



## Coupling ecology and evolution: malaria and the *S*-gene across time scales

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### Abstract

Malaria has long been a scourge to humans. The exceptionally high mortality in some regions has led to strong selection for resistance, even at the cost of increased risk of potentially fatal red blood cell deformities in some offspring. In particular, genes that confers resistance to malaria when they appear in heterozygous individuals are known to lead to sickle-cell anemia, or other blood diseases, when they appear in homozygous form. Thus, there is balancing selection against the evolution of resistance, with the strength of that selection dependent upon malaria prevalence. Over longer time scales, the increased frequency of resistance in a population might be expected to decrease the frequency of malaria and reduce selection for resistance. However, possession of the sickle-cell gene leads to longer-lasting parasitaemia in heterozygote individuals, and therefore the presence of resistance may actually increase infection prevalence. In this paper, we explore the interplay among these processes, operating over very different time scales. In particular, we show that on the fast time scale of malarial dynamics, the disease level reaches an equilibrium; on the slower, evolutionary time scale, this equilibrium tracks gene frequency. We analyze the slow time scale dynamics to investigate the impact of malaria on the evolution of resistance.

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## 1. Introduction

The dynamics of ecological communities require attention to the interplay between population dynamics and evolutionary change in interacting species [1]. In such systems, fitnesses are not constant, but may vary not only with gene frequencies, but also with species densities. Because of the tight interaction between individuals of two species, host–parasite interactions provide the ideal systems for investigating such coevolutionary interactions. Of particular interest has been the interplay between the evolution of virulence and resistance [2–7] or the maintenance of sex in species where parthenogenesis is possible [8–10]. These models tend to focus on the evolution of parasites, or the role of parasites on host evolution. Few models couple host evolution with parasite population dynamics, in part because parasites have shorter generation times, and thus evolve more quickly, meaning that the models must interface processes occurring at very different time scales [11–13].

A classic co-evolutionary dynamic occurs between humans and *Plasmodium falciparum* the mosquito-borne protozoan blood parasite that causes malaria. Falciparum malaria is a leading cause of global mortality, and mathematical models of malaria transmission have a long and rich history, dating back to Ross [14]. Malaria is also associated with several genetic blood disorders, notably sickle-cell anemia in individuals who are homozygous for the *S*-gene. The gene causing sickling provides a classic example of overdominance; heterozygotes are more fit than either homozygote when malaria is present [15,16]. Classical models demonstrating the stability of the balanced polymorphism appear in almost every basic course in population genetics, but with the assumption that the fitnesses of the three genotypes are constant. On the other hand, attention to the epidemiology of malaria typically leads to models that ignore explicit genetic structures in the host populations [17]. In this paper, we seek to bring these two perspectives into contact with each other, and to develop an understanding of the interplay among processes at very different time scales.

The special features of sickle-cell dynamics have not been addressed in the few previous mathematical studies of parasite–host coevolution in malaria [18] or more general infectious-disease terms [11–13,19]. Determining the quantitative relationship between the mortality rates from malaria and the frequency of the *S*-gene in a population is an old and difficult problem [15,16,20]. They are complicated because infectious-disease epidemiology and human demography occur on dramatically different temporal scales: parasite levels in infected humans fluctuate over hours to days, malaria incidence in a human population waxes and wanes from month to month and season to season, and human generations change over decades. Moreover, reproductive decisions by humans may change the fitness costs associated with the *S*-gene, so the classical formulas based on discrete generations are biased [21]. Also, though not considered here, other heritable hematological and immunological traits may influence individual response to malaria infection, so that actual levels of protection are likely to be polygenic.

The equilibrium frequency of the *S*-gene is a balance between excess mortality from malaria in individuals lacking the *S*-gene, and high mortality rates of *S*-gene homozygotes from sickle-cell disease. The different evolutionary time scales of hosts and parasites and the complicated biology raise interesting questions about the endemic dynamics of malaria. Increased frequency of the *S*-gene might produce marginal benefits to other individuals in the population if the lower parasitemia in *S*-gene heterozygotes reduces transmission of *P. falciparum* to mosquitoes. However,

since malaria selects for the *S*-gene, an *S*-gene acting ‘selfishly’ might evolve to enhance *Plasmodium* transmission, and thus increase its own frequency. Protective effects of the *S*-gene are associated with reduced parasitemia and clinical symptoms [22–25]. It is not clear whether the *S*-gene substantially changes susceptibility to infection or transmission to mosquitoes. Field and laboratory experiments indicate that, despite lower densities of the non-transmissible blood forms of the parasite, the infectivity of the transmissible blood forms is enhanced in sickle-cell individuals [26–29]. As it seems likely that this enhancement is mediated by reticulocytosis in the host, a life-history trade-off in the parasite, or both, it is at least circumstantially connected with a wealth of topics in malaria-parasite evolution, including speciation [30–32] and pathogenesis [33,34].

We develop a mathematical model that explicitly couples malaria transmission dynamics with changes in the frequency of the *S*-gene, and use the model to examine the temporal scales over which human population genetics respond to malaria. To deal with the complications of multiple temporal scales, we apply singular perturbation techniques to separate components into fast and slow parts, and analyze each separately. Similar methods have been used less formally to develop approximations to some aspects of malaria mortality [20].

## 2. Model

### 2.1. Model formulation

Although the population dynamics of malaria and the population genetics of the sickle-cell genes occur on very different time scales, it is straightforward to develop an appropriate model relating these. The high mortality associated with malaria has led to strong historical selection for resistance, and hence for single major genes conferring resistance in heterozygotes, despite the associated burden borne by homozygotes. We thus build on existing detailed knowledge of the genetics of resistance, focusing on a single locus with two alleles. Our foundation is thus the classical Ross–McDonald model for the spread of malaria, expanded to include the relevant genetic structure of the host.

Let  $u_1$  denote the density of uninfected humans of genotype *AA*. Similarly,  $u_2$  denotes the population density of genotype *AS*. Furthermore, let  $v_1$  and  $v_2$  represent the population densities of infected individuals of each genotype. We ignore *SS* individuals; high mortality rates from sickle-cell disease are typical in countries with high transmission rates of falciparum malaria, so these individuals rarely reach reproductive maturity. An extended model including the *SS* individuals can be studied using similar methods but it is very difficult to interpret the threshold conditions due to the complexity of the model. Finally, let  $z$  be the fraction of mosquitoes that are transmitting malaria. The fraction of the *AS* individuals in the population is

$$w = \frac{u_2 + v_2}{N},$$

where  $N$  is the total human population density,  $u_1 + v_1 + u_2 + v_2$ . The frequency of the *S* gene is  $q = w/2$  and the frequency of the *A* gene is denoted  $p = 1 - q$ .

