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Project-Team DRACULA

Multi-scale modelling of cell dynamics : application to hematopoiesis

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

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Modeling and Control for Life Sciences

Table of contents

Project-Team DRACULA

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

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

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2. Overall Objectives

2.1. Presentation

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

The Dracula project is devoted to multi-scale modeling in biology with applications to normal and pathological hematopoiesis (blood cell production). Multi-scale modeling implies simultaneous modeling of intra-cellular networks (molecular level), of cell behavior (cellular level), of the dynamics of cell populations (organ or tissue) with the control by other organs (organism) (see Figure 1). Such modeling represents one of the major challenges in modern science due to its importance and because of the complexity of biological phenomena and of the presence of very different scales.

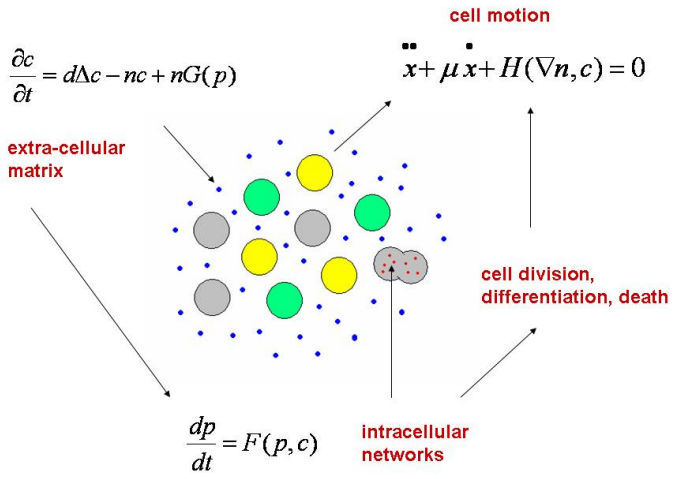

Figure 1. Schema of multi-scale models of cell dynamics: DPD-PDE-ODE models.

Hematopoiesis is a complex process that begins with primitive hematopoietic stem cells and results in formation of mature cells: red blood cells, white cells and platelets. Blood cells are produced in the bone marrow, from where mature cells are released into the blood stream. Hematopoiesis is based on a balance between cell proliferation (including self-renewal), differentiation and apoptosis (programmed cell death). The choice between these three possibilities is determined by intra-cellular regulatory networks and by numerous control mechanisms in the bone marrow (see Figure 2) or carried out by other organs. Intra-cellular regulatory networks are complex biochemical reactions involving proteins, enzymes and signalling molecules. Thus, hematopoiesis is a complex process which has a vital importance for the organism. Its malfunctioning can result in numerous blood diseases including leukemia.

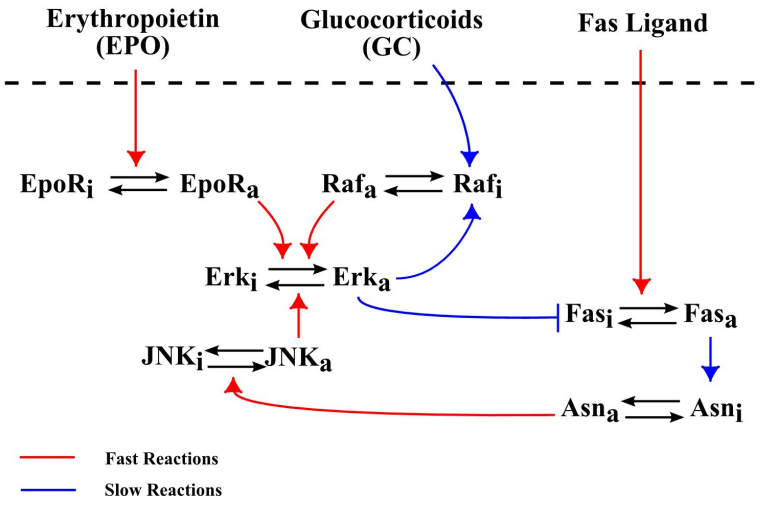

Figure 2. A schematic description of the intra-cellular molecular events that are relevant for decision making in an erythroid progenitor. The non active form of the protein is labeled i, the active form a. Blue lines indicate transcriptional regulation, red lines indicate biochemical regulation.

