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PARTIAL STABILITY IN A MODEL FOR ALLERGIC REACTIONS INDUCED BY CHEMOTHERAPY OF ACUTE LYMPHOBLASTIC LEUKEMIA*

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Dedicated to Dr. Dan Tiba on the occasion of his 70th anniversary

Abstract

A new model that captures the cellular evolution of patients undergoing maintenance therapy for acute lymphoblastic leukemia in connection with allergic reactions is considered. A previous model from is modified to include the cells involved in allergies induced by chemotherapy and desensitization.

Delay differential equations are used to model cell evolution. General properties of solutions are deduced, eventually proving partial stability of certain equilibria with respect to some of the variables. The immune system's functioning, as well as the therapeutic role for cancer cure without interference of allergic reactions caused by this treatment, are also evaluated using numerical simulations.

MSC: 34K20; secondary 34K12, 34K25, 92C37, 92C50.

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1 Introduction

Leukemia is a type of blood and bone marrow cancer characterized by an overabundance of abnormal white blood cells.

Acute lymphoblastic leukemia (ALL), also known as acute lymphocytic leukemia, is a type of cancer that arises from the early stages of lymphocyte cells known, as lymphoblasts, in the bone marrow. Leukemic cells normally infiltrate the bloodstream swiftly. They can spread to other organs such the lymph nodes, liver, spleen, etc[7].

Chemotherapy's goal is that, by using drugs, to stop or decrease the growth of cancerous cells. Following the first round of chemotherapy, front line of maintenance therapy is to give the patient 6-MT (mercaptopurine) orally[7, 21].

The more and more use of chemotherapy in recent time enhances hypersensitive responses (HSRs). Drug allergies can be lethal, limiting the use of first-line medicines and threatening patients' survival chance but also the quality of life. The reactions can range from minor cutaneous symptoms like itching and hives to potentially lethal anaphylaxis, which causes hypotension, oxygen deficiency, and cardiovascular collapse [9].

Mercaptopurine is a popular antimetabolite used to treat, besides acute lymphoblastic leukemia, the inflammatory bowel illness[26]. Mercaptopurine's side effects include myelosuppression, hepatotoxicity and hyperpigmentation. The example of a 36-year-old man with Philadelphia chromosome-negative pre-B-cell acute lymphoblastic leukemia who experienced a severe mercaptopurine-induced hypersensitivity reaction that required prolonged hospitalization as well as intensive laboratory tests and imaging is described in the literature[10].

According to [29], administration of oral 6-MP was associated with a 21 % increase in the percentage of CD4+ T cells, restoring the CD4/CD8 ratio. Prior to treatment with 6-MP, there was a T helper type 1(Th1) predominance, with the percentage of IFN-γ^{+} positive cells exceeding that of IL-4 cells. The percentage of CD4+ T cells that were interferon (IFN)-γ^{+} was reduced by 66%, moving the cytokine balance away from Th1 cells (known as proinflammatory) predominance.The IFN-γ^{+} /IL-4 ratio dropped [29]. IFN-γ^{+} is a cytokine which induces Th1 cells response while IL-4 is a cytokine which induces Th2 cells reponse (see [32]). Moreover 6-MP induces cytokines like IL-6 and TNF-alpha [27], where IL-6, the cytokine secreted by antigen-presenting cells, is able to polarize naive CD4+ T cells to effector Th2 cells, by inducing the initial production of IL-4 in CD4+ T cells [31].

According to [35] , Th2 cells stimulate IgE production, whereas Thl cells encourage IgG production (see [15]). So the shift from a Th2-dominated memory state to a Thl-dominated memory state shows a successful chemotherapy without the detection of allergic reactions.

There are several types of regulatory T cells, but the kind that appears to be essential in the context of allergic reactions is the so-called induced regulatory T cells (T_{reg}) [15]. These cells produce cytokines such as IL-10 and TGF-β, which can suppress both Th1 and Th2 immune responses, and they differentiate from naive T cells in the same way as the other subsets do. (see [15]).

The process of helping patients to accept drugs that previously produced hypersensitive reactions is known as drug desensitization. Desensitization, initially used to treat antibiotic hypersensitivity reactions, is now widely used to treat allergies to chemotherapy drugs and ambient sources , broadening the clinical applicability of a procedure that has been shown to be safe and effective in improving clinical outcomes, primarily by allowing patients to continue on their preferred first-line therapy.([34]). Drug desensitization is essentially a process in which an objectionable chemical is supplied in very small dose increments until the total dose equals the medication's initial target dose.

In order to mimic the ALL-immune dynamics under therapy, we use DDEs and some previous ideas (see [6],[7],[15]) to model the allergic reactions. We incorporate desensitization for mercaptopurine in our model to study the avoidance of hypersensitivity to this drug.

Following [37], the body is separated into two compartments: the central compartment, which contains the blood and well-perfused organs such as the heart, lungs, liver, and kidneys, and the peripheral compartment, which contains the weakly perfused tissues and organs.

2 The Model

The model consists of eleven nonlinear delay differential equations describing, in the first 4 equations, the temporal behavior of four variables implied in allergic reactions after allergen administration during treatment with 6-MP. The variables are: the concentration of naive CD4+ cells (N) and the concentrations of Th1, Th2 and T_{reg} cells, (T_1, T_2 and T_r respectively). The first four equations are essentially those from [15], but, following [37], we introduce a delay for the action of antigen presenting cells (APCs).

In Equations (5) and (6) we consider a process of maturation of APCs, denoted as A_1, A_2, after the contact with an allergen.Here we separate from [15] and use the approach in [24].

The rest of equations describe a compartment of erythropoiesis, on the lines in [11],[1], coupled with the dynamics of 6-MP used in the maintenance therapy ([21]). As in [21], we consider the whole population of erythrocytes to be affected by the drug. We denote by E the stem-like short-term erythroid cells, E_c the erythrocytes, E_p, the concentration of erythropoietin, L the loss during cell cycle, M_p the amount of 6-MP in plasma, I the concentration of induced cytokines during chemotherapy

$$\beta_e(x,y) = \quad \beta_0 \frac{1}{1+x^m} \frac{y}{1+y} \tag{1}$$

is the function that regulates the rate of self renewal.

The function

$$k_e(x) = \quad k_0 \tfrac{x}{1+x} \tag{2}$$

is the rate of differentiation.

The loss of stem-like cells is given by the function

$$h(t) = \frac{\gamma_0}{1+E_p(t)^\alpha} + \frac{\tilde{R}_m M_p(t)}{\tilde{R}_{50} + M_p(t)}, \tag{3}$$

such that $\tilde{R}_m = ER_m$ and $\tilde{R}_{50} = ECR_{50}$ (see [6]). Here $\tilde{R}_m$ is the maximum effect of drug on erythrocytes and $\tilde{R}_{50}$ is the saturation constant for drug on erythrocytes.

The loss during the cell cycle is given by:

$$v(t) = e^{-\int\limits_{t-\tau}^{t} h(s)ds}, \tag{4}$$

and a new variable will be introduced as $x_9 = v$.

The analysis above impose the consideration of four time delays:

- The first delay, τ_1, is due to the time for propagation of allergen from central compartment to peripheral compartment[37]. $\tau_1=\dfrac{arctg(\frac{2\pi}{K_{cp}})T}{2\pi}$. Here T is the infusion time interval and K_{cp} is a pharmacokinetic parameter related to the transition between central and peripheral compartment.
- The stem cell proliferation time will be denoted as τ_2.
- The time necessary for the development of the erythrocytes, τ_{RM}, (see[11]) is denoted as τ_3.
- τ_4 is the time necessary for the production of cytokines by the APCs, Naive cells and T cells.

