Analysis and Optimal control of deterministic Vector-Borne diseases model

by

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A dissertation submitted to the Graduate Faculty of
Auburn University
in partial fulfillment of the
requirements for the Degree of
Doctor of Philosophy

Auburn, Alabama
August 4, 2018

Keywords: vertically transmitted, sensitivity, Vector-borne, optimal control, basic reproduction number,

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Abstract

In this dissertation, two systems of deterministic differential equations are introduced to study the transmission of vector-borne diseases between a host and a vector. The total population of the host and the vector are divided into different compartments. The total population of host is divided into susceptible , exposed, infected, and treated groups. The total population of vector is divided into susceptible, exposed, and infected. In chapter 2, we introduce a model to study vertically transmitted vector-borne diseases with nonlinear system of differential equations. We analyze the model by finding the disease free equilibrium point E_0 and deriving the basic reproductive number R_0 by using the next generation matrix method. We study the local and global stability of E_0 and how the stability is related to R_0. We study the sensitivity of R_0 using the normalized forward sensitivity index and find the relation to the parameters in the model. We have numerical simulations to show the result we get from the analysis based on the dengue virus. In chapter 3, we introduce a model to study optimal control to find the best way to control viruses. We introduce two optimal controls, the prevention of contact between host and vector u_1 and the treatment of host u_2 in the model given in the chapter 2. We consider a cost functional related to the cost of the prevention and the treatment. We try to minimize the number of exposed and infected host groups and maximize the number of susceptible and treated host groups. We show the existence of u_1 and u_2 by using Carathodory's existence theorem. We find the explicit formula of u_1 and u_2 with the status variables and the adjoint variables from Hamiltonian by using Pontryagin's maximum principle. We find the numerical values of u_1 and u_2 by solving the given status system and the adjoint system derived from Hamiltonian. We use the forward-backward sweep method and the Runge-Kutta method in 3-dimension to solve the status system and the adjoint system. In the numerical simulation, we compare the result between the controlled case and uncontrolled case for each host and vector groups. Also we see which control among u_1 and u_2 is more effective to control the virus. In appendices, we show the Matlab code used in the numerical simulation.

Acknowledgments

I want to express my deepest appreciation and gratitude to my advisor Dr. Yanzhao Cao who guided me with patience and supported during the Ph.D course at Auburn University. I really thank for his effort, enthusiasm, and support through all the years. He continuously encouraged and convinced me that I could finish the research to get the Ph.D and I can do better on teaching. I could not write the dissertation without his guidance and persistent advise. I also thank the committee Dr. Xiayoing Han, Dr. Junshan Lin, Dr. Wenxian Shen, and the university reader Dr. Sang-Jin Suh who helped me to revise and improve the dissertation.

I also want to express my deepest appreciation to all members of the Department of Mathematics and Statistics at Auburn University. The faculty at the department have been really kind and available whenever I needed help and so I take the further steps to improve the research and the teaching. I am really glad that I am a part of the department.

I want to say thanks to my My wife, Hwanhee Lee, and two kids, Jason and Justin. I couldn't have accomplished my study without their love, support, and immense understanding.

I also want to say thanks to my father, mother, and brother who longed for my graduation. They always encouraged me to keep up the study and supported my life with everything they have.

I thank my friends who shared the knowledge and the friendship and encouraged me in the department and out of the department.

Above all, I thank the Almighty God who allow me to have the knowledge, the strength and the guidance to complete the Ph.D. I can not imagine the completion and the new job without his help.

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Chapter 1

Introduction

In this thesis, we study mathematical models for the dynamics of vector-borne diseases, especially dengue virus. We will provide a brief explanation for vector-borne diseases, mathematical modeling of vector-borne diseases, dengue virus, vertical transmission of dengue virus, analysis of the model, and optimal control approach to find the best way to control the virus.

Vectors are living organisms that can transmit infectious diseases between humans or from animals to humans. Many of these vectors are bloodsucking which ingest disease-producing microorganisms during a blood meal from an infected host (human or animal) and later inject it into a new host during their subsequent blood meal.

Vector-borne diseases are human illnesses caused by parasites, virus and bacteria that are transmitted by mosquitoes, sandflies, triatomic bugs, blackflies, ticks, tsetse flies, mites, snails and lice. Every year there are more than 700,000 deaths from diseases such as malaria, dengue, schistosomiasis, human African trypanosomiasis, leishmaniasis, Chagas disease, yellow fever, Japanese encephalitis and onchocerciasis globally. Since 2014, the major vector-born diseases are dengue, malaria, chikungunya, yellow fever, and Zika.

Changes in agricultural practices due to variation in temperature and rainfall can affect the transmission of vector-borne diseases. The growth of urban slums, lacking reliable piped water or adequate solid waste management, can render large populations in towns and cities at risk of viral diseases spread by mosquitoes. Together, such factors influence the reach of vector populations and the transmission patterns of disease-causing pathogens. [72]

Dengue fever is a mosquito-borne viral infection and is a severe, flu-like illness that affects infants, young children and adults [32, 71]. It occasionally develops into Severe dengue which

is the leading cause of serious illness and death among children. Classical dengue fever is generally observed in older children and adults and is characterized by sudden onset of fever, frontal headache, nausea, vomiting, and other symptoms. The actual illness last for 3 to 7 days is usually benign.

It is transmitted by the *Aedes aegypti mosquitoes and the Aedes albopictus mosquitoes. The Aedes aegypti mosquito lives in urban habitats and breeds mostly in man-made containers. Unlike other mosquitoes the Aedes aegypti mosquito is a day-time feeder. Therefore the peak biting periods are early in the morning and in the evening before dark. The Aedes albopictus mosquito lives mostly in Asia but due to the international trade, it has spread to North America and more than 25 countries in Europe.*

The virus is transmitted to humans through the bites of infected female mosquitoes. Infected symptomatic or asymptomatic humans are the main carriers and multipliers of the virus, serving as a source of the virus for uninfected mosquitoes. An infected mosquito is capable of transmitting the virus for the rest of its life. Mosquitoes' spread is due to its tolerance to temperature below freezing, hibernation, and ability to shelter in microhabitats.

At the present, there is no effective vaccine for the dengue fever. In late 2015 and early 2016, the first dengue vaccine was developed, but its efficacy depended on geographical settings. The main method to control or prevent the transmission of dengue virus is through controlling the environment including the mosquito's habitats, applying appropriate insecticides, using personal household protection, and monitoring and surveillance of vectors.

One of the difficulties to understand the dengue virus is how the virus can remain in human population even through long periods of extremely low incidence. One hypothesis is that the vertical transmission within the mosquito population allows the virus to persist during these times. Vertical transmission of dengue virus by mosquitoes was discovered at the end of the late 1970s. However, it is unclear how widespread it is in nature, and its importance in the epidemiology of the disease. Vertical transmission of dengue virus has been demonstrated in the lab for the several different mosquitoes. Numerous studies have provided clear evidence of vertical transmission of dengue in wild Aedes aegypti and Aedes albopictus mosquitoes. The laboratory experiments reviewed three ways of measuring vertical transmission. The first

is the vertical transmission rate (VTR) that is defined as the proportion of infected parents that produce at least one infected offspring. The second is the filial infection rate (FIR) that is defined as the proportion of infected progeny produced from infected parents, given that vertical transmission has occurred. The third is the vertical infection rate (VIR), which is the VTR multiplied by the FIR [1, 34].

Species	$v_t(\%)$	$f_t(\%)$	v(%)
Ae aegypti	3.0	0.13	0.039
Ae albopictus	41.2	2.9	.2

Table 1.1: Average Laboratory vertical infection (v), vertical transmission (v_t), and filial infection (f_t) rates for Aedes mosquitoes. [16]

Ross first described malaria transmission mathematically and Macdonald updated and extended Ross's theory and applied it to the Global Malaria Eradication Programme (GMEP). During the era of Macdonald, a quantitative theory, consisting of a set of linked concepts, notation and metrics for understanding and measuring mosquito-borne pathogen transmission and control were fully developed [61]. A number of factors that contribute to the rising of vector-borne diseases include (1) the ability of the anthropoids to adapt to new habitats, (2) development of insecticide and drug-resistant vectors, (3) global and rapid human movement (by jet airplanes), (4) building widespread irrigation and water-impoundment, (5) civil unrest and wars which lead to displacement of large masses of people who live for long periods of time under poor conditions, (6) rapid urbanization which concentrates many host on small area, (7) change in policies that took away resources for vector-control measures. In addition,the impact of climate change and global warming is a topic of significant debate. The emergence and reemergence of vector-borne diseases have promoted interest in their mathematical modeling. [70]

Mathematical models have become important tools for analyzing the spread and control of infectious diseases. The model formulation process clarifies assumptions, variables, and parameters. The models provide conceptual results such as thresholds, basic reproduction

numbers, contact numbers, and recovered numbers. Also computer simulations are useful experimental tools for building and testing the theories, assessing quantitative conjectures, determining sensitivities to changes in parameter values, and estimating key parameters from data. Mathematical models have been formulated for diseases such as measles, rubella, chickenpox, whooping cough, diphtheria, smallpox, malaria, onchocerciasis, filariasis, rabies, gonorrhea, herpes, syphilis, and HIV/AIDS [39].

The basic reproduction rate, R_0, is the number of secondary infections produced by one primary infection in a totally susceptible population. The traditional threshold condition is expressed in terms of relationship between S_0 and ρ. S_0 is the initial population of susceptible individuals and $\rho = \frac{\gamma}{\beta}$, where β is the transmission rate and γ is the recovery rate. If $S_0 > \rho$ the disease persists and if $S_0 < \rho$ the disease dies out. Because $R_0 = \frac{S_0}{\rho}$ the condition $S_0 > \rho$ is equivalent to the condition $R_0 > 1$. Similarly, the condition $S_0 < \rho$ is equivalent to the condition $R_0 < 1$. If $R_0 > 1$, then each infectious individual will pass the infection to more than one susceptible individual. Therefore the disease can be maintained in the population. If $R_0 < 1$, then the disease will die out in the population because it is not able to reproduce itself at a sufficient rate. This kind of information has proven that R_0 is a useful concept to determine effective control measures.

$$R_0 \propto \left(\frac{infectious}{contact}\right) \cdot \left(\frac{contact}{time}\right) \cdot \left(\frac{time}{infectious}\right) = \tau \cdot c \cdot d$$

where τ is the transmissibility, i.e., probability of infection given contact between a susceptible and infected individual, c is the average rate of contact between susceptible and infected individuals, and d is the duration of infectiousness.

A number of approaches have been used in the development of models analyzing the diseases. These approaches include 1) compartment models, 2) statistical approaches, 3) geographic approaches, and 4) economic models. Two classic epidemiology models are Epidemic and Endemic models. Epidemic models are used to describe rapid outbreaks that occur in less than one year. Endemic model are used for studying diseases over longer periods, during which there is a renewal of susceptible individuals by births or recovery from temporary immunity. The most common method in use is the compartment model. For example, there are SI, SIS,

SEI, SIR, SEIS, SIRS, SEIR, SEIRS, MSEIR, MSEIR, and MSEIRS models. The models consist of a number of compartment based on the disease status of an individual.

- *Passive immune (M): is composed by newborns that are temporarily passively immune due to antibodies transferred by their mothers.*
- *Susceptible (S): is the class of individuals who are susceptible to infection. This can include the passively immune individuals once they lose their immunity or, more commonly, any newborn infant whose mother has never been infected and therefore has not passed on any immunity.*
- *Exposed or Latent (E): compartment refers to the individuals that despite being infected, do not exhibit obvious signs of infection.*
- *Infected (I): in this class, the level of pathogen is sufficiently large within the host and there is potential for transmitting the infection to other susceptible individuals.*
- *Recovered or Resistant (R): includes all individuals who have been infected but have recovered.*

The process of building a mathematical model begins with a series of assumptions about how the disease process works and developing a simplified model to describe the process. The choice of which compartments to include in a model depends on the characteristics of the particular disease being studied and the purpose of the model. The exposed compartment is sometimes neglected when the latent period is very short. Additionally, the compartment of the recovered individuals cannot always be considered since there are diseases where the host does not become resistant [62]. The general transfer diagram for the MSEIR is given as the following.

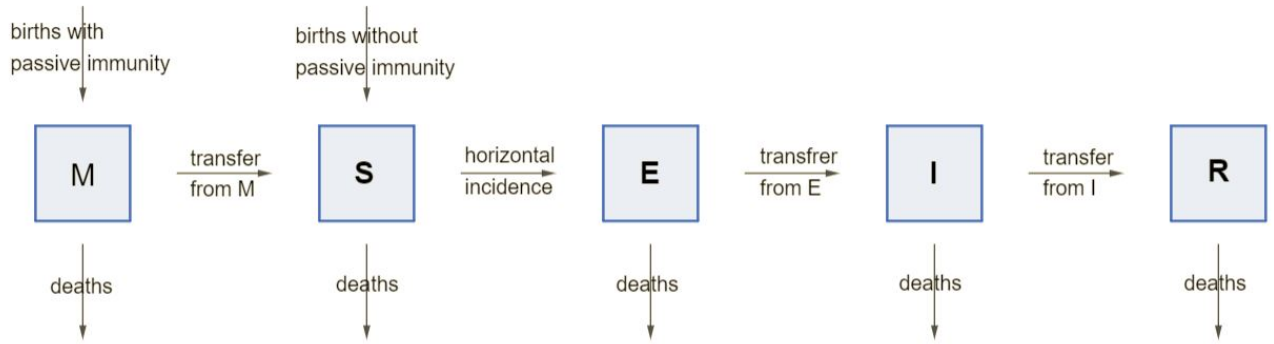

Figure 1.1: The general transfer diagram for the MSEIR model

The two classical epidemic and endemic SIR model provide an intuitive basis for understanding more complex epidemiology modeling results. For the classical SIR Epidemic model we assume that 1) Constant (closed) population size, N, 2) Constant rates (e.g., transmission, recovery rates), 3) No demography (i.e., births and deaths), and 4) Well-mixed population, where any infected individual has a probability of contacting any susceptible individual that is reasonably well approximated by the average. It is given by the initial value problem

$$\begin{aligned} \frac{dS}{dt} &= \frac{-\beta IS}{N}, & S(0) = S_0 \geq 0 \\ \frac{dI}{dt} &= \frac{\beta IS}{N} - \gamma I, & I(0) = I_0 \geq 0 \\ \frac{dR}{dt} &= \gamma I, & R(0) = R_0 \geq 0. \end{aligned} \tag{1.1}$$

where $S(t), I(t)$, and $R(t)$ are the number of susceptible, infectious, recovered, respectively and $N(t) = S(t) + I(t) + R(t)$. β is the effective contact rate, γ is the recovery rate. An epidemic occurs if the number of infected individuals increases, i.e., $\frac{dI}{dt} > 0$. Then we have $\frac{\beta IS}{N} - \gamma I > 0$ from the model (1.1)*. We assume that $\frac{S}{N} \approx 1$ because at the outset of an epidemic, nearly everyone is susceptible. Substituting $\frac{S}{N} = 1$, we have the basic reproduction number $R_0 = \frac{\beta}{\gamma} > 1$.*

The classic Endemic SIR model is almost the same as the SIR epidemic model, except that it has an inflow of newborns into the susceptible class at rate μN and deaths in the classes at

rates μS, μI, and μR. It is given by the initial value problem

$$\begin{aligned} \frac{dS}{dt} &= \mu N - \mu S \frac{-\beta IS}{N}, \quad S(0) = S_0 \geq 0 \\ \frac{dI}{dt} &= \frac{\beta IS}{N} - \gamma I - \mu I, \quad I(0) = I_0 \geq 0 \\ \frac{dR}{dt} &= \gamma I - \mu R, \quad R(0) = R_0 \geq 0. \end{aligned} \tag{1.2}$$

We find $R_0 = \frac{\beta}{\gamma+\mu}$ in the similar way from the endemic SIR model.

Since the two models are simple, we find the basic reproduction number, R_0 from $\frac{dI}{dt}$. For a complex model, we use the next generation method. The next generation method introduced by Diekmann (1990) is a general method of deriving R_0 in cases encompassing any situation in which the populations is divided into discrete, disjoint classes. In the next generation method, R_0 is defined as the spectral radius (dominant eigenvalue) of the next generation operator (matrix). Let us assume that there are n compartments of which m are infected. We define the vector $\bar{x} = \{x_i\}_{i=1}^n$ where x_i denotes the number of individuals in the ith compartment. Let $F_i(\bar{x})$ be the rate of appearance of new infections into compartment i, and let $V_i(\bar{x}) = V_i^-(\bar{x}) - V_i^+(\bar{x})$, where $V_i^+(\bar{x})$ is the rate of transfer of individuals into compartment i by all other means and $V^-(\bar{x})$ is the rate of transfer of individuals out of the ith compartment. The difference $F_i(\bar{x}) - V_i(\bar{x})$ gives the rate of change of x_i. We assume that F_i and V_i satisfy the conditions outlined in Van den Driessche [66]. We can form the next generation matrix FV^{-1} where

$$F = \left[\frac{\partial F_i(x_0)}{\partial x_j} \right] \tag{1.3}$$

and

$$V = \left[\frac{\partial V_i(x_0)}{\partial x_j} \right] \tag{1.4}$$

where $i, j = 1, \ldots, m$ and x_0 is the disease-free equilibrium. The entries of FV^{-1} give the rate at which infected individuals in x_j produce new infections in x_i, times the average length of time an individual spends in a single visit to compartment j. [38, 39, 41, 64].

We perform sensitivity analyses on a mathematical model to determine the relative importance of model parameters to disease transmission and prevalence. With the sensitivity, we can reduce human morbidity and control the disease. There are many methods available for

conducting sensitivity analysis such as differential analysis, response surface methodology, the Fourier amplitude sensibility test (FAST) and other variance decomposition, fast probability integration and sampling-based procedures. Nakul Chitnis [26] have evaluated the sensitivity indices of the basic reproduction number and the point of endemic equilibrium to the parameters in the model. We defines the normalized forward sensitivity index of a variable, u, that depends differentiable on a parameter, p, as

$$\gamma_p^u = \frac{\partial u}{\partial p} \times \frac{p}{u}. \tag{1.5}$$

These indices allow us to measure the relative change in a state variable when a parameter changes [63].

Optimal control theory is a powerful mathematical tool to make decision involving a complex system. For example, what percentage of the population should be vaccinated as times evolves in a given epidemic model to minimize both the number of infected people and the cost of implementing the vaccination strategy. Optimal control methods have been used to study the dynamics of diseases including malaria, yellow fever, and dengue.

A typical optimal control problem requires a performance index or cost functional, $J(x(\cdot), u(\cdot))$; a set of state variable, $x(\cdot) \in X$; and a set of control variable $u(\cdot) \in U$. The main goal consists in finding a piecewise continuous control $u(t)$, $t_0 \leq t \leq t_f$, and the associated state variable $x(t)$, to minimize (or maximize) the given objective functional. There are three well known equivalent formulations to describe an optimal control problem, which are the Lagrange, Mayer, and Bolza forms [24, 73].

