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Periodicity and synchronization in blood-stage malaria infection

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Abstract Malaria fever is highly periodic and is associated with the parasite replication cycles in red blood cells. The existence of periodicity in malaria infection demonstrates that parasite replication in different red blood cells is synchronized. In this article, rigorous mathematical analysis of an age-structured human malaria model of infected red blood cells (Rouzine and McKenzie, Proc Natl Acad Sci USA 100:3473–3478, 2003) is provided and the synchronization of *Plasmodium falciparum* erythrocytic stages is investigated. By using the replication rate as the bifurcation parameter, the existence of Hopf bifurcation in the age-structured malaria infection model is obtained. Numerical simulations indicate that synchronization with regular periodic oscillations (of period 48 h) occurs when the replication rate increases. Therefore, Kwiatkowski and Nowak's observation (Proc Natl Acad Sci USA 88:5111–5113, 1991) that synchronization could be generated at modest replication rates is confirmed.

Keywords Malaria · Age-structured model · Stability · Hopf bifurcation · Periodic solution · Synchronization

Mathematics Subject Classification (2000) 35B32 · 35Q92 · 92D30

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1 Introduction

Periodic occurrence of fever (and chills) is the hallmark symptom of malaria infection and the period of oscillation has been identified with the length of the parasite replication cycle (Rouzine and McKenzie 2003). Malaria parasite *Plasmodium falciparum* infects the liver first and then moves into the blood, where it multiplies and undergoes replication cycles in host red blood cells. The duration of each replication cycle is about 48 h. At the end of a cycle, the infected red blood cells burst and release free parasites, most of them will invade other red blood cells and the cycle is repeated. The attack of the parasites on red blood cells makes the person have high fever and the subsequent bursting of red blood cells makes the person have chills. When Alphones Laveran discovered the malaria parasites, he found that the attacks of fever coincide with the parasites in the blood coming to schizogony (Hawking et al. 1968). The phenomenon of periodic oscillations indicates that malaria parasite schizogony in different red blood cells is synchronized: malaria parasites enter and are released from these red blood cells at approximately the same times (Rouzine and McKenzie 2003).

Although the synchronous development of the erythrocytic stages of *Plasmodium falciparum* was accomplished in culture by sorbitol treatment (Lambros and Vanderberg 1989) and exposure to high temperature (Kwiatkowski 1989), respectively, this synchronization mechanism is still poorly understood. In the last decade, various mathematical models have been developed to study the periodicity and synchronization in blood-stage malaria infection. Kwiatkowski and Nowak (1991) proposed a 2-dimensional discrete model to show that the interaction between malaria parasites and red blood cells naturally tends to generate periodic solutions and explained that synchronization occurs at modest replication rates as the following features: (i) the innate response is promptly triggered by schizont rupture with a large number of schizonts causing a greater response than a small number; (ii) the innate response inhibits parasite growth with maximal effect on the later stages of the growth cycle. Gravenor and Kwiatkowski (1998) developed an age-structured coupled Markov chain model to describe the parasite erythrocyte cycle and its interaction with the host fever response and showed that different periodicities can result from different strengths of the innate fever response. Hosten et al. (2000) introduced a time delay into the basic model of Anderson et al. (1989), consisted of healthy red blood cells, infected red blood cells, malaria parasitemia, to produce periodic oscillations in host-parasites. See also a study by Mitchell and Carr (2010) on how a small delay in the activation of the immune response can lead to persistent oscillations in an intra-host malaria model of Recker et al. (2004). By considering a deterministic model consisted of four ordinary differential equations representing the healthy red blood cells, infected red blood cells, malaria parasitemia, and immune effectors, Li et al. (2010) studied how the proliferation rate of the immune cells induced by infected red blood cells contributes to the periodic occurrence of fever in the infected host.

Kwiatkowski and Nowak (1991) postulated that the critical components of the innate response are stimulated by and act upon two distinct phase intervals of the *Plasmodium falciparum* replication cycle: an inducing interval and a target interval. Based on these postulations, Rouzine and McKenzie (2003) used the following age-structured population model to expedite the identification of immunogens critical for controlling blood-stage malaria infection from observed oscillations:

$$\begin{cases} \frac{\partial n(\tau,t)}{\partial t} = -\frac{\partial n(\tau,t)}{\partial \tau} - [b(\tau) + d(\tau,t)]n(\tau,t), \\ n(0,t) = r(t) \int\limits_0^{+\infty} b(\tau)n(\tau,t)d\tau, \end{cases} \tag{1.1}$$

where t and τ are in units of replication cycle length 48 h, $n(\tau, t)$ is the density of infected cells in time phase τ of the parasites replication cycle at current time t, $b(\tau)$ and $d(\tau, t)$ are the burst and death rates of infected cells in phase τ, respectively, and $r(t)$ is the replication rate, i.e., the number of new cells infected by free parasites released from a bursting cell. We would like to mention that the unit of 48 h is used for t and τ, such a unit was also used by Molineaux et al. (2001) in a discrete *Plasmodium falciparum* parasitaemia model.

The goal of the present article is to show that the inherent synchronization of the infection by providing rigorous mathematical analysis of (1.1). We prove that periodic solutions exist in (1.1) when the replication rate $r(t)$ is relatively large. The existence of non-trivial periodic solutions in age-structured models has been a very interesting and difficult research topic. It is believed that such periodic solutions are induced by Hopf bifurcation. We establish the existence of Hopf bifurcation in (1.1) by using the Hopf bifurcation theorem for general age-structured models in Liu et al. (2010), which was established by using the center manifold theorem in Magal and Ruan (2009a) and the Hopf bifurcation theorem in Hassard et al. (1981).

