# Chapter 8
# Modeling Gene Regulatory Networks with Delayed Stochastic Dynamics

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## ABSTRACT

*We present a recently developed modeling strategy of gene regulatory networks (GRN) that uses the delayed stochastic simulation algorithm to drive its dynamics. First, we present experimental evidence that led us to use this strategy. Next, we describe the stochastic simulation algorithm (SSA), and the delayed SSA, able to simulate time-delayed events. We then present a model of single gene expression. From this, we present the general modeling strategy of GRN. Specific applications of the approach are presented, beginning with the model of single gene expression which mimics a recent experimental measurement of gene expression at single-protein level, to validate our modeling strategy. We also model a toggle switch with realistic noise and delays, used in cells as differentiation pathway switches. We show that its dynamics differs from previous modeling strategies predictions. As a final example, we model the P53-Mdm2 feedback loop, whose malfunction is associated to 50% of cancers, and can induce cells apoptosis. In the end, we briefly discuss some issues in modeling the evolution of GRNs, and outline some directions for further research.*

## INTRODUCTION

After sequencing the genomes of various organisms, understanding the integrated behavior of gene regulatory networks (GRN), taken in the large sense to comprise genes, RNA, proteins, microRNA and other molecules that mutually interact to control the dynamical behavior of the GRN within and between

DOI: 10.4018/978-1-60566-685-3.ch008

cells, has emerged as a fundamental problem in Systems Biology. So far there is only partial knowledge of the regulatory network structure and "logic" driving GRNs' dynamical behavior. Nevertheless, one can begin to address questions using the known features of these networks, by constructing the family, or ensemble, of all networks consistent with those observations.

This "ensemble" approach (Kauffman, 2004) studies the expected properties of members of the ensemble and predicts new observables to test against the dynamical behavior of cells and tissues. It is a further profound issue whether real networks are generic to any ensemble, given 3 billion years of evolution and natural selection.

There are three frameworks to analyze GRNs. At the most detailed level, one considers the chemical master equation of the detailed behavior of all components in members of some ensemble of networks. This can be done (McAdams et al, 1997) using the stochastic simulation algorithm (SSA) (Gillespie, 1977). Such models are inherently stochastic. Understanding the consequences of such noise is itself a critical problem and is focused in this chapter.

At a second level of abstraction, one considers systems of deterministic nonlinear ODEs (Mestl et al, 1995) capturing, in some sense, the mean field behavior of the real noisy stochastic networks. Since the number of copies of regulatory molecules in real system can be very small (from one to a few), such deterministic equations are, at best, an approximation, and several recent works have shown limitations of this method (Lipshtat et al, 2006). The addition of noise in Langevin equations (Toulouse et al, 2005), e.g., remains to be shown to capture the true nature of cellular dynamical noise.

At a still higher level of abstraction, one can consider models where gene states, time and other components are all discrete. While furthest from the detailed description, such models have the advantages of allowing the study of very large networks, with thousands of model genes. In particular, random Boolean networks (RBN) have been the subject of considerable analysis (Kauffman, 1969).

Here, we present the latest modeling strategy of GRNs (Ribeiro et al, 2006a), which aims to capture the relevant features of GRN to achieve simulations as realistic as possible. The dynamics is driven by the delayed SSA (Roussel & Zhu, 2006), which allows modeling multiple time-delayed reactions while maintaining a realistic account of molecular noise. We show evidence of its validity and accuracy at a detailed level.

The chapter is organized as follows. First, we describe recent experimental measurements that reveal key features that should be reflected in models of gene expression and gene-gene interactions. After that, we describe the SSA and the delayed SSA.

Next, a model for single gene expression is presented. It is shown that this model accurately reproduces recent measurements of gene expression at the single molecule level. Based on this model, a model of GRNs is proposed (Ribeiro et al, 2006a). Importantly, this modeling strategy allows applying the ensemble approach (Kauffman, 2004), which consists in simulating the dynamics of many GRNs with similar features, and extracting general properties of the dynamics from the resulting time series.

Subsequently, examples of applications of the modeling strategy are presented. A model of a toggle switch shows the relevance of including time delays in gene expression. To show the ability of modeling complex chemical pathways, we present a model of the P53-Mdm2 chemical feedback-loop, associated with important biochemical pathways in cells, responsible for responding to external stresses and apoptosis. The final section includes some preliminary studies on the evolution of these models of GRNs.