RESEARCH CENTRE

Inria Saclay Centre

2024 ACTIVITY REPORT

Project-Team LIFEWARE

Computational systems biology and optimization

DOMAIN

Digital Health, Biology and Earth

THEME

Computational Biology

Inria

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Project-Team LIFEWARE

Creation of the Project-Team: 2015 April 01

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1 Team members, visitors, external collaborators

Research Scientists

- François Fages [Team leader, INRIA, Senior Researcher, HDR]
- Virgile Andreani [INRIA, Starting Research Position, from Nov 2024]
- Jakob Ruess [INRIA, Researcher, HDR]
- Sylvain Soliman [INRIA, Researcher, HDR]
- Josue Tchouanti Fotso [INRIA, Starting Research Position, from Nov 2024]

Faculty Member

- Anna Niarakis [UNIV TOULOUSE III, Professor, until Aug 2024, Delegation, HDR]

Post-Doctoral Fellows

- Guillaume Ballif [INRIA, Post-Doctoral Fellow]
- Henri Mermoz Kouye [INRIA, Post-Doctoral Fellow]
- Maxime Mahout [INRIA, Post-Doctoral Fellow, until Jul 2024]
- Van Giang Trinh [INRIA, Post-Doctoral Fellow, from Oct 2024]

PhD Students

- Sacha E Silva-Saffar [UNIV EVRY]
- Alexandre Tan-Lhernould [SERVIER]

Technical Staff

- Mathieu Hemery [INRIA, Engineer]

Interns and Apprentices

- Yao Agbedoga [INRIA, Intern, from Apr 2024 until Aug 2024]
- Nolwenn Le Mehaute [INRIA, Intern, from Apr 2024 until Aug 2024]
- Solène Mansour [INRIA, Intern, until Jul 2024]

Administrative Assistant

- Melanie Da Silva [INRIA]

External Collaborators

- Anna Niarakis [UNIV TOULOUSE III, from Sep 2024, HDR]
- Denis Thieffry [ENS PARIS, HDR]

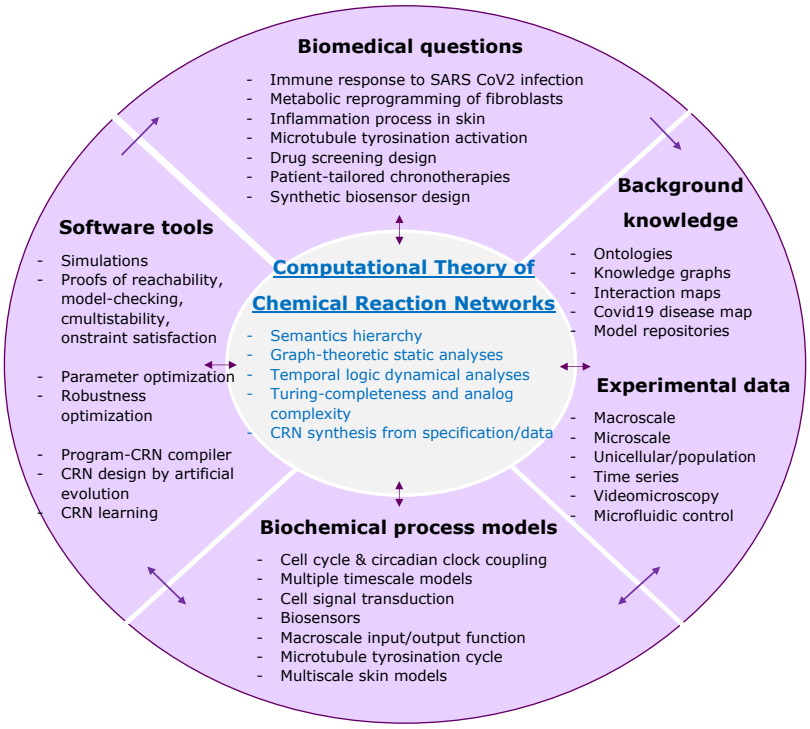

Figure 1: Overall picture of our Lifeware project centered on the development of a Computational Theory of Chemical Reaction Networks, in both perspectives of understanding natural cell processes in systems biology, and programming high-level functions in biochemistry and synthetic biology.

2 Overall objectives

This project aims at developing formal methods for understanding the cell machinery and establishing computational paradigms in cell biology and ecosystems. It is based on the vision of

cells as machines,
chemical reaction networks as programs,

and on the use of concepts from computer science to master the complexity of cell biochemical processes [9], [7].

We contribute to the development of a computational theory of chemical reaction networks (CRNs), by addressing fundamental research issues in computer science on the concepts of analog computation and analog computational complexity in biochemistry, and on the interplay between structure and dynamics in CRNs.

Since 2002, we develop a software platform, called the Biochemical Abstract Machine (BIOCHAM), for modeling, analyzing and now synthesizing CRNs, with some unique algorithmic contributions. The reaction rule-based language of BIOCHAM allows us to reason about CRNs at different levels of abstraction in the hierarchy of their stochastic, differential, Boolean and hybrid semantics. Various static analysis methods, most of them based on constraint solving or graph theory, provide useful information before going to simulations and dynamical analyses, for which quantitative temporal logic is used to formalize cell behaviors with imprecise data, and to constrain model building.

A tight integration between dry lab and wet lab efforts is also essential for the success of the project. This is achieved through collaborations with biologists and experimentalists, including partners from the pharmaceutical industry, on concrete biological and biomedical questions.

Because of the importance of declarative logic programming, constraint solving and optimization techniques in our approach, as well as the need for the rapid development of our symbolic computation software, we keep research and teaching activities on constraint logic programming. This is a fundamental programming paradigm for computing with partial information systems, and solving practical instances of NP-hard problems. For these reasons, BIOCHAM is implemented in Prolog with constraint solving libraries.

3 Research program

3.1 Chemical Reaction Network (CRN) Theory

Originally, Feinberg's mathematical theory of Chemical Reaction Networks (CRN), and Thomas's theory of influence networks, were created to provide sufficient and/or necessary structural conditions for various dynamical properties such as perfect adaptation, existence of multiple steady states, or of oscillations in complex interaction networks. Those conditions can be verified by static analyzers without knowing kinetic parameter values, nor making any simulation. In this first approach, most of our work consists in considering the **hypergraph structure** of a CRN (Petri net invariants, species-reaction labelled hypergraph, influence graph, reductions by subgraph epimorphisms) and analysing their interplay with the dynamics of CRNs in their different interpretations (Boolean, CTMC, ODE, time scale separations) which can be related in the framework of **abstract interpretation**[1]. For example, our study of the influence graphs of reaction systems [8] lead recently to sufficient graphical conditions ensuring rate-independence of CRN [5], or some time ago to the non-trivial generalization to reaction systems of Thomas' conditions of multi-stationarity and Soulé's proof given for influence systems, with much greater efficiency by several orders of magnitude for testing them when compared to current symbolic computation methods [3].

