Mathematical Models of Dengue Fever and Measures to Control It

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MATHEMATICAL MODELS OF DENGUE FEVER AND MEASURES TO CONTROL IT

By

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ABSTRACT

In this dissertation, we build a compartment model to investigate the dynamics of spread of dengue fever in both human and mosquito populations. We study the demographic factors that influence equilibrium prevalence, and perform a sensitivity analysis on the basic reproduction number. Among several intervention measures, the effects of two potential control methods for dengue fever are estimated: introducing Wolbachia to the mosquito population and introducing vaccines to the human population. A stochastic model for transmission of dengue fever is also built to explore the effect of some demographic factors.
CHAPTER 1

INTRODUCTION

1.1 Background information

When the incidence of an infectious disease starts to increase in any population, people start to look for methods that are best to combat the outbreak or at least control the number of infections. Experiments for producing and testing those control measures, such as vaccination, quarantining the infectives, or antiviral drugs, are costly and time consuming, so any tool that will enable us to predict the outcome is highly valuable.

Mathematical models are a powerful tool for investigating human infectious diseases, providing useful predictions about the potential transmission of a disease and the effectiveness of possible control measures.

Anderson and May [2] gave a comprehensive survey on the use of mathematics to study infectious diseases, and since then there has been an increasing number of mathematical epidemiology papers published. Many infectious diseases are spread by biting insects and ticks or other organisms, collectively known as vectors, which transfer pathogens between humans or other animals. The emergence or reemergence of such vector-borne diseases seems especially to have stimulated recent interest. Rogers et al. [40] reviewed the early vector-borne disease models, and many other authors have studied various particular vector-borne diseases, such as malaria [26, 42], West Nile virus [10], and dengue fever [17].

On the other hand, more recent publications tend to focus on the use of models with certain control measures for disease eradication or control. For example, Reluga [38] identified how individuals would make best use of social distancing and related self-protective behaviors during an epidemic. Althouse et al. [1] provided a quantitative framework for making allocation decisions in the presence of different externalities associated with control measures such as vaccination or antibiotic treatment. Elbasha et al. [15] explored how the vaccination programs should be designed to reduce the prevalence of the different HPV(Human Papilloma Virus) types. Mbah et al. [30] further studied the effects of both imitation behavior and contact heterogeneity on vaccination
coverage and disease dynamics.

Unfortunately, there are very limited control measures for most of the vector-borne diseases. Vaccines, available for only a few diseases (yellow fever, Japanese encephalitis, tick-borne encephalitis, tularemia, plague), are not widely used, and for some widespread diseases, such as West Nile virus, malaria, and dengue fever, vaccine is still not available. People have to depend on vector control programs including the removal of breeding sites generated by humans in households (e.g., old toys, water containers, and tires), larvicidal control, and malathion spraying to target adult vector populations. Other public health controls rely on shortening the mean vector life span or directly reducing the vector biting rate in humans through netting, screens, and application of insecticides to clothing or the application of insect repellents. However, these methods appear not to be sufficiently effective, as the frequency of outbreaks appears to be increasing in some areas, probably due to urbanization increasing the habitat of A. aegypti.

As a consequence of a lack of efficient control measures, mathematical models of vector-borne disease seldom incorporate the ideas of how to curb the disease, and mostly focus on the dynamic transmission of the diseases by using various approaches. Taking dengue fever as an example, Derouich et al. [14] studied the dynamics of the disease when caused by two different viruses, Favier et al. [19] explored the influence of spatial heterogeneity on the disease emergence, Focks et al. [20], de Castro Medeiros et al. [12] and Nuraini et al. [34] developed stochastic models to simulate the dengue infection, Degallier et al. [13] and Kongnuy et al. [27] investigated the dynamics of dengue by statistical methods with data from Brazil and Thailand respectively, and Perez et al. [35] investigated the numerical approaches of a dynamic system. In contrast, only very few publications briefly mentioned the effect of vector control on disease spreading [6, 37, 39].

However, with the research and development of biotechnology and medical technology, there have been several promising new attempts to control vector-borne diseases recently. For instance, Wolbachia is successfully used to control mosquitoes in the laboratory. Wolbachia is a bacterium that lives only within insect cells and is passed from one generation to the next through the insect’s eggs. It is present in up to 70% of all the different species of insects around us, including some mosquitoes that bite people, but not the major mosquito species involved in the transmission of diseases such as dengue and malaria. Vaccine is another control measure. There are a number of vaccine candidates in different stages of development for several diseases. For dengue fever, one of
the candidate vaccines has provided high coverage for some viruses strains, and for malaria, clinical and animal studies have shown that experimental vaccination has some degree of success when using attenuated viruses and using malaria vaccine candidate [16].

In this thesis, we aim to construct new mathematical models for vector-borne diseases, especially for dengue fever, and further investigate the impact of two kinds of control measures, introducing Wolbachia to the mosquito population and introducing vaccination to humans, on the epidemic’s progress.

1.2 Outline of thesis

We begin the thesis in Chapter Two with a traditional Susceptible-Infectious-Recovered (SIR) model built by Kermack et al. [25] in 1927. The basic reproduction number ($R_0$) is defined and discussed. Then we extend this model to an SEIR model with the letter E representing incubation or exposed state, during which an individual is infected but not yet infectious. With this SEIR model, we narrow our focus to modeling dengue fever by developing a coupled dynamics of disease prevalence in human beings and in mosquitoes. In the second chapter we also compute the basic reproduction number of the disease, and derive analytic forms for equilibrium points.

The third chapter builds a stochastic model based on the dengue transmission mechanism. Archived literature offers values for parameters in the dengue SEIR model, but the data suggest variation across different parts of the world. Therefore, we set some parameters in the stochastic model as constant while others follow a probability distribution. The host and vector populations are represented by a coupled individual-based SEIR model. The transitions between the S and E states are stochastically modeled. Several features are described by running 1000 times of simulation, and we compare several critical features of the results of the stochastic simulations and the numerical simulations from the deterministic model. Furthermore, we analyze the sensitivity of several parameters to the basic reproduction number. This general analysis gives important quantitative information about demographic factors that affect the persistence of disease. Sensitivity analysis will help us investigate how the parameters are implicated in determining the persistence of disease, and further search for alternative methods to control or eliminate dengue fever.

Chapter Four incorporates the effect of the bacterium Wolbachia into the SEIR model. The research question in this part is: “How does Wolbachia influence the mosquito population and
further the transmission of dengue viruses in human beings?" Dengue fever requires a relatively long extrinsic incubation period in its mosquito vector before transmission to a new human host, so the life expectation of infectious vectors strongly influences the spread of the disease. Previous work has shown that the frequency of \textit{Wolbachia}-infected mosquitoes will eventually reach a fixed positive value or decline to zero. By making this assumption, we build a model which subdivides the mosquito population into \textit{Wolbachia}-infected and \textit{Wolbachia}-uninfected parts with some fixed probabilities. We analyze the dynamics of human and vector populations in different compartments, and compute the basic reproduction number and equilibrium. The purpose of this model is to understand the relationship among the number of \textit{Wolbachia}-infected mosquitoes, the mosquito mortality rate, and the number of infectious humans at equilibrium. The relationship between the persistence of dengue fever and the mosquito survival profile is investigated.

In Chapter Five, vaccination is introduced, and game-theoretic analysis is applied to explore voluntary vaccination policy. Even though current candidate vaccines are imperfect, previous studies have shown that they would also drastically slow down the spread of the disease [21, 29]. We discuss how the vaccination would influence the dynamics of disease spread under different efficacy levels. On the other hand, one debate arises about whether to enforce vaccination or leave the decision to individuals. The choice of vaccination policy can cause different outcomes for the community as a whole. The best strategy for enforced vaccination may require a different proportion of the population vaccinated from what would occur if left to individuals to decide. Game-theoretic analysis helps to explain human decision-making with respect to vaccination.
CHAPTER 2

SIR AND EXTENDED SEIR MODELS WITH APPLICATION TO DENGUE FEVER

2.1 SIR model

2.1.1 Basic SIR model

Infectious disease ranges from childhood diseases like measles and chicken pox to deadly killers like AIDS (Acquired immune deficiency syndrome). The dynamics of an infectious disease has been questioned and studied for many years. In order to model the progress of an epidemic in a large population, comprising many different individuals in various fields, the population diversity must be reduced to a few key characteristics which are relevant to the infection under consideration.

In 1927, W. O. Kermack and A. G. McKendrick [25] created an SIR model for the number of people infected with a contagious disease in a closed population (i.e., no immigration or emigration) over time. It assumes that the population size is fixed (i.e., no births, deaths due to disease, or deaths by natural causes), incubation of the infectious agent is instantaneous, and duration of infection is same as length of the disease. It also assumes a completely homogeneous population with no age, spatial, or social structure. The model divides the host population into a small number of compartments, each containing individuals that are identical in terms of their status with respect to the disease. In their SIR model, there are three compartments:

- Susceptible: individuals who have not yet been infected with the disease, but are susceptible to the disease, and so might become infected if exposed

- Infectious: individuals who have been infected with the disease and are capable of spreading the disease to those in the susceptible category

- Recovered: individuals who have been infected and then recovered from the disease. Those in this category are not able to be infected again or to transmit the infection to others

It is traditional to denote the number of individuals at time $t$ in each of these compartments as $S(t)$, $I(t)$ and $R(t)$, respectively. The total host population size is $N = S + I + R$. 


The flow of this model may be considered as follows:

Having compartmentalized the host population, Kermack and McKendrick derived the following set of equations that specify how the sizes of the compartments change over time.

\[
\begin{align*}
\frac{dS}{dt} &= -\beta SI \\
\frac{dI}{dt} &= \beta SI - \gamma I \\
\frac{dR}{dt} &= \gamma I
\end{align*}
\] (2.1)

The infection rate, \( \beta \), is a measure of how fast susceptible people become infectious. The recovery rate, \( \gamma \), is a measure of how fast the infecteds recover.

Several assumptions were made in the formulation of these equations: Because of the assumption of homogeneity, an individual in the population must be considered to have the same probability as every other individual of contracting the disease. Therefore, an infected individual makes contact and is able to transmit the disease with \( \beta N \) others per unit time and the fraction of contacts by an infected with a susceptible is \( S/N \). The number of new infections in unit time per infective then is \( \beta N(S/N) \), giving the rate of new infections (or those leaving the susceptible category) as \( \beta N(S/N)I = \beta SI \). For the second and third equations, consider the population leaving the susceptible class as equal to the number entering the infected class. However, a fraction \( \gamma \) of infecteds is leaving this class (so that the mean infectious period is \( 1/\gamma \)) per unit time to enter the recovered class. These processes which occur simultaneously are referred to as the Law of Mass Action, a widely accepted idea that the rate of contact between two groups in a population is proportional to the size of each of the groups concerned [11].

Using this model, we will consider a mild, short-lived epidemic, e.g. influenza. Let us now consider a population which is naive with respect to this disease. What happens if a single infected individual is introduced into such a population? Is there going to be an epidemic? How many people will be infected? Equation (2.1) is a non-linear system of ordinary differential equations.
(ODE) which in general are hard to solve analytically. By implementing and simulating the model, we see that with various parameter sets, the results of the simulation are different (see Figure 2.2 and Figure 2.3).

![Figure 2.2: An epidemic simulated in the SIR model. Initial susceptible: 499, Initial infectious: 1, initial recovered: 0, $\beta$: 0.001, $\gamma$: 0.1](image1)

![Figure 2.3: A disease-free situation simulated in the SIR model. Initial susceptible: 499, Initial infectious: 1, initial recovered: 0, $\beta$: 0.0001, $\gamma$: 0.1](image2)

### 2.1.2 Basic reproduction number $R_0$

The different outcomes as shown in Figure 2.2 and 2.3 raise a question: What conditions are necessary for the outbreak of an epidemic?
A key parameter in epidemiology is the basic reproduction ratio, $R_0$. It is defined as the average number of secondary cases transmitted by a single infected individual that is placed into a fully susceptible population. In other words, $R_0$ tells us about the initial rate of spread of the disease. Hence, if $R_0 > 1$, there will be an epidemic, and if $R_0 < 1$, the introduced infections will recover (or die) without being able to replace themselves by new infections.

The explicit form of $R_0$ can be approached by the following analysis:

The model makes sense only so long as $S(t)$ and $I(t)$ remain non-negative. Thus if either $S(t)$ or $I(t)$ reaches zero we consider the system to have terminated. We observe that $S' < 0$ for all $t$ and $I' > 0$ if and only if $S > \gamma/\beta$. Thus $I$ increases so long as $S > \gamma/\beta$ but since $S$ decreases for all $t$, $I$ ultimately decreases and approaches zero. If $S(0) < \gamma/\beta$, $I$ decreases to zero (no epidemic), while if $S(0) > \gamma/\beta$, $I$ first increases to a maximum attained when $S = \gamma/\beta$ and then decreases to zero (epidemic). We consider introducing a small number of infectives into a susceptible population and ask whether there will be an epidemic. Thus quantity $\beta S(0)/\gamma$ is a threshold quantity. By replacing $S(0)$ with $N$ in Equation (2.1), this yields $\beta N/\gamma$. That is:

$$R_0 = \frac{\beta N}{\gamma} \quad (2.2)$$

Note that the result $R_0 = \beta N/\gamma$ derived above, applies only to the basic Kermack-McKendrick model. Alternative SIR models have different formulas for $dI/dt$ and hence for $R_0$: see, e.g., (2.4).

2.1.3 SIR with vital dynamics

The Kermack-McKendrick model explains a single epidemic well. However, almost all infectious diseases are recurrent with a certain period. For example, Figure 2.4 [18] shows the extinctions and re-emergences of dengue fever in Fortaleza, Brazil on a longer timescale. This cannot be explained by the basic SIR model. Why can’t a second epidemic occur in the model we’ve discussed? The infectious curve goes up and eventually declines because the pathogen is running out of susceptible individuals to infect. To simulate a second epidemic, there must be a source of susceptible individuals. Once people are recovered, they retain lifelong immunity to the virus. Therefore the only source of susceptibles is newborns.

If we expand the SIR model to the one including births and deaths, then our model becomes:
\[ \frac{\text{d}S}{\text{d}t} = \mu N - \beta SI - \mu S \]
\[ \frac{\text{d}I}{\text{d}t} = \beta SI - \gamma I - \mu I \]
\[ \frac{\text{d}R}{\text{d}t} = \gamma I - \mu R \]  

(2.3)

where \( \mu \) represents the birth and death rate, and newborn equals the natural mortality \( \mu N = \mu(S + I + R) \). We assume that the population size is constant during a disease epidemic because the timescale for population change is much longer than the infectious period. Again we implement and simulate the model. An example is shown in Figure 2.5, where we have taken the birth and death rate to be 0.0016. The rest of the parameters and initial conditions are the same as in the Figure 2.2.

