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INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Project-Team Contraintes

Constraint Programming

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Theme : Programs, Verification and Proofs

Table of contents

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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 processes in living cells, with logic programming concepts and program verification techniques.

2.2. Highlight: Model-checking generalized to constraint solving

In [16], we present a fundamental generalization of model-checking to temporal logic constraint solving, by considering temporal logic formulae with free variables over some domain D, and by computing a validity domain for the variables rather than a truth value for the formula. When D is a metric space, this allows us to define a continuous degree of satisfaction for a temporal logic formula in a given Kripke structure, opening up the field of model-checking to optimization.

This work originates from previous work in BIOCHAM on reverse engineering problems coming from systems biology. The algorithm used in BIOCHAM for solving Linear Time Logic constraints over the reals (LTL(R)) has been generalized to a fixpoint algorithm for branching time logics, namely for the quantifier-free first-order Computation Tree Logic over some arbitrary domain D (QFCTL(D)).

Our result shows that any constraint solver over some domain D can be lifted to a QFCTL(D) constraint solver over a finite Kripke structure over D, and that optimization techniques can be used to synthesize or parameterize deterministic as well as non-deterministic systems, in order to satisfy high-level QFCTL(D) specifications.

2.3. Highlight: Robustness measure of temporal logic properties

Robustness is the capacity of a system to maintain a function in the face of perturbations. It is essential for the correct functioning of natural as well as engineered biological systems. Robustness is generally defined in an *ad-hoc* problem-dependent manner, thus hampering the fruitful development of a theory of biological robustness, advocated by Kitano [Mol Syst Biol, 3:137, 2007].

In [7], we propose a general definition of robustness that applies to any biological function expressible in temporal logic LTL, and to broad model classes and perturbation types. Moreover, we propose a computational approach and an implementation in BIOCHAM 2.8 for the automated estimation of the robustness of a given behavior with respect to a given set of perturbations. The applicability and biological relevance of our approach is demonstrated by testing and improving the robustness of the timed behavior of a synthetic transcriptional cascade that could be used as a biological timer for synthetic biology applications.

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 :

$$\textit{biological model} = \textit{state transition system},$$
$$\textit{biological property} = \textit{temporal logic formula},$$
$$\textit{validation} = \textit{model-checking},$$
$$\textit{inference} = \textit{constraint solving}.$$

Our main research axis is thus the application of logic programming concepts and program verification techniques to the analysis 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 work 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. In this context, we have developed a rule-based modeling language, called Rules2CP, to express requirements in a declarative and flexible manner, and its compiler to efficient constraint programs using a global constraint dedicated to geometrical placement problems in high dimensions, together with reified finite-domain constraints.

4.2. In-silico cell processes

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 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 from temporal logic specification of the system's behavior as observed in biological experiments. 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 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 [5].

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 before his move to Lyon, 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.Along the same line of research, but in a different context, we collaborate with Pascal Hersen and Samuel Bottani, biophysicists at the Matière and Systèmes complexes lab, CNRS/Paris Diderot University, to design a prototypic platform and develop control software for the real-time control of gene expression in yeast.

5. Software

5.1. BIOCHAM

Participants: François Fages, Aurélien Rizk, Sylvain Soliman.

The Biochemical Abstract Machine BIOCHAM is a modeling and validation environment for molecular systems biology [30], under development since 2001, and distributed as open-source since 2003. Current version is v2.8.

BIOCHAM is compatible with the Systems Biology Markup Language (SBML) and adds precise semantics to biomolecular interaction maps at 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:

- a compositional rule-based language for modeling biochemical systems, allowing patterns for expressing set of rules in a compact form;
- numerical as well as 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 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 of the system;
- automatic conservation law detection, through constraint-based structural analysis of the underlying Petri-net.

  BIOCHAM was used in synergy with Beta WB and GINsim by the winning team of the *Biological Modelling Competition* of the *Formal Methods in Molecular Biology* workshop held in Dagstuhl in Feb. 2009.

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

5.2. Rules2CP

Participants: François Fages, Julien Martin, Thierry Martinez.

Rules2CP is a rule-based modelling language for constraint programming. Rules2CP is under development since 2006, and distributed as open-source since 2009.

Unlike other modelling languages, 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. We show that this is sufficient to model 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 rules' left-hand sides.

The expressiveness of Rules2CP is illustrated with a complete library for packing problems, called PKML, 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. 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 bootstrapped preprocessor for CHR implemented in Prolog.

