

ECOS-Chile cooperation program : **final report**

1 PROJECT DESCRIPTION

1.1 Identity

Project number: C16E01

Title: Automata networks: inverse problems and dynamics

1.2 Partners

in France: Université d'Aix-Marseille (AMU)

Laboratory (or research group): Laboratoire d'Informatique et Systèmes (LIS, UMR7020)

Head name: Frédéric BÉCHET

in Chile: Universidad Adolfo Ibañez (UAI)

Laboratory (or research group): Facultad de Ingeniería y Ciencias

1.3 Project coordinators

in France:

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in Chile:

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Grade: Professor

Address: Universidad Adolfo Ibañez, Diagonal las Torres 2640 Peñalolen, Santiago, Chile

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1.4 Project members

in France:

Florian BRIDOUX (PhD, since 2019/07/15, AMU)

Kévin PERROT (Associate Professor, AMU)

Pacôme PERROTIN (PhD candidate, since 2017/10/01, AMU)

Martín RÍOS WILSON (PhD candidate, since 2018/03/12, UAI/AMU cotutelle)

Sylvain SENÉ (Professor, AMU)

Guillaume THEYSSIER (Researcher, CNRS)

in Chile:

Eric GOLES (Professor, UAI)

Fabiola LOBOS (PhD, since 2019/12/09, UAI)

Stephanie MACLEAN (PhD, since 2020/01/13, UAI)

Marco MONTALVA (Assistant Professor, UAI)

Martín RÍOS WILSON (PhD candidate, since 2018/03/12, UAI/AMU cotutelle)

Gonzalo RUZ (Professor, UAI)

2 Project productions

The term “cosigned” is here comprehended as signed by both a Chilean and a French members of the project at least.

2.1 Publications

- 2.1.a Number of published (or in-press, or accepted) articles in international journals with editorial board and selection process: **10** among which **4** are cosigned.
- 2.1.b Number of published (or in-press, or accepted) articles in national journals with editorial board and selection process: 0.
- 2.1.c Number of published (or in-press, or accepted) articles in other sorts of journals: 0.
- 2.1.d Number of book chapters: 0.
- 2.1.e Number of books: 0.
- 2.1.f Number of audiovisual productions: 0.
- 2.1.g Other productions: 0.

2.2 Conference communications

- 2.2.a Number of published (or accepted) papers in the proceedings of international conferences with program committee: **6** among which **1** is cosigned.
- 2.2.b Number of published (or accepted) papers in the proceedings of national conferences with program committee: 0.

2.3 Theses

- 1. Number of PhD theses defended by Chilean students in France: 0.
- 2. Number of PhD theses defended by French students in Chile: 0.
- 3. Number of PhD theses defended by Chilean students: **2**.
- 4. Number of PhD theses defended by French students: **1**.
- 5. Number of MSc theses defended by Chilean students: 0.
- 6. Number of MSc theses defended by French students: 0.
- 7. Other kinds of theses: 0.

2.4 Other productions

The two coordinators of the project, Eric Goles and Sylvain Sené, participated to the Scientific committee of the International workshop on Boolean networks (IWBN2020) that took place in Concepción (Chile) from the 7th to the 10th of January 2020.

3 Project scientific presentation

3.1 Brief presentation

Travel details

Before we present the scientific results that have been obtained during the period of the project and partially funded by it, we give a recap of the travels funded by the project:

Year	Travels
2017	Gonzalo Ruz came to Marseille during 2 weeks Fabiola Lobos came to Marseille during 1 month Guillaume Theyssier went to Santiago during 2 weeks Florian Bridoux went to Santiago during 1 month
2018	Eric Goles came to Marseille during 2 weeks Stephanie MacLean came to Marseille during 1 month Kévin Perrot went to Santiago during 2 weeks Florian Bridoux went to Santiago during 1 month
2019	Marco Montalva came to Marseille during 2 weeks Martín Ríos Wilson came to Marseille during 1 month Guillaume Theyssier went to Santiago during 2 weeks Pacôme Perrotin went to Santiago during 1 month

Achieved scientific work

From the beginning of the project in January 2017, and until its end in December 2019, the members of the research group worked together on the two computational models at stake in the project: cellular automata and Boolean networks. They obtained relevant results on their dynamics that paved the way to new problematics that will demand specific attention in the future. Succinct presentations of the main results emerging from works in which French members of the project were directly involved are given below.