Let  $b(N)$  denote the human per-capita birth rate, possibly density dependent, with a constant per-capita natural mortality of  $m$ . To couple ecology and evolution, we make two assumptions. First, we assume that the ratio of mosquitoes to humans is a constant,  $c$ . This is a standard assumption in the modelling of malaria (ever since the original Ross–McDonald model). Any other assumption about variability in the ratio of mosquitoes to humans (M/H) would need to be justified. No evidence exists to suggest that the transmission dynamics of malaria have dramatically changed in hyper-endemic areas of Africa over the last several centuries. Malaria control has been mainly local, with no lasting effects on the long-term averages. M/H may have changed locally, but we have no evidence to support a general increase or decrease, despite changes in human population density. The main exception to all this may have been a decline in malaria mortality due to the use of chloroquine, a trend that has reversed with the spread of chloroquine resistance [35]. Most malaria mortality occurs in sub-Saharan Africa where *Anopheles gambiae* is the most important vector. *A. gambiae* thrives in and around the habitats created by humans, so humans create conditions favorable for *A. gambiae*. Over the time-scale of the last 200–300 years, the constant M/H assumption is a reasonable one, for any particular area, in part because of the ecology of *A. gambiae*. The most important exception to many of these rules is urban malaria, because of the concentration of humans into cities. The urbanization of Africa is a fairly recent phenomenon, and malaria remains endemic in many African cities [36]. Urbanization may affect M/H, but evidence is lacking. For now, the constant M/H assumption remains the reasonable null model and is valid over all the time scales being explicitly considered in this paper.

However, over the evolutionary time periods longer than those considered explicitly in this paper, this ratio surely will change, due to fluctuations about the mean as well as secular changes, for example associated with global climate change. Model predictions may be very sensitive to relaxation of the assumption. This simply reinforces the importance of investigating the dynamics of our baseline model, which can illuminate the factors sustaining the present quasi-steady state, so that future research can predict how climate change, by affecting the distribution of mosquitoes, might upset the balance between malaria dynamics, evolved resistance, and associated blood diseases. In this regard, it will also be important to incorporate spatial differences in climate and disease, and the importance of changing patterns of human mobility. Thus the model presented in this paper should be regarded as a foundation on which to build in a world of accelerating change.

Second, we assume that the fraction of each genotype born into the population is denoted  $P_i$  given by

$$P_1 = p^2, \quad P_2 = 2pq.$$

The transmission of malaria between humans and mosquitoes is governed by some basic epidemiological parameters. The human biting rate is denoted  $a$ , and average life of an infected mosquito is  $1/\delta$ . The probability that a human develops a parasitemia from a bite is denoted  $\theta_i$ ; we assume that  $\theta_1 \geq \theta_2$ . The disease induced death rate is denoted  $\alpha_i$ , and we assume that  $\alpha_1 \gg \alpha_2$ . In addition, we consider that *AS* individuals may die faster than *AA* individuals from causes other than malaria, and the excess rate of mortality for *AS* individuals is  $v$ . The probability that a mosquito acquires plasmodium from biting an individual of type  $i$  is denoted by  $\phi_i$ . The average time until a victim of malaria recovers, denoted  $1/\gamma_i$ , may be different in *AA* and *AS* individuals. We have listed all the variables and parameters in Table 1.

Table 1  
Definition of variables and parameters

Name	Description	Notes
$i = 1$	$AA$ individuals	
$i = 2$	$AS$ individuals	
$u_i$	Number of uninfected humans of genotype $i$	
$v_i$	Number of infected humans of genotype $i$	
$x_i$	Fraction of humans that are infected and have genotype $i$	$\frac{u_i}{N}$
$y_i$	Fraction of humans that are uninfected and have genotype $i$	$\frac{v_i}{N}$
$z$	Fraction of mosquitoes with plasmodium	
$w$	Frequency of $AS$ individuals	$x_2 + y_2$
$N$	Population size	
$q$	Frequency of $S$ -gene	$\frac{w}{2}$
$\theta_i$	Probability a human of type $i$ acquires a parasitemia per bite	$\theta_1 > \theta_2$
$\gamma_i$	Rate of recovery from malaria	$\gamma_1 < \gamma_2$
$a$	Biting rate per human per mosquito	
$c$	Number of mosquitoes per human	
$\phi_i$	Probability a mosquito acquires plasmodium from biting a human of type $i$	$\phi_1 > \phi_2$
$\delta$	Mosquito death rate	
$m$	Per-capita natural human death rate	
$\alpha_i$	Per-capita malaria-induced death rate of humans of type $i$	$\alpha_1 \geq \alpha_2$
$v$	Extra death rate of $AS$ individuals due to the sickle-cell genes	
$b(N)$	Per-capita Birth Rate of humans	
$P_1$	Fraction of total births of genotype $AA$	$1 - w + \frac{w^2}{4}$
$P_2$	Fraction of total births of genotype $AS$	$w\left(1 - \frac{w}{2}\right)$

The changes in population density of each genotype with each infection status are described by a set of five coupled ordinary differential equations:

$$\begin{aligned}
 \dot{u}_i &= P_i b(N)N - m_i u_i - a\theta_i c z u_i + \gamma_i v_i, \\
 \dot{v}_i &= a\theta_i c z u_i - (m_i + \gamma_i + \alpha_i) v_i, \\
 \dot{z} &= (1 - z) \left( a\phi_1 \frac{v_1}{N} + a\phi_2 \frac{v_2}{N} \right) - \delta z, \quad i = 1, 2,
 \end{aligned}
 \tag{1}$$

where  $m_1 = m$  and  $m_2 = m + v$ .

### 2.2. Mathematical analysis of the model

It is both mathematically convenient and biologically relevant to introduce new variables for prevalence of malaria infections in each genotype,  $x_i = u_i/N$  and  $y_i = v_i/N$ , as well as the frequency of the  $S$ -gene,  $w = x_2 + y_2 = 2q$ . The equations in the new variables are derived from the original (1) using the chain rule. We note for clarification that  $x_1 + y_1 + x_2 + y_2 = 1$  and  $x_1 + y_1 = 1 - w$ . We also introduce notation to reduce the number of parameters,  $\beta_{hi} = a\theta_i c$ ,

$\beta_{vi} = a\phi_i$ ,  $i = 1, 2$ . Then we obtain the following equivalent system to (1) in the terms that describe important epidemiological, demographic, and population genetic quantities,  $y_1$ ,  $y_2$ ,  $z$ ,  $w$ , and  $N$ :

$$\begin{cases} \dot{y}_1 = \beta_{h1}z(1 - w - y_1) - (m_1 + \gamma_1 + \alpha_1)y_1 - y_1\dot{N}/N, \\ \dot{y}_2 = \beta_{h2}z(w - y_2) - (m_2 + \gamma_2 + \alpha_2)y_2 - y_2\dot{N}/N, \\ \dot{z} = (1 - z)(\beta_{v1}y_1 + \beta_{v2}y_2) - \delta z, \\ \dot{w} = P_2b(N) - \alpha_2y_2 - m_2w - w\dot{N}/N, \\ \dot{N} = N((P_1 + P_2)b(N) - m_1(1 - w) - m_2w - \alpha_1y_1 - \alpha_2y_2). \end{cases} \quad (2)$$

Although most of the equations assume a general birth function  $b(N)$ , our detailed mathematical analysis for the specific case in which  $b(N)$  is a density dependent per-capita birth function,  $b(N) = b(1 - N/K)$ , where  $b$  is a constant (the maximum birth rate when population size is small) and  $K$  is approximately the density dependent reduction in birth rate.

