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Mathematical Modeling of Immune Dynamics in Chronic Myeloid Leukemia Therapy: Unraveling Allergic Reactions and T Cell Subset Modulation by Imatinib

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Abstract: This mathematical model delves into the dynamics of the immune system during Chronic Myeloid Leukemia (CML) therapy with imatinib. The focus lies in elucidating the allergic reactions induced by imatinib, specifically its impact on T helper (Th) cells and Treg cells. The model integrates cellular interactions, drug pharmacokinetics, and immune responses to unveil the mechanisms underlying the dominance of Th2 over Th1 and Treg cells, leading to allergic manifestations. Through a system of coupled delay differential equations, the interplay between healthy and leukemic cells, the influence of imatinib on T cell dynamics, and the emergence of allergic reactions during CML therapy are explored.

Keywords: chronic myeloid leukemia; imatinib therapy; mathematical modeling; immune system dynamics; T cell subset modulation; allergic reactions; pharmacokinetics; cellular interactions; Th1; Th2; Treg cells; stem-like; mature cell populations; time delays; differential equations; pharmacodynamics

MSC: 34K20; 92C50; 92D25

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1. Introduction

Chronic Myeloid Leukemia (CML) is a hematological malignancy characterized by the presence of the BCR-ABL fusion gene, which produces an abnormal tyrosine kinase protein. This protein is responsible for the uncontrolled proliferation of leukemic cells. The introduction of imatinib, a targeted tyrosine kinase inhibitor, has revolutionized the treatment of CML by specifically inhibiting this abnormal protein, leading to significant improvements in patient outcomes.

However, despite its efficacy, imatinib therapy is associated with a range of immune-related side-effects, including allergic reactions. These adverse effects are believed to result from the drug's impact on various components of the immune system, particularly T helper (Th) cells and regulatory T cells (Tregs). Understanding the underlying mechanisms of these immune responses is crucial for improving the management of CML patients undergoing imatinib therapy.

The significance of this study lies in its potential to bridge the gap in our understanding of the immune dynamics during imatinib treatment. By developing a comprehensive mathematical model, we aim to elucidate the interactions between imatinib, leukemic cells, and the immune system. This model incorporates cellular interactions, drug pharmacokinetics, and immune responses, providing a detailed framework to study the emergence of allergic reactions and other immune-related side-effects.

Previous studies, in which delay differential equations (DDEs) are used to model the CML-immune dynamics, have primarily focused on how to model the evolution of

healthy and leukemic cells and the direct effects of treatment on leukemic cells (see [1–13]). However, these studies offer limited exploration of its broader impact on the immune system. To address this, we added to the model new equations that account for allergic reactions, relying on [14–16]. The mathematical model introduced in this paper, bridges this gap by integrating the modulation of Th cell subsets and the resulting shift in immune balance. Specifically, we investigate the dominance of Th2 cells over Th1 and Treg cells, which is hypothesized to contribute to the allergic manifestations observed during therapy.

By employing a system of coupled delay differential equations, our model captures the temporal dynamics of cellular processes and drug interactions. This approach allows us to simulate the progression of CML and the corresponding immune responses over time, providing insights into the mechanisms driving the observed clinical outcomes.

2. The Mathematical Model

The mathematical model aims to capture the complexities of the immune response during CML therapy, with a specific focus on the alteration of T cell subsets, induced by imatinib. The model encompasses various cell populations, including stem-like healthy and leukemic cells, mature cells, and distinct T cell subsets (Th1, Th2, and Treg). Additionally, it incorporates the pharmacokinetics of imatinib, shedding light on its absorption and distribution within the body. Furthermore, the model explores the differentiation of naive T cells into effector states, considering positive growth and suppressive signals.

In what follows, we first discuss the biological aspects and assumptions and the mathematical implications of the said assumptions and then we introduce the model and describe its equations.

We integrate the modulation of naive APC cells by imatinib and leukemic cells. This integration suggests a potential shift in the balance of Th cell subsets, with a dominance of Th2 cells over Th1 and Treg cells. Understanding this shift is critical for elucidating the allergic reactions triggered during CML therapy. As shown by Segel [17], Th2 cells stimulate the production of IgE, while Th1 cells promote the production of IgG (refer to Behn [14]). Thus, a transition from a Th2-dominated memory state to a Th1-dominated memory state indicates successful chemotherapy without allergic reactions.

The model considers both healthy and leukemic cell populations, possessing self-renewal capabilities, denoted as x_1 and x_3, respectively. These are referred to as stem-like cells, assumed to undergo a brief period of quiescence categorized as short-term hematopoietic stem cells (ST-HSC).

Two additional populations, x_2 and x_4, represent mature healthy and leukemia leukocytes, respectively. The immune system is characterized by $x_5, \ldots, x_{13}$, representing naive APCs, mature APCs, naive CD4+, Th1, Th2, Th3, Tregs, naive CD8+, and CD8+ cytotoxic T cells actively targeting leukemic cells. The competition between healthy and leukemic blood cell populations for resources is considered in the feedback laws governing self-renewal and differentiation.

Thus, the rate of self-renewal is

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

(h for healthy and l for leukemia) with $\beta_{0\alpha}$ the maximal rate of self-renewal and $\theta_{1\alpha}$ half of the maximal value.

The rate of differentiation is

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

Now, $k_{0\alpha}$ is the maximal rate of differentiation and $\theta_{2\alpha}$ is half of the maximal value.

It is assumed that a fraction $\eta_{1\alpha}$, where $\alpha = h, l$, of short-term hematopoietic stem cells (ST-HSC) is prone to asymmetric division: one daughter cell undergoes differentiation, while the other re-enters the stem cell compartment. Another fraction, $\eta_{2\alpha}$, where $\alpha = h, l$, is inclined to differentiate symmetrically, yielding two cells that mature, while the remaining fraction $1 - \eta_{1\alpha} - \eta_{2\alpha}$, where $\alpha = h, l$, is predisposed to self-renewal, resulting in two stem-like cells after mitosis.

Moreover, the model includes feedback functions regulating the immune system, reflecting the modulation of naive APC cells by imatinib and the resulting shift in the balance of Th-cell subsets. Recognizing that active CD4+ T helper cells secrete positive growth/suppressive signals at varying rates, we introduce T-helper-dependent feedback functions. These functions model positive growth signals for T cells' self-development (autocrine loop) and stimulation of further division in T cytotoxic cells. Additionally, they account for suppressive signals resulting from the regulatory process. Here, the inhibitory effects of imatinib on Treg development are considered. Leukemic cells also exert an influence on the evolution of CD8+ cytotoxic T cells, suppressing the effect of the immune system.

The following feedback functions regulate the evolution of the immune system and its interaction with leukemic cells ([3,7]):

- $l_1(x) = \dfrac{1}{b_3 + x}$—it balances the effect of the immune system on the leukemic cells and it depends on the total number of leukemic cells (naive and mature);
- $l_2(x) = \dfrac{x}{b_3 + x}$—it controls the activation of APCs depending on the number of mature leukemic cells;
- $l_3(x) = \dfrac{1}{1 + x^2}$—it regulates the immune response through the number of mature leukemic cells;
- $\zeta(x) = \dfrac{x}{1 + x^2}$—it regulates the population CD8+ mature cells through T-reg cells.

The therapeutic strategy targeting the BCR-ABL gene is presumed to impact the apoptosis of leukemia cells and the proliferation rates of both healthy and leukemia cells. Its effect is considered constant over time, reflecting a period where, following an initial transitory stage, the cellular impact stabilizes. Imatinib plays a crucial role in modulating the maturation and proper functioning of Antigen-Presenting Cells (APCs) and, consequently, T cells within the immune system.

Treatment effects are incorporated into the model through the factor u_1 in terms controlling leukemic stem-like cell multiplication, and factors u_2, u_3, and u_4 in the equation of the immune system's cells. To determine the relationship between u_1, u_2, u_3, and u_4 and the drug concentration in the plasmatic compartment x_{15}, we rely on experimental data. Details on the choice of functions governing treatment influence on different cell lines can be found in [6]. Thus, $u_1(x_{15}) = \dfrac{1}{1 + (99/3.2^2)x_{15}^2}$ influences the leukemic stem cells. $u_2(x_{15}) = \dfrac{3.2^2}{3.2^2 + x_{15}^2}$ influences the APC. The activation of T cells is controlled by $u_3(x_{15}) = \dfrac{100/3}{100/3 + x_{15}^2}$. Finally, $u_4(x_{15}) = \dfrac{50/3}{50/3 + x_{15}^2}$ reduces the self-stimulation of T-helper cells.

As shown by Segel [17], Th2 cells stimulate the production of IgE, while Th1 cells promote the production of IgG (refer to Behn [14]). Consequently, a transition from a Th2-dominated memory state to a Th1-dominated memory state indicates successful chemotherapy without the occurrence of allergic reactions.

Among various regulatory T cells, the induced regulatory T cells (T_{reg}) are crucial in the context of allergic reactions (Behn [14]). These cells release cytokines like IL-10 and TGF-β, capable of suppressing both Th1 and Th2 immune responses. Their differentiation from naive T cells follows a similar process as observed in other subsets (see Behn [14]).

The procedure known as drug desensitization assists patients in tolerating medications that previously triggered hypersensitive reactions. According to [18], by employing a gradual desensitization approach, all patients successfully tolerated a daily dose of 400 mg of imatinib, and the dosage of prednisolone was systematically reduced. The proportions of imatinib-induced $CD4^+CD25^+CD134^+$ T cells declined from an initial mean (SD) of 11.3% (6.5%) and 13.4% (7.3%) to 3.2% (0.7%) and 3.0% (1.1%) following effective desensitization. This was observed when stimulating peripheral blood mononuclear cells with 1 and 2 mM of imatinib, respectively.

Time delays are incorporated to reflect the duration of cellular processes, introducing temporal dynamics to the model.

In order to model the CML-immune dynamics under therapy, we use a system of delayed differential equations (DDEs). We base the model on former work ([3,8,15]) and some classic models from the literature (see ([1,2,14,19])). We offer more details on the source of inspiration in the model description.

The complete model consists of the following equations:

$$\begin{aligned}\dot{x}_1 = &-\gamma_{1h}x_1 - (\eta_{1h}+\eta_{2h})k_h(x_2+x_4)x_1\\ &-(1-\eta_{1h}-\eta_{2h})\beta_h(x_1+x_3)x_1\\ &+2e^{-\gamma_{1h}\tau_1}(1-\eta_{1h}-\eta_{2h})\beta_h(x_{1\tau_1}+x_{3\tau_1})x_{1\tau_1}\\ &+\eta_{1h}e^{-\gamma_{1h}\tau_1}k_h(x_{2\tau_1}+x_{4\tau_1})x_{1\tau_1}\end{aligned} \tag{1}$$

$$\dot{x}_2 = -\gamma_{2h}x_2 + A_h(2\eta_{2h}+\eta_{1h})k_h(x_{2\tau_2}+x_{4\tau_2})x_{1\tau_2} \tag{2}$$

$$\begin{aligned}\dot{x}_3 = &-\gamma_{1l}x_3 - (\eta_{1l}+\eta_{2l})u_1(x_{15})k_l[(x_2+x_4)]x_3\\ &-(1-\eta_{1l}-\eta_{2l})\beta_l(x_1+x_3)x_3\\ &+2e^{-\gamma_{1l}\tau_3}(1-\eta_{1l}-\eta_{2l})\beta_l(x_{1\tau_3}+x_{3\tau_3})x_{3\tau_3}\\ &+\eta_{1l}e^{-\gamma_{1l}\tau_3}k_l[(x_{2\tau_3}+x_{4\tau_3})]x_{3\tau_3} - b_1x_3x_{13}l_1(x_3+x_4)\end{aligned} \tag{3}$$

$$\dot{x}_4 = -\gamma_{2l}x_4 + A_l(2\eta_{2l}+\eta_{1l})u_1(x_{15})k_l[(x_{2\tau_4}+x_{4\tau_4})]x_{3\tau_4} - b_2x_4x_{13}l_1(x_3+x_4) \tag{4}$$

$$\dot{x}_5 = c_1 - c_2x_5 - c_3x_5x_{15} - c_4x_5l_2(x_4) \tag{5}$$

$$\dot{x}_6 = -d_1x_6 + c_3x_5x_{15} \tag{6}$$

$$\dot{x}_7 = -d_1x_7 + c_4u_2(x_{15})x_5l_2(x_4) \tag{7}$$

$$\dot{x}_8 = \Lambda_1 - \beta_1x_8 - u_3(x_{15})x_8x_{6\tau_5}\left(\frac{x_9}{1+m_2x_{10}}\right) - pu_3(x_{15})x_8x_{6\tau_5}x_{10} - u_3(x_{15})\kappa x_8x_{6\tau_5}x_{11} \tag{8}$$

$$\dot{x}_9 = -\beta_2x_9 + \frac{\gamma_1u_4(x_{15})x_8x_{6\tau_5}}{1+m_rx_{11}}\left(\frac{x_9}{1+m_2x_{10}}\right) \tag{9}$$

$$\dot{x_{10}} = -\beta_3x_{10} + p\frac{\gamma_1u_4(x_{15})x_8x_{6\tau_5}}{1+m_rx_{11}}\left(\frac{x_{10}}{1+m_1\dfrac{x_9}{1+m_2x_{10}}}\right) \tag{10}$$

$$\dot{x_{11}} = -\beta_4x_{11} + u_4(x_{15})\kappa\gamma_1x_8x_{6\tau_5}x_{11} \tag{11}$$

$$\dot{x}_{12} = \Lambda_2 - a_1 x_{12} - \eta_1 u_3(x_{15}) x_7 x_{12} \tag{12}$$

$$\begin{aligned}\dot{x}_{13} = {} & 2^m \eta_1 u_3(x_{15}) x_{7\tau_6} x_{12\tau_6} - a_2 x_{13} \zeta(x_{11}) - a_3 x_{13} l_3(x_4) - \eta_2 u_3(x_{15}) x_{13} l_3(x_9 + x_{10} + x_{11} + x_{13}) + \\ & + 2^{n_1} \eta_2 u_3(x_{15}) x_{13\tau_7} l_3(x_{9\tau_7} + x_{10\tau_7} + x_{11\tau_7} + x_{13\tau_7})\end{aligned} \tag{13}$$

$$\dot{x}_{14} = -\lambda_0 x_{14} + K \tag{14}$$

$$\dot{x}_{15} = -\nu x_{15} + \lambda_0 x_{14} \tag{15}$$

The previous system can be written as

$$\dot{x}_i = f_i(x), i = 1, \ldots, 15, x = (x_1, \ldots, x_{15}) \tag{16}$$

In what follows, details are given on the form of the equations as well as on the occurring parameters.

Equation (1) represents the state variable x_1, the concentration of stem-like healthy cells, the rate of self-renewal $\beta_\alpha(X)$, and the rate of differentiation $k_\alpha(Y)$ with $\alpha = h, l$; where cell competition (healthy vs. leukemic) was taken into account, $X = x_1 + x_3$ and $Y = x_2 + x_4$ (see [1,2]). These first four equations were introduced in [8] (see also [3]).

Equation (2) represents the concentration of mature healthy cells x_2.

Equation (3) represents the concentration of stem-like leukemic cells x_3.

Equation (4) represents the concentration of mature leukemic cells x_4.

The last terms in Equations (3) and (4) stand for the mortality of the leukemic cells due to the interaction with the cytotoxic T cells (for a similar representation of this process, see [19]).

In Equation (5), x_5 represents the concentration of naive antigen-presenting cells (APCs). Here, c_1 is a constant supply of naive APCs even in the absence of any disease, and c_2 is the apoptosis rate of naive APCs. The third term accounts for the rate of APC activation by the antigen induced during therapy with imatinib. The last term represents the activation of naive APCs due to the encounter with leukemia cells. The treatment is involved in these activations through x_{15}.

In Equation (6), x_6 represents the concentration of mature APCs activated by the antigen induced by the drug. Here, d_1 denotes the apoptosis rate of mature APCs. The second term in the equation accounts for the influx of mature APCs from the naive pool due to activation by the antigen during therapy with imatinib.

Equation (7) represents the dynamics of APC cells activated by leukemic cells, x_7. The first term denotes natural degradation, and the second term refers to the activation of APC cells by leukemic cells.

In Equation (8), x_8 represents the concentration of naive CD4+ T cells, which are produced at a constant rate Λ. The second term represents the degradation of these naive cells. The last three terms stand for the differentiation of naive cells into Th1, Th2, and Treg, respectively, under the action of APCs [14].

In Equation (9), x_9 represents the variation in concentration of Th1 cells, which is proportional to the concentration of naive cells timed with the concentration of APCs stimulated by the allergen with a delay τ_5. The first term represents the degradation of Th1 cells, and the second term represents the differentiation of naive cells into Th1, diminished due to suppression by Treg and Th2 cells.

In Equation (10), x_{10} represents the concentration of Th2, which is proportional to the concentration of naive cells timed with the concentration of APCs and the concentration of their respective cytokines. The first term represents the degradation of Th2 cells, and the second term represents the differentiation of naive cells into Th2, divided by the suppression of Treg and Th1 cells. Remark that the suppression is modeled by factors of

the form $1/(1+x)$, where x stands for the concentration of cytokines produced by the suppressing population [14].

In Equation (11), x_{11} represents the concentration of Treg, which is proportional to the concentration of naive cells timed with the concentration of APCs. The first term represents the degradation of Treg cells, and the second term represents the differentiation of naive cells into Treg. In Equations (9)–(11), the parameter γ_1 determines how many differentiated T cells arise from a single naive cell. p and κ account for differences in autocrine action between the three subsets. The suppression strength of Th1, Th2, and Treg is controlled by the parameters m_1, m_2, m_r, in that order. The treatment effects are introduced in these equations through the factor u_4 that controls multiplication [20].

