CHAPTER 1

MALARIA MODELS WITH SPATIAL EFFECTS

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Abstract. In this chapter, we provide a brief review about some recent studies on mathematical modeling of malaria transmission in spatially heterogeneous environments. Deterministic models described by ordinary differential equations and reaction-diffusion equations are used to investigate the spatial spread of malaria between humans and mosquitoes. Selected topics include the importance of modeling spatial heterogeneity, basic models with infective immigrants, multi-patch models, and reaction-diffusion models. The chapter ends with a brief discussion about possible future research directions.

1.1 Introduction

Malaria, a vector-borne infectious disease caused by the *Plasmodium* parasite, is still endemic in more than 100 countries in Africa, South-East Asia, the Eastern Mediterranean, Western Pacific, Americas and Europe. In 2010 there were about 219 million malaria cases, with an estimated 660,000 deaths, mostly children under five in Sub-Saharan Africa (WHO 2012). The malaria parasite is transmitted to humans

via the bites of infected female mosquitoes of the genus *Anopheles*. Mosquitoes can become infected when they feed on the blood of infected humans. Thus the infection goes back and forth between humans and mosquitoes.

Mathematical modeling of malaria transmission has a long history. It has helped us to understand transmission mechanism, design and improve control measures, forecast disease outbreaks, etc. The so-called Ross-Macdonald model

$$\frac{dh(t)}{dt} = ab\frac{H-h(t)}{H}v(t) - rh(t)$$
$$\frac{dv(t)}{dt} = ac\frac{h(t)}{H}(V-v(t)) - dv(t)$$

is the earliest malaria model which was originally considered by Ross (1911) in 1911 and later extended by Macdonald (1952, 1956, 1957) in 1950s. Here H and V are the total populations of humans and mosquitoes, respectively, $h(t)$ and $v(t)$ are the numbers of infected humans and mosquitoes at time t, a is the rate of biting on humans by a single mosquito, b and c are the transmission probabilities from infected mosquitoes to susceptible humans and from infected humans to susceptible mosquitoes, respectively, $1/r$ is the duration of the disease in humans and d is the mortality rate of mosquitoes. On the basis of the modeling, Ross (1911) introduced the threshold density concept and concluded that "... in order to counteract malaria anywhere we need not banish *Anopheles* there entirely–we need only to reduce their numbers below a certain figure." Macdonald (1952, 1956, 1957) generalized Ross' basic model, introduced the concept of basic reproduction number as the average number of secondary cases produced by an index case during its infectiousness period, and analyzed several factors contributing to malaria transmission. The work of Macdonald had a very beneficial impact on the collection, analysis, and interpretation of epidemic data on malaria infection (Molineaux and Gramiccia 1980) and guided the enormous global malaria-eradication campaign of his era (Ruan et al. 2008). The Ross-Macdonald model is very useful and successful in the sense that it captures the essential features of malaria transmission process. The modeling structure is now frequently used to investigate the transmission dynamics of many other vector-borne diseases.

However, the Ross-Macdonald model is highly simplified and ignores many important factors of real-world ecology and epidemiology (Ruan et al. 2008). For example, it does not take into account the age structure and immunity in humans, latencies in both humans and mosquitoes, environmental factors, vital dynamics in humans, etc. Another omission is the spatial heterogeneity since both mosquitoes and humans are moving around which contributes to the spatial spread of the disease significantly. Malaria may vary spatially in the vectors that transmit it, in the species causing the disease, and in the level of intensity. It can be easily spread from one location to another due to extensive travel and migration (Martens and Hall 2000, Tatem et al. 2006, Stoddard et al. 2009). A possible reason for the failure of the Global Malaria Eradication Program (1955-1969) is due to human movement (Bruce-Chwatt 1968).

One way of introducing spatial effects into epidemic models is to divide the population into n subpopulations and allow infective individuals in one patch to infect susceptible individuals in another (see Lajmanovich amd Yorke 1976, Sattenspiel and Dietz 1995, Dushoff amd Levin 1995, Lloyd and May 1996, Arino 2009, Wang 2007, and the references cited therein). Spatial heterogeneities can be modeled by adding an immigration term where infective individuals enter the system at a constant rate. This certainly allows the persistence of the disease since if it dies out in one region then the arrival of an infective individual from elsewhere can trigger another epidemic. Spatial heterogeneities have also been incorporated into epidemiological models by using reaction-diffusion equations by some researchers (see, for example, Murray 1989). Smith and Ruktanonchai (2010), Mandal et al. (2011), and Reiner et al. (2013) have given comprehensive reviews on various mathematical models of malaria. In what follows, we only introduce some spatial models solely developed for malaria transmission. There are numerous spatial epidemic models for West Nile virus, dengue, and other vector-borne diseases which may be also applicable to malaria study, but are excluded from this chapter.

1.2 Malaria models with constant infective immigrants

In modern time, humans travel more frequently on scales from local to global. One million people are reported to travel internationally each day, and one million people travel from developed to developing countries (and vice versa) each week (Garrett 1996). A more recent report quoted a figure of 700 million tourist arrivals per year (Gössling 2002). These types of movements have the potential to spread disease pathogens and their vectors over long distances. Infected people from malaria-endemic regions can bring the disease to malaria-free regions and this has happened in the United States where an estimated 1,500 malaria cases are diagnosed annually in this country, of which about 60% are among U.S. travelers (Newman et al. 2004). Perhaps the simplest way to include spatial effects is to assume that there is a constant recruitment through human movement with a fraction of infective immigrants.

Tumwiine et al. (2010) developed such a model with the SIRS structure for humans and the SI structure for mosquitoes. Let $N_H(t)$ and $N_V(t)$ be the total numbers of mosquitoes and humans at time t, respectively. The human population is divided into three subclasses: susceptible, infectious and semi-immune, with numbers at time t in these classes given by $S_H(t), I_H(t)$ and $R_H(t)$, respectively. The mosquito population is divided into two subclasses: susceptible $S_V(t)$ and infectious $I_V(t)$. Thus $N_H(t) = S_H(t) + I_H(t) + R_H(t)$ and $N_V(t) = S_V(t) + I_V(t)$. A flow Λ of new members enters into the human population through birth or immigration with a fraction ϕ of infectives. It is assumed that there are no immigrants that enter the

immune class. The model takes the form

$$\begin{aligned}
\frac{dS_H}{dt} &= (1-\phi)\Lambda - ab\frac{S_H}{N_H}I_V + \nu I_H + \gamma R_H - \mu_h S_H,\\
\frac{dI_H}{dt} &= \phi\Lambda + ab\frac{S_H}{N_H}I_V - (\nu + r + \delta + \mu_h)I_H,\\
\frac{dR_H}{dt} &= rI_H - (\gamma + \mu_h)R_H,\\
\frac{dS_V}{dt} &= \lambda_v N_V - ac\frac{I_H}{N_H}S_V - \mu_v S_V,\\
\frac{dI_V}{dt} &= ac\frac{I_H}{N_H}S_V - \mu_v I_V,
\end{aligned} \tag{1.1}$$

where a is the number of humans a mosquito bites per unit time, b is the proportion of infected bites on humans that produce an infection, c is the transmission efficiency from humans to mosquitoes, μ_h and μ_v are the natural death rates for humans and mosquitoes, respectively, δ is the disease-induced death rate for humans, r is the progression rate that infectious humans become semi-immune, ν is the progression rate that infectious humans become susceptible, γ is the rate of loss of immunity for humans, and λ_v is the birth rate of mosquitoes.

Since a female mosquito takes a fixed number of blood meals per unit time independent of the abundance of the host, the mosquito-human ratio $m = \frac{N_V}{N_H}$ is taken as a constant. Set $s_h = \frac{S_H}{N_H}, i_h = \frac{I_H}{N_H}, r_h = \frac{R_H}{N_H}, s_v = \frac{S_V}{N_V}$ and $i_v = \frac{I_V}{N_V}$ as the proportions for classes S_H, I_H, R_H, S_V and I_V, respectively, so that

$$s_h + i_h + r_h = 1 \Rightarrow r_h = 1 - s_h - i_h \quad \text{and} \quad s_v + i_v = 1 \Rightarrow s_v = 1 - i_v.$$

Then system (1.1) reduces to

$$\begin{aligned}
\frac{ds_h}{dt} &= \gamma + (1-\phi)(\mu_h + \delta i_h) - [abmi_v + \mu_h + \gamma]s_h + (\nu - \gamma)i_h,\\
\frac{di_h}{dt} &= \phi(\mu_h + \delta i_h) + abms_h i_v - [\nu + r + \mu_h + \delta]i_h,\\
\frac{di_v}{dt} &= ac(1 - i_v)i_h - \lambda_v i_v
\end{aligned} \tag{1.2}$$

provided that $\frac{\Lambda}{N_H} = \mu_h + \delta i_h$. It can be shown that the biologically feasible region

$$T = \{(s_h, i_h, i_v) \in \mathbb{R}^3_+ : 0 \le s_h,\ 0 \le i_h, s_h + i_h \le 1,\ 0 \le i_v \le 1\}$$

is positively invariant with respect to system (1.2). Clearly, system (1.2) always has a disease-free equilibrium $E_0 = (1, 0, 0)$ when $\phi = 0$ (namely, there is no infective immigrants). So we can define a basic reproduction number

$$\mathcal{R}_0 = \sqrt{\frac{a^2 bmc}{\lambda_v(\nu + r + \mu_h + \delta)}}$$

for system (1.2) if $\phi = 0$. There exists a unique endemic equilibrium, denoted by E_1, if $\phi = 0$ and $\mathcal{R}_0 > 1$. For $\phi > 0$, system (1.2) has no disease-free equilibrium but has exactly one endemic equilibrium, denoted by $\tilde{E}_1$, for all parameter values. Following Tumwiine et al. (2010), we have the following results:

Theorem 1.1 *Let $\mathring{T}$ be the interior of T.*

(i) *If $\phi = 0$ and $\mathcal{R}_0 \leq 1$, then the disease-free equilibrium E_0 of system* (1.2) *is the only equilibrium in T and is globally asymptotically stable.*

(ii) *If $\phi = 0$ and $\mathcal{R}_0 > 1$, then the disease-free equilibrium E_0 of system* (1.2) *becomes unstable and there exists a unique endemic equilibrium E_1 which is globally asymptotically stable in $\mathring{T}$.*

(iii) *If $0 < \phi < 1$, then the unique endemic equilibrium $\tilde{E}_1$ of system* (1.2) *is globally asymptotically stable in $\mathring{T}$.*

The global stability of E_0 is proved by constructing a Lyapunov function and the global stabilities of E_1 and $\tilde{E}_1$ are proved by employing the geometrical approach developed in Li and Muldowney (1996). These indicate that a constant influx of infected immigrants plays a significant role in the spread and persistence of malaria and it could result in new disease outbreaks in area where malaria had once been eradicated.

