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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
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THEME
Observation, Modeling, and Control for Life Sciences

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Project-Team DRACULA

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

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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 modelling in biology with application to normal and pathological hematopoiesis (blood cell production). Multi-scale modelling implies simultaneous modelling of intra-cellular networks (molecular level), of cell behaviour (cellular level), of the dynamics of cell populations (organ or tissue) with the control by other organs (organism). Such modelling 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.

Hematopoiesis is a complex process that begins with primitive hematopoietic stem cells (HSC) and results in formation of mature cells: red blood cells, white blood cells and platelets. Blood cells are produced in the bone marrow, from where mature cells are released into the blood stream. Hematopoiesis is based on a balance between cell proliferation (including self-renewal), differentiation and apoptosis. The choice between these three possibilities is determined by intra-cellular regulatory networks and by numerous control mechanisms in the bone marrow or carried out by other organs. Intra-cellular regulatory networks are complex biochemical reactions involving proteins, enzymes and signalling molecules. Thus, hematopoiesis is a complex process which has a vital importance for the organism. Its malfunctioning can result in numerous blood diseases including leukemia.

2.2. Objectives

Our aim in this project is the development of modern tools of multi-scale modelling of biological phenomena (and in particular, for hematopoiesis). More precisely:

- Multi-scale modelling 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.
- 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. Scientific Foundations

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).

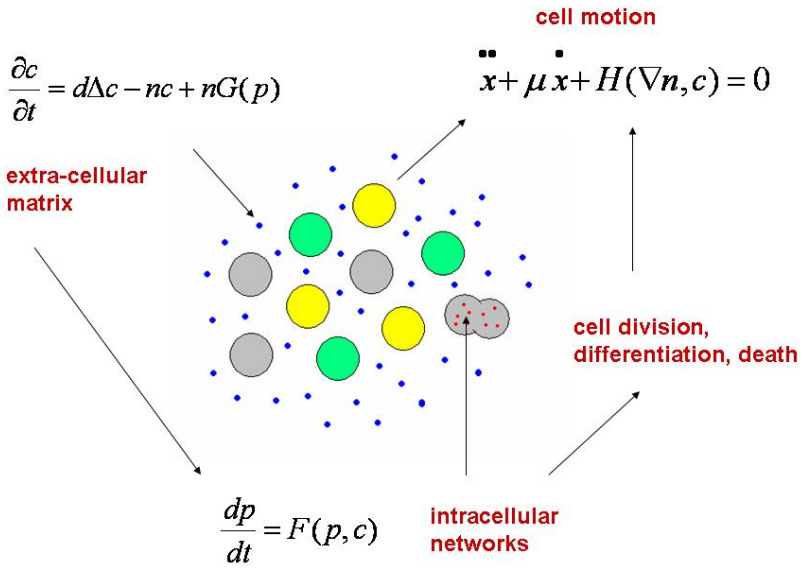

Figure 1. Schema of multi-scale models of cell dynamics: DPD-PDE-ODE models.

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 [35] 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 [36] 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 ([41], [43]), and they proved effective in hematopoiesis modelling ([30], [31], [33]). 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 [43]. The nonlocality can be either in the structure variable or in the time variable [30]. 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 [37].

3.5. Stochastic Equations

How identical cells perform different tasks may depend on deterministic factors, like external signals or pre-programming, or on stochastic factors. Intra-cellular processes are inherently noisy due to low numbers of molecules, complex interactions, limited number of DNA binding sites, the dynamical nature of molecular interactions, etc. Yet at the population level, deterministic and stochastic systems can behave the same way because of averaging over the entire population. This is why it is important to understand the causes and the roles of stochasticity in intra-cellular processes. In its simplest form, stochastic modelling of gene regulation networks considers the evolution of a low number of molecules (integer number) as they are synthesized, bound to other molecules, or degraded. The number n(t) of molecules at time t is a stochastic process whose probability transition to n+1 or n-1 is governed by a specific law. In some cases, master equations can yield analytical solutions for the probability distribution of n, P(n(t)). Numerically, efficient algorithms have been

developed (Gillespie algorithms and variants) to handle statistically exact solutions of biochemical reactions. Recently, these algorithms have been adapted to take into account time delays. This allows a stochastic description of delayed regulatory feedback loops, both at the intra-cellular and the population levels. Another approach with stochastic differential equation, using Langevin equations is relevant to study extrinsic sources of noise on a system. A thesis (R. Yvinec) supervised by L. Pujo-Menjouet and M.C. Mackey devoted to "stochastic differential equations", started in Lyon on October 2009.

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 intra-cellular 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 [38] 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. Lineage choice

Positive and negative feedbacks in intra-cellular regulatory networks create a bistable or multistable situation where different cell populations can co-exist. This allows the production of different blood cells beginning from stem cells. It is an important property of hematopoietic cell populations, which is not yet completely understood. We will focus on the erythroid/myelomonocytic choice, which is governed by a balance of lineage-affiliated transcription factors, such as GATA1 and PU.1. How the ratios of lineage-determining transcription factors stabilize progenitor cells and resolve their indeterminacy to commit them to discrete, mutually exclusive fates remains unexplained.

