Mathematical modeling and optimal control of a vector borne disease

by

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A thesis submitted to the

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National University of Sciences and Technology,
H-12, Islamabad, Pakistan

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Supervised by
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Abstract

This dissertation is concerned with mathematical modeling and optimal control of a vector borne disease. We derive and rigorously analyze mathematical models to better understand the transmission and spread of vector borne diseases. First, a mathematical model is formulated to evaluate the impact of biological control of a vector borne disease "malaria" by considering larvivorous fish as a sustainable larval control method. To evaluate the potential impacts of this biological control measure on malaria transmission, we investigate the model describing the linked dynamics between the predator-prey interaction and the host-vector interaction. The dynamical behavior with all possible equilibria of the model is presented. The model also exhibits backward bifurcation phenomenon which give rise to the existence of multiple endemic equilibria. The backward bifurcation phenomenon suggests that the reproductive number $\mathcal{R}_0 < 1$ is not enough to eliminate the disease from the population under consideration. So an accurate estimation of parameters and level of control measures is important to reduce the infection prevalence of malaria in an endemic region. Our control techniques for elimination of malaria in a community suggest that the introduction of larvivorous fish can in principle have important consequence for the control of malaria but also indicate that it would require a strong predator on larval mosquitoes. Then, a new epidemic model of a vector-borne disease which has both direct and the vector mediated transmissions is considered. The model incorporates bilinear contact rates between the mosquitoes vector and the humans host populations. Using Lyapunov function theory some sufficient conditions for global stability of both the disease-free equilibrium and the endemic equilibrium are obtained. We derive the basic reproduction number $\Re_0$

and establish that the global dynamics are completely determined by the values of $\Re_0$. For the basic reproductive number $\Re_0 < 1$, the disease free equilibrium is globally asymptotically stable, while for $\Re_0 > 1$, a unique endemic equilibrium exists and is globally asymptotically stable. The model is extended to assess the impact of some control measures, by using an optimal control theory. In order to do this, first we show the existence of the control problem and then use both analytical and numerical techniques to investigate that there are cost effective control efforts for prevention of direct and indirect transmission of disease. Finally, we present complete characterization and numerical simulations of the optimal control problem. In order to illustrate the overall picture of the epidemic, individuals under the optimal control and without control are shown in figures. Our theoretical results are confirmed by numerical simulations and suggest a promising way for the control of a vector borne disease.

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Abid Ali Lashari

Dedicated

To My Parents and Aino for all the joy they bring to my life

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Chapter 1

Introduction

Infectious diseases, also known as communicable diseases have long been recognized as a continuous threat to human beings all over the world. Mathematical modeling of the spread of communicable diseases has an increasing influence on the practice and theory of disease control and management [1]. Although vaccines have been developed for protection from many infectious diseases but infectious diseases are still a major cause of deaths of many people around the world. Recently, mosquito borne diseases are a major problem and are responsible for many life-threatening diseases such as malaria and dengue fever. The means of transmission of almost all infectious diseases from an infected to a susceptible individual is understood. However, the transmission interactions in a community are very complicated, hence it is very hard to understand the large size dynamics of the spread of disease without the proper structure of a mathematical model. Therefore, for understanding the underlying method by which diseases spread and cause epidemics is key for their control. This dissertation is concerned with the development of new mathematical models for the spread and control of a vector borne disease.

"Vector-borne disease" is the term commonly used to describe an illness caused by an infectious microbe that is transmitted to humans host by blood-sucking arthropods insects. The arthropods insects that serve as vectors include blood sucking insects such as mosquitoes, fleas, lice, biting flies and bugs [2]. It can, however, be directly transmitted from human to human through blood transfusions,

needle sharing and vertically from mother to child [3]. The term “vector” usually refers to any arthropod that transmits a disease from one host to other through feeding activity.

In recent years, vector-borne diseases have emerged as a serious public health problem in countries of the South-East Asia region including Pakistan [4,5]. Among these diseases dengue fever and malaria now occur in form of epidemics almost on an annual basis causing considerable morbidity and mortality. Dengue is spreading rapidly to newer areas and outbreaks occurring more frequently and explosively. A large outbreak in Lahore (Pakistan) this year took many lives [6]. Despite technological advances and increasing affluence in many regions, vector-borne infectious diseases remain amongst the most important causes of global health illness. The vectors of a number of infectious diseases, most prominent of which are malaria, dengue, Chikungunya, yellow fever, Japanese Encephalitic, St Louis Encephalitis, and West Nile Fever, caused by the West Nile Virus are mosquitoes [7]. There are also some other vectors like the assassin bugs, causing the Chagas disease, fleas transmitting the plague from its normal host to humans, or from human to human, and ticks which transmit the most prevalent vector-borne disease in North America.

Currently, dengue threatens up to 40% of the world’s population and there may be $50-100$ million cases annually [8]. A life-threatening vector borne disease "malaria" remains one of the world’s most prevalent vector-borne disease. Female blood sucker mosquito "Anopheles" is responsible for transmitting malaria between humans host population. Moreover, 40% of the world’s population live in malaria endemic regions. Malaria is responsible for killing about $700,000$ to 2.7 million people in a year, 75% of whom are children and belongs to poor countries specially in Africa [9]. Also due to continuous application of pesticides, mosquitoes have developed resistance to these chemicals which leads to an increase in the incidence of vector borne disease. Therefore, it is very important for us to understand the parameters which play a significant role in the transmission of the disease. Further, we need to develop effective control strategies for prevention of vector borne disease.

In this dissertation, we develop mathematical models to better understand the transmission mechanism and spread of vector borne diseases. The model presented will be a continuation of ideas from recent vector-host models [7, 10, 74, 98, 105]. We use ordinary differential equations to model the vector borne disease, where humans host and mosquitoes interact and transmit infection to each other. First, a mathematical model is formulated to evaluate the impact of a biological control of malaria by considering larvivorous fish as a sustainable larval control method. To evaluate the potential impacts of this biological control measure on malaria transmission, we investigate the model describing the linked dynamics between the predator-prey interaction and the host-vector interaction. For this, we will consider larvivorous fish as control variable in all possible breeding sites of mosquitoes. The model divides the human population into two classes namely: susceptible and infectious. The humans host population is recruited into the susceptible class by birth or immigration. Susceptible humans host contract the disease by interacting with infectious mosquitoes. Before re-entering the susceptible class, the infectious human host progress through an infectious class. Humans host leave the classes through natural mortality and emigration, and through a disease-related death out of the infectious class. There is one class of larvivorous fish and three classes for the mosquito population: larvae, susceptible, and infectious class of mosquitoes. Larvae enters the population at a rate gN_v, where g is egg laying rate of the mosquitoes. Larvae leaves the population through natural death, density dependent death, becoming adult with a maturation rate, and predation of larvae by larvivorous fish. Larvae becomes adult and enters the susceptible class. Then, mosquitoes gets infected by biting infectious humans and progress to the infectious class.

The above assumption and extensions leads to a system of five nonlinear ordinary differential equations with one dependent variable for each class. The different equilibria of the model are found and stability of these equilibria are discussed. The threshold quantity denoted by $\mathcal{R}_0$ is also defined for the model using the next generation operator approach. Numerical simulations are carried out and suggest that

the endemic equilibrium is stable for $\mathcal{R}_0 > 1$ and there is a trans-critical bifurcation at $\mathcal{R}_0 = 1$ where two branches of equilibrium points intersect and exchange stability. We prove that the bifurcation at $\mathcal{R}_0 = 1$ is supercritical (forward) and stable endemic equilibrium points exist for $\mathcal{R}_0 > 1$. For some values, there exists a subcritical (backward) bifurcation at $\mathcal{R}_0 = 1$ where stable positive endemic equilibrium points exist for $\mathcal{R}_0 < 1$. Thus, even when $\mathcal{R}_0 < 1$, disease can persist in the community in the presence of a locally asymptotically stable disease-free equilibrium. The model also exhibits backward bifurcation under certain restriction on parameters, which gives rise to existence of multiple endemic equilibria for $\mathcal{R}_0 < 1$. The backward bifurcation phenomenon suggests that the reproductive number $\mathcal{R}_0 < 1$ is not enough to eliminate the disease from the population under consideration. Therefore, an accurate estimation of parameters and level of control measures is important to reduce the infection prevalence of malaria in an endemic region.

Secondly, incorporating the fact that in human population the disease is not only spread by vector but also a human to human transmission (direct transmission) of the disease is possible. Based on this fact a new model with direct transmission in addition to vector mediated transmission is formulated to determine which factors are responsible for the spread of a vector borne disease. In this model, the human host population is split into different classes namely: susceptible host, exposed host, infectious host, and recovered (immune) host. People enters the susceptible class by birth or immigration. Susceptible host acquires infection not only by infectious vectors but also directly through humans by transfusion related transmission, blood transmission, transplantation related transmission, and needle-stick-related transmission. Then they enters the exposed, infectious, and immune classes. Each host leave the population through natural death, emigration out of each compartments, and infectious host leave the population by an additional disease-related death. Similarly, the vector population is subdivided in three classes: susceptible vector, exposed vector, and infectious vector. The mosquitoes vector are recruited into the susceptible class by birth. Vector gets infected after

sucking blood of an infectious host and then they enters the latent and infectious classes, respectively.

The model with direct transmission of the disease consists of a system of seven equations with four dependent variables representing host population and three dependent variables representing vector population. The disease free and endemic equilibrium points are found and the local and global stability of these equilibria are discussed. The basic reproduction number $\Re_0$ for this model is also defined. When $\Re_0 < 1$, the disease free equilibrium is asymptotically stable which means the introduction of a small number of infected individuals would not lead to an epidemic. When $\Re_0 > 1$, the unique positive endemic equilibrium exist and is asymptotically stable, which means the introduction of any infected individual would lead to an epidemic and disease persist in the community. Numerical simulations for various sets of parameters in terms of time series plots for each class are represented in detail. Then the model is further extended to incorporate some important epidemiological features, such as density-dependent birth rate in both host and vector populations and time dependent control functions. The extended model will then be used to determine cost-effective strategies for combating the spread of a vector-borne disease in a given population. In order to control the disease we use optimal control strategies by defining three control functions, one for vector-reduction strategies and the other two for personal (human) protection and blood screening, respectively. First, we show the existence of the control problem and then use both analytical and numerical techniques to investigate that there are cost effective control efforts for prevention of direct and indirect transmission of a vector borne disease. We also completely characterize the optimal control and compute the numerical solution of the optimality system using an iterative method. In order to illustrate the overall picture of the epidemic, individuals under the optimal control and without control are shown in figures.

1.1 How the vector borne disease spread

Vectors typically gets infected by a disease agent while feeding on the blood of infected birds, larger animals or humans and then the vector pass on the microbe to a susceptible human host or other animals. In almost all cases, an infectious microbe infect and multiply inside the vector body before the vector is able to transmit the disease to a susceptible host. The most deadly vector borne disease Malaria, Dengue, Chikungunya and West Nile virus kills million people annually and are carried by mosquitoes. Pool feeders such as the sand fly and black fly, vectors for Leishmaniasis and Onchocerciasis respectively, will make a hole in the host's skin, forming a small pool of blood from which they feed. Leishmania parasites then infect the host through the saliva of the sand fly. Triatomine bugs are responsible for the transmission of a trypanosome, Trypanosoma cruzi, which causes Chagas Disease.

An infected mosquito "Aedes Aegypti" which acts as the vector in transmitting the dengue virus, spread the virus (dengue) from one person to another when it takes a blood meal [4]. The mosquito gets infected by biting an infected person, then the mosquito vector pass the virus to a susceptible host. There is no way to tell which mosquito is carrying the dengue virus. Therefore people must protect themselves from all mosquito bites. Dengue viruses are common in Asia, Africa, Australia, the Pacific, and the United State. Dengue is most common in cities but can also be found in rural areas.

Malaria, which is a vector borne disease, is usually transmitted through the bite of an infected female "Anopheles" mosquito [9]. Malaria is not transmitted from one person to another person by casual contact, like common cold or flu. In the case of malaria, the incubation period for the disease (the period between infection and the beginning of symptoms) typically lasts between 10 days to four weeks.

West Nile Virus (WNV) is caused by the bite of an infected "Culex pipiens" mosquito vector [17]. Mosquitoes gets infected by biting an infectious bird. Infected mosquitoes vector then spread WNV to humans host and other animals by sucking

blood from their skin [18]. The most common amplifying hosts in the western hemisphere are American robin and the American crow, developing sufficient viral to spread the infection to mosquitoes which continue to pass the virus to other birds and also humans [19]. Birds can not transmit WNV directly to hosts, but in some cases WNV has been spread directly through blood transfusions and organ transplants, breastfeeding and even during pregnancy from mother to baby [20].

1.2 Historical perspective of vector borne disease

Vector borne diseases have been described in written history for thousands of years, including ancient Chinese, Indian, Greek and Roman writings. It was first recognized by workers in Queensland early in the 20th century that dengue is transmitted by the bite of an infected mosquito, particularly "Aedes Aegypti" a female mosquito. An estimated 50 million cases of dengue appears every year in the world [103]. In America, there were more than $616,000$ cases of dengue occurs in 1998, of which $11,000$ cases are of a life threatening form of dengue. Another vector borne disease "chikungunya" virus was first detected in 1953 in Tanzania (Africa) [13].

Malaria was found over $4,000$ years ago for the first time. The symptoms of malaria were discussed in ancient Chinese medical writings, and the disease was widely recognized in Greece by the fourth century. In 1880, Charles Louis Alphonse Laveran, a French army surgeon stationed in Constantine, Algeria, was the first to notice parasites in the blood of a patient suffering from malaria. For this discovery, Laveran was awarded the Nobel Prize in 1907.

An estimated $110 - 115$ million cases of malaria were reported in $1948 - 1950$. In $1950 - 1956$ some malaria control programme started and during $1960 - 1969$, tremendous success in eradicating the malaria has been achieved. But the control strategies failed to catch the increasing tendency of P. falciparum infection. In the start, there were 19.6% total infected individuals in 1970 but the ratio of infected increases to 41.3% in 1991.

WNV was identified for the first time in the United States in New York in 1999 [21], during an outbreak involving humans, horses, and birds. After this the virus has kept spreading rapidly to most parts of the United States [22]. In the United States, between 1999 and 2001, WNV was related with 149 cases of neurological diseases in humans host, 814 cases of equine encephalitis and 11,932 mortalities in the avian population. In 2003, about 9858 WNV cases in human host of which 14 deaths were reported [23].

1.3 Impact of vector borne disease on public health and economic

Vector borne disease and poverty are intimately connected. Estimating the economic impact of a vector borne disease is important in order to prioritize resources for research, prevention, and control. The research shows that the average family cost of treating on one child is approximately $61 including direct and indirect costs [24]. On average, the largest expenses were those related to the initial visit at a local general doctor, the hospital bill from children's hospital and loss of income for the parents. Malaria is the main cause of poverty in Indian subcontinent, Sri Lanka and Africa. The countries with high incidence of malaria are among the poorest in the world, and usually have very low economic growth. Malaria is a large expense for a family and can rightly be considered as a substantial socioeconomic burden in the world. More studies are needed to estimate the amount of the expenses related to a vector borne disease. It is effecting the way of living of Africans and is also preventing the improvement to live a standard life for future generations. Each year the economic growth of Africa is reduced by $1.3 million [25].

There was an outbreak of dengue fever in 1981 in Cuba and the estimated cost of this epidemic was approximately $103 million. This cost include the cost of control measures, hospitalization, the loss of productivity and salaries of 344,203 adult dengue victims [11]. Durig a dengue epidemic in Thailand (1994), about

51, 688 reported cases of dengue patients were reported with estimated cost of $6.9 million. Disability-adjusted life years are an age-weighted estimated measure of years of life lost from premature death, and years of life lived in less than full health. Globally there are estimated to be 50 million cases of dengue each year, equal to 528, 000 disability-adjusted life years [12]. In Thailand (2001), the impact of dengue fever on the relatives of victims hospitalized at the Kamphaeng Phet provincial hospital with confirmed dengue cases was assessed. It was estimated that each family loss approximately $61, which is more than the average monthly income in Thailand. The disability-adjusted life years were counted by a family level survey, which resulted in an estimated 427 disability-adjusted life years per million population in 2001.

1.3.1 Signs and symptoms

A vector borne disease "dengue fever" generally starts with a high fever, severe headache, rash on skin, joint and muscle pain. The first symptom of the disease appears about 5 to 7 days after a host is bitten by an infected mosquito vector. Usually rash on the skin appears 3 to 4 days after the start of the fever [9]. The disease can last up to 10 days, but the complete recovery from the disease can take a month.

The most common symptoms of malaria are similar to the flu. The human host may have: a headache, aching muscles, and weakness. A day or so later, the body temperature may rise (up to 40 degrees Celsius) and the host may have: a fever, shivers, mild chills, severe headache, vomiting, diarrhoea, and loss of appetite [16].

Symptoms of chikungunya start with a fever within 5 to 6 days after the bite of an infected mosquito. Symptoms include high-grade fever, severe headache, rashes on skin, severe joint and muscle pain [14]. Although not generally life threatening, symptoms include painful arthralgias that can persist for months and even years.

About one in 150 people infected with WNV will develop severe illness. The severe symptoms can include high fever, headache, neck stiffness, stupor, disorientation, coma, tremors, convulsions, muscle weakness, vision loss, numbness and

paralysis [17]. These symptoms may last several weeks, and neurological effects may be permanent. In case of mild illness, victim may have a fever and muscle aches and sometimes a skin rash. In the sever form of the disease, the infection may spread to the nervous system which results in a high fever, sever headache, and stiff neck. Children and young individuals are less likely to have severe symptoms than older adults.

1.3.2 How soon after bite do symptoms appear

The symptoms of dengue usually appears on averages 4 to 6 days after an individual is bitten by an infectious mosquito vector. If a person is infectious, he will be a source of dengue virus for about 6 days [103]. The symptoms of malaria, which often appear about 9 to 14 days after the bite of an infectious mosquito [9, 16].

In case of febrile stage of WNV the symptoms appears after 2 to 8 days. But generally symptoms of WNV appears about 2 to 15 days after exposure with an infectious mosquito [65]. The symptoms of chikungunya appears about $2-12$ days after an interaction with a vector carrying chikungunya [14].

1.4 Basic epidemiology of vector borne disease

Epidemiology is the branch of science that describes and explains the spread of diseases in a population. For example, who has the disease, how seriously, and when, where, and why he (she) gets the disease? The epidemiology of some of the life-threatening vector borne diseases is discussed below.

1.4.1 Malaria

Malaria is a potentially fatal disease caused by an infection with Plasmodium parasites. In most cases, the disease is transmitted through the bite of an infected female Anopheles mosquito, a vector for malaria. The Anopheles mosquito inserts its delicate mouthpart under the skin and feeds on its host's blood. The parasites which the mosquito carries are usually located in its salivary glands [16]. Therefore,

the parasites are transmitted directly into the host's blood stream. Malaria is a leading cause of death and disease worldwide, especially in developing countries. Each year, an estimated 300 to 500 million cases occur, and more than 1 million people die of the disease annually [9].

1.4.2 Dengue

Dengue fever, together with associated dengue haemorrhagic fever, is the world's fastest growing vector borne disease and the most important vector-borne viral disease affecting humans. The two species of the vector transmitting virus are "Aedes Aegypti" and "Aedes Albopictus" [63]. The mosquitoes that transmit dengue live among humans and breed in fresh water particularly in old tires, flower pots, old oil drums and tree hollows in urban areas [62]. The principal vector mosquito, aedes aegypti, prefers to feed on humans during the day time and most frequently is found in or near human habitations. There are two peak periods of biting activity, in the morning for several hours after daybreak and in the late afternoon for several hours before dark. The mosquito may feed at any time during the day [98].

1.4.3 West Nile virus

West Nile virus (WNV) is spread by the bite of infected vectors and infects humans, birds and horses. The vectors "Culex pipien" spread WNV and usually breeds rapidly in bottles, tanks, cans and gutters. A victim of WNV may cause inflammation of the brain, problems with the senses and polio like paralysis [21,64].

1.4.4 Chikungunya

Chikungunya is a third primatophilic virus (family Togaviridae) that is enzootic in African and perhaps Asian forests and transmitted by primatophilic mosquitoes. Transmission was part of a pandemic that spread through southern Asia, Indonesia and the Philippines. There have been an estimated 1.2 million cases in India alone, though apart from the highly publicised outbreaks in the Indian ocean there

has been little attention to this in the world press. The chikungunya outbreak highlighted a second forest vector species "Aedes Albopictus" that has adapted to the urban environment [14].

1.5 How can vector borne disease be prevented

There is no vaccine to protect individuals against most of the vector borne diseases [98]. Prevention centers on self protection from vectors bites when visiting the areas where a vector borne disease occurs. Eliminating mosquito breeding sites in these areas is another key prevention measure. Public health education forms an increasingly important component of management programs and initiatives, raising awareness about individual and communal actions that may control vectors, their breeding sites, prevent disease transmission, and provide access to treatment. Beside from directly impacting disease control, health education gives individuals greater control over their lives and therefore promotes cultural services.

1.5.1 Avoid mosquito bites when traveling in tropical areas

There is no vaccine for mosquito borne disease, one has to use alternative prevention measures. The most useful prevention measures include use of mosquito repellents on skin, mosquito nets and clothing. Before going outdoors during mosquitoes biting times, try to use repellents on parts of your body which are not covered with clothes. Use mosquito nets at the time of sleep if sleeping place is not screened. If any symptoms of a vector borne disease appears, immediately consult a doctor.

1.5.2 Eliminate mosquito breeding sites near your dwelling

Use spray and other chemicals at vectors breeding sites near your dwellings. Do not let the water to stay near your dwellings and throw away all items that can collect the water, especially old tires, uncovered barrels, buckets, flower pots, and cans. Daily change the water in pet animal water containers.

Chapter 2

Basic Epidemiology and Preliminaries

2.1 Introduction

Epidemiology deals with the study of disease in a population. Mathematical epidemiology uses mathematics to formulate the spread of epidemics, so that they can be understood and countered more effectively. It is well known that the spread of several infectious diseases in a population is one of the major problems in the modern society. Infectious diseases are the cause of the mortality of million peoples as well as the expenditure of a vast amount of money in health care and control of the disease [1]. Thus, it is essential that adequate attention must be paid to study and control of such infectious diseases. The transmission of a communicable disease in a population usually depends on: (i) the susceptible individuals, (ii) the exposed individuals, (iii) the infectious individuals, (iv) the recovered (removed) individuals and (v) the mode of transmission of the disease. In the following, we will provide brief information about transmission of an infectious disease [96].

- **Susceptible**: Those individuals in a population who are at risk of becoming infected by a disease.

- **Exposed**: Those individuals in a population who are infective but depending

on the type of the disease, may or may not transmit the infection.

- **Infectious**: Those collection of individuals who are already infected and can transmit the infection to other individuals.

- **Recovered**: Those individuals who have had the disease but now they are immune and may not catch or transmit the disease, either because they are no longer infectious, are naturally immune or have died.

- **Transmission** : The passing of a communicable disease from an infected host individual to a conspecific individual, regardless of whether the other individual was previously infected.

2.2 Compartmental modeling

Mathematical models are important tools in basic scientific research in many areas of biology, ecology, evolution, toxicology, immunology and natural resource management biology. The result obtained from analysis and simulation of epidemic models are used to test and extend biological theory, and to suggest new hypotheses or experiments. A lot of literature related to epidemiological modeling consider deterministic modeling where the population is divided into different classes called compartments based on their epidemiological status e.g. susceptible, infectious, recovered. The dynamics of several infections in these compartments are represented by differential equations. The categories in an SIR (Susceptible-Infected-Removed) models are assumed to be mutually exclusive and the transitions only occur from S to I and I to R. The number of compartments included in the model depends on the type of the disease. In case where susceptible individuals become infectious and then recover from the infection and recovered individuals directly go back to the corresponding susceptible class, then one needs SIS (Susceptible-Infected-Susceptible) models to represents this dynamics of the disease. More realistically, to model a disease dynamics in which people become infectious and recover later with the permanent acquired immunity to future infections after contracting the

disease, one need SIR model. If people recover with temporary immunity, so that they become susceptible again, then the simplest model to represents this dynamics is called an $SIRS$ (Susceptible-Infected-Removed-Susceptible) model. The SI (Susceptible-Infected) models are used if people do not recover from the disease. Generally, SIR models are suitable for viral diseases like, mumps, smallpox and measles, whereas SIS models are used for disease spread by bacterial agent such as plague, sexually transmitted diseases and meningitis. On the other hand, $SEIR$ (Susceptible-Exposed-Infected-Removed) model are appropriate for a disease transmission when infected (exposed) people go through a latent period (infected, but not yet infectious) before becoming infectious (disease like measles). Complete interaction and transfer diagram of some of the more common models which represent infectious disease dynamics is depicted in Figure (2.1).

Studies of the dynamical properties of such models usually consist of finding constant equilibrium solutions with conducting linearized analysis to determine their stability with respect to small disturbances. In mathematical modeling of the spread of infectious diseases, one needs an epidemic model to describe the behavior of disease which occur for a short period of time, while endemic models are needed to study the dynamics of a disease for long period of time [32].

2.3 The incidence function

The incidence in mathematical models of infectious disease is the rate at which susceptible individuals become infectious. If the time unit is day, then the daily contact rate denoted by $\beta(N)$ is defined as the average number of contacts of an infective per day sufficient to transmit the disease with other individuals. As $S(t)/N(t)$ is the susceptible fraction of the population, where $S(t)$ and $N(t)$ denotes the susceptible and the total number of individuals, respectively, in a population. Thus $\beta S(t)/N(t)$ is the average number of transmissions of infection per infective per unit of time and $\beta I(t)/N(t)$ is the average number of contacts with infectious individuals a susceptible individual makes per unit time. Thus, the number of new

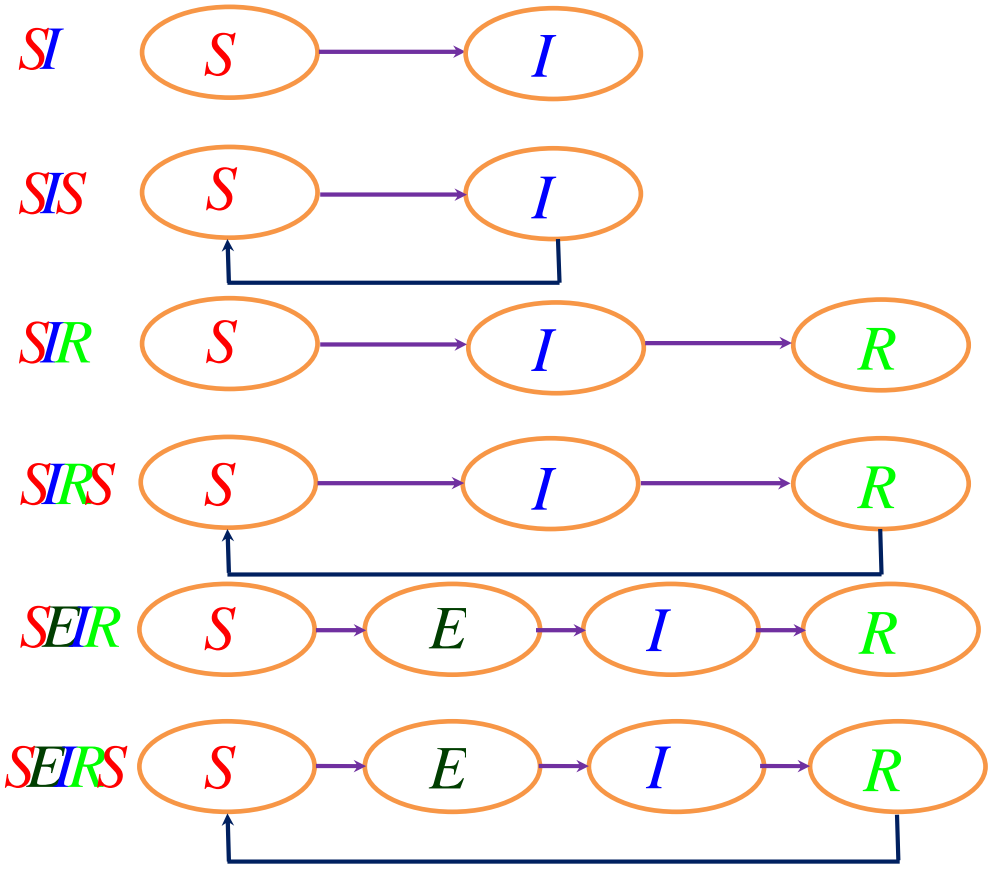

Figure 2.1: The transfer diagram for common models of infectious diseases with, the susceptible class S, the exposed class E, the infectious class I, and the recovered class R.

infections arising from the susceptibles is ξS, where $\xi = \beta(N)I/N$ is called the force of infection. If $\beta(N) = \beta N$ (that is, the contact rate depends on the size of the total population), then ξS is called mass action (bilinear) incidence [100]. When $\beta(N) = \beta$, a constant, then ξS is referred to as standard incidence function. The standard incidence $\beta S(t)I(t)/N(t)$, which is the average number of transmissions of infection by all infected individuals $I(t)$ per unit of time. When compared to the standard incidence, the simple mass action incidence implies that $\beta = \lambda/N$. Thus in case of mass action incidence β is proportional to the size of population.

