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Study of Malaria Transmission Dynamics by Mathematical Models

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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Applied Mathematics

STUDY OF MALARIA TRANSMISSION DYNAMICS BY MATHEMATICAL MODELS

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Abstract

This Ph.D thesis focuses on modeling transmission and dispersal of one of the most common infectious diseases, malaria.

Firstly, an integro-differential equation system is derived, based on the classical Ross-Macdonald model, to emphasize the impact of the disease latency on disease dynamics. The novelty lies in the fact that different distribution functions are used to describe the variance of individual latencies. The theoretical results of this project indicate that latencies reduce the basic reproduction number.

Secondly, a patch model is derived to examine how traveling by human beings affects the transmission and spread of malaria. Due to coexistence of latency and dispersal, the model turns out to be a system of delay differential equations on patches with non-local infections. The results from this work suggest that although malaria has been eradicated in many countries since the 1980s, re-emergence of the disease is still possible, and hence precautionary measures should be taken accordingly.

Thirdly, since there are more than five species of malaria parasites causing human malaria, and these are currently distributed in different geographic regions, co-invasion by multiple strains of malaria may arise. We propose multi-strain models to explore co-infection at the within-host level and co-existence at the between-host level. The analysis shows that competitive exclusion dominates at the within-host level, meaning that long term co-infection of a single host by multiple strains can be generically excluded. However, at the between-host level, long term co-existence of multiple strains in a region is possible.

Keywords: Infectious disease, malaria, latency, spatial dispersal, multi-species, mathematical modeling.

Statement of Co-Authorship

Charpter 2-4 of this thesis consist of the following papers:

Chapter 2: Yanyu Xiao and Xingfu Zou, Latencies in malaria infections and their impacts on the disease dynamics, submitted

Chapter 3: Yanyu Xiao and Xingfu Zou, Modeling malaria transmission in a patchy environment, in preparation

Chapter 4: Yanyu Xiao, Xingfu Zou, Can multiple malaria strains co-persist? — Analysis of ODE models, in preparation

The original draft for each of the above articles was prepared by the author. Subsequent revisions were performed by the author and Dr. Xingfu Zou. The analytical and numerical work was performed by the the author under the supervision of Dr. Xingfu Zou.

To my dearest parents

For their unconditional love, encouragement and support!

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Chapter 1

Introduction

Malaria is a widely spread infectious disease, which is also one of the most prevalent diseases in tropical and subtropical areas. Figure 1.1 is a map obtained from WHO Malaria Report 2010, and the shaded areas are the countries where malaria was endemic in 2009.

In addition to being widespread, malaria is also known as a massive killer, because annually 300 million to 500 million infections are reported, among which, 700,000 to 881,000 cases result in deaths as shown in Table 1.3. Most of deaths are either children under five or pregnant women.

Typical symptoms of malaria infections start with headache, followed by cyclical fevers and chills, and sometimes even coma (see, e.g., [31]). The period of cyclical fevers lasts several days, during which time a high probability of dying has been observed for children, since their immune systems are weak. Such fever can also lead to abortions of pregnant women. There are some other possible symptoms such as (refer to [31]) vague, sweating, anemia, bloody stools, convulsion, myalgia, diarrhea, nausea, and vomiting. All symptoms are caused by the intra-host development of members of eukaryotic protists of the genus *Plasmodium*, a family of protozoan parasites that are

responsible for malaria infection.

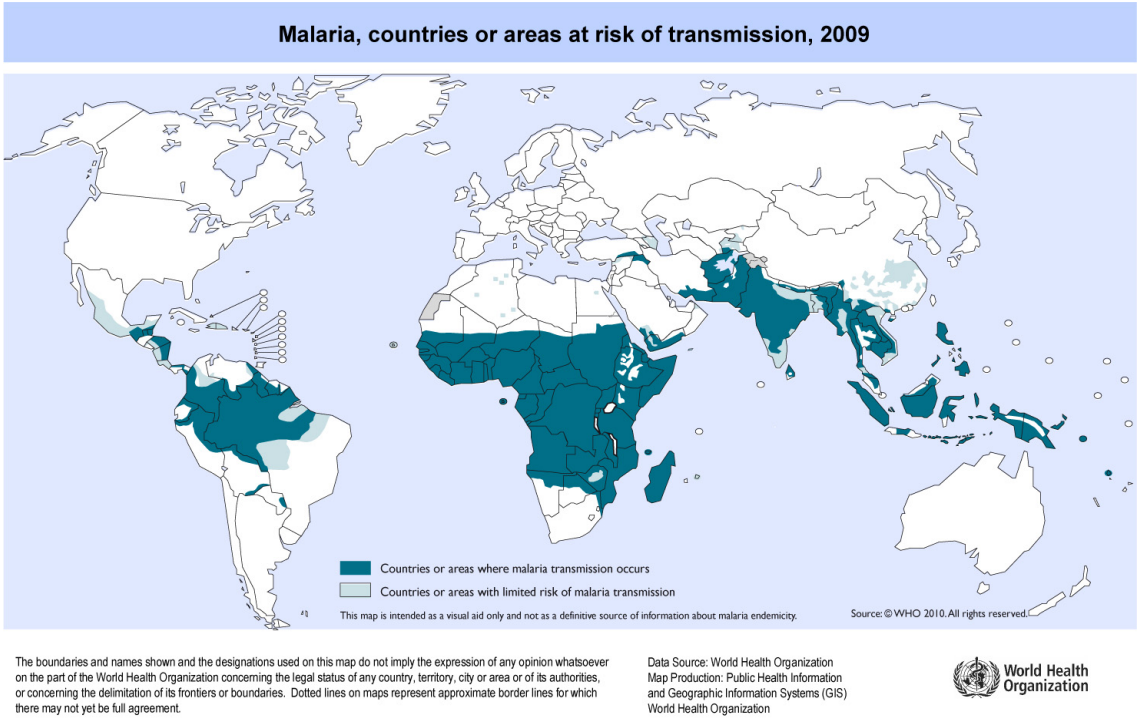

Figure 1.1: Malaria endemic countries in 2009

1.1 Life cycle of malaria parasites

Malaria is a vector-borne disease. Instead of transmitted directly from human to human, malaria parasites are transfered between humans through mosquitoes. The malaria parasite life cycle is divided into two parts, one is within host (human) body and the other is within vector (mosquito) body, as shown in Figure 1.2.

Human infection starts from a blood meal of an infectious female mosquito. The parasites existing in the infectious mosquito's saliva, called sporozoites at this stage, enter the bloodstream of the human though mosquito bites and migrate to the liver. Within minutes after entering in the human body, sporozoites infect hepatocytes, and

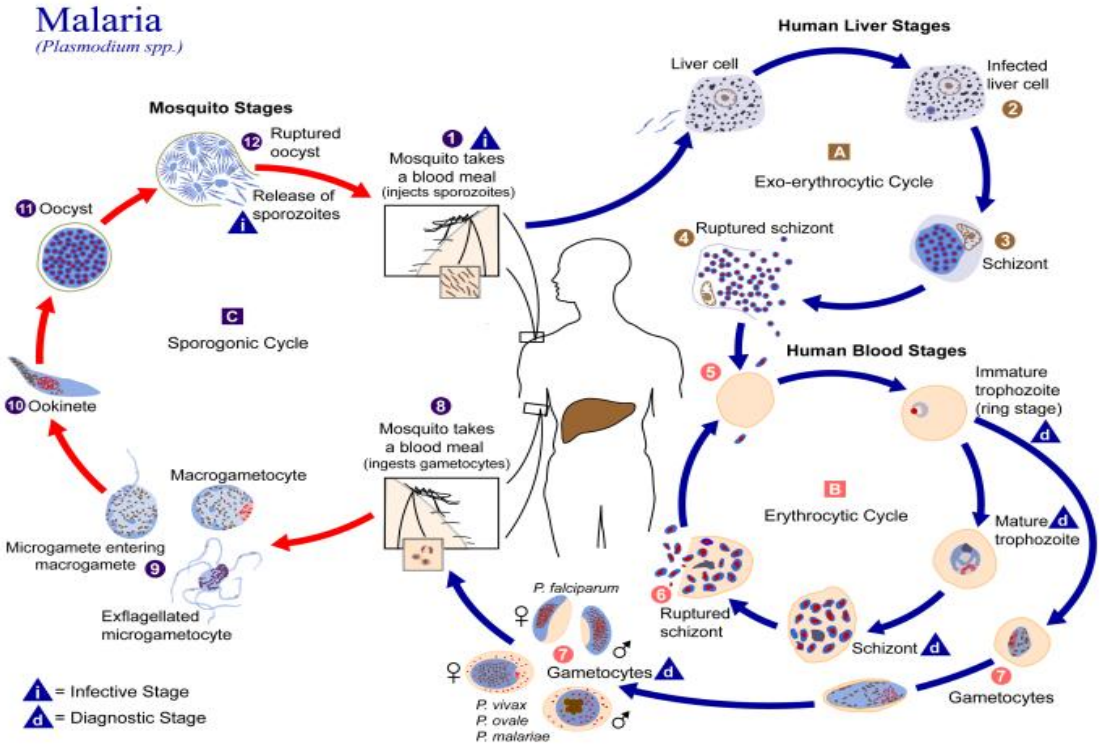

Figure 1.2: The life cycle of malaria parasites

multiply asexually and asymptomatically in liver cells for a period of $5-30$ days [6,9]. This period is called the exo-erythrocytic stage. At the end of this stage, thousands of merozoites (schizonts) emerge inside an infected liver cell. These merozoites rupture their host cells undetectably by wrapping themselves in the membrane of infected liver cells. Then, merozoites escape into the bloodstream and get ready to infect red blood cells. Once entering the bloodstream, free merozoites undergo the so-called erythrocytic stage, in which merozoites invade red blood cells to develop ring forms before experiencing asexual or sexual maturation. Within the red blood cells, a proportion of parasites keep multiplying asexually and periodically break out of infected old red blood cells to invade fresh red blood cells. Such amplification cycles may cause the symptom of waves of fever. The rest parasites follow sexual maturation and produce male (micro-) and female (macro-) gametocytes which may be taken up by bites of female mosquitoes.

When an uninfected female mosquito bites an infectious human, it ingests the human's blood cells with gametocytes. In the mosquito gut, exflagellated micro-gametocytes enter macro-gametocytes after being released from the human's red blood cells, and further form diploid zygotes, which develop into active ookinetes. Ookinetes burrow into the mosquito midgut wall and become oocysts. The growth and division of each oocyst produces thousands of active haploid forms called sporozoites. After $8-15$ days, the oocyst bursts and releases sporozoites into the body cavity of the mosquito, from where sporozoites travel to and invade the mosquito salivary glands. Then the malaria parasites once more undergoes a cycle of human infection when the mosquito takes a blood meal from another human, injecting the sporozoites from its salivary glands into the human bloodstream [33], and another round of the parasite life cycle starts.

	P. falciparum	P.vivax	P.ovale	P.malaria	P. knowlesi
Duration of primary exoerythrocytlc cycle (days)	5.5	8	9	14-15	8-9
Number of exoerythrocytlc merozoites	30 000	10 000	15 000	15 000	
Duration of erythrocytic cycle (hours)	48	48	50	72	24
Duration of mosquito cycle at 27°*C* (days)	10	8-9	12-14	14-15	

Table 1.1: Some comparative characters of the five human malaria parasites

1.2 Malaria species

There are more than one hundred species from the genus *Plasmodium* involved in malaria infection, but mainly five of them can cause human malaria: *P. falciparum*, *P. vivax*, *P. Ovale*, *P. Malaria* and *P. Knowles*. All of these species share a similar life cycle with various development time-frames (see Table 1.1 for the variance). Different maturation characters of these parasites are responsible for the variations in infection performances, vulnerable population groups and disease mortality rates. For instance, *P. falciparum* can invade and propagate in most ages of red blood cells, producing the largest numbers of exoerythrocytlc merozoites which leads itself to be the most fatal parasite among the five. Therefore, 90% of malaria induced deaths are contributed by *P. falciparum* infections. But this species is curable and can be eliminated completely in human bodies, due to the short exoerythrocytlc cycle that is approximated 6 days. This time period is exhibited as the latent period within humans. On the other hand, *P. vivax*, the one associated with a low disease mortality rate, can persist inside human bodies for an average human life time because of its ability to withstand a wide variation of temperature and the long exoerythrocytlc phase.

1.3 Geographical spread of malaria

Malaria is an ancient infectious diseases with a 10,000 year history [13]. Originally from different species of *Plasmodium* ancestors, the disease was first found in three places: West Africa, Central Africa, and Southeast Asia [10, 25]. From the time line of the disease dispersal in Table 1.2. [34], we noticed that the geographical spread of malaria has followed the dispersal or migration of human beings throughout history. More specifically, the growth of international trade in the sixteenth century in Europe, early trans-Pacific voyages, colonization of Central America and tropic areas and so on, all of them played an important role in helping the spread of malaria. In the early period of the last century, the total population of malaria infections has reached a very high level with more than one-half of the world's population at significant risk, and one out of ten was dying of this disease. Since the early 1950s, with the appearance of the effective insecticide DDT and medicines for malaria infection, the disease has almost gone extinction in North America and most European countries. Currently, deaths caused by malaria mainly happens in Africa. Although the disease incident rate is still high in India and Southeast Asia, the disease induced mortality rate is lower in contrast to that in Africa. The reason can be traced to the origin of malaria and the historical geographic distribution of different species of malaria parasites.

With the geographic expansion of the disease, malaria parasites have also experienced dispersal and evolution. Among the five main species that cause human infections, *P. falciparum* was original from West Africa, while *P.vivax* was first found in Asian and Central West Africa, independently [10, 25]. With the migration of human beings, *P. falciparum* has been spread towards north and east areas of Africa, and *P. vivax* has been spread from east to west via land (see Table 1.2.). And the spread of the parasites by sea followed the opposite direction.

Although both *P. vivax* and *P. malariae* had achieved the widest global distribution,

currently *P. vivax* and *P. falciparum* are the most common malaria parasites contributing more than 90% of infection cases. Almost 85% of the 300-500 million annual malaria cases occur in sub-Saharan Africa, and about 85% of the cases in Africa are caused by *P. falciparum*. *P. vivax* is still the most geographically prevalent parasite causing human malaria, estimated to account for 100-300 million clinical cases across much of Southeast Asia, Central and South America, the Middle East, causing $70-90\%$ of the infections in these areas. Infections caused by this particular species have low mortality rate but high probability of relapse, explaining why Southest Asians (including Indians) have a low death rate in contrast to Africa (exhibited in Table 1.3.).

Currently, there are roughly 108 countries endemic with malaria. Most of them are located in Africa and Southeast Asia. Although the eradication of malaria has been claimed in many western countries, shown in Table 1.3., there are still a few cases reported in these areas annually. The majority of reported cases are imported by travelers who have been to the regions where the disease persists. Increased travel would increases the chance of re-emergence of the disease in modern cities where malaria has been eradicated. Indeed, such re-emergence happened in Iquitos of Peru (see, [12]) once. Thus, the impact of increasing frequency and scale of traveling between regions, countries and continents on the disease dispersal, needs to be carefully evaluated, preferably by mathematical models.

1.4 Malaria control and treatments

According to the transmission procedure of malaria, there are three conditions for the prevalence of the disease:

(i) high density of *Anopheles* mosquitoes,

(ii) high density of human population,

(iii) large rate of transmission of parasites between human beings and mosquitoes.

Obviously, not too much can be done in respect to (ii). So, (i) and (iii) are naturally targeted. That is, either controlling the population of *Anopheles* female mosquitoes at a lower level, or avoiding biting by mosquitoes can reduce the chance of malaria becoming endemic. In the middle of the last century, people in Africa have already knew how to remove or poison the breeding grounds of mosquitoes or the aquatic habitats of the larva stages, such as by filling or applying oil to places with standing water, to control the population of mosquitoes [17]. Later, pesticide was widely employed to eliminate mosquitoes. On the other hand, mosquito nets, bedclothes and mosquito-repellent incense (indoor residual spraying) also help to keep mosquitoes far away from people and minimize the biting rate, greatly reducing the chance of infection and transmission of malaria.

There are some effective drugs for malaria patients currently. For example, *Chloroquine*, *Quinuine*, *Primaquine* and combinations of some other drugs like *sulfadoxine* and *pyrimethamine(SP)* are effective medicines for treating infections caused by the five major parasites. Although malaria is an entirely preventable or curable disease thanks to these effective medicines, there are still millions of people suffering from this disease, who are too poor to afford full treatments. Moreover, insufficient treatments due to poor economic conditions, may result in drug resistance and lead to emergence of new (drug resistant) strains of malaria parasites. For instance, the first case of resistance to *Chloroquine* was documented in 1957. *Chloroquine*, *Quinine* and *Sulfadoxine-pyrimethamine* resistance cases have been reported in almost all disease endemic areas [7]. The emergence of drug resistant species of malaria makes control and treatment of this disease harder and more challenging.

Once recovered, either naturally or after treatments, a human being does possess temporary immunity, but it only lasts a short time. And the cross-immunity of infections

caused by different species of malaria parasites [32] is complicated. The road to malaria vaccine clinics has been long and filled with darkness, even with the support of global funds. A completely effective vaccine has not yet been developed for malaria infection, although several vaccines are under clinical trials. Till recently, a vaccine appears to be within reach, following a successful large-scale phase III trial of RTS,S [27] in seven African countries. This latest achievement in trials shows the potential for a bright future for malaria vaccinations.

1.5 Mathematical models for malaria transmission

It is widely acknowledged that mathematical models can play a crucial role in predicting disease dynamics. The so-called Ross-MacDonald model (see, [28, 29, 22, 23, 24]) is the earliest attempt to quantitatively describe the dynamics of malaria transmission at a population level, given by the following system of ordinary differential equations:

$$\begin{cases} \dfrac{\mathrm{d}I_h}{\mathrm{d}t} = ae_1 I_m \dfrac{N - I_h}{N} - d_1 I_h, \\ \dfrac{\mathrm{d}I_m}{\mathrm{d}t} = ae_2 (M - I_m) \dfrac{I_h}{N} - d_2 I_m. \end{cases} \tag{1.5.1}$$

Here I_h and I_m represent the populations of the infectious classes of human beings and female mosquitoes, respectively. N and M are the total populations of human beings and female mosquitoes, which were assumed to be constants. The model ignores the latencies within both human hosts and mosquitoes, and assumes no immunity of the recovered individuals (thus, the terms $N - I_h$ and $M - I_m$ represent the populations of the susceptible humans and mosquitoes). The constant a is the mosquito biting rate; e_1 is the probability that a bite from an infective mosquito will cause infection of a susceptible human; and e_2 is the probability that a bite from a susceptible mosquito to an infective human individual will cause infection of the mosquito. It is assumed that

the average duration of infection for human beings and mosquitoes are $1/d_1$ and $1/d_2$, respectively. By analyzing this mathematical model, both Ross and McDonald found that it would be possible to eradicate the disease without killing all vector mosquitoes. This was in contrast to the traditional belief that malaria could be wiped out only by eradicating all vector mosquitoes, which would be impossible in practice. Indeed, by looking at the basic reproduction number for this model, given by

$$\mathcal{R}_0 = \frac{ae_1}{d_1}\,\frac{M}{N}\,\frac{ae_2}{d_2}, \tag{1.5.2}$$

one can show that any measure(s) that can bring $\mathcal{R}_0$ to a value less than 1 would eventually drive the disease to extinction. Obviously, among the possible measures are, for example, controlling the mosquito population M (e.g., by spraying mosquito pesticides) to a sufficiently lower level or controlling the biting rate a (e.g., by using mosquito nets).

The Ross-MacDonald model is a simple example that shows how mathematical modeling can provide insights into the dynamics of malaria transmission and spread, and suggest effective measures to control the disease. This simple model is fully mathematically tractable in the sense that the long term behavior of solutions of model (1.5.1) can be fully determined by the quantity $\mathcal{R}_0$, which is explicitly calculated from the model parameters. However, it is highly simplified and biologically inaccurate in the sense that many biological factors are omitted. In recent years, there have been efforts to incorporate these factors in models, resulting in various modifications of model (1.5.1). For instance, in [4, 8, 21], a discrete delay is introduced in models to account for the latency within mosquitoes. In [30], two discrete delays are introduced in model (1.5.1), one accounting for the latency in humans and the other for the latency in mosquitoes. In [19], a model with spatial diffusion and advection of mosquitoes and the seasonality of the model parameters is proposed and analyzed. In [20], age structure of the mosquitoes is incorporated in the model, and in [21], a spatially non-local model with

latency in mosquitoes is analyzed. Models that involve modification of model (1.5.1) to consider within a spatial environment (patchy), are discussed in [3, 11, 5].

In addition to modeling the disease transmission at host and vector population level, there are also works that study the replication of malaria parasites within the host. The first within-host model was proposed by Anderson et al. [2] (see also Hetzel and Anderson [14] and Anderson [1]). They described the interaction among healthy red blood cells, infected red blood cells and malaria parasites. These models have been generalized by many researchers for different purposes. We refer the reader to a review by Molineaux and Dietz [26] and Iggidr et. al. [15, 16] and the references therein on various such generalizations. Especially, the authors built a multi-stage and multi-species ordinary differential equation model for within-host dynamics of the malaria parasites, and showed that the basic reproduction number computed by the next generation matrix plays a global threshold role in [15]. The impact of the immune response on the infection of blood cells by malaria parasites is also discussed in [1, 14, 26, 18].

1.6 Thesis outline and objectives

Although some modifications of model (1.5.1) have appeared in the literature, there is much room to further improve the models to obtain a realistic description of the disease dynamics. In subsections 1.1 - 1.3 of this thesis, malaria transmission and spread is explored by deriving some more realistic models.

Taking the latency issue as an example, the model in [30] is the only one that has considered the latencies in both humans and mosquitoes. But a careful analysis of that model reveals that the model is indeed *not well posed*, because solutions starting with positive initial data may actually become negative. Also note that the latency actually differs from individual to individual, and such a variance in latency suggests that

latency distributions should be introduced. In Chapter 2, we derive a modified Ross-MacDonald model for the dynamics of malaria transmission by incorporating latencies in both human beings and female mosquitoes. Two general probability functions ($P_1(t)$ and $P_2(t)$) are introduced to reflect the variations of latencies among individual humans and individual mosquitoes, respectively. We justify the well-posedness of the new model, identify the basic reproduction number $\mathcal{R}_0$ for the model and analyze the dynamics of the model. The results show that latencies decrease the value of the basic reproduction number (BRN), and the BRN plays a threshold role in predicting whether the disease will die our or persist.

Chapter 3 deals with the spatial spread of malaria in a patchy environment. The existing works [3, 11, 5] ignore the latencies in their patch models. Moreover, in [11], the authors assume that not only humans but also mosquitoes disperse between patches. This may be justifiable if one considers small areas with aquatic environment as patches, but becomes unrealistic when cities or countries or continents are considered as patches because of the very limited distance that mosquitoes can fly [35]. In [5], the authors only consider the dispersal of infectious humans, but ignore that of susceptible humans—this also lacks justification. In Chapter 3, we derive a model built in a patchy environment where the distances between patches are far so that mosquitoes can not disperse between patches, but humans can. Latencies are assumed in humans and mosquitoes, and it is the mobility of people in latency that accounts for the scenario: a human being infected in one patch may become infectious, after a latent period, in another patch. This scenario is referred to as a non-local infection. By analyzing the model, both theoretically and numerically, we are able to explore the impact of the travel by susceptible, latent, and infectious humans on disease transmission and dispersal.

Chapter 4 is motivated by the current geographical distribution of the five main

Time Lines of invasion of malaria	Locations
>10000 years ago	Africa
	Mesopotamia
10000-5000 years ago	Indian peninsula
	South-East Asia
5000 years ago	China
3000 years ago	*P. falciparum* reaches India
2,500 - 2,000 years ago	the Mediterranean shores
1000-500 years ago	Northern Europe
end of 15th century AD	New World (North South America)
mid 18th century AD	Across North America
19th Century AD	all over the globe

Table 1.2: Time lines of malaria disease invasion in different regions.

species of malaria parasites, and the increasing mobility of human beings in the world. Travels by humans may bring the multiple species of malaria parasites into a single region, and hence, whether or not the multiple species can co-exist in that region turns to be an issue. In this chapter, we only consider two species for simplicity. We first set up a model to describe the interactions between two species at the within-host level. It turns out that the model demonstrates generic competitive exclusion. This means that generically, either both species will die out, or only one species will persist. Based on this result, we further set up another two-strain model at the population level. Analysis shows that for a range of model parameters, it is possible for the two species to co-exist in the same region.

We conclude the thesis with a conclusion in Chapter 5, where we summarize the main results (conclusions) of the thesis, and point out some possible topics for future work that of interest to the author.

Cases(in thousands)	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
African	173000	178000	181000	185000	187000	188000	187000	186000	181000	176000
Americas	2800	2300	2200	2100	1900	1900	1700	1500	1100	1100
Eastern Mediterranean	15000	16000	17000	16000	14000	12000	12000	12000	13000	12000
European	47	34	27	22	13	7	4	2	1	1
South-East Asia	38 000	38000	35000	35000	37000	39000	34000	32000	34000	34000
Western Pacific	2800	2500	2200	2500	2800	2300	2500	2100	1900	2300
World	233000	236000	237000	241000	243000	244000	238000	233000	231000	225000
min	181000	181000	182000	184000	185000	185000	179000	175000	171000	169000
max	302000	304000	308000	313000	314000	317000	310000	304000	298000	294000
Deaths(in thousands)	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
African	900	893	885	880	870	853	832	802	756	709
Americas	2.4	2.3	1.4	1.4	1.5	1.6	1.6	1.4	1.1	1.3
Eastern Mediterranean	18	18	21	19	17	17	16	15	16	16
European	0	0	0	0	0	0	0	0	0	0
South-East Asia	58	55	51	50	52	50	48	43	48	49
Western Pacific	6.8	5.8	5.2	5.9	6.5	4.9	5.4	4.7	4.2	5.3
World	985	974	963	957	947	927	904	867	826	781
min	797	785	775	769	765	744	725	694	662	628
max	1228	1214	1199	1191	1174	1153	1120	1075	1024	968

Table 1.3: Estimates of malaria cases and deaths by WHO region, 2000-2009

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Chapter 2

Latencies in malaria infections and their impacts on the disease dynamics

In this chapter, we modify the classic Ross-MacDonald model for malaria disease dynamics by incorporating latencies for both human beings and female mosquitoes. One novelty of our model is that we introduce two general probability functions ($P_1(t)$ and $P_2(t)$) to reflect the fact that the latencies differ from individual to individual. We justify the well-posedness of the new model, identify the basic reproduction number $\mathcal{R}_0$ for the model and analyze the dynamics of the model. We show that when $\mathcal{R}_0 < 1$, the disease free equilibrium E_0 is globally asymptotically stable, meaning that the disease will eventually die out; and if $\mathcal{R}_0 > 1$, E_0 becomes unstable. When $\mathcal{R}_0 > 1$, we consider two specific forms for $P_1(t)$ and $P_2(t)$: (i) $P_1(t)$ and $P_2(t)$ are both exponential functions; (ii) $P_1(t)$ and $P_2(t)$ are both step functions. For (i), the model reduces to a system of ordinary differential equations (ODEs), and for (ii), the long term disease dynamics are governed by a system of delayed differential equations (DDEs). In both cases, we are able to show that when $\mathcal{R}_0 > 1$, the disease persist; moreover if there is no recovery ($\gamma_1 = 0$), all admissible positive solutions will converge to the unique endemic equilibrium. A significant impact of the latencies is that they reduce the basic reproduction

number, regardless of the forms of the distributions.

2.1 Introduction

Malaria is an infectious disease and widespread in tropical and subtropical regions for thousands of years. Malaria is a vector-borne, caused by one or more of a family of protozoan called *Plasmodium*, mainly consisting of five species: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*. The malaria parasites can parasitize in blood cells and other tissues of both human beings and mosquitoes. The transmission of the disease between human beings and female mosquitoes is through biting by female mosquitoes of human beings. Based on such a transmission mechanism, it was initially widely believed that the disease could be wiped out only by eradicating all vector mosquitoes. This is impossible in practice.

It was Ross [18] who first used a mathematical model to quantitatively investigated the spread of malaria. Ross' model was later further extended and studies by McDonald [15, 16, 17], lead to the following system which has been referred to as the Ross-McDonald model

$$\begin{cases} \dfrac{\mathrm{d}I_1}{\mathrm{d}t} = ae_1 I_2(1 - \dfrac{I_1}{N}) - d_1 I_1, \\ \dfrac{\mathrm{d}I_2}{\mathrm{d}t} = ae_2(M - I_2)\dfrac{I_1}{N} - d_2 I_2. \end{cases} \tag{2.1.1}$$

Here I_1 and I_2 represent the populations of the infectious classes of human beings and female mosquitoes, respectively. N and M are the total populations of human beings and female mosquitoes, which are assumed to be constants. The coefficient a is the mosquito biting rate; e_1 is the probability that a bite by an infective mosquito will cause infection of a susceptible person; and e_2 is the probability that a bite from a susceptible mosquito on a infective human will cause infection of the mosquito. The parameters

d_1 and d_2 are the natural death rates of infectious human beings and mosquitoes, respectively. By analyzing this mathematical model, both Ross and McDonald found that it is possible to eradicate the disease without killing all vector mosquitoes. The basic reproduction number for this model is given by

$$\mathcal{R}_0 = \frac{ae_1 M}{d_1 N}\frac{ae_2}{d_2}, \tag{2.1.2}$$

one knows that any measure(s) that can bring $\mathcal{R}_0$ to a value less than 1 would eventually drive the disease to extinction, including controlling the mosquito population M to a sufficiently lower level. Obviously, the approach of mathematically modeling provides much insight into the spread of malaria, by which, effective measures to control the disease can be suggested. For example, in addition to decreasing M to a certain level (by spraying mosquito pesticides) which was Ross and McDonald's finding, decreasing the biting rate (achievable by using mosquito nets) can help eradicate malaria as well.

The Ross-McDonald model is mathematically tractable in the sense that long term solution behavior of the system (2.1.1) can be fully determined by the combined parameter $\mathcal{R}_0$. It is biologically inaccurate in the sense that many biological factors are omitted. One of the important factors is the latency in the transmission process. This can be seen from the life cycle of the malaria parasites. The cycle begins from a blood meal of a female mosquito from human beings. After bitten by an infected female mosquito, a person receives an inoculum of the malaria parasites (sporozoites). About half an hour later, liver cells of the person are invaded by sporozoites. The reproduction of parasites (merozoites) occurs in the liver cells again and again, releasing more free merozoites to infect more liver cells. The immature trophozoites (merozoites), become mature, developing either in a sexual or asexual way. Trophozoites that undergo asexual development will go through the erythrocytic cycle producing more immature trophozolie, while the others grow to gametocytes by sexual maturation and may be

transferred to a female mosquito after biting. Once they are ingested into a female mosquito, gametocytes differentiate into male or female gametes and then fuse in the mosquito gut. This produces ookinetes that penetrate the gut lining and are further developed to oocysts in the gut wall. When oocysts ruptures, they release sporozoites that migrate through the mosquito's body to the salivary glands, ready to undergo another life cycle. See, e.g. [1,21] for details on this topic. Several days to a couple of weeks are needed for the development of parasites inside humans and mosquitoes by the process described above.

Some modellers have noticed the omission of latencies in the Ross-McDonald model and proposed modifications in the form of DDEs, but most of these works only incorporate *a single delay*, representing the latency of the parasite in mosquitoes, see, e.g., [1, 2, 13]. Recently, Ruan and Xiao [19] modified the model (2.1.1) by adding *two delays* accounting for the latencies in both mosquitoes and humans, respectively. It results in the following delayed and rescaled system

$$\begin{cases} \dfrac{\mathrm{d}x(t)}{\mathrm{d}t} = ame_1 y(t-\tau_1)[1-x(t-\tau_1)]e^{-d_1\tau_1} - d_1 x(t), \\ \dfrac{\mathrm{d}y(t)}{\mathrm{d}t} = ae_2[1-y(t-\tau_2)]x(t-\tau_2)e^{-d_2\tau_2} - d_2 y(t), \end{cases} \tag{2.1.3}$$

where $m = M/N$, $x = I_1/N$ and $y = I_2/M$, and the term $e^{-d_1\tau_1}$ ($e^{-d_2\tau_2}$ resp.) accounts for the probability that an infected human host (mosquito resp.) can survive the latent period τ_1 (τ_2 resp). For this modified model, the basic reproduction number is adjusted to

$$\mathcal{R}_0 = \frac{a^2 e_1 e_2 m e^{-d_1\tau_1} e^{-d_2\tau_2}}{d_1 d_2}. \tag{2.1.4}$$

It is shown in [19] that when $\mathcal{R}_0 < 1$, then the disease free equilibrium $(0, 0)$ is stable; when $\mathcal{R}_0 \geq 1$, then $(0, 0)$ is unstable and there is an endemic equilibrium (x^*, y^*) which

is locally asymptotically stable provided that the two delays are small and

$$a^2 e_1 e_2 m < a e_2 d_1 + 2 d_1 d_2. \tag{2.1.5}$$

The inequality (2.1.5) is a mathematically technical condition without a biological explanation. Numerical simulations indicate that solutions of (2.1.3) with initial data from the region $[0, 1] \times [0, 1]$ can go outside of this region, causing confusion since $x(t)$ and $y(t)$ are proportional variables. This confusion suggests a careful revisit of the model. Moreover, the latencies of the malaria parasite in mosquitoes may differ from individual to individual, and so do the latencies in humans. This requires some mechanism in modeling to reflect such variances of the latencies.

The goal of this chapter is to derive a general and realistic model that incorporates not only the latencies of the malaria parasite in both mosquitoes and humans, but also the variances of the latencies. In Section 2.2, following the idea in [24], we formulate a more general model with two probability functions $P_1(t)$ and $P_2(t)$ describing the latency distributions for humans and mosquitoes, respectively. In Section 2.3, we analyze our new model mathematically. Under some reasonable assumptions, we address the well-posedness, identify the basic reproduction number $\mathcal{R}_0$ for the model, and prove that the disease free equilibrium is globally asymptotically stable if $\mathcal{R}_0 < 1$. When $\mathcal{R}_0 > 1$, the disease dynamics is more difficult to be determined for general $P_1(t)$ and $P_2(t)$, hence we consider two specific cases for $P_1(t)$ and $P_2(t)$. In Sub-Section 2.3.2, we consider the case that $P_1(t)$ and $P_2(t)$ are both exponential functions, resulting in a system of ODEs; in Sub-Section 2.3.3, we take $P_1(t)$ and $P_2(t)$ as step functions, leading to a system of DDEs. In both cases, we are able to obtain results on the disease dynamics. In Section 2.4, we summarize our main results and give some remarks discussing the modeling issue.

2.2 Model formulation for general latency distributions

Denote the size of the population of human beings by $N(t)$ and that of the female mosquitoes by $M(t)$. Let $S_1(t)$ and $I_1(t)$ be, respectively, the subpopulations of the susceptible and infectious classes of human hosts and $S_2(t)$ and $I_2(t)$ be the respective subpopulations of the susceptible and infectious classes of female mosquitoes. As mentioned in the introduction, there is a complicated development process of the malaria parasites in a host as well as in a mosquito, causing a latency in each part of the malaria life cycle. This requires introducing a third subpopulation for each populations: exposed class, consisting of those individuals who have been infected, but not infectious yet. Denote by $L_1(t)$ and $L_2(t)$ the subpopulations of the latent host and the latent female mosquito.

We consider a simple demographic scenario by assuming constant natural birth rates and death rates for both humans and the mosquitoes, denoted respectively by b_1, b_2 and d_1, d_2. As mentioned in the introduction, we use the constant a to denote the mosquito biting rate; e_1 to denote the probability that a bite from an infective mosquito will cause infection of a person; and e_2 to denote the probability that a biting by a susceptible mosquito of an infective human will cause infection of the mosquito. The malaria parasites only cause deaths in human beings, but not in mosquitoes, and this suggests introducing a disease related death rate for human beings, denoted by d. Infected human beings may recover, either due to the functioning of the immune system or through a treatment including taking anti-malaria drugs such as *Chloroquine*, *Quinine* and *Amodiaquine*. Let γ_1 be the recovery rate which is assumed to be a constant.

Now we introduce the latency distributions following the idea in [24]. Let $P_1(t)$ denote the probability (without taking death into account) that a latent host individual still remains in the latent class t time units after entering the latent class. Similarly, let $P_2(t)$ be the probability that a latent mosquito individual still remains in the latent class

t time units after entering the latent class. It is biological reasonable to assume that $P_1(t)$ and $P_2(t)$ possess the following properties:

(H): For $i = 1, 2$, $P_i : [0, \infty) \to [0, \infty)$ is non-increasing, piecewise continuous with possibly finitely many jumps and satisfy $P_i(0^+) = 1$, $\lim_{t\to\infty} P_i(t) = 0$ with $\int_0^\infty P_i(u)\,\mathrm{d}u$ positive and finite.

Assume that initially $S_1(0) > 0$, $I_1(0) \geq 0$, $S_2(0) > 0$, $I_2(0) \geq 0$ and $L_1(0) \geq 0$, $L_2(0) \geq 0$, then the equations governing the subpopulations are given by

$$\begin{cases} \dfrac{\mathrm{d}S_1}{\mathrm{d}t} = b_1 N(t) - ae_1 I_2(t)\dfrac{S_1(t)}{N(t)} + \gamma_1 I_1(t) - d_1 S_1(t), \\ L_1(t) = \displaystyle\int_0^t ae_1 I_2(\xi)\frac{S_1(\xi)}{N(\xi)} e^{(-d_1+d)(t-\xi)} P_1(t-\xi)\,\mathrm{d}\xi, \\ I_1(t) = N(t) - S_1(t) - L_1(t), \\ \dfrac{\mathrm{d}S_2}{\mathrm{d}t} = -ae_2 S_2 \dfrac{I_1}{N(t)} + b_2 M(t) - d_2 S_2(t), \\ L_2(t) = \displaystyle\int_0^t ae_2 S_2(\xi)\frac{I_1(\xi)}{N(\xi)} e^{-d_2(t-\xi)} P_2(t-\xi)\,\mathrm{d}\xi, \\ I_2(t) = M(t) - S_2(t) - L_2(t). \end{cases} \tag{2.2.1}$$

Here, the integrals are in the Riemann sense. This *SLIS* model can be visually illustrated by the diagram in Figure 2.1.

Since the emphasis of this chapter is the impact of latencies, we will follow the existing models in [15, 16, 17, 18, 19] to assume constant total populations for both human beings and female vector mosquitoes, i.e., $N(t) = N$ and $M(t) = M$ both are constants. This can be achieved by, for example, assuming that

(A1) Disease related deaths can be ignored (i.e., setting $d = 0$);

(A2) The natural birth and death rates balance the natural birth rates for both host and vector (i.e., $b_1 = d_1$ and $b_2 = d_2$).

