Activity Report 2011

Project-Team CONTRAINTES

Constraint programming

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THEME
Programs, Verification and Proofs

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Project-Team CONTRAINTES

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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.

This research field is born during the mid 80s from the combination of Logic Programming, Constraint Propagation techniques in Artificial Intelligence and Linear Programming in Operations Research. Thanks to its capability to combine heterogeneous resolution techniques (numerical, continuous, discrete, symbolic, deductive, heuristic) in a simple logical setting, this approach has shown particularly successful for solving combinatorial optimization problems ranging from pure academic problems to real-life problems in industry, commerce or biology.

The "Contraintes" group investigates the theoretical foundations, design, implementation and applications of rule-based languages and constraint solving techniques in two main domains: combinatorial optimization and computational systems biology. More generally in the later domain, Contraintes develops formal methods for systems biology and investigates the tight integration of *in silico* and *in vivo* approaches in systems and synthetic biology.

2.2. Highlight 2011 on the Subgraph Epimorphism Problem

The subgraph epimorphism (SEPI) problem is a variant of graph matching problem. Our interest in SEPIs 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. We have shown last year that in this setting, the notion of model reduction can be formalized as the existence of a sequence of vertex deletion and merge operations that transforms a first reaction graph into a second graph. 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.

This year we have shown that the SEPI existence problem between two graphs is NP-complete by reduction of the set covering problem [5] and on the algorithmic side, we provide a constraint satisfaction algorithm [10] that has been successfully used to solve SEPI matching problems on a large benchmark of reaction graphs extracted from the repository of systems biology models biomodels.net. In [5], we develop the theory of subgraph epimorphisms in general directed graphs. First, subgraph epimorphisms (SEPI), subgraph isomorphisms (SISO) and graph epimorphisms (EPI) are characterized in terms of graph transformation operations. Then the graph distance measures induced by these transformations are compared and shown to define metrics on graphs.

3. Scientific Foundations

3.1. Rule-based Languages

Logic programming in a broad sense is a declarative programming paradigm which relies on 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.

Concurrent Constraint Programming (CCP) extends CLP resolution 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. 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*. For solving combinatorial optimization problems, we use Gnu-Prolog (CLP family), Sicstus-Prolog or SWI-Prolog (CCP family), Rules2CP, a rule-based modeling language that we develop for non-programmers (CLP variant without recursion nor scope for variables), Comet^{TM}, another constraint modeling language, or SiLCC, our own implementation of LLCC. In the Biochemical Abstract Machine Language BIOCHAM we develop for Systems Biology, biochemical reactions between multisets of reactants and products are expressed with multi-headed rules (somewhat similar to CHR rules) but given 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. These domain reductions are the only way constraints communicate. Our research concerns different constraint domains, namely:

- 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;
- Kripke structures: temporal logic constraints (quantifier-free first order CTL constraints).

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 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 :

biological model = rule-based transition system,

biological property = temporal logic formula,

model validation = model-checking,

model inference = constraint solving.

[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.

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. 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 [26] and quantitative [27] – to the analysis of the large scale RB/E2F network [33], 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 Frédérique Clément, EPI SISYPHE, and Eric Reiter, INRA Tours, aims at understanding the structure and the dynamics of the follicule stimulating hormone (FSH) and angiotensine signal transduction in mammalian cells. The article [6] concludes our fruitful interactions done in the INRA AgroBi project INSIGHT (2006-2009) and in the AE REGATE.

- **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.

5. Software

5.1. BIOCHAM

Participants: François Fages, Steven Gay, Dragana Jovanovska, Aurélien Rizk, Sylvain Soliman.

The Biochemical Abstract Machine BIOCHAM [29] is a modeling environment for systems biology distributed as open-source since 2003. Current version is v3.3. 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 differential semantics (concentrations of molecules),
3. the stochastic semantics (discrete numbers 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 QFLTL(R) 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 [30].

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 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 comutation, or left aside, like unambiguous ODE to Petri net conversion, since a more general heuristic conversion is developped for BIOCHAM.

5.3. Spatio-temporal simulation environment (STSE)

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. YeastTracker

Participant: Jannis Uhlendorf.

YeastTracker is a software to follow single cells in movies and to quantify fluorescent images based on this tracking. It has been developed for yeast cells, but is also applicable to other cells that have a defined round shape. The software is written in Matlab and uses a circular Hough transform and binary integer programming to detect and follow cells. It allows to quantify the mean fluorescence of each cell as well as the co-localization of two different fluorescent markers. The software is available on request (jannis.uhlendorf@inria.fr).

5.5. Rules2CP

Participants: François Fages, Raphaël Martin.

