A Complex Delay Differential Equations Model for Acute Lymphoblastic Leukemia

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Abstract: In this paper, we introduce an innovative mathematical model designed to capture the dynamics of Acute Lymphoblastic Leukemia (ALL) under therapeutic interventions, employing delay-differential equations to account for the time delays inherent in biological processes. The model consists of 13 delay-differential equations, incorporating six distinct delays to represent various time-dependent factors such as drug effects, immune responses, and tumor growth cycles. To facilitate the analysis, we first identified the equilibrium points, which serve as critical benchmarks for understanding the system's behavior under steady-state conditions, followed by a detailed stability analysis to assess the robustness of these points against perturbations. Utilizing the critical case theorem, we translated the system by shifting the equilibrium point to zero, simplifying the stability examination. A series of transformations were applied to aid this process, allowing for deeper insights into the dynamics of ALL under treatment. Our findings contribute to understanding treatment efficacy and tumor progression, offering a mathematical framework that not only highlights the complex interplay between treatment, tumor dynamics, and time delays but also provides a foundation for future research aimed at optimizing therapeutic strategies for ALL management.

Key-Words: Acute Lymphoblastic Leukemia, mercaptopurine (6-MP), Erythrocytes, Leukocytes, Lymphoblasts, Equilibrium points, Critical Case, Stability Analysis.

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1 Introduction

Delay differential equations (DDEs) are a type of differential equation in which the rate of change of the variables depends on the values of the variables at the present time t and also on the values of the variables at previous time moments. The applications of DDEs cover important domains in engineering and life sciences. The introduction of delays in mathematical modelling opened new possibilities for a better approximation of the evolution of a natural phenomenon. DDEs have also been used with success in biology at a cellular level. Using time delays one obtains a more accurate description of the phenomena we want to model. The solutions of the delay differential equations are more faithful to the natural evolution of the quantities under study. The literature concerning the dynamics of DDEs, their properties, and applications is wide. For more information, one can refer to [1], [2], [3], and the references therein.

In 1977, a nonlinear delay-differential equation that describes the changes in the concentration of circulating blood cells was first introduced, [4].

In 2003, a model of the production and regulation of circulating blood neutrophils was proposed, [5].

In 2005, a more complex dynamics of blood cells in Chronic Myeloid Leukemia (CML) was described, [6]. The assumptions made in [5] regarding stem cells and the differentiation process were also used in [6].

Another important model was introduced, which differs from those introduced before through the fact that it is structured by age, thus offering a better perspective on the cell cycle, [7]. The authors took into account that there are two

phases in a cell cycle (the resting phase and the proliferating phase) and the fact that not all cells divide at the same age (depending on their type-pluripotent or committed stem cells).

In 2020, a physiological model of Acute Lymphoblastic Leukemia under treatment was studied [8]. The model was formed of three compartments: a compartment for erythropoiesis, a compartment for leukopoiesis, and a compartment for lymphopoiesis, coupled with the dynamics of 6-MP used in the maintenance therapy.

In this article, we propose a complex delay differential equations model for Acute Lymphoblastic Leukemia under treatment. The novelty of our model is that we take into account the physiological evolution of erythrocytes, leukocytes, and lymphocytes. The importance of this study is an introduction to studying the optimization of the treatment in the physiological model in order to determine the exact amount of medication needed at different stages of the disease.

Cancer, characterized as a genetic disease, arises from genetic alterations either inherited from parents or acquired throughout a person's lifetime. These genetic mutations lead to uncontrolled cell growth and the formation of tumors, which can ultimately cause significant bodily harm and mortality. The World Health Organization (WHO) identifies cancer as a leading cause of death globally, with approximately 10 million deaths in 2020, accounting for one in six fatalities. There are over 100 types of cancer, generally named based on the tissues or organs where they originate, [9].

Leukemia, a category of blood cancers, encompasses several types, including Chronic Myeloid Leukemia (CML), Chronic Lymphocytic Leukemia (CLL), Acute Myeloid Leukemia (AML), and Acute Lymphoblastic Leukemia (ALL). ALL, in particular, involves the malignant transformation and proliferation of lymphoid precursor cells in the bone marrow, blood, and other regions. This disease results in the production of approximately a trillion nonfunctional leukemia cells from the initial leukemia cell, which overcrowd healthy marrow cells and fail to perform normal cellular functions, [10]. Consequently, patients experience anemia, increased bleeding risk, and heightened susceptibility to infections due to reduced counts of red cells, platelets, and neutrophils. ALL rapidly invades the bloodstream and can spread to various organs, such as the liver, spleen, and lymph nodes, justifying its classification as an acute condition due to its swift progression, [11].

The primary treatment for ALL is chemotherapy, aimed at reducing or halting the growth of cancer cells. Unlike surgery and radiation, which target specific areas, chemotherapy affects the entire body, making it effective against cancer cells that have metastasized beyond the original tumor site, [12]. Chemotherapy's objectives include the complete destruction of cancer cells, controlling their growth and spread, alleviating symptoms by shrinking tumors, and preventing cancer recurrence. Following chemotherapy, maintenance therapy often involves oral administration of mercaptopurine (6-MP), which is crucial for slowing the growth of cancer cells. Research underscores the importance of maintenance therapy's intensity, as insufficient therapy can lead to persistent ALL, while overly aggressive treatment can result in severe side effects and secondary malignancies.

The complexity of ALL treatment is further compounded by genetic polymorphism in the enzyme Thiopurine Methyltransferase (TPMT), which plays a vital role in metabolizing 6-MP. 6-MP, a pro-drug, follows two metabolic pathways. The preferred pathway, catalyzed by the enzyme Hypoxanthine-Guanine Phosphoribosyltransferase (HGPRT), produces 6-thioguanine nucleotide (6-TGN). Conversely, TPMT converts 6-MP into methyl-mercaptopurines (MeMP). The relative activities of HGPRT and TPMT, determined by genetic factors, influence the concentration of active 6-TGN and, consequently, the treatment outcome, [8].

