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Computer Science Department

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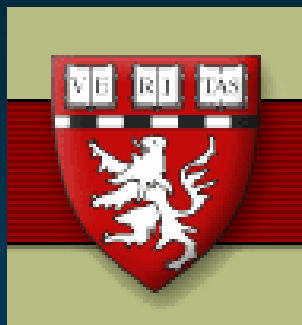
Aligning relationships in the UMLS Methods and preliminary results



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- ◆ **Alexa T. McCray**
Harvard Medical School
Boston, Massachusetts



- ◆ **Lowell Vizenor**
Ontology Works, Inc
Baltimore, Maryland

Overview

- ◆ The UMLS: A two-level structure
- ◆ Aligning relationships
 - Multiple approaches
 - Preliminary results
- ◆ Towards an ontology of relationships

The UMLS

A two-level structure



Unified Medical Language System

◆ SPECIALIST Lexicon

- 360,000 lexical items
- Part of speech and variant information

◆ Metathesaurus

- 6M names from over 100 terminologies
- 1.5M concepts
- 8M relations

◆ Semantic Network

- 135 high-level categories
- 7000 relations among them

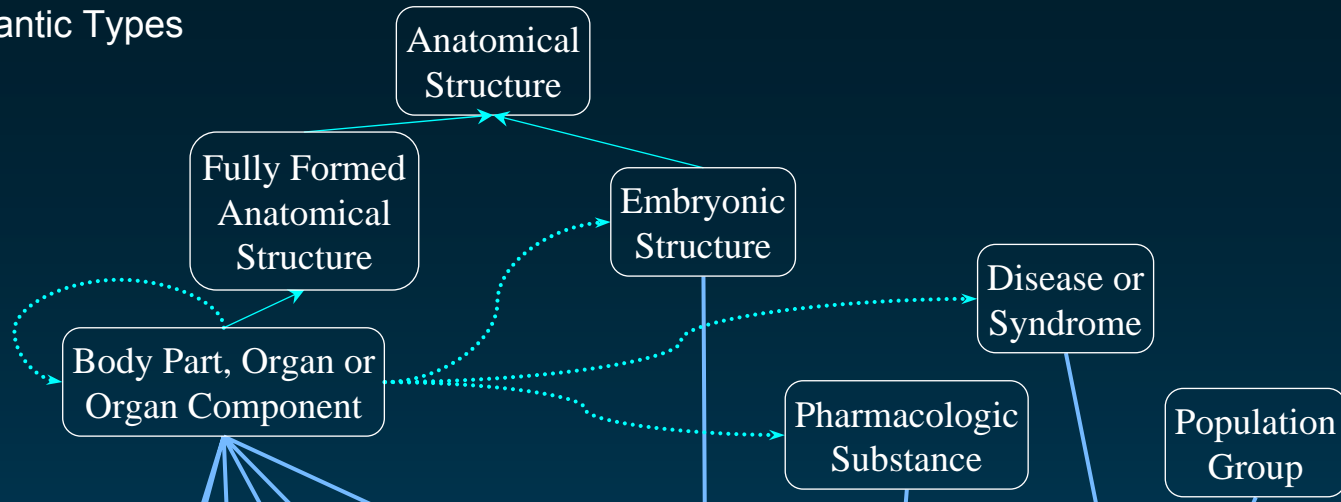
Lexical
resources

Terminological
resources

Ontological
resources



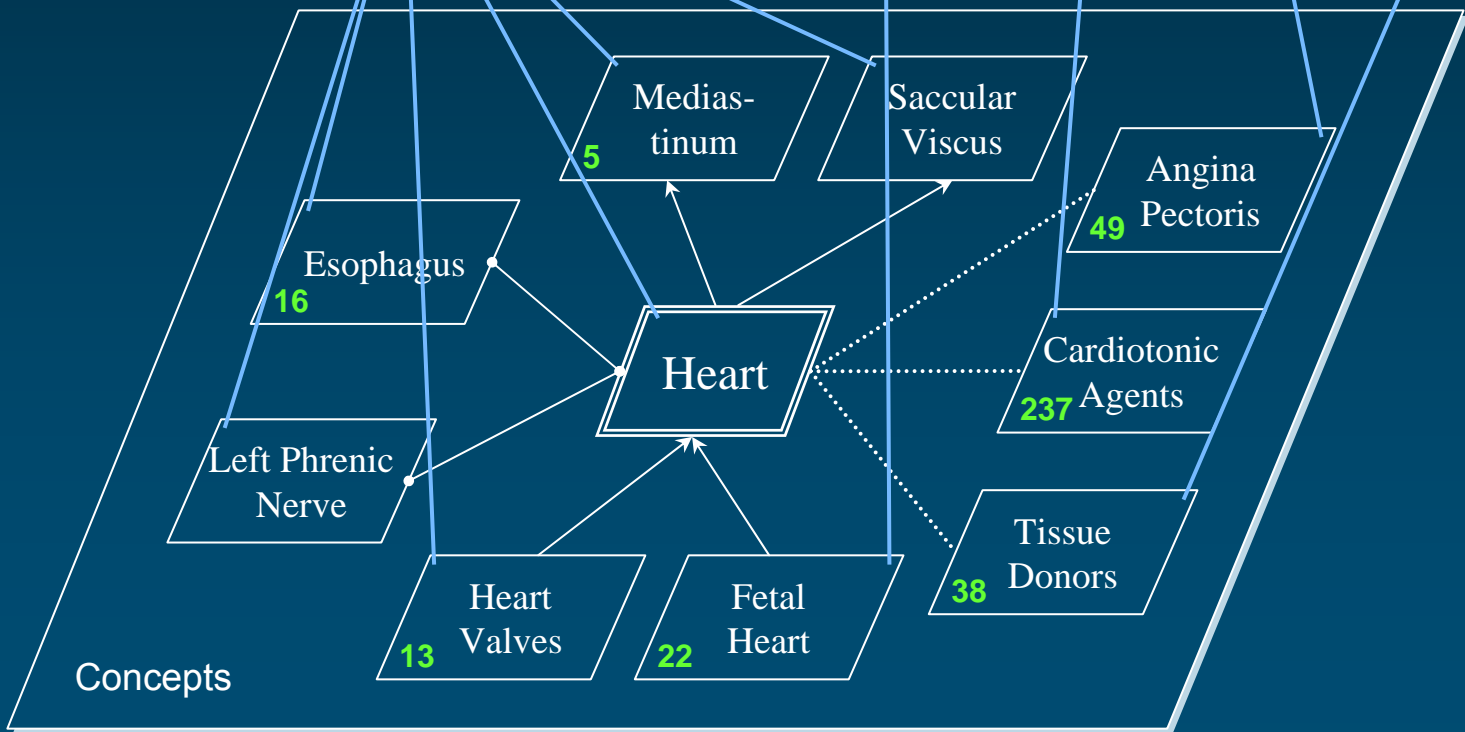
Semantic Types



Semantic Network



Metathesaurus



Concepts

UMLS Metathesaurus

Source Vocabularies

(2007AB)

- ◆ 143 source vocabularies
 - 17 languages
- ◆ Broad coverage of biomedicine
 - 5.9M names
 - 1.4M concepts
 - 8M relations
- ◆ Common presentation



Metathesaurus Basic organization

◆ Concepts

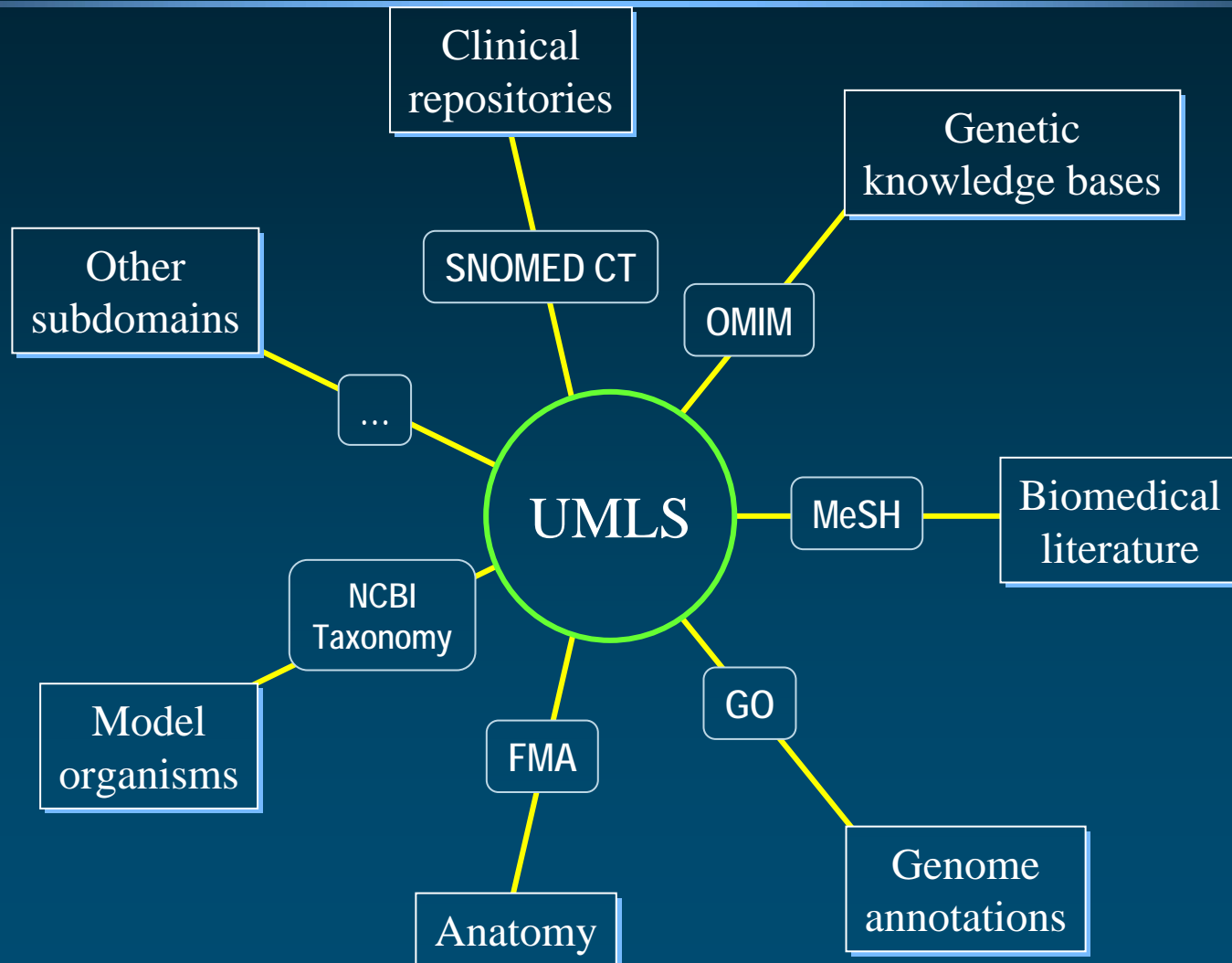
- Synonymous terms are clustered into a concept
- Properties are attached to concepts, e.g.,
 - Unique identifier
 - Definition

