Activity Report 2012

Project-Team CONTRAINTES

Constraint programming

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THEME
Programs, Verification and Proofs

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Project-Team CONTRAINTES

Keywords: Rule-based Languages, Formal Methods, Computational Biology, Combinatorial Optimization, Logic, Constraints, Hybrid Systems, Systems Biology, Synthetic Biology

Creation of the Project-Team: March 01, 2001 .

1. Members

Research Scientists

François Fages [Team Leader, Research Director (DR) Inria, HdR]
Grégory Batt [Research Associate (CR), Inria]
Sylvain Soliman [Research Associate (CR) Inria]

External Collaborators

Pascal Hersen [Research Scientist, MSC Lab., Univ. Paris Diderot]
Denis Thieffry [Professor, Ecole Normale Supérieure de Paris]

Engineers

Thierry Martinez [Engineer, since July 2012]
Raphaël Martin [Engineer]

PhD Students

François Bertaux [AMX scholarship, with EPI Bang]
Xavier Duportet [Inria scholarship and MIT]
David Fournier [CIFRE General Electric Transportation]
Steven Gay [Inria scholarship]
Artémis Llamosi [CNRS scholarship, MSC Lab. and Inria]
Jean-Baptiste Lugagne [Inria scholarship and CNRS MSC Lab.]
Pauline Traynard [AMX scholarship, with ENS]
Faten Nabli [Inria scholarship]
Jannis Uhlendorf [Inria scholarship and CNRS MSC Lab.]
Lumadaiara Do Nascimento Vitorino [Inria scholarship]

Post-Doctoral Fellows

Neda Saeedloei [PostDoc Inria, up to October 2012]
Francesco Santini [PostDoc Ercim, since October 2012]
Szymon Stoma [PostDoc Inria]
Edwin Jake Wintermute [PostDoc Inria, INSERM Tamara Lab, since December 2012]

Administrative Assistant

Stéphanie Aubin [Secretary (SAR) Inria]

Others

Hugues Asofa [Internship, Master 1, Ecole Polytechnique, Palaiseau]
Hui-Ju Chiang [Internship, Master 2, National Technical University, Taiwan]
Anthony Lins [Internship, Master 2, UNiversity of Pernambuco, Brazil]
Aishah Prastowo [Internship, Master 1 Approches interdisciplinaires du vivant, MSC Lab. and Inria, Paris]
Julianne Rieders [Internship, Master 1 Approches interdisciplinaires du vivant, MSC Lab. and Inria, Paris]
Joé Schaul [Internship, Master 2 student, MPRI, Paris, Inria and MSC Lab.]

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.

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 the study of formal methods coming from computer science to model and analyze biochemical reaction systems, with applications to cell biology, medicine and synthetic biology.

2.2. Highlight on modeling GPCR signaling, publication in Molecular Systems Biology with Robert Lefkowitz, recipient of the Nobel prize in Chemistry

In collaboration with Eric Reiter (UMR CNRS-INRA 6175) and Frédérique Clément (EPI SISYPHE) in the framework of the Initiative Action REGATE (2008-2012), and with Robert Lefkowitz (Duke University), recipient of the Nobel prize in Chemistry 2012 for his work on G-Protein Coupled Receptors (GPCR), we have combined experimental approaches with computational modeling to decipher the molecular mechanisms as well as the unexplained complex dynamics governing GPCR signaling, and more precisely the ERK activation by the angiotensin II type 1A receptor (AT1AR) in human embryonic kidney (HEK293) cells.

In [4], the molecular mechanisms and hidden dynamics governing ERK activation by the angiotensin II type 1A receptor are studied and deciphered, revealing a signal balancing mechanism that is found to be relevant to a wide range of important drug targets composed of other seven-transmembrane receptors. More precisely,

- An ODE-based dynamical model of ERK activation by the prototypical angiotensin II type-1A seven transmembrane receptor has been built and validated using BIOCHAM
- In order to deal with a limited number of experimental read-outs, unknown parameters have been inferred by simultaneously fitting control and perturbed conditions expressed in temporal logic LTL(R_{lin}) in BIOCHAM using the covariance method adaptive evolution strategy (CMAES) for continuous optimization (EPI TAO)
- In addition to its well-established function in G-protein uncoupling, G protein-coupled receptor kinase 2 has been shown to exert a strong negative effect on β-arrestin-dependent signaling and by doing so, to balance G-protein and β-arrestin signaling. The failure to fit some temporal constraints was the key to infer the existence of these interactions from the computational model.
- This novel function of G protein-coupled receptor kinase 2 has also been evidenced in primary vascular smooth muscle cells naturally expressing the AT1AR and in HEK293 cells expressing other 7TMRs.

