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Does evolution have a target morphology?

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Abstract

We suggest here that evolutionary and developmental processes differ primarily in scale. Both evolution and development are dynamical processes subject to bottom-up and top-down constraints, and both can be viewed as search processes in rugged landscapes with multiple attractors. An important aspect of regulative development and regeneration is the ability of the system to reach the same anatomical configuration from different starting points and despite perturbations – a robustness toward a specific "target morphology" as the set point of a homeostatic cycle. We propose that evolution can be viewed as a developmental process of life as a whole, and that principles of regulative development and regeneration can, therefore, be expected to be active at much larger spatio-temporal scales: the major evolutionary transitions, including endosymbiosis, multicellularity, and the emergence of social groups, can be regarded as features of a "target morphology" of organismal phylogeny that biological evolution can be expected to replicate starting from a wide range of initial states and under a wide range of environmental conditions. Each of these transitions, like anatomical homeostasis on the ontogenetic timescale, can be regarded as a solution to a single problem, the reduction of environmental uncertainty, as it is manifested at progressively larger scales.

Keywords: Free-energy principle, Major evolutionary transitions, Prediction, Scale-free biology

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Citation

When told that people say that it looked as if the sun went round the Earth, Wittgenstein asked, "what would it have looked like if it had looked as if the Earth turned on its axis?" -- Anscomb (1959, p. 151

1. Introduction

In multicellular organisms, development generally proceeds from a single-celled zygote through a succession of embryonic or immature forms until some stable, species- or variety-typical, adult morphology is achieved. In competent organisms, including starfish, planaria, salamanders, and deer, lost limbs, damaged organs, or even the entire body may be regenerated until this same stable, species- or variety-typical, adult morphology is restored (Birnbaum and Sánchez Alvarado, 2008). Thus, regeneration and regulative development are individual cases of a more general biological process: anatomical homeostasis, which is able to robustly achieve a specific large-scale geometry despite drastic perturbations such as amputation and from different starting conditions. For example, genomically-normal tadpoles altered to have their craniofacial organs in the wrong locations largely become normal frogs (Vandenberg, Adams and Levin, 2012). Similarly, some embryos can be cut in half, fused with others, or implanted with aggressive cancer cells, and still result in perfectly normal bodies (Mintz and Illmensee, 1975). These kinds

of examples illustrate how anatomical homeostasis can reach the same large-scale anatomy from diverse starting conditions and other perturbations (Pezzulo and Levin, 2016). We will refer to such a stable endpoint of development or regeneration, averaged over species- or variety-typical outcomes, as the "target morphology" of the species or variety (Levin, 2011). In regulative development and regeneration, the target morphology is operationally defined as that shape which, once achieved, causes further growth and remodeling to stop (Fig. 1). Individual organisms may alter their size once their target morphology is reached, but do not significantly alter their internal organization or external shape. Significant departures from target morphology, e.g. different numbers of digits or unusual craniofacial morphologies, are generally considered pathological, even if they may be long-term viable. Such departures must be possible, however, for morphology to evolve under natural selection; all speciation events and morphological innovations initially represented a "birth defect" relative to the parent lineage.

The concept of target morphology is clearly applicable below the scale of the whole, multicellular organism. Tissues and some organs have capacity to restore structure at their appropriate level. Individual cells, e.g. muscle cells or neurons, have characteristic morphologies that are the typical endpoints of differentiation for cells of that type in that organism or even across a major phylogenetic lineage. Metabolic cycles and gene regulatory networks have the capacity to retain their dynamics in the face of environmental changes and some mutations. One can even view the tertiary structures of macromolecules under typical physiological conditions (and short timescales) as target morphologies. As at

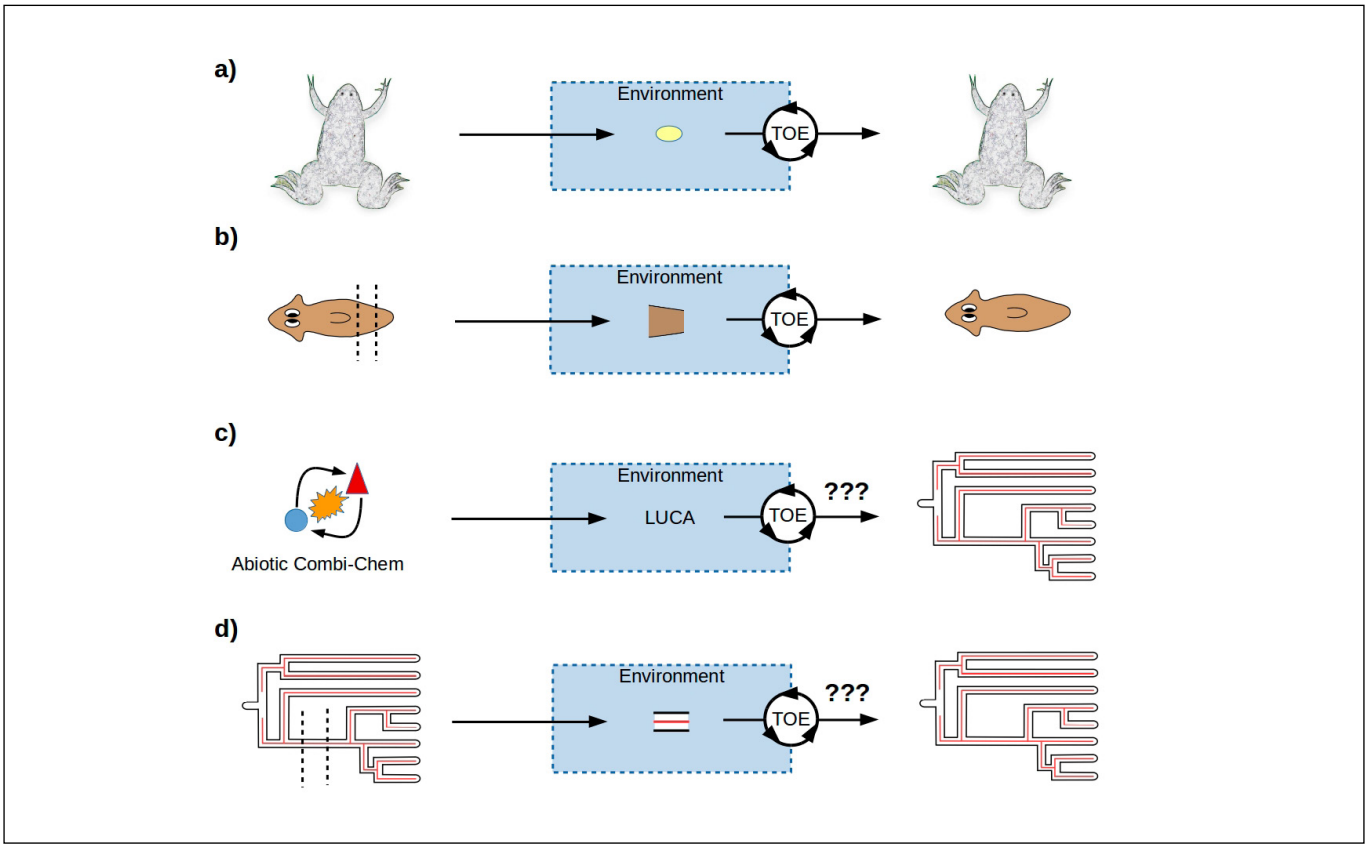

Fig. 1: The concept of target morphology. a) In sexually-reproducing organisms such as X. laevis , a single zygotic cell placed in an appropriate environment develops into an adult that replicates the morphology of the parent(s). At the cellular level, development involves a test-operate-exit (TOE) cycle that finds and fixes errors, thus maintaining the integrity of the process. b) A fragment excised from a regeneration-competent animal such as the planarian D. japonica and placed in an appropriate environment regenerates cells and tissues to replicate the adult form. c) Can the "shape" of the phylogeny of life since the last universal common ancestor (LUCA), including its major features such as endosymbiosis, multicellularity, and social organization be regarded as a "target morphology" of evolution? d) If some sample of the phylogeny of life since LUCA were to be placed in an appropriate planetary environment, would it "regenerate" a phylogenetic outcome with the same general characteristics?

the whole-organism scale, significant departures from target morphology by cells or macromolecules are generally considered pathological, and indeed generally disrupt "normal" function. But what about higher levels of organization and temporal scales larger than the lifetime of the individual organism?

Here, we ask whether the concept of target morphology could be usefully applied above the spatio-temporal scale characteristic of an individual organism. Can the typical sizes and organizations of ant hills, wolf packs, or human social groups, for example, be considered "targets" of inter-organism social interactions? Can climax communities be considered targets of inter-population interactions that constitute ecosystem-scale succession? Can biosphere-scale evolution, in particular, be considered to have a target morphology? What constraints did the structures of the last universal common ancestor (LUCA) and the environment in which it lived place on the evolutionary process that produced life as we know it? What constraints do molecular and cell biology place on evolution, and conversely, what aspects of information-processing at different scales facilitate robustness toward specific outcomes despite noise and uncertainty at lower scales? If the "tape" of Terrestrial evolution could, in Gould's (1989) metaphor, be run again, could we expect to see major transitions such as the rise of eukaryotes or multicellularity (Maynard Smith and Szathmáry, 1995; Szathmáry, 2015) replicated? Could we expect to see a "cognitive niche" (Pinker, 2010) occupied by an omnivorous, social generalist?

The idea that evolution might, like organismal development, be directed toward some target is obviously controversial and often rejected out of hand. Evolution must, after all, cope with unpredictable events such as bolide impacts causing mass extinctions (e.g. Schulte et al., 2010). It is important, however, to examine limitations on our observations which shape our intuitions on such questions. As Wittgenstein put it on being told that people say that it looked as if the sun went round the Earth, "what would it have looked like if it had looked as if the Earth turned on its axis?" (Anscomb, 1959, p. 151).

