Activity Report 2014

Team LIFEWARE

Computational systems biology and optimization

RESEARCH CENTER
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THEME
Computational Biology

Table of contents

Team LIFEWARE

Keywords: Systems Biology, Synthetic Biology, Rule-based Languages, Formal Methods, Optimization

Lifeware is a follow-up of the Contraintes project-team which stopped in 2013 December 31.

Creation of the Team: 2014 January 01.

1. Members

Research Scientists

François Fages [Team leader, Inria, Senior Researcher, HdR]
Grégory Batt [Inria, Researcher, HdR]
Sylvain Soliman [Inria, Researcher]

Engineers

François-Marie Floch [Inria ADT]
Philippe Morignot [Inria]
Thierry Martinez [Inria SED, part-time in Lifeware]

PhD Students

François Bertaux [Ecole Polytechnique, with EPI MAMBA]
Hui-Ju Chiang [National Taiwan University]
Xavier Duportet [Inria, until Jun 2014, with the Weiss lab (MIT)]
David Fournier [Cifre, General Electric Transportation, until Nov 2014]
Steven Gay [Post-Doc, Univ. Louvain la Neuve, Belgique]
Artémis Llamosi [CNRS, with MSC lab (CNRS/Paris7)]
Jean-Baptiste Lugagne [Inria, with MSC lab (CNRS/Paris7)]
Pauline Traynard [Ecole Polytechnique, with IBENS lab (ENS)]

Post-Doctoral Fellows

Szymon Stoma [Inria, until Mar 2014]
Valentina Peschetola [CNRS, with MSC lab (CNRS/Paris7)]

Visiting Scientists

Alexander Bockmayr [Prof Freie Univ. Berlin, until Mar 2014]
Pascal Hersen [CNRS, MSC lab (CNRS/Paris7), Researcher, HdR]
Denis Thieffry [ENS Paris, IBENS, Professor, HdR]

Administrative Assistants

Virginie Collette [Inria, from Nov 2014]
Assia Saadi [Inria, until Sep 2014]

Others

Melanie Kirch [Inria, Internship University of Erlangen-Nuremberg, from Nov 2014, with MSC lab (CNRS/Paris7)]
Agnes Koehler [Inria, Internship MPRI, from Mar 2014 to Aug 2014, with MSC lab (CNRS/Paris7)]
Ivy Uszynski [Inria, Internship Phelma INP Grenoble, from May 2014 to Aug 2014, with MSC lab (CNRS/Paris7)]
Jing Yang [Inria, Ecole Polytechnique, from Apr 2014 until Jun 2014]

2. Overall Objectives

2.1. Overall Objectives

This project aims at developing formal methods and experimental settings for **understanding the cell machinery** and establishing formal paradigms in cell biology. It is based on the vision of **cells as machines**, **biochemical reaction systems as programs**, and on the use of concepts and tools from computer science to master the complexity of cell processes. While for the biologist, as well as for the mathematician, the size of the biological networks and the number of elementary interactions constitute a complexity barrier, for the computer scientist the difficulty is not that much in the size of the networks than in the unconventional nature of biochemical computation. Unlike most programs, biochemical reaction systems involve transitions that are stochastic rather than deterministic, continuous-time rather than discrete-time, poorly localized in compartments instead of well-structured in modules, and created by evolution instead of by rational design. It is our belief however that some form of modularity is required by an evolutionary system to survive, and that the elucidation of these modules in biochemical computation is now a key to apply engineering methods in cell biology on a large scale.

Concretely, we keep developping a theory of biochemical computation and a prototype implementation in the Biochemical Abstract Machine BIOCHAM, a modeling and analysis platform for systems biology. The reaction rule-based language used in this system allows us to reason about biochemical reaction networks at different levels of abstraction, in either the **stochastic, differential, discrete, logical or hybrid semantics** of the reactions. This allows us to develop and apply a variety of **static analysis** methods, before going to simulations and **dynamic analyses**, for which we use **quantitative temporal logics** as a mean to formalize biological properties with imprecise data, constrain model building and calibrate models in high dimension by optimization methods.

A **tight integration between dry lab and wet lab** efforts is also essential for the success of the project. In collaboration with Pascal Hersen, MSC lab, we contribute to the development of an experimental platform for the closed-loop control of intracellular processes. This platform combines hardware (microfluidic device and microscope), software (cell tracking and model-based predictive control algorithms) and genetically modified living cells. It is used to investigate the possibilities to externalize the control of intracellular processes for systems and synthetic biology applications.

This project addresses fundamental research issues in computer science on the interplay between **structure and dynamics** in large interaction networks, and on the mixing of **continuous and discrete computation**. Many static analysis problems of biological networks are NP-hard. The recourse to constraint logic programming (CLP) to model and solve them, is our secret weapon, which probably explains our capability to experiment ideas in computational systems biology in very short time, by implementing them in CLP, integrating them as new components in our modeling platform BIOCHAM, and evaluating them directly on a large scale in systems biology model repositories such as BIOMODELS.NET.

The originality of this project also deals with the recourse to advanced micro-fluidic and **synthetic biology** technologies to perform accurate observations, modifications and real-time control at both single cell and cell population levels. For this to work, collaborations with top international leaders of these techniques have been established and consolidated with student exchange programs, especially in the framework of the Doctorate School “Frontiers in Life Sciences” to which we are affiliated, in addition to “Sciences Mathématiques de Paris-Centre”.

3. Research Program

3.1. Computational Systems Biology

Bridging the gap between the complexity of biological systems and our capacity to model and **quantitatively predict system behaviors** is a central challenge in systems biology. We believe that a deeper understanding of the concept and theory of biochemical computation is necessary to tackle that challenge. Progress in the theory is necessary for scaling, and enabling the application of static analysis, module identification and decomposition, model reductions, parameter search, and model inference methods to large biochemical reaction systems. A measure of success on this route will be the production of better computational modeling tools for elucidating the complex dynamics of natural biological processes, designing synthetic biological circuits and biosensors, developing novel therapy strategies, and optimizing patient-tailored therapeutics.

