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Activity Report 2014

Project-Team DRACULA

Multi-scale modelling of cell dynamics : application to hematopoiesis

IN COLLABORATION WITH: Institut Camille Jordan, Centre de Génétique et de Physiologie Moléculaire et Cellulaire

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Modeling and Control for Life Sciences

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Project-Team DRACULA

Keywords: Mathematical Biology, Systems Biology, Computational Biology, Multiscale Models, Regulatory Networks

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

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2. Overall Objectives

2.1. Presentation

Dracula is a joint research team between Inria, University of Lyon 1 (UCBL) and CNRS (ICJ, UMR 5208 and CGMC UMR 5534). It was created in January 2011.

The Dracula project is devoted to multi-scale modeling in biology with applications to normal and pathological hematopoiesis (blood cell production). Multi-scale modeling implies simultaneous modeling of intra-cellular networks (molecular level), of cell behavior (cellular level), of the 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 scales.

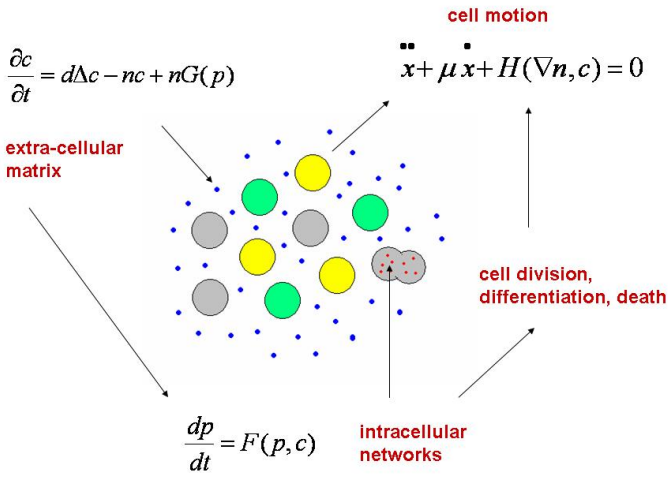

Figure 1. Schema of multi-scale models of cell dynamics: DPD-PDE-ODE models.

Hematopoiesis is a complex process that begins with primitive hematopoietic stem cells 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 (programmed cell death). The choice between these three possibilities is determined by intra-cellular regulatory networks and by numerous control mechanisms in the bone marrow (see Figure 2) or carried out by other organs. Intra-cellular regulatory networks are complex biochemical reactions involving proteins, enzymes and signalling molecules. Thus, hematopoiesis is a complex process which has a vital importance for the organism. Its malfunctioning can result in numerous blood diseases including leukemia.

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 behavior of hematopoietic stem cells under stress conditions, the understanding of deregulation

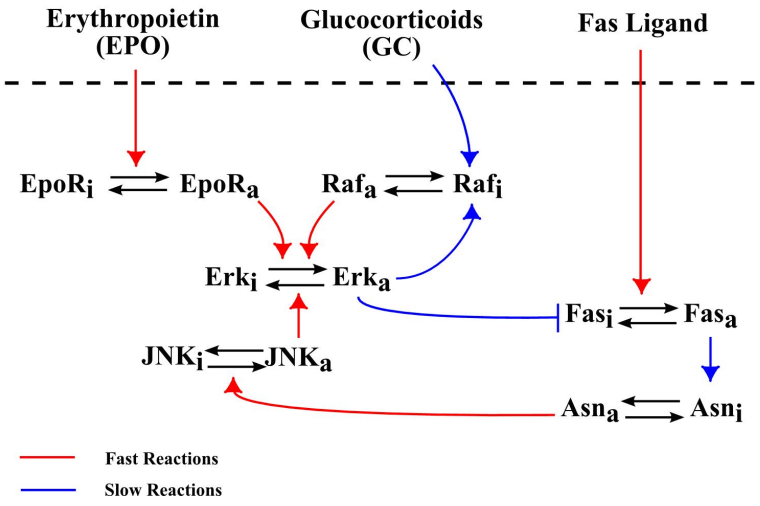

Figure 2. A schematic description of the intra-cellular molecular events that are relevant for decision making in an erythroid progenitor. The non active form of the protein is labeled i, the active form a. Blue lines indicate transcriptional regulation, red lines indicate biochemical regulation.

of erythropoiesis (the process of red blood cell production) under drag treatments (this can lead to lack of red blood cells (anemia), or a surplus of red blood cells), the understanding of immune response process under the control of T-cell activation and memory cell generation, in order to adapt infection prevention strategies.

On the other hand, the modeling methods developed here for hematopoiesis are relevant to study other complex biological systems. We pay a special attention on developing methods that are not restricted to hematopoiesis. In parallel with hematopoiesis modeling, most of members of Dracula keep on working on modeling of other biological phenomena, for example: tumor cells, prion disease, adaptive dynamics, atherosclerosis, and so on. Approaches developed in the present project are very likely relevant in these fields too.

An important part of our researches is in close collaboration with biologists and physicians in order to stay in close contact with the biological and medical goals. The presence, within the project, of a biologist (Olivier Gandrillon) that has acquired over the years the know-how required for interacting with mathematicians is probably one of the main asset of the project. He participates actively in many tasks of our program, especially involving description of biological process, and he is "consultant" for other biological aspects, in the other parts of the project.

2.2. Keywords

Multi-scale modeling; Mathematical Biology; Computational Biology; Hematopoiesis modeling; Erythropoiesis modeling; Leukemia modeling; Immune response modeling; Regulatory networks; Partial differential equations; Delay differential equations; Agent-based modeling; Dynamical systems.

2.3. Objectives

Our aim in this project is the development of modern tools of multi-scale modeling in biological phenomena (and in particular, for hematopoiesis). For the last four years, we have fixed the following objectives:

- Multi-scale modeling will be carried out on the basis of coupled DPD-PDE-ODE models, where dissipative particle dynamics (DPD) will be used in order to describe individual cells and relatively small cell populations, partial differential equations (PDE) will be used to describe concentrations of bio-chemical substances in the extra-cellular matrix, and ordinary differential equations (ODE, deterministic or stochastic) for intra-cellular regulatory networks (Figure 1).
- A new software "Cell dynamics" will be created in order to study these models numerically.
- Partial differential equations (PDE) will also be used to describe cell populations considered as continuous medium. We will study reaction-diffusion-convection equations with or without hydrodynamics, transport equations (hyperbolic PDEs) in which the structure can be age, size, maturity, protein concentration, etc. In some particular cases, transport equations will be reduced to delay differential equations (DDE) which are less difficult to investigate analytically.
- Numerical simulations will be compared with analytical studies of simplified test cases and model examples.
- Numerical simulations will also be compared to the "Cell dynamics" approach.
- Multi-scale models of hematopoiesis will be used to study normal situation or homeostasis where different cell types are in equilibrium with each other. This equilibrium is determined by intra-cellular regulatory networks and by numerous feedbacks by cell populations and other organs.
- Development and dynamics of blood diseases will be modeled taking into account disequilibrium of regulatory networks or feedbacks. On the other hand, we will model various approaches to treatment of these diseases (chemotherapy, chronotherapy). We will compare then the results with available biological and clinical information.

