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THE WITHIN-HOST DYNAMICS OF MALARIA INFECTION WITH IMMUNE RESPONSE

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Abstract. Malaria infection is one of the most serious global health problems of our time. In this article the blood-stage dynamics of malaria in an infected host are studied by incorporating red blood cells, malaria parasitemia and immune effectors into a mathematical model with nonlinear bounded Michaelis-Menten-Monod functions describing how immune cells interact with infected red blood cells and merozoites. By a theoretical analysis of this model, we show that there exists a threshold value R_0, namely the basic reproduction number, for the malaria infection. The malaria-free equilibrium is global asymptotically stable if $R_0 < 1$. If $R_0 > 1$, there exist two kinds of infection equilibria: malaria infection equilibrium (without specific immune response) and positive equilibrium (with specific immune response). Conditions on the existence and stability of both infection equilibria are given. Moreover, it has been showed that the model can undergo Hopf bifurcation at the positive equilibrium and exhibit periodic oscillations. Numerical simulations are also provided to demonstrate these theoretical results.

1. **Introduction.** Malaria is one of the three most dangerous infectious diseases worldwide (along with HIV/AIDS and tuberculosis). It is endemic in the tropical and subtropical regions of the world and caused an estimated 243 million cases led to an estimated 863,000 deaths in 2008 (WHO [42]). It is believed that half of the world's population is at risk of malaria (WHO [42]). Malaria infection in a host is caused by an inoculum of parasites from a blood-feeding female *Anopheles* mosquito carrying one or a combination of any of the four species of *Plasmodium* parasites: *P. falciparum, P. malariae, P. ovale,* and *P. vivax*. Among them, *P. falciparum* is

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responsible for almost all of the deaths attributed to malaria (McKenzie and Bossert [25]).

The malaria parasites first penetrate liver cells of the host and then move into the blood, where they multiply and undergo replication cycles in the red blood cells (or erythrocytes): the parasites multiply in the red blood cells which cause the infected red blood cells to burst and release a mass of new parasites (called merozoites) that quickly invade other red blood cells, and the cycle is repeated. When malaria parasites evolve in the host, they can stimulate the activity of immune cells in the host which produce an immune response to fight the infection. Immune response can either prevent the re-invasion of merozoites or increase the death rate of infected red blood cells (Stevenson and Riley [38] and Good et al. [12]).

Human immune system is composed of two subdivisions, the innate (non-specific) immune system and the adaptive (specific) immune system. The innate immune system is the first line of defense against invading pathogens while the adaptive immune system acts as a second line of defense which also provides protection against re-exposure to the same pathogen. Malaria infection triggers both innate and adaptive immune responses (Augustine et al. [6], Langhorne et al. [21], Malaguarnera and Musumeci [23]). Innate immune cells such as natural killer cells and dendritic cells are involved in the clearance of circulating parasites infected red blood cells (Cuban et al. [8], Augustine et al. [6]). Adaptive immune cells such as $CD4^+$ and $CD8^+$ are important for protection against malaria and B cell responses are induced by *Plasmodium* infection (Langhorne et al. [21], Augustine et al. [6]). The immune system has both cellular and humoral components by which they carry out their protective function. Cellular immunity is that T lymphocytes secrete proteins to act directly against the pathogens and stimulate cytotoxic T-cells which protect the host cells by lysis of infected cells and reduce the production of merozoites and gametocytes. Humoral immunity is the immune protection mediated by B lymphocytes which are activated by merozoites in blood and secrete antibodies into circulation as they remove merozoites from blood (Deans and Cohen [9] and Tumwiine et al. [40]). Though antibody-mediated immunity is more effective than cell-mediated immunity (Deans and Cohen [9]), extensive numerical analysis by Anderson et al. [4] suggested that it is very difficult to eradicate the parasites from the host by antibody-mediated attack against the free merozoites alone due to their short life-expectancy outside the erythrocytes.

In the last two decades, many mathematical models have been employed to describe the within-host dynamics of malaria infection, namely the dynamics of the blood stages of the malaria parasites and their interactions with red blood cells and immune effectors. The first models were proposed by Anderson et al. [4] (see also Hetzel and Anderson [16] and Anderson [3]) which consisted of healthy red blood cells, infected red blood cells, malaria parasitemia, without or with immune effectors. These models have been generalized by many researchers for different purposes, we refer to a review by Molineaux and Dietz [29] on various such generalizations and references.

Oscillations are common in the immune system (Stark et al. [37]), in particular when the host is infected by malaria parasites. Periodic occurrence of fever is the cardinal symptom of malaria and the period has been identified with the length of the replication cycle (Rouzine and Mckenzie [34]), which is 48 hours for *P. falciparum*. The periodicity indicates that malaria parasite replication in the red blood cells is synchronized: parasites enter and are released from the red blood cells at

approximately the same times (Rouzine and Mckenzie [34]). However, the mechanism of this synchronization is still not well-understood and quite a few models have been proposed to study the synchronization. For example, Kwiatkowsti and Nowak [20] proposed a 2-dimensional discrete model to show that the interaction between malaria parasites and red blood cells naturally tends to generate periodic fevers in the host when the replication rate is high. Rouzine and McKenzie [34] constructed an age-structured model to demonstrate that innate immune responses cause synchronization between the replication cycles of parasites in red blood cells which is reflected in periodic fevers in the host. Su et al. [39] proved the existence of Hopf bifurcation in the age-structured malaria infection model of Rouzine and McKenzie [34] by using the replication rate as the bifurcation parameter and showed numerically that synchronization with regular periodic oscillations (of period 48 h) occurs when the replication rate increases. Hoshen et al. [17] and Dong and Cui [11] introduced time delay into the basic model (without immune response) of Anderson et al. [4] to produce periodic oscillations in host-parasites. See also Mitchell and Carr [28]. When immune response is included in the basic model, via numerical simulations Anderson et al. [4] and Hetzel and Anderson [16] observed that periodic oscillations occur in the model with killing of infected red blood cells or with immune response directly against merozoites and infected red blood cells.

In this article we study the blood-stage dynamics of malaria in an infected host by incorporating healthy red blood cells, infected red blood cells, malaria parasitemia and immune effectors into a mathematical model. The model is a generalization of the basic models of Anderson et al. [4] and Anderson [3] with nonlinear bounded Michaelis-Menten-Monod functions describing how immune cells interact with the infected red blood cells and merozoites. We present some local analysis of the model, namely the existence and stability of the malaria-free, malaria infection (without specific immune response), and positive (with specific immune response) equilibria, in terms of the basic reproduction number. It is shown that if the basic reproduction numbers is greater than one, then the malaria parasites can infect the host and establish a persistent infection. The model also exhibits periodic oscillations due to Hopf bifurcation at the positive equilibrium by using the proliferation rate of the immune cells induced by infected red blood cells as the bifurcation parameter, which demonstrates that synchronicity is an inherent feature of malaria infection with immune response. Thus, we provide theoretical analysis and proof of the numerical observations of Anderson et al. [4] and Hetzel and Anderson [16] on the existence of periodic oscillations in the model with immune response. We also present some numerical simulations to illustrate out results.

This paper is organized as follows. In section 2 we propose a simple mathematical model for the within-host dynamics of malaria infection based on the basic understanding of biological interactions between malaria parasites, red blood cells, and immunity effectors, and some simple assumptions about the immune system. In section 3 we analyze the equilibria and obtain the basic reproduction numbers for malaria infection. We then present some numerical simulations and give some discussion in section 4.

2. **Mathematical modeling.**

In the malaria infection process of a host, there are four dynamical variables of populations: uninfected red blood cells $H(t)$, infected

red blood cells $I(t)$, free malaria parasites $M(t)$, and immunity effectors $E(t)$ (Anderson et al. [4], Chiyaka et al. [7], Hetzel and Anderson [16], Molineaux and Dietz [29], and McQueen and McKenzie [26]).

Red blood cells develop continuously from stem cells in the bone marrow through reticuloctyes to mature in about 7 days and live a total of about 120 days (Rapaport [33]). The population of uninfected red blood cells satisfies the equation $\frac{dH}{dt} = \lambda - d_1 H$ in the absence of any infection, which converges to a steady state $\frac{\lambda}{d_1}$, where λ is a constant product rate from the bone marrow and d_1 is the constant death rate of uninfected red blood cells, respectively. A density of about 5 million red blood cells per μl is maintained in adult males (Rapaport [33] and McQueen and McKenzie [26]).

