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MATHEMATICAL ANALYSIS OF A WITHIN-HOST MODEL OF MALARIA WITH IMMUNE EFFECTORS AND HOLLING TYPE II FUNCTIONAL RESPONSE

Abstract. In this paper, we consider a within-host model of malaria with Holling type II functional response. The model describes the dynamics of the blood-stage of parasites and their interaction with host cells, in particular red blood cells and immune effectors. First, we obtain equilibrium points of the system. The global stability of the disease-free equilibrium point is established when the basic reproduction ratio of infection is $R_0 < 1$. Then the disease is controllable and dies out. In the absence of immune effectors, when $R_0 > 1$, there exists a unique endemic equilibrium point. Global analysis of this point is given, which uses on the one hand Lyapunov functions and on the other hand results of the theory of competitive systems and stability of periodic orbits. Therefore, if $R_0 > 1$, the malaria infection persists in the host. Finally, in the presence of immune effectors, we find that the endemic equilibrium is unstable for some parameter values using the Routh–Hurwitz criterion; numerical simulations of the model also show the same results.

1. Introduction. Malaria is a mosquito-borne disease caused by any one of four different blood parasites, called *Plasmodia*. The disease is transmitted to people by the Anopheles mosquito. This disease is a leading cause of debilitating illness, with over 300-500 million cases and 1 million deaths each year around the world [4].

A female Anopheles mosquito carrying malaria-causing parasites feeds on a human and injects the parasites in the form of sporozoites into the bloodstream. The sporozoites travel to the liver and invade liver cells. Over 5-16 days, the sporozoites grow, divide, and produce tens of thousands of

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haploid forms, called *merozoites*, per liver cell. The merozoites exit the liver cells and re-enter the bloodstream, beginning a cycle of invasion of red blood cells, where they again multiply and burst the cells, each releasing 8-32 merozoites that invade more red blood cells and continue the cycle. Blood stage infection engages a network of interacting cells, cytokines, antibodies and other components of the immune system [16, 18].

Despite widespread efforts for malaria disease control in the world, there are still many problems due to malaria infection, particularly in Sub-Saharan Africa. Therefore, if we understand how the immune effectors react in a human body after malaria infection, we can take steps to develop new drugs or a vaccine. Our contribution is to propose new mathematical models of malaria infection and to analyze them. We use the original model of Anderson [1] with Holling type II functional response.

2. The model formulation. In Anderson's model, the interaction of malaria parasites, red blood cells and immune effectors is presented. The state variables are denoted by X, Y, M and I. The variable $X(t)$ denotes the density of uninfected red blood cells at time t, $Y(t)$ denotes the density of infected red blood cells at time t, $M(t)$ denotes the density of free merozoites in the blood at time t and $I(t)$ denotes the density of immune effectors at time t. The dynamic variable $I(t)$ represents the reaction of the immune system.

This model is given by the following system of differential equations:

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

Uninfected red blood cells are recruited from the red bone marrow at a constant rate Λ. The parameters μ_x, μ_y, μ_m and μ_i are respectively the natural death rates of uninfected red blood cells, infected red blood cells, free merozoites and immune effectors. The death of infected red blood cells results in the release of a number r of merozoites. The parameter k_s denotes the contact rate between uninfected red blood cells and free merozoites. The parameters μ_c and μ_h are the immuno-sensitivities of infected red blood cells and free merozoites, respectively. The immune effectors proliferate in response to contact with infected red blood cells and free merozoites at rates λ_y and λ_m, respectively. Usually the rate of infection in most malaria models

is assumed to be bilinear in the free merozoites M and the uninfected red blood cells X. However, the actual incidence rate is probably not linear over the entire range of M and X. Thus, it is reasonable to model the infection rate of malaria using Holling type II functional response, $\frac{k_s XM}{1+\alpha X}$, where $\alpha > 0$ is constant. Note that 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 effectors with Holling type II functional response is given by

$$\begin{aligned} \frac{dX}{dt} &= \Lambda - \mu_x X - \frac{k_s XM}{1+\alpha X}, \\ \frac{dY}{dt} &= \frac{k_s XM}{1+\alpha X} - \mu_y Y - \mu_c YI, \\ \frac{dM}{dt} &= r\mu_y Y - \mu_m M - \mu_h MI, \\ \frac{dI}{dt} &= [\lambda_y Y + \lambda_m M]I - \mu_i I. \end{aligned} \tag{2}$$

In this paper, we investigate stability of the equilibrium points of this system. These results enable us to discuss the nature of the disease.

3. The equilibrium points of the model. In this section, we will first find the equilibrium points of system (2). To compute them, we set the derivatives with respect to time in system (2) equal to zero. Hence, we get the following system of equations:

$$\begin{aligned} &\Lambda - \mu_x X - \frac{k_s XM}{1+\alpha X} = 0, \\ &\frac{k_s XM}{1+\alpha X} - \mu_y Y - \mu_c YI = 0, \\ &r\mu_y Y - \mu_m M - \mu_h MI = 0, \\ &[\lambda_y Y + \lambda_m M]I - \mu_i I = 0. \end{aligned} \tag{3}$$

From the fourth equation of (3), we obtain $I = 0$ or $\lambda_y Y + \lambda_m M - \mu_i = 0$.

In the absence of immune effectors, $I = 0$, the model reduces to a model with disease-free and endemic equilibrium points. For this model, we obtain the disease-free equilibrium point $E_0 = (\Lambda/\mu_x, 0, 0, 0)$ and the endemic equilibrium point $E_1 = (X^*, Y^*, M^*, 0)$, where

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

For the third equilibrium point $E_2 = (\tilde{X}, \tilde{Y}, \tilde{M}, \tilde{I})$ with immune effectors $\tilde{I} \neq 0$, we have

$$\begin{aligned} &\Lambda - \mu_x \tilde{X} - \frac{k_s \tilde{X} \tilde{M}}{1 + \alpha \tilde{X}} = 0, \\ &\frac{k_s \tilde{X} \tilde{M}}{1 + \alpha \tilde{X}} - \mu_y \tilde{Y} - \mu_c \tilde{Y} \tilde{I} = 0, \\ &r\mu_y \tilde{Y} - \mu_m \tilde{M} - \mu_h \tilde{M} \tilde{I} = 0, \\ &\lambda_y \tilde{Y} + \lambda_m \tilde{M} - \mu_i = 0. \end{aligned} \tag{5}$$

For existence of this equilibrium point, we have the following theorem.

THEOREM 1. *For small positive values of α, there exists an endemic equilibrium point $E_2 = (\tilde{X}, \tilde{Y}, \tilde{M}, \tilde{I}) \in \mathbb{R}^4_+$.*

Proof. For $\alpha = 0$, existence of at least one endemic equilibrium point $(\tilde{X}, \tilde{Y}, \tilde{M}, \tilde{I}) \in \mathbb{R}^4_+$ is proved in [18, Theorem 8]. By using this theorem and the implicit function theorem, we deduce that for small positive values of α, system (5) has a solution $E_2 = (\tilde{X}, \tilde{Y}, \tilde{M}, \tilde{I}) \in \mathbb{R}^4_+$. ∎

Notice that the equilibrium point E_2 exists provided that the density of immune effectors is not zero and the malaria infection persists within an infected host.

Now for the stability analysis of the equilibrium points, we will define the feasible region that is positively invariant. In order to do this, we use the following lemma.

LEMMA 1. *The region $Q = \{X(t) \geq 0, Y(t) \geq 0, M(t) \geq 0, I(t) \geq 0\}$ is positively invariant for solutions of system* (2).

