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On global stability of the intra-host dynamics of malaria and the immune system

J. Tumwiine [a], J.Y.T. Mugisha [b,*], L.S. Luboobi [b]

[a] *Department of Mathematics, Mbarara University of Science & Technology, Box 1410, Mbarara, Uganda*
[b] *Department of Mathematics, Makerere University, Box 7062, Kampala, Uganda*

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Abstract

In this paper we consider an intra-host model for the dynamics of malaria. The model describes the dynamics of the blood stage malaria parasites and their interaction with host cells, in particular red blood cells (RBC) and immune effectors. We establish the equilibrium points of the system and analyze their stability using the theory of competitive systems, compound matrices and stability of periodic orbits. We established that the disease-free equilibrium is globally stable if and only if the basic reproduction number satisfies $R_0 \leqslant 1$ and the parasite will be cleared out of the host. If $R_0 > 1$, a unique endemic equilibrium is globally stable and the parasites persist at the endemic steady state. In the presence of the immune response, the numerical analysis of the model shows that the endemic equilibrium is unstable.

Keywords: Global stability; Immune response; Reproduction number; Malaria parasites

1. Introduction

Many studies have been conducted using mathematical models for the within-host dynamics of malaria parasites. The within-host model of malaria infection involves alternating intracellular and extracellular parasite stages interacting with immune system. Human immune response predominantly acts on blood stage parasites, and are directed against the asexual forms. Gametocytes are benign and provoke little if any immune response [15,17]. The mortality of a gametocyte may depend on its age rather than on the immune status of individual [7].

The pioneering model is due to [3] in their attempts to address the blood stage asexual cycle of *Plasmodium*. Their model is defined by four compartments: density of uninfected red blood cells, density of infected cells, density of free merozoites and immune cells. They use a system of ordinary differential equations to describe the dynamics of the densities of these populations. Many other within-host malaria models have been proposed (see [4,6,9,10] based on the model proposed by [3].

* Corresponding author.
E-mail address: jytmugisha@math.mak.ac.ug (J.Y.T. Mugisha).

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The human immune response begins a few cycles after the initiation of the intra-erythrocytic phase. It acts in various ways to constrain the malaria parasite population growth and persistence. This may be reflected by either an increased death rate of infected red blood cells caused by non-specific (macrophage) response on signaled erythrocytes, or protection against the re-invading merozoites. It responds via two mechanisms, namely, humoral immunity and cell-mediated immunity. These two come into play at different stages of the parasite attack. Humoral immunity refers to immune protection mediated by B lymphocytes which are activated by the presence of merozoites in blood. The B-cells in turn secrete antibodies into circulation as they remove the merozoites from blood. It is humoral immunity that is more effective than the cell-mediated immunity [5]. Cell-mediated immunity acts as T lymphocytes secrete proteins called cytokines to act directly or indirectly against the pathogens and also stimulate cytotoxic T-cells. Cytotoxic T-cells play an important role of protecting the host cells by clearing (lysis) of infected cells, and thus reduce the production of merozoites and gametocytes.

The antibodies neutralize merozoites by attaching to their surface binding sites, blocking them from attaching to target cell receptors and so cell entry is inhibited. Additionally, antibodies are also involved in signalling macrophage cells of the immune system to engulf the bound merozoites. Since *Plasmodium* parasite lives inside red cells for much of its life cycle, it is able to avoid macrophage and antibodies. Thus, preventing cell entry of the merozoites would be the terminal event for malaria. However, humoral immunity is not entirely effective and so the host cells are infected with the malaria parasites.

Since malaria infection involves the absorption of the free merozoites into uninfected red blood cells, this results into a decrease in their density in the blood stream. The destruction of the parasitized red blood cells occurs in the spleen, where intra-erythrocytic parasites are removed. Some infected red cells leave the spleen intact, a process known as pitting [13]. This process occurs naturally *in vivo* when the host immune system can act but fails *in vitro* culture conditions in which leukocytes and the spleen are absent. The intracellular parasites depend on the host cell for survival and reproduction, but the host cell can be damaged either directly by the parasite, or by the immune response to parasite antigens which are expressed on the surface of infected cells [1]. Thus anemia is an inevitable consequence of malaria infection.

The interaction of malaria parasites and immune responses occurs on a dynamic land scape, in which a population of replicating parasites depletes a population of replenishing red blood cells [18]. However, malaria parasite also uses the parasite protein to stimulate the immune system for production of antibodies which protect the parasite against attack by the immune system. Knowledge of the factors that limit parasite numbers offers hope of better designed treatment and intervention strategies [16]. The dynamics of uninfected red blood cells, infected red blood cells destruction and immune activation are continuous processes which are best modelled by a system of differential equations. This is important in the analysis and interpretation for effective design of vaccines and drug treatment.

In this paper the model proposed by [3] is amplified incorporating the effect of both humoral and cell-mediated components of the immune system that target the different stages of parasite. We also modify the blanket death rate into death due to bursting of the infected red blood cells and natural death rate. There is also absorption of merozoites into the uninfected red blood cells during the process of infection and this decreases their density in blood.

2. Formulation of the model

In the model, the interaction of malaria parasites, red blood cells and immune response is presented. It is described by a system of four equations in the four variables that represent the density of uninfected red blood cells, X infected red blood cells, Y and free merozoites, M and the immune response, I. Uninfected red blood cells are recruited from the red bone marrow at a constant rate Λ and die at natural rate, $\mu_x X$ or are reduced at rate $k_s XM$ by contact with merozoites. The infected cells may die at natural rate, μ_1 or burst at a rate μ_y to release r merozoites per infected cell. The merozoites either die at a natural rate μ_m or are absorbed by uninfected red blood cells at a rate $k_s XM$.

The release of merozoites and their attack on red blood cells triggers an immune response to these (circulating) stages of the parasite. We incorporate specific immune response whose magnitude is proportional to the density of immune cells. The immune cells augment the clearance of merozoites and infected red blood cells from the body. The anti-blood stage immunity is T lymphocyte dependent that are constantly supplied from the thymus. They are recruited from their resting precursors by contact with the infected red blood cells. Thus, we have clearance rate of free-merozoites, $\mu_h MI$ due to B-cells and macrophages, clearance rate of infected red blood cells due to T-cells, $\mu_c YI$. The rate of change of density of immune cells is described by their proliferation and death rates. They proliferate in

response to contact with free-merozoites and infected red blood cells at rates $\lambda_m M$ and $\lambda_y Y$, respectively. The immune cells death is assumed to occur at a parasite-independent death rate $\mu_i I$. All the parameters of the model are assumed to be positive real numbers. With these definitions and assumptions, the interaction involving density of parasites, density of red blood cells and immune effector cells is given by the following system of differential equations:

$$\begin{aligned}
\frac{dX}{dt} &= \Lambda - \mu_x X - k_s M X,\\
\frac{dY}{dt} &= k_s M X - (\mu_1 + \mu_y) Y - \mu_c Y I,\\
\frac{dM}{dt} &= r\mu_y Y - k_s M X - \mu_m M - \mu_h M I,\\
\frac{dI}{dt} &= [\lambda_y Y + \lambda_m M] I - \mu_i I.
\end{aligned} \tag{1}$$

3. Analysis of the model

The equilibria are obtained by setting the right-hand side of system (1) equal to zero, giving the following:

$$\begin{aligned}
&\Lambda - \mu_x X - k_s M X = 0,\\
&k_s M X - (\mu_1 + \mu_y) Y - \mu_c Y I = 0,\\
&r\mu_y Y - k_s M X - \mu_m M - \mu_h M I = 0,\\
&[\lambda_y Y + \lambda_m M] I - \mu_i I = 0.
\end{aligned} \tag{2}$$

From the fourth equation of system (2), we have $I = 0$, or $Y = \frac{\mu_i - \lambda_m M}{\lambda_y}$.