We assume that the host response acts on free parasites only, that means $d(\tau, t) = 0$, and the response level increases gradually as the number of response-inducing cells grows, that is

$$r(t) = r_0 \exp\left(-c \int\limits_0^{+\infty} b(\tau)n(\tau,t)d\tau\right),$$

where r_0 is the maximum value of the replication ratio and $c > 0$ is a constant. For mathematical convenience we choose $b(\tau) = bX(\tau)$ with

$$X(\tau) = \begin{cases} 0, & \tau \in (0, \tau_0) \\ 1, & \tau \in [\tau_0, +\infty), \end{cases}$$

where b and τ_0 are the positive constants which represent the burst rate and the deviation of the burst time, respectively. Therefore, we consider the following problem:

$$\begin{cases} \frac{\partial n(\tau,t)}{\partial t} = -\frac{\partial n(\tau,t)}{\partial \tau} - bX(\tau)n(\tau,t), & \tau \in (0,+\infty),\ t > 0, \\ n(0,t) = r\left(\int\limits_0^{+\infty} bX(\tau)n(\tau,t)d\tau\right), & t \geq 0, \\ n(\cdot,0) = \phi(\tau) \in L^1(0,+\infty), \end{cases} \tag{1.2}$$

where $r(\phi) = r_0\phi \exp(-c\phi)$.

The rest of this paper is organized as follows. Some preliminary results and the existence of a disease equilibrium are given in Sect. 2. In Sect. 3, we analyze the eigenvalue problem. In Sect. 4, the stability of the disease equilibrium and the existence of Hopf bifurcation are discussed by using the standard perturbation argument in Thieme (1990b) or Magal and Ruan (2009b) and a Hopf bifurcation theorem for general age-structured models in Liu et al. (2010), respectively. Finally, some numerical simulations and discussions are given in Sect. 5.

2 Preliminary results

Consider the space $Y := \mathbb{R} \times L^1(0, +\infty)$ endowed with the following usual product norm

$$\left\| \begin{pmatrix} \alpha \\ \phi \end{pmatrix} \right\| = |\alpha| + \|\phi\|_{L^1(0,+\infty)}.$$

Define a linear operator $A : D(A) \subset Y \to Y$ by

$$A \begin{pmatrix} 0 \\ \phi \end{pmatrix} = \begin{pmatrix} -\phi(0) \\ -\phi' - bX(\tau)\phi \end{pmatrix} \quad \text{with } D(A) = \{0\} \times W^1(0, \infty)$$

and denote $Y_0 := \overline{D(A)} = \{0\} \times L^1(0, +\infty)$. Define $F : Y_0 \to Y$ by

$$F \begin{pmatrix} 0 \\ \phi \end{pmatrix} = \begin{pmatrix} r \left(\int_0^{+\infty} bX(\tau)\phi(\tau)d\tau \right) \\ 0 \end{pmatrix}.$$

Then by identifying $n(\cdot, t)$ with $u(t) = \begin{pmatrix} 0 \\ n(\cdot, t) \end{pmatrix}$, we can rewrite (1.2) as the following abstract Cauchy problem

$$\frac{du(t)}{dt} = Au(t) + F(u(t)) \quad \text{for } t \geq 0 \text{ and } u(0) = \begin{pmatrix} 0 \\ n(\cdot, 0) \end{pmatrix} \in Y_0. \tag{2.1}$$

By applying the results in Thieme (1990b), we can obtain the following result.

Lemma 2.1 $(-d, +\infty) \subset \rho(A)$. *More precisely, for any* $\lambda > -b$ *and any* $\begin{pmatrix} \alpha \\ \phi \end{pmatrix} \in Y$,

$$(\lambda - A)^{-1} \begin{pmatrix} \alpha \\ \phi \end{pmatrix} = \begin{pmatrix} 0 \\ \psi \end{pmatrix}$$
$$\Leftrightarrow \quad \psi(\tau) = \exp\left(-\int_0^\tau [\lambda + bX(s)]ds \right) \alpha + \int_0^\tau \exp\left(-\int_\ell^\tau [\lambda + bX(s)]ds \right) \phi(\ell)d\ell.$$

Moreover,

$$\|(\lambda - A)^{-n}\| \leq \frac{M}{(\lambda - \omega_A)^n} \quad \textit{for any } \lambda > -b \textit{ and any } n \geq 1$$

with $\omega_A := -b$ *and* $M = 1 + e^{b\tau_0}$.

Proof For any $\lambda > -b$ and any $\begin{pmatrix} \alpha \\ \phi \end{pmatrix} \in Y$, we have

$$\begin{aligned}
&\left\| (\lambda - A)^{-1} \begin{pmatrix} \alpha \\ \phi \end{pmatrix} \right\|_Y \\
&= \left\| \begin{pmatrix} 0 \\ \exp\left(-\int_0^\tau [\lambda + bX(s)]ds \right) \alpha + \int_0^\tau \exp\left(-\int_\ell^\tau [\lambda + bX(s)]ds \right) \phi(\ell) d\ell \end{pmatrix} \right\|_Y \\
&= \int_0^{+\infty} \left| \exp\left(-\int_0^\tau [\lambda + bX(s)]ds \right) \right| d\tau \cdot |\alpha| \\
&\quad + \int_0^{+\infty} \left| \int_0^\tau \exp\left(-\int_\ell^\tau [\lambda + bX(s)]ds \right) \phi(\ell) d\ell \right| d\tau.
\end{aligned}$$