Progress on the **coupling of models to data** is also necessary. Our approach based on quantitative temporal logics provides a powerful framework for formalizing experimental observations and using them as formal specification in model building. Key to success is a tight integration between *in vivo* and *in silico* work, and on the mixing of dry and wet experiments, enabled by novel biotechnologies. In particular, the use of microfluidic devices makes it possible to measure behaviors at both single-cell and cell population levels *in vivo*, provided innovative modeling, analysis and control methods are deployed *in silico*.

In synthetic biology, while the construction of simple intracellular circuits has shown feasible, the design of larger, **multicellular systems** is a major open issue. In engineered tissues for example, the behavior results from the subtle interplay between intracellular processes (signal transduction, gene expression) and intercellular processes (contact inhibition, gradient of diffusible molecule), and the question is how should cells be genetically modified such that the desired behavior robustly emerges from cell interactions.

3.2. Modeling of Cellular Processes

Since nearly two decades, a significant interest has grown for getting a quantitative understanding of the functioning of biological systems at the cellular level. Given their complexity, proposing a model accounting for the observed cell responses, or better, predicting novel behaviors, is now regarded as an essential step to validate a proposed mechanism in systems biology. Moreover, the constant improvement of stimulation and observation tools creates a strong push for the development of methods that provide predictions that are increasingly precise (single cell precision) and robust (complex stimulation profiles). In addition to the widely-used ordinary differential equation modeling framework, stochastic modeling frameworks, such as chemical master equations, and statistic modeling frameworks, such as ensemble models, are increasingly popular, since they enable to capture biological variability.

In all cases, dedicated mathematical and computational approaches are needed for the analysis of the models and their calibration to experimental data. One can notably mention global optimization tools to search for appropriate parameters within large spaces, moment closure approaches to efficiently approximate stochastic models, and (stochastic approximations of) the expectation maximization algorithm for the identification of mixed-effects models.

3.3. External Control of Cell Processes

External control has been employed since many years to regulate culture growth and other physiological properties. Recently, taking inspiration from developments in synthetic biology, closed loop control has been applied to the regulation of intracellular processes. Such approaches offer unprecedented opportunities to investigate how a cell process dynamical information by maintaining it around specific operating points or driving it out of its standard operating conditions. They can also be used to complement and help the development of synthetic biology through the creation of hybrid systems resulting from the interconnection of in vivo and in silico computing devices.

In collaboration with Pascal Hersen (CNRS MSC lab), we developed a platform for gene expression control that enables to control protein concentrations in yeast cells. This platform integrates microfluidic devices enabling long-term observation and rapid change of the cells environment, microscopy for single cell measurements, and software for real-time signal quantification and model based control. We demonstrated recently that this platform enables controlling the level of a fluorescent protein in cells with unprecedented accuracy and for many cell generations [1].

3.4. Chemical Reaction Network Theory

Feinberg's chemical reaction network theory and Thomas's influence network analyses provide sufficient and/or necessary structural conditions for the existence of multiple steady states and oscillations in regulatory networks, which can be predicted by static analyzers without making any simulation. In this domain, most of our work consists in analyzing the interplay between the **structure** (Petri net properties, influence graph, subgraph epimorphisms) and the **dynamics** (Boolean, CTMC, ODE, time scale separations) of biochemical reaction systems. In particular, our study of influence graphs of reaction systems, our generalization of Thomas' conditions of multi-stationarity and Soulé's proof to reaction systems [2], the inference of reaction systems from ODEs [8], the computation of structural invariants by constraint programming techniques, and the analysis of model reductions by subgraph epimorphisms [9], now provide solid ground for developing static analyzers, using them on a large scale in systems biology, and elucidating modules.

3.5. Logical Paradigm for Systems Biology

Our group was among the first ones in 2002 to apply **model-checking** methods to systems biology in order to reason on large molecular interaction networks, such as Kohn's map of the mammalian cell cycle (800 reactions over 500 molecules) [3]. The logical paradigm for systems biology that we have subsequently developped for quantitative models can be summarized by the following identifications :

biological model = transition system,

biological property = temporal logic formula,

model validation = model-checking,

model inference = constraint solving.

In particular, the definition of a continuous satisfaction degree for **first-order temporal logic** formulae with constraints over the reals, was the key to generalize this approach to quantitative models, opening up the field of model-checking to model optimization. This line of research continues with the development of patterns with efficient solvers [20], [19] and their generalization to handle stochastic effects.

3.6. Constraint solving and optimization

Optimization methods are important in our research. On the one hand, static analysis of biochemical reaction networks involves solving hard combinatorial optimization problems, for which **constraint programming** techniques have shown particularly successful, often beating dedicated algorithms and allowing to solve large instances from model repositories. On the other hand, parameter search and model calibration problems involve similarly solving hard continuous optimization problems, for which **evolutionary algorithms** such as the covariance matrix evolution strategy (CMA-ES) [4] has shown to provide best results in our context, for up to 100 parameters, for building challenging quantitative models, gaining model-based insights, revisiting admitted assumptions and contributing to biological knowledge [5]

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4. Application Domains

4.1. Preamble

Our collaborative work on biological applications is expected to serve as a basis for groundbreaking advances in cell functioning understanding, cell monitoring and control, and novel therapy design and optimization. We work mainly on eukaryotic cells. Our collaborations with biologists are focused on **concrete biological questions**, and on the building of predictive models of biological systems to answer them. Moreover, one important application of our research is the development of a **modeling platform** for systems biology.

4.2. Modeling platform for systems biology

Since 2002, we develop an open-source software environment for modeling and analyzing biochemical reaction systems. This software, called the Biochemical Abstract Machine (BIOCHAM), is compatible with SBML for importing and exporting models from repositories such as BioModels. It can perform a variety of static analyses, specify behaviors in Boolean or quantitative temporal logics, search parameter values satisfying temporal constraints, and make various simulations. While the primary reason of this development effort is to be able to **implement our ideas and experiment them quickly on a large scale**, BIOCHAM is used by other groups either for building models, for comparing techniques, or for teaching (see statistics in software section). BIOCHAM-WEB is a web application which makes it possible to use BIOCHAM without any installation. We plan to continue developing BIOCHAM for these different purposes and improve the software quality.

