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MALARIA MODEL WITH STAGE-STRUCTURED MOSQUITOES

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Abstract. A simple SEIR model for malaria transmission dynamics is formulated as our baseline model. The metamorphic stages in the mosquito population are then included and a simple stage-structured mosquito population model is introduced, where the mosquito population is divided into two classes, with all three aquatic stages in one class and all adults in the other class, to keep the model tractable in mathematical analysis. After a brief investigation of this simple stage-structured mosquito model, it is incorporated into the baseline model to formulate a stage-structured malaria model. A basic analysis for the stage-structured malaria model is provided and it is shown that a theoretical framework can be built up for further studies on the impact of environmental or climate change on the malaria transmission. It is also shown that both the baseline and the stage-structured malaria models undergo backward bifurcations.

1. **Introduction.** Malaria is by far the world's most important tropical parasitic disease. It is the 5th cause of death from infectious diseases worldwide (after respiratory infections, HIV/AIDS, diarrheal diseases, and tuberculosis), and the 2nd leading cause of death from infectious diseases in Africa after HIV/AIDS. It is a public health problem today in more than 109 countries and territories inhabited by some 3.3 billion people, and approximately half of the world's population is at risk of malaria, particularly those living in lower-income countries. There were 247 million cases of malaria in 2006, causing nearly one million deaths, mostly among African children, 190 - 311 million clinical episodes, and 708,000 - 1,003,000 deaths in 2008. Malaria has been eradicated in the United States since the early 1950's. However, 63 outbreaks of locally transmitted mosquito-borne malaria have occurred between 1957 and 2009, and 1500 cases of malaria, on average, are reported every year in the United States [7, 41].

Mathematical models for the transmission dynamics of infectious diseases have proven useful for the purpose of providing a logical structure within which to incorporate knowledge and test assumptions about the complex epidemics, in a way that could not be done by simple thought processes. Mathematical models for

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malaria have played an important role in helping researchers understand this epidemic, anticipate and plan for the future, and design and analyze control strategies. The earliest malaria mathematical model can be traced to the model formulated by Ross in 1911 [37]. MacDonald extended the Ross model in 1957 [28]. Since then, many other modeling attempts have been made to describe and to predict the transmission dynamics of malaria in the literature [1,3,10,11,30].

The sophistication of the epidemiological modeling efforts has grown steadily. A container-inhabiting mosquito simulation model was developed in [15]. Compartmental SEIR (susceptible-exposed-infected-recovered) differential equations models including asymptomatic immune humans were studied more recently in [32–34]. SEIR differential equations models with different levels of acquired immunity and the loss of immunity among human host populations were formulated, and the effects of social and economic conditions and temperature on the transmission were investigated by using numerical simulations in some of these studies [21,24,35,42,43]. However, in most mathematical malaria epidemic models, the mosquito populations are assumed to be homogeneous without distinguishing the stage difference among the mosquitoes.

Mosquitoes undergo complete metamorphosis going through four distinct stages of development during a lifetime: egg, pupa, larva, and adult [4]. While it is appropriate to assume that only mosquito adults are involved in the malaria transmission, the dynamics of the juvenile stages (pupae and larvae) have significant effects on the dynamics of the mosquito population, and hence the disease transmission dynamics [25].

Moreover, environmental change such as the change in temperature (global warming) has effects on the transmissions of many serious infectious diseases, and the incidence of malaria is among those diseases most sensitive to climate change. Mosquitoes at the juvenile stages respond to the climate change different from the response of adults. Therefore, to study the effects of environmental or climate change on malaria transmission, it is certainly necessary to include the stage structure in the mosquito populations.

In this paper, we first formulate a compartmental SEIR malaria transmission model as our baseline model, where the human population consists of susceptible, exposed (latent), infective, and recovered individuals, and the mosquito population only consists of susceptible, exposed (latent), and infective adults. We then include the stage structure in the mosquito population model. Realizing the difficulty in mathematical analysis for higher dimensional dynamical systems and the similarity of responses to the environmental or climate change among the mosquito juvenile stages, we divide the mosquito population into only two classes one of which consists of all aquatic stages and one of which consists of all adults. After fundamental mathematical analysis, we introduce the structured mosquitoes into the baseline malaria model. Further analysis is undertaken for the extended model. Based on the formula of the reproductive number, we provide a theoretical framework and basis for the study of the impact of environmental or climate change on the malaria transmission. Moreover, we show that the baseline model as well as the stage-structured malaria model both exhibit a backward bifurcation phenomenon which can make the disease control more difficult.

2. **The baseline malaria model.**

We first consider a baseline model for our study. In this model, we divide the human population into classes of susceptible, exposed

(latent), infective, and recovered individuals. Using the index h for the human host, we let S_h, E_h, I_h, and R_h be the numbers of susceptible, exposed, infective, and recovered humans, respectively. Here the exposed individuals are those who are infected but not yet infectious, and the infectives are those who are infected as well as infectious. We assume the recovered individuals are recovered from infection, but lose immunity with a certain rate [1, 24, 32, 34]. Note that the incubating or latent period is defined as the time from initial infection to the appearance of gametocytes in the blood [1].

To account the transmission dynamics between humans and mosquitoes, we divide the mosquito population into classes of susceptible, exposed, and infective individuals, where we only consider the mosquito population consisting of one stage of adults in this baseline model. Using the index v for the mosquitoes, we let S_v, E_v, and I_v denote the numbers of susceptible, exposed, and infective mosquitoes, respectively. Because the lifespan of mosquitoes is shorter than their infective period, we assume there are no recovered mosquitoes in the model.

