OPTIMAL CONTROL FOR A DELAY DIFFERENTIAL SYSTEM OF CHRONIC MYELOGENOUS LEUKEMIA

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Abstract. A mathematical model describing the time evolution of a Cancer cell population in Chronic Myelogenous Leukemia (CML) is extended: a function modeling the treatment approach of the disease is taken into account, allowing the investigation of the most appropriate cure protocol. Because CML is believed to arise in the hematopoietic stem cell (HSC) compartment, the study in this paper starts from a delay differential system modeling CML in the stem cell compartment. Optimal control is applied to this two-dimensional system with a molecular targeted therapy, such as imatinib. The objective in this work is to minimize the cancer cell population and the negative effects of the medication to the healthy cells of a certain patient. In order to solve the delayed optimal control problem, the system is discretized and its behavior is investigated for given sets of parameters. The obtained results are illustrated by numerical simulations and discussed in view of the optimal treatment approach.

AMS Classification: 49K21, 49K35, 93C23, 93C95, 92C50
Keywords: delay differential system, optimal control, Cancer cell population, Chronic Myelogenous Leukemia, imatinib.

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1. Introduction

Leukemia, a cancer of the blood or bone marrow characterized by an abnormal increase of blood cells, usually leukocytes (white blood cells), is often classified clinically on the basis of the character of the disease, which is acute or chronic. The acute or chronic nature of leukemia is based upon the rate of progression of the disease, meaning that with no treatment, a patient with acute leukemia will pass away within months, while a patient with chronic leukemia will die in years. This is due to the fact that while in acute leukemia the new cells, called blasts, remain very immature, being unable to accomplish their functions and increasing in number rapidly, in chronic leukemia there are some blast cells present, but they are more mature, being capable to perform some of their functions, and increasing in number less quickly, so the disease develops gradually.

One of the most common types of leukemia is Chronic Myelogenous Leukemia (CML). The disease is thought to arise from a stem cell in the earliest stages of blood cell development. In most cases of CML, the leukemic cells share a chromosomal abnormality not found in any normal cell of the human body. This abnormality is a reciprocal translocation between one chromosome 9 and one chromosome 22 [23]. The consequence is one chromosome 9 longer than normal and one chromosome 22 shorter than normal. The latter is called Philadelphia chromosome and is nominated Ph. The consequence of this process is a fusion gene, which causes the production of an abnormal tyrosine kinase protein, Bcr-Abl. This in turn causes the transformation of bone marrow cells to abnormal leukemic cells ([3], [5]). The precise course of the conversion from normal to cancerous cells at the molecular level is still not completely understood.

Chronic myeloid leukaemia (CML) includes five subtypes, namely [18]:

1. Chronic granulocytic leukemia (CGL) (95%);
2. Juvenile CML (extremely rare);
3. Chronic neutrophilic leukemia (CNL) (extremely rare);
4. Chronic myelomonocytic leukemia (CMML). CMML with low or normal leukocyte counts is classified as a myelodysplastic syndrome; CMML with high leukocyte count is both myelodysplastic and myeloproliferative;
5. Atypical CML (aCML). Intermediate between CGL and CMML but has distinctive features.

Many authors studied CML in their papers: Pujo-Menjouet and Mackey [19] (2005); Nanda, Moore and Lenhart [16] (2007); Roeder et al. [22] (2006); Sawyers [23] (1999); Shah et al. [24] (2008); Kim et al. [9] (2008); Halanay [7] (2010), [8] (2010); Angrstreic [1] (2004), Cortes et al. [2] (2005) etc.

There are few evidences pointing out that CML arises in the hematopoietic stem cell (HSC) compartment, which is the earliest stage of the blood cell formation. We base this statement on two facts:

- in CML, the Philadelphia chromosome is found in all the hematopoietic cell lines which descend from the hematopoietic stem cells [4];

- in one rare variety of CML, periodic oscillations appear in three forms of blood cells [19].

