IN PARTNERSHIP WITH:
CNRS

Université Claude Bernard (Lyon 1)

Activity Report 2017

Project-Team DRACULA

Multi-scale modeling of cell dynamics: application to hematopoiesis

IN COLLABORATION WITH: Institut Camille Jordan

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Modeling and Control for Life Sciences

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

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1. Personnel

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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.

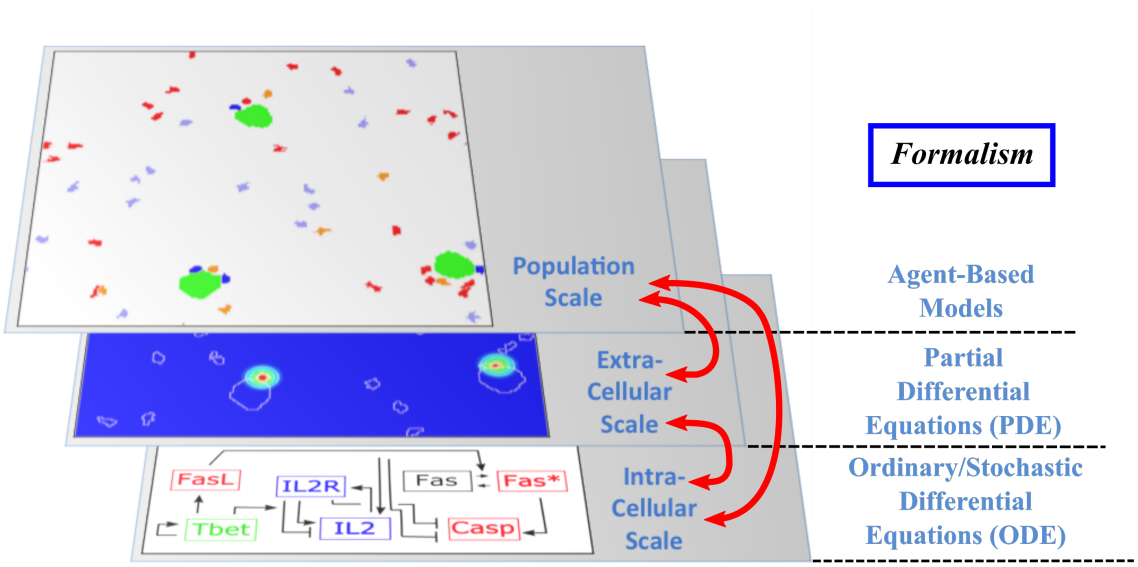

Figure 1. Scheme of multi-scale models of cell dynamics

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 sates, 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://www.inria.fr/en/teams/mamba), 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 Loeffer'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). 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 (2×100 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 (https://ceti.unm.edu/our-members/profile/alan-perelson.html) 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://www.inria.fr/en/teams/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 ([17]). 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 ([17]), 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 [21] 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 ([11], [12] and [34]). 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-though mechanism [11]. 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 Pujo-Menjouet, Nikolai Bessonov and Vitaly Volpert
- Contact: Vitaly Volpert

4.2. SiMuScale

We have developed within the team the *SiMuScale* platform, a software dedicated to exploring multi-scale population models (“SiMuScale” on researchgate, https://gforge.inria.fr/projects/simuscale). Coded in C++, *SiMuScale* is in active development since 2014. *SiMuScale* has been primarily developed to answer the need for an all-purpose, fast and flexible modeling tool for multiscale cell population dynamics. Biological agents (cells) are modeled by visco-elastic spheres, which are subject to mechanical constraints. Each cell possesses its own intracellular dynamics, coupled to other cells through bimolecular signals expressed at the surface of the cell. The internal state of the cell is also coupled to a behavioral state of the cell, which control the macroscopic fate: motility, growth, proliferation, death, etc. Mechanical interactions provide a 3D environment in which cells interact locally. *SiMuScale* is based on a core containing the simulator, and on plug-ins that contain the biological specifications of each cell. The core+plug-ins architecture makes it easier for the researcher to focus on the model and to capitalise on existing models, which all share the same framework and are compatible with each other. That way, *SiMuScale* makes the work of model writing and re-writing minimal and fits into reproducible research.

5. New Results

5.1. Cancer

5.1.1. Long-term treatment effects in chronic myeloid leukemia

We propose and analyze in [12] a simplified version of a partial differential equation (PDE) model for chronic myeloid leukemia (CML) derived from an agent-based model proposed by Roeder *et al.* in [38]. This model describes the proliferation and differentiation of leukemic stem cells in the bone marrow and the effect of the drug Imatinib on these cells. We first simplify the PDE model by noting that most of the dynamics occurs in a subspace of the original 2D state space. Then we determine the dominant eigenvalue of the corresponding linearized system that controls the long-term behavior of solutions. We mathematically show a

non-monotonous dependence of the dominant eigenvalue with respect to treatment dose, with the existence of a unique minimal negative eigen-value. In terms of CML treatment, this shows that there is a unique dose that maximizes the decay rate of the CML tumor load over long time scales. Moreover this unique dose is lower than the dose that maximizes the initial tumor load decay. Numerical simulations of the full model confirm that this phenomenon is not an artifact of the simplification. Therefore, while optimal asymptotic dosage might not be the best one at short time scales, our results raise interesting perspectives in terms of strategies for achieving and improving long-term deep response.

5.1.2. A model of interaction between the immune system and cancer cells in chronic myelogenous leukemia

We describe in [11] a simple model for the interaction between leukemic cells and the autologous immune response in chronic phase chronic myelogenous leukemia (CML). This model is a simplified version of the model we proposed in 2015 ([34]). Our simplification is based on the observation that certain key characteristics of the dynamics of CML can be captured with a three compartments model: two for the leukemic cells (stem cells and mature cells) and one for the immune response. We characterize the existence of steady states and their stability for generic forms of immunosuppres-sive effects of leukemic cells. We provide a complete co-dimension one bifurcation analysis. Our results show how clinical response to tyrosine kinase inhibitors treatment is compatible with the existence of a stable low-disease, treatment-free steady state.

