IOP Publishing Physical Biology

Phys. Biol. **4** (2007) 48–59 doi:10.1088/1478-3975/4/1/006

Propagation of extrinsic perturbation in a negatively auto-regulated pathway

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Received 13 November 2006
Accepted for publication 14 March 2007
Published 3 April 2007

Online at stacks.iop.org/PhysBio/4/48

Abstract
The apparent precision of the output in multi-step biochemical pathways in the face of external and intrinsic perturbations is non-obvious and conceptually difficult. Using a simple three-step negatively auto-regulated model pathway, we show that the effect of perturbation at different steps of the pathway and its transmission through the network is dependent on the context (i.e., the position) of the particular reaction step in relation to the topology of the regulatory network, stoichiometry of reactions, type of nonlinearity involved in the reactions and also on the intrinsic dynamical state of the pathway variables. We delineate the qualitative and quantitative changes in the pathway dynamics for constant ('bias') and random external perturbations acting on the pathway steps locally or globally to all steps. We show that constant perturbation induces qualitative change in dynamics, whereas random fluctuations cause significant quantitative variations in the concentrations of the different variables. Thus, the dynamic response of multi-step biochemical pathways to external perturbation depends on their biochemical, topological and dynamical features.