### 2.2.1. Fast dynamics of epidemics

The relevant parameters vary across many orders of magnitude. For example, the demographic parameters ( $b$  and  $m_i$ ) and the genetic parameters ( $\alpha_i$ ) are on the order of 1/decades, and the malaria disease parameters ( $\beta_{hi}$ ,  $\gamma_i$ ,  $\beta_{vi}$ , and  $\delta$ ) are on the order of 1/days. Hence, although the malaria disease dynamics and the changes in genetic composition are two coupled processes, the former occurs on a much faster time scale than the latter. Let  $m_i = \epsilon\tilde{m}_i$ ,  $\alpha_i = \epsilon\tilde{\alpha}_i$ , and  $b = \epsilon\tilde{b}$  with  $\epsilon > 0$  being small. We can use this fact to simplify the mathematical analysis of the full model with the use of singular perturbation techniques, which allows us to separate the time scales of the different processes (see Appendix A). By letting  $\epsilon = 0$  we obtain the following system for the fast dynamics (see Appendix A):

$$\begin{cases} \dot{y}_1 = \beta_{h1}z(1 - y_1 - w) - \gamma_1y_1, \\ \dot{y}_2 = \beta_{h2}z(w - y_2) - \gamma_2y_2, \\ \dot{z} = (1 - z)(\beta_{v1}y_1 + \beta_{v2}y_2) - \delta z, \end{cases} \quad (3)$$

which describes the epidemics of malaria for a given distribution of genotypes determined by  $w$ . Here, on the fast time scale,  $w$  is considered as a parameter. On the fast time scale, the basic reproductive number of malaria disease can be calculated as the leading eigenvalue of the next generation matrix [37] (see Appendix A):

$$\mathcal{R}_0 = \mathcal{R}_1(1 - w) + \mathcal{R}_2w, \quad (4)$$

where

$$\mathcal{R}_i = \frac{\beta_{hi}\beta_{vi}}{\gamma_i\delta}, \quad i = 1, 2 \quad (5)$$

involves parameters associated with malaria transmission between mosquitoes and humans of genotype  $i$ . In fact,  $\mathcal{R}_i$  (or  $\sqrt{\mathcal{R}_i}$ ) is the basic reproductive number when the population consists of entirely humans of genotype  $i$ . We show in Appendix A that, when  $\mathcal{R}_0 < 1$ , the disease-free equilibrium of the system (3) is locally asymptotically stable; and when  $\mathcal{R}_0 > 1$ , the system (3) has a unique non-trivial equilibrium  $E^* = (y_1^*, y_2^*, z^*)$  given by

$$y_1^* = \frac{T_{h1}z^*}{1 + T_{h1}z^*}(1 - w), \quad y_2^* = \frac{T_{h2}z^*}{1 + T_{h2}z^*}w, \quad (6)$$

where  $z^*$  is the unique positive solution of a quadratic equation whose coefficients are functions of  $w$  (see (A.7) and (A.8)), and

$$T_{hi} = \frac{\beta_{hi}}{\gamma_i}, \quad i = 1, 2. \tag{7}$$

2.2.2. Slow dynamics of population genetics

By using the re-scaled time  $\tau = \epsilon t$ , we can re-write the full system (2) as

$$\left\{ \begin{aligned} \epsilon \frac{dy_1}{d\tau} &= \beta_{h1}z(1 - y_1 - w) - \gamma_1y_1 - \epsilon y_1((\tilde{m}_1 - \tilde{m}_2)w \\ &\quad + \tilde{\alpha}_1(1 - y_1) - \tilde{\alpha}_2y_2 + (P_1 + P_2)\tilde{b}(N)), \\ \epsilon \frac{dy_2}{d\tau} &= \beta_{h2}z(w - y_2) - \gamma_2y_2 - \epsilon y_2((\tilde{m}_1 - \tilde{m}_2)(w - 1) \\ &\quad - \tilde{\alpha}_1y_1 + \tilde{\alpha}_2(1 - y_2) + (P_1 + P_2)\tilde{b}(N)), \\ \epsilon \frac{dz}{d\tau} &= (1 - z)(\beta_{v1}y_1 + \beta_{v2}y_2) - \delta z, \\ \frac{dw}{d\tau} &= ((1 - w)P_2 - wP_1)\tilde{b}(N) + (\tilde{m}_1 - \tilde{m}_2)w(1 - w) \\ &\quad + \tilde{\alpha}_1wy_1 - \tilde{\alpha}_2(1 - w)y_2, \\ \frac{dN}{d\tau} &= N((P_1 + P_2)\tilde{b}(N) - \tilde{m}_1(1 - w) - \tilde{m}_2w - \tilde{\alpha}_1y_1 - \tilde{\alpha}_2y_2). \end{aligned} \right. \tag{8}$$

This system has a two dimensional slow manifold (see Appendix A):

$$M = \{(y_1, y_2, z, w, N) : y_1 = y_1^*(w, N), y_2 = y_2^*(w, N), z = z^*(w, N)\},$$

which is normally hyperbolically stable as it consists of a set of such equilibria of the fast system (3).  $y_1^*$  and  $y_2^*$  are given in (6). The slow dynamics on  $M$  is described by the equations

$$\left\{ \begin{aligned} \frac{dw}{d\tau} &= ((1 - w)P_2 - wP_1)b(N) + (\tilde{m}_1 - \tilde{m}_2)w(1 - w) \\ &\quad + \tilde{\alpha}_1wy_1^* - \tilde{\alpha}_2(1 - w)y_2^*, \\ \frac{dN}{d\tau} &= N((P_1 + P_2)\tilde{b}(N) - \tilde{m}_1(1 - w) - \tilde{m}_2w - \tilde{\alpha}_1y_1^* - \tilde{\alpha}_2y_2^*). \end{aligned} \right. \tag{9}$$

Since  $M$  is normally hyperbolically stable, singular perturbation theory allows us to study the system (8) by studying the reduced slow system (9). In other words, if the dynamics of the system (9) can be characterized via bifurcations, then the bifurcating dynamics on the slow manifold  $M$  are structurally stable hence robust subject to perturbations. Therefore, results from the slow system will provide bifurcation properties of the system (8) as well as the full system (2).

For our bifurcation analysis of the slow dynamics, we choose the bifurcation parameter to be the fitness of the  $S$ -gene,  $\mathcal{F}$ , which we define to be

$$\mathcal{F} = \left( \frac{1}{w} \frac{dw}{d\tau} \right) \Big|_{w=0}. \tag{10}$$

Recall that  $w = 2q$ . Hence, we can use  $w$  to represent the abundance of the  $S$ -gene, and hence,  $\mathcal{F}$  represents the per-capita growth rate of sickle-cell genes when the gene is initially introduced into a population. That is,  $\mathcal{F}$  describes the invasion ability of the  $S$ -gene.