5.1.3. A hybrid computation model to describe the progression of multiple myeloma and its intra-clonal heterogeneity

Multiple myeloma (MM) is a genetically complex hematological cancer that is characterized by proliferation of malignant plasma cells in the bone marrow. MM evolves from the clonal premalignant disorder monoclonal gammopathy of unknown significance (MGUS) by sequential genetic changes involving many different genes, resulting in dysregulated growth of multiple clones of plasma cells. The migration, survival, and proliferation of these clones require the direct and indirect interactions with the non-hematopoietic cells of the bone marrow. We develop in [14], a hybrid discrete-continuous model of MM development from the MGUS stage. The discrete aspect of the model is observed at the cellular level: cells are represented as individual objects which move, interact, divide, and die by apoptosis. Each of these actions is regulated by intracellular and extracellular processes as described by continuous models. The hybrid model consists of the following submodels that have been simplified from the much more complex state of evolving MM: cell motion due to chemotaxis, intracellular regulation of plasma cells, extracellular regulation in the bone marrow, and acquisition of mutations upon cell division. By extending a previous, simpler model in which the extracellular matrix was considered to be uniformly distributed, the new hybrid model provides a more accurate description in which cytokines are produced by the marrow microenvironment and consumed by the myeloma cells. The complex multiple genetic changes in MM cells and the numerous cell-cell and cytokine-mediated interactions between myeloma cells and their marrow microenviroment are simplified in the model such that four related but evolving MM clones can be studied as they compete for dominance in the setting of intraclonal heterogeneity.

5.1.4. Fast and binary assay for predicting radiosensitivity based on the nucleoshuttling of ATM protein: development, validation and performances

The societal and clinical impact of post-radiotherapy adverse tissue events (AE) has highlighted the need of molecular parameters to predict individual radiosensitivity. Recent studies have stressed the role of the phosphorylated forms of the ATM protein (pATM) and its nucleoshuttling in response to radiation. The statistical performance of the pATM immunofluorescence assay to predict AE is promising. However, immunofluorescence requires a time-consuming amplification of cells. The purpose of the study in [24] was to develop a predictive assay based on the ELISA technique that renders faster the previous approach. Materials and methods This study was performed on 30 skin fibroblasts from 9 radioresistant and 21 AE patients. Patients were divided in 2 groups, radioresistant (toxicity grade<2) and radiosensitive (toxicity grade ≥ 2). The quantity of nuclear pATM molecules was assessed by ELISA method at 10 min and 1 h after 2 Gy and

compared to pATM immunofluorescence data. Results The pATM ELISA data were found in quantitative agreement with the immunofluorescence ones. A ROC analysis was applied first to two data sets (a training ($n = 14$) and a validating ($n = 16$) one) and thereafter to the whole data with a 2-fold cross-validation method. The assay showed an AUC value higher than 0.8, a sensitivity of 0.8 and a specificity ranging from 0.75 and 1, which strongly document the predictive power of the pATM ELISA assay. Conclusion This study showed that the assessment of nuclear pATM quantity after 2 Gy via ELISA technique can be the basis of a predictive assay with the highest statistical performance among the available predictive approaches.

5.2. Immune response

5.2.1. Identification of nascent memory CD8 T cells and modeling of their ontogeny

Primary immune responses generate short-term effectors and long-term protective memory cells. The delineation of the genealogy linking naive, effector and memory cells has been complicated by the lack of phenotypes discriminating effector from memory differentiation stages. Using transcriptomics and phenotypic analyses, we identify (see [17]) a novel marker combination that allows us to track nascent memory cells within the effector phase. We then use a formal approach based on mathematical models describing the dynamics of population-size evolutions to test potential progeny links and demonstrate that most cells follow a linear naive-early effector-late effector-memory pathway. Moreover, our mathematical model allows long-term prediction of memory cell numbers from a few early experimental measurements. Our work thus provides a phenotypic means to identify effector and memory cells, as well as a mathematical framework to investigate the ontology of their generation and to predict the outcome of immunization regimens in terms of memory cell numbers generated.

5.2.2. Modelling the dynamics of virus infection and immune response in space and time

Spreading of viral infection in the tissues such as lymph nodes or spleen depends on virus multiplication in the host cells, their transport and on the immune response. Reaction–diffusion systems of equations with delays in proliferation and death terms of the immune cells represent an appropriate model to study this process. The properties of the immune response and the initial viral load determine the regimes of infection spreading. In the proposed model [13], the proliferation rate of the immune cells is represented by a bell-shaped function of the virus concentration which increases for small concentrations and decreases if the concentration is sufficiently high. We use such a model system to show that an infection can be completely eliminated or it can remain present together with a decreased concentration of immune cells. Finally, immune cells can be completely exhausted leading to a high virus concentration in the tissue. In addition, we predicted two novel regimes of infection dynamics not observed before. Infection propagation in the tissue can occur as a superposition of two travelling waves: first wave propagates as a low level infection front followed by a high level infection front with a smaller speed of propagation. Both of the travelling waves can have a positive or a negative speed corresponding to infection advancement or retreat. These regimes can be accompanied by instabilities and the emergence of complex spatiotemporal patterns.

5.2.3. Estimates and impact of lymphocyte division parameters from CFSE data using mathematical modeling

Carboxyfluorescein diacetate succinimidyl ester (CFSE) labelling has been widely used to track and study cell proliferation. In [23], we use mathematical modeling to describe the kinetics of immune cell proliferation after an in vitro polyclonal stimulation tracked with CFSE. This approach allows us to estimate a set of key parameters, including ones related to cell death and proliferation. We develop a three-phase model that distinguishes a latency phase, accounting for non-divided cell behaviour, a resting phase and the active phase of the division process. Parameter estimates are derived from model results, and numerical simulations are then compared to the dynamics of in vitro experiments, with different biological assumptions tested. Our model allows us to compare the dynamics of CD4+ and CD8+ cells, and to highlight their kinetic differences. Finally we perform a sensitivity analysis to quantify the impact of each parameter on proliferation kinetics. Interestingly, we find that parameter sensitivity varies with time and with cell generation. Our approach can

help biologists to understand cell proliferation mechanisms and to identify potential pathological division processes.

