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A MATHEMATICAL MODEL OF TRANSMISSION OF PLASMODIUM VIVAX MALARIA WITH A CONSTANT TIME DELAY FROM INFECTION TO INFECTIOUS

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Abstract. This research is focused on a continuous epidemic model of transmission of *Plasmodium vivax* malaria with a time delay. The model is represented as a system of ordinary differential equations with delay. There are two equilibria, which are the disease-free state and the endemic equilibrium, depending on the basic reproduction number, R_0, which is calculated and decreases with the time delay. Moreover, the disease-free equilibrium is locally asymptotically stable if $R_0 < 1$. If $R_0 > 1$, a unique endemic steady state exists and is locally stable. Furthermore, Hopf bifurcation is applied to determine the conditions for periodic solutions.

1. Introduction

Malaria is a major public health problem in many countries. The malaria disease is due to a protozoan parasite from the genus *Plasmodium*, and is transmitted by infected *Anopheles* mosquitoes. Moreover, the malaria parasite can be found in several types of mammals. Malaria in humans is caused by four types of malaria parasites: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae* and *Plasmodium ovale* [5]. Most deaths from malaria are due to *Plasmodium falciparum* [15]. However, in this research, we focus on the type of malaria caused by *Plasmodium vivax*, since the resulting cases can present a latent infection (apparent recovery) and a subsequent relapse. In other words, a patient formerly infected by *Plasmodium vivax* can appear cured but may become infected again without any mosquito bites.

The *Plasmodium vivax* has a more complicated life cycle than the other malaria parasites. After an infected mosquito bites a human, *Plasmodium vivax* malaria is generated in the bloodstream in the sporozoite form. The sporozoites move to the liver and their cells divide generating merozoite and hypnozoite forms. Illness occurs when the merozoites invade the red blood cells. The clinical symptoms include fever, pain, chills, and sweats. Furthermore, the

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hypnozoites lay dormant in the liver and cause no symptoms. However, if the patient is weak, the hypnozoites evolve to merozoites, and the patient again will suffer the symptoms. This behavior is unique to *Plasmodium vivax* [10].

For several decades, numerous mathematical models have been developed and applied to comprehensively describe the transmission of malaria in human populations. One of the first well-known models was created by Ross [1, 19] who investigated the *Plasmodium falciparum* malaria. Ross constructed an uncomplicated model in the form of ordinary differential equations, in which the human population is divided into susceptible and infected compartments.

The first mathematical model to describe the transmission of *Plasmodium vivax* is in [8]. In this research, the human population was partitioned into four categories, namely susceptible, infected, dormant and recovered populations. The work focused on the basic reproduction number, R_0, as an indicator of equilibrium. Furthermore, two equilibrium points were obtained, for the disease-free and the endemic states. However, the stability analysis was not explored in this work. Subsequently, in order to pursue stability analysis, Kammanee [7] developed a mathematical model of transmission of *Plasmodium vivax* malaria where the human population is divided into three categories, with susceptible, infected and dormant disease statuses. Moreover, the mosquitoes, acting as disease vectors, fall into two classes: susceptible and infected mosquitoes. The chief assumption of this model is that an infected patient infects a susceptible mosquito when it bites. The basic reproduction number was also investigated. Two equilibrium points, for the disease-free and the endemic states, were also obtained, now with the stability analysis determined by R_0.

Later, Huo and Qiu [6] constructed a mathematical model of malaria transmission with relapse. The basic reproduction number was computed by the next generation matrix method. Moreover, the disease-free equilibrium was proved to be globally asymptotically stable if $R_0 \leq 1$, and the system was uniformly persistent if $R_0 > 1$.

The aforementioned models have however not been taken into account the time delay nature of a disease transmission. For malaria transmission, in general, there are two categories of time delay which can be introduced in a model. The first time delay is due to the extrinsic incubation period which occurs in mosquitoes. This is time taken the parasites to produce sporozoites and move to the mosquito's salivary glands. The second one is the intrinsic incubation period in the patients which is the period that sporozoites relocate to the liver of the patient and engender merozoites and hypnozoites, see [13]. One of the best work on the time delay in disease transmission is that of Wei et al. [23] who have formulated an epidemic model of a vector-borne disease with time delay. The basic reproduction number was assessed as an indicator of equilibrium stability. Furthermore, periodic solutions were considered through Hopf bifurcations.

Hence, for a reasonable malaria model, time delay should be taken into account. There are mathematical models of malaria with time delay in literature,

for example, Chamchod and Britton [2] focused on a dynamical system for *Plasmodium falciparum* malaria which includes the extrinsic incubation period in the model. Later, Wan and Cui [21] have constructed a mathematical model of *Plasmodium falciparum* malaria with two time delays, namely the extrinsic and intrinsic incubation period. They found that the basic reproduction number decreases with the two time delays. In addition, Wang and Zhao [22] presented a malaria model which takes into account the climate factors, the extrinsic incubation period, and the vector-bias effect.

For *Plasmodium vivax* malaria, Pongsumpun and Tang [18] have studied a mathematical model for *Plasmodium vivax* malaria with a constant delay in the mosquito compartment. Two equilibrium points, which are the disease-free state and the endemic state, were found. Furthermore, the numerical simulations showed limit cycles.