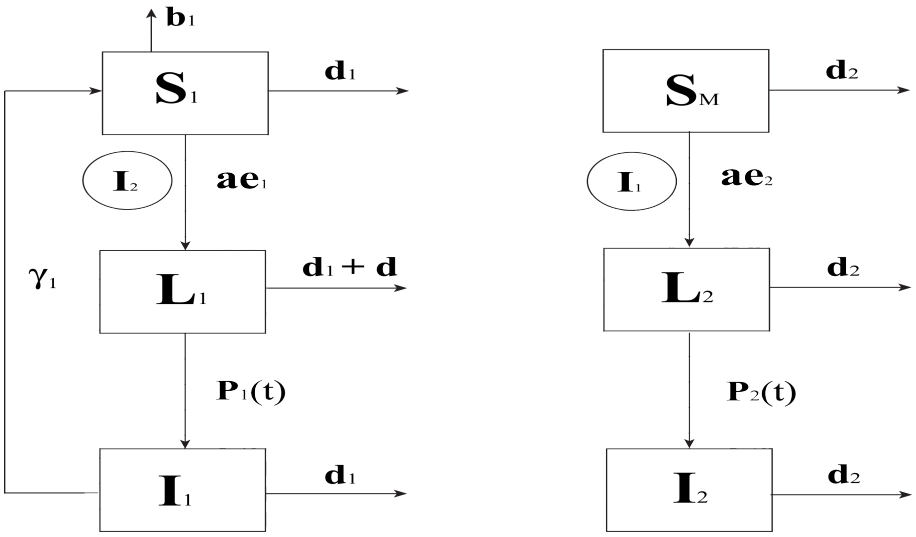

Figure 2.1: The transmission diagram of the host-vector SEIS model

There may be other situations that can lead to constant populations, (e.g., a compensation to the disease caused deaths by immigration of human hosts). However for simplicity of discussion, we simply assume (A1) and (A2) hold in the rest of the chapter. For a time scale that is not long, $N(t)$ and $M(t)$ vary only slightly, therefore, this case also constitutes a good scenario for approximating $N(t)$ and $M(t)$ by constants. With these assumptions, one only needs to work on four out of the six variables. We choose $S_1,\ I_1,\ S_2$ and I_2 for which the governing differential equations are derived as below.

Differentiating the L_1 and L_2 equations (in the sense of Riemann integral) leads to

$$\begin{cases} L_1'(t) = ae_1 I_2(t)\dfrac{S_1(t)}{N} + \displaystyle\int_0^t ae_1 I_2(\xi)\frac{S_1(\xi)}{N} e^{-d_1(t-\xi)} D_t P_1(t-\xi)\,\mathrm{d}\xi - d_1 L_1(t), \\ L_2'(t) = ae_2 S_2(t)\dfrac{I_1(t)}{N} + \displaystyle\int_0^t ae_2 S_2(\xi)\frac{I_1(\xi)}{N} e^{-d_2(t-\xi)} D_t P_2(t-\xi)\,\mathrm{d}\xi - d_2 L_2(t). \end{cases} \tag{2.2.2}$$

In the L_1 equation above, each term has its own biological meaning: the first term is the rate of new infections, the second term accounts for the rate at which the infected individuals move to the infectious class from the exposed class, and the third term is due to natural death. The terms in the L_2 equations can be explained in the same way.

Passing to the I_1 and I_2 equations and keeping the S_1 and S_2 equations (2.2.1) lead to the following reduced system

$$\begin{cases} \dfrac{\mathrm{d}S_1(t)}{\mathrm{d}t} = d_1 N - ae_1 I_2(t)\dfrac{S_1(t)}{N} + \gamma_1 I_1(t) - d_1 S_1(t), \\ \dfrac{\mathrm{d}I_1(t)}{\mathrm{d}t} = -\displaystyle\int_0^t ae_1 I_2(\xi)\frac{S_1(\xi)}{N} e^{-d_1(t-\xi)} D_t P_1(t-\xi)\,\mathrm{d}\xi - (d_1+\gamma_1) I_1(t), \\ \dfrac{\mathrm{d}S_2(t)}{\mathrm{d}t} = d_2 M - ae_2 S_2(t)\dfrac{I_1(t)}{N} - d_2 S_2, \\ \dfrac{dI_2(t)}{dt} = -\displaystyle\int_0^t ae_2 S_2(\xi)\frac{I_1(\xi)}{N} e^{-d_2(t-\xi)} D_t P_2(t-\xi)\,\mathrm{d}\xi - d_2 I_2(t). \end{cases} \tag{2.2.3}$$

Rescaling (2.2.3) by

$$\begin{cases} \dfrac{S_1(t)}{N} \to S_1(t), \quad \dfrac{L_1(t)}{N} \to L_1(t), \quad \dfrac{I_1(t)}{N} \to I_1(t), \\ \dfrac{S_2(t)}{M} \to S_2(t), \quad \dfrac{L_2(t)}{M} \to L_2(t), \quad \dfrac{I_2(t)}{M} \to I_2(t), \end{cases}$$

we have the following system

$$\begin{cases} \dfrac{\mathrm{d}S_1}{\mathrm{d}t} = d_1 - ae_1 m I_2(t) S_1(t) + \gamma_1 I_1(t) - d_1 S_1(t), \\ \dfrac{\mathrm{d}I_1}{\mathrm{d}t} = -\displaystyle\int_0^t ae_1 m I_2(\xi) S_1(\xi) e^{-d_1(t-\xi)} D_t P_1(t-\xi)\,\mathrm{d}\xi - (d_1+\gamma_1) I_1(t), \\ \dfrac{\mathrm{d}S_2}{\mathrm{d}t} = d_2 - ae_2 S_2(t) I_1(t) - d_2 S_2, \\ \dfrac{dI_2}{dt} = -\displaystyle\int_0^t ae_2 S_2(\xi) I_1(\xi) e^{-d_2(t-\xi)} D_t P_2(t-\xi)\,\mathrm{d}\xi - d_2 I_2(t), \end{cases} \tag{2.2.4}$$

with the following obvious constraints:

$$S_1(t) + L_1(t) + I_1(t) = 1, \quad S_2(t) + L_2(t) + I_2(t) = 1, \tag{2.2.5}$$

where $m = M/N$ represents the average mosquito number per person.

2.3 Mathematical analysis of the model

By the theory for integro-differential equations in [14], one knows that for any given initial values $S_i(0) \geq 0$ and $I_i(0) \geq 0$, $i = 1, 2$, system (2.2.4) admits a unique solution with $(S_1(t), I_1(t), S_2(t), I_2(t))$ satisfying the initial conditions. From the biological significance, we only need to consider system (2.2.4) in the set

$$\Omega := \left\{(S_1, I_1, S_2, I_2) \in R^4 : S_1 > 0,\ I_1 \geq 0,\ S_1 + I_1 \leq 1,\ \ S_2 > 0,\ I_2 \geq 0,\ S_2 + I_2 \leq 1.\right\}.$$

Indeed, one can easily show that the set Ω is positively invariant in the sense that stated in the following lemma.

Lemma 2.3.1 *If* $(S_1(0), I_1(0), S_2(0), I_2(0)) \in \Omega$ *satisfies* $S_1(0) + I_1(0) = 1$ *and* $S_2(0) + I_2(0) = 1$*, then system* (2.2.4) *has a unique solution* $(S_1(t), I_1(t), S_2(t), I_2(t))$ *satisfying the initial data* $(S_1(0), I_1(0), S_2(0), I_2(0))$*, which remains in* Ω *for all* $t \geq 0$*. Moreover, if* $I_1(0) + I_2(0) > 0$*, then* $I_1(t) > 0$ *and* $I_2(t) > 0$ *for* $t > 0$*.*

The proof of the lemma is by a standard argument, and is thus omitted here.

Let

$$\hat{P}_i := \lim_{t\to\infty} \int_0^t e^{-d_i u} P_i(u)\, \mathrm{d}u, \quad i = 1, 2.$$

Clearly, $\hat{P}_1$ (resp. $\hat{P}_2$) is the average time that an infected human being (resp. female mosquito) remains in the latent class before becoming infectious or dying (see [24]). By the properties of $P_i(u)$, it follows that

$$0 < \hat{P}_i < \lim_{t\to\infty} \int_0^t e^{-d_i u}\, \mathrm{d}u = 1/d_i, \quad i = 1, 2.$$

Actually, $\hat{P}_1 d_1$ (resp. $\hat{P}_2 d_2$) is the probability that an infected host (resp. mosquito) will die during the latent period. Hence, Q_1 (resp. Q_2) represents the proportion of the

exposed hosts (resp. vectors) that could survive during the latent period, where

$$\begin{aligned} Q_i &:= -\lim_{t\to\infty} \int_0^t e^{-d_i(t-\xi)} D_t P_i(t-\xi)\, \mathrm{d}\xi \\ &= 1 - d_i \hat{P}_i \in (0,1), \quad i = 1,2. \end{aligned}$$

Using Q_i, $i = 1, 2$, the basic reproduction number for the model (2.2.4) can then be defined as

$$\mathcal{R}_0 = m\frac{ae_1}{\gamma_1 + d_1} \cdot Q_1 \cdot \frac{ae_2}{d_2} \cdot Q_2, \tag{2.3.1}$$

accounting for the average number of secondary infections that a single infectious human being (or female mosquito), once introduced into a fully susceptible population of humans and mosquitoes, is expected to cause with respect to humans (female mosquitoes) during the infection period. Here, due to the transmission nature of this vector-host disease, $\mathcal{R}_0$ consists of two parts: $m\frac{ae_1}{\gamma_1+d_1} \cdot Q_1$ accounts for how many new infectious mosquitoes results from an infectious human being can result in during his infection period; and $\frac{ae_2}{d_2} \cdot Q_2$ explains how many new infectious human beings are infected by an infectious mosquito during its infection period.

System (2.2.4) has a disease free equilibrium E_0, given by $E_0 = (1, 0, 1, 0)$. In terms of the biological meaning of the basic reproduction number, $\mathcal{R}_0 = 1$ should be a threshold value for the stability/instability of E_0 for the model (2.2.4), as is confirmed in the following Theorem.

Theorem 2.3.1 *If $\mathcal{R}_0 < 1$, then E_0 is globally asymptotically stable in Ω; if $\mathcal{R}_0 > 1$, it is unstable.*

Proof. Let

$$\begin{aligned} B_1(z) &= \lim_{t\to\infty} \int_0^t ae_1 m e^{-(d_1+z)(t-\xi)} D_t P_1(t-\xi)\,\mathrm{d}\xi, \\ B_2(z) &= \lim_{t\to\infty} \int_0^t ae_2 e^{-(d_2+z)(t-\xi)} D_t P_2(t-\xi)\,\mathrm{d}\xi. \end{aligned}$$

Then the stability of E_0 is determined by the roots of the following characteristic equation of system (2.2.4) at E_0:

$$\mathbf{det}\begin{pmatrix} z+d_1 & -\gamma_1 & 0 & -ae_1 m \\ 0 & z+d_1+\gamma_1 & 0 & B_1(z) \\ 0 & -ae_2 & z+d_2 & 0 \\ 0 & B_2(z) & 0 & z+d_2 \end{pmatrix} = 0. \tag{2.3.2}$$

Expanding the determinant, equation (2.3.2) can be rewritten as

$$(z+d_1)(z+d_2)h(z) = 0, \tag{2.3.3}$$

where

$$h(z) = (z+d_2)(z+\gamma_1+d_1) - B_1(z)B_2(z). \tag{2.3.4}$$

Since $z = -d_1$ and $z = -d_2$ are two negative real roots of equation (2.3.3), the stability of E_0 is fully determined by the roots of $h(z) = 0$, which is equivalent to

$$z^2 + (d_1+\gamma_1+d_2)z + d_2(d_1+\gamma_1) = B_1(z)B_2(z). \tag{2.3.5}$$

Assume that $\mathcal{R}_0 < 1$. Then

$$\begin{aligned} & \left|z^2 + (d_1 + \gamma_1 + d_2)z + d_2(d_1 + \gamma_1)\right|^2 = |B_1(z)B_2(z)|^2 \\ \leq \;& (ae_1e_2mQ_1Q_2)^2 = [d_2(\gamma_1 + d_1)\mathcal{R}_0]^2 \\ < \;& [d_2(\gamma_1 + d_1)]^2. \end{aligned} \tag{2.3.6}$$

Let $z = x + iy$. If $x \geq 0$, then we have

$$\begin{aligned} & \left|z^2 + (d_1 + \gamma_1 + d_2)z + d_2(d_1 + \gamma_1)\right|^2 \\ = \;& \left|x^2 - y^2 + (d_1 + \gamma_1 + d_2)x + d_2(d_1 + \gamma_1) + i[2xy + (d_1 + \gamma_1 + d_2)y]\right|^2 \\ \geq \;& y^4 + y^2[2x^2 + 2x(d_1 + \gamma_1 + d_2) + d_1^2 + \gamma_1^2 + d_2^2 + 2d_1\gamma_1] + [d_2(d_1 + \gamma_1)]^2 \\ \geq \;& [d_2(d_1 + \gamma_1)]^2, \end{aligned} \tag{2.3.7}$$

which contradicts the inequality (2.3.6). Therefore, x (the real part of z) must be negative, implying that E_0 is locally asymptotically stable if $\mathcal{R}_0 < 1$.

Next, we show that E_0 is globally attractive when $\mathcal{R}_0 < 1$. To this end, we use the notation

$$x^\infty = \limsup_{t\to\infty} x(t) \quad \text{and} \quad x_\infty = \liminf_{t\to\infty} x(t)$$

for a function defined for all large t. Let $(S_1(t), I_1(t), S_2(t), I_2(t))$ be a solution of system (2.2.4) in Ω. By Lemma 2.3.1, we know that $S_1^\infty, I_1^\infty, S_2^\infty$ and I_2^∞ all exist and satisfy $0 < S_1^\infty \leq 1, 0 \leq I_1^\infty \leq 1, 0 < S_2^\infty \leq 1$ and $0 \leq I_2^\infty \leq 1$. By the Fluctuation Lemma [9], there is a sequence t_n with $t_n \to \infty$ as $n \to \infty$ such that

$$I_1(t_n) \to I_1^\infty, \quad \text{and} \quad I_1'(t_n) \to 0 \quad \text{as} \quad n \to \infty. \tag{2.3.8}$$

Rewrite the differential equation for $I_1(t)$ in model (2.2.4) as

$$I_1'(t) + (\gamma_1 + d_1)I_1(t) = -\int_0^t ae_1 mS_1(t-\xi)I_2(t-\xi)e^{-d_1\xi}D_t P_1(t-\xi)\,\mathrm{d}\xi. \tag{2.3.9}$$

Evaluating this equation at $t = t_n$ and letting $n \to \infty$ on both sides of the resulting equation, we obtain

$$(\gamma_1 + d_1)I_1^\infty \leq \limsup_{n\to\infty}\left(-\int_0^{t_n} ae_1 mS_1(t_n-\xi)I_2(t_n-\xi)e^{-d_1\xi}D_t P_1(t-\xi)\,\mathrm{d}\xi\right). \tag{2.3.10}$$

By the Lebesgue - Fatou Lemma (see [22], P468), it follows that

$$(\gamma_1 + d_1)I_1^\infty \leq ae_1 mS_1^\infty I_2^\infty Q_1. \tag{2.3.11}$$

Similarly, we can establish the following:

$$d_2 I_2^\infty \leq ae_2 S_2^\infty I_1^\infty Q_2. \tag{2.3.12}$$

The two inequalities (2.3.11) and (2.3.12) imply that either I_1^∞ and I_2^∞ are both positive or both zero. We show that the former is impossible if $\mathcal{R}_0 < 1$. Otherwise, (2.3.11) and (2.3.12) would yield

$$(\gamma_1 + d_1) \leq \frac{a^2 e_1 e_2 m S_1^\infty S_2^\infty Q_1 Q_2}{d_2}, \tag{2.3.13}$$

which is equivalent to

$$\frac{1}{\mathcal{R}_0} \leq S_1^\infty S_2^\infty.$$

This would lead to $1 < S_1^\infty S_2^\infty$ under $\mathcal{R}_0 < 1$, leading a contradiction to "$S_1^\infty \leq 1$ and $S_2^\infty \leq 1$". Therefore, $I_1^\infty = 0$ and $I_2^\infty = 0$, implying

$$I_1(t) \to 0, \;\; I_2(t) \to 0 \;\text{ as }\; t \to \infty. \tag{2.3.14}$$

Applying (2.3.14) and the theory of asymptotically autonomous systems (see, e.g., [3]) to the $S_i(t)$ equations in model (2.2.4), we conclude that

$$S_1(t) \to 1 \text{ and } \; S_2(t) \to 1 \text{ as } \quad t \to \infty. \tag{2.3.15}$$

Thus, E_0 is globally attractive, and hence, globally asymptotically stable in Ω provided that $\mathcal{R}_0 < 1$.

Next, assume that $\mathcal{R}_0 > 1$. To show that E_0 is unstable, it suffices to show that $h(z) = 0$ admits a positive real root. Consider $z = x > 0$ and let

$$T(x) = x^2 + (d_1 + \gamma_1 + d_2)x + d_2(d_1 + \gamma_1), \;\; B(x) = B_1(x)B_2(z). \tag{2.3.16}$$

Note that $T(x)$ is increasing in $x \geq 0$ and $T(0) = d_2(\gamma_1 + d_1)$ and $T(\infty) = \infty$. On the other side,

$$\begin{aligned} B(x) &= B_1(x)B_2(x) \\ &= \left(\lim_{t\to\infty} \int_0^t a e_1 m e^{-(d_1+x)(t-\xi)} D_t P_1(t-\xi)\, \mathrm{d}\xi\right)\left(\lim_{t\to\infty} \int_0^t a e_2 e^{-(d_2+x)(t-\xi)} D_t P_2(t-\xi)\, \mathrm{d}\xi\right) \\ &= \lim_{t\to\infty} \int_0^t\int_0^t a^2 e_1 e_2 m e^{-(d_1+x)(t-\xi)-(d_2+x)(t-\eta)} D_t P_1(t-\xi)\, D_t P_2(t-\eta)\, \mathrm{d}\xi\, \mathrm{d}\eta, \end{aligned} \tag{2.3.17}$$

is decreasing for $x > 0$, and $B(0) = a^2 e_1 e_2 m Q_1 Q_2$. Now $\mathcal{R}_0 > 1$ is equivalent to $T(0) < B(0)$ which implies that the equation $T(x) = B(x)$ has a positive real root, that is, $h(z) = 0$ has a positive real root. Therefore, E_0 is unstable if $\mathcal{R}_0 > 1$. The proof of the theorem is complete. □

When $\mathcal{R}_0 > 1$, for general functions $P_1(t)$ and $P_2(t)$, the dynamics of model (2.2.4) is difficult to determine. For example, even the issue of existence of an endemic equilibrium remains a problem: for some choices of $P_1(t)$ and $P_2(t)$, model (2.2.4) may allow an endemic equilibrium while for others choices, it may not. To proceed further, we consider two special cases of $P_1(t)$ and $P_2(t)$, for which we are able to obtain some further information about the dynamics of model (2.2.4).

2.3.1 Special case I — a system of ODEs

In this section, we set $P_i(t) = e^{-\varepsilon_i t}, i = 1, 2$ where ε_1 and ε_2 are positive constants. This means that the probabilities of infected hosts and vectors remaining in the latent classes follow negative exponential distributions with mean exposed times equal to $1/\varepsilon_1$ and $1/\varepsilon_2$, respectively. In this case, model (2.2.4) reduces to the following system of ODEs:

$$\begin{cases} \dfrac{\mathrm{d}S_1(t)}{\mathrm{d}t} = -ae_1 m S_1(t) I_2(t) + d_1 + \gamma_1 I_1(t) - d_1 S_1(t) \\ \dfrac{\mathrm{d}I_1(t)}{\mathrm{d}t} = \varepsilon_1 [1 - I_1(t) - S_1(t)] - (d_1 + \gamma_1) I_1(t), \\ \dfrac{\mathrm{d}S_2(t)}{\mathrm{d}t} = -ae_2 S_2 I_1(t) + d_2 - d_2 S_2(t), \\ \dfrac{\mathrm{d}I_2(t)}{\mathrm{d}t} = \varepsilon_2 [1 - I_2(t) - S_2(t)] - d_2 I_2(t). \end{cases} \tag{2.3.18}$$

The two survival factors Q_1 and Q_2 are now given by $Q_i = \frac{\varepsilon_i}{\varepsilon_i + d_i}$, $i = 1, 2$, and accordingly, the basic reproduction number becomes

$$\mathcal{R}_0 = \frac{ae_1 m}{\gamma_1 + d_1} \cdot \frac{ae_2}{d_2} \cdot \frac{\varepsilon_1}{\varepsilon_1 + d_1} \cdot \frac{\varepsilon_2}{\varepsilon_2 + d_2}. \tag{2.3.19}$$

By substitutions, we find system (2.3.18) admits only two equilibria, the disease free equilibrium E_0 and a non-trivial equilibrium E^*. When $\mathcal{R}_0 > 1$, E_0 is unstable, and the unique non-trivial equilibrium $E^* = (S_1^*, I_1^*, S_2^*, I_2^*)$, where

$$S_1^* = \frac{C_0}{C_1}, \quad I_1^* = \frac{\varepsilon_1 d_2(\mathcal{R}_0 - 1)}{C_1} \quad S_2^* = C_2, \quad I_2^* = \frac{\mathcal{R}_0 - 1}{C_3}, \tag{2.3.20}$$

and

$$\begin{aligned}
C_0 &= d_2 d_1 + d_2\gamma_1 + d_2\varepsilon_1 + \varepsilon_1 ae_2,\\
C_1 &= \frac{\varepsilon_1 ae_2}{(d_1+\varepsilon_1)(d_1+\gamma_1)(\varepsilon_2+d_2)}(\varepsilon_1\varepsilon_2\gamma_1 + \varepsilon_1\varepsilon_2 d_1 + \varepsilon_2 d_1^2 + \varepsilon_2\gamma_1 d_1 + \varepsilon_1\gamma_1 d_2\\
&\quad + \varepsilon_2 d_1 d_2 + d_1^2 d_2 + \gamma_1 d_1 d_2 + \varepsilon_1\varepsilon_2 e_1 am + \varepsilon_2 d_1 e_1 am + \varepsilon_2\gamma_1 e_1 am),\\
C_2 &= \frac{d_2}{\varepsilon_2 e_1 am(d_1 d_2 + \gamma_1 d_2 + \varepsilon_1 d_2 + \varepsilon_1 e_2 a)}\Big(\varepsilon_1\varepsilon_2\gamma_1 + \varepsilon_1\varepsilon_2 d_1 + \varepsilon_2 d_1^2 + \varepsilon_2\gamma_1 d_1\\
&\quad + \varepsilon_1\gamma_1 d_2 + \varepsilon_1 d_1 d_2 + d_1^2 d_2 + \gamma_1 d_1 d_2 + \varepsilon_1\varepsilon_2 e_1 am + \varepsilon_2 d_1 e_1 am + \varepsilon_2\gamma_1 e_1 am\Big),\\
C_3 &= \frac{ame_1}{\varepsilon_1 d_2(d_1+\varepsilon_1)(d_1+\gamma_1)(\varepsilon_2+d_2)}(\varepsilon_2 d_1 d_2 + d_1 d_2^2 + \gamma_1 d_2^2 + \varepsilon_2\gamma_1 d_2\\
&\quad + \varepsilon_1 d_2 ae_2 + \varepsilon_1\varepsilon_2 d_2 + \varepsilon_1 d_2^2 + \varepsilon_1\varepsilon_2 ae_2),
\end{aligned}$$

has all positive constants. If we retain L_1' and L_2' equations in system (2.3.18), we can solve L_1^* and L_2^* for the non-trivial equilibrium. The additions $S_1^* + L_1^* + I_1^* = 1$ and $S_2^* + L_2^* + I_2^* = 1$ lead the fact that each term does not exceed one. Hence, we have $E^* \in \Omega$. The following theorem shows that if $\gamma_1 = 0$, the global dynamics of system (2.3.18) is completely determined in terms of $\mathcal{R}_0$, which acts as a threshold in the global sense.

Theorem 2.3.2 *Consider system* (2.3.18). *If* $\mathcal{R}_0 > 1$, *the endemic equilibrium* E^* *is globally asymptotically stable among all positive solutions in* Ω, *provided that* $\gamma_1 = 0$.

Proof. To prove the global stability of E^*, we consider the full model system associated with the reduced system (2.3.18) by adding the latent classes:

$$\begin{cases} S_1'(t) = -\beta_{12} I_2(t) S_1(t) + d_1 + \gamma_1 I_1(t) - d_1 S_1(t), \\ L_1'(t) = \beta_{12} I_2(t) S_1(t) - (\varepsilon_1 + d_1) L_1(t), \\ I_1'(t) = \varepsilon_1 L_1(t) - (d_1 + \gamma_1) I_1(t), \\ S_2'(t) = -\beta_{21} S_2(t) I_1(t) + d_2 - d_2 S_2(t), \\ L_2'(t) = \beta_{21} S_2(t) I_1(t) - (d_2 + \varepsilon_2) L_2(t), \\ I_2'(t) = \varepsilon_2 L_2(t) - d_2 I_2(t), \end{cases} \tag{2.3.21}$$

where, for the convenience of notation, we have introduced the new parameters $\beta_{12} = ae_1m$ and $\beta_{21} = ae_2$. We will employ a Lyapunov function similar to those used in recent works [6, 10, 11]. To this end, we set $v_1 = \beta_{21} S_2^* I_1^*$ and $v_2 = \beta_{12} S_1^* I_2^*$ and let

$$\begin{aligned} V_1(t) = v_1 (S_1 - S_1^* - S_1^* \ln \frac{S_1}{S_1^*} + L_1 - L_1^* - L_1^* \ln \frac{L_1}{L_1^*}) \\ + v_2 (S_2 - S_2^* - S_2^* \ln \frac{S_2}{S_2^*} + L_2 - L_2^* - L_2^* \ln \frac{L_2}{L_2^*}), \end{aligned} \tag{2.3.22}$$

where S_i^* and I_i^*, $i = 1, 2$, are given in (2.3.20), and $L_1^* = (d_1 + \gamma_1) I_1^* / \varepsilon_1$ and $L_2^* = d_2 I_2^* / \varepsilon_2$ or equivalently, $L_i^* = 1 - S_i^* - I_i^*$, $i = 1, 2$. Differentiating $V_1(t)$ along any

positive solution of system (2.3.21) gives

$$
\begin{aligned}
V_1'(t) &= v_1\left[\left(1-\frac{S_1^*}{S_1}\right)S_1' + \left(1-\frac{L_1^*}{L_1}\right)L_1'\right] + v_2\left[\left(1-\frac{S_2^*}{S_2}\right)S_2' + \left(1-\frac{L_2^*}{L_2}\right)L_2'\right] \\
&= v_1\left[-\beta_{12}I_2S_1 + d_1 + \gamma_1 I_1 - d_1S_1 + \beta_{12}I_2S_1^* - d_1\frac{S_1^*}{S_1} - \gamma_1 I_1\frac{S_1^*}{S_1} + d_1S_1^*\right. \\
&\quad \left. +\beta_{12}I_2S_1 - (\varepsilon_1+d_1)L_1 - \beta_{12}I_2S_1\frac{L_1^*}{L_1} + (\varepsilon_1+d_1)L_1^*\right] \\
&\quad + v_2\left[-\beta_{21}S_2I_1 + d_2 - d_2S_2 + \beta_{21}S_2^*I_1 - d_2\frac{S_2^*}{S_2} + d_2S_2^*\right. \\
&\quad \left. +\beta_{21}S_2I_1 - (\varepsilon_2+d_2)L_2 - \beta_{21}S_2I_1\frac{L_2^*}{L_2} + (\varepsilon_2+d_2)L_2^*\right] \\
&= v_1\left[d_1 + \gamma_1 I_1 - d_1S_1 + \beta_{12}I_2S_1^* - d_1\frac{S_1^*}{S_1} - \gamma_1 I_1\frac{S_1^*}{S_1} + d_1S_1^* - (\varepsilon_1+d_1)L_1\right. \\
&\quad \left. -\beta_{12}I_2S_1\frac{L_1^*}{L_1} + (\varepsilon_1+d_1)L_1^*\right] + v_2\left[d_2 - d_2S_2 + \beta_{21}S_2^*I_1 - d_2\frac{S_2^*}{S_2}\right. \\
&\quad \left. +d_2S_2^* - (\varepsilon_2+d_2)L_2 - \beta_{21}S_2I_1\frac{L_2^*}{L_2} + (\varepsilon_2+d_2)L_2^*\right].
\end{aligned}
$$

Making use of the equations for the endemic equilibrium $\hat{E}^* = (S_1^*, L_1^*, I_1^*, S_2^*, L_2^*, I_2^*)$, we can further express $V_1'(t)$ as

$$
\begin{aligned}
V_1'(t) &= v_1\left[d_1S_1^* + \beta_{12}S_1^*I_2^* - \gamma_1 I_1^* + \gamma_1 I_1 - d_1S_1 + \beta_{12}S_1^*I_2 - d_1\frac{(S_1^*)^2}{S_1} + \gamma_1 I_1^*\frac{S_1^*}{S_1}\right. \\
&\quad \left. -\beta_{12}I_2^*\frac{(S_1^*)^2}{S_1} - \gamma_1 I_1\frac{S_1^*}{S_1} + d_1S_1^* - (\varepsilon_1+d_1)L_1 - \beta_{12}I_2S_1\frac{L_1^*}{L_1} + (\varepsilon_1+d_1)L_1^*\right] \\
&\quad + v_2\left[d_2S_2^* + \beta_{21}S_2^*I_1^* - d_2S_2 + \beta_{21}S_2^*I_1 - d_2\frac{(S_2^*)^2}{S_2} - \beta_{21}I_1^*\frac{(S_2^*)^2}{S_2}\right. \\
&\quad \left. +d_2S_2^* - (\varepsilon_2+d_2)L_2 - \beta_{21}I_1S_2\frac{L_2^*}{L_2} + (\varepsilon_2+d_2)L_2^*\right] \\
&= v_1\left\{d_1S_1^*\left(2 - \frac{S_1}{S_1^*} - \frac{S_1^*}{S_1}\right) + \beta_{12}S_1^*I_2 + \left[2\beta_{12}S_1^*I_2^* - \gamma_1 I_1^* + \gamma_1 I_1 - \beta_{12}I_2^*\frac{(S_1^*)^2}{S_1}\right.\right. \\
&\quad \left.\left. +\gamma_1 I_1^*\frac{S_1^*}{S_1} - \gamma_1 I_1\frac{S_1^*}{S_1} - \beta_{12}I_2S_1\frac{L_1^*}{L_1} - (\varepsilon_1+d_1)L_1\right]\right\} + v_2\left\{d_2S_2^*\left(2 - \frac{S_2}{S_2^*} - \frac{S_2^*}{S_2}\right)\right. \\
&\quad \left. +\beta_{21}S_2^*I_1 + \left[2\beta_{21}S_2^*I_1 - \beta_{21}I_1^*\frac{(S_1^*)^2}{S_2} - \beta_{21}S_2I_1\frac{L_2^*}{L_2} - (\varepsilon_2+d_2)L_2\right]\right\}.
\end{aligned}
$$

Further, we define

$$V_2(t) = v_1\frac{\varepsilon_1+d_1}{\varepsilon_1}\left(I_1 - I_1^* - I_1^*\ln\frac{I_1}{I_1^*}\right) + v_2\frac{\varepsilon_2+d_2}{\varepsilon_2}\left(I_2 - I_2^* - I_2^*\ln\frac{I_2}{I_2^*}\right). \tag{2.3.23}$$

Now we can construct the Lyapunov function $V = V_1 + V_2$. Straightforward calculation of the derivative of V along trajectories of system (2.3.21), after appropriate grouping, leads to

$$\begin{aligned}
V'(t) = {} & v_1\left\{d_1S_1^*\left(2 - \frac{S_1}{S_1^*} - \frac{S_1^*}{S_1}\right) + \beta_{12}S_1^*I_2 + \left[2\beta_{12}S_1^*I_2^* - \gamma_1I_1^* + \gamma_1I_1\right.\right.\\
& \left.-\beta_{12}I_2^*\frac{(S_1^*)^2}{S_1} + \gamma_1I_1^*\frac{S_1^*}{S_1} - \gamma_1I_1\frac{S_1^*}{S_1} - \beta_{12}I_2S_1\frac{L_1^*}{L_1} - (\varepsilon_1+d_1)L_1\right]\\
& \left.+\frac{\varepsilon_1+d_1}{\varepsilon_1}\left[\varepsilon_1L_1 - (d_1+\gamma_1)I_1 - \varepsilon_1L_1\frac{I_1^*}{I_1} + (d_1+\gamma_1)I_1^*\right]\right\}\\
& + v_2\left\{d_2S_2^*\left(2 - \frac{S_2}{S_2^*} - \frac{S_2^*}{S_2}\right) + \beta_{21}S_2^*I_1 + \left[2\beta_{21}S_2^*I_1 - \beta_{21}I_1^*\frac{(S_2^*)^2}{S_2}\right.\right.\\
& \left.\left.-\beta_{21}S_2I_1\frac{L_2^*}{L_2} - (\varepsilon_2+d_2)L_2\right] + \frac{\varepsilon_2+d_2}{\varepsilon_2}\left[\varepsilon_2L_2 - d_2I_2 - \varepsilon_2L_2\frac{I_2^*}{I_2} + d_2I_2^*\right]\right\}\\
= {} & v_1d_1S_1^*\left(2 - \frac{S_1}{S_1^*} - \frac{S_1^*}{S_1}\right) + v_2d_2S_2^*\left(2 - \frac{S_2}{S_2^*} - \frac{S_2^*}{S_2}\right)\\
& + v_1\left[\beta_{12}S_1^*I_2 - \frac{(\varepsilon_1+d_1)(d_1+\gamma_1)}{\varepsilon_1}I_1\right] + v_2\left[\beta_{21}S_2^*I_1 - \frac{d_2(\varepsilon_2+d_2)}{\varepsilon_2}I_2\right]\\
& + v_1\left[3\beta_{12}S_1^*I_2^* - \beta_{12}I_2^*\frac{(S_1^*)^2}{S_1} - \beta_{12}I_2S_1\frac{L_1^*}{L_1} - \beta_{12}S_1^*I_2^*\frac{L_1}{L_1^*}\frac{I_1^*}{I_1}\right]\\
& + v_1\gamma_1\left(I_1 - I_1^* + I_1^*\frac{S_1^*}{S_1} - I_1\frac{S_1^*}{S_1}\right)\\
& + v_2\left[3\beta_{21}S_2^*I_1^* - \beta_{21}I_1^*\frac{(S_2^*)^2}{S_2} - \beta_{21}S_2I_1\frac{L_2^*}{L_2} - \beta_{21}S_2^*I_1^*\frac{L_2}{L_2^*}\frac{I_2^*}{I_2}\right].
\end{aligned} \tag{2.3.24}$$

The third and fourth terms in system (2.3.24) cancel out:

$$\begin{aligned}
& v_1\left[\beta_{12}S_1^*I_2 - \frac{(d_1+\varepsilon_1)(d_1+\gamma_1)}{\varepsilon_1}I_1\right] + v_2\left[\beta_{21}S_2^*I_1 - \frac{d_2(\varepsilon_2+d_2)}{\varepsilon_2}I_2\right]\\
= {} & v_1v_2\left[\frac{I_2}{I_2^*} - \frac{I_1}{I_1^*}\right] + v_2v_1\left[\frac{I_1}{I_1^*} - \frac{I_2}{I_2^*}\right] = 0.
\end{aligned}$$

The sum of the fifth and seventh terms can be rewritten as

$$v_1 v_2 \left(6 - \frac{S_1^*}{S_1} - \frac{S_1}{S_1^*}\frac{I_2}{I_2^*}\frac{L_1^*}{L_1} - \frac{S_2^*}{S_2} - \frac{S_2}{S_2^*}\frac{I_1}{I_1^*}\frac{L_2^*}{L_2} - \frac{L_1}{L_1^*}\frac{I_1^*}{I_1} - \frac{L_2}{L_2^*}\frac{I_2^*}{I_2}\right).$$

The sixth term vanishes since $\gamma_1 = 0$ is assumed. Thus, $V'(t)$ can be simplified as

$$\begin{aligned} V'(t) = {} & v_1 d_1 S_1^* \left(2 - \frac{S_1}{S_1^*} - \frac{S_1^*}{S_1}\right) + v_2 d_2 S_2^* \left(2 - \frac{S_2}{S_2^*} - \frac{S_2^*}{S_2}\right) \\ & + v_1 v_2 \left(6 - \frac{S_1^*}{S_1} - \frac{S_1}{S_1^*}\frac{I_2}{I_2^*}\frac{L_1^*}{L_1} - \frac{S_2^*}{S_2} - \frac{S_2}{S_2^*}\frac{I_1}{I_1^*}\frac{L_2^*}{L_2} - \frac{L_1}{L_1^*}\frac{I_1^*}{I_1} - \frac{L_2}{L_2^*}\frac{I_2^*}{I_2}\right). \end{aligned} \tag{2.3.25}$$

By the relation of arithmetic mean and geometric mean, we conclude that $V'(t) \leq 0$ with the equality holding if and only if

$$\frac{S_1}{S_1^*} = \frac{L_1}{L_1^*} = \frac{I_1}{I_1^*} = \frac{S_2}{S_2^*} = \frac{L_2}{L_2^*} = \frac{I_2}{I_2^*} = 1.$$

By the Lyapunov-LaSalle Theorem, $\hat{E}^*$ is globally asymptotically stable for (2.3.21). Back to model (2.3.18), we conclude that E^* is globally asymptotically stable for (2.3.18) among all positive solutions in Ω, completing the proof. □

2.3.2 Special case II — a system of DDEs

Consider step functions for $P_1(t)$ and $P_2(t)$:

$$P_1(t) = \begin{cases} 1, & t \leq \tau_1, \\ 0, & t > \tau_1, \end{cases} \quad \text{and} \quad P_2(t) = \begin{cases} 1, & t \leq \tau_2, \\ 0, & t > \tau_2, \end{cases} \tag{2.3.26}$$

where $\tau_1 \geq 0$ and $\tau_2 \geq 0$ are constants. Although the latent period differs from individual to individual, choosing τ_1 and τ_2 as the respective average latencies for infected humans and female mosquitoes would make the above $P_1(t)$ and $P_2(t)$ reasonable ap-

proximations for the real situation.

With this pair of $P_1(t)$ and $P_2(t)$, the long term (e.g., for $t \geq \max\{\tau_1, \tau_2\}$) disease dynamics is governed by the following system of delay differential equations derived from model (2.2.4):

$$\begin{cases} \dfrac{\mathrm{d}S_1(t)}{\mathrm{d}t} = -ae_1 mS_1(t)I_2(t) + d_1 - d_1 S_1(t) + \gamma_1 I_1(t), \\ \dfrac{\mathrm{d}I_1(t)}{\mathrm{d}t} = ae_1 me^{-d_1\tau_1} S_1(t-\tau_1)I_2(t-\tau_1) - d_1 I_1(t) - \gamma_1 I_1(t), \\ \dfrac{\mathrm{d}S_2(t)}{\mathrm{d}t} = -ae_2 S_2(t)I_1(t) + d_2 - d_2 S_2(t), \\ \dfrac{\mathrm{d}I_2(t)}{\mathrm{d}t} = ae_2 e^{-d_2\tau_2} S_2(t-\tau_2)I_1(t-\tau_2) - d_2 I_2(t), \end{cases} \tag{2.3.27}$$

with

$$\begin{aligned} L_1'(t) &= ae_1 mS_1(t)I_2(t) - ae_1 me^{-d_1\tau_1} S_1(t-\tau_1)I_2(t-\tau_1) - d_1 L_1(t), \\ L_2'(t) &= ae_2 S_2(t)I_1(t) - ae_2 e^{-d_2\tau_2} S_2(t-\tau_2)I_1(t-\tau_2) - d_2 L_2(t). \end{aligned} \tag{2.3.28}$$

Accordingly, Q_i can be calculated as $Q_i = e^{-d_i\tau_i}$, $i = 1, 2$, resulting in the following explicit formula for the basic reproduction number:

$$\mathcal{R}_0 = \frac{ae_1 m}{(d_1 + \gamma_1)} \frac{ae_2}{d_2} e^{-d_1\tau_1} e^{-d_2\tau_2}. \tag{2.3.29}$$

For system (2.3.27), the uniqueness and the boundedness of its non-trivial equilibrium can be shown by a similar argument in previous case of ODEs. When $\mathcal{R}_0 > 1$, the components of the unique endemic equilibrium $E^* = (S_1^*, I_1^*, S_2^*, I_2^*)$ can be explicitly expressed as

$$\begin{aligned} S_1^* &= \frac{(d_1 + \gamma_1)D_1}{ae^{-d_1\tau_1} e_2 D_2}, \quad I_1^* = \frac{d_1(R_0 - 1)}{ae_2(d_1 + \gamma_1)d_2 D_2}, \\ S_2^* &= \frac{d_2 D_2}{ae_1 me^{-d2\tau_2} D_1}, \quad I_2^* = \frac{d_1(R_0 - 1)}{ae_1 m(d_1 + \gamma_1)d_2 D_1}, \end{aligned}$$

where

$$D_1 = \gamma_1 d_2(1 - e^{-d_1\tau_1}) + d_1 a e_2 e^{-d_1\tau_1} + d_1 d_2,$$

$$D_2 = a e_1 m\gamma_1 e^{-d_2\tau_2}(1 - e^{-d_1\tau_1}) + a e_1 m e^{-d_2\tau_2} d_1 + d_1\gamma_1 + d_1^2.$$

Theorem 2.3.1 has confirmed that the disease free equilibrium $E_0 = (1, 0, 1, 0)$ is globally asymptotically stable if $\mathcal{R}_0 < 1$ and it is unstable when $\mathcal{R}_0 > 1$. In the rest of this section, we explore the dynamics of system (2.3.27) when $\mathcal{R}_0 > 1$.