5.3. Erythropoiesis

5.3.1. Investigating the role of the experimental protocol in phenylhydrazine-induced anemia on mice recovery

Production of red blood cells involves growth-factor mediated regulation of erythroid progenitor apoptosis and self-renewal. During severe anemia, characterized by a strong fall of the hematocrit followed by a recovery phase, these controls allow a fast recovery of the hematocrit and survival of the organism. Using a mathematical model of stress erythropoiesis and an ad hoc numerical method, we investigate in [9] the respective roles of anemia-inducing phenylhydrazine injections and physiological regulation on the organism's recovery. By explicitly modeling the experimental protocol, we show that it mostly characterizes the fall of the hematocrit following the anemia and its severeness, while physiological process regulation mainly controls the recovery. We confront our model and our conclusions to similar experiments inducing anemia and show the model's ability to reproduce several protocols of phenylhydrazine-induced anemia. In particular, we establish a link between phenylhydrazine effect and the severeness of the anemia.

5.3.2. Numerical integration of an erythropoiesis model with explicit growth factor dynamics

Erythropoiesis, the red blood cell production process, involves interactions between cell populations with different differentiation states, mainly immature progenitor cells and mature erythrocytes, and growth factors such as erythropoietin and glucocorticoids, known to respectively inhibit cell apoptosis, stimulate proliferation and differentiation, and stimulate self-renewal. The feedback regulation of this process allows a very fast and efficient recovery in the case of a severe anemia. We consider in [8] an age-structured model of red blood cell production accounting for these feedback regulations and the dynamics of growth factors. We theoretically show the existence of a unique positive steady state for the model and we propose a numerical method to obtain an approximation to its solution. Experiments are reported to show numerically, on one hand, the optimal convergence order of the numerical scheme and, on the other hand, a fine approximation to real experimental data, with a suitable selection of the parameters involved.

5.4. Methodological developments

5.4.1. Traveling waves for a model of hematopoiesis

The formation and development of blood cells (hematopoiesis) is a very complex process. This process involves a small population of cells called hematopoietic stem cells (HSCs). The HSCs are undifferentiated cells, located in the bone marrow before they become mature blood cells and enter the blood stream. They have a unique ability to produce either similar cells (self-renewal), or cells engaged in one of different lineages of blood cells: red blood cells, white cells and platelets (differentiation). The HSCs can be either in a proliferating or in a quiescent phase. In [6], we distinguish between dividing cells that enter directly to the quiescent phase and dividing cells that return to the proliferating phase to divide again. We propose a mathematical model describing the dynamics of HSC population, taking into account their spatial distribution. The resulting model is an age-structured reaction-diffusion system. The method of characteristics reduces this model to a coupled reaction-diffusion equation and difference equation with delay. We study the existence of traveling wave fronts connecting the zero steady state with the unique positive uniform one. We use a monotone iteration technique coupled with the upper and lower solutions method.

5.4.2. A hybrid finite volume method for advection equations and its applications in population dynamics

We present in [30] a very adapted finite volume numerical scheme for transport type-equation. The scheme is an hybrid one combining an anti-dissipative method with down-winding approach for the flux ([35]; [36]) and an high accurate method as the WENO5 one ([37]). The main goal is to construct a scheme able to capture in

exact way the numerical solution of transport type-equation without artifact like numerical diffusion or without "stairs" like oscillations and this for any regular or discontinuous initial distribution. This kind of numerical hybrid scheme is very suitable when properties on the long term asymptotic behavior of the solution are of central importance in the modeling what is often the case in context of population dynamics where the final distribution of the considered population and its mass preservation relation are required for prediction.

5.4.3. Inferring gene regulatory networks from single-cell data: a mechanistic approach

The recent development of single-cell transcriptomics has enabled gene expression to be measured in individual cells instead of being population-averaged. Despite this considerable precision improvement, inferring regulatory networks remains challenging because stochasticity now proves to play a fundamental role in gene expression. In particular, mRNA synthesis is now acknowledged to occur in a highly bursty manner. We propose in [21] 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. We first explain how to build and simulate this network model based upon the coupling of genes that are described as piecewise-deterministic Markov processes. Our model is modular and can be used to implement various biochemical hypotheses including causal interactions between genes. However, a naive fitting procedure would be intractable. By performing a relevant approximation of the stationary distribution, we derive a tractable procedure that corresponds to a statistical hidden Markov model with interpretable parameters. This approximation turns out to be extremely close to the theoretical distribution in the case of a simple toggle-switch, and we show that it can indeed fit real single-cell data. As a first step toward inference, our approach was applied to a number of simple two-gene networks simulated in silico from the mechanistic model and satisfactorily recovered the original networks. Our results demonstrate that functional interactions between genes can be inferred from the distribution of a mechanistic, dynamical stochastic model that is able to describe gene expression in individual cells. This approach seems promising in relation to the current explosion of single-cell expression data.

5.5. Physiology

5.5.1. A multiscale modeling approach for the regulation of the cell cycle by the circadian clock

We present in [18] a multiscale mathematical model for the regulation of the cell cycle by the circadian clock. Biologically, the model describes the proliferation of a population of heterogeneous cells connected to each other. The model consists of a high dimensional transport equation structured by molecular contents of the cell cycle-circadian clock coupled oscillator. We propose a computational method for resolution adapted from the concept of particle methods. We study the impact of molecular dynamics on cell proliferation and show an example where discordance of division rhythms between population and single cell levels is observed. This highlights the importance of multiscale modeling where such results cannot be inferred from considering solely one biological level.

5.5.2. The lifespan and turnover of microglia in the human brain

The hematopoietic system seeds the CNS with microglial progenitor cells during the fetal period, but the subsequent cell generation dynamics and maintenance of this population have been poorly understood. We report in [25] that microglia, unlike most other hematopoietic lineages, renew slowly at a median rate of 28% per year, and some microglia last for more than two decades. Furthermore, we find no evidence for the existence of a substantial population of quiescent long-lived cells, meaning that the microglia population in the human brain is sustained by continuous slow turnover throughout adult life.