In the body system of an infected host, the invading parasites will infect the red blood cells of the host. We assume that malaria parasites infect the red blood cells at a rate proportional to the contact rate of their population size, αMH, where α is a positive constant which describes the rate or probability of successful infection by a malaria parasite. It has been reported that up to $500,000$ red blood cells per μl are parasitized with *P. falciparum* and only $25,000$ cells per μl with *P. vivax, P. ovale*, or *P. malariae* (Mandell et al. [24]). The infected cells die at rate δ_R per day so that $1/\delta$ is the life-expectancy of infected red blood cells (approximately 2 days, see Anderson et al. [4]).

Immune responses against malaria infections are complex and stage-specific. The malaria parasite induces a specific immune response which can stimulate the release of cytokines and activate the host's monocytes, neutrophils, T-cells, and natural killer cells to react to the different stage parasite (Malaguarnera and Musumeci [23]). It would be reasonable to include various innate, antibody and T-cell responses to malaria parasite in modeling the within-host dynamics (see McQueen and McKenzie [27] and Chiyaka et al. [7]). However, for the sake of simplicity and analysis, we only consider the immunity effectors $E(t)$ as the total capacity of the immune response of the host to infected cells by parasites.

Previously, the killing of infected cells by immunity effectors has been modeled by a simple mass-action term depending only on the product of the densities of the parasite and the immune cells which is an unbounded bilinear function (see Anderson et al. [4] and Hetzel and Anderson [16]). Taking into account the fact that cell proliferation can saturate and that there is a handling time in immune responses, the more reasonable nonlinear bounded Michaelis-Menten-Monod function was firstly used by Agur et al. [2] and Antia et al. [5] and late formally derived and proposed by De Boer and Perelson [10] and Pilyugin and Antia [32] to describe the interaction between immune cells and their targets (bacteria, parasites, viruses, etc.). Though there are no clinical or experimental data to support that the interaction between immune responses and malaria parasites satisfies the Michaelis-Menten-Monod function, we follow De Boer and Perelson [10], Pilyugin and Antia [32], and Chiyaka et al. [7] to use such a function $p_1 IE/(1+\beta I)$ to describe the killing of infected cells I by the immunity effectors E, where p_1 is the rate or possibility of successful removal of infected red blood cells I by immunity effectors and $1/\beta$ is a saturation constant that simulates immune cells to grow at half their maximum rate. It is also assumed that the presence of infected cells stimulates the proliferation of immune cells at a net rate $k_1 IE/(1+\beta I)$, where k_1 is the proliferation rate of lymphocytes. Immune effectors decay at a rate d_2. Free malaria parasites is produced from merozoites which replicate at a rate r in

an infected red blood cell and die at a rate μ. Note that the replication rate r is understood as the number (r_1) of merozoites produced by each infected red blood cell times the rate (δ) at which the infected red blood cells burst due to infection. We also assume that antibody-mediated attack directed against the free merozoites in the blood system (Anderson et al. [4]), given by $p_2ME/(1+\gamma M)$, and a net production rate of merozoite-specific antibodies of $k_2ME/(1+\gamma M)$. p_2 is the rate or possibility of successful removal of free merozoites M by immunity effectors, $1/\gamma$ is a saturation constant, and k_2 is the proliferation rate of lymphocytes due to the interactions between E and M.

The mathematical model for malaria parasites infection in a host consists of four ordinary differential equations:

$$\begin{aligned}
\frac{dH}{dt} &= \lambda - d_1H - \alpha HM,\\
\frac{dI}{dt} &= \alpha HM - \delta I - \frac{p_1IE}{1+\beta I},\\
\frac{dM}{dt} &= rI - \mu M - \frac{p_2ME}{1+\gamma M},\\
\frac{dE}{dt} &= -d_2E + \frac{k_1IE}{1+\beta I} + \frac{k_2ME}{1+\gamma M}.
\end{aligned} \tag{1}$$

The variables and their initial values are presented in Table 1. All parameters and their biological interpretations are given in Table 2.

Note that the terms $ME/(1+\gamma M)$ and $IE/(1+\beta I)$ describe, respectively, how the parasites and infected red cells simulate the activation of the immune effectors, they are regarded to describe the humoral and cell-mediated immunity, respectively (Anderson et al. [4], Murase et al. [30], Tumwiine et al. [40]).

We would like to make some remarks on the choice of parameter values and their units. Some parameters were adapted from other references directly, such as λ and d_2 from Anderson et al. [4]. Some other parameters were obtained by conversion and calculation of that from other references. For example, the term $\frac{k_1IE}{1+\beta I}$ appeared as $\frac{(k_1/\beta)IE}{(1/\beta)+\beta I}$ in Chiyaka et al. [7], so we calculated the parameter values correspondingly and changed their units accordingly.

Model (1) generalizes several known models, including the basic models in Anderson et al. [4] and Anderson [3], the pathogen-immune interaction model developed by Nowak and Bangham [31], and some variants in Liu [22], Murase et al. [30], and Tumwiine et al. [40]. When the immune response functions are unbounded bilinear functions, that is when $\beta = \gamma = 0$, Murase et al. [30] and Tumwiine et al. [40] studied the stability of these models. In particular, Kajiwara and Sasaki [19] proved that the models of Liu [22] and Murase et al. [30] are indeed globally stable. However, numerical simulations by Anderson et al. [4] and Hetzel and Anderson [16] indicated that periodic oscillations occur in the model with immune response. We shall study the existence and stability of the malaria-free, malaria infection, and positive equilibria and show that the model exhibits periodic oscillations via Hopf bifurcation at the positive equilibrium by using the proliferation rate of the immune cells induced by infected red blood cells as the bifurcation parameter.

3. **Mathematical analysis.**

In the section we study the dynamics of model (1) which imply various outcomes of malaria parasite infection within a host. Because of the biological meaning, we consider system (1) only in the first orthant $R^4_+ =$

TABLE 1. **Variables in Model (1)**

Symbols	*Variables*	*Initial Values*	*Ref.*
$H(t)$	population of red blood cells (RBC)	5×10^6cells/μl	[4, 7, 16, 26]
$I(t)$	population of infected RBC	0	[4, 7, 16, 26]
$M(t)$	population of malaria parasites	10^4cells/μl	[4, 7, 16, 26]
$E(t)$	population of immunity effectors	10^{-4}cells/μl	[4, 7, 16, 26]

TABLE 2. **Parameters in Model (1)**

Sym.	*Paras.*	*I.V.*	*Ref.*
λ	production rate of RBC	4.15×10^4 cells/μl/day	[4]
d_1	decay rate of RBC	8.3×10^{-3}/day	[4]
μ	decay rate of malaria parasites	48/day	[16]
d_2	decay rate of immunity effectors	0.05/day	[4]
α	infection of RBC by malaria parasites	2×10^{-9} μl/cell/day	[16]
δ	decay rate of $I(t)$	1.0/day	[16]
r	product rate of malaria parasites	12/day	[16]
p_1	removal rate of $I(t)$ by immune system	10^{-8} μl/cell/day	[16]
p_2	removal rate of $M(t)$ by immune system	10^{-8} μl/cell/day	[16]
k_1	proliferation rate of $E(t)$ by $I(t)$	2.5×10^{-5} μl/cell/day	[7]
k_2	proliferation rate of $E(t)$ by $M(t)$	4.69×10^{-5} μl/cell/day	[7]
β	$1/\beta$ half saturation constant for $I(t)$	5×10^{-4} μl/cell	[7]
γ	$1/\gamma$ half saturation constant for $M(t)$	6.67×10^{-4} μl/cell	[7]

$\{(H, I, M, E) : \ H \geq 0, I \geq 0, M \geq 0, E \geq 0\}$. We can show that the first orthant R^4_+ is positively invariant for flows of (1), i.e., every solution of model (1) with the initial values in R^4_+ will always stay there.

We first study the existence of equilibria of system (1) in R^4_+. Setting the right-hand sides of system (1) to zero, we have the following equations

$$\begin{aligned} \lambda - d_1 H - \alpha H M &= 0, \\ \alpha H M - \delta I - \tfrac{p_1 I E}{1+\beta I} &= 0, \\ r I - \mu M - \tfrac{p_2 M E}{1+\gamma M} &= 0, \\ -d_2 E + \tfrac{k_1 I E}{1+\beta I} + \tfrac{k_2 M E}{1+\gamma M} &= 0. \end{aligned} \tag{2}$$

Therefore, the existence of equilibria of system (1) in R^4_+ is equivalent to that of nonnegative solutions of equations (2). It can be checked that system (1) always has one equilibrium $P_0 = (\lambda/d_1, 0, 0, 0)$ for all parameters values, which represents the state in which there is no malaria infection in the host. Hence, we call P_0 the malaria-free equilibrium. Now we find malaria infection equilibria. There are two cases for these equilibria. One case is that the host lacks immune response as malaria parasites from a blood-feeding female *Anopheles* mosquito invade and produce infection in a host. Thus, $E = 0$. We denote this equilibrium by $P_1 = (H_1, I_1, M_1, 0)$. The other case is a positive equilibrium $P^* = (H^*, I^*, M^*, E^*)$ which implies that the host has immune response when malaria parasites invade

and produce infection in a host. Let

$$R_0 = \frac{r\alpha\lambda}{d_1\mu\delta}.$$

Following van den Driessche and Watmough [41] and Xiao and Bossert [43], we can see that R_0 is the basic reproduction number for the malaria infection in a host.