For system (2.3.27), the phase space is $X = C([-\tau_1, 0], R^2) \times C([-\tau_2, 0], R^2))$. The fundamental theory for such a system of DDEs can be found in [7]. For biological reasons, we consider the subset

$$X_+^1 = \left\{ \Phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X : \begin{array}{c} 0 \le \phi_1(\theta) \le 1,\ 0 \le \phi_2(\theta) \le 1 \ \text{ for, } \ \theta \in [-\tau_1, 0] \\ 0 \le \phi_3(\theta) \le 1,\ 0 \le \phi_4(\theta) \le 1 \ \text{ for, } \ \theta \in [-\tau_2, 0] \end{array} \right\}.$$

Let $X_+^0 = \{\Phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X_+^1 : \text{ either } \phi_2 \text{ or } \phi_4 \text{ is not identical to } 0\}$. Then for any $\Phi \in X_+^0$, the corresponding solution $(S_1(t), I_1(t), S_2(t), I_2(t))$ satisfies $0 < S_1(t) \le 1,\ 0 < I_1(t) \le 1,\ 0 < S_2(t) \le 1$ and $0 < I_2(t) \le 1$ for $t > 0$. We first show that if $R_0 > 1$, then the disease is weakly persistent in the sense stated in the following lemma.

Lemma 2.3.2 *Assume $R_0 > 1$. Then for any initial function $\Phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X_+^0$, the corresponding solution $(S_1(t), I_1(t), S_2(t), I_2(t))$ satisfies*

$$I_1^\infty > 0,\ I_2^\infty > 0,\ S_{1\infty} < 1,\ S_{2\infty} < 1.$$

Proof. By way of contradiction, we assume that the statement is false. We first show that the following equalities would all hold:

$$\lim_{t\to\infty} I_1(t) = 0, \quad \lim_{t\to\infty} I_2(t) = 0, \quad \lim_{t\to\infty} S_1(t) = 1, \quad \lim_{t\to\infty} S_2(t) = 1. \tag{2.3.30}$$

Indeed, if $I_1^\infty = 0$, then $I_1(t) \to 0$ as $t \to \infty$. Applying the theory of asymptotically autonomous systems (see, e.g., [3]) to the S_2 and I_2 equations in system (2.3.27), we conclude that $S_2(t) \to 1$ and $I_2(t) \to 0$, which further leads to, by the S_1 equation in system (2.3.27), $S_1(t) \to 1$. Similarly, $I_1^\infty = 0$ also leads to (2.3.30). If $S_{1\infty} = 1$, then $S_1(t) \to 1$ as $t \to \infty$. By $0 \le I_1(t) = I - S_1(t) - L_1(t) \le 1 - S_1(t)$, we know that $I_1(t) \to 0$ which in turn implies $I_2(t) \to 0$ and $S_2(t) \to 1$ as $t \to \infty$. Similarly, $S_{2\infty} = 1$ also leads to (2.3.30).

Now, for any $\delta \in (0, 1)$, by equalities in (2.3.30), there is $T > 0$ such that

$$I_1(t, \phi_2) < \delta, \quad I_2(t, \phi_4) < \delta, \quad S_1(t, \phi_1) > 1 - \delta, \quad S_2(t, \phi_3) > 1 - \delta, \quad \text{for } t \ge T. \tag{2.3.31}$$

By inequalities in (2.3.31) and the I_1 and I_2 equations in system (2.3.27), we have

$$\begin{cases} \dfrac{\mathrm{d}I_1(t)}{\mathrm{d}t} \ge ae_1 m e^{-d_1\tau_1} I_2(t - \tau_1)(1 - \delta) - (d_1 + \gamma_1) I_1(t), \\ \dfrac{\mathrm{d}I_2(t)}{\mathrm{d}t} \ge ae_2 e^{-d_2\tau_2} I_1(t - \tau_2)(1 - \delta) - d_2 I_2(t), \end{cases} \quad \text{for } t \ge T. \tag{2.3.32}$$

This suggests the following linear comparison system for $I_1(t)$ and $I_2(t)$:

$$\begin{cases} \dfrac{\mathrm{d}u_1(t)}{\mathrm{d}t} = ae_1 m e^{-d_1\tau_1} u_2(t - \tau_1)(1 - \delta) - (d_1 + \gamma_1) u_1(t), \\ \dfrac{\mathrm{d}u_2(t)}{\mathrm{d}t} = ae_2 e^{-d_2\tau_2} u_1(t - \tau_2)(1 - \delta) - d_2 u_2(t). \end{cases} \tag{2.3.33}$$

Since system (2.3.33) is monotone, the stability/instability of its trivial solution is the same as that of the linear system obtained by dropping the two delays in system (2.3.33) (see, e.g. Smith [20]) which is determined by the following characteristic equation:

$$\lambda^2 + (d_1 + \gamma_1 + d_2)\lambda + (d_1 + \lambda_1) d_2 \left[1 - (1 - \delta)^2 \mathcal{R}_0\right] = 0. \tag{2.3.34}$$

Because $\mathcal{R}_0 > 1$, one can choose $\delta \in (0, 1)$ sufficiently small so that $1 - (1 - \delta)^2 \mathcal{R}_0 < 0$,

and hence, equation (2.3.34) has a root with positive real part. This means that positive solutions of equation (2.3.34) are unbounded. On the other hand, the comparison theorem for delay differential equations (see, e.g., Smith [20]) implies that $I_1(t) \geq u_1(t)$ and $I_2(t) \geq u_2(t)$ where $(u_1(t), u_2(t))$ is the positive solution of system (2.3.34) with the initial function (ϕ_2, ϕ_4) and hence is unbounded. This contradicts with (2.3.30), and the contradiction completes the proof of the lemma. □

Next, we prove that if $\mathcal{R}_0 > 1$, then the disease is actually *uniformly strongly persistent*.

Theorem 2.3.3 *Assume that if* $\mathcal{R}_0 > 1$. *There exists an* $\eta > 0$ *such that for any initial function* $\Phi = (\phi_1, \phi_2, \phi_3, \phi_4) \in X_+^0$, *the corresponding solution* $(S_1(t), I_1(t), S_2(t), I_2(t))$ *satisfies*

(i) $\frac{d_1}{ae_1m+d_1} \leq S_{1\infty}$ *and* $\frac{d_2}{ae_2+d_2} \leq S_{2\infty}$;

(ii) $\eta \leq I_{1\infty}$ *and* $\eta \leq I_{2\infty}$.

Proof: Since $0 \leq I_1(t) \leq 1$ for $t \geq -\tau_2$ and $0 \leq I_2(t) \leq 1$ for all $t \geq -\tau_1$, the $S_1'(t)$ and $S_2'(t)$ equations in system (2.3.27) lead to

$$S_1'(t) \geq d_1 - ae_1mS_1(t) - d_1S_1(t) = d_1 - (ae_1m + d_1)S_1(t),$$
$$S_2'(t) \geq d_2 - ae_2S_2(t) - d_2S_2(t) = d_2 - (ae_2 + d_2)S_2(t).$$

By the standard comparison theorem (see, e.g., [20]), it follows that $S_1(t) \geq w_1(t)$, and $S_2(t) \geq w_2(t)$, where $(w_1(t), w_2(t))$ is the solution of

$$w_1'(t) = d_1 - ae_1mw_1(t) - d_1w_1(t),$$
$$w_2'(t) = d_2 - ae_2w_2(t) - d_2w_2(t).$$

with $w_1(0) \leq \phi_1(0),\ w_2(0) \leq \phi_3(0)$. Thus,

$$S_{1\infty} \geq\ w_{1\infty} = \frac{d_1}{ae_1 m + d_1},\ \text{ and }\ S_{2\infty} \geq\ w_{2\infty} = \frac{d_2}{ae_2 + d_2}. \tag{2.3.35}$$

Next, applying the Fluctuation Lemma (see, e.g., [9]) to the $S_1'(t)$ and $S_2'(t)$ equations in system (2.3.27) gives

$$I_1^\infty \geq \frac{d_2 - d_2 S_{2\infty}}{ae_2 S_{2\infty}},\ \ I_2^\infty \geq \frac{d_1 - d_1 S_{1\infty}}{ae_1 m S_{1\infty}}. \tag{2.3.36}$$

By Lemma 2.3.2 and the inequalities in (2.3.36), we know that $\partial X_+^1 = X_+^1/X_+^0$ is a uniform *weak* repeller for X_+^0. Applying Theorem 1.4 of [23] to the solution semi-flow $\mathbf{\Psi}(t, \Phi) = (S_1(t), I_1(t), S_2(t), I_2(t))$ of system (2.3.27) for $t \geq \max(\tau_1, \tau_2)$ with $\Phi \in X_+^0$, we conclude that ∂X_+^1 is also a uniform *strong* repeller for X_+^0, implying that the disease is uniformly strongly persistent. This means that there exists an $\eta > 0$ such that $I_{1\infty} \geq \eta,\ I_{2\infty} \geq \eta$, where η is independent of the initial function $\Phi \in X_+^0$. The proof is complete. □

The following theorem, parallels to Theorem 2.3.2 for (2.3.18), and confirms the global asymptotical stability of the endemic equilibrium E^* for system (2.3.27) under the assumption $\gamma_1 = 0$.

Theorem 2.3.4 *Consider system* (2.3.27). *Assume that* $R_0 > 1$. *Then the endemic equilibrium* E^* *is globally asymptotically stable in* X_+^0, *provided that* $\gamma_1 = 0$.

Proof. We use a Lyapunov functional to prove the theorem. Let

$$\begin{aligned} V &= ae_2e^{-d_2\tau_2}S_2^*I_1^*\left[e^{-d_1\tau_1}S_1^*\left(\frac{S_1}{S_1^*}-1-\ln\frac{S_1}{S_1^*}\right)+I_1^*\left(\frac{I_1}{I_1^*}-1-\ln\frac{I_1}{I_1^*}\right)\right] \\ &\quad +ae_1me^{-d_1\tau_1}S_1^*I_2^*\left[e^{-d_2\tau_2}S_2^*\left(\frac{S_2}{S_2^*}-1-\ln\frac{S_2}{S_2^*}\right)+I_2^*\left(\frac{I_2}{I_2^*}-1-\ln\frac{I_2}{I_2^*}\right)\right] \\ &\quad +ae_2e^{-d_2\tau_2}S_2^*I_1^*ae_1mS_1^*I_2^*e^{-d_1\tau_1}\int_{-\tau_1}^{0}g_1(S_1I_2)\,\mathrm{d}s \\ &\quad +ae_1me^{-d_1\tau_1}S_1^*I_2^*ae_2S_2^*I_1^*e^{-d_2\tau_2}\int_{-\tau_2}^{0}g_1(S_2I_1)\,\mathrm{d}s. \end{aligned}$$

where

$$g_1(x)=\frac{x(t+s)}{x^*}-1-\ln\frac{x(t+s)}{x^*},$$

and x^* is the endemic equilibrium term with respect to the component x in the solution of system (2.3.27).

The derivative of V along the trajectory of system (2.3.27) is

$$\begin{aligned} V' &= ae_2S_2^*I_1^*e^{-d_2\tau_2}\left[d_1e^{-d_1\tau_1}S_1^*\left(2-\frac{S_1}{S_1^*}-\frac{S_1^*}{S_1}\right)+e^{-d_1\tau_1}\gamma_1\left(I_1-I_1^*+I_1^*\frac{S_1^*}{S_1}-I_1\frac{S_1^*}{S_1}\right)\right. \\ &\quad +ae_1me^{-d_1\tau_1}I_2^*S_1^*+ae_1mI_2S_1^*e^{-d_1\tau_1}-ae_1me^{-d_1\tau_1}I_2^*\frac{(S_1^*)^2}{S_1}-(\gamma_1+d_1)I_1 \\ &\quad -ae_1me^{-d_1\tau_1}I_2(t-\tau_1)S_1(t-\tau_1)\frac{I_1^*}{I_1}+ae_1me^{-d_1\tau_1}I_2^*S_1^* \\ &\quad \left.-ae_1me^{-d_1\tau_1}\ln\frac{I_2S_1}{I_2(t-\tau_1)S_1(t-\tau_1)}\right] \\ &\quad +ae_1mS_1^*I_2^*e^{-d_1\tau_1}\left[d_2S_2^*e^{-d_2\tau_2}\left(2-\frac{S_2}{S_2^*}-\frac{S_2^*}{S_2}\right)+2ae_2S_2^*I_1^*e^{-d_2\tau_2}\right. \\ &\quad +ae_2S_2^*I_1e^{-d_2\tau_2}-ae_2S_2^*I_1^*e^{-d_2\tau_2}\frac{S_2^*}{S_2}-d_2I_2-ae_2e^{-d_2\tau_2}I_1(t-\tau_2)S_2(t-\tau_2)\frac{I_2^*}{I_2} \\ &\quad \left.-ae_2e^{-d_2\tau_2}\ln\frac{I_1S_2}{I_1(t-\tau_2)S_2(t-\tau_2)}\right]. \end{aligned}$$

Setting $c_1 = ae_2I_1^*S_2^*e^{-d_2\tau_2}$ and $c_2 = ae_1mI_2^*S_1^*e^{-d_1\tau_1}$, and reorganizing the above for-

mula, we obtain

$$\begin{aligned}
V' = {} & c_1 d_1 e^{-d_1\tau_1} S_1^* \left(2 - \frac{S_1}{S_1^*} - \frac{S_1^*}{S_1}\right) + c_2 d_2 e^{-d_2\tau_2} S_2^* \left(2 - \frac{S_2}{S_2^*} - \frac{S_2^*}{S_2}\right) \\
& + c_1 e^{-d_1\tau_1}\gamma_1 \left(I_1 - I_1^* + I_1^* \frac{S_1^*}{S_1} - I_1 \frac{S_1^*}{S_1}\right) \\
& + \left(a^2 e_1 e_2 m e^{-d_1\tau_1 - d_2\tau_2} I_1^* S_2^* I_2 S_1^* - a e_1 m I_2^* S_1^* e^{-d_1\tau_1} d_2 I_2\right) \\
& + \left[a^2 e_1 e_2 m e^{-d_1\tau_1 - d_2\tau_2} I_1 S_2^* I_2^* S_1^* - a e_2 I_1^* S_2^* e^{-d_2\tau_2}(d_1 + \gamma_1) I_1\right] \\
& + c_1 c_2 \left[4 - \frac{S_1^*}{S_1} - \frac{S_2^*}{S_2} - \frac{I_2(t-\tau_1)}{I_2^*}\frac{S_1(t-\tau_1)}{S_1^*}\frac{I_1^*}{I_1}\right. \\
& \left. - \frac{I_1(t-\tau_2)}{I_1^*}\frac{S_2(t-\tau_2)}{S_2^*}\frac{I_2^*}{I_2} - \ln\frac{I_2 S_1}{I_2(t-\tau_1)S_1(t-\tau_1)} - \ln\frac{I_1 S_2}{I_1(t-\tau_2)S_2(t-\tau_2)}\right].
\end{aligned}$$

The third term vanishes due to the assumption $\gamma_1 = 0$. Both the fourth and fifth terms are also zero by the equations for the equilibrium E^*. Now the sixth (last) term can be further rewritten as

$$c_1 c_2 \left[\left(1 - \frac{S_1^*}{S_1} + \ln\frac{S_1^*}{S_1}\right) + \left(1 - \frac{S_2^*}{S_2} + \ln\frac{S_2^*}{S_2}\right) + (1 - x + \ln x) + (1 - y + \ln y)\right],$$

where

$$x = \frac{I_2(t-\tau_1)}{I_2^*}\frac{S_1(t-\tau_1)}{S_1^*}\frac{I_1^*}{I_1}, \quad y = \frac{I_1(t-\tau_2)}{I_1^*}\frac{S_2(t-\tau_2)}{S_2^*}\frac{I_2^*}{I_2}.$$

Thus,

$$\begin{aligned}
V' = {} & c_1 d_1 e^{-d_1\tau_1} S_1^* \left(2 - \frac{S_1}{S_1^*} - \frac{S_1^*}{S_1}\right) + c_2 d_2 S_2^* e^{-d_2\tau_2} \left(2 - \frac{S_2}{S_2^*} - \frac{S_2^*}{S_2}\right) \\
& + c_1 c_2 \left[\left(1 - \frac{S_1^*}{S_1} + \ln\frac{S_1^*}{S_1}\right) + \left(1 - \frac{S_2^*}{S_2} + \ln\frac{S_2^*}{S_2}\right) + (1 - x + \ln x) + (1 - y + \ln y)\right].
\end{aligned} \tag{2.3.37}$$

Now, by the relation between arithmetic and geometric means, and the non-positivity of the function $g(u) = 1 - u + \ln u$, we conclude that $V' \leq 0$ and $V' = 0$ if and only if (S_1, I_1, S_2, I_2) is at E^*. It follows from the Lyapunov-LaSalle Theorem for DDEs

(see [7]) that E^* is globally asymptotically stable in X_+^0, completing the proof. □

2.4 Conclusion and discussion

In this chapter, we have modified the classic Ross-MacDonald model for the disease dynamics of Malaria by incorporating latencies within both human beings and female mosquitoes. The novelty of our model is that we have introduced two general probability functions ($P_1(t)$ and $P_2(t)$) to reflect the fact that the latencies of the malaria parasite differ from individual to individual in humans and mosquitoes. We have justified the well-posedness of the new model, identified the basic reproduction number $\mathcal{R}_0$ for the model and analyzed the dynamics of the model. We have shown, very naturally and as in most works on disease models, that when $\mathcal{R}_0 < 1$, the disease free equilibrium E_0 is globally asymptotically stable, meaning that the disease will eventually die out; and if $\mathcal{R}_0 > 1$, E_0 becomes unstable. When $\mathcal{R}_0 > 1$, the dynamics of the model become more difficult for general $P_1(t)$ and $P_2(t)$, and this forces us to consider some specific functions. When $P_1(t)$ and $P_2(t)$ are both exponential functions, the model reduces to a system of ODEs; when $P_1(t)$ and $P_2(t)$ are both step functions, the long term disease dynamics are governed by a system of DDEs. In both cases, we are able to show that when $\mathcal{R}_0 > 1$ then the disease will persist; moreover if there is no recovery ($\gamma_1 = 0$), then all admissible positive solutions will converge to the unique endemic equilibrium.

Our approach may provide a framework for dynamics of other mosquito-borne diseases. Taking Dengue as an example, since this disease is caused by the dengue *virus* (unlike the malaria protozoa), the recovered human beings will carry immunity, and hence not return to the susceptible class, implying $\gamma_1 = 0$ in the corresponding model. Therefore, our approach (actually results) can be easily applied to the corresponding

model(s) for dengue disease.

From the formula of the basic reproduction number $\mathcal{R}_0$ for our model, we can see that it is indeed smaller than the one obtained by ignoring the latencies (i.e., setting $Q_1 = 1$ and $Q_2 = 1$). In other words, if the latencies are neglected in modeling the disease dynamics, the basic reproduction number will be overestimated, regardless of what forms of the latency probability functions $P_1(t)$ and $P_2(t)$ are adopted

We point out that there is a mathematical theory for disease models which defines the basic reproduction number as the spectral radius of the so called next generation operator. Here in this chapter, our $\mathcal{R}_0$ is defined by the so called survival function [8]. The difference lies in that " the survival function gives the total number of infectives in the same class produced by a single infective of that class, while the next generation operator gives the mean number of new infectives per infective in any class per generation". The value corresponding to the latter definition thus depends on the number of infective classes in the infection cycle [8]. Taking the model (2.3.18) as an example, using the next generation operator (matrix in this case) approach from [4, 25], the basic reproduction number for model (2.3.18) is defined as

$$\mathcal{R}_0 = \sqrt{\frac{ae_1m}{\gamma_1 + d_1} \cdot \frac{ae_2}{d_2} \cdot \frac{\varepsilon_1}{\varepsilon_1 + d_1} \cdot \frac{\varepsilon_2}{\varepsilon_2 + d_1}}, \tag{2.4.1}$$

which is the square root of the formula in (2.3.19). Note that many researchers have used the survival function scenario to define basic reproduction numbers for vector-borne diseases, see e.g., [1, 8, 19] and the references therein. Note that because the threshold value for the basic reproduction number is at 1, such a difference does not cause any mathematical problem in exploring the threshold property of vector-borne disease models. For a detailed discussion on this topic, we refer readers to [4, 5, 8, 25].

We conclude this chapter by a remark that the way we have incorporated latencies in

this chapter may also help clarify the confusion for [19] mentioned in the introduction. Indeed, by adding $\tau_1 > 0$ and $\tau_2 > 0$ into the model, latent classes in both humans and mosquitoes are admitted and hence, the term $1 - x(t - \tau_1)$ and $1 - y(t - \tau_2)$ should be replaced by $1 - l_1(t - \tau_1) - x(t - \tau_1)$ and $1 - l_2(t - \tau_2) - y(t - \tau_2)$ respectively, where $l_1(t) = L_1(t)/N$ is the proportion of the latent human beings and $l_2(t) = L_2(t)/M$ is the proportion of the latent mosquitoes with both satisfying equations corresponding to equations (2.3.28). Since $1-x(t-\tau_1)$ is larger than $1-l_1(t-\tau_1)-x(t-\tau_1)$ and $1-y(t-\tau_2)$ is larger than $1 - l_2(t - \tau_2) - y(t - \tau_2)$, this may explain why the solutions of (1.3) with initial values from $[0, 1] \times [0, 1]$ may go beyond this region. When only considering a discrete latency in mosquitoes, Aron and May [1] discussed a similar model.

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Chapter 3

Modeling malaria transmission in a patchy environment

In this chapter, a mathematical model is derived to describe the transmission and spread of malaria over a patchy environment. The model incorporates two factors: disease latencies in both humans and mosquitoes, and dispersal of humans between patches. The basic reproduction number $\mathcal{R}_0$ is identified by the theory of the next generation operator for a structured disease model. The dynamics of the model is investigated in terms of $\mathcal{R}_0$. It is shown that the disease free equilibrium is asymptotically stable if $\mathcal{R}_0 < 1$, and it is unstable if $\mathcal{R}_0 > 1$; in the latter case, the disease is endemic in the sense that the variables for the infected compartments are uniformly persistent. For the case of two patches, some more explicit conditions are obtained, and impacts of dispersal rates in all different compartments on $\mathcal{R}_0$ are also explored. Some numerical simulations are performed which show that the impacts could be very complicated: in a certain range of the parameters, $\mathcal{R}_0$ is increasing with respect to a dispersal rate while in another range, it can be decreasing with respect to the same dispersal rate.

3.1 Introduction

Malaria is a mosquito-borne disease that has spread to more one hundred countries, mostly in tropical and sub-tropical regions. Each year, 300-500 million infection cases are reported, among which around a million cases result in deaths. Thus, malaria still remains a threat to human beings in many places in the world.

Mathematical models can help understand the dynamics of transmission and spread of the infectious disease and thereby, provide guides and suggestions for the control of the disease. In the context of malaria, the earliest model is the Ross-MacDonald model (see,e.g., [13,12] or [1]), which is given by the following system of ordinary differential equations:

$$\begin{cases} \dfrac{\mathrm{d}I_h}{\mathrm{d}t} = ac_1 I_m \dfrac{N - I_h}{N} - d_1 I_h, \\ \dfrac{\mathrm{d}I_m}{\mathrm{d}t} = ac_2 (M - I_m) \dfrac{I_h}{N} - d_2 I_m. \end{cases} \tag{3.1.1}$$

Here, I_h and I_m represent the populations of the infectious classes of human beings and female mosquitoes, respectively. N and M are the total populations of human beings and female mosquitoes, which were assumed to be constants. The model is a result of ignoring the latency within both hosts and mosquitoes and assuming no immunity of the recovered individuals (thus, the terms $N - I_h$ and $M - I_m$ present the populations of the susceptible humans and mosquitoes). The constant a is the mosquito biting rate; c_1 is the probability that a bite of an infective mosquito will cause infection of the human; and c_2 is the probability that a bite by a susceptible mosquito of an infective human individual will cause infection of the mosquito. It is assumed that the average durations of infection for human and mosquitoes are $1/d_1$ and $1/d_2$ individually. By analyzing this mathematical model, both Ross and Macdonald found that it would be possible to eradicate the disease without killing all vector mosquitoes. This was in contrast to the traditional belief that malaria could be wiped out only by eradicating all vector

mosquitoes, which turned out to be impossible in practice. Indeed, by looking at basic reproduction number for this model given by

$$\mathcal{R}_0 = \frac{ac_1}{d_1}\frac{M}{N}\frac{ac_2}{d_2}, \tag{3.1.2}$$

one knows that any measure(s) that can bring $\mathcal{R}_0$ to a value less than 1 would eventually drive the disease to extinction. Obviously, among the possible measures are, for example, controlling the mosquito population M (e.g., by spraying mosquito pesticides) to a sufficiently lower level and controlling the biting rate a (e.g., by using mosquito nets).

Ross-MacDonald model is a simple example of showing how mathematical modeling can provide insights into the mechanism of malaria transmission and spread, by which effective measures to control the disease can be suggested. This simple model is mathematically tractable in the sense that long term solution behavior of model (3.1.1) can be fully determined by the quantity $\mathcal{R}_0$ which is explicitly calculated by the model parameters. However, it is highly simplified and biologically inaccurate in the sense that many biological factors are omitted. Among such factors are latencies of the developments of malaria parasites within humans and mosquitoes, and the spatial heterogeneity of the habitats of humans and mosquitoes. In recent years, researchers consider these missing factors into the model, resulting in various forms of modification on model (3.1.1).

Along the line of latency, in [1,4,11], a discrete delay is introduced into their models to account for the latency within mosquitoes; in [14], two discrete delays are added into model (3.1.1), one accounting for the latency in humans and the other for that in mosquitoes; and two probability distributions are used to account for the variation of latencies in human and mosquito populations in [23].

We consider two forms of spatial heterogeneity: (A) continuous spatial heterogene-

ity and (B) discrete spatial heterogeneity. With respect to (A), a model in [10] with spatial diffusion and advection of mosquitoes was recently proposed and studied that also considered the seasonality of the model parameters, and a spatially non-local model in [11] with latency in mosquitoes was also discussed. In the context of case (B), some work on extensions of model (3.1.1) were included in [2, 3, 5]. However, patch models in [2, 3, 5] have all ignored the latencies which have been shown to have a significant impact on the disease dynamics. This motivates us to derive a more realistic patch model that not only contains dispersal of humans but also incorporates the latencies both in humans and in mosquitoes.

In this chapter, we will follow the approach in [8, 9] where patch models with non-local infections are derived and analyzed. Making use of the infection age as well as the typical method of characteristics for structured populations, we derive a model involving a patchy environment that has two discrete delays, accounting for the latencies in humans and mosquitoes, respectively. The model also contains spatially non-local term accounting for non-local infection resulting from the dispersal of humans during the latent period. We point out that, as in [2] and [3], we assume mosquitoes cannot fly the distances between the patches, and thus only humans can disperse between patches in our model. This is in contrast to the model in [5] where both humans and mosquitoes can disperse between patches.

The rest of the chapter is organized as below. In Section 3.2, we derive (not propose) the model rigorously, starting from an age structured system of first order partial differential equations and using the method of characteristics. In Section 3.3, we address the well-posedness by proving the non-negativeness and boundedness of solutions. In Section 3.4, we identify the basic reproduction number $\mathcal{R}_0$ of the model by using the abstract theory for structured disease models developed by Thieme [17]. As expected, $\mathcal{R}_0$ plays a threshold role in the sense that when $\mathcal{R}_0 < 1$, the disease free equilibrium

(DFE) is asymptotically stable (Section 4); if $\mathcal{R}_0 > 1$ the DFE is unstable and the disease is endemic in the sense that the infected components of the model are uniformly persistent (Section 3.5). In Section 3.6, we focus on the two-patch case where more explicit conditions are obtained, and impacts of dispersal rates in all different compartments on $\mathcal{R}_0$ are also explored. In the last section, Section 3.7, we summarize our main results and discuss the biological implications of our results.

3.2 Model formulation for general patch model with fixed latency

Consider human and *Anopheles* mosquito populations distributed over n patches. Here, depending on the situation, patches could be towns, cities or countries etc. Use N_i and M_i to denote the total population of human beings and female *Anopheles* mosquitoes in patch i, respectively. In the presence of malaria, the total populations are divided into compartments of susceptible and infected classes. Assume that there is a fixed infection latent period of length τ_1 within human beings and another fixed latent period τ_2 within mosquitoes. Latencies differ from individual to individual in general. For simplicity, here we assume fixed latencies which can be considered as an approximation of the mean latencies within the hosts and the vectors. We can also assume that $\tau_2 \leq \tau_1$, because it is known that the latency in humans is greater than that in mosquitoes. Due to latencies, the infected classes are further divided into latent classes and infectious classes for both hosts and vectors. Let S_{ij}, L_{ij} and I_{ij} be the sub-populations of the susceptible, latent and infectious classes respectively, with the first sub-index i specifying the i-th patch ($i = 1, 2, ..., n$), and the second sub-index j representing human for $j = 1$ and female mosquito for $j = 2$.

As we pointed out at the end of the introduction of this chapter, we assume that the

distances between two patches are sufficiently large so that the *Anopheles* mosquitoes cannot disperse between the patches. Then, the sub-populations of the mosquitoes can be described by the following differential equations:

$$\begin{cases} \dfrac{\mathrm{d}S_{i2}(t)}{\mathrm{d}t} = \beta_{i2}M_i(t) - d_{i2}S_{i2}(t) - a_i c_{i2} S_{i2}(t)\dfrac{I_{i1}(t)}{N_i(t)}, \\ \dfrac{\mathrm{d}L_{i2}(t)}{\mathrm{d}t} = -d_{i2}L_{i2}(t) + a_i c_{i2} S_{i2}(t)\dfrac{I_{i1}(t)}{N_i(t)} - a_i c_{i2} S_{i2}(t-\tau_2)\dfrac{I_{i1}(t-\tau_2)}{N_i(t-\tau_2)}e^{-d_{i2}\tau_2}, \\ \dfrac{\mathrm{d}I_{i2}(t)}{\mathrm{d}t} = -d_{i2}I_{i2}(t) + a_i c_{i2} S_{i2}(t-\tau_2)\dfrac{I_{i1}(t-\tau_2)}{N_i(t-\tau_2)}e^{-d_{i2}\tau_2}, \end{cases} \tag{3.2.1}$$

where β_{i2}, d_{i2} and a_i are the birth, death and biting rates respectively in patch i, and c_{i2} is the probability that a bite by a susceptible mosquito of an infectious human in patch i will cause infection. In this work, we further assume that $\beta_{i2} = d_{i2}$ for $i = 1, 2, \cdots, n$, so that the births and deaths of the mosquitoes are balanced in each patch, implying that the total mosquito population M_i in patch i remains a constant as $M_i'(t) = 0$ under the above assumption. Hence, we will simply write M_i to replace $M_i(t)$.

On the human being side, dispersal between patches is common. This, together with the latency within humans, will result in the so-called non-local infections, meaning that a human being may get infected in one patch, but start infecting mosquitoes in another patch. To model this phenomenon, we follow the ideas in [8, 9] to make use of the infection age a. Let $l_i(t, a)$ be the density of the infected human beings in patch i (i=1,2,...,n) with the infection age a at time t. Similar to the equations incorporating the natural age structure in Metz and Diekmann [6], the densities $l_i(t, a), (i = 1, 2, ...n)$ are described by the following system of first-ordered partial differential equations

$$\frac{\partial}{\partial t}l_i(t,a) + \frac{\partial}{\partial a}l_i(t,a) = -(d_{i1} + \bar{d}_{i1}(a) + \gamma_i)l_i(t,a) + \sum_{j=1}^{n} D_{ij}(a)l_j(t,a) - \sum_{j=1}^{n} D_{ji}(a)l_i(t,a) \tag{3.2.2}$$

where $D_{ij}(a)$ is the dispersal rate from patch j to patch i of the infected hosts at the

infection age a; d_{i1} is the natural death rate of the hosts, $\bar{d}_{i1}(a)$ stands for the malaria induced mortality rate and γ_i is the recovery rate, all in patch i. Here we neglect delays and loss for the movements of hosts between patches, otherwise things will become mathematically intractable.

From the definition of $l_i(t,a)$, the human population in the latent and infectious class in patch i at time t can be expressed by

$$L_{i1}(t) = \int_0^{\tau_1} l_i(t,a)\,\mathrm{d}a \text{ and } \quad I_{i1}(t) = \int_{\tau_1}^{\infty} l_i(t,a)\,\mathrm{d}a. \tag{3.2.3}$$

The fact that $d_{i1} + \bar{d}_{i1}(a) + \gamma_i$ is bounded below by the positive constant d_{i1} implies that

$$l_i(t,\infty) = 0. \tag{3.2.4}$$

Noting that the population with zero infection age equals to the population of new infections, we have

$$l_i(t,0) = a_i c_{i1} \frac{I_{i2}(t) S_{i1}(t)}{N_i(t)}, \tag{3.2.5}$$

where c_{i1} is the probability that a bite by an infectious mosquito of a susceptible human will result in a successful new infection of a susceptible human in patch i .

For convenience of showing the main idea to build the patch model, we further assume that the disease induced mortality rates and the dispersal rates in system (3.2.2) are piecewise constants:

$$\bar{d}_{i1}(a) = \begin{cases} 0, & 0 \le a \le \tau_1, \\ \mu_i, & a > \tau_1, \end{cases} \qquad D_{ij}(a) = \begin{cases} D_{ij}^L, & 0 \le a \le \tau_1, \\ D_{ij}^I, & a > \tau_1, \end{cases} \qquad i, j = 1, 2, ...n. \tag{3.2.6}$$

It follows from (3.2.2)-(3.2.4) and (3.2.6) that

$$\begin{aligned}\frac{\mathrm{d}I_{i1}(t)}{\mathrm{d}t} =& -\int_{\tau_1}^{\infty}\frac{\partial l_i(t,a)}{\partial a}\,\mathrm{d}a - \int_{\tau_1}^{\infty}\left(d_{i1}+\bar{d}_{i1}(a)\right)l_i(t,a)\,\mathrm{d}a\\ &+\int_{\tau_1}^{\infty}\sum_{j=1}^{n}D_{ij}(a)l_j(t,a)\,\mathrm{d}a - \int_{\tau_1}^{\infty}\sum_{j=1}^{n}D_{ji}(a)l_i(t,a)\,\mathrm{d}a\\ =& \, l_i(t,\tau_1) - (d_{i1}+\gamma_i+\mu_i)I_{i1}(t) + \sum_{j=1}^{n}D^I_{ij}I_{j1}(t) - \sum_{j=1}^{n}D^I_{ji}I_{i1}(t).\end{aligned} \tag{3.2.7}$$

Similarly, from (3.2.2)-(3.2.3) and (3.2.5)-(3.2.6), we obtain

$$\frac{\mathrm{d}L_{i1}(t)}{\mathrm{d}t} = a_i c_{i1} I_{i2}(t)\frac{S_{i1}(t)}{N_i(t)} - d_{i1}L_{i1}(t) - l_i(t,\tau_1) + \sum_{j=1}^{\infty}D^L_{ij}c_{j1}(t) - \sum_{j=1}^{\infty}D^L_{ji}c_{i1}(t). \tag{3.2.8}$$

The term $l_i(t,\tau_1)$ in (3.2.7) and (3.2.8) can be determined by applying the method of characteristics to (3.2.2) in the same way as in [8, 9], and we give the details below.

