INRIA

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Project-Team Contraintes

Constraint Programming

Paris - Rocquencourt

THEME SYM

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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.

Constraint Programming is a field 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, from pure problems to real problems in industry or commerce, owe much to the bringing of , on the one hand, new local consistency techniques, and, on the other hand, declarative languages which allow control on the mixing of heterogeneous resolution techniques: numerical, symbolic, deductive and heuristic.

The "Contraintes" group investigates the logical foundations, design, implementation, programming environments and applications of constraint programming 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 systems in living cells, with logic programming concepts and program verification technologies.

2.2. Highlight: Parameter Optimization w.r.t. Temporal Logic Constraints

Temporal logics and model-checking are at the core of our approach in BIOCHAM to express biological properties of complex biochemical systems and automatically verify their satisfaction in both qualitative and quantitative models. Last year, we introduced a fundamental generalization of model-checking to constraint solving by presenting a constraint solving algorithm for quantifier-free first-order temporal logic formulae with constraints over the reals, denoted by QFLTL(R). This algorithm computes the domain of the real valued variables occurring in a QFLTL(R) formula that makes it true in a model [3], [16].

Based on this result, we are now able to define a continuous degree of satisfaction of LTL(R) formulae in a given trace, as a distance to the validity domain of a corresponding QFLTL(R) formula. This opens up the field of continuous optimization methods to parameter search w.r.t. high-level specifications in temporal logic.

In [22], we show how this approach applies to searching several tenths of kinetic parameters from high-level specifications in reaction models of the cell cycle and of the MAPK signalling cascade (37 parameters). The Covariance Matrix Adaptation Evolutionary Strategy CMAES of Nikolaus Hansen from the TAO team used in these experiments let us hope to deal with a hundred of parameters.

2.3. Highlight: Second Participation to the IGEM Competition on Synthetic Biology

Organized by MIT since 2004, the iGEM competition gathers student teams from worldwide universities with the aim of inventing synthetic biological systems (see iGEM web site). iGEM has rapidly demonstrated its capability to attract on an original problem the best students in biology, chemistry, computer science, or engineering to research and entrepreneurship. For the second time, a Parisian team took part in the competition, with members of the "Contraintes" group supporting the team as Instructors or Advisors. The interdisciplinary team was made of a high-school student and of 13 Licence and Master students coming from various universities and "Grandes Ecoles" in the Paris area. Their project consisted in developing a genetically-controlled molecular assembly line (see the team wiki). To reach this goal, the team combined theoretical (mathematical and computational modelling) and experimental (wet lab) work This project was carried out at the Center for Interdisciplinary Research (Faculté de médecine, Université Paris Descartes) from May to September. For its work, the team has been awarded a bronze medal during the final Jamboree held in Boston.

3. Scientific Foundations

3.1. Concurrent constraint programming

The class of Concurrent Constraint programming languages (CC) was introduced a decade ago by Vijay Saraswat as a unifying framework for constraint logic programming and concurrent logic programming. The CC paradigm constitutes a representative abstraction of constraint programming languages, and thus allows a fine grained study of their fundamental properties.

CC generalizes the Constraint Logic Programming framework (CLP) by introducing a synchronization primitive, based on constraint entailment. It is 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 of the big successes 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. On the other hand, to use CC for programming reactive applications forces one to abandon the hypothesis of monotonic evolution of the constraint store; this is a strong motivation for new extensions of CC languages.

There are strong completeness theorems relating the execution of a CLP program and its translation in classical logic, which provide smooth reasoning techniques for such programs. However these theorems are 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. This allows the recovery of some completeness results about successes and stores; even suspensions may be characterized with the non-commutative logic of Ruet and Abrusci.

It is thus possible to address important issues for Constraint Programming:

- verifying CC programs;
- combining CLP and state-based programming;
- dealing with local search inside a global constraint solving procedure.

The last two cases rely on a natural extension of CC languages, called Linear Concurrent Constraint languages (LCC), which simply replaces constraint systems built onto classical logic by constraint systems built onto linear logic. This allows us to represent state changes thanks to the consumption of resources during the synchronization action, modeled by the linear implication.

3.2. Constraint solvers

Our domains of application use quite different constraint systems:

- finite domains (bounded natural numbers): primitive constraint of some finite domain membership, numerical, symbolic, higher order and global constraints;
- reals: polyhedral libraries and Simplex algorithm for linear constraints and interval methods otherwise;
- terms: subtyping constraints and ontologies;
- temporal constraints: CTL and LTL formulae, either propositional or with numerical constraints.

The project works on constraint resolution methods and their cooperation. The main focus is the declarativeness of the constraint solver (e.g. implemented by CHR rules), the efficiency of constraint propagation methods, the design of global constraints and the combination of constraint propagation with heuristic search.