However, we aim at development a computational theory of CRNs and biochemical programming. Our original method to infer CRNs from ODEs [6] showed the generality of CRNs, and lead us to prove the Turing-completeness of continuous CRNs over a finite set of molecular species, showing that any computable function over the real numbers (i.e. computable in arbitrary precision by a Turing machine) can be computed by a CRN over a finite set of molecular species [7] (Best paper award CMSB 2017, Prix La Recherche 2019). This result closed the last open problem on the computation power of CRNs in their different semantics and has opened a whole research avenue on CRN design by compilation of mathematical functions. This is illustrated by a series of publications since that date [12] (best paper award CMSB 2022), again this year [25] , and innovative applications in synthetic biology [4].

3.2 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) [2]. The logical paradigm for systems biology that we have subsequently developed for quantitative models can be summarized by the following identifications :

biological model = transition system K, initial state s
dynamical behavior specification = temporal logic formula ϕ
model validation = model-checking $K,\ s \models ?\ \phi$
model reduction = sub-model-checking, $K' \subset K$ s.t. $K'?,\ s \models \phi$
model prediction = formula enumeration, ϕ s.t. $K,\ s \models \phi?$
static experiment design = symbolic model-checking, $K,\ s? \models \phi$
model synthesis = constraint solving $K?,\ s \models \phi$
model inference = constraint solving $K?,\ s? \models \phi$

[1] François Fages, Sylvain Soliman. Abstract Interpretation and Types for Systems Biology. Theoretical Computer Science, 403(1):52–70, 2008. (preprint)

[2] N. Chabrier-Rivier, M. Chiaverini, V. Danos, F. Fages, V. Schächter. Modeling and querying biochemical interaction networks. Theoretical Computer Science, 325(1):25–44, 2004.

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 [3] [4]

This line of research continues with the development of temporal logic constraint patterns with efficient solvers, and their use for model building, in partnership with biologists to answer concrete questions in the biomedical domain[5] [6] [22, 21] and the pharmaceutical industry [11, 20, 19].

3.3 Constraint Logic Programming and Optimization

Declarative logic programming, constraint solving and optimization algorithms are important in our research. On the one hand, static analyses of CRNs often involve solving hard combinatorial optimization problems, for which we have shown that **constraint logic programming** techniques, including Answer Set Programming (ASP), are particularly successful, often beating dedicated algorithms on real-size instances from model repositories by orders of magnitude[7] [15, 23].

On the other hand, parameter search problems involve solving hard continuous optimization problems, for which evolutionary algorithms, and especially the covariance matrix evolution strategy (CMA-ES) (EPI RANDOPT) have shown to provide best results in our context. Constraint-based models and efficient constraint solvers are thus instrumental in our approach for building quantitative models, gaining model-based insights, revisiting biological hypotheses, and contributing to biological knowledge.

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. Our collaborations with biologists are focused on concrete biological questions, and on the building of mechanistic models of biological systems to answer them. Furthermore, one important application of our research is the development and distribution of a modeling software for computational systems biology and synthetic biology.

4.2 Modeling software for systems and synthetic biology at the cellular level

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, using rapid prototyping techniques based on constraint logic programming, BIOCHAM is distributed and used by other groups worldwide, for building CRN models, for comparing CRN analysis/synthesis techniques, and for teaching computational systems biology. A JUPYTER BIOCHAM KERNEL has been developed to use BIOCHAM on our web server without any installation which is heavily used for teaching.

[3] Aurélien Rizk, Grégory Batt, François Fages, Sylvain Soliman. Continuous Valuations of Temporal Logic Specifications with applications to Parameter Optimization and Robustness Measures. Theoretical Computer Science, 412(26):2827–2839, 2011.

[4] Aurélien Rizk, Grégory Batt, François Fages, Sylvain Soliman. A general computational method for robustness analysis with applications to synthetic gene networks. Bioinformatics, 12(25):il69–il78, 2009.

[5] Domitille Heitzler, Guillaume Durand, Nathalie Gallay, Aurélien Rizk, Seungkirl Ahn, Jihee Kim, Jonathan D. Violin, Laurence Dupuy and Christophe Gauthier, Vincent Piketty, Pascale Crépieux, Anne Poupon, Frédérique Clément, François Fages, Robert J. Lefkowitz, Eric Reiter. Competing G protein-coupled receptor kinases balance G protein and β-arrestin signaling. Molecular Systems Biology, 8(590), 2012.

[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.

[7] Steven Gay, François Fages, Thierry Martinez, Sylvain Soliman, Christine Solnon. On the subgraph Epimorphism Problem. Discrete Applied Mathematics, 162:214–228, 2014 (preprint

We plan to continue developing BIOCHAM for these different purposes with the recruitment of a research engineer to improve the software quality and animation of the community of users.

Since 2018, the CaSQ software complements this effort by providing an interface to import large interaction maps written in SBML using the CellDesigner tool and translate them into Boolean influence models with various tools compatible with the SBML-qual standard. It is also used in order to build hybrid models of metabolic networks and gene regulation in the MetaLo platform.

Since 2020, we participate in the CoLoMoTo notebook platform, which provides an integrated collection of software tools for the analysis of qualitative models, including CaSQ. This platform encourages the reproducibility of analysis by combining Docker images (reproducible software environment) and Jupyter notebooks (reproducible and shareable workflows).

These two last efforts play a central role in the global Covid-19 Disease Maps project.

4.3 Biomedical applications

We plan to continue to tackle challenging concrete biomedical questions with academic and industrial partners in an opportunist way, according to both the scope of the question on the international scene, and the relevance of our theoretical approaches to the question.

As mentioned above, our long-standing collaboration with F. Molina's CNRS-ALCEN lab on the design, optimization and industrialization of biochemical diagnosis vesicles [4] continues on a design methodology of robust CRNs including analog functions and derivative estimation [13].

Our successful collaboration with Servier on knowledge graphs and CRN model parameterizations using quantitative temporal logic for drug screening [11] continues with a new CIFRE thesis with Servier started this fall on CRN model learning from experimental data.

Our similarly successful collaboration with Johnson& Johnson Santé Beauté France on multi-scale modeling of the epidermis and multifactorial aspects of atopic dermatitis [19, 20] has revealed complex metastability behaviors in our population dynamics models and further emerging properties when combined with a multi-agent model at the tissue level. This research continued with O. Radulescu in Montpellier on the tropical algebraic analysis of quasi-stability in our model has led to a generalization of this phenomenon in population dynamicas models [20].

We also keep ready to continue our long-standing collaborations on chronotherapies as specialists of coupled models of the cell cycle and the circadian clock [14, 22] and their systemic regulators[8].

Last but not least, our group became very active in cooperative efforts at the European scale to design large molecular interaction maps for diseases such as Covid-19 [16] or rheumatoid arthritis [18] and derive from them Boolean dynamical models using the CaSQ software as well as developing hybrid models [1].

5 Social and environmental responsibility

5.1 Footprint of research activities

In synthetic biology, our approach based on analog computation target enzymatic reactions with proteins in artificial DNA-free RNA-free vesicles. This is an original approach to solving major safety issue for applications in medicine and the environment.

5.2 Impact of research results

Our multidisciplinary research rooted in fundamental computer science aims at contributing to biology and medicine by going quite far in the applications with partners from academia and pharma industry.

[8] 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.

6 Highlights of the year

6.1 Online analog computation in the cell with absolute functional robustness: algebraic characterization, function compiler and error control

Participants: François Fages, Mathieu Hemery.

