BABEŞ-BOLYAI UNIVERSITY CLUJ-NAPOCA
DOCTORAL SCHOOL OF MATHEMATICS AND COMPUTER SCIENCE

PhD THESIS SUMMARY

# ANALYSIS OF SOME MATHEMATICAL MODELS OF CELL DYNAMICS IN HEMATOLOGY

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# Contents

# Introduction

The purpose of the present thesis is the study of some mathematical models of cell dynamics and convex optimization problems applied to chronic myeloid leukemia, by taking into consideration basic concepts, methods and results from the theory of differential equations, such as: existence, uniqueness, boundedness, continuous dependence on data and stability of solutions.

## Mathematical modeling of hematological disorders

Mathematical models have been used in the last decades for a better understanding, prediction and control of biological processes. Specifically, cell proliferation related to blood production and hematological diseases has brought attention of several mathematicians such as S.I. Rubinow and J.L. Lebowitz [94, 95], M.C. Mackey and L. Glass [60], M.C. Mackey [59] and B. Djulbegovic and S. Svetina [28]. For more recent contributions we refer to A.S. Fokas et al. [32], B. Neiman [72], L.K. Andersen and M.C. Mackey [8], C. Colijn and M.C. Mackey [21], M. Adimy et al. [2], D. Dingli and F. Michor [27], P.S. Kim et al. [54], C. Foley and M.C. Mackey [33], A. Cucuianu and R. Precup [24], M. Doumic-Jauffret et al. [30], N.L. Komarova [56], T. Stiehl and A. Marciniak-Czochra [101], A.L. MacLean et al. [61, 62], F. Crauste [23], I.R. Radulescu et al. [88] and L.G. Parajdi et al. [76].

Over the years, the mathematical models that reproduce both normal and disturbed hematopoiesis have been proposed. The differential equations used for the models usually involve sigmoid or Hill functions, since hematopoiesis is a self-limiting process. For example, M.C. Mackey and L. Glass [60] have introduced the following mathematical model of blood production

$$p'(t) = \frac{ap(t-\tau)}{1+bp^n(t-\tau)} - cp(t),$$

where $p(t)$ is the density of mature cells in blood circulation, $\tau$ is the time delay between the production of immature cells in the bone marrow and their maturation and release in the blood stream, $a$ is the rate of cell production, $c$ is the cell turnover rate, $b$ and $n$ are positive numbers. The special form of the nonlinear term shows that the growth rate per cell $p'(t)/p(t-\tau)$ is approximately equal to $a$ as long the density of immature cells is close to zero, and decreases when $p(t-\tau)$ increases. Parameter $n$ controls the steepness of the response. The analogue equation without delay,

$$p'(t) = \frac{ap(t)}{1+bp^n(t)} - cp(t),$$

models the dynamic of an auto-limiting growth due to crowding inhibition, while the two-dimensional system

$$\begin{cases} x'(t) = \frac{ax(t)}{1+b(x(t)+y(t))} - cx(t) \\ y'(t) = \frac{Ay(t)}{1+B(x(t)+y(t))} - Cy(t). \end{cases} \tag{1}$$

introduced by D. Dingli and F. Michor [27] (see also the paper of A. Cucuianu and R. Precup

[24]) models the competition between normal and abnormal (or malignant) hematopoietic stem cells. Here, the model parameters $a, A, b, B, c$ and $C$ represent the nonrestrictive growth rates, the bone marrow microenvironment sensitivities, and the cell death rates (or cell turnover rates) of the two cell populations.

## Structure of the thesis

The thesis is structured in four chapters, each chapter being organized in several sections.

**Chapter 1** is entirely dedicated to a medical background which we need throughout this work. In Section 1.1 we present the concept of *Hematopoiesis*, which is the scientific name of the process of blood cell formation, while in Section 1.2 we shortly speak about leukemia, over-called cancer of the blood. Finally, in Section 1.3 we give an introduction to chronic myeloid leukemia.

In **Chapter 2** we propose a mathematical model of cell dynamics which shows us the transition process from the normal hematopoiesis to the chronic and accelerated acute stages in myeloid leukemia. This chapter contains six sections. First, we explain the contents of each section and we present the main tools and methods that are used.

Inspired by the paper of D. Dingli and F. Michor [27], in Section 2.1 we introduce a two-dimensional mathematical model

$$\begin{cases} x'(t) = \frac{ax(t)}{1+b_1x(t)+b_2y(t)} - cx(t) \\ y'(t) = \frac{Ay(t)}{1+B(x(t)+y(t))} - Cy(t), \end{cases} \tag{2}$$

which describes the evolution of normal $x(t)$ and abnormal (or leukemic) $y(t)$ stem cell populations in chronic myeloid leukemia. Based on this model, the normal hematopoietic state, the chronic and accelerated acute phases of chronic myeloid leukemia are mathematically characterized in terms of a parameter $D$ that incorporates the growth, the cell death and the sensitivity rates of the abnormal cells, and represents the equilibrium amount of abnormal cells. The bifurcation analysis involving this parameter yields two bifurcation points that from a mathematical point of view, correspond to the transition from the normal hematopoietic state to the chronic (also called indolent) leukemic phase, and from the chronic phase to the accelerated acute/blast phase.

In Section 2.2, we make a qualitative analysis of the two-dimensional mathematical model given in Section 2.1. Thus we prove: the existence and uniqueness of the solution of the initial value problem, the monotonicity and boundedness of the solutions, and their continuous dependence on data.

In Section 2.3, we determine the steady states of the model (2) and we discuss their local stability, while in Section 2.4, we study the global stability of those equilibrium points. Next, in Section 2.5, we provide some numerical simulations of the model, which confirm the already obtained theoretical results.

Finally in Section 2.6, the model is upgraded by six additional equations

$$\begin{aligned} x_1'(t) &= \tfrac{a_1x_1}{1+b_1x_1+b_2y_1} - c_1x_1 & y_1'(t) &= \tfrac{A_1y_1}{1+B(x_1+y_1)} - C_1y_1 \\ x_2'(t) &= a_2x_1 - c_2x_2 & y_2'(t) &= A_2y_1 - C_2y_2 \\ x_3'(t) &= a_3x_2 - c_3x_3 & y_3'(t) &= A_3y_2 - C_3y_3 \\ x_4'(t) &= a_4x_3 - c_4x_4 & y_4'(t) &= A_4y_3 - C_4y_4 \end{aligned}$$

so that, as in F. Michor et al. [68] and D. Dingli and F. Michor [27], it becomes able to describe the evolution of four types of cells:

- primitive stem cells,
- progenitor cells,

- differentiated cells,
- terminally differentiated cells.

The numerical simulations show the parallelism between the dynamics of primitive stem cells and that of the succeeding lines, which allows the analysis to be performed at any level, particularly to terminally differentiated cells, for which laboratory data can be obtained easier.

Our main contributions in Chapter 2 are as follows. In Section 2.2 we have: Theorem 2.2.1, about the existence and uniqueness of solutions of the Cauchy problem associated to the two-dimensional model (2); Theorem 2.2.2, about boundedness of solutions; Theorem 2.2.3 and Theorem 2.2.4, on continuous dependence of solutions on data, based on the classical method and also on a vector approach that uses vector-valued norms and matrices. The most relevant results in Section 2.3 are: Theorem 2.3.1 and Remark 2.3.2, which give information about the local stability of the equilibrium points of the two-dimensional system (2), using the first approximation Lyapunov's method, while the most relevant result in Section 2.4 is Theorem 2.4.1, which gives information about the global stability of those equilibrium points.

The results from this chapter are included in the papers L. Parajdi [73], L.G. Parajdi and R. Precup [75], L.G. Parajdi, R. Precup and E.A. Bonci [76] and R. Precup, D. Dima, C. Tomuleasa, M.A. Şerban and L.G. Parajdi [82].

The purpose of **Chapter 3** is to develop a mathematical approach of optimal therapy for individual patients in chronic myeloid leukemia, based on the two-dimensional mathematical model from Chapter 2. According to the Dingli-Michor model (1) from the paper [27], to eradicate the cancer of the blood (leukemia), the therapy should reverse the inequality $D > d$ which represents the acute leukemic phase, by decreasing the growth rate $A$ and/or increasing the sensibility rate $B$ and the turnover rate $C$, when acting against malignant cells (abnormal cells), and by increasing rate $a$ and/or decreasing parameters $b$ and $c$, when therapy is directed at normal cells.

In contrast to the paper of D. Dingli and F. Michor, in our work we deal with the chronic leukemic phase, characterized by the inequalities $d < D < d/s$. More realistically, instead of aiming at a complete eradication of leukemia by reversing the inequality $D > d$, we explore hypothetical therapies directed at abnormal cells that shift the steady state (or equilibrium) towards the normal hematopoiesis and thus confer an advantage to the normal hematopoietic stem cells over the abnormal cells.

The chapter is divided into four sections. After a general overview, in Section 3.1, we state a convex optimization problem based on the two-dimensional model introduced in Chapter 2.

In Section 3.2 we present two therapeutic scenarios related to the main objective of diminishing the ratio $y^*/x^*$ between abnormal and normal cells, under a prescribed threshold, while in Section 3.3 we consider a drug that acts on more than one parameter. The results obtained are compared with those from Section 3.2. Here, in Section 3.3, we prove that the use of a drug that inhibits simultaneously more than one kinetic parameter enables a smaller total dose, or toxicity, or cost, compared to the single-parameter inhibition. To solve the convex optimization problem we use the Kuhn-Tucker Theorem.

Finally, in Section 3.4 we consider an optimization problem based on the extended model to terminally differentiated cells, studied in Section 2.6. The most relevant result in this section, Conclusion 3.4.1, compares the results obtained when the drug acts over two classes of cells (progenitor cells and differentiated cells), to those obtained in case that the drug only acts on the single class of progenitor cells.

All results from Chapter 3 are original and are contained in the paper L.G. Parajdi, R. Precup, D. Dima, V. Moisoiu and C. Tomuleasa [77].

**Chapter 4** is all about the study of a mathematical model of stem cell dynamics after allogeneic bone marrow transplantation in chronic myeloid leukemia. The chapter is divided into four sections.

After a general overview in Section 4.1, based on the mathematical model from Chapter 2, we give

the three-dimensional mathematical model

$$\begin{cases} x'(t) = \frac{ax(t)}{1+b_1(x(t)+z(t))+b_2y(t)} \ \frac{x(t)+y(t)}{x(t)+y(t)+gz(t)} - cx(t) \\ y'(t) = \frac{Ay(t)}{1+B(x(t)+y(t)+z(t))} \frac{x(t)+y(t)}{x(t)+y(t)+Gz(t)} - Cy(t) \\ z'(t) = \frac{az(t)}{1+b_1(x(t)+z(t))+b_2y(t)} \frac{z(t)}{z(t)+h(x(t)+y(t))} - cz(t), \end{cases} \tag{3}$$

which describes the post-transplant cell evolution of normal host cells, whose population is denoted by $x(t)$, abnormal (or leukemic) host cells, denoted by $y(t)$, and donor cells, denoted by $z(t)$. Compared with the initial mathematical model given by R. Precup et al. [81], using our model we can make distinction between the chronic and accelerated acute phases at transplantation.

In Section 4.2, we make a qualitative analysis of the three-dimensional mathematical model (3). Thus we prove: the existence and uniqueness of the solution of the initial value problem, and the boundedness of the solutions.

In Section 4.3, we determine the steady states of the model (3), and we discuss their local stability, while in the last Section 4.4, we provide some numerical simulations, giving time-series representations and phase portraits of the dynamic system (3). The numerical simulations confirm the theoretical results.

The main results from Chapter 4 are as follows. In Section 4.2 we have: Theorem 4.2.1, an existence and uniqueness result, and Theorem 4.2.2, on boundedness of solutions. The most relevant results from Section 4.3 are: Theorem 4.3.1, a result about the admissibility of the steady states of the system (3); Theorem 4.3.2, about local stability of the equilibrium points of the three-dimensional system (3) in the chronic phase of CML; Theorem 4.3.4, about local stability of the equilibrium points of the three-dimensional system (3) in the accelerated acute phase of CML, both using the first approximation Lyapunov's method; Proposition 4.3.3 and Remark 4.3.5, about local stability on manifolds of the equilibrium points of the system (3) in the chronic and accelerated acute phases of CML.

These results from Chapter 4 are included in the paper L.G. Parajdi [74].

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Author's papers:

- L. Parajdi, *Modeling the treatment of tumor cells in a solid tumor*, J. Nonlinear Sci. Appl. **7** (2014), 188–195.
- L.G. Parajdi, *Stability of the equilibria of a dynamic system modeling stem cell transplantation*, submitted.
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- L.G. Parajdi, R. Precup and E.A. Bonci, *A mathematical model of the transition from the normal hematopoiesis to the chronic and accelerated acute stages in myeloid leukemia*, submitted.
- L.G. Parajdi, R. Precup, D. Dima, V. Moisoiu and C. Tomuleasa, *Theoretical basis of optimal therapy for individual patients in chronic myeloid leukemia. A mathematical approach*, submitted.
- R. Precup, D. Dima, C. Tomuleasa, M.A. Şerban and L.G. Parajdi, *Theoretical models of hematopoietic cell dynamics related to bone marrow transplantation*, In Frontiers in Stem Cell and Regenerative Medicine Research, Bentham Science Publishers-Sharjah, **8** (2018), 202–241.

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- Workshop for Young Researchers in Mathematics 7th edition (WYRM), Bucharest, Romania, May 17-20, 2017.
  http://math.univ-ovidius.ro/Workshop/2017/WYRM/Doc/Abstracts-Analysis.pdf?v=170515
- Workshop "Geometry and PDEs", West University of Timişoara, Romania, June 13-14, 2017.
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## Keywords

Stability, dynamical system, numerical simulations, mathematical modeling, cell dynamics, optimization problem, chronic myeloid leukemia, hematology.

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# Chapter 1
# Medical Background

The mathematical models introduced and studied in this thesis are inspired by some concrete biological processes. Thus, in order to make interpretations of the mathematical results in biological and medical terms, it is useful to shortly discuss these processes. Therefore in this chapter we present the process of blood cells formation, called hematopoiesis, and some disorders associated to it, namely leukemias, particularly the chronic myeloid leukemia.

## 1.1 Hematopoiesis

Hematopoiesis is the scientific name of the process of blood cells formation. The formation begins, like a whole process, in the intrauterine life in the mesoderm of the Yolk sack and goes on in the liver and the spleen between the second and seventh month. It then happens at the level of the bone marrow, where it will continue after birth. In early years of life, for example in childhood, hematopoiesis is happening in almost all bones, being replaced step by step with growth by fat tissue. In adults, hematopoiesis occurs only in the pelvis, vertebrae, sternum (see N. Young [109] and M. Howard et al. [44]) ribs, skull, proximal humerus and femur epiphysis (see K. Kaushansky et al. [52]).

Hematopoiesis can be viewed as an evolutionary tree that grows from one single *hematopoietic stem cell* (HSC). A HSC has several functions such as: it can renew itself, it can generate two other HSCs, it can lose the ability of self-renewal going through a process that yield two progenitor cells, or it can give birth to a progenitor cell and a HSC. Progenitor cells are able to initiate the differentiation towards one of the pathways that lead to the formation of various types of blood cells: *common lymphoid progenitor* (CLP) that will also pass through an evolution that means the differentiation and maturation into B- or T-lymphocytes and the *common myeloid progenitor* (CMP) that will also result leukocytes (white blood cells), erythrocytes (red blood cells) and platelets (see N. Young [109] and K. Kaushansky et al. [52]). Recent studies have shown there is a growing evidence that hematopoietic stem cells produce a common myeloid progenitor and a *common myelo-lymphoid progenitor* (CMLP) that in their turn produce a bipotential myeloid T progenitor and a myeloid B progenitor (see K. Kaushansky et al. [52]). Figure 1.1 gives the diagram of different compartments of cells from hematopoiesis.

The dynamics of HSCs depends of many factors: extrinsic cell factors (microenvironmental factors, humoral feedback, cytokines), and intrinsic cell factors, that is DNA alterations (see J.L. Abkowitz [1], N. Young [109], L. Zon [110], A. Cucuianu and R. Precup [24], K. Kaushansky et al. [52], M. Howard et al. [44] and P. Ramalingam et al. [91]).

