Activity Report 2013

Project-Team CONTRAINTES

Constraint programming

RESEARCH CENTER
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THEME
Architecture, Languages and Compilation

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Project-Team CONTRAINTES

Keywords: Systems Biology, Rule-based Languages, Formal Methods, Optimization, Synthetic Biology

Creation of the Project-Team: 2001 March 01, end of the Project-Team: 2013 December 31.

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2. Overall Objectives

2.1. Introduction

Constraint Logic Programming supports a great ambition for making of programming essentially a modeling task, with equations, constraints and logical formulas. Its foundation is the use of relations on mathematical variables to compute with partial information, using domain filtering algorithms and search.

Our EPI has evolved since its creation in 2001, from the study of concurrent constraint logic programming languages and their applications to solving combinatorial optimization problems in industry and biology, to a strong focus on computational systems biology, for the analysis and optimization of biochemical reaction systems, with applications to cell biology, medicine and synthetic biology.

2.2. Highlight: a Stronger Necessary Condition for the Multistationarity of Chemical Reaction Networks.

In the last thirty years, the conjecture of Thomas on the necessary presence of a positive circuit for the occurrence of multistationarity has opened a whole field of research, allowing better understanding of biochemical networks. In [5] we improve on the ten years old proof by Soulé. In particular, the obvious cases of multimolecular reactions where Thomas' condition was trivially satisfied can now easily be ruled out. The new condition makes it possible to use circuit analysis as an useful tool in the arsenal of the computational biologist, together with other structural methods.

2.3. Highlight: STL-based Analysis of TRAIL-induced Apoptosis Challenges the Notion of Type I/Type II Cell Line Classification

Extrinsic apoptosis is a programmed cell death triggered by external ligands, such as TRAIL. Depending on the cell line, the specific molecular mechanisms leading to cell death may significantly differ. These differences are attributed to the activation of one of two pathways, leading to classification of cell lines into two groups: type I and type II. In [6] we challenge this type I/type II cell line classification using signal temporal logic (STL), and reconciliate two apparently-conflicting views regarding the importance of either upstream or downstream processes for cell-type determination.

3. Research Program

3.1. Rule-based Modeling Languages

Logic programming in a broad sense is a declarative programming paradigm based on mathematical logic with the following identifications:

$$\textit{program} = \textit{logical formula},$$

$$\textit{execution} = \textit{proof search},$$

In Constraint Satisfaction Problems (CSP), the logical formulae are conjunctions of constraints (i.e. relations on variables expressing partial information) and the satisfiability proofs are computed by constraint solving procedures.

In Constraint Logic Programming (CLP), the logical formulae are Horn clauses with constraints (i.e. one headed rules for the inductive definitions of relations on variables) and the satisfiability proofs combine constraint solving and clause resolution. Gnu-Prolog and its modular extension EMoP that we develop, belong to this family of languages. We use them for solving combinatorial problems and for implementing Biocham.

In Concurrent Constraint Programming (CCP), CLP resolution is extended with a synchronization mechanism based on constraint entailment. The variables play the role of transmissible dynamically created communication channels. An agent may add constraints to the store or read the store to decide whether a constraint guard is entailed by the current store. Sicstus-Prolog and SWI-Prolog belong the this family of languages. We use them for solving combinatorial optimization problems and defining new global constraints.

Linear Logic Concurrent Constraint Programming (LLCC) is a generalization of CCP based on Jean-Yves Girard's Linear Logic [1], which allows for a non-monotonic evolution of the store of constraints and multi-headed rules like the Constraint Handling Rules (CHR) language of T. Frühwirth.

All these rule-based languages, of increasing expressivity, involve some form of *multiset rewriting*. We develop the following modeling languages:

- Rules2CP, a rule-based modeling language for solving constraint optimization problems, developed for non-programmers,
- SiLCC, our experimental implementation of LLCC,
- the Biochemical Abstract Machine BIOCHAM, a rule-based modeling language dedicated to Systems Biology, in which biochemical reactions between multisets of reactants and products are expressed with multi-headed rules (somewhat similar to CHR rules) and augmented with *kinetic expressions* from which one can derive quantitative interpretations by Ordinary Differential Equations (ODE), Continuous-Time Markov Chains (CTMC) or Hybrid Automata.

3.2. Constraint Solving Techniques

Constraint propagation algorithms use constraints actively during search for filtering the domains of variables and reducing the search space. These domain reductions are the only way constraints communicate between each other. Our research involves different constraint domains, namely:

- booleans: binary decision diagrams and SAT solvers;
- finite domains (bounded natural numbers): membership, arithmetic, reified, higher order and global constraints;
- reals: polyhedral libraries for linear constraints and interval methods;
- terms: subtyping constraints;
- graphs: subgraph epimorphism (SEPI) and isomorphism constraints; acyclicity constraint;
- Petri nets: P/T-invariants, siphons and traps;
- Kripke structures: temporal logic constraints (first-order Computation Tree Logic constraints over the reals).

We develop new constraints and domain filtering algorithms by using already existing constraint solving algorithms and implementations. For instance, we use the Parma Polyhedra Library PPL with its interface with Prolog for solving temporal logic constraints over the reals. Similarly, we use standard finite domain constraints for developing solvers for the new SEPI graph constraint.

3.3. Formal Methods for Systems Biology

At the end of the 90s, research in Bioinformatics evolved, passing from the analysis of the genomic sequence to the analysis of post-genomic interaction networks (expression of RNA and proteins, protein-protein interactions, transport, etc.). Systems biology is the name given to a pluridisciplinary research field involving biology, computer science, mathematics, physics, to illustrate this change of focus towards system-level understanding of high-level functions of living organisms from their biochemical bases at the molecular level.

[1] F. Fages, P. Ruet, S. Soliman. *Linear concurrent constraint programming: operational and phase semantics*, in "Information and Computation", 2001, vol. 165(1), pp.14-41.

Our group was among the first ones in 2002 to apply formal methods from computer science to systems biology in order to reason on large molecular interaction networks and get over complexity walls. The *logical paradigm for systems biology* that we develop can be summarized by the following identifications :

biological model = rule-based transition system,

biological property = temporal logic formula,

model validation = model-checking,

model inference = constraint solving.

Rule-based dynamical models of biochemical reaction networks are composed of a reaction graph (bipartite graph with vertices for species and reactions) where the reaction vertices are given with kinetic expressions (mass action law, Michaelis-Menten, Hill, etc.). Most of our work consists in analysing the *interplay between the structure* (reaction graphs) *and the dynamics* (ODE, CTMC or hybrid interpretations derived from the kinetic expressions).

