

The Inria logo is written in a red, cursive script font.

IN PARTNERSHIP WITH:  
**CNRS**

**Université Claude Bernard  
(Lyon 1)**

Activity Report 2019

## **Project-Team DRACULA**

Multi-scale modelling of cell dynamics :  
application to hematopoiesis

IN COLLABORATION WITH: Institut Camille Jordan

RESEARCH CENTER  
**Grenoble - Rhône-Alpes**

THEME  
**Modeling and Control for Life Sci-  
ences**



## Table of contents

<b>1. Team, Visitors, External Collaborators</b> .....	<b>1</b>
<b>2. Overall Objectives</b> .....	<b>2</b>
2.1. Presentation	2
2.2. Keywords	3
2.3. Research axis 1: Mathematical modeling for cell population dynamics	3
2.3.1. Executive summary	3
2.3.2. Project-team positioning	4
2.3.3. Collaborations	4
2.4. Research axis 2: Multi-scale modeling of hematopoiesis and leukemia	4
2.4.1. Executive summary	4
2.4.2. Project team positioning	5
2.4.3. Collaborations	5
2.5. Research axis 3: Multi-scale modeling of the immune response	6
2.5.1. Executive summary	6
2.5.2. Project-team positioning	6
2.5.3. Collaborations	7
2.6. Evolution of research direction during the last evaluation	7
2.6.1. Reminder of the objectives given for the last evaluation	7
2.6.2. Comments on these objectives over the evaluation period	8
2.6.3. Objectives for the next four years	8
<b>3. Research Program</b> .....	<b>8</b>
3.1. Mixed-effect models and statistical approaches	8
3.2. Development of a simulation platform	9
3.3. Mathematical and computational modeling	9
3.4. From hybrid dynamics to continuum mechanics	9
3.5. Structured partial differential equations	9
3.6. Delay differential equations	9
3.7. Multi-scale modeling of the immune response	10
3.8. Dynamical network inference from single-cell data	10
3.9. Leukemia modeling	10
<b>4. New Software and Platforms</b> .....	<b>11</b>
<b>5. New Results</b> .....	<b>11</b>
5.1. Mathematical models describing the interaction between cancer and immune cells in the lymph node	11
5.2. WASABI: a dynamic iterative framework for gene regulatory network inference	11
5.3. A multiscale model of platelet-fibrin thrombus growth in the flow	12
5.4. Mathematical modeling of platelet production	12
5.5. Nonlinear analysis of a model for yeast cell communication	13
5.6. Alzheimer's disease and prion: An in vitro mathematical model	13
5.7. Calibration, Selection and Identifiability Analysis of a Mathematical Model of the in vitro Erythropoiesis in Normal and Perturbed Contexts	13
5.8. Model-based assessment of the role of uneven partitioning of molecular content on heterogeneity and regulation of differentiation in CD8 T-cell immune responses	14
5.9. Spatial lymphocyte dynamics in lymph nodes predicts the cytotoxic T-Cell frequency needed for HIV infection control	14
5.10. Drugs modulating stochastic gene expression affect the erythroid differentiation process	14
5.11. Stochastic gene expression with a multistate promoter: breaking down exact distributions	15
5.12. Cell generation dynamics underlying naive T-cell homeostasis in adult humans	15

5.13. Erythroid differentiation displays a peak of energy consumption concomitant with glycolytic metabolism rearrangements	15
<b>6. Partnerships and Cooperations</b>	<b>16</b>
6.1. Regional Initiatives	16
6.2. National Initiatives	16
6.2.1. ANR	16
6.2.2. Other projects	16
6.3. European Initiatives	16
6.4. International Initiatives	16
6.4.1. Inria Associate Teams Not Involved in an Inria International Labs	16
6.4.2. Participation in Other International Programs	17
6.5. International Research Visitors	17
6.5.1. Visits of International Scientists	17
6.5.2. Visits to International Teams	17
<b>7. Dissemination</b>	<b>17</b>
7.1. Promoting Scientific Activities	17
7.1.1. Scientific Events: Organisation	17
7.1.1.1. General Chair, Scientific Chair	17
7.1.1.2. Member of the organizing Committees	17
7.1.2. Journal	17
7.1.2.1. Member of the Editorial Boards	17
7.1.2.2. Reviewer - Reviewing Activities	18
7.1.3. Invited Talks	18
7.1.4. Leadership within the Scientific Community	18
7.1.5. Research Administration	18
7.2. Teaching - Supervision - Juries	19
7.2.1. Teaching	19
7.2.2. Supervision	19
7.2.3. Juries	20
7.3. Popularization	20
7.3.1. Articles and contents	20
7.3.2. Interventions	21
<b>8. Bibliography</b>	<b>21</b>

# Project-Team DRACULA

*Creation of the Team: 2010 January 01, updated into Project-Team: 2011 January 01*

## Keywords:

### Computer Science and Digital Science:

- A6.1. - Methods in mathematical modeling
- A6.1.1. - Continuous Modeling (PDE, ODE)
- A6.1.2. - Stochastic Modeling
- A6.1.3. - Discrete Modeling (multi-agent, people centered)
- A6.1.4. - Multiscale modeling
- A6.2.1. - Numerical analysis of PDE and ODE
- A6.2.3. - Probabilistic methods
- A6.2.4. - Statistical methods
- A6.3.1. - Inverse problems

### Other Research Topics and Application Domains:

- B1.1.2. - Molecular and cellular biology
- B1.1.3. - Developmental biology
- B1.1.4. - Genetics and genomics
- B1.1.5. - Immunology
- B1.1.6. - Evolutionary biology
- B1.1.7. - Bioinformatics
- B1.1.8. - Mathematical biology
- B1.1.10. - Systems and synthetic biology
- B2.2.1. - Cardiovascular and respiratory diseases
- B2.2.3. - Cancer
- B2.2.5. - Immune system diseases
- B2.2.6. - Neurodegenerative diseases

## 1. Team, Visitors, External Collaborators

### Research Scientists

- Mostafa Adimy [Team leader, Inria, Senior Researcher, HDR]
- Samuel Bernard [CNRS, Researcher, HDR]
- Vincent Calvez [CNRS, Senior Researcher, from Jun 2019, HDR]
- Olivier Gandrillon [CNRS, Senior Researcher, HDR]
- Simon Girel [Univ de Lyon, Researcher, until Aug 2019]
- Thomas Lepoutre [Inria, Researcher, HDR]
- Vitaly Volpert [CNRS, Senior Researcher, HDR]

### Faculty Members

- Thibault Espinasse [Univ Claude Bernard, Associate Professor, from Jun 2019]
- Laurent Pujot-Menjouet [Univ Claude Bernard, Associate Professor, HDR]
- Léon Tine [Univ Claude Bernard, Associate Professor]

### PhD Students

- Ghada Abi Younes [Univ Claude Bernard, PhD Student, from Oct 2019]

Loïs Boullu [Univ Claude Bernard, PhD Student, until Aug 2019]  
Aurélien Canet [PhD Student, granted by CIFRE]  
Kyriaki Dariva [Univ Claude Bernard, PhD Student]  
Léonard Dekens [Univ Claude Bernard, PhD Student, from Sep 2019]  
Mete Demircigil [École Normale Supérieure de Paris, PhD Student, from Sep 2019]  
Ronan Duchesne [École Normale Supérieure de Lyon, PhD Student]  
Cheikh Gueye [PhD Student, from Oct 2019]  
Alexey Koshkin [Inria, PhD Student]  
Paul Lemarre [Univ Claude Bernard, PhD Student]  
Elias Ventre [École Normale Supérieure de Lyon, PhD Student, from Oct 2019]

#### **Interns and Apprentices**

Tasnim Fareh [Inria, Feb 2019]  
Nathan-Raynal Castang [Inria, from Mar 2019 until Jun 2019]

#### **Administrative Assistant**

Claire Sauer [Inria, Administrative Assistant]

#### **External Collaborator**

Fabien Crauste [CNRS, Senior Researcher, HDR]

## **2. Overall Objectives**

### **2.1. Presentation**

Dracula is a joint research team between Inria, Université Claude Bernard Lyon 1 (UCBL) and CNRS (Institut Camille-Jordan (ICJ, UMR 5208) and Laboratoire de Biologie et Modélisation de la Cellule (LBMC, UMR 5239)).

The Dracula project is devoted to multi-scale modeling in biology and medicine, and more specifically to the development of tools and methods to describe multi-scale processes in biology and medicine. Applications include normal and pathological hematopoiesis (for example leukemia), immune response, and other biological processes, like: tissue renewal, morphogenesis, atherosclerosis, prion disease, hormonal regulation of food intake, and so on. Multi-scale modeling implies simultaneous modeling of several levels of descriptions of biological processes: intra-cellular networks (molecular level), cell behavior (cellular level), dynamics of cell populations (organ or tissue) with the control by other organs (organism) (see Figure 1). Such modeling represents one of the major challenges in modern science due to its importance and because of the complexity of biological phenomena and of the presence of very different interconnected scales.

Although multi-scale modeling holds a great potential for biology and medicine, and despite the fact that a variety of techniques exists to deal with such problems, the complexity of the systems poses new challenges and needs the development of new tools. Moreover, different biological questions usually require different types of multi-scale modeling. The expected results of these studies are numerous. On one hand, they will shed new light on the understanding of specific biological and medical questions (for instance, what is the behavior of hematopoietic stem cells under pathological conditions? Or how to efficiently stimulate an immune response in order to design new vaccines?). On the other hand, the modeling methods developed here for specific processes are relevant to study other complex biological systems. We pay a special attention on developing methods that are not restricted to one or two applications.

An important part of our researches is performed in close collaboration with biologists and physicians in order to stay in contact with the biological and medical goals. The presence, within the project, of a biologist (Olivier Gandrillon) who has acquired over the years the know-how required for interacting with mathematicians is probably one of the main assets of the project. He participates actively in many tasks of our program, stimulates interactions between members of the project and biologists, and everyone benefits from his expertise in molecular and cell biology.

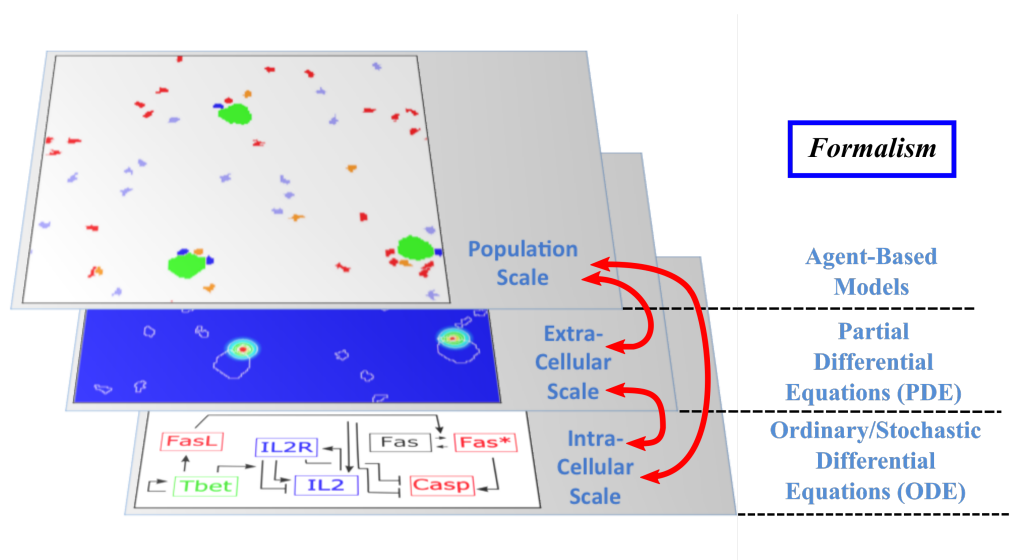


Figure 1. Scheme of multi-scale models of cell dynamics

## 2.2. Keywords

Multi-scale modeling; Hybrid modeling; Mathematical Biology; Computational Biology; Immune response modeling; Normal and pathological hematopoiesis; Multi-scale cancer modeling; Regulatory networks; Reaction-diffusion equation; Structured partial differential equations; Delay differential equations; Agent-based modeling; Dynamical systems.