However, we have

$$\begin{aligned}
&\int_0^{+\infty} \left| \int_0^\tau \exp\left(-\int_\ell^\tau [\lambda + bX(s)]ds \right) \phi(\ell) d\ell \right| d\tau \\
&\quad = \int_0^{\tau_0} \left| \int_0^\tau e^{-\lambda(\tau-\ell)} \phi(\ell) d\ell \right| d\tau + \int_{\tau_0}^{+\infty} \left| \int_0^\tau e^{-b(\tau-\tau_0)} e^{-\lambda(\tau-\ell)} \phi(\ell) d\ell \right| d\tau \\
&\quad = -\frac{1}{\lambda} e^{-\lambda\tau} \int_0^\tau e^{\lambda\ell} |\phi(\ell)| d\ell \Big|_0^{\tau_0} + \frac{1}{\lambda} \int_0^\tau |\phi(\tau)| d\tau \\
&\qquad + e^{b\tau_0} \left[-\frac{1}{\lambda + b} e^{-(\lambda+b)\tau} \int_0^\tau e^{\lambda\ell} |\phi(\ell)| d\ell \Big|_{\tau_0}^{+\infty} + \frac{1}{\lambda + b} \int_\tau^{+\infty} e^{-b\tau} |\phi(\tau)| d\tau \right] \\
&\quad \leq \frac{1}{\lambda + b} \int_0^{+\infty} |\phi(\tau)| d\tau
\end{aligned}$$

and

$$\begin{aligned}
&\int_0^{+\infty}\left|\exp\left(-\int_0^{\tau}[\lambda+bX(s)]ds\right)\right|d\tau\cdot|\alpha|\\
&=|\alpha|\left[\int_0^{\tau_0}e^{-\lambda\tau}d\tau+\int_{\tau_0}^{+\infty}e^{-\lambda\tau}e^{-b(\tau-\tau_0)}d\tau\right]\\
&=|\alpha|\left[-\frac{1}{\lambda}(e^{-\lambda\tau_0}-1)+\frac{e^{-\lambda\tau_0}}{\lambda+b}\right]\\
&=\frac{|\alpha|}{\lambda+b}\left[-\frac{b}{\lambda}(e^{-\lambda\tau_0}-1)+1\right].
\end{aligned}$$

It is not difficult to verify that the function $f(y)=(e^y-1)/y$ is an increasing function with y. Therefore, we can obtain that for $\lambda>-b$,

$$\int_0^{+\infty}\left|\exp\left(-\int_0^{\tau}[\lambda+bX(s)]ds\right)\right|d\tau\cdot|\alpha|\le\frac{e^{-b\tau_0}}{\lambda+b}|\alpha|.$$

In conclusion, we have

$$\left\|(\lambda-A)^{-1}\begin{pmatrix}\alpha\\ \phi\end{pmatrix}\right\|_Y\le\frac{1+e^{b\tau_0}}{\lambda+b}\left(|\alpha|+\|\phi\|_{L^1(0,+\infty)}\right).$$

The result follows. □

Since F is Lipschitz continuous on Y_0, the following lemma is a consequence of the results in Thieme (1990a).

Lemma 2.2 *There exists a unique continuous semiflow $\{U(t)\}_{t\ge0}$ on Y_0, such that for each $y\in Y_0$, the map $t\to U(t)y$ is an integrated solution of the Cauchy Problem (2.1), that is, $\int_0^t U(s)yds\in D(A)$ and*

$$U(t)y=y+A\int_0^t U(s)yds+\int_0^t F\left(U(s)y\right)ds.$$

Lemma 2.3 *When $r_0>1$, (2.1) has a unique positive steady state solution.*

Proof If $\begin{pmatrix}0\\ \bar{n}(\tau)\end{pmatrix}\in Y_0$ is a positive steady state solution of (2.1), then we have

$$\begin{pmatrix}0\\ \bar{n}(\tau)\end{pmatrix}\in D(A)\quad\text{and}\quad A\begin{pmatrix}0\\ \bar{n}(\tau)\end{pmatrix}+F\begin{pmatrix}0\\ \bar{n}(\tau)\end{pmatrix}=0, \tag{2.2}$$

which is equivalent to the following equations

$$\begin{cases} \bar{n}'(\tau) + bX(\tau)\bar{n}(\tau) = 0, \\ \bar{n}(0) = r_0 \left(\int_0^{+\infty} bX(\tau)\bar{n}(\tau)d\tau \right) \exp\left(-c \int_0^{+\infty} bX(\tau)\bar{n}(\tau)d\tau \right). \end{cases} \tag{2.3}$$

It follows that

$$\bar{n}(\tau) = \begin{cases} \bar{n}(0), & \tau \in (0, \tau_0) \\ \bar{n}(0)e^{-b(\tau-\tau_0)}, & \tau \in [\tau_0, +\infty). \end{cases} \tag{2.4}$$

Let $N = \int_{\tau_0}^{+\infty} \bar{n}(\tau)d\tau$ and integrate $\bar{n}(\tau)$ on $(\tau_0, +\infty)$, we obtain

$$N = r_0 bNe^{-cbN} \int_{\tau_0}^{+\infty} e^{-b(\tau-\tau_0)} ds.$$

It implies that $N = -\frac{1}{cb} \ln \frac{1}{r_0}$ which is larger than 0 if $r_0 > 1$. Thus,

$$\bar{n}(0) = r_0 bNe^{-cbN} = bN > 0.$$

It follows that $\bar{n}(\tau) > 0$ for $\tau > 0$. □

Throughout the paper we assume that $r_0 > 1$.