4.3. Couplings between the cell cycle and circadian clock

Recent advances in cancer chronotherapy techniques support the evidence that there exist important links between the cell cycle and the circadian clock genes. One purpose for modeling these links is to better understand how to efficiently target malignant cells depending on the phase of the day and patient characterictics. These questions are at the heart of our collaboration with Franck Delaunay (CNRS Nice) and Francis Lévi (Univ. Warwick, GB, formerly INSERM Hopital Paul Brousse, Villejuif) and of our participation in the ANR Hyclock project and in the submitted EU H2020 C2SyM proposal, following the former EU EraNet Sysbio C5SYS and FP6 TEMPO projects. In the past, we developed a coupled model of the Cell Cycle, Circadian Clock, DNA Repair System, Irinotecan Metabolism and Exposure Control under Temporal Logic Constraints [6]. We now focus on the bidirectional coupling between the cell cycle and the circadian clock and expect to gain fundamental insights on this complex coupling from computational modeling and single-cell experiments.

4.4. Biosensor design and implementation in non-living vesicles

In collaboration with Franck Molina (CNRS, Sysdiag, Montpellier) and Jie-Hong Jiang (NTU, Taiwan), we ambition to apply our techniques to the design and implementation of biosensors in non-living vesicles for medical applications. Our approach is based on protein computation and on our ability to compile controllers and programs in biochemical reactions. The realization will be prototyped using a microfluidic device at CNRS Sysdiag, which will allow us to precisely control the size of the vesicles and the concentrations of the injected proteins. It is worth noting that the choice of non-living chassis is also particularly appealing for security considerations in synthetic biology and compliance to forthcoming EU regulation.

5. New Software and Platforms

5.1. The Biochemical Abstract Machine

Participants: François Fages, François-Marie Floch, Thierry Martinez, Sylvain Soliman, Pauline Traynard.

[6] Elisabetta De Maria, François Fages, Aurélien Rizk, Sylvain Soliman. Design, Optimization, and Predictions of a Coupled Model of the Cell Cycle, Circadian Clock, DNA Repair System, Irinotecan Metabolism and Exposure Control under Temporal Logic Constraints. Theoretical Computer Science, 412(21):2108–2127, 2011.

5.1.1. BIOCHAM V3.6

The Biochemical Abstract Machine (BIOCHAM) is a software environment for modeling and analyzing biochemical reaction systems, making simulations, performing static analyses, specifying behaviors in temporal logic. It is distributed under the GPL license since 2002.

The new features of version v3.6 released in October 2014 include:

- Hybrid boolean-stochastic-continuous models and simulations
- Quantitative temporal logic patterns with dedicated solvers (based on [20])
- Trace simplifications (based on [19])
- `export_sbml3` added
- `curate_model` and `curate_sbml` added (based on [8])
- Refinements of the types for command arguments (no effect on Biocham models)
- Bug fixes

5.1.2. BIOCHAM-web

BIOCHAM-WEB is a web service which makes it possible to try BIOCHAM on line without any installation, through a spreadsheet. A new version BIOCHAM-web was released in March 2014 and is kept evolving since.

That web service will evolve to a complete graphical user interface, named BIOCHAM-gui, and will replace the current graphical user interface.

5.1.3. BIOCHAM-parallel

A (non-distributed) parallel version of BIOCHAM is also maintained for our own use on a cluster of 10000 cores at GENCI CINES. This version speeds-up (linearly in the number of processors) the search of parameter values by parallelizing the evaluation of the fitness function (computed by numerical integration) for both the different parameter sets and the different conditions (perturbations, gene knock down or stress).

5.2. ClpZinc

Participants: François Fages, Thierry Martinez, Philippe Morignot, Sylvain Soliman.

CLP2ZINC is a rule-based modeling language for constraint programming. It extends the MiniZinc modeling language with Horn clauses which can be used to express search strategies as constraints in the model. This system is developed in the framework of the ANR Net-WMS-2 project and is a follow-up of the RULES2CP modeling language.

5.3. CellStar: Long-term tracking of single cells from brightfield microscopy images

Participants: Grégory Batt, Pascal Hersen, Artémis Llamosi, Szymon Stoma.

In close collaboration with Kirill Batmanov, Cédric Lhoussaine and Cristian Versari from the LIFL (CNRS/Lille Univ), we developed CELLSTAR, a tool-chain for image processing and analysis dedicated to segmentation and tracking of yeast cells in brightfield time-lapse microscopy movies. To estimate algorithm quality we developed a benchmark made of manually-verified images illustrating various situations. On this benchmark, CELLSTAR outperformed 5 other state-of-the-art methods. The tool-chain is implemented in MATLAB and is provided together with the Python YEAST IMAGE TOOLKIT benchmark tool.

5.4. Other software

The team also develops several software primarily for internal use. Some of them are specific to particular hardware and are not distributed. Some others are general purpose and currently on the web page for free downloading.

6. New Results

6.1. Highlight: Xavier Duportet laureate of the AEF docteurs-entrepreneurs prize

Xavier Duportet has been awarded the AEF prize at the docteurs-entrepreneurs competition. His thesis, made jointly within Lifeware and the Weiss lab at MIT, was entitled "Developing new tools and platforms for mammalian synthetic biology: from the assembly and chromosomal integration of large genetic circuits to the engineering of artificial intercellular communication systems". He published his research in *Nucleic Acids Research* and *Nature Biotechnology* [7], [5]. In particular, he demonstrated the assembly and chromosomal integration in mammalian cells of the largest gene circuit integrated to date. Subsequently, he co-founded the startup company PhageX. He was also a laureate of the Concours National de Création d'Entreprises Innovantes and the Concours Mondial d'Innovation (personalized medicine track).

He is the president of the Hello Tomorrow challenge and vice-president of the Osons La France initiative. He has notably been featured in articles published in Le Monde, L'Obs, and L'Opinion. He has been an invited speaker at the prestigious 4th Congreso del Futuro in Santiago (Chili). [7]

6.2. Highlight: François Fages laureate of the French Academy of Sciences

François Fages was very honoured to receive the Michel Monpetit prize 2014 of the French Academy of Sciences for his contributions to fundamental computer science (unification theory and constraint logic programming) and computational systems biology (modeling of biochemical networks and design and supervision of the implementation of the BIOCHAM software).

