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Activity Report 2011

Project-Team DRACULA

Multi-scale modelling of cell dynamics: application to hematopoiesis

RESEARCH CENTER
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THEME
Observation, Modeling, and Control for Life Sciences

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Project-Team DRACULA

Keywords: Population Dynamics

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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 2011 was marked by the following events:

- The edition of 6 volumes of the journal MMNP (Mathematical Modelling of Natural Phenomena) on the following topics: Instability and patterns (dedicated to A. Golovin), Modelling of plant growth, Computational aerodynamics, Granular hydrodynamics, Complex fluids, Biomathematics Education (for more details see http://www.mmnp-journal.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).
- Organization of the international conference "Chance at the heart of the cell" (http://cgphimc.univ-lyon1.fr/CGPHIMC/CHC2), Lyon, 21-23 november 2011.

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).

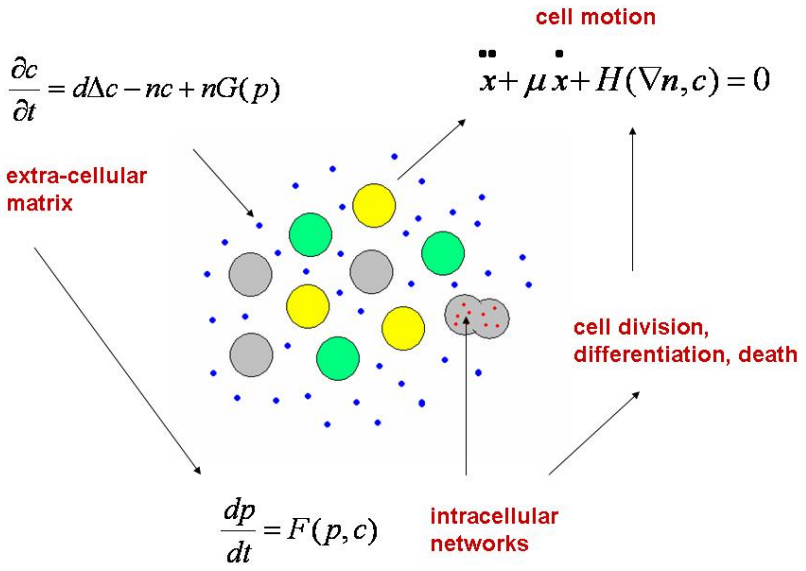

Figure 1. Schema of multi-scale models of cell dynamics: DPD-PDE-ODE models.

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 [24] 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 [25] 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 ([30], [32]), and they proved effective in hematopoiesis modelling ([19], [20], [22]). 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 [32]. The nonlocality can be either in the structure variable or in the time variable [19]. 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 [26].

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 [27] 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.

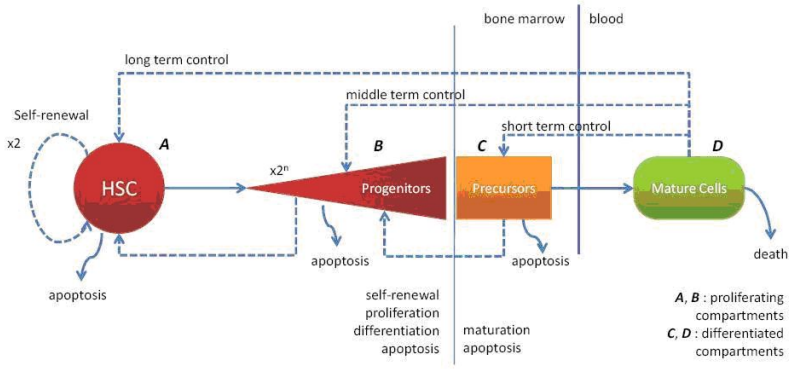

Figure 2. Scheme of Erythropoiesis Modelling. Without considering explicitly growth factor mediated regulation, all controls (proliferation, self-renewal, differentiation, apoptosis) are mediated by cell populations (dashed arrows). Mature cells can either regulate immature (HSC, progenitors) or almost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

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 [31]. 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 ([26], [23]), chronic myelogenous leukemia [28]).

