Activity Report 2015

Project-Team LIFEWARE

Computational systems biology and optimization

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Project-Team LIFEWARE

Creation of the Team: 2014 January 01, updated into Project-Team: 2015 April 01

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1. Members

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Grégory Batt [Inria, Researcher, HdR]
Sylvain Soliman [Inria, Researcher]

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Thierry Martinez [Inria SED]
Philippe Morignot [Inria, until Feb 2015]

PhD Students
François Bertaux [Ecole Polytechnique, with EPI MAMBA]
Katherine Chiang [NTU, Taiwan, until July 2015]
Artémis Llamosi [CNRS, with MSC lab (CNRS/Paris7)]
Jean-Baptiste Lugagne [Inria, with MSC lab (CNRS/Paris7)]
Jonas Sénizergues [Inria, from Oct 2015]
Pauline Traynard [Inria]

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Pascal Hersen [CNRS, MSC lab (CNRS/Paris7), Researcher]
Denis Thieffry [ENS Paris, Professor, HdR]

Administrative Assistants
Virginie Collette [Inria, up to Nov 2015]
Assia Saadi [Inria, since Dec 2015]

Others
Virgile Andréani [ENS Paris, Internship, from Oct 2015]
Ewen Corre [Inria, Internship Approches Interdisciplinaires du Vivant, with MSC lab (CNRS/Paris7), from Oct 2015]
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2. Overall Objectives

2.1. Overall Objectives

This project aims at developing formal methods and experimental settings for **understanding the cell machinery** and establishing formal paradigms in cell biology. It is based on the vision of **cells as machines**, **biochemical reaction systems as programs**, and on the use of concepts and tools from computer science to master the complexity of cell processes. While for the biologist, as well as for the mathematician, the size of the biological networks and the number of elementary interactions constitute a complexity barrier, for the computer scientist the difficulty is not that much in the size of the networks than in the unconventional nature of biochemical computation. Unlike most programs, biochemical reaction systems involve transitions that are stochastic rather than deterministic, continuous-time rather than discrete-time, poorly localized in compartments instead of well-structured in modules, and created by evolution instead of by rational design. It is our belief however that some form of modularity is required by an evolutionary system to survive, and that the elucidation of these modules in biochemical computation is now a key to apply engineering methods in cell biology on a large scale.

Concretely, we keep developping a theory of biochemical computation and a prototype implementation in the Biochemical Abstract Machine BIOCHAM, a modeling and analysis platform for systems biology. The reaction rule-based language used in this system allows us to reason about biochemical reaction networks at different levels of abstraction, in either the **stochastic, differential, discrete, logical or hybrid semantics** of the reactions. This allows us to develop and apply a variety of **static analysis** methods, before going to simulations and **dynamic analyses**, for which we use **quantitative temporal logics** as a mean to formalize biological properties with imprecise data, constrain model building and calibrate models in high dimension by optimization methods.

A **tight integration between dry lab and wet lab** efforts is also essential for the success of the project. In collaboration with Pascal Hersen, MSC lab, we contribute to the development of an experimental platform for the closed-loop control of intracellular processes. This platform combines hardware (microfluidic device and microscope), software (cell tracking and model-based predictive control algorithms) and genetically modified living cells. It is used to investigate the possibilities to externalize the control of intracellular processes for systems and synthetic biology applications.

This project addresses fundamental research issues in computer science on the interplay between **structure and dynamics** in large interaction networks, and on the mixing of **continuous and discrete computation**. Many static analysis problems of biological networks are NP-hard. The recourse to constraint logic programming (CLP) to model and solve them, is our secret weapon, which probably explains our capability to experiment ideas in computational systems biology in very short time, by implementing them in CLP, integrating them as new components in our modeling platform BIOCHAM, and evaluating them directly on a large scale in systems biology model repositories such as BIOMODELS.NET.

The originality of this project also deals with the recourse to advanced micro-fluidic and **synthetic biology** technologies to perform accurate observations, modifications and real-time control at both single cell and cell population levels. For this to work, collaborations with top international leaders of these techniques have been established and consolidated with student exchange programs, especially in the framework of the Doctorate School "Frontiers in Life Sciences" to which we are affiliated, in addition to "Sciences Mathématiques de Paris-Centre".

3. Research Program

3.1. Computational Systems Biology

Bridging the gap between the complexity of biological systems and our capacity to model and **quantitatively predict system behaviors** is a central challenge in systems biology. We believe that a deeper understanding of the concept and theory of biochemical computation is necessary to tackle that challenge. Progress in the theory is necessary for scaling, and enabling the application of static analysis, module identification and decomposition, model reductions, parameter search, and model inference methods to large biochemical reaction systems. A measure of success on this route will be the production of better computational modeling tools for elucidating the complex dynamics of natural biological processes, designing synthetic biological circuits and biosensors, developing novel therapy strategies, and optimizing patient-tailored therapeutics.

Progress on the **coupling of models to data** is also necessary. Our approach based on quantitative temporal logics provides a powerful framework for formalizing experimental observations and using them as formal specification in model building. Key to success is a tight integration between *in vivo* and *in silico* work, and on the mixing of dry and wet experiments, enabled by novel biotechnologies. In particular, the use of microfluidic devices makes it possible to measure behaviors at both single-cell and cell population levels *in vivo*, provided innovative modeling, analysis and control methods are deployed *in silico*.

In synthetic biology, while the construction of simple intracellular circuits has shown feasible, the design of larger, **multicellular systems** is a major open issue. In engineered tissues for example, the behavior results from the subtle interplay between intracellular processes (signal transduction, gene expression) and intercellular processes (contact inhibition, gradient of diffusible molecule), and the question is how should cells be genetically modified such that the desired behavior robustly emerges from cell interactions.

3.2. Modeling of Cellular Processes

Since nearly two decades, a significant interest has grown for getting a quantitative understanding of the functioning of biological systems at the cellular level. Given their complexity, proposing a model accounting for the observed cell responses, or better, predicting novel behaviors, is now regarded as an essential step to validate a proposed mechanism in systems biology. Moreover, the constant improvement of stimulation and observation tools creates a strong push for the development of methods that provide predictions that are increasingly precise (single cell precision) and robust (complex stimulation profiles). In addition to the widely-used ordinary differential equation modeling framework, stochastic modeling frameworks, such as chemical master equations, and statistic modeling frameworks, such as ensemble models, are increasingly popular, since they enable to capture biological variability.