The aim of our work is to explore the inclusion of time delay in the human compartment. Based on the model of [7], we shall introduce the intrinsic incubation period to the model. As we shall see later, this has a beneficial feature of the existence of a period solution, which was not found in the model presented in [7], without time delay. The periodic behavior in the transmission of *Plasmodium vivax* malaria is evidenced in the work of Kwak et al. [11] who have found that the number of patients is most commonly high in July and August during 2005–2009.

In order to improve the model, we apply an intrinsic incubation period to a model. This paper consists of five sections. In the next section, a mathematical model of *Plasmodium vivax* malaria with delay is constructed. The existence and uniqueness of equilibria are considered in Section 3. Moreover, the Hopf bifurcation analysis is also employed in this section. In order to demonstrate some theorems in Section 3, the numerical examples are presented in Section 4. Finally, in the last section, we provide some conclusion and discussion.

2. Mathematical model

In this section, we construct a mathematical model in order to study effects of the incubation period in human on the basic reproduction number. The model is based on SIRS for the human population and SI for the mosquito population, so we create an SIRS-SI model for the transmission of *Plasmodium vivax* malaria. In our model for the transmission of *Plasmodium vivax*, the host population (N_h) is divided into three compartments: susceptible (S'_h), infected (I'_h) and dormant (D'_h) population. Due to the fact that the immune system of a human can eliminate the disease, dormant cases can transform to susceptible. Infected cases can become dormant when the hypnozoites lie latently in the liver. Moreover, the mosquito vector population comprises two categories: susceptible (S'_v) and infected (I'_v). An infected mosquito is a carrier transmitting the pathogen into susceptible human population. We also assume that a new bite by an infected vector (mosquito) is unable to transform person

in the dormant compartment to an infected case. Moreover, an uninfected vector cannot become an infected mosquito by biting a person in the dormant group [7, 8, 18]. Furthermore, some infected patients can become susceptible (cured) when treated by doctors.

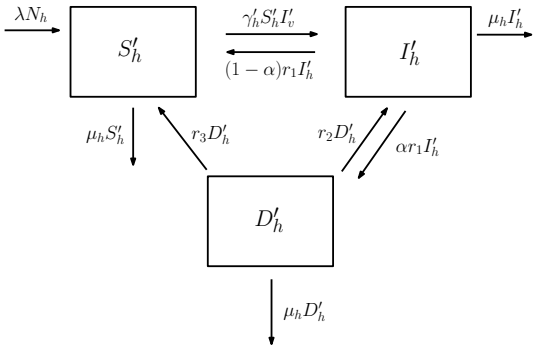

FIGURE 1. Flows in a compartmental model for the transmission of *Plasmodium vivax* malaria

A flowchart of the transmission of *Plasmodium vivax* is shown in Figure 1. The balance equation requires that the rate of change for any compartment is the rate of entering it minus the rate of leaving it (there is no internal generation, positive or negative). In the model, we assume that all parameters are nonnegative real numbers: λ is the natural birth rate; μ_h is the natural mortality rate; r_1 is the rate at which a person in the dormant category transforms to infected (without a bite); r_2^{-1} is the average life time for the parasite producing the illness; is the rate at which the immunity system can erase all parasites in the liver. Finally α is the probability of an infected patient becoming susceptible. Now we focus on the parameter γ'_h, which is the transmission rate at which the *Plasmodium vivax* parasite is contracted from an infected mosquito by a susceptible person. In 1998, Esteva et al. [4] have defined as

$$\gamma'_h = b\frac{\beta_h}{N_h + p}, \tag{1}$$

where b is the mean count of bites per mosquito per time; p is the population count of other animal species that the mosquito can feed on; and β_h is the probability that *Plasmodium vivax* goes to the blood stream on mosquito bite and thrives in the human.

We introduced a time delay into the model in [7], to represent the incubation time in humans, τ. A susceptible individual infected by a mosquito will not become infectious until τ time units later. During the incubation period, we assume that the human cannot recover. The term $e^{-\mu_h \tau}$ expresses the probability

of survival of the population during incubation phase, see [14]. Therefore, the incidence term of infectious mosquitoes is modified to $\gamma_h' I_v'(t-\tau)S_h'(t-\tau)e^{-\mu_h \tau}$.

From above assumptions, the model is

$$\frac{dS_h'}{dt} = \lambda N_h + (1-\lambda) r_1 I_h' + r_3 D_h' - \gamma_h' I_v'(t-\tau) S_h'(t-\tau) e^{-\mu_h \tau} - \mu_h S_h', \tag{2}$$

$$\frac{dI_h'}{dt} = \gamma_h' I_v'(t-\tau) S_h'(t-\tau) e^{-\mu_h \tau} + r_2 D_h' - (\mu_h + r_1) I_h', \tag{3}$$

$$\frac{dD_h'}{dt} = \alpha r_1 I_h' - (\mu_h + r_2 + r_3) D_h', \tag{4}$$

$$\frac{dS_v'}{dt} = A - \gamma_v' S_v' I_h' - \mu_v S_v', \tag{5}$$

$$\frac{dI_v'}{dt} = \gamma_v' S_v' I_h' - \mu_v I_v'. \tag{6}$$

The female *Anopheles* lays abundant eggs giving birth to larvae; however, only a small number of the larvae develop adults. Thus the recruitment rate A is not equal to $\lambda_v N_v$, where λ_v is the natural birth rate of mosquitoes and N_v is the number of mosquitoes. Moreover, γ_v' is the transmission rate at which susceptible mosquitoes biting an infected human become infected carrier vectors.