5.5.3. Impact of fat mass and distribution on lipid turnover in human adipose tissue

Differences in white adipose tissue (WAT) lipid turnover between the visceral (vWAT) and subcutaneous (sWAT) depots may cause metabolic complications in obesity. In [26], we compare triglyceride age and, thereby, triglyceride turnover in vWAT and sWAT biopsies from 346 individuals and find that subcutaneous triglyceride age and storage capacity are increased in overweight or obese individuals. Visceral triglyceride

age is only increased in excessively obese individuals and associated with a lower lipid removal capacity. Thus, although triglyceride storage capacity in sWAT is higher than in vWAT, the former plateaus at substantially lower levels of excess WAT mass than vWAT. In individuals with central or visceral obesity, lipid turnover is selectively increased in vWAT. Obese individuals classified as 'metabolically unhealthy' (according to ATPIII criteria) who have small subcutaneous adipocytes exhibit reduced triglyceride turnover. We conclude that excess WAT results in depot-specific differences in lipid turnover and increased turnover in vWAT and/or decreased turnover in sWAT may result in metabolic complications of overweight or obesity.

6. Bilateral Contracts and Grants with Industry

6.1. Bilateral Contracts with Industry

The industrial connections of the Dracula team have been made through the "Modeling of the immune response" project. Contacts have been established with both large pharmaceutical companies (Sanofi-Pasteur and Merial) and SMEs (AltraBio and the CosmoTech). The now finished ANR PrediVac project included the two aforementioned SMEs and therefore strengthened the ties between Dracula and its industrial local ecosystem. The same consortium applied to ANR grants on close research topics in 2017. Furthermore, the ties with CosmoTech have been strenghened through a joint CIFRE PhD (A. Bonnaffoux).

6.2. Bilateral Grants with Industry

- A recent cooperation has been initiated with the start up "Neolys Diagnostics" about radiotherapy effects on healthy cells and tumor cells. A PhD student, Aurélien Canet, has started his doctorate studies in January 2016 paid for one half by the start up and for the other half by the labex Milyon. Aurélien Canet is co-supervized by Larry Bodgi (from Neolys), Nicolas Foray (from Inserm) and Laurent Pujo-Menjouet.
- Celine Vial is scientific responsible of a contract with the European Consortium Eurokin and in collaboration with IFP "Energies nouvelles" on the topic: "Design experiments, sensibility and uncertainty analysis and kriging".

7. Partnerships and Cooperations

7.1. Regional Initiatives

In the context of the chair of applied mathematics "OQUAIDO", driven by Olivier Roustand (Mines de St Etienne), Celine Vial is the scientific responsible of a contract with the BRGM (Orléans) 2016-2018: "Study of a submergence problem: identify the critical offshore conditions for coastal flooding".

7.2. National Initiatives

7.2.1. ANR

- Olivier Gandrillon participates in the ANR (Investissement d'Avenir) Iceberg (head Gregory Batt (Inria)) "From population models to model populations: single cell observation, modeling, and control of gene expression". 2012-2017 (https://contraintes.inria.fr/~batt/iceberg/home.html).
- Thomas Lepoutre is a member of the ANR KIBORD (head L. Desvillettes) dedicated to "kinetic and related models in biology". 2014-2017: https://www.ljll.math.upmc.fr/kibord/.
- Céline Vial participates in the ANR PEPITO (head M. Henner) dedicated to "Design of Experiment for the Industry of transportation and Optimization". 2014-2018: http://www.agence-nationale-recherche.fr/?Project=ANR-14-CE23-0011.

7.2.2. Other projects

- Inria ADT : SiMuScale "Simulations Multi-Échelles de Populations Cellulaires", 2014-2017.
  Participants: Samuel Bernard [Coordinator], Fabien Crauste, Olivier Gandrillon, David Parsons.
- Association France Alzheimer Sciences Médicales: PAMELA “Prion et Alzheimer : Modélisation et Expérimentation d’une Liaison Agressive”, 2014-2017 (https://www.youtube.com/watch?v=X0mLf8IJhV4).
  Participants: Mostafa Adimy, Samuel Bernard, Thomas Lepoutre, Laurent Pujo-Menjouet [Coordinator], Léon Tine.
- Thomas Lepoutre is a member of the ERC MESOPROBIO (head V. Calvez) dedicated to "Mesoscopic models for propagation in biology". 2015-2020: http://cordis.europa.eu/project/rcn/193664_en.html.

7.3. International Initiatives

7.3.1. Inria Associate Teams Not Involved in an Inria International Labs

- Associate Teams Inria project, "Modelling Leukemia", 2014-2017.
  - Participants (Dracula): Mostafa Adimy, Samuel Bernard, Apollos Besse, Abdenasser Chekroun, Raouf El-Cheikh, Thomas Lepoutre [Coordinator], Laurent Pujo-Menjouet, Léon Tine, Céline Vial.
  - Partners: This is joint with Center for Scientific Computing and Applied Mathematical Modeling (Doron Levy) at University of Maryland (USA) (http://dracula.univ-lyon1.fr/modelling_leukemia.php).
  - The project Modelling Leukemia is devoted to the modeling of several aspects of Chronic Myeloid Leukemia. Leukemia is the most famous disease of the blood cell formation process (hematopoiesis). Chronic myeloid leukemia results in a uncontrolled proliferation of abnormal blood cells. As the hematopoiesis involves stem cells (not accessible to observations), mathematical modeling is here a great tool to test hypothesis. We want to add up the expertise of Inria team DRACULA specialized on the modeling of blood cell formation and the Center for Scientific Computation and Applied Mathematical Modeling (CSCAMM, University of Maryland, College Park).

7.4. International Research Visitors

7.4.1. Visits of International Scientists

- Claudia Pio Ferreira holded an Invited Professor position in the dracula team for two months (Octobre 14th - December 14th), she is affiliated to the Sao Paulo State University (UNESP), Institute of Biosciences, Department of Biostatistics, Botucatu, Brazil.

