Activity Report 2016

Project-Team LIFEWARE

Computational systems biology and optimization

RESEARCH CENTER
Saclay - Île-de-France

THEME
Computational Biology

Table of contents

Project-Team LIFEWARE

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

Keywords:

Computer Science and Digital Science:

- 2.1.1. - Semantics of programming languages
- 2.1.5. - Constraint programming
- 2.1.10. - Domain-specific languages
- 2.2.1. - Static analysis
- 2.3.2. - Cyber-physical systems
- 2.4. - Verification, reliability, certification
- 2.4.1. - Analysis
- 2.4.2. - Model-checking
- 2.4.3. - Proofs
- 6. - Modeling, simulation and control
- 6.1. - Mathematical Modeling
- 6.1.1. - Continuous Modeling (PDE, ODE)
- 6.1.2. - Stochastic Modeling (SPDE, SDE)
- 6.1.3. - Discrete Modeling (multi-agent, people centered)
- 6.1.4. - Multiscale modeling
- 6.1.5. - Multiphysics modeling
- 6.2.4. - Statistical methods
- 6.2.6. - Optimization
- 6.3.1. - Inverse problems
- 6.3.4. - Model reduction
- 7.2. - Discrete mathematics, combinatorics
- 7.3. - Optimization
- 7.4. - Logic in Computer Science
- 7.9. - Graph theory
- 8.7. - AI algorithmics

Other Research Topics and Application Domains:

- 1. - Life sciences
- 1.1.2. - Molecular biology
- 1.1.3. - Cellular biology
- 1.1.9. - Bioinformatics
- 1.1.10. - Mathematical biology
- 1.1.11. - Systems biology
- 1.1.12. - Synthetic biology
- 1.4. - Pathologies
- 2. - Health
- 2.2.3. - Cancer
- 2.4.1. - Pharmaco kinetics and dynamics

2.4.2. - Drug resistance
7. - Transport and logistics
9. - Society and Knowledge

1. Members

Research Scientists
François Fages [Team leader, Senior researcher, Inria, HDR]
Grégory Batt [Team co-leader, Researcher, Inria, HDR]
Jakob Ruess [Researcher, Inria, from Oct 2016]
Sylvain Soliman [Researcher, Inria, HDR]

PhD Students
Virgile Andreani [Ecole Polytechnique, with Duke Univ., from Sept 2016]
Jean Baptiste Caron [Inria, from Dec 2016]
Jean-Baptiste Lugagne [Inria, with MSC lab (CNRS/Paris7)]
Jonas Senizergues [Inria, until Aug 2016]
Pauline Traynard [Inria, until Feb 2016]

Post-Doctoral Fellows
Chiara Fracassi [Inria, with MSC lab (CNRS/Paris7)]
Artémis Llamosi [CNRS, with MSC lab (CNRS/Paris7), until Aug 2016]
Sucheendra Palaniappan [Inria, with EPI SUMO, from April to June 2016]

Visiting Scientists
David Rosenblueth [Univ. Mexico, from Mar 2016 to Sep 2016]
Denis Thieffry [ENS Paris, HDR]
Pascal Hersen [CNRS, MSC lab (CNRS/Paris7), HDR]
Thierry Martinez [Inria Paris, SED]
Laura Guyot [Dassault Systèmes]

Administrative Assistants
Régine Bricquet [Inria, until June 2016]
Corinne Petitot [Inria, from July 2016]

Others
Virgile Andreani [Inria, Internship, until Aug 2016]
Jean Baptiste Caron [MSC lab (CNRS/Paris7), Internship, from Apr 2016 to June 2016]
Ewen Corre [Inria, Internship, until Mar 2016]
Guillaume Le Guludec [Inria, Internship MPRI, Sup Telecom Paris, from Apr 2016 to Sep 2016]
Sebastian Ramon Sosa Carrillo [Inria, Internship, from Dec 2016]
Nicolas Vasselin [Inria Internship, Ecole Centrale de Paris, from Aug 2016]

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 developing a theory of biochemical computation with 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 makes it possible to apply a variety of **static analysis** methods, before going to simulations and **dynamical analyses**, for which we use **temporal logics** as a specification language to formalize biological behaviours with imprecise data, validate models w.r.t. observations, 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 biologists, we investigate concrete biological questions and develop computational models fitted to quantitative data which allow us to make quantitative predictions. 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, and perform accurate observations, modifications and real-time control at both single cell and cell population levels. We are affiliated with the Doctorate Schools “Frontières du vivant (FdV)” of University Sorbonne Paris Cité and “Sciences et technologies de l’information et de la communication (STIC)” of University Paris-Saclay.

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.

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 Phenotypic Heterogeneity in 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).

It is now fully apparent that cells do not respond identically to a same stimulation, even when they are all genetically-identical. This phenotypic heterogeneity plays a significant role in a number of problems ranging from cell resistance to anticancer drug treatments to stress adaptation and bet hedging.

Dedicated modeling frameworks, notably **stochastic** modeling frameworks, such as chemical master equations, and **statistic** modeling frameworks, such as ensemble models, are then needed to capture biological variability.

Appropriate mathematical and computational should then be employed for the analysis of these 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 [1], and (stochastic approximations of) the **expectation maximization** algorithm for the identification of mixed-effects models [2].

