First International Workshop on Formal Biomedical Knowledge Representation
(KR-MED2004), June 1, 2004, Whistler (Canada)

Towards a Computational Paradigm for Biological Structure

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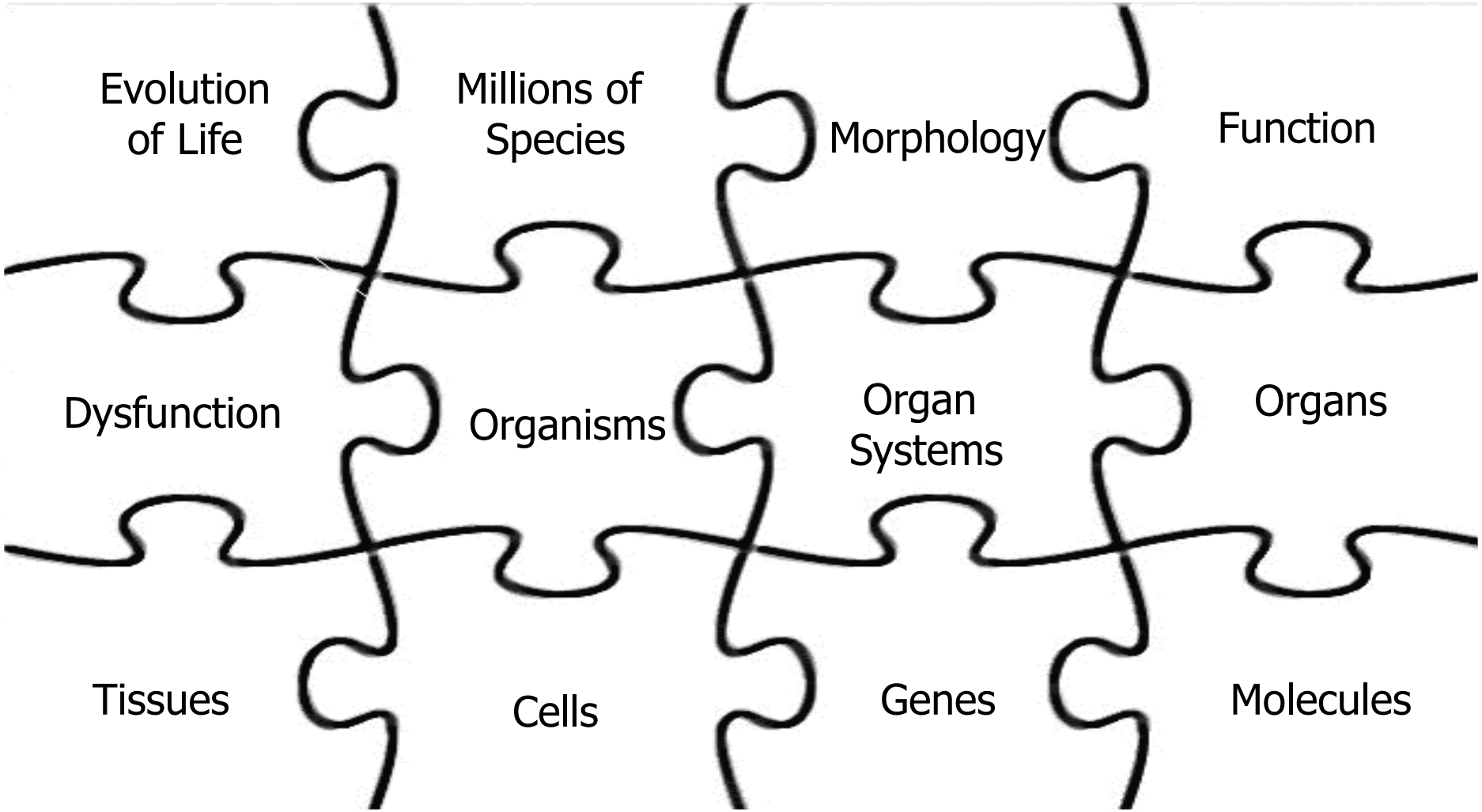
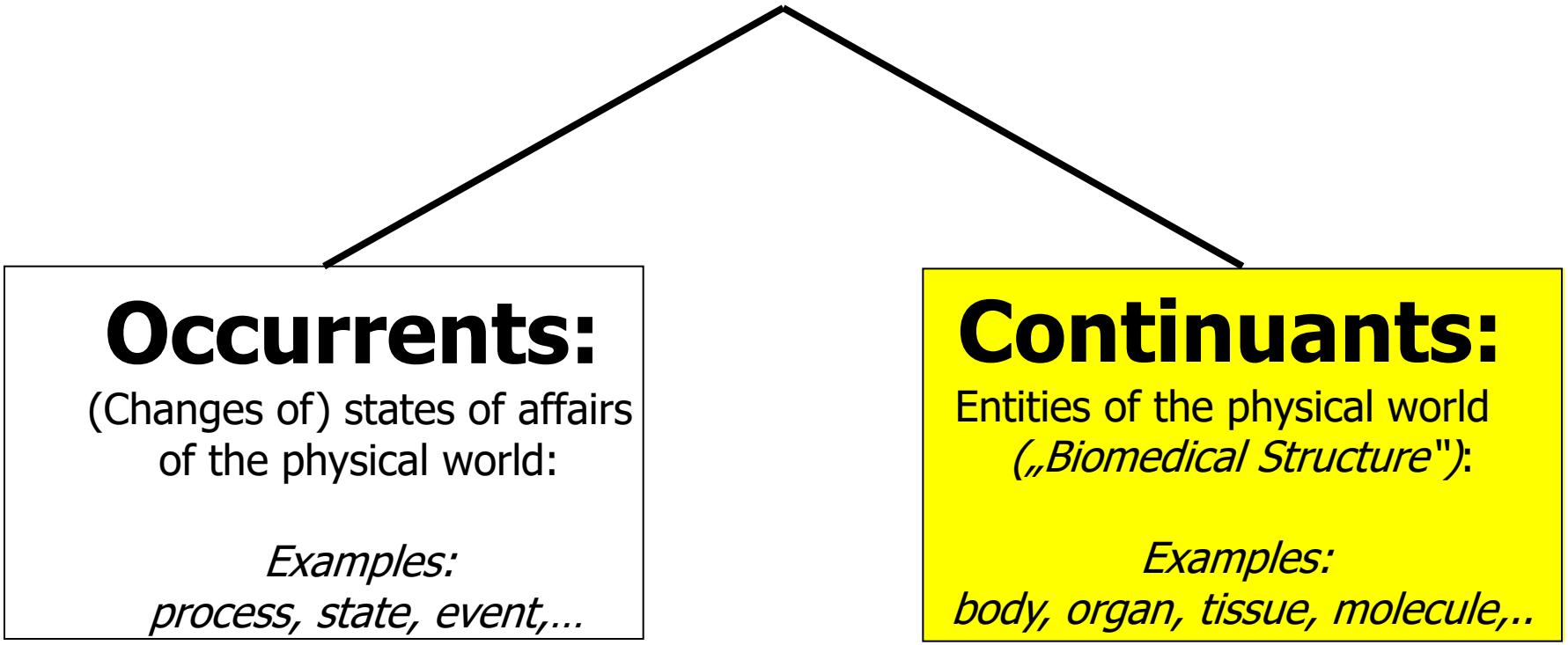
The World of Life Sciences…



…requires sophisticated organization

Bio-ontologies



What exists ?

- Human Anatomy
  - Foundational Model of Anatomy (FMA)
  - Portions of SNOMED, OpenGalen, MeSH
- Other Organisms
  - Open Biological Ontologies (OBO)
    - Mouse (developmental stages), Zebrafish, Drosophila,…
- Species-Independent
  - Gene Ontology: Cellular Component

Overlap

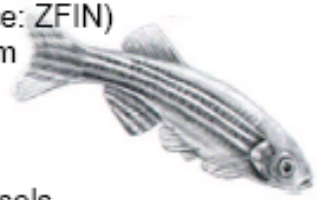
Mouse (embryonal stage TS11, source: MGI)
- cardiovascular system
- - heart
- - - cardiogenic plate

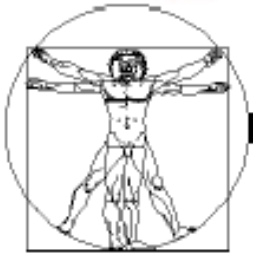
Mouse (embryonal stage TS18 , source: MGI)
- cardiovascular system
- - heart
- - - atrio-ventricular canal
- - - atrium
- - - bulboventricular groove
- - - bulbus cordis
- - - endocardial cushion tissue
- - - mesentery
- - - outflow tract
- - - pericardium
- - - primitive ventricle
- - - sinus venosus

Mouse (embryonal stage TS26 , source: MGI)
- cardiovascular system
- - heart
- - - aortic sinus
- - - atrio-ventricular canal
- - - atrio-ventricular cushion tissue
- - - atrium
- - - bulbar cushion
- - - endocardial cushion tissue
- - - endocardial tissue
- - - mesentery
- - - pericardium
- - - trabeculae carneae
- - - valve
- - - ventricle

Drosophila (adult, source FlyBase)
- circulatory system
- - heart
- - - heart muscle
- - - adult aortic funnel
- - - adult ostia
- - - dorsal diaphragm
- - - heart chamber
- - - terminal opening

Zebrafish (adult, source: ZFIN)
- cardiovascular system
- - heart
- - - atrium
- - - bulbus arteriosus
- - - hypobranchial vessels
- - - sinus venosus
- - - ventricle





Human, Adult, (source: FMA)
- cardiovascular system
- - heart
- - - wall of heart
- - - right atrium
- - - left atrium
- - - right ventricle
- - - left ventricle

} is-a organ chamber

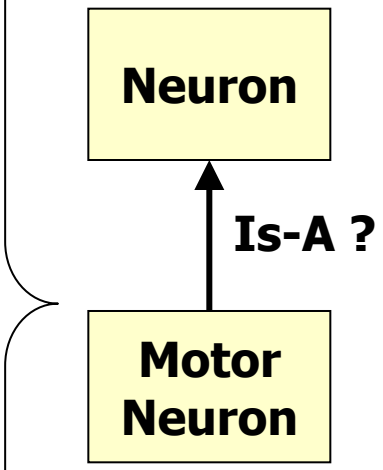
- - - right side of heart
- - - left side of heart
- - - fibrous skeleton of heart
- - - papillary muscle
- - - cardiac valve
- - - tricuspid valve
- - - mitral valve
- - - aortic valve
- - - pulmonary valve

} is-a cardiac valve

- - - interatrial septum
- - - (...)