Consider an observer gathering data at the individual cell level during embryogenesis. Imagine this observer had never heard of development and did not already know the fact, so obvious to us that we rarely question it, that it always ends up making the same large-scale anatomy. Seeing the amount of stochastic behavior, frequent failures, diversity of even genetically identical cells' behaviors, and variability in biochemical and biomechanical properties, would they be able to infer that despite all the noise, there is a single morphological attractor at which all of this messy activity will inevitably arrive, even if significantly perturbed? Would the #1 fact of embryogenesis – its invariant outcome – be apparent at a small scale of spatio-temporal observations? No such small-scale observations, we suggest, would reveal this emergent property, just as small-scale observations of gas molecules in the interior of a large but unobserved container would not reveal the gas pressure measurable outside the container or the inevitable large-scale outcomes of thermodynamic manipulations. Could it be that our observations of individual biological species and small – even with paleontology – numbers of generations are likewise too constrained by their small scale to make plausible the idea that evolutionary processes may also operate over a space with very strong attractors, to which populations converge despite the stochastic events at the mutation and selection levels? Are major transitions such as multicellularity, in particular, attractors in the landscape of evolution?

This controversy goes to the heart of evolutionary theory: it concerns whether the core evolutionary processes of variation and selection are mechanistically coupled. In organismal development, these processes clearly are coupled: only specific cell types are produced at any given stage, and these cells assemble into specific micro-environments into which later-developing cells are born or migrate and must afterwards function. Variation and selection are, in contrast, uncoupled in Darwinian evolution; while Darwin (1859) rejected "chance" variation in favor of unknown causes (e.g. p. 131), these causes are presented as prior to and hence independent of selection. The Neo-Darwinian movement of the mid-20th century largely discredited "orthogenetic" conceptions of evolutionary variation as somehow directed or constrained (see Ulett, 2014 for a historical review), replacing them with a conception of variation as strictly random. Selection, in this case, "does all the work" in evolution; as Monod (1972) puts it, "from a source of noise natural selection alone and unaided [draws] all the music of the biosphere" (p. 118). While the past five decades have yielded an increasingly mechanistic

and non-random understanding of variation at the level of the genome (e.g. Kitts et al., 1982; Lichten and Golsman, 1995; Hall et al., 1999; Foster, 2000; Callinan et al., 2005; Lemons and McGinnis, 2006; Mitchell et al., 2009; Stern and Orgogozo, 2009; Uller et al., 2018), if these mechanisms are both mutually uncorrelated and uncorrelated with later-acting selection, variation remains effectively random and evolutionary history remains purely contingent, producing diversity at all scales with selection as the sole constraint (McShea, 1994; McShea and Brandon, 2010). This Neo-Darwinian conclusion has its prominent critics, e.g. Conway-Morris (2003; 2010) and Orgogozo (2015) who point out that it cannot adequately explain observed cases of convergent evolution, but it nonetheless remains the dominant view within evolutionary biology. Astro/exobiologists and artificial life researchers, in contrast, make it their business to attempt predictions of how evolution might proceed from various initial conditions (e.g. DesMarais and Walter, 1999; Chyba and Hand, 2005; Kaltenegger, 2017; Lenton et al., 2018). The operational assumption in these fields is that evolution is not purely contingent, but can rather be characterized as a dynamical system governed by both bottom-up (e.g. variation) and top-down (e.g. selection) constraints. Given reasonable assumptions about the dynamics and the constraints, the possibility of some level of predictability is simply taken for granted.

Here we introduce two lines of argument for a deep mechanistic coupling between variation and selection, and hence for a view of evolutionary processes as search processes in a space with invariant attractors. The first is that the processes we characterize as "evolution" and "development" differ primarily in scale. Indeed as pointed out previously (Hermida, 2016; Fields and Levin, 2018; Mariscal and Doolittle, 2018), all of life since LUCA can be viewed as a single, continuous cell lineage; hence evolution can be viewed as a developmental process with LUCA as the "zygotic" founder cell. Viewing evolution as a developmental process naturally raises the questions of what variants are possible at each stage, and of how such variants might be expected to survive under selective constraints largely imposed by other organisms (Fields and Levin, 2020a). The second line of argument builds on Friston's (2013) observation that all living systems face a thermodynamic requirement to minimize the variational free energy (VFE) – effectively, the unpredictability – of their environments. We have argued previously that the transition to multicellularity can be viewed as a VFE minimization strategy (Fields and Levin, 2019). Briefly, reproductive (i.e. stem) cells can be expected to produce "bodies" comprising non-reproductive (i.e. somatic) progeny as protection against sufficiently-challenging environments. If the transition to multicellularity can be understood in effectively thermodynamic terms, as a general response to selective pressures that works independently of minor details or contingencies, might not the other major transitions be similarly understandable? Could we not expect any evolutionary "tape" run long enough to generate social multicellulars and a cognitive niche? Could we not expect that morphogenetic mechanisms developed at the cellular scale, e.g. developmental bioelectricity (Levin and Martyniuk, 2018), would be co-opted into whole-organism scale mechanisms, e.g. bioelectric mechanisms for controlling organism-scale behavior such as nervous systems (Fields, Bischof and Levin, 2020)?

In what follows, we first review target morphologies at the molecular (§2.1), organismal (§2.2) and ecosystem (§2.3) scales. In each case, we consider where and how the information specifying the target morphology is stored and how this information is accessed and expressed as the target morphology is being generated. We discuss, in each case, how top-down constraints arising at larger scales regulate processes at the scale of interest. We then address the question posed in our title, focusing specifically on the major transitions to cellularity (§3.1), endosymbiosis (§3.2), multicellularity (§3.3), social groups (§3.4), and finally the emergence of a cognitive niche (§3.5). In contrast to the standard, multilevel-evolution view that these transitions represent selection for increased cooperation (Buss, 1987; Maynard Smith and Szathmáry, 1995; Michod, 1999; Szathmáry, 2015), we suggest that in each transition cooperative structures develop once a toolkit of pre-adapted communication and regulation capabilities has been assembled. In line with our previous model of multicellularity (Fields and Levin, 2019), we suggest that the driver of this process is in every case VFE minimization, i.e. that the major transitions are thermodynamic at-

tractors. We outline, in §4, a new "picture" of evolution as a sequence of phase transitions that each incorporate smaller-scale systems into larger-scale organizations. As the larger-scale organizations are, in every case, micro-environments that both provide new resources and impose new selective constraints, the products of this evolutionary process are multi-scale, heterogeneous communities, i.e. holobionts (Bordenstein and Theis, 2015). We conclude in §5 by suggesting experimental approaches that could test these ideas.

2. Target morphologies: From macromolecules to ecosystems

Toward the end of Wonderful Life (1989), Gould speculates that had the early chordate Pikaia not survived the Middle Cambrian, "we are wiped out of future history – all of us, from shark to robin to orangutan" (p. 323). A tiny change in evolutionary history, in other words, could produce an entirely different later outcome. With no ability to rewind the "tape" of evolution of life on Earth and run it again, we are left with "just history" to explain the landscape of organisms and their relations that we see around us.

Contrast this with organismal development, where tiny changes occasionally produce informative monstrosities, but typically result in either no difference at all, minor variants, or lethality. We know this because we have, in fact, observed the tape run many times. Given only a genome, a zygote, or even an early embryo and required to employ first principles, not comparative methods, we might be no better off in predicting the adult form than we would be trying to predict humans from Pikaia. Yet developmental biology has the goal of achieving an understanding that supports such predictability. Why, as Conway-Morris (2010) asks, has evolutionary biology seemingly abandoned that goal?

It is perhaps useful to compare the situation in evolutionary biology to that in physical cosmology, another setting in which "rerunning the tape" is not possible. Like the evolution of life, the evolution of the physical universe is characterized by a sequence of major transitions (e.g. from pure radiation to elementary particles to atoms) that progressively generate a hierarchy of scale-specific structures (Hawking, 1988; Smolin, 1997). Theoretical models of this process postulate, at each scale, local physical interactions constrained by global boundary conditions. Central to these models are formal notions of complexity that capture organizational structure instead of, or in addition to, diversity of form (Lineweaver, Davies and Ruse, 2013). Such models have generated significant empirical predictions, many of which have been extensively tested (e.g. Cyburt et al., 2016). The success of such models suggests that a similar, multiscale approach may be useful for studying evolution. They demonstrate, for example, that "noise" on one scale may resolve into predictability at a smaller scale, or self-organize into predictability, in response to overlying constraints, at a larger scale.

In the sections that follow, we consider three scales at which biological processes uncontroversially generate target morphologies. All of these processes are obviously evolved processes, and the details of the morphologies that they produce have obviously been shaped by selection. The claim that they are evolved processes, however, tells us nothing about how they work. Understanding how they work, and indeed, understanding how selection might have shaped them, requires understanding them as combinations of underlying dynamics and overlying constraints, as emphasized by Polanyi (1968), Rosen (1986), Kaufmann (1993), McShea (2016), and many others. In such systems, the dynamics may be governed by large-scale attractors – i.e. target morphologies – that are undetectable by small-scale, local observations but are obvious when the system is observed at the scale of its overlying constraints. In none of the cases considered here has such an understanding of the coupling between dynamics and constraints been fully achieved, and it remains unknown whether it can be fully achieved. It has, however, in every case been partially achieved, and even this partial achievement yields substantial predictive power.

2.1 Macromolecular tertiary structure

Both RNAs and proteins fold into complex, sequence-specific secondary and tertiary structures as they are being synthesized. These structures are essential to function, and their integrity is maintained through the course of often-complex conformational changes involved in reversible binding and catalysis. It is reasonable

to regard these tertiary structures as "morphologies" and to regard the "correct" functional structure into which an RNA or protein polymer folds as the "target morphology" of that polymer. One can then ask what information specifies this target morphology and how that information is deployed to correctly construct the target morphology. Predictive answers to these questions not only have explanatory power for natural systems, but also clear medical and technological relevance.

Theoretical studies of RNA folding began with the assumption that the final structure was specified, under physiological conditions, by the RNA sequence (e.g. Tinoco, Uhlenbeck and Levine, 1971; DeLisi and Crothers, 1971). In the ensuing decades it has become clear that the sequence information is "read" in stages during folding, and that parts of the sequence can encode different "instructions" in the context of different partially-folded structures (Chen, 2008). It is also now clear that "bottom-up" sequence information is insufficient to specify the mature structure of most functional RNAs; a myriad of proteins, some specific to particular RNAs or classes of RNAs, are also required for correct folding (Pan and Sosnick, 2006). These ancillary proteins are, therefore, also contributors of instructive information to the folding process. From the RNA's perspective, they are parts of the environment that provide top-down information or, in the more usual language, constraints.

