RANK-ONE PERTURBATIONS AND STABILITY OF SOME EQUILIBRIUM POINTS IN A COMPLEX MODEL OF CELLS EVOLUTION IN LEUKEMIA

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The complex model of cells evolution in leukemia considers the competition between the populations of healthy and leukemic cells, the asymmetric division and the immune system's action in response to the disease. Delay differential equations are used to describe the dynamics of healthy and leukemic cells in case of CML (Chronic Myeloid Leukemia). The system consists of 9 delay differential equations, the first equations from 1 to 4 describe the hematopoietic healthy and leukemic cells evolution, equations 5 to 9 describe the evolution of the immune cell populations involved in the immune response against CML. The system has four possible types of equilibrium points, denoted E_1, E_2, E_3 and E_4. The study of stability is focused on E_3, when leukemia cells have entirely replaced the healthy ones and E_4, representing a chronic phase of the disease. A new technique is developed to handle the intractable characteristic equations in these cases.

1. Keywords

chronic myeloid leukemia, delay-differential equations, stability, first-rank perturbation

2. Introduction

Mathematical modelling of phenomena that occur in areas such as biology and medicine is more and more extended in recent years. One of the intense subjects of study is chronic myeloid leukemia (CML), which is a type of cancer of the blood characterized by an uncontrolled proliferation of white blood cells.

The role of the immune system during the evolution of leukemic cells has only recently been considered in studies. This is mainly due to the fact that the mechanism of the immune system is not entirely known and it's impact on the different types of leukemic cells (stem-like and mature cells) is still debated, especially when treatment takes place.These can also be seen as the

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reasons why modelling the action of the immune system in leukemia is very important.

In this paper we model the evolution of healthy and leukemic cells and the action of the immune system in CML. For this purpose, we use a system of delay differential equations. In what follows we briefly describe the mathematical model and analyze the stability of some equilibrium points after establishing a result on stability under a rank-one perturbation (see [9]).

3. **The model**

The model we study consists of 9 equations and was first introduced in [4], [1] and [2]. The first four equations describe the hematopoietic healthy and leukemic cells evolution, and the last five describe the evolution of the immune cell populations involved in the immune response against CML. The state variables represent the concentration of stem-like healthy and leukemic cells (x_1 and x_3), the concentration of mature healthy and leukemic cells (x_2 and x_4), the concentration of naive antigen presenting cells - APCs (x_5), the concentration of mature APCs (x_6), the concentration of naive T cells of 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 (x_9).

We consider all three types of cell division: symmetric self-renewal, asymmetric division and symmetric differentiation.

Two feedback loops regulate the self-renewal and the differentiation. These are introduced through the rate of self-renewal (β) and the rate of differentiation (k), where, considering competition,

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

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

with h - healthy and l - leukemic.

In order to model the immune system, we assume that the APCs are the first to activate, upon encountering mature leukemic cells. They, in turn, activate the T cells which differentiate into T-helper cells and CD8+ cytotoxic T-cells. The activation of the CD8+ cytotoxic T-cells is also stimulated by the T-helper cells. The cytotoxic T-cells are the cells that force the leukemic cells into apoptosis.

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

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

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

Taking into account all the above, we consider the system of DDEs below. For a more detailed description of the model, see [4], [1] and [2].