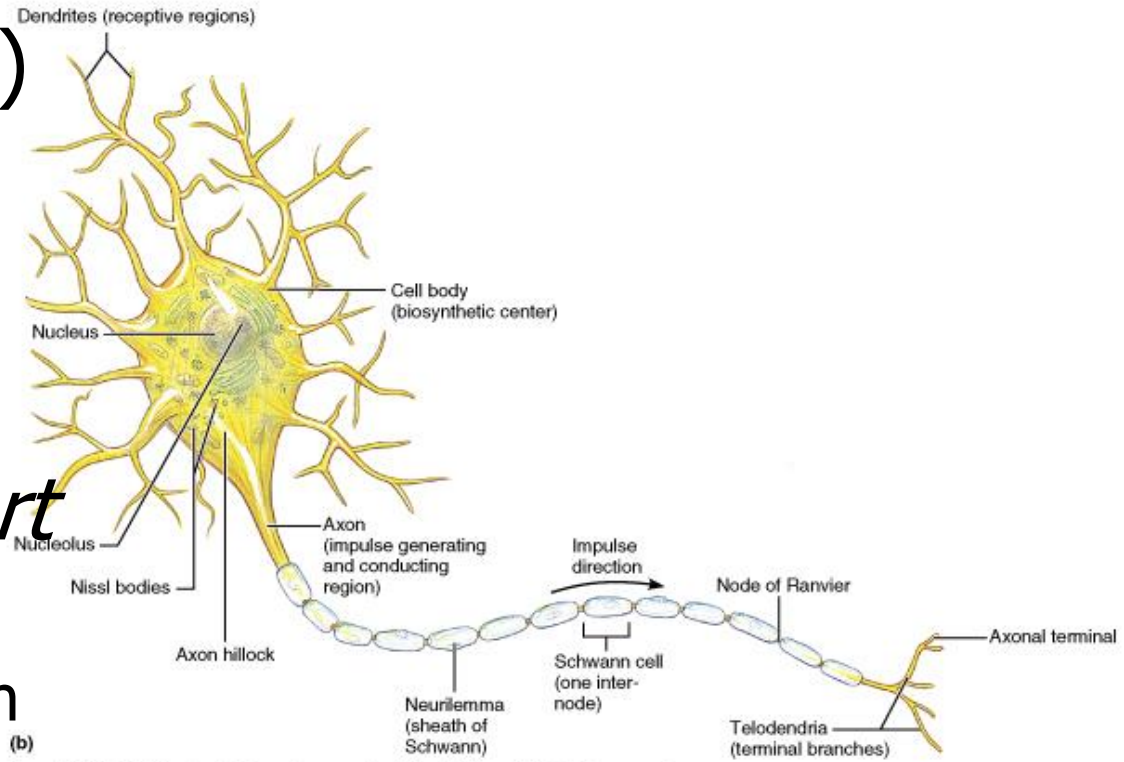
Same name – different meaning

- "*Motor Neuron instance-of Neuron*" (FlyBase)
- "*Motor Neuron narrower Neuron*" (MeSH)
- "*Motor Neuron subclass-of Neuron*" (FMA, OpenGALEN)



Same name – different meaning

- "*Cell has-part Axon*" (Gene Ontology)
  - Do cells without axons exist ?
  - Do axons without cells exist ?
- "*Neuron has-part Axon*" (FMA)
  - Does every neuron has an axon?



Deficiencies (II)

- "*Cell has-part Axon*" (Gene Ontology)
  - Do cells without axons exist ?
  - Do axons without cell exist ?
- "*Neuron has-part Axon*" (FMA)
  - Does every neuron has an axon?

"Keep in mind that part_of means can be a part of, not is always a part of "
GO Editorial Style Guide, Oct 2003

***"The part_of relationship (…) is usually necessarily* is_part"**
GO Editorial Style Guide, Jan 2004

"A part_of B if and only if: for any instance x of A there is some instance y of B which is such that x stands to y in the instance-level part relation, and vice versa".

Rosse & Smith MEDINFO 2004

Conflicting and / or underspecified conceptualizations hamper sharing and integration of ontologies

Semantic framework for biological structure…

- Foundational Relations
- General Attributes
- Theories

Semantic framework for biological structure…

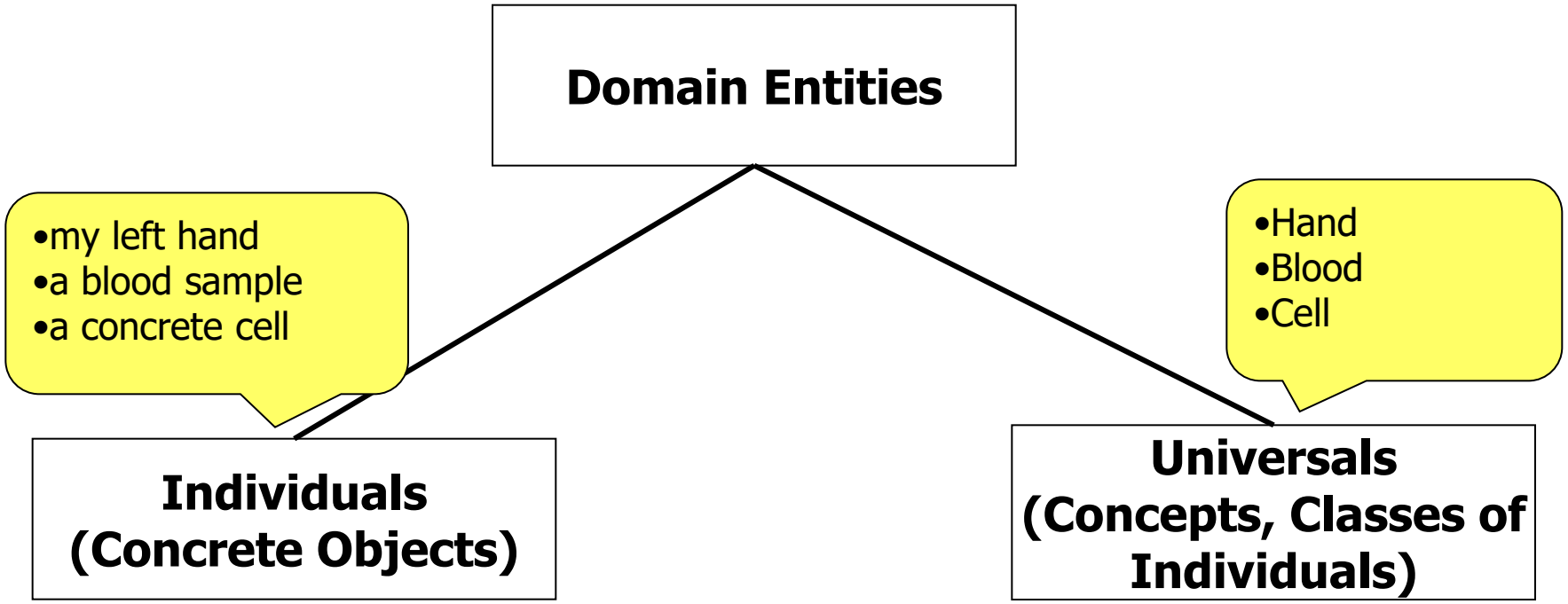
- Foundational Relations
- General Attributes
- Theories

Foundational Relations between Biological Structure

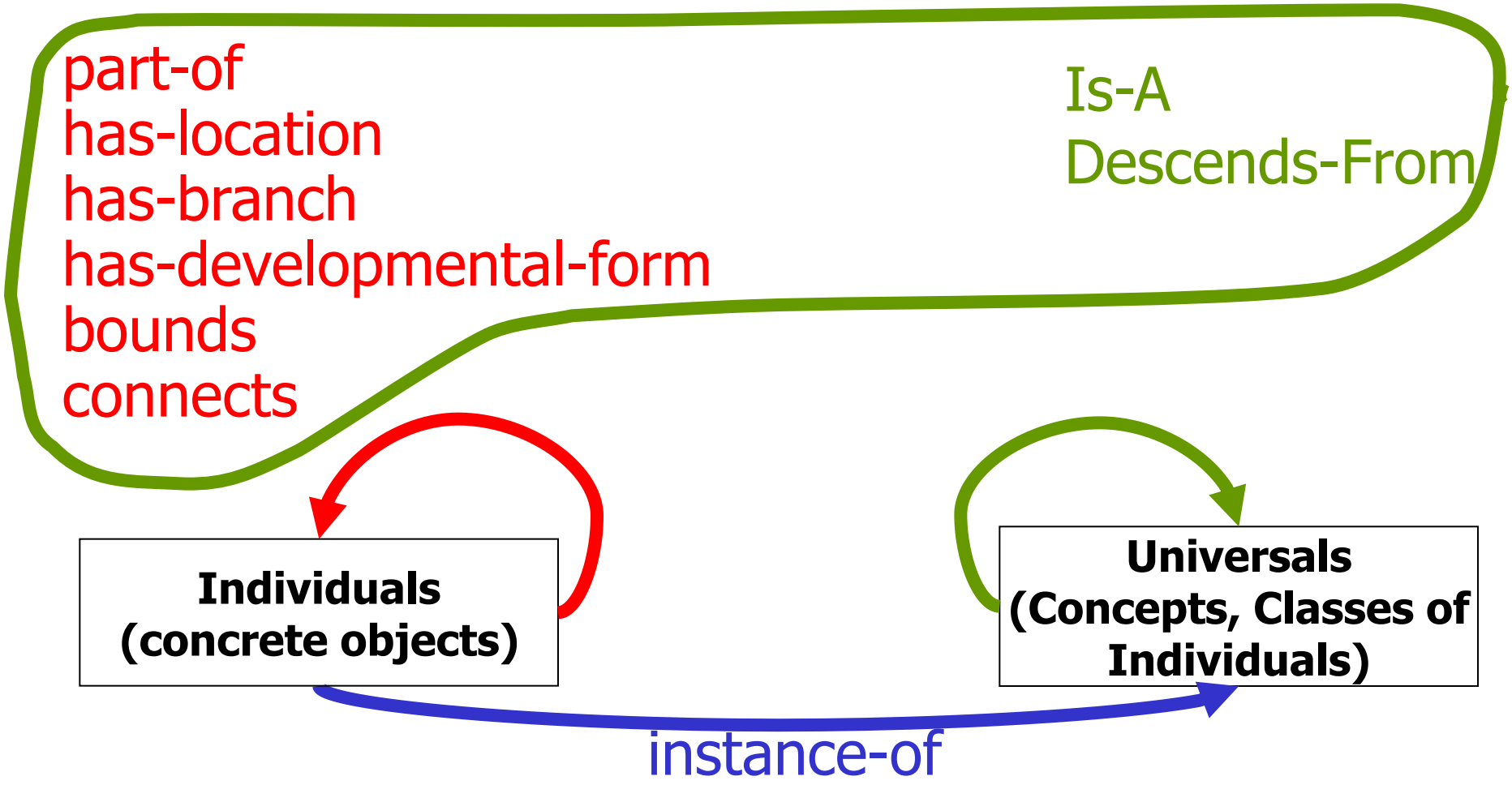
- is-a
- instance-of
- part-of / has-part
- has-location / location-of
- has-branch / branch-of
- has-developmental-form / is-developmental-form-of
- descends-from / has-descendant
- connects
- bounds / bounded by

