IN PARTNERSHIP WITH:
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Université Claude Bernard (Lyon 1)

Activity Report 2018

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 Sciences

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

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1. Team, Visitors, External Collaborators

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2. Overall Objectives

2.1. Presentation

Dracula is a joint research team between Inria, UniversitÃ© 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.

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.

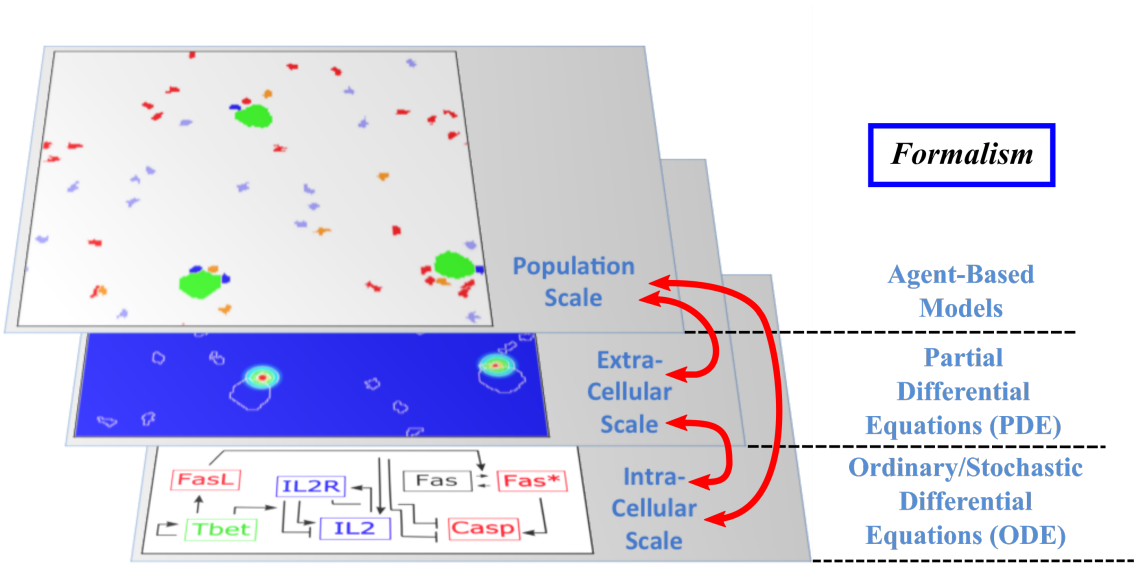

Figure 1. Scheme of multi-scale models of cell dynamics

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 (FranÃ§ois MorlÃ©, 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 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 GrÃ©goire 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 ([32]). 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 ([32]), 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 [34] 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 ([29], [30] and [31]). 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 [29]. 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

5. New Results

5.1. Oscillations and asymptotic convergence for a delay differential equation modeling platelet production

In [13], a model for platelet production is introduced for which the platelet count is described by a delay differential equation $P'(t) = -\gamma P(t) + f(P(t))g(P(t-r))$ where f and g are positive decreasing functions. First, the authors study the oscillation of the solutions around the unique equilibrium of the equation above, obtaining an inequality implying such an oscillation. They also obtain provide a condition such that this inequality is necessary and sufficient for oscillation. This result is compared to already existing results and the biological meaning of the inequality is studied. The authors also present a result on the asymptotic convergence of the solutions. This result depends on the behavior of the solution for $t \in [0, r]$, and the authors provide an analysis of the link between this behavior and the initial conditions in the case of a simpler model.

5.2. Meningioma growth dynamics assessed by radiocarbon retrospective birth dating

It is not known how long it takes from the initial neoplastic transformation of a cell to the detection of a tumor, which would be valuable for understanding tumor growth dynamics. We have assessed the age and growth dynamics in patients with WHO grade I meningiomas by combining retrospective birth-dating of cells by analyzing incorporation of nuclear-bomb-test-derived 14C, analysis of cell proliferation, cell density, MRI imaging and mathematical modeling. We provide an integrated model of the growth dynamics of benign meningiomas. The mean age of WHO grade I meningiomas was 22.1$\pm$ 6.5 years. We conclude that WHO grade I meningiomas are very slowly growing brain tumors, which are resected in average two decades after time of origination. [18]

5.3. Existence and stability of periodic solutions of an impulsive differential equation and application to CD8 T-cell differentiation

In this article [16], we study a scalar impulsive differential equation (IDE) with the aim of studying the effects of uneven molecular partitioning upon cell mitosis on CD8 T-cell differentiation. To do so, we introduce mathematical results that stand for a more general class of IDE, then apply them to our IDE and discuss those results with regard to the initial biological problem.