2.3.1 The epidemic SIR model

The SIR (Susceptible-Infected-Recovered) epidemic model is given by the following system of differential equations

$$\begin{cases} \dfrac{dS}{dt} = -\dfrac{\beta SI}{N}, & S(0) \geq 0, \\ \dfrac{dI}{dt} = \dfrac{\beta SI}{N} - \gamma I, & I(0) \geq 0, \\ \dfrac{dR}{dt} = \gamma I, & R(0) \geq 0, \end{cases} \tag{2.3.1}$$

where N is the size of the total population, β is the contact rate and $1/\gamma$ is an average infectious period for a given individual. The first SIR epidemic model was developed by Kermack and McKendrick in 1927 [38] to track disease outbreaks occurring over a short time span in a closed population of constant size.

2.3.2 The endemic SIR model

The classic SIR endemic model [96] with births and deaths is given by the following system of differential equations:

$$\begin{cases} \dfrac{dS}{dt} = \mu N - \dfrac{\beta SI}{N} - \mu S, & S(0) \geq 0, \\ \dfrac{dI}{dt} = \dfrac{\beta SI}{N} - \gamma I - \mu I, & I(0) \geq 0, \\ \dfrac{dR}{dt} = \gamma I - \mu R, & R(0) \geq 0. \end{cases} \tag{2.3.2}$$

The endemic model (2.3.2) is very much the same as the model (2.3.1) mentioned above, except that it incorporates recruitment of newly born individuals into the susceptible compartment and natural deaths in susceptible, infected and recovered class at rate μS, μI, and μR, respectively. Here $1/\mu$ is an average lifetime for a given individual. A model for disease with an exposed class and permanent immunity against re-infection would be called an $SEIR$ model and in case of a disease in which individuals can return to the susceptible class again after infection (or after immunity) would be called an SIS (or $SIRS$) model.

2.4 Brief literature survey on modeling of infectious diseases

In 1760 Daniel Bernoulli constructed a model to describe the disease dynamics of smallpox [1]. The mathematical theory of infectious disease pioneered by Ross, Kermack and McKendric, has been an important tool for the establishment of vaccination strategies. In 1906 Hamer formulated and analyzed a discrete time model to understand the recurrence of measles epidemics [26]. The model formulated by Hamer may have been the first to assume that the incidence of infection depends on the product of the susceptible and infectious individuals. Ross was interested in the spread and control of a vector borne disease malaria and he developed mathematical models for malaria as a host-vector disease in 1911 [55].

There have been many contributions involving modeling of specific infectious disease such as influenza [27], rubella [28] and AIDS [29]. A tremendous variety of models have now been formulated, rigourously analyzed, and applied to infectious diseases. The recent models [2, 34, 49–51] have involved important features such as regular loss of vaccine, passive immunity, disease related immunity, infection stages, disease transmission from mother to child, disease vectors, macro-parasitic loads, sexual mixing, vaccination and quarantine. Some important models to explain the epidemiology of infectious human disease such as measles, whooping cough, chickenpox, diphtheria, malaria, smallpox, onchocerciasis, gonorrhea, filariasis, rabies,

herpes and syphilis have been formulated (see [38–40] and the references therein).

The spread of an infectious disease in human population, generally, depends upon various factors such as the number of infectives, susceptibles, mode of transmission, social and economic factors, environmental, ecological and geographical conditions [30]. In the case of indirect transmission bacteria enter the environment and then contaminate food or water which may be later consumed by susceptibles, while in direct transmission susceptibles gets infected through meeting (kissing, shacking hands etc) with infectives [31, 35]. Many infectious disease like flu, smallpox, measles are spread by direct contact of susceptible and infectious individuals, while diseases like tuberculosis, typhoid, cholera etc are transmitted indirectly.

The compartmentalized deterministic model of an epidemic is based on modeling the rates involved in transmission of the disease, contact between members in the population, population growth, and rates of recovery. The dynamical behavior and role of optimal control theory using both bilinear incidence and standard incidence rate of an SIR model can be found in [1,33,34]. Trottier and Phillippe [36,37] discuss deterministic modeling such as SIR models, and the type of sensitivity analyses and repercussions of such tactics as immunization at birth. The stability analysis and asymptotic behavior of epidemic models have been investigated by many authors some of them are Huang et al [41], Dietz [42], Hethcote [43] and Kamper [44]. Hethcote discussed qualitative analysis of an SIR models by including several interaction terms. In [33, 36] the authors presented deterministic SIR models and analyzed the qualitative analysis.

In the modeling of the spread of infectious diseases, the interplay between epidemiological and demographic effects has been the central theme. Models with demographic structure have been analyzed by considering variable population, which involve birth, death and immigration rates [45]. In addition, mathematical models of sexually transmitted disease with vertical transmission, in which some of the children borne to infectious mothers are infectious, have been proposed and analyzed in [46, 47].

In recent years, epidemic models have been studied by many authors [33, 34,

50, 106, 107]. In order to model disease transmission process several authors have proposed many nonlinear incidence rates [48]. With these types of modified nonlinear incidence rates, many interesting and complicated transmission dynamics of epidemics such as multiple equilibria, periodic orbits and Hopf bifurcations have been studied [49]. The outbreak of infectious diseases causes deaths of millions of people as well as expenditure of enormous amount of money in health care and diseases control. It is, therefore, essential that attention must be paid to stop the spread of such infectious diseases. A number of studies in the literature have been made to study the role of vaccination and treatment on the spread of infectious diseases [50, 51].

Recently, some researchers reviews mathematical modeling of the spread of infectious disease and applied optimal control theory to control the spread of infectious diseases (see [52, 53, 107] and references therein). The optimal control efforts are used to limit the spread of the infectious diseases from the population. The analyzes of optimal control in mathematical models reveal the possibilities to develop strategies that manipulate the level of vaccination and treatment efforts [34]. By treating and vaccinating the peoples in a community at an appropriate time, it is possible to either reduce or eradicate the disease from the population.

Modeling the transmission of malaria, a vector borne disease, started in nineteenth century [54, 55]. Ross [56] constructed a mathematical model of a vector borne disease by proving that if the mosquito vector population density is decreased below a threshold, the rate of getting new infections would be less than the rate at which infected humans recover leading to the elimination of the disease from the community. The characteristic of variable population size and mortality due to disease are often ignored. Vector-host epidemic models with variable population and disease induced death rate have been proposed and rigorously analyzed in [57, 106] whereas models using the assumption of total constant population without disease related mortality are studied in [58, 59]. Some of the authors considered latent and infectious classes [58, 60] in a vector borne disease. No attention is paid to capture the effect of the length of partial immunity. The effect of partial human

immunity is very important in the transmission dynamics of a vector borne disease particularly malaria and is mathematically analyzed in a model proposed in [61]. The mathematical models for the spread of dengue and West Nile virus have been studied in [62, 63] and [64, 65], respectively. A dynamic model for dengue disease transmission is presented in [66], described by a set of nonlinear differential equations, that depend on the dynamics of the dengue mosquito vector, the number of infectious human host and host's motivation to combat the mosquito. Furthermore, an application of optimal control theory is also presented by considering an objective functional that depends on the costs of educational, sanitation campaigns and the costs related to medical treatment of the infectious human host.

2.5 Stability theory

In this section, we treat the stability concepts and conditions of autonomous systems consisting of differential equations. The most useful and general approach for studying the stability of nonlinear control systems is the theory introduced in the late 19th century by the Russian mathematician Alexandr Mikhailovich Lyapunov [95]. The aim of this section is to discuss the Lyapunov stability theory and its use in the analysis of nonlinear systems. Before addressing the main problems of defining and determining stability, let us discuss some relatively simple background issues.

2.5.1 Nonlinear dynamical systems and equilibrium points

A nonlinear autonomous dynamical system is the set of nonlinear differential equations expressing the rate of change of state in terms of state and time which does not explicitly involve time [95]. Generally mathematical models of infectious diseases are described by autonomous systems of differential equations, so we consider n-dimensional system of nonlinear first order ordinary differential equations in R^n,

$$\dot{\mathbf{X}}(t) = \mathbf{F}(\mathbf{X}(t)), \quad \mathbf{X}(t_0) = \mathbf{X}^0, \tag{2.5.1}$$

where the dot on $\mathbf{X}$ denotes the derivatives with respect to time t and $F : R^n \to R^n$ is $n \times 1$ nonlinear vector function continuous in $\mathbf{X}$, and $\mathbf{X}$ is the $n \times 1$ state vector. In terms of components, above system (2.5.1) can be written as

$$\begin{cases} \dot{x}_1 = f_1(x_1, x_2, ..., x_n), & x_1(t_0) = x_1^0, \\ \dot{x}_2 = f_2(x_1, x_2, ..., x_n), & x_2(t_0) = x_2^0, \\ \quad \vdots & \\ \dot{x}_n = f_n(x_1, x_2, ..., x_n), & x_n(t_0) = x_n^0, \end{cases}$$

where, each f_i for $i = 1, 2, ..., n$ is continuously differentiable function. A solution $\mathbf{X}(t)$ of the system (2.5.1) usually corresponds to a curve in state space as t varies from zero to infinity.

A linear system of differential equation is given by

$$\dot{\mathbf{X}}(t) = A\mathbf{X}(t) \tag{2.5.2}$$

where A is an $n \times n$ matrix. The linear system (2.5.2) is a special class of nonlinear system.

Definition 2.5.1. A solution $\mathbf{X}^*$ is called an equilibrium solution, steady state or a critical point of the system (2.5.1) if $\mathbf{X}^*$ satisfies $\mathbf{F}(\mathbf{X}^*) = 0$ [96].

2.5.2 Local stability in first order systems

In this subsection, we present some basic definitions to understand the behavior of the solutions near equilibria. Before we can generalize these observations to nonlinear systems, we need some definitions from dynamical systems theory (see Perko [94]).

Definition 2.5.2. (i) A steady state $\mathbf{X}^*$ is called stable if a solution which starts nearby stays nearby. More formally: an equilibrium solution $\mathbf{X}^*$ of the system (2.5.1) is said to be locally stable, if for each $\epsilon > 0$ there exists a $\delta > 0$ such that for any arbitrary solution $\mathbf{X}(t)$ of the system (2.5.1) satisfying the condition $||\mathbf{X}(t_0) - \mathbf{X}^*|| < \delta$, the inequality

$$||\mathbf{X}(t) - \mathbf{X}^*|| < \epsilon \tag{2.5.3}$$

holds for all $t \geq t_0$. Here, $||\cdot||$ denotes the Euclidean vector norm.

(ii) A steady state $\mathbf{X}^*$ is called asymptotically stable if it is stable and every solution starting near the equilibrium point converges to that equilibrium point. Mathematically: if

$$||\mathbf{X}(t) - \mathbf{X}^*|| \to 0 \quad \text{as} \quad t \to \infty \tag{2.5.4}$$

then the solution $\mathbf{X}^*$ is called locally asymptotically stable.

Roughly speaking an equilibrium $\mathbf{X}^*$ is stable if every solution starting near $\mathbf{X}^*$ stay nearby. If in addition nearby solution approach $\mathbf{X}^*$ as $t \to \infty$, then it is asymptotically stable.

2.5.3 Routh-Hurwitz criterion

A stable linear system requires that all the roots of the characteristic equation have negative real parts. In fact, the method determines only if there are roots that lie outside of the left half plane, it does not actually compute the roots. Routh-Hurwitz stability criterion is a test to ascertain without computing the roots, whether or not all roots of a polynomial have negative real parts. Routh-Hurwitz criterion gives the necessary and sufficient conditions for all roots of the characteristic polynomial to have negative real parts thus implying asymptotic stability [96].

Routh-Hurwitz Theorem 2.5.3. *Consider the characteristic equation*

$$|\lambda I - A| = \lambda^n + b_1\lambda^{n-1} + ... + b_{n-1}\lambda + b_n \tag{2.5.5}$$

determining the n eigenvalues λ of a real $n \times n$ square matrix A, where I is the identity matrix. Then all the eigenvalues λ have negative real parts iff

$$\triangle_1,\ \triangle_2, ...\triangle_n > 0, \tag{2.5.6}$$

where

$$\triangle_k = \begin{vmatrix} b_1 & 1 & 0 & 0 & 0 & 0 & \dots & 0 \\ b_3 & b_2 & b_1 & 1 & 0 & 0 & \dots & 0 \\ b_5 & b_4 & b_3 & b_2 & b_1 & 1 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ b_{2k-1} & b_{2k-2} & b_{2k-3} & b_{2k-4} & b_{2k-5} & b_{2k-6} & \vdots & b_k \end{vmatrix}.$$

Jacobian Matrix 2.5.4. Consider the function $\mathbf{F} : R^n \to R^n$, where $\mathbf{F}$ is the system as defined in (2.5.1). The variational matrix or Jacobian matrix of $\mathbf{F}(x_1, x_2, ..., x_n)$ denoted by $\mathcal{J}_{\mathbf{F}}$ is defined as follows

$$\mathcal{J}_{\mathbf{F}}(x_1, ..., x_n) = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \dots & \frac{\partial f_1}{\partial x_n} \\ \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \vdots & \frac{\partial f_n}{\partial x_n} \end{bmatrix},$$

where $\frac{\partial f_i}{\partial x_i}$ are partial derivatives of f_i with respect to x_i for $i = 1, 2, ..., n$. The importance of the Jacobian matrix lies in the fact that it represents the best linear approximation to a differentiable function near an equilibrium point [95].

2.6 Method for local stability of equilibria

Often one is able to determine the stability properties of the solution of the system (2.5.1) from the behavior of a linearized system. The linearization method help us to find the local stability of a nonlinear system around an equilibrium point.

Consider the autonomous system (2.5.1), and assume that $\mathbf{F}(\mathbf{X})$ is continuously differentiable. Then the system (2.5.1) can be expanded by Taylor series as follows

$$\dot{\mathbf{X}} = \left(\frac{\partial \mathbf{F}}{\partial \mathbf{X}}\right)_{\mathbf{X}^*=\mathbf{0}} \mathbf{X} + \mathbf{F}_{\text{Hig}}(\mathbf{X}) \tag{2.6.1}$$

where $\mathbf{F}_{\text{Hig}}(\mathbf{X})$ denotes the higher-order terms in $\mathbf{X}$. Note that the above Taylor expansion starts directly with the first-order term, due to the fact that $\mathbf{F}(\mathbf{0}) = \mathbf{0}$, which is the trivial equilibrium point of the system (2.5.1). This can always be achieved by displacing the origin into the equilibrium point. If the higher-order terms are dropped, then an approximate linear differential system is obtained

$$\mathcal{J}_{\mathbf{F}} = \left(\frac{\partial \mathbf{F}}{\partial \mathbf{X}}\right)_{\mathbf{X}^* = \mathbf{0}} \tag{2.6.2}$$

where $\mathcal{J}_{\mathbf{F}}$ is the variational matrix of $\mathbf{F}$. Then, the system

$$\dot{\mathbf{X}} = \mathcal{J}_{\mathbf{F}}\mathbf{X} \tag{2.6.3}$$

is called the variational system or the linearization of the original nonlinear system with respect to the soltion $\mathbf{X}^* = \mathbf{0}$.

The following theorem is referred to as the theorem on stability by linearization.

Theorem 2.6.1. *The equilibrium $\mathbf{X}^*$ of the system (2.5.1) is asymptotically stable if the Jacobian matrix $\mathcal{J}$ at the equilibrium is stable, that is, if the real parts of all its eigenvalues are negative otherwise the equilibrium is unstable if the real part of at least one eigenvalue is positive.*

A drawback of this theorem is that it does not settle the stability problem in the critical case where in addition to eigenvalues with negative real parts, we have eigenvalues with a zero real part. The method that has the possibility of solving these problems is called Lyapunov's direct method, or the method of Lyapunov functions. A function (Lyapunov function) satisfying some properties is constructed to prove the stability or asymptotic stability of an equilibrium in a given region. We shall now turn our attention toward the Lyapunov stability.

2.6.1 Lyapunov functions and LaSalle's invariance principle

Definition 2.6.2. Let $W \subset R^n$ be an open set containing the origin. A real valued function $V : W \to R$ with continuous first order partial derivatives is said to be positive definite on the set W if the following conditions hold:

- $V(\mathbf{X}) > 0$ for all $\mathbf{X} \in W$ with $\mathbf{X} \neq \mathbf{0}$.
- $V(\mathbf{0}) = 0$.
- V is called positive semi-definite if $V(\mathbf{X}) > 0$ for $\mathbf{X} \in W$.

Definition 2.6.3. A scalar positive definite function V with continuous first order partial derivatives in an open neighborhood W of the origin is called a Lyapunov function for the differential system (2.5.1) if $\dot{V} \leq 0$ for all $\mathbf{X} \in W - \{\mathbf{0}\}$ [95].

We formulate a fundamental theorem of Lyapunov's direct method [95].

Theorem 2.6.4. *(Lyapunov's stability Theorem). Let $\mathbf{X}^* = \mathbf{0}$ be a fixed point of the autonomous system $\dot{\mathbf{X}} = \mathbf{F}(\mathbf{X})$, $\mathbf{X} \in R^n$ and let $V : W \subset R^n \to R$ be continuously differentiable positive definite function in some neighborhood W of $\mathbf{X}^* = \mathbf{0}$.*

- *If $\dot{V}(\mathbf{Z}) \leq 0$ for $\mathbf{X} \in W - \{\mathbf{0}\}$, then $\mathbf{0}$ is stable.*
- *If $\dot{V}(\mathbf{X}) < 0$ for $\mathbf{X} \in W - \{\mathbf{0}\}$, then $\mathbf{0}$ is asymptotically stable.*
- *If $\dot{V} > 0$ for $\mathbf{X} \in W - \{\mathbf{0}\}$, then $\mathbf{0}$ is unstable.*

Definition 2.6.5. The equilibrium solution $\mathbf{X}^*$ of the system (2.5.1) is globally asymptotically stable, if every solution $\mathbf{X}(t)$ of the system (2.5.1) corresponding to an arbitrary choice of initial conditions satisfies

$$\lim_{t \to \infty} \mathbf{X}(t) = \mathbf{X}^*. \tag{2.6.4}$$

Definition 2.6.6. The set $H \subset R^n$ is said to be invariant with respect to the system (2.5.1) if for any initial value $\mathbf{X^0} \in H$ implies that the solution $\mathbf{X}(\mathbf{X^0}, t) \in H$ for all time t in the domain of the solution $\mathbf{X}(t)$. It is said to be positively invariant if $\mathbf{X^0} \in H$ implies $\mathbf{X}(\mathbf{X^0}, t) \in H$ for $t > 0$. That is if every solution starting in H remains in H for all t.

Theorem 2.6.7. *(LaSalle's Invariance Principle): Let $\Omega \subset H$ be a compact set that is positively invariant with respect to the system (2.5.1). Let $V : D \to R$ be a continuously differentiable function such that $\dot{V}(\mathbf{Z}) \leq 0$ on Ω. Let E be the set of all points in Ω such that $\dot{V}(\mathbf{Z}) = 0$. Let M be the largest invariant set in E. Then every solution starting in Ω approaches M as $t \to \infty$.*

Note that, in the above theorem, the word "largest" is understood in the sense of set theory, i.e., H is the union of all invariant sets.

2.7 Basic reproduction number

In epidemiology, the threshold for many mathematical models is the basic reproduction number of an infection which is defined as the expected number of secondary infections arising from a single infected case in a population with no immunity to the disease during the entire infectious period [1]. The basic reproductive number, usually denoted by R_0, is a key concept in epidemiology, and is inarguably one of the foremost and most valuable ideas that mathematician thinking has brought to epidemic theory. It tells us how easy or difficult it is to eliminate an infection from a population. Most importantly, R_0 serves as a threshold parameter that predicts whether a disease will spread in a community or not. When $R_0 < 1$, then, on average, a small number of infectious individuals introduced in a community produced less than one newly infected individual in their infectious period and the disease may be eradicated from the population in the long run. When $R_0 > 1$, introduction of each infectious produces more than one new infected cases, so in this case there will be an epidemic in the community. However, in simple words it is defined as the number of secondary cases caused by one infective individual during his entire infectious period.

The next generation method introduced in [15], is a general method for finding an expression for the basic reproduction number R_0. In order to find R_0, one needs to differentiate new infections from all other changes in a community. The vector $\mathbf{y} = (y_1, y_2, ..., y_n)^T$, where each $y_i > 0$ denotes the number of individuals in the ith class. Let us assume that there are n classes of which $m < n$ classes represent to infected individuals. Let Π_f be the set of all states which are free of disease i.e.

$$\Pi_f = \{\mathbf{y} > 0 | y_i = 0, i = 1, 2, ..., m\} \tag{2.7.1}$$

Let $\mathcal{F}_i(y)$ be the rate of appearance of new infection in ith class, $\mathcal{V}_i^+(\mathbf{y})$ be the rate of transfer of individuals into ith class by all other means, and $\mathcal{V}_i^-(\mathbf{x})$ be the rate of transfer of individuals out of ith class. Assume each function is at least twice differentiable in each variable. The epidemic model consists of the following system of first order ordinary differential equations together with non-negative

initial conditions:

$$\frac{d\mathbf{x}}{dt} = F_i(\mathbf{x}) = \mathcal{F}_i(\mathbf{x}) - \mathcal{V}_i(\mathbf{x}) \tag{2.7.2}$$

where $\mathcal{V}_i(\mathbf{x}) = \mathcal{V}_i^+(\mathbf{x}) - \mathcal{V}_i^-(\mathbf{x})$ and functions satisfy the following assumptions.

H_1: If $\mathbf{x} > 0$, then $\mathcal{F}_i(\mathbf{x}), \mathcal{V}_i^+(\mathbf{x}), \mathcal{V}_i^-(\mathbf{x}) \geq 0$ for $i = 1, 2, ..., n$.

H_2: If $\mathbf{x} = 0$, then $\mathcal{V}_i^-(\mathbf{x}) = 0$. In particular, if $\mathbf{x} \in \Pi_f$, then $\mathcal{V}_i^-(\mathbf{x}) = 0$ for $i = 1, 2, ..., m$.

H_3: $\mathcal{F}_i(\mathbf{x}) = 0$ for $i > m$.

H_4: $\mathbf{x} \in \Pi_f$, then $\mathcal{F}_i(\mathbf{x}) = 0$ and $\mathcal{V}_i^+(\mathbf{x}) = 0$ for $i = 1, 2, ..., m$.

H_5: If $\mathcal{F}_i(\mathbf{z})$ is set to zero, then all eigenvalues of the Jacobian matrix, evaluated at the free of disease equilibrium, have negative real parts.

The first assumption (H_1) implies that each of the function is non-negative and it represents transfer of individuals. In (H_2) it is assumed that individuals can not be transferred out of an empty class. (H_3) says that the class with no infection has zero incidence of infection and remain free of infection. Assumption (H_4) represents that if there is no disease in the community, then it will remain disease free. Finally (H_5) is concerned with the stability of $\mathcal{F}$ in the absence of new infections. That is the disease free equilibrium is locally asymptotically stable provided that the community has no new infection.

Following the idea of Diekmann et. al. [15], we call PQ^{-1} the next generation matrix for the model and set

$$R_0 = \rho(PQ^{-1}), \quad \text{where} \quad P = \frac{\partial \mathcal{F}_i(\mathbf{x_0})}{\partial x_j} \quad \text{and} \quad Q = \frac{\partial \mathcal{V}_i(\mathbf{x_0})}{\partial x_j}$$

with $i \geq 1$, is for the total number of classes and $j \leq m$ is only for those classes with infections and $\rho(PQ^{-1})$ is the spectral radius of the matrix PQ^{-1}.

For example if an infected individual is introduced into a class k of an infection free community. The (i, j) component of P matrix is the rate at which an infected individual in class j produce new infections in compartment i, and the (j, k) entry

of Q^{-1} is the average time an infected individual spends in class j during its lifetime in class k. Thus, the (i,k) component of the matrix PQ^{-1} is the expected number of new cases in ith class produced by the infected individual introduced into the kth class.

2.8 Bifurcation theory

If the dynamical behavior of a system of differential equations change by varying a parameter. A steady state (equilibrium) can become unstable and periodic solution arise or a new stable steady state may appear making the formerly stable steady state to an unstable one. If this happens we say that the system has undergone a bifurcation and the parameter that is varied is known as bifurcation parameter [67]. The analysis of bifurcation is concerned with study of how the behavior of an equilibrium solution change with a change in a parameter. We will consider only the case when a single parameter is varied.

Definition 2.8.1. (**The saddle-node bifurcation**): In case of saddle node bifurcation, as the bifurcation parameter passes through the bifurcation point, two equilibria disappear, so that there are no equilibria afterward. In this case one equilibria is stable and the other is unstable before they disappear. Consider the one parameter family of system

$$\dot{y} = -y^2 + \mu.$$

For $\mu < 0$ this equation has no equilibrium. At $\mu = 0$ the equilibrium $y = 0$ appears; it is called a saddle-node because it attracts solutions with positive initial values and repels those with negative ones. Clearly for $\mu > 0$ the equation has two equilibria: $y_1 = \sqrt{\mu}$ and $y_2 = -\sqrt{\mu}$, the first one is asymptotically stable and the second one is unstable. The situation in this simple example is generic; if a system has no equilibrium, a parameter is varied, and at a value of the parameter equilibria appear then they do this, usually, in pairs, with one stable and the other unstable.

2.9 Optimal control technique

Optimal control theory is a powerful mathematical technique derived from the calculus of variation. The behavior of a dynamical system is described by the state variable(s). The assumption is that there is a way to control the state variable(s) x, by acting upon it with a suitable control. Thus the dynamics of the system (state x) depends on the control u. The ultimate goal is to adjust control u to minimize or maximize a given objective functional, $J(u(t), x(t), t)$, that attains the desired goal and the required cost to achieving it. The optimal solution is then obtained when the most desired goal is achieved with least cost. The functional depends on the control and the state variables. There are a number of different methods for calculating the optimal control for specific model. Pontryagin's Maximum Principle for example allows the calculation of the optimal control for an ordinary differential equations system with given constraints. In [82,84] some powerful optimal control techniques have been derived for biological models consisting of differential equations.

2.9.1 The general optimal control problem

The general optimal control problem is given by

$$\min_{u} \left[\psi\big(T, \mathbf{y}(T)\big) + \int_0^T g\big(t, \mathbf{y}(t), \mathbf{u}(t)\big) dt \right],$$

where $\mathbf{y} = [y_1(t), y_2(t), ...y_n(t)]$ and $\mathbf{u} = [u_1(t), u_2(t), ...u_m(t)]$ are the state and control variables, respectively [84]. The dynamics of the state and control variables is given by the following system of first order ordinary differential equations

$$\frac{dy}{dt} = f(t, \mathbf{y}(t), \mathbf{u}(t)), \quad \mathbf{y_0} = \mathbf{y}(\mathbf{0}), \quad 0 \leq t \leq T. \tag{2.9.1}$$

2.9.2 Pontryagin's Maximum Principle

The Pontryagin's Maximum Principle [82] converts the minimization (maximization) of an objective functional denoted by J together with the state variable into

minimizing (maximizing) point-wise the Hamiltonian $\mathcal{H}$ with respect to the control variable $\mathbf{u}$.

Theorem 2.9.1. *If $\mathbf{y}^*(t)$ and $\mathbf{u}^*(t)$ are optimal state and control variables, respectively for control problem (2.9.1), then there exists adjoint variable denoted by $\lambda(t)$ such that*

$$\mathcal{H}(t, \mathbf{y}(t), \mathbf{u}(t), \lambda(t)) \leq \mathcal{H}(t, \mathbf{y}^*(t), \mathbf{u}^*(t), \lambda(t)),$$

here $\mathcal{H}$ is defined as

$$\mathcal{H} = f(t, \mathbf{y}(t), \mathbf{u}(t)) + \lambda(t) g(t, \mathbf{y}(t), \mathbf{u}(t)).$$

and

$$\frac{d\lambda(t)}{dt} = -\frac{\partial \mathcal{H}}{\partial \mathbf{y}}, \quad \lambda(T) = 0.$$

Where $\lambda(t)$ is the adjoint or co-state variable and T is the final time.

Necessary conditions

If $\mathbf{y}^*(t)$ and $\mathbf{u}^*(t)$ are optimal state and control variables, then they satisfy the following conditions

$$\begin{aligned} \frac{d\lambda(t)}{dt} &= -\frac{\partial \mathcal{H}}{\partial \mathbf{y}}, \\ \lambda(T) &= 0, \\ \frac{\partial \mathcal{H}}{\partial \mathbf{u}} &= 0. \end{aligned} \tag{2.9.2}$$

Sufficient conditions

If $\mathbf{y}^*(t)$, $\mathbf{u}^*(t)$ and $\lambda(T)$ satisfy the above conditions given in (2.9.2), then the control and the state variables are optimal.

