MANY-SORTED MODEL THEORY AS A CONCEPTUAL FRAMEWORK FOR SYSTEMS BIOLOGY

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An Early Application of Logic to Biology

- J. H. Woodger, *The Axiomatic Method in Biology* (1937)
- Took *Principia Mathematica* as a basis
- Presumes language of classes, relations and functions from the theory of types

Woodger (1937), cont'd

- Added ten basic predicates and relations, P, T, U,...
- "part of", "before in time", "organized unity", "related by divisions and fusions", "cell", "male", "female", "whole organism", "environment", "genetic property"

Woodger (1937), cont'd.

- Some of these notions apply only to cells, others only to higher organisms
- Formal explications of the concepts of gamete, zygote, allele, etc.
- Applications to Mendelian genetics

Barry Smith (et al.), Ontological Update of J. H.W.

- Formal ontology
- Mereology (theory of the part/whole relation)
- Criticism of Woodger: confuses formal notions (e.g., *part*) with biological notions (e.g., *cell*)

Smith, et al., cont'd

- Mereotopology: adds notions of *boundary* and *niche* (Smith and Varzi 1999)
- Incorporating *time* and *change* (Smith and Brogaard 2002)

Biological Systems, How Conceived I

- Taken as individuals: organized combinations of one or more cells
- Spatially bounded and genetically programmed to sustain themselves by drawing food, energy and other resources from the environment

Biological Systems, How Conceived II

- All biological systems whether singly or multiply celled consist of heterogeneous interacting materials
- Heterogeneity suggests the use of many-sorted model theory for the description of their structure.

Three Perspectives

- Bottom-up (chemical and genetic basis on up)
- Top-down (the systems and subsystems approach)
- Side-by-side (interacting subsystems, concurrent processes)

Many-Sorted Structures (aka Models)

- M= $(M_1,\ldots,M_n, R_1,\ldots,R_m, f_1,..,f_j, a_1,\ldots,a_k)$
- Signature σ with subsort relation
- Examples: typed hierarchies (simple, ramified, and cumulative); fields as vector spaces over subfields
- More examples: universes of operations and classes

Two Notions of Model

- A model in logic: a specific structure with specific objects, relations, etc.
- A model in science: a theoretical model of some part of reality

Theoretical Models

- Necessarily abstract and limited in scope, always subject to refinement
- There is no such thing as a complete model
- Scope of a model determined by aims, e.g. scientific, pedagogical, practical

Illustration: *Homo Sapiens*

- NB: Anatomy first, physiology later
- Top systems: musculoskeletal, nervous, respiratory, digestive, cardiovascular, endocrine, etc.
- Musculoskeletal subystem: skeleton, muscles, ligaments, tendons, etc.

Sorts and Subsorts for *Homo Sapiens* (expanded)

- Top sorts: Cells, Tissues, Organs, Organ Systems, Top Systems [preceding], Non-organic components
- Cells: bone marrow, muscle, blood, neurons,etc.
- Tissues: epithelial, connective (skin, cartilage, tendons, etc.), etc.

Sorts and Subsorts for *Homo Sapiens*, con't

- Organs: brain, heart, lungs, stomach, kidney, etc.
- An organ system--glands: thyroid, pituitary, hypothalamus, pancreas, etc.
- Non-organic components: water, oxygen, other gases, minerals, etc.

Adding Relations: Input and Output Relations

- For each constituent, tell what part of it admits input from the environment (e.g., fuel, information) and what part of it serves as output
- Tell for each what constitutes input and what forms output

Input and Output Examples

- Inputs for body as a whole: eyes, ears, nose, mouth, etc.
- Outputs for body as a whole: nose, mouth, urinary tract, rectum
- Heart inputs, outputs: veins, arteries
- Stomach inputs, outputs: esophagus, small intestine

An Aside: Organs as Black Boxes

- Given M of signature σ, restriction of M to a subsignature σ', $M|\sigma'$
- Organ as a black box: suppress all "internal" sorts that are specific to it
- Replacing an organ by another with the same inputs and outputs
- Examples: kidney transplant, artificial heart, appendix removal

Topological Relations

- Connectedness: "Dem bones...",
- Contiguity: liver and pancreas to stomach
- Boundary, interior, exterior: skin layers (dermis, epidermis, subcutaneous tissue)

More Relations

- Numbers and shape: numbers of teeth, how many of each kind, shape of jaw, etc.
- Orientation relations: left-right, anterior, posterior, etc.

Cf: The Foundational Model of Anatomy Project (FMA)

- Structural Informatics Group at the University of Washington
- http://xiphoid.biostr.washington.edu/fma/index.html
- "Over 120,000 terms, 168 relation types, 2.1 million relation instances"

Human Anatomy: Individual vs. Generic

- So far, just sortal-relational σ's
- Each individual human anatomy is given by a specific structure of sig. σ
- What is generic human anatomy?
- The 1st order theory of all adult human beings? Generic structures?

Comparative Anatomy

- Compare species S_1, S_2, sigs σ_1, σ_2, intersection σ
- Similarity notions $M_1|\sigma \approx M_2|\sigma$
- Possibility 1: Isomorphism
- Possibility 2: Elementary equivalence
- Possibility 3: Bisimilarity up to level n (n small)

Adding Constants

- For any specific M:
- Add Gender
- Add *The* heart, *the* lungs, *the* right kidney

Adding the Reals, Adding Time

- Add the reals as a basic sort
- Index M as a function of time
- Real valued time dependent constants: age, height, weight, blood pressure, temperature, white and red blood cell count, pH, etc.

Adding Functions

- Physiological vs. Mathematical Functions; the latter in signature
- Physiological function of the kidney: remove waste products from blood
- Mathematical function of the kidney: urine out as a function of blood in
- Heart: pump blood/contract-expand

To Explore

- Homeostasis as recursion theoretic fixed point
- Complexity notions for many-sorted structures with concurrent operations
- Physiological development: from embryo on [from zygote on??]

Other Approaches: Some References

- A. Burger et al., eds. (2008), *Anatomy Ontologies for Bioinformatics*
- C. Rosse and J. L.V. Mejino, Jr. (2008), The foundational model of anatomy ontology, in Burger (2008), 59-117
- B. Smith (2005), The logic of biological classification and the foundations of biomedical ontology (Proc. 10th ICLMPS, Oviedo, 2003)

Other Approaches (cont'd)

- B. Smith, et al. (2007), The OBO Foundry: coordinated evolution of ontologies to support biomedical data integration, *Nature Biotechnology 25*
- R. Winther (2006), Parts and theories in compositional biology, *Biology and Philosophy* 21
- R. Winther (2011), Part-whole science, *Synthese* 178.

The End