Multi-scale modeling in hematopoiesis holds a great potential. A variety of techniques exists to deal with this problem. However, the complexity of the system poses new difficulties and leads to the development of new tools. The expected results of this study are numerous. On one hand, it will shed new light on the different physiological mechanisms that converge toward the continuous regeneration of blood cells, for example: the behavior of hematopoietic stem cells under stress conditions, the understanding of deregulation of erythropoiesis (the process of red blood cell production) under drag treatments (this can lead to lack of red blood cells (anemia), or a surplus of red blood cells), the understanding of immune response process under the control of T-cell activation and memory cell generation, in order to adapt infection prevention strategies.

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

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

2.2. Keywords

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

2.3. Objectives

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

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

3. Research Program

3.1. Cell dynamics

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

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

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

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

3.2. From particle dynamics to continuum mechanics

DPD is well adapted to describe biological cells. However, it is a very time consuming method which becomes difficult to use if the number of particles exceeds the order of 10^5-10^6 (unless distributed computing is used). On the other hand, PDEs of continuum mechanics are essentially more efficient for numerical simulations. Moreover, they can be studied by analytical methods which have a crucial importance for the understanding of relatively simple test cases. Thus we need to address the question about the relation between DPD and PDE. The difficulty follows already from the fact that molecular dynamics with the Lennard-Jones potential can describe very different media, including fluids (compressible, incompressible, non-Newtonian, and so on) and solids (elastic, elasto-plastic, and so on). Introduction of dissipative terms in the DPD models can help to justify the transition to a continuous medium because each medium has a specific to it law of dissipation. Our first results [32] 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 [33] 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 ([38], [40]), and they proved effective in hematopoiesis modelling ([27], [28], [30]). 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 [40]. The nonlocality can be either in the structure variable or in the time variable [27]. 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 [34].

4. Application Domains

4.1. Normal hematopoiesis

4.1.1. Introduction

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

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

The basic mechanisms of our modelling approach are as follows:

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

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

4.1.2. Hematopoietic stem cells (HSC)

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

Our modelling approach will be based on two methods: deterministic and stochastic differential equations with delays (discrete and distributed), on one hand, and the DPD method using the individual based modelling on the other hand. The differential equation models based on the work initiated by Mackey [35] will describe the HSC compartment in normal conditions and the behaviour of these cells under some stress. The DPD method, as a complementary approach, will emphasize the spatial regulation of stem cell behaviour, and we will focus our attention to give a possible answer regarding their location in the bone marrow and the roles of the niche, their number in the system, their possible role under stress (that is their reaction under the different feedback controls).

4.1.3. Blood cell functions

(i) O2 transport: red lineage

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

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

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

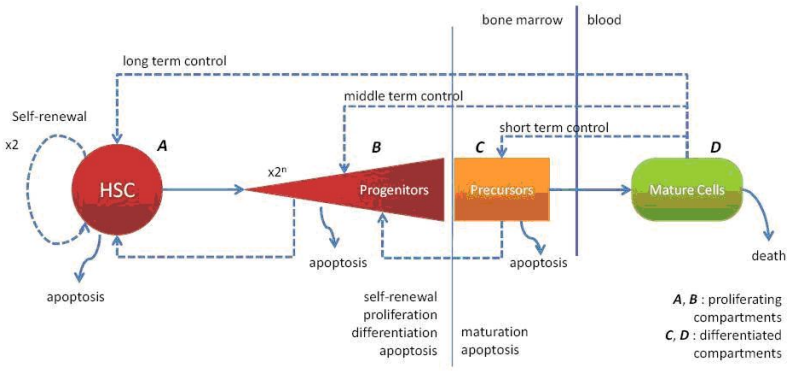

Figure 3. Scheme of Erythropoiesis Modelling. Without considering explicitly growth factor mediated regulation, all controls (proliferation, self-renewal, differentiation, apoptosis) are mediated by cell populations (dashed arrows). Mature cells can either regulate immature (HSC, progenitors) or almost 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 [39]. A first version of this model is shown in Figure 2.

