P systems–based Modelling of Cellular Signalling Pathways

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Abstract. Cellular signalling pathways are fundamental to the control and regulation of cell behaviour. Understanding the biosignalling network functions are crucial for studying different diseases and for designing effective therapeutic approaches to them. In this paper we present P systems as a feasible computational modelling tool for cellular signalling pathways that takes into consideration the inherent randomness occurring in biological phenomena and the discrete character of the components of the system. We illustrate these cellular models simulating the EGFR signalling cascade and the FAS–induced apoptosis using a deterministic strategy for evolution of P systems.

1 Introduction

The complexity of biomolecular cell systems is currently the focus of intensive experimental research, nevertheless the enormous amount of data about the function, activity, and interactions of such systems makes necessary the development of models able to provide a better understanding of the dynamics and properties of the systems.

A model is an abstraction of the real-world onto a mathematical/computational domain that highlights some key features while ignoring others that are assumed to be not relevant. A good model should have four properties: relevance, computability, understandability and extensibility. A model must be relevant capturing the essential properties of the phenomenon investigated; and computable so it can allow the simulation of its dynamic behaviour, as well as the qualitative and quantitative reasoning about its properties. An understandable model will correspond well to the informal concepts and ideas of molecular biology. Finally, a good model should be extensible to higher levels of organisations, like tissues, organs, organism, etc, in which molecular systems play a key role.

P systems are an unconventional model of computation inspired by the structure and the functioning of living cells which takes into consideration the discrete character of the quantity of components of the system by using rewriting rules on multisets of objects, that represent chemical substances, and strings, that represent the organisation of genes on the genome. The inherently randomness

in biological phenomena is captured by using stochastic strategies . We believe that P systems satisfy the above properties required to a good model.

Cellular signalling pathways are fundamental to the control and regulation of cell behaviour. Understanding the biosignalling network functions are crucial for studying different diseases and for designing effective therapeutic approaches to them. The characterization of properties about whole–cell functions requires mathematical/computational models that quantitatively describe the relationship between different cellular components.

Ordinary differential equations (ODEs) have been successfully used to model kinetics of conventional *macroscopic* chemical reactions. That is, the approach followed by ODEs is referred as macroscopic chemistry since they model the average evolution of the concentration of chemical substances across the whole system. In this approach each chemical concentration with time is described, implicitely assuming that the fluctuation around the average value of concentration is small relative to the concentration. This assumption of homogeneity may be reasonable in some circumstances but not in many cases due to internal structure and low numbers and non–uniform distributions of certain key molecules in the cell. While differential equations models may produce useful results under certain conditions, they provide a rather incomplete view of what is actually happening in the cell [1].

Due to the complexity of cellular signalling pathways, large number of linked ODEs are often necessary for a reaction kinetics model and the many interdependent differenttial equations can be very sensitive to their initial conditions and constants. Time delays and spatial effects (that play a important role on pathway behaviour) are difficult to include in a ODE model [8] in which are also very difficult to change and extend, because changes of network topology may require substantial changes in most of the basic equations [2].

Recently, different agent–based approaches are being used to model a wide variety of biological systems ([9], [10], [20]) and biological processes, including biochemical pathways [8].

The *microscopic* approach considers the molecular dynamics for each single molecule involved in the system taking into account their positions, momenta of atoms, etc . This approach is computationally intractable because of the number of atoms involved, the time scale and the uncertainty of initial conditions.

Our approach is referred as *mesoscopic* chemistry [19]. Like in the microscopic approach one considers individual molecules like proteins, DNA and mRNA, but ignores many molecules such as water and non-regulated parts of the cellular machinery. Besides the position and momenta of the molecules are not modelled, instead one deals with the statistics of which reactions occur and how often. This approach is more tractable than microscopic chemistry but it provides a finer and better understanding than the macroscopic chemistry.

This paper is organised as follows. In the next section we present a deterministic strategy for the evolution of P systems. In Section 3 and 4 a study of EGFR signalling cascade and of FAS–induced apoptotic signalling pathway are given. Finally, conclusions are presented in the last section.

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