3 Eigenvalue problems

The linearized equation of (2.1) at $\begin{pmatrix} 0 \\ \bar{n}(\tau) \end{pmatrix}$ is given by

$$\begin{cases} \frac{dv(t)}{dt} = Av(t) + DF \begin{pmatrix} 0 \\ \bar{n}(\tau) \end{pmatrix} (v(t)) \quad \text{for } t \geq 0, \\ v(0) = y \in Y_0, \end{cases} \tag{3.1}$$

where "D" is the Fréchet derivative operator, and for $\begin{pmatrix} 0 \\ w \end{pmatrix} \in Y_0$,

$$\begin{aligned} DF \begin{pmatrix} 0 \\ \bar{n} \end{pmatrix} \begin{pmatrix} 0 \\ w \end{pmatrix} &= \left(r' \left(\int_0^{+\infty} bX(\tau)\bar{n}(\tau)d\tau \right) \cdot \int_0^{+\infty} bX(\tau)\bar{n}(\tau)d\tau - bX(\tau)w(\tau) \right) \\ &= \begin{pmatrix} (1 + \ln \frac{1}{r_0}) \int_0^{+\infty} bX(\tau)w(\tau)d\tau \\ 0 \end{pmatrix}. \end{aligned}$$

Therefore, if we define an operator $B: D(A) \to Y$ by

$$B\begin{pmatrix} 0 \\ w \end{pmatrix} = \begin{pmatrix} (1+\ln\frac{1}{r_0})\int\limits_0^{+\infty} bX(\tau)w(\tau)d\tau \\ 0 \end{pmatrix},$$

then the linearized equation (3.1) can be rewritten as

$$\begin{cases} \frac{dv(t)}{dt} = (A+B)v(t) & \text{for } t \geq 0, \\ v(0) = y \in Y_0. \end{cases} \tag{3.2}$$

Following Magal and Ruan (2009a), we define the operator A_0, the part of A in $\overline{D(A)} = Y_0$, by

$$A_0\begin{pmatrix} 0 \\ \phi \end{pmatrix} = A\begin{pmatrix} 0 \\ \phi \end{pmatrix} \quad \text{for } \begin{pmatrix} 0 \\ \phi \end{pmatrix} \in D(A_0)$$

with

$$D(A_0) = \left\{ \begin{pmatrix} 0 \\ \phi \end{pmatrix} \in \{0\} \times W^{1,1}(0, +\infty) : \phi(0) = 0 \right\}.$$

Since A is a Hille-Yosida operator, we have the following lemma.

Lemma 3.1 *The linear operator A_0 is the infinitesimal generator of a strongly continuous semigroup of bounded linear operators $\{T_{A_0}(t)\}_{t\geq 0}$ on Y_0, and for each $t \geq 0$, the linear operator $T_{A_0}(t)$ is defined by*

$$T_{A_0}(t)\begin{pmatrix} 0 \\ \phi \end{pmatrix} = \begin{pmatrix} 0 \\ T_{\hat{A}_0}(t)\phi \end{pmatrix},$$

where $\{T_{\hat{A}_0}(t)\}_{t\geq 0}$ is a strongly continuous semigroup of bounded linear operators on $L^1(0, +\infty)$ and

$$T_{\hat{A}_0}(t)\phi(\tau) = \begin{cases} \exp\left(-\int\limits_{\tau - t}^{\tau} bX(s)ds \right) \phi(\tau - t), & \tau > t, \\ 0, & \tau \leq t. \end{cases}$$

Moreover, $\|T_{A_0}(t)\| \leq Me^{\omega_A t}$ for any $t \geq 0$.

For investigating the eigenvalues problem, we first state some definitions and theorems.

Definition 3.2 Let $L : D(L) \subset X \to X$ be the infinitesimal generator of a linear C_0-semigroup $\{T_L(t)\}_{t\geq 0}$ on a Banach space X. Define the *growth bound* $\omega_0(L) \in [-\infty, +\infty)$ of L by

$$\omega_0(L) := \lim_{t\to+\infty} \frac{\ln(\|T_L(t)\|_{\mathcal{L}(X)})}{t}.$$

Define the *essential growth bound* $\omega_{0,\text{ess}} \in [-\infty, +\infty)$ of L by

$$\omega_{0,\text{ess}}(L) := \lim_{t\to+\infty} \frac{\ln(\|T_L(t)\|_{\text{ess}})}{t},$$

where $\|T_L(t)\|_{\text{ess}}$ is the essential norm of $T_L(t)$ defined by

$$\|T_L(t)\|_{\text{ess}} = \kappa\left(T_L(t)B_X(0,1)\right).$$

Here, $B_X(0,1) = \{x \in X : \|x\|_X \leq 1\}$, and for each bounded set $B \subset X$,

$$\kappa(B) = \inf\{\varepsilon > 0 : \ B \text{ can be covered by a finite number of balls of radius} \leq \varepsilon\}$$

is the Kuratovsky measure of non-compactness.

Theorem 3.3 *Let $L : \ D(L) \subset X \to X$ be the infinitesimal generator of a linear C_0-semigroup $\{T_L(t)\}$ on a Banach space X. Then,*

$$\omega_0(L) = \max\left(\omega_{0,\text{ess}}(L), \max_{\lambda\in\sigma(L)\setminus\sigma_{\text{ess}}(L)} \text{Re}(\lambda)\right).$$

Assume in addition that $\omega_{0,\text{ess}} < \omega_0(L)$. Then, for each $\gamma \in (\omega_{0,\text{ess}}, \omega_0(L)]$, $\{\lambda \in \sigma(L) : \ \text{Re}(\lambda) \geq \gamma\} \subset \sigma_p(L)$ is non-empty, finite and contains only poles of the resolvent of L. Moreover, there exists a finite rank bounded linear projector $\Pi : \ X \to X$ satisfying the following properties:

(i) $\Pi(\lambda - L)^{-1} = (\lambda - L)^{-1}\Pi$, *for any* $\lambda \in \rho(L)$;
(ii) $\sigma(L_{\Pi(X)}) = \{\lambda \in \sigma \in \sigma(L) : \ \text{Re}(\lambda) \geq \gamma;\}$
(iii) $\sigma(L_{(I-\Pi)X}) = \sigma(L) \setminus \sigma(L_{\Pi(X)})$.