In this article, we present an innovative biological mathematical model for Acute Lymphoblastic Leukemia (ALL) under treatment, using delay-differential equations to represent the disease's progression and its reaction to therapy, similar to the approaches used in [8], [13], [14]. Our model comprises 13 delay-differential equations with six delays, offering a comprehensive framework to understand the interactions between leukemia cells, healthy cells, and treatment effects. We identify the equilibrium points of the system and conduct a stability analysis to evaluate the conditions under which the disease remains controlled or progresses. By translating the system to zero and performing several transformations, we apply the critical case theorem, [15], to gain insights into the model's behavior. This work contributes to the existing literature by providing a detailed and dynamic representation of ALL treatment,

potentially guiding future therapeutic strategies and improving patient outcomes.

Furthermore, recent advancements in fractional calculus have significantly enhanced our understanding of complex biological systems. Fractional differential equations, especially those involving fractional calculus and hybrid fractional models, offer a comprehensive framework for analyzing the stability and dynamics of various biological processes. These equations have proven effective in capturing the complexities of biological systems, providing critical insights into stability and solution behaviors. Future research could explore fractional delay models to extend these findings, while theoretical analysis of solutions could follow approaches similar to those outlined in [16], [17], [18], [19], [20], [21]. By integrating fractional calculus into our model, we aim to enhance its predictive capabilities and offer a more robust framework for studying the intricate dynamics of ALL and its treatment.

2 Mathematical Model and Equations for 6-Mercaptopurine Therapy Dynamics

In this section, we use $s_\tau = s(t-\tau)$ to denote delayed variables and employ delay-differential equations to model and analyze the dynamics of 6-Mercaptopurine (6-MP) used in maintenance therapy. The model consists of thirteen delay-differential equations (DDEs) incorporating six distinct time delays.

$$\dot{s} = f_i(s, s_{\tau_j});\ i = \overline{1,13},\ j = \overline{1,6}. \tag{1}$$

First Equation:

$$\begin{aligned}\dot{s}_1 \;=\; & -\frac{\delta_0}{1+s_3^{\varepsilon}}s_1 - \frac{R_1 s_7}{R_2+s_7}s_1 - (\upsilon_{1e}+\upsilon_{2e})\varpi_e(s_3)s_1 \\ & -(1-\upsilon_{1e}-\upsilon_{2e})\phi_e(s_1,s_3)s_1 \\ & +2s_4(1-\upsilon_{1e}-\upsilon_{2e})\phi_e(s_{1\tau_1},s_{3\tau_1})s_{1\tau_1} \\ & +\upsilon_{1e}s_4\varpi_e(s_{3\tau_1})s_{1\tau_1}.\end{aligned} \tag{2}$$

Description: This equation models the dynamics of stem-like short-term erythroid cells. The parameters include δ_0 for stem cell loss due to mortality, ε for the death rate, and υ_{1e} and υ_{2e} for the proportions of cells undergoing asymmetric and symmetric divisions, respectively.
Second Equation:

$$\dot{s}_2 = -\delta_2 s_2 + \tilde{B}_e\varpi_e(s_{3\tau_2})s_{1\tau_2}. \tag{3}$$

Description: This equation represents the uninfected erythrocytes. The term $-\delta_2 s_2$ accounts for the random loss of red blood cells, with $\tilde{B}_e$ as an amplification factor and τ_2 as the maturation time.
Third Equation:

$$\dot{s}_3 = -qs_3 + \frac{p_1}{1+s_2^n}. \tag{4}$$

Description: This equation describes the concentration of erythropoietin, where q is the absorption rate.
Fourth Equation:

$$\dot{s}_4 = s_4\left(-\frac{\delta_0}{1+s_3^{\varepsilon}} - \frac{R_1 s_7}{R_2+s_7} + \frac{\delta_0}{1+s_{3\tau_1}^{\varepsilon}} + \frac{R_1 s_{7\tau_1}}{R_2+s_{7\tau_1}}\right). \tag{5}$$

Description: This variable represents the loss during the cell cycle.
Fifth Equation:

$$\dot{s}_5 = -j_1 s_5 + p_2. \tag{6}$$

Description: This equation models the amount of 6-MP in the gut, with j_1 representing the absorption rate and p_2 the supply rate.
Sixth Equation:

$$\dot{s}_6 = j_1 s_5 - f_1 s_6 - \frac{g_1(1-f_2)}{g_2+s_6}s_6 - \frac{h_2 f_2}{h_1+s_6}s_6. \tag{7}$$

Description: This equation describes the amount of 6-MP in plasma. The parameters include f_1 for the elimination rate, g_1 and h_2 for conversion rates, and f_2 for the activity of the TPMT enzyme.
Seventh Equation:

$$\dot{s}_7 = \frac{j_2 g_1(1-f_2)}{g_2+s_6}s_6 - f_3 s_7. \tag{8}$$

Description: This equation represents the concentration of 6-TGN in red blood cells, with j_2 as the stoichiometric coefficient and f_3 as the elimination rate.
Eighth Equation:

$$\begin{aligned}\dot{s}_8 = & -\delta_{1l}s_8 - H_1 v_1(s_{11})s_8 - \upsilon_{1l}\varpi_l(s_9)s_8 \\ & -\upsilon_{2l}\varpi_l(s_9)s_8 - (1-\upsilon_{1l}-\upsilon_{2l})\phi_l(s_8)s_8 \\ & +2e^{-\delta_{1l}\tau_3}s_{10}(1-\upsilon_{1l}-\upsilon_{2l})\phi_l(s_{8\tau_3})s_{8\tau_3} \\ & +\upsilon_{1l}e^{-\delta_{1l}\tau_3}s_{10}\varpi_l(s_{9\tau_3})s_{8\tau_3}.\end{aligned} \tag{9}$$

Description: This equation models the concentration of short-term stem-like white blood cell precursors, accounting for mortality rate δ_{1l} and various rates of differentiation and renewal.