From equations (2), we can obtain the following lemma.

Lemma 3.1. *System (1) has a unique equilibrium which is the malaria-free equilibrium $P_0 = (\lambda/d_1, 0, 0, 0)$ if $R_0 \le 1$ and at least two equilibria if $R_0 > 1$. More precisely,*

(i) system (1) has only two equilibria: $P_0 = (\lambda/d_1, 0, 0, 0)$ and $P_1 = (H_1, I_1, M_1, 0)$ if $R_0 > 1$ and $d_2 \ge \frac{k_1}{\beta} + \frac{k_2}{\gamma}$, where $H_1 = \frac{\lambda}{d_1 R_0}, I_1 = \frac{\lambda}{\delta}\frac{(R_0-1)}{R_0}, M_1 = \frac{d_1}{\alpha}(R_0-1)$;

(ii) system (1) has three equilibria: $P_0 = (\lambda/d_1, 0, 0, 0)$, $P_1 = (H_1, I_1, M_1, 0)$ and $P^* = (H^*, I^*, M^*, E^*)$ if $R_0 > 1$, $\frac{k_2}{\gamma} \le d_2 \le \frac{k_1}{\beta}$ and $A_4M^4 + A_3M^3 + A_2M^2 + A_1M + A_0 = 0$ has a positive solution M^* with $0 < M^* < \min\{\frac{d_1}{\alpha}(R_0-1), L\}$, where

$$H^* = \frac{\lambda}{d_1 + \alpha M^*}, \quad I^* = \frac{d_2 + (d_2\gamma - k_2)M^*}{k_1 - \beta d_2 + (k_1\gamma + k_2\beta - d_2\beta\gamma)M^*},$$

$$E^* = (1+\gamma M^*)\frac{rd_2 + (rd_2\gamma - rk_2 - \mu k_1 + \mu\beta d_2)M^* - \mu(k_1\gamma + k_2\beta - d_2\beta\gamma){M^*}^2}{(k_1 - \beta d_2)p_2M^* + (k_1\gamma + k_2\beta - d_2\beta\gamma)p_2{M^*}^2}$$

$$A_4 = p_1\alpha\mu(k_2 - d_2)(k_1\gamma + k_2\beta - d_2\beta\gamma),$$

$$\begin{aligned} A_3 = {} & p_1\alpha(d_2 - k_2)(d_2\gamma - k_2 - \mu k_1 + \mu\beta d_2) - p_2k_1\alpha\lambda(k_1\gamma + k_2\beta \\ & - p_1\mu(d_1d_2 - d_1k_2 + \alpha d_2)(k_1\gamma + k_2\beta - d_2\beta\gamma) - d_2\beta\gamma) + p_2k_1\alpha\delta(d_2\gamma - k_2), \end{aligned}$$

$$\begin{aligned} A_2 = {} & p_1(d_1d_2 - d_1k_2 + \alpha d_2)(d_2\gamma - k_2 - \mu k_1 + \mu\beta d_2) - p_1d_1d_2\mu(k_1\gamma + k_2\beta - d_2\beta\gamma) \\ & + p_1d_2\alpha(d_2 - k_2) - p_2k_1(\alpha\lambda k_1 - \alpha\beta\lambda d_2 - \delta\gamma d_1d_2 - \delta d_1k_2 - \alpha\delta d_2), \end{aligned}$$

$$A_1 = p_1d_1d_2(d_2\gamma - k_2 - \mu k_1 + \mu\beta d_2) + p_1d_2(d_1d_2 - d_1k_2 + \alpha d_2) + p_2d_1d_2\delta k_1,$$

$$A_0 = p_1d_1d_2^2, \quad L = \frac{r(d_2\gamma - k_2) - \mu(k_1 - \beta d_2) + \sqrt{\triangle}}{2\mu(k_1\gamma + k_2\beta - d_2\beta\gamma)},$$

$$\triangle = \mu^2(k_1 - \beta d_2)^2 + r^2(d_2\gamma - k_2)^2 + 2\mu r k_1k_2 + 2\mu r\beta\gamma d_2\left(\frac{k_1}{\beta} + \frac{k_2}{\gamma} - d_2\right).$$

Proof. The existence of the equilibrium P_0 or P_1 can be obtained directly from (2) by setting $E = 0$. Thereby, we only need to seek conditions for the existence of the positive equilibrium $P^* = (H^*, I^*, M^*, E^*)$ of system (1).

Suppose that (H^*, I^*, M^*, E^*) is a positive solution of (2). Then from the last equation of (2) we have

$$d_2 = \frac{k_1I^*}{1 + \beta I^*} + \frac{k_2M^*}{1 + \gamma M^*},$$

which leads to

$$\frac{k_1}{\beta} + \frac{k_2}{\gamma} - d_2 = \frac{k_1}{\beta + \beta^2I^*} + \frac{k_2}{\gamma + \gamma^2M^*} > 0.$$

Hence, it is necessary for the existence of the positive equilibrium P^* that $d_2 < \frac{k_1}{\beta} + \frac{k_2}{\gamma}$, and

$$I^* = \frac{d_2 + (d_2\gamma - k_2)M^*}{k_1 - \beta d_2 + (k_1\gamma + k_2\beta - d_2\beta\gamma)M^*}. \tag{3}$$

On the other hand, from the second and the third equations of (2), we respectively have

$$\alpha H^* M^* - \delta I^* = \frac{p_1 I^* E^*}{1+\beta I^*} > 0,$$
$$r I^* - \mu M^* = \frac{p_2 M^* E^*}{1+\gamma M^*} > 0.$$

Thus, $\frac{\mu M^*}{r} < I^* < \frac{\alpha H^* M^*}{\delta}$. Note that $H^* = \frac{\lambda}{d_1+\alpha M^*}$ by the first equation of (2). Hence,

$$\frac{\mu M^*}{r} < I^* < \frac{\lambda\alpha M^*}{\delta(d_1+\alpha M^*)} < \frac{\lambda\alpha M^*}{\delta d_1}. \tag{4}$$

This gives the other necessary condition for the existence of the positive equilibrium P^* which is $R_0 > 1$. Therefore, if system (1) has a positive malaria infection equilibrium $P^* = (H^*, I^*, M^*, E^*)$, then $R_0 > 1$ and $d_2 < \frac{k_1}{\beta} + \frac{k_2}{\gamma}$.

In the following we discuss the sufficient conditions on the existence of the positive equilibrium P^*. From (2), we can obtain

$$\begin{aligned} H^* &= \frac{\lambda}{d_1+\alpha M^*}, \\ I^* &= \frac{d_2 + (d_2\gamma - k_2)M^*}{k_1 - \beta d_2 + (k_1\gamma + k_2\beta - d_2\beta\gamma)M^*}, \\ E^* &= \frac{k_1}{p_1 d_2}(\alpha H^* M^* - \delta I^*) + \frac{k_2}{p_2 d_2}(rI^* - \mu M^*) \\ &= (1+\gamma M^*)\frac{rd_2 + (rd_2\gamma - rk_2 - \mu k_1 + \mu\beta d_2)M^* - \mu(k_1\gamma + k_2\beta - d_2\beta\gamma){M^*}^2}{(k_1 - \beta d_2)p_2 M^* + (k_1\gamma + k_2\beta - d_2\beta\gamma)p_2 {M^*}^2}. \end{aligned} \tag{5}$$

It is clear that $H^* > 0$, $I^* > 0$, and $E^* > 0$ if the following conditions hold:

$$\begin{aligned} &M^* > 0, \ \frac{k_2}{\gamma} \le d_2 \le \frac{k_1}{\beta}, \\ &\alpha H^* M^* - \delta I^* > 0, \quad rI^* - \mu M^* > 0. \end{aligned} \tag{6}$$

From the last two inequalities of (6) and the expression of I^* in (5), we obtain that

$$\frac{\mu M^*}{r} < \frac{d_2 + (d_2\gamma - k_2)M^*}{k_1 - \beta d_2 + (k_1\gamma + k_2\beta - d_2\beta\gamma)M^*} < \frac{\lambda\alpha M^*}{\delta(d_1+\alpha M^*)}.$$

This is equivalent to the following inequalities

$$F(M^*) < 0, \ G(M^*) < 0, \tag{7}$$

where

$$F(M^*) \triangleq \mu(k_1\gamma + k_2\beta - d_2\beta\gamma){M^*}^2 + [\mu(k_1 - \beta d_2) - r(d_2\gamma - k_2)]\, M^* - rd_2,$$
$$G(M^*) \triangleq \alpha(d_2\gamma - k_2){M^*}^2 + [\alpha d_2 - d_1(d_2\gamma - k_2)(R_0 - 1)]\, M^* - d_1 d_2(R_0 - 1).$$

Note that $F(M^*) = 0$ has a negative root and a positive root L,

$$L = \frac{r(d_2\gamma - k_2) - \mu(k_1 - \beta d_2) + \sqrt{\triangle}}{2\mu(k_1\gamma + k_2\beta - d_2\beta\gamma)},$$

where $\triangle = \mu^2(k_1 - \beta d_2)^2 + r^2(d_2\gamma - k_2)^2 + 2\mu r k_1 k_2 + 2\mu r\beta\gamma d_2(\frac{k_1}{\beta} + \frac{k_2}{\gamma} - d_2)$.