In all cases, dedicated mathematical and computational approaches are needed for the analysis of the models and their calibration to experimental data. One can notably mention global optimization tools to search for appropriate parameters within large spaces, moment closure approaches to efficiently approximate stochastic models, and (stochastic approximations of) the expectation maximization algorithm for the identification of mixed-effects models.

3.3. External Control of Cell Processes

External control has been employed since many years to regulate culture growth and other physiological properties. Recently, taking inspiration from developments in synthetic biology, closed loop control has been applied to the regulation of intracellular processes. Such approaches offer unprecedented opportunities to investigate how a cell process dynamical information by maintaining it around specific operating points or driving it out of its standard operating conditions. They can also be used to complement and help the development of synthetic biology through the creation of hybrid systems resulting from the interconnection of in vivo and in silico computing devices.

In collaboration with Pascal Hersen (CNRS MSC lab), we developed a platform for gene expression control that enables to control protein concentrations in yeast cells. This platform integrates microfluidic devices enabling long-term observation and rapid change of the cells environment, microscopy for single cell measurements, and software for real-time signal quantification and model based control. We demonstrated recently that this platform enables controlling the level of a fluorescent protein in cells with unprecedented accuracy and for many cell generations [1].

3.4. Chemical Reaction Network Theory

Feinberg's chemical reaction network theory and Thomas's influence network analyses provide sufficient and/or necessary structural conditions for the existence of multiple steady states and oscillations in regulatory networks, which can be predicted by static analyzers without making any simulation. In this domain, most of our work consists in analyzing the interplay between the **structure** (Petri net properties, influence graph, subgraph epimorphisms) and the **dynamics** (Boolean, CTMC, ODE, time scale separations) of biochemical reaction systems. In particular, our study of influence graphs of reaction systems, our generalization of

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[1] Jannis Uhlendorf, Agnés Miermont, Thierry Delaveau, Gilles Charvin, François Fages, Samuel Bottani, Grégory Batt, Pascal Hersen. Long-term model predictive control of gene expression at the population and single-cell levels. Proceedings of the National Academy of Sciences USA, 109(35):14271–14276, 2012.

Thomas' conditions of multi-stationarity and Soulé's proof to reaction systems [2], the inference of reaction systems from ODEs [7], the computation of structural invariants by constraint programming techniques, and the analysis of model reductions by subgraph epimorphisms [2], now provide solid ground for developing static analyzers, using them on a large scale in systems biology, and elucidating modules.

3.5. Logical Paradigm for Systems Biology

Our group was among the first ones in 2002 to apply **model-checking** methods to systems biology in order to reason on large molecular interaction networks, such as Kohn's map of the mammalian cell cycle (800 reactions over 500 molecules) [3]. The logical paradigm for systems biology that we have subsequently developped for quantitative models can be summarized by the following identifications :

$$biological\ model = transition\ system,$$

$$biological\ property = temporal\ logic\ formula,$$

$$model\ validation = model\text{-}checking,$$

$$model\ inference = constraint\ solving.$$

In particular, the definition of a continuous satisfaction degree for **first-order temporal logic** formulae with constraints over the reals, was the key to generalize this approach to quantitative models, opening up the field of model-checking to model optimization. This line of research continues with the development of patterns with efficient solvers and their generalization to handle stochastic effects.

3.6. Constraint solving and optimization

Optimization methods are important in our research. On the one hand, static analysis of biochemical reaction networks involves solving hard combinatorial optimization problems, for which **constraint programming** techniques have shown particularly successful, often beating dedicated algorithms and allowing to solve large instances from model repositories. On the other hand, parameter search and model calibration problems involve similarly solving hard continuous optimization problems, for which **evolutionary algorithms** such as the covariance matrix evolution strategy (CMA-ES) [4] has shown to provide best results in our context, for up to 100 parameters, for building challenging quantitative models, gaining model-based insights, revisiting admitted assumptions and contributing to biological knowledge [5]

4. Application Domains

4.1. Preamble

Our collaborative work on biological applications is expected to serve as a basis for groundbreaking advances in cell functioning understanding, cell monitoring and control, and novel therapy design and optimization. We work mainly on eukaryotic cells. Our collaborations with biologists are focused on **concrete biological questions**, and on the building of predictive models of biological systems to answer them. However, one important application of our research is the development of a **modeling platform** for systems biology.

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[2]Sylvain Soliman. A stronger necessary condition for the multistationarity of chemical reaction networks. Bulletin of Mathematical Biology, 75(11):2289–2303, 2013.

[3]N. Chabrier-Rivier, M. Chiaverini, V. Danos, F. Fages, V. Schächter. Modeling and querying biochemical interaction networks. Theoretical Computer Science, 325(1):25–44, 2004.

[4]N. Hansen, A. Ostermeier (2001). Completely derandomized self-adaptation in evolution strategies. Evolutionary Computation, 9(2) pp. 159–195.

[5]Domitille Heitzler, Guillaume Durand, Nathalie Gallay, Aurélien Rizk, Seungkirl Ahn, Jihee Kim, Jonathan D. Violin, Laurence Dupuy, Christophe Gauthier, Vincent Piketty, Pascale Crépieux, Anne Poupon, Frédérique Clément, François Fages, Robert J. Lefkowitz, Eric Reiter. Competing G protein-coupled receptor kinases balance G protein and β-arrestin signaling. Molecular Systems Biology, 8(590), 2012.

4.2. Modeling platform for systems biology

Since 2002, we develop an open-source software environment for modeling and analyzing biochemical reaction systems. This software, called the Biochemical Abstract Machine (BIOCHAM), is compatible with SBML for importing and exporting models from repositories such as BioModels. It can perform a variety of static analyses, specify behaviors in Boolean or quantitative temporal logics, search parameter values satisfying temporal constraints, and make various simulations. While the primary reason of this development effort is to be able to **implement our ideas and experiment them quickly on a large scale**, BIOCHAM is used by other groups either for building models, for comparing techniques, or for teaching (see statistics in software section). BIOCHAM-WEB is a web application which makes it possible to use BIOCHAM without any installation. We plan to continue developing BIOCHAM for these different purposes and improve the software quality.