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.

5.6. SiLCC

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.

5.7. EMoP

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.

5.8. CHRat

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.

5.9. CLPGUI

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. Constraint Handling Rules and Linear Logic

Participants: François Fages, Thierry Martinez, Sylvain Soliman.

Implementations of Constraint Handling Rules (CHR) follow a committed-choice forward chaining execution model: the non-determinism of the abstract semantics is partly refined with extra-logical syntactic convention on the program order and possibly notations for weighted semantics (with priorities or probabilities), and partly left unspecified in the underlying compiler. In [13], we propose an alternative execution model which explores all the possible choices, by opposition to the committed-choice strategy. This execution model is angelic in the sense that if there exists a successful execution strategy (with respect to a given observable), then this strategy will be found. Formally, the set of computed goals is complete with respect to the set of the logical consequences of the interpretation of the initial goal in linear logic. In practice, this paper introduces a new data representation for sets of goals, the derivation nets. Sharing strategies between computation paths can be defined for derivation nets to make execution algorithmically tracktable in some cases where a naive exploration would be exponential. Control for refined execution is recovered with the introduction of user constraints to encode sequencing, fully captured in the linear-logic interpretation. As a consequence of angelic execution, CHR rules become decomposable while preserving accessibility properties. This decomposability makes natural the definition in angelic CHR of meta-interpreters to change the execution strategy. More generally, arbitrary computation can be interleaved during head matching, for custom user constraint indexation and deep guard definition.

6.2. Rule-based Modeling Language for Constraint Programming

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

Rules2CP is a rule-based modeling language which allows easy modeling of constraint satisfaction problems, together with specifications for search strategies and heuristic choice criterias by pattern matching. in [23], we study a new compilation scheme for Rules2CP which allows us to deal with dynamic ordering criteria and to generate procedural constraint programming code instead of flattened constraints. The comparison with the static expansion of Rules2CP models shows that the overhead at runtime is limited, with a gain in the size of the generated program which could be exponentially larger by static expansion.

The language Rules2CP is currently extended to deal with hybrid discrete and continuous domains and packing problems with complex shapes, in the framework of the ANR Net-WMS-2 project with KLS-Optim and EMN Inria EPI TASC. The compiler of Rules2CP is currently rewritten in Java in the framework of a collaboration with KLS-Optim supported by Inria DTI.

6.3. Trace Development Methodology

Participants: Pierre Deransart, Armando Gonçalves da Silva Junior.

We are working on a general theory of traces design taking traces as primary objects of study. It is based on the observation of the way trace files are accumulated as knowledge bases and elaborated in differents fields of activity like software engeneering, rule based systems and resolution, learning in context, or personal experience storing systems.

We worked on two main points: the development of an experimental tracer of CHR^v [11] (see TODAS project) and an application the notion of generic trace to standardization of constraints. In [17] we analyze, and occasionally correct, shortcomings of the former approach based on the generic trace format GENTra4CP, and show the interest that a generic tracer may bring to develop portable applications or to standardization efforts, in particular in the field of constraints.

6.4. Railway Time Tabling Optimization

Participants: François Fages, David Fournier, Sylvain Soliman.

Sustainable development is a key issue for our society. Optimization of resources, energy and costs (as admirably done in living organisms) has thus grown significantly over years to become a major field in industry. In collaboration with General Electric Transportation France which is a key-actor in the field of transportation all around the world, we investigate energy reduction for train and metro service providers through time tabling optimization. In [31], we describe and compare different optimization methods to reduce energy in mass rapid transits (MRT). Most of the literature deals with a special problematic arising in train services: the maximum traction energy. They show that for reducing costs and energy consumption, one method is the reduction of the peak energy over a time period. This objective function has been chosen for this study and the thesis depicts how to implement it on different paradigms, such as mixed-integer linear programming, constraint programming or local search. We conclude on promising approaches in terms of optimization methods for time tabling computation and real-time scheduling.

6.5. Petri Net Analysis of Biochemical Networks

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

Bridging the gap between quantitative and qualitative models, Petri nets (also known as place/transition graphs) have recently emerged as a promising tool for modeling and analysis of biochemical networks. In [14], we present a method to compute the minimal siphons and traps of a Petri net as a Constraint Satisfaction Problem (CSP). In our case, siphons and traps are purely structural properties that brings us information about the persistence of some molecular species. We present a constraint program that finds minimal siphons and traps containing specific set of places in a Petri net. This method is compared on models of the biomodels.net repository with other methods based on Mixed Integer Linear Programming (MILP) and Boolean Satisfiability (SAT). The flexibility brought by constraint programming, for instance in the declarative choice of variable enumeration heuristics, seems promising in further improving those results.