In the absence of immune response, substitution of $I = 0$ into the other three equations gives,

$$\begin{aligned}
&\Lambda - \mu_x X - k_s M X = 0,\\
&k_s M X - (\mu_1 + \mu_y) Y = 0,\\
&r\mu_y Y - k_s M X - \mu_m M = 0.
\end{aligned} \tag{3}$$

This gives two equilibria, $E_0 = (\Lambda/\mu_x, 0, 0, 0)$, that represents the state in which there is no infection and is known as the disease-free equilibrium point. The second equilibrium $E_1 = (X^*, Y^*, M^*, 0)$, where

$$\begin{aligned}
X^* &= \frac{\mu_m(\mu_y + \mu_1)}{k_s[\mu_y(r-1) - \mu_1]},\\
Y^* &= \frac{\Lambda}{\mu_1 + \mu_y} - \frac{\mu_m \mu_x}{k_s[\mu_y(r-1) - \mu_1]},\\
M^* &= \frac{\Lambda[\mu_y(r-1) - \mu_1]}{\mu_m(\mu_1 + \mu_y)} - \frac{\mu_x}{k_s}.
\end{aligned} \tag{4}$$

The third equilibrium point $E_2 = (\tilde{X}, \tilde{Y}, \tilde{M}, \tilde{I})$ for immune response $\tilde{I} \neq 0$ is calculated by substituting for $\tilde{Y} = \frac{\mu_i - \lambda_m \tilde{M}}{\lambda_y}$ into the other equations of system (2). This gives

$$\begin{aligned}
&\Lambda - \mu_x \tilde{X} - k_s \tilde{M} \tilde{X} = 0,\\
&k_s \tilde{M} \tilde{X} - \frac{(\mu_1 + \mu_y + \mu_c \tilde{I})(\mu_i - \lambda_m \tilde{M})}{\lambda_y} = 0,\\
&\frac{r\mu_y(\mu_i - \lambda_m \tilde{M})}{\lambda_y} - k_s \tilde{M} \tilde{X} - \mu_m \tilde{M} - \mu_h \tilde{M} \tilde{I} = 0.
\end{aligned} \tag{5}$$

This gives the equilibria

$$\tilde{X} = \frac{(\mu_m + \mu_h \tilde{I})(\mu_y + \mu_1 + \mu_c \tilde{I})}{k_s[\mu_y(r-1) - (\mu_1 + \mu_c \tilde{I})]},$$
$$\tilde{Y} = \frac{1}{\lambda_y}\left[\mu_i - \lambda_m\left(\frac{\Lambda[\mu_y(r-1) - (\mu_1 + \mu_c \tilde{I})]}{(\mu_m + \mu_h \tilde{I})(\mu_1 + \mu_y + \mu_c \tilde{I})} - \frac{\mu_x}{k_s}\right)\right],$$
$$\tilde{M} = \frac{\Lambda[\mu_y(r-1) - (\mu_1 + \mu_c \tilde{I})]}{(\mu_m + \mu_h \tilde{I})(\mu_1 + \mu_y + \mu_c \tilde{I})} - \frac{\mu_x}{k_s}. \tag{6}$$

The equilibrium point E_2 exists provided the density of the immune cells is not zero and the malaria infection persists within an infected individual. There will always be specific immune responses to check the infection. This will be achieved provided the condition $\lambda_m \tilde{M} + \lambda_y \tilde{Y} > \mu_i$ holds. The nature of stability of this equilibrium point is established based on numerical simulations.

3.1. Local and global stability of the disease-free equilibrium E_0

We discuss the local stability of the disease-free equilibrium by examining the linearized form of system (1) at the steady state E_0. The Jacobian matrix of system (1) is given by

$$J = \begin{bmatrix} -(\mu_x + k_s M^*) & 0 & -k_s X^* & 0 \\ k_s M^* & -(\mu_1 + \mu_y + \mu_c I^*) & k_s X^* & -\mu_c Y^* \\ -k_s M^* & r\mu_y & -(k_s X^* + \mu_m + \mu_h I^*) & -\mu_h M^* \\ 0 & \lambda_y I^* & \lambda_m I^* & \lambda_y Y^* + \lambda_m M^* - \mu_i \end{bmatrix}. \tag{7}$$

At the disease-free equilibrium point $E_0 = (\Lambda/\mu_x, 0, 0, 0)$, the system has the Jacobian matrix given by

$$J_{E_0} = \begin{bmatrix} -\mu_x & 0 & -k_s\Lambda/\mu_x & 0 \\ 0 & -(\mu_1 + \mu_y) & k_s\Lambda/\mu_x & 0 \\ 0 & r\mu_y & -(\mu_m + k_s\Lambda/\mu_x) & 0 \\ 0 & 0 & 0 & -\mu_i \end{bmatrix}. \tag{8}$$

It can be seen from the first and fourth columns that the Jacobian matrix has negative eigenvalues $-\mu_x$ and $-\mu_i$. The other two can be obtained by reducing the Jacobian matrix (8) into 2×2 matrix given by

$$J'_{E_0} = \begin{bmatrix} -(\mu_1 + \mu_y) & k_s\Lambda/\mu_x \\ r\mu_y & -(\mu_m k_s\Lambda/\mu_x) \end{bmatrix}. \tag{9}$$

The trace of the Jacobian matrix (9) is negative and for stability, we seek $J'_{E_0} > 0$. This gives the expression $(\mu_1 + \mu_y)(\mu_m + k_s\Lambda/\mu_x) > r\mu_y k_s\Lambda/\mu_x$ that is equivalent to $\frac{\Lambda k_s[\mu_y(r-1)-\mu_1]}{\mu_x\mu_m(\mu_1+\mu_y)} < 1$. Let us define the *basic reproduction number* of the infection as

$$R_0 = \frac{\Lambda k_s[\mu_y(r-1) - \mu_1]}{\mu_x\mu_m(\mu_1 + \mu_y)}.$$

We can state the following lemma using $R_0 < 1$ to indicate the stability of E_0.

Lemma 1. *The disease-free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$.*

The threshold quantity, R_0 is a measure of the number of secondary cells infected by a single infected cell in naive host [2]. It is an important parameter that plays a big role in the control of the malaria infection. The reduction of the infection in an individual targets the parameters that will bring its value to less than unity. When the reproduction number is less than unity, the disease-free equilibrium is locally asymptotically stable, and therefore, the disease dies out after some period of time. We also note that increased ability of an individual to fight off the infection is attained if: antibodies and macrophages clear the merozoites before they infect the red blood cells, the cytotoxic immune response clears the infected red blood cells before their lysis and the number of merozoites released by an infected red blood cell is reduced.

The global stability of the disease-free equilibrium E_0 is established from the following theorem.

Theorem 3.1. *The disease-free equilibrium* $E_0 = (\Lambda/\mu_x, 0, 0, 0)$ *of system* (1) *is globally asymptotically stable in* T *if* $R_0 \leqslant 1$*, and unstable if* $R_0 > 1$.