Proof. For simplicity of writing, model (2) can be written in the form $\dot{S}(t) = G(S(t))$, where $S(t) = (s_1, s_2, s_3, s_4)^T := (X, Y, M, I)$, $S(0) = (X(0), Y(0), M(0), I(0))^T \in Q$ and

$$G(S) = \begin{pmatrix} G_1(S) \\ G_2(S) \\ G_3(S) \\ G_4(S) \end{pmatrix} = \begin{pmatrix} \Lambda - \mu_x X - \frac{k_s X M}{1+\alpha X} \\ \frac{k_s X M}{1+\alpha X} - \mu_y Y - \mu_c Y I \\ r\mu_y Y - \mu_m M - \mu_h M I \\ [\lambda_y Y + \lambda_m M] I - \mu_i I \end{pmatrix}.$$

For $s_1 = 0$ in (2), we have $G_1(S) = \Lambda > 0$. Thus, no trajectory can pass through $X = 0$.

For $s_2 = 0$ in (2), we have $G_2(S) = \frac{k_s X M}{1+\alpha X} \geq 0$ provided that $X, M \geq 0$. That is, no trajectory can pass through $Y = 0$.

For $s_3 = 0$ in (2), we have $G_3(S) = r\mu_y Y \geq 0$ provided that $Y \geq 0$. Hence, no trajectory can pass through $M = 0$.

For $s_4 = 0$ in (2), we have $G_4(S) = 0$. Thus, no trajectory can pass through $I = 0$.

Due to the well known theorem by Nagumo [15], any solution of (2) with initial point $S(0) \in Q$, say $S(t) = S(t, S(0))$, is such that $S(t) \in Q$ for all $t > 0$. ∎

Remark 1. Notice that for biological reasons, the initial condition for system (2) must be non-negative. Thus by the above lemma, X, Y, M and I must be non-negative for $t \geq 0$.

From the first equation of (2), we obtain $X'(t) \leq \Lambda - \mu_x X(t)$. Thus

$$\limsup_{t\to\infty} X(t) \leq \frac{\Lambda}{\mu_x}.$$

Adding the first two equations of (2), we get

$$\begin{aligned}(X(t)+Y(t))' &= \Lambda - \mu_x X - \mu_y Y - \mu_c Y I \leq \Lambda - \mu_x X - \mu_y Y \\ &\leq \Lambda - m_1(X(t)+Y(t)),\end{aligned}$$

where $m_1 = \min\{\mu_x, \mu_y\}$. Thus,

$$\limsup_{t\to\infty}(X(t)+Y(t)) \leq M_1, \quad \text{where} \quad M_1 = \frac{\Lambda}{m_1}.$$

From the third equation of (2), we obtain

$$M'(t) \leq r\mu_y Y - \mu_m M \leq r\mu_y M_1 - \mu_m M.$$

Thus,

$$\limsup_{t\to\infty} M(t) \leq M_2, \quad \text{where} \quad M_2 = \frac{r\mu_y M_1}{\mu_m}.$$

Now, we set

$$V(t) = M(t) + \frac{\mu_h}{\lambda_m} I(t) + \frac{\lambda_y}{\mu_c}\,\frac{\mu_h}{\lambda_m} Y(t).$$

Calculating the derivative of V along the solutions of system (2), we have

$$\begin{aligned}\dot V(t) &= \dot M(t) + \frac{\mu_h}{\lambda_m}\dot I(t) + \frac{\lambda_y}{\mu_c}\,\frac{\mu_h}{\lambda_m}\dot Y(t) \\ &= r\mu_y Y(t) - \mu_m M(t) - \mu_h M(t) I(t) \\ &\quad + \frac{\mu_h}{\lambda_m}[\lambda_y Y(t) I(t) + \lambda_m M(t) I(t) - \mu_i I(t)] \\ &\quad + \frac{\lambda_y}{\mu_c}\,\frac{\mu_h}{\lambda_m}\left[\frac{k_s X(t) M(t)}{1+\alpha X(t)} - \mu_y Y(t) - \mu_c Y(t) I(t)\right] \\ &\leq r\mu_y Y(t) - \mu_m M(t) - \frac{\mu_h}{\lambda_m}\mu_i I(t) + \frac{\lambda_y}{\mu_c}\,\frac{\mu_h}{\lambda_m} k_s X(t) M(t) - \frac{\lambda_y}{\mu_c}\,\frac{\mu_h}{\lambda_m}\mu_y Y(t)\end{aligned}$$

$$\leq r\mu_y M_1 + \frac{\lambda_y}{\mu_c}\frac{\mu_h}{\lambda_m}k_s\left(\frac{\Lambda}{\mu_x}\right)M_2 - m_2\left(M(t) + \frac{\mu_h}{\lambda_m}I(t) + \frac{\lambda_y}{\mu_c}\frac{\mu_h}{\lambda_m}Y(t)\right)$$
$$= r\mu_y M_1 + \frac{\lambda_y}{\mu_c}\frac{\mu_h}{\lambda_m}k_s\left(\frac{\Lambda}{\mu_x}\right)M_2 - m_2 V(t),$$

where $m_2 = \min\{\mu_m, \mu_i, \mu_y\}$. Thus

$$\limsup_{t\to+\infty} V(t) \leq M_3, \quad \text{where} \quad M_3 = \frac{r\mu_y M_1 + \frac{\lambda_y}{\mu_c}\frac{\mu_h}{\lambda_m}k_s\left(\frac{\Lambda}{\mu_x}\right)M_2}{m_2}.$$

Therefore, the dynamics of system (2) can be analyzed in the following feasible region:

$$T = \left\{(X, Y, M, I) \in \mathbb{R}^4_+ : X \leq \frac{\Lambda}{\mu_x},\ X + Y \leq M_1,\ M \leq M_2,\right.$$
$$\left. M + \frac{\mu_h}{\lambda_m}I + \frac{\lambda_y}{\mu_c} \times \frac{\mu_h}{\lambda_m}Y \leq M_3\right\}.$$

Notice that the region T is positively invariant. In the next sections, we will investigate the stability of the above equilibrium points by considering the region T.

4. Local and global stability of the disease-free equilibrium point E_0. First of all, we discuss the local stability of the disease-free equilibrium point by examining the linearized form of system (2) at the equilibrium point E_0. The Jacobian matrix of system (2) is given by

(6)
$$J = \begin{bmatrix} -\left(\mu_x + \frac{k_s M}{(1+\alpha X)^2}\right) & 0 & \frac{-k_s X}{1+\alpha X} & 0 \\ \frac{k_s M}{(1+\alpha X)^2} & -(\mu_y + \mu_c I) & \frac{k_s X}{1+\alpha X} & -\mu_c Y \\ 0 & r\mu_y & -(\mu_m + \mu_h I) & -\mu_h M \\ 0 & \lambda_y I & \lambda_m I & \lambda_y Y + \lambda_m M - \mu_i \end{bmatrix}.$$

The Jacobian matrix at the disease-free equilibrium point $E_0 = (\Lambda/\mu_x, 0, 0, 0)$ is

(7)
$$J_{E_0} = \begin{bmatrix} -\mu_x & 0 & \frac{-k_s\frac{\Lambda}{\mu_x}}{1+\alpha\frac{\Lambda}{\mu_x}} & 0 \\ 0 & -\mu_y & \frac{k_s\frac{\Lambda}{\mu_x}}{1+\alpha\frac{\Lambda}{\mu_x}} & 0 \\ 0 & r\mu_y & -\mu_m & 0 \\ 0 & 0 & 0 & -\mu_i \end{bmatrix}.$$

From the first and fourth columns, we can see that J_{E_0} has negative eigenvalues $-\mu_x$ and $-\mu_i$. Removing the first and fourth rows and columns of

matrix (7), we obtain the matrix

$$J'_{E_0} = \begin{bmatrix} -\mu_y & \frac{k_s\Lambda}{\mu_x+\alpha\Lambda} \\ r\mu_y & -\mu_m \end{bmatrix}.$$

Since $\mu_x > 0$ and $\mu_i > 0$, the equilibrium point E_0 is locally asymptotically stable if

$$\mu_y\mu_m > r\mu_y\frac{k_s\Lambda}{\mu_x+\alpha\Lambda}, \quad \text{that is,} \quad \frac{rk_s\Lambda}{\mu_m(\mu_x+\alpha\Lambda)} < 1.$$

Let us define the *basic reproduction ratio of infection* as

$$R_0 = \frac{rk_s\Lambda}{\mu_m(\mu_x+\alpha\Lambda)}.$$

Thus, we have the following lemma.

