INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Project-Team Contraintes

Constraint programming

Paris - Rocquencourt

Theme : Programs, Verification and Proofs

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2. Overall Objectives

2.1. Introduction

Constraint Logic Programming supports a great ambition for programming: the one of making of programming essentially a modeling task, with equations, constraints and logical formulas. This research field is born during the mid 80s from Logic Programming, Linear Programming coming from Operations Research, and Constraint Propagation techniques coming from Artificial Intelligence. Its foundation is the use of relations on mathematical variables to compute with partial information.

The successes of Constraint Programming for solving combinatorial optimization problems, ranging from pure academic problems to real-life problems in industry or commerce, owe much to the bringing of both new local consistency techniques and new declarative languages which allow control on the mixing of heterogeneous resolution techniques: numerical, symbolic, deductive and heuristic.

Furthermore, this approach of combinatorial problems based on logical modeling can be fruitfully applied in systems biology to get over complexity walls and reason about large molecular interaction networks.

The "Contraintes" group investigates the logical foundations, design, implementation, programming environments and applications of constraint languages. The study of Concurrent Constraint languages is a core aspect of the project as they provide a conceptual framework for analyzing different issues of constraint programming, like constraint resolution techniques, concurrent modeling, reactive applications, etc. The main application domains investigated are combinatorial optimization problems and computational systems biology. In bioinformatics, our objective is not to work on structural biology problems which has been the main trend up to now, but to attack the great challenge of systems biology, namely to model the function, activity and interaction of molecular processes in living cells, with logic programming concepts and program verification techniques.

2.2. Highlight: Model Reductions as Subgraph Epimorphisms

In Systems Biology, an increasing collection of reaction rule based models of various biological processes is currently developed and made available in publicly accessible repositories, such as biomodels.net for instance (currently composed of 269 curated models), using common exchange formats such as the Systems Biology Markup Language (SBML). To date, however, there is no general method to relate different models to each other by abstraction or reduction relationships, and this task is left to the modeler for re-using and coupling models. In mathematical biology, model reduction techniques have been studied for a long time, mainly in the case where a model exhibits different time scales, or different spatial phases, which can be analyzed separately. These techniques are however far too restrictive to be applied on a large scale in systems biology, and do not take into account abstractions other than time or phase decompositions.

In [5], we propose a general computational method for relating models together, by considering primarily the structure of the interactions and abstracting from their dynamics in a first step. We present a graph-theoretic formalism in which model reductions are defined by finite sequences of operations of merging or deleting species or reaction vertices in the reaction graph. We show that the existence of such a graphical reduction between two graphs is equivalent to the existence of a subgraph epimorphism (i.e. morphism that is surjective on arcs and vertices). From this setting, we derive a constraint logic program over finite domains for deciding whether there exists a reduction from one reaction graph to another, and evaluate it on the computation of the reduction relationships between all SBML models of the biomodels.net repository. We show that biologically meaningful mappings between models are automatically inferred from the structure of the interactions.

Subgraph epimorphisms are also interesting combinatorial objects that we now study in their own rights. In collaboration with Christine Solnon (INSA Lyon), we develop their theory and compare them with the classical notions of subgraph isomorphisms, minors, etc.

3. Scientific Foundations

3.1. Concurrent Constraint Logic Programming

The class of Concurrent Constraint programming languages (CC) was introduced two decades ago by Vijay Saraswat as a unifying framework for constraint logic programming and concurrent logic programming. The CC paradigm constitutes a representative abstraction of practical constraint programming languages, allowing for a theoretical study of their fundamental properties.

CC extends the Constraint Logic Programming framework (CLP) by introducing a synchronization primitive, based on constraint entailment. This provides a model of concurrent computation, where agents communicate through a shared store, represented by a constraint, which expresses some *partial information* on the values of the variables involved in the computation. The variables play the role of transmissible dynamically created communication channels.

One important success of CC has been the simple and elegant reconstruction of finite domain constraint solvers, and the cooperation of several models to solve a single combinatorial problem. The programming of reactive applications however motivates new extensions, in particular for relaxing the hypothesis of monotonic evolution of the constraint store and expressing state change.