Besides this logical paradigm, we use the theory of abstract interpretation to relate the different interpretations of rule-based models and organize them in a hierarchy of semantics from the most concrete (CTMC stochastic semantics) to the most abstract (asynchronous Boolean transition system). This allows us to prove for instance that if a behavior is not possible in the Boolean semantics of the rules then it is not possible in the stochastic semantics for any kinetic expressions and parameter values. We also use the framework of abstract interpretation to formally relate rule-based reaction models to other knowledge representation formalisms such as, for instance, ontologies of protein functions, or influence graphs between molecular species. These formal methods are used to build models of biological processes, fit models to experimental data, make predictions, and design new biological experiments.

3.4. Tight Integration of In Silico and In Vivo Approaches

Bridging the gap between the complexity of biological systems and our capacity to model and predict systems behaviors is a central challenge in quantitative systems biology. We investigate using wet and dry experiments a few challenging biological questions that necessitate a tight integration between *in vivo* and *in silico* work. Key to the success of this line of research fundamentally guided by specific biological questions is the deployment of innovative modelling and analysis methods for the *in silico* studies.

Synthetic biology, or bioengineering, aims at designing and constructing *in vivo* biological systems that performs novel, useful tasks. This is achieved by reingeneering existing natural biological systems. While the construction of simple intracellular circuits has shown the feasibility of the approach, 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). How should cells be genetically modified such that the desired behavior robustly emerges from cell interactions? In collaboration with Dirk Drasdo (EPI BANG), we develop *abstraction methods for multiscale systems* to make the design and optimization of such systems computationally tractable and investigate the mammalian tissue homeostasis problem from a bioengineering point of view. Then, in collaboration with the Weiss lab (MIT), we construct and test *in vitro* the proposed designs in actively-growing mammalian cells.

The rational design of synthetic systems relies however on a good quantitative understanding of the functioning of the various processes involved. To acquire that knowledge, one observes the cell reaction to a range of external perturbations. However, current experimental techniques do not allow precise perturbations of cellular processes over a long time period. To make progress on this problem, we develop an experimental platform for the *closed-loop control* of intracellular processes. In collaboration with the MSC lab (CNRS/Paris Diderot U), we develop models of the controlled cellular system, generate quantitative data for parameter identification, and develop real-time control approaches. The integration of all these elements results in an original platform combining hardware (microfluidic device and microscope) and software (cell tracking and model predictive control algorithms). More specifically, by setting up an external, *in silico* feedback loop, we investigate

the strengths and time scales of natural feedback loops, responsible for cell adaptation to environmental fluctuations.

4. Application Domains

4.1. Combinatorial optimization

The number and economic impact of combinatorial optimization problems found in the industrial world are constantly increasing. They cover:

- resource allocation;
- placement, bin packing;
- scheduling;
- planning;
- transport;
- etc.

The last fifty years have brought many improvements in Operations Research resolution techniques. In this context, Constraint Programming can be seen as providing, on the one hand, constraint propagation algorithms that can be applied to various numerical or symbolic constraints, and on the other hand, declarative languages to model real-life problems and express complex resolution strategies. The latter point is crucial for designing new algorithms that cannot be defined without a sufficiently high-level language to express them. It allowed for better results than traditional methods, for instance in scheduling, and is promised to an even better future when thinking about the cooperation of global resolution, local consistency techniques and search methods.

The European FP6 Strep project Net-WMS that we have coordinated, has shown the benefit of combining discrete geometry constraints with rules to express physical, common sense and packing business constraints to solve packing problems in the context of warehouse management systems for the automotive industry. In this context, we have developed a rule-based modeling language, called Rules2CP, to express requirements in a declarative and flexible manner, and compile them to efficient constraint programs using reified constraints and a global constraint dedicated to geometrical placement problems in high dimension.

4.2. Computational Systems Biology

In partnership with biologists, we develop and experiment our modeling methods in five main leading applications:

- **Cancer chronotherapy optimization.** This research initiated in 2004 in partnership with Jean Clairambault, EPI BANG, and Francis Lévi INSERM, Hopital Paul Brousse, Villejuif, aims at understanding fundamental mechanisms involved in cancer and chronotherapies through mathematical modeling. Following the EU STREP project TEMPO (2006-2009) on "temporal genomics for patient tailored chronotherapeutics", coordinated by Francis Lévi, and in the framework of the Era-Net SysBio C5Sys project (2010-2013) coordinated by Francis Lévi and David Rand, University of Warwick, UK, we develop coupled models of the cell cycle, the circadian clock, the DNA repair system, irinotecan metabolism and drug injection optimization, focussing on the interactions between the cell cycle and the circadian clock in mammalian cells.
- **Mammalian cell cycle regulation.** This theme that is closely related to the previous one has lead to a formal collaboration in the framework of the ANR Syscomm project CALAMAR, started in 2009 on the "Compositional modeling and Analysis of LArge MoleculAr Regulatory networks". In partnership with Claudine Chaouiya, TAGC INSERM, Marseille, and Laurence Calzone, Institut Curie, Paris, this project aims at applying our computational techniques – both qualitative and quantitative – to the analysis of the large scale RB/E2F network, in order to elucidate various features of the human cell proliferation, especially in the case of healthy and bladder-tumor cells of different aggressiveness.

- **Real-time control of gene expression in yeast.** This research lead in the team by Grégory Batt investigates the possibilities to control gene expression in living cells. In collaboration with Pascal Hersen and Samuel Bottani, biophysicists at the Matière and Systèmes Complexes lab, CNRS/Paris Diderot University, we develop a microfluidic platform and control software for the real-time control of gene expression in yeast. In a larger initiative, we consider a similar problem but in mammalian cells, where the stochasticity of gene expression makes the control problem particularly challenging. The Iceberg Investissement d'Avenir project, coordinated by Grégory Batt, involves the MSC, BM2A, LIFL and PPS labs, and the Jacques Monod Institut. Similarly, the Contraintes research group is also involved in the Inria/INSERM large-scale initiative action COLAGE coordinated by Huges Berry, EPI COMBINING, with François Taddei, Ariel Lindner, INSERM Paris Necker, Hidde de Jong, Delphine Ropers, EPI IBIS, Jean-Luc Gouzé, and Madalena Chaves, EPI COMORE. In this project, we investigate the possibilities to control and reprogram growth and aging in bacteria *E. coli* using synthetic biology approaches.
- **Artificial tissue homeostasis in mammalian cells.** Artificial tissue design is a particularly challenging problem in synthetic biology since the system behavior results from the interplay between intra- and intercellular dynamics. In the framework of the Syne2arti ANR project, coordinated by Grégory Batt, and involving Dirk Draso, EPI BANG, Oded Maler, CNRS Verimag, and Ron Weiss, MIT, USA, we design and genetically-engineer mammalian cells to obtain a tissue having a desired cell density. The long-term correct functioning of the system relies several key aspects, including individual cell decisions, collective, spatial aspects, and cell-to-cell variability.
- **TGFβ signaling** In the framework of the BioTempo ANR project, we recently started to apply the different algorithms available in the BIOCHAM platform to the modeling of the TGFβ signaling network in collaboration with the SeRAIC lab (Rennes, France). The main challenge is to compare and understand crosstalks between the SMAD-dependent fast pathway and the MAPK-dependent slower pathway that is often related to cancer. Both the static network analyzers and the parameter learning methods of BIOCHAM are put to good use in this work.