6.6. Theory of Subgraph Epimorphisms

Participants: François Fages, Steven Gay, Thierry Martinez, 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 where 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 in [5]. We have shown that SEPIs preserve graph completeness and arc symmetry and that, just like SISO and EPI, SEPI is not a well quasi order. 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. This algorithm is implemented in BIOCHAM.

It is worth noticing that, given two graphs G and G', the greatest lower SEPI bounds and the least upper SEPI bounds are also interesting to compute since they represent "intersection" and "union" graphs for the SEPI relation. For instance, in our motivating application in systems biology, these objects correspond to the intersection (resp. union) of models at different levels of details for a given biochemical process. These graphs are not unique but we are confident that the constraint satisfaction algorithm presented in [10] can be interestingly generalized to compute them.

6.7. Parameter Search under Temporal Logic Constraints

Participants: Grégory Batt, Elisabetta De Maria, François Fages, Domitille Heitzler, Aurélien Rizk, Sylvain Soliman, Jannis Uhlendorf.

Our method for solving temporal logic constraints in the quantifier-free fragment of first-order linear time logic QFLTL(R), opens up the field of model-checking to optimization through the definition of a continuous degree of satisfaction for temporal logic formulae [8], [2]. This satisfaction degree can be used in a number of ways, e.g. as a fitness function with continuous optimization methods[2] to find unknown parameter values in a model with temporal logic constraints formalizing biological properties [4], [6], or to control a system from a temporal specification of its behavior [15], or to compute the robustness of a system w.r.t. a temporal property and a perturbation of the parameters.

This approach is implemented in BIOCHAM and is one unique feature of this modeling environment.

6.8. Model-based Optimization of Cancer Chronotherapies

Participants: Elisabetta De Maria, François Fages, Aurélien Rizk, Sylvain Soliman, Denis Thieffry.

Recent advances in cancer chronotherapy techniques support the evidence that there exist some links between the cell cycle and the circadian clock genes. One purpose for modeling the entrainment in period of the cell cycle by the circadian clock 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.

In [4] we show how temporal logic constraints, and the new features of BIOCHAM for parameter search (running on a cluster of 10000 processors at the GENCI) can be used to couple dynamical models in high dimension and more precisely to build a coupled model composed of:

- a four phases model of the mammalian cell cycle by Novak and Tyson,
- a circadian clock model by Leloup and Goldbeter,
- a DNA damage repair model by Ciliberto et al.,
- a model of irinotecan metabolism by Dimitrio and Ballesta,
- a simple model of drug administration control.

This coupled model allows us to minimize the toxicity of irinotecan on healthy cells, using BIOCHAM's parameter search method applied on the drug administration control law.

Our technology is ready to calibrate models on real patient data, evaluate model predictions and optimize patient-tailored chronotherapeutics. The collaboration currently focuses on the obtaining of consistent data in the C5Sys project and on the improvement of the cell cycle model.

6.9. Analysis of FSH and Angiotensine Signaling

Participants: François Fages, Domitille Heitzler, Aurélien Rizk, Sylvain Soliman.

In [6] in collaboration with Eric Reiter (UMR CNRS-INRA 6175) and Frédérique Clément (SISYPHE) in the framework of the Initiative Action REGATE, we have combined experimental approaches with computational modeling to decipher the molecular mechanisms as well as the hidden dynamics governing ERK activation by the angiotensin II type 1A receptor (AT1AR) in HEK293 cells. We have built in BIOCHAM a dynamical model that captures available knowledge and experimental data. The unknown kinetic parameters have been inferred using a temporal logic specification of experimental data in both control and perturbed conditions, using a cluster of 10000 processors at the GENCI.

The mathematical model predicts and experiments confirm that, for the AT1AR expressed in HEK293 cells: i) GRK2/3 and 5/6 regulate switching between the G protein and β-arrestin pathways as well as their distinct dynamics by phosphorylating the C- terminal region of the activated receptor; ii) GRK2/3 not only mediates desensitization of G protein activation but also exerts a strong restraining influence on β-arrestin signaling; iii) GRK5/6 exert little effect on G protein-stimulated ERK but are required for β-arrestin- mediated ERK activation; iv) the β-arrestin-dependent ERK pathway undergoes both activation and deactivation through amplified enzymatic processes.

[2] we use the Covariance Matrix Adaptation Evolutionary Strategy CMAES of Nikolaus Hansen from the EPI TAO. Morevoer, this year we have implemented a second method by Particle Swarm Optimization, PSO.

