A COMPLEX MODEL OF CELL EVOLUTION IN LEUKEMIA INCLUDING COMPETITION AND THE ACTION OF THE IMMUNE SYSTEM[*]

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Dedicated to Dr. Vasile Drăgan on the occasion of his 70th anniversary

Abstract

The model studied in this paper describes the competitive interaction between healthy and malignant cells in leukemia with the involvement of the immune system. The model consists of 9 delay-differential equations with 9 delays. Local stability is investigated for the equilibrium points of the system. Lyapunov-Krasovskii functionals related

to some of these points are constructed. The evolution of the disease is studied numerically within different scenarios that show that some particular circumstances can lead to recovery. This can be an important support for combined therapies that trigger the leukemia and at the same time stimulate the action of the immune system.
MSC: 34K20, 92D25, 92C50

keywords: delay differential equations, stability, chronic myelogenous leukemia, CD8+cytotoxic T-cells

1   Introduction

Leukemia is a cancer of the blood and bone marrow distinguished by a large number of white blood cells. Chronic myelogenous leukemia (CML), or chronic granulocytic leukemia, is a clonal stem cells disorder. It is characterized by the proliferation of granulocytes and their precursors in the bone marrow and the accumulation of these cells in the blood stream. The trigger of CML is a chromosomal abnormality, called the Philadelphia chromosome (denoted Ph) that causes the formation of the Bcr-Abl fusion gene. This gene is thought to be the one responsible for the abnormal myelocyte proliferation (see [16], [31]).

Although CML is one of the most studied types of leukemia (see [13], [3], [25], [12], [19]), only relatively recently has the immune system been included in models (see [8], [21], [22], [23],[26], [27]). This is mainly due to the fact that the immune system is very complex and its mechanism is not completely understood.

A description of the activation of the immune system and the effect of the immune system on the population of malignant cells can be found in [8]. The model presented in this paper is an extension of the model from [8]. In order to obtain a more accurate representation of the biological interactions that occur during CML, we included the competition between the healthy and the malignant cells. It is a novelty for cell competition to be considered. It is also the first time that a feedback action of the immune system is studied while taking into consideration the appropriate time delays. The paper [26] studies a model of ordinary differential equations (ODE) where only the dynamics of the mature leukemic cells related to the response of the immune system is considered. The approach in [21],[22],[23], [27], that partly inspired the present paper, consider another set of ODE equations for the leukemic cells and are different also in other aspects from the present

paper.

2 The model

The mathematical model we study was introduced in [7] (see also [5]), but without many details. It describes the dynamics of healthy and leukemic cells in CML in competition and the action of the immune system in response to the disease.

The model consists of 9 delay differential equations with 9 delays. The first four state variables are the stem-like healthy and leukemic cells (x_1 and x_3 respectively) and the mature healthy and leukemic cells (x_2 and x_4) in the white blood cells(myeloid) lineage. The next five variables represent the immune system, as follows: the concentration of naive APCs (x_5), the concentration of mature APCs (x_6), the concentration of naive T cells of both CD4+ and CD8+ phenotypes (x_7), the concentration of active CD4+ T-helper cells (x_8) and the concentration of active CD8+ cytotoxic T-cells (CTL) (x_9).

The stem-like cells are presumed to spend a relatively short period in the resting phase and will be deemed as short-term hematopoietic stem cells (ST-HSC). Following [5], [9],[24], [19], [30] and [32], we assume that a fraction $\eta_{1\alpha}$, $\alpha = h, l$ (h for healthy and l for leukemia), of these cells are susceptible for asymmetric division, meaning that one daughter cell proceeds to differentiate, while the other re-enters the stem-like cell population. Another percentage $\eta_{2\alpha}$, $\alpha = h, l$, is thought to be susceptible to differentiate symmetrically (both daughter cells are mature) while a percentage $1 - \eta_{1\alpha} - \eta_{2\alpha}$, $\alpha = h, l$, is susceptible to self-renewal (both daughter cells are stem-like cells).

The healthy and leukemic blood cell populations are seen in competition for resources and this is reflected in the fact that both feedback laws for self-renewal and differentiation depend on the sum of healthy and leukemic cells. For details, see [29].

Following [3] and [13], the rate of self-renewal is

$$\beta_\alpha(x_1 + x_3) = \beta_{0\alpha} \frac{\theta_{1\alpha}^{m_\alpha}}{\theta_{1\alpha}^{m_\alpha} + (x_1 + x_3)^{m_\alpha}}, \quad \alpha = h, l$$

(h for healthy and l for leukemia) with $\beta_{0\alpha}$ the maximal rate of self-renewal and $\theta_{1\alpha}$ half of the maximal value.

The rate of differentiation is

$$k_\alpha(x_2 + x_4) = k_{0\alpha} \frac{\theta_{2\alpha}^{n_\alpha}}{\theta_{2\alpha}^{n_\alpha} + (x_2 + x_4)^{n_\alpha}}, \quad \alpha = h, l.$$

where $k_{0\alpha}$ is the maximal rate of differentiation and $\theta_{2\alpha}$ is half of the maximal value.

The terms $m_\alpha, n_\alpha, \alpha = h, l$, control the sensitivity of β_α and k_α, $\alpha = h, l$ to changes in the population size.

The decrease of the healthy stem-like cell population is determined by a mortality rate γ_{1h} (the natural apoptosis), the percentage $\eta_{1h} + \eta_{2h}$ of the population that leaves to differentiate and the percentage $1 - \eta_{1h} - \eta_{2h}$ that leaves in order to go through self-renewal. The population increases by $2e^{-\gamma_{1h}\tau_1}(1 - \eta_{1h} - \eta_{2h})$ and $\eta_{1h}e^{-\gamma_{1h}\tau_1}$. These represent the cells that went through self-renewal and asymetric division. These cells return, after a time period of τ_1, to the stem-like cell population, diminished due to mortality during the cell cycle.

The dynamics of the healthy mature population is governed by a mortality rate γ_{2h} (the natural apoptosis) and by the percentage $2\eta_{2h} + \eta_{1h}$ of healthy stem-like cells that go through differentiation. The latter become mature cells after a period of time τ_2. The term A_h is an multiplication (amplification) factor.

The evolution of the leukemic cell populations mirrors those of the healthy cell populations, with the exception of the terms $b_6 x_3 x_9 l_1(x_4)$ in the third equation and $b_4 x_4 x_9 l_1(x_4)$ in the equation of x_4. These terms correspond to the mortality of the leukemic cells due to the interaction with the cytotoxic T-cells. They replace the exponential term considered in the models studied in [21], [28]

The following feedback functions regulate the evolution of the immune system and its interaction with leukemic cells:

$$\zeta_1(x) = \frac{1}{1 + x^p}, \quad \zeta_2(x) = \frac{x^2 + e_5}{x^2 + e_6},$$

$$l_1(x) = \frac{1}{b_1 + x^2}, \quad l_2(x) = \frac{x}{b_2 + x^2}, \quad l_3(x) = \frac{x}{b_3 + x^2}$$

The fifth equation describes the changes in the naive APCs population in the presence of leukemic cells. It is assumed that there is a constant supply (c_1) of naive APCs even in the absence of any disease and they die with an apoptosis rate c_2. When leukemic cells are detected, a fraction $c_3 l_2(x_4)$ mature into cells specialized to fight leukemia. We assume that, as the number of leukemic cells grows, the action of the immune system is supressed. This is expressed through the denominator of the feedback function $l_2(x_4)$. The mature APCs (x_6) have a mortality rate d_1.

The evolution of the naive T cells population, which contains both the naive CD4+ T cells and the naive CD8+ T cells, is depicted in the seventh

equation. It is assumed that there is a constant supply of naive T cells d_3 and a mortality rate d_2. By the law of mass action, when coming in contact with specialized mature APCs, a fraction d_{41} of the naive T cells mature into T-helpers (x_8). Another fraction d_{42} of the naive T cells mature into cytotoxic T-cells (x_9).