3. Research Program

3.1. Cell dynamics

We model dynamics of cell populations with two approaches, dissipative particle dynamics (DPD) and partial differential equations (PDE) of continuum mechanics. DPD is a relatively new method developed from molecular dynamics approach largely used in statistical physics. Particles in DPD do not necessarily correspond to atoms or molecules as in molecular dynamics. These can be mesoscopic particles. Thus, we describe in this approach a system of particles. In the simplest case where each particle is a sphere, they are characterized by their positions and velocities. The motion of particles is determined by Newton's second law (see Figure 1).

In our case, particles correspond to biological cells. The specific feature of this case in comparison with the conventional DPD is that cells can divide (proliferation), change their type (differentiation) and die by apoptosis or necrosis. Moreover, they interact with each other and with the extra-cellular matrix not only mechanically but also chemically. They can exchange signals, they can be influenced by various substances (growth factors, hormones, nutrients) coming from the extra-cellular matrix and, eventually, from other organs.

Distribution of the concentrations of bio-chemical substances in the extra-cellular matrix will be described by the diffusion equation with or without convective terms and with source and/or sink terms describing their production or consumption by cells. Thus we arrive to a coupled DPD-PDE model.

Cell behaviour (proliferation, differentiation, apoptosis) is determined by intra-cellular regulatory networks, which can be influenced by external signals. Intra-cellular regulatory networks (proteins controlling the cell cycle) can be described by systems of ordinary differential equations (ODE). Hence we obtain DPD-PDE-ODE models describing different levels of cell dynamics (see Figure 1). It is important to emphasize that the ODE systems are associated to each cell and they can depend on the cell environment (extra-cellular matrix and surrounding cells).

3.2. From particle dynamics to continuum mechanics

DPD is well adapted to describe biological cells. However, it is a very time consuming method which becomes difficult to use if the number of particles exceeds the order of 10^5-10^6 (unless distributed computing is used). On the other hand, PDEs of continuum mechanics are essentially more efficient for numerical simulations. Moreover, they can be studied by analytical methods which have a crucial importance for the understanding of relatively simple test cases. Thus we need to address the question about the relation between DPD and PDE. The difficulty follows already from the fact that molecular dynamics with the Lennard-Jones potential can describe very different media, including fluids (compressible, incompressible, non-Newtonian, and so on) and solids (elastic, elasto-plastic, and so on). Introduction of dissipative terms in the DPD models can help to justify the transition to a continuous medium because each medium has a specific to it law of dissipation. Our first results [39] show the correspondence between a DPD model and Darcy's law describing fluid motion in a porous medium. However, we cannot expect a rigorous justification in the general case and we will have to carry out numerical comparison of the two approaches.

An interesting approach is related to hybrid models where PDEs of continuum mechanics are considered in the most part of the domain, where we do not need a microscopical description, while DPD in some particular regions are required to consider individual cells.

3.3. PDE 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. These are more traditional models [40] with properties that depend on the particular problem under consideration and with many open questions, both from the point of view of their mathematical properties and for applications. In particular we are interested in the spreading of cell populations which describes the development of leukemia in the bone marrow and many other biological phenomena (solid tumors, morphogenesis, atherosclerosis, and so on). From the mathematical point of view, these are reaction-diffusion waves, intensively studied in relation with various biological problems. We will continue our studies of wave speed, stability, nonlinear dynamics and pattern formation. From the mathematical point of view, these are elliptic and parabolic problems in bounded or unbounded domains, and integro-differential equations. We will investigate the properties of the corresponding linear and nonlinear operators (Fredholm property, solvability conditions, spectrum, and so on). Theoretical investigations of reaction-diffusion-convection models will be accompanied by numerical simulations and will be applied to study hematopoiesis.

Hyperbolic problems are also of importance when describing cell population dynamics ([45], [47]), and they proved effective in hematopoiesis modelling ([34], [35], [37]). They are structured transport partial differential equations, in which the structure is a characteristic of the considered population, for instance age, size, maturity, protein concentration, etc. The transport, or movement in the structure space, simulates the progression of the structure variable, growth, maturation, protein synthesis, etc. Several questions are still open in the study of transport PDE, yet we will continue our analysis of these equations by focusing in particular on the asymptotic behaviour of the system (stability, bifurcation, oscillations) and numerical simulations of nonlocal transport PDE.

The use of age structure often leads to a reduction (by integration over the age variable) to nonlocal problems [47]. The nonlocality can be either in the structure variable or in the time variable [34]. In particular, when coefficients of an age-structured PDE are not supposed to depend on the age variable, this reduction leads to delay differential equations.

3.4. Delay differential Equations

Delay differential equations (DDEs) 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. Because these processes can take a certain time, the system depends on an essential way of its past state, and can be modelled by DDEs.

We explain hereafter how delays can appear in hematopoietic models. Based on biological aspects, we can divide hematopoietic cell populations into many compartments. We basically consider two different cell populations, one composed with immature cells, and the other one made of mature cells. Immature cells are separated in many stages (primitive stem cells, progenitors and precursors, for example) and each stage is composed with two sub-populations, resting (G0) and proliferating cells. On the opposite, mature cells are known to proliferate without going into the resting compartment. Usually, to describe the dynamic of these multi-compartment cell populations, transport equations (hyperbolic PDEs) are used. Structure variables are age and discrete maturity. In each proliferating compartment, cell count is controlled by apoptosis (programmed cell death), and in the other compartments, cells can be eliminated only by necrosis (accidental cell death). Transitions between the compartments are modelled through boundary conditions. In order to reduce the complexity of the system and due to some lack of information, no dependence of the coefficients on cell age is assumed. Hence, the system can be integrated over the age variable and thus, by using the method of characteristics and the boundary conditions, the model reduces to a system of DDEs, with several delays.

Leaving all continuous structures, DDEs appear well adapted to us to describe the dynamics of cell populations. They offer good tools to study the behaviour of the systems. The main investigation of DDEs are the effect of perturbations of the parameters, as cell cycle duration, apoptosis, differentiation, self-renewal, and re-introduction from quiescent to proliferating phase, on the behaviour of the system, in relation for instance with some hematological disorders [41].