The principal technique for an optimal control problem is to solve a set of necessary conditions that an optimal control and corresponding state must satisfy. The necessary conditions were developed by Pontryagin and his co-workers. Pontryagin introduced the idea of adjoint functions to append the differential equation to the objective functional. Adjoint functions have a similar purpose as Lagrange multipliers in multivariate calculus which append constraints to the functions of several variables to be maximized or minimized. We need to find the appropriate conditions that the adjoint function should satisfy and derive a characterization of the optimal control in terms of the optimal state and corresponding adjoint. We find the necessary

conditions from the Hamiltonian H, which is defined as follows.

$$\begin{aligned} H(t,x,u,\lambda) &= f(t,x,u) + \lambda g(t,x,u) \\ &= \textit{integrand } + \textit{ adjoint } * \textit{ RHS of the state equations}. \end{aligned} \tag{1.6}$$

We minimize (or maximize) H with respect to u at u^*, and the conditions can be written in terms of the Hamiltonian

$$\begin{aligned} &\frac{\partial H}{\partial u} = 0 \textit{ at } u^* \Rightarrow f_u + \lambda g_u = 0 \textit{ (optimality conditin)} \\ &\lambda' = -\frac{\partial H}{\partial \lambda} \Rightarrow \lambda' = -(f_x + \lambda g_x) \textit{ (adjoint equation)} \\ &\lambda(t_1) = 0 \textit{ (transversality condition)} \end{aligned} \tag{1.7}$$

There are two different ways to solve the optimal control problems in numerically 1) indirect method and 2) direct method. To apply an indirect method, it is necessary to explicitly get the adjoint equations, the control equations, and all of the transversality conditions if they exist. To solve the state and adjoint differential equations, we use the backward-forward sweep method and Rung-Kutta fourth order method . A direct method has been driven by the industrial need to solve large-scale optimization problems. This method constructs a sequence of points $x_1, x_2, \ldots, x^*$ such that the objective function F to be minimized satisfies $F(x_1) > F(x_2) > \cdots > F(x^*)$ and reformulates the problem as a standard nonlinear optimization problem (NLP). There are many well-known software programs that can handle it [47, 58, 62].

For the future research we consider periodicity and stochastic model. Periodicity and other oscillatory have been observed in the incidence of many infections diseases, including measles, mums, rubella, chickenpox, poliomyelitis, diphtheria, pertussis, and influenza. Many researches show that models with periodic coefficients can explain the periodicity and other oscillatory. For example, Contact rate vary seasonally for childhood diseases because of opening and closing of schools. Periodic changes in birth rate of populations are evidence in many biological works. Vaccinations program is also a source of periodicity. A natural and important problem associated with periodic epidemic model is to define and compute their basic reproduction numbers. Bacaër and Guernaoui [6] presented a general definition of the basic reproductions number in a periodic environment and show that it is a threshold parameter

for the local stability of the disease-free periodic solution and for the global dynamics under certain circumstances [55, 68].

Stochastic models are characterized by randomness, and variable states are described by probability distribution. If the environment is randomly varying and the population systems are often subject to environment noise, then parameters involved in epidemic models are not absolute constants, and they may fluctuate around some average values. If the initial population size is small then a stochastic model is more appropriate, since the likelihood that the population becomes extinct due to chance must be considered. Based on these factors, people began to be concerned about stochastic epidemic models. There are different possible approaches to including random effects in the model. In the future research, we will study the stochastic model based on our deterministic model [20, 33, 51].

This dissertation includes the analysis and the optimal control of the deterministic vertically transmitted vector-borne disease model. In chapter 2, we introduce a deterministic vertically transmitted vector-borne disease model that uses the SEIR model for the host and the SEI model for the vector. The basic reproduction number is derived using the next generation method and the local and global stability of the disease-free equilibrium point is discussed. Also, the sensitivity for R_0 is discussed. In chapter 3, we present the vertically transmitted vector-borne epidemic model with two controls to derive an optimal prevention of the contact between vector and host and an optimal treatment for host with the minimal implementation cost. We introduce an optimal control problem under the given epidemic model and discuss the existence of the optimal controls and the optimality system to find the optimal controls. In chapter 4, we consider controlling the number of mosquitoes and prevention of human-mosquito iteration. Similar to chapter 3, We introduce an optimal control problem under the given epidemic model and discuss the existence of the optimal controls and the optimality system to find the optimal controls. In each chapter, we provide the numerical results supporting the analytical conclusions.

Chapter 2

Analysis of Vertically transmitted vector-borne disease model

2.1 Vertically transmitted vector-borne disease Model

In this section, we formulate and analyze the vertically transmitted vector-borne disease model. We use SEIR type of structure for host and SIR type of structure for vector. The host population is grouped into four compartments: susceptible host (x_1), exposed host (no symptom, x_2), infectious (x_3), and treated (x_4). The total population of host is $N = x_1 + x_2 + x_3 + x_4$. The vector population is grouped into three compartments: susceptible vector (y_1), infectious vector (y_2). The total population of vector is $P = y_1 + y_2 + y_3$.

To formulate a model of a disease, we introduce parameters and assume the followings. We consider that the vertical transmission. That is, a disease is transmitted vertically from mother to child by blood transfusion, breast feeding, or complications during pregnancy and from mosquito to mosquito's eggs when they are infected. In the susceptible host, x_1, it is increased by a result of new recruits and birth from susceptible, exposed, and treated hosts, and treated hosts. It is decreased as a result of biting from infectious vectors and natural death. In the exposed host, x_2, it is increased by a result of biting from infectious vectors (at a rate of $\frac{\phi\beta y_3 x_1}{N}$) and birth from infected parents (at a rate of $\Lambda\zeta_1 x_3$). it is decreased by a result of natural death and becoming infectious host after the incubation period. In the infectious host, x_3, it is increased by a result of infectious host from an exposed host after the incubation period. It is decreased by a result of recovering, death induced by the disease, and natural death. In the treated host, x_4, it is increased by a result of recovering from infectious host. It is decreased by a result of becoming susceptible host after treated and natural death. In the susceptible

vector, y_1, it is increased by a result of new adult female and maturation from susceptible and exposed vector. It is decreased by a result of biting the exposed and infectious host and natural death. In the exposed vector, y_2, it is increased by a result of becoming a exposed vector from biting the exposed (at a rate of $\frac{\phi\theta_2 x_2}{N}$) and infectious host (at a rate of $\frac{\phi\theta_1 x_3}{N}$) and birth from infected parents. It is decreased by a result of becoming infectious after the incubation period and natural death. In the infectious vector, y_3, it is increased by a result of becoming infectious from exposed vector. It is decreased by natural death.

Parameter	Description (rates are per day)
μ	host death rate (when density is ignored)
ζ_1	vertical disease transmission rate (in the host)
ζ_2	vertical disease transmission rate (in the vector)
δ_0	average number of new adult female mosquitoes
δ_1	a factor for density dependent maturation of mosquitoes to adulthood
Λ	per capita(person) birth rate of host
r	host recovery rate
β	the probability that the disease is transmitted from an infected vector to a host per contact
ρ	host recruitment rate (by birth, assumed susceptible)
ϕ	the number of contacts between a host and a vector
α	disease-induced host death rate
ψ	fading rate of treatment to make hosts susceptible to the disease
γ	density independent death rate of vectors
ϵ	incubation rate of the disease in a vector
d	incubation rate of the disease in a host
θ_1	transmission efficacy of the disease from infectious host to vector
θ_2	transmission efficacy of the disease from exposed host to vector

Table 2.1: Parameters and description

We consider the following transmission between human and vector [11], [12].

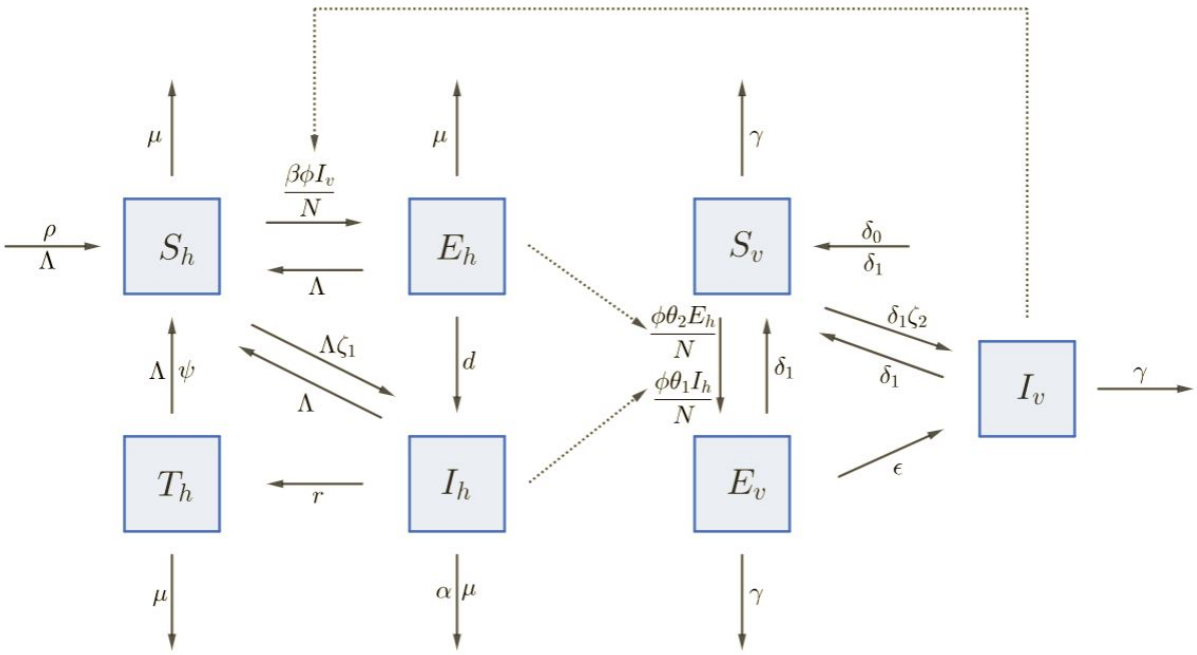

Figure 2.1: Compartment between human and vector where $S_h = x_1$, $E_h = x_2$, $I_h = x_3$, $T_h = x_4$, $S_v = y_1$, $E_v = y_2$, and $I_v = y_3$.

Based on the above figure, we can establish a model with the parameters in Table 2.1 as the following.

$$\begin{aligned}
\frac{dx_1}{dt} &= \rho + \Lambda(x_1 + x_2 + x_4) + \Lambda(1-\zeta_1)x_3 + \psi x_4 - \frac{\beta\phi y_3 x_1}{N} - \mu x_1 \\
\frac{dx_2}{dt} &= \frac{\beta\phi y_3 x_1}{N} + \Lambda\zeta_1 x_3 - dx_2 - \mu x_2 \\
\frac{dx_3}{dt} &= dx_2 - (r + \alpha + \mu)x_3 \\
\frac{dx_4}{dt} &= rx_3 - (\psi + \mu)x_4 \\
\frac{dy_1}{dt} &= \delta_0 + \delta_1(y_1 + y_2) + \delta_1(1-\zeta_2)y_3 - \frac{\phi\theta_1 x_3 y_1}{N} - \frac{\phi\theta_2 x_2 y_1}{N} - \gamma y_1 \\
\frac{dy_2}{dt} &= \frac{\phi\theta_1 x_3 y_1}{N} + \frac{\phi\theta_2 x_2 y_1}{N} + \delta_1\zeta_2 y_3 - \epsilon y_2 - \gamma y_2 \\
\frac{dy_3}{dt} &= \epsilon y_2 - \gamma y_3
\end{aligned} \tag{2.1}$$

with initial condition $x_i(0) \geq 0$, $i = 1, 2, 3, 4$ *and* $y_j(0) \geq 0$, $j = 1, 2, 3$ *and* $t \in [0, T]$.

To show that $\{x_1, x_2, x_3, x_4, y_1, y_2\}$ *are all bounded in a set, we find a positively invariant set with the state system* (2.1)*. We use the theorem from J.K. Hale. [37].*

Theorem 2.1 (Differential Inequality). *Let $\omega(t,u)$ be continuous scalar function on an open connected set $\Omega \in R^2$ and such that the initial value problem for the scalar equation*

$$\frac{du}{dt} = \omega(t,u)$$

has a uniques solution. If $u(t)$ is a solution of the above equation on $a \leq t \leq b$ and $v(t)$ is a solution of

$$\frac{dv}{dt} \leq \omega(t, v(t))$$

on $a \leq t \leq b$ with $v(a) \leq u(a)$, then $v(t) \leq u(t)$ for $a \leq t \leq b$.

Adding the first four equations in (2.1)*, we have the differential equations of the total population of host.*

$$\frac{dN}{dt} = \rho + \Lambda N - \alpha x_3 - \mu N \leq \rho + \Lambda N - \mu N. \tag{2.2}$$

Let $\frac{dz}{dt} = \rho + \Lambda z - \mu z$. Then it is one-dimensional differential equation with attracting set $[0, N^*]$, where $z^* = \frac{\rho}{\mu - \Lambda}$ is a positive equilibrium point. By the theorem 2.1, the equation (2.2) *implies that $N(t) \leq z(t)$ for $N(0) \leq z(0)$. Since $z(t)$ is an autonomous equation and N^* is the equilibrium solution, $N(t)$ remains in $[0, N^*]$ for $0 \leq N(0) \leq N^*$. Furthermore, if $N(0) > N^*$, then $N(t)$ approaches N^*.*

Similarly, adding the last three equation, yields

$$\frac{dP}{dt} = \delta_0 + \delta_1 P - \gamma P \tag{2.3}$$

with a positive equilibrium $P^* = \frac{\delta_0}{\gamma - \delta_1}$ and for $0 \leq P(0) \leq P^*$, $P(t)$ remains in $[0, P^*]$.

Let $X = (x_1, x_2, x_3, x_4)$, $Y = (y_1, y_2, y_3)$, and define

$$\Omega = \{(X,Y) \in R^4_+ \times R^3_+, \sum_{i=1}^{4} x_i \in [0, N^*], \sum_{i=1}^{3} y_1 \in [0, P^*]\} = [0, \frac{\rho}{\mu - \Lambda}] \times [0, \frac{\delta_0}{\gamma - \delta_1}] \tag{2.4}$$

The set Ω is forward invariant and attractor. Also, for $N(0) \geq N^* = \frac{\rho}{\mu - \Lambda}$, $N(t) \to N^* = \frac{\rho}{\mu - \Lambda}$ and for $P(0) \geq P^* = \frac{\delta_0}{\gamma - \delta_1}$, $P(t) \to P^* = \frac{\delta_0}{\gamma - \delta_1}$.

Theorem 2.2. *Ω is positively invariant under system* (2.1).

2.2 Disease free equilibrium point E_0 and R_0

In this section, we derive a disease free equilibrium point and the basic reproduction number, R_0. The basic reproduction number is defined as the average number of secondary infections produced when one infected individual is introduced into a host population [50, 53]. The basic reproduction number R0 is often considered as the threshold quantity that determines when an infection can invade and persist in a new host population [53].

To find the disease free equilibrium point of (2.1) *we set $x_2 = x_3 = x_4 = 0$ and $y_2 = y_3 = 0$. Let $E_0 = (x_1^*, 0, 0, 0, y_1^*, 0, 0)$ be the disease free equilibrium point. From the state system* (2.1)*, we obtain the following system.*

$$\begin{aligned} \frac{dx_1}{dt} &= \rho + \Lambda(x_1) - \mu x_1 \\ \frac{dx_2}{dt} &= \frac{dx_3}{dt} = \frac{dx_4}{dt} = 0 \\ \frac{dy_1}{dt} &= \delta_0 + \delta_1(y_1) - \gamma y_1 \\ \frac{dy_2}{dt} &= \frac{dy_3}{dt} = 0 \end{aligned} \tag{2.5}$$

Then the disease free equilibrium point is $E_0 = (x_1^*, 0, 0, 0, y_1^*, 0, 0)$ where $x_1^* = \frac{\rho}{\mu - \Lambda}, y_1^* = \frac{\delta_0}{\gamma - \delta_1}, \gamma > \delta_1, \mu > \Lambda$.

To find the epidemiology threshold R_0, we use the Next-Generation Approach [53, 66]. The key concept is that we need to average the expected number of new infectious over all possible infected types. Let G be a next generation matrix in which the ijth element of G, g_{ij}, is the expected number of secondary infectious of type i caused by a single infected individual of type j. That is, each element of the matrix G is a reproduction number, but one where who infects whom is accounted for. R_0 is the average of all the elements of G. [29]

1. *We consider equations in the state system* (2.1) *which correspond to the infected compartments which are related to x_2, x_3, x_4, y_2, y_3 and let $y_2 = x_5$ and $y_3 = x_6$.*

2. *We split the right-hand side in the infected compartments in the following way.*

$$\frac{dx_i}{dt} = F_i(x) - V_i(x), i = 2, 3, 4, 5, 6 \tag{2.6}$$

where

- $F_i(x)$ *is the rate of appearance of new infection compartment* i.
- $V_i(x) = V_i(x)^+ - V_i(x)^-$, $V_i(x)^+$ *is the rate of transfer of individuals into compartment* i *by all other means, and* V_i^- *is the rate of transfer of individuals out of compartment* i.

Note that this decomposition may not be unique. Different decompositions may occurred to different interpretations of each terms and may lead to a different basic reproduction number. The decomposition should satisfy the following properties.

- *if* $x_i \geq 0$, *then* $F_i(x), V_i(x)^+, V_i(x)^- \geq 0$ *for* $i = 2, 3, 4, 5, 6$.
- $x_i = 0$ *if and only if* $V_i(x)^- = 0$
- $F_i(x) = 0$ *and* $V_i(x) = 0$ *for* $i = 2, 3, 4$ *and* $x_5, x_6 \geq 0$
- $\sum_{i=2}^{6} V_i(x) \geq 0$ *for all* $x_i \geq 0$.

3. *Determine the matrices* F *and* V *with components.*

$$F = \left[\frac{\partial F_i(x)}{\partial x_j}\right]\Bigg|_{x=E_0} \text{ and } V = \left[\frac{\partial V_i(x)}{\partial x_j}\right]\Bigg|_{x=E_0}, \text{ for } i, j = 2, 3, 4, 5, 6 \tag{2.7}$$

where E_0 *is DEF.*

4. *The Next-Generation matrix,* K *is defined as*

$$K = FV^{-1} \tag{2.8}$$

5. *The basic reproduction number is defines as*

$$R_0 = \rho(FV^{-1}) \tag{2.9}$$

where $\rho(A)$ *denotes the spectral radius of A.*

Definition 2.1. *The spectral radius of a matrix* A *is defined as the maximum of the absolute values of the eigenvalues of A*

$$\rho(A) = sup\{|\lambda| : \lambda \in \sigma(A)\} \tag{2.10}$$

where $\sigma(A)$ *denotes the set of eigenvalues of A.*

By the next-generation approach, we can find $F_i(x)$ *and* $V_i(x)$ *and let* $\widetilde{F}(x) = (F_i(x))$ *and* $\widetilde{V}(x) = (V_i(x))$ *for* $i = 2, 3, 4, 5, 6$. *Then*

$$\begin{aligned}\widetilde{F}(x) &= \left(\frac{\beta\phi y_3 x_1}{N} + \Lambda\zeta_1 x_3, 0, 0, \frac{\phi\theta_1 x_3 y_1}{N} + \frac{\phi\theta_2 x_2 y_1}{N} + \delta_1\zeta_2 y_3, 0\right) \\ \widetilde{V}(x) &= (k_1 x_2, -dx_2 + k_3 x_3, -rx_3 + k_2 x_4, k_4 y_2, -\epsilon y_2 + \gamma y_3)\end{aligned} \tag{2.11}$$

where $k_1 = d + \mu, k_2 = \psi + \mu, k_3 = r + \alpha + \mu, k_4 = \epsilon + \gamma$.