8. Dissemination

8.1. Promoting Scientific Activities

8.1.1. Scientific Events Organisation

8.1.1.1. Member of the Organizing Committees

- Session of GDR “Mathématiques de la Modélisation du Vivant (Mamovi)”, Lyon (France), 27 - 29 Septembre 2017 (https://gdr-mamovi-2017.sciencesconf.org/). Organizer: Thomas Lepoutre.

- Conference “LyonSysBio/Meet the Industry” (Lyon Systems Biology), Lyon (France), 15-17 November 2017 (https://mti2017.sciencesconf.org/). Co-organizers: Fabien Crauste and Olivier Gandrillon.
- Journée Scientique "Modelisation du Vivant" de la Faculté des Sciences et Technologies de l’Universite Lyon 1, Lyon (France), 22 June 2017 (https://jsf2017.sciencesconf.org/). Co-organizers: Fabien Crauste.
- Semaine Etudes Mathématiques Entreprises (SEME) 2017, Lyon (France), 30 January - 3 February 2017 (https://semelyon2017.sciencesconf.org/). Co-organizers: Fabien Crauste and Céline Vial.
- Workshop “Population effects on languages (PopLang)”, Lyon (France), 20 November 2017 (https://poplang.sciencesconf.org/). Co-organizers: Laurent Pujo-Menjouet and Léon Tine.

8.1.2. Journal

8.1.2.1. Member of the Editorial Boards

- Mostafa Adimy: Journal of Nonlinear Systems and Applications; Chinese Journal of Mathematics.
- Olivier Gandrillon: BMC research Notes.
- Laurent Pujo-Menjouet: Journal of Theoretical Biology; Mathematical Modeling of Natural Phenomena.

8.1.2.2. Reviewer - Reviewing Activities

- Thomas Lepoutre: Nonlinear Analysis; Computational and Applied Mathematics; M2AN; Journal of Biological Dynamics.
- Samuel Bernard: Journal of Theoretical Biology.
- Fabien Crauste: Journal of Biological Systems; Journal of Theoretical Biology; Mathematical Methods in Applied Sciences; Plos One; Royal Society Open Science.
- Olivier Gandrillon: Plos Computational Biology; Progress in Biophysics and Molecular Biology; Journal of the Royal Society Interface; Journal of theoretical biology; Genes and npj Systems Biology and Applications.
- Mostafa Adimy: Journal of European Mathematical Society; Mathematical Methods in the Applied Sciences; Mathematical Modeling of Natural Phenomena.
- Léon Tine: Mathematical Modelling and Numerical Analysis.

8.1.3. Invited Talks

- Thomas Lepoutre: International conference on “PDMPs, theory and applications”, Seillac (France), May 29-June 2 2017; Workshop “Cross diffusion and kinetic equations for biology”, Vienna (Austria), 10-12 May 2017.
- Samuel Bernard: “Journée Scientifique de la faculté des Sciences et technologies de l’UCBL”, Lyon (France), 22 june 2017.
- Fabien Crauste: GDR Mamovi “Mathématiques de la Modélisation du Vivant”, Lyon (France), 27 - 29 Septembre 2017.
- Olivier Gandrillon: Workshop “Modelling, Noise and Development”, Bath (UK), 18-19 Mai 2017.
- Chloé Audebert: GDR Mamovi “Mathématiques de la Modélisation du Vivant”, Lyon (France), 27 - 29 Septembre 2017.
- Laurent Pujo-Menjouet: “ARC6 day”, Grenoble (France), 4 July 2017; “BIOMIM EXPO 2017”, Senlis (France), 29 - 30 June; “5ème édition des Congrès PSYRENE (PSYchologie, REcherche, NEurosciences)”, Lyon (France), 7 July 2017; “ECAL2017 (European Conference on Artificial Life)”, Lyon (France), 4-8 September; Workshop “Protein Aggregation: Biophysics and Mathematics”, Vienna (Austria), 6-8 June 2017.

8.2. Teaching - Supervision - Juries

8.2.1. Teaching

- Licence:
  - Thomas Lepoutre, Groupe de lecture, L3, ENS, Lyon.
  - Samuel Bernard, Linear and matrix algebra,30h ETD, INSA, Lyon.
  - Samuel Bernard, ODEs for neuroscience,10h ETD, INSA Lyon.
  - Laurent Pujo-Menjouet, Fondamentaux des mathématiques, 138h ETD, L1, UCBL, Lyon.
  - Laurent Pujo-Menjouet, Bio-mathématiques et modélisation, 10.5h ETD, L3, UCBL, Lyon.
  - Laurent Pujo-Menjouet, Introduction à l'analyse numérique, 60h ETD, L2, UCBL, Lyon.
  - Léon Tine, Fondamentaux des mathématiques, 80h ETD, L1, UCBL, Lyon.
  - Léon Tine, Techniques mathématiques de base, 70h ETD, L1, UCBL, Lyon.
  - Léon Tine, Maths pour enseignement, 10h ETD, 10h ETD, L3, UCBL, Lyon.
- Master:
  - Thomas Lepoutre, Agrégation, 30h ETD, M2, UCBL, Lyon.
  - Samuel Bernard, Cell population dynamics, 15h ETD, UCBL, Lyon.
  - Fabien Crauste, Population Dynamics, 9h ETD, M2, UCBL, Lyon.
  - Laurent Pujo-Menjouet, Systèmes Dynamiques, 72h ETD, M1, UCBL, Lyon.
  - Laurent Pujo-Menjouet, Network Algorithms for Molecular Biology, 7.5h ETD, Master 2 IXXI, ENS, Lyon.
  - Léon Tine, Épidémiologie, 30h ETD, M2, UCBL, Lyon.