These results convincingly illustrate the value of using computational modeling to decipher the complex signaling mechanisms elicited by 7TMRs [1]. This approach is applied more generally to G protein-coupled receptor signaling which is of great importance in pharmacology.

6.10. Multi-affine Hybrid Automaton Model of Cardiac Cells

Participant: Grégory Batt.

A fundamental question in the treatment of cardiac disorders, such as tachycardia and fibrillation, is under what circumstances does such a disorder arise? To answer to this question, in collaboration with E. Bartocci and R. Grosu at SUNY, Stony Brook, USA, we develop a multi-affine hybrid automaton (MHA) cardiac-cell model, and restate the original question as one of identification of the parameter ranges under which the MHA model accurately reproduces the disorder [12] . The MHA model is obtained from the minimal cardiac model of one of the authors, Fenton from Cornell University, by first bringing it into the form of a canonical genetic regulatory network, and then linearizing its sigmoidal switches in an optimal way. By leveraging the Rovergene tool for genetic regulatory networks, we are then able to successfully identify the parameter ranges of interest.

6.11. Real-time Control of Gene Expression in Yeast

Participants: Grégory Batt, François Fages, Jannis Uhlendorf.

To decipher the dynamical functioning of cellular processes, the method of choice is to observe the time response of cells subjected to well controlled perturbations in time and amplitude. Efficient methods, based on molecular biology, are available to monitor quantitatively and dynamically many cellular processes. In contrast, it is still a challenge to perturb cellular processes - such as gene expression - in a precise and controlled manner. In collaboration with Pascal Hersen at MSC lab (Paris Diderot University), in the framework of the Iceberg ANR project, we propose a first step towards *in vivo* control of gene expression: in real-time, we dynamically control the activity of a yeast signaling cascade thanks to an experimental platform combining a micro-fluidic device, an epi-fluorescence microscope and software implementing control approaches [15]. We experimentally demonstrate the feasibility of this approach, and we investigate computationally some possible improvements of our control strategy using a model of the yeast osmo-adaptation response fitted to our data.

6.12. Artificial Tissue Homeostasis in Mammalian Cells

Participants: Grégory Batt, François Bertaux, Xavier Duportet, François Fages, Szymon Stoma.

Cell-based gene therapy aims at creating and transplanting genetically-modified cells into a patient in order to treat a disease. Ideally, actively-growing cells are used to form a self-maintaining tissue in the patient, thus permanently curing the disease. However, before any real therapeutic use, robust mechanisms enforcing tissue homeostasis, that is, that the size of the newly-introduced tissue remains within admissible bounds, need to be developed. We proposed various designs and tested their robustness using *in silico* approaches. Preliminary results demonstrated that cell-to-cell variability plays a crucial role for tissue long-term maintenance. More extensive *in silico* characterizations require the development of efficient multiscale simulation methods. In parallel to the *in silico* work, done in collaboration with the Bang research group (Dirk Drasdo), we started the construction and *in vitro* experimental characterization of the most promising designs in collaboration with the Weiss lab (MIT) [24].

7. Contracts and Grants with Industry

7.1. Biointelligence

- OSEO BioIntelligence project (2009-2014) coordinated by Patrick Johnson, Dassault-Systèmes, with EPI ORPAILLEUR, SOBIOS, Aureus pharma, IPSEN, Pierre Fabre, Sanofi-Aventis, Servier, Bayer CropScience, INSERM, Genopole Evry.

7.2. Rules2Optim

- DTI ITI support for the industrialization of Rules2CP software with SME KLS-Optim.

7.3. General Electric Transportation

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

8. Partnerships and Cooperations

8.1. National Initiatives

- ANR Investissement Avenir Iceberg project (2011-2016) 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.
- ANR Syscomm project CALAMAR (2009-2011) "Compositional modeling and Analysis of LArge MoleculAr Regulatory networks - application to the control of human cell proliferation.", coordinated by C. Chaouiya, TAGC INSERM Marseille, L. Calzone, Institut Curie, Paris,
- AE REGATE (2008-) 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 cluster SGI of 10000 processors 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 International Partners

We have tight collaborations with the Weiss lab for synthetic biology at MIT, USA, through participation in the ANR Syne2arti project coordinated by Grégory Batt, and through the joint supervision of Xavier Duportet's PhD thesis.

We also have a starting 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).