1.3 Malaria models with discrete diffusion

Multi-patch models are widely used to model directly transmitted diseases as well as vector-borne diseases (see Arino 2009, Wang 2007). A patch may be referred to as a village, city, country, or some other geographical region. Either humans, mosquitoes or both are mobile, which case mainly depends on the spatial scale under consideration. Because mosquitoes have relatively lower mobility, we usually neglect mosquito movement in the large geographical scale, but consider both or mosquito movement in the small scale. In this section, we will first introduce some multi-path models with constant population size, then present multi-patch models with birth and death. At the end we will discuss a multi-strain model in a heterogeneous environment.

1.3.1 Multi-patch models without vital dynamics of humans

In the Ross-Macdonald model, both human and mosquito populations are constant and there is no latent period or partially-immune class. Its simplicity allows us to do some in-depth investigations. The early multi-patch malaria models follow the Ross-Macdonald structure (see Dye and Hasibeder 1986, Hasibeder and Dye 1988, Torres-Sorando and Rodríguez 1997, Rodríguez and Torres-Sorando 2001).

To take account of the non-homogeneous mixing between vectors and hosts, Dye and Hasibeder (1986, 1988) proposed and analyzed the following epidemic model

with m host patches and n vector patches

$$\begin{aligned}\frac{dS_i}{dt} &= \alpha\Big(\sum_j \gamma_{ji} I_j\Big)\Big(1-\frac{S_i}{H_i}\Big) - \rho S_i,\ 1 \le i \le m,\\ \frac{dI_j}{dt} &= \beta\Big(V_j - I_j\Big)\Big(\sum_i \gamma_{ji}\frac{S_i}{H_i}\Big) - \delta I_j,\ 1 \le j \le n,\end{aligned} \tag{1.3}$$

where H_i is the total host population size in patch i with S_i being infected and V_j is the total vector population size in patch j with I_j being infected, α and β are the transmission rates of infection from vectors to hosts and vice versa, γ_{ji} is the probability that a vector from patch j commutes to and bites in host patch i, ρ is the human recovery rate and δ is mosquito death rate. As far as we know, this is the first multi-patch malaria model which is somewhat different from those we will present later. A mosquito from any one of the n vector patches can bite any one of the m host patches. The nonnegative terms γ_{ji} are assumed to satisfy $\sum_{1\le i\le m}\gamma_{ji} = 1$ for $j = 1, 2, \cdots, n$.

We call model (1.3) a p/q model if $m = p$ and $n = q$. Let H and V be the total hosts and vectors over all patches. The following result suggests that nonuniform host selection by mosquitoes leads to basic reproduction numbers greater than or equal to those obtained under uniform host selection.

Theorem 1.2 (Theorem 2 in Hasibeder and Dye 1988) *The basic reproduction number $R(m/n)$ for the m/n model* (1.3) *can be estimated against the basic reproduction numbers $R(m/1), R(1/1), R(1/n)$ for the corresponding $m/1$, $1/1$, and $1/n$ models according to*

$$R(m/n) \ge R(m/1) \ge R(1/1) = R(1/n) = \alpha\beta V/\rho\delta H.$$

Moreover, the disease dynamics are completely determined by the basic reproduction number (Theorem 7 in Hasibeder and Dye 1988). Namely, the disease either goes extinct (if $R(m/n) \le 1$) or persists at an endemic equilibrium level (if $R(m/n) > 1$) in the whole system.

Torres-Sorando and Rodríguez (1997, 2001) clearly stated two types of mobility patterns in humans for malaria infection: migration between patches without return, and visitation in which the individuals return to their patch of origin after visiting other patches. Conditions for invasibility of the disease are obtained for the models under further assumptions. More recently, Auger et al. (2008) and Cosner et al. (2009) generalized the models in Dye and Hasibeder (1986, 1988), Torres-Sorando and Rodríguez (1997, 2001) to an even more general form. In particular, Cosner et al. (2009) studied the following visitation model

$$\begin{aligned}\frac{dX_i}{dt} &= \Big(\sum_{j=1}^{N} A_{ij}Y_j\Big)(H_i - X_i) - r_i X_i,\\ \frac{dY_i}{dt} &= \Big(\sum_{j=1}^{N} B_{ij}X_j\Big)(V_i - Y_i) - \mu_i Y_i,\end{aligned} \tag{1.4}$$

and migration model

$$\begin{aligned}\frac{dX_i}{dt} =& A_iY_i(H_i^* - X_i) - r_iX_i + \sum_{j=1}^{N} C_{ij}X_j,\\ \frac{dY_i}{dt} =& B_iX_i(V_i^* - Y_i) - \mu_iY_i + \sum_{j=1}^{N} D_{ij}Y_j,\end{aligned} \tag{1.5}$$

where $A_i = a_ib_ie^{-\mu_i\tau_i}/H_i^*$ and $B_i = a_ic_i/H_i^*$ for $i = 1, \cdots, N$. Here N is the number of patches in the network; X_i and Y_i are the numbers of infected humans and mosquitoes, respectively; H_i and V_i are the total numbers of humans and mosquitoes for the ith patch in isolation, respectively; r_i and μ_i are the recovery rate for humans and mortality rate of mosquitoes, respectively; A_{ij} and B_{ij} measure the rates that a vector from patch j bites and infects a host in patch i and a host in patch i gets infection from a vector in patch j, respectively; a_i and τ_i are the human feeding rate and the extrinsic incubation period of malaria within mosquitoes, respectively; b_i and c_i measure the transmission efficiencies from infected mosquitoes to susceptible humans and from infected humans to susceptible mosquitoes in patch i, respectively; C_{ij} and D_{ij} are the movement rates of humans and mosquitoes from patch j to patch i, $i \neq j$, respectively; $-C_{ii} = \sum_{j=1,j\neq i}^{N} C_{ji}$ and $-D_{ii} = \sum_{j=1,j\neq i}^{N} D_{ji}$ are the emigration rate of humans and mosquitoes in patch i, respectively; $(H_1^*, \cdots, H_N^*)$ and $(V_1^*, \cdots, V_N^*)$ are the equilibrium population size of humans and mosquitoes, which are the unique positive solutions to

$$\sum_{j=1}^{N} C_{ij}H_j^* = 0, i = 1, \cdots, N, \text{ and } \sum_{j=1}^{N} H_j^* = \sum_{j=1}^{N} H_j,$$
$$\sum_{j=1}^{N} D_{ij}V_j^* = 0, i = 1, \cdots, N, \text{ and } \sum_{j=1}^{N} V_j^* = \sum_{j=1}^{N} V_j,$$

respectively.

The basic reproduction number for each modeling approach is computed using the method of van den Driessche and Watmough (2002) and it is a threshold that determines the global dynamics of the disease.

Theorem 1.3 (Theorem 1 in Cosner et al. 2009) *Let $\mathscr{A} = ((A_{ij}H_i/\mu_j))$ and $\mathscr{B} = ((B_{ij}V_i/r_j))$, where the entries in $\mathscr{A}$ and $\mathscr{B}$ are taken from* (1.4)*. Assume that the matrices $\mathscr{A}$, $\mathscr{B}$ are irreducible. Then for* (1.4) *we may take $R_0^2 = \rho(\mathscr{A}\mathscr{B})$ where ρ is the spectral radius. If $R_0 < 1$ then the disease-free equilibrium in* (1.4) *is stable while if $R_0 > 1$ it is unstable. If the disease-free equilibrium in* (1.4) *is stable then there is no positive equilibrium and the disease-free equilibrium is globally stable among nonnegative solutions. If the disease-free equilibrium is unstable then there is a unique positive equilibrium which is globally stable among positive solutions.*

Theorem 1.4 (Theorem 2 in Cosner et al. 2009) *Consider the system* (1.5) *restricted to the invariant region $\{(X_1, \cdots, X_N, Y_1, \cdots, Y_N) : 0 \leq X_i \leq H_i^*, 0 \leq Y_i \leq$*

$V_i^*, i = 1, \cdots, N\}$. *Let* $C = ((C_{ij}))$ *and* $D = ((D_{ij}))$. *Let* $\mathscr{A}^* = ((A_i H_i^* \delta_{ij}))$, $\mathscr{B}^* = ((B_i V_i^* \delta_{ij}))$, $\mathscr{C}^* = ((C_{ij} - r_i \delta_{ij}))$, *and* $\mathscr{D}^* = ((D_{ij} - \mu_i \delta_{ij}))$, *where* δ_{ij} *is the Kronecker delta (i.e.,* 1 *when* $i = j$ *and* 0 *otherwise). Assume that the matrices* C *and* D *are irreducible. Then for* (1.5) *we may take* $R_0^2 = \rho(\mathscr{A}^* \mathscr{D}^{*-1} \mathscr{B}^* \mathscr{C}^{*-1})$. *If* $R_0 < 1$ *then the disease-free equilibrium in* (1.5) *is stable while if* $R_0 > 1$ *it is unstable. If the disease-free equilibrium in* (1.5) *is stable then there is no positive equilibrium and the disease-free equilibrium is globally stable among non-negative solutions. If the disease-free equilibrium is unstable then there is a unique positive equilibrium which is globally stable among positive solutions.*

An numerical example in Cosner et al. (2009) shows that a vector-borne disease can become endemic when humans move between patches, even though the disease dies out in each isolated patch. In fact, for a model consists of two identical patches we can show that the basic reproduction number of the isolated patch, labeled by $R_{i,0}$, is always less than or equal to the basic reproduction number R_0 of the two-patch model.