4. Application Domains

4.1. Normal hematopoiesis

4.1.1. Introduction

Modelling normal hematopoiesis will allow us to explore the dynamical appearance of the various cell types, originating from the stem cell compartment, through the bone marrow development up to the blood stream. The differentiated cell types will both fulfill physiological functions, and play a key role on the feedback control on homeostasis (balance of the system) in their own lineages. We will describe the hematopoiesis from three different points of view:

- The initial cell type, the hematopoietic stem cell (HSC);
- The lineage choice question;
- Three differentiated lineages that are responsible for specific function, namely oxygen transport, immune response and coagulation.

The basic mechanisms of our modelling approach are as follows:

- Any cell type can have two possibilities at each time step: to divide or to die.
- At any division step, the cell can either give rise to two daughter cells which are identical to the mother cell (self-renewal) or that are more advanced in their differentiation.

All these processes will be first modelled at the cellular level. In parallel, we will develop models of intracellular molecular networks (as some proteins controlling the cell cycle) influencing this decision making process, so as to be able to describe both micro-to-macro effects (molecules influencing the global cell behaviour) as well as macro-to-micro effects (like the global state of the cell population influencing the molecular behaviour).

4.1.2. Hematopoietic stem cells (HSC)

Although widely studied by biologists, HSC are still poorly understood and many questions remain open: How fast and how frequently do they divide? How many of them are in the bone marrow and where? How is their behaviour modified under stress conditions such as blood loss or transfusion?

Our modelling approach will be based on two methods: deterministic and stochastic differential equations with delays (discrete and distributed), on one hand, and the DPD method using the individual based modelling on the other hand. The differential equation models based on the work initiated by Mackey [42] will describe the HSC compartment in normal conditions and the behaviour of these cells under some stress. The DPD method, as a complementary approach, will emphasize the spatial regulation of stem cell behaviour, and we will focus our attention to give a possible answer regarding their location in the bone marrow and the roles of the niche, their number in the system, their possible role under stress (that is their reaction under the different feedback controls).

4.1.3. Blood cell functions

(i) O2 transport: red lineage

O_2 transport is provided by red blood cells (RBC) also called erythrocytes. Many different stages of maturity (including progenitors, precursors, reticulocytes and erythrocytes) are necessary to achieve the complete formation of RBC. These latter are then released in the blood stream where they transport oxygen. The whole process is tightly dependent on a robust well-balanced equilibrium called homeostasis.

It has been shown in the 1990's that apoptosis is regulated by EPO, a growth factor released by the kidneys under hypoxia. But also, under severe stress (like an important blood loss) some other molecules known as glucocorticoids can be released leading to an increase of the self-renewing rate for each generation. This led to the formulation of a first model, demonstrating the role of self-renewal.

The study of the red blood cell lineage will involve different scale levels, from the molecular one, with the effects of the hormones on the surface and internal parts of the cell, the cell contacts in each stage of RBC formation, and the red branch population in its whole with all the interactions taken into account (see Figure 3) in normal and stress conditions.

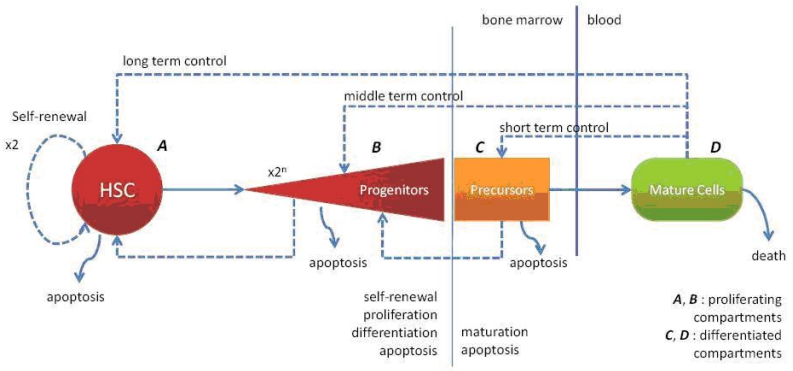

Figure 3. Scheme of Erythropoiesis Modelling ([33]). Without considering explicitly growth factor mediated regulation, all controls (proliferation, self-renewal, differentiation, apoptosis) are mediated by cell populations (dashed arrows). Mature cells can either regulate immature (HSC, progenitors) or almost mature (precursors) cells, precursors may act on progenitor dynamics, etc..

In order to couple the cellular behaviour to explicit molecular events, we will describe the events through a molecular network that is based upon the work of [46]. A first version of this model is shown in Figure 2.

(ii) Immune response

We will focus on the production of T-cells during an immune response. This represents an important activity of the lymphoid branch, part of leucopoiesis (white blood cell production). Several models of the myeloid branch of leucopoiesis have been investigated in the frame of specific diseases (for instance cyclical neutropenia ([41], [38]), chronic myelogenous leukemia [43]).

Time evolution of T-cell counts during an infection is well known: following the antigen presentation, the number of cells quickly increases (expansion), then decreases more slowly (contraction) and stabilizes around a value higher than the initial value. Memory cells have been produced, and will allow a faster response when encountering the antigen for a second time. Mechanisms that regulate this behaviour are however not well known.

A recent collaboration just started with immunologists (J. Marvel, Ch. Arpin) from the INSERM U851 in Lyon, who provide experimental data that are essential to assess the significance of models, based on strongly nonlinear ordinary differential equations, that can be proposed for T-cell production (Figure 4). By considering molecular events leading to cell activation when encountering a virus, we will propose a multi-scale model of the immune response.

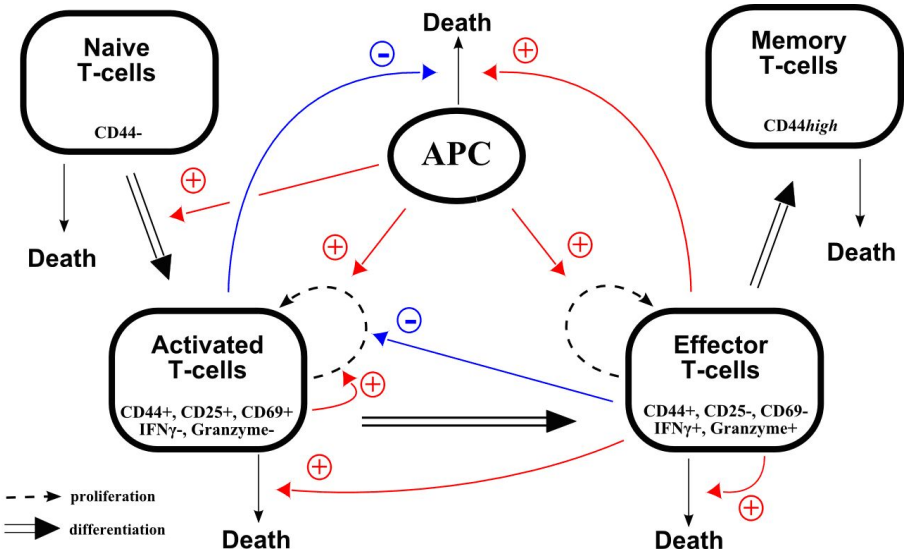

Figure 4. Model of the immune response resulting in the generation of CD8 memory T cells. The response starts with a viral infection resulting in the presentation of viral antigens through antigen presenting cells (APC) to naive T-cells. These latter, once activated, differentiate into activated cells which, under specific feedback loops will either die, differentiate into effector cells or self-renew. Differentiation of effector cells (killer cells) will result in the production of memory cells.