Even though mammals, humans included, have a stock of only $2 \times 10^4$ HSCs (see J.L. Abkowitz [1]), they can give birth and release into the blood stream approximately 2,5 billion erythrocytes/kg/day, 2,5 billion platelets/kg/day and 1 billion granulocytes/kg/day.

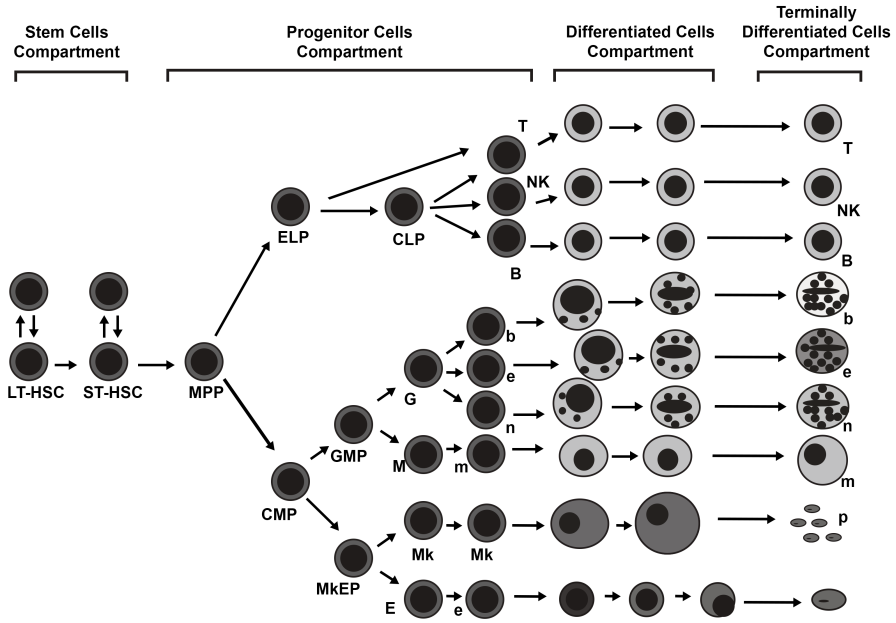



Figure 1.1: Diagram showing the compartments of different cells, from hematopoietic stem cells, to mature cells (or terminally differentiated cells).

## 1.2 What is leukemia?

Overcalled cancer of the blood, leukemias are an heterogeneous group of malignant disorders, arising from one mutant hematopoietic stem cell (mHSC) (see C. Lopez-Garcia et al. [57], H. Snippert et al. [100], A. Klein and B. Simons [55], G. Driessens et al. [31], M. Howard et al. [44] and A. Jilkine and R. Gutenkunst [47]). In this thesis, we are interested by mathematical aspects of cell dynamics and therefore, the complex biological processes on which the hematopoiesis is based are not completely involved.

There are four main types of leukemia (based on their progression - chronic or acute, and on the type of the affected cell - myeloid or lymphoid) (see B. Neiman [72]). Although current guidelines include a more comprehensive and detailed classification of leukemias (with types and subtypes of cells, mutations acquired, etc. see D. Arber et al. [9]), they are not the subject of this thesis, nor do they bring useful information to our mathematical models.

The mHSCs have an abnormal process of differentiation and particular characteristics compared to normal HSCs, due to their acquired genetic and epigenetic abnormalities: increased proliferation/growth advantage; lower sensitivity to apoptosis and to the environment; poor differentiation; squeeze out normal HSCs from bone marrow (see I. Roeder and M. d'Inverno [93]). All these can lead to a great variety of clinical results with major impact on patients health.

Without treatment, the life expectancy of patients with acute leukemia is on the order of weeks or months while in the case of chronic forms of leukemia the natural course of the disease leads to death in months or years.

## 1.3 Introduction to chronic myeloid leukemia

Chronic Myeloid Leukemia (CML) is an acquired myeloproliferative disorder (see B. Neiman [72] and M. Howard et al. [44]). The CML is most likely the first recognized leukemia, dating back to the 1840s (see N. Young [109]).

The CML represents 15% of all types of leukemia, annually occurring in every 2 out of 100.000 men and 1.1 out of 100.000 women (see K. Hemminki and Y. Jiang [39]). The diagnosis is usually established during routine blood tests, appearing more frequently after the fifth decade of life (see M. Howard et al. [44]). Through its signs and symptoms can be identified anemia, splenomegaly, weight loss, dyspnea on exertion. One of the risk factors, observed to have a role in developing CML is ionizing radiation (see N. Young [109]).

The hallmark of CML is the Philadelphia chromosome (Ph). Ph is characterized by a mutation in the normal hematopoietic stem cell population (see M. Howard et al. [44]), generated by one abnormal stem cell, with the t(9;22)(q34;q11) (see N. Young [109]) mutation, a reciprocal translocation of the ABL gene from chromosome 9 to chromosome 22, next to the BCR gene. This new born BCR-ABL gene codes a fusion protein with tyrosine kinase activity, that apparently influences whether the cell lives or dies, whether it proliferates or not.

This type of leukemia typically undergoes three phases: chronic (also called indolent) phase (CP-CML state), acceleration or transitory phase and acute/blast phase (see J.L. Abkowitz [1] and D. Arber et al. [9]). The next Figure 1.2 from the paper of B. Neiman [72], illustrates the time progression of these three phases. Notice that the chronic phase of CML involves periodic oscillations with a period of about three months (see C. Haurie et at. [36]), and usually progresses towards an acute phase. The graphic in Figure 1.2 shows a slow-progressing chronic phase, followed by an unstable phase, and by the transition to the acute phase.

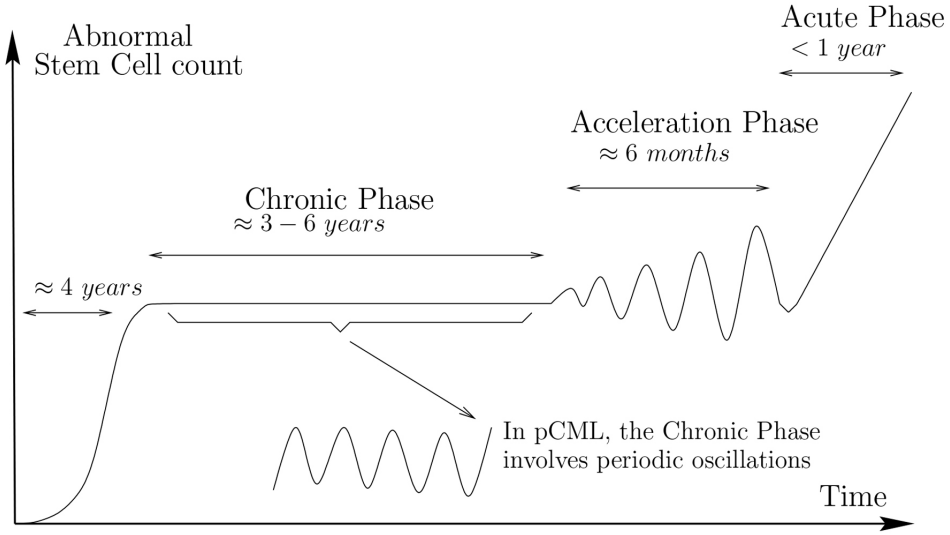



Figure 1.2: (B. Neiman [72]). There are three distinct phases of CML. The system reaches a steady state after a fast rise in the cell count. As years pass, an oscillatory instability appears and finally, this leads to the acute phase characterized by an increase in the cell count.

Due to the difficulty of separating acceleration phase from the blast phase one refers to them as a whole, naming it the *accelerated acute phase* (AAP-CML state). Most cases are diagnosed during the chronic phase and rarely during one of the other two phases. Once the mutation has occurred in one of the HSCs, it starts a series of divisions, followed by differentiation and maturation that no

longer obey the feedback and control mechanisms that apply to healthy HSCs. Therefore, the mutant cells divide at a quicker rate, producing a large number of thrombocytes and leukocytes, resulting in a population of cells where mHSCs are dominant.

At a certain point of CML, the occurence of other events (most probably the acquisition of other genetic mutations) leads to an instability of the mHSC population, that consequently follows an accelerated acute phase, resulting in an exponential increase of the number of immature stem cells. Cells multiply in a more accelerated manner and do not undergo differentiation, resulting in a blast phase, similar to various types of acute leukemias (myeloid - 70%, lymphoid - 20% and mixed type - 10%) in terms of symptoms and clinical findings (see B. Neiman [72], J.L. Abkowitz [1] and N. Young [109]). After reaching the accelerated or blastic phase, untreated patients have a median survival of 3 to 6 months (see H. Kantarjian et al. [49]).

In terms of treatment, even though tyrosinkinase inhibitors are effective in 70-80% of cases of CML, stem cell transplantation (SCT) seems to be the only curative treatment, nevertheless involving a high mortality rate due to complications (see E. Thomas [103] and M. Howard et al. [44]).

# Chapter 2
# Mathematical Modeling of Chronic Myeloid Leukemia

In a first approach, the analysis of mathematical models takes into consideration basic concepts, methods and results from the theory of differential equations, such as existence, uniqueness, continuous dependence on data, and stability of solutions. From the numerous works in this classical direction we mention those of A.L. Rabenstein [87], E.A. Coddington and N. Levinson [20], V.I. Arnold [10], I.A. Rus [96], R.P. Agarwal and D. O'Regan [4], V. Barbu [11] and R. Precup [80].

Concerning the applications of differential equations to biology and medicine, we mention the works of J. Berger et al. [12], J.D. Murray [70], D. Kaplan and L. Glass [50], C. Iancu and I.A. Rus [45], M.A. Horn et al. [43], L. Preziosi [86], R.W. Shonkwiler and J. Herod [98], D.S. Jones et al. [48], C.S. Chou and A. Friedman [17].

In this chapter of the thesis we propose a mathematical model of cell dynamics in chronic myeloid leukemia.

The chapter is structured in six sections. **Section 2.1** presents the two-dimensional mathematical model (2.4), which describes the evolution of normal $x(t)$ and abnormal $y(t)$ stem cell populations in myeloid leukemia, along with the biological interpretation of the parameters. This mathematical model shows us the transition process from the normal hematopoiesis to the chronic and accelerated acute stages in myeloid leukemia.

In **Section 2.2** we make a qualitative analysis of the given system, namely we deal with the existence and uniqueness of solutions, monotonicity and boundedness of solutions, and the continuous dependence of solutions on data, by means of two methods: the classical method and the method based on vector-valued norms and matrices.

In **Section 2.3** the steady states (or equilibrium points) of the system, and their local stability are discussed, while in the **Section 2.4** it is studied the global stability of those equilibrium points.

**Section 2.5** presents some numerical simulations of the considered system, which confirm the already obtained theoretical results.

In the last **Section 2.6**, we present an extended mathematical model to terminally differentiated cells. Some numerical simulations of the extended system are also given. This mathematical model describes the evolution of several normal and abnormal cell populations: primitive stem cell populations, progenitor cell populations, differentiated cell populations and terminally differentiated cell populations. The extended mathematical model gives us the possibility to understand the evolution of normal and abnormal cell populations at each stage of the process of forming blood cells.

The results in this chapter were published in the papers [73], [75], [76] and [82].

## 2.1 The basic mathematical model

The mathematical modeling of the time evolution of a population $p$ of any nature begins in a first approximation (assuming no constraints exist) with the Malthusian equation

$$p'(t) = ap(t) - cp(t),$$

where $p(t)$ is the population size at time $t$, and $a$ and $c$ are the growth and death (per capita) rates, respectively. Supposing that the growth rate is bigger than the death rate, the population will increase exponentially according to the law $p(t) = p_0 \exp((a-c)t)$, which is non-realistic in the long run, particularly for limited biological populations. Therefore, a more realistic approach is to consider that the growth (and/or death) rate will change during evolution by a self-limiting mechanism or exterior influences. For instance, the growth rate of a self-limiting population can be $a/(1+bp(t))$ depending on the population size itself. Here $b$ is a proportionality factor that shows how sensitive is that population with respect to its own size. This shows that the growth rate decreases as the population size $p(t)$ increases. In addition, the influence over $p$ of a competitive population $q$ can be simulated in the model by a growth rate of the form $a/(1+b_1p(t)+b_2q(t))$, where the ratio $b_2/b_1$ shows how strong the diminishing effect due to population $q$ is, compared to that of self-limiting.

Applied to the normal and abnormal stem cell populations denoted by $x$ and $z$, the above modeling choice leads to the following differential system

$$\begin{cases} x'(t) = \frac{ax(t)}{1+\beta_1 x(t)+\beta_2 z(t)} - cx(t) \\ z'(t) = \frac{Az(t)}{1+\gamma_1 x(t)+\gamma_2 z(t)} - Cz(t). \end{cases} \tag{2.1}$$

Here, since abnormal cells have a stronger diminishing effect on the growth rate of normal cells than on their own growth rate, it is natural to suppose that

$$\beta_2 > \gamma_2. \tag{2.2}$$

Also, the almost negligible effect of normal cells over the growth rate of population $z$ (i.e., $\gamma_1$ is much smaller than $\beta_1$) justifies the inequality

$$\frac{\gamma_2}{\gamma_1} > \frac{\beta_2}{\beta_1}. \tag{2.3}$$

For the mathematical analysis of most models, it is often convenient that the number of parameters is reduced as much as possible. Hence, in our case, we can reduce the number of parameters $\beta_1, \beta_2, \gamma_1, \gamma_2$ to three by making the change of variable

$$y = \frac{\gamma_2}{\gamma_1} z.$$

Substituting in (2.1) yields the system

$$\begin{cases} x'(t) = \frac{ax(t)}{1+\beta_1 x(t)+(\gamma_1/\gamma_2)\beta_2 y(t)} - cx(t) \\ y'(t) = \frac{Ay(t)}{1+\gamma_1 x(t)+\gamma_1 y(t)} - Cy(t), \end{cases}$$

which, with the notations

$$b_1 = \beta_1, \quad b_2 = \beta_2 \frac{\gamma_1}{\gamma_2}, \quad B = \gamma_1,$$

becomes

$$\begin{cases} x'(t) = \frac{ax(t)}{1+b_1 x(t)+b_2 y(t)} - cx(t) \\ y'(t) = \frac{Ay(t)}{1+B(x(t)+y(t))} - Cy(t). \end{cases} \tag{2.4}$$

In view of (2.3), one has $b_1 > b_2$, while (2.2) guarantees that $b_2 > B$. In consequence, in what follows we assume that

$$b_1 \geq b_2 > B. \tag{2.5}$$

The system (2.4) is our basic mathematical model. It expresses the time evolution of the normal and abnormal stem cell populations, denoted by $x(t)$ and $y(t)$, respectively. Here the model parameters $a$ and $A$ are the nonrestrictive *growth* rates (due to self-renewal) of normal and abnormal stem cells, respectively; $b_1, b_2$ and $B$ are the bone marrow microenvironment *sensitivities*; while $c$ and $C$ stand for their cell *death* rates (due to differentiation, apoptosis and other elimination mechanisms, see J. Domen [29], E. Vivier et al. [106], F.Q. Alenzi et al. [6], C. Riether et al. [92] and T. Cisneros et al. [18]). The terms

$$\frac{1}{1+b_1x+b_2y} \quad \text{and} \quad \frac{1}{1+B(x+y)}$$

model the *crowding effect* in the bone marrow microenvironment, introduce competition between normal and abnormal stem cells, and guarantee the homeostasis at the level of cell population. We assume that for both cell populations, the growth rate is greater than the death rate, that is

$$a > c \ \text{ and } \ A > C.$$

The eventual advantage of the abnormal cells of being less sensitive to the bone marrow microenvironment than normal cells, is expressed by (2.5).

Note that an alternative model for normal and abnormal cell dynamics in CML can be found in the paper of B. Neiman [72], where the role of the parameter $b_1/b_2$ is given by a parameter denoted by $g$ and assumed greater or equal to one.