$$
\begin{aligned}
\dot{x}_1 = {} & -\gamma_{1h}x_1 - (\eta_{1h}+\eta_{2h})k_h(x_2+x_4)x_1 - (1-\eta_{1h}-\eta_{2h})\beta_h(x_1+x_3)x_1 + \\
& +2e^{-\gamma_{1h}\tau_1}(1-\eta_{1h}-\eta_{2h})\beta_h(x_{1\tau_1}+x_{3\tau_1})x_{1\tau_1} + \\
& +\eta_{1h}e^{-\gamma_{1h}\tau_1}k_h(x_{2\tau_1}+x_{4\tau_1})x_{1\tau_1} \\
\dot{x}_2 = {} & -\gamma_{2h}x_2 + A_h(2\eta_{2h}+\eta_{1h})k_h(x_{2\tau_2}+x_{4\tau_2})x_{1\tau_2} \\
\dot{x}_3 = {} & -\gamma_{1l}x_3 - (\eta_{1l}+\eta_{2l})k_l(x_2+x_4)x_3 - (1-\eta_{1l}-\eta_{2l})\beta_l(x_1+x_3)x_3 + \\
& +2e^{-\gamma_{1l}\tau_3}(1-\eta_{1l}-\eta_{2l})\beta_l(x_{1\tau_3}+x_{3\tau_3})x_{3\tau_3} + \\
& +\eta_{1l}e^{-\gamma_{1l}\tau_3}k_l(x_{2\tau_3}+x_{4\tau_3})x_{3\tau_3} - b_1x_3x_9l_1(x_3+x_4) \\
\dot{x}_4 = {} & -\gamma_{2l}x_4 + A_l(2\eta_{2l}+\eta_{1l})k_l(x_{2\tau_4}+x_{4\tau_4})x_{3\tau_4} - b_2x_4x_9l_1(x_3+x_4) \\
\dot{x}_5 = {} & -c_2x_5 + c_1 - c_3x_5l_2(x_4) \\
\dot{x}_6 = {} & -d_1x_6 + c_3x_5l_2(x_4) \\
\dot{x}_7 = {} & -d_2x_7 + d_3 - d_4x_6x_7 \\
\dot{x}_8 = {} & -e_1x_8 - e_2\zeta_1(x_8)x_8 + 2e^{-e_1\tau_5}e_2\zeta_1(x_{8\tau_5})x_{8\tau_5} - e_3\zeta_2(x_8)x_8 + \\
& +2^{m_1}d_{41}x_{6\tau_7}x_{7\tau_7} \\
\dot{x}_9 = {} & -e_4x_9 - e_7\zeta_1(x_8)x_8x_9 + 2e^{-e_4\tau_6}e_7\zeta_1(x_{8\tau_6})x_{8\tau_6}x_{9\tau_6} - e_3\zeta_2(x_8)x_9 - \\
& -b_5x_9l_3(x_4) + 2^{n_1}e_8x_{9\tau_9}l_3(x_{4\tau_9}) + 2^{m_2}d_{42}x_{6\tau_8}x_{7\tau_8}
\end{aligned}
$$

The system has several types of equilibrium points $E = (x_1^*, x_2^*, x_3^*, x_4^*, x_5^*, x_6^*, x_7^*, x_8^*, x_9^*)$. The "death" equilibrium $x_j^* = 0, \forall j \neq 5, 7$ and the "health" equilibrium $x_3^* = x_4^* = 0$ have been studied in [1] and [2]. E_3, where $x_1^* = x_2^* = 0$, the case when leukemia cells have entirely replaced the healthy ones and E_4, where $x_j^* \neq 0\ \forall j = \overline{1,9}$, representing a chronic phase of the disease, have not been investigated until now using the characteristic equation due to its complexity. Sufficient conditions for delay-independent stability have been given, using Lyapunov-Krasovskii functionals, in [3].

4. **Stability study**

The characteristic equation of the linearized system is:

$$
\begin{aligned}
&\det(\lambda I_9 - A - Be^{-\lambda\tau_1} - Ce^{-\lambda\tau_2} - De^{-\lambda\tau_3} - Ee^{-\lambda\tau_4} - \\
&-Fe^{-\lambda\tau_5} - Ge^{-\lambda\tau_6} - He^{-\lambda\tau_7} - Ke^{-\lambda\tau_8} - Le^{-\lambda\tau_9}) = 0.
\end{aligned}
$$

Here, A is the matrix of partial derivatives with respect to undelayed state variables, while $B, C, \dots, L$ correspond to variables delayed by $\tau_1, \tau_2, \dots, \tau_9$ respectively.

