379h An Optimization-Based Method for the Design of Robust Synthetic Switches in Biological Networks

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One of the most challenging problems at the interface of biological sciences and engineering is to understand how the behaviors of living cells arise out of the dynamical properties of complex networks of genes and proteins. A fundamental understanding of how these networks are integrated and regulated, and how this regulation can be influenced, has important implications not only for reverse engineering their structure, but also for the forward engineering of novel structures in the context of the nascent field of ``Synthetic Biology.'' A central theme in this field is the idea of reassembling well-characterized genetic components into artificial networks that perform prescribed functions in vivo. Presently, these efforts are primarily driven by a rational approach to gene circuit design, where well-described parts are assembled based on predictions borne out of mathematical models of circuit behavior (e.g., see [6], [7], [10], [3]). The concept of engineering genetic networks has roots that date back nearly half a century [9]. It is relatively recent, however, that the fusion of experimental progress with precise analytical and computational tools has made the design and implementation of genetic networks amenable to quantitative analysis. Leading biologists have recognized that new systems-level knowledge is urgently needed to unravel and conceptualize the rich dynamic processes, feedback control loops and signal processing mechanisms of naturally-occurring networks on the one hand, and to systematically guide the design and implementation of synthetic networks that mimic naturally occurring ones, on the other.

The construction of synthetic networks is important for several reasons. One is the fact that it provides a first step towards logical cellular control, allowing DNA-level manipulation and monitoring of biological processes [2]. A second complementary motivation has to do with the valuable information regarding evolutionary design principles that can be gleaned from the study of simple networks decoupled from their complex, native biological environments. Such information can be useful in expediting biological discovery. Similar to the engineering of man-made control systems, however, the success of such an endeavor depends critically on the capability of predicting the full range of dynamical behavior expected from these designs. In particular, one of the most ubiquitous modules, or building blocks, in both natural and synthetic regulatory networks, are biological switches. Cells often use genetic switches to activate or repress expression of genes in response to certain stimuli as part of the mechanism that drives the overall adaptive response of a cell. A critical systems-level property that underlie switch-like behavior, and even relatively simple signaling networks have the potential to produce, is bistability. A bistable system is one that toggles between two discrete, alternative stable steady states, in contrast to a monostable system which slides along a continuum of steady states. Biological examples of bistable systems include the lambda phage lysis-lysogeny switch, the hysteretic lac repressor system, several mitogen-activated protein kinase (MAPK) cascades in animal cells, and cell cycle regulatory circuits. A bistable system always displays hysteresis, meaning that the stimulus must exceed a threshold to switch the system to another steady state, at which it may remain, when the stimulus decreases. Under proper conditions, bistability can arise from substrate inhibition or product activation in metabolic pathways, or from a a mutually inhibitory, double-negative feedback or positive feedback in artificial genetic circuits. A number of studies (e.g., see [4], [1]) have elucidated the underlying criteria for making a working switch, including conditions on the nonlinear functions that describe the interaction between network components.

A close examination of the literature, however, reveals that much of the effort in analyzing biological switches has been devoted to deciphering the networks' architectural and mechanistic features that predict the existence of a switch. By comparison, the problem of predicting the quality (i.e., performance and effectiveness) of a switch has received limited attention. For example, while the existence of multiple, stable steady states is a necessary condition for having a switch, multistability alone predicts

little about the quality of the switch. Some of the qualitative criteria for discerning the robustness of biological switches were first discussed in [4]. Examples include the proximity of steady states, both with respect to one another and with respect to the separatrix that divides their domains of attraction. In [5] it was shown, using general models of biological networks, how the relative position of the network trajectory at any given time with respect to the basins of attraction plays a critical role in deciding the fate of biological switches. According to [4], a large separation between the equilibria is desirable, both in terms of providing the switch with "immunity to stochastic fluctuations" [8] and helping bring about significant changes in gene expression levels.

The above discussion suggests that switch quality is an important factor that should be incorporated explicitly in the design of synthetic switches to ensure that they maintain their proper functionalities even under possible environmental stresses and uncertainty. So far, however, systematic approaches that take these robustness measures explicitly and quantitatively into account have yet to be developed. Motivated by this, we present in this work an optimization-based methodology for the analysis and design of robust synthetic switches in biological networks. We initially derive a general performance functional that measures quantitatively the various robustness criteria outlined in [4] and captures the tradeoffs between them. These criteria include the separation between the steady-states, the distance between each steady-state and the curve separating the basins of attraction, the switching time and the energy gap between the two states measuring the transition uncertainty. Exploiting the structure that typically characterizes models of biological networks, we use Lyapunov-based techniques to supply the link between the robustness criteria in the cost functional and the network states and parameters. With this performance measure, the synthesis problem is formulated as an optimization problem that maximizes the performance measure. In order to deal with this optimization problem, we initially analyze the behavior of the switch, with the aid of a general nonlinear model of synthetic switches, to identify possible tunable parameters that can serve as decision variables in the optimization formulation. Finally, we employ nonlinear optimization algorithms to optimize the performance measure through parameter tuning. The efficacy of the proposed optimization method is demonstrated through computer simulation studies using models of the toggle switch and the lac repressor system.

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