8.2.2. Supervision

- PhD in progress: Simon Girel, "Multiscale modeling of the immune response", Université Lyon, since September 2015, supervisor: Fabien Crauste.
- 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: Loïs Boullu, "Modélisation de la mégacaryopoïèse et applications aux maladies liées â la production des plaquettes", Université Lyon 1, October 2014, supervisors: Laurent Pujo-Menjouet and Jacques Bélair (co-tutelle avec l'Université de Montréal).
- PhD: Loïc Barbarroux, "Contributions to the multiscale modeling of the CD8 immune response : design, analysis, simulation and calibration of mathematical models", Université de Lyon 1, July 2017, supervisors: Mostafa Adimy and Phillipe Michel.
- PhD: Apollos Besse, "Mathematical Modeling of Chronic Myelogenous Leukemia", Université de Lyon, July 2017, supervisors: Samuel Bernard and Thomas Lepoutre.
- PhD in progress: Ulysse Herbach, "Modèles graphiques probabilistes pour l'inférence de réseaux de gènes", Université Lyon 1, since October 2015, supervisors: Olivier Gandrillon, Thibault Espinasse (ICJ) and Anne-Laure Fougères (ICJ).
- PhD in progress: Arnaud Bonnafoux, "Vers une inférence automatique de réseaux de gènes dynamiques à partir de "mégadonnées" temporelles discrètes acquises sur cellules uniques", Université Lyon 1, since November 2015, supervisors: Olivier Gandrillon (CIFRE with the COSMO company).
- PhD in progress: Ronan Duchesne, "Vers un modèle multi-échelle de la différentiation cellulaire : Application à la différentiation érythrocytaire", École normale supérieure de Lyon and Université Lyon 1, since September 2016, supervisors: Olivier Gandrillon and Fabien Crauste.

- PhD: Anass Bouchnita, “Mathematical modeling of blood coagulation and thrombus formation under flow in normal and pathological conditions”, Université Claude Bernard Lyon, Ecole Mohammadia d’Ingénieurs and Université Mohammed V de Rabat (Maroc), December 2017, supervisor: Vitaly Volpert.
- PhD: Tatiana Galochkina, “Mathematical modeling of blood inflammation processes and the problem of blood purification”, Université Claude Bernard Lyon and Moscow State University, Novmber 2017, supervisor: Vitaly Volpert.
- HDR: Samuel Bernard, “Structured differential equations and multiscale approaches for human cell population dynamics”, Université Claude Bernard Lyon, June 2017.
- HDR: Thomas Leoutre, “Contributions en dynamique de populations”, Université Claude Bernard Lyon, April 2017.

8.2.3. Juries

- Thomas Lepoutre was reviewer and member of the PhD of Athmane Bakhta (Université Paris Est), “Modèles mathématiques et simulation numérique de dispositifs photovoltaïques”.
- Samuel Bernard was member of Charles Rocabert PhD defense committee (INSA Lyon), “Etude de l’évolution des micro-organismes bactériens par des approches de modélisation et de simulation numériques”.
- Samuel Bernard was member of Apollos Besse PhD defense committee (INSA Lyon), “Modélisation Mathématique de la Leucémie Myéloïde Chronique".
- Olivier Gandrillon was president of the jury for the PhD of Alice Moussy (École Pratique des Hautes Études, Paris), “Caractérisation des premières étapes de différenciation des cellules hématopoïétiques à l’échelle de la cellule unique” and for the PhD of Coraline Petit (ENS Lyon), “Évolution et Développement d’un organe sériel : la molaire. Transcriptomique comparée des bourgeons de molaires chez les rongeurs”.
- Laurent Pujo-Menjouet was a jury member of the Habilitation thesis of Samuel Bernard (Université Claude Bernard Lyon 1), “Structured differential equations and multiscale approaches for human cell population dynamics”. He was also a jury member of the PhD of Tatiana Galochkina (université de Lyon et Université d’état de Moscou), “Structure spatiale des lipopolysaccharides et son rôle dans la coagulation sanguine”.
- Mostafa Adimy was member of Loïc Barbarroux PhD defense commitee (École Centrale de Lyon), “Contributions to the multiscale modeling of the CD8 immune response : design, analysis, simulation and calibration of mathematical models” and Walid Djema PhD defense commitee (Université Paris-Sud), “Understanding Cell Dynamics in Cancer from Control and Mathematical Biology Standpoints Particular Insights into the Modeling and Analysis Aspects in Hematopoietic Systems and Leukemia”.

8.3. Popularization

- Thomas Lepoutre is coorganizer of the scientific exhibition Mathalyon.
- Samuel Bernard: Conference “L’âge de nos cellules par tests nucle´aires", Université Ouverte Lycée Charles Foucault, Lyon, January 23, 2017.
- Olivier Gandrillon participated in the Declics 2017 activities (Lycée Jean Perrin and Lycée Juliette Récamier).
- Laurent Pujo-Menjouet: Conferences “Les langues en danger: les maths sur le bout de la langue”, Lycée Jean Puy, Roanne, March, 16, 2017; “Epidémies, quand les maths viennent en aide” , St Bonnet le château, April, 10, 2017; “Mathématiques et relations amoureuses: les jeux de l’amour sans le hasard, St Bonnet le château, April, 10, 2017; “Espèces en danger: quand les maths viennent à la rescousse”, Université ouverte, Lyon, January, 5, 2017; Animation of a stand on the “Salon des jeux mathématiques, Paris, May 27 to 30, 2017.

9. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] L. M. BARBARROUX. *Contributions to the multiscale modeling of the CD8 immune response : design, analysis, simulation and calibration of mathematical models*, Université de Lyon, July 2017, https://hal.archives-ouvertes.fr/tel-01569442

[2] S. BERNARD. *Structured differential equations and multiscale approaches for human cell population dynamics*, Université Claude Bernard Lyon 1, June 2017, Habilitation à diriger des recherches, https://hal.archives-ouvertes.fr/tel-01572434

[3] A. BESSE. *Mathematical Modeling of Chronic Myelogenous Leukemia*, Université de Lyon, July 2017, https://hal.archives-ouvertes.fr/tel-01561249

[4] A. BOUCHNITA. *Mathematical modelling of blood coagulation and thrombus formation under flow in normal and pathological conditions*, Université Lyon 1 - Claude Bernard ; Ecole Mohammadia d'Ingénieurs - Université Mohammed V de Rabat - Maroc, December 2017, https://hal.archives-ouvertes.fr/tel-01672317

[5] T. LEPOUTRE. *Contributions en dynamique de populations*, Université Claude Bernard (Lyon 1), April 2017, Habilitation à diriger des recherches, https://hal.inria.fr/tel-01524261