4.3. Couplings between the cell cycle and the circadian clock

Recent advances in cancer chronotherapy techniques support the evidence that there exist important links between the cell cycle and the circadian clock genes. One purpose for modeling these links is to better understand how to efficiently target malignant cells depending on the phase of the day and patient characterictics. These questions are at the heart of our collaboration with Franck Delaunay (CNRS Nice) and Francis Lévi (Univ. Warwick, GB, formerly INSERM Hopital Paul Brousse, Villejuif) and of our participation in the ANR Hyclock project and in the submitted EU H2020 C2SyM proposal, following the former EU EraNet Sysbio C5SYS and FP6 TEMPO projects. In the past, we developed a coupled model of the Cell Cycle, Circadian Clock, DNA Repair System, Irinotecan Metabolism and Exposure Control under Temporal Logic Constraints [6]. We now focus on the bidirectional coupling between the cell cycle and the circadian clock and expect to gain fundamental insights on this complex coupling from computational modeling and single-cell experiments.

4.4. Biosensor design and implementation in non-living vesicles

In collaboration with Franck Molina (CNRS, Sys2Diag, Montpellier) and Jie-Hong Jiang (NTU, Taiwan) we ambition to apply our techniques to the design and implementation of biosensors in non-living vesicles for medical applications. Our approach is based on purely protein computation and on our ability to compile controllers and programs in biochemical reactions. The realization will be prototyped using a microfluidic device at CNRS Sys2Diag which will allow us to precisely control the size of the vesicles and the concentrations of the injected proteins. It is worth noting that the choice of non-living chassis, in contrast to living cells in synthetic biology, is particularly appealing for security considerations and compliance to forthcoming EU regulation.

5. Highlights of the Year

5.1. Highlights of the Year

Four PhD Theses Defended this Year

Katherine Chiang defended her thesis [1] in three years at National Taiwan University and two internships with us in 2012 and 2013, on the computer-aided design of biomolecular systems, a subject co-supervised by Jie-Hong Jiang and François Fages which is of increasing importance in Lifeware and led to several publications this year [11], [6], [5].

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[6] Elisabetta De Maria, François Fages, Aurélien Rizk, Sylvain Soliman. Design, Optimization, and Predictions of a Coupled Model of the Cell Cycle, Circadian Clock, DNA Repair System, Irinotecan Metabolism and Exposure Control under Temporal Logic Constraints. Theoretical Computer Science, 412(21):2108 2127, 2011.

Artemis Llamosi defended his thesis [3] in three years also, on the modeling of cell-to-cell variability, a subject co-supervised by Grégory Batt and Pascal Hersen, which led to a major publication in *PLoS Computational Biology* [8] to appear in 2016, and a cooperation with Marc Lavielle (EP POPIX).

Steven Gay finally defended his thesis [2] on subgraph epimorphisms and model reductions, a subject co-supervised by François Fages and Sylvain Soliman, 18 months after he left us for taking a Post Doc position at Univ. Louvain-la-Neuve, Belgium.

Thierry Martinez defended his thesis [4] supervised by François Fages, on a logical kernel for constraint programming, with direct impact on the design of the ClpZinc modeling language and the rewriting of Biocham v4, for which he got engineer positions n the last years.

In addition, François Bertaux has sent to reviewers his thesis on the modeling of cell-to-cell variability and cell apoptosis, co-supervised by Dirk Draso and Grégory Batt. Sylvain Soliman has sent to reviewers his *Habilitation à Diriger des Recherches* on the dynamics of biochemical systems. Pauline Traynard is also finishing her thesis co-supervised by François Fages and Denis Thieffry, on temporal logic patterns and solvers and the modeling of the interactions between the cell cycle and the circadian clock, for a defense in early 2016 in three years and half. Jean-Baptiste Lugagne is also expected to defend his thesis in 2016.

These theses are the foundations of some major themes of Lifeware for the next years.

6. New Software and Platforms

6.1. BIOCHAM

The Biochemical Abstract Machine
KEYWORDS: Systems Biology - Bioinformatics
FUNCTIONAL DESCRIPTION

The Biochemical Abstract Machine (BIOCHAM) is a software environment for modeling and analyzing biochemical reaction systems, making simulations, performing static analyses, specifying behaviors in temporal logic.

- Participants: François Fages, François-Marie Floch, Thierry Martinez, Sylvain Soliman
- Contact: François Fages
- URL: http://lifeware.inria.fr/biocham/

6.2. BIOCHAM-WEB

KEYWORDS: Systems Biology - Bioinformatics
FUNCTIONAL DESCRIPTION

BIOCHAM-web is a web service which makes it possible to try BIOCHAM on line without any installation, through a spreadsheet.

- Participants: François Fages, François-Maris Floch and Thierry Martinez
- Contact: François Fages
- URL: http://lifeware.inria.fr/biocham/online/

6.3. CellStar

KEYWORDS: Systems Biology - Bioinformatics
FUNCTIONAL DESCRIPTION

In close collaboration with Kirill Batmanov, Cédric Lhoussaine and Cristian Versari from the LIFL (CNRS/Lille Univ) and with Pascal Hersen (MSC lab; CNRS/Paris 7), we developed CellStar, a tool-chain for image processing and analysis dedicated to segmentation and tracking of yeast cells in brightfield time-lapse microscopy movies. To estimate algorithm quality we developed a benchmark made of manually-verified images illustrating various situations. On this benchmark, CellStar outperformed 5 other state-of-the-art methods. The tool-chain is implemented in MATLAB and is provided together with the Python Yeast Image Toolkit benchmark tool.

- Participants: Pascal Hersen, Grégory Batt, Artémis Llamosi
- Contact: Grégory Batt
- URL: http://yeast-image-toolkit.biosim.eu/pmwiki.php

6.4. ClpZinc

FUNCTIONAL DESCRIPTION

CLP2Zinc is a rule-based modeling language for constraint programming. It extends the MiniZinc modeling language with Horn clauses which can be used to express search strategies as constraints in the model. This system is developed in the framework of the ANR Net-WMS-2 project and is a follow-up of the Rules2CP modeling language.

- Participants: Thierry Martinez, François Fages, Philippe Morignot and Sylvain Soliman
- Contact: Thierry Martinez
- URL: http://lifeware.inria.fr/~tmartine/clp2zinc/

7. New Results

7.1. Hybrid Simulation of Heterogeneous Biochemical Models in SBML

Participants: Katherine Chiang, François Fages, Sylvain Soliman.

