A LYAPUNOV-KRASOVSKII FUNCTIONAL FOR A COMPLEX SYSTEM OF DELAY-DIFFERENTIAL EQUATIONS

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This paper introduces a complex model that describes the competition between the populations of healthy and leukemic cells and the influence of the T-lymphocytes on the evolution of leukemia. The system consists of 5 delay differential equations derived from a Mackey-Glass approach. The main results of this work center around sufficient linear stability conditions for a nontrivial equilibrium point. These conditions arise from the construction of a Lyapunov-Krasovskii functional.

Keywords: linear stability, Lyapunov-Krasovskii functional, equilibrium points, delay-differential equations, leukemia

1. Introduction

Leukemia is a cancer of the blood and bone marrow, characterized by large and uncontrolled growth of white blood cells. The most studied type of leukemia, Chronic myelogenous leukemia (CML), involves granular leukocyte precursors, namely the myelocyte line. The trigger of CML is a chromosomal abnormality, called the Philadelphia chromosome (denoted Ph). The product of this chromosome is the formation of the Bcr–Abl fusion protein which is thought to be responsible for the dysfunctional regulation of myelocyte proliferation. The standard treatment of CML in recent years is Imatinib, a molecular targeted drug ([1]) that binds with Bcr-Abl and thus removes the proliferative advantage it provides to cancer cells ([1], [2]). Unfortunately some cells develop resistance to imatinib, so the treatment becomes inefficient ([3]).

Nowadays, it is well known that the immune system plays a fundamental role in tumor progression [4]. Clinical and experimental studies have documented the immune responses to leukemia. In CML, the biological literature reveals that T cells may play an important role in stemming the expansion of leukemic cells. The response of the immune system to leukemia is similar

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to the response to any other foreign substance that enter the body: the immune system reacts first through the activation of local Antigen-Presenting Cells (APCs). APCs (such as Dendritic cells, Macrophages, B-lymphocytes) are specialized blood cells that help fight off foreign substances ([5]). Mature APCs do not fight the leukemic cells directly, but they trigger the naive (CD4+ and CD8+) T cells. CD4+ T cells differentiate into T-helpers which, among other things, help to boost the activation of the CD8+ T cells. These differentiate into T-cytotoxic cells (CTL) which fight the leukemic cells.

In the paper [6], the authors found that leukemia-specific effectors CTLs were able to eliminate LSCs in vitro and in vivo in a setting with minimal leukemia load. The role of CD4+ T cells in leukemia is less clear, although in [7] the authors ascertained that some CML patients under imatinib-induced remission develop an anti-leukemia immune response involving both CD4+ and CD8+ T cells. Therefore, there is ample evidence that antigen-specific immune responses toward CML are elicited. Hence, our goal in this paper is to capture in a mathematical model the underlying dynamics of this disease by considering the evolution of healthy and leukemic cell populations along with one of the most important component of the cellular immune response to CML, namely T cell response.

Although a variety of mathematical papers have applied a range of modeling approaches to study tumor-immune interactions in general (see, for example the recent review [8]), only a few described the specific leukemia-immune interaction. Leukemia-immune models have been formulated using mostly ordinary differential equations (ODE) ([9], [10]) or delay differential equations (DDE) ([11], [12], [13], [14], [15], [16], [17]). Some models that specifically study the immune response to CML are [13], [11], [18] and [9]. In [13], Kim et al. analyzed a high order DDE model to account for the role of anti-leukemia specific response in CML dynamics. The authors concluded that the anti-leukemia T cell response may help maintain remission under Imatinib therapy and they proposed a treatment strategy involving vaccination. In [11], the authors analyzed a two-dimensional DDE model for the dynamics of CML cells and effectors T cells considering Imatinib therapy and immunotherapy. The focus in the paper [18] is on analyzing a DDE model in order to elucidate the transition of leukemia from the stable chronic phase to the unstable accelerated and acute phases and in [9], Moore and Li devise an ODE model and examine which model parameters are the most important in the success or failure of cancer remission.

However, none of the above papers have considered competition between healthy and leukemic cell populations, which is an important factor in CML dynamics. In the present work, we analyze the stability properties of certain equilibria of the CML competition model ([19]) with the immune interaction as a first step of a complex study.

