IN PARTNERSHIP WITH:
CNRS

Université Claude Bernard (Lyon 1)

Activity Report 2015

Project-Team DRACULA

Multi-scale modelling of cell dynamics : application to hematopoiesis

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

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Modeling and Control for Life Sciences

Table of contents

Project-Team DRACULA

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

Keywords:

Computer Science and Digital Science:

6.1. - Mathematical Modeling
6.1.1. - Continuous Modeling (PDE, ODE)
6.1.3. - Discrete Modeling (multi-agent, people centered)
6.1.4. - Multiscale modeling

Other Research Topics and Application Domains:

1. - Life sciences
1.1. - Biology
1.4. - Pathologies
2.4.2. - Drug resistance

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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.

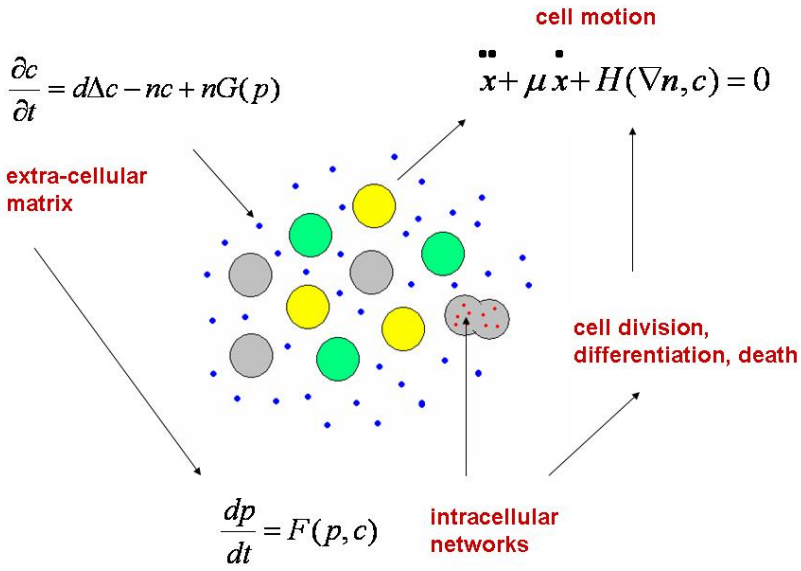

Figure 1. Schema of multi-scale models of cell dynamics: DPD-PDE-ODE models.

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.

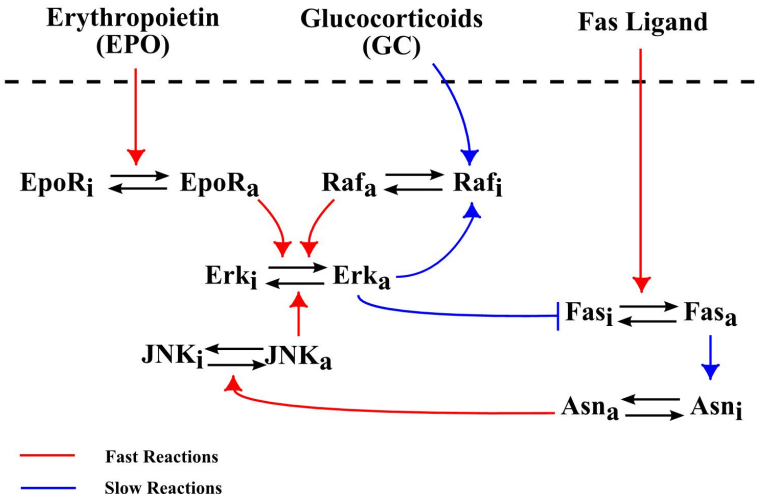

Figure 2. A schematic description of the intra-cellular molecular events that are relevant for decision making in an erythroid progenitor. The non active form of the protein is labeled i, the active form a. Blue lines indicate transcriptional regulation, red lines indicate biochemical regulation.

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 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 intracellular 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 [40] 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 [41] 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 ([46], [48]), and they proved effective in hematopoiesis modelling ([35], [36], [38]). 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 [48]. The nonlocality can be either in the structure variable or in the time variable [35]. 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 [42].

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 [43] 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.

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 [47]. 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 ([42], [39]), chronic myelogenous leukemia [44]).