3.3. 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 developed for quantitative models can be summarized by the following identifications :

$$\text{biological model = transition system } K$$

$$\text{dynamical behavior specification = temporal logic formula } \phi$$

$$\text{model validation = model-checking } \quad K,\ s \models ?\ \phi$$

$$\text{model reduction = sub-model-checking } \quad K'? \subset K,\ K',\ s \models \phi$$

$$\text{model prediction = formula enumeration } \quad K,\ s \models \phi?$$

$$\text{static experiment design = symbolic model-checking } \quad K,\ s? \models \phi$$

$$\text{model inference = constraint solving } \quad K?,\ s \models \phi$$

$$\text{dynamic experiment design = constraint solving } \quad K?,\ s? \models \phi$$

[1] Moment-based inference predicts bimodality in transient gene expression, C. Zechner C, J. Ruess, P. Krenn, S. Pelet, M. Peter, J. Lygeros, and H. Koeppl, Proceedings of the National Academy of Sciences USA, 9(5):109(21):8340-5, 2012

[2] What population reveals about individual cell identity: estimation of single-cell models of gene expression in yeast, A. Llamosi, A.M. Gonzalez-Vargas, C. Versari, E. Cinquemani, G. Ferrari-Trecate, P. Hersen, and G. Batt, PLoS Computational Biology, 9(5): e1003056, 2015

[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.

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 [4] This line of research continues with the development of temporal logic patterns with efficient constraint solvers and their generalization to handle stochastic effects.

3.4. 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 [5].

More recently, motivated by an analogy with a benchmark control problem, the stabilization of an inverted pendulum, we investigated the possibility to balance a genetic toggle switch in the vicinity of its unstable equilibrium configuration. We searched for solutions to balance an individual cell and even an entire population of heterogeneous cells, each harboring a toggle switch.

3.5. 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 Thomas' conditions of multi-stationarity and Soulé's proof to reaction systems [6], 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 now provide solid ground for developing static analyzers, using them on a large scale in systems biology, and elucidating modules.

3.6. Mixed Analog-Digital Computation with Biochemical Reactions

The continuous nature of many protein interactions leads us to consider models of analog computation, and in particular, the recent results in the theory of analog computability and complexity obtained by Amaury

[4] On a continuous degree of satisfaction of temporal logic formulae with applications to systems biology A. Rizk, G. Batt, F. Fages, S. Soliman International Conference on Computational Methods in Systems Biology, 251-268

[5] 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.

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

[7] François Fages, Steven Gay, Sylvain Soliman. Inferring reaction systems from ordinary differential equations. Journal of Theoretical Computer Science (TCS), Elsevier, 2015, 599, pp.64–78.

Pouly [8] and Olivier Bournez, establish fundamental links with digital computation. In [18], we derive from these results a Turing completeness result for elementary reaction systems (without polymerization) under the differential semantics. The proof of this result shows how mathematical functions described by Ordinary Differential Equations, namely by Polynomial Initial Value Problems (PIVP), can be compiled into elementary biochemical reactions, furthermore with a notion of analog computation complexity defined as the length of the trajectory to reach a given precision on the result. This opens a whole research avenue to analyze natural circuits in Systems Biology, transform behavioural specifications into biochemical reactions for Synthetic Biology, and compare artificial circuits with natural circuits acquired through evolution, from the novel point of view of analog computation complexity.

3.7. Constraint Solving and Optimization

Constraint solving and optimization methods are important in our research [17]. 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) [9] 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 [10].

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.

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.

[8] Amaury Pouly, "Continuous models of computation: from computability to complexity", PhD Thesis, Ecole Polytechnique, Nov. 2015.

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

[10] 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.

4.3. 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 [11]. 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 protocells

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

Creation of the Exploratory Action *InBio* with Pasteur Institute in Paris

The InBio project has been selected in the context of a call for new research groups organized by the Center for Bioinformatics, Biostatistics and Integrative Biology (C3BI) of Institut Pasteur.

The main scientific question investigated in InBio is how one can exploit cell-to-cell differences to better learn and control the functioning of biological systems. That is, instead of seeing phenotypic variability as undesired noise that beclouds the processes of interest, we will try to harness cellular heterogeneity. In particular for control problems, because one interacts with the system, it is important to be able to predict the dynamical evolution of phenotypic heterogeneity.

A second important scientific objective of InBio is to develop more rational and systematic interactions between experimental and computational work. The virtuous loop in which experiments nurture models, that in turn, orient further experiments is universally acclaimed and installing such a loop is a central objective of many research projects. In interdisciplinary research, it is expected that this exchange of information will emerge from the interactions between the two disciplinary groups. For both practical and theoretical reasons, this is actually often not the case. In InBio, we will adopt a multidisciplinary research approach and develop an integrated environment around the design-and-test loop. This will notably involve the rational design of cell stains and of experimental plans, so that experiments are maximally-informative, and of efficient model calibration and discrimination methods. This specific focus explains the full name given to the InBio group: “Experimental and Computational Methods for Modeling Cellular Processes” (InBio simply abridges integrative biology).

[11] 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.

InBio will be hosted at Institut Pasteur and will host experimental and theoretical research. It is a mixed structure between Inria (action exploratoire attached to Lifeware) and Institut Pasteur (research unit attached to the C3BI), and is headed by Grégory Batt.

The Dogma of the Control of the Cell Cycle by the Circadian Clock Revisited

Our long-standing and tight collaboration with Franck Delaunay's lab in Nice culminated this year with a revisiting of the dogma of the control of the cell cycle by the circadian clock. In [9] we showed, using a coupled reaction model of the cell cycle and the circadian clock and BIOCHAM analysers [4], that a selective upregulation of Reverb-α (or an inhibition of Bmal1) during mitosis is necessary to explain the period and phase data observed in NIH3T3 fibroblasts in different serum concentrations. This mechanism constitutes a reverse control of the circadian clock by the cell divisions which was previously outlooked but is overriding in some spontaneously dividing cell types such as non-confluent NIH3T3 fibroblasts.