Proof. Consider the Lyapunov function $L = r\mu_y Y + (\mu_1 + \mu_y)M$. Its derivative along the solutions of system (1) is

$$\begin{aligned}
L' &= r\mu_y Y' + (\mu_y + \mu_1)M' \\
&= r\mu_y\big(k_s MX - (\mu_1 + \mu_y)Y - \mu_c IY\big) + (\mu_1 + \mu_y)(r\mu_y Y - \mu_m M - \mu_h IM - k_s MX) \\
&= r\mu_y k_s MX - \mu_c IY - (\mu_1 + \mu_y)(k_s X + \mu_h I + \mu_m)M \\
&\leqslant r\mu_y k_s MX - (\mu_1 + \mu_y)(k_s X + \mu_m)M \\
&= r\mu_y k_s MX - (\mu_1 + \mu_y)k_s XM - \mu_m(\mu_1 + \mu_y)M \\
&= M\big[k_s X\big(\mu_y(r-1) - \mu_1\big) - \mu_m(\mu_1 + \mu_y)\big] \\
&= \mu_m(\mu_1 + \mu_y)M\left[\frac{k_s X(\mu_y(r-1) - \mu_1)}{\mu_m(\mu_1 + \mu_y)} - 1\right] \\
&= \mu_m(\mu_1 + \mu_y)M\left[\frac{k_s \Lambda(\mu_y(r-1) - \mu_1)}{\mu_x\mu_m(\mu_1 + \mu_y)} - 1\right] \\
&= \mu_m(\mu_1 + \mu_y)M[R_0 - 1] \leqslant 0 \quad \text{if } R_0 \leqslant 1.
\end{aligned} \tag{10}$$

We have established that $L' = 0$, if $R_0 \leqslant 1$ and the equality $L' = 0$ holds if and only if $R_0 = 1$ and $M = Y = I = 0$. If $R_0 > 1$, then $L' > 0$ when $X(t)$ is sufficiently close to Λ/μ_x except when $M = Y = I = 0$. Therefore the largest compact invariant set in $T = \{(X^*, Y^*, M^*, I^*) \in T\colon\ L' = 0\}$, where $R_0 \leqslant 1$, is the singleton $\{E_0\}$. On the boundary when $M = Y = I = 0$ (i.e. along X-axis), $X'(t) = \Lambda - \mu_x X(t)$ and $X(t) \to \Lambda/\mu_x$ as $t \to \infty$. From Lasalle–Lyapunov theorem (see [8]), every solution that starts in T approaches E_0 as $t \to \infty$. This proves the theorem and thus the disease-free equilibrium is globally asymptotically stable. □

3.2. Local and global stability of the endemic equilibrium E_1

The endemic equilibrium $E_1 = (X^*, Y^*, M^*, 0)$ is expressed in terms of R_0 with the components

$$\begin{aligned}
X^* &= \frac{\Lambda}{R_0\mu_x}, \\
Y^* &= \frac{\Lambda}{(\mu_1 + \mu_y)R_0}(R_0 - 1), \\
M^* &= \frac{\mu_x}{k_s}(R_0 - 1).
\end{aligned} \tag{11}$$

It is noted from the equations above that the system has no positive endemic equilibrium point if $R_0 < 1$. This is because both Y^* and M^* will assume negative values which is not biologically realistic. Thus, a positive endemic equilibrium point is achieved only when $R_0 > 1$.

The local stability of endemic equilibrium at E_1 is established from the eigenvalues of the Jacobian matrix (7). We observe from the last row that this matrix has the eigenvalue $\frac{\Lambda\lambda_y}{(\mu_1+\mu_y)R_0}(R_0 - 1) + \frac{\mu_x\lambda_m}{k_s}(R_0 - 1) - \mu_i < 0$, and the remaining eigenvalues derive from the 3×3 Jacobian matrix given by

$$J'_{E_1} = \begin{bmatrix} -R_0\mu_x & 0 & \frac{-k_s\Lambda}{\mu_x R_0} \\ \mu_x(R_0 - 1) & -(\mu_1 + \mu_y) & \frac{k_s\Lambda}{\mu_x R_0} \\ -\mu_x(R_0 - 1) & r\mu_y & -(\mu_m + \frac{k_s\Lambda}{\mu_x R_0}) \end{bmatrix}. \tag{12}$$

The characteristic polynomial of the Jacobian of the linearized system evaluated at this point is

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{13}$$

where

$$
\begin{aligned}
a_1 &= \mu_1 + \mu_y + \mu_m + R_0\mu_x + k_s\Lambda/R_0\mu_x,\\
a_2 &= R_0\mu_x(\mu_1 + \mu_y + \mu_m) + k_s\Lambda/R_0,\\
a_3 &= \mu_m(\mu_1 + \mu_y)(R_0 - 1)\mu_x.
\end{aligned} \tag{14}
$$

By the Routh–Hurwitz criterion, the eigenvalues of the matrix have negative real parts if and only if the inequalities $a_1 > 0$, $a_2 > 0$, $a_3 > 0$, $a_1a_2 > a_3$ hold for the coefficients of the characteristic equation (13).

From Eq. (14), we notice that a_1, a_2 and a_3 are positive. We compute

$$
\begin{aligned}
a_1a_2 - a_3 &= (\mu_1 + \mu_y + \mu_m + R_0\mu_x + k_s\Lambda/R_0\mu_x)\big(R_0\mu_x(\mu_1 + \mu_y + \mu_m) + k_s\Lambda/R_0\big)\\
&\quad - \mu_m(\mu_1 + \mu_y)(R_0 - 1)\mu_x\\
&= \big(R_0\mu_x(\mu_1 + \mu_y) + k_s\Lambda/R_0\big)(\mu_1 + \mu_y + \mu_m + R_0\mu_x + k_s\Lambda/R_0\mu_x)\\
&\quad + \mu_m\big[\mu_x(\mu_1 + \mu_y) + R_0\mu_x(\mu_m + R_0\mu_x + k_s\Lambda/R_0\mu_x)\big]\\
&\quad > 0.
\end{aligned} \tag{15}
$$

Since also $a_1 > 0, a_2 > 0, a_3 > 0$, then the characteristic equation (13) has negative real parts, and hence E_1 is locally asymptotically stable as long as the condition $\frac{\lambda_y\Lambda}{(\mu_1+\lambda_y)R0} + \frac{\lambda_m\mu_x}{k_s} < \frac{\mu_i}{R_0-1}$ holds. The endemic steady state, if it exists is always locally asymptotically stable. Thus, we have obtained the following result.

Lemma 2. *If $R_0 > 1$, then the endemic equilibrium E_1 is locally asymptotically stable.*

The global stability of the endemic equilibrium can be proved by applying the theory of competitive systems (see [20] and [11]) and additive compound matrices and differential equations [19] for the analysis of our system. This is because in the absence of immune cells, and without loss of generality, we can analyze system (1) by ignoring the last equation for the immune cells.

The second additive compound matrix of the Jacobian matrix (12) is given by

$$
J^{[2]}_{E_1} = \begin{bmatrix}
-[R_0\mu_x + \mu_1 + \mu_y] & \frac{k_s\Lambda}{\mu_x R_0} & \frac{k_s\Lambda}{\mu_x R_0}\\
r\mu_y & -[\mu_m + R_0\mu_x + \frac{k_s\Lambda}{\mu_x R_0}] & 0\\
\mu_x(R_0 - 1) & \mu_x(R_0 - 1) & -[\mu_1 + \mu_y + \mu_m + \frac{k_s\Lambda}{\mu_x R_0}]
\end{bmatrix}. \tag{16}
$$

We begin by giving the definition of a competitive system. Let $x \mapsto f(x)$ be a smooth vector field defined for x in an open set $D \subset \mathbf{R}^n$. The differential equation

$$
x' = f(x), \quad x \in D, \tag{17}
$$

is said to be competitive in D if, for some diagonal matrix $H = \operatorname{diag}(\epsilon_1, \epsilon_2, \ldots, \epsilon_n)$, where each ϵ_i is either 1 or -1, $H(\partial f/\partial x)H$ has nonpositive off-diagonal elements for all $x \in D$. If D is convex, the flow of a competitive system (12) preserves, for $t < 0$, the partial ordering in $\mathbf{R}^n$ defined by the orthant $K = \{(x_1, \ldots, x_n) \in \mathbf{R}^n\colon\ \epsilon_i x_i \geqslant 0\}$.