LEMMA 2. *The disease-free equilibrium E_0 is locally asymptotically stable if $R_0 < 1$, and it is unstable if $R_0 > 1$.*

The following theorem shows the global stability of the disease-free equilibrium point E_0.

THEOREM 2. *If $R_0 < 1$, the disease-free equilibrium point $E_0 = (\Lambda/\mu_x, 0, 0, 0)$ of system (2) is globally asymptotically stable in the invariant set T. If $R_0 > 1$, all solutions of system (2) starting sufficiently close to E_0 in T move away from E_0 except those solutions starting on the invariant set of the X-axis which approach E_0 along this axis.*

Proof. For simplicity, we set $X_0 = \Lambda/\mu_x$. Consider the continuously differentiable function

$$L = A_1\left(X - X_0 - X_0\ln\frac{X}{X_0}\right) + rY + M + A_2I,$$

where

$$A_1 = \frac{\mu_x\mu_m}{k_s\Lambda} \quad \text{and} \quad A_2 < \min\left\{\frac{r\mu_c}{\lambda_y}, \frac{\mu_h}{\lambda_m}\right\}.$$

Its derivative along the solutions of system (2) is

$$\begin{aligned}
\dot{L} &= A_1\left(\dot{X} - \frac{X_0}{X}\dot{X}\right) + r\dot{Y} + \dot{M} + A_2\dot{I} \\
&= A_1\left(\Lambda - \mu_xX - \frac{k_sXM}{1+\alpha X} - \frac{X_0}{X}\Lambda + \mu_xX_0 + \frac{k_sX_0M}{1+\alpha X}\right) \\
&\quad + r\left(\frac{k_sXM}{1+\alpha X} - \mu_yY - \mu_cYI\right) + r\mu_yY - \mu_mM - \mu_hMI \\
&\quad + A_2([\lambda_yY + \lambda_mM]I - \mu_iI)
\end{aligned}$$

$$
\begin{aligned}
&= A_1\mu_x X_0\left(2-\frac{X}{X_0}-\frac{X_0}{X}\right)-\frac{A_1k_sXM}{1+\alpha X}+\frac{A_1k_sX_0M}{1+\alpha X}+\frac{rk_sXM}{1+\alpha X}\\
&\quad -r\mu_cYI-\mu_mM-\mu_hMI+A_2([\lambda_yY+\lambda_mM]I-\mu_iI)\\
&= A_1\mu_x X_0\left(2-\frac{X}{X_0}-\frac{X_0}{X}\right)+\frac{rk_sXM-k_sXMA_1-\mu_m\alpha XM}{(1+\alpha X)}\\
&\quad -r\mu_cYI-\mu_hMI+A_2([\lambda_yY+\lambda_mM]I-\mu_iI)\\
&= A_1\mu_x X_0\left(2-\frac{X}{X_0}-\frac{X_0}{X}\right)+\frac{\frac{(R_0-1)\mu_m(\mu_x+\alpha\Lambda)}{\Lambda}XM}{(1+\alpha X)}\\
&\quad +(A_2\lambda_y-r\mu_c)YI+(A_2\lambda_m-\mu_h)MI-A_2\mu_iI.
\end{aligned}
$$

Since

$$
\begin{aligned}
2-\frac{X}{X_0}-\frac{X_0}{X}&<0, \quad X\neq X_0,\\
2-\frac{X}{X_0}-\frac{X_0}{X}&=0, \quad X=X_0,
\end{aligned}
$$

we have $\dot{L}\leq 0$ if $R_0<1$. Moreover $\dot{L}=0$ when $X=X_0$ and $M=I=0$. Let Σ_0 be the maximum invariant set in the set

$$
\begin{aligned}
\Sigma &= \{(X,Y,M,I):\dot{L}(X,Y,M,I)=0\}\\
&= \{(X,Y,M,I):X=X_0,\,Y\geq 0,\,M=I=0\}.
\end{aligned}
$$

From the third equation of (2) we have $\sum_0=\{E_0\}$, since otherwise for any orbit starting from a point with $Y>0$ in Σ, the M-component of this orbit must remain positive for $t>0$. From LaSalle's Theorem (see [6]), this implies that all solutions in T approach E_0 as $t\to\infty$. It follows that the disease-free equilibrium point E_0 is globally asymptotically stable. ∎

5. Local and global stability of the endemic equilibrium point E_1. In this section, we investigate the stability of the endemic equilibrium point $E_1=(X^*,Y^*,M^*,0)$. In terms of R_0, its coordinates are

$$
\begin{aligned}
X^* &= \frac{1}{\frac{\mu_x}{\Lambda}R_0+\alpha(R_0-1)},\\
Y^* &= \frac{1}{\mu_y}\frac{(\mu_x+\alpha\Lambda)(R_0-1)}{\frac{\mu_x}{\Lambda}R_0+\alpha(R_0-1)},\\
M^* &= \frac{r}{\mu_m}\frac{(\mu_x+\alpha\Lambda)(R_0-1)}{\frac{\mu_x}{\Lambda}R_0+\alpha(R_0-1)}.
\end{aligned}
\tag{8}
$$

From the above formulae, the system has no positive endemic equilibrium point if $R_0<1$; such a point is obtained only when $R_0>1$.

THEOREM 3. *Suppose that $R_0 > 1$. If $\lambda_y Y^* + \lambda_m M^* < \mu_i$, then the endemic equilibrium point $E_1 = (X^*, Y^*, M^*, 0)$ is locally asymptotically stable. If $\lambda_y Y^* + \lambda_m M^* > \mu_i$, then E_1 is unstable.*

Proof. The Jacobian matrix at $E_1 = (X^*, Y^*, M^*, 0)$ is

$$J_{E_1} = \begin{bmatrix} -\left(\mu_x + \frac{k_s M^*}{(1+\alpha X^*)^2}\right) & 0 & \frac{-k_s X^*}{1+\alpha X^*} & 0 \\ \frac{k_s M^*}{(1+\alpha X^*)^2} & -\mu_y & \frac{k_s X^*}{1+\alpha X^*} & -\mu_c Y^* \\ 0 & r\mu_y & -\mu_m & -\mu_h M^* \\ 0 & 0 & 0 & \lambda_y Y^* + \lambda_m M^* - \mu_i \end{bmatrix}. \tag{9}$$