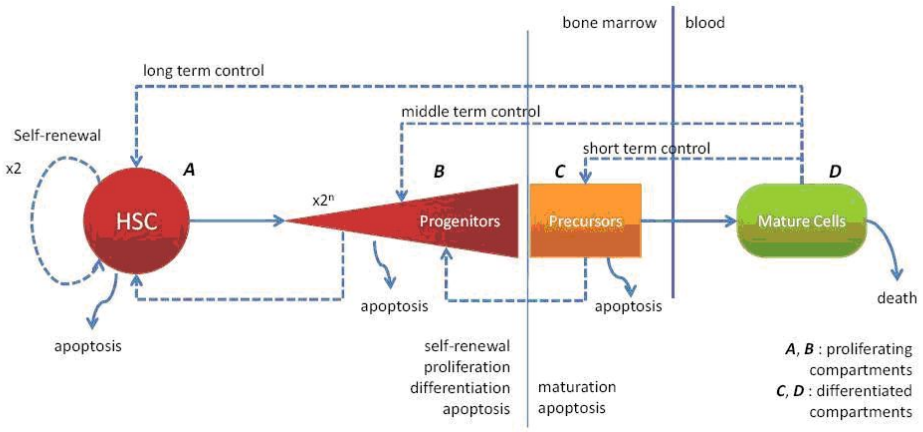

Figure 3. Scheme of Erythropoiesis Modelling ([34]). Without considering explicitly growth factor mediated regulation, all controls (proliferation, self-renewal, differentiation, apoptosis) are mediated by cell populations (dashed arrows). Mature cells can either regulate immature (HSC, progenitors) or almost mature (precursors) cells, precursors may act on progenitor dynamics, etc..

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.

(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

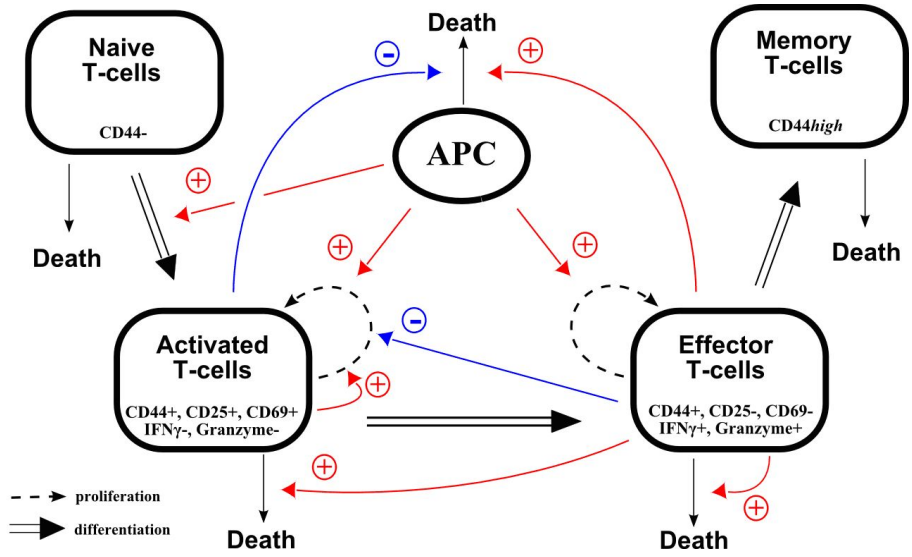

Figure 4. Model of the immune response resulting in the generation of CD8 memory T cells. The response starts with a viral infection resulting in the presentation of viral antigens through antigen presenting cells (APC) to naive T-cells. These latter, once activated, differentiate into activated cells 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.

The knowledge of hematopoiesis and related diseases has evolved to become a great deal in the past years, and Mackey's previous models (ref. [37]) 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 [45]. 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

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

6. New Results

6.1. Implication of the autologous immune system in BCR-ABL transcript variations in chronic myelogenous leukemia patients treated with Imatinib

Imatinib (IM) and other tyrosine kinase inhibitors (TKI) have improved treatment of chronic myelogenous leukemia (CML); however, most patients are not cured. Deeper mechanistic understanding may improve TKI combination therapies to better control the residual leukemic cell population. In analyzing our patients' data, we found that many patients who otherwise responded well to IM therapy still showed variations in their BCR-ABL transcripts. To investigate this phenomenon, we applied a mathematical model (see [14]) that integrates

CML and an autologous immune response to the patients' data. We define an immune window, or a range of leukemic loads for which the autologous immune system induces an improved response. Our modeling results in [14], suggest that, at diagnosis, a patient's leukemic load is able to partially or fully suppress the autologous immune response developed in a majority of patients, towards the CML clone(s). IM therapy drives the leukemic population into the "immune window", allowing the patient's autologous immune cells to expand and eventually mount an efficient recognition of the residual leukemic burden. This response drives the leukemic load below this immune window, allowing the leukemic population to partially recover until another weaker immune response is initiated. Thus, the autologous immune response may explain the oscillations in BCR-ABL transcripts regularly observed in patients on IM.