Chapter 3

Biological Control of Malaria: A Mathematical Model

3.1 Overview

In this chapter, theoretically we take a similar model as discussed in [74]. But here we consider all possible breeding sites of mosquitoes where biological control by larvivorous fish is being implemented in practice. Basically we divide the whole region under consideration into two parts based on breeding sites. The first region acts as reservoir for larvivorous fish stocking and harvested fish from this region are introduced to kill mosquito larvae in other region. Also we consider total human population variable which is more realistic as we are going to study the outcome of this method of control for longer duration. The objective is to determine whether or not the model for malaria exhibits the phenomenon of backward bifurcation. Our numerical simulations show the infection prevalence of malaria in endemic regions.

3.2 Introduction

In tropical and subtropical regions, mosquito borne diseases are a major problem and are responsible for many life-threatening diseases such as malaria, yellow

fever, dengue fever and chikungunya etc. Use of pesticides is in practice to control mosquitoes in these regions but environmental protection agencies have banned many pesticides as it harms non-targeted population too. Also, due to continuous application of pesticides, mosquitoes have developed resistance to these chemicals and now they are not so effective. This suggests us to look for an alternative method of control of mosquitoes and biological control seems to be environmental friendly method to control mosquito population. Biological control means introduction or manipulation of organisms to suppress vector population. Biological control, particularly using larvivorous fish plays a very positive role in controlling mosquitoes [68]. The method of control of mosquito using larvivorous fish is not new, it is being implemented since 1937 in many parts of the world. But control of mosquitoes using pesticides was fast so it suppressed this conventional method of control of mosquitoes. Now again this method of control is accepted and implemented in many parts of the world and one can refer [68–73] to see the positive outcome of this method of control. Although there are lots of experimental studies to see the efficacy of this method of control but not many researchers have explored mathematical modeling of this method of control of vectors. Recently, a mathematical model is formulated in [74] to study the efficacy of this method of control. But this model is simple in the sense that it didn't incorporate all breeding sites where in practice larvivorous fishes are introduced to kill mosquito larvae. It includes a specified region where fish can be stocked and simultaneously it can kill mosquito larvae in this specified region. But there are other breeding sites too such as rice fields, water tanks, ditches etc where larvivorous fishes are being introduced to control mosquito larvae but in this region stocking of larvivorous fishes are not possible as these are man made habitat for mosquito breeding which are temporary.

Recently, predatory fish that eat mosquito larvae, have been successfully employed against the malaria vector "Anopheles" as principal biological control agents that attack the initial larval stages of the mosquito [75]. Biological control may be effective if breeding sites are well known and limited in number but less feasible where they are numerous. Biological control thus provides a good illustration of

the importance of knowledge of local transmission ecology. Economic incentives may also be important in spurring initial interest in biological control mechanisms. In Asia, for instance, larvivorous fish have been effective where pisciculture can provide additional economic and agricultural benefits. In China, Wu et. al. [76] found that stocking edible fish in flooded parcel of arable land used for growing rice, supported significant fish production, and greatly reduced the number of malaria cases [77].

3.3 The model

In this section a long term scenario of biological control of malaria using larvivorous fish is presented in the form of differential equations. For this method of control, first step is to identify the mosquito breeding sites and then to apply this method of control. This includes rivers, ponds as well as man made habitats e.g. water storage tank, barrels, rice fields, ditches, irrigation channels, field wells, rain water in fallow lands etc. Field based experiments are carried out to observe the efficacy of this method of control in different parts of the world and it suggests us to include this method of control in our integrated control methodology.

Here, first we divide the whole breeding sites in two regions, namely region one which includes ponds and rivers where fish culture is possible and region two which includes man made habitats conducive to mosquito breeding such as water tank, rice fields, ditches etc, which are temporary habitat where fish can't survive for long. In fact stocking of larvivorous fish can be done in region one and harvested fish from region one can be transferred to region two to control mosquito larvae in this region. So obviously in region one dynamics of larvivorous fish and mosquito larvae follows predator prey type interaction. But as larvivorous fish population is not wholly dependent on mosquito larvae, they eat other insects larvae as well as plants etc. So in our model for larvivorous fish we have considered logistic growth as well as growth due to the predation of mosquito larvae. Here we assume that a fraction ν of the total breeding sites/area are lakes/pond rivers which can be considered

as region one. So region two will be $(1-\nu)$ fraction of total area. Accordingly, we assume that mosquito larvae density depends upon area of the breeding sites. So if L is the total larvae density in the whole region under consideration then νL will be distributed in region one and $(1-\nu)L$ will be distributed in region two. Furthermore, the population density of the larvivorous fish in region one is assumed to be $P(t)$. The prey-predator dynamics [96] of Larvae and Larvavorous fish is given by

$$\begin{cases} \dfrac{dL}{dt} = gN_v - dL - d_1L^2 - \lambda_v L - \alpha_1 L_1 P - \alpha_1\alpha_2 L_2\ qEP, \\ \dfrac{dP}{dt} = rP\left(1 - \dfrac{P}{K}\right) + \gamma\alpha_1 L_1 P - qEP, \end{cases} \tag{3.3.1}$$

where $L_1 = \nu L, L_2 = (1-\nu)L,\ L_1 + L_2 = L$. N_v is the total adult female mosquito which contributes to the growth of mosquito larvae. Here g is egg laying rate of the mosquitoes, d is the natural death rate of the mosquito larvae, d_1 corresponds to density dependent death rate constant of mosquito larvae, r is the intrinsic growth rate of the fish population and K is the carrying capacity of fish population in region one. As larvae of region one i.e. $\nu L = L_1(say)$ is subjected to predation by larvivorous fish so the term corresponding to this is $\alpha_1 L_1 P$ assuming linear response with a rate constant α_1. γ is the convention efficiency, q is the catchability constant and E is the harvesting effort to catch the larvivorous fish from region one. As the fish which are harvested from region one and α_2 fraction of it are introduced in region two to control the mosquito larvae form region two, so the term $\alpha_1\alpha_2 L_2\ qEP$ corresponds the predation of larvae of region two by harvested larvivorous fish with same predation rate constant α_1, λ_v is the maturation rate constant, i.e larvae become adult with this maturation rate constant.

Let us assume S_v and I_v as the population sizes of susceptible mosquitoes and infected mosquitoes and S_h and I_h as the population sizes of susceptible humans and infected humans. Assuming β as the mosquito biting rate, i.e., the average number of bites per mosquito per unit of time, the force of infection for susceptible mosquitoes can be represented as $c\beta S_v \frac{I_h}{N_h}$, where c is the transmission probability from infectious human to mosquitoes and N_h denotes the size of the total human

population. Assuming that the total number of bites made by mosquitoes equals to the number of bites received by humans, the average number of bites per human receives per unit of time is $\beta\frac{N_v}{N_h}$. Assuming the transmission probability per bite from infectious mosquitoes to human is b, the infection rate per susceptible human is given by

$$b\beta\frac{N_v}{N_h}\frac{I_v}{N_v} = b\beta\frac{I_v}{N_h}.$$

Now assuming criss-cross interaction between humans and mosquitoes, the rate of change per unit time in the number of susceptibles vector, infected vector, susceptibles host and infected host is governed by following set of differential equations:

$$\begin{cases} \dfrac{dS_v(t)}{dt} = \lambda_v L - c\beta S_v\dfrac{I_h}{N_h} - d_v S_v, \\ \dfrac{dI_v(t)}{dt} = c\beta S_v\dfrac{I_h}{N_h} - d_v I_v, \\ \dfrac{dS_h(t)}{dt} = \Gamma - b\beta S_h\dfrac{I_v}{N_h} - d_h S_h + \rho I_h, \\ \dfrac{dI_h(t)}{dt} = b\beta S_h\dfrac{I_v}{N_h} - (d_h + \rho + \mu)I_h, \end{cases} \tag{3.3.2}$$

where $S_v + I_v = N_v$, $S_h + I_h = N_h$. λ_v is the maturation rate constant of the mosquitoes vector and d_v is the constant death rate of the mosquitoes. Γ is the rate of recruitment and d_h is the constant death rate for the human population. ρ is the constant recovery rate and μ is the disease related death rate.

3.4 Existence of equilibria

In our proposed model, the total population of mosquitoes and human are $S_v + I_v = N_v$, $S_h + I_h = N_h$, respectively. We consider the following system of differential

equations for further analysis:

$$\begin{cases} \dfrac{dL(t)}{dt} = gN_v - dL - d_1L^2 - \lambda_v L - \alpha_1\nu LP - \alpha_1\alpha_2(1-\nu)L\ qEP, \\ \dfrac{dP(t)}{dt} = rP\left(1 - \dfrac{P}{K}\right) + \gamma\alpha_1\nu LP - qEP, \\ \dfrac{dI_v(t)}{dt} = c\beta(N_v - I_v)\dfrac{I_h}{N_h} - d_vI_v, \\ \dfrac{dN_v(t)}{dt} = \lambda_v L - d_vN_v, \\ \dfrac{dI_h(t)}{dt} = b\beta(N_h - I_h)\dfrac{I_v}{N_h} - (d_h + \rho + \mu)I_h, \\ \dfrac{dN_h(t)}{dt} = \Gamma - \mu I_h - d_hN_h. \end{cases} \tag{3.4.1}$$

Possible equilibria of the system (3.4.1) and their stability are explored here. The equilibria for our model are determined by setting right hand side of the model (3.4.1) to zero. The system (3.4.1) has five equilibria namely

$$\begin{cases} E_1 = \left(0, 0, 0, 0, 0\frac{\Gamma}{d_h}\right), \\ E_2 = \left(0, \frac{K}{r}(r - qE), 0, 0, 0, \frac{\Gamma}{d_h}\right), \\ E_3 = \left(L^*, 0, 0, \frac{\lambda_v L^*}{d_v}, 0, \frac{\Gamma}{d_h}\right), \\ E_4 = \left(L^*, P^*, 0, \frac{\lambda_v L^*}{d_v}, 0, \frac{\Gamma}{d_h}\right), \\ E_5 = \left(L^*, P^*, I_v^*, N_v^*, I_h^*, N_h^*\right), \end{cases} \tag{3.4.2}$$

where

$$\begin{cases} L^* = \dfrac{g\dfrac{\lambda_v}{d_v} - (d + \lambda_v) - \dfrac{K}{r}(r - qE)\{\alpha_1\nu + \alpha_1\alpha_2(1-\nu)qE\}}{d_1 + \dfrac{\gamma\alpha_1 K\nu}{r}\{\alpha_1\nu + \alpha_1\alpha_2(1-\nu)qE\}}, \\ N_v^* = \dfrac{\lambda_v}{d_v}L^*, \\ P^* = \dfrac{K}{r}\{(r - qE) + \gamma\alpha_1\nu L^*\}, \\ N_h^* = \dfrac{\Gamma - \mu I_h^*}{d_h}, \\ I_v^* = \dfrac{c\beta N_v^* I_h^*}{c\beta I_h^* + d_vN_h^*}. \end{cases}$$

I_h^* is the positive root of the following quadratic equation

$$D_1 I_h^2 + D_2 I_h + D_3 = 0, \tag{3.4.3}$$

where

$$\begin{aligned} D_1 &= (d_h + \rho + \mu)\left(\frac{\mu}{d_h}\right)\left(\frac{\mu d_v}{d_h} - \beta c\right), \\ D_2 &= bc\beta^2 N_v^*(\frac{\mu}{d_h} + 1) + (d_h + \rho + \mu)\left(\frac{\Gamma}{d_h}\right)\left(\beta c - \frac{2\mu d_v}{d_h}\right), \\ D_3 &= \left\{(d_h + \rho + \mu)d_v\frac{\Gamma}{d_h} - bc\beta^2 N_v^*\right\}\frac{\Gamma}{d_h}. \end{aligned}$$

The roots of this quadratic equation are given by

$$\frac{-(A_1 + A_2) \pm \sqrt{(A_1 - A_2)^2 + 4A_1 bc\beta^2 N_v^*}}{2D_1},$$

where $A_1 = (d_h+\rho+\mu)\left(\beta c - \frac{\mu d_v}{d_h}\right)\frac{\Gamma}{d_h}$, $A_2 = bc\beta^2 N_v^*\left(1 + \frac{\mu}{d_h}\right) - \mu\frac{d_v}{d_h}\frac{\Gamma}{d_h}(d_h+\rho+\mu)$. Next, depending upon the signs of D_1, D_2 and D_3, we may have unique, two or no positive roots. These findings are summarized in Table (3.1).

So, there exists unique positive root under the condition that the constant term in the last quadratic equation (3.4.3) is negative i.e.

$$(d_h + \rho + \mu)d_v\frac{\Gamma}{d_h} < bc\beta^2 N_v^*. \tag{3.4.4}$$

It is easy to visualize that the condition (3.4.4) corresponds to the basic reproduction number $\mathcal{R}_0^2 > 1$ which is discussed in detail in next section. Thus the endemic equilibrium point E_5 exists only when $\mathcal{R}_0^2 > 1$. From this discussion, it is easy to observe that we may get backward as well as forward bifurcation depending upon parameter values. Following two Figures $(3.1 - 3.2)$ are demonstrating this fact where the bifurcation parameter is taken as β and bifurcation diagram is drawn by finding corresponding values of $\mathcal{R}_0$. From Figure (3.1), it is concluded that the backward bifurcation leads to bi-stability phenomenon. The solutions of the system (3.4.1) converges to the disease free equilibria or the endemic equilibria depending on the initial population size. Infect, the phenomenon of bi-stability is very difficult to numerically simulate because the interval of $\mathcal{R}_0$ for the occurrence of backward bifurcation usually is very small and this results in very small range of parameters taken to make backward bifurcation to occur. The parameter values used in Figure (3.1) and (3.2) are given in Table (3.2) and (3.3) respectively.

Table 3.1: Conditions for existence of equilibria.

Conditions	sub-conditions	results
$D_3 > 0$		
i.e. $\mathcal{R}_0 < 1$	(a) $D_1 > 0$ & $D_2 > 0$	No positive roots
	(b)$D_1 < 0$ & $D_2 > 0$	Unique positive root but greater than $\frac{\Gamma}{\mu}$ so discarded
	(c) $D_1 > 0$ & $D_2 < 0$	No positive roots or two positive roots provided $D_2^2 - 4D_1D_3 < 0$ or $D_2^2 - 4D_1D_3 > 0$
	(d) $D_1 < 0$ & $D_2 < 0$	Unique positive root but greater than $\frac{\Gamma}{\mu}$ so discarded
$D_3 < 0$		
i.e. $\mathcal{R}_0 > 1$	(a) $D_1 > 0$ & $D_2 > 0$	Unique positive root
	(b)$D_1 < 0$ & $D_2 > 0$	Two positive roots as $D_2^2 - 4D_1D_3 > 0$ but larger root is greater than $\frac{\Gamma}{\mu}$ so discarded as for N_h to be positive $I_h < \frac{\Gamma}{\mu}$
	(c) $D_1 > 0$ & $D_2 < 0$	Unique positive root
	(d) $D_1 < 0$ & $D_2 < 0$	This case does not exist as $D_3 < 0$ & $D_1 < 0$ implies $D_2 > 0$

Table 3.2: Parameter values used in the numerical simulation of backward bifurcation.

Notation	Value	Notation	Value
g	60	d	0.05
Γ	0.7	d_1	0.02
ν	0.2	λ_v	0.0625
α_1	0.1	α_2	0.5
q	0.4	ρ	0.005
γ	0.1	r	0.01
c	0.5	K	20000
d_v	0.1	d_h	0.00003913
E	0.9	μ	0.002
b	0.5		

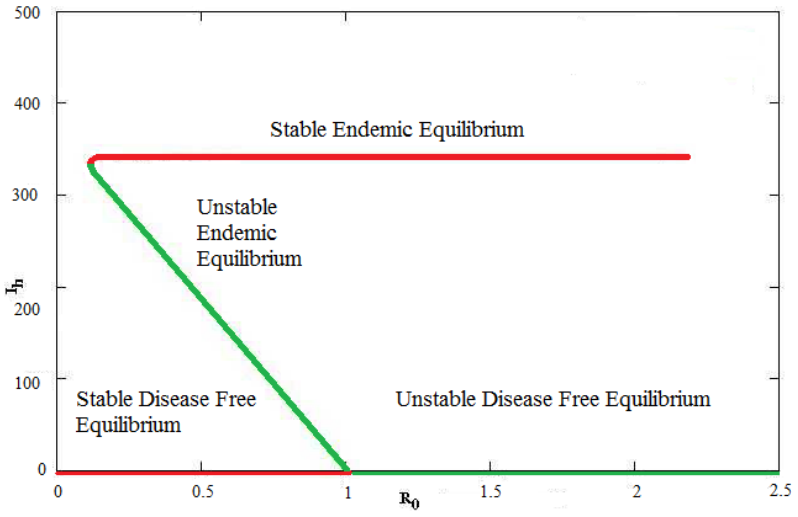

Figure 3.1: Variation of the equilibrium level of I_h with β showing the backward bifurcation from the disease-free equilibrium at $\mathcal{R}_0 = 1$, which leads to the existence of multiple endemic equilibria with parameter as in Table (3.2).

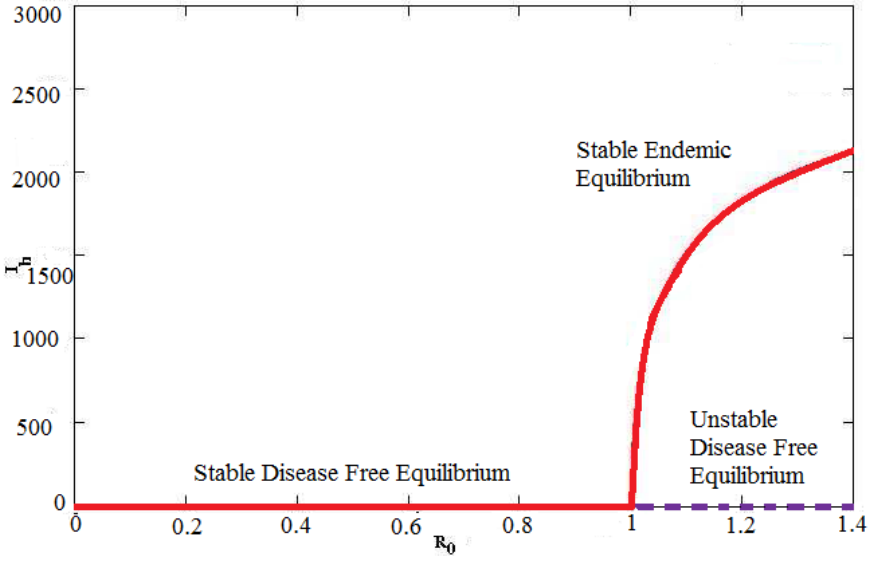

Figure 3.2: Variation of the equilibrium level of I_h with β showing the forward bifurcation for the parameter values as in Table (3.3).

Table 3.3: Parameter values used in the numerical simulation of forward bifurcation.

Notation	Value	Notation	Value
g	60	d	0.05
Γ	0.7	d_1	0.02
ν	0.2	λ_v	0.0625
α_1	0.2	ρ	0.005
q	0.4	E	0.9
γ	0.1	r	0.01
c	0.5	K	20000
d_v	0.1	d_h	0.00003913
α_2	0.5	μ	0.002
b	0.5		

3.5 The basic reproduction number $\mathcal{R}_0$

The basic reproduction number is defined as the number of secondary infections generated by a typical infected individual in an otherwise disease free population. The reproduction number ($\mathcal{R}_0$) for our model is computed using the method described in [15]. Here, the matrices $\mathcal{F}$ and $\mathcal{V}$ are the matrix of new infections and the matrix of transfers between compartments, respectively and are given by $\mathcal{V}$

$$\mathcal{F} = \begin{pmatrix} c\beta S_v \frac{I_h}{N_h} \\ b\beta S_h \frac{I_v}{N_h} \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} d_v I_v \\ (d_h + \rho + \mu) I_h \end{pmatrix}.$$

Now the matrix $\mathcal{F}$ and $\mathcal{V}$ evaluated at disease free equilibrium point are given by

$$\mathcal{F} = \begin{pmatrix} 0 & c\beta \frac{N_v^* d_h}{\Gamma} \\ b\beta & 0 \end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix} d_v & 0 \\ 0 & d_h + \rho + \mu \end{pmatrix}.$$

The matrix $\mathcal{F}\mathcal{V}^{-1}$ is given by

$$\begin{pmatrix} 0 & \frac{c\beta d_h N_v^*}{\Gamma(d_h + \rho + \mu)} \\ \frac{b\beta}{d_v} & 0 \end{pmatrix}$$

So the reproduction number $\mathcal{R}_0$ which is the spectral radius of the matrix $\mathcal{F}\mathcal{V}^{-1}$ is given by

$$\mathcal{R}_0 = \sqrt{\frac{c\beta d_h N_v^*}{\Gamma(d_h + \rho + \mu)} \frac{b\beta}{d_v}}.$$

3.6 Stability analysis

The local asymptotic stability of the equilibria are established using variational matrix method which is stated in the following theorem.

Theorem 3.6.1. *i. The equilibrium point $E_1 = (0, 0, 0, 0, 0, \frac{\Gamma}{d_h})$ is always unstable.*

ii. The equilibrium point $E_2 = \left(0, \frac{K}{r}(r - qE), 0, 0, 0, \frac{\Gamma}{d_h}\right)$ is locally asymptotically stable provided

$$d_v \left[d + \lambda_v + \{\alpha_1 \nu + \alpha_1 \alpha_2 qE(1 - \nu)\} \frac{K}{r}(r - qE) \right] > g\lambda_v,$$

which implies that L^* does not exist.

iii. The equilibrium point $E_3 = \left(L^*, 0, 0, \frac{\lambda_v L^*}{d_v}, 0, \frac{\Gamma}{d_h}\right)$ *is always unstable.*

Proof. *i*: The variational matrix corresponding to the system (3.4.1) at the equilibrium point $E_1 = \left(0, 0, 0, 0, 0, \frac{\Gamma}{d_h}\right)$ is given by

$$\begin{pmatrix} -(d+\lambda_v) & 0 & 0 & g & 0 & 0 \\ 0 & r-qE & 0 & 0 & 0 & 0 \\ 0 & 0 & -d_v & 0 & 0 & 0 \\ \lambda_v & 0 & 0 & -d_v & 0 & 0 \\ 0 & 0 & b\beta & 0 & -(d_h+\rho+\mu) & 0 \\ 0 & 0 & 0 & 0 & -\mu & -d_h \end{pmatrix}.$$

Here four roots of the characteristic polynomial are $-d_h, -(d_h+\rho+\mu), -d_v$ and $r - qE > 0$ and other two roots are given by the following quadratic equation,

$$\lambda^2 + (d + \lambda_v + d_v)\lambda + \{(d+\lambda_v)d_v - g\lambda_v\} = 0.$$

As one of the eigenvalues is positive so this equilibrium point E_1 is always unstable.

ii: The variational matrix at the equilibrium point $E_2 = \left(0, \frac{K}{r}(r-qE), 0, 0, 0, \frac{\Gamma}{d_h}\right)$ is given by

$$\begin{pmatrix} m_{11} & 0 & 0 & g & 0 & 0 \\ \gamma\alpha_1\nu\frac{r}{K}(r-qE) & -(r-qE) & 0 & 0 & 0 & 0 \\ 0 & 0 & -d_v & 070 & 0 & \\ \lambda_v & 0 & 0 & -d_v & 0 & 0 \\ 0 & 0 & b\beta & 0 & -(d_h+\rho+\mu) & 0 \\ 0 & 0 & 0 & 0 & -\mu & -d_h \end{pmatrix},$$

where $m_{11} = -\left[d + \lambda_v + \{\alpha_1\nu + \alpha_1\alpha_2 qE(1-\nu)\}\frac{K}{r}(r-qE)\right]$. Here also four roots of the characteristic polynomial of this variational matrix are $-d_h, -(d_h+\rho+\mu), -d_v$ and $-(r-qE)$ and other two roots are given by the following quadratic equation

$$\lambda^2 + K_1\lambda + K_2 = 0,$$

where

$$\begin{aligned} K_1 &= \left[d + \lambda_v + \{\alpha_1\nu + \alpha_1\alpha_2 qE(1-\nu)\}\frac{K}{r}(r-qE) + d_v\right], \\ K_2 &= d_v\left[d + \lambda_v + \{\alpha_1\nu + \alpha_1\alpha_2 qE(1-\nu)\}\frac{K}{r}(r-qE)\right] - g\lambda_v. \end{aligned} \tag{3.6.1}$$

This equilibrium point E_2 is locally asymptotically stable provided $K_2 > 0$, otherwise it is unstable. The stability of the equilibrium point E_2 corresponds to the case where L^* does not exist.

iii: The variational matrix at the equilibrium point $E_3 = \left(L^*, 0, 0, \frac{\lambda_v L^*}{d_v}, 0, \frac{\Gamma}{d_h}\right)$ is given by

$$\begin{pmatrix} -(d+\lambda_v+2d_1L^*) & -\{\alpha_1\nu+\alpha_1\alpha_2qE(1-\nu)\}L^* & 0 & g & 0 & 0 \\ 0 & r-qE+\gamma\alpha_1\nu L^* & 0 & 0 & 0 & 0 \\ 0 & 0 & -d_v & 0 & \frac{cd_h\beta N_v^*}{\Gamma} & 0 \\ \lambda_v & 0 & 0 & -d_v & 0 & 0 \\ 0 & 0 & b\beta & 0 & -(d_h+\rho+\mu) & 0 \\ 0 & 0 & 0 & 0 & -\mu & -d_h \end{pmatrix}.$$

Clearly two of the eigenvalues of this matrix are $-d_h$, $r-qE+\gamma\alpha_1\nu L^*$ and other four roots are given by the following quadratic equations in λ,

$$(d_h+\rho+\mu+\lambda)(d_v+\lambda) - \frac{bcd_h\beta^2N_v^*}{\Gamma} = 0,$$

$$(d+\lambda_v+2d_1L^*+\lambda)(d_v+\lambda) - g\lambda_v = 0.$$

As one of the eigenvalues is positive under the assumption that $r > qE$, so this equilibrium point is always unstable.

Theorem 3.6.2. *The disease free equilibrium point* $E_4 = \left(L^*, P^*, 0, \frac{\lambda_v L^*}{d_v}, 0, \frac{\Gamma}{d_h}\right)$ *is locally asymptotically stable provided* $\mathcal{R}_0 < 1$.

Proof. The variational matrix at the equilibrium point $E_4 = \left(L^*, P^*, 0, \frac{\lambda_v L^*}{d_v}, 0, \frac{\Gamma}{d_h}\right)$ is given by

$$\begin{pmatrix} -\frac{gN_v^*}{L^*}-d_1L^* & -\{\alpha_1\nu+\alpha_1\alpha_2qE(1-\nu)\}L^* & 0 & g & 0 & 0 \\ \gamma\alpha_1\nu P^* & \frac{-rP^*}{K} & 0 & 0 & 0 & 0 \\ 0 & 0 & -d_v & 0 & \frac{cd_h\beta N_v^*}{\Gamma} & 0 \\ \lambda_v & 0 & 0 & -d_v & 0 & 0 \\ 0 & 0 & b\beta & 0 & -(d_h+\rho+\mu) & 0 \\ 0 & 0 & 0 & 0 & -\mu & -d_h \end{pmatrix}.$$

Clearly one eigenvalue of this matrix is $-d_h$. Expanding the matrix along the fourth row leads to the following characteristic polynomial

$$\left(\lambda^2+(d_h+\rho+\mu+d_v)\lambda+(d_h+\rho+\mu)d_v-\frac{bcd_h\beta^2N_v^*}{\Gamma}\right)\left(\lambda^3+Q_1\lambda^2+Q_2\lambda+Q_3\right)=0.$$

where

$$\begin{aligned}
Q_1 &= d_v+\tfrac{gN_v^*}{L^*}+d_1L^*+\tfrac{r}{K}P^*,\\
Q_2 &= \left(\tfrac{gN_v^*}{L^*}+d_1L^*\right)\tfrac{r}{K}P^*+\gamma\alpha_1\nu P^*\{\alpha_1\nu+\alpha_1\alpha_2qE(1-\nu)\}L^*+d_v\left(d_1L^*+\tfrac{r}{K}P^*\right),\\
Q_3 &= d_v\left[\left(\tfrac{gN_v^*}{L^*}+d_1L^*\right)\tfrac{r}{K}P^*+\gamma\alpha_1\nu P^*\{\alpha_1\nu+\alpha_1\alpha_2qE(1-\nu)\}L^*\right]+g\lambda_v\tfrac{r}{K}P^*.
\end{aligned}$$

Two of the eigenvalues are given by the following quadratic equation in λ

$$\lambda^2+(d_h+\rho+\mu+d_v)\lambda+(1-\mathcal{R}_0^2)=0$$

So, roots of this quadratic equation will have negative real parts provided the basic reproduction number $\mathcal{R}_0<1$. The other three eigenvalues of this matrix are given by following cubic equation in λ,

$$\lambda^3+Q_1\lambda^2+Q_2\lambda+Q_3=0$$

Clearly, all Q_1, Q_2 and Q_3 are positive and it is easy to verify that $Q_1Q_2-Q_3$ is positive. So using Routh-Hurwitz criteria [95, 96], roots of this cubic equation will have negative real parts. Hence the equilibrium point E_4 is locally asymptotically stable provided $\mathcal{R}_0<1$.