8.3.2. Visits of International Scientists

8.3.2.1. Visiting Professor

Calin Belta, Boston University, USA (2 months),

8.3.2.2. Internships

Gopalakrishnan Kumar

Subject: Stochastic model of the yeast Met3 promoter

Institution: IIT Bombay (India)

Armando Gonçalves Da Silva Junior

Subject: Generating Explanatory Traces for Rule-Based Constraint Reasoning CHR

Institution: Federal University of Pernambuco (UFPE) (Brazil)

Philip Robin

Subject: Hybrid Simulations with Events

Institution: IIT New Delhi (India)

8.3.2.3. Short visits

Xuefeng Gao, University College, Cork, Ireland,

Neda Saeedloei, University of Texas, Dallas, USA

Yaakov Setty, Weizmann Institute, Revohot, Israel,

Szymon Stoma, Humboldt University, Berlin, Germany

8.3.3. Participation In International Programs

Program: STIC AmSud

Project acronym: TODAS

Project title: Trace Observation Driven Adaptive Solvers

Duration: janvier 2010 - décembre 2011

Coordinator: Pierre Deransart INRIA

Other partners: Eric Monfroy, UFSTM, Chile, Luis Menezes, UPE, Brazil, J. Robin, UFPE, Brazil, and F. Saubion, LERIA, U. Angers.

Abstract: The objective of the project is to define or improve self-adaptive constraint solving algorithms (Boolean, finite domains, local search or rules CHR) and their essential parameters, with an approach partly based on generic traces, to allow experimentation on different classes of solvers. At INRIA we worked in two directions: the development of a generic trace for CHR^v [11], and the integration of the approach of generic trace to describe different kinds of adaptive solvers.

9. Dissemination

9.1. Animation of the scientific community

- Grégory Batt's invited seminars:
  - Workshop on identification and control of biological interaction networks, Grenoble, Feb 08, invited talk
  - Rule-based modeling and application to biomolecular networks, École de recherche d'hiver en informatique fondamentale, ENS Lyon, Feb. 14 - 18, invited talk
  - Computational biology group, Instituto Gulbenkian de Ciência, Lisbon, May 16, invited seminar
  - Synthetic biology meeting of Societe Francaise de Biologie, Sept 21, invited talk
  - Biomolecular signaling and control group, ETHZ, Zurich, Oct 11, invited seminar
  - Automatique des systèmes hybrides, Supelec Rennes, Oct 17, invited seminar
  - Formal methods for bioinformatics workshop of "Approches Formelles des Systèmes Embarqués Communicants" group, Paris, Oct 19
  - P.S. Thiagarajan group seminar, NUS school of computing, Singapore, Nov 14, invited seminar
  - Computing department seminar, NUS school of computing, Singapore, Nov 15, invited seminar
  - Vasy team seminar, Autrans, Nov 28-30, invited seminar

  He was a reviewer for Bioinformatics, IEEE Transactions on Computational Biology and Bioinformatics, and Internal Journal of Robust and Nonlinear Control, and for CMSB'11, CDC'11, and ACC'11 conferences.

- Pierre Deransart is the General Secretary, past Chairman, of the "Association Française pour la Programmation par Contraintes" AFPC and contributes to the Members Council of ASTI AFPC.

  He is member of the program committee of the French Speaking Conference on Knowledge Engineering 2011 http://ic2011.liris.cnrs.fr/ and 2012. He organsised with Alain Mille in may 2011 a workshop on "Traces, Digital Traces, Knowledges and Cognition" http://pauillac.inria.fr/~deransar/ICAtelierIC1/IC2011AtelierTraces.html whose material will be published in a special issue of the review Intellectica in 2012.

- Xavier Duportet's invited seminar and contributed poster presentations:
  - Qu'est ce que la Biologie de Synthèse, Cité des Sciences, Paris, June 13, invited talk
  - Synthetic Biology 5.0 conference, Stanford, USA, Jun 15-17, poster
  - SynBerc retreat, Harvard Medical School, USA, October 19, poster

  technological transfer activities:
  - Young Entrepreneurs Initiatives competition, Boston, February - laureate
  - Concours de création d'entreprise innovante, Génopole Evry - ranked 3rd

- François Fages is a member of the Editorial Board of RAIRO Operations Research, and of the Steering Committee of the International Conference series on Computational Methods in Systems Biology (CMSB) in cooperation with the ACM.

  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 René Descartes, Paris 5,
  - the Laboratoire d'Informatique Fondamentale, University of Orléans.

  a member of the "Comité de pilotage" of the OSEO BioIntelligence project, coordinated by Dassault-Systèmes, of the "Comité d'animation du domaine STIC pour les sciences de la vie et de l'environnement" at Inria, and an assistant of the "inspecteurs de l'académie de Versailles pour le nouvel enseignement de l'informatique en terminale S".

