Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Biotechnology

Uncovering mechanisms of bistability in biological systems

Joseph R Pomerening

As the systems biology era progresses, theoreticians and experimentalists continue uncovering the molecular mechanisms that underlie the regulation of complex cellular phenomena, including those governing proliferation, differentiation, and death. The discovery of bistability in cellular responses and their signaling pathways has become a recurring theme, and prompted strong interest in understanding both the design and function of these networks. Modeling these systems has been crucial in assisting experimentalists to better understand how this and other types of behavior can emerge from a subset of regulators, and also to analyze and identify systems-level characteristics that would otherwise be difficult to intuit. In this review, recent advances in both theoretical and experimental work investigating the mechanistic as well as biological basis for bistability will be presented. These will include the role of positive feedback loops, the potential function of dual phosphorylation cycles, and substrate competition as a means of generating ultrasensitivity.

Addresses
Department of Biology and The Biocomplexity Institute, Indiana University, 212 South Hawthorne Drive, Simon Hall (SI-MSB), Room 043F, Bloomington, IN 47405-7003, United States

Corresponding author: Pomerening, Joseph R (jpomeren@indiana.edu)

Current Opinion in Biotechnology 2008, **19**:381–388

This review comes from a themed issue on
Systems biology
Edited by Jaroslav Stark

Available online 7th August 2008

0958-1669/$ – see front matter

DOI 10.1016/j.copbio.2008.06.009

Introduction

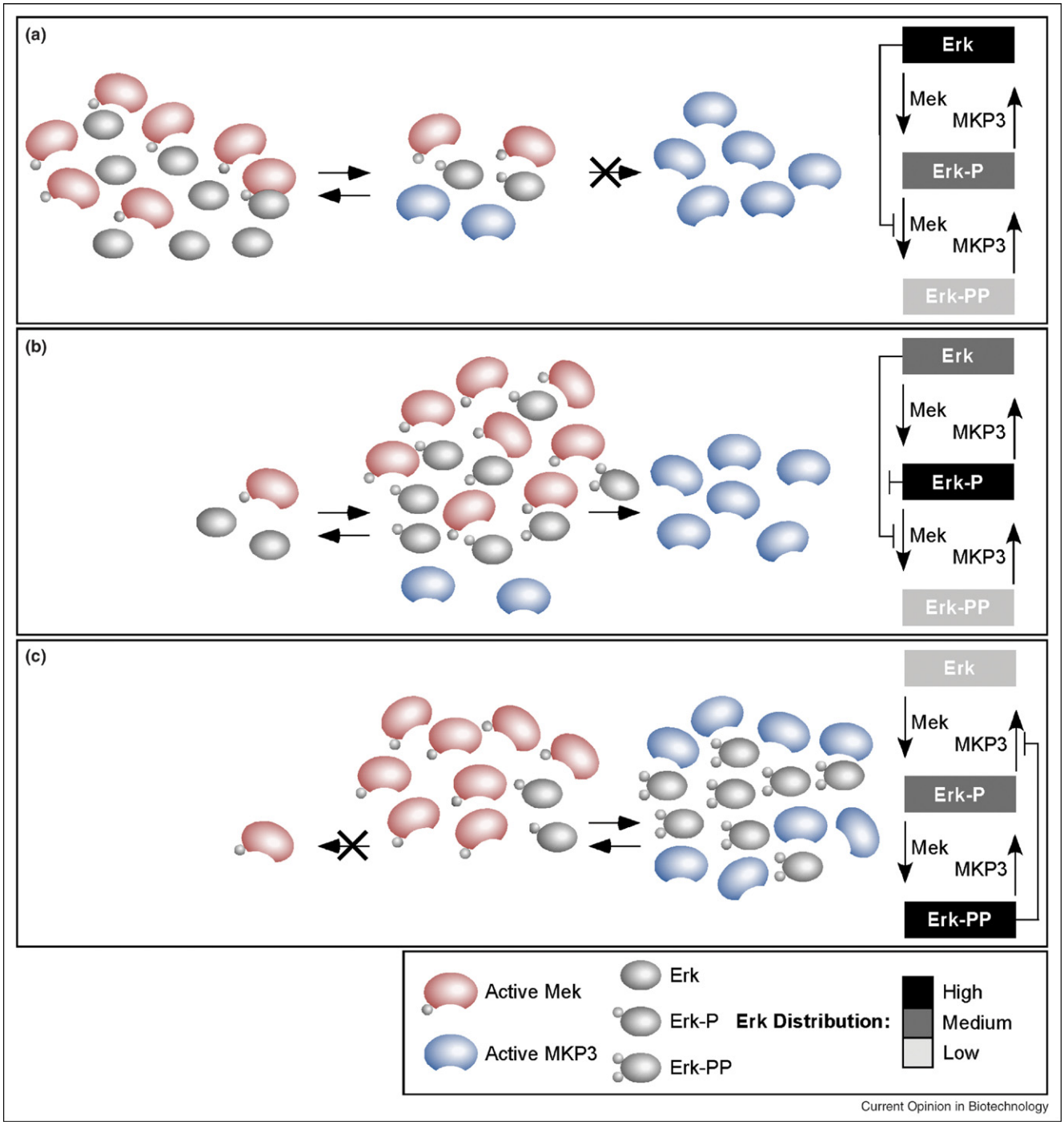
During the past decade, the focus of molecular biology has been shifting progressively from the identification of novel regulators and the pursuit of understanding their individual cellular functions, to discerning how subsets of proteins engage one another on the systems-level to receive, transmit, and process stimuli into complex biochemical and physiological outputs. Systems biology can be described as the global analysis of large-scale network structure and function [1]; at the other end of the spectrum is the drive to uncover emergent behaviors that can arise from merely a few regulators and lead to more sophisticated and often unexpected dynamics [2]. One virtue of systems biology, no matter the systems' scale, is the synergy that is gained by the combination of computational and experimental studies. As biologists continue to wire together the components and modules needed for cellular function, and as these systems become increasingly complex, the analytical and predictive power of computation cannot be denied. Indeed, the sketched-out cartoons, flow charts, and arrows have been undergoing their own quantitative evolution to no longer be merely useful depictions of biological pathways, but theoretical tools that give experimental biologists some crucial foresight into how systems behave [3]. One major area of quantitative biology for which this statement applies in both historical and present significance is the study of bistability in transcriptional and protein networks. Biochemical systems are pervaded with mechanisms that promote switch-like behaviors, and must often respond to situations that dictate the need for alternative stable steady states, otherwise known as multistability [4]. This review will highlight some recent theoretical and experimental advances that have garnered biologists a broader view of what is needed for a signal transduction pathway to exhibit bistability (and is thoroughly and clearly defined in some excellent past reviews [5,6]), and will describe why this systems-level behavior is fundamentally important in so many biological contexts.