These results are the outcome of a long-term collaboration initiated with Eric Reiter in 2004, during which we designed our formal methods for systems biology, and developed Biocham for supporting a tight integration between modeling and biological experiments.

2.3. Highlight: Cells driven by a computer, publication in PNAS

In collaboration with the Hersen group (MSC Lab), we have shown that it is possible to control in real-time gene expression in yeast cells. The main novelty resides in the use of a computer-driven feedback loop to control directly a small population of cells or even single cells. Our interface between cells and computer allowed us to drive the expression level of a given gene so that it follows a user-defined temporal profile over many cell generations and with an unprecedented accuracy. This approach opens perspectives for applications in synthetic biology and biotechnology domains.

This work has been published in the Proceedings of the National Academy of Sciences of the USA [6] , and has attracted the interest of the media (journal du CNRS, l'Humanité Dimanche, Phys.org).

3. Scientific Foundations

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.

CCP execution can be identified to deduction in J.Y. Girard's Linear Logic by interpreting multisets of constraints and agents as tensor product conjunctions and guards and rules as linear implications [1]. The logical completeness of CCP in LL continues to hold when considering linear logic constraint systems, i.e. constraint systems where constraints can be consumed by implication. This extension, named Linear Logic Concurrent Constraint Programming (LLCC), allows for a non-monotonic evolution of the store of constraints and can encode 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 have designed and continue developing 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.

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

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 [20], 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 [5], siphons and traps [10];
- 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.

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 :

$$\textit{biological model} = \textit{rule-based transition system},$$

$$\textit{biological property} = \textit{temporal logic formula},$$

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

$$\textit{model inference} = \textit{constraint solving}.$$

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 (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.
- **G-protein coupled receptor signal transduction**. This research initiated in 2004 in partnership with Eric Reiter, INRA Tours, and Frédérique Clément, EPI SISYPHE, aimed at understanding the structure and the dynamics of the follicule stimulating hormone (FSH) and angiotensine signal transduction in mammalian cells. It was first conducted in the INRA AgroBi project INSIGHT (2006-2009) and in the AE REGATE.

  The article [4] concludes our fruitful collaboration over this period of eight years, with a tightly coupled formal and experimental study of GPCR signaling, of particular importance in medicine since these receptors are the most common drug target.
- **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 and initiation of translation in sea urchin.** 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) and of the sea urchin's initiation of translation with Laboratoire Mer et Santé (Roscoff, France). In the first case, 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. In the second case there is a whole issue of parametrization even for small models since the data is quite sparse. The different parameter learning features of BIOCHAM, notably based on temporal logics, are therefore put to good use.

5. Software

5.1. BIOCHAM, biochemical abstract machine

Participants: François Fages, Steven Gay, Sylvain Soliman.

The Biochemical Abstract Machine BIOCHAM [18] 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;
- 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 GNU 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 [5] but has been further extended to allow import/export of various Petri nets formats. It provides as independent modules different features that can sometimes also be integrated in BIOCHAM, like SEPI computation, or left aside, like unambiguous ODE to Petri net conversion, since a more general heuristic conversion has been developed for BIOCHAM [8], [19].

5.3. STSE, spatio-temporal simulation environment

Participant: Szymon Stoma.

The overall goal of this project is to provide a software platform gathering 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

Participant: Szymon Stoma.

YeastImageToolkit is an extention of YeastTracker software started originally by Jannis Uhlendorf. It allows following single cells in movies and quantifying fluorescent images based on this tracking as well as creating cell lineages. The software is currently under development and is designed to be a CellProfiler plugin facilitating yeast cell tracking, lineage and fluorescent signal quantification. Project webpage is: http://yeast-segtrack.weebly.com/.

5.5. SBMC, systems biology model-checker

Participant: Szymon Stoma.

Systems Biology Model Checker (SBMC) is a webservice allowing to verify biological models (e.g. signaling pathways stored in SBML files) against their specifications given in Signal Temporal Logics (STL). This project aims at providing to a large audience the methods described in [21] and used to analyse extrensic apoptosis pathway. Project webpage is: SBMC.