The limit case $b_1 = b_2 =: b$ was considered by D. Dingli and F. Michor [27] and A. Cucuianu and R. Precup [24]. In this case there are only two non-zero steady states of the system, namely

$$(d, 0) \quad \text{and} \quad (0, D),$$

where $d$ and $D$ represent the homeostatic amounts of normal and abnormal stem cells, and they are given by

$$d = \frac{1}{b}\left(\frac{a}{c} - 1\right) \quad \text{and} \quad D = \frac{1}{B}\left(\frac{A}{C} - 1\right).$$

In what follows, we assume that $b_1 > b_2$. As we shall see, in this case, besides the non-zero steady states $(d, 0)$ and $(0, D)$, where this time

$$d = \frac{1}{b_1}\left(\frac{a}{c} - 1\right) \quad \text{and} \quad D = \frac{1}{B}\left(\frac{A}{C} - 1\right), \tag{2.6}$$

a third steady state $(x^*, y^*)$ could also exist with both positive components, i.e., $x^* > 0$ and $y^* > 0$. This makes the new model able to differentiate between chronic and accelerated acute phases in chronic myeloid leukemia.

## 2.2 Existence, uniqueness and continuous dependence on data

In this section we will discuss the initial value problem associated to system (2.4).

### Existence and uniqueness

**Theorem 2.2.1.** *For any $t_0 \geq 0$ and $u_0 = (x_0, y_0) \in (0, +\infty)^2$, there is a unique saturated solution $u = u(\cdot, t_0, u_0) = (x, y)$ of system (2.4) which is defined on the whole semiline $[t_0, +\infty)$, is of class $C^\infty$, with $x > 0$ and $y > 0$ on $[t_0, +\infty)$, and satisfies the initial condition*

$$u(t_0) = u_0.$$

## Monotonicity of the solutions

Let $(x, y)$ be any solution of system (2.4) with $x, y > 0$. The function $x(t)$ increases during the time intervals where $dx/dt > 0$, i.e.,

$$\frac{a}{1 + b_1 x(t) + b_2 y(t)} - c > 0, \quad \text{or equivalently,} \quad x(t) + \frac{b_2}{b_1} y(t) < d.$$

Thus, $x(t)$ increases as long as

$$x(t) + \frac{b_2}{b_1} y(t) < d, \quad \text{and decreases as long as} \quad x(t) + \frac{b_2}{b_1} y(t) > d.$$

Analogously, the function $y(t)$ increases as long as

$$\frac{A}{1 + B(x(t) + y(t))} - C > 0, \quad \text{or equivalently,} \quad x(t) + y(t) < D,$$

and decreases when $x(t) + y(t) > D$.

Therefore, the monotonicity of $x$ and $y$ is given by the weighted total of cells as compared with the homeostatic values $d$ and $D$.

## Boundedness of solutions

**Theorem 2.2.2.** *The solution $u = u(\cdot, t_0, u_0)$ is bounded on $[t_0, +\infty)$ for every $t_0 \geq 0$ and $u_0 \in (0, +\infty)^2$.*

## Continuous dependence on data

In practice, it is important to estimate the error between a solution of a given system and the solutions of a perturbed system. Let $u = (x, y)$ be the unique saturated solution of (2.4) satisfying the initial condition $u(t_0) = u_0$, where $t_0 \geq 0$ and $u_0 = (x_0, y_0) \in (0, +\infty)^2$, and let $v = (\overline{x}, \overline{y})$ be any solution of a Cauchy problem of the form

$$\begin{cases} v' = g(t, v) \\ v(t_0) = v_0, \end{cases} \tag{2.7}$$

where $v_0 = (\overline{x}_0, \overline{y}_0) \in \mathbb{R}^2_+$, $g = (g_1, g_2) \in C\left([t_0, t_0 + h] \times \mathbb{R}^2_+; \mathbb{R}^2_+\right)$, and it is assumed that $v$ exists on the interval $[t_0, t_0 + h]$.

We are interested to estimate the functions $x - \overline{x}$ and $y - \overline{y}$ in terms of the differences $x_0 - \overline{x}_0$, $y_0 - \overline{y}_0$, $f_1 - g_1$ and $f_2 - g_2$, where

$$\begin{aligned} f_1(x, y) &= \frac{ax}{1 + b_1 x + b_2 y} - cx, \\ f_2(x, y) &= \frac{Ay}{1 + B(x + y)} - Cy. \end{aligned}$$

By direct computation, we can show that $f_1, f_2$ satisfy the Lipschitz conditions

$$\begin{aligned} |f_1(w_1, w_2) - f_1(\overline{w}_1, \overline{w}_2)| &\leq l_{11} |w_1 - \overline{w}_1| + l_{12} |w_2 - \overline{w}_2|, \\ |f_2(w_1, w_2) - f_2(\overline{w}_1, \overline{w}_2)| &\leq l_{21} |w_1 - \overline{w}_1| + l_{22} |w_2 - \overline{w}_2|, \end{aligned} \tag{2.8}$$

with

$$\begin{aligned} l_{11} &= \max\{a - c, c\}, & l_{12} &= \tfrac{ab_2}{4b_1}, \\ l_{21} &= \tfrac{A}{4}, & l_{22} &= \max\{A - C, C\}. \end{aligned}$$

Denote

$$l = \max\{l_{11}, l_{12}\} + \max\{l_{21}, l_{22}\}.$$

**Theorem 2.2.3.** *Assume that*

$$\begin{aligned} |f_1(w_1,w_2)-g_1(t,w_1,w_2)| &\leq \eta_1 \\ |f_2(w_1,w_2)-g_2(t,w_1,w_2)| &\leq \eta_2 \end{aligned} \tag{2.9}$$

*for all* $w_1, w_2 \in \mathbb{R}_+$, $t \in [t_0, t_0+h]$, *and some numbers* $\eta_1, \eta_2 \geq 0$. *Then*

$$|x(t)-\overline{x}(t)| + |y(t)-\overline{y}(t)| \leq [|x_0-\overline{x}_0| + |y_0-\overline{y}_0| + (\eta_1+\eta_2)\,h]\, e^{hl} \tag{2.10}$$

*for all* $t \in [t_0, t_0+h]$.

Note that estimation (2.10) is given in terms of the norm

$$\|(x,y)\| = |x| + |y| \text{ on } \mathbb{R}^2.$$

With respect to the corresponding norm on $C\left([t_0,t_0+h],\mathbb{R}^2\right)$,

$$\|u\|_\infty = \max_{t\in[t_0,t_0+h]} \|u(t)\|,$$

it gives

$$\|u-v\|_\infty \leq (\|u_0-v_0\| + \|\eta\|\,h)\, e^{hl}. \tag{2.11}$$

Similar estimations hold with respect to other norms on $\mathbb{R}^2$. For example, if we consider the norms $\|(x,y)\| = \max\{|x|,|y|\}$ on $\mathbb{R}^2$ and the corresponding norm on $C\left([t_0,t_0+h],\mathbb{R}^2\right)$, $\|u\|_\infty = \max_{t\in[t_0,t_0+h]} \|u(t)\|$, we easily obtain (2.11), this time with $l = \max\{l_{11}+l_{12}, l_{21}+l_{22}\}$.

An estimation independent of the norm on $\mathbb{R}^2$ can be given in terms of vector-valued norms and matrices. In the end, let us consider the vector-valued norm on $\mathbb{R}^2$,

$$\|\!|(x,y)|\!\| = (|x|,|y|)^{tr}$$

and the corresponding vector-valued norm on $C\left([t_0,t_0+h],\mathbb{R}^2\right)$,

$$\|\!|u|\!\|_\infty = (\|x\|_\infty, \|y\|_\infty)^{tr}, \quad u=(x,y).$$

If we let $f=(f_1,f_2)$, the condition (2.8) can be written in the vector form

$$\|\!|f(w)-f(\overline{w})|\!\| \leq L\|\!|w-\overline{w}|\!\|$$

for all $w, \overline{w} \in \mathbb{R}^2_+$, where $L$ is the square matrix

$$L = \begin{bmatrix} \max\{a-c,c\} & \frac{ab_2}{4b_1} \\ \frac{A}{4} & \max\{A-C,C\} \end{bmatrix}.$$

Also condition (2.9) has the vector form

$$\|\!|f(w)-g(t,w)|\!\| \leq \eta$$

for all $w \in \mathbb{R}^2$, $t \in [t_0,t_0+h]$, where $\eta = (\eta_1,\eta_2)^{tr}$. Moreover, the inequalities

$$\begin{aligned} |x(t)-\overline{x}(t)| &\leq |x_0-\overline{x}_0| + \int_{t_0}^t |f_1(x(s),y(s)) - g_1(s,\overline{x}(s),\overline{y}(s))|\,ds \\ &\leq |x_0-\overline{x}_0| + \int_{t_0}^t |f_1(x(s),y(s)) - f_1(\overline{x}(s),\overline{y}(s))|\,ds \\ &\quad + \int_{t_0}^t |f_1(\overline{x}(s),\overline{y}(s)) - g_1(s,\overline{x}(s),\overline{y}(s)|\,ds \\ &\leq |x_0-\overline{x}_0| + \eta_1 h + l_{11}\int_{t_0}^t |x(s)-\overline{x}(s)|\,ds + l_{12}\int_{t_0}^t |y(s)-\overline{y}(s)|\,ds \end{aligned}$$

and

$$|y(t)-\overline{y}(t)| \quad \leq \quad |y_0-\overline{y}_0|+\eta_2 h+l_{21}\int_{t_0}^{t}|x(s)-\overline{x}(s)|\,ds+l_{22}\int_{t_0}^{t}|y(s)-\overline{y}(s)|\,ds,$$

can be put together under the vector inequality

$$\|u(t)-v(t)\| \leq \|u_0-v_0\|+h\eta+L\int_{t_0}^{t}\|u(s)-v(s)\|ds,$$

which from the vector version of Gronwall's inequality (see [80], p. 166) gives

$$\|u(t)-v(t)\| \leq e^{hL}\left(\|u_0-v_0\|+h\eta\right),$$

where $e^{hL}$ is a matrix exponential. Taking the maximum for $t\in[t_0,t_0+h]$ finally yields the following conclusion.

**Theorem 2.2.4.** *Under the above conditions, the following vector inequality holds:*

$$\|u-v\|_{\infty} \leq e^{hL}\gamma,$$

*where $\gamma$ is the column vector $\|u_0-v_0\|+h\eta$.*

## 2.3 Steady states and local stability

### Steady states

A steady state, an equilibrium, or a stationary solution of system (2.4) is a constant solution, i.e., a solution for which $dx/dt = dy/dt = 0$. Thus, the steady states of (2.4) are obtained by solving the algebraic system

$$\frac{ax}{1+b_1x+b_2y}-cx \quad = \quad 0, \tag{2.12a}$$

$$\frac{Ay}{1+B(x+y)}-Cy \quad = \quad 0. \tag{2.12b}$$

The solutions of the system (2.12a)-(2.12b) are the couples

$$(0,0),\quad (d,0),\quad (0,D)\quad \text{and}\quad (x^*,y^*),$$

where $d$, $D$ are given by (2.6),

$$x^*=-\frac{b_2c(A-C)-BC(a-c)}{BCc(b_1-b_2)} \quad \text{and} \quad y^*=\frac{b_1c(A-C)-BC(a-c)}{BCc(b_1-b_2)}.$$

Direct calculation leads to

$$x^*=\frac{b_1}{b_1-b_2}d-\frac{b_2}{b_1-b_2}D,\quad y^*=\frac{b_1}{b_1-b_2}\left(D-d\right).$$

It is easy to see that under the assumption that $b_1 > b_2$, both numbers $x^*$ and $y^*$ are positive (acceptable values from a biological point of view) if and only if

$$d<D<\frac{b_1}{b_2}d.$$

Thus, in this case, in addition to the non-zero steady states $(d,0)$ and $(0,D)$, a positive steady state $(x^*,y^*)$ appears, contrary to the case considered in the papers D. Dingli and F. Michor [27] and A. Cucuianu and R. Precup [24], where $b_1=b_2$.

### Local stability of steady states

We study the stability of the steady states of system (2.4) using the standard first approximation method (for details, see D. Kaplan and L. Glass [50], E.A. Coddington and N. Levinson [20] and D.S. Jones et al. [48]). According to this method, an equilibrium $(\alpha, \beta)$ is *asymptotically stable* if the Jacobian matrix $J(\alpha, \beta)$ is a Hurwitz matrix, i.e., Re $\lambda < 0$ for all its eigenvalues $\lambda$, and is *unstable* if Re $\lambda > 0$ for at least one of its eigenvalues.

From this study of local asymptotic stability of the stationary solutions of system (2.4), we obtain the following result:

**Theorem 2.3.1.** *(a) If $D < d$, then $(d, 0)$ is the only one steady state which is locally asymptotically stable.*

*(b) If $b_1 > b_2$ and $d < D < (b_1/b_2)d$, then $(x^*, y^*)$ is the only one steady state which is locally asymptotically stable.*

*(c) If $D > (b_1/b_2)d$, then $(0, D)$ is the only one steady state which is locally asymptotically stable.*

**Remark 2.3.2.** *In all of the three cases of the previous theorem, the steady state $(0, 0)$ is unstable as can be shown based on the assumptions $a > c$ and $A > C$.*

The above analysis shows a qualitative change of the system's behavior, more precisely a change of locally asymptotically stable equilibrium, as the parameter $D$ is varied. The values of this parameter at which the locally asymptotically stable equilibrium changes (called *bifurcation points*) are $D = d$ and $D = (b_1/b_2)d$. The bifurcation analysis of our system is illustrated by Figure 2.1.


Figure 2.1: Diagram of the transition from the normal hematopoiesis to the chronic and accelerated acute phases in chronic myeloid leukemia. Here CP-CML means the chronic phase of chronic myeloid leukemia and AAP-CML means the accelerated acute phase of chronic myeloid leukemia.

A condition like $D = d$ or $D = (b_1/b_2)d$ is physiologically very unstable, since small variations of the parameters can switch the normal state into chronic phase and vice versa, in case that $D = d$, and the chronic phase into the accelerated acute phase and vice versa, in case that $D = (b_1/b_2)d$. Also, from a medical point of view, the situations $D = d$ and $D = (b_1/b_2)d$ are practically undetectable.

## 2.4 Global stability

### Global asymptotic stability of steady states

In the previous section we studied the local stability of the equilibria of system (2.4) and we shown that there is only one locally asymptotically stable equilibrium in each one of the three states: normal, chronic and accelerated acute, namely $(d, 0)$, $(x^*, y^*)$ and $(0, D)$, respectively. It is the aim of this section to show that in fact the stability of these stationary solutions is a global one.

**Theorem 2.4.1.** *For any positive saturated solution $u = (x, y)$ of system (2.4) one has:*

$$\begin{aligned}
&(i) \quad u(t) \rightarrow (d, 0) \quad as \quad t \rightarrow +\infty, \quad in\ case \quad D < d;\\
&(ii) \quad u(t) \rightarrow (x^*, y^*) \quad as \quad t \rightarrow +\infty, \quad in\ case \quad d < D < (b_1/b_2)\, d;\\
&(iii) \quad u(t) \rightarrow (0, D) \quad as \quad t \rightarrow +\infty, \quad in\ case \quad (b_1/b_2)\, d < D.
\end{aligned}$$

## 2.5 Numerical simulations

Numerical simulations of system (2.4) illustrating the theoretical results have been performed in the paper of L.G. Parajdi et al. [76], using the Maple package.

### Parameter estimations

Parameter estimation provides applicability of the mathematical model and it is particularly important when the model is applied for real-time predictions. Some parameter estimations have been obtained in the paper of D. Dingli and F. Michor [27], where it is estimated that the number of stem cells in a healthy adult is approximately

$$d = 2 \times 10^4 \quad \text{(normal homeostatic state)}.$$

The stem cells divide every 200 days and die every 500 days. Therefore, the growth and death rates of normal stem cells (per capita, per day) could be taken

$$a = \frac{1}{200} = 0.005 \quad \text{and} \quad c = \frac{1}{500} = 0.002.$$

In the case of our system (2.4), the factor $b_1/b_2$ allows for the possibility that the abnormal stem cells are less sensitive to the bone marrow microenvironment than the normal stem cells. However, recent studies have shown different growth rates of hematopoietic stem cells (HSCs). One recent study concluded that HSCs divide on average every 40 weeks, with a range from 25 to 50 weeks (see S. Catlin et al. [13]). The parameter $b_1$ standing for the bone marrow microenvironment sensitivity of the normal stem cells can be estimated from the following relationship

$$b_1 = \frac{\frac{a}{c} - 1}{d} = 0.75 \times 10^{-4}.$$

For our numerical simulations we choose value 2 for $b_1/b_2$ and then we have $b_2 \simeq 0.38 \times 10^{-4}$.