6.3. Highlight: Pauline Traynard Best Student Paper Prize at CMSB 2014, for Trace Simplifications preserving Temporal Logic Formulae with Case Study in a Coupled Model of the Cell Cycle and the Circadian Clock

Participants: François Fages, Sylvain Soliman, Pauline Traynard.

Pauline Traynard was very pleased to receive the Best Student Paper Prize of the twelth International Conference on Computational Methods for Systems Biology, 17-19 November 2014, Univ. of Manchester, UK, for a communication on trace simplifications preserving temporal logic properties [19].

Calibrating dynamical models on experimental data time series is a central task in computational systems biology. When numerical values for model parameters can be found to fit the data, the model can be used to make predictions, whereas the absence of any good fit may suggest to revisit the structure of the model and gain new insights in the biology of the system. Temporal logic provides a formal framework to deal with imprecise data and specify a wide variety of dynamical behaviors. It can be used to extract information from numerical traces coming from either experimental data or model simulations, and to specify the expected behaviors for model calibration. The computation time of the different methods depends on the number of points in the trace so the question of trace simplification is important to improve their performance. In [19] we study this problem and provide a series of trace simplifications which are correct to perform for some common temporal logic formulae. We give some general soundness theorems, and apply this approach to period and phase constraints on the circadian clock and the cell cycle. In this application, temporal logic patterns are used to compute the relevant characteristics of the experimental traces, and to measure the adequacy of the model to its specification on simulation traces. Speed-ups by several orders of magnitude are obtained by trace simplification even when produced by smart numerical integration methods.

6.4. Highlight: Modeling Dynamics of Cell-to-Cell Variability in TRAIL-induced Apoptosis Explains Fractional Killing and Predicts Reversible Resistance

Participants: Grégory Batt, François Bertaux, Szymon Stoma.

Isogenic cells sensing identical external signals can take markedly different decisions. Such decisions often correlate with pre-existing cell-to-cell differences in protein levels. When not neglected in signal transduction models, these differences are accounted for in a static manner, by assuming randomly distributed initial protein levels. However, this approach ignores the *a priori* non-trivial interplay between signal transduction and the source of this cell-to-cell variability: temporal fluctuations of protein levels in individual cells, driven by noisy synthesis and degradation. Thus, modeling protein fluctuations, rather than their consequences on the initial population heterogeneity, would set the quantitative analysis of signal transduction on firmer grounds. Adopting this dynamical view on cell-to-cell differences amounts to recast extrinsic variability into intrinsic noise. In collaboration with Dirk Drasdo (EPI Mmaba), we proposed a generic approach to merge, in a systematic and principled manner, signal transduction models with stochastic protein turnover models. When applied to an established kinetic model of TRAIL-induced apoptosis, our approach markedly increased model prediction capabilities [4]. We obtained a mechanistic explanation of yet-unexplained observations on fractional killing and non-trivial robust predictions of the temporal evolution of cell resistance to TRAIL in HeLa cells. Our results provide an alternative explanation to survival via induction of survival pathways since no TRAIL-induced regulations are needed and suggest that short-lived anti-apoptotic protein Mcl1 exhibit large and rare fluctuations. More generally, our results highlight the importance of accounting for stochastic protein turnover to quantitatively understand signal transduction over extended durations, and imply that fluctuations of short-lived proteins deserve particular attention. [4]

6.5. Towards Real-time Control of Gene Expression at the Single Cell Level: A Stochastic Control Approach

Participants: Grégory Batt, Pascal Hersen.

Recent works have demonstrated the experimental feasibility of real-time gene expression control based on deterministic controllers. By taking control of the level of intracellular proteins, one can probe single-cell dynamics with unprecedented flexibility. However, single-cell dynamics are stochastic in nature, and a control framework explicitly accounting for this variability is presently lacking. In [21], we devised a stochastic control framework, based on Model Predictive Control, which fills this gap.

Based on a stochastic modelling of the gene response dynamics, our approach combined a full state-feedback receding-horizon controller with a real-time estimation method that compensated for unobserved state variables. Using previously developed models of osmostress-inducible gene expression in yeast, we showed *in silico* that our stochastic control approach outperformed deterministic control design in the regulation of single cells. This contribution lead to envision the application of the proposed framework to wet lab experiments in yeast.

This work was done in collaboration with Alfonso Carta (EPI BIOCORE), Eugenio Cinquemani (EPI IBIS), Lakshmeesh Maruthi and Ilya Tkachev (TU Delft), and Alessandro Abate (Oxford U).

6.6. A Platform for Rapid Prototyping of Synthetic Gene Networks in Mammalian Cells

Participants: Grégory Batt, Xavier Duportet, Pascal Hersen.

Mammalian synthetic biology may provide novel therapeutic strategies, help decipher new paths for drug discovery and facilitate synthesis of valuable molecules. Yet, our capacity to genetically program cells is currently hampered by the lack of efficient approaches to streamline the design, construction and screening of synthetic gene networks. To address this problem, we developed a framework for modular and combinatorial assembly of functional (multi)gene expression vectors and showed their efficient and specific targeted integration into a well-defined chromosomal context in mammalian cells.

In [7], in collaboration with the Weiss lab and the MSC lab, we demonstrated the potential of this framework by assembling and integrating different functional mammalian regulatory networks including the largest gene circuit built and chromosomally integrated to date (6 transcription units, 27kb), encoding an inducible memory device. Using a library of 18 different circuits as a proof of concept, we also demonstrated that our method enabled one-pot/single-flask chromosomal integration and screening of circuit libraries. This rapid and powerful prototyping platform is well suited for comparative studies of genetic regulatory elements, genes and multi-gene circuits as well as facile development of libraries of isogenic engineered cell lines.

6.7. Reconfigurable Circuitry in Biochemical Systems

Participants: Hui-Ju Chiang, François Fages, Sylvain Soliman.

