Queueing Entrainment – Downstream control of a synthetic oscillator

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***Short Abstract* — Using microfluidic experiments, stochastic simulations, and analytical theory, we investigate how a synthetic oscillator in *E. coli* can be entrained via modulation of its protein degradation pathway. The interaction occurs primarily through "queueing" of components for degradation, where proteins compete for the oscillator's primary protease, ClpXP, which effectively acts as a queueing server with a finite bandwidth. We find that periodically varying the production rate of an otherwise independent protein targeted to ClpXP can lead to entrainment, which we understand analytically using a degrade-and-fire formalism.**

Keywords — **Entrainment, queueing theory, oscillators, synthetic biology, systems biology**

I. Introduction

Biological oscillators permeate our daily life, ranging from circadian rhythms, to cell cycles, to our very heartbeats. Control over these systems is often done through entrainment [1], but detangling the mechanism of entrainment tends to be difficult in natural oscillators due to their complex web of interactions.

A complementary strategy to understanding biological entrainment is the synthetic biology approach, where genetically encoded circuits are constructed using known parts with (mostly) known interactions. Previously, investigators successfully leveraged a synthetic oscillator in *E. coli* as a model for transcriptional regulation-based entrainment [2]. In the following, we seek to extend this investigation to explore a particular form of post-translational entrainment, where competition of components for proteolytic machinery leads to the coupling of environment to oscillator. This entrainment mechanism may arise in a number of natural oscillators, since many natural oscillators include analogous proteolytic pathways as one of their essential components.

II. A Synthetic Oscillator and ClpXP Queueing

Our model synthetic oscillator in *E. coli* functions based on two primary ingredients: delayed negative feedback and enzymatic degradation [3]. Focusing on the latter, the oscillator depends on the cell's natural degradation pathways to remove proteins from the system quickly. This degradation is due to the processive protease ClpXP targeting genetically encoded tags on oscillator proteins.

Recent work has revealed that the finite bandwidth of ClpXP naturally leads to a queueing interpretation of protein degradation [4,5], whereby the protease acts as a server for proteins. A consequence is that the protease exhibits classical queueing regimes, such as underloaded and overloaded regimes where competition for the protease is low and high, respectively [6]. These regimes can be experimentally realized using synthetic means [4].

III. Queueing Entrainment

We utilize queueing to couple two sets of tagged proteins: the oscillator proteins and a protein controlled by an externally controlled inducer. Competition for the protease is the primary source of the interaction between the two sets of proteins. This coupling allows us to entrain the oscillator with a wide array of external signals with variable strengths and periods. Entrainment is demonstrated experimentally using a microfluidic platform, which allows for tightly controlled and highly repeatable experiments. The theoretical basis for entrainment stems from the ability for queueing coupling to either dilate or contract the oscillatory period, depending on oscillatory phase. This conclusion is supported by both stochastic simulations and analytic arguments.

IV. References

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