383c Understanding the Ultrasensitive Responses of Tricyclic Cascade Networks

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The ability of the mitogen-activated protein kinase (MAPK) cascade to generate switch-like (ultrasensitive) signals from graded stimuli is an often postulated and debated design principle of the ubiquitous signal transduction pathway. Despite the long history of study on the core module, the monocyclic interconvertible enzyme cascade, there is little evaluation of how the cascades interact in larger networks to generate and enhance switch-like responses. Here we study simple three-cascade networks, similar to the prototypical MAPK cascade, to determine the design principles for connecting ultrasensitive modules into ultrasensitive networks. Our results identify an essential balance between driving force for activation of the cascades, through concentration and enzyme affinities, and the minimization of enzyme-substrate complex formation as essential for generating high ultrasensitivity. When the system is properly balanced, through its dimensionless concentrations and enzyme affinities, a global maximum for the ultrasensitivity of the network is observed. Finally, we show how common modeling assumptions, such as neglect of enzyme-substrate complexes, can lead to vastly different predictions of cascade network principles.