Next we calculate F *and* V *which are Jacobian matrices of* $\widetilde{F}$ *and* $\widetilde{V}$ *respectively evaluated at DFE,* E_0, *with* $N = \frac{\rho}{\mu - \Lambda}$ *since* $x_1^* = N$ *at DFE.*

$$F = \begin{pmatrix} \frac{\partial F_1}{dx_2} & \frac{\partial F_1}{dx_3} & \frac{\partial F_1}{dx_4} & \frac{\partial F_1}{dy_2} & \frac{\partial F_1}{dy_3} \\ \frac{\partial F_2}{dx_2} & & \cdots & & \frac{\partial F_2}{dy_3} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \frac{\partial F_5}{dx_2} & & \cdots & & \frac{\partial F_5}{dy_3} \end{pmatrix} = \begin{pmatrix} 0 & \Lambda\zeta_1 & 0 & 0 & \beta\phi \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \frac{\theta_2\phi y_1}{x_1} & \frac{\theta_1\phi y_1}{x_1} & 0 & 0 & \zeta_2\delta_1 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} k_1 & 0 & 0 & 0 & 0 \\ -d & k_3 & 0 & 0 & 0 \\ 0 & -r & k_2 & 0 & 0 \\ 0 & 0 & 0 & k_4 & 0 \\ 0 & 0 & 0 & -\epsilon & \gamma \end{pmatrix} \tag{2.12}$$

Then we see that V *is a nonsingular* M*-matrix and we have* V^{-1}.

$$V^{-1} = \begin{pmatrix} \frac{1}{k_1} & 0 & 0 & 0 & 0 \\ \frac{d}{k_1 k_3} & \frac{1}{k_3} & 0 & 0 & 0 \\ \frac{dr}{k_1 k_2 k_3} & \frac{r}{k_2 k_3} & \frac{1}{k_2} & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{k_4} & 0 \\ 0 & 0 & 0 & \frac{\epsilon}{\gamma k_4} & \frac{1}{\gamma} \end{pmatrix} \tag{2.13}$$

Definition 2.2. *Let A be a $n \times n$ real Z-matrix. That is, $A = (a_{ij})$ where $a_{ij} \leq 0$ for all $i \neq j$, $1 \leq i, j \leq n$. Then matrix A is also a non-singular M-matrix if it can be expressed in the form $A = sI - B$, where $B = (b_{ij})$ with $b_{ij} \geq 0$ for all $1 \leq i, j \leq n$, where $s > \rho(B)$, and I is an identity matrix , and A is a singular M-matrix if $s = \rho(P)$.*

Definition 2.3. *A matrix A is called an M-matrix if*

- *A has Z-pattern, that is, the off-diagonal elements of A are nonpositive.*
- *The inverse A exists and has nonnegative elements: $A^{-1} \geq 0$.*

Lemma 2.1. *Let A be a non-singular M-matrix and suppose B and BA^{-1} are Z-matrices. Then B is a non-singular M-matrix if and only if BA^{-1} is a non-singular M-matrix.*

Since F is nonnegative matrix, $K = FV^{-1}$ is also nonnegative matrix. This implies that the next-generation matrix has its spectral radius as an eigenvalue and there are no other eigenvalues with lager modulus by the Perron-Frobenius theorem. This largest eigenvalues gives R_0. The basic reproduction number R_0 is defined as the spectral radius of

$$FV^{-1} = \begin{pmatrix} \frac{d\zeta_1\Lambda}{k_1k_3} & \frac{\zeta_1\Lambda}{k_3} & 0 & \frac{\beta\epsilon\phi}{k_4\gamma} & \frac{\beta\phi}{\gamma} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ \frac{dy_1\theta_1\phi}{k_1k_3x_1} + \frac{y_1\theta_2\phi}{k_1x_1} & \frac{y_1\theta_1\phi}{k_3x_1} & 0 & \frac{\delta_1\epsilon\zeta_2}{k_4\gamma} & \frac{\delta_1\zeta_2}{\gamma} \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \tag{2.14}$$

Thus, the spectral radius of FV^{-1} is

$$R_0 = R_0(\zeta_1, \zeta_2) = \rho(FV^{-1}) = \frac{1}{2}\left(\frac{\zeta_1\Lambda d}{k_1k_3} + \frac{\zeta_2\delta_1\epsilon}{\gamma k_4}\right) + \sqrt{\left[\frac{1}{2}(\frac{\zeta_1\Lambda d}{k_1k_3} - \frac{\zeta_2\delta_1\epsilon}{\gamma k_4})\right]^2 + R_h^2} \tag{2.15}$$

where $R_h = \phi\sqrt{\frac{\beta\epsilon(\theta_1 d + \theta_2 k_3)y_1^*}{\gamma k_1 k_3 k_4 x_1^*}}$.

2.3 Stability of disease free equilibrium point

In this section, we show that the disease free equilibrium point, E_0, is locally asymptotically stale and also globally asymptotically stable. First, we show the local stability of E_0.

To prove the local stability, we use the Hartman-Grobman theorem in Misha Guysinsky [36].

Theorem 2.3 (Hartman-Grobman theorem). *Let $U \subset \mathbb{R}^n$ be a neighborhood of 0, $f : U \to \mathbb{R}^n$ continuously differentiable with 0 as a hyperbolic fixed point. Then there is a homeomorphism h of a neighborhood of 0 with $h \circ f = Df_0 \circ h$ near 0.*

The theorem guarantees that the stability of the steady state of the original system is the same as the stability of the trivial steady state of the linearized system.

Also, we use the linear stability analysis. It is stated as the following theorem.

Theorem 2.4. *Given the differentia equations on $\mathbb{R}^n$*

$$x' = f(x)$$

Let x_0 be an equilibrium point of the above equation and $A = Df(x_0)$ be the Jacobian matrix of f at the equilibrium point x_0. If all eigenvalues of A have strictly negative real part, then x_0 is locally asymptotically stable.

We can see the local stability of E_0 from the theorem in P. van den Driessche [66] and the following theorems.

Theorem 2.5. *The disease-free equilibrium point E_0, of system* (2.1) *is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$, where R_0 is defined by* (2.15)

Next, we show the global stability of the disease free equilibrium point. To show that, we use the following theorem in Castillo-Chávez, C [22]. First, the System (2.1) *must be written in the form*

$$\begin{aligned} \frac{dx}{dt} &= F(x, I) \\ \frac{dI}{dt} &= G(x, I), \;\; G(x, 0) = 0 \end{aligned} \tag{2.16}$$

where $x \in \mathbb{R}^n$ denotes (its component) the number of uninfected individuals and $I \in \mathbb{R}^n$ denotes (its component) the number of infected individuals including exposed, infectious, etc.

The conditions (H1) and (H2) below must be to guarantee local asymptotic stability.

(H1) For $\frac{dx}{dt} = F(x, 0)$, x^* is globally asymptotically stable.

(H2) $G(x, I) = AI - \widehat{G}(x, I)$, $G(x, 0) = 0$ and $\widehat{G}(x, i) \geq 0$ for $(x, I) \in \Omega$.

where $A = D_I G(x^*, 0)$ is M-matrix (the off diagonal elements of A are nonnegative) and Ω is (2.4) *If the state system* (2.1) *satisfies the above two condition then the following theorem holds.*

Theorem 2.6. *The fixed point $E_0 = (x^*, 0)$ is globally asymptotically stable equilibrium of the state system* (2.1) *provided that $R_0 < 1$ and that assumptions (H1) and (H2) are satisfied.*

Proof. First, we define new variables and break the state system (2.1) into subsystems. Let $I = (x_2, x_3, y_2, y_3)$ and $x = (x_1, x_4, y_1)$. Then the state system (2.1) can be written as

$$\begin{aligned} \frac{dx}{dt} &= F(x, I) \\ \frac{dI}{dt} &= G(x, I) \end{aligned} \tag{2.17}$$

where

$$\begin{aligned} F(x, I) = \big\{ &\rho - \mu x_1 - \frac{\beta x_1 y_3 \phi}{N} + \Lambda(x_1 + x_2 + x_4) + (1 - \zeta_1)\Lambda x_3 + \psi x_4, r x_3 - x_4(\mu + \psi), \\ &\delta_0 - \frac{\theta_1 x_3 y_1 \phi}{N} - \frac{\theta_2 x_2 y_1 \phi}{N} + \gamma(-y_1) + \delta_1(y_1 + y_2) + \delta_1(1 - \zeta_2) y_3 \big\}^T \end{aligned} \tag{2.18}$$

$$\begin{aligned} G(x, I) = \big\{ &- d x_2 + \frac{\beta x_1 y_3 \phi}{N} - \mu x_2 + \zeta_1 \Lambda x_3, d x_2 - x_3(\alpha + \mu + r), \\ &\frac{\theta_1 x_3 y_1 \phi}{N} + \frac{\theta_2 x_2 y_1 \phi}{N} + \gamma y_2 - y_2 \epsilon + \delta_1 \zeta_2 y_3, y_2 \epsilon - \gamma y_3 \big\}^T \end{aligned} \tag{2.19}$$

where T is transpose. To show (2.17) satisfies the condition (H1), consider the system $\frac{dx}{dt} = F(x, 0)$

$$\begin{aligned} \frac{dx_1}{dt} &= (x_1 + x_4)\Lambda - x_1 \mu + \rho + x_4 \psi \\ \frac{dx_4}{dt} &= -x_4(\mu + \psi) \\ \frac{dy_1}{dt} &= -y_1 \gamma + \delta_0 + y_1 \delta_1 \end{aligned} \tag{2.20}$$

Then, $x^* = (x_1^*, x_4^*, y_1^*) = (\frac{\rho}{\mu - \Lambda}, 0, \frac{\delta_0}{\gamma - \delta_1})$. We see x^* is globally asymptotically stable under the system (2.20). To see that, we solve the second equation in (2.20) and obtain

$$x_4(t) = e^{-t(\mu + \psi)} x_4(0) \tag{2.21}$$

We have that $x_4(t) \to 0$ as $t \to \infty$. Similarly from the last equation, we obtain

$$y_1(t) = \frac{\delta_0}{\gamma - \delta_1} + e^{-t(\gamma - \delta_1)} y_1(0) \tag{2.22}$$

Since $\gamma > \delta_1$, we have that $y_1(t) \to \frac{\delta_0}{\gamma-\delta_1}$ as $t \to \infty$. By solving the first equation using $x_4(t)$, we obtain

$$x_1(t) = \frac{\rho}{\mu-\Lambda} - \frac{e^{-t(\mu+\psi)}}{\Lambda+\psi}x_4(0) - \Lambda\frac{e^{-t(\mu+\psi)}}{\Lambda+\psi}x_4(0) + e^{-t(\mu-\Lambda)}x_1(0) \tag{2.23}$$

Since $\mu > \Lambda$, we have that $x_1(t) \to \frac{\rho}{\mu-\Lambda}$ as $t \to \infty$.

We see that the convergence are independent of initial condition. Hence, the convergence of solutions of (2.20) is global and x^* is globally asymptotically stable.

Next, we show the system (2.17) satisfies the condition (H2). We see easily that $G(x, 0) = 0$. We find $A = D_I G(x^*, 0)$ and $\widehat{G}(x, I)$.

$$D_I G(x,I) = \begin{pmatrix} -d-\mu-\frac{x_1 y_3 \beta\phi}{N^2} & \zeta_1\Lambda - \frac{x_1 y_3 \beta\phi}{N^2} & 0 & \frac{x_1\beta\phi}{N} \\ d & -r-\alpha-\mu & 0 & 0 \\ \frac{y_1\theta_2\phi}{N} - \frac{x_3 y_1\theta_1\phi}{N^2} - \frac{x_2 y_1\theta_2\phi}{N^2} & \frac{y_1\theta_1\phi}{N} - \frac{x_3 y_1\theta_1\phi}{N^2} - \frac{x_2 y_1\theta_2\phi}{N^2} & -\gamma-\epsilon & \delta_1\zeta_2 \\ 0 & 0 & \epsilon & -\gamma \end{pmatrix} \tag{2.24}$$

Then, $A = D_i G(x^*, 0)$

$$A = \begin{pmatrix} -d-\mu & \zeta 1\Lambda & 0 & \beta\phi \\ d & -r-\alpha-\mu & 0 & 0 \\ \frac{\delta 0\theta 2(\mu-\Lambda)\phi}{(\gamma-\delta 1)\rho} & \frac{\delta 0\theta 1(\mu-\Lambda)\phi}{(\gamma-\delta 1)\rho} & -\gamma-\epsilon & \delta 1\zeta 2 \\ 0 & 0 & \epsilon & -\gamma \end{pmatrix} \tag{2.25}$$

and Let

$$\widehat{G}(x,I) = \begin{pmatrix} \frac{\beta y_3\phi(x_2+x_3+x_4)}{N} \\ 0 \\ \frac{\phi(\theta_2 x_2+\theta_1 x_3)(\delta_0 x1(\mu-\Lambda)+\delta_0 x2(\mu-\Lambda)+\delta_0(\mu-\Lambda)x_3+\delta_0(\mu-\Lambda)x_4+(\gamma-\delta_1)\rho y_1)}{\rho(\gamma-\delta_1)N} \\ 0 \end{pmatrix} \tag{2.26}$$

Since $\mu > \Lambda$ and $\gamma > \delta_1$, $\widehat{G}(x, I) \geq 0$ for $(x, I) \in \Omega$. We obtain $G(x, I) = AI - \widehat{G}(x, I)$.

Therefore, the disease free equilibrium point E_0 is globally asymptotically stable. □

2.4 Sensitivity analysis of R_0

In this section we perform sensitivity analysis of the basic reproduction number already obtained, (2.15)*, to identify the parameters which are important in contributing variability in the outcome of the basic reproduction number. There are several methods to perform the sensitivity analysis. We use the fixed point estimation used in Samsuzzoha [63]. Sensitivity analysis using the fixed point estimations has been applied to determine the relative importance of different parameters responsible for the disease transmission related to the basic reproductions number. Sensitivity indices for the basic reproduction number change with the change in parameters values. The normalized forward sensitivity index (in Nakul Chitnis [26]) of a variable to a parameter is the ratio of the relative change in the variable to the relative change in the parameter. For example, let* u *be a variable that depends on* p *a parameter and* $\delta > 0$ *be a small perturbation corresponding to* p*. We have*

$$\delta_u = u(p+\delta) - u(p) = \frac{u(p+\delta) - u(p)}{\delta}\delta \approx \delta\frac{\partial u}{\partial p} \tag{2.27}$$

We define the normalized forward sensitivity index , γ_p^u *as*

$$\gamma_p^u = \frac{\delta_u}{u}/\frac{\delta}{p} = \frac{p}{u}\frac{\partial u}{\partial p} \tag{2.28}$$

Definition 2.4. *The normalized forward sensitivity index of a variable ,* u*, that depends differentiably on a parameter,* p*, is defined as*

$$\gamma_p^u = \frac{\partial u}{\partial p} \times \frac{p}{u} \tag{2.29}$$

We evaluate the normalized forward sensitivity index for each parameters in R_0 *using the definitiom and the values of parameters in the table 2.2.*

Parameters	Values	Parameters	Values
γ	$[\frac{1}{17}, \frac{1}{10}]$	Λ	$(0, \mu)$
μ	$[\frac{1}{70(365)}, \frac{1}{45(365)}]$	θ_1	$[0, 1)$
ϕ	≥ 1	θ_2	$(0, \theta_1)$
ϵ	$[\frac{1}{14}, \frac{1}{7}]$	α	$(0, 0.001)$
r	$[0, \frac{1}{7}]$	ψ	$[0, 1)$
ζ_2	$[0, 1)$	β	$(0, 1)$
d	$[\frac{1}{14}, \frac{1}{3}]$	ζ_1	$[0, 1)$
δ_0	$[700, 10000]$	δ_1	$[0, 1)$

Table 2.2: Parameter estimation for dengue fever in [12, 13]. Rate is per day.

For the simplicity, we set we set $\zeta_1 = 0$ throughout the sensitivity. The sensitivity index $\gamma_{\zeta_1}^{R_0} \approx 1.91002 \times 10^{-6}$. It means that decreasing (or increasing) ζ_1 by 100% decreases (or increases) R_0 by $1.91002 \times 10^{-5}\%$. Since the formula for sensitivity index of parameters are complicate, we see the sensitivity index formula for ζ_2 as an example.

$$\gamma_{\zeta_2}^{R_0} = \frac{\delta_1 \zeta_2 \epsilon}{\sqrt{\epsilon \left(\frac{4\beta\gamma\delta_0\phi^2(\gamma+\epsilon)(\mu-\Lambda)(d\theta_1+\theta_2(\alpha+\mu+r))}{\rho(\gamma-\delta_1)(d+\mu)(\alpha+\mu+r)} + \delta_1^2\zeta_2^2\epsilon \right)}} \tag{2.30}$$

Using the definition 2.4 and the formula for each paramters, we evaluate the normalized forward sensitivity index of R_0.

Parameter	Sensitivity index
γ	-2.19232
δ_1	1.05291
ϕ	0.975482
μ	0.780124
δ_0	0.487741
β	0.487741
ρ	-0.487741
Λ	-0.292644
θ_1	0.25891
r	-0.258659
θ_2	0.22883
d	-0.22864
ϵ	0.163923
ζ_2	0.0245184
α	-0.000181061

Table 2.3: Sensitivity index for parameters in R_0. The parameters are orders from most sensitivity to least.Parameters are : $\theta_1 = 0.0083$, $\theta_2 = 0.00513$, $\mu = \frac{1}{70(365)}$, $\Lambda = \frac{0.375}{70(365)}$, $\rho = 205$, $\delta_0 = 1050$, $\beta = 0.2$, $r = \frac{1}{7}$, $\delta_1 = 0.0399$, $d = \frac{1}{10}$, $\psi = 0.00233$, $\zeta_2 = 0.0087$, $\alpha = 0.0001$, $\phi = 2$, $\epsilon = \frac{1}{8}$, $\gamma = \frac{1}{17}$

The most sensitive parameter is the host recovery rate, γ. Other important parameters include the factor for density dependent maturation of mosquitos to adulthood, δ_1, the number of contacts between a host and a vector, ϕ, and the host death rate, μ. Since $\gamma_\gamma^{R_0} = -2.19232$, decreasing (or increasing) γ by 10% increases (or decreases) R_0 by 21.92%. Similarly, as $\gamma_{\delta_1}^{R_0} = 1.05291$, increasing (or decreasing) δ_1 by 10% increases (or decreases) R_0 by 10.5%. The least important parameter is the disease-induced host date rate, α.

2.5 Numerical Simulations

In this section we perform simulation for the state system model (2.1)*. In this simulation, we consider initial conditions,* $x_1(0) = 100$*,* $x_2(0) = 20$*,* $x_3(0) = 20$*,* $x_4(0) = 10$*,* $y_1(0) = 1000$*,* $y_2(0) = 20$*, and* $y_3(0) = 30$*. These simulations are performed for different* γ*,* δ_1*,* ϕ*,* R_0*.* R_0 *is the basic reproduction number given by the equation* (2.15)*. The values of parameters, Table 2.4 are considered based on the dengue virus, Table 2.2.*

It is clear from Theorem 2.6 and 2.5 that the disease is endemic for $R_0 > 1$*. The numerical simulation shows that the number of exposed and infectious host increase when the number of the contact between a host and a vector,* ϕ*, increases.*

Parameters	Values	Parameters	Values
θ_1	0.0083	θ_2	0.00513
μ	$\frac{1}{70(365)}$	Λ	$\frac{0.375}{70(365)}$
ρ	205	δ_0	1050
β	0.2	r	$\frac{1}{7}$
δ_1	0.0399	d	$\frac{1}{10}$
ψ	0.00233	ζ_1	0.00001
ζ_2	0.0087	α	0.0001
ϕ	2	ϵ	$\frac{1}{8}$
γ	$\frac{1}{17}$		

Table 2.4: Parameter values for a dengue virus. In this case, $R_0 \approx 0.0838$.