At the equilibrium state, we found that $N_v = \frac{A}{\mu_v}$. Now we normalize all variables as $S_h = \frac{S_h'}{N_h}$, $I_h = \frac{I_h'}{N_h}$, $D_h = \frac{D_h'}{N_h}$, $S_v = \frac{S_v' \mu_v}{A}$ and $I_v = \frac{I_v' \mu_v}{A}$. For biological reasons, the solutions must be non-negative. Then the domain of the solutions is

$$\Lambda = \{(S_h, I_h, D_h, S_v, I_v) \in \mathbf{R}_+^5 \mid S_h + I_h + D_h = 1 \text{ and } S_v + I_v = 1\}, \tag{7}$$

where $\mathbf{R}_+^5$ denoted the non-negative cone of $\mathbf{R}^5$. Since the right-hand sides of (2)-(6) are continuous, the unique solution exists on the domain.

Due to (7), our model equations (2)-(6) correspond to the dynamical system

$$\begin{aligned} \frac{dI_h}{dt} &= \gamma_h I_v(t-\tau)(1 - I_h(t-\tau) - D_h(t-\tau)) e^{-\mu_h \tau} + r_2 D_h \\ &\quad - (\mu_h + r_1) I_h, \end{aligned} \tag{8}$$

$$\frac{dD_h}{dt} = \alpha r_1 I_h - (\mu_h + r_2 + r_3) D_h, \tag{9}$$

$$\frac{dI_v}{dt} = \gamma_v S_v I_h - \mu_v I_v. \tag{10}$$

The solutions for S_h and S_v are given by $S_h = 1 - I_h - D_h$ and $S_v = 1 - I_v$, respectively.

The reproduction number or the contact number [14, 23] is defined by

$$R_0 = \frac{(\mu_h + r_2 + r_3)\gamma_h \gamma_v \mathrm{e}^{-\mu_h \tau}}{\mu_v[(r_1 + \mu_h)(\mu_h + r_2 + r_3) - \alpha r_1 r_2]}. \tag{11}$$

It is the average number of secondary infections that a single infectious individual generates in a susceptible population of hosts and vectors. To see this notice that $\frac{\mu_h+r_2+r_3}{(r_1+\mu_h)(\mu_h+r_2+r_3)-\alpha r_1 r_2}$ is the average time that a patient is infectious. Moreover, $\gamma_v \frac{\mu_h+r_2+r_3}{(r_1+\mu_h)(\mu_h+r_2+r_3)-\alpha r_1 r_2}$ is the average rate of a susceptible mosquito being infected by biting an infectious person. Due to the incubation period τ in humans, during which some of them may die, a single infected mosquito can transmit the illness to $\gamma_h e^{-\mu_h \tau}/\mu_v$ hosts. Hence, the total number of secondary cases is the basic reproduction number $R_0 = \frac{(\mu_h+r_2+r_3)\gamma_h\gamma_v e^{-\mu_h\tau}}{\mu_v[(r_1+\mu_h)(\mu_h+r_2+r_3)-\alpha r_1 r_2]}$.

3. Existence and uniqueness of equilibria

Let $E = (I_h^*, D_h^*, I_v^*)$ be an equilibrium point of the model. In order to obtain an equilibrium point, the right-hand sides in (8)-(10) are set to zero (at equilibrium the rates of change are null). Now we have

$$D_h^* = \frac{\alpha r_1}{\mu_h + r_2 + r_3} I_h^* \quad \text{and} \quad I_v^* = \frac{\gamma_v}{\gamma_v I_h + \mu_v} I_h^*,$$

where I_h^* is computed as

$$\begin{aligned} &\gamma_h e^{\mu_h \tau} \left(\frac{\gamma_v I_h^*}{\gamma_v I_h^* + \mu_v} \right) \left(1 - I_h^* - \frac{\alpha r_1 I_h^*}{\mu_h + r_2 + r_3} \right) \\ &+ r_2 I_h^* \left(\frac{\alpha r_1}{\mu_h + r_2 + r_3} \right) - (\mu_h + r_1) I_h^* = 0. \end{aligned} \tag{12}$$

It is clear that there are two solutions to (12). One of them is $I_h^* = 0$ giving the disease-free equilibrium $E_0 = (0, 0, 0)$. If $I_h^* \neq 0$, then we obtain the endemic state $E_1 = (I_h^*, D_h^*, I_v^*)$ where

$$I_h^* = \frac{R_0 - 1}{R_0 M}$$

with $M = 1 + \frac{\alpha r_1(\gamma_h - r_2 e^{-\mu_h \tau})}{\gamma_h(\mu_h+r_2+r_3)} + \frac{(\mu_h+r_1)e^{-\mu_h\tau}}{\gamma_h}$.

3.1. Local stability of the disease-free state

In this section, we focus on the local stability of the disease-free equilibrium E_0 from the delay differential equation model.

