A MODEL FOR CELL EVOLUTION IN MALARIA UNDER TREATMENT CONSIDERING THE ACTION OF THE IMMUNE SYSTEM

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Abstract *In this paper, a complex system of delay differential equations modeling malaria evolution under treatment and considering the immune response, is introduced. The existence of the equilibrium points is investigated and the stability properties of the steady state representing the most aggravated phase of the disease are investigated, following a Lyapunov-Malkin approach and the study of a transcendental equation. The steady states representing the healthy state and an acute phase of the disease are investigated mostly through numerical simulations. Partial stability is revealed in all cases for a realistic set of parameters. Numerical results complete the study, emphasizing that the mathematical model is in line with medical evidence.*

Keywords: delay-differential equations, equilibrium points, partial stability, malaria, immune response

MSC2000: 34K18, 34K20, 37G05, 92C50, 92D30

1. Introduction

Malaria is a mosquito-borne infectious disease caused by parasitic protozoans belonging to the genus Plasmodium and it causes half a million deaths per year worldwide. The parasites penetrate liver cells, multiply, then enter the bloodstream and invade erythrocites or red blood cells (RBCs), where they again replicate. Afterwards, they burst the cells, releasing merozoites that invade more RBCs and continue the cycle. Moreover, other merozoites develop into immature gametocytes, which are the precursors of male and female gametes. When a mosquito bites an infected person, gametocytes reach the mosquito gut, where they mature, fuse and form motile zygotes which develop into new sporozoites that migrate to the insect's salivary glands. Later, when the mosquito takes a subsequent blood meal, it inoculates them into the skin of a new host. During the blood stage infection, as the parasitemia level increases, the number of RBCs drops, thus causing anemia and increasing demand for new erythrocytes formation [18].

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The process responsible for the production of new RBCs from hematopoietic blood cells (HSCs) is called erythropoiesis. Erythropoiesis is part of a more complex process, called hematopoiesis, responsible for the formation of all blood cells from HSCs, which are multipotent cells with self-renewal capacity and the ability to generate all blood cell types, following different differentiation pathways. During normal erythropoiesis, the committed erythroid progenitors give rise to erythroid burst-forming unit (BFU-E), the most immature haematopoietic cells that are already committed to the erythroid lineage, and then to erythroid colony-forming unit (CFU-E) cells. In the late stages of differentiation, cells turn into enucleated reticulocytes which eventually mature into erythrocytes. The regulation of erythropoiesis requires a precise control by means of intracellular proteins and growth factors. One of the most studied growth factor, playing the most important role in erythropoiesis regulation is the hormone erythropoietin (EPO), secreted by the kidneys in response to hypoxic conditions in bloodstream. While BFU-E cells respond to many hormones additional to EPO, the first phase of CFU-E erythroid differentiation is highly EPO dependent (see[14]). EPO stimulates proliferation and differentiation of red cell precursors, which activates increased erythropoiesis in the hemopoietic tissues, ultimately producing erythrocytes.

The response of the immune system to the invasion of merozoites is similar to the response to any other foreign substance that enters the body. Virtually, it triggers a series of molecular and cellular signals that activate cell-mediated immune responses. These signals (interferons, cytokines and inflammatory mediators) activate the local Antigen-Presenting Cells (APCs).

APCs are specialized blood cells that help to fight off foreign substances that enter the body. Resting (immature) APCs express membrane receptors that can capture and endocytose antigens. Activation converts the APCs into cells that are able to present antigens and activate naive T cells.

The adaptive immune response is initiated when naive T cells encounter specific antigens on the surface of an APC. Naive T cells fall under two large classes, namely Naive T cells that carry the CD8+ co-receptor on their surface and Naive T cells that bear the CD4+ co-receptor. So, mature APCs do not fight the leukemic cells directly, but they trigger the naive (CD4+ and CD8+) T cells.

CD4+ T cells differentiate into several subsets of effector T helper cells with a variety of different roles. The regulatory CD4+ T cells (Treg) are involved in controlling adaptive immune responses, including the activation and suppression of B lymphocytes ([23]). According to recent studies (see [13]), in moderate and severe forms of malaria, their number is considerably reduced.

Within this context, it is clear why a within-host mathematical model of malaria necessitates a framework able to properly approximate not only the blood stage of the infection but also the erythropoietic process that is responsible for overcoming the anemia induced by the disease. Henceforth, in this paper we introduce and study a complex mathematical model of erythropoiesis during malaria infection. The paper is organized as follows. In Section 1 the complex DDEs model of malaria

under treatment and with immune response is introduced and explained. In Section 2, the existence of various types of equilibrium points is discussed and in Section 3 their stability properties are investigated. Some relevant numerical results are presented in Section 4 and conclusions are drawn in Section 5.

2. **The model**

One DDE model of malaria can be found in the paper [6]. It contains a simplified equation for erythrocytes' evolution with respect to the model in [8]. In what follows, a more physiological model for erythropoiesis will be considered. We will concentrate only on the evolution of merozoites during malaria, since their number considerably overcomes that of gametocytes and their influence is responsible for the damaging effects of the disease.

The state variables of the system are: z_1 - the stem-like short-term erythroid cells, z_2 - the uninfected erythrocytes (RBC), z_3 - the concentration of erythropoietin, z_4 - a fictitious variable to be introduced later, z_5 - the number of infected red blood cells (iRBCs), z_6 - the number of free merozoites (extracellular malaria parazites), z_7 - the concentration of immature APCs, z_8 - the concentration of mature APCs, z_9 - the concentration of naive T cells of both CD4+ and CD8+ phenotype, z_{10} - the concentration of active CD4+ T-helper cells, z_{11} - the concentration of active B lymphocytes and CD8+ cytotoxic T-cells and z_{12} - the concentration of antibodies produced by the B cells. The following feedback functions are introduced

$$\beta(z_1, z_3) = \beta_0 \frac{\theta_1^m}{\theta_1^m + z_1^m} \frac{z_3}{1 + z_3}, \quad \beta_0 = \beta_{0s}\beta_{1e}$$

that regulates the rate of self renewal, the coefficient β_0 belonging to a feedback loop, with s standing from stem and e coming from the stimulation by erythropoietin and

$$k(z_3) = k_0 \frac{z_3}{1 + z_3},$$

that is responsible for differentiation of progenitors into mature cells. Moreover, it is assumed that a fraction η_1 of stem-like cells is susceptible to undergo an asymmetric division, a fraction η_2 is susceptible for symmetric differentiation while the rest will go to self renewal ([20]). The interaction between the parasites and the cells of the immune system is modeled by the functions

$$l_1(z) = \frac{1}{a_2 + z}, l_2(z) = \frac{z}{a_3 + z^2},$$

and the regulations of T-helper cells is given by

$$\zeta(z) = \frac{1}{1 + z}.$$

The loss of stem cells is modeled by the function

$$h(t) = \frac{\gamma_0}{1 + E(t)^\alpha}, \alpha > 0$$

(see [1], [2]) and, consequently, the loss during the cell cycle is given by

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

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

Recent studies ([11]) show that Plasmodium falciparum acts on both young and mature erythrocytes. With p the invasion rate, the law of masses results in the presence of the term $-pz_2z_6$ that is accountable for the infection process.