Theorem 1.5 *Consider system* (1.5) *with two identical patches connected by human movement, i.e.,* $a_i = a, b_i = b, c_i = c, \mu_i = \mu, r_i = r, \tau_i = \tau, H_i = H, V_i = V$, $i = 1, 2$, $C_{12} > 0$, $C_{21} > 0$ *and* $D_{12} = D_{21} = 0$. *Then* $R_0 \geq R_{1,0} = R_{2,0}$ *with equality if and only if* $C_{12} = C_{21}$.

Based on the above result, we present an example to illustrate this interesting phenomenon. For $i = 1, 2$, suppose $a_i = 0.2, b_i = 0.3, c_i = 0.3, \mu_i = 0.095$, $r_i = 0.07, \tau_i = 0$, $H_i = 1, V_i = 1.8$. Thus $R_{1,0} = R_{2,0} = 0.9871 < 1$ and the disease dies out in each isolated patch (see Figure 1.1). Now we allow humans to migrate between these two patches with $C_{12} = 0.1$ and $C_{21} = 0.5$. The basic reproduction number of the two-patch model is $R_0 = 1.0357 > 1$. Therefore, the disease becomes endemic in both patches (see Figure 1.2).

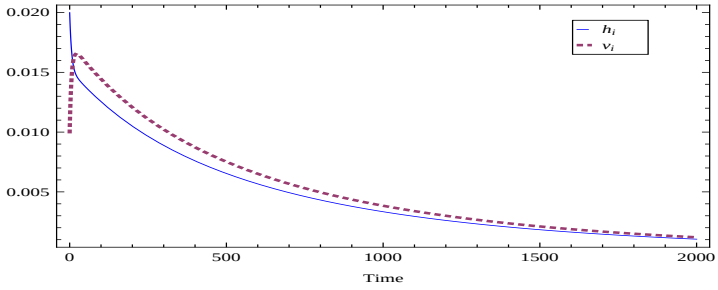

Figure 1.1 When there is no movement between the two patches, the disease disappears in both patches. Here $h_i(0) = 0.02, v_i(0) = 0.01, i = 1, 2$.

However, the scenario cannot happen for an SIS multi-patch model with standard incidence (see Gao and Ruan 2011) where the basic reproduction number of the full model is between the maximum and minimum of the basic reproduction numbers of

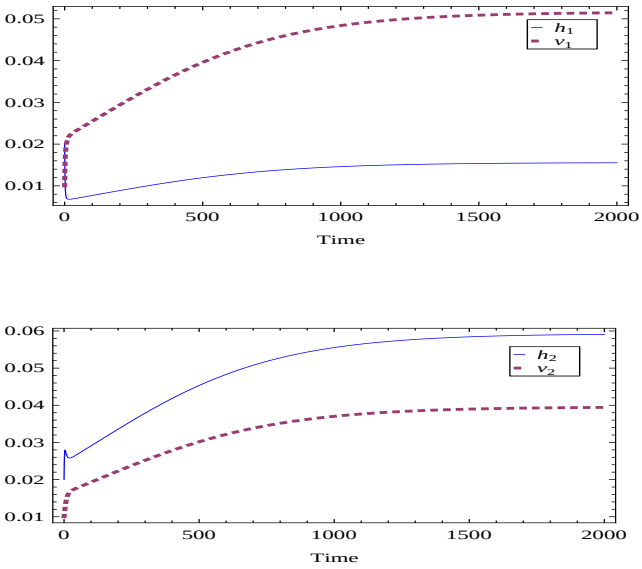

Figure 1.2 When nonsymmetric human movement occurs, the disease becomes endemic in both patches. Here $C_{12} = 0.1, C_{21} = 0.5, h_i(0) = 0.02$ and $v_i(0) = 0.01, i = 1, 2$.

each isolated patch, but can occur for an SIS multi-patch model with bilinear incidence (Wang and Zhao 2004) where we can rigorously establish a result on R_0 similar to Theorem 1.5 under the assumption that susceptible and infectious individuals have identical travel rates. In addition, this scenario does not exist for a multi-patch Ross-Macdonald model with constant mosquito-human ratio in each patch. The following conclusion follows from Proposition 2.2 in Gao and Ruan (2011).

Theorem 1.6 *Consider system* (1.5) *with arbitrary number of patches connected by human movement satisfying* $V_i/H_i = V_i^*/H_i^* = m_i$ *and* $D_{ij} = 0$ *for* $i, j = 1, \cdots, N$. *Then* $\min_{1\le i\le N} R_{i0} \le R_0 \le \max_{1\le i\le N} R_{i,0}$.

So the possible occurrence of the aforementioned scenario depends on the contact rate, namely, the scenario appears if the contact rate is a function of the total population and disappears if it is a constant. The other interesting observation with respect to system (1.5) is the non-monotone dependence of R_0 upon the travel rate. For example, using the same parameters as in Figure 1.1 except that $C_{12} = 0.2$ and $C_{21} = m$, the curve R_0 against m from 0.05 to 0.70 is given in Figure 1.3.

Auger et al. (2010) also considered an n-patch Ross-Macdonald model with host migration under the assumptions that the susceptible and infected hosts have different movement rates and the migration process is faster than the epidemic phenomenon. The model can possess multiple endemic equilibria when the basic reproduction number of the model is greater than one. Prosper et al. (2012) eliminated the

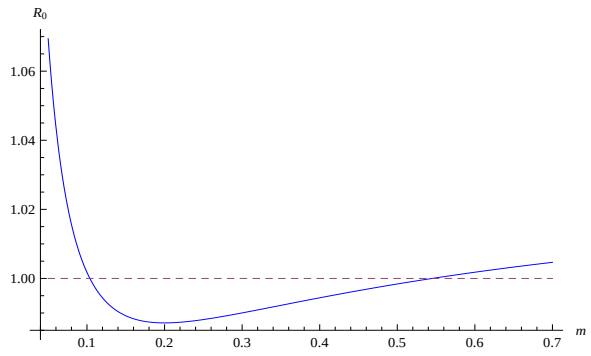

Figure 1.3 The relation between R_0 and $m = C_{21}$. The disease dies out when the travel rate from patch 1 to patch 2 is neither too small nor too large; it persists otherwise.

equation for infected mosquitoes from the classical Ross-Macdonald model provided that the infected mosquito population equilibrates much faster than the infected human population. When it extends to a patchy environment with human migration, a directly transmitted disease like model was derived. For the two-patch case, they found that the basic reproduction number of the whole system is between the basic basic reproduction numbers of the two patches in isolation. In fact, we can easily generalize this result to a system with an arbitrary number of patches and even establish the global dynamics of the system by using some earlier results in Gao and Ruan (2011).

1.3.2 Multi-patch models with vital dynamics of humans

In this subsection, we present two metapopulation models in which the acquired immunity in humans and the demographic process (births and deaths) of both humans and mosquitoes are incorporated and the transmission process is more complicated.

1.3.2.1 A multi-patch model with constant recruitment Arino et al. (2012) developed a multi-patch malaria model with SIRS and SI structures for the hosts and vectors, respectively. In the absence of disease and human migration, both humans and mosquitoes are modeled by a simple linear growth model with a constant recruitment rate and a constant natural death rate. It is assumed that a recovered person (asymptomatic carrier) is temporarily immune to the disease but who may be still infectious to mosquitoes. The total number of patches is n. At time t in patch i, there are $S_{H,i}(t)$ susceptible humans, $I_{H,i}$ infectious humans, $R_{H,i}$ recovered humans, $S_{V,i}$ susceptible mosquitoes and $I_{V,i}$ infectious mosquitoes. Let $H_i(t) = S_{H,i}(t) + I_{H,i}(t) + R_{H,i}(t)$ and $V_i(t) = S_{V,i}(t) + I_{V,i}(t)$ be the total human and mosquito populations in patch i at time t. Then the malaria transmission

dynamics are governed by the equations

$$\begin{aligned}
\frac{dS_{H,i}}{dt} =&\Lambda_{H,i} + \beta_{H,i}R_{H,i} + \rho_{H,i}I_{H,i} - \mu_{H,i}S_{H,i} - \Phi_{H,i}S_{H,i} + \sum_{j=1}^{n} m_{ij}^{S}S_{H,j},\\
\frac{dI_{H,i}}{dt} =&\Phi_{H,i}S_{H,i} - (\alpha_{H,i} + \gamma_{H,i} + \rho_{H,i} + \mu_{H,i})I_{H,i} + \sum_{j=1}^{n} m_{ij}^{I}I_{H,j},\\
\frac{dR_{H,i}}{dt} =&\alpha_{H,i}I_{H,i} - (\beta_{H,i} + \mu_{H,i})R_{H,i} + \sum_{j=1}^{n} m_{ij}^{R}R_{H,j},\\
\frac{dS_{V,i}}{dt} =&\Lambda_{V,i} - \mu_{V,i}S_{V,i} - \Phi_{V,i}S_{V,i},\\
\frac{dI_{V,i}}{dt} =&\Phi_{V,i}S_{V,i} - \mu_{V,i}I_{V,i},
\end{aligned} \tag{1.6}$$

where $\Phi_{H,i} = \Phi_{H,i}(S_{H,i}, S_{V,i}, I_{H,i}, R_{H,i}, I_{V,i})$ and $\Phi_{V,i} = \Phi_{V,i}(S_{H,i}, S_{V,i}, I_{H,i}, R_{H,i}, I_{V,i})$ are the forces of infection from mosquitoes to humans and from humans to mosquitoes, respectively. A classic form and a general form of $\Phi_{H,i}$ and $\Phi_{V,i}$ can be found in Ngwa and Shu (2000) and Chitnis et al. (2006), respectively.