Figure 2.5 shows what happens for one set of possible parameters and initial conditions. We see that the oscillations in the numbers in the three compartments damp out over time, eventually reaching an equilibrium \( (\hat{S}, \hat{I}, \hat{R}) \).

2.1.4 \( R_0 \), equilibria and their stability

The dynamics of model (2.3) are determined by the basic reproduction number \( R_0 \) which is defined as follows:

\[ R_0 = \frac{\beta N}{\gamma + \mu} \]  

(2.4)

We study the solutions of system (2.13) in the closed set
Figure 2.5: An epidemic simulated in the SIR model. Initial susceptible: 499, Initial infectious: 1, initial recovered: 0, $\beta$: 0.001, $\gamma$: 0.1, $\mu$: 0.0016

$\Omega = \{(S, I, R) \in \mathbb{R}_+^3 : S + I + R = N\}$.

The $\Omega$ set is positively invariant with respect to Equation (2.3). System (2.3) has at most two biologically meaningful equilibrium points.

$E = (S, I, R) \in \mathbb{R}_+^3$ is an equilibrium point for system (2.3) if it satisfies

$$
\begin{align*}
\mu N - \beta SI - \mu S &= 0 \\
\beta SI - \gamma I - \mu I &= 0 \\
\gamma I - \mu R &= 0
\end{align*}
$$

(2.5)

An equilibrium point $E$ is biologically meaningful if and only if $E \in \Omega$. The biologically meaningful equilibrium points are said to be disease-free or endemic depending on $I$: if there is no disease for the population ($I = 0$), then the equilibrium point is a disease-free equilibrium; otherwise, if $I > 0$, then the equilibrium point is called endemic.

The relationship between the basic reproduction number and the equilibrium is as follows:

When $R_0 \leq 1$ the infection will die out in the long run, which will give us a disease-free equilibrium $E_1$

$$
\lim_{t \to +\infty} (S(t), I(t), R(t)) = (N, 0, 0)
$$

(2.6)
When $R_0 > 1$, the model admits an endemic equilibrium $E_2$

$$\lim_{t \to +\infty} (S(t), I(t), R(t)) = (\mathcal{S}, \mathcal{I}, \mathcal{R})$$

$$= \left( \frac{\gamma}{\beta}, \frac{\mu(R_0-1)}{\beta}, \frac{\gamma R_0}{\beta} \right)$$

Figure 2.5 shows the dynamics of the model for one set of initial conditions. Will we get a different ending behavior, such as a different equilibrium or an oscillation without damping out, if we try a different set of initial conditions? The answer is no. The system will always undergo damped oscillations and converge to $(\mathcal{S}, \mathcal{I}, \mathcal{R})$ shown as in Figure 2.5.

**Theorem 2.1.1** The disease-free equilibrium $E_1$ and endemic equilibrium $E_2$ obtained from the previous system (2.3) are both locally stable.

**Proof** For $E_1$ the matrix of linearization (Jacobian matrix) is given by:

$$J_{E_1} = \begin{pmatrix}
-\mu & -\beta N & 0 \\
0 & \beta N - \gamma - \mu & 0 \\
0 & \gamma & -\mu
\end{pmatrix}.$$ 

Thus the eigenvalues of matrix $J_{E_1}$ are: $\lambda_{1,2} = -\mu$, $\lambda_3 = -\gamma - \mu + \beta N$.

Since $R_0 = \frac{\beta N}{\gamma + \mu} < 1$, $\lambda_3 < 0$, all the eigenvalues have negative real parts. Thus $E_1$ is locally stable.

For $E_2$ the matrix of linearization (Jacobian matrix) is given by:

$$J_{E_2} = \begin{pmatrix}
-\mu R_0 & -\frac{\beta N}{R_0} & 0 \\
\mu(R_0-1) & \frac{\beta N}{R_0} - \gamma - \mu & 0 \\
0 & \gamma & -\mu
\end{pmatrix}.$$ 

Thus the eigenvalues of matrix $J_{E_2}$ are: $\lambda_1 = -\mu$, $\lambda_{2,3} = \frac{1}{2R_0} \left( \beta N - \gamma R_0 - \mu R_0 - \mu R_0^2 \pm \sqrt{(-\beta N + \gamma R_0 + \mu R_0 + \mu R_0^2)^2 - 4R_0(-\beta \mu N + \gamma \mu R_0^2 + \mu^2 R_0^3)} \right)$.

Let us look at the first part in the parenthesis of $\lambda_{2,3}$.

Since $R_0 = \frac{\beta N}{\gamma + \mu}$, we have $\beta N - \gamma R_0 - \mu R_0 = 0$. So $\beta N - \gamma R_0 - \mu R_0 - \mu R_0^2 = -\mu R_0^2 < 0$.

For the second part in the square root,

$$-\beta \mu N + \gamma \mu R_0^2 + \mu^2 R_0^2 = \mu(-\beta N + (\gamma + \mu)R_0) = \beta \mu N(R_0 - 1) > 0$$

If the number in the square root is negative, we have a pair of conjugate eigenvalues whose real parts are negative.
If the number in the square root is positive,
\[
\sqrt{(-\beta N + \gamma R_0 + \mu R_0 + \mu R_0^2)^2 - 4R_0(-\beta \mu N + \gamma \mu R_0^2 + \mu^2 R_0^2)} < \sqrt{(-\beta N + \gamma R_0 + \mu R_0 + \mu R_0^2)^2} = -\beta N + \gamma R_0 + \mu R_0 + \mu R_0^2 = \mu R_0^2
\]

Then \( \lambda_{2,3} < 0 \). We have all the eigenvalues negative, so \( E_2 \) is locally stable.

2.2 SEIR Model: Extensions to Kermack et al. SIR model and its application to dengue fever

2.2.1 SEIR model

For many important infections there is a significant incubation period during which an individual has been infected but is not yet infectious. During this period the individual is in compartment \( E \) (for exposed).

\[
\begin{align*}
S & \xrightarrow{\beta SI} E & E & \xrightarrow{\alpha E} I & I & \xrightarrow{\gamma I} R
\end{align*}
\]

Figure 2.6: Scheme of the SEIR model. Boxes represent compartments, and arrows indicate flux between the compartments.

Consider now a more general model that also contains an exposed compartment, and we call the model SEIR model. We may think of infected susceptible individuals going into an exposed class, then proceeding from the exposed class to the infectious class, see Figure 2.6.

We assume that the incubation period is a random variable with exponential distribution with parameter \( \alpha \) (i.e. the average incubation period is \( \alpha^{-1} \)), and all the other assumptions and parameter sets are the same as in Equation (2.3). The model is given by the following system:

\[
\begin{align*}
\frac{dS}{dt} &= \mu N - \beta SI - \mu S \\
\frac{dE}{dt} &= \beta SI - \alpha E - \mu E \\
\frac{dI}{dt} &= \alpha E - \gamma I - \mu I \\
\frac{dR}{dt} &= \gamma I - \mu R \\
\end{align*}
\] (2.8)

Since the total population is constant in this model, we have \( S + E + I + R = N \).
**Force of infection**

Note that in the above model, the part $F = \beta I$ is the per capita rate at which susceptible individuals contact the infection, and it is directly proportional to the number of infectious individuals, so we call $F$ the force of infection. However, for large classes of infectious diseases, it is more realistic to consider a force of infection that does not depend on the absolute number of infectious individuals, but on their fraction with respect to the total constant population $N$. We let

$$F = \beta \frac{I}{N}$$

Then the model (2.8) becomes:

$$\frac{dS}{dt} = \mu N - \beta S \frac{I}{N} - \mu S$$
$$\frac{dE}{dt} = \beta S \frac{I}{N} - \alpha E - \mu E$$
$$\frac{dI}{dt} = \alpha E - \gamma I - \mu I$$
$$\frac{dR}{dt} = \gamma I - \mu R$$

(2.9)

The exposed compartment is a transitional state between susceptibles and infecteds, and individuals in this compartment are not infectious and thus do not contribute to the new infections, nor the decrease of susceptibles. The delay of becoming infectious is one that individuals have to experience once they get infected, but we are less interested in the dynamics of this compartment. Therefore, if the effect of the exposed compartment can be incorporated into expressions for other compartments, that will simplify the model. However, incubation is still a non-negligible process because if it acts on a very long time scale, then it is essential to include demographic effects, i.e., natural deaths in the exposed group.

We let $u(t)$ be the fraction of infected members with infection age $t$ who are not yet infective if alive. Then the fraction becoming infective at infection age $t$ if alive is $\mu u(t)$, and we have

$$\frac{du}{dt} = -\mu u(t), \quad u(0) = 1$$

(2.10)

The solution of the Equation (2.10) is

$$u(t) = e^{-\mu t}$$

(2.11)

Let us assume that the incubation period is a constant $\tau$. Then the individuals changing status from exposed to infecteds are those that were infecteds $\tau$ days before, and the recruitment number
of infecteds at time $t$ is related to the number of susceptibles and infecteds at time $(t - \tau)$, subject to surviving the incubation period, whose proportion is $e^{-\mu \tau}$.

Then system (2.9) becomes

$$\begin{align*}
\frac{dS}{dt} &= \mu N - \frac{\beta S(t)I(t)}{N} - \mu S(t) \\
\frac{dI}{dt} &= e^{-\mu \tau} \frac{\beta S(t-\tau)I(t-\tau)}{N} - \gamma I(t) - \mu I(t) \\
\frac{dR}{dt} &= \gamma I(t) - \mu R(t)
\end{align*} \tag{2.12}$$

This SEIR has played an important role in many disease studies, especially when the incubation period takes a large part of an individual’s whole life span. It not only studies infectious disease spread in human beings, but also in animals, insects, or between insects and human beings. For example, mosquitoes transmit many types of disease such as malaria, West Nile virus, and dengue fever. The incubation period of the disease in mosquito bodies is relatively long comparing to their life span, so SEIR model helps to study the dynamics of the disease development and transmission within the mosquito population, as well as between the mosquito and human populations.

In the next several chapters of this thesis, we will discuss a particular vector-borne infectious disease called dengue fever. We will use coupled SEIR models for both human and mosquito populations, and investigate certain measures to control dengue fever.

So, what is a vector-borne infectious disease? Here the term “vector” refers to any arthropod that transmits a disease through feeding activity. For example, fleas transmit bubonic plague, ticks transmit Lyme disease and Rocky Mountain spotted fever, and mosquitoes are vectors of malaria, dengue fever, and yellow fever, etc. Vector-borne infectious diseases are the illnesses caused by those vectors. They cause a significant fraction of the global infectious disease burden; indeed, nearly half of the world’s population is infected with at least one type of vector-borne pathogen [28].

Dengue fever is a typical vector-borne infectious disease.

2.2.2 Application to dengue fever

Dengue is transmitted by several species of mosquito, principally *Aedes aegypti*. Symptoms include fever, headache, muscle and joint pains, and a characteristic skin rash that is similar to measles. In a small proportion of cases the disease develops into the life-threatening dengue hemorrhagic fever (DHF), resulting in bleeding, low levels of blood platelets and blood plasma leakage, or into dengue shock syndrome (DSS), where dangerously low blood pressure occurs. Most
people with dengue recover without any ongoing problems. The mortality is $1 - 5\%$ without treatment, and less than $1\%$ with adequate treatment.

Figure 2.7: Global epidemiology of dengue fever: 2011. Courtesy of WHO, Denguenet.

Over the past few decades, the incidence of dengue fever has increased dramatically, with around 50 – 100 million people infected yearly. It is endemic in many countries in Africa, the Americas, the Eastern Mediterranean, Southeast Asia, and the Western Pacific (see Figure 2.7). Nowadays, dengue is a major public health problem in tropical and subtropical regions in more than 110 countries around the world.

Figure 2.8 shows the mechanism of transmission of dengue from one host to another via the vector. If a susceptible vector bites an infected person during the viremic period, it may become infected and subsequently transmit the virus to other healthy humans after an extrinsic incubation period of 7 to 12 days. Once infected, the female mosquito carries the virus during its life span. There is a 4 to 7 days intrinsic incubation period, during which infected human individuals are not contagious.

The transmission dynamics of dengue are modeled as in Anderson and May [2]. Favier et
al. extended [18] the model by incorporating the incubation periods. The model classifies hosts (humans) in four epidemiological states: susceptible ($S_h$), incubating or exposed ($E_h$), infectious ($I_h$), and recovered ($R_h$). Female vectors (mosquitoes) are classified as susceptible ($S_v$), incubating or exposed ($E_v$), and infectious ($I_v$). The total numbers of susceptible humans and adult susceptible mosquitoes are given by $N_h$ and $N_v$, respectively. The disease-induced mortality rate on humans is assumed negligible. The disease doesn’t have any effect on the life span of vectors. Once vectors are infected with dengue, the infectiousness lasts for the rest of their life.