For fixed $\xi > 0$, let

$$U_i^{\xi}(t) = l_i(t, t-\xi), \qquad \text{for } \xi \le t \le \xi+\tau_1, \;\; i = 1,2,...,n.$$

Then,

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}U_i^{\xi}(t) =& \frac{\partial}{\partial t}l_i(t,a)|_{a=t-\xi} + \frac{\partial}{\partial a}l_i(t,a)|_{a=t-\xi}\\ =& -(d_{i1}+\bar{d}_{i1}(t-\xi))l_i(t,t-\xi) + \sum_{j=1}^{n}D_{ij}(t-\xi)l_j(t,t-\xi)\\ &-\sum_{j=1}^{n}D_{ji}(t-\xi)l_i(t,t-\xi)\\ =& -d_{i1}l_i(t,t-\xi) + \sum_{j=1}^{n}D^L_{ij}l_j(t,t-\xi) - \sum_{j=1}^{n}D^L_{ji}l_i(t,t-\xi)\\ =& -d_{i1}U_i^{\xi}(t) + \sum_{j=1}^{n}D^L_{ij}U_i^{\xi}(t) - \sum_{j=1}^{n}D^L_{ji}U_i^{\xi}(t).\end{aligned} \tag{3.2.9}$$

Using vector notation $U^{\xi}(t) = \left(U_1^{\xi}(t), U_2^{\xi}(t), ..., U_n^{\xi}(t)\right)^T$ where T represents the transpose of a vector, (3.2.9) is rewritten as

$$\frac{\mathrm{d}}{\mathrm{d}t}U^{\xi}(t) = BU^{\xi}(t), \tag{3.2.10}$$

where the coefficient matrix B is given by

$$B = \begin{bmatrix} -d_{11} - \sum_{j=1}^{n} D_{j1}^{L} & D_{12}^{L} & \cdots & D_{1n}^{L} \\ D_{21}^{L} & -d_{21} - \sum_{j=1}^{n} D_{j2}^{L} & \cdots & D_{2n}^{L} \\ \vdots & \vdots & \ddots & \vdots \\ D_{n1}^{L} & D_{n2}^{L} & \cdots & -d_{n1} - \sum_{j=1}^{n} D_{jn}^{L} \end{bmatrix}.$$

Integrating system (3.2.10) for $t \in [\xi, \xi + \tau_1]$ yields

$$U^{\xi}(t) = e^{B(t-\xi)}\left(U_1^{\xi}(\xi), U_2^{\xi}(\xi), \cdots, U_n^{\xi}(\xi)\right)^T, \quad \xi \le t \le \xi + \tau_1. \tag{3.2.11}$$

From the definition of $U_i^{\xi}(t)$ and equalities (3.2.5), it follows that

$$\begin{aligned} U^{\xi}(t) =& e^{B(t-\xi)}\left(l_1(\xi, 0), l_2(\xi, 0), \cdots, l_n(\xi, 0)\right)^T \\ =& e^{B(t-\xi)}\left(a_1 c_{11} I_{1,2}(\xi)\frac{S_{1,1}(\xi)}{N_1(\xi)}, \cdots, a_n c_{n1} I_{n2}(\xi)\frac{S_{n1}(\xi)}{N_n(\xi)}, \right)^T, \quad \xi \le t \le \xi + \tau_1. \end{aligned} \tag{3.2.12}$$

For $t \ge \tau_1$, letting $l(t, \tau_1) = (l_1(t, \tau_1), l_2(t, \tau_1, \cdots, l_n(t, \tau_1)))^T$. Then

$$\begin{aligned} l(t, \tau_1) =& U^{t-\tau_1}(t) \\ =& e^{B\tau_1}\left(a_1 c_{11} I_{1,2}(t-\tau_1)\frac{s_{1,1}(t-\tau_1)}{N_1(t-\tau_1)}, \cdots, a_n c_{n1} I_{n2}(t-\tau_1)\frac{S_{n1}(t-\tau_1)}{N_n(t-\tau_1)}\right)^T. \end{aligned} \tag{3.2.13}$$

Denoting the matrix $e^{B\tau_1}$ by $P = [p_{ij}(\tau_1)]_{n\times n}$, (3.2.13) becomes

$$l_i(t,\tau_1) = \sum_{j=1}^{n} p_{ij}(\tau_1) a_j c_{j1} I_{j2}(t-\tau_1) \frac{S_{j1}(t-\tau_1)}{N_j(t-\tau_1)}. \tag{3.2.14}$$

Since our focus is not on demography of humans, we will adopt the simplest demographic equation $N_i'(t) = K_{i1} - d_{i1}N_i(t)$ for patch i ($i = 1, 2, \cdots, n$), which leads to the following equation for the susceptible human population in patch i:

$$\frac{\mathrm{d}S_{i1}(t)}{\mathrm{d}t} = K_{i1} - d_{i1}S_{i1}(t) + \gamma_i I_{i1}(t) - a_i c_{i1} I_{i2}(t)\frac{S_{i1}(t)}{N_i(t)} + \sum_{j=1}^{n} D_{ij}^S S_{j1}(t) - \sum_{j=1}^{n} D_{ji}^S S_{i1}(t). \tag{3.2.15}$$

Substituting equalities (3.2.14) back into the L_{i1} and I_{i1} equations in systems (3.2.7) and (3.2.8), and pulling together the resulting equations with (3.2.1) and (3.2.15), we know that the sub-populations in all compartments for $t \geq \tau_1$ are described by the following

system of delay differential equations (DDEs):

$$
\begin{cases}
\dfrac{\mathrm{d}S_{i1}(t)}{\mathrm{d}t} = K_{i1} - d_{i1}S_{i1}(t) + \gamma_i I_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^S_{ij}S_{j1}(t) - \sum_{j=1}^{n} D^S_{ji}S_{i1}(t) \\
\qquad\qquad - a_i c_{i1} I_{i2}(t)\dfrac{S_{i1}(t)}{N_i(t)}, \\
\dfrac{\mathrm{d}L_{i1}(t)}{\mathrm{d}t} = a_i c_{i1} I_{i2}(t)\dfrac{S_{i1}(t)}{N_i(t)} - d_{i1}L_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^L_{ij}L_{j1}(t) - \sum_{j=1}^{n} D^L_{ji}L_{i1}(t) \\
\qquad - \displaystyle\sum_{j=1}^{n} p_{ji}(\tau_1) a_i c_{i1} I_{i2}(t-\tau_1)\dfrac{S_{i1}(t-\tau_1)}{N_i(t-\tau_1)}, \\
\dfrac{\mathrm{d}I_{i1}(t)}{\mathrm{d}t} = -(d_{i1} + \gamma_i + \mu_i)I_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^I_{ij}I_{j1}(t) - \sum_{j=1}^{n} D^I_{ji}I_{i1}(t) \\
\qquad + \displaystyle\sum_{j=1}^{n} p_{ij}(\tau_1) a_j c_{j1} I_{j2}(t-\tau_1)\dfrac{S_{j1}(t-\tau_1)}{N_j(t-\tau_1)}, \\
\dfrac{\mathrm{d}S_{i2}(t)}{\mathrm{d}t} = d_{i2}M_i - d_{i2}S_{i2}(t) - a_i c_{i2} S_{i2}(t)\dfrac{I_{i1}(t)}{N_i(t)}, \\
\dfrac{\mathrm{d}L_{i2}(t)}{\mathrm{d}t} = -d_{i2}L_{i2}(t) + a_i c_{i2} S_{i2}(t)\dfrac{I_{i1}(t)}{N_i(t)} - a_i c_{i2} S_{i2}(t-\tau_2)\dfrac{I_{i1}(t-\tau_2)}{N_i(t-\tau_2)} e^{-d_{i2}\tau_2}, \\
\dfrac{\mathrm{d}I_{i2}(t)}{\mathrm{d}t} = -d_{i2}I_{i2}(t) + a_i c_{i2} S_{i2}(t-\tau_2)\dfrac{I_{i1}(t-\tau_2)}{N_i(t-\tau_2)} e^{-d_{i2}\tau_2},
\end{cases}
\tag{3.2.16}
$$

with $N_i = S_{i1} + L_{i1} + I_{i1}$ and $M_i = S_{i2} + L_{i2} + I_{i2}$, for $i = 1, 2, \cdots, n$. In the I_{i1} equation, we find that the recruitment consists of two parts: one directly results from travel of infectious individuals, while the other is a result of mobility of latent individuals with $p_{ij}(\tau_1)$ accounting for the probability that a host infected in patch j can survive during the latent period $[0, \tau_1]$, and has moved to patch i at the end of the latent period. For $n = 2$, the transmission dynamics described by system (3.2.16) can be visualized by the transmission diagram in Figure 3.1.

For $t \in [0, \tau_2)$, no new infected humans and mosquitoes will become infectious and

hence, the disease dynamics is governed by the following system of ODEs:

$$\begin{cases} \dfrac{\mathrm{d}S_{i1}(t)}{\mathrm{d}t} = K_{i1} - d_{i1}S_{i1}(t) + \gamma_i I_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^S_{ij}S_{j1}(t) - \sum_{j=1}^{n} D^S_{ji}S_{i1}(t) \\ \qquad\qquad - a_i c_{i1} I_{i2}(t)\dfrac{S_{i1}(t)}{N_i(t)}, \\ \dfrac{\mathrm{d}L_{i1}(t)}{\mathrm{d}t} = a_i c_{i1} I_{i2}(t)\dfrac{S_{i1}(t)}{N_i(t)} - d_{i1}L_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^L_{ij}L_{j1}(t) - \sum_{j=1}^{n} D^L_{ji}L_{i1}(t), \\ \dfrac{\mathrm{d}I_{i1}(t)}{\mathrm{d}t} = -(d_{i1} + \gamma_i + \mu_i)I_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^I_{ij}I_{j1}(t) - \sum_{j=1}^{n} D^I_{ji}I_{i1}(t), \\ \dfrac{\mathrm{d}S_{i2}(t)}{\mathrm{d}t} = d_{i2}M_i - d_{i2}S_{i2}(t) - a_i c_{i2} S_{i2}(t)\dfrac{I_{i1}(t)}{N_i(t)}, \\ \dfrac{\mathrm{d}L_{i2}(t)}{\mathrm{d}t} = -d_{i2}L_{i2}(t) + a_i c_{i2} S_{i2}(t)\dfrac{I_{i1}(t)}{N_i(t)}, \\ \dfrac{\mathrm{d}I_{i2}(t)}{\mathrm{d}t} = -d_{i2}I_{i2}(t), \end{cases} \tag{3.2.17}$$

while for $t \in [\tau_2, \tau_1)$, the disease dynamics is given by another system of DDEs:

$$\begin{cases} \dfrac{\mathrm{d}S_{i1}(t)}{\mathrm{d}t} = K_{i1} - d_{i1}S_{i1}(t) + \gamma_i I_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^S_{ij}S_{j1}(t) - \sum_{j=1}^{n} D^S_{ji}S_{i1}(t) \\ \qquad\qquad - a_i c_{i1} I_{i2}(t)\dfrac{S_{i1}(t)}{N_i(t)}, \\ \dfrac{\mathrm{d}L_{i1}(t)}{\mathrm{d}t} = a_i c_{i1} I_{i2}(t)\dfrac{S_{i1}(t)}{N_i(t)} - d_{i1}L_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^L_{ij}L_{j1}(t) - \sum_{j=1}^{n} D^L_{ji}L_{i1}(t), \\ \dfrac{\mathrm{d}I_{i1}(t)}{\mathrm{d}t} = -(d_{i1} + \gamma_i + \mu_i)I_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^I_{ij}I_{j1}(t) - \sum_{j=1}^{n} D^I_{ji}I_{i1}(t), \\ \dfrac{\mathrm{d}S_{i2}(t)}{\mathrm{d}t} = d_{i2}M_i - d_{i2}S_{i2}(t) - a_i c_{i2} S_{i2}(t)\dfrac{I_{i1}(t)}{N_i(t)}, \\ \dfrac{\mathrm{d}L_{i2}(t)}{\mathrm{d}t} = -d_{i2}L_{i2}(t) + a_i c_{i2} S_{i2}(t)\dfrac{I_{i1}(t)}{N_i(t)} - a_i c_{i2} S_{i2}(t-\tau_2)\dfrac{I_{i1}(t-\tau_2)}{N_i(t-\tau_2)}e^{-d_{i2}\tau_2}, \\ \dfrac{\mathrm{d}I_{i2}(t)}{\mathrm{d}t} = -d_{i2}I_{i2}(t) + a_i c_{i2} S_{i2}(t-\tau_2)\dfrac{I_{i1}(t-\tau_2)}{N_i(t-\tau_2)}e^{-d_{i2}\tau_2}, \end{cases} \tag{3.2.18}$$

Obviously, the long term disease dynamics are represented by the system of DDEs (3.2.16) which will be, therefore, the main focus of our analysis in the subsequent

sections.

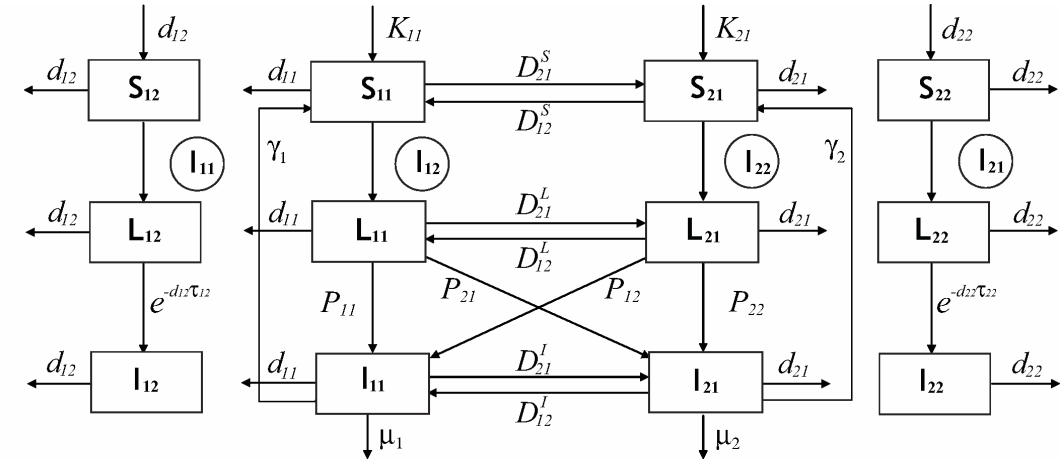

Figure 3.1: Transmission diagram for $t \geq \tau_1$ when there are only two patches.

It is natural to assume that the dispersal matrix $D^S = (D_{ij}^S)$ is irreducible, otherwise the patchy environment can be further split into smaller irreducible environments isolated from each other. As the behavior of individuals in latent period generally remains the same as that of susceptible individuals, we assume that $D^L = (D_{ij}^L)$ is also irreducible. Without loss of generality and for simplicity, we assume $D_{ij}^S \neq 0$, $D_{ij}^L \neq 0$, $D_{ij}^I \neq 0$ in the rest of the chapter.

3.3 Well-posedness

Realistically, initial values for all variables in the model should be non-negative:

$$S_{ij}(0) \geq 0, I_{ij}(t) \geq 0, L_{i1}(0) \geq 0, \quad \text{for } i = 1, 2, ..., n; j = 1, 2. \tag{3.3.1}$$

With such a set of initial values given, one can solve (3.2.17) to get a unique solution for $t \in [0, \tau_2]$ which can be easily shown to be non-negative in $[0, \tau_2]$. Using the values

of this solution in the inteval $[0, \tau_2]$, one can further solve the ODE system (3.2.17) to get a unique and non-negative solution defined for $t \in [\tau_2, \tau_1]$. The combination of these two solutions gives the initial function for the DDE system (3.2.16) on $[0, \tau_1] = [0, \tau_2] \cup [\tau_2, \tau_1]$. This non-negative initial function, by the fundamental theory of DDEs, will result in a unique solution of system (3.2.16) for $t \geq \tau_1$ which is also non-negative on the maximal interval of existence $[\tau_1, t_{max})$. Details of the theory validating the above argument is referred to, e.g., [7, 16]. For similar arguments, but for another non-vector-borne disease model with non-local infections on a patch environment, see [8].

Next, we show that the solutions of system (3.2.16) remain bounded. Firstly the boundedness of S_{i2}, L_{i2} and I_{i2} is obvious since $0 \leq S_{i2} \leq M_i$, $0 \leq L_{i2} \leq M_i$, $0 \leq I_{i2} \leq M_i$ and M_i is a constant. To prove the boundedness of S_{i1}, L_{i1} and I_{i1}, it suffices to show that N_i is bounded. Let $N(t)$ be the total population of humans in the n patches,i.e.,

$$N(t) = \sum_{i=1}^{n} N_i = \sum_{i=1}^{n} S_{i1}(t) + \sum_{i=1}^{n} L_{i1}(t) + \sum_{i=1}^{n} I_{i1}(t).$$

Then,

$$\begin{aligned} \dot{N}(t) &= \sum_{i=1}^{n} \dot{S}_{i1}(t) + \sum_{i=1}^{n} \dot{L}_{i1}(t) + \sum_{i=1}^{n} \dot{I}_{i1}(t) \\ &= \sum_{i=1}^{n} K_{i1} - \sum_{i=1}^{n} d_{i1} N_i(t) - \sum_{i=1}^{n} \mu_i I_{i1}(t) \\ &\leq \sum_{i=1}^{n} K_{i1} - \sum_{i=1}^{n} \underline{d}_1 N_i(t) \\ &= \bar{K}_1 - \underline{d}_1 N(t), \end{aligned} \tag{3.3.2}$$

where $\underline{d}_1 = \min_{1 \leq i \leq n}(d_{i1})$ and $\bar{K}_1 = \sum_{j=1}^{n} K_{i1}$. By the comparison theorem, we show that $N(t)$ is bounded with $\limsup_{t \to \infty} N(t) \leq \bar{K}_1 / \underline{d}_1$. Consequently, $N_i(t)$, $i = 1, 2, \cdots, n$ are also bounded, and so are S_{i1}, L_{i1} and I_{i1} by the relations $0 \leq S_{i1} \leq N_i$, $0 \leq L_{i1} \leq N_i$, $0 \leq I_{i1} \leq N_i$.

The prior boundedness of solutions to system (3.2.16) implies that all solutions with

initial conditions satisfying initial condition (3.3.1) exist globally, that is, exist for all $t \in [\tau, \infty)$ (see [7]).

Summarizing the above, we have established the following theorem.

Theorem 3.3.1 *For any given initial values satisfying initial condtion* (3.3.1)*, the model system consisting of* (3.2.16)-(3.2.18) *has a unique solution which is non-negative and bounded for all* $t \geq 0$*.*

As we have seen above, systems (3.2.18) and (3.2.17) only describe the disease dynamics on the transient intervals $[0, \tau]$ and $[\tau_2, \tau_1]$ respectively, and the long term disease dynamics is described by (3.2.16). In the rest of this chapter, we only need to investigate the dynamics of (3.2.16).

3.4 Disease free equilibrium and basic reproduction number

A disease free equilibrium of model (3.2.16) is the equilibrium with the infection related components being zeros. That is, such an equilibrium has the form

$$E_0 = (\bar{S}^0_{11}, \cdots, \bar{S}^0_{n1}, \bar{S}^0_{12}, \cdots, \bar{S}^0_{n2}, \underbrace{0, \cdots, 0}_{4n}).$$

Denote $\bar{S}^0_1 = (\bar{S}^0_{11}, \cdots, \bar{S}^0_{n1})$ and $\bar{S}^0_2 = (\bar{S}^0_{12}, \cdots, \bar{S}^0_{n2})$. It is immediately noticed that $\bar{S}^0_2 = (M_1, \cdots, M_n)$ and $\bar{S}^0_1$ satisfies the following linear algebraic system

$$Q\bar{S}^0_1 = K, \tag{3.4.1}$$

where $K = (K_{11}, \cdots, K_{n1})^T$ and

$$Q = \begin{pmatrix} d_{11} + \sum_{j=1}^{n} D^S_{j1} & -D^S_{12} & \cdots & -D^S_{1n} \\ -D^S_{21} & d_{21} + \sum_{j=1}^{n} D^S_{j2} & \cdots & -D^S_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ -D^S_{n1} & -D^S_{n2} & \cdots & d_{n1} + \sum_{j=1}^{n} D^S_{jn} \end{pmatrix}.$$

The irreducibility of D^S ensures that Q is also irreducible. Since Q has non-positive off-diagonal entries and positive column sums, Q is a non-singular M-matrix, and is thus invertible with $Q^{-1} > 0$. This shows that system (3.4.1) has a unique positive solution $\bar{S}^1_0 = Q^{-1}K > 0$, implying that system (3.2.16) has an unique disease free equilibrium E_0.

The basic reproduction number of a disease model is closely related the the stability of the disease free equilibrium. To proceed further, we linearize system (3.2.16), noting that the L_{i1} and L_{i2} equations decouple from the rest in the linearized system, so we drop the L_{i1} and L_{i2} equations, leading to the following system:

$$\begin{cases} \dfrac{\mathrm{d}}{\mathrm{d}t}S_{i1}(t) = -d_{i1}S_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^S_{ij}S_{j1}(t) - \sum_{j=1}^{n} D^S_{ji}S_{i1}(t) + \gamma_i I_{i1}(t) - a_i c_{i1} I_{i2}(t), \\ \dfrac{\mathrm{d}I_{i1}(t)}{\mathrm{d}t} = -(d_{i1} + \gamma_i + \mu_i)I_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^I_{ij}I_{j1}(t) - \sum_{j=1}^{n} D^I_{ji}I_{i1}(t) \\ \qquad\qquad + \displaystyle\sum_{j=1}^{n} p_{ij}(\tau_1)a_j c_{j1} I_{j2}(t-\tau_1), \\ \dfrac{\mathrm{d}}{\mathrm{d}t}S_{i2}(t) = -d_{i2}S_{i2}(t) - a_i c_{i2} I_{i1}(t)\dfrac{M_i}{\bar{S}^0_{i1}}, \\ \dfrac{\mathrm{d}I_{i2}(t)}{\mathrm{d}t} = -d_{i2}I_{i2}(t) + a_i c_{i2}\dfrac{M_i}{\bar{S}^0_{i1}} e^{-d_{i2}\tau_2} I_{i1}(t-\tau_2). \end{cases} \tag{3.4.2}$$

Let

$$\mathbf{F}_1 = \begin{pmatrix} 0 & F_1 \\ \\ 0 & 0 \end{pmatrix}, \quad \mathbf{F}_2 = \begin{pmatrix} 0 & 0 \\ \\ F_2 & 0 \end{pmatrix}, \quad \mathbf{V} = \begin{pmatrix} V_1 & 0 \\ \\ 0 & V_2 \end{pmatrix},$$

where the $n \times n$ matrices F_1, F_2, V_1 and V_2 are defined as below:

$$\begin{aligned}
&(F_1)_{ij} = p_{ij}(\tau_1) a_j c_{j1}, \quad i, j = 1, \cdots, n; \\
&F_2 = diag\left(a_1 c_{12} e^{-d_{12}\tau_2} \frac{M_1}{\bar{S}^0_{11}}, \cdots, a_n c_{n2} e^{-d_{n2}\tau_2} \frac{M_n}{\bar{S}^0_{n1}}\right), \\
&(V_1)_{ij} = \begin{cases} d_{i1} + \gamma_i + \mu_i + \sum_{k=1}^{n} D^I_{ki}, & \text{for} \quad j = i, \\ \\ -D^I_{ij} \quad \text{for} \quad j \neq i. \end{cases} \\
&V_2 = diag\,(d_{12}, d_{22}, \cdots, d_{n2}).
\end{aligned}$$

Denote $I_1(t) = (I_{11}, \cdots, I_{n1})$ and $I_2 = (I_{12}, \cdots, I_{n2})$ and let $I(t) = (I_1(t), I_2(t))$. Obviously, the equations in system (3.4.2) containing the components of $I(t)$ actually decouple from the rest, giving a subsystem containing $I(t)$ only:

$$\frac{\mathrm{d}}{\mathrm{d}t} I(t) = \mathbf{F}_1 I(t - \tau_1) + \mathbf{F}_2 I(t - \tau_2) - \mathbf{V} I(t). \tag{3.4.3}$$

Since system (3.2.16) (hence (3.4.3)) is not a system of ODEs, the recipe for calculating the spectral radius of the next generation *matrix* given in [20] cannot be directly applied to define the basic reproduction number for this model. Below, we will use the more general notion of the next generation *operator* which provides an analogue of the next generation *matrix* for structured models described by infinite dimensional systems, including system (3.2.16). We now follow the approach in [6, 17] to define the basic reproduction number $\mathcal{R}_0$ for our model. To this end, we need to identify the next generation operator for our model.

Assume that the populations of humans and female mosquitoes are settled at E_0 and there is no infectious individual before the time $t = 0$. Suppose that at $t = 0$, there are some infectious individuals introduced in this patchy environment. Then near E_0, the infectious populations $I_1(t)$ and $I_2(t)$ are governed by system (3.4.3). Note that the first two terms in system (3.4.3) track new infections while the last term takes care of evolution with respect to time, tracking the survival of the infected individuals.

Define a positive linear operator $\mathcal{F} : R^n_+ \times R^n_+ \to R^n_+ \times R^n_+$ by

$$\mathcal{F}(\sigma) = (F_1\sigma_2, F_2\sigma_1) \quad \text{for} \quad \sigma = (\sigma_1, \sigma_2) \in R^n_+ \times R^n_+.$$

Let $U(t) = (U_1(t), U_2(t))$ be the semi-group generated by

$$\frac{\mathrm{d}}{\mathrm{d}t} I(t) = -\mathbf{V} I(t),$$

that is

$$U(t)\sigma = (e^{-V_1 t}\sigma_1, e^{-V_2 t}\sigma_2), \quad \text{for} \quad \sigma = (\sigma_1, \sigma_2) \in R^n_+ \times R^n_+.$$

Now, let the initial distribution $I_0 = (I_0^1, I_0^2)$ where $I_0^1 = (I_{11}(0), \cdots, I_{n1}(0))$ and $I_0^2 = (I_{12}(0), \cdots, I_{n2}(0))$ be given. Due to the latency within humans, the production of new infectious humans will not occur before $t = \tau_1$, and hence, the number of the cumulative new infectious human beings is given by

$$\int_{\tau_1}^{\infty} F_1[U_2(t - \tau_1) I_0^2] \, \mathrm{d}t = \int_0^{\infty} F_1[U_2(t) I_0^2] \, \mathrm{d}t. \tag{3.4.4}$$

Similarly, new infections of female mosquitoes will not happen for $t < \tau_2$ and the number of the cumulative new infectious female mosquitoes is

$$\int_{\tau_2}^{\infty} F_2[U_1(t - \tau_2) I_0^1] \, \mathrm{d}t = \int_0^{\infty} F_2[U_1(t) I_0^1] \, \mathrm{d}t. \tag{3.4.5}$$

From equations (3.4.4) and (3.4.5), the distribution of all new infections caused by the initial distribution I_0 is

$$\int_0^\infty (F_1[U_2(t)I_0^2],\ F_2[U_1(t)I_0^1])\ \mathrm{d}t = \int_0^\infty \mathcal{F}U(t)I_0\ \mathrm{d}t.$$

This identifies the next generation operator $\mathcal{T}$ of the model:

$$\mathcal{T}(\sigma) := \int_0^\infty \mathcal{F}[U(t)\sigma]\,\mathrm{d}t, \quad \text{for} \quad \sigma = (\sigma_1, \sigma_2) \in R_+^n \times R_+^n. \tag{3.4.6}$$

The basic reproduction number is then defined as the spectral radius of $\mathcal{T}$: $\mathcal{R}_0 = \rho(\mathcal{T})$ (see, e.g. , [6, 17]). Note that (3.4.6) can be rewritten as

$$\mathcal{T}(\sigma) = \int_0^\infty \mathbf{F}e^{-\mathbf{V}t}\sigma\,\mathrm{d}t = (\int_0^\infty \mathbf{F}e^{-\mathbf{V}t}\,\mathrm{d}t)\sigma \quad \text{for} \quad \sigma = (\sigma_1, \sigma_2) \in R_+^n \times R_+^n, \tag{3.4.7}$$

where $\mathbf{F} = \mathbf{F}_1 + \mathbf{F}_2$. Thus, $\mathcal{R}_0$ can be further expressed as

$$\mathcal{R}_0 := \rho(\mathcal{T}) = \rho(\int_0^\infty \mathbf{F}e^{\text{-}\mathbf{V}t}\,\mathrm{d}t) = \rho(\mathbf{F}\int_0^\infty e^{\text{-}\mathbf{V}t}\,\mathrm{d}t) = \rho(\mathbf{F}\mathbf{V}^{-1}). \tag{3.4.8}$$

Now we consider the stability of E_0. It is easy to calculate the characteristic equation of system (3.4.2) as

$$|zE_{n\times n} + Q| \cdot |zE_{n\times n} + D_2| \cdot \left|(zE_{n\times n} + V_1)(zE_{n\times n} + V_2) - F_2e^{-z\tau_2}F_1e^{-z\tau_1}\right| = 0, \tag{3.4.9}$$

where $D_2 = diag\,(d_{12}, \cdots, d_{n2})$. The other matrices in (3.4.9) have been defined before. Let

$$\Delta_1(z) = |zE_{2n\times 2n} + Q|, \quad \Delta_2(z) = |zE_{2n\times 2n} + D_2|,$$
$$\Delta_3(z, \tau_1, \tau_2) = \left|(zE_{n\times n} + V_1)(zE_{n\times n} + V_2) - F_2e^{-z\tau_2}F_1e^{-z\tau_1}\right|.$$

Obviously $\Delta_2(z) = 0$ has roots $-d_{i2} < 0,\ i = 1, 2, \cdots, n$. Note that for the matrix

$Q = [Q_{ij}]_{n\times n}$,

$$\sum_{j\neq i}\left|-Q_{ji}\right| = \sum_{j=1}^{n} D^S_{ji} < d_i + \sum_{j=1}^{n} D^S_{ji} = \left|-d_i - \sum_{j=1}^{n} D^S_{ji}\right| = \left|-Q_{ii}\right|. \tag{3.4.10}$$

According to the Gershgorin Circle Theorem [21], any root z of $\Delta_1(z) = 0$ satisfies

$$|z + Q_{ii}| \leq \sum_{j\neq i}\left|-Q_{ji}\right| < |-Q_{ii}| = |Q_{ii}|$$

and hence, must have negative real part. Therefore, the stability of E_0 is fully determined by the distribution of the roots of the equation

$$\Delta_3(z, \tau_1, \tau_2) = 0 \tag{3.4.11}$$

which is nothing but the characteristic equation of (3.4.3). Noting that $\mathbf{F}_1$, $\mathbf{F}_2$ and $-\mathbf{V}$ all have non-negative off-diagonal entries, (3.4.3) is a monotone system, and hence the stability of the trivial solution is equivalent to that of the corresponding ODE system obtained by dropping the two discrete delays (see e.g., [15, 16]):

$$\frac{\mathrm{d}}{\mathrm{d}t}I(t) = (\mathbf{F}_1 + \mathbf{F}_2 - \mathbf{V})I(t) = (\mathbf{F} - \mathbf{V})I(t). \tag{3.4.12}$$

Then

$$\max\{Re(z) : \Delta_3(z, \tau_1, \tau_2) = 0\} < 0\ (>0) \quad \text{if and only if} \quad s(\mathbf{F} - \mathbf{V}) < 0\ (>0),$$

where $s(\mathbf{F} - \mathbf{V})$ is the stability modulus of $\mathbf{F} - \mathbf{V}$ defined as the maximal real part of all eigenvalues of the matrix $\mathbf{F} - \mathbf{V}$. By Theorem 2 in [20], $s(\mathbf{F} - \mathbf{V}) < 0\ (>0)$ is equivalent to $\rho(\mathbf{F}\mathbf{V}^{-1}) < 1\ (>1)$. Hence, E_0 is asymptotically stable when $\mathcal{R}_0 < 1$ and unstable when $\mathcal{R}_0 < 1$.

Summarizing the above, we have proved the following theorem.

Theorem 3.4.1 *If $\mathcal{R}_0 = \rho(\boldsymbol{F}\boldsymbol{V}^{-1}) < 1$, then E_0 is asymptotically stable, when $\mathcal{R}_0 > 1$, E_0 is unstable.*

3.5 Disease persistence and endemic equilibrium

We have seen that when $\mathcal{R}_0 > 1$, the DFE is unstable. In this section we will show that in this case, the disease will persist; and moreover, there exists an endemic equilibrium.

Note that in systems (3.2.16)-(3.2.18), L_{i2} actually decouples from the rest. We only need to consider the following subsystem as a result of omitting the $L'_{i2}(t)$ equations in (3.2.17), (3.2.18) and (3.2.16):

$$\begin{cases} \dfrac{\mathrm{d}S_{i1}(t)}{\mathrm{d}t} = K_{i1} - d_{i1}S_{i1}(t) + \gamma_i I_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^S_{ij}S_{j1}(t) - \sum_{j=1}^{n} D^S_{ji}S_{i1}(t) \\ \qquad\qquad - a_i c_{i1} I_{i2}(t)\dfrac{S_{i1}(t)}{N_i(t)}, \\ \dfrac{\mathrm{d}L_{i1}(t)}{\mathrm{d}t} = a_i c_{i1} I_{i2}(t)\dfrac{S_{i1}(t)}{N_i(t)} - d_{i1}L_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^L_{ij}L_{j1}(t) - \sum_{j=1}^{n} D^L_{ji}L_{i1}(t), \\ \dfrac{\mathrm{d}I_{i1}(t)}{\mathrm{d}t} = -(d_{i1} + \gamma_i + \mu_i)I_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^I_{ij}I_{j1}(t) - \sum_{j=1}^{n} D^I_{ji}I_{i1}(t), \\ \dfrac{\mathrm{d}S_{i2}(t)}{\mathrm{d}t} = d_{i2}M_i - d_{i2}S_{i2}(t) - a_i c_{i2} S_{i2}(t)\dfrac{I_{i1}(t)}{N_i(t)}, \\ \dfrac{\mathrm{d}I_{i2}(t)}{\mathrm{d}t} = -d_{i2}I_{i2}(t), \end{cases} \qquad t \in [0, \tau_2), \tag{3.5.1}$$

$$
\begin{cases}
\dfrac{\mathrm{d}S_{i1}(t)}{\mathrm{d}t} = K_{i1} - d_{i1}S_{i1}(t) + \gamma_i I_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^S_{ij}S_{j1}(t) - \sum_{j=1}^{n} D^S_{ji}S_{i1}(t) \\
\qquad\qquad - a_i c_{i1} I_{i2}(t)\dfrac{S_{i1}(t)}{N_i(t)}, \\
\dfrac{\mathrm{d}L_{i1}(t)}{\mathrm{d}t} = a_i c_{i1} I_{i2}(t)\dfrac{S_{i1}(t)}{N_i(t)} - d_{i1}L_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^L_{ij}L_{j1}(t) - \sum_{j=1}^{n} D^L_{ji}L_{i1}(t), \\
\dfrac{\mathrm{d}I_{i1}(t)}{\mathrm{d}t} = -(d_{i1} + \gamma_i + \mu_i)I_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^I_{ij}I_{j1}(t) - \sum_{j=1}^{n} D^I_{ji}I_{i1}(t), \\
\dfrac{\mathrm{d}S_{i2}(t)}{\mathrm{d}t} = d_{i2}M_i - d_{i2}S_{i2}(t) - a_i c_{i2} S_{i2}(t)\dfrac{I_{i1}(t)}{N_i(t)}, \\
\dfrac{\mathrm{d}I_{i2}(t)}{\mathrm{d}t} = -d_{i2}I_{i2}(t) + a_i c_{i2} S_{i2}(t-\tau_2)\dfrac{I_{i1}(t-\tau_2)}{N_i(t-\tau_2)}\, e^{-d_{i2}\tau_2},
\end{cases}
\qquad t \in [\tau_2, \tau_1), \tag{3.5.2}
$$

and

$$
\begin{cases}
\dfrac{\mathrm{d}S_{i1}(t)}{\mathrm{d}t} = K_{i1} - d_{i1}S_{i1}(t) + \gamma_i I_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^S_{ij}S_{j1}(t) - \sum_{j=1}^{n} D^S_{ji}S_{i1}(t) \\
\qquad\qquad - a_i c_{i1} I_{i2}(t)\dfrac{S_{i1}(t)}{N_i(t)}, \\
\dfrac{\mathrm{d}L_{i1}(t)}{\mathrm{d}t} = a_i c_{i1} I_{i2}(t)\dfrac{S_{i1}(t)}{N_i(t)} - d_{i1}L_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^L_{ij}L_{j1}(t) - \sum_{j=1}^{n} D^L_{ji}L_{i1}(t) \\
\qquad - \displaystyle\sum_{j=1}^{n} p_{ji}(\tau_1) a_i c_{i1} I_{i2}(t-\tau_1)\dfrac{S_{i1}(t-\tau_1)}{N_i(t-\tau_1)}, \\
\dfrac{\mathrm{d}I_{i1}(t)}{\mathrm{d}t} = -(d_{i1} + \gamma_i + \mu_i)I_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^I_{ij}I_{j1}(t) - \sum_{j=1}^{n} D^I_{ji}I_{i1}(t) \\
\qquad + \displaystyle\sum_{j=1}^{n} p_{ij}(\tau_1) a_j c_{j1} I_{j2}(t-\tau_1)\dfrac{S_{j1}(t-\tau_1)}{N_j(t-\tau_1)}, \\
\dfrac{\mathrm{d}S_{i2}(t)}{\mathrm{d}t} = d_{i2}M_i - d_{i2}S_{i2}(t) - a_i c_{i2} S_{i2}(t)\dfrac{I_{i1}(t)}{N_i(t)}, \\
\dfrac{\mathrm{d}I_{i2}(t)}{\mathrm{d}t} = -d_{i2}I_{i2}(t) + a_i c_{i2} S_{i2}(t-\tau_2)\dfrac{I_{i1}(t-\tau_2)}{N_i(t-\tau_2)}\, e^{-d_{i2}\tau_2},
\end{cases}
\qquad t \geq \tau_1. \tag{3.5.3}
$$

The break-down of the model into (3.5.1)-(3.5.3) starting with the ODE system

(3.5.1) seems to suggest that it is more convenient to establish persistence in $\mathfrak{R}^{5n}$. Consider the scenario in which there is no infectious individual in the patchy environment before $t = 0$. At $t = 0$, let $(S_1(0), S_2(0), L_1(0), I_1(0), I_2(0)) = (S_1^0, S_2^0, L_1^0, I_1^0, I_2^0)$ where $S_j^0 = (S_{1j}^0, \cdots, S_{nj}^0) \in \mathfrak{R}_+^n$, $L_1^0 = (L_{11}^0, \cdots, S_{n1}^0) \in \mathfrak{R}_+^n$ and $I_j^0 = (I_{1j}^0, \cdots, I_{nj}^0) \in \mathfrak{R}_+^n$ for $j = 1, 2$. With this initial condition, by Theorem 3.3.1 , there is a unique solution to the model (3.5.1)-(3.5.3), denoted by

$$\Big(S_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0),\ S_2(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0),\ L_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0),$$
$$I_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0),\ I_2(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0)\Big),$$

which is non-negative and bounded. For convenience of notation, we sometimes omit the initial values when referring to the solution and simply write $(S_1(t), S_2(t), L_1(t), I_1(t), I_2(t))$ if there is no confusion. Then we further have the following observations:

(O1) $S_j(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) \gg 0$ for $j = 1, 2$ and $t > 0$. Here and in the sequel, the notation $\gg$ means that all components are positive.

(O2) If $I_1^0 = 0$ and $I_2^0 = 0$, then $I_{i1}(t) = 0$ and $I_{i2}(t) = 0$ for all $t \geq 0$. This can be shown by applying the constant-variation formula to systems (3.5.1)-(3.5.3) consecutively.

(O3) Assume that either $I_1^0 > 0$ (i.e., $I_1^0 \geq 0$ but $I_1^0 \neq 0$, i.e., at least one component is positive) or $I_2^0 > 0$, meaning that the disease is brought to at least one patch either by humans or mosquitoes at $t = 0$. In this case, by system (3.5.1) we know that $I_1(t) > 0$ or $I_2(t) > 0$ for $t \in [0, \tau_2]$. Moving on to the interval $[\tau_2, \tau_1]$ and by (3.5.2), we further know that $I_1(t) > 0$ or $I_2(t) > 0$ for $t \in [0, \tau_1]$. Finally, for $t > \tau_1$, from system (3.5.3) and by the irreducibility and positivity of the matrix $P = e^{B\tau_1}$, we conclude that $I_1(t) \gg 0$ and $I_2(t) \gg 0$ for $t \geq \tau_1$. Thus components of $I_1(t)$ and $I_2(t)$ are positive for $t \geq \tau_1$.

(O4) If both $I_1^0 > 0$ and $I_2^0 > 0$, then repeating the argument for (O3) concludes that $I_1(t)$ and $I_2(t)$ are positive for $t \geq 0$.

(O5) If both $I_1^0 = 0$ and $I_2^0 = 0$, but $L_1^0 > 0$, then there is as least one component of L_1^0 that is positive. Assume $L_{i1} > 0$, $i \in \{1, 2, ..., n\}$,

$$L_{i1}(0) = \int_0^{\tau_1} l_i(0, a)\, \mathrm{d}a > 0,$$

which implies that $l_i(0, a_0) > 0$ for some $a_0 \in [0, \tau_1]$ and $i \in \{1, 2, ..., n\}$. By formula (3.2.2) for $l(t, a)$ and equation (3.2.13), we can extend $U^{\xi}t$ and $\xi > 0$ by $U^{-a_0}(t)$. Then

$$\begin{aligned} l(\tau_1 - a_0, \tau_1) = &\ U^{-a_0}(\tau_1 - a_0) \\ = &\ e^{B(\tau_1 - a_0)}\, (l_1(0, a_0),\ l_2(0, a_0),\ ...,\ l_n(0, a_0)) \\ > &\ 0. \end{aligned}$$

Further, due to the continuity of $l(t, a)$,

$$I_{i1}(\tau_1 - a_0) = \int_{\tau_1}^{\infty} l_i(\tau_1 - a_0, a)\, \mathrm{d}a > 0, \quad \text{for some } i \in \{1, 2, ..., n\}.$$

Repeating the argument for (O3) with a shifting of initial time, we conclude that $I_1(t)$ and $I_2(t)$ are positive for $t \geq 0$.