Ninth Equation:

$$\dot{s}_9 = -\delta_{2l} s_9 + \tilde{B}_l \varpi_l(s_{9\tau_4}) s_{8\tau_4}. \tag{10}$$

Description: This equation describes the dynamics of adult leukocytes, with $-\delta_{2l} s_9$ representing random loss and $\tilde{B}_l$ as an amplification factor.
Tenth Equation;

$$\dot{s}_{10} = s_{10} H_1 \left[v_1(s_{11\tau_3}) - v_1(s_{11}) \right]. \tag{11}$$

Description: This equation models the loss during the cycle of leukocytes, where H_1 represents the drug's maximum effect on white blood cells.
Eleventh Equation:

$$\dot{s}_{11} = \frac{j_2 g_1 (1 - f_2)}{g_2 + s_6} s_6 - g_3 s_{11}. \tag{12}$$

Description: This equation represents the concentration of 6-TGN in leukocytes, with g_3 as the elimination rate.
Twelfth Equation:

$$\dot{s}_{12} = -\delta_{1ll} s_{12} - (\upsilon_{1ll} + \upsilon_{2ll}) \varpi_{ll}(s_{13}) s_{12} \tag{13}$$

$$+\upsilon_{1ll} e^{-\delta_{1ll}\tau_5} \varpi_{ll}(s_{13\tau_5}) s_{12\tau_5}.$$

Description: This equation models short-term stem-like progenitor cells in leukocytes, accounting for mortality and differentiation rates.
Thirteenth Equation:

$$\dot{s}_{13} = -\delta_{2ll} s_{13} + \tilde{B}_{ll} \varpi_{ll}(s_{13\tau_6}) s_{12\tau_6}. \tag{14}$$

Description: This final equation describes mature leukocytes, with parameters δ_{2ll} and $\tilde{B}_{ll}$ defining loss and maturation rates, respectively.

2.1 Positivity of Solutions

The variables s in our model represent populations of cells. As such, it is essential that we ensure non-negative densities of cells, as negative values would be biologically meaningless. Therefore, demonstrating that the solutions to the system remain positive is a crucial characteristic for the validity of the original model (1).

Proposition 2.1. Let $\tau = \max\{\tau_J\}$, $j = \overline{1,6}$, and ϕ denote the initial conditions defined on the interval $[-\tau, 0]$. If the initial conditions ϕ of the system (1) are positive, then the solutions s of the system (1) remain positive for all $t \geq 0$.

Proof. Assume that the initial conditions ϕ for the system (1) are positive. To prove that the solutions remain positive, we must show that these solutions do not cross zero at any time $t > 0$. Suppose, for contradiction, that a solution becomes zero at some time $t_0 > 0$, i.e., $s(t_0) = 0$. Given that $s_{\tau j}(t_0) > 0$ for $j = \overline{1,6}$, it follows that

$$f_i(0, s_{\tau j}(t_0)) \geq 0 \Rightarrow \dot{s}(t_0) \geq 0, \tag{15}$$

where $i = \overline{1,13}$ and $j = \overline{1,6}$. Hence, the rate of change of the solution $\dot{s}(t_0)$ is non-negative at t_0. This implies that once the solution reaches zero, it cannot decrease further into negative values. Therefore, the solutions s of the system will remain positive for all $t \geq 0$, provided the initial values are positive. □

2.2 Analysis of Equilibrium Points

To identify the equilibrium points of the system, we solve the following equations:

$$f_i(s, s_{\tau_j}) = 0; \quad i = \overline{1,13},\ j = \overline{1,6} \tag{16}$$

At equilibrium points, the system reaches a steady state where variables do not change over time or with delays, implying that s equals s_{τ_j}. Therefore, the system equations at equilibrium are simplified as follows:

$$-\frac{\delta_0}{1 + s_3^{\varepsilon}} s_1 - \frac{R_1 s_7}{R_2 + s_7} s_1 - (\upsilon_{1e} + \upsilon_{2e}) \varpi_e(s_3) s_1$$

$$-(1 - \upsilon_{1e} - \upsilon_{2e}) \phi_e(s_1, s_3) s_1$$

$$+2 s_4 (1 - \upsilon_{1e} - \upsilon_{2e}) \phi_e(s_1, s_3) s_1 + \upsilon_{1e} s_4 \varpi_e(s_3) s_1 = 0. \tag{17}$$

$$-\delta_2 s_2 + \tilde{B}_e \varpi_e(s_3) s_1 = 0. \tag{18}$$

$$-q s_3 + \frac{p_1}{1 + s_2^n} = 0. \tag{19}$$

$$s_4 \left(-\frac{\delta_0}{1 + s_3^{\varepsilon}} - \frac{R_1 s_7}{R_2 + s_7} + \frac{\delta_0}{1 + s_3^{\varepsilon}} + \frac{R_1 s_{7\tau_1}}{R_2 + s_7} \right) = 0. \tag{20}$$

$$-j_1 s_5 + p_2 = 0. \tag{21}$$

$$j_1 s_5 - f_1 s_6 - \frac{g_1 (1 - f_2)}{g_2 + s_6} s_6 - \frac{h_2 f_2}{h_1 + s_6} s_6 = 0. \tag{22}$$

$$\frac{j_2 g_1 (1 - f_2)}{g_2 + s_6} s_6 - f_3 s_7 = 0. \tag{23}$$

$$-\delta_{1l} s_8 - H_1 v_1(s_{11}) s_8 - \upsilon_{1l} \varpi_l(s_9) s_8$$

$$-\upsilon_{2l} \varpi_l(s_9) s_8 - (1 - \upsilon_{1l} - \upsilon_{2l}) \phi_l(s_8) s_8$$