Based on Favier’s model, we incorporate the vital dynamics of humans and build the following homogeneous model, in which each mosquito can bite any person with equal probability. Variables and parameters are described in Table 2.1

$$
\begin{align*}
\frac{dS_h(t)}{dt} &= \mu_h N_h - mc\beta_{vh} \frac{S_h(t) I_v(t)}{N_h} - \mu_h S_h(t) \\
\frac{dI_h(t)}{dt} &= e^{-\mu_h \tau_i} mc\beta_{vh} \frac{S_h(t-\tau_i) I_v(t-\tau_i)}{N_h} - \gamma_h I_h(t) - \mu_h I_h(t) \\
\frac{dS_v(t)}{dt} &= \mu_v N_v - c\beta_{hv} \frac{I_h(t) S_v(t)}{N_v} - \mu_v S_v(t) \\
\frac{dI_v(t)}{dt} &= e^{-\mu_v \tau_e} c\beta_{hv} \frac{I_h(t-\tau_e) S_v(t-\tau_e)}{N_v} - \mu_v I_v(t)
\end{align*}
$$

Deaths are described in the last term in each equation. The total number of deaths is equal to the total number of births for both hosts and vectors. Each host can sustain a population of $m$ mosquitoes. Each day, each mosquito bites, on average, $c$ times ($c$ can be less than 1). Assuming that mosquitoes bite any host with equal probability, then the proportion of bites of viraemic mosquitoes biting susceptible hosts is equal to the proportion of viraemic mosquitoes in the population ($I_v/N_v$). Of these bites, only a fraction $\beta_{vh}$ will eventually lead to the infection of the
Table 2.1: Variables and parameters of dengue model (Equation (2.13))

<table>
<thead>
<tr>
<th>Notation</th>
<th>Description</th>
<th>Range in the literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_h(t), I_h(t)$</td>
<td>Number of susceptible and infectious hosts</td>
<td></td>
</tr>
<tr>
<td>$S_v(t), I_v(t)$</td>
<td>Number of susceptible and infectious vectors</td>
<td></td>
</tr>
<tr>
<td>$N_h$</td>
<td>Initial number of susceptible hosts</td>
<td>10000</td>
</tr>
<tr>
<td>$N_v$</td>
<td>Total number of vectors</td>
<td>0 – 30000</td>
</tr>
<tr>
<td>$m$</td>
<td>Relative density of vectors to hosts</td>
<td>0 – 3</td>
</tr>
<tr>
<td>$c$</td>
<td>Daily biting rate of the vectors</td>
<td>0 – 1 day$^{-1}$</td>
</tr>
<tr>
<td>$\beta_{vh}$</td>
<td>Probabilities of viral transmission from an infected vector to a susceptible host</td>
<td>0.1 – 0.9</td>
</tr>
<tr>
<td>$\beta_{hv}$</td>
<td>Probabilities of viral transmission from an infected host to a vector</td>
<td>0.4 – 0.9</td>
</tr>
<tr>
<td>$\tau_i$</td>
<td>Intrinsic incubation period (IIP)</td>
<td>4 – 7 days</td>
</tr>
<tr>
<td>$\tau_e$</td>
<td>Extrinsic incubation period (EIP: the time necessary for the virus to follow the cycle that brings it from the mosquito’s stomach to its salivary gland)</td>
<td>7 – 12 days</td>
</tr>
<tr>
<td>$\gamma_h$</td>
<td>Inverse of the duration of viremic</td>
<td>0.167 – 0.333 day$^{-1}$</td>
</tr>
<tr>
<td>$\mu_h$</td>
<td>Birth and death rate of hosts</td>
<td>0 – 0.005 day$^{-1}$</td>
</tr>
<tr>
<td>$\mu_v$</td>
<td>Birth and death rate of vectors</td>
<td>0.025 – 0.3 day$^{-1}$</td>
</tr>
</tbody>
</table>

Thus the rate of susceptible hosts getting infected is $mc\beta_{vh}I_v/H_v$. Hosts infected with dengue undergo an incubation period assumed to be of fixed length $\tau_i$, after which proportion $e^{-\mu_h\tau_i}$ of hosts survives, followed by an infectious period of mean duration $1/\gamma_h$. Similarly, susceptible mosquitoes become infected from an infectious host during probing and feeding at the rate $c\beta_{hv}I_h/N_h$, and infected mosquitoes experience an fixed extrinsic incubation period $\tau_e$. Their mean adult life span is $1/\mu_v$.

2.2.3 $R_0$ and equilibrium points

The basic reproduction number $R_0$ may be read as the average number of infections caused by a single infectious subject in a wholly susceptible population. At the beginning of the epidemic, to have dengue spread in both vector and human population, the number of infectious hosts and vectors need to increase. If either of them fails, the disease cannot persist in the population.

From Equation (2.13), when an epidemic occurs, we have

17
\[
\begin{align*}
\frac{dI_h(t)}{dt} |_{t=0} &> 0 \\
\frac{dI_v(t)}{dt} |_{t=0} &> 0
\end{align*}
\]  

(2.14)

or

\[
\begin{align*}
e^{-\mu_h\tau_i}mc\beta_{vh}S_h(t-\tau_i)I_v(t-\tau_i) &> \gamma_h I_h(t) - \mu_h I_h(t) \big|_{t=0} > 0 \\
e^{-\mu_v\tau_e}c\beta_{hv}I_h(t-\tau_e)S_v(t-\tau_e) &> \mu_v I_v(t) \big|_{t=0} > 0
\end{align*}
\]  

(2.15)

At the beginning of an epidemic, the number of non-susceptible hosts and vectors can be assumed negligible and

\[
S_h(t) \sim N_h \quad \text{and} \quad S_v(t) \sim N_v
\]  

(2.16)

Also, the number of infectious hosts at time \(t\) and \(t - \tau_e\) is almost the same, so is the number of infectious vectors at time \(t\) and \(t - \tau_i\).

\[
I_h(t) \sim I_h(t - \tau_e) \quad \text{and} \quad I_v(t) \sim I_v(t - \tau_i)
\]  

(2.17)

Then Equation (2.15) becomes

\[
\begin{align*}
e^{-\mu_h\tau_i}mc\beta_{vh}S_h \frac{I_h(t-\tau_i)}{N_h} &> (\gamma_h + \mu_h)I_h \\
e^{-\mu_v\tau_e}c\beta_{hv}I_h \frac{I_v(t-\tau_e)}{N_v} &> \mu_v I_v
\end{align*}
\]  

(2.18)

So we have

\[
e^{-(-\mu_h\tau_i - \mu_v\tau_e)}mc^2\beta_{vh}\beta_{hv}I_vI_h > (\gamma_h + \mu_h)\mu_v I_h I_v
\]

and

\[
\frac{mc^2\beta_{vh}\beta_{hv}e^{-(-\mu_h\tau_i - \mu_v\tau_e)}}{(\gamma_h + \mu_h)\mu_v} > 1
\]  

(2.19)

The above inequality is the condition for the disease to spread. So the expression of the basic reproduction number has the form:

\[
R_0 = \frac{mc^2\beta_{vh}\beta_{hv}e^{-(-\mu_h\tau_i - \mu_v\tau_e)}}{(\gamma_h + \mu_h)\mu_v}
\]  

(2.20)

We study the solutions of system (2.13) in the closed set

\[
\Omega = \{(S_h, I_h, S_v, I_v) \in \mathbb{R}_+^4 : S_h + I_h \leq N_h, S_v + I_v \leq N_v\}
\]

System (2.13) has at most two biologically meaningful equilibrium points.

\(E = (S_h, I_h, S_v, I_v) \in \mathbb{R}_+^4\) is an equilibrium point for system (2.13) if it satisfies

18
\[
\begin{align*}
\mu_h N_h - m c \beta_{vh} S_h(t) I_v(t) + \mu_h S_h(t) & = 0 \\
e^{\mu_h \tau_i} m c \beta_{vh} \frac{S_h(t) I_v(t) - \mu_h S_h(t)}{N_h} & = 0 \\
\mu_v N_v - c \beta_{hv} \frac{I_h(t) S_v(t) - \mu_v S_v(t)}{N_v} & = 0 \\
e^{-\mu_v \tau_e} c \beta_{hv} \frac{I_h(t) S_v(t) - \mu_v S_v(t)}{N_v} & = 0
\end{align*}
\] (2.21)

The biologically meaningful equilibrium points are said to be disease-free or endemic depending on \( I_h \) and \( I_v \): if there is no disease for both populations of humans and mosquitoes (\( I_h = I_v = 0 \)), then the equilibrium point is a disease-free equilibrium; otherwise, if \( I_h > 0 \) or \( I_v > 0 \), then the equilibrium point is called endemic.

The relationship between the basic reproduction number and the equilibrium is as follows:

If \( R_0 < 1 \), the disease-free equilibrium \( E_1 \) is obtained.

\[
E_1 = \lim_{t \to +\infty} (S_h(t), I_h(t), S_v(t), I_v(t)) = (N_h, 0, N_v, 0)
\] (2.22)

The endemic equilibrium \( E_2 \) is obtained if \( R_0 > 1 \).

\[
E_2 = \lim_{t \to +\infty} (S_h(t), I_h(t), S_v(t), I_v(t)) = (\hat{S}_h, \hat{I}_h, \hat{S}_v, \hat{I}_v)
\] with

\[
\begin{align*}
\frac{\dot{S}_h}{c \beta_{vh}} & = e^{\mu_v \tau_e} N_v \left(c \beta_{hv} \mu_h + c \beta_{vh} \mu_v + e^{\mu_v \tau_e} \mu_h \mu_v \right) \\
\frac{\dot{I}_h}{c \beta_{hv} \mu_v} & = e^{-\mu_h \tau_i} N_h \left(-c^2 m c \beta_{hv} \beta_{vh} + e^{\mu_h \tau_i} \mu_h \mu_v \right) \\
\frac{\dot{S}_v}{c \beta_{vh} \mu_h} & = e^{\mu_h \tau_i} N_v \left(\gamma_h + c \beta_{hv} \mu_v \right) \left( e^{\mu_h \tau_i} \mu_h \mu_v \right) \\
\frac{\dot{I}_v}{c \beta_{vh} \mu_h} & = e^{-\mu_v \tau_e} N_v \left(-c^2 m c \beta_{vh} \beta_{hv} + e^{\mu_v \tau_e} \mu_h \mu_v \right)
\end{align*}
\] (2.23)
CHAPTER 3

DETERMINISTIC AND STOCHASTIC MODELS OF DENGUE FEVER

3.1 Introduction

Our main purpose of studying the dynamics of dengue fever is to understand the epidemic phenomenon and to suggest strategies for the control of the disease in general. We are interested to investigate what happens if a few infections are introduced into the population. This illustrates, more or less, how an outbreak starts.

There are two parts we are going to explore: Numerical simulations of the deterministic model and stochastic simulations based on the dengue transmission mechanism.

3.2 Deterministic model

3.2.1 Numerical simulation

Now, we discuss the numerical simulation of the model (2.13) as the parameters in the system are varied. We have a range of values for each parameter (see Table 2.1) from archived literature and generally we obtain the result as in Figure 3.1. We perform all simulations and graphics with Mathematica. In Figure 3.1a and 3.1c, susceptible humans and vectors stay initially constant, then decline sharply to a nadir and subsequently oscillate to their equilibrium values. In Figure 3.1b and 3.1d, the dynamics of infectious populations shows an exponential growth phase followed by a peak and decay, and then increases again because there is a supply of new susceptible humans or vectors from newborns. After several oscillations the frequency of infections approaches an equilibrium. At this equilibrium, the numbers of infectious humans and vectors are 61 and 207, respectively. The human infection reached a peak between the 240th and the 250th day. The infection of the mosquitoes is delayed, with peak between the 260th and the 270th day.

3.2.2 Sensitivity analysis of basic reproduction number ($R_0$)

In system (2.13), the basic reproduction number is defined as:
Figure 3.1: Numerical simulation for susceptible humans (a), infectious humans (b), susceptible vectors (c) and infectious vectors (d) with the initial condition of 10000 susceptible humans, 1 infectious human, 10000 susceptible vectors and 0 infectious vector. The parameter values of this simulation are $\beta_{vh} = 0.16$, $\beta_{hv} = 0.48$, $c = 1$, $\gamma_h = 0.2$, $\tau_i = 6$, $\tau_e = 9$, $\mu_v = 1/14$, $\mu_h = 1/500$, $R_0 = 2.76527$. (See Table 2.1)

$$R_0 = \frac{mc^2\beta_{vh}\beta_{hv}e^{(-\mu_h\tau_i-\mu_v\tau_e)}}{\gamma_h + \mu_h}\mu_v$$

(3.1)

The magnitude of the basic reproduction number ($R_0$) is dependent on parameters that are associated with dengue fever epidemiology and human and mosquito traits.

Let us look at the possibility and necessity to modify those parameters in order to reduce the basic reproduction number. $m$ is the relative density of vectors to hosts, i.e. $m = \frac{N_v}{N_h}$. Reducing
can be achieved through controlling the number of mosquitoes, such as the removal of breeding sites generated by humans in households, malathion spraying to target adult mosquito populations and so on. \( c \) represents the biting rate per day per vector and per host. The ways to reduce the mosquito biting rate in humans include netting, screens, application of insecticides to clothing or the application of mosquito repellents. \( \beta_{vh} \) and \( \beta_{hv} \) are the probabilities of viral transmission from an infected vector to a susceptible host and from an infected host to a vector, respectively. These two values are usually fixed as they are the characteristics of dengue transmission, even though they may vary for different human races or at different places. \( \mu_h \) means the birth and death rate of hosts. It is inversely proportional to \( R_0 \), so reducing \( R_0 \) would have to be achieved by increasing the death rate of humans, which is a method that no one would like to do. \( \tau_i \) describes the days of intrinsic incubation period. Since its parameter \( \mu_h \) has range \( 0 \) – \( 0.005 \), changing \( \tau_i \) would make a very limited contribution towards \( R_0 \). \( \mu_v \) represents the birth and death rate of vectors. It is possible to raise this parameter by altering mosquitoes’ genes or some other biological techniques. \( \tau_e \) is the extrinsic incubation period, which is regarded as fixed and hard to change. \( \gamma_h \) is the inverse of the duration of viremic, which can be modified through applying medicine during the illness.

Therefore, in sum, there are four key parameters worth studying: (i) the relative density of vectors to hosts (\( m \)), (ii) the biting rate per day per vector and per host (\( c \)), (iii) the birth and death rate of vectors (\( \mu_v \)) and (iv) the inverse of the duration of viremic (\( \gamma_h \)).

In order to study the effect of these key parameters on \( R_0 \), we performed a sensitivity analysis on \( R_0 \) with respect to three parameters: \( m, \mu_v \) and \( \gamma_h \). \( c \) has the similar role to \( m \) in the formula, hence we only study \( m \) for brevity. The sensitivity index \( S_I \) is defined as

\[
S_I = \frac{\partial R_0}{\partial P} \cdot \frac{P}{R_0}
\]

where \( P \) is the parameter of interest. The larger the magnitude of the sensitivity index, the more sensitive \( R_0 \) was with respect to that parameter.

Sensitivity for the relative density of vectors to hosts (\( m \)) is positive for all values of \( m \) between 0 and 3; that is, \( R_0 \) increases as the relative vector density become larger. This is confirmed by the fact that higher mosquitoes density around the tropical areas (see Figure 2.7), corresponded to a higher prevalence of dengue fever. Furthermore, such dependence of \( R_0 \) on relative mosquito
density is even more pronounced when the birth and death rate of vectors is relatively low (Figure 3.2).

Figure 3.2: (a) Plot of $R_0$ vs. the relative density of vectors to hosts ($m$) and the birth and death rate of vectors ($\mu_v$). (b) Level curve of a basic reproduction number. Curve for $R_0 = 1$ is in red.

In contrast to the relative density of vectors to hosts ($m$), the sensitivity indexes for the birth and death rate of vectors ($\mu_v$) and for the inverse of the duration of viremic ($\gamma_h$) are negative. The latter means that, as indicated by $R_0$, the size of the epidemiological burden is likely to be less when individuals infected with dengue fever spend less time to recover (Figure 3.3). This is the
reason that medicine is critical to invent as fewer infectious days enable less secondary infection. Furthermore, the value of $R_0$ is found to be more sensitive to changes in the birth and death rate of vectors than changes in the inverse of the duration of viremic, which indicates a critical role of the birth and death rate, or mortality rate of vectors, in reducing the epidemiological burden of dengue fever.