The standard first-line treatment against CML is imatinib, a molecular-targeted drug [1]. It is well known, that imatinib is highly specific to binding with Bcr-Abl, blocking in this way the abnormal protein and thus removing the proliferative advantage that it provides to cancer cells [16]. Under imatinib, almost all patients attain hematological remission [12] and 75% attain cytogenetic remission [2]. Still, imatinib does not entirely eradicate residual leukemia cells and patients inevitably relapse after stopping treatment [9].

A variety of papers have proposed hypothesis regarding the effects of imatinib treatment on leukemia cells from a dynamical system point of view. Roeder et al. [22] (2006) develop a model for the interaction between leukemia and imatinib. In their model, they subdivided the leukemia stem cells in proliferating and quiescent cells and assumed that proliferating leukemia stem cells are affected by imatinib, while quiescent leukemia stem cells are not affected. Due to this additional assumption, the leukemic population under imatinib does not relapse without the effect of imatinib resistance mutations. Another approach is attained in the paper of Komorova and Wodarz [10] (2005), who develop a model that focuses on the drug resistance of leukemia cells. In their model, they implicitly assumed that imatinib affected all leukemia cells and that unavoidable relapse is a consequence of acquired imatinib resistance mutations. Moreover, recent experimental studies attest that in vitro, the Bcr-Abl inhibiting by imatinib or dasatinib is cytotoxic for CML cells [24].

However, it is worth mentioning that although imatinib has transformed CML from a life-threatening disease into a chronic condition, it is now known that this medicine rarely cures CML, and current recommendations dictate lifelong treatment with imatinib [21]. Although there are few hypotheses, the biology behind the failure of imatinib to fully eradicate CML is not completely understood.

As CML is believed to arise in the HSC compartment, our investigation of CML in this paper starts from a system of delay differential equations describing CML in the stem cell compartment. Section 2 displays the mathematical model and the facts that lead us to choose this model for study. We apply optimal control to this model with a molecular targeted therapy, such as imatinib. Our objective in this work is to minimize the cancer cell population and the negative effects of the medicine to the body of a certain patient. In order to achieve this objective, we discretize in Section 3 the optimal control problem and use in Section 4 Maple 14 software programming techniques to plot the graphs of the states, co-states and control. The results are discussed in Section 5 in view of the optimal treatment scheme.

2. The model

Because CML is believed to arise in the stem cell compartment in the bone marrow, we start our study from a mathematical model for stem cells to which we will further refer as "the Mackey model" ([13], [19], [20]). This model consists of a two-dimensional system of delay differential equations with a proliferating phase and a quiescent G_0 phase and starts from the following assertions: a cell entering in the proliferating stage has two choices: to replicate at a fixed time τ and produce two cells, or to die by apoptosis. After division, the two newly born cells enter the resting phase, in which they can either remain, or exit by one of two different ways: by differentiating into one of the committed cell lines (red cells, white cells, platelets), or by re-entering in the proliferating stage.

The Mackey model describing the time-evolution of the stem cells (proliferating and quiescent) is

$$\begin{cases} \dfrac{dx}{dt} = -\left(\beta_0 \dfrac{1}{1+x^n} + \delta\right) x + 2e^{-\gamma\tau}\beta_0 \dfrac{x_\tau}{1+x_\tau^n} \\ \dfrac{dy}{dt} = -\gamma y + \beta_0 \dfrac{x}{1+x^n} - e^{-\gamma\tau}\beta_0 \dfrac{x_\tau}{1+x_\tau^n}, \end{cases} \tag{1}$$

where x represents the density of resting cells, y is the density of proliferating cells and $x_\tau = x(t-\tau)$.

The meanings of the parameters are given below:

- γ represents the rate of apoptosis in the proliferating stage;

- δ is the rate of exit from the resting phase by differentiation;

- β_0 is the maximal rate of cell movement from the resting phase into proliferation;

- n is the parameter controlling the sensitivity of the mitotic re-entry rate β to changes in the size of G_0.