The following equations describe the evolution of the disease induced by Plasmodium falciparum (under treatment with Artemisinin).

$$\begin{aligned}
\dot{z}_1 = \; & -\tfrac{\gamma_0}{1+z_3^{\alpha}} z_1 - (\eta_1+\eta_2)k(z_3)z_1 - \\
& -(1-\eta_1-\eta_2)\beta(z_1,z_3)z_1 + \\
& +2z_4(1-\eta_1-\eta_2)\beta(z_{1\tau_1},z_{3\tau_1})z_{1\tau_1} + \eta_1 z_4 k(z_{3\tau_1})z_{1\tau_1} \\
\dot{z}_2 = \; & -\gamma_2 z_2 + \tilde{A}k(z_{3\tau_2})z_{1\tau_2} - pz_2z_6 \\
\dot{z}_3 = \; & -kz_3 + \tfrac{a_1}{1+z_2^r} \\
\dot{z}_4 = \; & z_4\left(-\tfrac{\gamma_0}{1+z_3^{\alpha}} + \tfrac{\gamma_0}{1+z_{3\tau_1}^{\alpha}}\right) \\
\dot{z}_5 = \; & pz_2z_6 - \gamma_3 z_5 - pz_{2\tau_3}z_{6\tau_3}S \\
\dot{z}_6 = \; & (1-c)\beta p z_{2\tau_3}z_{6\tau_3}S - pz_2z_6l_1(z_{12}) - \mu_M z_6 - b_1z_6z_{12} \\
\dot{z}_7 = \; & d_1 - c_2z_7 - b_2z_7l_2(z_6) \\
\dot{z}_8 = \; & -c_3z_8 + b_2z_7l_2(z_6) \\
\dot{z}_9 = \; & d_2 - c_4z_9 - b_3z_8z_9 \\
\dot{z}_{10} = \; & -c_5z_{10} - e_1\zeta(z_{10})z_{10}l_2(z_6) + 2e^{-c_5\tau_4}e_1\zeta(z_{10\tau_4})z_{10\tau_4}l_2(z_{6\tau_4}) + \\
& +2^{m_1}b_{41}z_{8\tau_6}z_{9\tau_6}l_2(z_{6\tau_6}) \\
\dot{z}_{11} = \; & -c_6z_{11} - e_2z_{10}z_{11}\zeta(z_{10}) + 2e^{-c_6\tau_5}e_2z_{10\tau_5}z_{11\tau_5}\zeta(z_{10\tau_5}) + \\
& +2^{m_2}b_{42}z_{8\tau_7}z_{9\tau_7}l_2(z_{6\tau_7}) \\
\dot{z}_{12} = \; & -c_7z_{12}z_6 + e_3z_{11}\tfrac{z_6}{a_4+z_6}
\end{aligned}$$

Here $r > 1$, $\beta = \beta_1 - \beta_d$, β_1 being the burst size in absence of treatment and β_d the effect of treatment with Artemisinin. Also, $\tilde{A} = A(2\eta_2 + \eta_1)$, with A the amplification factor. S accounts for the mortality of infected RBCs, and is influenced by treatment (see [18]). The interpretation and the values of parameters are given in Table 1. For more details on the model, please see [6] and [4].

3. **Equilibrium points**

Denote as $f_1, \ldots, f_{12}$ the right-hand members of the equations in the system above.

We notice first that, from $f_3 = 0, f_4 = 0, f_7 = 0$ and$f_9 = 0$ it follows that

$$\hat{z}_3 = \frac{a_1}{k}\frac{1}{1+z_2^r}$$
$$\hat{z}_4 = e^{-\left(\frac{\gamma_0}{1+\hat{z}_3^\alpha}\right)\tau_1} < 1$$
$$\hat{z}_7 = \frac{d_1}{c_2}$$
$$\hat{z}_9 = \frac{d_2}{c_4}$$

For $\hat{z}_1 = \hat{z}_2 = \hat{z}_5 = \hat{z}_6 = \hat{z}_8 = \hat{z}_{10} = \hat{z}_{11} = \hat{z}_{12} = 0$, we obtain further that $E_1 = (0, 0, \hat{z}_3, \hat{z}_4, 0, 0, \hat{z}_7, 0, \hat{z}_9, 0, 0, 0)$ is an equilibrium point, that can be interpreted as the equilibrium representing the last stage of the disease (i.e. close to the death of the patient). For different equilibrium points, we look for $(\hat{z}_1, \hat{z}_2) \neq (0, 0)$, while $z_5 = z_6 = z_8 = z_{10} = z_{11} = z_{12} = 0$. The following system must be verified by these points.

$$-\frac{\gamma_0}{1+\tilde{z}_3^\alpha} - (\eta_1+\eta_2)k(\tilde{z}_3) - (1-\eta_1-\eta_2)\beta(\tilde{z}_1, \tilde{z}_3) +$$
$$+2\tilde{z}_4(1-\eta_1-\eta_2)\beta(\tilde{z}_1, \tilde{z}_3) + \eta_1\tilde{z}_4 k(\tilde{z}_3) = 0$$
$$-\gamma_2\tilde{z}_2 + \tilde{A}k(\tilde{z}_3)\tilde{z}_1 = 0$$

The first equation becomes:

$$-\frac{\gamma_0}{1+\tilde{z}_3^\alpha} + k(\tilde{z}_3)(\eta_1\tilde{z}_4 - \eta_1 - \eta_2) + (2\tilde{z}_4 - 1)(1-\eta_1-\eta_2)\beta(\tilde{z}_1, \tilde{z}_3) = 0$$

Define

$$v_1(z_2) = \frac{a_1}{k(1+z_2^r)}$$
$$v_2(z_2) = e^{-\frac{\gamma_0\tau_1}{1+v_1(z_2)^\alpha}}$$
$$v_3(z_2) = \frac{\gamma_2 z_2}{\tilde{A}_e k[v_1(z_2)]}$$

Then $\tilde{z}_2$ can be obtained from the equation

$$-\frac{\gamma_0}{1+v_1(z_2)^\alpha} + k[v_1(z_2)](\eta_1 v_2(z_2) - \eta_1 - \eta_2) +$$
$$+(2v_2(z_2) - 1)(1-\eta_1-\eta_2)\beta[v_3(z_2), v_1(z_2)] = 0$$

and then $\tilde{z}_3 = v_1(\tilde{z}_2), \tilde{z}_4 = v_2(\tilde{z}_2), \tilde{z}_1 = v_3(\tilde{z}_2), \tilde{z}_7 = \hat{z}_7, \tilde{z}_9 = \hat{z}_9$.