5. Software and Platforms

5.1. BIOCHAM, biochemical abstract machine

Participants: François Fages, François-Marie Floch, Steven Gay, Sylvain Soliman.

The Biochemical Abstract Machine BIOCHAM is a modeling environment for systems biology distributed as open-source since 2003. Current version is v3.4, released in October. BIOCHAM uses a compositional rule-based language for modeling biochemical systems, allowing patterns for expressing set of rules in a compact form. This rule-based language is compatible with the Systems Biology Markup Language (SBML) and is interpreted with three semantics correspnding to three abstraction levels:

1. the boolean semantics (presence or absence of molecules),
2. the stochastic semantics (discrete numbers of molecules),
3. the differential semantics (concentrations of molecules).

Based on this formal framework, BIOCHAM features:

- Boolean and numerical simulators (Rosenbrock's method for the differential semantics, Gillespie's algorithm with tau lipping for the stochastic semantics);
- a temporal logic language (CTL for qualitative models and LTL(R_{lin}) with numerical constraints for quantitative models) for formalizing biological properties such as reachability, checkpoints, oscillations or stability, and checking them automatically with model-checking techniques;
- automatic search procedures to infer parameter values, initial conditions and even reaction rules from temporal logic properties;
- automatic detection of invariants, through constraint-based analysis of the underlying Petri net;
- automatic model reduction and comparison, through the use of subgraph epimorphisms [8];
- an SBGN-compatible reaction graph editor;
- an event handler allowing the encoding of hybrid models and formalisms.

BIOCHAM is implemented in GNU-Prolog and interfaced to the symbolic model checker NuSMV and to the continuous optimization tool CMAES developed by the EPI TAO.

5.2. Nicotine

Participant: Sylvain Soliman.

Nicotine is a Prolog framework dedicated to the analysis of Petri nets. It was originally built for the computation of invariants using GNU Prolog's CLP(FD) solver but has been further extended to allow import/export of various Petri nets formats. In 2013 it was ported to SWI Prolog, in order to use its more general FD solver for the satisfaction of the min-plus constraints coming from the tropical equilibration problem [13].

5.3. STSE (Spatio-Temporal Simulation Environment)

Participant: Szymon Stoma.

The overall goal of this software platform is to gather a set of open-source tools and workflows facilitating spatio-temporal simulations (preferably of biological systems) based on microscopy data. The framework currently contains modules to digitize, represent, analyze, and model spatial distributions of molecules in static and dynamic structures (e.g. growing). A strong accent is put on the experimental verification of biological models by actual, spatio-temporal data acquired using microscopy techniques. Project was initially started at Humboldt University Berlin and moved to Inria with its founder. Project webpage is: http://stse-software.org.

5.4. YeastImageToolkit

Participants: Szymon Stoma, Grégory Batt, Pascal Hersen, Artémis Llamosi.

Yeast Image Toolkit (YIT) is a set of tools facilitating segmentation and tracking of yeast cells in brightfield images. Toolkit consists of novel segmentation and tracking algorithm (CellStar), benchmark images and software allowing allowing to asses performance of the tracking. The software is currently under development and is designed to be a CellProfiler plugin. Project webpage is: http://yeast-image-toolkit.biosim.eu/.

5.5. FO-CTL(R_{lin}), first-order computation tree logic over the reals

Participants: François Fages, Thierry Martinez.

FO-CTL(R_{lin}) is a solver for full First-Order Computation Tree Logic with linear arithmetic over the reals in constrained transition systems (CTS). CTS are transition systems where both states and transitions are described with constraints. FO-CTL(R_{lin}) generalizes the implementation done in Biocham of LTL(R_{lin}) for linear traces to branching Kripke structure.

5.6. Rules2CP

Participants: François Fages, Raphaël Martin, Thierry Martinez.

Rules2CP is a rule-based modeling language for constraint programming. It is distributed since 2009 as open-source. Unlike other modeling languages for constraint programming, Rules2CP adopts a single knowledge representation paradigm based on rules without recursion, and a restricted set of data structures based on records and enumerated lists given with iterators. This allows us to model complex constraint satisfaction problems together with search strategies, where search trees are expressed by logical formulae and heuristic choice criteria are defined with preference orderings by pattern-matching on the rules' left-hand sides.

The expressiveness of Rules2CP has been illustrated in the FP6 Strep project Net-WMS by a complete library for packing problems, called PKML (Packing Knowledge Modeling Library), which, in addition to pure bin packing and bin design problems, can deal with common sense rules about weights, stability, as well as specific packing business rules.

5.7. SiLCC, linear concurrent constraint programming

Participant: Thierry Martinez.

SiLCC is an extensible modular concurrent constraint programming language relying upon linear logic. It is a complete implementation of the Linear logic Concurrent Constraint programming paradigm of Saraswat and Lincoln using the formal semantics of Fages, Ruet and Soliman. It is a single-paradigm logical language, enjoying concurrency, imperative traits, and a clean module system allowing to develop hierarchies of constraint systems within the language.

This software prototype is used to study the design of hierarchies of extensible libraries of constraint solvers. SiLCC is also considered as a possible implementation language for restructuring the code of BIOCHAM.

5.8. EMoP, existential modules for Prolog

Participant: Thierry Martinez.

EMoP is an extension of Prolog with first-class modules. These modules have the formal semantics of the LCC modules and provide Prolog with notions of namespaces, closures and objects within a simple programming model. Modules are also the support for user-definition of macros and modular syntax extensions. EMoP is bootstrapped and uses the GNU Prolog compilation chain as back-end.

5.9. CHRat, CHR with ask and tell

Participant: Thierry Martinez.

CHRat is a modular version of the well known Constraint Handling Rules language CHR, called for CHRat for CHR with *ask* and *tell*. Inspired by the LCC framework, this extension of CHR makes it possible to reuse CHRat components both in rules and guards in other CHRat components, and define hierarchies of constraint solvers. CHRat is a bootstrapped preprocessor for CHR which generates code for SWI/Prolog.

5.10. CLPGUI, constraint logic programming graphical user interface

Participant: François Fages.

CLPGUI is a generic graphical user interface written in Java for constraint logic programming. It is available for GNU-Prolog and SICStus Prolog. CLPGUI has been developed both for teaching purposes and for debugging complex programs. The graphical user interface is composed of several windows: one main console and several dynamic 2D and 3D viewers of the search tree and of finite domain variables. With CLPGUI it is possible to execute incrementally any goal, backtrack or recompute any state represented as a node in the search tree. The level of granularity for displaying the search tree is defined by annotations in the CLP program.