## 2.3. Research axis 1: Mathematical modeling for cell population dynamics

### 2.3.1. Executive summary

Stem cells are essential for development and keep the maintenance of many tissues homeostasis. They are characterized by their ability to self-renew as well as to produce differentiated cells. They vary enormously, for each organ, in their proliferation capacity, their potency to produce different cell lineage and their response to various environmental cues. How a cell will react to a given external signal does not depend only on its current state but also on its environment. Understanding the effect of cell-to-cell heterogeneity and the spatial organization of cell populations is therefore necessary to help keeping the normal function of an organ.

We develop mathematical tools and methods to study cell population dynamics and other biological processes: stability of steady states, existence of bifurcations, kinetic properties, spatial organization, in finely detailed cell populations. The main tools we use are hybrid discrete-continuous models, reaction-diffusion equations, structured models (in which the population is endowed with relevant structures or traits), delay differential systems, agent-based models. Our team has acquired an international expertise in the fields of analysis of reaction-diffusion and structured equations, particularly integro-differential and delay differential equations.

The mathematical methods we develop are not restricted to hematopoietic system (Research axis 2), and immune response (Research axis 3), rather we apply them in many other biological phenomena, for example: tissue renewal, morphogenesis, prion disease, atherosclerosis, hormonal regulation of food intake, cancer, and others.

### 2.3.2. Project-team positioning

The focus of this objective is the development, analysis and application of hybrid discrete-continuous, reaction-diffusion and structured partial differential models. The structured equations allow a fine description of a population as some structures (age, maturity, intracellular content) change with time. In many cases, structured equations can be partially integrated to yield integro-differential equations (ordinary or partial differential equations involving non-local integral terms), time-delay differential or time-delay partial differential, or coupled differential-difference models. Analysis of integro-differential and time-delay systems deals with existence of solutions and their stability. Applications are found in the study of normal and pathological hematopoietic system (Research axis 2), immune response (Research axis 3), morphogenesis, prion disease, cancer development and treatment, and generally in tissue renewal problems. Models based on structured equations are especially useful to take into account the effect of finite time cells take to divide, die or become mature. Reaction-diffusion equations are used in order to describe spatial distribution of cell populations. It is a well developed area of research in our team which includes qualitative properties of travelling waves for reaction-diffusion systems with or without delay, and complex nonlinear dynamics.

Our team has developed a solid expertise in mathematical analysis of reaction-diffusion with or without delay and structured equations (in particular, delay differential equations) and one of the most prolific. Other major groups are the teams of Benoit Perthame (Pierre et Marie CURIE University and Mamba, Paris, <https://team.inria.fr/mamba/fr/>), Emmanuel Grenier (Ecole normale supérieure de Lyon and NUMED, <https://www.inria.fr/en/teams/numed>), Odo Diekmann (Utrecht University, The Netherlands, <https://www.uu.nl/staff/ODiekmann>), Avner Friedman (The Ohio State University, USA, <https://people.math.osu.edu/friedman.158/>), Jianhong Wu (York University, Canada, <http://liam.lab.yorku.ca/>), Glenn Webb (Vanderbilt University, Nashville, USA, <https://as.vanderbilt.edu/math/bio/glenn-webb>), Philip K. Maini (University of Oxford, England, <https://people.maths.ox.ac.uk/maini/>), Mark Chaplain (University of St Andrews, Scotland, <http://www.mcs.st-andrews.ac.uk/~majc/>), Nicola Bellomo (University of Turin, Italy, <http://staff.polito.it/nicola.bellomo/index.html>). Most of the members of all these groups and of our team belong to the same mathematical community working on partial differential equations and dynamical systems with applications to biology and medicine.

### 2.3.3. Collaborations

- University of Toronto, Canada; Mathematical analysis and applications of reaction-diffusion equations (more than 30 joint papers).
- Institute of Problems of Mechanical Engineering, St.Petersburg, Russia; Dynamics of cell renewal (more than 10 joint papers).
- Department of Cell and Molecular Biology and Department of Forensic Medicine, Stockholm, Sweden; Dynamics of cell generation and turnover (3 joint papers).
- Universities of Tlemcen (Algeria) and Marrakech (Morocco); Delay differential equations (7 joint papers)

## 2.4. Research axis 2: Multi-scale modeling of hematopoiesis and leukemia

### 2.4.1. Executive summary

Hematopoiesis is a complex process that begins with hematopoietic stem cells (HSCs) and results in formation of mature cells: red blood cells, white cells and platelets. Blood cells are produced in the bone marrow, from where mature cells are released into the blood stream. Hematopoiesis is based on a balance between cell proliferation (including self-renewal), differentiation and apoptosis. The choice between these three possibilities is determined by intra-cellular regulatory networks and by numerous control mechanisms in the bone marrow or carried out by other organs. Intra-cellular regulatory networks are complex biochemical reactions involving proteins, enzymes and signalling molecules. The deregulation of hematopoiesis can result in numerous blood diseases including leukemia (a cancer of blood cells). One important type of leukemia is Chronic Myeloid Leukemia (CML). The strong tyrosine kinase activity of the BCR-ABL protein is the basis



for the main cell effects that are observed in CML: significant proliferation, anti-apoptotic effect, disruption of stroma adhesion properties. This explains the presence in CML blood of a very important number of cells belonging to the myeloid lineage, at all stages of maturation.

Multi-scale modeling in hematopoiesis holds a great potential. A variety of techniques exists to deal with this problem. However, the complexity of the system poses new difficulties and leads to the development of new tools. The expected results of this study are numerous. On one hand, it will shed new light on the different physiological mechanisms that converge toward the continuous regeneration of blood cells, for example: the understanding of deregulation of erythropoiesis (the process of red blood cell production) under drug treatments (this can lead to lack of red blood cells (anemia), or a surplus of red blood cells), the dynamic of leukemic cells under the action of drugs and the control of their resistance to these treatments.

#### 2.4.2. Project team positioning

Multi-scale modeling of hematopoiesis is one of the key points of the project that has started in the early stage of the Dracula team. Investigated by all the team members, it took many years of close discussion with biologists to get the best understanding of the key role played by the most important molecules, hormones, kinase cascade, cell communication up to the latest knowledge. One of the important questions here is to identify particular biological mechanisms (intracellular regulation, control mechanisms) and to integrate them in the different models. Our main work consisted in the development of a hybrid (continuous/discrete) model for red blood cell progenitor proliferation, survival/death, differentiation, and migration. Cells are modeled as discrete objects, and the extracellular medium is described by continuous equations for extracellular concentrations. This is to our knowledge the most complete model for erythropoiesis to date, and the only one using a multi-scale formalism. Other models published by our group and others for hematopoiesis are population-based models, mostly population structured equations (transport partial differential equations or delay differential equations). The interest in modeling hematopoiesis dates back to the 70's and two groups have been responsible for most of development in the past 40 years: Markus Loeffler's team in Leipzig, Germany (Wichmann et al. 1976, in *Mathematical Models in Medicine*) and Michael Mackey's team at McGill University, Montreal, Canada (Mackey 1978, *Blood*). Our model differs from population based models in that the regulation is directly modeled at the molecular level (See Figure 1) rather than acting on rates at the population level. Thus we can take into account non-predictable effects of interactions between different molecular pathways and between cells that would otherwise be lost in the global population rates.

Regarding modeling leukemia, we concentrated on Chronic Myeloid Leukemia (CML) and its treatment. We considered models based on ordinary differential equations for the action of the main proteins involved in CML (as BCR-ABL protein), and of transport equations (with or without delay, physiologically structured or not) to represent healthy and leukemic cell populations, take into account many interactions between proteins (especially BCR-ABL), cells (anti-apoptotic effect, etc.). The development of models for CML allowed us to interact with Franck Nicolini in Lyon (Centre Hospitalier de Lyon) and Doron Levy (Maryland University, <http://www.math.umd.edu/~dlevy/>). Different schools developed models for CML and its treatment. The three leading groups are the ones of Franziska Michor (Harvard School of public health, <http://michorlab.dfci.harvard.edu/>), Ingo Roeder (Institute for Medical Informatics and Biometry, Dresden, <https://tu-dresden.de/med/mf/imb/das-institut>) and Michael Mackey (McGill University, <http://www.mcgill.ca/mathematical-physiology-lab/>).

#### 2.4.3. Collaborations

Members of the team have worked for several years in collaboration with biologists (François Morlé, University Lyon 1) and hematologists (Charles Dumontet, Lyon and Mark Koury, Nashville, <http://www.hematology.org/Thehematologist/Authors/298.aspx>) on the Modelling of normal and pathological hematopoiesis .

The work on modeling Leukemia is based on two major collaborations: firstly, an ongoing (since 2011) mathematical collaboration with the University of Maryland through the program Associate Teams Inria project, "Modelling Leukemia" ([http://dracula.univ-lyon1.fr/modelling\\_leukemia.php](http://dracula.univ-lyon1.fr/modelling_leukemia.php)). Secondly, an ongoing (since 2012) collaboration with a clinician from Hospices Civils de Lyon (Dr. F.E. Nicolini). In this framework, we shall have soon access to the data of the clinical trial PETALs ( $2 \times 100$  patients).

## 2.5. Research axis 3: Multi-scale modeling of the immune response

### 2.5.1. Executive summary

Vaccination represents a worldwide health, social and economical challenge as it has allowed the eradication or the strong containment of several devastating diseases over the past century. However to date, most of the effective vaccines rely on the generation of neutralizing antibody responses and such vaccines have proven largely unsuccessful in the prevention against some pathogens, such as HIV or malaria. In such cases, vaccines geared towards the generation of CD8 T cell immunity may provide a better protection. The generation of memory CD8 T cells following antigenic immunization is a long process (lasting up to month in murine preclinical models), therefore strongly slowing the process of vaccine monitoring in preclinical studies. Thus, the dynamical modeling of the CD8 T cell immune response both at the cellular and molecular levels should provide an important tool to better understand the dynamics of the response and to speed-up the process and reduce costs of vaccine development.

