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A reductionist's systems biology

Opinion

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To tackle the complexity inherent in understanding large networks of interacting biomolecules, systems biology emphasizes cybernetic and systems theoretical approaches. The resulting focus on organization independent of physical manifestation threatens to throw away all that has been learned from molecular studies and ignores the reality that biologists are drawn together more by a shared interest in mechanism and structure than anything else. The field of reaction engineering suggests a reductionist approach to systems biology that fits easily within existing molecular paradigms but that can nonetheless be integrated into expansive physiological perspectives through the use of multi-scale modeling.

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Cybernetics, systems theory and systems biology

The emergence of systems biology [1] as a new discipline leaves many cell and molecular biologists unconvinced. Molecular biology emphasizes reductionist approaches to carefully delineated problems on the premise that important insights derive from deep mechanistic understanding. Molecular approaches also find practical application in mechanism-based drug discovery [2]. Systems biology, with its apparent emphasis on superficial analysis of large numbers of components, seems to discard the mechanistic view in favor of sweeping observations about networks and pathways. The well-developed field of reaction engineering suggests a future program for a 'reductionist systems biology' that should be more congenial to those of us with molecular training. Fortunately, reductionist (or bottom-up) approaches can be linked to cybernetic and systems-theoretical (top-down) approaches to yield multi-scale models combining detailed mechanism and wide biological scope [3].

Systems biology, as we use the term here, refers to the study of biology using a combination of mathematics, computation and empirical observation. The aim is to build numerical models of biological processes and test the models experimentally. The numerical emphasis is important, because only mathematical models have the power to capture dynamic behaviors of large sets of interacting components. Detailed knowledge of the parts of a system usually provides only limited insight into the dynamics of the system as whole. Systems biology, with its emphasis on formal numerical modeling, breaks with the tradition in genetics and molecular biology of anecdotal and pictorial models. The experimental emphasis in systems biology is also critical (and occasionally underappreciated), because it is only through experimentation that we can determine whether models accurately describe real biology. The experimental emphasis in systems biology distinguishes it from theoretical biology.

The analysis of biological phenomena in terms of cybernetics and systems theory traces its origins to Weiner [4] and von Bertalanffy [5] and has gained recent prominence through the work of Alon [6] Kaufmann [7] and others. Cybernetics and systems theory play a critical role in communications and computer design and it is natural to draw comparisons between information transfer in biology and electronics [8,9]. Moreover, systems theory provides a formal framework in which to study the structure of biological circuits in terms of error-correction, feedforward loops, bi-fans etc (e.g. [10,11]). However, the analogy is fraught with difficulty, not the least of which is that electronic circuits are designed whereas biological circuits have evolved. In a designed circuit the connectivity is known and well-defined abstraction layers are used to mask complexity as the system gets larger. In contrast, the connectivity of biological circuits remains largely unknown and methods to abstract design principles from known pathways are in their infancy. Indeed, the emphasis in systems theory on organization independent of instantiation (particular occurrences; see [12]) stands in marked contrast to the role that biomolecular structure and chemistry play in uniting geneticists, biophysicists and cell biologists.

Linking biomolecular and systems approaches

The branch of chemical engineering known as reaction engineering [13] fits well into the world-view of most cell and molecular biologists. Reaction engineers build and apply predictive numerical models of chemical reactions,

typically with the aim of controlling industrial processes. The chemical structures, concentrations, key kinetic constants, transport relationships and interactions of components are not known *a priori*, but must be determined empirically. Spatial distributions of reactants are critical in chemical systems as they are in biological systems. Moreover, reaction engineers retain a keen interest in the chemical properties of individual reactants, in part because *ab initio* calculation of thermodynamic and kinetic parameters is possible (something that is still not possible with most biomolecules). Mass action kinetics in physicochemical models are typically represented as a series of linked algebraic or differential equations (ordinary differential equations [ODEs] and partial differential equations). In a compartmentalized ODE network, chemical modification, assembly of multisubunit complexes and transport between compartments are all elementary 'reactions' to which rate equations are assigned. In chemical systems, reaction networks yield remarkable insight even when the system is only partially understood; physicochemical networks also appear promising in biological applications [14–17]. Of course, showing that the resulting numerical model is a good fit to experimental data, sensitive to important biological variables and unique with respect to topology is non-trivial. The model is subject to all of the errors and uncertainties in the underlying assumptions. Importantly, however, the process of creating a reaction network is intuitive for molecular and cell biologists (even if the mathematics is largely forgotten) and brings to the forefront assumptions and uncertainties that remain hidden in pictograms.

Drawing an analogy between systems biology and reaction engineering illuminates a number of interesting issues. First, far from being data-rich as often claimed, biology is extremely data-poor — particularly in terms of quantitative, time-dependent and spatially resolved measurements. It is not unusual for a reaction engineer to monitor a dozen or more critical reactants with millisecond resolution; in contrast, measuring the activities of a dozen kinases in a mammalian signal transduction circuit at even a few time points represents a major task for a PhD-level biologist. As a consequence, self-consistent, systematic experimental data sets are largely non-existent. Virtually all data, save gene and protein sequences, are verified only locally through the use of contemporaneous controls. Large-scale functional genomics lacks the emphasis on cell dynamics and rich data types necessary to solve this problem. Instead, it seems likely that truly informative systematic data sets can be developed only through the combined efforts of the general research community.

Second, it is almost certain that sharing biological models will become more important (and more interesting) than sharing data. Accurate models are much more effective, compact and portable as representations of dynamic processes than raw data itself. The pioneering work of Kee and the Sandia Combustion Research Facility [18,19] demonstrates how models can be shared across a community through the use of a common language and also evolve to encapsulate growing knowledge. As standards for sharing biological models are worked out, one can easily imagine biologists maintaining updated models of the processes they work on. This very prospect recently led to the creation of a new National Cancer Institute program in Integrated Cancer Biology [20].

Unification through multi-scale modeling

The reaction-based view of systems biology is appealing in its emphasis on mechanism and dynamics, but lacks an expansive genome-wide perspective. It is also ill-suited to describing the overall physiology of cells and organisms in which many reactions remain unknown. Multi-scale modeling comes to the rescue in the case, making it possible to fuse detailed reaction-based and large-scale systems-theoretical views of a complex process. Multi-scale models can also integrate information at different length and time scales, from proteins to cells and cells to organisms, while capturing both continuum processes (e.g. an abundant kinase phosphorylating a substrate) and discrete stochastic processes (the eventual effect on cell proliferation). Mathematical models of the human heart represent a beautiful example of integrating biochemistry and physiology using numerical methods, and the models are already influencing patient care [21].

Historically, some molecular biologists have preferred to work at the level of atomic-resolution structure and others at the level of whole-animal physiology. Both are equally valid and there is no reason to believe that this divergence of interest will disappear. However, in the future, the exciting possibility exists that detailed molecular study of biological reactions will proceed within the framework of multi-scale models that summarize knowledge of the broad biological context in an accurate and quantitative manner. By fusing cybernetic and reaction-based views of biological processes, systems biology will make it possible to tackle classic 19th century problems in physiology and disease with 21st century molecular technologies.

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