In this theorem, the existence of the projector was first proved by Webb (1985, 1987) and the fact that there is a finite number of points of the spectrum is proved by Engel and Nagel (2000).

Theorem 3.4 (Magal and Ruan 2009a) *If $\omega_{0,\text{ess}} < \omega_0(L)$, then $S := \{\lambda \in \sigma(L) : \text{Re}(\lambda) > \omega_{0,\text{ess}}(L)\} \subset \sigma_p(L)$, and each $\hat{\lambda} \in S$ is a pole of the resolvent of L. That is, $\hat{\lambda}$ is isolated in $\sigma(L)$, and there exists an integer $k_0 \geq 1$, such that Laurent's expansion of the resolvent takes the following form*

$$(\lambda I - L)^{-1} = \sum_{n=-k_0}^{\infty} (\lambda - \lambda_0)^n B_n^{\lambda_0},$$

where $\{B_n^{\lambda_0}\}$ are bounded linear operators on X, and the above series converges in the norm of operators whenever $|\lambda - \lambda_0|$ is small enough.

From Definition 3.2, it is easy to obtain that $\omega_0(A_0) \leq -b$. By Theorem 3.3, $\omega_{0,\mathrm{ess}}(A_0) \leq \omega_0(A_0)$. By using the result in Ducrot et al. (2008, Theorem 1.2), we deduce that

$$\omega_{0,\mathrm{ess}}\left((A+B)_0\right) \leq \omega_{0,\mathrm{ess}}(A_0) \leq -b. \tag{3.3}$$

Set $\Omega = \{\lambda \in \mathbb{C} : \operatorname{Re}(\lambda) > -b\}$, then by using Magal and Ruan (2009a, Lemma 2.1) and Theorem 3.4, we have

$$\sigma(A+B) \cap \Omega = \sigma_p(A+B) \cap \Omega. \tag{3.4}$$

Then we obtain the following lemma.

Lemma 3.5 *For $\lambda \in \mathbb{C} \cap \Omega$, $\lambda \in \sigma(A+B) \Leftrightarrow \Delta(\lambda) = 0$, where*

$$\Delta(\lambda) = 1 - \left(1 + \ln\frac{1}{r_0}\right)\frac{b}{\lambda + b}e^{-\lambda\tau_0}. \tag{3.5}$$

Furthermore, if $\lambda \in \mathbb{C} \cap \Omega$ with $\Delta(\lambda) \neq 0$, then

$$(\lambda I - (A+B))^{-1}\begin{pmatrix}\alpha\\ \psi\end{pmatrix} = \begin{pmatrix}0\\ \phi\end{pmatrix}$$

is equivalent to

$$\begin{aligned}\phi(\tau) = {} & \frac{1}{\Delta(\lambda)}\Bigg[(1+\ln\frac{1}{r_0})\int_0^{+\infty} bX(\tau) \\ & \times \int_0^{\tau}\exp\left(-\int_{\ell}^{\tau}[\lambda + bX(s)]ds\right)\psi(\ell)d\ell d\tau + \alpha\Bigg] \\ & + \int_0^{\tau}\exp\left(-\int_{\ell}^{\tau}[\lambda + bX(s)]ds\right)\psi(\ell)d\ell.\end{aligned} \tag{3.6}$$

Proof Note that $\lambda I - A$ is invertible for each $\lambda \in \mathbb{C} \cap \Omega$. It follows that $\lambda I - (A+B)$ is invertible if and only if $I - B(\lambda I - A)^{-1}$ is invertible and

$$(\lambda I - (A+B))^{-1} = (\lambda I - A)^{-1}[I - B(\lambda I - A)^{-1}]^{-1}.$$

However, using Lemma 2.1 we can obtain that

$$[I - B(\lambda I - A)^{-1}]\begin{pmatrix}\hat{\alpha}\\ \hat{\psi}\end{pmatrix} = \begin{pmatrix}\alpha\\ \psi\end{pmatrix} \Leftrightarrow \begin{cases} \hat{\alpha} = (1 + \ln \frac{1}{r_0}) \int\limits_0^{+\infty} bX(\tau)\gamma(\tau)d\tau + \alpha \\ \hat{\psi} = \psi, \end{cases}$$

where

$$\gamma(\tau) = \exp\left(-\int\limits_0^{\tau}[\lambda + bX(s)]ds\right)\hat{\alpha} + \int\limits_0^{\tau}\exp\left(-\int\limits_{\ell}^{\tau}[\lambda + bX(s)]ds\right)\hat{\psi}(\ell)d\ell.$$

It follows that

$$\Delta(\lambda)\hat{\alpha} = \alpha + \int\limits_0^{+\infty} bX(\tau)\int\limits_0^{\tau}\exp\left(-\int\limits_{\ell}^{\tau}[\lambda + bX(s)]ds\right)\hat{\psi}(\ell)d\ell d\tau.$$

Hence,

$$\hat{\alpha} = \frac{1}{\Delta(\lambda)}\left(\alpha + \int\limits_0^{+\infty} bX(\tau)\int\limits_0^{\tau}\exp\left(-\int\limits_{\ell}^{\tau}[\lambda + bX(s)]ds\right)\hat{\psi}(\ell)d\ell d\tau\right) \quad \text{if } \Delta(\lambda) \neq 0.$$

It follows that (3.6) can be obtained directly. It remains to show that for any λ with $\Delta(\lambda) = 0$, there is a $\begin{pmatrix}0\\ \phi\end{pmatrix} \in D(A)$ with $\phi \neq 0$, such that

$$(A + B)\begin{pmatrix}0\\ \phi\end{pmatrix} = \lambda\begin{pmatrix}0\\ \phi\end{pmatrix}.$$

