Optimization of Imatinib chronic myeloid leukemia's therapy via control theory

1 Introduction

The chronic myeloid leukemia (CML) is a clonal myeloproliferative human blood cancer that makes up approximately 15% of all leukemias in adults (cit). Different mathematical models were developed to study hematopoiesis, this is caused by the relative facility of sampling blood or bone marrow.

Some examples of this mathematical models are a discrete collection of ordinary differential equations, each of which describes a maturation stage of the cells [46, 67, 43]. Another group of models takes in account the stochasticity in the cell fate decision [61, 62].

Mathematical hierarchically models for the CML have proved useful for deriving prognostic informations the course of the disease and the parameters that describe the mechanism of the pathology [46, 67, 52, 58].

In this work we will consider a simple example of hierarchical model for leukemia [56], first we will study the equilibrium of the model in order to classify the patients in function of their parameters, and this will give to us the possibility to forecast the outcome of the therapy.

Then, since for this cancer exits a molecular target therapy (the tyrosine kinase inhibitor) that gives a dramatic improvement of the clinical situation of the patients; we will focus our attention about the optimization of the therapy, since therapy has different drawbacks, for example is not clear that if the therapy is able to completely eradicate the disease [46] so could be consider a life-long therapy and it is very expensive [14], this cost is so high that could limitate application of the therapy [26, 13], then a optimal therapy protocol would lower the prices of therapy and more patients will be able to afford it. The economic factor is not the only cost that is possible to consider when optimizing a protocol, for example we will also consider the toxicity, the possibility to develop a resistant mutation and the performance in reducing the tumor burden.

Then we will describe a mathematical framework to find the optimal protocol for any therapy where the mathematical model of the tumor dynamics and the pharmacokinetics of the drugs are known, to do that we will use the control theory, in particular we will consider a open loop optimization to solve the optimal control problem [39].

2 The mathematical model

2.1 Cell lineages

Many healthy tissues are characterized by a hierarchical organization, and this hierarchical organization could be treated as an ordered sequence of discrete maturation states. In various literatures, simple mathematical models are used to exploit this assumption for the study of healthy hematopoietic [43] and the dynamics involving the number of the cancer cells in a patient [67, 46, 1, 55, 56].

These models are built in the following ways: [67, 46, 58, 52, 1, 55, 56] we divide the cells of the tissue under the study in n_e in non-intersecting ensembles, with every ensemble representing a certain stage of cell differentiation. The time order of the differentiation stage defines a hierarchy of these ensembles. We define a *lineage* as a collection of ensembles that fully describe all the stages of differentiation of cells within a certain tissue.

For every ensemble, we define a function $c_{i,m}(t) : \mathbb{R} \longrightarrow \mathbb{R}^+$ with $i = 1, 2, \ldots, n_e$ and $m = 1, 2, \ldots, m_l$. These functions represent the number of cells in the i ensemble in the m lineage, at a time of t. Firstly, we divide the hematopoietic system into three different ensembles:

1. Stem cells (SC),

2. Progenitor cells (PC),

3. Terminally differentiated (or post-mitotic/mature) cells (TD)

a full model should consist of six different ensembles but, as stated, into [67, 56]. However, this assumption does not improve the agreement analyzing clinical data.

The next step is to study the transition between ensembles, since experimental data [46, 58, 52, 54] show that the proliferation of healthy cells, along with the blast, and the decline under therapy of the BCR-ABL expression are exponential. This implies that the dynamics of the number of cells should be described by first order differential equations (or by a binomial process, if one wants to use probabilistic dynamics).

We thus focus our attention on the fluxes between ensembles. Given the following constants:

- $p_{i,k}$ is the division rate of the cells in the i ensemble of the k lineage.

- $d_{i,k}$ is the death rate of the cells in the i ensemble of the k lineage.

- $a_{i,k} \in [0, 1]$. This factor represents the fact that when a cell divides itself with a probability of $a_{i,k}(t)$, both of its daughters belong to the i ensemble in the k lineage, with a probability $1 - a_{i,k}(t)$ to the $i+1$ ensemble. This, pertaining to the SC, is called self-renewal.

Then, considering only symmetric cells differentiation the flux between ensembles are as follows:

- $+2p_{i,k}a_{i,k}c_i(t)$ an in-going flux caused by the replication of cells in the i ensembles of the k lineage. This contribution is absent for the TD ensembles.

- $+p_{i-1,k}(1 - a_{i-1,k})c_{i-1,k}(t)$ an in-going flux due to the differentiation in the previous ensemble of the lineage. This is not present for the SC ($i = 1$),

- $-d_{i,k}c_{i,k}(t)$ an out-going flux due to the death of cells,

- $-p_{i,k}c_{i,k}(t)$. This is an out-going flux due to the differentiation,

It is well known that various kinds of feedback signal control the dynamics of cells proliferation [38, 45, 21]. In this work, we will consider a paracrine cytokine signal that controls the dynamics of cell self-renewal [43, 42, 56, 55], Furthermore, we suppose that this signal depends only on the number of mature cells ($c_{3,k}(t)$) present in the system [43]:

$$s(t) = \frac{1}{1 + \sum_{k=1}^{m_l} K_k c(t)_{3,k}}, \tag{1}$$

where K_k are constants that represent the different contributions from different mature cells of different cell lineages.

2

Next, the differential system that represents the dynamics of the healthy hematopoiesis is as follows:

$$
\begin{aligned}
\frac{dc_{1,h}(t)}{dt} &= [(2a_{1,h}s(t) - 1)p_{1,h} - d_{1,h}]c_{1,h}(t), \\
\frac{dc_{2,h}(t)}{dt} &= 2(1 - a_{1,h}s(t))p_{1,h}c_{1,h}(t) + [-d_{2,h} + (2a_{2,h}s(t) - 1)p_{2,h}]c_{2,h}(t), \\
\frac{dc_{3,h}(t)}{dt} &= 2(1 - a_{2,h}s(t))p_{2,h}c_{2,h}(t) - d_{3,h}c_{3,h}(t),
\end{aligned}
\tag{2}
$$

with $s(t)$ equal to:

$$
s(t) = \frac{1}{1 + K_h c(t)_{4,h}},
\tag{3}
$$

It is possible to add other feedback signals, such as for instance, an autocrine one. This would mean that the cells in one ensemble would control the dynamics of the ensemble they belong to. For example, this could be seen in the case of the hematopoietic SC (HSC), where an increased cell death could occur due to the competition for bone marrow space. This could be represented as a feedback signal that increases [25, 12, 72, 22] the death rate of HSC. However, for simplicity we will not consider such mechanics. The main reason in this choice of design is that the equilibrium structure would remain the same, and we would want to use the minimal set of parameters that could effectively represent all possible clinical situations.

2.2   Leukemic cell lineage

Furthermore, in the course of studying a cancer developing in hierarchically organized tissue, it is possible to hypothesize that it is hierarchically organized too. This means that if we impose that they are driven by a sub-population of tumor initiating cells (TIC), or cancer stem cells (CSC), (cit.) then every stage of differentiation will contain cancer cells. Since every cancer cell in the CML has a the BCR-ABL mutation, it is very easy to distinguish between a lineage of healthy cells and a lineage of cancer through experiments cells [46, 58, 52, 54].
This hypothesis could be generalized into m_l lineage. For example, in the case of representing subpopulations of tumor cells with different properties (e.g. a mutation that gives the resistance to a therapy or different parameters).
It is an open point if the differentiation of the CML cells is cytokine-dependent or cytokine-independent [55, 64, 63] (cit.others), this choice in the model would thus lead to a dramatic change in the response to the treatment and to the possible steady states of the system. Firstly, we are going to present two different possibilities to represent the dynamics of the leukemic cells lineage. For every case, we will show how a direct (from experiments) or indirect (from data analysis of the follow-up) estimation of the parameters could open the possibility for the simulating of a tumor growing phase, the therapy with a molecular inhibitor and the phase successive to the treatment. As stated in [67, 55] this estimation could be useful in predicting which steady states are possible for our patient, and we are going to point out that this makes it possible to predict the success of the therapy and to give a criterion for the interruption of the administration of the drug. That being said, an accurate estimation of the risk of the interruption is not the main scope of this work and further work would be necessary for the development of a more precise criterion.
Finally, since the common measurement during a follow up is a RQ-PCR between the BRC-ABL and a control gene [46, 58, 52, 54](cit. others), the experimental information is the relative value of the total number of cancer cells with respect to the total number of cells. As such, the figure of merit (FOM) of this study is the following:

$$
T(t) = \frac{\sum_{i=1}^{3} c_{i,l}(t)}{\sum_{i=1}^{3} \sum_{k=l}^{h} c_{i,k}(t)}.
\tag{4}
$$

