Chapter 7

Computational Approaches for Modeling Intrinsic Noise and Delays in Genetic Regulatory Networks

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ABSTRACT

This chapter focuses on the interactions and roles between delays and intrinsic noise effects within cellular pathways and regulatory networks. We address these aspects by focusing on genetic regulatory networks that share a common network motif, namely the negative feedback loop, leading to oscillatory gene expression and protein levels. In this context, we discuss computational simulation algorithms for addressing the interplay of delays and noise within the signaling pathways based on biological data. We address implementational issues associated with efficiency and robustness. In a molecular biology setting we present two case studies of temporal models for the Hes1 gene (Monk, 2003; Hirata et al., 2002), known to act as a molecular clock, and the Her1/Her7 regulatory system controlling the periodic somite segmentation in vertebrate embryos (Giudicelli and Lewis, 2004; Horikawa et al., 2006).

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1. INTRODUCTION

The mathematical modeling and simulation of genetic regulatory networks can provide insights into the complicated biological and chemical processes associated with genetic regulation. However, highly resolved computational models of such biochemical complexity can be very expensive and often infeasible and, thus, it is important that the models are kept simple but nevertheless capture the key processes.

Two vital aspects in modeling genetic regulatory networks are intrinsic noise and delays. Intrinsic noise arises in the system when there are small to moderate numbers of certain key molecules and is due to the uncertainty of knowing when a reaction occurs and which reaction it might be. Intrinsic noise is entirely different to extrinsic noise in which state changes are due to fluctuations in external conditions, such as temperature. These intrinsic noise effects can be modeled through the Stochastic Simulation Algorithm (SSA), first applied by Gillespie (1977) to simulate discrete chemical kinetics as the evolution of a discrete nonlinear Markov process.

Delays are intrinsic to slow biochemical processes that do not occur instantaneously and are often affected by spatial inhomogeneities. For instance, they are often associated with transcription and translation, two processes that imply other spatiotemporal processes often not explicitly modeled, such as (in eukaryotes) diffusion and translocation into and out of the nucleus, RNA polymerase activation, splicing, protein synthesis, and protein folding. These processes can take many minutes and so the effects are very important especially in the laying down of oscillating patterns of gene expression (Hirata et al., 2002). Monk (2003) notes that in mouse there is an average delay of 10–20 minutes between the action of a transcription factor on the promoter region of a gene and the appearance of the corresponding mRNA in the cytosol. Similarly, there is a delay of typically 1–3 minutes for the translation of a protein from mRNA.

By incorporating delays into the temporal model we can capture essential information on a macroscopic level, the delay can itself account for the multitude of biochemical processes and events on a microscopic time scale that render us unable to compute cell dynamics in real-time. Hence, we can expect more accurate and reliable predictions of cellular dynamics through the use of time delay models (Barrio et al., 2006).

One of the first people to consider feedback differential equation models for the regulation of enzyme synthesis was Goodwin (1965). An der Heiden (1979) then modified these ideas by including transport delays into Goodwin's model. The oscillatory behavior of the ensuing delay differential equations (DDEs) as a function of the size of delays was investigated by an der Heiden. However, these DDE models act in the continuous deterministic regime and this regime is not always appropriate when considering small numbers of molecules such as in the case of genetic regulation with small numbers of transcription factors.

In a lovely set of experiments, Hirata et al. (2002) measured the production of *hes1* mRNA and Hes1 protein in mice. This work forms the basis of one of our case studies in Section 4.1. Serum treatments on cultured cells result in oscillations in expression levels for *hes1* mRNA and Hes1 protein in a two hour cycle with a phase lag of approximately 15 minutes between the oscillatory profiles of mRNA and protein. The oscillations in expression continue for 6 to 12 hours.

In order to explain the observed behaviors, Hirata et al. modified a mathematical model developed by Elowitz and Leibler (2000) for a synthetic gene network constructed in *E. coli* cells by introducing one gene from λ-phage. By postulating a Hes1 interacting factor as a third molecular species Hirata et al. obtained a system of three Ordinary Differential Equations (ODEs) that gives rise to sustained

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