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Malaria dynamics with long incubation period in hosts

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ABSTRACT

Motivated by the empirical observation of the bimodal distribution of the incubation time of *P. vivax* in Korea, we analyze a mathematical model for malaria transmission dynamics that features two distinct exposed classes in the human population. The short-term incubation period is modeled by exponential distribution, while it is assumed that the long-term incubation period has fixed length. Then we formulate the model as a system of delay differential equations. We identify the basic reproduction number $\mathcal{R}_0$ and show that it is a threshold parameter for the global dynamics of the model. If $\mathcal{R}_0 \leq 1$, the disease-free equilibrium is globally attractive, while the disease uniformly persists in the human and mosquito populations when $\mathcal{R}_0 > 1$. Furthermore, for the special case of lifelong immunity, we prove that the endemic equilibrium is globally asymptotically stable.

1. Introduction

According to recent research, 104 countries or territories are at risk of malaria [1]. In addition to its health toll, malaria imposes a heavy economic burden on endemic countries [2]. One of the most common types of malaria is caused by *Plasmodium vivax*. The parasite *P. vivax* can remain dormant in liver cells in a form called *hypnozoite*, leading to an increased incubation period. *P. vivax* strains from different regions of the world have different length of incubation time [3]. Recent analyzes of the incubation period of *P. vivax* malaria in Korea have confirmed that the incubation times have a bimodal distribution, with a clear distinction of short-term and long-term incubations [4].

The basic models of Ross and Macdonald used ordinary differential equations to understand the dynamics of malaria transmission [5,6]. The incubation period was incorporated first by Sharpe and Lotka [7] as a discrete time delay. The delayed Ross–Macdonald model was later analyzed in [8,5,9]. It was concluded that prolonging the incubation periods reduces the prevalence of the disease. Other researchers expressed the incubation period by exponential distribution, letting the latent compartment decay exponentially in the absence of inflow from the infectious compartment [10,11], thus formulating the models by systems of ordinary differential equations.

Xiao and Zou [12] considered a general probability function $P(t)$ describing the latency distribution, in order to reflect the fact that the latency period varies from individual to individual. They show that when the basic reproduction number is less than one, the disease will eventually die out. When the basic reproduction number is greater than one, they consider two specific forms for $P(t)$: (i) $P(t)$ is an exponential function; (ii) $P(t)$ is a step function. In both cases, when the basic reproduction number is greater than one, they show that the disease will persist. Moreover, under additional conditions, all admissible positive solutions converge to the unique endemic equilibrium. They have generalized the conclusion of Ruan et al. [9] that longer incubation periods lead to lower prevalence of the infection, regardless of the specific form of the distributions.

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Based on empirical observation of the bimodality of the incubation times of *P. vivax* in Korea, Nah et al. [13] separated the exposed class in their model into short-term and long-term exposed classes. They describe $P(t)$ as a weighted sum of two exponential functions. However, according to the empirical investigations, no cases had incubation time between 15 and 32 weeks [4]. In this sense, it is more realistic to describe $P(t)$ as a weighted sum of an exponential function and a step function, as it provides a better approximation of the observed phenomenon.

In this paper, we analyze a *P. vivax* malaria transmission model describing $P(t)$ as a weighted sum of an exponential function and a step function, which means we model the short-term incubation periods by exponential distribution, while we assume that the long-term incubation period has fixed length. In Section 2, we construct the model and discuss its fundamental properties.

In Section 3, we define the basic reproduction number, and show that it is a threshold parameter determining the extinction or the persistence of the disease. Further, in the special case of lifelong immunity, we prove the global stability of endemic equilibrium when the basic reproduction number is greater than one.

2. Model description and basic properties

2.1. Model formulation

Let us denote by $e_H(t)$, $s_H(t)$ and $i_M(t)$ the fraction of exposed human population, the fraction of susceptible human population and the fraction of infective mosquito population at time t, respectively. We define the transmission coefficient as

$$\alpha := abm,$$

referring to Table 1 for the description of the parameters. Denote by ξ the mortality rate of human population. Then the fraction of the exposed human population at time t is given by

$$e_H(t) = \int_0^\infty \alpha s_H(t-u) i_M(t-u) P(u) e^{-\xi u} du,$$

where $P : \mathbb{R}_+ \to [0, 1]$ and $P(u)$ denotes the probability that an individual is still being in the exposed class u units of time after entering the exposed class, provided that this individual survived this period, which has probability $e^{-\xi u}$.

We separate the exposed individuals into two distinct classes. Following [14], we use the exponential distribution for the short-term incubation period (with average $1/\eta$), while we assume a fixed time τ for every individual with long-term incubation period. Let $p \in (0, 1)$ be the probability that an exposed individual experiences a short-term incubation period upon a successful contact with an infected mosquito. Then we can specify $P(u)$ as

$$P(u) = pP_s(u) + (1-p)P_l(u),$$

where

$$P_s(u) := e^{-\eta u}, \qquad P_l(u) := \begin{cases} 1, & u \in [0, \tau], \\ 0, & u \in (\tau, \infty). \end{cases}$$

Let us denote by $e_H^s(t)$ and $e_H^l(t)$ the fraction of exposed human population with short-term incubation period and with long-term incubation period at time t, respectively. It holds that

$$e_H(t) = e_H^s(t) + e_H^l(t).$$

Then we obtain

$$\begin{aligned} e_H^s(t) &= \int_0^\infty p\alpha s_H(t-u) i_M(t-u) P_s(u) e^{-\xi u} du \\ &= \int_0^\infty p\alpha s_H(t-u) i_M(t-u) e^{-(\eta+\xi)u} du, \end{aligned} \tag{1}$$

$$\begin{aligned} e_H^l(t) &= \int_0^\infty (1-p)\alpha s_H(t-u) i_M(t-u) P_l(u) e^{-\xi u} du \\ &= \int_0^\tau (1-p)\,\alpha s_H(t-u) i_M(t-u) e^{-\xi u} du. \end{aligned} \tag{2}$$

One can differentiate $e_H^s(t)$ with respect to t to get the ordinary differential equation

$$\frac{de_H^s(t)}{dt} = p\alpha s_H(t) i_M(t) - (\eta + \xi)\, e_H^s(t).$$

The fraction of human population progressing to the infectious class per unit of time at time t, after experiencing either the short- or long-term incubation period, is given by $\eta e_H^s(t) + (1-p)\alpha s_H(t-\tau) i_M(t-\tau) e^{-\xi\tau}$. We denote by $i_H(t)$ the fraction

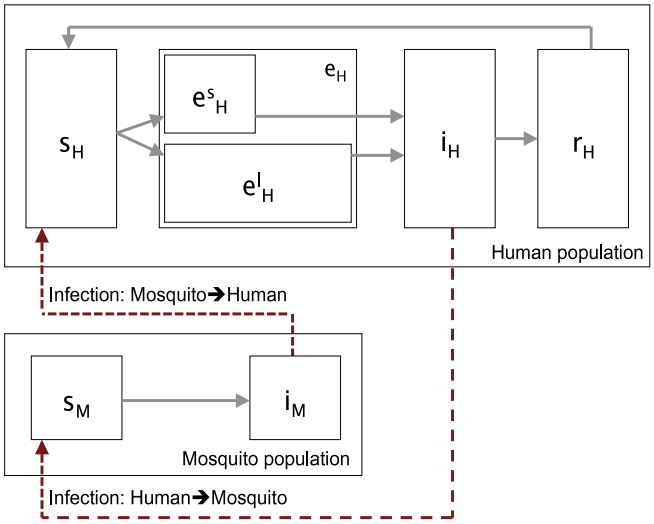


Fig. 1. Diagram for the disease transmission. The exposed class of humans is separated into two distinct classes according to the length of the incubation period.

Table 1
Description of parameters.