We mention that the term $2e^{-\gamma\tau}\beta_0\dfrac{x_\tau}{1+x_\tau^n}$ in the first equation represents the new daughter cells produced by the surviving mother cells and the term $e^{-\gamma\tau}\beta_0\dfrac{x_\tau}{1+x_\tau^n}$ in the second equation represents the fraction of surviving cells about to leave the proliferating phase that entered a time τ earlier. These terms can be justified technically as follows [19]: the system of differential equations (1) originates actually from an age-structured system of non-linear partial differential equations without delay; after integrating with respect to age, using the method of characteristics and considering some boundary conditions (see [15] for detailed computations), the terms with time delays $e^{-\gamma\tau}\beta_0\dfrac{x_\tau}{1+x_\tau^n}$ and $2e^{-\gamma\tau}\beta_0\dfrac{x_\tau}{1+x_\tau^n}$ appear naturally and have a simple biological explanation as stated above. The mitotic reentry rate from G_0 into proliferation is taken to be a monotone decreasing Hill function of x given by

$$\beta_o\frac{\theta^n}{\theta^n+x^n},$$

where θ is the G_0 stem cell population at which the rate of cell movement from G_0 into proliferation is one-half of its maximal value β_0.

For certain sets of values of parameters, the system of differential equations (1) models the time-evolution of CML stem cells.

In [19] the authors determine the local stability conditions and show under what conditions the Hopf bifurcation may occur. Moreover, they interpret the role of each parameter in loss of stability.

In the following, let us consider a function modeling the treatment with imatinib (or with another tyrosine kinase inhibitor, like dasatinib or nilotinib). Because the treatment with imatinib is thought to affect the stem cells only (or at least mostly) in the proliferative phase, we assume that only the proliferating leukemia cells are affected by this drug. For this reason, because we now expect that the number of

proliferating stem cells to decrease not only because the apoptosis rate, but also because the effect of the treatment itself, in the new control model, to the rate of apoptosis (γ) we add the control function $u(t)$. The control u represents the amount of the drug administered with the value $u = 0$ related to no treatment and $u = 1$ related to a maximum dosage. It is assumed that the amount of the drug stands in a direct relation to the fraction of cells which are being eradicated in the proliferative phase.

We introduce the optimal control model for CML stem leukemic cells:

$$\begin{cases} \dfrac{dx}{dt} = -\left(\beta_0 \dfrac{1}{1+x^n} + \delta\right) x + 2e^{-\tau(\gamma+u(t))}\beta_0 \dfrac{x_\tau}{1+x_\tau^n} \\ \dfrac{dy}{dt} = -\left(\gamma + u(t)\right) y + \beta_0 \dfrac{x}{1+x^n} - e^{-\tau(\gamma+u(t))}\beta_0 \dfrac{x_\tau}{1+x_\tau^n}, \end{cases} \tag{2}$$

where the function $u(t)$ is modeling the treatment with imatinib at time t.

Further, let us suppose that $x(t) = \varphi(t)$, $t \in [-\tau, 0]$ is the history of x.

Optimality in treatment might be defined in a variety of ways. In a number of studies, the total amount of the medicine administered is minimized. The common aim is to kill the tumor while keeping the patient healthy. In our model we choose to minimize the cancer mass at the end of an assumed fixed therapy interval and the cost in terms of the total quantity of the drug administered.

For that reason, the performance index or objective to be minimized is chosen as

$$J(u, x, y) = g\left(x(T), y(T)\right) + \int_0^T L\left(t, u(t)\right) dt \longrightarrow \min, \tag{3}$$

where $g : R^2 \to R$, $g\left(x(t), y(t)\right) = r_1 x(t) + r_2 y(t)$ and $L : [0, T] \times R \to R$, $L\left(t, u(t)\right) = u(t)$, $t \in [0, T]$, $0 \leq u(t) \leq 1$.

The coefficients r_i represents weights and the penalty term $r_1 x(T) + r_2 y(T)$ corresponds to a weighted average of the entire mass of cancer cells at the end of an assumed fixed therapy interval $[0, T]$. The integrand u corresponds to the fraction of the number of cancer cells killed. Given that the drug kills the healthy cells too, this is also used to model the harmful effect of the treatment on the normal tissues or its toxicity [11].

