Analysis of a Delay Differential Equation model of Allergic reactions in Acute Lymphoblastic Leukemia

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Abstract: In this article, we explore the cellular dynamics of Lymphoblasts in patients undergoing therapy for acute lymphoblastic leukemia, emphasizing potential allergic reactions. We also extend previous models to incorporate desensitization processes linked to hypersensitivity caused by chemotherapy. Furthermore, we analyze the interactions between the immune system and cancer progression, excluding allergies, using linear stability analysis and mathematical simulations.

Key-Words: Acute lymphoblastic leukemia, Allergies, Immune Response, Equilibrium Points, Stability Analysis, Critical Case.

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1 Introduction

Mathematical modeling is a process that converts real-world problems into mathematical expressions using systems of equations. This method offers a structured framework that enhances the comprehension of complex phenomena. The equations are designed to capture the behavior of parameters at every stage, emphasizing their importance, [1].

Throughout history, humanity has endured numerous catastrophes, both natural and human-induced. These disasters originate either from powerful natural forces or as a consequence of human actions and negligence. Natural disasters, in particular, result from severe environmental phenomena impacting specific regions, often worsened by human activities. Additionally, diseases have afflicted humankind for centuries, causing pain, suffering, and loss. Since the earliest civilizations, various illnesses have coexisted with humans, sometimes spreading and intensifying due to harmful or self-serving behaviors. Among these diseases, cancer has become one of the leading causes of death worldwide, particularly following the Second World War. According to the World Health Organization (WHO), global cancer cases surpassed 18 million in 2020, with nearly half or more of those diagnosed succumbing to the disease, [2]. However, dedicated specialists have been working tirelessly to change the outlook shaped by this disease. Their efforts are aimed at either curing and eliminating cancer or, at the very least, ensuring that patients can lead a dignified life.

Cancer is characterized by the uncontrolled growth and proliferation of abnormal cells, which can enter the bloodstream, damage healthy tissues, and disrupt organ function. With over 100 different types, cancer affects people of all ages, genders, and ethnic backgrounds. Common examples include breast cancer, lung cancer, colorectal cancer, and leukemia, among others. The disease originates from persistent

DNA mutations that multiply and spread during cell division, ultimately leading to tumor formation. These tumors can be either benign (non-cancerous) or malignant. Malignant tumors drive the aggressive spread of defective cells into nearby tissues and distant parts of the body through a process known as metastasis. At this stage, healthy cells either cease functioning or are forced to die, enabling the rapid expansion of damaged cells within an accelerated molecular cycle.

1.1 Acute Lymphocytic Leukemia

Leukemia is a type of cancer that originates from genetic alterations in the precursor cells of blood, occurring in the stem cells of the bone marrow. The bone marrow is a spongy tissue found in the center of bones and is responsible for housing hematopoietic stem cells, which produce blood cells. Blood, the fluid circulating throughout the body via vessels, consists of plasma, blood cells, and platelets. Plasma, the primary component, is a liquid composed of water, nutrients, proteins, ions, dissolved gases, and waste products. Platelets are cell fragments responsible for blood clotting. Blood cells are categorized into red and white cells, known as erythrocytes and leukocytes, respectively. Erythrocytes are specialized to transport oxygen (O_2) to tissues, while leukocytes play a critical role in defense and immune recognition, identifying and neutralizing foreign invaders. Blood cell production follows an asymmetric division process, meaning one daughter cell remains as a progenitor, while the other differentiates into specific stem cells: lymphoid or myeloid, each giving rise to distinct blood cell lineages, [3]. In leukemia, on the other hand, depending on these stem cells type and in their rate of reproduction, in cancerous plot, can be classified into myeloid or lymphocytic and acute or chronic relying, respectively, on cell provenance and velocity average. Consequently, acute lymphocytic leukemia (ALL) or also referred as acute lymphoblastic leukemia is a cancer emanated from lymphoblasts dispersed in an intense degree.

In acute lymphocytic leukemia (ALL), lymphoid stem cells develop into lymphoblasts, B lymphocytes, and T lymphocytes. However, during this process, a rapid and severe mutation occurs, leading to an overproduction of leukemia cells that are unable to defend the body effectively. Consequently, normal blood cells are outnumbered and suppressed, allowing the cancerous cells to infiltrate the nervous system, lymph nodes, spleen, liver, and other organs.

According to the American Cancer Society, projections for 2022 in the United States estimated 60,650 new cases of leukemia, with 6,660 cases attributed to ALL. Additionally, approximately 1,560 deaths were anticipated due to this specific type of leukemia, [4]. Acute lymphocytic leukemia (ALL) occurs more frequently in children under 5 years old and in adults over 50. While children experience a higher incidence of ALL, adults account for the majority of fatalities, with 4 out of every 5 deaths attributed to this age group. Despite these concerning statistics, survival rates for ALL have improved significantly over time.

The risk of developing leukemia, like other cancers, increases with exposure to high levels of radiation, certain chemicals, and genetic predispositions linked to specific mutations. These factors collectively heighten susceptibility and contribute to variations in incidence and mortality rates. In contrary, healing measures were designed to administer cancer treatments such as chemotherapy, radiation therapy and immunotherapy, being the first one the standard and most pertinent current alternative.

1.2 Chemotherapy and Medicines

Chemotherapy is a cancer treatment that utilizes drugs to disrupt the growth of cancer cells by either destroying them or inhibiting their division. However, chemotherapy drugs can also interfere with normal cell processes, leading to side effects. This treatment can be administered in different ways: into the bloodstream (orally or via injection), the cerebrospinal fluid, or directly into specific organs, referred to as systemic, intrathecal, and regional therapy, respectively. Additionally, chemotherapy may involve the use of multiple drugs, a strategy known as combination chemotherapy. In the initial phase of treatment, patients are often prescribed mercaptopurine, also known as 6MP. The primary goal is to sustain the success of the therapy while managing potential toxic effects that may arise.

Mercaptopurine is an important medication classified as a purine antagonist, commonly used to treat lymphocytic leukemia and inflammatory autoimmune diseases. It works by interfering with the production of adenosine and guanine triphosphates, essential components of DNA. Mercaptopurine (6MP) is metabolized into 6-thioguanine nucleotides (6TGN), which are activated to perform their anti-leukemic function. This conversion is facilitated by enzymes called thiopurine methyltransferase (TPMT) and

hypoxanthine-guanine phosphoribosyltransferase (HGPRT).

TPMT converts 6MP into methyl-thioinosine monophosphate (Me-TIMP), which is inactive against leukemia cells. In contrast, HGPRT converts 6MP into the active thioguanine nucleotides (6TGN) and thioinosine monophosphate (TIMP), which carry out the therapeutic action. The dosage of mercaptopurine is largely determined by an individual's TPMT levels. Higher TPMT activity requires lower doses of 6MP, while lower TPMT activity necessitates higher doses. However, higher dosages increase the risk of severe health complications, including hepatotoxicity, myelosuppression, pancreatitis, and leukopenia. Additionally, allergic reactions such as fever, rash, and nausea may occur, often depending on the dose consumed during treatment for acute lymphoblastic leukemia, [5]. The sustenance, accordingly, to sculp the entire conditions with a model is a must to formulate the ideal dose for selected patients.

