Simulating FAS-Induced Apoptosis by Using P Systems

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Abstract. In contrast to differential equations, P systems are an unconventional model of computation which takes into consideration the discrete character of the quantity of components and the inherent randomness that exists in biological phenomena. The key feature of the P systems is their compartmentalized structure which represents the heterogeneity of the structural organization of the cells, and where one can take into account the role played by membranes in the functioning of the system, for example signalling at the cell surface, selective uptake of substances from the media, diffusion across different compartments, etc.
We show here that the P systems can be a reliable tool for Systems Biology and could even outperform in some cases the current simulation techniques based on differential equations. We will also use a strategy that is based on the well known Gillespie's algorithm but running on more than one compartment and so it will be called *Multi-compartmental Gillespie Algorithm.*

1 Introduction

Understanding the biosignaling pathways is essential for designing effective therapeutic approaches to several important disease. For example the FAS-induced apoptotic signalling pathway was shown to be one of the most relevant processes for understanding and combating cancer, AIDS and neurodegenerative diseases such as Parkinson's disease, Alzheimer, etc. With several pathways unraveled in the last years, each one with its own unique structure and complexity, there is an increasing need to model these signalling cascades due to their complex nature. Because there is usually immense data collected for only one pathway, it is almost always hard to understand the pathway without the help of computer simulators. For better understanding of the FAS-induced apoptosis we are proposing a new way (actually two different approaches) of simulating the pathway by using P systems.

A typical group of biosignaling pathways is known to lead to *apoptosis* (also known as programmed cell death). Apoptosis is a mechanism which helps the unwanted, injured, or improperly developed cells to commit suicide playing a fundamental role in the fight of the organism against cancers. Thus, aberrations in apoptotic responses to death signals contribute to cancer development, resistance to treatment, but also the reverse problem: autoimmune diseases. One major mechanism for inducing the apoptosis is through the activation of death receptors. Among the death receptors the signaling pathways for FAS-induced apoptosis are best characterized at the moment. We believe that the only way to understand the complex signaling behavior of this pathway is by modeling it in computer simulators.

Modeling FAS-induced apoptosis (or any biosignaling pathway) can be done in many ways, the traditional approach being at the moment the use of differential equations. We argue that the use of differential equations is not the best approach for simulating processes that involve

low number of molecules/objects as the ordinary differential equations (ODEs) are assuming large populations of molecules and are modeling the *changes* in the concentration/numbers of molecules of a particular species. For low numbers of molecules we argue that the ODEs do not provide an accurate modeling. 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. A model must be relevant capturing the essential properties of the phenomenon investigated; and computable so it can allow the simulation of its dynamic behavior, 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 organizations, like tissues, organs, organism, etc, in which molecular systems play a key role. We believe that P systems posses all these properties.

The approach followed by differential equations is usually referred to as *macroscopic chemistry* since they model the average evolution of the concentration of chemical substances across the whole system.

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 in many of the cellular components.

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 other molecules like water and non-regulated parts of the cellular machinery. Besides this, the position and momenta of the molecules are also not modeled, 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.

Another observation is that the P system paradigm focuses on the compartmental structure that is exhibited by the cells; in each compartment one has different rules and objects, and the system moves from one configuration to the next one by obeying the rules and using only the objects available in each compartment. These are the features that we want to simulate in the signalling pathways, so using P systems is a natural approach.

References

1. Cheng, E.H., Wei, M.C., Weiler, S., Flavell, R.A., Mak, T.W., Lindsten, T., Korsmeyer, S.J. (2001). BCL-2, BCL-XL sequester BH3 domain-only molecules preventing BAX- and BAK-mediated mitochondrial apoptosis. *Molecular Cell*, **8**, 705–711.
2. Gillespie, D.T. (1976). A General Method for Numerically Simulating the Stochastic Time Evolution of Coupled Chemical Reactions. *Journal of Computational Physics*, **22**, 403–434.
3. Gillespie, D.T. (1977). Exact Stochastic Simulation of Coupled Chemical Reactions. *The Journal of Physical Chemistry*, **81**, 25, 2340–2361.
4. Gillespie, D.T. (2001). Approximate Accelerated Stochastic Simulation of Chemically Reacting Systems. *Journal of Chemical Physics*, **115**, 4, 1716–1733.
5. Gillespie, D.T. (2003). Improved Leap-size Selection for Accelerated Stochastic Simulation. *Journal of Chemical Physics*, **119**, 16, 8229–8234.
6. Hua, F., Cornejo, M., Cardone, M., Stokes, C., Lauffenburger, D. (2005). Effects of Bcl-2 Levels on FAS Signaling-Induced Caspase-3 Activation: Molecular Genetic Tests of Computational Model Predictions. *The Journal of Immunology*, **175**, 2, 985–995 and correction **175**, 9, 6235–6237.
7. Ibarra, O.H., Păun, A. (2005). Counting time in computing with cells. *Proceedings of DNA Based Computing, DNA11*, London, Ontario, 25–36.

8. Krammer, P.H. (2000). CD95's deadly mission in the immune system. *Nature*, **407**, 789–795.
9. Manca, V., Bianco, L., Fontana, F. (2005). Evolution and Oscillation in P Systems: Applications to Biological Phenomena, *Lecture Notes in Computer Science*, **3365**, 63 – 84.
10. Meng, T.C., Somani S., Dhar, P. (2004). Modelling and Simulation of Biological Systems with Stochasticity. *In Silico Biology*, **4**, 3, 293–309.
11. Oltavi, Z.N., Milliman, C.L., Korsmeyer, S.J. (1993). Bcl-2 heterodimerizes in vivo with a conserved homolog, Bax, that accelerates programmed cell death. *Cell*, **74**, 4, 609–619.
12. Philips, A., Cardelli. L. (2004). A Correct Abstract Machine for the Stochastic Pi-calculus. *Electronical Notes in Theoretical Computer Science*, to appear.
13. Priami, C., Regev, A., Shapiro, E., Silverman, W. (2001). Application of a Stochastic Name-Passing Calculus to Representation and Simulation of Molecular Processes. *Information Processing Letters*, **80**, 25–31.
14. Romero-Campero, F.J., Pérez-Jiménez, M.J. (2005). A Study of the Robustness of the EGFR Signalling Cascade using Continuous Membrane Systems. *Lecture Notes in Computer Science*, **3561**, 268 – 278.
15. Pérez-Jiménez, M.J., Romero-Campero, F.J. (2006) P Systems, a New Computational Modeling Tool for Systems Biology, *Transactions on Computational Systems Biology*, to appear.
16. Scaffidi, C., Fulda. S., Srinivasan, A., Friesen, C., Li, F., Tomaselli, K.J., Debatin, K.M., Krammer, P.H., Peter, M.E. (1998). Two CD95 (APO-1/Fas) signaling pathways. *The Embo Journal*, **17**, 1675–1687.
17. Stundzia, A.B., Lumsden, C.J. (1996). Stochastic Simulation of Coupled Reaction-Diffusion Processes. *Journal of Computational Physics*, **127**, 196–207.
18. The Stochastic Pi-Machine: `http://www.doc.ic.ac.uk/~anp/spim/`.
19. Van Kampen, N.G. (1992) Stochastic Processes in Physics and Chemistry. Elsevier Science B. V., Amsterdam, The Netherlands.
20. Wang, K., Yin, X.M., Chao, D.T., Milliman, C.L., Korsmeyer, S.J. (1996). BID: a novel BH3 domain-only death agonist. *Genes & Development*, **10**, 2859–2869.