$$+2 e^{-\delta_{1l}\tau_3} s_{10} (1 - \upsilon_{1l} - \upsilon_{2l}) \phi_l(s_8) s_8$$

$$+\upsilon_{1l} e^{-\delta_{1l}\tau_3} s_{10} \varpi_l(s_9) s_8 = 0. \tag{24}$$

$$-\delta_{2l} s_9 + \tilde{B}_l \varpi_l(s_9) s_8 = 0. \tag{25}$$

$$s_{10} H_1 [v_1(s_{11}) - v_1(s_{11})] = 0. \tag{26}$$

$$\frac{j_2 g_1 (1 - f_2)}{g_2 + s_6} s_6 - g_3 s_{11} = 0 \tag{27}$$

$$-\delta_{1ll}s_{12} - (\upsilon_{1ll} + \upsilon_{2ll})\varpi_{ll}(s_{13})s_{12} + \upsilon_{1ll}e^{-\delta_{1ll}\tau_5}\varpi_{ll}(s_{13})s_{12} = 0. \quad (28)$$

$$-\delta_{2ll}s_{13} + \tilde{B}_{ll}(2\upsilon_{2ll} + \upsilon_{1ll})\varpi_{ll}(s_{13})s_{12} = 0. \quad (29)$$

Solving these equations yields the equilibrium point $E(0, 0, \hat{s}_3, \hat{s}_4, \hat{s}_5, \hat{s}_6, \hat{s}_7, 0, 0, \hat{s}_{10}, \hat{s}_{11}, 0, 0)$. This equilibrium point corresponds to the model under treatment and represents the condition of patient mortality.

3 Linearizing the System

The Jacobian matrix for the undelayed variables is denoted as $A = [a_{ij}]$, where the non-zero entries are:

$$a_{11} = -\frac{\delta_0}{1+s_3^{\varepsilon}} - \frac{R_1 s_7}{R_2+s_7} - (\upsilon_{1e}+\upsilon_{2e})\varpi_e(s_3) - (1-\upsilon_{1e}-\upsilon_{2e})\left[\phi_e(s_1,s_3) + s_1\frac{\partial\phi_e}{\partial s_1}(s_1,s_3)\right]$$

$$a_{13} = \frac{\delta_0 s_1 \varepsilon s_3^{\varepsilon-1}}{(1+s_3^{\varepsilon})^2} - (\upsilon_{1e}+\upsilon_{2e})s_1\frac{\partial\varpi_e}{\partial s_3}(s_3) - (1-\upsilon_{1e}-\upsilon_{2e})s_1\frac{\partial\phi_e}{\partial s_3}(s_1,s_3)$$

$$a_{14} = 2(1-\upsilon_{1e}-\upsilon_{2e})\phi_e(s_1,s_3)s_1 + \upsilon_{1e}\varpi_e(s_3)s_1$$

$$a_{17} = -\frac{s_1 R_1 R_2}{(R_2+s_7)^2}$$

$$a_{22} = -\delta_2$$

$$a_{32} = -\frac{np_1 s_2^{n-1}}{(1+s_2^n)^2}$$

$$a_{33} = -q$$

$$a_{43} = \frac{\delta_0 s_4 \varepsilon s_3^{\varepsilon-1}}{(1+s_3^{\varepsilon})^2}$$

$$a_{47} = -\frac{s_4 R_1 R_2}{(R_2+s_7)^2}$$

$$a_{55} = -j$$

$$a_{65} = -j$$

$$a_{66} = -f_1 - \frac{g_1 g_2(1-f_2)}{(g_2+s_6)^2} - \frac{h_1 h_2 f_2}{(h_1+s_6)^2}$$

$$a_{76} = \frac{g_1 g_2 j_2(1-f_2)}{(g_2+s_6)^2}$$

$$a_{77} = -f_3$$

$$a_{88} = -\delta_{1l} - H_1\upsilon_1(s_{11}) - \upsilon_{1l}\varpi_l(s_9) - \upsilon_{2l}\varpi_l(s_9) - (1-\upsilon_{1l}-\upsilon_{2l})\left[\frac{\partial\phi_l}{\partial s_8}(s_8)s_8 + \phi_l(s_8)\right]$$

$$a_{89} = -(\upsilon_{1l}+\upsilon_{2l})s_8\frac{\partial\varpi_l}{\partial s_9}(s_9)$$

$$a_{8,10} = 2e^{-\delta_{1l}\tau_3}(1-\upsilon_{1l}-\upsilon_{2l})\phi_l(s_8)s_8 + \upsilon_{1l}e^{-\delta_{1l}\tau_3}\varpi_l(s_9)s_8$$

$$a_{8,11} = -H_1\upsilon_1'(s_{11})s_8$$

$$a_{99} = -\delta_{2l}$$

$$a_{10,11} = -s_{10}H_1\upsilon_1'(s_{11})$$

$$a_{10,16} = \frac{j_2 g_1 g_2(1-f_2)}{(g_2+s_6)^2}$$

$$a_{11,11} = -g_3$$

$$a_{12,12} = -\delta_{1ll} - (\upsilon_{1ll}+\upsilon_{2ll})\varpi_{ll}(s_{13})$$

$$a_{12,13} = -(\upsilon_{1ll}+\upsilon_{2ll})\frac{\partial\varpi_{ll}}{\partial s_{13}}s_{12}$$

$$a_{13,13} = -\delta_{2ll}$$

The matrix of partial derivatives with respect to the delayed variables is $B = [b_{ij}]$, where the non-zero terms are:

$$b_{11} = 2s_4(1-\upsilon_{1e}-\upsilon_{2e})\left[\frac{\partial\phi_e}{\partial s_1}(s_1,s_3)s_1 + \phi_e(s_1,s_3)\right] + \upsilon_{1e}s_4\varpi_e(s_3)$$

$$b_{13} = 2s_4(1-\upsilon_{1e}-\upsilon_{2e})\frac{\partial\phi_e}{\partial s_3}(s_1,s_3)s_1 + \upsilon_{1e}s_4\frac{\partial\varpi_e}{\partial s_3}(s_3)s_1$$