2.2.1 Unregulated CML cell lineage

Abnormalities of cytokine and/or growth factor are characteristic to all forms of leukemia. In fact, it would seem that the BCR-ABL oncogene increases the rate at which leukemic stem cells proliferate and differentiate into progenitors. As such, while using the equation (2) to simulate this behavior, we would still need to model this fact by giving a parameters advantage to the CML cell lineage or by neglecting all regulation mechanism for cancer cells. Next, the equations for the two lineages (healthy and leukemic) become uncoupled, and it is possible to study the dynamics of the tumor alone, with it being described by:

$$\begin{aligned}
\frac{dc_{1,l}(t)}{dt} &= \alpha c_{1,l}(t), \\
\frac{dc_{2,l}(t)}{dt} &= \beta c_{1,l}(t) + \delta c_{2,l}(t), \\
\frac{dc_{3,l}(t)}{dt} &= \gamma c_{2,l}(t) + \phi c_{3,l}(t),
\end{aligned} \tag{5}$$

where:

$$\begin{aligned}
\alpha &= (2a_{1,l} - 1)p_{1,l} - d_{1,l}, \quad \beta = 2(1 - a_{1,l})p_{1,l}, \\
\delta &= (2a_{2,l} - 1)p_{2,l} - d_{2,l}, \quad \gamma = 2(1 - a_{2,l})a_{2,l} \\
\phi &= -d_{3,l}.
\end{aligned} \tag{6}$$

This is a typical example of a linear autonomous system, and a good criterion for studying the stable points of the solution is to analyze the eigenvalues of the Jacobian. The Jacobian is provided as:

$$\mathbb{J} = \begin{bmatrix} \alpha & \beta & 0 \\ 0 & \delta & \gamma \\ 0 & 0 & \phi \end{bmatrix} \tag{7}$$

Then, α is an eigenvalue of $\mathbb{J}$.

Due to the Principle of linearized stability for autonomous system, only two equilibriums for this model exist: the first one is for $\alpha = 0$ (this is a center manifold) where the number of leukemic stem cells remains constant. The second is for $\alpha < 0$, and in this case, the tumor size for the $t \longrightarrow \infty$ goes to zero. For $\alpha > 0$, the number of leukemic stem cells goes to infinity. This would mean that the model presented in equation (5) neglects the hypothesis of the quiescent leukemic cells after the treatment [71, 73, 24, 11]. Suppose that the parameters are the same prior and post treatment. If that were the case, and if we impose $\alpha < 0$ during the treatment, the leukemic cells will decay, and this would imply that when treatment is stopped, $\alpha \geq 0$, As such, if the treatment does not eradicate the tumor in its entirety. Then, we have two possibilities: $\alpha = 0$, where the the leukemic cells remains constant, however, with this hypothesis the tumor should not develop before the treatment, or $\alpha > 0$ in which case we will see the relapse in every case, and it would thus be impossible to develop a subpopulations of quiescent stem cells.

Finally, since drugs, like Imatinib, induces apoptosis in the cancer cells [19, 70, 65] we model this effect as an increase of the death rate of the CML cell lineage. As such, these hypotheses will imply only two possible clinical out-comes:

1. Prior to the treatment, we have $\alpha > 0$, during the treatment, due to the drugs, we have $\alpha < 0$

2. Prior to the treatment, we have $\alpha > 0$, during the treatment, due to the drugs, we have $\alpha = 0$

In the first case, during the drug administration, we have a monotone decay of the tumor size, and it is possible to stop the therapy if all the leukemic cells are removed. In contrast, for the second case, during the treatment, the leukemic stem cells reached a new dynamical equilibrium and it is thus impossible to totally eradicate the tumor, this is an example of a long-life patient, since any interruption of the therapy could cause a relapse of the disease. Two examples obtained by numerical simulation are show in figure 1.
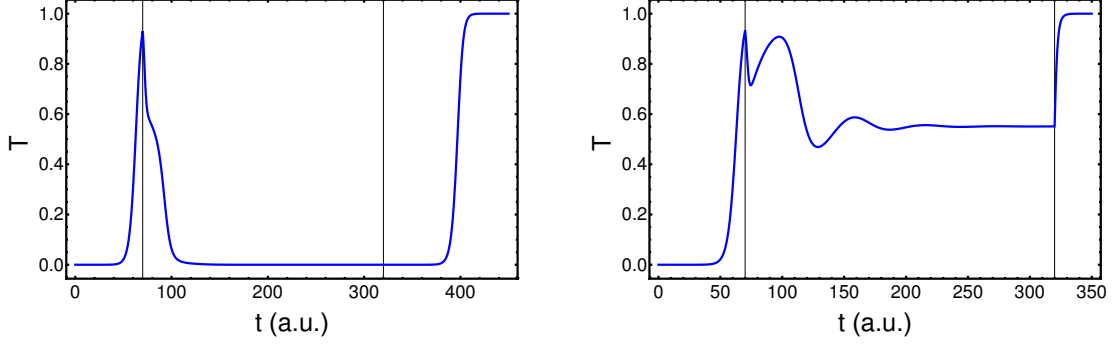
Figure 1: Figure of merit for different simulation of eq.s (5) and (2). We simulate an initial development of the leukemia into a healthy steady state from one TIC. Next, we simulate the therapy with a molecular inhibitor, like Imatinib, by raising the death rate of leukemic cells [19, 70, 65] Finally the interruption of the therapy, the black vertical lines represent the start and stop of the therapy. In both figures, the parameters are the same $d_{1,l} = d_{1,h} = 0.003$, $d_{2,l} = d_{2,h} = 0.005$, $d_{3,l} = d_{3,h} = 0.08$, $a_{1,l} = a_{1,h} = 0.65$, $a_{2,l} = a_{2,h} = 0.55$, $a_{3,l} = a_{3,h} = 0.55$, $p_{1,l} = p_{1,h} = 1$, $p_{2,l} = p_{2,h} = 1.2$, $p_{3,l} = p_{3,h} = 1.3$ and $K_l = K_h = 1.6 \times 10^{-10}$. The only difference between the two images is that on the Left, during the therapy $d_{1,l} > (2a_{a,l} - 1)p_{1,l}$ we see a monotone decay of the tumor burden, and it is only possible to stop the therapy if $m_{1,l}(t) = 0$. In contrast, the right shows that during the therapy, we have $d_{1,l} = (2a_{a,l} - 1)p_{1,l}$, so the tumor size becomes constant after a certain amount of time, In this case, it is impossible to interrupt the drug administration without causing a relapse.

2.2.2 Cytokine-dependent leukemic cell lineage

In this section, we suppose that the CML cells have a cytokine-dependent proliferation, and we assume that healthy cells and leukemic cells compete for environmental resources.
So, using only two lineages one for the healthy cells $(c_{i,h}(t))$ and one for the leukemic cells $(c_{i,l}(t))$, we have six first-order differential equations:

$$
\begin{aligned}
\frac{dc_{1,h}(t)}{dt} &= [(2a_{1,h}s(t) - 1)p_{1,h} - d_{1,h}]c_{1,h}(t), \\
\frac{dc_{2,h}(t)}{dt} &= 2(1 - a_{1,h}s(t))p_{1,h}c_{1,h}(t) + [-d_{2,h} + (2a_{2,h}s(t) - 1)p_{2,h}]c_{2,h}(t), \\
\frac{dc_{3,h}(t)}{dt} &= 2(1 - a_{2,h}s(t))p_{2,h}c_{2,h}(t) - d_{3,h}c_{3,h}(t), \\
\frac{dc_{1,l}(t)}{dt} &= [(2a_{1,l}s(t) - 1)p_{1,l} - d_{1,l}]c_{1,l}(t), \\
\frac{dc_{2,l}(t)}{dt} &= 2(1 - a_{1,l}s(t))p_{1,l}c_{1,l}(t) + [-d_{2,l} + (2a_{2,l}s(t) - 1)p_{2,l}]c_{2,l}(t), \\
\frac{dc_{3,l}(t)}{dt} &= 2(1 - a_{2,l}s(t))p_{2,l}c_{2,l}(t) - d_{3,l}c_{3,l}(t),
\end{aligned} \tag{8}
$$

with $s(t)$ equal to:

$$
s(t) = \frac{1}{1 + K_h c_{3,h}(t) + K_l c_{3,l}(t)}. \tag{9}
$$

The system (8) has three possible equilibriums [56]:

1. Leukemic steady state,

2. Healthy steady state,

3. Composite steady state.

First of all, we suppose that the parameters of the equations (8) are the same before and after the treatment. Indeed, if we discard this hypothesis, it is necessary to use stochastic
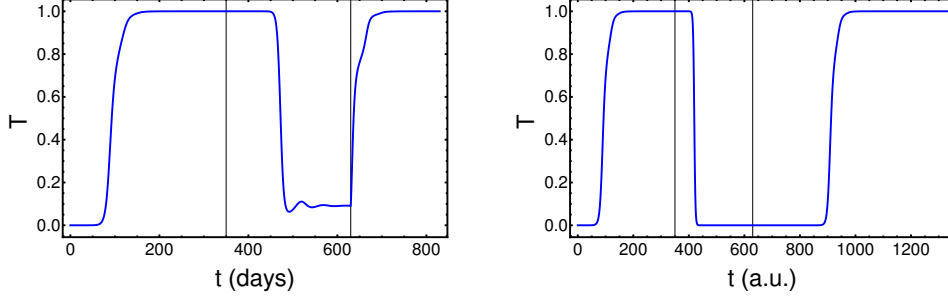
Figure 2: Figure of merit of the therapy and the stop, obtained by solving eq.s (8). We choose of parameters in order to have a composite steady state: $d_{1,l} = d_{1,h} = 0.003$, $d_{2,l} = d_{2,h} = 0.005$, $d_{3,l} = d_{3,h} = 0.08$, $a_{1,l} = a_{1,h} = 0.65$, $a_{2,l} = a_{2,h} = 0.55$, $a_{3,l} = a_{3,h} = 0.55$, $p_{1,l} > p_{1,h} = 1$, $p_{2,l} = p_{2,h} = 1.2$ and $p_{3,l} = p_{3,h} = 1.3$, $K_l = K_h = 1.6 \times 10^{-10}$.
In this case, the left shows the effects of the drugs that lead to a composite state, while the right is that of a pure healthy state.
In the first case, it is not possible to stop the therapy. In the second, this is possible only when the tumor is eradicated.

differential equations or probabilistic formalisms.

Since every patient had developed the leukemia in the past, this could append in two cases

a. We suppose that the BRC-ABL mutation gives a proliferation advantage to the leukemic cells. Next, the parameters of the patient imply that the leukemic steady state is possible and the healthy steady state is unstable in the direction of $c_{1,l}(t)$, i.e. $\frac{a_{1,l}p_{1,l}}{d_{1,l}+p_{1,l}} > \frac{a_{1,h}p_{1,h}}{d_{1,h}+p_{1,h}}$, $(2a_{1,l}-1)p_{1,l} > d_{1,l}$, $d_{3,l} > 0$, $\frac{a_{1,l}p_{1,l}}{d_{1,l}+p_{1,l}} > \frac{a_{2,l}p_{2,l}}{d_{2,l}+p_{2,l}}$ and $\frac{a_{1,l}p_{1,l}}{d_{1,l}+p_{1,l}} > \frac{a_{3,l}p_{3,l}}{d_{3,l}+p_{3,l}}$.

b. The patient specific parameters admit a steady composite state, i.e. $\frac{a_{1,h}p_{1,h}}{d_{1,h}+p_{1,h}} > \frac{a_{2,h}p_{2,h}}{d_{2,h}+p_{2,h}}$,

$\frac{a_{1,h}p_{1,h}}{d_{1,h}+p_{1,h}} > \frac{a_{3,h}p_{3,h}}{d_{3,h}+p_{3,h}}$, $d_{3,l} > 0$, $d_{3,h} > 0$ and $\frac{\frac{d_{1,l}}{p_{1,l}}+1}{2a_{1,l}} = \frac{\frac{d_{1,h}}{p_{1,h}}+1}{2a_{1,h}}$. In this case, the leukemia was developed due to the fluctuations in the population of the TIC [56] For an example, see figures 3 and 4.

Next, if we estimate that our patient is an a. type, we are able to have the same possibilities of the cytokine-independent model, as seen in figure 2.

In contrast, if the patient lies in the b. case, then the therapy will slowly eradicate the disease. However, it is possible to stop the therapy before, as the interruption will leave the patient in another composite state, defining $\alpha := (p_{1,l}d_{3,l} - p_{1,h}d_{3,h})(d_{3,h} - d_{3,l})$, we have three different possibilities [56]:

- $\alpha < 0$ the system is stable in the sense that it asymptotically approaches the center manifold if it starts in the neighborhood of it. This condition implies $p_{1,l}d_{3,l} > p_{1,h}d_{3,h}$ and $d_{3,h} > d_{3,l}$ or $p_{1,l}d_{3,l} < p_{1,h}d_{3,h}$ and $d_{3,h} < d_{3,l}$.

- $\alpha = 0$ if and only if either $p_{1,l}d_{3,l} = p_{1,h}d_{3,h}$ or $d_{3,l} = d_{3,h}$. In these cases, the system is stable in the sense that it will asymptotically approach the center manifold if it starts in the neighborhood of it, if

- $\alpha > 0$ and $K_l c_{3,h}(t)$ is small enough, then the system would be stable if it starts in the neighborhood of a center manifold.
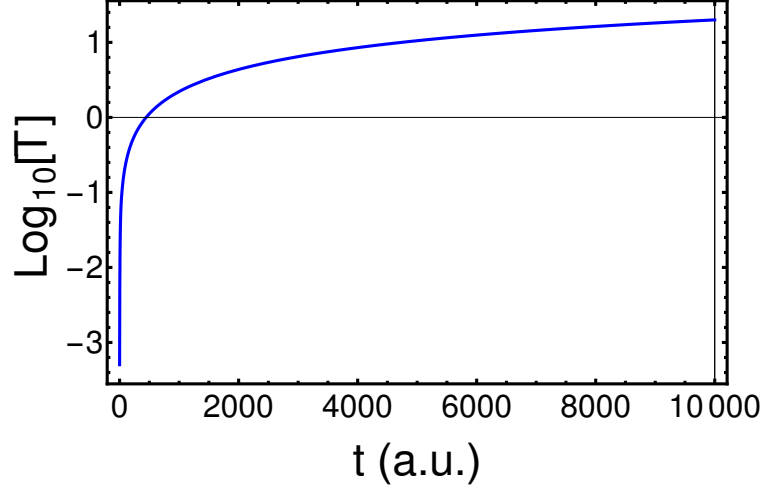
6

Figure 3: Figure of merit obtained solving eq.s (8). We added 10^4 TIC to a healthy steady state, and we chose the parameters required to have a composite steady state: $d_{1,l} = d_{1,h} = 0.003$, $d_{2,l} = d_{2,h} = 0.005$, $d_{3,l} = d_{3,h} = 0.08$, $a_{1,l} = a_{1,h} = 0.65$, $a_{2,l} = a_{2,h} = 0.55$, $a_{3,l} = a_{3,h} = 0.55$, $p_{1,l} = p_{1,h} = 1$, $p_{2,l} = p_{2,h} = 1.2$ and $p_{3,l} = p_{3,h} = 1.3$, $K_l = K_h = 1.6 \times 10^{-10}$. In this case, the we add random noise $x \in [-10^3, 10^3]$ to $c_{1,l}(t)$, Note that leukemia would not be able to develop without the fluctuations, but the fluctuations does not inherently imply the presence of the disease.
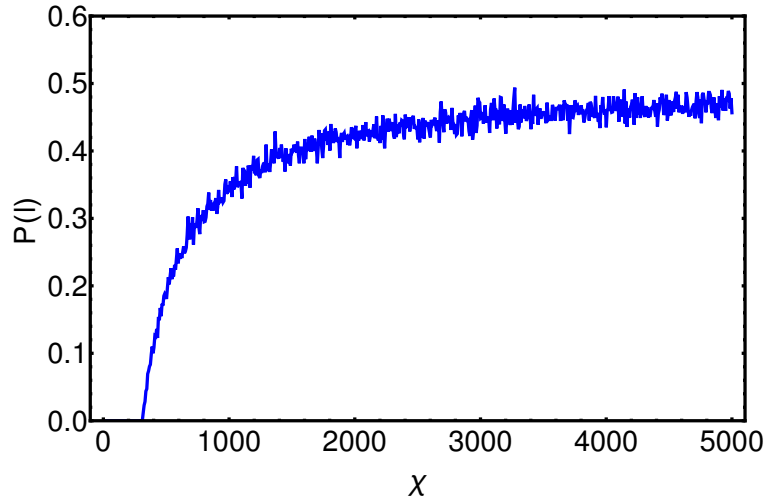

