Listening to the Noise: Random Fluctuations Reveal Gene Network Parameters

Brian Munsky[1], Brooke Trinh[2], and Mustafa Khammash[3]

***Short Abstract* — The goal of synthetic biology is to assemble genetic regulatory mechanisms to make cells do what we want them to do, when we want them to do it. However, before we can systematically design blueprints and control algorithms for such microscopic, living systems, we must first be able to fully characterize the behaviors of the individual components and identify the relevant kinetic parameters to describe the interplay of these components. While such mathematical descriptions initially appear extra complicated due to the inherent variability (often called "noise") of cellular processes, we show here that variability provides additional information that can actually help in the identification process. We use our approaches and flow cytometry measurements of cell variability to identify parameters and predict behaviors for the externally controlled regulation of the *lac* operon.**

***Keywords* —Genetic Regulatory Network, Stochastic Modeling, System Identification, *lac* regulation**

Cellular variability or "noise" (Elowitz, et al, 2002) leads to measurement fluctuations that may appear to complicate the analysis of gene regulatory networks. However, these fluctuations may be useful from the standpoint of system identification. In this talk we will discuss recent results regarding the identification of gene regulatory system parameters from this information regarding the variability in gene expression. In particular, we will discuss a number of findings that will help shape the use of such information in the identification of regulatory mechanisms.

First, we will use the common gene transcription/translation model from (Thattai & van Oudenaarden, 2001) and show that all parameters of this model are identifiable from cell population distributions of protein/mRNA measured at as few as two transient time instants. In contrast, two time measurements of mRNA/protein population averages are never sufficient for identifiability. Using the same model, we find that it is *impossible* to identify all parameters from stationary data. We show how taking multiple measurements in time and/or conducting additional experiments with perturbed initial conditions leads to better identification results in the presence of inaccurate measurements. This additional information can also help compensate for incomplete measurements, and we show how measurements of the protein mean and variance can be used to uniquely determine the dynamics of the protein *and* mRNA populations, thereby fully identifying the model parameters. Conversely, this identification is impossible without information regarding the protein variance. Thus, variability provides critical information that cannot be obtained from the mean behavior of the system.

We use these theoretical findings to suggest guidelines for subsequent identification studies on more realistic systems, in particular the regulation of the *lac* operon via externally applied Isopropyl-beta-D-thio-galactoside (IPTG). We grow cells with green fluorescent protein (GFP) and induce them at different times and with different levels of IPTG. These cells are then measured with flow cytometry at multiple transient time points, and the resulting histograms are used to fit parameters of a descriptive discrete stochastic model. The resulting model and the acquired parameters are used to extrapolate the response of the system under additional experimental conditions. The results of these experiments validate these predictions, and suggest that the identified model does indeed capture the important quantitative behaviors of the regulatory system. The proposed noise-based identification strategies offer a powerful means to quantitatively describe individual regulatory mechanisms. Eventually, we will quantify many more individual building blocks of systems biology, and the detailed quantification of this parts list will help researchers to systematically assemble more complicated, better characterized, and more easily controlled gene regulatory systems.

[1]Center for NonLinear Studies and CCS-3, Los Alamos National Lab. E-mail: brian.munsky@gmail.com

[2]Department of Molecular, Cellular and Developmental Biology, University of California at Santa Barbara.

[3]Department of Mechanical Engineering, University of California at Santa Barbara.

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