$$b_{43} = -\frac{\delta_0 s_4 \varepsilon s_3^{\varepsilon-1}}{(1+s_3^{\varepsilon})^2}$$

$$b_{47} = -\frac{s_4 R_1 R_2}{(R_2+s_7)^2}$$

The matrix $C = [c_{ij}]$ has non-zero terms:

$$c_{21} = \tilde{B}_e\varpi_e(s_3)$$

$$c_{23} = \tilde{B}_e\frac{\partial\varpi_e}{\partial s_3}(s_3)s_1$$

The matrix $D = [d_{ij}]$ has non-zero terms:

$$d_{88} = 2e^{-\delta_{1l}\tau_3}s_{10}(1-\upsilon_{1l}-\upsilon_{2l})\left[\frac{\partial\phi_l}{\partial s_8}(s_8)s_8 + \phi_l(s_8)\right] + \upsilon_{1l}e^{-\delta_{1l}\tau_3}s_{10}\varpi_l(s_9)$$

$$d_{89} = \upsilon_{1l}e^{-\delta_{1l}\tau_3}s_{10}\frac{\partial\varpi_l}{\partial s_9}(s_9)s_8$$

$$d_{1011} = s_{10}H_1\upsilon_1'(s_{11})$$

Let $E = [e_{ij}]$, where

$$E = \frac{\partial f}{\partial s_{\tau_4}}.$$

The non-zero terms of E are:

$$e_{98} = \tilde{B}_l \varpi_l(s_9)$$

$$e_{99} = \tilde{B}_l \frac{\partial \varpi_l}{\partial s_9}(s_9) s_8$$

Let $F = [f_{ij}]$, where

$$F = \frac{\partial f}{\partial s_{\tau_5}}.$$

The non-zero terms of F are:

$$f_{1212} = \upsilon_{1ll} e^{-\delta_{1ll}\tau_5} \varpi_{ll}(s_{13})$$

$$f_{1213} = \upsilon_{1ll} e^{-\delta_{1ll}\tau_5} \frac{\partial \varpi_{ll}}{\partial s_{13}}(s_{13}) s_{12}$$

Finally, let $G = [g_{ij}]$, where

$$G = \frac{\partial f}{\partial s_{\tau_6}}.$$

The non-zero terms of G are:

$$g_{1312} = \tilde{B}_{ll}(2\upsilon_{2ll} + \upsilon_{1ll}) \varpi_{ll}(s_{13})$$

$$g_{1313} = \tilde{B}_{ll}(2\upsilon_{2ll} + \upsilon_{1ll}) \frac{\partial \varpi_{ll}}{\partial s_{13}}(s_{13}) s_{12}$$

Stability analysis of the equilibrium point:
The general form of the characteristic is:

$$\det(\lambda I_n - A - Be^{-\lambda\tau_1} - Ce^{-\lambda\tau_2}) = 0$$

For the equilibrium point corresponding to $E(0, 0, \hat{s}_3, \hat{s}_4, \hat{s}_5, \hat{s}_6, \hat{s}_7, 0, 0, \hat{s}_{10}, \hat{s}_{11}, 0, 0)$ we have: the characteristic equation corresponding to E is:

$$\lambda^2(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})(\lambda - a_{22})$$
$$(\lambda - a_{33})(\lambda - a_{55})(\lambda - a_{66})(\lambda - a_{77})$$
$$(\lambda - a_{88} - d_{88}e^{-\lambda\tau_3})(\lambda - a_{99})(\lambda - a_{1111})$$
$$(\lambda - a_{1212} - f_{1212}e^{-\lambda\tau_5})(\lambda - a_{1313}) = 0$$

So, $\lambda = 0$ is a root, and we are in a critical case for the stability of the nonlinear system.

3.0.1 The real solutions of the characteristic equation

The real solutions of the characteristic equation are given by:

- $\lambda_1 = 0$
- $\lambda_2 = a_{22} = -\delta_2 < 0$
- $\lambda_3 = a_{33} = -q < 0$
- $\lambda_4 = a_{55} = -j_1 < 0$
- $\lambda_5 = a_{66} = -f_{1-\frac{g_1 g_2(1-f_2)}{(g_2+s_6)^2} - \frac{h_1 h_2 f_2}{(h_1+s_6)^2}} < 0$
- $\lambda_6 = a_{77} = -f_3 < 0$
- $\lambda_7 = a_{99} = -\delta_{2l} < 0$
- $\lambda_8 = a_{11,11} = -g_3 < 0$
- $\lambda_9 = a_{13,13} = -\delta_{2ll} < 0$

3.1 Critical Case

The characteristic equation corresponding to E has $\lambda = 0$ as a root, so we are in a critical case for the stability of the nonlinear system. Since we do not have the linear part equal to zero then so we will proceed to bring the system (1) to the canonical form. We perform a translation to zero by $x_i = s_i - \hat{s}_i$ for $i = \overline{1, 13}$.