3.3. Computational systems biology

Systems biology is a cross-disciplinary domain involving biology, computer science, logics, mathematics, and physics to elucidate the high-level functions of the cell from their biochemical bases at the molecular level.

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.

We are interested in the modeling and analysis of complex molecular processes in the cell, at different levels of abstraction, qualitative and quantitative. The most original aspect of our research can be summarized by the following identifications [24]:

$$\textit{biological model} = \textit{state transition system},$$

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

automatic validation = model-checking.

Our main research axis is thus the application of logic programming concepts and circuit or program verification techniques to the analysis (and synthesis) of complex biochemical 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. This last point is crucial for quickly developing complex combinations of algorithms, which is not possible without a language with a high level of abstraction. It allowed for better results, for instance in scheduling problems, than traditional methods, 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 CC 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 coordinate, makes us focus on pure and non-pure bin packing problems combining discrete geometry constraints with physical, common sense and packing business rules, in the context of warehouse management systems for the automotive industry.

4.2. In-silico cell

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 opens several new research avenues on the design and systematic validation of biological models.

In the 6th PCRD STREP project APrIL II (2004-2007) the focus was on probabilistic inductive logic programming for metabolic networks and we developed semi-automatic methods for model completion/revision [28] from temporal logic specification of the system's behavior as observed in biological experiments [3]. In the Network of Excellence REWERSE (2004-2008), the focus was on the application of the new Semantic Web technologies based on rules and constraints to bioinformatics. In this context, we developped type inference and abstract interpretation techniques [4] to relate biological models at different levels of abstraction, providing a formal ground for reusing and combining models available on the web. In the ARC MOCA (2006-2007) on "MOdularity, Compositionality and Abstraction in gene and protein networks", we studied with our partners the formal links between logical and numerical models of some parts of the cell cycle control, and modular decompositions based on control theory considerations [6].

Currently, we develop these technologies and apply them to new biological questions which we investigate in partnerships with biologists in three projects. First, the EU STREP project TEMPO (2006-2009) on "temporal genomics for patient tailored chronotherapeutics", coordinated by Francis Lévi INSERM Villejuif, where, in partnership with Jean Clairambault of the BANG project-team, we develop coupled models of the cell cycle, the circadian cycle and the effect of cytotoxic drugs in cancer therapies using BIOCHAM.

Second, the INRA AgroBi project INSIGHT, coordinated by Eric Reiter INRA Tours, where, in partnership with Frédérique Clément of the SISYPHE project-team, we develop models of FSH and GPCR signaling networks in mammalian cells. This research is now part of the AE REGATE coordinated by F. Clément SISYPHE.

Third, the AE COLAGE coordinated by Hughes Berry of the ALCHEMY project-team, with François Taddei, Ariel Lindner, INSERM Paris Necker, Hidde de Jong, Delphine Ropers, IBIS, J.L. Gouzé, and Madalena Chaves, COMORE, where we investigate the possibilities to control and reprogram growth and aging in bacteria *E. coli* using synthetic biology approaches.

5. Software

5.1. BIOCHAM

Participants: François Fages, Sylvain Soliman.

The Biochemical Abstract Machine BIOCHAM is a modeling and validation environment for molecular systems biology. BIOCHAM provides precise semantics to biomolecular interaction maps at three abstraction levels:

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

Based on this formal framework, BIOCHAM offers:

- a compositional rule-based language for modeling biochemical systems, allowing patterns and kinetic expressions when numerical data are available, compatible with the Systems Biology Markup Language SBML;
- numerical and boolean simulators (Rosenbrock's method for the differential semantics, Gillespie's algorithm with tau lipping for the stochastic semantics);

- a temporal logic language (CTL for qualitative models and LTL(R) 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 [22] and even reaction rules from temporal logic properties of the system;
- automatic conservation law detection, through constraint-based structural analysis of the underlying Petri-net [23].

BIOCHAM is fully implemented in GNU-Prolog and interfaced to the state-of-the-art symbolic model checker NuSMV and to the optimization tool CMAES.

5.2. 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 LLCC 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 preprocessor for CHR implemented in Prolog.

5.3. 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.

6. New Results

6.1. Design and Implementation of SiLCC and CHRat Programming Languages

Participants: Marcos Aurélio, François Fages, Cleyton Mario de Oliveira Rodrigues, Thierry Martinez, Sylvain Soliman.

We are developing SiLCC an imperative and concurrent constraint programming language based on a single paradigm: the one of Vijay Saraswat's concurrent constraint programming extended with constraint systems based on Jean-Yves Girard's Linear Logic. In the late 90's we developed the theory of this extension and we are now working on its implementation.