In Equation (12), x_{12} represents the concentration of the population of naive CD8+ cells. The first term denotes the supply rate, the second term denotes natural degradation, and the last term represents the loss due to maturation under the action of APCs activated by leukemic cells.

In Equation (13), x_{13} represents the concentration of mature CD8+ T cells. The first term represents the naive cells activated by APCs after m divisions, the second term represents the active CD8+ T cells that are suppressed by Tregs, the third term represents the suppression of the immune response by leukemia cells, and it is assumed that the level of down-regulation depends on the current leukemia population. This suppressive action is expressed by the presence of the mature population of leukemia cells in the denominator of the function l_3. The last two terms represent the stimulation of n_1 cell divisions due to positive growth signals induced by IL-2 secreted by both CD4+ and CD8+ mature cells. The time delays $\tau_6 = m\tau_T$ and $\tau_7 = n_1\tau_T$, where τ_T is the duration of the T cell division cycle, are supposed equal for naive and mature CD8+ cells.

In Equation (14), x_{14} represents equations for imatinib pharmacokinetics following [21]. Here, x_{14} stands for the amount of drug in the absorption compartment. λ_0 is the absorption rate in the first compartment, and K, the dose of drug administered in a unit of time, is taken to be constant.

In Equation (15), x_{15} represents the amount of drug in the plasmatic compartment. v is the total plasma clearance of the drug divided by the volume of distribution of the drug.

Let $\tau_{\max} = \max(\tau_1, \tau_2, \tau_3, \tau_4, \tau_5, \tau_6, \tau_7)$.

The delays for healthy and leukemia ST-HSC cells are τ_1 and τ_3, representing the duration of the cell cycle independent of the type of division. τ_2 and τ_4 denote the time needed for differentiation into mature leukocytes for healthy and leukemia cells, respectively. The fifth delay, τ_5, is due to the time for propagation of the allergen from the central compartment to the peripheral compartment [22]. If T is the infusion time interval and K_{cp} is a pharmacokinetic parameter related to the transition between the central and peripheral compartments, one has, following [22], $\tau_5 = \dfrac{\arctan(\frac{2\pi}{K_{cp}})T}{2\pi}$.

The delay τ_6 is the time necessary for naive CD8+ cell maturation, and τ_7 is the time necessary for n_1 divisions.

Define $\tau_{\max} = \max(\tau_1, \tau_2, \tau_3, \tau_4, \tau_5, \tau_6, \tau_7)$.

We refer to previous works [1,3,7] for parameter significance, interpretation, and justification.

The last two equations are decoupled from the rest of the system, so $x_{15} = P$ will be considered as an external parameter.

3. Positivity of Solutions

For the system (16), a Cauchy problem is defined by considering the initial data in $\varphi \in PC([-\tau, 0], \mathbb{R}^{15})$:

$$x(s) = \varphi(s) \ \forall \ s \in [-\tau, 0] \tag{17}$$

First of all, the essential positivity of the solutions will be established.

Proposition 1. *If the initial data* $\varphi \in PC([-\tau, 0], \mathbb{R}^{15})$ *satisfy* $\varphi_j(s) > 0 \ \forall \ s \in [-\tau, 0], j = 1, \ldots, 13$, *then the solution of the Cauchy problem (16) + (17) will satisfy* $x_j(t) \geq 0, j = 1, \ldots, 15$ *for all* $t \geq 0$ *in the domain of existence.*

Proof. From Equations (1)–(4) and (13) one can observe that, due to the delayed terms, if, for some $t_0 > 0$, one has $x_j(t_0) = 0$ for some $j = 1, 2, 3, 4$, then $x_j'(t_0) > 0$ and one cannot have negative values for $x_1, x_2, x_3, x_4, x_{13}$. The same reasoning works for x_5, x_6, x_{14}. Since

$$x_{15}(t) = x_{15}(0)e^{-\nu t} + \lambda_0 e^{-\nu t} \int_0^t e^{\nu s} x_{14}(s)\, ds$$

it follows that, once x_{14} is proved to be positive for all $t \geq 0$, if $x_{15}(0) > 0 \Rightarrow x_{15}(t) > 0 \ \forall \ t \geq 0$. Then, x_7, x_8, x_{12} result positive by the argument used at the beginning of the proof. Also, since

$$x_{11}(t) = x_{11}(0)e^{-\beta_4 t + \int_0^t u_4 k \gamma_1 x_8(s) x_6(s-\tau_6)\, ds}$$

it follows that $x_{11}(t) > 0 \ \forall \ t$ in the domain of existence. Similar formulae hold for x_9, x_{10} so, first, x_{10} results to be strictly positive and finally x_9 has the same property. □

4. Stability of Some Equilibria

4.1. The Equilibrium Point E_1

The first equilibrium point to be considered is $E_1 = (0, 0, 0, 0, \hat{x}_5, \hat{x}_6, 0, \hat{x}_8, 0, 0, 0, \hat{x}_{12}, 0, \hat{x}_{14}, \hat{x}_{15})$ corresponding to the death of the patient.

In order to study the characteristic equation, one has to compute the matrices $A = \dfrac{\partial f}{\partial x}$, the matrix of partial derivatives with respect to undelayed variables calculated in E_1, $B = \dfrac{\partial f}{\partial x_{\tau_1}}$, the matrix of partial derivatives with respect to τ_1 delayed variables, and similarly, $C = \dfrac{\partial f}{\partial x_{\tau_2}}$, $D = \dfrac{\partial f}{\partial x_{\tau_3}}$, $E = \dfrac{\partial f}{\partial x_{\tau_4}}$, $F = \dfrac{\partial f}{\partial x_{\tau_5}}$, $G = \dfrac{\partial f}{\partial x_{\tau_6}}$, $H = \dfrac{\partial f}{\partial x_{\tau_7}}$.

The elements of the matrices A, B, C, D, E, F, G, H are calculated in Appendix A.

The characteristic equation factorizes as

$$\begin{aligned}&(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})(\lambda - a_{22})(\lambda - a_{33} - d_{33}e^{-\lambda\tau_3})(\lambda - a_{44})(\lambda - a_{55})(\lambda - a_{66})(\lambda - a_{77})\\ &(\lambda - a_{88})(\lambda - a_{99})(\lambda - a_{10,10})(\lambda - a_{11,11})(\lambda - a_{12,12})(\lambda - a_{13,13}) = 0 \end{aligned} \tag{18}$$

The characteristic equation becomes:

$$\begin{aligned}&(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})(\lambda - a_{22})(\lambda - a_{33} - d_{33}e^{-\lambda\tau_3})(\lambda - a_{44})(\lambda - a_{55})(\lambda - a_{66})(\lambda - a_{77})\\ &(\lambda - a_{88})(\lambda - a_{99})(\lambda - a_{10,10})(\lambda - a_{11,11})(\lambda - a_{12,12})(\lambda - a_{13,13}) = 0\end{aligned}$$

Stability conditions: To study the stability of the equations $\lambda - a_{11} - b_{11}e^{-\lambda\tau_1} = 0$, $\lambda - a_{22} = 0$, and $\lambda - a_{33} - d_{33}e^{-\lambda\tau_3} = 0$, we apply the well-known criteria that can be found in [23,24].

Since $a_{11} < 0$, $a_{33} < 0$, $b_{11} > 0$, $d_{33} > 0$ (see Appendix A), one has stability for all positive τ_1, τ_3 if:

1. $a_{11} + b_{11} < 0$
2. $a_{33} + d_{33} < 0$
3. $a_{22} < 0$, $a_{44} < 0$, $a_{55} < 0$, $a_{66} < 0$, $a_{77} < 0$, $a_{88} < 0$, $a_{99} < 0$, $a_{10,10} < 0$, $a_{11,11} < 0$, $a_{12,12} < 0$, $a_{13,13} < 0$

4.2. The Equilibrium Point E_2

Consider next $E_2 = (\hat{x}_1, \hat{x}_2, 0, 0, \hat{x}_5, \hat{x}_6, 0, \hat{x}_8, 0, 0, 0, \hat{x}_{12}, 0, \hat{x}_{14}, \hat{x}_{15})$ that can be interpreted as a healthy state, with undetectable leukemia cells and no allergic reactions.

The nonzero terms in the matrices of partial derivatives calculated this time in E_2 are to be found in the Appendix A. The matrix

$$\lambda I_{13} - A - Be^{-\lambda\tau_1} - Ce^{-\lambda\tau_2} - De^{-\lambda\tau_3} - Ee^{-\lambda\tau_4} - Ge^{-\lambda\tau_6} - He^{-\lambda\tau_7}$$

is block triangular, so its determinant factors as

$$\begin{aligned} d = &(\lambda - a_{55})(\lambda - a_{66})(\lambda - a_{77})(\lambda - a_{88})(\lambda - a_{99}) \\ &(\lambda - a_{10,10})(\lambda - a_{11,11})(\lambda - a_{12,12})(\lambda - a_{13,13} - h_{13,13}e^{-\lambda\tau_7}) \\ &(\lambda - a_{14,14})(\lambda - a_{15,15})d_1 \end{aligned}$$

with

$$\begin{aligned} d_1 &= (\lambda - a_{33} - d_{33}e^{-\lambda\tau_3})(\lambda - a_{44})\Big[(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})(\lambda - a_{22} - c_{22}e^{-\lambda\tau_2}) - (a_{12} + b_{12}e^{-\lambda\tau_1})c_{21}e^{-\lambda\tau_2}\Big]. \\ &= (\lambda - a_{33} - d_{33}e^{-\lambda\tau_3})(\lambda - a_{44})(P_0(\lambda) + P_1(\lambda)e^{-\lambda\tau_1} + P_2(\lambda)e^{-\lambda\tau_2} + P_3(\lambda)e^{-\lambda(\tau_1+\tau_2)}) \end{aligned}$$

where

$$P_0(\lambda) = \lambda^2 - (a_{22} + a_{11})\lambda + a_{22}a_{11} \tag{19}$$

$$P_1(\lambda) = a_{22}b_{11} - b_{11}\lambda \tag{20}$$

$$P_2(\lambda) = a_{11}c_{22} - a_{12}c_{21} \tag{21}$$

$$P_3(\lambda) = b_{11}c_{22} - b_{12}c_{21} \tag{22}$$

According to the already cited criterion from [23,24], since $a_{33} < 0, a_{13,13} < 0$, and $b_{33} > 0, h_{13,13} > 0$, E_2 is stable if:

1. $a_{33} + d_{33} < 0$
2. $a_{13,13} + h_{13,13} < 0$
3. $a_{44}, \ldots, a_{15,15} < 0$
4. The roots of $P_0(\lambda) + P_1(\lambda)e^{-\lambda\tau_1} + P_2(\lambda)e^{-\lambda\tau_2} + P_3(\lambda)e^{-\lambda(\tau_1+\tau_2)} = 0$ have negative real parts.

We now study the roots of

$$F(\lambda) = P_0(\lambda) + P_1(\lambda)e^{-\lambda\tau_1} + P_2(\lambda)e^{-\lambda\tau_2} + P_3(\lambda)e^{-\lambda(\tau_1+\tau_2)} = 0 \tag{23}$$

with the aim of establishing when they have a negative real part (see also [25]).

Suppose that for $\tau_1 = \tau_2 = 0$, the Equation (23) is stable. Then, stability can be lost if, and only if, the roots of (23) cross the imaginary axis from left to right, as the delays vary. This can happen only if pure imaginary roots can appear, so consider the equation $F(iw) = 0$, $w \in \mathbb{R}$. The Equation (23) becomes:

$$\begin{aligned} F(iw) = &-w^2 + (a_{22} + a_{11})iw + a_{22}a_{11} + a_{22}b_{11}e^{-iw\tau_1} - b_{11}iwe^{-iw\tau_1} \\ &+ a_{11}c_{22}e^{-iw\tau_2} - a_{12}c_{21}e^{-iw\tau_2} + b_{11}c_{22}e^{-iw(\tau_1+\tau_2)} - b_{12}c_{21}e^{-iw(\tau_1+\tau_2)} = 0 \end{aligned}$$

Now, we look for conditions under which $F(iw)$ has no real roots w. We will analyze the equation and see if there are any specific conditions on the coefficients and parameters that would prevent the existence of real roots.

To solve $F(iw) = 0$, express the exponential terms in trigonometric form:

$$\begin{aligned} e^{-iw\tau_1} &= \cos(w\tau_1) - i\sin(w\tau_1) \\ e^{-iw\tau_2} &= \cos(w\tau_2) - i\sin(w\tau_2) \\ e^{-iw(\tau_1+\tau_2)} &= \cos(w(\tau_1+\tau_2)) - i\sin(w(\tau_1+\tau_2)) \end{aligned}$$

Substituting these expressions back into $F(iw)$, we obtain:

$$F(iw) = -w^2 - (a_{22} + a_{11})iw + a_{22}a_{11} + a_{22}b_{11}\cos(w\tau_1) - ia_{22}b_{11}\sin(w\tau_1)$$
$$- ib_{11}w\cos(w\tau_1) + b_{11}w\sin(w\tau_1) + a_{11}c_{22}\cos(w\tau_2) - ia_{11}c_{22}\sin(w\tau_2)$$
$$- a_{12}c_{21}\cos(w\tau_2) + ia_{12}c_{21}\sin(w\tau_2) + b_{11}c_{22}\cos(w(\tau_1 + \tau_2)) - ib_{11}c_{22}\sin(w(\tau_1 + \tau_2))$$
$$- b_{12}c_{21}\cos(w(\tau_1 + \tau_2)) + ib_{12}c_{21}\sin(w(\tau_1 + \tau_2)) = 0$$

Separate the real and imaginary parts of $F(iw)$ and then square each of them, following the approach in [26].

Introduce the real and imaginary parts through $F(iw) = R(w) + iI(w)$, where $R(w)$ is the real part and $I(w)$ is the imaginary part. Then,

$$R(w)^2 = [-w^2 + a_{22}a_{11} + a_{22}b_{11}\cos(w\tau_1) + b_{11}w\sin(w\tau_1) + (a_{11}c_{22} - a_{12}c_{21})\cos(w\tau_2)$$
$$+ (b_{11}c_{22} - b_{12}c_{21})\cos(w(\tau_1 + \tau_2))]^2$$
$$I(w)^2 = [-w(a_{11} + a_{22}) - a_{22}b_{11}\sin(w\tau_1) - b_{11}w\cos(w\tau_1) + (a_{12}c_{21} - a_{11}c_{22})\sin(w\tau_2)$$
$$+ (b_{12}c_{21} - b_{11}c_{22})\sin(w(\tau_1 + \tau_2))]^2$$

Condition 4 is verified if the following equation has no positive roots.

$$R(w)^2 + I(w)^2 = 0$$

Concerning the stability for $\tau_1 = \tau_2 = 0$, one has

$$P_0(\lambda) + P_1(\lambda) + P_2(\lambda) + P_3(\lambda) = \lambda^2 - \lambda(a_{11} + a_{22} + b_{11}) + a_{11}a_{22} + a_{22}b_{11} + a_{11}c_{22} + b_{11}c_{22}$$
$$-a_{12}c_{21} - b_{12}c_{21} = \lambda^2 + p_1\lambda + p_2$$

and (23) is stable for $\tau_1 = \tau_2 = 0$ if, and only if, $p_1 > 0$ and $p_2 > 0$.

4.3. Equilibrium Point E_3

Another interesting equilibrium point is $E_3 = (\hat{x}_1, \hat{x}_2, 0, 0, \hat{x}_5, \hat{x}_6, 0, \hat{x}_8, 0, \hat{x}_{10}, \hat{x}_{11}, \hat{x}_{12}, 0, \hat{x}_{14}, \hat{x}_{15})$, which represents a successful cure but with the persistence of allergic reactions.

The nonzero terms in the matrices of partial derivatives calculated in E_3 are found in the Appendix A.

To study the stability of E_3, remark that the matrix

$$\lambda I_{13} - A - Be^{-\lambda\tau_1} - Ce^{-\lambda\tau_2} - De^{-\lambda\tau_3} - Ee^{-\lambda\tau_4} - Fe^{-\lambda\tau_5} - Ge^{-\lambda\tau_6} - He^{-\lambda\tau_7}$$

is block triangular, so its determinant factors as

$$d = (\lambda - a_{55})(\lambda - a_{66})(\lambda - a_{99})(\lambda - a_{12,12})(\lambda - a_{14,14})(\lambda - a_{15,15})(\lambda - a_{13,13} - h_{13,13}e^{-\lambda\tau_7})d_1d_2$$

$$d_1 = (\lambda - a_{33} - d_{33}e^{-\lambda\tau_3})(\lambda - a_{44})[(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})(\lambda - a_{22} - c_{22}e^{-\lambda\tau_2}) - (a_{12} + b_{12}e^{-\lambda\tau_1})c_{21}e^{-\lambda\tau_2}]$$

$$d_2 = (\lambda - a_{77})[(\lambda - a_{88})(\lambda - a_{10,10})(\lambda - a_{11,11}) - a_{11,8}a_{8,11}(\lambda - a_{10,10}) + a_{10,11}(\lambda - a_{88})(a_{13,10} + h_{13,10}e^{-\lambda\tau_7})]$$

Remark that

$$d_1 = (\lambda - a_{33} - d_{33}e^{-\lambda\tau_3})(\lambda - a_{44})(P_0(\lambda) + P_1(\lambda)e^{-\lambda\tau_1} + P_2(\lambda)e^{-\lambda\tau_2} + P_3(\lambda)e^{-\lambda(\tau_1+\tau_2)})$$

with P_0, P_1, P_2, and P_3 defined in (19)–(22).