Parameter	Description
a	Contact rate of a mosquito with humans
b	Transmission efficacy of contact between an infected mosquito and a human individual
m	Proportion of mosquito population to human population
c	Transmission efficacy of contact between an infected human and a mosquito
p	Probability of an exposed human to experience short-term incubation period after infection
τ	Long-term incubation period of humans
ξ	Mortality rate of humans
μ	Mortality rate of mosquitoes
η	Rate of progression from the short-term exposed state to the infectious state
r	Recovery rate of humans
ω	Rate of loss of immunity for humans

of infectious human population. The following differential equation captures the dynamics of the fraction of the infective human population:

$$\frac{di_H(t)}{dt} = \eta e^s_H(t) + (1-p)\alpha s_H(t-\tau) i_M(t-\tau) e^{-\xi\tau} - (r+\xi)\, i_H(t).$$

By considering the recovered class of humans, $r_H(t)$, and the mosquito population dynamics, we arrive to

$$\frac{ds_H(t)}{dt} = \xi - \alpha s_H(t) i_M(t) - \xi s_H(t) + \omega r_H(t), \tag{3a}$$

$$\frac{de^s_H(t)}{dt} = p\alpha s_H(t) i_M(t) - (\eta+\xi)\, e^s_H(t), \tag{3b}$$

$$\frac{di_H(t)}{dt} = \eta e^s_H(t) + (1-p)\alpha s_H(t-\tau) i_M(t-\tau) e^{-\xi\tau} - (r+\xi)\, i_H(t), \tag{3c}$$

$$\frac{dr_H(t)}{dt} = r i_H(t) - (\omega+\xi)\, r_H(t), \tag{3d}$$

$$\frac{ds_M(t)}{dt} = \mu - \beta s_M(t) i_H(t) - \mu s_M(t), \tag{3e}$$

$$\frac{di_M(t)}{dt} = \beta s_M(t) i_H(t) - \mu i_M(t), \tag{3f}$$

where $\beta := ac$.

See also Fig. 1 for the disease transmission diagram and Tables 1 and 2 for the description of the parameters and the variables.

Table 2
Description of the dynamical variables. Each variable denotes a fraction of the population so that $s_H + (e^s_H + e^l_H) + i_H + r_H = 1$ and $s_M + i_M = 1$ hold.

Variable	Description
s_H	Susceptible human population
e_H	Exposed human population
e^s_H	Exposed human population having a short-term incubation period
e^l_H	Exposed human population having a long-term incubation period
i_H	Infectious human population
r_H	Recovered human population
s_M	Susceptible mosquito population
i_M	Infectious mosquito population

By differentiating both sides of (2) with respect to t, one can obtain

$$\frac{de^l_H(t)}{dt} = (1-p)\alpha s_H(t) i_M(t) - (1-p)\alpha s_H(t-\tau) i_M(t-\tau) e^{-\xi\tau} - \xi e^l_H(t). \tag{4}$$

Note that $e^l_H(t)$ does not appear in (3).

Let $C([-\tau, 0], \mathbb{R})$ be the space of real valued continuous functions on the interval $[-\tau, 0]$, and consider

$$\Omega := C([-\tau, 0], \mathbb{R}) \times \mathbb{R}^4 \times C([-\tau, 0], \mathbb{R}).$$

Assuming that the solution exists in Ω, it is convenient to introduce a standard notation from the theory of functional differential equations, see e.g [15,16]:

$$x_t := (s_{Ht}, e^s_H(t), i_H(t), r_H(t), s_M(t), i_{Mt}) \in \Omega,$$

where $s_{Ht} \in C([-\tau, 0], \mathbb{R})$ and $i_{Mt} \in C([-\tau, 0], \mathbb{R})$ are defined by the relations

$$s_{Ht}(\theta) = s_H(t+\theta), \qquad i_{Mt}(\theta) = i_M(t+\theta) \quad \text{for } \theta \in [-\tau, 0].$$

In what follows, we write $\hat{y}$ for the element of $C([-\tau, 0], \mathbb{R})$ satisfying $\hat{y}(\theta) = y$ for all $\theta \in [-\tau, 0]$. Let

$$\Omega_+ := C([-\tau, 0], \mathbb{R}_+) \times \mathbb{R}^4_+ \times C([-\tau, 0], \mathbb{R}_+).$$

Following the biological interpretation of our system, we prescribe the initial condition as

$$x_0 = \phi_0 \in \Omega_+. \tag{5}$$

Then system (3) can be written in the abstract form

$$\frac{dx(t)}{dt} = \mathcal{F}(x_t),$$

where $\mathcal{F} : \Omega \to \mathbb{R}^6$, with initial condition (5). We consider $\mathbb{R}^6$ equipped with the L^∞ norm and $C([-\tau, 0], \mathbb{R})$ equipped with the usual supremum norm denoted by $\|\cdot\|$. Now Ω is a Banach space with the norm

$$|\phi|_\Omega := \max\{\|f\|, |q_2|, |q_3|, |q_4|, |q_5|, \|g\|\},$$

for

$$\phi = (f, q_2, q_3, q_4, q_5, g) \in \Omega.$$

Then it is easy to show that $\mathcal{F}$ satisfies the local Lipschitz condition on each bounded subset of Ω, from which the local existence of solutions of (3) follows, see also Theorem 3.7 in Chapter 3 in [16]. Furthermore, it is straightforward to show that $x_t \in \Omega_+$ for sufficiently small t and it is easy to give an a priori bound for $|x_t|_\Omega$. Thus the solution x_t is continuable on $\mathbb{R}_+$. Consequently, (3) with (5) induces a continuous semiflow

$$\Phi : \mathbb{R}_+ \times \Omega_+ \to \Omega_+,$$

defined by

$$\Phi(t, \phi_0) = x_t(\phi_0).$$

Let

$$X := \left\{ \phi \;\middle|\; \begin{array}{l} 0 \le f(\theta),\ 0 \le g(\theta), \text{ for } \theta \in [-\tau, 0], \\ 0 \le q_j,\ j \in \{2, 3, 4, 5\}, \\ f(0) + \displaystyle\int_{-\tau}^{0} (1-p)\alpha f(s) g(s) e^{\xi s} ds + \sum_{j=2}^{4} q_j = 1, \\ q_5 + g(0) = 1. \end{array} \right\} \subset \Omega_+.$$

Proposition 1. *The set X is forward invariant under Φ, i.e.*

$$\Phi(t, X) \subset X, \quad t \in \mathbb{R}_+.$$

Proof. Let $\phi_0 \in X$. By Theorem 3.4 in [16], one can show that each component of $x_t(\phi_0)$ is nonnegative for all $t \geq 0$. Adding (3e) and (3f), we have $s'_M + i'_M = 0$, thus $s_M(t) + i_M(t)$ is a constant function. Since $s_M(0) + i_M(0) = 1$, we have $s_M(t) + i_M(t) = 1$ for all $t \geq 0$. Let

$$n(t) := s_H(t) + e^s_H(t) + i_H(t) + r_H(t) + \int_0^\tau (1-p)\alpha s_H(t-a) i_M(t-a) e^{-\xi a} da.$$

Note that from (2) and (4) we have

$$\begin{aligned}\frac{d}{dt}\int_0^\tau (1-p)\alpha s_H(t-a) i_M(t-a) e^{-\xi a} da &= \frac{d}{dt} e^I_H(t) \\ &= (1-p)\alpha s_H(t) i_M(t) - (1-p)\alpha s_H(t-\tau) i_M(t-\tau) e^{-\xi\tau} \\ &\quad - \xi \int_0^\tau (1-p)\alpha s_H(t-a) i_M(t-a) e^{-\xi a} da.\end{aligned}$$

Adding (3a)–(3d) and (4), one obtains

$$\frac{dn(t)}{dt} = \xi - \xi n(t)$$

with $n(0) = 1$. Thus $n(t) = 1$ for all $t \geq 0$, and the conclusion follows. □

The variables in (3) represent fractions of either the human population or the mosquito population. Thus, in X, the fractions of the human population sum up to 1, with all human compartments $(s_H, e^s_H, e^I_H, i_H, r_H)$ being nonnegative; and the fractions of mosquito populations sum up to 1, with all mosquito compartments (s_M, i_M) being nonnegative. Therefore X is exactly the biologically meaningful state space. In Sections 2 and 3 we consider the dynamics of system (3) in X.

2.2. Existence of equilibria

We define the basic reproduction number by

$$R_0 := \sqrt{\frac{\alpha\beta}{\mu(r+\xi)}\left((1-p)e^{-\xi\tau} + p\frac{\eta}{\eta+\xi}\right)}. \tag{6}$$

Here, α denotes the successful contact rate of an infected mosquito with humans. The term $(1-p)e^{-\xi\tau} + p\frac{\eta}{\eta+\xi}$ gives the probability that an infected human individual survives the exposed state and then becomes infectious. The expected infectious period of an infected mosquito is given by $1/\mu$. Therefore, the term $\frac{\alpha}{\mu}\left((1-p)e^{-\xi\tau} + p\frac{\eta}{\eta+\xi}\right)$ gives the expected number of infectious human generated by one infected mosquito during its expected lifetime.

Next, β denotes the successful contact rate of an infectious human with mosquitoes. The expected infectious period of an infected human is $\frac{1}{r+\xi}$. Thus $\frac{\beta}{r+\xi}$ gives the expected number of infectious mosquitoes generated by one infected human during the infectious period. Therefore R_0 has the usual biological interpretation, where we used the convention of taking the square root since reproduction takes two epidemiological generations.

