INRIA

INSTITUT NATIONAL DE RECHERCHE EN INFORMATIQUE ET EN AUTOMATIQUE

Team dracula

Multi-scale modelling of cell dynamics : application to hematopoiesis

Grenoble - Rhône-Alpes

Theme : Observation, Modeling, and Control for Life Sciences

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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 2010.

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.

2.3. Highlights of the year

The year 2010 was marked by the following events:

- The recruitment of Thomas Lepoutre as junior researcher (CR2 INRIA).
- The edition of 5 volumes of the journal MMNP (Mathematical Modelling of Natural Phenomena) on the following topics: ecology, reaction-diffusion waves, spectral problems, mathematical modeling in the medical sciences, mathematics and neuroscience, and cell migration.
- The co-organization of the Lyon's International Multidisciplinary Meeting on Post-Genomics (IPG'10), Lyon, 25-26 November.
- The co-organization of the second congress of the SM2A (Moroccan Society of Applied Mathematics), Rabat, Morocco, 28-30 June 2010.

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).

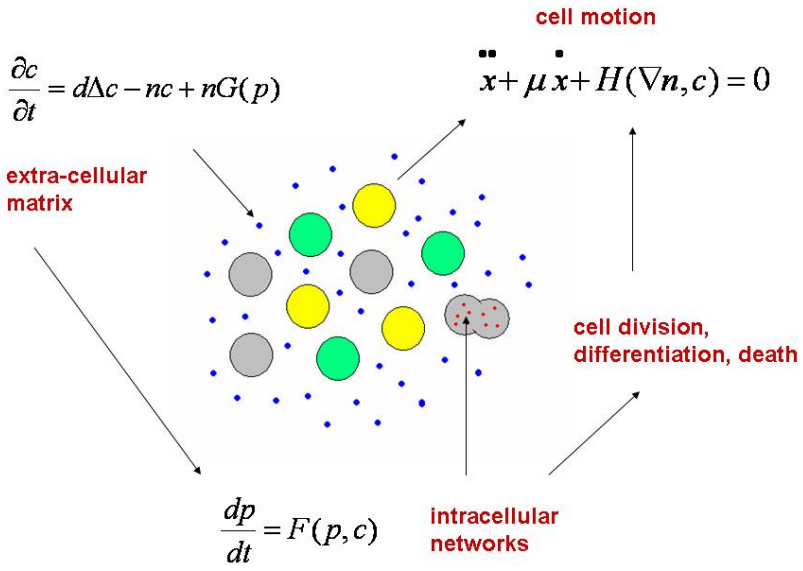

Figure 1. Schema of multi-scale models of cell dynamics: DPD-PDE-ODE models.

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 [26] 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 [28] 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 ([33], [35]), and they proved effective in hematopoiesis modelling ([22], [23], [27]). 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 [35]. The nonlocality can be either in the structure variable or in the time variable [22]. 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 [29].

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 [30] 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.

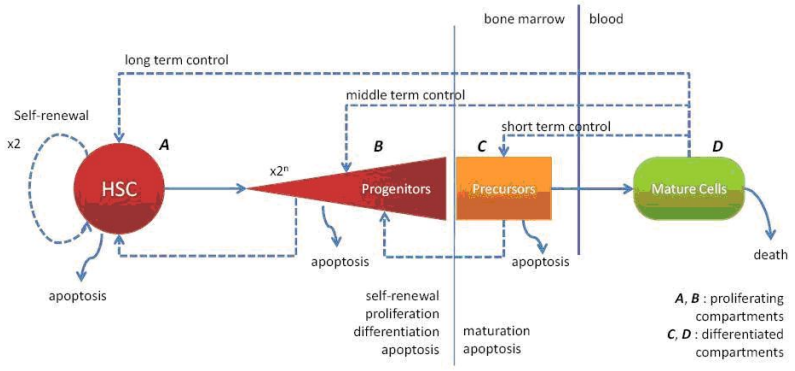

Figure 2. Scheme of Erythropoiesis Modelling. Without considering explicitly growth factor mediated regulation, all controls (proliferation, self-renewal, differentiation, apoptosis) are mediated by cell populations (dashed arrows). Mature cells can either regulate immature (HSC, progenitors) or almost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