The action of assisting patients to gradually decline, or overcome, drug reactions due to hypersensitivity is certified as desensitization. This technique was beneficial, initially, for antibiotic hypersensitivity reaction being extended to the treatment of allergies, most precisely originated from chemotherapy drugs, [6]. The fact that boosting a delicate region with remedial susceptive incentives -in a moderate manner- that flood the brain with supplement sensory information. Therefore, the party's ache after stimulation provokes a certain accommodation of the feelings. Once the body adjusts to these stimuli the doses are allowed, then, to be elevated until arriving the intended goal dosage.

1.3 Immune Response

In this section we provide some defendent tools adopted by the body to react when exposed to harmful or unusual scenarios following, [6], [7], [8], [9],[10].

The body is exposed to a variety of pathogens and infections, which differ depending on the specific areas they invade. To combat these threats, the immune system is divided into two branches: the innate and the adaptive immune systems. The innate immune system provides an immediate response to infections. It is fast, nonspecific, and often insufficient to completely control the infection. On the other hand, the adaptive immune system is more specific and includes humoral-mediated immunity and cell-mediated immunity, which rely on B cells and T cells, respectively. B cells play a key role in humoral immunity, which involves the body's fluids, or "humors." These cells secrete antibodies that circulate through the bloodstream and other body fluids to neutralize pathogens. However, humoral immunity is ineffective against infections that occur inside cells, which is where cell-mediated immunity comes into play. By combining the protection provided by B cells in the body's fluids and T cells inside the cells, the adaptive immune system ensures comprehensive protection throughout the body. Thus, the goal of the immune response is to control or completely eliminate infections, whether caused by bacteria or viruses.

In immunology, the restraining procedure takes place in distinct ways. In B cells domain these cells secrete antibodies which are proteins competent of binding with the pathogens and blocking its proliferation or preventing it to dive inwards the cells in a process known as opsonization. Moreover, the antibodies mark the cells for phagocytosis which is eventually the job attributed for phagocytic cells, descendent from the innate response. This transaction is developed as the macrophages round through the body noticing the opsonized cells and thus engulfing and exterminating them. For T cells precursors, otherwise, there are plenty of them in human body and an array of viral infections qualified to be repressed.

The variety of T cells is distinguished by the presence of $CD4$ and $CD8$ proteins, symbolized by $CD4+$ and $CD8+$ cells, which are the T helpers and the cytotoxic T cells, in this order. Once activated, they differentiate as memory cells or effector cells. These will be the laborer whereas that will be cloned and perpetuate their specificity waiting to be activated, if needed, in future attacks. While the T helpers mobilize B cells and release cytokines alerting the neighboring to reproduce promptly, the cytotoxic cells are stimulated by these cytokines and hence ready to act destroying cells and refraining their replication. Despite the fact that cytotoxic cells can kill cancerous cells and contain their spread, this scenario has a limitation and englobe a very squeezed range of pathogens each T cell can respond. Therefore, since helper T cells are involved in practically all adaptive immune reactions, they are the subset of most relevance.

Allergy is an extreme reaction of the immune system to the surrounding. It initiates through macrophages which analyze the body regularly for foreign substances that triggers severe

response, as in allergic plot. A naive cell, in peripherical lymphoid tissue, evolves with a definite and precise utility after being confronted by an accurate major histocompatibility complex (MHC). For naive T lymphoblasts, these receptors are entitled as MCH-II and are found on the periphery of the antigen presenting cells - the APCs. Furthermore, these cells assume a crucial role as they get differentiated into subtypes of effector helper T cells such as $Th1$, $Th2$ and $Treg$ determined by the cytokines released. If interleukin 12 ($IL-12$) is released the helper T cell matures to $Th1$ which can activate macrophages, motivate B cells to produce IgG antibodies and also cytotoxic T cells helper.

On the other hand, if the naive T helper becomes a $Th2$ cell, by the release of $IL-4$ from mast cells, it can stimulate B cells by secreting $IL-4$ which culminates contributing to the secretion of IgE antibodies as well as basophils and eosinophils. These IgE antibodies, moreover, bind with the mast cells as if they are indeed B cells. This is viable since IgE's fit ideally on the mast cells, so that every time exposed to the allergen it breaks through and inflammation occurs dropping an elevated quantity of histamine. In this sense, $Th2/Th1$ demonstrates itself higher which implies a larger quantity of IgE and a more brutal body experience, hence setting of the allergies. In contrary, there is a variety of T regulatory cells that would cooperate inverting the layout and thus the annulation of the allergy.

In lymph nodes, $Th1$ and $Treg$ are activated and literally happen to regulate the environment shutting down the immune system. Theoretically, as B cells are producing and secreting IgE, the $Treg$ would act by inducing a prosperous supply of proteins – the cytokines – most precisely the $IL-10$ and TGF-beta. These will promote the inhibition of IgE and the repress of the immune system. Concerning $Th1$ cells, in spite of, it would set motion to B cells to manufacture and dispense a distinguished IgG, more pointedly the IgG4. The emphasis of this antibody is that it will not be suitable for mast cells hinting apathy towards being attached to them. In addition, with the absence of antibodies binding into the mast cells, it will provoke a decreasing in IgE levels apart from an ascending volume of IgG4. Therefore, either the IgE's are converted into IgG4 or the $Tregs$ deactivate their production until they cease the allergic reaction.

Convincingly, in immunologic execution, the task underlying allergen exposure praise $Tregs$ that serve as backbone of healthy and immune response to allergies. By means of molecular secretion and absolute interaction between cells $Tregs$ impede the traditional T cells, APCs and B cells from functioning.

2 The Model

The model is constructed by 10 nonlinear equations and 4 delays. In order to put the model together, the first four equations discuss how well the four variables - concentration of Th1, Th2, Treg and of naive T helper cells - performed following the course of allergen management while receiving 6-MP treatment. We identify the expansion of APCs after the contact with the allergen in the fifth equation. The rest of the equations describe a compartment of lymphoblasts in ALL coupled with the dynamics of 6-MP used in the maintenance therapy [11],[12], [13].

2.1 The Equations

The model of lymphoblasts is given by the following equations:

$$\dot{E} = Z(E_i, E_{\tau_j}); \text{for } i = \overline{1,10} \text{ and } j = \overline{1,4} \quad (1)$$

$$\begin{aligned}
\dot{E}_1 = \; & -d_1 E_1 + \eta - E_1 E_{5_{\tau_1}} \left(\tfrac{E_2}{1+\alpha_2 E_3}\right) \\
& -\gamma E_1 E_{5_{\tau_1}} E_3 - \varphi E_1 E_{5_{\tau_1}} E_4 \\
\dot{E}_2 = \; & -d_2 E_2 + \tfrac{\pi_1 E_1 E_{5_{\tau_1}}}{1+\alpha_r E_4} \left(\tfrac{E_2}{1+\alpha_2 E_3}\right) - \beta_1 \tfrac{E_{10} E_2}{1+E_{10}} \\
\dot{E}_3 = \; & -d_3 E_3 + \tfrac{\gamma \pi_1 E_1 E_{5_{\tau_1}}}{1+\alpha_r E_4} \left(\tfrac{E_3}{1+\alpha_1 \frac{E_2}{1+\alpha_2 E_3}}\right) + \beta_2 \tfrac{E_{10} E_3}{1+E_{10}} \\
\dot{E}_4 = \; & -d_4 E_4 + \varphi \pi_1 E_1 E_{5_{\tau_1}} E_4 - \beta_r \tfrac{E_{10} E_4}{1+E_{10}} \\
\dot{E}_5 = \; & \kappa + d E_9 E_5 - \pi_2 E_5 - \alpha E_5 E_4
\end{aligned}$$