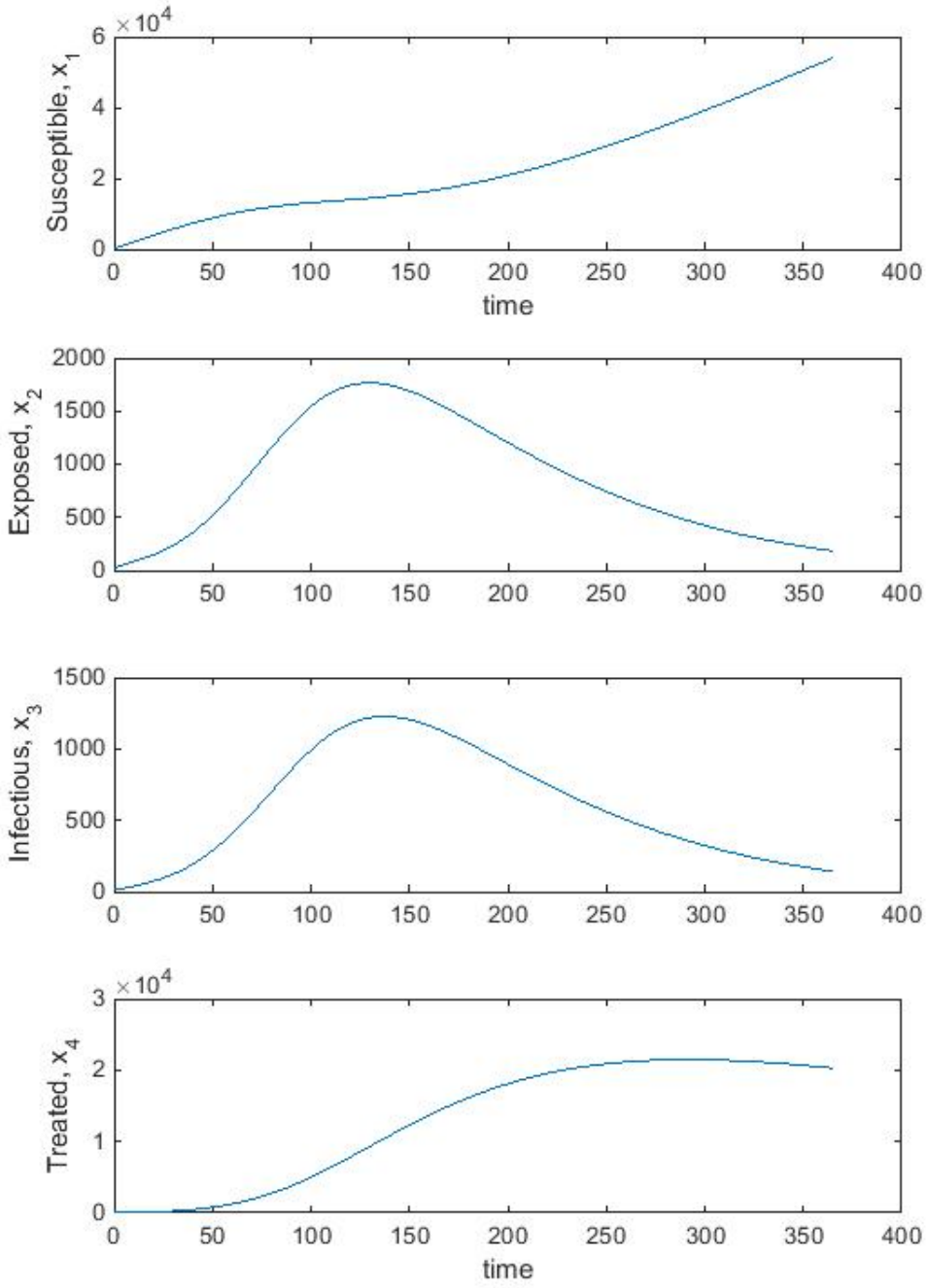

Figure 2.2: Solution for hosts, x_1, x_2, x_3, and x_4, with the values of the parameters in Table 2.4.

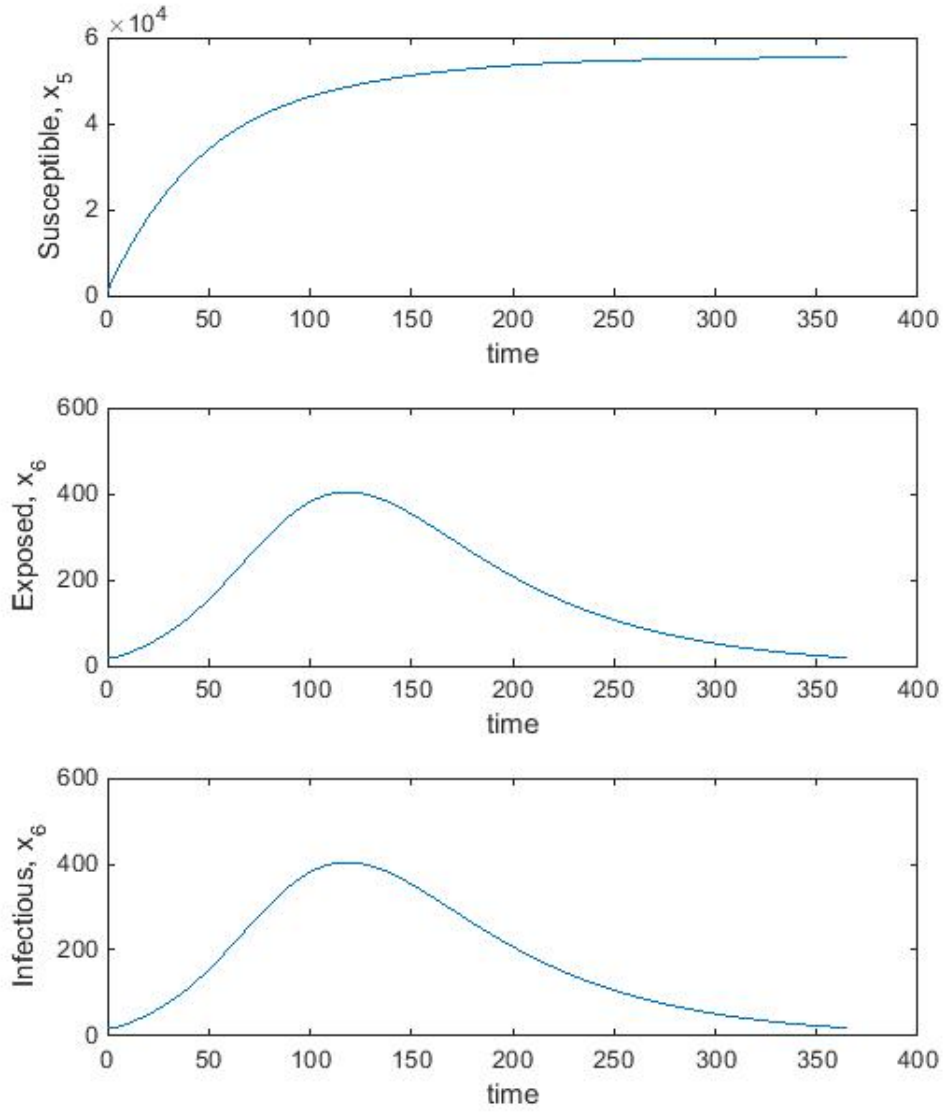

Figure 2.3: Solution for vectors y_1, y_2, and y_3, with the values of the parameters in Table 2.4.

The disease free equilibrium is stable for $R_0 < 1$ *as it is given by Theorem 2.6. Since* $R_0 \approx 0.0838 < 1$ *with the values of the parameters in Table 2.4, we can see in Figure 2.2 and 2.3 that the size of all exposed and infected groups in each population die out.*

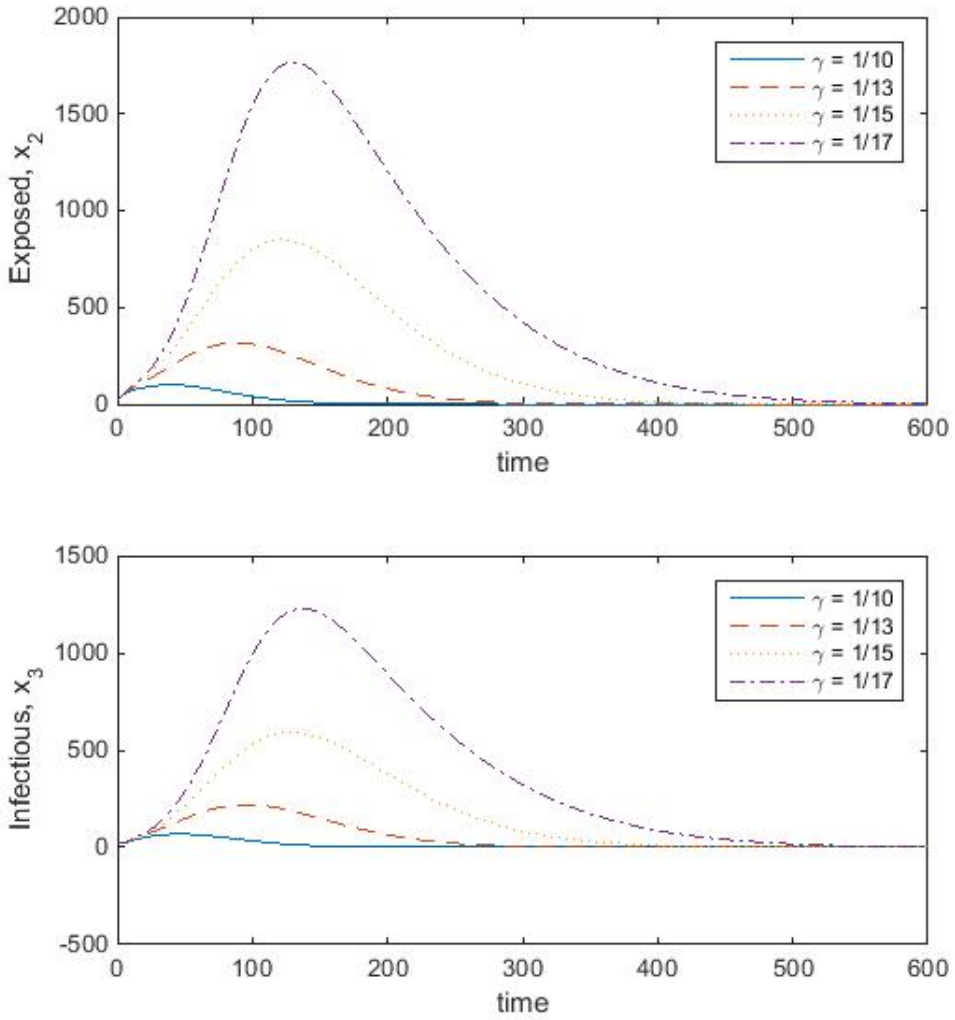

Figure 2.4: Solution for Exposed, x_2, and Infectious,x_3, host for $\gamma = \frac{1}{10}$, $\gamma = \frac{1}{13}$, $\gamma = \frac{1}{15}$, $\gamma = \frac{1}{17}$ with the values of the parameters in Table 2.4. In each cases, $R_0 \approx 0.0328$, $R_0 = 0.0502$, $R_0 = 0.065$, $R_0 = 0.0838$, respectively.

The decreased death rate of vectors, γ, is a factor for the increased size of exposed and infectious hosts in Figure 2.4. We see that the basic reproduction number R_0 is increasing as γ decreasing, as we studied in the section 2.4.

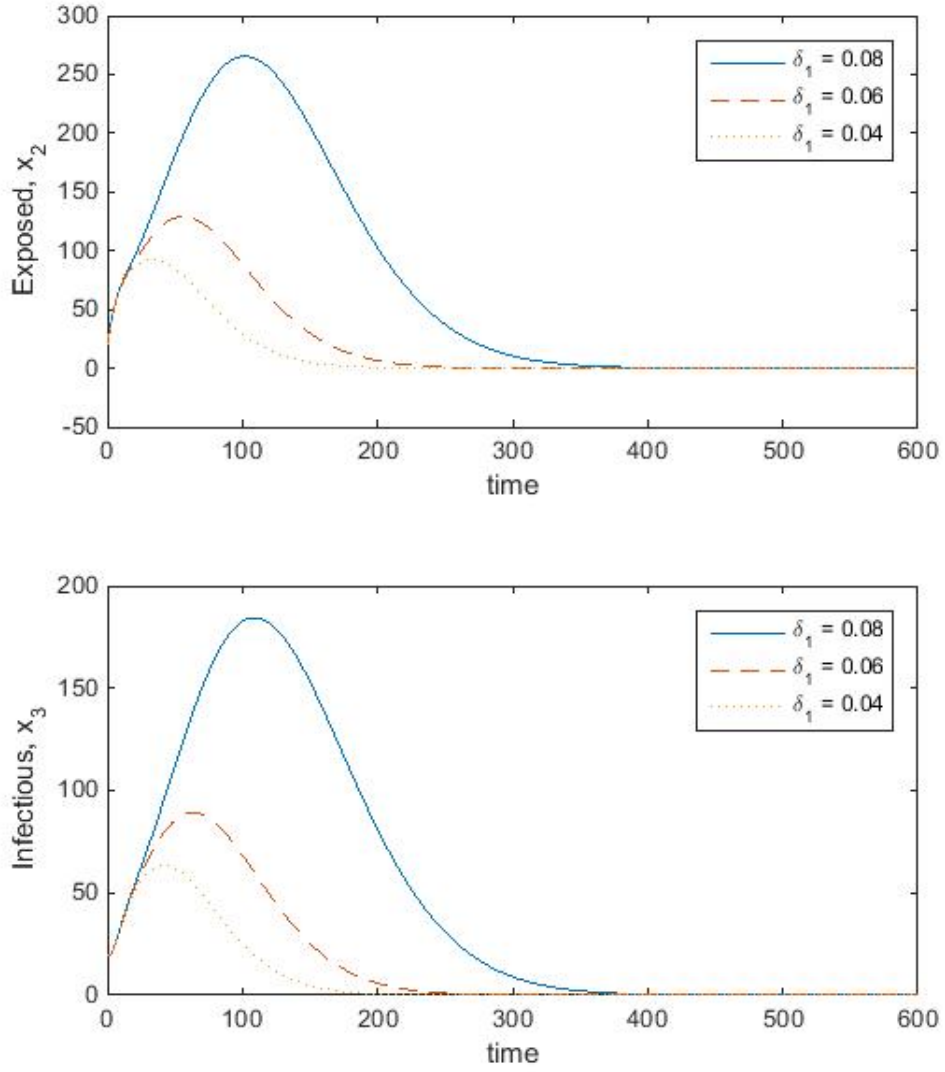

Figure 2.5: Solution for Exposed, x_2, and Infectious,x_3, host for $\delta_1 = 0.04$, $\delta_1 = 0.06$, $\delta_1 = 0.08$ with $\gamma = \frac{1}{10}$ and the values of the parameters in Table 2.4. In each cases, $R_0 \approx 0.0328$, $R_0 \approx 0.0405$, $R_0 \approx 0.0571$, respectively.

The decreased maturation of mosquitoes to adulthood, δ_1, is a factor for the decreased size of exposed and infectious hosts in Figure 2.5. We see that the basic reproduction number R_0 is increasing as δ_1 increasing, as we studied in the section 2.4.

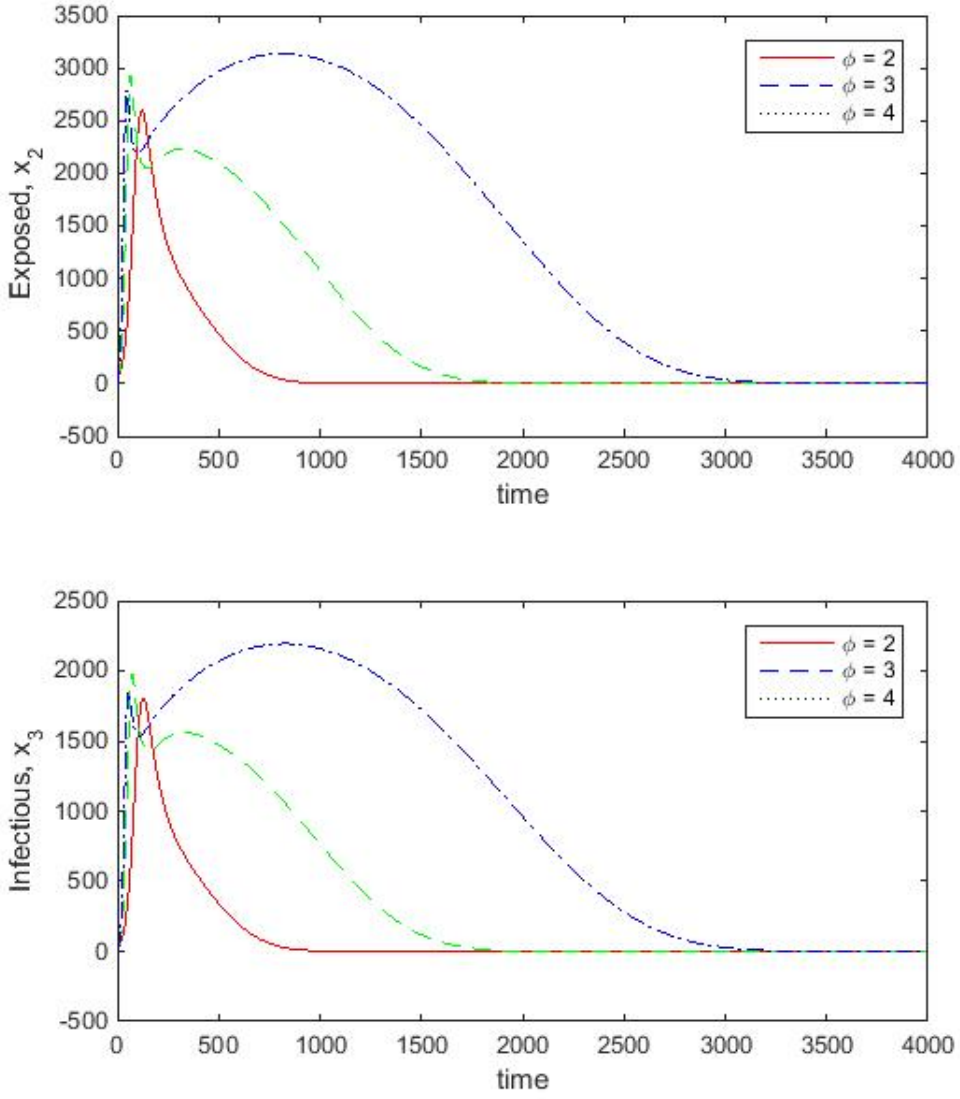

Figure 2.6: Solution for Exposed, x_2, and Infectious,x_3, host for $\phi = 2$, $\phi = 3$, $\phi = 4$ with $\delta_1 = 0.05$, $\gamma = \frac{1}{17}$, and the values of the parameters in Table 2.4. In each cases, $R_0 \approx 0.1223$, $R_0 \approx 0.1822$, $R_0 \approx 0.2421$, respectively.

The increased number of contacts between a host and a vector, ϕ, is a factor for the increased size of exposed and infectious hosts in Figure 2.6. We see that the basic reproduction number R_0 is increasing as δ_1 increasing, as we studied in the section 2.4.

