery in series, the combination shunted by a capacitance.

The structure described above forms a pn junction with a higher charge density within the phosphatidyl ethanolamine portion of the membrane. It is semipermeable to fundamental electrical charges but impervious to polar ions. This semipermeability is recognized when the membrane is placed between two electrolytes at different electrical potentials. Typically, the membrane will be conductive to electricity when the hydrophilic surface of the PE is made more negative than the hydrophilic PC surface. When the applied potential is reversed, the membrane acts as an insulator.

When examined in detail, the change from a conductor to an insulator is described by a simple exponential function. However, the transition from an insulator to a conductor may not occur at zero applied voltage. This fact suggests that the membrane may exhibit an intrinsic electrical potential. Such a potential will be defined as the intrinsic membrane potential. Note that this potential is not directly related to any plasma potential associated with a neuron.

When reverse biased, the insulating properties of the membrane can be defined in terms of its capacitance per unit area. When forward biased, this capacitance is of less importance at high bias potentials due to the high conductance of the membrane. The membrane may exhibit a variable capacitance at low applied potentials due to space-charge effects.

Note: The characteristics described here are those observed using a simple electrolytic system. They are not those of a membrane standing alone. The *system* consists of the membrane in series with the electrolytes on each side of the membrane and a polarizing external battery. The electrolytes need not be different.

1.4.2.3 Candidate situations for the electrolytics of membranes

Many models exist describing the electrolytic situation associated with an in-vivo membrane system. They rest on a variety of foundations. Most of them only address putative membranes that are permeable to ions. Knowledge concerning real biological membranes has advanced considerably in the last 50 years. This knowledge must be integrated into an overall view of the electrolytics of the biological membrane.

Three different generic BLM configurations can be developed based on the above chemistry plus one other optional condition. **Figure 1.4.2-4** illustrates several potential situations that may occur at the neural membrane-electrolyte interface. The figure is applicable to several of the discussion to follow in this chapter. The membranes are assumed to be without voids. Each electrolyte is complex. They contain single and multiple-valence simple ions, more complex ions and both ionized and unionized metabolites supporting the glutamate cycle. This figure does not address the boundary layers associated with the external electrodes.

The upper half of the figure involve electrochemical cells with an external potential applied. The lower half does not involve any external potential. A potential difference is generated across the membrane regardless of the character and concentration of the electrolytes.

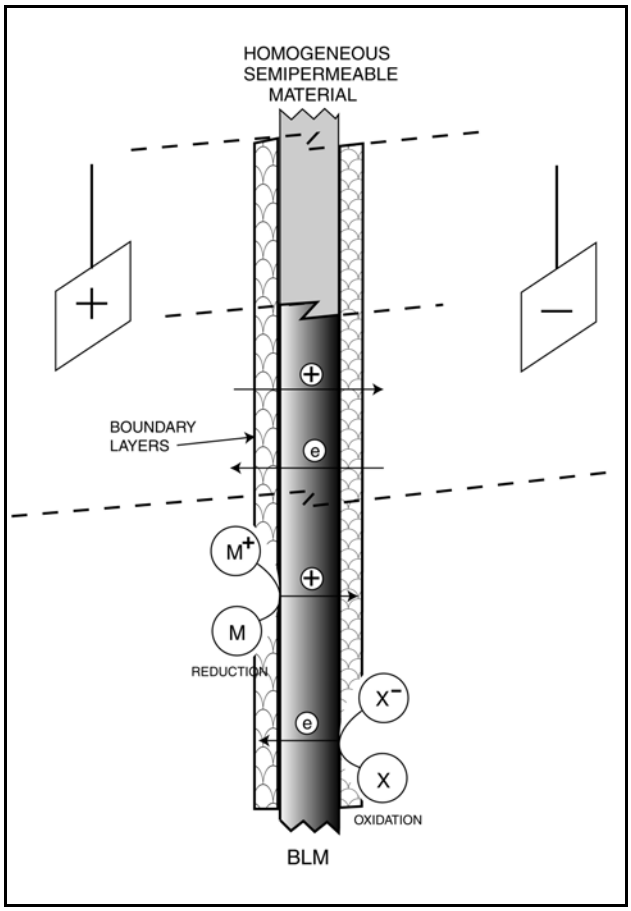

Figure 1.4.2-4 Potential situations at the membrane-electrolyte interface. The grey section of membrane represents the classical homogeneous semipermeable case. The remainder of the membrane represents a proposed biological bilayer membrane, BLM. See text.

The upper third of the figure addresses the conventional wisdom of a membrane as a homogeneous bulk material that is semipermeable to a variety of solutes. The material is void free. This is the conventional model addressed by Nernst, Donnan, Goldman and finally Hodgkin & Huxley. The permeability of this type of material by fundamental electrical charges, electrons and holes, is generally not addressed in the neuron, or basic cell, literature. It is this configuration that was applied to the lemmas of the neuron until recently. It is the configuration addressed in most of the literature referenced in **Section 1.1**. This configuration does not represent a real BLM.

The middle third of the figure is applicable to actual biological bilayer membranes , BLMs, when investigated in the laboratory. The material is void free. Such membranes are essentially impervious to ions and large molecules due to their hydrophobic core. It is also immersed between two electrolytes and an electrical potential is applied via the electrodes. The specific nature of the electrolytes is immaterial. However, electrons and positive charges, in the form of holes, can pass through such a membrane under appropriate electrical conditions.

1. When the membrane is a molecularly symmetrical BLM, the liquid-crystalline interface between the two bilayers is not conducive to the transmission of electrons or holes. The symmetrical BLM acts as a very high quality insulator, conducting neither electrons or holes. Electrically, the membrane acts as a pair of ideal electrical diodes wired back-to-back. The overall membrane configuration exhibits the reverse bias breakdown characteristic expected of such a configuration. This configuration corresponds to a type 1 BLM.

2. When the membrane is a molecularly asymmetrical BLM, the liquid-crystalline interface between the two bilayers is more flexible. Depending on the details of the asymmetry, the BLM is found to exhibit asymmetrical electrical performance from two perspectives. First, the BLM exhibits the electrical impedance characteristics of a high quality electrical diode. The electrical characteristic exhibits a finite reverse bias breakdown potential to be expected of such a configuration. The intrinsic value of the diode is determined by the mobility of both the electrons and holes moving through the membrane. Second, the BLM may exhibit an "intrinsic battery" that acts exactly like a conventional battery in the presence of an external polarization. In the absence of an external polarization, this "intrinsic battery" disappears. It cannot provide energy to an external load or perform work. in the thermodynamic sense. This configuration corresponds to a type 2 BLM.

Both of these configurations exhibit a capacitance in parallel with the conductive components due to the intrinsic dielectric properties of the membrane. However, the value of this capacitance must be calculated based on quantum-mechanical principles. The distance between the charges stored near the surfaces of the membrane is a function of the potential across the membrane.

The bottom third of the figure shows a situation similar to the middle third. However, no external bias is required to cause electrons and holes to pass through the BLM. The mechanisms marked reduction and oxidation are associated with an electrostenolytic process occurring at a stereospecific area of the membrane. They represents the typical oxidation and/or reduction reactions that can occur at the surface of a BLM. However, their stereospecific character only allows the reaction of specific chemicals at each site. If the BLM is of type 2 and the character "X" is replaced by glutamic acid, its oxidation will result in the left side of the membrane becoming negative with respect to the right side. Application of this configuration to an asymmetrical (type 2) BLM is key to the operation of the entire neural system in animals.

Reactions of this type are commonly called catalytic reactions in general chemistry with the membrane described as a substrate. However, in biochemistry, they are commonly called enzymatic reactions and the reactant is frequently described as the substrate.

The rate of this electrostenolytic reaction depends on many characteristics of the membrane, the potential reactants, and the availability of the reactants. It is proposed that the actual process taking place at the surface of many specialized regions of plasma membranes involves a portion of the Krebs cycle known as the glutamate shunt. This shunt involves the reduction of glutamic acid to GABA with the release of carbon dioxide.

The prevalence of glutamic acid in the vicinity of neurons and its purpose have long been mysteries in metabolism. The material has been conceptually associated with metabolism in the non-signaling portion of neural cells and in all other types of cells. This process is normally found occurring on the outside of cells where the required reactants are readily available from the blood stream and the local vascular matrix. The process appears to be the main source of the potential between the various plasmas of a cell and the surrounding environment. This reaction will be discussed in detail in **Section 3.2.**

When these reactions occur on the surfaces of the BLM as shown, charge will be transferred across the membrane. Whether the charge is transferred as an electron or as a hole is determined by the mobility of these species within the BLM. Since no electrical path exists through the electrolytes to an external circuit, the transferred charges will accumulate in a boundary layer associated with the BLM-electrolyte interface.

The charge transferred through the BLM is not able to flow freely into the electrolyte. That is not allowed by Gauss's Law of electrostatics. However, it can collect on the inner surface of the membrane and form an electrically charged boundary layer within the Helmholtz region (**Section 1.4.2.7.1**). Under steady state conditions, it is this electrostenolytic mechanism that provides the electrical potential of each plasma of the neural signaling system. It is also the source of potential in other chambers of neurons as well as other cells. Note that this electrostenolytic potential is not directly related to the "intrinsic battery" associated with the membrane and discussed in **Section 1.4.2.2.1.**

This configuration has been produced in the clinical research laboratory but without the investigator being completely aware of the precise situation. Tien discussed a combination of the above situations that included the electrostenolytic effect, an external potential bias and a BLM[299]. Tien describes that situation as involving a BLM that is electron conducting but highly resistive to the transport of ions. He did not address its electrical symmetry. Habib & Bockris describe an electrostenolytic situation (they call it an electrodic model) involving a pair of redox processes[300]. They combine the reduction and oxidation mechanisms of the above figure into a single mechanism. By eliminating one of these reactions, a potential is

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[299]Tien, H. (1974) Bilayer lipid membranes. (*also in* Marino, A. (1988) Modern bioelectricity. NY: Marcel Dekker, Chap 7 written by Zon & Tien, pg 191)

[300]Habib, M. & Bockris, J. *In* Gutmann, F. & Keyzer, H. (1986) Modern bioelectochemistry. NY: Plenum Press. pp. 82-83

found to exist across the membrane as discussed above.

The quantum-mechanical characteristics of symmetrical (type 1) BLMs make them impervious to electrical charges as well as most hydrophilic solutes. However, the quantum-mechanical properties of the asymmetrical (type 2) BLM do support the flow of fundamental charges through the BLM. More complex analyses, based on quantum-mechanics and available from semi-metallic semiconductor physics can be used to address this situation. Some of these techniques were introduced above and will continue to be used below.

1.4.2.3.1 Early attempts to apply classical diffusion theory to the axon

The names of three investigators appear repeatedly in the literature of osmotic diffusion in the presence of an electrical potential, Nernst (1890's), Donnan (1900's) and Goldman (1940's). There is a major problem in applying their work to the operation of the neuron.

The work of Hodgkin, Huxley & Katz has been appropriately recognized as monumental in their time. It was monumental in relation to the scope and perseverance shown in so many areas. However, like a tombstone in an unkempt cemetery, the monument is showing considerable wear.

Troshin provides a bibliography of the work between 1907 and 1959 exploring alternate theories related to the neuron. He quotes a key finding according to Fischer was "there is absolutely no free water in the protoplasm–all the water molecules form part of special complex organic compound of which the live substance is composed." Today, this complex is known as a liquid crystal. He also notes the attempts of the conservatives to salvage the classical theory by redefining the meaning of permeability to meet the needs of the concept (pgs 3, 7, 20-21, 28-29, 352-353). This is a common technique in biology that leads to mass confusion. Take a common word in the language and give it a unique technical meaning. Then fail to define the unique meaning upon first use of the term in ones writings. After about the third reference to the writing in the literature, all specificity associated with the unique definition is lost.

An example of the above methodology is the so-called "activated diffusion" theory of Danielli[301]. It moved from a conventional symmetrical non-crystalline semipermeable membrane to a membrane consisting of a continuous lipoid (liquid-crystalline) film completely without pores. His concept called for the penetration into the cell of a substance by passage via the interstices between the molecules of the lipoid film. This penetration was independent of the solubility of the material in lipoids. The permeating substance "punches" its way through, pushing apart the lipoid molecules in the membrane. The source of the energy behind the punch was not defined. It was an early version of a pore theory of lemma permeability.

> It is important to note the relative size of sugar molecules versus, the pitch of molecules in the liquid crystalline membranes versus the size of electrons. Any sugar, and even any hydrated sodium ion, is much larger than the pitch of the phospholipid spacing in a biological membrane. Similarly, an electron is infinitesimally smaller (1/1800th the diameter of a proton) than the diameter of any phospholipid molecule.

An alternate approach was supported by Michaelis based on dried colloidal membranes with a pore diameter sufficiently large to pass glucose molecules. He proposed the pores of his materials had a negative charge and were therefore impermeable to similarly charged particles–anions. A caveat frequently lost in subsequent discussions was that the Michaelis membranes were permeable to urea molecules although impermeable to monosaccharides. The fact that many living membranes are also permeable to disaccharides and other large molecules further undermines the simple Michaelis idea.

Troshin went on to focus on the protoplasm as a colloidal system incorporating a new

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[301]Danielli, J. (1984) Membranes *Internat. Rev Cytology*, vol 91 Academic Press

concept for the membrane. Initially, he labeled this the "new membrane theory." However, he gravitated to the label "phase theory" based on the proposals of Nasanov[302]. The term relates to the states of matter in the phase diagram as known then.

Nasanov was investigating the electrical properties of the biological membrane. His phase theory of bioelectric potentials is based on the idea that the disperse medium of the protoplasm behaves as a phase with respect to the surrounding solution of substances. Most of the electrolytes in the protoplasm (normally found in the state of rest) are in the bound and not the dissociated state.

After presenting sections on how various chemical agents passed through a cell membrane, Troshin summarized as follows. "According to the new membrane theory, the penetration into a cell of substances in most cases follows the scheme; substance A, dissolved in the medium, is converted in the cell membrane into substance B and in this form passes into the cell; in the cell this substance is reconverted into substance A (Ussing, 1949). This position concurs with many others (referenced later) that sodium and potassium ions cannot pass through a cell wall in a timely manner as simple ions. He also addresses the problem, that has remained such until now, concerning the asymmetrical distribution of substances between cell and medium. He describes "physiological permeability" as a mechanism relating to two simultaneous conditions. The mechanism operates when the passage of a substance into or out of a cell is accomplished against the concentration gradient and when its distribution between cell and medium cannot be explained by Donnan equilibrium. He notes, "In explaining these phenomena within the framework of the membrane theory writers have had to resort to postulating the existence in the cell of mechanisms for the 'expelling' or continuously 'pumping out' of the cell of some substances and of the 'active transport' into the cell of others." See **Section 1.4.2.9** for more on this conceptual framework.

Cole was a major player in the study of neural mechanisms in the middle of the last century. He probably had the strongest mathematical background of any researcher during that period, and was followed by his student, Rall (**Section 9.1.1.3**). Cole addresses many of the same problems as Troshin but from a more mathematically precise perspective[303].

Cole was one of the first investigators to include an electron micrograph of a cell wall in his publication. He also provided some observations he deduced from that image.

Writing in 1968, Cole closes with an interesting statement (pg 506). "The new challenge in the new era is to find what happens inside the membrane, the black box of the past."

Troshin and Cole, along with more recent results obtained with the electron microscope, are mandatory reading for any serious investigator of biological membranes. They form an essential base for separating the third person accounts (hear-say) found in many subsequent papers, books and textbooks purporting to explain the operation of the neuron.

The above discussion shows the slow advance of the membrane concept from a homogeneous semipermeable membrane between two dilute solvents in the direction of the current knowledge. The system involves a highly in-homogeneous bilayer membrane (with many unique electrical properties) separating two largely colloidal solutions where the protoplasm generally lacks ions free to physically move through the liquid medium via diffusion.

Even the above advances overlook at least three additional features that are critically important. First is the significantly different chemical and electronic properties of various portions of the differentiated biological membrane. Second are the unique chemical and electronic properties of parts of the differentiated biological bilayer membrane as it is known

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[302]Nasanov, D. (1959) Local reaction of the protoplasm and propagation excitation. *Izd Akad. Nauk SSSR*, Moscow-Leningrad, pp 1-434

[303]Cole, K. (1968) Membranes, Ions and Impulses. Berkeley, CA: University of California Press

today. Third is the further division of the colloidal state into the various forms of colloids and gels and the more critical state now known as the liquid crystalline state. This latter liquid crystalline state plays a critical role in the neural aspects of the cell that has evolved (differentiated) into the neuron.

The only valid conclusion is that nearly all of the literature before 1970 (and all subsequent textbooks based on that work–generally those published before 1995) should be discounted when studying the electrical parameters of the biological membrane system. The system actually consists of differentiated sections of membrane within a colloidal matrix. Each of the differentiated types of biological membrane, and their interaction with the colloidal matrix, must be analyzed based on its unique character.