Noticing that  $q = w/2$ ,  $p = 1 - w/2$  and

$$P_1 + P_2 = 1 - \frac{w^2}{4}, \quad (1 - w)P_2 - wP_1 = -\frac{1}{2}w^2\left(1 - \frac{w}{2}\right), \tag{11}$$

we can re-write the slow system (9) as

$$\begin{cases} \frac{dw}{d\tau} = -\frac{1}{2}\tilde{b}(N)w^2\left(1 - \frac{w}{2}\right) + g_1(w), \\ \frac{dN}{d\tau} = N\left(\tilde{b}(N)\left(1 - \frac{w^2}{4}\right) - g_2(w)\right), \end{cases} \tag{12}$$

where

$$\begin{aligned} g_1(w) &= (\tilde{m}_1 - \tilde{m}_2)w + \tilde{\alpha}_1wy_1^* - \tilde{\alpha}_2(1 - w)y_2^*, \\ g_2(w) &= \tilde{m}_1(1 - w) + \tilde{m}_2w + \tilde{\alpha}_1y_1^* + \tilde{\alpha}_2y_2^*. \end{aligned} \tag{13}$$

Then the following formula can be derived:

$$\left(\frac{1}{w} \frac{dw}{d\tau}\right)\Big|_{w=0} = (\tilde{m}_1 + W_1\tilde{\alpha}_1) - (\tilde{m}_2 + W_2\tilde{\alpha}_2), \tag{14}$$

where

$$W_1 = \frac{T_{h1}(\mathcal{R}_1 - 1)}{(1 + T_{h1})\mathcal{R}_1}, \quad W_2 = \frac{T_{h2}(\mathcal{R}_1 - 1)}{(1 + T_{h1})\mathcal{R}_1 + T_{h1} - T_{h2}}. \tag{15}$$

Let

$$\sigma_i = \tilde{m}_i + W_i\tilde{\alpha}_i. \tag{16}$$

Then  $\sigma_i \geq 0$  is the total per-capita death rate of type  $i$  individuals weighted by  $W_i$ , which depends only on malaria epidemiological parameters. The biological interpretation of  $\mathcal{F}$  suggests that, when the  $S$ -gene is initially introduced into a population, it may or may establish itself depending on whether the fitness is positive or negative, which is equivalent to whether  $\sigma_2 < \sigma_1$  or  $\sigma_2 > \sigma_1$ . This is indeed confirmed by both analytical and numerical studies of the slow system. Fig. 1 is a bifurcation diagram of the slow dynamics with  $\sigma_1$  and  $\sigma_2$  being the bifurcation parameters. In Fig. 1,  $\tilde{b}_1^*$  is a constant larger than the maximum per-capita birth rate  $\tilde{b}$  ( $=b/\epsilon$ );  $\sigma_2 = h(\sigma_1)$  is a decreasing function satisfying  $h(\tilde{b}) = \tilde{b}$  and  $h(\tilde{b}^*) = 0$ . Some of the results from this bifurcation diagram are summarized as follows:

*Case 1:  $\sigma_2 < \sigma_1$  (positive fitness).*

- (a) If  $\sigma_1 \leq \tilde{b}$ , or  $\tilde{b} < \sigma_1 < \tilde{b}^*$  and  $\sigma_2 < h(\sigma_1)$ , then there is a unique interior equilibrium  $E_* = (w_*, N_*)$  which is globally asymptotically stable (g.a.s.).



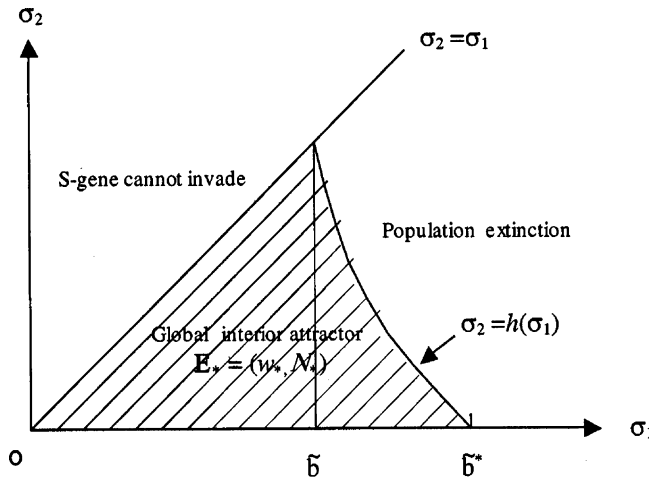


Fig. 1. Bifurcation diagram in the  $(\sigma_1, \sigma_2)$  plane. In the shaded region, there is a unique non-trivial equilibrium  $E_*$  which is a global attractor. In the region above the curve  $\sigma_2 = h(\sigma_1)$  and below the line  $\sigma_2 = \sigma_1$ , the total population size  $N(t)$  goes to zero as  $t \rightarrow \infty$ . In the region above the line  $\sigma_2 = \sigma_1$ , the  $S$ -gene will go extinction if its initial value is small. However, there maybe multiple equilibria in which case the  $S$ -gene may establish itself if its initial value is large.

- (b) If  $\tilde{b} < \sigma_1 < \tilde{b}^*$  and  $\sigma_2 > h(\sigma_1)$ , then the population will be wiped out (due to the death rates being too much higher than the ‘birth’ rate) with the fraction of  $AS$  individuals tending to a positive constant as  $t \rightarrow \infty$ .

Case 2:  $\sigma_2 > \sigma_1$  (negative fitness). The fraction of  $AS$  individuals will tend to zero as  $t \rightarrow \infty$ , whereas the total population size will tend to either  $K$  (when  $\sigma_2$  is small) or zero (when  $\sigma_2$  is large).

In either case, the system (9) has neither periodic solutions nor homoclinic loops.

An analytic proof of these results can be found in [39]. We point out that Case 1(b) is due to the standard incidence form of infection rate used in the  $z$  equation. Similar scenarios have been observed in other population models (see for example [38]), and such scenarios may not be present if the mass action form is used. The standard incidence form is more appropriate if the number of contacts is relatively constant, independent of density. Fig. 2 demonstrates some numerical calculations of solutions of the system (9) for  $(\sigma_1, \sigma_2)$  in the shaded region. Fig. 3 shows a couple of possible scenarios when  $\sigma_1 < \sigma_2$ . It is interesting to notice that, in Fig. 3(b), there are two locally asymptotically stable equilibria. One is the boundary equilibrium at which  $N > 0$  and  $w = 0$ , and the other one is one of the two interior equilibria. The regions of attraction of the two stable equilibria are divided by the separatrix formed by the stable manifold of the unstable interior equilibrium (see Fig. 4). This type of bi-stability can occur in several different ways, three of which are listed in Fig. 4. The three diagrams (a)–(c) in Fig. 4 are for cases when the system (9) has none, or one, or two equilibria on the positive  $w$ -axis. It shows that, if  $w(0)$  is small i.e., the initial population size of  $AS$  individuals is small, then the  $S$ -gene will go extinct due to a negative fitness. However, if for some reason (e.g. immigration of  $AS$  individuals)  $w$  suddenly becomes large (large

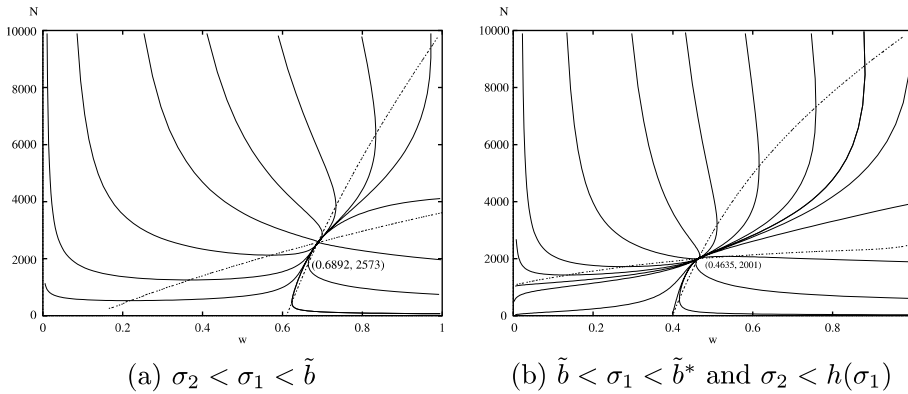


Fig. 2. Phase portraits of the slow system for  $(\sigma_1, \sigma_2)$  in the shaded region. In both cases the  $S$ -gene frequency will stabilize at a positive level.