The result on the existence of equilibria follows from algebraic calculation, see also [14].

Proposition 2. *If $R_0 \leq 1$, then system (3) has a unique equilibrium in X, the disease-free equilibrium $(\hat{1}, 0, 0, 0, 1, \hat{0})$. If $R_0 > 1$, there exist exactly two equilibria in X: the disease-free equilibrium and the endemic equilibrium, where each component is positive.*

Proof. The equilibria can be obtained from the following system of algebraic equations:

$$\begin{aligned}0 &= \xi - \alpha s_H i_M - \xi s_H + \omega r_H, \\ 0 &= p\alpha s_H i_M - (\eta+\xi) e^s_H, \\ 0 &= \eta e^s_H + (1-p)\alpha s_H i_M e^{-\xi\tau} - (r+\xi) i_H, \\ 0 &= r i_H - (\omega+\xi) r_H, \\ 0 &= \beta s_M i_H - \mu i_M.\end{aligned}$$

By straightforward, but rather lengthy calculations, one can find that a unique endemic equilibrium with strictly positive components exists if and only if $R_0 > 1$. □

3. Threshold dynamics: extinction and persistence of the disease

First we prove the global attractivity of the disease-free equilibrium for $R_0 \leq 1$. Let us define a subset of X by

$$G := \{\phi \in X | f(0) > 0, q_5 > 0\}.$$

It is easy to see that

$$\Phi(t, X) \subset G, \quad t > 0.$$

To prove the global attractivity, we construct a Lyapunov functional, for what we use, as a building block, the function

$$h(x) := x - 1 - \ln x \quad \text{for } x \in \mathbb{R}_+ \setminus \{0\}. \tag{7}$$

Note that $h(x) \geq 0$ for $x \in \mathbb{R}_+ \setminus \{0\}$ and that $h(x) = 0$ if and only if $x = 1$.

Theorem 1. *If $R_0 \leq 1$, then the disease-free equilibrium is globally attractive in X. Furthermore, if $R_0 < 1$ holds, then it is globally asymptotically stable in X.*

Proof. Consider the following functional $V : G \to \mathbb{R}_+$:

$$V(\phi) := c_1 h(f(0)) + c_2 q_2 + q_3 + c_3 h(q_5) + c_3 g(0) + c_4 \int_{-\tau}^{0} f(s) g(s) ds,$$

where

$$c_1 := \frac{\mu(r+\xi)}{\alpha\beta}, \qquad c_2 := \frac{\eta}{\eta+\xi}, \qquad c_3 := \frac{r+\xi}{\beta}, \qquad c_4 := (1-p)\alpha e^{-\xi\tau}.$$

We differentiate V with respect to t along solutions of (3):

$$\begin{aligned}
\frac{d}{dt}V(x_t) &= c_1(\xi - \alpha s_H(t) i_M(t) + \omega r_H(t) - \xi s_H(t)) + c_1\left(-\frac{\xi}{s_H(t)} + \alpha i_M(t) - \omega\frac{r_H(t)}{s_H(t)} + \xi\right) \\
&\quad + c_2(p\alpha s_H(t) i_M(t) - (\eta+\xi) e_H^s(t)) + \eta e_H^s(t) + (1-p)\alpha s_H(t-\tau) i_M(t-\tau) e^{-\xi\tau} \\
&\quad - (r+\xi) i_H(t) + c_3(\mu - \beta s_M(t) i_H(t) - \mu s_M(t)) + c_3\left(-\frac{\mu}{s_M(t)} + \beta i_H(t) + \mu\right) \\
&\quad + c_3(\beta s_M(t) i_H(t) - \mu i_M(t)) + c_4(s_H(t) i_M(t) - s_H(t-\tau) i_M(t-\tau)) \\
&= c_1\xi\left(2 - s_H(t) - \frac{1}{s_H(t)}\right) + c_3\mu\left(2 - s_M(t) - \frac{1}{s_M(t)}\right) + c_1\omega r_H(t)\left(1 - \frac{1}{s_H(t)}\right) \\
&\quad + (c_2 p\alpha + c_4 - c_1\alpha) s_H(t) i_M(t) + (\eta - c_2(\eta+\xi)) e_H^s(t) + (c_1\alpha - c_3\mu) i_M(t) \\
&\quad + (c_3\beta - (r+\xi)) i_H(t) + ((1-p)\alpha e^{-\xi\tau} - c_4) s_H(t-\tau) i_M(t-\tau) \\
&= c_1\xi\left(2 - s_H(t) - \frac{1}{s_H(t)}\right) + c_3\mu\left(2 - s_M(t) - \frac{1}{s_M(t)}\right) + c_1\omega r_H(t)\left(1 - \frac{1}{s_H(t)}\right) \\
&\quad + (c_2 p\alpha + c_4 - c_1\alpha) s_H(t) i_M(t).
\end{aligned}$$

Since $R_0 \leq 1$ is assumed, one can get

$$c_2 p\alpha + c_4 - c_1\alpha = \frac{\mu(r+\xi)}{\beta}(R_0^2 - 1) \leq 0.$$

Therefore we have $\frac{d}{dt}V(x_t) \leq 0$. For a given solution, we define a set

$$\overline{G} := \left\{\varphi \in G | V(\varphi) \leq V(x_{t_0})\right\},$$

for some $t_0 > 0$. One can see that $\overline{G}$ is closed and positively invariant. Thus the closure of $\overline{G}$ is itself and $\overline{G}$ contains x_t for all $t \geq t_0 > 0$. Since V is continuous on $\overline{G}$, V is a Lyapunov functional on G, see Chapter 5.3 in [15]. We define the set

$$E := \left\{\varphi \in \overline{G} | \dot{V}_{(3)}(\varphi) = 0\right\},$$

and one finds that

$$E = \left\{\phi \in \overline{G} | f(0) = 1,\ q_5 = 1\right\}.$$

Let M be the largest subset in E that is invariant with respect to (3). By LaSalle's invariance principle, the solution tends to M, see Theorem 3.2, Chapter 5.3 in [15]. We show that M consists of only the disease free equilibrium. From the invariance of M, for $\phi \in M$ one has $x_t(\phi) \in M \subset E$ for $t > 0$. Then $s_M(t) = 1$ and $i_H(t) = 0$ follow. From (3f), we obtain $\lim_{t\to\infty} i_M(t) = 0$. Then one can see that $\lim_{t\to\infty}\left(e_H^s(t), i_H(t), i_M(t)\right) = (0,0,0)$ and $\lim_{t\to\infty} s_H(t) = 1$. Thus, M consists

of only the disease-free equilibrium. Hence, every solution converges to the disease-free equilibrium. The local asymptotic stability of the disease-free equilibrium can be demonstrated by standard linearization: one can compute the characteristic equation (see [15,17]), and show that if $R_0 < 1$, then all roots of the characteristic equation have negative real parts. Here we omit the calculations. Thus the disease free equilibrium is globally asymptotically stable for $R_0 < 1$. □

Next we prove the persistence of the disease for $R_0 > 1$. Let us define

$$\rho := \sum_{i=1}^{4} \rho_i,$$

where $\rho_i : X \to \mathbb{R}_+$ for $i \in \{1, 2, 3, 4\}$ are given by

$$\rho_1(\phi) = q_2, \qquad \rho_2(\phi) = (1-p)\alpha \int_{-\tau}^{0} f(s)g(s)e^{\xi s} ds,$$
$$\rho_3(\phi) = q_3, \qquad \rho_4(\phi) = g(0).$$

Let

$$\tilde{X} := \{\phi \in X | \rho(\phi) > 0\}, \tag{8}$$
$$X_0 := \{\phi \in X | \rho(\phi) = 0\} = X \setminus \tilde{X}, \tag{9}$$

where X_0 is called the extinction space corresponding to ρ, for obvious reasons: X_0 is the collection of states where the disease is not present.