The dynamics of the malaria transmission is described by the system

$$\begin{aligned}
\frac{dS_h}{dt} &= \Lambda_h - (\mu_h + \lambda_h) S_h + \theta_h R_h, \\
\frac{dE_h}{dt} &= \lambda_h S_h - (\mu_h + \gamma_h) E_h, \\
\frac{dI_h}{dt} &= \gamma_h E_h - (\mu_h + \delta_h + \eta_h) I_h, \\
\frac{dR_h}{dt} &= \eta_h I_h - (\mu_h + \theta_h) R_h,
\end{aligned} \tag{2.1}$$

and

$$\begin{aligned}
\frac{dS_v}{dt} &= \Lambda_v - \mu_v S_v - \lambda_v S_v, \\
\frac{dE_v}{dt} &= \lambda_v S_v - (\mu_v + \gamma_v) E_v, \\
\frac{dI_v}{dt} &= \gamma_v E_v - \mu_v I_v,
\end{aligned} \tag{2.2}$$

where Λ_h and Λ_v are the input flows of the susceptible humans and mosquitoes including births, μ_h and δ_h are the natural and disease-induced death rates for humans, respectively; η_h is the recovery rate of humans, θ_h is the rate of loss of immunity for recovered humans, γ_h is the developing rate of exposed humans becoming infectious, such that $1/\gamma_h$ is the incubation period, λ_h is the infection rate or the incidence of infection from an infective mosquito to a susceptible human, μ_v is the natural death rate of the mosquitoes, γ_v is the rate of incubating mosquitoes becoming infectious; that is, $1/\gamma_v$ is the extrinsic incubation period of the parasite within the mosquito or the period of sporogony, and λ_h is the infection rate from an infective human to a susceptible mosquito.

The transmission of malaria is not directly from human to human, but through mosquitoes. Let $N_h = S_h + E_h + I_h + R_h$ be the total human population size, and $N_v = S_v + E_v + I_v$ the total mosquito population size. Then, the average number of mosquitoes per human host is N_v/N_h. Let r be the number of bites on a human by an individual mosquito per unit of time. Then, the proportion of infected bites on a human that produce an infection is rI_v/N_v. Suppose that the transmission probability to a human per infected bite is β_v. Then, the infection rate or the

incidence of infection of a human host, λ_h, is determined by

$$\lambda_h = \beta_v r \frac{I_v}{N_v}\frac{N_v}{N_h} = \beta_v r \frac{I_v}{N_h}. \tag{2.3}$$

The infection rate for mosquitoes can be determined in a similar way as for the humans such that

$$\lambda_v = r\frac{\beta_h I_h}{N_h}, \tag{2.4}$$

where β_h is the transmission probability per bite to a susceptible mosquito from an infective human.

Notice that if there is no infection, the human and mosquito populations both have asymptotically stable steady states, $\lim\limits_{t\to\infty} S_h = \Lambda_h/\mu_h$ and $\lim\limits_{t\to\infty} S_v = \Lambda_v/\mu_v$. We then derive the reproductive number for the baseline model (2.1) and (2.2).

The Jacobian matrix at the infection-free equilibrium $(S_h, R_h, I_h, E_h, I_v, E_v, S_v) = \left(S_h^0, 0, 0, 0, 0, 0, S_v^0\right)$, where $S_h^0 = \Lambda_h/\mu_h$ and $S_v^0 = \Lambda_v/\mu_v$, has the form of

$$J_0 := \begin{pmatrix} J_{01} & \cdot & 0 \\ 0 & J_{02} & 0 \\ 0 & \cdot & -\mu_v \end{pmatrix}, \tag{2.5}$$

where

$$J_{01} := \begin{pmatrix} -\mu_h & \theta_h \\ 0 & -\sigma_{h_3} \end{pmatrix}, \quad J_{02} := \begin{pmatrix} -\sigma_{h_2} & \gamma_h & 0 & 0 \\ 0 & -\sigma_{h_1} & r\beta_v & 0 \\ 0 & 0 & -\mu_v & \gamma_v \\ 0 & r\beta_h S_v^0/S_h^0 & 0 & -\sigma_v \end{pmatrix}, \tag{2.6}$$

and we write $\sigma_{h_1} := \mu_h + \gamma_h$, $\sigma_{h_2} := \mu_h + \delta_h + \eta_h$, $\sigma_{h_3} := \mu_h + \theta_h$, and $\sigma_v := \mu_v + \gamma_v$. Then, the infection-free equilibrium is locally asymptotically stable if the eigenvalues of J_{02} all have negative real part.

All off-diagonal elements of $-J_{02}$ are nonpositive, and the first three leading principal minors of $-J_{02}$ are σ_{h_2}, $\sigma_{h_1}\sigma_{h_2}$, and $\sigma_{h_1}\sigma_{h_2}\mu_v$, respectively, which are all positive. Then, it follows from M-matrix theory [5,22] that all eigenvalues of J_2 have negative real part, that is the infection-free equilibrium is locally asymptotically stable, if the determinant

$$\det J_{02} = \sigma_{h_1}\sigma_{h_2}\sigma_v\mu_v - r\beta_v\gamma_h r\beta_h S_v^0/S_h^0\gamma_v = \sigma_{h_1}\sigma_{h_2}\sigma_v\mu_v\left(1 - \frac{r^2\beta_h\beta_v\gamma_h\gamma_v S_v^0}{\sigma_{h_1}\sigma_{h_2}\sigma_v\mu_v S_h^0}\right)$$

is positive.

Define the reproductive number of infection for system (2.1) and (2.2) as

$$R_0 := \left(\frac{r^2\beta_h\beta_v\gamma_h\gamma_v S_v^0}{(\mu_h+\gamma_h)(\mu_h+\delta_h+\eta_h)(\mu_v+\gamma_v)\mu_v S_h^0}\right)^{1/2}. \tag{2.7}$$

Then if $R_0 < 1$, the infection-free equilibrium is locally asymptotically stable. On the other hand, if $R_0 > 1$, then the determinant of J_{02} is negative which implies that there exists at least one positive eigenvalue of J_{02}. Hence the infection-free equilibrium is unstable.