Realizing complex systems within a biochemical environment is a common pursuit in synthetic biology. Such systems achieve certain computation through properly designed biochemical reactions. Despite fruitful progress being made, most existing reaction designs have fixed target functionality. Their lack of reconfigurability can be disadvantageous, especially when a system has to adapt to a varying biochemical environment.

When control systems are of concern, linear control is one of the most widely applied control methods. Any linear control system can be realized with three elementary building blocks: integration, gain, and summation. Realizing linear control with biochemical reactions has been proposed in previous work, where reaction rates of the underlying reactions play a key role to achieve the desired building blocks. Essentially the reaction rates have to be matched exactly, and it imposes serious practicality restriction because in reality the reaction rates of available reactions are predetermined and can be limited. In [16] we devise a mechanism to make linear control systems configurable by adding auxiliary species as control knobs. The concentrations of the auxiliary species can be adjusted not only to compensate reaction rate mismatch, but also to reconfigure different control systems out of the same control architecture.

Furthermore, in [15] we propose an analog approach to economically construct a reconfigurable logic circuit similar to a silicon based field programmable gate array (FPGA). The effective "logic" and "interconnect" of the circuit can be dynamically reconfigured by controlling the concentrations of certain knob species. We study a potential biomedical application of our reconfigurable circuitry to disease diagnosis and therapy at a molecular level.

6.8. Inferring Reaction Systems from Ordinary Differential Equations

Participants: François Fages, Steven Gay, Sylvain Soliman.

In Mathematical Biology, many dynamical models of biochemical reaction systems are presented with Ordinary Differential Equations (ODE). Once kinetic parameter values are fixed, this simple mathematical formalism completely defines the dynamical behavior of a system of biochemical reactions and provides powerful tools for deterministic simulations, parameter sensitivity analysis, bifurcation analysis, etc. However, without requiring any information on the reaction kinetics and parameter values, various qualitative analyses can be performed using the structure of the reactions, provided the reactants, products and modifiers of each reaction are precisely defined. In order to apply these structural methods to parametric ODE models, we study a mathematical condition for expressing the consistency between the structure and the kinetics of a reaction, without restricting to Mass Action law kinetics. This condition, satisfied in particular by standard kinetic laws, entails a remarkable property of independence of the influence graph from the kinetics of the reactions. We derive from this study a heuristic algorithm which, given a system of ODEs as input, computes a system of reactions with the same ODE semantics, by inferring well-formed reactions whenever possible. We show how this strategy is capable of automatically curating the writing of ODE models in SBML, and present some statistics obtained on the model repository biomodels.net [8].

6.9. Model Reductions by Tropical Equilibration

Participants: François Fages, Sylvain Soliman.

Model reduction is a central topic in systems biology and dynamical systems theory, for reducing the complexity of detailed models, finding important parameters, and developing multi-scale models for instance. While singular perturbation theory is a standard mathematical tool to analyze the different time scales of a dynamical system and decompose the system accordingly, tropical methods provide a simple algebraic framework to perform these analyses systematically in polynomial systems. The crux of these methods is in the computation of tropical equilibrations. In [11] we show that constraint-based methods, using reified constraints for expressing the equilibration conditions, make it possible to numerically solve non-linear tropical equilibration problems, out of reach of standard computation methods. We illustrate this approach first with the detailed reduction of a simple biochemical mechanism, the Michaelis-Menten enzymatic reaction model, and second, with large-scale performance figures obtained on the http://biomodels.net webcite repository.

6.10. Model Reductions by Subgraph Epimorphisms

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

In [9] we follow another route based on a purely structural method and study the problem of deciding the existence of a subgraph epimorphism between two graphs. Our interest in this variant of graph matching problem stems from the study of model reductions in systems biology, where large systems of biochemical reactions can be naturally represented by bipartite digraphs of species and reactions. In this setting, model reduction can be formalized as the existence of a sequence of vertex deletion and merge operations that transforms a first reaction graph into a second graph. This problem is in turn equivalent to the existence of a subgraph (corresponding to delete operations) epimorphism (i.e. surjective homomorphism, corresponding to merge operations) from the first graph to the second. In this paper, we study theoretical properties of subgraph epimorphisms in general directed graphs. We first characterize subgraph epimorphisms (SEPI), subgraph isomorphisms (SISO) and graph epimorphisms (EPI) in terms of graph transformation operations. Then we study the graph distance measures induced by these transformations. We show that they define metrics on graphs and compare them. On the algorithmic side, we show that the SEPI existence problem is NP-complete by reduction of SAT, and present a constraint satisfaction algorithm that has been successfully used to solve practical SEPI problems on a large benchmark of reaction graphs from systems biology.

6.11. Temporal Logic Modeling of Dynamical Behaviors: First-Order Patterns and Solvers

Participants: François Fages, Pauline Traynard, Sylvain Soliman.

We have written a book chapter [20] to describe how quantitative temporal logic formulae can be used to formalize imprecise dynamical behaviors of biological systems, and how such a formal specification of experimental observations can be used to calibrate models to real data, in a more versatile way than with curve fitting algorithms, and with more efficient dedicated solvers than with generic temporal logic solvers.

Based on this article, we investigated the correctness of various trace simplification methods, as mentionned in the highlight section above [19].

6.12. Logical Modeling of the Mammalian Cell Cycle

Participants: François Fages, Pauline Traynard, Denis Thieffry.