We choose the matrix H as

$$
H = \begin{bmatrix}
1 & 0 & 0\\
0 & -1 & 0\\
0 & 0 & 1
\end{bmatrix}. \tag{18}
$$

Then from the matrix H and the Jacobian given in Eq. (12) we get

$$
H(J'_{E_1})H = \begin{bmatrix}
-R_0\mu_x & 0 & \frac{-k_s\Lambda}{\mu_x R_0}\\
-\mu_x(R_0 - 1) & -(\mu_1 + \mu_y) & \frac{-k_s\Lambda}{\mu_x R_0}\\
-\mu_x(R_0 - 1) & -r\mu_y & -(\mu_m + \frac{k_s\Lambda}{\mu_x R_0})
\end{bmatrix}. \tag{19}
$$

It can easily be seen that the system is competitive in ω, with respect to the partial order defined by the orthant $K = \{(X, Y, M) \in \mathbf{R}^3\colon\ X \geqslant 0,\ Y \leqslant 0,\ M \geqslant 0\}$. It is also proved in [12] and [20] that three-dimensional competitive systems that live in convex sets have the Poincaré–Bendixson property. That is, any non-empty compact omega limit set that contains no equilibria must be a closed orbit.

The following result is helpful in establishing that the endemic equilibrium E_1 is globally asymptotically stable (see [21]).

Theorem 3.2. *Assume $n = 3$ and D is convex. Suppose that* (17) *is competitive in D. Then it satisfies the Poincaré–Bendixson property.*

The endemic equilibrium E_1 is globally asymptotically stable in the interior of T so that the disease remains endemic. This is established by proving Theorem 3.3 below.

Theorem 3.3. *When $R_0 > 1$, the endemic equilibrium E_1 of system* (1) *is globally asymptotically stable in $\mathring{T}$. All solutions with initial data $(\Lambda/\mu_x, 0, 0, 0)$ approach the disease-free equilibrium E_0.*

Proof. It can easily be observed that all the trajectories starting from the boundary of ∂T of T enter $\mathring{T}$ of T except those on the $X-$ axis which converge to E_0 along this invariant axis. Thus, E_0 is the only $\omega-$ limit point on the boundary of T. It is enough to show that E_1 is globally asymptotically stable in $\mathring{T}$. Since system (1) is competitive, persistent for $R_0 > 1$ and E_1 is locally asymptotically stable, the result follows from Theorem 3.2 if we can show that system (1) has the property of stability of periodic orbits. This is derived from the criterion in [19] for the asymptotic orbital stability of a periodic orbit of a general autonomous system. It is sufficient to prove that the linear non-autonomous system

$$w'(t) = \big(J'^{[2]}_{E_1}\big(p(t)\big)\big)w(t) \tag{20}$$

is asymptotically stable, where $J'^{[2]}_{E_1}$ is the second additive compound matrix (16).

From Eq. (20), we have a linear system with respect to the solution $p(t) = (X(t), Y(t), M(t))$ given by

$$\begin{aligned}
w_1'(t) &= -(R_0\mu_x + \mu_1 + \mu_y)w_1(t) + \frac{k_s\Lambda}{\mu_x R_0}w_2(t) + \frac{k_s\Lambda}{\mu_x R_0}w_3(t),\\
w_2'(t) &= r\mu_y w_1(t) - \left(\mu_m + R_0\mu_x + \frac{k_s\Lambda}{\mu_x R_0}\right)w_2(t),\\
w_3'(t) &= \mu_x(R_0-1)w_1(t) + \mu_x(R_0-1)w_2(t) - \left(\mu_1 + \mu_y + \mu_m + \frac{k_s\Lambda}{\mu_x R_0}\right)w_3(t).
\end{aligned} \tag{21}$$

The following Lyapunov function is constructed in order to prove the asymptotic stability of system (21):

$$V\big(w_1(t), w_2(t), w_3(t); X(t), Y(t), M(t)\big) = \sup\left\{|w_1|, \frac{Y(t)}{M(t)}\big(|w_2| + |w_3|\big)\right\}.$$

By denoting the left hand derivative of $V(t)$ by D_+V, we obtain the following inequalities:

$$\begin{aligned}
D_+\big|w_1(t)\big| &\leqslant -(R_0\mu_x + \mu_1 + \mu_y)\big|w_1(t)\big| + \frac{k_s\Lambda}{\mu_x R_0}\big|w_2(t)\big| + \frac{k_s\Lambda}{\mu_x R_0}\big|w_3(t)\big|\\
&\leqslant -\big(R_0\mu_x + \mu_1 + \mu_y\big)\big|w_1(t)\big| + \frac{k_s\Lambda M(t)}{\mu_x R_0 Y(t)}\left(\frac{Y(t)}{M(t)}\big(\big|w_2(t)\big| + \big|w_3(t)\big|\big)\right),
\end{aligned} \tag{22}$$

$$D_+\big|w_2(t)\big| \leqslant r\mu_y\big|w_1(t)\big| - \left(\mu_m + R_0\mu_x + \frac{k_s\Lambda}{\mu_x R_0}\right)\big|w_2(t)\big|, \tag{23}$$

$$D_+\big|w_3(t)\big| \leqslant \mu_x(R_0-1)\big|w_1(t)\big| + \mu_x(R_0-1)\big|w_2(t)\big| - \left(\mu_1 + \mu_y + \mu_m + \frac{k_s\Lambda}{\mu_x R_0}\right)\big|w_3(t)\big|. \tag{24}$$

From Eqs. (23) and (24) we have

$$\begin{aligned}
&D_+\big(\big|w_2(t)\big| + \big|w_3(t)\big|\big)\\
&\quad\leqslant \big(r\mu_y + \mu_x(R_0-1)\big)\big|w_1(t)\big| - \left(\mu_m + \mu_x + \frac{k_s\Lambda}{\mu_x R_0}\right)\big|w_2(t)\big| - \left(\mu_1 + \mu_y + \mu_m + \frac{k_s\Lambda}{\mu_x R_0}\right)\big|w_3(t)\big|\\
&\quad\leqslant \big(r\mu_y + \mu_x(R_0-1)\big)\big|w_1(t)\big| - \Phi\big[\big|w_2(t)\big| + \big|w_3(t)\big|\big],
\end{aligned} \tag{25}$$

where $\Phi = \min\{(\mu_m + \mu_x + \frac{k_s\Lambda}{\mu_x R_0}), (\mu_1 + \mu_y + \mu_m + \frac{k_s\Lambda}{\mu_x R_0})\}$.