Articles in International Peer-Reviewed Journals

[6] M. ADIMY, A. CHEKROUN, B. KAZMIERCZAK. *Traveling waves in a coupled reaction-diffusion and difference model of hematopoiesis*, in "Journal of Differential Equations", 2017, vol. 262, pp. 4085 - 4128 [*DOI :* 10.1016/J.JDE.2016.12.009], https://hal.inria.fr/hal-01573613

[7] M. ADIMY, A. CHEKROUN, T. KUNIYA. *Delayed nonlocal reaction–diffusion model for hematopoietic stem cell dynamics with Dirichlet boundary conditions*, in "Mathematical Modelling of Natural Phenomena", 2017, vol. 12, n^{o} 6, pp. 1 - 22 [*DOI :* 10.1051/MMNP/2017078], https://hal.inria.fr/hal-01683636

[8] O. ANGULO, F. CRAUSTE, J. LÓPEZ-MARCOS. *Numerical integration of an erythropoiesis model with explicit growth factor dynamics*, in "Journal of Computational and Applied Mathematics", March 2018, vol. 330, pp. 770 - 782 [*DOI :* 10.1016/J.CAM.2017.01.033], https://hal.inria.fr/hal-01646786

[9] O. ANGULO, O. GANDRILLON, F. CRAUSTE. *Investigating the role of the experimental protocol in phenylhydrazine-induced anemia on mice recovery*, in "Journal of Theoretical Biology", January 2018, vol. 437, pp. 286 - 298 [*DOI :* 10.1016/J.JTBI.2017.10.031], https://hal.inria.fr/hal-01646792

[10] C.-A. AZENCOTT, T. AITTOKALLIO, S. ROY, A. AGRAWAL, E. BARILLOT, N. BESSONOV, D. CHASMAN, U. CZERWINSKA, A. F. SIAHPIRANI, S. FRIEND, A. GOLDENBERG, J. GREENBERG, M. HUBER, S. KASKI, C. KURZ, M. MAILICK, M. MERZENICH, M. MOROZOVA, A. MOVAGHAR, M. NAHUM, T. E. M. NORDLING, T. NORMAN, R. PENNER, K. SAHA, A. SALIM, S. SOROOSHYARI, V. SOUMELIS, A. STARK-INBAR, A. STERLING, G. STOLOVITZKY, S. S. SHIJU, J. TANG, A. TOSENBERGER, T. VIEET VAN, K. WENNERBERG, A. ZINOVYEV. *The inconvenience of data of convenience: computational*

research beyond post-mortem analyses, in "Nature Methods", September 2017, vol. 14, n^{o} 10, pp. 937 - 938 [*DOI :* 10.1038/NMETH.4457], https://hal.archives-ouvertes.fr/hal-01679028

[11] 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

[12] 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

[13] G. BOCHAROV, A. MEYERHANS, N. BESSONOV, S. TROFIMCHUK, V. VOLPERT. *Modelling the dynamics of virus infection and immune response in space and time*, in "International Journal of Parallel, Emergent and Distributed Systems", August 2017 [*DOI :* 10.1080/17445760.2017.1363203], https://hal.archives-ouvertes.fr/hal-01578907

[14] A. BOUCHNITA, F. E. BELMAATI, R. ABOULAICH, M. J. K. KOURY, V. A. VOLPERT. *A Hybrid Computation Model to Describe the Progression of Multiple Myeloma and Its Intra-Clonal Heterogeneity*, in "MDPI - Computation", 2017, vol. 5, n^{o} 1, 16 p. [*DOI :* 10.3390/COMPUTATION5010016], https://hal.archives-ouvertes.fr/hal-01565940

[15] A. BOUCHNITA, G. BOCHAROV, A. MEYERHANS, V. VOLPERT. *Towards a Multiscale Model of Acute HIV Infection*, in "Computation", 2017, vol. 5, n^{o} 1, 6 p. [*DOI :* 10.3390/COMPUTATION5010006], https://hal.archives-ouvertes.fr/hal-01570577

[16] A. BOUCHNITA, T. GALOCHKINA, P. KURBATOVA, P. NONY, V. VOLPERT. *Conditions of microvessel occlusion for blood coagulation in flow*, in "International Journal for Numerical Methods in Biomedical Engineering", 2017 [*DOI :* 10.1002/CNM.2850], https://hal.archives-ouvertes.fr/hal-01573775

[17] 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^{o} 3, pp. 306-317 [*DOI :* 10.1016/J.CELS.2017.01.014], https://hal.inria.fr/hal-01409637

[18] R. EL CHEIKH, S. BERNARD, N. EL KHATIB. *A multiscale modelling approach for the regulation of the cell cycle by the circadian clock*, in "Journal of Theoretical Biology", 2017, vol. 426, pp. 117-125 [*DOI :* 10.1016/J.JTBI.2017.05.021], https://hal.archives-ouvertes.fr/hal-01561617

[19] N. EYMARD, V. VOLPERT, P. KURBATOVA, N. BESSONOV, K. OGUNGBENRO, L. AARONS, P. JANIAUD, P. NONY, A. BAJARD, S. CHABAUD, Y. BERTRAND, B. KASSAÏ, C. CORNU. *Mathematical model of T-cell lymphoblastic lymphoma: disease, treatment, cure or relapse of a virtual cohort of patients*, in "Mathematical Medicine and Biology", 2017 [*DOI :* 10.1093/IMAMMB/DQW019], https://hal.archives-ouvertes.fr/hal-01568372

[20] T. GALOCHKINA, A. BOUCHNITA, P. KURBATOVA, V. VOLPERT. *Reaction-diffusion waves of blood coagulation*, in "Mathematical Biosciences", 2017, vol. 288, pp. 130 - 139 [*DOI :* 10.1016/J.MBS.2017.03.008], https://hal.archives-ouvertes.fr/hal-01567320

[21] 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^{o} 1, 105 p. [*DOI :* 10.1186/s12918-017-0487-0], https://hal.archives-ouvertes.fr/hal-01646910