The molecular networks controlling cell cycle progression in various organisms have been previously modelled, predominantly using differential equations. However, this approach meets various difficulties as one tries to include additional regulatory components and mechanisms. This led to the development of qualitative dynamical models based on Boolean or multilevel frameworks, which are easier to define, simulate, analyse and compose. In a poster presented at ECCB 2014, we revisit the Boolean model of Fauré et al. for the core network controlling G/S transition in mammalian cell cycle, taking into account recent advances in the characterisation of the underlying molecular networks to obtain a better qualitative consistency between model simulations

and documented mutants features. In particular, we introduced Skp2, the substrate recruiting component of the SCFSkp2 complex, which targets cell cycle control elements, such as p27, and is repressed by the tumour suppressor protein Rb. Furthermore, to supersede the limitations inherent to the Boolean simplifications, we have considered the association of multilevel logical components with key cell cycle regulators, including the tumour suppressor protein Rb. Indeed, it is well established that differently phosphorylated forms of Rb result in different effects on other components of the network, which can be faithfully modelled using a multilevel rather than a Boolean variable. To evaluate the dynamical properties of the resulting models, we perform synchronous and asynchronous simulations using the software GINsim (http://www.ginsim.org), for both the wild-type case and documented perturbations (e.g. combinations of loss- or gain-of-function mutations). In addition, we have designed a series of temporal logic queries (expressed in the CTL language), which enable an efficient and automatic verification of key dynamical properties (existence of a cyclic attractor or of a stable state, conditions on the order of changes of component levels, etc.), using the popular symbolic model checker NuSMV. This strategy greatly facilitates the dynamical analysis of increasingly detailed and complex cell cycle models. Our goal is to obtain a core cell cycle model consistent with the most relevant experimental results on mammalian cells, which will then be used as a module in more comprehensive cellular models, including cross-talks with the circadian clock network and key signalling pathways, whose deregulation underlies the development of various cancers.

6.13. A Greedy Heuristic for Optimizing Metro Regenerative Energy Usage compared to CMA-ES and MILP

Participants: François Fages, David Fournier.

When the regenerative braking energy cannot be stored by the metro producing it, it has to be used instantaneously on the network, otherwise it is lost. In this case, the accelerating and braking trains need be synchronized to fully benefit from the regenerative energy, and a metro timetable is energetically optimized when all the regenerative braking is utilized to power other trains. This synchronization consists in lining up each braking train with an accelerating one in its neighbourhood. Doing so, the latter will benefit from the regenerative energy of the former. In [17], [3] a fast greedy heuristic is proposed to tackle the problem of minimizing the energy consumption of a metro timetable by modifying solely the dwell times in stations. This heuristic is compared to a state-of-the-art meta heuristic called the covariance matrix adaptation evolution strategy (CMA-ES) and shows similar results with much faster computation time. Finally, it is shown that a run of the algorithm on a full timetable may reduce its energy consumption by 5.1%.

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contract with General Electric Transportation

Research contract on “Energy optimization in mass transport”. Accompagnying contract for the CIFRE thesis of David Fournier [3] (2011-2014).

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. ANR Projects

- ANR Blanc Hyclock (2014-2018) on “Hybrid modeling of time for Circadian Clock Biology and Chronopharmacology”, coordinated by F. Delaunay (CNRS, Nice), F. Lévi (INSERM Paris-Sud), G. Bernot (CNRS I3S, Nice), O. Roux (Ecle Centrale Nantes).

- ANR Blanc STOCH-MC (2014-2018) on "Stochastic Models: Scalable Model Checking", coordinated by Blaise Genest (Inria Rennes), with Grégory Batt, Wieslaw Zielonka (LIAFA), and Hugo Gimbert (LaBRI).
- ANR Investissement Avenir ICEBERG project (2011-2016) "From population models to model populations", coordinated by Grégory Batt, with Pascal Hersen (MSC lab, Paris Diderot Univ./CNRS), Reiner Veitia (Institut Jacques Monod, Paris Diderot Univ./CNRS), Olivier Gandrillon (BM2A lab, Lyon Univ./CNRS), Cédric Lhoussaine (LIFL/CNRS), and Jean Krivine (PPS lab, Paris Diderot Univ./CNRS).
- ANR Cosinus Syne2arti project (2010-2014) "From synthetic gene networks to artificial tissues" coordinated by Grégory Batt, with Oded Maler (CNRS Verimag), Dirk Drasdo (EPI Mamba), and Ron Weiss (MIT).
- ANR Blanc BIOTEMPO project (2010-2014) coordinated by Anne Siegel (EPI DYLISS), with Ovidiu Radulescu (U. Montpellier), O. Roux (Ecole Centrale de Nantes), Irina Rusu (U. Nantes).
- ANR Blanc NET-WMS-2 (2011-2015) on "constraint optimization in Wharehouse Management Systems", coordinated by F. Fages, with N. Beldiceanu (Ecole des Mines de Nantes, EPI TASC), and Abder Aggoun (KLS optim).

8.1.2. BPI-OSEO BioIntelligence Project

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

8.1.3. GENCI Contract

- GENCI (2009-) attribution of 300000 computation hours per year on the Jade cluster of 10000 cores of GENCI at CINES, Montpellier. Used for hardest parameter search problems in BIOCHAM-parallel.

8.2. International Initiatives

8.2.1. Inria Associate Teams

8.2.1.1. TISHOM

Title: Artificial tissue homeostasis: combining synthetic and computational biology approaches
Inria principal investigator: Grégory Batt
International Partner (Institution - Laboratory - Researcher):
Massachusetts Institute of Technology (United States) - Weiss Lab
Duration: 2012 - 2014

Cell-based gene therapy aims at creating and transplanting genetically-modified cells into a patient in order to treat an illness. Ideally, actively-growing cells are used to form a self-maintaining tissue in the patient, thus permanently curing the disease. Still, before any real therapeutic use, many important issues need to be addressed. In particular, one should guarantee tissue homeostasis, that is, that the size of the newly-introduced tissue remains within admissible bounds. The TISHOM project focused on developing methods and tools to facilitate the design and effective construction of artificial tissues.

In the context of his PhD, Xavier Duportet worked on three projects on engineering human cells. The first one, dealing with developing tools to facilitate the engineering of mammalian cells, has been published [7]. The two others deal with the development of communication systems and still need to be finalized. This experimental work raised a number of more theoretical questions, that were investigated by François Bertaux, together with Szymon Stoma. Two problems have been investigated. The first one dealt with accounting for protein fluctuations for the analysis of signal transduction systems over long time scales and has been published [4]. The second one dealt with the multiscale simulation of tissues and is still under way. During the course of the project, a third line of research emerged, to assist the design of a patterning system currently developed by the Weiss lab. On the computational side, the major issues have been addressed. On the experimental side, additional constructions and characterizations are still needed.