5.4. 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.

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. 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 Constraint Handling Rules (CHR) language of Thom Frühwirth shares many similarities with SiLCC. CHR (and its modular version CHRat [21]) and SiLCC are based on the same 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 [18], 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.

6.2. Rule-based Modeling of Constraint Satisfaction Problems

Participants: François Fages, Curtis Fonger, Julien Martin, Thierry Martinez, Surinderjeet Singh.

Rules2CP [29] is a rule-based modeling language which allows easy modelling of constraint satisfaction problems, together with specifications for search strategies and heuristic choice criterias. In [14], we describe the language and its compilation to constraint programs with a term rewriting system.

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 to study and solve higher-dimensional bin packing problems and placement constraints, including common sense, physical and industrial requirements expressed by rules [28], [27], [23], [32].

Furthermore, in [37], we look at the application of Rules2CP to solve Open-Shop Problem, which is at the core of many scheduling problems. In this approach we are able to solve many of the Open Shop instances which have only been closed very recently with minimal effort.

6.3. Modelling Search in Rules2CP

Participants: François Fages, Julien Martin, Thierry Martinez, Surinderjeet Singh.

One originality of Rules2CP as a modeling language is that it allows us to express search tree and labeling ordering heuristics declaratively by pattern matching on rule left-hand sides' derivation [15]. The search trees are expressed by logical formulae, and heuristic choice criteria are defined by preference orderings on variables and formulae. This approach to specifying ordering heuristics by pattern matching should be applicable to other modeling languages that use definitions, such as Zinc for instance.

In order to deal with dynamic ordering criteria, a new compilation scheme for Rules2CP is introduced in [17] for generating procedural constraint programming code, 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.

6.4. Symmetry Detection and Breaking in Constraint Satisfaction Problems

Participants: François Fages, Valentin Gatien-Baron.

In [33], a novel symmetry detection procedure is introduced for detecting symmetries not only in instanciated constraint satisfaction problems but in parametric constraint satisfaction programs or models. The method proceeds by normalization of expressions with a term rewriting system. The evaluation of the method on classical benchmark problems, expressed in the OPL modeling language, shows that the interesting symmetries that are easy to break with constraints are detected in a few seconds, or minutes for the generalized perfect square problem.

6.5. Trace Development Methodology

Participants: Pierre Deransart, Rafaël Oliveira.

We worked on a general theory of trace design 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 [39].

One of the important aspect of this research is to give a proper semantics to a trace, called "observational semantics" (OS). We followed two ways: the use of the simple fluent calculus as formalism for the OS, and the software component modeling approach to combine traces of components [12]. This approach is presently used to specify and implement a versatile trace r of CHR^v with several extensions, in the framework called CHROME-REF [31]. It includes three main component s: CHROME (input process), a Trace Driver (intermediator and trace query processor) and a Trace Analyzer (front-end). It is a useful experimental environment to contribute to elaborate a generic framework to generate explanatory traces for constraint solving and rule-based reasoning systems, as presented in [36].

6.6. Petri Net Representation of Biological Networks

Participants: François Fages, Faten Nabli, Sylvain Soliman, Denis Thieffry.

In [20], 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 (CSP). 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.

Other uses of Petri Nets structural properties computation were investigated in [35], and most notably an incomplete symbolic search for steady states based on T-invariants computation and other structural properties.

These developments are focused on the applications of the CALAMAR ANR project, where large models of the E2F/RB pathway and of other cancer-related processes are studied. This project also dwelves, on the formal side, on relationships between different formalisms, whether BIOCHAM-like reaction-centered, or regulation-centered like logical models [1] [6], the Petri Net level being common to both frameworks.

6.7. Model Reductions by Graph Transformations

Participants: François Fages, Steven Gay, 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 necessary conditions for oscillations (homeostasie) and multistability (cell differentiation).

In [19], model reduction techniques preserving the circuits in the influence graph are investigated and evaluated on a gene regulatory network responsible for segment polarity in Drosophilia. In [34], general structural model reduction techniques based on graph edition operations are investigated and evaluated on models of cell signalling. The perspective of these preliminary studies is to relate models at different levels of details by formal graph transformation operations, and design systematic model reduction/expansion strategies.

In [38], an extension of the syntax of reaction rules with antagonists is proposed for SBML and BIOCHAM in order to make visible in the rules the inhibitors of a reaction that are often hidden in the kinetic expression. This extension allows us to efficiently compute the influence graph of a reaction model and to compare models at different levels of details.