After finishing the minimal developmental program of m_1 cell divisions which lasts τ_7 days, the naive CD4+ T cells enter the active state with a term given by $2^{m_1} d_{41} x_{6\tau_7} x_{7\tau_7}$ (the last term in the eighth equation). The first term of the eighth equation represents the natural mortality of the cells. The second term illustrates the self-stimulation of T helpers for further division (the autocrine loop, represented by the function ζ_1). The time delay τ_5 represents the duration of one CD4+ T cell division after which the cells reenter the effector CD4+ population. The fourth term $(-e_3\zeta_2(x_8)x_8)$ is the number of active CD4+ cells that are suppressed by the regulatory mechanisms.

The naive CD8+ T cells also go through a minimal developmental program of m_2 cell divisions. This lasts τ_8 days. After this, the cells enter the mature CD8+ T cell population as $2^{m_2} d_{42} x_{6\tau_8} x_{7\tau_8}$ (the last term in the ninth equation). The mortality rate of the T-cytotoxic cells is e_4. The second term $(-e_7\zeta_1(x_8)x_8 x_9)$ is the rate at which CTLs are stimulated by positive growth signal (Il-2) secreted by CD4+T helper cells, for further division.

The third term $(2e^{-e_4\tau_6} e_7\zeta_1(x_{8\tau_6})x_{8\tau_6}x_{9\tau_6})$ is the number of cells that reenter the effector cytotoxic population after having divided once. The time delay τ_6 is the duration of one cycle of CD8+ T cells division.

The fourth term $(-e_3\zeta_2(x_8)x_9)$ gives the number of CTLs that are suppressed by the regulatory mechanisms, due especially to the action of Tregs. The fifth and sixth terms illustrate the interaction with the mature leukemic cells. Leukemia cells suppress anti-leukemia immune response. The precise mechanism is unknown. It is assumed that the level of down-regulation depends on the current leukemia population and this suppresive action is expressed by the presence of the mature population of leukemic cells (x_4) in the denominator of the function l_3 in the the fifth term $(-b_5x_9l_3(x_4))$. The sixth term in the ninth equation reflects the stimulation effect on the CD8+ T-cytotoxic cells due to the encounter with leukemia cells. n_1 is the number of divisions that take place in the time period $\tau_9 = n_1\tau_6$.

The model, taking into consideration the response of the immune system, is:

$$\dot{x}_1 = -\gamma_{1h}x_1 - (\eta_{1h} + \eta_{2h})k_h(x_2 + x_4)x_1 - (1 - \eta_{1h} - \eta_{2h})\beta_h(x_1 + x_3)x_1 +$$

$$+2e^{-\gamma_{1h}\tau_1}(1-\eta_{1h}-\eta_{2h})\beta_h(x_{1\tau_1}+x_{3\tau_1})x_{1\tau_1}+\eta_{1h}e^{-\gamma_{1h}\tau_1}k_h(x_{2\tau_1}+x_{4\tau_1})x_{1\tau_1}$$

$$\dot{x}_2 = -\gamma_{2h}x_2 + A_h(2\eta_{2h}+\eta_{1h})k_h(x_{2\tau_2}+x_{4\tau_2})x_{1\tau_2}$$

$$\dot{x}_3 = -\gamma_{1l}x_3 - (\eta_{1l}+\eta_{2l})k_l(x_2+x_4)x_3 - (1-\eta_{1l}-\eta_{2l})\beta_l(x_1+x_3)x_3+$$

$$+2e^{-\gamma_{1l}\tau_3}(1-\eta_{1l}-\eta_{2l})\beta_l(x_{1\tau_3}+x_{3\tau_3})x_{3\tau_3}+\eta_{1l}e^{-\gamma_{1l}\tau_3}k_l(x_{2\tau_3}+x_{4\tau_3})x_{3\tau_3}-$$

$$-b_6x_3x_9l_1(x_4)$$

$$\dot{x}_4 = -\gamma_{2l}x_4 + A_l(2\eta_{2l}+\eta_{1l})k_l(x_{2\tau_4}+x_{4\tau_4})x_{3\tau_4} - b_4x_4x_9l_1(x_4)$$

$$\dot{x}_5 = -c_2x_5 + c_1 - c_3x_5l_2(x_4)$$

$$\dot{x}_6 = -d_1x_6 + c_3x_5l_2(x_4)$$

$$\dot{x}_7 = -d_2x_7 + d_3 - d_4x_6x_7$$

$$\dot{x}_8 = -e_1x_8 - e_2\zeta_1(x_8)x_8 + 2e^{-e_1\tau_5}e_2\zeta_1(x_{8\tau_5})x_{8\tau_5} - e_3\zeta_2(x_8)x_8+$$

$$+2^{m_1}d_{41}x_{6\tau_7}x_{7\tau_7}$$

$$\dot{x}_9 = -e_4x_9 - e_7\zeta_1(x_8)x_8x_9 + 2e^{-e_4\tau_6}e_7\zeta_1(x_{8\tau_6})x_{8\tau_6}x_{9\tau_6} - e_3\zeta_2(x_8)x_9-$$

$$-b_5x_9l_3(x_4) + 2^{n_1}e_8x_{9\tau_9}l_3(x_{4\tau_9}) + 2^{m_2}d_{42}x_{6\tau_8}x_{7\tau_8}$$

The following notation was used for the delayed variables: $x_\tau = x(t-\tau)$.

Remark that, due to the presence of delayed terms, if the initial condition is positive, the solution will be positive on all the interval on which exists.

Several feedback functions are considered when modeling the action of the immune system. This is a major difference to the nonautonomous models in [22], [23].

3 Equilibrium points

We introduce the following notation for the previous system:

$$\dot{x}_i = f_i(x, x_{\tau_j}), i = \overline{1,9}, j = \overline{1,9}, x = (x_1, \ldots, x_9)$$

The equilibrium points are obtained solving the equations $f_i(x,x) = 0$, $i = \overline{1,9}$.

Solving the system, we get four possible types of equilibrium points:
$E_1 = (0,0,0,0,x_5^*,0,x_7^*,0,0)$ which corresponds to the "death of the patient",
$E_2 = (x_1^*, x_2^*, 0, 0, x_5^*, 0, x_7^*, 0, 0)$ which can be viewed as a healthy state,
$E_3 = (0, 0, \hat{x}_3, \hat{x}_4, \hat{x}_5, \hat{x}_6, \hat{x}_7, \hat{x}_8, \hat{x}_9)$ which reflects the situation where the leukemic cells have almost completely replaced the healthy cells and

$E_4 = (\tilde{x}_1, \tilde{x}_2, \tilde{x}_3, \tilde{x}_4, \tilde{x}_5, \tilde{x}_6, \tilde{x}_7, \tilde{x}_8, \tilde{x}_9)$ which corresponds to a chronic phase of the disease.

As we are modelling cell populations, these equilibrium points need to be positive. By solving the equations $f_i(x,x) = 0$, $i = \overline{1,9}$, we notice that in order for E_3 and E_4 to make sense biologically, the following condition must be met:

$$e_4 + e_3\zeta_2(x_8) + b_3l_3(x_4) > e_7\zeta_1(x_8)x_8 + 2e^{-e_4\tau_6}e_7\zeta_1(x_8)x_8 + 2^{n_1}e_8l_3(x_4)$$

4   Linear stability analysis

In this section we will give parameter conditions for stability and then present numerical simulations. The numerical results and simulations are obtained in MATLAB. A full list of parameters' value is given in section 7. The time units for all the simulations are considered as days and the units for the populations of cells are 10^3 *cells per microlitre of blood.*

Let $A = (a_{ij})_{i,j=\overline{1,9}}$ be the matrix of the derivatives of the system with respect to $x_1, x_2, x_3, x_4, x_5, x_6, x_7, x_8$ and x_9 calculated in an equilibrium point. For the same equilibrium point, we also consider the following matrices:

- $B_{\tau_1} = (b_{ij})_{i,j=\overline{1,9}}$ containing the derivatives with respect to $x_{1\tau_1}$, $x_{2\tau_1}$, $x_{3\tau_1}$, $x_{4\tau_1}, x_{5\tau_1}, x_{6\tau_1}, x_{7\tau_1}, x_{8\tau_1}$ and $x_{9\tau_1}$