However, currently published cellular models of the immune response are either over-simplified, not predicting important parameters of this response, or too complicated for most of their parameters to be accessible for experimental measurements, thus impeding their biological validation. Dynamical models of the CD8 T cell response at the molecular level are very scarce and there is no multi-scale model of the immune response giving insights into both the regulation at the molecular scale and the consequences on cell population dynamics.

The objective of this research axis is therefore to develop a predictive multi-scale model of the CD8 T cell response, by confronting the model at different stages to in vivo-acquired experimental data, in order to be able to investigate the influence of early molecular events on cell population dynamics few days or weeks later.

### 2.5.2. Project-team positioning

We are aiming at building and analyzing a multi-scale model of the CD8 T cell immune response, from the molecular to the cellular and potentially organismal scale. This consists in describing the dynamics at each scale with relevant formalisms as well as the careful description of the couplings between scales.

Only few research groups are actually working on the CD8 T cell immune response around the world, and none of them deals with multi-scale modeling of this response. A network developed around Alan Perelson's work in theoretical immunology in the last decades, at Los Alamos National Laboratory, and involves mainly people in various US universities or institutes. In Europe, Rob De Boer's group (<http://theory.bio.uu.nl/rdb/>) of theoretical immunology in Utrecht, Netherlands, is the historical leader in the CD8 T cell dynamics modeling. We considered the models developed in these groups when we started our project, and we contributed to improve them by using nonlinearities accounting for cell population interactions to regulate the response. Also, our initial focus was on the generation of memory cells associated with vaccine development so we modeled CD8 T cell responses against influenza and vaccinia viruses, whereas other groups usually consider LCMV in its chronic form.

Ron Germain's group at the NIH, and Grégoire Altan-Bonnet in subsequent works, focused on the molecular regulation of the CD4 and CD8 T cell immune responses. In particular, they built the *Simmune* software, which allows the modeling and simulation of molecular interactions (<https://www.niaid.nih.gov/research/simmune-project>). This software is not really devoted to multi-scale modeling yet it provides an interesting tool to describe molecular interactions. Since our aim is to couple molecular and cellular scales at the tissue level, and we do not want to consider large networks but rather small-simplified informative interaction networks, we are confident that our approach is complementary of these works.

Within Inria project-teams, NUMED develops multi-scale approaches for biological problems, and MAMBA and MONC (<https://team.inria.fr/monc/>) mention models of cancer progression and treatment including immune responses. In the first case the methodology is similar, and collaborations between NUMED and DRACULA already exist (both teams are located in Lyon), but applications differ. In the second case, MAMBA and MONC are mainly focused on cancer modeling and up to now are motivated by including an action of the immune system in the fight against cancer, which is very different from what we are developing. However, both modeling approaches are complementary and could lead to interactions, in particular in the

light of recent advances in medical research pointing towards an important role - and high expectations - of the immune reaction in fighting cancers. Finally, SISTM (<https://www.inria.fr/en/teams/sistm>) also focuses on the modeling of the immune response, mainly against HIV, but the motivation is very similar to ours: the objective is to provide tools and methods in order to efficiently develop vaccines. They consider the CD4 T cell response instead of the CD8 T cell response, and biostatistics to achieve their goals instead of multi-scale models, yet even though there is no interaction between SISTM and DRACULA at this moment our methods and objectives are close enough to foreshadow future collaborations.

### 2.5.3. Collaborations

On this topic our main collaborators are members of Jacqueline Marvel's team in Lyon in the CIRI (Centre International de Recherche en Infectiologie INSERM U1111): Dr. Jacqueline Marvel, head of the team, Dr. Christophe Arpin (CR CNRS), and other technicians and engineers of the team. They are all immunologists, specialists of the CD8 T cell response and of the generation of memory CD8 T cells.

We also interact with private companies: AltraBio (<http://www.altrabio.com/>), that provides tools for data analysis, and CosmoTech, that develops a modeling and simulating platform that should allow transferring our model on an easy-to-use platform devoted to commercial uses.

## 2.6. Evolution of research direction during the last evaluation

### 2.6.1. Reminder of the objectives given for the last evaluation

The aim of this project is the development of modern tools for multi-scale modeling in biological phenomena. During the period 2014-2017, the objectives we had fixed were to develop modern tools for multi-scale modeling of biological phenomena, as detailed hereafter:

1. **Multi-scale modeling of erythropoiesis**, the process of red blood cell production, in order to describe normal, stress, and pathological erythropoiesis, using mathematical and computational models. This led to:
2. **The modeling of hemoglobin instability** in dialysis patients: Thomas Lepoutre has been progressively taking part in this theme through a collaboration with P. Kim (University of Sydney, Australia);
3. **Multi-scale modeling of the CD8 T cell immune response**, in order to develop a predictive model of the CD8 T cell response, by confronting the model at different stages to in vivo-acquired experimental data;
4. **Population dynamics modeling**, with the aim to develop general mathematical tools to study them. The main tools we were using were structured equations, in which the cell population is endowed with relevant structures, or traits. We identified limitations in using these formalisms, this is why we started developing multi-scale approaches;
5. **Modeling of Chronic Myeloid Leukemia (CML) treatment**, using ordinary differential equations models. Our team had already developed a first model of mutant leukemic cells being resistant to chemotherapy. A next step would be to identify the parameters using experimental data;
6. **Multi-scale modeling carried out on the basis of hybrid discrete-continuous models**, where dissipative particle dynamics (DPD) are used in order to describe individual cells and relatively small cell populations, partial differential equations (PDE) are used to describe concentrations of biochemical substances in the extracellular matrix, and ordinary differential equations for intracellular regulatory networks (Figure 1). An emphasis would be made on developing codes that are both flexible and powerful enough to implement variants of the model, perform simulations, produce desired outputs, and provide tools for analysis; to do so:
7. We planned to contribute to a **recent project named chronos**, whose code (written in C++) represents heterogeneous populations of individual cells evolving in time and interacting physically and biochemically, and the objective is to make the code flexible enough to implement different formalisms within the same model, so that different components of the model can be represented in the most appropriate way;

8. **Partial differential equations (PDE) analysis**, with a focus on reaction-diffusion equations, transport equations (hyperbolic PDEs) in which the structure can be age, maturity, protein concentration, etc., with particular cases where transport equations are reduced to delay differential equations (DDE).

### 2.6.2. Comments on these objectives over the evaluation period

We have had strong contributions to objectives 1, 3, 4, 5, and consequently to objective 6, as well as to objective 8, as mentioned in previous sections. These contributions represented the core of the team's research activity over the evaluation period, as stressed by our publications. It is however noticeable that multi-scale modeling of the immune response and of pathological hematopoiesis (leukemia) has come to represent a proportionally more important part of our activity.

Objective 2 has been cancelled few months after the previous evaluation, following meetings with clinicians who did not show any particular interest in our approaches. The modeling of chronic myeloid leukemia instead took a bigger part of the team's research activity, both project being at the time coordinated by Thomas Lepoutre.

Objective 7 has been pursued, the project *chronos* evolved to a better defined project *SiMuScale* that is currently being developed and aims at structuring the team's activity and providing a simulation platform that could be adapted to various biological questions necessitating multi-scale modeling.

### 2.6.3. Objectives for the next four years

The main objectives for the next four years are to continue to improve the 3 previous points: **1)** Mathematical and computational modeling for cell population dynamics; **2)** Multi-scale modeling of hematopoiesis and leukemia; **3)** Multi-scale modeling of the immune response. In addition, we will pursue our effort to develop a simulation platform for multi-scale models (*SiMuScale*) and we intend to develop the use of mixed effect models and other statistical approaches to deal with the challenges offered by modern biology, in particular the generation of single cell data.

## 3. Research Program

### 3.1. Mixed-effect models and statistical approaches

Most of biological and medical data our team has to deal with consist in time series of experimental measurements (cell counts, gene expression level, etc.). The intrinsic variability of any biological system complicates its confrontation to models. The trivial use of means, eliminating the data variance, is but a second-best solution. Furthermore, the amount of data that can be experimentally generated often limits the use of classical mathematical approaches because model's identifiability or parameter identifiability cannot be obtained. In order to overcome this issue and to efficiently take advantage of existing and available data, we plan to use mixed effect models for various applications (for instance: leukemia treatment modeling, immune response modeling). Such models were initially developed to account for individual behaviors within a population by characterizing distributions of parameter values instead of a unique parameter value. We plan to use those approaches both within that frame (for example, taking into account longitudinal studies on different patients, or different mice) but also to extend its validity in a different context: we will consider different *ex vivo* experiments as being "different individuals": this will allow us to make the most of the experience-to-experience variations.

Such approaches need expertise in statistics to be correctly implemented, and we will rely on the presence of Céline Vial in the team to do so. Céline Vial is an expert in applied statistics and her experience already motivated the use of better statistical methods in various research themes. The increasing use of single cell technologies in biology make such approaches necessary and it is going to be critical for the project to acquire such skills.

## 3.2. Development of a simulation platform

We have put some effort in developing the *SiMuScale* platform, a software coded in  $C_{++}$  dedicated to exploring multiscale population models, since 2014. In order to answer the challenges of multi-scale modeling it is necessary to possess an all-purpose, fast and flexible modeling tool, and *SiMuScale* is the choice we made. Since it is based on a core containing the simulator, and on plug-ins that contain the biological specifications of each cell, this software will make it easier for members of the team – and potentially other modelers – to focus on the model and to capitalize on existing models, which all share the same framework and are compatible with each other. Within the next four years, *SiMuScale* should be widely accessible and daily used in the team for multi-scale modeling. It will be developed into a real-case context, the modeling of the hematopoietic stem cell niche, in collaboration with clinicians (Eric Solary, INSERM) and physicists (Bertrand Laforge, UPMC).

## 3.3. Mathematical and computational modeling

Multi-scale modeling of hematopoiesis is one of the key points of the project that has started in the early stage of the Dracula team. Investigated by the team members, it took many years of close discussion with biologists to get the best understanding of the key role played by the most important molecules, hormones, kinase cascade, cell communication up to the latest knowledge. An approach that we used is based on hybrid discrete-continuous models, where cells are considered as individual objects, intracellular regulatory networks are described with ordinary differential equations, extracellular concentrations with diffusion or diffusion-convection equations (see Figure 1). These modeling tools require the expertise of all team members to get the most qualitative satisfactory model. The obtained models will be applied particularly to describe normal and pathological hematopoiesis as well as immune response.

## 3.4. From hybrid dynamics to continuum mechanics

Hybrid discrete-continuous methods are well adapted to describe biological cells. However, they are not appropriate for the qualitative investigation of the corresponding phenomena. Therefore, hybrid model approach should be combined with continuous models. If we consider cell populations as a continuous medium, then cell concentrations can be described by reaction-diffusion systems of equations with convective terms. The diffusion terms correspond to a random cell motion and the reaction terms to cell proliferation, differentiation and death. We will continue our studies of stability, nonlinear dynamics and pattern formation. Theoretical investigations of reaction-diffusion models will be accompanied by numerical simulations and will be applied to study cell population dynamic.