(iii) Coagulation: platelet lineage

Thrombopoiesis, the process of production and regulation of platelets, is similar to erythropoiesis although important differences are observed. These two processes have an immature progenitor (MEP) in common. Platelets are involved in blood coagulation, and can be the source of blood diseases (thrombopenia, thrombocytosis). Their production is mainly regulated by thrombopoietin (TPO), a growth factor similar to EPO.

It is important to mention that very few experimental data exist in the literature, and mathematical modelling of thrombopoiesis did not attract so much attention in the past 20 years. However, collaboration with some leading hematologists in this domain will allow us to get updated and new data regarding this process.

Deterministic models, in the form of structured transport partial differential equations, will be proposed to describe platelet dynamics, through the description of HSC, megakaryocytic progenitor and megacaryocyte (platelet precursor) compartments. Circulating TPO, regulated by platelets, will induce feedback loops in thrombopoiesis, and we will investigate the dynamics of platelet production and emergence of platelet-related diseases.

4.2. Pathological hematopoiesis

The knowledge of hematopoiesis and related diseases has evolved to become a great deal in the past years, and Mackey's previous models (ref. [36]) do not allow us to correctly answer current questions that are clearly oriented toward the investigation of cell signalling pathways. These models nevertheless bring relevant ideas about the essential features of such modelling. It is also noteworthy that even though models of hematopoiesis have existed for quite a long time, their application to questions of explanation and prediction of hematopoiesis dynamics that are encountered in the clinic is still not sufficiently frequent, even though much progress has been achieved in the cooperation between hematologists and mathematicians [44]. This is in the optic of testable experimental predictions that the multi-scale model for pathological hematopoiesis will be developed. For instance, we will concentrate on myeloid leukemias (CML and AML) and their treatment.

4.2.1. Leukemia Modelling

(i) Chronic Myeloid Leukemia

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, genomic instability. This explains the presence in CML blood of a very important number of cells belonging to the myeloid lineage, at all stages of maturation.

We will consider models based on ordinary differential equations for the action of the main intra- and extra-cellular 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.), and their environment (disruption of stroma adhesion properties, for example). Transport pertains thus to cells from one compartment (or a group of compartments) to another compartment, with a determined speed of aging or maturation. These compartments may be detailed or not: the less mature are stem cells, then progenitor cells, etc.

(ii) Acute Myeloid Leukemia

The natural history of CML leads to its transformation ("blast crisis") in acute myeloid leukemia (AML), following supplementary genetic alterations that produce a maturation arrest (myeloid in $3/4$ of cases, lymphoid in $1/4$ of cases, confirming the insult to pluripotent stem cells), leading to an accumulation of immature cells in the bone marrow and in the general circulation, resulting in deep medullary impairment and fast fatal outcome, in spite of chemotherapy. This phenomenon is the same as the one observed in de novo AML, i.e., AML without a previous chronic phase.

The different modelling methods of AML will be similar to the ones described for CML, with some exceptions: the appearance of BCR-ABL mutations, which are not relevant in the case of AML, the appearance of a gene (spi-1) involved in the differentiation arrest, and constitutive activation of EPO receptor or Kit activating mutations promote proliferation and survival. This explains the accumulation of immature cells in the bone marrow and in the blood stream.

4.2.2. Treatment

As far as treatment of pathological hematopoiesis is concerned, two main strategies currently exist that aim at slowing down or eliminating damaged cell proliferation. The first of these strategies consists in launching the apoptotic process during the cell division cycle. This process is activated, for example when the cell is unable to repair damages, e.g., after exposure to cytostatic drugs. A typical example is apoptosis induced by chemotherapy-induced DNA damage: The damage is recognised by the cell, which then activates the sentinel

protein p53 ("guardian of the genome") that arrests the cell cycle to allow, if possible, damage repair. If the latter is unrecoverable, then p53 activates the endogenous apoptotic processes.

The second strategy aims at pushing damaged cells toward the differentiation that has been stopped in the course of their genetic mutation. Since a few years back, a new approach has been developed around the strategy of differentiation therapy. This therapy relies on molecules (growth factors and specific cytokines) that are able to re-initialise the cell differentiation programs that have been modified during malignant transformation. The cancer that is most concerned by the development of this differentiation therapy is AML whose malignant cells present highly undifferentiated features and the ones that present a translocation responsible for the differentiation (PML/RAR of the promyelocytic form, AML1/ETO and CBFbeta/MyH11, involving Core Binding Factors alpha and beta).

Mathematical models based on ordinary differential equations will be developed to describe the action of drugs (in the two cases mentioned above). They will take into account interactions between drugs and their environment. Our goal will be the optimization of possible synergies between drugs acting on distinct cellular targets, and the control of resistances to these treatments as well as their toxicities.

Curative and palliative strategies must take into account the dynamics of healthy and leukemic hematopoietic cells at multiple scales. In time, from optimal scheduling of combination therapy (hours) to avoiding the development of resistances and relapse (months to years). In space, from the stem cell niche to circulating blood. In organization, from gene and signalling networks (JAK/STAT, BCR-ABL) to cell populations and cytokine regulation (EPO, CSFs). Several recent qualitative models have provided insight in the complex dynamics of the disease and the response to treatments. Many of these models focus on the control or regulation processes that promote homeostasis or oscillatory behavior in cell number. However, as A. Morley points out, "once the control-systems features of hematopoiesis are accepted, the ability to construct a model that shows oscillatory behavior, even if the model incorporates the latest advances in hematopoietic cell biology, really adds little new knowledge. Rather, the challenge to modellers would seem to be to provide detailed predictions for the input-output characteristics of the different parts of the various control systems so that these predictions can be tested by experimental hematologists and a truly quantitative description of hematopoiesis can emerge".

