Jornada de Seguimiento de Proyectos, 2009
Programa Nacional de Tecnologías Informáticas

Desarrollo de Aplicaciones de la Computación Celular con Membranas y la Computación Biomolecular en la Biología TIN2006-15595

Alfonso Rodríguez-Patón [*]
Universidad Politécnica de Madrid
Dpto. de Inteligencia Artificial

Abstract

The aim of this project is to contribute both to the progress of Natural Computing and Systems Biology, using and developing: (1) the distributed computational model inspired in the living cell called "P System" (or membrane computing), (2) biomolecular computing, and (3) microfluidic systems. The contribution of this project to these scientific areas can be split into the following objectives:

1. Modelling of cellular and neurobiological processes developing new P systems.
2. Description and mathematical formalization of biomolecular processes using automata and formal language theory.
3. Resolution of computational problems with biological motivation using distributed molecular automata and microfluidic systems.

Keywords: Membrane computing, P Systems, biomolecular computing, DNA Computing, microfluidic systems, automata theory, formal languages

1 Project goals and objectives

The aim of this project is to contribute both to the progress of Natural Computing and Systems Biology, using and developing: (1) the distributed computational model inspired in the living cell called "P System" (or membrane computing), (2) biomolecular computing, and (3) microfluidic systems.

Natural computing can be described as a scientific area with two objectives: (1) understanding the computational processes that take place in Nature (particularly in biology), and (2) developing computational models inspired in Nature.

[*] Email: arpaton@fi.upm.es

On the other hand, the emerging Systems Biology faces the following challenge: to develop strong and precise mathematical models whose application allow describing, understanding and carrying out predictions over complex biological processes and systems.

Systems Biology, P Systems, and microfluidic systems are new and relevant scientific areas. Specifically, P Systems have been selected by the *Institute for Scientific Information* (ISI) as "Fast Emerging Research Front" in computer science in 2003, and one of our papers (coauthored by Andrei Paun) has been considered as "Fast Breaking Paper", highly cited and classified in the top 1% of the field (http://esi-topics.com/erf/october2003.html). Furthermore, *Science* journal (in its number of December 23rd, 2005) has catalogued Systems Biology as one of the "Breakthrough Of The Year". *MIT Technology Review* has elected microfluidic systems like one of 10 most promising emergent technologies of 2005.

The contribution of this project to these scientific areas can be split into the following objectives:

1. Modelling of cellular and neurobiological processes developing new P systems.
2. Description and mathematical formalization of biomolecular processes using automata and formal language theory.
3. Resolution of computational problems with biological motivation using distributed molecular automata and microfluidic systems.

Other expected benefits of carrying out this project will be: (1) to take advantage of the presence of two Ramon y Cajal researchers (Petr Sosík and Andrei Paun) in our Artificial Intelligent UPM group, (2) the incorporation to a future European consortium of cellular systems and biomolecular computing, (3) the opportunity to give formation to two researchers in these topics, and (4) the consolidation of collaborations with our EPOs : Harvard University (Yaakov Benenson's group) and Western Ontario University (Lila Kari's group).

The project team to carry out the objectives is formed by **5 researchers**. and 1 PhD student. Researchers: Alfonso Rodríguez-Patón, Daniel Manrique, Juan Ríos, Petr Sosík, Andrei Paun. Ph.D. Student: Jesús María Miró Bueno.

2 Success level reached in the project

Most of the objectives and goals planned initially in the project have been reached. We have gotten relevant scientific results related with the 3 main objectives of the project.

OBJECTIVE 1. Modelling of cellular and neurobiological processes developing new P systems.

Publications generated:

1. Andrei Paun, Alfonso Rodríguez-Patón: On Flip-Flop Membrane Systems with Proteins. Workshop on Membrane Computing 2007. *Lecture Notes in Computer Science* 4860, 414-427 (2007).