The new system becomes:

$$\dot{x} = f_i(x, x_{\tau_j}); \quad i = \overline{1, 13}, j = \overline{1, 6} \qquad (2)$$

where

$$\begin{aligned}
\dot{x}_4 &= -\frac{(x_4 + \hat{s}_4)\delta_0}{1 + (x_3 + \hat{s}_3)^{\varepsilon}} \\
&\quad - \frac{R_1(x_4 + \hat{s}_4)(x_7 + \hat{s}_7)}{R_2 + (x_7 + \hat{s}_7)} \\
&\quad + \frac{(x_4 + \hat{s}_4)\delta_0}{1 + (x_{3\tau_1} + \hat{s}_{3\tau_1})^{\varepsilon}} \\
&\quad + \frac{R_1(x_4 + \hat{s}_4)(x_{7\tau_1} + \hat{s}_{7\tau_1})}{R_2 + (x_{7\tau_1} + \hat{s}_{7\tau_1})} \\
&= g(x_3, x_4, x_7, x_{3\tau_1}, x_{7\tau_1})
\end{aligned}$$

with $g(0) = 0$ The matrices of partial derivatives are:

$$\begin{aligned}
A &= \frac{\partial f}{\partial x} = [a_{ij}], B = \frac{\partial f}{\partial x_{\tau_1}} = [b_{ij}], \\
C &= \frac{\partial f}{\partial x_{\tau_2}} = [c_{ij}], D = \frac{\partial f}{\partial x_{\tau_3}} = [d_{ij}], \\
E &= \frac{\partial f}{\partial x_{\tau_4}} = [e_{ij}], F = \frac{\partial f}{\partial x_{\tau_5}} = [f_{ij}] \text{ and} \\
G &= \frac{\partial f}{\partial x_{\tau_6}} = [g_{ij}]
\end{aligned}$$

The characteristic equation for the zero solution of the new system is exactly that one for E. And we have:

$$\frac{\partial g}{\partial x_3}(0) = \frac{\hat{s}_4 \delta_0 \varepsilon \hat{s}_3^{\varepsilon - 1}}{(1 + \hat{s}_3)^2}$$

$$\frac{\partial g}{\partial x_7}(0) = \frac{-R_1 R_2}{(R_2 + \hat{s}_7)^2}$$

$$\frac{\partial g}{\partial x_{3\tau_1}}(0) = \frac{-\hat{s}_4 \delta_0 \varepsilon \hat{s}_3^{\varepsilon - 1}}{(1 + \hat{s}_3)^2}$$

$$\frac{\partial g}{\partial x_{7\tau_1}}(0) = \frac{R_1 R_2}{(R_2 + \hat{s}_7)^2}$$

Then the Theorem is not applicable since the linear part is not equal to zero. Now, we write system in a form to which Theorem is applicable. Take:

$$\begin{aligned}\Gamma &= \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 \\ &+\beta_5 x_5 + \beta_6 x_6 + \beta_7 x_7 + \beta_8 x_8 \\ &+\beta_9 x_9 + \beta_{10} x_{10} + \beta_{11} x_{11} + \beta_{12} x_{12} + \beta_{13} x_{13}\end{aligned}$$

where $\dot{x} = Ax$, we have:

$$\begin{aligned}\dot{\Gamma} &= \beta_1 \dot{x}_1 + \beta_2 \dot{x}_2 + \beta_3 \dot{x}_3 + \beta_4 \dot{x}_4 \\ &+\beta_5 \dot{x}_5 + \beta_6 \dot{x}_6 + \beta_7 \dot{x}_7 + \beta_8 \dot{x}_8 \\ &+\beta_9 \dot{x}_9 + \beta_{10} \dot{x}_{10} + \beta_{11} \dot{x}_{11} \\ &+\beta_{12} \dot{x}_{12} + \beta_{13} \dot{x}_{13}\end{aligned}$$

so:

$$\begin{aligned}\dot{\Gamma} &= \beta_1 a_{11} x_1 + \beta_2 a_{22} x_2 + (\beta_3 a_{33} + \beta_4 a_{43}) x_3 \\ &+(\beta_5 a_{55} + \beta_6 a_{65}) x_5 \\ &+(\beta_6 a_{66+} \beta_7 a_{76} + \beta_{11} a_{116}) x_6 \\ &+(\beta_4 a_{47} + \beta_7 a_{77}) x_7 \\ &+\beta_8 a_{88} x_8 + \beta_9 a_{99} x_9 \\ &+(\beta_{10} a_{1011} + \beta_{11} a_{1111}) x_{11} \\ &+\beta_{12} a_{1212} x_{12} + \beta_{13} a_{1313} x_{13}\end{aligned}$$

Now, if one imposes $\dot{\Gamma} = 0$, it follows that:

$$\beta_1 = \beta_2 = \beta_9 = \beta_{12} = \beta_{13} = \beta_8 = 0$$

$$\beta_3 a_{33} + \beta_4 a_{43} = 0$$

$$\beta_5 a_{55} + \beta_6 a_{65} = 0$$

$$\beta_6 a_{66+} \beta_7 a_{76} + \beta_{11} a_{116} = 0$$

$$\beta_4 a_{47} + \beta_7 a_{77} = 0$$

$$\beta_{10} a_{1011} + \beta_{11} a_{1111} = 0$$

we get,

$$\beta_4 = 1 \& \ \beta_6 = 1$$

$$\beta_3 = \frac{-a_{43}}{a_{33}}$$

$$\beta_7 = \frac{-a_{47}}{a_{77}}$$

$$\beta_5 = \frac{-a_{65}}{a_{55}}$$

$$\beta_{11} = \frac{a_{47} a_{76} - a_{66} a_{77}}{a_{77} a_{116}}$$

$$\beta_{10} = \frac{-a_{11} a_{47} a_{76} + a_{11} a_{66} a_{77}}{a_{77} a_{116} a_{1011}}$$

Remark that:

$$\dot{x}_{3\tau 1} = a_{33} x_3 + B_{3\tau 1}$$

$$\dot{x}_{7\tau 1} = a_{77} x_7 + B_{7\tau 1}$$

with $B_{3\tau_1}$ and $B_{7\tau_1}$containing terms of order higher or equal to two. Now let,

$$\begin{aligned}\Gamma_1 &= \beta_3 x_3 + x_4 + \beta_5 x_5 + x_6 \\ &+\beta_7 x_7 + \beta_{10} x_{10} + \beta_{11} x_{11} \\ &-\frac{b_{43}}{a_{33}} x_{3\tau_1} - \frac{b_{47}}{a_{77}} x_{7\tau_1}\end{aligned}$$

Take $x_4 = \Gamma_1 + \frac{b_{43}}{a_{33}} x_{3\tau_1} + \frac{b_{47}}{a_{77}} x_{7\tau_1} - \beta_3 x_3 - \beta_5 x_5 - x_6 - \beta_7 x_7 - \beta_{10} x_{10} - \beta_{11} x_{11}$ and replace the forth equation in (3) by the previous equation of $\dot{\Gamma}_1$ so this equation has a zero linear part.