3. Discretization of the optimal problem

Further, we apply the numeric procedure from Gollmann et al. [6] (2009), in order to solve the delayed optimal control problem (2)+(3). For that matter, we may assume that the cost functional (3) is given in the Mayer form

$$J(u,x,y) = g\left(x(T), y(T)\right).$$

In our case, the reduction of the more general cost functional (3) to Mayer form proceeds by the introduction of the additional state variable z through the delayed equation

$$\dot{z}(t) = L\left(t, u(t)\right) \text{ or } \dot{z}(t) = u(t),\ z(0) = 0.$$

Then the cost functional (3) is rewritten in Mayer form

$$J\left(u,x,y\right) = g\left(x(T), y(T)\right) + z(T).$$

We use the Euler integration method with the step size $h = T/N$, where $N \in N_+$ and grid points $t_i = ih$, $i = 0, 1, ..., N$. Using the approximations $x(t_i) \simeq x_i \in R$, $y(t_i) \simeq y_i \in R$ and $u(t_i) \simeq u_i$, the delayed control problem (2)+(3) is converted into the nonlinear programming problem

$$\text{Minimize } J(u,x) = g(x_N) \tag{4}$$

subject to

$$\begin{cases} x_i - x_{i+1} + h\left[-\left(\beta_0 \dfrac{1}{1+x_i^n} + \delta\right) x_i + 2e^{-\tau(\gamma+u_i)}\beta_0 \dfrac{x_{i-k}}{1+x_{i-k}^n}\right] = 0, \\ y_i - y_{i+1} + h\left[-\left(\gamma + u_i\right) y_i + \beta_0 \dfrac{x_i}{1+x_i^n} - e^{-\tau(\gamma+u_i)}\beta_0 \dfrac{x_{i-k}}{1+x_{i-k}^n}\right] = 0, \end{cases} \tag{5}$$

$$i = \overline{0, N-1}.$$

Herein, the initial value profile φ provides the values

$$x_{-i} := \varphi(-ih),\ i = \overline{0,k}. \tag{6}$$

In this case, the optimization variable is represented by the vector

$$z := (u_0, x_1, y_1, u_1, x_2, y_2, ..., u_{N-1}, x_N, y_N) \in R^{3N}.$$

The Lagrangian function for NLP is given by

$$
\begin{aligned}
L(z,\lambda) \;:=\; & g(x_N)+\sum_{i=0}^{N-1}\lambda_{1i}^T\left\{x_i-x_{i+1}+h\left[-\left(\beta_0\frac{1}{1+x_i^n}+\delta\right)x_i+\right.\right.\\
& +\left.\left. 2e^{-\tau(\gamma+u_i)}\beta_0\frac{x_{i-k}}{1+x_{i-k}^n}\right]\right\}+\\
& +\sum_{i=0}^{N-1}\lambda_{2i}^T\left\{y_i-y_{i+1}+h\left[-(\gamma+u_i)\,y_i+\beta_0\frac{x_i}{1+x_i^n}-\right.\right.\\
& -\left.\left. e^{-\tau(\gamma+u_i)}\beta_0\frac{x_{i-k}}{1+x_{i-k}^n}\right]\right\},
\end{aligned}
\tag{7}
$$

with Lagrange multipliers $\lambda_{ji}=(\lambda_{j0},\lambda_{j1},...,\lambda_{jN-1})\in R^N$, $j=1,2$, $i=0,...,N-1$.