Also

$$\begin{aligned} d_2 &= (\lambda - a_{77})[\lambda^3 - (a_{10,10} + a_{11,11} + a_{88})\lambda^2 \\ &\quad + \lambda(a_{10,10}a_{11,11} + a_{88}a_{10,10} + a_{88}a_{11,11}) - a_{88}a_{10,10}a_{11,11} \\ &\quad - a_{11,8}a_{8,11}\lambda + a_{8,11}a_{10,10}a_{11,8} \\ &\quad + \lambda a_{13,10}a_{10,11} + \lambda h_{13,10}a_{10,11}e^{-\lambda\tau_7} - a_{10,11}a_{88}a_{13,10} - a_{88}a_{10,11}h_{13,10}e^{-\lambda\tau_7}] \\ &= (\lambda - a_{77})[Q_0(\lambda) + Q_1(\lambda)e^{-\lambda\tau_7}] \end{aligned} \tag{24}$$

with

$$\begin{aligned} Q_0(\lambda) &= \lambda^3 - (a_{10,10} + a_{11,11} + a_{88})\lambda^2 + \lambda(a_{10,10}a_{11,11} + a_{88}a_{10,10} + a_{88}a_{11,11} - a_{11,8}a_{8,11} + a_{13,10}a_{10,11}) \\ &\quad - a_{88}a_{10,10}a_{11,11} - a_{10,11}a_{88}a_{13,10} + a_{8,11}a_{10,10}a_{11,8} \\ Q_1(\lambda) &= \lambda h_{13,10}a_{10,11} - a_{88}a_{10,11}h_{13,10} \end{aligned} \tag{25}$$

Once again, since $a_{33} < 0, a_{13,13} < 0, b_{33} > 0, h_{13,13} > 0$, E_3 is stable if:

1. $a_{33} + d_{33} < 0$
2. a_{44}, a_{55}, a_{66}, a_{77}, a_{99}, $a_{12,12}$, $a_{14,14}$, $a_{15,15} < 0$
3. The roots of $P_0(\lambda) + P_1(\lambda)e^{-\lambda\tau_1} + P_2(\lambda)e^{-\lambda\tau_2} + P_3(\lambda)e^{-\lambda(\tau_1+\tau_2)} = 0$ have negative real parts
4. $a_{13,13} + h_{13,13} < 0$
5. The roots of $Q_0(\lambda) + Q_1(\lambda)e^{-\lambda\tau_7} = 0$ have negative real parts

The study of the roots of

$$F(\lambda) = P_0(\lambda) + P_1(\lambda)e^{-\lambda\tau_1} + P_2(\lambda)e^{-\lambda\tau_2} + P_3(\lambda)e^{-\lambda(\tau_1+\tau_2)} = 0 \tag{26}$$

is already performed for the study of the stability of E_2.

The analysis of condition 5 parallels the approach taken from Theorem 1 in [26] that we briefly recall.

Consider the equation $Q_0(\lambda) + Q_1(\lambda)e^{-\lambda\tau_7} = 0$, where Q_0 and Q_1 are analytic functions in the right half-plane Re$z > -\delta, \delta > 0$, which satisfy the following conditions:

1. $Q_0(z)$ and $Q_1(z)$ have no common imaginary zero.
2. $\overline{Q_0(-iy)} = Q_0(iy), \overline{Q_1(-iy)} = Q_1(iy)$, for real y (the upper bar denotes complex conjugate).
3. $Q_0(0) + Q_1(0) \neq 0$.
4. There are at most a finite number of roots of $Q_0(\lambda) + Q_1(\lambda)e^{-\lambda\tau_7} = 0$ in the right half-plane when $\tau_7 = 0$.
5. $F(y) \equiv |Q_0(iy)|^2 - |Q_1(iy)|^2$, for real y, has at most a finite number of real zeroes.

It is evident that the above conditions are verified in our setting.

Under these conditions, the following statements are true:

(a) Suppose that the equation $F(y) = 0$ has no positive roots. Then, if $Q_0(\lambda) + Q_1(\lambda)e^{-\lambda\tau_7} = 0$ is stable at $\tau_7 = 0$, it remains stable for all $\tau_7 \geq 0$, and if it is unstable at $\tau_7 = 0$, it remains unstable for all $\tau_7 \geq 0$.

(b) Suppose that the equation $F(y) = 0$ has at least one positive root and that each positive root is simple. As τ_7 increases, stability switches may occur. There exists a positive number τ_7^* such that the equation $Q_0(\lambda) + Q_1(\lambda)e^{-\lambda\tau_7} = 0$ is unstable for all $\tau_7 > \tau_7^*$. As τ_7 varies from 0 to τ_7^*, at most, a finite number of stability switches may occur.

In what follows, the condition for $F(y) \equiv |Q_0(iy)|^2 - |Q_1(iy)|^2 = 0$ to have no positive roots will be studied. Q_0 and Q_1 are given in (25).

We need to evaluate $|Q_0(iy)|, |Q_1(iy)|$, square them, and ensure that $F(y)$ remains non-positive for all positive y. Thus, we need to analyze the expression:

$$\begin{aligned} F(y) &= |Q_0(iy)|^2 - |Q_1(iy)|^2 \\ &= |Q_0(iy) + Q_1(iy)||Q_0(iy) - Q_1(iy)| \end{aligned}$$

After simplification, the condition for $F(y) = 0$:

$$\begin{aligned} &|Q_0(iy) + Q_1(iy)||Q_0(iy) - Q_1(iy)| = 0 \\ &\text{or} \\ &(Q_0(iy) + Q_1(iy))(Q_0(iy) - Q_1(iy)) = 0 \end{aligned}$$

This condition ensures that either $Q_0(iy) + Q_1(iy) = 0$ or $Q_0(iy) - Q_1(iy) = 0$ for all positive y.

We can expand these expressions:

$$\begin{aligned} &Q_0(iy) + Q_1(iy) = 0 \\ &\Rightarrow -iy^3 + (a_{10,10} + a_{11,11} + a_{88})y^2 \\ &\quad + iy[a_{10,10}a_{11,11} + a_{88}(a_{10,10} + a_{11,11}) - a_{11,8}a_{8,11} + a_{13,10}a_{10,11} + h_{13,10}a_{10,11}] \\ &\quad - a_{88}a_{10,10}a_{11,11} - a_{10,11}a_{88}a_{13,10} \\ &\quad + a_{8,11}a_{10,10}a_{11,8} - a_{88}a_{10,11}h_{13,10} = 0 \end{aligned}$$

and

$$\begin{aligned} &Q_0(iy) - Q_1(iy) = 0 \\ &\Rightarrow -iy^3 + (a_{10,10} + a_{11,11} + a_{88})y^2 \\ &\quad + iy[a_{10,10}a_{11,11} + a_{88}(a_{10,10} + a_{11,11}) - a_{11,8}a_{8,11} + a_{13,10}a_{10,11}] \\ &\quad - a_{88}a_{10,10}a_{11,11} - a_{10,11}a_{88}a_{13,10} \\ &\quad + a_{8,11}a_{10,10}a_{11,8} - (iyh_{13,10}a_{10,11} - a_{88}a_{10,11}h_{13,10}) = 0 \end{aligned}$$

The first equation, $Q_0(iy) + Q_1(iy) = 0$, becomes:

$$\begin{aligned} &(a_{10,10} + a_{11,11} + a_{88})y^2 - a_{10,11}a_{88}a_{13,10} + a_{8,11}a_{10,10}a_{11,8} - a_{88}a_{10,10}a_{11,11} - a_{88}a_{10,11}h_{13,10} \\ &\quad + i\Big\{y[a_{10,10}a_{11,11} + a_{88}(a_{10,10} + a_{11,11}) - a_{11,8}a_{8,11} + a_{13,10}a_{10,11} + h_{13,10}a_{10,11}] - y^3\Big\} = 0 \end{aligned}$$

To find the conditions such that the equation in y has no positive roots for the given complex equation, we need to analyze both the real and imaginary parts separately.

Real Part: The real part of the equation is:

$$(a_{10,10} + a_{11,11} + a_{88})y^2 - a_{10,11}a_{88}a_{13,10} + a_{8,11}a_{10,10}a_{11,8} - a_{88}a_{10,10}a_{11,11} - a_{88}a_{10,11}h_{13,10} = 0$$

For this quadratic equation, the condition to have no positive roots follows easily.

Imaginary Part: Set the imaginary part equal to zero:

$$y[a_{10,10}a_{11,11} + a_{88}(a_{10,10} + a_{11,11}) - a_{11,8}a_{8,11} + a_{13,10}a_{10,11} + h_{13,10}a_{10,11}] - y^3 = 0$$

Introduce $C_1 = a_{10,10}a_{11,11} + a_{88}(a_{10,10} + a_{11,11}) - a_{11,8}a_{8,11} + a_{13,10}a_{10,11} + h_{13,10}a_{10,11}$. If $C_1 < 0$ there are no positive roots of the imaginary part.

The second equation, $Q_0(iy) - Q_1(iy) = 0$, becomes:

$$\begin{aligned} &(a_{10,10} + a_{11,11} + a_{88})y^2 - a_{10,11}a_{88}a_{13,10} + a_{8,11}a_{10,10}a_{11,8} \\ &\quad - a_{88}a_{10,10}a_{11,11} + a_{88}a_{10,11}h_{13,10} \\ &\quad + i\Big\{y[a_{10,10}a_{11,11} + a_{88}(a_{10,10} + a_{11,11}) - a_{11,8}a_{8,11} + a_{13,10}a_{10,11} - h_{13,10}a_{10,11}] - y^3\Big\} = 0 \end{aligned}$$

To find the conditions such that the equation in y has no positive roots for the given complex equation, we need to analyze both the real and imaginary parts separately.

Real Part: The real part of the equation is:

$$(a_{10,10} + a_{11,11} + a_{88})y^2 - a_{10,11}a_{88}a_{13,10} + a_{8,11}a_{10,10}a_{11,8} - a_{88}a_{10,10}a_{11,11} + a_{88}a_{10,11}h_{13,10} = 0$$

For this quadratic equation, the condition to have no positive roots follows easily.

Imaginary Part: Set the imaginary part equal to zero:

$$y[a_{10,10}a_{11,11} + a_{88}(a_{10,10} + a_{11,11}) - a_{11,8}a_{8,11} + a_{13,10}a_{10,11} - h_{13,10}a_{10,11}] - y^3 = 0$$

Let us denote the coefficient term C_2 as:

$$C_2 = a_{10,10}a_{11,11} + a_{88}(a_{10,10} + a_{11,11}) - a_{11,8}a_{8,11} + a_{13,10}a_{10,11} - h_{13,10}a_{10,11}$$

So, the equation becomes:

$$-C_2 y + y^3 = 0$$

For the given cubic equation $-C_2 y + y^3 = 0$, there are no positive roots if $C_2 < 0$.

For $\tau_7 = 0$, $Q_0(\lambda) + Q_1(\lambda) = \lambda^3 + p_1\lambda^2 + p_2\lambda + p_3$. This will be a stable polynomial if, and only if, $p_1 > 0, p_2 > 0, p_3 > 0, p_1p_2 > p_3$ (the Routh–Hurwitz criterion).

4.4. Equilibrium Point E_4

The next equilibrium point, $E_4 = (\tilde{x}_1, \tilde{x}_2, 0, 0, \tilde{x}_5, \tilde{x}_6, 0, \tilde{x}_8, \tilde{x}_9, 0, \tilde{x}_{11}, \tilde{x}_{12}, 0, \tilde{x}_{14}, \tilde{x}_{15})$, represents a successful cure without allergic reactions. The conditions for its existence are listed in the Appendix A, together with the expressions of its components.

The nonzero terms in the matrices of partial derivatives calculated in E_4 are provided in Appendix A.

The determinant of the matrix

$$\lambda I_{13} - A - Be^{-\lambda\tau_1} - Ce^{-\lambda\tau_2} - De^{-\lambda\tau_3} - Ee^{-\lambda\tau_4} - Fe^{-\lambda\tau_5} - Ge^{-\lambda\tau_6} - He^{-\lambda\tau_7}$$

factors as

$$\begin{aligned} d = {} & (\lambda - a_{44})(\lambda - a_{55})(\lambda - a_{66})(\lambda - a_{77})(\lambda - a_{99})(\lambda - a_{10,10})(\lambda - a_{12,12}) \\ & (\lambda - a_{13,13} - h_{13,13}e^{-\lambda\tau_7})(\lambda - a_{14,14})(\lambda - a_{15,15})(\lambda - a_{33} - d_{33}e^{-\lambda\tau_3}) \\ & [(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})(\lambda - a_{22} - c_{22}e^{-\lambda\tau_2}) - (a_{12} + b_{12}e^{-\lambda\tau_1})c_{21}e^{-\lambda\tau_2}] \\ & [(\lambda - a_{88})(\lambda - a_{11,11}) - a_{8,11}a_{11,8}] \end{aligned}$$

Since in this case we also have $a_{33} < 0$, $b_{33} > 0$, $a_{13,13} < 0$, and $h_{13,13} > 0$, E_4 is stable if:

1. $a_{33} + d_{33} < 0$
2. $a_{13,13} + h_{13,13} < 0$
3. a_{44}, a_{55}, a_{66}, a_{77}, a_{99}, $a_{10,10}$, $a_{12,12}, a_{14,14}$, $a_{15,15} < 0$
4. The following equation has negative roots

$$(\lambda - a_{88})(\lambda - a_{11,11}) - a_{8,11}a_{11,8} = \lambda^2 - (a_{11,11} + a_{88})\lambda + a_{88}a_{11,11} - a_{8,11}a_{11,8}$$

i.e.,

$$a_{11,11} + a_{88} > 0 \text{ and } a_{88}a_{11,11} - a_{8,11}a_{11,8} > 0$$

5. The roots of

$$d_1 = [(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})(\lambda - a_{22} - c_{22}e^{-\lambda\tau_2}) - (a_{12} + b_{12}e^{-\lambda\tau_1})c_{21}e^{-\lambda\tau_2}]$$

have negative real parts.

For condition 5, we write d_1 as follows:

$$d_1 = P_0(\lambda) + P_1(\lambda)e^{-\lambda\tau_1} + P_2(\lambda)e^{-\lambda\tau_2} + P_3(\lambda)e^{-\lambda(\tau_1+\tau_2)} = 0$$

and use the analysis conducted for E_2.

5. Parameters Values, Numerical Calculations, and Simulations

The following parameters are taken mainly from [2,6,9,19], some of them being just estimated, especially for leukemia cells.

The production rate of naive CD4+ cells [19]	α	0.1
The strength of suppression rate of Th1 by Th2 [14]	m_2	0.1
The strength of suppression of Th2 by Th1 [14]	m_1	0.2
The strength of suppression rate by Treg [14]	m_r	0.5
The differences in the autocrine action of the three subsets [14]	p	0.05
The differences in the autocrine action of the three subsets [14]	κ	0.1
The death rate of *Th*1 cells [27]	β_2	$10^{-3}\ \mathrm{h}^{-1} = 0.0416 * 10^{-3}\ \mathrm{day}^{-1}$
The death rate of *Th*2 cells [27]	β_3	$10^{-3}\ \mathrm{h}^{-1} = 0.0416 * 10^{-3}\ \mathrm{day}^{-1}$
The death rate of *Treg* cells [27]	β_4	$10^{-3}\ \mathrm{h}^{-1} = 0.0416 * 10^{-3}\ \mathrm{day}^{-1}$
The proliferation rate of stimulated T cells [14]	γ_1	0.2
Time delay [22]	τ_5	0.0794
Initial number of immune cells [28]	φ_{13}	$7 * 10^5$ cells day^{-1} = 0.1 cells day^{-1} in microliter

5.1. *Numerical Simulations and Computations for* E_1

A numerical study of the conditions of stability for the equilibrium point E_1, based on the above-given parameters, gives the following:

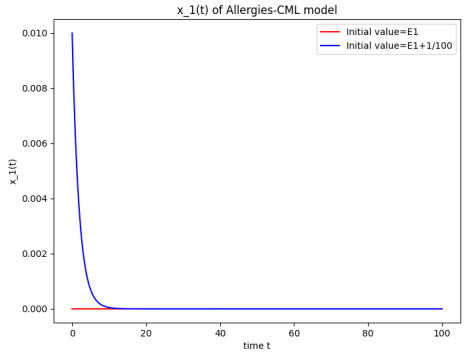
$$a_{11} + b_{11} = 0.6911$$

Recall that, in order for equilibrium point E_1 to be stable, the first condition is that $a_{11} + b_{11} < 0$. The numerical computations show that this condition does not hold. We conclude that this equilibrium point is not stable.

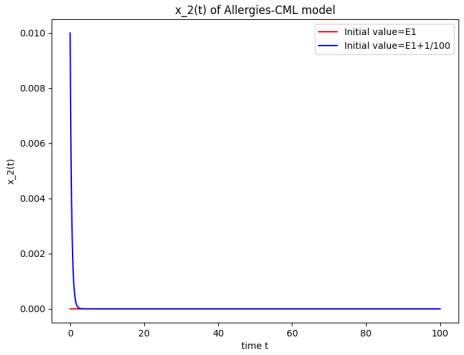
This result can also be seen in the numerical simulations below in Figure 1. Although the simulations start with the same concentration for Th1 cells and Th2 cells, the evolution shows an immunological destabilization, as the concentration of Th2 cells is greater than that of Th1 cells.