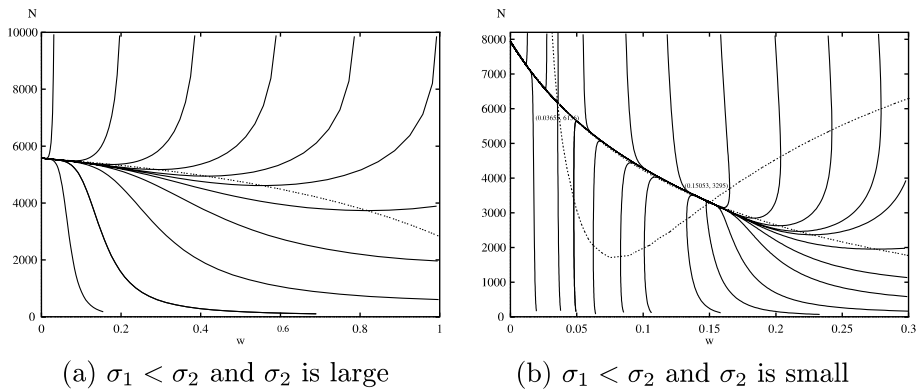


Fig. 3. Phase portraits of the slow system when the fitness is negative. (a) is for the case when  $\sigma_2$  is large. The  $S$ -gene goes extinction while the total population size goes to its carrying capacity. (b) is for the case when  $\sigma_2$  is small. There are two interior equilibria. The one with a lower value of  $w$  is unstable and the one with a higher value of  $w$  is stable.

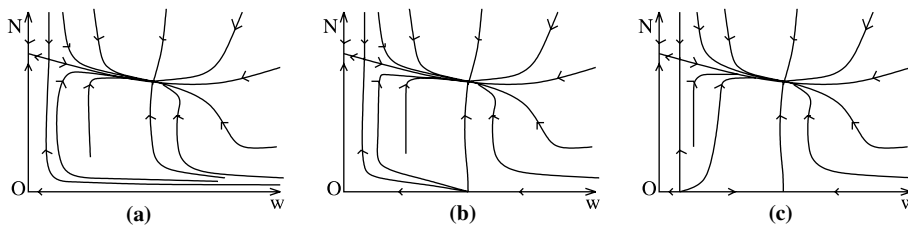


Fig. 4. Some bi-stability scenarios for  $\sigma_2 > \sigma_1$ . In (a) there is no non-trivial boundary equilibrium on the  $w$ -axis. In (b) there is one non-trivial boundary equilibrium on the  $w$ -axis. In (c) there are two non-trivial boundary equilibria on the  $w$ -axis.

enough to be on the right side of the separatrix), then the  $S$ -gene will be able to establish itself, even though the fitness is negative.

### 3. Evolution of associated traits

We see from the last section that whether or not the  $S$ -gene can invade and establish itself in a population is determined by whether the fitness coefficient is positive or negative. Recall that the fitness is given by the difference  $\sigma_1 - \sigma_2$ , where the total death rate  $\sigma_i$  is a sum of weighted death rates  $m_i$  and  $\alpha_i$  (see (16)) with the weight  $W_i$  given by (15). The quantity  $W_i$  contains all the malaria transmission parameters. Noticing that  $\tilde{m}_1 - \tilde{m}_2 = -\tilde{v}$  and using (10) and (15) we have

$$\mathcal{F} = -\tilde{v} + \frac{\tilde{\alpha}_1 T_{h1} (\mathcal{R}_1 - 1)}{(1 + T_{h1}) \mathcal{R}_1} - \frac{\tilde{\alpha}_2 T_{h2} (\mathcal{R}_1 - 1)}{(1 + T_{h1}) \mathcal{R}_1 + T_{h1} - T_{h2}}. \tag{17}$$

Let

$$T_{vi} = \frac{\beta_{vi}}{\delta}, \quad i = 1, 2. \tag{18}$$

Then  $\mathcal{R}_i = T_{hi} T_{vi}$  (see (5) and (7)). Notice that  $T_{hi}$  involves parameters related to malaria infection of humans of genotype  $i$  by mosquitoes, and  $T_{vi}$  involves parameters related to malaria infection of mosquitoes by humans of genotype  $i$ . Clearly, these transmission coefficients affect  $\mathcal{F}$  in non-linear ways. Fig. 5 illustrates how the fitness  $\mathcal{F}$  depends on the  $T_{h1}$  and  $T_{h2}$ . It shows that for any given value of  $T_{h1}$ , the fitness does not seem to change much with  $T_{h2}$ , which implies that any changes in malaria transmission rate  $\theta_2$  or in the recovery rate  $\gamma_2$  in  $AS$  individuals will unlikely change the fitness. On the other hand, an increase in the malaria transmission rate  $\theta_1$  or a decrease in the recovery rate  $\gamma_1$  in  $AA$  individuals will lead to a dramatic increase in the fitness. This illustrate one example of possible impact of malaria prevalence on the selection of the  $S$ -gene.

To asses how the frequency of  $S$ -gene may influence the endemic level of malaria, we examine the threshold quantity  $\mathcal{R}_0$  given in (4). Rewrite (4) as  $\mathcal{R}_0 = (\mathcal{R}_2 - \mathcal{R}_1)w + \mathcal{R}_1$ . It is easy to see that  $\mathcal{R}_0$  is either a decreasing function of  $w$  if  $\mathcal{R}_2 < \mathcal{R}_1$ , or an increasing function of  $w$  if  $\mathcal{R}_2 > \mathcal{R}_1$ .

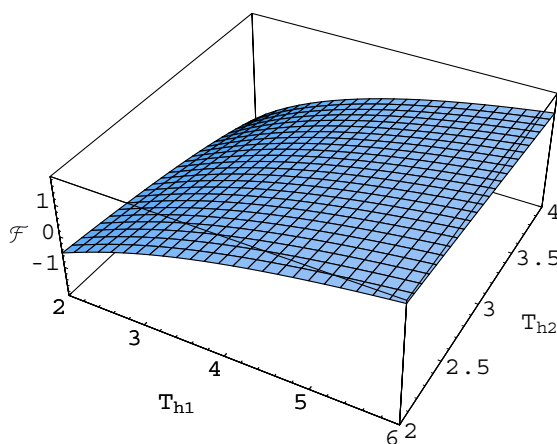


Fig. 5. Plot of the fitness  $\mathcal{F}$  vs. the transmission coefficient of humans of  $AA$  type ( $T_{h1}$ ) and the transmission coefficient of humans of  $AS$  type ( $T_{h2}$ ). The parameter values are:  $v = 0.00002, \alpha_1 = 0.0001, \alpha_2 = 0.00005, \epsilon = 10^{-4}, a = 1, \phi_1 = 0.05, \delta = 0.07$  (which gives  $T_{v1} = 0.7$ ). It shows that  $\mathcal{F}$  increases with  $T_{h2}$  and changes from negative to positive, but it is not very sensitive to changes in  $T_{h2}$  if  $T_{h2}$  is not too small.