◆ Relations

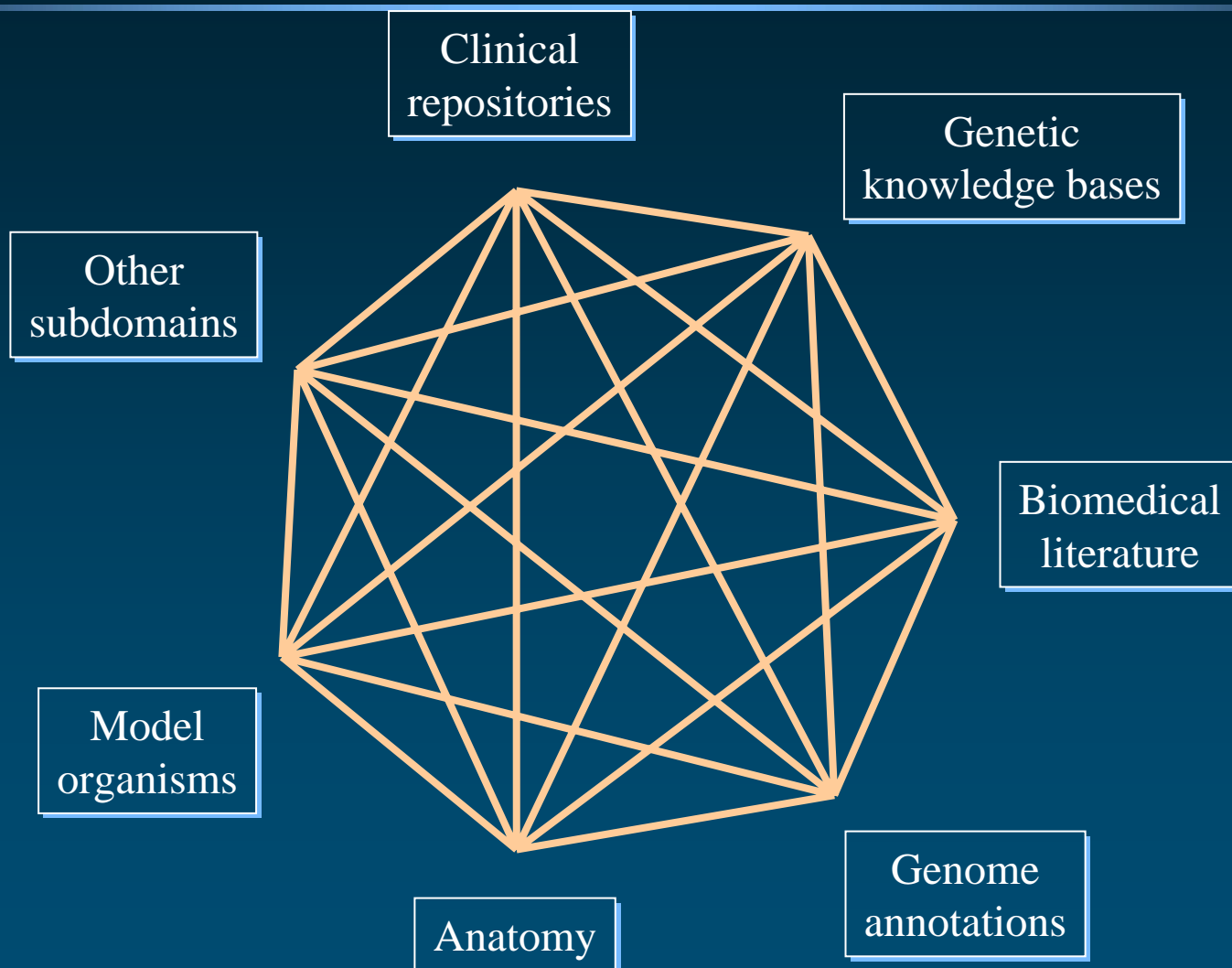
- Concepts are related to other concepts
- Properties are attached to relations, e.g.,
 - Type of relationship
 - Source



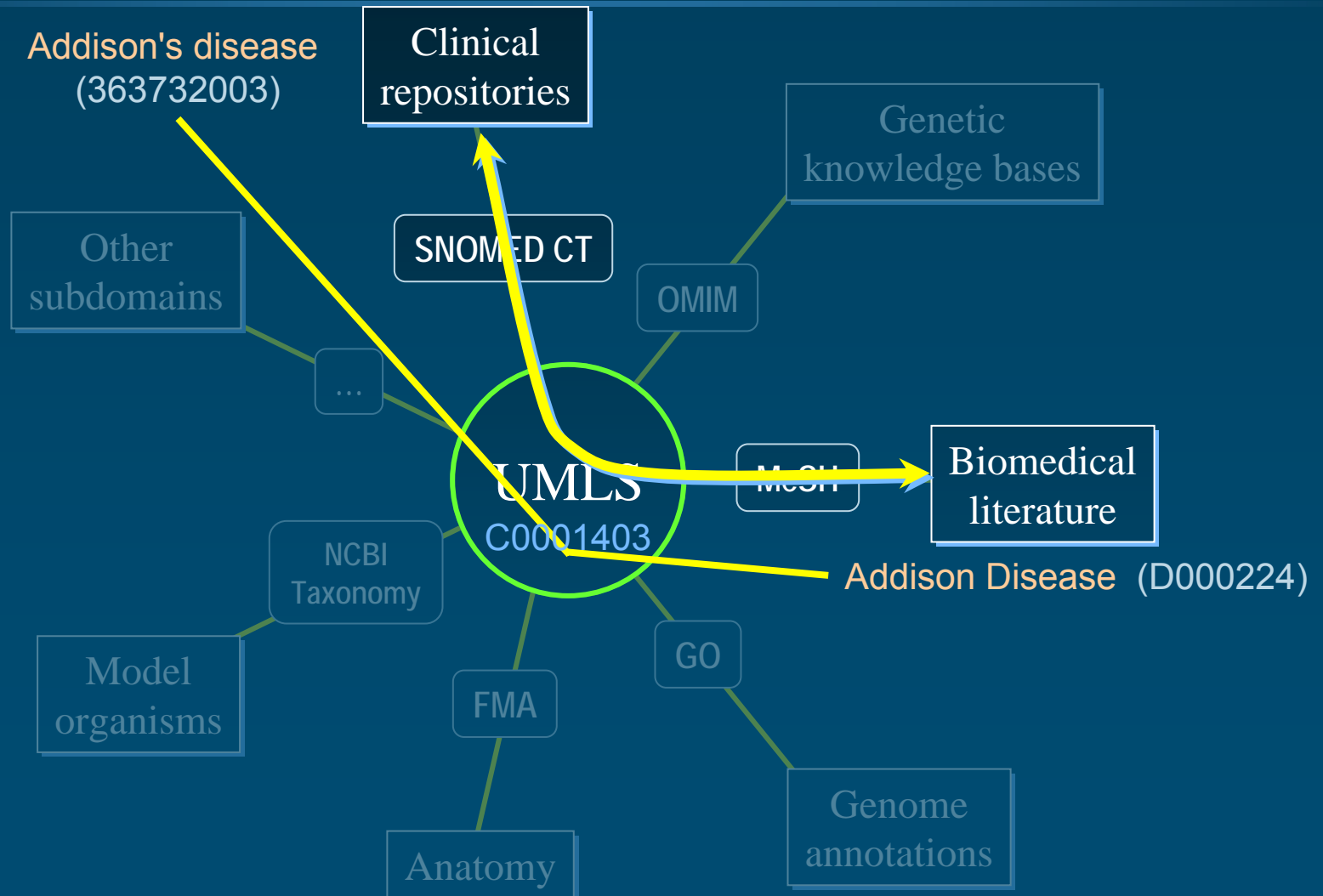
Integrating subdomains



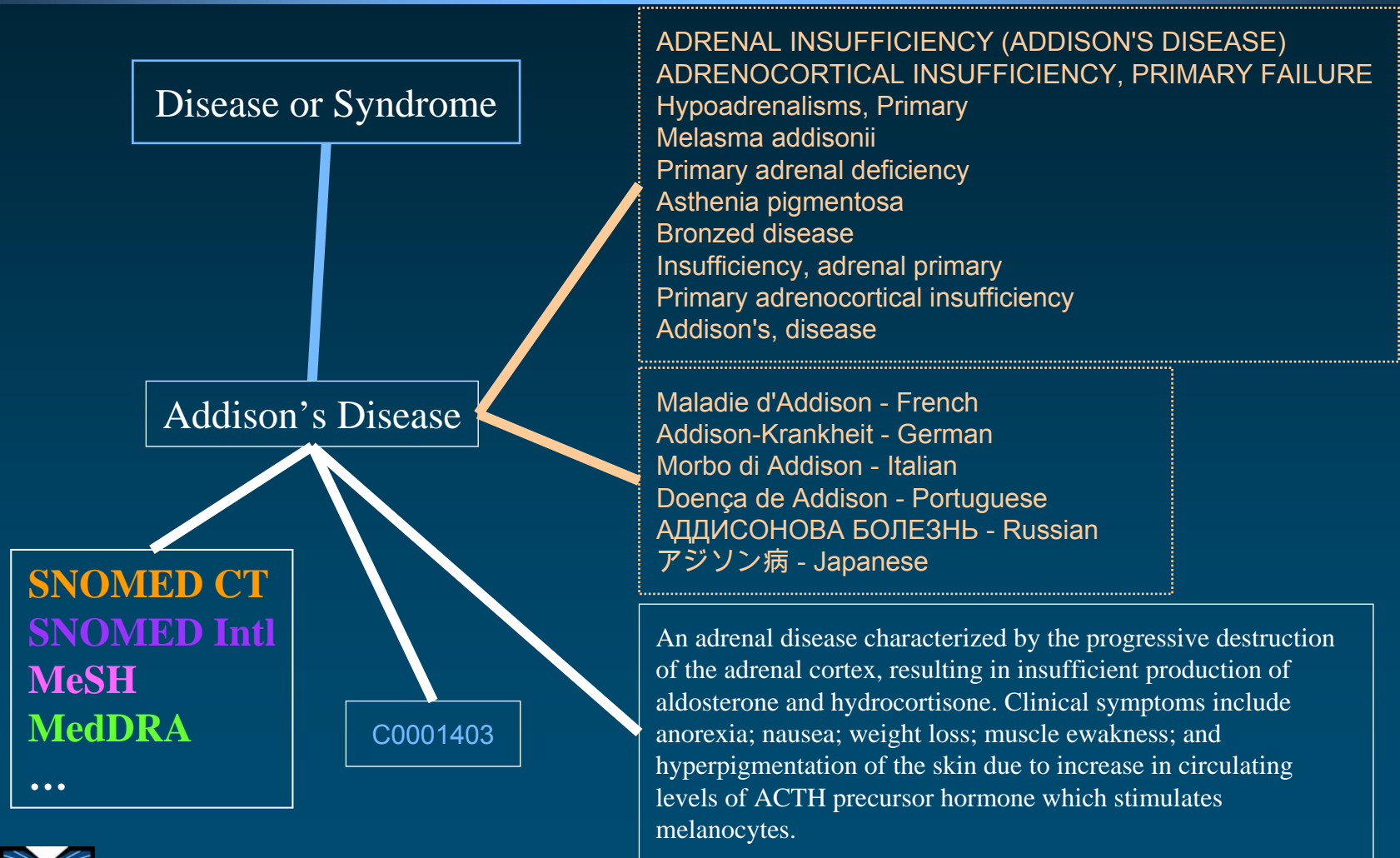
Integrating subdomains



Trans-namespace integration

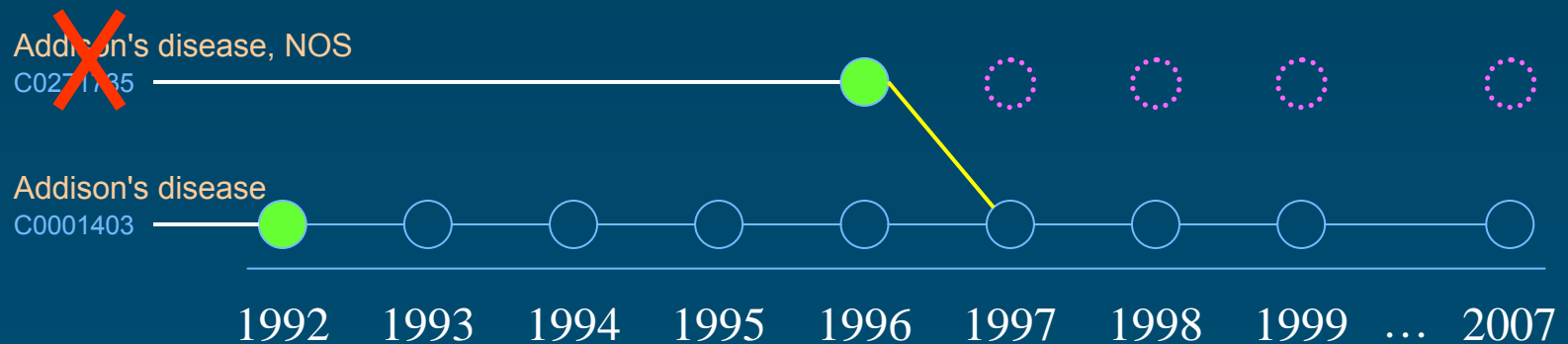


Addison's Disease: Concept



Metathesaurus Evolution over time

- ◆ Concepts never die (in principle)
 - CUIs are permanent identifiers
- ◆ What happens when they do die (in reality)?
 - Concepts can merge or split
 - Resulting in new concepts and deletions