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

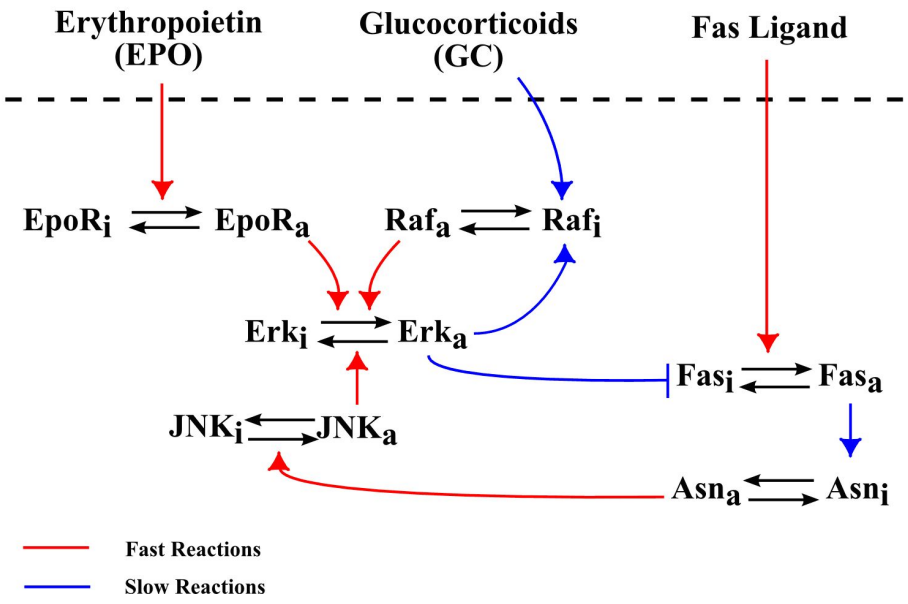

Figure 3. A schematic description of the intra-cellular molecular events that are relevant for decision making in an erythroid progenitor. The non active form of the protein is labeled i, the active form a. Blue lines indicate transcriptional regulation, red lines indicate biochemical regulation.

molecular events leading to cell activation when encountering a virus, we will propose a multi-scale model of the immune response.

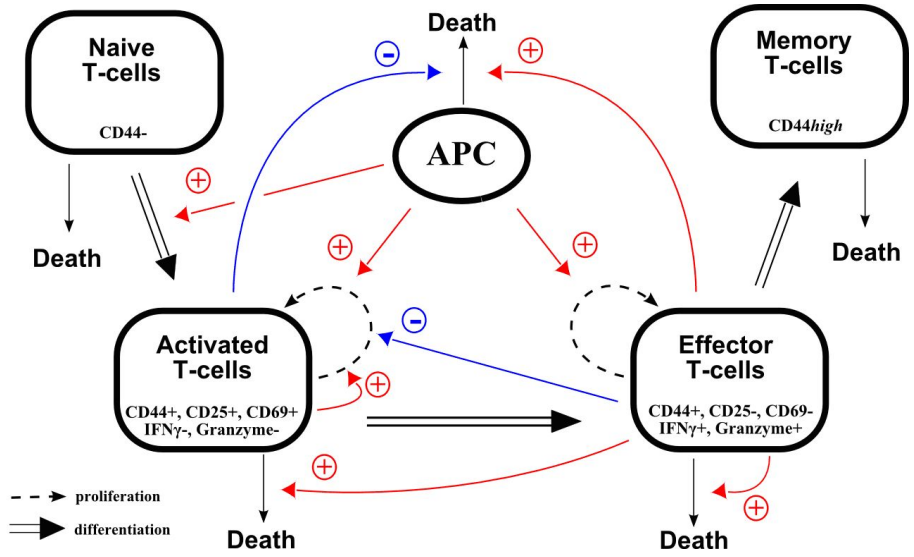

Figure 4. Model of the immune response resulting in the generation of CD8 memory T cells. The response starts with a viral infection resulting in the presentation of viral antigens through antigen presenting cells (APC) to naïve T-cells. These latter, once activated, differentiate into activated cells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

(iii) Coagulation: platelet lineage

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

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

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

4.2. Pathological hematopoiesis

The knowledge of hematopoiesis and related diseases has evolved to become a great deal in the past years, and Mackey's previous models (ref. [21]) 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 [29]. This is in the optic of testable experimental predictions that the multi-scale model for pathological hematopoiesis will be developed. For instance, we will concentrate on myeloid leukemias (CML and AML) and their treatment.

4.2.1. Leukemia Modelling

(i) Chronic Myeloid Leukemia

The strong tyrosine kinase activity of the BCR-ABL protein is the basis for the main cell effects that are observed in CML: significant proliferation, anti-apoptotic effect, disruption of stroma adhesion properties, genomic instability. This explains the presence in CML blood of a very important number of cells belonging to the myeloid lineage, at all stages of maturation.