Figure 4: Probability to develop a leukemia $P(l)$ with $T \geq 0.01$ after 5000 units of time in function of the range of a stochastic noise, $x \in [-\chi, \chi]$, added to $c_{1,l}(t)$ or $c_{1,h}(t)$. This probability was evaluated with 2000 repetitions for any value of χ. We started from a composite equilibrium with 10^4 TIC, where approximately 100% of the cells are healthy; the parameters of this simulation are: $d_{1,l} = d_{1,h} = 0.003$, $d_{2,l} = d_{2,h} = 0.005$, $d_{3,l} = d_{3,h} = 0.08$, $a_{1,l} = a_{1,h} = 0.65$, $a_{2,l} = a_{2,h} = 0.55$, $a_{3,l} = a_{3,h} = 0.55$, $p_{1,l} = p_{1,h} = 1$, $p_{2,l} = p_{2,h} = 1.2$ and $p_{3,l} = p_{3,h} = 1.3$, $K_l = K_h = 1.6 \times 10^{-10}$.
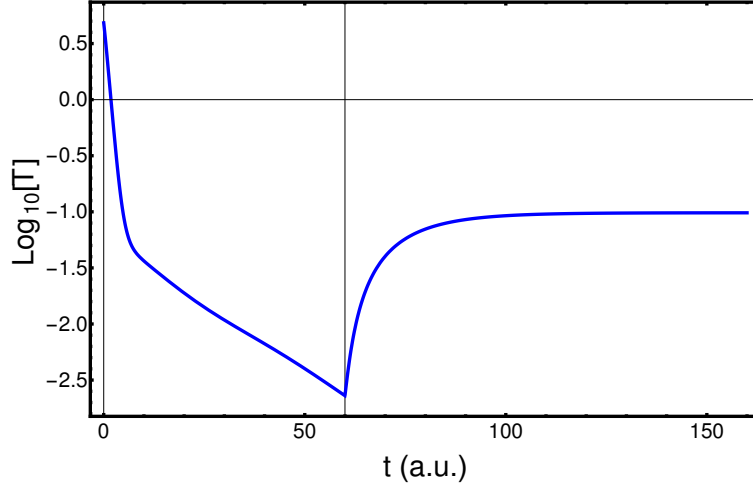
Figure 5: Figure of merit of the therapy and the stop, obtained by solving eq.s (8). We choose the parameters in order to have a composite steady state: $d_{1,l} = d_{1,h} = 0.003$, $d_{2,l} = d_{2,h} = 0.005$, $d_{3,l} = d_{3,h} = 0.08$, $a_{1,l} = a_{1,h} = 0.65$, $a_{2,l} = a_{2,h} = 0.55$, $a_{3,l} = a_{3,h} = 0.55$, $p_{1,l} = p_{1,h} = 1$, $p_{2,l} = p_{2,h} = 1.2$ and $p_{3,l} = p_{3,h} = 1.3$, $K_l = K_h = K_{sh} = K_{lh} = 1.6 \times 10^{-10}$. In this case we can see the typical decay with two slopes [46], this double decay it is due to a different slope of decay between HSC and PC. After the stop of the therapy, the vertical black line, the systems reaches a new composite steady state with less leukemic cells.

2.3   Pharmacodynamics and Pharmacokinetiks

In the previous section, we simplified the action of the molecular inhibitor, as an increasing of the death rate of not-TD CML cell lineage. However, works like [32, 69] suggest that the anti-leukemic activity of the treatment was time-dependent. As such, to better design the effects of the dosage, we model the concentration in the blood vs time as a Lasota [66] function:

$$C(t) = Ate^{-Bt} \tag{10}$$

where A and B are two real and positive constants.
Then, we model the effect of the concentration of Imatinib as an increment of the rate of death, which is modulated by a sigmodean-like function:

$$d_{i,l}(t) = \left(1 - \frac{2(1 - d_{i,l}^0)}{1 - CExp(-Ft)} \right) \tag{11}$$

where C and F are two real and positive constants and $d_{i,l}^0$ are the values of the death rate of the first two compartments of leukemic cells without treatment. Note that this function was chosen in order to obtain $d_{i,l}(t) = d_{i,l}^0$ when $C(t) = 0$ and $d_{i,l}(t) = 1$ when the concentration reached its maximum.
An example of the behavior of the equations (10) and (11) is shown in figure 6.
It is important to point out that since we integrated the system 8 for a long-time, with respect to the period of the function $C(t)$, it would be the same to consider any $L^1(\mathbb{R}, dt)$ function respective to (11), with the only relevant quantity being the value of the integral $N = \int_{t_0}^{t_1} d_{i,l}(t)dt$. Next, if we used a constant with the same numerical value (i.e. $\frac{\int_{t_0}^{t_1} d_{i,l}(t)}{(t_1 - t_0)} = d_{i,l}$) of the integral, the numerical solution of (8) will be the same. From the mathematical point of view, this approximation holds true only if the time lapse under study (integration) is slightly bigger with respect to the periodicity of the administration
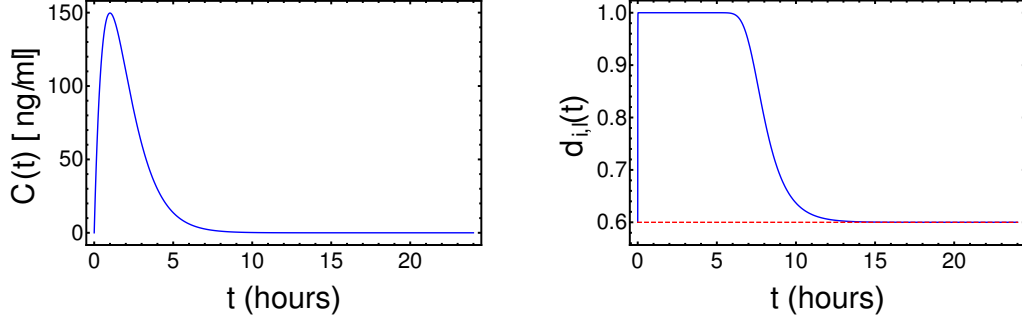
Figure 6: On the left is the simulation of the pharmacokinetics of 400 mg Imatinib administration, as stated in [32], and on the right are the effects of the therapy on the death rate of leukemic cells, the dashed red line is $d_{i,l}^0 = 0.60$. The parameters of equations (11) and (10) are $A = 407$, $B = 1$, $C = 1$ and $F = 1$

of the drugs, Instead from the biological point of view, this would reflect Haber's rule [47] $cost. = C \times t$, where C is the concentration of a substance and t is the length of time in which it is administered.

3   Tuning of the parameters

The model presented in the preceding section is thus able to give some predictive information regarding the course of the disease in a patient and to understand if the therapy can be stopped. However, this ability is limited by three factors

- The quantity studied in the experimental works (e.g. [46, 52]) is the molecular response (MR). Thus, it is an open question as to whether this quantity will always correlate with the cell count of tumor and if other measurement techniques would be better [54, 60, 35, 40, 27, 37].

- The experimental data is a relative information. Instead, the model requires quantitative information regarding the number of cells in a class.

- Discussion on the number of ensembles in a lineage with respect to the parameters.