Metathesaurus Relationships

- ◆ Symbolic relations: ~8 M pairs of concepts
 - ◆ Statistical relations : ~6 M pairs of concepts
(co-occurring concepts)
 - ◆ Mapping relations: ~150,000
-

- ◆ Categorization: Relationships between concepts and semantic types from the Semantic Network



Symbolic relations

- ◆ Relation
 - Pair of “atom” identifiers
 - Type
 - Attribute (if any)
 - List of sources (for type and attribute)
- ◆ Semantics of the relationship:
defined by its *type* [and *attribute*]
- ◆ Recorded bidirectionally

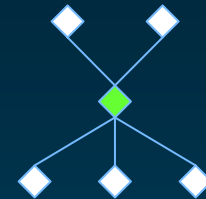
Symbolic relationships Type

◆ Hierarchical

- Parent / Child
- Broader / Narrower than

PAR / CHD

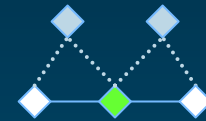
RB / RN



◆ Derived from hierarchies

- Siblings (children of parents)

SIB



◆ Associative

- Other

RO



◆ Various flavors of near-synonymy

- Similar
- Source asserted synonymy
- Possible synonymy

RL

SY

RQ

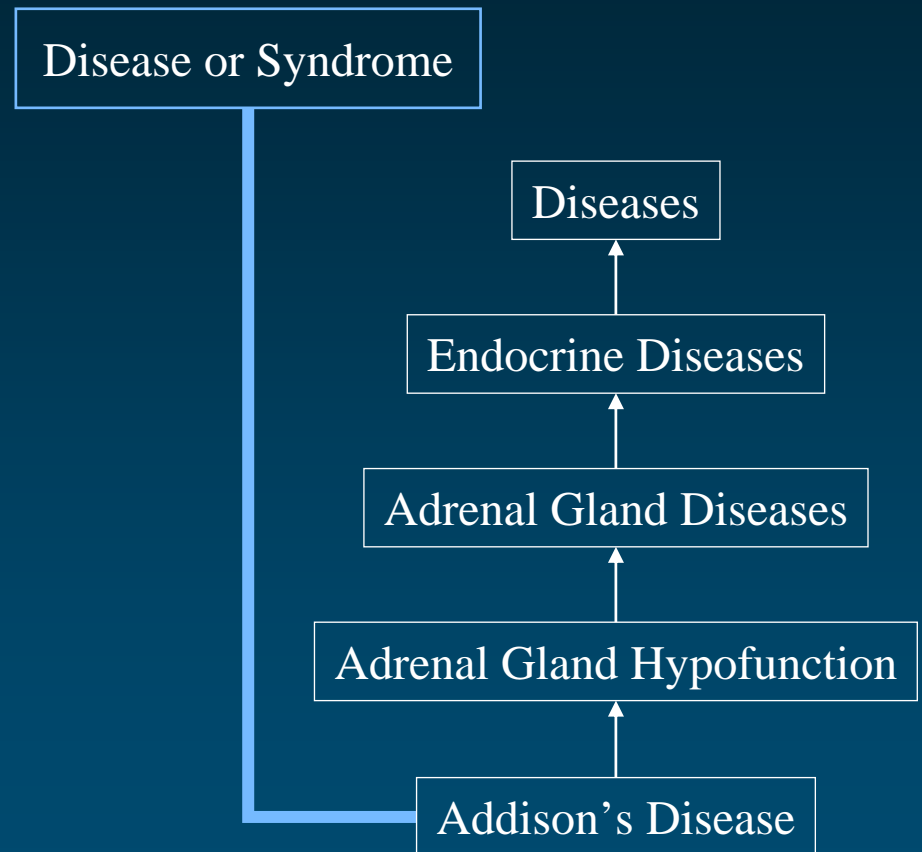


Symbolic relationships Attribute

- ◆ Hierarchical
 - isa (is-a-kind-of)
 - part-of
- ◆ Associative
 - location-of
 - caused-by
 - treats
 - ...
- ◆ Cross-references (mapping)

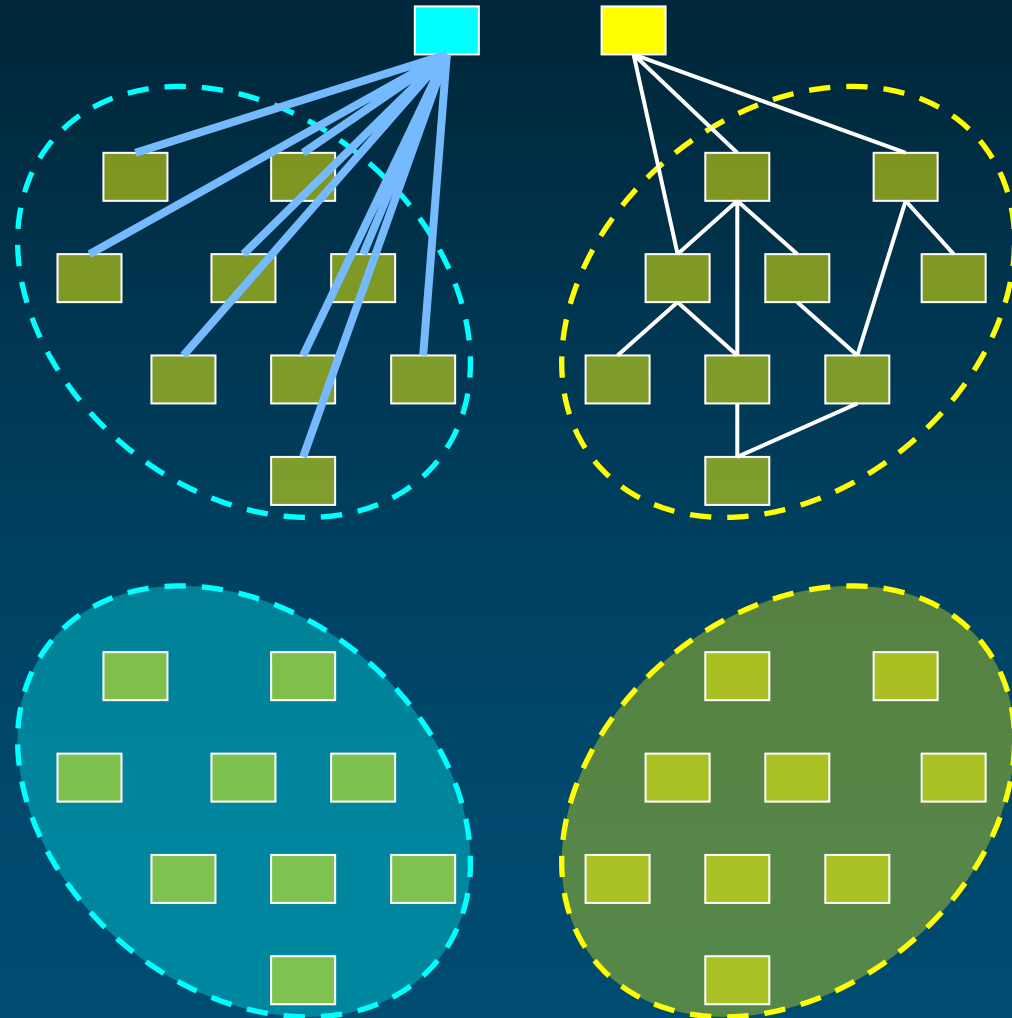
Categorize concepts

- ◆ High-level categories (semantic types)
- ◆ Assigned by the Metathesaurus editors
- ◆ Independently of the hierarchies in which these concepts are located



Categorization vs. hierarchies

- ◆ Semantic type
 - List of all concepts having this semantic type
- ◆ Concept
 - List of all descendants



UMLS Semantic Network

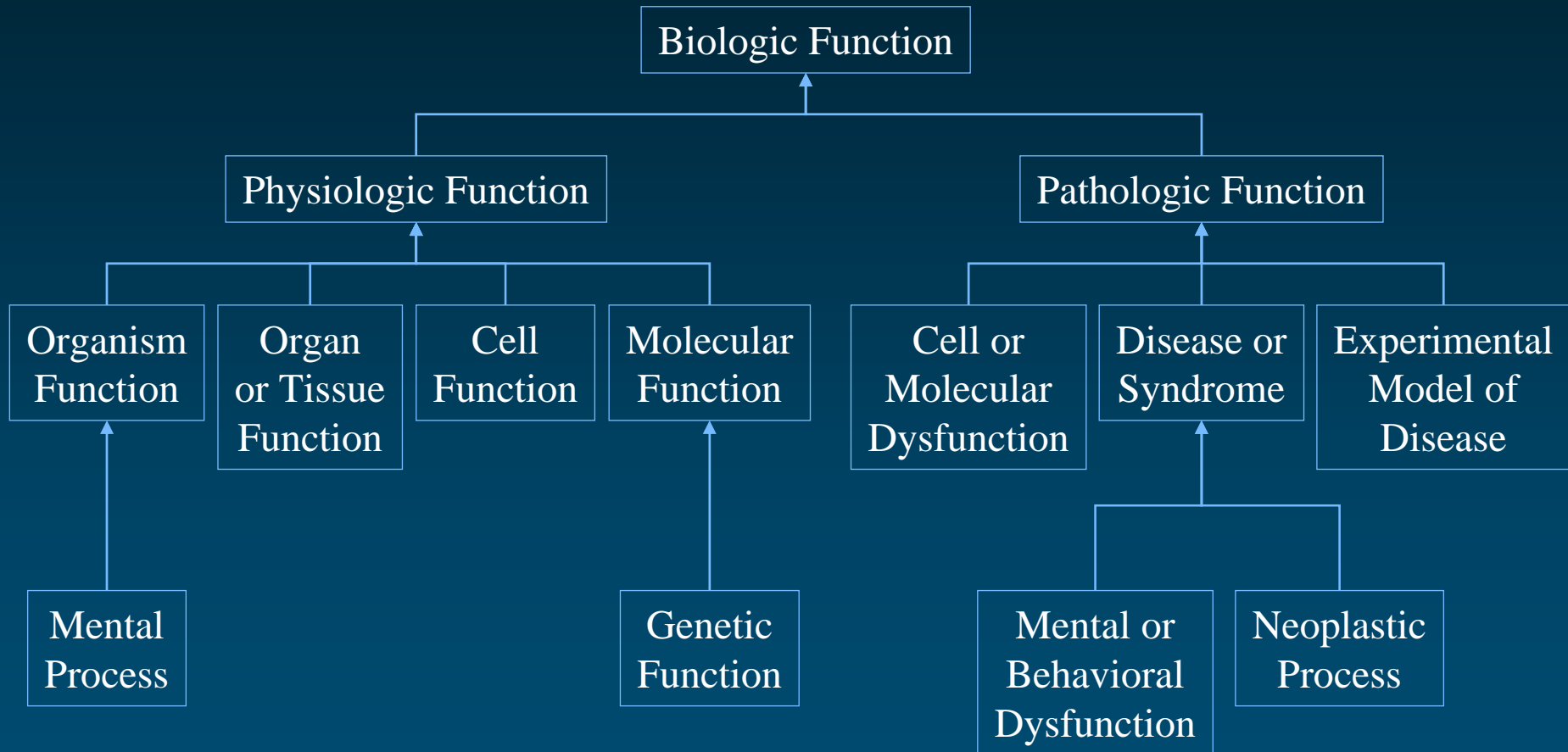
Semantic Network

- ◆ Semantic types (135)
 - tree structure
 - 2 major hierarchies
 - Entity
 - Physical Object
 - Conceptual Entity
 - Event
 - Activity
 - Phenomenon or Process

