

Hybrid Modeling and Simulation of Biomolecular Networks

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Abstract. In a biological cell, cellular functions and the genetic regulatory apparatus are implemented and controlled by a network of chemical reactions in which regulatory proteins can control genes that produce other regulators, which in turn control other genes. Further, the feedback pathways appear to incorporate switches that result in changes in the dynamic behavior of the cell. This paper describes a hybrid systems approach to modeling the intra-cellular network using continuous differential equations to model the feedback mechanisms and mode-switching to describe the changes in the underlying dynamics. We use two case studies to illustrate a modular approach to modeling such networks and describe the architectural and behavioral hierarchy in the underlying models. We describe these models using CHARON [2], a language that allows formal description of hybrid systems. We provide preliminary simulation results that demonstrate how our approach can help biologists in their analysis of noisy genetic circuits. Finally we describe our agenda for future work that includes the development of models and simulation for stochastic hybrid systems.¹

1 Introduction

In order to survive, organisms continuously monitor their surroundings and, if necessary, adjust traffic through simple or complex combinations of genetic and metabolic networks to respond to alterations in local conditions. Local conditions include both the physical environment, for example, temperature (the heat and cold shock response), nutrient and energy source concentrations (the stringent response), light (circadian rhythms), cell density (quorum sensing response) as well as the molecular environment of individual regulatory components. Examples of the latter include intracellular concentrations of transcription factors and allosteric effectors. The availability of complete genomic information for a wide variety of organisms and the consequent attention on proteomics has dramatically increased the number of systems and components of systems that are involved in these sensing and responding activities [4,10]. Understanding how

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these biological systems are integrated and regulated and how the regulation may be influenced, possibly for therapeutic purposes, remains a significant challenge.

In this paper we model and simulate examples of genetic and metabolic networks using a hybrid systems approach that combines concepts and tools from control theory and computer science. First we analyze a previously published plasmid-based genetic network that was designed and synthesized using three repressor transcription factors where one repressor negatively regulates the production of a subsequent repressor [7]. Then we model a biologically important genetic network that controls the quorum sensing response, an adaptive response of certain gram negative bacteria to local population density [13,17]. The quorum sensing response controls the luminescent behavior in certain strains of *Vibrio* which has been linked to the normal development of the bacterial host [18] as well as to medically important phenomena such as biofilm formation by *Pseudomonas aeruginosa*, an organism that can cause overwhelming pneumonia and septic shock [11,20].

2 Modeling

The genetic circuits and biomolecular networks considered here and elsewhere are remarkably similar to hybrid systems encountered in engineering, for example embedded systems. In particular, it is worth noting the following three key features:

Concurrency and communication. At the intra-cellular level, proteins and mRNAs are agents communicating with each other and influencing each other's behavior. At the inter-cellular level, cells can be viewed as networked agents interacting with each other via different communication mechanisms.

Discrete and continuous behaviors. At the lowest level, the evolution of entities such as proteins can be described by differential equations. Discreteness arises in two ways. First, a certain activity may be triggered only when the concentration of enabling quantities is above the desired threshold. This leads to discrete switching between active and dormant states. Second, different models may be appropriate at different levels of concentration.

Stochastic behavior. Evolution of entities is not deterministic, and is better captured by stochastic models that allow for uncertainty and noise.

These characteristics are typical of high-level models of embedded software such as autonomous communicating mobile robots. For describing such systems, we have developed the language CHARON [2] which incorporates ideas from concurrency theory (languages such as CSP [12]), object-oriented software design notations (such as Statecharts [9] and UML [3]), and formal models for hybrid systems (such as hybrid automata [1] and hybrid I/O automata [15]). The key features of CHARON are:

Architectural hierarchy. The building block for describing the system architecture is an *agent* that communicates with its environment via shared