We will analyze the dynamics of a binary fate decision governed by a gene-circuit containing auto-stimulation and cross-inhibition, as embodied by the GATA1-PU.1 paradigm. We will use mathematical models based on ordinary and partial differential equations and individually based modelling to study fundamental properties of hematopoiesis and its quantitative characteristics. We will also explore the fate decision process from a stochastic point of view.

4.1.4. 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 2) in normal and stress conditions.

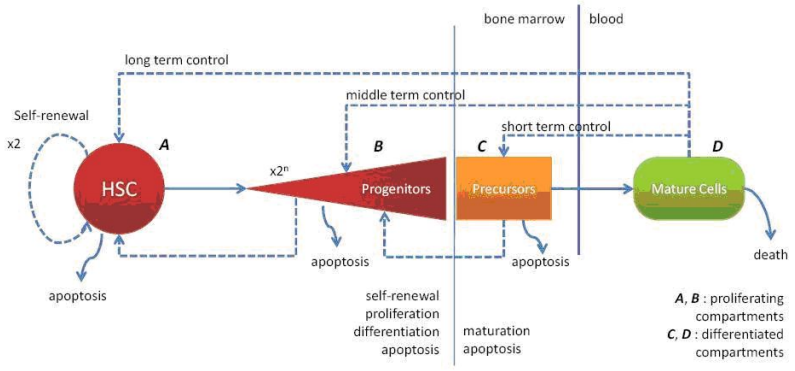

Figure 2. Scheme of Erythropoiesis Modelling. Without considering explicitly growth factor mediated regulation, all controls (proliferation, self-renewal, differentiation, apoptosis) are mediated by cell populations (dashed arrows). Mature cells can either regulate immature (HSC, progenitors) or almost mature (precursors) cells, precursors may act on progenitor dynamics, etc..

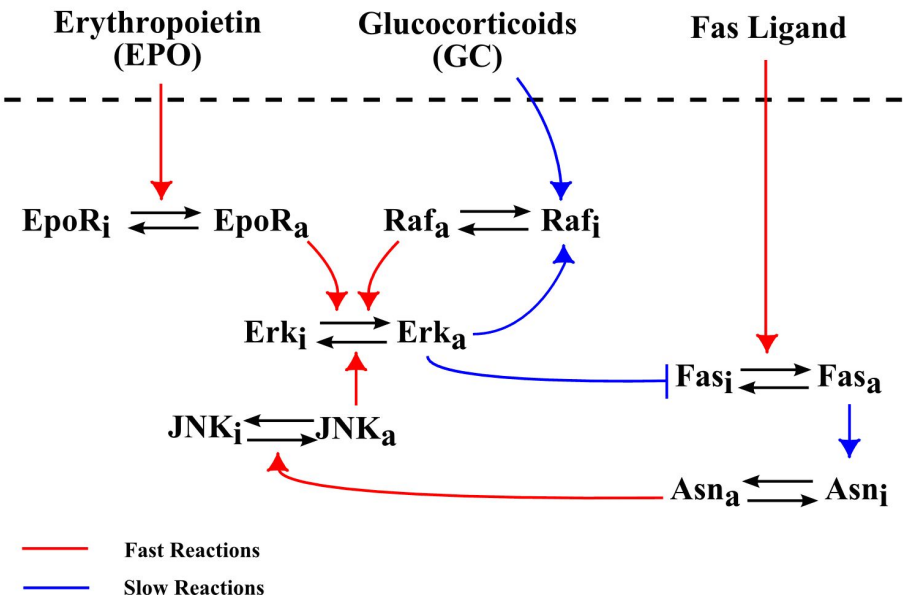

Figure 3. A schematic description of the intra-cellular molecular events that are relevant for decision making in an erythroid progenitor. The non active form of the protein is labeled i, the active form a. Blue lines indicate transcriptional regulation, red lines indicate biochemical regulation.

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 [42]. A first version of this model is shown in Figure 3.

(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 ([37], [34]), chronic myelogenous leukemia [39]).

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.

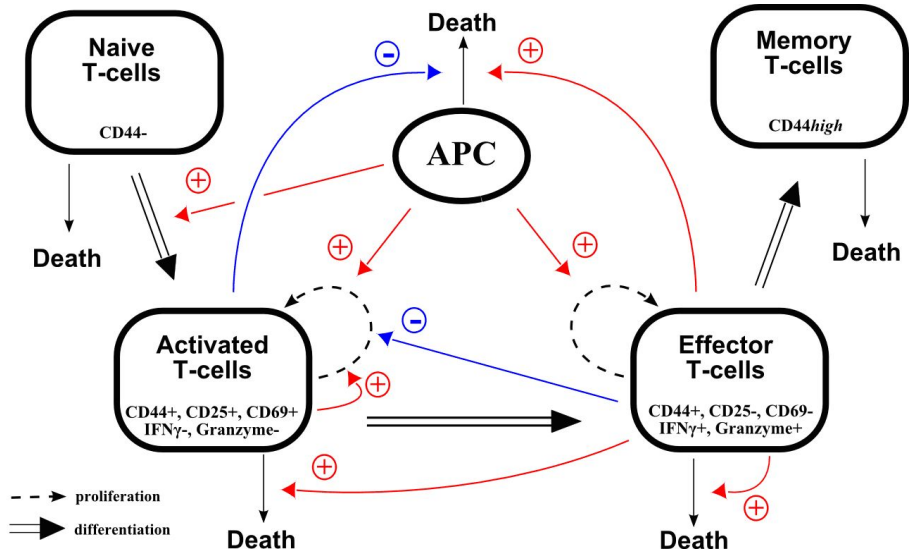

Figure 4. Model of the immune response resulting in the generation of CD8 memory T cells. The response starts with a viral infection resulting in the presentation of viral antigens through antigen presenting cells (APC) to naive T-cells. These latter, once activated, differentiate into activated cells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