![Figure 3.3](image1.png)

Figure 3.3: (a) Plot of $R_0$ vs. the relative density of vectors to hosts ($m$) and the inverse of the duration of viremic ($\gamma_h$). (b) Level curve of a basic reproduction number. Curve for $R_0 = 1$ is in red.

Specifically, the sensitivity indexes for $m$, $\mu_v$ and $\gamma_h$ are found to be 2.77, −1.64, and −0.99,
respectively, when all parameters are fixed at their baseline values (Figure 3.4). Therefore, for instance, if the mosquito mortality rate were to increase by 1%, then the value of $R_0$ would decrease by 1.64%. Similarly, a 1% decrease of the relative mosquito density would correspond to a 2.77% decrease, and 1% increase of the inverse of the duration of viremic would correspond to a 0.99% decrease in the value of $R_0$.

![Figure 3.4: Sensitivity analysis of the basic reproductive number. The sensitivity indices of the model parameters ($m$, $\mu_v$ and $\gamma_h$) are computed through local derivatives.](image)

### 3.3 Stochastic model

There are several papers simulating the dynamic transmission of dengue fever stochastically. Focks et al. [20] constructed a model that takes into account the majority of factors known to influence dengue epidemiology. The basis of their transmission model is the simulation of a human population growing in response to country- and age-specific birth and death rates. In contrast to most spatially homogeneous models, de Castro Medeiros et al. [12] developed a stochastic cellular automata model to simulate the spread of dengue fever in a dense community. Each cell corresponds to a built area, and has its identical pattern of local connections to other cells. Their model uses heterogeneous rules for human mobility.

Even though most previous stochastic models involve comprehensive factors that enable the models to be more realistic, seldom do they incorporate or compare with a deterministic system as a theoretical basis. Therefore, they are incapable of yielding the analytical form of several key
features of the model, such as the basic reproduction number and the equilibrium points.

Our stochastic model is based on a dengue transmission mechanism that is described as in the deterministic SEIR model, and includes certain elements of reality. Our analyses aim to build a bridge between the deterministic and stochastic models, compare some critical features of both models, and investigate the possibility that our future analysis of deterministic model could somewhat predict or be adopted in realistic situations through this bridge.

As the sensitivity of $R_0$ is analyzed with respect to several key factors in the last section, we want to see how those factors would influence the dynamics of the disease if they vary across different parts of the world. In addition, they even change from mosquito to mosquito in the same area. Among these factors, we mainly focus on the biting rate $c$, which will be regarded as a random variable instead of a fixed value.

We will explore an individual-based SEIR model which incorporates some important features of disease transmission in a discrete-time stochastic framework.

### 3.3.1 Description of model

The model we employ is based on the deterministic model (Equation (2.13)) but has some modifications to make it more realistic. Because the time scale for data on epidemics is usually daily at its finest, it is natural to use a discrete time model with a time step which is thought of as one day.

**Assumptions of model.**

(a) The total human population size is fixed at $N_h$, and the total mosquito population size is fixed at $N_v$.

(b) Human and mosquito populations are not age-structured, and vertical transmission and climate variability are not considered. Both human and vector populations are homogeneous mixtures.

(c) Time is discrete, with epochs $t = 0, 1, 2, \cdots$ The natural unit for the duration of an epoch is one day.

(d) If an individual gets infected, he enters the intrinsic incubation period ($\tau_i$) in which he cannot pass the disease to other mosquitoes. He stays in such a state for $\tau_i$ consecutive time points including the initial time point of getting the disease, where $\tau_i$ is a positive integer constant. Thus, if an individual gets the disease at epoch $t$, then he is diseased but not yet infectious for the epochs $\{t, t + 1, \ldots, t + \tau_i - 1\}$. In real life, if an individual is susceptible at time $t - 1$
and infected at time $t$ then it is assumed that he becomes infected somewhere in the interval $(t-1, t]$. At epoch $t + \tau_i$ such an individual enters the infectious compartment (I), and remains in this state for $1/\gamma_h$ time points, that is, at $\{t + \tau_i, t + \tau_i + 1, \ldots, t + \tau_i + 1/\gamma - 1\}$. At epoch $t + \tau_i + 1/\gamma_h$, this individual recovers (R) and cannot be re-infected. In general $\tau_i$ and $\gamma_h$ can be random variables, but this complication is ignored throughout for simplicity.

(e) If a mosquito gets infected, it enters the extrinsic incubation period (E) for $\tau_e$ days. It stays in the incubation for the epochs $\{t', t'+1, \ldots, t'+\tau_e - 1\}$ and becomes infectious (I) at time point $t' + \tau_e$. It will remain in this state for the rest of its life. Again, $\tau_e$ is set to be a constant instead of a random variable for simplicity.

(f) For individual $i$, $i = 1, \ldots, N_h$, the random process $X_i = \{X_i(t), t = 0, 1, 2, \ldots\}$ is such that $X_i(t) = 0$ if he is susceptible at time $t$, $X_i(t) = 1, 2, \ldots, \tau_i$ if he is in incubation period, $X_i(t) = \tau_i + 1, \tau_i + 2, \ldots, \tau_i + 1/\gamma_h$ if he is infectious, and $X_i(t) = \tau_i + 1/\gamma_h + 1$ if he is recovered. The value of $X_i(t)$ not only represents the states that an individual is in, but also indicates which day he is at. For example, $\tau_i + 3$ means an individual is at the 3rd day in infectious compartment. Thus the total number of humans in S, E, I, R compartments at time $t$ are

$$S_h(t) = \sum_{i=1}^{N_h} \mathbb{1}_{\{0\}}(X_i(t))$$

$$E_h(t) = \sum_{i=1}^{N_h} \mathbb{1}_{\{1, 2, \ldots, \tau_i\}}(X_i(t))$$

$$I_h(t) = \sum_{i=1}^{N_h} \mathbb{1}_{\{\tau_i + 1, \tau_i + 2, \ldots, \tau_i + 1/\gamma_h\}}(X_i(t))$$

$$R_h(t) = \sum_{i=1}^{N_h} \mathbb{1}_{\{\tau_i + 1/\gamma_h + 1\}}(X_i(t))$$

where $\mathbb{1}_A(\cdot)$ is an indicator function such that

$$\mathbb{1}_A(\omega) = \begin{cases} 1 & \text{if } \omega \in A \\ 0 & \text{if } \omega \notin A \end{cases}$$

There are a number of further constraints on the components as follows:

If we do not consider vital dynamics, then the number of exposed (infectious) humans at day $t$ equals the number of exposed (infectious) humans at day $t - 1$, and the number of recovered humans at day $t$ equals the number of recovered humans plus the number of humans who are
in their last infectious day at day \( t - 1 \). That is, for \( t = 1, 2, \ldots, \tau_e + 1 \):

\[
\sum_{i=1}^{N_h} \mathbb{1}_{k+1}(X_i(t)) = \sum_{i=1}^{N_h} \mathbb{1}_k(X_i(t - 1)), \quad k = 1, 2, \ldots, \tau_e + 1 / \gamma_h - 1
\]

\[
\sum_{i=1}^{N_h} \mathbb{1}_{\tau_e+1/\gamma_h+1}(X_i(t)) = \sum_{i=1}^{N_h} \mathbb{1}_{\tau_e+1/\gamma_h}(X_i(t - 1)) + \sum_{i=1}^{N_h} \mathbb{1}_{(\tau_e+1/\gamma_h+1)}(X_i(t - 1))
\]

(g) For mosquito \( j, j = 1, \ldots, N_v \), the random process \( Y_j = \{Y_j(t), t = 0, 1, 2, \ldots\} \) is such that

\( Y_j(t) = 0 \) if it is susceptible at time \( t \), \( Y_j(t) = 1, 2, \ldots, \tau_e \) if it is in incubation period, \( Y_j(t) = \tau_e + 1 \) if it is infectious. Thus the total number of mosquitoes in S, E, I compartments at time \( t \) are

\[
S_v(t) = \sum_{j=1}^{N_v} \mathbb{1}_{\{0\}}(Y_j(t))
\]

\[
E_v(t) = \sum_{j=1}^{N_v} \mathbb{1}_{\{1, 2, \ldots, \tau_e\}}(Y_j(t))
\]

\[
I_v(t) = \sum_{j=1}^{N_v} \mathbb{1}_{\{\tau_e+1\}}(Y_j(t))
\]

Again, there are the following constraints for \( t = 1, 2, \ldots, \):

\[
\sum_{i=1}^{N_v} \mathbb{1}_{k+1}(Y_j(t)) = \sum_{i=1}^{N_v} \mathbb{1}_k(Y_j(t - 1)), \quad k = 1, 2, \ldots, \tau_e - 1
\]

\[
\sum_{i=1}^{N_v} \mathbb{1}_{\tau_e+1}(Y_j(t)) = \sum_{i=1}^{N_v} \mathbb{1}_{\tau_e}(Y_j(t - 1)) + \sum_{i=1}^{N_v} \mathbb{1}_{(\tau_e+1)}(Y_j(t - 1))
\]

**Human and mosquito renewal rate.** Considering the initial dengue-free open population in the sense that human renewal is taken into account, after a dengue epidemic, the small number of susceptible individuals in addition to the births allows the maintenance of disease transmission, even at low rates. Through time, the number of susceptible humans increases until it is sufficient to initiate a new outbreak. The disease finally becomes endemic over time after several periods. We assume only positive or zero rates of human renewal. Theoretically, the daily number of human beings replaced by new susceptible ones would be \( N_h \cdot \mu_h \). Since our model considers only integers, the daily number of renewal humans is set as \( \lfloor N_h \cdot \mu_h \rfloor \). Similarly, the daily number of renewal mosquitoes is set as \( \lfloor N_v \cdot \mu_v \rfloor \).
Biting rate and target choice by mosquitoes. As we analyzed in the last section, the biting rate $c$ is a critical parameter with respect to the basic reproduction number $R_0$. However, this rate varies with time and mosquitoes. Some mosquitoes can take several meals within one day, while some may take no meal for several days. So, what distribution will the biting rate follow if it is not consistent from mosquito to mosquito? What will happen to the epidemic if the biting rate is a random variable?

Poisson distribution is a discrete probability distribution that expresses the probability of a given number of events occurring in a fixed interval of time if these events occur with a known average rate and independently of the time since the last event [22]. By this definition, $c$ follows a Poisson distribution and we assume the average biting rate is 1 per day:

$$c \sim \text{Pois}(1) \quad \text{and} \quad P(c = k) = \frac{e^{-1}}{k!} \quad \text{for} \quad k = 0, 1, 2, \ldots,$$

Based on above assumption, each mosquito’s biting rate follows a Poisson distribution daily. The random selection of the target humans by a mosquito is as follows:

If the biting rate of a mosquito $j$ at day $t$ is $c = k_j$, for example, then we uniformly randomly select $k_j$ person-times from $N_h$ humans since we only consider a homogeneous community, and each individual is allowed to be selected repeatedly within a day or by a same mosquito.

Transmission probabilities. During the process of interaction between humans and mosquitoes, each human can assume one of four states: S, E, I and R, and each mosquito can assume one of three states: S, E, I. If there is a contact between a susceptible human and an infectious mosquito, the human may become exposed with probability $\beta_{vh}$. On the other hand, if an infectious human has contact with a susceptible mosquito, the latter becomes exposed at a probability $\beta_{hv}$.

Stochastic model. Our stochastic model starts with the initial condition that all the humans and mosquitoes are susceptible except a small proportion of humans being infectious, who are at the very beginning of their infectious period. Every day, each mosquito has its biting rate and chooses targets to bite. The transmission probabilities from vectors to hosts and from hosts to vectors are described as above. By the end of that day, we randomly draw some hosts and vectors corresponding to their renewal rates, and remove them as dead. At the same time, we add new hosts and vectors with the same amount we removed to the susceptible state as newborns. We monitor the states of each host and each vector daily, as well as the interactions among them.
The daily flow chart and main algorithm are as follows. The development and implementation of the model are carried out using C++.

3.4 Model results and discussion

One important component in the transmission of dengue fever is the number of infectious humans over time. In the following analyses we are going to focus on the dynamics of infectious humans only.

Because stochastic events have randomness in the early phase of a mass-action phenomenon, repeated simulations with the same starting conditions do not always result in similar outcomes. This is most likely to occur as conditions become intermediate between favoring the loss of or rapid transmission of virus. Figure 3.6 shows two sample paths of the simulations. One of them finally perturbs around an equilibrium after an initial large peak followed by several damped oscillations. One of them drops to disease-free state after the first peak. It happens that the disease is eliminated.
Algorithm 1 Main algorithm to stochastic model (Pseudocode)

// Parameter setting: total number of vectors ($N_v$), total number of hosts ($N_h$), birth and death rate of vectors ($\mu_v$), birth and death rate of hosts ($\mu_h$), extrinsic incubation period ($\tau_e$), intrinsic incubation period ($\tau_i$), recovery rate ($\gamma_h$), transmissive rate from host to vector ($\beta_{hv}$), transmissive from vector to host ($\beta_{vh}$). A host is represented by $X_i(t)$, and he/she is in S when $X_i(t) = 0$, in E when $1 \leq X_i(t) \leq \tau_i$, in I when $\tau_i + 1 \leq X_i(t) \leq \tau_i + 1/\gamma_h$, and in R when $X_i(t) = \tau_i + 1/\gamma_h + 1$. A vector is denoted by $Y_j(t)$. It is in S when $Y_j(t) = 0$, in E when $1 \leq Y_j(t) \leq \tau_e$, and I when $Y_j(t) = \tau_e + 1$. We look at the dynamics of each group in 3000 days.

for $j = 1$ to 3000 do
  for $j = 1$ to $N_v$ do
    Is the vector Susceptible?
    If YES
      generate $c \sim \text{Pois}(1)$
      for $k = 1$ to $c$ do
        Randomly draw a host
        Is the host Infectious?
        If NO, nothing happens.
        If YES, generate $n \sim \text{Uniform}[0,1]$. If $n < \beta_{hv}$, the vector get infected, and $Y_j(t) = 1$.
        skip to step 2.
      end for
    end for
    Is the vector Exposed?
    If YES, $Y_j(t) = Y_j(t) + 1$, skip to step 2.
    If NO, the vector must be in Infectious compartment. Next step.
    generate $c \sim \text{Pois}(1)$
    for $k = 1$ to $c$ do
      Randomly draw a host.
      Is the host susceptible?
      If NO, nothing happens.
      If YES, generate $n \sim \text{Uniform}[0,1]$. If $n < \beta_{vh}$, the host get infected. $X_i(t) = 1$. skip to step 2.
    end for
  end for

// Step 2: Update hosts and mosquitoes each day considering the birth and death.
Accumulating all the $S_h$, $I_h$, $S_v$, and $I_v$ for each day, and
for $i = 1$ to $N_h$ do
  $X_i(t) = X_i(t) + 1$ if $X_i(t) \in \{1, 2, \ldots, \tau_i + 1/\gamma_h\}$.
end for
even though the basic reproduction number is greater than one in the stochastic model, because when the system runs out of susceptible humans, the renewal rate is too low to supply new infections before infectious mosquitoes die out.