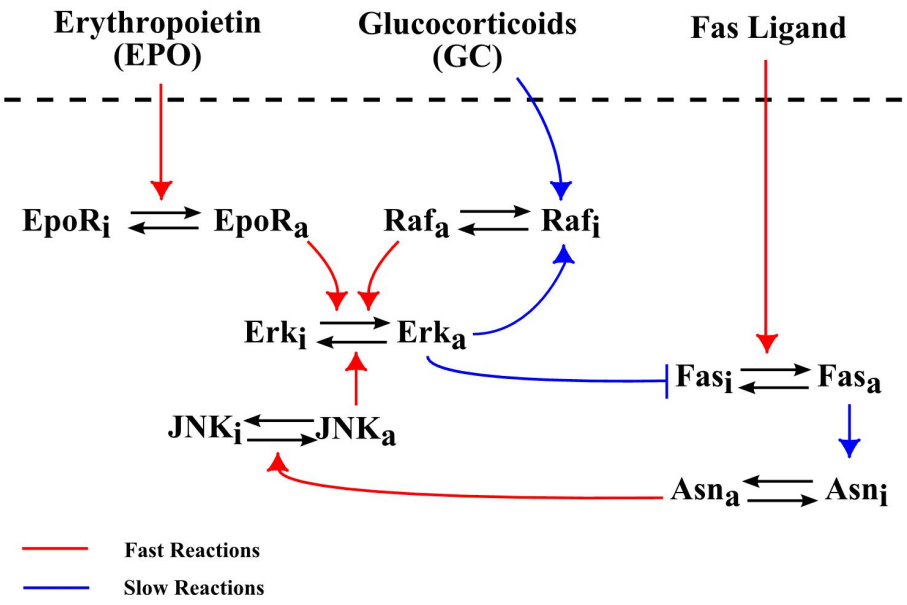

Figure 3. A schematic description of the intra-cellular molecular events that are relevant for decision making in an erythroid progenitor. The non active form of the protein is labeled i, the active form a. Blue lines indicate transcriptional regulation, red lines indicate biochemical regulation.

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 [34]. 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 ([29], [25]), chronic myelogenous leukemia [31]).

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.