$$\begin{aligned}
\dot{E}_6 = \; & -\gamma_{1ll} E_6 - g k(E_9) E_6 \\
& -(\eta_{1ll} + \eta_{2ll}) k_{ll}(E_7) E_6 \\
& +\eta_{1ll} e^{-\gamma_{1ll}\tau_2} k_{ll}(E_{7_{\tau_2}}) E_{6_{\tau_2}} E_8 \\
& -(1 - \eta_{1ll} - \eta_{2ll}) E_8 L(E_6) E_6 \\
& +2e^{-\gamma_{1ll}\tau_2}(1 - \eta_{1ll} - \eta_{2ll}) E_8 L(E_{6_{\tau_2}}) E_{6_{\tau_2}} \\
\dot{E}_7 = \; & -\gamma_{2ll} E_7 + A_{ll}(2\eta_{2ll} + \eta_{1ll}) k_{ll}(E_{7_{\tau_3}}) E_{6_{\tau_3}} \\
\dot{E}_8 = \; & E_8 g[k(E_{9_{\tau_2}}) - k(E_9)] \\
\dot{E}_9 = \; & b_2 - c E_9 - \tfrac{\alpha_1 E_9 E_7}{b_1 + E_9} \\
\dot{E}_{10} = \; & -\pi_3 E_{10} + \\
& a[E_{1_{\tau_4}} + E_{2_{\tau_4}} + E_{3_{\tau_4}} + E_{4_{\tau_4}} + E_{5_{\tau_4}}]
\end{aligned}$$

Moreover, we provide below, details regarding the equations' form and the occurrence of the parameters.

The first equation illustrates how the concentration of naive T-cells, which are generated at a steady rate η, varies. Naive cell deterioration is represented by the first term. The final three terms reflect the development of naive cells into Th1, Th2, and Treg, in that order, having that α_2 regulates the suppression power of Th2 cells.

The concentration of Th1 varies with the concentration of naive cells and the concentration of APCs activated by the allergen, as shown in the second equation. The time taken for allergens to move from the core compartment to the peripheral compartment is the origin of the initial delay, τ_1.Th1 cells breakdown are represented by the first term, while naive cells development into Th1 is lowered as a result of Treg and Th2 cells suppression with α_r being the suppression rate of strength of Treg cells. The final term refers to the blockage of Th1 by the cytokines that are generated during chemotherapy and the inhibition rate is indicated by β_1.

The fluctuation in Th2 concentration which is proportional to the concentration of naive cells, APC concentration, and cytokine concentration, is illustrated in the third equation. The destruction of Th2 cells is represented by the first term, and the transformation of naive cells into Th2 by the inhibition of Treg and Th1 cells is indicated by the second term, where α_1 regulates the suppression strength of Th1 cells. The last point refers to the activation of Th2, at a stimulation rate of β_2, by the produced cytokines during chemotherapy.

The fouth equation symbolizes the variation in Treg concentration, which is harmonious to the naive cell concentration and linked to the APC concentration. The destruction of Treg cells are represented by the first term, and the development of naive cells into Treg are shown by the second term. The final element represents the inhibition rate β_r of Treg by the produced cytokines throughout chemotherapy.

The fifth equation shows the number of mature APCs. The first term denotes the natality of these cells. The third expression, on the other hand, implies the mortality of mature APCs, while the second term illustrates the display of mature APCs excited by the antigen injected over chemotherapy. T cells control the opposite activation of these cells, which is indicated by the final term in the proportion α.

In the sixth equation , E_6 represents the short-term stem-like progenitors. The contraction of the healthy stem-like cells is determined by the fatality rate γ_{1ll}. The percentage $\eta_{1ll} + \eta_{2ll}$ is the portion of the population that leaves to differentiate. The population increases by $\eta_{1ll}e^{-\gamma_{1ll}\tau_2}$ and has a percentage of self renewal expressed by $1 - \eta_{1ll} - \eta_{2ll}$. The time needed to complete a cycle of self renewal asymmetric division or differentiation is given by τ_2. The functions k_{ll} and L give the rate differentiation regulate self renewal, respectively.

In equation seven, the mature cells, known as lymphoblasts, are represented by E_7. The arbitrary elimination of lymphoblasts at pace γ_{2ll} is represented by the first term, and A is the amplification factor. The cells pass through a developmental segment after completing amplification through cell division, and then eventually join the circulation by a period τ_4.

Equation eight expresses the loss through cell cycle and equation nine stands for the quantity of 6-MP present in plasma. The primary dose of 6-MP, rate at which the 6-MP desensitization dosage is removed from plasma, the withdrawel of the medication provinient from the battle with cancerous cells are considered in the ninth equation, following this sequence.

The last equation, represents the induced cytokine production during chemotherapy. The first term takes into consideration the cytokine mortality frequency as the second one displays the production of cells by mature APCs, naive T cells, Th1 cells, Th2 cells, and T reg cells, in this order, having that τ_4 is the specific delay required for these cells to secrete cytokines.

2.2 Equilibrium Points

In order to compute the equilibrium points of our model, we establish the equations of the system (1) as follows:

$$Z(E_i, E_{\tau_j}) = 0; \text{ for } i = \overline{1,10} \text{ and } j = \overline{1,4}$$

so we get,

$$\begin{aligned} 0 = \quad & -d_1E_1 + \eta - E_1E_{5_{\tau_1}}(\tfrac{E_2}{1+\alpha_2E_3}) \\ & -\gamma E_1E_{5_{\tau_1}}E_3 - \varphi E_1E_{5_{\tau_1}}E_4 \end{aligned}$$

$$
\begin{aligned}
0 = \; & -d_2E_2 + \tfrac{\pi_1E_1E_{5_{\tau_1}}}{1+\alpha_rE_4}(\tfrac{E_2}{1+\alpha_2E_3}) - \beta_1\tfrac{E_{10}E_2}{1+E_{10}} \\
0 = \; & -d_3E_3 + \tfrac{\gamma\pi_1E_1E_{5_{\tau_1}}}{1+\alpha_rE_4}(\tfrac{E_3}{1+\alpha_1\frac{E_2}{1+\alpha_2E_3}}) + \beta_2\tfrac{E_{10}E_3}{1+E_{10}} \\
0 = \; & -d_4E_4 + \varphi\pi_1E_1E_{5_{\tau_1}}E_4 - \beta_r\tfrac{E_{10}E_4}{1+E_{10}} \\
0 = \; & \kappa + dE_9E_5 - \pi_2E_5 - \alpha E_5E_4 \\
0 = \; & -\gamma_{1ll}E_6 - gk(E_9)E_6 - (\eta_{1ll}+\eta_{2ll})k_{ll}(E_7)E_6 \\
& +\eta_{1ll}e^{-\gamma_{1ll}\tau_2}k_{ll}(E_{7_{\tau_2}})E_{6_{\tau_2}}E_8 \\
& -(1-\eta_{1ll}-\eta_{2ll})E_8L(E_6)E_6 \\
& +2e^{-\gamma_{1ll}\tau_2}(1-\eta_{1ll}-\eta_{2ll})E_8L(E_{6_{\tau_2}})E_{6_{\tau_2}} \\
0 = \; & -\gamma_{2ll}E_7 + A_{ll}(2\eta_{2ll}+\eta_{1ll})k_{ll}(E_{7\tau_3})E_{6\tau_3} \\
0 = \; & E_8g[k(E_{9_{\tau_2}}) - k(E_9)] \\
0 = \; & b_2 - cE_9 - \tfrac{\alpha_1E_9E_7}{b_1+E_9} \\
0 = \; & -\pi_3E_{10} + \\
& a[E_{1_{\tau_4}} + E_{2_{\tau_4}} + E_{3_{\tau_4}} + E_{4_{\tau_4}} + E_{5_{\tau_4}}]
\end{aligned}
$$