Models of biochemical systems presented as a set of formal reaction rules can be interpreted in different for- malisms, most notably as either deterministic Ordinary Differential Equations, stochastic continuous-time Markov Chains, Petri nets or Boolean transition systems. While the formal composition of reaction systems can be syntactically defined as the (multiset) union of the reactions, the composition and simulation of models in different formalisms remains a largely open issue. In [5], we show that the combination of reaction rules and events, as already present in SBML, can be used in a non-standard way to define stochas- tic and boolean simulators and give meaning to the hybrid composition and simulation of heterogeneous models of biochemical processes. In particular, we show how two SBML reaction models can be composed into one hybrid continuous-stochastic SBML model through a high-level interface for composing reaction models and specifying their interpretation. Furthermore, we describe dynamic strategies for automatically partitioning reactions with stochastic or continuous interpretations according to dynamic criteria. The per- formances are then compared to static partitioning. The proposed approach is illustrated and evaluated on several examples, including the reconstructions of the hybrid model of the mammalian cell cycle regulation of Singhania et al. as the composition of a Boolean model of cell cycle phase transitions with a continuous model of cyclin activation, the hybrid stochastic-continuous models of bacteriophage T7 infection of Alfonsi et al., and the bacteriophage λ model of Goutsias, showing the gain in both accuracy and simulation time of the dynamic partitioning strategy.

7.2. Theoretical and Practical Complexities of Enumerating Minimal Siphons in Petri Nets

Participants: François Fages, Thierry Martinez, Sylvain Soliman.

Petri nets are a simple formalism for modeling concurrent computa- tion. They are also an interesting tool for modeling and analysing biochemical reaction systems, bridging the gap between purely qualitative and quantita- tive models. Biological networks can indeed be complex, large, and with many unknown kinetic parameters, which makes the development of quantitative models difficult. In [9], we focus on the Petri net representation of biochemical reactions and on two structural properties of Petri nets, siphons and traps, that bring us information about the persistence of some molecular species, independently of the kinetics. We first study the theoretical time com- plexity of minimal siphon decision problems in general Petri nets, and present three new complexity results: first, we show that the existence of a siphon of a given cardinality is NP-complete; second, we prove that deciding the Siphon- Trap property is co-NP-complete; third, we prove that deciding the existence of a minimal siphon containing a given set of places, deciding the existence of a siphon of a given cardinality and deciding the Siphon-Trap property can be done in linear time in Petri nets of bounded tree-width. Then, we present a Boolean model of siphons and traps, and two methods for enumerating all minimal siphons and traps of a Petri net, by using a SAT solver and a Con- straint Logic Program (CLP) respectively. On a benchmark of 345 Petri nets of hundreds of places and transitions, extracted from biological models from the BioModels repository, as well as on a benchmark composed of 80 Petri nets from the Petriweb database of industrial processes, we show that both the SAT and CLP methods are overall faster by one or two orders of magnitude com- pared to the state-of-the-art algorithm from the Petri net community, and are in fact able to solve all the enumeration problems of our practical benchmarks. We investigate why these programs perform so well in practice, and provide some elements of explanation related to our theoretical complexity results.

7.3. Abstraction-based Parameter Synthesis for Multiaffine Systems

Participant: Grégory Batt.

Multiaffine hybrid automata (MHA) represent a powerful formalism to model complex dynamical systems. This formalism is particularly suited for the representation of biological systems which often exhibit highly non-linear behavior. In [10], we consider the problem of parameter identification for MHA. We present an abstraction of MHA based on linear hybrid automata, which can be analyzed by the SpaceEx model checker. This abstraction enables a precise handling of time-dependent properties. We demonstrate the potential of our approach on a model of a genetic regulatory network and a myocyte model.

7.4. Tropical Algebra Methods for Model Reduction

Participants: François Fages, Jonas Sénizergues, Sylvain Soliman.

Jonas Sénizergues has just started a PhD Thesis on the design of model reduction techniques for systems biology based on tropical algebra. The idea is to reason on the orders of magnitude of both kinetic parameters and molecular concentrations in order to determine particular regimes exhibiting fast-slow decomposition and amenable to model reductions. Such model reductions generalize the quasi steady-state (QSSA) and quasi-equilibrium (QE) criteria, and lead to hybrid automata for chaining the reduced dynamics. The solving of tropical equilibration equations rely on previous work using constraint programming techniques [7] with collaboration with Ovidier Radulescu (Univ. Montpellier) and Andreas Weber (University of Bonn, Germany).

7.5. Modeling the Effect of the Cell Cycle on the Circadian Clock in Mouse Embryonic Fibroblasts

Participants: François Fages, Jonas Sénizergues, Denis Thieffry, Pauline Traynard, Sylvain Soliman.

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[7] Sylvain Soliman, François Fages, Ovidiu Radulescu. A constraint solving approach to model reduction by tropical equilibration. Algorithms for Molecular Biology, 9(24), 2014.

Experimental observations have put in evidence autonomous self-sustained circadian oscillators in most mammalian cells, and proved the existence of molecular links between the circadian clock and the cell cycle. Several models have been elaborated to assess conditions of control of the cell cycle by the circadian clock, in particular through the regulation by clock genes of Wee1, an inhibitor of the mitosis promoting factor, responsible for a circadian gating of mitosis and cell division period doubling phenomena. However, recent studies in individual NIH3T3 fibroblasts have shown an unexpected acceleration of the circadian clock together with the cell cycle when the milieu is enriched in FBS, the absence of such acceleration in confluent cells, and the absence of any period doubling phenomena. In [14], we try to explain these observations by a possible entrainment of the circadian clock by the cell cycle through the inhibition of transcription during mitosis. We develop a differential model of that reverse coupling of the cell cycle and the circadian clock and investigate the conditions in which both cycles are mutually entrained. We use the mammalian circadian clock model of Relogio et al. and a simple model of the cell cycle by Qu et al. which focuses on the mitosis phase. We show that our coupled model is able to reproduce the main observations reported by Feillet et al. in individual fibroblast experiments and use it for making some predictions. In [17], those hypothesis are revised in order to reproduce the phase data in addition to the period data and make new predictions.

7.6. Effects of repeated osmotic stress on gene expression and growth: from cell-to-cell variability to cellular individuality in the budding yeast *Saccharomyces cerevisiae*

Participants: Grégory Batt, Ewen Corre, Pascal Hersen, Artémis Llamosi.