Thus, the complete new model consists in the following equations:

$$\dot{N} = \Lambda - \beta_1 N - NA(t-\tau_1)\left(\frac{T_{1\eta}}{1+m_2T_2}\right) - pNA_2(t-\tau_1)T_2 - \kappa NA_2(t-\tau_1)T_r \tag{5}$$

$$\dot{T}_1 = -\beta_2 T_1 + \frac{\gamma_1 NA_2(t-\tau_1)}{(1+m_rT_r)}\left(\frac{T_1}{1+m_2T_2}\right) \tag{6}$$

$$\dot{T}_2 = -\beta_3 T_2 + p\frac{\gamma_1 NA_2(t-\tau_1)}{(1+m_rT_r)}\left(\frac{T_2}{1+m_1\dfrac{T_1}{1+m_2T_2}}\right) \tag{7}$$

$$\dot{T}_r = -\beta_4 T_r + \kappa\gamma_1 NA_2(t-\tau_1)T_r - \eta_r\frac{IT_r}{1+I} \tag{8}$$

$$\dot{A}_1 = \lambda - \beta M_p A_1 - \gamma_{21}A_1 \tag{9}$$

$$\dot{A}_2 = \beta M_p A_1 - \gamma_{22}A_2 - \mu A_2 T_r \tag{10}$$

$$\begin{aligned}\dot{E} = &-\frac{\gamma_0}{1+E_p^{\alpha_1}}E - \frac{\tilde{R}_m M_p}{\tilde{R}_{50}+M_p}E - (\eta_{1e}+\eta_{2e})k_e(E_p)E - (1-\eta_{1e}-\eta_{2e})\beta_e(E,E_p)E \\ &+ 2L(1-\eta_{1e}-\eta_{2e})\beta_e(E_{\tau_2},E_{p\tau_2})E_{\tau_2} + \eta_{1e}Lk_e(E_{p\tau_2})E_{\tau_2}\end{aligned} \tag{11}$$

$$\dot{E}_c = -\gamma_3 E_c + \tilde{A}_e k_e(E_{p\tau_3}) E_{\tau_3} \tag{12}$$

$$\dot{E}_p = -kE_p + \frac{a_1}{1 + E_c^n} \tag{13}$$

$$\dot{L} = L\left(-\frac{\gamma_0}{1 + E_p^{\alpha_1}} - \frac{\tilde{R}_m M_p}{\tilde{R}_{50} + M_p} + \frac{\gamma_0}{1 + E_{p\tau_2}^{\alpha_1}} + \frac{\tilde{R}_m M_{p\tau_2}}{\tilde{R}_{50} + M_{p\tau_2}}\right) \tag{14}$$

$$\dot{M}_p = a_2 - e_1 M_p - \frac{\mu_C M_p E_c}{c + M_p} \tag{15}$$

$$\dot{I} = -\gamma_4 I + k_1[A(t-\tau_4) + N(t-\tau_4) + T_1(t-\tau_4) + T_2(t-\tau_4) + T_r(t-\tau_4)] \tag{16}$$

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

Equation (5) represents the variation of concentration of naive T-cells which are produced at a constant rate Λ. The second term represents the degradation of naive cells. The last three terms stand for differentiation of naive cells into $Th1, Th2$ and T_{reg} respectively, under the action of APCs.

Equation (6) represents the variation of concentration of $Th1$, which is proportional to the concentration of naive cells timed the concentration of APCs stimulated by the allergen with a delay τ_1. The first term represents the degradation of $Th1$ cells, the second term represents the differentiation of naive cell into $Th1$ diminished due to suppression by T_{reg} and $Th2$ cells.

Equation (7) represents the variation of concentration of $Th2$, which is proportional to the concentration of naive cells timed the concentration of APCs and the concentration of their respective cytokines. The first term represent the degradation of Th2 cells, the second term represents the differentiation of naive cell into $Th2$ divided by the suppression of T_{reg} 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.

Equation (8) represents the variation of concentration of T_{reg}, which is proportional to the concentration of naive cells timed the concentration of APCs . The first term represents the degradation of Treg cells, the second term represents the differentiation of naive cell into T_{reg}. The last term stands for inhibition of T_{reg} by the induced cytokines during chemotherapy with inhibition rate η_r . 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 T_{reg} is controlled by the parameters m_1, m_2, and m_r, in that order.

In equation (9) the first term represents the supply rate of immature (naive) APCs, the second term accounts for the rate of APC activated by the antigen induced during maintenance therapy, the third term represents the death rate of naive APCs

In equation (10) the first term represents the influx of mature APCs from the naive pool due to activation by the antigen, the second term is the natural mortality and the last term represents the deactivation of mature APCs by regulatory T cells with a rate μ.

In equation (11) E represents the stem-like short-term erythroid cells. η_{2e} is the percentage of short term-hematopoietic stem cells (ST-HSC) supposed to undergo asymmetric division. η_{1e} is the percentage that goes to differentiation through symmetric division and $1 - \eta_{1e} - \eta_{2e}$ is the percentage of cells that self-renew through symmetric division. The factor 2 represents the division of each cell into 2 daughter cells. The time necessary for ST-HSC to complete a cycle of self renewal asymmetric division or differentiation is supposed to be same, τ_2.

In equation (12), E_c represents the uninfected erythrocytes. $-\gamma_3 E_c$ reflects the death of erythrocytes at a rate γ_3 and $\widetilde{A}_e = A_e(2\eta_{1e} + \eta_{2e})$ with A_e the amplification factor. Following the completion of amplification through cell division, the cells traverse a maturation period (duration in days denoted by τ_3) then enter the circulation.

In equation (13), $E_p(t)$ represents the concentration of erythropoietin and k represents the absorption rate of erythropoietin.

In equation (14), L is a new variable that represents the loss during the cell cycle.

In equation (15), M_p represents the amount of 6-MP in plasma. The first term accounts for the initial dose of 6MP, the second term represents the direct elimination rate of 6-MP from plasma [21], the third term accounts for the drug elimination from plasma due to the metabolizing into 6-TGP in the blood cells, where we modified the term given in [21] using some ideas from [17] to model the last action. In order to prevent the model to become too complicated, we suppose that elimination has a similar form for other blood cells than erythrocytes and adjust the constant μ_C to account for this.

In equation (16), I represents the production of induced cytokines during chemotherapy, where we follow [16] and consider as its sources the mature APCs and the naive and the mature CD4+ cells. Here the first term accounts for clearing rate of these cytokines, the second term represents the production of cytokines with a delay τ_4, by mature APCs, Naive T cells, Th1 cells, Th2 cells and T reg cells.

In order to facilitate the study of the DDE system, we introduce the following notations:
$x_1 =$ concentration of naive T-cells(N).
$x_2 =$ concentration of Th1 cells($T1$) .
$x_3 =$ concentration of Th2 cells($T2$) .
$x_4 =$concentration of T_{reg} cells($Treg$).
$x_5 =$ concentration of naive APCs(A_1).
$x_6 =$ concentration of mature APCs(A_2).
$x_7 =$concentration of stem-like short-term erythroid cells(E).
$x_8 =$ concentration of the erythrocyte(E_c).
$x_9 =$ concentration of erythropoietin(E_p).
$x_{10} =$ the loss during a cell cycle(L).
$x_{11} =$ the amount of 6-MP in plasma(M_p).
$x_{12} =$the concentration of induced cytokine during maintenance therapy(I).
Thus, the complete model with these new notations consists in the following equations:

$$
\begin{aligned}
&\dot{x_1} = \Lambda - \beta_1 x_1 - x_1 x_{6\tau_1}\left(\frac{x_2}{1+m_2x_3}\right) - p x_1 x_{6\tau_1} x_3 - \kappa x_1 x_{6\tau_1} x_4 \\
&\dot{x_2} = -\beta_2 x_2 + \frac{\gamma_1 x_1 x_{6\tau_1}}{(1+m_r x_4)}\left(\frac{x_2}{1+m_2x_3}\right) \\
&\dot{x_3} = -\beta_3 x_3 + p\frac{\gamma_1 x_1 x_{6\tau_1}}{(1+m_r x_4)}\left(\frac{x_3}{1+m_1\dfrac{x_2}{1+m_2x_3}}\right) \\
&\dot{x_4} = -\beta_4 x_4 + \kappa\gamma_1 x_1 x_{6\tau_1} x_4 - \eta_r\frac{x_{12}x_4}{1+x_{12}} \\
&\dot{x_5} = \lambda - \beta x_{11} x_5 - \gamma_{21} x_5 \\
&\dot{x_6} = \beta x_{11} x_5 - \gamma_{22} x_6 - \mu x_6 x_4 \\
&\dot{x_7} = -\frac{\gamma_0}{1+x_9^{\alpha_1}}x_7 - \frac{\tilde{R}_m x_{11}}{\tilde{R}_{50}+x_{11}}x_7 - (\eta_{1e}+\eta_{2e})k_e(x_9)x_7 \\
&-(1-\eta_{1e}-\eta_{2e})\beta_e(x_7,x_9)x_7 + 2x_{10}(1-\eta_{1e}-\eta_{2e})\beta_e(x_{7\tau_2},x_{9\tau_2})x_{7\tau_2} \\
&+\eta_{1e}x_{10}k_e(x_{9\tau_2})x_{7\tau_2} \\
&\dot{x_8} = -\gamma_3 x_8 + \tilde{A}_e k_e(x_{9\tau_3})x_{7\tau_3} \\
&\dot{x_9} = -kx_9 + \frac{a_1}{1+x_8^n} \\
&\dot{x}_{10} = x_{10}\left(-\frac{\gamma_0}{1+x_9^{\alpha_1}} - \frac{\tilde{R}_m x_{11}}{\tilde{R}_{50}+x_{11}} + \frac{\gamma_0}{1+x_{9\tau_2}^{\alpha_1}} + \frac{\tilde{R}_m x_{11\tau_2}}{\tilde{R}_{50}+x_{11\tau_2}}\right)
\end{aligned}
\tag{17}
$$

$$\dot{x}_{11} = a_2 - e_1 x_{11} - \frac{\mu_C x_{11} x_8}{c + x_{11}}$$

$$\dot{x}_{12} = -\gamma_4 x_{12} + k_1(x_{6\tau_4} + x_{1\tau_4} + x_{2\tau_4} + x_{3\tau_4} + x_{4\tau_4})$$

3 Equilibria

Setting the right-hand side of the equations in (17) to be equal to zero, the equilibrium points of our model are found. We choose only the non-negative equilibria, since only they have a biological meaning. Some of these equilibria will be presented next and analyzed from a medical point of view.