The equilibrium point $E_2 = (\tilde{z}_1, \tilde{z}_2, \tilde{z}_3, \tilde{z}_4, 0, 0, \tilde{z}_7, 0, \tilde{z}_9, 0, 0, 0)$ can be interpreted as the disease free equilibrium.

We look now for equilibrium points with all components non-zero.

From the third and the fourth equation,

$$z_3^* = \frac{a_1}{k}\frac{1}{1+z_2^{*r}} := u_1(z_2^*)$$
$$z_4^* = e^{-\left(\frac{\gamma_0\tau_1}{1+z_3^{*\alpha}}\right)} := u_2(z_2^*)$$

From the first equation it follows that

$$z_1^2 = \frac{\beta_0(1-\eta_1-\eta_2)(2z_4^*-1]z_3^*\theta_1^m}{(1+z_3^*)[\frac{\gamma_0}{1+u_1(z_2^*)^\alpha}+k(z_3^*)(\eta_2+\eta_1(1-z_4^*)]} - \theta_1^m$$

so, whenever the last expression is positive, one can calculate $z_1^* := u_3(z_2^*)$. Suppose this is the case. From the relations described above it follows that

$$z_6^* = \frac{-\gamma_2 z_2^* + \tilde{A}k(z_3^*)z_1^*}{pz_2^*} := u_4(z_2^*)$$
$$z_5^* = \frac{p(1-S)z_2^* z_6^*}{\gamma_3} := u_5(z_2^*)$$
$$z_7^* = \frac{d_1}{(c_2 + b_2 l_2(z_6^*))} := u_6(z_2^*)$$
$$z_8^* = \frac{b_2 u_6(z_2^*) l_2(z_6^*)}{c_3} := u_7(z_{2*})$$
$$z_9^* = \frac{d_2}{(c_4 + b_3 u_7(z_{2^*}))} := u_8(z_2^*)$$

and from the tenth equation one eventually obtains $z_{10} =: u_9(z_2^*)$. Then

$$z_{11}^* = \frac{2^{m_2} b_{42} z_8^* z_9^* l_2(z_6^*)}{c_6 + e_2(1-2e^{-c_6\tau_5})z_{10}^*\zeta(z_{10}^*)} := u_{10}(z_2^*)$$
$$z_{12}^* = \frac{e_3 z_{11}^*}{c_7(a_4 + z_6^*)} := u_{11}(z_2^*)$$

Finally z_2^* is obtained from the equation

$$(1-c)\beta p z_2^* S - p z_2^* l_1(u_{11}(z_2^*)) - \mu_M - b_1 u_{11}(z_2^*) = 0$$

We conclude that we have the following possible types of equilibrium points:

$$E_1 = (0, 0, \hat{z}_3, \hat{z}_4, 0, 0, \hat{z}_7, 0, \hat{z}_9, 0, 0, 0)$$
$$E_2 = (\hat{z}_1, \hat{z}_2, \hat{z}_3, \hat{z}_4, 0, 0, \hat{z}_7, 0, \hat{z}_9, 0, 0, 0).$$
$$E_3 = (z_1^*, z_2^*, z_3^*, z_4^*, z_5^*, z_6^*, z_7^*, z_8^*, z_9^*, z_{10}^*, z_{11}^*, z_{12}^*)$$

4. **Stability of equilibrium points**

When linearizing the system the following matrices are to be used in the study of the stability of equilibria. For these matrices, only the possible nonzero terms will be described. The values of the state variables must be replaced by the corresponding values of the equilibrium point under study.

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

$$a_{11} = -\frac{\gamma_0}{1+z_3^\alpha} - (\eta_1+\eta_2)k(z_3) - (1-\eta_{1e}-\eta_{2e})\left[\beta(z_1,z_3) + z_1\frac{\partial\beta}{\partial z_1}(z_1,z_3)\right]$$

$$a_{13} = \frac{\gamma_0 z_1 \alpha z_3^{\alpha-1}}{(1+z_3^\alpha)^2} - (\eta_1+\eta_2)z_1 k_e'(z_3) - (1-\eta_1-\eta_2)z_1\frac{\partial\beta}{\partial z_3}(z_1,z_3)$$

$$a_{14} = 2(1-\eta_1-\eta_2)\beta(z_1,z_3)z_1 + \eta_1 k(z_3)z_1$$

$$a_{22} = -\gamma_2 - pz_6,$$

$$a_{26} = -pz_2,$$

$$a_{32} = -\frac{a_1 r z_2^{r-1}}{(1+z_2^r)^2}$$

$$a_{33} = -k,$$

$$a_{43} = \frac{\gamma_0 z_4 \alpha z_3^{\alpha-1}}{(1+z_3^\alpha)^2}$$

$$a_{52} = pz_6, a_{55} = -\gamma_3, a_{56} = pz_2$$

$$a_{62} = -pz_6 l_1(z_{12}), a_{66} = -\mu_M - pz_2 l_1(z_{12}) - b_1 z_{12},$$

$$a_{6,12} = -pz_2 z_6 l_1'(z_{12}) - b_1 z_6$$

$$a_{76} = -b_2 z_7 l_2'(z_6), a_{77} = -c_2 - b_2 l_2(z_6)$$

$$a_{86} = b_2 z_7 l_2'(z_6), a_{87} = b_2 l_2(z_6), a_{88} = -c_3$$

$$a_{98} = -b_3 z_9, a_{99} = -c_4 - b_3 z_8$$

$$a_{10,6} = -e_1\zeta(z_{10}z_{10}l_2'(z_6), a_{10,10} = -c_5 - e_1 l_2(z_6)[\zeta(z_{10}) + z_{10}\zeta'(z_{10})]$$

$$a_{11,10} = -e_2 z_{11}[\zeta(z_{10} + z_{10}\zeta'(z_{10})], a_{11,11} = -c_6 - e_2 z_{10}\zeta(z_{10})$$

$$a_{12,6} = -c_7 z_{12} + e_3 z_{11}\frac{a_4}{(a_4+z_6)^2}, a_{12,11} = e_3\frac{z_6}{a_4+z_6}, a_{12,12} = -c_7 z_6.$$

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

$$b_{11} = 2z_4(1-\eta_1-\eta_2)\left[\beta(z_1,z_3) + z_1\frac{\partial\beta}{\partial z_1}(z_1,z_3)\right] + \eta_1 z_4 k(z_3),$$

$$b_{13} = 2(1-\eta_1-\eta_2)z_4 z_1\frac{\partial\beta}{\partial z_3} + \eta_1 k'(z_3)z_1$$

$$b_{43} = -\frac{\gamma_0 z_4 \alpha z_3^{\alpha-1}}{(1+z_3^\alpha)^2}$$

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

$$c_{21} = \tilde{A}k(z_3), c_{23} = \tilde{A}z_1k'(z_3)$$

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

$$d_{52} = -pz_6, d_{56} = -pz_2, d_{62} = (1-c)\beta pSz_6, d_{66} = (1-c)\beta pSz_2,$$