For patch i, $\Lambda_{H,i}$ and $\Lambda_{V,i}$ are the recruitment of humans and mosquitoes, respectively, $\alpha_{H,i}$ is the rate of progression from the infectious to the partially immune class, $\rho_{H,i}$ is the rate of recovery from being infectious, $\mu_{H,i}$ and $\mu_{V,i}$ are the natural death rates for humans and mosquitoes, respectively, $\gamma_{H,i}$ is the disease death rate, $\beta_{H,i}$ is the rate of loss of immunity for humans. Let $m_{ij}^{\pi}, \pi = S, I, R$, represent the travel rate of humans from patch j to patch i, for $i, j = 1, \cdots, n, i \neq j$, and $m_{ii}^{\pi} = -\sum_{j=1, j\neq i}^{n} m_{ji}^{\pi}$, for $\pi = S, I, R$ and $i = 1, \cdots, n$.. Assume that the travel rate matrices $M^{\pi} = (m_{ij}^{\pi})_{n\times n}$ are irreducible for $\pi = S, R$.

Let $S = (S_{H,1}, S_{V,1}, \cdots, S_{H,n}, S_{V,n})$ and $I = (I_{H,1}, R_{H,1}, I_{V,1}, \cdots, I_{H,n}, R_{H,n}, I_{V,n})$ denote the susceptible and infected states, respectively. It is easy to check that system (1.6) is well-posed and has a unique disease-free equilibrium $(S^*, 0)$ in $\Omega = \{(S, I) \in \mathbb{R}_{+}^{5n} : S_{H,i} > 0, S_{V,i} > 0, 1 \leq i \leq n\}$. Following the recipe of van den Driessche and Watmough (2002), we define the basic reproduction number of system (1.6) as

$$\mathcal{R}_0 = \rho(FV^{-1}) = \rho(\text{diag}\{F_{11}, \cdots, F_{nn}\}(V_{ij})_{n\times n}),$$

where submatrices

$$F_{ii} = \begin{bmatrix} 0 & 0 & \partial\Phi_{H,i}/\partial I_{V,i}S_{H,i}^{*} \\ 0 & 0 & 0 \\ \partial\Phi_{V,i}/\partial I_{H,i}S_{V,i}^{*} & \partial\Phi_{V,i}/\partial R_{H,i}S_{V,i}^{*} & 0 \end{bmatrix},$$

$$V_{ij} = \text{diag}\{-m_{ij}^{I}, -m_{ij}^{R}, 0\}, i \neq j, V_{ii} = \begin{bmatrix} \epsilon_{H,i} - m_{ii}^{I} & 0 & 0 \\ -\alpha_{H,i} & \delta_{H,i} - m_{ii}^{R} & 0 \\ 0 & 0 & \mu_{V,i} \end{bmatrix}$$

for $i, j = 1, 2, \cdots, n$.

The basic reproduction number $\mathcal{R}_0$ determines the local stability of the disease-free equilibrium but not the global behavior of system (1.6) since a backward bifurcation may occur at $\mathcal{R}_0 = 1$ if the disease related death rate is sufficiently high. Arino et al. (2012) used type reproduction numbers (Roberts and Heesterbeek 2003) to identify the reservoirs of infection where control measures would be most effective. The paper ends with applications to the disease spread from endemic to non-endemic areas and from rural to urban areas.

Zorom et al. (2012) introduced two control variables, prevention and treatment, to the model (1.6). By using the optimal control theory to a three-patch submodel, they numerically identified the best control strategy when the patch is a reservoir or not.

1.3.2.2 A multi-patch model with logistic growth To explore the effects of population dispersal on the spatial spread of malaria, Gao and Ruan (2012) formulated a multi-patch model based on that of Ngwa and Shu (2000) with an SEIR structure for humans and an SEI structure for mosquitoes. Both human and mosquito populations obey a logistic growth and migrate between n patches, with humans having additional disease induced death. The number of susceptible, exposed, infectious and recovered humans in patch i at time t, is denoted by $S_i^h(t), E_i^h(t), I_i^h(t)$ and $R_i^h(t)$, respectively. Let $S_i^v(t), E_i^v(t)$ and $I_i^v(t)$ denote, respectively, the number of susceptible, exposed and infectious mosquitoes in patch i at time t. $N_i^h(t)$ and $N_i^v(t)$ represent the total human and mosquito populations in patch i at time t. The interactions between hosts and vectors in patch i are given by the following system of $7n$ ordinary differential equations with nonnegative initial conditions satisfying $N_i^h(0) > 0$:

$$
\begin{aligned}
\frac{dS_i^h}{dt} &= \lambda_i^h N_i^h + \beta_i^h R_i^h + r_i^h I_i^h - \frac{c_i^{vh} a_i^v I_i^v}{N_i^h} S_i^h - f_i^h(N_i^h) S_i^h + \sum_{j=1}^{n} \varphi_{ij}^S S_j^h, \\
\frac{dE_i^h}{dt} &= \frac{c_i^{vh} a_i^v I_i^v}{N_i^h} S_i^h - (\nu_i^h + f_i^h(N_i^h)) E_i^h + \sum_{j=1}^{n} \varphi_{ij}^E E_j^h, \\
\frac{dI_i^h}{dt} &= \nu_i^h E_i^h - (r_i^h + \alpha_i^h + \gamma_i^h + f_i^h(N_i^h)) I_i^h + \sum_{j=1}^{n} \varphi_{ij}^I I_j^h, \\
\frac{dR_i^h}{dt} &= \alpha_i^h I_i^h - (\beta_i^h + f_i^h(N_i^h)) R_i^h + \sum_{j=1}^{n} \varphi_{ij}^R R_j^h, \\
\frac{dS_i^v}{dt} &= \lambda_i^v N_i^v - \frac{c_i^{hv} a_i^v I_i^h}{N_i^h} S_i^v - \frac{d_i^{hv} a_i^v R_i^h}{N_i^h} S_i^v - f_i^v(N_i^v) S_i^v + \sum_{j=1}^{n} \psi_{ij}^S S_j^v, \\
\frac{dE_i^v}{dt} &= \frac{c_i^{hv} a_i^v I_i^h}{N_i^h} S_i^v + \frac{d_i^{hv} a_i^v R_i^h}{N_i^h} S_i^v - (\nu_i^v + f_i^v(N_i^v)) E_i^v + \sum_{j=1}^{n} \psi_{ij}^E E_j^v,
\end{aligned}
\tag{1.7}
$$

$$\frac{dI_i^v}{dt} = \nu_i^v E_i^v - f_i^v(N_i^v) I_i^v + \sum_{j=1}^{n} \psi_{ij}^I I_j^v,$$

where λ_i^h and λ_i^v are the birth rates of humans and mosquitoes, respectively, $f_i^h(N_i^h) = \mu_i^h + \rho_i^h N_i^h$ and $f_i^v(N_i^v) = \mu_i^v + \rho_i^v N_i^v$ are the density-dependent death rates for humans and mosquitoes, respectively; γ_i^h is the disease-induced death rate for humans; a_i^v is the mosquito biting rate; c_i^{vh}, c_i^{hv} and d_i^{hv} are the transmission probabilities from infectious mosquito to a susceptible human, from an infectious human to a susceptible mosquito and from a recovered human to a susceptible mosquito, respectively; ν_i^h, α_i^h and β_i^h are the progression rates that exposed humans become infectious, infectious humans become recovered and recovered humans become susceptible, respectively; r_i^h is the rate of recovery from being infectious for humans; ν_i^v is the progression rate that exposed mosquitoes become infectious; $\varphi_{ij}^K \geq 0$ for $K = S, E, I, R$ is the immigration rate from patch j to patch i for $i \neq j$ of susceptible, exposed, infectious, and recovered humans, respectively; $\psi_{ij}^L \geq 0$ for $L = S, E, I$ is the immigration rate from patch j to patch i for $i \neq j$ of susceptible, exposed, and infectious mosquitoes, respectively; $-\varphi_{ii}^K \geq 0$ for $K = S, E, I, R$ is the emigration rate of susceptible, exposed, infectious, and recovered humans away from patch i, respectively; $-\psi_{ii}^L \geq 0$ for $L = S, E, I$, is the emigration rate of susceptible, exposed, and infectious mosquitoes in patch i, respectively.