Then, after some calculations, and respecting the biological meaning, we obtain the equilibrium point $E_p = (E_1^*, 0, 0, 0, E_5^*, 0, 0, E_8^*, E_9^*, E_{10}^*)$, where

$E_1^* = \frac{\eta}{d_1}$
$E_5^* = \frac{\kappa}{-dE_9+\pi_2}$
$E_8^* = e^{-gk(I_9)\tau_2}$
$E_9^* = \frac{b_2}{c}$
$E_{10}^* = \frac{a(E_{1_{\tau_4}}+E_{5_{\tau_4}})}{\pi_3}$

Linearizing, now, the system around the equilibrium point, the matrices of partial derivatives for the undelayed and with respect to the delayed variables are given as follows:

$$A = \frac{\partial Z}{\partial E} = [a_{ij}]$$

$$
\begin{aligned}
a_{11} = \; & -d_1 - E_5(\tfrac{E_2}{1+\alpha_2E_3}) - \gamma E_5E_3 - \varphi E_5E_4 \\
a_{12} = \; & -E_1E_5(\tfrac{1}{1+\alpha_2E_3}) \\
a_{13} = \; & \tfrac{\alpha_2E_1E_5E_2}{(1+\alpha_2E_3)^2} - \gamma E_1E_5 \\
a_{14} = \; & -\varphi E_1E_5 \\
a_{21} = \; & \tfrac{\pi_1E_5}{1+\alpha_rE_4}(\tfrac{E_2}{1+\alpha_2E_3}) \\
a_{22} = \; & -d_2 + \tfrac{\pi_1E_1E_5}{1+\alpha_rE_4}(\tfrac{1}{1+\alpha_2E_3}) - \beta_1\tfrac{E_{10}}{1+E_{10}} \\
a_{23} = \; & \tfrac{-\alpha_2\pi_1E_1E_5E_2}{(1+\alpha_rE_4)(1+\alpha_2E_3)^2} \\
a_{24} = \; & \tfrac{-\alpha_r\pi_1E_1E_5E_2}{(1+\alpha_rE_4)^2(1+\alpha_2E_3)} \\
a_{210} = \; & -\beta_1\tfrac{E_2}{(1+E_{10})^2} \\
a_{31} = \; & \tfrac{\gamma\pi_1E_5}{1+\alpha_rE_4}(\tfrac{E_3}{1+\alpha_1\frac{E_2}{1+\alpha_2E_3}}) \\
a_{32} = \; & -\tfrac{\gamma\pi_1E_1E_5E_3\alpha_1}{(1+\alpha_rE_4)(1+\alpha_2E_3)(1+\alpha_1\frac{E_2}{1+\alpha_2E_3})^2} \\
a_{33} = \; & -d_3 + \beta_2\tfrac{E_{10}}{1+E_{10}} \\
& +\tfrac{\gamma\pi_1E_1E_5}{(1+\alpha_2E_3+\alpha_1E_2)^2}\cdot \\
& .(\tfrac{1+2\alpha_2E_3+\alpha_1E_2+\alpha_2^2E_3^2+2\alpha_1\alpha_2E_2E_3}{1+\alpha_rE_4}) \\
a_{34} = \; & -\alpha_r\tfrac{\gamma\pi_1E_1E_5E_3}{(1+\alpha_1\frac{E_2}{1+\alpha_2E_3})(1+\alpha_rE_4)^2} \\
a_{310} = \; & \beta_2\tfrac{E_3}{(1+E_{10})^2} \\
a_{41} = \; & \varphi\pi_1E_5E_4 \\
a_{44} = \; & -d_4 + \varphi\pi_1E_1E_5 - \beta_r\tfrac{E_{10}}{1+E_{10}} \\
a_{410} = \; & -\beta_r\tfrac{E_4}{(1+E_{10})^2} \\
a_{54} = \; & -\alpha E_5 \\
a_{55} = \; & dE_9 - \pi_2 - \alpha E_4 \\
a_{59} = \; & dE_5 \\
a_{66} = \; & -\gamma_{1ll} - gk(E_9) - (\eta_{1ll}+\eta_{2ll})k_{ll}(E_7) \\
& -(1-\eta_{1ll}-\eta_{2ll})E_8L^{'}(E_6)E_6 \\
& -(1-\eta_{1ll}-\eta_{2ll})E_8L(E_6) \\
a_{67} = \; & -(\eta_{1ll}+\eta_{2ll})k_{ll}^{\prime}(E_7)E_6 \\
a_{68} = \; & \eta_{1ll}e^{-\gamma_{1ll}\tau_2}k_{ll}(E_7)E_6 \\
& -(1-\eta_{1ll}-\eta_{2ll})L(E_6)E_6 \\
& +2e^{-\gamma_{1ll}\tau_2}(1-\eta_{1ll}-\eta_{2ll})L(E_6)E_6 \\
a_{69} = \; & -gk^{'}(E_9)E_6 \\
a_{77} = \; & -\gamma_{2ll} \\
a_{89} = \; & -E_8gk^{'}(E_9) \\
a_{97} = \; & -\tfrac{\alpha_1E_9}{b_1+E_9} \\
a_{99} = \; & -c - \tfrac{\alpha_1E_7b_1}{(b_1+E_9)^2} \\
a_{1010} = \; & -\pi_3
\end{aligned}
$$

$$B = \frac{\partial Z}{\partial E_{\tau_1}} = [b_{ij}]$$

$$
\begin{aligned}
b_{15} &= -E_1\left(\tfrac{E_2}{1+\alpha_2 E_3}\right) - \gamma E_1 E_3 - \varphi E_1 E_4 \\
b_{25} &= \tfrac{\pi_1 E_1}{1+\alpha_r E_4}\left(\tfrac{E_2}{1+\alpha_2 E_3}\right) \\
b_{35} &= \tfrac{\gamma \pi_1 E_1}{1+\alpha_r E_4}\left(\tfrac{E_3}{1+\alpha_1 \frac{E_2}{1+\alpha_2 E_3}}\right) \\
b_{45} &= \varphi \pi_1 E_1 E_4
\end{aligned}
$$

$$C = \frac{\partial Z}{\partial E_{\tau_2}} = [c_{ij}]$$

$$
\begin{aligned}
c_{66} &= \eta_{1ll} e^{-\gamma_{1ll}\tau_2} k_{ll}(E_7) E_8 \\
&\quad + 2e^{-\gamma_{1ll}\tau_2}(1-\eta_{1ll}-\eta_{2ll}) E_8 L^{'}(E_6) E_6 \\
&\quad + 2e^{-\gamma_{1ll}\tau_2}(1-\eta_{1ll}-\eta_{2ll}) E_8 L(E_6) \\
c_{67} &= E_6 \eta_{1ll} e^{-\gamma_{1ll}\tau_2} k'_{ll}(E_7) E_8
\end{aligned}
$$

$$D = \frac{\partial Z}{\partial E_{\tau_3}} = [d_{ij}]$$

$$
\begin{aligned}
d_{76} &= A_{ll}(2\eta_{2ll} + \eta_{1ll}) k_{ll}(E_7) \\
d_{77} &= E_6 A_{ll}(2\eta_{2ll} + \eta_{1ll}) k'_{ll}(E_7)
\end{aligned}
$$

$$E = \frac{\partial Z}{\partial E_{\tau_4}} = [e_{ij}]$$

$e_{101} = e_{102} = e_{103} = e_{104} = e_{105} = a$

with all nonmentioned entries being null.