Theorem 3.1. *If $R_0 < 1$, then the disease-free equilibrium E_0 is locally asymptotically stable. Moreover, the disease-free equilibrium is unstable if $R_0 > 1$.*

Proof. For $\tau = 0$, the proof has already been given in [7]. Therefore, we only consider the case $\tau > 0$. First, assume that $R_0 > 1$. Linearizing the system (8)-(10) about E_0, the characteristic equation is

$$\begin{aligned} \lambda^3 + a_1\lambda^2 + a_2\lambda &= \mu_v[\alpha r_1 r_2 - (\mu_h + r_1)(\mu_h + r_2 + r_3)] \\ &\quad + [\gamma_v\gamma_h\lambda e^{-\mu_h\tau} + \gamma_v\gamma_h(\mu_h + r_2 + r_3)e^{-\mu_h\tau}]e^{-\lambda\tau}, \end{aligned} \tag{13}$$

where

$$a_1 = (\mu_h + r_2 + r_3) + \mu_v - (\mu_h + r_1),$$
$$a_2 = (\mu_h + r_1)(\mu_h + r_2 + r_3) + (\mu_h + r1)\mu_v + (\mu_h + r_2 + r_3)\mu_v - \alpha r_1 r_2.$$

We have to show that one solution to the characteristic equation is positive. We assume that λ is real. Denote the left-hand side of (13) by $F_1(\lambda)$ and the right-hand side by $G_1(\lambda)$. We can see that $F_1(0) = 0$ and $\lim_{\lambda\to\infty} F_1(\lambda) = \infty$. Next, it is clear that $G_1(0) = (R_0 - 1)\mu_v[(\mu_h + r_1)(\mu_h + r_2 + r_3) - \alpha r_1 r_2] > 0$ and $G_1(\lambda)$ decreases with λ. Therefore for some $\lambda = \widehat{\lambda} > 0$, graphs of the two functions must intersect, by the intermediate value theorem applied from 0 to some large value. Hence, at least one solution to (13) is positive, and the disease-free state is unstable when $R_0 > 1$.

Now we focus on the case $R_0 < 1$. Since $F_1(\lambda)$ is an increasing function for $\lambda \geq 0$ while $G_1(\lambda)$ is decreasing with $G_1(0) < 0$, the graphs cannot intersect with $\lambda > 0$. Hence, equation (13) does not have a non-negative real root. There are two possible cases for the roots of (13). The first one is that all roots are negative real numbers, and the other is having a pair of complex conjugate roots. In the first case, the disease-free state is stable. In the case of complex conjugate roots, this pair must cross the imaginary axis to provide non-negative real parts. Therefore, the characteristic equation (13) must have a pair of purely imaginary solutions for some $\tau > 0$. Without loss of generality, we assume that $\omega > 0$ and let $\lambda = i\omega$ be a root of (13). Thus we have

$$-\omega^3 i - a_1\omega^2 + a_2\omega i - \mu_v[\alpha r_1 r_2 - (\mu_h + r_1)(\mu_h + r_2 + r_3)]$$
$$- [\gamma_v\gamma_h \mathrm{e}^{-\mu_h\tau}\omega i + \gamma_v\gamma_h(\mu_h + r_2 + r_3)\mathrm{e}^{-\mu_h\tau}]\mathrm{e}^{-\lambda\tau}[\cos\omega\tau + i\sin\omega\tau] = 0.$$

Considering the real and imaginary parts, we get the following equations:

$$-\omega^3 + a_2\omega = \omega\gamma_h\gamma_v\mathrm{e}^{-\mu_h\tau}\cos(\omega\tau) - \gamma_h\gamma_v(\mu_v + r_2 + r_3)\mathrm{e}^{-\mu_h\tau}\sin(\omega\tau), \tag{14}$$

$$-a_1\omega^2 - \mu_v[\alpha r_1 r_2 - (\mu_h + r_1)(\mu_h + r_2 + r_3)] = \omega\gamma_h\gamma_v\mathrm{e}^{-\mu_h\tau}\sin(\omega\tau) + \gamma_h\gamma_v(\mu + r_2 + r_3)\mathrm{e}^{-\mu_h\tau}\cos(\omega\tau). \tag{15}$$

To get rid of the trigonometric functions, we square both sides of each equation and then add them together, to get an equation with a polynomial of degree six in ω:

$$\omega^6 + (a_1^2 - 2a_2)\omega^4$$
$$+ [a_2^2 + 2a_1\mu_v(\alpha r_1 r_2 - (\mu_h + r_1)(\mu_h + r_2 + r_3)) - \gamma_h^2\gamma_v^2\mathrm{e}^{-2\mu_h\tau}]\omega^2$$
$$+ \mu_v^2[\alpha r_1 r_2 - (\mu_h + r_1)(\mu_h + r_2 + r_3)]^2 - \gamma_h^2\gamma_v^2(\mu_h + r_2 + r_3)^2\mathrm{e}^{-2\mu_h\tau} = 0.$$

Let $z = \omega^2$ and the above equation becomes

$$z^3 + b_1 z^2 + b_2 z + b_3 = 0, \tag{16}$$

where

$$b_1 = (a_1^2 - 2a_2),$$
$$b_2 = [a_2^2 + 2a_1\mu_v(\alpha r_1 r_2 - (\mu_h + r_1)(\mu_h + r_2 + r_3)) - \gamma_h^2\gamma_v^2 \mathrm{e}^{-2\mu_h\tau}],$$
$$b_3 = \mu_v^2[\alpha r_1 r_2 - (\mu_h + r_1)(\mu_h + r_2 + r_3)]^2 - \gamma_h^2\gamma_v^2(\mu_h + r_2 + r_3)^2\mathrm{e}^{-2\mu_h\tau},$$
$$= \mu_v^2[\alpha r_1 r_2 - (\mu_h + r_1)(\mu_h + r_2 + r_3)]^2(1 - R_0^2).$$