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

$$e_{10,6} = 2e^{-c_5\tau_4}e_1\zeta(z_{10})z_{10}, e_{10,10} = 2e^{-c_5\tau_4}l_2(z_6)[\zeta(z_{10}) + z_{10}\zeta'(z_{10})]$$

$$F = \frac{\partial f}{\partial z_{\tau_5}}$$

$$f_{11,10} = 2e^{-c_6\tau_5}e_2[\zeta(z_{10}) + z_{10}\zeta'(z_{10})]z_{11}, f_{11,11} = 2e^{-c_6\tau_5}e_2\zeta(z_{10})z_{10}$$

$$G = \frac{\partial f}{\partial z_{\tau_6}}$$

$$g_{10,6} = 2^{m_1}b_{41}z_8z_9l_2'(z_6), g_{10,8} = 2^{m_1}b_{41}z_9l_2(z_6), g_{10,9} = 2^{m_1}b_{41}z_8l_2(z_6)$$

$$H = \frac{\partial f}{\partial z_{\tau_7}}$$

$$h_{11,6} = 2^{m_2}b_{42}z_8z_9l_2'(z_6), h_{11,8} = 2^{m_2}b_{42}z_9l_2(z_6), h_{11,9} = 2^{m_2}b_{42}z_8l_2(z_6)$$

The characteristic equation will be (see [10]:

$$\det(\lambda I - A - e^{-\lambda\tau_1}B - e^{-\lambda\tau_2}C - e^{-\lambda\tau_3}D - e^{-\lambda\tau_4}E - e^{-\lambda\tau_5}F - e^{-\lambda\tau_6}G - e^{-\lambda\tau_7}H) = 0$$

For the particular case of the equilibrium point E_1, since $a_{44} = 0, a_{12,12} = 0$, we have the equation:

$$(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})(\lambda - a_{22})(\lambda - a_{33})(\lambda - a_{55})\lambda^2(\lambda - a_{66})(\lambda - a_{77})(\lambda - a_{88})(\lambda - a_{99})$$
$$(\lambda - a_{10,10})(\lambda - a_{11,11}) = 0$$

and one can see that a critical case for stability by the first approximation theory appears.

The stability of the equation

$$\lambda - a_{11} - b_{11}e^{-\lambda\tau_1} = 0$$

is completely investigated in [5], [9].

From [9], and the form that the elements a_{11}, b_{11} take for E_1, the equation has all the roots in the left half-space of $\mathbb{C}$ if and only if

$$e^{-\frac{\gamma_e \tau_1 k^\alpha}{k^\alpha + a_1^\alpha}}[(2(1-\eta_{1e}-\eta_{2e})\beta(0,\hat{z}_3)+\eta_{1e}k(\hat{z}_3)] <$$
$$< \frac{\gamma_e}{1+\hat{z}_3^\alpha} + (1-\eta_{1e}-\eta_{2e})\beta(0,\hat{z}_3) + (\eta_{1e}+\eta_{2e})k(\hat{z}_3).$$

Since $a_{22} < 0, a_{33} < 0, a_{55} < 0, a_{66} < 0, a_{77} < 0, a_{88} < 0, a_{99} < 0, a_{10,10} < 0, a_{11,11} < 0$, the study of the stability can be settled using a critical-case theorem of Lyapunov-Malkin type that is proved in [3]. The result of this theorem is that, for a particular form of a system of DDE, the equilibrium is stable even in the critical case of a zero root of the characteristic equation if the other roots have real parts strictly negative. It is also proved in [3] that the system of DDE considered above can be brought, in a way similar to that used in [16], to the particular form needed for the application of the Lyapunov-Malkin type result.

The characteristic equations for E_2 and E_3 are more involved.

The characteristic equation for E_2, for example, has the following form:

$$d_1(\lambda)d_2(\lambda) = 0$$
$$d_1(\lambda) = \lambda(\lambda - a_{22})(\lambda - a_{33})(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1}) - \lambda a_{32}(\lambda - a_{11} - b_{11}e^{-\lambda\tau_1})$$
$$c_{23}e^{-\lambda\tau_2} - \lambda a_{32}c_{21}e^{-\lambda\tau_2}(a_{13} + b_{13}e^{-\lambda\tau_1}) - a_{32}a_{14}c_{21}e^{-\lambda\tau_2}(a_{43} + b_{43}e^{-\lambda\tau_1})$$
$$d_2(\lambda) = (\lambda - a_{66} - d_{66}e^{-\lambda\tau_3})(\lambda - a_{55})(\lambda - a_{77})(\lambda - a_{88})(\lambda - a_{99})$$
$$(\lambda - a_{10,10})(\lambda - a_{11,11})\lambda$$

Since $a_{43} = -b_{43}$ it follows that $\lambda = 0$ is also a root of $d_1(\lambda) = 0$, so, once again, the critical case of a double zero eigenvalue must be discussed as in the case of E_1.

As can be seen in figures 1 and 2, the simulations show that the analyzed equilibrium points exhibit *partial stability*, i.e. stability with respect to some of the variables. Consequently, let us recall the basic notions related to the concept of partial stability (see [22], [17]) relevant for our model. Consider a nonlinear time delay system

$$\dot{x} = f(x_t),$$

where $x_t : [-\tau, 0] \to \mathbb{R}^n, x_t(s) = x(t+s), t \geq 0$ represents the n-dimensional vector of state variables, with $x_t = (y_t, z_t) \in C := C([\tau, 0], \mathbb{R}^n)$. Here y_t represents the p-dimensional vector of state variables of interest with $p \leq n$, while z_t represents the $(n-p)$ - dimensional vector of auxiliary variables. Moreover, let $\varphi = (\varphi_y, \varphi_z) : [-\tau, 0] \to \mathbb{R}^n$ be the initial data. In the following, we assume that the vector field $f : C \to \mathbb{R}^n$, $f(0) = 0$, is continuous and satisfies the conditions of existence and uniqueness of solutions on the domain

$$\{x \in C | \, \|y\| < M, \|z\| < \infty\},$$

where M is a positive constant, with z defined for all $t \geq 0$ when $\|y(t)\| < M$ and that it satisfies the conditions necessary for the solution x to be defined on $[0, \infty)$.