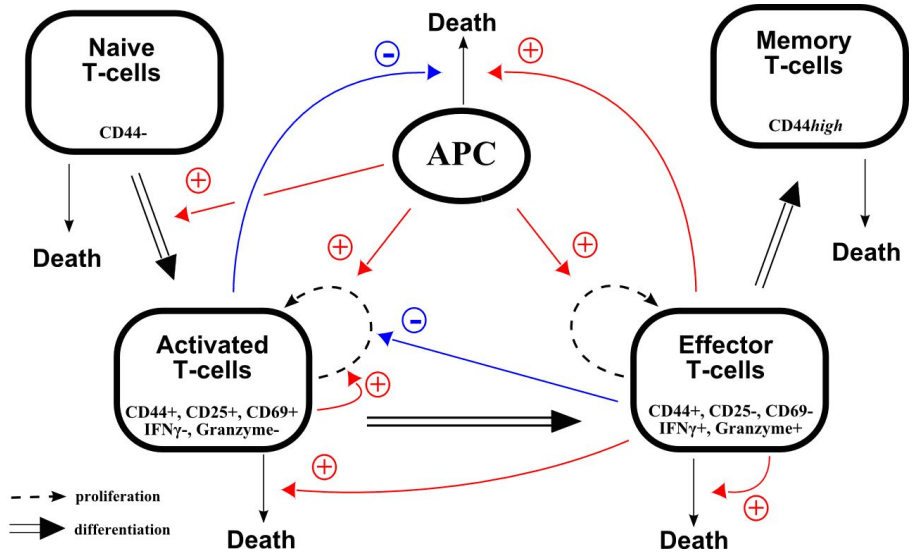

Figure 4. Model of the immune response resulting in the generation of CD8 memory T cells. The response starts with a viral infection resulting in the presentation of viral antigens through antigen presenting cells (APC) to naïve T-cells. These latter, once activated, differentiate into activated cells 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. [24]) 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 [32]. 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. Elastic cell model

Modelling in the framework of this project implies intensive numerical simulations. Cell dynamics modelling is one of the main approaches of this project. It corresponds to a multi-scale modelling which includes individual based modelling coupled with partial and ordinary differential equations. This modelling will be accompanied by the development of user friendly interfaces. They will allow the participants of the project as well as other possible users to apply the original software which will be developed. An example of such interfaces, which we already use for cell dynamics modelling, is shown in Figure 5.

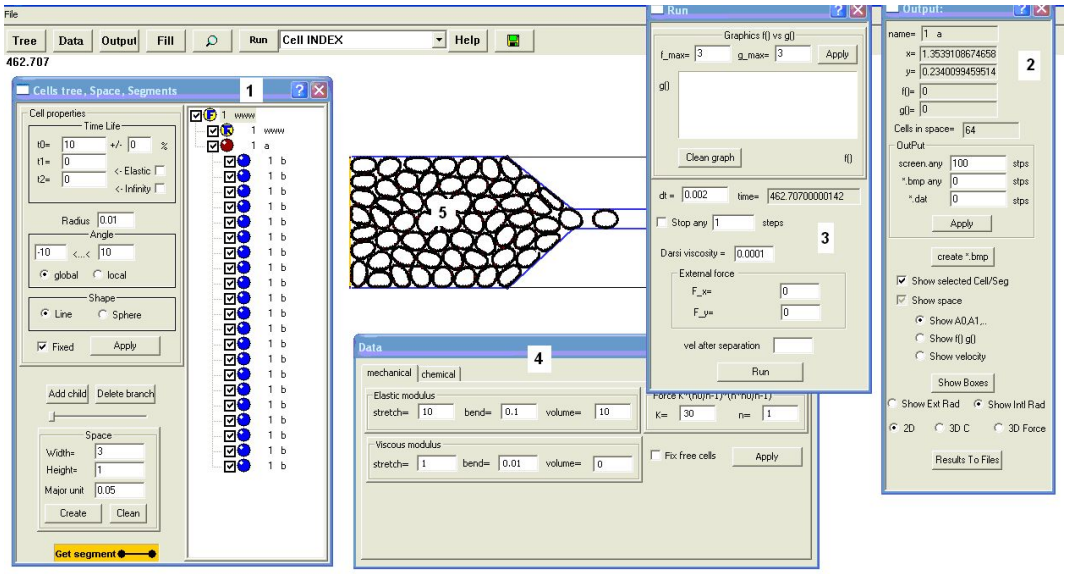

Figure 5. User interface for the software "Cell dynamics", the version "elastic cell model".

The interface includes the main window with the menu at the top of the screen and several other windows which can be open using the menu. These windows allow the user to specify the geometry of the domain and the properties of cells (1 in Figure 5), the values of parameters (3 and 4), the numerical and graphical output (2 and 5). Several versions of the software are now available. They include the "soft sphere model" and "elastic cell model". We discuss the possibility of the development of the 3D versions of the software.

6. New Results

6.1. Mathematical models of erythropoiesis

6.1.1. Mathematical study of feedback control roles and relevance in stress erythropoiesis

Participants: Fabien Crauste, Olivier Gandrillon, Vitaly Volpert.

In collaboration with Ivan Demin (PhD student, now modeler at Novartis Pharma in Basel, Switzerland).