Mueller & Rudin[304] published a large volume of work in the 1960's attempting to document the properties of synthetic bilayer membranes ascribed to the axolemma of Hodgkin & Huxley (**Section 1.5.5.1**). Being organic chemists, their exploratory focus was largely on the kinetics of the processes while adhering to the fundamental concept of the continuous bilayer biological membrane as the wall of a cell. On the other hand, they appear to be the first in the community to recognize the concept of a negative resistive impedance associated with their data. The magnification of the electron microscope available to this team was limited due to the time period. Their cross-sections of membranes were marginal for their purpose. As part of their work, they published a large collection of references and many measured parameters from various membranes[305]. The breakdown potential of 0.15 to 1.0×10^6 V/cm is of particular interest when discussing the electrical properties of the Activa and neuron of this work. Their material on permeability is extensive. It introduces the name translocators for modified (Type 3 in this work) membranes containing elements that can transport miscellaneous molecules and species across the membrane boundary. They constructed a potentially useful framework to describe these translocator materials. However, they noted that in 1969, "The molecular mechanisms of translocation and gating are unresolved." While their work did result in demonstration of a nonlinear and negative resistance characteristic in certain synthetic membranes, the characteristics were not those of the axolemma as proposed by Hodgkin & Huxley. In particular, the current density levels achieved were about 0.1% of those measured in biological samples and the current levels when the interior potential was positive with respect to the exterior did not remain at a low level until breakdown. Their portrayal of an action potential will be discussed in **Section 2.3.2**. While those authors offered no theoretical explanation for their results, there is little doubt they did achieve a quantum-mechanical process (tunneling) exhibited by a tunnel diode in a single synthetic bilayer membrane[306,307]. Their test configuration is described in an associated paper[308]. The papers should be considered simultaneously. The waveforms in their first paper compare favorably with a typical tunnel diode oscillator with a resistive load. The oscillatory waveforms exhibit time constants appropriate to the parameters of the test set, including the expected membrane capacitance, of the circuit. They also noted the liquid crystalline properties of their synthetic bilayer membranes.

A problem with the theoretical framework assumed by Mueller & Rudin is their assumption that all neurons generated action potentials. In fact, less than 5% of the neurons in Chordata generate action potentials. The other 95% of the neurons exhibit the current-voltage

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[304]Mueller, P. & Rudin, D. (1968) Resting and action potentials in experimental bimolecular lipid membranes *J Theor Biol* vol. 18, pp 222-258

[305]Mueller, P. & Rudin, D. (1969) Translocators in biomolecular lipid membranes: their role in dissipative and conservative bioenergy transductions *Cur Topics Bioenergetics* vol 3, pp 157-249

[306]Millman, J. & Halkias, C. (1972) Integrated Circuits: Analog and Digital Circuits & Systems. NY: McGraw-Hill pp 77-79, fig 3-18

[307]Mueller, P. & Rudin, D. (1968) Op. Cit. *Nature* vol. 217, pg 715

[308]Mueller, P. & Rudin, D. (1968) Resting and action potentials in experimental bimolecular lipid membranes *J Theor Biol* vol. 18, pp 222-258

characteristic expected of an analog circuit (see Parent in **Chapter 11**). These circuits do not exhibit the negative resistance feature they concentrated on creating. The second paper also says, with references but little discussion, oscillatory waveforms are also encountered in plant cells. Mueller & Rudin do provide a specific set of values (page 210) for the proposed electrical equivalent circuit of the axolemma proposed by Hodgkin & Huxley. They also address their interpretation of the theoretical status of the action potential on their page 214. This material will be addressed in **Sections 2.3.2** and in **Chapter 9**..

The analysis on page 246 of the paper in the Journal of Theoretical Biology relating to Ohm's Law should be reinterpreted based on the discussion at the beginning of this section. The correct laws are Kirchoff's Laws. The discussion of methods in their section 4.6 should be of value to the active researcher.

Adelman edited a large textbook in 1971[309]. While containing considerable data, the work is totally in line with the conventional assumptions concerning the operation of a biological membrane, based on chemistry and ionic diffusion through the membrane.

As noted above, Starzak published a treatise on membranes in 1984. While introducing many individual aspects of the electrical properties of the biological bilayer membrane, it suffers from a lack of continuity. This is apparently due to a lack of a consistent framework describing the membrane. In this respect, the author displayed little familiarity with the details of biological membranes and appears to rely upon much of the conceptual background (hear-say) discussed above. Little actual data from biological membranes appears in the book. The caption for his figure 4.4 lacks details and is not supported by a reference. It is proposed that the figure is not an action potential from an *in-vivo* squid neuron but a parametrically driven response using an axon prepared in the manner of Hodgkin & Huxley. Chapter 12 of the work focuses on the opposing ionic currents theory of Hodgkin & Huxley. He makes the interesting statement that "This may appear to be adequate information, because it does explain the transient behavior of the excitation process. However, on closer examination, it raises more questions than it answers." Starzak also surfaces the many problems associated with the earlier Donnan and Nernst theories based as they were on dilute solutions on opposite sides of a symmetrical semipermeable membrane (pg 253+).

Yeagle edited a large compendium on the biological membrane in 1992[310]. Noting that the Yeagle work did not address the electrical properties of the asymmetrical biological bilayer membrane is important. It did not address the electrolytic properties of membranes associated with the neurological class of cells at all. It remained focused on the chemical aspects of the biological membrane, although it did address the predominance of non-covalent bonding (generally hydrogen bonding) holding the individual molecules together in their unique liquid crystalline configuration. Yeagle is the first comprehensive work to recognize the liquid crystalline nature of the biological membrane. While Chapter one of Yeagle does recognize the liquid crystalline character of some differentiated portions of the biological bilayer membrane, and does develop the stereochemistry of the molecular structure associated with the bilayer, it does not delve into the electronic consequences of these arrangements. A comprehensive classification of lipids appears in his Table 1-1. Chapter two addresses the liquid crystalline characteristics of the biological membrane further. However, it also does not address the electronic properties of such membranes. While the second half of the book focuses on ionic transport through the biological membrane, it never addresses the transport of elementary charges (instead of heavy ions) through the membrane.

The later chapters in Yeagle are worthy of review. Chapter sixteen, entitled structural motifs for ion channels in membranes is unique. It is characterized by the predominance of

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[309]Adelman, W. *ed.* Biophysics and Physiology of Excitable Membranes NY: Van Nostrand Reinhold

[310]Yeagle, P. (1992) The Structure of Biological Membranes. Boca Raton, FL: CRC Press

caricatures of potential transport scenarios (with an absence of pictures, actual structural models or schematic models of membranes). Ionophoric agents (ionophores) are defined as organic molecules that can induce or facilitate ion transport across membranes (pg 722). The chapter contains several significant quotes. "Ionophores are classified either as ion carriers or channel-forming entities." "It should be stated that most ionophores are extremely toxic at the concentrations at which they are effective and are at present therapeutically useless (pg 722)." Ion carriers include the putative transport vesicle. The operation of these vesicles remains largely unresolved. The methods of material transport across the cell boundary (in either direction) are poorly understood at this time.

During the 1990's, Rapp and his associates undertook a major modeling effort related to the neuron[311]. It concentrated on passive modeling and the Hodgkin & Huxley characterization of the axon.

1.4.2.3.2 The community proposes to replace ionic permeability with gates and pores

Ling, writing in Gutmann & Keyzer, reviewed in detail the subject of colloidal chemistry as it applies to bioelectrochemistry[312]. He describes the development of an alternative lipoidal membrane theory based on totally hydrophobic thin films. He also develops the chronology of the work of Hodgkin & Huxley in electrolytics of membranes. A major step in their work was the modification of the Hodgkin-Huxley variant of the Goldman equation by Hodgkin & Huxley themselves. This ionic theory of cell potentials originally called for the permeability of the membranes they studied to chlorine ions. In their modification, the permeability of chlorine was omitted in order to more adequately match their data. However, dropping this factor without any theoretical justification has been criticized. Their modified equation led to the development of their "independence principle" regarding the movement of positively charge ions in opposite directions through a cell membrane in the presence of a single potential gradient. They assumed the membrane was a homogeneous isotropic medium and that no other ions were present. Subsequent experiments have not demonstrated such a mechanism. As a result, the community has undertaken the search for gates and pores compatible with a membrane that is semipermeable to large ions as a function of time and a poorly understood gate control mechanism. No positive demonstrable results related to this approach have been presented in the last twenty years.

As recently as May 2009, Bhattacharya noted[313], "When protein structures are published, they are mostly 'long sought' or 'eagerly awaited'." After 50 years, this is the situation for the "eagerly awaited" description of the sodium-selective and potassium-selective ion channels through the neural membranes. Their structural description, and even their imaging, have eluded both the cytologist and the crystallographer for a very long time. On the other hand, the conduction of an electrical charge down the molecular structures of the triglycerides has been documented widely for a long time.

Hille has provided an important discussion of how ionic channels have come to be named[314]. He pointed out, "The naming of ionic channels has not been systematic. . . . Finally, it is tacitly assumed that each component of the model corresponds to a type of channel, and the putative channels are given the same names as the permeability components in the original analysis." He then provides a back of the envelope calculation that the required change in the ionic concentration required to generate a 110 mV action potential in the giant squid

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[311]Rapp,M. Yarom, Y. & Segev, I. (1996) Modeling back propagation action potential in weakly excitable dendrites of neocortical pyramid cells *Proc Natl Acad Sci USA* vol. 93, pp 11985-11990

[312]Gutmann, F. & Keyzer, H. (1986) Modern bioelectochemistry. NY: Plenum Press. pp 45-49

[313]Bhattacharya, A. (2009) Structures of Desire *Nature* Vol 459(7243) pp 24-27

[314]Hille, B. (1984) Op. Cit. pp. 5-6

axon as only one part in 10^5. He points out that these minute changes are much below the changes in concentration that can be measured using available instrumentation. Dowling[315] made a similar calculation and determined the change in concentration was only two parts in 10^8. A change that he notes in not measurable with current techniques. No measurements have been made to date relating action potential generation to a change in chemical concentration within a neuron.

There have been few articles attempting to explain the putative mechanisms related to pores and gates. Horn attempted such an article in 1990[316]. As Horn notes with respect to individual studies of the problem, "Books have been written on this subject" (with citations). However, he obviously found it necessary to prepare a more cogent short discussion on this subject. The result is a paper with numerous caveats and approximations, but no data or even coordinate scales (except along one axis related to non-hydrated alkali-earth ions).

Hodgkin & Huxley did not demonstrate the movement of any ions (sodium or potassium) across the axolemma of the squid giant axon(either hydrated or non-hydrated. Recalculating the amount of charge on an absolute basis, the amounts of charge required to polarize a typical neuron plasma is far below the minimum number of ions (less than a micro-micro-micro mole) currently measurable by man). No reports have been found that claim to have measured a quantity of ions of this size moving through a BLM. **Chapter 3** describes in detail the movement of electrons across the neural membrane due to the electrostenolysis of glutamic acid (glutamate) into GABA.

1.4.2.3.3 Early efforts to define & demonstrate an ion pump as a bias source

By limiting their analyses to ions as charge transporters, Hodgkin & Huxley required an ion-pump to maintain the average potential between the inside and outside of the plasma membrane of an axon. This pump (or pumps) was responsible for the active transport of Na+ out of the axon and the simultaneous transport of K+ into the axoplasm. It had to operate on a time scale of hundredths of a second. They characterized this ion-pump as a mechanism imbedded in the plasma membrane. Their pump was apparently adopted from a much earlier proposal by Ostwald and by Bernstein in the 19th Century[317]. From the 1950's until the present, no confirmation of the existence of such an ion-pump related to the signaling operation of a neuron has appeared. This statement does not reflect on the use of an ion-pump in the metabolic aspects of the cell. Such a pump was recently discussed by Stein[318].

The study of the movement of ions across a BLM is more complex than the study of electron movement. While extensive studies of the movement of ions through various <u>non-biological</u> (and generally non-polarized) membranes have been well documented, substantive reports of the transfer of ions across a uniform BLM are rare. The hydrophobic core of such membranes essentially prohibit the transfer of water soluble ions across a BLM. To get around this problem, the literature frequently introduces other putative mechanisms. It speaks of the movement of ions across a BLM through "gates" or enclosed in specialized mobile vesicles. The gates are conceived of as channels in a membrane that are able to selectively isolate and allow ions to pass through a membrane. Similarly, many authors have suggested that vesicles can isolate a net charge (as ions of like charge) and move that charge across a

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[315]Dowling, J. (1992) Neurons and Networks. Cambridge, MA: Harvard University Press pg 75

[316]Horn, R. (1990) A primer of permeation and gating *In* Borsellino, A. Cervetto, L. & Torre, V. *eds*. Sensory Transduction. NY: Plenum pp 3-16

[317]Ling, G. (1986) The origin of cellular electrical potentials. *In*, Gutmann, F. & Keyzer, H. Modern Bioelectrochemistry. NY: Plenum Press pg 47

[318]Stein, W. (1991) Carrier kinetics show how the sodium pump uses ATP to render pumping of both sodium and potassium effective. *In* Yudilevich, D. Deves, R. et. al. Cell Membrane Transport. NY: Plenum Press Chap. 2, pp 21-38

heterogeneous membrane while enclosed in such a vesicle. Collectively, these gates and vesicles have been described under the label ion-pumps. To overcome the laws of electrostatics, these ion-pumps require a source of energy. To date, no such source of energy has been documented in the literature. Only various hypotheses based on chemical kinetics have appeared.

Note that the movement of non-ionized material (or a quantity of ionized materials with a net charge of zero) across a membrane requires much less energy. It only requires the energy needed to open and close the putative gate in the membrane or move the putative vesicle through the membrane. The existence of a transport mechanism for purposes of metabolism and cytogenesis is not disputed. Anderson & Fuchs were sited above in relation to the difficulty of moving large molecules through a membrane. Stein has recently discussed the kinetics of such a transport mechanism in the context of metabolism[319]. He notes the number of conflicts in the literature (page 25) and then makes a comment. "It is thermodynamics that determines whether or not pumping will occur, not kinetics." Note that chemical kinetics is a global technique. It cannot be used to determine the specific constituents of a reaction from among a large ensemble. Other techniques must be used to identify the actual materials involved in a reaction. Stein develops the possibility that the ions are transferred in an "occluded state." His analysis also suggests it may only be protons (rather than heavy ions) that move across the membrane barrier (page 32). If the quantum-mechanical concept of "holes" is adopted, the transport of a proton is replaced with the transport of a hole. The effective transport of a hole is actually due to the physical movement of electrons in the opposite direction.

Ling also addressed the subject of ion-pumps as they relate to the BLM. He did this because of the considerable confusion over the laboratory results related to this putative phenomena obtained during the 1980's. He provides some brief remarks on pages 49-62 of Gutmann & Keyzer and a thorough exposition in his own monograph.[320] He shows that the ion-pump is far from an accepted and verified solution to the ionic equilibrium problem of biological cells.

Habib & Bockris address the subject of the chicken and the egg on page 75 concerning the ion-pump. Relying on their interpretation of electrodics, they suggest another view. The concentration of alkali metal ions on the two sides of a membrane may be the result of the electrical potential across a membrane rather than the cause of that potential. ***This is a profound difference of view from the conventional wisdom***. They further suggest the initial potential may be due to anodic or cathodic processes that are "(different for membranes of varying function)." This is the view supported by this work.

Recently, Finkelstein crossed the intellectual bridge by emphatically and publicly noting the virtual impermeability of lipid bilayer membranes to small ions such as Na^+, K^+ and Cl^-.[321] However, he did not address the subject of the asymmetrical bilayer as a semiconductor. Wanting to accept the transport of ions through a membrane, he assigned this capability to proteinaceous pathways inserted into and through the membrane. In this position, he appears to be supporting the complex caricature of a BLM presented by Mackowski[322]. This caricature does not assign any quantum-mechanical properties to the membrane. Such gate structures are not seen at the molecular level in electron micrographs (or from x-ray

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[319]Stein, W. (1991) Carrier kinetics show how the sodium pump uses ATP to render pumping of both sodium and potassium effective. . . . *In* Yudilevich, D. et. al. *ed*. Cell Membrane Transport: Experimental Approaches and Methodologies. NY: Plenum Press. Chapter 2

[320]Ling, G. (1984) In search of the physical basis of life. NY: Plenum Press

[321]Finkelstein, A. (1987) Water movement through lipid bilayers, pores and plasma membranes. Volume 4 of the Distinguished Lecture Series of the Society of General Physiologists. NY: John Wiley & Sons. Chapter 6.

[322]Mackowski, L. Casper, L. Phillips, W. & Goodenough, D. (1977) Gap junction structure II: Analysis of x-ray diffraction data *J. Cell Biol*. vol. 74, pp 629-645

scatter analyses) of conduit membranes.

In summary, most of the neuroscience literature presents a picture of a fundamental BLM that is permeable to the ions of sodium and potassium, and generally chlorine, in spite of significant data to the contrary. The literature also assumes the membrane is an electrically symmetrical material with a uniform potential field gradient within it when subjected to an electrical bias. The most recent comprehensive books discussing the electrolysis of BLMs do not go beyond these two assumptions[323,324]. Possibly for pedagogical reasons, Habib & Bockris also stop with the consideration of paired redox reactions on the opposite sides of an undefined membrane. That membrane is apparently symmetrically conductive to electrons and/or holes. An alternate approach, involving a single redox reaction on one surface of an electrically asymmetrical membrane, was not addressed. This is the electrostenolytic approach presented in **Chapter 3**.

1.4.2.3.4 Summary discussion of the historical work

The Goldman, Donnan and Nernst Equations all assume a constant concentration field gradient within a membrane separating two dilute electrolytes. These conditions are not satisfied in biological membranes. A more comprehensive variable field theory must be used to describe biological membranes separating high concentration solutes.