Proposition 3. *The following assertions hold.*

1. *The set $\tilde{X}$ is forward invariant under Φ. Moreover, for each $i \in \{1, 2, 3, 4\}$ it holds that*

$$\rho_i(\Phi(t, \phi)) > 0 \quad \text{for } \phi \in \tilde{X} \text{ and } t > \tau. \tag{10}$$

2. *The extinction space X_0 is forward invariant under Φ.*

Proof. One can prove the first part by a comparison method and a contradiction argument, thus here we only prove the second part. Let $\phi \in X_0$. For $t \in [0, \tau]$ one can see that

$$(1-p)\alpha s_H(t-\tau) i_M(t-\tau) e^{-\xi\tau} = (1-p)\alpha f(t-\tau) g(t-\tau) e^{-\xi\tau} = 0.$$

Therefore, for $t \in [0, \tau]$, (3b)–(3d) are respectively reduced to

$$\begin{aligned} \frac{de_H^s(t)}{dt} &= p\alpha s_H(t) i_M(t) - (\eta + \xi)\, e_H^s(t), \\ \frac{di_H(t)}{dt} &= \eta e_H^s(t) - (r + \xi)\, i_H(t), \\ \frac{di_M(t)}{dt} &= \beta s_M(t) i_H(t) - \mu i_M(t) \end{aligned} \tag{11}$$

with $e_H^s(0) = i_H(0) = i_M(0) = 0$. Since $(e_H^s, i_H, i_M) = (0, 0, 0)$ is an equilibrium of (11), we get that

$$e_H^s(t) = i_H(t) = i_M(t) = 0, \quad t \in [0, \tau],$$

therefore

$$\begin{aligned} \int_{-\tau}^{0} s_{Ht}(s) i_{Mt}(s) e^{\xi s} ds &= \int_{t-\tau}^{t} s_H(s) i_M(s) e^{-\xi(t-s)} ds \\ &= \int_{t-\tau}^{0} f(s) g(s) e^{-\xi(t-s)} ds + \int_{0}^{t} s_H(s) i_M(s) e^{-\xi(t-s)} ds \\ &= 0, \quad t \in [0, \tau]. \end{aligned}$$

Hence we obtain $\rho(\Phi(t, \phi)) = 0$ for $t \in [0, \tau]$. By the method of steps, we arrive to the conclusion that $\rho(\Phi(t, \phi)) = 0$ holds for all $t \in \mathbb{R}_+$, i.e. $\rho(\Phi(t, \phi)) \in X_0$ for all $t \in \mathbb{R}_+$. □

We now introduce some terminology of persistence theory from Chapters 3.1 and 8.3 in [17].

Definition 1. Let X be a nonempty set and $\rho : X \to \mathbb{R}_+$.

1. A semiflow $\Phi : \mathbb{R}_+ \times X \to X$ is called uniformly weakly ρ-persistent, if there exists some $\epsilon > 0$ such that

$$\limsup_{t \to \infty} \rho(\Phi(t, x)) > \epsilon \quad \forall x \in X,\ \rho(x) > 0.$$

2. A semiflow Φ is called uniformly (strongly) ρ-persistent, if there exists some $\epsilon > 0$ such that

$$\liminf_{t\to\infty} \rho(\Phi(t,x)) > \epsilon \quad \forall x \in X,\ \rho(x) > 0.$$

3. A set $M \subset X$ is called weakly ρ-repelling if there is no $x \in X$ such that $\rho(x) > 0$ and $\Phi(t,x) \to M$ as $t \to \infty$.

Theorem 2. *If $R_0 > 1$, then the semiflow Φ is uniformly ρ-persistent.*

Proof. We apply Theorems 4.5 and 8.17 in [17]. First, we show that $(\hat{1}, 0, 0, 0, 1, \hat{0})$ is weakly ρ-repelling. Suppose that there exists $\psi_0 \in X$ such that $\rho(\psi_0) > 0$ with

$$\lim_{t\to\infty} \Phi(t, \psi_0) = (\hat{1}, 0, 0, 0, 1, \hat{0}). \tag{12}$$

We denote by $(s_{H_t}, e^s_H(t), i_H(t), r_H(t), s_M(t), i_{M_t})$ the solution at time t with initial state ψ_0. Since we have (12), there exists $T > 0$ such that $s_H(t) > \frac{1}{R_0}$ and $s_M(t) > \frac{1}{R_0}$ for all $t > T$. Let us define

$$U(t) := \frac{\eta}{\eta+\xi} e^s_H(t) + (1-p)\alpha e^{-\xi\tau} \int_{-\tau}^{0} s_{H_t}(s) i_{M_t}(s) ds + i_H(t) + R_0 \frac{r+\xi}{\beta} i_{M_t}(0).$$

Since $\rho(\psi_0) > 0$, by Proposition 3.1, $U(T) > 0$. We compute

$$\begin{aligned}
U'(t) &= \frac{\eta}{\eta+\xi}(p\alpha s_H(t) i_M(t) - (\eta+\xi) e^s_H(t)) + (1-p)\alpha e^{-\xi\tau}(s_H(t) i_M(t) - s_H(t-\tau) i_M(t-\tau)) \\
&\quad + \eta e^s_H(t) + (1-p)\alpha e^{-\xi\tau} s_H(t-\tau) i_M(t-\tau) - (r+\xi) i_H(t) + R_0 \frac{r+\xi}{\beta}(\beta s_M(t) i_H(t) - \mu i_M(t)) \\
&= \left(p\alpha \frac{\eta}{\eta+\xi} + (1-p)\alpha e^{-\xi\tau}\right) s_H(t) i_M(t) - (r+\xi) i_H(t) - R_0 \frac{(r+\xi)\mu}{\beta} i_M(t) + R_0 (r+\xi) s_M(t) i_H(t) \\
&= R_0 \frac{(r+\xi)\mu}{\beta} i_M(t)(R_0 s_H(t) - 1) + (r+\xi) i_H(t)(R_0 s_M(t) - 1) \\
&\geq 0
\end{aligned}$$

for $t > T$. Since U is increasing for $t > T$ and $U(T) > 0$, $U(t)$ does not converge to zero as $t \to \infty$. Thus, there is no $\psi_0 \in X$ such that $\rho(\psi_0) > 0$ and (12) holds. Therefore, $(\hat{1}, 0, 0, 0, 1, \hat{0})$ is weakly ρ-repelling.

By Proposition 3.1, together with the obvious statement $\cup_{\phi\in\chi_0} \omega(\phi) = (\hat{1}, 0, 0, 0, 1, \hat{0})$, one can see that Φ is uniformly weakly ρ-persistent using Theorem 8.17 in [17]. Since Φ has a compact global attractor on X, we can apply Theorem 4.5 in [17] to conclude that Φ is uniformly ρ-persistent. □

For a function $f : \mathbb{R} \to \mathbb{R}$, we use the notation

$$f^\infty = \limsup_{t\to\infty} f(t) \quad \text{and} \quad f_\infty = \liminf_{t\to\infty} f(t).$$

Theorem 3. *If $R_0 > 1$, then Φ is uniformly ρ_4-persistent.*

Proof. Let $\psi \in X$ with $\rho_4(\psi) > 0$. Since $\rho(\psi) \geq \rho_4(\psi) > 0$, by Theorem 2, there exists $\epsilon > 0$ such that $\liminf_{t\to\infty} \rho(\Phi(t,\psi)) > \epsilon$. Thus, one has $\limsup_{t\to\infty} \rho_i(\Phi(t,\psi)) > \epsilon$ for some $i \in \{1,2,3,4\}$.

First, assume that $e^{s\infty}_H > \epsilon$. By the Fluctuation method [16], we can take a sequence $\{t_j\}_{j=1}^\infty$ such that $e^{s\prime}_H(t_j) \to 0$, $e^s_H(t_j) \to e^{s\infty}_H$ as $j \to \infty$. From (3b), we get

$$\lim_{j\to\infty} s_H(t_j) i_M(t_j) = \lim_{j\to\infty} \left(\frac{1}{p\alpha} e^{s\prime}_H(t_j) + \frac{\eta+\xi}{p\alpha} e^s_H(t_j)\right)$$

and then

$$i^\infty_M \geq \lim_{j\to\infty} s_H(t_j) i_M(t_j) = \frac{\eta+\xi}{p\alpha} e^{s\infty}_H > \frac{(\eta+\xi)\epsilon}{p\alpha}, \tag{13}$$

thus we obtain the conclusion. Next we assume that $e^{I\infty}_H > \epsilon$. Then we have a sequence $\{t_m\}_{m=1}^\infty$ satisfying $e^{I\prime}_H(t_m) \to 0$, $e^I_H(t_m) \to e^{I\infty}_H$ as $m \to \infty$.