The mean duration of infection within the human population is

$$\bar{\tau}_h = \frac{\gamma_h}{(\mu_h+\gamma_h)(\mu_h+\delta_h+\eta_h)},$$

the mean number of bites per human from a mosquito is

$$\bar{r}_h = r\frac{S_v^0}{S_h^0},$$

and we write $\bar{\beta}_h = \beta_h$. Then the reproductive number of infection for the human population can be expressed as

$$R_0^h = \bar{r}_h \bar{\beta}_h \bar{\tau}^h.$$

Similarly, we can define the mean duration of infection within the mosquito population by

$$\bar{\tau}_v = \frac{\gamma_v}{\mu_v(\mu_v + \gamma_v)}.$$

Then, by writing $\bar{r}_v = r$ and $\bar{\beta}_v = \beta_v$, the reproductive number of infection for the mosquito population can be expressed as

$$R_0^v := \bar{r}_v \bar{\tau}_v \bar{\beta}_v.$$

Therefore, we can rewrite

$$R_0 = \left(R_0^h R_0^v\right)^{1/2}.$$

Model (2.1) and (2.2) may have an endemic equilibrium. The components of an endemic equilibrium need to satisfy the equations

$$\Lambda_h = (\mu_h + \lambda_h) S_h - \theta_h R_h, \tag{2.8a}$$
$$\lambda_h S_h = (\mu_h + \gamma_h) E_h, \tag{2.8b}$$
$$\gamma_h E_h = (\mu_h + \delta_h + \eta_h) I_h, \tag{2.8c}$$
$$\eta_h I_h = (\mu_h + \theta_h) R_h, \tag{2.8d}$$
$$\Lambda_v = (\mu_v + \lambda_v) S_v, \tag{2.8e}$$
$$\lambda_v S_v = (\mu_v + \gamma_v) E_v, \tag{2.8f}$$
$$\gamma_v E_v = \mu_v I_v. \tag{2.8g}$$

Solving equations (2.8a)-(2.8d), in terms of λ_h, we have

$$\begin{aligned} S_h &= \frac{\Lambda_h}{\mu_h + K_1\lambda_h}, & E_h &= \frac{\Lambda_h\lambda_h}{(\mu_h + K_1\lambda_h)\sigma_{h_1}}, \\ I_h &= \frac{\Lambda_h\lambda_h\gamma_h}{(\mu_h + K_1\lambda_h)\sigma_{h_1}\sigma_{h_2}}, & R_h &= \frac{\Lambda_h\lambda_h\gamma_h\eta_h}{(\mu_h + K_1\lambda_h)\sigma_{h_1}\sigma_{h_2}\sigma_{h_3}}, \end{aligned} \tag{2.9}$$

where $K_1 := 1 - \theta_h \frac{\eta_h\gamma_h}{\sigma_{h_1}\sigma_{h_2}\sigma_{h_3}} > 0$. We further write $K_2 := \frac{\sigma_{h_2}\sigma_{h_3} + \sigma_{h_3}\gamma_h + \gamma_h\eta_h}{\sigma_{h_1}\sigma_{h_2}\sigma_{h_3}}$. Then

$$N_h = \frac{\Lambda_h}{(\mu_h + K_1\lambda_h)}(1 + K_2\lambda_h). \tag{2.10}$$

Solving (2.8e)-(2.8g), we have

$$S_v = \frac{\Lambda_v}{\mu_v + \lambda_v}, \quad E_v = \frac{\Lambda_v\lambda_v}{\sigma_v(\mu_v + \lambda_v)}, \quad I_v = \frac{\gamma_v\Lambda_v\lambda_v}{\mu_v\sigma_v(\mu_v + \lambda_v)}. \tag{2.11}$$

Substituting (2.9), (2.10), and (2.11) into (2.3) and (2.4), respectively, we obtain

$$\lambda_h = \frac{r\beta_v(\mu_h + K_1\lambda_h)}{\Lambda_h(1 + K_2\lambda_h)} \frac{\gamma_v\Lambda_v\lambda_v}{\mu_v\sigma_v(\mu_v + \lambda_v)}, \tag{2.12}$$

$$\lambda_v = \frac{r\beta_h\gamma_h\lambda_h}{(1 + K_2\lambda_h)\sigma_{h_1}\sigma_{h_2}} = B_1\frac{\lambda_h}{1 + K_2\lambda_h}, \tag{2.13}$$

where $B_1 := \frac{r\beta_h\gamma_h}{\sigma_{h_1}\sigma_{h_2}}$.

We then substitute (2.13) into (2.12) and define the function

$$F(\lambda_h) := A_1 \frac{1 + K_3\lambda_h}{(1 + K_2\lambda_h)(1 + K_4\lambda_h)}, \tag{2.14}$$

where $A_1 := \frac{r\beta_v\Lambda_v\gamma_v r\beta_h\gamma_h\mu_h}{\Lambda_h\sigma_v\mu_v^2\sigma_{h_1}\sigma_{h_2}} = R_0^2$, $K_3 := \frac{K_1}{\mu_h}$ and $K_4 := K_2 + \frac{B_1}{\mu_v}$, such that there exists an endemic equilibrium for model (2.1) and (2.2) if and only if there is a positive solution to $F(\lambda_h) = 1$. Because

$$F(0) = A_1 = R_0^2, \quad \lim_{\lambda_h\to\infty} F(\lambda_h) = 0,$$

then there exists an endemic equilibrium if $R_0 > 1$.