No need to hide: dual phosphorylation/dephosphorylation cycles as a plausible generator of bistability

The mitogen-activated protein kinase (MAPK) pathway is an essential, three-tiered (MAPKKK → MAPKK → MAPK) eukaryotic signaling conduit that directs cells through many different decisions, including proliferation, differentiation, and programmed cell death [7•]. Even though positive feedback (or double-negative feedback) had long been considered requisite for bistability in a signaling system, Kholodenko and colleagues recently published a highly influential paper modeling a single level of the MAPK pathway — the regulation of MAPK (Erk) through the influence of the MAP kinase kinase (Mek) and the MAPK phosphatase (MKP3) — and demonstrating that dual phosphorylation/dephosphorylation cycles alone could confer hysteresis and bistability [8]. Markevich *et al.* used coupled ordinary differential equations parameterized with biologically realistic values for Erk phosphorylation and dephosphorylation rates by Mek and MKP3, respectively, to determine that a non-processive and (distributive) random two-collision cycle at this single level of the MAPK pathway would be sufficient to yield bistability. There were two constraints proposed by Markevich *et al.* for this dual phosphorylation

mechanism to yield bistability: first, at least one of the two enzymes (either kinase or phosphatase) must be saturated by substrate; next, the substrate of the first step must competitively inhibit conversion of the substrate at the second step. Although this mechanism would not rely on an allosteric feedback mechanism, *per se* (e.g. the further activation of upstream kinases by their downstream substrates, such as the activation of Mos by MAPK activation

Figure 1



Intrinsic positive feedback due to enzyme saturation, competitive inhibition, and feedforward inhibition. **(a)** A high concentration of Erk inhibits formation of Erk-PP as Erk-P is produced. **(b)** An increasing concentration of Erk-P relieves the inhibition of Mek caused previously by the high Erk concentration, resulting in a double-negative (positive) feedback and a burst of Erk-P production. **(c)** Increased production of Erk-PP causes it to compete with Erk-P for MKP3 phosphatase, inhibiting the conversion of Erk-P to Erk. This feedforward inhibition yields the equivalent of a positive feedback loop — any Erk-P formed by Erk-PP dephosphorylation will be re-phosphorylated by Mek.