The travel rate matrices $(\varphi_{ij}^K)_{n\times n}$ for $K = S, E, I, R$ and $(\psi_{ij}^L)_{n\times n}$ for $L = S, E, I$ are assumed to be irreducible. For convenience, suppose that individuals do not change their disease status and there is no birth or death during travel. So we have

$$\varphi_{ii}^K = -\sum_{\substack{j=1\\ j\neq i}}^{n} \varphi_{ji}^K, K = S, E, I, R, \text{ and } \psi_{ii}^L = -\sum_{\substack{j=1\\ j\neq i}}^{n} \psi_{ji}^L, L = S, E, I, \ 1 \leq i \leq n.$$

To avoid extinction of either humans or mosquitoes in the patchy environment, we further assume that

$$s(((\lambda_i^h - \mu_i^h)\delta_{ij} + \varphi_{ij}^S)_{n\times n}) > 0 \text{ and } s(((\lambda_i^v - \mu_i^v)\delta_{ij} + \psi_{ij}^S)_{n\times n}) > 0,$$

where s denotes the spectral bound of a matrix which is the largest real part of any eigenvalue of the matrix.

For any $t \geq 0$, denote the vector $(S_1^h(t), \ldots, S_n^h(t))$ by $S^h(t)$ and $E^h(t)$, $I^h(t)$, $R^h(t)$, $S^v(t)$, $E^v(t)$ and $I^v(t)$ can be introduced similarly. It is not difficult to show that system (1.7) is mathematically well-posed and epidemiologically reasonable. Applying the theory of monotone dynamical systems (Smith 1995), we find that system (1.7) has a disease-free equilibrium of the form $(S^{h*}, 0, 0, 0, S^{v*}, 0, 0)$. It follows the next generation method (Diekmann et al. 1990, van den Driessche and Watmough 2002) that the basic reproduction number of system (1.7) is

$$\mathcal{R}_0 = \sqrt{\rho(A_{64}A_{44}^{-1}A_{42}A_{22}^{-1}(A_{73} + A_{75}A_{55}^{-1}A_{53})A_{33}^{-1}A_{31}A_{11}^{-1})},$$

where

$$A_{11} = (\delta_{ij}(\nu_i^h + f_i^h(S_i^{h*})) - \varphi_{ij}^E)_{n\times n},\ A_{22} = (\delta_{ij}(\nu_i^v + f_i^v(S_i^{v*})) - \psi_{ij}^E)_{n\times n},$$
$$A_{31} = (\delta_{ij}\nu_i^h)_{n\times n},\ A_{33} = (\delta_{ij}(r_i^h + \alpha_i^h + \gamma_i^h + f_i^h(S_i^{h*})) - \varphi_{ij}^I)_{n\times n},$$
$$A_{42} = (\delta_{ij}\nu_i^v)_{n\times n},\ A_{44} = (\delta_{ij}f_i^v(S_i^{v*}) - \psi_{ij}^I)_{n\times n},\ A_{53} = (\delta_{ij}\alpha_i^h)_{n\times n},$$
$$A_{55} = (\delta_{ij}(\beta_i^h + f_i^h(S_i^{h*})) - \varphi_{ij}^R)_{n\times n},\ A_{64} = (\delta_{ij}c_i^{vh}a_i^v)_{n\times n},$$
$$A_{73} = (\delta_{ij}c_i^{hv}a_i^v S_i^{v*}/S_i^{h*})_{n\times n},\ A_{75} = (\delta_{ij}d_i^{hv}a_i^v S_i^{v*}/S_i^{h*})_{n\times n}.$$

Immediately, we know the disease-free equilibrium is locally asymptotically stable if $\mathcal{R}_0 < 1$ and is unstable if $\mathcal{R}_0 > 1$. Since system (1.7) is a high-dimensional nonlinear system, it is difficult to investigate the global dynamics of the system. However, under suitable conditions, we can use the techniques of persistence theory (Zhao 2003, Smith and Thieme 2011) to establish the uniform persistence of the disease in all patches provided that $\mathcal{R}_0 > 1$.

Theorem 1.7 (Theorem 3.7 in Gao and Ruan 2012) *Let $\mathcal{E}_{11}$ denote the disease-free equilibrium of* (1.7)*, $W^s(\mathcal{E}_{11})$ be the stable manifold of $\mathcal{E}_{11}$, and X_0 be $\mathbb{R}_+^n \times \mathrm{Int}\mathbb{R}_+^{3n} \times \mathbb{R}_+^n \times \mathrm{Int}\mathbb{R}_+^{2n}$. Suppose that $\mathcal{R}_0 > 1$, then $W^s(\mathcal{E}_{11}) \cap X_0 = \emptyset$. If, in addition, assume that*

(i) $\lambda_i^h - \mu_i^h - \gamma_i^h > 0$ *for* $i = 1, 2, \ldots, n$;

(ii) $\varphi_{ij}^K > 0$ *for* $K = S, E, I, R$, $i, j = 1, 2, \ldots, n$, $i \neq j$;

(iii) $\lambda_i^v - \mu_i^v > 0$ *for* $i = 1, 2, \ldots, n$ *(or* $\psi_{ij}^S = \psi_{ij}^E = \psi_{ij}^I$ *for* $i, j = 1, 2, \ldots, n$*).*

Then the disease is uniformly persistent among patches, i.e., there is a constant $\kappa > 0$ such that each solution $\Phi_t(\mathbf{x}_0) \equiv (S^h(t), E^h(t), I^h(t), R^h(t), S^v(t), E^v(t), I^v(t))$ of system (1.7) *with $\mathbf{x}_0 \equiv (S^h(0), E^h(0), I^h(0), R^h(0), S^v(0), E^v(0), I^v(0)) \in X_0$ satisfies*

$$\liminf_{t\to\infty}(E^h(t), I^h(t), R^h(t), E^v(t), I^v(t)) > (\kappa, \kappa, \ldots, \kappa)_{1\times 5n},$$

and (1.7) *admits at least one endemic equilibrium.*

Therefore, $\mathcal{R}_0$ gives a sharp threshold below which the disease-free equilibrium is locally stable and above which the disease persists in all patches. In order to eliminate the disease, we should seek a way to reduce $\mathcal{R}_0$ to be less than unity. A natural question about disease control in a discrete space is how the reproduction number depends on the travel rate matrices. This leads to a complicated eigenvalue problem. For the two-patch case, the basic reproduction number $\mathcal{R}_0$ varies monotonically with the travel rates of exposed, infectious, and recovered humans, which depend on the disease status. When the travel rate is independent of the disease status, but may or may not be independent of residence, the relationship between $\mathcal{R}_0$ and the travel rates of exposed, infectious and recovered humans becomes even more complicated and non-monotone dependence can occur.

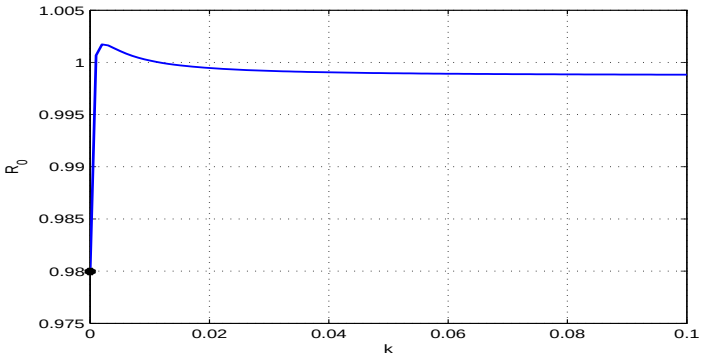

Figure 1.4 The basic reproduction number $\mathcal{R}_0$ in terms of $k = \varphi_{12}^E = \varphi_{12}^I = \varphi_{12}^R = \varphi_{21}^E = \varphi_{21}^I = \varphi_{21}^R$. Here all other parameters are fixed. The disease dies out when the exposed, infectious and recovered human travel rate is small or large, it persists otherwise.

Finally, for the two-patch submodel, three numerical examples were given to illustrate the impact of population dispersal for the disease spread. The first example is used to compare the importance of different disease states in the disease propagation. The optimal control strategy varies with the parameter setting. The second one indicates that suitable human movement can both promote and halt the disease spread even for two identical patches with the same initial conditions. In the last example, two patches which only differ in infectivity of humans and mosquitoes are concerned. Non-monotonicity of $\mathcal{R}_0$ in the exposed, infectious and recovered human travel rate which is independent of the residence and disease state is observed (see Figure 1.4). These results suggest that human movement plays a vital role in the spatial spread of malaria around the world. Since the travel of exposed humans can also spread the disease geographically and screening at borders usually can only help to identify those infected with symptom, inappropriate border control may make the disease spread even worse and to control or eliminate malaria we need strategies from regional to global.

1.3.3 Multi-patch and multi-strain malaria models

Most existing vector-borne disease models with population dispersal focus on the effect of spatial heterogeneity on the distribution and maintenance of infectious diseases. Few studies have addressed the impact of spatial heterogeneities on the evolution of pathogens to more resilient drug-resistant strains.

In a recent paper, Qiu et al. (2013) proposed a Ross-Macdonald type model with l competing strains on n discrete patches connected by human movement. In the i-th patch, the host population is divided into $l+1$ subclasses: susceptible, $S_i(t)$, and infected with strain j, $H_i^j(t)$, $j = 1, 2, \cdots, l$, while the vector population is classified as susceptible, $M_i(t)$, and infected with strain j, $V_i^j(t)$, $j = 1, 2, \cdots, l$.