The matrix for which we need to calculate the determinant has the form:

$$M = \begin{pmatrix} m_{11} & m_{12} & m_{13} & m_{14} & 0 & 0 & 0 & 0 & 0 \\ m_{21} & m_{22} & 0 & m_{24} & 0 & 0 & 0 & 0 & 0 \\ m_{31} & m_{32} & m_{33} & m_{34} & 0 & 0 & 0 & 0 & m_{39} \\ 0 & m_{42} & m_{43} & m_{44} & 0 & 0 & 0 & 0 & m_{49} \\ 0 & 0 & 0 & m_{54} & m_{55} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & m_{64} & m_{65} & m_{66} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & m_{76} & m_{77} & 0 & 0 \\ 0 & 0 & 0 & m_{84} & 0 & m_{86} & m_{87} & m_{88} & 0 \\ 0 & 0 & 0 & m_{94} & 0 & m_{96} & m_{97} & m_{98} & m_{99} \end{pmatrix}.$$

The dificulties in studying the characteristic equation arise from the presence of the elements m_{39} and m_{49}, with $m_{39} = a_{39} = b_1 x_3^* l_1(x_4^*)$ and $m_{49} = a_{49} = b_2 x_4^* l_1(x_4^*)$. In order to handle the stability study, we use the approach from [9] .

Let Δ_0 be the 9×9 matrix with all entries zero except for a_{39} on line 3, column 9 and a_{49} on line 4, column 9.

Define $A_1 = A - \Delta_0$, $M_1 = M - \Delta_0$. Then

$$\det M_1 = d_1 m_{55} m_{66} m_{77} m_{88} m_{99} \tag{1}$$

with

$$d_1 = \det \begin{pmatrix} m_{11} & m_{12} & m_{13} & m_{14} \\ m_{21} & m_{22} & 0 & m_{24} \\ m_{31} & m_{32} & m_{33} & m_{34} \\ 0 & m_{42} & m_{43} & m_{44} \end{pmatrix} \tag{2}$$

and

$$\begin{aligned} &m_{55} = \lambda - a_{55},\ m_{66} = \lambda - a_{66},\ m_{77} = \lambda - a_{77}, \\ &m_{88} = \lambda - a_{88} - f_{88} e^{-\lambda \tau_5} \end{aligned} \tag{3}$$

$$m_{99} = \lambda - a_{99} - g_{99} e^{-\lambda \tau_6} - l_{99} e^{-\lambda \tau_9}. \tag{4}$$

We use now the results from [11](see also [6]).

Consider the linear time-delay system

$$\dot{x}(t) = A_0 x(t) + \sum_{j=1}^{m} A_j x(t - \tau_j), \tag{5}$$

where $A_0, A_1, \dots, A_m \in M_n(\mathbb{R})$, with strictly positive delays $\tau_1, \dots, \tau_m$.

Define $\tau = \max\{\tau_1, \dots, \tau_m\}$ and let K be a fundamental matrix of solutions of the system (5), so $K(t) = 0$, $\forall t < 0$. If the system (5) is exponentially stable then $\exists M > 0$, $\omega > 0$, so that

$$||K(t)|| \le M e^{-\omega \tau}\ \forall t \ge 0.$$

In this situation, for every constant matrix W, the matrix function, called the Lyapunov matrix,

$$U(t) = \int_0^t K(t)^T W K(t+s)dt \tag{6}$$

is well defined for all $s \in \mathbb{R}$ (T means transpose).

Remark that for (5) asymptotic stability is equivalent to exponential stability (see [10]).

Let the matrices $A_0, A_1, \ldots, A_m$ be perturbed as $A_k + \Delta_k$, $k = 0, \ldots, m$ and consider the perturbed system

$$\dot{y}(t) = (A_0 + \Delta_0)y(t) + \sum_{j=1}^{m} (A_j + \Delta_j)y(t - \tau_j) \tag{7}$$

Suppose that the perturbations are bounded matrices

$$||\Delta_k|| \leq \rho_k \quad \forall k = 0, \ldots, m. \tag{8}$$

For positive definite matrices $W_0, W_1, \ldots, W_m, R_1, \ldots, R_m$, define

$$W = W_0 + \sum_{j=1}^{m} (W_j + \tau_j R_j) \tag{9}$$

and let U be the Lyapunov matrix defined by (6) with respect to this W. Define

$$\lambda_{min} = min\{inf\sigma(W_j), j = 0, \ldots, m, inf\sigma(R_j), j = 1, \ldots, m\}$$

and

$$v = max\{||U(t)||, t \in [0, \tau]\},$$
$$\rho = (\rho_0^2 + \cdots + \rho_m^2)^{1/2}$$

with $\sigma(M)$ the spectrum of the matrix M. The following theorem is proved in [11] using Lyapunov-Krasovskii functionals