## 3.5. Structured partial differential equations

Hyperbolic problems are also of importance when describing cell population dynamics. They are structured transport partial differential equations, in which the structure is a characteristic of the considered population, for instance age, size, maturity, etc. In the scope of multi-scale modeling, protein concentrations as structure variables can precisely indicate the nature of cellular events cells undergo (differentiation, apoptosis), by allowing a representation of cell populations in a multi-dimensional space. Several questions are still open in the study of this problem, yet we will continue our analysis of these equations by focusing in particular on the asymptotic behavior of the system (stability, oscillations) and numerical simulations.

## 3.6. Delay differential equations

The use of age structure in PDE often leads to a reduction (by integration over the age variable) to delay differential equations. Delay differential equations are particularly useful for situations where the processes are controlled through feedback loops acting after a certain time. For example, in the evolution of cell populations the transmission of control signals can be related to some processes as division, differentiation, maturation, apoptosis, etc. Delay differential equations offer good tools to study the behavior of the systems. Our main investigation will be the effect of perturbations of the parameters, as cell cycle duration, apoptosis, differentiation, self-renewal, etc., on the behavior of the system, in relation for instance with some pathological situations. The mathematical analysis of delay differential equations is often complicated and needs the development of new criteria to be performed.



### 3.7. Multi-scale modeling of the immune response

The main objective of this part is to develop models that make it possible to investigate the dynamics of the adaptive CD8 T cell immune response, and in particular to focus on the consequences of early molecular events on the cellular dynamics few days or weeks later: this would help developing predictive tools of the immune response in order to facilitate vaccine development and reduce costs. This work requires a close and intensive collaboration with immunologist partners.

We recently published a model of the CD8 T cell immune response characterizing differentiation stages, identified by biomarkers, able to predict the quantity of memory cells from early measurements ([40]). In parallel, we improved our multiscale model of the CD8 T cell immune response, by implementing a full differentiation scheme, from naïve to memory cells, based on a limited set of genes and transcription factors.

Our first task will be to infer an appropriate gene regulatory network (GRN) using single cell data analysis (generate transcriptomics data of the CD8 T cell response to diverse pathogens), the previous biomarkers we identified and associated to differentiation stages, as well as piecewise-deterministic Markov processes (Ulysse Herbach's PhD thesis, ongoing).

Our second task will be to update our multiscale model by first implementing the new differentiation scheme we identified ([40]), and second by embedding CD8 T cells with the GRN obtained in our first task (see above). This will lead to a multi-scale model incorporating description of the CD8 T cell immune response both at the molecular and the cellular levels (Simon Girel's PhD thesis, ongoing).

In order to further develop our multiscale model, we will consider an agent-based approach for the description of the cellular dynamics. Yet, such models, coupled to continuous models describing GRN dynamics, are computationally expensive, so we will focus on alternative strategies, in particular on descriptions of the cellular dynamics through both continuous and discrete models, efficiently coupled. Using discrete models for low cell numbers and continuous (partial differential equations) models for large cell numbers, with appropriate coupling strategies, can lead to faster numerical simulations, and consequently can allow performing intense parameter estimation procedures that are necessary to validate models by confronting them to experimental data, both at the molecular and cellular scales.

The final objective will be to capture CD8 T cell responses in different immunization contexts (different pathogens, tumor) and to predict cellular outcomes from molecular events.

### 3.8. Dynamical network inference from single-cell data

Up to now, all of our multiscale models have incorporated a dynamical molecular network that was build "by hand" after a thorough review of the literature. It would be highly valuable to infer it directly from gene expression data. However, this remains very challenging from a methodological point of view. We started exploring an original solution for such inference by using the information contained within gene expression distributions. Such distributions can be acquired through novel techniques where gene expression levels are quantified at the single cell level. We propose to view the inference problem as a fitting procedure for a mechanistic gene network model that is inherently stochastic and takes not only protein, but also mRNA levels into account. This approach led to very encouraging results [41] and we will actively pursue in that direction, especially in the light of the foreseeable explosion of single cell data.

### 3.9. Leukemia modeling

Imatinib and other tyrosine kinase inhibitors (TKIs) have marked a revolution in the treatment of Chronic Myelogenous Leukemia (CML). Yet, most patients are not cured, and must take their treatment for life. Deeper mechanistic understanding could improve TKI combination therapies to better control the residual leukemic cell population. In a collaboration with the Hospital Lyon Sud and the University of Maryland, we have developed mathematical models that integrate CML and an autologous immune response ([37], [38] and [39]). These studies have lent theoretical support to the idea that the immune system plays a rôle in maintaining remission over long periods. Our mathematical model predicts that upon treatment discontinuation, the

immune system can control the disease and prevent a relapse. There is however a possibility for relapse via a sneak-through mechanism [37]. Research in the next four years will focus in the Phase III PETALS trial. In the PETALS trial (<https://clinicaltrials.gov/ct2/show/NCT02201459>), the second generation TKI Nilotinib is combined with Peg-IFN, an interferon that is thought to enhance the immune response. We plan to: 1) Adapt the model to take into account the early dynamics (first three months). 2) Use a mixed-effect approach to analyse the effect of the combination, and find population and individual parameters related to treatment efficacy and immune system response. 3) Optimise long-term treatment strategies to reduce or cease treatment and make personalised predictions based on mixed-effect parameters, to minimise the long-term probability of relapse.

## 4. New Software and Platforms

### 4.1. CelDyn

KEYWORDS: Modeling - Bioinformatics - Biology

FUNCTIONAL DESCRIPTION: Software "Celdyn" is developed in order to model cell population dynamics for biological applications. Cells are represented either as soft spheres or they can have more complex structure. Cells can divide, move, interact with each other or with the surrounding medium. Different cell types can be introduced. When cells divide, the types of daughter cells are specified. A user interface is developed.

- Participants: Alen Tosenberger, Laurent Pujot-Menjouet, Nikolai Bessonov and Vitaly Volpert
- Contact: Vitaly Volpert

## 5. New Results

### 5.1. Mathematical models describing the interaction between cancer and immune cells in the lymph node

To study the interplay between tumor progression and the immune response, we develop in [5] two new models describing the interaction between cancer and immune cells in the lymph node. The first model consists of partial differential equations (PDEs) describing the populations of the different types of cells. The second one is a hybrid discrete-continuous model integrating the mechanical and biochemical mechanisms that define the tumor-immune interplay in the lymph node. We use the continuous model to determine the conditions of the regimes of tumor-immune interaction in the lymph node. While we use the hybrid model to elucidate the mechanisms that contribute to the development of each regime at the cellular and tissue levels. We study the dynamics of tumor growth in the absence of immune cells. Then, we consider the immune response and we quantify the effects of immunosuppression and local EGF concentration on the fate of the tumor.

### 5.2. WASABI: a dynamic iterative framework for gene regulatory network inference

Background Inference of gene regulatory networks from gene expression data has been a long-standing and notoriously difficult task in systems biology. Recently, single-cell transcriptomic data have been massively used for gene regulatory network inference, with both successes and limitations. In the work [8], we propose an iterative algorithm called WASABI, dedicated to inferring a causal dynamical network from time-stamped single-cell data, which tackles some of the limitations associated with current approaches. We first introduce the concept of waves, which posits that the information provided by an external stimulus will affect genes one-by-one through a cascade, like waves spreading through a network. This concept allows us to infer the network one gene at a time, after genes have been ordered regarding their time of regulation. We then demonstrate the ability of WASABI to correctly infer small networks, which have been simulated in silico using a mechanistic

model consisting of coupled piecewise-deterministic Markov processes for the proper description of gene expression at the single-cell level. We finally apply WASABI on in vitro generated data on an avian model of erythroid differentiation. The structure of the resulting gene regulatory network sheds a new light on the molecular mechanisms controlling this process. In particular, we find no evidence for hub genes and a much more distributed network structure than expected. Interestingly, we find that a majority of genes are under the direct control of the differentiation-inducing stimulus. Conclusions Together, these results demonstrate WASABI versatility and ability to tackle some general gene regulatory networks inference issues. It is our hope that WASABI will prove useful in helping biologists to fully exploit the power of time-stamped single-cell data.

### 5.3. A multiscale model of platelet-fibrin thrombus growth in the flow

Thrombosis is a life-threatening clinical condition characterized by the obstruction of blood flow in a vessel due to the formation of a large thrombus. The pathogenesis of thrombosis is complex because the type of formed clots depends on the location and function of the corresponding blood vessel. To explore this phenomenon, we develop in [9] a novel multiscale model of platelet-fibrin thrombus growth in the flow. In this model, the regulatory network of the coagulation cascade is described by partial differential equations. Blood flow is introduced using the Navier–Stokes equations and the clot is treated as a porous medium. Platelets are represented as discrete spheres that migrate with the flow. Each platelet can attach to the thrombus, aggregate, become activated, express proteins on its surface, detach, and/or become non-adhesive. The interaction of platelets with blood flow is captured using the Immersed Boundary Method (IBM). We use the model to investigate the role of flow conditions in shaping the dynamics of venous and arterial thrombi. We describe the formation of red and white thrombi under venous and arterial flow respectively and highlight the main characteristics of each type. We identify the different regimes of normal and pathological thrombus formation depending on flow conditions.

### 5.4. Mathematical modeling of platelet production

- In [10], we analyze the existence of oscillating solutions and the asymptotic convergence for a nonlinear delay differential equation arising from the modeling of platelet production. We consider four different cell compartments corresponding to different cell maturity levels: stem cells, megakaryocytic progenitors, megakaryocytes, and platelets compartments, and the quantity of circulating thrombopoietin (TPO), a platelet regulation cytokine.
- In [11], we analyze the stability of a differential equation with two delays originating from a model for a population divided into two subpopulations, immature and mature, and we apply this analysis to a model for platelet production. The dynamics of mature individuals is described by the following nonlinear differential equation with two delays:  $x'(t) = -\lambda x(t) + g(x(t - \tau_1)) - g(x(t - \tau_1 - \tau_2))e^{-\lambda\tau_2}$ . The method of  $D$ -decomposition is used to compute the stability regions for a given equilibrium. The center manifold theory is used to investigate the steady-state bifurcation and the Hopf bifurcation. Similarly, analysis of the center manifold associated with a double bifurcation is used to identify a set of parameters such that the solution is a torus in the pseudo- phase space. Finally, the results of the local stability analysis are used to study the impact of an increase of the death rate  $\gamma$  or of a decrease of the survival time  $\tau_2$  of platelets on the onset of oscillations. We show that the stability is lost through a small decrease of survival time (from 8.4 to 7 days), or through an important increase of the death rate (from 0.05 to 0.625 days<sup>-1</sup>).
- In [12], we analyze the stability of a system of differential equations with a threshold-defined delay arising from a model for platelet production. We consider a maturity-structured population of megakaryocyte progenitors and an age-structured population of platelets, where the cytokine thrombopoietin (TPO) increases the maturation rate of progenitors. Using the quasi-steady-state approximation for TPO dynamics and the method of characteristics, partial differential equations are reduced to a system of two differential equations with a state-dependent delay accounting for



the variable maturation rate. We start by introducing the model and proving the positivity and boundedness of the solutions. Then we use a change of variables to obtain an equivalent system of two differential equations with a constant delay, from which we prove existence and uniqueness of the solution. As linearization around the unique positive steady state yields a transcendental characteristic equation of third degree, we introduce the main result, a new framework for stability analysis on models with fixed delays. This framework is then used to describe the stability of the megakaryopoiesis with respect to its parameters. Finally, with parameters being obtained and estimated from data, we give an example in which oscillations appear when the death rate of progenitors is increased 10-fold.