We proposed in [10] a new multi-scale model of erythropoiesis. This model describes erythroid progenitor dynamics and intracellular regulatory network that determines erythroid cell fate (self-renewal, differentiation, death by apoptosis). All erythroid progenitors are divided into several sub-populations according to their maturity. Two intracellular proteins, Erk and Fas, are supposed to be determinant for the regulation of self-renewal, differentiation and apoptosis. Two growth factors, erythropoietin and glucocorticoids, are also taken into account in the modelling, as well as a membrane protein, Fas-ligand, playing an active role in erythroid progenitor death. The model consists of a nonlinear system of ordinary differential equations, with several feedback controls. We studied existence of biologically relevant steady states and their stability. We carried out computer simulations of anaemia and compared the obtained results with available experimental data on induced anaemia in mice. The main objective of this work was to evaluate the roles of the feedback controls in order to provide more insights into the regulation of erythropoiesis. Feedback by Epo on apoptosis was shown to be determinant in the early stages of the response to anaemia, whereas regulation through intracellular regulatory network, based on Erk and Fas, appeared to operate on a long-term scale.

Keywords: *anaemia, intracellular regulatory network, growth factor, bistability*.

6.1.2. Multi-scale model of erythropoiesis

Participants: Fabien Crauste, Olivier Gandrillon, Vitaly Volpert.

In collaboration with Ivan Demin (Novartis Pharma in Basel, Switzerland).

We investigated in [11] a multi-scale mathematical model of erythropoiesis. Erythroid progenitors were supposed to be able to self-renew. Three cellular processes were supposed to control erythropoiesis: self-renewal, differentiation and apoptosis. We described these processes and regulatory networks that govern them. Two proteins (ERK and Fas) were considered as the basic proteins participating in this regulation. All erythroid progenitors were divided into several sub-populations depending on their maturity level. Feedback regulations by erythropoietin, glucocorticoids and Fas ligand (FasL) were introduced in the model. The model consisted of a system of ordinary differential equations describing intracellular protein concentration evolution and cell population dynamics. We studied steady states and their stability. We carried out computer simulations of an anaemia situation and analysed the results.

Keywords: *erythropoiesis, multi-scale model, self-renewal, differentiation, bistability*.

6.1.3. Spacial distribution of cell populations in the processes of erythropoiesis

Participant: Vitaly Volpert.

In collaboration with I. Demin (Novartis Pharma in Basel, Switzerland), A. Ducrot (University of Bordeaux).

We studied in [16] spatial cell distribution in the bone marrow taking into account cell self-renewal, differentiation and apoptosis as well as cell motion resulting from cell proliferation. The model consisted of reaction-diffusion equations in a porous medium. The existence of stationary solutions corresponding to normal erythropoiesis was proved. In the leukemic case, this stationary solution becomes unstable. Malignant cells propagate as a travelling wave filling the marrow. We studied this phenomenon numerically in the 2D case. An analytical approximation for the wave speed was compared with the numerical solution of the full problem.

Keywords: *cell population, reaction-diffusion equations, porous medium, traveling waves*.

6.1.4. Hybrid model of erythropoiesis and leukemia treatment with cytosine arabinoside

Participants: Samuel Bernard, Fabien Crauste, Polina Kurbatova, Vitaly Volpert.

In collaboration with N. Bessonov (St. Petersburg, Russia), I. Demin (Novartis Pharma in Basel, Switzerland), Ch. Dumontet (Hospital E. Herriot, University of Lyon 1) and S. Fischer (University of Lyon 1).