6.2. Predicting pathogen-specific CD8 T cell immune responses from a modeling approach

The primary CD8 T cell immune response constitutes a major mechanism to fight an infection by intracellular pathogens. We aim at assessing whether pathogen-specific dynamical parameters of the CD8 T cell response can be identified, based on measurements of CD8 T cell counts, using a modeling approach. We generated experimental data consisting in CD8 T cell counts kinetics during the response to three different live intra-cellular pathogens: two viruses (influenza, vaccinia) injected intranasally, and one bacteria (Listeria monocytogenes) injected intravenously. All pathogens harbor the same antigen (NP68), but differ in their interaction with the host. In parallel, we developed in [16] a mathematical model describing the evolution of CD8 T cell counts and pathogen amount during an immune response. This model is characterized by 9 parameters and includes relevant feedback controls. The model outputs were compared with the three data series and an exhaustive estimation of the parameter values was performed. By focusing on the ability of the model to fit experimental data and to produce a CD8 T cell population mainly composed of memory cells at the end of the response, critical parameters were identified. We show that a small number of parameters $(2-4)$ define the main features of the CD8 T cell immune response and are characteristic of a given pathogen. Among these parameters, two are related to the effector CD8 T cell mediated control of cell and pathogen death. The parameter associated with memory cell death is shown to play no relevant role during the main phases of the CD8 T cell response, yet it becomes essential when looking at the predictions of the model several months after the infection.

6.3. Dynamics of cell generation and turnover in the human heart

The contribution of cell generation to physiological heart growth and maintenance in humans has been difficult to establish and has remained controversial. We report in [8] that the full complement of cardiomyocytes is established perinataly and remains stable over the human lifespan, whereas the numbers of both endothelial and mesenchymal cells increase substantially from birth to early adulthood. Analysis of the integration of nuclear bomb test-derived $14C$ revealed a high turnover rate of endothelial cells throughout life ($> 15\%$ per year) and more limited renewal of mesenchymal cells ($< 4\%$ per year in adulthood). Cardiomyocyte exchange is highest in early childhood and decreases gradually throughout life to $< 1\%$ per year in adulthood, with similar turnover rates in the major subdivisions of the myocardium. We provide an integrated model of cell generation and turnover in the human heart.

6.4. Travelling waves of cell differentiation

The paper [7] is devoted to modelling of cell differentiation in an initially homogeneous cell population. The mechanism which provides coexistence of two cell lineages in the initially homogeneous cell population is suggested. If cell differentiation is initiated locally in space in the population of undifferentiated cells, it can propagate as a travelling wave converting undifferentiated cells into differentiated ones. We suggest a model of this process which takes into account intracellular regulation, extracellular regulation and different cell types. They include undifferentiated cells and two types of differentiated cells. When a cell differentiates, its choice between two types of differentiated cells is determined by the concentrations of intracellular proteins.

Differentiated cells can either stimulate differentiation into their own cell lineage or into another cell lineage. In the case of the positive feedback, only one lineage of differentiated cells will finally appear. In the case of negative feedback, both of them can coexist. In this case a periodic spatial pattern emerges behind the wave.

6.5. Pattern regeneration based on cell memory

In [24], we present a new model of the cellular dynamics that enable regeneration of complex biological morphologies. Biological cell structures are considered as an ensemble of mathematical points on the plane. Each cell produces a signal which propagates in space and is received by other cells. The total signal received by each cell forms a signal distribution defined on the cell structure. This distribution characterizes the geometry of the cell structure. If a part of this structure is removed, the remaining cells have two signals. They keep the value of the signal which they had before the amputation (memory), and they receive a new signal produced after the amputation. Regeneration of the cell structure is stimulated by the difference between the old and the new signals. It is stopped when the two signals coincide. The algorithm of regeneration contains certain rules which are essential for its functioning, being the first quantitative model of cellular memory that implements regeneration of complex patterns to a specific target morphology. Correct regeneration depends on the form and the size of the cell structure, as well as on some parameters of regeneration.