When shifted to a stressful environment, cells are capable of complex response and adaptations. Although the cellular response to a single stress has been studied in great detail, very little is known when it comes to dynamically fluctuating stressful environments. In addition, in the context of stress response, the role of cell-to-cell variability in cellular processes and more specifically in gene expression is still unclear.

In his PhD thesis [3], Artémis Llamosi uses a systems and synthetic biology approach to investigate osmotic stress in *S. cerevisiae* at the single cell level. Combining microfluidics, fluorescent microscopy and advanced image analysis, we are able to subject cells to precise fluctuating osmolarity and monitor single-cell temporal response.

While much previous research in gene expression heterogeneity focused on its stochastic aspect, we consider here long-lasting differences between cells regarding expression kinetics. Using population models and state-of-the-art statistical analysis, we manage to represent both population and single-cell dynamics in a single concise modelling framework. This quantitative approach capturing stable individuality in gene expression dynamics can define a form of non-genetic cellular identity.

To improve our understanding of the biological interpretation of such identity, we investigate the relation between single-cell specificities in their gene expression with their phenotype and micro-environment. We then take a lineage based perspective and find this form of identity to be partially inherited.

Understanding the evolutionary consequences of inheritable non-genetic cellular identity requires a better knowledge of the impact of fluctuating stress on cell proliferation. Dissecting quantitatively the consequences of repeated stress on cell-cycle and growth gives us an overview of the energetic and temporal consequences of repeated stress. At last, technical and theoretical developments needed to carry this investigation further are presented.

7.7. Resistance to anti-cancer drugs by non-mutational mechanisms: insights from a cell-based multi-scale model of TRAIL-induced apoptosis

Participants: Virgile Andréani, Grégory Batt, François Bertaux.

The fact that tumors can acquire drug resistance by non-mutational mechanisms is increasingly gaining attention (Sharma et al., 2010; Pisco et al., 2013; Flusberg et al., 2013). Stochastic fluctuations in cellular states of different resistance and proliferative potential could play an important role in such resistance acquisition. Thus, to enable a quantitative, molecular-level understanding of those phenomena, modeling approaches that go beyond traditional, deterministic kinetic models of biological pathways are required.

An interesting and well-studied example of non-mutational resistance acquisition concerns the response of cancer cells to the agent TRAIL, a selective inducer of apoptotic cell death. In a previous work (Bertaux et al., 2014), we have developed a single-cell model of TRAIL-induced apoptosis that accounts for (1) protein-protein signaling reactions linking TRAIL exposure to commitment to apoptosis, (2) stochastic gene expression for the proteins involved in this signaling and (3) protein degradation. Under parsimonious and realistic assumptions for parameter values, fractional killing and transient resistance acquisition readily emerged from model simulations. Those two properties relating to TRAIL resistance are observed in-vitro for many different cancer cell lines.

Here, again in collaboration with Dirk Drasdo and Szymon Stoma, we investigate the long-term response of proliferating cancer cell populations repeatedly treated by TRAIL by integrating our single-cell model of TRAIL-induced apoptosis into a multi-cellular simulation framework. We predict that the long-term killing efficiency of repeated treatments is strongly reduced compared to the first treatment. A detailed analysis showed that resistance acquisition is caused mainly by the targeted degradation of activated pro-apoptotic proteins and an imbalance between the turnover of pro- and anti- apoptotic proteins. In addition, simulations of the treatment of multi-cellular spheroids suggested that limited TRAIL penetration is unlikely to be a driving cause of resistance, but that it can exacerbate the impact of cell-intrinsic resistance acquisition.

7.8. Controlling a genetic inverted pendulum

Participants: Grégory Batt, Catherine Eisenhauer, Pascal Hersen, Jean-Baptiste Lugagne.

The ability to routinely control complex genetic circuits in vivo and in real-time promises quantitative understanding of cellular processes of unprecedented precision, quality, and richness. With combined efforts in microfluidic design, microscope automation, image segmentation and analysis, and control theory, we propose a platform for real-time, single-cell, externalized in silico control and monitoring of genetic networks in E. coli. Computational framework and hardware are optimized for parallelizing the experiments and we use the platform to test and control an entire library of synthetic genetic circuits. The circuits we are trying to control are based on the genetic toggle switch, a foundational circuit in synthetic biology, which consists of two genes that repress each other. This genetic system features two stable equilibrium points where one of the genes has taken over. Our objective is to dynamically balance the circuit in single cells around a third, unstable equilibrium point at which no gene dominates and their mutual repression strengths are balanced. This is similar to the landmark problem in control theory of stabilizing an inverted pendulum. Although our work indicates that this real-time control approach can drive convoluted genetic networks towards states that are inaccessible to traditional genetic perturbations such as knock-outs and promoter induction, the a priori quantitative knowledge of the system required for achieving this control is minimal. We show that even a simple Proportional-Integral controller can stabilize the unstable point of the toggle switch in single cells. Finally, we demonstrate that manipulation, or even inversion, of the stability map of the network is possible, though counter intuitive, via the simultaneous stabilization of an entire population of toggle switch cells around their unstable point with a common dynamic input.

7.9. Synthesizing Configurable Biochemical Implementation of Linear Systems from Their Transfer Function Specifications

Participants: Katherine Chiang, François Fages, Sylvain Soliman.

The ability to engineer synthetic systems in the biochemical context is constantly being improved and has a profound societal impact. Linear system design is one of the most pervasive methods applied in control tasks, and its biochemical realization has been proposed by Oishi and Klavins and advanced further in recent years. However, several technical issues remain unsolved. Specifically, the design process is not fully automated from specification at the transfer function level, systems once designed often lack dynamic adaptivity to environmental changes, matching rate constants of reactions is not always possible, and implementation may be approximative and greatly deviate from the specifications. In [6], building upon the work of Oishi and Klavins, we overcome these issues by introducing a design flow that transforms a transfer-function specification of a linear system into a set of chemical reactions, whose input-output response precisely conforms to the specification. This system is implementable using the DNA strand displacement technique. The underlying configurability is embedded into primitive components and template modules, and thus the entire system is adaptive. Simulation of DNA strand displacement implementation confirmed the feasibility and superiority of the proposed synthesis flow.

7.10. Reconfigurable Neuromorphic Computation in Biochemical Systems

Participants: Katherine Chiang, François Fages.