3. **The stage-structured mosquito population model.** The mosquito population is assumed to be homogeneous without distinguishing their stage difference, and the density dependence is assumed to be based on the total mosquito population in model system (2.1) and (2.2). In fact, most of the works in the literature have also included only mosquito adults in malaria epidemic models and ignored their stage difference.

Mosquitoes undergo complete metamorphosis going through four distinct stages of development during a lifetime: egg, pupa, larva, and adult [4]. After drinking blood, adult females lay a raft of 40 to 400 tiny white eggs in standing water or very slow-moving water. Within a week, the eggs hatch into larvae (sometimes called wrigglers) that breathe air through tubes which they poke above the surface of the water. Larvae eat bits of floating organic matter and each other. Larvae molt four times as they grow; after the fourth molt, they are called pupae. Pupae (also called tumblers) also live near the surface of the water, breathing through two horn-like tubes (called siphons) on their back. Pupae do not eat. When the skin splits after a few days from a pupa, an adult emerges. The adult lives for only a few weeks and the full life-cycle of a mosquito takes about a month [31].

While interspecific competition and predation are rather rare events and could be discounted as major causes of larval mortality, intraspecific competition could represent a major density dependent source for them, and hence the effect of crowding could be an important factor in the population dynamics of mosquitoes [14,17,35]. Moreover, the total size of the mosquito population is usually regulated by the emergence rate of new adult mosquitoes. Furthermore, because of the metamorphic differences, the distinct stages respond to environment differently and have varied regulating factors to the population. Hence, to incorporate environmental factors into the modeling of the mosquito-borne diseases, the metamorphosis stage structure needs to be included.

Nevertheless, to keep our mathematical modeling as simple as possible, due to the fact that the first three stages in a mosquito's life cycle are aquatic, we group the three aquatic stages of mosquitoes into one class and divide the mosquito population into only two classes, one of which consists of the first three stages that we simply call the larvae, denoted by J_v, and one of which consists of all adults, denoted by S_v [25]. In addition, because the intraspecific competition represents a major density dependent source and the effect of crowding could be an important factor in the population dynamics of mosquitoes, we assume that the density dependence is based on larvae only.

We let the birth rate, that is, the oviposition rate of adults be constant, denoted by b_v. We assume the maturation rate for larvae to be a function of the larvae population size such that it is represented as $\alpha(1-g(J_v))$, where $\alpha > 0$ is the maximum emergence rate, $0 \le g(J_v) \le 1$, with $g(0) = 0$, $g'(J_v) > 0$, and $\lim_{J_v \to \infty} g(J_v) = 1$, is the functional response of the emergence due to the intraspecific competition. We let the death rate of larvae be a linear function as $d_0 + d_1 J_v$, where d_0 and d_1 are the density independent and dependent coefficients, respectively, and the death rate of adults be constant μ_v. Then we arrive at the following system which describes the population dynamics of the mosquitoes:

$$\begin{aligned} \frac{dJ_v}{dt} &= b_v S_v - \alpha\left(1 - g(J_v)\right) J_v - (d_0 + d_1 J_v) J_v, \\ \frac{dS_v}{dt} &= \alpha\left(1 - g(J_v)\right) J_v - \mu_v S_v. \end{aligned} \tag{3.1}$$

In particular, we take a functional response for $g(J_v)$ with such a simple form, that satisfies all of the assumptions, as

$$g(J_v) = \frac{J_v}{1 + J_v}.$$

Then system (3.1) becomes

$$\begin{aligned} \frac{dJ_v}{dt} &= b_v S_v - \frac{\alpha J_v}{1 + J_v} - (d_0 + d_1 J_v) J_v, \\ \frac{dS_v}{dt} &= \frac{\alpha J_v}{1 + J_v} - \mu_v S_v. \end{aligned} \tag{3.2}$$

The dynamics of system (3.2) are relatively simple. First, it is easy to see that the positive quadrant is positively invariant under the flow of system (3.2). Then the origin $(0, 0)$ is an equilibrium for system (3.2). Let

$$\hat{r} := \frac{b_v \alpha}{(\alpha + d_0)\mu_v}. \tag{3.3}$$

Simple linear stability analysis shows that the origin is a locally asymptotically stable node if $\hat{r} < 1$, and it is a saddle point if $\hat{r} > 1$. Hence $\hat{r}$ defines the intrinsic growth rate for the mosquito population.

Furthermore, system (3.2) has a positive equilibrium if

$$b_v \frac{\alpha J_v}{1 + J_v} = \mu_v \frac{\alpha J_v}{1 + J_v} + \mu_v (d_0 + d_1 J_v) J_v,$$

or

$$d_1 J_v^2 + (d_0 + d_1) J_v + (\alpha + d_0)\left(1 - \hat{r}\right) = 0. \tag{3.4}$$

Then, if $\hat{r} < 1$, there exists no positive equilibrium, and if $\hat{r} > 1$, there exists a unique positive equilibrium. This unique positive equilibrium, denoted by $(J_v^{(0)}, S_v^{(0)})$, can be analytically solved as

$$J_v^{(0)} = \frac{\left((d_0 + d_1)^2 - 4 d_1 (\alpha + d_0)(1 - \hat{r})\right)^{1/2}}{2 d_1} - \frac{d_0 + d_1}{2 d_1}, \qquad S_v^{(0)} = \frac{\alpha J_v^{(0)}}{\mu_v \left(1 + J_v^{(0)}\right)}. \tag{3.5}$$

The local stability of the positive equilibrium can be determined by the eigenvalues of the Jacobian matrix at the positive equilibrium which has the form of

$$J_2 := \begin{pmatrix} -d_0 - 2d_1 J_v - \dfrac{\alpha}{(1+J_v)^2} & b_v \\ \dfrac{\alpha}{(1+J_v)^2} & -\mu_v \end{pmatrix},$$

where we write, for simplicity, $J_v^{(0)} = J_v$. It is easy to show that $\mathrm{tr} J_2 < 0$, $\det J_2 > 0$, and $(\mathrm{tr} J_2)^2 > 4 \det J_2$. Hence the positive equilibrium is a locally asymptotically stable node.

