

Towards Probabilistic Model Checking on P Systems using PRISM

Francisco J. Romero-Campero^a, Marian Gheorghe^b,
Luca Bianco^c, Dario Pescini^d, Mario J. Pérez-Jiménez^a, Rodica Ceterchi^e

^aResearch Group on Natural Computing
Department of Computer Science and Artificial Intelligence
University of Seville, Avda. Reina Mercedes, 41012 Sevilla, Spain
Email: {fran,marper}@cs.us.es

^bDepartment of Computer Science, The University of Sheffield
Regent Court, Portobello Street, Sheffield S1 4DP, UK
Email: M.Gheorghe@dcs.shef.ac.uk

^cDepartment of Computer Science, University of Verona
Strada Le Grazie 15, 37134 Verona, Italy
Email: bianco@sci.univr.it

^dDipartimento di Informatica, Sistemistica e Comunicazione
Università degli Studi di Milano-Bicocca
Via Bicocca degli Arcimboldi 8, 20126 Milano, Italy
Email: pescini@disco.unimib.it

^eUniversity of Bucharest, Faculty of Mathematics and Computer Science
Academiei 14, 70109 Bucharest, Romania
Email: rc@funinf.cs.unibuc.ro

Abstract. In this paper it is presented the use of P systems and π -calculus to model interacting molecular entities and how they are translated into a probabilistic and symbolic model checker called PRISM.

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, an abstraction of the real-world onto a mathematical/computational domain, 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, [20]. 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, and 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.

In this paper we will deal with models developed within the framework of membrane computing. Membrane computing is an emergent branch of natural computing introduced by G. Păun in [15]. This new model of computation starts from the assumption that the processes taking place in the compartmental structure of a living cell can be interpreted as computations. The devices of this model are called P systems. Roughly speaking, a P

system consists of a cell-like membrane structure, in the compartments of which one places multisets of objects which evolve according to given rules.

Although most research in P systems concentrates on the computational power of the devices involved, lately they have been used to model biological phenomena within the framework of computational systems biology. In this case P systems are not used as a computing paradigm, but rather as a formalism for describing the behaviour of the system to be modelled. In this respect several P systems models have been proposed to describe oscillatory systems [8], signal transduction [17], gene regulation control [16], quorum sensing [12, 18, 21] and metapopulations [19]. These models differ in the type of the rewriting rules, membrane structure and the strategy applied to run the rules in the compartments defined by membranes. Some of these models using *metabolic algorithm* [5], *dynamical probabilistic P systems* [19] and *(multicompartmental) Gillespie Algorithm* [17] were applied in certain case studies.

As P systems are inspired from the structure and functioning of the living cell, it is natural to consider them as modelling tools for biological systems, within the framework of systems biology, being an alternative to more classical approaches like ordinary differential equations (ODEs) and to some recent approaches like Petri nets and π -calculus. Differential equations have been used successfully to model kinetics of conventional macroscopic chemical reactions where the main focus is on the average evolution of the concentration of chemical substances across the whole system. Nevertheless, there is an implicit assumption of continuously varying chemical concentration and deterministic dynamics. Two critical characteristics of this approach are that the number of molecules of each type in the reaction mix is large and that for each type of reaction in the system, the number of reactions is large within each observation interval, that is reactions are fast.

When the number of particles of the reacting species is small and reactions are slow, which is frequently the case in some biological systems, both of the previous assumptions are questionable and the deterministic continuous approach to chemical kinetics should be complemented by an alternative approach. In this respect, one has to recognise that the individual chemical reaction steps occur discretely and are separated by time intervals of random length. Stochastic and discrete approaches like the ones used with Petri nets [11], π -calculus [20] and P systems [17, 19] are more accurate in this situation. Nevertheless, these formalisms differs in some essential features that will be discussed briefly in this paper.

Most research in systems biology focuses on the development of models of different biological systems in order to be able to simulate them, accurate enough such as to be able to reveal new properties that can be difficult or impossible to discover through direct experiments. One key question is what one can do with a model, other than just simulate trajectories? This question has been considered in detail for deterministic models, but less for stochastic models. Stochastic systems defy conventional intuition and consequently are harder to conceive. The field is widely open for theoretical advances that help us to reason about systems in greater detail and with finer precision.

An attempt in this direction consists in using model checking tools to analyse in an automatic way various properties of the model. There are previous studies investigating the use of model checking for P system specifications [2, 7].

Our current attempt uses a probabilistic symbolic model checking approach based on PRISM (Probabilistic and Symbolic Model Checker) [22] and investigates continuous time P systems with Gillespie dynamics using protein-protein interaction rules.

Systems consisting of interacting molecular entities have been modelled by using π -calculus formalism [20] explaining the principles of transforming the biological system into a π -calculus model in a coherent way.