Each author developed a mathematical model that addressed a more complex situation than his predecessor. Nernst only addressed the static or zero current situation due to a single ion-pair in the electrolyte. Donnan addressed the equilibrium condition for two ion-pairs and Goldman provided the general solution for any number of simple well-behaved ions. All these mathematical solutions for the equilibrium condition were based on a symmetrical membrane that was semipermeable to ions. They were unaware of the internal structure of a BLM and did not address the permeability of the membrane to electrons or holes. The semipermeability to ions had to result in a constant ion density gradient that could be related to a constant potential field gradient within the membrane. Goldman later introduced a set of piece wise continuous equations that allowed for a less restrictive but still continuous field gradient. All of the solutions related to dilute solutions of electrolytes. These conditions are not compatible with biological membranes supporting the neural signaling process. Since type 1 and type 2 BLM's exhibit an absolute barrier to hydrophilic ions, **the required gradients are not present and the work of these investigators does not apply to type 1 and type 2 BLM's**. Cole said in 1968: "Since Goldman, there have been extensive developments of the electrodiffusion theory that are almost entirely without an anchor in experiments on artificial or living membranes[325]." This situation appears to remain true today. Starzak dedicated considerable space to developing each of the above equations and discussing their limitations (pp. 44-83 & 218-223). Matthews also reviewed the applicability of the work of each of the above investigators in a briefer format at an introductory level[326].

Habib & Bockris, writing on page 72 in Gutmann & Keyzer, stress that although examples of compliance with the Nernst-Planck equation certainly exist in the laboratory, they are rare. That equation and the subsequent Goldman and Hodgkin-Huxley equations are not consistent with most of the data concerning the BLM. Anderson & Fuchs have provided a

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[323]Gutmann, F. & Keyzer, H. (1986) Modern bioelectochemistry. NY: Plenum Press.

[324]Marino, A. (1988) Modern bioelectricity. NY: Marcel Dekker

[325]Cole, K. (1968) Membranes, Ions and Impulses. Berkeley, CA: University of California Press pg 200

[326]Matthews, G. (1991) Cellular physiology of nerve and muscle. Boston, MA: Blackwell Scientific Publications, pp. 27-50

particularly relevant paper[327]. They discuss the necessary changes to the Nernst-Planck model needed to represent a lipid bilayer. They also show that little or no ionic permeability exists on a steady state basis. They demonstrated the current due to a large lipophilic ion was exclusively a displacement current.

A. Katz (2011) has noted (page 372) the applicability of the Goldman-Hodgkin-Katz Equation for evaluating the potential across a membrane depends on the presence of an activity gradient across the membrane for, and the permeability of the membrane to, each of the ionic constituents in the equation. "The contribution of any ion to Em disappears if there is no activity gradient, or if permeability to the ion becomes zero."

Cullis & Hope have documented the remarkably limited permeability of lipid bilayers to Na+ and K+ ions[328]. Permeability coefficients of less than 10^{-10} cm/s are commonly observed, and they can be as small as 10^{-14} cm/s for Na+ and K+. For the example of a 100 nm diameter large unilamellar vesicles (LUV), this would correspond to a half-life for release of entrapped Na^+ of approximately 3.6 years.

As noted in **Section 1.4.2.3.2**, to avoid the limitations on the permeability of neural lemma to Na^+ and K^+, investigators have introduced the concept of pores in the lemma. It needs to be shown that a conventional continuous activity gradient is associated with these pores and that they do not operate like a vesicle that is only open to one fluid face of the lemma at a time (like a revolving door).

Yeagle has described a revolving door mechanism associated with the antibiotic, valinomycin, for transporting potassium ions through the BLM. Valinomycin is a dodecapeptide that forms a ring structure with an inner diameter very closely matched to the ionic radius of the dehydrated potassium ion. He describes a three-step process for the transport of the potassium through the BLM, involving potassium capture at one surface of the BLM, transport through the BLM and release of the potassium at the other surface. His caricature of the process (page 237) does not appear to be to scale. It is not clear how his ring structure, which is not a spherical Fullerene, isolates the potassium ion from the hydrophobic elements of the BLM. Typically, an organic encloses an inorganic through coordinate bonding. Such bonding does not change the ionic state of the ion itself.

Figure 1.4.2-5 presents the relative permeability of membranes to various molecules found in a biology textbook, and probably based on Table VII of Cullis & Hope. It clearly shows the minimal permeability of a membrane to sodium and potassium ions. Madigan et al. did not identify the specific form of membrane involved here. They note the virtual total lack of permeability of these membranes to polar molecules and ions except via the inclusion of putative membrane transport proteins. They assert, "The necessity for carrier-mediated transport mechanism in microorganisms can readily be appreciated." However, they fail to identify any of these mechanisms except at their conceptual level.

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[327]Anderson, O. & Fuchs, M. (1975) Potential energy barriers to ion transport within lipid bilayers. *Biophysic J* vol. 15, pp 795-829

[328]Cullis, P. & Hope, M. (1991) Physical properties and functional roles of lipids in membranes *In* Vance, D. & Vance, J. *eds.* Biochemistry of Lipids, Lipoproteins and Membranes. NY: Elsevier Chapter 1

Substance	Rate of permeability[a]
Water	100
Glycerol	0.1
Tryptophan	0.001
Glucose	0.001
Chloride ion (Cl^-)	0.000001
Potassium ion (K^+)	0.0000001
Sodium ion (Na^+)	0.00000001

[a]Relative scale—permeability with respect to permeability of water, given as 100.

Figure 1.4.2-5 Comparative permeability of membranes to various particles. From Madigan et al., 1997

They define an antiporter as a transporter that carries one substance across the membrane while simultaneously carrying a second substance across in the opposite direction. They note such active transport requires the expenditure of energy.

While they describe the membrane as a permeability barrier, Madigan et al. provide an interesting view that a biological membrane is highly permeable to water which they describe as "small and uncharged." Water is usually put in the class of highly polar if not charged. Their presentation appears suitable only for introductory pedagogy.

The findings of Anderson & Fuchs that the smaller the ion the less likely its ability to pass through a lipid bilayer is particularly interesting (page 797). Their potential barrier calculations (figure 1) are compatible with others. Gavach & Sandeaux also explored artificial bilayer membranes and provided an interesting quotation[329]. "The small values for the membrane resistance obtained with hydrophobic ions, as compared to those where inorganic ions are present in the aqueous solutions indicate that only the former ions can penetrate *into* [not through, editor] the membrane. This fact is corroborated by the sign of the Nernstian trans-membrane potential under zero current conditions."

In summary, since the intense work of the 1970's, it has been known that uninterrupted membranes of neural conduits are impervious to ions (even under pathological conditions).

1.4.2.4 The Nernst Equation and electrophoresis do not apply to the neurolemma

The findings of Karczmar et al. in **Section 1.2.1** and the caveat of Matthews in **Section 1.3.3** have already shown why the Nernst Equation does not apply to lemma in words. This section will provide more data to support the arguments. The following section will provide a more theoretical mathematical discussion.

The Nernst Equation describes the concentration gradient between two solutions on opposite sides of a symmetrical and homogenous membrane that is semipermeable to the solutes in the solutions. A condition of the application of the Nernst Equation is that the concentration gradient for each species of interest must be continuous. As documented by Anderson and Fuchs, both mathematically and illustratively, the typical bilayer lemma of a biological cell is not semipermeable to ions due to the very high energy differences found within the lemma[330]. **Figure 1.4.2-6** rearranges and expands their figure to stress specific features of their figure. Their potential energy is relative to the energy of the ion when in the dilute aqueous

[329]Gavach, C. & Sandeaux, R. (1975) Non-mediated zero voltage conductance of hydrophobic ions through bilayer lipid memberanes *Biochim Biophys Acta* vol. 413, pp 33-44

[330]Anderson, O. & Fuchs, M. (1975) Potential energy barriers to ion transport within lipid bilayers. *Biophysic J* vol. 15, pp 795-829

solution. The value of 5 electron-volts is a very high barrier in semiconductor physics, compared to the typical semiconductor barrier of about 1 electron-volt or less. Pure carbon in the form of a diamond, a very impervious material, has a band gap of 5.4 electron-volts.

They focused their calculations on the negative ion of 7×10^{-8}M tetraphenylborate and 0.1M sodium chloride in water solution. This solution obeys the rules of ionic electrochemistry. They noted, "Certain organic anions, e.g. tetraphenylborate, absorb strongly into the membrane-solution boundary regions. These ions will therefore provide information about the shape of the potential energy barrier in the middle of the membrane, independent of assumptions about what happens at the membrane-solution interfaces." They remarked the sodium ions did not show a proclivity to associate with their lemma like the tetraphenylborate ion did. As noted in **Section 8.4**, sodium does not exist as a simple ion in water at this molarity. It is complexed with the water to form a much larger structure, usually $Na^{+}\bullet(H_2O)_6$

They did not examine in detail the barrier layers usually associated with biological lemma as developed in **Sections 3.3 & 3.4.**

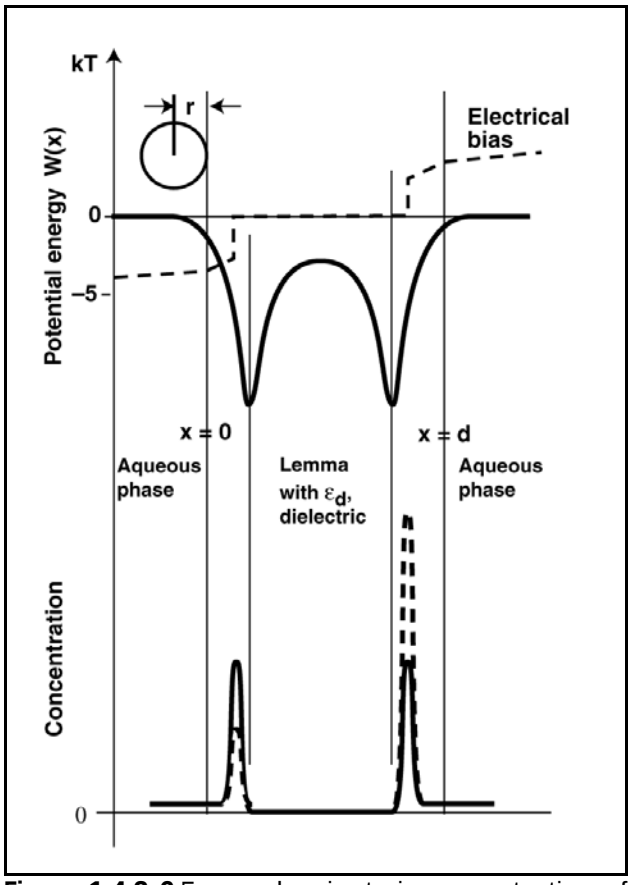

Figure 1.4.2-6 Energy barrier to ion penetration of a symmetrical lemma. Top; the energy barrier as a function of position. Also shown is the radius of an ion and the potential (dashed line) as a function of position after electrolytic equilibration. Bottom; the distribution of ions in the absence of any voltage applied between the solutions. Dashed shows distributions with an applied potential. See text. Expanded from Anderson & Fuchs, 1975.

The upper frame shows the potential energy profile across a lemma based on the combination of hydrophilic and lipophilic regions within the lemma. The solid line shows two very high energy barriers within the lemma in the absence of any electrical bias across their simple test cell (they also used a Ussing type cell initially for comparison purposes). These two energy barriers rise essentially asymptotically at the center of these regions and constitute discontinuities that introduce significant mathematical difficulties into any analyses requiring a continuous concentration gradient across a semipermeable barrier (such as the analyses of Nernst, of Donnan and of Goldman require). The dashed line shows the effective electrical bias imposed on the test cell after the transient following application of the bias. There is a small voltage gradient within the aqueous phases due to the IR drop while electrical charges move through the solvent in order to polarize the capacitance of the lemma. This gradient disappears as the capacitor becomes fully charged and the voltage drop across the aqueous phases returns to zero. All of the applied electrical bias now appears across the lemma capacitance.

> Anderson & Fuchs stressed the importance of the effective potential in their calculations. "An additional, but often overlooked, problem is that ion transport through membranes should be related to the effective potential influencing ion movement within the membrane, not to the applied potential."

The lower frame shows the concentration of tetraphenylborate ions within the test cell. In the

absence of any electrical bias (solid line), the concentration shows the affinity of the ion for the phosphatidylethanolamine bilayers of their lemma. Notice that the peak concentrations occur along the outer slopes of the potential energy barriers. No ions have actually penetrated the lemma. Upon application of an electrical bias (nominally 75 mV in their example), the concentrations of ions increase at one barrier and decrease at the other (dashed lines), effectively charging the capacitor formed by the lemma with its dielectric constant of about 2.0. Still no ions have actually crossed the lemma. Anderson & Fuchs describe the transient displacement current associated with this charging of the lemma capacitance (~6 x 10^{-9} F/mm^2). They demonstrate the only current present is this displacement current. They reported time constants of τ = 1.42 ms charging and τ = 1.95 ms discharging. However, their transient responses show a function that differs significantly from an exponential. Their analysis accounts for this difference. They note, "At higher concentrations we find that the apparent time constant increases with increasing $TphB^-$ concentration due to diffusion polarization. Diffusion polarization reflects the changing distance between the two centroids of ion concentration with changing potential. Alternately, it could be due to the inhibition of ion movement by the complex barrier layer usually encountered in biological lemma (**Section 3.4**). They speak of crossing the edges at x = 0 and x = d as passing through the membrane rather than the more correct, passing through the membrane wall or passing into the membrane. No steady state current was found that actually passed through their type 1 phosphatidylethanolamine bilayer lemma. Their graphs use the term conductance when their text refers to the" initial conductance" associated with a transient phenomenon that dies out.

Anderson & Fuchs focused on molarities below 3 x 10^{-7}M and noted other affects occurring at molarities above 10^{-6}M when discussing their figure 7. These molarities are still far from the electrolytic chemistry range.

Note the concentration of the solute is finite in the aqueous phase and rises and falls on the skirts of the energy barriers, but remains zero between the two barriers (unless sufficiently high bias fields are applied to cause electrical breakdown of the lemma dielectric). The concentration gradient is undefined at the barriers (mathematically discontinuous) and undefined or zero within the bulk of the lemma. Therefore, the Nernst Equation does not apply to their type 1 lemma. The work of Anderson and Fuchs is critically important to the study of bioelectrochemistry. Donnan, and later Goldman, have attempted to modify the Nernst Equation at the margins so that it provides numerical values equal to those measured on opposite sides of real membranes of real neurons under a specific set of conditions. The measured values were actually due to the electrical potential established within the axoplasm enclosed by the multi-port axolemma of a neuron due to current passing through the Activa (the first port) and the electrostenolytic process involved in biasing the Activa (at the second port) as illustrated in **Figure 1.2.2-2**.

Barenholz & Cevc[331] have provided similar data to Anderson & Fuchs but using a "chemical" scale for the vertical axis. They provided data similar to that above for the entrance into (but not penetration) of the membrane by oxygen, water, and NH_3. They note, "For water soluble substances, such as inorganic ions, the membrane interior is a permeability barrier maximum, for fat-soluble substances, such as organic ions, the same region acts as a trap. In either case, exchange of material between the aqueous compartments separated by a membrane is hindered."

Leermakers & Kleijn[332] have provided more recent but similar data to Anderson & Fuchs using electrostatic scales. They note the more asymptotic (and higher spatial resolution) character of the electrostatic potential given by the self-consistent-field (SCF) technique of calculation.

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[331]Barenholz, Y. & Cevc, G. (2000) Structure and properties of membranes in Baszkin, A. & Norde, W. eds. Physical Chemistry of Biological Interfaces. NY: Marcel Dekker Chap 7

[332]Leermakers, F. & Kleijn, J. (2004) Molecular modelling of biological membranes: structure and permeation properties *In* van Leeuwen, H. & Koster, W. *eds*. Physicochemical Kinetics and Transport at Biointerfaces. NY: John Wiley & Sons Chap 2

The Nernst, Donnan and Goldman variants of the basic Nernst Equation do not apply to the type 1, 2 and 4 lemma of neurons. To overcome this problem, recent investigators have proposed "pores" capable of opening and closing, under control of an unknown hand, to account for the transport of charged alkali and alkali earth ions across the lemma. There is not yet any demonstration of the validity of this concept. In this work, the type 3 lemma contains embedded proteins capable of transporting neutral molecules, but not ions, across the lemma by complexing with those molecules.

Electrophoresis is a very valuable laboratory analysis technique used to identify solutes in a solution empirically. The apparatus applies an electrical potential between the solutions containing the unknown solutes that are separated by a symmetrical semipermeable membrane in a Nernst Cell apparatus. The membrane is usually described as a "column." The column satisfies the requirement of concentration gradient continuity needed to satisfy the Nernst Equation. As a result, different solutes travel down (across) the column at velocities controlled by their net electrical energy, their physical size (related to molecular weight), and the potential gradient applied across the column. With time, the location of the solutes become separated within the column. The column is then removed from the electrical field and dried. The visibility of the various solutes is then made more visible using a variety of dyeing agents.

The process of electrophoresis plays a negligible role with regard to the lemma of neurons, and other cells, because the requirement of a continuous concentration gradient is not met within the lemma.

