

Understanding The Design Principles of Biological Networks Using Optimization

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Keywords: design principles, biological networks, dynamic optimization.

The emerging field of systems biology includes a strong focus on the network perspective of biological systems [1, 6, 2]. In this work we are exploring the development and application of fundamental tools to understand and probe biological networks using global optimization with embedded dynamics. These tools are being applied to study multiple mitogen-activated protein kinase (MAPK) networks from organisms ranging from yeast to mammals.

Optimization provides a powerful approach to interrogate network models and better understand the importance of interconnectivity between the players (small molecules, DNA, RNA, and proteins), as well as how connectivity relates to networks properties. This understanding may be useful in relating the observed structural differences of biological networks with their functional roles, in understanding trade-offs inherent in biological network design, and in developing therapeutic strategies for intervention and modulation of biological networks.

MAPK networks are chosen as a model system of study because these networks have been well studied, but some of the network structure and kinetic parameters remain incomplete. Despite the mounting number of molecular mechanisms [7, 4, 3, 5, 8] being observed in MAPK networks, little is known about the significance of subtle differences in their construction. The balance of available information and the puzzling significance of unexplained mechanisms make MAPK networks a good candidate for further study and, in particular, to apply optimization.

To understand biological networks, we pose the problem as a multiple objective optimization. MAPK is represented as a biochemical network, with nodes representing multiple binding and modification states of proteins, and arcs representing the transitions or reactions among these states. The arcs are described further by dynamic equations expressing mass-action kinetics and other relationships. To understand the structural differences in multiple MAPK networks, optimization is applied to a network superstructure — a network consisting of the union of observed structures — to generate and study alternative optimal structures, to elucidate underlying design principles, and to discover trade-offs inherent among multiple objectives. The optimization probes structures and dynamics to understand better the relative effectiveness of network components in producing specific signal-processing characteristics such as signal amplification, response time, and time shift. Methods to analyze the optimal results to extract design principles are being discussed along with optimization problem characteristics of MAPK networks. Results suggest that MAPK networks with multiple phosphorylation steps or multiple layers of kinases are more sluggish but are capable to produce more sophisticated responses.

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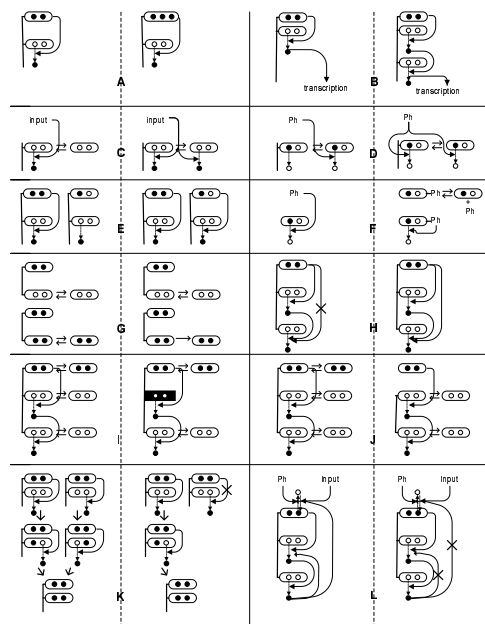


Figure 1: Components of network interconnectivity of the MAPK network super-structure.

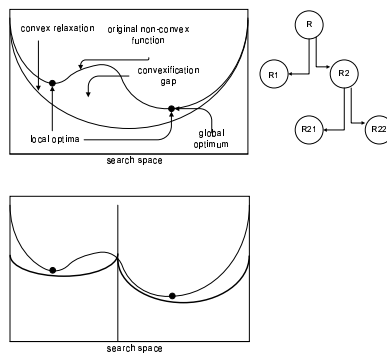


Figure 2: Illustration of the spatial branch and bound algorithm to solve global optimization.

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