Parameters $A, B$ and $C$ vary from patient to patient, and so does parameter $D$. Like in D. Dingli and F. Michor [27], we assume that the value of parameter $B$ is approximately half of $b_2$, hence $B \simeq 0.19 \times 10^{-4}$. As regards the parameters $A$ and $C$, several values are considered in our simulations such that all the previous relationships between the model parameters hold.

### Numerical simulation of the model

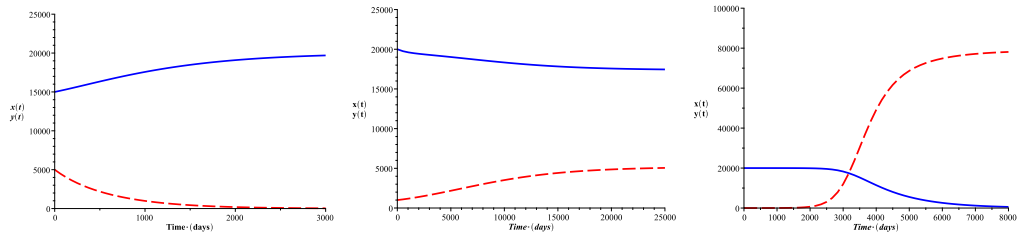
We shall numerically simulate the system (2.4) to investigate the behavior of normal and abnormal stem cell populations in the following cases: $D < d$ (normal state), $d < D < (b_1/b_2)d$ (chronic state) and $(b_1/b_2)d < D$ (accelerated acute state). The graphs of $x(t)$ (blue solid line) and $y(t)$ (red broken line) for a time interval $0 \leq t \leq T$, are represented for values of the model parameters: $a, b_1, b_2, c, A, B, C$, initial values $x(0)$, $y(0)$ and length $T$ of time interval. For example, if $a = 0.005$; $b_1 = 0.75 \times 10^{-4}$; $b_2 = 0.38 \times 10^{-4}$; $c = 0.002$; $A = 0.01$; $B = 0.19 \times 10^{-4}$ and $C = 0.004$.

| **Case I** | **Case II** | **Case III** |
|---|---|---|
| $a < A$ | $a < A$ | $a < A$ |
| $c < C$ | $c = C$ | $c > C$ |
| $b_1 > b_2 > B$ | $b_1 > b_2 > B$ | $b_1 > b_2 > B$ |

Table 2.1: The numerical simulation cases. $a, A$ = growth rates; $b_1, b_2, B$ = bone marrow microenvironment sensitivities; $c, C$ = death rates; $a, b_1, b_2, c$ = normal stem cell parameters and $A, B, C$ = abnormal (leukemic) stem cell parameters.

We shall restrict our simulations to the situations presented in Table 2.1. In all of the cases, we assume that the abnormal stem cells are less sensitive to environmental crowding (bone marrow microenvironment) than the normal stem cells, that is $b_1 > b_2 > B$.

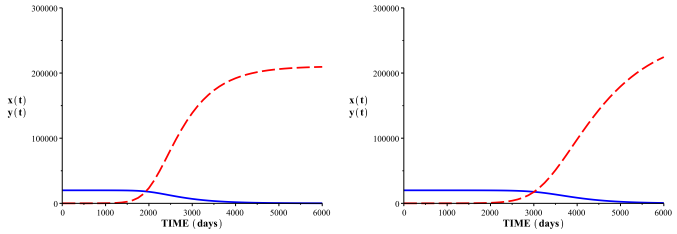
Case I : In this case the growth and death rates of normal stem cells are smaller than the growth and death rates of abnormal stem cells. Figure 2.2 (a) shows the behaviour in time ($T = 3000$ days) of the two cell populations for the parameter values from the first line of Table 2.2, which correspond to the normal hematopoietic state $D < d$. The normal stem cell population $x(t)$ (represented by blue solid line) tends to the value $d$ while the abnormal stem cell population $y(t)$ (represented by red broken line) tends towards 0. Biologically this mutant/leukemic cells extinction, due to random events, has been explained and demonstrated in several studies using stem cell lineages (see A. Jilkine and R. Gutenkunst [47], H. Snippert et al. [100], A. Klein et al. [55], G. Driessens et al. [31]). Figure 2.2 (b) shows the behaviour in time ($T = 25000$ days) of the two cell populations for the parameter values from the second line of Table 2.2, which correspond to the chronic state $d < D < (b_1/b_2)d$. The normal and abnormal stem cell populations $x(t)$, $y(t)$ tend toward $x^*$ and $y^*$, respectively. Figure 2.2 (c) shows the behavior in time ($T = 8000$ days) of the two cell populations for the corresponding parameter values from Table 2.2, which lead to the accelerated acute state $D > (b_1/b_2)d$. The normal stem cell population $x(t)$ tends towards 0, while the abnormal stem cell population $y(t)$ tends to the value $D$.




(a) Normal state (b) CP-CML state (c) AAP-CML state

Figure 2.2: Behaviour of the normal and abnormal stem cell populations in Case I. Initial conditions: (a) $x(0) = 1.5 \times 10^4$, $y(0) = 5 \times 10^3$; (b) $x(0) = 2 \times 10^4$, $y(0) = 1 \times 10^3$; (c) $x(0) = 2 \times 10^4$, $y(0) = 1$.

Case II and Case III : Assume now that in Case II the death rate of normal stem cells is equal to the death rate of abnormal stem cells and in Case III the death rate of normal stem cells is greater than the death rate of abnormal stem cells. In both cases the growth rate of normal stem cells is smaller than the growth rate of abnormal stem cells. Then $A/C > a/c$ and since $1/B > 1/b_2$, we immediately see that $(1/B)(A/C - 1) > (1/b_2)(a/c - 1)$, or equivalently $D > (b_1/b_2)d$. Hence, in this two cases only the accelerated acute state is possible. The Figures 2.3 (a) and 2.3 (b) show the behaviour in time ($T = 6000$ days) of the two cell populations for the corresponding parameter values from Table 2.2. As we can see, in the both cases the normal stem cell population $x(t)$ tends towards 0, while the abnormal stem cell population $y(t)$ tends to the value $D$.



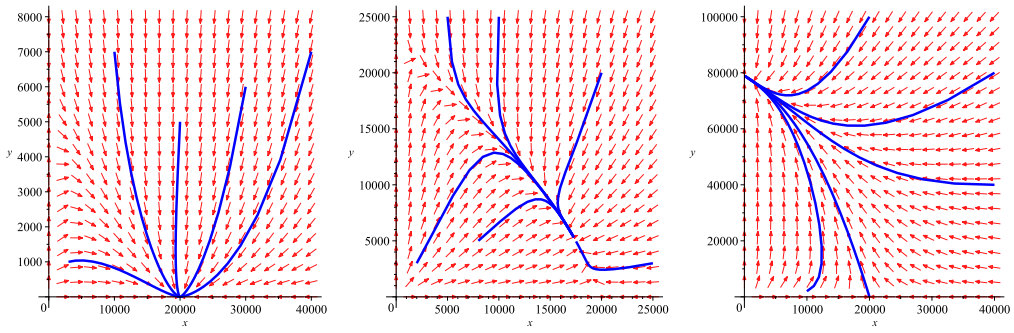

(a) AAP-CML state (b) AAP-CML state

Figure 2.3: Behavior of the normal and abnormal stem cell populations in Case II and Case III. Initial conditions: (a) $x(0) = 2 \times 10^4$, $y(0) = 1$; (b) $x(0) = 2 \times 10^4$, $y(0) = 1$.

| Fig. | $a$ | $b_1 \times 10^{-4}$ | $b_2 \times 10^{-4}$ | $c$ | $A$ | $B \times 10^{-4}$ | $C$ | $S - S$ |
|---|---|---|---|---|---|---|---|---|
| 2.2($a$) | 0.005 | 0.75 | 0.38 | 0.002 | 0.01 | 0.19 | 0.009 | $(d, 0)$ |
| 2.2($b$) | 0.005 | 0.75 | 0.38 | 0.002 | 0.01 | 0.19 | 0.007 | $(x^*, y^*)$ |
| 2.2($c$) | 0.005 | 0.75 | 0.38 | 0.002 | 0.01 | 0.19 | 0.004 | $(0, D)$ |
| 2.3($a$) | 0.005 | 0.75 | 0.38 | 0.002 | 0.01 | 0.19 | 0.002 | $(0, D)$ |
| 2.3($b$) | 0.005 | 0.75 | 0.38 | 0.002 | 0.006 | 0.19 | 0.001 | $(0, D)$ |

Table 2.2: Parameter values for simulations. S – S = steady state; $d = 2 \times 10^4$ (normal); D = variable parameter (abnormal).

Figure 2.4, shows the phase portrait of system (2.4) in the normal state $D < d$, in the chronic phase $d < D < (b_1/b_2)d$ and in the accelerated acute phase $(b_1/b_2)d < D$.




(a) Normal state (b) CP-CML state (c) AAP-CML state

Figure 2.4: The phase portrait of the two-dimensional system (2.4), in the normal state (a) $D < d$, in the CP-CML state (b) $d < D < (b_1/b_2)d$, and in the AAP-CML state (c) $(b_1/b_2)d < D$. The orbits $(x(t), y(t))$ approach the unique asymptotically stable equilibrium $(d, 0)$, in case (a); $(x^*, y^*)$, in case (b); and finally $(0, D)$, in case (c).

## 2.6 The extended model to terminally differentiated cells

Working at the level of primitive stem cells there is not a common way to determine the size of the two (normal and abnormal) cell populations. Therefore, it would be useful to have a reflection of the primitive stem cell evolution at the level of terminally differentiated cells, much easier to be estimated by current blood tests.

The idea first appears in F. Michor et al. [68], and applied to our mathematical model yields the extended system of eight equations

$$\begin{aligned}
&x_1'(t) = \tfrac{a_1 x_1}{1+b_1 x_1+b_2 y_1} - c_1 x_1 \quad \text{(NSC)} \qquad y_1'(t) = \tfrac{A_1 y_1}{1+B(x_1+y_1)} - C_1 y_1 \quad \text{(ASC)}\\
&x_2'(t) = a_2 x_1 - c_2 x_2 \qquad\qquad \text{(NPC)} \qquad y_2'(t) = A_2 y_1 - C_2 y_2 \qquad\qquad \text{(APC)}\\
&x_3'(t) = a_3 x_2 - c_3 x_3 \qquad\qquad \text{(NDC)} \qquad y_3'(t) = A_3 y_2 - C_3 y_3 \qquad\qquad \text{(ADC)}\\
&x_4'(t) = a_4 x_3 - c_4 x_4 \qquad\qquad \text{(NTC)} \qquad y_4'(t) = A_4 y_3 - C_4 y_4 \qquad\qquad \text{(ATC).}
\end{aligned}$$

Here $x_2(t)$, $y_2(t)$ stand for the normal (N) and abnormal (A) progenitor cell (PC) populations; $x_3(t)$, $y_3(t)$ stand for the normal and abnormal differentiated cell (DC) populations; and $x_4(t)$, $y_4(t)$ stand for the normal and abnormal terminally differentiated cell (TC) populations, respectively. The new parameters $a_2$, $A_2$ are the rates at which normal and abnormal progenitor cells are produced from normal and abnormal stem cells; $a_3$, $A_3$ are the rates at which normal and abnormal differentiated cells are produced from normal and abnormal progenitor cells; $a_4$, $A_4$ are the rates at which normal and abnormal terminally differentiated cells are produced from normal and abnormal differentiated cells and $c_2$, $c_3$, $c_4$, $C_2$, $C_3$, $C_4$ are the death rates of normal and abnormal progenitors, differentiated and terminally differentiated cells.

In the equilibrium state, we assume that in a healthy adult body the number of stem cells is $d = x_1^* = 2 \times 10^5$, the number of progenitor cells is $x_2^* = 1 \times 10^8$, the number of differentiated cells is $x_3^* = 1 \times 10^{10}$ and the number of terminally differentiated cells is $x_4^* = 1 \times 10^{12}$ (see F. Michor et al. [68]). Consequently, in the equilibrium state, we have for progenitor cells $a_2 x_1^* - c_2 x_2^* = 0$, whence $a_2/c_2 = x_2^*/x_1^* = 5 \times 10^2$, for differentiated cells $a_3 x_2^* - c_3 x_3^* = 0$, whence $a_3/c_3 = x_3^*/x_2^* = 1 \times 10^2$, and for terminally differentiated cells $a_4 x_3^* - c_4 x_4^* = 0$, hence $a_4/c_4 = x_4^*/x_3^* = 1 \times 10^2$. Therefore, if $c_2 = 0.008$, $c_3 = 0.05$ and $c_4 = 1$ (see F. Michor et al. [68]), then $a_2 = 4$, $a_3 = 5$, and $a_4 = 100$. Also we assume that $A_2 = 2a_2$, $A_3 = 2a_3$, $A_4 = a_4$ and $C_2 = c_2$, $C_3 = c_3$, $C_4 = c_4$.

Note that if

$$(x_{1E},\ y_{1E})$$

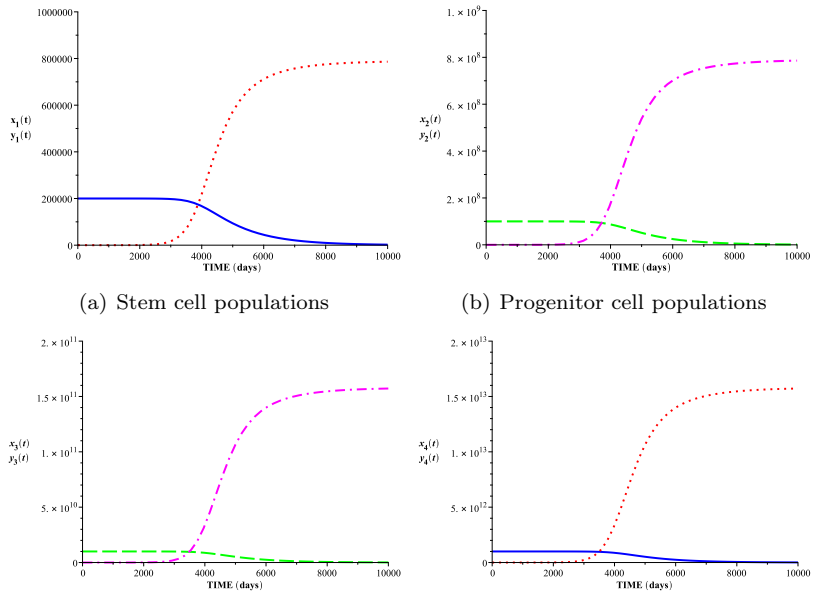
is any equilibrium (E) of the initial system (2.4), then

$$\begin{aligned}
&(x_{1E},\ y_{1E},\ a_2 x_{1E}/c_2,\ A_2 y_{1E}/C_2,\ a_2 a_3 x_{1E}/c_2 c_3,\ A_2 A_3 y_{1E}/C_2 C_3,\\
&a_2 a_3 a_4 x_{1E}/c_2 c_3 c_4,\ A_2 A_3 A_4 y_{1E}/C_2 C_3 C_4)
\end{aligned}$$

is an equilibrium of the extended system, and the two equilibria have the same stability property. Therefore, working at the level of primitive stem cells is equivalent to working at the level of any one of the succeeding classes of cells. Thus, if by blood tests one estimates the steady state ration $x_{4E}/y_{4E}$ between healthy and unhealthy terminally differentiated cells as being equal to $\lambda$, then we can immediately calculate the analogue steady state ratios of differentiated, progenitors and stem cells, as follows:

$$\frac{x_{3E}}{y_{3E}} = \lambda \frac{A_4 c_4}{a_4 C_4}, \quad \frac{x_{2E}}{y_{2E}} = \lambda \frac{A_3 A_4 c_3 c_4}{a_3 a_4 C_3 C_4}, \quad \frac{x_{1E}}{y_{1E}} = \lambda \frac{A_2 A_3 A_4 c_2 c_3 c_4}{a_2 a_3 a_4 C_2 C_3 C_4}.$$

Figures 2.5 (a)-(d) show that there is indeed a parallelism between the behaviours of normal and abnormal cell populations in all four cell compartments.