Note that $G(M^*) = 0$ also has a negative root and a positive root $\frac{d_1}{\alpha}(R_0 - 1)$. Therefore, when $0 < M^* < \min\{L, \frac{d_1}{\alpha}(R_0 - 1)\}$, we have $F(M^*) < 0$ and $G(M^*) < 0$.

We now discuss the conditions that M^* should satisfy. Substituting (5) into the second equation of (2), after some calculations we obtain the equation

$$A_4M^4 + A_3M^3 + A_2M^2 + A_1M + A_0 = 0, \tag{8}$$

where

$$\begin{aligned}
A_4 &= p_1\alpha\mu(k_2 - d_2)(k_1\gamma + k_2\beta - d_2\beta\gamma),\\
A_3 &= p_1\alpha(d_2 - k_2)(d_2\gamma - k_2 - \mu k_1 + \mu\beta d_2) - p_2k_1\alpha\lambda(k_1\gamma + k_2\beta - d_2\beta\gamma)\\
&\quad - p_1\mu(d_1d_2 - d_1k_2 + \alpha d_2)(k_1\gamma + k_2\beta - d_2\beta\gamma) + p_2k_1\alpha\delta(d_2\gamma - k_2),\\
A_2 &= p_1(d_1d_2 - d_1k_2 + \alpha d_2)(d_2\gamma - k_2 - \mu k_1 + \mu\beta d_2) - p_1d_1d_2\mu(k_1\gamma + k_2\beta - d_2\beta\gamma)\\
&\quad + p_1d_2\alpha(d_2 - k_2) - p_2k_1(\alpha\lambda k_1 - \alpha\beta\lambda d_2 - \delta\gamma d_1d_2 - \delta d_1k_2 - \alpha\delta d_2),\\
A_1 &= p_1d_1d_2(d_2\gamma - k_2 - \mu k_1 + \mu\beta d_2) + p_1d_2(d_1d_2 - d_1k_2 + \alpha d_2) + p_2d_1d_2\delta k_1,\\
A_0 &= p_1d_1d_2^2.
\end{aligned}$$

Therefore, if $R_0 > 1$, $\frac{k_2}{\gamma} \le d_2 \le \frac{k_1}{\beta}$ and equation (8) has a positive solution M^* with $0 < M^* < \min\{L, \frac{d_1}{\alpha}(R_0 - 1)\}$, then (2) has a positive solution (H^*, I^*, M^*, E^*), which implies statement (ii). We complete the proof. □

We now start to study the stability of these equilibria of system (1). We compute the Jacobian matrix of system (1) at point $P = (H, I, M, E)$, denoted by $J(P)$. Then

$$J(P) = \begin{pmatrix}
-d_1 - \alpha M & 0 & -\alpha H & 0\\
\alpha M & -\delta - \frac{p_1E}{(1+\beta I)^2} & \alpha H & -\frac{p_1I}{1+\beta I}\\
0 & r & -\mu - \frac{p_2E}{(1+\gamma M)^2} & -\frac{p_2M}{1+\gamma M}\\
0 & \frac{k_1E}{(1+\beta I)^2} & \frac{k_2E}{(1+\gamma M)^2} & \frac{k_1I}{1+\beta I} + \frac{k_2M}{1+\gamma M} - d_2
\end{pmatrix}.$$

3.1. **Local and global stability of the malaria-free equilibrium P_0.** At the malaria-free equilibrium $P_0 = (\lambda/d_1, 0, 0, 0)$, we have the Jacobian matrix

$$J(P_0) = \begin{pmatrix}
-d_1 & 0 & -\frac{\alpha\lambda}{d_1} & 0\\
0 & -\delta & \frac{\alpha\lambda}{d_1} & 0\\
0 & r & -\mu & 0\\
0 & 0 & 0 & -d_2
\end{pmatrix},$$

and its characteristic equation is

$$(\Lambda + d_1)(\Lambda + d_2)(\Lambda^2 + (\mu + \delta)\Lambda + \delta\mu - r\alpha\lambda/d_1) = 0. \tag{9}$$

From (9), it can be seen that all eigenvalues are negative if $R_0 < 1$ and one of the eigenvalues is positive if $R_0 > 1$. Therefore, we have the following lemma.

Lemma 3.2. *The malaria-free equilibrium P_0 of system (1) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.*

According to Lemma 3.1, we know that system (1) has a unique equilibrium P_0 if $R_0 \le 1$. We will show that the malaria-free equilibrium is globally stable in R^4_+ if $R_0 \le 1$.

Theorem 3.3. *The malaria-free equilibrium $P_0 = (\lambda/d_1, 0, 0, 0)$ is globally asymptotically stable in R^4_+ if $R_0 \le 1$.*

Proof. We first note the fact that $\frac{dH}{dt} < 0$ in R^4_+ if $H(t) \geq \frac{\lambda}{d_1}$, and system (1) has a unique equilibrium P_0 in R^4_+ since $R_0 \leq 1$. Thus, we only need to consider the stability of P_0 in the region

$$D = \{(H, I, M, E);\ 0 \leq H \leq \frac{\lambda}{d_1}, 0 \leq I, 0 \leq M, 0 \leq E\}.$$

Choosing the Liapunov function $V = rI + \delta M$ in the region D, we calculate the derivative of V along the solutions of system (1) as follows:

$$\begin{aligned}
\tfrac{dV}{dt}|_{(1)} &= r\tfrac{dI}{dt} + \delta\tfrac{dM}{dt} \\
&= r\left(\alpha HM - \delta I - \tfrac{p_1 IE}{1+\beta I}\right) + \delta\left(rI - \mu M - \tfrac{p_2 ME}{1+\gamma M}\right) \\
&= r\alpha HM - \mu\delta M - rp_1\tfrac{EI}{1+\beta I} - \delta p_2\tfrac{EM}{1+\gamma M} \\
&< r\alpha HM - \mu\delta M \\
&= M\mu\delta(\tfrac{r\alpha}{\mu\delta}H - 1) \\
&< M\mu\delta(\tfrac{r\alpha\lambda}{d_1\mu\delta} - 1) \\
&= \mu\delta M(R_0 - 1) \leq 0 \ \text{ if } \ R_0 \leq 1.
\end{aligned}$$

Also equation $\frac{dV}{dt}|_{(1)} = 0$ has a unique solution P_0 of system (1) in D. By LaSalle's Invariance Principle we know that the malaria-free equilibrium P_0 is globally asymptotically stable in R^4_+ if $R_0 \leq 1$. □

This result indicates that malaria infection cannot be established within a host if $R_0 \leq 1$ (see Figure 1).

3.2. **Local stability of the malaria infection equilibrium P_1 (without specific immune response).** If $R_0 > 1$, then system (1) has a malaria infection equilibrium $P_1 = (H_1, I_1, M_1, 0)$ with

$$H_1 = \frac{\lambda}{d_1 R_0}, I_1 = \frac{\lambda}{\delta}\frac{(R_0 - 1)}{R_0}, M_1 = \frac{d_1}{\alpha}(R_0 - 1).$$

The Jacobian matrix at P_1 is

$$J(P_1) = \begin{pmatrix}
-d_1R_0 & 0 & -\frac{\alpha\lambda}{d_1R_0} & 0 \\
d_1(R_0-1) & -\delta & \frac{\alpha\lambda}{d_1R_0} & -\frac{p_1\lambda(R_0-1)}{\delta R_0+\beta\lambda(R_0-1)} \\
0 & r & -\mu & -\frac{p_2d_1(R_0-1)}{\alpha+d_1\gamma(R_0-1)} \\
0 & 0 & 0 & \frac{k_1\lambda(R_0-1)}{\delta R_0+\beta\lambda(R_0-1)} + \frac{k_2d_1(R_0-1)}{\alpha+d_1\gamma(R_0-1)} - d_2
\end{pmatrix}.$$

The characteristic equation of $J(P_1)$ is

$$(\Lambda - \frac{k_1\lambda(R_0-1)}{\delta R_0+\beta\lambda(R_0-1)} - \frac{k_2d_1(R_0-1)}{\alpha+d_1\gamma(R_0-1)} + d_2)(\Lambda^3 + a_1\Lambda^2 + a_2\Lambda + a_3) = 0, \quad (10)$$

where $a_1 = d_1R_0 + \delta + \mu$, $a_2 = d_1R_0(\mu + \delta)$ and $a_3 = d_1\delta\mu(R_0 - 1)$.