It can be seen from the last row that J_{E_1} has eigenvalue $\lambda_y Y^* + \lambda_m M^* - \mu_i$ and the remaining eigenvalues can be derived from the 3×3 matrix

$$J'_{E_1} = \begin{bmatrix} -\left(\mu_x + \frac{k_s M^*}{(1+\alpha X^*)^2}\right) & 0 & \frac{-k_s X^*}{1+\alpha X^*} \\ \frac{k_s M^*}{(1+\alpha X^*)^2} & -\mu_y & \frac{k_s X^*}{1+\alpha X^*} \\ 0 & r\mu_y & -\mu_m \end{bmatrix}. \tag{10}$$

The characteristic polynomial for the matrix (10) is

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{11}$$

where

$$\begin{aligned} a_1 &= \mu_x + \frac{k_s M^*}{(1+\alpha X^*)^2} + \mu_y + \mu_m, \\ a_2 &= (\mu_y + \mu_m)\left(\mu_x + \frac{k_s M^*}{(1+\alpha X^*)^2}\right), \\ a_3 &= \frac{k_s M^*}{(1+\alpha X^*)^2}\mu_y\mu_m. \end{aligned}$$

It is clear that the constants a_1, a_2 and a_3 are positive. Now, we compute

$$\begin{aligned} a_1a_2 - a_3 &= \left(\mu_x + \frac{k_s M^*}{(1+\alpha X^*)^2} + \mu_y + \mu_m\right)(\mu_y + \mu_m)\left(\mu_x + \frac{k_s M^*}{(1+\alpha X^*)^2}\right) \\ &\quad - \frac{k_s M^*}{(1+\alpha X^*)^2}\mu_y\mu_m \\ &= \left(\mu_x + \frac{k_s M^*}{(1+\alpha X^*)^2} + \mu_y\right)(\mu_y + \mu_m)\left(\mu_x + \frac{k_s M^*}{(1+\alpha X^*)^2}\right) \\ &\quad + \mu_m\mu_x(\mu_y + \mu_m) + \mu_m^2\frac{k_s M^*}{(1+\alpha X^*)^2} > 0. \end{aligned}$$

Therefore, the Routh–Hurwitz conditions ($a_1 > 0, a_2 > 0, a_3 > 0, a_1a_2 > a_3$) for a polynomial of degree three are satisfied. Hence E_1 is locally asymptotically stable if $\lambda_y Y^* + \lambda_m M^* < \mu_i$. ∎

The global stability of the endemic equilibrium point can be proved by applying the theory of competitive systems (see [17] and [10]).

Note that in the absence of immune effectors, i.e. $I(t) = 0$, without loss of generality, we can analyze system (2) without the last equation. Then system (2) changes to

$$\begin{aligned} \frac{dX}{dt} &= \Lambda - \mu_x X - k_s X M, \\ \frac{dY}{dt} &= k_s X M - \mu_y Y, \\ \frac{dM}{dt} &= r\mu_y Y - \mu_m M. \end{aligned} \tag{12}$$

We begin with the definition of a competitive system. Let $D \subset \mathbb{R}^n$ be an open set and $x \mapsto f(x) \in \mathbb{R}^n$ be a C^1 function defined in D. We consider the autonomous system in $\mathbb{R}^n$ given by

$$x' = f(x). \tag{13}$$

We recall the definition of competitive system from [17].

Definition 1. System (13) is *competitive* in D if, for some diagonal matrix $H = (\epsilon_1, \dots, \epsilon_n)$, where each ϵ_i is either 1 or -1, $H \cdot Df(x) \cdot H$ has non-positive off-diagonal elements for $x \in D$, where $Df(x)$ is the Jacobian of (13).

It is shown in [17] that, if D is convex, the flow of such a system preserves for $t < 0$ the partial order in $\mathbb{R}^n$ defined by orthant

$$K = \{(x_1, \dots, x_n) \in \mathbb{R}^n : \epsilon_i x_i \geq 0\}.$$

By looking at the Jacobian matrix and choosing the matrix H as

$$H = \begin{bmatrix} 1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & 1 \end{bmatrix},$$

it can be easily seen that our system is competitive in T with respect to the partial order defined by the orthant

$$K = \{(X, Y, M) \in \mathbb{R}^3 : X \geq 0,\ Y \leq 0,\ M \geq 0\}.$$

Hirsch [9] and Smith [17] proved that three-dimensional competitive systems that live in convex sets have the Poincaré–Bendixson property [19]. That is, any non-empty compact ω-limit set that contains no equilibrium point must be a closed orbit.

For the definition of ω-limit set, the reader is referred to [6].

Here we recall additional definitions from [6] and [3], respectively, that we will use later.

DEFINITION 2. Suppose system (13) has a periodic solution $x = p(t)$ with minimal period $\omega > 0$ and orbit $\gamma = \{p(t) : 0 \leq t \leq \omega\}$. This orbit is *orbitally stable* if, for each $\epsilon > 0$, there exists a $\delta > 0$ such that any solution $x(t)$ for which the distance of $x(0)$ from γ is less than δ, remains at a distance less than ϵ from γ for all $t \geq 0$. It is *asymptotically orbitally stable* if the distance of $x(t)$ from γ also tends to zero as $t \to \infty$.

DEFINITION 3. System (13) is *persistent* if each solution $x(t)$ starting in $\text{int}(D)$ has the property that $\liminf_{t\to\infty} x(t)$ is at a positive distance from the boundary of D.

We also use the following definition in the next theorems.

DEFINITION 4. System (13) has the *property of stability of periodic orbits* if the orbit of any periodic solution $p(t)$, if it exists, is asymptotically orbitally stable.

In the following theorem, we will use the concept of second additive compound matrix. For the definition, the reader is referred to the Appendix of this paper.

THEOREM 4. *A sufficient condition for a periodic orbit* $\gamma = \{p(t) : 0 \leq t \leq \omega\}$ *of* (13) *to be asymptotically orbitally stable is that the linear system*

$$y'(t) = (Df^{[2]}(p(t)))y(t)$$

is asymptotically stable, where $Df^{[2]}$ *is the second additive compound matrix of the Jacobian* Df *of* f.

For the proof of Theorem 4, the reader is referred to [14, Theorem 4.2].

The following theorem is the main tool to prove the global stability of the endemic equilibrium E_1.

THEOREM 5. *Assume that* $n = 3$ *and* D *is convex and bounded. Moreover suppose that* (13) *is competitive, persistent and has the property of stability of periodic orbits. If* x_0 *is the only equilibrium point in* $\text{int}(D)$*, and if it is locally asymptotically stable, then it is globally asymptotically stable in* $\text{int}(D)$.

Proof. The proof is similar to the proofs of Theorems 2.1 and 4.2 in [12]. ∎

The endemic equilibrium point E_1 is globally asymptotically stable in the interior of $T_0 := T \cap \{I = 0\}$. This is shown in Theorem 6 below.

THEOREM 6. *If* $R_0 > 1$ *and* $\lambda_y Y^* + \lambda_m M^* < \mu_i$*, then the endemic equilibrium point* E_1 *of system* (12) *is globally asymptotically stable in* $\text{int}(T_0)$.

Proof. The relevant vector field is transversal to the boundary of T_0, except in the invariant set of the X-axis. On the X-axis, we have

$$X' = \Lambda - \mu_x X.$$

This equation implies that $X(t) \to \Lambda/\mu_x$ as $t \to \infty$. Therefore, E_0 is the only ω-limit point on the boundary of T_0. Notice that for $R_0 > 1$, E_0 cannot be the ω-limit point of any orbit in $\mathrm{int}(T_0)$. Therefore, system (12) is persistent when $R_0 > 1$ (see [13, Proposition 5.8]).