So, the linearized system around the equilibrium point can be written as:

$$\dot{E} = AE + BE_{_{\tau_1}} + CE_{_{\tau_2}} + DE_{_{\tau_3}} + EE_{_{\tau_4}} \quad (2)$$

with $E = (E_1, E_2, ..., E_{10})$, $E_{\tau_i} = (E_{1_{\tau_i}}, ..., E_{10_{\tau_i}})$ for $i = \overline{1,4}$ and A, B, C, D & E the matrices obtained from the linearization of system (1) with respect to the undelayed and delayed variables as above.

In what follows, we have:

$$
\begin{aligned}
M = &\ \lambda I_{10} - A - Be^{-\lambda\tau_1} - Ce^{-\lambda\tau_2} \\
&\ - De^{-\lambda\tau_3} - Ee^{-\lambda\tau_4}
\end{aligned}
$$

$$\det(M) = 0 \quad (3)$$

being the characterisctic equation designed for (2).

3 Stability analysis of the equilibrium point E_p

The stability at the specific equilibrium point, we substitute $E_p = (E_1^*, 0, 0, 0, E_5^*, 0, 0, E_8^*, E_9^*, E_{10}^*)$ in the matrices A, B, C, D and E achieved when linearizing the system (1). The nonzero values, thus, are given by:

$$
\begin{aligned}
a_{11} &= -d_1 \\
a_{12} &= -E_1^* E_5^* \\
a_{13} &= -\gamma E_1^* E_5^* \\
a_{14} &= -\varphi E_1^* E_5^* \\
a_{22} &= -d_2 + \pi_1 E_1^* E_5^* - \beta_1 \tfrac{E_{10}^*}{1+E_{10}^*} \\
a_{33} &= -d_3 + \gamma \pi_1 E_1^* E_5^* + \beta_2 \tfrac{E_{10}^*}{1+E_{10}^*} \\
a_{44} &= -d_4 + \varphi \pi_1 E_1^* E_5^* - \beta_r \tfrac{E_{10}^*}{1+E_{10}^*} \\
a_{54} &= -\alpha E_5^* \\
a_{55} &= dE_9^* - \pi_2 \\
a_{59} &= dE_5^* \\
a_{66} &= -\gamma_{1ll} - gk(E_9^*) - (\eta_{1ll} + \eta_{2ll}) k_{ll}(0) \\
&\quad - (1 - \eta_{1ll} - \eta_{2ll}) E_8^* L(0) \\
a_{77} &= -\gamma_{2ll} \\
a_{89} &= -E_8^* gk^{'}(E_9^*) \\
a_{97} &= -\tfrac{\alpha_1 E_9^*}{b_1 + E_9^*} \\
a_{99} &= -c \\
a_{1010} &= -\pi_3 \\
c_{66} &= \eta_{1ll} e^{-\gamma_{1ll}\tau_2} k_{ll}(0) E_8^* \\
&\quad + 2e^{-\gamma_{1ll}\tau_2}(1-\eta_{1ll}-\eta_{2ll}) E_8^* L(0) \\
d_{76} &= A_{ll}(2\eta_{2ll} + \eta_{1ll}) k_{ll}(0) \\
e_{101} &= e_{102} = e_{103} = e_{104} = e_{105} = a
\end{aligned}
$$

Then, the characteristic equation (3) corresponding to E_p can be written asfollows:

$$
\begin{aligned}
&\lambda(\lambda - a_{11})(\lambda - a_{22})(\lambda - a_{33}). \\
&(\lambda - a_{44})(\lambda - a_{55})(\lambda - a_{66} - c_{66}e^{-\lambda\tau_2}). \\
&(\lambda - a_{77})(\lambda - a_{99})(\lambda - a_{1010}) = 0
\end{aligned} \quad (4)
$$

so $\lambda = 0$ is a root, and we are in a critical case for the stability of the nonlinear system. In light of this situation, we will write the system in its canonical form.

For the purpose of using the theorem, we analyze the roots of (4) as folllows:

$$a_{11} = -d_1 < 0$$

$$a_{77} = -\gamma_{2ll} < 0$$

$$a_{99} = -c < 0$$

$$a_{1010} = -\pi_3 < 0$$

This yields us to impose some conditions to obtain only negative solutions as necessary prerequisites to apply the theorem of the critical case (see, [12]).

Proposition 3.1 *Consider the equilibrium point* $E_p = (E_1^*, 0, 0, 0, E_5^*, 0, 0, E_8^*, E_9^*, E_{10}^*)$. *If*

$$\pi_1 E_1^* E_5^* < d_2 + \beta_1 \frac{E_{10}^*}{1 + E_{10}^*}$$

$$\gamma\pi_1 E_1^* E_5^* < d_3 + \beta_2 \frac{E_{10}^*}{1 + E_{10}^*}$$

$$\varphi\pi_1 E_1^* E_5^* < d_4 + \beta_r \frac{E_{10}^*}{1 + E_{10}^*}$$

$$dE_9^* < \pi_2$$

then $\lambda_2 = a_{22}$, $\lambda_3 = a_{33}$, $\lambda_4 = a_{44}$ *and* $\lambda_5 = a_{55}$ *are, respectively, all negative roots.*

Inorder for the previous theorem to be applicable, we perform a translation to zero by $V_i = E_i - E_i^*$. Thus, the translated system can be written as:

$$\dot{V} = \widetilde{Z}_i(V, V_{\tau_j}) = 0; \text{for } i = \overline{1,10} \text{ and } j = \overline{1,4} \tag{5}$$