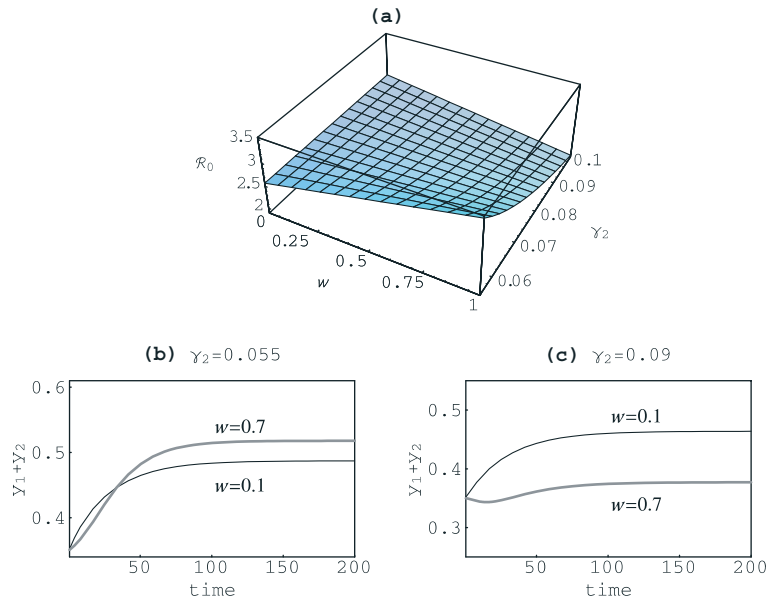


Fig. 6. (a) is a plot of  $\mathcal{R}_0$  vs.  $w$  and  $\gamma_2$ . It shows that  $\mathcal{R}_0$  decreases with  $w$  for smaller  $\gamma_2$  and increases with  $w$  for larger  $\gamma_2$ . (b) and (c) plot solutions of the fast system (3) for different values of  $\gamma_2$ .  $y_1 + y_2$  represents the fraction of the population infected with malaria. The parameter values are:  $\gamma_1 = 0.05$ ,  $\theta_1 = 0.06$ ,  $\theta_2 = 0.05$ ,  $\phi_1 = 0.05$ ,  $\phi_2 = 0.09$ ,  $b = 0.00004$ ,  $m = 0.00003$ . The values for other parameters are the same as that used for Fig. 5.

Recall that  $w = 2q$  and  $q$  is the frequency of  $S$ -gene in the population. Relative magnitudes of  $\mathcal{R}_1$  and  $\mathcal{R}_2$  are determined by several epidemiological parameters. Fig. 6(a) illustrates an example by changing  $\gamma_2$  ( $1/\gamma_2$  is the duration of malaria infection in  $AS$  individuals). It shows that  $\mathcal{R}_0$  increases with  $w$  for smaller values of  $\gamma_2$  and decreases with  $w$  for larger values of  $\gamma_2$ . In general, the disease prevalence increases with  $\mathcal{R}_0$ . This is confirmed by numerical simulations of the fast system (3), which is shown in Fig. 6(a)–(c).  $y_1 + y_2$  is the fraction of the population infected with malaria. Notice that in Fig. 6(b), higher  $S$ -gene frequencies corresponds to higher endemic levels of malaria at equilibrium.

Thus, increased duration of parasitaemia in heterozygotes (decreasing  $\gamma_2$ ) leads to higher endemic prevalence of malaria and increased selection for the  $S$ -gene. These changes have very little effect on  $\mathcal{F}$ . This raises the interesting question of whether traits that affect  $\gamma_2$  are under selection. Thus, traits associated with disease transmission may coevolve with traits associated with disease resistance.

#### 4. Discussion

By coupling the dynamics of the epidemiology of malaria and the genetics of sickle cell gene, our model allows for joint investigation of (1) impact of malaria on the selection of  $S$ -gene (2) influence of genetic composition of a population on the maintenance of malaria, and (3) evolution of associated traits. Our results are based on threshold conditions derived from our model by sepa-

rating malaria disease dynamics on the fast time scale and the dynamics of  $S$ -gene on the slow time scale and by conducting stability analysis. The epidemic threshold condition  $\mathcal{R}_0 > 1$  (under which malaria is endemic) is related to the  $S$ -gene frequency through  $w$ , and the threshold condition for the fitness of  $S$ -gene  $\mathcal{F} > 0$  (under which the rare gene is able to invade and maintain itself) depends on epidemiological parameters as well as the endemic level of malaria. We illustrate the uses of these thresholds for the studies of questions related to (1)–(3) in Section 3. These results cannot be obtained from epidemiology models without genetic or genetic models without epidemics.

Standard population genetic models often use discrete-generations, and assume that when both parents are heterozygous, a fourth of all births are  $S$ -gene homozygotes. In our models, compensatory reproductive decisions can reduce the fitness costs associated with the  $S$ -gene [21]. For example,  $S$ -gene homozygote children may be lost in utero or early in infancy. In these cases, the interbirth interval may be shorter following the birth of  $S$ -gene homozygote offspring. Alternatively, voluntary decisions to limit family size may reduce the fitness cost of the  $S$ -gene; pairings to  $S$ -gene heterozygotes will tend to have the same number of children. The net effect in both cases is a marginal delay in the birth rate, and the total fitness cost of the  $S$ -gene is somewhat lower than that predicted by the standard models.

The  $S$ -gene may affect the expression of several traits associated with malaria transmission dynamics. The  $S$ -gene can improve fitness by reducing the probability of becoming parasitaemic, by reducing the duration of a parasitaemia, or by reducing the probability of developing malaria per parasitaemia. If one of the former mechanism is responsible for the enhanced fitness of  $S$ -gene heterozygotes, the population would benefit from increased frequency of the  $S$ -gene because heterozygotes would be a sink for *Plasmodium*, serving the same function as alternative hosts. Alternatively, the  $S$ -gene may reduce disease, influencing the expression of traits that increase the selective pressure acting on it. The evidence is mixed, but tends to support the notion that the gene is acting selfishly. One experiment challenged individuals with infectious mosquitoes and showed that 2/15  $S$ -gene heterozygotes developed parasitaemia compared with 14/15 homozygotes lacking the  $S$ -gene [15]. On the other hand, the prevalence of parasitaemia is similar in  $S$ -gene heterozygotes compared with non- $S$  homozygotes [22–25]. If there is a real difference in the probability of becoming parasitaemic, but no real difference in the prevalence of parasitaemia, parasitaemia may last longer in  $S$ -gene heterozygotes. Other evidence suggests that transmission to mosquitoes is higher from  $S$ -gene heterozygotes [26–29]. On balance, it seems that increased frequency of the  $S$ -gene leads to enhanced transmission rates for *Plasmodium*.

There are several intrinsic shortcomings in the Macdonald [40] model of malaria transmission, on which our model is based. In particular, it does not account for the complex effects of acquired immunity on transmission [41], for fluctuations in transmission intensity [42], or for the existence of multiple parasite genotypes and meiotic recombination among them [43]. These shortcomings may have unexpected importance in the current context, in that recent evidence suggests that sickle-cell trait may differentially affect different parasite genotypes, as defined at immunogenic loci, and may influence superinfection frequencies [44,45]. Our model includes several other simplifications with respect to empirical data; for instance, our assumption that all sickle homozygotes ( $SS$ ) die is only an approximation [46]. Furthermore, relationships between malaria prevalence (or incidence) and malaria-induced mortality (or morbidity) are far more complex than assumed here: *Plasmodium* infection is necessary but by no means sufficient to produce disease in malaria [47,48].