It is equivalent to

$$\phi = \left(1 + \ln\frac{1}{r_0}\right)\int\limits_0^{+\infty} bX(\tau)\phi(\tau)d\tau \cdot \exp\left(-\int\limits_0^{\tau}[\lambda + bX(s)]ds\right).$$

If we fix $\int_{\tau_0}^{+\infty} b\phi(\tau)d\tau = C$ with C a nonzero constant and integrate the above equation from τ_0 to ∞, then we have $\Delta(\lambda)C = 0$. Due to $\Delta(\lambda) = 0$, the result follows. □

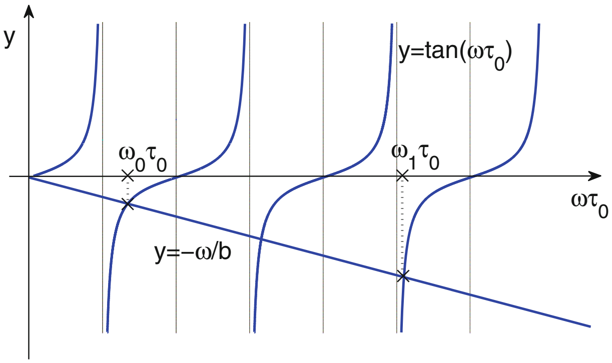

Fig. 1 Illustration of solutions of (4.2)

4 Stability and Hopf bifurcation

Let $\lambda_{1,2} = \pm i\omega$ with $\omega > 0$ be solutions of the characteristic equation $\Delta(\lambda) = 0$. Then we have

$$\begin{cases} \frac{1}{1+\ln\frac{1}{r_0}} = \cos\omega\tau_0 \\ \frac{-\omega}{b(1+\ln\frac{1}{r_0})} = \sin\omega\tau_0, \end{cases} \tag{4.1}$$

which leads to (see Fig. 1)

$$\tan\omega\tau_0 = \frac{-\omega}{b} \tag{4.2}$$

and

$$r_0 = \exp\left(1 - \frac{1}{\cos\omega\tau_0}\right).$$

Let $\omega_k \in \left((2k + \frac{1}{2})\pi/\tau_0, (2k+1)\pi/\tau_0\right)$, $k = 0, 1, \ldots$, be the roots of (4.2). Define

$$r_0^{(k)} = \exp\left(1 - \frac{1}{\cos\omega_k\tau_0}\right), \quad k = 0, 1, \ldots. \tag{4.3}$$

Then we know that $\pm i\omega_k$ are the purely imaginary roots of the characteristic equation with $r_0 = r_0^{(k)}$ and the characteristic equation with $r_0 > 1$ has no other purely imaginary roots. It is not difficult to verify that $r_0^{(k+1)} > r_0^{(k)}$ for $k = 0, 1, \ldots$. Clearly, $r_0^{(0)} > e^2$.

Let $\lambda(r_0) = \gamma(r_0) + i\omega(r_0)$ be the root of the characteristic equation satisfying $\gamma(r_0^{(k)}) = 0$ and $\omega(r_0^{(k)}) = \omega_k$, when r_0 is close to $r_0^{(k)}$, $k = 0, 1, \ldots$. Then we have the following transversality condition.

Lemma 4.1 $\gamma'(r_0^{(k)}) > 0$ *for any* $k = 0, 1, \ldots$.

Proof Substituting $\lambda(r_0)$ into the characteristic equation, taking the derivative associated with r_0, and replacing r_0 by $r_0^{(k)}$, we have

$$\begin{aligned}\gamma'(r_0^{(k)}) &= \mathrm{Re}\left(-\frac{\lambda+b}{r_0(1+\ln\frac{1}{r_0})[1+\tau_0(\lambda+b)]}\Big|_{r_0=r_0^{(k)}}\right)\\ &= -\frac{1}{r_0^{(k)}(1+\ln\frac{1}{r_0^{(k)}})}\mathrm{Re}\left(\frac{i\omega_k+b}{1+b\tau_0+i\omega_k}\right)\\ &= -\frac{b(b\tau_0+1)+\omega_k^2\tau_0}{r_0^{(k)}(1+\ln\frac{1}{r_0^{(k)}})[(1+b\tau_0)^2+\omega_k^2\tau_0^2]}.\end{aligned}$$

Obviously, $\gamma'(r_0^{(k)}) > 0$ because $\gamma_0^{(k)} > e^2$. □

The following lemma describes the distribution of the roots of the characteristic equation.

Lemma 4.2 (i) *If* $r_0 \in (1, r_0^{(0)})$, *then all roots of the characteristic equation have negative real parts.*

(ii) *The characteristic equation has purely imaginary roots if and only if* $r = r_0^{(k)}$, $k = 0, 1, \ldots$. *When* $r = r_0^{(0)}$ *all the roots, except* $\pm i\omega_0$, *have negative real parts.*

(iii) *When* $r_0 \in (r_0^{(k)}, r_0^{(k+1)}]$, $k = 0, 1, \ldots$, *the characteristic equation has exactly* $k+1$ *pairs of roots with positive real parts.*

Proof Firstly, it is easy to verify that all the roots of the characteristic equation have negative real parts when $r_0 = 1$ and 0 is not a root of the characteristic equation with any $r_0 > 1$. In addition, we know that $\pm i\omega_k$ are the purely imaginary roots of the characteristic equation with $r_0 = r_0^{(k)}$ and the characteristic equation with $r_0 > 1$ has no other purely imaginary roots. The results follow directly from Ruan and Wei (2003, Corollary 2.4). □

By using the standard perturbation argument in Thieme (1990b) or Magal and Ruan (2009b), the following stability result follows directly from (3.3), (3.4) and Lemma 4.2.

Theorem 4.3 *The positive steady state solution* $\begin{pmatrix}0\\ \bar{n}(\tau)\end{pmatrix}$ *of* (2.1) *is asymptotically stable when* $r \in (1, r_0^{(0)})$ *and unstable when* $r \in (r_0^{(0)}, +\infty)$.