The Turing completeness of continuous Chemical Reaction Networks (CRNs) states that any computable real function can be computed by a continuous CRN on a finite set of abstract molecular species, possibly restricted to elementary reactions, i.e. with at most two reactants and mass action law kinetics [7].

In [25], we introduce a more stringent notion of robust online analog computation, called Absolute Functional Robustness (AFR), for the CRNs that stabilize the concentration values of some output species to the result of one function of the input species concentrations, while allowing arbitrary perturbations for intermediate and output species throughout the attraction basin. We prove that the set of real functions stabilized by a CRN with mass action law kinetics is precisely the set of real algebraic functions.

In [34], we describe the corresponding CRN synthesis tool part of our CRN modeling and analysis software BIOCHAM (Biochemical Abstract Machine). This compiler transforms any elementary (resp. algebraic) real function into a formal finite CRN to compute it (resp. with absolute functional robustness), through a pipeline of symbolic computation steps, among which quadratization optimization plays a key role to restrict to elementary reactions with at most two reactants, over a minimum number of molecular species.

6.2 HDR Identification and control of stochastic reaction networks in single cells and microbial populations

Participants: Jakob Ruess.

One of the defining features in the evolution of life was the transition from single-cell to multicellular organisms. Multicellularity allows for division of labor and the optimization of fitness of an organism via specialization. The same principle can be extended to microorganisms living together in a population or microbial community. Here, diversification and specialization of function can be achieved either by (genetically) different types of microbes living together symbiotically to form a microbial consortium or by cells of an isogenic population displaying different phenotypes despite being genetically identical.

The latter is the subject of this HDR [37] carried out in the last years on developing methods to analyze, parametrize, and control the dynamics of stochastic reaction networks in single cells and the coupled dynamics of single-cell and population processes. Most of the methodology presented in this HDR has been used to aid the understanding, design, and control for two different synthetically constructed biological systems in bacteria and yeast.

7 New software, platforms, open data

7.1 New software

7.1.1 BIOCHAM

Name: The Biochemical Abstract Machine

Keywords: Bioinformatics, Systems Biology, Computational biology

Functional Description: The Biochemical Abstract Machine (BIOCHAM) is a software environment for modeling, analyzing and synthesizing biochemical reaction networks (CRNs) with respect to a

formal specification of the observed or desired behavior of a biochemical system. BIOCHAM is compatible with the Systems Biology Markup Language (SBML) and contains some unique features about formal specifications in quantitative temporal logic, sensitivity and robustness analyses and parameter search in high dimension w.r.t. behavioral specifications, static analyses, and synthesis of CRNs.

Release Contributions: – bug fix – multiple improvements of the commands and documentation

URL: http://lifeware.inria.fr/biocham4/

Contact: François Fages

Participants: François Fages, Mathieu Hemery, Sylvain Soliman

7.1.2 CaSQ

Name: CellDesigner as SBML-Qual

Keyword: Systems Biology

Functional Description: CaSQ is a tool that can convert a molecular interaction map built with CellDesigner, or any similar SBML-capable tool, to an executable Boolean model. CaSQ is developed in Python (download and install instructions can be found on the Python package index) and uses as source the xml file of CellDesigner, in order to infer preliminary Boolean rules based solely on network topology and semantic annotations (e.g., certain arcs are noted as catalysis, inhibition, etc.). The aim is to convert a Process Description representation, i.e., a reaction model, into a full logical model. The resulting structure is closer to an Activity Flow diagram, though not in a strict SBGN-PD to SBGN-AF notion. Moreover logical rules that make the model executable are also obtained. CaSQ was used on maps of the Rheumatoïd Arthritis, of the MAP-Kinase cascade, etc. and is now being used by the Covid-19 DiseaseMaps consortium to automatically obtain logical models from maps [2].

CaSQ has recently been added to the CoLoMoTo Docker image and can be used in such a notebook.

Release Contributions: Bug correction. Complete integration to the rhumatoid arthritis map pipeline.

URL: https://casq.readthedocs.io/en/stable/

Publications: hal-03385317, hal-02590714

Contact: Sylvain Soliman

Participants: Sylvain Soliman, Anna Niarakis, Aurélien Naldi

7.1.3 MetaLo

Name: Metabolic analysis of Logical models

Keywords: Flux Balance Analysis, Boolean model

Functional Description: MetaLo is a framework for the Metabolic analysis (FBA) of Logical models extracted automatically from detailed mechanistic maps.

Release Contributions: Packaged version for published article.

URL: https://pypi.org/project/metalo/

Publication: hal-04439008

Contact: Sylvain Soliman

Partners: Université d'Evry-Val d'Essonne, Université de Toulouse

7.1.4 trappist

Keywords: Boolean model, Petri nets

Functional Description: Trappist is a tool for computing minimal trap spaces of a Boolean model.

Release Contributions: Better performances.

URL: https://pypi.org/project/trappist/

Publications: hal-04167028, hal-04209296

Contact: Sylvain Soliman

Participant: Sylvain Soliman

Partner: Laboratoire d'Informatique et des Systèmes (LIS) Université Aix-Marseille

7.1.5 Pack modeling

Name: Prolog pack for constraint-based mathematical modeling

Keywords: Logic programming, Constraint-based programming, Generic modeling environment

Functional Description: Pack of Prolog libraries defining bounded quantifiers (quantifiers.pl), subscripted variables(arrays.pl), constraints on integer or real subscripted variables (clp.pl), and constraint-based mathematical models (modeling.pl)

URL: https://lifeware.inria.fr/wiki/Main/Software#modeling

Contact: François Fages

8 New results

8.1 Identification and control of stochastic reaction networks in single cells and microbial populations.

Participants: Virgile Andreani, Guillaume Ballif, Henri Mermoz Kouyé, Jakob Ruess, Josue Tchouanti.

In his *habilitation à diriger des recherches* [37], Jakob Ruess presents the work that he carried out in the last years on developing methods to analyze, parametrize, and control the dynamics of stochastic reaction networks in single cells and the coupled dynamics of single-cell and population processes. This is the subject of research conducted in his part of the team.

During the last years, he has worked in close collaboration with synthetic biologists. Accordingly, most of the methodology has been used to aid the understanding, design, and control for two different synthetically constructed biological systems in bacteria and yeast. The thesis is organized into four chapters. Chapter 1 presents methodological work on stochastic reaction networks. First, he discusses moment equations and moment closure methods and how they can be used for parameter inference for stochastic reactions networks. Second, he presents a method for estimating derivatives of model outputs to model parameters (i.e. local sensitivities) via stochastic simulation of the CTMC for cases when the reaction rate constant are random variables. In Chapter 2, he first demonstrates how single-cell models can be augmented to additionally capture population-level processes and then he shows how absorbing Markov chain theory can be deployed to study the resulting multi-scale models and to predict features of emerging population dynamics. Subsequently, some results are presented on optimal control of multi-scale models for protein bioproduction applications. Chapter 3 presents experimental results on two synthetically constructed single-cell systems and the deployment of the theoretical and methodological results described in the first two chapters for these systems. First, he introduces a light-controllable gene

expression system in bacteria and discusses our results on using model-predictive control to regulate its dynamics inside single cells. Second, he focusses on a recombination system in yeast that allows one to create and dynamically control simple microbial consortia emerging from a single yeast strain via light-inducible genetic rewiring. Finally, in Chapter 4, he presents a modeling framework for epidemiology that allows one to include mechanistic models of contact tracing within classical compartmental models such as the SIR model in a mathematically coherent fashion. Compartmental models in epidemiology are, from a mathematical perspective, equivalent to models of chemical reactions in cells. As such, this chapter provides an example of how it can be beneficial to exploit synergies between these fields.