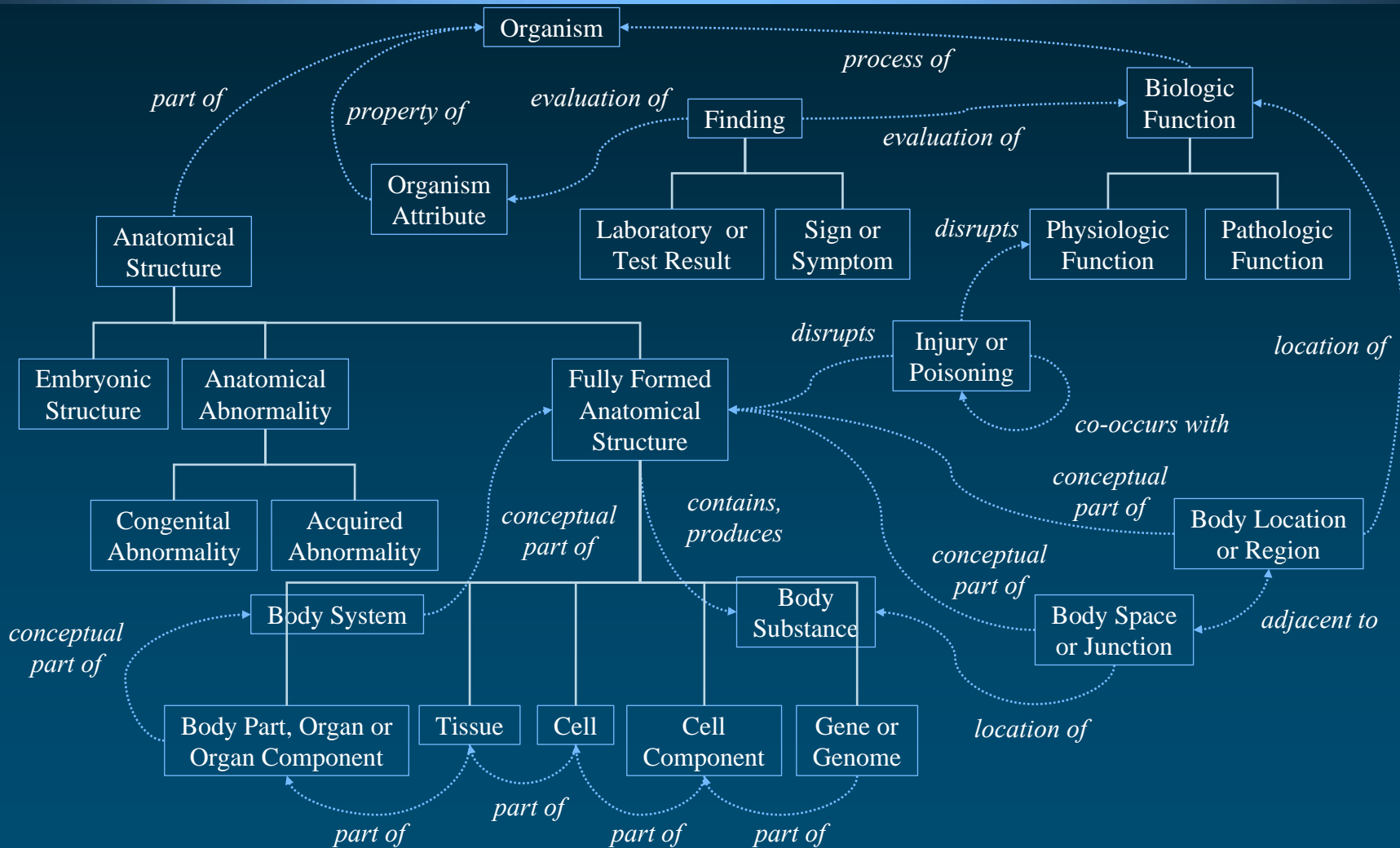
Semantic Network

- ◆ Semantic network relationships (54)
 - hierarchical (isa = is a kind of)
 - among types
 - *Animal isa Organism*
 - *Enzyme isa Biologically Active Substance*
 - among relations
 - *treats isa affects*
 - non-hierarchical
 - *Sign or Symptom diagnoses Pathologic Function*
 - *Pharmacologic Substance treats Pathologic Function*

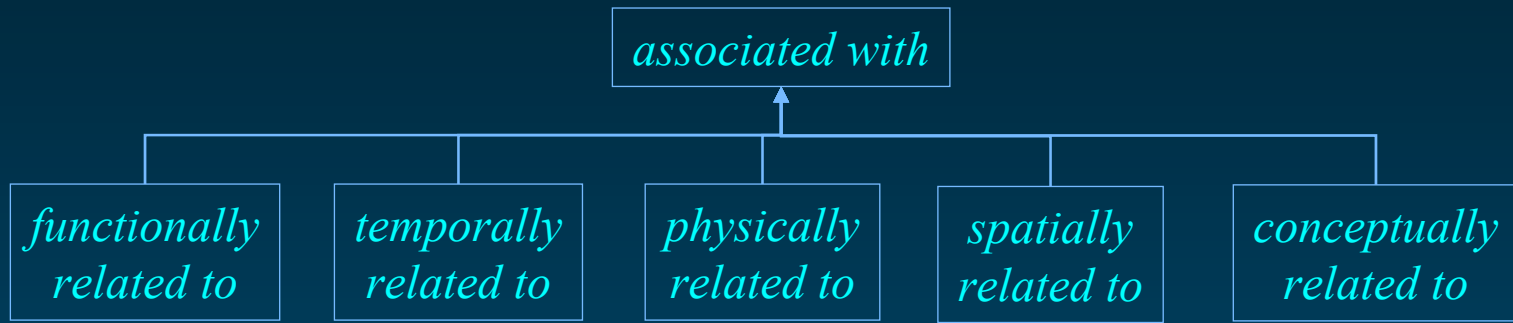
“Biologic Function” hierarchy (isa)