6.8. Analysis of Interlocked Positive Feedback Loops

Participants: François Fages, Sylvain Soliman.

The two element mutual activation and inhibitory positive feedback loops are a common motifs that occur in many biological systems in both isolated and interlocked form, as for example,in the cell division cycle and thymus differentiation in eukaryotes.

In[5], the properties of three element interlocked positive feedback loops that embeds both mutual activation and inhibition are studied indepth for their bistable properties by performing bifurcation and stochastic analysis. Codimension one and two bifurcations reveal important properties like robustness to parameter variations and adaptability under various conditions by its ability to fine tune the threshold to a wide range of values and to maintain a wide bistable regime. Furthermore, we show that in the interlocked circuit, mutual inhibition controls the decision to switch from OFF to ON state, while mutual activation enforces the decision. This view is supported through a concrete biological example Candida albicans, a human fungal pathogen that can exist in two distinctive cell types: one in the default white state and the other in an opaque form. Stochastic switching between these two forms takes place due to the epigenetic alternation induced by the

transcriptional regulators in the circuit, albeit without any rearrangement of the nuclear chromosomes. The transcriptional regulators constitute interlocked mutualactivation and inhibition feedback circuits that provide adaptable threshold and wide bistable regime. These positive feedback loops are shown to be responsible for robust noise induced transitions without chattering, persistence of particular phenotypes for many generations and selective exhibition of onep articular form of phenotype when mutated. Finally, we propose for synthetic biology constructs touse interlocked positive feedback loops instead of two element positive feedback loops because they are better controlled than isolated mutual activation and mutual inhibition feedback circuits.

6.9. Temporal Logic Constraint Solving

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 particular, linear time logic constraints (QFLTL($\mathbb{R}$)) are used to formalize the global behavior of the system known from biological experiments, and infer the unknown parameter values of the model.

In [16] we have studied the abstract properties of this approach and have given a general constraint solving algorithm for branching time logics (CTL) over arbitrary computation domains D. We have shown that the QFCTL constraint satisfiability problem is decidable in finite Kripke structures over an arbitrary computation domain with a decidable language of constraints, i.e. that any constraint solver can be lifted to a temporal logic constraint solver over finite Kripke structures. We have presented a generic QFCTL constraint solver which computes validity domains for the free variables of a formula, in quadratic time in the number of states. We show that when D is a metric space, this allows us to define a continuous degree of satisfaction for a temporal logic formula in a given Kripke structure, opening up the field of model-checking to optimization, in a very general setting.

6.10. Parameter Search w.r.t. Temporal Logic Properties

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

In BIOCHAM, 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[1] in order to find unknown parameter values in a model satisfying a set of biological properties formalized in temporal logic [13]. 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.

The study of similar metrics and methods for stochastic processes is under investigation.

6.11. Robustness Analysis w.r.t. Temporal Logic Properties

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

In [7], we propose a general definition of robustness that applies to any biological function expressible in temporal logic LTL, and to broad model classes and perturbation types. This measure of the robustness of a given behavior with respect to a given set of perturbations can be estimated with a constraint solving method, implemented in BIOCHAM v2.8, for computing the continuous degree of satisfaction of QFLTL(R) formulae. The applicability and biological relevance of our approach is demonstrated by testing and improving the robustness of the timed behavior of a synthetic transcriptional cascade that could be used as a biological timer for synthetic biology applications. These novel methods are evaluated on models of the cell cycle and of the MAPK signalling cascade. In , they are used to analyze a gene activation cascade in synthetic biology.

6.12. Automated selection of PADE models by symbolic model checking

Participant: Grégory Batt.

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

Qualitative piecewise-affine differential equation (PADE) models offer an attractive formalism for representing genetic regulatory networks in absence of precise information on parameter values. Predictions on systems behaviors can be obtained in the form of a discrete state transition system simply by using parameter relative order. In this work, we encode in a symbolic way the transition relation of the graph and use symbolic model checkers to automatically select the set of models whose parameter order is consistent with a set of observations. Because in PADE systems the dynamics in a state may be defined with respect to the dynamics in neighbouring states, the main difficulty was to obtain a purely state-based encoding of the transition relation, similar to those used by model checkers. This approach is applied to a synthetic gene network built in *E. coli* for *in vivo* benchmarking of reverse-engineering and modeling approaches (IRMA). This work is done in collaboration with Hidde de Jong and Michel Page in the IBIS research group (INRIA Rhône-Alpes/UPMF).