  François Fages has been the Conference and Program Chair of CMSB'11 and a member of the Program Committees of CHR'11, CompMod'11, CS2BIO'11, ICECCS'11, ICLP'11, JFPC'11, MELO'11, RuleML'11, SASB'11, WCB'11.

  François Fages was a reviewer for research grants of the Research Foundation Flanders - FWO, Belgium, of the EPSRC Programme Grant Applications, UK, of the CNRS-MPG postdoctoral awards, Germany, of several ANR project proposals, and of Inria "Primes d'Excellence Scientifique".

  He has been reviewer of the PhD Thesis of Loïc Paulevé, Ecole Centrale de Nantes, and a member of the PhD Thesis committee of Guillermo Rodrigo, University of Valencia, Spain.

  Invited seminars:
  - Andreas Draeger's group, University of Tubingen, Germany, Jan 28,
  - Torsten Schaub's group, Max Planck Institute, Potsdam, Germany, Feb 10,
  - University Federal De Pernambuco, Recife, Brazil, Dec 14,
  - University De Pernambuco, Recife, Brazil, Dec 15,
  - Lycée Jules Ferry, Versailles, France, Nov 30,
  - Lycée Essouriau, Les Ulis, France, Dec 3.

- Thierry Martinez acted as reviewer for ICLP'11, JFPC'11 and RULEML'11. He was also a member of the organizing committe of CMSB'11.

  Invited seminar:

  - Doctoral Seminar, Rocquencourt, “How to write and prove programs with constraints and linear logic”, Oct. 2011

- Faten Nabli, poster presentation:
  - Constraint Programming Conference Doctoral Program, Perugia, Italy, Sep 11
- Sylvain Soliman acted as reviewer for CMSB’11, TACAS’11, ICLP’11 and IET Systems Biology. He was also member of the organizing committe of CMSB’11
- Szymon Stoma was Mentor for the Google Summer School of Code 2011, Jun-Sep.

  Invited seminars:
  - Open phyllotaxis meeting, Virtualplants INRIA, Montpellier, June
  - Ann Carpenter’s group, Broad Institute/MIT, Boston, Nov
- 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 scientific committees for ECCB-ISMB 2011, JOBIM 2011, CMSB 2011, and SASB 2011;
  - Editor of BioSystems;
  - Associated Editor of PLoS Computational Biology;
  - Adviser for the PLoS Biology Education series.
- Jannis Uhlendorf poster presentation:
  - Basel computational biology conference, Basel, Switzerland, poster
  - Stochastic systems biology conference, Monte Verita, poster
  - Physics and biological system conference, Orsay, France, poster
  - Young Researchers in Life Sciences Congress, Paris, France, poster

9.2. Teaching

Contraintes is affiliated to the Doctoral school of Mathematical Science of the University of Paris 7, and to the interdiciplinary Doctoral school “Frontières du Vivant” of the University of Paris 5.

The following courses have been given by members of Contraintes:

Doctorate: Ecole Jeunes Chercheurs en Programmation “Programmation par Contraintes”, Dinard, François Fages (6h).

Master: Cell Systems Biology master curriculum at the Ecole Normale Supérieure, Paris, coordinated by Denis Thieffry.

Master M2 course C2-35-1 on *Constraint Programming*, Master Parisien de Recherche en Informatique (MPRI) Sylvain Soliman (responsible, 24h).

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 M2 course on *Constraint Programming*, Master d’Informatique d’Orléans, François Fages (3h).

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

Master M1 course on Synthetic Biology and Entrepreneurship, AgroParisTech, Xavier Duportet (6h)

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

Licence L1 TD on *Fondements de l’Informatique*, Université de Versailles-Saint-Quentin-en-Yvelines, Elisabetta De Maria (36h).

Licence L1 TD on *Fondements de l’Informatique*, Université de Versailles-Saint-Quentin-en-Yvelines, Aurélien Rizk (33h).

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

Alliance pour la recherche et l’innovation des industries de sante, Paris, bimonthly meetings for SynBio Scientific Commitee, Xavier Duportet

The following PhD theses have been supervised:

PhD : Domitille Heitzler, “Modélisation dynamique des mécanismes de signalisation cellualire induits oar l’hormone folliculo-stimulante et l’angiotensine”, Université Rabelais à Tours, Janvier 2011, Dir. Eric Reiter, Frédérique Clément, François Fages,

PhD : Aurélien Rizk, “Résolution de contraintes temporelles pour l’analyse de systèmes biologiques”, Université Paris Diderot, Paris, 6 juin 2011, Dir. François Fages,

PhD in progress : Thierry Martinez, “Concurrence, angélisme et contraintes pour la programmation en logique linéaire”,Université Paris Diderot, Paris, Dir. François Fages,

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 Diderot, Paris, octobre 2010, Dir. Grégory Batt, François Fages and Ron Weiss (MIT)

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

PhD in progress : David Fournier, Université Paris Diderot, Paris, octobre 2009, Dir. François Fages and Denis Mulard (General Electric),

PhD in progress : Thierry Martinez, Université Paris Diderot, Paris, octobre 2009, Dir. François Fages,

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

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

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] D. HEITZLER. *Modélisation dynamique des mécanismes de signalisation cellulaire induits par l'hormone folliculo-stimulante et l'angiotensine*, Univ. François Rabelais de Tours, January 2011.