CLPGUI has been mainly developped in 2001 and is distributed as third-party software on GNU-Prolog and SICStus Prolog web sites. In 2009, CLPGUI has been interfaced to Rules2CP/PKML and used in the FP6 Strep Net-WMS with a non-released version.

6. New Results

6.1. A Stronger Necessary Condition for the Multistationarity of Chemical Reaction Networks

Participant: Sylvain Soliman.

In the last thirty years, the conjecture of Thomas on the necessary presence of a positive circuit for the occurrence of multistationarity has opened a whole field of research, allowing better modeling and understanding of biochemical networks, especially in the emerging field of systems biology. However, if that aspect is striking in the field of discrete modeling of gene regulatory networks, it did not have the same impact in the Ordinary Differential Equations (ODE) based modeling community. This is mostly due to the fact that this necessary condition, the existence of a positive loop in the Jacobian of the ODE system, is almost always satisfied.

In [5] we improve on the ten years old proof by Soulé, using the structural information from the stoichiometric matrix of a biochemical reaction system. This allows us to state a more strict version of the famous Thomas' necessary condition for multistationarity. In particular, the obvious cases where Thomas' condition was trivially satisfied, mutual inhibition due to a multimolecular reaction and mutual activation due to a reversible reaction, can now easily be ruled out. The new condition makes it possible to use circuit analysis as an useful tool in the arsenal of the computational biologist, together with other structural methods.

6.2. Petri Net Analyses of Biochemical Reaction Networks using Constraint Logic Programming

Participants: François Fages, Thierry Martinez, Faten Nabli, Sylvain Soliman.

The Thesis of Faten Nabli [1] marks our achievements on the static analysis of biochemical reaction networks using Petri Net concepts and Constraint Logic Programming algorithms. This Thesis presents a Boolean model and two constraint-based methods for enumerating all minimal siphons and traps of a Petri net, by iterating the resolution of Boolean satisfiability problems executed with either a SAT solver or a CLP(B) program. The performances of these methods are compared with respect to a state-of-the-art algorithm from the Petri net community. On a benchmark with 80 Petri nets from the Petriweb database and 403 Petri nets from curated biological models of the Biomodels database, we show that miniSAT and CLP(B) solvers are overall both faster by two orders of magnitude with respect to the dedicated algorithm. Furthermore, we analyse why these programs perform so well on even very large biological models and show a polynomial time complexity result for Petri nets of fixed treewidth, using a similar theorem for constraint satisfaction problems with bounded treewidth constraint graphs. Faten Nabli has been hired with a Post-Doc position at Sanofi Paris.

6.3. Structural Model Reduction: CLP and SAT Solvers for Computing Subgraph Epimorphisms

Participants: François Fages, Steven Gay, Thierry Martinez, Francesco Santini, Sylvain Soliman.

This year, in [8], we have developed and compared CLP and SAT solvers on the NP-complete problem of deciding the existence of a subgraph epimorphism between two graphs. Our interest in this variant of graph matching problem stems from the study of model reductions in systems biology, where large systems of biochemical reactions can be naturally represented by bipartite digraphs of species and reactions. In this setting, model reduction can be formalized as the existence of a sequence of vertices, species or reaction, deletion and merge operations which transforms a first reaction graph into a second graph [2]. This problem is in turn equivalent to the existence of a subgraph (corresponding to delete operations) epimorphism (i.e. surjective homomorphism, corresponding to merge operations) from the first graph to the second. We show how subgraph epimorphism problems can be modeled as Boolean constraint satisfaction problems, and we compare CLP and SAT solvers on a large benchmark of reaction graphs from systems biology.

6.4. Quantitative Model Reduction: a CLP Solver for Computing Tropical Equilibrations

Participants: François Fages, Sylvain Soliman.

[2] Steven Gay, Sylvain Soliman, François Fages. A Graphical Method for Reducing and Relating Models in Systems Biology. Bioinformatics, 26(18):i575–i581, 2010.

Model reduction is a central topic in computational systems biology and dynamical systems theory, for reducing the complexity of quantitative models, finding important parameters, and developing multi-scale models for instance. While perturbation theory is a standard mathematical tool to analyze the different time scales of a dynamical system, and decompose the system accordingly, tropical methods provide a simple algebraic framework to perform these analyses systematically in polynomial systems. The crux of these tropicalization methods is in the computation of tropical equilibrations. In [13], we show that constraint-based methods, using reified constraints for expressing the equilibration conditions, make it possible to numerically solve non-linear tropical equilibration problems, out of reach of standard computation methods. We illustrate this approach first with the reduction of simple biochemical mechanisms such as the Michaelis-Menten and Goldbeter-Koshland models, and second, with performance figures obtained on a large scale on the model repository `biomodels.net`.

This work is done in collaboration with Ovidiu Radulescu, Univ. Montpellier, in the context of a larger project about symbolic methods in systems biology with François Boullier, LIFL and Andras Weber, Univ. Bonn.

6.5. Species Minimization in Biochemical Reaction Computing

Participants: Hui-Ju Chiang, François Fages.

Engineering biochemical reactions for computational purposes is a common pursue in synthetic biology. In such design tasks, molecular species have to be carefully engineered to ensure modularity and orthogonality, and are scarce resources. Minimizing the number of involved molecular species is crucial to accomplish a complex computation within a confined biochemical environment.

In [10], we investigate an approach to species minimization by reusing modular and regular reactions in an asynchronous time-multiplexed fashion. Our method enhances not only species utility, but also re-programmability and robustness in realizing various logic circuits. A case study demonstrates the ease of design in realizing general logic computation, and simulation confirms the feasibility and robustness of the proposed method.

This work is done in collaboration with Jie-Hong Jiang and Katherine Chiang from NTU Taiwan in the context of a common project about biochemical programming.

6.6. Hybrid Composition and Simulation of Heterogeneous Biochemical Models

Participants: Hui-Ju Chiang, François Fages, Sylvain Soliman.

Models of biochemical systems presented as a set of formal reaction rules with kinetic expressions can be interpreted with different semantics: as either deterministic Ordinary Differential Equations, stochastic continuous-time Markov Chains, Petri nets or Boolean transition systems. While the formal composition of reaction models can be syntactically defined as the (multiset) union of the reactions, the hybrid composition of models in different formalisms is a largely open issue.

In [7], we show that the combination of reaction rules with conditional events, as the ones already present in SBML, does provide the expressive power of hybrid automata and can be used in a non standard way to give meaning to the hybrid composition of heterogeneous models of biochemical processes. In particular, we show how hybrid differential-stochastic and hybrid differential-Boolean models can be compiled and simulated in this framework, through the specification of a high-level interface for composing heterogeneous models. This is illustrated by a hybrid stochastic-differential model of bacteriophage T7 infection, and by a reconstruction 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 and a differential model of cyclin activation.

6.7. Composition and Abstraction of Logical Influence Networks: Application to Multi-Cellular Systems

Participant: Grégory Batt.