By the Routh-Hurwitz criterion, the roots of (10) have negative real parts if and only if

$$\begin{aligned}
&\tfrac{k_1\lambda(R_0-1)}{\delta R_0+\beta\lambda(R_0-1)} + \tfrac{k_2d_1(R_0-1)}{\alpha+d_1\gamma(R_0-1)} - d_2 < 0, \\
&a_1 > 0,\ a_3 > 0,\ a_1a_2 - a_3 > 0.
\end{aligned}$$

Note that a_1, a_2 and a_3 are positive. We calculate

$$a_1a_2 - a_3 = d_1R_0\mu(d_1R_0 + \mu + \delta) + d_1\delta R_0(d_1R_0 + \delta) + d_1\mu\delta > 0.$$

Hence, P_1 is locally asymptotically stable if and only if $\frac{k_1\lambda(R_0-1)}{\delta R_0+\beta\lambda(R_0-1)}+\frac{k_2d_1(R_0-1)}{\alpha+d_1\gamma(R_0-1)}-d_2<0$. This inequality holds if $\frac{k_1}{\beta}+\frac{k_2}{\gamma}-d_2\le 0$. Thus, from Lemmas 3.1 and 3.2, we have the following result.

Theorem 3.4. *If $R_0>1$ and $d_2\ge\frac{k_1}{\beta}+\frac{k_2}{\gamma}$, then system (1) has only two equilibria P_0 and P_1, the malaria-free equilibrium P_0 is unstable and the malaria infection equilibrium P_1 is locally asymptotically stable. Moreover, both P_0 and P_1 are unstable if $R_0>1$ and*

$$\frac{k_1\lambda(R_0-1)}{\delta R_0+\beta\lambda(R_0-1)}+\frac{k_2d_1(R_0-1)}{\alpha+d_1\gamma(R_0-1)}-d_2>0.$$

This theorem implies that malaria infection (without specific immune response) can be established within a host if $R_0>1$ and $d_2\ge\frac{k_1}{\beta}+\frac{k_2}{\gamma}$ (see Figure 2).

3.3. **Local stability of the positive equilibrium P^* (with specific immune response).** From Lemma 3.1, we know that the coordinates of the two malaria infection equilibria $P_1=(H_1,I_1,M_1,0)$ and $P^*=(H^*,I^*,M^*,E^*)$ have the following relationships:

$$\begin{aligned}
&M^*<M_1=\tfrac{d_1}{\alpha}(R_0-1),\\
&H^*=\tfrac{\lambda}{d_1+\alpha M^*}>\tfrac{\lambda}{d_1+\alpha M_1}=H_1,\\
&I^*=\tfrac{\lambda-d_1H^*}{\delta}-\tfrac{p_1I^*E^*}{\delta(1+\beta I^*)}<\tfrac{\lambda-d_1H^*}{\delta}<\tfrac{\lambda-d_1H_1}{\delta}=I_1.
\end{aligned}$$

These imply that

$$\frac{k_1I_1}{1+\beta I_1}+\frac{k_2M_1}{1+\gamma M_1}-d_2=\frac{k_1I_1}{1+\beta I_1}+\frac{k_2M_1}{1+\gamma M_1}-(\frac{k_1I^*}{1+\beta I^*}+\frac{k_2M^*}{1+\gamma M^*})>0.$$

Thus, if the positive equilibrium P^* exists, then P_0 and P_1 are always unstable.

Now we study the stability of the positive equilibrium P^*. The local stability of P^* is established from the Jacobian matrix at P^* given by

$$J(P^*)=\begin{pmatrix}
-d_1-\alpha M^* & 0 & -\alpha H^* & 0\\
\alpha M^* & -\delta-\frac{p_1E^*}{(1+\beta I^*)^2} & \alpha H^* & -\frac{p_1I^*}{1+\beta I^*}\\
0 & r & -\mu-\frac{p_2E^*}{(1+\gamma M^*)^2} & -\frac{p_2M^*}{1+\gamma M^*}\\
0 & \frac{k_1E^*}{(1+\beta I^*)^2} & \frac{k_2E^*}{(1+\gamma M^*)^2} & 0
\end{pmatrix}.$$

The characteristic equation is

$$\lambda^4+b_1\lambda^3+b_2\lambda^2+b_3\lambda+b_4=0. \tag{11}$$

where

$$\begin{aligned}
b_1=\;& d_1+\mu+\delta+\alpha M^*+\tfrac{p_1E^*}{(1+\beta I^*)^2}+\tfrac{p_2E^*}{(1+\gamma M^*)^2},\\
b_2=\;& (d_1+\alpha M^*)(\delta+\tfrac{p_1E^*}{(1+\beta I^*)^2})+(d_1+\alpha M^*)(\mu+\tfrac{p_2E^*}{(1+\gamma M^*)^2})\\
&+(\delta+\tfrac{p_1E^*}{(1+\beta I^*)^2})(\mu+\tfrac{p_2E^*}{(1+\gamma M^*)^2})-\alpha rH^*\\
&+(\mu+\tfrac{p_2E^*}{(1+\gamma M^*)^2})+\tfrac{p_1k_1I^*E^*}{(1+\beta I^*)^3}+\tfrac{p_2k_2M^*E^*}{(1+\gamma M^*)^3},\\
b_3=\;& (d_1+\alpha M^*)(\delta+\tfrac{p_1E^*}{(1+\beta I^*)^2})(\mu+\tfrac{p_2E^*}{(1+\gamma M^*)^2})-rd_1\alpha H^*\\
&+(d_1+\alpha M^*)(\tfrac{p_1k_1I^*E^*}{(1+\beta I^*)^3}+\tfrac{p_2k_2M^*E^*}{(1+\gamma M^*)^3})+\tfrac{p_2k_1H^*M^*}{(1+\gamma M^*)(1+\beta I^*)^2}\\
&+\tfrac{p_1k_1I^*E^*}{(1+\beta I^*)^3}(\mu+\tfrac{p_2E^*}{(1+\gamma M^*)^2})+\tfrac{p_2k_2M^*E^*}{(1+\gamma M^*)^3}(\delta+\tfrac{p_1E^*}{(1+\beta I^*)^2})+\tfrac{p_1k_2rI^*E^*}{(1+\beta I^*)(1+\gamma M^*)},\\
b_4=\;& \tfrac{p_2k_1d_1\alpha H^*M^*E^*}{(1+\gamma M^*)(1+\beta I^*)^2}+\tfrac{p_1k_1I^*E^*}{(1+\beta I^*)^3}(d_1+\alpha M^*)(\mu+\tfrac{p_2E^*}{(1+\gamma M^*)^2})\\
&+\tfrac{p_2k_2M^*E^*}{(1+\gamma M^*)^3}(d_1+\alpha M^*)(\delta+\tfrac{p_1E^*}{(1+\beta I^*)^2})+\tfrac{p_1k_2rI^*E^*(d_1+\alpha M^*)}{(1+\beta I^*)(1+\gamma M^*)^2}.
\end{aligned}$$

Using the Routh-Hurwitz criterion, we obtain that the roots of (11) have negative real parts if and only if

$$\begin{aligned} &b_1 > 0,\ b_1b_2 - b_3 > 0,\ (b_1b_2 - b_3)b_3 - b_1^2b_4 > 0,\\ &(b_1b_2 - b_3)b_3b_4 - b_1^2b_4^2 > 0. \end{aligned} \tag{12}$$

Hence, we have the following theorem on the existence and stability of positive equilibrium by the conclusion (ii) of Lemma 3.1, which implies successful parasite invasion of the host even with the specific immune response.