1.4.2.4.1 Description of the mathematical solution of the real concentration gradient of a neurolemma

It is common for recent authors in the life sciences to discuss the mathematics of molecular motion across a membrane. Atkins & Paula are one of the most recent[333]. It should be noted their analysis is superficial. They begin with the second order linear differential equation known as the simple wave equation. They define a steady state situation such that all terms involving time are eliminated. They also define two boundary conditions, the concentration, [A], equal to $[A]_0$ at one surface of the membrane and equal to zero at the second surface. They then replace the generic term a^2 by D giving the ordinary differential equation of second order in one variable;

$$a^2 \partial^2[A] / \partial x^2 = D \partial^2[A] / \partial x^2$$

They then provide the first of two solutions to this equation, known as the general solution by solving the homogeneous equation (a differential equation with zero as the right hand term);

$$D \partial^2[A] / \partial x^2 = 0$$

They are correct, the general solution is;

$[A](x) = [A]_0 (1 - x/l)$ for $0 < x < l$, and they note, "which implies that [A] decreases linearly inside the membrane."

However, this is only the general solution. As noted by Churchill in his seminal book on boundary value problems[334], introductory courses in ordinary differential equations "stress the method of obtaining a solution of the problem as stated, and give less attention to the precise statement of the problem that would ensure that the solution found is the only one

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[333] Atkins, P. & Paula, J. (2006) Physical Chemistry for the Life Sciences. Oxford, UK: Oxford University Press Section 8.2

[334] Churchill, R. (1941) Fourier Series and Boundary Value Problems. NY: McGraw-Hill page 94

possible." That is the precise situation here. Atkins & Paula failed to state probably the most important boundary condition of all, the concentration gradient, F(x) within the membrane.

It is now necessary to determine the particular solution that describes the precise statement of concentration using the non-homogeneous equation (a differential equation with a function as the right hand term);

$$D\partial^2[A]/\partial x^2 = F(x)$$

within the membrane , ***and remove the "implication" stated by Atkins & Paula***. One example of this concentration for a real membrane, *F*(x), is shown above from Anderson and Fuchs. The complexity of this concentration does not lead to a compact mathematical solution. The two asymptotic conditions shown within the membrane are related to discontinuities in the concentration. The presence of such discontinuities falsify the assumptions of Nernst, of Donnan and of Goodman concerning the neurolemma. To account for these two asymptotes mathematically requires the use of residue techniques even beyond the applicability of conventional Fourier Series.

Graduate and post graduate investigators should not rely upon the general solution to a homogeneous differential equation. They must address the particular solution. The total solution of the simple wave equation for a neurolemma is the sum of the general and particular solutions, and the three boundary conditions, *F*(x) $[A]_0$ = [A] and $[A]_l$ = 0 and evaluated with the terminal boundary conditions..

1.4.2.5 The chemical and electrical characteristics of a simple membrane *system*

A simple cylindrical conduit plays a major role in the neural system. **Figure 1.4.2-7** illustrates the situation; (a) shows the chemical arrangement of the material forming the outer membrane, (b) shows the elementary electrical circuit applicable to the membrane, (c) shows a fundamental cell in topological form, both chemically and electrically. Also shown is the boundary layer between the wall and the enclosed electrolyte. This boundary layer was discussed earlier. Its significance will be discussed more fully in **Section 1.4.2.7.2**.

(a) emphasizes the geometric arrangement of the two phospholipids. The total thickness of the membrane is usually less than 100 Angstrom. The circles represent the polar heads of each molecular film and the two short lines represent the two hydrocarbon chains of the molecule. The inner core of the bilayer membrane is highly hydrophobic while the external surfaces are hydrophilic. As a result, the fundamental BLM is essentially impervious to ions. The case shown is asymmetrical with the outer layer containing PC and the inner layer containing PE.

(b) illustrates the equivalent electrical circuit of a molecularly asymmetrical bilayer membrane. As indicated above, the membrane is impervious to ionic charges. However, it is semipermeable to fundamental electrical charges. The diode allows a conventional current to flow easily from the inside the membrane to the outside. Thus, an enclosed membrane cannot support a positive potential on its inside surface. However, if the membrane is subjected to a bias such that the inside is negative, the diode is reverse-biased and no significant current will flow through it. A battery is shown in series with the diode. Based on experimental data, this battery is usually of less than 50 mV static potential and of either polarity depending on the particular phospholipids present. This battery represents the intrinsic membrane potential of a bilayer sandwich. This battery is due to a quantum-mechanical mechanism and is part of an *equivalent circuit*. *It does not exist alone or in the absence of a polarizing bias across the membrane*. Because of the thinness of the membrane, it exhibits a significant capacitance per unit area.

Kinnunen & Virtanen have described their concept for the transfer of electrons along properly arranged ethylenic double bonds of unsaturated nerve membrane lipids forming

liquid crystalline films[335]. Their configuration appears compatible with that defined above. However, there are alternatives to their ethylenic double bonds. Both hydrogen bonding and potentially tunneling have appeared in the literature as mechanisms for increasing the conductivity of lipids.

(c) illustrates a cross-section of an electrical conduit formed of a BLM. The left and right quadrants are drawn to show how the phospholipids form a hollow cylinder. This cylinder contains a lipophilic barrier to the movement of ionized particles as shown by the dashed line. The molecules are also in a closely packed liquid crystalline arrangement that makes a formidable barrier to penetration by any large particles.

For the molecularly asymmetrical bilayer shown, the electrical equivalent circuit shown in the top and bottom quadrants of the figure are appropriate.

An electrostenolytic process is shown by dotted lines in the lower quadrant of the frame. It effectively connects the interior electrolyte of the system to the external electrolyte. By proper choice of reactants, an electrical charge can be injected through the membrane and into the space labeled the boundary layer. If this charge consists of electrons, the interior of the membrane will develop a negative electrical potential compared with the interneural matrix, INM. Since the equivalent diode of the membrane is reverse biased, this potential will only decay slowly in the absence of continued electrostenolytic action. However, as Matthews postulated, a finite amount of electrostenolytic activity is required to maintain the interior cytoplasm at a quiescent potential compared with the INM[336]. The precise value of this intrinsic cytoplasm potential is given by the solution of the electrochemical equation for the current through the electrostenolytic process and the equivalent batteries and diodes as given by Kirchoff's Laws.

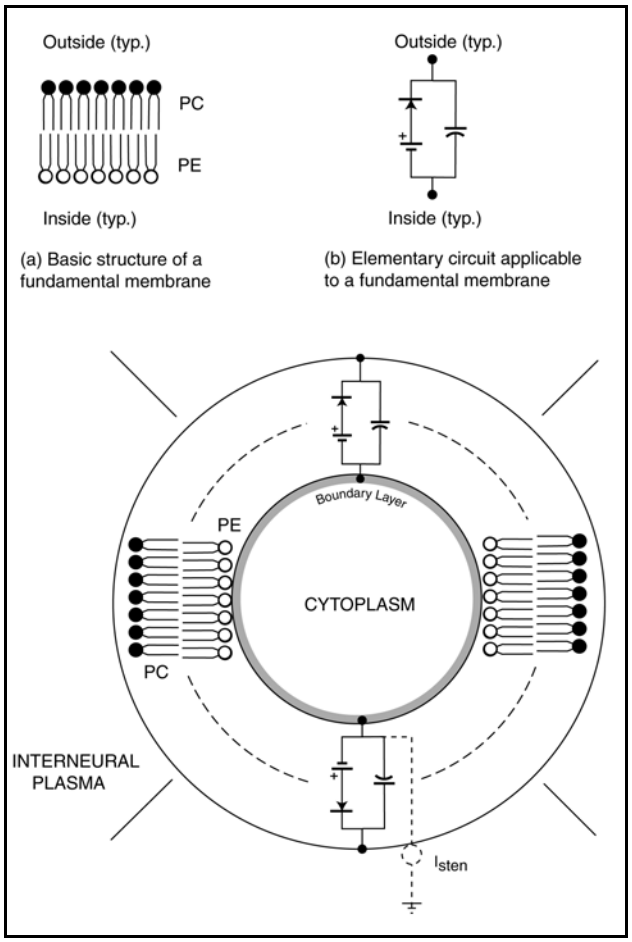

Figure 1.4.2-7 The physical and electrical structure of a typical cell conduit. (a) Basic molecular structure of the membrane. In asymmetrical membranes (type 2), the two phospholipids are different. When they are the same (type 1), the material is typically an electrical insulator. In either case, the hydrophobic core of the membrane is impervious to ions. Only type 2 membranes are shown in the figure. (b) Basic electrical network of membrane. (c) Caricature of conduit showing both molecular and electrical characteristics and the boundary layer between the wall and the electrolyte. The electrostenolytic process is shown dotted.

1.4.2.6 Equilibrium conditions for a biological membrane between two electrolytes

Any discussion of equilibrium should differentiate between static equilibrium and dynamic

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[335]Kinnunen, K. & Virtanen, J. (1986) *in* Gutmann, F. & Keyzer, H. Modern Bioelectrochemistry. NY: Plenum Press, pg 459

[336]Matthews, G. (1991) Op. Cit.

equilibrium. These are fundamentally different situations in neuroscience. Static, or quasi-static equilibrium, is most often encountered in the laboratory under *in-vitro* conditions. The term quasi-static equilibrium is introduced here to account for the fact that most *in-vitro* experiments cannot be maintained for very long because of the consumption of unknown and undocumented metabolic supplies. Dynamic equilibrium is encountered whenever *in-vivo* experiments are performed.

Some experimenters have attempted to move from quasi-static to dynamic *in-vitro* conditions through continuous oxygenation of their electrolytes. While this practice may have an observable effect, it probably has little direct effect on the anaerobic nature of the neural signaling process (**Section 1.4.3.xxx**).

The premise of Mathews must be carefully considered when discussing BLM systems[337]. His summary position is that animal cells are not at equilibrium because their ionic concentrations are not at equilibrium with their surroundings. Therefore, metabolic energy must be continually expended to maintain the quiescent condition. While his position is rational based on the conventional wisdom related to membranes porous to ions, it is irrelevant to neural conduits formed of fundamental BLMs that are impervious to ions. If the membrane is impervious to ions, the concept of osmotic equilibrium between the interior and exterior of a conduit does not apply.

However, a fundamental BLM is semipermeable to fundamental electrical charges. This condition could lead to a continuous lack of electrical equilibrium and a continuous requirement for the expenditure of energy to maintain a status quo. This condition is avoided by keeping the interior of the asymmetrical membrane at a negative potential. Such a condition requires no continuous expenditure of energy.

This situation justifies the need for a charge-pump but discounts the need for an ion-pump. In a non-neural cell, the need for a charge-pump is minimal. However, in a neuron, the continuous action of the Activa requires a more active charge-pump.

1.4.2.6.1 Affect of diffusion on the electrochemistry at the membrane-electrolyte boundary

The long term diffusion of ions and particles across selected regions of the neural membrane obviously occurs. Such movement supports cell genesis and metastasis. It is proposed that this process is found only in more specialized and complex regions of type 3 membrane described by others as "fluid mosaic zones" or using subunit models[338]. This diffusion generally occurs slowly and has no significant impact on neural signaling. It is proposed any ions must become associated with other molecular structures and achieve electrical neutrality before passage through the membrane (probably via proteins embedded in the membrane).

1.4.2.6.2 The complexity of the diffusion environment near the membrane

The complexity of the diffusion environments internal to and external to the membrane conduit and their ability to support the various electrostenolytic processes is closely tied to the morphology of the local neural structures. This subject will be addressed in detail in **Chapter 9** following the discussion of a variety of individual neural morphologies.

1.4.2.6.3 The mathematics of electrical equilibrium for a real membrane

The mathematics of electrical equilibrium related to a real membrane between two electrolytes can be quite complex. The equilibrium associated with each type of charged

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[337]Matthews, G. (1991) Cellular physiology of nerve and muscle. Boston, MA: Blackwell Scientific Publications, pg. 1

[338]Eckert, R. (1988) Op. Cit. pp. 69-71

species must be considered. However, the premise of this work is that only type 1, 2 & 4 membranes are relevant to signaling within the neural system. The internal lipophilic regions of these membranes make them impervious to polar ions. The resulting problem resolves down to the solution of the equilibrium condition associated with the flow of fundamental charged particles, electrons and holes.

For a fundamental BLM that is not a complete insulator to the flow of electrical charges, a quantum-mechanical potential barrier exists within the membrane. The potential gradient within the membrane is not constant with respect to position within the membrane. Written in differential calculus form, $dV/dx \neq V/a$ where V is the total potential across the membrane of thickness a and x is the position within a. This potential barrier results in an asymmetrical porosity with respect to charges that is not addressed by a constant field equation such as that of Goldman or Hodgkin & Huxley. The resulting variable field theory proposed here is based on this condition. It is not new. It is used throughout semiconductor physics.

This alternate theory related to fundamental charged particles can be summarized by comparing it with the derivation of the constant field theory of Goldman. Either the material of Starzak or a more concise presentation provided by Matthews can be applied to fundamental charges as easily as to ions[339]. The above inequality is taken as an equality in his equation B-4. Therefore, equation B-5 does not follow from equation B-3 and the appropriate differential equation is of a higher order than assumed by Goldman. In solving the equation of B-5, Goldman employed definite integrals. The limits he chose are appropriate but do not allow for the presence of an electrostenolytic process on one surface of the membrane. Such a process would introduce another fixed potential into the earlier equation B-1. Although this addition would not add significant complexity to the mathematics, it does change the form of his equation B-1. This changes the form of the equation following B-11, and after factoring, results in a new variable field equation describing a real asymmetrical membrane. The precise solution of this equation depends on the profile of dV/dx and will be left to others to define. See Anderson & Fuchs.

The primary concern of the variable field theory, particularly within the time span associated with neural signaling, is with the transit of electrons and holes and ***not ions***.

Turiv et al. have provided useful informaton concerning the flow of spherical particles along the long axis of nematic materials, a situation pertinent to this discussion and **Section 2.2.1.3**[340].

1.4.2.7 The interactions at a metal-electrolyte interface–electrodics

The theory of metal-electrolyte interfaces (electrodics), while not involved directly in the bioelectrochemistry of the neural system, provides a valuable point of reference. The concept of the Helmholtz layer (and its physical dimensions) will be play an important role in the operation of the three-terminal axon conduit developed in **Chapters 2 & 9**. This section will be brief. A more complete discussion can be found in a companion document on the world wide web[341].

Bauer has prepared a small book that provides a useful introduction to electrodics[342]. It provides definitions and a discussion of the limitations on the current art. It can serve as a

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[339]Matthews, G. (1991) Op. Cit. Appendix B

[340]Turiv, T.Lazo, I. Brodin, A. et al. (2013) Effect of Collective Molecular Reorientations on Brownian Motion of Colloids in Nematic Liquid Crystal *Science* 342, 1351-1353

[341]— www.sightresearch.net/pdf/10Morphology.pdf Section 10.1.3.2

[342]Bauer, H. (1972) Electrodics: Modern Ideas Concerning Electrode Reactions. Stuttgart: Georg Thieme

jumping off point to electrolytics to be developed below. There is a similar book by Fry[343]. Bauer devotes several pages to shortcomings in the theory in the 1970's time period. While the art has moved forward, it has not addressed the electrolytic interface discussed in this work.

Bauer noted a problem with the theory presented in his section 2.2.1. "The equations are written without a precise definition of the process to be described, other than it involves charge transfer." He notes this condition was not unique to his presentation but was common in the literature of the time.

1.4.2.7.1 The Helmholtz region or double layer at an electrolyte interface

When discussing the static condition of an axoplasm biased relative to the surrounding medium, the situation resembles the situation found in the double layer adjacent to a metal in a electrochemical cell[344]. However, the metal electrode is replaced by a dielectric with another electrolyte on its opposite surface. The condition resembles that shown at the top in **Figure 1.4.2-8**. The bilayer membrane forming the lemma is of type 1 and acts as a perfect insulator. The surfaces of the bilayer membrane are susceptible to adsorption by a variety of molecules found in both the axoplasm and the INM. In this case, only adsorption within the axoplasm is shown. For a more comprehensive discussion of the nature of the double layer at a fundamental level, see Bockris, et. al[345].

On the assumption that the type 1 bilayer membrane is molecularly symmetrical, and does not exhibit any space charge non-uniformity, the potential appearing in the vicinity of the membrane is shown at the bottom of the figure. If the membrane exhibited a variation in space charge, the diagonal line connecting the potential on each side of the membrane would not be a straight line. Under this condition, the membrane would also exhibit an additional capacitance beyond that calculated based on its geometry and permittivity.

Note that adsorption of ions (and molecules) on the surface of the membrane can change concentration of species near the membrane and thereby change the local potential drastically, even causing it to become more negative than the adjacent bulk electrolyte. This effect can affect the operation of the overall interface significantly.

The physical model presented here does not change significantly when the interneural matrix is replaced by a liquid crystalline material and the bilayer membrane is made asymmetrical. However, the electrical potential within the membrane will no longer be a linear function of position and may document the presence of a space charge variation as well.