## 5.5. Nonlinear analysis of a model for yeast cell communication

In [13], we study the non-linear stability of a coupled system of two non-linear transport-diffusion equations set in two opposite half-lines. This system describes some aspects of yeast pairwise cellular communication, through the concentration of some protein in the cell bulk and at the cell boundary. We show that it is of bistable type, provided that the intensity of active molecular transport is large enough. We prove the non-linear stability of the most concentrated steady state, for large initial data, by entropy and comparison techniques. For small initial data we prove the self-similar decay of the molecular concentration towards zero. Informally speaking, the rise of a dialog between yeast cells requires enough active molecular transport in this model. Besides, if the cells do not invest enough in the communication with their partner, they do not respond to each other; but a sufficient initial input from each cell in the dialog leads to the establishment of a stable activated state in both cells.

## 5.6. Alzheimer's disease and prion: An in vitro mathematical model

Alzheimer's disease (*AD*) is a fatal incurable disease leading to progressive neuron destruction. *AD* is caused in part by the accumulation in the brain of  $A\beta$  monomers aggregating into oligomers and fibrils. Oligomers are amongst the most toxic structures as they can interact with neurons via membrane receptors, including  $PrP^c$  proteins. This interaction leads to the misconformation of  $PrP^c$  into pathogenic oligomeric prions,  $PrP^{ol}$ . In [14], we develop a model describing in vitro  $A\beta$  polymerization process. We include interactions between oligomers and  $PrP^c$ , causing the misconformation of  $PrP^c$  into  $PrP^{ol}$ . The model consists of nine equations, including size structured transport equations, ordinary differential equations and delayed differential equations. We analyse the well-posedness of the model and prove the existence and uniqueness of solutions of our model using Schauder fixed point theorem and Cauchy-Lipschitz theorem. Numerical simulations are also provided to give an illustration of the profiles that can be obtained with this model.

## 5.7. Calibration, Selection and Identifiability Analysis of a Mathematical Model of the in vitro Erythropoiesis in Normal and Perturbed Contexts

The in vivo erythropoiesis, which is the generation of mature red blood cells in the bone marrow of whole organisms, has been described by a variety of mathematical models in the past decades. However, the in vitro erythropoiesis, which produces red blood cells in cultures, has received much less attention from the modelling community. In the paper [15], we propose the first mathematical model of in vitro erythropoiesis. We start by formulating different models and select the best one at fitting experimental data of in vitro erythropoietic differentiation obtained from chicken erythroid progenitor cells. It is based on a set of linear ODE, describing 3 hypothetical populations of cells at different stages of differentiation. We then compute confidence intervals for all of its parameters estimates, and conclude that our model is fully identifiable. Finally, we use this model to compute the effect of a chemical drug called Rapamycin, which affects all states of differentiation in the culture, and relate these effects to specific parameter variations. We provide the first model for the kinetics of in vitro cellular differentiation which is proven to be identifiable. It will serve as a basis for a model which will better account for the variability which is inherent to the experimental protocol used for the model calibration.

## 5.8. Model-based assessment of the role of uneven partitioning of molecular content on heterogeneity and regulation of differentiation in CD8 T-cell immune responses

Activation of naive CD8 T-cells can lead to the generation of multiple effector and memory subsets. Multiple parameters associated with activation conditions are involved in generating this diversity that is associated with heterogeneous molecular contents of activated cells. Although naive cell polarisation upon antigenic stimulation and the resulting asymmetric division are known to be a major source of heterogeneity and cell fate regulation, the consequences of stochastic uneven partitioning of molecular content upon subsequent divisions remain unclear yet. In [16], we aim at studying the impact of uneven partitioning on molecular-content heterogeneity and then on the immune response dynamics at the cellular level. To do so, we introduce a multiscale mathematical model of the CD8 T-cell immune response in the lymph node. In the model, cells are described as agents evolving and interacting in a 2D environment while a set of differential equations, embedded in each cell, models the regulation of intra and extracellular proteins involved in cell differentiation. Based on the analysis of *in silico* data at the single cell level, we show that immune response dynamics can be explained by the molecular-content heterogeneity generated by uneven partitioning at cell division. In particular, uneven partitioning acts as a regulator of cell differentiation and induces the emergence of two coexisting sub-populations of cells exhibiting antagonistic fates. We show that the degree of unevenness of molecular partitioning, along all cell divisions, affects the outcome of the immune response and can promote the generation of memory cells.

## 5.9. Spatial lymphocyte dynamics in lymph nodes predicts the cytotoxic T-Cell frequency needed for HIV infection control

The surveillance of host body tissues by immune cells is central for mediating their defense function. *In vivo* imaging technologies have been used to quantitatively characterize target cell scanning and migration of lymphocytes within lymph nodes (LNs). The translation of these quantitative insights into a predictive understanding of immune system functioning in response to various perturbations critically depends on computational tools linking the individual immune cell properties with the emergent behavior of the immune system. By choosing the Newtonian second law for the governing equations, we developed in [17] a broadly applicable mathematical model linking individual and coordinated T-cell behaviors. The spatial cell dynamics is described by a superposition of autonomous locomotion, intercellular interaction, and viscous damping processes. The model is calibrated using *in vivo* data on T-cell motility metrics in LNs such as the translational speeds, turning angle speeds, and meandering indices. The model is applied to predict the impact of T-cell motility on protection against HIV infection, i.e., to estimate the threshold frequency of HIV-specific cytotoxic T cells (CTLs) that is required to detect productively infected cells before the release of viral particles starts. With this, it provides guidance for HIV vaccine studies allowing for the migration of cells in fibrotic LNs.

## 5.10. Drugs modulating stochastic gene expression affect the erythroid differentiation process

To better understand the mechanisms behind cells decision-making to differentiate, we assessed in [18] the influence of stochastic gene expression (SGE) modulation on the erythroid differentiation process. It has been suggested that stochastic gene expression has a role in cell fate decision-making which is revealed by single-cell analyses but studies dedicated to demonstrate the consistency of this link are still lacking. Recent observations showed that SGE significantly increased during differentiation and a few showed that an increase of the level of SGE is accompanied by an increase in the differentiation process. However, a consistent relation in both increasing and decreasing directions has never been shown in the same cellular system. Such demonstration would require to be able to experimentally manipulate simultaneously the level of SGE and cell differentiation in order to observe if cell behavior matches with the current theory. We identified three drugs that modulate SGE in primary erythroid progenitor cells. Both Artemisinin and Indomethacin

decreased SGE and reduced the amount of differentiated cells. On the contrary, a third component called MB-3 simultaneously increased the level of SGE and the amount of differentiated cells. We then used a dynamical modelling approach which confirmed that differentiation rates were indeed affected by the drug treatment. Using single-cell analysis and modeling tools, we provide experimental evidence that, in a physiologically relevant cellular system, SGE is linked to differentiation.

### **5.11. Stochastic gene expression with a multistate promoter: breaking down exact distributions**

We consider in [19] a stochastic model of gene expression in which transcription depends on a multistate promoter, including the famous two-state model and refractory promoters as special cases, and focus on deriving the exact stationary distribution. Building upon several successful approaches, we present a more unified viewpoint that enables us to simplify and generalize existing results. In particular, the original jump process is deeply related to a multivariate piecewise-deterministic Markov process that may also be of interest beyond the biological field. In a very particular case of promoter configuration, this underlying process is shown to have a simple Dirichlet stationary distribution. In the general case, the corresponding marginal distributions extend the well-known class of Beta products, involving complex parameters that directly relate to spectral properties of the promoter transition matrix. Finally, we illustrate these results with biologically plausible examples.

### **5.12. Cell generation dynamics underlying naive T-cell homeostasis in adult humans**

Thymic involution and proliferation of naive T-cells both contribute to shaping the naive T-cell repertoire as humans age, but a clear understanding of the roles of each throughout a human life span has been difficult to determine. By measuring nuclear bomb test-derived  $^{14}\text{C}$  in genomic DNA, we determined in [22] the turnover rates of CD4+ and CD8+ naive T-cell populations and defined their dynamics in healthy individuals ranging from 20 to 65 years of age. We demonstrate that naive T-cell generation decreases with age because of a combination of declining peripheral division and thymic production during adulthood. Concomitant decline in T-cell loss compensates for decreased generation rates. We investigated putative mechanisms underlying age-related changes in homeostatic regulation of CD4+ naive T-cell turnover, using mass cytometry to profile candidate signaling pathways involved in T-cell activation and proliferation relative to CD31 expression, a marker of thymic proximity for the CD4+ naive T-cell population. We show that basal nuclear factor  $\kappa\text{B}$  (NF- $\kappa\text{B}$ ) phosphorylation positively correlated with CD31 expression and thus is decreased in peripherally expanded naive T-cell clones. Functionally, we found that NF- $\kappa\text{B}$  signaling was essential for naive T-cell proliferation to the homeostatic growth factor interleukin (IL)-7, and reduced NF- $\kappa\text{B}$  phosphorylation in CD4+ CD31- naive T cells is linked to reduced homeostatic proliferation potential. Our results reveal an age-related decline in naive T-cell turnover as a putative regulator of naive T-cell diversity and identify a molecular pathway that restricts proliferation of peripherally expanded naive T-cell clones that accumulate with age.

### **5.13. Erythroid differentiation displays a peak of energy consumption concomitant with glycolytic metabolism rearrangements**

Our previous single-cell based gene expression analysis pointed out significant variations of LDHA level during erythroid differentiation. Deeper investigations highlighted that a metabolic switch occurred along differentiation of erythroid cells. More precisely we showed in [26] that self-renewing progenitors relied mostly upon lactate-productive glycolysis, and required LDHA activity, whereas differentiating cells, mainly involved mitochondrial oxidative phosphorylation (OXPHOS). These metabolic rearrangements were coming along with a particular temporary event, occurring within the first 24h of erythroid differentiation. The activity of glycolytic metabolism and OXPHOS rose jointly with oxygen consumption dedicated to ATP production at 12-24h of the differentiation process before lactate-productive glycolysis sharply fall down and energy needs decline. Finally, we demonstrated that the metabolic switch mediated through LDHA drop and OXPHOS

upkeep might be necessary for erythroid differentiation. We also discuss the possibility that metabolism, gene expression and epigenetics could act together in a circular manner as a driving force for differentiation.

## 6. Partnerships and Cooperations

### 6.1. Regional Initiatives

- The Région ARA project INGERENCE dedicated to “INferring GENE REgulatory NEtworks from single CELL Data to improve vaccine design”, 2018-2021.  
**Participants:** Olivier Gandrillon, Fabien Crauste [Coordinator].

### 6.2. National Initiatives

#### 6.2.1. ANR

- ANR SinCity “Single cell transcriptomics on genealogically identified differentiating cells” (<https://anr.fr/Projet-ANR-17-CE12-0031>), 2017-2020.  
**Participant:** Olivier Gandrillon [Coordinator].
- Olivier Gandrillon participates in the ANR MEMOIRE (head Jacqueline Marvel) dedicated to “MultiscalE MOdeling of CD8 T cell Immune REsponses”, 2018-2021.