Theorem 3.5. *Assume that* $R_0 > 1$, $\frac{k_2}{\gamma} \le d_2 \le \frac{k_1}{\beta}$ *and* $A_4M^4 + A_3M^3 + A_2M^2 + A_1M + A_0 = 0$ *has a positive solution* M^* *with* $0 < M^* < \min\{\frac{d_1}{\alpha}(R_0 - 1), L\}$. *Then system (1) has a positive equilibrium* P^*, *which is locally asymptotically stable if the inequalities in (12) hold.*

We can find some parameters values for system (1) such that all conditions of Theorem 3.5 hold (see Figure 3). Thus, a persistent malaria infection with specific immune response can be established for system (1).

Next we shall determine when the positive equilibrium P^* becomes unstable and Hopf bifurcation occurs. Following the analysis of a fourth-order characteristic equation in Ruan and Wolkowicz [35], we look for conditions which guarantee characteristic equation (11) having two roots with negative real part and a pair of conjugate purely imaginary roots. After some calculations, we obtain that

$$b_1 > 0,\ b_4 > 0,\ b_1b_2 - b_3 > 0,\ (b_1b_2 - b_3)b_3 - b_1^2b_4 = 0. \tag{13}$$

To prove the occurrence of Hopf bifurcation at the positive equilibrium P^*, it remains to verify the transversal condition. We choose k_1 as a bifurcation parameter. Define

$$\psi(k_1) = (b_1(k_1)b_2(k_1) - b_3(k_1))b_3(k_1) - b_1^2(k_1)b_4(k_1). \tag{14}$$

Suppose that there exists a $k_1^* > 0$ such that $b_1(k_1^*) > 0$, $b_4(k_1^*) > 0$, $b_1(k_1^*)b_2(k_1^*) - b_3(k_1^*) > 0$ and $\psi(k_1^*) = 0$. Then equation (11) has four roots, $\pm\omega i$, λ_1 and λ_2, where $\omega = \sqrt{\frac{b_3(k_1^*)}{b_1(k_1^*)}}$, $\mathrm{Re}(\lambda_1) < 0$ and $\mathrm{Re}(\lambda_2) < 0$. When $0 < |k_1 - k_1^*| \ll 1$, we assume that equation (11) has four roots, $\nu(k_1) \pm \omega(k_1)i$, $\lambda_1(k_1)$ and $\lambda_2(k_1)$, where $\nu(k_1^*) = 0$, $\omega(k_1^*) = \omega$, $\lambda_1(k_1^*) = \lambda_1$ and $\lambda_2(k_1^*) = \lambda_2$. In the following we calculate the derivative of $\nu(k_1)$ with k_1 at k_1^*. Note that

$$\begin{aligned} (\nu(k_1) + i\omega(k_1))^4 + b_1(k_1)(\nu(k_1) + i\omega(k_1))^3 + b_2(k_1)(\nu(k_1)\\ +i\omega(k_1))^2 + b_3(k_1)(\nu(k_1) + i\omega(k_1)) + b_4(k_1) = 0. \end{aligned} \tag{15}$$

By (14) and some calculations, we obtain that

$$\frac{d\nu(k_1)}{dk_1}|_{k_1=k_1^*} = -\frac{b_1(k_1^*)}{2((b_1(k_1^*)b_2(k_1^*) - 2b_3(k_1^*))^2 + b_1(k_1^*)^3b_3(k_1^*))}\frac{d\psi(k_1)}{dk_1}|_{k_1=k_1^*}.$$

Hence, the transversal condition holds under some conditions. By the Hopf bifurcation theorem, we have the following result on bifurcation at the positive equilibrium P^*.

Theorem 3.6. *Assume that system (1) has a positive equilibrium at* P^*. *If there exists a* $k_1^* > 0$ *such that* $b_1(k_1^*) > 0$, $b_4(k_1^*) > 0$, $b_1(k_1^*)b_2(k_1^*) - b_3(k_1^*) > 0$, *and* $\psi(k_1^*) = 0$ *and* $\frac{d\psi(k_1)}{dk_1}|_{k_1=k_1^*} \neq 0$, *then Hopf bifurcation occurs and a periodic solution appears near* P^* *when* k_1 *passes through* k_1^*.

This result indicates that when the host is infected by malaria parasites, a persistent malaria infection with specific immune response can be established. Oscillations in the quantities of H, I, M and E in the host can be observed. We would like to mention that though the positive equilibrium $P^*(H^*, I^*, M^*, E^*)$ is not given explicitly in terms of parameters due to the complexity of the model, we have given some sufficient conditions symbolically for the stability of P^* and the existence of Hopf bifurcation in Theorems 3.5 and 3.6, respectively. In next section, numerical simulations will show validity of these theoretical results, that is, the positive equilibrium of system (1) is stable for some parameter values, and it will become unstable and a family of periodic solutions will bifurcate from the positive equilibrium via Hopf bifurcation when k_1 passes through a critical value (see Figures 3 and 4).

Remark 1. Notice that in the bifurcation analysis we selected k_1, the proliferation rate of the immune cells induced by infected red blood cells, as the bifurcation parameter. Similarly, we may choose k_2, the proliferation rate of immune cells due to the interactions between the immune response and merozoites, as the bifurcation parameter and obtain analogous results under certain conditions (such as $R_0 > 1$ and $\frac{k_2}{\gamma} < d_2 < \frac{k_1}{\beta}$)(see Figures 5 and 6). These agree with the numerical simulations by Anderson et al. [4] and Hetzel and Anderson [16] that periodic oscillations occur in the model with killing of infected red blood cells or with immune response directly against merozoites and infected red blood cells.

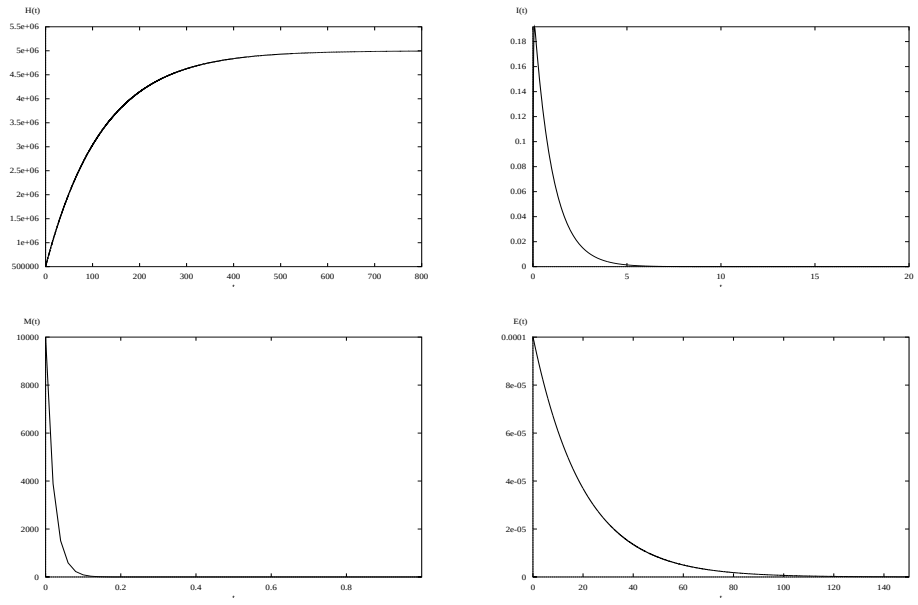

FIGURE 1. When $R_0 = 0.0025 < 1$, the disease-free equilibrium $P_0 = (5 \times 10^6, 0, 0, 0)$ is globally asymptotically stable. Here the parameter values are given in Table 2 and $H(0) = 5 \times 10^5$.

4. **Numerical simulations and discussion.** In this section we provide some numerical simulations to illustrate the dynamics of model (1). First, with parameter values giving in Table 2, we can verify that $R_0 = 0.0025 < 1$. Thus, Theorem 3.3 implies that the malaria-free equilibrium $P_0 = (5 \times 10^6, 0, 0, 0)$ is globally stable (see Figure 1).

Next, we choose $\alpha = 9\times10^{-7}, d_2 = 0.13$ and take all other parameters as in Table 2. Then we can verify that $R_0 = 1.125 > 1$ and $\frac{k_1}{\beta} + \frac{k_2}{\gamma} < d_2$. By Theorem 3.4, we know that the malaria infection equilibrium without specific immune response $P_1 = (4.44 \times 10^6, 4611, 1153, 0)$ is locally asymptotically stable (see Figure 2).