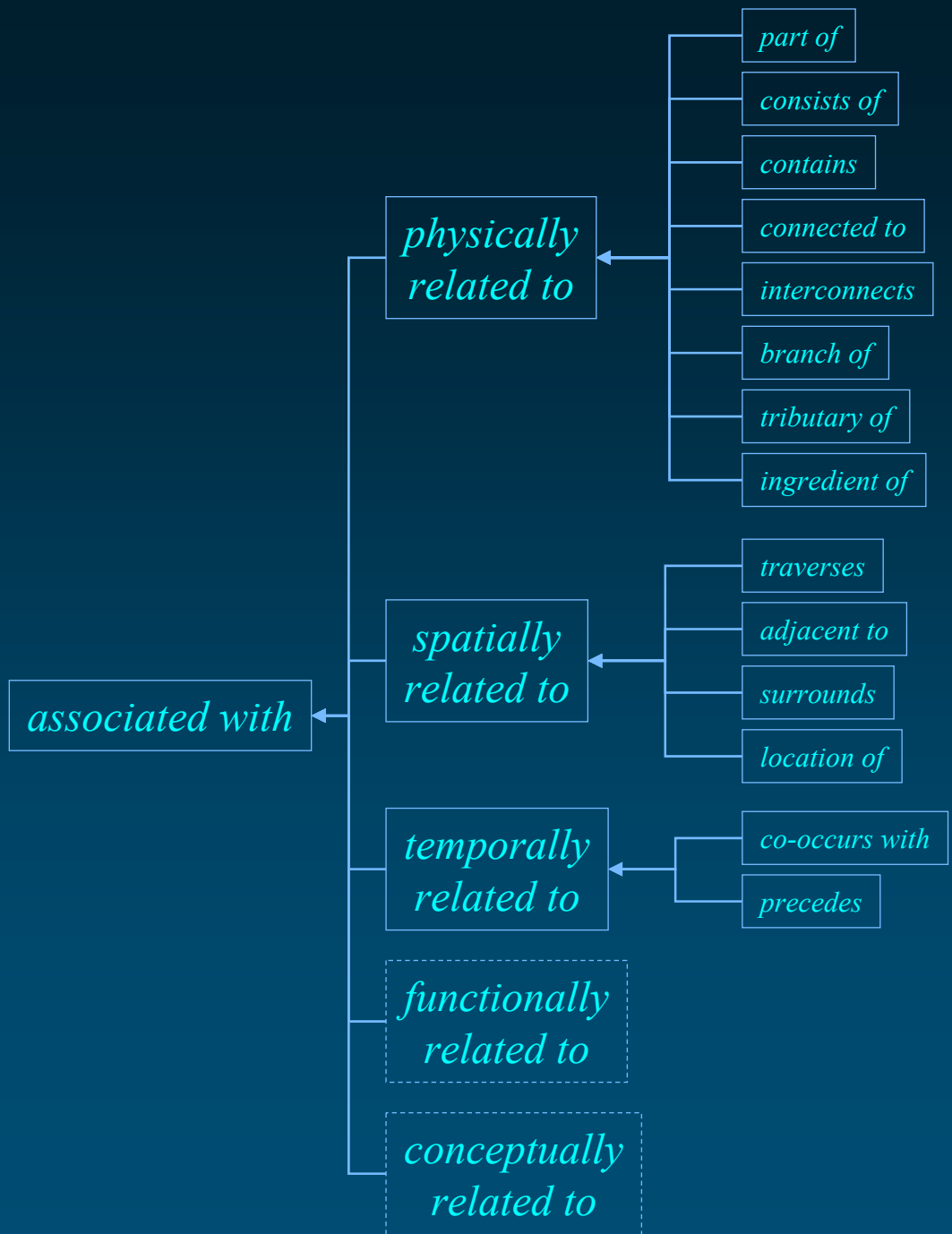


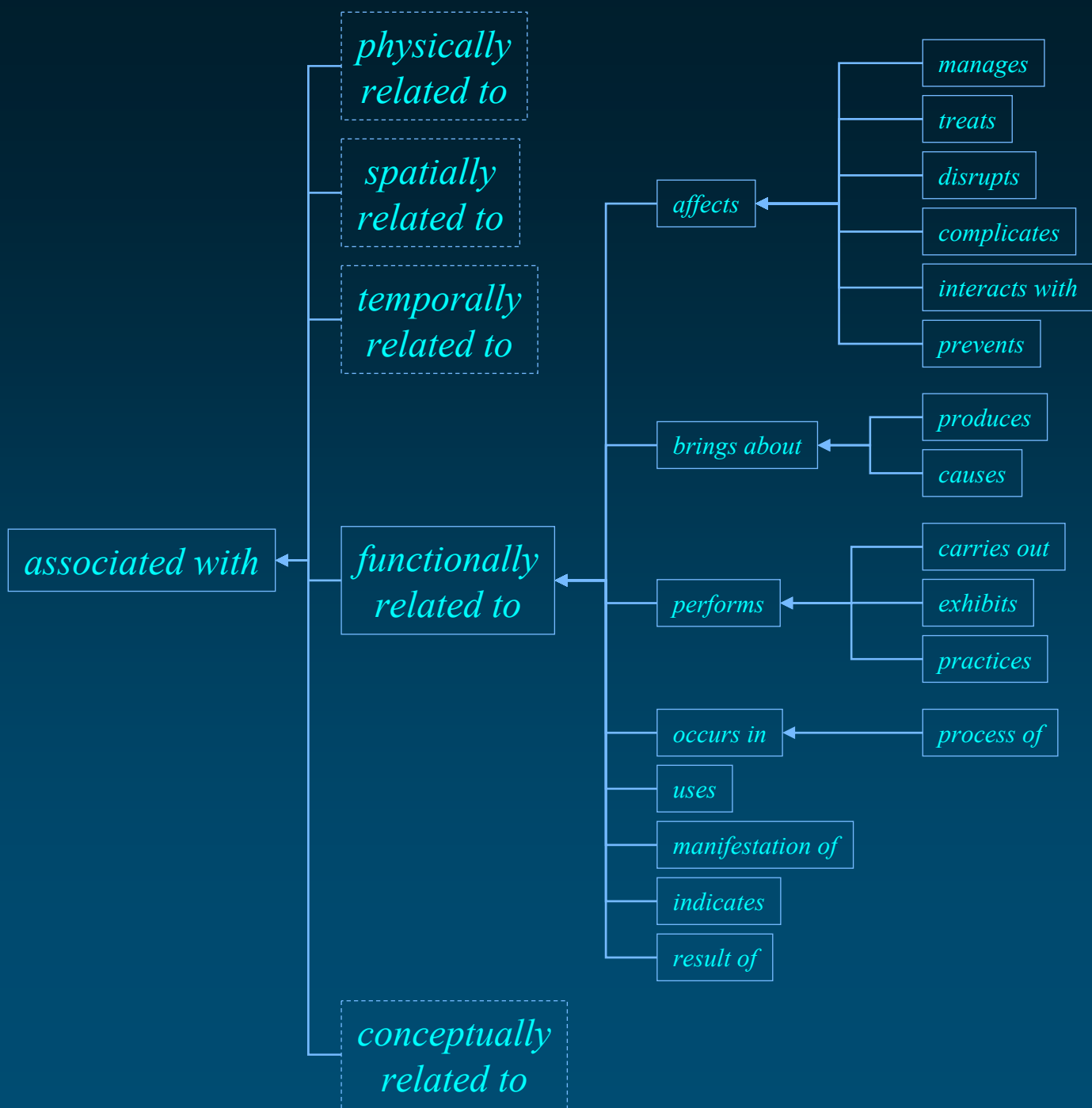
Associative (non-isa) relations

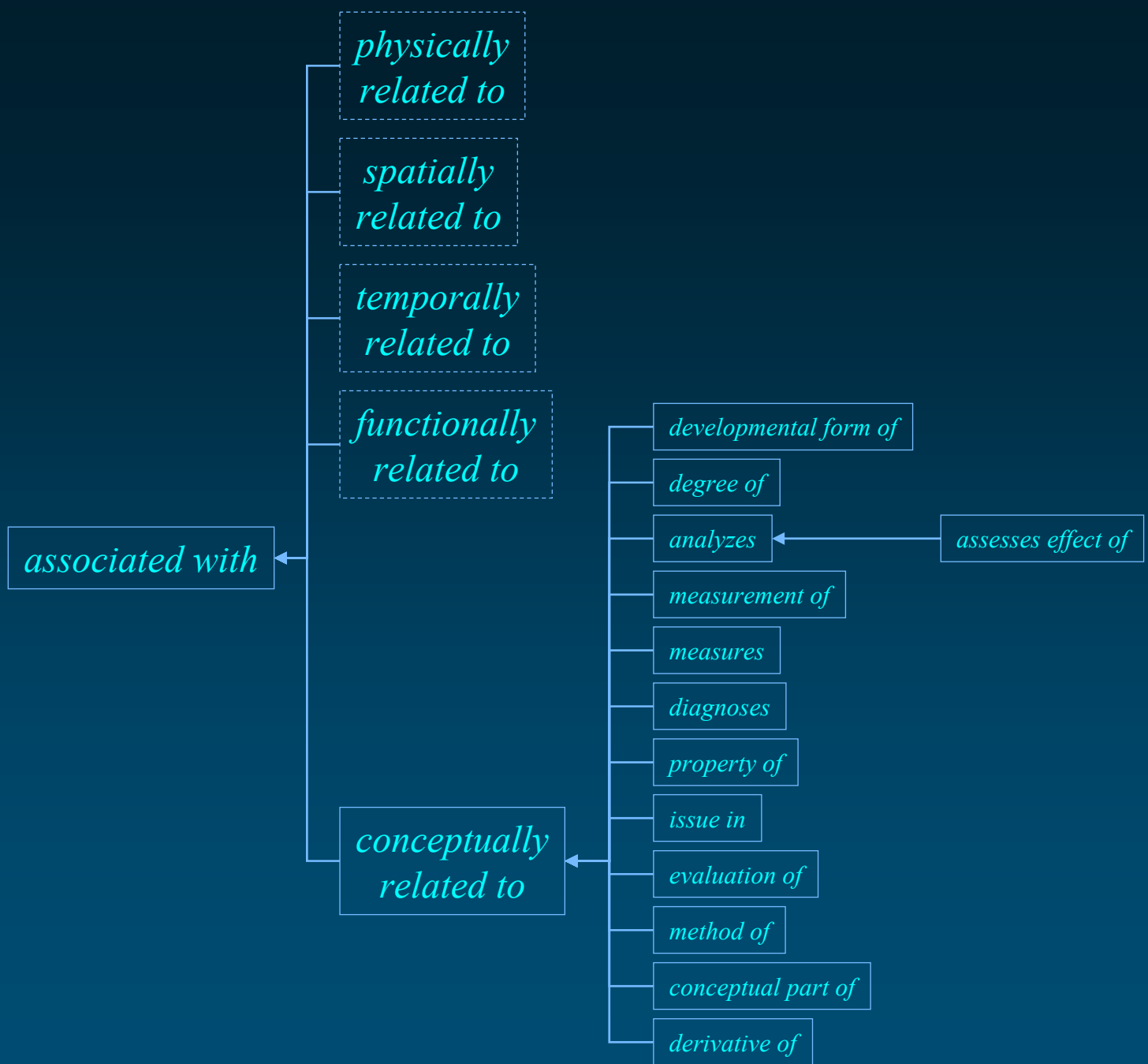


Relationship hierarchy





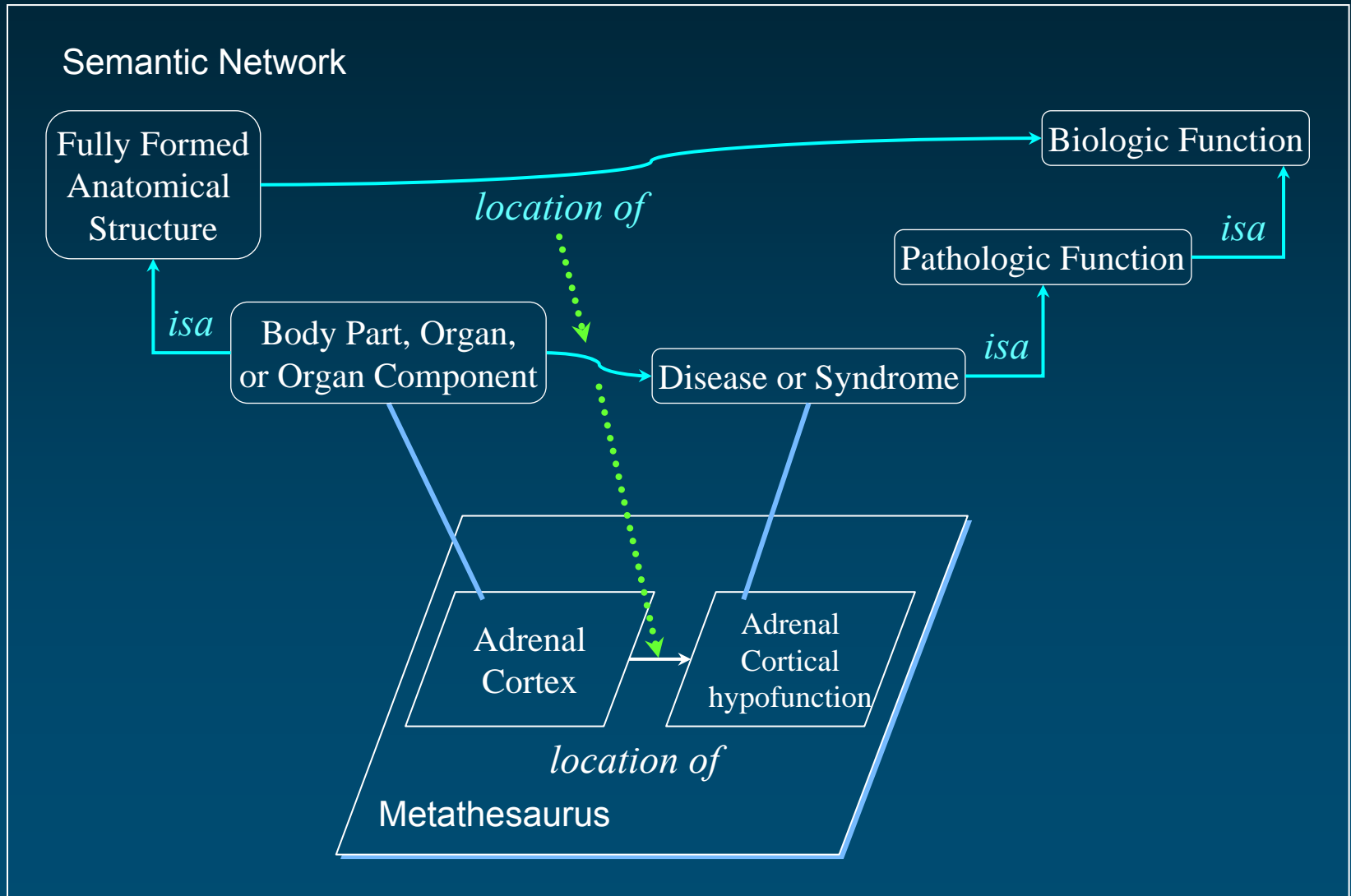




Why a semantic network?

- ◆ Semantic Types serve as high level categories assigned to Metathesaurus concepts, *independently of their position in a hierarchy*
- ◆ A relationship between 2 Semantic Types (ST) is a possible link between 2 concepts that have been assigned to those STs
 - The relationship may or may not hold at the concept level
 - Other relationships may apply at the concept level

Relationships can inherit semantics



Aligning relationships

Relationships in the UMLS

(2005AC)

◆ Metathesaurus

- 139 relationships
 - Thesaural
 - Specified
- No definition
- No organization

- *isa*
- *causes*
- *due to*
- *manifestation of*
- *icd asterisk*
- *associated finding of*
- *may treat*

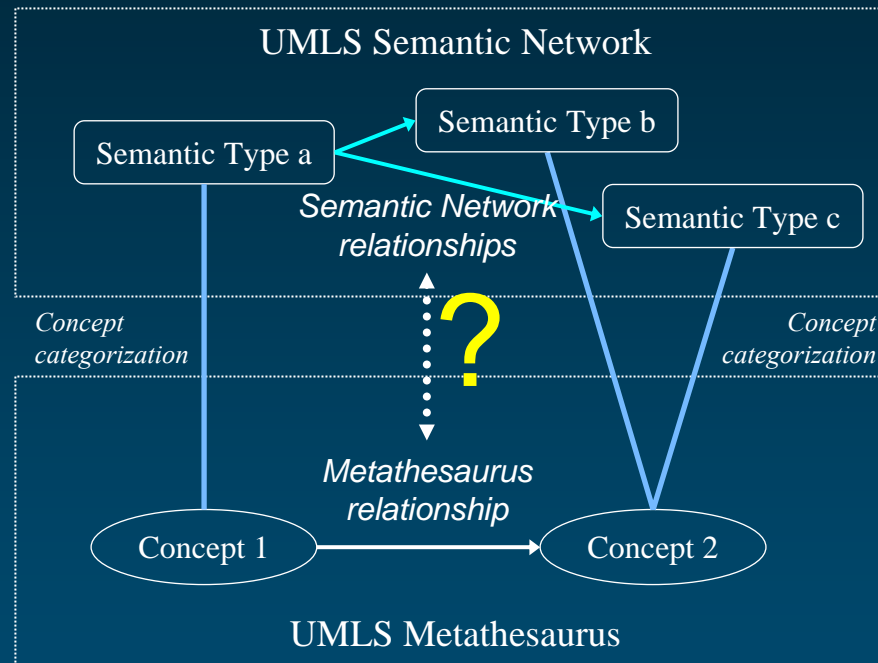
◆ Semantic Network

- 54 relationships
- Textual definition
- Organized in 5 hierarchies

- *isa*
- *associated with*
 - *functionally related to*
 - *physically related to*
 - *spatially related to*
 - *temporally related to*
 - *conceptually related to*



Concepts/Types vs. Relationships



Objectives

- ◆ Elicit the meaning of Metathesaurus relationships
- ◆ Establish
 - A correspondence between
 - Each of the 139 relationships in the Metathesaurus
 - And relationships in the Semantic Network
 - The nature of the correspondence
 - Equivalence, specialization, other
- ◆ Enrich SN relationships with relationships from the Metathesaurus
- ◆ Develop an ontology of relationships