- $C_{\tau_2} = (c_{ij})_{i,j=\overline{1,9}}$ containing the derivatives with respect to $x_{1\tau_2}$, $x_{2\tau_2}$, $x_{3\tau_2}, x_{4\tau_2}, x_{5\tau_2}, x_{6\tau_2}, x_{7\tau_2}, x_{8\tau_2}$ and $x_{9\tau_2}$

- $D_{\tau_3} = (d_{ij})_{i,j=\overline{1,9}}$ containing the derivatives with respect to $x_{1\tau_3}$, $x_{2\tau_3}$, $x_{3\tau_3}, x_{4\tau_3}, x_{5\tau_3}, x_{6\tau_3}, x_{7\tau_3}, x_{8\tau_3}$ and $x_{9\tau_3}$

- $E_{\tau_5} = (e_{ij})_{i,j=\overline{1,9}}$ containing the derivatives with respect to $x_{1\tau_4}$, $x_{2\tau_4}$, $x_{3\tau_4}, x_{4\tau_4}, x_{5\tau_4}, x_{6\tau_4}, x_{7\tau_4}, x_{8\tau_4}$ and $x_{9\tau_4}$

- $F_{\tau_5} = (f_{ij})_{i,j=\overline{1,9}}$ containing the derivatives with respect to $x_{1\tau_5}$, $x_{2\tau_5}$, $x_{3\tau_5}, x_{4\tau_5}, x_{5\tau_5}, x_{6\tau_5}, x_{7\tau_5}, x_{8\tau_5}$ and $x_{9\tau_5}$

- $G_{\tau_6} = (g_{ij})_{i,j=\overline{1,9}}$ containing the derivatives with respect to $x_{1\tau_6}$, $x_{2\tau_6}$, $x_{3\tau_6}, x_{4\tau_6}, x_{5\tau_6}, x_{6\tau_6}, x_{7\tau_6}, x_{8\tau_6}$ and $x_{9\tau_6}$

- $H_{\tau_7} = (h_{ij})_{i,j=\overline{1,9}}$ containing the derivatives with respect to $x_{1\tau_7}$, $x_{2\tau_7}$, $x_{3\tau_7}, x_{4\tau_7}, x_{5\tau_7}, x_{6\tau_7}, x_{7\tau_7}, x_{8\tau_7}$ and $x_{9\tau_7}$

- $K_{\tau_8} = (k_{ij})_{i,j=\overline{1,9}}$ containing the derivatives with respect to $x_{1\tau_8}$, $x_{2\tau_8}$, $x_{3\tau_8}, x_{4\tau_8}, x_{5\tau_8}, x_{6\tau_8}, x_{7\tau_8}, x_{8\tau_8}$ and $x_{9\tau_8}$

○ $L_{\tau_9} = (l_{ij})_{i,j=\overline{1,9}}$ containing the derivatives with respect to $x_{1\tau_9}$, $x_{2\tau_9}$, $x_{3\tau_9}$, $x_{4\tau_9}, x_{5\tau_9}, x_{6\tau_9}, x_{7\tau_9}, x_{8\tau_9}$ and $x_{9\tau_9}$

The caracteristic equation is:

$$\det(\lambda I_9 - A - B_{\tau_1}e^{-\lambda\tau_1} - C_{\tau_2}e^{-\lambda\tau_2} - D_{\tau_3}e^{-\lambda\tau_3} - E_{\tau_4}e^{-\lambda\tau_4} - F_{\tau_5}e^{-\lambda\tau_5} - G_{\tau_6}e^{-\lambda\tau_6} -$$

$$-H_{\tau_7}e^{-\lambda\tau_7} - K_{\tau_8}e^{-\lambda\tau_8} - L_{\tau_9}e^{-\lambda\tau_9}) = 0$$

4.1 Stability study of the equilibrium point E_1

In what follows, for the convenience of the reader, we briefly recall the main results from [5] where the stability of equilibrium point E_1 has been studied.

The characteristic equation corresponding to the linearization of the system relative to the E_1 is:

$$(\lambda - a_{22})(\lambda - a_{44})(\lambda - a_{55})(\lambda - a_{66})(\lambda - a_{77})(\lambda - a_{99})(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})\cdot$$

$$\cdot(\lambda - a_{33} - d_{33}e^{-\lambda\tau_3})(\lambda - a_{88} - f_{88}e^{-\lambda\tau_5}) = 0$$

It is well known (see [10], [17], [20]) that, in order for an equilibrium point to be stable, the roots of the characteristic equation must all have negative real parts. We notice that $a_{22} = -\gamma_{2h} < 0, a_{44} = -\gamma_{2l} < 0, a_{55} = -c_2 < 0, a_{66} = -d_1 < 0, a_{77} = -d_2 < 0$ and $a_{99} = -e_4 - e_3\dfrac{e_5}{e_6} < 0$. Thus, we only need to study the remaining four equations. The study of these equations with the method presented in [14] yields the following necessary and sufficient delay independent stability conditions for E_1:

$$\text{I.} \qquad \lambda - a_{11} - b_{11}e^{-\lambda\tau_1} = 0 \qquad (1)$$

Proposition 1. *Assume that the following condition is met:*

$$(1 - \eta_{1h} - \eta_{2h})\beta_{0h} < \gamma_{1h} + \eta_{2h}k_{0h}. \qquad (2)$$

Then equation (1) is stable for $\tau_1 = 0$ and it remains stable for all $\tau_1 > 0$.

$$\text{II.} \qquad \lambda - a_{33} - d_{33}e^{-\lambda\tau_3} = 0 \qquad (3)$$

Proposition 2. *Assume that the following condition is met:*

$$(1 - \eta_{1l} - \eta_{2l})\beta_{0l} < \gamma_{1l} + \eta_{2l}k_{0l}. \qquad (4)$$

Then equation (3) is stable for $\tau_3 = 0$ and it remains stable for all $\tau_3 > 0$.

$$\text{III.} \qquad\qquad \lambda - a_{88} - f_{88}e^{-\lambda\tau_5} = 0 \qquad\qquad (5)$$

Proposition 3. _Assume that the following condition is met:_

$$e_2 < e_1 + \frac{e_3 e_5}{e_6}. \qquad\qquad (6)$$

Then equation (5) is stable for $\tau_5 = 0$ and it remains stable for all $\tau_5 > 0$.

Remark 1. _The equilibrium point E_1 is stable if equations (1), (3) and (5) are stable._

4.1.1 Numerical simulations for equilibrium point E_1

The equilibrium point $E_1 = (0, 0, 0, 0, 0.9999, 0, 0.6666, 0, 0)$ is unstable, as neither of the conditions 2, 4 or 6 are met. We can also see this is figure 1, where we notice that the unstable equlibrium point is attracted by a healthy state. This is sometimes the case after chemotherapy. The pacient is left with only a small amount of neutrophiles in the system and still has a chance to recover.
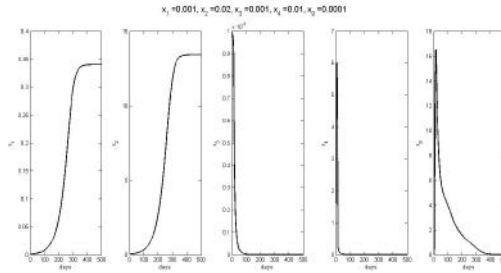

Figure 1: Evolution of healthy and leukemic cell populations starting near E_1

4.2 Stability study of the equilibrium point E_2

The characteristic equation corresponding to the linearization of the system with respect to the equilibrium E_2 is:

$$(\lambda - a_{44})(\lambda - a_{55})(\lambda - a_{66})(\lambda - a_{77})(\lambda - a_{99})(\lambda - a_{33} - d_{33}e^{-\lambda\tau_3})(\lambda - a_{88} - f_{88}e^{-\lambda\tau_5}) \cdot$$

$$\cdot [(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})(\lambda - a_{22} - c_{22}e^{-\lambda\tau_2}) - c_{21}e^{-\lambda\tau_2}(a_{12} + b_{12}e^{-\lambda\tau_1})] = 0$$

This characteristic equation decouples into 8 equations that can be studied separately, as follows.