(a) Stem cell populations

(b) Progenitor cell populations

(c) Differentiated cell populations

(d) Terminally differentiated cell populations

Figure 2.5: Behavior of (a) stem cell populations, (b) progenitor cell populations, (c) differentiated cell populations and (d) terminally differentiated cell populations for the parameter values: $a_1 = 0.005$, $a_2 = 4$, $a_3 = 5$, $a_4 = 100$, $b_1 = 0.75 \times 10^{-5}$, $b_2 = 0.38 \times 10^{-5}$, $c_1 = 0.002$, $c_2 = 0.008$, $c_3 = 0.05$, $c_4 = 1$, $A_1 = 0.01$, $A_2 = 8$, $A_3 = 10$, $A_4 = 100$, $B = 0.19 \times 10^{-5}$, $C_1 = 0.004$, $C_2 = c_2$, $C_3 = c_3$, $C_4 = c_4$, and initial conditions: $x_1(0) = 2 \times 10^5$, $x_2(0) = 1 \times 10^8$, $x_3(0) = 1 \times 10^{10}$, $x_4(0) = 1 \times 10^{12}$, $y_1(0) = y_2(0) = y_3(0) = y_4(0) = 1$.

# Chapter 3
# Optimization Problems in Chronic Myeloid Leukemia

Many authors have studied different types of optimization problems applied in natural sciences, such as Y. Cherruault [16], C.J.S. Alves et al. [7], Y. Wang et al. [108] and G. Cedersund et al. [15]. From the numerous works in which there are studied optimization problems and optimal control applied in chronic myeloid leukemia we mention those of S. Nanda et al. [71], B. Ainseba and C. Benosman [5], Q. He et al. [37], S.B. Mendrazitsky et al. [65, 66].

What we are going to elaborate in this chapter, based on model (2.4), is a mathematical approach of optimal therapy for individual patients in chronic myeloid leukemia. More realistically, instead of aiming at a complete eradication of cancer, we explore hypothetical therapies directed at abnormal cells that shift the equilibrium towards the normal hematopoiesis and thus confer an advantage to the normal hematopoietic stem cells over their abnormal counterparts.

This chapter is structured in four sections. In **Section 3.1** we present the optimization problem based on mathematical model (2.4) presented in Chapter 2.

**Section 3.2** presents two therapeutic scenarios which are related to the main *objective* of diminishing the ratio $y^*/x^*$ of abnormal and normal cells under a prescribed threshold. Next, in **Section 3.3** we consider a drug that acts on more than one parameters and the results are compared with those from Section 3.2. It is proved that using a drug that inhibits simultaneously more than one kinetic parameter enables a smaller total dose/toxicity/cost compared to the single-parameter inhibition.

In the last **Section 3.4** we present an application based on the extended model to terminally differentiated cells, studied in Section 2.6 from Chapter 2. The main result in this section compares the results obtained when the drug acts over two classes of cells: progenitor cells and differentiated cells, to those obtained in case that the drug only acts on the class of progenitor cells.

Most of the results in this chapter are contained in the paper [77].

## 3.1 The optimization problem

The Dingli-Michor mathematical model (1), as well as model (2.4), were developed to describe the dynamics in the stem cell compartment, but they can be equally used for any other compartment of the hematopoiesis, such as the progenitor cell, differentiated cell, terminally differentiated cell compartment. Of course, the model parameters are different from one layer to another. Moreover, at any layer, the turnover rates include the transition rates to the next layer and the death rates, while the growth rates depend on the cell proliferation in the previous compartment (except for the first layer of primitive stem cells, where growth means self-regeneration).

Next, we shall perform the analysis under the assumption that at any layer, the condition $D < d/s$ is satisfied. For simplicity, our analysis is carried out only for the stem cell compartment in the marrow

such that the chronicity condition

$$d < D < \frac{d}{s}$$

holds, where $s = b_2/b_1$ and $s < 1$. Naturally, a better outcome is possible if several layers are simultaneously treated.

Since our treatment only improves the balance between abnormal and normal cells, we need some criteria for estimating the degree of illness and the response to the treatment.

The degree of disease can be estimated by the location of $D$ in the interval $[d, d/s]$. The further $D$ is from $d$, the higher is the leukemic burden. A precise measure of this location is the ratio

$$\frac{D-d}{\frac{d}{s}-D}.$$

Similarly one may consider the ratio $y^*/x^*$. In virtue of the expressions

$$x^* = \left(\frac{1}{s}-1\right)^{-1}\left(\frac{d}{s}-D\right) \quad \text{and} \quad y^* = (1-s)^{-1}(D-d),$$

between the two indicators, there is the following relation

$$\frac{y^*}{x^*} = \frac{1}{s}\cdot\frac{D-d}{\frac{d}{s}-D}. \tag{3.1}$$

Both indicators depend on the ratio $D/d$, which can serve itself as a measure of the degree of disease. Similarly, one may consider the ratio

$$\beta = \frac{y^*}{2x^*+y^*}, \tag{3.2}$$

which can be put into connection with routine laboratory assays such as the BCR-ABL percentage. This assay measures the relative expression of the abnormal BCR-ABL gene compared to that of ABL. However, since the ABL amplicon is also contained in the BCR-ABL, the denominator is proportional to both malignant and non-malignant cells. The factor 2 in (3.2) is needed since every non-malignant cell contains two ABL genes. Thus, in order to gain information about the leukemic burden from a certain compartment, the analysis should be carried out on a subpopulation of cells. Such an analysis is possible due to the fact that the hierarchy of hematopoiesis is well understood (see E. Hideo et al. [41]) and that the different types of cells can be discriminated by flow activated cell sorting (using fluorescent antibodies against surface markers, see L.A. Herzenberg et al. [40]). Although such a strategy is not routinely used in the clinical setting, the technology needed for such an approach is already available. Consequently, we can consider that the BCR-ABL percentage can be estimated for the stem cell compartment using appropriate cell surface markers.

Considering (2.6), any therapy directed at abnormal cells should decreases $D$ by increasing the turnover and sensitivity parameters $C$ and $B$ and by decreasing the growth rate $A$. By contrary, if the therapy is directed at normal cells, then an increase of $d$ is expected by decreasing the turnover and sensitivity parameters $c$, $b_1$ and by increasing the growth rate $a$. This type of intervention can be modeled using an indirect pharmacodynamic response. Let $d_m$, $D_m$, $s_m$, $x_m^*$, $y_m^*$ be the values of $d$, $D$, $s$, $x^*$ and $y^*$ modified by the therapy, and let the factors $v_1$, $v_2$, $v_3$, $v_4, v_5$ give the amplitude of modifications according to the following formulas

$$D_m = \frac{1}{v_2 B}\left(v_1\frac{A}{C}-1\right), \quad d_m = \frac{1}{v_4 b_1}\left(v_3\frac{a}{c}-1\right) \quad \text{and} \quad s_m = v_5 s,$$

where

$$v_1, v_4 \le 1, \quad v_2, v_3 \ge 1 \quad \text{and} \quad v_5 < s^{-1}. \tag{3.3}$$

Then $d < d_m$, $D > D_m$, $s_m < 1$, and if the chronic state still persists, i.e., $d_m < D_m < s_m^{-1} d_m$, then the following new homeostatic levels are reached

$$x_m^* = \left(\frac{1}{s_m} - 1\right)^{-1} \left(\frac{d_m}{s_m} - D_m\right) \quad \text{and} \quad y_m^* = (1 - s_m)^{-1} (D_m - d_m).$$

Note that if $v_5 = 1$, then $s_m = s$ and consequently the inequality

$$D_m < s_m^{-1} d_m \tag{3.4}$$

holds. In the opposite case, if $v_5 > 1$, then $s_m > s$ and there is a risk that the system shifts to an accelerated acute state, hence the condition (3.4) should be added as a constraint.

Assume that a drug modifies one or more kinetic parameters. The response of the system to the intervention can be described by an indirect pharmacodynamic response (see N.L. Dayneka et al. [25]) such as,

$$v(t) = 1 - \frac{C_p(t)}{C_p(t) + IC_{50}},$$

where $C_p$ represents the plasmatic concentration of the drug (or any other pharmacokinetic parameter, such as the area under the curve (AUC)) and $IC_{50}$ represents a constant that can be interpreted as the drug concentration producing 50% of the maximum inhibition. More generally, the response function depends on the pharmacokinetic parameter according to the following formula

$$v(t) = 1 - \frac{C_p^{\frac{1}{\theta}}(t)}{C_p^{\frac{1}{\theta}}(t) + IC_{50}},$$

where $\theta$ represents a parameter that controls the steepness of the response. Consider that the steady state serum concentration of the drug is proportional to the **dose** $J$ through a constant $\alpha$ and also that the inhibitory term depends directly on the dose and hence we can exclude the time dependence. Therefore, the response function of the kinetic parameter depends on the dose according to the following formula

$$v = 1 - \frac{(\alpha J)^{\frac{1}{\theta}}}{(\alpha J)^{\frac{1}{\theta}} + IC_{50}}.$$

By dividing the second term by $\alpha^{\frac{1}{\theta}}$ and renaming $IC_{50}/\alpha^{\frac{1}{\theta}}$ as $p$, we get

$$v = 1 - \frac{J^{\frac{1}{\theta}}}{J^{\frac{1}{\theta}} + p}.$$

By expressing $J$ in terms of $v$ and $p$, we obtain

$$J = p \left(\frac{1}{v} - 1\right)^{\theta}. \tag{3.5}$$

The formula (3.5) can be applied to $v_1$ and $v_4$, which are $\leq 1$. In the case of $v_2$, $v_3$ and $v_5$, which are $\geq 1$, the response function can be written as

$$J = p\,(v - 1)^{\theta}. \tag{3.6}$$

By combining (3.5) and (3.6) for the general case of a drug which modifies all kinetic parameters, we get for the dose $J$, the expression

$$J = p_1 \left(\frac{1}{v_1} - 1\right)^{\theta_1} + p_2\,(v_2 - 1)^{\theta_2} + p_3\,(v_3 - 1)^{\theta_3} + p_4 \left(\frac{1}{v_4} - 1\right)^{\theta_4} + p_5\,(v_5 - 1)^{\theta_5}. \tag{3.7}$$

Here, the positive exponents $\theta_1, \theta_2, \theta_3, \theta_4$ and $\theta_5$ give the rapidity of the growth of $J$ as $1/v_1, v_2, v_3, 1/v_4, v_5$ increase to infinity, respectively, and $p_1,\ p_2,\ p_3,\ p_4,\ p_5$ are the proportionality factors of the dose. This type of response could easily be applied to model other parameters, such as the **cost**, or the **toxicity** of a drug.

In particular, we may consider the expression

$$J = p_1 \left(\frac{1}{v_1} - 1\right) + p_2 (v_2 - 1) + p_3 (v_3 - 1) + p_4 \left(\frac{1}{v_4} - 1\right) + p_5 (v_5 - 1), \tag{3.8}$$

or its quadratic version

$$J = p_1 \left(\frac{1}{v_1} - 1\right)^2 + p_2 (v_2 - 1)^2 + p_3 (v_3 - 1)^2 + p_4 \left(\frac{1}{v_4} - 1\right)^2 + p_5 (v_5 - 1)^2. \tag{3.9}$$

Compared to (3.8), the expression (3.9), and more general (3.7), is much more sensitive to values of the amplitudes $v_1, ..., v_5$ far-off from the non-action value 1.

Note that the value 1 of any inhibition term $v_i$ means that the corresponding kinetic parameter is non modified. Thus, we may consider treatment protocols which modify only one of the five kinetic parameters, two, three, four or all five of them, without changing the expression of the objective function $J$. In each case, the problem is to find the factors $v_1, ..., v_5$ such that the total **dose/toxicity/cost** is minimal and the disease indicator is smaller than a desired value. Of course, different treatment regimens can give more or less the same minimal **dose/toxicity/cost**. Consequently, supplementary criteria (besides dose/toxicity/cost) that influence the therapeutic decision could also be added to our model. Thus a problem of a medical interest is to compare these protocols with respect to different additional criteria.

According to the chosen indicator and to the number of kinetic parameters influenced by the drug, we consider first the problem of optimal dosage of a drug that modifies only one kinetic parameter (a selective drug), and next a non-selective drug that simultaneously influences more than one kinetic parameter.

## 3.2 Optimal personalized dosing of a selective drug

By a selective drug one means a drug that acts only on a single parameter.

Assuming that using appropriate assays, the BCR-ABL level $\beta$ is calculated for the stem cell compartment. From the mathematical expression (3.2), the ration $y^*/x^*$ can be obtained, namely

$$\frac{y^*}{x^*} = \frac{2\beta}{(1-\beta)}.$$

Using (3.1), where $s$ is assumed to be $< 1$ (see Chapter 2), for example we choose $s$ to be $1/2$, one obtains the value of $D$,

$$D = (1+\beta)d,$$

and we consider two different scenarios.

**The first scenario.**
In the first scenario, we consider a drug which acts only on the proliferation rate A from the system (2.4). The expression of $D$ from (2.6), where $B$ is known, gives the relative proliferation rate $\rho = A/C$, namely

$$\rho = 1 + (1+\beta)Bd.$$

After diagnosis, the patient is treated with a standard dose $J_0$ and the response is assessed some time later by the new BCR-ABL $\beta_0$, which as above, gives the after-treatment relative proliferation rate

$$\rho_0 = 1 + (1+\beta_0)\, Bd.$$

Thus, after the start of the treatment, the relative proliferation rate $\rho$ has been modified by the factor $v_0 = \rho_0/\rho$. We notice that in the case of chronic leukemia, the time needed for the system to reach its new equilibrium state can be several years long. Now, from the expression of dose given by (3.8),

$$J = p\left(\frac{1}{v} - 1\right)^{\theta},$$

we can find the proportionality dosage factor $p$, namely

$$p = J_0 / \left(\frac{1}{v_0} - 1\right)^{\theta} = J_0 \left(\frac{1 + (1+\beta_0)Bd}{(\beta - \beta_0)Bd}\right)^{\theta}.$$

At this stage we are able to prescribe the personalized dose for a given target $\beta_*$, some time after reaching a new equilibrium state (for example $\beta_* = 0.05\%$),

$$J_1 = J_0 \left(\frac{(\beta - \beta_*)(1 + (1+\beta_0)Bd)}{(\beta - \beta_0)(1 + (1+\beta_*)Bd)}\right)^{\theta}.$$

It remains to make a choice for the exponent $\theta$. This can be done if we set a minimal threshold in response to the maximal dose $J_{max}$, such that if the response is above this value, then the treatment is considered ineffective. In the case of the terminally differentiated cell compartment, the European LeukemiaNet (ELN) guidelines states that after 18 months, the BCR-ABL should be below 1%. In the case of stem cells, new guidelines should be developed. Here, we consider that after receiving a maximal dose, the new BCR-ABL level should be at least the average between the level at diagnosis and the target BCR-ABL $(\beta_* + \beta)/2$. Thus, with $J_{\max}$ instead of $J_1$ and $(\beta_* + \beta)/2$ in the place of $\beta_0$, and taking the logarithm, we obtain

$$\theta = \frac{\ln\left(J_{\max}/J_0\right)}{\ln \gamma},$$

where

$$\gamma = \frac{2 + (2 + \beta_* + \beta)Bd}{1 + (1+\beta_*)Bd}.$$

It is worth noting that the dependence of $\theta$ on initial patient's degree of disease $\beta$, and the dependence of both proportionality dosage factor $p$ and optimal dose $J_1$ on $\beta$ and $\beta_0$, i.e., on patient's degree of disease and on the patient's response to the standard dose.