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. [32]) 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 [40]. 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 extracellular 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. Software

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. Modelling of Erythroblastic Islands (red blood cell production)

Participants: Fabien Crauste [Contact person], Olivier Gandrillon, Vitaly Volpert.

In collaboration with N. Bessonov, S. Fischer and P. Kurbatova.

The production and regulation of red blood cells (erythropoiesis) occurs in the bone marrow where erythroid cells proliferate and differentiate within particular structures, called erythroblastic islands. A typical structure of these islands consists of a macrophage (white cell) surrounded by immature erythroid cells (progenitors), with more mature cells on the periphery of the island, ready to leave the bone marrow and enter the bloodstream.

We proposed a hybrid model [11], coupling a continuous model (ordinary differential equations) describing intracellular regulation through competition of two key proteins, to a discrete spatial model describing cell-cell interactions, with growth factor diffusion in the medium described by a continuous model (partial differential equations), to investigate the role of the central macrophage in normal erythropoiesis. Intracellular competition of the two proteins leads the erythroid cell either to proliferation, differentiation, or death by apoptosis. This approach allows considering spatial aspects of erythropoiesis, involved for instance in the occurrence of cellular interactions or the access to external factors, as well as dynamics of intracellular and extracellular scales of this complex cellular process, accounting for stochasticity in cell cycle durations and orientation of the mitotic spindle. The analysis of the model showed a strong effect of the central macrophage on the stability of an erythroblastic island, when assuming the macrophage releases prosurvival cytokines. Even though it is not clear whether or not erythroblastic island stability must be required, investigation of the model concludes that stability improves responsiveness of the model, hence stressing out the potential relevance of the central macrophage in normal erythropoiesis.

6.2. Modelling of the CD8 T cell Immune Response

Participants: Fabien Crauste [Contact person], Olivier Gandrillon, Emmanuelle Terry.

In collaboration with J. Marvel and C. Arpin.

The CD8 immune response is a specific immune response triggered by the organism when the innate response is unable to fight a pathogen. We proposed a new model of the CD8 T cell immune response based on the description of feedback controls exerted by the cytotoxic CD8 T cell population on the pathogen and the population itself [14]. This model, a system of ordinary and age-structured partial differential equations, allows describing a classical response, characterized by a cellular expansion following the pathogen-mediated activation, then a contraction phase and the generation of memory CD8 T cells. Moreover, we showed the global asymptotic stability of this system corresponding to the elimination of the virus. This situation is expected and describes for instance what is observed with the flu virus.

A simpler version of this model (based on nonlinear ordinary differential equations) has then been confronted to experimental data generated by Jacqueline Marvel's team in Lyon (immunology team), with 3 different pathogens. A parameter sweep has been performed and some parameters of the model, specific of cellular processes, have been shown to characterize CD8 immune responses against either a virus or a bacterium. This work is in progress and should be submitted soon.

6.3. Modelling of Platelet Thrombus Formation

Participants: Alen Tosenberger, Vitaly Volpert [Contact person].

In collaboration with F. Ataullakhanov, N. Bessonov, A. Butylin, G. Panasenko, M. Panteleev, E. Shnol, I. Sirakov and A. Tokarev.

An injury of a blood vessel requires quick repairing of the wound in order to prevent a loss of blood. This is done by the hemostatic system. The key point of its work is the formation of an aggregate from special blood elements, namely, platelets. The construction of a mathematical model of the formation of a thrombocyte aggregate with an adequate representation of its physical, chemical, and biological processes is an extremely complicated problem. A large size of platelets compared to that of molecules, strong inhomogeneity of their distribution across the blood flow, high shear velocities, the moving boundary of the aggregate, the interdependence of its growth and the blood flux hamper the construction of closed mathematical models convenient for biologists. We proposed a new PDE-based model of a thrombocyte aggregate formation [21], [22]. In this model, the movement of its boundary due to the adhesion and detachment of platelets is determined by the level set method. The model takes into account the distribution inhomogeneity of erythrocytes and platelets across the blood flow, the invertible adhesion of platelets, their activation, secretion, and aggregation. The calculation results are in accordance with the experimental data concerning the kinetics of the ADP-evoked growth of a thrombus in vivo for different flow velocities. The model constructed here can be easily extended to the case of other hemostatic mechanisms and can be integrated into different continuous blood flow models.

6.4. Reaction-Diffusion Model of Atherosclerosis Development

Participant: Vitaly Volpert [Contact person].

In collaboration with N. El Khatib, S. Genieys and B. Kazmierczak.