We propose for instance, to use models in the form of structured transport partial differential equations (with or without delay, physiologically structured or not) to represent the competition between target, resistant and healthy cell populations. The resulting models to describe the dynamic of these cell populations under the action of drugs are multi-scale systems of the form (Hyperbolic PDE)-ODE or DDE-ODE. For instance, we will develop mathematical models of chronotherapy and pharmacotherapy for CML and AML.

5. New Software and Platforms

5.1. CelDyn

Participants: Laurent Pujo-Menjouet, Alen Tosenberger, Vitaly Volpert [correspondant].

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.

6. New Results

6.1. Highlights of the Year

- Marine Jacquier and Fabien Crauste (in collaboration with C.O. Soulage and H.A. Soul) published a paper ([18], see also § 6.7) in PLoS ONE 2014.

- Sotiris Prokopiou, Loic Barbarroux, Samuel Bernard, Olivier Gandrillon and Fabien Crauste (in collaboration with J. Mafille, Y. Leverrier, C. Arpin and J. Marvel) published a paper ([21], see also § 6.2) in Computation 2014.
- We organized a session "Deterministic and stochastic models in biology and medicine" at 10th AIMS Conference on Dynamical Systems, Differential Equations and Applications, Madrid (Spain), 7 - 11 July 2014 http://www.aimsciences.org/conferences/2014/.
- Our project entitled "Prion and Alzheimer: mathematical modeling and experiments dealing with a dangerous liaison" has been granted by the French Association France Alzheimer, and has been selected with 3 other projects amongst 14 supported works to be part of a scientific popularizing broadcasting campaign through a short scientific cartoon http://www.francealzheimer.org/projets-soutenus-cette-ann%C3%A9e/lab-alz-comprendre-enjeux-recherche/964 and https://www.youtube.com/watch?v=X0mLf8IJhV4&list=PLCq-e7n2r6Wgo3kaseDHetNAPAG7y9B-d.

6.2. Multi-scale model of the CD8 T cell immune response

We presented in [21] the first multi-scale model of CD8 T cell activation in a lymph node, following an acute infection. CD8 T cell dynamics are described using a cellular Potts model (hence cells are discrete interacting objects), whereas intracellular regulation is associated with a continuous system of nonlinear ordinary differential equations focusing on the dynamics of key proteins. This model allows to reproduce the dynamics of CD8 T cells over a five days period (corresponding to the activation and differentiation into effector cells) and is currently used to characterize the generation of memory cells.

6.3. Mathematical model of hematopoiesis

We investigate in [5] a mathematical model of blood cell production in the bone marrow (hematopoiesis). The model describes both the evolution of primitive hematopoietic stem cells and the maturation of these cells as they differentiate to form the three kinds of progenitors and mature blood cells (red blood cells, white cells and platelets). The three types of progenitors and mature cells are coupled to each other via their common origin in primitive hematopoietic stem cells compartment. The resulting system is composed by eleven age-structured partial differential equations. To analyze this model, we don't take into account cell age-dependence of coefficients, that prevents a usual reduction of the structured system to an unstructured delay differential system. We study the existence of stationary solutions: trivial, axial and positive steady states. Then we give conditions for the local asymptotic stability of the trivial steady state and by using a Lyapunov function, we obtain a sufficient condition for its global asymptotic stability. In some particular cases, we analyze the local asymptotic stability of the positive steady state by using the characteristic equation. Finally, by numerical simulations, we illustrate our results and we show that a change in the duration of cell cycle can cause oscillations.

6.4. The role of spatial organization of cells in erythropoiesis

Erythropoiesis, the process of red blood cell production occurs mainly in the bone marrow. The functional unit of mammalian erythropoiesis, the erythroblastic island, consists of a central macrophage surrounded by adherent erythroid progenitor cells (CFU-E/Pro-EBs) and their differentiating progeny, the erythroblasts. Central macrophages display on their surface or secrete various growth or inhibitory factors that influence the fate of the surrounding erythroid cells. CFU-E/Pro-EBs have three possible fates : a) expansion of their numbers without differentiation, b) differentiation into reticulocytes that are released into the blood, c) death by apoptosis. CFU-E/Pro-EB fate is under the control of a complex molecular network, that is highly dependent upon environmental conditions in the erythroblastic island. In order to assess the functional role of space coupled with the complex network behavior in erythroblastic islands, we developed hybrid discrete-continuous models of erythropoiesis. In [13], a model was developed in which cells are considered as individual physical objects, intracellular regulatory networks are modeled with ordinary differential equations and extracellular concentrations by partial differential equations. We used this model to investigate the impact of an important

difference between humans and mice in which mature late-stage erythroblasts produce the most Fas-ligand in humans, whereas early-stage erythroblasts produce the most Fas-ligand in mice. Although the global behaviors of the erythroblastic islands in both species were similar, differences were found, including a relatively slower response time to acute anemia in humans. Also, our modeling approach was very consistent with in vitro culture data, where the central macrophage in reconstituted erythroblastic islands has a strong impact on the dynamics of red blood cell production. Conclusions: The specific spatial organization of erythroblastic islands is key to the normal, stable functioning of mammalian erythropoiesis, both in vitro and in vivo. Our model of a simplified molecular network controlling cell decision provides a realistic functional unit of mammalian erythropoiesis that integrates multiple microenvironmental influences within the erythroblastic island with those of circulating regulators of erythropoiesis, such as EPO and glucocorticosteroids, that are produced at remote sites.

6.5. Mathematical modelling of cell polarization

In [19], a fine description of the behaviour of a nonlinear drift diffusion model inspired from spontaneous cell polarization was performed. This model has Keller Segel type properties and in particular, quantitative proofs were obtained for the convergence to steady state or self similar profile or blow up. The behaviour depends on the mass of the initial data.

6.6. Numerical modelling of cell distribution in blood flow

Properties of blood cells and their interaction determine their distribution in flow. It is observed experimentally that erythrocytes migrate to the ow axis, platelets to the vessel wall, and leucocytes roll along the vessel wall. In [2], a three-dimensional model based on Dissipative Particle Dynamics method and a new hybrid (discrete-continuous) model for blood cells is used to study the interaction of erythrocytes with platelets and leucocytes in flow. Erythrocytes are modelled as elastic highly deformable membranes, while platelets and leucocytes as elastic membranes with their shape close to a sphere. Separation of erythrocytes and platelets in flow is shown for different values of hematocrit. Erythrocyte and platelet distributions are in a good qualitative agreement with the existing experimental results. Migration of leucocyte to the vessel wall and its rolling along the wall is observed.

6.7. Mathematical model of food intake dynamics

In [18], we propose a nonlinear mathematical model of food intake dynamics and body weight dynamics, involving the description of several regulating hormones (leptin, ghrelin, insulin). Using a temporal perturbation of food availability in groups of rats, this model is able to predict body weight and food intake variations by taking into account energy expenditure dynamics based on a memory of the previous food intake. This model also allowed us to estimate the memory lag to approximately 8 days. It also explains how important variations in food availability during periods longer than these 8 days can induce body weight gains.

