Metabolic gene regulation in a dynamically changing environment

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***Short Abstract* — We monitor the response of *S. cerevisiae* metabolic gene regulation to periodic changes in the external carbon source. We find that the system acts as a low-pass filter that reliably responds to a slowly changing environment, while effectively ignoring fluctuations that are too fast for the cell to efficiently respond. We use computational modeling to determine that frequency selection in the system is controlled by the interaction of coupled positive feedback networks governing the signal transduction of alternative carbon sources. Our findings establish a framework for probing organisms to reveal the mechanisms that mediate cellular responses to unpredictable environments.**

I. Introduction

Natural selection dictates that cells constantly adapt to dynamically changing environments in a context-dependent manner. For example, a sensitive response may be optimal when environmental changes are gradual while a slow response may enable cells to save energy by ignoring rapid, transient environmental fluctuations. Gene-regulatory networks often mediate cellular responses to perturbation, and an understanding of cellular adaptation will require experimental approaches aimed at subjecting cells to a dynamic environment that mimics their natural habitat [1-3].

In order to probe the response of a metabolic gene network to a fluctuating environment, we developed a microfluidic platform which can subject a population of cells to a continuously varying media supply. The device is designed to generate a fluctuating media signal by dynamically combining two media reservoirs according to a time-dependent function. Yeast cells with a fluorescent reporter protein fused to the *GAL1* promoter were subjected to sinusoidal glucose waves over a 0.2% galactose background, with varying glucose concentration from 0-0.25%. We used computational modeling to simulate the response and uncover key aspects of the network architecture that give rise to the observed behavior [4]. In particular, we were interested in how the interplay of the galactose and glucose utilization networks gives rise to low-pass filtering of carbon source fluctuations.

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II. Results

Time-lapse fluorescence imaging of the cell population in the growth chamber was used to calculate the amplitude ratio and phase shift of the cellular response relative to the glucose signal. The results showed that the metabolic network acts as a low-pass filter, with a maximum response frequency of about 5.6 rads/hr. For frequencies lower than this, the cells responded with a high amplitude response and a delayed phase shift near 0.4 rads. However, when the frequency of the perturbations was greater than 5.6 rads/hr, the amplitude of the response was very small, and usually imperceptible.

Calibration of the computational model to the experimental data led to several important observations that would not have arisen from an analysis of steady-state batch culture data. The large amplitude ratios observed at low frequencies suggested that when glucose was added to the system the degradation rates of the galactose network were greater than in the absence of glucose. Previous studies have suggested that components of the glucose network can actively decay mRNA produced by genes involved in the galactose/glucose switch [2]. We found that adding glucose-induced decay of the galactose network mRNA was crucial to obtaining a model that accurately predicted the response of the network to sinusoidal perturbations.

III. Conclusion

We have shown that the metabolic gene networks in *S. cerevisiae* act together to create a low-pass filter for dynamic changes in the environmental carbon source. Our computational modeling also provides further evidence suggesting network connections that are masked by steady-state, batch culture experiments.

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