Multiple complementary approaches

- ◆ Metathesaurus-centric
 - Manual elicitation
 - Abstraction at the level of high-level concepts
 - Abstraction at the level of Semantic Types
- ◆ Semantic Network-centric

1a

Manual elicitation

- ◆ Create random samples of a maximum of 50 relations per Metathesaurus relationship
- ◆ Review manually

causative agent of

causative_agent_of

C0014644	A3031273	Human herpesvirus 4	C0021345	A2933867	Infectious mononucleosis	[SNOMEDCT]
C0086776	A3899901	Genus Parvovirus	C0348332	A3056008	Parvovirus as the cause of diseases classified ...	[SNOMEDCT]
C1032649	A3321258	Mycobacterium tuberculosis complex	C0452162	A3130980	Female tuberculous pelvic inflammatory disease	[SNOMEDCT]
C0012802	A3076711	Thiazide diuretic	C0414005	A3243943	Chlorthalidone adverse reaction	[SNOMEDCT]
C0013227	A3627347	Pharmaceutical / biologic product	C0572072	A3273526	Overdose of dihydrocodeine	[SNOMEDCT]
C0007537	A2879568	Cefaclor	C0571453	A3246511	Cefaclor allergy	[SNOMEDCT]
C0038174	A2886834	Staphylococcus epidermidis	C1299601	A3718212	Staphylococcus epidermidis ventriculitis	[SNOMEDCT]
C0557858	A3185117	Plant material	C0275188	A2954926	Asaemia axillaris poisoning	[SNOMEDCT]
C0596004	A2882629	Hyoscyamine	C0573267	A3239847	Accidental hyoscyine overdose	[SNOMEDCT]
C0013227	A3627347	Pharmaceutical / biologic product	C0349155	A3086327	[X]Mental and behavioral disorders due to use o...	[SNOMEDCT]
C0003954	A2878725	Ascaris	C0348284	A3085798	[X]Ascariasis with other complications	[SNOMEDCT]
C0040615	A3639571	Anti-psychotic agent	C0568488	A3288971	Sulpiride poisoning of undetermined intent	[SNOMEDCT]
C0022237	A3188798	Propan-2-ol	C0161681	A3148996	Isopropyl alcohol causing toxic effect NOS	[SNOMEDCT]
C0443078	A3238891	Psychoactive substance of abuse - non-pharmaceu..	C0338784	A3019121	Episodic chronic alcoholism	[SNOMEDCT]
C0042036	A28887830	Urine	C1313946	A3883768	Urine induced contact dermatitis	[SNOMEDCT]
C0004611	A6917107	Bacteria	C0014736	A3019421	Erysipelothrix infection NOS	[SNOMEDCT]
C0013227	A6938913	Drug or medication	C0571249	A3247042	Hypromellose allergy	[SNOMEDCT]
C0040840	A2887564	Treponema pallidum	C0554634	A3037536	Late congenital neurosyphilis	[SNOMEDCT]
C0314732	A3034111	Infectious agent	C0438346	A3203670	Splinter of anus without major open wound, infe...	[SNOMEDCT]
C0026727	A2884274	Mucus	C0349471	A3048120	Neonatal aspiration of mucus	[SNOMEDCT]
C0360112	A3069840	Sedative/neuroleptic	C0413830	A3244725	Pericyazine adverse reaction	[SNOMEDCT]
C0314732	A3034111	Infectious agent	C0403738	A3904401	Penile prosthesis infection	[SNOMEDCT]
C0314732	A3034111	Infectious agent	C0410394	A3092303	Acute osteomyelitis-talus	[SNOMEDCT]
C0014383	A3899795	Genus Enterovirus	C1320186	A3898384	Enterovirus infection of the central nervous sy...	[SNOMEDCT]
C0038675	A2886949	Sulfadiazine	C0568989	A3288962	Sulfadiazine poisoning of undetermined intent	[SNOMEDCT]
C0314732	A3034111	Infectious agent	C1279224	A3034123	Infectious colitis, enteritis and gastroenterit...	[SNOMEDCT]
C0445932	A3078543	Treponema pallidum ss. endemicum	C0343841	A3014643	Dichuchwa	[SNOMEDCT]
C0322643	A3300132	Solenopotes	C0277353	A3512905	Infestation by Solenopotes	[SNOMEDCT]
C0019682	A3031279	Human immunodeficiency virus	C0276507	A2951799	AIDS with progressive multifocal leukoencephalo...	[SNOMEDCT]
C0030498	A2872800	Parasite	C0153328	A3053629	Other specified infectious or parasitic diseases	[SNOMEDCT]
C0314732	A3034111	Infectious agent	C1274152	A3512280	Infective dermatosis of lip	[SNOMEDCT]
C0040840	A2887564	Treponema pallidum	C0039130	A2888750	Cardiovascular syphilis	[SNOMEDCT]
C0314732	A3034111	Infectious agent	C0477692	A3228249	[X]Periostitis in other infectious diseases cla...	[SNOMEDCT]
C0042776	A2872734	Virus	C0276627	A2957806	Chronic aggressive viral hepatitis	[SNOMEDCT]
C0001617	A3374034	Corticoid preparation	C1274200	A3707306	Skin disease attributable to corticosteroid the...	[SNOMEDCT]
C0013227	A3627347	Pharmaceutical / biologic product	C0570403	A3243972	Clofibrate group adverse reaction	[SNOMEDCT]
C0360108	A3076386	Tetracyclic antidepressant	C0568289	A3250399	Tetracyclic antidepressant drug poisoning	[SNOMEDCT]
C0027573	A3162195	Neisseria gonorrhoeae	C0341755	A3026595	Gonococcal prostatitis	[SNOMEDCT]
C0443078	A3238891	Psychoactive substance of abuse - non-pharmaceu..	C0349179	A3086377	[X]Mental and behavioral disorders due to use o...	[SNOMEDCT]
C0013227	A3627347	Pharmaceutical / biologic product	C0573474	A3294922	Netilmicin overdose	[SNOMEDCT]
C0004611	A6917107	Bacteria	C0275554	A3461347	Acute bacterial arthritis	[SNOMEDCT]
C0001268	A2886726	Spectinomycin	C0571387	A3247542	Spectinomycin allergy	[SNOMEDCT]
C0589068	A3245937	Ingestible alcohol	C0033936	A3086293	[X]Mental and behavioral disorders due to use o...	[SNOMEDCT]
C0004382	A3755448	Autonomic agent	C0570914	A3247138	Lidoflazine allergy	[SNOMEDCT]
C0314754	A3026722	Gram-negative coccus	C0343489	A3007140	Chronic meningococccemia	[SNOMEDCT]
C0006463	A2879325	Busulfan	C0572494	A3260795	Busulfan overdose of undetermined intent	[SNOMEDCT]
C0314732	A3034111	Infectious agent	C0007684	A3512066	Infectious disease of central nervous system	[SNOMEDCT]
C0019704	A3031298	Human immunodeficiency virus type I	C0276500	A2967509	Human immunodeficiency virus I infection	[SNOMEDCT]
C0052322	A2993080	Argemone oil	C0413036	A3097680	Argemone oil causing toxic effect	[SNOMEDCT]
C0033808	A2885980	Pseudomonas	C1275136	A3577393	Neonatal pseudomonas infection	[SNOMEDCT]

Domain

Range

causative_agent_of

C0014644 A3031273 Human herpesvirus 4	C0021345 A2933967 Infectious mononucleosis	[SNOMEDCT]
C0086776 A3899901 Genus Parvovirus	C0348332 A3056008 Parvovirus as the cause of diseases classified ...	[SNOMEDCT]
C1032649 A3321258 Mycobacterium tuberculosis complex	C0452162 A3130980 Female tuberculous pelvic inflammatory disease	[SNOMEDCT]
C00076711 Thiiazide diuretic	C0571453 A324001 Cefaclor allergy	[SNOMEDCT]
C0007537 A2879568 Cefaclor	C0573267 A323947 Accidental hyoscine overdose	[SNOMEDCT]
C0007537 A2879568 Cefaclor	C0573267 A323947 Accidental hyoscine overdose	[SNOMEDCT]
C0596004 A2882639 Hyoscyamine	C0568488 A3288971 Sulpiride poisoning of undetermined intent	[SNOMEDCT]
C0040615 A3639571 Anti-psychotic agent	C1274152 A3512280 Infective dermatosis of lip	[SNOMEDCT]
C0042677 A2884274 Mucus	C0039130 A2888750 Cardiovascular syphilis	[SNOMEDCT]
C0360112 A3001322 Treponema pallidum	C0477740 A3328249 [X] Peritonitis in other infectious diseases cla...	[SNOMEDCT]
C0314732 A3034111 Infectious agent	C1274200 A3707306 Skin disease attributable to corticosteroid the...	[SNOMEDCT]
C0314732 A3034111 Infectious agent	C0341755 A3026597 Gonococcal proctitis	[SNOMEDCT]
C0014983 A3899788 Enterovirus	C0341755 A3026597 Gonococcal proctitis	[SNOMEDCT]
C0038675 A2886941 Sulfadiazine	C0570914 A3247138 Lidoflazine allergy	[SNOMEDCT]
C0314732 A3034111 Infectious agent	C0343489 A3007140 Chronic meningococccemia	[SNOMEDCT]
C0449932 A3078543 Treponema pallidum	C0572494 A3260795 Busulfan overdose of undetermined intent	[SNOMEDCT]
C0322643 A3300132 Treponema pallidum	C0007684 A3512066 Infectious disease of central nervous system	[SNOMEDCT]
C0019582 A3031279 Human immunodeficiency virus	C0276500 A2967509 Human immunodeficiency virus I infection	[SNOMEDCT]
C0030498 A3031279 Human immunodeficiency virus	C0413036 A3097680 Argemone oil causing toxic effect	[SNOMEDCT]
C0314732 A3034111 Infectious agent	C1275136 A3577393 Neonatal pseudomonas infection	[SNOMEDCT]
C0040940 A2887566 Treponema pallidum		
C0314732 A3034111 Infectious agent		
C0042676 A2884274 Mucus		
C0001611 A3374034 Corticoid preparation		
C0013227 A3627347 Pharmaceutical / biologic		
C0360108 A3076386 Tetracyclic antidepressant		
C0027573 A3162195 Neisseria gonorrhoeae		
C0443078 A3238891 Psychoactive substance of		
C0013227 A3627347 Pharmaceutical / biologic		
C0004611 A6917107 Bacteria		
C0001268 A2886726 Spectinomycin		
C0589068 A3245937 Ingestible alcohol		
C0004382 A3755448 Autonomic agent		
C0314754 A3026722 Gram-negative coccus		
C0006463 A2879325 Busulfan		
C0314732 A3034111 Infectious agent		
C0019704 A3031298 Human immunodeficiency virus type I		
C0052322 A2993080 Argemone oil		
C0033808 A2885980 Pseudomonas		

Virus
 Anti-psychotic agent
 Autonomic agent
 Ingestible alcohol

Chronic aggressive viral hepatitis
 Sulpiride poisoning of undetermined...
 Lidoflazine allergy
 Mental and behavioral disorders

Infectious agents and Pharmacologic substances

causes

Disorders

"Brings about a condition or an effect. Implied here is that an agent, such as for example, a pharmacologic substance or an organism, has brought about the effect"

causative agent of SNOMED CT ≡ causes SN

1b Abstraction at the level of high-level concepts

- ◆ Compute the lowest common ancestor(s) for concepts in the domain and range of the relationship, respectively