Now, it is sufficient to show that E_1 is globally asymptotically stable in $\mathrm{int}(T_0)$. Since system (12) is competitive, persistent for $R_0 > 1$ and E_1 is locally asymptotically stable, the result follows from Theorem 5 if we can show that system (12) has the property of stability of periodic orbits. This is derived from Theorem 4. It is enough to prove that the linear non-autonomous system

$$w'(t) = (Df^{[2]}(p(t)))w(t) \tag{14}$$

is asymptotically stable.

The Jacobian matrix of system (12) is given by

$$Df(X,Y,M) = \begin{bmatrix} -\left(\mu_x + \frac{k_s M}{(1+\alpha X)^2}\right) & 0 & \frac{-k_s X}{1+\alpha X} \\ \frac{k_s M}{(1+\alpha X)^2} & -\mu_y & \frac{k_s X}{1+\alpha X} \\ 0 & r\mu_y & -\mu_m \end{bmatrix}. \tag{15}$$

The second additive compound matrix of (15) is

$$\begin{aligned} &Df^{[2]}(X,Y,M) \\ &= \begin{bmatrix} -\left(\mu_x + \frac{k_s M}{(1+\alpha X)^2} + \mu_y\right) & \frac{k_s X}{1+\alpha X} & \frac{k_s X}{1+\alpha X} \\ r\mu_y & -\left(\mu_x + \frac{k_s M}{(1+\alpha X)^2} + \mu_m\right) & 0 \\ 0 & \frac{k_s M}{(1+\alpha X)^2} & -(\mu_y + \mu_m) \end{bmatrix}. \end{aligned} \tag{16}$$

For the solution $p(t) = (X(t), Y(t), M(t))$, equation (14) becomes

$$\begin{aligned} w_1'(t) &= -\left(\mu_x + \frac{k_s M}{(1+\alpha X)^2} + \mu_y\right) w_1(t) + \frac{k_s X}{1+\alpha X} w_2(t) \\ &\quad + \frac{k_s X}{1+\alpha X} w_3(t), \\ w_2'(t) &= r\mu_y w_1(t) - \left(\mu_x + \frac{k_s M}{(1+\alpha X)^2} + \mu_m\right) w_2(t), \\ w_3'(t) &= \frac{k_s M}{(1+\alpha X)^2} w_2(t) - (\mu_y + \mu_m) w_3(t). \end{aligned} \tag{17}$$

In order to demonstrate that (17) is asymptotically stable, we consider the

Lyapunov function $V(t)$ and the norm $\|\ \|$ defined as follows:

$$\|(w_1, w_2, w_3)\| = \sup\{|w_1|, |w_2| + |w_3|\},$$
$$V(t) = V(w_1(t), w_2(t), w_3(t); X(t), Y(t), M(t))$$
$$= \left\| \begin{bmatrix} 1 & 0 & 0 \\ 0 & \frac{Y(t)}{M(t)} & 0 \\ 0 & 0 & \frac{Y(t)}{M(t)} \end{bmatrix} \begin{bmatrix} w_1 \\ w_2 \\ w_3 \end{bmatrix} \right\| = \sup\left\{ |w_1|, \frac{Y(t)}{M(t)}(|w_2| + |w_3|) \right\}.$$

The function $V(t)$ is positive, but not differentiable everywhere. Fortunately, this lack of differentiability can be remedied by using the right derivative of $V(t)$, denoted as $D_+V(t)$.

Suppose that the solution $p(t) = (X(t), Y(t), M(t))$ is periodic of minimal period ω. Since system (12) is persistent for $R_0 > 1$, the orbit γ of $p(t)$ remains at a positive distance from the boundary of T_0. Thus

$$Y(t) \geq \epsilon \quad \text{and} \quad M(t) \geq \epsilon \quad \text{with } 0 < \epsilon \leq 1.$$

Hence the function V is well defined along $p(t)$ and there exists a constant $c > 0$ such that

$$V(w_1, w_2, w_3; X, Y, M) \geq c\, \|(w_1, w_2, w_3)\| \tag{18}$$

for all $(w_1, w_2, w_3) \in \mathbb{R}^3$ and $(X, Y, M) \in \gamma$.

We have the following inequalities:

$$\begin{aligned} D_+|w_1| &\leq -\left(\mu_x + \frac{k_s M}{(1+\alpha X)^2} + \mu_y\right)|w_1(t)| + \frac{k_s X}{1+\alpha X}|w_2(t)| \\ &\quad + \frac{k_s X}{1+\alpha X}|w_3(t)| \\ &\leq -\left(\mu_x + \frac{k_s M}{(1+\alpha X)^2} + \mu_y\right)|w_1(t)| \\ &\quad + \frac{k_s X M(t)}{(1+\alpha X)Y(t)}\left(\frac{Y(t)}{M(t)}(|w_2(t)| + |w_3(t)|)\right), \end{aligned} \tag{19}$$

$$D_+|w_2| \leq r\mu_y|w_1(t)| - \left(\mu_x + \frac{k_s M}{(1+\alpha X)^2} + \mu_m\right)|w_2(t)|, \tag{20}$$

$$D_+|w_3| \leq \frac{k_s M}{(1+\alpha X)^2}|w_2(t)| - (\mu_y + \mu_m)|w_3(t)|. \tag{21}$$

From (20) and (21) we obtain

$$\begin{aligned} D_+(|w_2(t)| + |w_3(t)|) &\leq r\mu_y|w_1(t)| - (\mu_x + \mu_m)|w_2(t)| - (\mu_y + \mu_m)|w_3(t)| \\ &\leq r\mu_y|w_1(t)| - \phi[|w_2(t)| + |w_3(t)|] \end{aligned} \tag{22}$$

where $\phi = \min\{\mu_x + \mu_m, \mu_y + \mu_m\}$.

By using (22), we obtain

$$
\begin{aligned}
(23)\quad & D_+\frac{Y(t)}{M(t)}(|w_2(t)|+|w_3(t)|)\\
&=\left(\frac{Y'(t)}{Y(t)}-\frac{M'(t)}{M(t)}\right)\frac{Y(t)}{M(t)}(|w_2(t)|+|w_3(t)|)+\frac{Y(t)}{M(t)}D_+(|w_2(t)|+|w_3(t)|)\\
&\le \frac{Y(t)}{M(t)}r\mu_y|w_1(t)|+\left(\frac{Y'(t)}{Y(t)}-\frac{M'(t)}{M(t)}-\phi\right)\frac{Y(t)}{M(t)}(|w_2(t)|+|w_3(t)|).
\end{aligned}
$$

We assert that (19) and (23) lead to

$$
D_+V(t)\le \sup\{h_1(t),h_2(t)\}V(t), \tag{24}
$$

where

$$
\begin{aligned}
h_1(t)&=-\left(\mu_x+\frac{k_sM}{(1+\alpha X)^2}+\mu_y\right)+\frac{k_sXM}{(1+\alpha X)Y},\\
h_2(t)&=\frac{Y(t)}{M(t)}r\mu_y+\left(\frac{Y'(t)}{Y(t)}-\frac{M'(t)}{M(t)}-\phi\right).
\end{aligned}
$$

Since $\mu_y>\mu_x$ and the second and third equations of system (12) are respectively

$$
\frac{k_sXM}{(1+\alpha X)Y}=\frac{Y'}{Y}+\mu_y \quad\text{and}\quad \frac{M'}{M}=\frac{r\mu_yY}{M}-\mu_m,
$$

we have

$$
\begin{aligned}
h_1(t)&=\frac{Y'}{Y}-\left(\mu_x+\frac{k_sM}{(1+\alpha X)^2}\right),\\
h_2(t)&=\frac{Y'}{Y}-\mu_x.
\end{aligned}
$$