Under dose $J_1$, the BCR-ABL level should be maintained under the desired level $\beta_*$. However, in time, patients can develop resistance to the drug. In such a situation, a supplementary doses may be taken into consideration as a first alternative. The optimal supplementary dose $J_s$ can be determined by repeating the above procedure and is given by

$$J_s = J_{0s}\left(\frac{(\beta_n - \beta_*)(1 + (1+\beta_{n+1})Bd)}{(\beta_n - \beta_{n+1})(1 + (1+\beta_*)Bd)}\right)^{\theta_1},$$

where $\beta_n$ is the transcript level at the last *n-th* monitoring test, higher than the target one $\beta_*$, $J_{0s}$ is any supplementary testing dose, and $\beta_{n+1}$ is the response to the dose $J_1 + J_{0s}$. Also

$$\theta_1 = \frac{\ln\left(J_{\max} - J_1/J_{0s}\right)}{\ln \gamma_1}, \quad \gamma_1 = \frac{2 + (2 + \beta_* + \beta_n)Bd}{1 + (1+\beta_*)Bd}.$$

Hence the treatment should continue with the new dose $J_1 + J_s$. Theoretically, a supplementary dose may be considered at each monitoring test which shows a transcript level above $\beta_*$, provided that the equilibrium state has been achieved.

**The second scenario**.
In the second scenario, we consider a drug which acts only on the microenvironment sensitivity B from the system (2.4). Using (3.1), where $s$ is 1/2, we obtain the value for B,

$$B = \frac{A - C}{(1 + \beta)Cd},$$

which gives the sensitivity of abnormal cells.

We applied the same procedures like in the first scenario and we have the after-treatment value of the microenvironment sensitivity

$$B_0 = \frac{A - C}{(1 + \beta_0)Cd}.$$

After the treatment, the value of microenvironment sensitivity B has been modified by the factor $v_0 = B_0/B$.

We can find the proportionality dosage factor $p$ from

$$J_0 = p\,(v_0 - 1)^{\theta},$$

namely

$$p = J_0 \left(\frac{1 + \beta_0}{\beta - \beta_0}\right)^{\theta},$$

and we are able to prescribe the personalized dose for a given target $\beta_*$, that is

$$J_1 = J_0 \left(\frac{(\beta - \beta_*)(1 + \beta_0)}{(\beta - \beta_0)(1 + \beta_*)}\right)^{\theta}.$$

It remains to determine the exponent $\theta$ by applying the same idea like in the first scenario. In the same way we obtain

$$\theta = \frac{\ln\left(J_{max}/J_0\right)}{\ln \gamma}, \quad \text{where} \quad \gamma = \frac{2 + \beta_* + \beta}{1 + \beta_*}.$$

## 3.3 Non-specific drug optimization problems

In this section we refer to non-specific drugs, i.e., drugs that act over more than one parameters.

**First non-specific drug optimization problem.**
The recent improvement in drug manufacturing knowledge has led to the development of targeted therapies which can alter a specific pathway of the disease. Although this strategy could decrease toxicity by lowering the off-target effects, using targeted therapies can also lead to a decrease in efficacy by enabling the tumor more escape mechanisms.

Our first multi-drug scenario has as main objective to guarantee, with minimal **dose/toxicity/cost**, that the ratio between the modified and the initial leukemic homeostatic values $D_m$ and $D$ is under a chosen number $q < 1$, and that the ratio between the modified and the initial normal homeostatic values $d_m$ and $d$ is larger than some given number $r > 1$, that is

$$D_m \leq qD \quad \text{and} \quad d_m \geq rd.$$

The above-mentioned inequalities give

$$\frac{D_m}{d_m} \leq qr^{-1}\frac{D}{d},$$

where $qr^{-1} < 1$, ensuring an improved degree of the disease with respect to the estimation indicator $D/d$. For simplicity, we assume that the relative sensitivity parameter $s$ is not modified, hence $v_5 = 1$,

which guarantees that the system remains in the chronic leukemic state $D_m < s^{-1}d_m$. Thus, for the first non-specific drug optimization problem, the **dose/toxicity/cost** function of type (3.8) is

$$J = p_1\left(\frac{1}{v_1} - 1\right) + p_2\left(v_2 - 1\right) + p_3\left(v_3 - 1\right) + p_4\left(\frac{1}{v_4} - 1\right).$$

Finding the parameters $v_1, v_2, v_3$ and $v_4$ means to solve the **constrained convex optimization problem** with the objective function $J$,

$$\begin{array}{l} \text{Minimize} \;\; J \\ \text{Subject to} \;\; \varphi_i\left(v\right) \leq 0, \quad i = 1, .., 6, \end{array}$$

where $v = (v_1, v_2, v_3, v_4) \in \mathbb{R}^4_+$,

$$\begin{aligned} \varphi_1\left(v\right) &= v_1 - 1, \quad \varphi_2\left(v\right) = 1 - v_2, \\ \varphi_3\left(v\right) &= v_1\frac{A}{BC} - v_2 q\left(\frac{A}{BC} - \frac{1}{B}\right) - \frac{1}{B}, \\ \varphi_4\left(v\right) &= 1 - v_3, \quad \varphi_5\left(v\right) = v_4 - 1, \\ \varphi_6\left(v\right) &= -v_3\frac{a}{b_1 c} + v_4 r\left(\frac{a}{b_1 c} - \frac{1}{b_1}\right) + \frac{1}{b_1}. \end{aligned}$$

To solve this problem, we use the Kuhn-Tucker Theorem (see V.G. Karmanov [51] and M. Luptáčik [58]). Let $L\left(v, u\right)$ be the Lagrangian associated to the convex optimization problem

$$L\left(v, u\right) = J\left(v\right) + \left\langle u, \varphi\left(v\right)\right\rangle,$$

where $u \in \mathbb{R}^6_+$, $\varphi\left(v\right)$ is the vector $\left(\varphi_1\left(v\right), .., \varphi_6\left(v\right)\right)$ and by $\left\langle u, \varphi\left(v\right)\right\rangle$ we mean $u_1\varphi_1\left(v\right) + .. + u_6\varphi_6\left(v\right)$. Then, a solution of the optimization problem is a point $v \in \mathbb{R}^4_+$ for which there is $u \in \mathbb{R}^6_+$ such that the couple $u, v$ is a saddle point of the Lagrangian

$$\begin{aligned} \nabla_v L\left(v, u\right) &\geq 0, \\ \left\langle v, \; \nabla_v\left(v, u\right)\right\rangle &= 0, \\ \nabla_u L\left(v, u\right) &\leq 0, \\ \left\langle u, \; \nabla_u\left(v, u\right)\right\rangle &= 0. \end{aligned} \tag{3.10}$$

Assume that $v_i \neq 1$ for $i = 1, .., 4$, meaning that the first four parameters are all effectively altered. Since $\nabla_u L\left(v, u\right)$ is the vector

$$\begin{array}{c} \left(v_1 - 1, \; 1 - v_2, \; v_1\frac{A}{BC} - v_2 q\left(\frac{A}{BC} - \frac{1}{B}\right) - \frac{1}{B}, \right. \\ \left. 1 - v_3, \; v_4 - 1, \; -v_3\frac{a}{b_1 c} + v_4 r\left(\frac{a}{b_1 c} - \frac{1}{b_1}\right) + \frac{1}{b_1}\right), \end{array}$$

from the last two conditions in (3.10), we find

$$u_1 = u_2 = u_4 = u_5 = 0,$$

while from the first two conditions in (3.10),

$$\nabla_v L\left(v, u\right) = 0,$$

that is

$$\begin{aligned} -\frac{p_1}{v_1^2} + u_3\frac{A}{BC} &= 0, \\ p_2 - u_3 q\left(\frac{A}{BC} - \frac{1}{B}\right) &= 0, \\ p_3 - u_6\frac{a}{b_1 c} &= 0, \\ -\frac{p_4}{v_4^2} + u_6 r\left(\frac{a}{b_1 c} - \frac{1}{b_1}\right) &= 0. \end{aligned}$$

Solving yields

$$u_3 = \frac{p_2 BC}{q(A-C)}, \quad u_6 = \frac{p_3 b_1 c}{a}\ , \quad v_1 = \left(\frac{p_1 q(A-C)}{p_2 A}\right)^{\frac{1}{2}}, \quad v_4 = \left(\frac{a p_4}{p_3 r\,(a-c)}\right)^{\frac{1}{2}}.$$

Finally, since $u_3 \neq 0$ and $u_6 \neq 0$, using again the first two conditions in (3.10) one obtains $v_2$ and $v_3$, and thus the optimal solution

$$\begin{aligned} v_1 &= \left(\frac{p_1 q(A-C)}{p_2 A}\right)^{\frac{1}{2}}, \quad v_2 = \frac{\left(\frac{p_1 q A(A-C)}{p_2}\right)^{\frac{1}{2}} - C}{q(A-C)}, \\ v_3 &= \frac{\left(\frac{p_4 r a(a-c)}{p_3}\right)^{\frac{1}{2}} + c}{a}, \quad v_4 = \left(\frac{a p_4}{p_3 r\,(a-c)}\right)^{\frac{1}{2}}. \end{aligned}$$

It is worth mentioning that the conditions on $v_i$ ensure that the corresponding optimal solution is different from 1, meaning that the *i-th* parameter is modified. Thus, in terms of the relative growth rates $A/C$ and $a/c$ of abnormal and normal cells, we have

$$\begin{aligned} v_1 &< 1 \quad \text{if and only if} \quad \frac{p_1}{p_2} > \frac{\left(q\left(\frac{A}{C}-1\right)+1\right)^2}{q\frac{A}{C}\left(\frac{A}{C}-1\right)}, \\ v_2 &> 1 \quad \text{if and only if} \quad \frac{p_1}{p_2} < \frac{\frac{A}{C}}{q\left(\frac{A}{C}-1\right)}, \\ v_3 &> 1 \quad \text{if and only if} \quad \frac{p_4}{p_3} > \frac{\frac{a}{c}-1}{r\frac{a}{c}}, \\ v_4 &< 1 \quad \text{if and only if} \quad \frac{p_4}{p_3} < \frac{r\left(\frac{a}{c}-1\right)}{\frac{a}{c}}. \end{aligned}$$

Despite the above given analytical solution, a numerical one is possible and easy to obtain using Matlab, Maple or Mathematica computer software.

**Second non-specific drug optimization problem.**
Our second non-specific drug scenario uses a similar approach to the previous one, but this time the response is evaluated in terms of $y^*/x^*$. Therefore, we impose a condition on the ratio $y^*/x^*$

$$\frac{y_m^*}{x_m^*} \leq k\frac{y^*}{x^*} \tag{3.11}$$

where $y^*/x^*$, $y_m^*/x_m^*$ are the pre-treatment and after-treatment disease indicators, respectively, and $k < 1$ is a target coefficient. Thus, in this case, the problem is to optimize the objective function $J$ given by (3.8) (or (3.9)) under the constraints (3.3), (3.4) and (3.11). The results of this optimization problem are similar to the previous one.

## 3.4 Optimal personalized dosing of a selective drug based on the extended model to terminally differentiated cells

Here we consider the following extended mathematical model, presented in Section 2.6, where we include the modifications of parameters due to the treatment by the factors $v_0$ and $v_1$:

$$\begin{aligned}
&x_1'(t) = \tfrac{a_1 x_1}{1+b_1x_1+b_2y_1} - c_1x_1 \quad \text{(NSC)} \qquad y_1'(t) = \tfrac{A_1y_1}{1+B(x_1+y_1)} - C_1y_1 \quad \text{(ASC)}\\
&x_2'(t) = a_2x_1 - c_2x_2 \qquad\qquad \text{(NPC)} \qquad y_2'(t) = v_0A_2y_1 - C_2y_2 \qquad\quad \text{(APC)}\\
&x_3'(t) = a_3x_2 - c_3x_3 \qquad\qquad \text{(NDC)} \qquad y_3'(t) = v_1A_3y_2 - C_3y_3 \qquad\quad \text{(ADC)}\\
&x_4'(t) = a_4x_3 - c_4x_4 \qquad\qquad \text{(NTC)} \qquad y_4'(t) = A_4y_3 - C_4y_4 \qquad\quad \text{(ATC).}
\end{aligned}$$

First we assume that the drug (for example Imatinib) acts over parameters $A_2$ and $A_3$ (see F. Michor et al. [68]). Note that the effect over other parameters of Imatinib and of other used drugs, is not clarified in the literature.

The BCR-ABL percentage is given by the formula

$$\beta = \frac{y_4^*}{2x_4^* + y_4^*}, \tag{3.12}$$

whence

$$\frac{y_4^*}{x_4^*} = \frac{2\beta}{1-\beta}.$$

Furthermore, using the eight-dimensional system from Section 2.6, we obtained the product $\rho = A_2A_3$ of the rate at which abnormal progenitor cells and abnormal differentiated cells proliferate, in terms of $\beta$ and of the other parameters, namely

$$\rho = \frac{2\beta\,(d-sD)\,C_2C_3C_4a_4a_3a_2}{(1-\beta)\,(D-d)\,A_4c_2c_3c_4}.$$

After diagnosis, the patient is treated with a standard dose $J_0$ (for example $J_0 = 400$ mg) and the response is assessed some time later (for example 2 years later), by the new BCR-ABL $\beta_0$, which gives the after-treatment product of the rate at which abnormal progenitor cells and abnormal differentiated cells proliferate,

$$\rho_0 = \frac{2\beta_0\,(d-sD)\,C_2C_3C_4a_4a_3a_2}{(1-\beta_0)\,(D-d)\,A_4c_2c_3c_4}.$$

Hence, we have

$$v_0v_1 = \frac{\rho_0}{\rho} = \frac{\beta_0\,(1-\beta)}{\beta\,(1-\beta_0)}.$$

Let us consider for the one-drug dose, the following expression

$$J = p\left(\frac{1}{v_0v_1} - 1\right)^{\theta}.$$

Then the proportionality dosage factor $p$ is

$$p = J_0/\left(\frac{1}{v_0v_1} - 1\right)^{\theta} = J_0\left(\frac{\beta_0\,(1-\beta)}{\beta-\beta_0}\right)^{\theta}.$$

At this stage we are able to prescribe the personalized dose of the drug for a given target $\beta_* = 0.005\%$, some time after at reaching a new equilibrium state:

$$J_1 = p\left(\frac{\beta-\beta_*}{\beta_*\,(1-\beta)}\right)^{\theta} = J_0\left(\frac{\beta_0\,(\beta-\beta_*)}{\beta_*\,(\beta-\beta_0)}\right)^{\theta}. \tag{3.13}$$

A maximal dose $J_{max}$ is prescribed in the case of an admissible response to the standard dose $J_0$, equal to or less than 10%, where it is consider that the drug is inefficient and thus it has to be replaced if the response is above 10% (see Table 6 from A. Hochhaus et al. [42]).

In order that the personalized dose expresion (3.13) be effective, we need to determine the exponent $\theta$. To this aim, with $J_{max}$ instead of $J_1$ and 10% in the place of $\beta_0$, and taking the logarithm, we obtain

$$\theta = \frac{\ln\left(J_{\max}/J_0\right)}{\ln\gamma}, \quad \text{where} \quad \gamma = \frac{0.1\left(\beta-\beta_*\right)}{\beta_*\left(\beta-0.1\right)}.$$

Next, we perform numerical simulations using the optimal personalized dose formula.

| BCR-ABL of untreated patient | BCR-ABL after standard dose $[0.01\% - 0.1\%]$ | BCR-ABL the target value $< 0.01\%$ | $J_{max}$ maximum dose | $J_0$ initial standard dose | $J_{opt}$ optimal dose |
|---|---|---|---|---|---|
| $\beta = 99\%$ | $\beta_0 = 0.09\%$ | $\beta_* = 0.005\%$ | 800 mg | 400 mg | 518.78 mg |
| $\beta = 96\%$ | $\beta_0 = 0.05\%$ | $\beta_* = 0.005\%$ | 800 mg | 400 mg | 492.00 mg |
| $\beta = 99\%$ | $\beta_0 = 0.04\%$ | $\beta_* = 0.005\%$ | 800 mg | 400 mg | 482.27 mg |
| $\beta = 98\%$ | $\beta_0 = 0.03\%$ | $\beta_* = 0.005\%$ | 800 mg | 400 mg | 469.93 mg |
| $\beta = 97\%$ | $\beta_0 = 0.09\%$ | $\beta_* = 0.005\%$ | 800 mg | 400 mg | 518.74 mg |

Table 3.1: Simulations of optimal personalized dose formula based on the extended mathematical model.