The interactions between hosts and vectors in patch i ($i = 1, 2, \cdots, n$) are described by the following differential equations:

$$\begin{aligned}
\frac{dS_i(t)}{dt} =& \nu_i N_i - b_i \left(\sum_{j=1}^{l} \alpha_j V_i^j \right) \frac{S_i}{N_i} + \sum_{j=1}^{l} \gamma_i^j H_i^j + \sum_{k=1}^{n} m_{ik} S_k - \nu_i S_i, \\
\frac{dH_i^j(t)}{dt} =& b_i \alpha_j V_i^j \frac{S_i}{N_i} - \gamma_i^j H_i^j + \sum_{k=1}^{n} m_{ik} H_k^j - \nu_i H_i^j, \ j = 1, 2, \cdots, l, \\
\frac{dM_i(t)}{dt} =& \Lambda_i - b_i \left(\sum_{j=1}^{l} \beta_j H_i^j \right) \frac{M_i}{N_i} - \mu_i M_i, \\
\frac{dV_i^j(t)}{dt} =& b_i \beta_j M_i \frac{H_i^j}{N_i} - \mu_i V_i^j, \ j = 1, 2, \cdots, l, \\
N_i =& S_i + \sum_{j=1}^{l} H_i^j, \ T_i = M_i + \sum_{j=1}^{l} V_i^j,
\end{aligned} \tag{1.8}$$

where ν_i is the birth and death rate of the hosts, b_i is the biting rate of vectors on hosts, α_j and β_j are the transmission efficiencies from infected vectors with strain j to susceptible hosts and from infected hosts with strain j to susceptible vectors, respectively, γ_i^j is the recovery rate of infected hosts with strain j, Λ_i is the vector recruitment into the susceptible class, μ_i is the mortality rate of the vectors. In addition, m_{ik} represents the migration rate from patch k to patch i for susceptible and infected hosts, $1 \le i, k \le n$ and $i \ne k$. We assume that the travel rate matrix $(m_{ik})_{n\times n}$ is irreducible with $m_{ii} = -\sum_{k=1,k\neq i}^{n} m_{ki}$, otherwise the n patches can be separated into two independent groups.

Since the total host and vector populations in patch i satisfy

$$\frac{dN_i(t)}{dt} = \sum_{k=1}^{n} m_{ik} N_k, 1 \le i \le n, \text{ and } \frac{dT_i(t)}{dt} = \Lambda_i - \mu_i T_i, \ 1 \le i \le n, \tag{1.9}$$

respectively, it follows from Cosner et al. (2009), Auger et al. (2008) that the subsystem composed of the first n equations of (1.9) has a unique positive equilibrium, labeled by $\bar{N} = (\bar{N}_1, \bar{N}_2, \cdots, \bar{N}_n)^T$, which is globally asymptotically stable, and the subsystem composed of the last n equations of (1.9) also admits a unique positive equilibrium, labeled by $\bar{T} = (\bar{W}_1, \bar{W}_2, \cdots, \bar{W}_n)^T = (\frac{\Lambda_1}{\mu_1}, \frac{\Lambda_2}{\mu_2}, \cdots, \frac{\Lambda_n}{\mu_n})^T$, which is also globally asymptotically stable. System (1.8) is then qualitatively equivalent to the following $2ln$-dimensional system

$$\begin{aligned}
\frac{dH_i^j(t)}{dt} &= b_i \alpha_j V_i^j \frac{\bar{N}_i - \sum_{j=1}^{l} H_i^j}{\bar{N}_i} - \gamma_i^j H_i^j + \sum_{k=1}^{n} m_{ik} H_k^j - \nu_i H_i^j, \\
\frac{dV_i^j(t)}{dt} &= b_i \beta_j \left(\bar{W}_i - \sum_{j=1}^{l} V_i^j \right) \frac{H_i^j}{\bar{N}_i} - \mu_i V_i^j,
\end{aligned} \tag{1.10}$$

where $i = 1, 2, \cdots, n, j = 1, 2, \cdots, l$. Set

$$\Omega = \left\{ (I^1, I^2, \cdots, I^l) \in \mathbb{R}_+^{2ln} : \sum_{j=1}^{l} H_i^j \le \bar{N}_i, \sum_{j=1}^{l} V_i^j \le \bar{W}_i, \ i = 1, 2, \cdots, n \right\},$$

where $I^j = (H_1^j, H_2^j, \cdots, H_n^j, V_1^j, V_2^j, \cdots, V_n^j)$. Thus Ω is positively invariant for (1.10).

In the context of no host migration, model (1.10) becomes a simple multi-strain model

$$\begin{aligned} \frac{dH_i^j(t)}{dt} &= b_i \alpha_j V_i^j \frac{N_i^0 - \sum_{j=1}^{l} H_i^j}{N_i^0} - \gamma_i^j H_i^j - \nu_i H_i^j, \ 1 \le j \le n, \\ \frac{dV_i^j(t)}{dt} &= b_i \beta_j \left(\bar{W}_i - \sum_{j=1}^{l} V_i^j \right) \frac{H_i^j}{N_i^0} - \mu_i V_i^j, \ 1 \le j \le n \end{aligned} \tag{1.11}$$

and the respective basic reproduction number for strain j in patch i is

$$R_i^j = \sqrt{\frac{b_i^2 \alpha_j \beta_j \bar{W}_i}{(\gamma_i^j + \nu_i)\mu_i N_i^0}},$$

where $N_i^0 = N_i(0), 1, 2, \cdots, n$. Qiu et al. (2013) proved the following theorem which implies that competitive exclusion of the strains is the only outcome on a single patch.

Theorem 1.8 (Theorem 3.1 in Qiu et al. 2013) *For a given $i \in \{1, 2, \cdots, n\}$, system* (1.11) *has the following:*

(1) *if $R_i^j < 1$ for all $1 \le j \le l$, then the disease for all strains will eventually die out, i.e., the disease-free equilibrium of the system* (1.11) *is globally asymptotically stable;*

(2) *if $R_i^j > 1$ for some $1 \le j \le l$ and assume that there exists $j^* \in \{1, 2, \cdots, l\}$ such that $R_i^{j^*} > R_i^j$ for all $j = 1, 2, \cdots, l$, $j \ne j^*$, then*

$$\lim_{t \to +\infty} H_i^{j^*}(t) = \frac{[b_i^2 \alpha_{j^*} \beta_{j^*} \frac{\bar{W}_i}{N_i^0} - \mu_i(\gamma_i^{j^*} + \nu_i)] N_i^0}{b_i \beta_{j^*} (\gamma_i^{j^*} + \nu_i + b_i \alpha_{j^*} \frac{\bar{W}_i}{N_i^0})},$$

$$\lim_{t \to +\infty} V_i^{j^*}(t) = \frac{[b_i^2 \alpha_{j^*} \beta_{j^*} \frac{\bar{W}_i}{N_i^0} - \mu_i(\gamma_i^{j^*} + \nu_i)] N_i^0}{b_i \alpha_{j^*} (b_i \beta_{j^*} + \mu_i)},$$

and

$$\lim_{t \to +\infty} H_i^j(t) = 0, \lim_{t \to +\infty} V_i^j(t) = 0$$

for all $j = 1, 2, \cdots, l, j \neq j^*$.

Next, for the case when the patches are connected, define

$$\Gamma^c = \{(I^1, I^2, \cdots, I^l) \in \Omega : \ I^j = 0, j \neq c\}$$

for $c \in \{1, 2, \cdots, l\}$. Then Γ^c is positively invariant for (1.10) and system (1.10) in Γ^c becomes

$$\begin{aligned} \frac{dH_i^c(t)}{dt} &= b_i \alpha_c V_i^c \frac{\bar{N}_i - H_i^c}{\bar{N}_i} - \gamma_i^c H_i^c + \sum_{k=1}^{n} m_{ik} H_k^c - \nu_i H_i^c, \\ \frac{dV_i^c(t)}{dt} &= b_i \beta_c (\bar{W}_i - V_i^c) \frac{H_i^c}{\bar{N}_i} - \mu_i V_i^c, \ i = 1, 2, \cdots, n. \end{aligned} \tag{1.12}$$

Note that system (1.12) a special case of the migration model (1.5). The multi-patch basic reproduction number of subsystem (1.12) is given by

$$\mathcal{R}_0^c = \sqrt{\rho(\mathscr{F}_{12}^c (\mathscr{V}_{22}^c)^{-1} \mathscr{F}_{21}^c (\mathscr{V}_{11}^c)^{-1})}$$

for strain c, where

$$\begin{aligned} \mathscr{F}_{12}^c &= \text{diag}\{b_1 \alpha_c, b_2 \alpha_c, \cdots, b_n \alpha_c\}, \\ \mathscr{F}_{21}^c &= \text{diag}\{b_1 \beta_c \frac{\bar{W}_1}{\bar{N}_1}, b_2 \beta_c \frac{\bar{W}_2}{\bar{N}_2}, \cdots, b_n \beta_c \frac{\bar{W}_n}{\bar{N}_n}\}, \\ \mathscr{V}_{11}^c &= ((\gamma_i^c + \nu_i)\delta_{ik} - m_{ik})_{n \times n}, \ \mathscr{V}_{22}^c = \text{diag}\{\mu_1, \mu_2, \cdots, \mu_n\}. \end{aligned}$$

The dynamics of system (1.10) in Γ^c are completely determined by the respective basic reproduction number $\mathcal{R}_0^c$.

Theorem 1.9 (Theorem 3.2 in Qiu et al. 2013) *If* $\mathcal{R}_0^c \leq 1$*, then the disease-free equilibrium* E_0 *of the system* (1.10) *is globally asymptotically stable in* Γ^c.

If $\mathcal{R}_0^c > 1$*, then system* (1.10) *has a unique equilibrium* $E_{I^c}(I^c = \bar{I}^c > 0, I^j = 0, j \neq c)$ *which is globally asymptotically stable in* $\Gamma^c \backslash \{O\}$.