We obtain

$$
\begin{aligned}
(25)\quad \sup\{h_1(t),h_2(t)\}&=\sup\left\{\frac{Y'}{Y}-\left(\mu_x+\frac{k_sM}{(1+\alpha X)^2}\right),\frac{Y'}{Y}-\mu_x\right\}\\
&\le \frac{Y'}{Y}-\mu_x.
\end{aligned}
$$

Thus

$$
\int_0^\omega \sup\{h_1(t),h_2(t)\}\,dt\le \ln Y(t)\big|_0^\omega-\mu_x\omega=-\mu_x\omega<0. \tag{26}
$$

This fact together with (24) implies that $V(t)\to 0$ as $t\to\infty$. By (18) it turns out that

$$
(w_1(t),w_2(t),w_3(t))\to 0 \quad \text{as } t\to\infty.
$$

As a result, the linear system (17) is asymptotically stable and the periodic solution $(X(t),Y(t),M(t))$ is asymptotically orbitally stable. ∎

6. Local stability of the endemic equilibrium point E_2. In this section, we study the stability properties of the endemic equilibrium point in the presence of immune effectors, i.e., E_2. The Jacobian matrix of system (2) at $E_2 = (\tilde{X}, \tilde{Y}, \tilde{M}, \tilde{I})$ for $\tilde{I} \neq 0$ is given by

$$J_{E_2} = \begin{bmatrix} -\left(\mu_x + \frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2}\right) & 0 & \frac{-k_s\tilde{X}}{1+\alpha\tilde{X}} & 0 \\ \frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2} & -(\mu_y + \mu_c\tilde{I}) & \frac{k_s\tilde{X}}{1+\alpha\tilde{X}} & -\mu_c\tilde{Y} \\ 0 & r\mu_y & -(\mu_m + \mu_h\tilde{I}) & -\mu_h\tilde{M} \\ 0 & \lambda_y\tilde{I} & \lambda_m\tilde{I} & \lambda_y\tilde{Y} + \lambda_m\tilde{M} - \mu_i \end{bmatrix}. \tag{27}$$

In order to determine its determinant, the following simplified form of system (3) evaluated at $E_2 = (\tilde{X}, \tilde{Y}, \tilde{M}, \tilde{I})$ is used:

$$\begin{aligned} &\mu_y + \mu_c\tilde{I} = \frac{k_s\tilde{X}\tilde{M}}{(1+\alpha\tilde{X})\tilde{Y}}, \\ &\mu_m + \mu_h\tilde{I} = \frac{r\mu_y\tilde{Y}}{\tilde{M}}, \\ &\lambda_y\tilde{Y} + \lambda_m\tilde{M} - \mu_i = 0 \quad \text{for } \tilde{I} \neq 0. \end{aligned} \tag{28}$$

By using (27) and (28), we have

$$J_{E_2} = \begin{bmatrix} -\left(\mu_x + \frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2}\right) & 0 & \frac{-k_s\tilde{X}}{1+\alpha\tilde{X}} & 0 \\ \frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2} & \frac{-k_s\tilde{X}\tilde{M}}{(1+\alpha\tilde{X})\tilde{Y}} & \frac{k_s\tilde{X}}{1+\alpha\tilde{X}} & -\mu_c\tilde{Y} \\ 0 & r\mu_y & \frac{-r\mu_y\tilde{Y}}{\tilde{M}} & -\mu_h\tilde{M} \\ 0 & \lambda_y\tilde{I} & \lambda_m\tilde{I} & 0 \end{bmatrix}. \tag{29}$$

The characteristic polynomial of the linearized system is

$$p(\lambda) = \det \begin{bmatrix} -\left(\mu_x + \frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2} + \lambda\right) & 0 & \frac{-k_s\tilde{X}}{1+\alpha\tilde{X}} & 0 \\ \frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2} & -\left(\frac{k_s\tilde{X}\tilde{M}}{(1+\alpha\tilde{X})\tilde{Y}} + \lambda\right) & \frac{k_s\tilde{X}}{1+\alpha\tilde{X}} & -\mu_c\tilde{Y} \\ 0 & r\mu_y & -\left(\frac{r\mu_y\tilde{Y}}{\tilde{M}} + \lambda\right) & -\mu_h\tilde{M} \\ 0 & \lambda_y\tilde{I} & \lambda_m\tilde{I} & -\lambda \end{bmatrix} = 0. \tag{30}$$

This can be written as

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0,$$

where

$$
\begin{aligned}
a_1 &= \left(\mu_x + \frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2}\right) + \frac{k_s\tilde{X}\tilde{M}}{(1+\alpha\tilde{X})\tilde{Y}} + \frac{r\mu_y\tilde{Y}}{\tilde{M}},\\
a_2 &= \left(\mu_x + \frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2}\right)\frac{k_s\tilde{X}\tilde{M}}{(1+\alpha\tilde{X})\tilde{Y}} + \left(\mu_x + \frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2}\right)\frac{r\mu_y\tilde{Y}}{\tilde{M}}\\
&\quad + \lambda_m\tilde{I}\mu_h\tilde{M} + \mu_c\tilde{Y}\lambda_y\tilde{I},\\
a_3 &= \left(\mu_x + \frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2}\right)\lambda_m\tilde{I}\mu_h\tilde{M} + \left(\mu_x + \frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2}\right)\mu_c\tilde{Y}\lambda_y\tilde{I}\\
&\quad + \frac{k_s\tilde{X}\tilde{M}}{(1+\alpha\tilde{X})\tilde{Y}}\lambda_m\tilde{I}\mu_h\tilde{M} + \frac{k_s\tilde{X}}{1+\alpha\tilde{X}}\mu_h\tilde{M}\lambda_y\tilde{I} + \mu_c\tilde{Y}r\mu_y\lambda_m\tilde{I}\\
&\quad + \mu_c\tilde{Y}\lambda_y\tilde{I}\frac{r\mu_y\tilde{Y}}{\tilde{M}} + \frac{k_s\tilde{X}}{1+\alpha\tilde{X}}\,\frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2}r\mu_y,\\
a_4 &= \left(\mu_x + \frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2}\right)\frac{k_s\tilde{X}\tilde{M}}{(1+\alpha\tilde{X})\tilde{Y}}\lambda_m\tilde{I}\mu_h\tilde{M} + \mu_x\frac{k_s\tilde{X}}{1+\alpha\tilde{X}}\mu_h\tilde{M}\lambda_y\tilde{I}\\
&\quad + \left(\mu_x + \frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2}\right)\mu_c\tilde{Y}r\mu_y\lambda_m\tilde{I}\\
&\quad + \left(\mu_x + \frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2}\right)\mu_c\tilde{Y}\lambda_y\tilde{I}\frac{r\mu_y\tilde{Y}}{\tilde{M}}.
\end{aligned}
$$

For convenience, we adopt the following notation:

$$
A_1 = \mu_x + \frac{k_s\tilde{M}}{(1+\alpha\tilde{X})^2},\quad A_2 = \frac{k_s\tilde{X}\tilde{M}}{(1+\alpha\tilde{X})\tilde{Y}},\quad A_3 = \frac{r\mu_y\tilde{Y}}{\tilde{M}},\quad A_4 = \mu_h\tilde{M},
$$

$$
A_5 = \lambda_m\tilde{I},\quad A_6 = \mu_c\tilde{Y},\quad A_7 = \lambda_y\tilde{I},\quad A_8 = \frac{k_s\tilde{X}}{1+\alpha\tilde{X}},\quad A_9 = r\mu_y.
$$