Moreover, if we let the two equations on the right hand side of (3.2) be $f_1(J_v, S_v)$ and $f_2(J_v, S_v)$, respectively, then it is easy to check that

$$\partial_{J_v} f_1(J_v, S_v) + \partial_{S_v} f_2(J_v, S_v) = -\alpha \frac{1}{(1+J_v)^2} - d_0 - 2d_1 J_v - \mu_v < 0.$$

Hence, by the Bendixson-Dulac Principle [12], system (3.2) has no closed orbits in the positive quadrant of the JS-plane. In summary, we have the following results.

Theorem 3.1. *If $\hat{r} < 1$, the trivial equilibrium $(0, 0)$ of system (3.2) is a globally asymptotically stable node, and there exists no positive equilibrium. If $\hat{r} > 1$, the trivial equilibrium $(0, 0)$ of system (3.2) is unstable, and there exists a unique positive equilibrium, given in (3.5), which is a globally asymptotically stable node.*

4. **The malaria model with two mosquito stages.** We combine the baseline malaria model and the population model for the mosquitoes with two stages to formulate a new stage-structured malaria model in this section.

We use the same equations for humans and include the equations for the mosquito stages in (3.2) in system (2.2). Then we arrive at the following system for the malaria transmissions where the dynamics for humans are governed by the equations

$$\begin{aligned} \frac{dS_h}{dt} &= \Lambda_h - (\mu_h + \lambda_h) S_h + \theta_h R_h, \\ \frac{dE_h}{dt} &= \lambda_h S_h - (\mu_h + \gamma_h) E_h, \\ \frac{dI_h}{dt} &= \gamma_h E_h - (\mu_h + \delta_h + \eta_h) I_h, \\ \frac{dR_h}{dt} &= \eta_h I_h - (\mu_h + \theta_h) R_h, \end{aligned} \tag{4.1}$$

and the dynamics for mosquitoes are governed by the equations

$$\begin{aligned} \frac{dJ_v}{dt} &= b_v N_v - \frac{\alpha J_v}{1+J_v} - (d_0 + d_1 J_v) J_v, \\ \frac{dS_v}{dt} &= \frac{\alpha J_v}{1+J_v} - \mu_v S_v - \lambda_v S_v, \\ \frac{dE_v}{dt} &= \lambda_v S_v - (\mu_v + \gamma_v) E_v, \\ \frac{dI_v}{dt} &= \gamma_v E_v - \mu_v I_v, \end{aligned} \tag{4.2}$$

where $N_v = S_v + E_v + I_v$. Here we denote the mosquito larvae by J_v, and assume $\hat{r} > 1$, that is, $b_v \alpha > \mu_v(\alpha + d_0)$, such that the trivial solution is unstable.

Again we first determine the reproductive number for model (4.1) and (4.2) by investigating the eigenvalues of the Jacobian matrix at the infection-free equilibrium

$(S_h, R_h, I_h, E_h, I_v, E_v, S_v, J_v) = \left(S_h^0, 0, 0, 0, 0, 0, S_v^{(0)}, J_v^{(0)}\right)$, with $S_h^0 = \Lambda_h/\mu_h$, and $J_v^{(0)}$ and $S_v^{(0)}$ given in (3.5),

$$J_3 := \begin{pmatrix} J_{01} & \cdot & 0 \\ 0 & J_{02} & 0 \\ 0 & \cdot & J_{03} \end{pmatrix},$$

where J_{01} and J_{02} are the same as in (2.6) and

$$J_{03} := \begin{pmatrix} -\mu_v & \dfrac{\alpha}{\left(1+J_v^{(0)}\right)^2} \\ b_v & -d_0 - 2d_1 J_v^0 - \dfrac{\alpha}{(1+J_v^{(0)})^2} \end{pmatrix}. \tag{4.3}$$

We assume that $(J_v^{(0)}, S_v^{(0)})$ is an asymptotically stable node for system (3.2) such that the eigenvalues of J_{03} both have negative real part. The stability of J_3 then is determined only by that of J_{02}, and hence we have the following formula for the reproductive number

$$R_0 := \left(\frac{r^2 \beta_h \beta_v \gamma_h \gamma_v S_v^{(0)}}{(\mu_h+\gamma_h)(\mu_h+\delta_h+\eta_h)(\mu_v+\gamma_v)\mu_v S_h^0} \right)^{1/2}. \tag{4.4}$$

We then look for an endemic equilibrium for system (4.1) and (4.2) and consider the equations

$$\Lambda_h = (\mu_h + \lambda_h)\, S_h - \theta_h R_h, \tag{4.5a}$$
$$\lambda_h S_h = (\mu_h + \gamma_h)\, E_h, \tag{4.5b}$$
$$\gamma_h E_h = (\mu_h + \delta_h + \eta_h)\, I_h, \tag{4.5c}$$
$$\eta_h I_h = (\mu_h + \theta_h)\, R_h, \tag{4.5d}$$
$$b_v N_v = \frac{\alpha J_v}{1+J_v} + (d_0 + d_1 J_v) J_v, \tag{4.5e}$$
$$\frac{\alpha J_v}{1+J_v} = (\mu_v + \lambda_v) S_v, \tag{4.5f}$$
$$\lambda_v S_v = (\mu_v + \gamma_v) E_v, \tag{4.5g}$$
$$\gamma_v E_v = \mu_v I_v. \tag{4.5h}$$