classify by domain / range ?

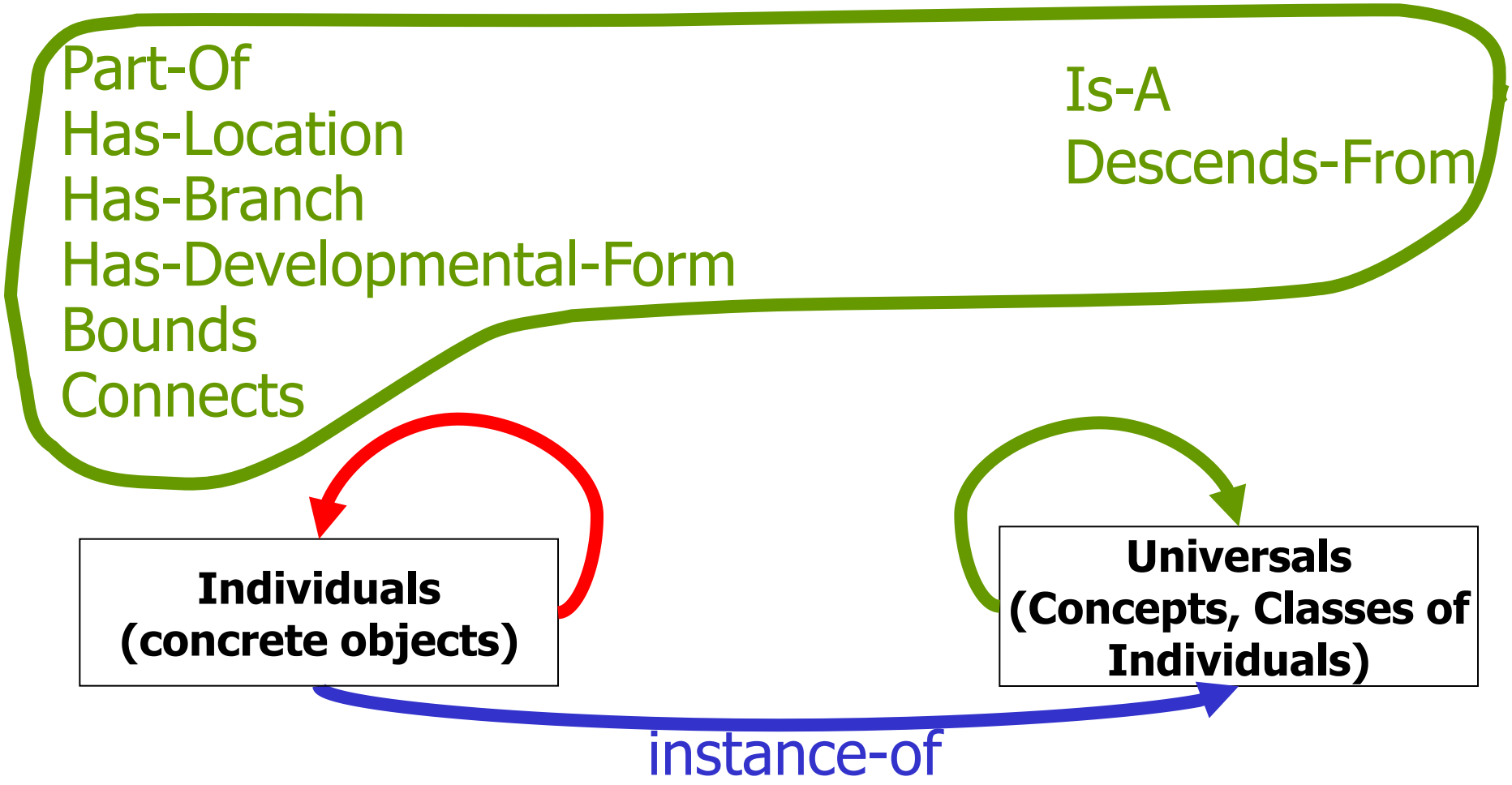
Two kinds of entities



Classification of Foundational Relations



Classification of Foundational Relations



From Instance-to-Instance relations to Class-to-Class Relations

A, B are classes, $inst\text{-}of$ = class membership

rel: relation between instances Rel: relation between classes

$Rel\ (A, B) =_{def}$

1. $\exists x: inst\text{-}of\ (x, A) \wedge inst\text{-}of\ (y, B) \wedge rel\ (x, y)$ **OR**
2. $\forall x: inst\text{-}of(x, A) \rightarrow \exists y: inst\text{-}of\ (y, B) \wedge rel\ (x, y)$ **OR**
3. $\forall y: inst\text{-}of(y, B) \rightarrow \exists x: inst\text{-}of\ (x, A) \wedge rel\ (x, y)$

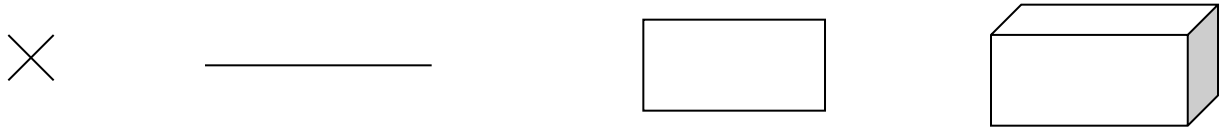
cf.
Schulz & Hahn (KR 2004, June 2, 11am)
Rosse & Smith (MEDINFO 2004)

Semantic framework for biological structure…

- Foundational Relations
- General Attributes
- Theories

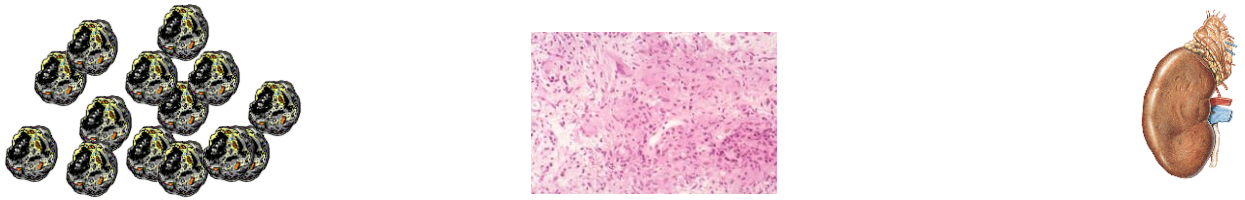
General Attributes (mutually disjoint classes)

- Dimensionality: Point, 1-D, 2-D, 3-D



- Solids vs. hollow spaces, vs. Boundaries

- Collections vs. Masses vs. Count Objects



cf. Schulz & Hahn, FOIS 01

Semantic framework for biological structure…

- Foundational Relations
- General Attributes
- Theories

Theories

- A set of formal axioms which describe a restricted (local) domain.
- Four orthogonal theories for Biological Structure
  - **Granularity**
  - **Species**
  - **Development**
  - **Canonicity**

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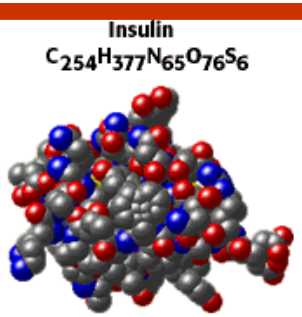
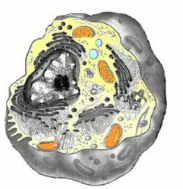
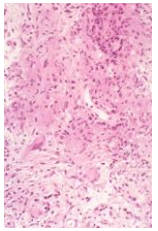
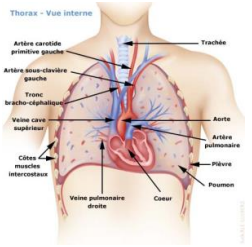
Granularity



- Level of detail (molecular, cellular, tissue, organ)
- Change in Granularity level may be non-monotonous
  - Change of sortal restrictions:
    - 3-D $\rightarrow$ 2-D boundary
    - Count concept $\rightarrow$ Mass concept
  - Change of relational attributions:
    - disconnected $\rightarrow$ connected