In this sense, we provide the substitution $E_i = V_i + E_i^*$ in system (1) and get:

$$\begin{aligned}
\dot{V}_1 &= -d_1(V_1 + E_1^*) + \eta \\
&\quad -(V_1 + E_1^*)(V_{5_{\tau_1}} + E_5^*)\left(\tfrac{(V_2+E_2^*)}{1+\alpha_2(V_3+E_3^*)}\right) \\
&\quad -\gamma(V_1 + E_1^*)(V_{5_{\tau_1}} + E_5^*)(V_3 + E_3^*) \\
&\quad -\varphi(V_1 + E_1^*)(V_{5_{\tau_1}} + E_5^*)(V_4 + E_4^*) \\
\dot{V}_2 &= -d_2(V_2 + E_2^*) \\
&\quad +\tfrac{\pi_1(V_1+E_1^*)(V_{5_{\tau_1}}+E_5^*)}{1+\alpha_r(V_4+E_4^*)}\left(\tfrac{(V_2+E_2^*)}{1+\alpha_2(V_3+E_3^*)}\right) \\
&\quad -\beta_1 \tfrac{(V_{10}+E_{10}^*)(V_2+E_2^*)}{1+(V_{10}+E_{10}^*)} \\
\dot{V}_3 &= -d_3(V_3 + E_3^*) \\
&\quad +\tfrac{\gamma\pi_1(V_1+E_1^*)(V_{5_{\tau_1}}+E_5^*)}{1+\alpha_r(V_4+E_4^*)}\left(\tfrac{(V_3+E_3^*)}{1+\alpha_1\frac{(V_2+E_2^*)}{1+\alpha_2 E_3}}\right) \\
&\quad +\beta_2 \tfrac{(V_{10}+E_{10}^*)(V_3+E_3^*)}{1+(V_{10}+E_{10}^*)} \\
\dot{V}_4 &= -d_4(V_4 + E_4^*) \\
&\quad +\varphi\pi_1(V_1 + E_1^*)(V_{5_{\tau_1}} + E_5^*)(V_4 + E_4^*) \\
&\quad -\beta_r \tfrac{(V_{10}+E_{10}^*)(V_4+E_4^*)}{1+(V_{10}+E_{10}^*)} \\
\dot{V}_5 &= \kappa + d(V_9 + E_9^*)(V_5 + E_5^*) \\
&\quad -\pi_2(V_5 + E_5^*) - \alpha(V_5 + E_5^*)(V_4 + E_4^*) \\
\dot{V}_6 &= -\gamma_{1l}(V_6 + E_6^*) - gk((V_9 + E_9^*))(V_6 + E_6^*) \\
&\quad -(\eta_{1l} + \eta_{2l})k_l((V_7 + E_7^*))(V_6 + E_6^*) \\
&\quad +\eta_{1l}e^{-\gamma_{1l}\tau_2}k_l((V_{7_{\tau_2}} + E_7^*)). \\
&\quad .(V_{6_{\tau_2}} + E_6^*)(V_8 + E_8^*) \\
&\quad -(1 - \eta_{1l} - \eta_{2l})(V_8 + E_8^*). \\
&\quad .L(V_6 + E_6^*)(V_6 + E_6^*) \\
&\quad +2e^{-\gamma_{1l}\tau_2}(1 - \eta_{1l} - \eta_{2l})(V_8 + E_8^*). \\
&\quad .L(V_{6_{\tau_2}} + E_6^*)(V_{6_{\tau_2}} + E_6^*) \\
\dot{V}_7 &= -\gamma_{2l}(V_7 + E_7^*) \\
&\quad +A_l(2\eta_{2l}+\eta_{1l})k_l((V_{7_{\tau_3}}+E_7^*))(V_{6_{\tau_3}}+E_6^*) \\
\dot{V}_8 &= (V_8 + E_8^*)g[k((V_{9_{\tau_2}} + E_9^*)) - k((V_9 + E_9^*))] \\
\dot{V}_9 &= b_2 - c(V_9 + E_9^*) - \tfrac{\alpha_1(V_9+E_9^*)(V_7+E_7^*)}{b_1+(V_9+E_9^*)} \\
\dot{V}_{10} &= -\pi_3(V_{10} + E_{10}^*) \\
&\quad +a[(V_{1_{\tau_4}}+E_1^*)+(V_{2_{\tau_4}}+E_2^*)+(V_{3_{\tau_4}}+E_3^*) \\
&\quad +(V_{4_{\tau_4}} + E_4^*) + (V_{5_{\tau_4}} + E_5^*)]
\end{aligned}$$

by letting

$f(V_8, V_9, V_{9_{\tau_2}}) = \dot{V}_8$
$= (V_8 + E_8^*)g[k((V_{9_{\tau_2}} + E_9^*)) - k((V_9 + E_9^*))]$

we achieve that $f(0) = 0$.

The partial derivatives matrices around zero are as the calculated before,

$$A = \frac{\partial \widetilde{Z}}{\partial V} = [a_{ij}]$$

$$B = \frac{\partial \widetilde{Z}}{\partial V_{\tau_1}} = [b_{ij}]$$

$$C = \frac{\partial \widetilde{Z}}{\partial V_{\tau_2}} = [c_{ij}]$$

$$D = \frac{\partial \widetilde{Z}}{\partial V_{\tau_3}} = [d_{ij}]$$

$$E = \frac{\partial \widetilde{Z}}{\partial V_{\tau_4}} = [e_{ij}]$$

The zero solution of the new system's characteristic equation fits E_1.

Conversely, we accomplish that

$$\frac{\partial f}{\partial V_9}(0) = -E_8^* g k'(E_9^*)$$

$$\frac{\partial f}{\partial V_{9_{\tau_2}}}(0) = E_8^* g k'(E_9^*)$$

showing that the linear component is not zero and creating, once again, a scenario in which the theorem is not applicable.

We, then, readjust the system (5) to make the suitable adoption of the theorem.

Take $\upsilon = \alpha_1 V_1 + \alpha_2 V_2 + ... + \alpha_{10} V_{10}$ such that $\dot{V} = \overline{A}V$.

So, after some calculations we get

$$\begin{bmatrix}\dot{V}_1\\ \dot{V}_2\\ \dot{V}_3\\ \dot{V}_4\\ \dot{V}_5\\ \dot{V}_6\\ \dot{V}_7\\ \dot{V}_8\\ \dot{V}_9\\ \dot{V}_{10}\end{bmatrix} = \begin{bmatrix} a_{11}V_1 + a_{12}V_2 + a_{13}V_3 + a_{14}V_4\\ a_{22}V_2\\ a_{33}V_3\\ a_{44}V_4\\ a_{54}V_4 + a_{55}V_5 + a_{59}V_9\\ a_{66}V_6\\ a_{77}V_7\\ a_{89}V_9\\ a_{97}V_7 + a_{99}V_9\\ a_{1010}V_{10}\end{bmatrix}$$

and thus, we have

$$\dot{v} = \alpha_1\dot{V}_1 + \alpha_2\dot{V}_2 + ... + \alpha_{10}\dot{V}_{10}$$

Following the requirements, we get:

$$\begin{aligned}\dot{v} &= \alpha_1(a_{11}V_1 + a_{12}V_2 + a_{13}V_3 + a_{14}V_4)\\ &\quad +\alpha_2 a_{22}V_2 + \alpha_3 a_{33}V_3 + \alpha_4 a_{44}V_4\\ &\quad +\alpha_5(a_{54}V_4 + a_{55}V_5 + a_{59}V_9)\\ &\quad +\alpha_6 a_{66}V_6 + \alpha_7 a_{77}V_7 + \alpha_8 a_{89}V_9\\ &\quad +\alpha_9(a_{97}V_7 + a_{99}V_9) + \alpha_{10}a_{1010}V_{10}\end{aligned}$$

Fixing $\dot{v} = 0$ and arraging the equation, we have:

$$\begin{aligned}0 &= \alpha_1 a_{11}V_1 + (\alpha_1 a_{12} + \alpha_2 a_{22})V_2\\ &\quad +(\alpha_1 a_{13} + \alpha_3 a_{33})V_3\\ &\quad +(\alpha_1 a_{14} + \alpha_4 a_{44} + \alpha_5 a_{54})V_4\\ &\quad +\alpha_5 a_{55}V_5 + \alpha_6 a_{66}V_6\\ &\quad +(\alpha_7 a_{77} + \alpha_9 a_{97})V_7\\ &\quad +(\alpha_5 a_{59} + \alpha_8 a_{89} + \alpha_9 a_{99})V_9\\ &\quad +\alpha_{10}a_{1010}V_{10}\end{aligned}$$