Sickle cell (HbS) is a hemoglobinopathy, specifically a variant hemoglobin, and there is some evidence that other variant hemoglobins (HbC in West Africa, and HbE or HbF – persistent fetal hemoglobin – in SE Asia and the SW Pacific) are protective against malaria as well. Individuals with one *S* and one *C* allele are not uncommon in West Africa, and, at least in vitro, parasite growth in *SC* cells is especially poor. The thalassemias are also hemoglobinopathies, and may be the most common monogenic diseases of humans. Perhaps the best recent evidence for their malaria-protective effects is through ‘micro-epidemiological’ studies on alpha-thalassemias in the SW Pacific; there is also some evidence for milder anemias and increased survivorship in concurrent alpha-thalassemic/sickle relative to sickle-trait patients. Beta-thalassemias are fairly common in the formerly malarious Mediterranean/Middle East; it has been argued that their lower frequencies in Africa are due to ‘competition’ with sickle. A red-blood-cell cytoskeletal defect (ovalocytosis, in SE Asia) appears to produce resistance – though not complete blockage – of cell invasion by parasites. G6PD deficiency (a maternally transmitted hereditary alteration in the host NADPH pathway used by the parasite) and several inherited immunological characteristics (e.g. specific HLA haplotypes) seem to affect malaria infections as well. We have not considered any possible interactions of sickle-cell and other malaria-protective traits (e.g. [49]). Our model does represent significant progress toward solving the old and difficult problems noted in the Introduction, however, and, we hope, toward the solutions of more general problems related to host heterogeneity and its influence on infectious-disease agents. Finally, it provides a foundation upon which an investigation on the challenges posed by environmental changes associated with climate and land use can be based.

### Acknowledgements

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### Appendix A. Calculation of $\mathcal{R}_0$ and separation of scales

Let  $E_0 = (0, 0, 0)$  be the disease-free equilibrium of the fast system (3). Then from the Jacobian matrix at  $E_0$  we obtain the next generation matrix (see [37,38]):

$$\begin{pmatrix} 0 & 0 & \frac{\beta_{h1}(1-w)}{\delta} \\ 0 & 0 & \frac{\beta_{h2}w}{\delta} \\ \frac{\beta_{v1}}{\gamma_1} & \frac{\beta_{v2}}{\gamma_2} & 0, \end{pmatrix}$$

whose leading eigenvalue is

$$\sqrt{\frac{\beta_{v1}\beta_{h1}(1-w)}{\delta\gamma_1} + \frac{\beta_{v2}\beta_{h2}w}{\delta\gamma_2}}.$$

This quantity gives the basic reproductive number. However, to simplify the notation we define our  $\mathcal{R}_0$  to be this number squared:

$$\mathcal{R}_0 = \frac{\beta_{v1}\beta_{h1}(1-w)}{\delta\gamma_1} + \frac{\beta_{v2}\beta_{h2}w}{\delta\gamma_2} = \mathcal{R}_1(1-w) + \mathcal{R}_2w.$$

The threshold condition remains the same, i.e.,  $E_0$  is l.a.s if  $\mathcal{R}_0 < 1$  and unstable if  $\mathcal{R}_0 > 1$ .

Assume that the demographic parameters ( $m_i, \alpha_i$  and  $b$ ) are much smaller than malaria-related disease parameters. Let  $m_i = \epsilon\tilde{m}_i, \alpha_i = \epsilon\tilde{\alpha}_i$ , and  $b = \epsilon\tilde{b}$  with  $\epsilon$  being small. Rewrite the system (2) in the form

$$\frac{dU}{dt} = G(U) + \epsilon F(U), \tag{A.1}$$

where

$$U = \begin{pmatrix} y_1 \\ y_2 \\ z \\ w \\ N \end{pmatrix}, \quad G(U) = \begin{pmatrix} \beta_{h1}z(1-w-y_1) - \gamma_1y_1 \\ \beta_{h2}z(w-y_2) - \gamma_2y_2 \\ (1-z)(\beta_{v1}y_1 + \beta_{v2}y_2) - \delta z \\ 0 \\ 0 \end{pmatrix}, \tag{A.2}$$

and

$$F = \begin{pmatrix} F_1 \\ F_2 \\ F_3 \\ F_4 \\ F_5 \end{pmatrix} = \begin{pmatrix} -(\tilde{m} + \tilde{\alpha}_1)y_1 - y_1\tilde{f}(N) \\ -(\tilde{m} + \tilde{\alpha}_2)y_2 - y_2\tilde{f}(N) \\ 0 \\ P_2\tilde{b}(N) - \tilde{\alpha}_2y_2 - \tilde{m}_2w - w\tilde{f}(N) \\ N((P_1 + P_2)\tilde{b}(N) - \tilde{m}_1(1-w) - \tilde{m}_2w - \tilde{\alpha}_1y_1 - \tilde{\alpha}_2y_2) \end{pmatrix}, \tag{A.3}$$

where

$$\tilde{f}(N) = (P_1 + P_2)\tilde{b}(N) - \tilde{m}_1(1-w) - \tilde{m}_2w - \tilde{\alpha}_1y_1 - \tilde{\alpha}_2y_2.$$

The fast dynamics at the disease scale are given by (A.1) when taking  $\epsilon = 0$ :

$$\frac{dU}{dt} = G(U), \tag{A.4}$$

which is equivalent to the system (3). Recall that (see (5), (7), and (18))

$$T_{hi} = \frac{\beta_{hi}}{\gamma_i}, \quad T_{vi} = \frac{\beta_{vi}}{\delta}, \quad \mathcal{R}_i = T_{hi}T_{vi}, \quad i = 1, 2. \tag{A.5}$$

Let  $E^* = (y_1^*, y_2^*, z^*, w, N)$  be a non-trivial equilibrium of (A.4) with  $w$  and  $N$  being parameters. Setting the right hand side of (3) equal to zero we get

$$y_1^* = \frac{T_{h1}z^*}{1 + T_{h1}z^*}(1-w), \quad y_2^* = \frac{T_{h2}z^*}{1 + T_{h2}z^*}w, \tag{A.6}$$

and  $z^*$  is a solution of the equation

$$k_0z^2 + k_1z + k_2 = 0 \tag{A.7}$$

with

$$\begin{aligned} k_0 &= T_{h1}T_{h2} + \mathcal{R}_1T_{h2}(1 - w) + \mathcal{R}_2T_{h1}w, \\ k_1 &= T_{h1} + T_{h2} + \mathcal{R}_1(1 - T_{h2})(1 - w) + \mathcal{R}_2(1 - T_{h1})w, \\ k_2 &= 1 - \mathcal{R}_1(1 - w) - \mathcal{R}_2w. \end{aligned} \tag{A.8}$$

If  $\mathcal{R}_0 = \mathcal{R}_1(1 - w) + \mathcal{R}_2w < 1$ , then  $k_2 = 1 - \mathcal{R}_0 > 0$ . To show that Eq. (A.7) has no positive solution, it suffices to show that  $k_1 > 0$ . Let  $T_0 = \max\{T_{h1}, T_{h2}\}$ . Then  $T_{h1} + T_{h2} - T_0\mathcal{R}_0 \geq 0$ . Hence,

$$k_1 = T_{h1} + T_{h2} + \mathcal{R}_0 - \mathcal{R}_1T_{h2}(1 - w) - \mathcal{R}_2T_{h1}w \geq T_{h1} + T_{h2} + \mathcal{R}_0 - T_0\mathcal{R}_0 > 0,$$

and hence,  $E^*$  is not biologically feasible.