From (4), we have

$$\lim_{m\to\infty} \left(s_H(t_m) i_M(t_m) - s_H(t_m-\tau) i_M(t_m-\tau) e^{-\xi\tau}\right) = \lim_{m\to\infty} \left(\frac{1}{(1-p)\alpha} e^{I\prime}_H(t_m) + \frac{\xi}{(1-p)\alpha} e^I_H(t_m)\right).$$

Then we deduce that

$$\begin{aligned} i_M^\infty &\geq \limsup_{m\to\infty} s_H(t_m) i_M(t_m) - \liminf_{m\to\infty} s_H(t_m-\tau) i_M(t_m-\tau) e^{-\xi\tau} \\ &\geq \limsup_{m\to\infty} \left(s_H(t_m) i_M(t_m) - s_H(t_m-\tau) i_M(t_m-\tau) e^{-\xi\tau} \right) \\ &= \frac{\xi}{(1-p)\alpha} e_H^{I\infty} \\ &> \frac{\xi\epsilon}{(1-p)\alpha}. \end{aligned} \tag{14}$$

Finally we assume that $i_H^\infty > \epsilon$. Then there is a sequence $\{t_l\}_{l=1}^\infty$ such that $i_H'(t_l) \to 0$, $i_H(t_l) \to i_H^\infty$ as $l \to \infty$. From (3c), one has

$$\lim_{l\to\infty} \left(\frac{\eta}{\alpha} e_H^s(t_l) + (1-p) s_H(t_l-\tau) i_M(t_l-\tau) e^{-\xi\tau} \right) = \lim_{l\to\infty} \left(\frac{1}{\alpha} i_H'(t_l) + \frac{r+\xi}{\alpha} i_H(t_l) \right). \tag{15}$$

Moreover,

$$i_M^\infty \geq p i_M^\infty + (1-p) e^{-\xi\tau} i_M^\infty.$$

Since inequality (13) implies $i_M^\infty \geq \frac{\eta+\xi}{p\alpha} e_H^{s\infty}$,

$$\begin{aligned} i_M^\infty &\geq \frac{\eta+\xi}{\alpha} e_H^{s\infty} + (1-p) e^{-\xi\tau} \limsup_{l\to\infty} s_H(t_l-\tau) i_M(t_l-\tau) \\ &\geq \frac{\eta}{\alpha} e_H^{s\infty} + (1-p) e^{-\xi\tau} \limsup_{l\to\infty} s_H(t_l-\tau) i_M(t_l-\tau) \\ &\geq \lim_{l\to\infty} \left(\frac{\eta}{\alpha} e_H^s(t_l) + (1-p) s_H(t_l-\tau) i_M(t_l-\tau) e^{-\xi\tau} \right). \end{aligned}$$

By (15), we get

$$i_M^\infty \geq \frac{r+\xi}{\alpha} i_H^\infty > \frac{r+\xi}{\alpha}\epsilon.$$

Therefore, Φ is uniformly weakly ρ_4-persistent. From the uniformly weak persistence, the uniform persistence follows by Theorem 4.5 in [17]. □

Theorem 4. *If $R_0 > 1$, then Φ is uniformly ρ_3-persistent.*

Proof. Let $\psi \in X$ with $\rho_3(\psi) > 0$. Since $\rho(\psi) \geq \rho_3(\psi) > 0$, by Theorem 2, there exists $\epsilon > 0$ such that $\liminf_{t\to\infty} \rho(\Phi(t,\psi)) > \epsilon$. Then, $\limsup_{t\to\infty} \rho_i(\Phi(t,\psi)) > \epsilon$ for some $i \in \{1,2,3,4\}$.

Assume that $i_M^\infty > \epsilon$. By (3f), with a sequence $\{t_k\}_{k=1}^\infty$ such that $i_M'(t_k) \to 0$, $i_M(t_k) \to i_M^\infty$ as $k \to \infty$, we have

$$\lim_{k\to\infty} s_M(t_k) i_H(t_k) = \lim_{k\to\infty} \left(\frac{1}{\beta} i_M'(t_k) + \frac{\mu}{\beta} i_M(t_k) \right).$$

This implies

$$i_H^\infty \geq \lim_{k\to\infty} s_M(t_k) i_H(t_k) = \frac{\mu}{\beta} i_M^\infty > \frac{\mu}{\beta}\epsilon. \tag{16}$$

Next we assume that $e_H^{s\infty} > \epsilon$. Similar as in (13), we get

$$i_M^\infty \geq \frac{\eta+\xi}{p\alpha} e_H^{s\infty}. \tag{17}$$

By (16) and (17), we find

$$i_H^\infty \geq \frac{\mu}{\beta} i_M^\infty \geq \frac{\mu}{\beta} \frac{\eta+\xi}{p\alpha} e_H^{s\infty} > \frac{\mu}{\beta} \frac{\eta+\xi}{p\alpha}\epsilon.$$

Next we assume that $e_H^{I\infty} > \epsilon$. Similar as in (14), we get

$$i_M^\infty \geq \frac{\xi}{(1-p)\alpha} e_H^{I\infty}. \tag{18}$$

By (16) and (18), one has

$$i_H^\infty \geq \frac{\mu}{\beta} i_M^\infty \geq \frac{\mu}{\beta} \frac{\xi}{(1-p)\alpha} e_H^{I\infty} > \frac{\mu}{\beta} \frac{\xi}{(1-p)\alpha} \epsilon.$$

From uniformly weak persistence, the uniform persistence follows by Theorem 4.5 in [17]. □

Lemma 1. *There exists $T > 0$ such that $s_H(t) > \frac{1}{2}\frac{\xi}{\alpha+\xi}$ for all $t \geq T$.*

Proof. From the first equation of (3), we have

$$s_H' = \xi - \alpha s_H i_M + \omega r_H - \xi s_H \geq \xi - \alpha s_H - \xi s_H$$

and thus $s_{H\infty} \geq \frac{\xi}{\alpha+\xi} > 0$. □

Theorem 5. *If $R_0 > 1$, then Φ is uniformly ρ_2-persistent.*

Proof. Let $\psi \in X$ with $\rho_2(\psi) > 0$. By Proposition 3.1, there exist $t^* > \tau$ such that $\rho_4(x_{t^*}(\psi)) > 0$.

Then, by Theorem 3, there exists $\epsilon > 0$ such that

$$\liminf_{t\to\infty} \rho_4(\Phi(t,\psi)) = \liminf_{t\to\infty} \rho_4(\Phi(t, x_{t^*}(\psi))) > \epsilon.$$

From now on, we denote by $(s_{H_t}, e_H^s(t), i_H(t), r_H(t), s_M(t), i_{M_t})$ the solution with initial state ψ. There exists $T_1 > 0$ such that $i_{M_t}(0) > \frac{1}{2}\epsilon$ for all $t \geq T_1$. Take $T_2 > 0$ such that $s_{H_t}(0) > \frac{1}{2}\frac{\xi}{\alpha+\xi}$ for all $t \geq T_2$. Then,

$$\int_{-\tau}^{0} s_{H_t}(s) i_{M_t}(s) e^{\xi s} ds > \frac{1}{4}\frac{\xi}{\alpha+\xi}\epsilon \int_{-\tau}^{0} e^{\xi s} ds$$

for all $t > \max\{T_1, T_2\} + \tau$. Therefore,

$$\liminf_{t\to\infty} (1-p)\alpha \int_{-\tau}^{0} s_{H_t}(s) i_{M_t}(s) e^{\xi s} ds \geq \frac{1}{4}(1-p)\alpha \frac{\xi}{\alpha+\xi}\epsilon \int_{-\tau}^{0} e^{\xi s} ds > 0. \quad \square$$

Theorem 6. *If $R_0 > 1$, then Φ is uniformly ρ_1-persistent.*

Proof. Let $\psi \in X$ with $\rho_1(\psi) > 0$. By Proposition 3.1, there exist $t^* > \tau$ such that $\rho_4(x_{t^*}(\psi)) > 0$. Then, by Theorem 3, there exists $\epsilon > 0$ such that

$$\liminf_{t\to\infty} \rho_4(\Phi(t,\psi)) = \liminf_{t\to\infty} \rho_4(\Phi(t, x_{t^*}(\psi))) > \epsilon.$$

From now on, we denote by $(s_{H_t}, e_H^s(t), i_H(t), r_H(t), s_M(t), i_{M_t})$ the solution with initial state ψ. There exists $T_1 > 0$ such that $i_H(t) > \frac{1}{2}\epsilon$ for all $t \geq T_1$. Take $T_2 > 0$ such that $s_H(t) > \frac{1}{2}\frac{\xi}{\alpha+\xi}$ for all $t \geq T_2$. Then,

$$\frac{d}{dt} e_H^s(t) = p\alpha s_H(t) i_M(t) - (\eta+\xi) e_H^s(t) \geq \frac{1}{4} p\alpha \frac{\xi}{\alpha+\xi}\epsilon - (\eta+\xi) e_H^s(t)$$

for all $t > \max\{T_1, T_2\}$, thus $e_{H\infty}^s \geq \frac{p\alpha\xi\epsilon}{4(\eta+\xi)(\alpha+\xi)}$. □

Combining Theorems 3–6 and Proposition 3.1, we immediately obtain the following result.