Using Eq. (25), we simplify the following expression:

$$
\begin{aligned}
&D_+\frac{Y(t)}{M(t)}\big(|w_2(t)|+|w_3(t)|\big)\\
&=\left(\frac{Y'(t)}{Y(t)}-\frac{M'(t)}{M(t)}\right)\frac{Y(t)}{M(t)}\big(|w_2(t)|+|w_3(t)|\big)+\frac{Y(t)}{M(t)}D_+\big(|w_2(t)|+|w_3(t)|\big)\\
&\leqslant \frac{Y(t)}{M(t)}\big(r\mu_y+\mu_x(R_0-1)\big)|w_1(t)|+\left(\frac{Y'(t)}{Y(t)}-\frac{M'(t)}{M(t)}-\Phi\right)\frac{Y(t)}{M(t)}\big(|w_2(t)|+|w_3(t)|\big).
\end{aligned}
\tag{26}
$$

We observe from Eqs. (22) and (26) that

$$
D_+V(t)\leqslant \sup\big\{h_1(t),h_2(t)\big\}V(t),
\tag{27}
$$

where

$$
h_1(t)=-(R_0\mu_x+\mu_1+\mu_y)+\frac{k_s\Lambda M(t)}{\mu_x R_0 Y(t)}=\frac{Y'(t)}{Y(t)}-R_0\mu_x
\tag{28}
$$

and

$$
\begin{aligned}
h_2(t)&=\frac{Y(t)}{M(t)}\big(r\mu_y+\mu_x(R_0-1)\big)+\left(\frac{Y'(t)}{Y(t)}-\frac{M'(t)}{M(t)}-\mu_m-\mu_x-\frac{k_s\Lambda}{\mu_x R_0}\right),\\
h_2(t)&=\frac{Y'(t)}{Y(t)}+\frac{\Lambda k_s(R_0-1)}{(\mu_1+\mu_y)R_0}-\mu_x
\end{aligned}
\tag{29}
$$

since $\mu_1+\mu_y>\mu_x$, and the second and third equations of system (1) are respectively given by $\frac{k_sM(t)X(t)}{Y(t)}=\frac{k_sM(t)\Lambda}{R_0\mu_xY(t)}=\frac{Y'(t)}{Y(t)}+\mu_1+\mu_y$ and $\frac{M'(t)}{M(t)}=r\mu_y\frac{Y(t)}{M(t)}-\frac{\Lambda k_s}{R_0\mu_x}-\mu_m$ for $I=0$.

Let $\mu=\min\{R_0\mu_x,\frac{\Lambda k_s(R_0-1)}{(\mu_1+\mu_y)R_0}-\mu_x\}$,

$$
\sup\big\{h_1(t),h_2(t)\big\}\leqslant\frac{Y'(t)}{Y(t)}-\mu.
\tag{30}
$$

From Eq. (30), we have

$$
\int_0^\omega \sup\big\{h_1(t),h_2(t)\big\}\,dt\leqslant\big[\ln Y(t)\big]_0^\omega-\mu\omega=-\mu\omega<0.
\tag{31}
$$

This shows that the periodic solution $(X(t),Y(t),M(t))$ is asymptotically stable. □

3.3. Local stability of the endemic equilibrium E_2

In this section, we study the stability properties of endemic equilibrium in the presence of the immune response. The local stability of E_2 is established from the Jacobian (7) evaluated at $E_2=(\tilde{X},\tilde{Y},\tilde{M},\tilde{I})$ for $\tilde{I}\neq 0$. This is given by

$$
J_{E_2}=\begin{bmatrix}
-(\mu_x+k_s\tilde{M}) & 0 & -k_s\tilde{X} & 0\\
k_s\tilde{M} & -(\mu_1+\mu_y+\mu_c\tilde{I}) & k_s\tilde{X} & -\mu_c\tilde{Y}\\
-k_s\tilde{M} & r\mu_y & -(k_s\tilde{X}+\mu_m+\mu_h\tilde{I}) & -\mu_h\tilde{M}\\
0 & \lambda_y\tilde{I} & \lambda_m\tilde{I} & \lambda_y\tilde{Y}+\lambda_m\tilde{M}-\mu_i
\end{bmatrix}.
\tag{32}
$$

In order to determine the determinant of Jacobian matrix J_{E_2}, the following simplified form of system (2) evaluated at $E_2=(\tilde{X},\tilde{Y},\tilde{M},\tilde{I})$ is used:

$$\mu_x + k_s\tilde{M} = \frac{\Lambda}{\tilde{X}},$$

$$\mu_1 + \mu_y + \mu_c\tilde{I} = \frac{k_s\tilde{M}\tilde{X}}{\tilde{Y}},$$

$$k_s\tilde{X} + \mu_m + \mu_h\tilde{I} = \frac{r\mu_y\tilde{Y}}{\tilde{M}},$$

$$\lambda_y\tilde{Y} + \lambda_m\tilde{M} - \mu_i = 0, \quad \text{for } \tilde{I} \neq 0. \tag{33}$$

Then from the Jacobian matrix (32) and relations (33), we have

$$J_{E_2} = \begin{bmatrix} -\frac{\Lambda}{\tilde{X}} & 0 & -k_s\tilde{X} & 0 \\ k_s\tilde{M} & -\frac{k_s\tilde{M}\tilde{X}}{\tilde{Y}} & k_s\tilde{X} & -\mu_c\tilde{Y} \\ -k_s\tilde{M} & r\mu_y & -\frac{r\mu_y\tilde{Y}}{\tilde{M}} & -\mu_h\tilde{M} \\ 0 & \lambda_y\tilde{I} & \lambda_m\tilde{I} & 0 \end{bmatrix}. \tag{34}$$

This gives a characteristic polynomial of the linearized system given by

$$P(\lambda) = \det\begin{bmatrix} -\frac{\Lambda}{\tilde{X}} - \lambda & 0 & -k_s\tilde{X} & 0 \\ k_s\tilde{M} & -\frac{k_s\tilde{M}\tilde{X}}{\tilde{Y}} - \lambda & k_s\tilde{X} & -\mu_c\tilde{Y} \\ -k_s\tilde{M} & r\mu_y & -\frac{r\mu_y\tilde{Y}}{\tilde{M}} - \lambda & -\mu_h\tilde{M} \\ 0 & \lambda_y\tilde{I} & \lambda_m\tilde{I} & -\lambda \end{bmatrix}. \tag{35}$$

This simplifies to the equation

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0, \tag{36}$$

where

$$a_1 = \frac{\Lambda}{\tilde{X}} + \frac{k_s\tilde{M}\tilde{X}}{\tilde{Y}} + \frac{r\mu_y\tilde{Y}}{\tilde{M}},$$

$$\begin{aligned} a_2 &= \lambda_m\tilde{I}\mu_h\tilde{M} + \lambda_y\tilde{I}\mu_c\tilde{Y} + \left(\frac{\Lambda}{\tilde{X}} + \frac{k_s\tilde{M}\tilde{X}}{\tilde{Y}}\right)\frac{r\mu_y\tilde{Y}}{\tilde{M}} + \frac{\Lambda}{\tilde{X}}\frac{k_s\tilde{M}\tilde{X}}{\tilde{Y}} - r\mu_y k_s\tilde{X} - k_s\tilde{X}k_s\tilde{M} \\ &= \lambda_m\tilde{I}\mu_h\tilde{M} + \lambda_y\tilde{I}\mu_c\tilde{Y} + \frac{\Lambda}{\tilde{X}}(\mu_m + \mu_h\tilde{I} + \mu_1 + \mu_y + \mu_c\tilde{I}) + k_s\tilde{X}\left(\frac{\Lambda}{\tilde{X}} - k_s\tilde{M}\right) \\ &= \lambda_m\tilde{I}\mu_h\tilde{M} + \lambda_y\tilde{I}\mu_c\tilde{Y} + \frac{\Lambda}{\tilde{X}}\left(\frac{k_s\tilde{M}\tilde{X}}{\tilde{Y}} + \mu_m + \mu_h\tilde{I}\right) + k_s\mu_x\tilde{X}, \end{aligned}$$