From a constraint programming point of view, the unique combination of constraint programming with imperative features opens many new possibilities, among which:

- the capability of programming constraint solvers in the language, making them extensible by the user,
- making a fully bootstrapped implementation of a constraint programming language (for the first time since Prolog)
- combining constraint reasoning with state change;
- embedding program declarations, modules and closures as agents;
- proving program correctness using Linear Logic.

The main step realized this year has been done in the framework of the well-known Constraint Handling Rules (CHR) language of Tom Fruhwirth which share many similarities with SiLCC. In [12], [13], we introduce a modular version of the Constraint Handling Rules language CHR, called CHRat for modular CHR with *ask* and *tell*. Any constraint defined in a CHRat component can be reused both in rules and guards in another CHRat component to define new constraint solvers. Unlike previous work on modular CHR, our approach is completely general as it does not rely on an automatic derivation of conditions for checking entailment in guards, but on a programming discipline for defining both satisfiability (*tell*) and entailment (*ask*) checks by CHRat rules for each constraint. We define the operational and declarative semantics of CHRat, provide a transformation of CHRat components to flat CHR programs, and prove the preservation of the semantics. We then provide examples of the modularization of classical CHR constraint solvers.

In [10], we show how default reasoning and negation as failure can be integrated in CHR with disjunction.

6.2. Design and Implementation of the Rules2CP Modeling Language

Participants: François Fages, Julien Martin.

In the framework of the Net-WMS European project, we study higher-dimensional bin packing problems and placement constraints taking into account specific industrial requirements. In [15], [14], [31], we introduce a general purpose rule-based modeling language for constraint programming, named Rules2CP. One orignality of Rules2CP as a modeling language is that it allows us to express search strategies and heuristics as preference orderings on variables, values, and *and/or* formulae. This language is used in the project to define the Packing Knowledge Modeling Language PKML and express non-pure bin packing problems including common sense, physical and industrial requirements with rules. PKML rules are translated to constraint programs with the Rules2CP compiler. Furthermore, a large subset of PKML can be very efficiently compiled in the geometrical constraint kernel geost [11], [30].

6.3. Traces

Participant: Pierre Deransart.

It is common understanding that a process equipped with a tracer produces a single trace. It is indeed here what we call *actual trace*, the one that has a physical sense. It is less obvious to involve another trace that we qualify of *virtual* because it has no physical existence but only a conceptual one, which results from an abstraction of observed artefacts. The virtual trace can be seen in two ways: as a result of a succession of abstract states of the observed process equipped with a tracer (observational semantics), or as an interpretation of the events of the actual trace (Interpretative Semantics). It is these relationships between these two forms of traces that we study here. This conceptual loop of trace construction is the basis of the way trace are practically elaborated with the purpose to understand observed processes.

This approach is based on the concept of *full trace* (actual or virtual), full in the sense that the totality of knowledge regarding the observed process is there explicitly or implicitly contained. This constitutes a basis for studying the modular construction of tracers and traces, using only the notions of trace enrichment, sub-trace, fusion, trace abstraction. We also study the notion of genericity of a trace, i.e. the possibility to give semantics to a tracer, which covers a family of observed processes.

We started to elaborate a general theory of trace construction 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 are currently investigating the use of the fluent calculus as modeling tool for the observational semantics in the framework of the projets C4RBCP. At the moment only working documents have been produced [32].

6.4. Petri Net Representation of Biological Networks

Participants: François Fages, Sylvain Soliman, Denis Thieffry.

In [23], we present a way to compute the minimal semi-positive invariants of a Petri net representing a biological reaction system, as a Constraint Satisfaction Problem. The use of Petri-nets to manipulate reaction models,and make available a variety of tools is quite old, and recently analyses based on invariant computation for biological models have become more and more frequent, especially in the context of module decomposition. In our case, this analysis brings both qualitative and quantitative information on the models, in the form of conservation laws and consistency checking, thanks to finite domain constraint programming. It is noticeable that some of the most recent optimizations of standard invariant computation techniques in Petri-nets correspond to well-known techniques in CSPs, like symmetry-breaking. A simple prototype based on GNU-Prolog's FD solver, and including symmetry detection and breaking, was incorporated into the BIOCHAM modelling environment.

In [2], we show how the Petri Net approach to modelling can be extended to gene regulatory networks.

6.5. Reaction Models and Influence Graphs

Participants: François Fages, Sylvain Soliman, Denis Thieffry.

Biologists use diagrams to represent interactions between molecular species, and on the computer, diagrammatic notations are also more and more employed in interactive maps. These diagrams are fundamentally of two types: reaction graphs and positive/negative influence graphs. The analysis of circuits in the influence graphs has been introduced by René Thomas in the late 70's with some conjectures on necessary conditions for oscillations (homeostasie) and multistability (cell differentiation). These conjectures have been proven under various conditions in the setting of ordinary differential setting.equations, and more recently in [8] by Rémy, Ruet and Thieffry in the setting of boolean logical models.