5.6. 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.

5.7. 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.

5.8. 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.

5.9. 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.

5.10. 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.

5.11. 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. Inferring Reaction Rule Models from Ordinary Differential Equations

Participants: François Fages, Steven Gay, Sylvain Soliman.

Many models in Systems Biology are described as Ordinary Differential Equations (ODEs), which allow for numerical integration, bifurcation analyses, parameter sensitivity analyses, etc. However, before fixing the kinetics and parameter values and going to simulations, various analyses can be performed based only on the structure of the model. This approach has rapidly developed in Systems Biology in the last decade, with for instance, the analyses of structural invariants in Petri net representation, model reductions by subgraph epimorphims, qualitative attractors in logical dynamics or temporal logic properties by analogy to circuit and program verification. These complementary analysis tools do not rely on kinetic information, but on the structure of the model with reactions.

In [8], [19], we present a symbolic computation algorithm for inferring a reaction model from an ODE system, based a general compatibility condition between the kinetic expression and the structure of a reaction, and report on its use for automatically curating the writing in SBML of the models in the respository biomodels.net. SBML is now a standard for sharing and publishing reaction models. However, since SBML does not enforce any coherence between the structure and the kinetics of a reaction, an ODE model can be transcribed in SBML without reflecting the real structure of the reactions, hereby invalidating many structural analyses. We show that the automatic writing in SBML of the models of biomodels.net allows us to reduce the percentage of models with a non well-formed reaction from 66% to 28%.

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

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

Petri nets are a simple formalism for modeling concurrent computation. Recently, they have emerged as a promising tool for modeling and analyzing biochemical interaction networks, bridging the gap between purely qualitative and quantitative models. Biological networks can indeed be large and complex, which makes their study difficult and computationally challenging.

In [10], we focus on two structural properties of Petri nets, siphons and traps, that bring us information about the persistence of some molecular species. We present 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. We compare the performances of these methods 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.

In [5] we present a method to compute the minimal semi-positive invariants of a Petri net representing a biological reaction system, as resolution of a Constraint Satisfaction Problem. This analysis brings both qualitative and quantitative information on the models, in the form of conservation laws, consistency checking, etc. thanks to finite domain constraint programming. It is noticeable that some of the most recent optimizations of standard invariant computation techniques in Petri nets correspond to well-known techniques in constraint solving, like symmetry-breaking. A simple implementation based on GNU-Prolog's finite domain solver, and including symmetry detection and breaking, was incorporated into the BIOCHAM modelling environment and in the independent tool Nicotine. Some illustrative examples and benchmarks are provided.

6.3. Subgraph Epimorphisms

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

The operations of deleting and merging vertices are natural operations for reducing a graph. While graph reductions through a sequence of vertex deletions (resp. mergings) characterize subgraph isomorphisms (resp. graph epimorphisms), sequences of both vertex deletion and merging operations characterize subgraph epimorphisms. Our proposal is thus to use subgraph epimorphism for comparing graphs in applications in systems biology and image analysis, when a more flexible notion than the classical notion of subgraph isomorphism is required.

In collaboration with Christine Solnon (INSA Lyon), we have developed the theory of subgraph epimorphisms. We have defined the SEPI, EPI and SISO distances between two graphs as the size of the largest SEPI (resp. EPI, SISO) lower bound graphs. These distances are equal to the minimum number of respectively vertex deletion and/or merging operations that are necessary to obtain isomorphic graphs. They are also metrics on graphs and we have $d_d \geq d_{md}$ and $d_m \geq d_{md}$. From a computational point of view, we have shown that the existence of a SEPI between two graphs is an NP-complete problem and have presented a constraint satisfaction algorithm for solving it.

Our algorithm is implemented in BIOCHAM and is currently improved for better performance on large graphs and generalized as a SEPI graph constraint propagation algorithm for computing SEPI lower and upper bounds.

6.4. Parameter Search with Temporal Logic Constraints

Participants: Grégory Batt, François Fages, Anthony Lins, Sylvain Soliman, Pauline Traynard, Jannis Uhlendorf, Luma Vittorino.

Our method for solving temporal logic constraints in first-order linear time logic LTL(R_{lin}), opens up the field of model-checking to optimization through the definition of a continuous degree of satisfaction for temporal logic formulae. This satisfaction degree can be used in a number of ways, e.g. as a fitness function with continuous optimization methods to find unknown parameter values in a model, to perform sensitivity analyses and compute the robustness of a system w.r.t. a temporal property and a perturbation of the parameters. or to find control parameters.