In what follows we prove that the same results are obtained in case that the drug acts only on $A_2$ which is the rate at which abnormal progenitor cells are produced from abnormal stem cells. Hence, we assume that $v_1 = 1$, and the extended mathematical model reduces to,

$$\begin{aligned}
&x_1'(t) = \tfrac{a_1 x_1}{1+b_1 x_1+b_2 y_1} - c_1 x_1 \quad \text{(NSC)} \qquad y_1'(t) = \tfrac{A_1 y_1}{1+B(x_1+y_1)} - C_1 y_1 \quad \text{(ASC)}\\
&x_2'(t) = a_2 x_1 - c_2 x_2 \qquad\qquad \text{(NPC)} \qquad y_2'(t) = v_0 A_2 y_1 - C_2 y_2 \qquad\quad \text{(APC)}\\
&x_3'(t) = a_3 x_2 - c_3 x_3 \qquad\qquad \text{(NDC)} \qquad y_3'(t) = A_3 y_2 - C_3 y_3 \qquad\quad \text{(ADC)}\\
&x_4'(t) = a_4 x_3 - c_4 x_4 \qquad\qquad \text{(NTC)} \qquad y_4'(t) = A_4 y_3 - C_4 y_4 \qquad\quad \text{(ATC).}
\end{aligned}$$

The BCR-ABL percentage is given by the formula (3.12), where the ration

$$\frac{y_4^*}{x_4^*} = \frac{2\beta}{1-\beta}.$$

From the extended model presented in Section 2.6, we obtained the rate $\rho = A_2$, at which abnormal progenitor cells are produced from abnormal stem cells, namely

$$\rho = \frac{2\beta\left(d-sD\right)C_2C_3C_4a_4a_3a_2}{\left(1-\beta\right)\left(D-d\right)A_4A_3c_2c_3c_4}.$$

After diagnosis, the patient is treated whit a standard dose $J_0$ (for example $J_0 = 400$ mg) and the response is assessed some time later (for example 2 years later), by the new BCR-ABL $\beta_0$, which gives the after-treatment rate at which abnormal progenitor cells proliferate,

$$\rho_0 = \frac{2\beta_0\left(d-sD\right)C_2C_3C_4a_4a_3a_2}{\left(1-\beta_0\right)\left(D-d\right)A_4A_3c_2c_3c_4}.$$

Hence, we have

$$v_0 = \frac{\rho_0}{\rho} = \frac{\beta_0\left(1-\beta\right)}{\beta\left(1-\beta_0\right)}.$$

From the expression of one-drug dose

$$J = p\left(\frac{1}{v_0} - 1\right)^{\theta},$$

we have the proportionality dosage factor $p$, namely

$$p = J_0\left(\frac{\beta_0\,(1-\beta)}{\beta - \beta_0}\right)^{\theta}.$$

Next, we are able to prescribe the personalized dose of drug for a given target $\beta_* = 0.005\%$, some time after reaching a new equilibrium state (for example at 5 years later)

$$J_1 = p\left(\frac{\beta - \beta_*}{\beta_*\,(1-\beta)}\right)^{\theta} = J_0\left(\frac{\beta_0\,(\beta - \beta_*)}{\beta_*\,(\beta - \beta_0)}\right)^{\theta}.$$

A maximal dose $J_{max}$ is prescribed in the case of an admissible response to the standard dose $J_0$, equal to or less than 10%, where it is consider that the drug is inefficient and thus it has be replaced if the response is above 10%. With $J_{max}$ instead of $J_1$ and 10% in the place of $\beta_0$ and taking the logarithm, we obtain

$$\theta = \frac{\ln\left(J_{\max}/J_0\right)}{\ln\gamma}, \quad \text{where} \quad \gamma = \frac{0.1\,(\beta - \beta_*)}{\beta_*\,(\beta - 0.1)}.$$

Therefore, we have the following conclusion:

**Conclusion 3.4.1.** *The product of the factors $v_0$, $v_1$ giving the amplitude of modifications when the drug acts simultaneously over $A_2$ and $A_3$, is equal with the modification factor when the drug is assumed to act only on the class of progenitor cells, if we consider for the one-drug dose, the following expression:*

$$J = p\left(\frac{1}{v} - 1\right)^{\theta},$$

*where $v$ can be equal with the product of $v_0$ and $v_1$ or with $v_0$ in the second case.*

# Chapter 4
# Mathematical Modeling of Stem Cell Transplantation in CML

Among the important papers which approach the topic regarding mathematical modeling of stem cell transplantation, we mention the following: P.C. Vincent et al. [105], R. De Conde et al. [26], P.S. Kim et al. [53], A. Marciniak-Czochra and T. Stiehl [63], R. Precup et al. [81, 84], R. Precup [79] and T. Stiehl et al. [102]. Some review works on mathematical models for cancer, particularly for chronic myeloid leukemia, are the papers of H. Moore and N.K. Li [69], E. Afenya [3], F. Michor [67], C. Foley and M.C. Mackey [33], G. Clapp and D. Levy [19].

In this chapter of the thesis we give a mathematical model of stem cell dynamics after allogeneic bone marrow transplantation in chronic myeloid leukemia. This model is essentially based on the basic model (2.4) from Chapter 2.

The chapter is structured in four sections. In the first **Section 4.1** we present the three-dimensional mathematical model (4.1), which describes the dynamics of normal host $x(t)$, abnormal host $y(t)$ and donor $z(t)$ stem cell populations after bone marrow transplantation in myeloid leukemia, along with the biological interpretation of the parameters.

In **Section 4.2** we make a qualitative analysis of the three-dimensional system (4.1), namely we deal with the existence and uniqueness of solutions, and boundedness of solutions.

**Section 4.3** presents the steady states of the system, and their local stability.

The last **Section 4.4** presents a number of time-series representations and phase portraits of the three-dimensional system, which confirm the already obtained theoretical results.

The results in this chapter are contained in the paper [74].

## 4.1 The mathematical model

The basic idea of mathematical modeling of stem cell transplantation appears in the papers of R. Precup et al. [85, 81]. The idea consists in adding, at time $t = 0$, in competition with $x_0$ and $y_0$ (host cells) a new population $z_0$ (donor cells). If the combativeness of $z$ against $x$ and $y$ (graft versus host and graft versus leukemia) compensates that of the $x$ and $y$ against $z$ (anti graft effect), and if the initial conditions $x_0$ and $y_0$ are small enough as compared with $z_0$, then in time, host cells are eliminated and they are replaced by donor cells, guaranteeing the elimination of leukemia. Mathematically, a new equation in $z$ was added to the basic model of Dingli-Michor in order to incorporate the new competition between the donor cell population noted by $z$ and normal respectively abnormal cell populations noted by $x$ and $y$, respectively. It is supposed that intrinsic growth rate, bone marrow microenvironment sensitivity and the death rate of the donor cell population are those of the normal host cell population, namely $a$, $b$ and $c$.

In this chapter, a similar model of stem cell transplantation is introduced starting from the more refined system (2.4). Compared with the initial model considered by R. Precup et al. [81], our

mathematical model makes distinction between the chronic and accelerated acute/blast phases at transplantation.

Therefore, based on the normal-abnormal system (2.4), we consider the following mathematical model for the post-transplant cell evolution

$$\begin{cases} x'(t) = \frac{ax(t)}{1+b_1(x(t)+z(t))+b_2y(t)} \ \frac{x(t)+y(t)}{x(t)+y(t)+gz(t)} - cx(t) \\ y'(t) = \frac{Ay(t)}{1+B(x(t)+y(t)+z(t))} \frac{x(t)+y(t)}{x(t)+y(t)+Gz(t)} - Cy(t) \\ z'(t) = \frac{az(t)}{1+b_1(x(t)+z(t))+b_2y(t)} \frac{z(t)}{z(t)+h(x(t)+y(t))} - cz(t), \end{cases} \tag{4.1}$$

where $x$, $y$ and $z$ stands for normal host cells, abnormal (or leukemic) host cells, and donor cells. The growth inhibitory factors

$$\frac{1}{1+g\frac{z}{x+y}}, \quad \frac{1}{1+G\frac{z}{x+y}} \quad \text{and} \quad \frac{1}{1+h\frac{x+y}{z}}$$

take into consideration the cell-cell interactions, quantitatively by ratio $z/(x+y)$ and $(x+y)/z$ and qualitatively by parameters $h$, $g$ and $G$ which represents the intensity of the anti-host, anti-leukemia and anti-graft effects.

The parameters $a$, $b_1$, $b_2$, $c$, $A$, $B$, $C$, $g$, $G$, and $h$ are assumed to be positive, with $a > c$, $A > C$, and $b_1 > b_2 > B$. Recall from Chapter 2 that the chronic phase of chronic myeloid leukemia is characterized by the inequality

$$d < D < \alpha d,$$

while the accelerated acute phase corresponds to the inequality

$$\alpha d < D,$$

where

$$d = \frac{1}{b_1}\left(\frac{a}{c} - 1\right), \quad D = \frac{1}{B}\left(\frac{A}{C} - 1\right) \quad \text{and} \quad \alpha = \frac{b_1}{b_2}$$

with $\alpha > 1$.

## 4.2 Existence and uniqueness of solutions

As for the two-dimensional system (2.4), we discuss the initial value problem associated to system (4.1).

### Existence and uniqueness

**Theorem 4.2.1.** *For any $t_0 \geq 0$ and $u_0 = (x_0, y_0, z_0) \in (0, +\infty)^3$, there is a unique saturated solution $u = u(\cdot, t_0, u_0) = (x, y, z)$ of system (4.1) which is defined on the whole semiline $[t_0, +\infty)$, is of class $C^\infty$, with $x > 0$, $y > 0$ and $z > 0$ on $[t_0, +\infty)$, and satisfies the initial condition*

$$u(t_0) = u_0.$$

### Boundedness of solutions

**Theorem 4.2.2.** *The solution $u = u(\cdot, t_0, u_0)$ is bounded on $[t_0, +\infty)$ for every $t_0 \geq 0$ and $u_0 \in (0, +\infty)^3$.*

## 4.3 Steady states and stability

### Steady states

The steady states of system (4.1) are obtained by solving the algebraic system

$$U(x,y,z) \equiv \frac{ax}{1+b_1x+b_2y+b_1z}\,\frac{x+y}{x+y+gz} - cx = 0 \tag{4.2a}$$

$$V(x,y,z) \equiv \frac{Ay}{1+B(x+y+z)}\,\frac{x+y}{x+y+Gz} - Cy = 0 \tag{4.2b}$$

$$W(x,y,z) \equiv \frac{az}{1+b_1x+b_2y+b_1z}\,\frac{z}{z+h(x+y)} - cz = 0. \tag{4.2c}$$

We solve this algebraic system looking successively for solutions having first $x=0$, then $y=0$, $z=0$, and finally when $x,y,z$ are different from zero.

We obtain seven solutions:

$$\begin{aligned} &P_1(d,0,0); \quad P_2(0,D,0); \quad P_3(0,0,d); \quad P_4(x^*,y^*,0);\\ &P_5(x^+,0,z^+); \quad P_6(0,y^{++},z^{++}) \ \text{ and } \ P_7(x^\#,y^\#,z^\#). \end{aligned} \tag{4.3}$$

Here

$$x^* = \frac{b_2}{b_1-b_2}(\alpha d - D), \quad y^* = \frac{b_1}{b_1-b_2}(D-d), \tag{4.4}$$

$$x^+ = \frac{\frac{a}{c(1+\sqrt{gh})}-1}{b_1\left(1+\sqrt{\frac{h}{g}}\right)}, \quad z^+ = \sqrt{\frac{h}{g}}x^+, \tag{4.5}$$

$$x^\# = \frac{b_1\left(1+\sqrt{\frac{g}{h}}\right)\left(1+G\sqrt{\frac{h}{g}}\right)\left(d-\frac{1}{b_1}\sqrt{gh}\right)-\left(1+\sqrt{gh}\right)\left(b_1+b_2\sqrt{\frac{g}{h}}\right)\left(D-\frac{G}{B}\sqrt{\frac{h}{g}}\right)}{(b_1-b_2)\left(1+\sqrt{gh}\right)\left(1+\sqrt{\frac{g}{h}}\right)\left(1+G\sqrt{\frac{h}{g}}\right)}, \tag{4.6}$$

$$y^\# = \frac{b_1}{b_1-b_2}\left(\frac{\left(1+\sqrt{gh}\right)\left(D-\frac{G}{B}\sqrt{\frac{h}{g}}\right)-\left(1+G\sqrt{\frac{h}{g}}\right)\left(d-\frac{1}{b_1}\sqrt{gh}\right)}{\left(1+G\sqrt{\frac{h}{g}}\right)\left(1+\sqrt{gh}\right)}\right) \tag{4.7}$$

and

$$z^\# = \frac{D-\frac{G}{B}\sqrt{\frac{h}{g}}}{\left(1+\sqrt{\frac{g}{h}}\right)\left(1+G\sqrt{\frac{h}{g}}\right)}, \tag{4.8}$$

while $(y^{++},z^{++})$ represents the solution of the two-dimensional algebraic system

$$\begin{cases} \frac{A}{1+B(y+z)}\frac{y}{y+Gz} - C = 0\\ \frac{a}{1+b_2y+b_1z}\frac{z}{z+hy} - c = 0. \end{cases} \tag{4.9}$$

We are only interested into solutions with nonnegative components. Such solutions are called *admissible* for system (4.1) from biological reasons. We now discuss the positivity of the solutions of algebraic system (4.2a)-(4.2c) for each one of the cases: chronic, and accelerated acute.

**Admissible steady states in the chronic case:**
We consider the system (4.1) in the chronic case. Hence

$$a > c, \quad A > C, \quad b_1 > b_2 > B \ \text{ and } \ d < D < \alpha d. \tag{4.10}$$

We have the following conclusions.

**Theorem 4.3.1.** *Let the assumptions* (4.10) *hold.*
*(i) The steady states* $P_1(d,0,0)$, $P_2(0,D,0)$, $P_3(0,0,d)$, *and* $P_4(x^*,y^*,0)$ *are admissible.*
*(ii) The steady state* $P_5(x^+,0,z^+)$ *is admissible if and only if*

$$gh < \left(\frac{a}{c}-1\right)^2.$$

*(iii) The steady state* $P_6(0,y^{++},z^{++})$ *is admissible if and only if*

$$Gh < \left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right).$$

*(iv) The steady state* $P_7(x^{\#},y^{\#},z^{\#})$ *is admissible if and only if*

$$Gh < \left(\frac{A}{C}-1\right)\sqrt{gh} < \left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right),$$

*and*

$$\frac{1+\sqrt{gh}}{1+G\sqrt{\frac{h}{g}}} > \frac{d-\frac{1}{b_1}\sqrt{gh}}{D-\frac{G}{B}\sqrt{\frac{h}{g}}} > \frac{\left(1+\sqrt{gh}\right)\left(b_1+b_2\sqrt{\frac{g}{h}}\right)}{b_1\left(1+\sqrt{\frac{g}{h}}\right)\left(1+G\sqrt{\frac{h}{g}}\right)}.$$

**Admissible steady states in the accelerated acute case:**
Let system (4.1) be in the accelerated acute case, that is

$$a > c, \quad A > C, \quad b_1 > b_2 > B \quad \text{and} \quad \alpha d < D. \tag{4.11}$$

In this case we have the same conclusions about the admissibility of the steady states of system (4.1) like in the chronic case, except the point $P_4(x^*,y^*,0)$ which is not admissible since $x^* < 0$, in view of the condition $\alpha d < D$.

## Local stability of steady states

The discussion which follows is about the local stability of the steady states of system (4.1). We study the local stability in each one of the two cases: chronic and accelerated acute.