Lemma 4.4 *The purely imaginary eigenvalues of the operator* $A + B$ *are simple.*

Proof Assume $\hat{\lambda} = i\omega$ is an eigenvalue of $A + B$. $\hat{\lambda}$ is simple means it is a pole of order 1 of the resolvent of $A + B$ and $B_{-1}^{\hat{\lambda}}$, the projector on the generalized eigenspace of $A + B$ associated to $\hat{\lambda}$, has rank 1. From Yosida (1980, Theorems 1 and 2, pp.

298–299) or Liu et al. (2008, p. 1799), we only need to show that the following limit exists

$$B_{-1}^{\hat{\lambda}}\begin{pmatrix}\alpha\\ \psi\end{pmatrix} = \lim_{\lambda\to\hat{\lambda},\lambda\neq\hat{\lambda}} (\lambda-\hat{\lambda})\,(\lambda I-(A+B))^{-1}\begin{pmatrix}\alpha\\ \psi\end{pmatrix}.$$

By using Lemma 3.5, we know that if $\frac{d\Delta(\hat{\lambda})}{d\lambda}\neq 0$, then the above limit exists, and we have

$$B_{-1}^{\hat{\lambda}}\begin{pmatrix}\alpha\\ \psi\end{pmatrix}$$
$$=\begin{pmatrix} 0 \\ \left(\frac{d\Delta(\hat{\lambda})}{d\lambda}\right)^{-1}\left[\alpha+(1+\ln\frac{1}{r_0})\int_0^{+\infty} bX(\tau)\int_0^{\tau}\exp\left(-\int_{\ell}^{\tau}[\lambda+bX(s)]ds\right)\psi(\ell)d\ell d\tau\right]\end{pmatrix}.$$

However,

$$\frac{d\Delta(\hat{\lambda})}{d\lambda}=0\Leftrightarrow b\left(1+\ln\frac{1}{r_0}\right)\left(\frac{e^{-i\omega\tau_0}}{i\omega+b}+\tau_0e^{-i\omega\tau_0}\right)=0$$

which leads to $\tau_0=0$ or $b=0$ and $\omega=0$. This is a contradiction. The result thus follows. □

By combining (3.3), Lemmas 4.2 and 4.4, we are in a position to apply the Hopf bifurcation theorem for general age-structured models in Liu et al. (2010) to obtain the following main result of this paper.

Theorem 4.5 *A generic Hopf bifurcation occurs for* (2.1) *with* $r_0=r_0^{(k)}$ *at the positive steady state solution* $\begin{pmatrix}0\\ \bar{n}(\tau)\end{pmatrix}$ *for each* $k=0,1,\ldots$. *Moreover, the period of the bifurcating periodic solutions is close to* $2\pi/\omega_k$.

The results in Theorems 4.3 and 4.5 indicate that there is a critical value $r_0^{(0)}$ for the maximum value of the parasite replication ratio r_0. When $r_0<r_0^{(0)}$, the positive steady state solution $\begin{pmatrix}0\\ \bar{n}(\tau)\end{pmatrix}$ of system (2.1) or $\bar{n}(\tau)$ of the model (1.2) is asymptotically stable; when $r_0=r_0^{(0)}$, $\bar{n}(\tau)$ loses its stability and Hopf bifurcation occurs; when $r_0>r_0^{(0)}$, $\bar{n}(\tau)$ is unstable, a family of periodic solutions bifurcates from $\bar{n}(\tau)$, and the period of the bifurcating periodic solutions is approximately equal to $2\pi/\omega_0$, where ω_0 is the purely imaginary part of the eigenvalue.

5 Numerical simulations and discussion

In this section, we first present some numerical simulations to illustrate the results obtained in the previous section. Consider (1.2) with $b=8.2$, $c=0.5$, $\tau_0=0.4$ and

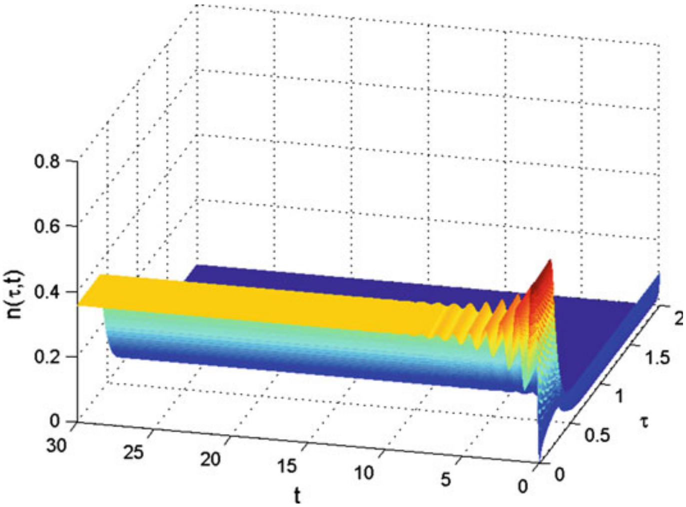

Fig. 2 When $r_0 = 9$, the positive steady state is asymptotically stable

$\phi(\tau) = 0.1$. From (4.2), (4.3) and Lemma 2.3, we obtain that the bifurcating value $r_0^{(0)} \approx 9.5436$, the purely imaginary part $\omega_0 \approx 6.2297$, and the periodic the bifurcating periodic solution of the Hopf bifurcation approaches to $2\pi/\omega_0 \approx 1.0086$ as r_0 approaches $r_0^{(0)}$. By the results in Theorems 4.3 and 4.5 we know that the positive steady state solution of model (1.2) is asymptotically stable when $r_0 \in (1, 9.5426)$, which is shown in Fig. 2 with $r_0 = 9$. We can see that the value of the steady state in Fig. 2 is close to $\bar{n}(0)$. When $r_0 > r_0^{(0)}$ the steady state becomes unstable and Hopf bifurcation occurs, the period of the periodic solution is about 1 unit (48 h), see Fig. 3 with $r_0 = 11$. When r_0 is relatively large, solutions approach a time-periodic solution with period 1 unit (48 h) and larger amplitude, see Fig. 4 with $r_0 = 60$.