2. Oscar H. Ibarra, Andrei Paun, Gheorghe Paun, Alfonso Rodríguez-Patón, Petr Sosík, Sara Woodworth: Normal forms for spiking neural P systems. *Theoretical Computer Science* 372(2-3): 196-217 (2007). Journal in **JCR** index of ISI Web.

3. Ludek Cienciala, Lucie Ciencialová, Pierluigi Frisco, Petr Sosík: On the Power of Deterministic and Sequential Communicating P Systems. *Int. J. Found. Comput. Sci.* 18(2): 415-431 (2007). Journal in **JCR** index of ISI Web.

4. García-Arnau, M; Pérez, D; Rodríguez-Patón, A; Sosík, P. On the power of elementary features in spiking neural P systems. *Natural Computing*, 7(4): 471-483 (2008).

5. Oscar H. Ibarra, Andrei Paun: Computing with cells: membrane systems - some complexity issues. *International Journal of Parallel, Emergent and Distributed Systems* (IJPEDS) 23(5): 347-365 (2008).

6. Jack, J; Rodríguez-Patón, A; Ibarra, OH; Paun, A**.** Discrete nondeterministic modeling of the FAS pathway. *International Journal of Foundations of Computer Science*, 19(5):1147 - 1162 (2008). Journal in **JCR** index of ISI Web.

7. Oscar H. Ibarra, Sara Woodworth, Fang Yu, Andrei Paun: On spiking neural P systems and partially blind counter machines. *Natural Computing* 7(1): 3-19 (2008).

---

8. Haiming Chen, Mihai Ionescu, Tseren-Onolt Ishdorj, Andrei Paun, Gheorghe Paun, Mario J. Pérez-Jiménez: Spiking neural P systems with extended rules: universality and languages. *Natural Computing* 7(2): 147-166 (2008).
9. John Jack, Andrei Paun, Alfonso Rodríguez-Patón: Effects of HIV-1 Proteins on the Fas-Mediated Apoptotic Signaling Cascade: A Computational Study of Latent CD4+ T Cell Activation. Workshop on Membrane Computing 2008, *Lecture Notes in Computer Science* 5391 Springer 2009: 246-259.

Short description of the papers:

Paper 1: We consider the membrane systems with proteins (objects) on membranes. We improve previous results in the area and also define a new variant of these systems based on time as the output of the computation. The new model allows (due to its flexibility) even stronger improvements with respect to the number of proteins needed to perform the computation.

Paper 2: The spiking neural P systems are a class of computing devices recently introduced as a bridge between spiking neural nets and membrane computing. In this paper we prove a series of normal forms for spiking neural P systems, concerning the regular expressions used in the firing rules, the delay between firing and spiking, the forgetting rules used, and the outdegree of the graph of synapses. In all cases, surprising simplifications are found, without losing the computational completeness — sometimes at the price of (slightly) increasing other parameters which describe the complexity of these systems.

Paper 3: We characterize the computational power of several restricted variants of communicating P systems. We show that 2-deterministic communicating P systems with 2 membranes, working in either minimally or maximally parallel mode, are computationally universal. Considering the sequential mode, 2 membranes are shown to characterize the power of partially blind multicounter machines. Next, a characterization of the power of 1-deterministic communicating P systems is given. Finally, we show that the non-deterministic variant in maximally parallel mode is universal already with 1 membrane.

Paper 4: Since their first publication in 2006, spiking neural (SN) P systems have already attracted the attention of a lot of researchers. This might be owing to the fact that this abstract computing device follows basic principles known from spiking neural nets, but its implementation is discrete, using membrane computing background. Among the elementary properties which confer SN P systems their computational power one can count the unbounded fan-in (indegree) and fan-out (outdegree) of each "neuron", synchronicity of the whole system, the possibility of delaying and/or removing spikes in neurons, the capability of evaluating arbitrary regular expressions in neurons in constant time and some others. In this paper we focus on the power of these elementary features. Particularly, we study the power of the model when some of these features are disabled. Rather surprisingly, even very restricted SN P systems keep their universal computational power. Certain important questions regarding this topic still remain open.