The first one is $E_1 = (x_1^*, 0, 0, 0, x_5^*, x_6^*, 0, 0, x_9^*, x_{10}^*, x_{11}^*, x_{12}^*)$ with

$x_1^* = \dfrac{\Lambda}{\beta_1}, x_5^* = \dfrac{\lambda}{\gamma_{21} + \beta x_{11}^*}, x_6^* = \dfrac{\beta x_{11}^* x_5^*}{\gamma_{22}}$

$x_9^* = \dfrac{a_1}{k}$

$x_{10}^* = e^{-\left(\dfrac{\gamma_0}{1 + x_8^{*\alpha_1}} + \dfrac{\tilde{R}_m x_{11}^*}{\tilde{R}_{50} + x_{11}^*}\right)\tau_2}$

$x_{11} = \dfrac{a_2}{e_1}, x_{12}^* = \dfrac{k_1(x_6^* + x_1^*)}{\gamma_4}$

E_1 corresponds to the death of the patient since there are no more erythrocytes nor T_{reg}.

The second equilibrium point, $E_2 = (x_1^*, x_2^*, 0, 0, x_5^*, x_6^*, 0, 0, x_9^*, x_{10}^*, x_{11}^*, x_{12}^*)$, illustrates a situation when there is still a critical condition but there are no allergic effects because we see that the number of Th1-cells is different from zero but that of Th2-cells is equal to zero.

Here,

$x_1 = \dfrac{\beta_2}{\gamma_1 x_6^*}, x_2^* = \dfrac{\Lambda - \beta_1 x_1^*}{x_1^* x_6^*}, x_5^* = \dfrac{\lambda}{\gamma_{21} + \beta x_{11}^*}, x_6^* = \dfrac{\beta x_{11}^* x_5^*}{\gamma_{22}}$

$x_9^* = \dfrac{a_1}{k}$

$x_{10}^* = e^{-\left(\dfrac{\gamma_0}{1 + x_8^{*\alpha_1}} + \dfrac{\tilde{R}_m x_{11}^*}{\tilde{R}_{50} + x_{11}^*}\right)\tau_2}$

$x_{11}^* = \dfrac{a_2}{e_1}, x_{12}^* = \dfrac{k_1(x_5^* + x_1^* + x_2^*)}{\gamma_4}$

$E_3 = (x_1^*, x_2^*, 0, 0, x_5^*, x_6^*, x_7^*, x_8^*, x_9^*, x_{10}^*, x_{11}^*, x_{12}^*)$ corresponds to a healthy state of the patient with no allergic reactions (because in E_3 we see that the Th1 (x_2) cells are not equal to zero so in this way Th1 will dominate Th2 cells that are zero)[32].

Here,
$x_1^* = \dfrac{\beta_2}{\gamma_1 x_6^*}, x_2^* = \dfrac{\Lambda - \beta_1 x_1^*}{x_1^* x_6^*}, x_5^* = \dfrac{\lambda}{\gamma_{21} + \beta x_{11}^*}, x_6^* = \dfrac{\beta x_{11}^* x_5^*}{\gamma_{22}}$
$x_{10}^* = e^{-\left(\dfrac{\gamma_0}{1 + x_8^{*\alpha_1}} + \dfrac{\tilde{R}_m x_{11}^*}{\tilde{R}_{50} + x_{11}^*}\right)\tau_2}$
$x_{12}^* = \dfrac{k_1(x_6^* + x_1^* + x_2^*)}{\gamma_4}$
The values of x_1^*, x_7^*, x_8^*, x_9^*, x_{11}^* are calculated numerically in the last section.

$E_4 = (x_1^*, 0, x_3^*, 0, x_5^*, x_6^*, x_7^*, x_8^*, x_9^*, x_{10}^*, x11^*, x_{12}^*)$ corresponds to a healthy state of the patient with allergic effects that might still persist (because in E4 we see that the Th2(x_3) cells are not equal to zero so in this way Th2 dominate the Th1 cells and T reg cells that are zero)[32].
$x_1^* = \dfrac{\beta_3}{p\gamma_1 x_6^*}, x_3^* = \dfrac{\Lambda - \beta_1 x_1^*}{p x_1^* x_6^*}, x_5^* = \dfrac{\lambda}{\gamma_{21} + \beta x11^*}, x_6^* = \dfrac{\beta x_{11}^* x_5^*}{\gamma_{22}},$
$x_{10}^* = e^{-\left(\dfrac{\gamma_0}{1 + x_8^{*\alpha_1}} + \dfrac{\tilde{R}_m x_{11}^*}{\tilde{R}_{50} + x_{11}^*}\right)\tau_2}$
$x_{12}^* = \dfrac{k_1(x_5^* + x_1^* + x_3^*)}{\gamma_4}$
The values of x_7^*, x_8^*, x_9^* and x_{11}^* are also calculated numerically in the last section.

The linearized system around an equilibrium point is written as:

$$\dot{x} = Ax + Bx_{\tau_1} + Cx_{\tau_2} + Dx_{\tau_3} + Ex_{\tau_4} \tag{18}$$

with $x = (x_1, \cdots, x_{12}), \quad x_{\tau_i} = (x_{1\tau_i}, \cdots, x_{12\tau_i}), \quad i = 1, 2, 3, 4$

$$A = \left.\frac{\partial f}{\partial x}\right|_{E_i}, \quad B = \left.\frac{\partial f}{\partial x_{\tau_1}}\right|_{E_i}, \quad C = \left.\frac{\partial f}{\partial x_{\tau_2}}\right|_{E_i}, \quad D = \left.\frac{\partial f}{\partial x_{\tau_3}}\right|_{E_i}, \quad E = \left.\frac{\partial f}{\partial x_{\tau_4}}\right|_{E_i} \tag{19}$$

The characteristic equation corresponding to (18) is :

$$det\left(\lambda I_{11} - A - Be^{-\lambda\tau_1} - Ce^{-\lambda\tau_2} - De^{-\lambda\tau_3} - Ee^{-\lambda\tau_4}\right) = 0 \tag{20}$$

To study the stability of an equilibrium point we should use this characteristic equation. It is known that if all the roots of the characteristic equation have negative real parts, then the equilibrium point is uniformly asymptotically stable. If there exist at least one root with a positive real part then the equilibrium point is unstable . The matrices introduced above will be calculated below. The values of the state variables must be replaced by the values corresponding to the equilibrium point under study.

$$A = \frac{\partial f}{\partial x}$$

$$a_{11} = -\beta_1 - x_6 \frac{x_2}{1+m_2x_3} - px_6x_3 - \kappa x_6 x_4$$
$$a_{12} = -\frac{x_1x_6}{1+m_2x_3}$$
$$a_{13} = \frac{m_2x_1x_6x_2}{(1+m_2x_3)^2} - px_1x_6$$
$$a_{14} = -\kappa x_1 x_6$$
$$a_{21} = \frac{\gamma_1 x_6 x_2}{(1+m_r x_4)(1+m_2x_3)}$$
$$a_{22} = -\beta_2 + \frac{\gamma_1 x_1 x_6}{(1+m_r x_4)(1+m_2x_3)}$$
$$a_{23} = \frac{-\gamma_1 m_2 x_6 x_1 x_2}{(1+m_r x_4)(1+m_2x_3)^2}$$
$$a_{24} = \frac{-\gamma_1 m_r x_6 x_1 x_2}{(1+m_r x_4)^2(1+m_2x_3)}$$
$$a_{31} = \frac{p\gamma_1 x_6 x_3}{(1+m_r x_4)(1+m_1 \frac{x_2}{1+m_2x_3})}$$
$$a_{32} = -\frac{p\gamma_1 x_1 x_6 x_3 m_1 (1+m_2x_3)}{(1+m_r x_4)(1+m_2x_3+m_1x_2)^2}$$
$$a_{33} = -\beta_3 + \frac{p\gamma_1 x_1 x_6}{1+m_r x_4} \frac{1+m_2x_3+m_2^2x_3^2+m_1x_2+2m_1m_2x_2x_3}{(1+m_1x_2+m_2x_3)^2})$$
$$a_{34} = -\frac{pm_r\gamma_1 x_1 x_6 x_3}{(1+m_r x_4)^2(1+m_1 \frac{x_2}{1+m_2x_3})}$$
$$a_{41} = \kappa\gamma_1 x_6 x_4$$
$$a_{44} = -\beta_4 + \kappa\gamma_1 x_6 x_1 - \frac{\eta_r x_{12}}{1+x_{12}}$$
$$a_{4,12} = -\frac{\eta_r x_4}{(1+x_{12})^2}$$
$$a_{55} = \beta x_{11} - \gamma_{21}$$
$$a_{5,11} = -\beta x_5$$
$$a_{64} = -\mu x_6$$
$$a_{65} = \beta x_{11}$$
$$a_{66} = -\gamma_{22}$$
$$a_{6,11} = \beta x_5$$
$$a_{77} = -\frac{\gamma_0}{1+x_9^{\alpha_1}} - \frac{\tilde{R}_m x_{11}}{\tilde{R}_{50}+x_{11}} - (\eta_{1e}+\eta_{2e})k_e(x_9)$$
$$-(1-\eta_{1e}-\eta_{2e})\left[\beta_e(x_7,x_9) + \frac{\partial \beta_e(x_7,x_9)}{\partial x_7} x_7\right]$$