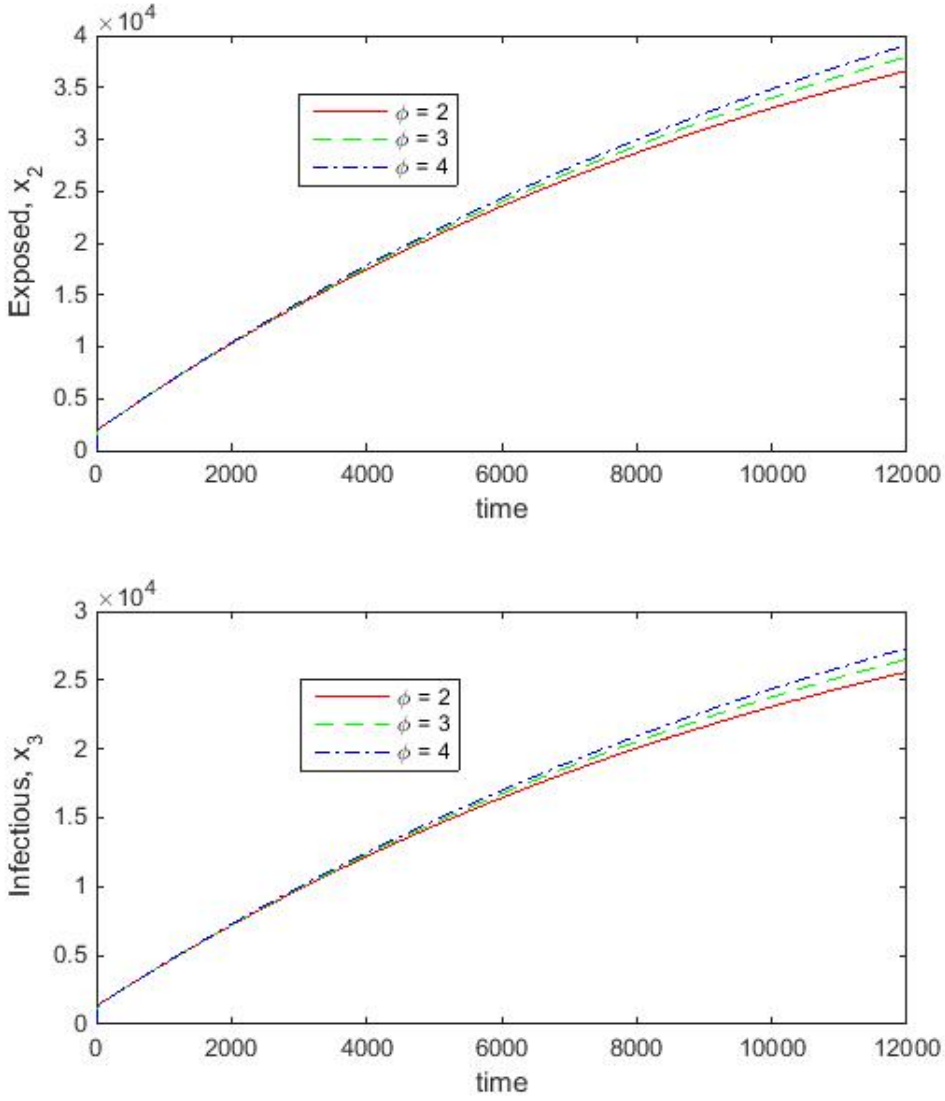

Figure 2.7: Solution for Exposed, x_2, and Infectious,x_3, host for $\phi = 17$, $\phi = 18$, $\phi = 19$ with $\delta_1 = 0.05$, $\gamma = \frac{1}{17}$, and the values of the parameters in Table 2.4. In each cases, $R_0 \approx 1.0209$, $R_0 \approx 1.0808$, $R_0 \approx 1.1407$, respectively.

Since $R_0 > 1$ for each ϕ, the disease free equilibrium point is unstable. In Figures 2.4, 2.5, 2.6, 2.7, we see that the number of exposed and infectious host are changing as γ, δ_1, and ϕ is changing. However, it does not necessarily result in the spread of the disease among hosts. This is shown by the phase portrait for $\phi = 17$ in Figure 2.8.

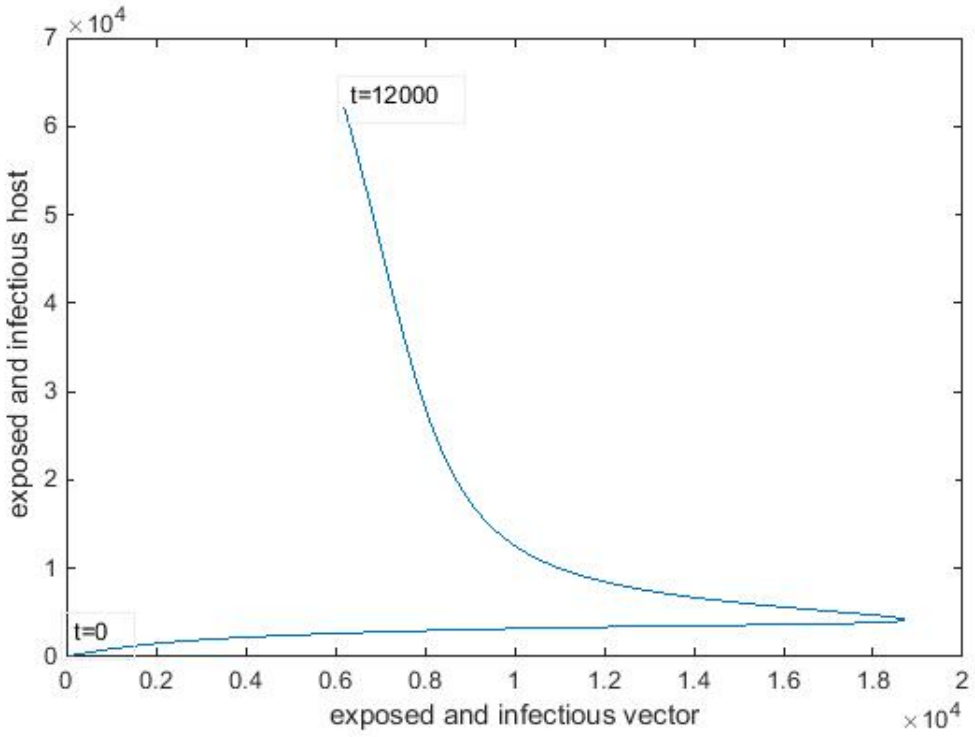

Figure 2.8: A phase plane portrait for the Exposed and the Infectious host,$x_2 + x_3$, against the Exposed and the Infectious vector, $y_2 + y_3$, where $\phi = 17$.

From the figure 2.8, we see that an increase in exposed and infected vectors does not necessarily in the spread of the disease among hosts. Also, we see that the opposite case is not necessary. So, we can not say about the change of the number of exposed and infected hosts just looking at the change of the number of exposed and infected vectors.

Chapter 3

Optimal control for Vertically transmitted vector-borne disease:treament and prevention of human-mosquito interaction

3.1 A Model for Optimal Control of vertically transmitted vector-borne disease

In this section, we formulate an optimal control model for vertically transmitted vector-borne disease to drive an optimal prevention of the contact between host and vector and an optimal treatment for host with the minimal implementation cost. The control functions, u_1 *and* u_2*, represent time dependent efforts of prevention and treatment respectively on a time interval* $[0, T]$*. For the prevention, we can do the followings;*

- *Aware of the areas that are heavily infested and avoid*
- *Wear long-sleeved shirts and pants in neutral colors*
- *Inspect vehicles before entering*
- *Avoid bushes*
- *Use insect repellent*

For the treatment, we can do the followings;

- *Screen patient*
- *Administer drug intake and patients' condition*

We will introduce u_1 *and* u_2 *into the model* (2.1). *The transmission model of the vertically transmitted vector-borne disease with the prevention and the treatment controls is given by*

$$\begin{aligned}
\frac{dx_1}{dt} &= \rho + \Lambda(x_1 + x_2 + x_4) + \Lambda(1-\zeta_1)x_3 + \psi x_4 - \frac{\beta\phi y_3 x_1(1-u_1(t))}{N} - \mu x_1 \\
\frac{dx_2}{dt} &= \frac{\beta\phi y_3 x_1(1-u_1(t))}{N} + \Lambda\zeta_1 x_3 - dx_2 - \mu x_2 \\
\frac{dx_3}{dt} &= dx_2 - (r + \alpha + \mu + r_0 u_2(t))x_3 \\
\frac{dx_4}{dt} &= (r + r_0 u_2(t))x_3 - (\psi + \mu)x_4 \\
\frac{dy_1}{dt} &= \delta_0 + \delta_1(y_1 + y_2) + \delta_1(1-\zeta_2)y_3 - \frac{\phi\theta_1 x_3 y_1(1-u_1(t))}{N} - \frac{\phi\theta_2 x_2 y_1(1-u_1(t))}{N} - \gamma y_1 \\
\frac{dy_2}{dt} &= \frac{\phi\theta_1 x_3 y_1(1-u_1(t))}{N} + \frac{\phi\theta_2 x_2 y_1(1-u_1(t))}{N} + \delta_1\zeta_2 y_3 - \epsilon y_2 - \gamma y_2 \\
\frac{dy_3}{dt} &= \epsilon y_2 - \gamma y_3
\end{aligned} \tag{3.1}$$

with initial condition $x_i(0) \geq 0$, $i = 1, 2, 3, 4$ *and* $y_j(0) \geq 0$, $j = 1, 2, 3$ *and* $t \in [0, T]$.

In the model (3.1), $1 - u_1(t)$ *describes the failure rate of prevention efforts. The per capita recovery rate is* $r_0 u_2(t)$, *where* $0 \leq r_0 \leq 1$ *is the proportion of effective treatment.*

We discuss the boundedness of the host and vector population. From the model (3.1), *we have that by adding the first four equation,*

$$\frac{dN}{dt} = \rho - \alpha x_3 + (\Lambda - \mu)N \leq \rho + (\Lambda - \mu)N \tag{3.2}$$

By the theorem (2.1), $N \leq \frac{\rho}{\mu - \Lambda}$ *for the initial value* $N(0) \leq \frac{\rho}{\mu - \Lambda}$. *Similarly, adding the last three equations, we have*

$$\frac{dP}{dt} = \delta_0 - (\gamma - \delta_1)P \tag{3.3}$$

Thus, for the initial value $P(0) \leq \frac{\delta_0}{\gamma - \delta_1}$, *we have* $P \leq \frac{\delta_0}{\gamma - \delta_1}$.

Let $X = (x_1, x_2, x_3, x_4)$ *and* $Y = (y_1, y_2, y_3)$ *and define a set*

$$\Omega = \{(X, Y) |\, \mathbb{R}^4_+ \times \mathbb{R}^3_+, 0 \leq N \leq \frac{\rho}{\mu - \Lambda}, 0 \leq P \leq \frac{\delta_0}{\gamma - \delta_1}\} \tag{3.4}$$

Theorem 3.1. Ω *is positively invariant under system* (3.1)

Proof. First, we show that the solutions with an initial values in Ω remains nonnegative for all $t \geq 0$. Let $C_1 = -\beta\phi - \mu$, $C_2 = -d - \mu$, $C_3 = -\gamma - \alpha - \mu$, and $C_4 = -\psi - \mu$. Then we

have the following inequalities

$$\frac{dx_i}{dt} \geq C_i x_i \text{ for } i = 1, 2, 3, 4 \tag{3.5}$$

Similarly, let $D_1 = -\phi\theta_1 - \phi\theta_2 - \gamma$, $D_2 = -\epsilon - \gamma$, and $D_3 = -\gamma$. Then we have the following inequalities

$$\frac{dy_i}{dt} \geq D_i y_i \text{ for } i = 1, 2, 3 \tag{3.6}$$

It implies that the solutions with an initial values in Ω remains nonnegative for all $t \geq 0$. From (3.2), (3.3) we have $N \leq \frac{\rho}{\mu - \Lambda}$ and $\frac{\delta_0}{\gamma - \delta_1}$. Since $N = \sum_{i=0}^{4} x_i$ and $P = \sum_{i=0}^{3} y_i$, Ω is positively invariant under the system (3.1). □

3.2 Optimal Control Problem

We consider an optimal control problem with the objective (cost) functional given by

$$J(u_1, u_2) = \int_0^T (A_1 x_2(t) + A_2 x_3(t) + B_1 u_1^2(t) + B_2 u_2^2(t))dt + l(x_1(T), x_4(T)) \tag{3.7}$$

where A_1 and A_2 are positive weight constants of the susceptible and infectious group, respectively and B_1 and B_2 are positive weight constants for prevention and treatment efforts, respectively. We choose a quadratic for the cost on the controls for the technical reason and that is similar in other literature, that is, $B_1 u_1^2$ is the cost of prevention, and $B_2 y_2^2$ is the cost of the treatment effort. $l(x_1(T), x_4(T))$ is the fitness of the susceptible and treated group at the end of the process as a result of the prevention and the treatment efforts and we want to maximize while the cost function J is minimized. We seek an optimal control pair (u_1^*, u_2^*) such that

$$J(u_1^*, u_2^*) = \min\{J(u_1, u_2) | (u_1, u_2) \in \Gamma\} \tag{3.8}$$

where the control set is

$$\Gamma = \{(u_1, u_2) | u_i(t) \text{ is piecewise continuous on} [0, T], a_i \leq u_i(t) \leq b_i, i = 1, 2\} \tag{3.9}$$

where a_i and b_i , $i = 1, 2$ are constants in $[0, 1]$. We discuss the existence of the optimal control and then the optimal system.

3.3 Existence of an Optimal Control

In this section, we show that the optimal control exists by using a result from Fleming and Rishel [33] and Carathodory's existence theorem [49].

Theorem 3.2 (Carathodory's existence theorem). *Consider the differential equation*

$$y'(t) = f(t, y(t)), y(t_0) = y_0 \tag{3.10}$$

with f defined in the rectangular domain $R = \{(t, y)||t - t_0| \leq a, |y - y_0| \leq b\}$. If the function f satisfies the following three conditions

- *$f(t, y)$ is continuous in y for each fixed t.*
- *$f(t, y)$ is measurable in t for each fixed y.*
- *there is a Lebesgue-integrable function $m(t)$, $|t - t_0| \leq a$, such that $|f(t, y)| \leq m(t)$ for all $(t, y) \in R$.*

then, the differential equation has a solution in the extended sense in a neighborhood of the initial condition.

Theorem 3.3. *Consider the objective functional $J(u_1, u_2)$ given by* (3.7) *with $(u_1, u_2) \in \Gamma$ subjected to the system* (3.1)*. There exists $(u_1^*, u_2^*) \in \Gamma$ such that $J(u_1^*, u_2^*) = \min\{J(u_1, u_2)|(u_1, u_2) \in \Gamma\}$.*

Proof. By a result from Fleming and Rishel [33], if the following conditions are satisfied, then there exist $(u_1^*, u_2^*) \in \Gamma$.

1. The set of controls and corresponding state variables are non-empty.
2. Γ is convex and closed
3. The right hand side of (3.1) is bounded by a linear function in the state and control.
4. The integrand of the equation (3.7) is convex on Γ and is bounded below by $c_1(|u_1|^2 + |u_2|^2)^{\frac{\beta}{2}} - c_2$ where $c_1 > 0$, $c_2 > 0$, and $\beta > 1$.

5. The function l is continuous.

Carathodory's existence theorem for the state system (3.1) with bounded coefficients gives the first condition. The control set Γ is convex and closed by definition. The right hand side of the system (3.1) satisfies the third condition as the state solutions are bounded from Theorem 3.1. The integrand in the objective functional 3.7 is convex. Let $L(t, x_1, x_2, u_1, u_2) = A_1x_2(t) + A_2x_3(t) + B_1u_1^2 + B_2u_2^2$. We show that

$$\begin{aligned} &L(t, x_1, x_2, \lambda u_1 + (1-\lambda)u_1', \lambda u_2 + (1-\lambda)u_2') \\ &\qquad \leq \lambda L(t, x_1, x_2, u_1, u_2) + (1-\lambda)L(t, x_1, x_2, u_1', u_2') \end{aligned} \tag{3.11}$$

for $\lambda \in [0, 1]$ and $(u_1, u_2), (u_1', u_2') \in \Gamma$. By the definition, we have that

$$\begin{aligned} &L(t, x_1, x_2, \lambda u_1 + (1-\lambda)u_1', \lambda u_2 + (1-\lambda)u_2') \\ &\quad = A_1x_2(t) + A_2x_3(t) + B_1(\lambda u_1 + (1-\lambda)u_1')^2 + B_2(\lambda u_2 + (1-\lambda)u_2')^2 \end{aligned} \tag{3.12}$$

and

$$\begin{aligned} &\lambda L(t, x_1, x_2, u_1, u_2) + (1-\lambda)L(t, x_1, x_2, u_1', u_2') \\ &= A_1x_2(t) + A_2x_3(t) + \lambda B_1u_1^2 + \lambda B_2u_2^2 + B_1(1-\lambda)u_1'^2 + B_2(1-\lambda)u_2'^2 \end{aligned} \tag{3.13}$$

Then we get that

$$\begin{aligned} &A_1x_2(t) + A_2x_3(t) + B_1(\lambda u_1 + (1-\lambda)u_1')^2 + B_2(\lambda u_2 + (1-\lambda)u_2')^2 \\ &\quad \leq A_1x_2(t) + A_2x_3(t) + \lambda B_1u_1^2 + \lambda B_2u_2^2 + B_1(1-\lambda)u_1'^2 + B_2(1-\lambda)u_2'^2 \end{aligned} \tag{3.14}$$

It means that we need to show that

$$\begin{aligned} &B_1(\lambda u_1 + (1-\lambda)u_1')^2 + B_2(\lambda u_2 + (1-\lambda)u_2')^2 \\ &\qquad \leq \lambda B_1u_1^2 + \lambda B_2u_2^2 + B_1(1-\lambda)u_1'^2 + B_2(1-\lambda)u_2'^2 \\ &\qquad = B_1(\lambda u_1^2(1-\lambda)u_1'^2) + B_2(\lambda u_2^2 + (1-\lambda)u_2'^2) \end{aligned} \tag{3.15}$$

We show that $(\lambda u_1 + (1-\lambda)u_1')^2 \leq \lambda u_1^2 + (1-\lambda)u_1'^2$.

$$\begin{aligned}(\lambda u_1 + (1-\lambda)u_1')^2 &= \lambda^2 u_1^2 + 2\lambda(1-\lambda)u_1 u_1' + (1-\lambda)^2 u_1'^2 \\ &= \lambda(\lambda - 1 + 1)u_1^2 + 2\lambda(1-\lambda)u_1 u_1 + (1-\lambda)(1-\lambda)u_1'^2 \\ &= \lambda u_1^2 + \lambda(\lambda-1)u_1^2 + 2\lambda(1-\lambda)u_1 u_1' + (1-\lambda)u_1'^2 + \lambda(\lambda-1)u_1'^2 \\ &= \lambda u_1^2 + (1-\lambda)u_1'^2 + \lambda(\lambda-1)(u_1^2 - 2u_1 u_1' + u_1'^2) \\ &= \lambda u_1^2 + (1-\lambda)u_1'^2 + \lambda(\lambda-1)(u_1 - u_1')^2 \\ &\leq \lambda u_1^2 + (1-\lambda)u_1'^2 \end{aligned} \tag{3.16}$$

Similarly, we can show that $(\lambda u_2 + (1-\lambda)u_2')^2 \leq \lambda u_2^2 + (1-\lambda)u_2'^2$. Thus, the integrand in the objective functional , $A_1 x_2(t) + A_2 x_3(t) + B_1 u_1^2 + B_2 u_2^2$, is convex on Γ. Since the state variables are bounded, there are $c_1 > 0$, $c_2 > 0$ and $\beta > 1$ satisfying

$$A_1 x_2(t) + A_2 x_3(t) + B_1 u_1^2 + B_2 u_2^2 \geq c_1(|u_1|^2 + |u_2|^2)^{\frac{\beta}{2}} - c_2$$

We want to maximize the function $l(x_1(T), x_4(T))$ while the cost functional J is minimized. If we define the function l as follows,

$$l(x_1(T), x_4(T)) = -Q_1 x_1(T) - Q_2 x_4(T), Q_1 \geq 0, Q_2 \geq 0 \tag{3.17}$$

Then the function l is clearly continuous. Finally there exists an optimal control pair (u_1^*, u_2^*) that minimizes the objective functional $J(u_1, u_2)$. □

3.4 Optimality System

We present the optimality system using a result from Lewis and Syrmos [48] and Pontryagin's Maximum Principle. From the theorems in Lenhart and Workman [47] and Clarke [28], the optimality system can be used to compute candidates for the optimal control pair.

