Spatio-temporal Measurements and Modeling of Genetic Expression

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***Short Abstract* — Recent advances in fluorescent tagging of single messenger RNA transcripts have provided the means to rapidly probe and generate statistical information on gene expression in large populations of single-cells [1-4]. Here, we present our work in which we quantify the importance of different types of fluctuations: temporal, spatial within individual cells, or cell-to-cell. We use this understanding to infer more useful gene expression models and design more informative gene expression experiments.**

***Keywords* — multiplexed smFISH, spatial stochastic modeling, gene expression**

I. Background

Single-molecule, single-cell studies of genetic expression have provided key insights into how cells respond to external stimuli [1]. By directly measuring copy numbers of individual biomolecules in cells, such as the number of individual messenger RNA transcripts, it is now possible to obtain statistical measures of the spatio-temporal distributions of key signaling and regulatory molecules. Such comprehensive datasets can be used to infer system-level models that yield quantitative insight into cellular regulation, predict cellular responses in new experimental conditions, and suggest more revealing experiments to uncover regulatory dynamics. The integration of single-molecule spectroscopy, biochemistry, and numerical modeling is a powerful multi-disciplinary approach to investigating cellular response at the genetic level.

We have constructed a microscope and data analysis package capable of automated, multiplexed measurements of mRNA transcripts tagged via smFISH [4,5]. This capability enables visualizing the spatial distribution of single mRNA transcripts in large populations of single cells and builds rich datasets for gene expression pathways. In turn, these data sets allow quantitative explorations of spatio-temporal fluctuations of mRNA within cells. A key issue we seek to address is what types of fluctuations are most informative about the underlying gene regulatory process. In other words, how much experimental resources should be spent to measure (i) *temporal*, (ii) *spatial*, or (iii) *cell-to-cell* fluctuations? As an example, we studied Interluekin 1-alpha (IL1α) mRNA expression within human THP-1 cells during stimulus response to lipopolysaccharide (LPS). By spatially resolving mRNA within thousands of individual cells at multiple times points, we quantified all three fluctuation types [5].

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II. Results

Model. We expanded the common bursting gene expression model [6] and derived a set of linear ODEs to describe the mean, variance, and co-variance of nuclear and cytoplasmic IL1α mRNA. We fit this model to the full single-cell data set from above. Next, we used this baseline model to simulate limited data sets that contain different combinations of the three fluctuation types. Comparing models inferred from each simulated data set, we are able to draw conclusions on which fluctuation types are most revealing about the underlying system's mechanisms and parameters.

Experimental Design. Using the results of this computational investigation, we are able to design the next round of experiments to provide maximal discrimination power between competing archetypes of IL1α mRNA production and regulation.

III. Conclusion

The approach developed here is applicable to any eukaryotic gene expression pathway. With careful integration of discrete spatial stochastic analyses and single-molecule experimental measurements of mRNA expression, one can design more informative experiments, capture spatial, temporal and cell-to-cell fluctuations, and uncover new insight into gene regulatory phenomena.

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