Graded and hysteretic responses in bacterial signaling networks: mechanisms and design principles

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***Short Abstract* — A key property of living cells is their ability to react to internal or external signals with specific biochemical responses. The nature of these responses can only be understood by studying the dynamics of the underlying biochemical networks involving reactions and interactions of genes, proteins and other biochemical components of the cell. Many naturally occurring networks display graded responses in which continuous variation of an input signal results in continuous change of the system output. Alternatively, biochemical networks can exhibit bistable or hysteretic responses so that over a range of signals the network possesses two stable steady states. We discuss several examples of naturally occurring switches, focusing on the design principles that allow cells to achieve the physiologically desired response.**

***Keywords* — hysteresis, bistability, graded response, sigma factors, two-component systems, sporulation, stress response**

I. Background

MANY examples of hysteretic developmental switches have been identified in naturally occurring systems or those constructed synthetically. The generic theme underlying the existence of hysteretic responses in all these circuits is the same – the existence of a positive feedback and signal amplification by an underlying non-linearity. Such bistable designs would be desirable to networks controlling irreversible cell-fate decisions but can be deleterious for networks for environment sensing. Recently we constructed several mathematical models illustrating how the feedback architecture of the networks coupled to post-translational regulation leads to the physiologically desired response. These models include (A) partner-switching mechanisms controlling factors σ^F and σ^B in *Bacillus subtilis* and related bacteria [1], (B) posttranslational bistability in two-component signal transduction systems and (C) the network controlling proteases expression in populations of *B. subtilis* under nutrient limiting conditions.

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II. Results

A. Partner-switching networks

The activities of commitment to sporulation (σ^F) and general stress response (σ^B) sigma factors are controlled post-translationally by the networks containing σ, anti-σ and anti-anti-σ factors. The phosphorylation state of the latter defines the state of the network. We demonstrate that bistable responses in the σ^F-network originate on the post-translational level because of self-enhancing formation of a "dead-end" complex between anti-σ^F and anti-anti-σ^F with ADP in the catalytic site [1]. This mechanism does not function in the homologous σ^B-network, which displays a graded response over a wide range of signals despite the presence of positive feedbacks on the transcriptional level. These feedbacks originate from σ^B transcriptional control of the operon containing σ^B itself and its network partners.

B. Two-component systems

In bacteria, two component systems (TCS) are the key signal transduction networks regulating global responses to environmental changes. The network involves a sensory kinase (SK) that autophosphorylates in response to a signal and then transfers the phosphate to its cognate response regulator (RR). We show that formation of a dead-end complex between SK and RR can lead to bistable responses. However this possibility is eliminated by the network design of many classical TCS. Indeed, in many instances SK is bifunctional and, when unphosphorylated, it is also capable of dephosphorylating RR. This interaction leads to a negative feedback loop that suppresses the bistability.

C. Protease production in starving B. subtilis cells

When the bacterium *Bacillus subtilis* faces conditions of nutrient limitation, it employs a number of adaptive strategies. We constructed a mathematical model that explains heterogeneous expression of extracellular proteases in isogenic populations. The model shows how positive feedback leads to slow and noisy kinetics of activation of DegU – RR controlling the production proteases.

1. Igoshin, O. A., Price, C.W., Savageau, M.A., Mol. Microbiol. **61** (2006)165-184