The defense was part of a rich seminar with the jury members.

In [38], a tribute was written in memory of Elisabeta Vergu who worked at INRAE in bioinformatics and epidemiology.

8.2 Evolution of a trait distributed over a large fragmented population: Propagation of chaos meets adaptive dynamics

Participants: Josue Tchouanti.

In [39], we consider a metapopulation made up of K demes, each containing N individuals bearing a heritable quantitative trait. Demes are connected by migration and undergo independent Moran processes with mutation and selection based on trait values. Mutation and migration rates are tuned so that each deme receives a migrant or a mutant in the same slow timescale and is thus essentially monomorphic at all times for the trait (adaptive dynamics).

In the timescale of mutation/migration, the metapopulation can then be seen as a giant spatial Moran model with size K that we characterize. As $K \to \infty$ and physical space becomes continuous, the empirical distribution of the trait (over the physical and trait spaces) evolves deterministically according to an integro-differential evolution equation. In this limit, the trait of every migrant is drawn from this global distribution, so that conditional on its initial state, traits from finitely many demes evolve independently (propagation of chaos).

Under mean-field dispersal, the value X_t of the trait at time t and at any given location has a law denoted μ_t and a jump kernel with two terms: a mutation-fixation term and a migration-fixation term involving μ_{t-} (McKean-Vlasov equation).

In the limit where mutations have small effects and migration is further slowed down accordingly, we obtain the convergence of X, in the new migration timescale, to the solution of a stochastic differential equation which can be referred to as a new canonical equation of adaptive dynamics. This equation includes an advection term representing selection, a diffusive term due to genetic drift, and a jump term, representing the effect of migration, to a state distributed according to its own law.

8.3 On a model of online analog computation in the cell with absolute functional robustness: algebraic characterization, function compiler and error control

Participants: François Fages, Mathieu Hemery.

The Turing completeness of continuous Chemical Reaction Networks (CRNs) states that any computable real function can be computed by a continuous CRN on a finite set of molecular species, possibly restricted to elementary reactions, i.e. with at most two reactants and mass action law kinetics. In [25], we introduce a more stringent notion of robust online analog computation, called Absolute Functional Robustness (AFR), for the CRNs that stabilize the concentration values of some output species to the result of one function of the input species concentrations, while allowing arbitrary perturbations for intermediate and output species throughout the attraction basin. We prove that the set of real functions stabilized by a CRN with mass action law kinetics is precisely the set of real algebraic functions. Based on this result, we present a compiler which takes as input any algebraic function (defined by one polynomial

and one point for selecting one branch of the algebraic curve defined by the polynomial) and generates an abstract CRN to stabilize it. Furthermore, we provide error bounds to estimate and control the error of an unperturbed system, under the assumption that the environment inputs are driven by k-Lipschitz functions.

8.4 On BIOCHAM Symbolic Computation Pipeline for Compiling Mathematical Functions into Biochemistry

Participants: François Fages, Mathieu Hemery, Sylvain Soliman.

Chemical Reaction Networks (CRNs) are a standard formalism used in chemistry and biology to model complex molecular interaction systems. In the perspective of systems biology, they are a central tool to analyze the high-level functions of the cell in terms of their low-level molecular interactions. In the perspective of synthetic biology, they constitute a target programming language to implement in chemistry new functions either in vitro, in artificial vesicles, or in living cells. In [34], we describe the CRN synthesis tool part of our CRN modeling and analysis software BIOCHAM (Biochemical Abstract Machine). This compiler transforms any elementary (resp. algebraic) real function into a formal finite CRN to compute it (resp. with absolute functional robustness), through a pipeline of symbolic computation steps, among which quadratization optimization plays a key role to restrict to elementary reactions with at most two reactants and a minimum number of molecular species.

8.5 Graphical Conditions ensuring Equality between Differential and Mean Stochastic Dynamics

Participants: Hugo Buscemi, François Fages.

Complex systems can be advantageously modeled by formal reaction systems (RS), a.k.a. chemical reaction networks in chemistry. Reaction-based models can indeed be interpreted in a hierarchy of semantics, depending on the question at hand, most notably by Ordinary Differential Equations (ODEs), Continuous Time Markov Chains (CTMCs), discrete Petri nets and asynchronous Boolean transition systems. The last three semantics can be easily related in the framework of abstract interpretation. The first two are classically related by Kurtz's limit theorem which states that if reactions are density-dependent families, then, as the volume goes to infinity, the mean reactant concentrations of the CTMC tends towards the solution of the ODE. In the more realistic context of bounded volumes, it is easy to show, by moment closure, that the restriction to reactions with at most one reactant ensures similarly that the mean of the CTMC trajectories is equal to the solution of the ODE at all time points.

In [30], we generalize that result in presence of polyreactant reactions, by introducing the Stoichiometric Influence and Modification Graph (SIMG) of an RS, and by showing that the equality between the two interpretations holds for the variables that belong to distinct SIMG ancestors of polyreactant reactions. We illustrate this approach with several examples. Evaluation on BioModels reveals that the condition for all variables is satisfied on models with no polymolecular reaction only. However, our theorem can be applied selectively to certain variables of the model to provide insights into their behaviour within more complex systems. Interestingly, we also show that the equality holds for a basic oscillatory RS implementing the sine and cosine functions of time.

8.6 Computing Thermodynamically Consistent Elementary Flux Modes with Answer Set Programming

Participants: Maxime Mahout.

Elementary Flux Modes (EFM) allow the description of the minimal sets of reactions in a metabolic network under steady-state conditions, representing unique and feasible pathways. They fully characterize the solution space but a combinatorial explosion prevents their calculation when the network is large. Furthermore, it is not necessary to calculate all of them, as many of them are not biologically relevant. In [31], we present the software aspefm which combines the use of Answer Set Programming and Linear Programming, proposes to integrate different types of constraints in the EFM computation such as equilibrium constants, Boolean regulatory rules, growth yields and growth medium. The addition of constraints makes it possible to cut off research pathways that lead to non-relevant EFMs. The computation of the EFMs of interest significantly reduces the computational time and saves space. In this article, we have added thermodynamic constraints in terms of the Gibbs energy of reactions, which constrain metabolite concentrations within a chosen interval. This constraint is added as a theory propagator and it reduces the enumeration during the computation. We applied our tool to the central carbon metabolism of E. coli and showed that the Gibbs energy constraints suppress a large number of non-relevant EFMs.

8.7 Scalable Enumeration of Trap Spaces in Boolean Networks via Answer Set Programming

Participants: Sylvain Soliman, Van Giang Trinh.