In [18], we study the formal relationship between reaction graphs and influence graphs. We consider systems of biochemical reactions with kinetic expressions, as written in the Systems Biology Markup Language SBML, and interpreted by a system of Ordinary Differential Equations over molecular concentrations. We show that under a general condition of increasing monotonicity of the kinetic expressions, and in absence of both positive and negative influences between a pair of molecules, the influence graph inferred from the stoichiometric coefficients of the reactions is equal to the one defined by the signs of the coefficients of the Jacobian matrix. Under these conditions, satisfied by mass action law, Michaelis-Menten and Hill kinetics, the influence graph is thus independent of the precise kinetic expressions, and is computable in linear time in the number of reactions. We apply these results to Kohn's map of the mammalian cell cycle (500 variables and 800 rules) and to the MAPK signalling cascade. Then we propose a syntax for denoting antagonists in reaction rules and generalize our results to this setting.

6.6. Abstract Interpretation for Systems Biology

Participants: François Fages, Sylvain Soliman.

Abstract interpretation is a theory of abstraction that has been introduced for the analysis of programs. In particular, it has proved useful for organizing the multiple semantics of a given programming language in a hierarchy of semantics corresponding to different detail levels, and for defining type systems for programming languages and program analyzers in software engineering. We have investigated the application of these concepts to systems biology formalisms.

More specifically, we consider the Systems Biology Markup Language SBML, and the Biochemical Abstract Machine BIOCHAM with its differential, stochastic, discrete and boolean semantics [17]. In [4], we show how all of these different semantics, except the differential one, can be formally related by simple Galois connections. This provides a simple algebraic setting for relating the different interpretations of biochemical networks, and a formal ground for conducting precise analyses. In particular, we study the inference/checking of protein functions, influence graphs and compartment topology in reaction models.

6.7. Temporal Logic Constraint Solving in QFLTL(R)

Participants: François Fages, Aurélien Rizk.

Temporal logics and model-checking are at the core of BIOCHAM to express biological properties of complex biochemical systems and automatically verify their satisfaction in both qualitative and quantitative models. In [3], we go beyond model-checking and present a constraint solving algorithm for quantifier-free first-order temporal logic formulae with constraints over the reals, denoted by QFLTL(R). This algorithm computes the domain of the real valued variables occurring in a formula that makes it true in a model. We illustrate this approach for the automatic generation of a temporal logic specification from biological data time series. We provide a set of biologically relevant patterns of formulae, and apply them to numerical data time series of models of the cell cycle control and MAPK signal transduction. We show in these examples that this approach infers automatically semi-qualititave semi-quantitative information about concentration thresholds, amplitude of oscillations, stability properties, checkpoints and influences between species.

6.8. Parameter Search and Robustness Analysis w.r.t. Temporal Logic Properties

Participants: Grégory Batt, François Fages, Sylvain Soliman, Aurélien Rizk.

Finding mathematical models satisfying a specification built from the formalization of biological experiments, is a central task of the modeller that techniques like model-checking help solving, in the qualitative but also in the quantitative case. In [22], we show how the previous method for QFLTL(R) constraint solving can be used to define a continuous degree of satisfaction of LTL(R) formulae in a given trace. We then show how such a satisfaction measure can be used as a fitness function with state-of-the-art search methods[1] in order to find biochemical kinetic parameter values satisfying a set of biological properties formalized in temporal logic. We also show how it can be used to define a measure of robustness of a biological model with respect to some specification. These novel methods are evaluated on models of the cell cycle and of the MAPK signalling cascade. In [26], [27], they are used to analyze a gene activation cascade in synthetic biology.

6.9. Temporal Logic Analysis of Gene Networks under Parameter Uncertainty

Participant: Grégory Batt.

The lack of precise numerical information for the values of biological parameters severely limits the development and analysis of models of genetic regulatory networks. To deal with this problem, we propose in [1], a method for the analysis of genetic regulatory networks under parameter uncertainty. We consider models based on piecewise-multiaffine differential equations, dynamical properties expressed in temporal logic, and intervals for the values of uncertain parameters. The problem is then either to guarantee that the system satisfies the expected properties for every possible parameter value – the corresponding parameter set is then called valid – or to find valid subsets of a given parameter set. The proposed method uses discrete abstractions and model checking, and allows for efficient search of the parameter space. However, the abstraction process creates spurious behaviors in the abstract systems, along which time does not progress. Consequently, the verification of liveness properties, expressing that something will eventually happen, and implicitly assuming progress of time, often fails. A solution to this second problem is proposed using the notion of transient regions. This approach has been implemented in a tool for robust verification of gene networks (RoVerGeNe) and applied to the tuning of a synthetic network built in *E. coli*.

