iSimBioSys :An 'In Silico' Discrete Event Simulation Framework for Modeling Biological Systems

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Abstract

The genome projects have provided comprehensive information about the basic building blocks of life. The next challenge is to understand how biological functions emerge from complex interactions of these building blocks. In this work, we present a generic, extensible in silico *simulation framework which allows the experimenter to test various hypotheses of an experiment* 'in silico' *and develop a model for subsequent wet test analysis. Undertaking a systems approach, we abstract a biological process as a set of interacting functions driven in time by a set of* discrete events. *We focus on three two-component gene regulatory networks, (a) PhoP/PhoQ network (b) barA/sirA network and (c) pmrB/pmrA network involved in bacterial pathogenesis in Salmonella Typhimurium and capture their interactions in various stages of infection. We report results on the expression of various gene and gene products from these pathways. We conclude that such a stochastic framework can provide insight into how collective interaction of different molecules manifests in physiology and diseases.*

1. Introduction

During the last decade, tremendous advancements in high-throughput biological experiments have generated an explosive amount of empirical data on the molecular foundations of biological structures and functions [1]. However, as more and more data become available, biologists are now looking beyond assigning functions to individual genes. Although individual functions and their mechanisms have been studied and characterized, most functions in biological systems involve extremely complex interactions of other biological processes and functions. The challenge [1] is to develop a comprehensive model integrating molecular and genetic data for a quantitative understanding of physiology and behavior of biological processes at multiple scales - starting from cell , to tissue, and finally to the whole organism.

In this paper, we present an illustrative example of a system engineering approach to develop a generic framework for modeling complex biological processes.

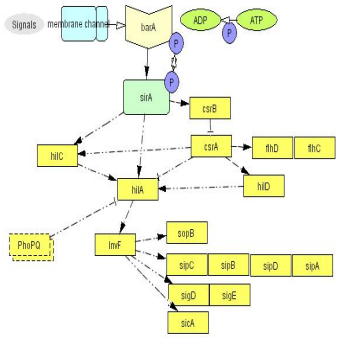

Figure 1. barA/sirA gene regulatory pathway in Salmonella

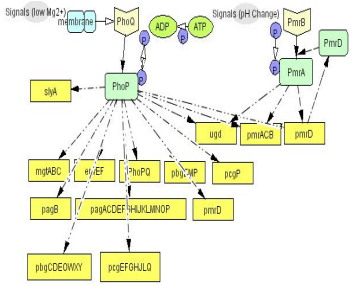

Figure 2. phoPQ and pmrAB gene regulatory pathway in Salmonella

2. Discrete Event Simulation

In stochastic discrete-event simulation paradigm, the dynamics of a complex system are captured by discrete (temporal) state variables, where an *event* is a combined process of large number of state transitions between a set of state variables accomplished within the event execution time. The key idea is to segregate the complete state-space into a disjoint set of independent events that can be executed simultaneously without any interaction. The application of discrete-event based system modeling techniques in large-scale computer and communication networks has demonstrated the accuracy of this approach for higher order system dynamics within the limits of input data, state partitioning algorithms, uncertainty of information propagation and highly mobile entities.

We identify a biological process as a system of resources (which can typically be the various molecules, ions, etc.

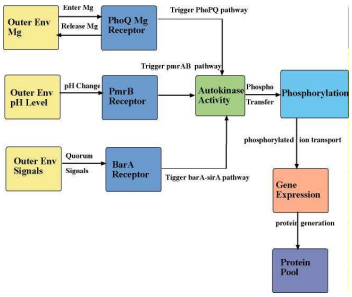

Figure 3. *iSimBioSys* Simulation Framework

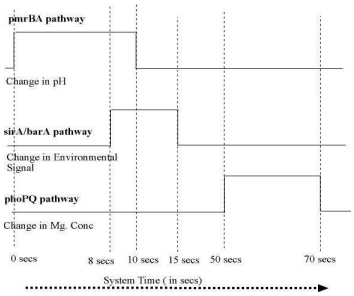

Figure 4. Timing Diagram of various environmental signals

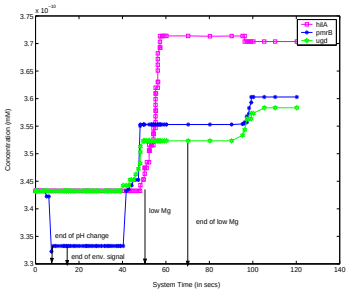

Figure 5. Dynamics of gene expression on the various pathways

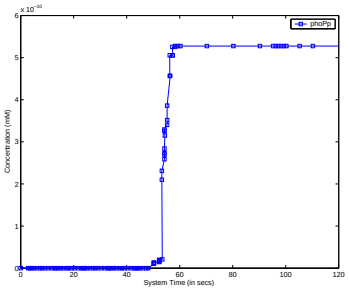

Figure 6. Enhanced activity of PhoPQ pathway in low Magnesium

involved in the system) that periodically change between 'busy' and 'free' states, based on the underlying resource usage algorithms, i.e the processes in which these resources are used. The transitions from one state to another are governed by transition flow rates of the functions involved in the process. The process is initiated by a set of input signals from the external world to the system. These input signals initiate the creation of dynamic events that drive the simulation in *time* domain, capturing how the system resources change states dynamically. The key challenges in this approach include the identification of biological discrete events based on system knowledge, the set of resources involved, and estimation of the time required to complete a biological discrete event, which is termed as the *event holding time*.

In the rest of the paper, we apply this technique to simulate interaction of virulence regulatory pathways in Salmonella Typhimurium.

3. Salmonella Pathogenesis and iSimBioSys

Bacterial pathogenesis in Salmonella typhimurium involves the complex interaction of regulatory pathways which play different roles in various stages of infection [3]. We focus on three two-component regulatory pathways involved in pathogenesis : (a) barA/sirA system which plays active role in epithelial cell invasion (b) phoPQ system and (c) pmrAB system, involved in survival in macrophage cells and acidic environments. We show how these pathways interact (manifested in change in concentration of gene products) as the bacterial cell infects.

We have developed a multi-threaded discrete-event simulation framework, called *iSimBioSys*, which models the biological processes involved in the pathways. As mentioned earlier, the key steps in the simulation are identification of the functional blocks, the discrete events driving the blocks and estimation of the block holding times. Fig.3 depicts the schematic diagram of *iSimBioSys* framework. As can be seen from the figure, the key functions driving the process have been abstracted, together with the *events* involved in driving the functions. The functions or entities, and the events define the discrete-event simulation framework. The simulation has been developed using the SimJava [4] Java-based web discrete event simulation together with a real-time graphical user interface showing the simulation run. In the next section, we report some results of the simulation of Salmonella pathogenesis on *iSimBioSys*.

4. Results

In order to capture the dynamics of the three pathways, we modeled the system holding-time of the different blocks of Fig.3, as given in [2]. The concentration of the various gene products were reported during the simulation. Fig.4 shows a timing diagram representing the duration of the various environmental signals. Based on these signals, Fig.5 captures the change in concentration of a few illustrative genes as the simulation progressed through the different pathways. Fig.6 shows the enhanced activation of the PhoPQ pathway, expressed by the rise in concentration of phosphorylated PhoP (phoPp), in low Magnesium concentration [3]. Fig.5 and Fig.6 show that *iSimBioSys* can capture the dynamic interaction of various pathways involved in Salmonella pathogenesis in terms of changing concentration of their gene products with time. We conclude that such a discrete event simulation framework, together with modeling of various biological processes, can provide an *in silico* tool for testing hypotheses prior to wet-test experiments.

References

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