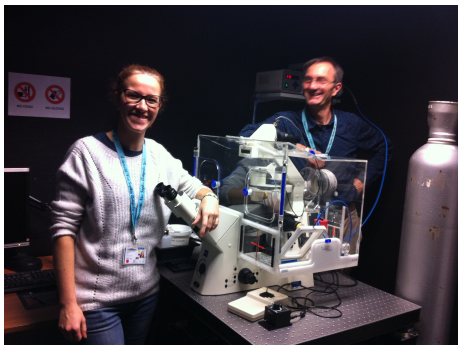

Figure 1.

Céline Feillet and Franck Delaunay, CNRS Nice,

with the large-scale time-lapse video microscope which produced the unicellular 72h data studied in [9].

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, performing static analyses, making simulations, specifying behaviors in temporal logic and searching parameter values in high dimension.

This year BIOCHAM has been completely rewritten with a modular architecture. The new version v4.0 will be released soon with new features for synthesizing biochemical reaction systems from input/output function specifications.

- Participants: François Fages, Guillaume Le Guludec, Thierry Martinez Sylvain Soliman
- Contact: François Fages
- URL: http://lifeware.inria.fr/biocham/

6.2. CellStar

KEYWORDS: Systems biology - Bioinformatics
FUNCTIONAL DESCRIPTION

In close collaboration with Kirill Batmanov, Cédric Lhoussaine and Cristian Versari (LIFL, CNRS/Lille Univ), with Szymon Stoma (Inria; now ETHZ), and with Pascal Hersen (MSC, CNRS/Paris7), 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 tools. 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 and Szymon Stoma
- Contact: Grégory Batt
- URL: http://cellstar-algorithm.org/

6.3. CLP2Zinc

KEYWORDS: Modeling language - Constraint programming - Search
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 was 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 and Sylvain Soliman
- Contact: Thierry Martinez
- URL: http://lifeware.inria.fr/~tmartine/clp2zinc/

7. New Results

7.1. Analog computation in the cell: specifications, compilation into biochemical reactions and computational complexity

Participants: François Fages, Guillaume Le Guludec.

The continuous nature of many protein interactions leads us to consider mixed analog-digital computation methods, for which the recent results in the theory of analog computability and complexity obtained by Amaury Pouly [12] and Olivier Bournez, establish fundamental links with digital computation. In [18], we derive from these results a Turing completeness result for elementary reaction systems (without polymerization) under the differential semantics, and present a compiler of behavioural specifications into biochemical reactions which can be compared to natural circuits acquired through evolution. We illustrate this approach through the example of the MAPK signaling module which has a function of analog-digital converter in the cell, and through the cell cycle control.

The biochemical compiler is implemented in BIOCHAM v4.0 which will be soon released. We plan to use it in the ANR-MOST project BIOPSY on "Biochemical Programming" for the design of artificial biosensors and the programming of (non-living) protocells in collaboration with Franck Molina, CNRS Sys2diag lab, Montpellier.

[12] Amaury Pouly, "Continuous models of computation: from computability to complexity", PhD Thesis, Ecole Polytechnique, Nov. 2015.

7.2. Influence systems vs reaction systems

Participants: François Fages, Thierry Martinez, David Rosenblueth, Sylvain Soliman, Denis Thieffry.

In Systems Biology, modelers develop more and more reaction-based models to describe the mechanistic biochemical reactions underlying cell processes. They may also work, however, with a simpler formalism of influence graphs, to merely describe the positive and negative influences between molecular species. The first approach is promoted by reaction model exchange formats such as SBML, and tools like CellDesigner, while the second is supported by other tools that have been historically developed to reason about boolean gene regulatory networks. In practice, modelers often reason with both kinds of formalisms, and may find an influence model useful in the process of building a reaction model. In [11], we introduce a formalism of influence systems with forces, and put it in parallel with reaction systems with kinetics, in order to develop a similar hierarchy of boolean, discrete, stochastic and differential semantics. We show that the expressive power of influence systems is the same as that of reaction systems under the differential semantics, but weaker under the other interpretations, in the sense that some discrete behaviours of reaction systems cannot be expressed by influence systems. This approach leads us to consider a positive boolean semantics which we compare to the asynchronous semantics of gene regulatory networks à la Thomas. We study the monotonicity properties of the positive boolean semantics and derive from them an efficient algorithm to compute attractors.

7.3. What population reveals about individual cell identity: Single-cell parameter estimation of models of gene expression in yeast

Participants: Grégory Batt, Pascal Hersen, Artémis Llamosi.

Significant cell-to-cell heterogeneity is ubiquitously observed in isogenic cell populations. Consequently, parameters of models of intracellular processes, usually fitted to population-averaged data, should rather be fitted to individual cells to obtain a population of models of similar but non-identical individuals. In [6], we propose a quantitative modeling framework that attributes specific parameter values to single cells for a standard model of gene expression. We combine high quality single-cell measurements of the response of yeast cells to repeated hyperosmotic shocks and state-of-the-art statistical inference approaches for mixed-effects models to infer multidimensional parameter distributions describing the population, and then derive specific parameters for individual cells. The analysis of single-cell parameters shows that single-cell identity (e.g. gene expression dynamics, cell size, growth rate, mother-daughter relationships) is, at least partially, captured by the parameter values of gene expression models (e.g. rates of transcription, translation and degradation). Our approach shows how to use the rich information contained into longitudinal single-cell data to infer parameters that can faithfully represent single-cell identity. This is the first demonstration that biologically-meaningful values for parameter of intracellular processes can be attributed to individual cells.