Boolean Networks (BNs) are widely used as a modeling formalism in several domains, notably systems biology and computer science. A fundamental problem in BN analysis is the enumeration of trap spaces, which are hypercubes in the state space that cannot be escaped once entered. Several methods have been proposed for enumerating trap spaces, however they often suffer from scalability and efficiency issues, particularly for large and complex models. To our knowledge, the most efficient and recent methods for the trap space enumeration all rely on Answer Set Programming (ASP), which has been widely applied to the analysis of BNs. In [35], motivated by these considerations, we present a new method for enumerating trap spaces in BNs using ASP. We evaluate the method on a mix of 250+ real-world and 400+ randomly generated BNs, showing that it enables analysis of models beyond the capabilities of existing tools (namely pyboolnet, mpbn, trappist, and trapmvn).

8.8 Metabolic analysis of Logical models extracted from molecular interaction maps

Participants: Anna Niarakis, Sylvain Soliman.

Molecular interaction maps (MIMs) are static graphical representations depicting complex biochemical networks that can be formalized using one of the Systems Biology Graphical Notation languages. Regardless of their extensive coverage of various biological processes, they are limited in terms of dynamic insights. However, MIMs can serve as templates for developing dynamic computational models. In [24], we present MetaLo, an opensource Python package that enables the coupling of Boolean models inferred from process description MIMs with generic core metabolic networks. MetaLo provides a framework to study the impact of signaling cascades, gene regulation processes, and metabolic flux distribution of central energy production pathways. MetaLo computes the Boolean model's asynchronous asymptotic behavior, through the identification of trap-spaces (using the trappist tool [35] described in the above section), and extracts metabolic constraints to contextualize the generic metabolic network. MetaLo is able to handle largescale Boolean models and genome-scale metabolic models without requiring kinetic information or manual tuning. The framework behind MetaLo enables in depth analysis of the regulatory model, and may allow tackling a lack of omics data in poorly addressed biological fields to contextualize generic metabolic networks along with improper automatic reconstructions of cell-and/or disease-specific metabolic networks. at MetaLo is available under the terms of the GNU General Public License v3.

8.9 Drug-target identification in COVID-19 disease mechanisms using computational systems biology approaches

Participants: Anna Niarakis, Sylvain Soliman.

In [27], we report on the COVID-19 Disease Map project, a large-scale community effort uniting 277 scientists from 130 Institutions around the globe. We use high-quality, mechanistic content describing SARS-CoV-2-host interactions and develop interoperable bioinformatic pipelines for novel target identification and drug repurposing. Extensive community work allowed an impressive step forward in building interfaces between Systems Biology tools and platforms. Our framework can link biomolecules from omics data analysis and computational modelling to dysregulated pathways in a cell-, tissue- or patient-specific manner. Drug repurposing using text mining and AI-assisted analysis identified potential drugs, chemicals and microRNAs that could target the identified key factors. Results revealed drugs already tested for anti-COVID-19 efficacy, providing a mechanistic context for their mode of action, and drugs already in clinical trials for treating other diseases, never tested against COVID-19. The key advance is that the proposed framework is versatile and expandable, offering a significant upgrade in the arsenal for virus-host interactions and other complex pathologies.

8.10 Digital Twins and Rheumatoid Arthritis

Participants: Anna Niarakis.

Digital twins represent a key technology for precision health. Medical digital twins consist of computational models that represent the health state of individual patients over time, enabling optimal therapeutics and forecasting patient prognosis. Many health conditions involve the immune system, so it is crucial to include its key features when designing medical digital twins. The immune response is complex and varies across diseases and patients, and its modelling requires the collective expertise of the clinical, immunology, and computational modelling communities. [26] outlines the initial progress on immune digital twins and the various initiatives to facilitate communication between interdisciplinary communities. We also outline the crucial aspects of an immune digital twin design and the prerequisites for its implementation in the clinic. We propose some initial use cases that could serve as "proof of concept" regarding the utility of immune digital technology, focusing on diseases with a very different immune response across spatial and temporal scales (minutes, days, months, years). Lastly, we discuss the use of digital twins in drug discovery and point out emerging challenges that the scientific community needs to collectively overcome to make immune digital twins a reality.

Rheumatoid arthritis is a complex disease marked by joint pain, stiffness, swelling, and chronic synovitis, arising from the dysregulated interaction between synoviocytes and immune cells. Its unclear etiology makes finding a cure challenging. The concept of digital twins, used in engineering, can be applied to healthcare to improve diagnosis and treatment for complex diseases like rheumatoid arthritis. In [29, 28], we pave the path towards a digital twin of the arthritic joint by building a large, modular biochemical reaction map of intra- and intercellular interactions. This network, featuring over 1000 biomolecules, is then converted to one of the largest executable Boolean models for biological systems to date. Validated through existing knowledge and gene expression data, our model is used to explore current treatments and identify new therapeutic targets for rheumatoid arthritis.

8.11 On Teaching Constraint-based Modeling and Algorithms for Decision Support in Prolog

Participants: Francois Fages.

Constraint programming techniques are particularly successful at solving discrete optimization problems such as resource allocation, scheduling or transport problems which are ubiquitous in the industry. Although historically introduced in the mid 80's with the generalization of Prolog to the class of Constraint Logic Programming languages, those techniques are mainly used today through constraint solving libraries in standard programming languages such as C++, Java, Python, and mainly taught with constraint-based modeling languages such as MiniZinc or Essence, in the tradition of algebraic modeling languages developed for mixed integer linear programming. Nonetheless, the foundations of both constraint solvers and constraint-based models in first-order logic should make of Prolog with its constraint-solving libraries a unique language to teach all aspects of constraint programming, provided missing higher-level MiniZinc-like mathematical modeling language constructs are added to Prolog libraries. This is what I have developed for teaching purposes in SWI-Prolog through a package named modeling [33]. This package contains libraries for defining shorthand functional notations, subscripted variables (arrays in addition to lists), set comprehension (bounded iteration and quantifiers compatible with constraints, in addition to recursion), front-end to constraint solving libraries for shorthand expansions on arrays and reification, and search tree tracing and visualization. This approach makes it possible to teach constraint-based modeling, search programming, and constraint solving with a unique high-level modeling/programming language, Prolog.

8.12 A Constraint-based Mathematical Modeling Library in Prolog with Answer Constraint Semantics

Participants: Francois Fages.

Constraint logic programming emerged in the late 80's as a highly declarative class of programming languages based on first-order logic and theories with decidable constraint languages, thereby subsuming Prolog restricted to equality constraints over the Herbrand's term domain. This approach has proven extremely successfull in solving combinatorial problems in the industry which quickly led to the development of a variety of constraint solving libraries in standard programming languages. Later came the design of a purely declarative front-end constraint-based modeling language, MiniZinc, independent of the constraint solvers, in order to compare their performances and create model benchmarks. Beyond that purpose, the use of a high-level modeling language such as MiniZinc to develop complete applications, or to teach constraint programming, is limited by the impossibility to program search strategies, or new constraint solvers, in a modeling language, as well as by the absence of an integrated development environment for both levels of constraint-based modeling and constraint solving.