Paper 5: Membrane systems have a great potential for implementing massively concurrent systems in an efficient way that would allow us to solve currently intractable problems once future biotechnology gives way to a practical bio-realization. In this paper we survey some interesting and fundamental complexity issues such as universality vs. nonuniversality, determinism vs. nondeterminism, membrane and alphabet size hierarchies, characterizations of context-sensitive languages and other language classes and various notions of parallelism.

Paper 6: Computer modeling of molecular signaling cascades can provide useful insight into the underlying complexities of biological systems. We present a refined approach for the discrete modeling of protein interactions within the environment of a single cell. The technique we offer utilizes the Membrane Systems paradigm which, due to its hierarchical structure, lends itself readily to mimic the behavior of cells. Since our approach is nondeterministic and discrete, it provides an interesting contrast to the standard deterministic ordinary differential equations techniques. We argue that our approach may outperform ordinary differential equations when modeling systems with relatively low numbers of molecules – a frequent occurrence in cellular signaling cascades.
Refinements over our previous modeling efforts include the addition of nondeterminism for handling reaction competition over limited reactants, increased efficiency in the storing and sorting of reaction waiting times, and modifications of the model reactions. Results of our discrete simulation of the type I and type II Fas-mediated apoptotic signaling cascade are illustrated and

compared with two approaches: one based on ordinary differential equations and another based on the well-known Gillespie algorithm.

Paper 7: A k-output spiking neural P system (SNP) with output neurons, (O1 ; . . . ; Ok) , generates a tuple (n_1 ; . . . ; n_k) of positive integers if, starting from the initial configuration, there is a sequence of steps such that during the computation, each Oi generates exactly two spikes aa (the times the pair a a are generated may be different for different output neurons) and the time interval between the first a and the second a is n_i. After the output neurons generate their pairs of spikes, the system eventually halts. We give characterizations of sets definable by partially blind multicounter machines in terms of k-output SNPs operating in a sequential mode. Slight variations of the models make them universal.

Paper 8: We consider spiking neural P systems with rules allowed to introduce zero, one, or more spikes at the same time. The motivation comes both from constructing small universal systems and from generating strings; previous results from these areas are briefly recalled. Then, the computing power of the obtained systems is investigated, when considering them as number generating and as language generating devices. In the first case, a simpler proof of universality is obtained, while in the latter case we find characterizations of finite and recursively enumerable languages (without using any squeezing mechanism, as it was necessary in the case of standard rules). The relationships with regular languages are also investigated.

Paper 9: We present a new model for simulating Fas-induced apoptosis in HIV-1-infected CD4+ T cells. Moreover, the reactivation of latently infected cells is explored. The work, an extension of our previous modelling efforts, is the first attempt in systems biology for modelling the Fas pathway in the latently infected cells. We provide results, using the Nondeterministic Waiting Time (NWT) algorithm, from the model, simulating the infection of activated CD4+ T cells as well as the reactivation of the latently infected cells.

OBJECTIVE 2. Description and mathematical formalization of biomolecular processes using automata and formal language theory.

Publications generated:

10. Michael Domaratzki, Petr Sosík, Alfonso Rodríguez-Patón. Algebraic properties of substitution on trajectories. *Theoretical Computer Science*, Volume 369, Issues 1-3, 15 December 2006, Pages 183-196. Journal in **JCR** of ISI Web.

11. Andrei Paun: On the Hopcroft's minimization algorithm CoRR abs/0705.1986: (2007).

12. Andrei Paun, Mihaela Paun, Alfonso Rodríguez-Patón: Hopcroft's Minimization Technique: Queues or Stacks?. CIAA 2008 *Lecture Notes in Computer Science* 5148: 78-91 (2008).

13. Jorge Couchet, Daniel Manrique, Luis Porras: Grammar-Guided Neural Architecture Evolution. IWINAC (1) 2007, *Lecture Notes in Computer Science* 4527, 437-446 (2007).