7.4. The cost of cellular adaptation to stress: tradeoff between short-term and long-term adaptation to osmotic stress in yeast

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

Upon stress, cells have evolved complex adaptation strategies to environmental variations which include sensing, information processing and modification of metabolic and transcriptional activity. The reaction of yeast cells to hyperosmotic stress spans several timescales and includes massive gene-expression changes, bio-compatible osmolyte production, and direct action on the cell cycle. Despite a detailed knowledge of molecular events, the impact of stress-response on cellular resources is poorly known. In particular, strong and fast adaptation which alter proliferation in the short term while conferring advantage on the long term are important drivers of stress-response evolution.

In this study, we use microfluidics to vary dynamically both the source of cost (osmotic stress) and the available metabolic resources (glucose) while monitoring cellular proliferation. We show that, under hyper-osmotic stress, metabolic resources are rerouted towards the production of glycerol through activation of an essential enzyme in glycerol production. This reveals the nature of the burden imposed by osmotic stress and, more generally, allows us to better understand the evolutionary tradeoffs between stress response and proliferation.

7.5. Balancing a genetic inverted pendulum

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

The ability to routinely control complex genetic circuits in vivo and in real-time promises quantitative understanding of cellular processes of unprecedented precision and quality. With combined efforts in microfluidic design, microscope automation, image analysis, modeling and control theory, we propose a platform for real-time, single-cell, *in silico* control of genetic networks in *E. coli*. The circuit we are trying to control is a 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 in its upright position. 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 maintain in a balanced state the toggle switch in single cells. Finally, we demonstrate that similar results can be obtained by applying periodic inductions, identical to all cells in the population. Given the fact that all cells behave differently, this result was highly unexpected. It can however be understood as an example of dynamic stabilization, analogous to the solution proposed by Kapitza for the inverted pendulum.

These results are presented in the PhD thesis of Jean-Baptiste Lugagne [2].

7.6. A look-ahead simulation algorithm for DBN models of biochemical pathways

Participants: Grégory Batt, Sucheendra Palaniappan.

Dynamic Bayesian Networks (DBNs) have been proposed as an efficient abstraction formalism of biochemical models. They have been shown to approximate well the dynamics of biochemical models, while offering improved efficiency for their analysis. In [14], we compare different representations and simulation schemes on these DBNs, testing their efficiency and accuracy as abstractions of biological pathways. When generating these DBNs, many configurations are never explored by the underlying dynamics of the biological systems. This can be used to obtain sparse representations to store and analyze DBNs in a compact way. On the other hand, when simulating these DBNs, singular configurations may be encountered, that is configurations from where no transition probability is defined. This makes simulation more complex. We initially evaluate two simple strategies for dealing with singularities: first, re-sampling simulations visiting singular configurations; second filling up uniformly these singular transition probabilities. We show that both these approaches are error prone. Next, we propose a new algorithm which samples only those configurations that avoid singularities by using a look-ahead strategy. Experiments show that this approach is the most accurate while having a reasonable run time.

7.7. Logical model specification aided by model-checking techniques: application to the mammalian cell cycle regulation

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

Understanding the temporal behaviour of biological regulatory networks requires the integration of molecular information into a dynamical model. However, the analysis of model dynamics faces a combinatorial explosion as the number of regulatory components and interactions increases. In [8], we use model-checking techniques to verify sophisticated dynamical properties resulting from the model influence structure in the absence of kinetic assumption. We demonstrate the power of this approach by analysing a Boolean influence model of the molecular network controlling mammalian cell cycle. This approach enables a systematic analysis of model properties, the delineation of model limitations, and the assessment of various refinements and extensions based on recent experimental observations. The resulting logical model accounts for the main irreversible transitions between cell cycle phases, the sequential activation of cyclins, and the inhibitory role of Skp2, and further emphasizes the multifunctional role for the cell cycle inhibitor Rb.

7.8. Model-based investigation of the circadian clock and cell cycle coupling in mouse embryonic fibroblasts: prediction of RevErb–α up-regulation during mitosis

Participants: François Fages, Sylvain Soliman, Pauline Traynard.

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. Some mathematical models have also been built to assess conditions of control of the cell cycle by the circadian clock. However, recent studies in individual NIH3T3 fibroblasts have shown an unexpected acceleration of the circadian clock together with the cell cycle when the culture medium is enriched with growth factors, and the absence of such acceleration in confluent cells. In [9], in order to explain these observations, we study a possible entrainment of the circadian clock by the cell cycle through a regulation of clock genes around the mitosis phase. We develop a computational model and a formal specification of the observed behavior to investigate the conditions of entrainment in period and phase. We show that either the selective activation of RevErb-α or the selective inhibition of Bmal1 transcription during the mitosis phase, allow us to fit the experimental data on both period and phase, while a uniform inhibition of transcription during mitosis seems incompatible with the phase data. We conclude on the arguments favouring the RevErb-α up-regulation hypothesis and on some further predictions of the model.

7.9. Stochastic continuous optimization backend for the constraint modelling language MiniZinc with applications to geometrical placement problems

Participants: François Fages, Thierry Martinez, Sylvain Soliman.

MiniZinc is a solver-independent constraint modeling language which is increasingly used in the constraint programming community. It can be used to compare different solvers which are currently based on either Constraint Programming, Boolean satisfiability, Mixed Integer Linear Programming, and recently Local Search. In [12], [13] we present a stochastic continuous optimization backend for MiniZinc models over real numbers. More specifically, we describe the translation of FlatZinc models into objective functions over the reals, and their use as fitness functions for the Covariance Matrix Adaptation Evolution Strategy (CMA-ES) solver. We illustrate this approach with the declarative modeling and solving of hard geometrical placement problems [16], motivated by packing applications in logistics [10] involving mixed square-curved shapes and complex shapes defined by Bézier curves.