This approach is implemented in BIOCHAM and is one unique feature of this modeling environment. In this implementation, the continuous optimization procedure we use is the Covariance Matrix Adaptation Evolutionary Strategy CMAES of Nikolaus Hansen from the EPI TAO. A parallel version of Biocham implements this method on the Jade cluster of 10000 cores at GENCI for running our most challenging parameter search problems.

This year, in collaboration with Fernando Buarque, we have explored another continuous optimization method of the family of Particle Swarm Optimization (PSO), called Fish School Optimization (FSS). In [13], we report on our first results which are encouraging for using FSS for decreasing the sensitivity of the method to initial conditions and being able to maintain several swarms of solutions.

6.5. 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 imortant 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 investigated the effect of transcription inhibition during mitosis, as a reverse coupling from the cell cycle to the circadian clock. We use 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.

6.6. STL-based Analysis of TRAIL-induced Apoptosis

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, leading to classification of cell lines into two groups (type I and type II). In [21], we challenge this type I/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. Then, STL-guided parameter search is used to solve the few inconsistencies found between model and data. 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 rather than being considered as defining criteria for cell type classification, these three distinguishing behaviors should be merely considered as type I or II features. On the methodological point of view, this work illustrates the biological relevance of STL-diagrams, STL population data, and STL-guided parameter search. Such tools are well adapted to the ever-increasing availability of heterogeneous knowledge on complex signal transduction pathways.

6.7. Real-time Control of Gene Expression in Yeast

Participants: Grégory Batt, François Fages, Jannis Uhlendorf, Jean-Baptiste Lugagne, Artémis Llamosi, Pascal Hersen.

Gene expression plays a central role in the orchestration of cellular processes. The use of inducible promoters to change the expression level of a gene from its physiological level has significantly contributed to the understanding of the functioning of regulatory networks. However, from a quantitative point of view, their use is limited to short-term, population-scale studies to average out cell-to-cell variability and gene expression noise and limit the nonpredictable effects of internal feedback loops that may antagonize the inducer action. In this project, in collaboration with the Hersen Lab at MSC (Paris Diderot University), we show that, by implementing an external feedback loop, one can tightly control the expression of a gene over many cell generations with quantitative accuracy. To reach this goal, we developed a platform for real-time, closed-loop control of gene expression in yeast that integrates microscopy for monitoring gene expression at the cell level, microfluidics to manipulate the cells environment, and original software for automated imaging, quantification, and model predictive control. By using an endogenous osmostress responsive promoter and playing with the osmolarity of the cells environment, we show that long-term control can, indeed, be achieved for both time-constant and time-varying target profiles at the population and even the single-cell levels [6]. Importantly, we provide evidence that real-time control can dynamically limit the effects of gene expression stochasticity. We anticipate that our method will be useful to quantitatively probe the dynamic properties of cellular processes and drive complex, synthetically engineered networks.

6.8. Genome Engineering of Mammalian Cells: Targeted and Efficient Integration of Multi-unit Genetic Payloads

Participants: Grégory Batt, Xavier Duportet.

Targeted integration of multi-unit genetic payloads would greatly benefit elucidating complex cellular mechanisms and implementing new functions in mammalian cells. Current technologies are however time-consuming and require tedious post-integration controls. To address this problem, we propose a modular framework to assemble large multi-unit genetic payloads and target their integration into either one or both alleles of a chromosomal locus of choice. To achieve this, we combine in a two-step process the customizable targeting properties of homing endonucleases with the efficiency and specificity of a large serine recombinase. We have demonstrated that an optimized version of BxB1 recombinase allows the targeted integration of large genetic circuits (up to 7 transcription units, 60kb) into a preintegrated landing pad in the AAVS1 locus, with a significant increase in efficiency compared to other site-specific recombination systems (integration in 10% of transfected cells without selection) . By reducing the time and efforts to generate large populations of isogenic stable cell lines adapted to study multi-component genetic systems, our framework is a valuable tool for mammalian synthetic biology and offers great potential for a broad range of biotechnology and therapeutic applications.

6.9. Reifying Global Constraints

Participants: François Fages, Raphaël Martin, Thierry Martinez, Sylvain Soliman.

