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Mini-Review

Systems Biology: To Meet Challenges for Biology in the Twenty-first Century

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Genomics, structural biology, and bioinformatics deal with identification, cataloguing and characterization of the components that make up a cell. The focus on individual genes and proteins, which has proven so powerful for the molecular genetics in the past century, is in itself inadequate to describe the dynamic processes involving interactions among tens, hundreds and even thousands of components. Cell function, including growth, differentiation, division, and apoptosis, are temporal processes and we will only be able to understand them if we treat them as dynamic systems. There is a general agreement that systems approach is necessary to understand the causal and functional relationships that generate the dynamics of biological networks and pathways.

Reductionism, which has dominated last century biological research in molecular biology, has provided a wealth of knowledge about the components of the cell to describe its structural organization and their functions. Despite its enormous success, it is increasingly clear that a discrete biological function can only rarely be attributed to an individual molecule. Instead, most biological characteristics arise from complex interactions between the cell's numerous constituents, such as proteins, DNA, RNA and small molecules. Therefore, a key challenge for biology in the twenty-first century is to understand the structure and the dynamics of the complex intercellular web of interactions that contribute to the structure and function of a living cell (Sontag., 2005; Mesarovic and Sreenath., 2006; Wolkenhauer., 2003). Complex systems display properties, often called "emergent properties," that are not demonstrated by their individual components and cannot be predicted even with full understanding of the components alone. A comprehensive understanding of such emergent properties requires systems-level perspectives and cannot be gleaned from simple reductionist approaches (Bhalla and Iyengar., 1999).

Molecular Networks are Dynamical Systems

The capacity of a cell to change in space and time is crucial to survival and reproduction. The dynamic properties of a cell are implicit in the topology of the metabolic, signaling and transcription-regulatory networks (Dibrov *et al*., 1982; Dibrov *et al*., 1982; Lauffenburger, 2000). These networks of interacting molecules are intrinsically dynamic: they describe how a cell changes in space and time to respond to

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stimuli, grow and reproduce, differentiate, and do all the other remarkable tricks that are necessary to stay alive and perpetuate the species (Olaf Wolkenhauer and Mihailo Mesarovia 2005). In the past year, many prominent molecular biologists have pointed out the pressing need for theoretical and computational tools to show the spatial and temporal organization implicit in the way that macromolecules are 'wired together' to create a living cell. The wiring diagram of molecular networks implies a set of dynamic relationships among its components and, therefore, demands to be converted into a set of mathematical equations that describe the temporal and spatial evolution of the system (Wolkenhauer *et al*., 2005; Cho and Walkenhauer., 2003).

Mathematical Modeling as Central Component in Systems Biology

Human minds are incapable of inferring the emergent properties of a system from thousands of data points, but we have evolved to intelligently interpret an enormous amount of visual information. The data is therefore transferred to visualization programs. Formulation of detailed graphical or mathematical models, allows us to formalize and integrate existing knowledge in a precise way, providing formal methods of analysis, and therefore forms a central component in systems biology (Heinrich *et al*., 2002).

There are two main modeling approaches in systems biology. One is construction of large-scale models, incorporating as many details as have been uncovered experimentally on a given pathway or signaling system and on a detailed cartography of various networks, another useful approach in systems biology is construction of small-scale models of limited complexity, containing a reduced number of variables (2 to 20), and aiming at addressing specific questions (Hlavacek *et al*., 2006). From these small-scale models, one can often derive conclusions of more general significance, e.g. concerning cellular rhythms, cell signaling and cell cycle dynamics, especially when including dynamic phenomena: multi- stability, oscillations, spatial and spatio-temporal patterns (e.g. in morphogenesis and cell to cell communication) (Lauffenburger, 2000; Tindall *et al*., 2008). Both approaches have merits and limitations, and they can converge by putting small-scale models (modules) into a common framework. Model standardization is vital, but should not be used to suppress creative approaches. Models should also be closely tied with existing and new experimental data (Eungdamrong and Iyengar, 2004).