6.8. Long time existence of weak solutions to cross diffusion models

We pointed out a general entropy structure in cross diffusion systems. We used this structure with duality arguments to build a general framework in which weak solutions exist for a long time. This led to two research articles (one [10] in Siam Journal of Mathematical Analysis and one and [32] recently accepted in Comm. In PDE). This was conducted with the help of the ANR KIBORD.

6.9. Mathematics of Darwin's diagram

Darwin illustrated his theory about emergence and evolution of biological species with a diagram. It shows how species exist, evolve, appear and disappear. Our goal in [8] is to give a mathematical interpretation of this diagram and to show how it can be reproduced in mathematical models. It appears that conventional models in population dynamics are not sufficient, and we introduce a number of new models which take into account local, nonlocal and global consumption of resources, and models with space and time dependent coefficients.

6.10. A micellar on-pathway intermediate step explains the kinetics of prion amyloid formation

In [16], we used a strong interdisciplinary collaboration between mathematicians and biologists to exhibit a new element taking an important role in the development of the pathological prion formation. Indeed, in a previous work by Alvarez-Martinez et al. (2011), the authors pointed out some fallacies in the mainstream interpretation of the prion amyloid formation. It appeared necessary to propose an original hypothesis able to reconcile the in vitro data with the predictions of a mathematical model describing the problem. Here, a model is developed accordingly with the hypothesis that an intermediate on-pathway leads to the conformation of the prion protein into an amyloid competent isoform thanks to a structure, called micelles, formed from hydrodynamic interaction. The authors also compared data to the prediction of their model and proposed a new hypothesis for the formation of infectious prion amyloids.

7. Bilateral Contracts and Grants with Industry

7.1. 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 Cosmo). The current ANR PrediVac incorporates the two aforementioned SMEs and therefore strengthens the ties between Dracula and its industrial local ecosystem.

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. ANR

Projects coordination by a member of Dracula

- ANR (jeunes chercheurs) ProCell "Mathematical Methods for Erythropoiesis Modelling: from Proteins to Cell Populations", 2009-2014.
  Participants: Samuel Bernard, Fabien Crauste [Coordinator], Olivier Gandrillon, Thomas Lepoutre, Philippe Michel, Laurent Pujo-Menjouet, Vitaly Volpert.
- ANR BIMOD "Hybrid models of cell populations. Application to cancer modelling and treatment", 2010-2014.
  Participants: Mostafa Adimy, Fabien Crauste, Vitaly Volpert [Coordinator].
- ANR STOCHAGENE "Role of the chromatin dynamics on the stochasticity in gene expression in higher eukaryotic cells", 2011-2015.
  Participant: Olivier Gandrillon [Coordinator].

Collaboration in other projects

- ANR RPIB PrediVac "Innovative modeling tools for the prediction of CD8 T cell based vaccine efficacy", 2013-2015. Partners: U1111 Inserm (J. Marvel, coordinator), Dracula, Altrabio (small company), CoSMo (small company). For Dracula, the budget from 2013 to 2015 is 198 keuros, including three one-year post-doc positions (one post-doc has been recruited in April 2014 (Xuefeng Gao)), and the members are Fabien Crauste and Olivier Gandrillon.
- Thomas Lepoutre participates in the ANR (jeunes chercheurs) MODPOL (head Vincent Calvez (ENS Lyon)) "Cell polarization modeling", 2011-2015.
- Thomas Lepoutre is a member of the ANR KIBORD (head L. Desvillettes) dedicated to "kinetic and related models in biology". 2012-2016.
- 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".

8.1.2. Other projects

- Inria ADT : SiMuScale "Simulations Multi-Échelles de Populations Cellulaires", 2014-2016.
  Participants: Samuel Bernard [Coordinator], Fabien Crauste, David Parsons.
- Association France Alzheimer Sciences Médicales 2014 : PAMELA "Prion et Alzheimer : Modélisation et Expérimentation d'une Liaison Agressive", 2014. Partners: UR0892 VIM (Virologie et Immunologie Moléculaires), INRA Domaine de Vilvert, Jouy-en-Josas.
  Participants: Mostafa Adimy, Samuel Bernard, Thomas Lepoutre, Laurent Pujo-Menjouet [Coordinator], Léon Tine.

8.2. European Initiatives

8.2.1. Collaborations in European Programs, except FP7 & H2020

- Research program PHC POLONIUM (2014-2015) "Applications of reaction-diffusion equations in biology and medicine". Partners: Warsaw, Poland (Slawomir Bialecki, Jolanta Ciesielska, Bogdan Kazmierczak (coordinator), Marek Kochanczyk, Tomasz Lipniacki).
  Participants: Mostafa Adimy, Abdennasser Chekroun, Laurent Pujo-Menjouet [Coordinator], Alen Tosenberger, Vitaly Volpert.

8.2.2. Collaborations with Major European Organizations

- University of Valladolid (Spain). Collaboration with Oscar Angulo, Juan Carlos Lopez-Marcos and Miguel Ange Lopez-Marcos, on the analysis of an age-structured model describing erythropoiesis, and its numerical resolution.
- Karolinska University Hospital of Stockholm (Sweden). Collaboration with Peter Arner, Mats Eriksson, Erik Arner, Mikael Rydén and Kirsty L. Spalding, on the study of dynamics of human adipose lipid turnover in health and metabolic disease.

8.3. International Initiatives

8.3.1. Inria Associate Teams

8.3.1.1. Modelling leukemia

Title: Modeling quiescence and drug resistance in Chronic Myeloid Leukemia

International Partner (Institution - Laboratory - Researcher):

Center for Scientific Computation And Mathematical Modelling, University of Maryland (United States).

Duration: 2013 - 2015.

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

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 will join 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). The theoretical and modeling experience of team DRACULA and the numerical expertise combined with the links with experimentalists of members of CSCAMM will allow us to study deeply evolution of leukemia. We will especially focus on the behavior of leukemic stem cells and their possibility of becoming quiescent (dormant). Then we will study (using the knowledge obtained on leukemic stem cells) the phenomenon of drug resistance and its propagation over time and finally the mechanisms of multidrug resistance.