6.10. Approximating Continuous Systems by Timed Automata

Participant: Grégory Batt.

The above-mentionned work aims at overapproximating a continuous dynamical system by an automaton. To obtain finer abstractions, we develop a new technique for over-approximating (in the sense of timed trace inclusion) continuous dynamical systems by *timed automata* [21]. The essence of our technique is the partition of the state space into cubes and the allocation of a clock for each dimension. This allows us to get much better approximations of the behavior. We specialize this technique to multi-affine systems, a class of nonlinear systems of primary importance for the analysis of biochemical systems and demonstrate its applicability on an example taken from synthetic biology.

[1] namely the Covariance Matrix Adaptation Evolutionary Strategy CMAES of Nikolaus Hansen from the TAO project-team.

6.11. Coupled Model of the Cell Cycle and the Circadian Cycle in Mammalian Cells

Participants: François Fages, Sriram Krishnamachari, Aurélien Rizk, Sylvain Soliman, Denis Thieffry.

Recent advances in cancer chronotherapy techniques support the evidence that there exist some links between the cell and the circadian cycles. Both cycles have been successfully modeled, however, as of today, there are no precise models describing the coupling of the two cycles. One purpose of a coupled model is to better understand how to efficiently target malignant cells depending on the phase of the day. This is at the heart of our participation in the EU STREP project TEMPO.

Building on our previous model of the entrainment in period of the cell cycle by the circadian cycle, our model is currently composed of a model the circadian cycle from Leloup and Goldbeter, a model of the mammalian cell cycle from Novak and Tyson, and a model fo the effect of the Irinotecan drug. The new features of BIOCHAM for parameter search [22], [3], [28] are used to adjust the coupling of these models.

In [19], different logical models of the cell cycle in eukaryotes are compared, and in [20] a modular approach is proposed for the logical modelling of the budding yeast cell cycle.

6.12. Connectivity and Dynamics of the FSH Signalling Network in Granulosa Cells

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

In collaboration with Frédérique Clément (SISYPHE) and Eric Reiter (UMR CNRS-INRA 6175), in the framework of the INRA AgroBI INSIGHT project, we analyse the connectivity and dynamics of the FSH signalling network in its target cells, and embedding the network within a multi-scale representation, from the molecular up to the organic level. We are examining the relative contributions of different pathways to the cell response to FSH signal, in order to determine how each pathway controls downstream cascades and which mechanisms are involved in the transition between different cellular states [25]. BIOCHAM is used first at the boolean level, to formalise the network of interactions corresponding to the FSH-induced signalling events on the cellular scale, and then at the differential semantics level, to predict continuous dynamical behaviors. In order to find and fine-tune the structure of the network and the values of the kinetic parameters, model-checking techniques are applied to undertake a systematic comparison between the model behaviour and the results of experiments. In particular, the new method for parameter search [22], [3], [28] provides better performance than classical numerical methods in this context.

6.13. Qualitative dynamical modelling of biological regulatory networks

Participant: Denis Thieffry.

The logical analysis of gene regulatory networks provides surprisingly informative results on their qualitative dynamical properties. This approach is developped in several study cases: in [5] for the analysis of the formation of the anterior-posterior compartment boundary in the Drosophila wing imaginal disc, in [9] for the segmentation of the fly embryo and the logical analysis of the role of the Segment Polarity cross-regulatory module, and in [7] for the functional organisation of *E. coli* transcriptional regulatory network

7. Other Grants and Activities

7.1. National contracts

- ANR project CALAMAR (2008-2010) “Compositional modelling and Analysis of LArge MoleculAr Regulatory networks - application to the control of human cell proliferation.”, coordinated by C. Chaouiya, INSERM Marseille, L. Calzone, Institut Curie, Paris,

- INRA project AgroBi (2006-2008) on the" modeling of FSH signaling", coordinated by Eric Reiter, INRA Tours, with F. Clément SISYPHE.
- 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.

7.2. European contracts

- 6th PCRD STREP Net-WMS (2006-2009) 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;
- 6th PCRD STREP TEMPO (2006-2009) on "temporal genomics for tailored chronotherapeutics", coordinated by Francis Lévi at INSERM Villejuif, with J. Clairambault BANG, F. Delaunay, CNRS Sophia-Antipolis, L. Meijer, CNRS Roscoff, CINBO Chieti, Hospital Services Aprilla, Helios Biosciences, Physiomics.
- 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.