Global constraints were introduced two decades ago as a means to model some core aspects of combinatorial problems with one single constraint for which an efficient domain filtering algorithm can be provided, possibly using a complete change of representation. However, global constraints are just constraint schemas on which one would like to apply usual constraint operations such as reification, i.e. checking entailment, disentailment and negating the constraint. This is currently not the case in state-of-the-art tools and was not considered in the global constraint catalog until recently. In [20], we propose a general framework for reifying global constraints and apply it to some important constraints of the catalog, such as the cumulative constraint for instance. We show that several global constraints that were believed to be hard to negate can in fact be efficiently negated, and that entailment and disentailment can be efficiently tested. We also point out some new global constraints that are worth studying from this point of view and provide some performance figures obtained with an implementation in Choco.

This scheme is currently used for compiling the Rules2CP constraint modeling language to Choco, and to internalize search in CSPs through constraint reification.

6.10. Railway Time Tabling Optimization

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

Metros are able to generate electricity on a metro line by braking. This energy is immediately available in the third rail and is lost if no metro in the neighbourhood can consume it. It is thus possible to decrease the total energy consumption of a metro line by synchronizing the accelerations and braking of the metros. In [2], [9], we propose a classification of energy optimization timetable problems and we present a model for optimizing energy consumption which does not significantly alter the quality of service, by subtly modifying dwell times. We show however that this optimization problem is NP-hard. We present a hybrid genetic/linear programming algorithm for computing the distribution of braking metros. In this hybridization, the objective function is computed by a linear program and by a heuristic, and the dwell times are modified by a genetic algorithm. On a typical example with real data, the savings exceed 7%. Furthermore, on a benchmark of the literature for a simpler problem, we discuss the results obtained with our genetic algorithm, a tabu search algorithm and the mixed integer linear program used by the authors.

7. Bilateral Contracts and Grants with Industry

7.1. Dassault-Systèmes, BioIntelligence project

- The OSEO Biointelligence project coordinated by Dassault-Systèmes, with EPI Orpailleur, Sobios, Aureus pharma, Ipsen, Pierre Fabre, Sanofi-Aventis, Servier, Bayer CropScience, INSERM, Genopole Evry (2009-2014).

7.2. KLS-Optim, Rules2Optim project

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

7.3. General Electric Transportation, Cifre contract

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

8. Partnerships and Cooperations

8.1. National Initiatives

- 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 (2010-2013) coordinated by Anne Siegel, CNRS IRISA Rennes, with Ovidiu Radulescu, U. Montpellier, Irina Rusu, U. Nantes.
- AE REGATE (2008-2012) 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-) 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, 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: mars 2010 - mars 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

Title: Artificial tissue homeostasis: combining synthetic and computational biology approaches (TISHOM)

Inria principal investigator: Gregory Batt

International Partner (Institution - Laboratory - Researcher):

Massachusetts Institute of Technology (United States) - Weiss Lab - Ron Weiss

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.

8.3.2. Inria International Partners

We also have a collaboration with the Center for Systems and Control at the Delft University of Technology (The Netherlands) on developing formal probabilistic approaches for robust control of gene expression. This collaborative project is funded by the Frans/Nederlandse Academie as part of the van Gogh Programm (Coordination Alessandro Abate/Grégory Batt).

8.4. International Research Visitors

8.4.1. Visits of International Scientists

8.4.1.1. Visits of International Scientists

Prof. Fernando Buarque (from February 2012 until April 2012)

Subject: Fish School Optimization

Institution: University of Pernambuco, Brazil

8.4.1.2. Internships

Hui-Ju Katherine CHIANG (from Jul 2012 until Oct 2012)

Subject: Theory of temporal logic constraint solving

Institution: National Taiwan University (Taiwan)

Anthony LINS (from Mar 2012 until Jun 2012)

Subject: Particle swarm optimization for systems biology

Institution: Federal University of Pernambuco (Brazil)

8.4.1.3. Short visits

Andreas Weber, University of Bonn, Germany

Chris Banks, University of Edinburgh, UK

Francesco Santini, CWI, Amsterdam, Netherlands

Ron Weiss, MIT, USA

Alessandro Abate and Ilya Tkachev, TU Delft, Netherlands

Liu Bing, National University of Singapore, Singapore

8.4.2. Visits to International Teams

Xavier Duportet: 6 months with the Weiss lab at MIT

Szymon Stoma: two times two weeks with the Weiss lab at MIT

François Bertaux: two times two weeks with the Weiss lab at MIT

9. Dissemination

9.1. Scientific Animation

- Grégory Batt has organized an international workshop on Design, optimization and control in systems and synthetic biology at ENS Paris during two days (15 speakers, 230 registered participants, 14 nationalities).

