In Silico Cell Signaling Underground

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Signaling was somewhat an underground topic at the recent International Conference on Systems Biology at the Karolinska Institute in Stockholm, Sweden. The meeting focused on mathematical and computational modeling of biological systems (*1*). The topics of the oral presentations were diverse, including modeling cis-regulatory logic, inter- and intracellular gradients, gene networks, chemical pathways, localization of proteins in the cell, and theoretical foundations. But the posters demonstrated a large and healthy swell of interest in modeling and simulating various aspects of cell signaling. These posters are the focus of this review.

Signal transduction is a complex process that can be better understood by modeling the processes and computing the dynamics. The simulated dynamics can then be compared with experimental data. If experimental data match the in silico predictions, we gain a useful confirmation of the model. If there is only a partial matchup, the modeler can go back and modify either the model or numerical parameters within the model. These cycles of modeling and experimental validation gradually result in the convergence of the model's predictions with the measured parameters of the natural biological system. However, there is a deeper reason to use computational modeling for complex biological processes like cell signaling. The very process of formalizing a biological process forces a new perspective on the subject matter. One can no longer tolerate intuitive, vague models. One is forced to look at the consequences of theoretical assumptions. In other words, the process of mathematical and computational modeling can lead to a deeper understanding of the structure and dynamics of signal transduction.

Modeling in general, and signal network and transduction pathway modeling in particular, can be done at different levels of abstraction and ontology. The focus of interest influences the model as well. Some models of cellular signaling processes are created with more abstract, less detailed views in mind. For example, some use Boolean networks and rules to describe global properties of a signaling network or signal transduction pathway, whereas others use a much more detailed approach such as ordinary differential equations (ODEs) to model detailed quantitative relationships. The latter might be called the "engineering" perspective on cell signaling, whereas the former is a more abstract logical perspective. An engineering perspective is good if one has plenty of data, but a logical or qualitative perspective allows the modeling of phenomena for which we depend on phenomenological data that are hard to quantify. Both perspectives have their value, and they can be complementary.

Certain cancers, such as breast and ovarian cancers, involve the epidermal growth factor (EGFR) family of receptors, including HER2. To better understand the quantitative relationships between the amounts of EGFR and HER2 expressed and the degree of aberrant cell behavior, B. Hendriks (MIT, Boston) modeled the relationship between HER2 overexpression and the resulting effects on EGFR signaling. His models are particularly useful because they incorporate receptor trafficking to account for dynamic changes in the abundance and distribution of cellular receptors, including their creation, placement into the cell wall, removal into the cytoplasm, recycling, and destruction. Hendricks applied models of receptor trafficking to an analysis of relevant experimental signaling data [see also (*2*)].

The tumor necrosis factor-α (TNF-α) signaling network, which can induce apoptosis (cell death), was the focus of the modeling effort by S. Gaudet (MIT) and colleagues using ODEs. They found that signaling networks with the same connectivity (structure) and kinetic parameters, but that differ only in concentrations of some components [in this case, the proteases caspase-8 and caspase-3, FLIP (FADD-like interleukin-1-converting enzyme (FLICE)-like inhibitory protein), inhibitor of apoptosis (cIAP), X-linked inhibitor-of-apoptosis protein (XIAP)] can result in very different responses of the signaling network. Hence, they argue that their model leads to a systematic classification of cell types in terms of the concentrations of key components. This, they argue, can explain how the same cell type can respond to the same signal with cell death in one instance but not in another.

In a different approach, Markov chains are being used by M. Said (MIT) and colleagues to model networks that make up the cell death machinery including those of the worm (*Caenorhabditis elegans*), the fruit fly (*Drosophila*), and humans (*3*). Markov chains are sequences of states in which the probability of each succeeding state depends on the preceding state. A Markov chain can thus be used to define a pathway of interactions based on their probabilities. These investigators are attempting to make evolutionary comparisons among these signaling networks to clarify their function and complexity. Said and her colleagues are interested more in the topology, or general structure, of signaling networks than the individual component reactions. Markov chain models emphasize the topological, or structural, differences in signaling networks and their evolution.