Corollary 1. *If $R_0 > 1$, there exists $\epsilon > 0$ such that*

$$e_{H\infty}^s > \epsilon, \qquad e_{H\infty}^I > \epsilon, \qquad i_{H\infty} > \epsilon \quad \text{and} \quad i_{M\infty} > \epsilon$$

for every $\phi_0 \in \tilde{X}$, i.e. the disease uniformly persists in each infected compartments of the human and mosquito populations.

4. Global stability of the endemic equilibrium

In the special case of $\omega = 0$, which means that individuals acquire permanent immunity after recovering from the infection, we show that the endemic equilibrium is indeed globally asymptotically stable, provided that the basic reproduction number is greater than one.

Theorem 7. *Assume that $\omega = 0$. If $R_0 > 1$, then the endemic equilibrium is globally asymptotically stable in $\tilde{X}$.*

Proof. First we define a subset of X as

$$\tilde{G} := \left\{ \phi \in X \,\middle|\, \begin{array}{l} f(\theta) > 0,\ g(\theta) > 0,\ \theta \in [-\tau, 0], \\ q_j > 0,\ j \in \{2, 3, 4, 5\}. \end{array} \right\}.$$

From Proposition 3 one can see that

$$\Phi(t, \tilde{X}) \subset \tilde{G}, \quad t > \tau.$$

To prove the theorem we construct a Lyapunov functional on $\tilde{G}$. Let us denote by

$$\left(s_H, e_H^s, i_H, r_H, s_M, i_M\right)$$

the endemic equilibrium of (3), where each component is strictly positive. We define

$$c_1 := \frac{1}{\alpha i_M}(k_1 + k_2), \qquad c_2 := \left(\frac{\alpha s_H i_M}{e_H^s}\right)^{-1} \frac{\eta}{\eta + \xi}, \qquad c_3 := \left(\frac{\alpha s_H i_M}{i_H}\right)^{-1},$$

$$c_4 := \frac{1}{\beta i_H}(k_1 + k_2), \qquad c_5 := \left(\frac{\beta s_M i_H}{i_M}\right)^{-1} (k_1 + k_2),$$

where k_1 and k_2 are constants defined as

$$k_1 := p\frac{\eta}{\eta + \xi}, \ k_2 := (1 - p)\, e^{-\xi\tau}.$$

For $\phi = (f, q_2, q_3, q_4, q_5, g) \in \tilde{G}$, we consider the following functional:

$$V_e(\phi) := c_1 h\left(\frac{f(0)}{s_H}\right) + c_2 h\left(\frac{q_2}{e_H^s}\right) + c_3 h\left(\frac{q_3}{i_H}\right) + c_4 h\left(\frac{q_5}{s_M}\right) + c_5 h\left(\frac{g(0)}{i_M}\right) + k_2 U_e(\phi),$$

where

$$U_e(\phi) := \int_{-\tau}^{0} h\left(\frac{f(s)g(s)}{s_H i_M}\right) ds$$

and h is defined as in (7) in Section 3. We differentiate V_e with respect to t along the solution of (3). Since one has $\xi = \alpha s_H i_M + \xi s_H$ from the first equation of (3), we compute

$$\begin{aligned} \frac{d}{dt} h\left(\frac{s_H(t)}{s_H}\right) &= \frac{1}{s_H}\left(1 - \frac{s_H}{s_H(t)}\right)\left(\alpha s_H i_M + \xi s_H - \alpha s_H(t) i_M(t) - \xi s_H(t)\right) \\ &= \frac{1}{s_H}\left(1 - \frac{s_H}{s_H(t)}\right)\left\{\alpha s_H i_M\left(1 - \frac{s_H(t) i_M(t)}{s_H i_M}\right) + \xi s_H\left(1 - \frac{s_H(t)}{s_H}\right)\right\} \\ &= \frac{1}{s_H}\left\{\alpha s_H i_M\left(1 - \frac{s_H}{s_H(t)}\right)\left(1 - \frac{s_H(t) i_M(t)}{s_H i_M}\right) + \xi s_H\left(1 - \frac{s_H}{s_H(t)}\right)\left(1 - \frac{s_H(t)}{s_H}\right)\right\} \\ &= \alpha i_M\left(1 - \frac{s_H(t) i_M(t)}{s_H i_M} - \frac{s_H}{s_H(t)} + \frac{i_M(t)}{i_M}\right) + \xi\left(1 - \frac{s_H}{s_H(t)}\right)\left(1 - \frac{s_H(t)}{s_H}\right). \end{aligned} \tag{19}$$

From (3b), one has

$$0 = p\alpha s_H i_M - (\eta + \xi)\, e_H^s, \tag{20}$$

hence

$$\eta + \xi = \frac{p\alpha s_H i_M}{e_H^s}.$$

Then

$$\begin{aligned} \frac{d}{dt} h\left(\frac{e_H^s(t)}{e_H^s}\right) &= \frac{1}{e_H^s}\left(1 - \frac{e_H^s}{e_H^s(t)}\right)\left(p\alpha s_H(t) i_M(t) - p\alpha s_H i_M \frac{e_H^s(t)}{e_H^s}\right) \\ &= p\frac{\alpha s_H i_M}{e_H^s}\left(1 - \frac{e_H^s}{e_H^s(t)}\right)\left(\frac{s_H(t) i_M(t)}{s_H i_M} - \frac{e_H^s(t)}{e_H^s}\right) \\ &= p\frac{\alpha s_H i_M}{e_H^s}\left(\frac{s_H(t) i_M(t)}{s_H i_M} - \frac{e_H^s(t)}{e_H^s} - \frac{e_H^s}{e_H^s(t)}\frac{s_H(t) i_M(t)}{s_H i_M} + 1\right). \end{aligned} \tag{21}$$

From (3c), one can get

$$r+\xi=\frac{1}{i_H}\left\{\eta e_H^s+(1-p)\,\alpha e^{-\xi\tau}s_H i_M\right\}.$$

Then we obtain

$$\frac{di_H(t)}{dt}=\eta e_H^s\left(\frac{e_H^s(t)}{e_H^s}-\frac{i_H(t)}{i_H}\right)+(1-p)\,\alpha e^{-\xi\tau}s_H i_M\left(\frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M}-\frac{i_H(t)}{i_H}\right).$$

We compute

$$\begin{aligned}\frac{d}{dt}h\left(\frac{i_H(t)}{i_H}\right)&=\frac{1}{i_H}\left(1-\frac{i_H}{i_H(t)}\right)\left\{\eta e_H^s\left(\frac{e_H^s(t)}{e_H^s}-\frac{i_H(t)}{i_H}\right)+(1-p)\,\alpha e^{-\xi\tau}s_H i_M\left(\frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M}-\frac{i_H(t)}{i_H}\right)\right\}\\&=\frac{\eta e_H^s}{i_H}\left(1-\frac{i_H}{i_H(t)}\right)\left(\frac{e_H^s(t)}{e_H^s}-\frac{i_H(t)}{i_H}\right)\\&\quad+(1-p)\,\frac{\alpha e^{-\xi\tau}s_H i_M}{i_H}\left(1-\frac{i_H}{i_H(t)}\right)\left(\frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M}-\frac{i_H(t)}{i_H}\right).\end{aligned}$$

From (20), one finds that

$$\eta e_H^s=p\alpha s_H i_M\frac{\eta}{\eta+\xi}=\alpha s_H i_M k_1.$$

Therefore

$$\begin{aligned}\frac{d}{dt}h\left(\frac{i_H(t)}{i_H}\right)&=\frac{\alpha s_H i_M}{i_H}\left\{k_1\left(1-\frac{i_H}{i_H(t)}\right)\left(\frac{e_H^s(t)}{e_H^s}-\frac{i_H(t)}{i_H}\right)+k_2\left(1-\frac{i_H}{i_H(t)}\right)\left(\frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M}-\frac{i_H(t)}{i_H}\right)\right\}\\&=\frac{\alpha s_H i_M}{i_H}\left\{k_1\left(\frac{e_H^s(t)}{e_H^s}-\frac{i_H(t)}{i_H}-\frac{i_H}{i_H(t)}\frac{e_H^s(t)}{e_H^s}+1\right)\right.\\&\quad\left.+k_2\left(\frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M}-\frac{i_H(t)}{i_H}-\frac{i_H}{i_H(t)}\frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M}+1\right)\right\}.\end{aligned}$$