Theorem 3.6.3. *The equilibrium point $E_5=(L^*,P^*,I_v^*,\ N_v^*,I_h^*,N_h^*)$ which exists for $\mathcal{R}_0>1$ is locally asymptotically stable.*

Proof.

The variational matrix at the equilibrium point $E_5\,(L^*,P^*,I_v^*,N_v^*,I_h^*,N_h^*)$ is given by

$$\begin{pmatrix} m_{11} & m_{12} & 0 & g & 0 & 0 \\ m_{21} & m_{22} & 0 & 0 & 0 & 0 \\ 0 & 0 & m_{33} & m_{34} & m_{35} & m_{36} \\ \lambda_v & 0 & 0 & -d_v & 0 & 0 \\ 0 & 0 & m_{53} & 0 & m_{55} & m_{56} \\ 0 & 0 & 0 & 0 & -\mu & -d_h \end{pmatrix}$$

where

$$\begin{aligned}
m_{11} &= -\left[(d+\lambda_v) + 2d_1L^* + \alpha_1\nu P^* + \alpha_1\alpha_2 qE(1-\nu)P^*\right], \\
m_{12} &= -\{\alpha_1\nu + \alpha_1\alpha_2 qE(1-\nu)\}L^*, \\
m_{21} &= \gamma\alpha_1\nu P^*, \\
m_{22} &= r - \frac{2rP^*}{K} + \gamma\alpha_1\nu L^* - qE, \\
m_{33} &= -(\frac{c\beta I_h^*}{N_h^*} + d_v), \\
m_{34} &= \frac{c\beta I_h^*}{N_h^*}, \\
m_{35} &= \frac{c\beta(N_v^* - I_v^*)}{N_h^*}, \\
m_{36} &= -\frac{c\beta(N_v^* - I_v^*)I_h^*}{N_h^{*2}}, \\
m_{53} &= \frac{b\beta(N_h^* - I_h^*)}{N_h^*}, \\
m_{55} &= -(\frac{b\beta I_v^*}{N_h^*} + d_h + \rho + \mu), \\
m_{56} &= \frac{b\beta I_h^* I_v^*}{N_h^{*2}}.
\end{aligned}$$

Expanding the variational matrix along the fourth row and after some rearrangement, we have the following characteristic equation in λ

$$\left(\lambda_v g(m_{22}-\lambda)+(d_v+\lambda)\big((m_{11}-\lambda)(m_{22}-\lambda)-m_{12}m_{21}\big)\right)\begin{vmatrix} m_{33}-\lambda & m_{35} & m_{36} \\ m_{53} & m_{55}-\lambda & m_{56} \\ 0 & -\mu & -d_h-\lambda \end{vmatrix}.$$

This equation can be written as a product of the following two cubic equations,

$$\lambda^3 + F_1\lambda^2 + F_2\lambda + F_3 = 0, \text{ and } \lambda^3 + G_1\lambda^2 + G_2\lambda + G_3 = 0,$$

where

$$\begin{aligned} F_1 &= d_v - (m_{11} + m_{22}) > 0, \\ F_2 &= m_{11}m_{22} - d_v(m_{11} + m_{22}) - m_{12}m_{21} - \lambda_v g > 0, \\ F_3 &= d_v(m_{11}m_{22} - m_{12}m_{21}) + \lambda_v g m_{22} > 0, \\ G_1 &= d_h - (m_{33} + m_{55}) > 0, \\ G_2 &= m_{33}m_{55} - d_h(m_{33} + m_{55}) + \mu m_{56} - m_{53}m_{35}, \\ G_3 &= m_{33}m_{55}d_h m_{53}m_{36}\mu - m_{33}m_{56}\mu - m_{53}m_{35}d_h. \end{aligned} \tag{3.6.2}$$

It is to verify that $F_1F_2 - F_3 > 0$ and $G_1G_2 - G_3 > 0$ provided $\mathcal{R}_0 > 1$. So using Routh-Hurwitz criteria, this equilibrium point is stable under the condition that $\mathcal{R}_0 > 1$.

3.7 Backward bifurcation analysis

In this section we consider the system (3.4.1) and establish the conditions on parameter values that cause a backward bifurcation. For classic disease transmission models with associated reproduction number $\mathcal{R}_0$ less than unity is necessary condition for disease elimination. However, in case of backward bifurcation this requirement may not always be sufficient, where a stable endemic equilibrium co-exists with a stable disease-free equilibrium for $\mathcal{R}_0 < 1$. This phenomenon has been observed in numerous disease transmission models [93, 98]. In a backward bifurcation situation, disease control depend on the initial sizes of the various sub-populations of the model. The occurrence of a backward bifurcation has an important implications for epidemiological control measures, since an epidemic may persist at steady state even if $\mathcal{R}_0 < 1$. It is instructive to determine whether or not such phenomenon occurs in the mosquito-fish-human cycle, by analyzing the basic model (3.4.1). A method, based on the use of Centre Manifold theory [78], will be used to investigate the possibility of backward bifurcation when $\mathcal{R}_0 = 1$.

For this, we consider the following theorem introduced in [78] and based on the use of centre manifold theory [79].

Theorem 3.7.1. *Let us consider the following general system of ordinary differential equations with a parameter* $\phi = \beta - \beta^*$

$$\frac{dx}{dt} = f(x, \phi), \quad f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n, \quad f \in C^2(\mathbb{R} \times \mathbb{R}). \tag{3.7.1}$$

Without loss of generality, it is assumed that $x = 0$ *is an equilibrium for system (3.7.1) for all values of the parameter* ϕ*. Assume that*

A1. $A = D_x f(0, 0)$ *is the linearized matrix of the system (3.7.1) around the equilibrium* $x = 0$ *with* ϕ *evaluated at* 0*. Zero is a simple eigenvalue of* A *and all other eigenvalue of* A *have negative real parts;*

A2. Matrix A *has a non-negative right eigenvector* w *and a left eigenvector* v *corresponding to the zero eigenvalue.*

Let f_k *be the* k*th component of* f *and*

$$a = \sum_{i,j,k=1}^{5} v_k w_i w_j \frac{\partial^2 f_k(0,0)}{\partial x_i \partial x_j}, \quad b = \sum_{i,k=1}^{5} v_k w_i \frac{\partial^2 f_k(0,0)}{\partial x_i \partial \beta_h}$$

The local dynamics of the system (3.7.1) around 0 *are totally determined by* a *and* b*.*

(i) In the case where $a > 0$*,* $b > 0$*, we have that when* $\phi < 0$ *with* $|\phi|$ *close to zero,* $x = 0$ *is unstable; when* $0 < \phi \ll 1$*,* $x = 0$ *is unstable and there exists a negative and locally asymptotically stable equilibrium;*

(ii) In the case where $a < 0$*,* $b < 0$*, we have that when* $\phi < 0$ *with* $|\phi|$ *close to zero,* $x = 0$ *is locally asymptotically stable and there exists a positive unstable equilibrium; when* $0 < \phi \ll 1$*,* $x = 0$ *is locally asymptotically stable, and there exists a positive unstable equilibrium;*

(iii) In the case where $a > 0$*,* $b < 0$*, we have that when* $\phi < 0$ *with* $|\phi|$ *close to zero,* $x = 0$ *is unstable and there exists a locally asymptotically stable negative equilibrium; when* $0 < \phi \ll 1$*,* $x = 0$ *is stable and a positive unstable equilibrium appears;*

(iv) In the case where $a < 0$, $b > 0$, we have that when $\phi < 0$ changes from negative to positive, $x = 0$ changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable. Particularly, if $a > 0$ and $b > 0$, then a backward bifurcation occurs at $\phi = 0$.

To apply the centre manifold method, the following simplification and change of variables are made on the model (3.4.1). First, we consider, $x_1 = L$, $x_2 = P$, $x_3 = I_v$, $x_4 = N_v$, $x_5 = I_h$ and $x_6 = N_h$. Further, by using the vector notation $X = (x_1, x_2, x_3, x_4, x_5, x_6)^T$, the system (3.4.1) can be written in the form $\frac{dX}{dt} = \mathcal{F}(X)$, with $\mathcal{F} = (f_1, f_2, f_3, f_4, f_5, f_6)^T$, as follows:

$$\begin{cases} \dfrac{dx_1}{dt} = f_1 = gx_4 - dx_1 - d_1x^2 - \lambda_v x_1 - \alpha_1 v x_1 x_2 - \alpha_1\alpha_2(1-v)x_1 qEx_2, \\ \dfrac{dx_2}{dt} = f_2 = \gamma x_2(1 - \dfrac{x_2}{K}) + \gamma\alpha_1 v x_1 x_2 - qEx_2, \\ \dfrac{dx_3}{dt} = f_3 = c\beta(x_4 - x_3)\dfrac{x_5}{x_6} - d_v x_3, \\ \dfrac{dx_4}{dt} = f_4 = \lambda_v x_1 - d_v x_4, \\ \dfrac{dx_5}{dt} = f_5 = b\beta(x_6 - x_5)\dfrac{x_3}{x_6} - (d_h + \rho + \mu)x_5, \\ \dfrac{dx_6}{dt} = f_6 = \Gamma - d_h x_5 - d_h x_6. \end{cases} \tag{3.7.2}$$

In order to explore the possibility of backward bifurcation, we consider β as a bifurcation parameter, by solving for β from $\mathcal{R}_0 = 1$ gives

$$\beta = \beta^* = \sqrt{\frac{d_v\Gamma(d_h + \rho + \mu)}{cd_h N_v^* b}}.$$

The Jacobian matrix at the disease free equilibrium E_4 with $\beta = \beta^*$ is

$$J_{\beta^*} = \begin{pmatrix} -\frac{gN_v^*}{L^*} - d_1 L^* & -\{\alpha_1\nu + \alpha_1\alpha_2 qE(1-\nu)\}L^* & 0 & g & 0 & 0 \\ \gamma_h\alpha_1 vP & -\frac{\gamma P}{K} & 0 & 0 & 0 & 0 \\ 0 & 0 & -d_v & 0 & \frac{c\beta N_v}{N_h} & 0 \\ \lambda_v & 0 & 0 & -d_v & 0 & 0 \\ 0 & 0 & b\beta & 0 & -(d_h+\rho+\mu) & 0 \\ 0 & 0 & 0 & 0 & -\mu & -d_h \end{pmatrix}.$$

The characteristic equation of the Jacobian matrix J_{β^*} is given by

$$\big(\lambda^2 + (d_h+\rho+\mu+d_v)\lambda + d_v(d_h+\rho+\mu)(1-\mathcal{R}_0^2)\big)\big(\lambda^3 + Q_1\lambda^2 + Q_2\lambda + Q_3\big) = 0.$$

It can be easily seen that the Jacobian matrix J_{β^*} with $\beta = \beta^*$ of the linearized system (3.7.2) has a simple zero eigenvalue and all other eigenvalues have negative real parts (see proof of Theorem 3.6.2). Hence, the center manifold theory can be used to analyze the dynamics of the system (3.7.2) near $\beta = \beta^*$. For the case when $\mathcal{R}_0 = 1$, it can be shown, using technique in Castillo-Chavez and Song [78], that the matrix J_{β^*} has a right eigenvector (corresponding to the zero eigenvalue), given by $\mathbf{w} = [w_1\ w_2\ w_3\ w_4\ w_5\ w_6]^T$, where

$$w_1 = w_2 = 0,\ w_3 = \frac{c\beta N_v^*}{N_h^* d_v} w_5,\ w_4 = 0,\ w_6 = \frac{\mu}{d_h} w_5,\ w_5 = w_5 > 0. \tag{3.7.3}$$

Similarly, the matrix J_{β^*} has a left eigenvector (corresponding to the zero eigenvalue), denoted by $\mathbf{v} = [v_1\ v_2\ v_3\ v_4\ v_5\ v_6]$, where

$$v_1 = v_2 = v_4 = v_6 = 0,\ v_3 = \frac{b\beta}{d_v} v_5,\ v_5 = v_5 > 0. \tag{3.7.4}$$

The local bifurcation analysis near the bifurcation point is determined by the signs of two associated constants, denoted by a and b, defined (respectively) by

$$a = \sum_{i,j,k=1}^{5} v_k w_i w_j \frac{\partial^2 f_k(0,0)}{\partial x_i \partial x_j},\ \text{and}\ b = \sum_{i,k=1}^{5} v_k w_i \frac{\partial^2 f_k(0,0)}{\partial x_i \partial \beta_h}.$$

Computation of a. For the transformed model (3.7.2), the associated non-zero partial derivatives of f_i for $i = 1, 2, ..., 6$ evaluated at the disease free equilibrium

(DFE) which we need in the computation of a are given by (since $v_1 = v_2 = v_4 = v_6 = 0$) we only need the following for the computation of a

$$\begin{aligned} \frac{\partial^2 f_3}{\partial x_3 \partial x_5} &= \frac{\partial^2 f_3}{\partial x_5 \partial x_3} = -c\beta/N_h^*, \ \frac{\partial^2 f_3}{\partial x_5 \partial x_6} = \frac{\partial^2 f_3}{\partial x_6 \partial x_5} = \frac{-c\beta N_v *}{N_h^{*2}}, \\ \frac{\partial^2 f_5}{\partial x_3 \partial x_5} &= \frac{\partial^2 f_5}{\partial x_5 \partial x_3} = \frac{-b\beta}{N_h} \end{aligned} \tag{3.7.5}$$

all other second order derivatives are zero. After some algebraic manipulations, it follows that

$$a = v_3\left(\frac{-2c\beta}{N_h^*} w_3 w_5 - \frac{-2c\beta N_v^*}{N_h^{*2}} w_5 w_6) + v_5(\frac{-2b\beta}{N_h^*} w_3 w_5)\right).$$

Substituting the values of v_3, w_3, w_6 and after some re-arrangements we have

$$a = 2\frac{bc\beta^2 d_h^2 \lambda_v L^*}{d_v^2 \Gamma^2} v_5 w_5^2 (\frac{-c\beta}{d_v} + \frac{\mu}{d_h} - 1).$$

Computation of b. Substituting the vectors $\mathbf{v}$ and $\mathbf{w}$ and the respective partial derivatives (evaluated at the disease free equilibrium) into the expression for b and after simplifications

$$b = v_3 w_5 \frac{c\beta N_v}{N_h} + v_5 w_3 b\beta$$

b is automatically positive. Hence, the coefficient $a > 0$ if and only if

$$-c\beta d_h + \mu d_v - d_h d_v > 0.$$

Thus, the following result is established.

Theorem 3.7.2. *The model exhibits backward bifurcation at $\mathcal{R}_0 = 1$ whenever the coefficient a, is positive.*

The model (3.7.2) undergoes backward bifurcation at $\mathcal{R}_0 = 1$ if the inequality ($a > 0$) is satisfied. Simulations are carried out, using a suitable set of parameter values (so that $a > 0$ is satisfied), to illustrate the backward bifurcation property of the model (3.7.2) (see Figure (3.1) and Figure (3.2)).

3.8 Numerical simulation and discussion

The system (3.4.1) is simulated for the set of parameters in Table (3.4), in this case the disease free equilibrium point E_4 is stable and for the set of parameter values in Table (3.4) it is computed as $(23.28, 1431.2, 0, 29.1, 0, 12778)$.

The value of basic reproduction number for this set of parameter values is 0.8054848 which does not satisfy the backward bifurcation condition $a > 0$. Phase portrait of this system in $N_h - I_h$, $N_v - I_v$ and $P - L$ planes are shown in Figures $(3.3) - (3.5)$, respectively.

Again, the system (3.4.1) is simulated for the set of parameters in Table (3.5). This set of parameters gives $\mathcal{R}_0 = 0.3523$ which satisfied the backward bifurcation condition $(a > 0, b > 0)$. The two nontrivial equilibria are
$E_1^* = (177.459, 983.672, 69.084, 110.912, 341.899, 414.0147)$ and
$E_2^* = (177.459, 983.672, 8.887, 110.912, 241.510, 5545.071)$, where one of them in particular E_1^* is stable and E_2^* is unstable. The unstable equilibrium is shown as a triangle in Figure (3.6). In addition to these equilibria, we have disease free equilibrium say $E_0^*(177.46, 983.67, 0, 110.912, 0, 17889)$. This equilibrium point E_0^* is locally asymptotically stable which is shown in Figure 3.7, which is demonstrating all three equilibria in $N_v - I_v$ plane.

To see the stability of endemic the equilibrium point for $\mathcal{R}_0 > 1$, the system (3.4.1) is simulated for the set of parameters in Table (3.6). For this set of parameters $R_0 = 1.342475$ and the endemic equilibrium point E_5 comes out to be $(23.28, 1431.2, 7.6814, 29.1, 425.75, 75, 7122.7)$. The phase portrait of this equilibrium point in $N_h - I_h$, $N_v - I_v$ and $P - L$ planes are shown in Figures $(3.8) - (3.10)$.

Table 3.4: Parameter values used in the numerical simulations.

Notation	Value	Notation	Value
g	60	d	0.05
Γ	0.5	d_1	0.02
ν	0.2	λ_v	0.0625
α_1	0.2	α_2	0.5
q	0.3	E	0.5
r	0.2	d_v	0.05
c	0.5	K	2000
β	0.6	d_h	0.00003913
γ	0.1	ρ	0.005
b	0.5	μ	0.00005

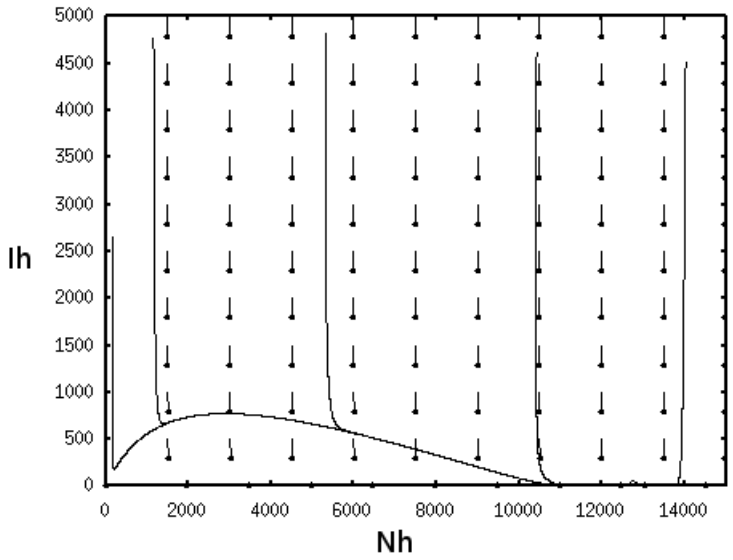

Figure 3.3: Phase plot of I_h verses N_h showing the stability of the disease free equilibrium.

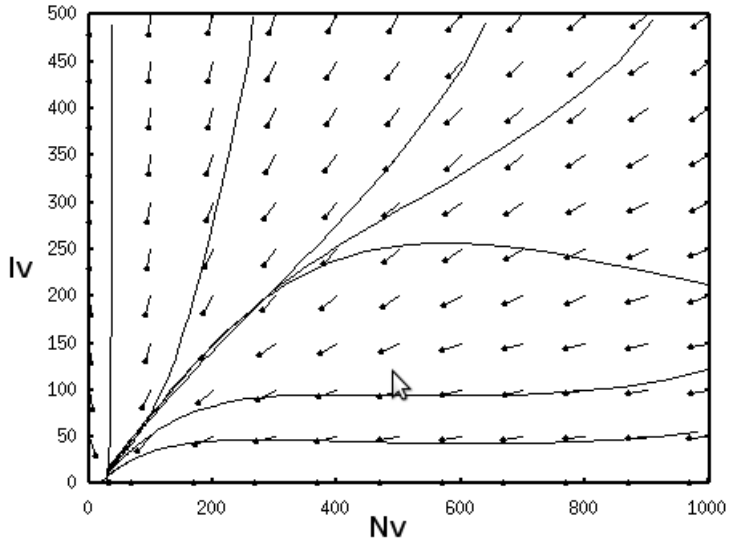

Figure 3.4: Phase plot of I_v verses N_v showing the stability of the disease free equilibrium.

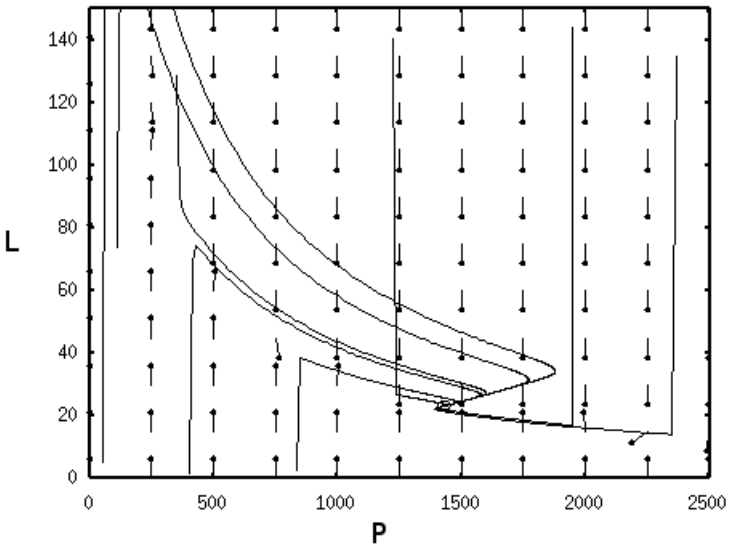

Figure 3.5: Phase portrait of the system in $P - L$ plane.

Table 3.5: Parameter values used in the numerical simulations.

Notation	Value	Notation	Value
g	60	d	0.05
Γ	0.7	d_1	0.02
ν	0.2	λ_v	0.0625
α_1	0.1	α_2	0.5
q	0.4	E	0.9
γ	0.1	r	0.01
c	0.5	K	2000
β	0.4	d_h	0.00003913
d_v	0.1	ρ	0.005
b	0.5	μ	0.002

Table 3.6: Parameter values used in the numerical simulations.

Notation	Value	Notation	Value
g	60	d	0.05
Γ	0.3	d_1	0.02
ν	0.2	λ_v	0.0625
α_1	0.2	α_2	0.5
q	0.3	E	0.5
r	0.2	d_v	0.05
c	0.5	K	2000
β	0.6	d_h	0.00003913
γ	0.1	ρ	0.005
b	0.5	μ	0.00005

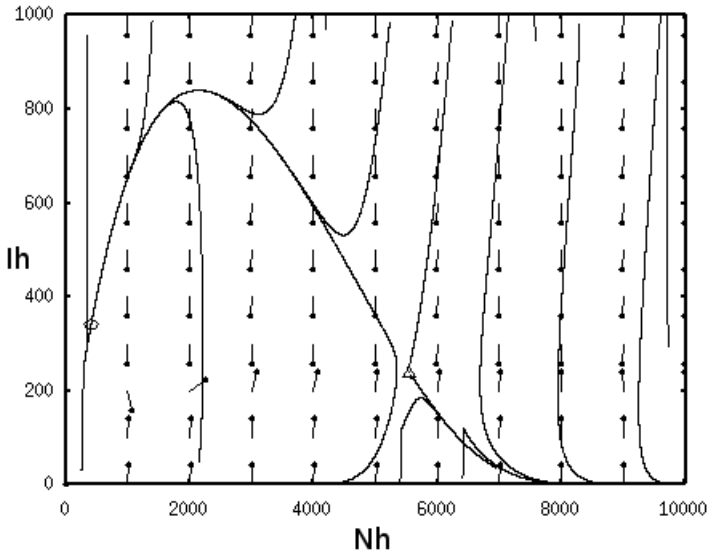

Figure 3.6: Phase portrait in $N_h - I_h$ plane for $R_0 < 1$ and the backward bifurcation condition $a > 0, b > 0$.

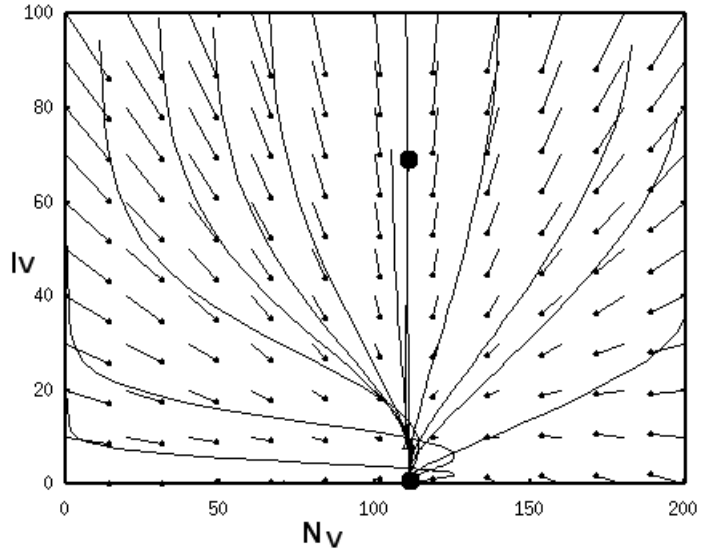

Figure 3.7: Phase portrait in $N_v - I_v$ plane for $R_0 < 1$ showing bi-stability.

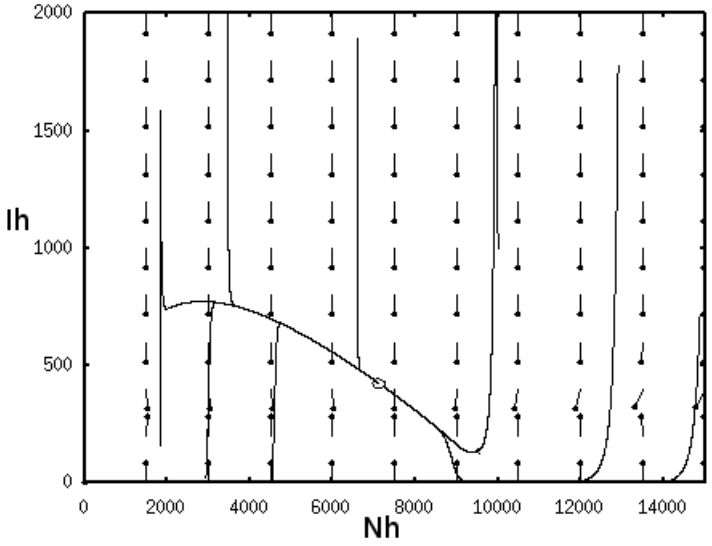

Figure 3.8: The phase portrait of endemic equilibrium point E_5 in $N_h - I_h$ plane.

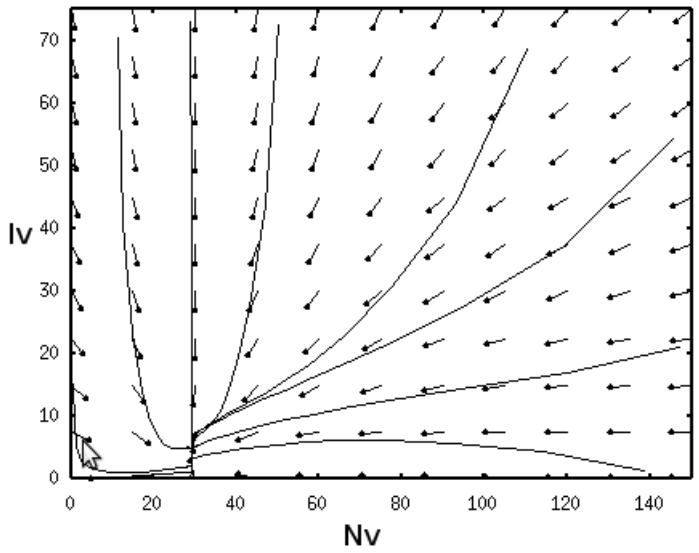

Figure 3.9: The phase portrait of endemic equilibrium point E_5 in $N_v - I_v$ plane.