Memory Boolean networks (MBNs) In [3] (an article accepted in 2018 but not published yet), E. Goles, F. Lobos, G. Ruz and S. Sené introduced a new model of Boolean networks (BNs), namely MBNs (or BNs with firing memory). MBNs are BNs whose vertices are updated synchronously depending on their proper Boolean local transition functions so that each vertex remains at its firing state a finite number of steps (a delay). They proved in particular that these networks have the same computational power than the classical ones: any MBN composed of m vertices can be simulated by a BN by adding vertices to it. They also proved general results on specific classes of networks: the existence of at least one delay greater than 1 in disjunctive networks makes such networks have only fixed points as attractors; for arbitrary networks composed of two vertices, they characterised the delay phase space. Finally, they analysed two classical biological models by introducing delays: the model of the immune control of the λ -phage and that of the genetic control of the floral morphogenesis of the plant *Arabidopsis thaliana*. Following these lines, in [13], E. Goles, and M. Ríos Wilson, together with P. Montealegre, focused on symmetric (non-directed) conjunctive networks and proved that some such networks exhibit attractors of non-polynomial period. They also proved the PSPACE-completeness of the prediction problem that consists in determining if some vertex will eventually change its state given an initial configuration.

Evolutionary computation and BN reconstruction One of the first popular applications of BNs for genetic networks is that of the control of the floral morphogenesis of the plant *Arabidopsis thaliana* introduced by Mendoza and Alvarez-Buylla at the end of the 1990s, whose specific formal attractors correspond to biological floral tissues (sepals, petals, carpels and stamens). In [16], E. Goles, G. Ruz and S. Sené considered this model and a reduced and equivalent version of it in order to reconstruct synthetic threshold BNs that admit the same asymptotic behaviour as these base models. To do so,

they exploited an evolution strategy to search for neighbouring solutions. Thanks to this strategy, they were able to find solutions, *i.e.* new BNs computing the genetic control of the floral morphogenesis, with fewer edges (model reduction) as well as networks with more balanced distributions of basins of attractions (more sound models since more likely to produce the floral tissues). Overall, the results showed the effectiveness of using evolutionary computation in this application to explore alternative solutions with desired properties.

Synchronism sensitivity in elementary cellular automata (ECA) K. Perrot and M. Montalva, together with P. de Oliveira and E. Ruivo, worked on the sensitivity of some Boolean automata networks to changes in their dynamics against deterministic update perturbations [6, 8, 7]. Due to their large number of different dynamics, they can be extremely sensitive to update schedule perturbations, which renders them not robust in this sense, a feature often undesirable in many applications. In these works, in order to restrain the entire set of possibilities, they studied in particular the maximum number of different dynamics in ECA, with fixed cyclic lattices, and with infinite lattices. This led to a complete classification of the ECA rule space according to their maximum sensitivity to update schedules. Some finer quantitative measurements of synchronism sensibility are under investigation, as well as generalizations of the “one-step” sensitivity under consideration so far.

Complexity of counting distinct block-sequential schedules on BNs Classical updating modes with which BNs are studied are block-sequential updating modes, *i.e.* defined as ordered partitions of their set of vertices. Informally, such modes are such that vertices are separated in disjoint blocks, vertices of a same block are updated in parallel and blocks are iterated sequentially, one after the other. Since the works of Aracena et. al between 2009 and 2013, it is known that update digraphs are pertinent objects to study non-equivalent block-sequential updating modes. In [14], K. Perrot and S. Sené, together with C. Noûs and L. Venturini, proved the #P-completeness of the counting problem that consists in counting the number of induced equivalence classes, that is a tight upper bound on the synchronism sensitivity of a given network. However, thanks to a decomposition method, they also proved that the problem is computable in quasi-quadratic time for specific classes of BNs, notably those whose interactions between vertices can be modelled as oriented cacti, or oriented series-parallel graphs.

Complexity of fixed points problems on BNs An interesting question on discrete dynamical systems (DDSs), consists in understanding towards which specific behaviours they tend to evolve. In the framework of BNs, since they are finite DDS instances, these asymptotic behaviours are either fixed points or limit cycles, and have relevant meanings in the context of genetic regulation modelling: fixed points may be associated with differentiated cellular types and limit cycles with specific biological rhythms. Furthermore, given a BN $f : \{0, 1\}^n \rightarrow \{0, 1\}^n$ composed of n vertices, the architecture of the interactions between its vertices is classically represented by a signed interaction graph (SIG). In this SIG, if vertex i has a positive (resp. negative) influence on component j , then j tends to mimic (resp. negate) i . One important fact is that whilst a BN admits one SIG, a SIG may correspond to several distinct BNs. Thanks to experiments, molecular biologists often discover the SIG they do not know. A classical question they ask to their colleagues (mathematicians or computer scientists) is: given that SIG, can it correspond to a BN having at least k fixed points? In [11], F. Bridoux and K. Perrot, together with N. Durbec and A. Richard, proved that answering to this question is a computational problem that is in P or complete for NP, NP^{#P} or NEXPTIME depending on the given SIG, and can thus be intractable.