Then

$$
\begin{aligned}
a_1 &= A_1 + A_2 + A_3,\\
a_2 &= A_1(A_2 + A_3) + (A_4A_5 + A_6A_7),\\
a_3 &= A_1(A_4A_5 + A_6A_7) + A_5(A_2A_4 + A_6A_9) + A_4A_7A_8\\
&\quad + A_6A_7A_3 + (A_1 - \mu_x)A_8A_9,\\
a_4 &= A_1A_5(A_2A_4 + A_6A_9) + \mu_xA_4A_7A_8 + A_1A_6A_7A_3.
\end{aligned}
$$

Notice that as $A_1 - \mu_x > 0$, all a_i for $1 \le i \le 4$ are positive. Therefore, we get

$$
\begin{aligned}
H_2 &= A_1(A_1 + A_2 + A_3)(A_2 + A_3) + A_7(A_2A_6 - A_4A_8)\\
&\quad + A_5(A_3A_4 - A_6A_9) - (A_1 - \mu_x)A_8A_9,
\end{aligned}
$$

$$
\begin{aligned}
H_3 = {} & (A_1 + A_2 + A_3) \\
& \times \big\{ A_1^2 A_2 A_6 A_7 + A_1^2 A_5 (A_3 A_4 - A_6 A_9) \\
& + (A_2 + A_3)[A_1 A_4 A_7 A_8 + A_1 A_8 A_9 (A_1 - \mu_x)] \\
& - (A_1 + A_2 + A_3)\mu_x A_4 A_7 A_8 \big\} \\
& + [A_7(A_2 A_6 - A_4 A_8) + A_5(A_3 A_4 - A_6 A_9) - (A_1 - \mu_x) A_8 A_9] \\
& \times \big\{ A_1(A_4 A_5 + A_6 A_7) + A_5(A_2 A_4 + A_6 A_9) + A_4 A_7 A_8 \\
& \qquad + A_6 A_7 A_3 + (A_1 - \mu_x) A_8 A_9 \big\}.
\end{aligned}
$$

It is obvious that all coefficients a_1, a_2, a_3 and a_4 are positive. Moreover, for our characteristic polynomial, the Hurwitz determinants are $H_1 = a_1$, $H_2 = a_1 a_2 - a_3$, $H_3 = (a_1 a_2 - a_3)a_3 - a_1^2 a_4$ and $H_4 = a_4 H_3$. It can be easily seen that the Hurwitz conditions depend on the parameter values. Thus, the Hurwitz determinants H_2, H_3 and H_4 may be positive or negative. Hence, the Routh–Hurwitz criterion [11] for some parameters values gives local asymptotic stability of E_2. In fact, due to the positivity of a_i, the only condition of stability is $H_3 > 0$. Therefore, the endemic equilibrium point E_2 can be locally asymptotically stable or unstable, depending on the parameter values. In the following we give some examples related to this point.

Examples. Let $\mu_x = 0.0083$, $k_s = 2.5 \times 10^{-10}$, $\mu_y = 0.025$, $\mu_m = 48$, $\mu_i = 0.05$, $r = 16$, $\mu_c = \mu_h = 10^{-8}$, $\lambda_y = 2 \times 10^{-8}$ and $\lambda_m = 3 \times 10^{-8}$. We have the following numerical results:

1. For $\Lambda = 2.5 \times 10^8$ and $\alpha = 5 \times 10^{-11}$, we have

$$H_1 = 48.033376, \quad H_2 = 19.148383, \quad H_3 = 0.0000189, \quad H_4 = 1.412 \times 10^{-11}.$$

Thus in this case the real parts of all of the eigenvalues are negative, and therefore the endemic equilibrium point E_2 is locally asymptotically stable.

2. For $\Lambda = 2.5 \times 10^{25}$ and $\alpha = 10^{-12}$, we have

$$H_1 = 51.985224, \qquad H_2 = 22.426866,$$
$$H_3 = -1.421 \times 10^{-14}, \qquad H_4 = -6.057 \times 10^{-16}.$$

Thus in this case at least one of the eigenvalues has a positive real part. This means that the endemic equilibrium point E_2 is unstable.

7. Numerical analysis. In this section, using the initial data for variables and parameter values given in Table 1, numerical simulations are carried out to demonstrate the dynamics of system (2). First, we choose $\alpha = 0.99$ and take all other parameters as in Table 1. Then, we can verify that $R_0 = 8.4175 \times 10^{-11} < 1$. Fig. 1 reveals that the disease-free equilibrium point E_0 is globally asymptotically stable when $R_0 < 1$. In Figs. 2 and 3, we choose $\alpha = 10^{-11}$ and take all other parameters as in Table 1. Then we have $R_0 = 1.9290 > 1$. Fig. 2 shows that if $R_0 > 1$, the endemic equilibrium

point E_1 is globally asymptotically stable, whereas observing Fig. 3, we find that E_2 is unstable.

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

Parameters and variables	Value	Ref.
Λ	2.5×10^8 cells/day/ml	[8]
μ_x	0.0083/day	[2]
k_s	2.5×10^{-10}/day	[8]
μ_y	0.025/day	[7]
μ_m	48/day	[8]
μ_i	0.05/day	[8]
r	16	[2, 5]
μ_c	10^{-8}/day	[8]
μ_h	10^{-8}/day	[8]
λ_y	2×10^{-8}/day	[8]
λ_m	3×10^{-8}/day	[8]
$X(0)$	3×10^{10} cells/ml/day	[8]
$Y(0)$	0 cells/ml/day	[8]
$M(0)$	2×10^5 cells/ml/day	[8]
$I(0)$	0.0001 cells/ml/day	[8]

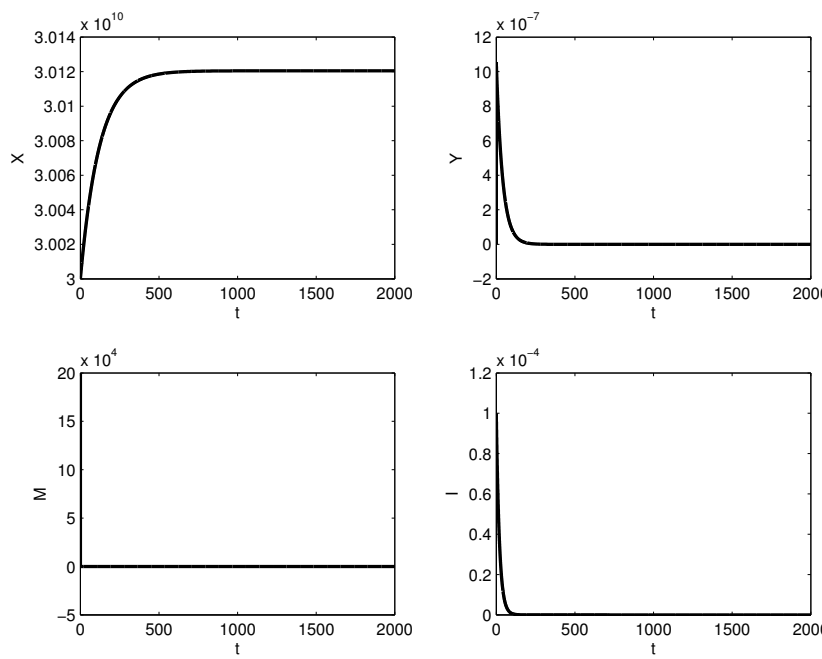

Fig. 1. The equilibrium point E_0 is globally asymptotically stable when $R_0 < 1$.