A hybrid model of cell population dynamics, where cells are discrete elements whose dynamics depend on continuous intracellular and extracellular processes, was developed in [21] to simulate the evolution of immature red blood cells in the bone marrow. Cell differentiation, self-renewal or apoptosis were determined by an intracellular network, based on two proteins Erk and Fas and described by ordinary differential equations, and by local extracellular regulation performed by Fas-ligand, a protein produced by mature cells whose concentration evolution was represented by a partial differential equation. The model was used to study normal and leukemic red blood cell production (erythropoiesis), and treatment of leukemia. Normal cells were supposed to have a circadian rhythm, that influences their cell cycle durations, whereas leukemic cells, appart from being characterized by excessive proliferation and insufficient differentiation and apoptosis, were supposed to escape circadian rhythms. We considered a treatment based on periodic administration of Ara-C, an anti-cancer agent targeting cells in DNA synthesis. A pharmacodynamic/pharmacokinetic model of Ara-C was then proposed, and used to simulate the treatment. Influences of the period of the treatment and the day delivery time on the outcome of the treatment were investigated and stressed the relevance of considering chronotherapeutic treatments to cure leukemia.

Keywords: *hybrid model, leukemia treatment, chronotherapy, regulatory networks, cell cycle*.

6.2. Mathematical models of hematopoietic stem cell dynamics

6.2.1. Asymptotic behavior and stability switch for a mature-immature model of cell differentiation

Participants: Mostafa Adimy, Fabien Crauste.

In collaboration with C. Marquet (University of Pau).

We investigated in [3] the stability of a delay differential model describing hematopoietic cell dynamics. The framework we considered was a nonlinear age-structured model describing the dynamics of a cell population divided into mature and immature cells. Immature cells, that can be either proliferating or non-proliferating, differentiate in mature cells, that in turn control the immature cell population through a negative feedback. The initial system was reduced to two delay differential equations, and we investigated the asymptotic stability of the trivial and the positive steady states. By constructing a Lyapunov function, the trivial steady state was proven to be globally asymptotically stable when it is the only equilibrium of the system. The asymptotic stability of the positive steady state is related to a delay-dependent characteristic equation. Existence of a Hopf bifurcation and stability switch for the positive steady state was established. We illustrated the stability with numerical simulations.

Keywords: *mature and immature cells, hematopoiesis, asymptotic stability, lyapunov function, delay-dependent characteristic equation, stability switch, Hopf bifurcation.*

6.2.2. Stability and Hopf bifurcation for a cell population model with state-dependent delay

Participants: Mostafa Adimy, Fabien Crauste.

In collaboration with H. Hbid (University of Marrakech), R. Qesmi (University of Toronto, Canada).

We proposed in [2] a mathematical model describing the dynamics of a hematopoietic stem cell population. The method of characteristics reduced the age-structured model to a system of differential equations with a state-dependent delay. A detailed stability analysis was performed. A sufficient condition for the global asymptotic stability of the trivial steady state was obtained using a Lyapunov-Razumikhin function. A unique positive steady state was shown to appear through a transcritical bifurcation of the trivial steady state. The analysis of the positive steady state behavior, through the study of a first order exponential polynomial characteristic equation, concluded the existence of a Hopf bifurcation and gave criteria for stability switches. A numerical analysis confirmed the results and stressed the role of each parameter involved in the system on the stability of the positive steady state.

Keywords: *hematopoietic stem cells, functional differential equation, state-dependent delay, Lyapunov-Razumikhin function, Hopf bifurcation.*

6.2.3. Boundedness and Lyapunov function for a nonlinear system of hematopoietic stem cell dynamics

Participants: Mostafa Adimy, Fabien Crauste.

In collaboration with A. El Abdllaoui (University of Pau).

We investigated in [1] a system of nonlinear differential equations with distributed delays, arising from a model of hematopoietic stem cell dynamics. We stated uniqueness of a global solution under a classical Lipschitz condition. Sufficient conditions for the global stability of the population were obtained, through the analysis of the asymptotic behavior of the trivial steady state and using a Lyapunov function. Finally, we gave sufficient conditions for the unbounded proliferation of a given cell generation.