2. The model

In this paper, we consider a mathematical model that aims to capture the dynamics of the healthy and leukemic stem-like short-term and mature leukocytes in CML (see [20], [21]) while taking into account the competition for resources (between the healthy and leukemic cells) and the action of the immune system in response to the disease. The model consists of 5 delay differential equations (DDEs) with 5 delays. Two of the state variables are stem-like cell populations, i.e. cell populations with self-renewal ability. These cell populations are supposed to spend a relatively short period in the resting phase and will be termed as short-term hematopoietic stem cells (ST-HSC). The state variables are: x_1 and x_3- the healthy and leukemic ST-HSC, x_2 and x_4 - mature healthy and leukemic leukocytes and x_5 - the concentration of active anti-leukemia T-cells. The time evolution of the state variables is described by the following DDEs system:

$$\begin{aligned}
\dot{x}_1 = \; & -\gamma_{1h}x_1 - (\eta_{1h}+\eta_{2h})k_h(x_2+x_4)x_1 - (1-\eta_{1h}-\eta_{2h})\beta_h(x_1+x_3)x_1 + \\
& +2e^{-\gamma_{1h}\tau_1}(1-\eta_{1h}-\eta_{2h})\beta_h(x_{1\tau_1}+x_{3\tau_1})x_{1\tau_1} + \\
& +\eta_{1h}e^{-\gamma_{1h}\tau_1}k_h(x_{2\tau_1}+x_{4\tau_1})x_{1\tau_1} \\
\dot{x}_2 = \; & -\gamma_{2h}x_2 + A_h(2\eta_{2h}+\eta_{1h})k_h(x_{2\tau_2}+x_{4\tau_2})x_{1\tau_2} \\
\dot{x}_3 = \; & -\gamma_{1l}x_3 - (\eta_{1l}+\eta_{2l})k_l(x_2+x_4)x_3 - (1-\eta_{1l}-\eta_{2l})\beta_l(x_1+x_3)x_3 + \\
& +2e^{-\gamma_{1l}\tau_3}(1-\eta_{1l}-\eta_{2l})\beta_l(x_{1\tau_3}+x_{3\tau_3})x_{3\tau_3} + \\
& +\eta_{1l}e^{-\gamma_{1l}\tau_3}k_l(x_{2\tau_3}+x_{4\tau_3})x_{3\tau_3} - b_1x_3x_5l_1(x_3+x_4) \\
\dot{x}_4 = \; & -\gamma_{2l}x_4 + A_l(2\eta_{2l}+\eta_{1l})k_l(x_{2\tau_4}+x_{4\tau_4})x_{3\tau_4} - b_2x_4x_5l_1(x_3+x_4) \\
\dot{x}_5 = \; & a_1 - a_2x_5 - a_3x_5l_2(x_4) + 2^{n_1}a_4x_{5\tau_5}l_2(x_{4\tau_5})
\end{aligned}$$

The healthy and leukemic 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 leukemia cells. Following [20] and [21], 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, and 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. For more details about the competition modeling between healthy and CML cell populations, please see [19].

As in [22] and [19], it is assumed that a fraction $\eta_{1\alpha}$, $\alpha = h, l$, of ST-HSC is susceptible to asymmetric division: one daughter cell proceeds to differentiate and the other re-enters the stem cell compartment. A fraction $\eta_{2\alpha}$, $\alpha = h, l$, is susceptible to differentiate symmetrically with both cells that result following a phase of maturation and the fraction $1 - \eta_{1\alpha} - \eta_{2\alpha}$, $\alpha = h, l$, is susceptible to self-renewal so both cells that results after mitosis are stem-like cells (see [23], [24]).

The immune system inhibits CML cells and leukemic cells stimulate the immune system for a certain range of leukemic concentration, called "optimal load zone" (for details, see [13]). As the immune system is not stimulated for too low or too high CML cell concentration, we choose the following feedback functions to model the interaction between the leukemic and the T cell populations:

$$l_1(x) = \frac{1}{b_3 + x}, \quad l_2(x) = \frac{x}{b_4 + x^2}$$

The duration of the cell cycle for healthy and leukemic ST-HSC cells, independent of the type of division, is represented through the delays τ_1 and τ_3. The time required for differentiation into mature leukocytes for healthy and, respectively, leukemia cells is reflected through the delays τ_2 and τ_4 . The delay τ_5 is the time necessary for the activation of anti-leukemia T cells.