Early research on protein folding similarly assumed that the information specifying the final structure resided in the sequence (e.g. Kuntz, 1972; Nagano, 1973). The most straightforward interpretation of this assumption, that protein folding minimizes the free energy of interaction of its amino acids, is computationally intractable (e.g. Fraenkel, 1993), raising the question of how Nature could efficiently solve this problem. There is now considerable evidence that proteins fold incrementally, with already-folded domains providing higher-level constraints on the folding of later domains as well as on domain assembly (Dill and MacCallum, 2012). Additional high-level constraints may be provided by chaperone proteins (Saibil, 2013) or other cofactors present in the "typical" environment. Hence as in the case of RNA, information at multiple scales is required to achieve the molecular-scale target morphology.

2.2 Organismal morphology

By considering the genome to be the sole carrier of inherited information, Modern Synthesis evolutionary theory committed itself to the genome as the sole driver of development. Hence we have, for example, "[d]evelopmental biology can be seen as the study of how information in the genome is translated into adult structure, and evolutionary biology of how the information came to be there in the first place" (Szathmáry and Maynard Smith, 1995, p. 231). This extreme view has been criticized from multiple perspectives (e.g. Pigliucci and Müller, 2010; Danchin et al., 2011; Laland et al., 2015; Booth, Mariscal and Doolittle, 2016; Gawne, McKenna and Nijhout, 2018) but still remains prominent.

That supra-genomic information can be inherited has been known at least since the work of Beisson and Sonneborn (1965) demonstrating inheritance of experimentally-induced alterations of cortical pattern in Paramecium (see Harold, 2005; Fields and Levin, 2018 for reviews of multiple studies along these lines that illustrate the stable and yet re-writable nature of target morphology on a single cell level). Indeed it is clear that any daughter cell, even if produced by asymmetric cleavage, inherits not only multiple active cytosolic molecules, including mRNAs, but also intact cytoskeletal components, an organized cell membrane, and organelles from its parent. We have previously termed this spatially-organized, functionally-intact information the "architectome" and shown that it is inherited in addition to the genome, transcriptome, and proteome (Fields and Levin, 2018). Evolution is, therefore, not just the evolution of the genome and its products, but also the evolution of the architectome. The genome and architectome scales are coupled bottom-up over evolutionary time by the incorporation of evolved gene products into the evolving architectome; they can also be expected to be coupled top-down through constraints on gene expression imposed by the architectome (Pezzulo and Levin, 2016).

Bioelectricity provides one mechanism for top-down control of gene expression. Bioelectric fields have long been known to influence morphological changes in single cells and developmental processes in multicellular organisms (Matthews, 1903; Burr and Northrop, 1935; Lund, 1947; Waris, 1950). More recently, electric circuits in non-neural cell groups have been revealed as

containing instructive information for organ morphogenesis and axial patterning in a wide range of animal models and human channelopathies (Bates, 2015; see Levin, Pezzulo and Finkelstein, 2017; McLaughlin and Levin, 2018 for more recent reviews). It has now been shown, using regenerating planaria (Dugesia) as a model system, that stable tissue-wide bioelectric prepatterns can drive a global change of the bodyplan to a two-headed symmetrical form, and are heritable without genetic change (Durant et al, 2017; Durant et al, 2019). Additional examples of the target morphology being specifically re-written include trophic memory in deer antlers and crab claws (reviewed in Lobo et al., 2014), as well as the results of repeated amputations in salamanders (Bryant et al., 2017).

Single genomes can support multiple target morphologies, in unicells (e.g. amoeboid and flagellate forms in Naegleria gruberi, Brunet and King, 2017) and facultative multicellulars (e.g. choanoflagellates) as well as in obligate multicellulars including metazoa. Target morphology can be preserved despite significant genetic change, e.g. in planaria (Dugesia) which maintained a fixed morphology and behavioral repertoire over 20 years of asexual reproduction despite the accumulation of non-synonymous codon substitutions in 74% of predicted genes (Nishimura et al., 2015). On the other hand, small changes in the genome, or in environmental conditions including bioelectric signaling, diet, toxins, parasites, and commensal bacteria etc. can produce large changes in final morphology as well as function. Homeotic transformations can move substantial components of intact, functional morphology from one part of the body to another through the localized co-regulation of large numbers of genes (e.g. Gehring and Hiromi, 1986). In planaria, homeotic replacements of posterior structures with anterior structures can be effected by either genetic or bioelectric manipulations (Lobo and Levin, 2015), with bioelectrically-induced replacements typically more accurately-scaled that genetically-induced replacements (Durant et al., 2019).

The development of mechanistic models, typically incorporating assumptions about physical forces as well as biochemical and/or cellular communication processes, has been a mainstay of developmental biology for decades (e.g. Thompson, 1942; Turing, 1952; Wolpert, 1969; Gierer and Meinhardt, 1972) and has flourished more recently as sophisticated gene-regulatory network (GRN, e.g. Engler et al., 2009; Hecker et al., 2009; Briscoe and Kicheva, 2017; Herrera-Delgado et al., 2018) and organism-scale cell-cell communication (e.g. Pietak and Levin, 2016) models have become feasible. Such models all incorporate, either explicitly or implicitly, both bottom-up and top-down constraints on the developmental dynamics at the scale of interest. While the assumptions and mechanisms implemented by such models are inevitably simplified compared to the actual biology, they are nonetheless capable of correctly predicting the outcomes of not-yet performed experiments, and hence of motivating and directing experimental work (e.g. Raspopovic et al., 2014; Chernet, Fields and Levin, 2015; Lobo and Levin, 2015; Pai et al., 2018; Streichan et al., 2018; Lee, Richtsmeier and Kraft, 2019; Pietak et al., 2019).

2.3 Ecosystem-level structure

Recognizable large-scale ecosystems such as grasslands or forests have been known to develop by long-term successional processes for over a century (for a historical review, see Connell and Slayter, 1977). The stable, “climax” endpoints of such processes have well-defined structures and internal self-stabilizing dynamics, and can be considered “target morphologies” in a natural sense. Smaller-scale multi-organism communities that incorporate abiotic materials in specific, reproducible configurations, such as termite mounds, have well-defined target morphologies in an even more obvious sense, and have been proposed to be individual “extended organisms” with heterogeneous genomes (Turner, 2004). With the discovery of ubiquitous, obligate microbiomes and the rise of the holobiont concept (Guerrero, Margulis and Berlanga, 2013; Gilbert, 2014; Bordenstein and Theis, 2015), it is now clear that all multicellular organisms are “ecosystems” in some sense, making the analogy between organismal morphology and ecosystem morphology even more direct. Stereotypical changes in microbiome structure as the “host” body ages (e.g. Miller, 2016) suggest that the concepts of “succession” and “development” are strongly coupled within holobionts. For example, the activity of commensal microbiota can strongly influence the morphogenesis of its host organism, such as the induction of second heads and alteration of visual system

structure by bacteria in regenerating planaria (Williams et al., 2020).

As in the case of organismal development, studies of ecosystem succession have relied on mathematical modeling almost since their inception (Connell and Slayter, 1977). Such models typically employ abstract "spaces" with dimensions, e.g. principal components, representing populations or subpopulations or their properties (Lockwood and Lockwood, 1993; Levin et al., 1997; Logofet and Lesnaya, 2000; Fukami et al., 2005). "Morphology" in this case corresponds to a probability distribution, or a stable dynamics over such distributions in a system such as Lotka-Volterra, in this abstract space. In considering the possibility of a target morphology for an evolutionary process, we can expect this more abstract, organizational sense of morphology to be more relevant than the idea of a three-dimensional shape.

3. Are major evolutionary transitions predictable?

The central idea of cladistics is that any correct phylogeny depicts an organismal lineage. As noted earlier, if we think of a phylogeny of life on Earth as depicting a cell lineage, it becomes clear that all of life can be considered a single, spatio-temporally extended living entity. This entity has, in particular, a spatio-temporally continuous cytoplasm enclosed by a spatio-temporally continuous membrane (Fields and Levin, 2018). This

