

### **383b Biological Network Design Principles: Discovery through Optimization**

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The emerging field of systems biology includes a strong focus on the network perspective of biological systems. In this work we explore the development and application of tools that can be used to discover structure--function relationships in biological networks, to discover design principles and to design synthetic studies of new and modified networks. Mathematical optimization provides a powerful set of methods to achieve these goals of network analysis, interrogation, and design.

We illustrate these approaches in the context of MAP kinase networks, for which there is a strong foundation of experimental and theoretical study, but about which many questions remain. In particular, subtle and significant differences exist between individual MAP kinase cascades that may correspond to important context-specific functional differences.

To understand MAP kinase networks, we posed the problem as a multiple-objective optimization with embedded dynamics. The dynamics of MAP kinase is modeled as a biochemical network, with dynamic equations expressing mass-action kinetics and other relationships. Optimization was applied to a set of network structures, the optimal networks were examined to elucidate underlying design principles, and multiple objectives were imposed to discover inherent trade-offs. The optimization probes structures and dynamics to understand the effectiveness of networks in producing specific signal-processing characteristics such as signal amplification, response time, and noise filtering.

Results suggest that MAP kinase networks with multiple phosphorylation steps and multiple layers of kinases are more sluggish but better at rejecting noise while maintaining rapid (but delayed) responses. Furthermore, the non-linear networks in MAP kinase may exhibit very high order dynamics, a behavior that is typically observed in a cascade of Continuously-Stirred Tank Reactors and useful for noise-filtering. The additional phosphorylation steps and layers of kinases allow additional controls for trade-off between the high order dynamic behavior and signal amplification.