Atherosclerosis begins as an inflammation in blood vessel walls (intima). The inflammatory response of the organism leads to the recruitment of monocytes. Trapped in the intima, they differentiate into macrophages and foam cells leading to the production of inflammatory cytokines and further recruitment of white blood cells. This self-accelerating process, strongly influenced by low-density lipoproteins (cholesterol), results in a dramatic increase of the width of blood vessel walls, formation of an atherosclerotic plaque and, possibly, of its rupture. We suggested a 2D mathematical model of the initiation and development of atherosclerosis which takes into account the concentration of blood cells inside the intima and of pro- and anti-inflammatory cytokines [18]. The model represents a reaction-diffusion system in a strip with nonlinear boundary conditions which describe the recruitment of monocytes as a function of the concentration of inflammatory cytokines. We proved the existence of travelling waves described by this system and confirmed our previous results which suggest that atherosclerosis develops as a reaction-diffusion wave.

6.5. Hematopoietic model with feedback control

Participants: Mostafa Adimy [Contact person], Lila Sebaa.

In collaboration with O. Angulo and C. Marquet.

We investigate 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 types of blood cells (red blood cells, white cells and platelets). The primitive hematopoietic stem cells and the first generations of each line (progenitors) are able to self-renew, and can be either in a proliferating or in a resting phase (G_0-phase). These properties are gradually lost while cells become more and more mature. The three types of progenitors and mature cells are coupled to each other via their common origin in primitive hematopoietic stem cells compartment. Peripheral control loops of primitive hematopoietic stem cells and progenitors as well as a local autoregulatory loop are considered in the model. 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 investigate some fundamental properties of the solutions of this system, such as boundedness and positivity. 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 [7]. 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. This can be related to observations of some periodical hematological disease such as chronic myelogenous leukemia, cyclical neutropenia, cyclical thrombocytopenia, etc.

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

The MIREV project, on the "Modeling of the Immune Response to support Efficient Vaccine development", submitted in 2011 to the BioAster IRT, is still in the selection process. Partners include: Sanofi-Pasteur, Altrabio, Antagene, The Cosmo Company, INSERM-I2V and Dracula Team.

8. Partnerships and Cooperations

8.1. Regional Initiatives

Collaboration with the Immune Lab of Jacqueline Marvel in Lyon (Immunité, Infection et Virus), one paper published together in 2012 and one grant obtained from the FINOVI foundation.

8.2. National Initiatives

8.2.1. ANR

Projects coordination by a member of Dracula

+ ANR (jeunes chercheurs) MADCOW "Modelling amyloid dynamics and computation output work: applications to Prion and Alzheimer's disease", 2008-2012.
Participants: Samuel Bernard, Fabien Crauste, Erwan Hingant, Laurent Pujo-Menjouet [Coordinator], Vitaly Volpert.

+ ANR (jeunes chercheurs) ProCell "Mathematical Methods for Erythropoiesis Modelling: from Proteins to Cell Populations", 2009-2013.
Participants: Samuel Bernard, Fabien Crauste [Coordinator], Olivier Gandrillon, Laurent Pujo-Menjouet, Emmanuelle Terry, 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

+ Thomas Lepoutre participates in the ANR project (jeunes chercheurs) MODPOL "cell polarization modeling", 2011-2015, Vincent Calvez (ENS Lyon) [Coordinator].

+ Olivier Gandrillon participates in the ANR (Investissement d'Avenir) Iceberg "From population models to model populations: single cell observation, modeling, and control of gene expression", Gregory Batt (Inria) [Coordinator].

8.3. European Initiatives

8.3.1. Collaborations in European Programs

Program: PICS CNRS - RUSSIE

Project title: Mathematical modelling of blood diseases

Duration: 2010-2012
Participants: Samuel Bernard, Fabien Crauste, Laurent Pujo-Menjouet, Alen Tosenberger, Vitaly Volpert [Coordinator].

8.3.2. 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.

8.4. International Initiatives

8.4.1. Participation In International Programs

8.4.1.1. 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.

8.5. International Research Visitors

8.5.1. Visits of International Scientists

- Michal Komorowski - Institute of Fundamental Technological Research of Polish Academy of Science, Warsaw, Pologne - February 2012.
- Oscar Angulo - University of Valladolid, Spain - March 2012.
- Konstantinos Tzirakis - Institute of Applied and Computational Mathematics, Foundation for Research and Technology, Greece - April 2012.
- Thomas Höfer - German Cancer Research Center, Heidelberg - April 2012.
- John Lygeros - Automatic Control Laboratory, ETH Zurich, Switzerland - June 2012.
- Hassan Hbid - University of Marrakech - June 2012.
- Khalil Ezzinbi (chercheurs invités) - University of Marrakech - September 2012.
- Michael C. Mackey - McGill University, Montréal, Canada - September 2012.
- Marta Tyran-Kaminska - University of Silesia, Pologne - September 2012.
- Sergei Fedotov - School of Mathematics, The University of Manchester, UK - October 2012.
- Amira Kebir - Institut Pasteur de Tunis - December 2012.