Figure 3.6: Two sample paths of the infectious humans in the stochastic simulation (black, red), as well as the means of 1000 paths at all the time points (blue). Here $N_v = 8000$, $N_h = 4000$, $\mu_v = 1/24$, $\mu_h = 1/500$, EIP$= \tau_e = 9$, IIP$= \tau_i = 6$, $\gamma_h = 0.2$, $\beta_{hv} = 0.4$, and $\beta_{vh} = 0.197$. Initial conditions are: initial infectious hosts=50, and the rest of the humans and mosquitoes are all in susceptible state.

In order to explore the general behavior of the dynamics of the disease, a total of 1000 replicates of the stochastic model are run. We find that repeated runs typically give similar results regarding dates of onset and duration of the epidemic and extent of infection within the population.

Among these 1000 sample paths, we extract the paths that do not drop to 0 at time 2000 so that the disease-free and endemic cases are separated. Then we calculate the mean of those extracted paths at every time point and compare it with the curve from the deterministic model.

Figure 3.7 shows the similarities and differences between the results of the two models. Comparing with the deterministic model, the first peak of the stochastic model is lower and later; there are several humps after the first peak instead of one; the curve oscillates around a level, although the amplitude is small. However, they share several similarities: Both of them increase sharply at the
beginning and arrive at a peak. Then both of them drop significantly followed by some oscillations. Eventually infectious human number ($I_h$) in the deterministic model reaches its equilibrium 35.79, and in the stochastic model, $I_h$ oscillates around its equilibrium 38.60 with variance 0.3356.

Figure 3.7: Comparison of the deterministic model (blue) and the stochastic model (red). Here $N_v = 8000$, $N_h = 4000$, $\mu_v = 1/24$, $\mu_h = 1/500$, EIP = $\tau_e = 9$, IIP = $\tau_t = 6$, $\gamma_h = 0.2$, $\beta_{hv} = 0.4$, and $\beta_{vh} = 0.197$. Both models have the same initial conditions: initial infectious hosts=50, and the rest of the humans and mosquitoes are all in susceptible state.

Our study shows that the results of both deterministic model and stochastic model share several critical features of the dynamics of dengue fever. The equilibriums are close even though the biting rate is set as a random variable in the stochastic model. Therefore, we expect that any methods for the sake of disease elimination, that are analyzed and implemented by the deterministic model, will quantitatively predict the behavior of the results of the stochastic model, which is more realistic, to a certain extent. It might happen that the results of both models have differences, but at least we could assure that the methods we use will not have no effect or opposite effect on fighting the disease.
CHAPTER 4

A MODEL OF DENGUE FEVER WITH WOLBACHIA IN VECTOR POPULATION

4.1 Introduction: Aedes aegypti and Wolbachia

*Aedes aegypti* is a domesticated mosquito that prefers to live in and around human habitation, thriving in crowded cities and biting primarily at dusk and dawn. Humans also provide nutrients needed for mosquitoes to reproduce through stagnant water. In urban areas, *Aedes* mosquitoes breed in water containers such as plastic cups, discarded tires, broken bottles, and flower vases. With urbanization, crowded cities, high population density, and poor sanitation, environmental conditions foster the spread of the disease [39].

Female mosquitoes acquire infection by taking blood meals from infected humans. These infected mosquitoes pass the disease to other susceptible humans. Female mosquitoes lay their eggs on wet inner walls of containers. Eggs hatch to become larvae. In the following days, the larvae feed on microorganisms involved in the degradation of leaves and other organic matter in water. When a larva has acquired enough energy and size, metamorphosis changes the larva into a pupa. The adult mosquito emerges from the mature pupa as it floats at the water surface. The entire life cycle, from the aquatic phase (eggs, larvae, pupae) to the adult phase, lasts from 8 to 10 days at room temperature, depending on the level of feeding. However, when the seasons are freezing or waterless, the eggs or larvae delay their development, and carry on their life cycle only when there is enough water or warmth. For example, the eggs of some species of *Aedes* remain unharmed in diapause if they dry out, and hatch later when they are covered by water.

It is very difficult to control or eliminate *Aedes aegypti* mosquitoes because they quickly adapt to changes in the environment and bounce back to initial numbers after droughts or prophylactic measures. The transmission thresholds and the extent of dengue transmission are determined by various factors, including the level of herd immunity in the human population, survival, feeding behavior, abundance of *Aedes aegypti*, climate and human density, distribution, and movement. Currently, there are two primary methods of prevention: larval control and adult mosquito control.
Larvicide treatment is an effective control of the vector larvae, together with mechanical control, which is related to educational campaigns to remove still water from domestic receptacles and eliminate possible breeding sites. However, educational campaigns are hard to promote widely and continuously, especially in some rural areas. The application of insecticides can reduce the mosquito vector population. However, the efficacy is often constrained by the difficulty in achieving enough coverage of resting surfaces, and remains insufficient since it only permits to delay the outbreak of the epidemic [14].

While controlling or eliminating the mosquito population in all the endemic areas doesn’t seem feasible, another sensitive component of a vector’s role in pathogen transmission is its daily probability of survival. Disease control strategies that aim to increase vector mortality are expected to be more efficient in reducing pathogen transmission than alternative ways, because relatively small changes in daily survival can result in relatively large changes in the basic reproduction number, as well as in the number of new human infections.

For disease transmission to occur, pathogens have to undergo a significant period of development in their insect vector before they can be transmitted to a new host. After a female mosquito ingests an infectious blood meal, dengue arboviruses penetrate the mosquito’s midgut and replicate in various tissues before infecting the salivary glands, where they are transmitted to a new host during subsequent blood-feeding. This time period from pathogen ingestion to biological infectivity is termed the extrinsic incubation period (EIP) and lasts for 7 to 12 days, which take up a large period of a mosquito’s whole life span. A trait in a vector population that shortens life span is critical because it not only decreases the vector survival through EIP, but also shortens the expectation of infective life, or the number of days a vector is capable of spreading the disease. What trait would shorten life span and make vectors unable to respond and adapt to it in their future generations? Some bacteria in the genus Wolbachia potentially satisfy that requirement.

Wolbachia are bacteria that live within insect cells and are passed from one generation to the next through the insect’s eggs. Wolbachia pipiens was first observed in the ovaries and testes of the mosquito, Culex pipiens in the 1920s. Early studies showed that it was not a pathogen of mammals but instead a naturally occurring and harmless symbiotic bacterium of insects. Since those early studies it has been determined that it is extremely common in insects, with estimates suggesting that up to 60% of all insect species naturally carry different strains of Wolbachia. Considering that
there may be 2 – 5 million different insect species on the planet, *Wolbachia* is a very successful and pervasive insect bacterium.

In some systems, *Wolbachia* does not seem to confer major fitness costs to its arthropod host. However, a pathogenic *Wolbachia* strain called popcorn or *wMelPop* has been shown to kill adult *Drosophila melanogaster* by over-replicating in the central nervous system. Average adult life span of infected flies is approximately one-half that of uninfected flies. If popcorn or a popcorn-like *Wolbachia* strain were transferred into disease vectors such as mosquitoes, it might be possible to reduce the potential for dengue transmission by increasing vector mortality. However, life-shortening *Wolbachia* strains do not occur in mosquitoes naturally.

McMeniman et al. [31] successfully infected *A. aegypti* with the *wMelPop* strain, and showed that *wMelPop* strain halved the average life span of laboratory *A. aegypti*. Thus, *wMelPop* may be able to shorten *A. aegypti* life span in the wild, and skew mosquito population age structure toward younger individuals, thereby reduce pathogen transmission without eradicating the mosquito population.

McMeniman’s experiments also tested a particular reproductive phenotype of *Wolbachia* known as cytoplasmic incompatibility (CI), a type of embryonic lethality that results from crosses between infected males with uninfected females. Figure 4.1 explains CI and how by releasing a limited number of mosquitoes with *Wolbachia* to breed with wild type mosquitoes, over a small number of generations, will result in all the mosquitoes having *Wolbachia*. Their results show that only 2 eggs hatched from more than 4400 embryos obtained from crosses between *Wolbachia*-infected males and uninfected females. It revealed that the *wMelPop* infection induced very strong CI.

In McMeniman’s experiments, they also verified high maternal inheritance of *Wolbachia* from infected females to their progeny. The proportion of *Wolbachia*-infected progeny from *Wolbachia*-infected females mating with uninfected males is above 99.45%. Their data suggest that the maternal transmission rate predicts stable prevalence of the infection once *Wolbachia* has invaded a population under the action of CI.

Under laboratory conditions, McMeniman et al. verified that with strong CI and high maternal inheritance, *Wolbachia* strains, such as *wMelPop*, could invade and subsequently maintain a high prevalence in mosquito populations, even if they confer a fitness cost such as shortened life span and increased mortality.
Figure 4.1: The diagram [36] above explains Cytoplasmic Incompatibility and how by releasing a limited number of mosquitoes with Wolbachia to breed with wild type mosquitoes, over a small number of generations, will result in all the mosquitoes having Wolbachia.

a) When male mosquitoes with Wolbachia mate with female wild mosquitoes that don’t have Wolbachia those females will have eggs but they won’t hatch.

b) When male mosquitoes with Wolbachia mate with females that are already carrying Wolbachia the mating will be normal and the offspring will all have Wolbachia.

c) When female mosquitoes with Wolbachia mate with males without Wolbachia all her offspring will have Wolbachia.

Nevertheless, field cage trials conducted under semi-natural conditions are needed to gain a quantitative estimate of the potential efficacy of this strategy.

Walker et al. [45] tested the invasion of Wolbachia in a semi-field facility providing environments that simulate the natural habitat of A. aegypti in north Queensland, Australia. They tested the potential of the wMelPop strain to invade uninfected mosquito populations at a starting frequency of 0.65 and with additional near-weekly supplementary additions of Wolbachia-infected mosquitoes. Their results show that wMelPop increased and reached fixation after 40 days. It exploits the potential of a practical approach to Wolbachia invasion in mosquito population.

Vertically inherited parasites are predicted to evolve toward reduced virulence over time. However, unlike chemical insecticides, biological agents that induce mortality in late life, such as wMelPop, are expected to impose relatively weak selection pressures for the evolution of resistance. This is because the majority of individuals in the population are able to initiate several
reproductive cycles before death, minimizing costs to reproductive output. Moreover, since the initial description of \textit{wMelPop} in \textit{D. melanogaster} over 10 years ago, no signs of resistance to life-shortening have emerged in laboratory stocks.

A comparison of results from these experimental studies with simulations from recent theoretical models, which examine the potential of life-shortening \textit{Wolbachia} to modify mosquito population age structure, suggests that \textit{wMelPop} should be able to initiate a population invasion of \textit{A. aegypti} \cite{6, 8, 37}.

There are two opposing phenomena affecting the ability of life-shortening \textit{Wolbachia} to spread in a population. First, because \textit{wMelPop} shortens life span, \textit{Wolbachia}-infected mosquitoes may have lower fitness than longer lived uninfected mosquitoes. Previous empirical analyses have regarded fecundity reduction out of shortened life span as the major measure of fitness reduction. If this is the case, \textit{Wolbachia} will not spread through the mosquito population and dengue transmission will persist. On the other hand, many \textit{Wolbachia} induce sperm-egg cytoplasmic incompatibility (CI) in their hosts. Therefore, when the proportion of \textit{Wolbachia}-infected mosquitoes is large, infected females produce a greater number of viable embryos than uninfected mosquitoes, conferring a reproductive advantage over uninfected females. Thus, the fitness increase due to CI can offset the life-shortening effects of \textit{wMelPop}, resulting in a fitness trade-off for mosquitoes infected with \textit{wMelPop}.

The effect of this trade-off on population dynamics was first considered by Caspari and Watson \cite{7}. They examined fitness advantage due to CI ($s_h$), as opposed to the fitness reduction due to life-shortening effects ($s_f$), in accordance with earlier analysis concerning fecundity reduction, on the host. Assuming random mating, discrete generations and perfect maternal transmission, when \textit{Wolbachia} reduces host fitness from 1 to $1 - s_f < 1$ and when mating with a \textit{Wolbachia}-infected male reduces a non-carrier’s fitness from 1 to $1 - s_h < 1$, the frequency of infected adults ($p$) at generation $t + 1$ (details in Appendix A) has been described to be:

$$p_{t+1} = \frac{p_t (1 - s_f)}{1 - s_f p_t - s_h p_t (1 - p_t)}$$  \hspace{1cm} (4.1)

This formula predicts three equilibrium points for \textit{Wolbachia} infection frequency. There are stable equilibrium points at $p = 0$ and 1, and an unstable equilibrium at $p = s_f / s_h$. 

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The unstable equilibrium $s_f/s_h$ is a threshold infection frequency, above which *Wolbachia* is expected to spread to fixation 1, but below which its frequency is expected to decline to 0. Therefore, for *Wolbachia* to spread into a host population, the reproductive benefit due to cytoplasmic incompatibility ($s_h$) must be greater than the fitness reduction in life span ($s_f$) associated with the infection, and the initial prevalence ($p_t$) of infected adults must be greater than the ratio $s_f/s_h$.

Turelli and Hoffmann [44] extended the analysis of Caspari and Watson to deduce the equilibrium points when transmission is not perfect. Let $\mu$ denote the fraction of offspring from *Wolbachia*-infected mother that are non-carriers, then the recursion becomes (details in Appendix B)

$$p_{t+1} = \frac{p_t(1 - \mu)(1 - s_f)}{1 - s_f p_t - s_h p_t(1 - p_t) - \mu s_h p_t^2 (1 - s_f)}. \quad (4.2)$$

Thus, the equilibrium frequencies for *Wolbachia*-infected mosquitoes are $p = 0$ and the roots of

$$s_h(1 - \mu + \mu s_f)p^2 - (s_f + s_h)p + s_f + \mu - \mu s_f = 0. \quad (4.3)$$

First note that if $\mu = 0$, corresponding to perfect maternal transmission, this equation yields two equilibrium points: $p = 1$ and $p = s_f/s_h$, which are the same as what we obtained from Equation (4.1).

