Introduction to monitoring and manipulating signaling networks

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A seminal issue in better understanding how cells respond to a variety of physiological cues is to elucidate how signaling cascades, and more generally biochemical networks, work and how they interact with one another. Eventually, it would be desirable to model signaling cascades quantitatively and with sufficient precision as to be able to predict, *a priori*, how a cell will adapt to a given stimulus. That worthy goal may be a long way off, but it already serves as an organizing principle for the emerging area of systems biology. This special thematic issue of *Molecular BioSystems*, "Monitoring and Manipulating Signaling Networks", provides a flavor of the many exciting advances being made along this long road. In the spirit of the mission of this journal, most of the articles were chosen to reflect common themes in systems biology but we've made some idiosyncratic choices in order to drive home the message that chemists have a great deal to contribute to this emerging field.

One of the best-developed "toolboxes" available to study cellular responses on a global scale is microarray-based expression profiling. Thomas and his co-workers employ this technique in combination with another microarray-based experiment called the ChIP on chip (pp. 627–639) to better understand the stress response mediated by the transcription factor HSF1. The ChIP on chip employs the well-known chromatin immunoprecipitation (ChIP) technique, but rather than probing for the immunoprecipitation (IP) of a specific promoter with a transcription factor, the entire set of co-IP'd DNAs are amplified and hybridized to an array of DNA probes for promoter sequences, allowing visualization of the binding sites of the transcription factor of interest. The combination of expression profiling and the ChIP on chip is a powerful method to distinguish direct and indirect effects of a given transcription factor.

A highlight article by Hendrik Luesch (p. 609) provides a compelling presentation and perspective on how novel large-scale genomic and genetic strategies are being utilized to ask global questions about the modes of actions of small molecules on the cell. As Luesch rightly explains in his introduction, in recent years the notion of drug "target" has gone from the molecular to the systems level. That is, genome-wide analyses of small molecule actions on the cell allow us to ask what are the direct and indirect effects of drugs on cellular metabolic and regulatory networks. Do multiple effects represent action on many, unknown targets or the massive integration of the many cellular subsystems? What are the consequences of large-scale analysis on cells to our ability to predict potential therapeutic or dilatory effects of molecules on humans? There are no simple answers to these questions. Luesch provides an overview on the technologies that are being applied, the questions these methods raise and how approaches that have been developed in simple model organisms like bakers yeast are being now developed in human cells.

Of course, as the experimental tools begin to provide data of suitable quality for predicting network behavior *in silico*, advanced models for this purpose must be developed. A daunting problem in this regard is the tremendous complexity of any given signaling cascade, let alone interactions between different pathways. Thus, simplification is required. But how to achieve this without "throwing the baby out with the bathwater"? Or put another way, what subset of all of the possible protein levels, interactions, rate constants, *etc.* must be measured in order to provide a reasonably accurate model of the system? The groups of Tidor and Kell consider this issue on pp. 650–659 and 640–649, respectively. Adiwijaya, *et al.* explore an approach that theoretic chemists will find appealing and which has become a common theme in systems biology. They describe a strategy to optimize kinetic parameters around repeated "motifs" sets of reciprocal enzymatic reactions that are commonly found, for example in signal transduction pathways. They show that several types of solutions and adaptations have been found for the same motif in different contexts. These adaptations, both evolutionary and differential among different cell types could reflect simple ways for adaptations, for example environmental stress or nutrient sources may rapidly occur. The general approach described should also be of value to studying the spectrum of motifs that have been discovered in biochemical networks. The paper by Yue *et al.* presents a different, but equally important perspective on the problem of parametizing variables and the association of variables in complex biochemical pathways, most importantly describing how to identify those dynamic variables that are most important in describing and predicting the behavior of a signal transduction pathway.

At a practical level, systems approaches are all about process. It is one thing to talk about modeling the composition and states of many proteins in the cell and another to actually assemble the data necessary to get there. Proteomics, particularly mass-spectroscopic analysis of cellular protein compositions and complexes are among the most extraordinary examples of the challenges involved. Lee and Cooper (p. 621) review

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this problem and the specific challenges arising in applying these techniques to plants. It is particularly interesting to read this example because while plant biochemistry may be foreign to many readers, the lessons to be learned from doing proteomic analysis on the complex and varied tissues that plants represent are perhaps more general and more useful to those that are interested in how these approaches can be applied beyond the model organisms that we are most aware of.

Finally, we couldn't help but slip in an overview on Molecular Modeling by Barril and Soliva. Why? In the end we are interested in molecules and from a systems perspective, how they interact with other molecules, whether through simple binary complexes or through multiple target effects on whole systems. We look forward to a day when the notion of "structure–function" will evolve to accommodate the system level interactions of molecules with the cellular machinery of life and that what we can model about molecules, whether simpler or more elaborate may even allow us to predict systems effects.

In summary, this collection of articles provides a small glimpse of the enormous efforts currently underway to gain a quantitative understanding of signaling pathways and biochemical networks in general . The long-term goal is to harness the technical and conceptual tools that chemists have applied to complex systems for decades; to acquire predictive power while learning also from other disciplines what information we can obtain and what it is thought to mean to these disciplines. Success would have a huge impact on our basic understanding of cellular function, drug development a variety of other fields. *Molecular BioSystems* remains committed to focusing on this area for some time to come.

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