We notice that $a_{44} = -\gamma_{2l} < 0, a_{55} = -c_2 < 0, a_{66} = -d_1 < 0, a_{77} = -d_2 < 0$ and $a_{99} = -e_4 - e_3\dfrac{e_5}{e_6} < 0$.

As for E_1, the 6th and 7th equations can be studied through the theorems presented in [14], [17].

$$\text{I.} \qquad\qquad \lambda - a_{33} - d_{33}e^{-\lambda\tau_3} = 0 \qquad\qquad (7)$$

Proposition 4. *Assume that the following condition is met:*

$$(1 - \eta_{1l} - \eta_{2l})\beta_l(x_1^*) < \gamma_{1l} + \eta_{2l}k_l(x_2^*). \qquad\qquad (8)$$

Then equation (7) is stable for $\tau_3 = 0$ and it remains stable for all $\tau_3 > 0$.

Proof. For the equilibrium point E_2 we have:

$$a_{33} = -\gamma_{1l} - (\eta_{1l} + \eta_{2l})k_l(x_2^*) - (1 - \eta_{1l} - \eta_{2l})\beta_l(x_1^*)$$

$$d_{33} = e^{-\gamma_{1l}\tau_3}[2(1 - \eta_{1l} - \eta_{2l})\beta_l(x_1^*) + \eta_{1l}k_l(x_2^*)].$$

For $\tau_3 = 0$ the equation (7) becomes:

$$\lambda - (1 - \eta_{1l} - \eta_{2l})\beta_l(x_1^*) + \gamma_{1l} + \eta_{2l}k_l(x_2^*)$$

Equation (7) is stable for $\tau_3 > 0$ if

$$(1 - \eta_{1l} - \eta_{2l})\beta_l(x_1^*) < \gamma_{1l} + \eta_{2l}k_l(x_2^*).$$

When $\tau_3 > 0$, since $d_{33} > 0$, the following conditions must hold for stability:

1. $a_{33} < \dfrac{1}{\tau_3}$

2. $a_{33} + d_{33} < 0$

The first condition is fulfilled since $a_{33} < 0 < \dfrac{1}{\tau_3}$. For the second condition to hold we must have:

$$e^{-\gamma_{1l}\tau_3} < \frac{\gamma_{1l} + (\eta_{1l} + \eta_{2l})k_l(x_2^*) + (1 - \eta_{1l} - \eta_{2l})\beta_l(x_1^*)}{2(1 - \eta_{1l} - \eta_{2l})\beta_l(x_1^*) + \eta_{1l}k_l(x_2^*)}. \qquad (9)$$

We notice that condition (9) holds if (8) holds. $\qquad\square$

Remark 2. *If condition (8) does not hold, then there might be a stability switch if condition (9) holds for some $\tau_3 > 0$.*

II. $$\lambda - a_{88} - f_{88}e^{-\lambda\tau_5} = 0 \qquad (10)$$

Proposition 5. *Assume that the following condition is met:*

$$e_2 < e_1 + \frac{e_3 e_5}{e_6}. \qquad (11)$$

Then equation (10) is stable for $\tau_5 = 0$ and it remains stable for all $\tau_5 > 0$.

Proof. Similarly to the proof of Proposition 4, we recall that for the equilibrium point E_2 we have:

$$a_{88} = -e_1 - e_2 - \frac{e_3 e_5}{e_6}$$

$$f_{88} = 2e^{-e_1\tau_5}e_2$$

Equation (10) is stable for $\tau_5 = 0$ if

$$e_2 < e_1 + \frac{e_3 e_5}{e_6}.$$

For $\tau_5 > 0$, since $f_{88} > 0$ and $a_{88} < 0$, the following stability condition must be met:

$$2e^{-e_1\tau_5}e_2 < e_1 + e_2 + \frac{e_3 e_5}{e_6}. \qquad (12)$$

We notice that, if condition (11) holds, then (12) holds. $\qquad\square$

Next, we study the following equation:

$$(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})(\lambda - a_{22} - c_{22}e^{-\lambda\tau_2}) - c_{21}e^{-\lambda\tau_2}(a_{12} + b_{12}e^{-\lambda\tau_1}) = 0 \quad (13)$$

Proposition 6. *Assume that the following conditions hold:*

$$a_{11} + b_{11} + a_{22} + c_{22} < 0$$
$$(a_{11} + b_{11})(a_{22} + c_{22}) - c_{21}(a_{12} + b_{12}) > 0 \qquad (14)$$

Then equation (13) is stable for $\tau_1 = \tau_2 = 0$.

Proof. For $\tau_1 = \tau_2 = 0$ equation (13) becomes:

$$\lambda^2 - \lambda(a_{11} + b_{11} + a_{22} + c_{22}) + (a_{11} + b_{11})(a_{22} + c_{22}) - c_{21}(a_{12} + b_{12}) = 0 \quad (15)$$

In order for both roots of equation (15) to be in the left half-plane, the following conditions must hold:

$$a_{11} + b_{11} + a_{22} + c_{22} < 0$$
$$(a_{11} + b_{11})(a_{22} + c_{22}) - c_{21}(a_{12} + b_{12}) > 0$$

$\qquad\qquad\square$

To simplify the calculations, we introduce the following notations:

$$\alpha_1 = a_{11} + b_{11} + a_{22}$$

$$\beta_1 = a_{22}(a_{11} + b_{11})$$

$$\alpha_2 = -c_{22}$$

$$\beta_2 = c_{22}(a_{11} + b_{11}) - c_{21}(a_{12} + b_{12})$$

Proposition 7. *If either condition*

$$(\alpha_1^2 - 2\beta_1 - \beta_2^2)^2 - 4(\beta_1^2 - \alpha_2^2) > 0 \tag{16}$$

or condition

$$\alpha_1^2 - 2\beta_1 - \beta_2^2 < 0 \tag{17}$$

does not hold, then, if equation (13) is stable for $\tau_1 = \tau_2 = 0$, it will remain stable for $\tau_1 = 0$ and $\tau_2 > 0$.

Proof. Consider $\tau_1 = 0$ and $\tau_2 > 0$. Equation (13) becomes:

$$\lambda^2 - \alpha_1\lambda + \beta_1 + e^{-\lambda\tau_2}(\beta_2 + \alpha_2\lambda) = 0 \tag{18}$$

In order to study this equation we use Theorem 1 from [15]. We define

$$P(z) = z^2 - \alpha_1 z + \beta_1$$

$$Q(z) = \alpha_2 z + \beta_2$$

Note that conditions (ii) and (iii) from the theorem are satisifed and conditions (i), (iv) and (v) are most likely to hold.

The stability of equation (18) depends on the roots of the equation:

$$|P(iy)|^2 = |Q(iy)|^2 \tag{19}$$

If equation (19) has no $y > 0$ as a root then, if (18) is stable with $\tau_2 = 0$, it will be stable for all $\tau_2 > 0$. If equation (19) has at least one positive root and all the positive roots are simple, as τ_2 increases there might be stability switches. Thus, if (18) is stable at $\tau_2 = 0$, it may become unstable when $\tau_2 = \tau_2^*$.

Let $P(iy) = P_R(y) + iP_I(y)$ and $Q(iy) = Q_R(y) + iQ_I(y)$, with P_R, P_I, Q_R, Q_I real valued.