Parameter for the β function for healthy cells	β_{0h}	1.77
Parameter for the β function for leukemia cells	β_{0l}	2
Parameter for the function k for healthy cells	k_{0h}	0.1
Parameter for the function k for leukemia cells	k_{0l}	0.4
The maximum value of the β function for leukemic cells	θ_{1l}	0.5
The maximum value of the β function for healthy cells	θ_{1h}	0.5
The maximum value of the function k for leukemic cells	θ_{2l}	36
The maximum value of the function k for healthy cells	θ_{2h}	36
Parameter of the Hill function β_h	m_h	2
Parameter of the Hill function k_h	n_h	2
Parameter of the Hill function β_l	m_l	2
Parameter of the Hill function k_l	n_l	2
Loss of stem cells due to mortality and differentiation in other lines for leukemic cells	γ_{1l}	0.04
Loss of stem cells due to mortality and differentiation in other lines for healthy cells [2]	γ_{1h}	0.1
Rate of asymmetric division for leukemic cells	η_{1l}	0.1
Rate of asymmetric division for healthy cells	η_{1h}	0.7
Rate of symmetric division for leukemic cells	η_{2l}	0.7
Rate of symmetric division for healthy cells	η_{2h}	0.1
Loss of stem cells due to cytotoxic T cells	b_1	0.03
Instant mortality of mature leukemic leukocytes	γ_{2l}	1.2, 0.15
Instant mortality of mature normal leukocytes	γ_{2h}	2.4
Amplification factor for leukemic leukocytes	A_l	1400
Amplification factor for normal leukocytes [2]	A_h	1200
Loss of mature leukocytes due to cytotoxic T cells	b_2	0.6
Standard half-saturation in a Michaelis–Menten low	b_3	6
Supply rate of immature APCs	c_1	0.3/day
Death/turnover rate of immature APCs	c_2	0.03/day
Coefficient of the activation due to imatinib	c_3	1
Coefficient of the activation due to leukemia cells	c_4	2
Death/turnover rate of mature APCs	d_1	0.8/day
Supply rate of naive T cells CD4+ phenotype	Λ_1	2
Death/turnover rate of naive CD4+ cells	β_1	0.03/day
Death/turnover rate of effector CD4+ T helper cells	e_1	0.23/day
Supply rate of naive T cells CD8+ phenotype	Λ_2	2
Death/turnover rate of naive CD8+ cells	a_1	0.23/day
Kinetic coefficient	η_1	0.2
Coefficient of the positive growth signal [19]	η_2	20
The number of antigen depending divisions	n_1	6
Coefficient of inhibition due to Treg cells	a_2	1
Coefficient of inhibition due to leukemic cells	a_3	1.2 or 50
Number of divisions in minimal CD8+ developmental program	m	4
First-order absorbtion rate	λ_0	0.61 h^{-1}
Dose of administrated drug	K	0.2824 $\mu M\ h^{-1}$
Clearance rate	ν	0.0412 h^{-1}
Duration of cell cycle for leukemia stem-like cells	τ_3	5.5
Duration of cell cycle for normal stem-like cells	τ_1	2.8
Duration of leukocyte cycle for leukemic cells	τ_4	5.4
Duration of leukocyte cycle for normal cells	τ_2	3.5
Duration of one CD4+ T cell division (bifurcation parameter)	τ_5	2.4 days
Duration of one CD8+ T cell division	τ_T	1.4 days
Duration of minimal developmental program,	$\tau_6 = 4\tau_T$	5.6
Duration of minimal developmental program,	$\tau_7 = 6\tau_T$	8.4

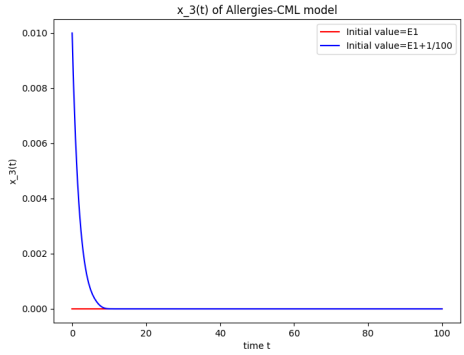
Furthermore, the simulations do not show a promising evolution of the patient's condition, as both the healthy and the leukemic cells decrease to zero.



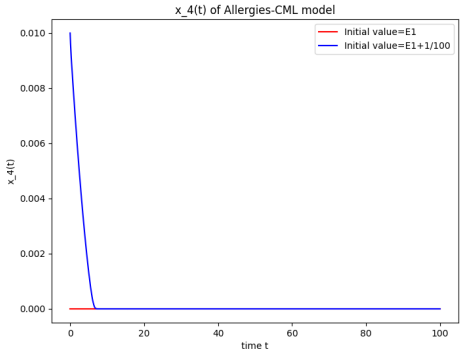
(**a**)



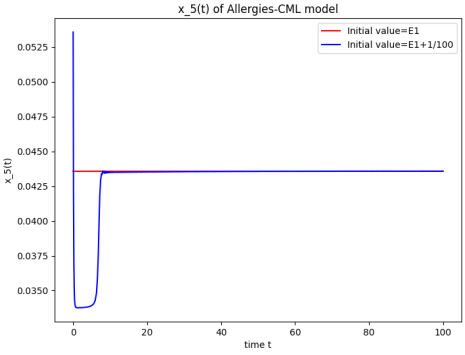
(**b**)



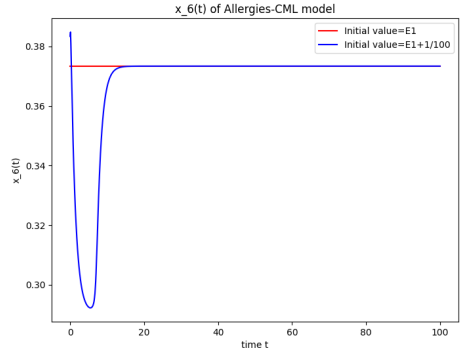
(**c**)



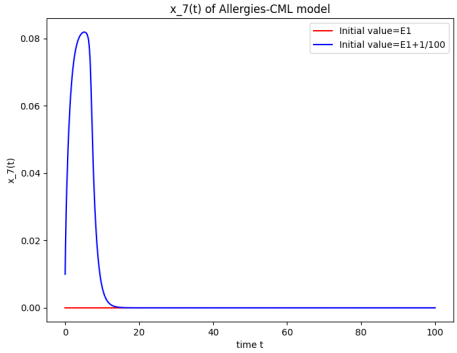
(**d**)



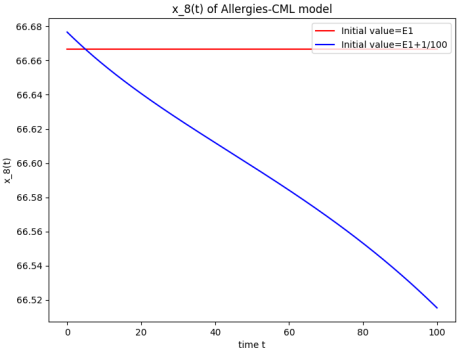
(**e**)



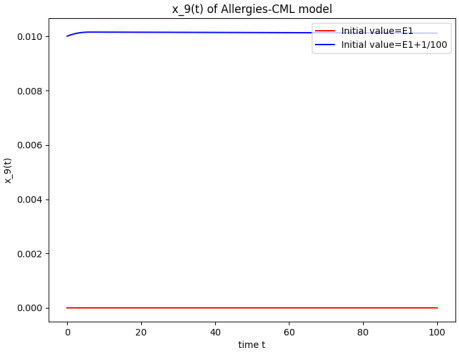
(**f**)


x_7(t) of Allergies-CML model
Initial value=E1
Initial value=E1+1/100
x_7(t)
time t

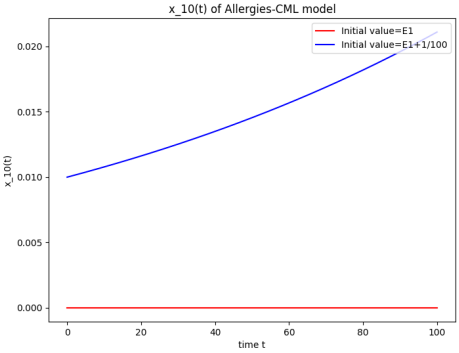
(g)


x_8(t) of Allergies-CML model
Initial value=E1
Initial value=E1+1/100
x_8(t)
time t

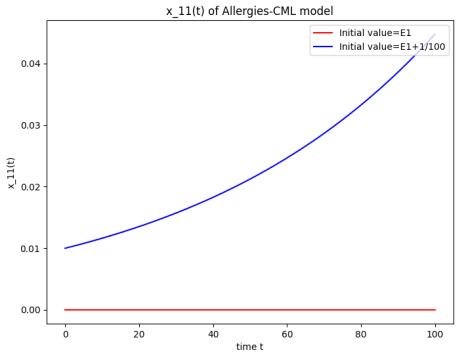
(h)


x_9(t) of Allergies-CML model
Initial value=E1
Initial value=E1+1/100
x_9(t)
time t

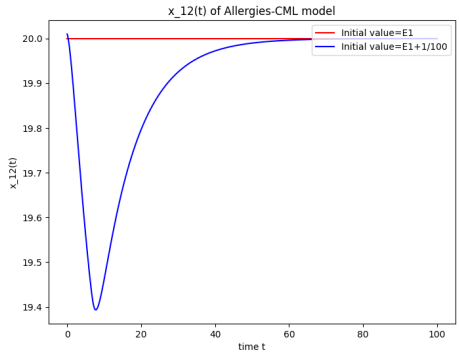
(i)


x_10(t) of Allergies-CML model
Initial value=E1
Initial value=E1+1/100
x_10(t)
time t

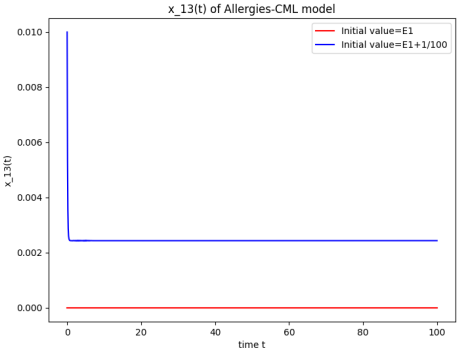
(j)


x_11(t) of Allergies-CML model
Initial value=E1
Initial value=E1+1/100
x_11(t)
time t

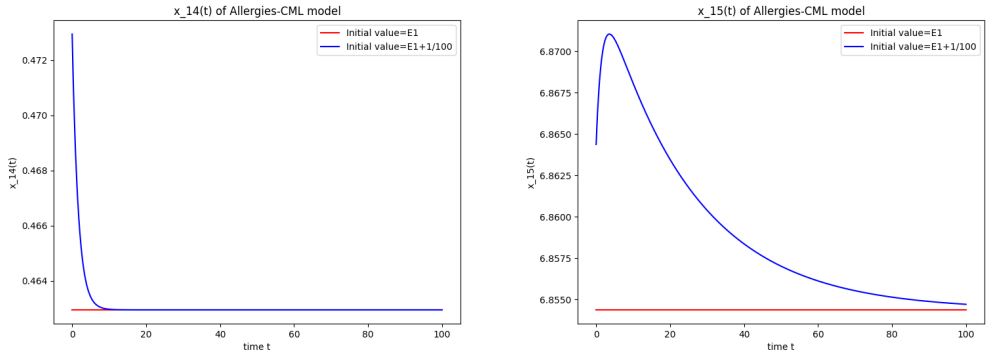
(k)


x_12(t) of Allergies-CML model
Initial value=E1
Initial value=E1+1/100
x_12(t)
time t

(l)


x_13(t) of Allergies-CML model
Initial value=E1
Initial value=E1+1/100
x_13(t)
time t

(m)



(**n**) (**o**)

Figure 1. Stability around the equilibrium point E_1. (**a**) The concentration of stem-like healthy cells around E_1. (**b**) The concentration of mature healthy cells around E_1. (**c**) The concentration of stem-like leukemic cells around E_1. (**d**) The concentration of mature leukemic cells around E_1. (**e**) The concentration of naive APCs around E_1. (**f**) The concentration of mature APCs activated by the drug around E_1. (**g**) The concentration of mature APCs activated by the leukemic cells around E_1. (**h**) The concentration of naive CD4+ T cells around E_1. (**i**) The concentration of Th1 cells around E_1. (**j**) The concentration of Th2 cells around E_1. (**k**) The concentration of Treg cells around E_1. (**l**) The concentration of naive CD8+ T cells around E_1. (**m**) The concentration of mature CD8+ T cells around E_1. (**n**) The amount of drug in the absorbtion compartment around E_1. (**o**) The amount of drug in the plasmatic compartment around E_1.

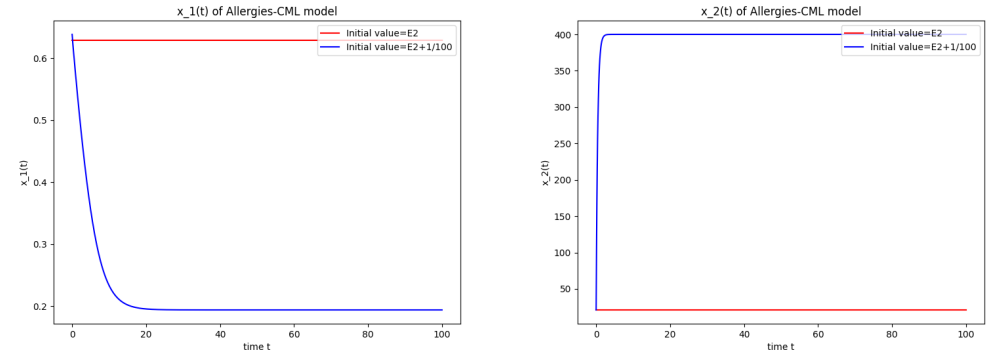
5.2. Numerical Simulations and Computations for E_2

The equilibrium point E_2 is stable if:

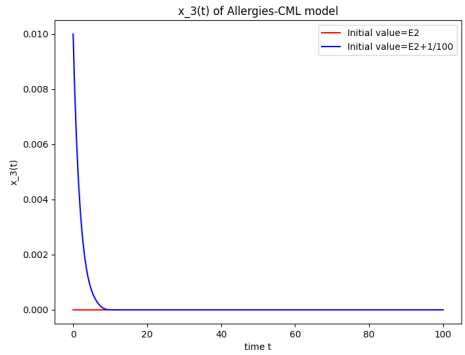
1. $a_{33} + d_{33} < 0$
2. $a_{13,13} + h_{13,13} < 0$
3. $a_{44}, \ldots, a_{15,15} < 0$
4. The roots of $P_0(\lambda) + P_1(\lambda)e^{-\lambda\tau_1} + P_2(\lambda)e^{-\lambda\tau_2} + P_3(\lambda)e^{-\lambda(\tau_1+\tau_2)} = 0$ have negative real parts.

Numerical computations show that $a_{13,13} + h_{13,13} = 521.736225 > 0$. Therefore, E_2 is not stable.

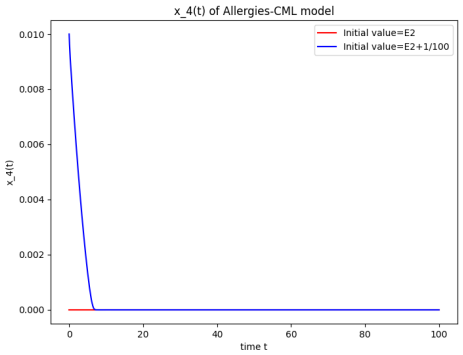
The numerical simulations performed around the equilibrium point E_2 indicate instability, validating the computations (Figure 2). It remains a healthy evolution, as the leukemic cells reduce to undetectable values and the healthy cells are attracted to a positive state. The balance of Th1–Th2 cells is towards Th2, so there are allergic reactions present.