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[343]Fry, A. (1972) Synthetic Organic Electrochemistry. NY: Harper & Row

[344]Mohilner, D. (1966) The electrical double layer *In* Bard, A. Electroanalytical chemistry, vol. 1. NY: Marcel Dekker, Inc. pp 243 & 310-311

[345]Bockris, J. Devanathan, M. & Muller, K. (1963) On the structure of charged interfaces Proc Royal Soc London vol. 274, pp 55-89

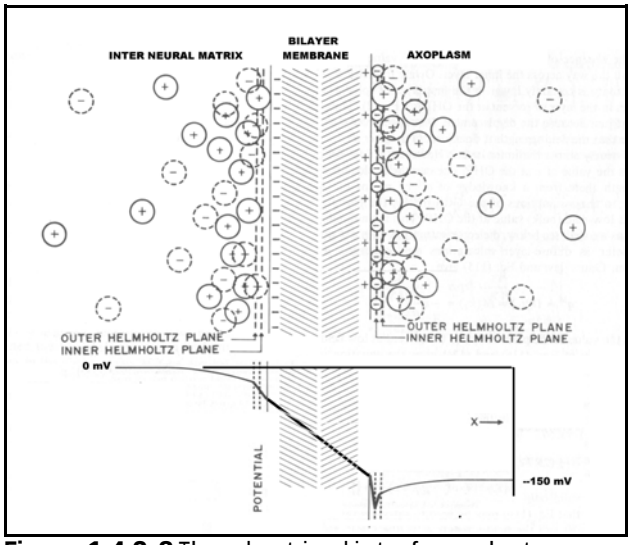

Figure 1.4.2-8 The electrical interfaces between a dielectric lemma and the adjacent electrolytes (plasmas). Dotted circles represent "ghosts" of anions repelled in diffuse layer. The left half assumes the absence of specific adsorption. The right half assumes adsorption at the dielectric interface. Built from information in Mohilner, 1966.

The inner and outer Helmholtz layers are quite thin in electrolytes of reasonable concentration. A table of the overall thickness of the charge layer is provided by Mohilner (page 247) and is reproduced in modified form as **Figure 1.4.2-9**. It applies to the concentrations of typical axoplasms. Sea water is often correlated with axoplasm. If the difference in viscosity between the two does not lead to a difference in electrical diffusibility, the electrolyte concentration (dominated by the sodium ion) near the wall of a BLM-axoplasm interface should be about 0.45 M. Based on this value, the thickness of the total diffuse layer thickness at the inner wall of the lemma is about 0.002 microns. The calculated molarity of sea water is based on Sverdrup, et. al[346].

A thickness of only 0.002 microns (2 nanometers or 20 Angstrom) in the thickness of the Helmholtz region has a major effect on the transport of electrons along the wall of the axolemma, as will be discussed in **Chapter 9**.

Electrolyte* Concentration	Ionic Charge	Thickness of Layer (99.99% of diffuse-layer effect)	
10^{-6}M	1	28 000 A^{O}	**2.8 microns**
	2	14 000	**1.4**
	3	9 400	
10^{-4}	1	2 800	
	2	1 400	**0.14**
	3	940	
10^{-2}	1	280	
	2	140	**0.014**
	3	94	
10^{-1}	1	88	
	2	44	
	3	30	**0.003**
0.45	**1**	**19**	**~0.002 ****

*z-z-valent electrolyte considered
****NaCl in sea water**

Figure 1.4.2-9 Effective thickness of the diffuse layer for z–z electrolytes at 25 C. Note change in concentration interval.

1.4.2.8 More detailed electrical circuit of the plasma membrane

The electrical model of the neural membrane is somewhat more complex than generally described in the literature when the Helmholtz region is considered. Rather than consisting of a resistive material in parallel with a capacitance as shown in frame **A** of **Figure 1.4.2-10**, it is more appropriately shown as in **B** or **C**. The circuit shown in A is usually modified by replacing G_m by a series of parallel G_m's in parallel in order to provide a piecewise linear representation of the experimental data. **B** shows the preferred electrical description of a type 1 BLM and **C** shows the preferred description of a type 2 BLM. In **B**, the membrane will exhibit an extremely high resistance due to the back to back diodes. In **C**, the series impedance of the single equivalent diode, D_m, will be much lower than in **B**. Equally important, the impedance associated with D_m is identical to the data used to establish the piecewise linear approximation used in **A**. G_s and C_s represent the conductance and capacitance of the solution and C_p represents any stray capacitance associated with the test set.

[346] Sverdrup, Johnson & Fleming (1942) The Oceans. NY: Prentice-Hall *In* Handbook of Chemistry & Physics, 56th ed. Raton, FL: CRC Press pg F-199

When measurements are made on type 2 BLM, it is important to note the character of the overall electrical circuit. Particularly when making AC measurements, the overall circuit of **C**, without considering the properties of the metal-electrolyte interfaces, can act as a clamp circuit. This action can cause the measured capacitance, $C_m + C_{sc}$, to be a function of the frequency of the AC waveform. A similar situation is encountered in most measurements where a DC path is maintained through the test configuration.

The complex circuits discussed here can help explain the non-exponential transient responses recorded by Anderson & Fuchs.

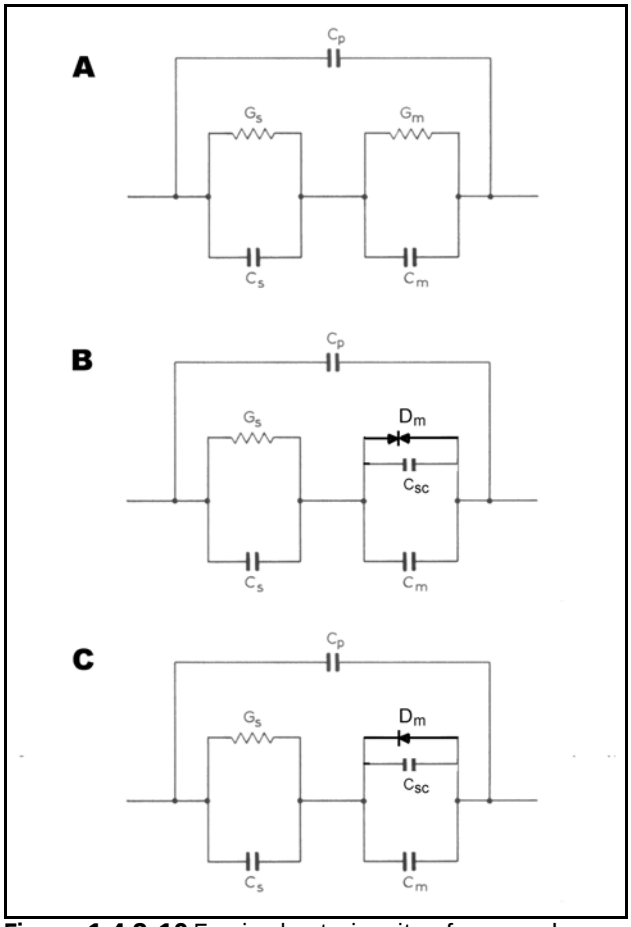

Figure 1.4.2-10 Equivalent circuits of a membrane and its adjacent solution. A; the simple circuit of many texts. B; the more detailed circuit of a type 1 BLM. C; the detailed circuit of a type 2 BLM. See text.

1.4.2.9 The generic transmembrane material pump

It is likely that water molecules are transferred through the plasmalemma of a cell by embedded cholesterol, and potentially other sterols.

With the immense powers of the nucleus of a cell, and surrounding regions within the soma, to manufacture individual proteins and perform glycolysis, it is only necessary to transfer a small number of chemicals through the plasmalemma of a neuron. These include;

1. Oxygen, glycogen, H_2O, CO_2,

2. Either a variety of amino acids or a source of ammonia suitable for building amino acids,

3. A source of phosphoric acid or a variety of phospho-triglycerides.

4. And a variety of materials providing trace amounts of other critical atoms.

Most theories associate the transfer of this limited list of chemicals to the formation of protein based areas as discussed above. Many additional chemical reactions can occur on the external surface of the plasmalemma in support of neural operation. Only those additional chemical transformations occurring within the cell require the transport of additional reactants through the plasmalemma.

Lacking an adequate electron microscope image of a transmembrane material transfer mechanism, the community has been free to speculate on the mechanism. This speculation has spawned an endless variety of block diagrams and caricatures. Each variant has been supported primarily by kinetic evidence, frequently drawn from experiments on a different but chemically related species. Some evidence has been obtained from gross measurements of concentration changes, usually under *in-vitro* conditions. Such approaches are awkward. The proposed hypothetical mechanisms are frequently labeled pumps in the vernacular as a convenience. A generic kinase is frequently associated with the mechanism in the absence of any additional understanding. This is the case in **Figure**

1.4.2-11 with apologies to Mullins who presented a similar block diagram in 1971[347]. The labels have been made more generic than in the original as the diagram seems compatible with almost any chemical species. Several additional arrows were provided in the original drawing. These suggested a variety of other materials might augment the basic machinery. The arrows associated with the rightmost pump are reproduced as in the original. The two pumps on the left can be considered as independent or as coupled depending on the argument to be made. If they are coupled, it is frequently proposed that the coupling is complicated and not representative of a one-to-one transfer process.

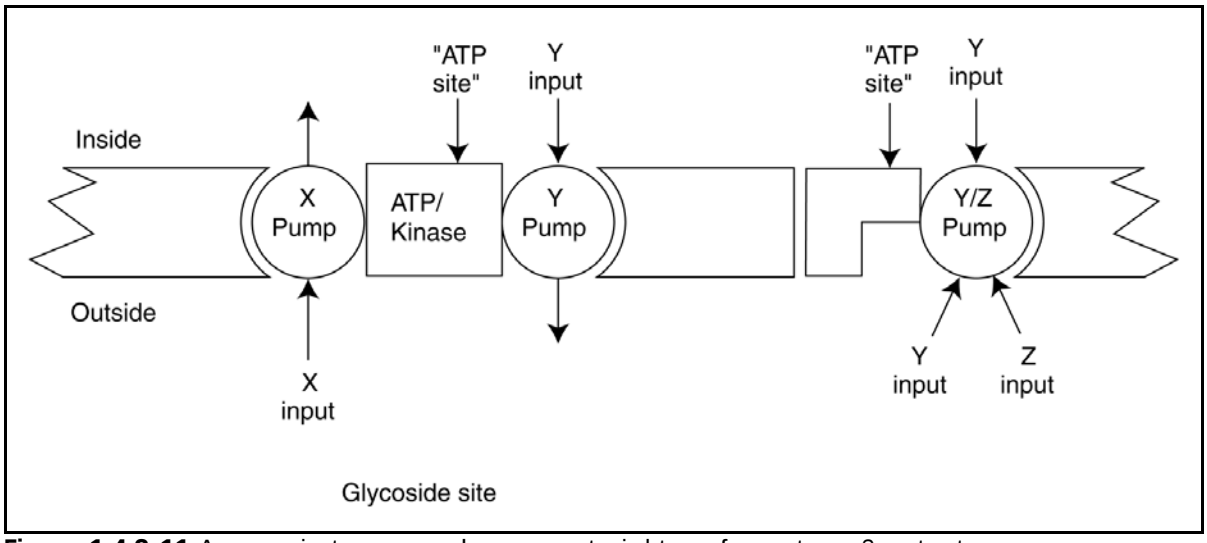

Figure 1.4.2-11 A generic transmembrane material transfer system. See text.

The description of this type of block diagram in caricature is where the fun begins. Are individual pumps provided for each species? If the pumps are coupled, how are they coupled and with respect to what species? In the chemical domain? In the physical domain? In the electronic domain? In the neural domain? Does one kinase support the transfer of two distinctly different materials in opposite direction? Virtually all of the above approaches have been proposed in the literature of biological transmembrane transfer.

Do the pumps represent a vesicle type structure that can either penetrate the membrane or do they represent an embedded vesicle that can access both the internal and external plasmas? If the pumps represent a pore, how is control of the species to be transferred accomplished? In either case, can the mechanism transfer a free ion or only complete (electrostatically neutral) molecules?

A fundamental framework that explains the transmembrane transfer of a variety of materials is desperately needed at this time.

1.4.2.10 Caricatures of a membrane pore from the literature

Caricatures of a pore composed of a protein material forming a cylindrical aperture passing through a BLM have been common for a very long time. Some X-ray crystallography has been interpreted as supporting such a configuration. Unfortunately, no electron micrograph of such a pore has appeared. Unwin has carried the caricature of the acetylcholine receptor (pore) the farthest. His data was gathered from the post synaptic membranes of the electric organ of the torpedo ray, *Squaliformes Torpedo nobiliana*. The Order defines the

[347]Mullins, L. (1971) *in* Bolis, C. et. al. *ed*. Permeability and function of biological membranes. Amsterdam, North-Holland Pub. Co, pg 200.

sharks. He assumes this data is generic to all synapses of other animals. No details were provided about where within the post synaptic membrane (inside or outside the gap junction) the proposed pores were located. His 1993 review provided proposed dimensions based on calculated sizes of various proteins[348]. The proposed pore is 80 Angstrom in diameter and 110 Angstrom long with about 55 Angstrom extending into the extracellular space. This latter dimension causes a problem. If the pore was present within the gap junction, the pore would extend across the entire width of the gap. Unwin does define a separate structure, a porin, as occurring within the gap junction. Based on this, it can be assumed his ligand-gated pores do not occur within the gap junction.

The review clearly defines the exploratory and conceptual nature of the field. The paper highlights the wide variety of purported neurotransmitters and the leading caricature of a pore. The description relies heavily on words like may, must, is likely to be, thought to be, despite, do not know, it is possible and another possibility. The review also defines two separate classes of pores, putative voltage-gated ion channels and putative ligand-gated ion channels.

Stephenson & Strange have provided a slightly modified version of Unwin's conceptual drawing of a pore[349].

The largely conceptual framework for the pore as a physical mechanism associated with neural signaling does not compete with the measured data associated with the BLM as an electrical diode. If operated as a gate, the pore continues to rely upon a difference in concentration density for the driving force behind the transfer of ions. The "three-dimensional image" in Unwin's figure 4 may be a caricature based on computer modeling with artificial surface reflectance added to provide detail not available in an electron micrograph.

The comments of Unwin on page 32 concerning the receptor sites of glutamate are encouraging. However, he is unable to associate these sites with a pore or channel. No references were provided for his comments.

Before the introduction of the electron microscope, no method was available to image the BLM in detail. Since then, new images appear regularly. However, most images have centered on the synaptic region and the Nodes of Ranvier. These images have shown the unique electronic configuration of these regions along with a nearly uniform bilayer biological membrane (**Sections 10.6.3** & **10.7.1**). Little or no sign of vesicles or other pores in the membrane have been recorded. This is probably understandable for two reasons. First, little functional reason exists for such metabolic material transfer mechanisms to be found in these regions. Second, if they occurred in these regions, their highly transient nature (required if they are to support a 100-1000 Hertz bandwidth signaling function) would be difficult to record. The problem would be aggravated by the sample preparation procedures required in current electron microscopy.

Ritchie and Rogart have provided a calibration for the difference between type 2 and type 1 BLM based on their pharmacological experiments[350]. They measured the relative binding of tritiated saxitoxin to rabbit sciatic nerve membrane. They note the physiological inhomogeneity of myelinated neuron, even when demyelinated. Speaking of an axon segment, they say that nodal membrane has an electrical conductivity per square micron 500 times higher than internodal membrane based on this relative binding. While they associate this phenomenon with a difference in putative density, 12,000 vs 25 channels per

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[348]Unwin, N. (1993) Neurotransmitter action: opening of ligand-gated ion channels *Neuron* vol. 10 (suppl) pp 31-41

[349]Stephenson, F. & Strange, P. (1993) Receptors for neurotransmitters, *Chapter 2 in* Shinitzky, M. Biomembranes. NY: Balaban Publishers

[350]Ritchie, J. & Rogart, R. (1977) Density of sodium channels in mammalian myelinated neerve fibers and nature of the axonal membrane under the myelin sheath *Proc Natl Acad Sci USA* vol. 74, no. 1, pp 211-215

square micron, of sodium channels (in accordance with the chemical theory of the neuron), it is more easily described by one of two quite different situations.

1. The relative ability of the saxitoxin to bind to sites associated with the asymmetrical molecular structure of the type 2 BLM, and particularly sites of electrostenolytic activity.

2. The relative ability of the saxitoxin to bind to sites associated with type 3 BLM involved in molecular transport through the membrane.

Their extended discussion of the potential areas of the putative gates compared to the total size of the available membrane and the precision of their calculations (factors of two or larger) testify to the tentativeness of their conclusions.

A more extensive examination of the regions of the plasmalemma of a neuron may expose the location of regions dedicated to the transport of metabolic materials. However, examining the total surface area of a neuron at the required resolution is a time-consuming process.

1.5 Measured electronic characteristics of <u>type 2</u> membranes

The biological literature, without being specific, has long represented the equivalent electrical circuit of a BLM by a battery in series with a variable resistor (sometimes shunted by a capacitor). This representation is an oversimplification. To compensate for this difficulty, authors describing the lemma of an axon have frequently resorted to using multiple current paths with each path represented by a battery and a variable resistor in series. Justification for this representation has relied upon the "independence principle" introduced by Hodgkin & Huxley (**Section 1.3.2.1**) but never defended or demonstrated. This principle is not found in or supported by the principles of electrical engineering. It is merely an attempt to introduce a mechanism justifying their hypothesis concerning the axon. The correct representation for a single region of a type 2 membrane is a single intrinsic battery in series with a single diode and its associated shunt capacitance.