$$a_{79} = \frac{\alpha_1\gamma_0 x_7 x_9^{\alpha_1-1}}{(1+x_9^{\alpha_1})^2} - (\eta_{1e}+\eta_{2e})k_e'(x_9)x_7 - (1-\eta_{1e}-\eta_{2e})x_7\frac{\partial\beta_e}{\partial x_9}(x_7,x_9)$$
$$a_{7,10} = 2(1-\eta_{1e}-\eta_{2e})x_7\beta_e(x_7,x_9) + \eta_{1e}k_e(x_9)x_7$$
$$a_{7,11} = -\tilde{R}_m x_7 \frac{\tilde{R}_{50}}{(\tilde{R}_{50}+x_{11})^2}$$
$$a_{88} = -\gamma_3$$
$$a_{98} = -\frac{a_1 n x_8^{n-1}}{(1+x_8)^2}$$
$$a_{99} = -k$$
$$a_{10,9} = \frac{\gamma_0\alpha_1 x_{10} x_9^{\alpha_1-1}}{(1+x_9^{\alpha_1})^2}$$
$$a_{10,11} = -\tilde{R}_m x_{10}\frac{\tilde{R}_{50}}{(\tilde{R}_{50}+x_{11})^2}$$
$$a_{11,8} = -\frac{\mu_C x_{11}}{c+x_{11}}$$
$$a_{11,11} = -e_1 - \frac{\mu_C x_8 c}{(c+x_{11})^2}$$
$$a_{12,12} = -\gamma_4$$

and the other values are zeros

$$B = \frac{\partial f}{\partial x_{\tau_1}}$$

$$b_{16} = -\frac{x_1x_2}{1+m_2x_3} - px_1x_3 - \kappa x_1x_4$$
$$b_{26} = \frac{\gamma_1 x_1 x_2}{(1+m_r x_4)(1+m_2x_3)}$$
$$b_{36} = \frac{p\gamma_1 x_1 x_3}{(1+m_r x_4)(1+m_1\frac{x_2}{1+m_2x_3})}$$
$$b_{46} = \kappa\gamma_1 x_1 x_4$$

and the other values are zero.

$$C = \frac{\partial f}{\partial x_{\tau_2}}$$

$$c_{77} = 2x_{10}(1-\eta_{1e}-\eta_{2e})\left[\beta_e(x_7,x_9) + \frac{\partial\beta_e(x_7,x_9)}{\partial x_7}x_6\right] + \eta_{1e}x_{10}k_e(x_9)$$
$$c_{79} = 2x_{10}(1-\eta_{1e}-\eta_{2e})\left[\frac{\partial\beta_e(x_7,x_9)}{\partial x_9}x_7\right] + \eta_{1e}x_{10}x_7k_e'(x_9)$$
$$c_{10,9} = -\frac{\gamma_0\alpha_1 x_{10} x_9^{\alpha_1-1}}{(1+x_9^{\alpha_1})^2}$$

$c_{10,11} = \dfrac{x_{10}\tilde{R}_{50}\tilde{R}_m}{(\tilde{R}_{50} + x_{11})^2}$
and the other values are zero.

$$D = \frac{\partial f}{\partial x_{\tau_3}}$$

$d_{87} = \tilde{A}_e k_e(x_9)$
$d_{89} = \tilde{A}_e x_7 k_e'(x_9)$
and the other values are zero.

$$E = \frac{\partial f}{\partial x_{\tau_4}}$$

$e_{12,1} = e_{12,2} = e_{12,3} = e_{12,4} = e_{12,6} = k_1$

and the other values are zero.

3.1 Stability Analysis of E_1

The characteristic equation (20) corresponding to E_1 becomes:

$$\begin{vmatrix}
k_1 & -a_{12} & -a_{13} & -a_{14} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & k_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & k_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & k_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & k_5 & 0 & 0 & 0 & 0 & 0 & -a_{5,11} & 0 \\
0 & 0 & 0 & -a_{64} & -a_{65} & k_6 & 0 & 0 & 0 & 0 & -a_{6,11} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & k_7 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & -d_{87}e^{-\lambda\tau_2} & k_8 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_9 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -a_{10,9} - c_{10,9}e^{-\lambda\tau_2} & k_{10} & -a_{10,11} - c_{10,11}e^{-\lambda\tau_2} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -a_{11,8} & 0 & 0 & k_{11} & 0 \\
-e_{12,1}e^{-\lambda\tau_4} & -e_{12,2}e^{-\lambda\tau_4} & -e_{12,3}e^{-\lambda\tau_4} & -e_{12,4}e^{-\lambda\tau_2} & 0 & -e_{12,6}e^{-\lambda\tau_4} & 0 & 0 & 0 & 0 & 0 & k_{12}
\end{vmatrix} = 0$$

where

$$\begin{aligned}
k_1 &= \lambda - a_{11} \\
k_2 &= \lambda - a_{22} \\
k_3 &= \lambda - a_{33} \\
k_4 &= \lambda - a_{44} \\
k_5 &= \lambda - a_{55} \\
k_6 &= \lambda - a_{66} \\
k_7 &= \lambda - a_{77} - c_{77}e^{-\lambda\tau_2} \\
k_8 &= \lambda - a_{88} \\
k_9 &= \lambda - a_{99} \\
k_{10} &= \lambda \\
k_{11} &= \lambda - a_{11,11} \\
k_{12} &= \lambda - a_{12,12}
\end{aligned}$$

Expanding the above determinant we get the following form of the equation:

$$d_1(\lambda) = \lambda(\lambda - a_{11})(\lambda - a_{22})(\lambda - a_{33})(\lambda - a_{44})(\lambda - a_{55})(\lambda - a_{66})$$
$$(\lambda - a_{77} - c_{77}e^{-\lambda\tau_2})(\lambda - a_{88})(\lambda - a_{99})(\lambda - a_{11,11})(\lambda - a_{12,12}) = 0.$$

Remark that a critical case for stability appears since $\lambda = 0$ is a root. If one can apply the results from [3], E_1 has a regular asymptotic behavior if $a_{11},\ a_{22},\ a_{33},\ a_{44},\ a_{55},\ a_{66},\ a_{88},\ a_{99}, a_{11,11}, a_{12,12}$ are negative and all the roots of the equation

$$\lambda - a_{77} - c_{77}e^{-\lambda\tau_2} = 0 \tag{21}$$

have negative real parts.
According to [12] a necessary and sufficient condition in order that all roots of equation(21) have negative real parts is that:

- $a_{77}\tau_2 < 1$
- $a_{77}\tau_2 < -c_{77}\tau_2 < (\theta^2 + a_{77}^2\tau_2^2)^{\frac{1}{2}}$

where, since $a_{77} \neq 0, \theta$ is the unique root of the equation $\theta = a_{66}\tau_2\ tan(\theta)$.
Since we do not have an equation with the linear part equal to zero, the theorem in [3] is not directly applicable, so we should proceed to bring the system to the canonical form to which this theorem can be applied (see the details in [3], [6]).
But, according to the numerical values of the parameters, we get :
$a_{22} = 1.8991,\ a_{33} = 0.0722$ so E_1 is not stable, therefore we will study its partial stability below.