To overcome this problems, we make the following assumptions. Regarding the first one, we suppose that the proportionality between MR and cell counts holds. Indeed, only further experiments can solve any further problems with this supposition.
The second problem is trickier, as if one tries to make a fit between the FOM and the values, as reported in the data, he will struggle with the fact that it is necessary to make a non-trivial guess on the initial conditions, and consequently, the value of the parameters that he will obtain would be dependent on this initial guess. Furthermore, by minimizing some notion of distance one will find the FOM closer to the data, and this FOM $F(\mathbb{A}, \mathbf{x}_0)$ would be completely described by the collection of its parameters $\mathbb{A}$ and initial condition $\mathbf{x}_0$. However, a couple of $(\mathbb{A}', \mathbf{x}_0')$ will exist such that $F(\mathbb{A}, \mathbf{x}_0) = F(\mathbb{A}', \mathbf{x}_0')$. For these reasons, every result obtained with this model should be treated with attention. Since every estimation of the parameters depends on an arbitrary guess, the values of the parameters that is obtained through a data analysis will be one of the possible solutions with the same FOM. As such, the focus during data analysis should be to address the behavior, not the absolute values of the results. This will hold true till will be accessible the information about the cell count in

particular at the start of the therapy, and it is only through this condition will the tuning of the parameters in order to be consistent with the international scale for MR [68].

First of all, we are going to reduce the attention on the biologically relevant range of parameters [56]:

$$\frac{1}{2} < \bar{s} < 1, \quad 0 \leq K_l \bar{c}_{3,l} \leq (2a_{1,l}), \quad 0 \leq K_h \bar{c}_{3,h} \leq (2a_{1,h}), \tag{12}$$

then, supposing that the relevant experimental data is not the absolute value of the MR, but it variation (the behavior), we made the data analysis in the following way: We gave n data for a follow up, while $O(t_i)$ for $i = 1, \ldots n$ and the FOM $T(t_i, \mathbb{A})$ was obtained by numerically solving the system at t_i for a certain collection of parameters $\mathbb{A}$, Next, we defined a matrix of F_K, which elements were given by:

$$F_{K,ij} = (1 - \delta_{ij}) \frac{K_i - K_j}{t_i - t_j} \tag{13}$$

where δ_{ij} is the Kronecker delta and $K_i = O(t_i), \quad T(t_i, \mathbb{A})$.

This symmetric matrix contains the value of all the incremental ratios contained in the experimental data. Finally, we minimized the 2-norm distance between F_O and F_T, i.e.:

$$D = \sum_{i=1}^{n} \sum_{j=1}^{n} \sqrt{(|F_{O,ij}|^2 - |F_{T,ij}|^2)}. \tag{14}$$

We chose to study this quantity as minimizing the differences between the theoretical and observed incremental ratio between the pair of neighbor points will promote local trends from the derivatives.

The minimization was performed by a random search algorithm that worked in the following way:

1. Make a random initial guess on the parameters $\mathbb{A}$

2. Make a random step in the parameters space $\mathbb{A} \longrightarrow \mathbb{A}'$

3. Solve the system (8) using $\mathbb{A}'$

4. Evaluate D

5. If D evaluated with $\mathbb{A}'$ is lesser than D evaluated using $\mathbb{A}$, then go back to 2 and use $\mathbb{A}'$ as an initial guess, or else go back to 2.

If $\mathbb{A}$ and $\mathbb{A}'$ had the same D, we chose the case that minimized:

$$\chi^2 = 1 - \sum_{i}^{n} \frac{O(t_i) - T(t_i)}{T(t_i)} \tag{15}$$

In order to have a more robust procedure, we added a super iteration (SI) on the initial guess. Both random seeds were obtained using the Sobol sequence [7]. An example of the analysis of a patient of [46] is shown in figure 7. In this case, due to the time-span of the follow up and the periodic dosage of the molecular inhibitor we modeled the Pharmacodynamics that we used with a constant reduction estimated in [46].
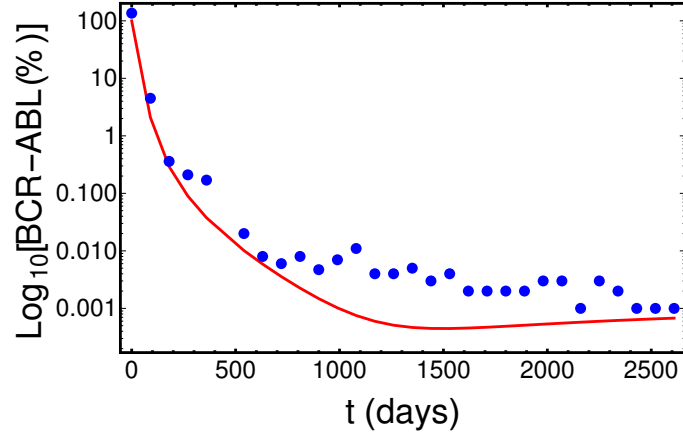
Figure 7: The blue points are data of a follow up from [46], and the red solid line is the best fit obtained using the procedure described in this work, with a 500 SI and 1100 iteration of the algorithm. In this example, we fixed the initial condition, and fixed the death rate $d_{i,k}$ from the work [46] then $d_{i,l} = d_{i,h}$ for $i = 1, 2, 3, 4$ with $d_1 = 0.003$ per day, $d_2 = 0.008$ per day, $d_3 = 0.05$ per day, and $d_4 = 1$ per day, the probability of self-renewal was fixed $a_{i,l} = a_{i,h}$ for $i = 1, 2, 3, 4$ $a_1 = 0.7$, $a_2 = 0.65$, $a_3 = 0.55$ and $a_4 = 0.55$, $K = 1.3 \times 10^{-7}$. Finally, we suppose that during the treatment $p_{1,h} = 2p_{1,l}/100$, $p_{2,h} = 2p_{2,l}/750$ and $p_{3,h} = p_{3,l}$. The obtained values were $p_{1h} = 6.986$ per day, $p_{2,h} = 0.0137$ per day, $p_{3h} = 2.014$ per day and $\lambda = 2.2 \times 10^{-8}$ per day. The results of the two tests were $\chi = 0.990$ and $D = 2.602$. Note that the final state was reached from an analysis of the eigenvalue of the Jacobian results unstable, in fact if the simulation is performed for later times, it reached a stable state higher than the final state and this stable state was different from the minimum of T. The minimum was reached just after the first 3-fold decay. This peculiar behavior was caused by the signal, as it had a big increase just after this decline.

4 Optimization of the therapy

A mathematical model of the disease and its therapy gave the possibility of making a *in silico* optimization of the therapy [59, 51]. With regarding to the optimization, we mean balancing certain therapy costs against performance. For example, the cost of the therapy could be an economic cost [14, 34, 26, 13, 23] or toxicity of the therapy [74, 29, 10, 15] and the reduction in the tumor burden of a patient could be used as the performance. Such a kind of study could be very useful, in particular for the CML, as the treatment is very expensive [14, 34, 13] such that it could limit the patient's access to therapy [23, 26] and lowering the prices of therapy will allow more patients to afford it and maintain a long-term health care policy [20]. It is also possible that sub-clonal resistant mutation could arise and would make it necessary to manage the switch to a new molecular therapy [16] In this case, we suppose that the therapy fails in eradicating the disease (then it is life-long therapy) and a low dosage could be useful in minimize the toxicity of the therapy [18].

To perform this optimization, we will use the control theory, in particular we will use an open loop control. A key aspect of this theory is the cost. As such, we defined the following cost function:

$$\mathbb{J}(t) := \int_{t_{in}}^{t_{fin}} \left(\mathbf{A}(d(t)) + \mathbf{B}(d(t)) + \mathbf{C}(T(t)) + \mathbf{D}(R(t)) \right) dt \tag{16}$$

where t_{in} and t_{fin} are initial and final time of the interval under study, $\mathbf{A}(d(t))$ represents the economic cost of the therapy, $\mathbf{B}(d(t))$ represents the cumulative toxicity of the therapy, $\mathbf{C}(T(t))$ represents the cost in quality of life due to the burden of cancer during the therapy, and $\mathbf{D}(R(t))$ is the cost of the risk of developing a resistant mutation.