7.3. International contracts

- Project C4RBCP, with Jacques Robin from the UFPE, in the framework of the bilateral cooperation with Brazil (funded under the FACEPE/INRIA agreement). In this project, we investigate the synergy between two hitherto unrelated areas of computer science: Rule-Based Constraint Programming (RBCP) and Component-Based Software Engineering (CBSE). These two areas bring complementary principles to the general issue of software reuse for Automated Reasoning (AR). We investigate how these CBSE concepts can be adapted to the RBPC language CHR$\vee$(Constraint Handling Rules with Disjunctive bodies, a simple yet powerful extension of CHR) and implemented in the adaptive CHR$\vee$ engine CHROME (CHR Online Model-driven Engine) currently under development at CIn-UFPE. The project is driven by complementary skills of both teams: CBSE at UFPe and Constraint Logic Programming, CHR and Trace development methodology at INRIA.

7.4. Invitations

Have been invited for short visits :

- Jacques Cohen, Brandeis University, USA
- Elisabetta De Maria, University of Udine, Italy
- Jacques Robin, Universidade Federal de Pernambuco, Brazil
- Jacques-Alexandre Sepulchre, CNRS, INLN Nice

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 are given by Contraintes members:

- 24h M2 course on *Constraint Programming*, Master Parisien de Recherche en Informatique (MPRI) Sylvain Soliman (18h, resp.), François Fages (6h).
- 48h M2 course on *Computational Systems Biology*, Master Parisien de Recherche en Informatique (MPRI) François Fages (12h, co-resp.), Grégory Batt (12h).
- Master modules *Programming applied to Biology and Dynamical modelling of biological regulatory networks*, University of the Mediterranean, Marseille, Denis Thieffry (30h).
- L1 course on *Introduction à l'informatique (C2i)* Université Paris 1 Panthéon-Sorbonne, Thierry Martinez (48h)
- L1 course on *Introduction to Programming Languages*, Licence Mathématiques, Informatique, Technologies, Sciences de l'Information et de la Communication (MITSIC), University of Paris 8 Vincennes–Saint-Denis, Julien Martin (40h)
- L1 TD *Mathematics*, Université FranÃ§ois Rabelais, Tours, Domitille Heitzler (22h)

8.2. Leadership within scientific community

- Grégory Batt was an instructor of the Paris iGEM team and a judge at the 5th iGEM competition on Synthetic Biology, MIT, Boston USA. He co-organized a satellite workshop on Dynamical Modelling and Simulation of Biological Networks of the JOBIM conference, Lille, July 2008.
- 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 worked as "Brazil Correspondent" in the DRI (INRIA's International Relations Direction) and organized several INRIA visits and activities related to INRIA-Brazil scientific cooperation Brazil.
- François Fages is member of the Editorial Board of RAIRO Operations Research and since this year, member of the Steering Committee of the Computational Methods in Systems Biology (CMSB), member of the Scientific Committee of the Integrative Post-Genomique (IPG) conference, and co-organizer with Alfonso Jaramillo, Ecole Polytechnique, and Franck Molina, CNRS Montpellier, of the Epigenomics project "New tools for Synthetic Biology", at the Genopole of Evry. Up to June 2008, he was the Chairman of the ERCIM Working Group on Constraints.

  François Fages was the Conference Chair with Laurent Perron, ILOG, of the Fifth International Conference on Integration of AI and OR Techniques in Constraint Programming for Combinatorial Optimization Problems CP-AI-OR'08 (150 part.), Paris, May 2008, and the Conference Chair with Marc Vidal, Harvard Medical School, of the European American Innovation Day on "From Modeling to Engineering Biological Processes" EAID'08 (150 part.), Boston, USA, December 2008. He co-organized with Nicolas Beldiceanu and Mats Carlsson the first International Workshop on Bin Packing and Placement Constraints BPPC'08, and with Rolf Backofen and Agostino Dovier the International Workshop on Constraints in Bioinformatics WCB'08, both associated to CP-AI-OR'08 in Paris, May 2008.

  François Fages gave a lecture at Collège de France in the framework of Gérard Berry Chair, on "Machines abstraites, vérification formelle et biochimie cellulaire", Paris, May 2008.
- Aurélien Rizk participated as advisor for the Paris team in the 5th IGEM competition on Synthetic Biology organized by the MIT, USA.
- Sylvain Soliman was the Secretary of the ERCIM Working Group on Constraints up to June 2008. with François Fages and Francesca Rossi ha was editor of a special issue of the Recent Advances in Constraints LNCS series with revised selected papers from CSCLP 2007 [29].

- Denis Thieffry is Vice-Chair of the Scientific Committee of the ANR (French Agence Nationale pour la Recherche) SYSCOMM (Complex Systems) funding program, 2008, Associated Editor of BioSystems (since July 2008), member of the CNRS ATIP Scientific Committee (young group leader grant scheme) Chair of Systems Biology call, member of the INSERM Workshop Scientific Committee, and member of the scientific committees of the European Conference of Computational Biology 2008.