It has been well-known since ancient time that fever associated with human malaria is periodic but the mechanism has been unclear. Malaria fever is associated with the parasite replication cycle in red blood cells. After a constant period (48 h) of replication a parasite makes the infected red blood cell to burst and release new parasites to invade other red blood cells. Simultaneous rupture of a large number of parasites stimulates a host fever response (Kwiatkowski and Nowak 1991). Based on our theoretical results, for any fixed burst rate b or fixed deviation of the burst time τ_0, under the assumption that the replication period of malaria parasites in the blood-stage is 48 h ($2\pi/\omega_0 = 1$), using (4.2) and (4.3) we can obtain the critical value $r_0^{(0)}$ of the maximum value of the replication ratio which gives the smallest replication rate such that the synchronization (i.e. Hopf bifurcation) is generated.

Recently, many researchers have proposed various mathematical models to study the interaction between malaria parasites and the host fever response, we refer to Kwiatkowski and Nowak (1991), Hosten et al. (2000), Gravenor and Kwiatkowski (1998), Rouzine and McKenzie (2003), Molineaux et al. (2001), and the references cited therein. Kwiatkowski and Nowak (1991) and Gravenor and Kwiatkowski (1998)

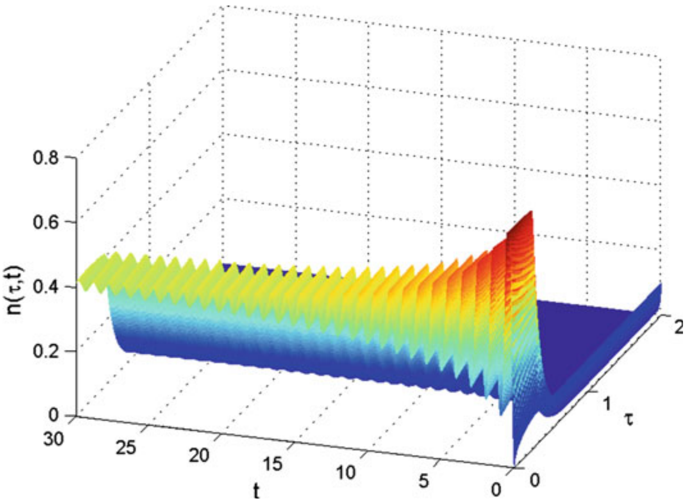

Fig. 3 When $r_0 = 11$, the positive steady state is unstable and a time-periodic solution with small amplitude exists via Hopf bifurcation

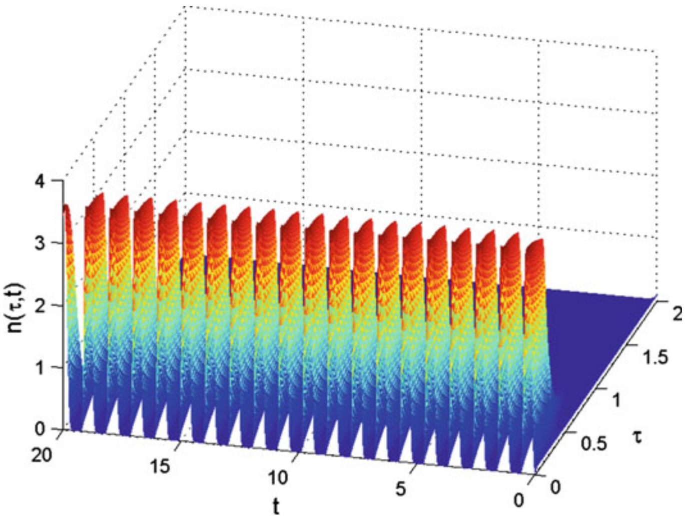

Fig. 4 When $r_0 = 60$, solutions converge to a time-periodic solution with larger amplitude and period 1 unit (48 h)

estimated the model parameters using clinical data and observed synchronization by simulating the solutions of their mathematical models and showed that the synchronization of the malaria infection is an inherent feature of infection from different points of view. It is worth mentioning that Kwiatkowski and Nowak (1991) showed that synchronization of the infections occurs when the replication rate is modest. Molineaux et al. (2001) focused on the malaria therapy. In this article, we provided rigorous mathematical analysis of the age-structured model of Rouzine and McKenzie (2003). Using the Hopf bifurcation theorem for general age-structured models in Liu et al. (2010), we proved that the model exhibits periodic solutions via Hopf bifurcation when the maximum value of the replication ratio r_0 is close to a critical value $r_0^{(0)}$. We have found some inherent link between the burst rate and the critical value of replication ratio such that the phenomenon of synchronization occurs and given a method to estimate the critical value. For any fixed burst rate b we can calculate $r_0^{(0)}$ by using (4.2) and (4.3). Notice that when the burst rate is bigger, the critical value of replication ratio is smaller. Therefore, the synchronization with regular periodic oscillations (of period 48 h) is generated when the replication rate is modest high, which confirmed the observation by Kwiatkowski and Nowak (1991).

It is a remarkable fact that the numerical simulations seem to suggest that the bifurcating periodic solutions are stable and the Hopf bifurcation exists globally. However, the stability of the bifurcating periodic solutions and the global existence of the Hopf bifurcation in age-structured models remain open. We leave this for future consideration.

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