BN (de)composition and modules BNs can be viewed as a generalisation of Boolean cellular automata that are well known to be Turing universal. So, any theorem describing the way BNs compute information would be a strong tool that could be applied to a wide range of models of computation. In [6], K. Perrot, P. Perrotin and S. Sené followed this idea and explored and proposed a way of working with BNs that involves adding external inputs to the base model (via modules), and more importantly, a way to link networks together using the above mentioned inputs (via wirings). The

aim was to develop a powerful formalism for BN (de)composition. They obtained three results: the first one proves that the formalism is complete, which means that any BN can be created from modules and wirings; the second one uses modules/wirings to prove simulation results amongst BNs (in particular, it proves that composing with local simulations (of modules) is sufficient to simulate the dynamics of a whole BN; the third one expresses the complexity (CoNP-completeness) of the relation between modularity and the dynamics of modules. In [15], following these lines, they provided other results that offer an upper bound on the number of attractors in an acyclic module when the latter is wired recursively into a BN, and a diversity of complexity results on decision problems related to the existence of a fixed point or a limit cycle of a given length depending on the number of inputs, that can be fixed parameter tractable, or NP-complete as the case may be.

Intrinsic simulation of automata networks (ANs) An AN is a generalisation of a BN, in which the states of the vertices are not in $\{0, 1\}$ but in a set Q . Concisely, it is defined as a function $f : Q^n \rightarrow Q^n$. In [12], F. Bridoux and G. Theyssier, together with M. Gadouleau, studied how some (sets of) automata networks can be simulated by some other (set of) automata networks with prescribed updating mode or interaction graph. The goal was to better understand the computational power of sequential and asynchronous updating modes. So, they proved that, for non-Boolean alphabets and any network size, there are intrinsically non-sequential transformations (that cannot be obtained as composition of sequential updates of some network); there are no universal ANs that can produce all non-bijective functions via compositions of asynchronous updates; there are universal ANs for sequential updates if one allows to use a larger alphabet and then use either projection onto or restriction to the original alphabet. They also characterised the set of functions that are generated by non-bijective sequential updates as well as the SIGs whose transformation semigroup is the full semigroup of transformations on Q^n , and showed that they are the same for either sequential updates only or all asynchronous updates.

3.2 Relations between proposed and achieved objectives

The project C16E01 that was funded by ECOS was entitled “Automata networks: inverse problem and dynamics”. Its general problematics can be summed up in *developing mathematical and algorithmic methods to study two classes of ANs, cellular automata and BNs, through their ability to model genetic regulation networks and the complexity of some computational problems*. To this extent, the works led and the results obtained during the project period do constitute an achievement of the objectives proposed in 2016, but not only, in the sense that other thematics were addressed, such as intrinsic simulation.

Firstly, in relation to the computational models viewed as models of genetic regulation networks, notice that the works on MBNs are directly linked with biological problematics since they are issued from a concise and complete mathematical formalisation of a model of regulation networks integrating the actions of genes and proteins; besides, in [3], two applications of this new formalism were made on both the immune control of the bacteriophage λ on the bacterium *Escherichia coli* and the morphogenetic control of the flower development of *Arabidopsis thaliana*. On the latter, a reconstruction process were also developed using evolutionary computation to obtain synthetic BNs with the same asymptotic features, but reduced and more sound with respect to developmental biology phenomenology [16]. In [6], a cell cycle sequence of the fission yeast model was used to emphasise the relevance of the BN (de)composition formalism in a biological context. Eventually, even if they have not been discussed in the report, notice that other biological problems were addressed during the period: (i) using a reconstruction process similar to the one used in [16] based on the neutral space computation, the project led to better suited BNs for modelling the *Clostridium difficile* infection [9]; and (ii) deriving from the studies on the influence of updating modes on the dynamics of BNs, [1] highlighted the importance of focusing on more general update methods to capture biological clocks by modelling the morphogenesis of the Chilean tree *Araucaria araucana* and the cardio-respiratory pace.