Theorem 1 ([11], Th. 3.12). *Suppose (5) is exponentially stable. Let the positive-definite matrices $W_0, W_1, \ldots, W_m, R_1, \ldots, R_m$ be given and let U be the Lyapunov matrix defined in (6) for W defined in (9). Then (7) is also exponentially stable for all perturbations that verify*

$$\rho \leq \frac{\lambda_{min}}{2v(1 + \sum_{k=1}^{m} \tau_k ||A_k||)^{1/2}} \tag{10}$$

This theorem is applied to the study of the asymptotic stability of equilibrium E_3 and E_4 using the linearized system and the Theorem on stability by the first approximation.

Consider Δ_0 as defined above and $\Delta_k = 0$, $k = 1, \ldots, 9$. Then

$$||\Delta_0|| \leq (m_{39}^2 + m_{49}^2)^{1/2}$$

so

$$\rho = (m_{39}^2 + m_{49}^2)^{1/2}. \tag{11}$$

The following result is obtained:

Theorem 2. *Suppose that for d_1, m_{88} and m_{99} defined in (2), (3) and (4) the equations $d_1 = 0$, $m_{88} = 0$ and $m_{99} = 0$ have all the roots λ with $Re\,\lambda < 0$. Then, if ρ defined in (11) verifies (10), the equilibrium points E_3 and E_4 are asymptotically stable.*

Proof. The result follows from (1) and from the considerations above since $a_{55} < 0$, $a_{66} < 0$ and $a_{77} < 0$. □

Remark. Since $a_{39} = -b_6\hat{x}_3 l_1(\hat{x}_4)$ and $a_{49} = -b_4\hat{x}_4 l_1(\hat{x}_4)$, one way to have (10) satisfied is to have $|b_6| + |b_4|$ small enough.

From Ch. III, §7, Th. II in [8], if the zero solution of the linearised system is unstable due to the presence of a root λ of the characteristic equation with $\mathrm{Re}\,\lambda > 0$, the zero solution of the nonlinear system is also unstable.

In what follows, we present the stability study for the equilibrium point $E_3 = (0, 0, x_3^*, x_4^*, x_5^*, x_6^*, x_7^*, x_8^*, x_9^*)$. In this case, the equation $d_1 = 0$ decouples into:

$$(\lambda - a_{22})(\lambda - a_{55})(\lambda - a_{66})(\lambda - a_{77})(\lambda - a_{88} - f_{88}e^{-\lambda\tau_5})\cdot$$
$$\cdot(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})(\lambda - a_{99} - f_{99}e^{-\lambda\tau_6} - l_{99}e^{-\lambda\tau_9})\cdot$$
$$\cdot[(\lambda - a_{33} - d_{33}e^{-\lambda\tau_3})(\lambda - a_{44} - e_{44}e^{-\lambda\tau_4}) - e_{43}e^{-\lambda\tau_4}(a_{34} + d_{34}e^{-\lambda\tau_3})] = 0$$

The first four equations have negative real roots. We will study the rest of the equations following [5], [6] and [7].

I.

$$\lambda - a_{11} - b_{11}e^{-\lambda\tau_1} = 0. \tag{9}$$

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

$$a_{11} + b_{11} < 0.$$

Then equation (9) is stable for $\tau_1 = 0$ and it remains stable for all $\tau_1 > 0$.

Proof. For $\tau_1 = 0$ the equation becomes: $\lambda - a_{11} - b_{11} = 0$ and we have negative roots if $a_{11} + b_{11} < 0$.
If $\tau_1 > 0$ we use the method presented in [6]. As $b_{11} > 0$, the following conditions must hold for stability:

$$a_{11} < \frac{1}{\tau_1},$$
$$a_{11} + b_{11} < 0.$$

The first condition holds as $a_{11} < 0$ and the second one holds if the equation is stable for $\tau_1 = 0$. □

II.