Differential Equations to Study the Dynamics of Biochemical Networks

Differential equations have been one of the most widely used mathematical modeling techniques in systems biology (Dibrov *et al*., 1982). In this approach, the state of the biochemical networks is expressed in terms of concentrations of its molecular species, which are positive real numbers. Mathematical model representing temporal dynamics of the biological system is obtained using mass balance. The differential equations represent the growth / decay of the concentrations of various species with respect to time (Wolkenhauer *et al*., 2005). The solution of differential equation is obtained using appropriate initial conditions giving the concentrations of molecules at any given point in time. Models employing differential equations can be grouped into three subgroups:

- Pure chemical kinetics systems completely disregarding any spatial aspect

- Compartmental models couple a set of non-spatial systems in order to achieve a coarse grained spatial resolution
- Diffusion-reaction systems exploit fine - grained spatial information

If the system under consideration can be assumed as a well-stirred reactor, one can ignore spatial aspects and use ODEs only. The basic dynamic equation describing the change in concentration C of a molecular species is obtained as

$$\frac{dC}{dt} = (generation) - (consumption)$$

The term on the right hand side sums up all effects of reactions producing C minus the effect of all reactions consuming C. Such equations are developed for each component (molecular species) of the system. Generally, the system of equations so obtained is coupled and nonlinear. Analytical solution of a nonlinear coupled system of ordinary differential equations with suitable initial conditions is not possible always. Numerical techniques are used to solve the differential equations (Olaf Wolkenhauer and Mihailo Mesarovia, 2005; Sundaramurthy P and Sunita G, 2010). The ODE formulation from a biological context is relatively easy and numerical methods for solving them are well developed. Therefore, ODE models are heavily used in modeling biochemical networks (Cho and Wolkenhauer, 2003).

In the second approach, cell is divided into several compartments. For each compartment, a set of ODE are developed to describe the dynamics in the compartment of the cell. Fluxes across various compartments are then specified. In this framework, the state variables are still functions of time only and issues related with space can be coarsely resolved using compartments keeping the computational advantages of the non-spatial approach (Suresh Babu *et al*., 2006).

In contrast, partial differential equations (PDEs) address spatial variations explicitly. The concentration now depends on both time and space, where movement in space is separated into diffusion and convection:

$$\frac{dC}{dt} = D\frac{\partial^2 C}{\partial x^2} - v\frac{\partial C}{\partial x} + (generation) - (consumption)$$

This framework allows to model phenomena like wave propagation and pattern formation, but it heavily increases the computational effort required for solving the equations. In the context of biochemical networks, PDEs are currently used only to model spatial processes explicitly.

Stochastic Modeling

Due to the small number of molecules involved in some biochemical networks, their approximation as continuous processes via differential equations cannot always be valid. In contrast to analytical approach, stochastic models explicitly account for the uncertainty that is involved in molecular processes, and allow making predictions not only about the average behavior of a system, but also about its standard deviation from that behavior (Steven *et al*., 2004). However, this knowledge comes at a cost: stochastic processes tend to be more expensive to simulate on a computer, and their mathematical analysis is usually not straightforward.

In stochastic modeling, two fields can be distinguished. On one hand, stochastic simulation algorithms (SSA) have been developed in which reactions have associated kinetic rates depending on the concentration of their substrates, similar to ODE models (Ullah and Wolkenhauer., 2009). Here, the kinetic rate of reaction is interpreted as the probability of its reaction taking place in a certain time interval. On the

other hand, biochemical systems have been interpreted as Markov chains, in which the state of the chain is represented by the number of molecules present, and reactions are modeled as transitions between these states (Dominic *et al*., 2006). As long as there is no feedback in the system, the analysis of Markov chains is well developed and information can be gained on the steady state probability distribution of the process. Feedback, which is an inherent feature of many biochemical networks, poses problems for the analysis since a steady-state distribution of the system does not have to exist in this case (Steven *et al*., 2004).

Scope, Limitation and Conclusion

Systems biology is a comprehensive quantitative analysis of the manner in which all the components of a biological system interact functionally over time. Impressive advances have been made in modeling a number of individual processes in immunology, physiology, development, and neurobiology. Increasingly however, modeling of molecular processes, involving most or all genes, gene products and metabolites is being used to understand complex disease processes. Knowledge of disease-perturbed networks will facilitate drug discovery, and pharmacological intervention will focus on preventing disease-mediated transitions. This predictive and preventive medicine will lead naturally to personalized medicine, in which therapeutic strategies will be tailored to individual needs. In this sense, systems biology will fundamentally transform society.

While during these genomics and bioinformatics tasks we indeed encounter "large volumes of data", in systems biology and particularly cell signaling, it is often the lack of quantitative, sufficiently rich time course datasets that is a, if not the major, problem (Harsharani et al., 2005). Parameters such as enzyme concentrations and reaction rates vary from cell to cell, even among cells of the same type. Some of the parameters available in the literature are based on rough guesses or on data from different and perhaps inconsistent sources, and usually are obtained from in vitro experiments. In cell modeling, models should not depend on tight values for parameters. One should avoid "pseudo-exactness," which is meaningless in that context. Only models that display desired behaviors over relatively large ranges of parameters can be valid.

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