Since $R_0 < 1$, it is easy to see that b_1, b_2 and $b_3 > 0$. By Descartes' rule of signs, equation (16) has no positive real root. Moreover, since, by direct computation we can show that $b_1b_2 - b_3 > 0$, by the Routh-Hurwitz criteria equation (16) has complex conjugate roots with negative real parts. Therefore, there is no real ω with $i\omega$ a solution of the characteristic equation (13). By Rouché's theorem [12], the real parts of all the roots of the characteristic equation are negative, for any value of the delay $\tau \geq 0$. We deduce that the disease-free state is asymptotically locally stable if $R_0 < 1$. □

3.2. Local stability of the endemic state

In this section, we assume that $R_0 > 1$, and show that an endemic equilibrium exits. Furthermore, we will also demonstrate a Hopf bifurcation by using the time delay τ as the bifurcation parameter. Like for the disease-free state, we linearize the model (8)-(10) about the point E_1. The characteristic equation is

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = -e^{-\lambda\tau}(a_4\lambda^2 + a_5\lambda + a_6), \tag{17}$$

where

$$a_1 = (\mu_h + r_1) + (\mu_h + r_2 + r_3) + (\gamma_v I_h^* + \mu_v),$$
$$a_2 = (\mu_h + r_1)(\mu_h + r_2 + r_3 + \gamma_v I_h^* + \mu_v) + (\mu_h + r_2 + r_3)(\gamma_v I_h^* + \mu_v) - \alpha r_1 r_2,$$
$$a_3 = ((\mu_h + r_1)(\mu_h + r_2 + r_3) - \alpha r_1 r_2(\gamma_v I_h^* + \mu_v),$$
$$a_4 = -\gamma_h I_h^* \mathrm{e}^{-\mu_h\tau},$$
$$a_5 = (1 - I_h^* - D_h^*)(1 - I_v^*)\mathrm{e}^{-\mu_h\tau} - \alpha r_1\gamma_h I_h^*\mathrm{e}^{-\mu_h\tau} - a_4[(\mu_h + r_2 + r_3) + (\gamma_v I_h^* + \mu_v)],$$
$$a_6 = (\mu_h + r_2 + r_3)(1 - I_h^* - D_h^*)(1 - I_v^*)\mathrm{e}^{-\mu_h\tau} - \alpha r_1\gamma_h I_h^* e - \mu_h\tau(\gamma_v I_h^* + \mu_v) - a_4(\mu_h + r_2 + r_3)(\gamma_v I_h^* + \mu_v).$$

In the case $\tau = 0$, the proof is available in [7], so here we consider the case $\tau > 0$. We restate equation (17) by moving the positive terms on the right-hand side to the left-hand side. Then, we obtain:

$$\lambda^3 + a_1\lambda^2 + \overline{a}_2\lambda + \overline{a}_3 = \mathrm{e}^{\lambda\tau}(a_4\lambda^2 + \overline{a}_5\lambda + \overline{a}_6), \tag{18}$$

where

$$\overline{a}_2 = a_2 - \mathrm{e}^{\lambda\tau}(1 - I_h^* - D_h^*)(1 - I_v^*)\mathrm{e}^{-\mu_h\tau},$$

$$\overline{a}_3 = a_3 - \mathrm{e}^{\lambda\tau}(\mu_h + r_2 + r_3)(1 - I_h^* - D_h^*)(1 - I_v^*)\mathrm{e}^{-\mu_h\tau},$$
$$\overline{a}_5 = a_5 - \mathrm{e}^{\lambda\tau}(1 - I_h^* - D_h^*)(1 - I_v^*)\mathrm{e}^{-\mu_h\tau},$$
$$\overline{a}_6 = a_6 - \mathrm{e}^{\lambda\tau}(\mu_h + r_2 + r_3)(1 - I_h^* - D_h^*)(1 - I_v^*)\mathrm{e}^{-\mu_h\tau}.$$

It is clear that $a_1 > 0$, $\overline{a}_2 >$ and $\overline{a}_3 > 0$ for all $\lambda \geq 0$. Let $F_2(\lambda)$ be the left-hand side of (18) and $G_2(\lambda)$ be its right-hand side. Since, $F_2(\lambda) > 0$ for all $\lambda \geq 0$ while $G_2(\lambda) < 0$ for all $\lambda \geq 0$, there is no intersection point for $\lambda \geq 0$. Hence, there are no non-negative real roots. Now we assume that the solution of (17) is pure imaginary, say, $\lambda = i\omega$ with $\omega > 0$. Substituting $\lambda = i\omega$ in (17), we obtain

$$-i\omega^3 - a_1\omega^2 + a_2\omega i + a_3 = (-a_2\omega^2 + ia_5\omega + a_6)(\cos(\omega\tau) + i\sin(\omega\tau)). \tag{19}$$

Separating the real and imaginary parts, we have

$$a_2\omega - \omega^3 = a_5\omega\cos(\omega\tau) - (a_6 - a_4\omega^2)\sin(\omega\tau), \tag{20}$$

$$a_3 - a_1\omega^2 = (a_6 - a_4\omega^2)\cos(\omega\tau) + a_5\omega\sin(\omega\tau). \tag{21}$$

In order to eliminate the trigonometric terms, we square these equations and then sum them together. This gives a polynomial in ω of degree six:

$$\omega^6 + (a_1^2 - 2a_2 - a_4^2)\omega^4 + (a_2^2 - 2a_1a_3 + 2a_4a_6 - a_5^2)\omega^2 + (a_3^2 - a_6^2) = 0. \tag{22}$$

By setting $z = \omega^2$, we can reduce the degree of polynomial equation. Then we have

$$h(z) = z^3 + b_1z_2^2 + b_2z + b_3 = 0, \tag{23}$$

where

$$b_1 = a_1^2 - 2a_2 - a_4^2,$$
$$b_2 = a_2^2 - 2a_1a_3 + 2a_4a_6 - a_5^2,$$
$$b_3 = a_3^2 - a_6^2.$$

In order to prove that the endemic state E_1 is locally stable, we must demonstrate that there is no positive solution for equation (23).