One solution to this problem was found by considering the logical semantics of CC languages. The completeness theorems which relate the execution of a CLP program to its translation in classical logic are indeed broken by the synchronization operation of CC. Looking for a logical semantics of CC programs in the general paradigm of logic programming,

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

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

leads to a translation in Jean-Yves Girard's linear logic, in which the CC operational transitions are identified to linear implications (in the opposite direction of the classical CLP logical semantics). The associated completeness theorems for successes and accessible stores (and suspensions in the non-commutative logic of Ruet and Abrusci) continue to hold for linear logic constraint systems which allow for non monotonic evolution of the constraint store.

In this theoretical framework, called LCC for Linear Logic Concurrent Constraint programming[1], it is thus possible to address important issues for Constraint Programming:

- verifying CC programs;
- combining CC and state-based programming;
- defining extensible libraries of constraint solvers without changing of programming language.

3.2. Constraint Filtering Algorithms

The project works on constraint resolution methods and their cooperation. The main focus is the declarativeness of the constraint solver, the efficiency of constraint propagation methods, the design of global constraints and the combination of constraint propagation with heuristic search.

Our application domains involve quite different constraint domains on which we use or contribute with new constraint filtering algorithms for

- finite domains (bounded natural numbers): membership, arithmetic, reified, higher order and global constraints;
- reals: polyhedral libraries for linear constraints and interval methods otherwise;
- terms: subtyping constraints;
- graphs: subgraph epimorphism and isomorphism constraints;
- Kripke structures: temporal logic constraints (QFCTL and QFLTL formulae with free variables).

3.3. Logical Paradigm for Systems Biology

At the end of the Nineties, 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, etc). The complexity of these networks requires a large research effort to develop symbolic notation and analysis tools for biological processes and data. In order to scale-up, and get over the complexity walls to reason about biological systems, there is a general feeling that beyond providing tools to biologists, computer science has much to offer in terms of concepts and methods. Systems biology is the name given to a pluridisciplinary domain involving biology, computer science, mathematics, physics,... and aiming at elucidating the high-level functions of the living organisms from their biochemical bases at the molecular level.

Our main research axis in this field since 2002 has been the application of logic programming concepts and program verification techniques to the modeling and analysis of complex biochemical processes in the cell. The logical paradigm for systems biology that we develop can be summarized by the following identifications :

[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.

biological model = (quantitative) state transition system,

biological property = temporal logic formula,

model validation = model-checking,

model inference = constraint solving.

This original approach can combine different levels of abstraction, both qualitative and quantitative, for reasoning about cell processes. It has proven successful for the modeling, analysis and even optimization of complex molecular processes in the cell.

4. Application Domains

4.1. Combinatorial optimization problems

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 forty years have brought many improvements in Operations Research resolution techniques. In this context, Constraint Programming can be seen as providing, on the one hand, local consistency techniques 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 project builds upon its knowledge of constraint languages, constraint solvers and their implementation to work in these directions. The LCC paradigm offers at the same time a theoretical framework for analysis, and a valuable guide for practical language design and implementation. The work on programming environments helps to integrate the Constraint Programming tools into this application domain.

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 [30]. 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 2002 , we started a Collaborative Research Initiative ARC CPBIO on “Process Calculi and Biology of Molecular Networks”. By working on well understood biological models, we sought:

- to identify in the family of competitive models coming from the Theory of Concurrency and from Logic Programming (Constraint Logic Programming, Concurrent Constraint languages and their extensions to discrete and continuous time, TCC, HCC), the ingredients of a language for the modular and multi-scale representation of biological processes;
- to provide a series of examples of biomolecular processes transcribed in formal languages, and a set of biological questions of interest about these models;
- to design and apply to these examples formal computational reasoning tools for the simulation, the analysis and the querying of the models.