**Stability analysis for the chronic phase of CML**

**Theorem 4.3.2.** *Let* $a, b_1, b_2, c, A, B, C, g, G, h$ *be positive parameters such that* (4.10) *holds. Then:*
(a) $P_1(d,0,0)$ *and* $P_2(0,D,0)$ *are unstable equilibria;*
(b) $P_3(0,0,d)$ *and* $P_4(x^*,y^*,0)$ *given by* (4.4)*, are locally asymptotically stable equilibria;*
(c) *When* $P_5(x^+,0,z^+)$ *given by* (4.5) *and* $P_6(0,y^{++},z^{++})$ *given by* (4.9) *are admissible, they are unstable equilibria;*
(d) *When* $P_7\left(x^{\#},y^{\#},z^{\#}\right)$ *given by* (4.6), (4.7) *and* (4.8) *is admissible, it is locally asymptotically stable if and only if*

$$\delta_1 > 0, \ \delta_3 > 0 \quad \textit{and} \quad \delta_1\delta_2 > \delta_3,$$

*where* $\delta_1, \delta_2, \delta_3$ *are given by*

$$\begin{aligned}
\delta_1 &= -J_{11} - J_{22} - J_{33} = -tr(J),\\
\delta_2 &= J_{11}J_{22} + J_{22}J_{33} + J_{11}J_{33} - J_{13}J_{31} - J_{32}J_{23} - J_{21}J_{12},\\
\delta_3 &= -J_{11}J_{22}J_{33} - J_{21}J_{32}J_{13} - J_{31}J_{12}J_{23} + J_{13}J_{22}J_{31} + J_{23}J_{32}J_{11} +\\
&+ J_{33}J_{12}J_{21} = -\det(J)
\end{aligned}$$

*and* $J_{ij},\ i,j = 1,2,3$ *are the elements of the Jacobian matrix calculated at* $(x^{\#},y^{\#},z^{\#})$.

Recall that the equilibrium $P_5\left(x^+,0,z^+\right)$ is admissible if and only if

$$gh<\left(\frac{a}{c}-1\right)^2,$$

and the equilibrium $P_6\left(0,y^{++},z^{++}\right)$ is admissible if and only if

$$Gh<\left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right).$$

Hence only one, or both $P_5\left(x^+,0,z^+\right)$ and $P_6\left(0,y^{++},z^{++}\right)$ could be admissible. When they are admissible, they are unstable and their local stability on manifolds is specified by the following proposition.

**Proposition 4.3.3.** *Assume that $h\geq 1$. Then*

(1) *If $P_5\left(x^+,0,z^+\right)$ is admissible and $P_6\left(0,y^{++},z^{++}\right)$ is not, then $P_5\left(x^+,0,z^+\right)$ has a two-dimensional locally stable invariant manifold.*

(2) *If $P_6\left(0,y^{++},z^{++}\right)$ is admissible and $P_5\left(x^+,0,z^+\right)$ is not, then $P_6\left(0,y^{++},z^{++}\right)$ has a two-dimensional locally stable invariant manifold.*

(3) *Assume that both $P_5\left(x^+,0,z^+\right)$ and $P_6\left(0,y^{++},z^{++}\right)$ are admissible. Then*

(a) *If $f(\sqrt{\frac{g}{h}})>0$, then $P_5\left(x^+,0,z^+\right)$ has a one-dimensional locally stable invariant manifold, and $P_6\left(0,y^{++},z^{++}\right)$ has a two-dimensional locally stable invariant manifold.*

(b) *If $f(\sqrt{\frac{g}{h}})<0$ and*

$$\frac{(b_1-b_2)\sqrt{gh}}{b_1b_2(\sqrt{gh}+\alpha h)}\left(\frac{a}{c}\frac{1}{1+\sqrt{gh}}-1\right)>-f\left(\sqrt{\frac{g}{h}}\right),$$

*then $P_5\left(x^+,0,z^+\right)$ has a one-dimensional locally stable invariant manifold, and $P_6\left(0,y^{++},z^{++}\right)$ has a one-dimensional locally stable invariant manifold.*

(c) *If $f(\sqrt{\frac{g}{h}})<0$ and*

$$\frac{(b_1-b_2)\sqrt{gh}}{b_1b_2(\sqrt{gh}+\alpha h)}\left(\frac{a}{c}\frac{1}{1+\sqrt{gh}}-1\right)<-f\left(\sqrt{\frac{g}{h}}\right),$$

*then $P_5\left(x^+,0,z^+\right)$ has a two-dimensional locally stable invariant manifold, and $P_6\left(0,y^{++},z^{++}\right)$ has a one-dimensional locally stable invariant manifold.*

**Stability analysis for the accelerated acute phase of CML**

**Theorem 4.3.4.** *Let $a,b_1,b_2,c,A,B,C,g,G,h$ be positive parameters such that (4.11) holds. Then:*

(a) *$P_1(d,0,0)$ is unstable equilibrium;*

(b) *$P_2(0,D,0)$ and $P_3(0,0,d)$ are locally asymptotically stable equilibria;*

(c) *When $P_4\left(x^+,0,z^+\right)$ given by (4.5) and $P_5\left(0,y^{++},z^{++}\right)$ given by (4.9) are admissible, they are unstable equilibria;*

(d) *When $P_6\left(x^{\#},y^{\#},z^{\#}\right)$ given by (4.6), (4.7) and (4.8) is admissible, it is locally asymptotically stable if and only if*

$$\delta_1>0,\ \delta_3>0\ \ \text{and}\ \ \delta_1\delta_2>\delta_3,$$

*where $\delta_1,\delta_2,\delta_3$ are given by*

$$\begin{aligned}
\delta_1 &= -J_{11}-J_{22}-J_{33}=-tr(J),\\
\delta_2 &= J_{11}J_{22}+J_{22}J_{33}+J_{11}J_{33}-J_{13}J_{31}-J_{32}J_{23}-J_{21}J_{12},\\
\delta_3 &= -J_{11}J_{22}J_{33}-J_{21}J_{32}J_{13}-J_{31}J_{12}J_{23}+J_{13}J_{22}J_{31}+J_{23}J_{32}J_{11}+\\
&+ J_{33}J_{12}J_{21}=-\det(J).
\end{aligned}$$

**Remark 4.3.5.** *Notice that the stability on manifolds of the equilibria $P_4\left(x^+,0,z^+\right)$ and $P_5\left(0,y^{++},z^{++}\right)$ is the same as for the equilibria $P_5\left(x^+,0,z^+\right)$ and $P_6\left(0,y^{++},z^{++}\right)$ from the chronic case.*

## 4.4 Numerical simulations

In this section, we perform numerical simulations of system (4.1) in two cases: first in the chronic case and then in the accelerated acute case. We also visualize the separation surface between the basins of attraction of the asymptotically stable steady states.

To illustrate and verify the theoretical results, we perform **time-series** representations using Maple *software* [38], and **phase portraits** in three dimensions using Matlab *software*, more precisely a modified version of the LaguerreEig package [104].

We use the physiological values of parameters from [81]. A discussion about the doze level $z(0)$ of infused cells necessary after a non-myeloablative conditioning can be found in [64] and [99]. For example, see [64], a recommended dose is of $3-6\times10^{8}$/kg nucleated cells.

As shown in the paper of R. Precup et al. [83], the control of the separation surface between the basins of attraction of the asymptotically stable equilibria is essential for the correction scenarios after stem cell transplantation.

### Numerical simulations in the chronic case

Case (a): Assume that $P_5\left(x^+,0,z^+\right)$ is not admissible and $P_6\left(0,y^{++},z^{++}\right)$ is admissible. Consider the following values of the parameters:

$$\begin{array}{lll} a=0.23, & b_1=2.2\times10^{-8}, & b_2=1.1\times10^{-8}, \quad c=0.01,\\ A=0.33, & B=5.5\times10^{-9}, & C=0.03,\\ g=25, & G=4, & h=20, \end{array}$$

for which

$$d=10^{9},\quad D=1.81\times10^{9},\quad \alpha d=2\times10^{9},$$

and the following conditions hold

$$\begin{array}{c} a>c,\quad A>C,\quad b_1>b_2>B \quad \text{and}\\ d<D<\alpha d \quad \text{(chronic case)}. \end{array}$$

Also, the computations

$$gh=500>\left(\frac{a}{c}-1\right)^{2}=484,$$

$$Gh=80<\left(\frac{A}{C}-1\right)\left(\frac{a}{c}-1\right)=220,$$

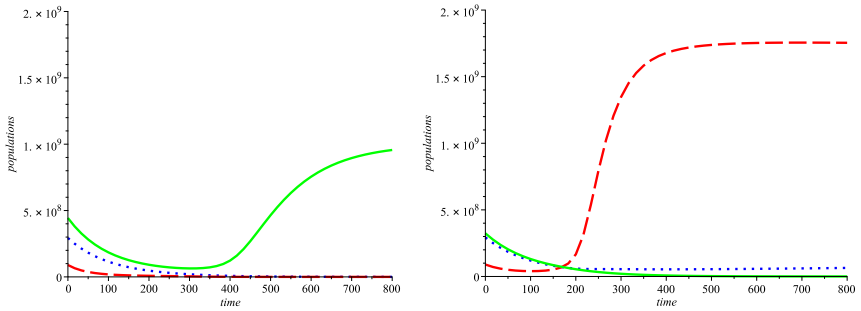
confirm that $P_5\left(x^+,0,z^+\right)$ is not admissible and $P_6\left(0,y^{++},z^{++}\right)$ is admissible. In addition, the condition for the admissibility of $P_7\left(x^{\#},y^{\#},z^{\#}\right)$ does not hold since

$$\begin{aligned} \frac{1+\sqrt{gh}}{1+G\sqrt{\frac{h}{g}}} &= 5.10313>\frac{d-\frac{1}{b_1}\sqrt{gh}}{D-\frac{G}{B}\sqrt{\frac{h}{g}}}=-0.01404\\ &\not> \frac{\left(1+\sqrt{gh}\right)\left(b_1+b_2\sqrt{\frac{g}{h}}\right)}{b_1\left(1+\sqrt{\frac{g}{h}}\right)\left(1+G\sqrt{\frac{h}{g}}\right)}=3.75625. \end{aligned}$$

Hence, for this simulation, we have no $P_5\left(x^+,0,z^+\right)$ and $P_7\left(x^{\#},y^{\#},z^{\#}\right)$ as admissible equilibria, but there exists the admissible equilibrium $P_6\left(0,\ 1.85935\times10^{7},\ 3.48656\times10^{7}\right)$ for which the eigenvalues of the corresponding Jacobian matrix are $-0.005412297301854$, $0.034764565551854$,

$-0.007563470039000$. Thus $P_6\,(0, y^{++}, z^{++})$ is an unstable equilibrium.

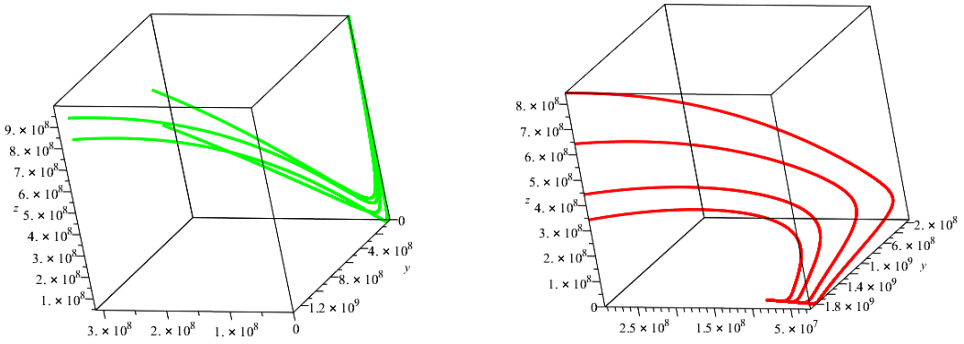
First we obtain the time-series representations of solutions using the above values of the parameters and some initial conditions. Figure 4.1 (a), shows that host normal cell population $x(t)$ (blue dotted line) and abnormal (or leukemic) cell population $y(t)$ (red dashed line) are eliminated, while the donor cell population $z(t)$ (green solid line) becomes arbitrarily close to the normal homeostatic amount $d$. This case corresponds to a successful transplant. In Figure 4.1 (b), donor cell population $z(t)$ approaches 0, while the normal and abnormal cell populations $x(t)$ and $y(t)$ tend toward $x^* = 1.818181818 \times 10^8$ and $y^* = 1.636363636 \times 10^9$, respectively. This means that in this case the transplant is unsuccessful.




(a) Successful transplant (b) Unsuccessful transplant

Figure 4.1: Behavior of the normal, abnormal and donor cell populations with the initial data: (a) $x(0) = 2.932\times10^8$, $y(0) = 0.896\times10^8$, $z(0) = 4.438\times10^8$; (b) $x(0) = 2.932\times10^8$, $y(0) = 0.896\times10^8$, $z(0) = 3.238\times10^8$.

Figures 4.2 (a) and (b) represents the phase portraits of system (4.1). Figure (a) shows that the orbits move towards the 'good' attractor $(0, 0, d)$, while Figure (b) shows that the orbits move towards the 'bad' attractor $(x^*, y^*, 0)$, depending on the initial conditions (initial cell concentrations) $(x(0), y(0), z(0))$.




(a) The 'good' attractor (b) The 'bad' attractor

Figure 4.2: The phase portrait of the three-dimensional system (4.1) in the chronic state, $d < D < \alpha d$.

Figure 4.3 illustrates the phase portrait of system (4.1). In black it is represented the separation surface between the basin of attraction of the 'good' equilibrium $P_3(0, 0, 10^9)$ and the basin of attraction of the 'bad' equilibrium $P_4(1.818181818 \times 10^8,\ 1.636363636 \times 10^9,\ 0)$. The orbits starting

from initial points located in the 'good' basin (green orbits in Figure 4.3) remain entirely in that basin and in time approach $P_3(0,0,d)$. Similarly, the orbits starting from initial points located in the 'bad' basin (red orbits in Figure 4.3) remain entirely in that basin and in time approach $P_4\left(x^*,y^*,0\right)$.

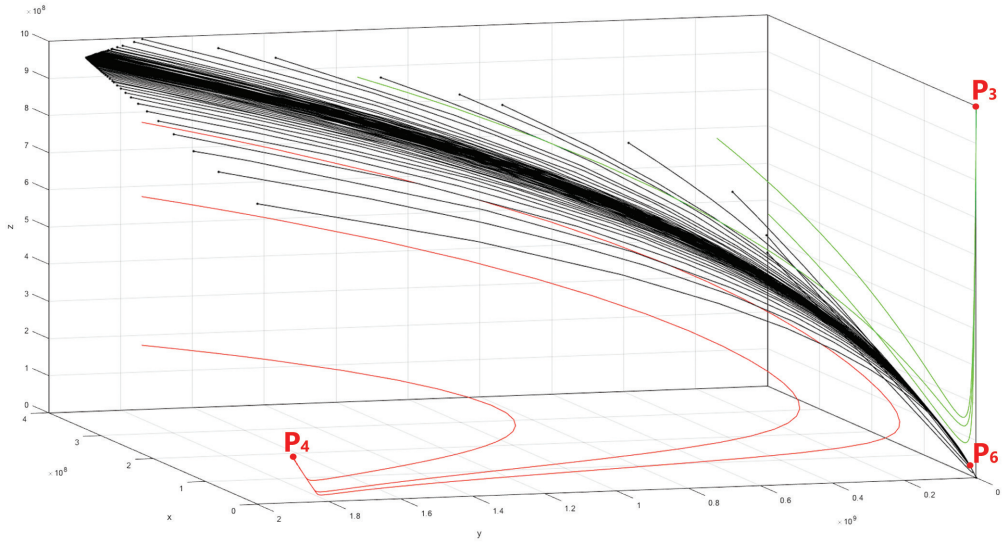



Figure 4.3: The separation surface between the 'good' and the 'bad' basins of attraction in the chronic case. (Matlab code source can be found in Appendix)

Similar simulations can be performed
Case $(b)$: When $P_5\left(x^+,0,z^+\right)$ is admissible and $P_6\left(0,y^{++},z^{++}\right)$ is not admissible, and
Case $(c)$: When both $P_5\left(x^+,0,z^+\right)$ and $P_6\left(0,y^{++},z^{++}\right)$ are admissible.

We can perform similar simulations in the accelerated acute case. These numerical simulations confirm the importance for the transplant success of the initial concentration of cells at the moment of transplantation.

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