We will consider models based on ordinary differential equations for the action of the main intra- and extra-cellular proteins involved in CML (as BCR-ABL protein), and of transport equations (with or without delay, physiologically structured or not to represent healthy and leukemic cell populations, take into account many interactions between proteins (especially BCR-ABL), cells (anti-apoptotic effect, etc.), and their environment (disruption of stroma adhesion properties, for example). Transport pertains thus to cells from one compartment (or a group of compartments) to another compartment, with a determined speed of aging or maturation. These compartments may be detailed or not: the less mature are stem cells, then progenitor cells, etc.

(ii) Acute Myeloid Leukemia

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

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

4.2.2. Treatment

As far as treatment of pathological hematopoiesis is concerned, two main strategies currently exist that aim at slowing down or eliminating damaged cell proliferation. The first of these strategies consists in launching the apoptotic process during the cell division cycle. This process is activated, for example when the cell is unable to repair damages, e.g., after exposure to cytostatic drugs. A typical example is apoptosis induced by chemotherapy-induced DNA damage: The damage is recognised by the cell, which then activates the sentinel protein p53 ("guardian of the genome") that arrests the cell cycle to allow, if possible, damage repair. If the latter is unrecoverable, then p53 activates the endogenous apoptotic processes.

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

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

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

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

5. Software

5.1. CelDyn

Participants: Nikolai Bessonov, 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)

The production of red blood cells, erythropoiesis, occurs in the bone marrow, where immature erythroid cells differentiate and produce red blood cells. Differentiation and maturation of immature red blood cells occurs in very specific spatial structures called erythroblastic islands. They consists of a macrophage (big white blood cell) surrounded by immature cells and providing them with survival factors. Using a hybrid model, made of a discrete model describing cell-cell interactions and accounting for spatial interactions, and a continuous model describing intracellular protein regulation (deciding for cell fate), we showed the importance of the central macrophage in the erythroblastic island, in order to prevent unstable islands leading either to cell populations extinction or excessive proliferation. This result is actually under review (Journal of Theoretical Biology), partial results have been already published (Math. Model. Nat. Phenom.)

6.2. Modelling of the CD8 T cell Immune Response

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. This model, a system of ordinary and age-structured partial differential equations, allows to describe 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. We are now confronting the model to experimental data being generated by Jacqueline Marvel's team in Lyon (immunology team). The analysis of the model and the first results have been published in Journal of Biological Systems

6.3. Particle Dynamics Methods of Blood Flow Simulations

Various particle methods are widely used to model dynamics of complex media. In our work molecular dynamics and dissipative particles dynamics are applied to model blood flows composed of plasma and erythrocytes. The properties of the homogeneous particle fluid are studied. Capillary flows with erythrocytes are investigated.

6.4. Periodic linear cell cycle models

Several results on periodic linear cell cycle models were obtained in collaboration with Frederique Billy (Inria Bang), Jean Clairambault (Inria Bang), Olivier Fercoq (Inria Maxplus), Stéphane Gaubert (Inria Maxplus) and Thomas Ouillon (Ensta). Those results are currently in revision (minor modifications requested). It deals with the property of the growth rate in such models. Several aspects are discussed, among wich: effect of the variability of the division process on the growth rate, fitting coefficients to data obtained by FUCCI methodology and optimization procedure for the growth rate.

6.5. Relaxed cross diffusion models

A general well posedness result for relaxed cross diffusion models was obtained by members of our team in collaboration with Michel Pierre and Guillaume Rolland (IRMAR, Rennes). A paper in this subject has been submitted.

7. Contracts and Grants with Industry

7.1. Contracts with Industry

Two contracts have been written with the industry:

- FUI project "Calvax" ("Development of a vaccine against canine visceral leishmaniasis using a system's biology approach "; partners: Merial, Altrabio, Antagene, The Cosmo Company, CNRS-ICJ, INSERM-I2V et CNRS-CGPHIMC).
- IRT project "MIREV" ("Modeling of the Immune Response to support Efficient Vaccine development"; partners: Merial, Sanofi-Pasteur, Altrabio, Antagene, The Cosmo Company, CNRS-ICJ, INSERM-I2V et CNRS-CGPHIMC).

7.2. Grants with Industry

- We got a grant with Merial (10 keuros), it allowed us to pay an internship for 4.5 months (Adour Mikirditsian).
- We are actually working on an application to a FUI (Fonds Unique Interministériel) contract, involving Merial; The application occurred in november, and we still have no answer.
- We also applied to the IRT program, with Merial and Sanofi-Pasteur, decisions are expected in the first semester of 2012.