This work lead us to the design and implementation of the Biochemical Abstract Machine BIOCHAM that has the unique feature of providing formal languages corresponding to different qualitative and quantitative levels of abstraction for, on the one hand, modeling biomolecular interaction diagrams with reaction rules, and on the other hand, modeling the biological properties of the system in temporal logic. This double formalization of both the model and the biological properties of the system at hand has opened several new research avenues on the design and systematic validation of biological models.

In partnership with biologists, we develop and experiment our modeling technology in three domains:

- **Modeling of cell cycle and optimization of cancer therapies.** 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, our development in BIOCHAM of original coupled models of the cell cycle, the circadian clock, the DNA repair system, irinotecan metabolism and drug injection optimization, continues in the Era-Net SysBio C5Sys project (2010-2013) coordinated by Francis Lévi and David Rand, University of Warwick, UK, by focussing on the interactions between the cell cycle and the circadian clock in mammalian cells.
- **Modeling and analysis of 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 FSH and angiotensine signal transduction in mammalian cells. Our article submitted to Science Signaling [6] concludes our fruitful interactions done in the INRA AgroBi project INSIGHT (2006-2009) and in the AE REGATE.
- **Control of gene expression and synthetic biology.** This research lead in the team by Grégory Batt investigates the possibilities to control and reprogram 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 design a microfluidic platform and develop control software for the real-time control of gene expression in yeast. In the AE 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, we investigate similarly the possibilities to control and reprogram growth and aging in bacteria *E. coli* using synthetic biology approaches. Finally, in collaboration with Ron Weiss at MIT, USA, we have started a project on the synthetic control of the population density in a mammalian cellular tissue.

5. Software

5.1. BIOCHAM

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

The Biochemical Abstract Machine BIOCHAM [32] is a modeling environment for systems biology [39], [17], under development since 2001, and distributed as open-source since 2003. Current version is v3.2. 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 [21], [20].

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. Rules2CP

Participants: François Fages, Julien 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.

5.3. 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.

5.4. 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 implemented in Prolog.

5.5. 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 FP6 Strep Net-WMS with a non-released version.

6. New Results

6.1. Linear Logic Concurrent Constraint Programming and Constraint Handling Rules

Participants: François Fages, Thierry Martinez, Sylvain Soliman.

The Constraint Handling Rules (CHR) language of Thom Frühwirth shares many similarities with SiLCC [34]. CHR (and its modular version CHRat) and SiLCC are based on a similar model of concurrent computation, where agents communicate through a shared constraint store, with a synchronization mechanism based on constraint entailment. In particular, the Constraint Simplification Rules (CSR) subset of CHR and the flat subset of LCC, where agent nesting is restricted, are very close syntactically and semantically.

In [13], we analyze these similarities by providing translations between CSR and flat-LCC, on the one hand, and a transformation from the full LCC language to flat-LCC, on the other hand. This transformation is similar to λ-lifting in functional languages. In conjunction with the equivalence between CHR and CSR with respect to naive operational semantics, these results lead to semantics-preserving translations from full LCC to CHR and conversely. Immediate consequences of this work include new proofs for CHR linear logic and phase semantics, relying on corresponding results for LCC, plus an encoding of the λ-calculus in CHR.

All the proofs of this paper are currently developed in the Coq proof assistant with interactions with the EPI GALLIUM.

6.2. Rule-based Modeling for Constraint Programming

Participants: Nicolas Beldiceanu, François Fages, Julien Martin, Thierry Martinez.

Rules2CP [33] is a rule-based modeling language which allows easy modeling of constraint satisfaction problems, together with specifications for search strategies and heuristic choice criterias [2]. The expressiveness and effectiveness of Rules2CP have been illustrated through the development of the Packing Knowledge Modeling Language PKML as a library on top of Rules2CP, dedicated to bin packing problems. PKML language is used in the FP6 Strep Net-WMS [30]. to study and solve higher-dimensional bin packing problems and placement constraints, including common sense, physical and industrial requirements expressed by rules

One originality of Rules2CP as a modeling language is its capability to express complex search strategies, by defining search trees with logical formulae and heuristic choice criteria by pattern matching on rule left-hand sides' derivation. in [29], we study a new compilation scheme for Rules2CP which allows us to deal with dynapmic 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.

