Quantitative properties of post-translationally regulated genetic circuits

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Genetic regulatory circuits often possess distinct quantitative properties. While the relationships between the structure and dynamical features of transcriptionally regulated circuits have been extensively studied, the rules governing the dynamics of genetic circuits involving post-translational regulation have remained largely unexplored. Here we examine how the choice of the target of post-translational regulation determines the dynamical properties of the circuits' response. We use the comparative dynamics methodology to gain insights into the quantitative properties of circuits involving the recently emerged broad class of bacterial post-translational regulators termed connector proteins.

***Keywords*: mathematical modeling, gene expression, signal transduction, post-translational regulation, protein–protein interactions, connector proteins**

Transcription factors activate or repress expression of their target genes either directly – by binding to a gene's promoter – or indirectly, via complex regulatory circuits that may involve transcriptional cascades, positive and negative feedback loops, and feedforward architectures [1,2,4]. It has been established that differences in regulatory circuit structure result in differences in quantitative properties of the circuits' response [1,2,4]. However, general rules that define the relationship between circuit structure and circuit dynamics require further studies, particularly for newly discovered classes of regulatory circuits with non-intuitive dynamic properties.

Here we investigate the quantitative properties of genetic regulatory circuits that involve post-translational mechanisms based on protein–protein interactions. While such mechanisms are wide-spread in bacteria and eukaryotes, their quantitative properties remain largely unexplored. Our goal is to obtain insights into how the choice of protein–protein interaction target in a circuit influences the circuit's activation and deactivation dynamics, as well as the steady state properties. We address this question for the recently emerged class of bacterial post-translational regulators termed connector proteins, which facilitate signal integration in bacterial signal transduction systems, and play central roles in physiological processes such as nutrient limitation response and antibiotic resistance [3].

The targets of connectors are two-component systems, which constitute a prevalent class of bacterial signal transduction mechanisms [3]. A two-component system contains a sensor kinase, which responds to a specific signal by modifying the phosphorylated state of its cognate response regulator. This allows the regulator to mediate a specific biological function in the cell (typically, by acting as a transcription factor). We studied connectors that target either the response regulator (by protecting its phosphorylated form) or the sensor kinase (by increasing its kinase activity or decreasing its phosphatase activity towards the phosphorylated response regulator) [3].

We constructed mathematical models for the three mechanisms of connector action using available information about the known connectors and two-component systems. By analyzing activation and deactivation response curves for the models, we established that the regulator-targeting circuit exhibited a large deactivation delay (i.e., increased expression persistence) in comparison with the sensor-targeting circuits. This property was independent of the presence of transcriptional positive autoregulation in the circuits, and robust to parameter variations. By performing parameter scans, we demonstrated that increased expression persistence of the regulator-targeting circuit is ultra-robust to variations in the connector–target complex formation and dissociation rates. Moreover, we obtained insights into the factors contributing to increased persistence of expression.

The differences in output levels for the three circuits strongly depend on the parameter values and thus are not robust characteristics of connector action mechanisms. Furthermore, the distinct connector action mechanisms appear to possess nearly equivalent noise properties. Thus, in our comparisons, increased expression persistence exhibited by the regulator-targeting circuit was the most distinctive quantitative feature resulting from the differences in connector action mechanisms.

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