

A phase diagram of regulatory strategies

Matthew Thomson¹ and David A. Sivak²

Short Abstract — Any organism is embedded in an environment (specifying for example the concentrations of basic nutrients) that changes over time. The timescale for and information content of environmental change, the precision with which the organism can detect its environment, and the timescale for effective regulation all will affect the suitability of different regulatory strategies, such as ignore, monitor-and-respond, or predict. We propose a general framework to predict the optimal regulatory strategy given the statistics of environmental and measurement fluctuations, and apply this analysis to the enzymatic regulation of metabolism. This perspective promises a theoretical framework for interpreting molecular signal processing algorithms.

Keywords — Regulation, inference, prediction.

I. PURPOSE

ANY organism is embedded in an environment (specifying for example the concentrations of basic nutrients) that changes over time, in ways typically outside its control. In response to such changing environmental conditions, organisms dynamically regulate expression of their genomes to meet physiological demands [1]. For example, many organisms implement circuits of signal transduction and regulatory molecules that collect information from the environment and modulate expression of metabolic enzymes to convert environmental nutrients into energy.

For environmental sensing and gene regulation, regulatory circuits often employ complex information processing and control algorithms [2] that can be schematically classified into broad qualitative classes including: insensitivity to environmental conditions, adaptation, temporal averaging, after-the-fact response to changes, stochastic switching, or prediction of future changes on the basis of past conditions. An important goal of systems biology is to catalog the molecular circuits [3] and corresponding information processing algorithms [4] used by a range of microorganisms and to understand how information processing algorithms are adapted to particular cellular tasks like metabolic regulation as well as particular environmental niches.

Organisms occupy a diverse range of environmental niches, so that characteristic time scales of environmental change range over many orders of magnitude. Temporal

correlations in environmental structure emerge through day and night cycles, seasons, weather patterns, timescales of host dynamics, and complex physical processes like fluid flow, turbulence, and diffusion. Quantitative biology would benefit from a quantitative picture for how various architectures of sensing and control circuits differ in their suitability across a range of environmental time scales and statistical patterns. Put simply, when does it make sense to trust one's immediate senses, to do more complicated inference, or predict the future?

II. RESULTS

Here, we develop a general theoretical framework for deriving optimal regulatory algorithms for a model cellular task, the regulation of expression of a single enzyme in response to a time-varying environmental nutrient concentration, given the statistics of environmental and measurement fluctuations.

The timescales for environmental change and effective regulation, the information content of the environment, and the precision with which the organism can detect its environment all will affect the suitability of different regulatory strategies. We demonstrate how different regimes of these basic physical properties of the environment and organism demarcate common signal processing strategies.

For example, with perfect nutrient sensors, it is optimal for the cell to simply respond to the measured concentration of a nutrient signal. As sensors become noisy, the optimal strategy switches to one of internalization (through Bayesian priors) of the statistics of environmental dynamics, which overcomes inherent physical limitations in sensing (an organism's measurement of nutrient signals) and response (carrying out a regulatory program).

Using this framework, we also derive novel regulatory algorithms by considering environments with complex temporal correlations motivated by the ecology of microorganisms.

III. CONCLUSIONS

This perspective provides computational tools for predicting optimal regulatory strategies in the presence of complex statistical patterns and promises a theoretical framework for interpreting existing biomolecular signal processing algorithms.

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Center for Systems and Synthetic Biology, University of California, San Francisco, California 94158.

¹E-mail: matthew.thompson@ucsf.edu

²E-mail: david.sivak@ucsf.edu