9. Dissemination

9.1. Scientific Animation

The year 2012 was marked by the following events:

- The edition of 6 volumes of the journal MMNP (Mathematical Modelling of Natural Phenomena) on the following topics: cancer modeling, solitary waves, epidemiology, modelling phenomena on micro- and nano-scale, immunology, biological oscillations (see http://journals.cambridge.org/action/displayJournal?jid=MNP).
- The co-organization of a monthly seminar (INRIabcd, every last friday), jointly with Inria team BEAGLE, and the organization of a seminar on biomathematics (on thursday, twice a month) (see archives for 2012 : http://bsmc.insa-lyon.fr/~M3B/fr/seminaire.php?annee=2012).

- Organization of the Third International Conference of the Moroccan Society of Applied Mathematics (SM2A), Marrakesh, 10-13 September (see http://sm2a-2012.ucam.ac.ma/en/index.html).
- Organization of a workshop dedicated to "cell population dynamics", Tunis, 26-28 November 2012 (http://euromedbiomaths.org/atelier-M3CD-Tunis/).
- Organization of a summer school dedicated to the interactions between stochastic and deterministic approach for population dynamics, Paris, 06-14 September 2012 (see http://www.cmap.polytechnique.fr/~ecolemathbio2012/index.php).

9.2. Teaching - Supervision

9.2.1. Teaching

Licence : Thomas LEPOUTRE, Dynamique de populations, 12h, L3, ENS Lyon.
Licence : Thomas LEPOUTRE, Dynamique de populations structurées, 9h, L3, ENS Cachan, Paris.
Licence : Samuel BERNARD, Algèbre linéaire et analyse matricielle, 38h, L3, INSA Lyon.
Licence : Laurent PUJO-MENJOUET, EDP réaction-diffusion, 15h, L3, UCBL Lyon.
Licence : Laurent PUJO-MENJOUET, EDO-Systèmes dynamiques, 40h, L3, INSA Lyon.
Licence : Laurent PUJO-MENJOUET, Équations différentielles et EDP, 36h, L3, UCBL Lyon.
Licence : Laurent PUJO-MENJOUET, Fonctions de plusieurs variables, 36h, L2, UCBL Lyon.
Licence : Laurent PUJO-MENJOUET, Suite et série de fonctions, 36h, L2, UCBL Lyon.
Licence : Laurent PUJO-MENJOUET, Projet Etudiant, 09h, L2, UCBL Lyon.
Licence : Romain Yvinec, Équations différentielles Ordinaires, 18h, L2, UCBL Lyon.
Licence : Romain Yvinec, Mesure et intégration, 24h, L3, UCBL Lyon.
Licence : Philippe MICHEL, Analyse appliquée, 56h, L3, ECL Lyon.
Licence : Philippe MICHEL, Analyse numérique, 16h, L3, ECL Lyon.
Licence : Philippe MICHEL, Probabilités et statistique, 16h, L3, ECL Lyon.
Licence : Philippe MICHEL, Optimisation 16h en L3, ECL Lyon.
Licence : Philippe MICHEL, Projet d'études, 20h, L3, ECL Lyon.
Master : Thomas LEPOUTRE, Préparation à l'agrégation, calcul scientifique, 30h, M2, UCBL Lyon.
Master : Thomas LEPOUTRE, Equations de Hamilton Jacobi, 18h, M2, ENS Lyon.
Master : Fabien CRAUSTE, Equations structurées et hématopoïèse, 2h, M2, UCBL Lyon.
Master : Samuel BERNARD: Modélisation en biologie, 4h, M2, ENS Lyon.
Master : Laurent PUJO-MENJOUET, Modélisation en biologie et médecine, 4h, M2, ENS Lyon.
Master : Laurent PUJO-MENJOUET, EDP et modélisation, 30h, M1, INSA Lyon.
Master : Laurent PUJO-MENJOUET, Projets tutorés, 3h, M1, UCBL Lyon.
Master : Laurent PUJO-MENJOUET, Systèmes dynamiques, 27h, M1, UCBL Lyon.
Master : Laurent PUJO-MENJOUET, EDP et Structures biologiques, 18h, M2, UCBL Lyon.
Master : Laurent PUJO-MENJOUET, EDP pour l'hématopoïèse, 18h, M2, UCBL Lyon.
Master : Romain YVINEC, Equations de transport en biologie, 12h, M2, UCBL Lyon.
Master : Philippe MICHEL, Algorithmes pour la décision en entreprise, 16h, M2, ECL Lyon.
Master : Philippe MICHEL, Mathématiques appliquées à la biologie, 20h, M1, ECL Lyon.
Master : Philippe MICHEL, Systèmes embarqués collaboratifs, 12h, M1, ECL Lyon.
Master : Philippe MICHEL, Projet Application - Recherche, 10h, M1, ECL Lyon.

9.2.2. Supervision

PhD : Erwan Hingant, Contributions à la modélisation mathématique et numérique de problèmes issus de la biologie - Applications aux Prions et à la maladie d'Alzheimer, Université Claude Bernard, Lyon 1, September 17th 2012, co-advised by Ionel Sorin Ciuperca and Laurent Pujo-Menjouet.

PhD : Emmanuelle Terry, Modélisation mathématique des dynamiques de la réponse immunitaire T CD8, aux échelles cellulaire et moléculaire, Université Claude Bernard, Lyon 1, October 12th 2012, co-advised by Fabien CRAUSTE and Olivier GANDRILLON.