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Linnean Taxonomy of Species

Deuterostomia
- Echinodermata
- Hemichord
- Chordata
  - ?– Calcichordata †
  - Urochordata (tunicates)
  - Cephalochordata (a
  - Yunnanozoon †
  - Craniata — Hyperotreti, Vertebrata
    - Hyperoartia (lampreys)
    - ?– Euconodonta †
    - Pteraspidomorphi †
    - ?≡ Thelodonti †
    - ?– Anaspida †
    - Galeaspida †
    - ?– Pituriaspida †
    - Osteostraci †
    - Gnathostomata
      - Sarcopterygii
      - Actinopterygii
      - Acanthodii †
      - Chondrich
      - Placoderm
        - ?– Onychodontiformes †
        - Coelacanthimorpha
        - Porolepimorpha †
        - Dipr taxon links
        - Rhizodontimorpha †
        - Osteolepimorpha †
        - Terrestrial Vertebrates

Ecdysozoa
- Arthropoda
- Onychophora (velvet worms)
- Tardigrada (water bears)
- Nematoda (roundworms)
- Nematomorpha (horsehair worms)
- Kinorhyncha
- Loricifera
- Priapulida (penis worms)

Lophotrochozoa
- ?– Platyhelminthes (flatworms, tapeworms, flukes)
- ?– Chaetognatha (arrow worms)
- ?– Gastrotricha
- ?– Rotifera (rotifers)
- ?– Gnathostomulida (jaw worms)
- ?– Micrognathozoa
- ?– Cycliophora
- ?– Mesozoa
- Annelida (bristleworms, ragworms, earthworms, leeches and their allies)
- Sipuncula (peanut worms)
- Mollusca (snails, clams, squids, etc.)
- Nemertea (ribbon worms)
- Bryozoa (moss animals)
- Entoprocta (kamptozoans)

THE TREE OF LIFE WEB PROJECT
http://tolweb.org

Linnean Taxonomy of Species

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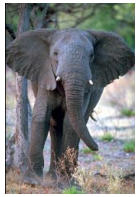
Linnean Taxonomy of Species

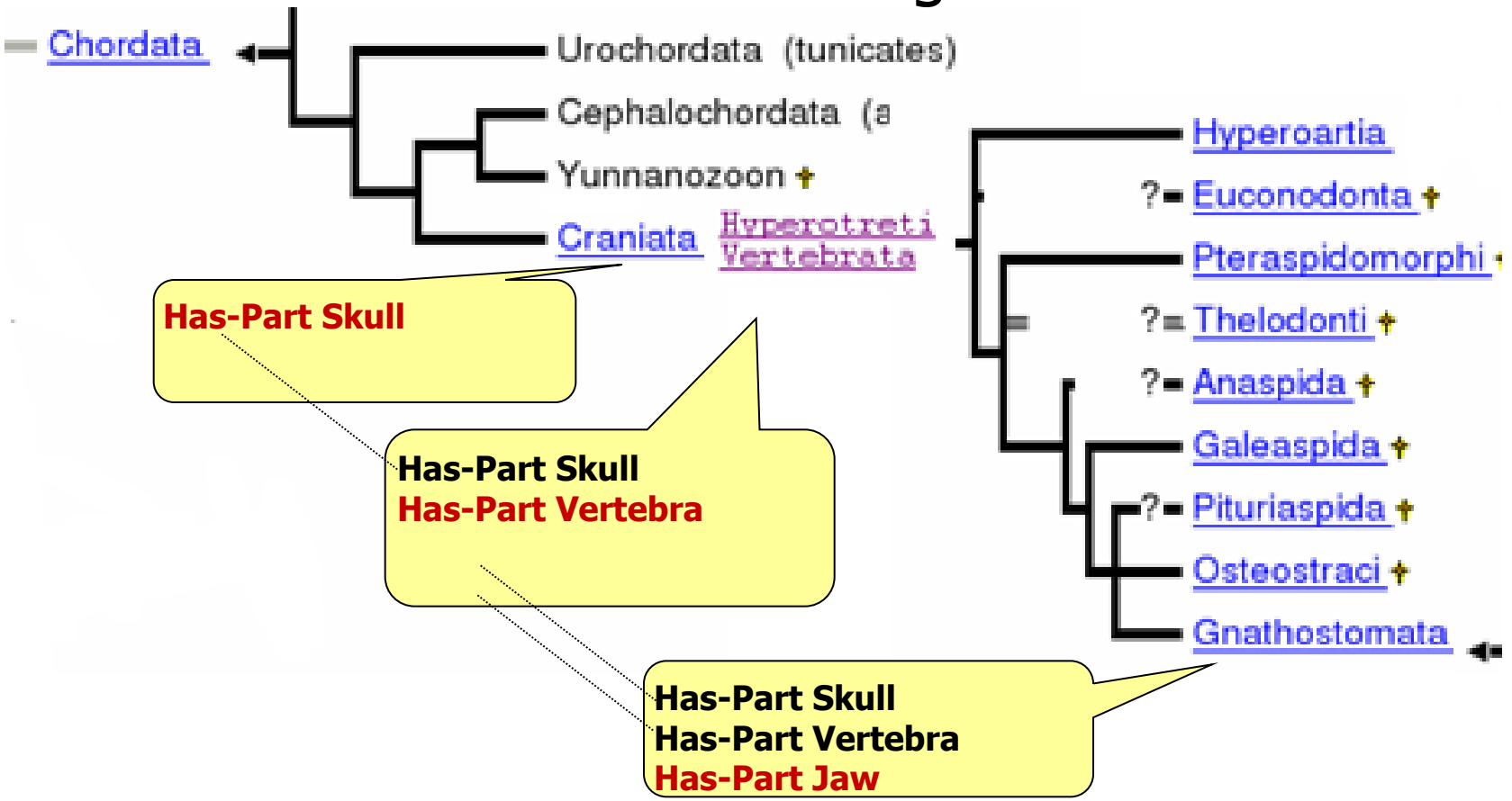


taxon links

- Triconodonts †
- Monotremata
- Multituberculata
- Marsupialia
- Palaeoryctoids †
- Eutheria
  - Edentata (anteaters, sloths, armadillos)
  - Pholidota (pangolins)
  - Glires
    - Lagomorpha (rabbits, hares, and pikas)
    - Rodentia (mice)
    - Macroscelidea
  - Primates
    - Platyrrhini
    - Catarrhini
      - Cercopithecidae
      - Hominidae
        - Pongo (orangutan)
        - Pan (chimpanzee and bonobo)
        - Ardipithecus †
        - Australopithecus †
        - Homo (humans)
        - Gorilla
      - Hylobatidae
    - Tarsii
    - Strepsirhini
  - Scandentia
  - Chiroptera (bats)
  - Dermoptera (colugos or flying lemurs)
  - Insectivora (shrews, moles, hedgehogs, etc.)
  - Creodonta †
  - Carnivora (dogs, cats, bears, raccoons, weasels, mongooses, hyenas, seals, walruses)
  - Condylarthra †
  - Artiodactyla (pigs, deer, cattle, goats, sheep, hippopotamuses, camels, etc.)
  - Cetacea (whales, dolphins, porpoises)
  - Tubulidentata (aardvark)
  - Perissodactyla (horses, tapirs, rhinoceroses)
  - Hyracoidea (hyraxes, dassies)
  - Sirenia (manatees, dugong, sea cow)
  - Desmostylia †
  - Embrythopoda †
  - Proboscidea (elephants, mammoths, mastodons, etc.)

Species

Introduction of Axioms at the highest common level



Theories

- A set of formal axioms which describe a restricted (local) domain.
- Four orthogonal theories for Biological Structure
  - **Granularity**
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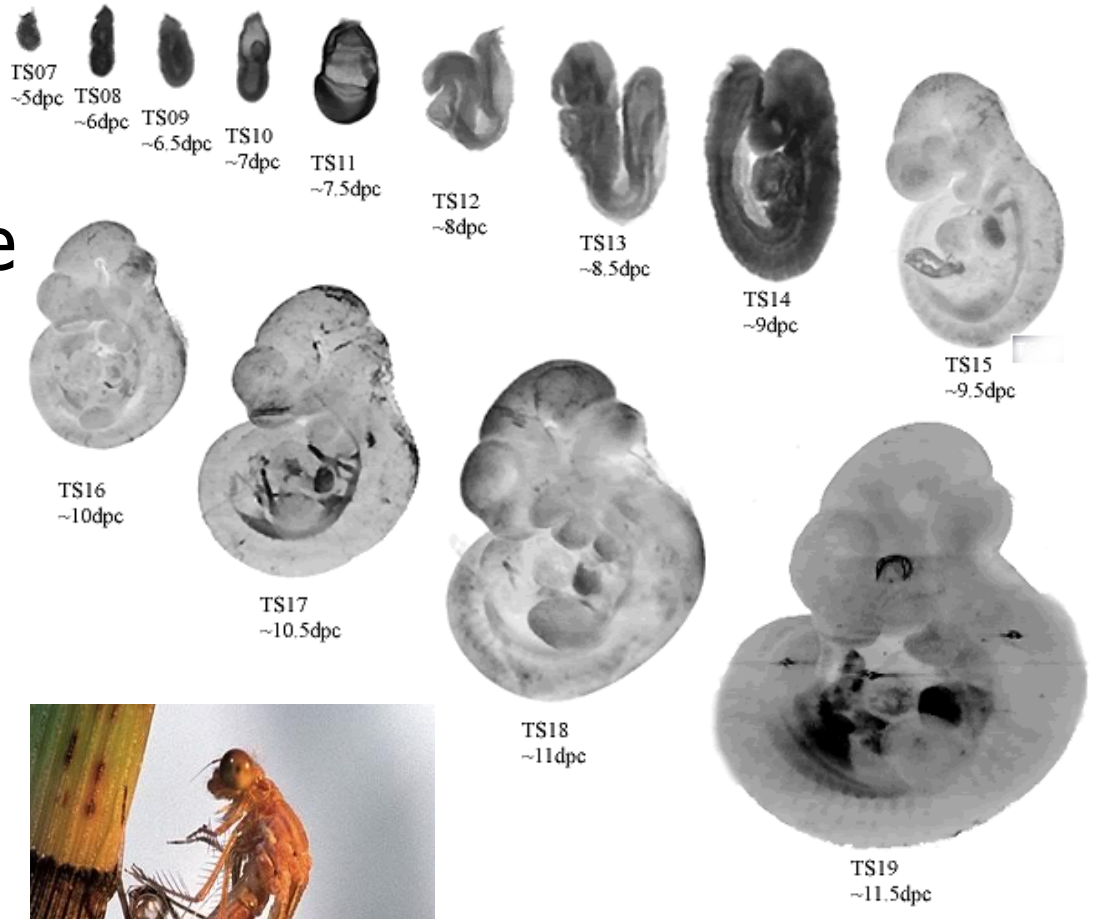
  - **Development**
  - **Canonicity**