14. Jorge Couchet, Daniel Manrique, Juan Rios, Alfonso Rodríguez-Patón: Crossover and mutation operators for grammar-guided genetic programming. *Soft Comput.* 11(10): 943-955 (2007). Journal in **JCR** index of ISI Web.

15. Marc García-Arnau, Daniel Manrique, Juan Rios, Alfonso Rodríguez-Patón: Initialization method for grammar-guided genetic programming. *Knowl.-Based Syst.* 20(2): 127-133 (2007). Journal in **JCR** index of ISI Web.

16. Peter Sebestyén, Petr Sosík: Modelling Multiple Robots in Space: An Adaptive Eco-Grammar System. *Fundamenta Informaticae* 76(3): 367-381 (2007). Journal in **JCR** index of ISI Web.

17. Lila Kari, Petr Sosík: On the weight of universal insertion grammars. *Theoretical Computer Science* 396(1-3): 264-270 (2008). Journal in **JCR** index of ISI Web.

Short description of the papers:

Paper 10: Language operations on trajectories provide a generalization of many common operations such as concatenation, quotient, shuffle and others. A trajectory is a syntactical condition determining positions where an operation is applied. Besides their elegant language-theoretical properties, the operations on trajectories have been used to solve problems in coding theory, bio-informatics and concurrency theory. We focus on algebraic properties of substitution on trajectories. Their characterization in terms of language-theoretical properties of the associated sets of trajectories is given. The transitivity property is of particular interest. Unlike, e.g., shuffle on trajectories, in the case of substitution the transitive closure of a regular set of trajectories is again regular. This result has consequences in the above-mentioned application areas.

Papers 11, 12: We consider the absolute worst case time complexity for Hopcroft's minimization algorithm applied to unary languages (or a modification of this algorithm for cover automata minimization). We show that in this setting the worst case is reached only for deterministic automata or cover automata following the structure of the de Bruijn words.

Paper 13: This article proposes a context-free grammar to be used in grammar-guided genetic programming systems to automatically design feed-forward neural architectures. This grammar has three important features. The sentences that belong to the grammar are binary strings that directly encode all the valid neural architectures only. This rules out the appearance of illegal points in the search space. Second, the grammar has the property of being ambiguous and semantically redundant. Therefore, there are alternative ways of reaching the optimum. Third, the grammar starts by generating small networks. This way it can efficiently adapt to the complexity of the problem to be solved. From the results, it is clear that these three properties are beneficial to the convergence process of the grammar-guided genetic programming system.

Paper 14: This paper proposes a new grammar-guided genetic programming (GGGP) system by introducing two original genetic operators: crossover and mutation. The first, the so-called grammar-based crossover operator, strikes a good balance between search space exploration and

exploitation capabilities and, therefore, enhances GGGP system performance. And the second is a gram- mar-based mutation operator, based on the crossover, which has been designed to generate individuals that match the syntactical constraints of the context-free grammar that defines the programs to be handled. The use of these operators together in the same GGGP system assures a higher convergence speed and less likelihood of getting trapped in local optima than other related approaches.

Paper 15: new tree-generation algorithm for grammar-guided genetic programming that includes a parameter to control the maximum size of the trees to be generated.

Paper 16: We present a multi-robot model suitable for study of interactions and emergence of rational behavior. We focus on a grammatical approach, and to demonstrate its advantages, we design a model of an adaptive multi-robot community in terms of eco-grammar systems. We show that this grammatical model, based on the blackboard architecture, can naturally involve reinforcement collective learning. We test two learning algorithms in a common environment with almost reactive co-operating robots. Experimental results show that using the grammatical model, the robot community can be successfully trained to find a close-to-optimal solution to a given NP-complete task of a truss construction.

Paper 17: We study the computational power of pure insertion grammars. We show that pure insertion grammars of weight 3 can characterize all recursively enumerable languages. This is achieved by either applying an inverse morphism and a weak coding, or a left (right) quotient with a regular language. We also study an application in DNA computing and improve some known results concerning the power of insertion–deletion DNA systems.