Hence,

$\alpha_1 = 0$
$\alpha_1 a_{12} + \alpha_2 a_{22} = 0$
$\alpha_1 a_{13} + \alpha_3 a_{33} = 0$
$\alpha_1 a_{14} + \alpha_4 a_{44} + \alpha_5 a_{54} = 0$
$\alpha_5 = 0$
$\alpha_6 = 0$
$\alpha_7 a_{77} + \alpha_9 a_{97} = 0$
$\alpha_5 a_{59} + \alpha_8 a_{89} + \alpha_9 a_{99} = 0$
$\alpha_{10} = 0$

Thus, $\alpha_1, \alpha_5, \alpha_6$ and α_{10} are equal to 0 suggesting explicitly that $\alpha_2 = \alpha_3 = \alpha_4 = 0$.

Now, setting $\alpha_8 = 1$, we obtain $\alpha_9 = -\frac{a_{89}}{a_{99}}$ which implies that

$$\alpha_7 = -\frac{\alpha_9 a_{97}}{a_{77}} = \frac{a_{89}a_{97}}{a_{99}a_{77}}$$

Remark that:

$$\dot{V}_{9_{\tau_2}} = a_{99}V_{9_{\tau_2}} + M_{9_{\tau_2}}$$

with $M_{9_{\tau_2}}$ containing terms of order higher or equal to 2.

Then, we consider

$$\upsilon_1 = \alpha_7 V_7 + V_8 + \alpha_9 V_9 - \frac{c_{89}}{a_{99}}V_{9_{\tau_2}}$$

following, we have that

$$\begin{aligned}\dot{\upsilon}_1 &= c_{89}V_{9_{\tau_2}} - \frac{c_{89}}{a_{99}}\dot{V}_{9_{\tau_2}} + M_8^{(1)}\\ &= c_{89}V_{9_{\tau_2}} - \frac{c_{89}}{a_{99}}(a_{99}V_{9_{\tau_2}} + M_{9_{\tau_2}})\\ &= M_8^{(2)}(V, V_{_{\tau_2}})\end{aligned}$$

In order to avoid the linear part in the 8^{th} equation of (5), we exchange it by the equation of $\dot{\upsilon}_1$ and let

$$V_8 = \upsilon_1 - \alpha_7 V_7 - \alpha_9 V_9 + \frac{c_{89}}{a_{99}}V_{9_{\tau_2}}$$

We, then, have that the new system is exactly formed by the equations of the system (5) except for V_8 as presented below:

$$\begin{aligned}\dot{V}_1 &= -d_1(V_1 + E_1^*) + \eta\\ &\quad -(V_1 + E_1^*)(V_{5_{\tau_1}} + E_5^*)(\tfrac{(V_2+E_2^*)}{1+\alpha_2(V_3+E_3^*)})\\ &\quad -\gamma(V_1 + E_1^*)(V_{5_{\tau_1}} + E_5^*)(V_3 + E_3^*)\\ &\quad -\varphi(V_1 + E_1^*)(V_{5_{\tau_1}} + E_5^*)(V_4 + E_4^*)\\ \dot{V}_2 &= -d_2(V_2 + E_2^*)\\ &\quad +\tfrac{\pi_1(V_1+E_1^*)(V_{5_{\tau_1}}+E_5^*)}{1+\alpha_r(V_4+E_4^*)}(\tfrac{(V_2+E_2^*)}{1+\alpha_2(V_3+E_3^*)})\\ &\quad -\beta_1\tfrac{(V_{10}+E_{10}^*)(V_2+E_2^*)}{1+(V_{10}+E_{10}^*)}\\ \dot{V}_3 &= -d_3(V_3 + E_3^*)\\ &\quad +\tfrac{\gamma\pi_1(V_1+E_1^*)(V_{5_{\tau_1}}+E_5^*)}{1+\alpha_r(V_4+E_4^*)}(\tfrac{(V_3+E_3^*)}{1+\alpha_1\frac{(V_2+E_2^*)}{1+\alpha_2 E_3}})\\ &\quad +\beta_2\tfrac{(V_{10}+E_{10}^*)(V_3+E_3^*)}{1+(V_{10}+E_{10}^*)}\end{aligned}$$

$$\begin{aligned}\dot{V}_4 &= -d_4(V_4 + E_4^*)\\ &\quad +\varphi\pi_1(V_1 + E_1^*)(V_{5_{\tau_1}} + E_5^*)(V_4 + E_4^*)\\ &\quad -\beta_r\tfrac{(V_{10}+E_{10}^*)(V_4+E_4^*)}{1+(V_{10}+E_{10}^*)}\\ \dot{V}_5 &= \kappa + d(V_9 + E_9^*)(V_5 + E_5^*)\\ &\quad -\pi_2(V_5 + E_5^*) - \alpha(V_5 + E_5^*)(V_4 + E_4^*)\\ \dot{V}_6 &= -\gamma_{1ll}(V_6 + E_6^*)\\ &\quad -gk((V_9 + E_9^*))(V_6 + E_6^*)\\ &\quad -(\eta_{1ll} + \eta_{2ll})k_{ll}((V_7 + E_7^*))(V_6 + E_6^*)\\ &\quad +\eta_{1ll}e^{-\gamma_{1ll}\tau_2}k_{ll}((V_{7_{\tau_2}} + E_7^*))(V_{6_{\tau_2}} + E_6^*).\\ &\quad .(\upsilon_1 - \alpha_7 V_7 - \alpha_9 V_9 + \tfrac{c_{89}}{a_{99}}V_{9_{\tau_2}})\end{aligned}$$

$$
\begin{aligned}
&-(1-\eta_{1ll}-\eta_{2ll}).\\
&.(\upsilon_1-\alpha_7V_7-\alpha_9V_9+\tfrac{c_{89}}{a_{99}}V_{9_{\tau_2}}).\\
&.L(V_6+E_6^*)(V_6+E_6^*)\\
&+2e^{-\gamma_{1ll}\tau_2}(1-\eta_{1ll}-\eta_{2ll}).\\
&.(\upsilon_1-\alpha_7V_7-\alpha_9V_9+\tfrac{c_{89}}{a_{99}}V_{9_{\tau_2}}).\\
&.L(V_{6_{\tau_2}}+E_6^*)(V_{6_{\tau_2}}+E_6^*)
\end{aligned}
$$

$$\dot{V}_7=-\gamma_{2ll}(V_7+E_7^*)+A_{ll}(2\eta_{2ll}+\eta_{1ll})k_{ll}((V_{7_{\tau_3}}+E_7^*))(V_{6_{\tau_3}}+E_6^*)$$

$$
\begin{aligned}
\dot{\upsilon}_1 &= c_{89}V_{9_{\tau_2}}-\frac{c_{89}}{a_{99}}\dot{V}_{9_{\tau_2}}+M_8^{(1)}\\
&= c_{89}V_{9_{\tau_2}}-\frac{c_{89}}{a_{99}}(a_{99}V_{9_{\tau_2}}+M_{9_{\tau_2}})\\
&= M_8^{(2)}(V,V_{\tau_2})
\end{aligned}
$$

$$\dot{V}_9=b_2-c(V_9+E_9^*)-\frac{\alpha_1(V_9+E_9^*)(V_7+E_7^*)}{b_1+(V_9+E_9^*)}$$

$$
\begin{aligned}
\dot{V}_{10}=&-\pi_3(V_{10}+E_{10}^*)\\
&+a[(V_{1_{\tau_4}}+E_1^*)+(V_{2_{\tau_4}}+E_2^*)+(V_{3_{\tau_4}}+E_3^*)+(V_{4_{\tau_4}}+E_4^*)+(V_{5_{\tau_4}}+E_5^*)]
\end{aligned}
$$