P. Gennemark (Chalmers University of Technology, Göteborg, Sweden) presented an algorithm that generates a model from data automatically (*4*). Thus, not only are the parameters for the model determined by the data, but the model structure itself is created through a model identification algorithm. In this application, the model is based on the high osmolarity glycerol (HOG) response pathway in yeast. These models not only summarize existing knowledge, but also can be used to plan experimental strategies.

Cross-talk between two signaling pathways, transforming growth factor-β (TGF-β) and platelet-derived growth factor-β (PDGF-β), was the focus of the modeling effort by E. Fredlund (Lundberg Laboratory for Cancer Research, Gothenburg,

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Sweden). These pathways were connected through a model of the Ras-Raf-mitogen-activated protein kinase (MAPK) or extracellular signal-regulated protein kinase (ERK) kinase (MEK)-ERK pathway (*5*).

Ras signaling is controlled by way of the MAPK cascade (H. Herzel, Humboldt University, Berlin). A model of this cascade showed its signaling module to be multifunctional, in that in can act as a switch, amplifier, or feedback controller (*6*) .

A Monte Carlo probabilistic method was used by W. Hlavacek (Los Alamos National Lab) to model high-affinity immunoglobulin-ε (Igε) receptor (FcεRI)-mediated signal transduction, which is involved in allergic reactions (*7*). This system consists of multiple interacting components (a ligand, the receptor, and the tyrosine kinases Lyn and Syk) and leads to the activation of Syk. Hlavacek and colleagues found that many possible combinations of reactions could lead to the same result; no one combination dominated. Hence, given this combinatorial complexity, this group concluded that the FcεRI signal transduction cascade is better described as a network than as a single path. Multiple concurrent paths can be active at the same time. Interestingly, Hlavacek claimed that knockout experiments showing one component as upstream or downstream from another component do not necessarily impose a temporal order on signaling events.

A hybrid approach that combines a graphical method with ODEs was used to model explicitly the TNF-α pathway (*8*) mediated by the transcription factor nuclear factor κB (NF-κB). The graphical approach was was complemented by the use of ODEs to quantitatively model the pathway (K.-H. Cho, S.-Y. Shin, H.-W. Lee, University of Ulsan, Korea; O. Wolkenhauer, University of Manchester Institute of Science and Technology, UK) (*9*). This group is also modeling the Ras-Raf-MEK-ERK pathway in collaboration with W. Kolch (University of Glasgow).

As Wolkenhauer explained, whereas bioinformaticians grapple with a flood of data, those who are modeling signal transduction systems face no excess of data. Rather, they often lack detailed data to describe crucial processes. Still, modeling can provide the life scientist with valuable information that aids experimental design. A systems approach makes hypotheses about functional, causal relationships. To find those causal relationships, says Wolkenhauer, "We need to systematically perturb or manipulate the system; this implies a change of the way experimental scientists conduct their experiments." The focus then shifts from the components of the cell themselves to how those components interact to form a dynamic system.

Another hybrid approach combined ODEs with a probabilistic rule-based system to mathematically model T cell responses to signaling. In this way, G. Ciobanu (National University of Singapore) and B. Tanasa (Romanian Academy, Iasi, Romania) and colleagues get both a qualitative and quantitative description of the system.

Integrating cell signaling with development was the subject of two posters. Plant developmental signaling in *Arabidopsis thaliana* in the shoot apical meristem (SAM) was the focus of H. Jönsson (CalTech, Pasadena, CA) (*10*), whereas developmental signaling in *C. elegans* was the subject of U. Platzer (Deutsches Krebsforschungszentrum, Heidelberg) (*11*). Platzer uses Boolean networks to describe the signaling network in combination with rules for how cells react. In contrast, Jönsson uses a neural network-inspired regulatory network to describe protein distribution in cells. Interestingly, both of these workers couple the gene regulatory network with mechanical networks.

This fascination with cell signaling is understandable. The involvement of cell signaling in important diseases, such as autoimmune diseases and cancer, makes a systematic understanding of signal transduction pathways and networks essential. There is much to be done. A systems approach provides both a qualitative and quantitative understanding of such complex cellular phenomena. It is not an overstatement to call this refocusing on systems as opposed to components a new paradigm. As such, it holds great promise and opportunity like none we have had before.

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