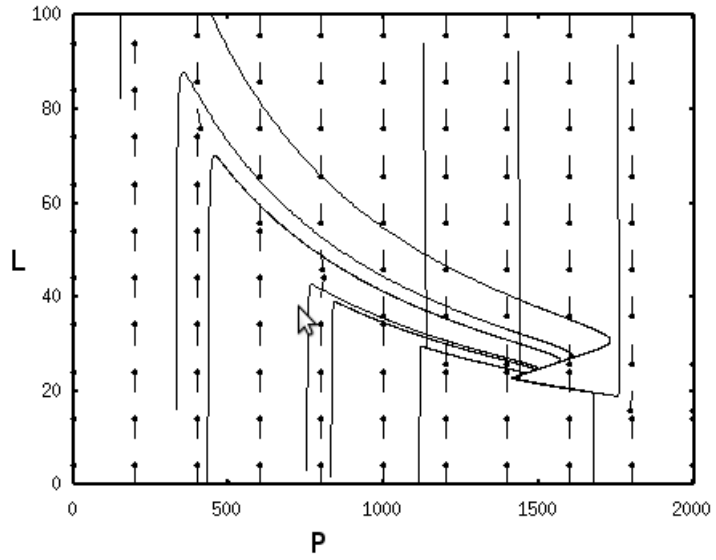

Figure 3.10: The phase portrait of endemic equilibrium point E_5 in $L - P$ plane.

Finally to see the effect of introduction of larvivorous fish, we change the parameter α_1 and keep all other parameters as in Table (3.5). The variation of infected human population with time for different α_1 is shown in Figure (3.11). It is observed that for small value of α_1 the equilibrium level of I_h is high and as we increase α_1, the equilibrium level of infected human population decreases and finally further increase in α_1 makes $\mathcal{R}_0 < 1$ and which makes the disease free equilibrium point E_4 to be stable and hence the infected human population tends to zero.

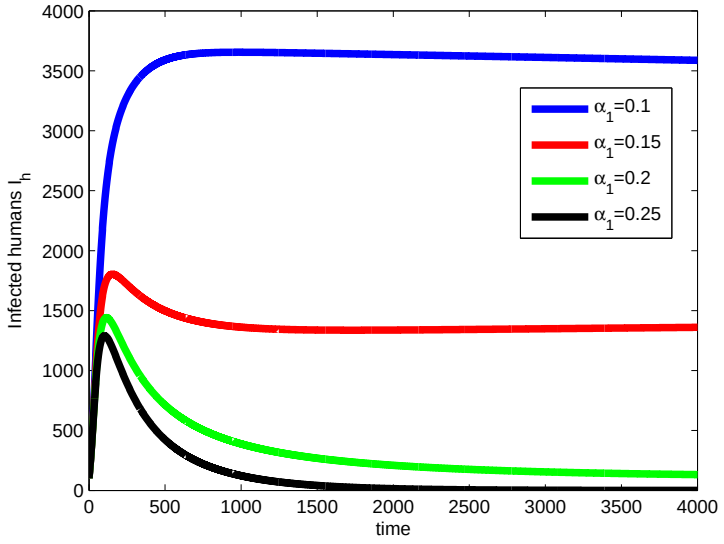

Figure 3.11: The variation of infected human population with time for different values of α_1.

3.9 Conclusions

In this chapter, we have developed and analyzed a nonlinear mathematical model for malaria which incorporates the introduction of predatory fish as a biological control agent. For mosquitoes population we consider two stages, i.e. larvae and adult so that control can be applied to both stages of mosquitoes population. Equilibria of the model are found and stability of these equilibria are discussed using variational matrix method. The disease free equilibrium is locally asymptotically stable whenever $\mathcal{R}_0 < 1$ and is unstable for $\mathcal{R}_0 > 1$. For $\mathcal{R}_0 > 1$ the endemic equilibrium point is always locally asymptotically stable. As this model exhibits backward bifurcation, so $\mathcal{R}_0 < 1$ is not sufficient to eliminate the disease from the population and we need another threshold less than one and $\mathcal{R}_0$ should be reduced below this threshold to eliminate the disease from the population. This fact is demonstrated in the backward bifurcation diagram. Usually, in case of forward

bifurcation, disease dies out when the reproduction number is less than unity while in case of backward bifurcation disease may persist even the reproduction number is less than unity. Also it is observed that with the introduction of predatory fish, the equilibrium level of larvae population decreases which causes the decrease in the equilibrium level of adult mosquito population and this decreases the basic reproduction number. So introduction of larvivorous fish has positive impact in controlling the transmission of malaria. Further, numerical simulation is performed to demonstrate the analytical results.

Chapter 4

Formulation of a Vector Borne Disease Model with Direct Transmission

4.1 Overview

The work in this chapter is based on the design and analysis of suitable compartmental model for the transmission dynamics of a vector borne disease in a population. A basic model which allows direct and indirect transmission is formulated and rigorously analysed. The model consider the transmission of the disease between two different populations, human host population, and mosquito vector population. It has a locally-asymptotically stable disease-free equilibrium whenever the basic reproduction number ($\Re_0$) is less than unity. Using Lyapunov function theory some sufficient conditions for global stability of both the disease-free equilibrium and the endemic equilibrium are obtained. For the basic reproductive number $\Re_0 > 1$, a unique endemic equilibrium exists and is globally asymptotically stable. Finally, using Matlab, numerical simulations are carried out to investigate the influence of the key parameters on the spread of the vector born disease, to support the analytical conclusion and illustrate possible behavioral scenarios of the model.

4.2 Introduction

Mathematical modeling involves the use of mathematics to describe, explain, or predict behavior or phenomena in the real world. It is particularly useful in investigating questions or testing ideas within complex systems. A mathematical model is an abstraction of a physical system that uses precise language to describe the system's behavior. The model is then analyzed, solved, or simulated on a computer. The results can be interpreted in physical terms to aid understanding of the underlying system or to point the parts of the system that might be targeted for change.

The model first proposed by Ross [55] and subsequently modified by Macdonald [90] has influenced both the modeling and the application of control strategies to a vector-borne disease malaria. Models of malaria that investigate complications arising from host superinfection, immunity, and other factors [1, 7, 91, 92] are based on the fundamental model proposed by Ross. This model has also influenced the mathematical analysis of many other vector-borne diseases [63, 97]. In almost all the contribution in modeling the spread of a vector borne disease, many of the contributes consider that vector borne disease such as malaria, dengue fever, West Nile virus, and so forth, are only transmitted to the human host population through the bite of infected mosquitoes. However some evidences have shown that direct transmission (transfusion related transmission, blood transmission, transplantation related transmission, and needle-stick-related transmission) of a vector borne disease is also possible [3]. An account of the modeling with direct transmission in addition to mosquitoes vector transmission can be found in [7, 10]. The assumption of constant population size in epidemiological models is relatively valid for diseases of short duration with limited effects on mortality. However, this assumption fails to hold for diseases that are endemic in a population with changing population size, and for diseases which raise the mortality rate. Considering this situation, the effects of changing population size and disease induced mortality are far from negligible in the modeling of epidemics especially a vector borne disease [80]. In

this chapter, we extend the model of Cai and Li [10] to include exposed individuals, disease induced death rate and time dependent total population size in both host and vector populations.

4.3 Model frame work

To develop a compartmental model, we consider the transmission of the disease between two different populations, human host population, $N_h(t)$, and mosquito vector population, $N_v(t)$. In our compartmental model, we sub-divided the total humans host and mosquito vectors populations into different sub-populations. The total humans host population at time (t), denoted by $N_h(t)$ is split into four distinct epidemiological subclasses of individuals which are: susceptible $S_h(t)$, exposed $E_h(t)$, infectious $I_h(t)$ and recovered, $R_h(t)$, so that $N_h = S_h + E_h + I_h + R_h$. People recruited in the susceptible class either through birth or through immigration. Susceptible human can be infected via two routes of transmission, that is directly through a contact with an infectious individual (possibly as a result of transfusion related transmission, transplantation related transmission, or needle-stick-related transmission etc) and through being bitten by an infectious vector. The interactions between humans host and mosquitoes vector have been assumed a mass-action type interaction [85]. The host enters the exposed class from the susceptible class after bitten by an infectious mosquito vector. After a certain period of time exposed humans host develop symptoms of the disease and then enter to the infectious class. After some time, the infectious humans recover and move to the recovered class. The recovered human host are assumed to acquire permanent immunity and there is no transfer from the recovered class back to the susceptible class. Humans host leave the population through natural and due to disease induced death rates.

The total mosquito vectors population is divided into three sub-classes: susceptible vector, exposed vector and infectious vector, with densities denoted by $S_v(t)$, $E_v(t)$ and $I_v(t)$, respectively. Here $N_v = S_v + E_v + I_v$ denotes the number of

the total vector population at time t. The recovered (immune) class in the vector population does not exist, since the mosquitoes once infected never recover from infection, that is, their infection period ends with their death. The mosquito vectors enter the susceptible class through birth. Newly infected mosquitoes vector move to the exposed class E_v from the susceptible class S_v, with some probability, after biting an infectious human host. After some period of time the mosquito progress from the exposed class to the class of symptomatic mosquitoes vector I_v. The mosquito remains infectious for life. Mosquitoes leave the population through natural death and disease induced death rates. The model also includes human disease-induced death rate because mortality for a vector borne disease in areas of high transmission can be high. The dynamics of the disease in human host and mosquito vector populations is depicted in Figure (4.1).

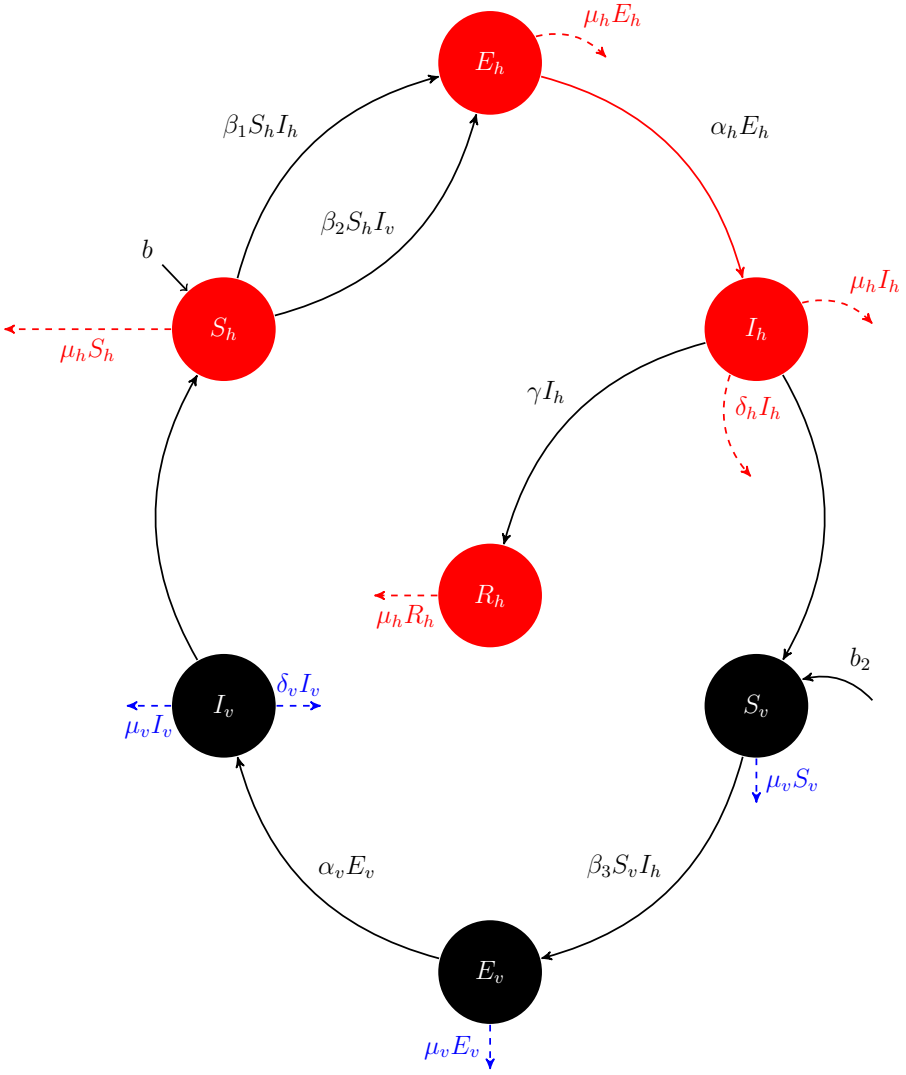

Figure 4.1: The schematic flow chart of a vector borne disease transmission model representing the interaction and transfer of both human and vector populations.

This model has three differences from those reported in the previous model (chapter 3). The first is that exposed (latent) and immune classes in host population denoted by E_h and R_h, respectively and an exposed E_v class in vector population is incorporated. The second is that, in order to keep things simple the incidence term is assumed to be of the bilinear mass-action form and a disease induced death rate in vector population denoted by δ_v is included. Finally, susceptible human hosts can get infected via direct route of transmission, through

a contact with an infectious individual in addition to an indirect transmission, through being bitten by an infectious vector. Also rigorous qualitative analysis will be presented for the resulting vector host epidemic model.

The transfer diagram Figure (4.1) and the assumptions above lead to the following epidemic model consisting of nonlinear system of seven ordinary differential equations:

$$\begin{cases} \dfrac{dS_h}{dt} = b_1 - \beta_1 S_h I_h - \beta_2 S_h I_v - \mu_h S_h, \\ \dfrac{dE_h}{dt} = \beta_1 S_h I_h + \beta_2 S_h I_v - \alpha_h E_h - \mu_h E_h, \\ \dfrac{dI_h}{dt} = \alpha_h E_h - \gamma_h I_h - \mu_h I_h - \delta_h I_h, \\ \dfrac{dR_h}{dt} = \gamma_h I_h - \mu_h R_h, \\ \dfrac{dS_v}{dt} = b_2 - \beta_3 S_v I_h - \mu_v S_v, \\ \dfrac{dE_v}{dt} = \beta_3 S_v I_h - \alpha_v E_v - \mu_v E_v, \\ \dfrac{dI_v}{dt} = \alpha_v E_v - \mu_v I_v - \delta_v I_v, \end{cases} \tag{4.3.1}$$

with initial conditions

$$S_h(0) \geq 0,\ E_h(0) \geq 0,\ I_h(0) \geq 0,\ R_h(0) \geq 0,\ S_v(0) \geq 0,\ E_v(0) \geq 0,\ I_v(0) \geq 0. \tag{4.3.2}$$

The parameters used in the model are shown in Table 4.1.

As in the terms, $\beta_1 S_h I_h$ denotes the rate at which the human hosts S_h get infected by infectious human hosts I_h, $\beta_2 S_h I_v$ denotes the rate at which the human hosts S_h get infected by infectious mosquitoes vector I_v, and $\beta_3 S_v I_h$ denotes the rate at which the mosquitoes vector S_v get infected by infectious humans host I_h. All parameters are assumed to be strictly positive except the disease-related death rates which are assume to be nonnegative.

Table 4.1: Parameter definitions for the model (4.3.1).

b_1:	The human host input (birth) rate.
β_1 :	The rate of direct transmission of the disease.
β_2:	The rate of transmission of the disease from mosquito to human.
β_3	The rate of transmission of the disease from human to mosquito.
μ_h:	Natural death rate of humans.
α_h:	Progression rate from E_h to I_h class.
γ_h:	Recovery rate for humans.
δ_h:	Disease-induced death rate for humans.
b_2:	Recruitment rate of mosquitoes.
μ_v:	Natural death rate of mosquito.
α_v:	Progression rate from E_v to I_v class.
δ_v:	Disease-induced death rate for mosquitoes.

4.4 Mathematical analysis of the model

4.4.1 Positivity of solutions

In this section, we will analyze the general properties of the system (4.3.1) with positive initial conditions. The model (4.3.1) describes the human host and mosquito vector population, and, therefore, it is very important to prove that all variables describing the dynamics of the populations will be positive. In particular, the objective is to prove that all solutions of the system (4.3.1) with positive initial conditions will be positive for all $t > 0$.

Theorem 4.4.1. *Let the initial conditions be given by (4.3.2). Then the solutions* $(S_h, E_h, I_h, R_h, S_v, E_v, I_v)$ *of the system (4.3.1) are positive for all* $t > 0$.

Proof. Let us take

$$t^* = \sup\{t > 0 : \ S_h > 0, \ E_h \geq 0, \ I_h \geq 0, \ R_h > 0, \ S_v > 0, \ E_v \geq 0, \ I_v \geq 0\}.$$

Thus, $t^* > 0$. Then, from the first equation of the system (4.3.1) we have

$$\begin{aligned}\frac{dS_h}{dt} &= b_1 - \beta_1 S_h I_h - \beta_2 S_h I_v - \mu_h S_h, \\ &= b_1 - (\beta_1 I_h + \beta_2 I_v + \mu_h) S_h.\end{aligned}$$

Letting $f(t) = \beta_1 I_h(t) + \beta_2 I_v(t)$, above equation can be written as

$$\frac{d}{dt}\left(S_h \exp\left\{\int_0^t f(u)du + \mu_h t\right\}\right) = b_1 \exp\left\{\int_0^t f(u)du + \mu_h t\right\},$$

integrating both sides from $t = 0$ to $t = t^*$

$$S_h(t^*)\exp\left\{\int_0^{t^*} f(u)du + \mu_h t^*\right\} - S_h(0) = \int_0^{t^*} b_1 \exp\left\{\int_0^x f(x)dx + \mu_h y\right\}dy,$$

multiplying both sides by $\exp\left\{-\int_0^{t^*} f(u)du - \mu_h t^*\right\}$

$$\begin{aligned}S_h(t^*) &= S_h(0)\exp\left\{-\int_0^{t^*} f(u)du - \mu_h t^*\right\} + \exp\left\{-\int_0^{t^*} f(u)du - \mu_h t^*\right\} \\ &\quad \times \int_0^{t^*} b_1 \exp\left\{\int_0^x f(x)dx + \mu_h y\right\}dy > 0.\end{aligned}$$

Thus $S_h(t^*)$ being the sum of positive terms is positive. By the same argument it can be proved that the quantities $E_h,\ I_h,\ R_h,\ S_v,\ E_v$, and I_v are positive for all time $t > 0$.

4.4.2 Invariant region

Proposition 4.4.2. *Let $(S_h, E_h, I_h, R_h, S_v, E_v, I_v)$ be the solution of the system (4.3.1) with initial conditions (4.3.2) and the biologically-feasible region $\Omega = \Omega_h \times \Omega_v$ with*

$$\Omega_h = \{(S_h, E_h, I_h, R_h) \in R_+^4 : N_h \leq \frac{b_1}{\mu_h}\},$$

and

$$\Omega_v = \{(S_v, E_v, I_v) \in R_+^3 : N_v \leq \frac{b_2}{\mu_v}\}.$$

Then Ω is positively invariant and attracting under the flow described by the system (4.3.1).

Proof. Adding the expressions in the right-hand sides of the equations in the model (4.3.1) gives

$$\big(\frac{dN_h}{dt}, \frac{dN_v}{dt}\big) = (b_1 - \mu_h N_h - \delta_h I_h, b_2 - \mu_v N_v - \delta_v I_v). \tag{4.4.1}$$

Since $0 \leq I_h \leq N_h$ and $0 \leq I_v \leq N_v$,

$$\begin{cases} \dfrac{dN_h}{dt} \leq b_1 - \mu_h N_h \leq 0, & \text{for } N_h \geq \frac{b_1}{\mu_h}, \\ \dfrac{dN_v}{dt} \leq b_2 - \mu_v N_v \leq 0, & \text{for } N_v \geq \frac{b_2}{\mu_v}. \end{cases} \tag{4.4.2}$$

It follows from (4.4.2) that $\big(\frac{dN_h}{dt} \leq 0, \frac{dN_v}{dt} \leq 0\big)$. Since $\frac{dN_h}{dt} \leq b_1 - \mu_h N_h$ and $\frac{dN_v}{dt} \leq b_2 - \mu_v N_v$, a standard comparison theorem [101] can be used to show that $(0,0) \leq (N_h, N_v) \leq \big(N_h(0)e^{-\mu_h t} + \frac{b_1}{\mu_h}(1 - e^{-\mu_h t}), N_v(0)e^{-\mu_v t} + \frac{b_2}{\mu_v}(1 - e^{-\mu_v t})\big)$. If $N_h(0) \leq \frac{b_1}{\mu_h}$ and $N_v(0) \leq \frac{b_2}{\mu_v}$, then $N_h(t) \leq \frac{b_1}{\mu_h}$ and $N_v(t) \leq \frac{b_2}{\mu_v}$. Hence, the set Ω is positively-invariant (i.e., all initial solutions in Ω remain in Ω for all $t > 0$). Thus as $t \to \infty$, $0 \leq (N_h, N_v) \leq (\frac{b_1}{\mu_h}, \frac{b_2}{\mu_v})$ and we can conclude that Ω is an attracting set. $\square$

Thus, every solution of the model (4.3.1), with initial condition in Ω remains there for $t > 0$. Furthermore, in Ω the usual existence, uniqueness and continuation results hold for the system, so that the system (4.3.1), is well-posed mathematically and epidemiologically [1]. Hence, it is sufficient to study the dynamics of the flow generated by the model (4.3.1) in Ω.

4.5 Disease free equilibrium and its stability

Disease-free equilibrium points are steady state solutions where there is no disease in either the human host or mosquito vector populations. In order to understand dynamical behavior of the system (4.3.1), we set right hand side of all equations in the system (4.3.1) equal to zero. Direct calculations shows that the system (4.3.1) has a disease free equilibrium point given by

$$\mathcal{E}_f = (S_h^0, 0, 0, 0, S_v^0, 0, 0),$$

where $S_h^0 = \frac{b_1}{\mu_h}$ and $S_v^0 = \frac{b_2}{\mu_v}$. The disease free steady states has a strong influence on the behavior of disease transmission in a community. If we are looking for the elimination of the disease, we have to establish the conditions under which the disease free equilibrium is stable.

The dynamics of the disease is described by the quantity $\Re_0$ as follows:

$$\Re_0 = \frac{b_1}{\mu_h}\left(\frac{\alpha_h \alpha_v b_2 \beta_2 \beta_3}{\mu_v Q_1 Q_2 Q_3 Q_4} + \frac{\alpha_h \beta_1}{Q_1 Q_2}\right), \tag{4.5.1}$$

with

$$\begin{cases} Q_1 = \alpha_h + \mu_h, \\ Q_2 = \gamma_h + \mu_h + \delta_h, \\ Q_3 = \alpha_v + \mu_v, \\ Q_4 = \mu_v + \delta_v. \end{cases}$$

The threshold quantity $\Re_0$, is called the basic reproduction number of the disease [39,99]. It represents the expected average number of new infections produced directly and indirectly by a single infective when introduced into a completely susceptible population. For classical epidemic models, it is common that the basic reproduction number is threshold in a sense that, when the basic reproduction number $\Re_0 < 1$, on average each infected individual infects fewer than one individual, and the disease dies out. If $\Re_0 > 1$, on average each infected individual, infects more than one other individual, so we would expect the disease to spread. It is standard in epidemiologic modeling to focus on $\Re_0$ as a stability criterion. Thus, to investigate control strategies, the approach adopted in [34] consists of studying parameters values for which R_0 was either above or below unity.

To prove stability results at the disease free equilibrium $\mathcal{E}_f$, we calculate the Jacobian matrix $\mathcal{J}(\mathcal{E}_f)$ at $\mathcal{E}_f$.

Theorem 4.5.1. *If $\Re_0 < 1$, then the disease-free equilibrium point $\mathcal{E}_f$ of the model (4.3.1) is locally asymptotically stable, otherwise unstable.*

Proof. In order to examine the local stability of the disease-free equilibrium, the Jacobian matrix should be evaluated at the equilibrium point $\mathcal{E}_f$. Linearizing the

system (4.3.1) around $\mathcal{E}_f$ gives the following Jacobian matrix

$$\mathcal{J}(\mathcal{E}_f) = \begin{pmatrix} -\mu_h & 0 & -\beta_1\frac{b_1}{\mu_h} & 0 & 0 & 0 & -\beta_2\frac{b_1}{\mu_h} \\ 0 & -Q_1 & \beta_1\frac{b_1}{\mu_1} & 0 & 0 & 0 & \beta_2\frac{b_1}{\mu_h} \\ 0 & \alpha_h & -Q_2 & 0 & 0 & 0 & 0 \\ 0 & 0 & \gamma_h & -\mu_h & 0 & 0 & 0 \\ 0 & 0 & -\beta_3\frac{b_2}{\mu_v} & 0 & -\mu_v & 0 & 0 \\ 0 & 0 & \beta_3\frac{b_2}{\mu_v} & 0 & 0 & -Q_3 & 0 \\ 0 & 0 & 0 & 0 & 0 & \alpha_v & -Q_4 \end{pmatrix}. \tag{4.5.2}$$

Routh-Hurwitz Criteria [96] insures that the stability at the disease free equilibrium will be obtained if all the eigenvalues of the Jacobian matrix $\mathcal{J}(\mathcal{E}_f)$ have negative real parts. The characteristic equation of the above matrix is

$$(\lambda+\mu_h)(\lambda+\mu_h)(\lambda+\mu_v)(\lambda^4+a_1\lambda^3+a_2\lambda^2+a_3\lambda+a_4)=0, \tag{4.5.3}$$

where

$$\begin{aligned} a_1 &= Q_1+Q_2+Q_3+Q_4, \\ a_2 &= Q_1Q_2+Q_1Q_3+Q_1Q_4+Q_2Q_3+Q_2Q_4+Q_3Q_4-\frac{b_1\alpha_h\beta_1}{\mu_h}, \\ a_3 &= Q_1Q_3Q_4+Q_2Q_3Q_4+(Q_3+Q_4)(Q_1Q_2-\frac{b_1\alpha_h\beta_1}{\mu_h}), \\ a_4 &= Q_1Q_2Q_3Q_4(1-R_0). \end{aligned}$$

There are seven eigenvalues corresponding to equation (4.5.3). Three of the eigenvalues, $-\mu_h$ with multiplicity two and $-\mu_v$, have negative real part. The other four eigenvalues are the solutions of the fourth-order polynomial equation

$$\delta(\lambda)=\lambda^4+a_1\lambda^3+a_2\lambda^2+a_3\lambda+a_4. \tag{4.5.4}$$

Now, from the stability point of view, we want to know whether there is a solution λ of the polynomial (4.5.4) with positive real part. If such a solution λ of the polynomial (4.5.4) exist, then the equilibrium point E_f is unstable, otherwise, it is locally asymptotically stable. The coefficients a_1, a_2 are always positive but a_3, a_4 could be negative. It is easily verified that if $\Re_0 < 1$, $a_4 > 0$ and $Q_1Q_2 > b_1\alpha_h\beta_1/\mu_h$, hence $a_3 > 0$. Thus, all $a_i > 0$ for $i = 1, 2, 3, 4$ and the positivity of all the coefficient

a_i imply that there are no positive real solutions for the polynomial equation (4.5.4). The necessary and sufficient conditions for the local stability follows by applying Routh-Hurwitz criteria to the characteristic equation (4.5.4). Since $a_i > 0$, all roots have negative real parts if and only if

$$\begin{aligned}
\triangle_1 &= a_1 > 0 \\
\triangle_2 &= \begin{vmatrix} a_1 & 1 \\ 0 & a_2 \end{vmatrix} > 0, \\
\triangle_3 &= \begin{vmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ 0 & 0 & a_3 \end{vmatrix} > 0, \\
\triangle_4 &= \begin{vmatrix} a_1 & 1 & 0 & 0 \\ a_3 & a_2 & a_1 & 1 \\ 0 & a_4 & a_3 & a_2 \\ 0 & 0 & 0 & a_4 \end{vmatrix} > 0.
\end{aligned}$$

It is clear that $a_1, a_2 > 0$, provided $\Re_0 < 1$, hence $\triangle_1, \triangle_2 > 0$. For the disease free equilibrium $\mathcal{E}_f$ to be stable, we only need here to prove that $\triangle_3, \triangle_4 > 0$.

$$\begin{aligned}
\triangle_3 = a_1a_2 - a_3 = &\big(Q_1 + Q_2 + Q_3 + Q_4\big)\big(Q_1Q_2 + Q_1Q_3 + Q_1Q_4 \\
&+Q_2Q_3 + Q_2Q_4 + Q_3Q_4 - \frac{b_1\alpha_h\beta_1}{\mu_h}\big) - \big(Q_1Q_3Q_4 + Q_2Q_3Q_4 \\
&+(Q_3 + Q_4)(Q_1Q_2 - \frac{b_1\alpha_h\beta_1}{\mu_h})\big).
\end{aligned} \tag{4.5.5}$$

Rewriting equation (4.5.5) with some little rearrangement, we get the following equation

$$\begin{aligned}
\triangle_3 = &(Q_1 + Q_2)\big(Q_1Q_2 + Q_1Q_3 + Q_1Q_4 + Q_2Q_3 + Q_2Q_4 + Q_3Q_4 \\
&-\frac{b_1\alpha_h\beta_1}{\mu_h}\big) + Q_3\big(Q_1Q_3 + Q_1Q_4 + Q_2Q_3 + Q_2Q_4 + Q_3Q_4\big) \\
&+Q_4^2(Q_1 + Q_2 + 3Q_4).
\end{aligned} \tag{4.5.6}$$

Lastly,

$$\begin{aligned}\triangle_4 &= a_3(a_1a_2 - a_3) - a_1^2a_4 = \frac{\alpha_h\alpha_v b_1 b_2\beta_2\beta_3}{\mu_h\mu_v}(Q_1+Q_2+Q_3+Q_4)^2 \\ &\quad +(Q_3+Q_4)^2 + 2(Q_1Q_3+Q_1Q_4+Q_2Q_3+Q_2Q_4\frac{b_1\alpha_h\beta_1}{\mu_h})Q_3Q_4.\end{aligned} \tag{4.5.7}$$

Since $Q_1Q_2 > b_1\alpha_h\beta_1/\mu_h$, whenever $\Re_0 < 1$. Consequently from the equations (4.5.6) and (4.5.7), it is clear that $\triangle_3$ and $\triangle_4$ being the sum of positive terms are positive. Thus, by Routh-Hurwitz criteria [96] all the eigenvalues of the Jacobian matrix $\mathcal{J}(\mathcal{E}_f)$ have negative real parts whenever $\Re_0 < 1$, which shows that the disease free equilibrium $\mathcal{E}_f$ is locally asymptotically stable.