3.2 Stability Analysis of E_2

The characteristic equation (20) corresponding to E_2 becomes:

$$\begin{vmatrix}
k_1 & -a_{12} & -a_{13} & -a_{14} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-a_{21} & k_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & k_3 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & k_4 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & k_5 & 0 & 0 & 0 & 0 & 0 & -a_{5,11} & 0 \\
0 & 0 & 0 & -a_{64} & -a_{65} & k_6 & 0 & 0 & 0 & 0 & -a_{6,11} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & k_7 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & -d_{87}e^{-\lambda\tau_2} & k_8 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & k_9 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -a_{10,9} - c_{10,9}e^{-\lambda\tau_2} & k_{10} & -a_{10,11} - c_{10,11}e^{-\lambda\tau_2} & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & -a_{11,8} & 0 & 0 & k_{11} & 0 \\
-e_{12,1}e^{-\lambda\tau_4} & -e_{12,2}e^{-\lambda\tau_4} & -e_{12,3}e^{-\lambda\tau_4} & -e_{12,4}e^{-\lambda\tau_2} & 0 & -e_{12,6}e^{-\lambda\tau_4} & 0 & 0 & 0 & 0 & 0 & k_{12}
\end{vmatrix} = 0$$

where,

$$
\begin{aligned}
k_1 = &\quad \lambda - a_{11}\\
k_2 = &\quad \lambda - a_{22}\\
k_3 = &\quad \lambda - a_{33}\\
k_4 = &\quad \lambda - a_{44}\\
k_5 = &\quad \lambda - a_{55}\\
k_6 = &\quad \lambda - a_{66} - c_{66}e^{-\lambda\tau_2}\\
k_7 = &\quad \lambda - a_{77}\\
k_8 = &\quad \lambda - a_{88}\\
k_9 = &\quad \lambda\\
k_{10} = &\quad \lambda - a_{1010}
\end{aligned}
$$

This time, the determinant above gives the following equation:

$$
\begin{aligned}
d_2(\lambda) = \lambda[\lambda^2 - \lambda(a_{11} + a_{22}) + a_{11}a_{22} - a_{12}a_{21}]&\\
\times (\lambda - a_{33})(\lambda - a_{44})(\lambda - a_{55})(\lambda - a_{66})(\lambda - a_{77} - c_{77}e^{-\lambda\tau_2})&\\
\times (\lambda - a_{88})(\lambda - a_{99})(\lambda - a_{11,11})(\lambda - a_{12,12}) = 0.&
\end{aligned}
$$

Therefore, using the approach for the critical case as before, necessary conditions for stability of E_2 are
$a_{33},\ a_{44},\ a_{55},\ a_{77},\ a_{88}, a_{10,10},\ a_{11,11}$ to be negative and all the roots of the equations

$$\lambda - a_{77} - c_{77}e^{-\lambda\tau_2} = 0 \tag{22}$$

$$\lambda^2 - (a_{11} + a_{22})\lambda + a_{11}a_{22} - a_{12}a_{21} = 0 \tag{23}$$

have negative real parts.
Once again, according to numerical calculations, using the parameters listed at the end of the paper, the solutions of equation (23) are $\lambda_1 = 2.3799$ and $\lambda_2 = 0.0239$ and since both of them are positive, E_2 is unstable.

4 General properties of the solutions

Define $\tau = max\{\tau_1, \tau_2, \tau_3, \tau_4\}$ and let $PC([-\tau, 0], \mathbb{R}^{12})$ denote the space of piecewise continuous functions defined on $[-\tau, 0]$ with values in $\mathbb{R}^{12}$. The norm in $PC([-\tau, 0], \mathbb{R}^{12})$ will be defined by

$$||\varphi||_\tau = sup\{||\varphi(t)||_2 | t \in [-\tau, 0]\},$$

with $|| \cdot ||_2$ the euclidean norm in $\mathbb{R}^n$. For (17)consider the initial data

$$x(s) = \varphi(s), s \in [-\tau, 0] \tag{24}$$

Proposition 1. *If the initial data $\varphi \in PC([-\tau,0],\mathbb{R}^{11})$ satisfy $\varphi_j(s) > 0 \;\forall\; s \in [-\tau,0], j = 1,\dots,10$ then the solution of the Cauchy problem ((17)+(24)) will satisfy $x_j(t) \geq 0, j = 1,\dots,10$ for all t in the domain of existence.*

Proof. Since $x_j(0) > 0 \;\forall\; j = 1,\dots,12$ there $t_0 > 0$ so that

$$x_j(t) > 0 \;\forall\; t \in [0,t_0),\; \forall\; j = 1,\dots,11.$$

It follows that $x_1(t) > 0 \;\forall\; t \in [-\tau,t_1), t_1 \geq t_0$.
If $x_1(t_1) = 0$ one has $x_1'(t_1) = \Lambda > 0$ so x_1 will increase for $t > t_1$ and consequently, $x_1(t) > 0 \;\forall\; t$ in the domain of existence. The same reasoning applies to x_5 and x_{11}.
In the same vein we see that if

$$x_{12}(t_0) = 0 \Rightarrow x_{12}'(t_0) > 0 \Rightarrow x_{12}(t) > 0 \;\forall\; t \in [t_0,t_{12}) t_{12} > t_0$$

$$\to 1 + x_{12}(t) > 0 \; for \; t \in (0,t_{12})$$

Then, since

$$x_4(t) = x_4(0)e^{-\int_0^t [\beta_4 - k\gamma_1 x_1(s)x_5(s-\tau_1) + \eta_r \frac{x_{12}(s)}{1+x_{12}(s)}]ds}$$

one has $x_4(t) > 0 \;\forall\; t \in [0,t_{11})$.
Remark that we have

$$1 + m_2 x_3(t) > 0, 1 + m_1 x_2(t) + m_2 x_3(t) > 0 \;\forall\; t \in [0,t_2) \subset [0,t_{12}), t_2 \geq t_0$$

Then

$$x_3(t) = x_3(0)e^{\int_0^t [-\beta_3 + p\gamma_1 \frac{x_1(s)x_5(s-\tau_1)[1+m_2 x_3(s)]}{[1+m_r x_4(s)][1+m_1 x_2(t)+m_2 x_3(t)]}]ds} > 0 \;\forall\; t \in [0,t_2).$$

Since $x_3(t_2) = 0$ is clearly impossible we conclude that $x_3(t) > 0 \;\forall\; t \in [0,t_{12})$.
Similarly,

$$x_2(t) = x_2(0)e^{-\int_0^t [\beta_2 - \gamma_1 \frac{x_1(s)x_5(s-\tau_1)}{[1+m_r x_4(s)][1+m_2 x_3(s)]}]ds}$$

we conclude that $x_2(t) > 0 \;\forall\; t \in [0,t_{12})$.
$x_{10}(t) > 0$ by its definition.
If $x_6(t_6) = 0 \Rightarrow x_s'(t_6) > 0 \Rightarrow x_6(t) > 0 \;\forall\; t$ in the domain of existence.
The same reasoning apply to x_7, x_8 so they are also strictly positive on the whole interval of existence and then $x_9 > 0$ on the whole interval of existence.
From now on, the initial data for (17) will be supposed positive. □

Proposition 2. *If*

$$\frac{5k_1}{\gamma_4} < 1, \tag{25}$$

then,
$x_1, x_5, x_6, x_9, x_{10}, x_{11}$ *are bounded on the whole interval of existence.*

Proof. From (17) it follows that

$$\dot{x_1}(t) = \Lambda - \beta_1 x_1(t) - x_1(t)p_1(t)$$

with $p_1(t) \geq 0$ for positive initial data. Then

$$x_1(t) = x_1(0)e^{-\beta_1 t - \int_0^t p_1(s)ds} + \Lambda \left(\int_0^t e^{\beta_1 s} e^{\int_0^s p_1(r)dr} ds \right) e^{-\beta_1 t} e^{-\int_0^t p_1(s)ds}$$

and we have the following estimation for the second term

$$\Lambda \left(\int_0^t e^{\beta_1 s} e^{\int_0^s p_1(r)dr} ds \right) e^{-\beta_1 t} e^{-\int_0^t p_1(s)ds} \leq$$

$$\leq \Lambda \left(\int_0^t e^{\beta_1 s} e^{\int_0^t p_1(r)dr} ds \right) e^{-\beta_1 t} e^{-\int_0^t p_1(s)ds} = \Lambda \tfrac{1-e^{-\beta_1 t}}{\beta_1} \leq \tfrac{\Lambda}{\beta_1}\ \forall\ t \geq 0$$

It follows that $|x_1(t)| \leq M_1$ for some positive M_1.
For $x_{11}(t)$ we introduce

$$p_{11}(t) = \mu_C \frac{x_8(t)}{c + x_{11}(t)}$$

and we can write

$$\begin{aligned}
&x_{11}(t) = x_{11}(0)e^{-e_1 t - \int_0^t p_{11}(s)ds} + a_2 \left(\int_0^t e^{e_1 s + \int_0^s p_{11}(r)dr} ds \right) e^{-e_1 t - \int_0^t p_{11}(s)ds} \leq \\
&\leq x_{11}(0) + a_2 \left(\int_0^t e^{e_1 s} ds \right) e^{\int_0^t p_{11}(r)dr} e^{-e_1 t} e^{-\int_0^t p_{11}(s)ds} = \\
&= x_{11}(0) + a_2 \tfrac{e^{e_1 t} - 1}{e_1} e^{-e_1 t} \leq x_{11}(0) + \tfrac{a_2}{e_1} = M_{11}
\end{aligned}$$