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

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

$$a_{88} + f_{88} < 0.$$

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

Proof. For $\tau_5 = 0$ the equation becomes: $\lambda - a_{88} - f_{88} = 0$ and we have negative roots if $a_{88} + f_{88} < 0$.
If $\tau_5 > 0$ we use the method presented in [6]. As $f_{88} > 0$, the following conditions must hold for stability:

$$a_{88} < \frac{1}{\tau_5},$$
$$a_{88} + f_{88} < 0.$$

The first condition holds as $a_{88} < 0$ and the second one holds if the equation is stable for $\tau_5 = 0$. □

III.

$$\lambda - a_{99} - f_{99}e^{-\lambda\tau_6} - l_{99}e^{-\lambda\tau_9} = 0. \qquad (11)$$

Proposition 3. *Assume that the following condition is satisfied:*

$$a_{99} + f_{99} + l_{99} < 0.$$

Then equation (11) is stable for $\tau_6 = 0$ *and* $\tau_9 = 0$.

Proof. For $\tau_6 = 0$ and $\tau_9 = 0$ the equation becomes: $\lambda - a_{99} - f_{99} - l_{99} = 0$ and we have negative roots if $a_{99} + f_{99} + l_{99} < 0$. □

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

$$a_{99} + f_{99} < \frac{1}{\tau_9}.$$

Then, if the equation (11) is stable for $\tau_6 = 0$ *and* $\tau_9 = 0$, *it will remain stable for* $\tau_6 = 0$ *and* $\tau_9 > 0$.

Proof. For $\tau_6 = 0$ and $\tau_9 > 0$ the equation becomes: $\lambda - a_{99} - f_{99} - l_{99}e^{-\lambda\tau_9} = 0$. We will, as before, use the method presented in [6]. We notice that $l_{99} < 0$, so the following conditions must hold for stability:

$$a_{99} + f_{99} < \frac{1}{\tau_9},$$
$$a_{99} + f_{99} + l_{99} < 0.$$

If the equation (11) is stable for $\tau_6 = 0$ and $\tau_9 = 0$, then the second condition is satisfied. □

Proposition 5. *Consider the equation:*

$$y^2 - 2g_{99}y\sin y\tau_6^* + 2a_{99}g_{99}\cos y\tau_6^* + a_{99}^2 + g_{99}^2 = 0. \quad (12)$$

Assume that equation (12) has no positive real roots. Then, if the equation (11) is stable for $\tau_6 = \tau_6^*$ and $\tau_9 = 0$, it will remain stable for $\tau_6 = \tau_6^*$ and $\tau_9 > 0$.

Proof. The proof comes from Theorem 1 from [7], with the correction given by [5]. □

IV.

$$(\lambda - a_{33} - d_{33}e^{-\lambda\tau_3})(\lambda - a_{44} - e_{44}e^{-\lambda\tau_4}) - e_{43}e^{-\lambda\tau_4}(a_{34} + d_{34}e^{-\lambda\tau_3}) = 0. \quad (13)$$

Proposition 6. *Assume that the following conditions are satisfied:*

$$\begin{aligned} &a_{33} + d_{33} + a_{44} + e_{44} < 0, \\ &(a_{33} + d_{33})(a_{44} + e_{44}) - e_{43}(a_{34} + d_{34}) > 0. \end{aligned} \quad (14)$$

Then equation (13) is stable for $\tau_3 = \tau_4 = 0$.

Proof. For $\tau_3 = \tau_4 = 0$ equation (13) becomes:

$$\lambda^2 - \lambda(a_{33} + d_{33} + a_{44} + e_{44}) + (a_{33} + d_{33})(a_{44} + e_{44}) - e_{43}(a_{34} + d_{34}) = 0. \quad (15)$$

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

$$\begin{aligned} &a_{33} + d_{33} + a_{44} + e_{44} < 0, \\ &(a_{33} + d_{33})(a_{44} + e_{44}) - e_{43}(a_{34} + d_{34}) > 0. \end{aligned}$$

□

To simplify the calculations, we introduce the following notations:

$$\begin{aligned} \alpha_1 &= a_{33} + d_{33} + a_{44} \\ \beta_1 &= a_{44}(a_{33} + d_{33}) \\ \alpha_2 &= -e_{44} \\ \beta_2 &= e_{44}(a_{22} + d_{22}) - e_{43}(a_{34} + d_{34}). \end{aligned}$$

Proposition 7. *If either the condition*

$$(\alpha_1^2 - 2\beta_1 - \beta_2^2)^2 - 4(\beta_1^2 - \alpha_2^2) > 0 \quad (16)$$

or condition

$$\alpha_1^2 - 2\beta_1 - \beta_2^2 < 0 \quad (17)$$

does not hold, then, if equation (13) is stable for $\tau_3 = \tau_4 = 0$, it will remain stable for $\tau_3 = 0$ and $\tau_4 > 0$.