Equation (19) becomes:

$$P_R^2(y) + P_I^2(y) = Q_R^2(y) + Q_I^2(y)$$

We have the following 4th degree equation:

$$y^4 + y^2(\alpha_1^2 - 2\beta_1 - \beta_2^2) + \beta_1^2 - \alpha_2^2 = 0 \tag{20}$$

For $x = y^2$ we get

$$x^2 + x(\alpha_1^2 - 2\beta_1 - \beta_2^2) + \beta_1^2 - \alpha_2^2 = 0 \tag{21}$$

In order for equation (20) to have at least one positive simple real root, the following conditions must hold:

$$\Delta = (\alpha_1^2 - 2\beta_1 - \beta_2^2)^2 - 4(\beta_1^2 - \alpha_2^2) > 0$$

$$\alpha_1^2 - 2\beta_1 - \beta_2^2 < 0$$

For the equation to be stable, at least one of the above conditions must not be met. □

We next consider $\tau_1 = \tau_1^*$ fixed and $\tau_2 > 0$. Equation (13) becomes:

$$(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1^*})(\lambda - a_{22} - c_{22}e^{-\lambda\tau_2}) - c_{21}e^{-\lambda\tau_2}(a_{12} + b_{12}e^{-\lambda\tau_1^*}) = 0 \tag{22}$$

The above equation can be rewritten as:

$$P(\lambda) + Q(\lambda)e^{-\lambda\tau_2} = 0$$

where

$$P(\lambda) = \lambda^2 - (a_{11} + a_{22})\lambda + a_{11}a_{22} - (b_{11}\lambda + a_{22}b_{11})e^{-\lambda\tau_1^*}$$

$$Q(\lambda) = -c_{22}\lambda + a_{11}c_{22} - a_{12}c_{21} + (b_{11}c_{22} - b_{12}c_{21})e^{-\lambda\tau_1^*}.$$

Remark 3. *Assume that equation $|P(iy)|^2 - |Q(iy)|^2 = 0$ has no positive real roots. Then, if equation (22) is stable for $\tau_1 = 0$ and $\tau_2 = 0$, it will remain stable for $\tau_1 = \tau_1^*$ and all $\tau_2 > 0$.*

As $P(z)$ and $Q(z)$ are analytic functions, we can apply the results of Theorem 1 from [15]. Like before, for $z = iy$, we are interested in the roots of the following equation:

$$F(y) = |P(iy)|^2 - |Q(iy)|^2.$$

We have:

$$F(y) = y^4 + 2b_{11}y^3\sin(\tau_1^*y) + k_1y^2 + 2a_{11}b_{11}y^2\cos(\tau_1^*y)+$$

$$+k_2 y \sin(\tau_1^* y) + k_3 \cos(\tau_1^* y) + k_4, \tag{23}$$

where

$k_1 = a_{11}^2 + a_{22}^2 + b_{11}^2 - c_{22}^2$

$k_2 = 2a_{22}^2 b_{11} - 2b_{11} c_{22}^2 + 2b_{12} c_{21} c_{22}$

$k_3 = 2a_{11} b_{12} c_{21} c_{22} + 2a_{11} a_{22}^2 b_{11} - 2a_{11} b_{11} c_{22}^2 - 2a_{12} b_{12} c_{21}^2 + 2a_{12} b_{11} c_{21} c_{22}$

$k_4 = a_{11}^2 a_{22}^2 + a_{22}^2 b_{11}^2 - a_{11}^2 c_{22}^2 - a_{12}^2 c_{21}^2 - b_{11}^2 c_{22}^2 - b_{12}^2 c_{21}^2 + 2a_{11} a_{12} c_{21} c_{22} +$

$\quad + 2b_{11} b_{12} c_{21} c_{22}$

If equation (23) has no $y > 0$ as a root then, if (13) is stable with $\tau_1 = 0$ and $\tau_2 = 0$, it will be stable for all $\tau_2 > 0$ and $\tau_1 = \tau_1^*$.

Remark 4. *The equilibrium point E_2 is stable if equations (7), (10), (18) and (22) are all stable.*

4.2.1 Numerical simulations for equilibrium point E_2

The equilibrium point $E_2 = (0.7168, 22.9413, 0, 0, 0.9999, 0, 0.6666, 0, 0)$ is asymptotically stable. Figure 2 shows the evolution of cell populations when there is a very small burden of leukemic cells.
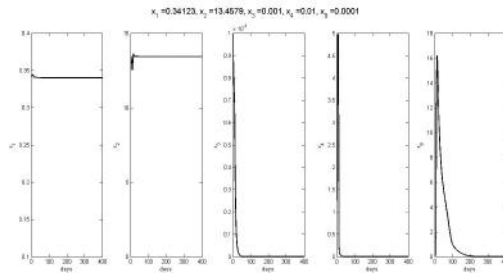

Figure 2: Evolution of healthy and leukemic cell populations starting near E_2

4.3 Stability study for the equilibrium points E_3 and E_4 - a Lyapunov-Krasovskii approach

The Lyapunov-Krasovskii functional presented in [6] for the reduced model can be generalized for the physiological model. We obtain sufficient conditions for local stability.

We perform a translation to zero: $y_i = x_i - \hat{x}_i, \ i = \overline{1, 9}$.

For $\dot{y}_i = h_i(y, y_{\tau_j})$, we consider the following candidate Lyapunov-Krasovskii functional defined on the state space $C\left([-\tau, 0], \mathbb{R}^n\right)$, where $\tau = \max\{\tau_j\}$, $j = \overline{1,9}$:

$$V(\phi) = \sum_{i=1}^{9} \alpha_i \phi_i^2(0) + \sum_{j=1}^{9}\left(\beta_j \int_{t-\tau_j}^{t} \phi_j^2(s)ds + \sum_{i \neq j} \delta_{ij} \int_{t-\tau_j}^{t} \phi_i^2(s)ds \right),$$

with $\alpha_i \geq 0, \beta_j \geq 0, \forall i = \overline{1,9}, j = \overline{1,9}$ and $\delta_{ij} \geq 0$ for $i \neq j$.

For $V^*(t) = V(y_t)$, as $y_t(0) = y(t)$, we have:

$$V = \sum_{i=1}^{9} \alpha_i y_i^2 + \sum_{j=1}^{9}\left(\beta_j \int_{t-\tau_j}^{t} y_j^2(s)ds + \sum_{i \neq j} \delta_{ij} \int_{t-\tau_j}^{t} y_i^2(s)ds \right),$$

with $\alpha_i \geq 0, \beta_j \geq 0, \forall i = \overline{1,9}, j = \overline{1,9}$ and $\delta_{ij} \geq 0$ for $i \neq j$.

As we are working in the framework of stability in the first approximation, consider one of the former equilibrium points $(\bar{x}_1, \bar{x}_2, \bar{x}_3, \bar{x}_4, \bar{x}_5, \bar{x}_6, \bar{x}_7, \bar{x}_8, \bar{x}_9)$ and denote the system in deviations as

$$\dot{y}_i = g_i(y, y_{\tau_j}),$$

where

$$g_i(y) = \sum_{k=1}^{9} \frac{\partial f_i}{\partial y_k}(\bar{x}) y_k + \sum_{k,j} \frac{\partial f_i}{\partial y_{k\tau_j}}(\bar{x}) y_{k\tau_j}$$

By denoting the coefficients in g_i, $i = \overline{1,9}$ we obtain:

$$
\begin{aligned}
g_1(y) =& \ v_{11}y_1 + v_{12}y_2 + v_{13}y_3 + v_{12}y_4 + v_{14}y_{1\tau_1} + \\
& +v_{15}y_{2\tau_1} + v_{16}y_{3\tau_1} + v_{15}y_{4\tau_1} \\
g_2(y) =& \ v_{21}y_2 + v_{22}y_{1\tau_2} + v_{23}y_{2\tau_2} + v_{23}y_{4\tau_2} \\
g_3(y) =& \ v_{31}y_3 + v_{32}y_1 + v_{33}y_2 + v_{34}y_4 + v_{35}y_9 + \\
& +v_{36}y_{3\tau_3} + v_{37}y_{1\tau_3} + v_{38}y_{2\tau_3} + v_{38}y_{4\tau_3} \\
g_4(y) =& \ v_{41}y_4 + v_{42}y_3 + v_{43}y_{4\tau_4} + v_{44}y_{2\tau_4} + v_{45}y_{3\tau_4} \\
g_5(y) =& \ v_{51}y_5 + v_{52}y_4 \\
g_6(y) =& \ v_{61}y_6 + v_{62}y_4 + v_{63}y_5
\end{aligned}
$$

$$g_7(y) = v_{71}y_7 + v_{72}y_6$$

$$g_8(y) = v_{81}y_8 + v_{82}y_{6\tau_7} + v_{83}y_{7\tau_7} + v_{84}y_{8\tau_5}$$

$$g_9(y) = v_{91}y_9 + v_{92}y_8 + v_{93}y_4 + v_{94}y_{7\tau_8} + v_{95}y_{6\tau_8} +$$

$$+ v_{96}y_{9\tau_6} + v_{97}y_{8\tau_6} + v_{98}y_{9\tau_9} + v_{99}y_{4\tau_9}$$