Keywords: *hematopoiesis, time-delay systems, Lyapunov function.*

6.3. Cell turnover in slowly renewing tissues in humans

Participant: Samuel Bernard.

In collaboration with Karolinska Institutet, Stockholm, Sweden.

The year 2010 was also marked by a consolidation of long-running projects, with three offshoot papers from the collaborations of S. Bernard in Stockholm. The first is a study of metabolic risk based on fat tissue morphology [5]. The second is a study rebutting recent controversial claims that cardiac muscle cells renew at a high rate throughout life [6], and the third one is a methodology paper for estimating turnover rates in biological systems [8].

Keywords: *cardiomyocyte renewal, ploidy, pericentriolar material 1, cardiac Troponin, Iododeoxyuridine, 14C, bomb pulse, cell turnover, Tissue maintenance, fat mass, adipocyte.*

6.4. Circadian rhythm and cell population growth

Participant: Thomas Lepoutre.

In collaboration with J. Clairambault and S. Gaubert, BANG (INRIA Rocquencourt).

We proved in [20] a convexity property of the Floquet eigenvalue. It extends the classical Kingman's inequality for positive matrices. On a modelling point of view, it gives a generic argument for chronotherapy, since at the toxicity level, this implies that periodic treatment are in general (that is on average) less toxic than constant treatment.

6.5. Nonlinear dynamics of travelling waves for reaction-diffusion equations

6.5.1. Existence of waves for a nonlocal reaction-diffusion equation

Participant: Vitaly Volpert.

In collaboration with I. Demin (Novartis Pharma in Basel, Switzerland).

We studied in [17] a nonlocal reaction-diffusion equation arising in population dynamics. The integral term in the nonlinearity describes nonlocal stimulation of reproduction. We proved existence of travelling wave solutions by the Leray-Schauder method using topological degree for Fredholm and proper operators and special a priori estimates of solutions in weighted Hölder spaces.

Keywords: *integro-differential equation, travelling waves, Leray-Schauder method.*

6.5.2. Linear stability analysis of reaction fronts propagation in liquids with vibrations

Participant: Vitaly Volpert.

In collaboration with K. Allali, F. Bikany and A. Taik (University of Mohammedia, Morocco).

Influence of vibrations on the onset of convective instability of reaction fronts in a liquid medium was studied in [14]. The model consisted of a reaction-diffusion system coupled with the Navier-Stokes equations under the Boussinesq approximation. Linear stability analysis of the problem was fulfilled, and the convective instability boundary was found.

Keywords: *convective instability, reaction front propagation, vibrations.*

6.6. Qualitative properties of elliptic problems in unbounded domains

Participant: Vitaly Volpert.

In collaboration with V. Vougalter (University of Notre Dame, Indiana, USA).

We obtained in [18] solvability conditions for some elliptic equations involving non Fredholm operators, which are sums of second order differential operators with the methods of spectral theory and scattering theory for Schrödinger type operators.

Keywords: *solvability conditions, non Fredholm operators, elliptic problems.*

6.7. Differential and partial differential equations with delay

6.7.1. Stability and Hopf bifurcation for a first-order linear delay differential equation with distributed delay

Participant: Fabien Crauste.

F. Crauste published in Complex-Time Delay Systems (Ed F. Atay, Springer), a chapter on the stability and the existence of a Hopf bifurcation for delay differential equations with distributed delay [19]. This class of equations is widely used in many research fields such as automatic, economic, and, for our purpose, in biological modelling because it can be associated with problems in which it is important to take into account some history of the state variable (e.g., gestation period, cell cycle durations or incubation time). When few data are available, this history is usually assumed to be discrete (so one gets a discrete delay equation, well studied in the literature). Yet, in most cases very few is known about it, and how it can be distributed, so very abstract assumptions lead to equations with distributed delay. The paper focused on stability properties of such equations, that is under which conditions on the parameters do all solutions converge toward zero? And, as a consequence, how is it possible to destabilize the equation? Can oscillating or periodic solutions appear? All these questions arise from needs to understand how many systems can be destabilized, or how can they stay stable for a long time.