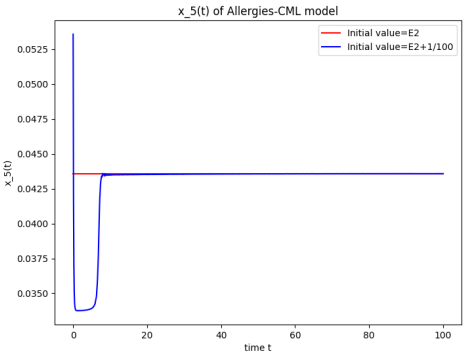
(**a**) (**b**)


x_3(t) of Allergies-CML model
Initial value=E2
Initial value=E2+1/100
x_3(t)
time t

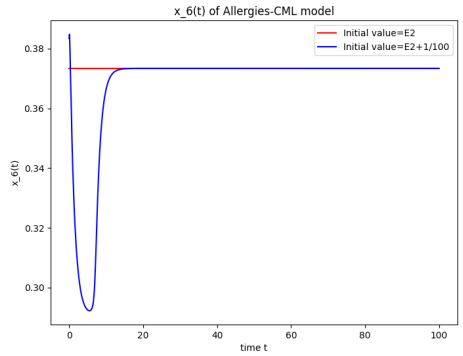
(**c**)


x_4(t) of Allergies-CML model
Initial value=E2
Initial value=E2+1/100
x_4(t)
time t

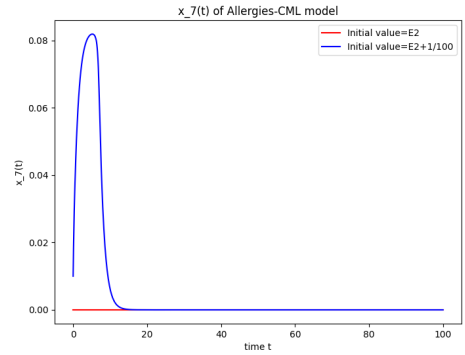
(**d**)


x_5(t) of Allergies-CML model
Initial value=E2
Initial value=E2+1/100
x_5(t)
time t

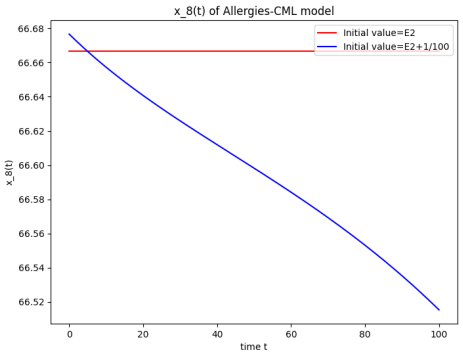
(**e**)


x_6(t) of Allergies-CML model
Initial value=E2
Initial value=E2+1/100
x_6(t)
time t

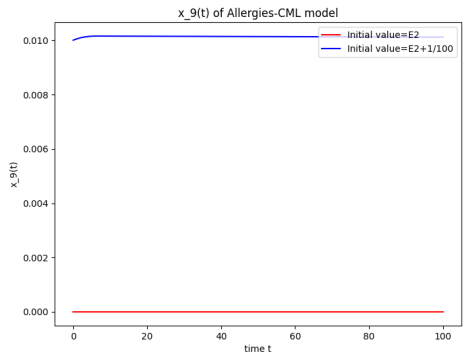
(**f**)


x_7(t) of Allergies-CML model
Initial value=E2
Initial value=E2+1/100
x_7(t)
time t

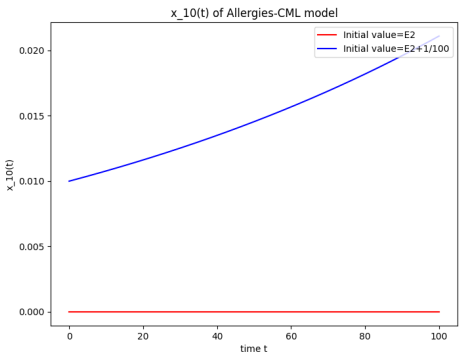
(**g**)


x_8(t) of Allergies-CML model
Initial value=E2
Initial value=E2+1/100
x_8(t)
time t

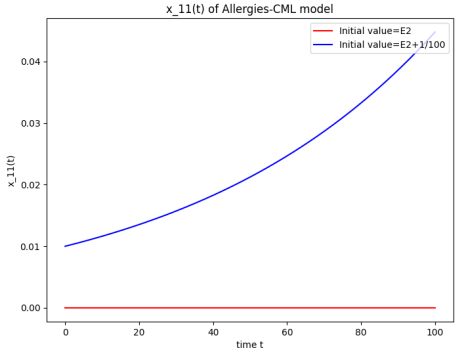
(**h**)


x_9(t) of Allergies-CML model
Initial value=E2
Initial value=E2+1/100
x_9(t)
time t

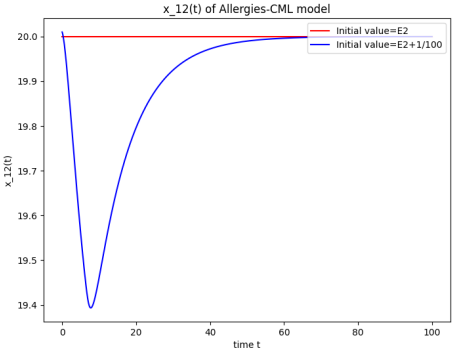
(**i**)


x_10(t) of Allergies-CML model
Initial value=E2
Initial value=E2+1/100
x_10(t)
time t

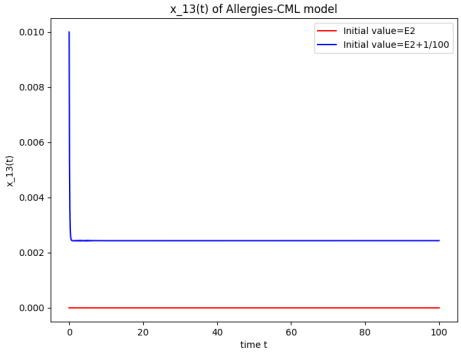
(**j**)



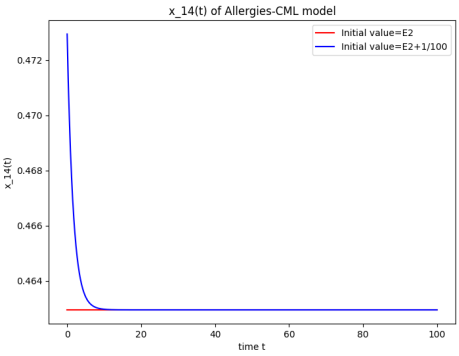
(**k**)



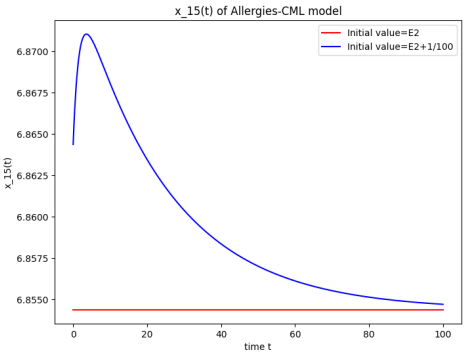
(**l**)



(**m**)



(**n**)



(**o**)

Figure 2. Stability around the equilibrium point E_2. (**a**) The concentration of stem-like healthy cells around E_2. (**b**) The concentration of mature healthy cells around E_2. (**c**) The concentration of stem-like leukemic cells around E_2. (**d**) The concentration of mature leukemic cells around E_2. (**e**) The concentration of naive APCs around E_2. (**f**) The concentration of mature APCs activated by the drug around E_2. (**g**) The concentration of mature APCs activated by the leukemic cells around E_2. (**h**) The concentration of naive CD4+ T cells around E_2. (**i**) The concentration of Th1 cells around E_2. (**j**) The concentration of Th2 cells around E_2. (**k**) The concentration of Treg cells around E_2. (**l**) The concentration of naive CD8+ T cells around E_2. (**m**) The concentration of mature CD8+ T cells around E_2. (**n**) The amount of drug in the absorbtion compartment around E_2. (**o**) The amount of drug in the plasmatic compartment around E_2.

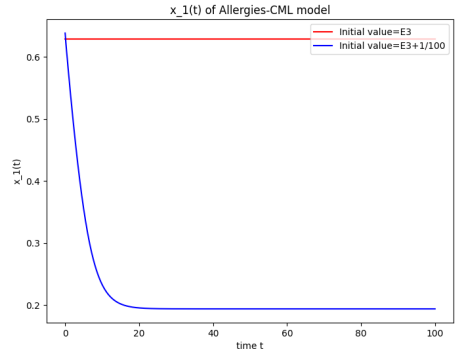
5.3. Numerical Simulations and Computations for E_3

The equilibrium point E_3 is stable if the following parameter conditions hold:

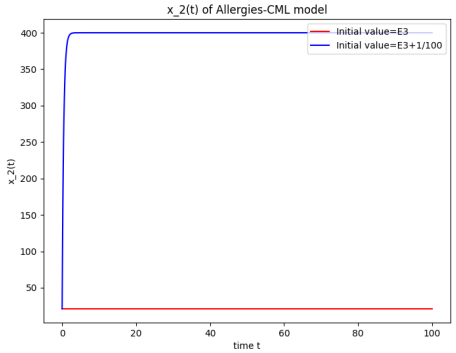
1. $a_{33} + d_{33} < 0$
2. a_{55}, a_{66}, a_{77}, a_{99}, $a_{12,12} < 0$
3. The roots of $P_0(\lambda) + P_1(\lambda)e^{-\lambda\tau_1} + P_2(\lambda)e^{-\lambda\tau_2} + P_3(\lambda)e^{-\lambda(\tau_1+\tau_2)} = 0$ have negative real parts
4. $a_{13,13} + h_{13,13} < 0$
5. The roots of $Q_0(\lambda) + Q_1(\lambda)e^{-\lambda\tau_7} = 0$ have negative real parts

According to the numerical calculations, $a_{99} = 0.0001378815942 > 0$. Therefore, E_3 is not stable.

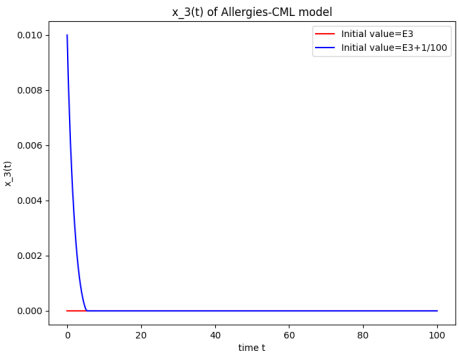
The numerical simulations performed around the equilibrium point E_3 also seem to indicate instability (Figure 3). It has a positive evolution, as the leukemic cells die out and the concentration of Th1 cells shows rapid growth. The allergic reactions are still present due to the large concentration of Th2 cells, which greatly outnumber the Th1 cells.



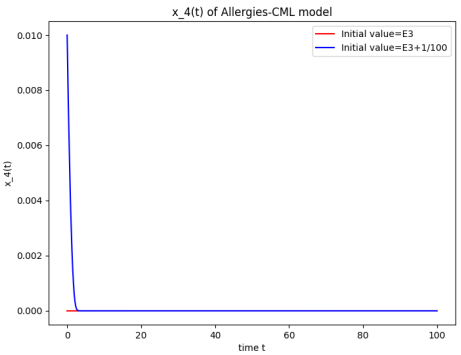
(**a**)



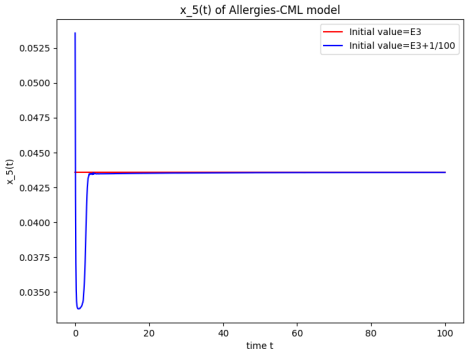
(**b**)



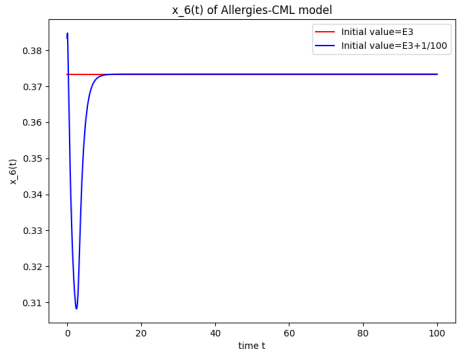
(**c**)



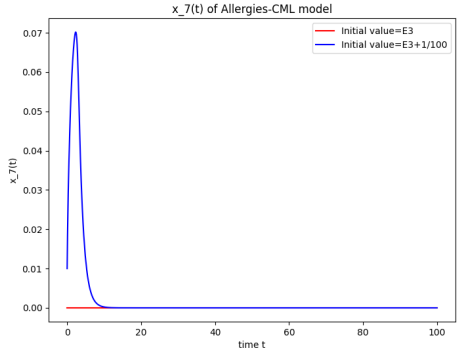
(**d**)



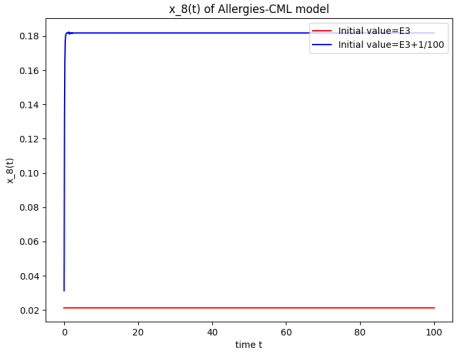
(**e**)



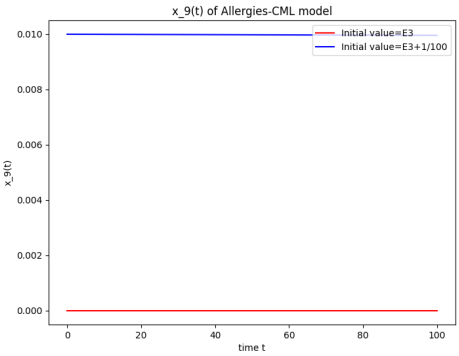
(**f**)


x_7(t) of Allergies-CML model
Initial value=E3
Initial value=E3+1/100
x_7(t)
time t

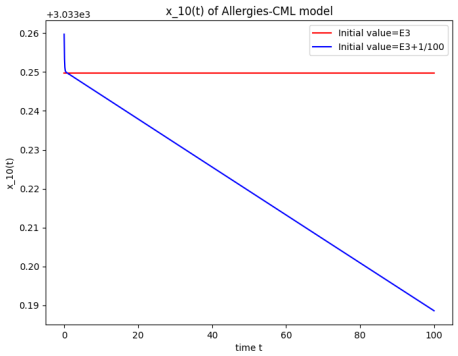
(g)


x_8(t) of Allergies-CML model
Initial value=E3
Initial value=E3+1/100
x_8(t)
time t

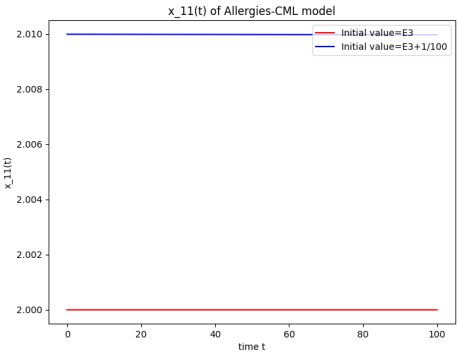
(h)


x_9(t) of Allergies-CML model
Initial value=E3
Initial value=E3+1/100
x_9(t)
time t

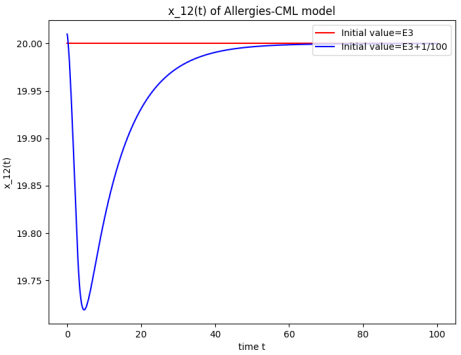
(i)


+3.033e3
x_10(t) of Allergies-CML model
Initial value=E3
Initial value=E3+1/100
x_10(t)
time t

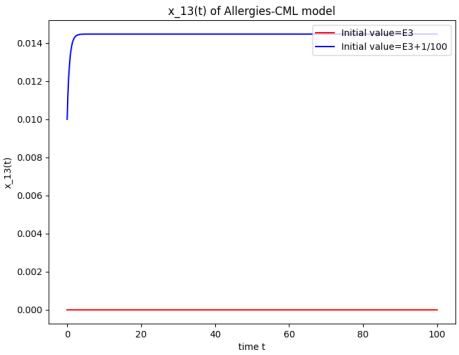
(j)


x_11(t) of Allergies-CML model
Initial value=E3
Initial value=E3+1/100
x_11(t)
time t

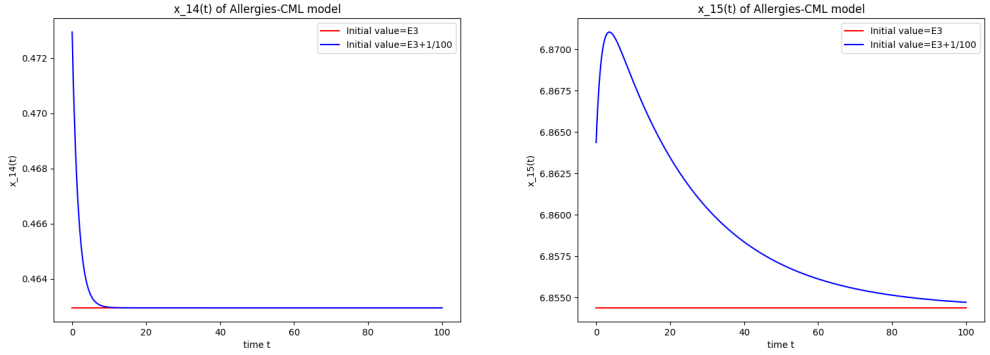
(k)


x_12(t) of Allergies-CML model
Initial value=E3
Initial value=E3+1/100
x_12(t)
time t

(l)


x_13(t) of Allergies-CML model
Initial value=E3
Initial value=E3+1/100
x_13(t)
time t

(m)



(**n**) (**o**)

Figure 3. Stability around the equilibrium point E_3. (**a**) The concentration of stem-like healthy cells around E_3. (**b**) The concentration of mature healthy cells around E_3. (**c**) The concentration of stem-like leukemic cells around E_3. (**d**) The concentration of mature leukemic cells around E_3. (**e**) The concentration of naive APCs around E_3. (**f**) The concentration of mature APCs activated by the drug around E_3. (**g**) The concentration of mature APCs activated by the leukemic cells around E_3. (**h**) The concentration of naive CD4+ T cells around E_3. (**i**) The concentration of Th1 cells around E_3. (**j**) The concentration of Th2 cells around E_3. (**k**) The concentration of Treg cells around E_3. (**l**) The concentration of naive CD8+ T cells around E_3. (**m**) The concentration of mature CD8+ T cells around E_3. (**n**) The amount of drug in the absorbtion compartment around E_3. (**o**) The amount of drug in the plasmatic compartment around E_3.