  Grégory Batt's invited seminars:

  – Summer school Naturel et artificiel: le vivant et ses représentations, Berder, Apr 03, invited talk

  – Model-based analysis and control of cellular processes workshop, Purdue, IN, USA, Oct 09, contributed talk

  – Perspectives en Biologie de Synthèse, Aviesan/Allenvi workshop, Paris, Dec 11, invited talk

  He has been a member of the Program Committee of the JOBIM'12 conference. He was a reviewer for Bioinformatics, IEEE Transactions on Computational Biology and Bioinformatics, and Biosystems.

- François Bertaux was invited to short working visits at the Weiss Lab (MIT, Boston, USA) - March and May/June.
- Xavier Duportet's invited seminar and contributed poster presentations:
  - La Biologie de Synthèse, Bar des Sciences, Paris, April 06, invited talk
  - SynBerc retreat, MIT, USA, October 11, poster

  He has been involved in technological transfer activities:
  - Provisional patent application: High-throughput discovery of recombinase sites towards the engineering of recombinase specificity
  - Gen9 Inaugural G-Prize, 3rd place winner, Cambridge, MA

  He is a member of Synthetic Biology Scientific Committee at Alliance pour la recherche et l'innovation des industries de santé (ARIIS), Paris.
- 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).

  He is a member of the Scientific Advisory Boards of
  - the Center for Systems Biology at Edinburgh, Scotland,
  - the Doctorate School Frontières du Vivant of the University Paris Descartes
  - the Laboratoire d'Informatique Fondamentale, University of Orléans.

  and a member of the
  - "Comité de pilotage" of the OSEO BioIntelligence project, coordinated by Dassault-Systèmes

  François Fages has co-organized the fourth international workshop on "Bin packing and placement constraints" BPPC'12 associated to CPAIOR'12 in Nantes, June 2012.

  He was member of the program committees of CHR'12, CMSB'12, CS2BIO'12, FHIES'12, ICORES'12, SASB'12 and WCB'12. He has reviewed articles for the following journals: ACM Transactions on Computational Logics, Artificial Intelligence, Constraints, BioMedCentral systems biology, Constraints, PLOS One, Rairo OR.

  François Fages was reviewer of research grants for
  - the Agence Nationale de la Recherche (ANR),
  - the Royal Society (London),
  - and the Swiss National Science Foundation (SNSF).

  Invited seminars:
  - Dagstuhl's seminar on formal methods for chemical reaction networks, Schloss Dagstuhl, Germany, October 2012.
  - Formal methods in systems biology workshop, associated to CAV'12, Berkeley, USA, July 2012.
  - Symposium Biointelligence, Sophia-Antipolis, July 2012.
  - CP meets CAV workshop, Turunc, Turkey, June 2012.
  - 25 ans du LIFO, Orléans, March 2012.
- Thierry Martinez acted as a member of the Program Committee of CHR'12.

- Sylvain Soliman acted as reviewer for CMSB'12 and BMC Systems Biology, as member of the Program Committee of JFPC'12. He was also expert/reviewer for the French PEPS biologie-mathématiques-informatique call (CNRS/INSERM/Inria).

  He gave an invited seminar at Institut Curie's bioinformatics team. "Reaction Graphs to Regulatory Networks - Theory to practice".
- Szymon Stoma was invited to short working visits at the Weiss Lab (MIT, Boston, USA) - March and May/June.
- Denis Thieffry is currently
  - member of the Comité Scientifique Sectoriel of the Department *Biologie et Santé* of the ANR;
  - member of the Comité de Pilotage of the LabEx MemoLife (involving teams from IBEns, Collège de France, and ESPCI);
  - member of the CNRS/INSERM ATIP/Avenir Scientific Committee (young group leader grant scheme);
  - member of the board of the PhD Program Complexity in Post-Genomic Biology of the University of Torino;
  - member of the program committees for ECCB-ISMB, JOBIM, CMSB, and SASB;
  - Editor of BioSystems;
  - Associated Editor of PLoS Computational Biology;
  - Adviser for the PLoS Biology Education series.
- Jannis Uhlendorf gave an invited seminar at the BioComputing group of the Laboratoire d'Informatique Fondamentale de Lille on Real-time control of gene expression in February 2012.