In this chapter, F. Crauste presented a state of the art on the topic and the most recent advances in the stability analysis of differential equations with distributed delay. It is noticeable that only partial results have been proved up to now. Mainly, only sufficient conditions for the stability - which is sometimes enough - have been obtained.

Keywords: *time-delay systems, asymptotic stability, delay-dependent characteristic equation, stability switch, Hopf bifurcation*.

6.7.2. Extrapolation spaces and partial neutral functional Differential Equations with infinite delay

Participant: Mostafa Adimy.

In collaboration with M. Alia and K. Ezzinbi (University of Marrakech, Morocco).

We studied in [4] the existence regularity and stability of solutions for some nonlinear partial functional differential equations with infinite delay. We supposed that the linear term was a Hille-Yosida operator on a Banach space and the nonlinear function took its values on some spaces larger than the initial Banach space, namely the extrapolated Favard class corresponding to the semigroup generated by the linear part. Our approach was based on the theory of the extrapolation. We gave also a linearized stability principle to study the behavior of solutions near the equilibriums of the model.

Keywords: *partial functional differential equations, infinite delay, extrapolation spaces, semigroup, linearized stability*.

7. Other Grants and Activities

7.1. Regional Initiatives

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

Financial support from FINOVI (Fondation Innovations en Infectiologie) for project entitled "Multi-scale modelling of CD8 T-cell response"

7.2. National Initiatives

- ANR (jeunes chercheurs) MADCOW "Modelling amyloid dynamics and computation output work: applications to Prion and Alzheimer's disease", 2008-2011.
  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, Polina Kurbatova, 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, Polina Kurbatova, Vitaly Volpert [Coordinator].
- ANR Anatools "Analytical tools for cancer chemotherapy improvement", 2007-2010 (coordinator: C. Perigaud from the university of Montpelier 2).
  Participants: Laurent Pujo-Menjouet, Vitaly Volpert.

7.3. European Initiatives

- PAI France-Pologne "Reaction diffusion equations in biology", 2010-2011, with Instytut Podstawowych Problemòw Techniki, Varsovie.
  Participants: Stéphane Génieys [Coordinator], Vitaly Volpert.
- PAI France-Grece "Patient specific modelling of atherosclerotic lesions leading to vascular stenosis", 2010-2011, with Institute of Applied and Computational Mathematics, Heraklion-Crete.
  Participants: Stéphane Génieys [Coordinator], Vitaly Volpert.

7.4. International Initiatives

- Project PICS CNRS RUSSIE "Mathematical modelling of blood diseases", 2010-2012.
  Participants: Samuel Bernard, Fabien Crauste, Polina Kurbatova, Laurent Pujo-Menjouet, Vitaly Volpert [Coordinator].
- French-Moroccan program CNRS/CNRST "Reduction of complexity in differential equations arising from population dynamics", 2008-2010.
  Participants: Mostafa Adimy [Coordinator], Fabien Crauste.

8. Dissemination

8.1. Animation of the scientific community

- F. Crauste and O. Gandrillon have participated in the organization of the yearly IPG conference (IPG'10: Integrative Post-Genomics), in Lyon, 27-30 September 2010. This conference has been sponsored by INRIA.
- M. Adimy has participated in the organization of RIMM-2010, First International Workshop on the Role and Impact of Mathematics in Medicine, in Paris, 10-12 June 2010. This conference has been sponsored by INRIA.
- M. Adimy and F. Crauste have organized a biomathematics session in the second congress of the "Société Marocaine de Mathématiques Appliquées" (SM2A), in Rabat (Morocco), 28-30 June 2010.
- F. Crauste has organized a biomathematics session in the "10ème Colloque Franco-Roumain de Mathématiques Appliquées", in Poitiers, 26-31 August 2010.

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