Beyond these applications to packing problem, our real motivation for these developments is the solving of parameter search problems in computational systems biology and its implementation in BIOCHAM.

7.10. Mixture model CMA-ES

Participants: François Fages, Nicolas Vasselin.

In [19], we report on our attempt to improve the CMA-ES global optimization algorithm based on two ideas: first the use of Sobol's quasi-random low discrepancy numbers instead of pseudo-random numbers, second the design of a mixture model extension of CMA-ES (MM-CMA-ES) which, instead of doing restarts with an important loss of information at each restart, evolves a dynamic set of multivariate normal distributions in parallel, using an EM clustering algorithm at each step to decide of population splittings and mergings. On the standard Coco benchmark for evaluating global stochastic optimization methods, the use of Sobol numbers shows a quite uniform improvement by 30% as was already shown by Teytaud last year [13]. On the other hand, MM-CMA-ES does not show speed-up w.r.t. CMA-ES with IBOP restart strategy, even on objective functions with many local minima such as the Rastragin function. The reason is the overhead in the number of evaluation of the objective functions, introduced by the MM strategy, and the very subtle effect of the adaptive step size strategy of CMA-ES to escape from the covering of several local minima by one (large) normal distribution.

[13] O. Teytaud. Quasi-random numbers improve the CMA-ES on the BBOB testbed. Artificial Evolution (EA2015), 2015, Lyon, France. Springer Verlag, pp.13

7.11. Metro energy optimization through rescheduling

Participants: François Fages, Thierry Martinez.

The use of regenerative braking is a key factor to reduce the energy consumption of a metro line. In the case where no device can store the energy produced during braking, only the metros that are accelerating at the same time can benefit from it. Maximizing the power transfers between accelerating and braking metros thus provides a simple strategy to benefit from regenerative energy without any other hardware device. In [15], we use a mathematical timetable model to classify various metro energy optimization problems studied in the literature and prove their NP-hardness by polynomial reductions of SAT. We then focus on the problem of minimizing the global energy consumption of a metro timetable by modifying the dwell times in stations. We present a greedy heuristic algorithm which aims at locally synchronizing braking trains along the timetable with accelerating trains in their time neighbourhood, using a non-linear approximation of energy transfers. On a benchmark of the litterature composed of six small size timetables, we show that our greedy heuristics performs better than CPLEX using a MILP formulation of the problem with a linear approximation of the objective function. We also show that it runs ten times faster than a state-of-the-art evolutionary algorithm, called the covariance matrix adaptation evolution strategy (CMA-ES), using the same non-linear objective function on these small size instances. On real data leading to 10000 decision variables on which both MILP and CMA-ES do not provide solutions, our dedicated algorithm computes solutions with a reduction of energy consumption ranging from 5% to 9%.

This work done in 2014 in the Cifre PhD Thesis of David Fournier with General Electric Transportation has received this year the Gold Medal of the *Annual Alstom Contest* "I Nove You" in the "Green Innovation" category.

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. ANR Projects

- ANR-MOST BIOPSY (2016-2020) on "Biochemical Programming System", coordinated by F. Molina (CNRS, Sys2diag, Montpellier) and J.H. Jiang (National Taiwan University), with F. Fages.
- ANR MEMIP (2016-2020) on "Mixed-Effects Models of Intracellular Processes", coordinated by G. Batt, with P. Hersen, (CNRS/Paris7), E. Cinquemani (Inria EPI IBIS) and M. Lavielle (Inria/CNRS/Polytechnique, EPI XPOP).
- ANR COGEX (2016-2019) on "Computer Aided Control of Gene Expression" coordinated by P. Hersen (MSC lab, CNRS/Paris7), with G. Batt and G. Truan (LISBP, CNRS/INSA).
- ANR Blanc HYCLOCK (2014-2018) on "Hybrid modeling of time for Circadian Clock Biology and Chronopharmacology", coordinated by F. Delaunay (CNRS, Nice), with F. Lévi (INSERM Paris-Sud), G. Bernot (CNRS I3S, Nice), O. Roux (Ecole Centrale Nantes), F. Fages and S. Soliman.
- 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).

8.1.2. GENCI Contract

- GENCI (2009-2016) 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. Informal International Partners

In the context of the PhD thesis of Virgile Andréani, we initiated a collaboration with the lab of Lingchong You in the Biomedical Engineering department of Duke University (NC, USA).

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 a sabbatical stay of six months

- Prof. David Rosenblueth, University of Mexico, Mexico.

We also received for short visits:

- Prof. Mark Chaplain, University of St-Andrews, UK,
- Prof. Attila Attila Csikász-Nagy, King's College London,
- Dr. Jakob Ruess, IST Austria,
- Dr. Amaury Pouly, Univ. Oxford, UK,
- Dr. Christoph Zechner, ETH Zurich,
- Prof. Natalio Krasnogor, Newcastle University, UK,

8.3.1.1. Research Stays Abroad

Virgile Andréani visited Lingchong You's lab (Duke U.) for two weeks in March 2016.