The term $\gamma_{1\alpha}, \alpha = h, l$ is the natural apoptosis. A_α is an amplification factor and m_α, n_α control the sensitivity of respectively β_α and k_α to changes in the size of stem-like and respectively mature populations.

3. **Linear stability analysis**

By making the right hand terms in the system equal to zero, we can determine the following types of equilibria:

$$E_1 = (0, 0, 0, 0, x_5^*) \qquad E_2 = (x_1^*, x_2^*, 0, 0, x_5^*)$$
$$E_3 = (0, 0, \hat{x}_3, \hat{x}_4, \hat{x}_5) \quad E_4 = (\tilde{x}_1, \tilde{x}_2, \tilde{x}_3, \tilde{x}_4, \tilde{x}_5)$$

Equilibria E_1 is usually associated with the death of the patient. The second type of equilibria, E_2, represents healthy states, since there are no leukemic cells. In E_3 the leukemic cells have completely replaced the healthy cells and E_4 corresponds to the chronic phase of the disease.

The first step in linear stability analysis of equilibrium points is the study of their characteristic equation which, for delay-differential equations, is a transcedental equation. It is known (see [25],[26], [27]) that, in order for the equilibrium point to be stable, the roots of the characteristic equation must all have negative real parts.

To determine the characteristic equation for an equilibrium point, we must first linearize the system around that equilibrium point. Let $A = (a_{ij})_{i,j=\overline{1,5}}$ be the matrix of the derivatives of the system with respect to x_1, x_2, x_3, x_4 and x_5 calculated in an equilibrium point. For a certain equilibrium point, we also consider the following matrices:

- $B_{\tau_1} = (b_{ij})_{i,j=\overline{1,5}}$ containing the derivatives with respect to $x_{1\tau_1}, x_{2\tau_1}, x_{3\tau_1}, x_{4\tau_1}, x_{5\tau_1}$
- $C_{\tau_2} = (c_{ij})_{i,j=\overline{1,5}}$ containing the derivatives with respect to $x_{1\tau_2}, x_{2\tau_2}, x_{3\tau_2}, x_{4\tau_2}, x_{5\tau_2}$
- $D_{\tau_3} = (d_{ij})_{i,j=\overline{1,5}}$ containing the derivatives with respect to $x_{1\tau_3}, x_{2\tau_3}, x_{3\tau_3}, x_{4\tau_3}, x_{5\tau_3}$
- $E_{\tau_5} = (e_{ij})_{i,j=\overline{1,5}}$ containing the derivatives with respect to $x_{1\tau_4}, x_{2\tau_4}, x_{3\tau_4}, x_{4\tau_4}, x_{5\tau_4}$
- $F_{\tau_5} = (f_{ij})_{i,j=\overline{1,5}}$ containing the derivatives with respect to $x_{1\tau_5}, x_{2\tau_5}, x_{3\tau_5}, x_{4\tau_5}, x_{5\tau_5}$

The characteristic equation has the general form:

$$det(\lambda I_5 - A - B_{\tau_1}e^{-\lambda\tau_1} - C_{\tau_2}e^{-\lambda\tau_2} - D_{\tau_3}e^{-\lambda\tau_3} - E_{\tau_4}e^{-\lambda\tau_4} - F_{\tau_5}e^{-\lambda\tau_5}) = 0$$

For equilibrium points E_1 and E_2 the characteristic equations decouple nicely and can be studied through the methods presented in [28], [29] and [30].

Unfortunately, for E_3 and E_4 the characteristic equation does not decouple. Usually, in the event of multiple delays and for nontrivial equilibrium points, the characteristic equation proves too complex for stability conditions to be found from investigating it. The alternative is constructing a Lyapunov-Krasovskii functional.

In what follows we are going to give sufficient conditions for linear stability using a Lyapunov-Krasovskii functional.

We perform a translation to zero and consider:

$$y_i = x_i - \hat{x}_i,\ i = \overline{1,5}$$

We thus obtain the system:

$$\begin{aligned}
\dot{y}_1 = \ & -\gamma_{1h}(y_1+\hat{x}_1) - (\eta_{1h}+\eta_{2h})k_h[(y_2+\hat{x}_2)+(y_4+\hat{x}_4)](y_1+\hat{x}_1) - \\
& -(1-\eta_{1h}-\eta_{2h})\beta_h[(y_1+\hat{x}_1)+(y_3+\hat{x}_3)](y_1+\hat{x}_1) + \\
& +2e^{-\gamma_{1h}\tau_1}(1-\eta_{1h}-\eta_{2h})\beta_h[(y_{1\tau_1}+\hat{x}_1)+(y_{3\tau_1}+\hat{x}_3)](y_{1\tau_1}+\hat{x}_1) + \\
& +\eta_{1h}e^{-\gamma_{1h}\tau_1}k_h[(y_{2\tau_1}+\hat{x}_2)+(y_{4\tau_1}+\hat{x}_4)](y_{1\tau_1}+\hat{x}_1) \\
\dot{y}_2 = \ & -\gamma_{2h}(y_2+\hat{x}_2) + A_h(2\eta_{2h}+\eta_{1h})k_h[(y_{2\tau_2}+\hat{x}_2)+(y_{4\tau_2}+\hat{x}_4)](y_{1\tau_2}+\hat{x}_1) \\
\dot{y}_3 = \ & -\gamma_{1l}(y_3+\hat{x}_3) - (\eta_{1l}+\eta_{2l})k_l[(y_2+\hat{x}_2)+(y_4+\hat{x}_4)](y_3+\hat{x}_3) - \\
& -(1-\eta_{1l}-\eta_{2l})\beta_l[(y_1+\hat{x}_1)+(y_3+\hat{x}_3)](y_3+\hat{x}_3) + \\
& +2e^{-\gamma_{1l}\tau_3}(1-\eta_{1l}-\eta_{2l})\beta_l[(y_{1\tau_3}+\hat{x}_1)+(y_{3\tau_3}+\hat{x}_3)](y_{3\tau_3}+\hat{x}_3) + \\
& +\eta_{1l}e^{-\gamma_{1l}\tau_3}k_l[(y_{2\tau_3}+\hat{x}_2)+(y_{4\tau_3}+\hat{x}_4)](y_{3\tau_3}+\hat{x}_3) - \\
& -b_1(y_3+\hat{x}_3)(y_5+\hat{x}_5)l_1((y_3+\hat{x}_3)+(y_4+\hat{x}_4)) \\
\dot{y}_4 = \ & -\gamma_{2l}(y_4+\hat{x}_4) + A_l(2\eta_{2l}+\eta_{1l})k_l[(y_{2\tau_4}+\hat{x}_2)+(y_{4\tau_4}+\hat{x}_4)](y_{3\tau_4}+\hat{x}_3) - \\
& -b_2(y_4+\hat{x}_4)(y_5+\hat{x}_5)l_1((y_3+\hat{x}_3)+(y_4+\hat{x}_4)) \\
\dot{y}_5 = \ & a_1 - a_2(y_5+\hat{x}_5) - a_3(y_5+\hat{x}_5)l_2(y_4+\hat{x}_4) + 2^{n_1}a_4(y_{5\tau_5}+\hat{x}_5)l_2(y_{4\tau_5}+\hat{x}_4)
\end{aligned}$$

Consider the following type of Lyapunov-Krasovskii functional:

$$V=\sum_{i=1}^{5}\alpha_i y_i^2+\sum_{j=1}^{5}\beta_j\int\limits_{t-\tau_j}^{t}y_j^2(s)ds+\sum_{i\neq j}\delta_{ij}\int\limits_{t-\tau_j}^{t}y_i^2(s)ds$$

with $\alpha_i>0,\beta_j>0,\forall i=\overline{1,5},j=\overline{1,5}$ and $\delta_{ij}>0$ for $i\neq j$

As we know from [31], a Lyapunov-Krasovskii functional needs to be positively defined and $\dfrac{dV}{dt}<0$.

$$\frac{dV}{dt}=\sum_{i=1}^{5}2\alpha_i y_i\dot{y}_i+\sum_{j=1}^{5}\beta_j\left[y_j^2(t)-y_j^2(t-\tau_j)\right]+\sum_{i\neq j}\delta_{ij}\left[y_i^2(t)-y_i^2(t-\tau_j)\right]$$

Let $\dot{y}_i=g_i,i=\overline{1,5}$. As we are working in the framework of stability in the first approximation (see [31]), we have:

$$\frac{dV}{dt}=\sum_{i=1}^{5}2\alpha_i y_i f_i(y)+\sum_{j=1}^{5}\beta_j\left[y_j^2(t)-y_j^2(t-\tau_j)\right]+\sum_{i\neq j}\delta_{ij}\left[y_i^2(t)-y_i^2(t-\tau_j)\right]$$

where

$$f_i(y)=\sum_{k=1}^{5}\frac{\partial g_i}{\partial y_k}(\hat{x})y_k+\sum_{k,j}\frac{\partial g_i}{\partial y_{k\tau_j}}(\hat{x})y_{k\tau_j}$$