With incomplete maternal transmission ($\mu > 0$) and $s_h > s_f[1 - 2\mu(1 - s_f)]$, both roots of Equation (4.3) are between 0 and 1. The larger root is a stable equilibrium $p^*$ and the smaller one $\hat{p}$ is unstable. The values of $\hat{p}$ and $p^*$ are given by

$$\hat{p} = \frac{s_f + s_h - \sqrt{(s_f + s_h)^2 - 4(\mu(1 - s_f) + s_f)(1 - \mu(1 - s_f))s_h}}{2(1 - \mu(1 - s_f))s_h} \quad (4.4)$$

$$p^* = \frac{s_f + s_h + \sqrt{(s_f + s_h)^2 - 4(\mu(1 - s_f) + s_f)(1 - \mu(1 - s_f))s_h}}{2(1 - \mu(1 - s_f))s_h} \quad (4.5)$$

Information from field-collected females suggests that $s_h \approx 0.45$ and $s_f \approx 0.05$, and Hoffmann’s [23] data suggest that reasonable estimates are $s_h = 0.3–0.45$ and $s_f = 0.05–0.2$. Using the extreme parameter combinations, $s_f = 0.2$ and $s_h = 0.3$ vs. $s_f = 0.05$ and $s_h = 0.45$, Equation (4.5) requires that $\mu$ be between 0 and 0.061, and the stable equilibrium $p^*$ is between 0.65 and 1. Note that our upper bound for $\mu$ is much larger than the one in archived papers, such as $\mu = 0.039$ by Hoffmann et al. [23]. The estimation from laboratory experiments is much smaller, for example, $\mu$ approximates to 0.0026 – 0.0055 by McMeniman et al. [31].
Recent models have included life-shortening effects and examined the feasibility of using *Wolbachia*, through its effects on *A. aegypti* life span, to control dengue fever. Brownstein et al. [6] studied the age distribution of mosquitoes and associated reduction in disease transmission after introducing *Wolbachia*. Rasgon et al. [37] explored varying patterns and degrees of induced mortality from *Wolbachia* to mosquitoes and quantified the resultant reduction in pathogen transmission. Jansen et al. [24] and Schraiber et al. [41] modeled the requirements for spread of *wMelPop* and the associated reduction in disease transmission.

However, most of the papers mainly focused on the *Wolbachia* invasion in mosquito populations and generally analyzed its effect on dengue control. None of the literature incorporates the effect of *Wolbachia* in the dengue SEIR model to see how it will change the dynamics and endemics of dengue fever in human populations.

In this chapter we describe and explore, using a quantitative modeling framework, the dynamics of dengue fever in human and vector populations after introducing *Wolbachia*, compute the basic reproduction number and new equilibrium points, and quantify the reduction in dengue transmission expected to result from such an introduction under various levels of *Wolbachia*.

### 4.2 Model

Because of the reproductive advantage conferred to *Wolbachia*-infected females, CI can drive *wMelPop* infection through vector population to high frequency despite fitness costs under certain conditions. When the maternal transmission is imperfect, introducing *Wolbachia* may lead its coverage to either drop to 0, or increase to fixation $p^*$, depending on the initial prevalence of *Wolbachia*-infected females, and a critical threshold $s_f/s_h$.

Many papers have simulated the spread of *Wolbachia* in mosquito populations. Their results are similar, as we have stated above. So we are only interested in the situations that when *Wolbachia*-infected mosquitoes arrive to fixation in the population, how it will influence the dynamics of the spread of dengue fever, how the basic reproduction number will change, and the possibility to reduce or eliminate the disease in human population.

Before we incorporate the effect of *Wolbachia* in our SEIR model, there are several assumptions we are going to make.
Firstly, we assume that the vector population keeps at a constant number before and after introducing \textit{Wolbachia}. This is because previous experiments show that the hatch rate of mosquitoes depends on the environmental conditions such as climate, amount of breeding sites, and so on. For example, if we were to eliminate all larvae, pupae, and adult \textit{A. aegypti} at once from a site, its population could recover two weeks later as a result of egg hatching following rainfall or the addition of water to containers harboring eggs. Therefore we assume that the egg supply is always sufficient but the environmental capacity determines the vector population.

Second, we assume that the proportion of \textit{Wolbachia}-infected mosquitoes in the whole population has arrived to its equilibrium. If it declines to 0, \textit{Wolbachia} has no effect on the vectors, and the case is the same as the model we have in Chapter Three. If \textit{Wolbachia} is spread to fixation $p^*$, from our earlier analysis, we assume the range of $p^*$ is between 0.65 and 1.

Third, we denote the mortality rate of \textit{Wolbachia}-infected mosquitoes by $\mu_w$ and assume that its value satisfies $\mu_v \leq \mu_w \leq 2\mu_v$. This assumption is based on McNemann’s [31] laboratory experiments, in which their results show that \textit{wMelPop} strain halved the average life span of both female and male \textit{A. aegypti}. However, the laboratory provided a good environment for mosquitoes to live, and we expect the life span of mosquitoes in wild to be shorter as a result of limited source of food, existence of predators and so on. Therefore, \textit{Wolbachia} non-carriers have a shorter life span than the ones in laboratory, and the life-shortening effect of \textit{Wolbachia} is not as strong as it was observed in lab.

Finally, we assume that the birth rate of \textit{Wolbachia}-infected mosquitoes is higher than that of \textit{Wolbachia} non-carriers. This is because infected mosquitoes have fitness advantage due to cytoplasmic incompatibility, which is greater than the fitness reduction due to life-shortening effect. In addition, the reproductive benefit of \textit{Wolbachia}-infected mosquitoes is high enough to offset the their high mortality so that the \textit{Wolbachia} in the vector population keeps at a fixed level. For \textit{Wolbachia} non-carriers, their fecundity decreases out of the crosses between infected males with uninfected females, but the relative hatch rate increases since more source of food or hatch space is available for each egg, so that the rate of eggs becoming adult mosquitoes is the same as their mortality. Therefore, we assume the birth and death rate of \textit{Wolbachia}-infected mosquitoes are both $\mu_w$, and those of uninfected mosquitoes are $\mu_v$.

Based on the above assumptions, we separate the mosquito population into two groups: \textit{Wol-}
Wolbachia-infected mosquitoes and Wolbachia non-carriers. We want to look at the dynamics of infectious mosquitoes within each group, and see for different proportions of Wolbachia-infected mosquitoes, how the infectious human number will change.

In terms of Equation (2.13), we have the following system (4.6). The change of susceptible humans depends on the infectious number of both Wolbachia-infected and uninfected mosquitoes. We assume the Wolbachia level in mosquitoes has already reached to a fixed number \( p^* \) before dengue is introduced into the human population, therefore the birth rates of Wolbachia-infected and non-carriers are \( \mu_v p^* N_v \) and \( \mu_v (1 - p^*) N_v \), respectively. \( S_w \) and \( I_w \) represent the number of susceptible and infectious Wolbachia-infected mosquitoes, and \( I_v \) and \( S_v \) are the corresponding numbers for Wolbachia non-carriers.

\[
\begin{align*}
\frac{dS_h(t)}{dt} &= \mu_h N_h - m c \beta_{vh} \left( I_v(t) + I_w(t) \right) S_h(t) - \mu_h S_h(t) - \gamma_h I_h(t) - \mu_h I_h(t) \\
\frac{dI_h(t)}{dt} &= e^{-\mu_h \tau_e} c \beta_{vh} \left( I_v(t) + I_w(t) \right) S_h(t) - \gamma_h I_h(t) - \mu_h I_h(t) \\
\frac{dS_v(t)}{dt} &= \mu_v (1 - p^*) N_v - c \beta_{hv} I_v(t) S_v(t) - \mu_v S_v(t) \\
\frac{dI_v(t)}{dt} &= e^{-\mu_v \tau_e} c \beta_{hv} I_v(t) S_v(t) - \mu_v I_v(t) \\
\frac{dS_w(t)}{dt} &= \mu_w p^* N_v - c \beta_{hw} I_w(t) S_w(t) - \mu_w S_w(t) \\
\frac{dI_w(t)}{dt} &= e^{-\mu_w \tau_e} c \beta_{hw} I_w(t) S_w(t) - \mu_w I_w(t)
\end{align*}
\] (4.6)

In the system (4.6), two groups of mosquitoes are closely related to each other. Because of the imperfect maternal transmission, Wolbachia-infected females will still give birth to Wolbachia non-carrier offspring. On the other hand, cytoplasmic incompatibility is not perfect either, and Wolbachia non-carrier females still have Wolbachia-infected progeny hatch when they mate with male mosquitoes who are carrying Wolbachia. Hence the transition between two groups of mosquitoes is available, whereas it may not be frequent under strong CI and high maternal transmission.

### 4.3 Results and discussion

To investigate the effect of introducing Wolbachia to the dynamics of infectious humans, we choose various Wolbachia levels in the mosquito population: \( p^* = 0, 0.7, 0.85, \) and 1. For the sake of simplicity, we set the mortality rate of Wolbachia-infected mosquitoes equal to twice the mortality of uninfected mosquitoes, i.e. \( \mu_w = 2\mu_v \). We performed all simulations and graphics with Mathematica.
4.3.1 Numerical solution

Figure 4.2 shows the dynamics of susceptible, infectious humans and vectors when \( p^* \) changes. In Figure 4.2b, all the curves have a similar behavior. They increase to a peak and decay, then oscillate around and eventually approach to an equilibrium. Moreover, as \( p^* \) increases, the first peak becomes smaller and more delayed, and the equilibrium also decreases. A Wolbachia level that is less than 1 is sufficient to lower infection to 0.

4.3.2 Basic reproduction number \( R'_0 \)

At which level is Wolbachia high enough to eliminate the dengue fever? The easiest way to see it is to calculate the basic reproduction number. Here we still set \( \mu_w = 2\mu_v \). At the beginning of an endemic, non-susceptible humans or vectors are negligible, so \( S_h(0) \approx N_h, S_v(0) \approx N_v(1 - p^*), \) and \( S_w(0) \approx N_v p^* \). The same as the deduction in Equation (2.18), the dengue will spread if and only if

\[
\begin{align*}
    e^{-\mu_h \tau_i} mc \beta_{vh} \frac{N_h(I_v + I_w)}{N_v} &> (\gamma_h + \mu_h) I_h \\
    e^{-\mu_v \tau_e} c \beta_{hv} \frac{I_h(1-p^*) N_v}{N_h} &> \mu_v I_v \\
    e^{-\mu_w \tau_e} c \beta_{hw} \frac{I_h p^* N_v}{N_h} &> \mu_w I_w
\end{align*}
\]

Dividing the second and third inequalities by \( \mu_v \) and \( \mu_w \) on both sides respectively, summing them up, and multiplying by the first inequality, we have

\[
mc^2 \beta_{hv} \beta_{vh} e^{-\mu_h \tau_i} \left( e^{-\mu_v \tau_e} (1 - p^*)/\mu_v + e^{-\mu_w \tau_e} p^*/\mu_w \right) > \gamma_h + \mu_h
\]

and

\[
mc^2 \beta_{hv} \beta_{vh} e^{-\mu_h \tau_i} \left( e^{-\mu_v \tau_e} \frac{1-p^*}{\mu_v} + e^{-\mu_w \tau_e} \frac{p^*}{\mu_w} \right) > \frac{\gamma_h + \mu_h}{\gamma_h + \mu_h} > 1
\]

Therefore, the new basic reproduction number after introducing Wolbachia is

\[
R'_0 = \frac{mc^2 \beta_{hv} \beta_{vh} e^{-\mu_h \tau_i} \left( e^{-\mu_v \tau_e} \frac{1-p^*}{\mu_v} + e^{-\mu_w \tau_e} \frac{p^*}{\mu_w} \right)}{\gamma_h + \mu_h}
\]

(4.8)

To study how the Wolbachia level \( p^* \) will affect \( R'_0 \), we pick the parameter values the same as in Figure 3.1. Figure 4.3 shows the relationship between \( p^* \) and \( R'_0 \). The basic reproduction number decreases as \( p^* \) increases, and arrives to 1 when \( p^* = 0.866 \). In other words, when the proportion of
Figure 4.2: Numerical simulation of dynamics of (a) susceptible humans, (b) infectious humans, (c) susceptible vectors and (d) infectious vectors for different *Wolbachia* levels in vector population. The initial condition is: $S_h = 10000$, $I_h = 1$, $S_v = 10000$ and $I_v = 0$. The parameter value of this simulation: $\beta_{vh} = 0.2$, $\beta_{hv} = 0.6$, $c = 0.8$, $\tau_i = 6$, $\tau_e = 9$, $\mu_v = 1/14$, $\mu_h = 1/500$, $\mu_w = 1/7$. (See Table 2.1)
Figure 4.3: The basic reproduction number with Wolbachia vs. Wolbachia level. The intercept of the curve and $R'_0 = 1$ is at $p^* = 0.866$.

Wolbachia-carriers is greater than 86.6%, the dengue fever can be eliminated from the populations based on our current parameter values.

Note that the Wolbachia level $p^*$ predicted by Hoffmann et al. [23] and McMenimann’s [31] experiments are much higher than 0.886, which means under our assumptions, using Wolbachia to fight dengue has a high success rate.

4.3.3 Equilibrium points

Another feature we are interested in is the equilibrium points when Wolbachia is incorporated into the SEIR model. Among the equilibrium points in the four compartments, we mainly focus on the infectious human number. System (4.6) has two more useful parameters comparing with Equation (2.13): $\mu_w$ and $p^*$. The first one reflects the life-shortening effect of Wolbachia on mosquitoes, and the second one reflects the composition of the mosquito population, with its effect on the dynamics of the disease and $R'_0$ is analyzed above. Both of them are critical to the possibility of removing dengue fever.

In previous analysis, we assume the mortality rate of Wolbachia-infected mosquitoes is double of uninfected ones, i.e. $\mu_w = 2\mu_v$. However, under field condition, the life-shortening effect of Wolbachia is not as strong as it was observed in lab. So what will happen for different Wolbachia levels if $\mu_w \leq 2\mu_v$? Will introducing Wolbachia still get rid of dengue if its life-shortening effect is not that obvious?
Figure 4.4: Size of infectious human at equilibrium (\(\hat{I}_h\)) vs. mortality of Wolbachia-infected mosquitoes (\(\mu_w\)) and Wolbachia level (\(p^*\))

Figure 4.4 shows the relationship among \(\mu_w\), \(p^*\) and \(\hat{I}_h\). In general, the infectious human population at equilibrium falls as \(p^*\) or \(\mu_w\) increases, but when the mortality rate \(\mu_w\) is not high enough, for example, \(\mu_w = 0.1\), even all the mosquitoes are infected with Wolbachia, dengue fever will still persist in the human population. However, introducing Wolbachia contributes to controlling the disease no matter the value of \(p^*\).
VACCINATION AGAINST DENGUE FEVER: A PROSPECTIVE ANALYSIS

5.1 Background

Vaccination is of critical importance in reducing the severity of many infectious diseases, especially vector-borne diseases such as yellow fever, Japanese encephalitis, and tick-borne encephalitis. Although there is no commercially available vaccine to protect against dengue fever, a number of dengue vaccine candidates are in different stages of development.