8.3.2. Participation In other International Programs

8.3.2.1. M3CD

Program: Euromediterranean 3+3

Title: Mathematical Models and Methods in Cell Dynamics

Inria principal investigator: Mostafa Adimy

International Partners (Institution - Laboratory - Researcher):

Institut Pasteur de Tunis (Tunisia) - Slimane Ben Miled

Consiglio Nazionale delle Ricerche- Istituto per le Applicazioni del Calcolo Mauro Picone (Italy) - Istituto per le Applicazioni del Calcolo Mauro Picone - Roberto Natalini

Cadi Ayyad University (Morocco) - Populations Dynamics Laboratory - Moulay Lhassan Hbid

Duration: Jan 2012 - Dec 2015

The aim of this project is to establish a network working on mathematical and computational models in cell dynamics. This network consists of five groups which have already established close bilateral relations. Those are the Inria teams Bang and Dracula in Paris and Lyon, France, the team IAC-CNR in Rome, Italy, the laboratory of Mathematical Population Dynamics (LMDP) from the university of Marrakech in Morocco, and the team of Mathematical Modelling and Computing in Biology (MoMinBi) from the Pasteur Institute in Tunis. Modelling cell dynamics and related processes is one of the main subjects of interest for the partners for many years. The issues addressed in the present project can be divided into five parts:

1) Analysis of structured models in cell population dynamics ;

2) Dynamics of normal and pathological haematopoiesis ;

3) Dynamics of Darwinian adaptation, in particular by drug resistance in competing cell or parasite populations, healthy and pathological / pathogenic (cancer, bacteria, parasites) ;

4) Dynamics of chemical and physical determinants of filament formation and intracellular spatial organisation of the cytoskeleton conformation ;

5) Coupling of the molecular mechanisms of control of the cell division cycle and cell proliferation.

The first part has been developed for many years by all the partners in this project. It tackles issues related to cell dynamics and biological mechanisms, physiological and chemical properties of cells and cell populations. The other four aspects of the project have been studied in the past by the Inria teams "Bang" and "Dracula" (**2**, **4**, **5**) and the IAC-CNR team (Rome), or are a rapidly emergent theme in Bang (**3**, cell Darwinism) with possible and natural connections with the other teams, in particular IAC-CNR and MoMinBi in Tunisia. Themes (**2**, **4**, **5**) have also been initiated (for their fundamental part) in a recent collaboration between Dracula and the teams from Morocco and Tunisia. The objectives of the present project are to pursue and deepen the study of cell proliferation dynamics and cellular mechanisms using structured models that take into account some new structure variables. The development of computer models will also be investigated in this project. Training and research activities related to these topics are currently underway between the Inria teams and the teams from Marrakech and Tunis, and between the Italian team and Bang. Two co-supervised theses are currently in progress, a Spring school on this subject will be organised by the partners in 2012. This program comes at the right time to give a new impetus to this collaboration. It will lead to the establishment of a multi-site laboratory expertise in population dynamics modelling, especially in cellular dynamics. This project will also allow the teams from Morocco and Tunisia to use their knowledge on mathematics applied to cell dynamics.

8.3.2.2. FCRF

Program: Fonds France Canada pour la recherche (FFCR)- France Canada research fund (FCRF) "New research collaboration" 2014-2015.

Title: Mathematical modelling of megakaryopoiesis and applications to platelet related diseases

Participants: Mostafa Adimy, Fabien Crauste, Laurent Pujo-Menjouet [Coordinator].
International Partners : Canada (Jiguo Cao, Nemanja Kosovalic, Jianhong Wu).

8.4. International Research Visitors

8.4.1. Visits of International Scientists

8.4.1.1. Internships

Anass Bouchnita

Subject: Numerical simulations of blood flows and blood coagulation
Date: from March 2014 until May 2014
Institution: École Mohammadia d'Ingénieurs (EMI), Rabat, Morocco

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific events organisation

9.1.1.1. Member of the organizing committee

- Conference "LyonSysBio" (Lyon Systems Biology), Lyon (France), 19 - 21 November 2014 (http://lyonsysbio.sciencesconf.org/?lang=fr). Co-organizers : Fabien Crauste and Olivier Gandrillon.
- 12ème Colloque Franco-Roumain de Mathématiques Appliquées, Lyon (France), 25 - 30 August 2014 (http://cfr2014.univ-lyon1.fr/). Co-organizer : Fabien Crauste.
- 10th AIMS Conference on Dynamical Systems, Differential Equations and Applications, Madrid (Spain), 7 - 11 July 2014 (http://www.aimsciences.org/conferences/2014/). Co-organizers of the session "Deterministic and stochastic models in biology and medicine" : Mostafa Adimy, Fabien Crauste and Laurent Pujo-Menjouet.
- Regular Semovi seminar series (http://www.biosyl.org/news/semovi), 5 seminars organized in 2014. Co-organizer : Olivier Grandrillon. BioSyL (http://www.biosyl.org) worshops organization. Co-organizer : Olivier Grandrillon.

9.1.2. Journal

9.1.2.1. Member of the editorial board

- Mostafa Adimy : Journal of Nonlinear Systems and Applications (JNSA); The Scientific World Journal; Chinese Journal of Mathematics.
- Fabien Crauste : Computational and Mathematical Methods in Medicine (HPG)
- Laurent Pujo-Menjouet : Mathematical modelling natural phenomena; Frontiers Mathematics and Computers in Simulation

9.1.2.2. Reviewer

- Fabien Crauste : Abstract and Applied Analysis, Computational and Applied Mathematics, Journal of Mathematical Biology, Journal of Theoretica Biology, Mathematical Biosciences and Engineering, Mathematical Methods in the Applied Sciences, Mathematical Biosciences.

- Laurent Pujo-Menjouet : ISRN Biomathematics, Mathematical Biosciences, Mathematical Biosciences and Engineering, Mathematics and Computers in Simulation, Mathematical Methods in the Applied Sciences, Zeitschrift fuer Angewandte Mathematik und Physik (ZAMP).
- Olivier Gandrillon : Gene, Journal of the Royal Society Interface, PLOS Computational Biology, BMC research notes.
- Phillipe Michel : Nonlinear Analysis, PLOS One
- Samuel Bernard : PLOS Computational Biology, Biophysical Journal, Journal of Theoretical Biology, PLOS One, BMC Systems Biology, Mathematics and Computers in Simulations.
- Thomas Lepoutre : Siam Journal of Mathematical Analysis, Numerical Methods in PDE, Journal of Mathematical Biology.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