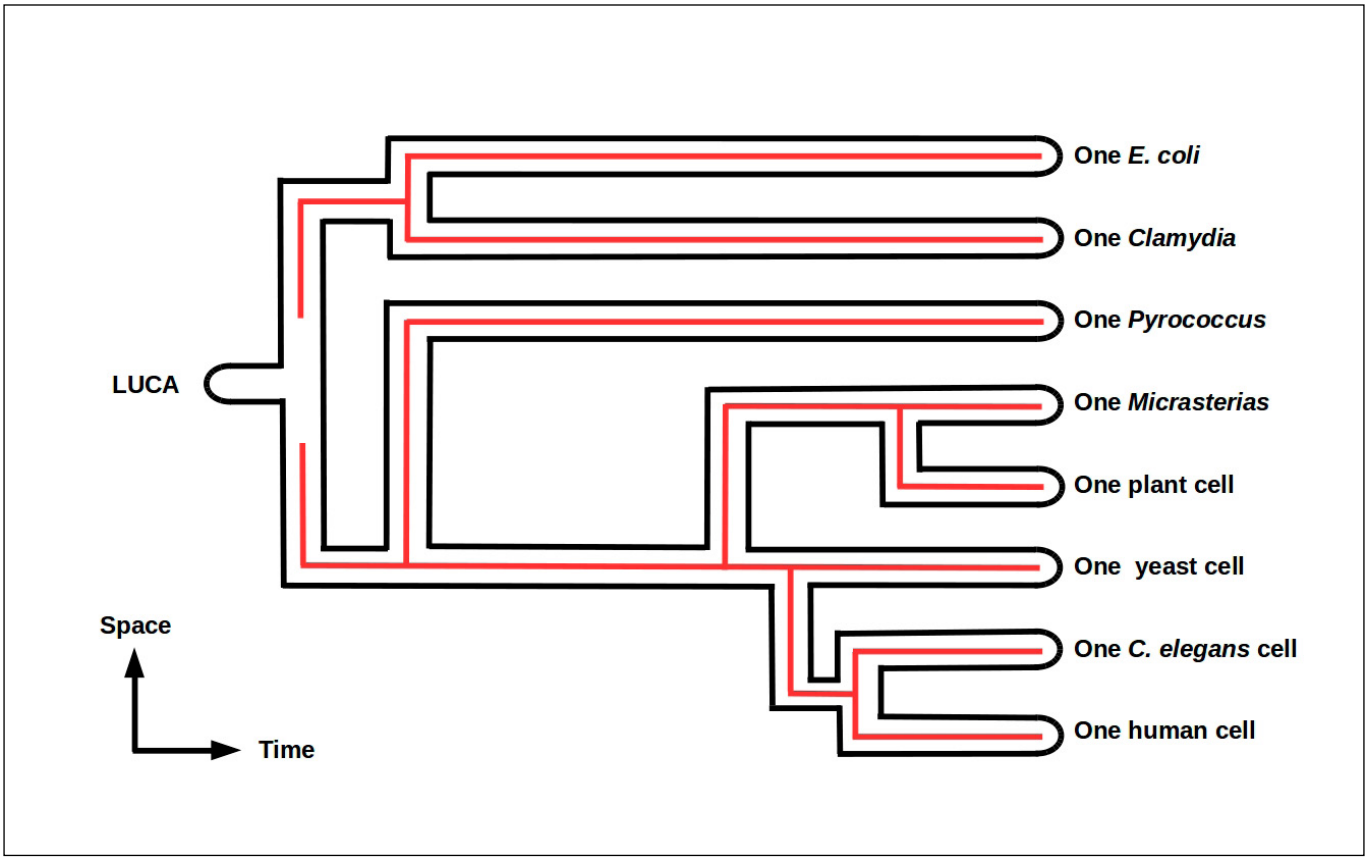

Fig. 2: Representation of a sample of phylogeny as a cell lineage starting from LUCA. Whether LUCA had a DNA genome (red lines) is left open. Endosymbiotic events are not shown; see Fields and Levin (2018) for lineage diagrams that include them.

is illustrated in Fig. 2. The analogy with a cell lineage describing a developmental process is obvious.

When we think of life as a single entity in this way, evolution becomes an interaction between processes internal to this entity, including variation, competition, and cooperation, and processes external to this entity. In this it is fully analogous to development, where variation is differentiation, cooperation is well recognized – to the extent of defining biological individuals as units of maximum cooperation (Queller and Strassmann, 2009; Strassmann and Queller, 2010) – and competition is increasingly being demonstrated (Gogna, Shee and Moreno, 2015; Madan, Gogna and Moreno, 2018; Gawne, McKenna and Levin, 2020). While the developmental processes of individual organisms are "evolved" while evolution itself clearly is not, this distinction as noted above has no explanatory power. Evolution is, moreover, increasingly recognized to be a learning process, one that results not only in adaptation, but also in increased evolvability (Watson and Szathmáry, 2016; Kouvaris et al., 2017).

Viewing evolution as a space- and time-dependent interaction between a living entity and its environment allows powerful and general information-theoretic tools to be brought to bear on the question of its predictability. Friston (2013) argued that all living systems face a thermodynamic requirement to minimize the variational free energy (VFE) – effectively, the unpredictability – of their environments. Environmental VFE is, moreover, defined at a specific locus: the boundary through which the system interacts with its environment, characterized in mathematical terms as a Markov blanket (MB, Pearl, 1988; see Friston, 2013; Friston et al., 2015; Fields and Levin, 2018 for further discussion). Kuchling et al. (2019) showed that MBs can be defined, and VFE minimization within the MB characterized in terms of approximate Bayesian inference, in systems satisfying very general physical assumptions; these assumptions can be generalized still further when the system-environment interaction is describing using quantum instead of classical physics (Fields and Marcianò, 2019; Fields and Glazebrook, 2020). We have shown previously that under appropriate environmental conditions, MBs can support phase transitions to more complex internal organizations (Fields and Levin, 2019). We argue in what follows that such conditions occur ubiquitously and at multiple scales over evolutionary history, and drive a sequence of phase transitions to larger and more complex organizational structures.

3.1 Cellularity

Origin-of-life proposals are notoriously diverse and controversial, and the structure of the biosphere prior to LUCA remains primarily a topic of speculation (Cornish-Bowden and Cárdenas, 2017; Bartlett and Wong, 2020). Whether life had one origin or many, and whether LUCA was the product of a single lineage or many both remain unclear. The structure of LUCA itself is largely unknown, though it seems reasonable to assume that LUCA was a membrane-bound cell (or protocell, Szathmáry, 2015) with both nucleic acids and proteins.

Selection clearly favored cellular life. Are there, however, principles on the basis of which we could expect cellular life to develop an any suitable environment? Friston (2013) offers a heuristic "proof" that any system with an MB will approach a stable, self-sustaining dynamics within the MB, concluding that as living systems at least approximately satisfy the conditions required to maintain an MB, life is "(almost) inevitable" (p. 1). An MB, however, is a set of states, not a physical structure such as a membrane. Hence given Friston's result, the key question becomes that of principles on the basis of which we could expect the emergence of physical boundaries, the states of which constitute MBs for whatever systems the boundaries enclose. All current cells are bounded by membranes, but it cannot be ruled out that earlier "cells" – ancestors of LUCA – were bounded by protein capsids, other non-lipid biotic structures, or even abiotic structures.

It is useful to think of this question of boundaries in more abstract, cybernetic terms. Homeostasis can be considered a form of memory, a record of what has worked in the past (Ashby, 1956). The processes that maintain homeostasis can, as Friston (2013) emphasizes, be considered inferential: they are processes that compare external conditions to the memory and adjust one or the other, what Friston calls "active inference." The most fundamental requirement of any such process is that "external conditions" and "memory" be separately accessible. Maintaining homeostasis, therefore, requires a boundary. Some approaches to the origin of

life postulate abiotic boundaries, e.g. mineral surfaces (Szathmáry, 2015), but any free-living life form requires a boundary that it can regenerate, particularly following replication. Hence the origin of the chemistry required to regenerate boundaries may be the principle problem to be solved by emergent protocellular life forms. As Cornish-Bowden and Cárdenas (2017) put it, "Understanding how the transition to an organism with a large coding capacity can have happened is a more challenging problem than understanding how LUCA could have evolved to Homo sapiens" (p. 72).

Importantly, we are just starting to understand how a sufficiently protected not-yet-cellular system could have been both stable and sufficiently robust to explore the space of possibilities leading to cellularity. Recent work has highlighted the capabilities of subcellular components, such as molecular networks that show learning and adaptation (Watson et al., 2010; Herrera-Delgado et al., 2018), cell-free systems that show complex self-assembly of cytoskeletal structures (Cheng and Ferrell, 2018), and dynamic, responsive motile behavior of cell fragments (Albrecht-Buehler, 1980; Euteneuer and Schliwa, 1984; Sun et al., 2013). Moreover, syncytial systems like Physarum (Vallverdú et al., 2018), giant cells such as algae (Coneva and Chitwood, 2015), Acetabularia (Mandoli, 1998), and glass sponges (Leys, 2015) demonstrate how flexible the idea of a "cell" is. Evolution clearly pushes the limits of cellularity to make it look and behave like multicellularity.

3.2 Endosymbiosis

Once regenerable boundaries become available, the logic of VFE minimization is sufficient to drive increases in complexity. One need only postulate a sufficiently variable environment and an ability of cells to exchange information.

Within a VFE minimization or active inference framework, the primary driver of evolution is predictability (Friston, 2013; Friston et al., 2015; Kuchling et al., 2019). For a cell equipped with a memory, the most predictable state is the state of its own memory: homeostasis is precisely the process of keeping this state fixed. If cells are capable of both communicating the states of their memories to other cells and receiving such communications, then the states of other cells also become predictable. Cell-surface markers and diffusible signals are such means of communication. As a means of communicating not just the state of the memory, but a functional component of the memory, lateral gene transfer (LGT) is an even more efficient means of increasing mutual predictability, one that microbes make particular use of in challenging environments (Robbins, Krishtalka and Wooley, 2016). Indeed LGT can be viewed as "endosymbiosis" at the scale of the genome.

If the states of other cells are more predictable than the state of the open environment, any cell that associates closely with other cells achieves an increase in predictive success, i.e. a decrease in VFE. Hence facultative multicellularity is a direct prediction of the VFE minimization framework. Any evolutionary process capable of producing cellular life can be expected to generate facultatively multicellular life. The appearance of microbial stromatolites 3,500 million years ago (MYA), i.e. shortly after LUCA (Stal, 2012), is therefore not surprising.

Facultatively-multicellular microbial systems exhibit division of labor, even in single-species systems such as Myxobacteria (Muñoz-Dorado et al., 2016). In many systems, division of labor includes both division of metabolic labor and differential exposure to the open environment (Stal, 2012; Ereshefsky and Pedroso, 2015). If such systems are considered "individuals" as Ereshefsky and Pedroso (2015) suggest, their "internal" protected components have many of the features of endosymbionts: internal location, specific metabolic functions, and only partial reproductive independence (Booth and Doolittle, 2015). Such facultative endosymbiosis appears both quite common and very old.

The transition from facultative endosymbiosis to the obligate, cellular endosymbiosis found in eukaryotes represents, from a VFE perspective, an increase in predictive power. Cellular symbiosis renders the presence and contribution of the metabolic partner secure from the "host" perspective, and the availability of protection from the open environment secure from the endosymbiont's perspective. Hence this transition can be expected in any evolutionary process driven by VFE minimization. As Booth and Doolittle (2015) point out, the idea that eukaryogenesis was unique and highly improbable may largely be the result of ascertainment bias.