[2] A. RIZK. *Résolution de contraintes temporelles pour l'analyse de systèmes biologiques*, Université Denis Diderot, Paris, May 2011.

Articles in International Peer-Reviewed Journal

[3] R. CHARNEY, J. COHEN, A. RIZK. *Efficient synthesis of a class of Boolean programs from I-O data: Application to genetic networks*, in "Discrete Applied Mathematics", March 2011, vol. 159, n^{o} 6, p. 410–419, http://dx.doi.org/10.1016/j.dam.2010.10.009.

[4] E. DE MARIA, F. FAGES, A. RIZK, S. SOLIMAN. *Design, Optimization, and Predictions of a Coupled Model of the Cell Cycle, Circadian Clock, DNA Repair System, Irinotecan Metabolism and Exposure Control under Temporal Logic Constraints*, in "Theoretical Computer Science", May 2011, vol. 412, n^{o} 21, p. 2108–2127, http://dx.doi.org/10.1016/j.tcs.2010.10.036.

[5] S. GAY, F. FAGES, T. MARTINEZ, S. SOLIMAN, C. SOLNON. *On the subgraph Epimorphism Problem*, in "Discrete Applied Mathematics", 2011, submitted.

[6] D. HEITZLER, G. DURAND, 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. *GRKs: molecular switches controlling the balance between G protein and β-arrestin-mediated signaling by 7TMRs*, in "Molecular Systems Biology", 2011, submitted.

[7] A. MIERMONT, J. UHLENDORF, M. MCCLEAN, P. HERSEN. *The dynamical systems properties of the HOG signaling cascade*, in "Journal of Signal Transduction", 2011, n^{o} 2011, 930940.

[8] A. RIZK, G. BATT, F. FAGES, S. SOLIMAN. *Continuous Valuations of Temporal Logic Specifications with applications to Parameter Optimization and Robustness Measures*, in "Theoretical Computer Science", June 2011, vol. 412, n^{o} 26, p. 2827–2839, http://dx.doi.org/10.1016/j.tcs.2010.05.008.

[9] S. STOMA, M. FROHLICH, S. GERBER, E. KLIPP. *STSE: Spatio-temporal simulation environment dedicated to biology*, in "BMC Bioinformatics", 2011, n^{o} 12, 126.

International Conferences with Proceedings

[10] S. GAY, T. MARTINEZ, S. SOLIMAN, F. FAGES. *A Constraint Program For Subgraph Epimorphisms with Application to Identifying Model Reductions in Systems Biology*, in "Proceedings of the seventh Workshop on Constraint Based Methods for Bioinformatics WCB'11, colocated with CP 2011", September 2011, p. 59–66.

[11] A. GONÇALVES, M. A. A. D. SILVA, P. DERANSART, J. ROBIN. *Towards a Generic Trace for Rule Based Constraint Reasoning*, in "Eighth International Workshop on Constraint Handling Rules (CHR2011)", J. SNEYERS (editor), TR, German University in Cairo, Egypt, 2011.

[12] R. GROSU, G. BATT, F. FENTON, J. GLIMM, C. LE GUERNIC, S. SMOLKA, E. BARTOCCI. *From cardiac cells to genetic regulatory networks*, in "23rd International Conference on Computer Aided Verification, CAV'11", Cliff Lodge, 2011.

[13] T. MARTINEZ. *Angelic CHR*, in "Proceedings of the Eighth International Workshop on Constraint Handling Rules CHR'11", J. SNEYERS (editor), September 2011, http://contraintes.inria.fr/tmartine/papers/martinez11chr.pdf.

[14] F. NABLI. *Finding minimal siphons as a CSP*, in "CP'11: The Seventeenth International Conference on Principles and Practice of Constraint Programming, Doctoral Program", September 2011, p. 67–72.

[15] J. UHLENDORF, S. BOTTANI, F. FAGES, P. HERSEN, G. BATT. *Towards real-time control of gene experession: controlling the HOG signaling cascade*, in "Proceedings of the 16th Pacific Symposium on Biocomputing (PSB 2011)", Hawaii, USA, January 2011, p. 338–349.