Definition: ([22], [17])
The trivial equilibrium of the delay system

$$\dot{x} = f(x_t),$$

is said to be *asymptotically y-stable* if
- it is y-stable, i.e. for $(\forall)\varepsilon > 0, (\exists)\delta = \delta_\varepsilon > 0$ such that

$$\|\varphi\| < \delta \Longrightarrow \|y(t)\| < \varepsilon, (\forall)t > 0,$$

- $(\exists)\Delta > 0$ such that the solutions with $\|\varphi\| < \Delta$ satisfy

$$\lim_{t\to\infty} \|y(t)\| = 0.$$

The analytical study of partial stability uses specific Lyapunov-Krasovskii functionals. The construction of such functionals will be the target of future work. The numerical simulations that follow, considered here for the first time, have the merit of pointing a new field of investigation related to the models under consideration.

5. Numerical simulations

In this section, the trajectories of the dynamical system starting from a neighborhood of the equilibrium E_1, E_2 and E_3 are plotted. The values and the interpretation of the parameters are given in Table 1.

Table 1. Parameters of the model

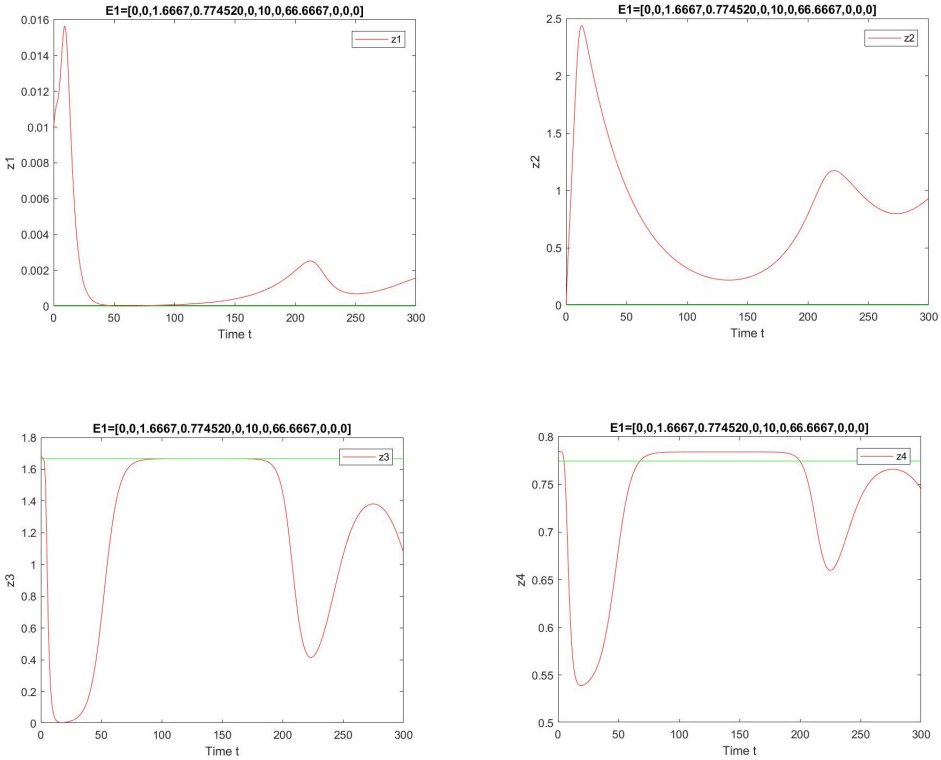
Maximal value of the β function [8], [2]	β_0	1.5
Maximal value of the function k [2]	k_0	0.1
Parameter for the β function [8]	θ_1	0.5
Loss of stem cells due to mortality [2]	γ_0	0.2
Rate of asymmetric division (estimated)	η_1	0.3
Rate of symmetric division (estimated)	η_2	0.3
Parameter in the Hill function (estimated)	m	2
Standard half-saturation in a Michaelis-Menten low (estimated)	a_2	3
Instant mortality of mature erythrocytes [6]	γ_2	0.025
Amplification factor [8]	A_e	563
Coefficient in the negative feedback [2]	a_1	1
Parameter in the negative feedback [1]	r	7
Disappearance rate of EPO [2]	k	0.6
Parameter of the death rate [2]	α	0.8
Survival of infected red blood cells [6]	S	0.9
Maximal invasion rate [21]	p	$2 * 10^{-9}$

Conversion rate from merozoites to gametocytes [6]	c	$4 * 10^{-4}$
Burst size [21] [19]	β	32
Infected RBCs death rate [6]	γ_3	0.025
Merozoites death rate [6]	μ_M	48/5000
Rate of distruction [15] of merozoites by antibodies	b_1	10^{-8}
Supply daily rate of immature APCs [12]	d_1	0.3
Death/turnover daily rate of immature APCs [12]	c_2	0.03
Coefficient of the feedback function [4]	a_3	2
Coefficient of feedback maturation of immature APCs [4]	b_2	1
Death/turnover dayly rate of mature APCs	c_3	0.01
Supply rate of naive T cells of both fenotypes [12]	d_2	2
Death/turnover dayly rate of naive CD4+ and CD8+ T cells [12]	c_4	0.03
Kinetic coefficient [12]	b_3	20
Kinetic coefficients [12]	b_{41}, b_{42}	10, 10
Death/turnover daily rate of effector CD4+ T helper cells [12]	c_5	0.23
Death/turnover rate of effector CD8+ T cytotoxic cells [12]	c_6	0.4/day
Number of divisions in minimal CD4+ developmental program [12]	m_1	2
Number of divisions in minimal CD8+ developmental program [12]	m_2	7
Coefficient of the autocrine loop function [4]	e_1	0.2
Coefficient of the positive growth signal function [12]	e_2	40
Maximum reproduction rate [15]	e_3	0.6
Decay rate of antibodies [15]	c_7	$5 * 10^{-10}$
Population when the antibodies grow half of its max growth rate [15]	a_4	1500
Duration of stem cells' cycle of self-renewall [8]	τ_1	2.8
Duration of stem cells' cycle of differentiation [8]	τ_2	3.5
Time to burst on infected red blood cells [6]	τ_3	2
Duration of one $CD4 + T$ cell division	τ_4	2.6
Duration of one $CD8 + T$ cell division	τ_5	1.4
Duration of minimal developmental program, $1 + (m_1 - 1)\tau_4$	τ_6	3.6
Duration of minimal developmental program, $1 + (m_2 - 1)\tau_4$	τ_7	16.6

In Figure 1, the trajectories starting in a neighborhood of equilibrium E_1, representing the most aggravated phase of the disease, are plotted. In this case, $a_{11} = -0.49234$ and $b_{11} = 0.595412$ so, the left hand side of the inequality giving the stability of E_1 is equal with 0.595412, while the right hand side is 0.49234, hence the inequality is not satisfied. Moreover, one can easily notice that for small disturbances in initial conditions near E_1, the simulations show that one has only partial stability ([7], [22]) with respect to state variables $z_5 - z_8$, z_{10}, z_{11}.

From a medical point of view, this might translate into the recovery of the patient, as the optimal evolution of the state variables trajectories is towards a healthy state, mainly involving the vanishing of the merozoites and of the infected erythrocytes and the recovering of the healthy erythrocyte population.