[22] M. MARION, V. VOLPERT. *Existence of Pulses for the System of Competition of Species*, in "Journal of Dynamics and Differential Equations", 2017, vol. 14, pp. 1–18 [*DOI :* 10.1007/s10884-017-9582-6], https://hal.archives-ouvertes.fr/hal-01573773

[23] P. MAZZOCCO, S. BERNARD, L. PUJO-MENJOUET. *Estimates and impact of lymphocyte division parameters from CFSE data using mathematical modelling*, in "PLoS ONE", June 2017, vol. 12, n^{o} 6, e0179768 p. , https://hal.archives-ouvertes.fr/hal-01561667

[24] S. PEREIRA, L. BODGI, M. DUCLOS, A. CANET, M. L. FERLAZZO, C. DEVIC, A. GRANZOTTO, S. DENEUVE, G. VOGIN, N. FORAY. *Fast and binary assay for predicting radiosensitivity based on the nucleoshuttling of ATM protein: development, validation and performances*, in "International Journal of Radiation Oncology - Biology - Physics", October 2017 [*DOI :* 10.1016/j.ijrobp.2017.10.029], https://hal.inria.fr/hal-01647135

[25] P. RÉU, A. KHOSRAVI, S. BERNARD, J. E. MOLD, M. SALEHPOUR, K. ALKASS, S. PERL, J. TISDALE, G. POSSNERT, H. DRUID, J. FRISÉN. *The Lifespan and Turnover of Microglia in the Human Brain*, in "Cell Reports ", July 2017, vol. 20, n^{o} 4, pp. 779 - 784 [*DOI :* 10.1016/j.celrep.2017.07.004], https://hal.archives-ouvertes.fr/hal-01572438

[26] K. L. SPALDING, S. BERNARD, E. NÄSLUND, M. SALEHPOUR, G. POSSNERT, L. L. APPELSVED, K.-Y. FU, K. ALKASS, H. DRUID, A. THORELL, M. RYDÉN, P. ARNER. *Impact of fat mass and distribution on lipid turnover in human adipose tissue*, in "Nature Communications", May 2017, vol. 8, 15253 p. [*DOI :* 10.1038/ncomms15253], https://hal.archives-ouvertes.fr/hal-01561605

[27] V. VOLPERT, S. PETROVSKII, A. ZINCENKO. *Interaction of human migration and wealth distribution*, in "Nonlinear Analysis: Hybrid Systems", 2017, vol. 159, pp. 408 - 423 [*DOI :* 10.1016/j.na.2017.02.024], https://hal.archives-ouvertes.fr/hal-01565519

[28] V. VOUGALTER, V. VOLPERT. *Existence of stationary solutions for some systems of integro-differential equations with superdiffusion*, in "Rocky Mountain Journal of Mathematics", 2017, vol. 47, n^{o} 3, pp. 955-970 [*DOI :* 10.1216/RMJ-2017-47-3-955], https://hal.archives-ouvertes.fr/hal-01564763

[29] V. VOUGALTER, V. VOLPERT. *Solvability in the sense of sequences for some non Fredholm operators related to the superdiffusion*, in "Journal of Pseudo-Differential Operators and Applications", 2017, vol. 160, pp. 1–22 [*DOI :* 10.1007/s11868-017-0204-1], https://hal.archives-ouvertes.fr/hal-01573772

[30] C. YANG, L. M. TINE. *A Hybrid Finite Volume Method for Advection Equations and Its Applications in Population Dynamics*, in "Numerical Methods for Partial Differential Equations", February 2017, vol. 33, n^{o} 4, pp. 1114 - 1142 [*DOI :* 10.1002/num.22134], https://hal.archives-ouvertes.fr/hal-01646859

Other Publications

[31] M. AHMED, V. MAUME-DESCHAMPS, P. RIBEREAU, C. VIAL. *Spatial Risk Measure for Max-Stable and Max-Mixture Processes*, June 2017, https://arxiv.org/abs/1706.08244 - working paper or preprint, https://hal.archives-ouvertes.fr/hal-01546570

[32] T. BOURGERON, V. CALVEZ, J. GARNIER, T. LEPOUTRE. *Existence of recombination-selection equilibria for sexual populations*, March 2017, working paper or preprint, https://hal.archives-ouvertes.fr/hal-01489695

[33] V. CALVEZ, T. LEPOUTRE, N. MEUNIER, N. MULLER. *Two models for yeast cell communication*, March 2017, working paper or preprint, https://hal.archives-ouvertes.fr/hal-01498673

References in notes

[34] 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^{o} 19, pp. 4053-62 [*DOI :* 10.1158/0008-5472.CAN-15-0611], https://hal.inria.fr/hal-01251396

[35] B. DESPRÉS, F. LAGOUTIÈRE. *Un schéma non linéaire anti-dissipatif pour l'équation d'advection linéaire*, in "Comptes Rendus de l'Académie des Sciences - Series I - Mathematics", 1999, vol. 328, n^{o} 10, pp. 939 - 943 [*DOI :* 10.1016/S0764-4442(99)80301-2], http://www.sciencedirect.com/science/article/pii/S0764444299803012

[36] T. GOUDON, F. LAGOUTIÉRE, L. M. TINE. *Simulations of the Lifshitz-Slyozov equations: The role of coagulation terms in the asymptotic behavior*, in "Mathematical Models and Methods in Applied Sciences", 2013, vol. 23, n^{o} 07, pp. 1177-1215, http://www.worldscientific.com/doi/abs/10.1142/S0218202513500061

[37] G.-S. JIANG, C.-W. SHU. *Efficient Implementation of Weighted ENO Schemes*, in "Journal of Computational Physics", 1996, vol. 126, n^{o} 1, pp. 202 - 228 [*DOI :* 10.1006/JCPH.1996.0130], http://www.sciencedirect.com/science/article/pii/S0021999196901308

[38] I. ROEDER, M. HORN, I. GLAUCHE, A. HOCHHAUS, M. C. MUELLER, M. LOEFFLER. *Dynamic modeling of imatinib-treated chronic myeloid leukemia: functional insights and clinical implications*, in "Nature Medicine", 10 2006, vol. 12, pp. 1181 EP -, http://dx.doi.org/10.1038/nm1487