OBJECTIVE 3. Resolution of computational problems with biological motivation using distributed molecular automata and microfluidic systems.

Publications generated:

18. Marc García-Arnau, Daniel Manrique, Alfonso Rodríguez-Patón, Petr Sosík. A P system and a constructive membrane-inspired DNA algorithm for solving the Maximum Clique Problem. *Biosystems*, Volume 90, Issue 3, November-December 2007, Pages 687-697. Journal in **JCR** of ISI Web.

19. Petr Sosík, Alfonso Rodríguez-Patón: Membrane computing and complexity theory: A characterization of PSPACE. *J. Comput. Syst. Sci.* 73(1): 137-152 (2007). Journal in **JCR** index of ISI Web.

20. Marc García-Arnau, Daniel Manrique, Alfonso Rodríguez-Patón: A Parallel DNA Algorithm Using a Microfluidic Device to Build Scheduling Grids. IWINAC 2007. *Lecture Notes in Computer Science* 4527, 193-202 (2007).

21. Marc García-Arnau, Daniel Manrique, Alfonso Rodríguez-Patón, Petr Sosík: Towards a Robust Biocomputing Solution of Intractable Problems. DNA 2007. *Lecture Notes in Computer Science* 4848, 221-230 (2008).

22. Miró, JM; Rodríguez-Patón, A. "Biomolecular computing devices in Synthetic Biology", in Porto, A; Pazos, A; Buño, W (Eds.), IGI Global. Book: Advancing Artificial Intelligence through Biological Process Applications. Pages: 250 - 267. Medical Information Science Reference (2008).

Short description of the papers:

Paper 18: We present a P system with replicated rewriting to solve the Maximum Clique Problem for a graph. Strings representing cliques are built gradually. This involves the use of inhibitors that control the space of all generated solutions to the problem. Calculating the maximum clique for a graph is a highly relevant issue not only on purely computational grounds, but also because of its relationship to fundamental problems in genomics. We propose to implement the designed P system by means of a DNA algorithm. This algorithm is then compared with two standard papers that addressed the same problem and its DNA implementation in the past. This comparison is carried out on the basis of a series of computational and physical parameters. Our solution features a significantly lower cost in terms of time, the number and size of strands, as well as the simplicity of the biological implementation.

Paper 19: We show that confluent P systems with active membranes solve in polynomial time exactly the class of problems **PSPACE**. Consequently, these P systems prove to be equivalent (up to a polynomial time reduction) to the alternating Turing machine or the PRAM computer. Similar results were achieved also with other models of natural computation, such as DNA computing or genetic algorithms. Our result, together with the previous observations, suggests that the class **PSPACE** provides a tight upper bound on the computational potential of biological information processing models.

Paper 20: This article proposes a parallel algorithm that uses DNA and a distributed microfluidic device to generate scheduling grids in polynomial time. Rather than taking a brute force approach, the algorithm presented here uses concatenation and separation operations to gradually build the DNA strings that represent a Multiprocessor Task scheduling problem grids. The microfluidic device used makes for an autonomous system, also enabling it to solve the problem without the need of external control.

Paper 21: An incremental approach to construction of biomolecular algorithms solving intractable problems is presented. The core idea is to build gradually the space of candidate solutions and remove invalid solutions as soon as possible. We demonstrate two examples of this strategy: a P system with replication and inhibitors for solving the Maximum Clique Problem for a graph, and an incremental DNA algorithm for the same problem inspired by the membrane solution. The DNA implementation is based on the parallel filtering DNA model featuring error-resistance of the employed operations. The algorithm is compared with two standard papers that addressed the same problem and its DNA implementation in the past. The comparison is carried out on the basis of a series of computational and physical parameters. The incremental algorithm features a dramatically lower cost in terms of time, the number and size of DNA strands, together with a high error-resistance. A probabilistic analysis shows that physical parameters (volume of the DNA pool, concentration of the solution-encoding strands) and error-resistance of the algorithm should allow to process *in vitro* instances of graphs with hundreds to thousands of vertices.