Logical (Boolean or multi-valued) modelling is widely employed to study regulatory or signalling networks. Even though these discrete models constitute a coarse, yet useful, abstraction of reality, the analysis of large networks faces a classical combinatorial problem. In [4], we proposed to take advantage of the intrinsic modularity of inter-cellular networks to set up a compositional procedure that enables a significant reduction of the dynamics, yet preserving the reachability of stable states. To that end, we relied on process algebras, a well-established computational technique for the specification and verification of interacting systems.

We developed a novel compositional approach to support the logical modelling of interconnected cellular networks. First, we formalised the concept of logical regulatory modules and their composition. Then, we made this framework operational by transposing the composition of logical modules into a process algebra framework. Importantly, the combination of incremental composition, abstraction and minimisation using an appropriate equivalence relation (here the safety equivalence) yields huge reductions of the dynamics. We illustrated the potential of this approach with two case-studies: the Segment-Polarity and the Delta-Notch modules.

6.8. Identification of Biological Models from Single Cell Data: a Comparison between Mixed-Effects and Moment-based Inference

Participants: Grégory Batt, Andres Mauricio Gonzalez Vargas, Pascal Hersen, Artémis Llamosi, Jannis Uhlendorf.

Experimental techniques in biology such as microfluidic devices and time-lapse microscopy allow tracking of the gene expression in single cells over time. So far, few attempts have been made to fully exploit these data for modeling the dynamics of biological networks in cell populations. In [9], we compare two modeling approaches capable to describe cell-to-cell variability: Mixed-Effects (ME) models and the Chemical Master Equation (CME). We discuss how network parameters can be identified from experimental data and use real data of the HOG pathway in yeast to assess model quality.

For CME we rely on the identification approach proposed by Zechner et al. (PNAS, 2012), based on moments of the probability distribution involved in the CME. ME and moment-based (MB) inference will be also contrasted in terms of general features and possible uses in biology.

6.9. STL-based Analysis of TRAIL-induced Apoptosis Challenges the Notion of Type I/Type II Cell Line Classification

Participants: Grégory Batt, François Bertaux, Szymon Stoma.

Extrinsic apoptosis is a programmed cell death triggered by external ligands, such as the TNF-related apoptosis inducing ligand (TRAIL). Depending on the cell line, the specific molecular mechanisms leading to cell death may significantly differ. Precise characterization of these differences is crucial for understanding and exploiting extrinsic apoptosis. Cells show distinct behaviors on several aspects of apoptosis, including (i) the relative order of caspases activation, (ii) the necessity of mitochondria outer membrane permeabilization (MOMP) for effector caspase activation, and (iii) the survival of cell lines overexpressing Bcl2. These differences are attributed to the activation of one of two pathways, leading to classification of cell lines into two groups: type I and type II.

In [6] we challenge this type I/type II cell line classification. We encode the three aforementioned distinguishing behaviors in a formal language, called signal temporal logic (STL), and use it to extensively test the validity of a previously-proposed model of TRAIL-induced apoptosis with respect to experimental observations made on different cell lines. After having solved a few inconsistencies using STL-guided parameter search, we show that these three criteria do not define consistent cell line classifications in type I or type II, and suggest mutants that are predicted to exhibit ambivalent behaviors. In particular, this finding sheds light on the role of a feedback loop between caspases, and reconciliates two apparently-conflicting views regarding the importance of either upstream or downstream processes for cell-type determination. More generally, our work suggests that these three distinguishing behaviors should be merely considered as type I/II features rather

than cell-type defining criteria. On the methodological side, this work illustrates the biological relevance of STL-diagrams, STL population data, and STL-guided parameter search implemented in the tool Breach. Such tools are well-adapted to the ever-increasing availability of heterogeneous knowledge on complex signal transduction pathways.

6.10. Single Cell Models and Models of Populations: A Mixed Effect Approach

Participants: Grégory Batt, Andres Mauricio Gonzalez Vargas, Pascal Hersen, Artémis Llamosi.

For a long time, experiments and models of gene expression were mainly based on the mean behavior of a population of cells. Although observed early, it is only recently that experimental technique allowed detailed investigation of variability in this process. Since the pioneering work of Elowitz and colleagues, a distinction is drawn between what is called intrinsic and extrinsic variability or noise. Intrinsic noise originates in the randomness of chemical reactions within a cell whether extrinsic noise is the variation in between cells at a given time. Extrinsic variability is associated with population heterogeneity in the concentrations of ribosomes or other molecular players or processes relevant to gene expression (RNAPolII concentration, degradation and dilution rates etc.).

In this work, we propose a modelling framework for gene expression based on a system of ODEs with random parameters following a distribution across the population of cells. In this context, each cell has its own identity which is represented by the value of its parameters. With this model we ask how much of the long term variability can be explained by extrinsic variability alone. We produced long term, time lapse and single-cell data of repeated gene induction in Saccharomyces cerevisiae. One experiment was treated as learning set whereas two were used as test sets. From the learning set, we are able to infer single cell parameters and population distributions which represent accurately in terms of mean and variance the variability in the population. These learned population distributions allowed good predictions on both the learning and test sets.

Our study demonstrates also that the way inference of single cell parameters and distributions is performed is crucial to achieve good performance. Best results being found by joint estimation of the parameters for single cells and for the whole population. With this technique, we noted that very decent fits of the population dynamics can be obtained by estimating only on a very limited number of cells. Concerning the quality of single cell parameters inferred, we validated the presence of an expected significant correlation between the dilution rate and the measured single cell growth rate. This motivates the use of this tool in order to investigate the origins of extrinsic noise, by correlating single cell parameters with measured candidate factors of gene expression variability such as cell density, cell size or age.

6.11. Coupled Model of the Cell Cycle and Circadian Clock

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

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. This is at the heart of our participation in collaboration with the EPI BANG in the EraNet SysBio project C5Sys, follow up of the former EU STREP project TEMPO.

This year we have pursued the investigation of the effect of transcription inhibition during mitosis, as a reverse coupling from the cell cycle to the circadian clock. We use quantitative temporal logic constraints and the parallel version of BIOCHAM for parameter search, running on the Jade cluster of 10000 processors at the GENCI CINES, to couple dynamical models in high dimension and fit models to experimental data time series obtained in Franck Delaunay's lab in Nice, CNRS. We are defining a series of common temporal logic patterns and *ad hoc* schemes for computing their validity domain on a given trace, more efficiently than by the generic method implemented in BIOCHAM.

6.12. Solving Mixed Shapes Packing Problems by Continuous Optimization with the CMA Evolution Strategy

Participants: François Fages, Thierry Martinez, Lumadaiara Do Nascimento Vitorino.