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific Events Selection

9.1.1.1. Member of the Conference Program Committees

- Grégory Batt was member of the program committees of:
  - FOSBE'16 6th IFAC Conference on Foundations of Systems Biology in Engineering, Laboratory for Systems Theory and Automatic Control, Otto von Guericke University, Magdeburg, Germany, 9th - 12th October 2016.
  - CMSB'16 14th International Conference on Computational Methods in Systems Biology, Computer Laboratory, University of Cambridge, UK, 21st - 23rd September 2016.
  - HSB'16 5th international workshop on Hybrid Systems Biology, Grenoble, October 20-21, 2016.
- François Fages was member of the program committees of:

  - CIE'16 Computability in Europe, Paris, 2016.
  - CMSB'16 14th International Conference on Computational Methods in Systems Biology, Computer Laboratory, University of Cambridge, UK, 21st - 23rd September 2016.
  - CP'16 22nd International Conference on Principles and Practice of Constraint Programming, Toulouse, France, September 5-9, 2016.
  - HSB'16 5th international workshop on Hybrid Systems Biology, Grenoble, October 20-21, 2016.
  - IJCAI'16 25th International Joint Conference on Artificial Intelligence, New York, 2016.
  - SASB'16 The Seventh International Workshop on Static Analysis and Systems Biology, September 8–10, 2016, Edinburgh, UK
  - WCB'16 12th International Workshop on Constraint-Based Methods for Bioinformatics, Toulouse, 2016.
- Sylvain Soliman was member of the program committees of:
  - CP'16 22nd International Conference on Principles and Practice of Constraint Programming, Toulouse, France, September 5-9, 2016.
  - WCB'16 12th International Workshop on Constraint-Based Methods for Bioinformatics, Toulouse, 2016.
- Sucheendra K. Palaniappan was member of the program committee of Formal Methods for Biological and Biomedical Systems (FMBBS 2016), Shenzhen, China, December 2016.

9.1.2. Journal

9.1.2.1. 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.

9.1.2.2. Reviewer - Reviewing Activities

Beyond their Editorial Board and Program Committee duties,

- Grégory Batt reviewed an article for *ACS Synthetic Biology*
- François Fages reviewed articles for *BMC Systems Biology*, *Fundamenta Informaticae*, *BioSystems*, *PLOS-One* and *Computers and Industrial Engineering*.
- Sylvain Soliman reviewed articles for *BMC Systems Biology*, *BioSystems* and *AMS Math Reviews*.

9.1.3. Invited Talks

- François Fages gave invited talks at
  - Workshop on Symbolic Computation for Biological Systems, "Biochemical Programs and Mixed Analog-Digital Algorithms in the Cell", Univ. Bonn, 22 November 2016
  - Bilille scientific day on Systems Biology, "Biochemical Programs and Mixed Analog-Digital Algorithms in the Cell", Univ. Lille, 15 November 2016,
  - Colloque de Cérisy, Sciences de la vie, science de l'information, "Biochemical Programs and Mixed Analog-Digital Algorithms in the Cell", 20 September 2016,
  - Workshop on Formal Verification of Real-Time Systems, "Continuous Valuations of Temporal Logic Specifications with applications to Parameter Optimization and Robustness Measures", ENSTA Brest, 28 June 2016,
  - Workshop on Verification of Biological Systems, "Hybrid Analog/Digital Computation with Biochemical Reaction Systems", ENS Cachan, 17 May 2016,

  - International Worskhop on Entropy and Information, “Digital/Analog Computation in the Cell”, Univ Paris-Diderot, 9 May 2016.
  - GT TheorBio, “Computational Systems Biology and Optimization”, Orsay, 9 Février 2016.
- Grégory Batt gave invited talks at
  - Seminar at Systems Biology group, Clinical Pharmacology, Roche Pharma Research, on “Multi-scale modeling of TRAIL-induced apoptosis”, March 2016, Basel
  - Seminar at Control Theory and Systems Biology Lab, Department of Biosystems Science and Engineering, ETHZ, on “Multi-scale modeling of TRAIL-induced apoptosis”, March 2016, Basel
  - Journées Inria Cancer, Modeling dynamics of cell-to-cell variability in TRAIL-induced apoptosis explains fractional killing and predicts reversible resistance, March 2016, Paris
  - Third International Workshop on Synthesis of Complex Parameters, “What population reveals about individual cell identity: Single-cell parameter estimation of models of gene expression in yeast”, April 2016, Eindhoven
  - Open University: systèmes hybrides et systèmes biologiques, “Predicting long-term effects of apoptosis-inducing drug treatments”, May 2016, ENS Cachan, France
  - Journées scientifiques Inria, “What population reveals about individual cell identity: Single-cell parameter estimation of models of gene expression in yeast”, June 2016, Rennes
  - Second Conference of the French Research Group on Synthetic Biology, “Balancing a genetic toggle switch by real-time control or periodic stimulations”, June 2016, Bordeaux
  - Second Conference of the French Research Group on Symbolic Systems Biology, “Multi-scale modeling of TRAIL-induced apoptosis”, July 2016, Lyon
  - Pasteur Quantitative Biology Symposium, “Balancing a genetic toggle switch by real-time control or periodic stimulations”, Oct 2016, Paris
  - Bililleb scientific day on Systems Biology, “Balancing a genetic toggle switch by real-time control or periodic stimulations”, Nov 2016, Lille
- Jakob Ruess gave invited talks at
  - Dracula seminar, “Towards real-time in vivo mathematical biology at the level of single cells”, Nov 2016, Lyon

9.1.4. 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
  - co-animator of the French working group on Symbolic Systems Biology GT BIOSS
- François Fages is a member of
  - the Steering Committee of the International Conference on Computational Methods for Systems Biology since 2008,
  - the Scientific Council of the *Doctorate School “Frontières Du Vivant”* at *Center for Research and Interdisciplanirity*, Universities Paris Descartes and Paris Diderot, since 2010,
  - The Scientific Commmittee of the Summer School Ecole Thématique Modélisation Formelle des Réseaux de Régulation Biologique since 2010.