In [32], we propose to solve those issues by taking Prolog with its constraint solving libraries, as a unified relation-based modeling and programming language. We present a Prolog library for high-level constraint-based mathematical modeling, inspired by MiniZinc, using subscripted variables (arrays) in addition to lists and terms, quantifiers and iterators in addition to recursion, together with a patch of constraint libraries in order to allow array functional notations in constraints. We show that this approach does not come with a significant computation time overhead, and presents several advantages in terms of the possibility of focussing on mathematical modeling, getting answer constraints in addition to ground solutions, programming search or constraint solvers if needed, and debugging models within a unique modeling and programming environment.

8.13 Graphical conditions for the existence, unicity and number of regular models

Participants: François Fages, Sylvain Soliman, Van Giang Trinh.

The regular models of a normal logic program are a particular type of partial (i.e. 3-valued) models which correspond to stable partial models with minimal undefinedness. In [36], we explore graphical conditions on the dependency graph of a finite ground normal logic program to analyze the existence,

unicity and number of regular models for the program. We show three main results: 1) a necessary condition for the existence of non-trivial (i.e. non-2-valued) regular models, 2) a sufficient condition for the unicity of regular models, and 3) two upper bounds for the number of regular models based on positive feedback vertex sets. The first two conditions generalize the finite cases of the two existing results obtained by You and Yuan (1994) for normal logic programs with wellfounded stratification. The third result is also new to the best of our knowledge. Key to our proofs is a connection that we establish between finite ground normal logic programs and Boolean network theory.

9 Bilateral contracts and grants with industry

9.1 Bilateral contracts with industry

9.1.1 Institut de Recherches Servier

Participants: François Fages, Alexandre Than-Lhernould, Mathieu Hemery, Sylvain Soliman.

Cifre PhD thesis of Alexandre Than-Lhernould on "Inference of biological models from temporal data for drug screening".

9.1.2 IBM research, France

Participants: François Fages, Sylvain Soliman.

The PhD thesis of Marine Collery at IBM France on "Expressive classification rule learning with an emphasis on learning from sequential data." was defended last year and the contract finished this year.

10 Partnerships and cooperations

10.1 International initiatives

10.1.1 Participation in other International Programs

Jakob Ruess collaborates with Hwayeon Ryu (Elon University, USA) through a programm co-funded by the NSF and the ERC project BridgingScales that enables research visits of Hwayeon Ryu to Inria.

On the topics of the ERC project BridgingScales, Jakob Ruess collaborates with experimental biologists at the University of Exeter, UK (Remy Chait) and the Univsersity of Pavia, Italy (Lorenzo Pasotti).

10.2 International research visitors

10.2.1 Visits of international scientists

Other international visits to the team

Hwayeon Ryu

Status researcher

Institution of origin: Elon Univ.

Country: USA

Dates: 12-21 December 2024

Context of the visit: visiting professor

Mobility program/type of mobility: collaboration

Virgile Andreani

Status researcher

Institution of origin: Boston Univ.

Country: USA

Dates: 21 May 2024

Context of the visit: Lifeware public seminar

Mobility program/type of mobility: lecture

Heinz Koeppl

Status researcher

Institution of origin: TU Darmstadt

Country: Germany

Dates: 18-19 March 2024

Context of the visit: HDR defense of Jakob Ruess

Mobility program/type of mobility: lecture

Mustafa Khammash

Status researcher

Institution of origin: ETH Zurich

Country: Switzerland

Dates: 18-19 March 2024

Context of the visit: HDR defense of Jakob Ruess

Mobility program/type of mobility: lecture

Ramon Grima

Status researcher

Institution of origin: University of Edinburgh

Country: United Kingdom

Dates: 18-19 March 2024

Context of the visit: HDR defense of Jakob Ruess

Mobility program/type of mobility: lecture

Philipp Thomas

Status researcher

Institution of origin: Imperial College London

Country: United Kingdom

Dates: 18-19 March 2024

Context of the visit: HDR defense of Jakob Ruess

Mobility program/type of mobility: lecture

Guido Sanguinetti

Status researcher

Institution of origin: SISSA

Country: Italy

Dates: 18-19 March 2024

Context of the visit: HDR defense of Jakob Ruess

Mobility program/type of mobility: lecture

Ovidiu Radulescu

Status researcher

Institution of origin: Univ. of Montpellier

Country: France

Dates: 18-19 March 2024

Context of the visit: HDR defense of Jakob Ruess

Mobility program/type of mobility: lecture

Christian Jendreiko

Status researcher

Institution of origin: Univ. Dusseldorf

Country: Germany

Dates: 19-20 February 2024

Context of the visit: Lifeware seminar on rule-based generative AI

Mobility program/type of mobility: lecture

10.3 European initiatives

10.3.1 Horizon Europe

BridgingScales BridgingScales project on cordis.europa.eu

Title: From single cells to microbial consortia: bridging the gaps between synthetic circuit design and emerging dynamics of heterogeneous populations

Duration: From May 1, 2023 to April 30, 2028

Partners:

- INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET AUTOMATIQUE (INRIA), France

Inria contact: Jakob Ruess

Coordinator:

Summary: A key turning point in the evolution of life was the transition from single-cell to multicellular organisms and the optimization of fitness via division of labour and specialization. Similarly, microorganisms have evolved equivalent strategies by forming communities or consortia. Division of labour in isogenic microbial populations is often implemented by mechanisms that create or act upon population heterogeneity to diversify functionality. Rational design in synthetic biology, on the other hand, is focused on the engineering of gene circuits with deterministically predictable functionality within single cells. While synthetic biology has certainly come a long way, predictable functionality of circuits in growing microbial populations still remains elusive or limited to tightly constrained operating conditions. We will develop novel mathematical methods to characterize and control the dynamics of synthetic gene circuits within growing microbial populations. We will develop a modelling framework and novel computational methods that take both stochasticity of single-cell processes and consequences of heterogeneity for population dynamics into account. On the mathematical side, this necessitates coupling single-cell stochastic processes to state dependent population processes such as growth or selection. We will develop methods for parameter inference, experimental design and control for such models. This will enable the construction of models that can be used to design synthetic circuits that function as specified within growing populations and that can be deployed to regulate single-cell processes such that desirable dynamics emerge at the scale of populations and consortia. We will apply the methodology for bioproduction problems in which proteins that are hard to fold need to be produced. Overproducing such proteins impairs cellular growth, which creates couplings between single-cell and population processes and raises the need to feedback control production.

10.4 National initiatives

10.4.1 ANR Project: Opt-MC

Participants: Guillaume Ballif, Henri Mermoz Kouyé, Jakob Ruess.

ANR Opt-MC - Optogenetic control of microbial communities (2023-2026) coord. Jakob Ruess, with Frédéric Bonnans, Laurent Pfeiffer (DISCO).

10.4.2 ANR Project: Difference

Participants: François Fages, Mathieu Hemery, Sylvain Soliman.

ANR δIFFERENCE on "Complexity theory with discrete ODEs", coordinated by Olivier Bournez, Ecole Polytechnique, with F. Fages, F. Chyzak (EP MATHEXP), A. Durand Univ. Paris-Diderot, F. Madelaine P. Valarché Univ. Créteil, Jerôme Durand-Lose, Orléans -Moulay Barkatou Thomas Cluzeau, Limoges - Mathieu Sablik, Toulouse.

11 Dissemination

Participants: François Fages, Mathieu Hemery.

