

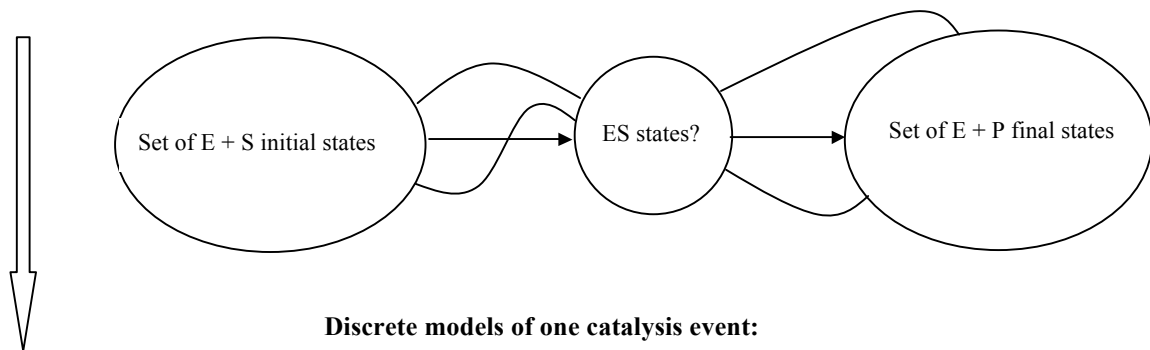
Difficult Concepts in Systems Biology II: Levels and Reductions

1.10.2008

Motivation. System Biology is very much in the vogue. This is partly because full modelling of biological systems is now a possibility. The literature of systems biology has elements that are very well defined, such as the different forms of high throughput data, knowledge of biological structures and dynamical modelling. Moreover, there are concepts at work here like “robustness”, “complexity”, “redundancy” and “evolvability” that can be used in a sloppy fashion, but can also be defined properly with a little effort. However, this literature is also dominated by concepts that can only be described as elusive and that in many contexts appear unnecessary. Such concepts are “Life”, “Function”, “Emergence”, “Purpose”, “Modularity”, “Reduction”, “Interpretation”, “Level”, “Analyzability”, “Explanation”, “Understanding”, “Cause” and “Disease/Dysfunction”. There are most likely others. These concepts are problematic since they are frequently used by the majority of the bio-science community, but there is no consensus about their definition or even their necessity or irreducibility. We will define a series of projects with the primary aim of clarifying these concepts. (Cautionary note: The literature on the topic is extensive and the articles often appear in philosophical journals. The articles read should be chosen with serious care to avoid being overwhelmed.)

Biological Levels and Reductions. Biological concepts are frequently arranged in levels, where the concept at one level (for example, an enzyme) is autonomous in the sense that its behaviour (as described by Michaelis-Mentens’ constant, for example) can be summarized with properties that do not need reference to lower levels (for instance its constituent atoms). These concepts and levels are naturally defined during biological research and this process is not part of an explicit meta-scientific program, although these concepts are often central to such debates. For example the distinction between levels is a necessity both for modelling and for understanding. Using kinetics to describe enzyme behaviour instead of molecular dynamics allows an acceleration of more than 8 orders of magnitude in calculations. Using the concept “enzyme” allows a much lower dimensional representation that can be handled intellectually in contrast to a more complete description, in many cases humanly inaccessible.

A molecular dynamics sample path involving one catalysis event:



Discrete models of one catalysis event:

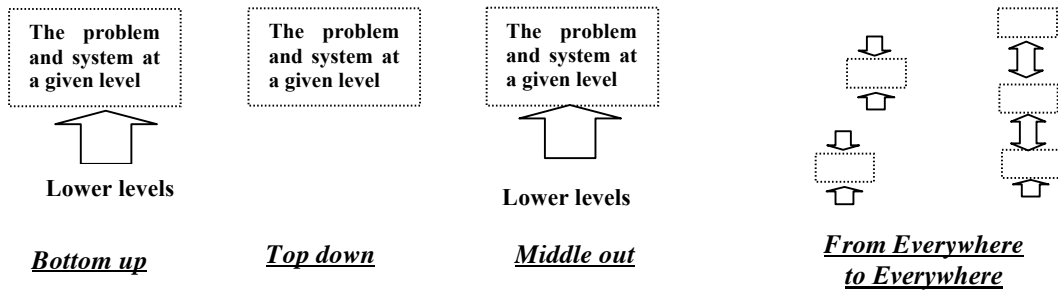


The first models of enzymatic action were published in the first decades of the 20th century by Michaels, Menten, Henry, Haldane and others. These are models with a few states and interactions and lead to simple equations allowing explicit analysis of their dynamics. It is clear that the real picture is vastly more complicated and has started to be analyzed only in the last decade of the 20th century by molecular dynamics. A naïve MD simulation could have 10^3 - 10^4 atomic positions (enzyme, substrate, water and ions) and would in principle be simulated for 10^9 steps of 10^{-15} second duration. Clever techniques such as Transition Path Sampling (Bolhuis et al, 2002) can improve significantly on this and force dynamic trajectory toward a desired end state and still allow rates to be calculated and identification of key interacting groups.

Making discrete approximations have also been applied to other complex molecular events such as protein folding (Fersht, 2004). These are simple illustrations of events and objects formulated at different levels. As computational modelling becomes increasingly dominant in biology, stringent definitions of levels, objects and their dynamics could be increasingly necessary.