(ii) Immune response

We will focus on the production of T-cells during an immune response. This represents an important activity of the lymphoid branch, part of leucopoiesis (white blood cell production). Several models of the myeloid branch of leucopoiesis have been investigated in the frame of specific diseases (for instance cyclical neutropenia ([34], [31]), chronic myelogenous leukemia [36]).

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

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

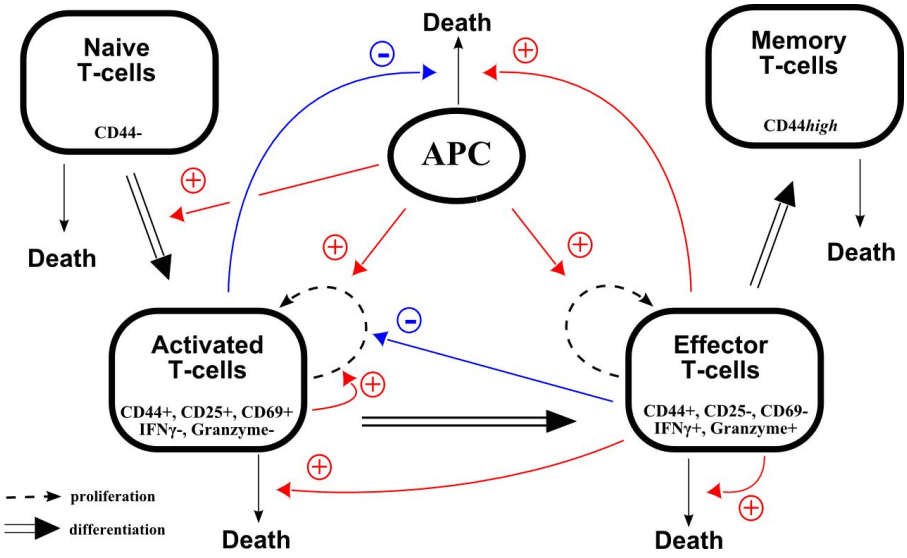

Figure 4. Model of the immune response resulting in the generation of CD8 memory T cells. The response starts with a viral infection resulting in the presentation of viral antigens through antigen presenting cells (APC) to naive T-cells. These latter, once activated, differentiate into activated cells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

(iii) Coagulation: platelet lineage

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

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

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

4.2. Pathological hematopoiesis

The knowledge of hematopoiesis and related diseases has evolved to become a great deal in the past years, and Mackey's previous models (ref. [29]) 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 [37]. 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 and Platforms

5.1. CelDyn

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

Software "Celdyn" is developed in order to model cell population dynamics for biological applications. Cells are represented either as soft spheres or they can have more complex structure. Cells can divide, move, interact with each other or with the surrounding medium. Different cell types can be introduced. When cells divide, the types of daughter cells are specified. A user interface is developed.

6. New Results

6.1. Mathematical modeling in chronobiology

Circadian clocks are autonomous oscillators entrained by external Zeitgebers such as light-dark and temperature cycles. On the cellular level, rhythms are generated by negative transcriptional feedback loops. In mammals, the suprachiasmatic necleus (SCN) in the anterior part of the hypothalamus plays the role of the central

circadian pacemaker. Coupling between individual neurons in the SCN leads to specify self-sustained oscillations even in the absence of external signals. These neuronal rhythms orchestrate the phasing of circadian oscillations in peripheral organs. Altogether, the mammalian circadian system can be regarded as a network of coupled oscillators. In order to understand the dynamic complexity of these rhythms, mathematical models successfully complement experimental investigations. In [19], we discuss basic ideas of modeling on three different levels: (i) rhythm generation in single cells by delayed negative feedbacks, (ii) synchronization of cells via external stimuli or cell-cell coupling, and (iii) optimization of chronotherapy.