Lastly, the associated team also helped to organize the workshop Design, optimization and control in systems and synthetic biology. Nearly 200 researchers and students attended this event. Although of relatively modest size, this event was attended by a number of leaders of the field and had a significant international visibility.

8.2.2. Inria International Partners

8.2.2.1. Collaboration with National Taiwan University

Since 2012, we have a collaboration with Prof. Jie-Hong Jiang, National Taiwan University first on hybrid simulations of biochemical reaction systems and now on the design of a compiler of digital programs and analog circuits in biochemical reactions. Our preliminary results and common publications on this topic [15], [16] are encouraging but a lot of work is needed to minimize the number of necessary species and reactions. Our aim, in partnership with Franck Molina (CNRS, Sysdiag, Montpellier) is to design a biosensor using our biochemical programming compiler, implement the generated code in a liposome using a microfluidic device, and test its efficacy *in vitro*.

8.3. International Research Visitors

8.3.1. Invited Professors

Prof. Alexander Bockmayr from Freie Universitat, Berlin, Germany, visited us from January to March 2014 for common work on constraint-based methods in computational systems biology, and teaching in our MPRI Master C2.19 course on computational methods for systems and synthetic biology.

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific events organisation

9.1.1.1. General chair, scientific chair

- François Fages was co-Chair of BPPC'14, Fifth International Workshop in Bin Packing and Placement Constraints, associated to CPAIOR'14, Cork Ireland, May 2014.

9.1.1.2. Member of the organizing committee

- François Fages was member of the organizing committee and session co-chair of SFC'14, the 44ième Congrès de la Société Francophone de Chronobiologie, ESPCI ParisTech, Oct. 29-31 2014.

9.1.2. Scientific events selection

9.1.2.1. Chair of conference program committee

- François Fages was co-PC-Chair of FMMB'14, First International Conference on Formal Methods for Macro Biology, joint to ICSB'14, Noumea, Nouvelle Calédonie, September 2014.

9.1.2.2. Member of the conference program committee

- François Fages was member of the program committees of :
  - CMSB'14, Twelth International Conference on Computational Methods in Systems Biology – Nov. 17-19, Manchester, 2014.
  - WCB'14 10th Workshop on Constraint-based methods for Bioinformatics, associated to CP, Lyon France, September 2014.
  - VEMDP'14 The 1st International Workshop on Verification of Engineered Molecular Devices and Programs – An affiliated workshop of CAV 2014 hosted in Vienna, Austria on July 17, 2014.

  - HSB'14 Third workshop Hybrid Systems Biology – Vienna Summer of Logic, July 23-24, 2014.
  - CHR'14 11th International Workshop on Constraint Handling Rules — Vienna Summer of Logic, July 18, 2014.
- Grégory Batt was member of the program committee of HSB'14, the third workshop on Hybrid Systems Biology – Vienna Summer of Logic, July 23-24, 2014.

9.1.2.3. Reviewer

- Grégory Batt was member of the review panel of ERASynBio, an ERA-NET from the seventh framework program for the development and coordination of synthetic biology in the European research area (Lisbon, Jan 2014).
- François Fages was reviewer for the Luxembourg National Research Fund.

9.1.3. Journal

9.1.3.1. Member of the editorial board

- François Fages is member of
  - the Editorial Board of the Computer Science area of the Royal Society Open Science journal since 2014
  - the Steering Committee of the international conference series Computational Methods in Systems Biology since 2008
  - the Editorial Board of the journal RAIRO OR Operations Research since 2004

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Lifeware is affiliated to the Doctoral school of Mathematical Science of the University Paris Diderot, and to the interdiciplinary Doctoral school "Frontières du Vivant" of the University Paris Descartes.

The following courses have been given by members of Lifeware:

Master: course C2-19 on *Computational Methods for Systemic and Synthetic Biology*, Master Parisien de Recherche en Informatique (MPRI) François Fages (responsible, 12h), Grégory Batt (12h), Denis Thieffry (12h).

Master: Interdisciplinary Master in Life Science at the Ecole Normale Supérieure, Paris. Denis Thieffry (coordinator), Grég ory Batt (6h).

Master: course C2-35-1 on *Constraint Programming*, Master Parisien de Recherche en Informatique (MPRI) Sylvain Soliman (responsible, 24h) [beginning of the 2013-2014 academic year].

Master: *Computational Biology* at Master Approches Interdisciplinaires du Vivant (AIV), Grégory Batt (coordinator, 48h).

Master: *Statistics* at Master Approches Interdisciplinaires du Vivant (AIV), Valentina Peschetola (24h).

Grégory Batt has been selected to participate to the first workshop on Teaching Through Research of the Leadership Program, organised by the Centre for Research and Interdisciplinarity under the auspice of the "learning science" UNESCO chair (April 2014, Paris).

9.2.2. Supervision

HDR: Grégory Batt, *Design, optimization and control in systems and synthetic biology*, Université Paris Diderot, March 7, 2014. Jury: Vincent Danos (Edinburgh U), Frédéric Devaux (Paris5 U), Hidde de Jong (Inria), Olivier Gandrillon (CNRS), Mustafa Khammash (ETHZ), and Reiner Veitia (Paris7).

PhD in progress : François Bertaux, Université Pierre et Marie Curie, Paris, Sept 2011, Dir. Dirk Drasdo (EPI Mamba) and Grégory Batt

PhD: Xavier Duportet, *Developing new tools and platforms for mammalian synthetic biology: from the assembly and chromosomal integration of large genetic circuits to the engineering of artificial intercellular communication systems*, Université Paris Descartes (Oct. 2010), Paris, Dir. Grégory Batt and Ron Weiss (MIT), Nov 14, 2014. Jury: Grégory Batt, Diego di Bernardo (Tigem), Tim Lu (MIT), Didier Mazel (Pasteur), Franck Molina (CNRS), Reiner Veitia (Paris 7), and Ron Weiss

PhD: David Fournier, *Metro Regenerative Braking Energy Optimization through Rescheduling: Mathematical Model and Greedy Heuristics Compared to MILP and CMA-ES*, Université Paris Diderot, Paris (Oct 2011), Dir. François Fages and Denis Mulard (General Electric), 27 Nov 2014. Jury: Thierry Benoist (Innovation24), Xavier Delorme (Ecole des Mines de Saint Etienne), Roberto Di Cosmo (U. Paris-Diderot), François Fages, Narendra Jussien (Telecom Lille), Denis Mulard (General Electric).

