**208g Dynamical Analysis of an Integrated Signaling Network at a Genome-Scale**

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Recent advances in genomic technologies have generated more detailed descriptions of the critical components of signaling networks. Though many important components of different biological networks have been identified and quantified, a holistic approach to understanding of interactions inside a network and between different cellular networks is essential to enable more intelligent design of therapeutic agents for treatment of human diseases arising from defects in cellular signaling mechanisms.

In this presentation, we perform in silico analysis of a cellular signaling network. Two fundamental challenges remain for the genome-scale analysis of cellular signaling networks: (1) how to interface cellular signaling reconstructions with metabolic and regulatory networks; and (2) how to analyze dynamic properties of signaling networks at a genome-scale. To address these issues, we characterize time-scales of important network components (e.g., chemical reactions, signaling events, etc.) in the Saccharomyces cerevisiae signaling system.

Because the integrated cellular network is characterized by different time scales, the system is ill-conditioned. To predict dynamic responses correctly, proper separation of time-scales is necessary. We begin with quasi steady-state assumptions for the chemical reactions and events that are “relatively” fast. This gives us an idea of how slow modes of the integrated network are responding to external signals or perturbations. However, for complex systems, specifying quasi steady-state modes by examining every reaction kinetic would be laborious and difficult to implement. To predict dynamic behavior of such a large system, either a singular perturbation method [1] or a model reduction technique [2] that systematically separates slow/fast modes can be integrated. With the characterized dynamics, temporal integration and/or Monte Carlo simulation approaches can allow us to identify what events and reactions are important for a particular cellular function.

Finally, cellular objective functions (hypotheses) for the integrated cellular network are evaluated to analyze global biological design principles.

References

[1] Kumar, A. & Daoutidis, P. (2002). Nonlinear dynamics and control of process systems with recycle. Journal of Process Control 12, 475–484.

[2] Shvartsman, S. Y. & Kevrekidis, I. G. (1998). Nonlinear model reduction for control of distributed systems: a computer-assisted study. AIChE Journal 44, 1579–1595.