Finkelstein & Cass were probably the first to raise the following question[351]. "Does the very thinness of the membrane, irrespective of its organization, necessitate the consideration of physical phenomena that can generally be ignored in the discussion of 'macroscopic' membranes (such as ion exchange membranes or dialysis tubing)?" The following material (and the papers of Mueller & Rudin–see **Section 1.4.2**) will confirm the answer is yes.

Type 2 biological bilayer membrane is defined by its *molecularly asymmetrical structure*. The overall membrane remains impervious to the flow of ions. However, this asymmetry at the molecular level has a profound effect on the quantum-mechanical properties of the membrane and provides it a unique set of electrical characteristics.

The molecularly asymmetrical BLM can be represented by three electrical elements, an "intrinsic" battery in series with the parallel combination of a diode and a capacitor. As indicated earlier, <u>the combination of the battery and a diode is an equivalent circuit resulting from quantum-mechanical mechanisms</u>. They do not exist in the absence of an external potential across the membrane. **This combination of circuit elements cannot perform thermodynamic work when connected to an external circuit**.

While requiring conductive electrolytes on both sides of the type 2 membrane for electrical circuit continuity, the properties and operation of the type 2 BLM is independent of the chemical nature of the electrolytes.

The impedance associated with an electrical element consists of two parts, a resistive part and a reactive part. These are the usual terms used in electrical engineering. They are used

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[351]Finkelstein, A. & Cass, A. (1987) *in* Finkelstein, A. Water movement through lipid bilayers, pores and plasma membranes. NY: John Wiley & Sons. pg 145

to separate the "resistive" (normally dissipative) component of the impedance from the energy storage (or non-dissipative) component of the impedance. The latter consist of capacitances and inductances. These parts can be isolated by applying an alternating potential across the element, or network of elements. The resistive part is characterized by the fact the current flowing through it is in phase with the applied voltage. The reactive part is characterized by the fact the current flowing through it is in quadrature with the applied voltage. The total current flowing through an arbitrary network of more than two passive electrical elements can exhibit any phase angle between –90 and +90 degrees (first and fourth quadrants) relative to the applied voltage. With the addition of active components, the phase angle can move into the second and third quadrants. This section will discuss the "resistive" part of the impedance and then the "reactive" part.

As will be shown in **Chapter 9**, the typical *in-vivo* axolemma cannot be described using only resistive and capacitive elements. It also exhibits inductance, a diode characteristic and a current source associated with electrostenolysis.

1.5.1 The resistive character of the fundamental membrane in electrolyte

Terminology is a problem in the literature concerning the impedances of membranes. Many authors have been inconsistent in the units they associated with the terms resistance, conductance and resistivity. The terms resistance and conductance are associated with a parameter measured between two discreet points in a circuit. They are reciprocal. The resistance is defined with units of Ohms. These terms are normally associated with fixed values associated with electrically linear and bilateral materials.

Resistivity is a measure of the bulk electrical properties of a material. It is typically proportional to the thickness of the material and inversely proportional to the cross sectional area that a current passes through traversing the material. Thus, it has the units of Ohms per unit length times the unit cross section, or typically Ohm-cm in the CGS system. The conductivity is the reciprocal of the resistivity. A problem can arise when discussing a BLM with a nominally fixed thickness. In this case, several experimenters have used resistivity with the units of Ohms times the unit cross section without including the unit length term. As a result, they use the expression Ohms-cm^2 to indicate resistivity. This is an incorrect (shorthand) expression prevalent during the 1930–1960's. The expression Ohms-cm^2 refers to an alternate parameter, the resistivity per unit membrane thickness. The resistivity per membrane thickness can be given the name "thin-film resistivity." With a typical membrane thickness of 100 Angstrom, the thin-film resistivity, or resistivity per membrane thickness (with units of Ohm-cm^2) is typically 10^6 smaller than the true resistivity of an equivalent bulk material (with units of Ohm-cm).

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Cole provided an elementary discussion of the properties of a single membrane versus sea water in 1968[352]. It highlights the above problem with units. The terms in parentheses have been added for clarity. "Membrane conductances range from very small values beyond the negative resting potential (reverse biased) to much larger maximum values at positive potentials (forward biased). The nominal value of 1000 Ohm-cm^2 (resistivity per membrane thickness) at rest corresponds to a column of sea water 50 cm long. A maximum conductance equivalent to 5 Ohm–cm^2 (resistivity per membrane thickness) is approached in a number of membranes under positive voltage clamp, and 0.1 Ohm-cm^2 (or less, see **Section 9.4**) has been found for a node (electrotonic synapse). A nominal value of 1 Ohm-cm^2 (resistivity per membrane thickness) is then equivalent to a 0.5 mm of sea water." The value for the synapse (a pair of uniquely juxtaposed BLMs) shows it can have a conductance 10,000 times greater than for a single BLM. This performance is explained by the synapse acting as an "active diode" as defined in **Section 2.4**.

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[352]Cole, K. (1968) Membranes, Ions and Impulses. Berkeley, CA: University of California Press pp 520-522

Cole also considered the operating and breakdown potentials of a membrane. "The values of the average (high forward bias) and the breakdown (reverse bias) field strengths in the membrane are of the order of 10^5 V/cm. This average value for the normal operations of the membrane is certainly striking. It may well be highly significant as more becomes known of the behavior of other systems under such conditions." Cole was entirely correct. The fact that the breakdown potential is about +200 mV for a 100 Angstrom thick membrane is also important when stimulating the membrane artificially in the laboratory.

Cole concludes: "Considerable effort was devoted to the expression of membrane parameters in terms of centimeters and seconds but we have reached a stage at which molecular units may be more immediately significant." This work will return to that theme after the next paragraph.

1.5.1.1 The electrical characteristics of a theoretical diode

The literature contains an immense amount of data showing that the fundamental impedances found in vision research are inherently nonlinear and are symbolized by a perfect diode. This is also true of the fundamental BLM. The perfect diode is characterized by a very simple algebraic equation, $I = f(e^V)$ or more specifically, $I = I_o(\exp((V - V\gamma)/\eta V_T) - 1)$. The terms in this equation are discussed below.

Others could argue that the nonlinear characteristics found in the literature are not those of diodes. Historically, the impedance has been described as a variable resistor (using a symbol with a sweeper but no hand to control the sweep)[353]. However, the evidence is overwhelming. There is a critical test that the exponential hypothesis passes with flying colors. The natural base e has a unique property in the calculus in that it is its own derivative. Therefore, if the current-voltage characteristic of an impedance is described by the above equation, its derivative will also be described by an equation of the same form. No other simple mathematical function exhibits this property. Figure 6 and 7 of paper number III of Millecchia & Mauro[354] provide just such results. Their plots of the differential, $\Delta I/\Delta V$ versus V are identical in form to the original I versus V plots.

Figure 1.5.1-1 displays the current-voltage characteristic of a diode. The frame on the left shows the exponential characteristic on a single set of linear scales. The frame on the right is frequently used to highlight the features of the diode. The lower portion is at a much finer current scale than the top. The general equation for this function contains three parameters, the offset parameter, $V\gamma$, the thermal parameter, ηV_T, and the scaling parameter, I_o. By using a split scale, the reverse current value (I_o) can be illustrated on the same graph with the much more prominent offset parameter and the forward current value. It also makes a more convenient graph for illustrating the reverse voltage breakdown characteristic of the diode, usually labeled V_Z. These four parameters, and the capacitance of the device, completely characterize any diode. In many situations, the static impedance, shown by the line labeled Z(static) is of interest. In other situations, the dynamic impedance, shown by the line labeled Z(dynamic) is of interest. Note the dynamic impedance is normally lower than the static impedance.

The offset parameter, $V\gamma$, is the potential of the intrinsic battery associated with a membrane.

Comparing these figures with that of a simple resistor is useful. The current-voltage characteristic of any resistor is a straight line through the origin on these graphs. The line describes the voltage across the resistor divided by the current through the resistor and given by the relationship V/I. There is no reason to use an expanded scale with a resistor. A high value of resistance is shown by a nearly horizontal line in the left frame while a low value of resistance is shown by a nearly vertical line.

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[353]Eckert, R. & Randall, D. (1978) Op. Cit. pg 118

[354]Millecchia, R. & Mauro, A. (1969) The ventral photoreceptor cells of Limulus. J. Gen. Physiol. vol. 54, paper II-pp. 310-330 and paper III-331-351

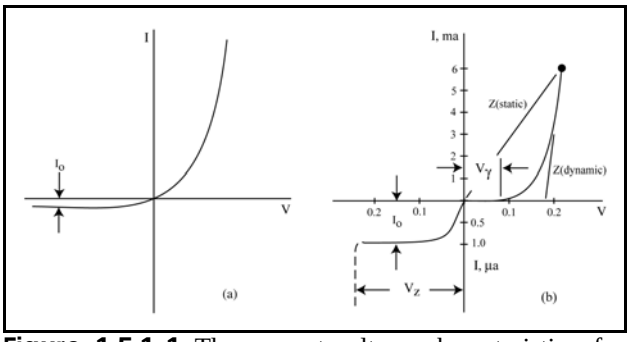

Figure 1.5.1-1 The current-voltage characteristic of a diode EDIT. The left frame employs linear axes. The right frame has a break in the scale of the vertical axis to highlight the reverse current through the diode. See text for other features of the graphs.

Defining a fixed resistance for the resistive component of a diode is not possible since the equation cannot be written in the form V/I. However, it is possible to define an effective resistance (actually two) at a given voltage (or current). The first, the static resistance (also known as the large signal resistance) can be defined as (V-V(0))/(I-I(0)) where V(0) and I(0) are defined as equal to the zero point on the graph of I versus V (or any other point if desired). The second can be defined as the small signal (also known as the small signal or dynamic) resistance given by the slope of the graph of V versus I at a given voltage (current), $\Delta V/\Delta I = K \bullet e^{-V}$. Alternately, the small signal conductance is, at a given voltage, $\Delta I/\Delta V = (1/K) \bullet e^{V}$. Both the static and dynamic impedances of the diode play important roles in the neural system.

> Occasional discussions appear in the literature as to whether a particular biological impedance is a function of the current through it or of the voltage across it. Clearly, such a distinction is meaningless.

The diode is seen to represent a very high resistive impedance when it is reverse biased (that is defined by the reverse current, I_0, for any large value of voltage). Alternately, it exhibits a very low resistive impedance (approaching an asymptotic value) when it is forward biased. The limitation of the current to I_0 says the diode is not equivalent to a fixed resistor at high reverse voltages. Up to the point of breakdown, the calculated resistance will be proportional to the voltage applied.

1.5.1.2 Measured resistive impedance of a real BLM

The goal of this section is to determine whether the fundamental BLM can be defined using a Donnan–Nernst symmetrical but semipermeable membrane or is more properly defined using an asymmetrical semiconducting membrane that is impermeable to ions. In the Donnan–Nernst context, the membrane is electrically symmetrical and the asymmetrical electrical properties are due to the difference in concentrations and permeabilities of the two electrolytes. In the semiconducting membrane approach, the membrane itself is electrically asymmetrical to the flow of electrons regardless of the adjacent electrolytes. It need not be conductive to any ions present in the solutes.

While performing experiments with a different purpose, Eliasof, et. al. have provided a useful set of voltage-current characteristics for a simple membrane-electrolyte system[355]. The data was captured using a special voltage clamp technique known as the patch clamp technique. This technique allows the analysis of very small areas (but not necessarily areas of one unique type) of a BLM. The details of their test configuration were not provided. Their figure 4 is reproduced in **Figure 1.5.1-2** with the addition of several curves to the frame labeled sEAAT2B. These will be discussed below. Their figures 5 through 7 are also instructive. The membrane is the plasmalemma of an oocyte of salamander, *Xenopus*, and not that of a neuron. However, it is a premise of this work that the plasmalemma of all animal cells share a common structure whether the cell has evolved into a neuron or not. The electrolyte associated with the electrical contact was KCl at a concentration of 3 M. This configuration gave an electrode resistance of "less than one K-Ohm." The initial interior plasma was native to the cloned oocyte.

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[355]Eliasof, S. et. al. (1998) Localization and function of five glutamate transporters cloned from the salamander retina. *Vision Res*. vol. 38, pp 1443-1454

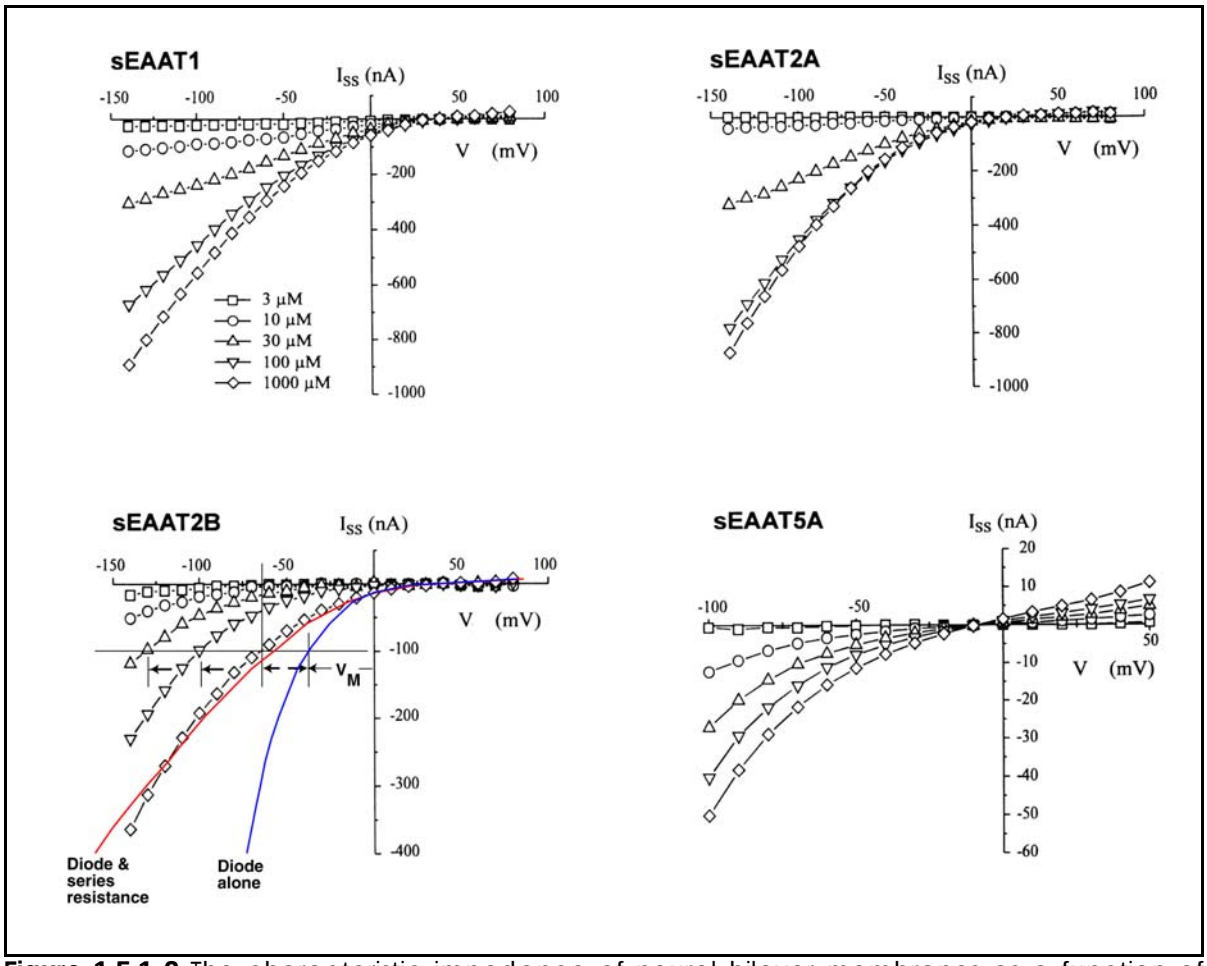

Figure 1.5.1-2 The characteristic impedance of neural bilayer membranes as a function of electrolyte concentration. A reinterpretation of Eliasof (1998). One electrolyte was modified to contain L-glutamate at the concentrations shown. Note the distinct crossover at minus 10 millivolts for the lower right sample. The labels of the voltage scales have been changed and labeling added to the lower left quadrant. The "series resistance" is the resistance attributable to the lemma as well as that of the two bulk electrolytes and the electrodes.

Unfortunately, at least two problems relate to this data. First, Eliasof, et. al. used a patch clamp approach. This approach is a variant of the simple Leyden Jar technique and similar to those suggested in Kotyk & Janacek[356]. A better approach would use a Ussing apparatus discussed in **Section 1.3.3.** The Leyden Jar approach results in the total recorded voltage being a function of three elements, the conductivity of the sample membrane, the conductivity of the electrolytes employed and the ½-potentials (and conductances) of the test set electrodes. Because of these unknowns, it is not possible to ascertain the exact impedance characteristic of just the membrane. Following this rationale, the data can be interpreted as the result of a combination of an electrical diode (the membrane), a conductance (the bulk electrolyte plus the electrode electrolyte) and one or more batteries (the electrodes and any intrinsic membrane potential) in series.

