A DELAY DIFFERENTIAL EQUATIONS MODEL FOR MAINTENANCE THERAPY IN ACUTE LYMPHOBLASTIC LEUKEMIA

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We introduce a mathematical model which captures the cellular evolution in the case of patients diagnosed with acute lymphoblastic leukemia and who are under maintenance therapy. We develop the model using a system of delay-differential equations. The main goal of this paper is to describe the complex biological model by considering three different compartments for the processes of erythropoiesis, leukopoiesis and lymphopoiesis. We discuss the existence and the stability of some equilibrium points.

Keywords: delay-differential equations, acute lymphoblastic leukemia, treatment in ALL, linear stability

1. Introduction

1.1. Background on ALL

Hematopoiesis is the biological process by which blood cells are produced. This includes the formation, development and differentiation of cells. All cellular blood components originate from hematopoietic stem cells which are located in the bone marrow. Each stem cell will go through either symmetric self-renewal, asymmetric division or symmetric differentiation. Hematopoietic stem cells generate two major progenitors cell lineages: myeloid and lymphoid. While the Myeloid line contains cells such as granulocytes, monocytes, erythrocytes or platelets, the lymphoid line is associated with the immune system. Lymphocytes include natural killer cells, T-cells and B-cells. The role of the immune system is very important when studying blood diseases and infections.

Cancer is a result of a sequence of molecular events that affect the normal characteristics of cells. In cancer, normal cells are prevented from growth and must compete with the malignant ones. Cancer cells usually result from mutations in the DNA. Consequently, mutations begin to increase in the cell, causing further abnormalities in that cell and the daughter cells. Some of these mutated cells die, but other may give the abnormal cell an advantage to multiply much more rapidly than the normal cells.

Leukemia is a cancer of the blood and bone marrow distinguished by a large number of disfunctional white blood cell.

Acute lymphoblastic leukemia (ALL), also called acute lymphocytic leukemia, is a cancer that starts from the early version of lymphocyte cells, called lymphoblasts, in the bone marrow. Leukemia cells usually invade the blood fairly quickly. They can then spread to other parts of the body, including the lymph nodes, liver, spleen, central nervous system (brain and spinal cord), and testicles (in males). Other types of cancer also can start in these organs and then spread to the bone marrow, but these cancers are not leukemia.

The term "acute" means that the leukemia can progress quickly, and if not treated, would be fatal within a few months. Lymphocytic means it develops from early (immature)

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forms of lymphocytes, a type of white blood cell. This is different from acute myeloid leukemia (AML), which develops in other white blood cell types found in the bone marrow.

In Acute lymphoblastic leukemia, too many stem cells become modified lymphoblasts. These cells are called leukemia cells. These leukemia cells are not able to fight infection very well. Also, as the number of leukemia cells increases in the blood and bone marrow, there is less room for healthy white blood cells, red blood cells, and platelets. Mutant lymphoblasts, precursors of B and T lymphocytes, proliferate uncontrollably and perturb the development of other cell lines, mainly the erythrocytes and the leukocytes.

1.2. Treatment in ALL

Chemotherapy is a type of treatment that includes a medication to treat cancer. The aim of chemotherapy is to stop or slow down the growth of cancerous cells, but it may affect the whole body. Chemotherapy medications attack rapidly growing cancer cells and they can also affect healthy cells that grow rapidly. The chemotherapy has serious side effects and the study of a physiological model may lead to a reduced toxicity while preserving efficiency ([11]-[4]). After first phase chemotherapy, the treatment consists of an oral administration of 6-MT (mercaptopurine). This is not biologically active but becomes so when converted by the enzymes HGPRT and TPMT into 6-TGN. While TPMT converts 6-MT into MeMP (metil-mercaptopurine), that has no effect on leukemic cells, HGPRT converts the rest into the active substance. The quantity of TPMT depends heavily on each human genotype. The patients with high rate of TPMT will receive a quantity of 6-TGN too small to be effective, those with a lower TPMT activity, and these are the majority, are exposed to higher toxicity, sometimes incompatible with life. This underpins the necessity of modeling the whole process in order to find the optimal dose for each patient ([11],[12] and [8]).

2. The Mathematical Model

The DDE mathematical model will contain a compartment for erythropoiesis coupled with the dynamics of 6-MP used in the maintenance therapy, a compartment for leukopoiesis coupled with the dynamics of 6-MP and a compartment for lymphopoiesis.

When modeling the hematopoiesis, the three types of cell divisions mentioned above will be considered. The treatment consists in oral administration of 6-MT (mercaptopurine).