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

Erythropoiesis, the process of production of red blood cells, is performed through complex regulatory processes. We proposed an earlier model describing stress erythropoiesis in mice [33]. This model, based on the description of erythroid progenitor and erythrocyte dynamics using delay equations, led us to conclude on the quantitative importance of self-renewal. In [6], we refined this previous approaches by taking into account a more mechanistic description of the induction of anemia via phenylhydrazine injection. This led us to revisit some of our initial hypothesis regarding self-renewal regulation.

5.5. Generalizing a mathematical model of prion aggregation allows strain coexistence and co-stability by including a novel misfolded species

Prions are proteins capable of adopting misfolded conformations and transmitting these conformations to other normally folded proteins. A distinct feature of prion propagation is the existence of different phenotypical variants, called strains. In order to conform to biological observations of strain coexistence and co-stability, we develop in [19] an extension of the classical model by introducing a novel prion species consistent with biological studies.

5.6. Analysis and Numerical Simulation of a Polymerization Model with Possible Agglomeration Process

The purpose of [20] is to provide analytical and numerical results for a general polymerization model with lengthening process by agglomeration. 2D spatial diffusion of monomers is taken into account for the mass transfer between monomers and polymers. The analysis of the model is performed thanks to a double fixed point theorem. Adequate numerical scheme based on a generalization of the anti-dissipative method developed in Goudon (Math. Models Methods Appl. Sci. 23:1177–1215, 2013

5.7. The Origin of Species by Means of Mathematical Modelling

Darwin described biological species as groups of morphologically similar individuals. These groups of individuals can split into several subgroups due to natural selection, resulting in the emergence of new species. Some species can stay stable without the appearance of a new species, some others can disappear or evolve. In [10] we have developed a model which allows us to reproduce the principal patterns in Darwin's diagram. Some more complex evolutionary patterns are also observed. The relation between Darwin's definition of species, stated above, and Mayr's definition of species (group of individuals that can reproduce) is also discussed.

5.8. Improved duality estimates in the time discrete case for cross diffusion models

In [28], time discrete versions of the duality estimates derived by Canizo et al. for parabolic systems have been obtained. They allow the construction of solution with superquadratic reactions terms for cross diffusion models with bounded pressure.

6. Partnerships and Cooperations

6.1. National Initiatives

6.1.1. ANR

- ANR SinCity "Single cell transcriptomics on genealogically identified differentiating cells", 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.
- Fabien Crauste participates in the ANR MEMOIRE (head Jacqueline Marvel) dedicated to "MultiscalE MOdeling of CD8 T cell Immune REsponses". 2018-2021.
- Thomas Lepoutre is a member of the ANR KIBORD (head L. Desvillettes) dedicated to “kinetic and related models in biology". 2014-2018: https://www.ljll.math.upmc.fr/kibord/.

6.1.2. Other projects

- 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: .

6.2. European Initiatives

6.2.1. FP7 & H2020 Projects

Fabien Crauste and Olivier Gandrillon participates 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

6.3. International Initiatives

6.3.1. MODELLING_LEUKEMIA

Title: Modeling quiescence and drug resistance in Chronic Myeloid Leukemia

International Partner (Institution - Laboratory - Researcher):

University of Maryland (United States) - Center for Scientific Computation and Mathematical Modeling (CSCAMM) - Levy Doron

Start year: 2016

See also: http://dracula.univ-lyon1.fr/modelling_leukemia.php

This project is dedicated to the mathematical modelling of chronic myeloid leukemia and treatment effects. We focus especially on the interplay between the immune response and treatment. This has a potential impact on the study of treatment cessation. This work is conducted in close collaboration with a clinician.