[356]Kotyk, A. & Janacek, K. (1975) Cell membrane transport, 2nd ed. NY: Plenum Press pp. 303-304

The second problem relates to the electrolyte used. It appears the concentrations given refer to the concentration of L-glutamate in an undefined solvent, probably distilled water. If this is the case, no sodium was present on either side of the membranes. The quality (pH) of the water could be significant in precise measurements. This author was unable to determine unequivocally from the paper how the solution was applied to the oocytes, topically or by injection. Because of the participation of L-glutamate in the electrostenolytic process of a typical cell, it was a poor choice for purposes of this analysis. However, the experimental goal of Eliasof, et. al. and their protocol assumed the role of L-glutamate was that of a neurotransmitter, not a neuro-facilitator. For the immediate purpose, it is only necessary that L-glutamate (glutamic acid) is highly ionized at the concentrations used. The analysis below confirms this is the case.

In spite of these problems, the data appears to provide good relative data regarding the plasma membrane of the oocytes of salamander. The individual frames published all show a common underlying mechanism except for sample sEAAT5A. Note the scale change for this sample. Eliasof, et. al. discussed the problems with their experiments involving sample sEAA5A. The curves for this sample show a symmetry between the first and third quadrants about the value –10 mV. They also show a total impedance 10-25 times higher than for the other frames. The data suggests the portion of membrane captured within the voltage clamp apparatus was dominated by type 1 membrane and not type 2 membrane like in the other frames. The –10 mV offset cannot be explained based only on the data in their paper.

Omitting sEAAT5A for the moment, the question remains whether the data supports the symmetrical membrane proposition based on Donnan and Nernst or the semiconductor diode proposition of this work. Starzak has recently reproduced the mathematics of the Goldman constant field equations (pg 220-223) that reflect the Donnan and Nernst models. He notes that the symmetrical membrane model can act as a "rectifier" due to the difference in permeabilities and concentrations of the electrolytes. However, he does not provide any support for how this assymetrical phenomenon is achieved using symmetrical materials. Unfortunately, the models of Starzak, Donnan, Nernst and others have not included the resistive impedance associated with the electrolytes acting as conduits to the test set electrodes.

Starzak has provided a theoretical description of the current-voltage characteristic of a putative BLM based on the hypothesis that the membrane is a symmetrical semipermeable material[357]. He developed a complete equation for his symmetrical membrane configuration (eq. 9.98) but did not plot it explicitly (with data points), preferring to discuss its asymptotic limits. This was probably because his equations are discontinuous at zero potential. A discontinuity in a mathematical analog of a continuous process is not a desirable feature, particularly when small values of the independent variable are particularly important. Such a discontinuity says the equation, while describing the data, is not that used in the underlying mechanism.

The results of Starzak's analysis shows that the impedance of the cell absent the electrolytes becomes a fixed resistance represented by a straight line passing through the origin for equal electrolyte concentrations on each side of the membrane. His analysis did not include any finite resistances due to the current paths between the surfaces of the membrane and the electrodes. He recognized the need for this in more complicated models found in practice.

Starzak used the term rectifier in its generic form by saying it exhibits a different asymptotic resistance in opposing quadrants of the voltage-current characteristic. This definition is similar to the large signal approximation used in industrial rectifiers, Z(static) in the earlier paragraph. This definition is significantly different from the definition of a diode (acting as a rectifier) as used in low voltage circuits. The mathematical characteristic of a diode is a simple (and continuous) exponential extending over all voltage values. When passing current in the forward direction, the diode exhibits a resistance approaching zero with increasing current. However, it exhibits a limiting absolute current, I_0, when opposing the flow of current. These conditions are significantly different from the "rectifier" defined by Starzak.

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[357]Starzak, M. (1984) The physical chemistry of membranes. NY: Academic Press, pg. 223

It is useful to consider the asymptotes related to the data of Eliasof, et. al. as they help define the boundary conditions of the underlying mechanisms. By evaluating each frame of the figure graphically, it is possible to discern the contribution of the membrane, the electrolyte and the electrodes. Assuming the electrolyte and the electrodes used to introduce the electrical potential into the cell are symmetrical with respect to polarity (a questionable assumption), the impedance associated with the test set alone is symmetrical with respect to the current and no extraneous potential source is introduced at zero current through the cell.

It is clear from the upper and left frames of the figure that the test configuration does not exhibit the detailed properties of a Starzak (Goldman–Donnan–Nernst) rectifier. The curves in the first quadrant exhibit an asymptote at a current, I_0 rather than an asymptote described by a constant resistance passing through the origin. The asymptotes of each curve do not appear to pass through the origin. This feature is a characteristic of a diode rectifier.

Looking at the third quadrant of the frames is also instructive. The sets of curves are consistent with part of the asymptotic condition defined by Starzak for a "rectifier" however, the asymptotes do not pass through the origin. They appear to converge near -70 mV.
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The curves are amenable to further analysis. It is proposed that the overall characteristic of a BLM separated by two electrolytes of finite path length is that of a diode rectifier in series with a finite resistance due to the electrolytes. Under these condition, the equation describing the curves in the figure would be given by:

$$V - V\gamma = I(Z + R) = IZ + IR = V_m + V_e$$

where Z is a perfect diode with an impedance that is an exponential function of the current. It represents the membrane. R represents the resistive impedance associated with the electrodes and the electrolytes. $V\gamma$ is the offset parameter associated with a semiconducting diode. V_m and V_e represent the voltages across the membrane and the electrolyte and electrodes respectively. The last relationship has been plotted on the lower left frame of the figure. The total voltage, at a given current, between the copper wire terminals of the test set is given by the sum of the voltage across the membrane, V_m, and the voltage V_e representing the appropriate concentration for the test electrolytes. For the asymmetrical membrane (that is impervious to ions) assumption, the current is less than I_0 for any potential that is opposed by the diode. Significant current through the test set should only be found in the lower left quadrant of each frame.

For a very dilute electrolyte, the resistivity of the electrolyte is high. For R>>Z, the curve is a straight line given by $V - V\gamma = IR = V_e$. Such a line approaches horizontal in this graphical presentation.

As the electrolyte concentration rises, its electrical conductivity also rises and its resistivity drops. As the concentration continues to rise the voltage drop across the electrolyte becomes negligible and the curve becomes representative of only the membrane. The curve is an exponential given by $V - V\gamma = IZ = V_m$. This function is described by the line marked "diode alone" in the lower left frame of the figure.

The lower left frame has been overlaid by the response of a perfect semiconductor diode and a perfect semiconductor diode in series with a resistance. The diode limits the reverse current in quadrant one to its reverse current parameter, I_0, regardless of the resistive impedance present. This value appears to be on the order of 10 nA or less (see figure 6 in Eliasof, et. al.). The current in the forward direction is limited by the effective resistance of the diode (that varies with applied voltage) and the resistance of the electrolytes in series. While this configuration does exhibit an asymptote as described for a "rectifier," it also exhibits a specific shape defined by the current-voltage characteristics of the diode and resistor combination. The curve labeled diode & series resistance corresponds to the condition for a diode in series with a resistance of 650 Ohms calculated at –100 nA . This number is in excellent agreement with the "less than one K-Ohm" value given by Eliasof, et. al. for their test set. It also suggests that the curve marked 1000 μM is in fact the asymptotic value for this test configuration. Further increasing the concentration of the L-gluamate electrolyte would

have negligible effect.

The curve marked diode & series resistance is within 10% of the measured response for 1000 μM over the entire range of measurement.

> **The data of Eliasof, et. al. is highly supportive of the fact that the BLM is an electrically asymmetrical diode element that is independent of the environment external to the membrane (except that it be of low electrical impedance in order to provide an electrical path to the electrodes of the test set). The BLM need not be (and generally is not) permeable to ions!** The equations of Donnan, Nernst, Goldman and Starzak do not apply to the real *in-vivo* BLM. They do not exhibit an absolute asymptote limiting the reverse current through the system. The asymptotes applicable to the BLM are those illustrated in **Figure 1.5.2-1**.

The individual frames suggest the diode characteristic is accompanied by an offset parameter, $V\gamma$, but the data is not consistent enough to clearly define this parameter. Yau, et. al. presented data that leads to a more explicit definition of the offset parameter, $V\gamma$. They employed different solutions on the two sides of the membrane[358]. With "Normal Ringer's solution" on one side and a pseudo intracellular solution on the other side, they measured a very precise +10 mV for the offset parameter, regardless of the amount of Ca^{2+} or Mg^{2+} added during the experiment. When the same complex solution was provided on both sides of a different membrane of larger size, the offset parameter was found to be zero (and the currents were much larger). This stresses the importance of evaluating the diode equation of a membrane under *in-vivo* conditions and in specifying both the type and physical dimensions of the membrane sample.

> The data of Yau, et. al. was all obtained under Leyden jar conditions. Pending better data based on experiments using a Ussing apparatus, the offset parameter (intrinsic battery potential) of the in-vivo biological diode will be taken as +10 mV at 300 Kelvin, much less than the values in conventional germanium or silicon diodes.

Starzak proceeded to present several additional scenarios based on the symmetrical semipermeable membrane assumption. These appear to be totally academic with regard to the electrically asymmetrical ionically impermeable nature of the BLM.

Neither the analysis by Starzak nor the graph by Eliasof, et. al. address the second order process of dielectric breakdown in a diode at high reverse voltage leading to the parameter V_Z. However, Mueller & Rudin[359] have provided the complete electrical characteristic of a "biomolecular lipid membrane."

Figure 1.5.1-3 documents the findings of Mueller & Rudin for a bilayer membrane made from synthetic sphingomyelin (a family name not a specific molecular formula) using the method of Yeda. The tocopherol was also synthetic. The membrane potential describes the inside potential minus the outside potential. A positive current is "outward."Thus, the third quadrant would be the operational quadrant in a biological cell. The characteristic in the third quadrant shows dielectric breakdown at –170 mV occurring before the diode current becomes significant because of the symmetry of the bilayers. The first quadrant shows the material biased to prevent current flow. The rapid rise in this quadrant near 76 mV is due to dielectric breakdown in this membrane. The wording in their text is a bit brief as to whether this sample contained alamethicin or was the reference sample. Alamethicin is a cyclopeptide antibiotic containing a variety of amino-acids and at least one carboxyl group.

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[358]Yau, K-W. Haynes, L & Nakatani, K. (1986) Roles of calcium and cyclic GMP in visual transduction. *In* Luttgau, H. *ed.* Membrane Control of Cellular Activity. Stuttgart: Gustav Fischer pp 343-366 *Reported in* Yau, K. (1994) Phototransduction mechanism in retinal rods and cones, *Invest. Ophthal. & Vis. Sci.* Vol. 35, no. 1, pp 9-32

[359]Mueller, P. & Rudin, D. (1968) Action potentials induced in biomolecular lipid membranes *Nature* vol. 217, pp 713-719

It may attack the sphingomyelin or associate with it stereochemically like glutamate does. Note the very small currents per square cm through this membrane. These currents are about 0.1% of those reported for the average current through a large piece of the lemma of the giant axon of *Loligo*. The (thin film) resistivity for this synthetic material is about 2×10^5 Ohms-cm^2. The low current level, and linear current change, for potentials between +76 and –170 mV strongly suggests the bilayer membrane consisted only of sphingomyelin and was therefore symmetrical. The membrane is a very high quality Type 1 BLM (a near perfect insulator). The asymmetry of breakdown potential may be due to the presence of alamethicin in one of the electrolytes.

Mueller & Rudin describe a variety of Excitation Inducing Materials (EIM's). They also reported "Membranes made from purified lecithin (PC) dissolved in decane are not suitable for the study of the action potentials reported here, the EIM gating mechanism being poorly developed." The reader is cautioned concerning Mueller & Rudin's definition of an action potential and of their EIM gating mechanisms.

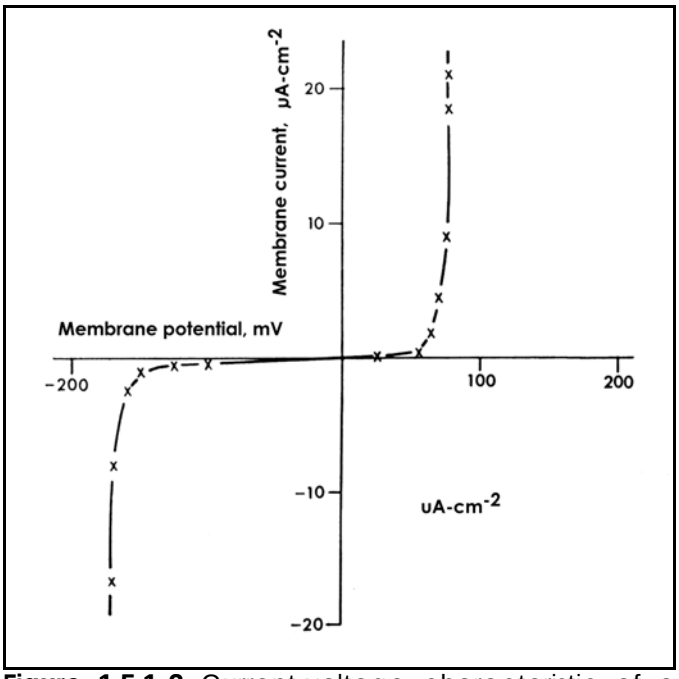

Figure 1.5.1-3 Current-voltage characteristic of a bilayer of sphingomyelin prepared from a bath of 2.5% sphingomyelin dissolved in tocopherol:chloroform:methanol::5:3:2. 0.1 M sodium chloride as the electrolyte on both sides. The asymmetry is purported to be due to the addition of 10^{-7} g/ml of alamethicin to one of the electrolytes. From Mueller & Rudin, 1968.

1.5.2 The reactive character of the fundamental membrane in electrolyte

The reactive component of the total impedance of a membrane depends critically on its geometry. While an artificial membrane prepared as a planar layer on a fluid surface may exhibit negligible inductance, it will exhibit a significant capacitance because of its thinness and its quantum-mechanical properties. If that same membrane is formed into a cylindrical tube, its capacitance will change due to its new geometry and the membrane will exhibit a significant inductance per unit length of the tube. Only planar films will be addressed in this section.

The inductance of a fundamental membrane is a function of the geometry of the membrane. In the case of the long cylindrical axon, the inductance is a significant parameter. For most neurites, the inductance is much smaller and very difficult to calculate due to their complex geometry. Certain neurites exhibit geometries very similar to axons and exhibit similar inductances. The inductance of an axon, or neurite, is primarily an operational concern. It will be addressed in detail in **Chapter 9**.

1.5.2.1 The capacitive character of fundamental membrane in electrolyte

The capacitive impedance found in a neuron is calculated conventionally (based on the actual geometry involved). It can vary between regions of the membrane and varies significantly if the INM is separated from the membrane by a myelin sheath. Typical values found in the literature for unmyelinated membrane range from 1 to 3 μF/cm^2. The measured values reported in the literature varies between 10% and 1000% of these values (See pg 13 in Troshin for early references). The wide range could be due to the primitive methods of

measuring the thickness of the BLMs and the lack of good values for their dielectric constants. There are also significant charge density variations associated with the calculation of the capacitance of a membrane. These variations are found within the membrane at the quantum-mechanical levels associated with a diode. They are also found in the adjacent electrolytes where they are generally described as Maxwellian layers. These variations are bias-potential sensitive.

In spite of the above range, the nominal value is very large. It is due primarily to the extreme thinness of a single membrane, typically 100-150 Angstroms[360] or less. In terms more appropriate to a neuron, the capacitance is about 10^{-8} μF/micron^2. The effective capacitance of a region of membrane is frequently reduced by a factor of more than 100 if a myelin sheath is present.

The capacitance of type 1 and type 2 regions of membrane are significantly different. In type 1 regions, the symmetrical bilayer represents a very high quality capacitor that is largely unaffected by the voltage across it up to the point of dielectric breakdown. Type 2 regions are significantly different. The asymmetric bilayer forms an electrical diode. Such a diode exhibits a change in capacitance as a function of the reverse potential across the diode[361]. This change is known to be incremental in character. This transition region capacitance is given by the equation: $C_T = |dQ/dV|$ and not the conventional $C = Q/V$. As a result, there is a displacement current $i = C_T(dV/dt)$ that is proportional to the rate of change of the applied potential. The transition region capacitance is a function of the applied reverse potential. The total capacitance associated with a membrane is therefore C_M (the DC capacitance) plus C_T (the displacement capacitance). This may account for some of the variation in values in the literature. The literature does not normally specify the potential (or the method) used to measure the capacitance. Precise values must specify both the potential and whether a DC (relaxation) or an AC (steady state) technique was used in the determination.

The transition capacitance can dominate the DC capacitance in specially prepared man-made diodes. Those devices are known as varactor diodes or varicaps.

For purposes of this section, the capacitance will be taken as 1.0 microfarad per square centimeter, the nominal value found to describe a range of about 0.5 to 3.0 μF/cm^2 found throughout the literature.

1.5.3 The intrinsic RC time constant of a typical membrane

The concept of a time constant is drawn from the simple exponential response exhibited by a two-element electrical circuit involving linear components. Such linear components exhibit impedance properties that are independent of the voltages applied to them. Type 1 BLM can be evaluated using this simple concept. Type 2 BLM is an electrical diode. A diode is not a linear component and this simple concept does not apply to a circuit containing a diode. To accommodate circuits containing a diode, various re-definitions of the term time constant have been used. They generally fall into two categories, the large scale or DC approximation and the small scale or AC approximation.