2.1. A model of Erythropoiesis in ALL under treatment

Let us denote by z_1, the stem-like short-term erythroid cells, z_2 the erythrocytes, $z_3(t) = E(t)$, the concentration of erythropoietin, z_5 the amount of $6-MP$ in Gut, z_6 the amount of $6-MP$ in plasma and z_7 the concentration of $6-TGN$ (tioguanine nucleotide) in red blood cells (RBCs)(see [7], [8], [6], [1]).

The loss of stem cells is given by the function

$$h(t) = \frac{\gamma_0}{1+E(t)^\alpha} + \frac{\tilde{R}_m z_7(t)}{\tilde{R}_{50} + z_7(t)},$$

were $\tilde{R}_m = ER_m$ and $\tilde{R}_{50} = ECR_{50}$ from [8].

The loss during the cell cycle is given by

$$v(t) = e^{-\int_{t-\tau}^{t} h(s)ds},$$

and a new variable is introduced as $z_4 = v$.

We work under the assumption of a constant dose administration of the drug.

In what follows, the stem cell proliferation time, τ_e, will be denoted as τ_1 and the time necessary for the development of the erythrocytes, $\tau_{RM} = 6$ (see [6]) as τ_2.

2.**1**.1. *The equations.*

The model that takes into consideration the response of the treatment is:

$$\dot{z} = f_i(z, z_{\tau_j}), i = \overline{1,7}, j = \overline{1,2} \tag{1}$$

$$\begin{aligned}
\dot{z}_1 = & -\frac{\gamma_0}{1+z_3^\alpha} z_1 - \frac{\tilde{R}_m z_7}{\tilde{R}_{50}+z_7} z_1 - (\eta_{1e}+\eta_{2e}) k_e(z_3) z_1 - (1-\eta_{1e}-\eta_{2e}) \beta_e(z_1, z_3) z_1 \\
& +2 z_4 (1-\eta_{1e}-\eta_{2e}) \beta_e(z_{1\tau_1}, z_{3\tau_1}) z_{1\tau_1} + \eta_{1e} z_4 k_e(z_{3\tau_e}) z_{1\tau_1} \\
\dot{z}_2 = & -\gamma_2 z_2 + \tilde{A}_e k_e(z_{3\tau_2}) z_{1\tau_2} \\
\dot{z}_3 = & -k z_3 + \frac{a_1}{1+z_2^r} \\
\dot{z}_4 = & z_4 \left(-\frac{\gamma_0}{1+z_3^\alpha} - \frac{\tilde{R}_m z_7}{\tilde{R}_{50}+z_7} + \frac{\gamma_0}{1+z_{3\tau_1}^\alpha} + \frac{\tilde{R}_m z_{7\tau_1}}{\tilde{R}_{50}+z_{7\tau_1}} \right) \\
\dot{z}_5 = & -k_a z_5 + d \\
\dot{z}_6 = & k_a z_5 - k_{el} z_6 - \frac{k_{pt}(1-e_{rel})}{K_t+z_6} z_6 - \frac{k_m e_{rel}}{K_m+z_6} z_6 \\
\dot{z}_7 = & \frac{v_{pt} k_{pt}(1-e_{rel})}{K_t+z_6} z_6 - k_{te} z_7
\end{aligned}$$

Here

$$\beta_e(z_1, z_3) = \beta_0 \frac{1}{1+z_1^{m1l}} \frac{z_3}{1+z_3} \quad , \ \beta_0 = \beta_{0l}\beta_{1e}$$

$$k_e(z_3) = k_0 \frac{z_3}{1+z_3} \quad , \ k_0 = k_{0l} k_{1e}$$

2.**1**.2. *Positivity of solutions.*

The state variables z are populations of cells and we cannot talk about negative densities of cells. Therefore, the positivity of the solution corresponding to the system is a very important characteristic for the original model (1) to have.

Proposition 2.1. *Let* $\tau = \max\{\tau_i\}$ $j = \overline{1,2}$ *and* ϕ *be the initial condition defined on* $[-\tau, 0]$. *If the initial condition* ϕ *of the system (1) is positive, then the solution* z *of the system (1) is positive for all* $t > 0$.