6.3.2. Participation in Other International Programs

6.3.2.1. Indo-French Center of Applied Mathematics

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

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

International Partner (Institution - Laboratory - Researcher):

(India)- Subhas Khajanchi

Duration: 2018 - 2021

Start year: 2018

6.4. International Research Visitors

6.4.1. Visits of International Scientists

Antone dos Santos Benedito, PHD student on Adding temperature and anthropogenic actions in the study of spatial-temporal behavior of insectplague Chrysodeixis Includens. Institute of Biosciences, São Paulo State University (UNESP), Botucatu, Brazil not a team member but visiting for 6 months (from September 1st 2018 to February 28, 2019)

6.4.2. Visits to International Teams

Paul Lemarre is visiting University of Merced in 2018-2019.

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 2018, Lyon, France http://icsb2018-france.com/.

7.1.1.2. Member of the Organizing Committees

- Fabien Crauste, International Conference of Systems Biology 2018, Lyon, France http://icsb2018-france.com/.
- Laurent Pujo Menjouet, co-organization of the minisymposium « Hematopoiesis and its disease » at ECMTB 2018, 11th European Conference on Mathematical and Theoretical Biology, Lisbon, Portugal, 23 – 27 July , 2018

7.1.2. Scientific Events Selection

7.1.2.1. Reviewer

M .Adimy : 2nd International Conference on Applied Mathematics (ICAM 2018), 2018 Fez-Morocco,

7.1.3. Journal

7.1.3.1. Member of the Editorial Boards

- O. Gandrillon Associate editor for BMC research notes
- M. Adimy Journal of Nonlinear Systems and Applications; Chinese Journal of Mathematics.
- L. Pujo Menjouet :Associate editor of PLOS ONE Journal of Thoerical Biology, Mathematical modelling of natural phenomena

7.1.3.2. Reviewer - Reviewing Activities

- O. Gandrillon : BioEssays, BioTechniques, BMC Bioinformatics, BMC Genomics, Cell Biology and Toxicology, Genes, Genomics, Journal of the Royal Society Interface, Journal of Theoretical Biology, Molecular BioSystems, Nature Communications, npj Systems Biology and Applications, Plos Computational Biology and Progress in Biophysics and Molecular Biology
- L. Tine Journal of Theoretical Biology
- T. Lepoutre Applied Mathematical Letters, Journal of Differential Equations, Siam Journal of Mathematical Analysis, Marrow
- L. Pujo Menjouet Journal of Theoretical Biology Bulletin of mathematical biology Journal of mathematical biology Plos computational biology
- S. Bernard J Theor Biol, Comput and Appl Math, J Roy Soc Interface

7.1.4. Invited Talks

- S Bernard, Modélisation mathématique de la croissance et de la réparation tissulaire, Fondation Les Treilles, Tourtour FR, 12-17/11/2018
- S Bernard, Workshop Mathematics of Biological rhythms, Northunbria University, Newcastle, 3-5/12/2018
- Thomas Lepoutre : Mathematical perspetives in the biology and therapeutics of cancer, Cirm, Luminy France, https://mathscancer.sciencesconf.org/
- Thomas Lepoutre : Mathematical Challenges in the Analysis of Continuum Models for Cancer Growth, Evolution and Therapy, CMO, Oaxaca MEXICO, https://www.birs.ca/events/2018/5-day-workshops/18w5115
- Mostafa Adimy, 2nd International Conference on Applied Mathematics (ICAM 2018), Fez-Morocco.
- Mostafa Adimy, 2ème Colloque des Mathématiciens Marocains à l'étranger, Marrakech-Morocco.
- Mostafa Adimy, 8th Mathematical and Biological School (Programa Argentino BIOMAT), Córdoba-Argentina.
- Mostafa Adimy, Mathematical Challenges in the Analysis of Continuum Models for Cancer Growth, Evolution and Therapy, Oaxaca, Mexico. https://www.birs.ca/events/2018/5-day-workshops/18w5115
- Laurent Pujo Menjouet, talk at the minisymposium « Topics in structured population dynamics » ECMTB 2018, 11th European Conference on Mathematical and Theoretical Biology, Lisbon, Portugal, 23 – 27 Juillet , 2018
- Laurent Pujo Menjouet, LIAM-IRC-MfPH 2018 Symposium in Structured population models: theory, numerics and applications, 27-29 août 2016

7.1.5. Leadership within the Scientific Community

- O . Gandrillon : Director of BioSyL, the Federative Research Structure for Systems Biology attached to University of Lyon
- T. Lepoutre : Head of the Groupe de Recherches CNRS MAMOVI on applied mathematical modelling in Life Sciences.