The Karush-Kuhn-Tucker (KKT) necessary optimality conditions for NLP (4)+(5) imply the existence of Lagrange multipliers satisfying the following equations

$$
\begin{cases}
\dfrac{\partial L}{\partial x_i}(z,\lambda)=0, \quad \dfrac{\partial L}{\partial y_i}(z,\lambda)=0, & i=\overline{0,N},\\
\dfrac{\partial L}{\partial u_i}(z,\lambda)=0, & i=\overline{0,N-1},
\end{cases}
$$

or equivalently

$$
\begin{aligned}
\lambda_{1i}^T-\lambda_{1i-1}^T &= -h\left\{-\delta\lambda_{1i}^T+\beta_0\frac{1+(1-n)x_i^n}{(1+x_i^n)^2}\left[-\lambda_{1i}^T+\lambda_{2i}^T+\right.\right.\\
&+\left.\left. e^{-\tau(\gamma+u_{i+k})}\left(-2\lambda_{1i+k}^T-\lambda_{2i+k}^T\right)\right]\right\}, i=\overline{1,N-k-1},\\
\lambda_{1i}^T-\lambda_{1i-1}^T &= -h\left\{-\delta\lambda_{1i}^T+\beta_0\frac{1+(1-n)x_i^n}{(1+x_i^n)^2}\left[-\lambda_{1i}^T+\lambda_{2i}^T\right]\right\}, i=\overline{N-k,N-1},\\
\lambda_{2i}^T-\lambda_{2i-1}^T &= -h\lambda_{2i}^T u_i, \qquad i=\overline{1,N-1}\\
\lambda_{1N-1}^T &= g_x(x_N),\\
\lambda_{2N-1}^T &= g_x(y_N).
\end{aligned}
$$

We applied the above numerical procedure and obtain in the next section the graphs of the time-evolution of the model.

4. Numerical simulations for the optimal problem

In this section, we used Maple 14 software programming techniques for the values of the parameters taken from estimates in the literature ([13], [19]). For $\delta=0.024,\gamma=0.228,\beta_0=0.053,\tau=1.41,n=4,r_1=r_2=1,T=3.6$ and

$x(t) = 10^{-4}$, $t \in [-\tau, 0], y(0) = 10^{-4}, u(0) = 1$, we obtain the evolution in time for the states, costates and control in Fig. 1-3.

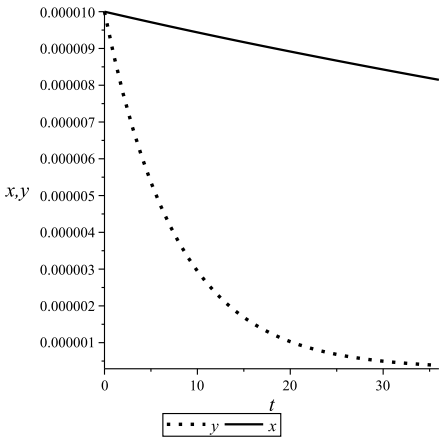

Fig. 1 - The states

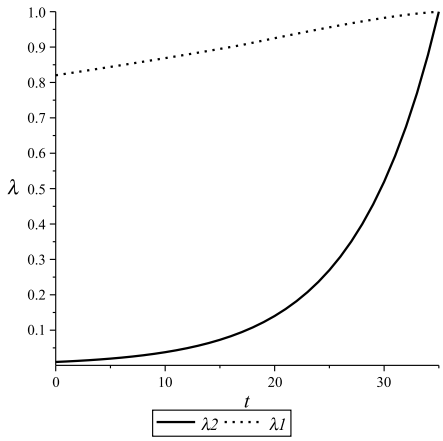

Fig. 2 - The costates

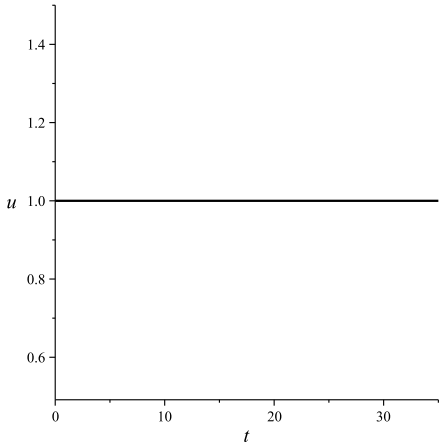

Fig. 3 - The control

In Fig. 4 we choose the same values as in Fig. 3, except for the initial value of the control function which was chosen $u(0) = 0$ (i.e. no treatment at $t_0 = 0$). Because in this case the control function rapidly increases to a peak value $u(t) = 1$ one can easily states that the optimal approach to handle the cure protocol is to start the treatment with the maximal dose of the medicine.

