QUANTITATIVE PERFORMANCE AND TRADEOFFS IN THE MAP KINASE SIGNALING MODULE

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Stephen Chapman

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ABSTRACT

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Stephen Chapman, B.S. University of California, Berkeley

M.S., Chemical Engineering, California Institute of Technology

Ph.D., Chemical Engineering, California Institute of Technology

Intracellular signal transduction networks propagate and integrate the information that cells sense from environmental stimuli. The quantitative performance of signaling networks regulates cell decisions, and aberrations in network performance lead to pathologies such as cancer. The mitogen-activated protein (MAP) kinase cascade is a highly-conserved signaling module that regulates diverse cellular processes, such as proliferation, differentiation, and apoptosis in eukaryotic species ranging from yeast to human. While the principal components and mechanisms that define the MAP kinase module are well established, our understanding of and ability to tune its quantitative performance is limited. Here, we probe more deeply how the quantitative properties of the MAP kinase module may be affected by variations in the expression levels of the key constituents of the cascade—kinases, phosphatases and scaffolds.

Using a computational approach, we delineate how four quantitative properties—responsiveness to input, dynamic range of output, signal amplification, and signal

lifetime—depend on the relative abundances of the two core components of the MAPK module, kinases and phosphatases. We identify a reduced metric termed the 'resistance to activation' that predicts the quantitative properties of the module across a wide range of parameter values. Its predictive utility extends to dynamic properties such as signal lifetime, which often dictates the MAP kinase's effect on cell function. Our analysis highlights tradeoffs in design, as not all quantitative attributes of the module can be simultaneously optimized. Thus, the resistance to activation captures the fundamental principles that determine cascade behavior and can be exploited to guide quantitative redesign of the MAP kinase module.

In addition to the expression levels of kinases and phosphatases, scaffolds play a key role in signal propagation through the MAP kinase module. Protein scaffolds bring together multiple components of a signaling pathway, thereby promoting signal flux along a common physical "backbone." Scaffolds figure prominently in natural signaling pathways and are emerging as a promising platform for synthetic circuits. To better understand how scaffolding quantitatively affects signal transmission, we conducted an *in vivo* experimental sensitivity analysis of MAP kinase response to broad perturbations in the expression level of Ste5, an exemplar scaffold of the yeast mating pathway. Our results demonstrate that the expression level of Ste5 significantly affects several quantitative aspects of signal propagation, including signal throughput, pathway ultrasensitivity, and baseline leakage. These new insights into the quantitative role of scaffolding in MAP kinase signaling suggest advantages and limitations in designing synthetic scaffold-based regulatory networks.

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