6.13. Modeling the Cell Cycle

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

Recent advances in cancer chronotherapy techniques support the evidence that there exist some links between the cell cycle and the circadian clock genes [10]. 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. This is at the heart of our participation in the EU STREP project TEMPO in collaboration with the BANG project-team.

In [11], [24] we show how temporal logic constraints, and the new features of BIOCHAM for parameter search, can be used to couple dynamical models. 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.

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.

In [2], [3], purely qualitative models of the cell cycle are shown to provide other useful information, and surprisingly informative results. In [8], a model of the G1/S transition of the cell cycle is used to find targets for drug resistance.

One important perspective that is common to all this modeling work around the cell cycle is the promise of patient-tailored therapeutics [9].

6.14. Modeling G protein-Coupled Signal Transduction

Participants: François Fages, Steven Gay, 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 signalling network in its target cells, and embedding the network within a multi-scale representation, from the molecular up to the organic level.

We study 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.

A systems biology approach is followed using BIOCHAM's features for rule-based modeling with temporal logic constraints used for searching unknown kinetic parameter values. In [4], this approach is applied more generally to G protein-coupled receptor signalling which is of great importance in pharmacology.

7. Other Grants and Activities

7.1. National contracts

- ANR project CALAMAR (2009-2011) “Compositional modelling 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.

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.

7.3. International contracts

- FACEPE/INRIA project C4RBCP (2007-2009), with Jacques Robin from the UFPE, on “Constraint, Object and Rule based Reasoning Engine with Components and Tracing” in the framework of the bilateral cooperation with Brazil.

7.4. Invitations

Have been invited for short visits :

- Claudine Chaouiya, Instituto Gulbenkian de Ciência - Oeiras, Portugal
- Alexis Saurin, University of Torino, Italy

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) [26]. .
- 48h M2 course on *Computational Methods for Systemic and Synthetic Biology*, Master Parisien de Recherche en Informatique (MPRI) François Fages (12h, co-resp.) [25], Grégory Batt (12h).
- 24h M1/M2 course on *Computational Biology*, Master Approches Interdisciplinaires du Vivant (AIV), Grégory Batt (course and TD/TP), Sylvain Pradalier (TD/TP).
- 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 François Rabelais, Tours, Domitille Heitzler (22h)
- L1 TD on *Fondements de l'Informatique*, Université de Versailles-Saint-Quentin-en-Yvelines, Elisabetta De Maria (30h)

8.2. Leadership within scientific community

- Grégory Batt is member of the JOBIM 2009 program commitee, and was an instructor of the 2009 Paris iGEM team. The team won a Gold medal and a special price for Best Human Practices. He co-organized a workshop on constructing gene networks: observation, analysis and control and a satellite workshop on dynamical modelling and simulation of biological networks of the JOBIM conference, Nantes, June 2009.
- 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.

  Pierre Deransart co-organised with Jean-Loïc Delhaye (DPE) and Philippe Navaux of the University of Rio Grande do Sul (UFRGS) the coloquium COLIBRI (COLloque d'Informatique: BRésil / INRIA, Coopérations, Avancées et Défis), in the framework of the year of France in Brazil 2009. It happened 22-24th of July 2009, and around 150 researcher of both coutries have contributed.
- François Fages is member of the Editorial Board of RAIRO Operations Research, member of the Steering Committee of the Computational Methods in Systems Biology (CMSB) conference, member of the Scientific Counsil of the Integrative Post-Genomique (IPG) conference, co-organizer with Alfonso Jaramillo, CNRS Evry, and Franck Molina, CNRS Montpellier, of the Epigenomics project "New tools for Synthetic Biology", at the Genopole of Evry, and since October 09, member of the "Comité d'animation du domaine STIC pour les sciences de la vie et de l'environnement" of INRIA.

  François Fages co-organized with Nicolas Beldiceanu and Mats Carlsson the second International Workshop on Bin Packing and Placement Constraints BPPC'09, assocated to CP'09 in Lisbon Portugal. François Fages participated to a public meeting on "Enjeux cognitifs de la biologie synthétique" in April 2009 at Agora Beaubourg, Centre Georges Pompidou, Paris.
- 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 member of the Evaluation Committee AERES of the LIRMM, UMR CNRS University Montpellier 2. Sylvain Soliman was with François Fages and Francesca Rossi editor of a special issue of the Recent Advances in Constraints LNCS series with revised selected papers from CSCLP 2008 [22].

- 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.

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