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:

Summer school Scientific Trends at the Interfaces: Biomathematics - Bioinformatics, Roscoff, Grégory Batt (6h) and François Bertaux (6h).

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).

Master: Cell Systems Biology master curriculum at the Ecole Normale Supérieure, Paris. Denis Thieffry (coordinator).

Master M2 course C2-35-1 on *Constraint Programming*, Master Parisien de Recherche en Informatique (MPRI) Sylvain Soliman (responsible, 24h) [end of the 2011-2012 academic year].

Master M1 course on *Computational Biology*, Master Approches Interdisciplinaires du Vivant (AIV), Grégory Batt (coordinator, 40h).

Master M1 course on Synthetic Biology, AgroParisTech, Xavier Duportet (12h).

Master M1 course on Synthetic Biology, Faculté de Médecine de Paris, Xavier Duportet (4h).

Licence L2 Cours/TD *Informatique*, Université de Paris Dauphine, Faten Nabli (72h).

Science, Innovation and Entrepreneurship non for profit organization: 4 conferences (400 people), Paris, Xavier Duportet (12h)

9.2.2. Supervision

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 : Thierry Martinez, Université Paris Diderot, Paris, Oct 2009, Dir. François Fages,

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

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

PhD in progress : Jannis Uhlendorf, Université Paris Diderot, Paris, Oct 2009, Dir. Grégory Batt, François Fages and Pascal Hersen (MSC)

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

9.2.3. Juries

PhD Thesis committee of Roberto Amato, Ankita Chaurasia, Francesca Fioretti, Filippo Menolascina, and Alessandra Vigilante, University of Naples, Italy, Member Grégory Batt.

HDR of Khallil Djelloul, University of Orléans. Reviewer François Fages.

PhD Thesis defense of Andrés A. Aristizàbal, Ecole Polytechnique. Chairman François Fages.

PhD Thesis committee of Adrien Basso-Blandin, University of Evry. Member François Fages.

PhD Thesis defense of Emmanuel Halloit, University of Nice, Villefranche sur Mer, décembre 2012. Member Denis Thieffry.

PhD Thesis defense of Guillaume Baptist, Université Joseph Fourrier, Grenoble, août 2012. Reviewer Denis Thieffry.

PhD Thesis defense of Mohamed Hedi Ben Amor, Université Joseph Fourrier, Grenoble, juillet 2012. Member Denis Thieffry.

9.3. Popularization

Our PNAS article attracted the attention of the media. Articles entitled “Ils contrôlent le vivant avec des ordinateurs !”, “Des cellules qui obéissent au doigt et à l’oeil”, “Focusing the phenotype - Controlling genetic expression through external feedback” appeared in l’Humanité Dimanche, le journal du CNRS, and Phys.org. Also, Grégory Batt participated to the radio program “Autour de la question” (RFI).

Two posters, “(Re)programmer le vivant” and “Des cellules pilotées par ordinateur”, were presented during the Fête de la science to a broad audience during two days by Grégory Batt.

Denis Thieffry has two books in press:

- Thieffry D. Gene networks, logical modelling, and regulatory motifs entries. In: Hancock JM, Zvelebil MJ (eds). Dictionary of Bioinformatics and Computational Biology. New York: John Wiley & Sons.
- Faur A, Thieffry D. Cell cycle modelling using logical rules. In: Dubitzky W, Wolkenhauer O, Cho K-H, Yokota H (eds.) Encyclopedia of Systems Biology. Springer.

10. Bibliography

Publications of the year

Articles in International Peer-Reviewed Journals

[1] S. BISTARELLI, F. SANTINI. *Coalitions of Arguments: An Approach with Constraint Programming*, in "Fundamenta Informaticae, IOS Press", 2012, to appear.

[2] D. FOURNIER, T. MARTINEZ, F. FAGES, D. MULARD. *Energy optimization of metro timetables: a hybrid approach*, in "RAIRO operations research", 2012, Submitted.

[3] S. GAY, F. FAGES, T. MARTINEZ, S. SOLIMAN, C. SOLNON. *On the subgraph Epimorphism Problem*, in "Discrete Applied Mathematics", 2012, submitted.