By coupling reproductive cycles, obligate endosymbiosis assures that components that work well together stay together. From an information-processing perspective, this represents an increase in computational power, one that enables more efficient search of fitness landscapes that are rugged on multiple scales (Watson and Pollack, 2003). A capability for more efficient search is, effectively, evolvability. Hence one can expect evolutionary processes to generate, via endosymbiotic or other reproductive-coupling processes, systems that are progressively more evolvable. Multicellular organisms possessing obligate, endosymbiotic microbiomes, and hence living and reproducing as holobionts, are not surprising from this perspective.

3.3 Multicellularity

We extend the above considerations of the advantages for predictability of facultative multicellularity to the case of obligate multicellularity in Fields and Levin (2019). In obligate multicellulars, there is an asymmetry in the benefits conferred by communication, one also observed in facultative multicellulars such as Myxobacteria and Dictyostelium: only a fraction of the cells involved get to reproduce. This fraction ranges from roughly 30% in asexual planaria (Elliott and Sánchez Alvarado, 2012) to roughly 5% in C. elegans hermaphrodites (Sulston and Horvitz, 1977) to much less than 1% in insects or vertebrates.

Why would evolution generate large, complex, multicellular systems in which most of the component cells have zero individual reproductive fitness? We suggested in Fields and Levin (2019) that reproductive (i.e. stem) cells faced with suitably-challenging environments assemble somatic bodies out of expendable, reproductively-suppressed progeny to keep the environment at bay while avoiding the risk of competition for their protected status and reproductive fitness. This "imperial" model of multicellularity requires a means of enforcing reproductive suppression over long distances, a problem for which specialized signaling systems including neurons provide a solution (Fields, Bischof and Levin, 2020; Fields and Levin, 2020b). Here again, VFE minimization and hence the preservation of memory correlates with signaling capability. As in the case of facultative multicellulars that limit reproduction to only some cells, the division of labor between stem and somatic cells is extreme from a fitness point of view, and the signaling can be regarded as coercive instead of cooperative.

3.4 Social groups

Microbial stromatolites are arguably the first social groups; indeed any facultative multicellular can be regarded as a "social group" at the cellular level. Such groups are held together by specific forms of communication – in this case, intercellular signaling with emergent "conventions" such as quorum sensing – and typically exhibit division of labor.

Beyond the cellular level, a VFE minimization framework favors social group formation whenever it increases net predictability, i.e. whenever the states or behavior of other in-group members are more predictable, by the average in-group member, than the states or behaviors of out-group members, including the open environment. While increased predictability is expected to be the case in general within a species, predictability is also high in "extended organism" cooperatives (e.g. Turner, 2004) and in the vast array of symbiotic, mutualist, and facilitated arrangements between disparate species (e.g. Bronstein, 2009). From this perspective, non-social organisms are the exception requiring explanation, e.g. in terms of required range size or hunting style for solitary carnivores.

3.5 The cognitive niche

When interactions between cells and multicellular organisms are conceptualized in terms of memory, information processing, and communication, it is natural to regard them as "cognitive" (Pattee, 1982; Stewart, 1996; Baluška and Levin, 2016; Levin, 2019). Indeed, the idea that VFE minimization implements approximate Bayesian inference originated in cognitive neuroscience (Friston, 2010). If evolution is viewed as driven at multiple scales by VFE minimation as suggested in the previous sections, all of life can be regarded as occupying a cognitive niche, an idea reminiscent of both the Gaia hypothesis (Lovelock and Margulis, 1974; Len-

ton et al., 2018) and biosemiotic thinking (Maturana and Varela, 1980; Kull et al., 2011).

The term "cognitive niche" is nonetheless applied primarily to the niche we humans occupy, one that demands abstraction, analogical reasoning, and planning as well as memory, perceptual processing, and situation-appropriate action. It is often identified specifically with human-like generative language capabilities (Pinker, 2010). Can we expect such a niche to be occupied, eventually, in a generic evolutionary scenario allowed to run long enough?

As higher cognitive capabilities are clearly useful for reducing environmental uncertainty, including uncertainty about what other organisms and particularly conspecifics (Adolphs, 2009) are likely to do next, one might expect an "advanced" cognitive niche to arise and be filled purely on VFE minimization grounds. However, one would also expect to see substantial pre-adaptation in organisms occupying niches that required lesser, but still significant, cognitive capabilities. Studies in both cognitive ethology, e.g. of analogical reasoning in tool use (Fields, 2011), and comparative genetics, e.g. of the role of FOXP2 in communication ability (Fisher and Scharff, 2009) provide compelling evidence for such pre-adaptation. Both molecular and bioelectric signaling, for example, enormously pre-date their employment by neurons. The earliest function of neurons, moreover, may have been the control of cell proliferation and differentiation, functions that neurons still provide today (Fields, Bischof and Levin, 2020). Hence nervous systems themselves may be a pre-adaptation for complex behaviors and hence general intelligence.

4. Reassessing evolutionary "direction"

As Orgogozo (2015) emphasizes, the question of the predictability of evolution can be posed at different scales and levels of abstraction. Here we have posed the question both abstractly and at large scale: are the major transitions of Terrestrial evolution predictable? Would we expect a generic evolutionary process running anywhere to produce cells, facultative multicellulars, endosymbionts, obligate multicellulars, and social groups? If we regard the predicted outcome as a target morphology, the "morphology" being targeted in this case is a multi-scale organizational structure. We are asking, effectively, if we can expect a generic evolutionary process to produce smart, social holobionts.

As discussed above, the basic ingredients needed to get such a process off the ground are boundaries, memory, information processing, and communication. The boundary must be impermeable to whatever implements the memory but permeable to whatever implements communication: these are the conditions that define an MB. Within the MB, it is sufficient that the information processing system implement VFE minimization, i.e. that its fundamental goal is to increase predictability.

Given such a starting point – a bounded "cell" that can talk to other cells – an evolutionary process will display major transitions if it is able to replicate this basic organizational structure on larger and larger scales. The key to achieving larger scales is, however, built into the system. Aggregating small entities will produce a large entity, and small entities can be expected to aggregate for protection from their environment. The pre-adaptation needed by the small entities to act as a larger unit is communication. This communication can be cooperative, but can also be coercive. Both communication styles were discovered, on Earth, by bacteria. We would expect them to be discovered at an early stage in any evolutionary process.

These considerations suggest that the "direction" of evolution is not toward higher complexity per se as often believed, but rather toward larger scales. Dynamics at larger scales is not more complex than dynamics at smaller scales; large-scale dynamics rather replicates smaller-scale dynamics using larger components. Complexity at the whole-system level increases due to the hierarchization resulting from this embedding (McShea, 2016).

The basic algorithm driving both evolution and development, VFE minimization, remains at least approximately fixed across scales. Evidence that phenomena as diverse as GRNs and metabolic networks (Agrawal, 2002; Barabási and Oltvai, 2004), functional networks in the mammalian brain (Bassett and Bullmore, 2006), and human social networks (Newman, 2001) all share the same small-world architecture suggests that the architecture of memory may also be fixed across scales.

Whether communication capabilities are similarly fixed, e.g. whether cell-cell communication systems have a "grammar" with structural properties resembling those of human languages, remains to be determined.

5. Future work and predictions

These ideas suggest a number of experimental approaches. First, it will be important to develop multiscale computer models that include both developmental and evolutionary scales. Some of this has been done in the field of artificial life (via "artificial embryogeny" e.g. Stanley and Miikkulainen, 2003; Andersen, Newman and Otter, 2006; 2009; Stanley, 2007; Cussat-Blanc et al., 2010; Pollack and Lowell, 2018) but further advances will require richer, more biorealistic virtual environments specifically including cells as allostatic agents pursuing infotaxis and surprise minimization, and the ability to form multicellular collectives whose large-scale shape and behavior are subject to selection. In such simulations, we predict the scaling of simple, adaptive homeostatic loops at the cellular level to multicellular anatomical homeostasis, and the discovery of similar plasticity toward system-level targets on multiple scales including the physiological, anatomical, and even evolutionary.

Second, wetlab experiments in synthetic morphology, especially those incorporating evolutionary dynamics (Kriegman et al., 2020), and model systems used for the study of origins of multicellularity (Ratcliff et al., 2012; Libby et al., 2016) should enable specific tests of our hypothesis regarding the stability of specific evolutionary transitions to the vagaries and noise of events at the lower levels. An especially interesting context is the use of bioelectric dynamics in bacterial biofilms (Prindle et al., 2015; Ratcliff et al., 2015; Humphries et al., 2017; Yang et al, 2020), suggesting experiments in repeated evolution of bacterial and yeast populations to determine how frequently discoveries, such as using bioelectrics to organize structure and physiology in such "proto-bodies", occur despite variable genetic and environmental conditions.

6. Conclusions

We have suggested here that reconceptualizing evolutionary biology to look more like developmental biology leads to novel insights and predictions (see also Fields and Levin, 2020b) and that such a reconceptualization is indeed underway already. Target morphologies in the form of large-scale attractors are to be expected in this setting; we suggest that the major evolutionary transitions are such attractors, and that their replication in multiple "rounds" of evolution could be expected. New theoretical and experimental technologies offer the possibility of testing evolutionary processes in controlled settings with known initial states and adjustable constraints. Both physics and computer science, in particular, have well-developed theoretical vocabularies and toolkits that have yet to be applied extensively to biological problems.

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Conflict of interest

The authors declare no conflicts of interest regarding this work.

References

1. Albrecht-Buehler, G 1980, "Autonomous movements of cytoplasmic fragments", Proceedings of the National Academy of Sciences USA, vol. 77, 6639-6643.

2. Andersen, T, Newman, R & Otter, T 2006, "Development of virtual embryos with emergent self-repair", in S Kumar, GS Hornby, J Bongard (eds) Developmental Systems: Papers from the AAAI Fall Symposium (Technical Report FS-06-03), AAAI, Palo Alta, CA.

3. Andersen, T, Newman, R & Otter, T 2009, "Shape homeostasis in virtual embryos", Artificial Life, vol. 15, 161-183.

4. Anscomb, GEM 1959, An Introduction to Wittgenstein's Tractatus, Hutchinson, London.

5. Ashby, WR 1956, Introduction to Cybernetics. Chapman and Hall, London.

6. Agrawal, H 2002, "Extreme self-organization in networks constructed from gene expression data", Physical Review Letters, vol. 89, 268702.