We now use $\mu=\beta s_M i_H+\mu s_M$ from (3e). Then

$$\begin{aligned}\frac{d}{dt}h\left(\frac{s_M(t)}{s_M}\right)&=\frac{1}{s_M}\left(1-\frac{s_M}{s_M(t)}\right)\left(\beta s_M i_H+\mu s_M-\beta s_M(t)i_H(t)-\mu s_M(t)\right)\\&=\frac{1}{s_M}\left(1-\frac{s_M}{s_M(t)}\right)\left\{\beta s_M i_H\left(1-\frac{s_M(t)i_H(t)}{s_M i_H}\right)+\mu s_M\left(1-\frac{s_M(t)}{s_M}\right)\right\}\\&=\beta i_H\left(1-\frac{s_M(t)i_H(t)}{s_M i_H}-\frac{s_M}{s_M(t)}+\frac{i_H(t)}{i_H}\right)+\mu\left(1-\frac{s_M}{s_M(t)}\right)\left(1-\frac{s_M(t)}{s_M}\right).\end{aligned}\tag{22}$$

Finally, from (3f) one has $0=\beta s_M i_H-\mu i_M$, thus

$$\mu=\frac{\beta s_M i_H}{i_M}$$

follows. Then

$$\begin{aligned}\frac{d}{dt}h\left(\frac{i_M(t)}{i_M}\right)&=\frac{1}{i_M}\left(1-\frac{i_M}{i_M(t)}\right)\left(\beta s_M(t)i_H(t)-\mu i_M(t)\right)\\&=\frac{1}{i_M}\left(1-\frac{i_M}{i_M(t)}\right)\left(\beta s_M(t)i_H(t)-\beta s_M i_H\frac{i_M(t)}{i_M}\right)\\&=\frac{\beta s_M i_H}{i_M}\left(1-\frac{i_M}{i_M(t)}\right)\left(\frac{s_M(t)i_H(t)}{s_M i_H}-\frac{i_M(t)}{i_M}\right)\\&=\frac{\beta s_M i_H}{i_M}\left(\frac{s_M(t)i_H(t)}{s_M i_H}-\frac{i_M(t)}{i_M}-\frac{i_M}{i_M(t)}\frac{s_M(t)i_H(t)}{s_M i_H}+1\right).\end{aligned}\tag{23}$$

Finally, we can compute that

$$\begin{aligned}\frac{d}{dt}U_e(x_t) &= h\left(\frac{s_H(t)i_M(t)}{s_H i_M}\right) - h\left(\frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M}\right)\\ &= \frac{s_H(t)i_M(t)}{s_H i_M} - \ln\left(\frac{s_H(t)i_M(t)}{s_H i_M}\right) - \frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M} + \ln\left(\frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M}\right)\\ &= \frac{s_H(t)i_M(t)}{s_H i_M} - \frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M} + \ln\left(\frac{s_H(t-\tau)i_M(t-\tau)}{s_H(t)i_M(t)}\right). \end{aligned} \tag{24}$$

From (19)–(24) we get

$$\begin{aligned}\frac{d}{dt}V_e(x_t) &= (k_1+k_2)\frac{\xi}{\beta i_M}\left(1-\frac{s_H}{s_H(t)}\right)\left(1-\frac{s_H(t)}{s_H}\right) + (k_1+k_2)\frac{\mu}{\beta i_H}\left(1-\frac{s_M}{s_M(t)}\right)\left(1-\frac{s_M(t)}{s_M}\right)\\ &\quad + (k_1+k_2)C_0(t) + k_1C_1(t) + k_2C_2(t),\end{aligned}$$

where

$$\begin{aligned}C_0(t) &= \left(1-\frac{s_H(t)i_M(t)}{s_H i_M} - \frac{s_H}{s_H(t)} + \frac{i_M(t)}{i_M}\right) + \left(1-\frac{s_M(t)i_H(t)}{s_M i_H} - \frac{s_M}{s_M(t)} + \frac{i_H(t)}{i_H}\right)\\ &\quad + \left(\frac{s_M(t)i_H(t)}{s_M i_H} - \frac{i_M(t)}{i_M} - \frac{i_M}{i_M(t)}\frac{s_M(t)i_H(t)}{s_M i_H} + 1\right),\\ C_1(t) &= \left(\frac{s_H(t)i_M(t)}{s_H i_M} - \frac{e_H^s(t)}{e_H^s} - \frac{e_H^s}{e_H^s(t)}\frac{s_H(t)i_M(t)}{s_H i_M} + 1\right) + \left(\frac{e_H^s(t)}{e_H^s} - \frac{i_H(t)}{i_H} - \frac{i_H}{i_H(t)}\frac{e_H^s(t)}{e_H^s} + 1\right),\end{aligned}$$

and

$$\begin{aligned}C_2(t) &= \left(\frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M} - \frac{i_H(t)}{i_H} - \frac{i_H}{i_H(t)}\frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M} + 1\right)\\ &\quad + \left(\frac{s_H(t)i_M(t)}{s_H i_M} - \frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M} + \ln\left(\frac{s_H(t-\tau)i_M(t-\tau)}{s_H(t)i_M(t)}\right)\right).\end{aligned}$$

One can respectively simplify $C_{0,1,2}(t)$ as

$$C_0(t) = \left(1-\frac{s_H(t)i_M(t)}{s_H i_M} - \frac{s_H}{s_H(t)}\right) + \left(1-\frac{s_M}{s_M(t)} + \frac{i_H(t)}{i_H}\right) + \left(-\frac{i_M}{i_M(t)}\frac{s_M(t)i_H(t)}{s_M i_H} + 1\right), \tag{25}$$

$$C_1(t) = \left(\frac{s_H(t)i_M(t)}{s_H i_M} - \frac{e_H^s}{e_H^s(t)}\frac{s_H(t)i_M(t)}{s_H i_M} + 1\right) + \left(-\frac{i_H(t)}{i_H} - \frac{i_H}{i_H(t)}\frac{e_H^s(t)}{e_H^s} + 1\right), \tag{26}$$

$$C_2(t) = \left(\frac{s_H(t)i_M(t)}{s_H i_M} - \frac{i_H(t)}{i_H} - \frac{i_H}{i_H(t)}\frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M} + 1\right) + \ln\left(\frac{s_H(t-\tau)i_M(t-\tau)}{s_H(t)i_M(t)}\right). \tag{27}$$

From (25)–(27) one can compute

$$\begin{aligned}(k_1+k_2)C_0(t) + k_1C_1(t) + k_2C_2(t) &= (k_1+k_2)\left\{\left(1-\frac{s_H}{s_H(t)}\right) + \left(1-\frac{s_M}{s_M(t)}\right) + \left(-\frac{i_M}{i_M(t)}\frac{s_M(t)i_H(t)}{s_M i_H} + 1\right)\right\}\\ &\quad + k_1\left\{\left(-\frac{e_H^s}{e_H^s(t)}\frac{s_H(t)i_M(t)}{s_H i_M} + 1\right) + \left(-\frac{i_H}{i_H(t)}\frac{e_H^s(t)}{e_H^s} + 1\right)\right\}\\ &\quad + k_2\left(-\frac{i_H}{i_H(t)}\frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M} + 1 + \ln\left(\frac{s_H(t-\tau)i_M(t-\tau)}{s_H(t)i_M(t)}\right)\right).\end{aligned}$$

Let us define

$$\begin{aligned}L(t) &:= (k_1+k_2)\left(\ln\left(\frac{s_H}{s_H(t)}\right) + \ln\left(\frac{s_M}{s_M(t)}\right) + \ln\left(\frac{i_M}{i_M(t)}\frac{s_M(t)i_H(t)}{s_M i_H}\right)\right)\\ &\quad + k_1\left(\ln\left(\frac{e_H^s}{e_H^s(t)}\frac{s_H(t)i_M(t)}{s_H i_M}\right) + \ln\left(\frac{i_H}{i_H(t)}\frac{e_H^s(t)}{e_H^s}\right)\right)\\ &\quad + k_2\left(\ln\left(\frac{i_H}{i_H(t)}\frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M}\right) - \ln\left(\frac{s_H(t-\tau)i_M(t-\tau)}{s_H(t)i_M(t)}\right)\right).\end{aligned}$$

We claim that $L(t) = 0$ holds. Indeed, one can calculate

$$\begin{aligned} L(t) &= (k_1+k_2)\ln\left(\frac{s_H}{s_H(t)}\frac{i_M}{i_M(t)}\frac{i_H(t)}{i_H}\right) + k_1\ln\left(\frac{s_H(t)i_M(t)}{s_H i_M}\frac{i_H}{i_H(t)}\right) + k_2\left\{\ln\left(\frac{i_H}{i_H(t)}\right) + \ln\left(\frac{s_H(t)i_M(t)}{s_H i_M}\right)\right\} \\ &= k_2\left\{\ln\left(\frac{s_H}{s_H(t)}\frac{i_M}{i_M(t)}\frac{i_H(t)}{i_H}\right) + \ln\left(\frac{i_H}{i_H(t)}\right) + \ln\left(\frac{s_H(t)i_M(t)}{s_H i_M}\right)\right\} \\ &= 0. \end{aligned}$$