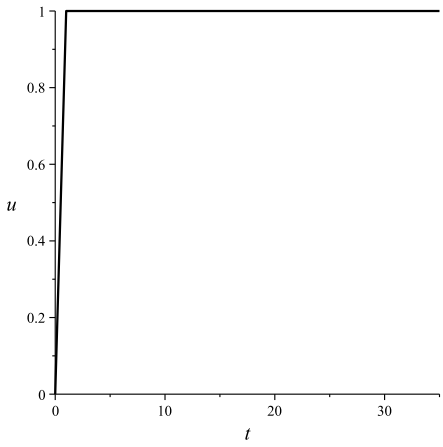

Fig. 4 - The control

For Fig. 5-7 the values of the parameters are $\delta = 0.01, \gamma = 0.069, \beta_0 = 0.020, \tau = 4.25, n = 4, r_1 = r_2 = 1, T = 3.4$ and $x(t) = 10^{-4}$, $t \in [-\tau, 0], y(0) = 10^{-4}, u(0) = 1$ and for Fig. 8-10 we have $\delta = 0.038, \gamma = 0.599, \beta_0 = 0.077, \tau = 1.15, n = 4$, $r_1 = r_2 = 1, T = 3.6$ and $x(t) = 10^{-4}$, $t \in [-\tau, 0], y(0) = 10^{-4}, u(0) = 1$.