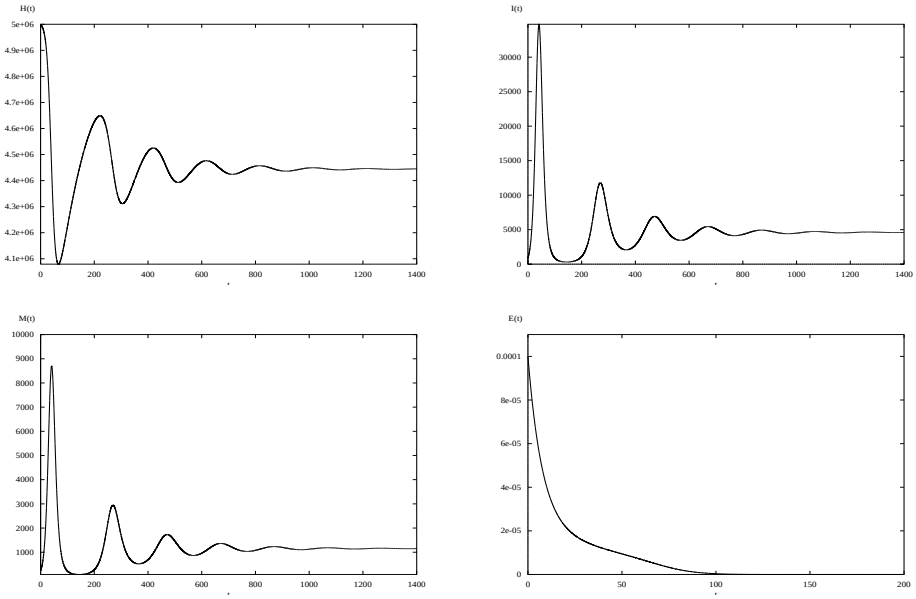

FIGURE 2. Taking $\alpha = 9 \times 10^{-7}, d_2 = 0.13$ and the other parameter values as in Table 2, then $\frac{k_1}{\beta} + \frac{k_2}{\gamma} < d_2$ and $R_0 = 1.125 > 1$. The malaria infection equilibrium without specific immune response $P_1 = (4.44 \times 10^6, 4611, 1153, 0)$ is stable.

For malaria infection equilibrium with specific immune response P^*, we choose $\alpha = 9 \times 10^{-7}, d_2 = 0.09, k_1 = 4.5001 \times 10^{-5}$ and take all other parameters as in Table 2. Thus, we have $k_1^* = 4.5045409 \times 10^{-5}$. In this case, $R_0 = 1.125 > 1$ and $\frac{k_2}{\gamma} < d_2 < \frac{k_1}{\beta}$. The equilibrium $P^* = (4.49 \times 10^6, 4209, 1052, 2.94 \times 10^6)$ is stable (see Figure 3).

While k_1 increases and passes through $k_1^* = 4.5045409 \times 10^{-5}$, for example, $k_1 = 9.5\times10^{-5}$, we have $R_0 = 1.125 > 1$, $\frac{k_2}{\gamma} < d_2 < \frac{k_1}{\beta}$ and the positive equilibrium $P^* = (4.82 \times 10^6, 1363, 340, 1.39 \times 10^7)$ which becomes unstable. Theorem 3.5 implies that system (1) undergoes Hopf bifurcation and a periodic solution appears (see Figure 4).

Finally, as mentioned in Remark 1 we can choose k_2 as a bifurcation parameter to obtain Hopf bifurcation at P^*. For example, choose $\alpha = 9\times10^{-7}, d_2 = 0.04, k_2 = 1.03 \times 10^{-5}$ and take all other parameters as in Table 2, we have $k_2^* = 1.033488 \times$

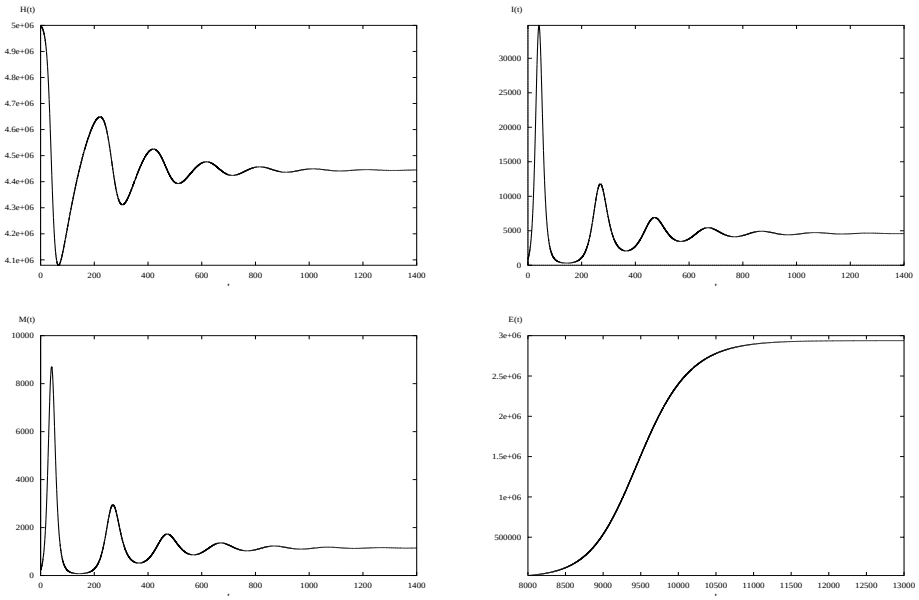

FIGURE 3. When $R_0 = 1.125 > 1$, $\frac{k_2}{\gamma} < d_2 < \frac{k_1}{\beta}$ and $k_1 < k_1^*$, The malaria infection equilibrium with specific immune response $P^* = (4.49\times10^6, 4209, 1052, 2.94\times10^6)$ is stable when $k_1 = 4.5001\times10^{-5}$.

10^{-5}. In this case, $R_0 = 1.125 > 1$ and $\frac{k_2}{\gamma} < d_2 < \frac{k_1}{\beta}$. The equilibrium $P^* = (4.49 \times 10^6, 4134, 1033, 3.44 \times 10^6)$ is stable (see Figure 5).

While k_2 increases and passes through $k_2^* = 1.033488\times10^{-5}$, for example, choose $k_2 = 2.305 \times 10^{-5}$, we have $R_0 = 1.125 > 1$, $\frac{k_2}{\gamma} < d_2 < \frac{k_1}{\beta}$ and the positive equilibrium $P^* = (4.65 \times 10^6, 2778, 693, 1.06 \times 10^7)$ which becomes unstable and a periodic solution appears (see Figure 6).

The conditions for the existence of Hopf bifurcation can be stated as follows: $R_0 = \frac{r\alpha\lambda}{d_1\mu\delta} > 1$, $\frac{k_2}{\gamma} < d_2 < \frac{k_1}{\beta}$, there exists a $k_1^* > 0$ such that (13) hold and $\psi'(k_1^*) \neq 0$. Rewrite the first condition as $\frac{r}{\mu}\frac{\lambda}{d_1}\frac{\alpha}{\delta} > 1$. Recall the biological meaning of these parameters, we know that $\frac{\lambda}{d_1}$ is the initial density of red blood cells (RBCs), $\frac{r}{\mu}$ represents the successful invasion of the malaria parasites during their life time, and $\frac{\alpha}{\delta}$ describes the successful infection of RBCs in that process. Thus, $R_0 > 1$ means that, before encountering immune response, with given initial density of RBCs, when there are enough numbers of malaria parasites that cause successful infection of RBCs, then the host is infected with malaria. The second condition indicates that the decay rate d_2 is somehow balanced between the proliferations induced by the malaria parasites $\frac{k_2}{\gamma}$ and infected RBCs $\frac{k_1}{\beta}$. The remaining conditions are mainly on the proliferation rate of the immune cells induced by infected red blood cells k_1, which roughly means that there is a critical value of k_1, once it is reached periodic oscillations in all components will occur. This demonstrates that synchronicity is an inherent feature of malaria infection with immune response.

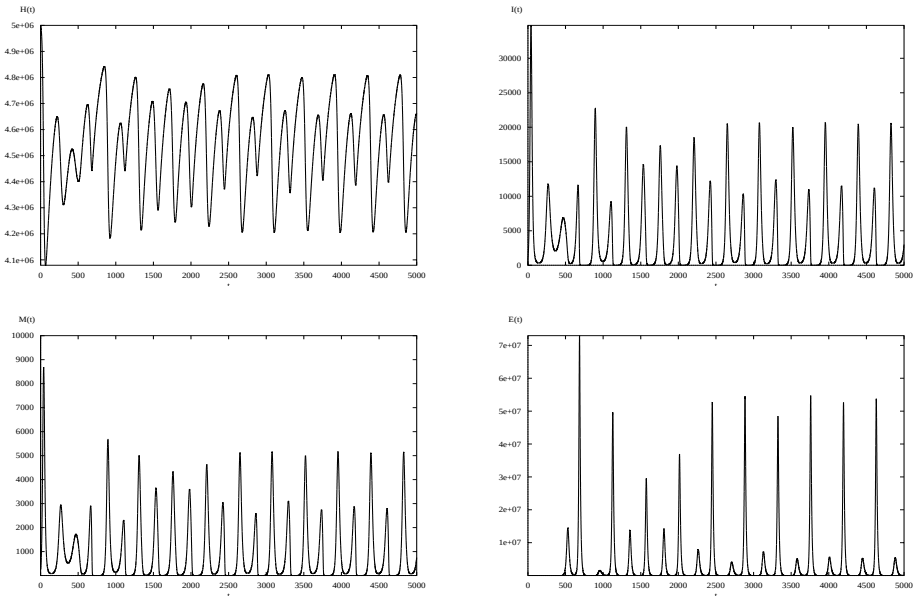

FIGURE 4. When $R_0 = 1.125 > 1$, $\frac{k_2}{\gamma} < d_2 < \frac{k_1}{\beta}$ and $k_1 > k_1^*$, there is a periodic solution bifurcated from the positive equilibrium $P^* = (4.82 \times 10^6, 1363, 340, 1.39 \times 10^7)$ when $k_1 = 9.5 \times 10^{-5}$.