Solving equations (4.5a)-(4.5d), in terms of λ_h, we have the same formulas for S_h, E_h, I_h, and R_h, as in (2.9). To find the components at the endemic equilibrium for mosquitoes, it first follows from (4.5g) and (4.5h) that

$$N_v = \left(1 + \frac{\lambda_v}{\mu_v+\gamma_v} + \frac{\gamma_v \lambda_v}{\mu_v(\mu_v+\gamma_v)}\right) S_v = \frac{\mu_v + \lambda_v}{\mu_v} S_v. \tag{4.6}$$

Then, substituting (4.6) into (4.5e) and from (4.5f) yields

$$d_1 J_v^2 + (d_0+d_1) J_v + d_0 + \alpha - \frac{\alpha b_v}{\mu_v} = d_1 J_v^2 + (d_0+d_1) J_v + (d_0+\alpha)(1-\hat{r}) = 0. \tag{4.7}$$

which is the same as (3.4). Thus, there exists a unique positive solution $J_v > 0$ if and only if $\hat{r} > 1$.

We next solve equations (4.5f)-(4.5h), in terms of λ_v and J_v, and obtain

$$S_v = \frac{\alpha J_v}{(1+J_v)(\mu_v+\lambda_v)},\ E_v = \frac{\alpha J_v \lambda_v}{(1+J_v)(\mu_v+\lambda_v)\sigma_v},\ I_v = \frac{\alpha\gamma_v J_v \lambda_v}{(1+J_v)(\mu_v+\lambda_v)\sigma_v\mu_v}. \tag{4.8}$$

Similarly as in Section 2, we have

$$\lambda_h = \frac{r\beta_v(\mu_h+K_1\lambda_h)}{\Lambda_h(1+K_2\lambda_h)}\frac{\alpha\gamma_v J_v\lambda_v}{(1+J_v)(\mu_v+\lambda_v)\sigma_v\mu_v}, \tag{4.9}$$

$$\lambda_v = \frac{r\beta_h\gamma_h\lambda_h}{(1+K_2\lambda_h)\sigma_{h_1}\sigma_{h_2}}. \tag{4.10}$$

By substituting (4.10) into (4.9), we arrive at

$$B_2\frac{1+K_3\lambda_h}{(1+K_2\lambda_h)(1+K_4\lambda_h)}\frac{J_v}{1+J_v} = 1,$$

that is,

$$\frac{(1+K_2\lambda_h)(1+K_4\lambda_h)}{1+K_3\lambda_h} = R_0^2, \tag{4.11}$$

where $B_2 := \frac{r^2\beta_v\alpha\gamma_v\beta_h\gamma_h\mu_h}{\Lambda_h\sigma_v\mu_v\sigma_{h_1}\sigma_{h_2}\mu_v} = \frac{1+J_v}{J_v}R_0^2$. Hence, as in Section 2, there exists an endemic equilibrium if $R_0 > 1$.

It is widely accepted that environmental change, particularly, climate change, is real and has significant influence on human health and on emerging arbovirus diseases ([18, 20]. More specifically, the potential effects of the environmental or climate change on the malaria transmission are substantial, especially through the mosquito population. The development of the three aquatic stages and their emergence to adults are strongly temperature dependent. The length of time required, e.g. for the eggs of some mosquito species to hatch is one, three, and ten days, at temperature 30°C, 20°C, and 10°C, respectively, and the embryonic development cannot be completed at 4°C. Water temperature regulates the speed of mosquito breeding. The larvae of some mosquito species hatch in spring time when the water temperature reaches 10°C and the hatching rate reaches its peak at 15°C. To develop common malaria mosquito first instar larvae take 65 days, at temperature $T = 12$°C to emerged adults, but only 7.3 days at $T = 31$°C [4, 8].

The duration of larval and pupal stages is also temperature-dependent such that it takes about 30-40 days at the water temperature 10-15°C, but only 6-7 days at 30°C [4, 8]. The duration for an egg to reach the adult stage of an anopheline mosquito gets prolonged at lower temperature and is reduced as the temperature increases. The minimum and maximum thresholds for the development of the aquatic stages are 11°C to 35°C. It only takes about 10 days at an optimum temperature of 28°C [9, 27, 29, 40].

While there have been long history and great efforts on mathematical modeling of malaria transmissions, there are not many works that incorporate the effects of climate change in the literature. The existing climate-related malaria models have made progress to help our understanding the effects of climate change and in predicting the future transmission patterns [26]. However, because of the complexity of the effects, analysis becomes mathematically intractable in some of those models [21, 38].

The stage-structured model given in system (4.1) and (4.2), nevertheless, provides a theoretical framework for incorporating environmental or climate change into a

reasonably simplified and mathematically tractable malaria model and can help us gain insight into the effects of climate change on the malaria transmission.

Due to the fact that many factors are involved in the malaria transmission and there is lack of complete data available, we focus on only a few major factors and demonstrate how sensitivity analysis can be done in the stage-structured model (4.1) and (4.2).

The extrinsic incubation period of the parasite within the mosquito, or the period of sporogony, determined by the $1/\gamma_v$ in system (4.2), is one of the major factors that affects the malaria transmission because it influences the number of infected mosquitoes that live long enough to become infectious, and it is extremely temperature sensitive [28, 36]. The other parameters in our model that are more temperature or climate sensitive are the birth rate of the mosquitoes, the maximum emergence rate of mosquito larvae to adults, and the density-independent death rate of the larvae.