Proof. Suppose that the initial condition ϕ of system (1) is positive. Then, in order to have a negative values, a solution has to cross through zero at a time $t_0 > 0$. Since for $t = t_0$ we have $z(t_0) = 0$ and $z_{\tau_j}(t_0) > 0$, then it can be easily seen that

$$f_i(0, z_{\tau_j}(t_0)) \geq 0 \Longrightarrow \dot{z}(t_0) \geq 0$$

with $i = \overline{1,7}, j = \overline{1,2}$. But then the components of the solution can not decrease to negative values. This means that the solution of the system will always be positive for positive initial values. □

2.**1**.3. *The equilibrium points.*

The equilibrium points are obtained by solving the following system:

$$f_i(z,z) = 0, i = \overline{1,7}.$$

After some calculations, we get:

$$[-\frac{\gamma_0}{1+z_3^\alpha} - \frac{\tilde{R}_m z_7}{\tilde{R}_{50}+z_7} - (\eta_{1e}+\eta_{2e})k_e(z_3) - (1-\eta_{1e}-\eta_{2e})\beta_e(z_1,z_3)$$
$$+2z_4(1-\eta_{1e}-\eta_{2e})\beta_e(z_1,z_3) + \eta_{1e}z_4k_e(z_3)]z_1 = 0$$

$$-\gamma_2 z_2 + \tilde{A}_e k_e(z_3)z_1 = 0$$

$$z_3 = \frac{a_1}{k}\frac{1}{1+z_2^r}$$

$$z_4\left(-\frac{\gamma_0}{1+z_3^\alpha} - \frac{\tilde{R}_m z_7}{\tilde{R}_{50}+z_7} + \frac{\gamma_0}{1+z_3^\alpha} + \frac{\tilde{R}_m z_{7\tau_e}}{\tilde{R}_{50}+z_7}\right) = 0$$

$$z_5 = \frac{d}{k_a}$$

$$k_a z_5 - k_{el}z_6 - \frac{k_{pt}(1-e_{rel})}{K_t+z_6}z_6 - \frac{k_m e_{rel}}{K_m+z_6}z_6 = 0$$

$$\frac{v_{pt}k_{pt}(1-e_{rel})}{K_t+z_6}z_6 - k_{te}z_7 = 0$$

It follows that:

$$\hat{z}_3 = \frac{a_1}{k}\frac{1}{1+\hat{z}_2^r}$$

$$\hat{z}_4 = e^{-\left(\frac{\gamma_0}{1+\hat{z}_3^\alpha}+\frac{\tilde{R}_m\hat{z}_7}{\tilde{R}_{50}+\hat{z}_7}\right)\tau_e} < 1$$

$$\hat{z}_5 = \frac{d}{k_a}$$

$$\hat{z}_7 = \frac{1}{k_{te}}\frac{v_{pt}k_{pt}(1-e_{rel})\hat{z}_6}{K_t+\hat{z}_6},$$

where the value of $\hat{z}_6$ can be calculated from:

$$d(K_t+\hat{z}_6)(K_m+\hat{z}_6)-k_{el}\hat{z}_6(K_t+\hat{z}_6)(K_m+\hat{z}_6)-k_{pt}(1-e_{rel})\hat{z}_6(K_m+\hat{z}_6)$$
$$-k_m e_{rel}\hat{z}_6(K_t+\hat{z}_6)=0$$

For $\hat{z}_1=\hat{z}_2=0, E=(0,0,\hat{z}_3,\hat{z}_4,\hat{z}_5,\hat{z}_6,\hat{z}_7)$ is an equilibrium point.

For different equilibrium points, we look for $(\hat{z}_1,\hat{z}_2)\neq(0,0)$, such that these points must verify equations (2) and (3).

$$-\frac{\gamma_0}{1+\hat{z}_3^{\alpha}}-\frac{\tilde{R}_m\hat{z}_7}{\tilde{R}_{50}+\hat{z}_7}-(\eta_{1e}+\eta_{2e})k_e(\hat{z}_3)-(1-\eta_{1e}-\eta_{2e})\beta_e(\hat{z}_1,\hat{z}_3)+$$
$$+2\hat{z}_4(1-\eta_{1e}-\eta_{2e})\beta_e(\hat{z}_1,\hat{z}_3)+\eta_{1e}\hat{z}_4k_e(\hat{z}_3)=0 \tag{2}$$

$$-\gamma_2\hat{z}_2+\tilde{A}_ek_e(\hat{z}_3)\hat{z}_1=0 \tag{3}$$

Then,

$$\hat{z}_2=\frac{\tilde{A}_ek_e(\hat{z}_3)\hat{z}_1}{\gamma_2}$$

In equation (2), consider $A_1=\dfrac{\gamma_0}{1+\hat{z}_3^{\alpha}}+\dfrac{\tilde{R}_m\hat{z}_7}{\tilde{R}_{50}+\hat{z}_7}>0$. Thus, equation (2) becomes:

$$-A_1+k_e(\hat{z}_3)(\eta_{1e}\hat{z}_4-\eta_{1e}-\eta_{2e})-(1-2\hat{z}_4)(1-\eta_{1e}-\eta_{2e})\beta_e(\hat{z}_1,\hat{z}_3)=0$$

Since $\hat{z}_4<1$, we know that

$$\eta_{1e}\hat{z}_4-\eta_{1e}-\eta_{2e}<0.$$

For $2\hat{z}_4<1\Longrightarrow\nexists(\hat{z}_1,\hat{z}_2)\neq(0,0)$ and for $2\hat{z}_4>1$ it is possible that $\hat{z}_1>0$ exists. In this case, we will also have $\hat{z}_2>0$.