6.6. Target morphology and cell memory

Despite the growing body of work on molecular components required for regenerative repair, we still lack a deep understanding of the ability of some animal species to regenerate their appropriate complex anatomical structure following damage. A key question is how regenerating systems know when to stop growth and remodeling – what mechanisms implement recognition of correct morphology that signals a stop condition? In [11], we review two conceptual models of pattern regeneration that implement a kind of pattern memory. In the first one, all cells communicate with each other and keep the value of the total signal received from the other cells. If a part of the pattern is amputated, the signal distribution changes. The difference from the original signal distribution stimulates cell proliferation and leads to pattern regeneration, in effect implementing an error minimization process that uses signaling memory to achieve pattern correction. In the second model, we consider a more complex pattern organization with different cell types. Each tissue contains a central (coordinator) cell that controls the tissue and communicates with the other central cells. Each of them keeps memory about the signals received from other central cells. The values of these signals depend on the mutual cell location, and the memory allows regeneration of the structure when it is modified. The purpose of these models is to suggest possible mechanisms of pattern regeneration operating on the basis of cell memory which are compatible with diverse molecular implementation mechanisms within specific organisms.

6.7. Transplanted bone marrow-derived cells contribute to human adipogenesis

Because human white adipocytes display a high turnover throughout adulthood, a continuous supply of precursor cells is required to maintain adipogenesis. Bone marrow (BM)-derived progenitor cells may contribute to mammalian adipogenesis; however, results in animal models are conflicting. In [22], we demonstrate in 65 subjects who underwent allogeneic BM or peripheral blood stem cell (PBSC) transplantation that, over the entire lifespan, BM/PBSC-derived progenitor cells contribute 10% to the subcutaneous adipocyte population. While this is independent of gender, age, and different transplantation-related parameters, body fat mass exerts a strong influence, with up to 2.5-fold increased donor cell contribution in obese individuals. Exome and whole-genome sequencing of single adipocytes suggests that BM/PBSC-derived progenitors contribute to adipose tissue via both differentiation and cell fusion. Thus, at least in the setting of transplantation, BM serves as a reservoir for adipocyte progenitors, particularly in obese subjects.

6.8. Modelling of platelet–fibrin clot formation in flow

The paper [23] is devoted to mathematical modelling of clot growth in blood flow. Great complexity of the hemostatic system dictates the need of usage of the mathematical models to understand its functioning in the normal and especially in pathological situations. In this work we investigate the interaction of blood flow, platelet aggregation and plasma coagulation. We develop a hybrid DPD–PDE model where dissipative particle dynamics (DPD) is used to model plasma flow and platelets, while the regulatory network of plasma coagulation is described by a system of partial differential equations. Modelling results confirm the potency of the scenario of clot growth where at the first stage of clot formation platelets form an aggregate due to weak inter-platelet connections and then due to their activation. This enables the formation of the fibrin net in the centre of the platelet aggregate where the flow velocity is significantly reduced. The fibrin net reinforces the clot and allows its further growth. When the clot becomes sufficiently large, it stops growing due to the narrowed vessel and the increase of flow shear rate at the surface of the clot. Its outer part is detached by the flow revealing the inner part covered by fibrin. This fibrin cap does not allow new platelets to attach at the high shear rate, and the clot stops growing. Dependence of the final clot size on wall shear rate and on other parameters is studied.

6.9. Conceptual model of morphogenesis and regeneration

The paper [24] is devoted to computer modelling of the development and regeneration of multicellular biological structures. Some species (e.g. planaria and salamanders) are able to regenerate parts of their body after amputation damage, but the global rules governing cooperative cell behaviour during morphogenesis are not known. Here, we consider a simplified model organism, which consists of tissues formed around special cells that can be interpreted as stemcells. We assume that stem cells communicate with each other by a set of signals, and that the values of these signals depend on the distance between cells. Thus the signal distribution characterizes location of stem cells. If the signal distribution is changed, then the difference between the initial and the current signal distribution affects the behaviour of stem cells—e.g. as a result of an amputation of a part of tissue the signal distribution changes which stimulates stem cells to migrate to new locations, appropriate for regeneration of the proper pattern. Moreover, as stem cells divide and form tissues around them, they control the form and the size of regenerating tissues. This two-level organization of the model organism, with global regulation of stem cells and local regulation of tissues, allows its reproducible development and regeneration.