7. Baluška, F & Levin, M 2016, "On having no head: cognition throughout biological systems", Frontiers in Psychology, vol. 7, 902.

8. Barabási, A-L & Oltvai, ZN 2004, "Network biology: Understanding the cell's functional organization", Nature Reviews Genetics, vol. 5, 101-114.

9. Bartlett, S & Wong, ML 2020, "Defining Lyfe in the Universe: From three privileged functions to four pillars", Life, vol. 10, 42.

10. Bassett, DS & Bullmore, E 2006, "Small world brain networks", The Neuroscientist, vol. 12, 512-523.

11. Bates, E 2015, "Ion channels in development and cancer", Annual Review of Cell and Developmental Biology, vol. 31, 231-247.

12. Beisson, J & Sonneborn, TM 1965, "Cytoplasmic inheritance of the organization of the cell cortex in Paramecium aurelia", Proceedings of the National Academy of Sciences USA, vol. 53, no. 2, 275-282.

13. Birnbaum, KD & Sánchez Alvarado, A 2008, "Slicing across kingdoms: Regeneration in plants and animals", Cell, vol. 132, no. 4, 697-710.

14. Booth, A & Doolittle, WF 2015, "Eukaryogenesis, how special really?" Proceedings of the National Academy of Sciences USA, vol. 112, 10278-10285.

15. Booth, A, Mariscal, C & Doolittle, WF 2016, "The Modern Synthesis in the light of microbial genomics", Annual Review of Microbiology, vol. 70, 279-297.

16. Bordenstein, SR & Theis, KR 2015, "Host biology in light of the microbiome: Ten principles of holobionts and hologenomes", PLoS Biology, vol. 13, no. 8, e1002226.

17. Briscoe, J & Kicheva, A 2017, "The physics of development 100 years after D'Arcy Thompson's "On Growth and Form", Mechanisms of Development, vol. 145, 26-31.

18. Bronstein, JL 2009, "The evolution of facilitation and mutualism". Journal of Ecology, vol. 97, 1160-1170.

19. Brunet, T & King N 2017, "The origin of animal multicellularity and cell differentiation" Developmental Cell, vol. 43, 124-140.

20. Bryant, DM, Sousounis, K, Farkas, JE, Bryant, S, Thao, N, Guzikowski, AR, Monaghan, JR, Levin, M & Whited, JL 2017, "Repeated removal of developing limb buds permanently reduces appendage size in the highly-regenerative Axolotl", Developmental Biology, vol. 424, 1-9.

21. Burr, HS & Northrop, FSC 1935, "The electro-dynamic theory of life", Quarterly Review of Biology, vol. 10, no. 3, 322-333.

22. Buss, LW 1987, The Evolution of Individuality. Princeton Univ Press, Princeton, NJ.

23. Callinan, PA, Wang, J, Herke, SW, Garber, RK, Liang, P & Batzer, MA 2005, "Alu retrotransposition- mediated deletion", Journal of Molecular Biology, vol. 348, 791-800.

24.

25. Chen, S-J 2008, "RNA folding: Conformational statistics, folding kinetics, and ion electrostatics", Annual Review of Biophysics, vol. 37, 197-214.

26. Cheng, X & Ferrell, JE 2018, "Spontaneous emergence of cell-like organization in Xenopus egg extracts", Science, vol. 366, 631-637.

27. Chernet, BT, Fields, C & Levin, M 2015, "Long-range gap junctional signaling controls oncogene-mediated

tumorigenesis in Xenopus laevis embryos", Frontiers in Physiology: Biophysics, vol. 5, 519.

28. Chyba, CF & Hand, KP 2005, "Astrobiology: The study of the living universe", Annual Review of Astronomy and Astrophysics, vol. 43, 31-74.

29. Coneva, V & Chitwood, DH 2015, "Plant architecture without multicellularity: quandaries over patterning and the soma-germline divide in siphonous algae", Frontiers in Plant Science, vol. 6, 287.

30. Connell, JH & Slayter, RO 1977, "Mechanisms of succession in natural communities and their role in community stability and organization", American Naturalist, vol. 111, 1119-1144.

31. Conway-Morris, S 2003, Life's Solution: Inevitable Humans in a Lonely Universe. Cambridge University Press, Cambridge, UK.

32. Conway-Morris, S 2010, "Evolution: Like any other science it is predictable", Philosophical Transactions of the Royal Society B, vol. 365, 133-145.

33. Cornish-Bowden, A & Cárdenas, M 2017, "Life before LUCA", Journal of Theoretical Biology, vol. 434, 68-74.

34. Cussat-Blanc, S, Pascalie, J, Luga, H & Duthen, Y 2010, "Three simulators for growing artificial creatures", IEEE Congress on Evolutionary Computation, pp. 1-8. IEEE, New York.

35. Cyburt, RH, Fields, BD, Olive, KA & Yeh, TH 2016, "Big bang nucleosynthesis: Present status", Reviews of Modern Physics, vol. 88, 015004.

36. Danchin, E, Charmantier, A, Champagne, FA, Mesoudi, A, Pujol, B & Blanchet, S 2011, "Beyond DNA: Integrating inclusive inheritance into an extended theory of evolution", Nature Reviews Genetics, vol. 12, 475-486.

37. Darwin, C 1859, On the Origin of Species by Means of Natural Selection, or the Preservation of Favoured Races in the Struggle for Life. Murray, London. Available online at http://darwin-online.org.uk/Variorum/1859

38. DeLisi, C & Crothers, DM 1971, "Prediction of RNA secondary structure", Proceedings of the National Academy of Sciences USA, vol. 68, 2682-2685.

39. DesMarais, DJ & Walter, MR 1999, "Astrobiology: Exploring the origins, evolution, and distribution of life in the universe", Annual Review of Ecology and Systematics, vol. 30, 397-420.

40. Dill, KA & MacCallum, JL 2012, "The Protein-folding problem, 50 years on", Science, vol. 338, 1042-1046.

41. Durant, F, Morokuma, J, Fields, C, Williams, K, Adams, DS & Levin M. 2017, "Long-term, stochastic editing of regenerative anatomy via targeting endogenous bioelectric gradients", Biophysical Journal, vol. 112, no. 10, 2231-2243.

42. Durant, F, Bischof, J, Fields, C, Morokuma, J, LaPalme, J, Hoi, A & Levin, M 2019, "The role of early bioelectric signals in the regeneration of planarian anterior/posterior polarity", Biophysical Journal, vol. 116, 948-961.

43. Elliott, SA & Sánchez Alvarado, A 2012, "The history and enduring contributions of planarians to the study of animal regeneration", Wiley Interdisciplinary Reviews: Developmental Biology, vol. 2, no. 3, 301-326.

44. Engler, AJ, Humbert, PO, Wehrle-Haller, B & Weaver, VM 2009, "Multiscale modeling of form and function", Science, vol. 324, 208-212.

45. Ereshefsky, M & Pedroso, M 2015, "Rethinking evolutionary individuality", Proceedings of the National Academy of Sciences USA, vol. 112, 10126-10132.

46. Euteneuer, M & Schliwa, M 1984, "Persistent, directional motility of cells and cytoplasmic fragments in the absence of microtubules", Nature, vol. 310, 58-61.

47. Fields, C 2011, "Implementation of structure mapping by event-file binding and action planning: A model of tool-improvisation analogies", Psychological Research, vol. 75, 129-142.

48. Fields, C, Bischof, J & Levin, M 2020 Morphological coordination: A common ancestral function unifying neural and non-neural signaling", Physiology, vol. 35, 16-30.

49. Fields, C & Glazebrook, JF 2020, "Representing measurement as a thermodynamic symmetry breaking. Symmetry, vol. 12: 810.

50. Fields, C & Levin, M 2018, "Multiscale memory and bioelectric error correction in the cytoplasm-cytoskeleton-membrane system", Wiley Interdisciplinary Reviews: Systems Biology and Medicine, vol. 10, e1410.

51. Fields, C & Levin, M 2019, "Somatic multicellularity as a satisficing solution to the prediction-error minimization problem", Communicative and Integrative Biology, vol. 12, 119-132.

52. Fields, C & Levin, M 2020a, "Integrating evolutionary and developmental thinking into a scale-free biology", BioEssays, in press (doi: 10.1002/bies.201900228).

53. Fields, C & Levin, M 2020b, "Does regeneration recapitulate phylogeny? Planaria as a model of body-axis specification in ancestral eumetazoa", Communicative and Integrative Biology, vol. 13, 27-38.

54. Fields, C & Marcianò, A 2019, "Markov blankets are general physical interaction surfaces", Physics of Life Reviews, in press (doi: 10.1016/j.plrev.2019.08.004).

55. Fisher, SE & Scharff, C 2009, "FOXP2 as a molecular window into speech and language", Trends in Genetics, vol. 25, 166-177.

56. Foster, PL 2000, "Adaptive mutation: Implications for evolution", BioEssays, vol. 22, 1067-1074.

57. Fraenkel, AS 1993, "Complexity of protein folding", Bulletin of Mathematical Biology, vol. 55, 1199-1210.

58. Friston, KJ 2010, "The free-energy principle: A unified brain theory?" Nature Reviews Neuroscience, vol. 11, 127-138.

59. Friston, KJ 2013, "Life as we know it", Journal of the Royal Society Interface, vol. 10, 20130475.

60. Friston, K, Levin, M, Sengupta, B & Pezzulo, G 2015, "Knowing one's place: A free-energy approach to pattern regulation", Journal of the Royal Society Interface, vol. 12, 20141383.

61. Fukami, T, Bezemer, TM, Mortimer, SR & van der Putten, WH 2005, "Species divergence and trait convergence in experimental plant community assembly", Ecology Letters, vol. 8, 1283-1290.

62. Gawne, R, McKenna, KZ & Nijhout, HF 2018, "Unmodern synthesis: Developmental hierarchies and the origin of phenotypes", BioEssays, vol. 40, 1600265.

63. Gawne, R, McKenna, K & Levin, M 2020, "The strategies of the parts: Competitive and coordinative interactions between characters produce adaptive developmental outcomes", BioEssays, in press (doi: 10.1002/bies.201900245).