Remark . For $R_0 \geq 1$ or equivalently $a_4 < 0$, we have $\delta(0) < 0$ and $\lim \delta(\lambda) \to +\infty$ when $\lambda \in \mathbb{R}$ and $\lambda \to +\infty$. Then, there exists $\lambda^* > 0$ such that $\delta(\lambda^*) = 0$, which proves the instability of the disease-free equilibrium.

4.6 Existence of the endemic equilibria

Endemic (positive) equilibria are steady state solutions where the disease persists in the population (all state variables are positive). In order to find equilibria (endemic equilibria) of the system (4.3.1) where at least one of the infective components of the system (4.3.1) is non-zero, we need to take the following steps.

Let $\mathcal{E}_+ = (S_h^*, E_h^*, I_h^*, R_h^*, S_v^*, E_v^*, I_v^*)$ represents any arbitrary endemic equilibrium of the model (4.3.1). Solving the equations of the system (4.3.1) at steady,

we get

$$\begin{cases} S_h^* = \dfrac{Q_1Q_2Q_3Q_4(\mu_v + \beta_3 I_h^*)}{\alpha_h\beta_1Q_3Q_4(\mu_v + \beta_3 I_h^*) + \alpha_h\alpha_v b_2\beta_2\beta_3}, \\ E_h^* = \dfrac{Q_2}{\alpha_h} I_h^*, \\ R_h^* = \dfrac{\gamma_h}{\mu_h} I_h^*, \\ S_v^* = \dfrac{b_2}{\mu_v + \beta_3 I_h^*}, \\ E_v^* = \dfrac{\beta_3 b_2 I_h^*}{Q_3(\mu_v + \beta_3 I_h^*)}, \\ I_v^* = \dfrac{\beta_3\alpha_v b_2 I_h^*}{Q_3Q_4(\mu_v + \beta_3 I_h^*)}. \end{cases}$$

If $I_h^* \neq 0$, then substituting $S_h^*,\ I_v^*$ in the second equation of the system (4.3.1) at steady state, we obtain after some calculations the following quadratic equation:

$$f(I_h) = aI_h^2 + bI_h + c = 0, \tag{4.6.1}$$

where

$$\begin{aligned} a &= \beta_1\beta_3Q_1Q_2Q_3Q_4, \\ b &= (\beta_1\mu_v + \beta_3\mu_h)Q_1Q_2Q_3Q_4 + b_2\alpha_v\beta_2\beta_3Q_1Q_2 - b_1\alpha_h\beta_1\beta_3Q_3Q_4, \\ c &= \mu_h\mu_vQ_1Q_2Q_3Q_4(1 - R_0). \end{aligned} \tag{4.6.2}$$

For a positive endemic equilibrium $\mathcal{E}_+ > 0$, we need $a > 0$ and $c < 0$. Clearly the coefficient a is always positive, and c is positive (negative) if $\Re_0$ is less than (greater than) unity, respectively. It is easy to see from the theory of quadratic equations if y_1 and y_2 are the roots for the quadratic equation (4.6.1), then the product of the roots is $y_1y_2 = \frac{c}{a}$; and if $\frac{c}{a} < 0$ then we have one positive root of the equation (4.6.1). Since a is always positive and $c < 0$ when $\Re_0 > 1$, hence we have one and only one positive root for the equation (4.6.1) when $\Re_0 > 1$. If $\Re_0 > 1$, then there are two roots of the equation (4.6.1) of which one root is positive and thus there is a unique endemic equilibrium. Thus we have established the following result.

Lemma 4.6.1. *If $\Re_0 > 1$, then the model (4.3.1) has a unique positive endemic equilibrium $\mathcal{E}_+ > 0$ in Ω.*

In the following Section, we study the global behavior of the equilibrium solution for the system (4.3.1).

4.7 Global stability analysis

To ensure that disease elimination is independent of the initial sizes of the sub-populations, it is necessary to show that the disease free equilibrium is globally-asymptotically stable if $\Re_0 < 1$. The following theorem provides the global property of the disease free equilibrium $\mathcal{E}_f$ of the system (4.3.1).

Theorem 4.7.1. *If $\Re_0 \leq 1$, then the disease free equilibrium of the system (4.3.1) is globally asymptotically stable on Ω.*

Proof. The global stability of the disease-free equilibrium in Ω if $\Re_0 < 1$ can be shown by considering a new dependent variable (Lyapunov function) as follows:

$$V(t) = W_1\big(S_h - S_h^0 - S_h^0 \log\frac{S_h}{S_h^0}\big) + W_2E_h + W_3I_h + W_4\big(S_v - S_v^0 - S_v^0 \log\frac{S_v}{S_v^0}\big) + W_5E_v + W_6I_v, \tag{4.7.1}$$

where W_i, for i=1, 2...6 are some positive constants to be chosen later. Calculating the Lyapunov derivative of V along the solutions of system (4.3.1), we obtain

$$\begin{aligned} V'(t) = \; & W_1(\frac{S_h - S_h^0}{S_h})[b_1 - \beta_1 S_h I_h - \beta_2 S_h I_v - \mu_h S_h] + W_2[\beta_1 S_h I_h + \beta_2 S_h I_v - Q_1 E_h] \\ & + W_3[\alpha_h E_h - Q_2 I_h] + W_4(\frac{S_v - S_h^0}{S_v})[b_2 - \beta_3 S_v I_h - \mu_v S_v] + W_5[\beta_3 S_v I_h - \\ & Q_3 E_v] + W_6[\alpha_v E_v - Q_4 I_v], \end{aligned} \tag{4.7.2}$$

where $'$ denotes the derivative with respect to time t. Using the values $S_h^0 = \frac{b_1}{\mu_h}$ and $S_v^0 = \frac{b_2}{\mu_v}$ in (4.7.2), we have

$$\begin{aligned} V'(t) \; = \; & -\mu_h W_1 \frac{(S_h - S_h^0)^2}{S_h} - \mu_v W_4 \frac{(S_v - S_v^0)^2}{S_v} + (W_5 - W_4)\beta_3 S_v I_h + \\ & (W_2 - W_1)[\beta_1 S_h I_h + \beta_2 S_h I_v] + (W_3\alpha_h - W_2 Q_1)E_h \\ & + (W_6\alpha_v - W_5 Q_3)E_v + [\frac{W_4 b_2 \beta_3}{\mu_v} + \frac{W_1 b_1 \beta_1}{\mu_h} - W_3 Q_2]I_h \\ & [\frac{W_1 b_1 \beta_2}{\mu_h} - W_6 Q_4]I_v. \end{aligned} \tag{4.7.3}$$

Let us choose $W_1 = W_2 = \alpha_h/Q_1$, $W_3 = 1$, $W_4 = W_5 = \dfrac{b_1\alpha_h\alpha_v\beta_2}{\mu_h Q_1 Q_3 Q_4}$, $W_6 = \alpha_h b_1 \beta 2/\mu_h Q_1 Q_4$ and rewriting equation (4.7.3) with some little rearrangement, we get

$$V'(t) = -\frac{\alpha_h\mu_h}{Q_1}\frac{(S_h - S_h^0)^2}{S_h} - \frac{b_1\alpha_h\alpha_v\beta_2\mu_v}{\mu_h Q_1 Q_3 Q_4}\frac{(S_v - S_v^0)^2}{S_v} - Q_2(1 - R_0)I_h. \qquad (4.7.4)$$

Thus $V'(t)$ is negative if $\Re_0 \leq 1$. Also note that, $V'(t) = 0$ if and only if $S_h = S_h^0$, $S_v = S_v^0$, $E_h = I_h = R_h = 0$, $E_v = I_v = 0$. Therefore the largest compact invariant set in $\{(S_h, E_h, I_h, R_h, S_v, E_v, I_v) \in \Omega : V'(t) = 0\}$ is the singleton $\{E_1\}$, where $\mathcal{E}_f$ is the disease-free equilibrium point. It follows by the Lyapunov-Lasalle theorem [95], that every solution to the equations in the system (4.3.1), with initial conditions in Ω, approaches the disease free equilibrium $\mathcal{E}_f$ as $t \to \infty$. Further, the region Ω is positively-invariant, thus disease-free equilibrium $\mathcal{E}_f$ is globally asymptotically stable in Ω if $\Re_0 \leq 1$. This completes the proof. $\square$

The epidemiological importance of the above result is that the disease will be wiped-out from the population if $\Re_0 < 1$, regardless of the initial number of infected individuals.

The next result concerns the global stability of the endemic equilibrium $\mathcal{E}_+$ of the system (4.3.1). To establish the global stability of the endemic equilibrium, we follow closely the ideas used in [112].

Theorem 4.7.2. *If $\Re_0 > 1$, then the endemic equilibrium $\mathcal{E}_+$ of the system (4.3.1) is globally asymptotically stable on Ω if*

$$\begin{cases} \mu_h = \dfrac{b_1}{S_h^*}, \\ \mu_v = \dfrac{b_2}{S_v^*}, \\ \alpha_h = \dfrac{Q_1 Q_2}{2\beta_1 S_h^*}, \\ \alpha_v = \dfrac{Q_3 Q_4 \beta_1}{\beta_2 \beta_3 S_v^*}. \end{cases} \qquad (4.7.5)$$

Proof. Define the Lyapunov function

$$\begin{aligned} L(t) &= \frac{1}{\beta_1 S_h^*}(S_h - S_h^* \log S_h) + \frac{1}{\beta_3 S_v^*}(S_v - S_v^* \log S_v) + \frac{1}{\beta_1 S_h^*} E_h + \frac{2}{Q_2} I_h \\ &\quad + \frac{1}{\beta_3 S_v^*} E_v + \frac{\beta_2}{Q_4 \beta_1} I_v. \end{aligned} \tag{4.7.6}$$

Calculating the time derivative of L along the solutions of the system (4.3.1), we obtain

$$\begin{aligned} L'(t) &= \frac{1}{\beta_1 S_h^*}(S_h - S_h^*)(\frac{b_1}{S_h} - \beta_1 I_h - \beta_2 I_v - \mu_h) + \frac{1}{\beta_3 S_v^*}(S_v - S_v^*)(\frac{b_2}{S_v} - \beta_3 I_h - \mu_v) \\ &\quad + \frac{1}{\beta_1 S_h^*}(\beta_1 S_h I_h + \beta_2 S_h I_v - Q_1 E_h) + \frac{2}{Q_2}(\alpha_h E_h - Q_2 I_h) + \frac{1}{\beta_3 S_v^*}(\beta_3 S_v I_h \\ &\quad - Q_3 E_v) + \frac{\beta_2}{Q_4 \beta_1}(\alpha_v E_v - Q_4 I_v). \end{aligned} \tag{4.7.7}$$

After some rearrangement we have

$$L'(t) = -\frac{\mu_h}{\beta_1}\big(\frac{S_h}{S_h^*} + \frac{S_h^*}{S_h} - 2\big) - \frac{\mu_v}{\beta_3}\big(\frac{S_v}{S_v^*} + \frac{S_v^*}{S_v} - 2\big). \tag{4.7.8}$$

Since the arithmetic mean is greater than or equal to the geometric mean, we have

$$\frac{S_h}{S_h^*} + \frac{S_h^*}{S_h} \geq 2 \quad and \quad \frac{S_v}{S_v^*} + \frac{S_v^*}{S_v} \geq 2. \tag{4.7.9}$$

Thus, the condition (4.7.5) ensures that $L'(t) \leq 0$ for all $(S_h, E_h, I_h, R_h, S_v, E_v, I_v) \in \Omega$, and the strict equality $L'(t) = 0$ holds only for $S_h = S_h^*$, $S_v = S_v^*$, $E_h = E_h^*$ $I_h = I_h^*$, $R_h = R_h^*$, $E_v = E_v^*$, and $I_v = I_v^*$. Then, the equilibrium state $\mathcal{E}_+$ is the only positively invariant set of the system (4.3.1) contained entirely in $\Omega = \{(S_h, E_h, I_h, R_h, S_v, E_v, I_v),\ S_h = S_h^*, S_v = S_v^*, E_h = E_h^*, I_h = I_h^*, R_h = R_h^*, E_v = E_v^*\}$ and hence by the asymptotic stability theorem [95], the positive endemic equilibrium state $\mathcal{E}_+$ is globally asymptotically stable on Ω. □

The epidemiological importance of the above result is that the disease continued to spread in the population.

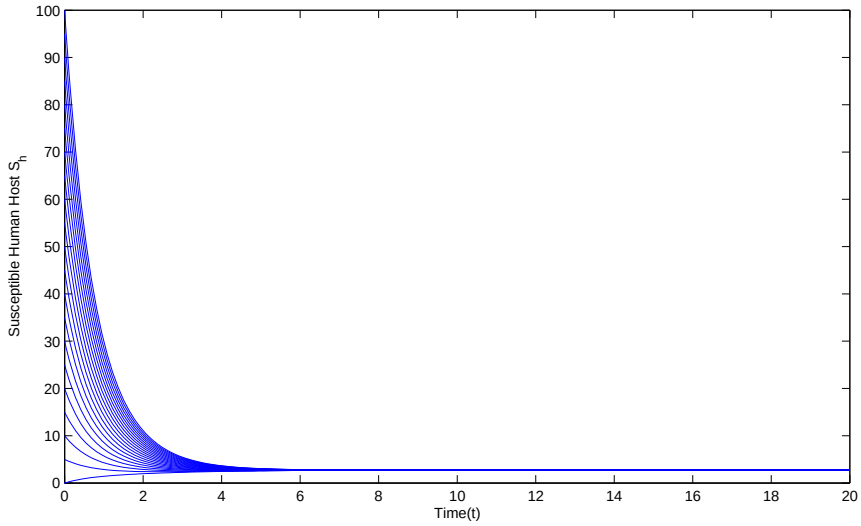

Figure 4.2: Time series plot of the model (4.3.1) with different initial conditions for the susceptible human host population S_h.

4.8 Numerical results and discussion

In this section the model is solved using Runge-Kutta fourth order scheme. The techniques in [102] can be used for solving a wide range of problems whose mathematical models yield system of differential equations.

To explore the behavior of the system and to demonstrate the stability of the disease free equilibrium, we consider the parameter values in Table (4.2). As evident from Figures $(4.2 - 4.8)$, the solution profiles converge to the disease free equilibrium. In Figures $(4.2 - 4.8)$, the result of Theorem (4.7.1) is illustrated using time series plot by simulating the model 4.3.1 and using parameter values for the case $\Re_0 < 1$ and various initial conditions. When $\Re_0 < 1$, all solutions of the system (4.3.1) converge to the disease free equilibrium, which implies that the disease is globally eradicated.

The stability of the endemic equilibrium in which the disease persist in both host and vector populations is represented in Figures $(4.9 - 4.14)$, using the parameter

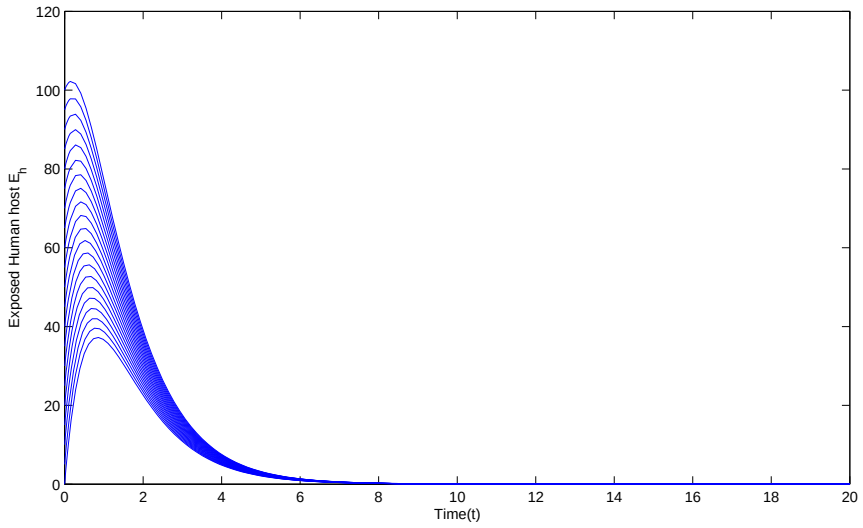

Figure 4.3: Time series plot of the model (4.3.1) with different initial conditions for the exposed human host population E_h.

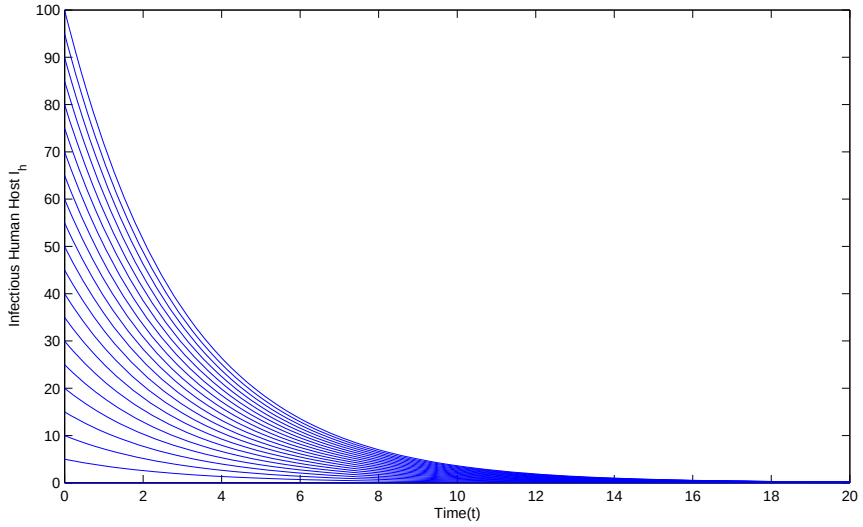

Figure 4.4: Time series plot of the model (4.3.1) with different initial conditions for the infected human host population I_h.

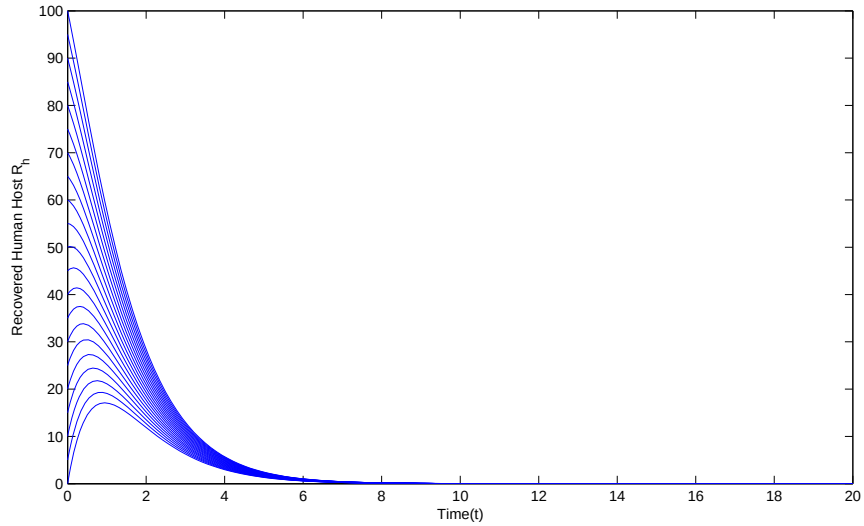

Figure 4.5: Time series plot of the model (4.3.1) with different initial conditions for the recovered human host population R_h.

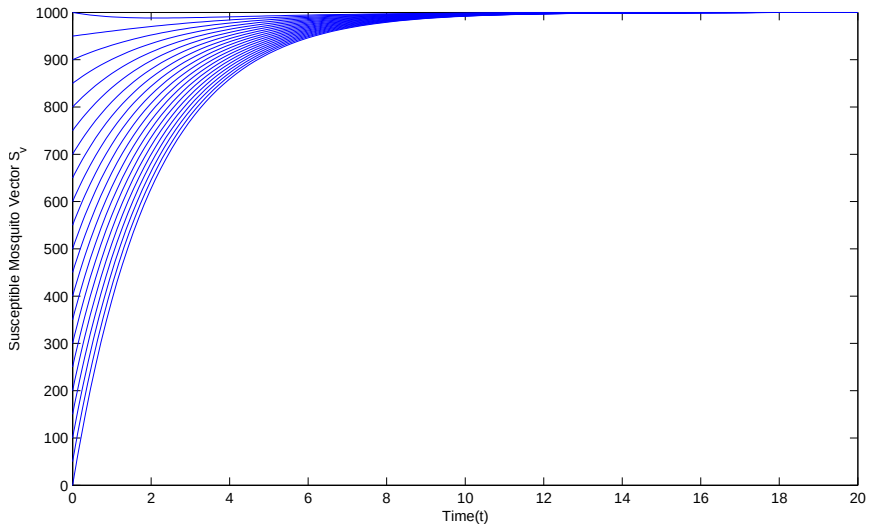

Figure 4.6: Time series plot of the model (4.3.1) with different initial conditions for the susceptible mosquito vector population S_v.

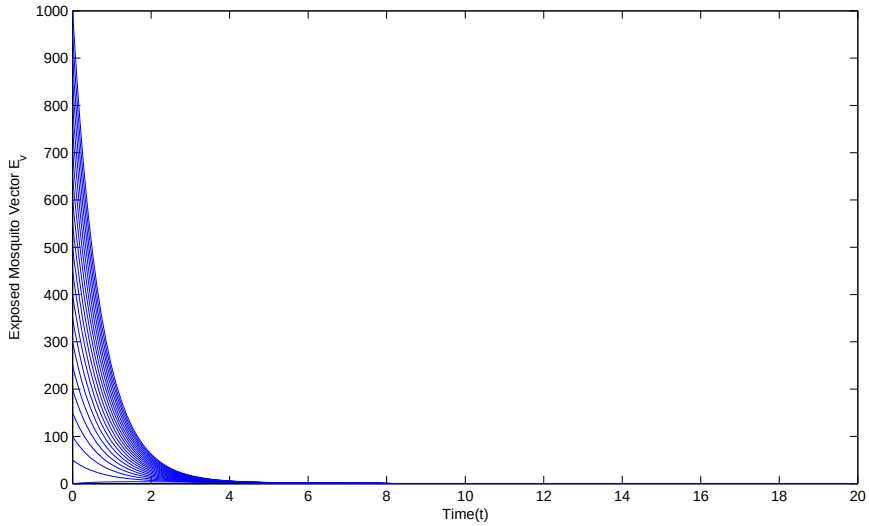

Figure 4.7: Time series plot of the model (4.3.1) with different initial conditions for the exposed mosquito vector population E_v.

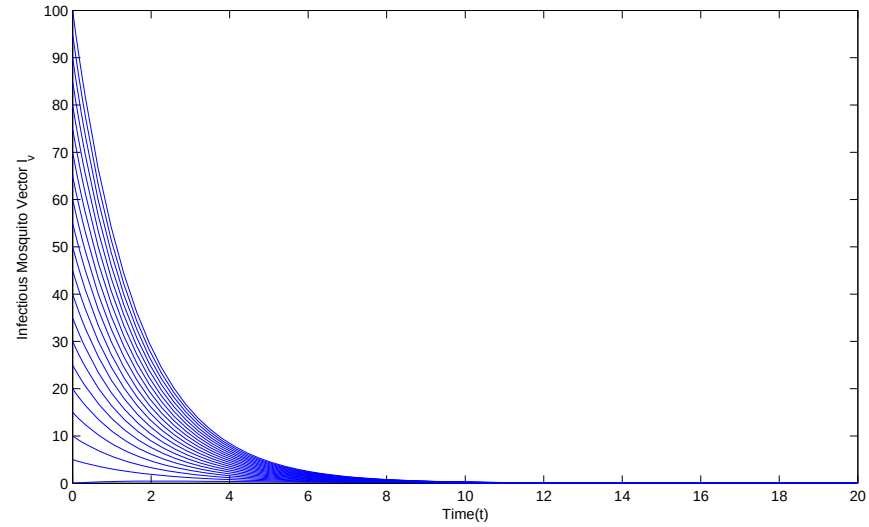

Figure 4.8: Time series plot of the model (4.3.1) with different initial conditions for the infected mosquito vector population I_v.

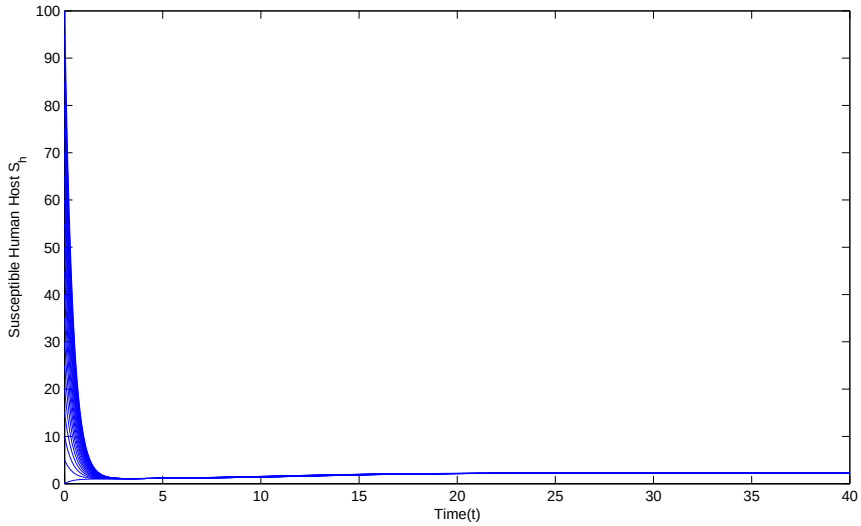

Figure 4.9: Time series plot of the model (4.3.1) with different initial conditions for the susceptible human host population S_h.

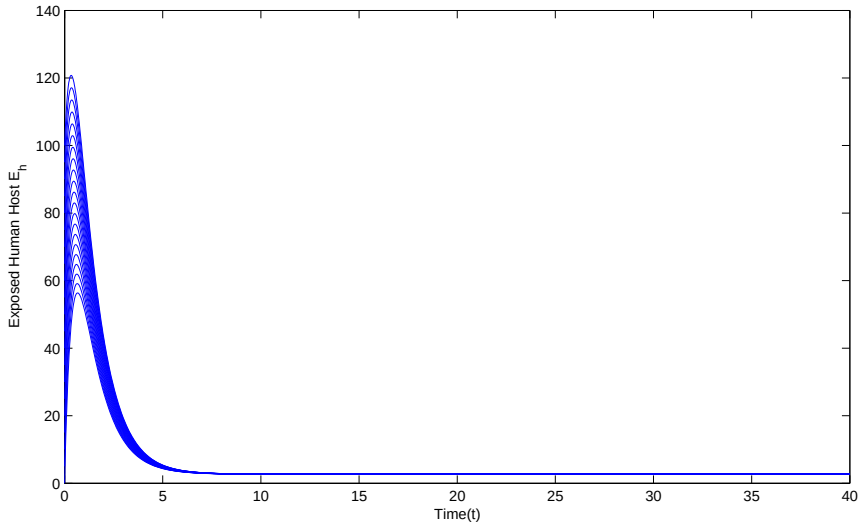

Figure 4.10: Time series plot of the model (4.3.1) with different initial conditions for the exposed human host population E_h.