Denote

$$\mathbf{X} = \mathfrak{R}_+^{5n} = \{(X_1, X_2, Y_1, Z_1, Z_2) : X_j \in \mathfrak{R}_+^n,\ Y_1 \in \mathfrak{R}_+^n,\ Z_j \in \mathfrak{R}_+^n,\ j = 1, 2\}$$

$$\mathbf{X}_0 = \{(X_1, X_2, Y_1, Z_1, Z_2) \in X : Y_1 \gg 0,\ Z_1 \gg 0,\ Z_2 \gg 0\},$$

and let $\partial\mathbf{X}_0 = \mathbf{X} \setminus \mathbf{X}_0$. Then

$$\partial\mathbf{X}_0 = \{(X_1, X_2, Y_1, Z_1, Z_2) \in \mathbf{X} : Z_{i1} = 0 \text{ or } Z_{i2} = 0 \text{ or } Y_{i1} = 0, \text{ at least for one } i\}.$$

We have seen from the above that both $\mathbf{X}$ and $\mathbf{X}_0$ are positive invariant sets for the solution semi-flow $\Phi(t)$ of model (3.5.1)-(3.5.3). It is obvious that $\partial\mathbf{X}_0$ is relatively closed in $\mathbf{X}$. Theorem 3.1 also confirms that systems (3.5.1)-(3.5.3) are point dissipative in $\mathbf{X}$.

Next, let

$$\Omega_{\partial 1} = \{(S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) \in \mathbf{X} : (S_1(t), S_2(t), L_1(t), I_1(t), I_2(t)) \in \partial\mathbf{X}_0\}.$$

We first prove the following lemma which shows that $\Omega_{\partial 1}$ can also be characterized by the following set

$$\Omega_{\partial 2} = \Big\{(S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) \in X : I_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) = 0,\ I_2(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) = 0,$$
$$L_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) = 0 \text{ for } t \geq 0\Big\}.$$

Lemma 3.5.1 $\Omega_{\partial 2} = \Omega_{\partial 1}$.

Proof. Indeed $\Omega_{\partial 2} \subset \Omega_{\partial 1}$ is obvious, so we only need to show $\Omega_{\partial 1} \subset \Omega_{\partial 2}$. Let $(S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) \in \Omega_{\partial 1}$. We need to show that $I_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) = 0$ and $I_2(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) = 0$ for all $t \geq 0$. Assume the opposite, that is, there exist an i and a $t_0 \geq 0$ such that either (A) $I_{i1}(t_0, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) > 0$; or (B) $I_{i2}(t_0, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) > 0$; or (C) $L_{i1}(t_0, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) > 0$. We show below that each of these three cases will lead to a contradiction.

With respect to (A), we have three cases: (A-1) $t_0 \in [0, \tau_2)$; (A-2) $t_0 \in [\tau_2, \tau_1)$; (A-3)

$t_0 \in [\tau_1, \infty)$. In case (A-1), similar to (O3) above, we know from system (3.5.1) that

$$I_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0)) > 0, \quad I_2(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) \geq 0 \text{ for } t \in [t_0, \tau_2);$$

and from system (3.5.2) that

$$I_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0)) > 0, \quad I_2(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) > 0 \text{ for } t \in [\tau_2, \tau_1);$$

and finally from system (3.5.3) that,

$$I_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0)) \gg 0, \quad I_2(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) \gg 0 \text{ for } t \in [\tau_1, \infty).$$

This implies that for $t \geq \tau_1$,

$$\Big(S_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0),\ S_2(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0),\ I_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0),$$
$$I_2(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0)\Big) \in \mathbf{X}_0,$$

a contradiction to $(S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) \in \Omega_{\partial 1}$. For (A-2), by system (3.5.2), we have

$$I_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0)) > 0, \quad I_2(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) \geq 0 \text{ for } t \in [t_0, \tau_1);$$

and by system (3.5.3),

$$I_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0)) > 0, \quad I_2(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) > 0 \text{ for } t \in [\tau_1, \tau_1 + \tau_2);$$

and finally by system (3.5.3),

$$I_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0)) \gg 0, \quad I_2(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) \gg 0 \text{ for } t \in [\tau_1 + \tau_2, \infty),$$

also a contradiction. For (A-3), by system (3.5.3), we have

$$I_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0)) > 0, \;\; I_2(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) > 0 \;\text{ for }\; t \in [t_0, t_0 + \tau_2);$$

and by system (3.5.3) again,

$$I_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0)) \gg 0, \;\; I_2(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) \gg 0 \;\text{ for }\; t \in [t_0 + \tau_2 + \tau_1, \infty),$$

also a contradiction.

With respect to (B), there are also three cases: (B-1) $t_0 \in [0, \tau_2)$; (B-2) $t_0 \in [\tau_2, \tau_1)$; (B-3) $t_0 \in [\tau_1, \infty)$. By similar arguments, each of these cases will lead to a contradiction as well. Therefore, $I_1(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) = 0$ and $I_2(t, S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) = 0$ for all $t \geq 0$, meaning that $(S_1^0, S_2^0, L_1^0, I_1^0, I_2^0) \in \Omega_{\partial 2}$. This proves $\Omega_{\partial 1} = \Omega_{\partial 1}$.

Upon the case of (C), by the observation of (O5) and similar arguments, we can get $\Omega_{\partial 1} = \Omega_{\partial 1}$.

In conclusion, we have $\Omega_{\partial 1} = \Omega_{\partial 1}$. □

The next lemma establishes weak persistence of the disease in the sense that both I_1 and I_2 persist.

Lemma 3.5.2 *Assume that $\mathcal{R}_0 > 1$. Then there is an $\varepsilon > 0$ such that for any solution of model* (3.5.3) *with initial conditions in X_0 that eventually enters X_0, we have*

$$\limsup_{t \to \infty} \max\{I_{ij}(t), i = 1, \cdots, n; j = 1, 2\} \geq \varepsilon. \tag{3.5.4}$$

Proof. For the sake of contradiction, assume that (3.5.4) is false. Then, there is a

$T_1 > \tau_1$ such that

$$0 < I_{ij}(t) < \varepsilon \text{ for } t \geq T_1, \ i = 1, \cdots, n; j = 1, 2. \tag{3.5.5}$$

It follows from (3.5.3) that

$$\frac{\mathrm{d}S_{i1}}{\mathrm{d}t} \geq (K_{i1} - a_i c_{i1}\varepsilon) - d_{i1}S_{i1} + \sum_{j=1}^{n} D_{ij}^{S} S_{j1} - \sum_{j=1}^{n} D_{ji}^{S} S_{i1}, \ \ t \geq T_1, \tag{3.5.6}$$

and

$$\frac{\mathrm{d}S_{i1}}{\mathrm{d}t} \leq (K_{i1} + \gamma_i\varepsilon) - d_{i1}S_{i1} + \sum_{j=1}^{n} D_{ij}^{S} S_{j1} - \sum_{j=1}^{n} D_{ji}^{S} S_{i1}, \ \ t \geq T_1. \tag{3.5.7}$$

The above suggests the following two comparison systems for $S_1(t)$:

$$\frac{\mathrm{d}Y_{i2}}{\mathrm{d}t} = (K_{i1} - a_i c_{i1}\varepsilon) - d_{i1}S_{i2} + \sum_{j=1}^{n} D_{ij}^{S} Y_{j2} - \sum_{j=1}^{n} D_{ji}^{S} Y_{i2}, \ \ t \geq T_1, \tag{3.5.8}$$

and

$$\frac{\mathrm{d}Y_{i3}}{\mathrm{d}t} = (K_{i1} + \gamma_i\varepsilon) - d_{i1}S_{i1} + \sum_{j=1}^{n} D_{ij}^{S} Y_{j3} - \sum_{j=1}^{n} D_{ji}^{S} Y_{i3}, \ \ t \geq T_1. \tag{3.5.9}$$

The comparison theorem (see, e.g., [16]) shows that

$$Y_2(t) \leq S_1(t) \leq Y_3(t), \ \text{ for } t \geq T_1. \tag{3.5.10}$$

Similarly, from the $L_1(t)$ equation in (3.5.3), we have

$$\frac{\mathrm{d}L_{i1}(t)}{\mathrm{d}t} \leq a_i c_{i1}\varepsilon - d_{i1}L_{i1}(t) + \sum_{j=1}^{n} D_{ij}^{L} L_{j1}(t) - \sum_{j=1}^{n} D_{ji}^{L} L_{i1}(t), \ \ t \geq T_1. \tag{3.5.11}$$

Hence, $L_1(t) \le Y_4(t)$ for large t, where $Y_4(t)$ satisfies

$$\frac{\mathrm{d}Y_{i4}(t)}{\mathrm{d}t} = a_i c_{i1}\varepsilon - d_{i1}Y_{i4}(t) + \sum_{j=1}^{n} D^L_{ij}Y_{j4}(t) - \sum_{j=1}^{n} D^L_{ji}Y_{i4}(t), \ \ t \ge T_1, \tag{3.5.12}$$

leading to

$$0 \le L_1(t) \le Y_4(t), \ \ \text{for} \ \ t \ge T_1, \tag{3.5.13}$$

by the comparison theorem.

Note system (3.5.8) has a globally asymptotically stable equilibrium $\bar{Y}_2(\varepsilon) = Q_s^{-1}K_2(\varepsilon)$ where $K_2(\varepsilon) = (K_{11} + \gamma_1\varepsilon, \cdots, K_{n1} + \gamma_n\varepsilon)$, and system (3.5.9) has a globally asymptotically equilibrium $\bar{Y}_3(\varepsilon) = Q_s^{-1}K_3(\varepsilon)$ where $K_3(\varepsilon) = (K_{11} - a_1c_{11}\varepsilon, \cdots, K_{n1} - a_nc_{n1}\varepsilon)$. Similarly, system (3.5.12) also has a globally asymptotically stable positive equilibrium $\bar{Y}_4(\varepsilon)$. Notice that $Y_2(\varepsilon)$, $Y_3(\varepsilon)$ and $\bar{Y}_4(\varepsilon)$ are all continuous in ε with $\bar{Y}_2(\varepsilon) \to \bar{S}^0_1$, $\bar{Y}_3(\varepsilon) \to \bar{S}^0_1$ and $\bar{Y}_4(\varepsilon) \to 0$ as $\varepsilon \to 0$. Hence, for any given $\eta > 0$, there is an $\varepsilon_0 \le \eta$ such that

$$\bar{S}^0_1 - \hat{\eta} \le \bar{Y}_2(\varepsilon), \ \ \bar{Y}_3(\varepsilon) \le \bar{S}^0_1 + \hat{\eta} \ \ \text{and} \ \ 0 \le \bar{Y}_4(\varepsilon) \le 2\hat{\eta} \ \ \text{for} \ \ \varepsilon \in (0, \varepsilon_0), \tag{3.5.14}$$

where $\hat{\eta}$ denotes the n-dimensional vector with all components equal to η. Thus, for t sufficiently large, we have

$$\bar{S}^0_1 - \hat{\eta} \le S_1(t) \le \bar{S}^0_1 + \hat{\eta} \ \ \text{and} \ \ 0 \le L_1(t) \le \hat{\eta}. \tag{3.5.15}$$

Choose $\eta < \min\{\bar{S}^0_{i1} : i = 1, \cdots, n\}$. Then for t sufficiently large,

$$0 < \bar{S}^0_{i1} - \eta < N_i(t) = S_{i1}(t) + L_{i1}(t) + I_{i1}(t) \le \bar{S}^0_{i1} + 3\eta, \ \ i = 1, \cdots, n. \tag{3.5.16}$$

Next consider the $S_2(t)$ equation in system (3.5.3). By relations (3.5.5), (3.5.15) and (3.5.16), we know that for sufficiently large t,

$$\frac{I_{i1}(t)}{N_i(t)} \leq \frac{\varepsilon}{\bar{S}^0_{i1} - \eta} \leq \frac{\eta}{\bar{S}^0_{i1} - \eta}.$$

This together with system (3.5.3) leads to

$$\frac{\mathrm{d}S_{i2}(t)}{\mathrm{d}t} \geq d_{i2}M_i - d_{i2}S_{i2}(t) - a_i c_{i2}\frac{\eta}{\bar{S}^0_{i1} - \eta}S_{i2}(t). \tag{3.5.17}$$

By an analogous argument, we conclude that for t sufficiently large,

$$S_{i2}(t) \geq \frac{d_i(\bar{S}^0_{i1} - \eta)}{d_i(\bar{S}^0_{i1} - \eta) + a_i c_{i1}\eta}M_i =: \bar{Y}_{i5}(\eta). \tag{3.5.18}$$

Obviously, $Y_{i5}(\eta)$ is continuous in η and $Y_{i5}(0) = M_i$.

We now apply the above estimates to the $I'_{i1}(t)$ and $I_{i2}(t)$ equations in system (3.5.3), yielding the following

$$\begin{cases} \dfrac{\mathrm{d}I_{i1}}{\mathrm{d}t} \geq -(d_{i1} + \gamma_i + \mu_i)I_{i1}(t) + \displaystyle\sum_{j=1}^{n} D^I_{ij}I_{j1}(t) - \sum_{j=1}^{n} D^I_{ji}I_{i1}(t) \\ \qquad\qquad + \displaystyle\sum_{j=1}^{n} p_{ij}(\tau_1)a_j c_{j1}h_j(\eta)I_{j2}(t - \tau_1), \\ \dfrac{\mathrm{d}I_{i2}}{\mathrm{d}t} \geq -d_{i2}I_{i2} + a_i c_{i2}\, e^{-d_{i2}\tau_2}g_i(\eta)I_{i1}(t - \tau_2), \end{cases} \tag{3.5.19}$$

where

$$h_i(\eta) = \frac{\bar{S}^0_{i1} - \eta}{\bar{S}^0_{i1} + 3\eta}, \quad g_i(\eta) = \frac{\bar{Y}_{i5}(\eta)}{\bar{S}^0_{i1} + 3\eta}, \quad i = 1, \cdots, n.$$

Consider the following comparison system obtained from the right-hand side of system (3.5.19):

$$\frac{\mathrm{d}W(t)}{\mathrm{d}t} = \mathbf{G}_1(\eta)W(t - \tau_1) + \mathbf{G}_2(\eta)W(t - \tau_2) - \mathbf{V}W(t) \tag{3.5.20}$$

where the matrix $\mathbf{V}$ is as in Section 3.4, and

$$\mathbf{G}_1(\eta) = \begin{pmatrix} 0 & G_1(\eta) \\ 0 & 0 \end{pmatrix} \quad \mathbf{G}_1(\eta) = \begin{pmatrix} 0 & 0 \\ G_1(\eta) & 0 \end{pmatrix}$$

with

$$G_1(\eta) = \begin{pmatrix} b_{11}(\tau_1)a_1c_{11}h_1(\eta) & b_{12}(\tau_1)a_2c_{21}h_2(\eta) & \cdots & b_{1n}(\tau_1)a_nc_{n1}h_n(\eta) \\ b_{21}(\tau_1)a_1c_{11}h_1(\eta) & b_{22}(\tau_1)a_2c_{21}h_2(\eta) & \cdots & b_{2n}(\tau_1)a_nc_{n1}h_n(\eta) \\ \vdots & \vdots & \ddots & \vdots \\ b_{n1}(\tau_1)a_1c_{11}h_1(\eta) & b_{n2}(\tau_1)a_2c_{21}h_2(\eta) & \cdots & b_{nn}(\tau_1)a_nc_{n1}h_n(\eta) \end{pmatrix},$$

$$G_2(\xi) = \begin{pmatrix} a_1c_{12}e^{-d_{12}\tau_2}g_1(\eta) & 0 & \cdots & 0 \\ 0 & a_2c_{22}e^{-d_{22}\tau_2}g_2(\eta) & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & a_nc_{n2}e^{-d_{n2}\tau_2}g_n(\eta) \end{pmatrix}.$$

This linear delay system is monotone and hence, the stability/instability of the trivial solution is independent of τ_1 and τ_2. Let $\mathbf{G}(\eta) = \mathbf{G}_1(\eta) + \mathbf{G}_2(\eta)$. By the same argument for the stability of system (3.4.12), we know that if $\rho(\mathbf{G}(\eta)\mathbf{V}^{-1}) > 1$, then the trivial solution of system (3.5.20) is unstable, implying that system (3.5.20) has unbounded solutions, since it is a linear system. Note that $h_i(\eta)$ and $g_i(\eta)$ are continuous in η with $h_i(0) = 1$ and $g_i(0) = M_i/\bar{S}^0_{i1}$. This implies that $\mathbf{G}_1(\eta) \to \mathbf{F}_1(\eta)$ and $\mathbf{G}_2(\eta) \to \mathbf{F}_2(\eta)$, and hence, $\mathbf{G}(\eta) \to \mathbf{F}$ as $\eta \to 0$. Now since $\mathcal{R}_0 = \rho(\mathbf{F}\mathbf{V}^{-1}) > 1$, by continuity, we can choose η sufficiently small so that $\rho(\mathbf{G}(\eta)\mathbf{V}^{-1}) > 1$, and therefore, system (3.5.20)

has unbounded solutions; by (3.5.19) and the comparison theorem for delay differential equations (see, e.g., [16]), system (3.5.3) also has unbounded solutions, contradicting the results in Theorem 3.3.1. This contradiction proves the lemma. □

We are now in the position to state and prove the main results in this section.

Theorem 3.5.1 *Assume that $\mathcal{R}_0 > 1$. Then the disease is uniformly persistent in the sense that there exists an $\varepsilon > 0$ such that for any solution of system* (3.5.3) *with initial data in $\boldsymbol{X_0}$ that eventually enters $\boldsymbol{X_0}$, we have*

$$\liminf_{t\to\infty} I_{ij}(t) \geq \varepsilon \ \textit{for} \ \ i = 1, \cdots, n; \ j = 1, 2. \tag{3.5.21}$$

Moreover, there exists a positive (endemic) equilibrium, that is, an equilibrium with all components positive.

Proof. Note that $\bar{S}^0 = (\bar{S}_1^0, \bar{S}_2^0)$ is globally asymptotically stable in $\Re_+^{2n}/\{0\}$ for the system consisting of the S_{i1} and S_{21} equations resulting from setting $I_{i1} = 0$ and $I_{21} = 0$ in (3.2.16). Moreover, by Lemmas 3.5.1-3.5.2, E_0 is an isolated invariant set in $\mathbf{X}$, and the stable manifold of E_0 does not intersect the interior of $\mathbf{X}_0$. Also note that every orbit in Ω_1 converges to E^0 (hence E_0 is an isolated invariant set in $\mathbf{X}$). By Theorem 4.6 in Thieme [19], it follows that the model system (3.5.1)-(3.5.3) is uniformly persistent with respect to $(\mathbf{X}_0, \partial\mathbf{X}_0)$, and hence (3.5.21) holds. Further by Theorem 2.4 in Zhao [24], there is an equilibrium in $\mathbf{X}_0$, denoted by $E^* = (S_1^*, S_2^*, I_1^*, I_2^*)$, where $S_1^* \geq 0$, $S_2^* \geq 0$ and $I_1^* \gg 0$ and $I_2^* \gg 0$. From the I_{i2} equations in system (3.5.3) and the fact that $I_1^* \gg 0$ and $I_2^* \gg 0$, it follows that $S_2^* \gg 0$. So, it remains to show that $S_1^* \gg 0$ as well. Firstly, claim that $S_1^* > 0$, because otherwise,the S_{i1} equations would lead to

$I^*_{i1} = -K_{i1}/\gamma_i < 0$, a contradiction. Rewrite the $S'_{i1}(t)$ equations as

$$S'_1(t) = [Q - Q_1(t)]S_1(t) + [K + M(t)]$$

where Q and K as in Section 3.2, $M(t) = (\gamma_1 I_{11}(t), \cdots, \gamma_n I_{21}(t))^T$ and

$$Q_1(t) = diag\left(\frac{a_1 c_{11} I_{12}(t)}{N_1(t)}, \frac{a_2 c_{21} I_{22}(t)}{N_2(t)}, \cdots, \frac{a_n c_{n1} I_{n2}(t)}{N_n(t)}\right).$$

Since $S^*_1 = S_1(t, S^*_1, S^*_2, I^*_1, I^*_2)$, S^*_1 can be expressed by

$$S^*_1 = e^{\int_0^t [Q - Q_1(\xi)]\, d\xi} S^*_1 + \int_0^t e^{\int_s^t [Q - Q_1(\xi)]\, d\xi} [K + M(\xi)]\, d\xi.$$

By the cooperative and irreducible property of the matrix Q and the positivity of $[K + M(\xi)]$, we conclude that $S^*_1 \gg 0$. Thus, E^* is positive, completing the proof. □

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3.6 A simple case: two-patch model

In the previous sections, we saw that $\mathcal{R}_0 = \rho(\mathbf{F}\mathbf{V}^{-1})$ plays the role of a threshold. All parameters in system (3.2.16) are included in the two matrices $\mathbf{F}$ and $\mathbf{V}$, directly or indirectly. We particularly emphasize that the dispersal rates in the three compartments (susceptible, latent and infectious) enter $\mathbf{F}$ and $\mathbf{V}$ in differential ways, and hence, we expect they affect $\mathcal{R}_0$ in different ways. Unfortunately, for general n, it is very difficult (if not impossible) to investigate the impact of these dispersal rates on $\mathcal{R}_0$ in explicit form. In this section, we will focus on the simplest patchy environment: two patches, with the hope of obtaining some more explicit and helpful information on how $\mathcal{R}_0$ depends on the various dispersal rates.

When $n = 2$, the matrix B becomes

$$B = \begin{bmatrix} -d_{11} - D_{21}^L & D_{12}^L \\ D_{21}^L & -d_{21} - D_{12}^L \end{bmatrix},$$

and in consequence, we get

$$P(\tau_1) = \begin{bmatrix} \frac{e^{-d_{11}\tau_1}\left(D_{12}^L + D_{21}^L e^{-\left(D_{12}^L + D_{21}^L\right)\tau_1}\right)}{D_{12}^L + D_{21}^L} & \frac{e^{-d_{11}\tau_1} D_{12}^L\left(1 - e^{-\left(D_{12}^L + D_{21}^L\right)\tau_1}\right)}{D_{12}^L + D_{21}^L} \\ \frac{e^{-d_{21}\tau_1} D_{21}^L\left(1 - e^{-\left(D_{12}^L + D_{21}^L\right)\tau_1}\right)}{D_{12}^L + D_{21}^L} & \frac{e^{-d_{21}\tau_1}\left(D_{12}^L e^{-\left(D_{12}^L + D_{21}^L\right)\tau_1} + D_{21}^L\right)}{D_{12}^L + D_{21}^L} \end{bmatrix}.$$

Further, we give the matrices $\mathbf{F}$ and $\mathbf{V}$ as the following expressions:

$$\mathbf{F} = \begin{bmatrix} 0 & 0 & p_{11}(\tau_1) a_1 c_{11} & p_{12}(\tau_1) a_2 c_{21} \\ 0 & 0 & p_{21}(\tau_1) a_1 c_{11} & p_{22}(\tau_1) a_2 c_{21} \\ \frac{a_1 c_{12} e^{-d_{12}\tau_2} M_1}{S_{11}^0} & 0 & 0 & 0 \\ 0 & \frac{a_2 c_{22} e^{-d_{22}\tau_2} M_2}{S_{21}^0} & 0 & 0 \end{bmatrix},$$

and

$$\mathbf{V} = \begin{bmatrix} d_{11} + \gamma_1 + \mu_1 + D_{21}^I & -D_{12}^I & 0 & 0 \\ -D_{21}^I & d_{21} + \gamma_2 + \mu_2 + D_{12}^I & 0 & 0 \\ 0 & 0 & d_{12} & 0 \\ 0 & 0 & 0 & d_{22} \end{bmatrix}.$$

where

$$\bar{S}_{11}^0 = \frac{D_{12}K_{21} + D_{12}K_{11} + d_{21}K_{11}}{d_{21}d_{11} + d_{21}D_{21} + D_{12}d_{11}}, \quad \bar{S}_{21}^0 = \frac{d_{11}K_{21} + D_{21}K_{21} + D_{21}K_{11}}{d_{21}d_{11} + d_{21}D_{21} + D_{12}d_{11}} \tag{3.6.1}$$

is the solution of $Qx = K$, regardless of the irreducibility of the matrix Q. Therefore,

with Maple's help, the basic reproduction number is calculated as

$$\mathcal{R} = \rho(\mathbf{F}\mathbf{V}^{-1}) = \frac{1}{2}\sqrt{2r_3s_2 + 2c_4s_4 + 2r_1s_1 + 2r_2s_3 + 2\sqrt{Z}}$$

where

$$\begin{aligned}
Z &= {r_3}^2{s_2}^2 + 2r_3s_2r_4s_4 + 2r_3s_1r_1s_2 - 2r_3s_2r_2s_3 + {r_4}^2{s_4}^2 - 2r_4s_4r_1s_1 \\
&\quad + 2r_4s_3r_2s_4 + {r_1}^2{s_1}^2 + 2r_1s_1r_2s_3 + {r_2}^2{s_3}^2 + 4r_3s_1r_2s_4 + 4r_4s_3r_1s_2, \\
r_1 &= a_1c_{12}\mathrm{e}^{-d_{12}\tau_2}M_1(d_{21} + \gamma_2 + \mu_2 + D^I_{12})/\left(\det(V_1)\,S^0_{11}\right), \\
r_2 &= a_1c_{12}\mathrm{e}^{-d_{12}\tau_2}M_1D^I_{12}/\left(\det(V_1)\,S^0_{11}\right), \\
r_3 &= a_2c_{21}\mathrm{e}^{-d_{22}\tau_2}M_2D^I_{21}/\left(\det(V_1)\,S^0_{21}\right), \\
r_4 &= a_2c_{21}\mathrm{e}^{-d_{22}\tau_2}M_2(d_{21} + \gamma_1 + \mu_1 + D^I_{21})/\left(\det(V_1)\,S^0_{21}\right), \\
s_1 &= p_{11}(\tau_1)a_1c_{11}/d_{12}, \quad s_2 = p_{12}(\tau_1)a_2c_{21}/d_{22}, \\
s_3 &= p_{21}(\tau_1)a_1c_{11}/d_{12}, \quad s_4 = p_{22}(\tau_1)a_2c_{21}/d_{22}.
\end{aligned}$$

The expression of the basic reproduction number is still complicated. For simplicity, we only consider two simple scenarios that make the two patches with dispersal: (i) only the susceptible individuals disperse; (ii) only the susceptible and exposed groups disperse. For the case when all three classes of humans disperse, we only explore the topic numerically.

It is natural and helpful to compare with these cases when the two patches are isolated, that is, D^S, D^L and D^I are all zero matrices. In this case, the disease free equilibrium is $E^1_0 = (K_{11}/d_{11},\ K_{21}/d_{21},\ M_1,\ M_2, 0,\ 0,\ 0,\ 0,\ 0,\ 0)$ and the basic reproduction number is

$$\mathcal{R}^1_0 = \max(R^1_1,\ R^1_2), \tag{3.6.2}$$

where

$$R_1^1 = \sqrt{\frac{{a_1}^2 c_{12} c_{11} \mathrm{e}^{(-d_{11}\tau_1 - d_{12}\tau_2)} M_1}{\frac{K_{11}}{d_{11}} (d_{11} + \gamma_1 + \mu_1) d_{12}}}, \quad R_2^1 = \sqrt{\frac{{a_2}^2 c_{22} c_{21} \mathrm{e}^{(-d_{21}\tau_1 - d_{22}\tau_2)} M_2}{\frac{K_{21}}{d_{21}} (d_{21} + \gamma_2 + \mu_2) d_{22}}}. \tag{3.6.3}$$

Clearly, R_1^1 and R_2^1 are the local basic reproduction numbers for each patch. Applying the results in work [23] (Chapter 2) to each patch, we have the following theorem on the the disease dynamics in each patch.

Theorem 3.6.1 *If $R_i^1 < 1$, then the disease free equilibrium (DFE): $(K_{i1}/d_{i1},\ 0,\ 0,\ M_i,\ 0,\ 0)$ is asymptotically stable; moreover if $\mu_i = \gamma_i = 0$, then the DFE is globally asymptotically stable. If $R_i^1 > 1$, the disease uniformly persists in the population.*

3.6.1 Only susceptible individuals disperse

When only susceptible individuals can travel between patches, the dispersal matrices D^L and D^I are zero matrices. Such an assumption may hold for the situation when all infected individuals are prohibited (e.g., by health authorities) from traveling. In this case, the matrix B and P are reduced to

$$B = \begin{bmatrix} -d_{11} & 0 \\ 0 & -d_{21} \end{bmatrix}, \quad P = \begin{bmatrix} \mathrm{e}^{-d_{11}\tau_1} & 0 \\ 0 & \mathrm{e}^{-d_{21}\tau_2} \end{bmatrix}.$$

Hence, the basic reproduction number is in the following form according to the next generation operator:

$$\mathcal{R}_0^2 := \max\left(R_1^2, R_2^2\right) \tag{3.6.4}$$

where

$$R_i^2 = \sqrt{\frac{{a_i}^2 c_{i1} c_{i2} \mathrm{e}^{-d_{i1}\tau_1} \mathrm{e}^{-d_{i2}\tau_1} M_i}{\bar{S}_{i1}^0 d_{i2} (d_{i1} + \gamma_i + \mu_i)}}$$

and $(\bar{S}^0_{11}, \bar{S}^0_{21})$ are the same as given by the expression in (3.6.1). Here, R_i^2 can be explained as a dispersal mediate reproduction number in patch i.

With the assumptions that $K_{11}/d_{11} = K_{21}/d_{21}$ and further $R_1^1 = R_2^1$, we can explore the impact of human dispersal on the global basic reproduction number (GBRN) in the case that all other parameters are fixed. Comparing $\mathcal{R}_0^2$ with $\mathcal{R}_0^1$, we can obtain the following relations:

(i) If $D_{21}^S < D_{12}^S$, $\bar{S}^0_{21} < K_{21}/d_{11} = K_{11}/d_{11} < \bar{S}^0_{11}$. By the formula of R_i^2, $i = 1, 2$, we have

$$R_1^2 < R_1^1 = R_2^1 < R_2^2,$$
$$\mathcal{R}_0^2 = R_2^2 = \max(R_1^2, R_2^2) > \max(R_1^1, R_2^1) = \mathcal{R}_0^1;$$

(ii) If $D_{21}^S > D_{12}^S$, similarly we have

$$R_1^2 > R_1^1 = R_2^1 > R_2^2,$$
$$\mathcal{R}_0^2 = R_1^2 = \max(R_1^2, R_2^2) > \max(R_1^1, R_2^1) = \mathcal{R}_0^1;$$

(iii) If $D_{21}^S = D_{12}^S$, similarly we have

$$R_1^2 = R_1^1 = R_2^1 = R_2^2,$$
$$\mathcal{R}_0^2 = R_1^2 = \max(R_1^2, R_2^2) = \max(R_1^1, R_2^1) = \mathcal{R}_0^1.$$

In the first two cases, the GBRN is increased by the dispersal of susceptible people. Biologically, the relations can be interpreted as: the asymmetric dispersal between patches leads to an increase of the GBRN, and in turn increases the possibility of disease persistence (when $\mathcal{R}_0^2$ exceeds one). The disease final size will be affected as well. Moreover, the stronger the asymmetry of the dispersal between patches, the faster $\mathcal{R}_0^2$ increases (shown in Figure 3.2. and 3.3.). Focusing on the disease dynamics in one patch, we can easily understand that when more susceptible people migrate in, the disease incidence rate decreases by decreasing the percentage of infectious individuals in

the patch. Mosquitoes have less chance to bite an infectious human and gets infected.

Next we relax the assumptions $K_{11}/d_{11} = K_{21}/d_{21}$ and $R_1^1 = R_2^1$. The numerical simulation for the general case is shown in Figure 3.4 (a-d). The dispersal rate D_{12}^S from patch 2 to patch 1 is fixed. By increasing D_{21}^S, we find that the GBRN with dispersal in the susceptible class is always greater than that in the case when patches are isolated. Unless the difference between D_{12}^S and D_{21}^S is small (weak asymmetry), then K_{11}/d_{11}, K_{21}/d_{21} dominate the relation of $K_{21}D_{21}^S/d_{11}$ and $K_{11}D_{21}^S/d_{11}$ and may even reduce $\mathcal{R}_0^2$. The following relations:

(i) if $K_{11}D_{21}^S/d_{11} < K_{21}D_{12}^S/d_{21}$, then $\bar{S}_{11}^0 > K_{11}/d_{11}$ and $\bar{S}_{21}^0 < K_{21}/d_{11}$. In consequence, by the formula for R_i^1 and R_i^2, $i = 1, 2$, we have

$$R_1^1 > R_1^2, \quad R_2^1 < R_2^2,$$

(ii) if $K_{11}D_{21}^S/d_{11} > K_{21}D_{12}^S/d_{21}$, similarly we have

$$R_1^1 < R_1^2, \quad R_2^1 > R_2^2.$$

In these cases, if $\mathcal{R}_0^1 = \max(R_1^1, R_2^1) = R_1^1$ and $K_{11}D_{21}^S/d_{11} < K_{21}D_{12}^S/d_{21}$, then we get $\mathcal{R}_0^2 = \max(R_1^2, R_2^2) < \max(R_1^1, R_2^1) = \mathcal{R}_0^2$.

With different dispersal rates, the GBRN may change in various ways. As indicated in Figure 3.4 (a-d), when we increase the dispersal rate D_{12}^S from patch 2 to 1, i.e. $D_{12}^S = 0, 0.1, 0.5, 0.9$, the curve of $\mathcal{R}_0^2$ changes from monotonically increasing to monotonically decreasing, with respect to the dispersal rate D_{21}^S from patch 1 to 2. Similarly, we have the same relation between $\mathcal{R}_0^2$ and D_{12}^S, if D_{21}^S is fixed. Figure 3.5 shows a case that two patches are isolated, and the disease will die out as both local basic reproduction number are less than 1: $R_1^2 = 0.5966$, $R_2^2 = 0.7208$. By traveling,

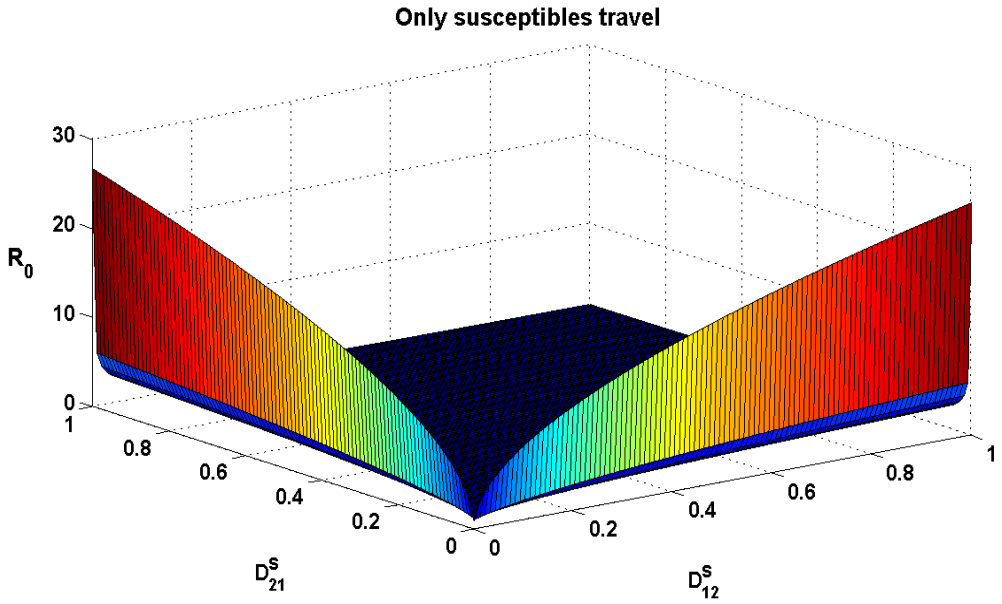

Figure 3.2: The relation between D^S and $\mathcal{R}_0^2$. For parameters $K_{11} = K_{21} = 0.72$, $d_{11} = 0.001$, $d_{12} = 0.011$, $d_{21} = 0.2$, $d_{22} = 0.2$, $a_1 = 0.5$, $a_2 = 0.4$, $e_{11} = 0.5$, $e_{12} = 0.45$, $e_{21} = 0.5$, $e_{22} = 0.45$, $\gamma_1 = 0.4$, $\gamma_2 = 0.4$, $\tau_1 = 20$, $\tau_2 = 6$, $\mu_1 = 0.08$, $\mu_2 = 0.08$, $M_1 = 2000$, $M_2 = 2000$.

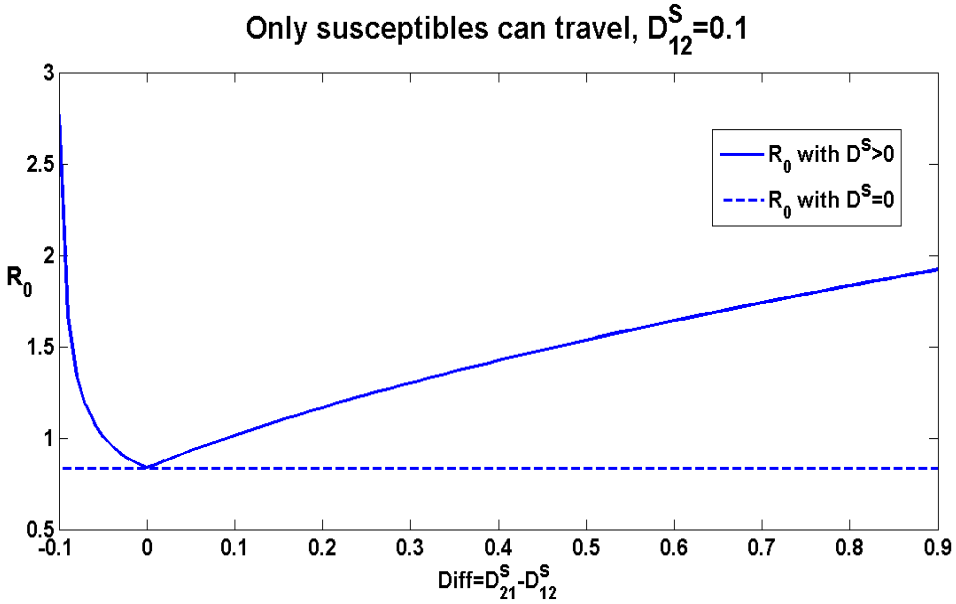

Figure 3.3: All the coefficients remains the same as in Figure 3.2, except diff=$D_{12}^S - D_{21}^S$, and D_{21}^S is fixed at 0.1, so the range of diff is from $[-0.1, 0.9]$

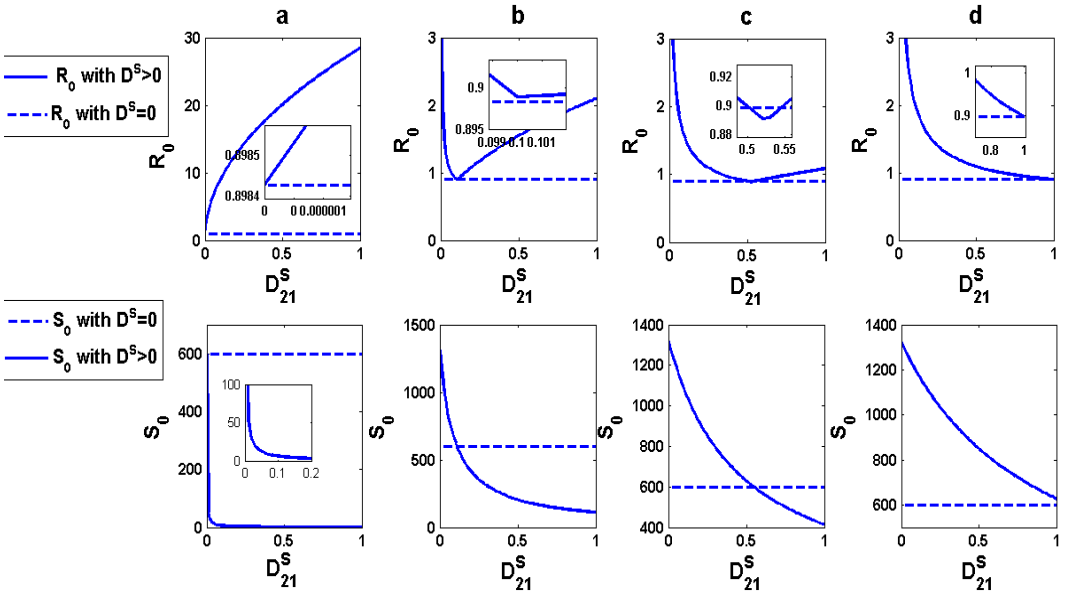

Figure 3.4: The top row of a,b,c,d are mappings of the 3-D curve on the plain $D_{12}^S = 0$ with different values of D_{12}^S; and the bottom row shows the size of the populations in both patches at the disease free steady state. All the coefficients are as follows $K_{11} = K_{21} = 0.72$, $d_{11} = 0.001$, $d_{12} = 0.011$, $d_{21} = 0.2$, $d_{22} = 0.2$, $a_1 = 0.5$, $a_2 = 0.4$, $e_{11} = 0.5$, $e_{12} = 0.4$, $e_{21} = 0.5$, $e_{22} = 0.45$, $\gamma_1 = 0.3$, $\gamma_2 = 0.4$, $\tau_1 = 20$, $\tau_2 = 6$, $\mu_1 = 0.08$, $\mu_2 = 0.1$, $M_1 = 2000$, $M_2 = 2000$.

the GBRN changes from 0.7208 (no connection) down to 0.7190 (low dispersal rates for both directions), then up to 1.1070 (dispersal with strong asymmetry). This can be explained as the fact that with a highly asymmetric dispersal between susceptible people, disease can persist in the population.