From a mathematical perspective, this translates into the following dynamical behavior of trajectories starting near E_1: a stable state for the variables z_5 (the infected RBC population) and z_6 (free merozoites population) and an unstable state for the variables z_1 and z_2 (healthy erythrocyte population and precursors).



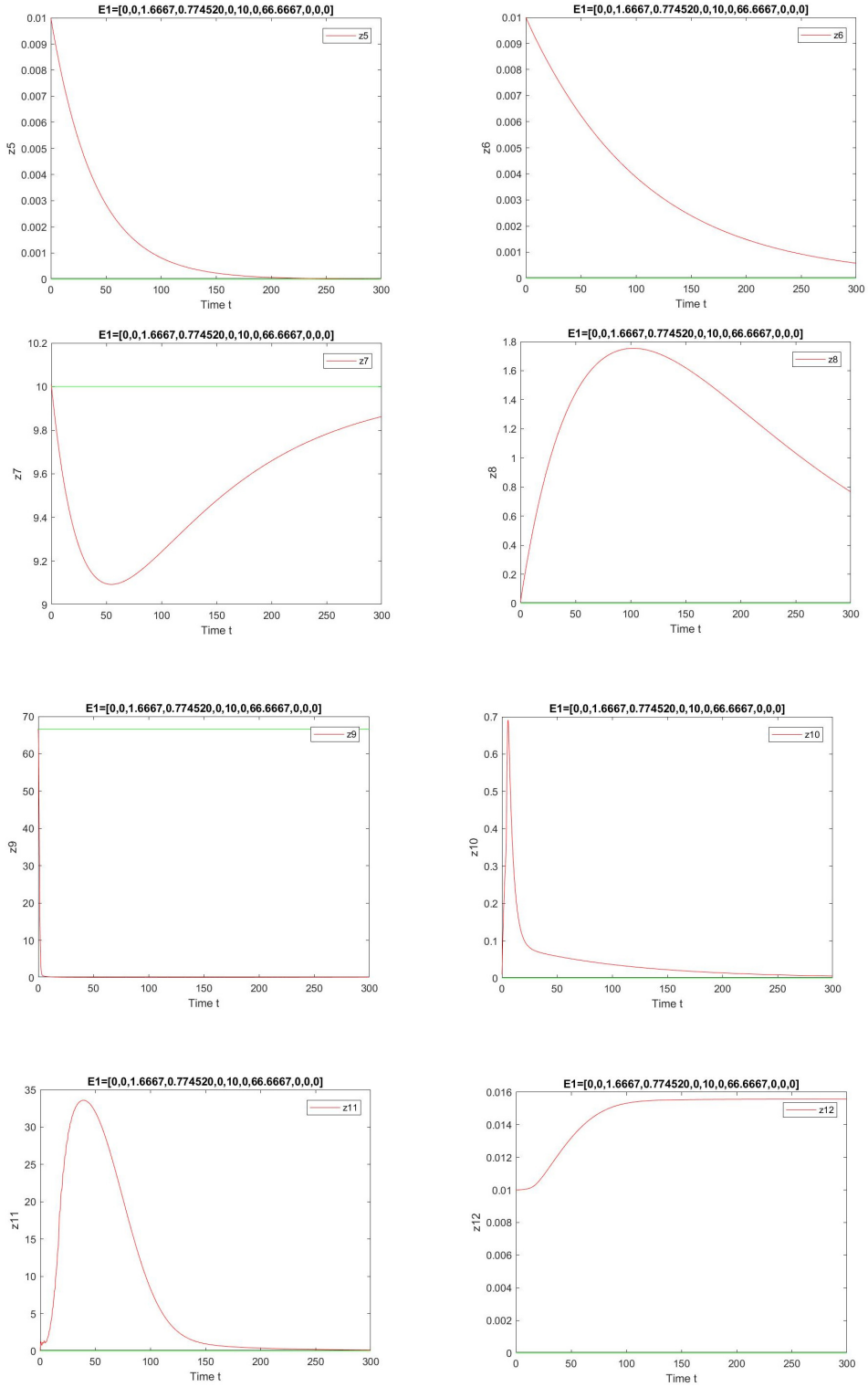
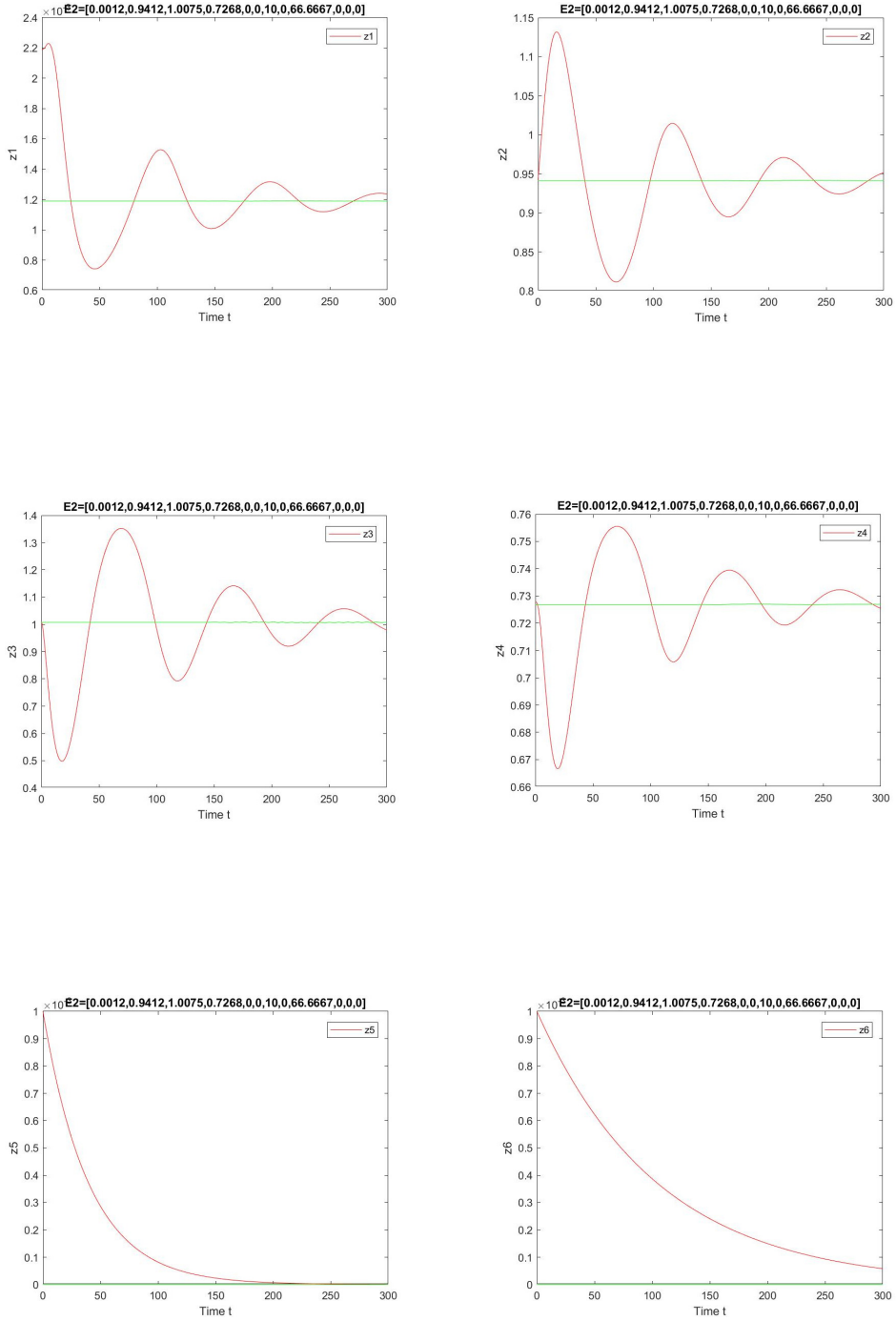