Paper 22: Synthetic biology and biomolecular computation are disciplines that fuse when it comes to designing and building information processing devices. In this chapter, we study several devices that are representative of this fusion. These are three gene circuits implementing logic gates, a DNA nanodevice and a biomolecular automaton.

Other scientific achievements:

Jesús Miró is doing his Ph.D. in this topic (DNA Computing and Synthetic Biology). We have already several preliminary results that we hope to publish along this year in one journal and a couple of conferences. One of our new designs is an **oscillator** made only with DNA strands that we have sent to Friedrich Simmel's group in the Technical University of Munich to implement in his lab. The oscillator can be used as a clock in synthetic genetic circuits. Our oscillator is robust and its frequency can be tuned. The implementation is not been easy but our relationship with Friedrich Simmel is been very positive and very promising.
The other preliminary results are based on the technique called "competitive hybridization" and consist in implementing reversible and configurable computations with biomolecules (mainly with DNA). We have preliminary designs of **Fredkin and Toffoli reversible gates** made with DNA strands using as basic operation competitive hybridization between strands. If the designs work well in the lab we would considerate the case of patenting these designs.

Another relevant result related with this objective is our contacts with professor **Milan Stojanovic** from Columbia University and **Alfonso Jaramillo** from Ecole Politechnique Paris. We have agreed in a project proposal and will apply for a Human Frontier Science Program grant this next month. Professors Stojanovic and Jaramillo will give a seminar in our Ph.D. program this year. Jaramillo gave a seminar also last year.

We have planed to present a proposal to the Call 4 of the FET Proactive program of FP7. I have been in the ICT's proposer day in Budapest, 2009 and in the FET Proactive Workshop.

We also maintain our relationship with professor **Yaakov Benenson** from Harvard University. He came in 2007 and he will come again to Madrid to give a seminar in our Ph.D. program in 2009.

Marc García Arnau (a past student of our group) obtained the DEA. He stopped his Ph.D. studies (at least for a couple of years) because he approved the air controller examinations and he is doing the preparation course.

José María Font is a new Ph.D. student in the group. He has just won a FPI grant for making his Ph.D. The topic of his thesis is "in silico evolution of genetic circuits".

Petr Sosík is collaborating in a paper with Leonard Adleman (one of the inventors of the RSA and the pioneer of the DNA Computing) trying to solve open questions about the decidability of Self-assembly. This is an important theoretical problem presented in the construction of DNA assembles in nano-bio-technology, for example.

3 Indicators of results

Degree of success in planned objectives

The different papers published in 2007 and 2008 show that we have achieved a good completion of the goals and objectives of the project. The objectives are almost complete.

The remaining and more important goals for 2009 are related to the Objective 3. We have some drafts and some preliminary interesting results that we want to publish soon (but we also want to implement some of them in a wet lab so it would take some time). We also have prepared a couple of papers related to Objective 1 to be presented in conferences this next summer.

The Objective 3 is also the main topic of research in our future project proposal in the Call 4 of the FET Proactive Initiative: Bio-chemistry based Informatoin Technology(CHEM-IT) (deadline: 1 April 2009). http://cordis.europa.eu/fp7/ict/fet-proactive/calls_en.html
We plan also to apply (in collaboration with two other groups) for a research grant in the Human Frontier Science Program. www.hfsp.org

Relevance and originality of the results: Our results has been published in international journals and presented in recognized International conferences.

Scientific publications

 # Publications in total (2007-2008): 21
10 papers in journals included in the JCR of the ISI Web
4 papers in international journals (not in JCR)
6 papers in international conferences published in LNCS
1 chapter of a book

 # Publications related to Objective 1: 9
- 3 papers in JCR journals
- 4 papers in international journals (not in JCR).
- 2 papers in international conferences covered in LNCS

 # Publications related to Objective 2: 7
- 2 papers in JCR journals
- 5 papers in international conferences covered in LNCS

 # Publications related to Objective 3: 5
- 2 papers in JCR journals
- 2 papers in international conferences covered in LNCS

- 1 chapter in a book.