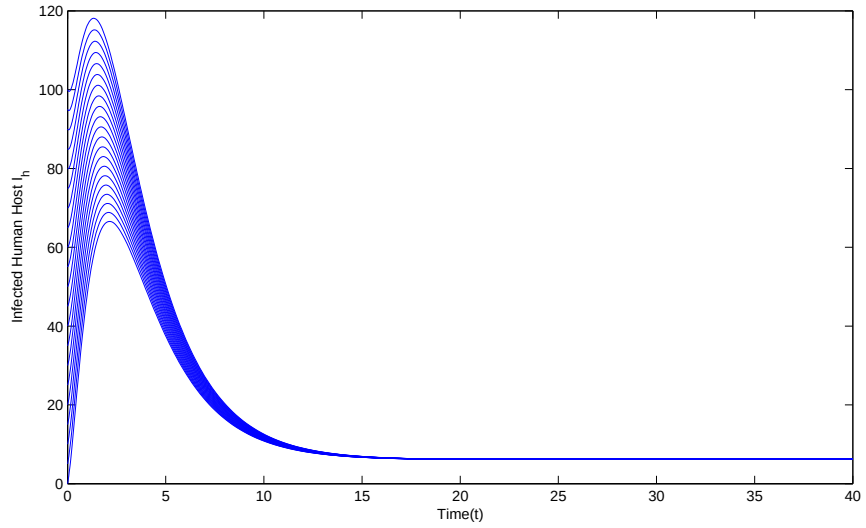

Figure 4.11: Time series plot of the model (4.3.1) with different initial conditions for the infected human host population I_h.

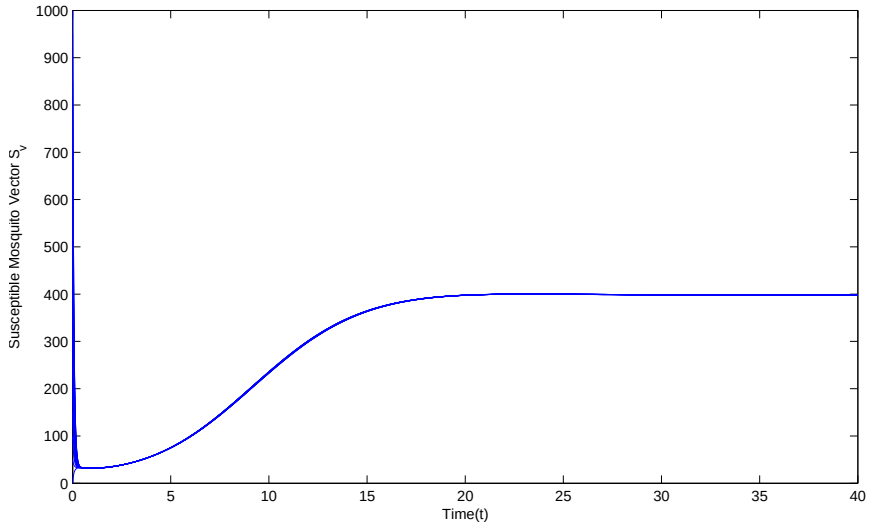

Figure 4.12: Time series plot of the model (4.3.1) with different initial conditions for the susceptible mosquito vector population S_v.

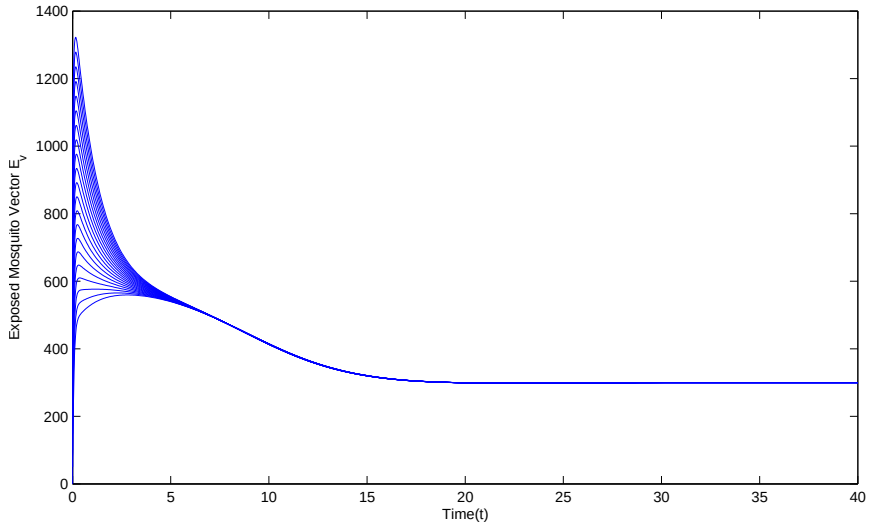

Figure 4.13: Time series plot of the model (4.3.1) with different initial conditions for the exposed mosquito vector population E_v.

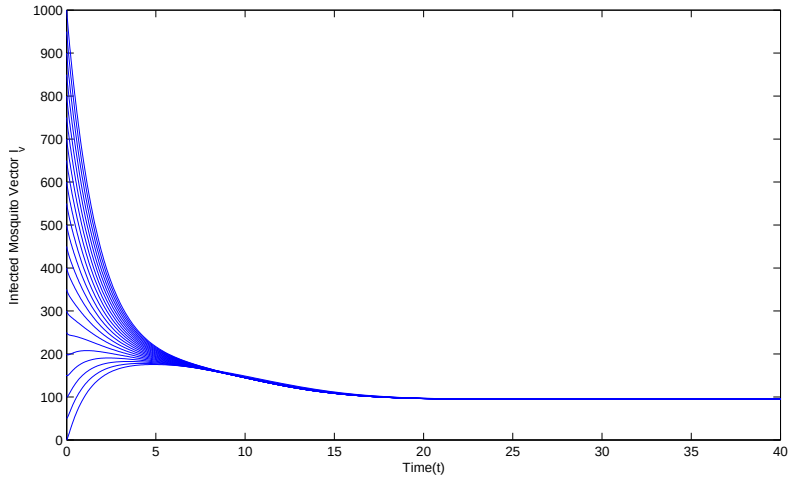

Figure 4.14: Time series plot of the model (4.3.1) with different initial conditions for the infected mosquito vector population I_v.

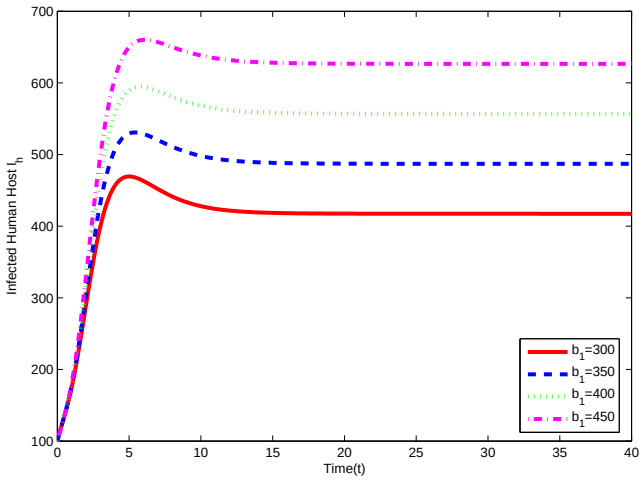

Figure 4.15: Variation of the infective human host population with time for different b_1 where other parameters are $b_2 = 1500$; $\beta_1 = 0.00002$; $\beta_2 = 0.0012$; $\beta_3 = 0.01$; $\mu_h = 0.09$; $\mu_v = 0.3$; $\alpha_h = 0.71$; $\alpha_v = 0.4$; $\delta_h = 0.001$; $\delta_v = 0.0001$; $\gamma_h = 0.53$.

values in Table (5.1), by the time series plots for the case where $\Re_0 > 1$. The solution profile converges to the unique positive endemic equilibrium.

Since the basic reproduction number $\Re_0$ depends upon the parameters of the model. In order to see the effect of some important parameters on the equilibrium, we change some of the parameters and keep all other parameters fixed. In Figures $(4.15 - 4.16)$, we change the parameter b_1 by keeping all other parameters fixed. It is observed that for large value of b_1 the equilibrium level of I_h and I_v is high and as we increase b_1, the equilibrium level of infected human and vectors population increases. The variation of infected human and vectors population with time for different values of b_2 is shown in Figures $(4.17-4.18)$, respectively. While in Figures $(4.19 - 4.21)$ the effect of β_1, β_2 and β_3, respectively, on the equilibrium level of the infected humans host population is presented. It is observed that for small value of these parameters the equilibrium level of I_h is small and as we decrease β_1, β_2 or β_3, the equilibrium level of infected human population decreases. Finally further decrease in β_1, β_2 or β_3 makes $\Re_0 < 1$, which makes the disease free equilibrium

Table 4.2: Parameters used for numerical simulation

Notation	Parameter description	Value
b_1	The human host input (birth) rate	25
β_1	The rate of direct transmission of the disease	0.0001
β_2	The rate of transmission of the disease from mosquito to human	0.0012
β_3	The rate of transmission of the disease from human to mosquito	0.001
μ_h	Natural death rate of humans	0.09
α_h	Transfer rate from E_h to I_h class	0.001
γ_h	Recovery rate for humans	0.3
δ_h	Disease-induced death rate for humans	0.9
b_2	Recruitment rate of mosquitoes	500
μ_v	Natural death rate of mosquito	0.003
α_v	Transfer rate from E_v to I_v class	0.04
δ_v	Disease-induced death rate for mosquitoes	0.8

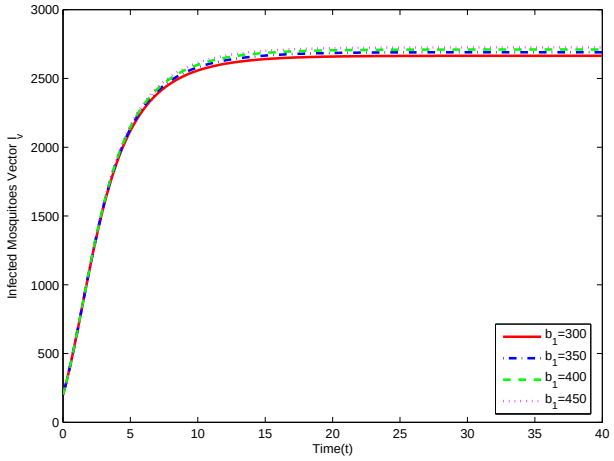

Figure 4.16: Variation of the infective mosquito vector population with time for different values of b_1 and other parameters are $b_2 = 1500$; $\beta_1 = 0.00002$; $\beta_2 = 0.0012$; $\beta_3 = 0.01$; $\mu_h = 0.09$; $\mu_v = 0.3$; $\alpha_h = 0.71$; $\alpha_v = 0.4$; $\delta_h = 0.001$; $\delta_v = 0.0001$; $\gamma_h = 0.53$.

point to be stable and hence the infected population tends to zero. Further, in Figures $(4.22 - 4.24)$ the effect of β_1, β_2 and β_3, respectively, on the equilibrium level of the infected mosquitoes vector population is presented. It is observed that for small value of these parameters the equilibrium level of I_v is small and as we decrease β_1, β_2 or β_3, the equilibrium level of infected mosquito population decreases. Further decrease in β_1, β_2 or β_3 makes $\Re_0 < 1$, which makes the disease free equilibrium point to be stable and hence the infected mosquito population tends to zero.

Table 4.3: Parameters used for numerical simulation

Notation	Parameter description	Value
b_1	The human host input (birth) rate	250
β_1	The rate of direct transmission of the disease	0.0001
β_2	The rate of transmission of the disease from mosquito to human	0.002
β_3	The rate of transmission of the disease from human to mosquito	0.01
μ_h	Natural death rate of humans	0.003
α_h	Transfer rate from E_h to I_h class	0.0001
γ_h	Recovery rate for humans	0.33
δ_h	Disease-induced death rate for humans	0.0001
b_2	Recruitment rate of mosquitoes	500
μ_v	Natural death rate of mosquito	0.003
α_v	Transfer rate from E_v to I_v class	0.2
δ_v	Disease-induced death rate for mosquitoes	0.00001

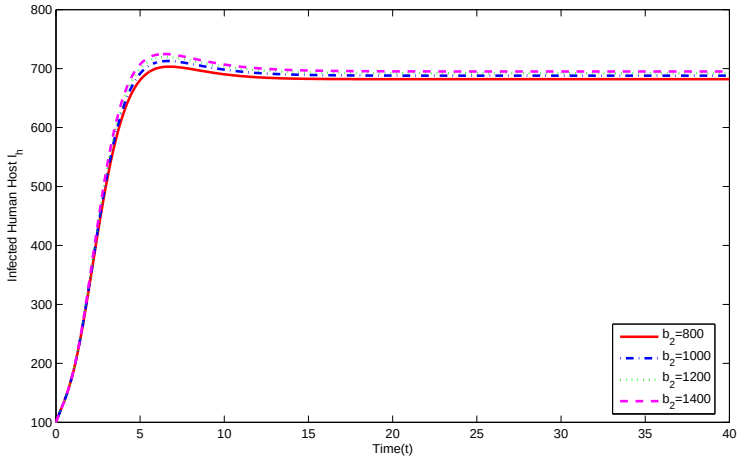

Figure 4.17: Variation of the infective human host population with time for different values of b_2 and other parameters are $b_1 = 500$; $\beta_1 = 0.00002$; $\beta_2 = 0.0012$; $\beta_3 = 0.01$; $\mu_h = 0.09$; $\mu_v = 0.3$; $\alpha_h = 0.71$; $\alpha_v = 0.4$; $\delta_h = 0.001$; $\delta_v = 0.0001$; $\gamma_h = 0.53$.

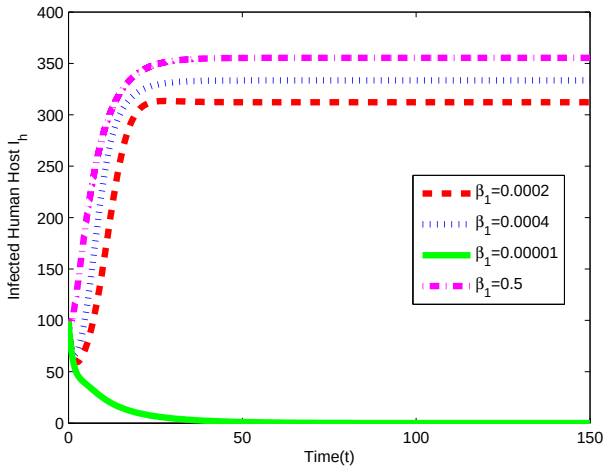

Figure 4.19: Variation of the infective human host population with time for different values of β_1 and other parameters are $b_1 = 500$; $b_2 = 1500$; $\beta_2 = 0.0012$; $\beta_3 = 0.01$; $\mu_h = 0.09$; $\mu_v = 0.3$; $\alpha_h = 0.71$; $\alpha_v = 0.4$; $\delta_h = 0.001$; $\delta_v = 0.0001$; $\gamma_h = 0.53$.

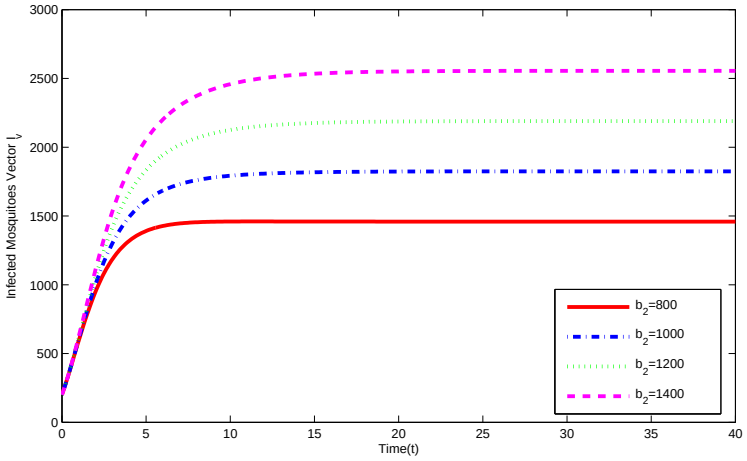

Figure 4.18: Variation of the infective mosquito vector population with time for different values of b_2 and other parameters are $b_1 = 500$; $\beta_1 = 0.00002$; $\beta_2 = 0.0012$; $\beta_3 = 0.01$; $\mu_h = 0.09$; $\mu_v = 0.3$; $\alpha_h = 0.71$; $\alpha_v = 0.4$; $\delta_h = 0.001$; $\delta_v = 0.0001$; $\gamma_h = 0.53$.

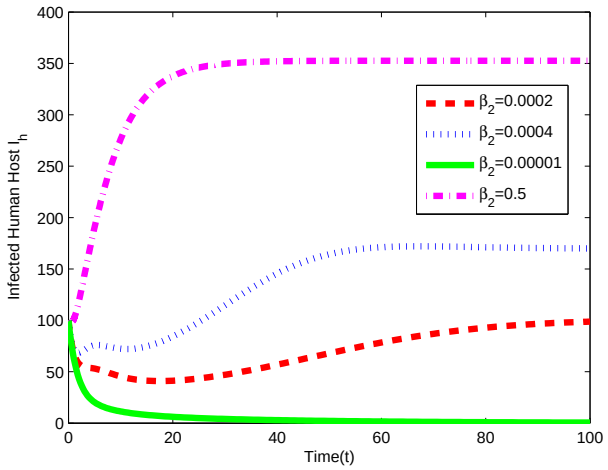

Figure 4.20: Variation of the infective human host population with time for different values of β_2 and other parameters are $b_1 = 500$; $b_2 = 1500$; $\beta_1 = 0.00002$; $\beta_3 = 0.01$; $\mu_h = 0.09$; $\mu_v = 0.3$; $\alpha_h = 0.71$; $\alpha_v = 0.4$; $\delta_h = 0.001$; $\delta_v = 0.0001$; $\gamma_h = 0.53$.

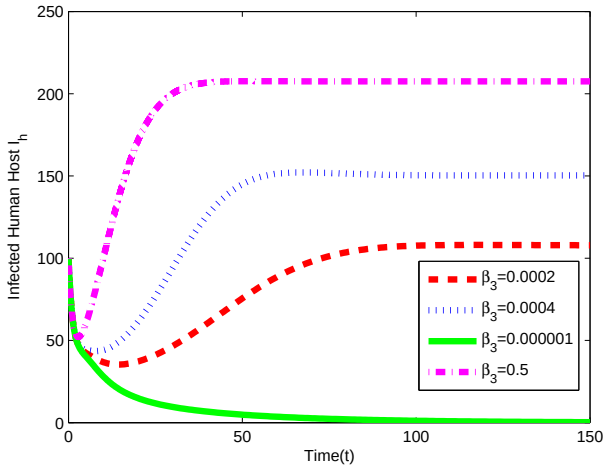

Figure 4.21: Variation of the infective human host population with time for different values of β_3 and other parameters are $b_1 = 500$; $b_2 = 1500$; $\beta_1 = 0.00002$; $\beta_2 = 0.0012$; $\mu_h = 0.09$; $\mu_v = 0.3$; $\alpha_h = 0.71$; $\alpha_v = 0.4$; $\delta_h = 0.001$; $\delta_v = 0.0001$; $\gamma_h = 0.53$.

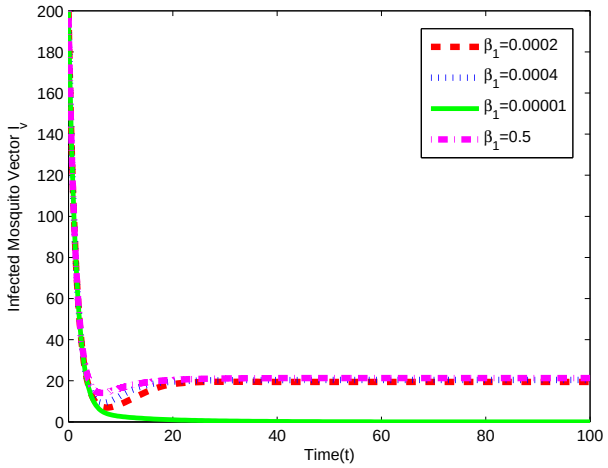

Figure 4.22: Variation of the infective vector population with time for different values of β_1 and other parameters are $b_1 = 500$; $b_2 = 1500$; $\beta_2 = 0.0012$; $\beta_3 = 0.01$; $\mu_h = 0.09$; $\mu_v = 0.3$; $\alpha_h = 0.71$; $\alpha_v = 0.4$; $\delta_h = 0.001$; $\delta_v = 0.0001$; $\gamma_h = 0.53$.

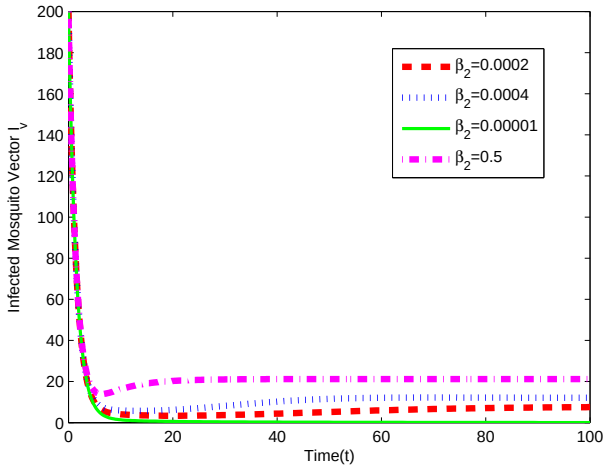

Figure 4.23: Variation of the infective vector population with time for different values of β_2 and other parameters are $b_1 = 500$; $b_2 = 1500$; $\beta_1 = 0.00002$; $\beta_3 = 0.01$; $\mu_h = 0.09$; $\mu_v = 0.3$; $\alpha_h = 0.71$; $\alpha_v = 0.4$; $\delta_h = 0.001$; $\delta_v = 0.0001$; $\gamma_h = 0.53$.

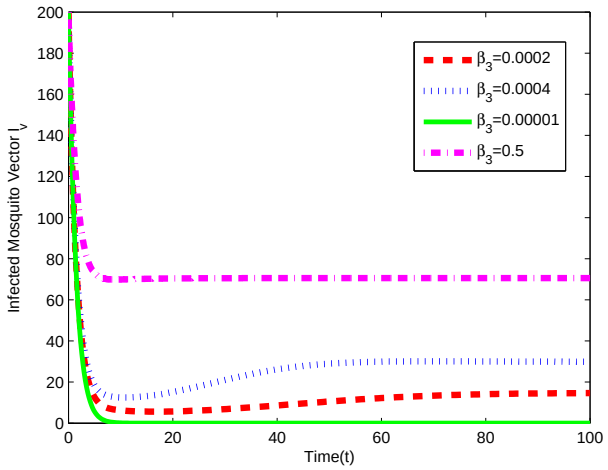

Figure 4.24: Variation of the infective vector population with time for different values of β_3 and other parameters are $b_1 = 500$; $b_2 = 1500$; $\beta_1 = 0.00002$; $\beta_2 = 0.0012$; $\mu_h = 0.09$; $\mu_v = 0.3$; $\alpha_h = 0.71$; $\alpha_v = 0.4$; $\delta_h = 0.001$; $\delta_v = 0.0001$; $\gamma_h = 0.53$.

4.9 Conclusions

In this chapter, we analyzed a 7-dimensional ordinary differential equation model for the transmission of a vector borne disease, which allow a direct mode of transmission, with 4 variables for humans host population and 3 variables for vectors population. It is shown that there exists a domain where the model is epidemiologically and mathematically well-posed.

As in epidemiological models, the model has two steady states, an uninfected steady state where the disease is not present; and an endemically infected steady state. We first established local stability results and obtained that there are two equilibria which are the disease-free equilibria and the endemic equilibria.

Then, we have developed Lyapunov functions to present the global stability of both the disease free and endemic steady states. It is proved that the global dynamics are completely determined by the basic reproduction number $\Re_0$. Our main results indicated that when $\Re_0 < 1$, the disease-free equilibrium is globally asymptotically stable, namely, the disease will die out of the population. When $\Re_0 > 1$, a unique endemic equilibrium exists and is globally asymptotically stable, which implies that the disease will always persist. From epidemiology point of view, the results in this chapter shows that a vector borne disease can be cleared from the community whenever the associated threshold parameter $\Re_0$ is brought to (and maintained at) a value less unity. If $\Re_0 > 1$, then the disease can not be eliminated and will spread in the population.

Chapter 5

Optimal Control of a Vector Borne Disease

5.1 Overview

The goal of this chapter is to incorporate some important epidemiological features, such as density-dependent birth rate in both host and vector populations and time dependent control functions, in our previous model presented in chapter 4. The extended model will then be used to determine cost-effective strategies for combatting the spread of a vector-borne disease in a given population. First, we show the existence of the control problem and then use both analytical and numerical techniques to investigate that there are cost effective control efforts for prevention of direct and indirect transmission of disease. In order to do this three control functions are used, one for vector-reduction strategies and other two for personal (human) protection and blood screening, respectively, to reduce the exposed, infectious humans and the total number of mosquitoes. Finally, we characterize the optimal control and compute numerical solution of the optimality system using an iterative method.

5.2 Introduction

Optimal control theory is a powerful mathematical tool to make decision involving complex dynamical systems [84]. For example, what percentage of the population should be vaccinated as time evolves in a given epidemic model to minimize both the number of infected people and the cost of implementing the vaccine strategy. The desired outcome depends on the particular situation. New drug treatments and combinations of drugs are under constant development. The optimal treatment scheme for patients remains the subject of intense debate. Application of control theory to epidemics is a very large field. A comprehensive survey of control theory applied to epidemiology was performed by Wick [86]. Many different epidemiological models with different objective functions have been proposed (see [34, 87–89]). Furthermore, optimal control methods have been used to study the dynamics of some diseases [104, 105], no such methods have been used, to the author's knowledge, to determine optimal control measures for a vector-host epidemic with direct transmission.

5.3 Application of optimal control to a vector borne disease

In this section, optimal control strategies for the following vector-host epidemic model [107] with direct and vector mediated transmission is presented.

$$\begin{aligned}
\frac{dS_h}{dt} &= b_1 - \beta_1 S_h I_h - \beta_2 S_h I_v - \mu_h S_h, \\
\frac{dE_h}{dt} &= \beta_1 S_h I_h + \beta_2 S_h I_v - \alpha_h E_h - \mu_h E_h, \\
\frac{dI_h}{dt} &= \alpha_h E_h - \gamma_h I_h - \mu_h I_h - \delta_h I_h, \\
\frac{dR_h}{dt} &= \gamma_h I_h - \mu_h R_h, \\
\frac{dS_v}{dt} &= b_2 - \beta_3 S_v I_h - \mu_v S_v, \\
\frac{dE_v}{dt} &= \beta_3 S_v I_h - \alpha_v E_v - \mu_v E_v, \\
\frac{dI_v}{dt} &= \alpha_v E_v - \mu_v I_v - \delta_v I_v.
\end{aligned} \tag{5.3.1}$$

In this system, we modified the recruitment rate in each susceptible population by including the density effects. In order to do this, we replace the previous recruitment rates by

$$b_1 \to b_1 + cN_h \quad \text{and} \quad b_2 \to b_2 N_v$$

where c is the proportionality constant showing the impact of density on the recruitment rate. In the absence of recruitment of new humans (i.e., $b_1 = 0$), the parameter c represent the per capita birth rate of human hosts.