Among these candidates, the leading one to become the world’s first vaccine against dengue fever was developed by Sanofi and Thailand’s Mahidol University. However, it was only 30 percent effective in its first large clinical trial. The main problem was that there are four serotypes of dengue virus, and Sanofi’s vaccine candidate was shown to be 61.2% effective against dengue virus type 1, 81.9% against type 3 and 90% type 4, but failed to provide any protection against type 2. It turned out that type 2 was the prevalent type in that region at the time of the study, and failing to provide protection against type 2 reduced the vaccine’s overall efficacy to 30%.

Even though the efficacy is low for the leading candidate vaccine, we still consider this option, since its eventual success is not precluded in the medium and long term, when more research that focuses on increasing the vaccine’s protection against serotype 2 has been done. Therefore, prospects for a dengue fever vaccine are good, and mathematical models of the effect of vaccine on dengue fever will be helpful in predicting the trend of disease prevalence, and thus facilitate vaccination policy.

In this chapter we consider two such models. The first is an epidemiological model with vaccination. We will study the conditions under which dengue fever can be controlled or eliminated. In this model, individuals are effectively treated as entities that obey prescribed laws rather than as humans with free-will. In contrast, human perceptions about risks associated with disease and vaccination may strongly influence vaccination decisions from the interests of the individuals under voluntary vaccination policy. When the interests of the individual diverge from the interests of the
group as a whole, such an epidemiological model cannot by itself explain the impact of vaccination on disease control. But methods from game theory [32] have provided valuable insights into interactions between epidemiology and human decision-making [3]. Accordingly, a second, game-theoretic model will be used to demonstrate how population-scale dynamic model can be coupled to individual-scale decision model.

### 5.2 Epidemiological model

The major focus of vaccination is direct individual protection. When the vaccine uptake level is sufficiently high, population effects also provide protection for unprotected individuals. The more vaccinated people, the less likely a susceptible person will come into contact with infectious people. With the introduction of a vaccine, the SEIR model from system (2.13) in Chapter Two becomes the following epidemiological model:

\[
\begin{align*}
\frac{dS_h(t)}{dt} &= \mu_h (1 - w) N_h - mc \beta_{vh} S_h(t) I_v(t) - \mu_h S_h(t) \\
\frac{dI_h(t)}{dt} &= e^{-\mu_h \tau_i} mc \beta_{vh} \frac{S_h(t) I_v(t)}{N_v} - \gamma_h I_h(t) - \mu_h I_h(t) \\
\frac{dS_v(t)}{dt} &= \mu_v N_v - c \beta_{hv} \frac{I_h(t) S_v(t)}{N_h} - \mu_v S_v(t) \\
\frac{dI_v(t)}{dt} &= e^{-\mu_v \tau_e} c \beta_{hv} \frac{I_h(t) S_v(t)}{N_h} - \mu_v I_v(t)
\end{align*}
\]

(5.1)

We suppose vaccination is continuous with a constant proportion of newborns, and the frequency of the effectively vaccinated individuals is \( w \). so the proportion of human population that enters the susceptible state becomes \( \mu_h (1 - w) \), and the proportion \( \mu_h w \) goes to the recovered state directly.

This system yields two equilibrium points, the disease-free state \((S^0_h, I^0_h, S^0_v, I^0_v) = (N_h (1 - w), 0, N_v, 0)\), and an endemic state \((\hat{S}_h, \hat{I}_h, \hat{S}_v, \hat{I}_v)\), where the number of infectious humans is

\[ \hat{I}_h = \frac{N_h \mu_h \{(1 - w) mc \beta_{hv}^2 \beta_{vh} e^{-\mu_h \tau_i} - e^{\mu_v \tau_e} \mu_v (\gamma_h + \mu_h)\}}{c \beta_{hv} (\gamma_h + \mu_h) (c m \beta_{vh} + e^{\mu_v \tau_e} \mu_h)} \]

Figure 5.1 shows simulations for various effective vaccine levels. Other possible intervention measures such as Wolbachia-infected mosquitoes were excluded. We see that the peak becomes lower and more delayed as \( w \) increases. For 63.84% of the population vaccinated, the vaccine eliminates the disease spread when all parameters are fixed at their baseline values.
5.3 Vaccination and theory of games

When the vaccine is firstly released in the population, we expect the vaccine uptake level to be high under voluntary vaccination policy. As vaccine-derived herd immunity builds, the probability of being infected declines but the perceived risk of vaccination remains constant. Hence, rational individuals may exempt themselves from vaccination once herd immunity is sufficiently strong. This has been described as a conflict between self interest and group interest and may make it difficult to eliminate a vaccine-preventable infection [4, 43].

One approach to the study of self interest in a group is population game theory. An early example of the use of game theory for studying vaccination [3], in which individual risk and population dynamics were explicitly modeled, was motivated by concerns for the safety of childhood-disease vaccines. A growing number of papers expanded on this idea, applied it to different kind of infectious diseases and investigated how various factors can favorably or unfavorably influence vaccination practices and health outcomes [5, 9, 43]. However, none of them has applied this idea to the vaccination of vector-borne diseases, and few of them have considered the case in which the vaccine is imperfect.

Generalization of Bauch’s work has led to the model studied here. Our model starts with the
introduction of a population game.

5.3.1 Description of game

Game theory is the study of strategic behavior, when the outcome of an individual’s action depends on actions taken by other individuals. In our game, each individual is trying to find the vaccination strategy that brings the largest benefit to oneself based on others’ strategy. In this population game, we regard Player 1 as an arbitrary focal individual who is one of only very few individuals that may deviate from the population norm, and Player 2 as the remaining individuals in the population.

Each player has a set of feasible plans of action – or strategies. Both Player 1 and Player 2 could choose from two pure strategies, to vaccinate or not to vaccinate, and their strategy set is a mixture of the pure strategies with certain probability [33]. Specifically, playing a strategy \( p \) is defined as selecting vaccinate with probability \( p \), and hence not vaccinate with probability \( 1 - p \).

Here, we assume Player 1 (P1) adopts a \( p \)-strategy, which is an rare strategy that only one or very few individuals use, and Player 2 (P2) is a \( q \)-strategist, who represents the behavior adopted by almost all of the population.

When individuals with the rare strategy are surrounded by ones with the popular strategy, what is their best reply? The answer depends on the rewards that \( p \)-strategists get. \( p \)-strategists are going to maximize their rewards by adjusting their strategy based on others’.

Before introducing these rewards, we first look at the payoffs for different strategies. Let \( r_i \) be the morbidity risk from not undergoing vaccination, and let \( \pi(q) \) be the probability that an unvaccinated individual will eventually be infected when the population strategy is \( q \). Here \( \pi(q) \) is a decreasing function of \( q \). Then the payoff for not taking vaccine is

\[
E_{II}(q) = -r_i \pi(q).
\]

Let \( r_v \) be the morbidity risk from vaccination, so that \(-r_v \) is the payoff of taking vaccine. Different from model (5.1), we suppose the vaccine is imperfect, and the efficacy of vaccine is \( \xi \leq 1 \), hence a proportion \( 1 - \xi \) of players who choose to take the vaccine still may get the disease. Therefore, the payoff for taking vaccine becomes

\[
E_{I}(q) = -r_v + (1 - \xi)(-r_i \pi(q)).
\]
Let \( f(p, q) \) denote the reward to a \( p \)-strategist in a monomorphic population of \( q \)-strategists, so that
\[
f(p, q) = pE_I(q) + (1 - p)E_{II}(q) = E_{II}(q) + (E_I(q) - E_{II}(q))p \tag{5.2}
\]
Here, \( E_I(q) - E_{II}(q) = -r_v + (1 - \xi)(-r_i\pi(q)) - (-r_i\pi(q)) = -r_v + \xi r_i\pi(q) \).

Nash equilibrium.

**Definition** A Nash equilibrium, is a strategy combination, such that no player has an incentive to unilaterally change her action. Players are in equilibrium if a change of strategy by any one of them would lead that player to earn less than if she retained her current strategy.

Let \( R_1 \) be the set of all strategy combination \((p, q)\) such that, for player 1, \( p \) is a best reply or best response to \( q \),
\[
R_1 = \{(p, q) \in D|f(p, q) = \max_p f(\tilde{p}, q)\} = \{(p, q) \in D|p = B(q)\}
\]
where \( D \) is the decision set \([0, 1] \times [0, 1]\), which denotes the set of all feasible strategy combinations.

For a 2-player continuous population game, \( f(p, q) = f(q, p) \) by symmetry, and therefore the set of all feasible strategy combinations \((p, q)\) such that, for Player 2, \( q \) is a best response to \( p \),
\[
R_2 = \{(p, q) \in D|f(q, p) = \max_q f(\tilde{q}, p)\} = \{(p, q) \in D|q = B(p)\}
\]
We call \( R_i \) Player \( i \)'s reaction set.

Now, any Nash equilibrium, denoted by \((p^*, q^*)\), can be found from the condition
\[
(p^*, q^*) \in R_1 \cap R_2
\]
The Nash equilibrium(s) obtained by this method ensures that
\[
f(p^*, q^*) \geq f(p, q^*) \quad \text{for all } (p, q^*) \in D
\]
and
\[
f(q^*, p^*) \geq f(q, p^*) \quad \text{for all } (p^*, q) \in D \tag{5.3}
\]
Theorem 5.3.1 (Nash’s Existence Theorem) Nash proved that if we allow mixed strategies, then every game with a finite number of players in which each player can choose from finitely many pure strategies has at least one Nash equilibrium.

To find the Nash equilibrium(s) in this model, there are several conditions we need to take account of.

Let us first suppose that $E_I(0) - E_{II}(0) \leq 0$ or $-r_v + \xi r_i \pi(0) \leq 0$.

Since $\pi(q)$ is a decreasing function, the coefficient $E_I(q) - E_{II}(q)$ of $p$ is always negative or 0. Hence, for given $q$, $f(p,q)$ is maximized by $p = 0$, and so

$$R_1 = \{(p,q)|p = 0, 0 \leq q \leq 1\}$$

See solid blue in Figure 5.2a. By symmetry, $f(p,q)$ is maximized by any $q = 0$ for any given $p$, and so

$$R_2 = \{(p,q)|0 \leq p \leq 1, q = 0\}$$

See dash blue in Figure 5.2a. Thus the unique intersection of $R_1$ and $R_2$ is $(0,0)$, which is the Nash equilibrium. This result makes sense because if $\xi r_i \pi(0) \leq r_v$, then the probability of dying from the vaccine is greater than the probability of dying from an disease outbreak, and so getting vaccinated is pointless.

Let us now suppose that $E_I(0) - E_{II}(0) > 0$ and $E_I(1) - E_{II}(1) < 0$, or $-r_v + \xi r_i \pi(0) > 0$ and $-r_v + \xi r_i \pi(1) < 0$.

In this case, there must exist $q^* \in (0,1)$ such that $E_I(q^*) - E_{II}(q^*) = 0$ or $-r_v + er_i \pi(q^*) = 0$. So the best response of $p$ to given $q$ is

$$p = B(q) = \begin{cases} 1 & \text{if} \ 0 < q < q^* \\ \text{any} & \text{if} \ q = q^* \\ 0 & \text{if} \ q^* < q < 1 \end{cases}$$

The set of all $(p,q)$ that satisfy the above equation consists of three straight line segments joining $(0,1)$ to $(0,q^*)$ to $(1,q^*)$ to $(1,0)$, as shown solid blue in Figure 5.2b. As we mentioned before that for a continuous population game, the best response of $q$ to given $p$ is the reflection of $B(q)$ with respect to the line $p = q$, as shown dash blue in Figure 5.2b. The intersections of
Figure 5.2: The reaction set and Nash equilibria

these two lines are Nash equilibriums. So, there are three Nash equilibrium points, namely, $(0, 1)$, $(q^*, q^*)$, and $(1, 0)$.

Lastly, when $E_I(1) - E_{II}(1) \geq 0$ or $-r_v + \xi r_i \pi(1) \geq 0$, the coefficient $E_I(q) - E_{II}(q)$ of $p$ is always positive or 0. Hence, for given $q$, $f(p, q)$ is maximized by $p = 1$, and so

$$R_1 = \{(p, q) | p = 1, 0 \leq q \leq 1\}$$

By symmetry,

$$R_2 = \{(p, q) | q = 1, 0 \leq p \leq 1\}$$

The only Nash equilibrium is the point $(1, 1)$. This result is illustrated by Figure 5.2c.

**Evolutionary stable strategy.** Suppose that proportion $1 - \epsilon$ of the population is going to be $q$-strategists, and proportion $\epsilon$ is trying out the rare strategy $p$, where $\epsilon$ is a small positive
number. Then the overall vaccine coverage has been perturbed from \( q \) to

\[
\bar{q} = \epsilon p + (1 - \epsilon)q.
\]

Will the minority \( p \)-strategists proliferate, will they stay and keep their behavior, or will even those few rare players decide to return to the popular strategy?

In Equation (5.2), we defined \( f(p, q) \) to be the reward to \( p \) in a \( q \) population, assuming that the frequency of \( p \) is almost zero. Now let’s extend the definition:

The reward to strategy \( p \) in a population playing \( \bar{q} \) is denoted by \( f(p, \bar{q}) \), and the reward to \( q \) in the same population is denoted by \( f(q, \bar{q}) \), where the first component of the rewards function is a strategy and the second component is a strategy mix.

We assume that

\[
f(p, \bar{q}) = f(p, \epsilon p + (1 - \epsilon)q) = \epsilon f(p, p) + (1 - \epsilon) f(p, q),
\]

which is interpreted to be the reward to being rare when surrounded by \( p \) with small probability \( \epsilon \) and by \( q \) with large probability \( 1 - \epsilon \). Correspondingly,

\[
f(q, \bar{q}) = f(q, \epsilon p + (1 - \epsilon)q) = \epsilon f(q, p) + (1 - \epsilon) f(q, q)
\]

is the reward of being popular \( q \)-strategists in a population with strategy mix \( \bar{q} \).