6.10. Delay differential-difference system for hematopoietic stem cell dynamics

We investigate in [2] and [3] a mathematical model of hematopoietic stem cell dynamics. We take two cell populations into account, quiescent and proliferating one, and we note the difference between dividing cells that enter directly to the quiescent phase and dividing cells that return to the proliferating phase to divide again. The resulting mathematical model is a system of two age-structured partial differential equations. By integrating this system over age and using the characteristics method, we reduce it to a delay differential-difference system, and we investigate the existence and stability of the steady states. We give sufficient conditions for boundedness and unboundedness properties for the solutions of this system. By constructing a Lyapunov function, the trivial steady state, describing cell's dying out, is proven to be globally asymptotically stable when it is the only equilibrium. The stability analysis of the unique positive steady state, the most biologically meaningful one, and the existence of a Hopf bifurcation allow the determination of a stability area, which is related to a delay-dependent characteristic equation. Numerical simulations illustrate our results on the asymptotic behavior of the steady states and show very rich dynamics of this model. This study may be helpful in understanding the uncontrolled proliferation of blood cells in some hematological disorders.

6.11. Discrete limit and monotonicity properties of the Floquet eigenvalue in an age structured cell division cycle model

We consider in [19] a cell population described by an age-structured partial differential equation with time periodic coefficients. We assume that division only occurs after a minimal age (majority) and within certain

time intervals. We study the asymptotic behavior of the dominant Floquet eigenvalue, or Perron-Frobenius eigenvalue, representing the growth rate, as a function of the majority age, when the division rate tends to infinity (divisions become instantaneous). We show that the dominant Floquet eigenvalue converges to a staircase function with an infinite number of steps, determined by a discrete dynamical system. As an intermediate result, we give a structural condition which guarantees that the dominant Floquet eigenvalue is a nondecreasing function of the division rate. We also give a counter example showing that the latter monotonicity property does not hold in general.

6.12. Optimal linear stability condition for scalar differential equations with distributed delay

Linear scalar differential equations with distributed delays appear in the study of the local stability of nonlinear differential equations with feedback, which are common in biology and physics. Negative feedback loops tend to promote oscillations around steady states, and their stability depends on the particular shape of the delay distribution. Since in applications the mean delay is often the only reliable information available about the distribution, it is desirable to find conditions for stability that are independent from the shape of the distribution. We show in [9] that for a given mean delay, the linear equation with distributed delay is asymptotically stable if the associated differential equation with a discrete delay is asymptotically stable. We illustrate this criterion on a compartment model of hematopoietic cell dynamics to obtain sufficient conditions for stability.

6.13. A mathematical model of leptin resistance

Obesity is often associated with leptin resistance, which leads to a physiological system with high leptin concentration but unable to respond to leptin signals and to regulate food intake. We propose in [20] a mathematical model of the leptin-leptin receptors system, based on the assumption that leptin is a regulator of its own receptor activity, and investigate its qualitative behavior. Based on current knowledge and previous models developed for body weight dynamics in rodents, the model includes the dynamics of leptin, leptin receptors and the regulation of food intake and body weight. It displays two stable equilibria, one representing a healthy state and the other one an obese and leptin resistant state. We show that a constant leptin injection can lead to leptin resistance and that a temporal variation in some parameter values influencing food intake can induce a change of equilibrium and a pathway to leptin resistance and obesity.

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. Furthermore, the ties with the COSMO companies have been strenghened through a joint CIFR pHD (see below).

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. ANR

Projects coordination by a member of Dracula

- 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", 2013-2016. Partners: U1111 Inserm (J. Marvel, coordinator), Dracula, Altrabio (small company), CoSMo (small company). For Dracula, the budget from 2013 to 2016 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.
- Thomas Lepoutre is a member of the ERC MESOPROBIO (head V. Calvez) dedicated to "Mesoscopic models for propagation in biology". 2015-2020.
- 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 2014-2015 : PAMELA "Prion et Alzheimer : Modélisation et Expérimentation d'une Liaison Agressive", 2014-2015. 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 not involved in an Inria International Labs

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).

9. Dissemination

9.1. Promoting Scientific Activities

9.1.1. Scientific events organisation

9.1.1.1. Member of the organizing committees

- Conference "LyonSysBio" (Lyon Systems Biology), Lyon (France), 18 - 20 November 2015 (http://lyonsysbio2015.sciencesconf.org/?lang=en). Co-organizers : Fabien Crauste and Olivier Gandrillon.
- Regular Semovi seminar series (http://www.biosyl.org/news/copy_of_semovi), 4 seminars organized in 2015. Co-organizer : Olivier Grandrillon and Fabien Crauste.
- BioSyL (http://www.biosyl.org) worshops organization. Co-organizer : Olivier Grandrillon.
- Equadiff conference, Lyon (France), 6-10 July 2015 (http://equadiff2015.sciencesconf.org/). Co-organizers : Thomas Lepoutre and Laurent Pujo-Menjouet.