Bin packing is a classical combinatorial optimization problem which has a wide range of real-world applications in industry, logistics, transport, parallel computing, circuit design and other domains. While usually presented as discrete problems, in [12] we consider continuous packing problems including curve shapes, and model these problems as continuous optimization problems with a multi-objective function combining non-overlapping with minimum bin size constraints. More specifically, we consider the covariance matrix adaptation evolution strategy (CMA-ES) with a nonoverlapping and minimum size objective function in either two or three dimensions. Instead of taking the intersection area as measure of overlap, we propose other measures, monotonic with respect to the intersection area, to better guide the search. In order to compare this approach to previous work on bin packing, we first evaluate CMA-ES on Korf's benchmark of consecutive sizes square packing problems, for which optimal solutions are known, and on a benchmark of circle packing problems. We show that on square packing, CMA-ES computes solutions at typically 14% of the optimal cost, with the time limit given by the best dedicated algorithm for computing optimal solutions, and that on circle packing, the computed solutions are at 2% of the best known solutions. We then consider generalizations of this benchmark to mixed squares and circles, boxes, spheres and cylinders packing problems, and study a real-world problem for loading boxes and cylinders in containers. These hard problems illustrate the interesting trade-off between generality and efficiency in this approach.

6.13. Railway Time Tabling Optimization with CMA-ES and Greedy Heuristics

Participants: François Fages, David Fournier, Thierry Martinez, Sylvain Soliman.

The problem of reducing energy consumption in public transportation has received increasing attention over the last years. Most metros have energy regenerative braking systems, which allow them to produce electric energy when they brake. We study the problem of optimizing the energy consumption of a metro line by modifying the timetable, in order to maximize the actual reuse of the regenerative energy. This is achieved by synchronizing the braking and acceleration phases of the metros, through slight modifications of the stopping times in stations. In an article in preparation, we present a constraint-based model of the electric network of the line, which is used to evaluate the energy consumption at each instant, and to compute a distribution matrix for approximating the potential energy transfers between metros. The optimization of the timetable is then performed by an evolutionary algorithm using the Covariance Matrix Adaptation Evolution Strategy (CMA-ES from Nikolaus Hansen, EPI TAO). On real data, this strategy shows energy savings ranging from 2.38% to 4.54%. Furthermore, these savings are shown to be robust with respect to perturbations of the dwell times.

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

- Cifre PhD accompanying contract with General Electric Transportation on urban railway time tabling optimization (2011-2014).

7.2. Bilateral Grants with Industry

- DTI ITI support for the industrialization of our Rules2CP modeling software and technological transfer to SME KLS-Optim (2011-2013).

8. Partnerships and Cooperations

8.1. National Initiatives

- The OSEO BioIntelligence coordinated by Dassault-Systèmes, with EPI Orpailleur, Sobios, Aureus pharma, Ipsen, Pierre Fabre, Sanofi-Aventis, Servier, Bayer CropScience, INSERM, Genopole Evry (2009-2014).
- 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), Cedric 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.
- ANR Cosinus Syne2arti project (2010-2013) coordinated by Grégory Batt, with Oded Maler, CNRS Verimag, Dirk Drasdo, EPI Bang, and Ron Weiss, MIT.
- ANR Blanc BioTempo project (2010-2014) coordinated by Anne Siegel, CNRS IRISA Rennes, with Ovidiu Radulescu, U. Montpellier, Irina Rusu, U. Nantes.
- AE REGATE (2008-2013) on the "REgulation of the GonAdoTropE axis", coordinated by Frédérique Clément, SISYPHE, with E. Reiter, INRA Tours, J.P. Françoise, Univ. Paris 6, B. Laroche Orsay, P. Michel Centrale Lyon, N. Ayache ASCLEPIOS, A. Goldbeter, ULB Bruxelles.
- AE COLAGE (2008-2013) on the "control of growth and aging in *E. coli* using synthetic biology approaches", coordinated by H. Berry, COMBINING, with F. Taddei, A. Lindner, INSERM Necker, H. de Jong, D. Ropers, IBIS, H. Geiselmann, Grenoble Univ., J.-L. Gouzé, and M. Chaves, COMORE.
- GENCI (2009-) attribution of 300000 computation hours per year on the Jade cluster of 10000 processors of GENCI at CINES, Montpellier.

8.2. European Initiatives

8.2.1. Collaborations in European Programs, except FP7

Program: EraNet SysBio

Project acronym: C5Sys

Project title: Circadian and cell cycle clock systems in cancer

Duration: march 2010 - march 2013

Coordinator: Francis Lévi, INSERM Hopital Paul Brousse, Villejuif, France and David Rand, Warwick Systems Biology, UK,

Other partners: EPI BANG, Erasmus University Medical Center, Rotterdam, University College London, UK, CNRS Nice, and L2S, Orsay.

Abstract: Mammalian cells are endowed with biological oscillators which time their activities. The circadian clock (circa, about; dies, day) generates a 24-hour rhythm which controls both cellular metabolism and cell division. The cell division cycle is an oscillator which times DNA synthesis, mitosis, and related apoptosis and DNA repair. Our understanding of the molecular mechanisms at work in both oscillators has greatly improved. In sharp contrast, little is known about how these two crucial oscillators interact, and how these interactions affect cellular proliferation in normal or cancer cells. On the one hand, the disruption of circadian clocks impairs cell physiology and quality of life. On the other hand, disruption of cell cycle, DNA repair or apoptosis impacts on cell

and organism survival. Experimental and clinical data show that circadian disruption accelerates malignant proliferation, and that DNA damage can reset the circadian clock. The central question addressed is how interactions between the circadian clock and cell cycle affect cellular proliferation and genotoxic sensitivity in normal and cancer cells, and how this knowledge translates into new prevention or therapeutic applications. Seven teams in France, Netherlands and United Kingdom integrate experimental, mathematical and bioinformatic approaches, so as to develop novel cell lines, biomarker monitoring methods and mathematical tools. C5Sys triggers innovative chronotherapeutic research for human cancers and advances systems medicine for improving patient care.

8.3. International Initiatives

8.3.1. Inria Associate Teams

8.3.1.1. TISHOM

Title: Artificial tissue homeostasis: combining synthetic and computational biology approaches

Inria principal investigator: Grégory Batt

International Partner (Institution - Laboratory - Researcher):

Massachusetts Institute of Technology (United States) - Weiss Lab

Duration: 2012 - 2014

See also: TISHOM

Cell-based gene therapy aims at creating and transplanting genetically-modified cells into a patient in order to treat an illness. Ideally, actively-growing cells are used to form a self-maintaining tissue in the patient, thus permanently curing the disease. Propelled forward by the development of stem cell biology, this research domain has recently attracted significant interest. Still, before any real therapeutic use, many important issues need to be addressed. In particular, one should guarantee tissue homeostasis, that is, that the size of the newly-introduced tissue remains within admissible bounds.

Using a synthetic biology approach, we propose to reprogram mammalian cells so as to enforce tissue homeostasis. The proposed design relies on growth control and cell-cell communication mechanisms. The design and tuning of such engineered tissues are particularly challenging. Indeed, the correct functioning of the system depends on its specific molecular implementation. To relate cell population behavior with molecular details, extensive modelling work and in-depth in silico analysis are needed. Therefore, a tight integration between dry lab and wet lab efforts will be essential for the success of the project.