6.2. Hybrid Models of Cell Population

The paper [20] is devoted to hybrid discrete-continuous models of cell populations dynamics. Cells are considered as individual objects which can divide, die by apoptosis, differentiate and move under external forces. Intra-cellular regulatory networks are described by ordinary differential equations while extracellular species by partial differential equations. We illustrate the application of this approach to some model examples and to the problem of tumor growth. Hybrid models of cell populations present an interesting nonlinear dynamics which is not observed for the conventional continuous models.

6.3. Multiscale Model in Biology

Biological processes span several scales in space, from the single molecules to organisms and ecosystems. Multiscale modelling approaches in biology are useful to take into account the complex interactions between different organisation levels in those systems. We present in [6] several single- and multiscale models, from the most simple to the complex ones, and discuss their properties from a multiscale point of view. Approaches based on master equations for stochastic processes, individual-based models, hybrid continuous-discrete models and structured PDE models are presented.

6.4. Model of hematopoiesis

In [2], a model of blood cell production in the bone marrow (hematopoiesis), has been investigated. It describes both the evolution of primitive hematopoietic stem cells and the maturation of these cells as they differentiate to form the three kinds of progenitors and mature blood cells (red blood cells, white cells and platelets). The three types of progenitors and mature cells are coupled to each other via their common origin in primitive hematopoietic stem cells compartment. The resulting system is composed by eleven age-structured partial differential equations. To analyze this model, we don't take into account cell age-dependence of coefficients, that prevents a usual reduction of the structured system to an unstructured delay differential system. We study the existence of stationary solutions: trivial, axial and positive steady states. Then we give conditions for the local asymptotic stability of the trivial steady state and by using a Lyapunov function, we obtain a sufficient condition for its global asymptotic stability. In some particular cases, we analyze the local asymptotic stability of the positive steady state by using the characteristic equation. Finally, by numerical simulations, we illustrate our results and we show that a change in the duration of cell cycle can cause oscillations.

6.5. Analysis of radiocarbon to facilitate identification of unknown decedents

The characterization of unidentified bodies or suspected human remains is a frequent and important task for forensic investigators. However, any identification method requires clues to the person's identity to allow for comparisons with missing persons. If such clues are lacking, information about the year of birth, sex and geographic origin of the victim, is particularly helpful to aid in the identification casework and limit the search for possible matches. We present in [4] results of stable isotope analysis of $(13)C$ and $(18)O$, and bomb-pulse $(14)C$ analyses that can help in the casework. The $(14)C$ analysis of enamel provided information of the year of birth with an average absolute error of 1.8 ± 1.3 years. We also found that analysis of enamel and root from the same tooth can be used to determine if the $(14)C$ values match the rising or falling part of the bomb-curve. Enamel laydown times can be used to estimate the date of birth of individuals, but here we show that this detour is unnecessary when using a large set of crude $(14)C$ data of tooth enamel as a reference. The levels

of $(13)C$ in tooth enamel were higher in North America than in teeth from Europe and Asia, and Mexican teeth showed even higher levels than those from USA. DNA analysis was performed on 28 teeth, and provided individual-specific profiles in most cases and sex determination in all cases. In conclusion, these analyses can dramatically limit the number of possible matches and hence facilitate person identification work.

7. Bilateral Contracts and Grants with Industry

7.1. Bilateral Contracts with Industry

The industrial connections of the Dracula team have been made through the "Modeling of the immune response" project. Contacts have been established with both large pharmaceutical companies (Sanofi-Pasteur and Merial) and SMEs (Altrabio and Cosmo). The current ANR PrediVac incorporates the two aforementioned SMEs and will therefore strengthen the ties between Dracula and its industrial local ecosystem.