We conclude that the types of equilibrium points corresponding to the model of Erythropoiesis in ALL under treatment are:
$E_1=(0,0,\hat{z}_3,\hat{z}_4,\hat{z}_5,\hat{z}_6,\hat{z}_7)$, corresponds to the "death of the patient" and
$E_2=(\hat{z}_1,\hat{z}_2,\hat{z}_3,\hat{z}_4,\hat{z}_5,\hat{z}_6,\hat{z}_7)$, corresponds to a "chronic phase of the disease".

In what follows, we will perform a linearization of system (1). The matrix of partial derivatives calculated in equilibria, for the undelayed variables, is:

$$A=\frac{\partial f}{\partial z}=[a_{ij}]$$

$$a_{11}=-\frac{\gamma_0}{1+z_3^{\alpha}}-\frac{\tilde{R}_m z_7}{\tilde{R}_{50}+z_7}-(\eta_{1e}+\eta_{2e})k_e(z_3)-(1-\eta_{1e}-\eta_{2e})\left[\beta_e(z_1,z_3)+z_1\frac{\partial\beta_e}{\partial z_1}(z_1,z_3)\right]$$
$$a_{12}=0$$
$$a_{13}=\frac{\gamma_0 z_1\alpha z_3^{\alpha-1}}{(1+z_3^{\alpha})^2}-(\eta_{1e}+\eta_{2e})z_1k_e'(z_3)-(1-\eta_{1e}-\eta_{2e})z_1\frac{\partial\beta_e}{\partial z_3}(z_1,z_3)$$
$$a_{14}=2(1-\eta_{1e}-\eta_{2e})\beta_e(z_1,z_3)z_1+\eta_{1e}k_e(z_3)z_1$$
$$a_{15}=a_{16}=0$$
$$a_{17}=-\tilde{R}_m z_1\frac{\tilde{R}_{50}}{\left(\tilde{R}_{50}+z_7\right)^2}$$
$$a_{21}=0, a_{22}=-\gamma_2, a_{23}=\cdots=a_{27}=0$$
$$a_{31}=0, a_{32}=-\frac{a_1 r z_2^{r-1}}{(1+z_2^r)^2}, a_{33}=-k, a_{34}=\cdots=a_{37}=0$$

$a_{41} = a_{42} = 0, a_{43} = \dfrac{\gamma_0 \alpha z_4 z_3^{\alpha-1}}{(1+z_3^\alpha)^2}, a_{44} = \cdots = a_{46} = 0, a_{47} = -\dfrac{\tilde{R}_m \tilde{R}_{50} z_4}{(\tilde{R}_{50}+z_7)^2}$

$a_{51} = a_{52} = a_{53} = a_{54} = 0, a_{55} = -k_a, a_{56} = a_{57} = 0$

$a_{61} = \cdots = a_{64} = 0, a_{65} = k_a, a_{66} = -k_{el} - \dfrac{k_{pt}(1-e_{rel})K_t}{(K_t+z_6)^2} - \dfrac{k_m e_{rel} K_m}{(K_m+z_6)^2}$

$a_{67} = 0$

$a_{71} = \cdots = a_{75} = 0, a_{76} = \dfrac{v_{pt} k_{pt}(1-e_{rel})K_t}{(K_t+z_6)^2}$

$a_{77} = -k_{te}$

The matrices of the partial derivatives with respect to the delayed variables are:

$$B = \frac{\partial f}{\partial z_{\tau_1}} = [b_{ij}]$$

$b_{11} = 2z_4(1-\eta_{1e}-\eta_{2e})\left[\beta_e(z_1,z_3) + z_1 \dfrac{\partial \beta_e}{\partial z_1}(z_1,z_3)\right] + \eta_{1e} z_4 k_e(z_3)$

$b_{12} = 0$

$b_{13} = 2(1-\eta_{1e}-\eta_{2e}) z_4 z_1 \dfrac{\partial \beta_e}{\partial z_3}(z_1,z_3) + \eta_{1e} z_4 k_e'(z_3) z_1$