6.3. Theory of Traces

Participants: Pierre Deransart, François Fages.

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. The state of this work is regularly updated on [40].

We worked on two main points: the development of a versatile tracer of CHR^v with several extensions, in the framework called CHROME-REF (see TODAS project) and an application field we called "exo-memory". In [10] we present an experimentation with a continuously updated textual exo-memory used to assist the natural memory of a subject. It is shown how trace theory could be used to improve the device. Main characteristics of such a memory aid are maintenance by the subject, limited size, plasticity, and persistence of the recall quality in the long term.

6.4. Model Reductions as Subgraph Epimorphisms

Participants: François Fages, Steven Gay, Sylvain Soliman.

In [5], we study the subgraph epimorphism problem and a constraint programming approach to solving it. Our interest in this particular variant of graph matching problem originates from the study of model reductions in systems biology. Large systems of biochemical reactions can indeed be naturally modelled as (bipartite) graphs of biomolecular compounds and react ions, and the notion of model reduction can be formalized in this setting as the existence of a sequence of delete and merge operations for species and reactions which transform a first reaction graph in a second graph. This problem is in turn equivalent to the existence of a subgraph (corresponding to delete operations) epimorphism (i.e. morphism, corresponding to merge operations, which is onto) from the first graph to the second. From this setting, we derive a constraint logic program over finite domains for deciding whether there exists a reduction from one reaction graph to another, and evaluate it on the computation of the reduction relationships between all SBML models of the biomodels.net repository. We show that biologically meaningful mappings between models can be automatically inferred from the structure of the interactions.

In collaboration with Christine Solnon (INSA Lyon), we develop the theory of subgraph epimorphisms and compare them with the classical notions of subgraph isomorphisms, minors, etc.

6.5. Steady-State Analyses and Petri Nets

Participants: François Fages, Faten Nabli, Sylvain Soliman.

In Systems Biology, very few analyses permit to extract information about the dynamics of quantitative models lacking precise parameter values, when pure symbolic computations fails. In [14], [25], we present a way to generalize well-known results about the steady-state analysis of some symbolic Ordinary Differential Equations systems by taking into account the structure of the reaction network. The study of the underlying Petri net, usually used mostly for metabolic flux analysis, provides classes where the analytic computation of some steady states of the system is possible, even though the original symbolic model did not form an S-system and was not solvable by state-of-the-art symbolic computation software. This new method is then illustrated on some models of the Biomodels repository.

Some other links between Petri nets and various Systems Biology modelling formalisms are studied in the framework of the ANR CALAMAR [36] leading, among other things, to the definition of conditions for the uniqueness of the mapping from differential equations to a structured model.

Indeed, structure-related qualitative analysis techniques have become increasingly popular in recent years, like qualitative model checking or pathway analysis (elementary modes, invariants, flux balance analysis, graph-based analyses, chemical organization theory, etc.). They do not rely on kinetic information but require a well-defined structure as stochastic analysis techniques equally do. In [9], we look into the structure inference problem for a model described by a system of Ordinary Differential Equations and provide conditions for the uniqueness of its solution. We describe a method to extract a structured reaction network model, represented as a bipartite multigraph, for example, a continuous Petri net (CPN), from a system of Ordinary Differential

Equations (ODEs). A CPN uniquely defines an ODE, and each ODE can be transformed into a CPN. However, it is not obvious under which conditions the transformation of an ODE into a CPN is unique, that is, when a given ODE defines exactly one CPN. We provide biochemically relevant sufficient conditions under which the derived structure is unique and counterexamples showing the necessity of each condition. Our method is implemented and available; we illustrate it on some signal transduction models from the BioModels database. Our results yield a new recommendation for the import/export feature of tools supporting the SBML exchange format.

6.6. Numerical Parameter Inference from Temporal Logic Properties

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

In BIOCHAM [39], our method for solving QFLTL(R) constraints allows us to define a continuous degree of satisfaction of LTL(R) formulae in a given trace, and use it as a fitness function in continuous optimization methods[2] in order to find unknown parameter values in a model satisfying a set of biological properties formalized in temporal logic [8]. This approach is heavily used in BIOCHAM for inferring unknown kinetic parameter values, initial concentrations, and/or control parameters from a formalization of the global behavior of the system in temporal logic [7], [6], [15].