8. Partnerships and Cooperations

8.1. National Initiatives

8.1.1. ANR

Projects coordination by a member of Dracula

- ANR (jeunes chercheurs) ProCell "Mathematical Methods for Erythropoiesis Modelling: from Proteins to Cell Populations", 2009-2013.
  Participants: Samuel Bernard, Fabien Crauste [Coordinator], Olivier Gandrillon, Laurent Pujo-Menjouet, Vitaly Volpert.
- ANR (jeunes chercheurs) MADCOW "Modelling amyloid dynamics and computation output work: applications to Prion and Alzheimer's disease", 2008-2013.
  Participants: Samuel Bernard, Fabien Crauste, Laurent Pujo-Menjouet [Coordinator], Vitaly Volpert.
- ANR BIMOD "Hybrid models of cell populations. Application to cancer modelling and treatment", 2010-2014.
  Participants: Mostafa Adimy, Fabien Crauste, Vitaly Volpert [Coordinator].
- ANR STOCHAGENE "Role of the chromatin dynamics on the stochasticity in gene expression in higher eukaryotic cells", 2011-2015.
  Participant: Olivier Gandrillon [Coordinator].

Collaboration in other projects

- ANR RPIB PrediVac "Innovative modeling tools for the prediction of CD8 T cell based vaccine efficacy", 2013-2015. Partners: U1111 Inserm (J. Marvel, coordinator), Dracula, Altrabio (small company), CoSMo (small company). For Dracula, the budget in 2013 is 88 keuros, including two one-year post-doc positions, recruited in February (Floriane Lignet) and in April (Sotiris Prokopiou).
- Thomas Lepoutre participates in the ANR (jeunes chercheurs) MODPOL (head Vincent Calvez (ENS Lyon)) "Cell polarization modeling", 2011-2015.
- Thomas Lepoutre is a member of the ANR KIBORD (head L. Desvillettes) dedicated to "kinetic and related models in biology". 2012-2016.
- Olivier Gandrillon participates in the ANR (Investissement d'Avenir) Iceberg (head Gregory Batt (Inria)) "From population models to model populations: single cell observation, modeling, and control of gene expression".

8.2. European Initiatives

8.2.1. Collaborations with Major European Organizations

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

8.3. International Initiatives

8.3.1. Inria Associate Teams

8.3.1.1. Modeling leukemia

Title: Modeling quiescence and drug resistance in Chronic Myeloid Leukemia

Inria principal investigator: Thomas Lepoutre

International Partner (Institution - Laboratory - Researcher):

University of Maryland (United States), Center for Scientific Computation and Mathematical Modeling.

Leukemia is the most famous disease of the blood cell formation process (hematopoiesis). Chronic myeloid leukemia results in a uncontrolled proliferation of abnormal blood cells. As the hematopoiesis involves stem cells (not accessible to observations), mathematical modeling is here a great tool to test hypothesis. We will join the expertise of Inria team DRACULA specialized on the modeling of blood cell formation and the Center for Scientific Computation and Applied Mathematical Modeling (CSCAMM, University of Maryland, College Park). The theoretical and modeling experience of team DRACULA and the numerical expertise combined with the links with experimentalists of members of CSCAMM will allow us to study deeply evolution of leukemia. We will especially focus on the behavior of leukemic stem cells and their possibility of becoming quiescent (dormant). Then we will study (using the knowledge obtained on leukemic stem cells) the phenomenon of drug resistance and its propagation over time and finally the mechanisms of multidrug resistance.

8.3.2. Participation In other International Programs

8.3.2.1. M3CD

Program: Euromediterranean 3+3

Title: Mathematical Models and Methods in Cell Dynamics

Inria principal investigator: Mostafa Adimy

International Partners (Institution - Laboratory - Researcher):

Institut Pasteur de Tunis (Tunisia) - Slimane Ben Miled

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

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

Duration: Jan 2012 - Dec 2015

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

1) Analysis of structured models in cell population dynamics ;

2) Dynamics of normal and pathological haematopoiesis ;

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

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

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

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

8.4. International Research Visitors

8.4.1. Visits of International Scientists

8.4.1.1. Internships

Evgenia Babushkina

Subject: Numerical simulations of blood flows and blood coagulation

Date: from Apr 2013 until Jul 2013

Institution: St. Petersburg State University (Russia (Russian Federation))

