Chapter 9
Process Algebra Models in Biology: The Case of Phagocytosis

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ABSTRACT

Process algebras are formal languages, which were originally designed to study the properties of complex reactive computer systems. Due to highly parallelized interactions and stochasticity inherit in biological systems, programming languages that implement stochastic extensions of processes algebras are gaining increasing attention as modeling and simulation tools in systems biology. The author discusses stochastic process algebras from the point of view of their broader potential as unifying instruments in systems biology. They argue that process algebras can help to complement conventional more established approaches to systems biology with new insights that emerge from computer science and software engineering. Along these lines, the author illustrates on examples their capability of addressing a spectrum of otherwise challenging biological phenomena, and their capacity to provide novel techniques and tools for modeling and analysis of biological systems. For the example models, they resort to phagocytosis, an evolutionarily conserved process by which cells engulf larger particles.

INTRODUCTION

Systems biology is a relatively recent term, which is often used to describe the general interdisciplinary effort in using techniques from biology, mathematics, physics and computing to provide insight into the workings of biological systems (Boogerd et al., 2007). Thus, the paradigm of systems biology covers a broad range of approaches, including those for obtaining massive amounts of information about whole biology systems. Another line of research in systems biology aims at building, with such a data, a science of principles

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of operation that is based on the interactions between components of biological systems. In this chapter, we discuss this latter consideration from the point of view of computer science (Cardelli, 2005; Fisher & Henzinger, 2007), in particular, of process algebras (Priami et al., 2001; Regev & Shapiro, 2002; Priami, 2009).

Biological systems are evolutionarily engineered, highly structured systems (Oltvai & Barabási, 2002). The underlying mechanisms enjoy an immense complexity, which is necessary for their functioning and survival, but difficult to reverse engineer. One of the reasons for this difficulty lies in obtaining 'complete' and 'accurate' data on these systems or their components for conceptualizing the acquired knowledge in (formal or informal) models. Another difficulty is that, in the presence of such data, the principles and analysis techniques imported from other disciplines are often not directly applicable to cover their complexity in an obvious way, and require an adjustment to the characteristics of the particular biological system being studied.

One of the main stream approaches for modeling and simulating the dynamics of biological systems is using differential equations, which can be traced back to the sixties (Noble, 1960) and earlier (Lotka, 1927; Volterra, 1926), and has its roots in Newton's physics. Being equipped with well understood analysis techniques, differential equations provide the 'deterministic' approach (as opposed to the stochastic approach) for modeling and simulating biological systems. In comparison to stochastic simulations, simulations with differential equation models are advantageous in terms of computational cost. However, differential equation models are inherently difficult to change, extend and upgrade, when modification to the model structure is required. For example, as new data about the modeled system is acquired, local changes in the structure of a model need to be carried over to all the equations that describe the structure of the model. Moreover, differential equations have limitations in expressivity when, for example, complexations of unbounded number of (diverse) entities are being modeled. Because of these reasons, differential equation models are better suited for models with a smaller size and fewer number of species (Danos et al., 2007). In addition, within the last few years, a general consensus has emerged that noise and stochastic effects, which are not directly captured by ordinary differential equations, are essential attributes of biological systems, especially when molecule numbers of certain species are smaller (Blossey et al, 2008; Shahrezaei & Swain, 2008).

Biological systems are massively parallel, highly complex systems, in which system components interact with each other in various ways. Similarly, complex reactive systems, as they are studied in computer science, maintain ongoing interactions with their environment rather than producing some final value upon termination. This observation points to an analogy, which provides means to study biological systems as complex reactive systems. The basic idea here is to describe the interactions of biological system components and the consequences of these interactions by means of computer language constructs in models and run simulations on these models. Such an algorithmic treatment (Priami, 2009) results in a mechanistic, systems-level consideration of the modeled biological system. In such a setting, the computer simulations can be seen as in silico experiments that are performed prior to in vitro wet-lab experiments to make predictions and guide the wet-lab experiments. Then, the newly obtained biological knowledge serves as feedback to improve the models for new predictions. In return, this approach provides feedback to develop and adapt the computer science technologies with respect to the needs of the modeled systems.

In recent years, pioneered by Regev and Shapiro's (2002) seminal work, there has been a considerable amount of research on applying computer science technologies to modeling biological systems. Various languages with stochastic simulation capabilities based on, for example,