Obviously, we need an explicit formula for every elements of the cost. For the economic cost, we imposed that it is linear respect to the dose $\mathbf{A}(d(t)) = Ad(t)$, As such, it can be argued that if the cost was about $120,000\$$ year at 400 mg per day [13], the cost for 1 mg of Imatinib was about $0,8333\$$, thus fixing the value of A.

Regarding the cumulative toxicity of the drugs, Imatinib could cause a grade $3/4$ (Common Terminology Criteria for Adverse Events (CTCAE) V5.0) Adverse Events (AE), and dose-limiting toxicity was not observed [15]. However, only to a small fraction of AE was attributed to Imatinib [15]. Then, for this case, we suppose that the long-term adverse effects are negligible, and they are quite acceptable [50]. i.e. $\mathbf{B}(d(t)) = 0$. Finally, since an accidental Imatinib over-dosage could cause reversible bilirubin and transaminase elevation [15] we bound the maximum dose at 900 mg per day.

During the therapy, we saw a great improvement of the quality of life after the first 3-fold decay, i.e. when $T(t) < 0.0001$ (cit.). Under this threshold no big improvements are observed. To model this behavior, we used the following function:

$$\mathbf{C}(T(t)) = C_1 e^{C_2(T(t)-T_0)}, \tag{17}$$

where C_i for $i = 1, 2$ are two real constants. This function gives the exponential cost if $T(t) > T_0$. However, as we will see below, C_1 could be set to 0.

Finally, we need to study the function that represents the risk associated to developing a resistant mutation $\mathbf{D}(R(t))$. We suppose that every CSC, when proliferating, has a certain probability r to develop a resistant mutation. In such cases, it would generate a resistant CSC. Thus, we estimate the risk of having a resistant mutation as the number of resistant cancer cells in respect to the total number of cells of the system, and to evaluate this quantity, we use a third cell lineage $c_{i,r}(t)$ (servono test per capire se é meglio cosí oppure conviene porre una quantitá direttamente proporzionale alle CSC, la seconda dovrebbe essere migliore in realtá).

References

[1] Philipp M Altrock, Lin L Liu, and Franziska Michor. "The mathematics of cancer: integrating quantitative models". In: *Nature Reviews Cancer* 15.12 (2015), p. 730.

[2] Eugene Asarin, Thao Dang, and Antoine Girard. "Reachability Analysis of Nonlinear Systems Using Conservative Approximation". In: *HSCC*. 2003.

[3] Sarit Assouline and Jeffrey H Lipton. "Monitoring response and resistance to treatment in chronic myeloid leukemia". In: *Current Oncology* 18.2 (2011), e71.

[4] Ehab Atallah, Charles A Schiffer, Kevin P Weinfurt, Mei-Jie Zhang, Jerald P Radich, Vivian G Oehler, Javier Pinilla-Ibarz, Michael WN Deininger, Li Lin, Richard A Larson, et al. "Design and rationale for the life after stopping tyrosine kinase inhibitors (LAST) study, a prospective, single-group longitudinal study in patients with chronic myeloid leukemia". In: *BMC cancer* 18.1 (2018), p. 359.

[5] M Baccarani, S Pileri, J-L Steegmann, M Muller, S Soverini, M Dreyling, and ESMO Guidelines Working Group. "Chronic myeloid leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up". In: *Annals of oncology* 23.suppl_7 (2012), pp. vii72–vii77.

[6] Michele Baccarani, Jorge Cortes, Fabrizio Pane, Dietger Niederwieser, Giuseppe Saglio, Jane Apperley, Francisco Cervantes, Michael Deininger, Alois Gratwohl, François Guilhot, et al. "Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet". In: *Journal of clinical oncology* 27.35 (2009), p. 6041.

[7] James Bergstra and Yoshua Bengio. "Random search for hyper-parameter optimization". In: *Journal of Machine Learning Research* 13.Feb (2012), pp. 281–305.

[8] Pavan Kumar Bhamidipati, Hagop Kantarjian, Jorge Cortes, A Megan Cornelison, and Elias Jabbour. "Management of imatinib-resistant patients with chronic myeloid leukemia". In: *Therapeutic advances in hematology* 4.2 (2013), pp. 103–117.

[9] Susan Branford, David T Yeung, David M Ross, Jodi A Prime, Chani R Field, Haley K Altamura, Alexandra L Yeoman, Jasmina Georgievski, Bronte A Jamison, Stuart Phillis, et al. "Early molecular response and female sex strongly predict stable undetectable BCR-ABL1, the criteria for imatinib discontinuation in patients with CML". In: *Blood* 121.19 (2013), pp. 3818–3824.

[10] Massimo Breccia, Caterina Stefanizzi, Laura Cannella, Roberto Latagliata, Anna Maria Frustaci, Ida Carmosino, Michelina Santopietro, and Giuliana Alimena. "Differences in hematological and non-hematological toxicity during treatment with imatinib in patients with early and late chronic phase chronic myeloid leukemia". In: *Leukemia & lymphoma* 49.12 (2008), pp. 2328–2332.

[11] I Bruns, A Czibere, JC Fischer, F Roels, RP Cadeddu, S Buest, D Bruennert, AN Huenerlituerkoglu, NH Stoecklein, R Singh, et al. "The hematopoietic stem cell in chronic phase CML is characterized by a transcriptional profile resembling normal myeloid progenitor cells and reflecting loss of quiescence". In: *Leukemia* 23.5 (2009), p. 892.

[12] LM Calvi, GB Adams, KW Weibrecht, JM Weber, DP Olson, MC Knight, RP Martin, E Schipani, P Divieti, F Rv Bringhurst, et al. "Osteoblastic cells regulate the haematopoietic stem cell niche". In: *Nature* 425.6960 (2003), p. 841.

[13] Christopher T Chen and Aaron S Kesselheim. *Journey of generic imatinib: a case study in oncology drug pricing*. 2017.

[14] Experts in Chronic Myeloid Leukemia et al. "The price of drugs for chronic myeloid leukemia (CML) is a reflection of the unsustainable prices of cancer drugs: from the perspective of a large group of CML experts". In: *Blood* 121.22 (2013), pp. 4439–4442.

[15] Martin H Cohen, Grant Williams, John R Johnson, John Duan, Jogarao Gobburu, Atiqur Rahman, Kimberly Benson, John Leighton, Sung K Kim, Rebecca Wood, et al. "Approval summary for imatinib mesylate capsules in the treatment of chronic myelogenous leukemia". In: *Clinical Cancer Research* 8.5 (2002), pp. 935–942.

[16] Jorge E Cortes, Jeffrey H Lipton, Carole B Miller, Lambert Busque, Luke P Akard, Javier Pinilla-Ibarz, Christopher Keir, Ghulam Warsi, Felice P Lin, and Michael J Mauro. "Evaluating the impact of a switch to nilotinib on imatinib-related chronic low-grade adverse events in patients with CML-CP: the ENRICH study". In: *Clinical Lymphoma, Myeloma and Leukemia* 16.5 (2016), pp. 286–296.

[17] Cosimo Cumbo, Luciana Impera, Crescenzio Francesco Minervini, Paola Orsini, Luisa Anelli, Antonella Zagaria, Nicoletta Coccaro, Giuseppina Tota, Angela Minervini, Paola Casieri, et al. "Genomic BCR-ABL1 breakpoint characterization by a multi-strategy approach for "personalized monitoring" of residual disease in chronic myeloid leukemia patients". In: *Oncotarget* 9.13 (2018), p. 10978.

[18] Edgar Faber, Martina Divoká, Ivana Skoumalová, Martin Novák, Ivana Marešová, Kateřina Mičová, David Friedeck, Tomáš Adam, Marie Jarošová, and Karel Indrák. "A lower dosage of imatinib is sufficient to maintain undetectable disease in patients with chronic myeloid leukemia with long-term low-grade toxicity of the treatment". In: *Leukemia & lymphoma* 57.2 (2016), pp. 370–375.

[19] Guofu Fang, Caryn Naekyung Kim, Charles L Perkins, Nimmanapalli Ramadevi, Elliott Winton, Sylvie Wittmann, and Kapil N Bhalla. "CGP57148B (STI-571) induces differentiation and apoptosis and sensitizes Bcr-Abl–positive human leukemia cells to apoptosis due to antileukemic drugs". In: *Blood* 96.6 (2000), pp. 2246–2253.

