Engineering circuits for temporal control

Jaline Gerardin[1] and Wendell A. Lim[2]

Signaling circuits in cells are capable of generating complex outputs in response to simple inputs. In this study, we explore coarse-grained design principles behind input duration filters and sequential activators, which may elucidate mechanisms behind T cell sensitivity and selectivity as well as temporal control in the cell cycle.

***Keywords* — circuit design, input duration filter, kinetic proofreading, sequential activation**

I. Motivation

BIOLOGICAL SYSTEMS CAN EXHIBIT COMPLEX BEHAVIOR IN RESPONSE TO SIMPLE STIMULI, and forward engineering of synthetic circuits in cells requires an understanding of the coarse-grained, simple circuit architectures capable of achieving the desired performance. How are the various modules of a signaling system wired to achieve the appropriate response? We seek to understand the core circuit architectures capable of generating interesting and biologically relevant behavior. This has been accomplished recently for the function of perfect adaptation [1].

In this study, we turn our attention to two signaling behaviors that exhibit temporal control. In an input duration filter, the signaling system is capable of ignoring short input pulses and responding only to long inputs. In a sequential activator, activation of signaling components are carefully modulated such that only one component is active at a time. Elucidating the driving circuit architectures behind these functions will lead to greater understanding of biological signaling as well as enable sophisticated future synthetic endeavors where different functional modules are hooked up to engineer complex behaviors.

II. Overview

T cells are able to respond extremely sensitively to non-self ligands, yet they also ignore large volumes of weaker self ligand binding. It has been proposed that T cells' extraordinary selectivity may be due to a kinetic proofreading scheme [2], where all ligands activate a fast negative feedback loop that dampens downstream signaling while only non-self ligands bind to receptors long enough to activate a slow positive feedback loop that eventually activates the cell for irreversible differentiation [3].

A detailed version of this model has been shown to recapture key features of T cell signaling [3], but it remains unclear what general features allow the circuit to distinguish between short-binding and long-binding ligands. We seek to comprehensively search a coarse-grained circuit space to characterize all topologies with input duration filtration function.

Biological systems may respond to a signal by executing a precise sequence of events. In some cases, such as the cell cycle, upstream modules are deactivated as downstream modules are activated, resulting in a sequentially activating system with exquisite temporal control of events. Little is known of what circuitry may give rise to this function; we seek to describe simple network architectures that result in sequentially activating and deactivating circuit components.

III. Methods

Signaling circuits are represented by a 3-node quasi-steady state enzymatic system of differential equations integrated in response to a step input.

A. Input duration filter

Each circuit topology and parameter set is subjected to a series of inputs of varying duration. The resulting (maximal) response-duration curve is fit to a Hill function, and a circuit's performance is quantified by its apparent Hill and response strength. Topologies are compared by their robustness: the number of parameter sets whose apparent Hill and response strength lie above certain thresholds.

Low-pass filters are characterized by steep Bode plots; a complementary approach to simulating ODEs is to analytically generate a series of Bode plots for each topology and select those circuit architectures that robustly generate steep Bode plots.

B. Sequential activator

Circuit trajectories are solved by integrating ODEs for each topology and parameter set in response to a step input. Sequential activation is quantified by minimizing the integral of the product of two nodes while simultaneously maximizing each node's response strength.

References

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[1]Program in Biophysics, University of California, San Francisco. E-mail: jaline.gerardin@ucsf.edu

[2]Department of Cellular and Molecular Pharmacology, University of California, San Francisco, and Howard Hughes Medical Institute. E-mail: lim@cmp.ucsf.edu