Using Stochastic Models to Control Gene Expression Under a Microscope

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***Abstract*— With the advent of easy-to-use reading and writing of genetic material, advanced microscopy platforms, and computational approaches, experimental platforms which integrate real-time measurements with computational algorithms to actuate and actively perturb biological systems require new computational tools. We present case studies for automated microscopy experiments developed using MicroMator, a Python software package for reactive microscopy. As a key example of the capability of this software, we use the optogenetic transcription factor EL222 to perform feedback control in individual yeast cells.**

***Index Terms*— Model predictive control, synthetic biology, automated microscopy**

I. Background

Modern microscopy platforms are provide a new wealth of quantitative information about how genes are regulated in synthetic and natural systems. From the synthetic biology perspective, optogenetically activated proteins enable precise perturbations of biological systems. These tools have been brought together to perform real-time control of gene expression in populations of cells, and more recently at the single-cell level [1], [2]. However, previous studies either do not make use of stochastic model based controllers [1] or were performed in mother machines in which segmentation and tracking are not necessary [2]. Here, we demonstrate single-cell control in a growing and dividing population of *S. cerevisae* using a quantitative stochastic model, with real-time segmentation and tracking of cells under the microscope. Furthermore, we demonstrate how these experiments can be implemented in our open Python-based reactive microscopy software MicroMator [3].

II. Results

We use the EL222 optogenetic gene expression system in *S. cerevisae* to control the production of a red fluorescent protein in single cells. We start by formulating a quantitative stochastic model using the finite state projection (FSP) approach to solving the chemical master equation [4], which describes the production and decay of the EL222 transcription factor and the light-activated production of a red fluorescent protein. We show that this model can be used to quantitatively predict fluorescent protein levels in individual cell, and use it as the model in a model predictive control framework. We then use Bayesian filtering based on the FSP model to estimate molecule numbers from single-cell fluorescence measurements. to perform a stochastic model predictive control of simulated fluorescence trajectories of the system. This validation of the approach on simulated data is shown in Fig. 1 (a-c). Finally, we test the single-cell control algorithm in up to 100 yeast simulataneously as they grow and divide in a microfluidic device Fig. 1(d), and compare this control strategy to other population based control strategies. Online segmentation, tracking, state estimation, and control were all implemented in open-source reactive microscopy software, MicroMator [3].

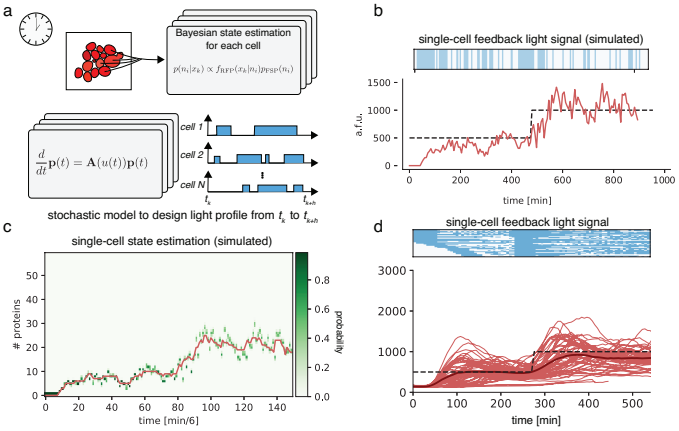

Fig. 1. (a) Overview of the FSP based model predictive control. (b) Application of the FSP-based model predictive control strategy applied to a single cell. (c) Bayesian state estimation of protein number from the trajectory in (b). (d) Single-cell fluoresence trajectories in individual yeast controlled using our FSP-based MPC algorithm.

III. Conclusion

This work brings together quantitative modeling, optogenetic synthetic biology, and reactive microscopy to control the production of protein in single cells, demonstrating how the MicroMator software can be used to program complex experiments.

References

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