Secondly, concerning the axis related to computational problems, even if complexity results have been obtained during the period, some changes were made regarding to the decision problems initially intended. Indeed, where we told that that we would work especially on the PRED et ATTRACT problems in the framework of CA, we finally worked on computational problems (counting and decision ones) related to BNs. This comes essentially from (i) the first advances we made during the first year and a half of the project on (M)BNs about the ways of organising updates over time; and (ii) the wish to obtain theoretical results as general as possible and certainly more useful in the context of biological modelling. Indeed, in discrete modelling, the organisation of updates over time is essential. It is all the more essential to pay attention to it since literature in biology does not give strong results about the way genes express over time, except a strong hypothesis centred on the chromatin dynamics. Of course, if we want to reach results susceptible to help/consolidate biologists, the first step is to know to which extent we can comprehend the intrinsic changes operated by updating modes on the dynamics of BNs. That is why in [14], the focus was put on the counting problem aiming at knowing how many update graphs equivalence classes do exist, which led to show that its complexity remains tractable, even if it is among the most difficult tractable problems. And that is why in [11, 15], the focus was put on decision problems related to attractors (fixed points and limit cycles), which showed that such problems remain very often intractable.

3.3 Scientific and economic benefits

The economic axis is not discussed here, simply because it does not make sense for a project like C16E01. At the scientific level, the main already acquired benefits have just been discussed but let us sum up them, while presenting what is certainly more interesting at present, namely the future expected benefits. Broadly speaking, this project led to results that solved questions of importance for the domain of finite dynamical systems, in particular the ones related to complexity theory. It also helped the research group to open questions (and to solve some of them) about intrinsic simulation, a concept that was not studied so far in the framework of ANs. This concept paves the way to a lot of further studies that should lead to begin to know well the subtleties of the computational expressiveness of these objects. Moreover, the developments around MBNs provided a new way to consider temporal actions in the BN universe. This model remains clearly not well comprehended, notably because it induces updating modes that are far more general than the classical ones, which gives a lot of opportunities for progressing on it from the theoretical point of view. To finish, it is obvious that the main part of the efforts made during the project was made on theoretical aspects combining discrete mathematics and fundamental computer science. As a matter of fact, whilst they undoubtedly show the relevance of the work done, the applications to biology evoked in this report could develop more in the future to become more impacting and affect substantially other disciplines.

3.4 Formation and research benefits for the research group

The project created the opportunity to consolidate the existing collaboration between the Chilean group in Santiago and the French group in Marseille. This consolidation notably materialised in the cotutelle of the PhD thesis of M. Ríos Wilson who is co-supervised by A. Maass and E. Goles (on the Chilean side) and by G. Theyssier and S. Sené (on the French side), and who should be able to defend his PhD during the first semester of 2021. Also, the thematics addressed reinforced the doctoral program in Computer science and complex systems at UAI, and participated in creating a course on “Discrete dynamical systems and Models of computation” at the Master 2 degree in Computer science and discrete mathematics at AMU.

3.5 Perspectives of the collaboration

Scientific perspectives The three years collaboration has opened a lot of scientific perspectives, among which the following theoretical ones that seem very pertinent:

- The introduction of MBNs in [3] as well as the positions developed in [1] about block-parallel updating modes open several research tracks on the organisation of updates over time in discrete dynamical systems. If one consider updating modes with the more general standpoint, they are defined for a given BAN as the set of infinite sequences of subsets of its vertices, which represents an uncountably infinite set. Of course, it is inconceivable to begin working on such a set. That is why DDSs are classically studied with restricted (deterministic or not) families of updating modes. The most known are the block-sequential ones (regrouping the parallel one and the sequential ones). But MBNs whose vertices are subjected to sorts of independent local clocks, and block-parallel modes, are more general deterministic modes that deserve to be studied in depth, all the more because their features fit quite well to real biological phenomena. That is the first perspective.
- The computational problems that were dealt with in the project closed questions related to complexity theory. But numerous other problems could be addressed. For instance, in [11], the problem was to understand, for a given SIG, if it could admit a BN evolving towards at least (resp. at most) k fixed points. A direct perspective of this work is to address similar questions concerning limit cycles. Such works should be much more difficult because the appearing of limit cycles as attractors of a BN is not as well understood as that of fixed points. Another more long term perspective on this theme comes from the results obtained in [14] about the complexity of counting the equivalence classes induced by block-sequential questions. If one succeeded in making advances about the dynamical properties generated by more general updating modes, it would be natural to tackle similar questions in this framework.

Future of the collaboration On the scientific perspectives presented above, the Chilean and French researchers who compose the research group of the project will keep working together whatever the funding context, as they have had the habits since years. Even if it has not been discussed at present, the submission of an ANR project is a possible scenario. Such a project could group together researchers who work on such DDSs from France (Marseille, Nice, Paris-Saclay, Bordeaux), Chile (Santiago, Concepción), and England (Durham).