#### 6.2.2. Other projects

- Thomas Lepoutre is a member of the ERC MESOPROBIO (head Vincent Calvez) dedicated to “Mesoscopic models for propagation in biology”, 2015-2020: (<http://vcalvez.perso.math.cnrs.fr/mesoprobio.html>).

### 6.3. European Initiatives

#### 6.3.1. FP7 & H2020 Projects

- Olivier Gandrillon and Alexey Koshkin participate in the EU RTN network COSMIC (head Antpoine van Kampen) dedicated to “Combatting disorders of adaptive immunity with systems medicine”, 2018-2021, <https://cosmic-h2020.eu>

### 6.4. International Initiatives

#### 6.4.1. Inria Associate Teams Not Involved in an Inria International Labs

##### 6.4.1.1. MathModelingHematopoiesis

Title: Mathematical modeling of hematopoietic stem cell dynamics in normal and pathological hematopoiesis with optimal control for drug therapy

International Partner (Institution - Laboratory - Researcher):

Presidency University, Kolkata (India) - Subhas Khajanchi

Start year: 2019

The project proposes to develop and analyse new mathematical models of Hematopoietic Stem Cell population dynamics in normal and pathological hematopoiesis. Two important questions will be explored in this project: i) the biological data concerning the hematopoiesis process evolves constantly, and new understanding modifies the established mathematical models, ii) modeling constraints us to simplify the complicated biological scenarios, which moving away from the reality, but enabling us to reach a certain comprehension of the hematopoiesis process.

The project will shed new light on the different physiological mechanisms that converge toward the continuous regeneration of blood cells, for example: the behavior of hematopoietic stem cells under stress conditions, the understanding of deregulation of erythropoiesis under drug treatments (this can lead to lack of red blood cells (anemia), or a surplus of red blood cells (erythrocytoses)), the appearance of oscillations in patients with Chronic Myeloid Leukemia (CML); Or, the overproduction of blasts in patients with Acute Myeloid Leukemia (AML)). The effect of the immune system and drug therapy in the presence of CML or AML will be included in the model and optimal control method will also be used.

#### **6.4.2. Participation in Other International Programs**

##### *6.4.2.1. Indo-French Center of Applied Mathematics*

Title: Mathematical modeling of hematopoiesis process in application to chronic and acute myelogenous leukemia

International Partner (Institution - Laboratory - Researcher):

Department of Mathematics - Presidency University, Kolkata (India) - Subhas Khajanchi

Duration: 2018 - 2021

Start year: 2018

### **6.5. International Research Visitors**

#### **6.5.1. Visits of International Scientists**

Jairo Gomes da Silva, PhD student at Institute of Biosciences, São Paulo State University (UNESP), Botucatu, Brazil, visiting the team for 6 months (from September 2019 to February 2020).

#### **6.5.2. Visits to International Teams**

Paul Lemarre is visiting University of California, Merced, USA, in 2019-2020.

## **7. Dissemination**

### **7.1. Promoting Scientific Activities**

#### **7.1.1. Scientific Events: Organisation**

##### *7.1.1.1. General Chair, Scientific Chair*

- Olivier Gandrillon, International Conference of Systems Biology 2019, Lyon, <http://www.ens-lyon.fr/evenement/recherche/icsb-2018-19th-international-conference-systems-biology>

##### *7.1.1.2. Member of the organizing Committees*

- Laurent Pujo-Menjouet, The Society for Mathematical Biology, Annual Meeting and Conference, Montreal, Canada, mini-symposium co-organizer, 21-26 July 2019

#### **7.1.2. Journal**

##### *7.1.2.1. Member of the Editorial Boards*

- Mostafa Adimy, Journal of Nonlinear Systems and Applications
- Olivier Gandrillon, Associate editor for BMC research notes
- Vincent Calvez, Journal of Mathematical Biology; SIAM Journal of Mathematical Analysis
- Laurent Pujo-Menjouet, Associate editor of PLOS ONE; Journal of Theoretical Biology; Mathematical modelling of natural phenomena

#### 7.1.2.2. Reviewer - Reviewing Activities

- Mostafa Adimy, Canadian Journal of Mathematics; PLOS Neglected Tropical Diseases; Journal of Mathematical Modeling of Natural Phenomena
- Olivier Gandrillon, Plos Computational Biology; Progress in Biophysics and Molecular Biology; Journal of the Royal Society Interface; Journal of theoretical biology; Systems Biology and Applications; Genes
- Vincent Calvez, Inventiones Mathematicae; Duke Math Journal; Journal of the EMS; Nature Physics; Ecology Letters
- Laurent Pujo-Menjouet, Journal of Theoretical Biology; Plos One, Plos Computational Biology; Journal of Mathematical Modeling of Natural Phenomena; Journal of Mathematical Biology; Bulletin of Mathematical Biology; Computational and applied mathematics; Mathematical Biosciences and Engineering

#### 7.1.3. Invited Talks

- Mostafa Adimy, International Conference on Mathematical Modelling in Biomedicine, Moscow - Russia, 30 September - 04 October, 2019, <http://eng.rudn.ru/science/conferences/9370>
- Mostafa Adimy, 9ème colloque, Tendances dans les Applications Mathématiques (TAMTAM), Tlemcen - Algeria, 24 - 27 February 2019, <https://tamtam2019-univ-tlemcen.weebly.com/accueil.html>
- Vincent Calvez, BIOMAT Granada, Patterns in Life and Social Sciences, Granada - Spain, June 17-19, <http://www.ugr.es/~kinetic/biomat/>
- Vincent Calvez, Colloque d'ouverture 50 ans du Laboratoire J.L. Lions, Roscoff - France, 4-8 mars 2019 <https://ljl-roscoff.sciencesconf.org>
- Vincent Calvez, Journées Aussois Chaire MMB, Aussois - France, 19 - 23 May <http://www.cmap.polytechnique.fr/chaire-mmb/Aussois2019.html>
- Vincent Calvez, LMS Research School, PDEs in Mathematical Biology: Modelling and Analysis, ICMS, Edinburgh - UK, 29 April – 3 May 2019, [https://www.icms.org.uk/LMS\\_PDEsmathbio.php](https://www.icms.org.uk/LMS_PDEsmathbio.php)
- Laurent Pujo-Menjouet, Mathématiques étonnantes, SMF conference, Lyon, 9 December, <https://smf.emath.fr/conference-coeur>

#### 7.1.4. Leadership within the Scientific Community

- Olivier Gandrillon, Director of BioSyL, the Federative Research Structure for Systems Biology attached to University of Lyon, <http://www.biosyl.org>
- Thomas Lepoutre, Head of the Groupe de Recherches CNRS MAMOVI on applied mathematical modelling in Life Sciences

#### 7.1.5. Research Administration

- Léon Tine, Membre conseil du département de Mathématiques, UCBL 1
- Léon Tine, Co-responsable de l'enseignement TMB ( Techniques Mathématiques de Base) du portail PCSI, UCBL 1
- Mostafa Adimy, Comité scientifique (COS) du centre Inria Rhône-Alpes
- Mostafa Adimy, Comité scientifique (CS) de l'Institut Camille Jordan, UCBL 1

- Mostafa Adimy, Comité des thèses de l'Institut Camille Jordan, UCBL 1
- Laurent Pujo-Menjouet, Responsable de la filière mathématiques pour la biologie et la médecine pour le master M2 Maths en Actions à l'UCBL 1
- Laurent Pujo-Menjouet, Correspondant mobilité international pour le département de mathématiques à l'UCBL 1
- Laurent Pujo-Menjouet, Directeur du portail mathématiques et informatique à l'UCBL 1
- Thomas Lepoutre member of the CORDI-S commission of Inria.

## 7.2. Teaching - Supervision - Juries

### 7.2.1. Teaching

- Licence: Laurent Pujo-Menjouet, Fondamentaux des mathématiques, 138h EQTD, L1, UCBL 1
- Licence: Laurent Pujo-Menjouet, 3ème année biosciences BIM, Systèmes Dynamiques et EDP, 45h EQTD, INSA Lyon
- Licence : Léon Tine, Techniques mathématiques de base, 53h (EqTD), niveau L0, UCBL 1
- Licence : Léon Tine, Techniques mathématiques de base, 62h (EqTD), niveau L1, UCBL 1
- Licence : Léon Tine, Initiation LaTeX+ stage, 12h (EqTD), niveau L3, UCBL 1
- Licence : Vincent Calvez, Cours de math pour étudiants médecins, cursus Médecine-Sciences (2e année fac de médecine), 40h, Lyon Est/Sud
- Master : Samuel Bernard, Population Dynamics, 36h ETD, M2, UCBL 1
- Master : Mostafa Adimy, Population Dynamics, 9h ETD, M2, UCBL, UCBL 1
- Master : Mostafa Adimy, Epidemiology, 21h ETD, M2, UCBL, UCBL 1
- Master: Thomas Lepoutre, préparation à l'option pour l'agrégation, 45 h eq TD, M2 UCBL 1
- Master: Laurent Pujo-Menjouet, Systèmes Dynamiques, 72 h EQTD, M1, UCBL1
- Master: Laurent Pujo-Menjouet, Systèmes complexes: modelling biology and medicine, M2, 9h EQTD, ENS-Lyon
- Master: Laurent Pujo-Menjouet, 4ème année biosciences BIM: ED-EDP, 24h EQTD, INSA Lyon
- Master: Léon Tine, Maths en action, Remise à niveau analyse, 12h (EqTD), niveau M2, UCBL 1
- Master: Léon Tine, Maths en action, épidémiologie, 18h (EqTD), niveau M2, UCBL 1
- Master: Vincent Calvez, Modèles mathématiques et analyse pour Ecologie et Evolution, 24h, niveau M2 avancé, ENS-Lyon
- Master: Olivier Gandrillon, Systems Biology, 8h, niveau M2 Génopopath, UCBL 1

### 7.2.2. Supervision

- PhD in progress: Aurélien Canet, "Contribution à l'étude de la quantification de la réponse d'une tumeur solide après un traitement par radiothérapie", Université Lyon, since January 2016, supervisors: Larry Bodgi, Nicolas Foray and Laurent Pujo-Menjouet
- PhD in progress: Kyriaki Dariva, "Modélisation mathématique des interactions avec le système immunitaire en leucémie myéloïde chronique". Université Lyon 1, since September 2018, supervisor: Thomas Lepoutre
- PhD in progress: Ronan Duchesne, "Vers un modèle multi-échelle de la différenciation cellulaire : Application à la différenciation érythrocytaire", École normale supérieure de Lyon and Université Lyon 1, Décembre 2019, supervisors: Olivier Gandrillon and Fabien Crauste
- PhD in progress: Alexey Koshkin, "Inferring gene regulatory networks from single cell data", ENS de Lyon, since September 2018, supervisors: Olivier Gandrillon and Fabien Crauste



- PhD in progress: Paul Lemarre, “Modélisation des souches de prions”. Université Lyon 1, since May 2017, supervisors: Laurent Pujo-Menjouet et Suzanne Sindi (University of California, Merced)
- PhD in progress: Léonard Dekens, “Adaptation d’une population avec une reproduction sexuée à un environnement hétérogène : modélisation mathématique et analyse asymptotique dans un régime de petite variance”, Université Lyon 1, since September 2019, supervisor: Vincent Calvez.
- PhD in progress: Mete Demircigil, “Etude du mouvement collectif chez Dictyostelium Discoideum et autres espèces. Modélisation, Analyse et Simulation”, ENS-Lyon, since September 2019, supervisor: Vincent Calvez.
- PhD in progress: Ghada Abi Younes, “Modélisation mathématique des maladies inflammatoires”, Université Lyon, since November 2019, supervisor: Vitaly Volpert.
- PhD in progress: Elias Ventre, “Paysage et trajectoire - des réseaux de régulation génique aux trajectoires cellulaires”, ENS - Lyon, since October 2019, supervisors: Olivier Gandrillons and Thibault Espinasse.
- PhD in progress: Cheikh Gueye, “Problèmes inverses pour l’estimation de paramètre de modèles mathématiques”, Université Lyon, since October 2019, supervisors: Laurent Pujo-Menjouet and Léon Tine.