8.4.1.2. Visits of other international scientists

- Malay Banerjee - Kanpur, India - from May 2013 until June 2013.
- Dana-Adriana Botesteanu - University of Maryland, USA - from May 2013 until June 2013
- Peter Kim - University of Sydney, Australia - from January 2013 until February 2013
- Nemanja Kosovalic - York University, Canada - March 2013

- Michael Mackey - McGill University, Canada - February 2013
- Jianhong Wu - York University, Canada - March 2013

9. Dissemination

9.1. Scientific Animation

The year 2013 was marked by the following events:

- The edition of 4 volumes of the journal MMNP (Mathematical Modelling of Natural Phenomena) on the following topics: Harmonic analysis; Anomalous diffusion; Front Propagation; Plant growth modelling (see http://journals.cambridge.org/action/displayJournal?jid=MNP).
- The co-organization of a monthly seminar (INRIabcd, every last friday), jointly with Inria team BEAGLE, and the organization of a seminar on biomathematics (on thursday, twice a month) (see archives : http://dracula.univ-lyon1.fr/news_old.php).
- The organization of the Semovi seminar (http://www.biosyl.org/news/semovi). Two editions (March and October) in 2013, Olivier Gandrillon.
- Thematic program: Mathematical Biology

  Our team has been the co-organizer of a thematic program on "Mathematical Biology", in Lyon (France) from March 4th to June 14th (3 months), 2013:
  http://mathbio2013.sciencesconf.org/
  These activities are funded in part by the "Laboratoire d'Excellence", labex MILYON an initiative from the French ministry of research.
  The main topics of this program are: Cell biology, population dynamics, quantitative modeling for drug development, systems biology, and evolutionary biology.

  The highlights of the program are:

  - Systems Biology Approach to Infectious Processes, Lyon (France), May 13-15 (part of the thematic program Mathematical Biology), Fabien Crauste, Olivier Gandrillon.

  - ESMTB-EMS Summer school "Multiscale modeling in the life sciences", Lyon (France), May 27-31 (part of the thematic program Mathematical Biology), Thomas Lepoutre, Vitaly Volpert.

  - Conference in honour of Michael Mackey's 70th birthday, Lyon (France), June 3-6 (part of the thematic program Mathematical Biology), Samuel Bernard, Fabien Crauste, Laurent Pujo-Menjouet.

9.2. Teaching - Supervision - Juries

9.2.1. Teaching

Licence : Léon MATAR TINE, Analyse, fonctions de plusieurs variables, Prepa L2, 60h, University Lyon 1.

Licence : Léon MATAR TINE, Analyse numérique, L3, 36h, University Lyon 1.

Licence : Laurent PUJO-MENJOUET, EDP réaction-diffusion, 10.5h, L3, University Lyon 1.

Licence : Laurent PUJO-MENJOUET, EDO-Systèmes dynamiques, 40h, L3, INSA Lyon.

Licence : Laurent PUJO-MENJOUET, Equations différentielles et EDP, 36h, L3, University Lyon 1.

Licence : Laurent PUJO-MENJOUET, Fonctions de plusieurs variables, 36h, L1, University Lyon 1

Licence : Laurent PUJO-MENJOUET, Suite et série de fonctions, 36h, L2, University Lyon 1.

Licence : Laurent PUJO-MENJOUET, Projet Etudiant, 03h, L2, University Lyon 1.

Licence : Philippe MICHEL, Analyse appliquée, 56h, L3, Ecole Centrale de Lyon.

Licence : Philippe MICHEL, Analyse appliquée, 56h, L3, Ecole Centrale de Lyon.

Licence : Philippe MICHEL, Probabilités et statistique, 32h, L3, Ecole Centrale de Lyon.

Licence : Philippe MICHEL, Projet d'études, 10h, L3, Ecole Centrale de Lyon.

Master : Mostafa ADIMY, Dynamique des populations : application aux populations de cellules, 15h, M2, University Lyon 1.

