Modelling EGFR signalling network using continuous membrane systems

M.J. Pérez-Jiménez; F.J. Romero-Campero

Research Group on Natural Computing
Department of Computer Science and Artificial Intelligence
University of Sevilla
Avda. Reina Mercedes s/n, 41012, Sevilla, Spain
{marper,fran}@us.es

Abstract. The complexity of networks of biological signalling pathways is such that the development of simplifying models is essential in trying to understand the wide-ranging cellular responses they can generate. In this paper a continuous variant of membrane systems is introduced and used to model the epidermal growth factor receptor signalling network which is known to play a key role in tumour cell proliferation, angiogenesis and metastasis.

Keywords: membrane computing, EGFR signalling network, signal transduction

1 Introduction

Membrane Computing is an emergent branch of Natural Computing introduced by G. Păun in [7]. Since then it has received an important attention from the scientific community. In fact, Membrane Computing has been selected by the Institute for Scientific Information, USA, as a fast *Emerging Research Front* in Computer Science, and [6] was mentioned in [11] as a highly cited paper in October 2003.

This new non-deterministic 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 in a synchronous non-deterministic maximally parallel manner.

Most variants of membrane systems have been proved to be computationally complete, that is equivalent in power to Turing machines, and computationally efficient, that is being able to solve computationally hard problems in polynomial time. P systems as a discrete model of computation have also been used to model biological phenomena (see the volume in [1]); and as a continuous model in [5]. A first formalization of non-discrete P system and a way to approximate them was introduced in [2].

In this paper we introduce a continuous variant of P systems different from that in [5] and we use it to model the epidermal growth factor receptor (EGFR) signalling network. Up to now the usual mathematical formalization of biochemical signalling networks has been done using differential equations. This paper introduces a novel formalization of these phenomena in a computational framework.

The epidermal growth factor receptor (EGFR) belongs to the tyrosine kinase family of receptors. Binding of the epidermal growth factor (EGF) to the extracellular domain of EGFR induces receptor dimerization and autophosphorylation of intracellular domains. Then a multitude of signaling proteins are recruited starting a complex signalling cascade that transfers the activation signal from the receptor to the nucleus. Dysregulated EGFR expression, ligand production and signalling have been proved to have a strong association with tumourgenesis. As a result of this, EGFR has been identified as a key biological target for the development of novel anticancer therapies.

The paper is organised as follows. Continuous P systems are introduced in the next section. In section 3 we discuss how continuous P systems can be approximated by discrete systems in order to implement them in computers; a description of the EGF signalling network is given in section 4. In section 5 the model of the EGF signalling network is presented. Some results are exposed in the next section. Finally, conclusions and future work are given in the last section.

References

1. Ciobanu, G.; Păun, Gh.; Pérez-Jiménez, M.J.: *Applications of Membrane Computing*, Springer-Verlag (2005) in press.
2. Cordón-Franco, A.; Sancho-Caparrini, F.: Approximating Non-Discrete P Systems. In G. Mauri, Gh. Păun, M.J. Pérez-Jiménez, Gr. Rozenberg, A. Salomaa (eds.) *Membrane Computing, International Workshop, WMC5, Milan, Italy, June 2005, Revised Papers*. Lecture Notes in Computer Science, Springer, **3365**, in press.
3. Kholodenko, B.G. et al.: Quantification of short term signalling by the epidermal growth factor receptor. *J. Biol. Chem.*, **274** (1999) 30169–30181.
4. Miller, J.H.; Zheng, F.: Large-scale simulations of cellular signaling processes, *Parallel Computing* **30** (2004) 1137–1149.
5. Nishida, T.Y.: Simulations of photosynthesis by a K-Subset transforming system with membranes, *Fundamenta Informaticae*, **49**, 1 (2002), 101–113.
6. Păun, A.; Păun, Gh.: The power of communication: P systems with symport/antiport, *New Generation Computing*, **20**, 3 (2002), 295–305.
7. Păun, Gh.: Computing with membranes, *Journal of Computer and System Sciences*, **61**(1) (2000) 108 – 143.
8. Păun, Gh.: *Membrane Computing. An introduction*, Springer-Verlag Berlin, 2002.
9. Plank, M.J.; Sleeman, B.D.: Tumour-Induced Angiogenesis: A Review, *Journal of Theoretical Medicine*, in press.
10. Schoeberl, C. et al.: Computatinal modeling of the dynamics of the MAP kinase cascade activated by surface and internalized EGF receptors, *Nature Biotech.* **20** (2002) 370–375.

11. ISI web page http://esi-topics.com/erf/october2003.html
12. P systems web page http://psystems.disco.unimib.it/