Substitute x_4 in the equations of the system: Now take

$$\Gamma_2 = \gamma_1 z_1 + \gamma_2 z_2 + \gamma_3 z_3 + \gamma_4 \Gamma_1 + \gamma_5 z_5 + ... + \gamma_{13} z_{13},$$

where $\dot{z} = \ddot{A} z$ so,

$$\dot{\Gamma}_2 = \gamma_1 \dot{z}_1 + \gamma_2 \dot{z}_2 + \gamma_3 \dot{z}_3 + \gamma_4 \dot{\Gamma}_1 + \gamma_5 \dot{z}_5 + ... + \gamma_{13} \dot{z}_{13}$$

Now since Γ_1 has no linear part in the system in the z variables, it follows that:

$$\begin{aligned}\dot{\Gamma}_2 &= \gamma_1 a_{11} z_1 + \gamma_2 a_{22} z_2 + \gamma_3 a_{33} z_3 \\ &+(\gamma_5 a_{55} + \gamma_6 a_{65}) z_5 + \\ &(\gamma_6 a_{66} + \gamma_7 a_{76} + \gamma_{11} a_{116}) z_6 \\ &+\gamma_7 a_{77} z_7 + \gamma_8 a_{88} z_8 \\ &+\gamma_9 a_{99} z_9 + (\gamma_{10} a_{1011} + \gamma_{11} a_{1111}) z_{11} \\ &+\gamma_{12} a_{1212} z_{12} + \gamma_{13} a_{1313} z_{13}\end{aligned}$$

If one imposes $\dot{\Gamma}_2 = 0$ it follows that:

$$\gamma_{10} a_{1011} + \gamma_{11} a_{1111} = 0$$

for $\gamma_{10} = 1$,it follows that

$$\gamma_{11} = -\frac{a_{1111}}{a_{1011}}$$

We also have:

$$\gamma_6 a_{66} + \gamma_7 a_{76} + \gamma_{11} a_{116} = 0$$

which indicates that:

$$\gamma_6 = \frac{a_{1111} a_{116}}{a_{1011} a_{66}}$$

We also have:

$$\gamma_5 a_{55} + \gamma_6 a_{65} = 0,$$

which means that:

$$\gamma_5 = -\frac{a_{1111}a_{116}a_{65}}{a_{1011}a_{66}a_{55}}$$

Then

$$\Gamma_2 = \gamma_5 z_5 + \gamma_5 z_6 + z_{10} + \gamma_{11} z_{11},$$

so the equation of Γ_2 has no linear part. That is $\dot{\Gamma}_2 = R_4^{(1)}$ with $R_4^{(1)}$ containing only terms of order greater or equal to two. Take

$$z_{10} = \Gamma_2 - \gamma_5 z_5 - \gamma_6 z_6 - \gamma_{11} z_{11}$$

Replacing the tenth equation by $\dot{\Gamma}_2$ so this equation has a zero linear part. Substitute z_{10} in the equations of the new system, so the linear part of the tenth equation does not contain Γ_2 and the other equations do not contain Γ_2 at all . Therefore, the Theorem of critical case can be applied (see [15]) to study the stability of the zero solution of system (2) and its conclusions transferred to the study of stability of the equilibrium point E of system (1).

Since $a_{22} < 0, a_{33} < 0, a_{55} < 0, a_{66} < 0, a_{77} < 0, a_{99} < 0, a_{11,11} < 0$ and $a_{13,13} < 0$ then the stability depends on the study of the transcendental term in the characteristic equation.

Now consider the transcendental equations,

$$\lambda - a_{11} - b_{11}e^{-\lambda\tau_1} = 0 \qquad (3)$$

The stability analysis of Equation (3) is classical (see, for example, [1]).

$$b_{11} = 2\hat{s}_4(1-\upsilon_{1e}-\upsilon_{2e})\phi_e(0,\hat{s}_3)+\upsilon_{1e}s_4\varpi_e(\hat{s}_3) > 0$$

$$\begin{aligned} a_{11} &= -\frac{\delta_0}{1+s_3^{\varepsilon}} - \frac{R_{1\hat{s}7}}{R_2+\hat{s}_7} \\ &\quad -(\upsilon_{1e}+\upsilon_{2e})\varpi_e(\hat{s}_3) \\ &\quad -(1-\upsilon_{1e}-\upsilon_{2e})\phi_e(0,\hat{s}_3) < 1. \end{aligned}$$

for $\tau_1 = 0$, we have $a_{11} < 0 < \frac{1}{\tau_1}$ and $b_{11} > 0$. Therefore equation (3) becomes:

$$\lambda - a_{11} - b_{11} = 0$$

$$\begin{aligned} 0 &= \lambda + \frac{\delta_0}{1+\hat{s}_3^{\varepsilon}} + \frac{R_{1\hat{s}7}}{R_2+\hat{s}_7} \\ &\quad +(\upsilon_{1e}+\upsilon_{2e})\varpi_e(\hat{s}_3) + (1-\upsilon_{1e}-\upsilon_{2e})\phi_e(0,\hat{s}_3) \\ &\quad -2\hat{s}_4(1-\upsilon_{1e}-\upsilon_{2e})\phi_e(0,\hat{s}_3) \\ &\quad -\upsilon_{1e}\,\hat{s}_4\varpi_e(\hat{s}_3). \end{aligned}$$