Lemma 3.2. *If one of the following conditions holds*:

(1) $b_1 \geq 0$, $b_2 \geq 0$ *and* $b_3 \geq 0$,

(2) $b_3 \geq 0$ *and* $h(z_1) > 0$ *where* $z_1 = \frac{-b_1 + \sqrt{b_1^2 - 3b_2}}{3}$,

then there is no positive root of the equation (23).

Proof. If the first condition holds, then the proof is clear by applying Descartes' rule of signs. Next we consider the case with the second condition is satisfied. The y-intercept is $(0, b_3)$, which is above the x-axis, and the local minimum point $(z_1, h(z_1))$ is also above the x-axis. Therefore, there is no x-intercept at any $x > 0$. □

If the coefficients in (23) satisfy assumptions of the above Lemma, there is no root $i\omega$ for (17). Therefore, the real parts of all the eigenvalues of (17) are negative, for any $\tau \geq 0$ by Rouché's theorem [12]. Therefore, we get the following theorem.

Theorem 3.3. *If $R_0 > 1$ and the hypothesis of Lemma 3.2 is satisfied, then the endemic equilibrium E_1 is asymptotically local stable for all $\tau \geq 0$.*

3.3. Hopf bifurcation analysis

By Theorem 3.3, it is clear that if all parameters satisfy the conditions in Lemma 3.2, then the endemic state is asymptotically stable for any time delay. Nevertheless, if the conditions are not satisfied, then stability of the endemic equilibrium may depend on the time delay. Therefore, some time delays may cause oscillations. When some assumptions made do not hold, for example $b_3 < 0$, then equation (23) can have at least one positive root, say κ_0. Furthermore, then there exists a purely imaginary $\lambda = i\omega_0 = i\sqrt{\kappa_0}$ as a solution of the characteristic equation (17). We found oscillating solutions numerically, and in this section we focus on Hopf bifurcation analysis.

We chose the time delay τ as the bifurcation parameter. Let $\lambda(\tau) = \rho(\tau) + i\omega(\tau)$ be an eigenvalue of (17). Assuming $\omega_0 > 0$, we set $\rho(\tau_0) = 0$ and $\omega(\tau_0)$ as initial values matching the bifurcation parameter τ_0. In order to find values of τ, we eliminate the sine functions in (20) and (21), because the range of arccos is positive. Then we obtain

$$\tau_k = \frac{1}{\omega_0} \arccos\left[\frac{(a_1a_4 - a_5)\omega_0^4 + (a_2a_5 - a_3a_4 - a_1a_6)\omega_0^2 + a_3a_6}{a_5^2\omega_0^2 + (a_6 - a_4\omega_0^2)^2}\right] + \frac{2k\pi}{\omega_0} \tag{24}$$

for $k \in \mathbf{N}$.

Due to continuity of $Re(\lambda(\tau))$, when the real part of $\lambda(\tau)$ changes from negative ($\tau < \tau_0$) to positive ($\tau > \tau_0$), so does the equilibrium point, if the transversality condition

$$\left.\frac{d\mathrm{Re}(\lambda(\tau))}{d\tau}\right|_{\tau=\tau_0} \neq 0 \tag{25}$$

holds. Furthermore, a Hopf bifurcation happens while τ passes through the bifurcation point τ_0, see [9].

Theorem 3.4. *Let ω_0 be the largest positive simple root of (22). Then $i\omega(\tau_0) = i\omega_0$ is a simple root of (17) and $\lambda(\tau) = \rho(\tau) + i\omega(\tau)$ is differentiable with respect to τ in some open ball $B(\tau_0, \varepsilon)$ for some $\varepsilon > 0$.*

The proof of Theorem 3.4 has been given in [16].

Lemma 3.5. *Let c be the largest real solution of*

$$g(x) = x^3 + \alpha x^2 + \beta x + \gamma = 0. \tag{26}$$

Then $g'(c) > 0$.