(for positive initial data, $x_8(t)$ & $x_{11}(t)$ are positive according to proposition 1.)
For x_5, remark that

$$\begin{aligned}
&x_5(t) = x_5(0)e^{-\gamma_{21} t - \beta \int_0^t x_{11}(s)ds} + \lambda \left(\int_0^t e^{\gamma_{21} s} e^{\beta \int_0^s x_{11}(r)dr} ds \right) e^{-\gamma_{21} t} e^{-\beta \int_0^t x_{11}(s)ds} \leq \\
&\leq x_5(0) + a \left(\int_0^t e^{\gamma_{21} s} ds \right) e^{\beta \int_0^t x_{11}(r)dr} e^{-\gamma_{21} t} e^{-\beta \int_0^t x_{11}(s)ds} \\
&= x_5(0) + \frac{a}{\gamma_{21}}(1 - e^{-\gamma_{21} t}) \leq \\
&\leq x_5(0) + \frac{a}{\gamma_{21}} = M_5.
\end{aligned}$$

With similar arguments one obtains that x_6 is bounded:

$$x_6(t) = x_6(0)e^{-\gamma_{22}t-\mu\int_0^t x_4(s)ds} + \beta\left(\int_0^t x_{11}(s)x_5(s)e^{\gamma_{22}s}e^{\mu\int_0^s x_4(r)dr}ds\right) \cdot e^{-\gamma_{22}t}e^{-\mu\int_0^t x_4(s)ds}.$$

Then

$$x_6(t) \leq x_6(0) + \beta M_{11}M_5\left(\int_0^t e^{\gamma_{12}s}ds\right)e^{\mu\int_0^t x_4(s)ds}e^{-\gamma_{22}t}e^{-\mu\int_0^t x_4(s)ds} \leq$$
$$\leq x_6(0) + \frac{\beta_0}{\gamma_{22}}M_{11}M_5 = M_6$$

Passing to x_9, one has the following estimations,

$$x_9(t) = x_9(0)e^{-kt} + \big(\int_0^t \frac{a_1}{1+x_8^n(s)}e^{ks}ds\big)e^{-kt}$$

But

$$x_8(t) > 0 \Rightarrow \frac{a_1}{1+x_8^n(s)} < a_1$$

So we get the following estimations

$$x_9(t) \leq ||\varphi||_\tau + \frac{a_1}{k}\left(1-e^{-kt}\right) \leq ||\varphi||_\tau + \frac{a_1}{k} = M_9$$

so $x_9(t)$ is bounded
$x_{10}(t)$ is bounded by its definition since $h(t) > 0$,

$$x_{10}(t) \leq M_{10} \leq 1$$

$\square$

Proposition 3. *The solution of (17) exists on* $[-\tau, \infty)$.

Proof. The Proposition will follow from a slight generalization of Theorem 1.2. in [23] where the conditionon f that ensures global existence is supposed to hold only for the solutions of (17), this being used in the proof. So we need to prove that, with $\varphi = (\varphi_1, \ldots, \varphi_{11})$ a solution of (17) and $f = (f_1, \ldots, f_{11})$ the right-hand side of (17), one has

$$|f_j(\varphi)| \leq h(||\varphi||_\tau), j = 1, \ldots, 11, \int_{r_0}^{\infty} \frac{1}{h(r)}dr = \infty, \forall\, r_0 > 0.$$

We will show that there exist constants K_1, K_2 so that
$|f_j(\varphi)| \leq K_1 + K_2||\varphi||_\tau, j = 1, \ldots, 11$ and the Proposition will result.

$$|f_1(\varphi)| \leq |\Lambda| + \beta_1 M_1 + M_1 M_6 |\varphi_2(t)| + pM_1 M_6 |\varphi_3(t)| + \kappa M_1 M_6 |\varphi_4(t)| \leq$$

$$\leq |\Lambda| + \beta_1 M_1 + (M_1 M_6 + pM_1 M_6 + \kappa M_1 M_6)||\varphi||_\tau$$

$$|f_2(\varphi)| \leq (\beta_2 + \gamma_1 M_1 M_6)||\varphi||_\tau$$

$$|f_3(\varphi)| \leq (\beta_3 + p\gamma_1 M_1 M_6)||\varphi||_\tau$$

$$|f_4(\varphi)| \leq (\beta_4 + \kappa\gamma_1 M_1 M_6 + \eta_r)||\varphi||_\tau$$

$$|f_5(\varphi)| \leq \lambda + \gamma_{21} M_5 + \beta M_5 M_{11},$$

$$|f_6(\varphi)| \leq \gamma_{22} M_6 + \beta M_5 M_{11} + \mu M_6 ||\varphi||_{tau}$$

$$|f_7(\varphi)| \leq [\gamma_0 + \tilde{R_m} + (\eta_{1e} + \eta_{2e})k_0 + (1 - \eta_{1e} - \eta_{2e})\beta_0$$
$$+2M_{10}(1 - \eta_{1e} - \eta_{2e})\beta_0 + \eta_{1e} k_0 M_{10}]||\varphi||_\tau$$

$$|f_8(\varphi)| \leq (\gamma_3 + \tilde{A}_e k_e(M_8))||\varphi||_\tau$$

$$|f_9(\varphi)| \leq a_1 + kM_9,$$

$$|f_{10}(\varphi)| \leq (2\gamma_0 + 2\tilde{R}_m)M_{10},$$

$$|f_{11}(\varphi)| \leq a_2 + e_1 M_{11} + \mu_C ||\varphi||_\tau$$
$$|f_{12}(\varphi)| \leq (\gamma_4 + 5k_1)||\varphi||_\tau,$$

□

4.1 Partial Stability of E_1

In this section we will derive delay-independent partial stability conditions for the equilibrium E_1 of the considered system.
We recall first the necessary definitions and results from [33], [2], [13]. Consider the system

$$\dot{x} = X(t, x_t), x_{t_0} = \varphi \tag{26}$$

We assume that $\tau > 0$ is a given real number, $x_t : [-\tau, 0] \to \mathbb{R}^n$ is defined by $x_t(s) = x(t+s)$, with the norm

$$||x(t)||_2 = \sqrt{x_1^2(t) + \cdots + x_n^2(t)}$$

We introduce the partition:
$x = (z, u)^T$ (T denotes transposition), where $z \in \mathbb{R}^m$, $u \in R^{n-m}(1 \leq m < n)$.
$X : \mathbb{R} \times C \to \mathbb{R}^n$ is assumed to be continuous and X maps every $\mathbb{R}\times$ (bounded set) into a bounded set, in the domain D defined by

$$t \geq 0, \quad ||z||_\tau \leq h, \quad ||u||_\tau < \infty \tag{27}$$

The solutions of (26) are assumed to be unique and u-continuable: the solutions are defined for every $t \geq t_0$ where $||z(t; t_0, \varphi)||_2 \leq h$. If we suppose that (27) holds for all $t \geq t_0$ then the solution $x(t; t_0, \varphi)$ is defined for all $t \geq t_0$.
Taking into account the above partitions, the system (26) can be represented as:

$$\dot{z}(t) = Z(t, y_t, z_t), \dot{u}(t) = U(t, y_t, z_t) \tag{28}$$

Suppose that

$$Z(t, 0, 0) = 0, \;\; U(t, 0, 0) = 0 \; \forall \; t \geq t_0 \tag{29}$$

Let $x(t; t_0, \varphi)$ denote a solution of the system (26) with initial condition $x(t_0; \varphi)$.The same notation will be applied for the solutions of each of the two equations in (28).

Definition ([33], [13], [2]). The equilibrium point x = 0 of system (26), & (28) is called

1. z-stable, if for every $t_0 \geq 0$ and every $\epsilon > 0$, there exists a $\delta(\epsilon; t_0) > 0$ such that $||\varphi||_\tau < \delta$ implies $||z(t; t_0; \varphi)||_2 < \epsilon$ for all $t \geq t_0$. It is called uniformly y-stable if δ does not depend on t_0,

2. asymptotically z-stable if it is z-stable and for every $t_0 \geq 0$ there exists a $\Delta(t_0) > 0$ such that for every solution $x(t; t_0; \varphi)$ of system (26),& (28) that satisfies $||\varphi||_\tau < \Delta(t_0)$ the following holds true

$$\lim_{t\to\infty} ||z(t; t_0; \varphi)|| = 0 \tag{30}$$

3. uniformly asymptotically z-stable, if it is uniformly z-stable with respect to t_0 in terms of point (1) and one can find $\Delta > 0$ such that relation (30) is met uniformly with respect to (t_0, φ) from the domain $t_0 \geq 0, ||\varphi||_\tau < \Delta$ (for any numbers $\eta > 0$, $t_0 \geq 0$ one can find the number $T = T(\eta) > 0$ such that $||z(t; t_0, \varphi)|| < \eta$ for all $t \geq t_0 + T$, $||\varphi||_\tau < \Delta$)

The following theorem will be used to prove asymptotic stability of E_2 with respect to some of its variables.

Theorem 4. ([33], Th.5.2.1.)