8.4. International Research Visitors

8.4.1. Internships

Hui-Ju Katherine Chiang (from Jul 13 until Sep 13) on program compilation in biochemical reaction networks.

8.4.2. Visits to International Teams

Grégory Batt: one week with the Weiss lab at MIT

François Bertaux: two weeks with the Weiss lab at MIT

Xavier Duportet: 3 months and 1 week with the Weiss lab at MIT

9. Dissemination

9.1. Scientific Animation

- Grégory Batt's invited seminars:
  - Long-term model predictive control of gene expression, in *Bison seminar*, ETHZ, Zurich, March 2013
  - Modeling intrinsic and extrinsic variability: models, model identification methods and noise conversion, *Haredhol seminar*, ENS Paris, Paris, April 2013
  - Comprendre et contrôler le fonctionnement des cellules: apport de la biologie computationnelle, Seminar *Groupement de recherche interdisciplinaire sur les systèmes biologiques (Grisbi)*, Montpellier, Oct 2013
  - Comprendre et contrôler le fonctionnement des cellules: apport de la biologie computationnelle, *Symposium franco-britannique sur la biologie de synthèse*, London, Oct 2013
  - Cells driven by computers. *Pharmacometry and Bioinformatics Day*, Sanofi, Paris, Dec 2013

  He has been a member of the EraSynBio evaluation committee (Lisbon), judge at iGEM competition (Lyon), and animator of the axis "Modélisation des réseaux biologiques, biologie systémique et synthétique" of the Groupement de Recherche "Bioinformatique moléculaire" (GdR BIM). He was member of the PhD advisory committees of Adrien Henry (laboratoire de génétique végétale du Moulon, Orsay) and of Géraldine Célière (Bang group, Inria Paris-Rocquencourt). He was a reviewer for Integrative Biology, PLoS Computational Biology, ACS Synthetic Biology, European Conference on Control, and Computational Methods in Systems Biology conference
- Xavier Duportet's invited seminar and contributed poster presentations:
  - Keystone Symposia on Precision Genome Engineering and Synthetic Biology, Colorado, USA, March 17-22
  - Synthetic Biology conference (SB6.0), London, July 9-12

  He has been involved in technological transfer activities:
  - Provisional patent application: High-throughput discovery of recombinase sites towards the engineering of recombinase specificity
  - Consulting on mammalian synthetic circuit design for Lung LLC, USA

  Xavier is also the President of a non-profit organization to promote science and technology entrepreneurship among European students and scientists and organizing the Hello Tomorrow Challenge, a European startup competition.
- François Fages is a member of
  - Editorial Board of RAIRO Operations Research,
  - Steering Committee of the International Conference series on Computational Methods in Systems Biology (CMSB).
  - Scientific Advisory Board of the Doctorate School Frontières du Vivant of the University Paris Descartes
  - "Comité de pilotage" of the OSEO BioIntelligence project, coordinated by Dassault-Systèmes
  - "Comité scientifique du LIFO", University of Orléans
  - "Commission de spécialistes", University of Lille.

  He was member of the program committees of CHR'13 (Tenth International Workshop on Constraint Handling Rules Berlin, Germany – July 13th, 2013), CMSB'13 (Eleventh Conference on Computational Methods in Systems Biology, IST Klosterneuburg, Austria, September 2013), FroCoS'13 (Frontiers of Combining Systems, co-located with Tableaux 2013, Nancy, France, September 18-20, 2013), HSB'13 (Second International Workshop on Hybrid Systems and Biology associated to ECAL 2013, Taormina, Italy, September 2, 2013), ICLP'13 (29th International Conference on Logic

Programming 24 - 29 August 2013, Istanbul, Turkey), WCB'13 (Workshop on Constraint-Based-Methods for Bioinformatics, Budapest, Hungary, co-located with CP'13, Uppsala, Sweden September 16-20, 2013), ICORES'13 (second International Conference on Operations Research and Enterprise Systems, held in conjunction with h ICAART 2013 and ICPRAM 2013, Barcelona, Spain, Feb 2013).

He has reviewed articles for the following journals: ACM Transactions on Computational Logics, Artificial Intelligence, Journal of Logic and Computation, PLOS Computational Biology, Annals of Operations Research, Information and Computation, Journal of Mathematical Biology, Constraints, BMC Systems Biology,

François Fages was reviewer of research grants for
- the Netherlands Organisation for Scientific Research (NWO),
- the Research Foundation Flanders (FWO)

Invited talks:
- BRICS-CCI, 1st BRICS Countries Conference on Computational Intelligence, Recife, Brazil, October 2013.
- Symposium Biointelligence, Sophia-Antipolis, July 2013.
- Interdisciplinary Symposium on Signals and Systems for Medical Applications, Paris, 3-4 Jun 2013.

- Thierry Martinez was member of the Program Committee of CHR'13. He acted as reviewer for the journal Constraints, and for the conferences Concur'13, FROCOS'13 and ICLP'13.
- Sylvain Soliman acted as reviewer for LICS'13, and CMSB'13, and as member of the Program Committees of WLPE'13, JFPC'13 and SASB'13. He was also reviewer for the Austrian Science Fund (FWF) stand alone project proposals.
- Denis Thieffry is currently
  - member of the INSERM CSS2 evaluation/recruitment commission;
  - member of the board of the PhD Program Complexity in Post-Genomic Biology of the University of Torino;
  - member of the program committees for ISMB, JOBIM, CMSB, and SASB;
  - Editor of BioSystems;
  - Associated Editor of PLoS Computational Biology; as well as of BMC Systems Biology;
  - Adviser for the PLoS Biology Education series.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Contraintes is affiliated to the Doctoral school of Mathematical Science of the University Paris Diderot, and to the interdiciplinary Doctoral school "Frontières du Vivant" of the University Paris Descartes.

The following courses have been given by members of Contraintes:

Ecole thématique CNRS "Biologie des Réseaux", Ile de Porqueroles, François Fages (6h), Denis Thieffry (4h).

Master M2 course C2-19 on *Computational Methods for Systemic and Synthetic Biology*, Master Parisien de Recherche en Informatique (MPRI) François Fages (responsible, 12h), Grégory Batt (12h), Denis Thieffry (12h).

Interdisciplinary Master in Life Science at the Ecole Normale Supe´rieure, Paris. Denis Thieffry (coordinator).

Master M2 course C2-35-1 on *Constraint Programming*, Master Parisien de Recherche en Informatique (MPRI) Sylvain Soliman (responsible, 24h) [beginning of the 2013-2014 academic year].

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

Master M2 course *Dynamical Modelling of Cellular Regulatory Networks*, Master of Biology of Cellular Systems, Grégory Batt (6h).