PhD : Romain Yvinec, Modélisation probabiliste en biologie moléculaire et cellulaire, Université Claude Bernard, Lyon 1, October 05th 2012, co-advised by Mostafa Adimy and Laurent Pujo-Menjouet.

PhD : Latifa Bouguerra, University of Alger, Algerian government scholarship, started October 2012, co-advised by Mostafa Adimy and Rachid Boudchich.

PhD : Youssef Bourfia, University of Marrakech, IRD grant, started October 2010, co-advised by Mostafa Adimy and Hassan Hbid.

PhD : Abdennasser Chekroun, ICJ UMR 5208, Lyon 1, Algerian government scholarship, started October 2012, advised by Mostafa Adimy.

PhD : Raouf El Cheikh, ICJ UMR 5208, Lyon 1, salarié, started October 2011, advised by Samuel Bernard.

PhD : Nathalie Eymard, ICJ UMR 5208, Lyon 1, salariée, started October 2009, advised by Vitaly Volpert.

PhD : Mohamed Helal, University of Sidi Bel Abbes, Algeria, Algerian government scholarship, started October 2011, co-advised by Laurent Pujo-Menjouet and Abdelkader Lakmeche.

PhD : Marine Jacquier, ICJ UMR 5208, Lyon 1, started October 2012, co-advised by Mostafa Adimy and Fabien Crauste.

PhD : Lila Sebaa, University of Alger, Algerian government scholarship, started October 2009, co-advised by Mostafa Adimy and Rachid Boudchich.

PhD : Alen Tosenberger, ICJ UMR 5208, Lyon 1, advised by Vitaly Volpert.

9.3. Popularization

Thomas Lepoutre is a member of the website Images des Mathématiques (see, http://www.cmap.polytechnique.fr/~ecolemathbio2012/index.php), reviewing press articles concerning mathematics. He also participated to the programm MathaLyon, spending one day in Collège de l'Isle à Vienne (38), animating Mathematical stands for students.

10. Bibliography

Publications of the year

Doctoral Dissertations and Habilitation Theses

[1] E. HINGANT. *Contributions à la modélisation mathématique et numérique de problèmes issus de la biologie - Applications aux Prions et à la maladie d'Alzheimer*, Université Claude Bernard - Lyon I, September 2012, http://hal.inria.fr/tel-00763444.

[2] E. TERRY. *Modélisation mathématique des dynamiques de la réponse immunitaire T CD8, aux échelles cellulaire et moléculaire*, Université Claude Bernard - Lyon I, October 2012, http://hal.inria.fr/tel-00763897.

[3] R. YVINEC. *Modélisation probabiliste en biologie moléculaire et cellulaire*, Université Claude Bernard - Lyon I, October 2012, http://hal.inria.fr/tel-00749633.

Articles in International Peer-Reviewed Journals

[4] M. ADIMY, O. ANGULO, J. C. LOPEZ-MARCOS, M. A. LOPEZ-MARCOS. *Asymptotic behaviour of a mathematical model of hematopoietic stem cell dynamics*, in "International Journal of Computer Mathematics", 2013, http://hal.inria.fr/hal-00767161.

[5] M. ADIMY, F. CRAUSTE. *Delay Differential Equations and Autonomous Oscillations in Hematopoietic Stem Cell Dynamics Modeling*, in "Mathematical Modelling of Natural Phenomena", 2012, vol. 7, n^{o} 6, p. 1-22 [*DOI :* 10.1051/MMNP/20127601], http://hal.inria.fr/hal-00766339.

[6] M. ADIMY, K. EZZINBI, C. MARQUET. *Center manifolds for some partial functional differential equations with infinite delay in fading memory spaces*, in "Journal of Concrete and Applicable Mathematics", 2012, vol. 10, n^{o} 3-4, p. 168-185, http://hal.inria.fr/hal-00763166.

[7] M. ADIMY, C. MARQUET. *On the stability of hematopoietic model with feedback control*, in "Comptes Rendus Mathématique", February 2012, vol. 350, n^{o} 3-4, p. 173-176, http://hal.inria.fr/hal-00763154.

[8] O. BERGMANN, J. LIEBL, S. BERNARD, K. ALKASS, M. S. Y. YEUNG, P. STEIER, W. KUTSCHERA, L. JOHNSON, M. LANDÉN, H. DRUID, K. L. SPALDING, J. FRISÉN. *The age of olfactory bulb neurons in humans.*, in "Neuron", May 2012, vol. 74, n^{o} 4, p. 634-9 [*DOI :* 10.1016/J.NEURON.2012.03.030], http://hal.inria.fr/hal-00755464.

[9] O. BERGMANN, S. ZDUNEK, J. FRISÉN, S. BERNARD, H. DRUID, S. JOVINGE. *Cardiomyocyte renewal in humans.*, in "Circulation Research", January 2012, vol. 110, n^{o} 1, e17-8; author reply e19-21 [*DOI :* 10.1161/CIRCRESAHA.111.259598], http://hal.inria.fr/hal-00755465.