[4] D. HEITZLER, G. DURAND, N. GALLAY, A. RIZK, S. AHN, J. KIM, J. D. VIOLIN, L. DUPUY, C. GAUTHIER, V. PIKETTY, P. CRÉPIEUX, A. POUPON, F. CLÉMENT, F. FAGES, R. J. LEFKOWITZ, E. REITER. *Competing G protein-coupled receptor kinases balance G protein and β-arrestin signaling*, in "Molecular Systems Biology", June 2012, vol. 8, n^{o} 590, http://dx.doi.org/10.1038/msb.2012.22.

[5] S. SOLIMAN. *Invariants and Other Structural Properties of Biochemical Models as a Constraint Satisfaction Problem*, in "Algorithms for Molecular Biology", May 2012, vol. 7, n^{o} 15, http://dx.doi.org/10.1186/1748-7188-7-15.

[6] J. UHLENDORF, A. MIERMONT, T. DELAVEAU, G. CHARVIN, F. FAGES, S. BOTTANI, G. BATT, P. HERSEN. *Long-term model predictive control of gene expression at the population and single-cell levels*, in "Proceedings of the National Academy of Sciences USA", 2012, vol. 109, n^{o} 35, p. 14271–14276.

International Conferences with Proceedings

[7] S. BISTARELLI, G. GOSTI, F. SANTINI. *Solving Fuzzy Distributed CSPs: An Approach with Naming Games*, in "DALT", M. BALDONI, L. DENNIS, V. MASCARDI, W. VASCONCELOS (editors), Lecture Notes in Computer Science, Springer, 2012.

[8] F. FAGES, S. GAY, S. SOLIMAN. *Inferring Reaction Models from ODEs*, in "CMSB'12: Proceedings of the tenth international conference on Computational Methods in Systems Biology", Lecture Notes in BioInformatics, Springer-Verlag, October 2012, vol. 7605, p. 370–373.

[9] D. FOURNIER, D. MULARD, F. FAGES. *Optimisation énergétique de tables horaires de métros: une approche hybride*, in "Actes de Journées Francophones de Programmation par Contraintes JFPC'12", Toulouse, France, 2012, p. 127–130.

[10] F. NABLI, F. FAGES, T. MARTINEZ, S. SOLIMAN. *A Boolean Model for Enumerating Minimal Siphons and Traps in Petri-nets*, in "Proceedings of CP'2012, 18th International Conference on Principles and Practice of Constraint Programming", Lecture Notes in Computer Science, Springer-Verlag, October 2012, vol. 7514, p. 798–814, http://contraintes.inria.fr/~tmartine/papers/NFMS12cp.pdf.

[11] N. SAEEDLOEI, G. GUPTA. *An Extension of π-Calculus with Real-Time and its Realization in Logic Programming*, in "Proceedings of Logic Based Program Synthesis and Transformation, LOPSTR'12", 2012.

[12] N. SAEEDLOEI, G. GUPTA. *Coinductive Constraint Logic Programming*, in "Proceedings of FLOPS'12", Lecture Notes in Computer Science, Springer-Verlag, 2012, vol. 7294, p. 243–259.

[13] A. J. DA C. C. LINS, F. B. DE LIMA NETO, F. FAGES, C. J. A. B. FILHO. *A Comparative Analysis of FSS with CMA-ES and S-PSO in Ill-Conditioned Problems*, in "Intelligent Data Engineering and Automated Learning - 13th International Conference IDEAL", Lecture Notes in Computer Science, Springer, 2012, vol. 7435, p. 416–422, http://dx.doi.org/10.1007/978-3-642-32639-4_51.

National Conferences with Proceeding

[14] F. NABLI, F. FAGES, T. MARTINEZ, S. SOLIMAN. *Un modèle Booléen pour l'énumération des siphons et des pièges minimaux dans les réseaux de Petri*, in "Actes de Journées Francophones de Programmation par Contraintes JFPC'12", Toulouse, France, 2012, http://contraintes.inria.fr/~tmartine/papers/NFMS12jfpc.pdf.

Conferences without Proceedings

[15] N. SAEEDLOEI, G. GUPTA. *Timed π-Calculus and its Realization in Coinductive Constraint Logic Programming*, in "Proceedings of the first Coinductive Logic Programming Workshop Co-LP'12", 2012.

Scientific Books (or Scientific Book chapters)

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