Development

- Represents time-dependent "snapshots" from the life cycle of an organism, e.g., zygote, embryo, fetus, child, adult
- Granularity stages are species-dependent e.g. metamorphosis



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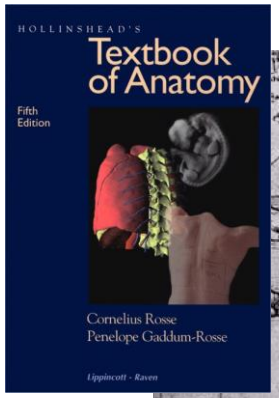
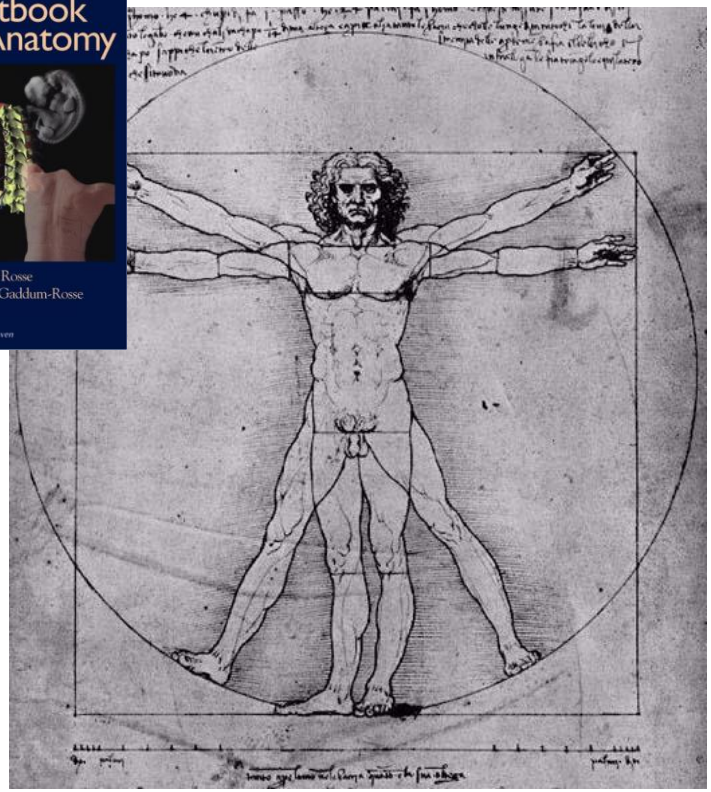
Canonicity

- Degrees of "Wellformedness" of Biological Structure:
  - Canonic structure





Canonicity

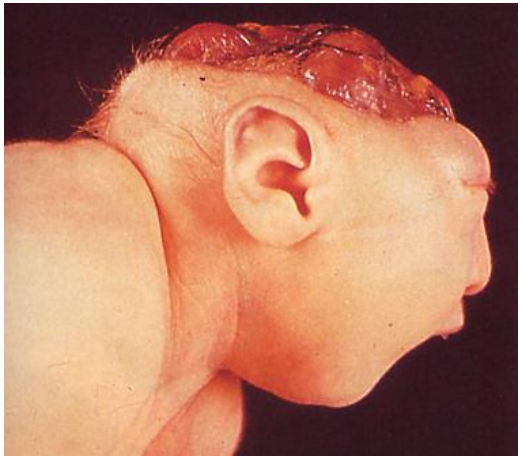
- Degrees of "Wellformedness" of Biological Structure:
  - Canonic structure
  - Structural Variations

Canonicity

- Degrees of "Wellformedness" of Biological Structure:
  - Canonic structure
  - Structural Variations
  - Pathological Structure

Canonicity

- Degrees of "Wellformedness" of Biological Structure:
  - Canonic structure
  - Structural Variations
  - Pathological Structure
  - Lethal Structure



Canonicity

- Degrees of "Wellformedness" of Biological Structure:
  - Canonic structure
  - Structural Variations
  - Pathological Structure
  - Lethal Structure
  - Derivates of biological structure

Canonicity

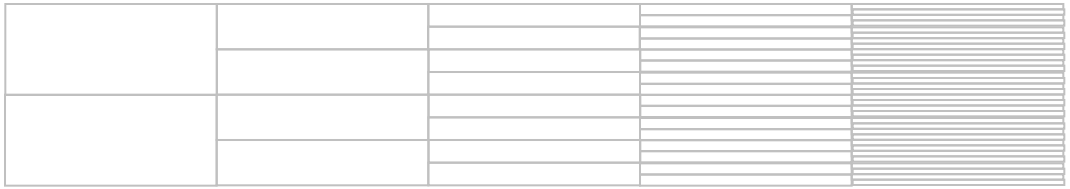
- Five canonicity levels: each level introduces axioms valid for higher levels

Level	1	2	3	4	5
Theory	any amount of matter, if of biological origin	any living or dead organism	any living organism	living organism without pathologic modifications	ideal organism
Set of Axioms	n_1	n_2 $n_1 \subset n_2$	n_3 $n_2 \subset n_3$	n_4 $n_3 \subset n_4$	n_5 $n_4 \subset n_5$