By the comparison principle and the result on asymptotically autonomous systems, we find that a strain cannot invade the patchy environment and dies out over the whole system if the multi-patch basic reproduction number for that strain is less than one, and it can if it is the only strain whose reproduction number is greater than one.

Theorem 1.10 (Theorem 3.3 in Qiu et al. 2013) (1) *If* $\mathcal{R}_0^j \leq 1$ *for all* $1 \leq j \leq l$*, then the disease-free equilibrium* E_0 *of the system* (1.10) *is globally asymptotically stable in* Ω.

(2) *If there exists* $c \in \{1, 2, \cdots, l\}$ *such that* $\mathcal{R}_0^c > 1$ *and* $\mathcal{R}_0^j \leq 1$ *for* $1 \leq j \leq l, j \neq c$*, then the boundary equilibrium* $E_{I^c}(I^c = \bar{I}^c > 0, I^j = 0, j \neq c)$ *is globally asymptotically stable in* $\Omega \backslash \{(I^1, I^2, \cdots, I^l) : I^c = 0\}$.

When two or more strains have their multi-patch basic reproduction numbers greater than one, they compete for the same limiting resource, the susceptible hosts and vectors. For simplicity, we consider the two-strain multi-patch model

$$\begin{aligned}\frac{dH_i^j(t)}{dt} &= b_i\alpha_j V_i^j\frac{\bar{N}_i - H_i^1 - H_i^2}{\bar{N}_i} - \gamma_i^j H_i^j + \sum_{k=1}^{n} m_{ik}H_k^j - \nu_i H_i^j,\\ \frac{dV_i^j(t)}{dt} &= b_i\beta_j(\bar{W}_i - V_i^1 - V_i^2)\frac{H_i^j}{\bar{N}_i} - \mu_i V_i^j,\end{aligned} \tag{1.13}$$

where $i = 1, 2, \cdots, n, j = 1, 2$.

We are interested in the case when both $\mathcal{R}_0^1 > 1$ and $\mathcal{R}_0^2 > 1$, since otherwise by Theorem 1.10 one or both strains will die out. By Theorem 1.9, the system (1.13) has a disease-free equilibrium $E_0(0, 0)$ and two boundary equilibria $E_{I^1}(\bar{I}^1, 0), E_{I^2}(0, \bar{I}^2)$. Define the invasion reproduction number for strain j as

$$\mathscr{R}_j^i = (\rho(\mathscr{M}_j^i))^{\frac{1}{2}},$$

where

$$\begin{aligned}\mathscr{M}_j^i =& \text{diag}\left\{b_1\beta_i\frac{\bar{W}_1 - \bar{V}_1^j}{\bar{N}_1}, b_2\beta_i\frac{\bar{W}_2 - \bar{V}_2^j}{\bar{N}_2}, \cdots, b_n\beta_i\frac{\bar{W}_n - \bar{V}_n^j}{\bar{N}_n}\right\}\\ &\times (\mathscr{V}_{11}^i)^{-1}\text{diag}\left\{b_1\alpha_i\frac{\bar{N}_1 - \bar{H}_1^j}{\bar{N}_1\mu_1}, b_2\alpha_i\frac{\bar{N}_2 - \bar{H}_2^j}{\bar{N}_2\mu_2}, \cdots, b_n\alpha_i\frac{\bar{N}_n - \bar{H}_n^j}{\bar{N}_n\mu_n}\right\}.\end{aligned}$$

for $1 \le i, j \le 2$ and $i \ne j$. Here $\mathscr{V}_{11}^i$, $i = 1, 2$ are defined in $\mathcal{R}_0^i$. Obviously, $\mathscr{R}_j^i < \mathcal{R}_0^i$.

Using some results from the theory of M-matrices, we can prove that the Jacobian matrix for the system (1.13) at E_{I^j} is unstable (stable) if $\mathscr{R}_j^i > 1$ ($\mathscr{R}_j^i < 1$). So is the equilibrium E_{I^j}. Moreover, it is proved that both strains are uniformly persistent among patches when $\mathscr{R}_2^1 > 1$ and $\mathscr{R}_1^2 > 1$.

Theorem 1.11 (Theorem 4.2 in Qiu et al. 2013) *If $\mathscr{R}_2^1 > 1$ and $\mathscr{R}_1^2 > 1$, then there exists an $\varepsilon > 0$ such that for every $(I^1(0), I^2(0)) \in \text{Int}\mathbb{R}_+^{4n}$ the solution $(I^1(t), I^2(t))$ of system* (1.13) *satisfies that*

$$\liminf_{t\to+\infty} H_i^j(t) \ge \varepsilon,\ \liminf_{t\to+\infty} V_i^j(t) \ge \varepsilon$$

for all $i = 1, 2, \cdots, n, j = 1, 2$. Moreover, system (1.13) *admits at least one (component-wise) positive equilibrium.*

A combination of Theorem 1.8 and 1.11 suggests that host migration among patches, i.e., the spatial heterogeneity, is a possible mechanism that can lead to the coexistence of multiple competing strains in a common area. In addition, by applying the theory of type-K monotone dynamical systems (Smith 1995), Qiu et al. (2013) investigated the global dynamics of system (1.13) with two patches under certain restraints.

1.4 Malaria models with continuous diffusion

Reaction-diffusion type models have been developed to describe motion of individuals in a continuous space (Wu 2008, Ruan and Wu 2009). The population density now becomes a function of two variables: time and location. When malaria is concerned, the simplest model of this kind is the standard Ross-Macdonald model with a diffusion term. Lou and Zhao (2010) extended it to a reaction-diffusion-advection malaria model with seasonality

$$\begin{aligned}\frac{\partial h(t,x)}{\partial t} =& a(t)b\frac{H-h(t,x)}{H}v(t,x) - d_h h(t,x) + D_h\frac{\partial^2 h(t,x)}{\partial x^2},\\ \frac{\partial v(t,x)}{\partial t} =& a(t)c\frac{h(t,x)}{H}(M(t)-v(t,x)) - d_v(t)v(t,x)\\ &+ D_v\frac{\partial^2 v(t,x)}{\partial x^2} - g\frac{\partial}{\partial x}v(t,x).\end{aligned} \tag{1.14}$$

The density of humans and mosquitoes at location x and time t are H and $M(t)$, $h(t,x)$ and $v(t,x)$ of whom are infected, respectively. Let $a(t)$ be the mosquito biting rate at time t, $1/d_h$ and $1/d_v(t)$ be the human infectious period and the life expectancy of mosquitoes, respectively, b and c be the transmission efficiencies from infectious vectors to humans and from infectious humans to vectors, D_h and D_v be the diffusion rates for humans and mosquitoes, respectively, g be the constant velocity flux. The time-dependent parameters, $a(t), d_v(t)$ and $M(t)$, are ω-periodic functions while b, c, H, d_h, g, D_h and D_v are positive constants.

In the case of an unbounded domain, the spreading speeds and travelling waves for system (1.14) are studied. With respect to a bounded domain, the model exhibits a threshold behavior on the global attractivity of either the disease-free equilibrium or the positive periodic solution.

Consideration of certain practical factors in the study of malaria is sometimes necessary and even critical. In another paper, Lou and Zhao (2011) derived a reaction-diffusion malaria model with incubation period in the vector population

$$\begin{aligned}\frac{\partial u_1(t,x)}{\partial t} =& D_h\Delta u_1(t,x) + \frac{c\beta(x)}{H(x)}(H(x)-u_1(t,x))u_3(t,x) - (d_h+\rho)u_1(t,x),\\ \frac{\partial u_2(t,x)}{\partial t} =& D_m\Delta u_2(t,x) + \mu(x) - \frac{b\beta(x)}{H(x)}u_2(t,x)u_1(t,x) - d_m u_2(t,x),\\ \frac{\partial u_3(t,x)}{\partial t} =& e^{-d_m\tau}\int_\Omega \Gamma(D_m\tau,x,y)\frac{b\beta(y)}{H(y)}u_2(t-\tau,y)u_1(t-\tau,y)dy\\ &+ D_m\Delta u_3(t,x) - d_m u_3(t,x), x\in\Omega, t>0,\\ \frac{\partial u_i}{\partial n} =& 0, \forall x\in\partial\Omega, t>0, i=1,2,3,\end{aligned} \tag{1.15}$$

where $u_1(t,x), u_2(t,x)$ and $u_3(t,x)$ are the population densities of infected humans, susceptible and infectious mosquitoes, respectively, D_h and D_m are the diffusion coefficients of humans and mosquitoes, respectively, b and c are the transmission

probabilities from infectious humans to susceptible mosquitoes and from infectious mosquitos to susceptible humans, respectively, $\beta(x)$ is the habitat-dependent biting rate, $H(x)$ is the total human density at point x, d_h and d_m are the human and mosquito death rates, respectively, ρ is the human recovery rate, $\mu(x)$ is the habitat-dependent mosquito recruitment rate, τ is the incubation period in mosquitoes, Γ is the Green function associated with the Laplacian operator Δ and the Neumann boundary condition, Ω is a spatial habitat with smooth boundary $\partial\Omega$.