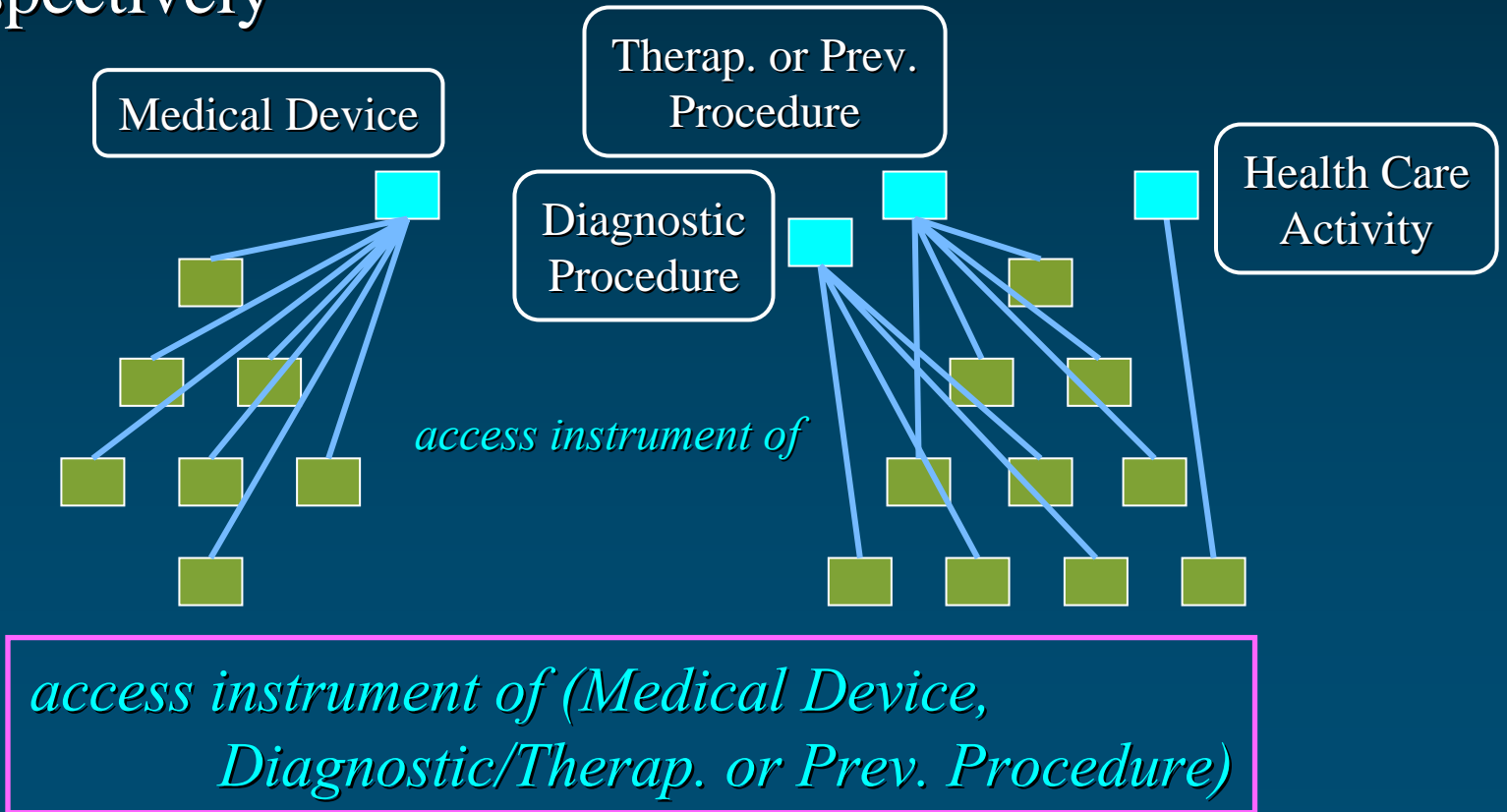


access instrument of (Endoscope, Procedure)

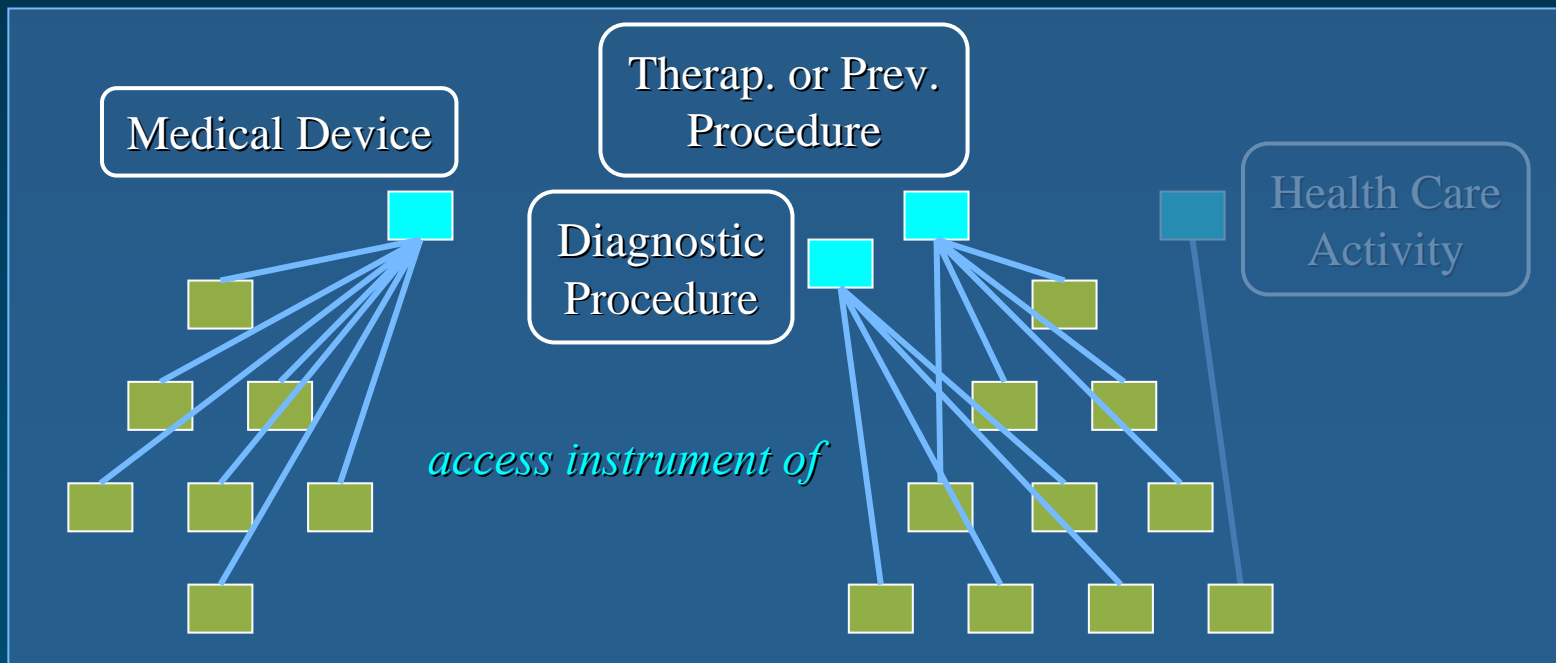
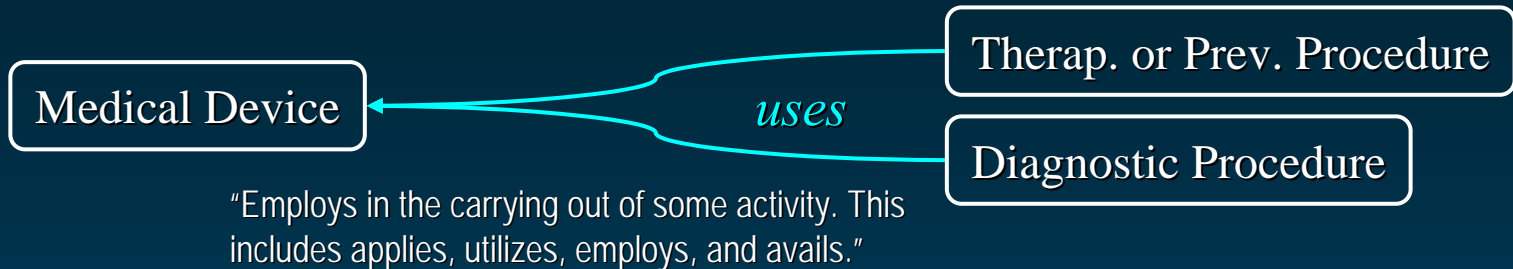
1c

Abstraction at the level of STs

- ◆ Compute the distribution of the STs for concepts in the domain and range of the relationship, respectively



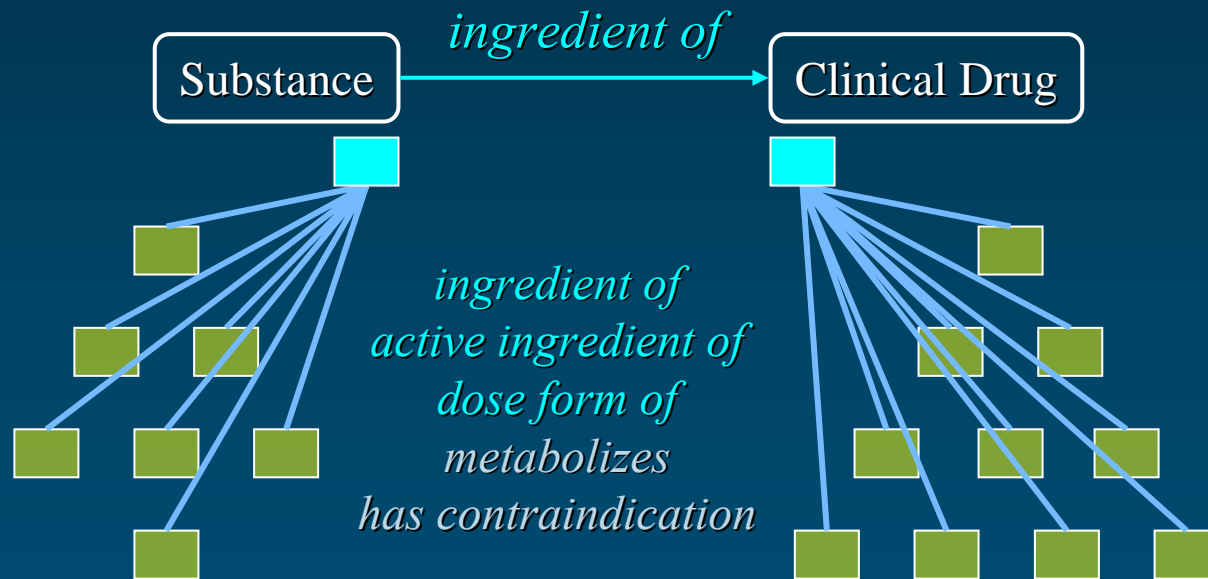
Identifying candidates in the SN



$$\text{access instrument of}_{SNOMED CT} \equiv \text{inv}(\text{uses}_{SN})$$

② Semantic Network-centric approach

- ◆ For a given relationship between two STs in the SN, list all the relationships between concepts categorized by these STs



$\{ \textit{ingredient of}_*, \textit{active ingredient of}_{SNOMEDCT}, \textit{dose form of}_*, \} \equiv \textit{ingredient of}_{SN}$

Results Materials

(2005AC)

- ◆ 139 specified relationships (RELA) in the Metathesaurus
- ◆ Major contributors
 - SNOMED CT (62)
 - LOINC (15)
 - NDF-RT (15)
- ◆ Most relationships are specific to one vocabulary
 - 116 specific to one vocabulary
 - 23 found in at least 2 vocabularies



Results Alignment

- ◆ 80 relationships (58%) could be aligned
 - Identical
 - *affects, process of, ingredient of*
 - Roughly equivalent to
 - *focus of_{SNOMEDCT} ≡ issue in_{SN}*
 - More specific than
 - *metabolic site of_{NDFRT} < functionally related to_{SN}*
- ◆ Non aligned (non-semantic relationships)
 - Lexical relationships (e.g., *british form of**, *suffix of_{LOINC}*)
 - Mapping relationships (e.g., *see from_{CRISP}, mapped to**)
 - Vocabulary management (e.g., *replaces_{SNOMEDCT}*)