Consider a factor that is closely related to environmental or climate change, such as temperature or humidity, and use it as an independent variable, denoted by τ. Assume that extrinsic incubation period of the parasite within the mosquito, the birth rate of the mosquitoes, the maximum emergence rate of mosquito larvae to adults, and the larvae death rate are functions of this factor such that $\gamma_v = \gamma_v(\tau)$, $b_v = b_v(\tau)$, $\alpha = \alpha(\tau)$, and $d_0 = d_0(\tau)$. Then, this factor is incorporated into the reproductive number as

$$R_0(\tau) := \left(\frac{r^2 \beta_h \beta_v \gamma_h \gamma_v(\tau) S_v^0(\tau)}{(\mu_h + \gamma_h)(\mu_h + \delta_h + \eta_h)(\mu_v + \gamma_v(\tau))\mu_v S_h^0} \right)^{1/2} := C \left(\frac{\gamma_v(\tau) S_v^0(\tau)}{\mu_v + \gamma_v(\tau)} \right)^{1/2},$$

where C is a combination of other parameters that are assumed less sensitive to this environmental factor,

$$S_v^0(\tau) = \frac{\alpha(\tau) J_v^0(\tau)}{\mu_v (1 + J_v^0(\tau))}$$

is the number of adult mosquitoes at the infection-free equilibrium with the number of mosquito larvae $J_v^0(\tau)$ determined by

$$J_v^0(\tau) = \frac{\left((d_0(\tau) - d_1)^2 \mu_v^2 + 4 d_1 \mu_v \alpha(\tau)(b_v(\tau) - \mu_v) \right)^{1/2} - (d_0(\tau) + d_1)\mu_v}{2 d_1 \mu_v}.$$

The sensitivity of R_0 with respect to the environmental factor τ can be described by the derivative of R_0 with respect to τ as

$$\frac{1}{C^2} \frac{\partial (R_0(\tau))^2}{\partial \tau} = \frac{\mu_v S_v^{(0)}(\tau)}{(\mu_v + \gamma_v(\tau))^2} \frac{\partial \gamma_v(\tau)}{\partial \tau} + \frac{\gamma_v(\tau)}{\mu_v + \gamma_v(\tau)} \frac{\partial S_v^{(0)}(\tau)}{\partial \tau}, \tag{4.12}$$

where

$$\begin{aligned} \frac{\partial S_v^{(0)}(\tau)}{\partial \tau} &= \frac{\partial \alpha(\tau)}{\partial \tau} \frac{J_v^0(\tau)}{\mu_v (1 + J_v^0(\tau))} + \frac{\alpha(\tau)}{\mu_v (1 + J_v^0(\tau))^2} \frac{\partial J_v^0(\tau)}{\partial \tau} \\ &= \frac{1}{\mu_v (1 + J_v^0(\tau))} \left(J_v^0(\tau) \frac{\partial \alpha(\tau)}{\partial \tau} + \frac{\alpha(\tau)}{1 + J_v^0(\tau)} \frac{\partial J_v^0(\tau)}{\partial \tau} \right). \end{aligned} \tag{4.13}$$

A complete analysis for the sensitivity of the reproductive number on the key factors is still complex depending on the formulas of the factors and available data. However the expression (4.12) with (4.13) provides a theoretical framework and an analytic basis for further investigation of effects of environmental or climate change on the malaria transmission.

5. **Forward or backward bifurcation.** In most classical epidemic models, as the reproductive number is less than one, the infection-free equilibrium is the only equilibrium and is globally asymptotically stable. As the reproductive number is increased and exceeds one, the infection-free equilibrium becomes unstable and a stable positive endemic equilibrium is bifurcated. Such a phenomenon is referred to as forward bifurcation. There, however, have appeared a good number of epidemic models in the literature where an unstable positive endemic equilibrium bifurcates through a transcritical bifurcation when the reproductive number is less than one, which is referred to as backward bifurcation [2, 6, 13, 16, 19, 39]. In this section, we show that both the baseline model (2.1) and (2.2) and the stage-structured model (4.1) and (4.2) undergo backward bifurcation.

As it is shown in Section 2 and 4, the endemic equilibria of system (2.1) and (2.2) satisfies equation $F(\lambda_h) = 1$ and the endemic equilibria of system (4.1) and (4.2) satisfies (4.11). These endemic equilibria correspond to the positive roots λ_h of the equation

$$(1+K_2\lambda_h)(1+K_4\lambda_h)-R_0^2(1+K_3\lambda_h) = K_2K_4\lambda_h^2+(K_2+K_4-A_1K_3)\lambda_h+1-R_0^2 = 0. \tag{5.1}$$

If $R_0 > 1$, there exists a unique positive root of (5.1), that is, a unique endemic equilibrium of (2.1) and (2.2), or (4.1) and (4.2).

For $R_0 \le 1$, we introduce $c := R_0^2 - 1$ and consider the quadratic equation

$$F_1(\lambda, c) := K_2K_4\lambda^2 + \big(K_2 + K_4 - (1 + c)K_3\big)\lambda - c = 0. \tag{5.2}$$

The curve of (5.2) hence corresponds to the bifurcation curve of λ as a function of c or R_0.

For convenience, we solve (5.2) for c in terms of λ and get

$$c(\lambda) = \frac{K_2K_4\lambda^2 + (K_2 + K_4 - K_3)\lambda}{1 + K_3\lambda}, \tag{5.3}$$

for $\lambda \ge 0$. Then, a positive solution $\lambda > 0$ to $c(\lambda) = 0$ corresponds to an endemic equilibrium of (2.1) and (2.2), or (4.1) and (4.2).

Equation $c(\lambda) = 0$ has a nonzero root

$$\lambda^* = \frac{K_3 - (K_2 + K_4)}{K_2K_4}. \tag{5.4}$$

Hence, if

$$K_2 + K_4 > K_3,$$

the nonzero root is negative and thus there is no backward bifurcation. If

$$K_2 + K_4 < K_3, \tag{5.5}$$

there exists a positive root $\lambda^* > 0$, which implies that a backward bifurcation appears.