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 2011.
- Our team is a partner of the recently accepted ANR project MODPOL (head Vincent Calvez, CNRS member of Inria Numed).

8.2. European Initiatives

- PAI France-Pologne "Reaction diffusion equations in biology", 2010-2011, with Instytut Podstawowych Problemòw Techniki, Varsovie.
- PAI France-Grece "Patient specific modelling of atherosclerotic lesions leading to vascular stenosis", 2010-2011, with Institute of Applied and Computational Mathematics, Heraklion-Crete.
- Collaboration with Oscar Angulo Torga, from the math department of the University of Valladolid (Spain), on the analysis of a age-structured model describing erythropoiesis, and its numerical resolution.

8.3. International Initiatives

8.3.1. INRIA International Partners

Two weeks of Thomas Lepoutre in Santiago (Chile) by Salome Martinez (CMM) for a joint work on cross diffusion models.

Programme explorateur: five weeks collaboration with Pr Doron Levy (College Park, Maryland, USA).

8.3.2. Visits of International Scientists

8.3.2.1. Internships

Vsevolod Salnikov (from May 2011 until Sep 2011)

Subject: Hybrid models of cell population dynamics

Institution: Laboratoire Poncelet (Russia (Russian Federation))

8.3.2.2. Visits of International Scientists

- Glenn Webb (June 2011)
  - Subject: Analysis of a model for transfer phenomena in biological populations
  - Institution: Vanderbilt University, Nashville, USA
- Marc Chaplain (24-25 November 2011)

  - Subject: Mathematical modelling of intracellular negative feedback systems
  - Institution: Division of Mathematics, University of Dundee, Scotland

- Grégoire Altan-Bonnet (16-17 November 2011)
  - Subject: Enforcing a reliable immune response with unreliable lymphocytes
  - Institution: ImmunoDynamics Group, Programs in Computational Biology and Immunology, Memorial Sloan-Kettering Cancer Center, New York NY, USA

- Marc-Thorsten Hutt (08-09 September 2011)
  - Subject: How few elements can systematically shape large-scale patterns
  - Institution: Jacobs University, Bremen, Germany

- Pal Westermark (22-23 June 2011)
  - Subject: Descriptive analysis of cellular circadian rhythms, and some scenarios for coupling and synchronization
  - Institution: Institute for Theoretical Biology, Berlin, Germany

- Philip Maini (25-27 May 2011)
  - Subject: Mathematical modelling of tumour dynamics
  - Institution: Oxford University, United Kingdom

- Ingmar Glauche (25-26 May 2011)
  - Subject: Systems biology of stem cell fate decisions
  - Institution: TU Dresden, Germany

- Peter Swain (04-05 December 2011)
  - Subject: Noise and fluctuations in gene expression
  - Institution: Center for Systems Biology at Edinburgh, United Kingdom

- Roeland M.H. Merks (29-30 March 2011)
  - Subject: Cell-based computer modeling of angiogenesis and vasculogenesis
  - Institution: Life Science Group, CWI, and NCSB-NISB, Amsterdam, The Netherlands

- Thomas Stiehl (02-03 March 2011)
  - Subject: A Mathematical Model for Cell Differentiation and its Applications to Hematopoiesis and Stem Cell Transplantation
  - Institution: Heidelberg University, Germany

8.3.3. Participation In International Programs

- Project PICS CNRS RUSSIE "Mathematical modelling of blood diseases", 2010-2012.
  Participants: Samuel Bernard, Fabien Crauste, Polina Kurbatova, Laurent Pujo-Menjouet, Vitaly Volpert [Coordinator].

9. Dissemination

9.1. Animation of the scientific community

- Organization of the international conference "Chance at the heart of the cell" (http://cgphimc.univ-lyon1.fr/CGPHIMC/CHC2), Lyon, 21-23 november 2011.
- 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).
- Participation to the "Fête de la Science" sur le campus de la Doua.
- A conference entitled "Quand les cellules tueuses se réveillent..." in the "Université Ouverte" cycle of conferences for a wide audience, organized by the Université Lyon 1 (April 19th, 2011).
- Associate editor of the volume "Modelling Plant Growth" (volume 6, number 2) of Math. Model. Nat. Phenom., published in 2011.
- Reviewer for several applied mathematics journal and biomathematics journals (Interntaional journal of biomathematics, Mathematicl Biosciences, SIAM Journal on Control and Optimization, Journal of Mathematical Biology, etc.)

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