7.1.6. Scientific Expertise

- L. Pujo Menjouet: reviewer for ANR

7.1.7. Research Administration

- L.M. Tine :Membre conseil du département de Mathématiques, Lyon 1
- L.M. Tine Co-responsable de l'enseignement TMB (Techniques Mathématiques de Base) du portail PCSI.
- M. Adimy : Comité scientifique (COS) du centre Rhône-Alpes.
- M. Adimy : Comité scientifique (CS) de l'Institut Camille Jordan.
- M. Adimy : Comité des thèses de l'Institut Camille Jordan.
- M. Adimy : Comité d'évaluation de l'Université de Guyane.
- L. Pujo- Menjouet : Responsable de la filière mathématiques pour la biologie et la médecine pour le master 2 math en actions à l'université Claude Bernard Lyon 1,
- L. Pujo- Menjouet : correspondant mobilité international pour le département de mathématiques à l'université Claude Bernard Lyon 1,
- L. Pujo- Menjouet : directeur du portail mathématiques et informatique à l'université Claude Bernard Lyon 1,
- T. Lepoutre member of the CORDI-S commission.

7.2. Teaching - Supervision - Juries

7.2.1. Teaching

Licence: Samuel Bernard: Algèbre Linéaire, 15h, L3, INSA

Licence: Samuel Bernard: EDO-EDP, 15h, L3, INSA

Licence : Ronan Duchesne, Anglais, 5h, L3

Licence : Ronan Duchesne, Modélisation des systèmes biologiques, 22h, L3

Licence : Ronan Duchesne, Bioinformatique, 20h, L3

Licence : Ronan Duchesne, Développement, 4h, L3

Licence : Simon Girel, Fondamentaux des mathématiques 1, 86h, L1, Université Lyon 1, France

Licence : Simon Girel, Introduction à l'analyse numérique, 10h, L1, Université Lyon 1, France

Licence: Laurent Pujo Menjouet, Fondamentaux des mathématiques I, 138h EQTD, L1, UCBL 1, FRANCE

Licence: Laurent Pujo Menjouet, Introduction à l'analyse numérique, 62h EQTD, L2, UCBL 1, FRANCE

Licence: Laurent Pujo Menjouet, bio-mathématiques et modélisation BISM, 10.5h EQTD, L3 UCBL 1, FRANCE

Licence: Laurent Pujo Menjouet, 3ème année biosciences BIM: EDO, 35h EQTD, INSA Lyon, FRANCE

Licence : L. M. Tine, Techniques mathématiques de base, 53h (EqTD), niveau L0, Lyon 1, France.

Licence : L. M. Tine, Techniques mathématiques de base, 62h (EqTD), niveau L1, Lyon 1, France.

Licence : L. M. Tine, Initiation LaTex+ stage, 12h (EqTD), niveau L3, Lyon 1, France.

Master : Samuel Bernard, Population Dynamics, 36h ETD, M2, UCBL, Lyon.

Master : Mostafa Adimy, Population Dynamics, 9h ETD, M2, UCBL, Lyon.

Master : Mostafa Adimy, Epidemiology, 12h ETD, M2, UCBL, Lyon.

Master : Ronan Duchesne, Biologie du développement, 12h, M1

Master : Ronan Duchesne, Statistiques, 2h, M1

Master : Ronan Duchesne, Adaptation, 2h, M1

Master : Ronan Duchesne, Practicals in statistics and modelling for the biosciences, 28h, M2

Master: Thomas Lepoutre, préparation à l'option pour l'agrégation, 45 h eq TD, M2 UCBL 1, FRANCE

Master: Laurent Pujo Menjouet, maths appliquées et statistiques: Systèmes dynamiques, 78h EQTD, M1, UCBL 1, FRANCE,

Master: Laurent Pujo Menjouet, master modélisation des systèmes complexes: modelling biology and medicine, M2, 9h EQTD, ENS-Lyon, FRANCE

Master: Laurent Pujo Menjouet,INSA 4ème année biosciences BIM: ED-EDP, 22h EQTD, M1 INSA Lyon, FRANCE

Master: L. M. Tine, Maths en action, Remise à niveau analyse, 12h (EqTD), niveau M2, Lyon 1, France.