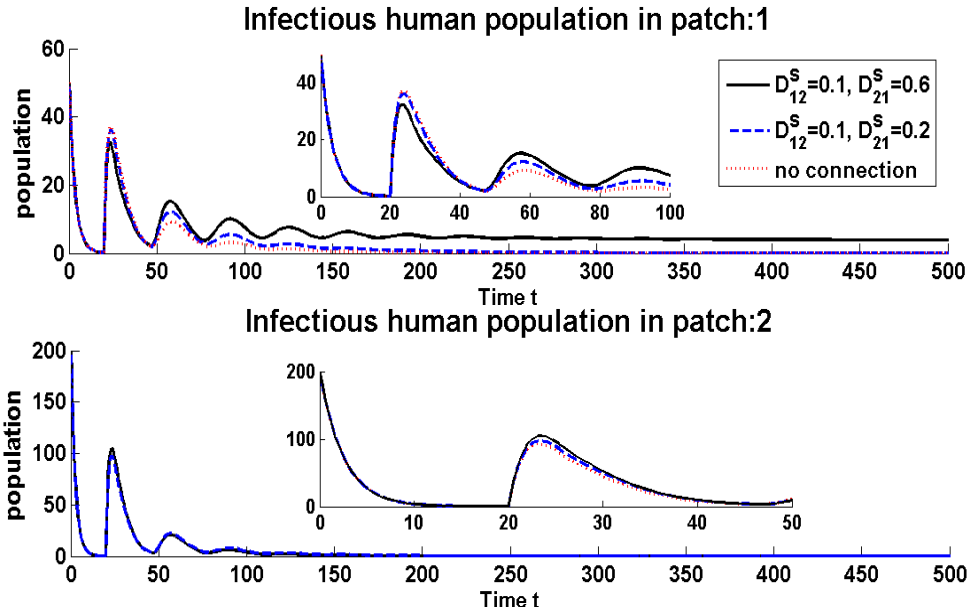

Figure 3.5: Solid lines: the GBRN is 1.1070; dash lines: the GBRN is 0.7190; dot lines: the GBRN is 0.7208. The other coefficients and initial conditions are $N_1(0) = 500$, $N_2(0) = 600$, $M_1 = 2000$, $M_2 = 6000$, $S_{11}(0) = 450$, $S_{21}(0) = 400$, $S_{12}(0) = 1800$, $S_{22}(0) = 5000$, $E_{11}(0) = 0$, $E_{21}(0) = 0$, $I_{11}(0) = 50$, $I_{21}(0) = 200$, $I_{12}(0) = 200$, $I_{22}(0) = 1000$, $K_{11} = 0.6$, $K_{21} = 0.72$, $d_{11} = 0.001$, $d_{12} = 0.011$, $d_{21} = 0.2$, $d_{22} = 0.2$, $a_1 = 0.3$, $a_2 = 0.3$, $e_{11} = 0.5$, $e_{12} = 0.4$, $e_{21} = 0.5$, $e_{22} = 0.45$, $\gamma_1 = 0.3$, $\gamma_2 = 0.4$, $\tau_1 = 20$, $\tau_2 = 6$, $\mu_1 = 0.01, \mu_2 = 0.02$, $D^L = D^I = 0$. Time unit: days.)

3.6.2 Only susceptibles and individuals in exposed group can disperse

When patients become infectious, they usually have disease symptoms that limit their outdoor activities. But when they are in the disease latency, they may travel without knowing they have been infected. Therefore, under these circumstances, both sus-

ceptible and latent individuals disperse between patches, i.e.,D^S and D^L are non-zero matrices, when the infectious groups are quarantined, i.e., D^I is a zero matrix. Then, the GBRN is

$$\mathcal{R}_0^3 := \rho(\mathbf{F}\mathbf{V}^{-1}) = \frac{1}{2}\sqrt{2\,h_2 j_4 + 2\,h_1 j_1 + 2\,\sqrt{\Gamma_2}}$$

where

$$\begin{aligned}
\Gamma_2 =& h_2{}^2 j_4{}^2 - 2\,h_2 j_4 h_1 j_1 + h_1{}^2 j_1{}^2 + 4\,h_2 j_3 h_1 j_2,\\
j_1 =& p_{11}(\tau_1)a_1 c_{11}/d_{12}, \quad j_2 = p_{12}(\tau_1)a_2 c_{21}/d_{22},\\
j_3 =& p_{21}(\tau_1)a_1 c_{11}/d_{12}, \quad j_4 = p_{22}(\tau_1)a_2 c_{21}/d_{22},\\
h_1 =& \frac{a_1 c_{12}\mathrm{e}^{-d_{12}\tau_2} M_1}{\vec{s}_{11}^{\,0}\,(d_{11}+\gamma_1+\mu_1)}, \quad h_2 = \frac{a_2 c_{22}\mathrm{e}^{-d_{22}\tau_2} M_2}{\vec{s}_{21}^{\,0}\,(d_{21}+\gamma_2+\mu_2)}.
\end{aligned}$$

Notice that $\mathcal{R}_0^3$ can be re-arranged and given terms of R_1^2 and R_2^2 as

$$\mathcal{R}_0^3 := \frac{1}{2}\sqrt{2\,R_1^2\eta_1 + 2\,R_1^2\eta_2 + 2\,\sqrt{\Gamma_3}} \tag{3.6.5}$$

where

$$\Gamma_3 = (R_1^2\eta_1)^2 - 2\,R_1^2\eta_1 R_2^2\eta_2 + (R_2^2\eta_2)^2 + 4\,R_1^2\,R_2^2\,\eta_1\,\eta_2\frac{p_{12}(\tau_1)p_{21}(\tau_1)}{p_{11}(\tau_1)p_{22}(\tau_1)}$$

and $\eta_i = p_{ii}(\tau_1)/\mathrm{e}^{-d_{i1}\tau_1}$. where $\eta_i = p_{ii}(\tau_1)/\mathrm{e}^{-d_{i1}\tau_1}$.

When individuals in latency can travel, the impact of dispersal rates for susceptible people is similar as we discussed in section 3.6.1. The movements of people in exposed class also changes the GBRN in various ways as well. By our observations, we get

$\eta_i < 1$, and according to the derivation of the probability matrix P, we further have

$$\begin{aligned}\frac{p_{12}(\tau_1)p_{21}(\tau_1)}{p_{11}(\tau_1)p_{22}(\tau_1)} &= \frac{D_{12}^L D_{21}^L (\mathrm{e}^{-(D_{12}^L+D_{21}^L)}-1)^2}{(D_{12}^L + D_{21}^L \mathrm{e}^{-(D_{12}^L+D_{21}^L)})(D_{12}^L \mathrm{e}^{-D_{12}^L-D_{21}^L} + D_{21}^L)} \\ &\leq \frac{D_{12}^L D_{21}^L (\mathrm{e}^{-(D_{12}^L+D_{21}^L)}-1)^2}{D_{12}^L D_{21}^L} \\ &\leq \frac{D_{12}^L D_{21}^L}{D_{12}^L D_{21}^L} \\ &\leq 1.\end{aligned}$$

Therefore

$$\max\{R_1^2\eta_1,\, R_2^2\eta_2\} \leq \mathcal{R}_0^3 \leq R_1^2\eta_1 + R_2^2\eta_2.$$

If we fix the dispersal rate of susceptible people, and vary that of the latent population. We observe the impact of D^L on $\mathcal{R}^3$. It is unlikely that $D^S = 0$ while $D^L > 0$, as there is no indication that infected people have a higher preference for traveling than susceptible humans. Figures 3.6., 3.7. and 3.8. exhibit the relationship between D^L and $\mathcal{R}^3$, with $K_{11} = 0.6$, $K_{21} = 0.72$, $d_{11} = 0.001$, $d_{12} = 0.011$, $d_{21} = 0.2$, $d_{22} = 0.2$, $a_1 = 0.6$, $a_2 = 0.4$, $e_{11} = 0.5$, $e_{12} = 0.4$, $e_{21} = 0.5$, $e_{22} = 0.45$, $\gamma_1 = 0.3$, $\gamma_2 = 0.4$, $\tau_1 = 16$, $\tau_2 = 16$, $\mu_1 = 0.08$, $\mu_2 = 0.1, D_{12}^S = 0.3$, $D_{21}^S = 0.5$, $M_1 = 2000$, $M_2 = 6000$.

There is a special situation that the dispersal rate of people in latency is proportional to that for the susceptible groups. The proportion affects the disease persistence as well, and its relationship with $\mathcal{R}^3$ is shown in Figure 3.9 and 3.10. We set $K_{11} = 0.6$, $K_{21} = 0.72$, $d_{11} = 0.001$, $d_{12} = 0.011$, $d_{21} = 0.2$, $d_{22} = 0.2$, $a_1 = 0.6$, $a_2 = 0.4$, $e_{11} = 0.5$, $e_{12} = 0.4$, $e_{21} = 0.5$, $e_{22} = 0.45$, $\gamma_1 = 0.3$, $\gamma_2 = 0.4$, $\tau_1 = 16$, $\tau_2 = 16$, $\mu_1 = 0.08$, $\mu_2 = 0.1$, $M_1 = 2000$, $M_2 = 6000$.

Another possible phenomenon is: the dispersal is unidirectional for individuals in the latent period. Hence, we have either $D_{12}^L = 0$ or $D_{21}^L = 0$. Here, we assume $D_{21}^L = 0$.

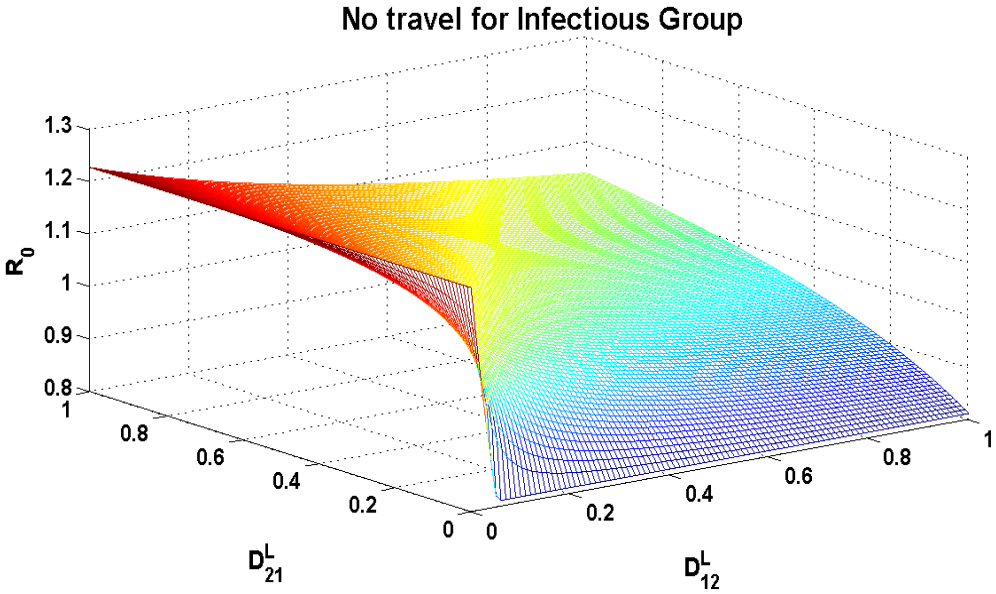

Figure 3.6: The relation between D^L and $\mathcal{R}^3$ when both susceptible and latent groups travel, and susceptible individuals travel at fixed rates between patches.

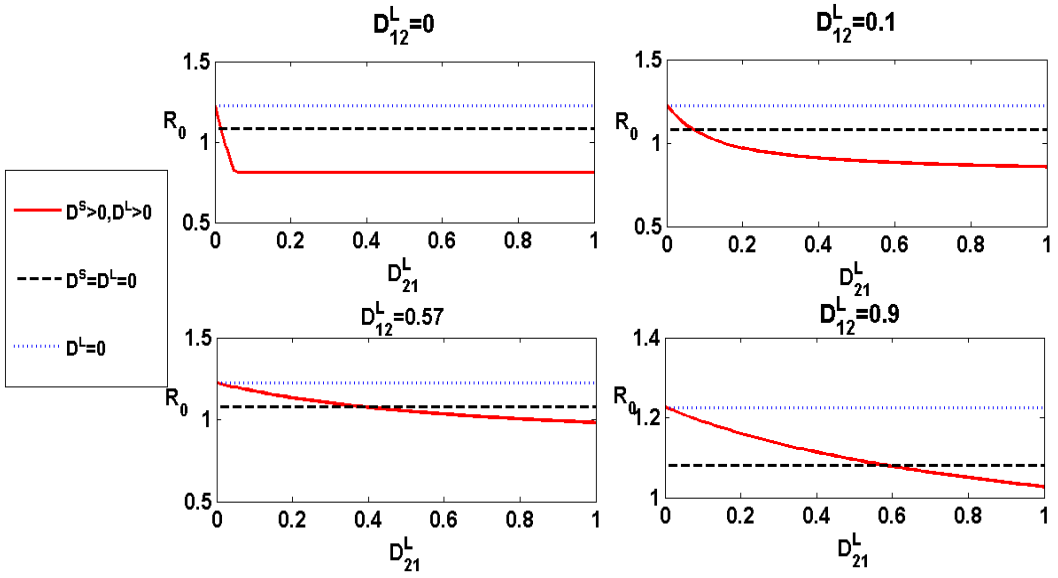

Figure 3.7: The 2D mapping of figure 3.6. From a-d, the dispersal rate from patch 2 to 1 set as D_{12}^L = 0, 0.1, 0.57, 0.9.

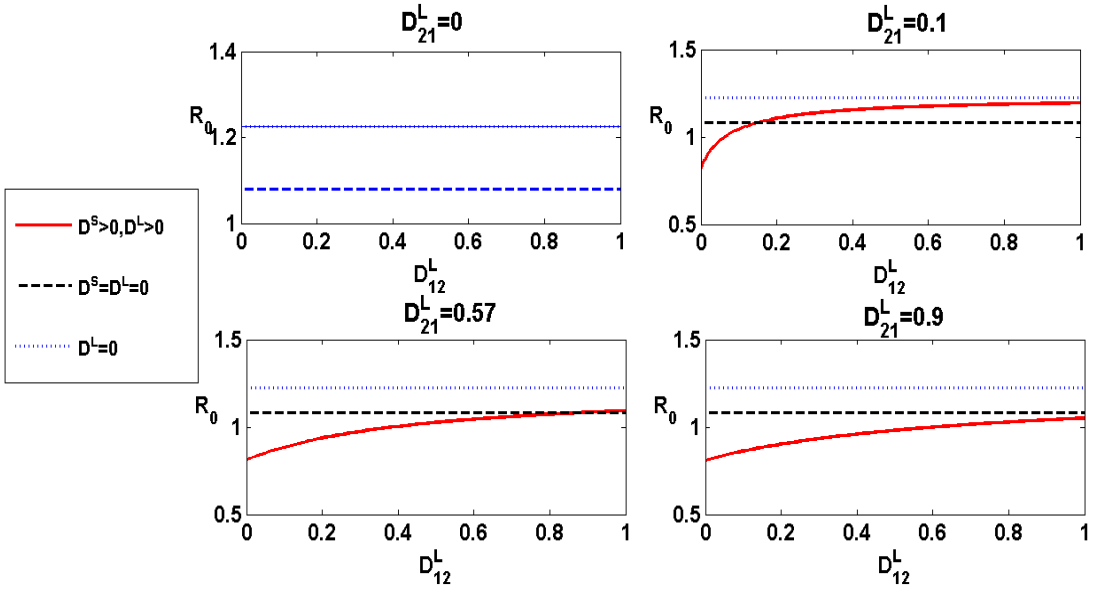

Figure 3.8: The 2D mapping of figure 3.6. From a-d, the dispersal rate from patch 2 to 1 is set as $D^L_{21} = 0, 0.1, 0.57, 0.9$. In a, the line of the basic reproduction number for both case $D^S > 0$, $D^L > 0$ and $D^L = 0$ coincide.

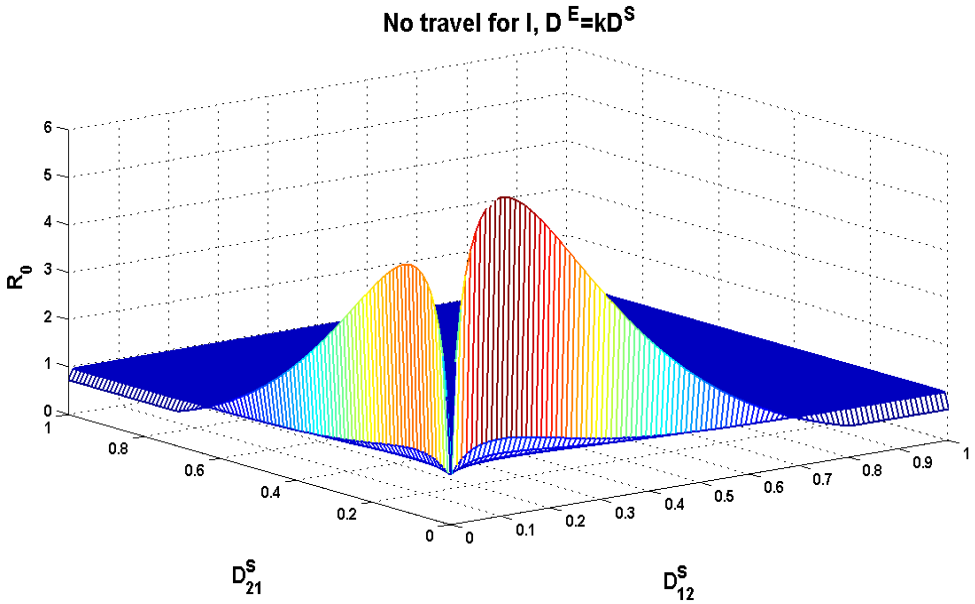

Figure 3.9: The relation between D^S and $\mathcal{R}^3$ when the travel rate for people in latency is proportional to that for healthy group. The proportion rate $k = 0.6$.

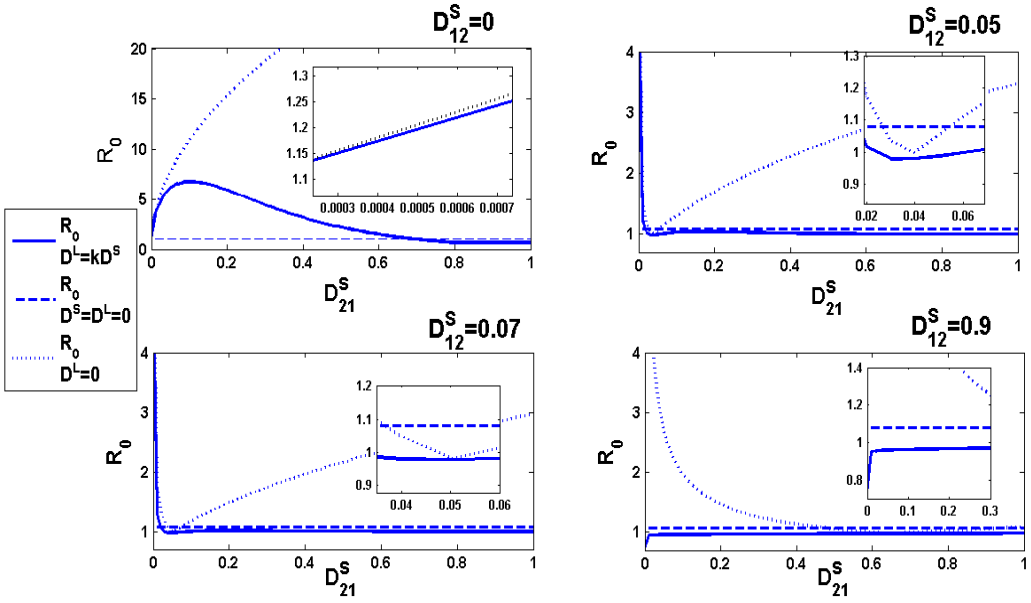

Figure 3.10: The 2D mapping of Figure 3.9. From a-d, the dispersal rate from patch 2 to 1 is set as $D_{12}^S = 0,\ 0.1,\ 0.5,\ 0.9$.

Then, it follows by

$$B = \begin{bmatrix} -d_{11} & D_{12}^L \\ 0 & -d_{21} - D_{12}^L \end{bmatrix}.$$

and in consequence, we have

$$P(\tau_1) = \begin{bmatrix} \mathrm{e}^{-d_{11}\tau_1} & \mathrm{e}^{-d_{11}\tau_1}(1 - \mathrm{e}^{-D_{12}^L\tau_1}) \\ 0 & \mathrm{e}^{-d_{11}\tau_1}\mathrm{e}^{-D_{12}^L\tau_1} \end{bmatrix}$$

Therefore, the basic reproduction number is

$$\begin{aligned} \bar{\mathcal{R}}_0^3 &:= \frac{1}{2}\sqrt{2\,R_1^2\,\eta_1 + 2\,R_1^2\,\eta_2 + 2\,\sqrt{(R_1^2\eta_1)^2 - 2\,R_1^2\eta_1 R_2^2\eta_2 + (R_2^2\eta_2)^2}} \\ &= \max\,(R_1^2\,\eta_1, R_2^2\,\eta_2). \end{aligned} \tag{3.6.6}$$

Obviously, $\bar{\mathcal{R}}_0^3 < \mathcal{R}_0^2$. This may explain why while there are currently many disease endemic areas in the world, the disease has not yet spread and does not persist glob-

ally. The zero or low local basic reproduction of those disease-free cities and countries reduce the value of the global(average) basic reproduction number.

3.6.3 Two patches are fully connected

In this case, we have given the expression for $\mathcal{R}$ at the beginning of this section. With the complicated form of the basic reproduction number, we only give numerical results to explain the impact of movement on persistence of the disease here. We know that if more infected humans come into a patch, more susceptible humans locally may get infected instantly and vice versa. The dispersal of infectious groups between two patches has a similar impact on the disease persistence with that of groups in the latent period. In Figure 3.11, we compare the GBRN between the two cases which are with or without dispersal in infectious class. When D^L is fixed, by introducing a dispersal rate between infectious groups in two patches, if the dispersal rate of susceptible class from patch 2 to 1 is low, then the global basic reproduction rate actually less than that in the situation with no dispersal in infectious group. Otherwise if D^S_{12} is high, the impact from movement of susceptible class plays a dominant role.

Next, if we compare the weights of the impacts of dispersal between individuals in latency and in infectious period on the disease persistence. We find that with a fixed dispersal rate between healthy people, $D^S_{12} = 0.3$, $D^S_{21} = 0.5$, when the connections between either group in latency or infectious group is not strong, then due to the instant infection and latent period, the travel activities of individual in latent period is less harmful than that of infected individuals. However, if the connections between latent or infectious groups are strong in both groups, the disease induced mortality rate dominates the GBRN and reduce the impact on GBRN caused by traveling of infectious group (Figure 3.12). In practice, the dispersal rate members of the population in the latent and infectious class is usually less or at least no more than that of susceptible

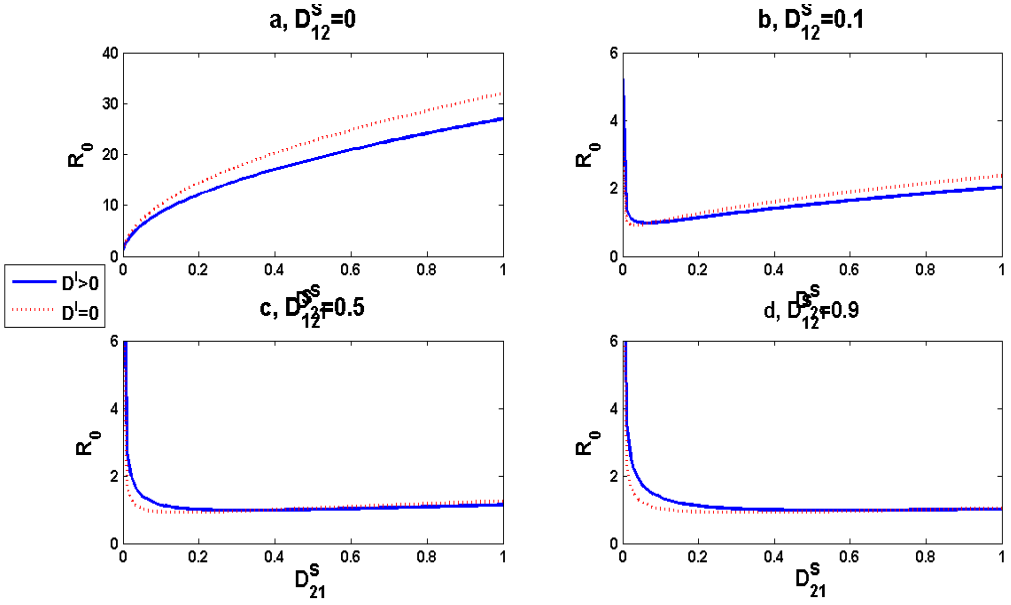

Figure 3.11: From a-d, the dispersal rate from patch 2 to 1 set as $D_{12}^S = 0$, 0.1, 0.5, 0.9, and $D_{12}^L = 0.42, D_{21}^L = 0.6$. $D_{12}^I = 0.1, D_{21}^I = 0.2$ for the dot line and $D_{12}^I = D_{21}^I = 0$ for the solid line. The other parameters are set as $K_{11} = 0.6$, $K_{21} = 0.72$, $d_{11} = 0.001$, $d_{12} = 0.011$, $d_{21} = 0.2$, $d_{22} = 0.2$, $a_1 = 0.6$, $a_2 = 0.4$, $e_{11} = 0.5$, $e_{12} = 0.4$, $e_{21} = 0.5$, $e_{22} = 0.45$, $\gamma_1 = 0.3$, $\gamma_2 = 0.4$, $\tau_1 = 16$, $\tau_2 = 16$, $\mu_1 = 0.08$, $\mu_2 = 0.1$, $M_1 = 2000$, $M_2 = 6000$.

people. So we are more interested in the case with small dispersal rates between latent and infectious groups individually (a and b in Figure 3.12) under the condition that $D_{12}^S = 0.3$, $D_{21}^S = 0.5$.

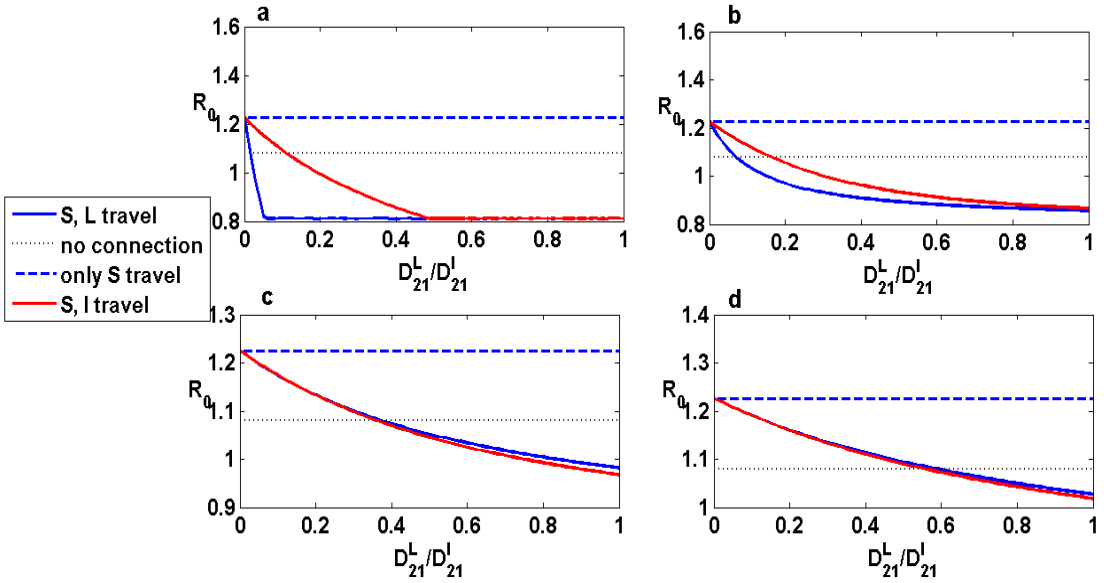

Figure 3.12: From a-d, the dispersal rate from patch 2 to 1 set as $D_{12}^L = D_{12}^I = 0, 0.1, 0.5, 0.9$. All the other coefficients remain the same as in Figure 3.11.

3.7 Conclusion and Discussion

In this chapter, we have proposed an epidemic model to simulate the dynamics of malaria transmission under the influence of population dispersal between patches. Population dispersal can be interpreted as human beings traveling and migrating by transportation from one city (country, continent) to another. However, female mosquitoes cannot move from patch to patch as the distance between patches is consider to be beyond the flying ability of the insects. We have incorporated constant latent periods into the model for the additional purpose of exploring how the movement of individuals in the latent period will affect the disease dispersal. We build a system of DDEs for n

patches. For the model, we applied the theorem of the next generation operator [18] to compute its GBRN. We have shown that a small scale of disease invasion is unsuccessful for n patches if $\mathcal{R}_0 < 1$; while if $\mathcal{R}_0 > 1$, the disease will uniformly persist in every patch. In the special case of two patches, we have considered different types of human dispersal: (i) only susceptible population can move; (ii) only susceptibles and persons in the disease latent period can travel and migrate. When only the susceptible group can travel, disease will not disperse from one patch to another. However, if the movements are between patches where malaria is endemic, the disease may persist between patches even if the local basic reproduction rates are less than one in both patches, i.e., the disease would die out when patches were isolated. When groups in the latent or infective period can travel, the disease can be spread from patches with disease to the other disease free areas, causing the persistence of malaria in other places, shown in Figure 3.13.

We have assumed that in different patches, the latent periods are fixed and identical for all human beings and all female mosquitoes, respectively. It is biologically reasonable to consider various latent periods for both hosts in patches, as climate and geographic impacts in each patch may be different. The theorem of the next generation operator theorem can still apply in this case, but the probability matrix $P(\tau)$ of dispersal of individuals in the latent period is much more complicated. We leave this as future work.

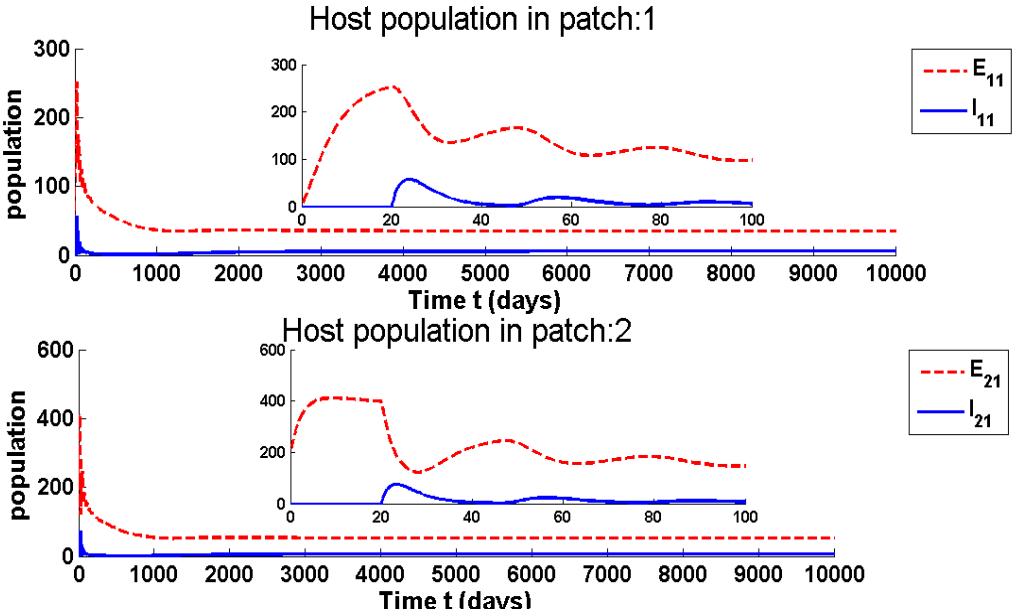

Figure 3.13: Patch 1 with $S_1^0 = 500$, $M_1 = 2000$ is disease free at time 0, and patch 2 with $S_2^0 = 600$, $M_2 = 6000$ with a population of 50 human in latency and 200 mosquitoes infected initially. There are infectious humans at the beginning. $K_{12} = 0.7$, $K_{21} = 0.72$, $d_{11} = 0.001$, $d_{12} = 0.011$, $d_{21} = 0.2$, $d_{22} = 0.2$, $a_1 = 0.4$, $a_2 = 0.4$, $e_{11} = 0.5$, $e_{12} = 0.4$, $e_{21} = 0.5$, $e_{22} = 0.45$, $\gamma_1 = 0.3$, $\gamma_2 = 0.4$, $\tau_1 = 16$, $\tau_2 = 16$, $\mu_1 = 0.08$, $\mu_2 = 0.1$, $D_{12}^S = 0.1$, $D_{21}^S = 0.7$, $D_{12}^L - 0.1$, $D_{21}^L = 0.15$, $D^I = 0$.

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Chapter 4

Can multiple malaria species co-persist? — Analysis of ODE models

There are several species of malaria protozoa spreading in different regions. On the other hand, the world becomes more highly connected by travel than ever before. This raises a natural concern of possible epidemics caused by multiple species of malaria parasites in one region. In this study, we use mathematical models to explore such a possibility. Firstly, we propose a model to govern the within-host dynamics of two species. Analysis of this model practically excludes the possibility of co-persistence (or super-infection) of the two species in one host. Then we move on to set up another model to describe the dynamics of disease transmission between human and mosquito populations without the co-infection class (using the results in Section 4.2). By analyzing this model, we find that epidemics involving both species in a single region is possible.

4.1 Introduction

Malaria is widespread and the most prevalent infectious disease in the world. It causes millions of infections every year, 90% of which are either children age under five or pregnant women. Since the 1980s, this disease has been claimed to have been eradicated in many developed countries, such as United States, Canada and some European countries. Althogh mortality rate associated with malaria infection have been reduced from more than a million to an estimated 700,000-881,000 per year, according to the latest report from the *Roll Back Malaria* partnership of the World Health Organization [30], the disease still remains endemic in most tropical and subtropical areas (about 108 countries), and is associatesd with the poverty in these places.

The malaria pathogen is consisted of members of eukaryotic protisists of the genus *Plasmodium*. Humans, reptiles, birds and various mammals are potential hosts for more than 100 species of plasmodium. Among these species, there are five major species that have been reported to cause malaria infections in humans with significant number of infections. They are *P. falciparum*, *P. vivax*, *P. ovale*, *P. malaria* and *P. knowles*. These protozoan are transferred from the mosquito salivary glands to human bloodstream via bites of mosquito, hence malaria is a mosquito-borne disease. Due their different ring forms, malaria parasites have different characteristics during the infection process. For example, *P. falciparum* infections have the highest disease-induced mortality rate and this protozoan is responsible for 90% of malaria induced deaths. Because *P. falciphrum* has strong parasitic ability in red blood cells (Rbcs) of all ages (other species are restricted to Rbcs at particular stages of development), it can therefore cause high rates of parasitaemia [27]. The other species *P. vivax* has a wider range for its survival temperature.

Tracing back to ten thousand years ago, *P. falciparum* was original from West

Africa, while *P.vivax*, co-evolved with non-human primates, i.e. Asian macaques, and was originally found in Asian and Central West Africa independently [5,18]. Currently, the geographical distribution of *Plasmodium* infections is as follows. Nearly 85% of cases in Africa are caused by *P. falciparum*. The remaining cases are caused by the other three species. *P. vivax* has the widest geographically distribution, existing in most countries in Asia, Central and South America, and the Middle East, where 70 – 90% of malaria infections is caused by this species and the rest is mainly due to *P. falciparum* [2,20]. *P. malariae* causes sporadic infections in Africa, parts of India, the western Pacific and South America, whereas *P. ovale* is restricted to tropical Africa, New Guinea, and the Philippines [2]. P. knowlesi has been reported in Eastsouth Asian countries such as Malaysia, Thailand, Vietnam, Myanmar and Philippines [6, 7, 19, 21, 26]. In some regions, more than one malaria species has been found and this raises a natural concern: can such a co-existence of multiple malaria species persist in a single region?

This concern has been debated by researchers since the first case of co-existence was reported. Maitland and Williams [15] argued that newly transmitted *P. falciparum* infections were suppressing patient infections (either new or latent) with *P. vivax*. Nosten et al. [17] found that on the Thai-Burma border, pregnant women whose first attack of malaria during pregnancy was caused by *P. vivax* had a significantly lower risk of developing *P. falciparum* infections later in the pregnancy. Moreover, statistical analysis by McKenzie and Bossert [16] showed that the number of mixed infections did not weigh significantly compared with that of single infection cases for *P.falciparum - P.vivax*. On the other hand, based on the data they collected, McKenzie and Bossert [16] claimed that at the level of human populations, four malaria species had been established in the populations in Madagascar and New Guinea.