9.2.2. Supervision

PhD : Faten Nabli, “Approches de programmation par contraintes pour l’analyse des propriétés structurelles des réseaux de Petri et application aux réseaux biochimiques”, Université Paris Diderot, Paris, 10/07/2013, Dir. François Fages and Sylvain Soliman

PhD : Jannis Uhlendorf, “Real-time feedback control of gene expression”, Paris Diderot University, Paris, 19/04/2013, Dir. Grégory Batt and Pascal Hersen (MSC)

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

PhD in progress : Xavier Duportet, Université Paris Descartes, Paris, Oct 2010, Dir. Grégory Batt, François Fages and Ron Weiss (MIT)

PhD in progress : Steven Gay, Université Paris Diderot, Paris, Oct 2009, Dir. François Fages and Sylvain Soliman,

PhD in progress : David Fournier, Université Paris Diderot, Paris, Oct 2011, Dir. François Fages and Denis Mulard (General Electric),

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

PhD in progress : Artemis Llamosi, Université Paris Diderot, Paris, Nov 2012, Dir. Grégory Batt, Jean-Marc di Meglio and Pascal Hersen (MSC)

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

PhD in progress : Luma Vittorino, Université Paris Diderot, Paris, Oct 2012, Dir. François Fages,

9.2.3. Juries

HDR of Cédric Lhoussaine, University of Lille. Dec 2013. Reviewer François Fages.

HDR of Nicolas Le Novère, University of Bordeaux. Nov 2013. Reviewer François Fages and Denis Thieffry.

PhD Thesis defense of Geoffrey Andrieux. University of Rennes. Jul 2013. François Fages.

PhD Thesis defense of Sucheendra Palaniappan, NUS, Singapore. June 2013. Reviewer Grégory Batt.

PhD Thesis defense of Andreas Milias-Argeitis, ETHZ. March 2013. Reviewer Grégory Batt.

MSc Thesis defenses of Lakshmeesh Maruthi and Yifan Pan, TU Delft. September 2013. Grégory Batt.

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] F. NABLI. , *Approches de programmation par contraintes pour l’analyse des propriétés structurelles des réseaux de Petri et application aux réseaux biochimiques*, Université Paris-Diderot - Paris VII, July 2013, http://hal.inria.fr/tel-00924445

[2] J. UHLENDORF. , *Real-time feedback control of gene expression*, Université Paris-Diderot - Paris VII, April 2013, http://hal.inria.fr/tel-00850778

Articles in International Peer-Reviewed Journals

[3] P. GUYE, Y. LI, L. WROBLEWSKA, X. DUPORTET, R. WEISS. *Rapid, modular and reliable construction of complex mammalian gene circuits*, in "Nucleic Acids Research", 2013, vol. 41, n^{o} 16 [*DOI :* 10.1093/NAR/GKT605], http://hal.inria.fr/hal-00926598

[4] N. D. MENDES, F. LANG, Y.-S. LE CORNEC, R. MATEESCU, G. BATT, C. CHAOUIYA. *Composition and abstraction of logical regulatory modules: application to multicellular systems*, in "Bioinformatics", January 2013, vol. 29, n^{o} 6, pp. 749-757 [*DOI :* 10.1093/BIOINFORMATICS/BTT033], http://hal.inria.fr/hal-00785564

[5] S. SOLIMAN. *A stronger necessary condition for the multistationarity of chemical reaction networks*, in "Bulletin of Mathematical Biology", November 2013, vol. 75, n^{o} 11, pp. 2289-2303 [*DOI :* 10.1007/s11538-013-9893-7], http://hal.inria.fr/hal-00772438

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International Conferences with Proceedings

[7] K. CHIANG, F. FAGES, J.-H. JIANG, S. SOLIMAN. *On the Hybrid Composition and Simulation of Heterogeneous Biochemical Models*, in "CMSB - 11th International Conference on Computational Methods for Systems Biology - 2013", Klosterneuburg, Austria, A. GUPTA, T. A. HENZINGER (editors), Lecture Notes in Computer Science, Springer, September 2013, vol. 8130, pp. 192–205 [*DOI :* 10.1007/978-3-642-40708-6_15], http://hal.inria.fr/hal-00913292

[8] S. GAY, F. FAGES, F. SANTINI, S. SOLIMAN. *Solving Subgraph Epimorphism Problems using CLP and SAT*, in "WCB - ninth Workshop on Constraint Based Methods for Bioinformatics, colocated with CP 2013", Uppsala, Sweden, 2013, pp. 67–74, http://hal.inria.fr/hal-00908973

[9] A. GONZALEZ, J. UHLENDORF, J. SCHAUL, E. CINQUEMANI, G. BATT, G. FERRARI-TRECATE. *Identification of biological models from single-cell data: a comparison between mixed-effects and moment-based inference*, in "ECC - 12th European Control Conference - 2013", Zurich, Switzerland, 2013, http://hal.inria.fr/hal-00831641

[10] R.-Y. HUANG, D.-A. HUANG, H.-J. KATHERINE, J.-H. JIANG, F. FAGES. *Species Minimization in Computation with Biochemical Reactions*, in "IWBDA'13: Proceedings of the fifth International Workshop on Bio-Design Automation", Imperial College, London, United Kingdom, 2013, http://hal.inria.fr/hal-00935829

[11] J.-B. LUGAGNE, D. A. OYARZÚN, G.-B. STAN. *Stochastic simulation of enzymatic reactions under transcriptional feedback regulation*, in "European Control Conference (ECC)", Zurich, Switzerland, July 2013, pp. 3646-3651, http://hal.inria.fr/hal-00935727

[12] T. MARTINEZ, L. VITORINO, F. FAGES, A. AGGOUN. *On Solving Mixed Shapes Packing Problems by Continuous Optimization with the CMA Evolution Strategy*, in "BRICS-CCI 2013 - First BRICS countries congress on Computational Intelligence", Recife, Brazil, 2013, http://hal.inria.fr/hal-00934917

[13] S. SOLIMAN, F. FAGES, O. RADULESCU. *A Constraint Solving Approach to Tropical Equilibration and Model Reduction*, in "WCB - ninth Workshop on Constraint Based Methods for Bioinformatics, colocated with CP 2013", Uppsala, Sweden, 2013, pp. 27–36, http://hal.inria.fr/hal-00906419

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[14] F. BERTAUX, S. STOMA, D. DRASDO, G. BATT. , *Dynamics of cell-to-cell variability in TRAIL-induced apoptosis explains fractional killing and predicts reversible resistance*, February 2014, http://hal.inria.fr/hal-00942885

[15] A. GONZALEZ, J. UHLENDORF, J. SCHAUL, E. CINQUEMANI, G. BATT, G. FERRARI-TRECATE. , *Identification of biological models from single-cell data: a comparison between mixed-effects and moment-based inference*, Inria, April 2013, n^{o} RR-8288, http://hal.inria.fr/hal-00817582