Figure 1. For small disturbances in initial conditions near E_1 the system exhibits partial stability.

The trajectories starting in a neighborhood of equilibrium E_2 are plotted in Figure 2. One can easily notice that in this case the equilibrium exhibits partial stability with respect to state variables $z_1 - z_8$, z_{10}, z_{11}. As this stationary point represents the disease-free state of the disease, here the stability of z_1 and z_2 together with stability of z_5 and z_6 is the awaited outcome.



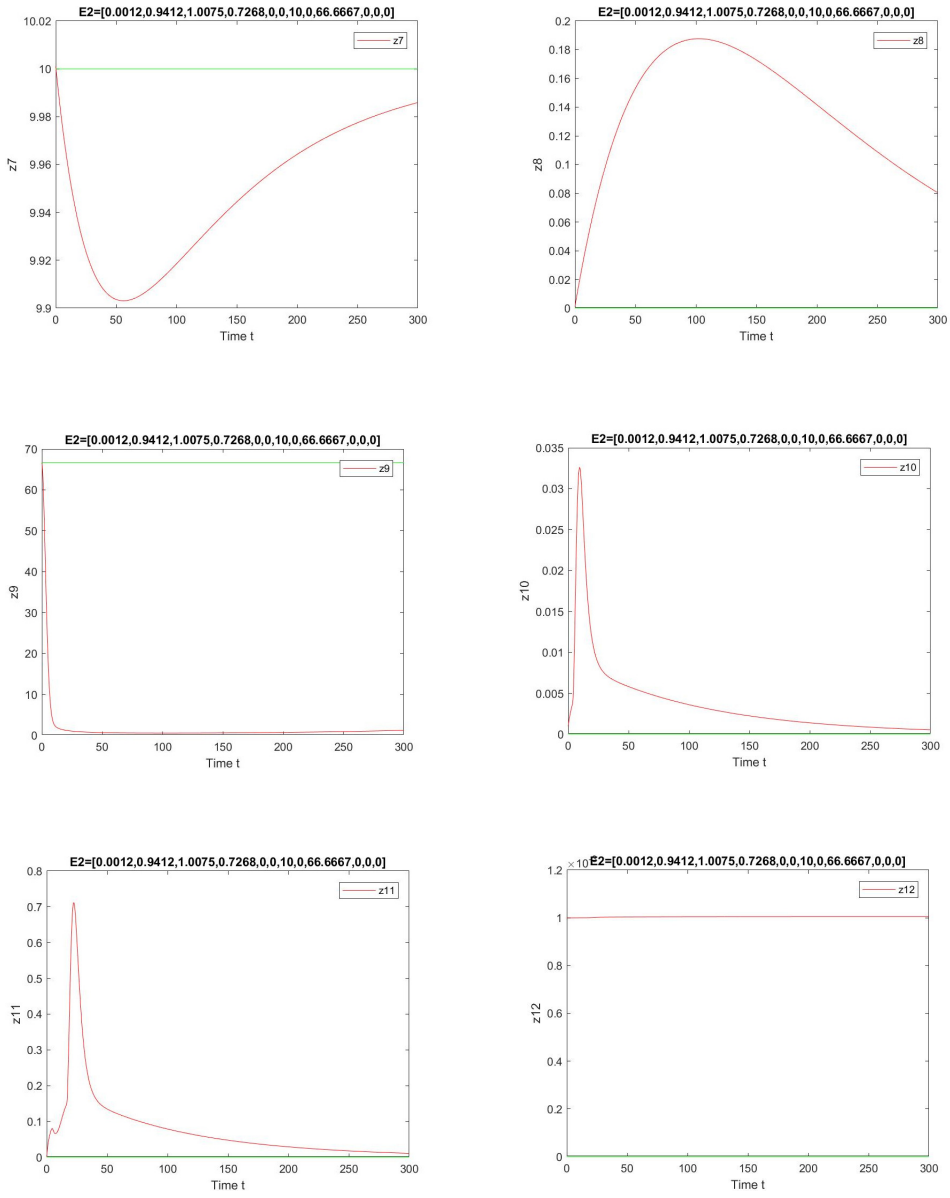
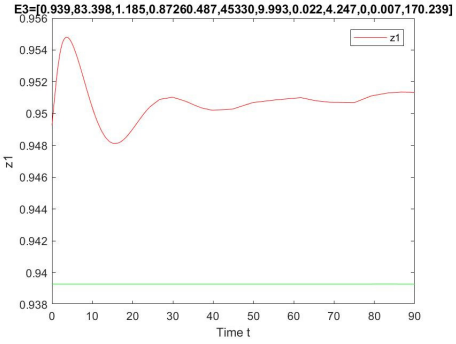
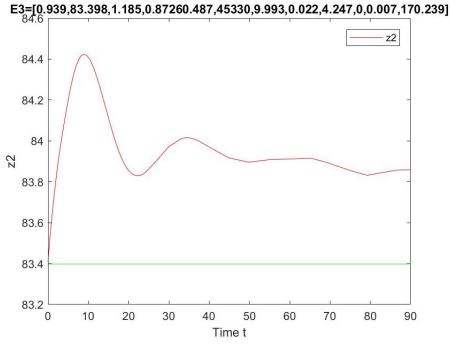


Figure 2. For small disturbances in initial conditions near E_2 the system exhibits partial stability.

Analogously, in Figure 3, the trajectories starting in a neighborhood of the steady state E_3 are plotted. In this case the equilibrium exhibits partial stability with respect to state variables $z_7 - z_{11}$.

For all the stationary points, Figures 1, 2 and 3 establish that the dynamics of the components of the immune system might have different behaviors: the antibodies cell population might remain high for a long period, while some other components of the immune response will die out. From an immunological perspective, this is also the expected evolution.