9.1.5. Scientific Expertise

François Fages

- is a member of the jury for the *Prix de thèse Gilles Kahn* of the *Société Informatique de France*, since 2015,
- reviewed one research project for the **Israel Science Foundation**.

Grégory Batt has been a member of the selection committee for Junior research scientists (CR2) at Inria Rennes - Bretagne Atlantique in 2016.

9.1.6. Research Administration

François Fages is member of the "Bureau du Comité des Projets" of Inria Saclay-IdF.

Sylvain Soliman is member of

- the "Commission Scientifique" of Inria Saclay-IdF
- and of the AAP Digiteo/Digicosme Ph.D. grant jury.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Master: Grégory Batt (coordinator and teacher: 48h) and Jakob Ruess (24h), *Computational Biology*, M1, Master Approches Interdisciplinaires du Vivant (AIV).

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

Master/PhD: Grégory Batt (co-coordinator 80h, teacher 8h) and Jakob Ruess (8h), *Modeling and engineering of biological systems*, M2/PhD, Institut de Technologie et d'Innovation of Paris Sciences et Lettres (PSL-ITI), Paris.

Master: Chiara Fracassi (48h), *Experimental Methods in Biophysics*, M1, Master Approches Interdisciplinaires du Vivant (AIV).

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

Doctorate: François Fages (6h), *Méthodes formelles pour la biologie des systèmes*, Ecole Thématique Modélisation Formelle des Réseaux de Régulation Biologique, Ile de Porquerolles, 6-10 June 2016

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 : Pauline Traynard, *Model Building by Temporal Logic Constraint Solving: Investigation of the Coupling between the Cell Cycle and the Circadian Clock*, Université Paris Diderot, Paris (Oct 2012), Dir. François Fages and Denis Thieffry (ENS), 10 May 2016.

PhD : François Bertaux. *Cell-based multi-scale modeling for systems and synthetic biology: from stochastic gene expression in single cells to spatially organized cell populations*. Université Paris - Diderot, Dir. Dirk Drasdo (EPI MAMBA) and Grégory Batt, 15 May 2016.

PhD : Jean-Baptiste Lugagne, Université Paris Diderot, Paris (Oct 2012), Dir. Grégory Batt and Pascal Hersen (CNRS, MSC), 13 Dec 2016.

PhD in progress: Jonas Sénizergues, Université Paris Diderot, Paris (Oct 2015, until August 2016), Dir. François Fages and Sylvain Soliman.

PhD in progress (Sept 2016-): Virgile Andréani, Ecole Polytechnique, Paris , Dir. Grégory Batt and Lingchong You (Duke U.).

PhD in progress (Dec 2016-): Jean-Baptiste Caron, relais thèse Inria, Dir. Grégory Batt.

9.2.3. Juries

- HDR: Morgan Magnin, "Contributions à l'élaboration de connaissances qualitatives en bio-informatique", Ecole Centrale de Nantes, *François Fages, Reviewer*, 28 avril 2016.
- Ph.D.: Simona Catozzi, "Retroactivity in Signal Transduction", Univ. Nice Sophia-Antipolis, *François Fages, Examiner*, 15 Dec. 2016.
- Ph.D.: Alexandre Temperville, "Bases creuses en algèbre linéaire exacte et simplification algorithmique de modèles biologiques", Université de Lille, *François Fages, Reviewer*, 11 juillet 2016.
- Ph.D.: Ignacio Salas, "Packing Curved Objects with Interval Methods", Ecole des Mines de Nantes, *François Fages, Reviewer, Chairman of the Jury*, 29 avril 2016.
- Ph.D.: Louis Fippo Fitime, "Modélisation hybride, Analyse et Vérification Quantitative des grands réseaux de régulation biologique", École Centrale de Nantes, *Sylvain Soliman, Examiner*, November 28, 2016.
- Ph.D.: Adel Mezine, "Conduite d'expériences par apprentissage actif pour l'identification de systèmes dynamiques biologiques", Paris-Saclay University, *Grégory Batt, Reviewer*, October 11, 2016.

9.3. Popularization

François Fages

- wrote a book chapter "AI and Biological Modeling" [17], for an encyclopedic book entitled "A guided tour to Artificial Intelligence Research" to appear next year,
- participated in the **Colloque de Cérisy** "Sciences du vivant, sciences de l'information", 20 Septembre 2016, with a conference and an article [18] to appear in a book next year,
- wrote an article for ERCIM news [16],
- and received a schoolgirl for one afternoon in our research team.

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] F. BERTAUX. *Cell-based multi-scale modeling for systems and synthetic biology: from stochastic gene expression in single cells to spatially organized cell populations*, Université Pierre & Marie Curie - Paris 6, June 2016, https://tel.archives-ouvertes.fr/tel-01405430

[2] J.-B. LUGAGNE. *Real-time control of a genetic toggle switch*, Université Paris 7, December 2016, https://tel.archives-ouvertes.fr/tel-01417700

[3] S. SOLIMAN. *A structural perspective on the dynamics of biochemical systems*, Université Paris Sud - Orsay, December 2016, Habilitation à diriger des recherches, https://tel.archives-ouvertes.fr/tel-01403712

[4] P. TRAYNARD. *Model Building by Temporal Logic Constraint Solving: Investigation of the Coupling between the Cell Cycle and the Circadian Clock*, Université Paris Diderot, May 2016, https://tel.archives-ouvertes.fr/tel-01404060