5.4. Numerical Simulations and Computations for E_4

The equilibrium point E_4 is stable if:

1. $a_{33} + d_{33} < 0$
2. $a_{44}, \ldots, a_{13,13} < 0$
3. The following equation has negative roots

$$\begin{aligned}&(\lambda - a_{88})(\lambda - a_{11,11}) - a_{8,11}a_{11,8}\\ &= \lambda^2 - (a_{11,11} + a_{88})\lambda + a_{88}a_{11,11} - a_{8,11}a_{11,8}\end{aligned}$$

i.e.,

$$a_{11,11} + a_{88} > 0 \quad \text{and} \quad a_{88}a_{11,11} - a_{8,11}a_{11,8} > 0$$

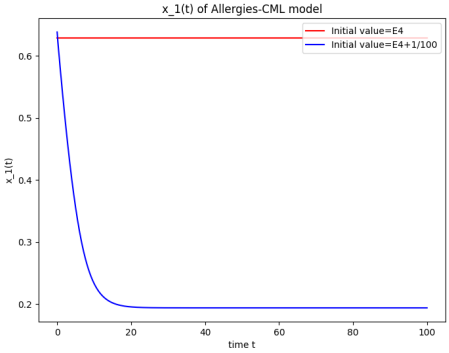
4. The roots of

$$d_1 = \left[(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})(\lambda - a_{22} - c_{22}e^{-\lambda\tau_2}) - (a_{12} + b_{12}e^{-\lambda\tau_1})c_{21}e^{-\lambda\tau_2}\right]$$

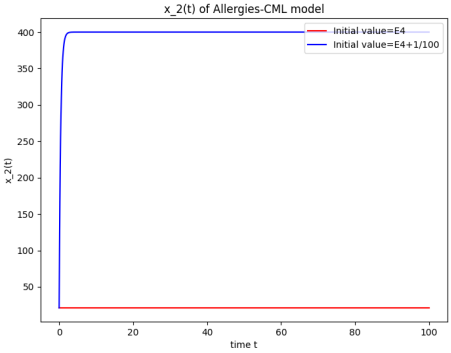
have negative real parts.

The numerical computations have again found that $a_{99} = 0.00003469487448016272 > 0$. Therefore, E_4 is not stable.

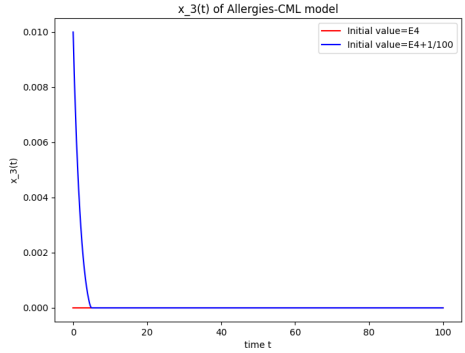
This can also be seen in the numerical simulations (Figure 4). Again, the progression of the solution is a favorable one, seeing as the leukemic cells diminish to zero. There is no presence of allergic reactions; the concentration of Th1 cells greatly outnumbers that of Th2.


x_1(t) of Allergies-CML model
Initial value=E4
Initial value=E4+1/100
x_1(t)
time t

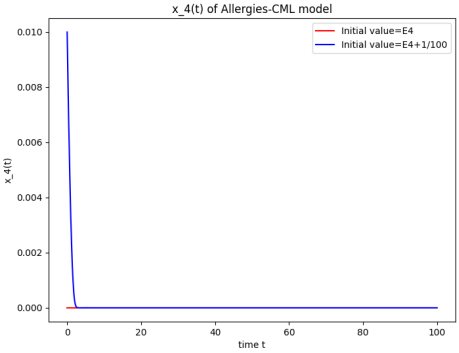
(**a**)


x_2(t) of Allergies-CML model
Initial value=E4
Initial value=E4+1/100
x_2(t)
time t

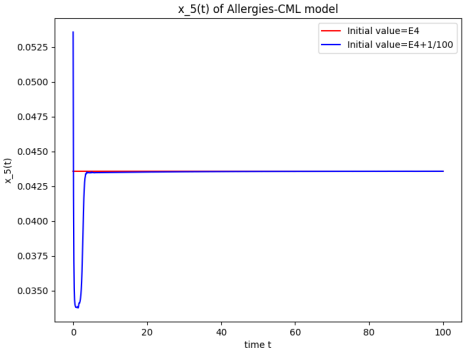
(**b**)


x_3(t) of Allergies-CML model
Initial value=E4
Initial value=E4+1/100
x_3(t)
time t

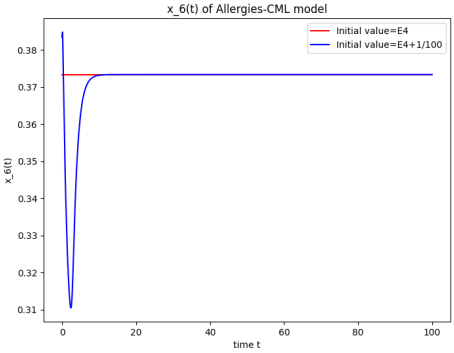
(**c**)


x_4(t) of Allergies-CML model
Initial value=E4
Initial value=E4+1/100
x_4(t)
time t

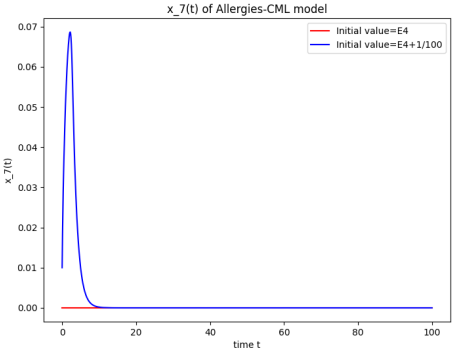
(**d**)


x_5(t) of Allergies-CML model
Initial value=E4
Initial value=E4+1/100
x_5(t)
time t

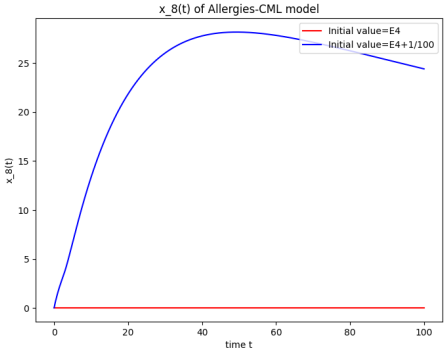
(**e**)


x_6(t) of Allergies-CML model
Initial value=E4
Initial value=E4+1/100
x_6(t)
time t

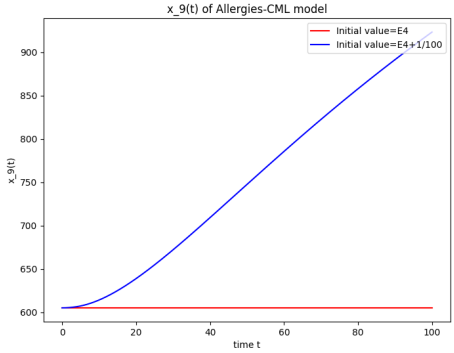
(**f**)


x_7(t) of Allergies-CML model
Initial value=E4
Initial value=E4+1/100
x_7(t)
time t

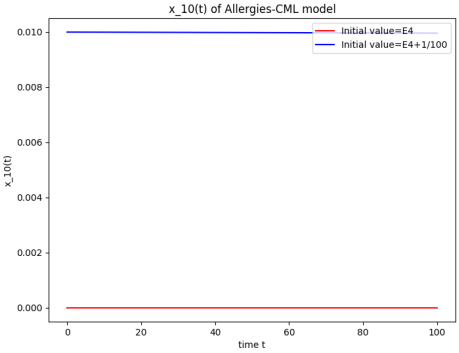
(**g**)


x_8(t) of Allergies-CML model
Initial value=E4
Initial value=E4+1/100
x_8(t)
time t

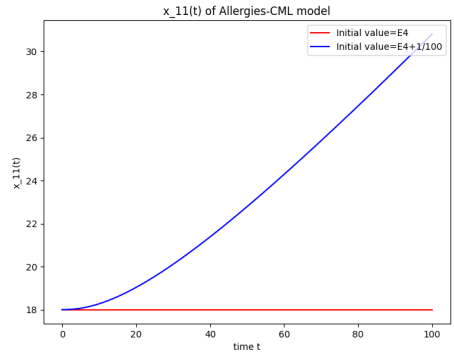
(**h**)


x_9(t) of Allergies-CML model
Initial value=E4
Initial value=E4+1/100
x_9(t)
time t

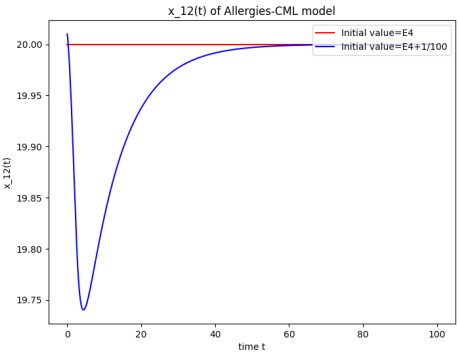
(**i**)


x_10(t) of Allergies-CML model
Initial value=E4
Initial value=E4+1/100
x_10(t)
time t

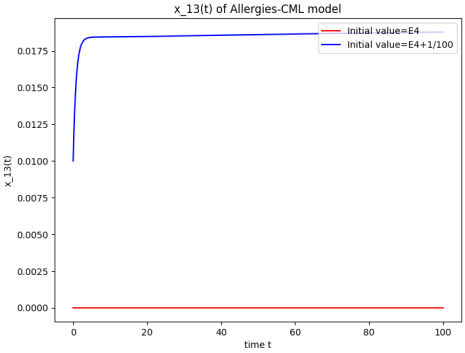
(**j**)


x_11(t) of Allergies-CML model
Initial value=E4
Initial value=E4+1/100
x_11(t)
time t

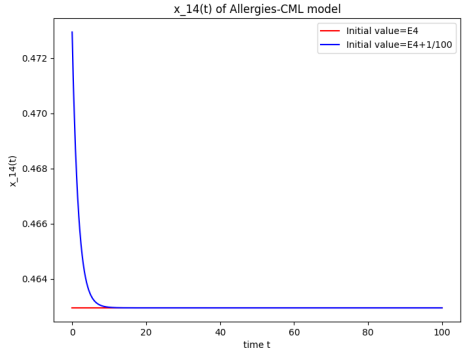
(**k**)


x_12(t) of Allergies-CML model
Initial value=E4
Initial value=E4+1/100
x_12(t)
time t

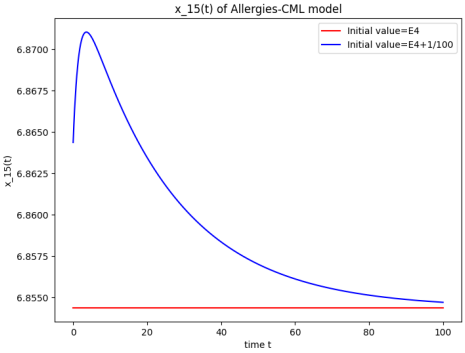
(**l**)



(**m**)



(**n**)



(**o**)

Figure 4. Stability around the equilibrium point E_4. (**a**) The concentration of stem-like healthy cells around E_4. (**b**) The concentration of mature healthy cells around E_4. (**c**) The concentration of stem-like leukemic cells around E_4. (**d**) The concentration of mature leukemic cells around E_4. (**e**) The concentration of naive APCs around E_4. (**f**) The concentration of mature APCs activated by the drug around E_4. (**g**) The concentration of mature APCs activated by the leukemic cells around E_4. (**h**) The concentration of naive CD4+ T cells around E_4. (**i**) The concentration of Th1 cells around E_4. (**j**) The concentration of Th2 cells around E_4. (**k**) The concentration of Treg cells around E_4. (**l**) The concentration of naive CD8+ T cells around E_4. (**m**) The concentration of mature CD8+ T cells around E_4. (**n**) The amount of drug in the absorbtion compartment around E_4. (**o**) The amount of drug in the plasmatic compartment around E_4.

Our numerical simulations reveal several characteristics of immune dynamics during imatinib therapy:

- Simulations indicate that in some scenarios, the concentration of Th2 cells exceeds that of Th1 cells, leading to allergic reactions. In these cases, both healthy and leukemic cell populations diminish to zero.
- In other scenarios, while leukemic cells reduce to undetectable levels, healthy cells stabilize at positive values. However, an imbalance favoring Th2 cells still results in allergic reactions.
- Some simulations show a positive evolution with leukemic cells dying out and a rapid increase in Th1 cell concentration. Yet, high Th2 cell concentrations indicate persistent allergic reactions.
- Importantly, there are scenarios where leukemic cells are eliminated without triggering allergic reactions. In these cases, the concentration of Th1 cells greatly outnumbers Th2 cells, providing a more favorable therapeutic outcome.

6. Conclusions and Future Work

This article presents a mathematical model that describes the dynamics of both healthy and leukemic cells, along with the role of the immune system, in the context of Chronic Myeloid Leukemia (CML) under treatment. The goal is to study the occurrence of allergic reactions to imatinib treatment by investigating the underlying mechanism behind the dominance of Th2 cells over Th1 and Treg cells.

Delay differential equations were used because time delays aid in accurately capturing the timing of biological processes. The model offers detailed insights into the inner workings of the immune system, including the behavior and activation of the cells responsible for the immune response (APCs, CD4+ T cells, CD8+ T cells, Th1 cells, Th2 cells, Treg cells).

Demonstrating the positivity of solutions is crucial when dealing with variables that represent cell populations. Section 3 of this paper covers the problem of positivity. We successfully demonstrated that, when the initial data have positive values, the solutions will remain positive throughout.

We identified the potential equilibria of the system and conducted an exhaustive local stability analysis around these points. Section 4 provides the mathematical calculations and findings regarding the four distinct equilibrium points uncovered. Biologically, these correspond to the following scenarios: patient demise, a healthy condition, a cured state with allergic reactions, and a cured state without allergic reactions.

We performed numerical simulations for four equilibrium points. The first equilibrium point is unstable, which is desirable since it describes the death of the patient (or possibly the state immediately following a bone marrow transplant). Unfortunately, the evolution of healthy cells in this configuration is not favorable.

The second equilibrium point is also unstable. Nonetheless, the simulations describe a positive evolution where leukemic cell counts decrease to undetectable levels, and healthy cells gravitate towards a positive state. Despite starting with equivalent concentrations of Th1 and Th2 cells in simulations, the evolutionary trend demonstrates immunological destabilization, evidenced by a higher concentration of Th2 cells compared to Th1 cells. Thus, although the patient has a favorable evolution as the leukemic burden diminishes, we expect allergic reactions to appear.

The numerical computations and simulations conducted around the third equilibrium point suggest instability. Despite this, there is a positive trend observed as leukemic cells diminish and the concentration of Th1 cells experiences rapid growth. Allergic reactions persist due to the significant concentration of Th2 cells, which greatly surpasses that of Th1 cells. This situation may change, as there seems to be a decreasing trend in the population of Th2 cells.

The last equilibrium point is unstable, according to the numerical computations and simulations. The simulations show a promising evolution, with no allergic reactions.

While the current parameter configuration renders all equilibrium points unstable, we can detect partial stability in certain variables of the system. This paves the way for new mathematical studies aimed at exploring the circumstances under which specific variables remain stable independent of others.

Mathematically simulating allergic reactions in the context of drug allergies is a critical area of research that holds substantial importance in both pharmacology and clinical medicine. This approach offers multiple benefits, from enhancing our understanding of allergic mechanisms to improving patient safety. Based on the findings outlined in this article, the next step involves exploring various parameter scenarios to gain a holistic understanding of the correlation between drug concentration and the onset of allergic reactions.

In summary, this study aims to provide a nuanced understanding of the immune system's behavior during CML therapy with imatinib. By addressing the current gaps in knowledge and offering a detailed mathematical framework, we hope to contribute to the development of more effective treatment strategies and the management of immune-related side-effects in CML patients.

Author Contributions: Conceptualization, R.A.; Validation, I.B.; Data curation, L.F.; Writing—original draft, R.A.; Writing—review & editing, R.A. and A.H. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding authors.

Conflicts of Interest: The authors declare no conflicts of interest.

Appendix A

In the following, the matrices of partial derivatives calculated in equilibria will be listed. Everywhere, the state variables are calculated in equilibria.

The equilibrium point $E_1 = (0, 0, 0, 0, \hat{x}_5, \hat{x}_6, 0, \hat{x}_8, 0, 0, 0, \hat{x}_{12}, 0, \hat{x}_{14}, \hat{x}_{15})$.