[20] Tito Fojo and Christine Grady. "How much is life worth: cetuximab, non–small cell lung cancer, and the 440 billion question". In: *Journal of the National Cancer Institute* 101.15 (2009), pp. 1044–1048.

[21] Walter Fried. "Erythropoietin and erythropoiesis". In: *Experimental hematology* 37.9 (2009), pp. 1007–1015.

[22] Sara M Garrido, Frederick R Appelbaum, Cheryl L Willman, and Deborah E Banker. "Acute myeloid leukemia cells are protected from spontaneous and drug-induced apoptosis by direct contact with a human bone marrow stromal cell line (HS-5)". In: *Experimental hematology* 29.4 (2001), pp. 448–457.

[23] Andrés Gomez-de-León, David Gómez-Almaguer, Guillermo J Ruiz-Delgado, and Guillermo J Ruiz-Arguelles. "Insights into the management of chronic myeloid leukemia in resource-poor settings: a Mexican perspective". In: *Expert review of hematology* 10.9 (2017), pp. 809–819.

[24] Susan M Graham, Heather G Jørgensen, Elaine Allan, Charlie Pearson, Michael J Alcorn, Linda Richmond, and Tessa L Holyoake. "Primitive, quiescent, Philadelphia-positive stem cells from patients with chronic myeloid leukemia are insensitive to STI571 in vitro". In: *Blood* 99.1 (2002), pp. 319–325.

[25] JD Griffin and B Lowenberg. "Clonogenic cells in acute myeloblastic leukemia". In: *Blood* 68.6 (1986), pp. 1185–1195.

[26] David U Himmelstein, Deborah Thorne, Elizabeth Warren, and Steffie Woolhandler. "Medical bankruptcy in the United States, 2007: results of a national study". In: *The American journal of medicine* 122.8 (2009), pp. 741–746.

[27] A Hochhaus, F Lin, A Reiter, H Skladny, PJ Mason, PC Shepherd, NC Allan, R Hehlmann, JM Goldman, NC Cross, et al. "Quantification of residual disease in chronic myelogenous leukemia patients on interferon-alpha therapy by competitive polymerase chain reaction." In: *Blood* 87.4 (1996), pp. 1549–1555.

[28] Tessa L Holyoake and David Vetrie. "The chronic myeloid leukemia stem cell: stemming the tide of persistence". In: *Blood* 129.12 (2017), pp. 1595–1606.

[29] Wenyue Hu, Shuyan Lu, Indrawan McAlpine, Joseph D Jamieson, Dong U Lee, Lisa D. Marroquin, Jonathan R Heyen, and Bart A Jessen. "Mechanistic investigation of imatinib-induced cardiac toxicity and the involvement of c-Abl kinase". In: *Toxicological Sciences* 129.1 (2012), pp. 188–199.

[30] Timothy P Hughes, Andreas Hochhaus, Hagop M Kantarjian, Francisco Cervantes, François Guilhot, Dietger Niederwieser, Philipp D le Coutre, Gianantonio Rosti, Gert Ossenkoppele, Clarisse Lobo, et al. "Safety and efficacy of switching to nilotinib 400 mg twice daily for patients with chronic myeloid leukemia in chronic phase with suboptimal response or failure on front-line imatinib or nilotinib 300 mg twice daily". In: *haematologica* 99.7 (2014), pp. 1204–1211.

[31] Timothy P Hughes, Carla Maria Boquimpani, Naoto Takahashi, Noam Benyamini, Nelma Cristina D Clementino, Vasily Shuvaev, Sikander Ailawadhi, Jeffrey H Lipton, Anna G Turkina, Elena Beatriz Moiraghi, et al. "Treatment-free remission in patients with chronic myeloid leukemia in chronic phase according to reasons for switching from imatinib to nilotinib: subgroup analysis from ENESTop". In: (2016).

[32] Yoji Ishida, Kazunori Murai, Kohei Yamaguchi, Takuto Miyagishima, Motohiro Shindo, Kazuei Ogawa, Takahiro Nagashima, Shinji Sato, Reiko Watanabe, Satoshi Yamamoto, et al. "Pharmacokinetics and pharmacodynamics of dasatinib in the chronic phase of newly diagnosed chronic myeloid leukemia". In: *European journal of clinical pharmacology* 72.2 (2016), pp. 185–193.

[33] Elias J Jabbour, Jay Lin, Lisa R Siegartel, Melissa Lingohr-Smith, Brandy Menges, and Dinara Makenbaeva. "Evaluation of healthcare resource utilization and incremental economic burden of patients with chronic myeloid leukemia after disease progression to blast phase". In: *Journal of medical economics* 20.9 (2017), pp. 1007–1012.

[34] Elias J Jabbour, Jay Lin, Lisa R Siegartel, Melissa Lingohr-Smith, Brandy Menges, and Dinara Makenbaeva. "Evaluation of healthcare resource utilization and incremental economic burden of patients with chronic myeloid leukemia after disease progression to blast phase". In: *Journal of medical economics* 20.9 (2017), pp. 1007–1012.

[35] László Kereskai, János A Vass, Maria Kneif, and László Pajor. "Correlation between BCR-ABL expression and tumor burden is restricted to the transition from minor to major cytogenetic response in interferon treated CML patients". In: *Pathology Oncology Research* 9.3 (2003), pp. 174–179.

[36] Ashu Kumari, Cornelia Brendel, Andreas Hochhaus, Andreas Neubauer, and Andreas Burchert. "Low BCR-ABL expression levels in hematopoietic precursor cells enable persistence of chronic myeloid leukemia under imatinib". In: *Blood* 119.2 (2012), pp. 530–539.

[37] Susan Latham, Paul A Bartley, Bradley Budgen, David M Ross, Elizabeth Hughes, Susan Branford, Deborah White, Timothy P Hughes, and Alexander A Morley. "BCR-ABL1 expression, RT-qPCR and treatment decisions in chronic myeloid leukaemia". In: *Journal of clinical pathology* (2016), jclinpath–2015.

[38] Judith E Layton, Helen Hockman, William P Sheridan, and George Morstyn. "Evidence for a novel in vivo control mechanism of granulopoiesis: mature cell-related control of a regulatory growth factor". In: *Blood* 74.4 (1989), pp. 1303–1307.

[39] Suzanne Lenhart and John T Workman. *Optimal control applied to biological models.* Crc Press, 2007.

[40] T Lion, A Gaiger, T Henn, E Hörth, OA Haas, K Geissler, and H Gadner. "Use of quantitative polymerase chain reaction to monitor residual disease in chronic myelogenous leukemia during treatment with interferon." In: *Leukemia* 9.8 (1995), pp. 1353–1360.

[41] François-Xavier Mahon, Delphine Réa, Joëlle Guilhot, François Guilhot, Françoise Huguet, Franck Nicolini, Laurence Legros, Aude Charbonnier, Agnès Guerci, Bruno Varet, et al. "Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial". In: *The lancet oncology* 11.11 (2010), pp. 1029–1035.

[42] Anna Marciniak-Czochra and Thomas Stiehl. "Mathematical models of hematopoietic reconstitution after stem cell transplantation". In: *Model Based Parameter Estimation*. Springer, 2013, pp. 191–206.

[43] Anna Marciniak-Czochra, Thomas Stiehl, Anthony D Ho, Willi Jäger, and Wolfgang Wagner. "Modeling of asymmetric cell division in hematopoietic stem cells—regulation of self-renewal is essential for efficient repopulation". In: *Stem cells and development* 18.3 (2009), pp. 377–386.

[44] Michele Massimino, Stefania Stella, Elena Tirrò, Chiara Romano, Maria Stella Pennisi, Adriana Puma, Livia Manzella, Antonino Zanghì, Fabio Stagno, Francesco Di Raimondo, et al. "Non ABL-directed inhibitors as alternative treatment strategies for chronic myeloid leukemia". In: *Molecular cancer* 17.1 (2018), p. 56.

[45] Donald Metcalf. "Hematopoietic cytokines". In: *Blood* 111.2 (2008), pp. 485–491.

[46] Franziska Michor, Timothy P Hughes, Yoh Iwasa, Susan Branford, Neil P Shah, Charles L Sawyers, and Martin A Nowak. "Dynamics of chronic myeloid leukaemia". In: *Nature* 435.7046 (2005), p. 1267.