Proposition 8. *Assume the following conditions hold:*

$$\left[\frac{v_{14}^2}{\beta_1} + \frac{v_{15}^2}{\delta_{21}} + \frac{v_{16}^2}{\delta_{31}} + \frac{v_{15}^2}{\delta_{41}} + 2v_{12}^2 + v_{13}^2 \right] \alpha_1^2 + 2v_{11}\alpha_1 + (\beta_1 + \delta_{12} + \delta_{13} + 1) < 0$$

$$\left[\frac{v_{23}^2}{\beta_2} + \frac{v_{22}^2}{\delta_{12}} + \frac{v_{23}^2}{\delta_{41}} \right] \alpha_2^2 + 2v_{21}\alpha_2 + (\beta_2 + \delta_{21} + \delta_{23} + \delta_{24} + 2) < 0$$

$$\left[\frac{v_{36}^2}{\beta_3} + \frac{v_{37}^2}{\delta_{13}} + \frac{v_{38}^2}{\delta_{23}} + \frac{v_{38}^2}{\delta_{43}} + v_{32}^2 + v_{33}^2 + v_{34}^2 + v_{35}^2 \right] \alpha_3^2 + 2v_{31}\alpha_3 + (\beta_3 + \delta_{31} + \delta_{34} + 2) < 0$$

$$\left[\frac{v_{43}^2}{\beta_4} + \frac{v_{44}^2}{\delta_{24}} + \frac{v_{45}^2}{\delta_{34}} + v_{42}^2 \right] \alpha_4^2 + 2v_{41}\alpha_4 + (\beta_4 + \delta_{41} + \delta_{42} + \delta_{43} + \delta_{49} + 4) < 0$$

$$v_{52}^2\alpha_5^2 + 2v_{51}\alpha_5 + 1 < 0$$

$$\left[v_{62}^2 + v_{63}^2 \right] \alpha_6^2 + 2v_{61}\alpha_6 + (\delta_{67} + 1) < 0$$

$$v_{72}^2\alpha_7^2 + 2v_{71}\alpha_7 + (\beta_7 + \delta_{78}) < 0$$

$$\left[\frac{v_{83}^2}{\beta_7} + \frac{v_{82}^2}{\delta_{67}} + \frac{v_{84}^2}{\delta_{85}} \right] \alpha_8^2 + 2v_{81}\alpha_8 + (\delta_{85} + \delta_{86} + 1) < 0$$

$$\left[\frac{v_{98}^2}{\beta_9} + \frac{v_{94}^2}{\delta_{78}} + \frac{v_{95}^2}{\delta_{68}} + \frac{v_{96}^2}{\delta_{96}} + \frac{v_{97}^2}{\delta_{86}} + \frac{v_{99}^2}{\delta_{49}} + v_{92}^2 + v_{93}^2 \right] \alpha_9^2 + 2v_{91}\alpha_9 + (\beta_9 + \delta_{96}) < 0.$$

Then the equilibrium points E_3 and E_4 are stable, independent of delays.

Proof. The derivative of V with respect to time is:

$$\frac{dV}{dt} = \sum_{i=1}^{9} 2\alpha_i y_i g_i(y) + \sum_{j=1}^{9} \left(\beta_j \left[y_j^2(t) - y_j^2(t - \tau_j) \right] + \sum_{i \neq j} \delta_{ij} \left[y_i^2(t) - y_i^2(t - \tau_j) \right] \right).$$

Sufficient stability conditions are obtained by forcing $\dfrac{dV}{dt}$ to be negative. We will only show the calculations corresponding to the terms that come from $g_1(y)$, as all the others are done similarly.

The stability conditions arise from:

$$2\alpha_1 v_{11} y_1^2 + 2\alpha_1 v_{12} y_1 y_2 + 2\alpha_1 v_{13} y_1 y_3 + 2\alpha_1 v_{12} y_1 y_4 + 2\alpha_1 v_{14} y_1 y_{1\tau_1} +$$

$$+2\alpha_1 v_{15} y_1 y_{2\tau_1} + 2\alpha_1 v_{16} y_1 y_{3\tau_1} + 2\alpha_1 v_{15} y_1 y_{4\tau_1} + \beta_1 y_1^2 - \beta_1 y_{1\tau_1}^2 - \quad (24)$$

$$-\delta_{21} y_{2\tau_1}^2 - \delta_{31} y_{3\tau_1}^2 - \delta_{41} y4\tau_1^2 + \delta_{21} y_2^2 + \delta_{31} y_3^2 + \delta_{41} y_4^2 < 0$$

We create perfect squares by adding and substracting terms, such as:

$$2\alpha_1 c_{14} y_1 y_{1\tau_1} - \beta_1 y_{1\tau_1}^2 + \frac{\alpha_1^2 c_{14}^2}{\beta_1} y_1^2 - \frac{\alpha_1^2 c_{14}^2}{\beta_1} y_1^2 = -\left(\frac{\alpha_1 c_{14}}{\sqrt{\beta_1}} y_1 - \sqrt{\beta_1} y_{1\tau_1} \right)^2 + \boxed{\frac{\alpha_1^2 c_{14}^2}{\beta_1} y_1^2}$$

and

$$2\alpha_1 c_{12} y_1 y_2 + \alpha_1^2 c_{12}^2 y_1^2 - \alpha_1^2 c_{12}^2 y_1^2 + y_2^2 - y_2^2 = -\left(\alpha_1 c_{12} y_1 - y_2 \right)^2 + \boxed{\alpha_1^2 c_{12}^2 y_1^2} + \boxed{y_2^2}$$

The term y_2^2 will be taken into account in the conditions that come from studying $g_2(y)$. In doing so with every problematic term in (24), we restrict the coefficient of y_1^2 as follows:

$$\left[\frac{v_{14}^2}{\beta_1} + \frac{v_{15}^2}{\delta_{21}} + \frac{v_{16}^2}{\delta_{31}} + \frac{v_{15}^2}{\delta_{41}} + 2v_{12}^2 + v_{13}^2 \right] \alpha_1^2 + 2v_{11}\alpha_1 + (\beta_1 + \delta_{12} + \delta_{13} + 1) < 0$$

By applying the same method with the next 8 parts of $\dfrac{dV}{dt}$ corresponding to the functions $g_i(y)$, $i = \overline{2,9}$, we obtain the *sufficient stability conditions*:

$$\left[\frac{v_{23}^2}{\beta_2} + \frac{v_{22}^2}{\delta_{12}} + \frac{v_{23}^2}{\delta_{41}} \right] \alpha_2^2 + 2v_{21}\alpha_2 + (\beta_2 + \delta_{21} + \delta_{23} + \delta_{24} + 2) < 0$$

$$\left[\frac{v_{36}^2}{\beta_3} + \frac{v_{37}^2}{\delta_{13}} + \frac{v_{38}^2}{\delta_{23}} + \frac{v_{38}^2}{\delta_{43}} + v_{32}^2 + v_{33}^2 + v_{34}^2 + v_{35}^2 \right] \alpha_3^2 + 2v_{31}\alpha_3 + (\beta_3 + \delta_{31} + \delta_{34} + 2) < 0$$

$$\left[\frac{v_{43}^2}{\beta_4} + \frac{v_{44}^2}{\delta_{24}} + \frac{v_{45}^2}{\delta_{34}} + v_{42}^2\right]\alpha_4^2 + 2v_{41}\alpha_4 + (\beta_4 + \delta_{41} + \delta_{42} + \delta_{43} + \delta_{49} + 4) < 0$$