Suppose that there exists a function $V : \mathbb{R} \times C \to \mathbb{R}$ of class C^1 and continuous strictly increasing functions

$a, b : \mathbb{R}^+ \to \mathbb{R}^+$ with $a(0) = b(0) = 0$ so that, in the domain (27), for small h,

$$V(t, \varphi)) \geq a(||\varphi_v(0))||), \quad \dot{V}(t, x_t) \leq 0. \tag{31}$$

where $\dot{V}$ denotes the derivative along the system (26). Then the equilibrium point x = 0 of system (26) is z-stable.

If, in addition,

$$V(t, \varphi)) \leq b(||\varphi||_\tau), \tag{32}$$

then the z-stability is uniform.

Theorem 1. *([33], Th.5.2.2.) Suppose that there exists* $V : \mathbb{R} \times C \to \mathbb{R}$ *of class* C^1 *and* $a, b, w : \mathbb{R}^+ \to \mathbb{R}^+$, *continuous strictly increasing functions for* $t > 0$, *with* $a(0) = b(0) = w(0) = 0$ *so that*

$$a(||\varphi_v(0)||) \leq V(t, \varphi) \leq b(||\varphi||_\tau), \dot{V}(t, x_t) \leq -w(||z(t)||) \tag{33}$$

$\forall\ (t, \varphi) \in D\ (see(27))$ *with* h *small enough and*

$$||Z(t, \varphi)|| \leq M\ \forall\ (t, \varphi) \in D. \tag{34}$$

($\dot{V}$ *means the derivative of* V *along system (26)). Then the zero solution of (26) is uniformly asymptotically stable with respect to* z.

Proposition 4. *If*

$$p\gamma_1 x_1^* x_6^* < \beta_3,\ k\gamma_1 x_1^* x_6^* < \beta_4\ \&\ \beta(x_5^* + x_{11}^*) < 2\gamma_{22} \tag{35}$$

E_1 *is uniformly asymptotically partially stable with respect to variables* $x_3, x_4, x_5, x_6, x_{11}$ *and with respect to the invariant manifold of solutions with positive components.*

Proof. Translate the equilibrium E_1 into zero by $y_i = x_i - x_i^*$, for $i = 1, \dots, 12$. We are interested only in equations $3, 4, 5, 6$, and 11.

$$\begin{aligned}
\dot{y_3} &= -\beta_3 y_3 + p\frac{\gamma_1(y_1+x_1^*)(y_{6\tau_1}+x_6^*)}{(1+m_r y_4)}\left(\frac{y_3}{1+m_1\dfrac{y_2}{1+m_2y_3}}\right)\\
\dot{y}_4 &= -\beta_4 y_4 + \kappa\gamma_1(y_1+x_1^*)(y_{6\tau_1}+x_6^*)y_4 - \eta_r\tfrac{(y_{12}+x_{12}^*)y_4}{1+y_{12}+x_{12}^*}\\
\dot{y}_5 &= -\gamma_{21}y_5 - \beta y_{11}y_5 - \beta x_{11}^* y_5 - \beta x_5^* y_{11}\\
\dot{y}_6 &= -\gamma_{22}y_6 + \beta y_5 y_{11} + \beta x_5^* y_{11} + \beta x_{11}^* y_5 - \mu y_4 y_6 - \mu x_6^* y_4\\
\dot{y}_{11} &= -e_1 y_{11} - \mu_C\frac{y_8(y_{11}+x_{11}^*)}{c+y_{11}+x_{11}^*}
\end{aligned} \tag{36}$$

Remark first that for bounded $(y_3, y_4, y_5, y_6, y_{11})$, the right-hand expressions in (36) are also bounded. Consider the candidate Lyapunov function

$$V(y_3,y_4,y_5,y_6,y_{11}) = \alpha_1\frac{y_3^2}{2}+\alpha_2\frac{y_4^2}{2}+\alpha_3\frac{y_5^2}{2}+\alpha_4\frac{y_6^2}{2}+\alpha_5\frac{y_{11}^2}{2}$$

with $\alpha_1, \alpha_2, \alpha_3, \alpha_4, \alpha_5 \in (0, \infty)$ subject to further constraints. Remark that one has

$$m||(y_3,y_4,y_5,y_6,y_{11})||_2 \le V(y_3,y_4,y_5,y_6,y_{11}) \le M||y||_{tau}^2, y=(y_1,\dots,y_{12})$$

for some $m, M > 0$. The derivative of V along (36) is given by

$$\begin{aligned}
\frac{dV}{dt} =& -\alpha_1\beta_3 y_3^2 + \alpha_1 p\frac{\gamma_1(y_1+x_1^*)(y_{6\tau_1}+x_6^*)}{(1+m_r y_4)}\left(\frac{y_3^2}{1+m_1\frac{y_2}{1+m_2y_3}}\right)\\
&-\alpha_2\beta_4 y_4^2 + \alpha_2 k\gamma_1 y_1 y_4^2 y_{6\tau_1} + \alpha_2 k\gamma_1 y_1 y_4^2 x_6^* + \alpha_2 k\gamma_1 x_1^* y_4^2 y_{6\tau_1}\\
&+\alpha_2 k\gamma_1 x_1^* y_4^2 x_6^* - \alpha_2\eta_r\frac{y_4^2(y_{12}+x_{12}^*)}{1+y_{11}+x_{12}^*} - \alpha_3\gamma_{21}y_5^2 - \alpha_3\beta y_5^2 y_{11}\\
&-\alpha_3\beta x_{11}^* y_5^2 - \alpha_3\beta x_5^* y_5 y_{11} - \alpha_4\gamma_{22}y_6^2 + \alpha_4\beta y_5 y_6 y_{11} + \alpha_4\beta x_5^* y_6 y_{11}\\
&+\alpha_4\beta x_{11}^* y_5 y_6 - \alpha_4\mu y_4 y_6^2 - \alpha_4\mu x_6^* y_4 y_6 - \alpha_5 e_1 y_{11}^2\\
&-\mu_c\frac{y_8 y_{11}(y_{11}+x_{11}^*)}{c+y_{11}+x_{11}^*}
\end{aligned}$$

Then , neglecting some negative terms and using the inequality

$$ab \le \frac{a^2}{2}+\frac{b^2}{2}$$

one obtains

$$\begin{aligned}
\frac{dV}{dt} <& (-\alpha_1\beta_3 + \alpha_1 p\gamma_1 x_1^* x_6^*) y_3^2 + (-\alpha_2\beta_4 + \alpha_2 k\gamma_1 x_1^* x_6^*) y_4^2 \\
&+ \alpha_1 p\gamma_1 y_1 y_{6\tau_1} y_3^2 + \alpha_1 p\gamma_1 y_1 x_6^* y_3^2 + \alpha_1 p\gamma_1 x_1^* y_{6\tau_1} y_3^2 \\
&+ \alpha_2 k\gamma_1 y_1 y_4^2 y_{6\tau_1} + \alpha_2 k\gamma_1 y_1 y_4^2 x_6^* \\
&+ \alpha_2 k\gamma_1 x_1^* y_4^2 y_{6\tau_1} - \alpha_3(\beta x_{11}^* + \gamma_{21}) y_5^2 \\
&- \alpha_4\gamma_{22} y_6^2 + \alpha_4\beta y_5 y_6 y_{11} + \alpha_4\beta x_5^* \frac{y_{11}^2}{2} \\
&+ \alpha_4\beta x_5^* \frac{y_6^2}{2} + \alpha_4\beta x_{11}^* \frac{y_5^2}{2} \\
&+ \alpha_4\beta x_{11}^* \frac{y_6^2}{2} - \alpha_5 e_1 y_{11}^2 \\
=& (-\alpha_1\beta_3 + \alpha_1 p\gamma_1 x_1^* x_6^*) y_3^2 + (-\alpha_2\beta_4 + \alpha_2 k\gamma_1 x_1^* x_6^*) y_4^2 \\
&+ \left(-\alpha_3\beta x_{11}^* - \alpha_3\gamma_{21} + \frac{\alpha_4\beta x_{11}^*}{2}\right) y_5^2 \\
&+ \alpha_4 \left(-\gamma_{22} + \frac{\beta x_5^*}{2} + \frac{\beta x_{11}^*}{2}\right) y_6^2 \\
&+ \left(\frac{\alpha_4\beta x_5^*}{2} - \alpha_5\right) y_{11}^2 + \alpha_4\beta y_5 y_6 y_{11}
\end{aligned}$$