64. Gehring, WJ & Hiromi, Y 1986, "Homeotic genes and the homeobox", Annual Review of Genetics, vol. 20, 147-173.

65. Gierer, A & Meinhardt, H 1972, "A theory of biological pattern formation", Kybernetik, vol. 12, no.1, 30-39.

66. Gilbert, SF 2014, "Symbiosis as the way of eukaryotic life: The dependent co-origination of the body", Journal of Biosciences, vol. 39, 201-209.

67. Gogna, R, Shee, K & Moreno, E 2015, "Cell competition during growth and regeneration", Annual Review of Genetics, vol. 49, 697-718.

68. Gould, SJ 1989, Wonderful Life. Norton, New York.

69. Guerrero, R, Margulis, L & Berlanga, M 2013, "Symbiogenesis: The holobiont as a unit of evolution", International Microbiology, vol. 16, 133-143.

70. Hall, RM, Collis, CM, Kim, M-J, Partridge, SR, Recchia, GD &. Stokes, HW 1999, "Mobile gene cassettes and integrons in evolution", Annals of the New York Academy of Sciences, vol. 870, 68-80.

71. Hawking, SW 1988, A Brief History of Time, Bantam Dell, New York.

72. Hecker, M, Lambeck, S, Toepfer, S, van Someren, E & Guthke, R 2009, "Gene regulatory network inference: Data integration in dynamic models – A review", Biosystems, vol. 96, 86-103.

73. Hermida, M 2016, "Life on Earth is an individual", Theory in the Biosciences, vol. 135, 37-44.

74. Herrera-Delgado, E, Perez-Carrasco, R, Briscoe, J & Sollich, P 2018, "Memory functions reveal structural properties of gene regulatory networks", PLoS Computational Biology, vol. 14, no. 2, e1006003.

75. Humphries, J, Xiong, L, Liu, J, Prindle, A, Yuan, F, Arjes, HA, Tsimring, L & Süel, GM 2017, "Species-independent attraction to biofilms through electrical signaling", Cell, vol. 168, 200-209.

76. Kaltenegger, L 2017, "How to characterize habitable worlds and signs of life", Annual Review of Astronomy and Astrophysics, vol. 55, 433-485.

77. Kauffman, SA 1993, The Origins of Order, Oxford University Press, Oxford, UK.

78. Kitts, P, Symington, L,Burke, M, Reed, R & Sherratt, D 1982, "Transposon-specified site-specific recombination", Proceedings of the National Academy of Sciences USA, vol. 79, 46-50.

79. Kouvaris K, Clune J, Kounios L, Brede M & Watson RA 2017, "How evolution learns to generalise: Using the principles of learning theory to understand the evolution of developmental organisation", PLoS Computational Biology, vol. 13, no. 4, e1005358.

80. Kriegman, S, Blackiston, D, Levin, M & Bongard, J 2020, "A scalable pipeline for designing reconfigurable organisms", Proceedings of the National Academy of Sciences USA, vol. 117, 1853-1859.

81. Kuchling, F, Friston, K, Georgiev, G & Levin, M 2020, "Morphogenesis as Bayesian inference: A variational approach to pattern formation and control in complex biological systems", Physics of Life Reviews, in press. https://doi.org/10.1016/j.plrev.2019.06.001

82. Kull, K, Deacon, T, Emmeche, C, Hoffmeyer, J & Stjernfelt, F 2011, "Theses on biosemiotics: Prolegomena to a theoretical biology" in C Emmeche, K Kull (eds) Towards a Semiotic Biology: Life Is the Action of Signs, pp. 25-41. Imperial College Press: London, UK.

83. Kuntz, ID 1972, "Protein folding", Journal of the American Chemical Society, vol. 94, 4009-4012.

84. Laland, KN, Uller, T, Feldman, MW, Sterelny, K,Müller, GB, Moczek, A, Jablonka, E & Odling-Smee, J 2015, "The extended evolutionary synthesis: its structure, assumptions and predictions", Proceedings of the Royal Society B, vol. 282: 20151019.

85. Lee, C, Richtsmeier, JT & Kraft, RH 2019, "A coupled reaction-diffusion-strain model predicts cranial vault formation in development and disease", Biomechanics and Modeling in Mechanobiology, vol. 18, 1197-1211.

86. Lemons, D & McGinnis, W 2006, "Genomic evolution of Hox gene clusters", Science, vol. 313, 1918-1922.

87. Lenton, TM, Daines, SJ, Dyke, JG, Nicholson, AE, Wilkinson, DM & Williams, HTP 2018, "Selection for Gaia across multiple scales", Trends in Evolution and Ecology, vol. 33, 633-645.

88. Levin, M 2011, "The wisdom of the body: future techniques and approaches to morphogenetic fields in regenerative medicine, developmental biology and cancer", Regenerative Medicine, vol. 6: 667- 673.

89. Levin, M 2014a, "Molecular bioelectricity: How endogenous voltage potentials control cell behavior and instruct pattern regulation in vivo", Molecular Biology of the Cell, vol. 25, no. 24, 3835-3850.

90. Levin, M 2014b, "Endogenous bioelectrical networks store non-genetic patterning information during development and regeneration", Journal of Physiology, vol. 592, no. 11, 2295-2305.

91. Levin, M 2019, "The computational boundary of a "self": Developmental bioelectricity drives multicellularity and scale-free cognition", Frontiers in Psychology, vol. 10, 2688.

92. Levin, M & Martyniuk, CJ 2018, "The bioelectric code: An ancient computational medium for dynamic control of growth and form", Biosystems, vol. 164, 76-93.

93. Levin, M, Pezzulo, G & Finkelstein, JM 2017, "Endogenous bioelectric signaling networks: Exploiting voltage gradients for control of growth and form", Annual Review of Biomedical Engineering, vol. 19, 353-387.

94. Levin, S, Greenfell, B, Hastings, A & Perelson, AS 1997, "Mathematical and computational challenges in population biology and ecosystems science", Science, vol. 275, 334-343.

95. Leys, SP 2015, "Elements of a 'nervous system' in sponges", Journal of Experimental Biology, vol. 218, 581-591.

96. Libby, E, Conlin, PL, Kerr, B & Ratcliff, WC 2016, "Stabilizing multicellularity through ratcheting", Proceedings of the Royal Society B, vol. 371, 20150444.

97. Lichten, M & Golsman, ASH 1995, "Meiotic recombination hotspots", Annual Review of Genetics, vol. 29, 423-444.

98. Lineweaver, CH, Davies, PCW & Ruse, M 2013 "What is complexity? Is it increasing?" in CH Lineweaver, PCW. Davies & M Ruse (eds) Complexity and the Arrow of Time, pp. 3-16. Cambridge University Press, Cambridge, UK.

99. Lobo, D & Levin, M 2015, "Inferring regulatory networks from experimental morphological phenotypes: A computational method reverse-engineers planarian

regeneration", PLoS Computational Biology, vol. 11, e1004295.

100. Lobo, D, Solano, M, Bubenik, GA & Levin, M 2014, "A linear-encoding model explains the variability of the target morphology in regeneration", Journal of the Royal Society Interface, vol. 11, 20130918.

101. Lockwood, JA & Lockwood, DR 1993, "Catastrophe theory: A unified paradigm for rangeland ecosystem dynamics", Journal of Rangeland Management, vol. 46, no. 4, 282-288.

102. Logofet, DO & Lesnaya, EV 2000, "The mathematics of Markov models: What Markov chains can really predict in forest successions", Ecological Modelling, vol. 126, 285-298.

103. Lovelock, JE & Margulis, L 1974, "Atmospheric homeostasis by and for the biosphere: The Gaia hypothesis", Tellus, vol. 26, no. 1-2, 2-10.

104. Lund, EJ 1947, Bioelectric Fields and Growth. University of Texas Press, Austin, TX.

105. Madan, E, Gogna, R & Moreno, E 2018, "Cell competition in development: Information from flies and vertebrates", Current Opinion in Cell Biology, vol. 55, 150-157.

106. Mandoli, DF 1998, "Elaboration of body plan and phase change during development of Acetabularia: How is the complex architecture of a giant cell built?" Annual Review of Plant Physiology and Plant Molecular Biology, vol. 49, 173-198.

107. Mariscal, C & Doolittle, WF 2018, "Life and life only: A radical alternative to life definitionism", Synthese, in press. https://doi.org/10.1007/s11229-018-1852-2

108. Mathews, AP 1903, "Electrical polarity in the hydroids", American Journal of Physiology, vol. 8, no. 4, 294-299.

109. Maturana, HR & Varela, FJ 1980, Autopoiesis and Cognition: The Realization of the Living. D. Reidel, Dordrecht.

110. Maynard Smith, J & Szathmáry, E 1995, The Major Transitions in Evolution. Oxford University Press, Oxford, UK.

111. McLaughlin, KA & Levin, M 2018, "Bioelectric signaling in regeneration: Mechanisms of ionic controls of growth and form", Developmental Biology, vol. 433, no. 2, 177-189.

112. McShea, DW 1994, "Mechanisms of large-scale evolutionary trends", Evolution, vol. 48, 1747-1763.

113. McShea, DW 2016, "Hierarchy: The source of teleology in evolution", in N Eldredge, T Pievani, E Serrelli, I Temkin (eds), Evolutionary Theory: A Hierarchical Perspective, pp. 86-102. University of Chicago Press, Chicago.

114. McShea, DW and Brandon, RN 2010, Biology's First Law, University of Chicago Press, Chicago.

115. Miller, WB 2016, "The eukaryotic microbiome: Origins and implications for fetal and neonatal life", Frontiers in Pediatrics, vol. 4, 96.

116. Mitchell, A,Romano, GH, Groisman, B, Yona, A, Dekel, E, Kupiec, M, Dahan, O & Pilpel, Y 2009, "Adaptive prediction of environmental changes by microorganisms", Nature, vol. 460, 220-224.

117. Michod, RE 1999, Darwinian Dynamics. Princeton University Press, Princeton, NJ.

118. Mintz, B & Illmensee, K 1975, "Normal genetically mosaic mice produced from malignant teratocarcinoma cells", Proceedings of the National Academy of Sciences USA, vol. 72, no. 9, 3585-3589.