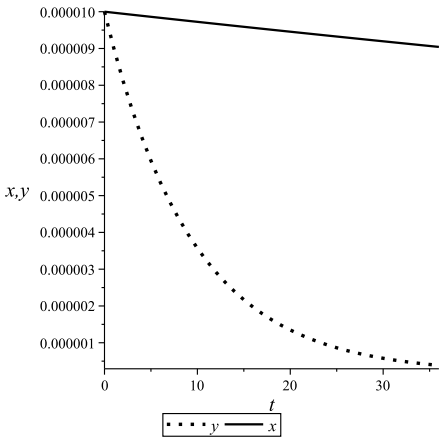

Fig. 5 - The states

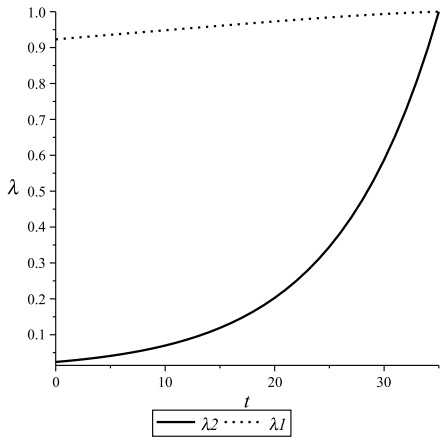

Fig. 6 - The costates

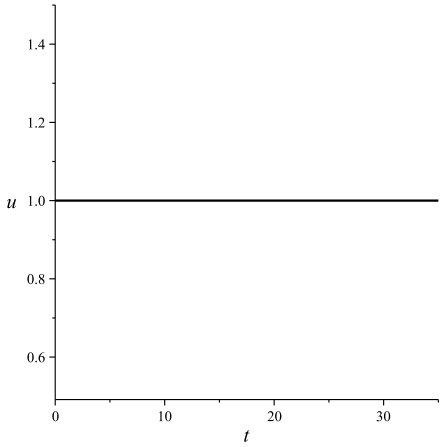

Fig. 7 - The control

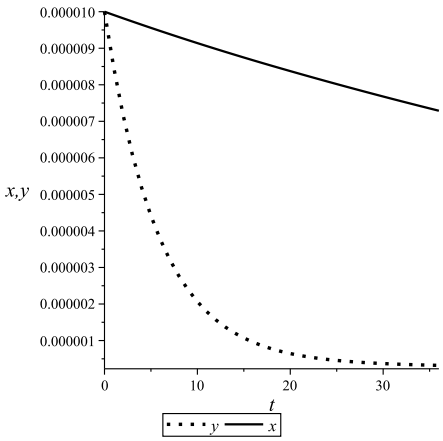

Fig. 8 - The states

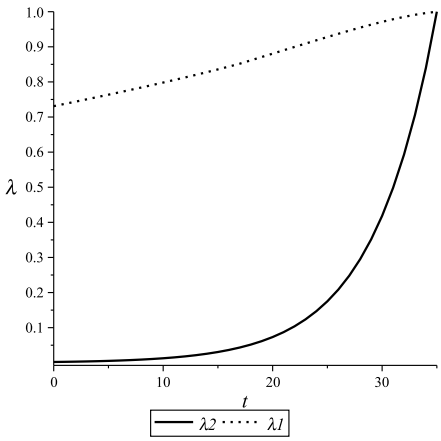

Fig. 9 - The costates

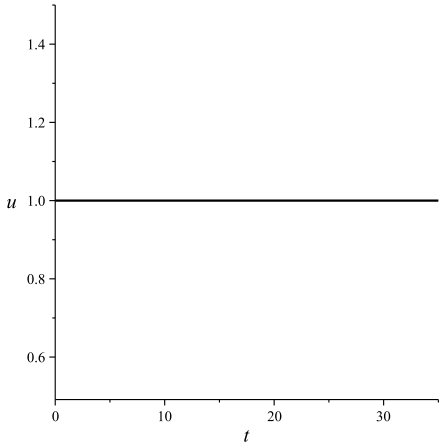

Fig. 10 - The control

An interesting remark is that if we increase the value of δ (from $\delta = 0.3$ in Fig. 11 to $\delta = 0.9$ in Fig.12 and to $\delta = 1.4$ in Fig. 13) and keep the other parameters as in Fig. 1-3, the graph of x changes drastically, indicating, as in the case of y, a major decrease.

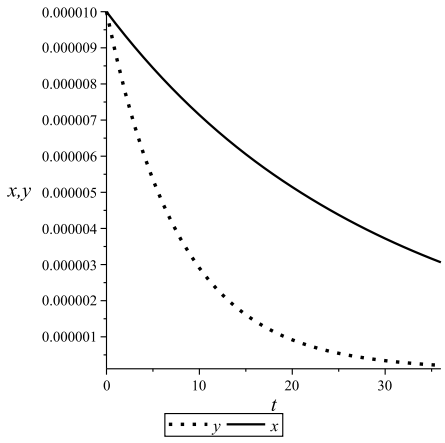

Fig. 11 - The states with $\delta = 0.3$

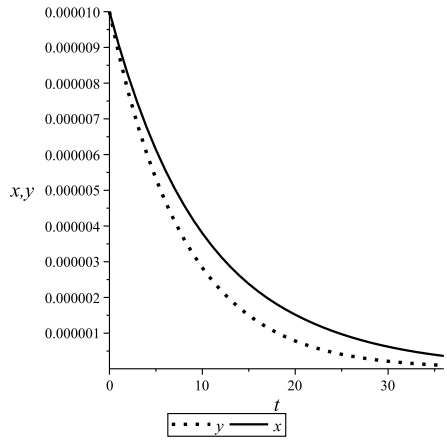

Fig. 12 - The states with $\delta = 0.9$

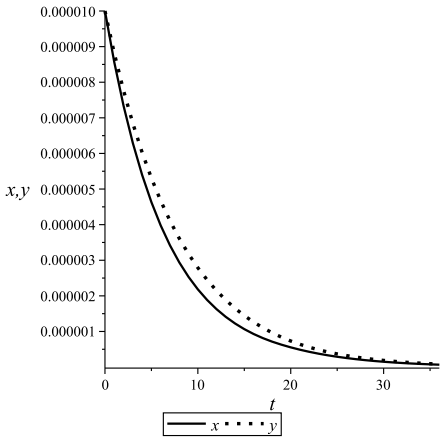

Fig. 13 - The states with $\delta = 1.4$

Also, as we may expect, increasing the value of the maximal rate of cell movement from the resting phase into proliferation from $\beta_0 = 0.053$ (Fig. 1) to $\beta_0 = 0.4$ (Fig. 14) and to $\beta_0 = 0.9$ (Fig.15) and keep the other parameters as in Fig. 1-3, leads to a increasingly faster decrease of the graph of x.