These are helpful for us to better understand how immune response defends against the malaria parasite infection and possibly causes the periodic fevers in the host.

We would like to make some remarks about our model (1). The model is a generalization of the basic model of Anderson et al. [4] and Anderson [3] with a nonlinear bounded Michaelis-Menten-Monod function describing the interaction between healthy red blood cells, infected red blood cells, malaria parasitemia and immune effectors. Since the replication rate of merozoites is described by the number of merozoites produced by each infected red blood cell times the rate at which the infected red blood cells burst due to infection, Soul [36] pointed out the possible unrealistic large growth of parasites in the absence of immunity by the model in Anderson et al. [4] considering the parasite growth cycle (which is 48 hours for *P. falciparum*). To address this problem, Gravenor and Lloyd [13] (see also Gravenor et al. [14, 15]) proposed to estimate the dynamics of malaria parasites by using multiple stages for the infected red blood cells. The overall parasite life-span is now described by a sum of n exponential distributions and the modified multiple stage model is a system of $n + 2$ ordinary differential equations. Interestingly, Gravenor and Lloyd [13] found that the basic model of Anderson et al. [4] leads to equilibrium solutions that are identical to those obtained from the multiple stage model. Adda et al. [1] and Iggidr et al. [18] preformed global stability analysis of the multiple stage model and showed the existence and global stability of a unique endemic equilibrium which rules out the existence of possible oscillations via bifurcations. Our model predicts periodic oscillations in all components that are induced by Hopf bifurcation at the positive equilibrium by using the proliferation rate of the immune

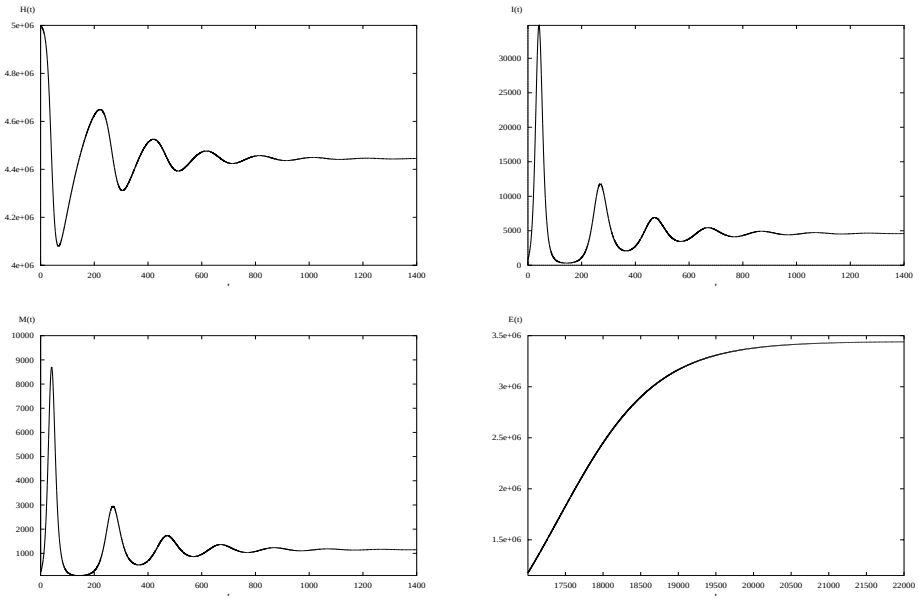

FIGURE 5. When $R_0 = 1.125 > 1$, $\frac{k_2}{\gamma} < d_2 < \frac{k_1}{\beta}$ and $k_2 < k_2^*$, The endemic equilibrium $P^* = (4.49 \times 10^6, 4134, 1033, 3.44 \times 10^6)$ is stable when $k_2 = 1.03 \times 10^{-5}$.

cells induced by infected red blood cells as the bifurcation parameter. Notice that immune response was not included in the multiple stage model of Gravenor and Lloyd [13]. It will be interesting to see if the immune system can also induce Hopf bifurcation in their model. Another option is, as did in Hoshen et al. [17], Dong and Cui [11], and Mitchell and Carr [28], to introduce a time delay into the basic model of Anderson et al. [4] to describe the parasite growth cycle which will produce the observed periodic oscillations in host-parasite dynamics.

Another remark we would like to make is that in model (1) we used only one component $E(t)$ to represent the total capacity of the immune response of the host to infected cells by parasites for the sake of simplicity and analysis. Immune responses against malaria infections are complex and stage-specific. The malaria parasite induces a specific immune response which can stimulate the release of cytokines and activate the host's monocytes, neutrophils, T-cells, and natural killer cells to react to the different stage parasites (Malaguarnera and Musumeci [23]). It would be more reasonable to model cellular and humoral immune responses separately by including various innate, antibody and T-cell responses to malaria parasites in modeling the within-host dynamics (see McQueen and McKenzie [27] and Chiyaka et al. [7]). However, that would increase the number of equations in the model and make the analysis much more difficult if it is not impossible. Our work focuses on studying the nonlinear dynamics of a basic simple model including the essential parameters of within-host malaria by a single compartment of parasites. This study provides an example of how basic mathematical frameworks may be used to explore the mechanisms of complex parasite dynamics within their hosts.

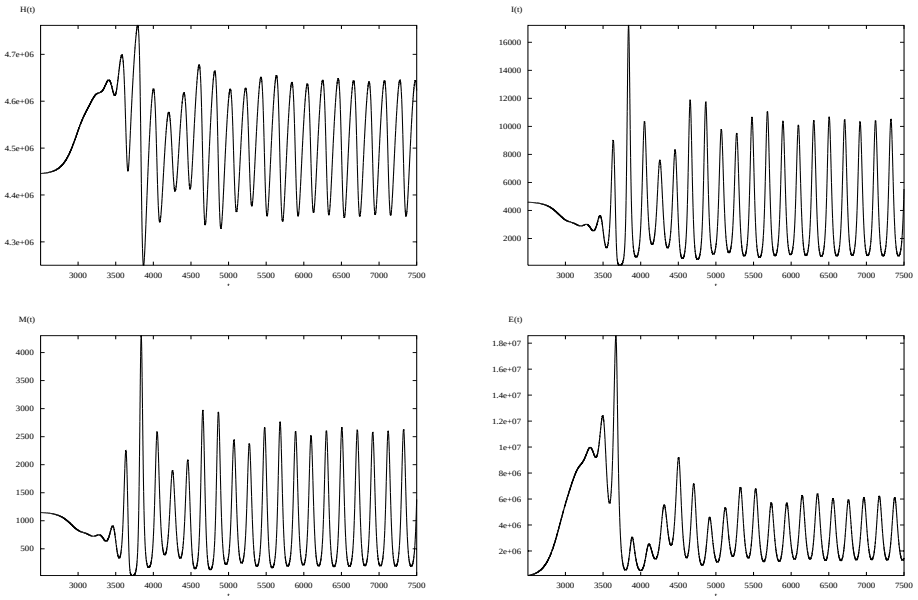

FIGURE 6. When $R_0 = 1.125 > 1$, $\frac{k_2}{\gamma} < d_2 < \frac{k_1}{\beta}$ and $k_2 > k_2^*$, there is a periodic solution bifurcated from the positive equilibrium $P^* = (4.65 \times 10^6, 2778, 693, 1.06 \times 10^7)$ when $k_2 = 2.305 \times 10^{-5}$.

As pointed out by Augustine et al. [6], many coinfections that have profound effects on the immune system, such as infection with human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* (TB), are common in people living malaria endemic regions. It will be interesting to study the effect of immune response to the coinfection of malaria and HIV (Xiao and Bossert [43]) or TB. We leave this for future consideration.

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