Effect of Noise and Parametric Variations on Gene Regulatory Circuit Dynamics

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***Short Abstract* — We study the effect of both the noise and the parametric variations on the gene regulatory circuit (GRC) dynamics by integrating stochastic analysis in the *Ra*ndom *Ci*rcuit *Pe*rturbation (RACIPE) method. Our two sampling schemes, one based on constant noise simulations and the other based on simulated annealing, enable estimation of both the basins of attraction as well as the relative stability of different gene expression states of the GRC. This systematic investigation of various GRC topologies sheds light on noise-induced hybrid states.**

***Keywords* — gene regulatory circuits, gene expression noise, simulated annealing, network robustness, sRACIPE.**

I. Introduction

NOISE or stochastic fluctuations in molecular components play an important role in biological systems [1-3]. The dynamics of a gene regulatory circuit (GRC), a functional regulatory network motif of a small set of interconnected regulators, can be modeled using different mathematical frameworks like stochastic simulation algorithms such as Gillespie algorithm, stochastic differential equation-based methods, asynchronous random Boolean network models, and hybrid methods [4]. Most of these methods require a fixed set of kinetic parameters whose estimations are difficult and thus any uncertainty in these parameters limits the accuracy of the models as well.

*Ra*ndom *ci*rcuit *pe*rturbation (RACIPE) is an ordinary differential equation-based method that overcomes the uncertainty in parameter estimation by generating an ensemble of models with random kinetic parameters [5-6]. Gene expression patterns obtained from the statistical analysis of this ensemble of models correspond to the distinct functional states of the GRC. To generalize the RACIPE method to capture the stochasticity of cellular processes, we have incorporated stochastic analysis in RACIPE in our method, sRACIPE [7]. Such stochastic analysis allows us to analyze changes in the gene expression patterns in different gene expression clusters at different noise levels. Crucially, sRACIPE also allows us to compare the stability of various states, which is not feasible in RACIPE in which all states are considered equally probable. This is accomplished by a simulated annealing-based approach where the GRC is first simulated at a high noise, and then the noise is decreased gradually to zero. Next, we discuss the results obtained by application of sRACIPE to various GRCs.

II. Results

Statistical analysis of sRACIPE models revealed that the changes in gene expression patterns due to parametric variations are qualitatively different from those arising due to stochasticity of molecular components. While parameter variations result in an increase in the spread of the gene expression clusters, large noise alters both the number of clusters as well as the gene expression patterns within the clusters. We observed merger of distinct states at high noise levels and creation of new hybrid states. The basin of attraction of the states can be estimated by using multiple initial conditions and simulating the GRC at a constant noise. Similar findings were observed for cascaded toggle switches and other large networks. Simulated annealing revealed relative stability of the states as well as the most stable state of a GRC as high noise enables the GRC to access all possible states and then it gets trapped in the most stable state as the noise is reduced [7].

III. Conclusion

We have developed a method to study the gene expressions of stochastic GRCs and provided a publically available R-package for applying this method to any GRC.

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