$$v_{52}^2\alpha_5^2 + 2v_{51}\alpha_5 + 1 < 0$$

$$\left[v_{62}^2 + v_{63}^2\right]\alpha_6^2 + 2v_{61}\alpha_6 + (\delta_{67} + 1) < 0$$

$$v_{72}^2\alpha_7^2 + 2v_{71}\alpha_7 + (\beta_7 + \delta_{78}) < 0$$

$$\left[\frac{v_{83}^2}{\beta_7} + \frac{v_{82}^2}{\delta_{67}} + \frac{v_{84}^2}{\delta_{85}}\right]\alpha_8^2 + 2v_{81}\alpha_8 + (\delta_{85} + \delta_{86} + 1) < 0$$

$$\left[\frac{v_{98}^2}{\beta_9} + \frac{v_{94}^2}{\delta_{78}} + \frac{v_{95}^2}{\delta_{68}} + \frac{v_{96}^2}{\delta_{96}} + \frac{v_{97}^2}{\delta_{86}} + \frac{v_{99}^2}{\delta_{49}} + v_{92}^2 + v_{93}^2\right]\alpha_9^2 + 2v_{91}\alpha_9 + (\beta_9 + \delta_{96}) < 0.$$

$$\square$$

The stability conditions concern the linear system. From the *Stability in the first approximation theorem*, a stability result is transfered to the nonlinear system. The study of stability of equilibria for equations with multiple delays has been approached by many authors . Especially interesting are the recent papers [27], [4], [11], [28].

4.3.1   Numerical simulations for equilibrium points E_3 and E_4

While $E_{31} = (0, 0, 0.0027, 13.7986, 0.8066, 0.5800, 0.0017, 0.0538, 6.0394)$ and $E_4 = (0.7812, 10.5986, 0.0493, 44.1989, 0.9299, 0.2102, 0.0047, 0.0536, 5.0211)$ are unstable, $E_{32} = (0, 0, 1.2462, 103.4748, 0.9687, 0.0936, 0.0105, 0.0531, 4.6697)$ is asymptotically stable.

Equilibrium points E_{31} and E_4 display different behaviours depending on the initial conditions. In figures 3 and 5 we clearly see that the pacient's condition improves. Figures 4 and 6 show the case in which the patient has taken a turn for the worse. Both situations occur in the neighborhoods of E_{31} and E_4 respectively. In the first situation, E_{31} and E_4 are attracted to a healthy state. In the latter case, the patient's blood cell populations stabilize around equilibrium point E_{32}.
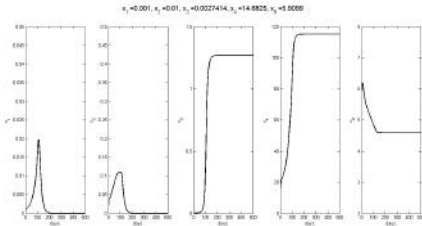

Figure 3: Evolution of healthy and leukemic cell populations starting near E_{31} (the patient recovers)
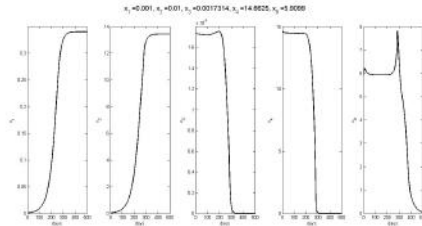

Figure 4: Evolution of healthy and leukemic cell populations starting near E_{31} (the patient's condition worsened)
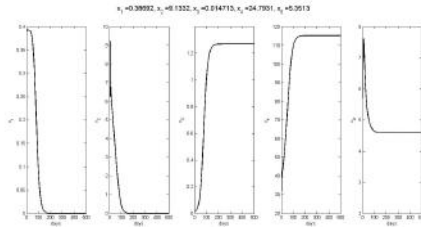
Figure 5: Evolution of healthy and leukemic cell populations starting near E_4 (the patient's condition worsened)
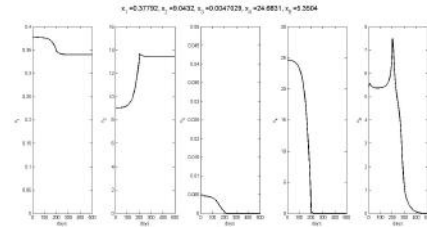
Figure 6: Evolution of healthy and leukemic cell populations starting near E_4 (the patient recovers)

5   The immune system and different scenarios for the evolution of the disease

Figures 7 and 8 show the evolution of the healthy and leukemic cell populations with and without the influence of the immune system (when $b_4 = 0$). We can see that the response of the immune system to the leukemic cells is important. It helps slow down the growth of leukemic cells and the decrease of healthy cells until treatment can be administrated.
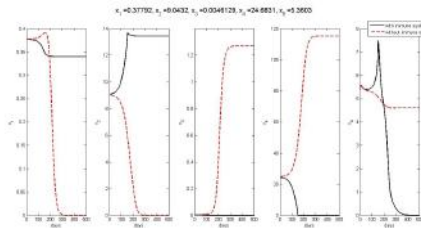

Figure 7: Evolution of healthy and leukemic cell populations with and without the influence of the immune system starting near E_4
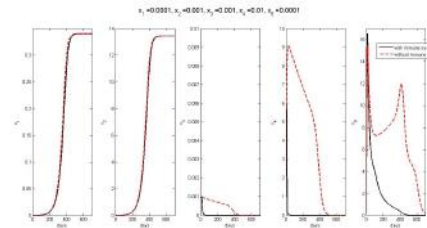
Figure 8: Evolution of healthy and leukemic cell populations with and without the influence of the immune system starting near E_1

In real life, there are not two persons with the same parameters. This is why the evolution of any disease is different from pacient to pacient. Even for the same person, the parameters may change with time. Accordingly, it is important to see the progression of the disease for different parameter values. To do so, we considered two other scenarios. These will be presented

as compared to the configuration of the initial parameters. We will refer to the latter as the default scenario.

○ *Scenario 2* - a more aggressive evolution of the leukemic cells

For some people, leukemia has a faster evolution. To illustrate this, we considered a lower apoptosis rate ($\gamma_{2l} = 0.1$) and higher multiplication (amplification) rate for the mature leukemic cells ($A_l = 4800$). We also increased the predisposition of stem-like leukemic cells to go through differentiation($\theta_{1l} = 0.8$, $\theta_{2l} = 20$).
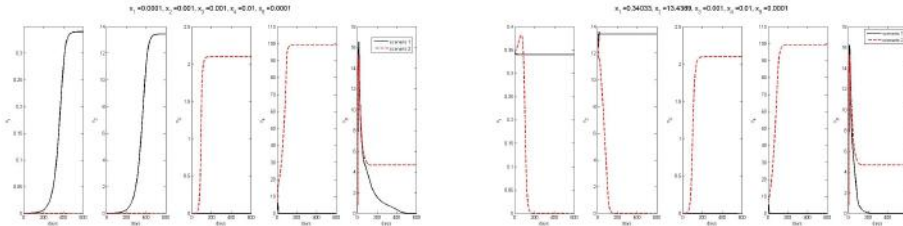

Figure 9: Scenario 2 ($\gamma_{2l} = 0.1$, $A_l = 4800$, $\theta_{1l} = 0.8$, $\theta_{2l} = 20$)

Figure 10: Scenario 2 ($\gamma_{2l} = 0.1$, $A_l = 4800$, $\theta_{1l} = 0.8$, $\theta_{2l} = 20$)

As it can be seen in figures 9 and 10, a more aggressive evolution of leukemic cells can lead to the patient's death.