PhD in progress : Steven Gay, *Subgraph Epimorphisms: Theory and Application to Model Reductions in Systems Biology*, Université Paris Diderot, Paris (Oct 2009), Dir. François Fages and Sylvain Soliman, defense in March 2015

PhD in progress : Jean-Baptiste Lugagne, Université Paris Diderot, Paris, Oct 2012, Dir. Grégory Batt and Pascal Hersen

PhD in progress : Artemis Llamosi, Université Paris Diderot, Paris, Nov 2012, Dir. Grégory Batt and Pascal Hersen

PhD in progress : Thierry Martinez, *Execution models for Constraint Programming: kernel language design through semantics equivalence*, Université Paris Diderot, Paris (Oct 2009), Dir. François Fages, Defense in March 2015

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

9.2.3. Juries

- HDR Pascal Hersen, Université Paris-Diderot, Examiner: François Fages
- PhD Adrien Basso-Blandin, Université d'Evry, November 2014, Examiner: François Fages
- PhD Benjamin Gyori, National University of Singapore, October 2014, Reviewer: Grégory Batt
- PhD Santiago Videla, Université de Rennes, July 2014, Reviewer: Grégory Batt
- PhD Alejandro Vignoni, Universitat Politecnica de Valencia, May 2014, Reviewer: Grégory Batt

9.3. Popularization

- Grégory Batt has been an invited speaker at the citizen science workshop Worldviews and Values in Synthetic Biology, Paris, June 2014.
- Grégory Batt had a stand at *Rencontres Inria Industries*, Lyon, May 2014.
- Xavier Duportet has been invited to speak at the *4th Congreso del Futuro* (Santiago, Chili), together with renown change makers (*e.g.* J. Rifkin, T. Piketty)
- Xavier Duportet is the cofounder and president of Hello Tomorrow, an international non-profit organization to promote technology entrepreneurship, with hubs in more than 80 cities worldwide and organizing one of the largest global startup competition.

- Xavier Duportet is the vice president of *Osons La France*, a forum to promote scientific innovation (Grand Palais, Paris, Dec 2014).
- Xavier Duportet has been featured in *Le Monde, L'Obs, Europe1, L'Opinion (2x), SoonSoonSoon, L'Atelier*, and *Widoobiz*.
- François Fages gave an invited talk at *Forum des Lauréats en Informatique et Mathématiques Appliquées*, Collège de France, Paris, Dec 2014.
- François Fages gave an invited talk at *Deuxième Journée Biologie et Mathématiques sur la Montagne*, Collège de France, Paris, Oct 2014.
- Artémis Llamosi is the co-foundeur and general secretary of the OpenLab, and organizer of related events on product industrialization. He provides scientific expertise to hosted startups.

Our research has also been presented at many scientific venues, in invited talks at the

- 21st European Conference on Artificial Intelligence, ECAI'14 (Prague, Aug 2014, François Fages),
- 10th International Conference on Distributed Computing and Internet Technology ICDCIT'14 (Bhubanesvar, Feb 2014, François Fages),

contributed talks

- in LyonSysBio conference (Nov. 2014, François Bertaux),
- International Workshop on Image-based Systems Biology (Jena, Sept. 2014, Szymon Stoma),

invited seminars

- Irisa Rennes and LISBP Toulouse (Grégory Batt),

and posters at

- the Systems Biology of Human Diseases workshop (Harvard, June 2014, François Bertaux),
- q-bio summer conference (Santa Fe, Aug. 2014, François Bertaux),
- Stochastic Biology (IST Austria, May 2014, François Bertaux),
- Image Bioinformatics (Leuven, Oct. 2014, Szymon Stoma),
- European Conference on Computational Biology (Strasbourg, Sep 2014, Denis Thieffry, Pauline Traynard),
- International Conference on Systems Biology (Melbourne, Sep 2014, François Fages, Pauline Traynard).

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] G. BATT. *Design, optimization and control in systems and synthetic biology*, Université Paris-Diderot - Paris VII, March 2014, Habilitation à diriger des recherches, https://tel.archives-ouvertes.fr/tel-00958566

[2] X. DUPORTET. *Developing new tools and platforms for mammalian synthetic biology: From the assembly and chromosomal integration of complex DNA circuits to the engineering of artificial intercellular communication systems*, Université Paris Diderot (Paris 7), November 2014, https://tel.archives-ouvertes.fr/tel-01108520

[3] D. FOURNIER. *Metro Regenerative Braking Energy Optimization through Rescheduling: Mathematical Model and Greedy Heuristics Compared to MILP and CMA-ES*, Paris-VIII, November 2014, https://tel.archives-ouvertes.fr/tel-01102408

Articles in International Peer-Reviewed Journals

[4] F. BERTAUX, S. STOMA, D. DRASDO, G. BATT. *Modeling Dynamics of Cell-to-Cell Variability in TRAIL-Induced Apoptosis Explains Fractional Killing and Predicts Reversible Resistance*, in "PLoS Computational Biology", 2014, vol. 10, n° 10, 14 p. [*DOI :* 10.1371/JOURNAL.PCBI.1003893.S016], https://hal.inria.fr/hal-00942885

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Invited Conferences

[12] G. BATT. *Cells driven by computers: long-term model predictive control of gene expression in yeast (keynote talk)*, in "HSCC - Proceedings of the 17th international conference on Hybrid Systems: Computation and Control", Berlin, Germany, ACM, April 2014, 2 p. [*DOI :* 10.1145/2562059.2562144], https://hal.archives-ouvertes.fr/hal-01104055

[13] F. FAGES. *Cells as Machines: Towards Deciphering Biochemical Programs in the Cell (keynote talk)*, in "21st European Conference on Artificial Intelligence", Prague, Czech Republic, 2014, https://hal.inria.fr/hal-01103333

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