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Design principles of protein networks

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Understanding the protein networks that perform computations within the cell (signal transduction networks) is a central problem in molecular biology. From the point of view of physics, these networks offer the challenge of understanding the collective behavior of interacting molecular machines designed to operate with remarkable precision under strong biological constraints. Our new lab studies these intracellular networks using a combined experimental and theoretical approach, aiming to uncover general underlying principles that govern their functioning.

One approach is to study relatively simple networks in detail. Several model systems, such as some sensory and genetic regulation pathways in the bacterium *Escherichia coli*, have been well characterized on the level of the protein components and their interactions. One can use these systems to ask questions about how network-level functions, such as adaptation, integration of different signals and amplification of weak signals, arise from the interplay of individual components. These systems lend themselves to experimental study, using powerful techniques for genetic manipulations of protein circuits and for measuring the organism behavior (the output of the network). In parallel, techniques for mathematical modeling and simulations of the network will be developed to explore such questions as: Are there architectures of protein networks which make their essential function impervious to fluctuations in conditions and biochemical parameters? A model for such studies is our work on robustness in bacterial chemotaxis (Alon et al., 1999), where an experiment, motivated by a theoretical analysis, showed that the chemotaxis network is designed so that an essential feature (precise adaptation) survives large variations in the concentrations of the network components. Further directions to explore include the ways that networks withstand the noise inherent in the coupling to the rest of the cell, and noise due to their being composed of discreet, stochastically synthesized elements. Focusing on suitable systems, we can ask whether there are isolated modules within the network that act as robust amplifiers, switches etc., with the aim of uncovering recurring "building blocks" that underlie many signaling networks.

A second approach is to employ emerging experimental techniques that utilize information on complete genomes, to attempt to understand an entire microorganism as a vast genetic network. For example, it is now becoming possible to monitor the expression level of all genes in *E. coli* in parallel. In a challenging long-term project, an experimental system capable of monitoring the expression of all genes, at a temporal resolution of minutes, is being developed. One way to achieve this is through the construction a set of plasmids, each bearing a fluorescent reporter (such as fast-folding GFP) downstream of one of the ~2000 promoters in *E. coli* (known from its completed genome sequence). Levels of gene expression from each promoter can then be monitored in parallel by the fluorescence of colonies of cells, each bearing one of the plasmids. Additional data will be collected using high-density oligonucleotide arrays. The cells are systematically subjected to various environmental stimuli and genetic perturbations, and a large data set of the resulting gene expression patterns will be compiled. Theoretical tools for analyzing this data, and integrating it with the substantial existing knowledge on genetic pathways, are being developed, to attempt to piece together a map of the genetic circuits of the cell. For example, this approach allowed us to order the genes in the *E. coli* flagella pathway without need for the standard methods of mutant analysis [Kalir et al., 2001] . We expect that the new analysis methods that will be developed for this "reverse engineering" of *E. coli* will be applicable in mapping the genetic regulation networks of other cell types. Such an undertaking should yield insights into the general motifs of organism-wide computation.

Selected Publications

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