Implementing application-specific computation and con- trol tasks within a biochemical system has been an important pursuit in synthetic biology. Most synthetic designs to date have focused on realiz- ing systems of fixed functions using specifically engineered components, thus lacking flexibility to adapt to uncertain and dynamically-changing environments. To remedy this limitation, an analog and modularized approach to realize reconfigurable neuromorphic computation with biochemical reactions is presented in [11]. We propose a biochemical neural network consisting of neuronal modules and interconnects that are both reconfigurable through external or internal control over the concentrations of certain molecular species. Case studies on classification and machine learning applications using the DNA strain displacement technology demonstrate the effectiveness of our design in both reconfiguration and autonomous adaptation.

7.11. Search by Constraint Propagation

Participants: François Fages, Thierry Martinez, Sylvain Soliman.

Constraint programming is traditionally presented as the combination of two components: a constraint model and a search procedure. In [13] we show that tree search procedures can be fully internalized in the constraint model with a fixed enumeration strategy. This approach has several advantages: 1) it makes search strategies declarative, and modeled as constraint satisfaction problems; 2) it makes it possible to express search strategies in existing front-end modeling languages supporting reified constraints without any extension; 3) it opens up constraint propagation algorithms to search constraints and to the implementation of novel search procedures based on constraint propagation. We illustrate this approach with a Horn clause extension of the MiniZinc modeling language and the modeling in this language of a variety of search procedures, including dynamic symmetry breaking procedures and limited discrepancy search, as constraint satisfaction problems. We show that this generality does not come with a significant overhead, and can in fact exhibit exponential speedups over procedural implementations, thanks to the propagation of the search constraints.

7.12. Execution models for Constraint Programming and Semantics Equivalence

Participants: François Fages, Thierry Martinez, Sylvain Soliman.

Logic programming and constraint programming are two declarative programming paradigms which rely on the identification of programs to theories, and programming to modeling. Execution models result from the operational interpretation of logical provability in logic programming, and of constraint propagation in constraint programming. However, the control of execution is crucial for the practicability of these schemes and extra-logical traits are thus added in those programming systems, with the classical slogans "logic program = logical theory + control", "constraint program = constraint model + search".

In his thesis [4], Thierry Martinez investigates execution models in which control and search can be shifted into the logic or the constraint model, while preserving the semantics. The three parts of the thesis correspond to the three semantics equivalence that are showed: the first between two committed-choice forward-chaining logic languages, the second between constraint logic programs and constraint models, and the third between guard semantics in angelic settings. Each of these equivalence is constructive in the sense that there exists an encoding that enables the compilation from one of the paradigm to the other.

7.13. On Translating MiniZinc Constraint Model into Fitness Functions: Application to Continuous Placement Problems.

Participants: François Fages, Thierry Martinez, Bao Duy Tran.

MiniZinc is a solver-independent constraint modeling lan- guage which is increasingly used in the constraint programming com- munity. It can be used to compare different solvers which are currently based on either constraint programming, Boolean satisfiability or mixed integer linear programming. In [12], we show how MiniZinc models can be compiled into fitness functions for evolutionary algorithms. More specifically, we describe the translation of FlatZinc models into fitness functions over the reals and their use in the Covariance Matrix Adapta- tion Evolution Strategy (CMA-ES) solver. We illustrate this approach, and evaluate it, on the modeling and solving of complex shape continuous placement problems.

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. ANR Projects

- ANR Blanc HYCLOCK (2014-2018) on "Hybrid modeling of time for Circadian Clock Biology and Chronopharmacology", coordinated by F. Delaunay (CNRS, Nice), F. Lévi (INSERM Paris-Sud), G. Bernot (CNRS I3S, Nice), O. Roux (Ecle Centrale Nantes).
- ANR Blanc STOCH-MC (2014-2018) on "Stochastic Models: Scalable Model Checking", coordinated by Blaise Genest (Inria Rennes), with Grégory Batt, Wieslaw Zielonka (LIAFA), and Hugo Gimbert (LaBRI).
- ANR Investissement Avenir ICEBERG project (2011-2016) "From population models to model populations", coordinated by Grégory Batt, with Pascal Hersen (MSC lab, Paris Diderot Univ./CNRS), Reiner Veitia (Institut Jacques Monod, Paris Diderot Univ./CNRS), Olivier Gandrillon (BM2A lab, Lyon Univ./CNRS), Cédric Lhoussaine (LIFL/CNRS), and Jean Krivine (PPS lab, Paris Diderot Univ./CNRS).
- ANR Blanc NET-WMS-2 (2011-2015) on "constraint optimization in Wharehouse Management Systems", coordinated by F. Fages, with N. Beldiceanu (Ecole des Mines de Nantes, EPI TASC), and Abder Aggoun (KLS optim).

8.1.2. GENCI Contract

- GENCI (2009-) attribution of 300000 computation hours per year on the Jade cluster of 10000 cores of GENCI at CINES, Montpellier. Used for our hardest parameter search problems in BIOCHAM-parallel.

8.2. International Initiatives

8.2.1. Inria International Partners

8.2.1.1. Collaboration with National Taiwan University

Since 2012, we develop a collaboration with Prof. Jie-Hong Jiang, National Taiwan University which culminated this year with the defence of the PhD Thesis of Katherine Chiang [1], co-supervised by Jie-Hong Jiang and François Fages with two internships in 2012 and 2013, and with several publications [5], [11], [6]. Our aim is to pursue our collaboration on the concept of biochemical programming and the development of biochemical programming tools, in particular for the design of artificial biosensors in partnership with Franck Molina (CNRS, Sys2diag, Montpellier).

8.2.2. Participation In other International Programs

- French-German PROCOPE (2015-2017) grant on "Réduction de modèle et analyse de grands réseaux biochimiques par des méthodes stoechiométriques et tropicales", coord. Prof Andreas Weber, University of Bonn, Germany, and Prof. Ovidiu Radulescu, Univ. Montpellier, France.

8.3. International Research Visitors

8.3.1. Visits of International Scientists

Our group received for short visits of a few days

- Prof. Hugo Fort, Univ. Montevideo, Uruguay
- Prof. Andreas Weber, Univ. Bonn, Germany
- Damien Woods, Caltech, USA

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific events organisation

9.1.1.1. General chair, scientific chair

- Grégory Batt, Pascal Hersen, and Denis Thieffry organized the 2nd International Conference on Design, optimization and control in systems and synthetic biology, DOC'15, November 12-13, 2015, ENS, Paris.
- François Fages was co-chair with Nicolas Beldiceanu of the 6th International Workshop on Bin Packing and Placement Constraints, BPPC'15 associated to CP'15, 31st August 2015, Cork, Ireland.
- François Fages is member of the Steering Committee of the International Conference on Computational Methods for Systems Biology since 2008.