11.1 Promoting scientific activities

Chair of conference program committees. François Fages is co-PC chair with Sabine Peres of the 23rd int. conf. CMSB 2025, Lyon, 10-12 Sep. 2025.

Member of the conference program committees. François Fages was PC member of CMSB'24 and Simultech'24 conferences.

Grant and award reviews. Jakob Ruess was reviewer for the "prix de these des systemes complexes 2024" organised by the Société Française des Systèmes Complexes.

Jakob Ruess was grant reviewer for the UKRI (UK Research and Innovation) Funding Service.

11.1.1 Journal

Member of the editorial boards. François Fages was member of the editorial board of Royal Society Open Science from 2014 to 2024.

Sylvain Soliman is an associate editor for PLOS Computational Biology.

Reviewer - reviewing activities. François Fages was reviewer for eLife, ACM Computing Surveys, PLOS Computational Biology.

Jakob Ruess was reviewer for Bioinformatics (journal), BMC Bioinformatics, and the Journal of Mathematical Biology.

Mathieu Hemery was reviewer for Cloud Computing and Data Science, Physical Review X - Life (2 reviews), Physical Review E (2 reviews), the Journal of the Royal Society Interface and Theoretical Computer Science.

Virgile Andreani was reviewer for PLOS One.

11.1.2 Invited talks

François Fages gave invited talks at

- Workshop on Differential Algebra and Modeling associated to ISSAC'24, Raleigh, NC USA, July 20-21 2024, "On modeling dynamical systems with reaction systems and their hierarchy of semantics"
- Journées synthèse de programmes, 26-27 November 2024, Bordeaux, "Local vs Global Approaches to Model Learning: Algorithms, Failures and Theorem"
- Janis Toth seminar, 9 April 2024, Budapest, Hungary, "Chemical Reaction Networks as a Programming Language"
- MAX team seminar, 11 March 2024, LIX, Palaiseau, "On rule-based models of dynamical systems"

Jakob Ruess gave invited talks at

- Keynote speaker at the Journées du GT Bioss, May 27-29, 2024, Paris. "From single cells to microbial consortia and back: stochastic chemical kinetics coupled to population dynamics".
- Speaker at the European conference on mathematical and theoretical biology (ECMTB), July 22-26, 2024, Toledo, Spain. "From single cells to microbial consortia and back: stochastic chemical kinetics coupled to population dynamics".
- Speaker at the Cellular trajectories workshop at Imperial College, London, UK, 5-6 September, 2024. "Using single-cell models to understand and control emerging population dynamics of an artificial differentiation system in yeast".

Virgile Andreani gave a talk at

- LCQB seminar, 17 December 2024, Paris. "Understanding and designing systems in synthetic biology, from promoter to protein to antibiotic resistance."

11.1.3 Leadership within the scientific community

François Fages is Chairman of the Steering Committee of the Int. Conf. on Computational Methods in Systems Biology .

11.1.4 Scientific expertise

François Fages is member of AFNOR CN 22 group on Programming Languages, where he acts as expert for the evolution of the ISO-Prolog norm.

11.1.5 Research administration

François Fages represents Inria at ED IPP to facilitate the registration of Inria PhD candidates.

11.2 Teaching - Supervision - Juries

11.2.1 Teaching

- Master 2: François Fages (coordinator 24h and teacher 12h), Jérôme Feret (12h) *C2-19 - Biochemical Programming*, Master Parisien de Recherche en Informatique (MPRI), Paris.
- Cycle ingénieur Ecole Polytechnique, Master 1: François Fages (coordinator, 18h lectures), Mathieu Hemery (18h TD) CSC-51055-EP - Constraint-based Modeling and Algorithms for Decision Making Problems Master Artificial Intelligence, Master Science and Technology, Ecole Polytechnique.
- Bachelor 3: François Fages (coordinator, 12h lectures), Mathieu Hemery (12h TD), CSC-3F007-EP - Relational Programming, Ecole Polytechnique.

11.2.2 Supervision

François Fages supervised the Master 2 internship of Solène Mansour.
Jakob Ruess supervised the Master 2 internships of Nolwenn Le-mehaute and Yao Agbedoga.

11.2.3 Juries

Fançois Fages participated in the juries of

- HDR Gleb Pogudin, "Symbolic Transformations of Dynamical Models" (Reviewer), 5 December 2024,Ecole Polytechnique
- PhD thesis of Florian Régin "Programmation Par Contraintes Générative" (Reviewer), 16 December 2024, Univ. Nice.

- PhD thesis of Jovial Cheukam Ngouonou, "Apprentissage automatique de cartes d'invariants d'objets combinatoires avec une application pour la synthèse d'algorithmes de filtrage" (Reviewer), 3 October 2024, Univ. Laval, Quebec, Canada
- PhD thesis of Kerian Thuillier, "Méthodes de satisfiabilité hybrides pour l'inférence de régulations booléennes contrôlant des réseaux métaboliques" (Reviewer), 27 September 2024, Univ. Rennes

Jakob Ruess participated in the juries of

- Thesis advisory committee of Emrys Reginato, Inria Grenoble.
- Reviewer of the PhD thesis of Tommaso Bianucci, Max-Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany.

11.3 Popularization

11.3.1 Specific official responsibilities in science outreach structures

Mathieu Hemery is co-organizer of scientific outreach commission at Inria Saclay.

11.3.2 Productions (articles, videos, podcasts, serious games, ...)

François Fages participated to the creation of a video on CIFRE theses by ANRT.

11.3.3 Participation in Live events

Mathieu Hemery gave 4 Chiches presentation and participated to the "Fête de la Science".

11.3.4 Others science outreach relevant activities

Mathieu Hemery was a member of the scientific committee for the "Maths & Jeux" mediation exposure based on various off-the-shelf boardgames to introduce mathematical concepts.

12 Scientific production

12.1 Major publications

[1] S. Aghakhani, S. E. Silva-Saffar, S. Soliman and A. Niarakis. 'Hybrid computational modeling highlights reverse warburg effect in breast cancer-associated fibroblasts'. In: *Computational and Structural Biotechnology Journal* 21 (19th Aug. 2023), pp. 4196–4206. DOI: 10.1016/j.csbj.2023.08.015. URL: https://inria.hal.science/hal-04192259 (cit. on p. 7).

[2] S. Aghakhani, S. Soliman and A. Niarakis. 'Metabolic Reprogramming in Rheumatoid Arthritis Synovial Fibroblasts: a Hybrid Modeling Approach'. In: *PLoS Computational Biology* 18.12 (12th Dec. 2022), e1010408. DOI: 10.1371/journal.pcbi.1010408. URL: https://inria.hal.science/hal-03880870.

[3] A. Baudier, F. Fages and S. Soliman. 'Graphical Requirements for Multistationarity in Reaction Networks and their Verification in BioModels'. In: *Journal of Theoretical Biology* 459 (14th Dec. 2018), pp. 79–89. DOI: 10.1016/j.jtbi.2018.09.024. URL: https://hal.archives-ouvertes.fr/hal-01879735 (cit. on p. 5).