Andrei Paun (invited speaker):
Princeton University (NSF workshop on Emerging Models and Technologies for Computation: Bio-Inspired Computing and the Biology and Computer Science Interface) June 2008
Title: *Discrete nondeterministic modeling of cellular pathways*
• The Microsoft Research - University of Trento: Centre for Computational and Systems Biology (COSBI) Martie 2008,
Title: *Discrete nondeterministic modeling of cellular pathways*
• IBM T.J. Watson Research Center, March 2007.
Title: *Membrane systems and automata*

Alfonso Rodríguez-Patón (invited lecturer/professor in Federation of European Bioscience (FEBS) course in New Developments in Quantitative Molecular Bioscience). 10-17 September 2008.

Human resources development

We have two Ph.D. students with FPI grants making their Ph.D. thesis in topics related to the project. Jesús María Miró Bueno got an FPI grant associated with this project. José María Font has just started an FPI grant from the UPM.
José María Larrea (Ph.D. student) has just started to collaborate with our group.

Collaborations with other European or international groups

- Gheorghe Paun (Instituto de Matemáticas de la Academia de Ciencias de Rumanía)
- Mario J. Pérez Jiménez (Prof. Titular de la Univ de Sevilla y Responsable del grupo de investigación en Computación Natural de la Univ. de Sevilla)
- Oscar H. Ibarra (Catedrático de la Universidad de Santa Barbara, USA)
- Lila Kari (Professor and Canada Research Chair in Biocomputing. Department of Computer Science. University of Western Ontario, Canadá)
- Yaakov Benenson (Fellow Researcher, FAS Center for Systems Biology, Universidad de Harvard, USA).
- Alfonso Jaramillo (Ecole Polytechnique. CNRS Francia).
- Friedrich C. Simmel (Professor in the Technische Universität München, Munich, Germany).
- Milan Stojanovic (Associate Professor in Columbia University, NY, USA).

Project Management

No problems in the management of the project except the just cancelled collaboration of a researcher that finally choose another position. We are looking for another researcher. José María Larrea (Ph.D. student) has just started to collaborate in partial time with our team.

TIN2006-15595

References

1. Andrei Paun, Alfonso Rodríguez-Patón: On Flip-Flop Membrane Systems with Proteins. Workshop on Membrane Computing 2007. *Lecture Notes in Computer Science* 4860, 414-427 (2007).

2. Oscar H. Ibarra, Andrei Paun, Gheorghe Paun, Alfonso Rodríguez-Patón, Petr Sosík, Sara Woodworth: Normal forms for spiking neural P systems. *Theoretical Computer Science* 372(2-3): 196-217 (2007). Journal in **JCR** index of ISI Web.

3. Ludek Cienciala, Lucie Ciencialová, Pierluigi Frisco, Petr Sosík: On the Power of Deterministic and Sequential Communicating P Systems. *Int. J. Found. Comput. Sci.* 18(2): 415-431 (2007). Journal in **JCR** index of ISI Web.

4. García-Arnau, M; Pérez, D; Rodríguez-Patón, A; Sosík, P. On the power of elementary features in spiking neural P systems. *Natural Computing*, 7(4): 471-483 (2008).

5. Oscar H. Ibarra, Andrei Paun: Computing with cells: membrane systems - some complexity issues. *International Journal of Parallel, Emergent and Distributed Systems* (IJPEDS) 23(5): 347-365 (2008).

6. Jack, J; Rodríguez-Patón, A; Ibarra, OH; Paun, A**.** Discrete nondeterministic modeling of the FAS pathway. *International Journal of Foundations of Computer Science*, 19(5):1147 - 1162 (2008). Journal in **JCR** index of ISI Web.