9.1.2. Scientific events selection

9.1.2.1. Member of the conference program committees

- Grégory Batt was member of the program committees of :
  - HSB'15 Fourth International Workshop on Hybrid Systems Biology, Madrid, Spain, September 3-4, 2015
  - CMSB'15, 13th International Conference on Computational Methods in Systems Biology, Nantes, France, Sept. 16-18, 2015.
- François Fages was member of the program committees of :
  - IJCAI'16 25th International Joint Conference on Artificial Intelligence, New York, USA, 2016.
  - CIE'16 Computability in Europe, Paris, 2016.
  - HSB'15 Fourth International Workshop on Hybrid Systems Biology, Madrid, Spain, September 3-4, 2015
  - CP'15 21st International Conference on Principles and Practice of Constraint Programming, Cork, Ireland, Aug 31-Sep 4, 2015.
  - ICLP'15 31st International Conference on Logic Programming, Cork, Ireland, Aug 31-Sep 4, 2015.
  - WCB'15 11th Workshop on Constraint-based methods for Bioinformatics, associated to CP'15, Cork, Ireland, August 31st 2015.

- CMSB'15, 13th International Conference on Computational Methods in Systems Biology, Nantes, France, Sept. 16-18, 2015.
- LMBS'15, 1st International Workshop on Logical Modeling of Biological Systems, satellite workshop of CMSB'15, Nantes, France, Sept. 18, 2015.
- VEMDP'15, Verification of Engineered Molecular Devices and Programs, July 19, 2015, San Francisco, USA.
- FroCoS'15, Wroclaw, Poland, 15-19 Sep 2015.

- Sylvain Soliman was member of the program committee of:
  - WCB'15 11th Workshop on Constraint-based methods for Bioinformatics, associated to CP'15, Cork, Ireland, August 31st 2015.

9.1.3. Journal

9.1.3.1. Member of the editorial boards

François Fages is member of

- the Editorial Board of the Computer Science area of the Royal Society Open Science journal since 2014
- the Editorial Board of the journal RAIRO OR Operations Research since 2004

9.1.3.2. Reviewer - Reviewing activities

- Grégory Batt and Jean-Baptiste Lugagne were reviewers for the journal *ACS Synthetic Biology*. Grégory Batt was reviewer for the *Journal of Molecular Biology*.
- Chiara Fracassi was reviewer for the journal *Epidemiology and Infection*.
- François Fages and Pauline Traynard were reviewers for *Theoretical Computer Science*. François Fages was reviewer for *PLoS Computational Biology, Transaction on Computational Biology and Bioinformatics, Theoretical Computer Science, Acta Biotheoretica, Transactions on Computational Logic,* and *Journal of Constraints*.

Sylvain Soliman was reviewer for *BMC Systems Biology, AMS Math Reviews, PLoS One*, and *Bioinformatics*.

9.1.4. Invited talks

- Virgile Andréani gave an invited talk at the Journée nationale du groupe de travail BIOSS, 23 Nov 2015.
- Grégory Batt gave invited talks at
  - workshop Integrative cell models: Bridging microbial physiology and systems biology, Leiden, the Netherlands (short talk), January 2015
  - Institute of Genetics and Development of Rennes, Reverse Engineering Cell Division team, February 2015
  - Interdisciplinary Computing and Complex BioSystems group, Newcastle University, UK, May 2015
  - Laboratoire de Biologie Moléculaire de la Cellule, ENS Lyon, October 2015
- François Bertaux gave an invited talk at the conference Design, Optimization and Control of Systems and Synthetic Biology, ENS Paris, Nov 2015.
- François Fages gave invited talks at
  - University of Bonn, Bioinformatics Seminar, Germany, 11 December 2015,
  - CNRS Sys2Diag lab, Montpellier, 8 December 2015,
  - Journée nationale du groupe de travail BIOSS, Paris, 23 November 2015,
  - National Taiwan University, Biology Dept., Taipei, Taiwan, 14 July 2015
  - National Taiwan University, Electrical Engineering Dept., Taipei, Taiwan, 15 July 2015

     – CIRM, "Méthodes de réduction de modèles discrets", Marseille, 28 May 2015

     – aSSB'15 Thematic Research School, Strasbourg, 23-27 March 2015

- Artemis Llamosi gave an invited talk at the Conference Lyon SysBio 2015, November 2015

- Jean-Baptiste Lugagne gave an invited talk at the conference Design, Optimization and Control of Systems and Synthetic Biology, ENS Paris, Nov 2015.

- Chiara Fracassi gave an invited talk at BioSynSys'15, the first conference of the GDR Synthetic and Systems Biology, Paris Diderot U, Sept 2015.

9.1.5. Leadership within the scientific community

- Grégory Batt is a member of
  - the IEEE/CSS Technical Committee on Systems Biology,
  - the scientific board of the GDR de Biologie de Synthèse et des Systèmes
  - the GDR de Bioinformatique Moléculaire, in charge of the axis on Biological network modelling, systems biology and synthetic biology

- François Fages is a member of the Steering Committee of the international conference series Computational Methods in Systems Biology since 2008

9.1.6. Scientific expertise

Grégory Batt was member of the review and selection panels of ERASysAPP, an ERA-NET for Systems Biology Applications (Gothenborg, April 2015). He was also a reviewer for ANR blanc programme. He is a member of the scientific committee of the Advanced Lecture Course on Computational Systems Biology summer school. He has also served as a mentor in the workshop Teaching Through Research of the Leadership Program, organised by the Centre for Research and Interdisciplinarity under the auspice of the "learning science" UNESCO chair (April 2015, Paris).

François Fages is a member of the Scientific Council of the *Doctorate School "Frontières Du Vivant"* at *Center for Research and Interdisciplanirity*, Universities Paris Descartes and Paris Diderot (since 2010). He was a member of the *Comité de Sélection* for a Professorship position in Section 27 in Lille and member of the jury for the *Prix de thèse Gilles Kahn* of the *Société Informatique de France*.

9.1.7. Research administration

François Fages is member of the "Bureau du Comité des Projets" of Inria Paris-Rocquencourt.