$b_{14} = \cdots = b_{37} = 0$

$b_{41} = b_{42} = 0, b_{43} = -\dfrac{\gamma_0 z_4 \alpha z_3^{\alpha-1}}{(1+z_3^\alpha)^2}$

$b_{44} = b_{45} = b_{46} = 0, b_{47} = \dfrac{\tilde{R}_m \tilde{R}_{50} z_4}{\left(\tilde{R}_{50}+z_7\right)^2}$

$b_{51} = \cdots = b_{77} = 0$

$$C = \frac{\partial f}{\partial z_{\tau_2}} = [c_{ij}]$$

$c_{11} = \cdots = c_{17} = 0$

$c_{21} = \tilde{A}_e k_e(z_3)$

$c_{22} = 0, c_{23} = \tilde{A}_e z_1 k_e'(z_3)$

$c_{24} = \cdots = c_{77} = 0$

The characteristic equation will be:

$$\det(\lambda I - A - e^{-\lambda\tau_1} B - e^{-\lambda\tau_2} C) = 0$$

It is easy to see that, for E_1, a critical case of a zero root for the characteristic equation must be analyzed.

2.2. The leukopoiesis model

Now x_1 represents the concentration of short-term stem-like white blood cells precursors and x_2 the adult leukocytes. Treatment is present through

$$l_1(x_6) = \frac{x_6}{L_{1S0}+x_6}$$

(see [8]). Once again a non-constant rate of elimination of stem cells is encountered and this leads to the consideration of a new variable:

$$x_3(t) = e^{-T_1 \int_{t-\tau_3}^{t} l_1(s) ds}$$

2.**2**.1. *The equations.*

The model that takes into consideration the response of the treatment is:

$$\dot{x} = \tilde{f}_i(x, x_{\tau_j}), i = \overline{1,6}, j = \overline{3,4} \tag{4}$$

$$\begin{aligned}
\dot{x}_1 = \; & -\gamma_{1l}x_1 - T_1 l_1(x_6)x_1 - \eta_{1l}k_l(x_2)x_1 - \eta_{2l}k_l(x_2)x_1 - \\
& (1-\eta_{1l}-\eta_{2l})\beta_l(x_1)x_1 + 2e^{-\gamma_{1l}\tau_3}x_3(1-\eta_{1l}-\eta_{2l})\beta_l(x_{1\tau_3})x_{1\tau_3} + \\
& +\eta_{1l}e^{-\gamma_{1l}\tau_3}x_3 k_l(x_{2\tau_3})x_{1\tau_3} \\
\dot{x}_2 = \; & -\gamma_{2l}x_2 + \tilde{A}_l k_l(x_{2\tau_4})x_{1\tau_4} \\
\dot{x}_3 = \; & x_3 T_1[l_1(x_{6\tau_3}) - l_1(x_6)] \\
\dot{x}_4 = \; & -k_a x_4 + d \\
\dot{x}_5 = \; & k_a x_4 - k_{el}x_5 - \frac{k_{pt}(1-e_{rel})}{K_t + x_5}x_5 - \frac{k_m e_{rel}}{K_m + x_5}x_5 \\
\dot{x}_6 = \; & \frac{\nu_{pt}k_{pt}(1-e_{rel})}{K_t + x_5}x_5 - k_{tl}x_6
\end{aligned}$$

where

$$\beta_l(x_1) = \beta_{0l}\frac{1}{1+x_1^{m_{1l}}}, k_l(x_2) = k_{0l}\frac{1}{1+x_2^{m_{2l}}}, \tilde{A}_l = A_l(2\eta_{1l}+\eta_{2l})$$

2.**2**.2. *The equilibrium points.*

The equilibrium points of (4) are obtained solving the equations

$$\tilde{f}_i(x,x) = 0, i = \overline{1,6}.$$

So, we have:

$$[-\gamma_{1l} - T_1 l_1(x_6) - \eta_{1l}k_l(x_2) - \eta_{2l}k_l(x_2) - (1-\eta_{1l}-\eta_{2l})\beta_l(x_1) +$$

$$+2e^{-\gamma_{1l}\tau_3}x_3(1-\eta_{1l}-\eta_{2l})\beta_l(x_1) + \eta_{1l}e^{-\gamma_{1l}\tau_3}x_3 k_l(x_2)]x_1 = 0$$

$$-\gamma_{2l}x_2 + \tilde{A}_l k_l(x_2)x_1 = 0$$

$$x_3 T_1[l_1(x_6) - l_1(x_6)] = 0$$

$$x_4 = \frac{d}{k_a}$$

$$k_a x_4 - k_{el}x_5 - \frac{k_{pt}(1-e_{rel})}{K_t + x_5}x_5 - \frac{k_m e_{rel}}{K_m + x_5}x_5 = 0$$