We obtain sufficient stability conditions by forcing $\dfrac{dV}{dt}$ to be negative. The functions f_1,f_2,f_3,f_4 and f_5 are :

$$\begin{aligned}
f_1(y)=\ & \{-\gamma_{1h}-(\eta_{1h}+\eta_{2h})k_h(x_2^*+x_4^*)-(1-\eta_{1h}-\eta_{2h})\left[\beta_h(x_1^*+x_3^*)+\right.\\
&\left.+\beta_h^{'}(x_1^*+x_3^*)x_1^*\right]\}y_1+\left[-(\eta_{1h}+\eta_{2h})k_h^{'}(x_2^*+x_4^*)x_1^*\right]y_2+\\
&+\left[-(1-\eta_{1h}-\eta_{2h})\beta_h^{'}(x_1^*+x_3^*)x_1^*\right]y_3+\left[-(\eta_{1h}+\eta_{2h})k_h^{'}(x_2^*+x_4^*)x_1^*\right]y_4+\\
&+\left\{2e^{-\gamma_{1h}\tau_1}(1-\eta_{1h}-\eta_{2h})\left[\beta_h(x_1^*+x_3^*)+\beta_h^{'}(x_1^*+x_3^*)x_1^*\right]+\right.\\
&\left.+\eta_{1h}e^{-\gamma_{1h}\tau_1}k_h(x_2^*+x_4^*)\right\}y_{1\tau_1}+\left[\eta_{1h}e^{-\gamma_{1h}\tau_1}k_h^{'}(x_2^*+x_4^*)x_1^*\right]y_{2\tau_1}+\\
&+\left[2e^{-\gamma_{1h}\tau_1}(1-\eta_{1h}-\eta_{2h})\beta_h^{'}(x_1^*+x_3^*)x_1^*\right]y_{3\tau_1}+\\
&+\left[\eta_{1h}e^{-\gamma_{1h}\tau_1}k_h^{'}(x_2^*+x_4^*)x_1^*\right]y_{4\tau_1}\\
f_2(y)=\ & -\gamma_{2h}y_2+\left[A_h(2\eta_{2h}+\eta_{1h})k_h(x_2^*+x_4^*)\right]y_{1\tau_2}+\\
&+\left[A_h(2\eta_{2h}+\eta_{1h})k_h^{'}(x_2^*+x_4^*)x_1^*\right]y_{2\tau_2}+\\
&+\left[A_h(2\eta_{2h}+\eta_{1h})k_h^{'}(x_2^*+x_4^*)x_1^*\right]y_{4\tau_2}
\end{aligned}$$