It does not pay to switch from \( q \) to \( p \) when \( f(q, \bar{q}) > f(p, \bar{q}) \) or

\[
f(q, \epsilon p + (1 - \epsilon)q) > f(p, \epsilon p + (1 - \epsilon)q)
\]

The population strategy \( q^* \) is said to be an evolutionary stable strategy or ESS if it does not pay to switch from \( q^* \) to any \( p \neq q^* \), for all sufficiently small \( \epsilon > 0 \). Hence, setting \( q = q^* \) for the first argument in (5.6), we find that \( q^* \) is an ESS if \( f(q^*, q^*) > f(p, q^*) \) for all \( p \neq q^* \). An equivalent statement is as follows:

**Theorem 5.3.2** For \( q^* \) to be an ESS, two conditions need to be met:

\[
f(q^*, q^*) \geq f(p, q^*) \quad \text{for all} \quad p
\]

and, for all \( p \neq q^* \), either

\[
f(q^*, q^*) > f(p, q^*)
\]
On the other hand, setting \( q = q^* \) in (5.6) and taking the limit as \( \epsilon \to 0 \), a necessary condition for \( q^* \) to be an ESS is that

\[
f(q^*, q^*) \geq f(p, q^*)
\]

for all \( p \). Comparing with (5.3) and recalling that \( f(p, q) = f(q, p) \) for a 2-player continuous population game, we see that a necessary condition for \( q^* \) to be an ESS is that \((q^*, q^*)\) be a Nash equilibrium. Thus candidates for evolutionary stability correspond to symmetric Nash equilibria.

Therefore, by Theorem 5.3.2, we can find the ESS for various conditions.

When \( E_I(0) - E_{II}(0) \leq 0 \), the only Nash equilibrium is \((0, 0)\), and so \( q^* = 0 \) is the unique ESS.

When \( E_I(1) - E_{II}(1) \geq 0 \), the only Nash equilibrium is \((1, 1)\), and so \( q^* = 1 \) is the unique ESS.

When \( E_I(0) - E_{II}(0) > 0 \) and \( E_I(1) - E_{II}(1) < 0 \), we see that 0 or 1 is the unique best reply to 1 or 0, respectively, and \( q^* \) is the unique best reply to itself. By Theorem 5.3.2, we are only interested in the symmetric Nash equilibrium, and so \( q^* \) is the only candidate for ESS. However, \( q^* \) is not the unique best reply to itself. There are infinitely many alternative best replies for \( p \) given \( q = q^* \), so \( f(q^*, q^*) > f(p, q^*) \) does not hold. Nevertheless, for all \( p \neq q^* \), let us look at the sign of \( f(q^*, p) - f(p, p) \).

\[
f(q^*, p) - f(p, p) = q^*E_I(p) + (1-q^*)E_{II}(p) - \{pE_I(p) + (1-p)E_{II}(p)\}
\]

Here both \( q^* - p \) and \( E_I(p) - E_{II}(p) \) are strictly decreasing and change sign from positive to negative at \( p = q^* \), so \( f(q^*, p) - f(p, p) \) is always positive for all \( p \neq q^* \), and \( f(q^*, p) > f(p, p) \). Hence \( q^* \) is an ESS.

The payoff gain to an individual playing \( p \) while the majority playing \( q \) in such a population is

\[
\Delta f = f(p, q) - f(q, q) = \epsilon(p-q)[E_I(p) - E_{II}(p)] + (1-\epsilon)(p-q)[E_I(q) - E_{II}(q)]
\]

The payoff gain \( \Delta f \) is a measure of the incentive for an individual to change strategies from \( q \) to \( p \). If most of the population adopts strategy \( q \), and the rare population adopts the evolutionary
steady strategy \( q^* \), so that \( E_I(q^*) - E_{II}(q^*) = 0 \) as we obtained. Then \( \Delta f = (1-\epsilon)(q^*-q)[E_I(q) - E_{II}(q)] \) is strictly positive for \( q \neq q^* \), all \( \epsilon \) and efficacy \( \xi \), where \( 0 \leq \epsilon \leq 1 \) and \( 0 \leq \xi \leq 1 \). In this case, the rare population always has higher reward than the \( q \)-strategists. We can also conclude that for any \( p \neq q^* \) and \( q \neq q^* \), if \( p \) is closer than \( q \) to the ESS \( q^* \), individuals adopting \( p \) obtain a higher reward than those adopting \( q \).

### 5.3.2 Incorporation of epidemic model

To find out the infection probability \( \pi(q) \), we look at the epidemiological model (5.1) again. The non-trivial stable state is \((\hat{S}_h, \hat{I}_h, \hat{S}_v, \hat{I}_v)\), where

\[
\hat{S}_h(w) = \frac{e^{\mu_v \tau_e} N_h \{c_\beta_{hv} \mu_h (1-w) + e^{\mu_h \tau_i} (\mu_h + \gamma_h) \mu_v \}}{c_\beta_{hv} (cm \beta_{vh} + e^{\mu_v \tau_e} \mu_h)}
\]

and

\[
\hat{I}_v(w) = \frac{e^{-\mu_v \tau_e} N_v \mu_h \{ (1-w)c_\beta_{hv} \beta_{vh} - e^{\mu_v \tau_e} \beta_{vh} (\gamma_h + \mu_h) \mu_v \}}{cm \beta_{vh} \{ (1-w) c_\beta_{hv} \mu_h + e^{\mu_h \tau_i} (\gamma_h + \mu_h) \mu_v \}}
\]

Therefore, the probability that an unvaccinated individual will eventually be infected is:

\[
\frac{mc_\beta_{vh} \hat{S}_h(w)/N_v}{mc_\beta_{vh} \hat{S}_h(w)/N_v + \mu_v \hat{S}_h(w)}
\]

When the population strategy is \( q \), the effective vaccine uptake level is \( w = \xi q \), so

\[
\pi(q) = \frac{c^2 m(\xi q-1) \beta_{hv} \beta_{vh} + e^{\mu_v \tau_e} (\gamma_h + \mu_h) \mu_v}{c(\xi q-1) \beta_{hv} (cm \beta_{vh} + e^{\mu_v \tau_e} \mu_h)}
\]

The value of ESS \( q^* \) is obtained by solving the equation \( \pi(q^*) = \frac{r_v}{\xi r_i} \).

\[
q^* = \frac{c^2 m \beta_{hv} \beta_{vh} (\xi r_i - r_v) - ce^{\mu_v \tau_e} \beta_{hv} \mu_h r_v - e^{\mu_v \tau_e} \mu_h \xi \mu_v r_i (\mu_h + \gamma_h)}{c \beta_{hv} \xi (cm \beta_{vh} (\xi r_i - r_v) - e^{\mu_v \tau_e} r_v \mu_h))}
\]

We interpret \( r_i \) and \( r_v \) as morbidity risks from infection and the vaccination. We can eliminate one of the parameters, leaving only the relative risk as

\[
r_0 = \frac{r_v}{r_i}
\]

In addition, we define the adjusted relative risk as

\[
r_{adj} = \frac{r_v}{\xi r_i}
\]

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The adjusted relative risk involves the contribution of efficacy in the relative risk. For example, if \( \xi = 0.5 \), which mean half of the vaccine uptake humans still under the risk of infection, then the relative risk is doubled and we denote it as adjusted relative risk.

Thus, we can rewrite

\[
q^* = \frac{c^2 m \beta_{hv} \beta_{vh} (1 - r_{adj}) - c e^{\mu_v \tau_e} \beta_{hv} \mu_h r_{adj} - e^{\mu_v \tau_v + \mu_h \tau_e} \mu_v (\mu_h + \gamma_h)}{c \beta_{hv} \xi \{ cm \beta_{vh} (1 - r_{adj}) - e^{\mu_v \tau_e} r_{adj} \mu_h \}}
\]

5.3.3 Results and discussion

As the vaccine candidate developed by Sanofi failed to provide protection against type 2, which is the prevalent type in the trial region, the efficacy of the vaccine was reduced to 30%. However, in other regions, where the prevalent type is not type 2, we would expect the efficacy to be higher. Therefore, we want to investigate the expected vaccine coverage for any relative risk \( r_0 \), or adjusted relative risk \( r_{adj} \) with various values of vaccine efficacy \( \xi \).

![Figure 5.3: ESS vaccine uptake level \((q^*)\) vs. adjusted relative risk when the vaccine efficacy varies.](image)

Figure 5.3 shows that the vaccine uptake level at the ESS is more sensitive to a change in adjusted relative risk \( (r_{adj}) \) when the vaccine efficacy \( (\xi) \) becomes lower. When the adjusted relative risk is above 0.62, no one would like to take the vaccine. Since the expression of \( r_{adj} \) contains \( \xi \), it is hard to tell the direct relationship between the mortality risk from vaccine and the mortality risk from infection. Figure 5.4 plots ESS vaccine uptake level vs. (unadjusted) relative risk instead.
In Figure 5.4, for a fixed relative risk, increasing efficacy enables a decrease in the vaccine uptake level at the ESS. This makes sense because higher efficacy raises the level of immune individuals, and the ESS vaccine uptake level drops by herd immunity.

The grid surface in Figure 5.5 shows the basic reproduction number when humans’ vaccination strategy is at the ESS $q^*$. We see that within the domain of relative risk and efficacy, the basic reproduction number is always greater than 1. This finding formalizes an argument that has previ-
ously been predicted, namely, it is impossible to eradicate a disease through voluntary vaccination when individuals act according to their own interests [4].
CHAPTER 6

CONCLUSION AND FUTURE WORK

In Chapter Three, we investigated the demographic factors that could control or eliminate dengue fever. Particularly, we studied the relationship among the number of infectious humans, the mosquito mortality rate, and the relative density of mosquitoes to humans. Based on the process of the deterministic model, we further built a stochastic model which involves comprehensive demographic factors, and compared the results with the numerical solution of the deterministic model. The results of the two models highlighted the similarity of several critical features, which could serve as a bridge between the theoretical basis and realistic applications.

Chapters Four and Five explored two potential intervention measures: introducing the bacterium *Wolbachia* to the mosquito population, and introducing vaccines to the human population. In the former case, we considered the life-shortening effect of *Wolbachia* on mosquitoes, and found that the persistence of dengue fever sensitively depends on the mosquito survival profile. In the latter case, when vaccine is introduced into the human population, herd immunity makes people exempt themselves from vaccination. We used game theory to study decision-making by individuals and evaluated the level of disease control under voluntary vaccination policy.

Because our goal is to elucidate the most fundamental issues, we have focused on the simplest possible epidemiological model appropriate for vector-borne diseases and have assumed that seasonal forcing, population age-structure, social structure all have negligible effects.

More demographic factors could be set as random variables in the stochastic model, such as the relative density of mosquitoes to humans, the probabilities of viral transmission from an infected vector to a susceptible host or from an infected host to a susceptible vector, and the incubation period. Stochastic simulations were carried out to the basic compartment model without any intervention measures such as introducing *Wolbachia* or vaccines, and future work could incorporate those control measures.

Even though we incorporated the effect of *Wolbachia* in the SEIR model, assuming the *Wolbachia* level has arrived to fixation in the mosquito population, the case of how the *Wolbachia*
spreads into the mosquito population to further perturb the endemic of dengue fever in human
population has not been studied. In the game-theoretic model, perceived relative risk is usually
different from actual relative risk. How perceived relative risk shifts the ESS vaccine uptake level
and influences disease control will provide guidance in running education programs.
APPENDIX A

FREQUENCY OF WOLBACHIA-INFECTED MOSQUITOES FROM ONE GENERATION TO NEXT (EQUATION (4.1))

Let \( p_t \) denote the frequency of Wolbachia-infected adults in generation \( t \). Let \( F = 1 - s_f \) denote the relative fecundity of Wolbachia-infected females. Then \( p_t(1 - s_f) \) is the amount of Wolbachia-infected mosquitoes in the next generation.

In the next generation, the amount of mosquito reduction is composed of two parts: \( s_f p_t \) is the amount of mosquito reduction from reduced fitness due to life-shortening effect. \( s_h p_t(1 - p_t) \) is the amount of mosquito reduction from reduced hatch rate due to incompatible fertilizations (i.e., fertilizations of Wolbachia-infected males with Wolbachia-infected females). Therefore, \( 1 - s_f p_t - s_h p_t(1 - p_t) \) is the amount of total mosquitoes in the next generation.

Assuming random mating and equal viabilities for both incompatibility types, the frequency of Wolbachia-infected adults in generation \( t + 1 \) is the ratio of the amount of Wolbachia-infected adults and the amount of total mosquitoes. We have the recursions:

\[
p_{t+1} = \frac{p_t(1 - s_f)}{1 - s_f p_t - s_h p_t(1 - p_t)}
\]

(A.1)
APPENDIX B

FREQUENCY OF WOLBACHIA-INFECTED MOSQUITOES FROM ONE GENERATION TO NEXT (EQUATION (4.2))

The definitions of $p_t$ and $F = 1 - s_f$ are the same as we defined in Appendix A. In addition, we let $\mu$ denote the fraction of offspring from Wolbachia-infected mother that are Wolbachia non-carriers. Then $p_t(1 - \mu)(1 - s_f)$ is the amount of Wolbachia-infected mosquitoes in the next generation.

In the next generation, the amount of mosquito reduction is composed of three parts: $s_f p_t$ and $s_h p_t (1 - p_t)$ are the same as we described in Appendix A, the amount of mosquito reduction from reduced fitness due to life-shortening effect, and from reduced hatch rate due to incompatible fertilizations, respectively. $\mu s_h p_t^2 (1 - s_f)$ is the amount of mosquito reduction due to incompatible fertilizations in part that imperfect maternal transmission happens. Therefore, $1 - s_f p_t - s_h p_t (1 - p_t) - \mu s_h p_t^2 (1 - s_f)$ is the amount of total mosquitoes in the next generation.

Therefore, when maternal transmission is imperfect, the frequency of Wolbachia-infected adults in generation $t + 1$ is the ratio of the amount of Wolbachia-infected adults and the amount of total mosquitoes. We have the recursions:

$$p_{t+1} = \frac{p_t(1 - \mu)(1 - s_f)}{1 - s_f p_t - s_h p_t (1 - p_t) - \mu s_h p_t^2 (1 - s_f)}.$$


BIOGRAPHICAL SKETCH

Yingyun Shen was born in Hangzhou, Zhejiang, China, the city where the famous West Lake is located. She studied mathematics and applied mathematics in Zhejiang University at Hangzhou. After obtaining her bachelor’s degree in mathematics, the dream of using mathematics to solve biological problems motivated her to the Biomathematics graduate program in the Department of Mathematics at Florida State University, where she had a six-year wonderful time in the world’s most beautiful sunshine.