[16] J. UHLENDORF, P. HERSEN, G. BATT. *Towards real-time control of gene expression: in silico analysis*, in "18th IFAC World Congress, WC'11", Milan, 2011.

National Conferences with Proceeding

[17] P. DERANSART. *Traces génériques et contraintes, GenTra4CP revisité*, in "Septièmes Journées Francophones de Programmation par Contraintes (JFPC 2011)", 2011, p. 105–114.

Conferences without Proceedings

[18] G. BATT. *Towards Real-Time Control of Gene Expression (invited talk)*, in "International Workshop Towards Systems Biology", Grenoble, France, May 2011.

[19] F. FAGES. *A graphical method for reducing and relating models in systems biology (invited talk)*, in "International Workshop Towards Systems Biology", Grenoble, France, May 2011.

[20] F. FAGES. *Formal cell biology in Biocham (keynote talk)*, in "International Symposium on Symbolic Systems Biology ISSSB'11", Shonan Village, Japan, November 2011.

[21] F. FAGES. *Hiérarchie de formalismes et de modèles en biologie systémique (exposé invité)*, in "Journée ITMO CMN Inria", Paris, France, March 2011.

[22] F. FAGES. *Une méthode graphique pour réduire et relier les modèles en biologie des systèmes*, in "Symposium Biointelligence", Sophia-Antipolis, France, July 2011.

Scientific Books (or Scientific Book chapters)

[23] J. MARTIN, T. MARTINEZ, F. FAGES. *Static Expansion vs Procedural Code Generation in Rule-based Modeling Languages*, in "Recent Advances in Constraints", J. LARROSA, B. O'SULLIVAN (editors), LNAI, Springer-Verlag, 2011, n^{o} 6384, p. 38–58.

[24] A. RANDALL, P. GUYE, S. GUPTA, X. DUPORTET, R. WEISS. *Design and connection of robust genetic circuits*, in "Methods in Enzymology", C. VOIGT (editor), Elsevier, 2011, n° 497, p. 159–186.

Books or Proceedings Editing

[25] F. FAGES (editor). *Proc. of the 9th International Conference on Computational Methods in Systems Biology CMSB'11*, ACM in cooperation Conference Proceedings, ACM Digital Libray, Paris, France, September 2011.

Research Reports

[26] L. CALZONE, C. CHAOUIYA, É. REMY, S. SOLIMAN. *Qualitative Modelling of the RB/E2F network*, ANR CALAMAR (ANR-08-SYSC-003), February 2011, n° D3.1, http://tagc.univ-mrs.fr/welcome/IMG/pdf/livrable-3-1.pdf.

[27] L. CALZONE, S. SOLIMAN. *Quantitative Modelling of the RB/E2F network*, ANR CALAMAR (ANR-08-SYSC-003), September 2011, n° D3.2.

[28] P. DERANSART. *Generic Traces and Constraints, GenTra4CP revisited*, Inria HAL report, 2011, http://hal.inria.fr/hal-00597033/en.

[29] F. FAGES, D. JOVANOVSKA, A. RIZK, S. SOLIMAN. *BIOCHAM v3.3 Reference Manual*, INRIA, 2011, http://contraintes.inria.fr/BIOCHAM/.

[30] F. FAGES, P. ROBIN, S. SOLIMAN. *Simulations hybrides*, OSEO project BioIntelligence, 2011, n° INR-04-L3-D14.

[31] D. FOURNIER. *Constraint Modeling of Trains Supervision and Timetabling*, Chalmers University, Sweden, Ecole des Mines d'Ales, INRIA, France, September 2011.

[32] S. SOLIMAN. *Constraint Programming for the Dynamical Analysis of Biochemical Systems – A Survey*, ANR CALAMAR (ANR-08-SYSC-003), February 2011, n° D1.6, http://tagc.univ-mrs.fr/welcome/IMG/pdf/Livrable-1-6.pdf.

[33] S. SOLIMAN, A. ZINOVYEV. *Reduction of differential models*, ANR CALAMAR (ANR-08-SYSC-003), September 2011, n° D1.2.

Other Publications

[34] F. FAGES. *Aspects sémantiques et algorithmiques du vivant*, in "Séminaire Jacques Morgenstern", INRIA Sophia-Antipolis, January 2011, video and slides, http://www-sop.inria.fr/colloquium/.

[35] F. FAGES. *Programmation Logique avec Contraintes*, 2011, Ecole Jeunes Chercheurs en Programmation CNRS, http://contraintes.inria.fr/fages/Teaching/EJC.