Theorem 3.4. *If $u^*(t)$ and $x^*(t)$ are optimal for*

$$\begin{gathered} min_u \int_{t_0}^{t_1} f(t, x(t), u(t))dt \\ \textit{subjected to } x'(t) = g(t, x(t), u(t)) \\ x(t_0) = x(0) \textit{ and } x(t_1) \textit{ free}. \end{gathered} \tag{3.18}$$

,then there exists a piecewise differentiable adjoint variable $\lambda(t)$ *such that*

$$H(t, x^*(t), u^*(t), \lambda(t)) \leq H(t, x^*(t), u(t), \lambda(t)) \tag{3.19}$$

for all controls u *at each time* t*, where Hamiltonian* H *is*

$$H = f(t, x(t), u(t)) + \lambda(t) g(t, x(t), u(t)) \tag{3.20}$$

and

$$\begin{aligned} \lambda'(t) &= -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x} \\ \lambda(t_1) &= 0 \end{aligned} \tag{3.21}$$

Theorem 3.5. *Suppose that* $f(t, x, u)$ *and* $g(t, x, u)$ *are noth continuously differentiable functions in their three arguments and concave in* u*. Suppose* u^* *is an optimal control for problem* (3.18)*, with associated state* x^**, and* λ *a piecewise differentiable function with* $\lambda(t) \geq 0$ *for all* t*. Suppose for all* $t_0 \leq t \leq t_1$

$$0 = H_u(t, x^* t(t), u^*(t), \lambda(t)). \tag{3.22}$$

Then for all controls u *and each* $t + 0 \leq t \leq t_1$*, we have*

$$H(t, x^*(t), u^*(t), \lambda(t)) \leq H(t, x^*(t), u(t), \lambda(t)) \tag{3.23}$$

We have introduced an adjoint variable λ*, which is similar to a Lagrange multiplier. It attaches the differential equations information onto the minimization of the objective functional* (3.7)*. To apply the theory, we follow an outline.*

1. *Form the Hamiltonian for the problem.*

2. *Write the adjoint differential equation, termianl boundary condition, and the optimiality condition. Now there are three unknowns,* u^**,* x^**, and* λ*.*

3. *Try to eliminate* u^* *by using the optimality equation* $H_U = 0$*, i.e., solve for* u^* *in terms of* x^* *and* λ*.*

4. *Solve the two differential equations for* x^* *and* λ *with two boundary conditions, substituting* u^* *in the differential equations with the expression for the optimal control from the previous step.*

5. *After finding the optimal state and adjoint, solve for the optimal control.*

We define a Lagrangian which is the Hamiltonian augmented with penalty terms for the control constraints. Let $Z = (X, Y) \in \Omega$ *and* $U = (u_1, u_2) \in \Gamma$*, where* $X = (x_1, x_2, x_3, x_4)$ *and* $Y = (y_1, y_2, y_3)$*, where* Ω *is defined by* (3.4) *and* Γ *is defined by* (3.9)*.*

$$
\begin{aligned}
H(Z, U, \Pi) =& A_1 x_2(t) + A_2 x_3(t) + B_1 u_1^2 + B_2 u_2^2 \\
&+ \lambda_1 \left(\rho + \Lambda(x_1 + x_2 + x_4) + \Lambda(1 - \zeta_1) x_3 + \psi x_4 - \frac{\beta \phi y_3 x_1 (1 - u_1(t))}{N} - \mu x_1 \right) \\
&+ \lambda_2 \left(\frac{\beta \phi y_3 x_1 (1 - u_1(t))}{N} + \Lambda \zeta_1 x_3 - d x_2 - \mu x_2 \right) \\
&+ \lambda_3 \left(d x_2 - (r + \alpha + \mu + r_0 u_2(t)) x_3 \right) \\
&+ \lambda_4 \left((r + r_0 u_2(t)) x_3 - (\psi + \mu) x_4 \right) \\
&+ \lambda_5 \left(\delta_0 + \delta_1 (y_1 + y_2) + \delta_1 (1 - \zeta_2) y_3 - \frac{\phi \theta_1 x_3 y_1 (1 - u_1(t))}{N} - \frac{\phi \theta_2 x_2 y_1 (1 - u_1(t))}{N} - \gamma y_1 \right) \\
&+ \lambda_6 \left(\frac{\phi \theta_1 x_3 y_1 (1 - u_1(t))}{N} + \frac{\phi \theta_2 x_2 y_1 (1 - u_1(t))}{N} + \delta_1 \zeta_2 y_3 - \epsilon y_2 - \gamma y_2 \right) \\
&+ \lambda_7 \left(\epsilon y_2 - \gamma y_3 \right) \\
&- \omega_{11}(u_1 - a_1) - \omega_{12}(b_1 - u_1) - \omega_{21}(u_2 - a_2) - \omega_{22}(b_2 - u_2)
\end{aligned}
\tag{3.24}
$$

where the adjoint variable $\Pi = (\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7)$ *and the penalty multipliers* $\omega_{ij}(t) \geq 0$ *satisfying*

$$\omega_{11}(u_1(t) - a_1) = \omega_{12}(t)(b_1 - u_1(t)) = 0 \text{ at optimal control } u_1^*$$

and

$$\omega_{21}(u_2(t) - a_2) = \omega_{22}(t)(b_2 - u_2(t)) = 0 \text{ at optimal control } u_2^*$$

We can check the concavity condition of H *that minimizes the objective functional;*

$$\frac{\partial^2 H}{\partial u_i^2} = 2B_i > 0 \text{ at } u_i^* \text{ for } i = 1, 2. \tag{3.25}$$

Theorem 3.6. *Given an optimal control pair,* (u_1^*, u_2^*)*,and solutions,* $x_1, x_2, x_3, x_4, y_1, y_2$ *and* y_3 *of the corresponding state system* (3.1)*, there exist adjoint variables* Π *satisfying*

$$\begin{aligned}
\dot{\lambda_1} &= -\Bigg(\lambda_1\left(\Lambda-\mu+\frac{\beta(1-u_1)x_1y_3\phi}{N^2}-\frac{\beta(1-u_1)y_3\phi}{N}\right)+\lambda_2\left(\frac{\beta(1-u_1)y_3\phi}{N}-\frac{\beta(1-u_1)x_1y_3\phi}{N^2}\right)\\
&\quad+\lambda_5\left(\frac{\theta_2(1-u_1)x_2y_1\phi}{N^2}+\frac{\theta_1(1-u_1)x_3y_1\phi}{N^2}\right)+\lambda_6\left(-\frac{\theta_2(1-u_1)x_2y_1\phi}{N^2}-\frac{\theta_1(1-u_1)x_3y_1\phi}{N^2}\right)\Bigg)\\
\dot{\lambda_2} &= -\Bigg(A_1+d\lambda_3+\lambda_2\left(-d-\mu-\frac{\beta(1-u_1)x_1y_3\phi}{N^2}\right)+\lambda_1\left(\Lambda+\frac{\beta(1-u_1)x_1y_3\phi}{N^2}\right)\\
&\quad+\lambda_5\left(\frac{\theta_2(1-u_1)x_2y_1\phi}{N^2}+\frac{\theta_1(1-u_1)x_3y_1\phi}{N^2}-\frac{\theta_2(1-u_1)y_1\phi}{N}\right)\\
&\quad+\lambda_6\left(-\frac{\theta_2(1-u_1)x_2y_1\phi}{N^2}-\frac{\theta_1(1-u_1)x_3y_1\phi}{N^2}+\frac{\theta_2(1-u_1)y_1\phi}{N}\right)\Bigg)\\
\dot{\lambda_3} &= -\Bigg(A_2+\lambda_3\left(-\alpha-\mu-r_0u_2-r\right)+\lambda_4\left(r_0u_2+r\right)+\lambda_1\left((1-\zeta_1)\Lambda+\frac{\beta(1-u_1)x_1y_3\phi}{N^2}\right)\\
&\quad+\lambda_2\left(\zeta_1\Lambda-\frac{\beta(1-u_1)x_1y_3\phi}{N^2}\right)+\lambda_5\left(\frac{\theta_2(1-u_1)x_2y_1\phi}{N^2}+\frac{\theta_1(1-u_1)x_3y_1\phi}{N^2}-\frac{\theta_1(1-u_1)y_1\phi}{N}\right)\\
&\quad+\lambda_6\left(-\frac{\theta_2(1-u_1)x_2y_1\phi}{N^2}-\frac{\theta_1(1-u_1)x_3y_1\phi}{N^2}+\frac{\theta_1(1-u_1)y_1\phi}{N}\right)\Bigg)\\
\dot{\lambda_4} &= -\Bigg(\lambda_4(-\mu-\psi)+\lambda_1\left(\Lambda+\frac{\beta(1-u_1)x_1y_3\phi}{N^2}+\psi\right)-\frac{\beta\lambda_2(1-u_1)x_1y_3\phi}{N^2}\\
&\quad+\lambda_5\left(\frac{\theta_2(1-u_1)x_2y_1\phi}{N^2}+\frac{\theta_1(1-u_1)x_3y_1\phi}{N^2}\right)+\lambda_6\left(-\frac{\theta_2(1-u_1)x_2y_1\phi}{N^2}-\frac{\theta_1(1-u_1)x_3y_1\phi}{N^2}\right)\Bigg)\\
\dot{\lambda_5} &= -\Bigg(\lambda_5\left(-\gamma+\delta_1-\frac{\theta_2(1-u_1)x_2\phi}{N}-\frac{\theta_1(1-u_1)x_3\phi}{N}\right)+\lambda_6\left(\frac{\theta_2(1-u_1)x_2\phi}{N}+\frac{\theta_1(1-u_1)x_3\phi}{N}\right)\Bigg)\\
\dot{\lambda_6} &= -\Bigg(\lambda_6(-\gamma-\epsilon)+\delta_1\lambda_5+\lambda_7\epsilon\Bigg)\\
\dot{\lambda_7} &= -\Bigg(-\gamma\lambda_7+\delta_1\left(1-\zeta_2\right)\lambda_5+\delta_1\zeta_2\lambda_6-\frac{\beta\lambda_1(1-u_1)x_1\phi}{N}+\frac{\beta\lambda_2(1-u_1)x_1\phi}{N}\Bigg)
\end{aligned} \tag{3.26}$$

with the terminal conditions,

$$\lambda_1(T)=\left.\frac{\partial l}{\partial x_1}\right|_T,\ \lambda_4(T)=\left.\frac{\partial l}{\partial x_4}\right|_T,\ \lambda_i(T)=0,\ \textit{for } i=2,3,5,6,7. \tag{3.27}$$

Furthermore, u_1^* *and* u_2^* *are represented by*

$$\begin{aligned}
u_1^* &= \max\left(a_1,\min\left(b_1,\frac{\beta\lambda_1(-x_1)y_3\phi+\beta\lambda_2x_1y_3\phi+\left(\lambda_6-\lambda_5\right)y_1\phi\left(\theta_2x_2+\theta_1x_3\right)}{2B_1N}\right)\right)\\
u_2^* &= \max\left(a_2,\min\left(b_2,\frac{\left(\lambda_3-\lambda_4\right)r_0x_3}{2B_2}\right)\right)
\end{aligned} \tag{3.28}$$

Proof. We differentiate the Lagrangian H with respect to states, $Z = (x_1, x_2, x_3, x_4, y_1, y_2, y_3)$. Then the adjoint system can be written as

$$\dot{\lambda}_1 = -\frac{\partial L}{\partial x_1}, \quad \dot{\lambda}_2 = -\frac{\partial L}{\partial x_2}, \quad \dot{\lambda}_3 = -\frac{\partial L}{\partial x_3},$$
$$\dot{\lambda}_3 = -\frac{\partial L}{\partial x_4}, \quad \dot{\lambda}_5 = -\frac{\partial L}{\partial y_1}, \quad \dot{\lambda}_6 = -\frac{\partial L}{\partial y_2}, \quad \dot{\lambda}_7 = -\frac{\partial L}{\partial y_3}$$

The terminal condition of the adjoint equations can be given by

$$\frac{\partial l}{\partial Z} - \Pi = 0, \qquad \text{at } t = T.$$

To obtain the optimality conditions, we differentiate the Lagrangian H with respect to $U = (u_1, u_2)$ and set it equal to zero.

$$\begin{aligned} \frac{\partial L}{\partial u_1} &= 2B_1 u_1 + \frac{\beta\lambda_1 x_1 y_3 \phi}{N} - \frac{\beta\lambda_2 x_1 y_3 \phi}{N} + \lambda_5 \left(\frac{\theta_2 x_2 y_1 \phi}{N} + \frac{\theta_1 x_3 y_1 \phi}{N} \right) \\ &\quad + \lambda_6 \left(-\frac{\theta_2 x_2 y_1 \phi}{N} - \frac{\theta_1 x_3 y_1 \phi}{N} \right) - \omega_{11} + \omega_{12} = 0 \\ \frac{\partial L}{\partial u_2} &= 2B_2 u_2 - \lambda_3 r_0 x_3 + \lambda_4 r_0 x_3 - \omega_{21} + \omega_{22} = 0 \end{aligned} \tag{3.29}$$

Solving for the optimal control, we obtain

$$\begin{aligned} u_1^* &= \frac{N(\omega_{11} - \omega_{12}) + \beta\lambda_1(-x_1)y_3\phi + \beta\lambda_2 x_1 y_3 \phi + (\lambda_6 - \lambda_5) y_1 \phi (\theta_2 x_2 + \theta_1 x_3)}{2B_1 N} \\ u_2^* &= \frac{(\lambda_3 - \lambda_4) r_0 x_3 + \omega_{21} - \omega_{22}}{2B_2} \end{aligned} \tag{3.30}$$

We consider the following three cases to have an explicit expression for the optimal control. For the optimal control u_1^*,

1. On the set $\{t | a_1 < u_1^*(t) < b_1\}$, we have $\omega_{11}(t) = \omega_{12} = 0$. Hence the optimal control is

$$u_1^* = \frac{\beta\lambda_1(-x_1)y_3\phi + \beta\lambda_2 x_1 y_3 \phi + (\lambda_6 - \lambda_5) y_1 \phi (\theta_2 x_2 + \theta_1 x_3)}{2B_1 N}$$

2. On the set $\{t | u_1^*(t) = b_1\}$, we have $\omega_{11}(t) = 0$. Hence

$$b_1 = u_1^* = \frac{N(-\omega_{12}) + \beta\lambda_1(-x_1)y_3\phi + \beta\lambda_2 x_1 y_3 \phi + (\lambda_6 - \lambda_5) y_1 \phi (\theta_2 x_2 + \theta_1 x_3)}{2B_1 N}$$

Since $\omega_{12}(t) \geq 0$, we have that

$$\frac{\beta\lambda_1(-x_1)y_3\phi + \beta\lambda_2 x_1 y_3 \phi + (\lambda_6 - \lambda_5) y_1 \phi (\theta_2 x_2 + \theta_1 x_3)}{2B_1 N} \geq b_1$$

3. On the set $\{t|u_1^*(t) = a_1\}$, we have $\omega_{12}(t) = 0$. Hence

$$a_1 = u_1^* = \frac{N(\omega_{11}) + \beta\lambda_1(-x_1)y_3\phi + \beta\lambda_2 x_1 y_3\phi + (\lambda_6 - \lambda_5)\, y_1\phi\,(\theta_2 x_2 + \theta_1 x_3)}{2B_1 N}$$

Since $\omega_{11}(t) \geq 0$, we have that

$$\frac{\beta\lambda_1(-x_1)y_3\phi + \beta\lambda_2 x_1 y_3\phi + (\lambda_6 - \lambda_5)\, y_1\phi\,(\theta_2 x_2 + \theta_1 x_3)}{2B_1 N} \leq a_1$$

Combining these three cases, the optimal control u_1^* is characterized as

$$u_1^* = \max\left(a_1, \min\left(b_1, \frac{\beta\lambda_1(-x_1)y_3\phi + \beta\lambda_2 x_1 y_3\phi + (\lambda_6 - \lambda_5)\, y_1\phi\,(\theta_2 x_2 + \theta_1 x_3)}{2B_1 N}\right)\right)$$

For the optimal control u_2^*,

1. On the set $\{t|a_2 < u_2^*(t) < b_2\}$, we have $\omega_{21}(t) = \omega_{22} = 0$. Hence the optimal control is

$$u_2^* = \frac{(\lambda_3 - \lambda_4)\, r_0 x_3}{2B_2}$$

2. On the set $\{t|u_2^*(t) = b_2\}$, we have $\omega_{21}(t) = 0$. Hence

$$b_2 = u_2^* = \frac{(\lambda_3 - \lambda_4)\, r_0 x_3 - \omega_{22}}{2B_2}$$

Since $\omega_{22}(t) \geq 0$, we have that

$$\frac{(\lambda_3 - \lambda_4)\, r_0 x_3}{2B_2} \geq b_2$$

3. On the set $\{t|u_2^*(t) = a_2\}$, we have $\omega_{22}(t) = 0$. Hence

$$u_2^* = \frac{(\lambda_3 - \lambda_4)\, r_0 x_3 + \omega_{21}}{2B_2}$$

Since $\omega_{21}(t) \geq 0$, we have that

$$\frac{(\lambda_3 - \lambda_4)\, r_0 x_3}{2B_2} \geq a_2$$

Combining these three cases, the optimal control u_2^* is characterized as

$$u_2^* = \max\left(a_2, \min\left(b_2, \frac{(\lambda_3 - \lambda_4)\, r_0 x_3}{2B_2}\right)\right)$$

□

3.5 The forward-backward sweep method Algorithm

In this section , we introduce a numerical algorithm to find an optimal control, u^**. We break the time interval* $[t_0, t_1]$ *into pieces with specific points of interest* $t_0 = b_1, b_2, \ldots, b_N, b_{N+1} = t_1$*. These points will usually be equally spaced. The approximation will be a vector* $\overrightarrow{u} = (u^1, u^2, \ldots, u^N, u^{N+1})$ *where* $u^i = (u_1(b_i), u_2(b_i))^T$*. There are various methods to solve optimal control problem. For example, Rodrigues and Monteiro [62], Wang [69], or Betts [10]. We use the forward-backwardsweep method introduced in Anita and Capasso [3] or Lenhart and Workman [47]. We consider a control problem.*

$$min_u J(u) = \int_{t_0}^{t_1} f(t, x(t), u(t))dt \tag{3.31}$$

subjected to

$$\begin{cases} x'(t) = g(t, u(t), x(t)), t \in (t_0, t_1) \\ x(t_0) = x_0 \end{cases} \tag{3.32}$$

and

$$\begin{cases} \lambda'(t) = -\frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x} \\ \lambda(t_1) = 0 \end{cases} \tag{3.33}$$

where $G(t, u, x)$ *is the integrand of the cost functional. Then the forward-backward sweep method is*

S0: Choose $u^{(0)} \in \Gamma$*. Set* $k = 0$

S1: Compute $x^{(k)}$ *the solution to* (3.32) *corresponding to* $u = u^{(k)}$

S2: Compute $\lambda^{(k)}$ *the solution to* (3.33) *corresponding to* $u = u^{(k)}$

S3: Compute $u^{(k+1)}$ *the solution to the equation*

$$G_u(t, u(t), x^{(k)}(t)) + f_u^*(t, u(t), x^{(k)}(t))\lambda^{(k)} = 0$$

S4: (The stopping criterion)

If $\min(\delta\|u^{(k+1)}\|_1 - \|u^{(k+1)} - u^{(k)}\|_1, \delta\|x^{(k+1)}\|_1 - \|x^{(k+1)} - x^{(k)}\|_1, \delta\|\lambda^{(k+1)}\|_1 - \|\lambda^{(k+1)} - \lambda^{(k)}\|_1) > 0$

then Stop

else $k = k + 1$ *go to S0.*

Here, $\|\cdot\|_1$ *refers to the* l^1 *norm for vectors, i.e.,*

$$\|u - oldu\| = \sum_{i=1}^{N+1} |u_i - oldu_i|. \tag{3.34}$$

Many types of convergence tests exist for S5. We use the stopping criterion explained in Lenhart and Workman [47]. It requires the relative errors to be small,

$$\begin{aligned} \frac{\|u - oldu\|_1}{\|u\|_1} &\leq \delta \\ \frac{\|x - oldx\|_1}{\|x\|_1} &\leq \delta \\ \frac{\|\lambda - old\lambda\|_1}{\|\lambda\|_1} &\leq \delta \end{aligned} \tag{3.35}$$

where δ *is the accepted tolerance. To allow the zero for the controls, multiply both sides by* $\|u\|_1$ *in* (3.35) *to remove it from the denominator. Then we have*

$$\delta\|u\|_1 - \|u - oldu\| \geq 0$$

or

$$\delta \sum_{i=1}^{N+1} |u_i| - \sum_{i=1}^{N+1} |u_i - oldu_i| \geq 0. \tag{3.36}$$

In the same reason, we have

$$\delta\|x\|_1 - \|x - oldx\| \geq 0$$

$$\delta\|\lambda\|_1 - \|\lambda - old\lambda\| \geq 0$$

This method has two restrictions as explained in Lenhart and Workman [47], 1) the Lipschitz constants for the state, adjoint, and control is small enough and 2) the time interval is small. Because of these restrictions, we choose the parameters and t_1 *very carefully. The convergence and stability of the forward-backward sweep algorithm can be found in Mcasey [54].*