Examples

Granularity

Species



Development

Canonicity

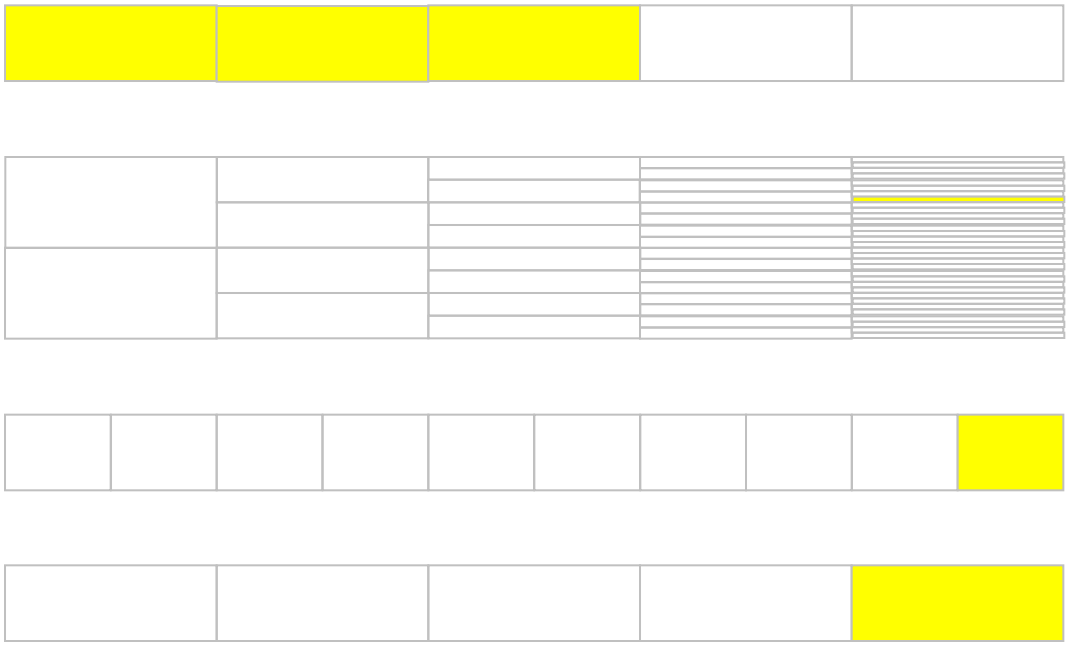
Coverage: Foundational Model of Anatomy

Granularity

Species

Development

Canonicity



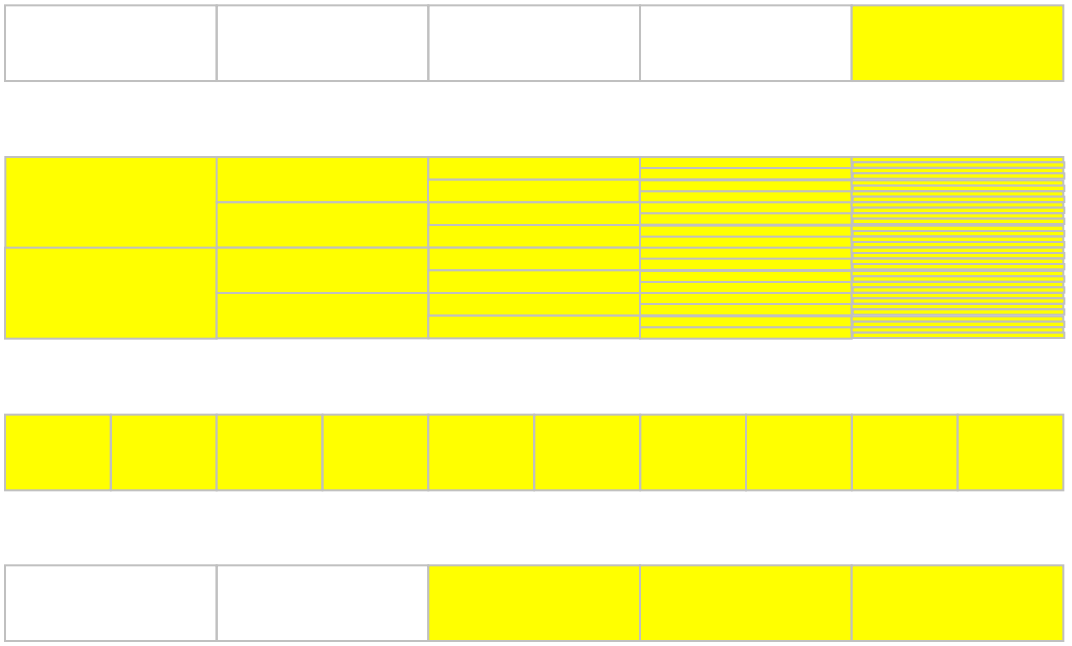
Coverage:
Gene Ontology

Granularity

Species

Development

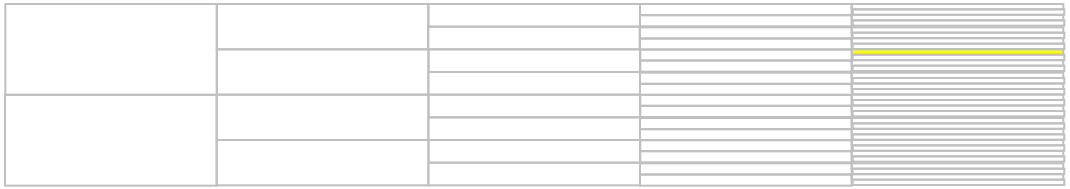
Canonicity



Coverage:
Mouse Anatomy

Granularity

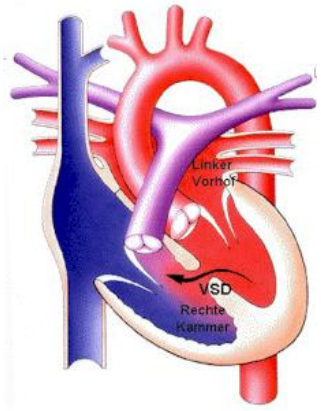
Species



Development

Canonicity

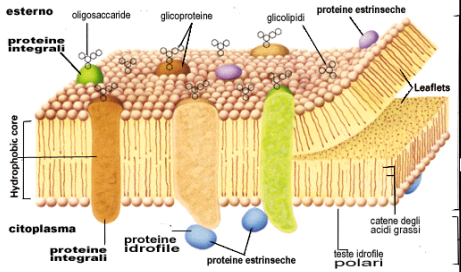
Examples



Connects(RightVentricle, Left Ventricle)

Granularity	**= normal**	**false**
Species	**= mammal**	
Development	**= adult**	
Canonicity	**= 4-5**	

Granularity	**= any**	**true**
Species	**= vertebrate**	
Development	**= early embryo**	
Canonicity	**= any**	



Is-A(Membrane, 3-D object)

Granularity	**= normal**	**true**
Species	**= any**	
Development	**= any**	
Canonicity	**= any**	

Granularity	**= lowest**	**false**
Species	**= any**	
Development	**= any**	
Canonicity	**= any**	

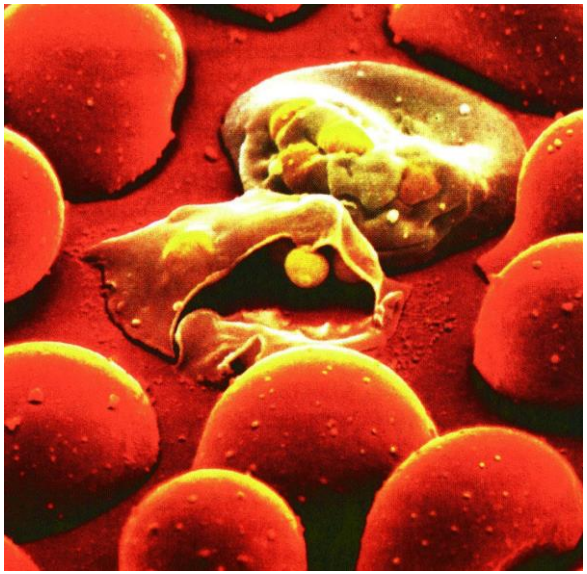
Conclusion

- Integration of bio-ontologies requires
  - Uncontroversial semantics of relations and attributes
  - Clear commitment to theories, such as granularity, species, development and canonicity
- Redundancy can be avoided
  - Encoding axioms at the highest common level in the species taxonomy (e.g. vertebrates, arthropods, primates) and benefit from inheritance in subsumption hierarchies

…requires sophisticated organization

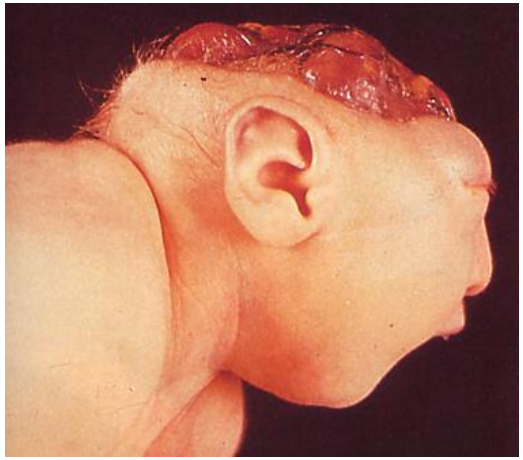
- Formalization and Standardization of Clinical Terminologies
- Basis for the Annotation of Genes and Gene Products
- Semantic reference for scientific communication
- Machine-supported reasoning and decision-support

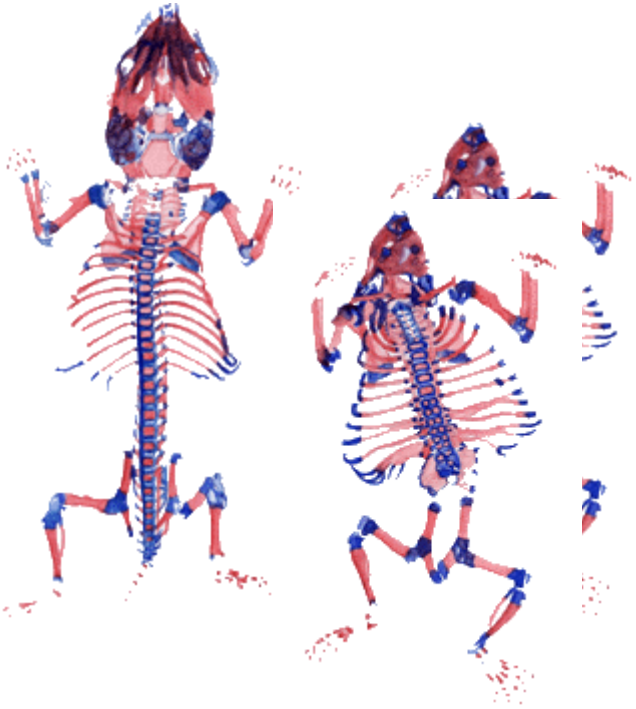
Bio-ontologies !

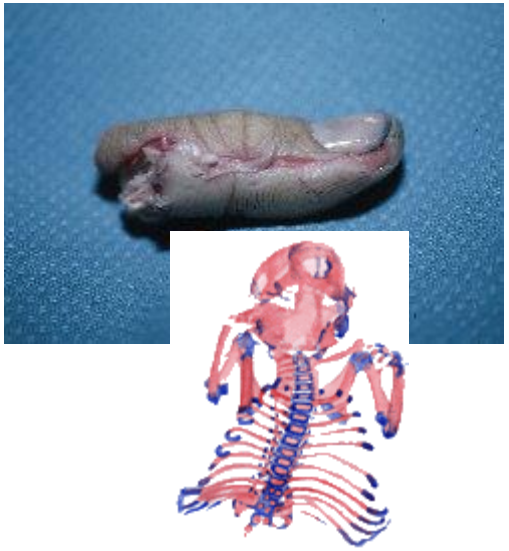


Upper level classification of entities

	Individuals (concrete objects)	**Universals (Concepts, Classes of Individuals)**
Continuants (physical objects,…)	• my left hand • a blood sample • a concrete cell	• Hand, • Blood • Cell
Occurrents (events, processes, actions…)	• Peter's diabetes • appendectomy of Patient #12345	• Diabetes mellitus • Appendectomy