$$\begin{aligned} a_3 &= \left(\frac{\Lambda}{\tilde{X}} + \frac{k_s\tilde{M}\tilde{X}}{\tilde{Y}}\right)\lambda_m\tilde{I}\mu_h\tilde{M} + \frac{\Lambda}{\tilde{X}}\frac{k_s\tilde{M}\tilde{X}}{\tilde{Y}}\frac{r\mu_y\tilde{Y}}{\tilde{M}} + \frac{\Lambda}{\tilde{X}}\mu_c\tilde{Y}\lambda_y\tilde{I} + \mu_c\tilde{Y}\left(r\mu_y\lambda_m\tilde{I} + \lambda_y\tilde{I}\frac{r\mu_y\tilde{Y}}{\tilde{M}}\right) \\ &\quad + \lambda_y\tilde{I}\mu_h\tilde{M}k_s\tilde{X} + r\mu_y k_s\tilde{X}k_s\tilde{M} - \frac{\Lambda}{\tilde{X}}r\mu_y k_s\tilde{X} - k_s\tilde{X}k_s\tilde{M}\frac{k_s\tilde{M}\tilde{X}}{\tilde{Y}} \\ &= \frac{\Lambda}{\tilde{X}}\lambda_m\tilde{I}\mu_h\tilde{M} + \frac{\Lambda}{X}\lambda_y\tilde{I}\mu_c\tilde{Y} + \frac{\mu_c\tilde{Y}r\mu_y(\lambda_m\tilde{M} + \lambda_y\tilde{Y})\tilde{I}}{\tilde{M}} + \frac{k_s\tilde{X}\mu_h\tilde{M}((\lambda_m\tilde{M} + \lambda_y\tilde{Y}))\tilde{I}}{\tilde{Y}} \\ &\quad + k_s\tilde{X}k_s\tilde{M}(\mu_m + \mu_h\tilde{I})\frac{\tilde{M}}{\tilde{Y}} \end{aligned}$$

$$
\begin{aligned}
&= \frac{\Lambda}{\tilde{X}}(\lambda_m \tilde{I}\mu_h \tilde{M} + \lambda_y \tilde{I}\mu_c \tilde{Y}) + \lambda_m \tilde{I}\left(\mu_c \tilde{Y} r\mu_y + \frac{k_s \tilde{X}\tilde{M}}{\tilde{Y}}\mu_h \tilde{M}\right) + \frac{r\mu_y \tilde{Y}}{\tilde{M}}\lambda_y \tilde{I}\mu_c \tilde{Y} \\
&\quad + \frac{k_s \tilde{X}\tilde{M}}{\tilde{Y}} k_s \tilde{M}(\mu_m + \mu_h \tilde{I}) + \mu_h \tilde{M}\lambda_y \tilde{I} k_s \tilde{X}, \\
a_4 &= \frac{\Lambda}{\tilde{X}}\frac{k_s \tilde{M}\tilde{X}}{\tilde{Y}}\lambda_m \tilde{I}\mu_h \tilde{M} + \frac{\Lambda}{\tilde{X}}\mu_c \tilde{Y}\left(r\mu_y \lambda_m \tilde{I} + \lambda_y \tilde{I}\frac{r\mu_y \tilde{Y}}{\tilde{M}}\right) + \frac{\Lambda}{\tilde{X}} k_s \tilde{X}\lambda_y \tilde{I}\mu_h \tilde{M} - k_s \tilde{X} k_s \tilde{M}\lambda_y \tilde{I}\mu_h \tilde{M} \\
&\quad - k_s \tilde{X}\mu_c \tilde{Y} k_s \tilde{M}\lambda_y \tilde{I} \\
&= \frac{\Lambda}{\tilde{X}}\frac{k_s \tilde{M}\tilde{X}}{\tilde{Y}}\lambda_m \tilde{I}\mu_h \tilde{M} + \frac{\Lambda}{\tilde{X}}\mu_c \tilde{Y} r\mu_y \lambda_m \tilde{I} + \mu_c \tilde{Y}\lambda_y \tilde{I}\left(\frac{\Lambda}{\tilde{X}}\frac{r\mu_y \tilde{Y}}{\tilde{M}} - k_s \tilde{X} k_s \tilde{M}\right) + \lambda_y \tilde{I}\mu_h \tilde{M} k_s \tilde{X}\left(\frac{\Lambda}{\tilde{X}} - k_s \tilde{M}\right) \\
&= \frac{\Lambda}{\tilde{X}}\frac{k_s \tilde{M}\tilde{X}}{\tilde{Y}}\lambda_m \tilde{I}\mu_h \tilde{M} + \frac{\Lambda}{\tilde{X}}\mu_c \tilde{Y} r\mu_y \lambda_m \tilde{I} + \lambda_y \tilde{I}\mu_c \tilde{Y}\left(\mu_x k_s \tilde{X} + \frac{\Lambda}{\tilde{X}}(\mu_m + \mu_h \tilde{I})\right) + \mu_x \lambda_y \tilde{I}\mu_h \tilde{M} k_s \tilde{X}.
\end{aligned}
$$

For convenience, we adopt the following notation and then rewrite the coefficients of the characteristic polynomial:

$$
\begin{aligned}
&A_1 = \frac{\Lambda}{\tilde{X}}, \qquad A_2 = \frac{k_s \tilde{M}\tilde{X}}{\tilde{Y}}, \qquad A_3 = \frac{r\mu_y \tilde{Y}}{\tilde{M}}, \qquad A_4 = \lambda_m \tilde{I}, \qquad A_5 = \mu_h \tilde{M}, \qquad A_6 = \lambda_y \tilde{I}, \\
&A_7 = \mu_c \tilde{Y}, \qquad A_8 = k_s \tilde{M}, \qquad A_9 = k_s \tilde{X}, \qquad A_{10} = \mu_m + \mu_h \tilde{I}, \qquad A_{11} = r\mu_y. \\
&a_1 = A_1 + A_2 + A_3, \\
&a_2 = A_4 A_5 + A_6 A_7 + A_1(A_2 + A_{10}) + \mu_x A_9, \\
&a_3 = A_1(A_4 A_5 + A_6 A_7) + A_4(A_2 A_5 + A_7 A_{11}) + A_3 A_6 A_7 + A_2 A_8 A_{10} + A_5 A_6 A_9, \\
&a_4 = A_1 A_4(A_2 A_5 + A_7 A_{11}) + \mu_x A_6 A_9(A_5 + A_7) + A_1 A_6 A_7 A_{10}.
\end{aligned}
$$

Then we have

$$
\begin{aligned}
H_2 &= A_1 A_2^2 + \left(A_1^2 + A_1 A_2\right)(A_2 + A_{10}) + \mu_x\left[A_9(A_1 + A_2 + A_3) + A_2 A_{10}\right] + A_7(A_2 A_6 - A_4 A_{11}) \\
&\quad + A_5(A_3 A_4 - A_6 A_9), \\
H_3 &= \mu_x A_9(A_1 + A_2 + A_3) \\
&\quad \times \left\{A_4 A_5(A_1 + A_2) + A_2 A_8 A_{10} + A_5 A_6 A_9 + A_4 A_7 A_{11} - \left[A_2 A_6 A_7 + A_5 A_6(A_1 + A_2 + A_3)\right]\right\} \\
&\quad + A_1 A_{10}(A_1 + A_2 + A_3)\left\{A_4 A_5(A_1 + A_2) + A_2 A_8 A_{10} + A_5 A_6 A_9 + A_4 A_7 A_{11} - A_2 A_6 A_7\right\} \\
&\quad + \left\{A_3 A_4 A_5 - \left(A_6 A_7(A_1 + A_3) + A_2 A_8 A_{10} + A_5 A_6 A_9 + A_4 A_7 A_{11}\right)\right\} \\
&\quad \times \left\{A_4 A_5(A_1 + A_2) + A_6 A_7(A_1 + A_3) + A_2 A_8 A_{10} + A_5 A_6 A_9 + A_4 A_7 A_{11} - A_1 A_2(A_1 + A_2 + A_3)\right\} \\
&\quad + A_7(A_1 + A_2 + A_3)\left\{A_6\left[A_4 A_5(A_1 + A_2) + A_6 A_7(A_1 + A_3) + A_2 A_8 A_{10} + A_5 A_6 A_9 + A_4 A_7 A_{11}\right]\right. \\
&\quad \left. - A_1 A_4 A_{11}(A_1 + A_2 + A_3)\right\}.
\end{aligned}
$$

It is clear that all the coefficients a_1, a_2, a_3, and a_4 are positive. The Routh–Hurwitz criterion that are necessary and sufficient for the local asymptotic stability of the endemic equilibrium E_2 are that the coefficients are positive and the Hurwitz determinants are positive [14]. For a fourth degree characteristic polynomial the Hurwitz determinants are $H_1 = a_1$, $H_2 = (a_1 a_2 - a_3)$, $H_3 = (a_1 a_2 - a_3)a_3 - a_1^2 a_4 > 0$, and $H_4 = a_4 H_3 > 0$. However, depending on the parameter values the Hurwitz conditions H_2, H_2 and H_4 may not be positive and hence all the Hurwitz conditions are not satisfied. Thus, the endemic equilibrium E_2 can be locally unstable for some parameter values.

