Abstract Submitted
for the MAR06 Meeting of
The American Physical Society

Intrinsic Fluctuations, Robustness and Tunability in Signaling Cycles. JOSEPH LEVINE, Caltech, HAO YUAN KUEH, Harvard Univ., LEONID MIRNY, MIT — Covalent modification cycles (e.g. phosphorylation) underlie most cellular signaling. Low molecular copy number, arising from compartmental segregation and slow diffusion between compartments, potentially renders these cycles vulnerable to intrinsic chemical fluctuations. How can a cell operate reliably in the presence of this inherent stochasticity? How do changes in extrinsic parameters lead to variability of response? Can cells exploit these parameters to tune cycles to different ranges of stimuli? We study the dynamics of an isolated phosphorylation cycle. Our model shows that the cycle transmits information reliably if it is tuned to an optimal parameter range, in spite of intrinsic fluctuations and even for small input signal amplitudes. At the same time, the cycle is sensitive to changes in the concentration and activity of kinases and phosphatases. This sensitivity can lead to significant cell-to-cell response variability Our results show that signaling cycles possess a surprising combination of robustness and tunability. This combination makes them ubiquitous in eukaryotic signaling, optimizing signaling in the presence of fluctuations using their inherent flexibility. On the other hand, cycles tuned to suppress intrinsic fluctuations can be fragile to changes in the number and activity of kinases and phosphatases. Such trade-offs in robustness to fluctuations can influence the evolution of signaling cascades, making them the weakest links in cellular circuits.

Leonid Mirny
MIT

Date submitted: 30 Nov 2005 Electronic form version 1.4