This nonlocal and time-delayed reaction-diffusion model admits a basic reproduction number $\mathcal{R}_0$ which serves as a threshold between the extinction and persistence of the disease when Ω is a bounded region. Wu and Xiao (2012) studied the corresponding Cauchy problem in an unbound domain and showed that there exist travelling wave solutions connecting the the disease-free steady state and the endemic steady state if $\mathcal{R}_0 > 1$ (i.e., malaria can invade the domain), and there is no travelling wave solution connecting the disease-free steady state itself if $\mathcal{R}_0 < 1$. By assuming that infectious humans are more attractive to mosquitoes than susceptible humans, Xu and Zhao (2012) modified the model of Lou and Zhao (2010) with a vector-bias term, i.e., change the terms $(H(x) - u_1(t,x))/H(x)$ and $u_1(t,x)/H(x)$ in (1.15) to

$$\frac{l[H(x) - u_1(t,x)]}{pu_1(t,x) + l[H(x) - u_1(t,x)]} \text{ and } \frac{pu_1(t,x)}{pu_1(t,x) + l[H(x) - u_1(t,x)]},$$

respectively. Here p (l) is the probability that a mosquito bites a human if that human is infectious (susceptible) and $p > l$. They obtained some similar results as before. Additionally, in 2005 Bacaër and Sokhna (2005) developed a reaction-diffusion type model describing the geographical spread of drug resistance due to the mobility of mosquitoes.

1.5 Discussion

Human and mosquito movement plays an important role in the spread and persistence of malaria around the world. It brings a big challenge to the prevention and control of malaria. Mathematical modeling of malaria with population dispersal could provide insights into the link of disease transmission between different places, identify key patches or populations, and therefore help us design more effective antimalarial strategies.

In the case of discrete spaces, multi-patch models with migration or commuting have been used by many researchers. The transmission dynamics are much simpler if human population dynamics are ignored (Dye and Hasibeder 1986, Hasibeder and Dye 1988, Torres-Sorando and Rodríguez 1997, Rodríguez and Torres-Sorando 2001, Cosner et al. 2009, Auger et al. 2008). This is probably okay for short term prediction and control. However, we have to add demographic effects into the model for studies with a longer time scale. Models with variable human and mosquito populations become more complicated with richer dynamics (Arino et al. 2012, Gao and Ruan 2012). Little is known about the global stability, the multiplicity or unique-

ness of the endemic steady states. In many cases, fortunately, it is possible to define the basic reproduction number $\mathcal{R}_0$ based on the procedure of van den Driessche and Watmough (2002) and show the existence of an endemic equilibrium as well as the uniform persistence of the disease when $\mathcal{R}_0 > 1$.

Table 1.1 Overview of some malaria models with spatial heterogeneity. The meaning of each column is: Article-which paper, Year-publication year, Eqns-type of model equations (ordinary differential equations-ODE, delay differential equations-DDE or reaction-diffusion equations-RDE), Host-model structure in host, Vector-model structure in vector, Mobility-who has mobility (vector, host, or both), Approach-modeling approach (migration model or visitation model), Rate-is travel rate independent of disease status, Vital-does the model consider vital dynamics in humans. The articles are ordered first by the type of model equations, then by the publication year with an exception of the model in the last article which is a single patch model with constant immigration of infectives.

Article	Year	Eqns	Host	Vector	Mobility	Approach	Rate	Vital
[11]	1986	ODE	SIS	SI	vector	visitation	yes	no
[17]	1988	ODE	SIS	SI	vector	visitation	yes	no
[48]	1997	ODE	SIS	SI	host	both	yes	no
[37]	2001	ODE	SIS	SI	host	visitation	yes	no
[42]	2004	ODE	SIS	SE_1E_kI	vector	migration	yes	no
[28]	2005	ODE	SIS	SEI	vector	migration	yes	no
[3]	2008	ODE	SIS	SI	host	migration	yes	no
[8]	2009	ODE	SIS	SI	both	both	yes	no
[4]	2010	ODE	SIS	SI	host	migration	no	no
[1]	2012	ODE	SIRS	SI	host	migration	no	yes
[33]	2012	ODE	SIS	SI	host	migration	yes	no
[14]	2012	ODE	SEIRS	SEI	both	migration	no	yes
[60]	2012	ODE	SIRS	SI	host	migration	no	yes
[34]	2013	ODE	SIS	SI	host	migration	yes	no
[12]	2014	ODE	SIS	SI	host	migration	yes	no
[57]	2013	DDE	SEIS	SEI	host	migration	no	yes
[5]	2005	RDE	$SI_1(I_2)R(J)S$	$SI_1(I_2)$	vector	n/a	yes	yes
[21]	2010	RDE	SIS	SI	both	n/a	yes	no
[22]	2011	RDE	SIS	SEI	both	n/a	yes	yes
[58]	2012	RDE	SIS	SEI	both	n/a	yes	yes
[55]	2012	RDE	SIS	SEI	both	n/a	yes	yes
[49]	2010	ODE	SIRS	SI	host	n/a	n/a	yes

With respect to continuous spaces, reaction-diffusion equations models have been developed to study the spatial spread of malaria, but so far only a very limited number of works are available. Using the theory of next generation operators we can still define a basic reproduction number $\mathcal{R}_0$, and prove that there exist traveling wave solutions connecting the disease-free state and the endemic state if $\mathcal{R}_0 > 1$ or show the global attractivity of the disease-free steady state or the endemic steady state under special conditions.

In Table 1.1 we give a summary of the malaria models we mentioned in this survey. The study of malaria transmission with spatial heterogeneity is far from well-established. In general, questions such as the global dynamics of multi-patch model with demographic structure, the dependence of $\mathcal{R}_0$ on the diffusion rate and the validity of spatial models are still unanswered. There are some interesting future research directions that we would like to mention as follows.

1. Multi-patch models with time-varying parameters. The mosquito ecology and behavior are strongly driven by climate factors such as rainfall, temperature and humidity. An obvious fact is that mosquito densities are usually higher during the rainy season than in the dry season. To reflect these features, we might use time-varying model parameters instead of constant parameters. Gao et al. (2014) proposed a periodic malaria model in a fragmented habitat which is a generalization of the multi-patch Ross-Macdonald model studied by Auger et al. (2008) and Cosner et al. (2009). Each mosquito is confined to one of the n patches while humans can seasonally migrate from one patch to another. At time t, there are $H_i(t)$ humans with $h_i(t)$ being infected and $V_i(t)$ mosquitoes with $v_i(t)$ being infected in patch i. The human feeding rate $a_i(t)$, mosquito recruitment rate $\epsilon_i(t)$, mosquito death rate $d_i(t)$, and human migration rate $m_{ij}(t)$, are assumed to be periodic and continuous functions with the same period $\omega = 365$ days. The transmission probabilities from infectious mosquitoes to susceptible humans, b_i, from infectious humans to susceptible mosquitoes, c_i, and the human recovery rate, r_i, are positive constants. The periodic malaria model then has the form

$$\begin{aligned}
\frac{dH_i(t)}{dt} &= \sum_{j=1}^{p} m_{ij}(t)H_j(t), \;\; 1 \le i \le p,\\
\frac{dV_i(t)}{dt} &= \epsilon_i(t) - d_i(t)V_i(t), \;\; 1 \le i \le p,\\
\frac{dh_i(t)}{dt} &= b_i a_i(t)\frac{H_i(t) - h_i(t)}{H_i(t)}v_i(t) - r_i h_i(t) + \sum_{j=1}^{p} m_{ij}(t)h_j(t), \;\; 1 \le i \le p,\\
\frac{dv_i(t)}{dt} &= c_i a_i(t)\frac{h_i(t)}{H_i(t)}(V_i(t) - v_i(t)) - d_i(t)v_i(t), \;\; 1 \le i \le p,
\end{aligned} \tag{1.16}$$

where the emigration rate of humans in patch i, $-m_{ii}(t) \ge 0$, satisfies $\sum_{j=1}^{p} m_{ji}(t) = 0$ for $i = 1, \ldots, p$ and $t \in [0, \omega]$ and the matrix $(\int_0^\omega m_{ij}(t)dt)_{p\times p}$ is irreducible.

According to the framework presented in Wang and Zhao (2008), we define the basic reproduction number $\mathcal{R}_0$ for system (1.16) and show that either the disease disappears or becomes established at a unique positive periodic solution, depending on $\mathcal{R}_0$. It provides a possible explanation to the fact that the number of malaria cases show seasonal variations in most endemic areas.

2. Time delays in humans and mosquitoes. Another interesting extension is to introduce delays to account for the latencies in humans and/or mosquitoes. This leads to non-local infections, meaning an infection that is caused by an infectious individual from other location who was exposed before arriving at the current site. Xiao and Zou (2013) derived a system of delay differential equations to depict malaria transmission in a large scale patchy environment in which the latent periods within both hosts and vectors are explicitly included. Since mosquitoes have limited mobility, only host migration is concerned. Within a single patch, the disease progression in humans and mosquitoes are modeled by an SEIS model and an SEI model, respectively. It follows the theory of the next generation operator for structured disease models that the basic reproduction number is defined and shown to be a threshold for the dynamics of the model.

3. More realistic spatial models. Models of malaria in heterogeneous environments has been developed rapidly in recent years. Researchers incorporate acquired immunity, vital dynamics, time delays and environmental factor into the multi-patch Ross-Macdonald model and obtain conditions for disease persistence and extinction. However, these models are still lack of reality and practicality. Models with increasing reality become less mathematically tractable, but they are still useful as long as we can solve them in a numerical way. For example, Smith et al. (2004) proposed a multi-patch malaria model with seasonally varying mosquito birth rate, multi-stage incubation in humans and the movement of mosquitoes. The emigration rate of mosquitoes in one patch is not a constant, but a decreasing function of the number of humans in that patch. They performed simulations for a linear array of 17 patches and found that the two risk factors of human infection, the human biting rate and the proportion of mosquitoes that are infectious, may be negatively corrected in a heterogeneous environment. Their model was modified by Menach et al. (2005) by incorporating a more detailed description of mosquito oviposition behaviour.

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