[10] I. CIUPERCA, E. HINGANT, L. PALADE, L. PUJO-MENJOUET. *Fragmentation and monomer lengthening of rod-like polymers, a relevant model for prion proliferation*, in "Discrete and Continuous Dynamical Systems - Series B", May 2012, vol. 17, n^{o} 3, p. 775-799 [*DOI :* 10.3934/DCDSB.2012.17.775], http://hal.inria.fr/hal-00653362.

[11] S. FISCHER, P. KURBATOVA, N. BESSONOV, O. GANDRILLON, V. VOLPERT, F. CRAUSTE. *Modeling erythroblastic islands: using a hybrid model to assess the function of central macrophage.*, in "Journal of Theoretical Biology", April 2012, vol. 298, p. 92-106 [*DOI :* 10.1016/J.JTBI.2012.01.002], http://hal.inria.fr/hal-00709848.

[12] O. GANDRILLON, D. KOLESNIK-ANTOINE, J.-J. KUPIEC, G. BESLON. *Chance at the heart of the cell.*, in "Prog Biophys Mol Biol", May 2012, p. 1-4 [*DOI :* 10.1016/J.PBIOMOLBIO.2012.05.006], http://hal.inria.fr/hal-00720052.

[13] T. LEPOUTRE, M. PIERRE, G. ROLLAND. *Global well-posedness of a conservative relaxed cross diffusion system.*, in "SIAM Journal on Mathematical Analysis", 2012, vol. 44, n^{o} 3, p. 1674-1693, http://hal.inria.fr/hal-00683006.

[14] E. TERRY, J. MARVEL, C. ARPIN, O. GANDRILLON, F. CRAUSTE. *Mathematical model of the primary CD8 T cell immune response: stability analysis of a nonlinear age-structured system.*, in "Journal of Mathematical

Biology", August 2012, vol. 65, p. 263-291 [*DOI :* 10.1007/s00285-011-0459-8], http://hal.inria.fr/hal-00649219.

[15] J. VIÑUELAS, G. KANEKO, A. COULON, G. BESLON, O. GANDRILLON. *Towards experimental manipulation of stochasticity in gene expression.*, in "Prog Biophys Mol Biol", May 2012, p. 44-53 [*DOI :* 10.1016/J.PBIOMOLBIO.2012.04.010], http://hal.inria.fr/hal-00720054.

[16] V. VOLPERT, N. APREUTESEI. *Existence of travelling waves for a class of integro-differential equations from population dynamics*, in "International Electronic Journal of Pure and Applied Mathematics", November 2012, vol. 5, n^{o} 2, p. 53-67, http://hal.inria.fr/hal-00753095.

[17] V. VOLPERT, N. BESSONOV, N. EYMARD, P. KURBATOVA. *Mathematical modelling of erythropoiesis in vivo with multiple erythroblastic islands.*, in "Applied Mathematics Letters", November 2012, p. 1217-1221 [*DOI :* 10.1016/J.AML.2012.02.053], http://hal.inria.fr/hal-00753093.

[18] V. VOLPERT, N. EL KHATIB, S. GÉNIEYS, B. KAZMIERCZAK. *Reaction-Diffusion Model of Atherosclerosis Development.*, in "J. Math. Biol.", November 2012, vol. 65, n^{o} 2, p. 349-374 [*DOI :* 10.1007/s00285-011-0461-1], http://hal.inria.fr/hal-00753096.

[19] V. VOLPERT, P. KURBATOVA, G. PANASENKO. *Asymptotic numerical analysis of the diffusion-discrete absorption equation.*, in "Math. Methods Appl. Sci.", November 2012, vol. 35, n^{o} 4, p. 438-444 [*DOI :* 10.1002/MMA.1572], http://hal.inria.fr/hal-00753097.

[20] V. VOLPERT, N. K. THAKUR. *Propagation of Turing patterns in a plankton model.*, in "J. Biol. Dynamics", November 2012, p. 1-15 [*DOI :* 10.1080/17513758.2012.655327], http://hal.inria.fr/hal-00753094.

[21] V. VOLPERT, A. TOKAREV, G. SIRAKOV, G. PANASENKO, E. SCHNOL, A. BUTYLIN, F. ATAULLAKHANOV. *Continuous Mathematical Model of Platelet Thrombus Formation in Blood Flow.*, in "Russian Journal of Numerical Analysis and Mathematical Modelling", November 2012, vol. 27, n^{o} 2, p. 192-212 [*DOI :* 10.1515/RNAM-2012-0011], http://hal.inria.fr/hal-00753091.

[22] V. VOLPERT, A. TOSENBERGER, F. ATAULLAKHANOV, N. BESSONOV, M. A. PANTELEEV, A. TOKAREV. *Modelling of thrombus growth and growth stop in flow by the method of dissipative particle dynamics.*, in "Russian Journal of Numerical Analysis and Mathematical Modelling", November 2012, vol. 27, n^{o} 5, p. 507-522, http://hal.inria.fr/hal-00753089.

[23] V. VOLPERT, V. VOUGALTER. *On the existence of stationary solutions for some systems of non-Fredholm integro-differential equations.*, in "Discontinuity, Nonlinearity and Complexity", November 2012, p. 197-209, http://hal.inria.fr/hal-00753090.