119. Monod, J 1972, Chance and Necessity. Random House, New York.

120. Muñoz-Dorado, J, Marcos-Torres, FJ, García-Bravo, E, Moraleda-Muñoz, A & Pérez J 2016, "Myxobacteria: Moving, killing, feeding, and surviving together", Frontiers in Microbiology, vol. 7, 781.

121. Nagano, K 1973, "Logical analysis of the mechanism of protein folding: I. Predictions of helices, loops and β-structures from primary structure", Journal of Molecular Biology, vol. 75, 401-420.

122. Newman, MEJ 2001, "The structure of scientific collaboration networks", Proceedings of the National Academy of Sciences USA, vol. 98, 404–409.

123. Nishimura, O, Hosoda, K, Kawaguchi, E, Yazawa, S, Hayashi, T, Inoue, T, et al. 2015, "Unusually large number of mutations in asexually reproducing clonal planarian Dugesia japonica", PLoS One, vol. 10, no. 11, e0143525.

124. Orgogozo, V 2015, "Replaying the tape of life in the twenty-first century", Interface Focus, vol. 5, 20150057.

125. Pai, VP, Pietak, A, Willocq, V, Ye, B, Shi, N-Q & Levin, M 2018, "HCN2 Rescues brain defects by enforcing endogenous voltage pre-patterns", Nature Communications, vol. 9, 998.

126. Pan, T & Sosnick, T 2006, "RNA folding during transcription", Annual Review of Biophysics and Biolmolecular Structure, vol. 35, 161-175.

127. Pattee, HH 1982, "Cell psychology", Cognition and Brain Theory, vol. 5, 325-341.

128. Pearl, J 1988, Probabilistic Reasoning in Intelligent Systems: Networks of Plausible Inference. Morgan Kaufmann, San Mateo, CA.

129. Pezzulo, G & Levin, M 2016, "Top-down models in biology: Explanation and control of complex living systems above the molecular level", Journal of the Royal Society Interface, vol. 13, 20160555.

130. Pietak, A & Levin, M2016, "Exploring instructive physiological signaling with the Bioelectric Tissue Simulation Engine", Frontiers in Bioengineering and Biotechnology, vol. 4, 55.

131. Pietak, A, Bischof, J, LaPalme, J, Morokuma. J & Levin, M 2019, "Neural control of body-plan axis in regenerating planaria", PLoS Computational Biology, vol. 15, no. 4, e1006904

132. Pigliucci, M & Müller, CB 2010, "Elements of an extended evolutionary synthesis" in M Pigliucci & CB Müller (eds) Evolution – The Extended Synthesis, pp. 3-17. MIT Press, Cambridge, MA.

133. Pinker, S 2010, "The cognitive niche: Coevolution of intelligence, sociality, and language", Proceedings of the National Academy of Sciences USA, vol. 107, 8993-8999.

134. Polanyi, M 1968, "Life's irreducible structure. Live mechanisms and information in DNA are boundary conditions with a sequence of boundaries above them", Science, vol. 160, 1308-1312.

135. Pollack, J & Lowell, J 2018, "Developmental encodings promote the emergence of hierarchical modularity", Proceedings of ALIFE 2016: The Fifteenth International Conference on the Synthesis and Simulation of Living Systems, pp. 344-351. MIT Press, Cambridge, MA.

136. Prindle, A, Liu, J, Asally, M, Ly, S, Garcia-Ojalvo, J & Süel, GM 2015, "Ion channels enable communication in bacterial communities", Nature, vol. 527, 59-63.

137. Queller, DC & Strassmann, JE 2009, "Beyond society: The evolution of organismality", Philosophical Transactions of the Royal Society B, vol. 364, 3143-3155.

138. Raspopovic, J, Marcon, L, Russo, L & Sharpe, J 2014, "Modeling digits. Digit patterning Is controlled by a Bmp-Sox9-Wnt Turing network modulated by morphogen gradients", Science, vol. 345, 566-570.

139. Ratcliff, WC, Denison, RF, Borello, M & Tavisano, M 2012, "Experimental evolution of multicellularity", Proceedings of the National Academy of Sciences USA, vol. 109, 1595-1600.

140. Ratcliff, WC, Fankhauser, JD, Rogers, DW, Greig, D & Tavisano, M 2016, "Origins of multicellular evolvability in snowflake yeast", Nature Communications, vol. 6, 6102.

141. Robbins, RJ, Krishtalka, L & Wooley, JC 2016, "Advances in biodiversity: Metagenomics and the unveiling of biological dark matter", Standards in Genomic Science, vol. 11, 69.

142. Rosen, R 1986, "On information and complexity, in JL Casti & A Karlqvist (eds) Complexity, Language, and Life: Mathematical Approaches, pp. 174-196. Springer, Berlin.

143. Saibil, H 2013, "Chaperone machines for protein folding, unfolding and disaggregation", Nature Reviews Molecular Cell Biology, vol. 14, 630-642.

144. Schulte, P, Alegret, L, Arenillas, I, Arz, JA et al. 2010, "The Chicxulub asteroid impact and mass extinction at the Cretaceous-Paleogene boundary", Science vol. 327, 1214-1218.

145. Smolin, L 1997, The Life of the Cosmos, Oxford University Press, Oxford, UK.

146. Stal, LJ 2012, "Cyanobacterial mats and stromatolites" in BA Whitton (ed) Ecology of Cyanobacteria II: Their Diversity in Space and Time, pp. 65-125. Springer, Berlin.

147. Stanley, KO 2007, “Compositional pattern producing networks: A novel abstraction of development”, Genetic Programming and Evolvable Machines, vol. 8, 131-162.

148. Stanley, KO & Miikkulainen, R 2003, “A taxonomy for artificial embryology”, Artificial Life, vol. 9, 93-130.

149. Stern, DL & Orgogozo, V 2009, “Is evolution predictable?” Science, vol. 323, 746-751.

150. Stewart, J 1996, “Cognition = Life: Implications for higher-level cognition”, Behavioral Processes, vol. 35, 311-326.

151. Strassmann, JE & Queller, DC 2010, “The social organism: Congresses, parties and committees”, Evolution, vol. 64, 605-616.

152. Streichan, SJ, Lefebvre, MF, Noll, N, Wieschaus, EF & Shraiman, BI 2018, “Global morphogenetic flow is accurately predicted by the spatial distribution of myosin motors”, Elife, vol. 7, e27454.

153. Sulston, JE & Horvitz, HR 1977, “Post-embryonic cell lineages of the nematode, Caenorhabditis elegans”, Developmental Biology, vol. 56, 110-156.

154. Sun, Y, Do, H, Gao, J, Zhao, R, Zhao, M & Mogilner, A 2013, “Keratocyte fragments and cells utilize competing pathways to move in opposite directions in an electric field”, Current Biology, vol. 23, 569-574.

155. Szathmáry, E 2015, “Toward major evolutionary transitions theory 2.0”, Proceedings of the National Academy of Sciences USA, vol. 112, 10104-10111.

156. Szathmáry, E & Maynard Smith, J 1995, “The major evolutionary transitions”, Nature, vol. 374, 227-232.

157. Thompson, DAW 1942, On Growth and Form. Cambridge University Press, Cambridge, UK.

158. Tinoco, I, Uhlenbeck, O & Levine, MD, 1971, “Estimation of secondary structure in ribonucleic acids”, Nature, vol. 230, 362-367.

159. Turing, AM 1952, “The chemical basis of morphogenesis”, Philosophical Transactions of the Royal Society B, vol. 237, 37-72.

160. Turner, JS 2004, “Extended phenotypes and extended organisms”, Biological Philosophy, vol. 19, 327-352.

161. Ulett, MA 2014, “Making the case for orthogenesis: The popularization of definitely directed evolution (1890–1926)”, Studies in the History and Philosophy of Biology and Biomedical Science, vol. 45, 124-132.

162. Uller, T, Moczek, AP, Watson, RA, Brakefield, PM & Laland, KN 2018, “Developmental bias and evolution: A regulatory network perspective”, Genetics, vol. 209, 949-966.

163. Vallverdú, J, Castro, R, Mayne, R, Talanov, M, Levin, M, Baluška, F, Gunji, Y, Dussutour, A, Zenil, H & Adamatzky, A 2018, “Slime mould: The fundamental mechanisms of biological cognition”, Biosystems, vol. 165, 57-70.

164. Vandenberg, LN, Adams, DS & Levin, M 2012, “Normalized shape and location of perturbed craniofacial structures in the Xenopus tadpole reveal an innate ability to achieve correct morphology”, Developmental Dynamics vol. 241, no. 5, 863-878.

165. Waris, H 1950, “Cytophysiological studies on Micrasterias II. The cytoplasmic framework and its mutation”, Physiologia Plantarum, vol. 3, no. 3, 236-246.

166. Watson, RA, Buckley, CL, Mills, R & Davies, A 2010, “Associative memory in gene regulation networks”, Proceedings of the Alife XII Conference, pp. 194-202. MIT Press, Cambridge, MA.

167. Watson, RA & Pollack, JB 2003, “A computational model of symbiotic composition in evolutionary transitions”, BioSystems, vol. 69, 187-209.

168. Watson, RA & Szathmáry, E 2016, “Can evolution learn?” Trends in Ecology and Evolution, vol. 31, 147-157.

169. Williams, K, Bischof, J, Lee, F, Miller, K, LaPalme, J, Wolfe, B & Levin, M 2020, “Regulation of axial and head patterning during planarian regeneration by a commensal bacterium”, Mechanisms of Development, vol. 163, 103614.

170. Wolpert, L 1969, “Positional information and the spatial pattern of cellular differentiation”, Journal of Theoretical Biology, vol. 25, no. 1, 1-47.

171. Yang, C-Y, Bialecka-Fornal, M, Weatherwax, C, Larkin, JW, Prindle, A, Liu, J, Garcia-Ojavlo, J & Süel, GM 2020, “Encoding membrane-potential-based memory within a microbial community”, Cell Systems, vol. 10, 417-423.