In the next section, we use numerical analysis to illustrate the long term behavior of the system.

3.4. Numerical analysis

With the initial data and parameters values in Table 1, numerical simulations are carried out to illustrate the behavior of the system at equilibrium points. Fig. 1 reveals that in the absence of immune response, there is a sudden rise in the densities of infected red blood cells and merozoites that results in the decrease in the density of uninfected red blood cells. However, this later on drops down as the death rate of the cells is greater than the recruitment rate. The

Table 1
Parameter estimates and initial data values for the model of malaria

Parameters and variables	Value	Ref.
Λ rate of red blood cells production	2.5×10^8 cells/day/ml	[10]
μ_x natural death rate of un infected red blood cells	0.0083/day	[3]
κ_s infection rate of red blood cells by merozoites	2.5×10^{-10}/day	[10]
μ_y natural death rate of infected red blood cells	0.025/day	[9]
μ_m natural death rate of free merozoites	48/day	[10]
μ_i natural death rate of immune cells	0.05/day	[10]
μ_1 differentiation rate of asexual form into merozoites	0.5/day	[3]
r merozoites released per dying infected erythrocyte	16	[3,7]
μ_c activation rate of immune cells by contact with infected cells	10^{-8}/day	[10]
μ_h activation rate of immune cells by contact with merozoites	10^{-8}/day	[10]
λ_y proliferation rate of immune cells in response to infected red blood cells	2×10^{-8}/day	[10]
λ_m proliferation rate of immune cells in response to merozoites	3×10^{-8}/day	[10]
$X(0)$ Initial density of uninfected red blood cells	3×10^{10} cells/ml/day	[10]
$Y(0)$ Initial density of infected red blood cells	0 cells/ml/day	[10]
$M(0)$ Initial density of free merozoites	2×10^5 cells/ml/day	[10]
$I(0)$ Initial density of immune cells	0.0001 cells/ml/day	[10]

equilibrium E_1 converges to a steady state that is asymptotically stable whereas E_2 does not converge to a steady state and so is unstable (see Figs. 1 and 2).

4. Discussion

Our model captures the dynamics of malaria infection within an infected individual described by a system of differential equations. We incorporate the effect of both cell-mediated and humoral immune response against the blood stage of the disease.

We obtained three equilibria. The first equilibrium corresponds to the disease-free or uninfected state, the second one is the infected state in the absence of the specific immune response and the third one represents the infected state in which immune cells are present. The conditions for the establishment of the disease based on the eigenvalues of the system evaluated at the disease-free equilibria revealed that it is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. Global stability analysis of the model was carried out based on a Lyapunov function and it was established that the infection disappears from an infected individual if $R_0 \leqslant 1$. This can be explained that on average an infected individual cell produces less than one new infected individual cell over the course of its infectious period, and the infection cannot grow. Considering an infected individual that initially consists of susceptible and infected red blood cell populations, there is convergence to a disease-free steady state as infected red blood cells die off and are replaced by uninfected ones.

The second equilibrium represents a state in which the infection exists in the absence of the specific immune cells. Its other components are positive only when $R_0 > 1$. The necessary and sufficient conditions for its local stability provided by Routh–Hurwitz criteria confirm that it is always asymptotically stable if it exists. It is also proved using the theory of competitive systems that the equilibrium is globally asymptotically stable. Numerical simulations reveal that the second equilibrium always converges (see Fig. 1) to an endemic steady state. This implies that non-immunocompetent individuals will be unable to fight off the malaria infection. From Fig. 2 we established that the third equilibrium E_2 does not always converge to a steady state and so is unstable. The reason may be that immunocompetent individuals are able to withstand the malaria infection and the immune system eventually is able to clear off the infection.

The stability of the equilibria is important for disease control. This can be achieved through disrupting propagation of the infection to the point that $R_0 < 1$. This can be achieved through antimalarials that kill infected red blood cells and merozoites. This having been accomplished, the malaria infection will die out of its own accord, as the system tends to the "no infection" state at the new stabilized point.