3.6 The Runge-Kutta method in 3-dimension

In this section, we introduce a numerical method required to solve in S1 and S2 in the previous section. To solve the state (3.1) *, the Runge-Kutta method is applied and we consider a modified Runge-Kutta to solve the adjoint* (3.26)*. We solve the state* (2.1) *forward in time and the adjoint*

(3.26) *backward in time. We consider 4th order Runge-Kutter methods. Let* $x'(t) = f(t, x(t))$. *Then the 4th order Runge-Kutta method is*

$$x_{n+1} = x_n + \frac{h}{6}(k_1 + 2k_2 + 2k_3 + k_4) \text{ for } n = 0, 1, 2, 3, \ldots.$$

where

$$\begin{aligned} k_1 &= f(t_n, x_n) \\ k_2 &= f(t_n + \frac{h}{2}, x_n + \frac{k_1}{2}h) \\ k_3 &= f(t_n + \frac{h}{2}, x_n + \frac{k_2}{2}h) \\ k_4 &= f(t_n + h, x_n + hk_3) \end{aligned} \tag{3.37}$$

To find k_2 *in* (3.37), x_n *is replaced with* $x_n + \frac{k_1}{2}h$ *and* t_n *is replaced with* $t_n + \frac{h}{2}$. *So, to calculate a control,* u, *we should consider* $u_n + \frac{h}{2}k_2$. *However, there is no explicit dependence on* t *in the differential equation for* u. *So this value is not assigned by our vector. There are many ways to approximate this value. For example, an interpolating polynomial or spline of* u *could be generated. In most of the literature, it usually suffices to approximate it as the following*

$$u_n(1 - c_n) + u_{n+1}c_n \tag{3.38}$$

where n *is the current iteration and* $0 < c_n < 1$. *This is weighted average, where the weight shifts each iteration towards the current iteration. In our numerical experiment, we use the average*

$$\frac{u_n + u_{n+1}}{2}. \tag{3.39}$$

We consider the 4th order Runge-Kutta for 3 inputs, so we can solve the states forward in time,

$$\begin{aligned} k_1 &= f(t_n, x_n, u_n) \\ k_2 &= f(t_n + \frac{h}{2}, x_n + \frac{h}{2}k_1, \frac{1}{2}(u_n + u_{n+1})) \\ k_3 &= f(t_n + \frac{h}{2}, x_n + \frac{h}{2}k_2, \frac{1}{2}(u_n + u_{n+1})) \\ k_4 &= f(t_n + h, x_n + hk_3, u_{n+1}) \end{aligned} \tag{3.40}$$

To solve the adjoints backward in time,

$$\begin{aligned} l &= N + 2 - n \\ k_1 &= f(t_l, \lambda_l, x_l, u_l) \\ k_2 &= f(t_l - \frac{h}{2}k_1, \frac{1}{2}(x_l + x_{l-1}), \frac{1}{2}(u_l + u_{l-1})) \\ k_3 &= f(t_l - \frac{h}{2}k_2, \frac{1}{2}(x_l + x_{l-1}), \frac{1}{2}(u_l + u_{l-1})) \\ k_4 &= f(t_l - h, \lambda_l - hk_3, x_{l-1}, u_{l-1}) \\ \lambda_{l-1} &= \lambda_l - \frac{h}{6}(k_1 + 2k_2 + 3k_3 + k_4) \end{aligned} \tag{3.41}$$

where h is the step size between time, t, N is the total number of time steps, $n = 1, 2, 3 \ldots, N$, and $l = N + 1, N, \ldots, 2$.

The error for the 4th order Runge-Kutta method is $O(h^4)$. The stability and accuracy of the 4th order Runge-Kutta method is found in Butcher [17, 18].

3.7 Numerical Results

In this section, we perform a simulation for the state system (3.1)*, the adjoint system* (3.26)*, and the optimal control* (3.30)*. The model considered in the experiment is tested with data taken from the dengue virus. The optimality system is a two-point boundary problem because of the initial condition $Z(0)$ of the state system* (3.1) *and the terminal condition $\Pi(0)$* (3.26)*. First, we make an initial guess for the control functions. Second, we solve the initial valued state system forward in time. Then, using the same guess for the control functions, we solve the adjoint system with the terminal conditions backeard in time. The controls are updated in each iteration using the optimality conditions* (3.30)*. To focus on the controls, we choose weight constant values $A_1 = A_2 = 1, B_1 = B_2 = 50$, and $Q_1 = Q_2 = 0.1$ in the objective functional* (3.7) *and the Hamitonian* (3.24)*.*

We consider the initial conditions $x_1(0) = 100, x_2(0) = 20, x_3(0) = 20, x_4(0) = 10, y_1(0) = 1000, y_2(0) = 20$ and $y_3(0) = 30$. For the boundary of prevention and treatment efficiency we choose $a_1 = a_2 = 0$ and $b_1 = b_2 = 1$.

Parameter	Value	Parameter	Value
ϵ	$\frac{1}{12}$	δ_0	1050
γ	$\frac{1}{15}$	r	$\frac{1}{7}$
β	0.2	$r0$	0.04
ζ_2	0.67	δ_1	0.0399
θ_1	0.0082	d	$\frac{1}{10}$
θ_2	0.0289	ψ	0.0014
μ	$\frac{1.01}{70*365}$	ζ_1	0
Λ	$\frac{0.379}{70*365}$	α	0.0238
ρ	205	ϕ	3

Table 3.1: Parameter values are estimated based on a dengue virus.

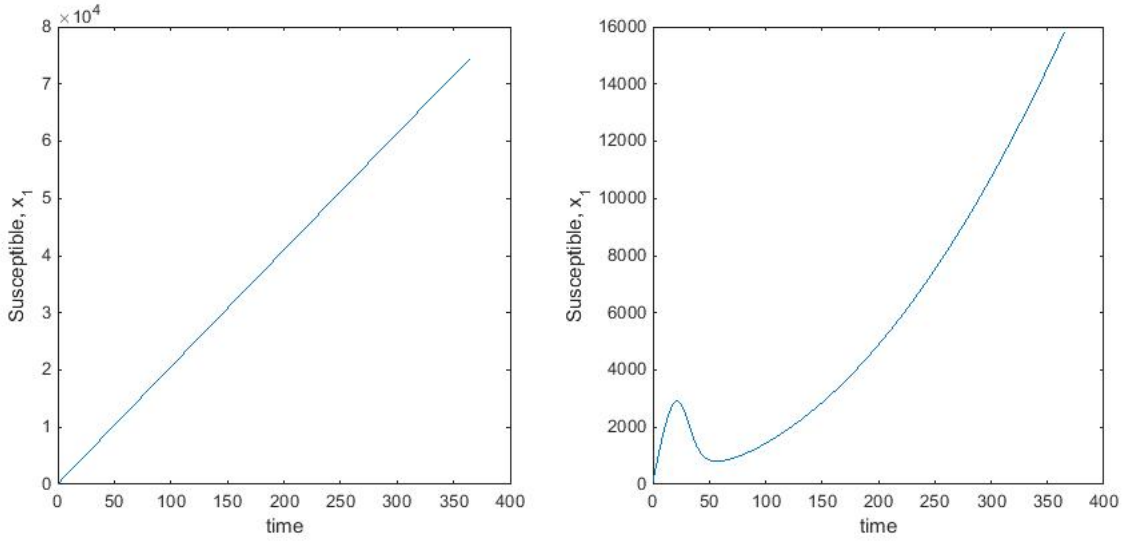

Figure 3.1: Comparison between Controlled(left) and Uncontrolled(right) for susceptible host

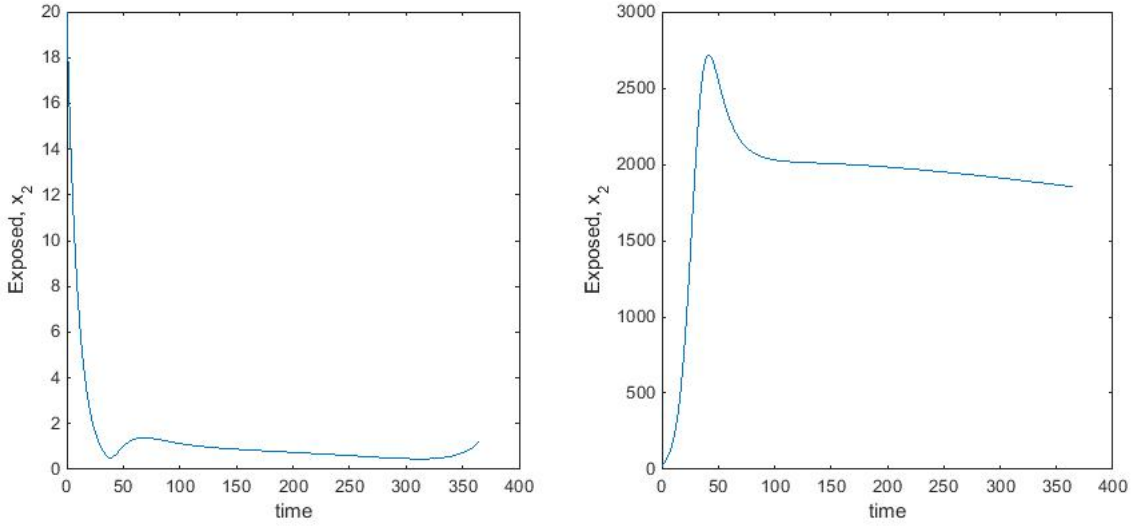

Figure 3.2: Comparison between Controlled(left) and Uncontrolled(right) for exposed host

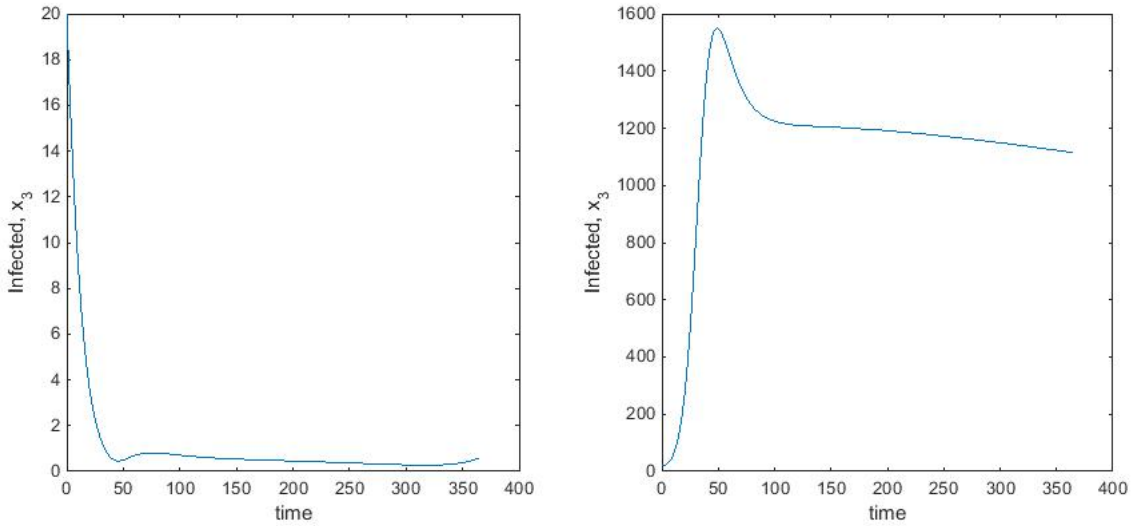

Figure 3.3: Comparison between Controlled(left) and Uncontrolled(right) for infected host

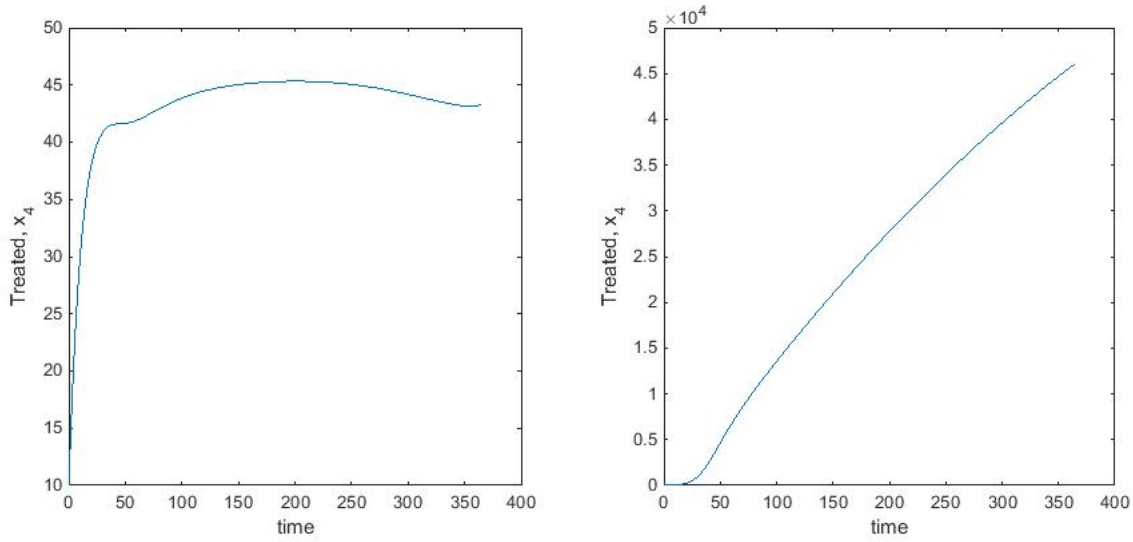

Figure 3.4: Comparison between Controlled(left) and Uncontrolled(right) for treated host

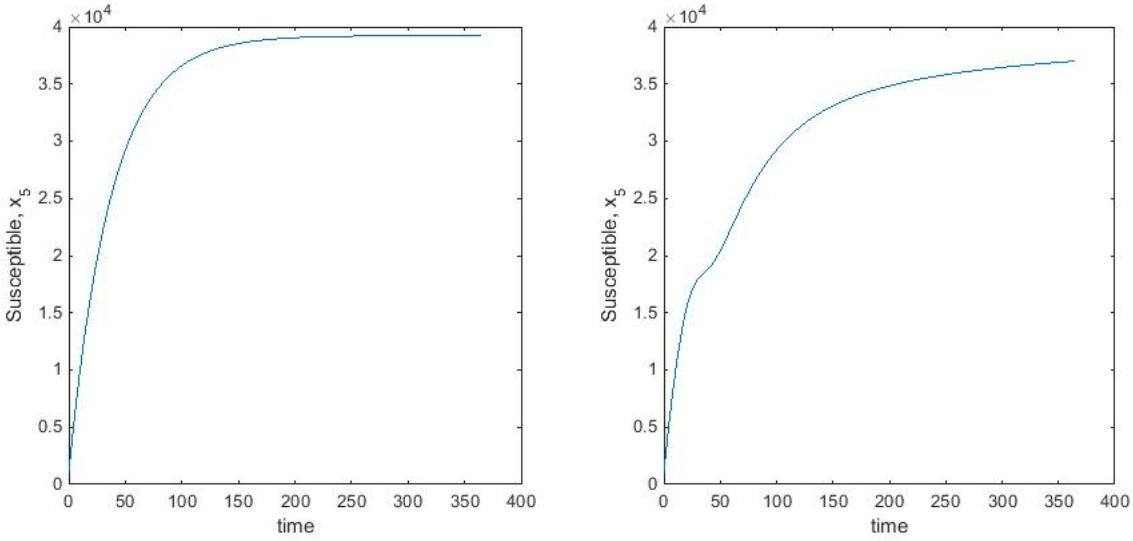

Figure 3.5: Comparison between Controlled(left) and Uncontrolled(right) for susceptible vector

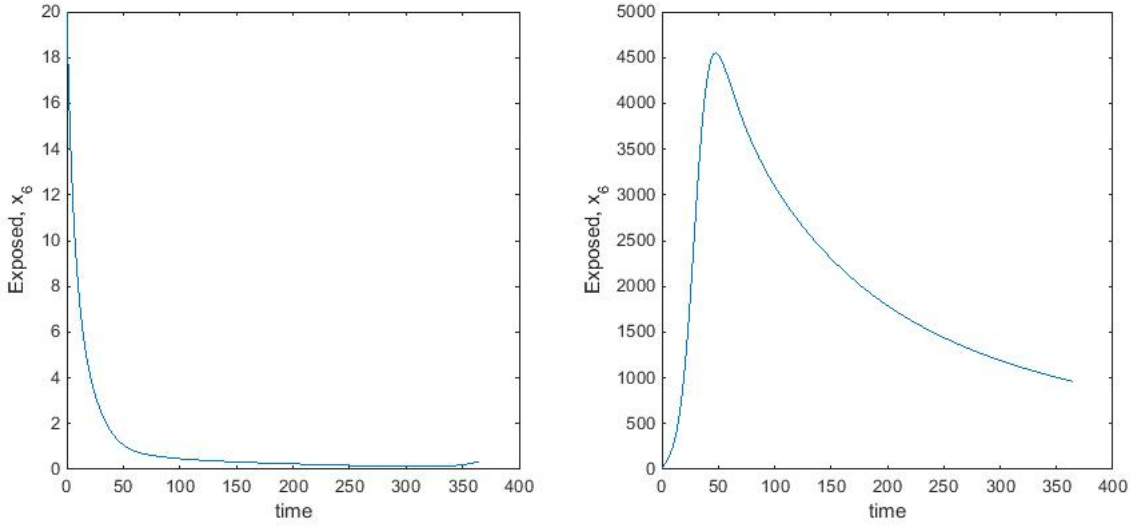

Figure 3.6: Comparison between Controlled(left) and Uncontrolled(right) for exposed vector

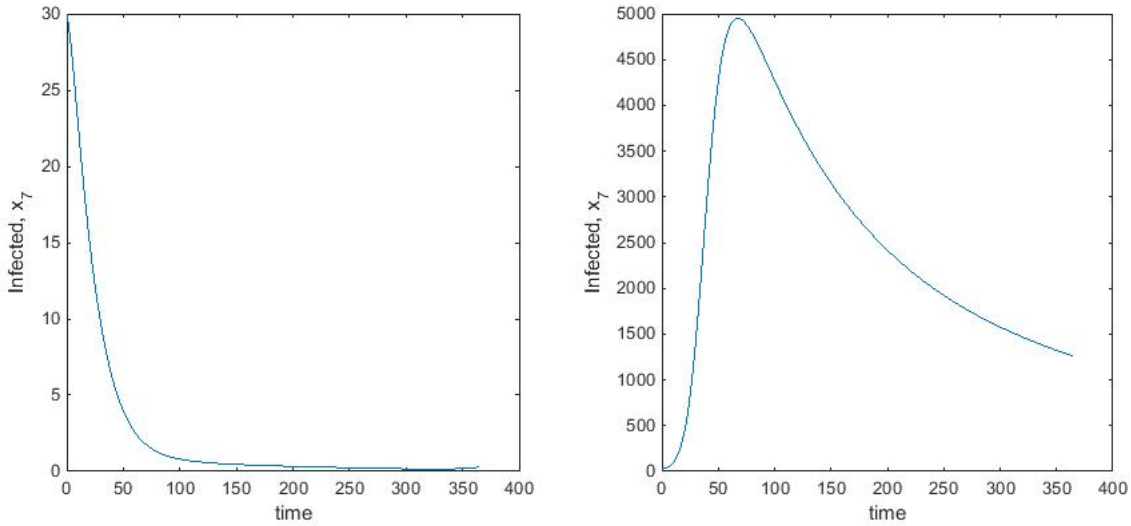

Figure 3.7: Comparison between Controlled(left) and Uncontrolled(right) for infected vector

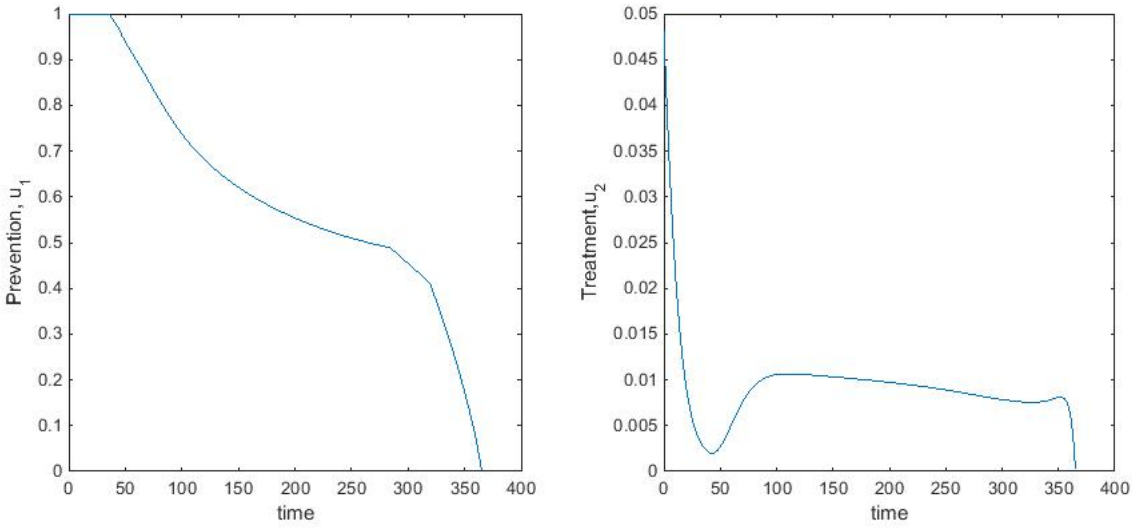

Figure 3.8: Optimal Control u_1(left) and u_2(right)

From 3.3 and 3.4, we see that the number of exposed and infected host are reduced in very short time compare to the result without controls. Also, From 3.6 and 3.7, we see that the number of exposed and infected vector are reduced in vary short time compare to the result without controls. We see that from the figures 3.1 - 3.7, the result with the optimal controls, u_1 *and* u_2 *are better than the result without the optimal control.*

From 3.8, we see that the effectiveness of the prevention is higher than the effectiveness of the treatment. So, we see the numerical result with only with the prevention u_1.