9.1.2. Journal

9.1.2.1. Member of the editorial boards

- 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.
- Olivier Gandrillon: BMC research Notes.

9.1.2.2. Reviewer

- Mostafa Adimy : Zeitschrift fuer Angewandte Mathematik und Physik (ZAMP); Funkcialaj Ekvacioj, Journal of Fixed Point Theory and Applications.

- Fabien Crauste : Journal of Mathematical Biology, Plos Comp Biol.
- Olivier Gandrillon : Genes, Gene, BioEssays, Nature, Journal of the Royal Society Interface, Plos Comp Biol.
- Thoms Lepoutre : Bulletin of mathematical biology, Communications in Mathematical Sciences, Networks and Heterogeneous Media, Kinetic and Related Models.

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: Fabien Crauste, Dynamique des populations cellulaires, 15h, 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

- 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 : Loïc Barbarroux, 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 : Alvaro Mateso Gonzales, Models for anomalous diffusion, ENS Lyon, October 2014, Thomas Lepoutre, Hugues Berry and Vincent Calvez (Alvaro is not member of Dracula team).
- 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).
- PhD in progress : Simon Girel, Contribution à la modélisation multi-échelles de la réponse immunitaire : Analyse d'équations aux dérivées partielles et identiabilité paramétrique, Université de Lyon (LabEx), Septembre 2015, Fabien Crauste
- PhD in progress : Ulysse Herbach, Modèles graphiques probabilistes pour l'inférence de réseaux de gènes, Université Lyon 1, October 2015, Olivier Gandrillon, Thibault Espinasse (ICJ) and Anne-Laure Fougères (ICJ).
- PhD in progress : Arnaud Bonnafoux, Vers une inférence automatique de réseaux de gènes dynamiques à partir de « mégadonnées » temporelles discrètes acquises sur cellules uniques, Université Lyon 1, November 2015, Olivier Gandrillon (CIFRE with the COSMO company).

9.2.3. Juries

- Fabien Crauste was reviewer and member of the PhD of Ana Jarne Munoz (Université de Bordeaux), Modeling the effect of exogenous Interleukin 7 in HIV patients under antiretroviral therapy with low immune reconstitution.
- Mostafa Adimy was reviewer and member of the PhD of Patrice Ndambomve (University of Abuja, Nigeria), Contributions to control theory of nonlinear systems and split feasibility problems.
- Mostafa Adimy was reviewer of the PhD of Abdelkarim Nidal Akdad (University of Marrakesh, Morocco), Contribution to quantitative and qualitative analysis for neutral partial functional differential equations - Existence and regularity.

9.3. Popularization

- Fabien Crauste : conference "grippe saisonnière, épidémie, pandémie : quel apport des mathématiques ?" à l'Université Ouverte, Lyon, 20 January 2015.
- Thomas Lepoutre is one of the organizer of Mathalyon (Mathematcial exhibitions in highschool with 4 researchers, 20 days of intervention in 2015).

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] P. MAZZOCCO. *Applications of mathematical modeling for optimization of chemotherapy delivery protocols, to treat low-grade glioma patients*, Université Grenoble Alpes, September 2015, https://tel.archives-ouvertes.fr/tel-01235541

Articles in International Peer-Reviewed Journals

[2] M. ADIMY, A. CHEKROUN, T.-M. TOUAOULA. *A delay differential-difference system of hematopoietic stem cell dynamics*, in "Comptes Rendus Mathématique", April 2015, vol. 353, n^{o} 4 [*DOI :* 10.1016/J.CRMA.2015.01.018], https://hal.inria.fr/hal-01249894

[3] M. ADIMY, A. CHEKROUN, T.-M. TOUAOULA. *Age-structured and delay differential-difference model of hematopoietic stem cell dynamics*, in "Discrete and Continuous Dynamical Systems - Series B", November 2015, vol. 20, n^{o} 9, 27 p. [*DOI :* 10.3934/DCDSB.2015.20.2765], https://hal.inria.fr/hal-01249892

[4] K. ALLALI, F. BIKANY, A. TAIK, V. VOLPERT. *Numerical simulations of heat explosion with convection in porous media*, in "Combustion Science and Technology", 2015 [*DOI :* 10.1080/00102202.2014.948619], https://hal.archives-ouvertes.fr/hal-01238489

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