$$\frac{\nu_{pt}k_{pt}(1-e_{rel})}{K_t + x_5}x_5 - k_{tl}x_6 = 0$$

From the above equations and the definition of x_3, we obtain:

$$\hat{x}_3 = e^{-T_1 l_1(\hat{x}_6)\tau_3}$$

$$\hat{x}_4 = \frac{d}{k_a}$$

$$\hat{x}_6 = \frac{1}{k_{tl}} \frac{v_{pt} k_{pt} (1 - e_{rel})}{K_t + \hat{x}_5} \hat{x}_5,$$

where $\hat{x}_5$ can be calculated from:

$$d(K_t + \hat{x}_5)(K_m + \hat{x}_5) - k_{el}\hat{x}_5(K_t + \hat{x}_5)(K_m + \hat{x}_5) - k_{pt}(1 - e_{rel})\hat{x}_5(K_m + \hat{x}_5)$$

$$-k_m e_{rel}\hat{x}_5(K_t + \hat{x}_5) = 0$$

For $\hat{x}_1 = \hat{x}_2 = 0, \tilde{E} = (0, 0, \hat{x}_3, \hat{x}_4, \hat{x}_5, \hat{x}_6)$ is an equilibrium point. For different equilibrium points, we look for $(\hat{x}_1, \hat{x}_2) \neq (0, 0)$.

The following equations, (5) and (6), must be verified by these points.

$$\begin{aligned} &-\gamma_{1l} - T_1 l_1(x_6) - \eta_{1l} k_l(x_2) - \eta_{2l} k_l(x_2) - (1 - \eta_{1l} - \eta_{2l})\beta_l(x_1) + \\ &+2e^{-\gamma_{1l}\tau_3} x_3 (1 - \eta_{1l} - \eta_{2l})\beta_l(x_1) + \eta_{1l} e^{-\gamma_{1l}\tau_3} x_3 k_l(x_2) = 0 \end{aligned} \tag{5}$$

$$-\gamma_{2l} x_2 + \tilde{A}_l k_l(x_2) x_1 = 0 \tag{6}$$

We conclude that the two types of equilibrium points corresponding to the model of leukopoiesis are:

$$\tilde{E}_1 = (0, 0, \hat{x}_3, \hat{x}_4, \hat{x}_5, \hat{x}_6)$$
$$\tilde{E}_2 = (\hat{x}_1, \hat{x}_2, \hat{x}_3, \hat{x}_4, \hat{x}_5, \hat{x}_6)$$

When linearizing the system, we consider, as before, $\tilde{A}$, the matrix of partial derivatives with respect to undelayed variables:

$\tilde{a}_{11} = -\gamma_{1l} - T_1 l_1(\hat{x}_6) - (\eta_{1l} + \eta_{2l}) k_l(\hat{x}_2) - (1 - \eta_{1l} - \eta_{2l})\beta_l(\hat{x}_1) - (1 - \eta_{1l} - \eta_{2l})\beta_l'(\hat{x}_1)\hat{x}_1$

$\tilde{a}_{12} = -(\eta_{1l} + \eta_{2l})\hat{x}_1 k_l'(\hat{x}_2)$
$\tilde{a}_{13} = e^{-\gamma_{1l}\tau_3} \left[2(1 - \eta_{1l} - \eta_{2l})\beta_l(\hat{x}_1) + \eta_{1l} k_l(\hat{x}_2)\right] \hat{x}_1$
$\tilde{a}_{14} = \cdots = \tilde{a}_{15} = 0$
$\tilde{a}_{16} = -x_1 T_1 l_1'(\hat{x}_6)$
$\tilde{a}_{21} = 0$
$\tilde{a}_{22} = -\gamma_{2l}$
$\tilde{a}_{23} = \cdots = \tilde{a}_{26} = 0$
$\tilde{a}_{31} = \cdots = \tilde{a}_{35} = 0$
$\tilde{a}_{36} = -\hat{x}_3 T_1 l_1'(\hat{x}_6)$
$\tilde{a}_{41} = \cdots = \tilde{a}_{43} = 0$
$\tilde{a}_{44} = -k_a$
$\tilde{a}_{45} = \tilde{a}_{46} = 0$
$\tilde{a}_{51} = \cdots = \tilde{a}_{53} = 0$
$\tilde{a}_{54} = k_a$
$\tilde{a}_{55} = -k_{el} - \dfrac{k_{pt}(1 - e_{rel})K_t}{(K_t + \hat{x}_5)^2} - \dfrac{k_m e_{rel} K_m}{(K_m + \hat{x}_5)^2}$
$\tilde{a}_{56} = 0$
$\tilde{a}_{61} = \cdots = \tilde{a}_{64} = 0$
$\tilde{a}_{65} = \dfrac{\nu_{pt} k_{pt}(1 - e_{rel})K_t}{(K_t + \hat{x}_5)^2}$
$\tilde{a}_{66} = -k_{tl}$