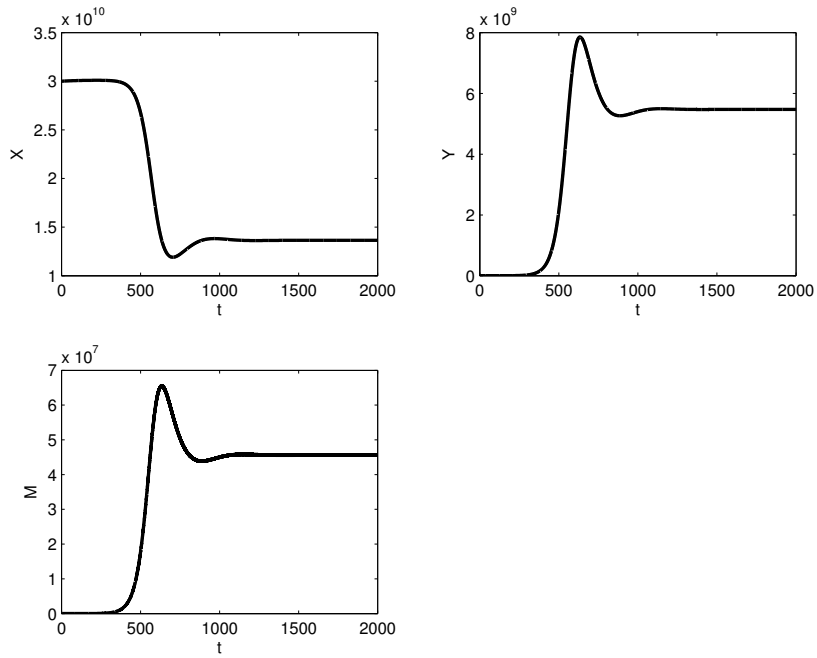

Fig. 2. The equilibrium point E_1 is globally asymptotically stable in the absence of immune effectors when $R_0 > 1$.

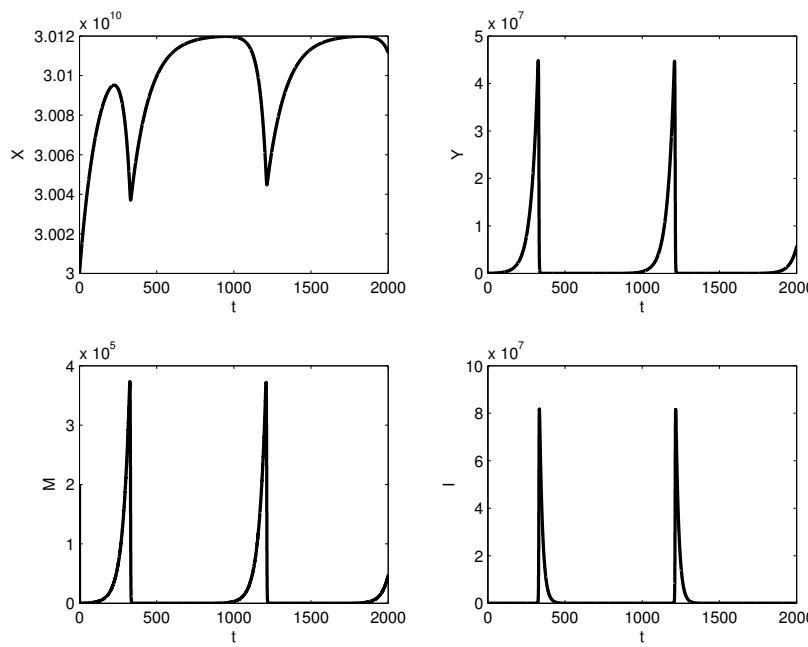

Fig. 3. The equilibrium point E_2 is not globally asymptotically stable in the presence of immune effectors.

8. Discussion. In this paper, we investigated a within-host model of malaria with Holling type II functional response. Our model described the dynamics of malaria infection within an infected host by a system of ordinary differential equations.

We got three equilibrium points. The first and second equilibrium were obtained in the absence of immune effectors, whereas the third one was achieved in the presence of immune response. By constructing Jacobian matrix at the first equilibrium point which corresponds to the disease-free or uninfected state, we could define the basic reproduction ratio of infection, R_0. Then by applying the conditions of local asymptotic stability to this matrix, we deduced that the disease-free equilibrium point is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. Global stability analysis of this point was carried out based on an invariant set and LaSalle's Theorem. It was established that the infection disappears from an infected host if $R_0 < 1$. Numerical simulations reveal that the disease-free equilibrium is always globally asymptotically stable as long as the condition $R_0 < 1$ holds (see Fig. 1).

The second equilibrium point reflects the state in which the infection exists but there are no immune effectors. The components of this point are expressed in terms of R_0 and they are positive only when $R_0 > 1$. By considering one more condition and using the Routh–Hurwitz criterion, we proved the local asymptotic stability of the second equilibrium point. It is also demonstrated using the theory of competitive systems that the equilibrium point is globally asymptotically stable (see Fig. 2). This implies that without the presence of immune effectors, the body will be unable to get rid of the malaria infection.

For the third equilibrium point, we found that the Hurwitz conditions depend on the parameter values and thus they may not be satisfied. Since the necessary and sufficient conditions for local asymptotic stability of an equilibrium point are provided by the Routh–Hurwitz criterion, the third equilibrium can be unstable for some parameter values. Also from Fig. 3 we see that the third equilibrium point does not always converge to a steady state and so is unstable. The reason may be that with the presence of immune effectors, the body is able to tolerate the malaria infection and finally the immune system can clear the infection.

Appendix. Compound matrices. In this appendix, we shall give the definition of an additive compound matrix. A survey of properties of additive matrices together with their connections to differential equations may be found in [12, 14].

We start by recalling the definition of a kth exterior power or multiplicative compound of a matrix.

DEFINITION 5. Let A be any $n \times m$ matrix of real of complex numbers, and let $a_{i_1,\dots,i_k,j_1,\dots,j_k}$ be the minor of A determined by the rows $(i_1,\dots,i_k)$ and the columns $(j_1,\dots,j_k)$, where $1 \le i_1 < \cdots < i_k \le n$ and $1 \le j_1 < \cdots < j_k \le m$. The kth *multiplicative compound matrix* $A^{(k)}$ of A is the $\binom{n}{k} \times \binom{m}{k}$ matrix whose entries written in the lexicographic order are $a_{i_1,\dots,i_k,j_1,\dots,j_k}$. In particular, when A is an $n \times k$ matrix with columns $a_1,\dots,a_k$, $A^{(k)}$ is the exterior product $a_1 \wedge \cdots \wedge a_k$.

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

DEFINITION 6. Let A be an $n \times n$ matrix. The 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 differentiation with respect to h.

If $B = A^{[k]}$, then the following formula for $b_{i,j}$ can be deduced from the above equation. For any $i = 1,\dots,\binom{n}{k}$, let $(i) = (i_1,\dots,i_k)$ be the ith member in the lexicographic ordering of all k-tuples of integers such that $1 \le i_1 < \cdots < i_k \le n$. Then

$$b_{i,j} = \begin{cases} a_{i_1,j_1} + \cdots + a_{i_k,j_k} & \text{if } (i) = (j), \\ (-1)^{r+s} a_{i_s,j_r} & \text{if exactly one entry } i_s \text{ in (i) does not occur} \\ & \text{in } (j) \text{ and } j_r \text{ does not occur in } (i), \\ 0 & \text{if } (i) \text{ differs from } (j) \text{ in two or more entries.} \end{cases}$$

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

$$A^{[1]} = A,$$

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

$$A^{[3]} = a_{11} + a_{22} + a_{33}.$$

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