w1118
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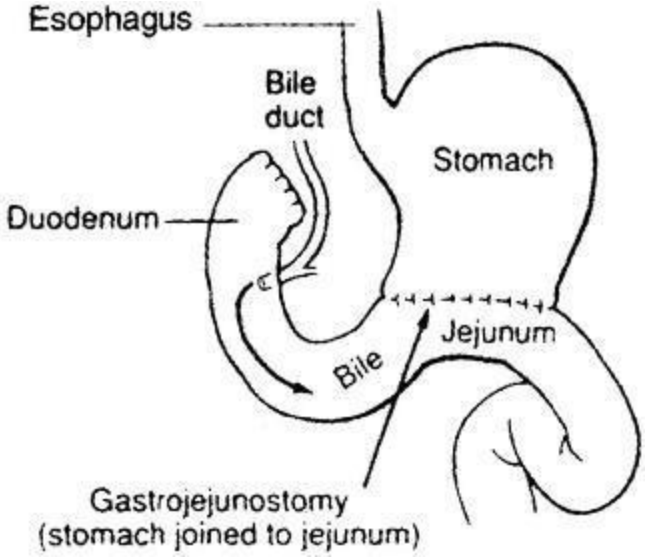
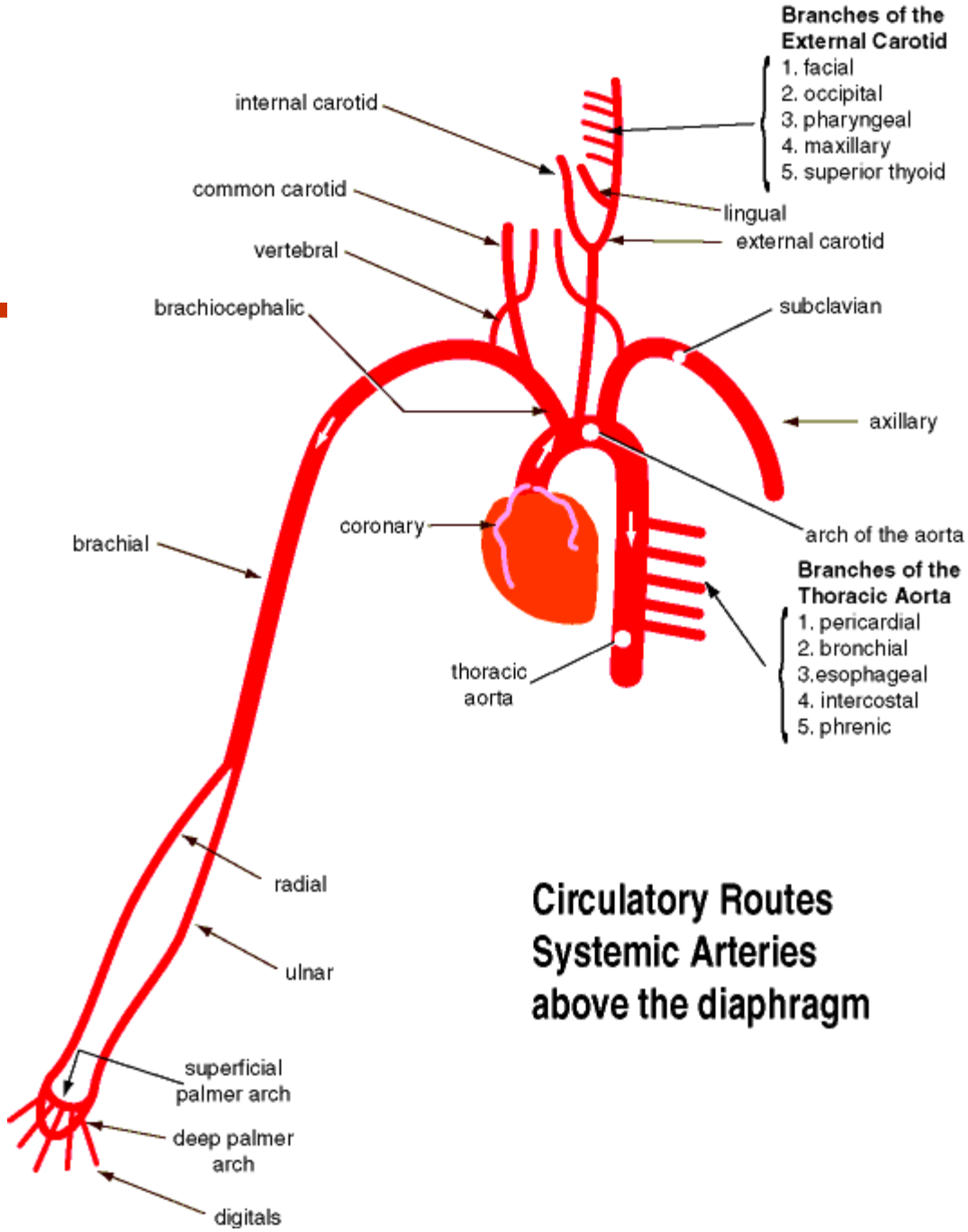

Esophagus
Bile duct
Stomach
Duodenum
Jejunum
Bile
Gastrojejunostomy
(stomach joined to jejunum)

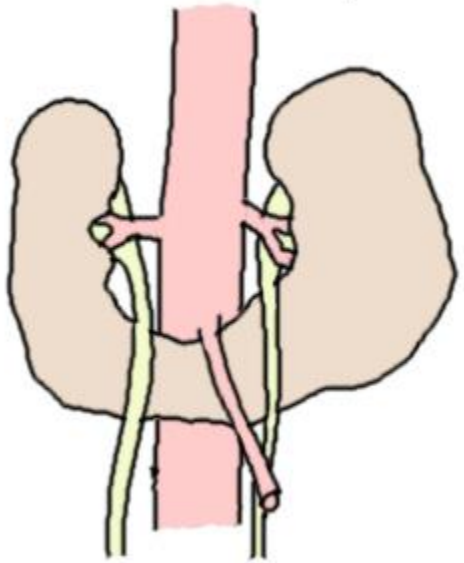


Circulatory Routes
Systemic Arteries
above the diaphragm

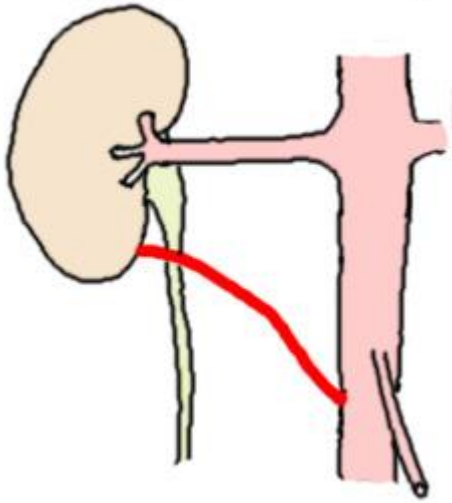

b
c


b

Horseshoe Kidney



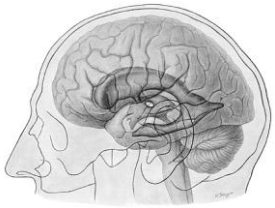
Accessory Renal Artery



Mereotopological Quiz

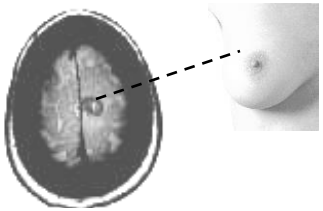
- Cranial Cavity *has-location* Head
  Is Cranial Cavity part-of Head ? ☺☹

- Brain *has-location* Cranial Cavity
  Is Brain part of Cranial Cavity ? ☺☹



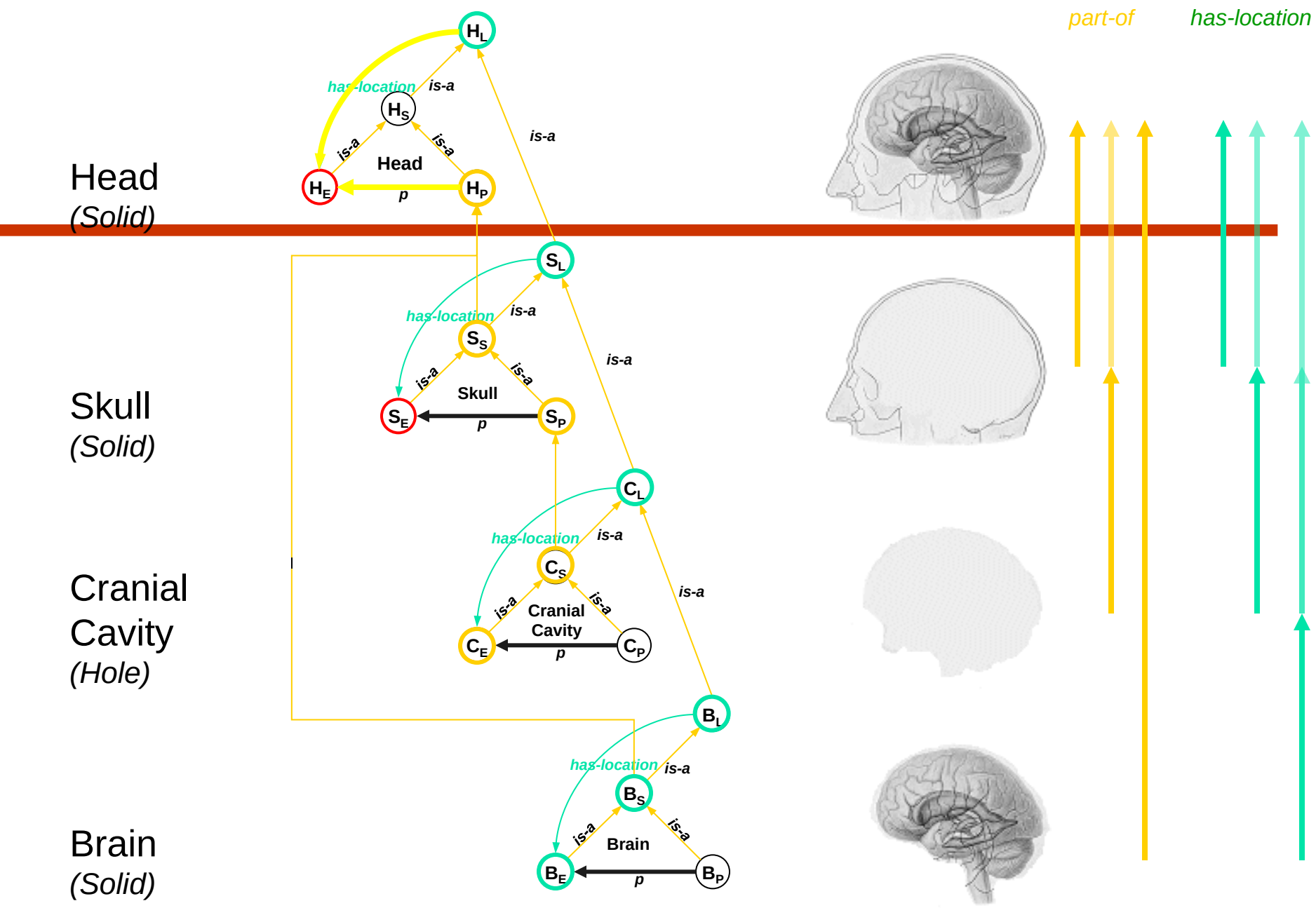
- Glioblastoma *has-location* Brain
  Glioblastoma part-of Brain? ☺☹