Following this route, similar metrics and methods are currently developed for stochastic processes [35].

Consistency techniques for hybrid ODE-stochastic simulations are also studied in this perspective [16].

6.7. Parameter Inference for Qualitative Models of Regulatory Networks

Participant: Grégory Batt.

Investigating the relation between the structure and behavior of complex biological networks often involves posing the question if the hypothesized structure of a regulatory network is consistent with the observed behavior, or if a proposed structure can generate a desired behavior. In [3], we recast the above questions into a parameter search problem for qualitative models of regulatory networks. We develop a method based on symbolic model checking that avoids enumerating all possible parametrizations, and show that this method performs well on real biological problems, using the IRMA synthetic network and benchmark datasets. We test the consistency between IRMA and time-series expression profiles, and search for parameter modifications that would make the external control of the system behavior more robust.

6.8. Modeling the cell cycle and 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 the EraNet SysBio project C5Sys, follow up of the former EU STREP project TEMPO, in collaboration with the EPI BANG.

In [7], [22], [23] 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. This approach is illustrated by 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.

[2] namely the Covariance Matrix Adaptation Evolutionary Strategy CMAES of Nikolaus Hansen from the EPI TAO.

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. Modeling and analysis of FSH and Angiotensine Signaling Networks

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

In collaboration with Eric Reiter (UMR CNRS-INRA 6175) and Frédérique Clément (SISYPHE) in the framework of the Initiative Action REGATE, we analyse the connectivity and dynamics of the FSH signaling network in its target cells, and embedding the network within a multi-scale representation, from the molecular up to the organic level.

In [6] 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 built in BIOCHAM an abstracted ODE-based model that captured the available knowledge and experimental data. We inferred the unknown parameters by simultaneously fitting experimental data generated 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 $\hat{I}^2$-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 $\hat{I}^2$-arrestin signaling; iii) GRK5/6 exert little effect on G protein-stimulated ERK but are required for $\hat{I}^2$-arrestin- mediated ERK activation; iv) the $\hat{I}^2$-arrestin-dependent ERK pathway undergoes both activation and deactivation through amplified enzymatic processes.

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. Control of the HOG signaling cascade

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 [26], [27], [28], 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.

We have experimentally demonstrated the feasibility of this approach and investigated computationally some possible improvements of our control strategy using a model of the yeast osmo-adaptation response fitted to our data [15].

7. Other Grants and Activities

7.1. National contracts

- 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.
- 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.
- 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, ALCHEMY, 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.

7.2. European contracts

- EraNet SYsBio C5Sys (2010-2013) on "Circadian and cell cycle clock systems in cancer", coordinated by Franci Lévi, INSERM Hopital Paul Brousse, Villejuif, France, and David Rand, Warwick Systems Biology, UK, EPI BANG, Erasmus University Medical Center, Rotterdam, University College London, UK, CNRS Nice, and L2S, Orsay.
- 6th PCRD STREP Net-WMS (2006-2010) on "constraint optimization in Wharehouse Management Systems", ERCIM coord, F. Fages scientific coordinator, N. Beldiceanu, Ecole des Mines de Nantes, M. Carlsson, SICS, Abder Aggoun, KLS optim, CEA, MindBiz, Widescope, CRF Fiat, PSA;

7.3. International contracts

- TODAS STIC-AmSud Project, INRIA, MAEE, CONICYT, CAPES (2010-2012) on "Trace Observation Driven Adaptive Solvers", coordinated by Pierre Deransart, with Eric Monfroy, UFSTM, Chile, J. Robin, UFPE, Brazil, Luis Menezes, UPE, Brazil, and F. Saubion, LERIA, U. Angers.