The nonzero elements in A are:

$$
\begin{aligned}
&a_{11} = -\gamma_{1h} - (\eta_{1h} + \eta_{2h})k_{0h} - (1 - \eta_{1h} - \eta_{2h})\beta_{0h}\\
&a_{22} = -\gamma_{2h}, a_{33} = -\gamma_{1l} - (\eta_{1l} + \eta_{2l})u_1(x_{15})k_{0l} - (1 - \eta_{1l} - \eta_{2l})\beta_{0l}\\
&a_{44} = -\delta_{2l}, a_{54} = \frac{-c_4 x_5}{b_3}, a_{55} = -c_2 - c_3 x_{15}, a_{5,15} = -c_3 x_5\\
&a_{65} = c_3 u_2(x_{15}), a_{66} = -d_1, a_{74} = \frac{c_4 u_2(x_{15}) x_5}{b_3}, a_{77} = -d_1, a_{88} = -\beta_1\\
&a_{99} = -\beta_2, a_{10,10} = -\beta_3, a_{11,11} = -\beta_4, a_{12,7} = -\eta_1 u_3(x_{15}) x_{12}\\
&a_{12,12} = -a_1, a_{13,13} = -a_3 - \eta_2 u_3(x_{15}), a_{14,14} = -\lambda_0, a_{15,14} = \lambda_0, a_{15,15} = -\nu
\end{aligned}
$$

$$
A = \begin{bmatrix}
a_{11} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & a_{22} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & a_{33} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & a_{44} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & a_{54} & a_{55} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{5,15}\\
0 & 0 & 0 & 0 & 0 & a_{66} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & a_{74} & 0 & 0 & a_{77} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{88} & 0 & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{99} & 0 & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{10,10} & 0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{11,11} & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & a_{12,7} & 0 & 0 & 0 & 0 & a_{12,12} & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{13,13} & 0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\lambda_0 & 0\\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & \lambda_0 & -\nu
\end{bmatrix}
$$

The nonzero element in B is

$$b_{11} = 2e^{-\gamma_{1h}\tau_1}(1 - \eta_{1h} - \eta_{2h})\beta_{0h} + k_{0h}\eta_{1h}e^{-\gamma_{1h}\tau_1}$$

The nonzero element in C is

$$c_{21} = A_h(2\eta_{2h} + \eta_{1h})k_{0h}.$$

The nonzero element in D is

$$d_{33} = 2e^{-\gamma_{1l}\tau_3}(1 - \eta_{1l} - \eta_{2l})\beta_{0l} + k_{0l}\eta_{1l}e^{-\gamma_{1l}\tau_3}.$$

The nonzero element in E is

$$e_{43} = A_l(2\eta_{2l} + \eta_{1l})k_{0l}u_1(x_{15}).$$

The nonzero element in G is

$$g_{13,7} = 2^m \eta_1 u_3(x_{15}) x_{12}.$$

The nonzero element in H is

$$h_{13,7} = 2^{n_1} \eta_2 u_3(x_1 5).$$

F **is zero**.
The equilibrium point $E_2 = (\hat{x_1}, \hat{x_2}, 0, 0, \hat{x_5}, \hat{x_6}, 0, \hat{x_8}, 0, 0, 0, \hat{x_{12}}, 0, \hat{x_{14}}, \hat{x_{15}})$.
The nonzero elements in A are:

$$a_{11} = -\gamma_{1h} - (\eta_{1h} + \eta_{2h}) \frac{K_{0h} \theta_{2h}^{n_h}}{\theta_{2h}^{n_h} + \hat{x_2}^{n_h}} (1 - \eta_{1h}\eta_{2h} - \eta_{2h}) \frac{\beta_{0h} \theta_{1h}^{m_h}}{\theta_{1h}^{mh} + (\hat{x_1})^{m_h}}$$

$$a_{12} = \frac{n_h(\eta_{1h} + \eta_{2h}) k_{0h} \theta_{2h}^{n_h} \hat{x_1} \hat{x_2}^{n_h - 1}}{\left(\theta_{2h}^{n_h} + \hat{x_2}^{n_h}\right)^2}$$

$$a_{13} = \frac{-(1 - \eta_{1h} - \eta_{2h}) \hat{x_1}^{m_h} \beta_{0h} \theta_{1h}^{m_h}}{\left[\theta_{1h}^{m_h} + (\hat{x_1})^{m_h}\right]^2}$$

$$a_{14} = \frac{(\eta_{1h} + \eta_{2h}) n_h (\hat{x_2})^{n_h - 1} k_{0h} \theta_{2h}^{n_h} \hat{x_1}}{\left[\theta_{2h}^{n_h} + (x_2)^{n_h}\right]^2}$$

$$a_{22} = -\gamma_{2h}$$

$$a_{33} = -\gamma_{1l} - \frac{(\eta_{1l} + \eta_{2l}) u_1(\hat{x_{15}}) k_{0l} \theta_{2l}^{n_l}}{\theta_{2l}^{n_l} + (\hat{x_2})^{n_l}} - \frac{(1 - \eta_{1l} - \eta_{2l}) \beta_{0l} \theta_{1l}^{m_l}}{\theta_{1l}^{m_l} + (\hat{x_1})^{m_l}}$$

$$a_{44} = -\gamma_{2l}$$

$$a_{54} = \frac{-c_4 \hat{x_5}}{b_3}$$

$$a_{55} = -c_2 - c_3 \hat{x_{15}}$$

$$a_{5,15} = -c_3 \hat{x_{15}}$$

$$a_{65} = c_3 \hat{x_{15}}$$

$$a_{66} = -d_1$$

$$a_{6,15} = c_3 \hat{x_5}$$

$$a_{74} = \frac{c_4 u_2(\hat{x_{15}}) \hat{x_5}}{b_3}$$

$$a_{77} = -d_1$$

$$a_{88} = -\beta_1$$

$$a_{89} = -u_3(\hat{x_{15}}) \hat{x_8} \hat{x_6}$$

$$a_{8,11} = -u_3(\hat{x_{15}}) k \hat{x_8} \hat{x_6}$$

$$a_{8,10} = -p u_3(\hat{x_{15}}) \hat{x_8} \hat{x_6}$$

$$a_{99} = -\beta_2 + \gamma_1 u_4(\hat{x_{15}}) \hat{x_8} \hat{x_6}$$

$$a_{10,10} = -\beta_3 + p \gamma_1 u_4(\hat{x_{15}}) \hat{x_8} \hat{x_6} (1 + 2m_2)$$

$$a_{11,11} = -\beta_4 + u_4(\hat{x_{15}}) k \gamma_1 \hat{x_8} \hat{x_6}$$

$$a_{12,7} = -\eta_1 u_3(\hat{x_{15}}) \hat{x_{12}}$$

$$a_{12,12} = -a_1 - \eta_1 u_3(\hat{x_{15}}) \hat{x_7} = -a_1$$

$$a_{13,13} = -a_3 - \eta_2 u_3(\hat{x_{15}})$$

$$a_{14,14} = -\lambda_0$$

$$a_{15,14} = \lambda_0$$

$$a_{15,15} = -v$$

$$A = \begin{bmatrix} a_{11} & a_{12} & a_{13} & a_{14} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & a_{22} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & a_{33} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & a_{44} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & a_{54} & a_{55} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{5,15} \\ 0 & 0 & 0 & 0 & a_{65} & a_{66} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{6,15} \\ 0 & 0 & 0 & a_{74} & 0 & 0 & a_{77} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{88} & a_{89} & a_{8,10} & a_{8,11} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{99} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{10,10} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{11,11} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & a_{12,7} & 0 & 0 & 0 & 0 & a_{12,12} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{13,13} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{14,14} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{15,14} & a_{15,15} \end{bmatrix}$$

The nonzero elements in B are:

$$b_{11} = \frac{2e^{-\gamma_1\tau_1}(1-\eta_{1h}-\eta_{2h})\beta_{0h}\theta_{1h}^{m_h}}{\theta_{1h}^{m_h}(x_1)^{mh}} + \frac{\eta_{1h}e^{-\gamma_1\tau_1}k_{0h}\theta_{2h}^{n_h}}{\theta_{2h}^{n_h h} + (\hat{x}_2)^{n_h}}$$

$$b_{12} = \frac{-\eta_{1h}e^{-\gamma_{1h}\tau_1}k_{0h}\theta_{2h}^{n_h}(\hat{x}_2)^{n_h-1}\hat{x}_1}{\left[\theta_{2h}^{n_h} + (\hat{x}_2)^{n_h}\right]^2}$$

$$b_{13} = \frac{-2e^{-\gamma_{1h}\tau_1}(1-\eta_1 h-\eta_{2h})\beta_{0h}\theta_{1_h}^{m_h}(\hat{x}_1)^{m_h}}{\left[\theta_{1h}^{m_h} + (\hat{x}_1)^{m_h}\right]^2}$$

$$b_{14} = \frac{-\eta_{1h}\cdot e^{-\gamma_{1h}\tau_1}k_{0h}\hat{x}_1(\hat{x}_2)^{n_h-1}\theta_{2h}^{n_h}}{\left[\theta_{2h}^{n} + (\hat{x}_2)^{n_h}\right]^2}$$

The nonzero elements in C are:

$$c_{21} = \frac{A_h(2\eta_{2h}+\eta_{1h})K_{0h}\theta_{2h}^{n_h}}{\theta_{2h}^{n_h} + (\hat{x}_2)^{n_h}}$$

$$c_{22} = \frac{-A_h n_h(2\eta_{2h}+\eta_{1h})\hat{x}_1 k_{0h}\theta_{2h}^{n_h}(\hat{x}_2)^{n_h-1}}{\left[\theta_{2h}^{n_h} + (\hat{x}_2)^{n_h}\right]^2}$$

$$c_{24} = \frac{-A_h n_h(2\eta_{2h}+\eta_{1h})\hat{x}_1 k_{0h}\theta_{2h}^{n_h}(\hat{x}_2)^{n_h-1}}{\left[\theta_{2h}^{n_h} + (\hat{x}_2)^{n_h}\right]^2}$$

The nonzero element in D is:

$$d_{33} = \frac{2e^{-\gamma_{1l}\tau_3}(1-\eta_{1l}-\eta_{2l})\beta_{0l}\theta_{1l}^{m_l}}{\theta_{1l}^{m_l} + (\hat{x_1})^{m_l}} + \frac{\eta_{1l}e^{-\gamma_{1l}\tau_3}k_{0l}\theta_{2l}^{m_l}}{\theta_{2l}^{n_l} + (\hat{x}_2)^{n_l}}$$

The nonzero element in E is:

$$e_{43} = \frac{A_l(2\eta_{2l}+\eta_{1l})u_1(\hat{x}_{15})k_{0l}\theta_{2l}^{n_l}}{\theta_{2l}^{nl} + (\hat{x}_2)^{n_l}}$$

The nonzero element in G is:

$$g_{13,7} = 2^m\eta_1 u_3(\hat{x}_{15})\hat{x}_{12}$$

The nonzero element in H is:

$$h_{13,13} = 2^{n_1}\eta_2 u_3(\hat{x_{15}})$$

The equilibrium point $E_3 = (\hat{x}_1, \hat{x}_2, 0, 0, \hat{x}_5, \hat{x}_6, 0, \hat{x}_8, 0, \hat{x}_{10}, \hat{x}_{11}, \hat{x}_{12}, 0, \hat{x}_{14}, \hat{x}_{15})$.
The nonzero elements in A are:

$$a_{11} = -\gamma_{1h} - (\eta_{1h} + \eta_{2h})\frac{K_{0h}\theta_{2h}^{n_h}}{\theta_{2h}^{n_h} + \hat{x_2}^{n_h}}(1 - \eta_{1h}\eta_{2h} - \eta_{2h})\frac{\beta_{0h}\theta_{1h}^{m_h}}{\theta_{1h}^{mh} + (\hat{x_1})^{m_h}}$$

$$a_{12} = \frac{n_h(\eta_{1h} + \eta_{2h})k_{0h}\theta_{2h}^{n_h}\hat{x_1}\hat{x_2}^{n_h-1}}{\left(\theta_{2h}^{n_h} + \hat{x}_2^{n_h}\right)^2}$$

$$a_{13} = \frac{-(1 - \eta_{1h} - \eta_{2h})\hat{x}_1^{m_h}\beta_{0h}\theta_{1h}^{m_h}}{\left[\theta_{1h}^{m_h} + (\hat{x}_1)^{m_h}\right]^2}$$

$$a_{14} = \frac{(\eta_{1h} + \eta_{2h})n_h(\hat{x}_2)^{n_h-1}k_{0h}\theta_{2h}^{n_h}\hat{x}_1}{\left[\theta_{2h}^{n_h} + (x_2)^{n_h}\right]^2}$$

$$a_{22} = -\gamma_{2h}$$

$$a_{33} = -\gamma_{1l} - \frac{(\eta_{1l} + \eta_{2l})u_1(\hat{x_{15}})k_{0l}\theta_{2l}^{n_l}}{\theta_{2l}^{n_l} + (\hat{x}_2)^{n_l}} - \frac{(1 - \eta_{1l} - \eta_{2l})\beta_{0l}\theta_{1l}^{m_l}}{\theta_{1l}^{m_l} + (\hat{x}_1)^{m_l}}$$

$$a_{44} = -\gamma_{2l}$$

$$a_{54} = \frac{-c_4\hat{x}_5}{b_3}$$

$$a_{55} = -c_2 - c_3\hat{x}_{15}$$

$$a_{5,15} = -c_3\hat{x}_{15}$$

$$a_{65} = c_3\hat{x}_{15}$$

$$a_{66} = -d_1$$

$$a_{6,15} = c_3\hat{x}_5$$

$$a_{74} = \frac{c_4u_2(\hat{x}_{15})\hat{x}_5}{b_3}$$

$$a_{77} = -d_1$$

$$a_{89} = \frac{-u_3(\hat{x}_{15})\hat{x}_6\hat{x}_8}{1 + m_2\hat{x}_{10}}$$

$$a_{8,10} = -pu_3(\hat{x}_{15})\hat{x}_6\hat{x}_8$$

$$a_{8,11} = -u_3(\hat{x}_{15})k\hat{x}_6\hat{x}_8$$

$$a_{8,15} = \frac{200\hat{x}_6\hat{x}_8}{3\left(\frac{100}{3} + \hat{x}_{15}^2\right)^2}(p\hat{x}_{10} + \hat{x}_{11}k)$$

$$a_{99} = -\beta_2 + \frac{\gamma_1u_4(x_{15})\hat{x}_6\hat{x}_8}{(1 + m_r\hat{x}_{11})(1 + m_2\hat{x}_{10})}$$

$$a_{10,8} = \frac{p\gamma_1u_4(\hat{x}_{15})\hat{x}_{10}\hat{x}_6(1 + m_2\hat{x}_{10})}{(1 + m_r\hat{x}_{11})(1 + m_2\hat{x}_{10})}$$

$$a_{10,9} = \frac{-p\gamma_1u_4(\hat{x}_{15})\hat{x}_{10}\hat{x}_6(1 + m_2\hat{x}_{10})m_1}{(1 + m_r\hat{x}_{11})(1 + m_2\hat{x}_{10})^2}$$

$$a_{10,10} = \frac{-\beta_3 + p\gamma_1u_4(\hat{x}_{15})\hat{x}_8\hat{x}_6(1 + m_2\hat{x}_{10})}{(1 + m_r\hat{x}_{11})(1 + m_2\hat{x}_{10})}$$

$$a_{10,11} = \frac{-(p\gamma_1\mu_4(\hat{x}_{15})\hat{x}_8\hat{x}_6\hat{x}_{10})(1+m_2\hat{x}_{10})m_r}{(1+m_2\hat{x}_{10})(1+m_r\hat{x}_{11})^2}$$
$$a_{10,15} = \frac{100p\gamma_1\hat{x}_8\hat{x}_6\hat{x}_{10}\hat{x}_{15}}{3(1+m_r\hat{x}_{11})(1+m_2\hat{x}_{10})\left(50/3+\hat{x}_{15}^2\right)^2}$$
$$a_{11,8} = u_4(\hat{x}_{15})k\gamma_1\hat{x}_6\cdot\hat{x}_{11}$$
$$a_{11,11} = -\beta_4 + u_4(\hat{x}_{15})k\gamma_1\hat{x}_6\hat{x}_8$$
$$a_{11,15} = \frac{-100k\gamma_1\hat{x}_6\hat{x}_8\hat{x}_{11}\hat{x}_{15}}{3\left(\frac{50}{3}+\hat{x}_{15}^2\right)^2}$$
$$a_{12,7} = -\eta_1 u_3(\hat{x}_{15})\hat{x}_{12}$$
$$a_{12,12} = -a_1$$
$$a_{13,13} = \frac{-a_2\hat{x}_{11}}{1+\hat{x}_{11}} - a_3 - \frac{\eta_2 u_3(\hat{x}_{15})}{1+\hat{x}_{10}+\hat{x}_{11}}$$
$$a_{14,14} = -\lambda_0$$
$$a_{15,14} = \lambda_0$$
$$a_{15,15} = -v$$

$$A = \begin{bmatrix}
a_{11} & a_{12} & a_{13} & a_{14} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & a_{22} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & a_{33} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & a_{44} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & a_{54} & a_{55} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{5,15} \\
0 & 0 & 0 & 0 & a_{65} & a_{66} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{6,15} \\
0 & 0 & 0 & a_{74} & 0 & 0 & a_{77} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{89} & a_{8,10} & a_{8,11} & 0 & 0 & 0 & a_{8,15} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{99} & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{10,8} & a_{10,9} & a_{10,10} & a_{10,11} & 0 & 0 & 0 & a_{10,15} \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{11,8} & 0 & 0 & a_{11,11} & 0 & 0 & 0 & a_{11,15} \\
0 & 0 & 0 & 0 & 0 & 0 & a_{12,7} & 0 & 0 & 0 & 0 & a_{12,12} & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{13,13} & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{14,14} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{15,14} & a_{15,15}
\end{bmatrix}$$