  Denis Thieffry organized with K Leon, R Mulet and G Carneiro, the 2nd Havana School on Biological Networks, La Havana, Cuba., November 2008, and with S. Brauckmann, C. Brandt and GB Müller, an interdisciplinary workshop on BioGraphs (II), Max Planck Institute for History of Sciences, Berlin, Germany. June 2008.

9. Bibliography

Year Publications

Articles in International Peer-Reviewed Journal

[1] G. BATT, C. BELTA, R. WEISS. *Temporal logic analysis of gene networks under parameter uncertainty*, in "IEEE Transactions on Circuits and Systems and IEEE Transactions on Automatic Control", vol. 58, n^{o} Joint Special Issue on Systems Biology, 2008, p. 215–229.

[2] C. CHAOUIYA, E. REMY, D. THIEFFRY. *Petri net modelling of biological regulatory networks*, in "Journal of Discrete Algorithms", vol. 6, n^{o} 2, June 2008, p. 165–177.

[3] F. FAGES, A. RIZK. *On Temporal Logic Constraint Solving for the Analysis of Numerical Data Time series*, in "Theoretical Computer Science", vol. 408, n^{o} 1, November 2008, p. 55–65.

[4] F. FAGES, S. SOLIMAN. *Abstract Interpretation and Types for Systems Biology*, in "Theoretical Computer Science", vol. 403, n^{o} 1, 2008, p. 52–70.

[5] A.-G. GONZÁLEZ, C. CHAOUIYA, D. THIEFFRY. *Qualitative dynamical modelling of the formation of the anterior-posterior compartment boundary in the Drosophila wing imaginal disc*, in "Bioinformatics", vol. 24, 2008, p. 234–240.

[6] S. KRISHNAMACHARI, F. FAGES, S. SOLIMAN. *Dynamics of the interlocked positive feedback loops explaining the robust epigenetic switching in Candida albicans*, in "Journal of Theoretical Biology", submitted 2008.

[7] A. MARTÍNEZ-ANTONIO, S. C. JANGA, D. THIEFFRY. *Functional organisation of Escherichia coli transcriptional regulatory network*, in "Journal of Molecular Biology", vol. 381, n^{o} 1, 2008, p. 238–247.

[8] E. REMY, P. RUET, D. THIEFFRY. *Graphic requirements for multistability and attractive cycles in a Boolean dynamical framework*, in "Advances in Applied Mathematics", vol. 41, n^{o} 3, 2008, p. 335–350.

[9] L. SÁNCHEZ, C. CHAOUIYA, D. THIEFFRY. *Segmenting the fly embryo: logical analysis of the role of the Segment Polarity cross-regulatory module*, in "International Journal of Developmental Biology", vol. 52, 2008, p. 1059–1075.

International Peer-Reviewed Conference/Proceedings

[10] M. AMEDIA, F. FAGES, J. ROBIN. *Default Reasoning in CHR∨*, in "Proceedings of the fifth Constraint Handling Rules Workshop CHR'08", T. FRÜHWIRTH, T. SCHRIJVERS (editors), 2008.

[11] M. CARLSSON, N. BELDICEANU, J. MARTIN. *A Geometric Constraint over k-Dimensional Objects and Shapes Subject to Business Rules*, in "Proceedings of CP'2008", P. J. STUCKEY (editor), Lecture Notes in Computer Science, vol. 5202, Springer, 2008, p. 220–234.

[12] F. FAGES, C. M. DE OLIVEIRA RODRIGUES, T. MARTINEZ. *Modular CHR with ask and tell*, in "Proceedings of the fifth Constraint Handling Rules Workshop CHR'08", T. FRÜHWIRTH, T. SCHRIJVERS (editors), 2008.

[13] F. FAGES, C. M. DE OLIVEIRA RODRIGUES, T. MARTINEZ. *Modular CHR with ask and tell*, in "Proceedings of the 13th International Workshop on Constraint Solving and Constraint Programming CSCLP'08, Roma, Italy", 2008.

[14] F. FAGES, J. MARTIN. *Des règles aux contraintes avec le langage de modélisation Rules2CP*, in "Actes de Journées Francophones de Programmation par Contraintes JFPC'08, Nantes, France", 2008.

[15] F. FAGES, J. MARTIN. *From Rules to Constraint Programs with the Rules2CP modeling language*, in "Proceedings of the 13th International Workshop on Constraint Solving and Constraint Programming CSCLP'08, Roma, Italy", 2008.

[16] F. FAGES, A. RIZK. *Analyse de Séries Temporelles par Résolution de Contraintes de Logique Temporelle*, in "Actes de Journées Francophones de Programmation par Contraintes JFPC'08, Nantes, France", 2008.