Articles in International Peer-Reviewed Journals

[5] O. BÉTHOUX, A. LLAMOSI, S. TOUSSAINT. *Reinvestigation of Protelytron permianum (Insecta; Early Permian; USA) as an example for applying reflectance transformation imaging to insect imprint fossils*, in "Fossil Record", 2016, vol. 20, n° 1, pp. 1 - 7 [*DOI :* 10.5194/FR-20-1-2016], https://hal.inria.fr/hal-01406082

[6] A. LLAMOSI, A. GONZALEZ, C. VERSARI, E. CINQUEMANI, G. FERRARI-TRECATE, P. HERSEN, G. BATT. *What population reveals about individual cell identity: Single-cell parameter estimation of models of gene expression in yeast*, in "PLoS Computational Biology", February 2016, vol. 12, n° 2, e1004706 [*DOI :* 10.1371/JOURNAL.PCBI.1004706], https://hal.inria.fr/hal-01248298

[7] 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", April 2016, vol. 21, n° 2, pp. 251–276 [*DOI :* 10.1007/S10601-015-9190-1], https://hal.archives-ouvertes.fr/hal-01170962

[8] P. TRAYNARD, A. FAURÉ, F. FAGES, D. THIEFFRY. *Logical model specification aided by model- checking techniques: application to the mammalian cell cycle regulation*, in "Bioinformatics", 2016, vol. 32, n° 17, pp. i772-i780 [*DOI :* 10.1093/BIOINFORMATICS/BTW457], https://hal.archives-ouvertes.fr/hal-01378465

[9] P. TRAYNARD, C. FEILLET, S. SOLIMAN, F. DELAUNAY, F. FAGES. *Model-based investigation of the circadian clock and cell cycle coupling in mouse embryonic fibroblasts: Prediction of RevErb-α up-regulation during mitosis*, in "BioSystems", November 2016, vol. 149, pp. 59–69 [*DOI :* 10.1016/J.BIOSYSTEMS.2016.07.003], https://hal.archives-ouvertes.fr/hal-01378466

International Conferences with Proceedings

[10] A. AGGOUN, A. RHIAT, F. FAGES. *Panorama of real-life applications in logistics embedding bin packing optimization algorithms, robotics and cloud computing technologies*, in "GOL'16 - 3rd IEEE International Conference on Logistics Operations Management", Morocco, Morocco, May 2016 [*DOI :* 10.1109/GOL.2016.7731693], https://hal.archives-ouvertes.fr/hal-01378469

[11] F. FAGES, T. MARTINEZ, D. ROSENBLUETH, S. SOLIMAN. *Influence Systems vs Reaction Systems*, in "CMSB'16: Proceedings of the fourteenth international conference on Computational Methods in Systems Biology", Cambridge, UK, United Kingdom, E. BARTOCCI, P. LIO, N. PAOLETTI (editors), Lecture Notes in Computer Science, Springer-Verlag, September 2016, vol. 9859, pp. 98-115 [*DOI :* 10.1007/978-3-319-45177-0_7], https://hal.archives-ouvertes.fr/hal-01378470

[12] T. MARTINEZ, F. FAGES, A. AGGOUN. *A Stochastic Continuous Optimization Backend for MiniZinc with Applications to Geometrical Placement Problems*, in "Proceedings of the 13th International Conference on Integration of Artificial Intelligence and Operations Research Techniques in Constraint Programming, CPAIOR'16", Banff, Canada, C.-G. QUIMPER (editor), Springer, May 2016, vol. 9676, pp. 262-278 [*DOI :* 10.1007/978-3-319-33954-2_19], https://hal.archives-ouvertes.fr/hal-01378468

[13] T. MARTINEZ, F. FAGES, A. AGGOUN. *Un solveur d'optmization stochastique pour MiniZinc avec des applications à des problèmes de placements géométriques*, in "Douzièmes Journées Francophones de Programmation par Contraintes JFPC'16", 2016, https://hal.archives-ouvertes.fr/hal-01378467

[14] S. K. PALANIAPPAN, M. PICHENÉ, G. BATT, E. FABRE, B. GENEST. *A Look-Ahead Simulation Algorithm for DBN Models of Biochemical Pathways*, in "Hybrid Systems Biology, 5th International Workshop, HSB 2016", Grenoble, France, E. CINQUEMANI, A. DONZÉ (editors), Lecture Notes in Computer Science, October 2016, vol. 9957, pp. 3-15 [*DOI :* 10.1007/978-3-319-47151-8_1], https://hal.inria.fr/hal-01406115

Research Reports

[15] D. FOURNIER, T. MARTINEZ, F. FAGES, D. MULARD. *Metro Energy Optimization through Rescheduling: Mathematical Models and Heuristic Algorithm Compared to MILP and CMA-ES* , Inria Saclay Ile de France, December 2016, https://hal.inria.fr/hal-01420311

Scientific Popularization

[16] A. AGGOUN, N. BELDICEANU, G. CHABERT, F. FAGES. *Packing with Complex Shapes*, in "ERCIM News", 2016, n^{o} 105, 32 p. , https://hal.archives-ouvertes.fr/hal-01378471

Other Publications

[17] F. FAGES. *AI in Biological Modelling*, November 2016, working paper or preprint, https://hal.inria.fr/hal-01409753

[18] F. FAGES, G. LE GULUDEC. *Programmes biochimiques et algorithmes mixtes analogiques-digitaux dans la cellule*, October 2016, working paper or preprint, https://hal.inria.fr/hal-01409743

[19] N. VASSELIN, F. FAGES. *Mixture Model-CMA-ES* , December 2016, internship report, https://hal.inria.fr/hal-01420342