○ *Scenario 3* - a slower evolution of the leukemic cells

In this scenario, the leukemic cells have a more similar evolution to the healthy cells. The mortality rates for both the naive and mature cells are the same as the ones for the healthy cells ($\gamma_{1l} = 0.1$, $\gamma_{2l} = 1.5$). The rates of symmetric and asymmetric division are closer in value to those of healthy cells ($\eta_{1l} = 0.2$, $\eta_{2l} = 0.5$).
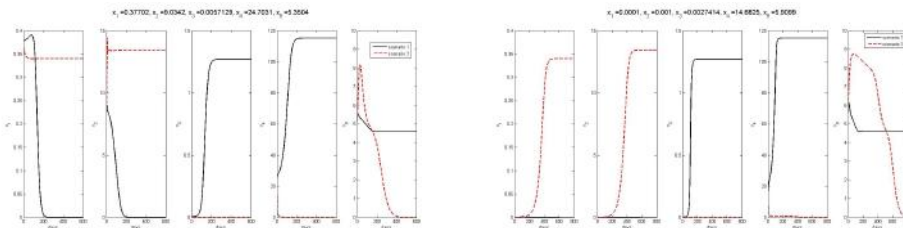

Figure 11: Scenario 3 ($\gamma_{1l} = 0.1$, $\gamma_{2l} = 1.5$, $\eta_{1l} = 0.2$, $\eta_{2l} = 0.5$)

Figure 12: Scenario 3 ($\gamma_{1l} = 0.1$, $\gamma_{2l} = 1.5$, $\eta_{1l} = 0.2$, $\eta_{2l} = 0.5$)

For these parameter values, the patient has more chances to reaching a healthy state, as can be seen in figures 11 and 12.

6   Conclusions

In this paper, it is for the first time that the dynamics of leukemic and healthy cell populations in CML is analyzed, taking into account the effect of cell competition and the complex involvement of the immune system. In the construction of the mathematical model, using delay differential equations, two important assumptions are made: i) leukemic cells suppress anti-leukemia immune response, ii) only cytotoxic T-cells actively fight leukemic cells. Four types of steady states were found analytically. We infer that each of them corresponds to a certain phase, namely: 1) to the disease free (healthy) situation - equilibria E_2; 2) to an incipient or middle stage of the disease when there are still enough healthy cells - equilibria E_4; 3) to an aggravated phase of leukemia when the healthy cell populations were subject to a serious decline - equilibria E_3 and 4) to the last condition, corresponding to death - equilibria E_1. Two steady states of type E_3 (denoted E_{31} and E_{32}) are found numerically, for certain sets of parameters values. The equilibrium point E_{31} corresponds to a less aggravated phase, while E_{32} corresponds to a more aggravated one. The stability of the steady states is analyzed through the decomposition of the characteristic equation or by constructing Lyapunov-Krasovskii functionals.

Numerical simulations validate the model and show the importance of the immune system in the fight against the illness. Before the leukemic cell population grows large enough in order to be able to inhibit the immune system, the cytotoxic T-cells slow the growth of leukemic cells. As expected, the immune system is not sufficient to cure CML, but it plays an important role in the evolution of the disease.

The tumor burden at the time of the diagnosis - related to some type of the equilibrium and the features of the disease accompanied by the possible determination of some of the parameters, might be an important decision factor in planning the treatment strategy. This strategy might involve the type and/or the dose of the medicine, in order to affect some of the cell multiplication rates. Certainly, this could also include combinations of drugs.

From our analysis, we observe that the dynamics of the system around the equilibrium points is highly dependent on the parameters' values. In order to get a better view of the evolution of leukemia, three different parameter configurations (scenarios) are considered. For the first scenario, the

parameter values were taken mainly from literature. This is called the default scenario. The next two scenarios illustrate a more aggressive leukemia, respectively a less aggressive one. As expected, the results varied significantly. This is important, as the disease progresses differently for every patient. For example, comparing scenario 2 with the default scenario, one can notice that for the same type of equilibria (E_2 - Fig. 8, respectively E_4 - Fig. 9), the dynamics of the system changes drastically. The same conclusion stands when comparing the scenario 3 with the default scenario (equilibria E_{31} - Fig. 10, equilibria E_4 - Fig. 11). These findings suggest that, from a clinical point of view, not only the tumor amount at the moment of the diagnosis is important, but also the characteristics of the patients leukemia. From a treatment perspective, developing some technical means in order to compute the important specific parameters for a certain patient, would create the premise for a better treatment strategy, adapted to the disease phase and features. However, this is a challenging task and it still belongs to the medicine of the future.

7 List of parameter values

Coefficient of the feedback function l_1	b_1	2
Coefficient of the feedback function l_2	b_2	1.5
Coefficient of the feedback function l_3	b_3	5
Loss of mature leukemic leukocytes due to cytotoxic T cells	b_4	0.6
Coefficient for apopthosis rate and regulatory mechanism	b_5	0.8
Loss of stem-like leukemic cells due to cytotoxic T cells	b_6	0.06

Supply dayly rate of immature APCs ([23])	c_1	0.3
Death/turnover daily rate of immature APCs ([23])	c_2	0.3
Coefficient of the feedback function	c_3	1
Death/turnover daily rate of mature APC ([23])	d_1	0.1
Supply rate of naive T cells both fenotypes ([23])	d_3	0.02
Death/turnover daily rate of naive CD4+ and CD8+ T cells ([23])	d_2	0.03
Kinetic coefficient ([22])	d_4	20
Kinetic coefficients ([22])	d_{41}, d_{42}	10, 10

The number of antigen depending divisions	n_1	2
Number of divisions in minimal CD4+ developmental program	m_1	2
Number of divisions in minimal CD8+ developmental program	m_2	7
Coefficient of the positive growth signal (Il2), ζ_1	p	2

Maximal value of the β_h function	β_{0h}	1.77
Maximal value of the β_l function	β_{0l}	2
Maximal value of the function k_h	k_{0h}	0.1
Maximal value of the function k_l	k_{0l}	0.4
Parameter for the β_h function	θ_{1h}	0.5
Parameter for the β_l function	θ_{1l}	0.5
Parameter for the function k_h	θ_{2h}	36
Parameter for the function k_l	θ_{2l}	36
Parameter for the β_h function	m_h	2
Parameter for the β_l function	m_l	2
Parameter for the function k_h	n_h	2
Parameter for the function k_l	n_l	4
Loss of stem cells due to mortality for healthy cells	γ_{1h}	0.1
Loss of stem cells due to mortality for leukemic cells	γ_{1l}	0.04
Rate of asymmetric division for healthy cells	η_{1h}	0.7
Rate of asymmetric division for leukemic cells	η_{1l}	0.1
Rate of symmetric division for leukemic cells	η_{2l}	0.7
Rate of symmetric division for healthy cells	η_{2h}	0.1
Instant mortality of mature leukemic leukocytes	γ_{2l}	0.15
Instant mortality of mature normal leukocytes	γ_{2h}	2.4
Multiplication (amplification) factor for leukemic leukocytes	A_l	1440
Multiplication (amplification) factor for normal leukocytes	A_h	1200

Duration of cell cycle for normal stem cells	τ_1	2.8
Duration of cell cycle for normal leukocytes	τ_2	3.5
Duration of leukocyte cycle for leukemic cells	τ_3	2.7
Duration of leukocyte cycle for normal cells	τ_4	1.4
Duration of one CD4+ T cell division	τ_5	1.4
Duration of one CD8+ T cell division	τ_6	1
Duration of minimal developmental program	τ_7	$1 + (m_1 - 1)\tau_5$
Duration of minimal developmental program	τ_8	$1 + (m_2 - 1)\tau_6$
Duration of minimal developmental program	τ_9	$n_1\tau_6$

Death/turnover dayly rate of effector CD4+ T helper cells ([23])	e_1	0.23
Coefficient of the autocrine loop function	e_2	0.2
Coefficient of the regulatory process function, ζ_2 (([22]),[23])	e_3	60
Death/turnover rate of effector CD8+ T cytotoxic cells ([23])	e_4	0.4
Coefficient of the "regulatory process" function, ζ_2	e_5	0.2
Coefficient of the "regulatory process" function, ζ_2	e_6	3.48
Coefficient of the "positive growth signal" function ζ_1 ([23])	e_7	40
Coefficient of the level of down-regulation due to leukemic cells ([21])	e_8	0.4

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