Levels are partially ordered since objects in one can consist of many objects from a lower level. This has led to characterisations of the approaches to modelling. *Bottom-up* will start with thorough descriptions of low level and move to higher levels always explaining higher level objects in terms of lower level objects. This approach is also often called reductionism. *Top-down* is used in biology, when the function of an object (for instance a network) is assumed known and lower level (for instance a specific enzyme in the network) is then explained by serving a purpose at the higher level. Sydney Brenner and Denis Noble (Noble, 2006) often describes much practical modelling as *middle-out* in the sense that one starts at the level of interest and refers of lower levels for reductionist explanations and to higher levels to establish purpose.



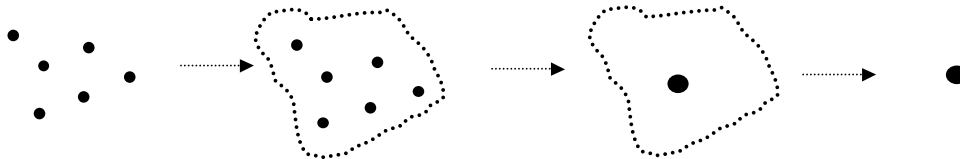


In systems biology and the analysis of throughput data, there is often a lack of an initial driving question and an emphasis on global modelling where top-down and bottom-down approaches will be applied simultaneously at many levels in an approach that could rather be called from everywhere to everywhere.

Physical-chemical, Stochastic and Dynamical Modelling Techniques. Due to the size of biological systems modelling is done at many levels: Quantum Mechanical for small sets of atoms involved for instance enzymatic reactions; Classical Force Fields for motions and interactions of molecules involving hundreds to many thousands of atoms; Stochastic Chemical Kinetics for reactions involving tens to a thousand molecules; and Deterministic Kinetics for larger number of molecules. Kinetic Models are often combined to integrate network models used to describe a regulation, metabolic pathways and more. Diffusion Models describe transport and thermal noise in biological systems.

Biological Systems are physical systems, and physics has a hierarchy of models. Berendsen (2007) describes one eleven-level hierarchy starting with relativistic quantum dynamics and ending with steady flow fluid dynamics. There is not easy identification between biological hierarchies and physical hierarchies, although they do intersect and some biological objects can be identified with naturally defined physical objects. Biological concepts are partially historical constructs, where certain entities have been elevated to the status of "biological object" and its behaviour described and predicted by useful rules and equations.

Defining or recognizing Biological Objects



For computational and conceptual reasons it is convenient to identify a series of objects (for instance atoms or molecules that can be view as a unit with properties that can be defined from the component. Often this is straight forward – a molecule is a set of atoms bound by covalent bonds and a concentration is the number of a specific type of molecule per volume. In other cases it can be harder and the quality of modelling is at risk as when coarse graining in MD simulations.

Since all biological objects are physical a reduction is possible in principle, but can be computationally prohibitive or even detrimental as it would erase central qualities in its biological definition. In modelling biological objects a series of essential decisions has to be made. As systems biology typically involves many levels, models can be mixed and typically are. Useful models arise in a trade-off between tractability and reductive realism, so experience or testing can allow certain aspects to be simplified to, for instance, Boolean networks, if the underlying model is sufficiently switch-like. The complexity of integrated models is no virtue and regaining the simplicity of single-level models is often attempted by observing that the dynamics of different levels occur at very different scales where fast dynamics levels can be assumed to be at equilibrium relative to boundary conditions determined by slow dynamic levels. Recently Ball et al. (2006) have also used multi-level models for enzymatic reactions, where the stochastic dynamics moves between different for instance Poisson and Diffusion Processes dependent on the number of molecules in the system.

Project Goals

- Read key literature.
- Find examples of reductions in biology. Find and discuss specific examples of reductions and the size of the systems necessary to them to appear. This will imply independent critical literature search.
- Computational aspects of reductions. Formulate simple dynamical models and investigate the probability of the standard emergent properties. This could for instance be done by sampling linear dynamical systems (Hirsch et al., 2004) and asking what is the probability that a random dynamical system possesses stability, robustness, oscillations,....
- Automatic search for reductions.
- Answer the question: 'Is the concept of reductions necessary and useful?'

Some Key Philosophical Literature

Couch, M.B. (2005), "Functional properties and convergence in biology", *Philosophy of Science* 72:1041–1051.

- Craver, C.F. (2005), "Beyond reduction: mechanisms, multifield integration and the unity of neuroscience", *Studies in History and Philosophy of Biological and Biomedical Sciences* 36:373–395.
- Craver, C.F., and W. Bechtel (2007), "Top-down causation without top-down causes", *Biology and Philosophy* 22:547–563
- Delehanty, M. (2005), "Emergent properties and the context objection to reduction", *Biology and Philosophy* 20:715–734
- Dupré, J. (1993), *The disorder of things: metaphysical foundations of the disunity of science*. Cambridge, MA: Harvard University Press
- Jaeger, G., and S. Sarkar (2003), "Coherence, entanglement, and reductionist explanation in quantum physics", in A. Ashtekar, R.S. Cohen, D. Howard, J. Renn, S. Sarkar and A. Shimony (eds.), *Revisiting the foundations of relativistic physics: Festschrift in honor of John Stachel*, Dordrecht: Kluwer, 523–542.
- Kim, J. (1992), "Multiple realization and the metaphysics of reduction", *Philosophy and Phenomenological Research* 52:1–26.
- (1998), *Mind in a physical world*. Cambridge, MA: MIT Press.
- (2005), *Physicalism, or something near enough*. Princeton: Princeton University Press
- Nagel, T. (1998), "Reductionism and antireductionism", in G.R. Bock and J.A. Goode (eds.), *The limits of reductionism in biology*, Chichester: John Wiley & Sons, 3–10.
- Noble, D. (1998), "Reduction and integration in understanding the heart", in G.R. Bock and J.A. Goode (eds.), *The limits of reductionism in biology*, Chichester: John Wiley & Sons, 56–72.