### 7.2.3. Juries

- Laurent Pujo-Menjouet: PhD of Hugo Martin, Étude de données et analyse de modèles intégrodifférentiels en biologie cellulaire, Laboratoire Jacques-Louis Lions - Sorbonne Université, examiner.
- Vincent Calvez: PhD of Pierre Roux, Équations aux dérivées partielles de type Keller-Segel en dynamique des populations et de type Fokker-Planck en neurosciences, Laboratoire de mathématiques d’Orsay - Université Paris-Sud, reviewer
- Vincent Calvez: PhD of Xiaoming Fu, Reaction-diffusion Equations with Nonlinear and Nonlocal Advection Applied to Cell Co-culture, Institut de Mathématiques de Bordeaux, Université de Bordeaux, examiner
- Olivier Gandrillon: PhD of Ronan Duchesne, Erythroid differentiation in vitro under the lens of mathematical modelling, ENS-Lyon, examiner.

## 7.3. Popularization

### 7.3.1. Articles and contents

- Laurent Pujo-Menjouet : Radio (France Inter), la tête au carré, <https://www.franceinter.fr/emissions/la-tete-au-carre/la-tete-au-carre-10-mai-2019>
- Laurent Pujo-Menjouet : Radio (Europe 1), Wendy Bouchard, <https://www.europe1.fr/emissions/on-fait-le-tour-de-la-question-avec-wendy-bouchard/wendy-bouchard-aujourd'hui-alchimie-equation-formule-magique-lamour-est-il-le-fruit-du-hasard-3905606>
- Laurent Pujo-Menjouet : Radio (Québec), <https://www.qub.radio/balado?id=6bb8beb9-9bb3-493f-abe3-aa7100f60a73&episode=3f6e7a5c-b11a-45ff-aa28-aa96015f517b&fbclid=IwAR2DUNgo-QvKh3z9oGeslTJOnCa3f5GzTYWIIGrYSe5hrm7ydSgc1gW6Z5g>
- Laurent Pujo-Menjouet : Radio Canada, <https://ici.radio-canada.ca/premiere/emissions/region-zero-8/episodes/439145/audio-fil-du-vendredi-26-juillet-2019/10>
- Laurent Pujo-Menjouet : Presse écrite (L’Express), [https://www.lexpress.fr/actualite/sciences/le-livre-qui-veut-modeliser-l-amour-par-les-mathematiques\\_2075520.html](https://www.lexpress.fr/actualite/sciences/le-livre-qui-veut-modeliser-l-amour-par-les-mathematiques_2075520.html)
- Laurent Pujo-Menjouet : Presse écrite (Le Figaro), <http://www.lefigaro.fr/sciences/le-bonheur-conjugal-c-est-simple-comme-une-equation-differentielle-20190506>



- Laurent Pujo-Menjouet : Presse écrite (Slate), <http://www.slate.fr/story/178140/maths-livre-jeu-amour-hasard-laurent-pujo-menjouet>
- Laurent Pujo-Menjouet : Presse écrite (Le Parisien), <http://www.leparisien.fr/societe/et-si-l-amour-n-etait-pas-le-fruit-du-hasard-10-06-2019-8090055.php>
- Laurent Pujo-Menjouet : Presse écrite (Montreal Gazette), <https://montrealgazette.com/news/local-news/equations-can-predict-the-success-of-relationships-mathematician-says>
- Laurent Pujo-Menjouet : Presse écrite (Society), <http://math.univ-lyon1.fr/~pujo/Society.pdf>
- Laurent Pujo-Menjouet : Presse écrite (Le matin dimanche, Suisse), <https://twitter.com/lpmenjouet/status/1130474006312890373/photo/1>
- Laurent Pujo-Menjouet : Presse écrite (Le journal de Montréal), <https://www.journaldemontreal.com/2019/07/30/et-si-lamour-se-maintenait-avec-des-equations-mathematiques>

### 7.3.2. Interventions

- Thomas Lepoutre: Visite de l'inria pour les stagiaires de 3e de l'ICJ (plusieurs fois dans l'année, une matinée en général).
- Thomas Lepoutre participation to MathaLyon intervention
- Laurent Pujo-Menjouet participation to "Math en Jeans", Collège-Lycée Lacassagne, Lyon and Collège Gratte-Ciel, Villeurbanne
- Laurent Pujo-Menjouet participation to "Mathématiques étonnantes, SMF conférence", Lyon
- Laurent Pujo-Menjouet participation to TEDx, Montrouge [https://www.youtube.com/watch?v=xJ8wE\\_wmtUY](https://www.youtube.com/watch?v=xJ8wE_wmtUY)

## 8. Bibliography

### Publications of the year

#### Doctoral Dissertations and Habilitation Theses

- [1] R. DUCHESNE. *Erythroid differentiation in vitro under the lens of mathematical modelling*, Université de Lyon, December 2019, <https://hal.archives-ouvertes.fr/tel-02440831>

#### Articles in International Peer-Reviewed Journals

- [2] M. ADIMY, A. CHEKROUN, T. KUNIYA. *Coupled reaction-diffusion and difference system of cell-cycle dynamics for hematopoiesis process with Dirichlet boundary conditions*, in "Australian Journal of Mathematical Analysis and Applications", November 2019, vol. 479, n<sup>o</sup> 1, pp. 1030-1068 [DOI : 10.1016/J.JMAA.2019.06.066], <https://hal.inria.fr/hal-02448738>
- [3] M. ADIMY, A. CHEKROUN, C. PIO FERREIRA. *Global dynamics of a differential-difference system: a case of Kermack-McKendrick SIR model with age-structured protection phase*, in "Mathematical Biosciences and Engineering", 2020, vol. 17, n<sup>o</sup> 2, pp. 1329-1354 [DOI : 10.3934/MBE.2020067], <https://hal.inria.fr/hal-02431660>
- [4] P. ARNER, S. BERNARD, L. APPELSVED, K.-Y. FU, D. ANDERSSON, M. SALEHPOUR, A. THORELL, M. RYDÉN, K. SPALDING. *Adipose lipid turnover and long-term changes in body weight*, in "Nature Medicine", September 2019, vol. 25, n<sup>o</sup> 9, pp. 1385-1389 [DOI : 10.1038/s41591-019-0565-5], <https://hal.archives-ouvertes.fr/hal-02317491>

- [5] M. A. BENCHAI, A. BOUCHNITA, V. VOLPERT, A. MAKHOUTE. *Mathematical Modeling Reveals That the Administration of EGF Can Promote the Elimination of Lymph Node Metastases by PD-1/PD-L1 Blockade*, in "Frontiers in Bioengineering and Biotechnology", May 2019, vol. 7, pp. 1-18 [DOI : 10.3389/FBIOE.2019.00104], <https://hal.archives-ouvertes.fr/hal-02363404>
- [6] N. BESSONOV, A. BEUTER, S. TROFIMCHUK, V. VOLPERT. *Cortical waves and post-stroke brain stimulation*, in "Mathematical Methods in the Applied Sciences", June 2019, vol. 42, n<sup>o</sup> 11, pp. 3912-3928 [DOI : 10.1002/MMA.5620], <https://hal.archives-ouvertes.fr/hal-02363412>
- [7] N. BESSONOV, A. BEUTER, S. TROFIMCHUK, V. VOLPERT. *Estimate of the travelling wave speed for an integro-differential equation*, in "Applied Mathematics Letters", February 2019, vol. 88, pp. 103-110 [DOI : 10.1016/J.AML.2018.07.037], <https://hal.archives-ouvertes.fr/hal-01941455>
- [8] A. BONNAFFOUX, U. HERBACH, A. RICHARD, A. GUILLEMIN, S. GONIN-GIRAUD, P.-A. GROS, O. GANDRILLON. *WASABI: a dynamic iterative framework for gene regulatory network inference*, in "BMC Bioinformatics", April 2019, vol. 20, n<sup>o</sup> 1, pp. 1-19 [DOI : 10.1186/s12859-019-2798-1], <https://hal.archives-ouvertes.fr/hal-02159694>
- [9] A. BOUCHNITA, V. VOLPERT. *A multiscale model of platelet-fibrin thrombus growth in the flow*, in "Computers & Fluids", April 2019, vol. 184, pp. 10-20 [DOI : 10.1016/J.COMPFLUID.2019.03.021], <https://hal.archives-ouvertes.fr/hal-02363406>
- [10] L. BOULLU, M. ADIMY, F. CRAUSTE, L. PUJO-MENJOUET. *Oscillations and asymptotic convergence for a delay differential equation modeling platelet production*, in "Discrete and Continuous Dynamical Systems - Series B", 2019, vol. 24, n<sup>o</sup> 6, pp. 2417-2442 [DOI : 10.3934/DCDSB.2018259], <https://hal.inria.fr/hal-01835435>
- [11] L. BOULLU, L. PUJO-MENJOUET, J. BÉLAIR. *Stability analysis of an equation with two delays and application to the production of platelets*, in "Discrete and Continuous Dynamical Systems - Series S", 2019, pp. 1-24, forthcoming [DOI : 10.3934/DCDSS.2020131], <https://hal.inria.fr/hal-02109546>
- [12] L. BOULLU, L. PUJO-MENJOUET, J. WU. *A model for megakaryopoiesis with state-dependent delay*, in "SIAM Journal on Applied Mathematics", July 2019, vol. 79, n<sup>o</sup> 4, pp. 1218-1243 [DOI : 10.1137/18M1201020], <https://hal.inria.fr/hal-02123621>
- [13] V. CALVEZ, T. LEPOUTRE, N. MEUNIER, N. MULLER. *Non-linear analysis of a model for yeast cell communication*, in "ESAIM: Mathematical Modelling and Numerical Analysis", 2019, pp. 1-32, forthcoming [DOI : 10.1051/M2AN/2019065], <https://hal.inria.fr/hal-02372511>
- [14] I. S. CIUPERCA, M. DUMONT, A. LAKMECHE, P. MAZZOCCO, L. PUJO-MENJOUET, H. REZAEI, L. TINE. *Alzheimer's disease and prion: An in vitro mathematical model*, in "Discrete and Continuous Dynamical Systems - Series B", October 2019, vol. 24, n<sup>o</sup> 10, pp. 5225-5260 [DOI : 10.3934/DCDSB.2019057], <https://hal.archives-ouvertes.fr/hal-02414635>
- [15] R. DUCHESNE, A. GUILLEMIN, F. CRAUSTE, O. GANDRILLON. *Calibration, Selection and Identifiability Analysis of a Mathematical Model of the in vitro Erythropoiesis in Normal and Perturbed Contexts*, in "In Silico Biology", May 2019, vol. 13, n<sup>o</sup> 1-2, pp. 55-69 [DOI : 10.3233/ISB-190471], <https://hal.archives-ouvertes.fr/hal-02309925>