Suppose condition (5.5) is satisfied. Then function $c(\lambda)$ in (5.3) has the unique positive critical point

$$\begin{aligned}\bar{\lambda} =& \frac{-K_2K_4 + \big(K_2K_4\left(K_2K_4 + K_3^2 - K_3(K_2 + K_4)\right)\big)^{1/2}}{K_2K_3K_4} \\ =& \frac{-K_2K_4 + (K_2K_4(K_3 - K_2)(K_3 - K_4))^{1/2}}{K_2K_3K_4},\end{aligned}$$

and simple straightforward calculation yields

$$c(\bar{\lambda}) = -K_2K_4(\bar{\lambda})^2.$$

If we define

$$R_b^2 = 1 + c(\bar{\lambda}) = \frac{K_3(K_2+K_4) - 2K_2K_4 + 2\left(K_2K_4(K_3-K_4)(K_3-K_2)\right)^{1/2}}{K_3^2}, \tag{5.6}$$

then model system (2.1) and (2.2) has a backward bifurcation at $R_0 = 1$ such that there are two endemic equilibria for $R_b < R_0 < 1$, if $K_2 + K_4 < K_3$.

We can also describe the bifurcation curve, through the graph of λ as a function of R_0, as follows.

Suppose a backward bifurcation appears. Then there exist two solutions to equation (5.2)

$$\lambda(c) = \frac{(1+c)K_3 - (K_2+K_4) \pm \left(\left((1+c)K_3 - (K_2+K_4)\right)^2 + 4K_2K_4c\right)^{1/2}}{2K_2K_4}, \tag{5.7}$$

for $R_b < R_0 < 1$.

It follows from

$$\frac{\partial F_1(\lambda, c)}{\partial c} = \left(2K_2K_4\lambda + K_2 + K_4 - (1+c)K_3)\right)\frac{d\lambda}{dc} - K_3\lambda - 1 = 0,$$

that, at the solutions of (5.2),

$$\left(2K_2K_4\lambda + K_2 + K_4 - (1+c)K_3)\right)\frac{d\lambda}{dc} = K_3\lambda + 1 > 0. \tag{5.8}$$

Substituting (5.7) into the left hand side of (5.8), we have

$$\pm\left(\left((1+c)K_3 - (K_2+K_4)\right)^2 + 4K_2K_4c\right)^{1/2} \frac{d\lambda}{dc} > 0,$$

where the plus and minus signs correspond to the larger and smaller solutions of (5.2), respectively. Then, for the larger (smaller) solution λ, we have $\frac{d\lambda}{dc} > (<)\ 0$. That is, the slope of the bifurcation curve is positive at the point with the larger λ, and negative at the point with the smaller λ, for each R_0 between R_b and 1.

We summarize the results about endemic equilibria as follows.

Theorem 5.1. *System (2.1) and (2.2), or (4.1) and (4.2), has a unique endemic equilibrium if $R_0 > 1$. Under the condition of $K_2 + K_4 < K_3$, there exists a positive number, $0 < R_b < 1$, given in (5.6), such that system (2.1) and (2.2), or (4.1) and (4.2), has no endemic equilibrium if $R_0 < R_b$, a unique endemic equilibrium if $R_0 = R_b$, and two endemic equilibria, which implies a backward bifurcation, if $R_b < R_0 < 1$. On the other hand, if $K_2 + K_4 \geq K_3$, there exists no endemic equilibrium for either system, and backward bifurcation cannot occur for $R_0 < 1$.*

We have not been able to show the stability of the endemic equilibrium corresponding to the larger λ, for $R_0 < 1$. However, because the bifurcation at $R_0 = 1$ is a transcritical bifurcation, the endemic equilibrium corresponding to the smaller λ, for $R_0 < 1$, is unstable [23].

6. **Conclusion.** To build a theoretical framework and a fundamental analytic basis for incorporating the impact of environmental or climate change on the malaria transmission, we first formulate a baseline compartmental malaria model with homogeneous mosquito population in Section 2. We derive a formula for the reproductive number R_0 and give a basic study of the malaria transmission dynamics. We then consider the metamorphosis of mosquitoes with distinct stages during their lifetime. To keep our model more tractable in mathematical analysis, we combine the first three aquatic stages of mosquitoes into one class, and divide the mosquito population into only two classes, the larvae and the adults, and formulate a simple stage-structured mosquito population model in Section 3. After a simple mathematical analysis on the stage-structured mosquito population model, we introduce the structured mosquitoes into the baseline malaria model and formulate a stage-structured malaria model in Section 4. We derive the formula of the reproductive number for the stage-structured malaria model, and then explore how the impact of environmental or climate change on the malaria transmission can be incorporated. We focus on a few major parameters that are more sensitive to environmental or climate change and consider them as functions of factors that represent environmental or climate changes. We demonstrate that the sensitivity of the reproductive number, including the major parameters, to those factors can lead to our better understanding. While our study is only preliminary, with further data of environmental or climate change on the malaria transmission parameters available, a deeper understanding may be achieved based on our fundamental analytic results.

As backward bifurcation has been exhibited in many epidemic models, we also show, in Section 5, that both of the baseline and the stage-structured malaria models undergo backward bifurcation although our stability analysis is not complete. The different dynamical behavior of the models in this study, compared to the behavior of most classical epidemiological models, and the possible occurrence of backward bifurcation make control of malaria more difficult, as pointed out in [6]. More attention should be drawn with regard to such a phenomenon. Further investigation is needed and is planned in our further studies.

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