Therefore, we obtain

$$\begin{aligned} (k_1+k_2)C_0(t) + k_1C_1(t) + k_2C_2(t) &= (k_1+k_2)C_0(t) + k_1C_1(t) + k_2C_2(t) + L(t) \\ &= -(k_1+k_2)\left\{h\left(\frac{s_H}{s_H(t)}\right) + h\left(\frac{s_M}{s_M(t)}\right) + h\left(\frac{i_M}{i_M(t)}\frac{s_M(t)i_H(t)}{s_M i_H}\right)\right\} \\ &\quad - k_1\left\{h\left(\frac{e_H^s}{e_H^s(t)}\frac{s_H(t)i_M(t)}{s_H i_M}\right) + h\left(\frac{i_H}{i_H(t)}\frac{e_H^s(t)}{e_H^s}\right)\right\} \\ &\quad - k_2 h\left(\frac{i_H}{i_H(t)}\frac{s_H(t-\tau)i_M(t-\tau)}{s_H i_M}\right) \\ &\le 0. \end{aligned}$$

Thus it follows that $\frac{d}{dt}V_e(x_t) \le 0$. If x_0 is the function identically equal to the endemic equilibrium, then obviously $x_t = \left(\hat{s_H}, e_H^s, i_H, r_H, s_M, \hat{i_M}\right)$ for $t > 0$. Let us assume that x_t is not identically equal to the endemic equilibrium. Then there exists $c > 0$ such that $c = V_e(x_{t_0})$ for some $t_0 > \tau$. We define

$$G_c := \left\{\phi \in \tilde{G} | V_e(\phi) \le c = V_e(x_{t_0})\right\}.$$

We see that G_c is closed and positively invariant, thus the closure of G_c is itself and G_c contains x_t for all $t \ge t_0$. Since V_e is continuous on G_c, V_e is a Lyapunov functional on G_c, see Chapter 5.3 in [15]. We define the set

$$\Sigma := \left\{\phi \in G_c | \dot{V}_{e(3)}(\phi) = 0\right\}.$$

We obtain

$$\Sigma = \left\{\phi \,\middle|\, \begin{array}{l} f(0) = s_H,\ q_5 = s_M, \\ \dfrac{q_2}{e_H^s} = \dfrac{q_3}{i_H} = \dfrac{g(0)}{i_M} = \dfrac{f(-\tau)g(-\tau)}{s_H i_M} \end{array}\right\}.$$

Let L be the largest subset in Σ that is invariant with respect to (3). One can see that L is the set of initial functions satisfying

$$0 = \frac{ds_M(t)}{dt} = \mu - \beta s_M i_H(t) - \mu s_M,$$

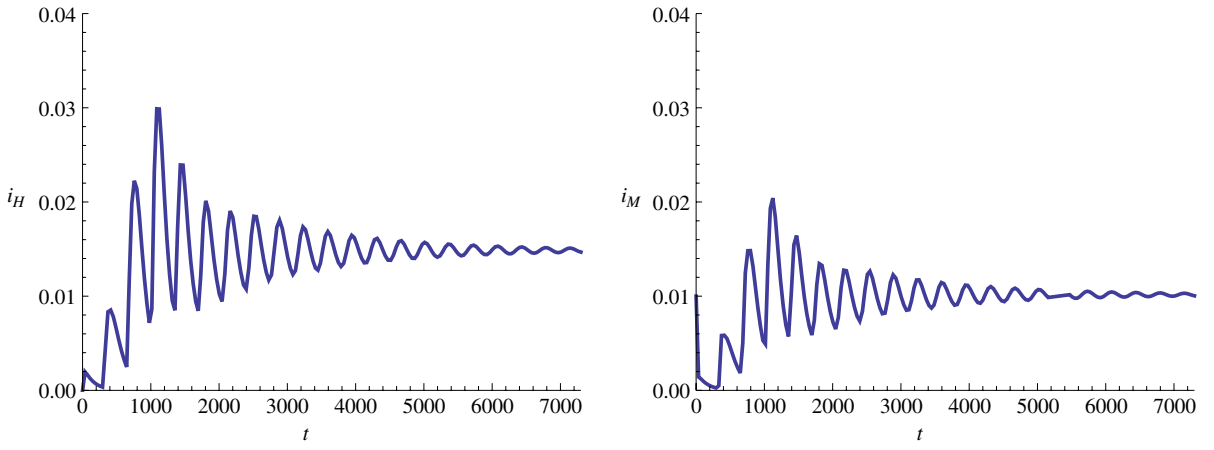
for any t, thus one can identify the element $(f, q_2, q_3, q_4, q_5, g) \in L$ as $q_3 = i_H$. Then we get $q_2 = e_H^s$ and $g(0) = i_M$. Next one can see that

$$\begin{aligned} \frac{ds_H(t)}{dt} &= \xi - \alpha s_H i_M - \xi s_H = 0, \\ \frac{di_M(t)}{dt} &= \beta s_M i_H - \mu i_M = 0, \end{aligned}$$

thus $f(\theta) = s_H$ and $g(\theta) = i_M$ for every $\theta \in [-\tau, 0]$. Then, by LaSalle's invariance principle, see Theorem 3.1 in [15], we conclude that the solution tends to the endemic equilibrium of (3). Since for every solution we can choose such a c, the positive equilibrium is globally attractive. Similarly as we mentioned in the proof of Theorem 1, for the stability of the endemic equilibrium, one can compute the characteristic equation and show that if $R_0 > 1$ and $\omega = 0$ hold, then all roots of the characteristic equation have negative real parts. Thus the endemic equilibrium is globally asymptotically stable. □

5. Discussion

We have analyzed a malaria transmission model that features two distinct exposed classes in human population, the class having short-term incubation period and the class having long-term incubation period. Short-term incubation period is modeled by exponential distribution, while it is assumed that the long-term incubation period has fixed length, to capture the characteristics of the empirically observed distribution of incubation periods in temperate regions for *P. vivax*. The



(a) Infectious human dynamics.

(b) Infectious mosquito dynamics.

Fig. 2. Solution of system (3) with initial condition $s_H(t) = 1$ and $s_M(t) = 1$ for $t < 0$, $(s_H, e_H^s, e_H^l, i_H, r_H, s_M, i_M)(0) = (1, 0, 0, 0, 0, 0.09, 0.01)$. We observe that the solution converge to the endemic equilibrium. Parameter values are $\xi = 0.00004$, $p = 0.25$, $a = 0.3$, $b = 0.5$, $c = 0.23$ $\tau = 330$, $\eta = 0.04$, $\mu = 0.1$, $r = 0.07$, $m = 2$ and $\omega = 1/365$, obtained from empirical observation in Korea, see [14].

basic reproduction number, R_0 was identified from model parameters. When $R_0 \leq 1$, it was shown that the disease-free equilibrium is globally attractive, which means the disease dies out. When $R_0 > 1$, the disease uniformly persists. Moreover, in the special case of lifelong immunity, the endemic equilibrium is globally asymptotically stable. We observe from numerical simulations that the solutions converge to the endemic equilibrium also in the case without the specific assumption of lifelong immunity (see Fig. 2).

From (6), we observe that R_0 increases with respect to p if $\frac{\eta}{\eta+\xi} > e^{-\xi\tau}$, and decreases with respect to p otherwise. In reality, it is natural to assume that the average short incubation time is less than the length of long term incubation time, i.e., $\frac{1}{\eta} < \tau$. With this restriction, we have

$$\frac{\eta}{\eta+\xi} = \frac{1}{1+\frac{\xi}{\eta}} > \frac{1}{1+\xi\tau} > e^{-\xi\tau},$$

which leads to the conclusion that R_0 is an increasing function of p. Note that R_0 will be overestimated if we ignore the long term incubation period in modeling. It further indicates that for parasites, inducing long term incubation period in humans is not beneficial for their reproduction. The observed bimodality of the incubation periods suggests that an another underlying mechanism plays a role, possibly seasonal effects, which are relevant in malaria transmission in Korea [4].

It is known that *hypnozoites* are responsible for late relapses in *P. vivax* infections as well as long incubation. Some previous studies considered relapse in the transmission model [18–20]. For future works on more realistic *P. vivax* transmission modeling, the effect of multiple blood stage infections and seasonality is a natural next step to be investigated. However, both has its inherent difficulties (such as analysis of time periodic delay differential equations). Our study shows that it is possible to perform a rigorous mathematical analysis when the basic malaria transmission model is extended to include short and long term incubation in humans, thus it is a step toward more realistic *P. vivax* models in the future.

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