7.4. Invitations

Have been invited for short visits :

- Radu Grosu, SUNY at Stony Brook, USA
- Adam Halasz, West Virginia University - Department of Mathematics
- Vianney le Clément, UCL Louvain, Belgique

8. Dissemination

8.1. 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:

- M2 course C2-4-1 on *Constraint Programming*, Master Parisien de Recherche en Informatique (MPRI) Sylvain Soliman (responsible, 15h), François Fages (6h), Thierry Martinez (3h).
- M2 course C2-19 on *Computational Methods for Systemic and Synthetic Biology*, Master Parisien de Recherche en Informatique (MPRI) François Fages (responsible, 12h) [41], Grégory Batt (12h), Denis Thieffry (12h).
- M2 course on *Computational Biology*, Master Approches Interdisciplinaires du Vivant (AIV), Grégory Batt (24h).
- Cell Systems Biology master curriculum at the Ecole Normale Supérieure, Paris, coordinated by Denis Thieffry.
- Ecole Jeunes Chercheurs "Modélisation formelle des réseaux de régulation biologique", Ile de Porquerolles, François Fages (8h).
- Tutorial on *New Computational Methods for Systems Biology* at the International Conference on Systems Biology, Edinburgh, UK, François Fages (3h), Sylvain Soliman (1h) [17].
- M2 course on *Constraint Programming*, Master d'Informatique d'Orléans, François Fages (3h).
- L2 Cours/TD *Informatique*, Université de Paris Dauphine, Faten Nabli (72h).
- L1 TD on *Fondements de l'Informatique*, Université de Versailles-Saint-Quentin-en-Yvelines, Elisabetta De Maria (36h).
- L1 TD on *Fondements de l'Informatique*, Université de Versailles-Saint-Quentin-en-Yvelines, Aurélien Rizk (33h).

8.2. Leadership within scientific community

- Grégory Batt co-organized a satellite workshop on Dynamical modeling and simulation of biological networks of the JOBIM conference in Montpellier, September 2010. He was also a member of the Thesis committee of Zohra Khalis (Evry Univ., Dec. 2010)
- 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.
- François Fages is a member of the Editorial Board of RAIRO Operations Research, and of the Steering Committees of the Computational Methods in Systems Biology (CMSB) and of the Integrative Post-Genomique (IPG) conferences. He is a member of the Scientific Councils of the Doctorate School Frontières du Vivant of the University René Descartes, Paris 5, and of the department of Computer Science at Ecole Centrale de Paris. He is a member of the "Comité d'animation du domaine STIC pour les sciences de la vie et de l'environnement" of INRIA.

  François Fages was a reviewer for two senior grants of the European Research Council in 2010. He was a reviewer of the PhD Theses of Judith Zamborszky, Univ. of Trento, Italy, Peter Van Weert, KUL, Belgium, a member of Thesis committee of Jérémie Vautard, Univ. Orléans, and chairman of the Thesis committee of Carito Guziolowski, Univ. Rennes.

  François Fages co-organized with Nicolas Beldiceanu and Mats Carlsson the third International Workshop on Bin Packing and Placement Constraints BPPC'10, assocated to CP-AI-OR'10 in Bologna, Italy. He is the Program Chair of CMSB'11 conference that will be held in September 2011 in Paris.
- Denis Thieffry is member of the Comité Scientifique Sectoriel of the Life and Health Department of the ANR, Associated Editor of PLoS Computational Biology (since 2010) and of BioSystems (since 2008), adviser for the PLoS Biology Education series (since 2010). member of the CNRS ATIP Scientific Committee (young group leader grant scheme), member of the INSERM Workshop Scientiï¬c Committee, and member of the scientiï¬c committee of the European Conference

of Computational Biology (2010). Participation to the AERES Evaluation Committee of the CNRS UMR 5534 - CGMC. Lyon, France. January 2010. Participation to the AERES Evaluation Committee of the SFRs 41, 128 and Lyon-Est (the three life science federative research structures in Lyon). Lyon, France. June 2010.

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[2] J. MARTIN. *Un langage de modélisation à base de règles pour la programmation par contraintes*, Université Pierre et Marie Curie, Paris, July 2010.

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