In this paper it is shown how π -calculus and P systems can model systems consisting of reactions with biochemical entities. The specification is translated into PRISM and various properties are studied. Some simulations obtained using the the PRISM simulator as well as a P system simulator with Gillespie dynamics are presented.

The paper is organised as follows: in section 2 a brief overview of PRISM is presented; section 3 deals with P system specifications in PRISM, section 4 presents a case study representing the cell cycle in eukaryotes described using a P system specification and a π -calculus definition; both are then translated into PRISM and contrasted in section 5; conclusions are drawn in section 6.

References

1. Alur, R., Henzinger, T.A. (1999) Reactive Modules. *Formal Methods in System Design* **15** 7–48.
2. Andrei, O., Ciobanu, G., Lucanu, D. (2005) Executable Specifications of P Systems. In: *Proc. 5th Workshop on Membrane Computing*.
3. Bernardini, F., Manca, V. (2003) P Systems with Boundary Rules. *Lecture Notes in Computer Science*, **2597**, 107–118.
4. Bernardini, F., Gheorghe, M. (2004) Population P Systems. *J. UCS* **10(5)** 509–539.
5. Bianco, L., Fontana, F., Manca, V. (2006) P Systems with Reaction Maps, *International Journal of Foundations of Computer Science*, **17** (1) 27–48.
6. Calder, M., Vyshemirsky, V., Gilbert, D., Orton, R. Analysis of Signalling Pathways using Continuous Time Markov Chains, *Transactions on Computational Systems Biology*, to appear.
7. Dang, Z., Ibarra, O.H., Li, C., Gaoyan, X. Decidability of Model-Checking P Systems. *Journal of Automata, Languages and Combinatorics*, 126–145.
8. Fontana, F., Bianco, L., Manca, V. (2005) P Systems and the Modeling of Biochemical Oscillations, *Workshop on Membrane Computing*, 199 – 208.
9. Gillespie, D.T. (1976). A General Method for Numerically Simulating the Stochastic Time Evolution of Coupled Chemical Reactions. *J Comput Physics*, **22**, 403–434.
10. Gillespie, D.T. (1977). Exact Stochastic Simulation of Coupled Chemical Reactions. *The Journal of Physical Chemistry*, **81**, 25, 2340–2361.
11. Goss, P.J.E., Peccoud, J. (1998) Quantitative modeling of stochastic systems in molecular biology using stochastic Petri nets. *Proc. Natl. Acad. Sci. USA*, **95**, 6750–6755.
12. Krasnogor, N., Gheorghe, M., Terrazas, G., Diggle, S., Williams, P., Camara, M. (2005) An appealing Computational Mechanism Drawn from Bacterial Quorum Sensing. *Bulletin of the EATCS*, **85**, 135–148.
13. Lecca, P., Corrado, P. Cell Cycle Control in Eukaryotes: A BioSpi Model, *Electronic Notes in Theoretical Computer Science*, to appear.
14. Novak, B., Csikasz-Nagy, A., Gyorffy, B., Nasmyth, K., Tyson, J.J. Model Scenarios for Evolution of the Eukaryotic Cell Cycle, (1998) *Phil. Trans. R. Soc. Lond.*, **353**, 2063–2076.
15. Păun, Gh. (2000). Computing with Membranes, *Journal of Computer and System Sciences*, **61**(1) 108 – 143.
16. Pérez-Jiménez, M.J., Romero-Campero, F.J. Modelling Gene Expression Control Using P Systems: The Lac Operon, A Case Study, submitted.
17. Pérez-Jiménez, M.J., Romero-Campero, F.J. (2006) P Systems, a New Computational Modelling Tool for Systems Biology, *Transactions on Computational Systems Biology*, to appear.
18. Pérez-Jiménez, M.J., Romero-Campero, F.J. A Model of the Quorum Sensing System in *Vibrio fischeri* using P Systems, submitted.
19. Pescini, D., Besozzi, D., Mauri, G., Zandron, C. (2006) Dynamical probabilistic P systems, *International Journal of Foundations of Computer Science*, **17** (1) 183–195.
20. Regev, A., Shapiro, E. The π -calculus as an abstraction for biomolecular systems. In Gabriel Ciobanu and Grzegorz Rozenberg, editors, *Modelling in Molecular Biology*. Springer 2004.
21. Terrazas, G., Krasnogor, N., Gheorghe, M., Bernardini, F., Diggle, S., Camara, M. (2005) An Environment Aware P-System Model of Quorum Sensing. *CIE 2005, Lecture Notes in Computer Science*, **3526**, 473–485.

22. PRISM Web Site: <http://www.cs.bham.ac.uk/~dyp/prism/>
23. The P Systems Web Site: <http://psystems.disco.unimib.it>
24. SciLab Web Site <http://scilabsoft.inria.fr/>
25. <http://www.dcs.shef.ac.uk/~marian>