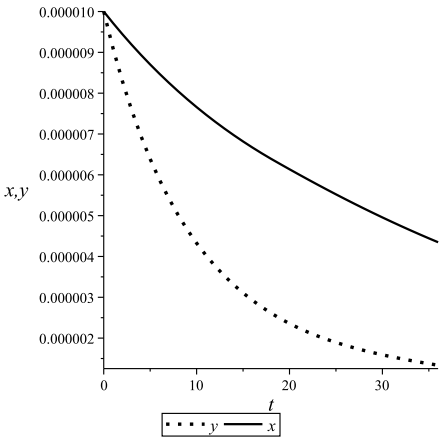

Fig. 14 - The states with $\beta_0 = 0.4$

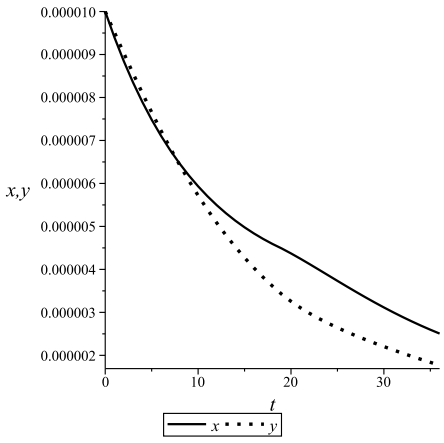

Fig. 15 - The states with $\beta_0 = 0.9$

5. Discussion

All the graphs for the states plotted in the previous section attest that the number of both the proliferating (y) and the resting (x) cancerous cell decrease as the

treatment is initiated, even though the number of resting cells decreases much slower than the number of proliferating cells.

The most important conclusion based on the figures plotted in the previous section indicate that the optimal treatment scheme for CML with imatinib or dasatinib should attain its highest value from the first dose and sustain it to the entire treatment-time.

At the present, for patients with chronic-phase CML, imatinib is initiated at a daily oral dose of 400 mg, a procedure that begins as soon as the diagnosis is made [17]. Nevertheless, the maximum dose allowed for treatment with imatinib is 800 mg daily, a dosage which because of the higher cost and more severe adverse effects is rarely recommended.

However, experimental and clinical studies suggest that a major goal of therapy with imatinib should be to achieve an early major molecular response, the treatment with high-dose imatinib (i.e. 800 mg) being the most significant aspect associated with an increased probability of achieving a molecular response, particularly at earlier time points (i.e. 12 months) [2].

The numerical results of this study are in concordance with recent clinical studies, indicating that the dosages of imatinib administered to a patient with CML should be invariable and at a maximum dose allowed. Of course, the sensibility of each patient to the adverse effects of the drugs should be taken into consideration. Furthermore, the reality that some patients relapse after stopping the treatment with imatinib may possibly be a consequence of the fact showed by the graphs that the number of resting cells decreases extremely slowly.

In that respect, we varied (increased or decreased) the value of a certain parameter (keeping the others constant) in order to see what changes produce major modifications in the behavior of x and y. The most important positive change was noticed when we increased the value of δ (see Fig. 11-13). In that case, both x and y decreased in time, indicating that a possible approach to overcome the disease by killing both proliferating and resting leukemia stem cells is finding a drug that increases the differentiation rate δ. Of course, because we assumed that only the proliferating stem cells are affected by imatinib, another approach in order to eradicate CML stem cells would be to increase the maximal rate of cell movement from the resting into proliferating stage β_0, as we observe from Fig. 14-15.

In conclusion, in order to completely overcome CML, the treatment scheme with imatinib should be enhanced with an additional medicine designed to decrease the number of resting cancerous cells using one of the two methods described above.

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