3.6 Publication list

In this section are listed all the publications published by the members of the project in the context of this French-Chilean collaboration founded by ECOS (which is therefore acknowledged at the end of these papers). The presentation is done following the subsections of Section 2.

Articles in international journals

- [1] Jacques Demongeot and Sylvain Sené. About block-parallel Boolean networks: a position paper. *Natural Computing*, 19:5–13, 2020.
- [2] Enrico Formenti and Kévin Perrot. How hard is it to predict sandpiles on lattices? A survey. *Fundamenta Informaticæ*, 171:189–219, 2020.
- [3] Eric Goles, Fabiola Lobos, Gonzalo A. Ruz, and Sylvain Sené. Boolean networks with firing memory. *Natural Computing*. Accepted.
- [4] Stephanie MacLean, Marco Montalva-Medel, and Eric Goles. Block invariance and reversibility of one dimensional linear cellular automata. *Advances in Applied Mathematics*, 105:83–101, 2019.
- [5] Kévin Perrot, Marco Montalva-Medel, Pedro P. B. de Oliveira, and Eurico L. P. Ruivo. Maximum sensitivity to update schedules of elementary cellular automata over periodic configurations. *Natural Computing*, 19:51–90, 2020.
- [6] Kévin Perrot, Pacôme Perrotin, and Sylvain Sené. On Boolean automata networks (de)composition. *Fundamenta Informaticæ*. Accepted.

- [7] Eurico L. P. Ruivo, Pedro P. B. de Oliveira, Marco Montalva-Medel, and Kévin Perrot. Maximum sensitivity to update schedules of elementary cellular automata over infinite configurations. *Information and Computation*, 2020. In press.
- [8] Eurico L. P. Ruivo, Marco Montalva-Medel, Pedro P. B. de Oliveira, and Kévin Perrot. Characterisation of the elementary cellular automata in terms of their maximum sensitivity to all possible asynchronous updates. *Chaos, Solitons & Fractals*, 113:209–220, 2018.
- [9] Dante Travisany, Eric Goles, Mauricio Latorre, María-Paz Cortés, and Alejandro Maass. Generation and robustness of Boolean networks to model *Clostridium difficile* infection. *Natural Computing*, 19:111–134, 2020.
- [10] André P. Vieira, Eric Goles, and Hans J. Herrmann. Dynamics of extended Schelling models. *Journal of Statistical Mechanics: Theory and Experiment*, 2020:013212, 2020.

Papers in international conferences

- [11] Florian Bridoux, Nicolas Durbec, Kévin Perrot, and Adrien Richard. Complexity of maximum fixed point problem in Boolean networks. In *Proceedings of CiE'19*, volume 11558 of *LNCS*, pages 132–143. Springer, 2019.
- [12] Florian Bridoux, Maximilien Gadouleau, and Guillaume Theyssier. Simulation of automata networks. In *Proceedings of CiE'20*, 2020. Accepted.
- [13] Eric Goles, Pedro Montealegre, and Martín Ríos Wilson. On the effects of firing memory in the dynamics of conjunctive networks. In *Proceedings of AUTOMATA'19*, volume 11525 of *LNCS*, pages 1–19. Springer, 2019.
- [14] Camille Noûs, Kévin Perrot, Sylvain Sené, and Lucas Venturini. #P-completeness of counting update digraphs, cacti, and series-parallel decomposition method. In *Proceedings of CiE'20*, 2020. Accepted.
- [15] Kévin Perrot, Pacôme Perrotin, and Sylvain Sené. On the complexity of acyclic modules in automata networks. In *Proceedings of TAMC'20*, 2020. Accepted.
- [16] Gonzalo A. Ruz, Eric Goles, and Sylvain Sené. Reconstruction of Boolean regulatory models of flower development exploiting an evolution strategy. In *Proceedings of CEC'18*, pages 1–8. IEEE Press, 2018.

Theses

- [17] Florian Bridoux. *Simulations intrinsèques et complexités dans les réseaux d'automates*. PhD thesis, Université d'Aix-Marseille, 168 pages, 2019.
- [18] Fabiola Lobos. *Dynamics of Automata Networks: Theory and numerical experiments*. PhD thesis, Universidad Adolfo Ibáñez & Universidade Presbiteriana Mackenzie, 137 pages, 2020.
- [19] Stephanie MacLean. *Dynamics of Automata under different update schedules*. PhD thesis, Universidad Adolfo Ibáñez, 93 pages, 2019.