Master : Thomas LEPOUTRE, Préparation à l'agrégation, calcul scientifique, 30h, M2, University Lyon 1.

Master : Thomas LEPOUTRE, Dynamique des proteines, 18h, M2, University Lyon 1.

Master : Thomas LEPOUTRE, Equations de Hamilton Jacobi, 18h, M2, ENS Lyon.

Master : Samuel BERNARD: Dynamique des populations : application aux populations de cellules, 15h, M2, University Lyon 1.

Master : Laurent PUJO-MENJOUET, Modélisation en biologie et médecine, 4h, M2, ENS Lyon.

Master : Laurent PUJO-MENJOUET, EDP et modélisation, 30h, M1, INSA Lyon.

Master : Laurent PUJO-MENJOUET, Projets tutorés, 3h, M1, University Lyon 1.

Master : Laurent PUJO-MENJOUET, Systèmes dynamiques, 27h, M1, University Lyon 1.

Master : Laurent PUJO-MENJOUET, EDP pour l'hématopoïèse, 18h, M2, University Lyon 1.

Master : Philippe MICHEL, Algorithmes pour la décision en entreprise, 16h, M2, Ecole Centrale de Lyon.

Master : Philippe MICHEL, Systèmes embarqués collaboratifs, 14h, M1, Ecole Centrale de Lyon.

Master : Philippe MICHEL, Projet Application - Recherche, 10h, M1, Ecole Centrale de Lyon.

Master : Philippe MICHEL, Méthodes variationnelles pour les EDP, 36h , M2, Ecole Centrale de Lyon.

9.2.2. Supervision

PhD in progress: Loic Barbarroux, Ecole Centrale de Lyon, French ministry scholarship, since October 2013, co-supervised by Mostafa Adimy and Philippe Michel.

PhD in progress: Latifa Bouguerra, University of Alger, Algerian scholarship, since October 2012, co-supervised by Mostafa Adimy and Rachid Boudchich.

PhD in progress: Abdennasser Chekroun, University Lyon 1, Algerian scholarship, since October 2012, supervised by Mostafa Adimy.

PhD in progress: Raouf El Cheikh, University Lyon 1, salarié, since October 2011, supervised by Samuel Bernard.

PhD : Mohamed Helal, Contributions aux équations et inclusions différentielles et applications a des problèmes issus de la biologie cellulaire, University of Sidi Bel Abbes, Algeria, September 2013, co-supervised by Laurent Pujo-Menjouet and Abdelkader Lakmeche.

PhD in progress: Marine Jacquier, University Lyon 1, since October 2012, co-supervised by Mostafa Adimy and Fabien Crauste.

PhD in progress: Alen Tosenberger, University Lyon 1, CNRS scholarship, supervised by Vitaly Volpert.

9.2.3. Juries

- Mostafa Adimy was member and reviewer of the following PhD: Dhaou Lassoued (University of Paris 1 (Panthéon-Sorbonne)), December 2013; Souhila BOUDJEMA (University of Paris 1 (Panthéon-Sorbonne)), September 2013; Yuan HE (University of Bordeaux), November 2013; Ousmane SEYDI (University of Bordeaux), November 2013; Mohamed HELAL (University of Sidi Bel Abbes, Algeria), 22 September 2013; Naamat ALI (University of La Rochelle), July 2013.

- Mostafa Adimy was reviewer of the following PhD: William DIMBOUR (University of Antilles et de la Guyane), May 2013.
- Samuel Bernard was member of the following PhD: Anne-Sophie LESART (University of Grenoble), November 2013.
- Samuel Bernard was acting as a co-director for the following PhD: Stephan FISCHER (University of Lyon) December 2013.
- Olivier Gandrillon was acting as a director for the following PhD: Gael Kaneko (University of Lyon), Septembre 2013.
- Olivier Gandrillon was member and reviewer of the following PhD: Benoit Robisson (University of Marseille), November 2013; Lydia Boudaréne (ENS Paris), March 2013.
- Olivier Gandrillon was member of the following PhD: Adrien Senecal (ENS Paris), September 2013.

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