7. Oscar H. Ibarra, Sara Woodworth, Fang Yu, Andrei Paun: On spiking neural P systems and partially blind counter machines. *Natural Computing* 7(1): 3-19 (2008).
8. Haiming Chen, Mihai Ionescu, Tseren-Onolt Ishdorj, Andrei Paun, Gheorghe Paun, Mario J. Pérez-Jiménez: Spiking neural P systems with extended rules: universality and languages. *Natural Computing* 7(2): 147-166 (2008).
9. John Jack, Andrei Paun, Alfonso Rodríguez-Patón: Effects of HIV-1 Proteins on the Fas-Mediated Apoptotic Signalling Cascade: A Computational Study of Latent CD4+ T Cell Activation. Workshop on Membrane Computing 2008, *Lecture Notes in Computer Science* 5391 Springer 2009: 246-259.

---

10. Michael Domaratzki, Petr Sosík, Alfonso Rodríguez-Patón. Algebraic properties of substitution on trajectories. *Theoretical Computer Science*, Volume 369, Issues 1-3, 15 December 2006, Pages 183-196. Journal in **JCR** of ISI Web.

11. Andrei Paun: On the Hopcroft's minimization algorithm CoRR abs/0705.1986: (2007).

12. Andrei Paun, Mihaela Paun, Alfonso Rodríguez-Patón: Hopcroft's Minimization Technique: Queues or Stacks?. CIAA 2008 *Lecture Notes in Computer Science* 5148: 78-91 (2008).

13. Jorge Couchet, Daniel Manrique, Luis Porras: Grammar-Guided Neural Architecture Evolution. IWINAC (1) 2007, *Lecture Notes in Computer Science* 4527, 437-446 (2007).

14. Jorge Couchet, Daniel Manrique, Juan Rios, Alfonso Rodríguez-Patón: Crossover and mutation operators for grammar-guided genetic programming. *Soft Comput.* 11(10): 943-955 (2007). Journal in **JCR** index of ISI Web.

15. Marc García-Arnau, Daniel Manrique, Juan Rios, Alfonso Rodríguez-Patón: Initialization method for grammar-guided genetic programming. *Knowl.-Based Syst.* 20(2): 127-133 (2007). Journal in **JCR** index of ISI Web.

16. Peter Sebestyén, Petr Sosík: Modelling Multiple Robots in Space: An Adaptive Eco-Grammar System. *Fundamenta Informaticae* 76(3): 367-381 (2007). Journal in **JCR** index of ISI Web.

17. Lila Kari, Petr Sosík: On the weight of universal insertion grammars. *Theoretical Computer Science* 396(1-3): 264-270 (2008). Journal in **JCR** index of ISI Web.

18. Marc García-Arnau, Daniel Manrique, Alfonso Rodríguez-Patón, Petr Sosík. A P system and a constructive membrane-inspired DNA algorithm for solving the Maximum Clique Problem. *Biosystems*, Volume 90, Issue 3, November-December 2007, Pages 687-697. Journal in **JCR** of ISI Web.

19. Petr Sosík, Alfonso Rodríguez-Patón: Membrane computing and complexity theory: A characterization of PSPACE. *J. Comput. Syst. Sci.* 73(1): 137-152 (2007). Journal in **JCR** index of ISI Web.

20. Marc García-Arnau, Daniel Manrique, Alfonso Rodríguez-Patón: A Parallel DNA Algorithm Using a Microfluidic Device to Build Scheduling Grids. IWINAC 2007. *Lecture Notes in Computer Science* 4527, 193-202 (2007).

21. Marc García-Arnau, Daniel Manrique, Alfonso Rodríguez-Patón, Petr Sosík: Towards a Robust Biocomputing Solution of Intractable Problems. DNA 2007. *Lecture Notes in Computer Science* 4848, 221-230 (2008).

22. Miró, JM; Rodríguez-Patón, A. "Biomolecular computing devices in Synthetic Biology", in Porto, A; Pazos, A; Buño, W (Eds.), IGI Global. Book: Advancing Artificial Intelligence through Biological Process Applications. Pages: 250 - 267. Medical Information Science Reference (2008).