Calling

$$
\begin{aligned}
&f(E_6,E_{6_{\tau_2}},E_7,E_{7_{\tau_2}},E_9,E_{9_{\tau_2}},\chi_1)=\\
&-\gamma_{1ll}(V_6+E_6^*)-gk((V_9+E_9^*))(V_6+E_6^*)\\
&-(\eta_{1ll}+\eta_{2ll})k_{ll}((V_7+E_7^*))(V_6+E_6^*)\\
&+\eta_{1ll}e^{-\gamma_{1ll}\tau_2}k_{ll}((V_{7_{\tau_2}}+E_7^*))(V_{6_{\tau_2}}+E_6^*).\\
&.(-\alpha_7V_7-\alpha_9V_9+\tfrac{c_{89}}{a_{99}}V_{9_{\tau_2}})\\
&-(1-\eta_{1ll}-\eta_{2ll})(-\alpha_7V_7-\alpha_9V_9+\tfrac{c_{89}}{a_{99}}V_{9_{\tau_2}}).\\
&.L(V_6+E_6^*)(V_6+E_6^*)\\
&+2e^{-\gamma_{1ll}\tau_2}(1-\eta_{1ll}-\eta_{2ll}).\\
&.(-\alpha_7V_7-\alpha_9V_9+\tfrac{c_{89}}{a_{99}}V_{9_{\tau_2}}).\\
&.L(V_{6_{\tau_2}}+E_6^*)(V_{6_{\tau_2}}+E_6^*)\\
&+[\eta_{1ll}e^{-\gamma_{1ll}\tau_2}k_{ll}((V_{7_{\tau_2}}+E_7^*))\\
&-(1-\eta_{1ll}-\eta_{2ll})L(V_6+E_6^*)](V_{6_{\tau_2}}+E_6^*)\upsilon_1\\
&+2e^{-\gamma_{1ll}\tau_2}(1-\eta_{1ll}-\eta_{2ll})L(V_{6_{\tau_2}}+E_6^*).\\
&.(V_{6_{\tau_2}}+E_6^*)]\upsilon_1
\end{aligned}
$$

we, so, remark that the linear part of f doesn't contain υ_1.

Having this outline set, since the other equations, except that of υ_1, do not contain η_1 at all, we conclude that theorem (*) can be applied. Moreover, the stability of the equilibrium point depends, now, on the examination of the transcendental expressions which are part of the characteristic equation (4).

The transcendental equations of the characteristic equation

Consider the equation,

$$\lambda-a_{66}-c_{66}e^{-\lambda\tau_2}=0 \tag{6}$$

Proposition 3.2 *Assume that the following condition is true:*

$$\gamma_{1ll}+gk(E_9)+\eta_{2ll}k_{ll}(0)>(1-\eta_{1ll}-\eta_{2ll})E_8^*L(0) \tag{7}$$

Then the equation (6) is stable for $\tau_2=0$ and it remains stable for all $\tau_2>0$.

Proof: At the equilibrium we have:

$$
\begin{aligned}
a_{66}=&-\gamma_{1ll}-gk(E_9^*)-(\eta_{1ll}+\eta_{2ll})k_{ll}(0)\\
&-(1-\eta_{1ll}-\eta_{2ll})E_8^*L(0)\\
c_{66}=&\ \eta_{1ll}e^{-\gamma_{1ll}\tau_2}k_{ll}(0)E_8^*\\
&+2e^{-\gamma_{1ll}\tau_2}(1-\eta_{1ll}-\eta_{2ll})E_8^*L(0)
\end{aligned}
$$

Letting $\tau_2=0$, the equation (6) can be written as:

$$
\begin{aligned}
&\lambda-(-\gamma_{1ll}-gk(E_9)-(\eta_{1ll}+\eta_{2ll})k_{ll}(0)\\
&-(1-\eta_{1ll}-\eta_{2ll})E_8^*L(0)-(\eta_{1ll}k_{ll}(0)\\
&+2(1-\eta_{1ll}-\eta_{2ll})E_8^*L(0)) &&=0
\end{aligned}
$$

Reordering the terms, we get

$$
\begin{aligned}
&\lambda+\gamma_{1ll}+gk(E_9)+\eta_{2ll}k_{ll}(0)\\
&-(1-\eta_{1ll}-\eta_{2ll})E_8^*L(0) &&=0
\end{aligned}
$$

As $\tau_2=0$, the equation (6) is stable if $\gamma_{1ll}+gk(E_9)+\eta_{2ll}k_{ll}(0)>(1-\eta_{1ll}-\eta_{2ll})E_8^*L(0)$

Knowing that $c_{66}>0$,it is enough to prove the first and the second conditions of theorem in (**) while $\tau_2>0$.

So, we need to show that:

1. $a_{66}\tau_2<1$
2. $a_{66}+c_{66}<0$

For 1:

Having $a_{66}=-\gamma_{1ll}-gk(E_9^*)-(\eta_{1ll}+\eta_{2ll})k_{ll}(0)-(1-\eta_{1ll}-\eta_{2ll})E_8^*L(0)<0<\frac{1}{\tau_2}$.

This shows that condition 1 of theorem in ([14]) is satisfied.

As for condition 2, we get

$$
\begin{aligned}
a_{66}+c_{66}=&-\gamma_{1ll}-gk(E_9^*)-(\eta_{1ll}+\eta_{2ll})k_{ll}(0)\\
&-(1-\eta_{1ll}-\eta_{2ll})E_8^*L(0)\\
&+\eta_{1ll}e^{-\gamma_{1ll}\tau_2}k_{ll}(0)E_8^*\\
&+2e^{-\gamma_{1ll}\tau_2}(1-\eta_{1ll}-\eta_{2ll})E_8^*L(0)\\
&<0
\end{aligned} \tag{8}
$$

which indicates that if (7) is true, then (8) is also true. □

4 Conclusion

This study developed a mathematical model for allergies derived from chemotherapy of Acute Lymphoblastic Leukemia (ALL) treatment based on delay-differential equations. The model, consisting of ten equations with four distinct delays, successfully represents the intricate interactions between leukemia cells, healthy cells, and therapeutic interventions. By performing stability analysis and applying the critical case theorem, we determined equilibrium points and established the conditions that govern either disease suppression or progression.

Our results underline the value of mathematical modeling in clarifying leukemia

dynamics and supporting treatment strategies. Moreover, we suggested incorporating fractional calculus into the framework to strengthen its predictive accuracy and resilience, as fractional differential equations have proven effective in describing complex biological systems.

In summary, this work introduces a novel and dynamic approach to modeling leukemia treatment, underscoring the essential role of mathematical models in advancing cancer therapies and improving patient outcomes.

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