Chapter 4

Summary

In this dissertation we studied a vertically transmitted deterministic vector-borne disease model and the optimal control of the deterministic model. The deterministic model is a compartment model. We consider SEIR model for the host and SEI model for the host. We divide the total host population into susceptible, exposed, infectious, and treated groups. Similarly, the total vector population is divided into susceptible, exposed, and infectious groups. By studying which elements affect the transmission between a host and a vector and how the disease is transmitted from one compartment to another, we develop a system of nonlinear differential equations that describes the epidemiology of vector-borne disease.

In chapter 2, we analyzed the vertically transmitted deterministic vector-borne disease model. We find the disease free equilibrium point E_0 by setting the number of exposed, infectious, and treated groups is equal to zero. Then, we calculated the basic reproduction number (or the epidemiology threshold) R_0 using the Next-Generation Approach which is finding the spectral radius of the next-generation matrix. We proved that if $R_0 < 1$, the disease free equilibrium points is locally and globally asymptotically stable and the disease is extinguished. If $R_0 > 1$, then the disease free equilibrium point is unstable. We also studied the sensitivity of R_0. We studied that which parameter make the value of R_0 change most and least using the normalized forward sensitivity index γ_p^u with a variable u that depends differentiably on a parameter p. We found that the change of host recovery rate γ, a factor for density dependent maturation of mosquitoes to adulthood δ_1, and the number of contacts between a host and a vector α affect the value of R_0 most and the change of disease-induced host death rate α and vertical disease transmission rate in the vector ζ_2 least. We do the numerical experiment for the

different value of parameters to explain the analytic results. We had the numerical experiments for $R_0 < 1$ and $R_0 > 1$ and we see that for $R_0 < 1$, the disease die out and for $R_0 > 1$, the disease persist.

In chapter 3, we studied the optimal control for the vertically transmitted deterministic vector-borne disease model. We consider the two optimal control functions ,The prevention u_1 and the treatment u_2, which are piecewise continuous on a certain time interval. We introduce these two controls into the deterministic model in chapter 2, which u_1 is related to susceptible, exposed host groups, susceptible, and exposed vector groups and u_2 is related to infectious and treated host groups. We find u_1 and u_2 by minimizing the cost $J(u_1, u_2)$ which minimizes the number of exposed and infected host groups and the cost for the prevention and the treatment and maximizes the number of susceptible and treatment host groups at the final time step. We shoe the existence of the optimal control functions using Carathodory's existence theorem. We calculate the optimal controls by finding the optimal system. We formulate Hamiltonian to find the optimal system with the deterministic model, the integrand of the cost functional with the adjoint variables which is similar to a Lagrange multiplier using Pontry-yagins Maximum Principle. We find the explicit formula for u_1 and u_2 in terms of the status variables and the adjoint variables. For the numerical simulation, we use the forward-backward sweep method since the status system which is the deterministic model with the optimal controls has the initial condition and the system of adjoint variables has the final condition. We solve the status system and the adjoint system using the Runge-Kutta method in 3-dimensions. In the numerical simulation, we focus on the effectiveness of the controls u_1 and u_2. We choose the parameters based on the dengue virus. We compared the result between when we control the disease and the case when we don't. We see that when the controls are included, the disease die out faster than the result without the controls and we archive more the number of susceptible and treated host groups faster than without controls. We also see the effectiveness of each controls. The effectiveness of the prevention is higher than the treatment.

In the future, we will study for the periodic model and the stochastic model of the deterministic model in chapter 2. The transmission of a disease is affected by the season and the temperature which is periodic. We expect that we can get the better result which fits the result

from the real life. Also, we can study the transmission in the small number of host and vector by considering the stochastic model.

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Appendices

.1 Matlab Code

Matlab code for the numerical simulation of the optimal control. main.m

```
clc
clear

epsilon = 1/12;
gamma = 1/15;
beta = 0.2;
theta1 = 0.0082;
theta2 = 0.0289;
mu = 1.01/(70*365);
Lambda = 0.379/(70*365);
rho = 205;
delta0 = 1050;
r= 1/7;
r0 = 0.04;
delta1 = 0.0399;
d = 1/10;
psi = 0.0014;
zeta1 = 0;
zeta2 = 0.67;
alpha = 0.0238;
```

```
21 phi = 3;
22 A1 = 1;
23 A2 = 1;
24 B1 = 50;
25 B2 = 50;
26 T = 365; %final time
27 N = 200;
28 x0 = [100; 20; 20; 10; 1000; 20; 30]; %initial value of x
29 u0 = [0; 0]; %initial value of u
30 lambdafinal =[-0.1;0;0;-0.1;0;0;0]; %final values of lambda
31 t = linspace(0,T,N+1);
32 h = T/N;
33 x = zeros(7,N+1); %initialize x
34 u = zeros(2,N+1); %initialize u
35 lambda = zeros(7,N+1); %initialize x
36 x(:,1) = x0; %assign the x0
37 u(:,1) = u0; %assign the u0
38 lambda(:,N+1) = lambdafinal; %assign the lambdafinal
39
40 %R0
41 %1/2*(zeta1 * Lambda*d/(k1*k2) + zeta2 * delta1*epsilon/(gamma*k4))...
42 %+sqrt((1/2 *(zeta1*Lambda*d/(k1*k3)-zeta2*delta1*epsilon/(gamma*k4)))^2...
43 %+phi^2 * (beta*epsilon*(theta1*d+theta2*k3)*(delta0/(gamma-delta1)))/(gamma*
       k1*k3*k4*(rho/(mu-Lambda))))
44
45 parameters=[epsilon,gamma,beta,theta1,theta2,mu,Lambda,rho,delta0,r, r0, ...
46       delta1, d, psi, zeta1, zeta2,alpha,phi,A1,A2,B1,B2];
47
```

```
k = 1;%counter of the iteration
delta = 0.001; %error bound
test = -1; %error
while (test<0 && k<1000)
    oldx = x;
    oldu = u;
    oldlambda = lambda;

    %forward Runge-Kutta 4th with 3 input algorithm for state
    for i = 1:N
        k1(1:7,1) = state(t(i),x(:,i),u(:,i),parameters);
        k2(1:7,1) = state(t(i)+h/2,x(:,i)+h*k1/2,(u(:,i)+u(:,i+1))/2,parameters);
        k3(1:7,1) = state(t(i)+h/2,x(:,i)+h*k2/2,(u(:,i)+u(:,i+1))/2,parameters);
        k4(1:7,1) = state(t(i)+h,x(:,i)+h*k3,u(:,i+1),parameters);
        x(:,i+1) = x(:,i)+ (h/6) * (k1+2*k2+2*k3+k4);
    end

    %backward Runge-Kutta 4th with 3 input algorithm for adjoint
    for i = 1:N
        j = N+2-i;
        k1(1:7,1) = adjoint(t(j), lambda(:,j), x(:,j),u(:,j),parameters);
        k2(1:7,1) = adjoint(t(j)-h/2, lambda(:,j)-h*k1/2,(x(:,j)+x(:,j-1))/2 ...
            ,(u(:,j)+u(:,j-1))/2,parameters);
        k3(1:7,1) = adjoint(t(j)-h/2,lambda(:,j)-h*k2/2,(x(:,j)+x(:,j-1))/2 ...
            ,(u(:,j)+u(:,j-1))/2,parameters);
        k4(1:7,1) = adjoint(t(j)-h/2, lambda(:,j)-h*k3/2,x(:,j-1),u(:,j-1),
            parameters);
        lambda(:,j-1) = lambda(:,j) - (h/6) *(k1+2*k2+2*k3+k4);
```

```
75      end
76
77      %Find controls
78      for  i = 1:N+1
79          u(1,i) = max(0,min(1,(beta*lambda(1,i)*(-x(1,i))*x(7,i)*phi...
80              +beta*lambda(2,i)*x(1,i)*x(7,i)*phi ...
81              +(lambda(6,i)-lambda(5,i))*x(5,i)*phi*(theta2*x(2,i) ...
82              +theta1*x(3,i)))/(2*B1*(x(1,i)+x(2,i)+x(3,i)+x(4,i)))));
83          u(2,i) = max(0,min(1,(lambda(3,i)-lambda(4,i))*r0*x(3,i)/(2*B2)));
84      end
85
86      %updates Control
87      c = 0.8;
88      u = (1-c)*u + c*oldu;
89  %   for  i=1:N+1
90  %       if(u(1,i) > oldu(1,i))
91  %           u(1,i) = (1 - c) + oldu(1,i)*c;
92  %       else
93  %           u(1,i) = oldu(1,i)*c;
94  %       end
95  %       if(u(2,i) > oldu(2,i))
96  %           u(2,i) = (1 - c) + oldu(2,i)*c;
97  %       else
98  %           u(2,i) = oldu(2,i)*c;
99  %       end
100 %   end
101
102     %error bewteen old and new
```

```
103     tempu = min(delta*sum(abs(u),2)-sum(abs(oldu-u),2));
104     tempx = min(delta*sum(abs(x),2)-sum(abs(oldx-x),2));
105     templambda = min(delta*sum(abs(lambda),2)-sum(abs(oldlambda-lambda),2));
106     test  = min(tempu,min(tempx,templambda))
107
108     %The cost
109     %trapz(A1*oldx(2,:)+A2*oldx(3,:)+B1*oldu(1,:).^2+B2*oldu(2,:).^2)...
110     %    -0.1*oldx(1,N+1)- 0.1*oldx(4,N+1)
111     %trapz(A1*x(2,:)+A2*x(3,:)+B1*u(1,:).^2+B2*u(2,:).^2) ...
112     %    -0.1*x(1,N+1)-0.1*x(4,N+1)
113
114     k=k+1;
115 end
116
117
118 plot(t,x(3,:),t,x(7,:))
119  title('infectious')
120 legend('host','vector')
```

The Matlab code for the system of the status (state.m).

```
function dxdt = state(t,x,u,parameters)
parameters = num2cell(parameters);
[epsilon,gamma,beta,theta1,theta2,mu,Lambda,rho,delta0,r, r0,
   ...
   delta1, d, psi, zeta1, zeta2,alpha,phi,A1,A2,B1,B2] = deal(
      parameters{:});

dxdt = zeros(7,1);
dxdt(1) = rho + Lambda*(x(1)+x(2)+x(4)) + Lambda*(1-zeta1)*x
   (3)+psi*x(4)...
   -beta * phi*x(7)*x(1)*(1-u(1))/(x(1)+x(2)+x(3)+x(4)) - mu *
       x(1);
dxdt(2) = beta*phi*x(7)*x(1)*(1-u(1))/(x(1)+x(2)+x(3)+x(4)) +
   Lambda*zeta1*x(3)-d*x(2)-mu*x(2);
dxdt(3) = d*x(2) - (r + alpha + mu+r0*u(2))*x(3);
dxdt(4) = (r+r0*u(2))* x(3)- (psi + mu)*x(4);
dxdt(5) = delta0 + delta1*(x(5)+x(6)) + delta1*(1-zeta2)*x(7)
   ...
   - phi*theta1*x(3)*x(5)*(1-u(1))/(x(1)+x(2)+x(3)+x(4)) ...
   - phi*theta2*x(2)*x(5)*(1-u(1))/(x(1)+x(2)+x(3)+x(4)) -
      gamma*x(5);
dxdt(6) = phi*theta1*x(3)*x(5)*(1-u(1))/(x(1)+x(2)+x(3)+x(4))
   ...
   + phi*theta2*x(2)*x(5)*(1-u(1))/(x(1)+x(2)+x(3)+x(4))...
   + delta1*zeta2*x(7)-epsilon*x(6)-gamma*x(6);
dxdt(7) = epsilon*x(6)-gamma*x(7);
```

The Matlab code for the system of the adjoint (adjoint.m).

```
function dlambdadt = adjoint(t,lambda,x,u,parameters)
parameters = num2cell(parameters);
[epsilon,gamma,beta,theta1,theta2,mu,Lambda,rho,delta0,r, r0,
   ...
   delta1, d, psi, zeta1, zeta2,alpha,phi,A1,A2,B1,B2] = deal(
      parameters{:});

dlambdadt = zeros(7,1);
dlambdadt(1) = -(lambda(1)*(Lambda-mu+beta*(1-u(1))*x(1)*x(7)*
   phi/(x(1)+x(2)+x(3)+x(4))^2 ...
       -beta*(1-u(1))*x(7)*phi/(x(1)+x(2)+x(3)+x(4))) ...
   +lambda(2)*(beta*(1-u(1))*x(7)*phi/(x(1)+x(2)+x(3)+x(4))
      ...
       -beta*(1-u(1))*x(1)*x(7)*phi/(x(1)+x(2)+x(3)+x(4))^2)...
   +lambda(5)*(theta2*(1-u(1))*x(2)*x(5)*phi/(x(1)+x(2)+x(3)+x
      (4))^2 ...
       +theta1*(1-u(1))*x(3)*x(5)*phi/(x(1)+x(2)+x(3)+x(4))^2)
          ...
   +lambda(6)*(-theta2*(1-u(1))*x(2)*x(5)*phi/(x(1)+x(2)+x(3)+
      x(4))^2 ...
       -theta1*(1-u(1))*x(3)*x(5)*phi/(x(1)+x(2)+x(3)+x(4))^2))
          ;
dlambdadt(2) = -(A1+d*lambda(3) ...
   +lambda(2)*(-d-mu-beta*(1-u(1))*x(1)*x(7)*phi/(x(1)+x(2)+x
      (3)+x(4))^2) ...
   +lambda(1)*(Lambda+beta*(1-u(1))*x(1)*x(7)*phi/(x(1)+x(2)+x
      (3)+x(4))^2) ...
```

```
18      +lambda(5)*(theta2*(1-u(1))*x(2)*x(5)*phi/(x(1)+x(2)+x(3)+x
            (4))^2 ...
19          +theta1*(1-u(1))*x(3)*x(5)*phi/(x(1)+x(2)+x(3)+x(4))^2
                ...
20          -theta2*(1-u(1))*x(5)*phi/(x(1)+x(2)+x(3)+x(4))) ...
21      +lambda(6)*(-theta2*(1-u(1))*x(2)*x(5)*phi/(x(1)+x(2)+x(3)+
            x(4))^2 ...
22          -theta1*(1-u(1))*x(3)*x(5)*phi/(x(1)+x(2)+x(3)+x(4))^2
                ...
23          +theta2*(1-u(1))*x(5)*phi/(x(1)+x(2)+x(3)+x(4)));
24  dlambdadt(3) = -(A2+lambda(3)*(-alpha-mu-r0*u(2)-r)+lambda(4)
        *(r0*u(2)+r)...
25      +lambda(1)*((1-zeta1)*Lambda+beta*(1-u(1))*x(1)*x(7)*phi/(x
            (1)+x(2)+x(3)+x(4))^2)...
26      +lambda(2)*(zeta1*Lambda-beta*(1-u(1))*x(1)*x(7)*phi/(x(1)+
            x(2)+x(3)+x(4))^2)...
27      +lambda(5)*(theta2*(1-u(1))*x(2)*x(5)*phi/(x(1)+x(2)+x(3)+x
            (4))^2 ...
28          +theta1*(1-u(1))*x(3)*x(5)*phi/(x(1)+x(2)+x(3)+x(4))^2
                ...
29          -theta1*(1-u(1))*x(5)*phi/(x(1)+x(2)+x(3)+x(4)))...
30      +lambda(6)*(-theta2*(1-u(1))*x(2)*x(5)*phi/(x(1)+x(2)+x(3)+
            x(4))^2 ...
31          -theta1*(1-u(1))*x(3)*x(5)*phi/(x(1)+x(2)+x(3)+x(4))^2
                ...
32          +theta1*(1-u(1))*x(5)*phi/(x(1)+x(2)+x(3)+x(4)));
33  dlambdadt(4) = -(lambda(4)*(-mu-psi)+...
```

```
34    lambda(1)*(Lambda+beta*(1-u(1))*x(1)*x(7)*phi/(x(1)+x(2)+x
          (3)+x(4))^2+psi)...
35    -lambda(2)*(beta*(1-u(1))*x(1)*x(7)*phi/(x(1)+x(2)+x(3)+x
          (4))^2)  ...
36    +lambda(5)*(theta2*(1-u(1))*x(2)*x(5)*phi/(x(1)+x(2)+x(3)+x
          (4))^2  ...
37        +theta1*(1-u(1))*x(3)*x(5)*phi/(x(1)+x(2)+x(3)+x(4))^2)
              ...
38    +lambda(6)*(-theta2*(1-u(1))*x(2)*x(5)*phi/(x(1)+x(2)+x(3)+
          x(4))^2)...
39        -theta1*(1-u(1))*x(3)*x(5)*phi/(x(1)+x(2)+x(3)+x(4))^2);
40 dlambdadt(5) = -(lambda(5)*(-gamma+delta1-theta2*(1-u(1))*x(2)
       *phi/(x(1)+x(2)+x(3)+x(4))  ...
41    -theta1*(1-u(1))*x(3)*phi/(x(1)+x(2)+x(3)+x(4)))  ...
42    +lambda(6)*(theta2*(1-u(1))*x(2)*phi/(x(1)+x(2)+x(3)+x(4))
          ...
43    +theta1*(1-u(1))*x(3)*phi/(x(1)+x(2)+x(3)+x(4))));
44 dlambdadt(6) = -(lambda(6)*(-gamma-epsilon)+delta1*lambda(5)+
       lambda(7)*epsilon);
45 dlambdadt(7) = -(-gamma*lambda(7) +delta1*(1-zeta2)*lambda(5)+
       delta1*zeta2*lambda(6)...
46    -beta*lambda(1)*(1-u(1))*x(1)*phi/(x(1)+x(2)+x(3)+x(4))...
47    +beta*lambda(2)*(1-u(1))*x(1)*phi/(x(1)+x(2)+x(3)+x(4)));
```