The nonzero elements in B are:

$$b_{11} = \frac{2e^{-\gamma_1\tau_1}(1-\eta_{1h}-\eta_{2h})\beta_{0h}\theta_{1h}^{m_h}}{\theta_{1h}^{m_h}(x_1)^{mh}} + \frac{\eta_{1h}e^{-\gamma_1\tau_1}k_{0h}\theta_{2h}^{n_h}}{\theta_{2h}^{n_h}h + (\hat{x}_2)^{n_h}}$$
$$b_{12} = \frac{-\eta_{1h}e^{-\gamma_{1h}\tau_1}k_{0h}\theta_{2h}^{n_h}(\hat{x}_2)^{n_h-1}\hat{x}_1}{\left[\theta_{2h}^{n_h}+(\hat{x}_2)^{n_h}\right]^2}$$
$$b_{13} = \frac{-2e^{-\gamma_{1h}\tau_1}(1-\eta_1 h-\eta_{2h})\beta_{0h}\theta_{1_h}^{m_h}(\hat{x}_1)^{m_h}}{\left[\theta_{1h}^{m_h}+(\hat{x}_1)^{m_h}\right]^2}$$
$$b_{14} = \frac{-\eta_{1h}\cdot e^{-\gamma_{1h}\tau_1}k_{0h}\hat{x}_1(\hat{x}_2)^{n_h-1}\theta_{2h}^{n_h}}{\left[\theta_{2h}^{n}+(\hat{x}_2)^{n_h}\right]^2}$$

The nonzero elements in C are:

$$c_{21} = \frac{A_h(2\eta_{2h} + \eta_{1h})K_{0h}\theta_{2h}^{n_h}}{\theta_{2h}^{n_h} + (\hat{x}_2)^{n_h}}$$
$$c_{22} = \frac{-A_h n_h(2\eta_{2h} + \eta_{1h})\hat{x}_1 k_{0h}\theta_{2h}^{n_h}(\hat{x}_2)^{n_h-1}}{\left[\theta_{2h}^{n_h} + (\hat{x}_2)^{n_h}\right]^2}$$
$$c_{24} = \frac{-A_h n_h(2\eta_{2h} + \eta_{1h})\hat{x}_1 k_{0h}\theta_{2h}^{n_h}(\hat{x}_2)^{n_h-1}}{\left[\theta_{2h}^{n_h} + (\hat{x}_2)^{n_h}\right]^2}$$

The nonzero element in D is:

$$d_{33} = \frac{2e^{-\gamma_{1l}\tau_3}(1 - \eta_{ll} - \eta_{2l})\beta_{0l}\theta_{1l}^{m_l}}{\theta_{1l}^{m_l} + (\hat{x}_1)^{m_l}} + \frac{\eta_{1l}e^{-\gamma_{1l}\tau_3}k_{0l}\theta_{2l}^{m_l}}{\theta_{2l}^{n_l} + (\hat{x}_2)^{n_l}}$$

The nonzero element in E is:

$$e_{43} = \frac{A_l(2\eta_{2l} + \eta_{1l})u_1(\hat{x}_{15})k_{0l}\theta_{2l}^{n_l}}{\theta_{2l}^{nl} + (\hat{x}_2)^{n_l}}$$

The nonzero elements in F are:

$$f_{86} = -pu_3(\hat{x}_{15})\hat{x}_6\hat{x}_8\hat{x}_{10-}u_3(\hat{x}_{15})k\hat{x}_6\hat{x}_8\hat{x}_{11}$$
$$f_{10,6} = \frac{p\gamma_1 u_1(\hat{x}_{15})\hat{x}_8\hat{x}_{10}}{1 + m_r\hat{x}_{11}}$$
$$f_{11,6} = u_4(\hat{x}_{15})k\gamma_1\hat{x}_8\hat{x}_{11}$$

The nonzero element in G is:

$$g_{13,7} = 2^m\eta_1 u_3(\hat{x}_{15})\hat{x}_{12}$$

The nonzero elements in H are:

$$h_{13,10} = \frac{-2^{n+1}\eta_2 u_3(\hat{x}_{15})\hat{x}_{13}\hat{x}_{10}}{\left(1 + \hat{x}_{10}^2 + \hat{x}_{11}^2 + \hat{x}_{13}^2\right)^2}$$
$$h_{13,11} = \frac{-2^{n+1}\eta_2 u_3(x_{15})\hat{x}_{11}\hat{x}_{13}}{\left(1 + \hat{x}_{10}^2 + x_{11}^2 + \hat{x}_{13}^2\right)^2}$$
$$h_{13,13} = \frac{2^{n_1}\eta_2 u_3(\hat{x}_{15})}{1 + \hat{x}_{10}^2 + \hat{x}_{11}^2 + \hat{x}_{13}^2}\left(1 - \frac{2\hat{x}_{13}^2}{1 + \hat{x}_{10}^2 + \hat{x}_{11}^2 + \hat{x}_{13}^2}\right)$$

The equilibrium point $E_4 = (\tilde{x}_1, \tilde{x}_2, 0, 0, \tilde{x}_5, \tilde{x}_6, 0, \tilde{x}_8, \tilde{x}_9, 0, \tilde{x}_{11}, \tilde{x}_{12}, 0, \tilde{x}_{14}, \tilde{x}_{15})$.
The nonzero elements in A are:

$$a_{11} = -\gamma_{1h} - (\eta_{1h} + \eta_{2h})\frac{K_{0h}\theta_{2h}^{n_h}}{\theta_{2h}^{n_h} + \tilde{x_2}^{n_h}}(1 - \eta_{1h}\eta_{2h} - \eta_{2h})\frac{\beta_{0h}\theta_{1h}^{m_h}}{\theta_{1h}^{mh} + (\tilde{x_1})^{m_h}}$$
$$a_{12} = \frac{n_h(\eta_{1h} + \eta_{2h})k_{0h}\theta_{2h}^{n_h}\tilde{x_1}\tilde{x_2}^{n_h-1}}{\left(\theta_{2h}^{n_h} + \tilde{x}_2^{n_h}\right)^2}$$
$$a_{13} = \frac{-(1 - \eta_{1h} - \eta_{2h})\tilde{x}_1^{m_h}\beta_{0h}\theta_{1h}^{m_h}}{\left[\theta_{1h}^{m_h} + (\tilde{x}_1)^{m_h}\right]^2}$$

$$a_{14} = \frac{(\eta_{1h} + \eta_{2h}) n_h (\tilde{x}_2)^{n_h - 1} k_{0h} \theta_{2h}^{n_h} \tilde{x}_1}{\left[\theta_{2h}^{n_h} + (\tilde{x}_2)^{n_h}\right]^2}$$

$$a_{22} = -\gamma_{2h}$$

$$a_{33} = -\gamma_{1l} - \frac{(\eta_{1l} + \eta_{2l}) u_1(\tilde{x_{15}}) k_{0l} \theta_{2l}^{n_l}}{\theta_{2l}^{n_l} + (\tilde{x}_2)^{n_l}} - \frac{(1 - \eta_{1l} - \eta_{2l}) \beta_{0l} \theta_{1l}^{m_l}}{\theta_{1l}^{m_l} + (\tilde{x}_1)^{m_l}}$$

$$a_{44} = -\gamma_{2l}$$

$$a_{54} = \frac{-c_4 \tilde{x}_5}{b_3}$$

$$a_{55} = -c_2 - c_3 \tilde{x}_{15}$$

$$a_{5,15} = -c_3 \tilde{x}_{15}$$

$$a_{65} = c_3 \tilde{x}_{15}$$

$$a_{66} = -d_1$$

$$a_{6,15} = c_3 \tilde{x}_5$$

$$a_{74} = \frac{c_4 u_2(\tilde{x}_{15}) \tilde{x}_5}{b_3}$$

$$a_{77} = -d_1$$

$$a_{88} = -\beta_1 - u_3(\tilde{x}_{15}) \tilde{x}_6 \tilde{x}_9 - u_3(\tilde{x}_{15}) k \tilde{x}_8 \tilde{x}_6 \tilde{x}_{11}$$

$$a_{89} = -u_3(\tilde{x}_{15}) \tilde{x}_6 \tilde{x}_8$$

$$a_{8,10} = u_3(\tilde{x}_{15}) \tilde{x}_6 \tilde{x}_8 (m_2 - p)$$

$$a_{8,11} = -k u_3(\tilde{x}_{15}) \tilde{x}_6 \tilde{x}_8$$

$$a_{8,15} = \frac{200 \tilde{x}_{15} \tilde{x}_6 \tilde{x}_8}{3\left(\frac{100}{3} + \tilde{x}_{15}^2\right)^2} (\tilde{x_9} - k \tilde{x}_{11})$$

$$a_{98} = \frac{\gamma_1 u_4(\tilde{x}_{15}) \tilde{x}_6 \tilde{x}_9}{1 + m_r \tilde{x}_{11}}$$

$$a_{99} = -\beta_2 + \frac{\gamma_1 u_4(\tilde{x}_{15}) \tilde{x}_6 \tilde{x}_8}{1 + m_r \tilde{x}_{11}}$$

$$a_{9,10} = \frac{-\gamma_1 u_4(\tilde{x}_{15}) \tilde{x}_6 \tilde{x}_8 \tilde{x}_9 m_2}{(1 + m_r \tilde{x}_{11})}$$

$$a_{9,11} = \frac{-\gamma_1 u_4(\tilde{x}_{15}) \tilde{x}_6 \tilde{x}_8 \tilde{x}_9 m_r}{(1 + m_r \tilde{x}_{11})^2}$$

$$a_{9,15} = \frac{-100 \gamma_1 \tilde{x}_6 \tilde{x}_8 \tilde{x}_9 \tilde{x}_{15}}{3(1 + m_r \tilde{x}_{11})\left(\frac{50}{3} + \tilde{x}_{15}^2\right)^2}$$

$$a_{10,10} = -\beta_3 + \frac{p \gamma_1 u_4(\tilde{x}_{15}) \tilde{x}_6 \tilde{x}_8}{(1 + m_r \tilde{x}_{11})(1 + m_1 \tilde{x}_9)}$$

$$a_{11,8} = u_4(\tilde{x}_{15}) k \gamma_1 \tilde{x}_6 \tilde{x}_{11}$$

$$a_{11,11} = -\beta_4 + u_4(\tilde{x}_{15}) k \gamma_1 \tilde{x}_8 \tilde{x}_6$$

$$a_{11,15} = \frac{100 k \gamma_1 \tilde{x}_6 \tilde{x}_8 \tilde{x}_{11} \tilde{x}_{15}}{3\left(\frac{50}{3} + \tilde{x}_{15}^2\right)^2}$$

$$a_{12,7} = -\eta_1 u_3(\tilde{x}_{15}) \tilde{x}_{12}$$

$$a_{12,12} = -a_1$$

$$a_{13,9} = \frac{2 \eta_2 u_3(\tilde{x}_{15}) \tilde{x}_{13} \tilde{x}_9}{\left(1 + \tilde{x}_9^2 + \tilde{x}_{11}^2 + \tilde{x}_{13}^2\right)^2}$$

$$a_{13,11} = -a_2\tilde{x}_{13}\left[\frac{1-\tilde{x}_{11}^2}{\left(1+\tilde{x}_{11}^2\right)^2}\right] + \frac{2\eta_2\mu_3(\tilde{x}_{15})\tilde{x}_{13}\tilde{x}_{11}}{\left(1+\tilde{x}_9^2+\tilde{x}_{11}^2+\tilde{x}_{13}^2\right)^2}$$

$$a_{13,13} = -a_2\zeta(\tilde{x}_{11}) - \frac{a_3u_3(\tilde{x_{15}})\eta_2}{1+\tilde{x}_9^2+\tilde{x}_{11}^2+\tilde{x}_{13}^2}$$

$$a_{13,15} = \frac{-200\eta_2\tilde{x}_{13}\tilde{x}_{15}}{3\left(1+\tilde{x}_9^2+\tilde{x}_{11}^2+\tilde{x}_{13}^2\right)\left(\frac{100}{3}+\tilde{x}_{15}^2\right)}$$

$$a_{14,14} = -\lambda_0$$

$$a_{15,14} = \lambda_0$$

$$a_{15,15} = -v$$

$$A = \begin{bmatrix} a_{11} & a_{12} & a_{13} & a_{14} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & a_{22} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & a_{33} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & a_{44} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & a_{54} & a_{55} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{5,15} \\ 0 & 0 & 0 & 0 & a_{65} & a_{66} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{6,15} \\ 0 & 0 & 0 & a_{74} & 0 & 0 & a_{77} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{88} & a_{89} & a_{8,10} & a_{8,11} & 0 & 0 & 0 & a_{8,15} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{98} & a_{99} & a_{9,10} & a_{9,11} & 0 & 0 & 0 & a_{9,15} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{10,10} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{11,8} & 0 & 0 & a_{11,11} & 0 & 0 & 0 & a_{11,15} \\ 0 & 0 & 0 & 0 & 0 & 0 & a_{12,7} & 0 & 0 & 0 & 0 & a_{12,12} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{13,9} & 0 & a_{13,11} & 0 & a_{13,13} & 0 & a_{13,15} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{14,14} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_{15,14} & a_{15,15} \end{bmatrix}$$

The nonzero elements in B are:

$$b_{11} = \frac{2e^{-\gamma_1\tau_1}(1-\eta_{1h}-\eta_{2h})\beta_{0h}\theta_{1h}^{m_h}}{\theta_{1h}^{m_h}(\tilde{x}_1)^{mh}} + \frac{\eta_{1h}e^{-\gamma_1\tau_1}k_{0h}\theta_{2h}^{n_h}}{\theta_{2h}^{n_h}h+(\tilde{x}_2)^{n_h}}$$

$$b_{12} = \frac{-\eta_{1h}e^{-\gamma_{1h}\tau_1}k_{0h}\theta_{2h}^{n_h}(\tilde{x}_2)^{n_h-1}\tilde{x_1}}{\left[\theta_{2h}^{n_h}+(\tilde{x}_2)^{n_h}\right]^2}$$

$$b_{13} = \frac{-2e^{-\gamma_{1h}\tau_1}(1-\eta_1 h-\eta_{2h})\beta_{0h}\theta_{1_h}^{m_h}(\tilde{x}_1)^{m_h}}{\left[\theta_{1h}^{m_h}+(\tilde{x}_1)^{m_h}\right]^2}$$

$$b_{14} = \frac{-\eta_{1h}e^{-\gamma_{1h}\tau_1}k_{0h}\tilde{x}_1(\tilde{x}_2)^{n_h-1}\theta_{2h}^{n_h}}{\left[\theta_{2h}^{n}+(\tilde{x}_2)^{n_h}\right]^2}$$

The nonzero elements in C are:

$$c_{21} = \frac{A_h(2\eta_{2h}+\eta_{1h})K_{0h}\theta_{2h}^{n_h}}{\theta_{2h}^{n_h}+(\tilde{x}_2)^{n_h}}$$

$$c_{22} = \frac{-A_hn_h(2\eta_{2h}+\eta_{1h})\tilde{x}_1k_{0h}\theta_{2h}^{n_h}(\tilde{x}_2)^{n_h-1}}{\left[\theta_{2h}^{n_h}+(\tilde{x}_2)^{n_h}\right]^2}$$

$$c_{24} = \frac{-A_hn_h(2\eta_{2h}+\eta_{1h})\tilde{x}_1k_{0h}\theta_{2h}^{n_h}(\tilde{x}_2)^{n_h-1}}{\left[\theta_{2h}^{n_h}+(\tilde{x}_2)^{n_h}\right]^2}$$

The nonzero element in D is:

$$d_{33} = \frac{2e^{-\gamma_{1l}\tau_3}(1-\eta_{ll}-\eta_{2l})\beta_{0l}\theta_{1l}^{m_l}}{\theta_{1l}^{m_l}+(\tilde{x_1})^{m_l}} + \frac{\eta_{1l}e^{-\gamma_{1l}\tau_3}k_{0l}\theta_{2l}^{m_l}}{\theta_{2l}^{n_l}+(\tilde{x}_2)^{n_l}}$$

The nonzero element in E is:

$$e_{43} = \frac{A_l(2\eta_{2l} + \eta_{1l})u_1(\tilde{x}_{15})k_{0l}\theta_{2l}^{n_l}}{\theta_{2l}^{nl} + (\tilde{x}_2)^{n_l}}$$

The nonzero elements in F are:

$$f_{86} = -u_3(\tilde{x_{15}})\tilde{x}_8\tilde{x}_9 - u_3(\tilde{x_{15}})k\tilde{x}_8\tilde{x}_6\tilde{x}_{11}$$
$$f_{96} = \frac{\gamma_1 u_4(\tilde{x}_{15})\tilde{x}_8\tilde{x}_9}{1 + m_r\tilde{x}_{11}}$$
$$f_{11,6} = u_4(\tilde{x}_{15})k\gamma_1\tilde{x}_8\tilde{x}_{11}$$

The nonzero elements in G is:

$$g_{13,7} = 2^m\eta_1 u_3(\tilde{x}_{15})\tilde{x}_{12}$$

The nonzero elements in H are:

$$h_{13,9} = \frac{-2^{n_1+1}\eta_2 u_3(\tilde{x}_{15})\tilde{x}_{13}\tilde{x}_9}{\left(1 + \tilde{x_9}^2 + \tilde{x_{11}}^2 + \tilde{x_{13}}^2\right)^2}$$
$$h_{13,11} = \frac{-2^{n_1+1}\eta_2 u_3(\tilde{x}_{15})\tilde{x}_{13}\tilde{x}_{11}}{\left(1 + \tilde{x}_9^2 + \tilde{x}_{11}^2 + \tilde{x}_{13}^2\right)^2}$$
$$h_{13,13} = \frac{2^{n_1}\eta_2 u_3(\tilde{x_{15}})}{1 + \tilde{x}_9^2 + \tilde{x}_{11}^2 + \tilde{x}_{13}^2}$$

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