$$
\begin{aligned}
f_3(y) = \; & \{-\gamma_{1l} - (\eta_{1l}+\eta_{2l})k_l(x_2^*+x_4^*) - (1-\eta_{1l}-\eta_{2l})\left[\beta_l(x_1^*+x_3^*)+\right. . \\
& \left.+\beta_l^{'}(x_1^*+x_3^*)x_3^*\right] - b_1x_5^*\left[l_1(x_3^*+x_4^*)+l_1^{'}(x_3^*+x_4^*)x_3^*\right]\} y_3 + \\
& + \left[-(1-\eta_{1l}-\eta_{2l})\beta_l^{'}(x_1^*+x_3^*)x_3^*\right] y_1 + \left[-(\eta_{1l}+\eta_{2l})k_l^{'}(x_2^*+x_4^*)x_3^*\right] y_2 + \\
& + \left[-(\eta_{1l}+\eta_{2l})k_l^{'}(x_2^*+x_4^*)x_3^* - b_1x_3^*x_5^*l_1^{'}(x_3^*+x_4^*)\right] y_4 + \\
& + \left[-b_1x_3^*l_1(x_3^*+x_4^*)\right] y_5 + \{2e^{-\gamma_{1l}\tau_3}(1-\eta_{1l}-\eta_{2l})\left[\beta_l(x_1^*+x_3^*)+\right. \\
& \left.+\beta_l^{'}(x_1^*+x_3^*)x_3^*\right] + \eta_{1l}e^{-\gamma_{1l}\tau_3}k_l(x_2^*+x_4^*)\} y_{3\tau_3} + \\
& + \left[2e^{-\gamma_{1l}\tau_3}(1-\eta_{1l}-\eta_{2l})\beta_l^{'}(x_1^*+x_3^*)x_3^*\right] y_{1\tau_3} + \\
& + \left[\eta_{1l}e^{-\gamma_{1l}\tau_3}k_l^{'}(x_2^*+x_4^*)x_3^*\right] y_{2\tau_3} + \left[\eta_{1l}e^{-\gamma_{1l}\tau_3}k_l^{'}(x_2^*+x_4^*)x_3^*\right] y_{4\tau_3} \\
f_4(y) = \; & \left\{-\gamma_{2l} - b_2x_5^*\left[l_1(x_3^*+x_4^*)+l_1^{'}(x_3^*+x_4^*)x_4^*\right]\right\} y_4 + \\
& + \left[-b_2x_5^*x_4^*l_1^{'}(x_3^*+x_4^*)\right] y_3 + \left[-b_2x_4^*l_1(x_3^*+x_4^*)\right] y_5 \\
& \left[A_l(2\eta_{2l}+\eta_{1l})k_l^{'}(x_2^*+x_4^*)x_3^*\right] y_{2\tau_4} + \\
& + \left[A_l(2\eta_{2l}+\eta_{1l})k_l(x_2^*+x_4^*)\right] y_{3\tau_4} + \\
& + \left[A_l(2\eta_{2l}+\eta_{1l})k_l^{'}(x_2^*+x_4^*)x_3^*\right] y_{4\tau_4} \\
f_5(y) = \; & \left[-a_2 - a_3l_2(x_4^*)\right] y_5 + \left[-a_3x_5^*l_2^{'}(x_4^*)\right] y_4 + \left[2^{n_1}a_4x_5^*l_2^{'}(x_4^*)\right] y_{4\tau_5} + \\
& + \left[2^{n_1}a_4l_2(x_4^*)\right] y_{5\tau_5}
\end{aligned}
$$

To simplify the calculations, we introduce special notations for the coefficients in f_1, f_2, f_3, f_4 and f_5 as follows:

$$
\begin{aligned}
f_1(y) = \; & c_{11}y_1 + c_{12}y_2 + c_{13}y_3 + c_{12}y_4 + c_{14}y_{1\tau_1} + c_{15}y_{2\tau_1} + c_{16}y_{3\tau_1} + c_{15}y_{4\tau_1} \\
f_2(y) = \; & c_{21}y_2 + c_{22}y_{1\tau_2} + c_{23}y_{2\tau_2} + c_{23}y_{4\tau_2} \\
f_3(y) = \; & c_{31}y_3 + c_{32}y_1 + c_{33}y_2 + c_{34}y_4 + c_{35}y_5 + c_{36}y_{3\tau_3} + c_{37}y_{1\tau_3} + c_{38}y_{2\tau_3} + c_{38}y_{4\tau_3} \\
f_4(y) = \; & c_{41}y_4 + c_{42}y_3 + c_{43}y_5 + c_{44}y_{4\tau_4} + c_{44}y_{2\tau_4} + c_{45}y_{3\tau_4} \\
f_5(y) = \; & c_{51}y_5 + c_{52}y_4 + c_{53}y_{5\tau_5} + c_{54}y_{4\tau_5}
\end{aligned}
$$

The construction will be exemplified considering only the terms from V that come from $f_1(y)$ and those from the other equations that combine with them, since all the other ones are handled in a similar manner.

Sufficient stability conditions arise from:

$$
\begin{aligned}
& 2\alpha_1c_{11}y_1^2 + 2\alpha_1c_{12}y_1y_2 + 2\alpha_1c_{13}y_1y_3 + 2\alpha_1c_{12}y_1y_4 + 2\alpha_1c_{14}y_1y_{1\tau_1} + 2\alpha_1c_{15}y_1y_{2\tau_1} + \\
& + 2\alpha_1c_{16}y_1y_{3\tau_1} + 2\alpha_1c_{15}y_1y_{4\tau_1} + \beta_1y_1^2 - \beta_1y_{1\tau_1}^2 - \delta_{21}y_{2\tau_1}^2 - \delta_{31}y_{3\tau_1}^2 - \delta_{41}y_{4\tau_1}^2 < 0
\end{aligned}
$$