We consider $\tilde{B}$, the matrix of partial derivatives with respect to variables delayed by τ_3:

$\tilde{b}_{11} = e^{-\gamma_{1l}\tau_3}\hat{x}_3\left[2(1-\eta_{1l}-\eta_{2l})\beta_l(\hat{x}_1) + 2(1-\eta_{1l}-\eta_{2l})\hat{x}_1\beta_l'(\hat{x}_1) + \eta_{1l}k_l(\hat{x}_2)\right]$
$\tilde{b}_{12} = \eta_{1l}e^{-\gamma_{1l}\tau_3}\hat{x}_3k_l'(\hat{x}_2)\hat{x}_1$
$\tilde{b}_{13} = \cdots = \tilde{b}_{16} = 0$
$\tilde{b}_{21} = \cdots = \tilde{b}_{26} = 0$
$\tilde{b}_{31} = \cdots = \tilde{b}_{35} = 0$
$\tilde{b}_{36} = \hat{x}_3T_1l_1'(\hat{x}_6)$
$\tilde{b}_{41} = \cdots = \tilde{b}_{66} = 0$

We consider $\tilde{C}$, the matrix of partial derivatives with respect to variables delayed by τ_4:

$\tilde{c}_{11} = \cdots = \tilde{c}_{16} = 0$
$\tilde{c}_{21} = \tilde{A}_lk_l(\hat{x}_2)$
$\tilde{c}_{22} = \tilde{A}_lk_l'(\hat{x}_2)\hat{x}_1$
$\tilde{c}_{23} = \cdots = \tilde{c}_{66} = 0$

The characteristic equation is given by:

$$\det(\lambda I - \tilde{A} - e^{-\lambda\tau_3}\tilde{B} - e^{-\lambda\tau_4}\tilde{C}) = 0$$

We notice that zero is, again, a root of the characteristic equation in the particular case of equilibrium point E_1.

2.3. The lymphoblasts model

In [10], the authors prove that the curative action of the therapy in ALL is exerted by induction of a higher rate of differentiation that ultimately results in the extinction of the malignant clone.

Lymphopoiesis is present in an extended DDE model of hematopoiesis given in [2].

2.3.1. *The equations.*

The model for the evolution of ALL cell population will contain two delay differential equations, one for the Stem-Like progenitors, u_1, and another for more mature cells, the lymphoblasts , u_2. In the first compartment only asymmetric division and differentiation will be considered.

The system of equations is:

$$\dot{u} = \hat{f}_i(u, u_{\tau_{jll}}), i = 1, 2,\ j = 1, 2 \tag{7}$$

$$\begin{aligned}\dot{u}_1 = &\ -\gamma_{1ll}u_1 - (\eta_{1ll}+\eta_{2ll})k_{ll}(u_2)u_1 + \eta_{1ll}e^{-\gamma_{1ll}\tau_{1ll}}k_{ll}(u_{2\tau_{1ll}})u_{1\tau_{1ll}}\\ \dot{u}_2 = &\ -\gamma_{2ll}u_2 + A_{ll}(2\eta_{2ll}+\eta_{1ll})k_{ll}(u_{2\tau_{2ll}})u_{1\tau_{2ll}}\end{aligned}$$

with $k_{ll}(u) = \dfrac{k_{0,ll}}{1+u^m}$

2.**3**.2. *Equilibrium points.*

We determine the equilibrium points by solving the following system of equations:

$$-\gamma_{1ll}u_1 - (\eta_{1ll}+\eta_{2ll})k_{ll}(u_2)u_1 + \eta_{1ll}e^{-\gamma_{1ll}\tau_{1ll}}k_{ll}(u_2)u_1 = 0$$

$$-\gamma_{2ll}u_2 + A_{ll}(2\eta_{2ll}+\eta_{1ll})k_{ll}(u_2)u_1 = 0$$

It is clear that $\hat{E}=(0,0)$ is the only meaningful biological equilibrium point.