If  $\mathcal{R}_0 > 1$ , then  $k_2 = 1 - \mathcal{R}_0 < 0$ . It is easy to show that  $k_0 > 0$  as  $0 < w < 1$ . Hence, when  $\mathcal{R}_0 > 1$  Eq. (A.7) has a unique positive solution which we denote by  $z^*$ . Let  $h(z)$  denote the function of  $z$  given by the left hand side of (A.7). Notice that  $h(0) = k_2 < 0$ ,  $h(1) = 1 + T_{h1}T_{h2} + T_{h1} + T_{h2} > 0$ , and  $h(z^*) = 0$ . Hence,  $0 < z^* < 1$ . From (A.6) we also have that  $0 < y_i^* < 1, i = 1, 2$ . It follows that an endemic equilibrium  $E^* = (y_1^*, y_2^*, z^*)$  exists and is unique.

The stability of  $E^*$  is determined by the eigenvalues of the following matrix  $H$  (which is the upper left block of the Jacobian matrix  $DG(E^*)$ ):

$$H = \begin{pmatrix} -(\beta_{h1}z^* + \gamma_1) & 0 & \beta_{h1}(1 - w - y_1^*) \\ 0 & -(\beta_{h2}z^* + \gamma_2) & \beta_{h2}(w - y_2^*) \\ \beta_{v1}(1 - z^*) & \beta_{v2}(1 - z^*) & -(\beta_{v1}y_1^* + \beta_{v2}y_2^* + \delta) \end{pmatrix}.$$

The matrix  $H$  can be written in the form  $H = M - D$ , where

$$\begin{aligned} M &= \begin{pmatrix} 0 & 0 & \beta_{h1}(1 - w - y_1^*) \\ 0 & 0 & \beta_{h2}(w - y_2^*) \\ \beta_{v1}(1 - z^*) & \beta_{v2}(1 - z^*) & 0 \end{pmatrix}, \\ D &= \begin{pmatrix} \beta_{h1}z^* + \gamma_1 & 0 & 0 \\ 0 & \beta_{h2}z^* + \gamma_2 & 0 \\ 0 & 0 & \beta_{v1}y_1^* + \beta_{v2}y_2^* + \delta \end{pmatrix}. \end{aligned}$$

Notice that  $M \geq 0$ , i.e., all elements of  $M$  are non-negative (recall that  $1 - w - y_1 = x_1 > 0$  and  $w - y_2 = x_2 > 0$ ) and  $D$  is a diagonal matrix with positive diagonal elements. It is known (see [37]) that all eigenvalues of  $H$  have negative real parts if and only if the dominant eigenvalue of the matrix  $MD^{-1}$  is less than one. The eigenvalues of  $MD^{-1}$  are

$$\lambda_0 = 0,$$

and

$$\lambda_{\pm} = \pm \sqrt{\left(\frac{\beta_{h1}(1 - w - y_1^*)}{\beta_{v1}y_1^* + \beta_{v2}y_2^* + \delta}\right)\left(\frac{\beta_{v1}(1 - z^*)}{\beta_{h1}z^* + \gamma_1}\right) + \left(\frac{\beta_{h2}(w - y_2^*)}{\beta_{v1}y_1^* + \beta_{v2}y_2^* + \delta}\right)\left(\frac{\beta_{v2}(1 - z^*)}{\beta_{h2}z^* + \gamma_2}\right)}.$$

Obviously,  $\lambda_0 < 1$  and  $\lambda_- < 1$ . Using the following equalities (which are obtained by setting the right hand side of (3) equal to zero):



$$z_1^* = \frac{\beta_{v1}y_1^* + \beta_{v2}y_2^*}{\beta_{v1}y_1^* + \beta_{v2}y_2^* + \delta} = \frac{\gamma_1 y_1^*}{\beta_{h1}(1 - w - y_1^*)},$$

$$z_2^* = \frac{\beta_{v1}y_1^* + \beta_{v2}y_2^*}{\beta_{v1}y_1^* + \beta_{v2}y_2^* + \delta} = \frac{\gamma_2 y_2^*}{\beta_{h2}(w - y_2^*)},$$

and noticing that  $\beta_{hi}z^* + \gamma_i > \gamma_i, i = 1, 2$ , and that  $0 < z^* < 1$ , we get

$$\lambda_+^2 < \frac{\gamma_1 y_1^*}{\beta_{v1}y_1^* + \beta_{v2}y_2^*} \frac{\beta_{v1}(1 - z^*)}{\gamma_1} + \frac{\gamma_2 y_2^*}{\beta_{v1}y_1^* + \beta_{v2}y_2^*} \frac{\beta_{v2}(1 - z^*)}{\gamma_2} = 1 - z^* < 1.$$

It follows that  $\lambda_+ < 1$  and that  $E^*$  is locally asymptotically stable. Thus, the system (A.1) for  $\epsilon = 0$  contains a two-dimensional stable manifold of steady states

$$U_0(w, N) = (y_1^*, y_2^*, z^*, w, N)^T. \tag{A.9}$$

The equations for the slow dynamics can be derived following the approach of [12]. Assume that the solutions to (A.1) have the form

$$U(t) = U_0(w(t), N(t)) + \epsilon U_1(t, \epsilon), \tag{A.10}$$

and let  $\frac{dU_0}{dt} = (0, 0, 0, \frac{dw}{dt}, \frac{dN}{dt})^T$ . Then using Eqs. (A.1) and (A.10) we have

$$\frac{dU}{dt} = \frac{dU_0}{dt} + \epsilon \frac{\partial U_1}{\partial t} = G(U_0(w, N)) + \epsilon DG(U_0(w, N))U_1 + \epsilon F(U_0(w, N)) + O(\epsilon^2), \tag{A.11}$$

where  $DG(U_0(w, N))$  denotes the Jacobian matrix of  $G$  at  $U_0(w, N)$ . Notice that  $G(U_0(w, N)) = 0$ . Also notice that  $DG(U_0(w, N))$  has three eigenvalues with negative real part and two zero eigenvalues. Two left eigenvectors of  $DG(U_0(w, N))$  corresponding to the two zero eigenvalues can be computed as

$$V_1 = (0, 0, 0, 1, 0), \quad V_2 = (0, 0, 0, 0, 1). \tag{A.12}$$

Let  $V = \begin{pmatrix} V_1 \\ V_2 \end{pmatrix}$ . Then using similar arguments given in [12] we know that in (A.10) the variable  $U_1$  can be chosen such that  $V \frac{\partial U_1}{\partial t} = 0$ . Hence, when neglecting higher order terms in  $\epsilon$ , (A.11) yields

$$V \frac{dU_0}{dt} = \epsilon VF. \tag{A.13}$$

Let  $\tau = \epsilon t$ . Then (A.13) can be written as

$$V \frac{dU_0}{d\tau} = VF, \tag{A.14}$$

which is exactly the system (9) in Section 2. Using perturbation results by Hoppensteadt [50,51] we know that the system (A.14) provides a good approximation to the slow dynamics of (A.1) when  $\epsilon$  is small. The separation of scales can also be justified using geometric theory of singular perturbations due to Fenichel [52] (see [39] for more details).

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