Proof. Consider $\tau_3 = 0$ and $\tau_4 > 0$. Equation (13) becomes:

$$\lambda^2 - \alpha_1\lambda + \beta_1 + e^{-\lambda\tau_2}(\beta_2 + \alpha_2\lambda) = 0. \quad (17)$$

In order to study this equation we use Theorem 1 from [7]. We define

$$P(z) = z^2 - \alpha_1 z + \beta_1,$$
$$Q(z) = \alpha_2 z + \beta_2.$$

Note that conditions (i)- (v) from the Theorem are satisfied. The stability of equation (17) depends on the roots of the equation:

$$|P(iy)|^2 = |Q(iy)|^2. \quad (18)$$

Let $P(iy) = P_R(y) + iP_I(y)$ and $Q(iy) = Q_R(y) + iQ_I(y)$, where P_R, P_I, Q_R, Q_I are real valued. Equation (18) becomes:

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

This leads to the following 4th degree equation:

$$y^4 + y^2(\alpha_1^2 - 2\beta_1 - \beta_2^2) + \beta_1^2 - \alpha_2^2 = 0. \quad (19)$$

For $x = y^2$ we get

$$x^2 + x(\alpha_1^2 - 2\beta_1 - \beta_2^2) + \beta_1^2 - \alpha_2^2 = 0. \quad (20)$$

In order for equation (19) 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 (13) to be stable, at least one of the above conditions must not hold. □

We next consider $\tau_3 = \tau_3^*$ fixed and $\tau_4 > 0$. Equation (13) becomes:

$$(\lambda - a_{33} - d_{33}e^{-\lambda\tau_3^*})(\lambda - a_{44} - e_{44}e^{-\lambda\tau_4}) - e_{43}e^{-\lambda\tau_4}(a_{34} + d_{34}e^{-\lambda\tau_3^*}) = 0. \quad (21)$$

The above equation can be rewritten as:

$$P(\lambda) + Q(\lambda)e^{-\lambda\tau_4} = 0,$$

where

$$P(\lambda) = \lambda^2 - (a_{33} + a_{44})\lambda + a_{33}a_{44} - (d_{33}\lambda + a_{44}d_{33})e^{-\lambda\tau_3^*}$$
$$Q(\lambda) = -e_{44}\lambda + a_{33}e_{44} - a_{34}e_{43} + (d_{33}e_{44} - d_{34}e_{34})e^{-\lambda\tau_3^*}.$$

As $P(z)$ and $Q(z)$ are analytic functions, we can apply the results of Theorem 1 from [7]. As before, for $z = iy$, we are interested in the roots of the equation

$$F(y) = |P(iy)|^2 - |Q(iy)|^2 = 0.$$

If the equation $F(y) = 0$ has no positive root then, if (13) is stable with $\tau_3 = \tau_3^*$ and $\tau_4 = 0$, it will be stable for all $\tau_4 > 0$ and $\tau_3 = \tau_3^*$.

5. **Numerical simulations**

Numerical simulations using the packeges Biftool and DDE in Matlab show that there are two equilibrium points of the type E_3.

While $E_{31} = (0, 0, 0.0017, 14.6724, 0.8159, 0.5522, 0.0018, 0.0538, 5.9097)$ is unstable, $E_{32} = (0, 0, 1.2696, 115.15, 0.9718, 0.0843, 0.0116, 0.0530, 4.6057)$ is asymptotically stable. The solutions starting in the neighbourhood of E_{31} display different behaviours depending on the initial conditions. In Figures 1 and 3 we clearly see that the pacient's condition improves. Figures 2 and 4 show the case in which the patient has taken a turn for the worse. 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}.