- Brain metastasis *has-location* Brain
  Brain metastasis part-of Brain? ☺☹



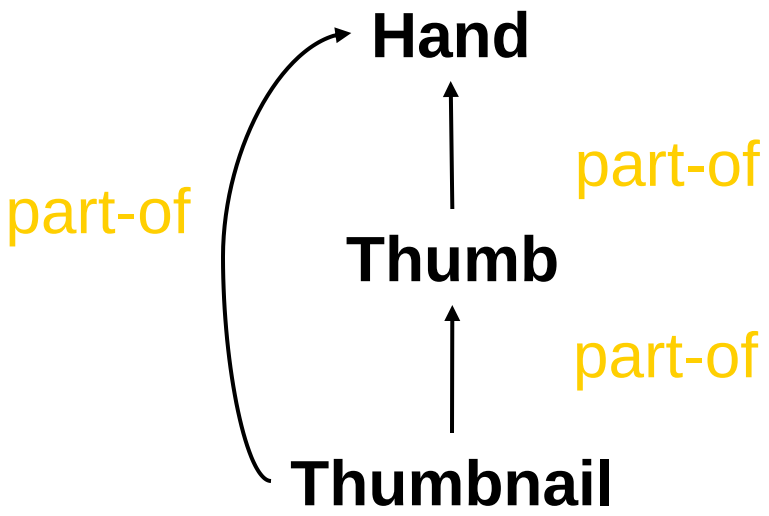
- Embryo *has-location* Uterus
  Embryo part-of Uterus ? ☺☹

Images from: Sobotta CD-ROM


part-of
has-location
Head
(Solid)
Skull
(Solid)
Cranial
Cavity
(Hole)
Brain
(Solid)
H_L
H_S
H_E
H_P
Head
p
S_L
S_S
S_E
S_P
Skull
p
C_L
C_S
C_E
C_P
Cranial
Cavity
p
B_L
B_S
B_E
B_P
Brain
p
has-location
is-a
transitive closure by taxonomic subsumption

Subtheories of an Ontology of Biological Structure

1. Taxonomy „is-a“ 2. Mereology „part-of“ 3. Topology „connection“

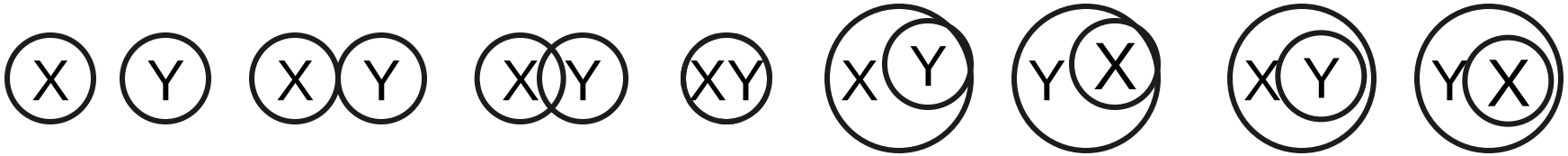


Subtheories of an Ontology of Biological Structure

1. Taxonomy — 2. Mereology — 3. Topology

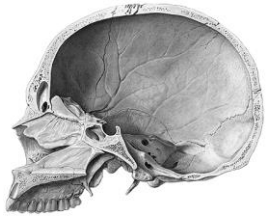
„is-a“ *„part-of“* *„connection“*

- Canonical relationships



(Schulz et al. AMIA 2000)

- Topological Primitives:

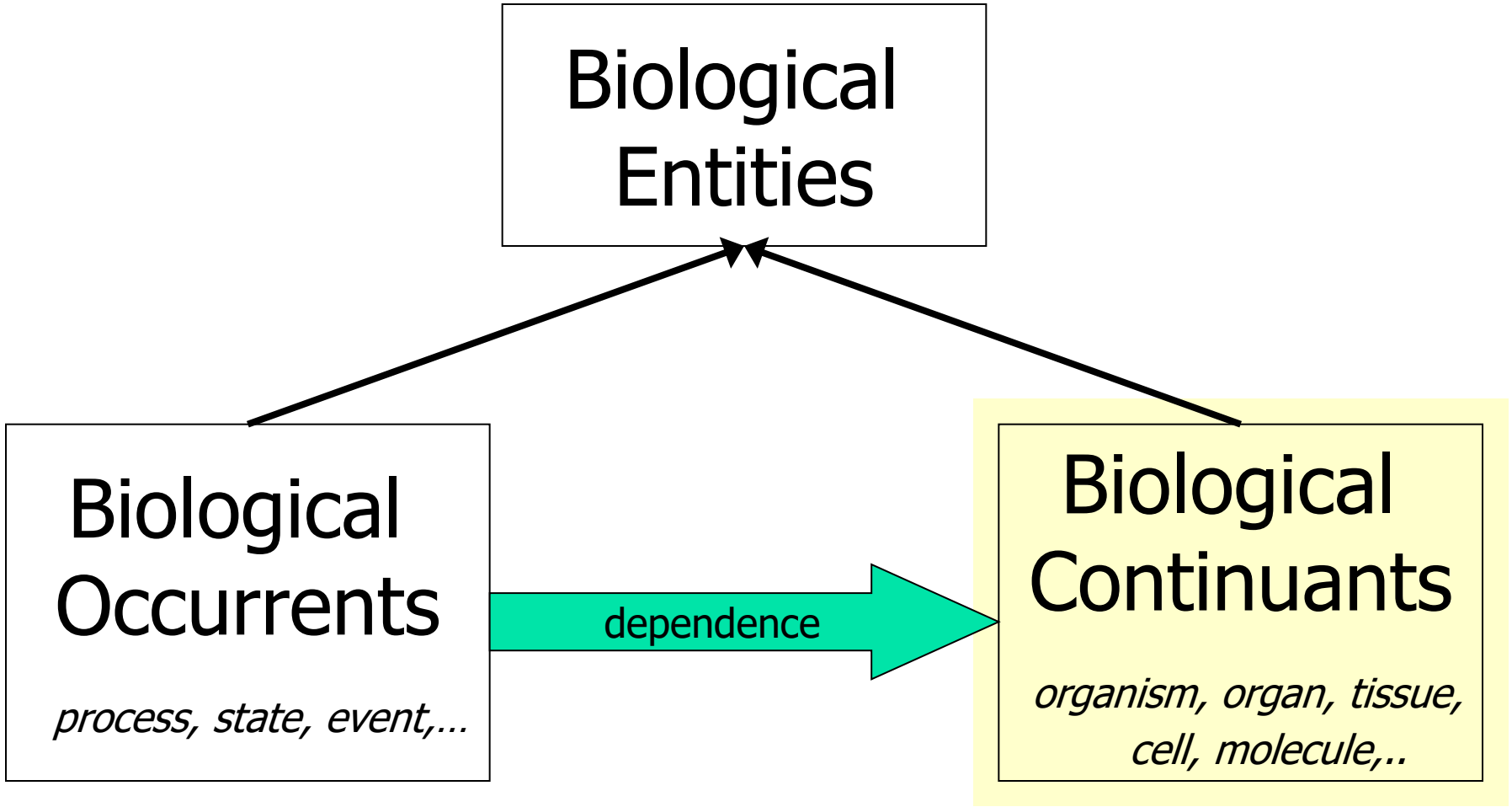


Structure of Talk

- Introduction
- Foundational Relations
- Foundational Attributes
- Theories
  - Granularity
  - Species
  - Development
  - “Canonicity”

The World of Life Sciences…

Generalized Representation of Living Systems: Top Level

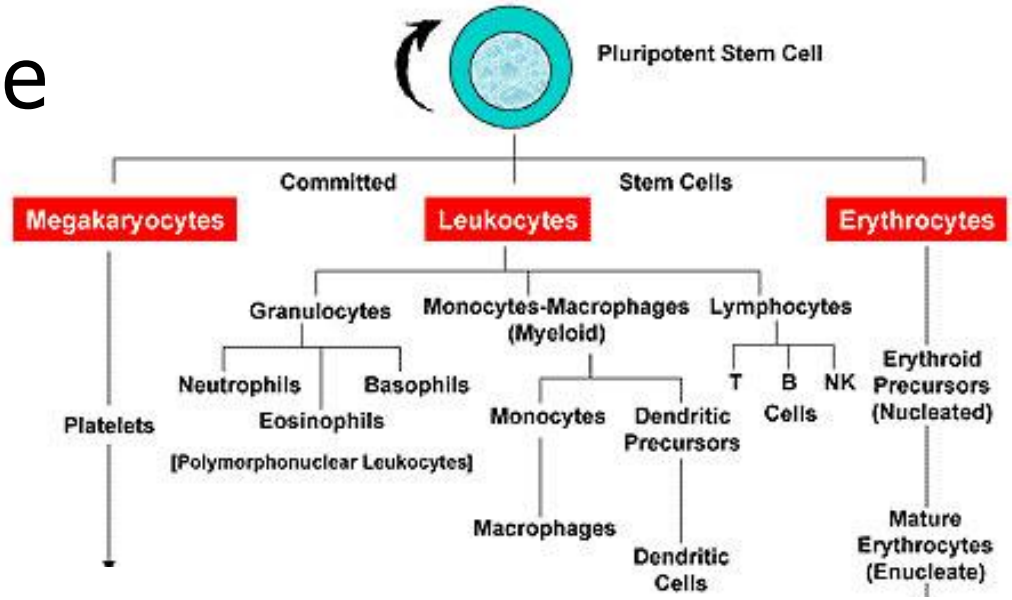


Ontological Account for Biological Continuants

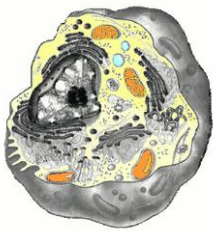
- Foundational Relations
- Foundational Attributes
- Theories
  - Granularity
  - Species
  - Development
  - "Canonicity"

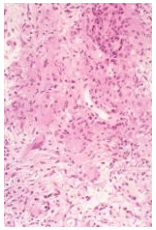
Granularity

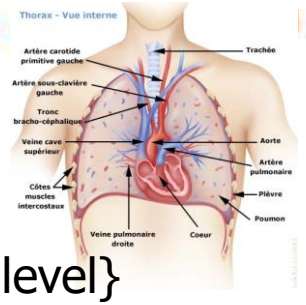
- Taxonomic: degree of specialization



- Mereologic: degree of dissection







{molecular level, cellular level, tissue level, organ level, population level}

Change in Granularity level may be non-monotonous

- Change of sortal restrictions:
  - 3-D $\rightarrow$ 2-D boundary
  - Count concept $\rightarrow$ Mass concept
- Change of relational attributions:
  - disconnected $\rightarrow$ connected
-