In this chapter, we address the concern of co-existence of multiple species by using mathematical models. For simplicity, we only consider two species, but we believe

that the approach can be applied to the situation with more than two species. Further justification for just choosing two species is because that the two major species, *P. falciparum* and *P. vivax*, contribute 90% of malaria infections in most areas. In Section 4.2, we propose a model represented by a system of ordinary differential equations (ODEs), describing the life cycle of malaria parasites at the erythrocytic phase. The dynamics of the model predicts that generically co-infection within a host cannot persist. In Section 4.3, we model the malaria transmission at the human and mosquito population level. We first propose another model of ODEs for a single-species case containing the recovered class for humans, and then, extend this model to a two-species version in a natural way. Notice that the cross-immunity between species is complicated, e.g., there is no cross immunity between *P. falciparum* and *P. vivax* [31]. Hence, we need to incorporate extra terms in the two-species model to reflect this fact. For both one-species and two-species models, we address well-posedness, identify the basic reproduction numbers and show the threshold role these numbers play. Moreover, we explore the long term dynamics including the stability of various equilibria and persistence of the model systems. Our results shows that although two species of malaria parasites cannot co-exist within a single host, but both can persist in a single region at the population level. We finish the chapter in Section 4.4, where we summarize the main results and discuss the biological implications as well as some possible future work. Some numerical simulation results are also given to support our conclusion on persistence at the population level.

4.2 Within-host level

The life cycle of malaria parasites inside human bodies consists of two phases: an exo-erythrocytic and an erythrocytic phase. The exoerythrocytic procedure involves infection of the hepatic system (liver). After an effective bite, a mosquito injects sporozoites,

which rapidly attach to and enter the liver cells though the bloodstream. An asymptomatic period follows, during which parasite mature and multiply asexually within the liver cells, forming hepatic schizonts (see, e.g., [27]). Once hepatic schizonts rupture the liver cells, and release merozoites back into the bloodstream. After entering the erythorocytic phase, the free merozoites penetrate Rbcs, where they develop to ring forms and undergo sexual or asexual maturation. Sexual maturation produces male and female gametocytes, and sexually propagates infectious gametocytes, that wait for piercing by female mosquitoes. Asexual maturation forms schizonts, which invade healthy Rbcs and repeat the cycle again and again, causing the well-recognized pattern of cyclical fevers in humans.

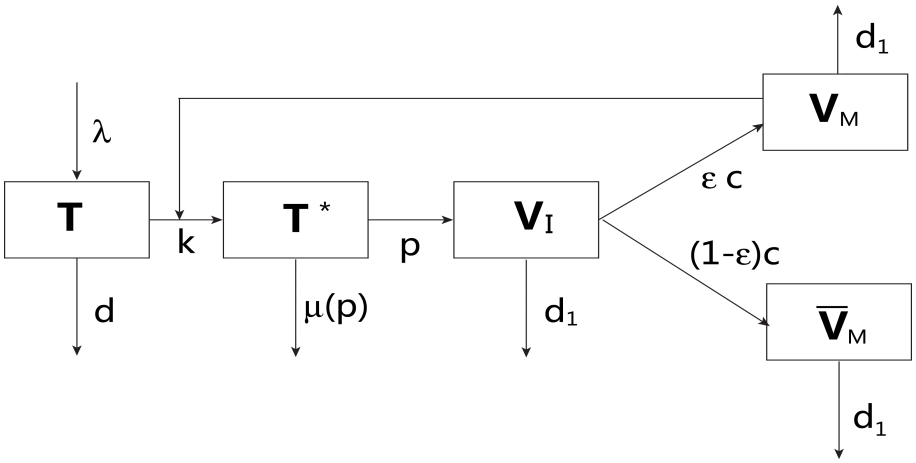

Figure 4.1: One-species case.

From the above description, the developmental process of malaria parasites within a host can be illustrated by the diagram in Figure 4.1. Here T, T^*, V_I, V_M and $\bar{V}_M$ represent the populations of healthy Rbcs, infected Rbcs, immature merozoites, asexually mature merozoites, sexually mature gametocytes, respectively. It is assumed that (i) the health Rbcs are recruited at a constant rate λ; (ii) uninfected target cells die at rate d; (iii) parasites at all phases die at a rate d_1; (iv) asexually mature merozoites infect healthy Rbcs according to a mass-action law with constant rate k; (v) infected Rbcs

then produce immature merozoites at rate p and are killed (ruptured) at rate $\mu(p)$ associated with the production rate; and finally, (vi) a proportion ϵc of immature merozoites remains asexual and keep searching for healthy Rbcs, whereas the rest mature sexually in the bloodstream.

Translating the diagram into differential equations, we obtain the following model system

$$\begin{cases} \dot{T}(t) = \lambda - dT - kV_M T, \\ \dot{T}^*(t) = kV_M T - \mu(p)T^*, \\ \dot{V}_I(t) = pT^* - d_1 V_I - cV_I, \\ \dot{V}_M(t) = \epsilon_1 cV_I - d_1 V_M, \\ \dot{\bar{V}}_M(t) = (1-\epsilon_1)cV_I - d_1 \bar{V}_M. \end{cases} \tag{4.2.1}$$

Clearly, the last equation in system (4.2.1) is decoupled from the others. Hence, we only need to consider the following reduced system

$$\begin{cases} \dot{T}(t) = \lambda - dT - kV_M T, \\ \dot{T}^*(t) = kV_M T - \mu(p)T^*, \\ \dot{V}_I(t) = pT^* - d_1 V_I - cV_I, \\ \dot{V}_M(t) = \epsilon_1 cV_I - d_1 V_M. \end{cases} \tag{4.2.2}$$

When a host is infected by two different species of malaria parasites, the dynamics of the Rbcs and the parasites of the two species within the host can be described by the following system of ODEs which is a very straightforward expansion of the one species

model (4.2.2):

$$\begin{cases} \dot{T}(t) = \lambda - dT - k_1 V_{M1} T - k_2 V_{M2} T, \\ \dot{T}_1^*(t) = k_1 V_{M1} T - \mu(p_1) T_1^*, \\ \dot{T}_2^*(t) = k_2 V_{M2} T - \mu(p_2) T_2^*, \\ \dot{V}_{I1}(t) = p_1 T_1^* - d_1 V_{I1} - c_1 V_{I1}, \\ \dot{V}_{I2}(t) = p_2 T_2^* - d_2 V_{I2} - c_2 V_{I2}, \\ \dot{V}_{M1}(t) = \epsilon_1 c_1 V_{I1} - d_1 V_{M1}, \\ \dot{V}_{M2}(t) = \epsilon_2 c_2 V_{I2} - d_2 V_{M2}. \end{cases} \tag{4.2.3}$$

Here the meanings of all variables and parameters are similar to those in system (4.2.2) and self-explanatory, with the integer subscripts 1 and 2 denoting species 1 and 2 respectively. Similarly, the model system (4.2.3) is demonstrated by the diagram in Figure 4.2.

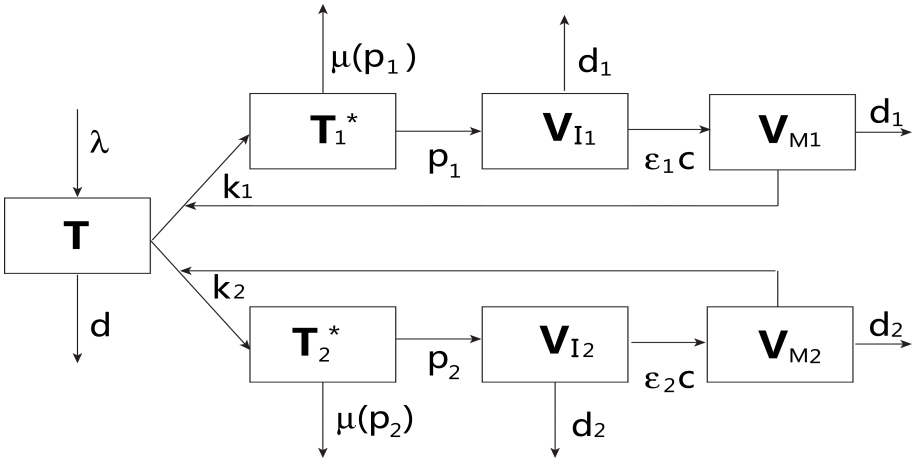

Figure 4.2: Two-species case.

The form of the model system (4.2.3) is a special case of a more general system studied in [10] where n strains and k development stages are considered. Hence, we can use the results in [10] to obtain the dynamics of system (4.2.2). To this end, we

introduce the following two quantities

$$\mathcal{R}_i = \frac{\lambda k_i \epsilon_i c_i p_i}{d d_i \mu(p_i)(d_i + c_i)}, \ i = 1, 2.$$

Each of them is the respective basic reproduction number for the corresponding parasite species in the absence of the other species. Then, $\mathcal{R}_0 = \max(\mathcal{R}_1, \mathcal{R}_2)$, gives the full basic reproduction number for model (4.2.3) (see, [10]). Applying Theorem 3.1 in [10] to (4.2.3), it follows that the dynamics of model (4.2.3) can be described by the following theorem:

Theorem 4.2.1 *For* (4.2.3)*, the following hold.*

(i) If $\mathcal{R}_0 \leq 1$, then the infection free equilibrium (IFE) $E_0 = (\lambda/d, 0, 0, 0, 0, 0, 0,)$ is globally asymptotically stable in $\mathfrak{R}^7_+$;

(ii) If $\mathcal{R}_0 > 1$, then E_0 becomes unstable. In this case, there are the following possibilities:

(ii)-1 If $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$, then in addition to the IFE, there is the species 1 endemic equilibrium E_1, which is globally asymptotically stable in $\mathfrak{R}^7_+ \setminus \{E_0\}$;

(ii)-2 If $\mathcal{R}_2 > 1$ and $\mathcal{R}_1 < 1$, then in addition to the IFE, there is the species 1 endemic equilibrium E_2, which is globally asymptotically stable in $\mathfrak{R}^7_+ \setminus \{E_0\}$;

(ii)-3 If both $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 > 1$, but $\mathcal{R}_1 > \mathcal{R}_2$, then in addition to the IFE, there are the species 1 endemic equilibrium E_1 and species 2 endemic equilibrium E_2; but E_2 is unstable and E_1 is globally asymptotically stable in $\mathfrak{R}^7_+ \setminus \{E_0, E_2\}$;

(ii)-3 If both $\mathcal{R}_1 > 1$ *and* $\mathcal{R}_2 > 1$*, but* $\mathcal{R}_2 > \mathcal{R}_1$*, then in addition to the DFE, there are the species 1 endemic equilibrium* E_1 *and species 2 endemic equilibrium* E_2*; but* E_1 *is unstable and* E_2 *is globally asymptotically stable in* $\mathfrak{R}^7_+ \setminus \{E_0, E_1\}$*;*

Theorem 4.2.1 shows that both of the malaria parasites will all die out (when $\mathcal{R}_0 \leq 1$), or competitive exclusion generically holds when $\mathcal{R}_0 > 1$—"generic" in the sense of $\mathcal{R}_1 \neq \mathcal{R}_2$. In [10], no results were obtained for the case when there are more than one species that have the same value of its species-specific reproduction number. Turning to the two species case, this corresponds to the case $\mathcal{R}_1 = \mathcal{R}_2 > 1$. Some tedious but straightforward calculations show that in such a critical situation, in addition to E_0, E_1 and E_2, there will be infinitely many co-existence equilibria (positive equilibria where all components are positive). This and the results in Theorem 4.2.1 are demonstrated in Figure 4.3, where the equilibria shown by bold font are the stable ones.

Although the global dynamics of system (4.2.3) are unknown when $\mathcal{R}_1 = \mathcal{R}_2 > 1$, we conjecture that the asymptotical behavior of a solution depends on the initial data. Since $\mathcal{R}_1$ and $\mathcal{R}_2$ contain more than ten model parameters, the equation $\mathcal{R}_1 = \mathcal{R}_2 > 1$ is indeed a very sensitive condition and is unlikely to hold in reality. Therefore, we conclude that generically, two species of the malaria parasites cannot co-persist within a single host. This suggests that when modeling the spread of malaria at the population level, we can exclude the class of hosts that carry two species of the malaria parasites.

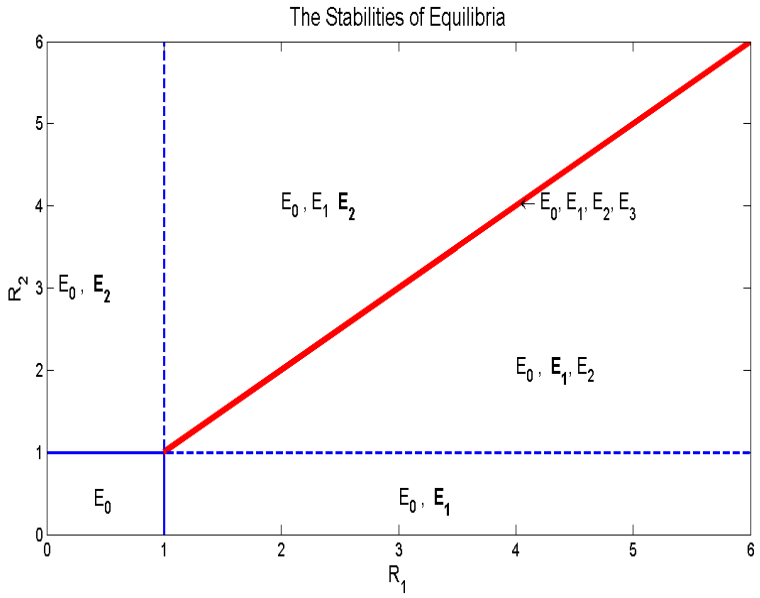

Figure 4.3: Summary of equilibria and their stabilities: only those in bold font are stable. Red line represents the co-existence.

4.3 Between-host level

In this section, we explore the spread of two species of the malaria parasites between the human and mosquito populations. To this end, we need a basic model for a single species and then extend it to a model for two species, as we did for the within host level in the previous section .

4.3.1 A single species model

For a single species, we propose the following model, which is a modification of the classic Ross-Macdonald model:

$$\begin{cases} S'_H = b_H N_H - d_H S_H - ac_1 \dfrac{S_H}{N_H} I_M + \beta R_H, \\ I'_H = ac_1 \dfrac{S_H}{N_H} I_M - d_H I_H - \gamma I_H, \\ R'_H = \gamma I_H - d_H R_H - \beta R_H, \\ S'_M = b_M N_M - d_M S_M - ac_2 S_M \dfrac{I_H}{N_H}, \\ I'_M = ac_2 S_M \dfrac{I_H}{N_H} - d_M I_M. \end{cases} \tag{4.3.1}$$

Here, the host population is divided into three classes: susceptible (S_H), infectious (I_H) and recovered (R_H), with $N_H = S_H + I_H + R_H$ being the total host population; the mosquito population is divided into two classes: susceptible (S_H) and infectious (I_H), with $N_M = S_M + I_M$ being the total mosquito population. Our emphasis in this work is the interaction of two species, thus we ignore the latency since incorporation of latency will result in a model that is an infinite dimensional system, and hence, increase the level of difficulty.

The model parameters are explained below:

- b_H and b_M are the birth rates of humans and mosquitoes (for humans, "birth" is in a general sense including other recruitments besides natural birth), and d_H and d_M are the death rates of humans and mosquitoes;
- a is the biting rate, c_1 is the probability that a bite by an infectious mosquito of a susceptible human being will cause infection, and c_2 is the probability that a bite by a susceptible mosquito of an infectious human being will cause infection;
- γ is the combined recover rate including the natural recovery and the recovery

due to treatments;

- the temporary immunity of the recovered hosts follows a negative exponential distribution $e^{-\beta t}$, hence recovered hosts return to the susceptible class at rate β.

It is known that malaria causes deaths of humans. Here, to make the model more mathematically tractable, we also assume that sufficient and effective treatments are available so that there will be no deaths caused by malaria. We further assume that in the absence of the disease, recruitment and death for both human and mosquito populations are balanced so that the total populations of host and mosquitoes remain constants. This is achieved by assuming $b_H = d_H$ and $b_M = d_M$ in (4.3.1).

Under the above scenarios, the total populations of human beings and mosquitoes are constants since $S'_H + I'_H + R'_H = b_H N_H - d_H(S_H + I_H + R_H) = b_H N_H - d_H N_H = 0$ and $S'_M + I'_M = b_M N_M - d_M(S_M + I_M) = b_M N_M - d_M N_M = 0$. This allows us to replace the term R_H by $N_H - S_H - I_H$ and $S_M = 1 - I_M$ to reduce the system. Rescaling the system by $\frac{S_H}{N_H} \to S_H$, $\frac{I_H}{N_H} \to I_H$ and $\frac{I_M}{N_M} \to I_M$ leads to

$$\begin{cases} S'_H = d_H - d_H S_H - a c_1 m S_H I_M + \beta(1 - S_H - I_H), \\ I'_H = a c_1 m S_H I_M - d_H I_H - \gamma I_H, \\ I'_M = a c_2 (1 - I_M) I_H - d_M I_M. \end{cases} \tag{4.3.2}$$

where $m = N_M/N_H$. By the standard method (see, e.g., Smith [16] or Thieme [24]), one can show that for any given initial values $x_0 = (S_H(0), I_H(0), I_M(0))$ satisfying

$$0 \le S_H(0) \le 1, \;\; 0 \le I_H(0) \le 1, \;\; 0 \le I_M(0) \le 1, \tag{4.3.3}$$

the system (4.3.2) has a unique solution $(S_H(t, x_0), I_H(t, x_0), I_M(t, x_0))$ satisfying

$(S_H(0, x_0), I_H(0, x_0), I_M(0, x_0)) = x_0$ and

$$0 \le S_H(t, x_0) \le 1, \;\; 0 \le I_H(t, x_0) \le 1, \;\; 0 \le I_M(t, x_0) \le 1, \tag{4.3.4}$$

for all $t \ge 0$. Thus, model (4.3.2) (and hence (4.3.1)) is well-posed.

Obviously, system (4.3.2) admits the disease free equilibrium: $E_0 = (1, 0, 0)$. Linearizing system (4.3.2) at E_0 leads to the following linear system

$$\begin{cases} S_H' = -(d_H + \beta)S_H - \beta I_H - ac_1 m I_M, \\ I_H' = -(d_H + \gamma)I_H + ac_1 m I_M \\ I_M' = ac_2 I_H - d_M I_M, \end{cases} \tag{4.3.5}$$

from which, we can obtain the next generation matrix FV^{-1} where

$$F = \begin{pmatrix} 0 & ac_1 \\ ac_2 m & 0 \end{pmatrix}, \quad V = \begin{pmatrix} (d_H + \gamma) & 0 \\ 0 & d_M \end{pmatrix}.$$

By the next generation method [25], the basic reproduction number of the model (4.3.2) is given as the spectral radius of FV^{-1}:

$$\mathcal{R}_0 = r(FV^{-1}) = \sqrt{\frac{a^2 c_1 c_2 m}{d_M(d_H + \gamma)}} \tag{4.3.6}$$

The stability of E_0 is fully determined by $\mathcal{R}_0$, as is confirmed in the following theorem.

Theorem 4.3.1 *The disease free equilibrium E_0 is globally asymptotically stable if $\mathcal{R}_0 < 1$, and it is unstable when $\mathcal{R}_0 > 1$.*

Proof. The local asymptotic stability of E_0 when $\mathcal{R}_0 < 1$ and the instability of

E_0 when $\mathcal{R}_0 > 1$ follow directly from Theorem 2 in [25]. We only need to show the global attractiveness of E_0 when $\mathcal{R}_0 < 1$. Applying (4.3.4) to the I'_H and I'_M equations in (4.3.2), we see that (4.3.4) has the following as an upper comparison system for the I'_H and I'_M equations in system (4.3.2):

$$\begin{cases} I'_H = ac_1 mI_M - (d_H + \gamma)I_H, \\ I'_M = ac_2 I_H - d_M I_M, \end{cases} \tag{4.3.7}$$

which has the matrix representation $I'(t) = (F - V)I(t)$ where $I = (I_H, I_M)$. Clearly, system (4.3.7) is the I'_H and I'_M equations in (4.3.5). Note that $\mathcal{R}_0 = r(FV^{-1}) < 1$ if and only if $\sigma(F - V) < 0$ where $\sigma(F - V)$ is the stability modulus of the matrix $F - V$, that is,

$$\sigma(F - V) = \max\{Re(\lambda) : \lambda \text{ is an eigenvalue of } F - V\}.$$

Since system (4.3.7) is linear, the local stability of the trivial solution implies its global stability, that is, every solution of system (4.3.7) approaches the trivial solution. On the other hand, system (4.3.7) is cooperative. By the comparison theorem (see, e.g., Theorem 2.1 in [16]), for every solution satisfying system (4.3.3), its I_H and I_M components will be bounded from above by the solution of system (4.3.7) that has the same initial values, and thus, they will approach zero as well. Now, applying the theory of asymptotically autonomous systems (see, e.g., [3]) to the S_H and S_M equations in (4.3.2), we conclude that $S_H(t) \to 1$ as $t \to \infty$. This implies that E_0 is indeed globally attractive if $\mathcal{R}_0 < 1$, and completes the proof. □

When $R_0 > 1$, by explicitly solving the algebraic system for equilibria of system (4.3.2), we find that the system (4.3.2) has a unique endemic equilibrium $E^* =$

(S_H^*, I_H^*, I_M^*) where

$$
\begin{aligned}
S_H^* &= \frac{N_H (d_H + \gamma)(d_M d_H + d_M \gamma + \beta d_M + d_H a e_{21} + \epsilon_1 a c_2)}{a c_2 \left(a c_1 N_M d_H + a c_1 N_M \gamma + \beta N_H d_H + \beta N_H \gamma + {d_H}^2 N_H + d_H N_H \gamma + \beta a c_1 N_M\right)}, \\
I_H^* &= \frac{N_H d_M (d_H + \gamma_1)(d_H + \beta)(R_0 - 1)}{\left(a c_1 N_M d_H + a e_{11} N_M \gamma + \beta N_H d_H + \beta N_H \gamma + {d_H}^2 N_H + d_H N_H \gamma + \beta a c_1 N_M\right) c_2 a}, \\
I_M^* &= \frac{N_H d_M (d_H + \gamma_1)(d_H + \beta)(R_0 - 1)}{d_M d_H + d_M \gamma + \beta d_M + d_H a e_{21} + \beta a c_2}.
\end{aligned}
\tag{4.3.8}
$$

Moreover, by a similar argument to that in the proof of Theorem 3.3 in [28], we can show that if $\mathcal{R}_0 > 1$, then the I_H and I_M components of solutions of (4.3.2) are uniformly strongly persistent in the sense stated in the following theorem.

Proposition 4.3.1 *Assume that $\mathcal{R}_0 > 1$. Then I_H and I_M are uniformly persistent in the sense that there exists an $\eta > 0$ such that for every solution of system* (4.3.2) *with $I_H(0) > 0$ and $I_M(0) > 0$,*

$$\liminf_{t\to\infty} I_H(t) \geq \eta, \quad \liminf_{t\to\infty} I_M(t) \geq \eta.$$

Proof. The proof is almost a duplicate of that of Theorem 3.3 in [28], and hence is omitted here in order to save space. □

Let

$$\Gamma := \left\{x(t) = (S_H, I_H, I_M) \in R_+^3 : S_H + I_H \leq 1, I_M \geq 1\right\}$$

and denote the interior of Γ by Γ_0. The following theorem gives sufficient conditions that ensure the global stability of E^* in Γ_0.

Theorem 4.3.2 *Assume that $R_0 > 1$. Then the unique endemic equilibrium E^* of system*

(4.3.2) *is globally stable in* Γ_0 *provided that*

$$d_H + d_M - \max(-\beta, \beta - \gamma) > 0. \tag{4.3.9}$$

Proof. We will apply the main theorem in [11] to prove the global asymptotic stability of the unique endemic equilibrium E^*. To this end, we need to verify the so called Bendixson criteria: $\bar{q} < 0$, where the definition of $\bar{q}$ will be given later as we proceed. For the reader's convenience, we will adopt the same notations and terminology as used in [11]. The theory has also been applied to some other disease models to prove the global asymptotic stability of the unique endemic equation (see, e.g., [12])

Firstly, applying the comparison method to the S_H equation in system (4.3.2), we can easily show that S_H is also uniformly persistent. This together with Proposition 4.3.1 leads to the uniform persistence of system (4.3.2) in the bounded set Γ, which implies the existence of a compact $K \subset \Gamma_0$ that is absorbing with respect to system (4.3.2) in Γ. Namely, for every compact set $K_0 \subset \Gamma_0$, we have $x(t, K_0) \subset K$ for sufficiently large t, where $x(t, x_0)$ represents the solution of (4.3.2) with the initial condition $x_0 \in K$ (see, e.g., [1]).

The Jacobian matrix J of model system (4.3.2) associated with a general solution $x(t) = (S_H(t), I_H(t), I_M(t))$ is

$$J = \begin{pmatrix} -d_H - ac_1 mI_M - \beta & -\beta & -ac_1 mS_H \\ ac_1 mI_M & -d_H - \gamma & ac_1 mS_H \\ 0 & ac_2(1 - I_M) & -ac_2 I_H - d_M \end{pmatrix},$$

and its second additive compound matrix (see [12] for the definition; also refer to the

Appendix of [12] for detailed calculations) can be calculated as

$$\begin{pmatrix} -2d_H - ac_1mI_M - \beta - \gamma & ac_1mS_H & ac_1mS_H \\ ac_2(1 - I_M) & -d_H - d_M - \beta - ac_1mI_M - ac_2I_H & -\beta \\ 0 & ac_1mI_M & -d_H - d_M - ac_2I_H - \gamma \end{pmatrix}.$$

Let $A(x) = diag(1, I_H/I_M, I_H/I_M)$. Then A is C^1 and nonsingular in Γ_0. Let $f = (f_1, f_2, f_3)$ denote the vector field of system (4.3.2). Then,

$$A_f A = diag(0, \frac{I_M}{I_H}(\frac{I_H}{I_M})_f, \frac{I_M}{I_H}(\frac{I_H}{I_M})_f),$$

where A_f is the matrix resulting from replacing each of the entries of A by its directional derivative along f. Here for a scalar function $g = g(S_H, I_H, I_M)$, its directional derivative along f is

$$g_f = \left(\frac{\partial g}{\partial S_H}, \frac{\partial g}{\partial I_H}, \frac{\partial g}{\partial I_M}\right) \cdot f = \frac{\partial g}{\partial S_H} f_1 + \frac{\partial g}{\partial I_H} f_2 + \frac{\partial g}{\partial I_M} f_3.$$

Following [12], we construct the matrix $B = (B_{ij})_{3\times 3}$ in terms of

$$\begin{aligned} B_{11} &= -2d_H - ac_1mI_M - \beta - \gamma, \\ B_{12} &= \left(ac_1mS_H\frac{I_M}{I_H}, ac_1mS_H\frac{I_M}{I_H}\right), \\ B_{21} &= \left(ac_2(1 - I_M)\frac{I_H}{I_M}, 0\right)^T, \\ B_{22} &= \begin{pmatrix} b_{11} & -\beta \\ ac_1mI_M & b_{22} \end{pmatrix}, \\ b_{11} &= \frac{I_M}{I_H}(\frac{I_H}{I_M})_f - d_H - d_M - \beta - ac_1mI_M - ac_2I_H, \\ b_{22} &= \frac{I_M}{I_H}(\frac{I_H}{I_M})_f - d_H - d_M - \gamma - ac_2I_H. \end{aligned}$$

We select the vector norm in R^3 to be

$$\|(u, v, w)\|_0 = \sup\{|u|,\ |v| + |w|\},$$

and let κ_0 denote the Lozinskiĭ measure induced by this vector norm (for the definition see e.g., [13]). By [14], the following estimate holds:

$$\kappa_0(B) \leq \sup\{g_1,\ g_2\}, \tag{4.3.10}$$

where

$$g_1 = B_{11} + \|B_{12}\|_r = -2d_H - ac_1 mI_M - \beta - \gamma + \frac{ac_1 mS_H I_M}{I_H}, \tag{4.3.11}$$

and

$$\begin{aligned} g_2 =& \kappa_1(B_{22}) + \|B_{21}\|_l = \frac{I_M}{I_H}(\frac{I_H}{I_M})_f - d_H - d_M - ac_2 I_H \\ &+ \max\{-\beta, \beta - \gamma\} + \frac{ac_1(1 - I_M)I_H}{I_M}. \end{aligned} \tag{4.3.12}$$

Here, for $\|(u, v)\|_r = \max\{|u|, |v|\}$, $\|(u, v)^T\|_l = |u| + |v|$, and κ_1 is the Lozinskiĭ measure with respect to the l_1 norm in R^2. Thus, $\kappa_1(B_{22})$ is calculated by the following procedure: add the absolute value of the off-diagonal elements to the diagonal one in each column of B_{22}, then take the maximum of the two sums [4].

From the equation (4.3.2), we find

$$\frac{I_M}{I_H}(\frac{I_H}{I_M})_f = \frac{I'_H}{I_H} - \frac{I'_M}{I_M}, \tag{4.3.13}$$

and

$$\frac{ac_1 mS_H I_M}{I_H} = \frac{I'_H}{I_H} + d_H + \gamma, \tag{4.3.14}$$

$$\frac{ac_2(1-I_M)I_H}{I_M} = \frac{I'_M}{I_M} - d_M I_M. \tag{4.3.15}$$

The uniform persistence of the solution in Proposition 4.3.1 ensures that there are $\eta > 0$ and $T_0 > 0$, for any solution of (4.3.2), regardless of the initial condition in K (the absorbing set), satisfying

$$I_H(t) > \eta, \quad I_M(t) > \eta, \quad \text{for } t > T_0. \tag{4.3.16}$$

Substituting equalities (4.3.13)-(4.3.15) into (4.3.11)-(4.3.12) and making use of inequalities (4.3.16), we obtain

$$\begin{aligned} g_1 &= -2d_H - ac_1 m I_M - \beta - \gamma + \frac{ac_1 m S_H I_M}{I_H} \\ &\leq -2d_H - ac_1 m\eta - \beta - \gamma + \frac{I'_H}{I_H} + d_H + \gamma \\ &\leq \frac{I'_H}{I_H} - (d_H + \beta) \text{ for } t > T_0, \end{aligned} \tag{4.3.17}$$

and

$$\begin{aligned} g_2 &= \frac{I'_H}{I_H} - \frac{I'_M}{I_M} - d_H - d_M + \max\{-\beta, \beta-\gamma\} - ac_2 I_H + \frac{ac_2(1-I_M)I_H}{I_M} \\ &= \frac{I'_H}{I_H} - d_M I_M - d_H - d_M + \max\{-\beta, \beta-\gamma\} - ac_2 I_H \\ &\leq \frac{I'_H}{I_H} - d_H\eta - d_M - d_M + \max\{-\beta, \beta-\gamma\} - ac_2\eta \\ &\leq \frac{I'_H}{I_H} - (d_H + d_M - \max\{-\beta, \beta-\gamma\}) \text{ for } t > T_0. \end{aligned} \tag{4.3.18}$$

Let $\delta_1 = d_H + \beta$ and $\delta_2 = d_H + d_M - \max\{-\beta, \beta-\gamma\}$, and set $\delta = \min\{\delta_1, \delta_2\}$. Then under the condition (4.3.9), $\delta > 0$ and

$$\kappa_0(B) \leq \frac{I'_H}{I_H} - \delta \text{ for } t > T_0.$$

Thus, along each solution (S_H, I_H, I_M) to (4.3.2) such that $(S_H(0), I_H(0), I_M(0)) \in K$ and for $t > T_0$, we get

$$\frac{1}{t}\int_0^t \kappa_0(B(s))\,\mathrm{d}s \le \frac{1}{t}\int_0^T \kappa_0(B(s))\,\mathrm{d}s + \frac{1}{t}\log\frac{I_H(t)}{I_H(T)} - \delta\frac{t-T}{t} \to -\delta < 0 \ \text{ as } \ t \to \infty.$$

Therefore, we have

$$\bar{q} := \limsup_{t\to\infty} \sup_{x_0\in\Gamma_0} \frac{1}{t}\kappa_0(B(s, x_0))\,\mathrm{d}s \le -\frac{\delta}{2},$$

verifying the Bendixson criterion. By theorem 2.3 and 3.1 in [11], we conclude that E^* is globally asymptotically stable in Γ_0, and the proof is complete. □

Remark 4.3.1 *Relation* (4.3.9) *can be guaranteed by some more explicit condition. For example, each of the following is such a condition:*

(C1) $\beta < \frac{r}{2}$;

(C2) $\frac{\gamma}{2} \le \beta < d_H + d_M + \gamma$.

Remark 4.3.2 *Translating the results in Theorems 4.3.1 and 4.3.2 for* (4.3.2) *to* (4.3.1)*, parallel conclusions can be drawn for system* (4.3.1) *in* $\mathfrak{R}^4_+$ *space in a straightforward way by adding the component* $S_m = 1 - I_m$.

4.3.2 A two-species model

In this subsection, we consider the situation in which two species of malaria parasites have been brought into the same region. We would like to know if both two species can persist in the region. We naturally wish to expand the one-species model (4.3.1) to this case by adding another set of variables corresponding to the second species. In other

words, we will adopt all assumptions in Subsection 4.3.1 leading to system (4.3.1), and accordingly propose the following two-species model

$$\begin{cases} S'_H = d_H N_H - d_H S_H - ae_{11}\dfrac{S_H}{N_H} I_{M1} - ae_{12}\dfrac{S_H}{N_H} I_{M2} + \beta_1 R_{H1} + \beta_2 R_{H2}, \\ I'_{H1} = ae_{11}\dfrac{S_H}{N_H} I_{M1} - d_H I_{H1} - \gamma_1 I_{H1} + ae_1 \dfrac{R_{H2}}{N_H} I_{M1}, \\ R'_{H1} = \gamma_1 I_{H1} - ae_2 \dfrac{R_{H1}}{N_H} I_{M2} - d_H R_{H1} - \beta_1 R_{H1}, \\ I'_{H2} = ae_{12}\dfrac{S_H}{N_H} I_{M2} - d_H I_{H2} - \gamma_2 I_{H2} + ae_2 \dfrac{R_{H1}}{N_H} I_{M2}, \\ R'_{H2} = \gamma_2 I_{H2} - ae_1 \dfrac{R_{H2}}{N_H} I_{M1} - d_H R_{H2} - \beta_2 R_{H2}, \\ S'_M = d_M N_M - d_M S^*_M - ae_{21} S_M \dfrac{I_{H1}}{N_H} - ae_{22} S^*_M \dfrac{I_{H2}}{N_H}, \\ I'_{M1} = ae_{21} S_M \dfrac{I_{H1}}{N_H} - d_M I_{M1}, \\ I'_{M2} = ae_{22} S_M \dfrac{I_{H2}}{N_H} - d_M I_{M2}. \end{cases} \tag{4.3.19}$$

Here, all variables and parameters are self-explanatory and are as in (4.3.1), but some have integer subscripts that distinguish species 1 and species 2, respectively, except for the last term in the I'_{H1} and I'_{H2} equations. These two new terms are the result of the complication of cross immunity between two species. Indeed, immunization studies in [9, 31] with *P. vivax* and *P. falciparum* RAS performed with human volunteers did not seem to support cross immunity, meaning that individuals recovered from infection by one speciesn do not gain extra protection from the other species. Another study shown in [8] conducted in Southeast Asia actually showed that the incidence of *P.vivax* infection after treatment of *P.falciparum* infection is substantially greater than that would be expected on the basis of entomological inoculation rates, and this motivates us to use a probability parameter e_1 different from e_{11}, and e_2 different from e_{12}. Clearly, $e_1 = 0 = e_2$ corresponds to the situation of complete cross immunity, and in this case the model is of competitive nature. However, when $e_1 > 0$ and $e_2 > 0$, the

model demonstrates not only *competitive* but also *cooperative* interactions between the two species.

This model can be graphically illustrated by the diagram in Figure 4.4.

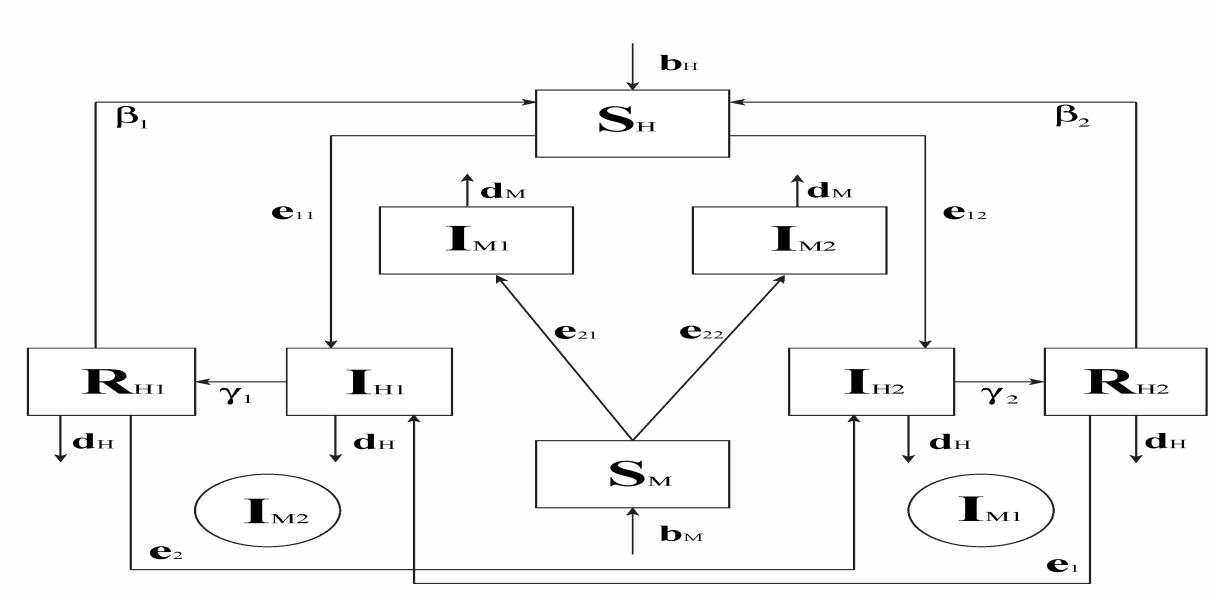

Figure 4.4: Two species case at population level

We still denote by N_H the total population of human beings, by N_M the total population of the female mosquitoes. Addition still gives $S'_H + I'_{H1} + R'_{H1} + I'_{H2} + R'_{H2} = b_H N_H - d_H N_H = 0$ and $S'_M + I'_{M1} + I'_{H1} = b_H N_M - d_H N_M = 0$, that is, N_H and N_M remain constants. As usual, we rescale the variables in system (4.3.19) by

$$\frac{S_H}{N_H} \to S_H, \quad \frac{I_{Hi}}{N_H} \to I_{Hi}, \quad \frac{R_{Hi}}{N_H} \to R_{Hi}, \quad i = 1, 2,$$

and

$$\frac{S_M}{N_M} \to S_M, \quad \frac{I_{Mi}}{N_M} \to I_{Mi}, \quad i = 1, 2.$$

yielding

$$\begin{cases} S'_H = d_H - d_H S_H - ae_{11} m S_H I_{M1} - ae_{12} m S_H I_{M2} + \beta_1 R_{H1} + \beta_2 R_{H2}, \\ I'_{H1} = ae_{11} m S_H I_{M1} - d_H I_{H1} - \gamma_1 I_{H1} + ae_1 m R_{H2} I_{M1}, \\ R'_{H1} = \gamma_1 I_{H1} - ae_2 m R_{H1} I_{M2} - d_H R_{H1} - \beta_1 R_{H1}, \\ I'_{H2} = ae_{12} m S_H I_{M2} - d_H I_{H2} - \gamma_2 I_{H2} + ae_2 m R_{H1} I_{M2}, \\ R'_{H2} = \gamma_2 I_{H2} - ae_1 n R_{H2} I_{M1} - d_H R_{H2} - \beta_2 R_{H2}, \\ S'_M = d_M - d_M S_M - ae_{21} S_M I_{H1} - ae_{22} S_M I_{H2}, \\ I'_{M1} = ae_{21} S_M I_{H1} - d_M I_{M1}, \\ I'_{M2} = ae_{22} S_M I_{H2} - d_M I_{M2}. \end{cases} \tag{4.3.20}$$

where $m = N_M/N_H$.