[24] V. VOLPERT, V. VOUGALTER. *On the solvability conditions for the diffusion equation with convection terms.*, in "Comm. Pure and Applied Analysis", November 2012, vol. 11, n^{o} 1, p. 365–373, http://hal.inria.fr/hal-00753098.

[25] V. VOLPERT, V. VOUGALTER. *Solvability Conditions for a Linearized Cahn-Hilliard Equation of Sixth Order.*, in "Math. Model. Nat. Phenom.", November 2012, vol. 7, n^{o} 2, p. 146–154 [*DOI :* 10.1051/MMNP/20127212], http://hal.inria.fr/hal-00753092.

[26] V. VOLPERT, V. VOUGALTER. *Solvability conditions for some linear and nonlinear non-Fredholm elliptic problems.*, in "Anal. Math. Phys.", November 2012, p. 473-496 [*DOI :* 10.1007/s13324-012-0046-1], http://hal.inria.fr/hal-00753099.

Articles in National Peer-Reviewed Journals

[27] S. BERNARD. *Né pour sentir [Born to smell].*, in "médecine/sciences", November 2012, vol. 28, n^{o} 11, p. 937-9 [*DOI :* 10.1051/MEDSCI/20122811012], http://hal.inria.fr/hal-00767595.

International Conferences with Proceedings

[28] P.-N. MOUGEL, C. RIGOTTI, O. GANDRILLON. *Finding Collections of k-Clique Percolated Components in Attributed Graphs*, in "Pacific-Asia Conference on Knowledge Discovery and Data Mining (PAKDD)", Kuala Lumpur, Malaisie, LNCS, 2012, vol. 7302, p. 181–192, http://hal.inria.fr/hal-00758843.

[29] P.-N. MOUGEL, C. RIGOTTI, O. GANDRILLON. *Finding Collections of Protein Modules in Protein-Protein Interaction Networks*, in "Bioinformatics and Computational Biology (BICoB)", Las Vegas, États-Unis, 2012, p. 216-222, http://hal.inria.fr/hal-00758858.

References in notes

[30] M. ADIMY, F. CRAUSTE. *Global stability of a partial differential equation with distributed delay due to cellular replication*, in "Nonlinear Analysis", 2003, vol. 54, n^{o} 8, p. 1469-1491.

[31] M. ADIMY, F. CRAUSTE, L. PUJO-MENJOUET. *On the stability of a maturity structured model of cellular proliferation*, in "Discrete Contin. Dyn. Syst. Ser. A", 2005, vol. 12, n^{o} 3, p. 501-522.

[32] R. APOSTU, M. C. MACKEY. *Understanding cyclical thrombocytopenia: A mathematical modelling approach*, in "Journal of Theoretical Biology", 2008, vol. 251, n^{o} 2, p. 297-316.

[33] J. BELAIR, M. C. MACKEY, J. MAHAFFY. *Age-structured and two-delay models for erythropoiesis*, in "Mathematical Biosciences", 1995, vol. 128, n^{o} 1-2, p. 317-346.

[34] S. BERNARD, J. BELAIR, M. C. MACKEY. *Oscillations in cyclical neutropenia: new evidence based on mathematical modelling*, in "J. Theor. Biol.", 2003, vol. 223, n^{o} 3, p. 283-298.

[35] N. BESSONOV, L. PUJO-MENJOUET, V. VOLPERT. *Cell modelling of hematopoiesis*, in "Math. Model. Nat. Phenomena", 2006, vol. 1, n^{o} 2, p. 81-103.

[36] A. DUCROT, V. VOLPERT. *On a model of leukemia development with a spatial cell distribution*, in "Math. Model. Nat. Phenomena", 2007, vol. 2, n^{o} 3, p. 101-120.

[37] C. HAURIE, D. DALE, M. C. MACKEY. *Cyclical Neutropenia and Other Periodic Hematological Disorders: A Review of Mechanisms and Mathematical Models*, in "Blood", 1998, vol. 92, n^{o} 8, p. 2629-2640.

[38] M. C. MACKEY. *Unified hypothesis for the origin of aplastic anemia and periodic hematopoiesis*, in "Blood", 1978, vol. 51, n^{o} 5, p. 941-956.

[39] M. C. MACKEY, C. OU, L. PUJO-MENJOUET, J. WU. *Periodic Oscillations of Blood Cell Populations in Chronic Myelogenous Leukemia*, in "SIAM Journal on Mathematical Analysis", 2006, vol. 38, n^{o} 1, p. 166-187.

[40] F. MICHOR, T. HUGHES, Y. IWASA, S. BRANFORD, N. SHAH, C. SAWYERS. *Dynamics of chronic myeloid leukaemia*, in "Nature", 2005, vol. 435, n^{o} 7046, p. 1267-1270.

[41] B. PERTHAME. *Transport Equations in Biology*, Birkhauser Basel, 2006.

[42] C. RUBIOLO, D. PIAZZOLLA, K. MEISSL, H. BEUG, J. HUBER, A. KOLBUS. *A balance between Raf-1 and Fas expression sets the pace of erythroid differentiation*, in "Blood", 2006, vol. 108, n^{o} 1, p. 152-159.

[43] G. WEBB. *Theory of Nonlinear Age-Dependent Population Dynamics*, Marcel Dekker, 1985.