[17] F. FAGES, S. SOLIMAN. *Formal Cell Biology in BIOCHAM*, in "8th Int. School on Formal Methods for the Design of Computer, Communication and Software Systems: Computational Systems Biology SFM'08, Bertinoro, Italy", M. BERNARDO, P. DEGANO, G. ZAVATTARO (editors), Lecture Notes in Computer Science, vol. 5016, Springer-Verlag, February 2008, p. 54–80.

[18] F. FAGES, S. SOLIMAN. *From reaction models to influence graphs and back: a theorem*, in "Proceedings of Formal Methods in Systems Biology FMSB'08", Lecture Notes in Computer Science, n^{o} 5054, Springer-Verlag, February 2008.

[19] A. FAURÉ, A. NALDI, C. CHAOUIYA, A. CILIBERTO, D. THIEFFRY. *Comparative analysis of logical models of the cell cycle in eucaryotes*, in "Proceedings of the International Conference on Systems Biology ICSB'08", 2008.

[20] A. FAURÉ, A. NALDI, F. LOPEZ, C. CHAOUIYA, A. CILIBERTO, D. THIEFFRY. *Logical modelling of the budding yeast cell cycle: a modular approach.*, in "Proceedings of European Conference on Computational Biology ECCB'08", 2008.

[21] O. MALER, G. BATT. *Approximating continuous systems by timed automata*, in "First International Workshop on Formal Methods in Systems Biology, FMSB'08", J. FISHER (editor), Lecture Notes in Bioinformatics, vol. 5054, Springer, 2008, p. 77–89.

[22] A. RIZK, G. BATT, F. FAGES, S. SOLIMAN. *On a Continuous Degree of Satisfaction of Temporal Logic Formulae with Applications to Systems Biology*, in "CMSB'08: Proceedings of the fourth international conference on Computational Methods in Systems Biology", M. HEINER, A. UHRMACHER (editors), Lecture Notes in Computer Science, vol. 5307, Springer-Verlag, October 2008, p. 251–268, http://contraintes.inria.fr/~fages/Papers/RGFS08cmsb.pdf.

[23] S. SOLIMAN. *Finding minimal P/T-invariants as a CSP*, in "Proceedings of the fourth Workshop on Constraint Based Methods for Bioinformatics WCB'08, associated to CPAIOR'08", May 2008, http://wcb08.dimi.uniud.it/PAPERS/Soliman.pdf.

Workshops without Proceedings

[24] F. FAGES. *A logical paradigm for systems biology applied to modeling tool design*, in "European American Innovation Day EAID'08 From Modeling to Engineering Biological Processes, Harvard Medical School, Boston, USA", December 2008.

[25] D. HEITZLER, G. DURAND, L. DUPUY, C. GAUTHIER, V. PIKETTY, P. CRÉPIEUX, A. RIZK, S. SOLIMAN, F. FAGES, F. CLÉMENT, E. REITER. *Modelling of FSHR-induced Signalling Network*, in "Poster, International Conference on Gonadotropins and Receptors IGCR'08, London, UK", 2008.

[26] A. RIZK, G. BATT, F. FAGES, S. SOLIMAN. *Towards a general computational method for robustness analysis*, in "International Conference Frontiers in Synthetic Biology, Boston", 2008.

[27] A. RIZK, G. BATT, F. FAGES, S. SOLIMAN. *Towards a general computational method for robustness analysis*, in "Poster, International Conference Synthetic Biology 4.0, Hong Kong", 2008.

Scientific Books (or Scientific Book chapters)

[28] F. FAGES, S. SOLIMAN. *Model Revision from Temporal Logic Properties in Systems Biology*, in "Probabilistic Inductive Logic Programming", Lecture Notes in Computer Science, vol. 4911, Springer-Verlag, 2008, p. 287–304.

Books or Proceedings Editing

[29] F. FAGES, S. SOLIMAN, F. ROSSI (editors). *Proceedings of the 12th Annual ERCIM International Workshop on Constraint Solving and Constraint Logic Programming CSCLP'07*, Lecture Notes in Computer Science, vol. 5129, Springer-Verlag, Rocquencourt, France, 2008.

Research Reports

[30] M. CARLSSON, N. BELDICEANU, J. MARTIN. *A Geometric Constraint over k-Dimensional Objects and Shapes Subject to Business Rules*, SICS Technical Report, n^{o} T2008:04, Swedish Institute of Computer Science, 2008.

[31] F. FAGES, J. MARTIN. *From Rules to Constraint Programs with the Rules2CP Modelling Language*, INRIA Research Report, n^{o} RR-6495, Institut National de Recherche en Informatique, April 2008, http://hal.inria.fr/inria-00270326/fr/.

Other Publications

[32] P. DERANSART. *Semantic View of Tracers and their Traces, and Applications*, Document interne, August 2008, http://contraintes.inria.fr/~deransar.