Some issues

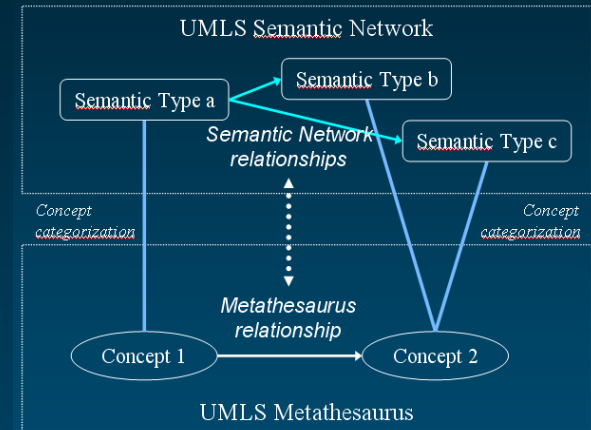
- ◆ Manual elicitation
 - Manual review by experts required
- ◆ Abstraction at the level of high-level concepts
 - Lowest common ancestor = root of the terminology (heterogeneous set of concepts)
- ◆ Abstraction at the level of Semantic Types
 - Multiple STs for a set of concepts
 - Multiple relationships for a given pair of STs
- ◆ Semantic Network-centric approach
 - Multiple relationships in the Metathesaurus between the concepts corresponding to a given pair of STs

Towards an ontology of relationships

Motivation

◆ Consistency checking

- Relations asserted between STs in the SN should provide constraints for relations between Metathesaurus concepts categorized by these STs



◆ Effective subsumption reasoning

- Requires explicit equivalence between identical relationships (e.g., $\text{inv}(\textit{due to}) = \textit{cause of} \equiv \textit{causes}$)
- Requires explicit subProperty relations

Existing resources

- ◆ Semantic Network relationships
 - 54 relationships, not formally defined, organized into a shallow hierarchy
 - <http://semanticnetwork.nlm.nih.gov/>
- ◆ GALEN relationships
 - Over 500 relationships, semi-formally defined, organized into a hierarchy
 - <http://www.opengalen.org/>
- ◆ OBO relation ontology
 - 10 relationships, formally defined
 - <http://obofoundry.org/ro/>

GALEN relations *isIngredientOf*

tree structure:

- + topLinkClass
- Attribute
 - DomainAttribute
 - ConstructiveAttribute
 - InversePartitiveAttribute
 - InverseStructuralPartitiveAttribute
 - + IsDivisionOf
 - makesUp
 - x specificallyMakesUp
 - isIngredientOf
 - x isSpecificIngredientOf
 - x isMultipleIngredientOf
 - x isNotIngredientOf
 - x isNotChemicalSubgroupOf
 - + inverseProcessPartitiveAttribute
 - + InverseStructuralAttribute
 - + involves
 - + FunctionalAttribute
 - x hasReference
 - x hasFrameOfReference
 - + hasPhysicalMeans
 - + hasPersonPerforming
 - x records
 - x hasEmployer
 - + WrapperAttribute
 - + TemporalAttribute
 - + ModifierAttribute
 - + SpecificationLevelAttribute
 - + ApplicationAttribute

Name:	isIngredientOf
Inverse:	hasIngredient
Cardinality:	manyMany
Properties:	inverse, transitive
Transits:	makesUp
Transitive orbits:	makesUp

Attribute Pretty: on Filter: on

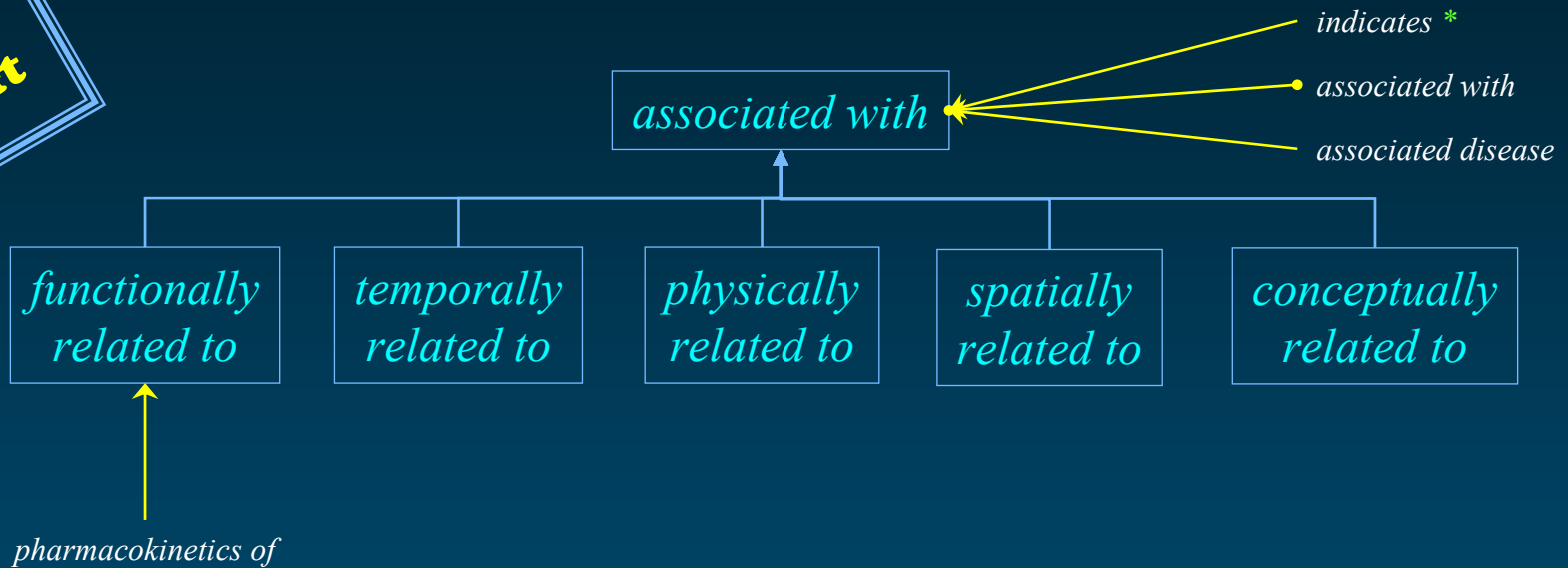
OBO relations

Summary Table

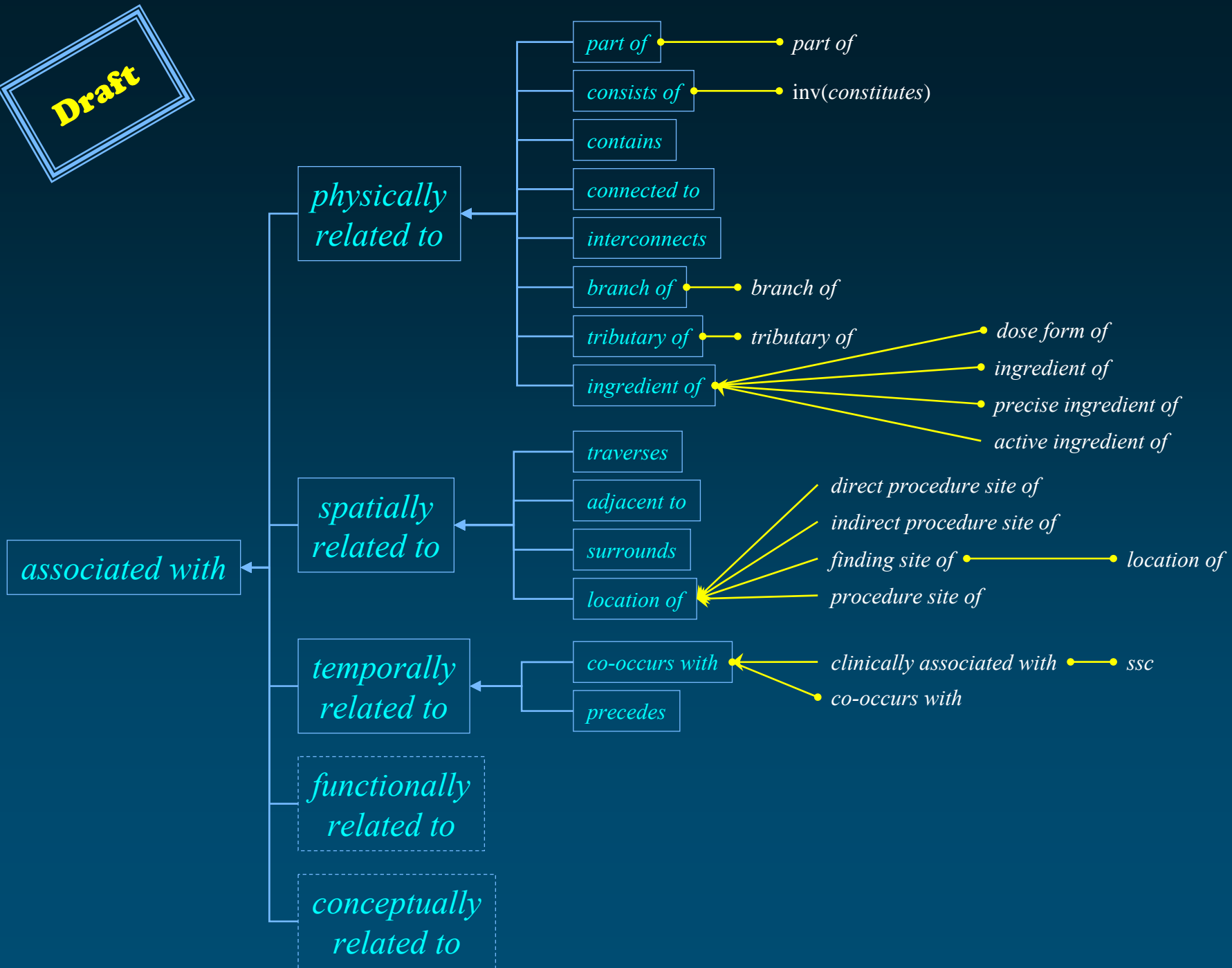
name	transitive	symmetric	reflexive	anti-symmetric	documentation
is_a	+		+	+	View detailed summary
part_of	+		+	+	View detailed summary
integral_part_of	+		+	+	View detailed summary
proper_part_of	+				View detailed summary
located_in	+		+		View detailed summary
contained_in					View detailed summary
adjacent_to					View detailed summary
transformation_of	+				View detailed summary
derives_from	+				View detailed summary
preceded_by	+				View detailed summary
has_participant					View detailed summary
has_agent					View detailed summary
instance_of					View detailed summary

Extending the SN relationship hierarchy

Draft



Draft



Draft

physically related to

spatially related to

temporally related to

associated with

functionally related to

conceptually related to

metabolic site of

metabolizes

affects

affects

has physiologic effect

has direct morphology

has indirect morphology

brings about

performs

occurs in

occurs in

has direct substance

uses

manifestation of

indicates

result of

manages

treats

disrupts

complicates

interacts with

prevents

produces

causes

carries out

exhibits

practices

process of

instrument of

definitional manifestation of

interprets

has specimen procedure

occurs after

may treat
treats

may prevent

encodes gene product

causative agent of
cause of

exhibits

process of
pathological process of

access instrument of
direct device of
indirect device of
procedure device of

inv

Draft

physically related to

spatially related to

temporally related to

functionally related to

associated with

conceptually related to

is differential diagnostic for — *ddx*

contraindicated with — *contraindicated with*

form of ← *developmental form of*
← *form of*

~~*developmental form of*~~

degree of

analyzes ← *analyzes*
← *assesses effect of*

measurement of — *specimen of*

measures — *measures*

diagnoses — *diagnoses* — *may diagnose*

property of — *manifestation of **

issue in — *focus of*

evaluation of — *evaluation of*

method of ← *measurement method of*
← *method of*

conceptual part of — *conceptual part of*

derivative of — *component of*

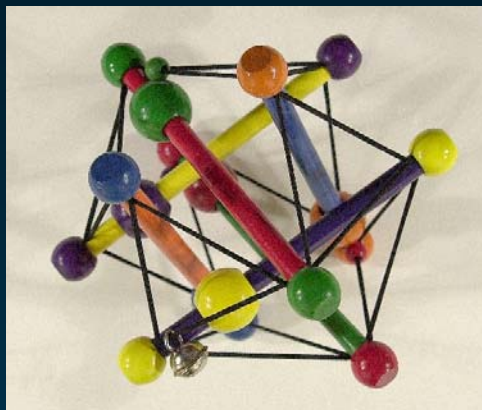
process of — *process of*

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