Proof. There are two cases of its roots. The first case is that all roots are real, say $a < b < c$. The $g(x)$ can be rewritten as $g(x) = (x-a)(x-b)(x-c)$. It is clear that $g'(c) = (c-a)(c-b) > 0$. The others is complex conjugate roots, say $a \pm bi$ where $b > 0$, and one real root, say c. Then the other form of $g(x)$ is $g(x) = ((x-a)^2 + b)(x-c)$. Now we have $g'(c) = (c-a)^2 + b > 0$. □

We will apply the previous Lemma to show that $\frac{d}{d\tau}\mathrm{Re}(\lambda(\tau))|_{\tau=\tau_0} > 0$. On taking the derivative with respect to τ of (17):

$$\frac{d\lambda}{d\tau} = \frac{-\lambda \mathrm{e}^{-\lambda\tau}(a_4\lambda^2 + a_5\lambda + a_6)}{(3\lambda^2 + 2a_1\lambda + a_2) - \mathrm{e}^{-\lambda\tau}(2a_4\lambda + a_5) + \tau\mathrm{e}^{-\lambda\tau}(a_4\lambda^2 + a_5\lambda + a_6)}.$$

In order to eliminate the exponential term by applying equation (17), we have

$$\begin{aligned}\left(\frac{d\lambda}{d\tau}\right)^{-1} &= \frac{3\lambda^2 + 2a_1\lambda + a_2}{-\lambda e^{-\lambda\tau}(a_4\lambda^2 + a_5\lambda + a_6)} + \frac{2a_4\lambda + a_5}{\lambda(a_4\lambda^2 + a_5\lambda + a_6)} - \frac{\tau}{\lambda} \\ &= \frac{2\lambda^3 + a_1\lambda^2 - a_3}{-\lambda^2(\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3)} + \frac{a_4\lambda^2 - a_6\lambda}{\lambda^2(a_4\lambda^2 + a_5\lambda + a_6)} - \frac{\tau}{\lambda}.\end{aligned}$$

Hence,

$$\begin{aligned}&\mathrm{Sign}\left\{\frac{d\mathrm{Re}(\lambda)}{d\tau}\right\}_{\lambda=i\omega_0} = \mathrm{Sign}\left\{\mathrm{Re}\left(\frac{d\mathrm{Re}(\lambda)}{d\tau}\right)^{-1}\right\}_{\lambda=i\omega_0} \\ &= \mathrm{Sign}\left\{\mathrm{Re}\left[\tfrac{2\lambda^3+a_1\lambda^2+a_3}{-\lambda^2(\lambda^3+a_1\lambda^2+a_2\lambda+a_3)}\right]_{\lambda=i\omega_0} + \mathrm{Re}\left[\tfrac{a_4\lambda^2+a_6}{\lambda^2(a_4\lambda^2+a_5\lambda+a_6)}\right]_{\lambda=i\omega_0}\right\} \\ &= \mathrm{Sign}\left\{\mathrm{Re}\left[\tfrac{-a_3-i(2\omega_0^3+a_1\omega_0^2)}{\omega_0^2[(a_3-a_1\omega_0^2)+i(a_2\omega_0-\omega_0^3)]}\right] + \mathrm{Re}\left[\tfrac{-a_4\omega_0^2-a_6}{\omega_0^2[(a_6-a_4\omega_0^2)+a_5\omega_0 i]}\right]\right\} \\ &= \mathrm{Sign}\left\{\frac{3\omega_0^4 + 2(a_1^2 - 2a_2 + a_4^2)\omega_0^2 + (a_2^2 - 2a_1a_3 + 2a_4a_6 - a_5^2)}{(a_3 - a_1\omega^2)_0^2 + (a_2\omega_0 - \omega_0^3)^2}\right\}. \quad (27)\end{aligned}$$

The numerator of the right-hand side of (27) is the derivative of (23) whose the largest real root is ω_0. By Lemma 3.2, we have $\frac{d\mathrm{Re}\lambda}{d\tau}\big|_{\omega=\omega_0} > 0$. Now we can conclude as follows.

Theorem 3.6. *Assume that $R_0 > 1$, and either $b_3 < 0$ or $b_3 > 0$ and $h(z_1) < 0$ where $z_1 = \frac{-b_1+\sqrt{b_1^2-3b_2}}{3}$. Let ω_0 is the largest positive real root of* (23). *The parameter τ_0 is defined by*

$$\tau_0 = \frac{1}{\omega_0}\arccos\left[\frac{(a_1a_4 - a_5)\omega_0^4 + (a_2a_5 - a_3a_4 - a_1a_6)\omega_0^2 + a_3a_6}{a_5^2\omega_0^2 + (a_6 - a_4\omega_0^2)^2}\right].$$

Then the endemic state E_1 is asymptotically stable for $\tau < \tau_0$ and unstable for $\tau \geq \tau_0$. Moreover, a Hopf bifurcation occurs at $\tau = \tau_0$. In addition, there exists a positive number ε such that the our model under study possesses periodic solutions for $\tau \in (\tau_0, \tau_0 + \varepsilon)$.

The periodic solution is a limit cycle in the case of $\tau \in (\tau_0\tau_0 + \varepsilon)$. The radius of the cycle will increase with τ, see [3, 16, 17].

4. Numerical implementation

In order to demonstrate the above theorem, we provide some numerical simulations using suitable parameters that satisfy the conditions of the previous section. A set of realistic parameters is $\mu_h = 0.0000457\,\text{year}^{-1}$ $\mu_v = 0.04\,\text{year}^{-1}$, $r_1 = 0.077\,\text{year}^{-1}$, $r_2 = 0.0057\,\text{year}^{-1}$, $r_3 = 0.005\,\text{year}^{-1}$ see in [7]. However, an appropriate set of parameters is $\gamma_h = 1.19\,\text{year}^{-1}$, $\gamma_v = 0.25\,\text{year}^{-1}$. The simulation program was implemented in MatLab and employed Runge-Kutta of order 4 for the delay differential equations, see [20].