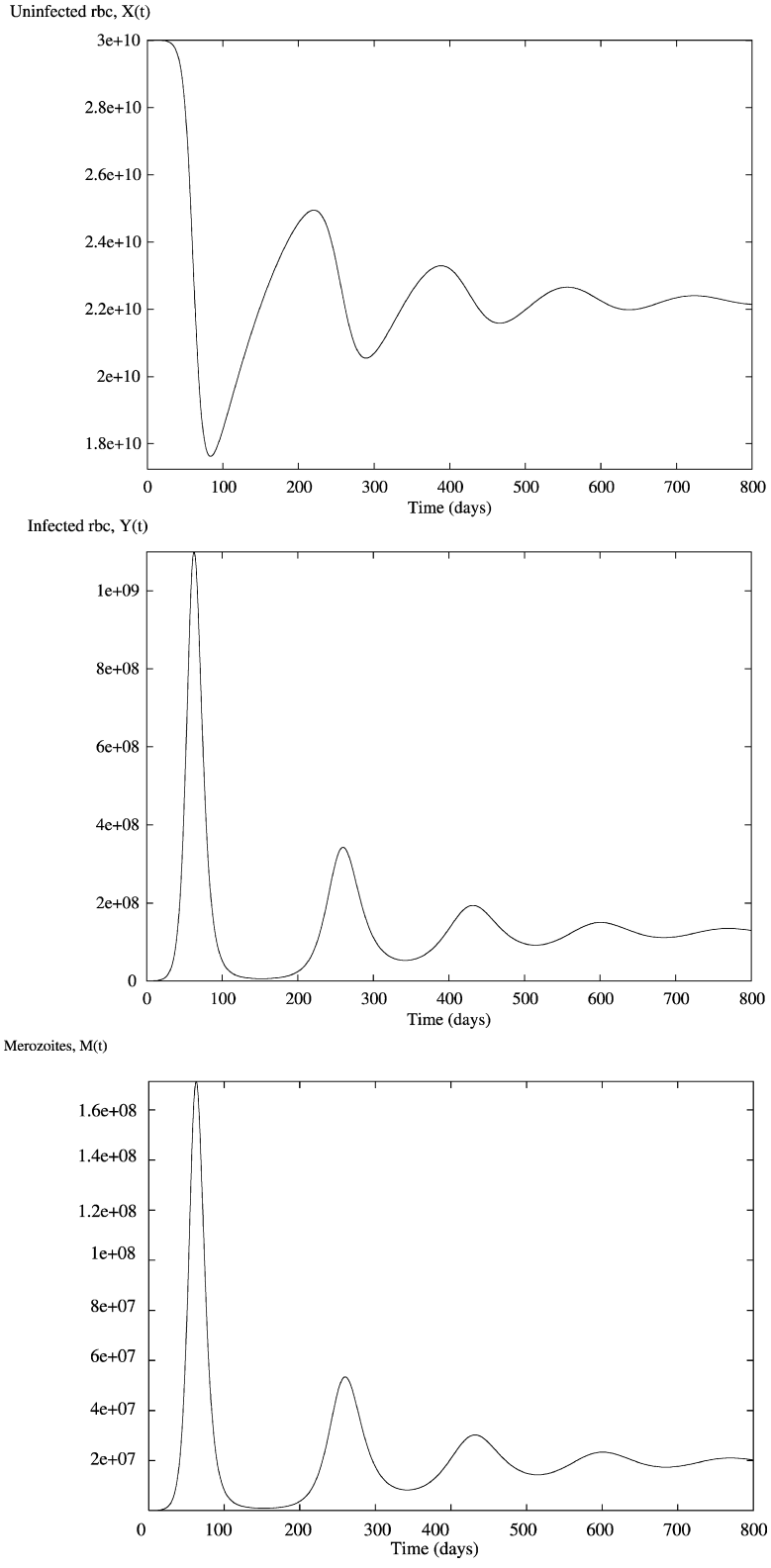

Fig. 1. Equilibrium point E_1 tends to the endemic steady state in the absence of immune response.

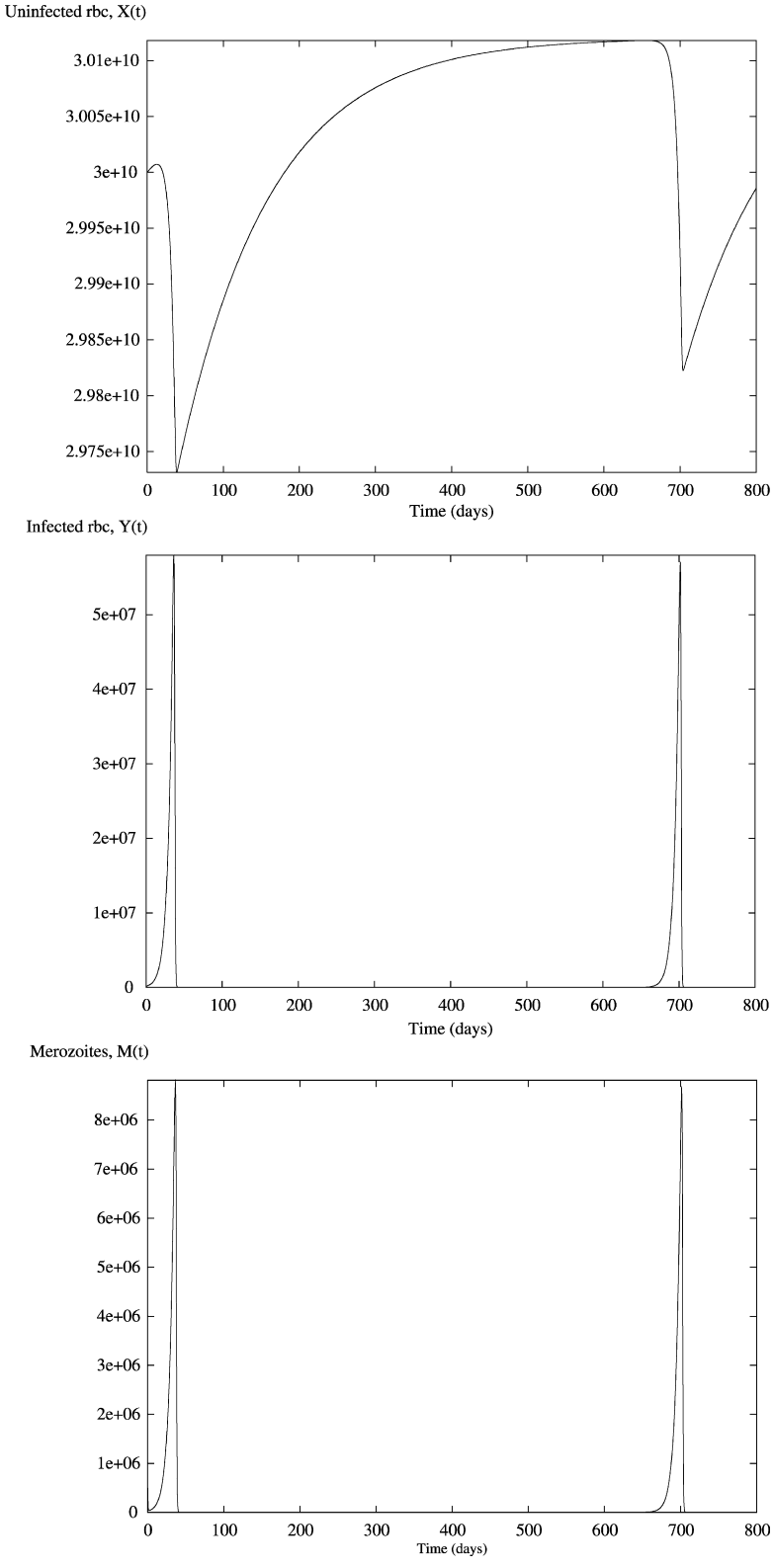

Fig. 2. Equilibrium point E_2 does not converge to a steady state in the presence of immune response.

Appendix A. Compound matrices

In this section, we give the definition of an additive compound matrix. The details of compound matrices and ordinary differential equations are given in [19].

Definition A.1. Let A be any $n \times m$ matrix of real and complex numbers, and let $a_{i_1,\dots,j_k}$ be the minor of A determined by the rows $(i_1,\dots,i_k)$ and the columns $(j_1,\dots,j_k)$, $1 \leqslant i_1 < i_2 < \cdots < j_k \leqslant n$, $1 \leqslant j_1 < j_2 < \cdots < j_k \leqslant m$. The kth multiplicative compound matrix of A^k of A is the $\binom{n}{k} \times \binom{m}{k}$ matrix whose entries, written in a lexicographic order are $a_{i_1,\dots,j_k}$. When A is a $n \times m$ matrix with columns $a_1, a_2, \dots, a_k$, A^k is the exterior product $a_1 \wedge a_2 \wedge \cdots \wedge a_k$.

For the case $m = n$, the additive compound matrices are defined in the following way.

Definition A.2. If $A = a_{ij}$ be an $n \times n$ matrix, its kth additive compound $A^{[k]}$ of A is the $\binom{n}{k} \times \binom{n}{k}$ matrix given by

$$A^{[k]} = D(I + hA)^{(k)}\big|_{h=0},$$

where D is the differentiation with respect to h. For any integer $i = 1, \dots, \binom{n}{k}$, let $(i) = (i_1, \dots, i_k)$ be the ith member in the lexicographic ordering of all k-tuples of integers such that $1 \leqslant i_1 < i_2 < \cdots < i_k \leqslant i_n$. Then

$$b_{ij} = \begin{cases} a_{i_1 i_1} + \cdots + a_{i_k i_k} & \text{if } (i) = (j), \\ (-1)^{r+s} a_{i_s, i_r} & \text{if exactly one entry of } i_s \text{ in } (i) \text{ does not occur in } (j) \text{ and } j_s \text{ does not occur in } (i), \\ 0 & \text{if } (i) \text{ differs from } (j) \text{ in two or more entries.} \end{cases}$$

In the special cases $k = 1$, $k = n$, we find $A^{[1]} = A$, $A^{[n]} = \operatorname{Tr} A$. For $n = 3$, the matrices $A^{[k]}$ are as follows:

$$A^{[1]} = A, \qquad A^{[2]} = \begin{bmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{bmatrix}, \qquad A^{[3]} = a_{11} + a_{22} + a_{33}.$$

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