In the human population, the associated force of infections are reduced by factors of $\big(1 - u_1(t)\big)$ and $\big(1 - u_2(t)\big)$, respectively, where $u_1(t)$ measures the level of successful precautions effort or a basic-practice blood-donation procedure that disallows the donations of infected donors and $u_2(t)$ measures the level of successful prevention (personal protection) efforts. The transfusion related transmission can

be controlled effectively by implementing a basic-practice blood-donation procedure that disallows the donations of infected donors and standard precautions for needle-stick injuries are the best preventive measures for needle-stick-related transmission. Thus the control $u_1(t)$ represents the basic precaution or implementation of a basic-practice blood-donation procedure that disallows the donations of infected donors. As there is no effective vaccine for most of vector-borne disease at the moment [108], efforts are underway to develop one (e.g., drugs or vaccine). Consequently the control variable $u_2(t)$ represents the use of drugs or vaccine which are alternative preventive measures to minimize or eliminate mosquito-human contacts (such as the use of insect repellents). Finally, we describe the role of the third control variable $u_3(t)$. Most of the vector use favorable climatic conditions to flourish, particularly during hot and wet seasons [105]. These problems are less pressing during cold seasons. Therefore, we can use a time-dependent mosquito control, preferably applied in seasons favorable for mosquito outbreak. The control variable $u_3(t)$ represents the level of larvicide and adulticide used for mosquito control administered at mosquito breeding sites to eliminate specific breeding areas. It follows that the reproduction rate of the mosquito population is reduced by a factor of $(1 - u_3(t))$. Also, it is assumed that under the successful control efforts the mortality rate of mosquitoes vector population increases at a rate proportional to the control variable $u_3(t)$, where $r_0 > 0$ is a rate constant. Note that the controls are fully effective when $u_i(t) = 1$ for $i = 1, 2, 3$ whereas no control is effective when $u_i(t) = 0$. Taking into account the assumptions and extensions made above, the dynamics of the control problem is given

$$
\begin{aligned}
\frac{dS_h}{dt} &= b_1 + cN_h - \beta_1 S_h I_h(1-u_1) - \beta_2 S_h I_v(1-u_2) - \mu_h S_h, \\
\frac{dE_h}{dt} &= \beta_1 S_h I_h(1-u_1) + \beta_2 S_h I_v(1-u_2) - \alpha_h E_h - \mu_h E_h, \\
\frac{dI_h}{dt} &= \alpha_h E_h - \gamma_h I_h - \mu_h I_h - \delta_h I_h, \\
\frac{dR_h}{dt} &= \gamma_h I_h - \mu_h R_h, \\
\frac{dS_v}{dt} &= b_2 N_v(1-u_3) - \beta_3 S_v I_h(1-u_2) - \mu_v S_v - r_0 u_3 S_v, \\
\frac{dE_v}{dt} &= \beta_3 S_v I_h(1-u_2) - \alpha_v E_v - \mu_v E_v - r_0 u_3 E_v, \\
\frac{dI_v}{dt} &= \alpha_v E_v - \mu_v I_v - \delta_v I_v - r_0 u_3 I_v.
\end{aligned} \tag{5.3.2}
$$

The above system (5.3.2) for the human host and mosquito vector populations is also equipped with initial conditions as follows: $S_h(0) = S_{h0}$, $E_h(0) = E_{h0}$, $I_h(0) = I_{h0}$, $R_h(0) = R_{h0}$, $S_v(0) = S_{v0}$, $E_v(0) = E_{v0}$ and $I_v(0) = I_{v0}$. We seek to minimize the number of exposed host, infected host, total number of mosquito (vector) and the cost of applying the controls. We use bounded lebesgue measurable control and the objective functional is given by

$$
J(u_1, u_2, u_3) = \int_0^T \left(A_1 E_h + A_2 I_h + A_3 N_v + \frac{1}{2}(B_1 u_1^2 + B_2 u_2^2 + B_3 u_3^2) \right) dt, \tag{5.3.3}
$$

subject to the state system given in (5.3.2). The total cost includes not only the consumption for every individual but also the cost of organization, management, and cooperation etc. Hence, the objective (cost) function should be nonlinear. In this paper, a quadratic function is implemented for measuring the control cost by referenced to many literatures in epidemics control [81–83]. The objective of our work is to minimize the exposed and infectious human population, the total number of vector population and the cost of implementing the control by using

possible minimal control variables u_i for $i = 1, 2, 3$. This functional includes the number of exposed, infectious and the total number of mosquito populations, respectively, as well as the social costs related to the resources needed for, personal protection $B_1u_1^2$, treatment $B_2u_2^2$, and spraying of insecticides operations, $B_3u_3^2$. In words, we are minimizing the number of exposed, infectious human and susceptible, exposed and infectious mosquito populations as well as the cost based on the implementation of the control functions. We choose to model the control efforts via a linear combination of quadratic terms, $u_i^2(t)(i = 1, 2, 3)$. In the objective functional the quantities A_1, A_2 represent the weight constants of the exposed and infected human population, respectively and A_3 represent the weight constant of the total vector population while B_1, B_2 and B_3 are weight constants for blood donor screening, personal protection (reduction of vector and human contacts) and vector control, respectively. The terms $1/2\, B_1u_1^2$, $1/2\, B_2u_2^2$ and $1/2\, B_3u_3^2$ describe the costs associated with the blood donor screening, prevention of vector-human contacts and vector control, respectively. The cost associated with the first control could come from donor screening systems. The cost associated with the second control could come from cost of mosquito repellents which can be spread on the skin or incorporated in soap, mosquito coils, electric mats, burning of local plants, and distribution of mosquito nets. The cost associated with third control could arise from applying conventional chemical pesticides, such as the organophosphate compound temephos, mosquitocidal oils, such as Bonide Mosquito Larvicide, kill mosquito larvae and pupae by interfering with air intake at the water surface and adulticiding. We assume that the costs are proportional to the square of the corresponding control function. The objective of the optimal control problem is to seek optimal control functions $(u_1^*(t), u_2^*(t), u_3^*(t))$ such that

$$J(u_1^*, u_2^*, u_3^*) = \min\{J(u_1, u_2, u_3),\ (u_1, u_2, u_3) \in U\} \tag{5.3.4}$$

subject to the system (5.3.2), where the control set is defined as

$$U = \{(u_1, u_2, u_3) | u_i(t) \text{ is Lebesgue measurable on } [0, 1],\ 0 \leq u_i(t) \leq 1,\ i = 1, 2, 3\}. \tag{5.3.5}$$

Pontryagin's Maximum Principle is used to solve this optimal control problem and the derivation of the necessary conditions. First we prove the existence of an optimal control for the system (5.3.2) and then derive the optimality system.

5.4 Existence of control problem

In this section, we consider the control system (5.3.2) with initial conditions at $t = 0$ to show the existence of the control problem. Note that for bounded Lebesgue measurable controls and non-negative initial conditions, non-negative bounded solutions to the state system exists (see [109]).

Pontryagin's Maximum Principle converts the control problem into a problem of minimizing a Hamiltonian function H point-wise with respect to (u_1, u_2, u_3):

$$\begin{aligned} H &= A_1E_h + A_2I_h + A_3N_v + 1/2(B_1u_1^2 + B_2u_2^2 + B_2u_3^2) \\ &+\lambda_1\Big[b_1 + cN_h - \beta_1S_hI_h(1-u_1) - \beta_2S_hI_v(1-u_2) - \mu_hS_h\Big] \\ &+\lambda_2\Big[\beta_1S_hI_h(1-u_1) + \beta_2S_hI_v(1-u_2) - \alpha_hE_h - \mu_hE_h\Big] \\ &+\lambda_3\Big[\alpha_hE_h - \gamma_hI_h - \mu_hI_h - \delta_hI_h\Big] + \lambda_4\Big[\gamma_hI_h - \mu_hR_h\Big] \\ &+\lambda_5\Big[b_2N_v(1-u_3) - \beta_3S_vI_h(1-u_2) - \mu_vS_v - r_0u_3S_v\Big] \\ &+\lambda_6\Big[\beta_3S_vI_h(1-u_2) - \alpha_vE_v - \mu_vE_v - r_0u_3E_v\Big] \\ &+\lambda_7\Big[\alpha_vE_v - \mu_vI_v - \delta_vI_v - r_0u_3I_v\Big]. \end{aligned} \tag{5.4.1}$$

where $\lambda_i, i = 1, ..., 7$ are the adjoint variables.

For the existence of our control problem, we state and prove the following theorem.

Theorem 5.4.1. *There exists an optimal control* $u^* = (u_1^*, u_2^*, u_3^*) \in U$ *such that*

$$J(u_1^*, u_2^*, u_3^*) = \min_{(u_1,u_2,u_3)\in U} J(u_1, u_2, u_3),$$

subject to the control system (5.3.2) with the initial conditions at $t = 0$.

Proof. To prove the existence of an optimal control we use the result in [34, 110]. Note that the control and the state variables are nonnegative values. In this minimizing problem, the necessary convexity of the objective functional J is satisfied. The set of all the control variables $(u_1, u_2, u_3) \in U$ is also convex and closed by definition. The optimal system is bounded which determines the compactness needed for the existence of an optimal control. In addition, the integrand in the functional (5.3.3), $A_1E(t) + A_2I(t) + A_3N_v(t) + 1/2(B_1u_1^2 + B_2u_2^2 + B_3u_3^2)$ is convex on the control set U. Also we can easily see that, there exist a constant $\rho > 1$ and positive numbers ω_1, ω_2 such that

$$J(u_1, u_2, u_3) \geq \omega_1(|u_1|^2 + |u_2|^2 + |u_3|^2)^{\rho/2} - \omega_2,$$

because, the state variables are bounded, which completes the existence of an optimal control. □

In order to find the optimal solution we apply the Pontryagin's Maximum Principle [111] as follows:
If (x, u) is an optimal solution of an optimal control problem, then there exists a non trivial vector function $\lambda = (\lambda_1, \lambda_2, ..., \lambda_n)$ satisfying the following inequalities.

$$\begin{aligned} \frac{dx}{dt} &= \frac{\partial H(t, x, u, \lambda)}{\partial \lambda}, \\ 0 &= \frac{\partial H(t, x, u, \lambda)}{\partial u}, \\ \frac{d\lambda}{dt} &= -\frac{\partial H(t, x, u, \lambda)}{\partial x}. \end{aligned} \tag{5.4.2}$$

Pontryagin's Maximum Principle provides the necessary conditions for an optimal control problem. This principle converts (5.3.2), (5.3.3), and (5.3.4) into a problem of minimizing point-wise Hamiltonian H, with respect to the control variables

(u_1, u_3, u_3). We, now derive the necessary conditions that optimal control functions and corresponding states must satisfy. In the following theorem, we present the adjoint system and the control characterization by applying the necessary conditions to the Hamiltonian H.

Theorem 5.4.2. *Given an optimal control $u^* = (u_1^*, u_2^*, u_3*)$ and a solution $y = (S_h, E_h, I_h,\ R_h, S_v, E_v, I_v)$ of the corresponding optimal control problem (5.3.2)-(5.3.3). Then there exists adjoint variables λ_i, $i = 1, ..., 7$ satisfying*

$$\begin{aligned}
\frac{d\lambda_1(t)}{dt} &= (\lambda_1 - \lambda_2)\big(\beta_1(1-u_1)I_h + \beta_2(1-u_2)I_v\big) + \mu_h\lambda_1 - c\lambda_1,\\
\frac{d\lambda_2(t)}{dt} &= -c\lambda_1 + \alpha_h(\lambda_2 - \lambda_3) + \mu_h\lambda_2 - A_1,\\
\frac{d\lambda_3(t)}{dt} &= -c\lambda_1 + \beta_1(\lambda_1 - \lambda_2)(1-u_1)S_h + \gamma_h(\lambda_3 - \lambda_4) + (\delta_h + \mu_h)\lambda_3\\
&\quad +\beta_3(\lambda_5 - \lambda_6)(1-u_2)S_v - A_2,\\
\frac{d\lambda_4(t)}{dt} &= -c\lambda_1 + \mu_h\lambda_4,\\
\frac{d\lambda_5(t)}{dt} &= -b_2\lambda_5(1-u_3) + \beta_3(\lambda_5 - \lambda_6)(1-u_2)I_h + \mu_v\lambda_5 + r_0\lambda_5 u_3 - A_3,\\
\frac{d\lambda_6(t)}{dt} &= -b_2\lambda_5(1-u_3) + \alpha_v(\lambda_6 - \lambda_7) + \mu_v\lambda_6 + r_0\lambda_6 u_3 - A_3,\\
\frac{d\lambda_7(t)}{dt} &= \beta_2(\lambda_1 - \lambda_2)(1-u_2)S_h - b_2\lambda_5(1-u_3) + (\mu_v + \delta_v)\lambda_7 + r_0\lambda_7 u_3 - A_3.
\end{aligned} \tag{5.4.3}$$

with transversality conditions (or boundary conditions)

$$\lambda_i(T) = 0, \quad i = 1,\ 2, ...,\ 7. \tag{5.4.4}$$

Furthermore, the control functions u_1^*, u_2^*, and u_3^* are given by

$$u_1^* = \max\{\min\{\mathcal{R}_1, 1\}, 0\}, \tag{5.4.5}$$

$$u_2^* = \max\{\min\{\mathcal{R}_2, 1\}, 0\}, \tag{5.4.6}$$

$$u_3^* = \max\{\min\{\mathcal{R}_3, 1\}, 0\}, \tag{5.4.7}$$

where

$$\begin{aligned}
\mathcal{R}_1 &= \frac{\beta_1(\lambda_2 - \lambda_1)S_h^* I_h^*}{B_1}, \\
\mathcal{R}_2 &= \frac{\beta_2(\lambda_2 - \lambda_1)S_h^* I_v^* + \beta_3(\lambda_6 - \lambda_5)S_v^* I_h^*}{B_2}, \\
\mathcal{R}_3 &= \frac{b_2\lambda_5 N_v^* + r_0(\lambda_5 S_v^* + \lambda_6 E_v^* + \lambda_7 I_v^*)}{B_3}.
\end{aligned}$$

Proof. To determine the adjoint equations and the transversality conditions we use the Hamiltonian H in equation (5.4.1). The adjoint system results from the Pontryagin's Maximum Principle [111].

$$\frac{d\lambda_1(t)}{dt} = -\frac{\partial H}{\partial S_h}, \quad \frac{d\lambda_2(t)}{dt} = -\frac{\partial H}{\partial E_h}, ..., \quad \frac{d\lambda_7(t)}{dt} = -\frac{\partial H}{\partial I_v}$$

with $\lambda_i(T) = 0, i = 1, 2, 3, ..., 7$

To get the characterization of the optimal control given by (5.4.5)- (5.4.7), solving the equations,

$$\frac{\partial H}{\partial u_1} = 0, \quad \frac{\partial H}{\partial u_2} = 0 \text{ and } \frac{\partial H}{\partial u_3} = 0,$$

on the interior of the control set and using the property of the control space U, we can derive the desired result (5.4.5)-(5.4.7).

The system (5.4.3) is obtained by differentiating the Hamiltonian function, evaluated at the optimal control. Here, we call formulas (5.4.5)-(5.4.7) for u^* the characterization of the optimal control. The optimal control and the state are found by solving the optimality system, which consists of the state system (5.3.2), the adjoint system (5.4.3), initial conditions at $t = 0$, boundary conditions (5.4.4), and the characterization of the optimal control problem (5.4.5)-(5.4.7). To solve the optimality system we use the initial and transversality conditions together with

the characterization of the optimal control (u_1^*, u_2^*, u_3^*) given in (5.4.5)-(5.4.7). In addition, the second derivatives of the integrand with respect to u_1, u_2 and u_3, respectively, are positive, which shows that the optimal problem is minimum at controls u_1^*, u_2^* and u_3^*. By substituting the values of u_1^*, u_2^* and u_3^* in the control system (5.3.2) we get the following system

$$\begin{aligned}
\frac{dS_h^*}{dt} &= b_1 + cN_h^* - \beta_1 S_h^* I_h^* (1 - \max\{\min\{\mathcal{R}_1, 1\}, 0\}) \\
&\quad -\beta_2 S_h^* I_v^* (1 - \max\{\min\{\mathcal{R}_2, 1\}, 0\}) - \mu_h S_h^*, \\
\frac{dE_h^*}{dt} &= \beta_1 S_h^* I_h^* (1 - \max\{\min\{\mathcal{R}_1, 1\}, 0\}) \\
&\quad +\beta_2 S_h^* I_v^* (1 - \max\{\min\{\mathcal{R}_2, 1\}, 0\}) - \alpha_h E_h^* - \mu_h E_h^*, \\
\frac{dI_h^*}{dt} &= \alpha_h E_h^* - \gamma_h I_h^* - \mu_h I_h^* - \delta_h I_h^*, \\
\frac{dR_h^*}{dt} &= \gamma_h I_h^* - \mu_h R_h^*, \\
\frac{dS_v^*}{dt} &= b_2 N_v^* (1 - \max\{\min\{\mathcal{R}_3, 1\}, 0\}) - \beta_3 S_v^* I_h^* - \mu_v S_v^* \\
&\quad -r_0 \max\{\min\{\mathcal{R}_3, 1\}, 0\} S_v^*, \\
\frac{dE_v^*}{dt} &= \beta_3 S_v^* I_h^* - \alpha_v E_v^* - \mu_v E_v^* - r_0 \max\{\min\{\mathcal{R}_3, 1\}, 0\} 0\} E_v^*, \\
\frac{dI_v^*}{dt} &= \alpha_v E_v^* - \mu_v I_v^* - \delta_v I_v^* - r_0 \max\{\min\{\mathcal{R}_3, 1\}, 0\} I_v^*,
\end{aligned} \tag{5.4.8}$$

Table 5.1: Parameter values used in the numerical simulations to the optimal control

Notation	Parameter description	Value
δ_v	Disease-induced death rate for mosquitoes vector	negligible.
μ_h	Natural death rate of humans host.	0.0000409
γ_h	Recovery rate for humans host.	0.1428
μ_v	Average lifespan of mosquitoes vector.	$[4, 14]$
b_1	Recruitment rate of humans host.	2.5
δ_h	Disease-induced death rate for humans host.	10^{-3}
α_h	Progression rate from E_h to I_h class.	$(0, 1)$

with H^* at $(t, S_h^*, E_h^*, I_h^*, R_h^*, S_v^*, E_v^*, I_v^*, u_1^*, u_2^*, u_3^*, \lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5, \lambda_6, \lambda_7)$:

$$\begin{aligned} H^* = {} & A_1 E_h^* + A_2 I_h^* + A_3 N_v^* + \tfrac{1}{2}\big(B_1(\max\{\min\{\frac{\beta_1(\lambda_2-\lambda_1)S_h^* I_h^*}{B_1}, 1\}, 0\})^2 \\ & + B_2(\max\{\min\{\frac{\beta_2(\lambda_2-\lambda_1)S_h^* I_v^*}{B_2}, 1\}, 0\})^2 \\ & + B_3(\max\{\min\{\frac{b_2\lambda_5 N_v^* + r_0(\lambda_5 S_v^* + \lambda_6 E_v^* + \lambda_7 I_v^*)}{B_3}, 1\}, 0\})^2\big) + \lambda_1 \frac{dS_h^*}{dt} \\ & + \lambda_2 \frac{dE_h^*}{dt} + \lambda_3 \frac{dI_h^*}{dt} + \lambda_4 \frac{dR_h^*}{dt} + \lambda_5 \frac{dS_v^*}{dt} + \lambda_6 \frac{dE_v^*}{dt} + \lambda_7 \frac{dI_v^*}{dt}. \end{aligned} \tag{5.4.9}$$

To find out the optimal control and state, we will numerically solve the above systems (5.4.8) and (5.4.9).

5.5 Numerical results and discussion

In this section, the optimality system is solved using Runge-Kutta fourth order scheme. We, show the numerical simulations of the impacts of the optimal control

strategies on a vector borne disease transmission. The optimal strategy is obtained by solving the state system, adjoint system and the transversality conditions. In our numerical simulation, first we start to solve the state equations (5.3.2) using Runge-Kutta fourth order forward in time with a guess for the controls over the simulated time. Then, using the current iteration of the state equations, the adjoint equations in the system (5.4.3) are solved by a backward method with the transversality conditions (5.4.4). We update the controls by using a convex combination of the controls in the previous iteration and the value from the characterizations of the systems (5.4.5)-(5.4.7). This process is repeated and iterations are stopped if the values of unknowns at the previous iteration are very close to the ones at the present iteration [84]. We may also refer the readers to see [34] such iterative algorithms for more detail.

Parameter values used in the numerical simulations are estimated based on a dengue disease as given in Table (5.1). The values of some of the parameters in the model are dictated by reality, e.g. the death rates of the human host and mosquito vector, the duration of the infectious period in the humans host, disease induced death rate of human host and mosquito vector, etc. Other parameters are arbitrarily chosen with $b_2 = 0.045$, $\beta_1 = 0.0004$, $\beta_2 = 0.0006$, $\beta_3 = 0.009$, and $\alpha_v = 0.042$. For illustration purpose, we consider the parameters values in Table 4.1 for numerical simulation. When viewing the graphs, remember that each of the individuals without control is marked by un-dashed lines. The individuals with control are marked by dash-dotted lines. The weight constant values in the objective functional are $A_1 = 0.008$, $A_2 = 0.001$, $A_3 = 0.004$, $B_1 = 100$, $B_2 = 50$ and $B_3 = 100$.

Figure (5.1), represents the population of susceptible, exposed, infected and recovered individuals (human) in two systems, (5.3.1) without control and (5.3.2) with control. The solid line denotes the population of individuals in the system (5.3.1) without control while the dotted line denotes the population of individuals in the system (5.3.2) with control. The population of infected individuals with control is more sharply decreased after 6 days than the individuals without control.

Figure (5.2) represents the population of susceptible, exposed, infected and the total vector in the two systems (5.3.1) without control and (5.3.2) with control. The population of susceptible vector with control is more sharply decreased than without control and becomes very small. The population of exposed and infected vector with control is more sharply decreased than the vector population without control. Figure (5.3) represent the optimal controls u_1^*, u_2^* and u_3^*. The control vanishes in day 30 and there remains a very small number of susceptible, exposed and infected vector.

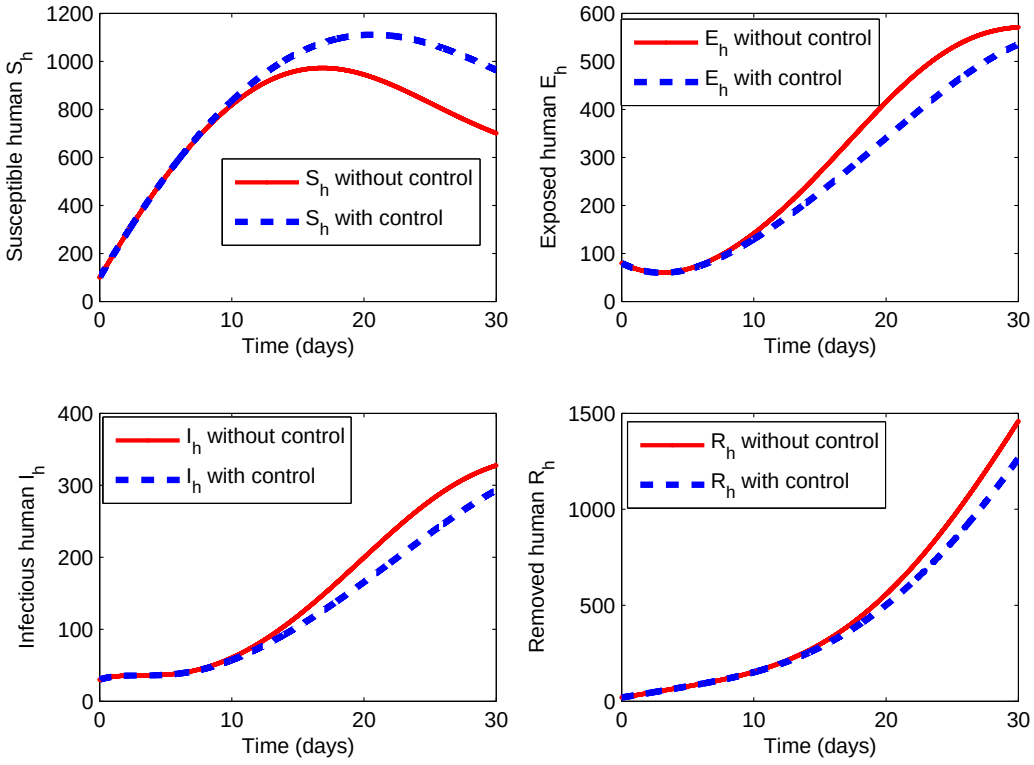

Figure 5.1: The plot represents population of susceptible, exposed, infected and recovered human host both with control and without control.

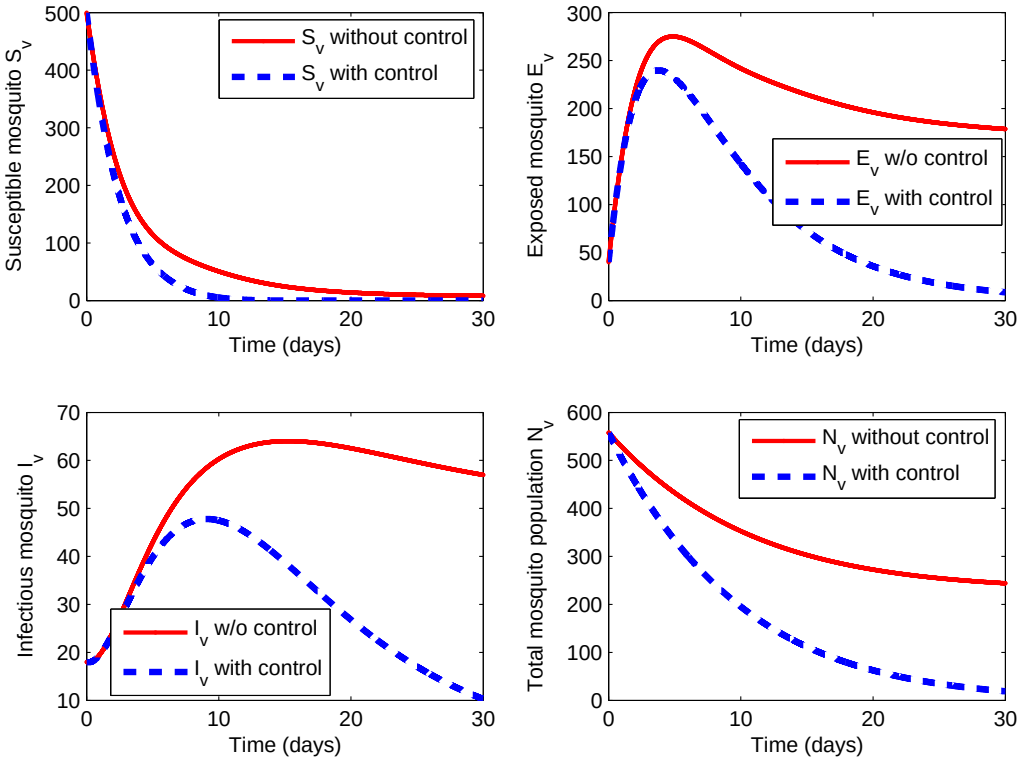

Figure 5.2: The plot represents population of susceptible, exposed, infected and the total number of mosquito vector both with control and without control.

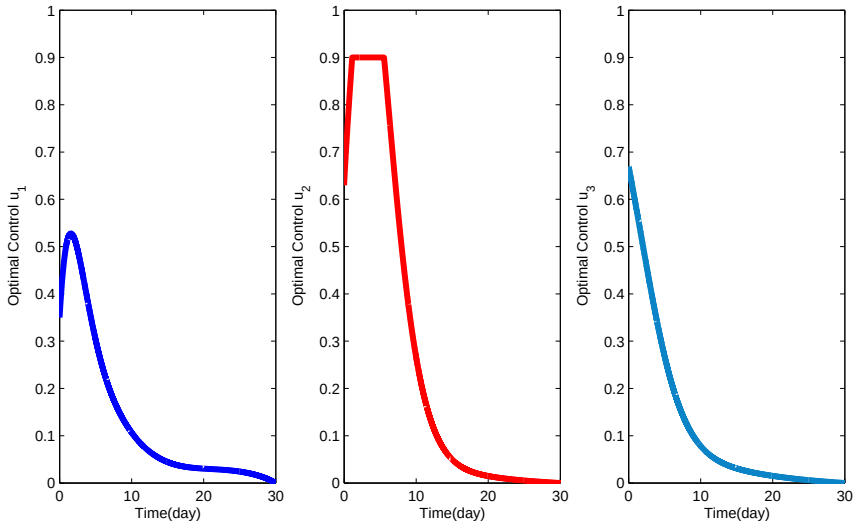

Figure 5.3: Optimal controls given by (5.4.5)-(5.4.7).

5.6 Conclusions

A comprehensive, continuous model for the transmission dynamics of a vector borne disease has been presented. We sought to determine control strategies that would minimize not only the exposed, infected human host, and susceptible, exposed, infected mosquitoes (vector) but also the cost of implementation of the control as well. An optimal control strategy has been presented. Our model incorporates three types of control measures associated with blood donor screening, personal protection and the vector reduction strategies. We analyzed the optimal control using the objective functional J in terms of quadratic forms. Minimizing the cost we obtained the optimal controls u_1, u_2 and u_3 where J was minimized. Using Pontryagin's Maximum Principle the control system is analyzed to determine the necessary conditions for existence of an optimal control. Using the state and adjoint system together with the characterization of the optimal control, we solved the problem numerically via a numerical method. A comparison between optimal control and without control dynamics is presented. It is easy to see that

the optimal control has a very desirable effect upon the population for reducing number of exposed and infected humans host population and the total number of mosquitoes vector population. In order to illustrate the overall picture of the disease, the numbers of exposed, infected human population and susceptible, exposed, infected mosquito population under the optimal control and without control are shown in figures. The results indicates that preventive practices are very effective in reducing the incidence of infectious hosts and vectors.

5.7 Areas of possible improvement to our model

Our present model does not consider some other factors listed below which may influence the spread of vector borne disease. These factor(s) when properly incorporated in the model, may provide a better understanding of the transmission dynamics of vector borne disease and its control.

- **Climate change**: The impact of climate change on the transmission dynamics of vector borne diseases. This allows us to investigate the relationship between the spread of vector borne diseases and climate change.

- **Partial immunity to reinfection**: In malaria infection, it is a commonly observed phenomenon for the recovered individuals to reinfection. In order to have more accurate representation of the dynamics of a vector borne disease in the society, our model could be improved to include partial immunity to reinfection in order to describe the transmission dynamics of malaria with reinfection in the recovered humans.

- **Vaccination**: It is expected that any future vector borne disease vaccine would be imperfect (that is, it would not offer 100% protection against infection in all people). This will allow us to study, via mathematical modeling, the potential impact of an imperfect vector borne disease vaccine. So the model could be extended to incorporate an imperfect vaccine against a vector borne disease.

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