[47] Frederick J Miller, Paul M Schlosser, and Derek B Janszen. "Haber's rule: a special case in a family of curves relating concentration and duration of exposure to a fixed level of response for a given endpoint". In: *Toxicology* 149.1 (2000), pp. 21–34.

[48] Helen Moore and Natasha K Li. "A mathematical model for chronic myelogenous leukemia (CML) and T cell interaction". In: *Journal of theoretical biology* 227.4 (2004), pp. 513–523.

[49] Tariq I Mughal and John M Goldman. "Molecularly targeted treatment of chronic myeloid leukemia: beyond the imatinib era". In: *Front Biosci* 11 (2006), pp. 209–220.

[50] Tariq I Mughal and Andrew Schrieber. "Principal long-term adverse effects of imatinib in patients with chronic myeloid leukemia in chronic phase". In: *Biologics: targets & therapy* 4 (2010), p. 315.

[51] Seema Nanda, Helen Moore, and Suzanne Lenhart. "Optimal control of treatment in a mathematical model of chronic myelogenous leukemia". In: *Mathematical biosciences* 210.1 (2007), pp. 143–156.

[52] Adam Olshen, Min Tang, Jorge Cortes, Mithat Gonen, Timothy Hughes, Susan Branford, Alfonso Quintás-Cardama, and Franziska Michor. "Dynamics of chronic myeloid leukemia response to dasatinib, nilotinib, and high-dose imatinib". In: *haematologica* (2014), haematol–2013.

[53] Alfonso Quintás-Cardama, Fabio Pires De Souza Santos, Hagop Kantarjian, Susan O'brien, Stefan Faderl, Ahmed Awais, Gautam Borthakur, and Jorge Cortes. "Dynamics and management of cytopenias associated with dasatinib therapy in patients with chronic myeloid leukemia in chronic phase after imatinib failure". In: *Cancer* 115.17 (2009), pp. 3935–3943.

[54] Alessia Rainero, Fabrizio Angaroni, Andrea Conti, Cristina Pirrone, Giovanni Micheloni, Lucia Tararà, Giorgia Millefanti, Emanuela Maserati, Roberto Valli, Orietta Spinelli, et al. "gDNA qPCR is statistically more reliable than mRNA analysis in detecting leukemic cells to monitor CML". In: *Cell death & disease* 9.3 (2018), p. 349.

[55] Thomas Stiehl, Anthony D Ho, and Anna Marciniak-Czochra. "Mathematical modeling of the impact of cytokine response of acute myeloid leukemia cells on patient prognosis". In: *Scientific reports* 8.1 (2018), p. 2809.

[56] Thomas Stiehl and Anna Marciniak-Czochra. "Mathematical modeling of leukemogenesis and cancer stem cell dynamics". In: *Mathematical Modelling of Natural Phenomena* 7.1 (2012), pp. 166–202.

[57] Moshe Talpaz, Giuseppe Saglio, Ehab Atallah, and Philippe Rousselot. "Dasatinib dose management for the treatment of chronic myeloid leukemia". In: *Cancer* (2018).

[58] Min Tang, Mithat Gonen, Alfonso Quintas-Cardama, Jorge Cortes, Hagop Kantarjian, Chani Field, Timothy P Hughes, Susan Branford, and Franziska Michor. "Dynamics of chronic myeloid leukemia response to long-term targeted therapy reveal treatment effects on leukemic stem cells". In: *Blood* 118.6 (2011), pp. 1622–1631.

[59] Allen R Tannenbaum, Tryphon Georgiou, Joseph Deasy, and Larry Norton. "Control and the Analysis of Cancer Growth Models". In: *bioRxiv* (2018), p. 244301.

[60] Andrei Tchirkov, Michel Giollant, FranÇoise Tavernier, Georges BrianÇon, Olivier Tournilhac, Fabrice Kwiatkowski, Pierre Philippe, Bachra Choufi, FranÇois DemÉocq, Philippe Travade, et al. "Interphase cytogenetics and competitive RT-PCR for residual disease monitoring in patients with chronic myeloid leukaemia during interferon-α therapy". In: *British journal of haematology* 101.3 (1998), pp. 552–557.

[61] James E Till, Ernest A McCulloch, and Louis Siminovitch. "A stochastic model of stem cell proliferation, based on the growth of spleen colony-forming cells". In: *Proceedings of the National Academy of Sciences* 51.1 (1964), pp. 29–36.

[62] Cristian Tomasetti and Doron Levy. "Role of symmetric and asymmetric division of stem cells in developing drug resistance". In: *Proceedings of the National Academy of Sciences* 107.39 (2010), pp. 16766–16771.

[63] Richard A Van Etten. "Aberrant cytokine signaling in leukemia". In: *Oncogene* 26.47 (2007), p. 6738.

[64] Richard A Van Etten. "Oncogenic signaling: new insights and controversies from chronic myeloid leukemia". In: *Journal of Experimental Medicine* 204.3 (2007), pp. 461–465.

[65] Paolo Vigneri and Jean YJ Wang. "Induction of apoptosis in chronic myelogenous leukemia cells through nuclear entrapment of BCR–ABL tyrosine kinase". In: *Nature medicine* 7.2 (2001), p. 228.

[66] M Wazewska-Czyzewska and A Lasota. "Matematyczne problemy dynamiki ukladu krwinek czerwonych". In: *Matematyka Stosowana VI* (1976), pp. 23–40.

[67] Benjamin Werner, Jacob G Scott, Andrea Sottoriva, Alexander RA Anderson, Arne Traulsen, and Philipp M Altrock. "The cancer stem cell fraction in hierarchically organized tumors can be estimated using mathematical modeling and patient-specific treatment trajectories". In: *Cancer research* 76.7 (2016), pp. 1705–1713.

[68] Helen E White, John Hedges, Israel Bendit, Susan Branford, Dolors Colomer, Andreas Hochhaus, Timothy Hughes, Suzanne Kamel-Reid, Dong-Wook Kim, Vijay Modur, et al. "Establishment and validation of analytical reference panels for the standardization of quantitative BCR-ABL1 measurements on the international scale". In: *Clinical chemistry* 59.6 (2013), pp. 938–948.

[69] Hiroyuki YOSHITSUGU, Yasuhiko IMAI, Taku SERIU, and Masaki HIRAOKA. "Markov chain Monte Carlo Bayesian analysis for population pharmacokinetics of dasatinib in Japanese adult subjects with chronic myeloid leukemia and Philadelphia chromosome positive acute lymphoblastic leukemia". In: *Rinsho yakuri/Japanese Journal of Clinical Pharmacology and Therapeutics* 43.1 (2012), pp. 29–41.

[70] Chunrong Yu, Geoffrey Krystal, Paul Dent, and Steven Grant. "Flavopiridol potentiates STI571-induced mitochondrial damage and apoptosis in BCR-ABL-positive human leukemia cells". In: *Clinical Cancer Research* 8.9 (2002), pp. 2976–2984.

[71] Bin Zhang, Adam C Strauss, Su Chu, Min Li, Yinwei Ho, Keh-Dong Shiang, David S Snyder, Claudia S Huettner, Leonard Shultz, Tessa Holyoake, et al. "Effective targeting of quiescent chronic myelogenous leukemia stem cells by histone deacetylase inhibitors in combination with imatinib mesylate". In: *Cancer cell* 17.5 (2010), pp. 427–442.

[72] Jiwang Zhang, Chao Niu, Ling Ye, Haiyang Huang, Xi He, Wei-Gang Tong, Jason Ross, Jeff Haug, Teri Johnson, Jian Q Feng, et al. "Identification of the haematopoietic stem cell niche and control of the niche size". In: *Nature* 425.6960 (2003), p. 836.

[73] Hong Zhou and Rongzhen Xu. "Leukemia stem cells: the root of chronic myeloid leukemia". In: *Protein & cell* 6.6 (2015), pp. 403–412.

[74] Yu Zhu and Si-Xuan Qian. "Clinical efficacy and safety of imatinib in the management of Ph+ chronic myeloid or acute lymphoblastic leukemia in Chinese patients". In: *OncoTargets and therapy* 7 (2014), p. 395.