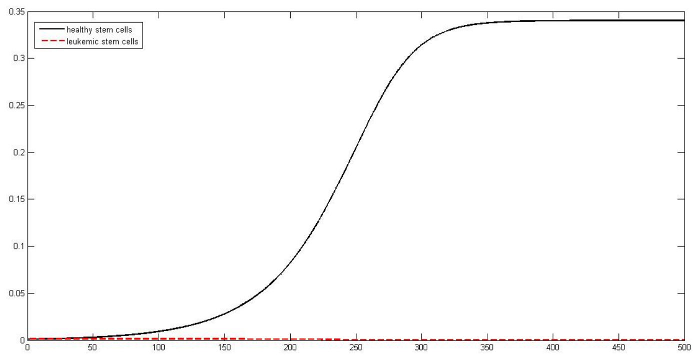

FIGURE 1. The evolution of healthy and leukemic stem cell populations starting near E_{31} (the patient recovers)

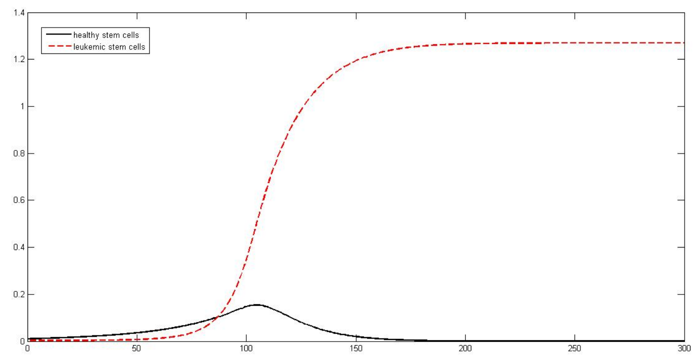

FIGURE 2. The evolution of healthy and leukemic stem cell populations starting near E_{31} (the patient's condition worsened)

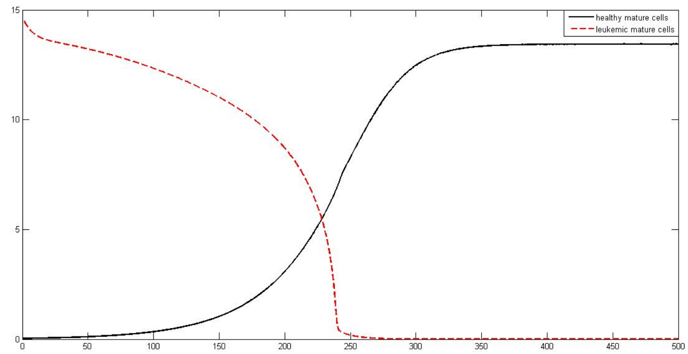

FIGURE 3. The evolution of healthy and leukemic mature cell populations starting near E_{31} (the patient recovers)

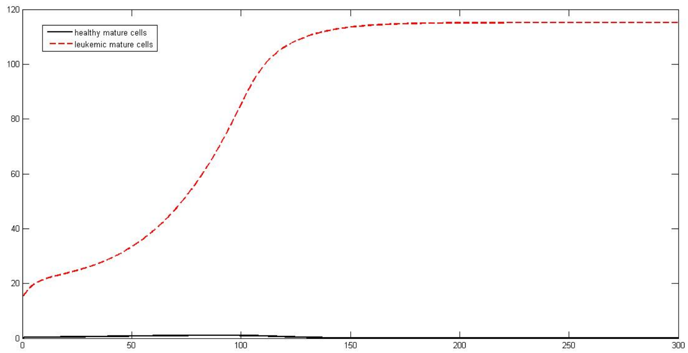

FIGURE 4. The evolution of healthy and leukemic mature cell populations starting near E_{31} (the patient's condition worsened)

6. Conclusions

Because of the complexity and the dimension of the DDEs system, a stability study using directly the characteristic equation is intractable for some of the equilibrium points.

Based on [11] we use a perturbed version of the matrix associated with the characteristic equation of the system. This facilitates the study of the characteristic equation and allows us to find sufficient conditions in parameter space than ensure linear stability.

From a medical point of view, numerical simulations show that in the case of a low population of healthy cells, the patient's condition can worsen or the patient can recover depending mainly on the population of leukemic cells.

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