So,

$$\begin{aligned} \lambda &= -\frac{\delta_0}{1+\hat{s}_3^{\varepsilon}} - \frac{R_{1\hat{s}7}}{R_2+\hat{s}_7} \\ &\quad -\varpi_e(\hat{s}_3)(-\upsilon_{1e}-\upsilon_{2e}+\upsilon_{1e}\hat{s}_4) \\ &\quad +(2\hat{s}_4-1)(1-\upsilon_{1e}-\upsilon_{2e})\phi_e(0,\hat{s}_3). \end{aligned}$$

Then if

$$\begin{aligned} &-\frac{\delta_0}{1+\hat{s}_3^{\varepsilon}} - \frac{R_1\hat{s}_7}{R_2+\hat{s}_7} - \\ &\varpi_e(\hat{s}_3)(-\upsilon_{1e}-\upsilon_{2e}+\upsilon_{1e}\hat{s}_4) \\ &+(2\hat{s}_4-1)(1-\upsilon_{1e}-\upsilon_{2e})\phi_e(0,\hat{s}_3) \\ <\ & 0 \end{aligned}$$

then equation (3) is stable for $\tau_1 = 0$ and remains stable for $\tau_1 > 0$.

Now Consider the equation:

$$\lambda - a_{88} - d_{88}e^{-\lambda\tau_3} = 0 \qquad (4)$$

$$\begin{aligned} d_{88} &= 2e^{-\delta_{1l}\tau_3}\hat{s}_{10}(1-\upsilon_{1l}-\upsilon_{2l})\phi_l(\hat{s}_8) \\ &\quad +\upsilon_{1l}e^{-\delta_{1l}\tau_3}\hat{s}_{10}\varpi_l(\hat{s}_9) \\ &> 0 \end{aligned}$$

$$\begin{aligned} a_{88} &= -\delta_{1l} - H_1\upsilon_1(\hat{s}_{11}) - \upsilon_{1l}\varpi_l(\hat{s}_9) \\ &\quad -\upsilon_{2l}\varpi_l(\hat{s}_9) - (1-\upsilon_{1l}-\upsilon_{2l})\phi_l(\hat{s}_8) \\ &< 0 \end{aligned}$$

for $\tau_3 = 0$, we have $a_{88} < 0 < \frac{1}{\tau 3}$ and $d_{88} > 0$. Therefore equation (4) becomes:

$$\lambda - a_{88} - d_{88} = 0$$

$$\begin{aligned} \lambda &= -\delta_{1l} - H_1\upsilon_1(\hat{s}_{11}) + \\ &\quad +(e^{-\delta_{1l}\tau_3}\hat{s}_{10}-1)\upsilon_{1l}\varpi_l(\hat{s}_9) - \upsilon_{2l}\varpi_l(\hat{s}_9) \\ &\quad +(2e^{-\delta_{1l}\tau_3}\hat{s}_{10}-1)(1-\upsilon_{1l}-\upsilon_{2l})\phi_l(\hat{s}_8). \end{aligned}$$

So, if

$$\begin{aligned} &-\delta_{1l} - H_1\upsilon_1(\hat{s}_{11}) + \\ &+(e^{-\delta_{1l}\tau_3}\hat{s}_{10}-1)\upsilon_{1l}\varpi_l(\hat{s}_9) - \upsilon_{2l}\varpi_l(\hat{s}_9) \\ &+(2e^{-\delta_{1l}\tau_3}\hat{s}_{10}-1)(1-\upsilon_{1l}-\upsilon_{2l})\phi_l(\hat{s}_8) \\ <\ & 0 \end{aligned}$$

then equation (4) is stable for $\tau_3 = 0$ and remains stable for $\tau_3 > 0$.

Now, consider the equation:

$$\lambda - a_{1212} - f_{1212}e^{-\lambda\tau_5} = 0 \qquad (5)$$

$$f_{1212} = \upsilon_{1ll}e^{-\delta_{1ll}\tau_5}\varpi_{ll}(\hat{s}_{13}) > 0$$

$$a_{1212} = -\delta_{1ll} - (\upsilon_{1ll} + \upsilon_{2ll})\varpi_{ll}(\hat{s}_{13}) < 0$$

for $\tau_5 = 0$, we have $a_{12,12} < 0 < \frac{1}{\tau_5}$ and $d_{12,12} > 0$. Therefore equation (5) becomes:

$$\lambda - a_{12,12} - f_{12,12} = 0$$

$$\lambda + \delta_{1ll} + (\upsilon_{1ll} + \upsilon_{2ll})\varpi_{ll}(\hat{s}_{13}) - \upsilon_{1ll}e^{-\delta_{1ll}\tau_5}\varpi_{ll}(\hat{s}_{13}) = 0$$

$$\lambda = -\delta_{1ll} + (\upsilon_{1ll}e^{-\delta_{1ll}\tau_5} - \upsilon_{1ll} - \upsilon_{2ll})\varpi_{ll}(\hat{s}_{13}).$$

So, if

$$-\delta_{1ll} + (\upsilon_{1ll}e^{-\delta_{1ll}\tau_5} - \upsilon_{1ll} - \upsilon_{2ll})\varpi_{ll}(\hat{s}_{13}) < 0,$$

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

Conclusion 3.1. The equilibrium point E is stable if equations (3), (4) and (5) are stable.

4 Conclusion

This study presented a detailed mathematical model for Acute Lymphoblastic Leukemia (ALL) treatment using delay-differential equations. Our model, comprising 13 delay-differential equations with six delays, effectively captures the complex interactions between leukemia cells, healthy cells, and treatment. Through stability analysis and the application of the critical case theorem, we identified equilibrium points and the conditions for disease control or progression.

Our findings highlight the importance of mathematical modeling in understanding ALL dynamics and guiding therapeutic strategies. Additionally, we proposed integrating fractional calculus into our model to enhance its predictive capabilities and robustness, given the effectiveness of fractional differential equations in capturing biological complexities.

In conclusion, this work provides a novel and dynamic representation of ALL treatment, emphasizing the role of mathematical models in advancing cancer therapy and improving patient outcomes.

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