Using Noise to Differentially Control Single Cells

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***Abstract*— Optogenetics provides powerful possibilities to engineer synthetic cell systems to exhibit complex and externally controllable behaviors. However, these systems are subject to substantial biochemical noise due to the discrete and random nature of gene regulation. A so-called "Optogenetic Maxwells Demon" (OMD) was recently proposed to exploit noise and force different cells toward different fates despite those cells exhibiting identical probabilistic rules and using only a single-input-multiple-output controller. In this presentation, we extend this theoretical analysis to exploit noise and control cells to track dynamic and asynchronous reference signals.**

***Index Terms*— Noise, Optogenetic Feedback Control, Maxwell's Demon, Synthetic Biology**

I. Introduction

The study of optogenetics combines synthetically engineered biological circuits (Fig A) with light-activated promoters to control gene activity using a modulated light source. So called "cyber-organic" systems extend these optogenetic biocircuits with electronically-modulated light sources to enable computer-based control of cellular behavior. In particular, the development of an optogenetically controllable T7 polymerase was recently used to activate genes in the presence of light [1]. Incorporating these features with optical microscopy could enable new feedback control methods where the state of the system is measured using fluorescent reporter proteins.

Synthetic biocircuits have been used myriad engineering applications where intrinsic gene regulation noise has reduced circuit performance. As such, much research has been devoted to develop circuits or control methods that mitigate or eliminate noise. However, noise can be more than just a nuisance. Recent work shows that an OMD (Fig B1) could theoretically control two identical cells to achieve two different *specified* fates by exploiting noise and nonlinearity in the rate equations while implementing feedback based on transiently-observed molecular counts. The OMD can accomplish this by observing the state of some or all cells and modulating a *single global light input* until all cells reach their desired states. Using stochastic analyses based on the Chemical Master Equation (CME), we optimize noise-exploiting controllers to reshape the joint probability distribution for multiple cells' behavior [2], [3].

*Research reported in this publication was supported by the National Institute of General Medical Sciences of the National Institutes of Health under award number R35GM124747.

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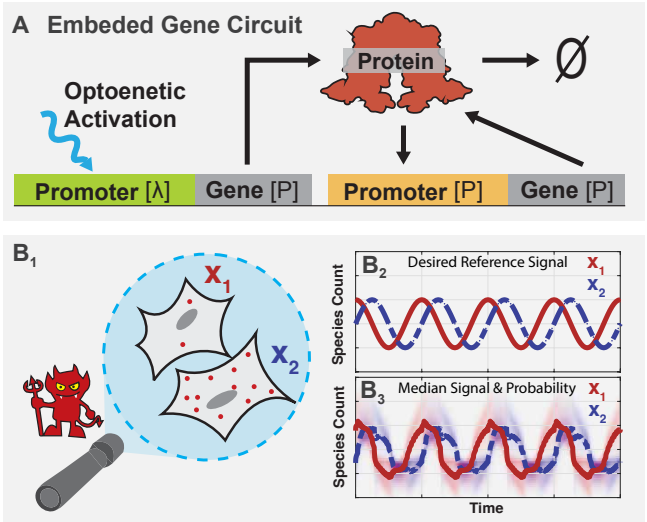

Fig. 1. A) Optogenetic T7 promoter circuit extended to include nonlinear auto-activation. B1) OMD differentially controls the fates of two cells (x_1 and x_2) by modulating a single global light input. (B2) The desired reference signal for x_1 and x_2. (B3) The median controlled value of x_1 and x_2 versus time (red and blue lines), as well as their probability distributions. Figure adapted from [4].

II. Results

We extend the development of a transient OMD controller which now forces multiple cells to track periodic reference cycles (Fig B2). The control law is generated by breaking the dynamic reference signal into a set of N quasi-steady reference points and cycling through the controllers over time. Our results indicate that for a system of cells that exhibits nonlinearity and noise, a single feedback control input (Fig A) can force multiple different cells to track different dynamic reference signals (Fig B2 and B3). We also show that the different cells can be forced to follow reference signals with different frequencies or asymmetric phase shifts. We discuss future work to improve the system response speed through eigenvalue decomposition of the CME and consideration of relaxation dynamics between shifts in the control law.

References

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