If, besides the conditions (35) that involve only the parameters of the system, we choose α_3, α_4, and α_5 so that

$$\alpha_4\beta x_{11}^* < 2\alpha_3(\beta x_{11}^* + \gamma_{21}), \alpha_4\beta x_5^* < \alpha_5 \tag{37}$$

the quadratic terms in $\frac{dV}{dt}$ give a negative definite quadratic form. Introduce $z = (y_3, y_4, y_5, y_6, y_{11})$. It follows that

$$\tfrac{dV}{dt} \leq -\omega(||z||_2^2) + G(z_t)$$

where ω is strictly positively defined and,

$$\begin{aligned}
|G(z_t)| =& \alpha_1 p\gamma_1 y_1 y_{6\tau_1} y_3^2 + \alpha_1 p\gamma_1 y_1 x_6^* y_3^2 + \alpha_1 p\gamma_1 x_1^* y_{6\tau_1} y_3^2 \\
&+ \alpha_2 k\gamma_1 y_1 y_4^2 y_{6\tau_1} + \alpha_2 k\gamma_1 y_1 y_4^2 x_6^* + \alpha_2 k\gamma_1 x_1^* y_4^2 y_{6\tau_1} + \alpha_4\beta y_5 y_6 y_{11} \\
\leq& M||z_t||_\tau^3
\end{aligned}$$

Then the derivative of V along the shifted system (17) is strictly negatively defined for small norm initial data, and uniform asymptotic partial stability is proved (see also [36], [33], [13], [18], [19], [2]) □

5 List of Parameters and Numerical Simulations.

The production rate of naive cells. [24]	Λ	0.1
The strength of suppression rate of $Th1$ by $Th2$ [15]	m_2	0.1
The strength of suppression of $Th2$ by $Th1$ [15]	m_1	0.2
The strength of suppression rate by T_{reg} [15]	m_r	0.25
The differences in the autocrine action at $Th2$ level [30]	p	1.02
The differences in the autocrine action atT_{reg} level[15]	κ	0.8
The death rate of Naive T cells [24]	β_1	0.03
The death rate of Th_1 cells [25]	β_2	$5 * 24 * 10^{-3}$
The death rate of Th_2 cells [25]	β_3	$5 * 24 * 10^{-3}$
The death rate of T_{reg} cells [25]	β_4	$5 * 24 * 10^{-3}$
The proliferation rate of stimulated T-cells [15]	γ_1	8
Natural decay of induced cytokine during chemotherapy [28]	γ_4	0.4152
Inhibition rate of Treg cells by the induced cytokines [20]	η_r	0.4
First time delay [37]	τ_1	0.0794
Second time delay [7]	τ_2	2.8
Third time delay [6]	τ_3	6
Forth time delay [28]	τ_4	0.25
The production rate of induced cytokines [22]	k_1	1
The birth rate of naive APCs[24]	λ	0.3
Rate of APC activation by the antigen[14]	β	0.001
Rate of immature APC natural mortality [24]	γ_{21}	0.08
Rate of mature APC natural mortality [24]	γ_{22}	0.8
Rate of APC inhibition by regulatory T cells [14]	μ	10^{-2}
Maximal value of the function β_0 [7]	β_0	1.5
Maximal value of the function β_0 [7]	k_0	0.18
Parameter for the death rate [7]	α_1	0.8
Loss of stem cells due to mortality [7]	γ_0	0.1
Rate of asymmetric/symmetric division [7]	η_{1e}, η_{2e}	0.3
Parameter in the hill function [7]	m	2
Standard half saturation(estimated) [7]	a_1	3
Instant mortality of mature erythrocytes [7]	γ_3	0.025
Amplification factor [7]	$\tilde{A}$	2400
Maximum effect of drug on erythrocytes [7]	$\tilde{R_m}$	0.0022
Saturation constant for drug on erythrocytes [7]	$\tilde{R_{50}}$	82.2
Supply rate of 6-MP	a_2	0.2
6-MP elimination rate from the plasma [21][7]	e_1	5
deactivation rate of drug due to cancer cells killing [17]	μ_C	0.1
drug concentration that produces half of the maximum activity of drug[17](estimated)	c	6
Clearance rate of EPO [1]	k	0.6
Parameter in the negative feedback [5]	m	2

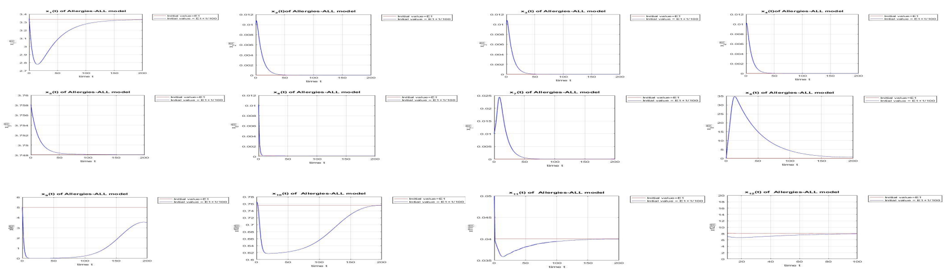

Figure 1: Simulation of a small disturbance in initial conditions near E_1. The equilibrium exhibits partial stability. E_1 corresponds to the death of the patient. In the simulations, we chose $a_2 = 0.2$ to ensure stability for most of the variables. Note that this specific choice of a_2 was made based on prior analysis and experimental observations. E_1= (3.3333, 0, 0, 0, 3.7481, 1.8741×10^{-4} 0, 0, 5, 0.7558, 0.0400, 17.0555).

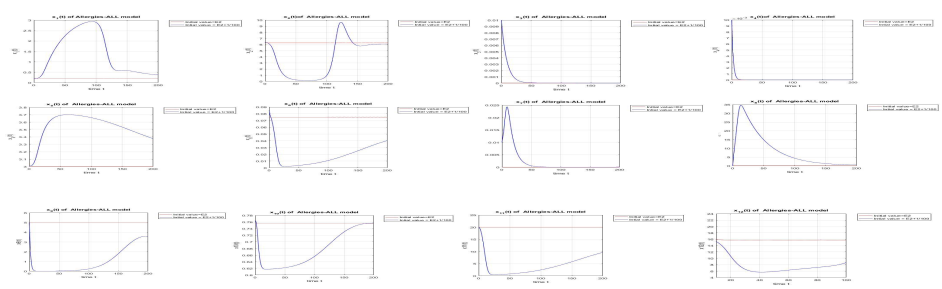

Figure 2: Simulation of a small disturbance in initial conditions near E_2. The equilibrium exhibits partial stability. E_2 corresponds to the case when there is still a critical condition without the detection of allergic reactions because Th1 cells dominate TH2 cells. E_2= (0.2000, 6.2667, 0, 0, 3.0000, 0.0750, 0, 0, 5, 0.7549, 20, 22.8003)

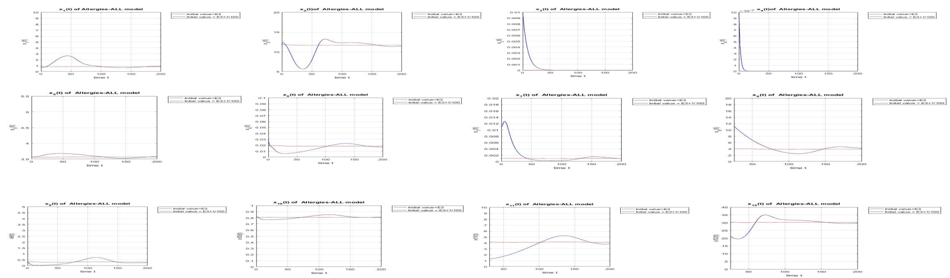

Figure 3: Simulation of a small disturbance in initial conditions near E_3. The equilibrium exhibits stability. As E_3 refers to the cure of the patient without the detection of allergies, the stability means that we have a successful therapy. This means that small quantities of allergens do not harm. E_3=(0.7869, 11.7596, 0, 0, 3.5594, 0.0191, 9.8143×10^{-4}, 3.7723, 0.3283, 0.8089, 4.2846, 38.7906)

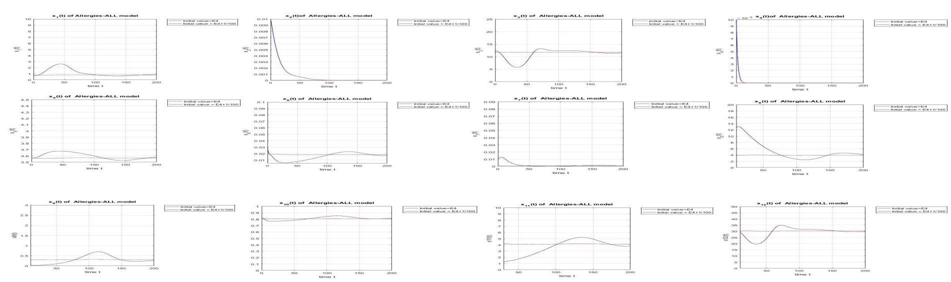

Figure 4: Simulation of a small disturbance in initial conditions near E_4. The equilibrium exhibits partial stability. E_4 represents the cure of the patient with the presence of allergic reactions as we can figure that in E_4 the Th2 cells dominate Th1 cells initially which means that there is an allergic reaction in this case. E_4= (0.7714, 0, 11.7905, 0, 3.5594, 0.0191, 9.8143×10^{-4}, 3.7722, 0.3283, 0.8089, 4.2846, 10.4306)

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