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

$$
2\alpha_1c_{14}y_1y_{1\tau_1} - \beta_1y_{1\tau_1}^2 + \frac{\alpha_1^2c_{14}^2}{\beta_1}y_1^2 - \frac{\alpha_1^2c_{14}^2}{\beta_1}y_1^2 = -\left(\frac{\alpha_1c_{14}}{\sqrt{\beta}_1}y_1 - \sqrt{\beta}_1y_{1\tau_1}\right)^2 + \boxed{\frac{\alpha_1^2c_{14}^2}{\beta_1}y_1^2}
$$

and

$$
2\alpha_1c_{12}y_1y_2 + \alpha_1^2c_{12}^2y_1^2 - \alpha_1^2c_{12}^2y_1^2 + y_2^2 - y_2^2 = -\left(\alpha_1c_{12}y_1 - y_2\right)^2 + \boxed{\alpha_1^2c_{12}^2y_1^2} + \boxed{y_2^2}
$$

The term y_2^2 will be taken into account in the conditions that come from studying $f_2(y)$.

In doing so with every problematic term in the derivative of the Lyapunov-Krasovskii functional, we restrict the coefficient of y_1^2 as follows:

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

We denote the coefficient of α_1^2 by p_1, the coefficient of α_1 by q_1, and the free term by r_1 and we consider the following equation:

$$p_1\alpha_1^2+q_1\alpha_1+r_1=0$$

with $p_1>0$ and $r_1>0$.

This second degree equation has real roots if $\boxed{q_1^2-4p_1r_1>0}$.

As the product of the roots is positive $P=\dfrac{r_1}{p_1}$, the roots have the same sign. In order for the roots to be positive, the sum of the roots must be positive:

$$S=-\frac{q_1}{p_1}\Rightarrow\boxed{q_1<0}$$

Let α_{11} and α_{12} be the roots of the equation. Since $p_1>0$, then $\boxed{\alpha_1\in(\alpha_{11},\alpha_{12})}$ for $p_1\alpha_1^2+q_1\alpha_1+r_1<0$.

The same calculations are made for y_i, $i=\overline{2,5}$ and we obtain:

$$\left[\frac{c_{23}^2}{\beta_2}+\frac{c_{22}^2}{\delta_{12}}+\frac{c_{23}^2}{\delta_{42}}\right]\alpha_2^2+2c_{21}\alpha_2+(\beta_2+\delta_{21}+\delta_{23}+\delta_{24}+2)<0$$

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

$$\left[\frac{c_{44}^2}{\beta_4}+\frac{c_{44}^2}{\delta_{24}}+\frac{c_{45}^2}{\delta_{34}}+c_{42}^2\right]\alpha_4^2+2c_{41}\alpha_4+(\beta_4+\delta_{41}+\delta_{42}+\delta_{43}+\delta_{45}+3)<0$$

$$\left[\frac{c_{53}^2}{\beta_5}+\frac{c_{54}^2}{\delta_{45}}+c_{52}^2\right]\alpha_5^2+2c_{51}\alpha_5+(\beta_5+2)<0$$

We ultimately give the following sufficient stability conditions:

$$\begin{aligned}
&q_1^2-4p_1r_1>0,\quad q_1<0,\quad \alpha_1\in(\alpha_{11},\alpha_{12})\\
&q_2^2-4p_2r_2>0,\quad q_2<0,\quad \alpha_2\in(\alpha_{21},\alpha_{22})\\
&q_3^2-4p_3r_3>0,\quad q_3<0,\quad \alpha_3\in(\alpha_{31},\alpha_{32})\\
&q_4^2-4p_4r_4>0,\quad q_4<0,\quad \alpha_4\in(\alpha_{41},\alpha_{42})\\
&q_5^2-4p_5r_5>0,\quad q_5<0,\quad \alpha_5\in(\alpha_{51},\alpha_{52})
\end{aligned}$$

4. Conclusions

In this paper we have introduced a model that tries to capture the dynamics of the competition between healthy and leukemic cells and the response of immune system in CML.

Four types of equilibria were found for this system. The stability of the first two (E_1 and E_2) can be studied through their characteristic equation and will be studied in further work.

For the other two (E_3 and E_4), sufficient linear stability conditions were found using a Lyapunov-Krasovskii functional.

Also in further work, the effect of treatment on the populations of leukemic cells will be introduced in the model.

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