[4] A. Courbet, P. Amar, F. Fages, E. Renard and F. Molina. 'Computer-aided biochemical programming of synthetic microreactors as diagnostic devices'. In: *Molecular Systems Biology* 14.4 (26th Apr. 2018). DOI: 10.15252/msb.20177845. URL: https://hal.inria.fr/hal-01779791 (cit. on pp. 5, 7).

[5] E. Degrand, F. Fages and S. Soliman. 'Graphical Conditions for Rate Independence in Chemical Reaction Networks'. In: *Proceedings CMSB 2020: The 18th International Conference on Computational Methods in Systems Biology*. CMSB 2020 - 18th International Conference on Computational Methods in Systems Biology. Konstanz / Online, Germany, 23rd Sept. 2020. URL: https://hal.inria.fr/hal-02900758 (cit. on p. 5).

[6] F. Fages, S. Gay and S. Soliman. 'Inferring reaction systems from ordinary differential equations'. In: *Theoretical Computer Science* 599 (Sept. 2015), pp. 64–78. DOI: 10.1016/j.tcs.2014.07.032. URL: https://hal.inria.fr/hal-01103692 (cit. on p. 5).

[7] F. Fages, G. Le Guludec, O. Bournez and A. Pouly. 'Strong Turing Completeness of Continuous Chemical Reaction Networks and Compilation of Mixed Analog-Digital Programs'. In: CMSB 2017 - 15th International Conference on Computational Methods in Systems Biology. Vol. Lecture Notes in Computer Science. Proceedings of the fiveteen international conference on Computational Methods in Systems Biology, CMSB 2017 10545. Darmstadt, Germany, 27th Sept. 2017, pp. 108–127. URL: https://hal.inria.fr/hal-01519828 (cit. on pp. 4, 5, 8).

[8] F. Fages, T. Martinez, D. A. Rosenblueth and S. Soliman. 'Influence Networks compared with Reaction Networks: Semantics, Expressivity and Attractors'. In: *IEEE/ACM Transactions on Computational Biology and Bioinformatics* PP.99 (2018), pp. 1–14. DOI: 10.1109/TCBB.2018.2805686. URL: https://hal.inria.fr/hal-01510216 (cit. on p. 5).

[9] F. Fages and F. Molina. 'The Cell: A Chemical Analog Calculator'. In: *Symbolic Approaches to Modeling and Analysis of Biological Systems*. 1. Wiley, 10th Aug. 2023. DOI: 10.1002/9781394229086.ch7. URL: https://hal.science/hal-04310569 (cit. on p. 4).

[10] E. Greugny. 'Computational modeling approaches to multifactorial aspects of atopic dermatitis'. Institut Polytechnique de Paris, 4th Oct. 2022. URL: https://pastel.hal.science/tel-03906902.

[11] J. Grignard, V. Lamamy, E. Vermersch, P. Delagrange, J.-P. Stephan, T. Dorval and F. Fages. 'Mathematical modeling of the microtubule detyrosination/tyrosination cycle for cell-based drug screening design'. In: *PLoS Computational Biology* 18.6 (27th June 2022), e1010236. DOI: 10.1371/journal.pcbi.1010236. URL: https://inria.hal.science/hal-03707809 (cit. on pp. 6, 7).

[12] M. Hemery and F. Fages. 'Algebraic Biochemistry: a Framework for Analog Online Computation in Cells'. In: CMSB 2022 - International Conference on Computational Methods in Systems Biology. Bucarest, Romania, 14th Sept. 2022. URL: https://hal.science/hal-03696273 (cit. on p. 5).

[13] M. Hemery and F. Fages. 'On Estimating Derivatives of Input Signals in Biochemistry'. In: CMSB 2023 - 21st International Conference on Computational Methods in Systems Biology. Luxembourg City, Luxembourg, 2023. URL: https://inria.hal.science/hal-04154923 (cit. on p. 7).

[14] J. Martinelli. 'On learning mechanistic models from time series data with applications to personalised chronotherapies'. Institut Polytechnique de Paris, 18th Feb. 2022. URL: https://theses.hal.science/tel-03686289 (cit. on p. 7).

[15] F. Nabli, T. Martinez, F. Fages and S. Soliman. 'On Enumerating Minimal Siphons in Petri nets using CLP and SAT solvers: Theoretical and Practical Complexity'. In: *Constraints* 21.2 (Apr. 2016), pp. 251–276. DOI: 10.1007/s10601-015-9190-1. URL: https://hal.archives-ouvertes.fr/hal-01170962 (cit. on p. 6).

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[17] J. Ruess, G. Ballif and C. Aditya. 'Stochastic chemical kinetics of cell fate decision systems: from single cells to populations and back'. In: *The Journal of Chemical Physics* 159.18 (8th Nov. 2023). DOI: 10.1063/5.0160529. URL: https://inria.hal.science/hal-04275681.

[18] V. Singh, A. Naldi, S. Soliman and A. Niarakis. 'A large-scale Boolean model of the rheumatoid arthritis fibroblast-like synoviocytes predicts drug synergies in the arthritic joint'. In: *npj Systems Biology and Applications* 9.33 (15th July 2023). DOI: 10.1038/s41540-023-00294-5. URL: https://inria.hal.science/hal-04187223 (cit. on p. 7).

[19] E. Thibault Greugny, J. Bensaci, F. Fages and G. Stamatas. 'Computational modeling predicts impaired barrier function and higher sensitivity to skin inflammation following pH elevation'. In: *Experimental Dermatology* (2nd Nov. 2022). DOI: 10.1111/exd.14698. URL: https://inria.hal.science/hal-03909897 (cit. on pp. 6, 7).

[20] E. Thibault Greugny, F. Fages, O. Radulescu, P. Szmolyan and G. Stamatas. 'A Skin Microbiome Model with AMP interactions and Analysis of Quasi-Stability vs Stability in Population Dynamics'. In: *Theoretical Computer Science* (Nov. 2023), p. 114294. DOI: 10.1016/j.tcs.2023.114294. URL: https://inria.hal.science/hal-04253028 (cit. on pp. 6, 7).

[21] P. Traynard, A. Fauré, F. Fages and D. Thieffry. 'Logical model specification aided by model- checking techniques: application to the mammalian cell cycle regulation'. In: *Bioinformatics* 32.17 (2016), pp. i772–i780. DOI: 10.1093/bioinformatics/btw457. URL: https://hal.archives-ouvertes.fr/hal-01378465 (cit. on p. 6).

[22] P. Traynard, C. Feillet, S. Soliman, F. Delaunay and F. Fages. 'Model-based investigation of the circadian clock and cell cycle coupling in mouse embryonic fibroblasts: Prediction of RevErb-α up-regulation during mitosis'. In: *BioSystems* 149 (Nov. 2016), pp. 59–69. DOI: 10.1016/j.biosystems.2016.07.003. URL: https://hal.archives-ouvertes.fr/hal-01378466 (cit. on pp. 6, 7).

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12.2 Publications of the year

International journals

[24] S. Aghakhani, A. Niarakis and S. Soliman. 'MetaLo: metabolic analysis of Logical models extracted from molecular interaction maps'. In: *Journal of Integrative Bioinformatics* 21.1 (6th Feb. 2024), p. 20230048. DOI: 10.1515/jib-2023-0048. URL: https://inria.hal.science/hal-04439008 (cit. on p. 13).

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