Sylvain Soliman is president of the "Comité de Suivi Doctoral" and of the "Commission de Dévelopement Technologique" of Inria Paris-Rocquencourt.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Master: Grégory Batt, *Computational Biology*, coordinator 48h, M1, Master Approches Interdisciplinaires du Vivant (AIV).

Master: Grégory Batt (6h), Denis Thieffry (coordinator), *Dynamical Modelling of Cellular Regulatory Networks*, M2, Interdisciplinary Master in Life Science at the Ecole Normale Supérieure, Paris.

Master: François Fages (coordinator module 48h, teaching 12h), Grégory Batt (12h), Denis Thieffry (12h), C2-19 *Computational Methods for Systemic and Synthetic Biology*, Master Parisien de Recherche en Informatique (MPRI), Paris.

Master: Chiara Fracassi, *Dynamics of Living Systems*, 24h, M1, Master Approches Interdisciplinaires du Vivant (AIV).

Master: Thierry Martinez, *Développement logiciel*, 17h, M1, Ecole des Ponts et Chaussée, Champs-sur-Marne.

Master: Sylvain Soliman, C2-35-1 *Constraint Programming*, coordinator and teaching 24h, M2, Master Parisien de Recherche en Informatique (MPRI), Paris.

Master: Pauline Traynard, *Introduction to Linux and Programming with Python and R*, M1, M2, 30h, master IMaLiS du département de biologie de l'ENS,

9.2.2. Supervision

PhD : Katherine Chiang, *Biomolecular Computing System Design: Architecture, Synthesis, and Simulation*, National Taiwan University, Taipei, Taiwan (Sep 2012), Dir. Jie-Hong Jiang and François Fages, 13 July 2015.

PhD : Steven Gay, *Subgraph Epimorphisms: Theory and Application to Model Reductions in Systems Biology*, Université Paris Diderot, Paris (Oct 2009), Dir. François Fages and Sylvain Soliman, 26 May 2015.

PhD : Artémis Llamosi, Université Paris Diderot, Paris (Nov 2012), Dir. Grégory Batt and Pascal Hersen (MSC), 15 Dec 2015.

PhD : Thierry Martinez, *Execution models for Constraint Programming: kernel language design through semantics equivalence*, Université Paris Diderot, Paris (Oct 2009), Dir. François Fages, 17 December 2015

PhD in progress : François Bertaux, Université Pierre et Marie Curie, Paris (Sept 2011), Dir. Dirk Drasdo (EPI MAMBA) and Grégory Batt

PhD in progress : Jean-Baptiste Lugagne, Université Paris Diderot, Paris (Oct 2012), Dir. Grégory Batt and Pascal Hersen (CNRS, MSC)

PhD in progress : Jonas Sénizergues, Université Paris Diderot, Paris (Oct 2015), Dir. François Fages and Sylvain Soliman

PhD in progress : Pauline Traynard, Université Paris Diderot, Paris (Oct 2012), Dir. François Fages and Denis Thieffry (ENS)

9.2.3. Juries

- PhD Alexis Courbet, "Engineering autonomous and programmable biosensors through synthetic biology: integrating multiplexed biomarker detection and biomolecular signal processing into next-generation diagnostics", Univ. Montpellier, 7 December 2015, Invited Examiner: François Fages

- PhD Christopher Banks, "Spatio-temporal Logic for the Analysis of Biochemical Models", 28 Jan 2015, Univ. of Edimburgh, Scotland, Reviewer: François Fages

- PhD Erwan Bigan, "Minimal conditions for protocell growth", Dec 2015, Ecole Polytechnique, France, Reviewer: Gregory Batt

9.3. Popularization

Pascal Hersen and Artémis Llamosi are founders of the *OpenLab* at the *Center for Research and Interdisciplinarity* in Paris, and organizers of related events on product industrialization. They provide scientific expertise to hosted startups.

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] K. CHIANG. *Biomolecular System Design: Architecture, Synthesis, and Simulation*, National Taiwan University, June 2015, https://hal.inria.fr/tel-01237638

[2] S. GAY. *Subgraph Epimorphisms: Theory and Application to Model Reductions in Systems Biology*, Université Paris Diderot, May 2015, https://hal.inria.fr/tel-01236291

[3] A. LLAMOSI. *Effects of repeated osmotic stress on gene expression and growth: from cell-to-cell variability to cellular individuality in the budding yeast Saccharomyces cerevisiae*, Université Paris Diderot, December 2015, https://tel.archives-ouvertes.fr/tel-01253235

[4] T. MARTINEZ. *Execution models for Constraint Programming: kernel language design through semantics equivalence.* , Paris Diderot, December 2015, https://hal.inria.fr/tel-01251695

Articles in International Peer-Reviewed Journals

[5] H.-J. CHIANG, F. FAGES, J.-H. JIANG, S. SOLIMAN. *Hybrid Simulations of Heterogeneous Biochemical Models in SBML*, in "ACM Transactions on Modeling and Computer Simulation", April 2015, vol. 25, n° 2, pp. 14:1-14:22 [*DOI :* 10.1145/2742545], https://hal.archives-ouvertes.fr/hal-01170947

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[9] F. NABLI, T. MARTINEZ, F. FAGES, S. SOLIMAN. *On Enumerating Minimal Siphons in Petri nets using CLP and SAT solvers: Theoretical and Practical Complexity*, in "Constraints", 2015, pp. 1–26 [*DOI :* 10.1007/S10601-015-9190-1], https://hal.archives-ouvertes.fr/hal-01170962

International Conferences with Proceedings

[10] S. BOGOMOLOV, C. SCHILLING, E. BARTOCCI, G. BATT, H. KONG, R. GROSU. *Abstraction-Based Parameter Synthesis for Multiaffine Systems*, in "11th International Haifa Verification Conference, HVC 2015, Haifa, Israel, November 17-19, 2015, Proceedings", Haifa, Israel, Springer International Publishing, November 2015, vol. 11, pp. 19-35 [*DOI :* 10.1007/978-3-319-26287-1_2], https://hal.inria.fr/hal-01242371

[11] H.-J. CHIANG, J.-H. JIANG, F. FAGES. *Reconfigurable Neuromorphic Computation in Biochemical Systems*, in "EMBC 2015 - 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society", Milano, Italy, August 2015, pp. 937 - 940 [*DOI :* 10.1109/EMBC.2015.7318517], https://hal.archives-ouvertes.fr/hal-01236265

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Other Publications

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