E3=[0.939,83.398,1.185,0.87260.487,45330,9.993,0.022,4.247,0,0.007,170.239]
z1
Time t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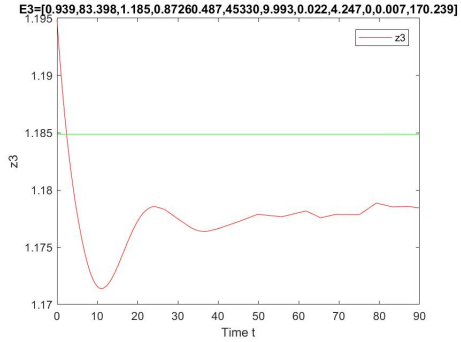
z2
Time t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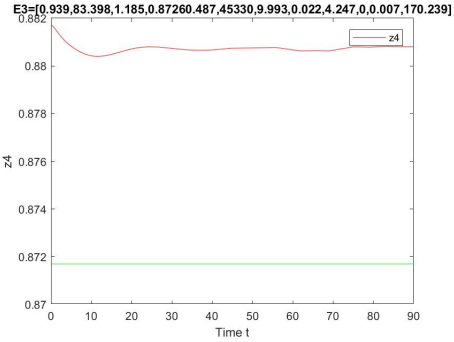
z3
Time t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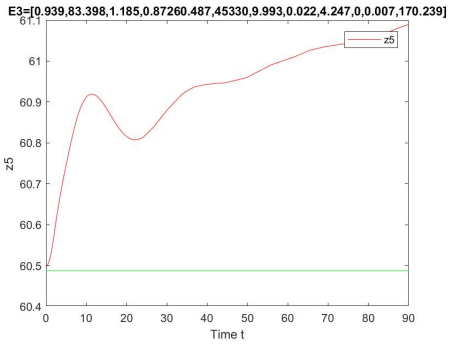
z4
Time t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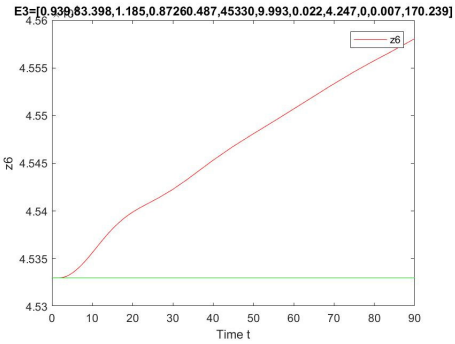
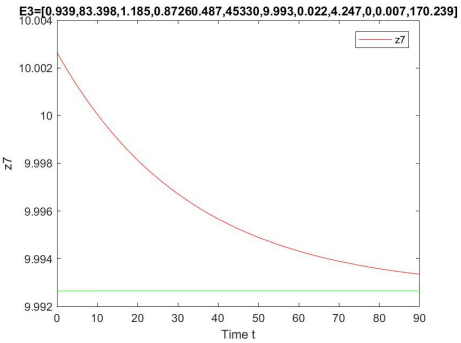
z5
Time t


E3=[0.939,83.398,1.185,0.87260.487,45330,9.993,0.022,4.247,0,0.007,170.239]
z6
Time t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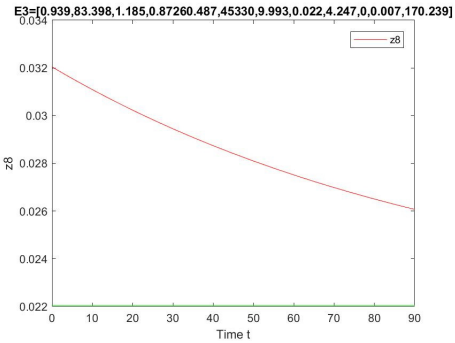
z7
Time t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z8
Time t

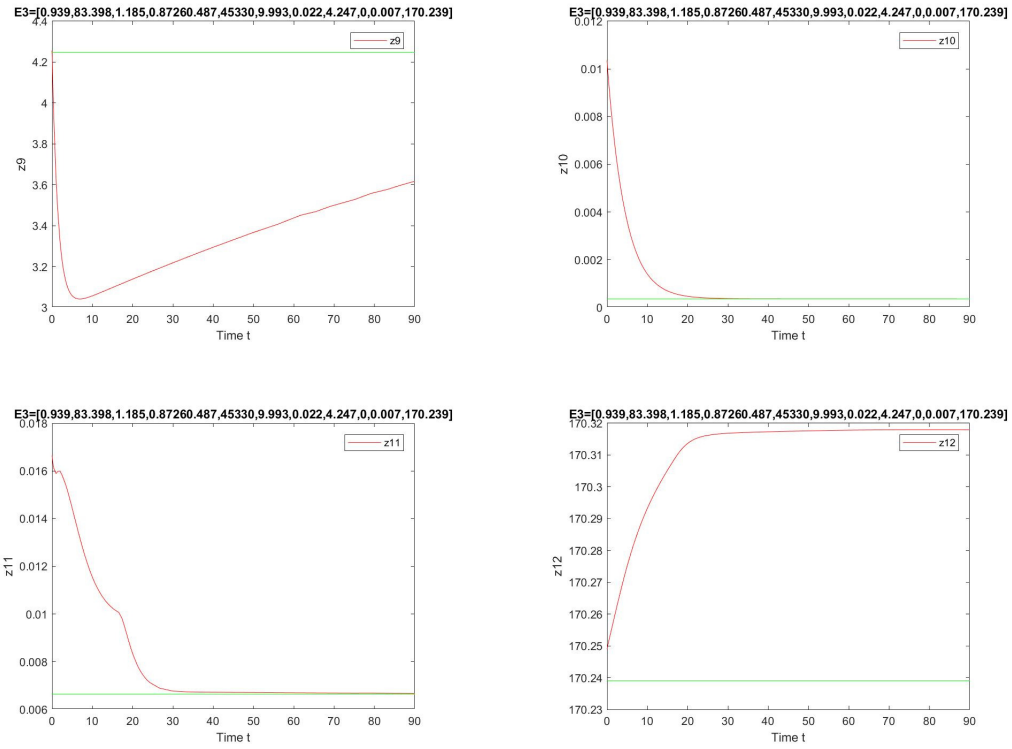

Figure 3. For small disturbances in initial conditions near E_3 the system exhibits partial stability.

6. Conclusions

In this paper a complex model of DDEs for the evolution of malaria infection with treatment and immune response is introduced and its dynamical properties are investigated. The stability properties of the equilibrium E_1, representing the most aggravated phase of the disease (i.e close to death) are investigated using the characteristic equation, following a Lyapunov-Malkin approach and the study of a transcendental equation. The steady states E_2 and E_3 are studied through numerical simulations. Partial stability is revealed in all cases for a realistic set of parameters. The numerical simulations show a dynamical behavior of the system in accordance with medical reality and so the model is correct to a good extent.

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