Finkelstein has measured ohmic resistivities as high as 10^{12}–10^{13} Ohm–cm^2 for membranes that appear to be of type 1. When combined with the nominal capacitance of such a membrane (1.0 μF/cm^2), the resulting intrinsic time constant is on the order of 10^6–10^7 seconds (10^5 minutes, 3000 hours or 100 days). Such a free-standing membrane has little significance to the operation of a neural system.

Finkelstein & Cass have reported resistivities of 10^6–10^9 Ohm–cm^2 for membranes that appear to be of type 2. When combined with the nominal capacitance of a membrane, the resulting intrinsic time constant of this type of membrane is on the order of one second to a millisecond. This is a significant value when considering the operation of a neural circuit.

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[360]Eckert, R. & Randall, D. (1978) Animal Physiology San Francisco CA: W. H. Freeman pg. 114

[361]Millman, J. & Halkias, C. (1972) Op. Cit. pg 63-67

1.5.4 The shape factor in total lemma impedance

The geometry of a lemma plays an important role in its impedance. As an example, a cylindrical capacitor of unit length, with a given average circumference does not have the same capacitance as a planar capacitor of unit length and a width equal to that circumference. In fact a cylindrical capacitor also exhibits a significant inductance.

The treatment of the total impedance of a conduit formed of a biological membrane is complex if it involves multiple regions with different electrical properties. The treatment is also different depending on the type of signal being considered. Cole has provided extensive information on the individual components of the total impedance, including the reactive component associated with an inductance[362]. The more complex treatments will be found in **Chapters 2 & 9.**

1.5.5 Additional measured electrical data for bilayer membranes

A variety of individual BLM types are widely dispersed within a neuron and it is difficult to identify their properties at the molecular level. **Section 1.4.2.5** discusses the role of these different BLMs. The lack of such a model in previous writings has made it difficult to rationalize the data in the literature[363]. While the use of the patch clamp technique offers the potential of measuring carefully differentiated areas of plasmalemma, defining areas of uniform characteristics is very difficult at this time. As a result the characteristics of generic samples presented in the literature, based on this technique, have been inconsistent.

Little data exists in the literature taken directly from real BLMs. Caution is required in the analysis of the available data because of the susceptibility of membranes of liquid crystalline material to rupture or change by external agents. Precisely quantifying both the values and circumstances associated with the values are important. The values of Zon & Tien for example are prefaced by the words "typical" and "greater than" when speaking of a mixed group of bilayer membranes[364]. They do not specify the area of the membrane used to determine the capacitance and resistance.

Equally important are the criteria for determining the impedances within a complex circuit. The Laws of Kirchoff and Ohm require explicit conditions if accurate results are to be obtained. Most of the conductivity changes reported in the biological literature are due to the presence of diodes (not variable resistors) and voltage sources within the circuits examined. All voltage (and current) sources within the circuit must be accounted for before impedance measurements can be attempted using Kirchoff's Laws. If Ohm's Law is to be used, all diodes and other nonlinear elements must also be removed from the circuit.

Pethig has provided one of the few descriptions of the permittivity of biological tissue as a function of frequency[365]. However, it is described as "typical" and suggests the sample has a permittivity extending over six orders of magnitude corresponding to a frequency range of eleven orders of magnitude. Little additional description and no additional references were provided. The reader should review this data considering the possibility that the data represents several capacitive element in series of drastically different size. See Pethig, pages

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[362]Cole, K. (1968) Op. Cit.

[363]Finkelstein, A. & Cass, A. Permeability and electrical properties of thin lipid membranes. *In* Finkelstein, A. (1987) Water movement through lipid bilayers, pores and plasma membranes. Volume 4 of the Distinguished Lecture Series of the Society of General Physiologists. NY: John Wiley & Sons. pg. 147s-172s

[364]Zon, J. & Tien, H. Electronic properties of natural and modeled bilayer membranes. In Marino, A. (1988) Modern bioelectricity. Chapter 7, pg. 208

[365]Pethig, R. (1979) Dielectric and Electronic Properties of Biological Materials. NY: John Wiley pg 226

15-17. This condition may separate the individual components on a plot of this type without actually requiring changes of permittivity of such extreme values. As an example, most investigators of myelin report relative permittivity values of only 2-3.

Page 139 of Pethig provides the complex permittivity of both water and ice. His method of presentation is unconventional, but for a valid reason. The real part of the permittivity corresponds to the capacitive effect and the imaginary corresponds to the loss component. The data shows the real portion of the permittivity of ice to be about 96 up to a frequency of about 1000 Hz compared to about 80 for water up to a frequency of over 1000 mHz (note the m in the second frequency limit). Mohilner gives the relative permittivity of water as 78.49 at 25 C[366].

1.5.5.1 Synthetic analogs of natural membranes

In the early 1960's, Mueller, et. al. prepared bilayer membranes of phospholipid material plus hydrocarbon additives designed to represent prototypical biological membranes. In the late 1960's, Finkelstein & Cass reported detailed information on their synthesis of artificial bilayer membranes based on the methods of Mueller, et. al. The work involved a complicated protocol. It was designed to measure the physical permeability of these prototypical biological membranes to a variety of particles (water, neutral solutes, ions, ions in the presence of their unionized atoms). It was also designed to make measurement of the electrical characteristics of the membranes in the presence of various solutions containing the above materials. Lecithin (PC) based membranes were prepared in the presence of a variety of hydrocarbons, including cholesterol. Their primary finding was stated unequivocally in their abstract; **"The unmodified membrane is virtually impermeable to ions and small 'hydrophilic' solutes, but relatively permeable to water and 'lipophilic' molecules."**[367] They found the rate of ion movement to be immeasurably small through the prototypical membrane because of the extreme insolubility of ions in the hydrophobic region. They presented electrical resistivities per unit membrane thickness of 10^6-10^9 Ohms–cm^2. These membranes had a typical thickness of less than 100 Angstrom.

Finally, they established that these prototypical membranes, and most of those prepared earlier by others from extracts of natural samples, did not exhibit "pores" through which particles could pass.

When they prepared a membrane in the presence of cholesterol, they found the filtration (osmotic) permeability coefficient, P_f, for water to be a significant function of the molar concentration of the constituents.

Ehrenstein, writing in Adelman, reviewed the properties of synthetic lipid membranes versus real axon membranes[368]. It appears from the electrical resistance measurement given that the artificial lipid membrane was probably symmetrical (type 1) and therefore an electrical insulator five orders of magnitude higher than the real membrane (of unknown and probably mixed type).

1.5.5.2 Modified synthetic analogs of real membranes

Finkelstein & Cass also explored the modification of synthetic membranes after their formation from various materials, mostly complex organics. However, their methods were more likely to introduce inclusion between the two bilayers or penetrations of only one bilayer than they were to emulate a natural membrane. Little reason exists to suggest their penetrations of the total membrane, if any, had the complexity of real penetrations at the molecular level.

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[366]Mohilner, D. (1966) The electrical double layer *In* Bard, A. *ed.* Electroanalytical Chemistry, vol 1 pg 313

[367]Finkelstein, A. & Cass, A. (1987) Op. Cit., pg. 145s

[368]Ehrenstein, G. (1971) Excitability in lipid bilayer membranes *in* Adelman, W. Biophysics and Physiology of Excitabel Membranes. NY: Van Nostrand Reinhold Chapter 21

They noted that many detergents simply disrupt the membrane structure and destroy the film. Many other organics lowered the apparent ion permeability of the membranes, frequently accompanied by the appearance of "black regions" within or on the surface of the films (pg 163s). [The appearance of a black film is a very strong indication of electrostenolytic activity at the surface of the membrane.] These changes in permeability were significant, varying by the sixth to tenth power of the concentration of the additional constituent. Because of these changes, the membranes showed a typical leaky diode current-voltage characteristic at 32 degree centigrade and major, repeatable changes in conductance as a function of temperature. Their work suggests the permeability to ions of prototypical and real membranes is highly sensitiveity of to the presence of complex organics.

1.6 Imaging techniques have provided a new level of whole brain understanding

Recent advances in imaging of both the static properties and the dynamic rates of energy consumption within the animal body (particularly the human body) have led to spectacular new knowledge about and means of treating the body. The ability to see the activity level within the brain during a variety of intellectual activities has led to new knowledge. The techniques currently available remain relatively crude with regard to the neural system. Specifically, they illustrate the energy consumed as it relates to oxygen consumption (the aerobic aspect of neural cell homeostasis (and possibly the aerobic consumption of associated glia in producing glutamate). However, they do not currently focus on the actual signaling within the neural system (involving essentially anaerobic processes). Recall that the oxidation of glutamic acid to GABA and CO_2 does not involve the consumption of oxygen at that time. The glutamate was formed earlier by glycolosis.

Stenger has provided a current description of the BOLD fMRI technique at the technical level[369]. This is the technique providing the most spectacular images of oxygen consumption in the brain in real time.

> As noted by Adolphs et al. fMRI with a 3.0 Tesla magnet still exhibits a resolution about 100 times less than achievable with electrophysiological probing[370]. The images are typically at the 2 x 2 x 2 mm pixel resolution. **Section 4.3.5.3** discusses the non-invasive tools (PET, CATS, MRI and fMRI) available in greater detail and provides a 2012 resolution update.
>
> Rose & Rose have provided a complimentary set of numbers[371], "At its best, fMRI averages activity over about two seconds in a small block of brain tissue about 0.5 mm across. Although this block of tissue seems tiny, so complex is the brain that the tiny block contains some 5.5 million neurons, 22 kilometers of their dendrites, and up to 55 billion connections."
>
> In imaging experiments with small animals, 7.0 Tesla magnets have been used to explore volumes no larger than 30 cm on a side. This is marginally large enough for a human head and the first Atlas of the human brain at this level has now appeared[372].

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[369]Stenger, V. (2006) Technical considerations for BOLD fMRI of the orbitofrontal cortex *In* Zald, D. & Rauch, S. *eds*. The Orbitofrontal Cortex. Oxford: Oxford Univ Press Chapter 17

[370]Adolphs R. Kawasaki, H. Oya, H. & Howard, M. (2006) Intracranial electrophysiology of the human orbitofrontal cortex *In* Zald, D. & Rauch, S. *eds*. The Orbitofrontal Cortex. Oxford: Oxford Univ Press. page 357

[371]Rose, H. & Rose, S. (2012) Genes, Cells and Brains. NY: Verso Chapter 8 The irresistible rise of the neurotechnosciences

[372]Cho, Z-H. *ed*. (2010) 7.0 Tesla MRI brain atlas. NY: Springer

> The resolution achieved at 7.0 Tesla should be improved by at least a factor of two (down to one or two million neurons per resolution element. A second book focused on the white matter (the commissure) is currently in press[373].

Zimmerman et al. have provided a massive book on virtually all aspects of neuro-imaging, but with little emphasis on the neurological system as such[374]. Source citations are sparse in the work. What is described as the quadrigeminal "plate" is shown in medial view on pages 503-510, 527, 969 & 971, probably at T = 1.5 Tesla. A higher resolution image would show the complex structure of this group.

Rose & Rose have also discussed the limitations on the fMRI technique in the midst of the excessive exuberance over the cranial maps appearing regularly.

> "The dramatic false-color images that grace the journal articles and media reports of fMRI studies are the result of extensive mathematical transformation of the raw observations of blood flow and *a priori* assumptions about which regions to study and how to select sample sizes. One critical analysis that rocked the social neuroscience community examined fifty-four of its most prestigious papers and described them as voodoo correlations, showing 'implausibly high correlations through statistically inappropriate selection of data' (despite the authors being persuaded to change their original title to something more anodyne, the damage was done[375]). Worse still, a group of students reported getting apparently meaningful fMRI images from a dead salmon[376]."

1.7 Conclusions to be drawn from Chapter 1 EDIT OUT

Up until now, the neurological literature has focused on an elementary concept of the BLM enclosing a cell that has not been sufficiently compartmentalized. As a result, most discussions of the BLM in a chemical context are archaic. They assume a set of conditions not found in real neurons.

Efforts in the neurological community have continued to focus on a chemical explanation for signaling within the neural system. These efforts have not resulted in a framework that can guide future investigations.

When different investigators attempt to explain the operation of a cell membrane based on their data, they have generally assumed a simplified membrane that conflicts with those of other investigators. No satisfactory generic membrane has appeared to date.

To avoid the increasing evidence that free ions cannot move across a majority of the plasmalemma of a cell, efforts have been increased to find a pore structure adequate to the task. Improvements in electron microscopy have failed to support such proposals, particularly in the areas (the junctional-tissue) separating two or more neurons.

It is time to move on to a biological bilayer membrane that is regionalized where each region serves a different purpose. To achieve these purposes, the molecular character of the regions vary.

The most complex models found in the current literature do not do justice to the BLM.

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[373]Cho, Z-H. Calamante, F. & Chi, J-G. (2013-14) 7.0 Tesla MRI Brain White Matter Atlas. Panmun.

[374]Zimmerman, R. Gibby, W. Carmody, R. eds. (2000) Neuroimaging: Clinical and Physical Principles. NY: Springer

[375]Vul, E. Harris, C. Winlielman, P & Pashler, H. (2009) Puzzlingly high correlations in fMRI studies of emotion, personality and social cognition *Perspec Psychol Sci* vol 4, pp 274-290

[376]Bennett, C. Baird, A. Miller, M. & Wolford, G. (2009) Neural correlates of interspecies perspectiv taking in the post-mortem Atlantic Salmon: An argument for multiple comparisons correction *Soc Neurosci Abstr*

Specifically, they do not address the subject of hydrophobic membranes or membranes containing a hydrophobic phase, such as BLMs. Nor did they allow for the presence of complex organic ions, within the solvents, capable of resonance among their ionic states. Nor did they address the presence of ions such as calcium that can exhibit two different valences. Finally, they do not address the two fundamental and crucial conditions. They do not consider the presence of electrostenolytic processes which could skew their electrochemical equations and they do not address the quantum-mechanical properties of such thin membranes. In neurons, these last two conditions are the most crucial.

Two facts must be accepted to understand the operation of the neural membrane. First, quantum-mechanical principles apply to these membranes. Second, the permeability of these membranes to electrons and holes is far more important than their permeability to ions and large uncharged particles. It is their quantum-mechanical distribution of charge that accounts for both their asymmetrical electrical properties and their non-uniform potential field gradient as a function of transverse distance.

> The result is a membrane structure that is not directly addressed by the Nernst-Donnan-Goldman theories, or the Hodgkin-Huxley modifications to those equations (due to their underlying constant field assumption). Adjustments to the lipoidal membrane theory are required as well (due the quantum-mechanical characteristics of a membrane).

The last two conditions lead to two key facts. First, each of the cited authors derivations, related to diffusion through a membrane, assumed a constant potential field gradient within the membrane. This condition requires an electrically symmetrical membrane. Such a constant gradient is only found in relatively uniform heterogeneous material. Second, none of the authors allowed for the presence of a chemical source of electrons on the surface of the operational membrane.

It is now time to rationalize the above materials and to recognize that bilayer membranes of two phosphoglyceride leaves form a special class. They consist of hydrophilic surfaces with a hydrophobic interior. When the two bilayers are symmetrical, the material is an exceptionally good insulator and it is impervious to the movement of both heavy ions and fundamental charged particles. When the two bilayers are asymmetrical, they remain impervious to heavy ions. Electrically, membranes are liquid crystalline and are so thin that they are subject to quantum-mechanical effects. Such membranes are susceptible to the transport of fundamental charges and exhibit a non uniform potential gradient between their two surfaces. In fact the gradient is a characteristic of an electrical diode.

The thinness and electrical asymmetry of membranes also place them in a special category with respect to electrolytic chemistry. Employing a pair of redox equations to explain the transfer of charge through a membrane is not necessary. If it did electrodeless electroplating onto the surface of a substrate would be impossible. Such electroplating is frequently observed in retinas and is an important industrial process.

A single reaction can generate free electrons, transport those electrons through the membrane (by quantum-mechanical tunneling or otherwise) and leave them on the surface of the membrane in an isolated state. Due to the extremely high impedance of the now reverse biased electrical diode character of the membrane, these isolated charges can maintain a potential across the capacitance of the membrane for a long time. The result is a non-equilibrium electrical condition that is not dependent on any chemical or diffusion related condition involving heavy ions.

Recognizing that a continuous symmetrical bilayer membrane of phospholipid material is impervious to virtually all ions and an extremely good insulator (10^{12}-10^{13} Ohms/cm^2 based on some extremely difficult measurements) **is necessary.** Asymmetrical bilayer membranes are also impervious to ions. Only when the membranes are asymmetrical do they exhibit a lower *and asymmetrical* electrical impedance. Recognizing the great sensitivity of bilayer membranes of liquid crystalline materials to attack by a wide range of chemicals is also necessary. A wide variety of both ionic and non-ionic detergents can disrupt them. Even micro-molar amounts of many organic compounds will disturb their electrical characteristics

by many orders of magnitude.[377] This sensitivity, and electron microscopy, suggest that real BLMs do not include significant proteinaceous pathways. Finally, noting the likelihood that different regions of a given membrane may be optimized, at the molecular level, for specific functions is appropriate.

Based on the above, one can describe a membrane in much greater detail than previously done in the terminology of the 1950's. It appears that type 1 and type 2 membranes form a majority of the conduits associated with neural signaling and type 3 membranes are found primarily in regions of the plasmalemma associated with the homeostasis of the overall cell.

[377]Finkelstein, A. (1987) Water movement through lipid bilayers, pores and plasma membranes. NY: John Wiley & Sons. pp. 109

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