- [16] S. GIREL, C. ARPIN, J. MARVEL, O. GANDRILLON, F. CRAUSTE. *Model-based assessment of the Role of Uneven Partitioning of Molecular Content on Heterogeneity and Regulation of Differentiation in CD8 T-cell Immune Responses*, in "Frontiers in Immunology", 2019, pp. 1-41, <https://arxiv.org/abs/1903.01233>, forthcoming [DOI : 10.3389/FIMMU.2019.00230], <https://hal.archives-ouvertes.fr/hal-02008705>
- [17] D. GREBENNIKOV, A. BOUCHNITA, V. VOLPERT, N. BESSONOV, A. MEYERHANS, G. BOCHAROV. *Spatial Lymphocyte Dynamics in Lymph Nodes Predicts the Cytotoxic T Cell Frequency Needed for HIV Infection Control*, in "Frontiers in Immunology", June 2019, vol. 10, pp. 1-15 [DOI : 10.3389/FIMMU.2019.01213], <https://hal.archives-ouvertes.fr/hal-02363399>
- [18] A. GUILLEMIN, R. DUCHESNE, F. CRAUSTE, S. GONIN-GIRAUD, O. GANDRILLON. *Drugs modulating stochastic gene expression affect the erythroid differentiation process*, in "PLoS ONE", November 2019, vol. 14, n<sup>o</sup> 11, pp. 1-19 [DOI : 10.1371/JOURNAL.PONE.0225166], <https://hal.archives-ouvertes.fr/hal-02375801>
- [19] U. HERBACH. *Stochastic Gene Expression with a Multistate Promoter: Breaking Down Exact Distributions*, in "SIAM Journal on Applied Mathematics", June 2019, vol. 79, n<sup>o</sup> 3, pp. 1007-1029 [DOI : 10.1137/18M1181006], <https://hal.archives-ouvertes.fr/hal-02159699>
- [20] T. LEPOUTRE. *Improved duality estimates: time discrete case and applications to a class of cross-diffusion systems*, in "Communications in Mathematical Sciences", 2019, vol. 17, n<sup>o</sup> 2, pp. 1-17, <https://arxiv.org/abs/1812.01296>, <https://hal.inria.fr/hal-01943576>
- [21] M. MARION, V. VOLPERT. *Existence of Pulses for the System of Competition of Species*, in "Journal of Dynamics and Differential Equations", September 2019, vol. 31, n<sup>o</sup> 3, pp. 1653-1670 [DOI : 10.1007/s10884-017-9582-6], <https://hal.archives-ouvertes.fr/hal-02363423>
- [22] J. E. MOLD, P. RÉU, A. OLIN, S. BERNARD, J. MICHAELSSON, S. RANE, A. YATES, A. KHOSRAVI, M. SALEHPOUR, G. POSSNERT, P. BRODIN, J. FRISÉN. *Cell generation dynamics underlying naïve T cell homeostasis in adult humans*, in "PLoS Biology", October 2019, vol. 17, n<sup>o</sup> 10, e3000383 p. [DOI : 10.1101/635995], <https://hal.archives-ouvertes.fr/hal-02160888>
- [23] N. RATTO, M. MARION, V. VOLPERT. *Existence of pulses for a reaction-diffusion system of blood coagulation in flow*, in "Mathematical Biosciences and Engineering", 2019, vol. 16, n<sup>o</sup> 5, pp. 4196-4212, forthcoming [DOI : 10.3934/MBE.2019209], <https://hal.archives-ouvertes.fr/hal-02084120>
- [24] N. RATTO, M. MARION, V. VOLPERT. *Existence of pulses for a reaction-diffusion system of blood coagulation*, in "Topological Methods in Nonlinear Analysis", 2019, forthcoming, <https://hal.archives-ouvertes.fr/hal-02089011>
- [25] N. RATTO, M. MARION, V. VOLPERT. *Existence of Waves for a Bistable Reaction–Diffusion System with Delay*, in "Journal of Dynamics and Differential Equations", 2019, vol. 16, n<sup>o</sup> 5, pp. 4196-4212 [DOI : 10.1007/s10884-019-09751-4], <https://hal.archives-ouvertes.fr/hal-02363403>
- [26] A. RICHARD, E. VALLIN, C. ROMESTAING, D. ROUSSEL, O. GANDRILLON, S. GONIN-GIRAUD. *Erythroid differentiation displays a peak of energy consumption concomitant with glycolytic metabolism rearrangements*, in "PLoS ONE", September 2019, vol. 14, n<sup>o</sup> 9, e0221472 p. [DOI : 10.1371/JOURNAL.PONE.0221472], <https://hal-univ-lyon1.archives-ouvertes.fr/hal-02318812>

- [27] M. SEN, V. VOLPERT, V. VOUGALTER. *Existence of waves for a reaction–diffusion–dispersion system*, in "Nonlinear Analysis: Theory, Methods and Applications", March 2019, vol. 180, pp. 52-66 [DOI : 10.1016/J.NA.2018.09.011], <https://hal.archives-ouvertes.fr/hal-01941461>
- [28] S. TROFIMCHUK, V. VOLPERT. *Global continuation of monotone waves for bistable delayed equations with unimodal nonlinearities*, in "Nonlinearity", July 2019, vol. 32, n<sup>o</sup> 7, pp. 2593-2632 [DOI : 10.1088/1361-6544/AB0E23], <https://hal.archives-ouvertes.fr/hal-02363393>
- [29] M. YEUNG, M. DJELLOUL, E. STEINER, S. BERNARD, M. SALEHPOUR, G. POSSNERT, L. BRUNDIN, J. FRISÉN. *Dynamics of oligodendrocyte generation in multiple sclerosis*, in "Nature", January 2019, n<sup>o</sup> 566, pp. 538–542 [DOI : 10.1038/s41586-018-0842-3], <https://hal.archives-ouvertes.fr/hal-02002274>

### Conferences without Proceedings

- [30] M. ANDRADE-RESTREPO, P. LEMARRE, L. PUJO-MENJOUET, L. TINE, S. I. CIUPERCA. *Modeling the spatial propagation of A $\beta$  oligomers in alzheimer's disease*, in "CEMRACS 2018 - Numerical and mathematical modeling for biological and medical applications: deterministic, probabilistic and statistical descriptions", Marseille, France, 2019, pp. 1 - 10, <https://hal.archives-ouvertes.fr/hal-02414660>

### Scientific Books (or Scientific Book chapters)

- [31] M. CALÉRO, I. S. CIUPERCA, L. PUJO-MENJOUET, L. MATAR TINE. *Alzheimer Disease: Convergence Result from a Discrete Model Towards a Continuous One*, in "Trends in Biomathematics: Mathematical Modeling for Health, Harvesting, and Population Dynamics", Springer, 2019, pp. 397-431 [DOI : 10.1007/978-3-030-23433-1\_25], <https://hal.archives-ouvertes.fr/hal-02414726>
- [32] K. GRZESIK, K. ENG, F. CRAUSTE, S. BATTAGLIA. *In Silico Methods for Studying T Cell Biology*, in "Int. Rev. Cell. Mol. Biol. 342", Elsevier, 2019, pp. 265-304 [DOI : 10.1016/BS.IRCMB.2018.07.005], <https://hal.archives-ouvertes.fr/hal-02237891>
- [33] L. PUJO-MENJOUET. *Le jeu de l'amour sans le hasard Mathématiques du couple*, Des Equateurs, May 2019, pp. 1-248, <https://hal.archives-ouvertes.fr/hal-02414777>
- [34] L. PUJO-MENJOUET. *Passer notre amour à la machine*, in "Futures of Love", August 2019, <https://hal.archives-ouvertes.fr/hal-02414758>

### Scientific Popularization

- [35] L. PUJO-MENJOUET. *Est-ce par hasard s'il a le cœur qui s'égaré*, in "Pour la science", November 2019, <https://hal.archives-ouvertes.fr/hal-02414752>

### Other Publications

- [36] C. ROCABERT, G. BESLON, C. KNIBBE, S. BERNARD. *Phenotypic Noise and the Cost of Complexity*, November 2019, EvoLyon 2019, Poster, <https://hal.archives-ouvertes.fr/hal-02402443>

### References in notes

- [37] A. BESSE, G. D. CLAPP, S. BERNARD, F. E. NICOLINI, D. LEVY, T. LEPOUTRE. *Stability Analysis of a Model of Interaction Between the Immune System and Cancer Cells in Chronic Myelogenous Leukemia*,

- in "Bulletin of Mathematical Biology", 2017, pp. 1–27 [DOI : 10.1007/s11538-017-0272-7], <https://hal.archives-ouvertes.fr/hal-01539364>
- [38] A. BESSE, T. LEPOUTRE, S. BERNARD. *Long-term treatment effects in chronic myeloid leukemia*, in "Journal of Mathematical Biology", 2017, pp. 1-26 [DOI : 10.1007/s00285-017-1098-5], <https://hal.archives-ouvertes.fr/hal-01447781>
- [39] G. D. CLAPP, T. LEPOUTRE, R. EL CHEIKH, S. BERNARD, J. RUBY, H. LABUSSIÈRE-WALLET, F. E. NICOLINI, D. LEVY. *Implication of the Autologous Immune System in BCR-ABL Transcript Variations in Chronic Myelogenous Leukemia Patients Treated with Imatinib.*, in "Cancer Research", October 2015, vol. 75, n<sup>o</sup> 19, pp. 4053-62 [DOI : 10.1158/0008-5472.CAN-15-0611], <https://hal.inria.fr/hal-01251396>
- [40] F. CRAUSTE, J. MAFILLE, L. BOUCINHA, S. DJEBALI, O. GANDRILLON, J. MARVEL, C. ARPIN. *Identification of Nascent Memory CD8 T Cells and Modeling of Their Ontogeny*, in "Cell Systems", February 2017, vol. 4, n<sup>o</sup> 3, pp. 306-317 [DOI : 10.1016/J.CELS.2017.01.014], <https://hal.inria.fr/hal-01409637>
- [41] U. HERBACH, A. BONNAFFOUX, T. ESPINASSE, O. GANDRILLON. *Inferring gene regulatory networks from single-cell data: a mechanistic approach*, in "BMC Systems Biology", November 2017, vol. 11, n<sup>o</sup> 1, 105 p. [DOI : 10.1186/s12918-017-0487-0], <https://hal.archives-ouvertes.fr/hal-01646910>