- Licence : Phillipe Michel, Analyse appliquée, 56h, L3, Ecole Centrale de Lyon.
- Licence : Phillipe Michel, Probabilités et statistique, 30h, L3, Ecole Centrale de Lyon.
- Licence: Samuel Bernard, Algèbre linéaire et matricielle, 45h, L3, INSA Lyon.
- Licence : Laurent Pujo-Menjouet, les réels et les fonctions, 36h, L1, Université Lyon 1.
- Licence : Laurent Pujo-Menjouet, suites et séries de fonctions, 36h, L1, Université Lyon 1.
- Licence : Laurent Pujo-Menjouet, Equations Différentielles, 18h, L2, Université Lyon 1.
- Licence : Laurent Pujo-Menjouet, Projet de l'étudiant de Licence, 14h, L2, Université Lyon 1.
- Licence : Laurent Pujo-Menjouet, Biomathématiques et modélisation, 10h, L3, Université Lyon 1.
- Licence : Laurent Pujo-Menjouet, Equations différentielles et aux dérivées partielles, 36h, L3, Université Lyon 1.
- Licence: Léon Matar Tine, Techniques mathématiques de base (TMB), 42h, L1, Université Lyon 1.
- Licence: Léon Matar Tine, Maths PMI-Analyse, 42h, L2, Université Lyon 1.
- Licence: Léon Matar Tine, Analyse Numérique, 36h, L3, Université Lyon 1.
- Master : Phillipe Michel, Algorithmes pour la décision en entreprise, 15h, M2, Ecole Centrale de Lyon.
- Master : Phillipe Michel, Méthodes variationnelles pour les EDP, 35h, M2, ECL, Ecole Centrale de Lyon.
- Master : Phillipe Michel, Systèmes embarqués collaboratifs, 14h, M1, Ecole Centrale de Lyon.
- Master: Mostafa Adimy, Dynamique des populations cellulaires, 20h, M2, Université Lyon 1.
- Master: Samuel Bernard, Dynamique des populations cellulaires, 20h, M2, Université Lyon 1.
- Master : Laurent Pujo-Menjouet, Modélisation en biologie et médecine, 8h, M2, Université Lyon 1.
- Master : Laurent Pujo-Menjouet, Gestion de projet en ingénierie mathématique, 3h, M1, Université Lyon 1.
- Master : Laurent Pujo-Menjouet, Systèmes dynamiques, 66h, M1, Université Lyon 1.
- Master : Laurent Pujo-Menjouet, Projet tutoré en Mathématiques, 3h, M2, Université Lyon 1.
- Master: Léon Matar Tine, Dynamique des protéine, 18h, M2, Université Lyon 1.
- Master: Thomas Lepoutre, Dynamique des protéine, 18h, M2, Université Lyon 1.

9.2.2. Supervision

- HdR : Fabien Crauste, Équations à retard et modèles de dynamiques de populations cellulaires, Université Lyon 1, December 2014.

- PhD in progress : Marine Jacquier, Contribution à l'étude de modèles à retards modélisant l'impact physiologique du comportement de prise alimentaire, Université Lyon 1, October 2012, Mostafa Adimy and Fabien Crauste.
- PhD in progress : Abdennasser Chekroun, Équations différentielles et aux différences à retard pour des modèles de dynamique des cellules souches hématopoïétiques, Université Lyon 1, October 2012, Mostafa Adimy.
- PhD in progress : Barbaroux Loic, modélisation mathématique de la réponse immunitaire chez un individu en vue d'optimiser des stratégies de vaccination, Université de Lyon 1, October 2013, Mostafa Adimy and Phillipe Michel.
- PhD in progress : Raouf El Cheikh, Multiscale modelling of the interaction between the cell cycle and the circadian clock, Université Lyon 1, October 2011, Samuel Bernard and Vitaly Volpert.
- PhD in progress : Apollos Besse, The role of tumor-immune interaction in combined treatments for chronic myeloid leukemia, Université Lyon 1, October 2014, Samuel Bernard and Thomas Lepoutre.
- PhD in progress : Flavien Duparc, Etude d'un modèle mathématiques de régulation de l'hémoglobine chez les patients dialysés, Université Lyon 1, October 2014, Mostafa Adimy 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, Laurent Pujo-Menjouet and Jacques Bélair (co-tutelle avec l'Université de Montréal).

9.2.3. Juries

- Mostafa Adimy was member and reviewer of the following PhD : Modou Lo (University of Saint-Louis, Senegal), February 2014; Jose Luis Avila Alonso (University of Paris-Sud XI), July 2014; Benjamin Aymard (University of Paris 6), October 2014; Mathieu Leroy-Lereêtre (University of Toulouse), October 2014.
- Mostafa Adimy was reviewer of the PhD of Ahmed Fadili (University of Agadir, Morocco), December 2014.
- Mostafa Adimy was reviewer of the HDR of Samir Fatajou (University of Marrakech, Morocco), November 2014.
- Mostafa Adimy was member of the juries : Fabien Crauste, HDR (University of Lyon), December 2014; Nathalie Eymard, PhD (University of Lyon), December 2014.

9.3. Popularization

- Fabien Crauste : Cycle "Mathématiques et médecine" de l'Université Ouverte "Grippe saisonnière, épidémie, pandémie : quel apport des mathématiques ?", 25 March 2014.
- Olivier Grandrillon : Participation in the café des sciences "La recherche en génétique, entre prouesses et promesses", in Lyon (Samedi 11 octobre)
- Samuel Bernard : Participation in Conférence à l'Université Ouverte "Garder le rythme, c'est garder la santé" and "L'âge de nos cellules par test nucléaire", in Lyon.
- Thomas Lepoutre : Cycle "Mathématiques et médecine" de l'Université Ouverte.
- Thomas Lepoutre is one of the organizer of Mathalyon (Mathematcial exhibitions in highschool with 4 researchers, 20 days of intervention every year).
- Thomas Lepoutre : Intervention at Cité Scolaire Internationale (Highschool in Lyon) to explain what is a researcher's job.
- Laurent Pujo-Menjouet : Cycle "Mathématiques et médecine" de l'Université Ouverte "Le bonheur est dans le pré, les vaches folles aussi", 16 September, 2014.
- Laurent Pujo-Menjouet : supervising junior high school students for the "MathenJeans" program http://www.mathenjeans.fr (academic year 2014-2015).

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] F. CRAUSTE. *Delay Equations and Models of Cell population Dynamics*, Université Claude Bernard Lyon 1, December 2014, Habilitation à diriger des recherches, https://hal.inria.fr/tel-01092352

[2] A. TOSENBERGER. *Blood flow modelling and applications to blood coagulation and atherosclerosis*, Université Claude Bernard - Lyon 1 Institut Camille Jordan - CNRS UMR 5208, February 2014, https://tel.archives-ouvertes.fr/tel-01101607

Articles in International Peer-Reviewed Journals

[3] M. ADIMY, M. ALIA, K. EZZINBI. *Functional differential equations with unbounded delay in extrapolation spaces*, in "Electronic Journal of Differential Equations", 2014, vol. 2014, pp. 1 - 16, https://hal.inria.fr/hal-01096950

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