Master: L. M. Tine, Maths en action, épidémiologie, 18h (EqTD), niveau M2, Lyon 1, France.

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, encadrants: Larry Bodgi, Nicolas Foray and Laurent Pujo Menjouet.

PhD in progress: Kyriaki Dariva , "Modélisation mathématique des interactions avec le système immunitaire en leucémie myéloide chronique". Université Lyon 1, September 2018, supervisor : Thomas Lepoutre

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 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 : Arnaud Bonnafoux, Vers une inférence automatique de réseaux de gènes dynamiques à partir de « mégadonnées » temporelles discrètes acquises sur cellules uniques, Université Lyon 1, October 2018, Olivier Gandrillon (CIFRE with the COSMOTECH).

PhD : Loïs Boullu, Modélisation de la mégacaryopoïèse et applications aux maladies liées â la production des plaquettes, Université Lyon 1, November 2018, Laurent Pujo Menjouet and Jacques Bélair (co-tutelle avec l'Université de Montréal).

PhD : Simon Girel, Modélisation de la réponse immunitaire T CD8 : analyse mathématique et modèles multi-échelles, Université de Lyon, November 2018 , encadrant: Fabien Crauste.

PhD : Ulysse Herbach, Modèles graphiques probabilistes pour l'inférence de réseaux de gènes, Université Lyon 1, September 2018, Olivier Gandrillon, Thibault Espinasse (ICJ) and Anne-Laure Fougères (ICJ).

7.2.3. Juries

We separate the juries of team members from external participations. PhD Defense within the team in 2018

- Arnaud Bonnaffoux (O. Gandrillon supervisor),
- Lois Boullu (L. Pujo Menjouet supervisor, M. Adimy and F. Crauste examiners),
- Ulysse Herbach (O. Gandrillon supervisor)
- Simon Girel (F. Crauste supervisor L. Pujo Menjouet examiner).

- M. Adimy: PhD of Linlin Li, Mathematical analysis of a model of partial differential equations describing the adaptation of mosquitoes facing the usage of insecticides, University of Bordeaux, reviewer.
- M. Adimy: PhD of Zhengyang Zhang, A class of state-dependent delay differential equations and applications to forest growth, University of Bordeaux, examiner.
- V. Volpert: PhD of Guillaume Cantin, Étude de réseaux complexes de systèmes dynamiques dissipatifs ou conservatifs en dimension finie ou infinie. Application à l'analyse des comportements humains en situation de catastrophe. Université Le Havre Normandie, examiner.
- S. Bernard : Charles Rocabert, Etude de l'évolution de micro-organismes bactériens par des approches de modélisation et de simulation informatique, INSA Lyon, (examiner)

7.3. Popularization

7.3.1. Articles and contents

- L. Pujo Menjouet : interview dans Causette (hors série Juillet-Août 2018)
- L. Pujo Menjouet : interview dans le magazine Society (fin juillet 2018)

7.3.2. Interventions

- T. Lepoutre: Visite de l'inria pour les stagiaires de 3e de l'ICJ (plusieurs fois dans l'année, une matinée en général).
- T. Lepoutre: présentation de l'antenne et des équipes à deux classes lors du congrès Maths en Jeans (mars 2018)
- T. Lepoutre participation to MathaLyon interventions
- L. Pujo Menjouet : participation à Math en Jeans édition 2018 (collège de la côte Roannaise, Renaison)
- L. Pujo Menjouet : présentation de deux conférences au collège de Saint Bonnet le château le 21 juin 2018

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Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] A. BONNAFFOUX. *Inferring gene regulatory networks from dynamic multi-scale data*, Université de Lyon, October 2018, https://hal.archives-ouvertes.fr/tel-01920262

[2] L. BOULLU. *Study of delay differential equations with applications to the regulation of blood platelet production*, Université de Lyon, November 2018, https://hal.inria.fr/tel-01948726

[3] S. GIREL. *Modeling the CD8 T-cell Immune Response : Mathematical Analysis and Multiscale Models*, Université de Lyon, November 2018, https://hal.archives-ouvertes.fr/tel-01941850

[4] U. HERBACH. *From stochastic modelling of gene expression to inference of regulatory networks*, Université de Lyon, September 2018, https://tel.archives-ouvertes.fr/tel-01930398

Articles in International Peer-Reviewed Journals

[5] 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

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