From the biological meaning of all variables in system (4.3.20), we only need to consider system (4.3.20) within the set

$$X = \left\{ \begin{array}{l} (S_H, I_{H1}, R_{H1}, I_{H2}, R_{H2}, S_M, I_{M1}, I_{M2}) \in \mathfrak{R}^8 : \\ 0 \le S_H, S_M I_{H1}, R_{H1}, I_{H2}, R_{H2}, I_{M1}, I_{M2} \le 1, \\ S_H + I_{H1} + R_{H1} + I_{H2} + R_{H2} = 1,\ S_M + I_{M1} + I_{M1} = 1. \end{array} \right\}.$$

Since the right-hand side contains only polynomial functions, by the standard ODE theory, for any initial vector

$$x_0 = (S_H(0), I_{H1}(0), R_{H1}(0), I_{H2}(0), R_{H2}(0), S_M, I_{M1}(0), I_{M2}(0)) \in \mathfrak{R}^8,$$

system (4.3.20) has a unique solution

$$x(t) = (S_H(t, x_0), I_{H1}(t, x_0), R_{H1}(t, x_0), I_{H2}(t, x_0), R_{H2}(t, x_0), S_M(t, x_0), I_{M1}(t, x_0), I_{M2}(t, x_0)),$$

satisfying $x(0) = x_0$. Denote by $\Phi(t)$ the semi-flow generated by the solutions of system (4.3.20), i.e.,

$$\begin{aligned}\Phi(t)x_0 &= x(t, x_0)\\ &= (S_H(t, x_0), I_{H1}(t, x_0), R_{H1}(t, x_0), I_{H2}(t, x_0), R_{H2}(t, x_0),\\ &\quad S_M(t, x_0), I_{M1}(t, x_0), I_{M2}(t, x_0)) .\end{aligned}$$

By the standard argument on invariance of semi-flows (see, e.g., Smith [16]), we can easily show that the set X is positively invariant for system (4.3.20) in the sense that if $x_0 \in X$, then $\Phi(t)x_0 \in X$ for all $t \geq 0$. This is justification that the model (4.3.20) is well-posed and is thus biologically meaningful. In the rest of this chapter, we will discuss the long term dynamics of (4.3.20) in X.

4.3.3 A two-species model—disease free equilibrium and basic reproduction number

The model (4.3.20) has a disease free equilibrium (DFE), given by $\bar{E}_0 = (1, 0, 0, 0, 0, 1, 0, 0,)$. Here in this section, we will add a bar to the notation for the equilibria and basic reproduction numbers to distinguish the two-species case from the one-species case in section 4.3.1.

To explore the possibilities of other equilibria, we define

$$\mathcal{R}_i = \sqrt{\frac{a^2 e_{1i} e_{2i} m}{d_M(d_H + \gamma_i)}},\ i = 1, 2.$$

Clearly, $\mathcal{R}_i$ is the i-species basic reproduction number for the malaria parasite in the absence of species j ($j \neq i$). Therefore, by the results in Section 4.3.1, we know that if

$\mathcal{R}_1 > 1$, then there is the species 1 endemic equilibrium

$$\bar{E}_1^* = (S_{H1}^*, I_{H1}^*, R_{H1}^*, 0, 0, S_{M1}^*, I_{M1}^*, 0)$$

where S_{H1}^*, I_{H1}^*, S_M^* and I_{M1}^* are all positive constants given by formulas similar to (4.3.8), but with those species specific parameters associated to species 1, and $R_{H1}^* = 1 - S_{H1}^* - I_{H1}^*$. Similarly, when $\mathcal{R}_2 > 1$, there is the species 2 endemic equilibrium

$$\bar{E}_2^* = (S_{H2}^*, 0, 0, I_{H2}^*, R_{H2}^*, 0, S_{M2}^*, I_{M12}^*)$$

with $R_{H2}^* = 1 - S_{H2}^* - I_{H2}^*$.

Linearizing system (4.3.20) at $\bar{E}_0$ leads to

$$\begin{cases} S_H' = -d_H S_H - ae_{11} m I_{M1} - ae_{12} m I_{M2} + \beta_1 R_{H1} + \beta_2 R_{H2}, \\ I_{H1}' = ae_{11} m I_{M1} - (d_H + \gamma_1) I_{H1} \\ R_{H1}' = \gamma_1 I_{H1} - (d_H + \beta_1) R_{H1}, \\ I_{H2}' = ae_{12} m I_{M2} - (d_H + \gamma_2) I_{H2}, \\ R_{H2}' = \gamma_2 I_{H2} - (d_H + \beta_2) R_{H2}, \\ S_M' = -d_M S_M - ae_{21} I_{H1} - ae_{22} I_{H2}, \\ I_{M1}' = ae_{21} I_{H1} - d_M I_{M1}, \\ I_{M2}' = ae_{22} I_{H2} - d_M I_{M2}. \end{cases} \tag{4.3.21}$$

Note that in system (4.3.21), the four equations for I_{H1}', I_{H2}, I_{M1} and I_{M2} are decoupled

from the other four equations, forming the following sub-system:

$$\begin{cases} I'_{H1} = ae_{11}mI_{M1} - d_H I_{H1} - \gamma_1 I_{H1}, \\ I'_{M1} = ae_{21}I_{H1} - d_M I_{M1}, \\ I'_{H2} = ae_{12}mI_{M2} - d_H I_{H2} - \gamma_2 I_{H2}, \\ I'_{H1} = ae_{22}I_{H2} - d_M I_{M2}. \end{cases} \tag{4.3.22}$$

Let $\bar{I} = (I_{H1}, I_{M1}, I_{H2}, I_{M2})$. Note that we have switched the order of I_{M1} and I_{H2} in $\bar{I}$. Obviously, system (4.3.22) can be represented by the matrix form

$$\bar{I}'(t) = (\bar{F} - \bar{V})\bar{I}(t). \tag{4.3.23}$$

where $\bar{F}$ is the new infection matrix given by

$$\bar{F} = \begin{pmatrix} 0 & ae_{11}m & 0 & 0 \\ ae_{21} & 0 & 0 & 0 \\ 0 & 0 & 0 & ae_{12}m \\ 0 & 0 & ae_{22} & 0 \end{pmatrix},$$

and

$$\bar{V} = \begin{pmatrix} (d_H + \gamma_1) & 0 & 0 & 0 \\ 0 & d_M & 0 & 0 \\ 0 & 0 & (d_H + \gamma_2) & 0 \\ 0 & 0 & & d_M \end{pmatrix}.$$

Following [25], the next generation matrix for the model (4.3.20) is then given by

$$\bar{F}\bar{V}^{-1} = \begin{pmatrix} 0 & ae_{11}m/d_M & 0 & 0 \\ ae_{21}/(d_H+\gamma_1) & 0 & 0 & 0 \\ 0 & 0 & 0 & ae_{12}m/d_M \\ 0 & 0 & ae_{22}/(d_H+\gamma_2) & 0 \end{pmatrix},$$

and the basic reproduction number is the spectral radius of this matrix:

$$\bar{\mathcal{R}}_0 = r(\bar{F}\bar{V}^{-1}) = \max\left\{\sqrt{\frac{a^2e_{11}e_{21}m}{d_M(d_H+\gamma_1)}},\ \sqrt{\frac{a^2e_{12}e_{22}m}{d_M(d_H+\gamma_2)}}\right\} = \max\{\mathcal{R}_1, \mathcal{R}_2\}. \quad (4.3.24)$$

The following theorem is a direct result of Theorem 2 in [25], which confirms that the stability of the DFE is fully determined by $\bar{\mathcal{R}}_0$.

Theorem 4.3.3 . *If $\bar{\mathcal{R}}_0 < 1$, then the disease free equilibrium is asymptotically stable. If $\bar{\mathcal{R}}_0 > 1$, it is unstable.*

4.3.4 A two-species model—disease persistence

When $\bar{\mathcal{R}}_0 > 1$, at least one of the two individual basic reproduction numbers $\mathcal{R}_1$ and $\mathcal{R}_2$ is larger than 1. If $\mathcal{R}_1 > 1$, we have seen in the above subsection that $\bar{E}_1^* = (S_{H1}^*, I_{H1}^*, R_{H1}^*, 0, 0, S_{M1}^*, I_{M1}^*, 0)$ exists. We introduce the following quantity

$$\bar{\mathcal{R}}_{21} = \frac{a^2e_{12}e_{22}mS_{H1}^*S_{M1}^* + a^2e_{22}e_2mS_{M1}^*R_{H1}^*}{d_M(d_H+\gamma_2)},$$

which measures the number of secondary infections by species 2, assuming that species 1 is settled at $\bar{E}_1^*$. We may call $\bar{\mathcal{R}}_{21}$ *the species 1 mediated basic reproduction number for species 2*. Symmetrically, if $\mathcal{R}_2 > 1$, then $\bar{E}_2^* = (S_{H2}^*, 0, 0, I_{H2}^*, R_{H1}^*, 0, S_{M2}^*, I_{M2}^*)$ exists and we can define *the species 2 mediated basic reproduction number for species*

1 by

$$\bar{\mathcal{R}}_{12} = \frac{a^2 e_{11} e_{21} m S^*_{H2} S^*_{M2} + a^2 e_{21} e_1 m S^*_{M2} R^*_{H2}}{d_M(d_H + \gamma_2)}.$$

We point out that the *cooperative effects* between the two species due to the lack of cross immunity is also reflected in the fact that $\bar{\mathcal{R}}_{21}$ and $\bar{\mathcal{R}}_{12}$ are different from $\bar{\mathcal{R}}_0$.

The following theorem provides some information on the disease dynamics under $\bar{\mathcal{R}}_0 > 1$.

Theorem 4.3.4 . *Assume that* $\bar{\mathcal{R}}_0 > 1$.

(i) In the case $\mathcal{R}_1 > 1$*: if* $\bar{\mathcal{R}}_{21} > 1$*, then* $\bar{E}^*_1$ *is unstable; if* $\bar{\mathcal{R}}_{21} < 1$*, then* $\bar{E}^*_1$ *is asymptotically stable provided that*

$$d_H + d_M - \max(-\beta_1, \beta_1 - \gamma_1) > 0. \tag{4.3.25}$$

(ii) In the case $\mathcal{R}_2 > 1$*: if* $\bar{\mathcal{R}}_{12} > 1$*, then* $\bar{E}^*_2$ *is unstable; if* $\bar{\mathcal{R}}_{12} < 1$*, then* $\bar{E}^*_1$ *is asymptotically stable provided that*

$$d_H + d_M - \max(-\beta_2, \beta_2 - \gamma_2) > 0. \tag{4.3.26}$$

Proof: We only give the proof of (i), as the proof of (ii) is similar.

Linearizing system (4.3.20) at $\bar{E}^*_1$ and expanding the determinant defining the characteristic equation, after some tedious calculations, the characteristic equation $H_2(z) = 0$ is given by

$$H(z) = (z + d_M)(z + d_H)(z + \beta_2 + a e_1 n I^*_{M_1}) h_1(z) h_2(z), \tag{4.3.27}$$

and where

$$h_1(z) = z^2 + (\gamma_1 + d_M + d_H)z + (d_M d_H + d_M\gamma_1 - a^2 e_{12}e_{22}mS^*_{H1}S^*_{M1} - a^2 e_{22}e_2 mS^*_{M1}R^*_{H1}),$$

$$h_2(z) = z^3 + Q_1 z^2 + Q_2 z + Q_3,$$

$$\begin{aligned}
Q_1 =\ & ac_2 I^*_{H1} + \gamma_1 + ac_1 mI^*_{M1} + d_M + 2\,d_H + \beta_1,\\
Q_2 =\ & \beta\, d_M + \gamma_1 d_M + ac_1 mI^*_{M1}d_M + 2\,d_M d_H + a^2 c_1 mI_{M1}c_2 I^*_{H1} + \gamma_1 ac_2 I^*_{H1}\\
& - a^2 c_2 S^*_{M1}c_1 mS^*_{H1} + ac_1 mI^*_{M1}\gamma_1 + \beta_1\gamma_1 + ac_1 mI^*_{M1}\beta_1 + 2ac_2 I^*_{H1}d_H + d_H\gamma_1\\
& + ac_1 mI^*_{M1}d_H + \beta_1\, d_H + d_H^2 + ac_2 I^*_{H1}\beta_1\\
Q_3 =\ & d_M\beta_1\gamma_1 + ac_2 I^*_{H1}d_H^2 + d_M ac_1 mI^*_{M1}d_H + ac_2 I^*_{H1}d_H\beta_1 + a^2 c_1 mI^*_{M1}c_2 I^*_{H1}d_H\\
& - \beta_1\, a^2 c_2 S^*_{M1}c_1 mS^*_{H1} + d_M d_H^2 + a^2 c_1 mI^*_{M1}\beta_1\, c_2 I^*_{H1} - d_H a^2 c_2 S^*_{M1}c_1 mS^*_{H1}\\
& + a^2 c_1 mI^*_{M1}\gamma_1\, c_2 I^*_{H1} + ac_1 mI_{M1}\beta_1\, d_M + d_M ac_1 mI^*_{M1}\gamma_1 + d_M d_H\beta_1 + d_M d_H\gamma_1\\
& + \beta_1\,\gamma_1\, ac_2 I^*_{H1} + d_H\gamma_1\, ac_2 I^*_{H1},
\end{aligned}$$

which are obtained in *Maple*. By tedious calculations (with the help of *Maple*), we can show that $Q_i > 0$ for $i = 1, 2, 3$. Since there is only difference in notation between $h_2(z)$ and the characteristic equation of system (4.3.2) at the endemic equilibrium E^*, we can show that

$$Q_1 Q_2 - Q_3 > 0 \tag{4.3.28}$$

by Theorem 4.3.2 and Routh-Hurwitz criteria. Inequality (4.3.28) implies that all roots of $h_2(z) = 0$ have negative real parts. Hence, the stability of $\bar{E}^*_1$ is fully determined by the roots of $h_1(z) = 0$. It is easily seen that if $\bar{\mathcal{R}}_{21} < 1$ then the two roots of $h_1(z) = 0$ have negative real parts, implying that $\bar{E}^*_1$ is locally asymptotically stable; and if $\bar{\mathcal{R}}_{21} > 1$ then $h_1(z) = 0$ has a positive real root implying that $\bar{E}^*_1$ unstable. The proof is complete.

□

Conditions conditions (4.3.9), (4.3.25) and (4.3.26) can also be expressed by some explicit conditions, similar to those in Remark 4.3.1.

The next theorem gives conditions under which one species of the malaria parasites can persist in the host and vector populations.

Theorem 4.3.5 *Suppose* $\bar{\mathcal{R}}_0 > 1$.

(i) If either (A1) $\bar{\mathcal{R}}_1 > 1$ *and* $\bar{\mathcal{R}}_2 < 1$*; or (B1)* $\bar{\mathcal{R}}_2 > 1$, $\bar{\mathcal{R}}_{12} > 1$ *and condtion* (4.3.26) *holds, then* I_{H1} *and* I_{M1} *are uniformly persistent in the sense that there is a positive constant* $\eta_1 > 0$ *such that for every solution of system* (4.3.20) *with* $I_{H1}(0) > 0$ *and and* $I_{M1}(0) > 0$*, there hold*

$$\liminf_{t\to\infty} I_{H1}(t) \geq \eta_1, \quad \liminf_{t\to\infty} I_{M1}(t) \geq \eta_1.$$

(ii) If either (A2) $\bar{\mathcal{R}}_2 > 1$ *and* $\bar{\mathcal{R}}_1 < 1$*; or (B2)* $\bar{\mathcal{R}}_1 > 1$, $\bar{\mathcal{R}}_{21} > 1$ *and condition* (4.3.25) *holds, then* I_{H2} *and* I_{M2} *are uniformly persistent in the sense that there is a positive constant* $\eta_2 > 0$ *such that for every solution of system* (4.3.20) *with* $I_{H2}(0) >$ *and and* $I_{M2}(0) > 0$*, there hold*

$$\liminf_{t\to\infty} I_{H2}(t) \geq \eta_2, \quad \liminf_{t\to\infty} I_{M2}(t) \geq \eta_2.$$

Proof: We will only show the proof for case (i), as the proof the case (ii) is similar.

Denote

$$X_0 = \{(S_H, I_{H1}, R_{H1}, I_{H2}, R_{H2}, S_M, I_{M1}, I_{M2}) \in X : I_{H1} > 0 \text{ and } I_{M1} > 0\},$$

$$\partial X_0 = X/X_0 = \{(S_H, I_{H1}, R_{H1}, I_{H2}, R_{H2}, S_M, I_{M1}, I_{M2}) \in X, I_{H1} = 0 \text{ or } I_{M1} = 0\}.$$

By the form of system (4.3.20), it is easy to see that both X_0 and X are positively

invariant. Obviously, ∂X_0 is relatively closed in X. The boundedness of the solution established in Section 4.3.2 confirms that system (4.3.20) is a point dissipative system.

Set

$$M_\partial = \left\{ \begin{array}{l} (S_H(0), I_{H1}(0), R_{H1}(0), I_{H2}(0), R_{H2}(0), S_M(0), I_{M1}(0), I_{M2}(0)) \in X : \\ (S_H(t), I_{H1}(t), R_{H1}(t), I_{H2}(t), R_{H2}(t), S_M(t), I_{M1}(t), I_{M2}(t)) \text{ satisfies (4.3.20)} \\ \text{and belongs } \partial X_0, \forall t \geq 0. \end{array} \right\},$$

and let

$$M_0 = \{(S_H, I_{H1}, R_{H1}, I_{H2}, R_{H2}, S_M, I_{M1}, I_{M2}) \in X : I_{H1} = 0,\ I_{M1} = 0\}.$$

We show that $M_\partial = M_0$. Clearly, we have $M_\partial \supset M_0$, so we only need to prove $M_\partial \subset M_0$. Suppose not, then there exists x_0 such that $x_0 \in M_\partial$ but $x_0 \notin M_0$. Then, either the second or the seventh component is positive. For the former, by the seventh equation in system (4.3.20), $I_{M1}(t)$ is activated (nonzero) for $t > 0$ which in turn activates $I_{H1}(t)$, implying that $x_0 \notin M_\partial$, a contradiction. For the later, by the second equation in system (4.3.20), $I_{H1}(t)$ is activated for $t > 0$ which in turn activates $I_{M1}(t)$, implying that $x_0 \notin M_\partial$, also a contradiction. Thus, we have shown $M_\partial = M_0$.

Next, we show that for every solution in X_0, the I_H and I_M components are weakly persistent in the sense that

$$\limsup_{t\to\infty} I_{H1}(t) > 0 \quad \text{and} \quad \limsup_{t\to\infty} I_{M1}(t) > 0. \tag{4.3.29}$$

For the sake of contradiction, we assume that inequalities (4.3.29) does not hold. Then either (P1) $\lim_{t\to\infty} I_{H1}(t) = 0$, or (P2) $\lim_{t\to\infty} I_{H1}(t) = 0$. For (P1), applying the theory of asymptotically autonomous systems to the $I'_M(t)$ equation, we conclude (P2) also

holds. Similarly, (P2) also implies (P1). Further applying the theory of asymptotically autonomous systems to the $R_{H1}(t)$ equation, it follows that $R_{H1}(t) \to 0$ as $t \to \infty$. Thus, either (P1) or (P2) leads to

$$\lim_{t\to\infty} I_{H1}(t) = 0, \quad \lim_{t\to\infty} I_{M1}(t) = 0, \quad \text{and} \quad \lim_{t\to\infty} R_{H1}(t) = 0. \tag{4.3.30}$$

Therefore, the S_H, I_{H2}, R_{H2}, S_M and I_{M2} equations in system (4.3.20) have the following as limiting system:

$$\begin{cases} S'_H = d_H - d_H S_H - a e_{12} m S_H I_{M2} + \beta_2 R_{H2}, \\ I'_{H2} = a e_{12} m S_H I_{M2} - d_H I_{H2} - \gamma_2 I_{H2}, \\ R'_{H2} = \gamma_2 I_{H2} - d_H R_{H2} - \beta_2 R_{H2}, \\ S'_M = d_M - d_M S_M - a e_{22} S_M I_{H2}, \\ I'_{M2} = a e_{22} S_M I_{H2} - d_M I_{M2}. \end{cases} \tag{4.3.31}$$

Case (A1) : $\mathcal{R}_1 > 1$ and $\mathcal{R}_2 < 1$. By Theorem 4.3.1, $(1, 0, 0, 1, 0)$ is an equilibrium of system (4.3.31) and it is globally asymptotically stable if $\mathcal{R}_2 < 1$. Therefore, for any $\bar{\epsilon}_1 > 0$, there exists $\bar{T}_1 > 0$ such that

$$S_H(t) \geq 1 - \bar{\epsilon}_1, \quad S_M(t) \geq 1 - \bar{\epsilon}_1, \quad , R_{H2}(t) \geq \bar{\epsilon}_1, \quad \text{for } t > \bar{T}_1. \tag{4.3.32}$$

Applying the inequalities in (4.3.32) to the I_{H1} and I_{M1} equations in the original system (4.3.20), we obtain

$$\begin{aligned} I'_{H1} &\geq a e_{11} m (1 - \bar{\epsilon}_1) I_{M1} - d_H I_{H1} - \gamma_1 I_{H1}, \\ I'_{M1} &\geq a e_{21} (1 - \bar{\epsilon}_1) I_{H1} - d_M I_{M1}, \end{aligned} \quad \text{for } t > \bar{T}_1. \tag{4.3.33}$$

This suggests the following linear comparison system

$$\begin{cases} u_1' = ae_{11}m(1-\bar{\epsilon}_1)u_2 - (d_H+\gamma_1)u_1, \\ u_2' = ae_{21}(1-\bar{\epsilon}_1)u_1 - d_M u_2. \end{cases} \tag{4.3.34}$$

Because $\mathcal{R}_1 > 1$, by continuity, we can choose $\bar{\epsilon}_1$ sufficiently small so that

$$\frac{a^2 e_{11}e_{21}m(1-\bar{\epsilon})^2}{d_M(d_H+\gamma_1)} > 1, \tag{4.3.35}$$

which implies that the stability modulus of system (4.3.34) is positive. Therefore the positive solutions of system (4.3.34) are unbounded. On the other hand, system (4.3.34) is cooperative and hence, by the comparison theorem (see, e.g., [16] or [23]), we have $I_{H1}(t) \geq u_1(t)$ and $I_{M1}(t) \geq u_2(t)$, where $(u_1(t),\, u_2(t))$ is the positive solution of (4.3.34) with initial condition $(I_{H1}(0),\, I_{M1}(0))$. Now the unboundedness of $(u_1(t), u_2(t))$ implies unboundedness of $(I_{H1}, I_{M1}(t))$, a contradiction.

Case (B1): $\mathcal{R}_2 > 1$, $\bar{\mathcal{R}}_{12} > 1$ and condition (4.3.26) holds. Apply Theorem 4.3.2 to system (4.3.31) (under $\mathcal{R}_2 > 1$ and condtion (4.3.26)), we have $S_H(t) \to S^*_{H2}$, $I_{H2}(t) \to I^*_{H2}$, $R_{H2}(t) \to R^*_{H2}$, $S_M(t) \to S^*_{M2}$, $I_{M2}(t) \to I^*_{M2}$. Hence, for any $\bar{\epsilon}_2 > 0$, there exists $\bar{T}_2 > 0$ such that

$$S_H(t) \geq S^*_{H2} - \bar{\epsilon}_2, \quad S_M(t) \geq S^*_{M2} - \bar{\epsilon}_2, \quad , R_{H2}(t) \geq R^*_{H2} - \bar{\epsilon}_2, \quad \text{for } t > \bar{T}_2. \tag{4.3.36}$$

Applying the inequalities in (4.3.36) to I_{H1} and I_{M1} equations in the original system (4.3.20), we obtain

$$\begin{aligned} I_{H1}' &\geq ae_{11}m(S^*_{H2} - \bar{\epsilon}_2)I_{M1} - d_H I_{H1} - \gamma_1 I_{H1} + ae_1 m(R^*_{H2} - \bar{\epsilon}_2)I_{M1}, \\ I_{M1}' &\geq ae_{21}(S^*_{M2} - \bar{\epsilon}_2)I_{H1} - d_M I_{M1}, \end{aligned} \quad \text{for } t > \bar{T}_2 \tag{4.3.37}$$

This suggests the following linear comparison system

$$\begin{cases} v_1' = [ae_{11}m(S^*_{H2} - \bar{\epsilon}_2) + ae_1 m(R^*_{H2} - \bar{\epsilon}_2)]v_2 - (d_H + \gamma_1)v_1, \\ v_2' = ae_{21}(S^*_{M2} - \bar{\epsilon}_2)v_1 - d_M v_2. \end{cases} \tag{4.3.38}$$

Since $\bar{\mathcal{R}}_{12} > 1$, by continuity, we can choose $\bar{\epsilon}_2$ sufficiently small so that

$$\begin{aligned} &\frac{[ae_{11}m(S^*_{H2} - \bar{\epsilon}_2) + ae_1 m(R^*_{H2} - \bar{\epsilon}_2)]ae_{21}(S^*_{M2} - \bar{\epsilon}_2)}{d_M(d_H + \gamma_2)} \\ =&\frac{a^2 e_{11}e_{21}m(S^*_{H2} - \bar{\epsilon}_2)(S^*_{M2} - \bar{\epsilon}_2) + a^2 e_{21}e_1 m(S^*_{M2} - \bar{\epsilon}_2)(R^*_{H2} - \bar{\epsilon}_2)}{d_M(d_H + \gamma_2)} \\ >&1. \end{aligned}$$

This implies that the characteristic equation of the linear system (4.3.38) has a positive real root, which means the positive solutions of (4.3.34) are unbounded. Similar to the proof of case (A1), this would further imply that $(I_{H1}(t), I_{M1}(t))$ is unbounded, also a contradiction.

Combining the above, we have proved that (4.3.29) is valid. In the case of (A1), $\bar{E}_0$ is the only equilibrium in M_0, and every forward orbit in M_0 converges to $\bar{E}_0$. Note that (4.3.29) implies that $\bar{E}_0$ is an isolated invariant set in X, $W^S(\bar{E}_0) \cap X_0$ is empty where W^S is a stable manifold. By [[24], Theorem 4.6] , we conclude that system (4.3.20) is uniformly persistent with respect to $(X_0, \partial X_0)$. Under condition (B1), there are only two equilibria $\bar{E}_0$ and $\bar{E}^*_2$ in M_0. From (4.3.29) and the fact that $M_\partial = M_0$, we know that these two equilibria are isolated in X, and $W^S(\bar{E}_0) \cap X_0$ and $W^S(\bar{E}^*_2) \cap X_0$ are empty, and so every forward orbit in M_0 converges to either $\bar{E}_0$ or $\bar{E}^*_2$. Moreover $\bar{E}_0$ and $\bar{E}^*_2$ are acyclic in M_0. Again, by [[24], Theorem 4.6], we conclude that system (4.3.20) is uniformly persistent with respect to $(X_0, \partial X_0)$. Therefore, under either (A1) or (B1), we have I_H and I_M are uniformly persistent, the proof is complete. □

Combining (i) and (ii) in the above theorem, we have the following results on persistence of both species of the malaria parasites.

Theorem 4.3.6 *Assume one of the following holds,*

(i) $\bar{\mathcal{R}}_1 > 1,\ \bar{\mathcal{R}}_2 < 1,\ \bar{\mathcal{R}}_{21} > 1$ *and condition* (4.3.25) *holds;*

(ii) $\bar{\mathcal{R}}_2 > 1,\ \bar{\mathcal{R}}_1 < 1,\ \bar{\mathcal{R}}_{12} > 1$ *and condition* (4.3.26) *holds; and*

(iii) $\bar{\mathcal{R}}_1 > 1,\ \bar{\mathcal{R}}_2 > 1,\ \bar{\mathcal{R}}_{12} > 1,\ \bar{\mathcal{R}}_{21} > 1$ *and conditions* (4.3.25), (4.3.26) *hold;*

then both species are uniformly persistent in the sense that there is a positive constant $\bar{\eta}$*, such that every solution* $(S_H, I_{H1}, R_{H1}, I_{H2}, R_{H2}, S_M, I_{M1}, I_{M2})$ *with initial condition in* $\bar{X}_0$ *satisfies,*

$$\liminf_{t\to\infty} I_{Hi} \geq \eta, \quad \liminf_{t\to\infty} I_{Mi} \geq \eta, \quad i = 1, 2,$$

where $\bar{X}_0 = \{(S_H, I_{H1}, R_{H1}, I_{H2}, R_{H2}, S_M, I_{M1}, I_{M2}) | \, 0 < S_H,\, S_M \leq 1,\, 0 \leq R_{H1},\, R_{H2} < 1,\ 0 < I_{H1} < 1,\, 0 < I_{M1} < 1,\, 0 < I_{H2} < 1,\, 0 < I_{M2} < 1\}$. *Moreover, system (*(4.3.20)*) admits at least one positive equilibrium(co-existence equilibrium).*

Proof The uniform existence of both species is a consequence of Theorem 4.3.5. The existence of the positive equilibrium follows from the uniform persistence and the existence theorem in [29]. □

4.4 Conclusion and discussion

We have set up a ODE model (4.3.20) to describe the dynamics of disease transmission involving two species of malaria parasites in a well mixed human and mosquito environment. The model is a natural expansion of a one-species model (4.3.1) but with the fact of ”no cross immunity” incorporated. The model also makes use of the result

from a within-host model (i.e. (4.2.3)) for two species which generically excludes persistence of both species within a single host. This allows us to ignore the co-infected class in our two-species model.

We have investigated the dynamics of both systmes (4.3.1) and (4.3.20). More specifically, we have identified the basic reproduction numbers and showed their threshold role for both models by studying the stabilities of equilibiria and the persistence of the model systems. Our analysis on the two-species model (4.3.20) shows that two species of the malaria parasites may both persist in the region under certain circumstances reflected by the conditions in Theorem 4.3.6. These conditions are all expressed in terms of inequalities, and hence, are robust in terms of parameters. This is in contrast to the two-species model (4.2.3) at within-host level, for which competition exclusion holds unless an identity ($\mathcal{R}_1 = \mathcal{R}_2$) holds. The persistence of both species claimed in Theorem 4.3.6 can be observed in numeric simulations, see, e.g., Figure 4.5.

The persistence of both species can be partially attributed to the cooperative effect in the model (4.3.20) which is due to the lack of cross immunity. This is reflected in the conditions in Theorems 4.3.5 and Theorem 4.3.6. For example, in Theorem 4.3.5, either (A1) or (B1) can lead to the persistence of species 1. While (A1) accounts for the case that species 1 outcompetes species 2, (B1) provides a scenario that species 2 not only can survive itself but can also help species 1 survive.

Under the conditions in Theorem 4.3.6, there is a positive equilibrium for (4.3.20). Unfortunately we are unable to study the stability of this positive equilibrium, and the global dynamics of the model (4.3.20) under these conditions. We leave this as a possible future work.

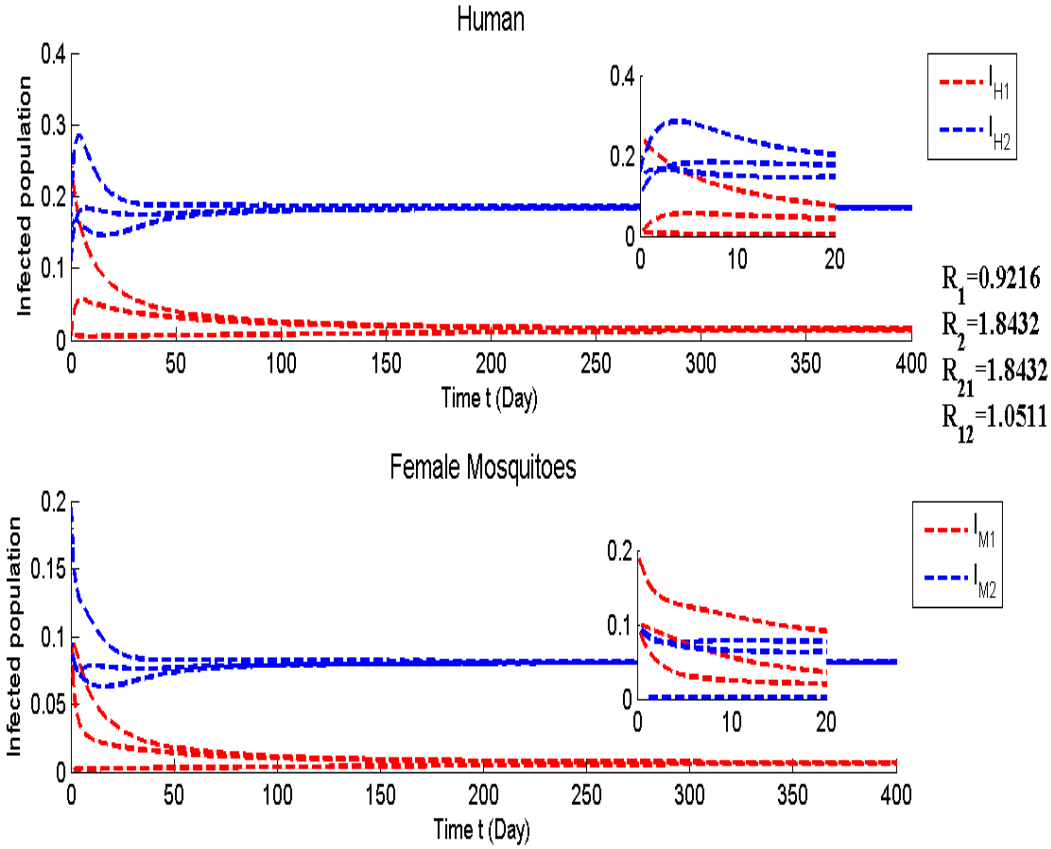

Figure 4.5: Both species can persist at the population level. Simulations are done with the following parameter values and initial conditions: $a = 0.5$, $e_1 = 0.9$, $e_2 = 0.5$, $e_{11} = 0.4$, $e_{21} = 0.2$, $e_{12} = 0.5$, $e_{22} = 0.5$, $n = 7.25$, $\gamma_1 = 0.3$, $\gamma_2 = 0.21$, $d_H = 0.001$, $d_M = 0.2$, $\beta_1 = 1/3$, $\beta_2 = 1/6$; $S_H = 0.6$, $I_{H1} = 0.25$, $R_{H1} = 0$, $I_{H2} = 0.15$, $R_{H2} = 0$, $S_M = 0.8$, $I_{M1} = 0.1$, $I_{M2} = 0.1$.

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Chapter 5

Conclusion and future work

5.1 Conclusion

Based on the classical Ross-Macdonald model [5, 6, 7], three types of models were proposed focusing on the infection latency in both hosts and vectors, disease dispersal with latency in a spatially heterogeneous environment and infections by multi-species of malaria parasites.

In Chapter 2, we derived a model that incorporates, not only the latencies of the malaria parasites in both mosquitoes and humans, but also the variation of the latencies by introducing two general probability functions ($P_1(t)$ and $P_2(t)$). For the general integro-differential system, the basic reproduction number was computed, ans shown to function as a threshold for the disease dynamics. When this threshold is less than one, without any interventions, the disease will eventually die out from the population, in the sense that the disease free equilibrium is globally asymptotically stable; when the reproduction number is greater than one, the disease free equilibrium is no longer stable. Under this circumstance, two types of survival functions were adopted for detailed mathematical analysis.To model the case that the probability that an infected individ-

ual leaves the exposed class decreases gradually with respect to time, we used the the negative exponential probability function. Then the model was reduced to a system of ODEs. If the latent period is fixed, then we adopted the step function as the survival probability function, and the system becomes a model of DDEs. In both cases, we were able to show that the disease will uniformly persist in the community if the basic reproduction rate is greater than one. Additionally, if the disease recovery rate is zero, all the solutions will converge to a unique endemic equilibrium, meaning that the disease will persist at a stable steady state. Moreover, from the expressions of the basic reproduction number, we confirmed the significant impact of the latencies on disease transmissions, regardless the various forms of survival functions. The longer the latent period, the smaller the basic reproduction number. The results indicate that the disease reproduction rate is over-estimated by the classical Ross-Macdonald model.

The heterogeneity of spatial environments can be either discrete or continuous. In Chapter 3, we considered discrete diffusion between patches. A system of DDEs was derived to describe the population dispersal. The distances between patches was assumed to be beyond the flying ability of female mosquitoes and so the model only included the dispersal terms for humans. Thus the focus was on the impact of human dispersal on the disease transmission and spread. In addition to the linear dispersion terms, non-local infection terms, reflecting the mobility of the individuals during the latent period, were added as well. The equations for the latent and infective classes were derived from that of the infected group with infection age structure. Using the next generation operator [3, 4], we computed the global basic reproduction number for all patches, and showed it is a threshold for the disease dynamics. We pointed out that for small scale disease invasion fails of n patches, a global basic reproduction number is less than one and the disease does not become endemic; however if the threshold is greater than one, then the disease uniformly persists in the different patches when

the patches are well connected. We focused on the two patch model, and theoretically and numerically analyzed the relations between the dispersals from different disease compartments (susceptible, latent, infectious) and the dynamics of the disease transmission and persistence. When only the susceptible group can travel, the disease does not disperse from one patch to another. However, the movement of susceptible and latent individuals between patches, where the disease is in epidemic, may lead to the persistence of malaria, even if the disease would not persist locally (the local basic reproduction rates are less than one) when patches are isolated. When people in the latent or infective period migrate, the disease can spread between patches and cause the persistence of malaria in other places.

In chapter 4, we proposed a multi-species model based on the fact that there are at least five species of malaria parasites causing human infections. The work answered one question, whether multi-species of the parasite can persist. We set up models addressed to the co-existence issue at both within- and between- host level. We were able to find that competition exclusion leads the co-infection of multiple species of parasites impossible within one host; however, the co-operative behavior may dominant the competitive behavior at the population level, resulting in the co-existence of multiple species in a community. This is consistent with the results reported by biologists and epidemiologist. What is more, for a single species model at the population level, we showed the global asymptotic stability of the unique endemic equilibrium. This which further helps to introduce the species-mediate reproduction number for each species. These two additional thresholds decide whether an invader species can survive or not if the resident species has settled at its stable endemic state.

5.2 Future work

As mentioned in the discussion part of each chapter, there are still some interesting but challenging problems that remain open and are worth exploring in the future.

For the work in [8] addressed in Chapter 2, we did not get the global stability of the disease endemic equilibrium when the disease recovery rate is nonzero. However, in our numerical analysis, the endemic equilibria in both sub-cases seem to be globally asymptotically stable when the basic reproduction number exceeds one. Therefore, it would be interesting to work on the global stabilities of both endemic equilibria.

In Chapter 3, we were able to get the asymptotic stability of the disease free equilibrium, but its global stability and the stability of other possible equilibria has not yet been determined. For the two patch model, there are still many other interesting sub-cases with various dispersal forms between patches to work on.

The work on disease infections by multi-species did not incorporate the disease latencies for the different species of *Plasmodium*. Different species of parasites have different infection latencies, i.e. the average latency of *P. falciphrum* infection is $5-6$ days and that of *P. vivax* is longer [1, 2]. It would be interesting to consider a variety of latencies in the model, and explore whether multi-species can survive in the same region.

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