In Figure 2, the numerical results from the main model under study are shown for the case of endemic state where $R_0 > 1$ and $\tau = 2.5$, below the bifurcation value $\tau_0 = 2.7$. In Figure 3, a numerical example with a limit cycle is demonstrated, namely at the bifurcation point $\tau_0 = 2.7$. According to Theorem 3.6, the solution trajectory tends to a limit cycle surrounding the endemic point, as a theoretical prediction.

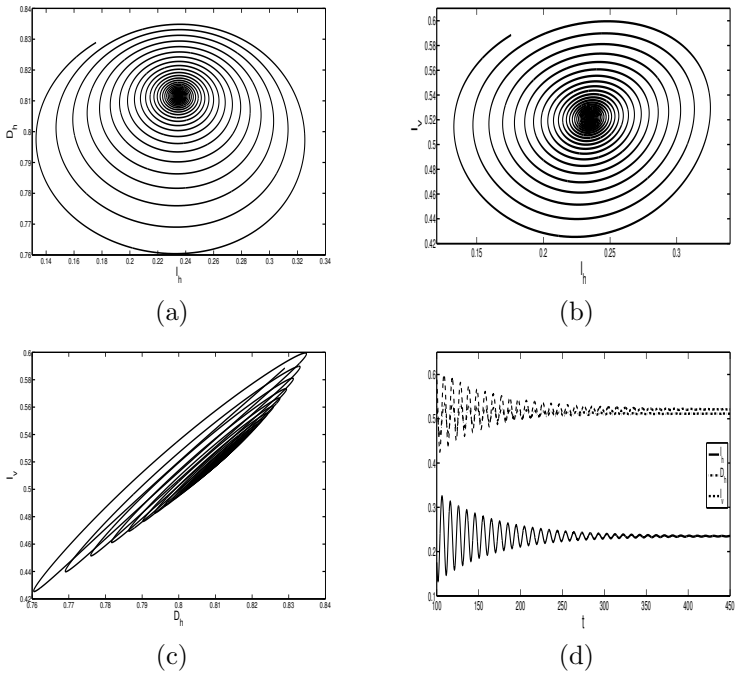

FIGURE 2. Computer simulations of the model equations (8)-(10) demonstrating the case $R_0 > 1$ and $\tau < \tau_0$ with a stable endemic state. The plots show time traces of the solution in (a) (I_h, D_h)-plane (b) (I_h, Iv)-plane, (c) (D_h, I_v)-plane and (d) plotting $I_h(-)$, $D_h(--)$, $I_v(..)$ versus t.

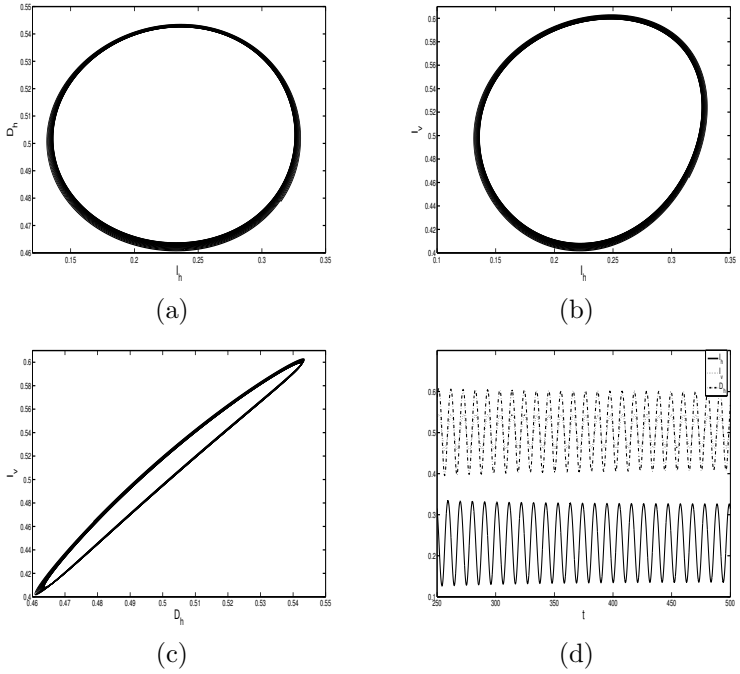

FIGURE 3. Computer simulations of the model equations (8)-(10) demonstrating a case with $R_0 > 1$ and $\tau = \tau_0$ (i.e., the bifurcation point) with a limit cycle expected theoretically. The plots show time traces in (a) (I_h, D_h)-plane (b) (I_h, Iv)-plane, (c)(D_h, I_v)-plane and (D) plotting $I_h(-)$, $D_h(--)$, $I_v(..)$ versus t.

5. Conclusion

A mathematical model for the transmission of *Plasmodium vivax* with a constant time delay was constructed. The time delay represents the intrinsic incubation period which is the time taken for a human from contracting infection to becoming infectious. An analysis of the model equations shows two equilibria, namely the disease-free equilibrium and the endemic equilibrium. Furthermore, the basic reproduction number was derived in symbolic form, and it determines the dynamics of the model: if $R_0 < 1$, the disease-free state is locally stable and the disease vanishes, while if $R_0 > 1$, a unique endemic equilibrium occurs and is locally stable. Moreover, the time delay was considered as a bifurcation parameter. According to Hopf bifurcation analysis, the endemic equilibrium is locally stable for suitably small time delays. However, the stability of the endemic state is lost when the time delay increases. One of

the key features of our model is the existence of a periodic solution, which is consistent with the behavior of malaria transmission observed in nature.

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