When linearizing the system (7), we denote by $\hat{A}$ the matrix of partial derivatives for the undelayed variables:

$\hat{a}_{11} = -\gamma_{1ll} - (\eta_{1ll}+\eta_{2ll})k_{ll}(u_2)$
$\hat{a}_{12} = -u_1(\eta_{1ll}+\eta_{2ll})k'_{ll}(u_2)$
$\hat{a}_{21} = 0$
$\hat{a}_{22} = -\gamma_{2ll}$

and the matrices of the partial derivatives with respect to the delayed variables are:

$$\hat{B} = \frac{\partial f}{\partial u_{\tau_{1ll}}} = [\hat{b}_{ij}]$$

$\hat{b}_{11} = \eta_{1ll}e^{-\gamma_{1ll}\tau_{1ll}}k_{ll}(u_2)$
$\hat{b}_{12} = u_1\eta_{1ll}e^{-\gamma_{1ll}\tau_{1ll}}k'_{ll}(u_2)$
$\hat{b}_{21} = 0$
$\hat{b}_{22} = 0$

$$\hat{C} = \frac{\partial f}{\partial u_{\tau_{2ll}}} = [\hat{c}_{ij}]$$

$\hat{c}_{11} = 0$
$\hat{c}_{12} = 0$
$\hat{c}_{21} = A_{ll}(2\eta_{2ll}+\eta_{1ll})k_{ll}(u_2)$

$\hat{c}_{22} = u_1A_{ll}(2\eta_{2ll}+\eta_{1ll})k'_{ll}(u_2)$

The characteristic equation has the general form:

$$\det(\lambda I - \hat{A} - e^{-\lambda\tau_{1ll}}\hat{B} - e^{-\lambda\tau_{2ll}}\hat{C}) = 0$$

For the particular case of equilibrium point $\hat{E}=(0,0)$, the characteristic equation is:

$$\left(\lambda - \hat{a}_{11} - e^{-\lambda\tau_{1ll}}\hat{b}_{11}\right)(\lambda - \hat{a}_{22}) = 0$$

The equilibrium point is stable if the roots of the characteristic equation all have negative real parts (see [9],[3]).

The characteristic equation decouples into

$$\lambda - \hat{a}_{22} = 0 \tag{8}$$

and

$$\lambda - \hat{a}_{11} - e^{-\lambda\tau_{1ll}}\hat{b}_{11} = 0 \tag{9}$$

We notice that $\lambda = \hat{a}_{22} = -\gamma_{2ll} < 0$. Thus, we only need to study equation (9).

Proposition 2.2. *The equation (9) is stable for $\tau_{1ll}=0$ and remains stable for $\tau_{1ll}>0$.*

Proof. We recall that, for the equilibrium point $\hat{E}$ we have:

$$\hat{a}_{11} = -\gamma_{1ll} - (\eta_{1ll} + \eta_{2ll})k_{0,ll}$$

$$\hat{b}_{11} = \eta_{1ll}e^{-\gamma_{1ll}\tau_{1ll}}k_{0,ll}$$

For $\tau_{1ll} = 0$, equation (9) becomes:

$$\lambda + \gamma_{1ll} + (\eta_{1ll} + \eta_{2ll})k_{0,ll} - \eta_{1ll}k_{0,ll} = 0$$

so

$$\lambda = -\gamma_{1ll} - \eta_{2ll}k_{0,ll} < 0$$

Since $\hat{b}_{11} > 0$, according to ([3],[5]), the following conditions must hold for stability when $\tau_{1ll} > 0$:

1. $\hat{a}_{11} < \frac{1}{\tau_{1ll}}$
2. $\hat{a}_{11} + \hat{b}_{11} < 0$.

We notice that $\hat{a}_{11} < 0 < \frac{1}{\tau_{1ll}}$, so the first condition holds. We compute:

$$\hat{a}_{11} + \hat{b}_{11} \quad = -\gamma_{1ll} - \eta_{2ll}k_{0,ll} - \eta_{1ll}k_{0,ll}\left(1 - e^{-\gamma_{1ll}\tau_{1ll}}\right) < 0$$

Thus, the second condition hold. □

In conclusion, the equilibrium point $(0, 0)$ is locally asymptotically stable. So, the model ensures the patient's recovery when the leukemic burden is not very high.

3. **Conclusion**

A physiological model describing erythropoiesis, leukopoiesis and lymphopoiesis during the maintenance therapy with 6-MP is developed using delay differential equations to account for the cell cycle and amplification. It contains the three types of division of cells and allows for a realistic prognosis of the leukemic lymphoblasts' evolution, that means healing, if the therapy is tolerated. The critical case for stability encountered as well as the stability of chronic equilibria will be analyzed in future works.

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