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# Models Linking Epidemiology with Immunology and Ecology

Eric Shu Numfor
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To the Graduate Council:

I am submitting herewith a dissertation written by Eric Shu Numfor entitled "Models Linking Epidemiology with Immunology and Ecology." I have examined the final electronic copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Mathematics.

Suzanne M. Lenhart, Major Professor

We have read this dissertation and recommend its acceptance:

Judy Day, Yulong Xing, Shigetoshi Eda

Accepted for the Council:
Dixie L. Thompson

Vice Provost and Dean of the Graduate School

(Original signatures are on file with official student records.)

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# Models Linking Epidemiology with Immunology and Ecology

A Dissertation Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

Eric Shu Numfor

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*This dissertation is dedicated to the Almighty God, for providing me with the rudiments to pursue the difficult and turbulent route of academics.*

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# Abstract

Optimal control can be used to design intervention strategies for the control of infectious diseases and predator-prey systems. In this dissertation, we studied models encapsulating two relatively new areas of mathematical biology, which combine epidemiology with immunology and ecology.

We formulated immuno-epidemiological models of coupled *within-host* model of ordinary differential equations and *between-host* model of ordinary differential equations and partial differential equations, using the Human Immunodeficiency Virus (HIV) for illustration, and set a framework for optimal control of immuno-epidemiological models. By constructing an iterative sequence from a representation formula for a solution to the linked model and using the fixed-point argument, existence and uniqueness of solution to the immuno-epidemiological model are obtained. An explicit expression for the basic reproduction number, $\mathcal{R}_0$ (R zero), of the linked model is derived, and local asymptotic and global stability results are obtained when $\mathcal{R}_0 < 1$. When $\mathcal{R}_0 > 1$, it is shown that the endemic equilibrium point is locally asymptotically stable. An optimal control problem with drug-treatment control on the within-host system is formulated and analyzed; these results are novel for optimal control of ODEs linked with such first order PDEs. Numerical simulations based on a forward-backward sweep method are obtained. Our analysis and control techniques give a new tool for investigating immuno-epidemiological models for other diseases.

An eco-epidemiological model of predator and prey, motivated by cats and birds on the Marion Island, is formulated and analyzed. Basic and demographic reproduction numbers are obtained, and stability analysis of equilibria is investigated. An optimal control problem involving scalar and time-dependent controls is formulated and analyzed. Existence, characterization and uniqueness results are obtained. Numerical simulations based on a forward-backward sweep method illustrate the possibility of eradicating predators and conserving prey when a combination of control strategies are applied.

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# Chapter 1

# Introduction

This dissertation studies stability analysis and optimal control theory with its applications to mathematical models in ecology, immunology and epidemiology. We focus on formulating and analyzing epidemiological models linked with immunological and ecological models, which are relatively new areas of mathematical biology, called immuno-epidemiology and eco-epidemiology, respectively.

## 1.1 Immuno-epidemiology

The term immuno-epidemiology originates primarily from studies on macroparasitic infections [17, 27, 53, 57, 101, 112], often including mathematical models [16, 111]. Linking immunological mechanisms to epidemiological patterns takes into account the interrelationshp between individual and population levels, and creates new perspectives [63]. It translates individual characteristics such as immune status and pathogen load to population level and traces their epidemiological significance. Immunological models coupled with epidemiological models can be used to study questions related to virulence and evolution of disease life history. Since parasite transmission, parasite induced-mortality (or virulence) and infection recovery rate are the three most important quantities related to disease [4, 87], in coupling the immunological and epidemiological models in Chapters 2 and 3, we focus on linking immunological dynamics to the additional host mortality, recovery rate and transmission rate of infection of the epidemiological model.

## 1.2 Eco-epidemiology

Ecology and epidemiology are major fields of study in their own right, but in the presence of an infectious disease, the relationship between predator and prey, for example, becomes complex [20]. Anderson and May [2] were the first to merge these fields of study by formulating a predator-prey model where prey species were infected with an infectious disease[10, 14]. On the other hand, Hadeler and Freedman [56] were the first to model the spread of a disease amongst interacting populations, where both predator and prey were infected by an infectious disease [105].

Eco-epidemiology is a branch of mathematical biology that deals with ecological and epidemiological aspects simultaneously. This branch of mathematics is relatively new, and within the last two decades, some work has been devoted to the study of the effects of disease on a predator-prey system [9, 11, 19, 64, 105]. In most of these models, the effect of a disease is investigated in the prey population or predator population or both predator-prey populations.

We shall formulate a predator-prey model with the introduction of feline immunodeficiency virus (FIV) in the predator population, and investigate optimal harvesting and disease-related control strategies. This model is motivated by the need for management of cat populations which are damaging the bird populations on certain remote islands.

## 1.3 Optimal Control Theory

Optimal control theory is an extension of calculus of variations, which is a mathematical optimization method for deriving control/management policies. Optimal control has many applications in biology, public health, economics and engineering.

An optimal control problem consists of an objective functional, which is a function of state and control functions, subject to a dynamical system. The state function stisfies a differential equation which depends on the control function. The control function is adjusted in order to achieve a specified goal, and the dynamical system can be modeled with: ordinary differential equations, partial differential equations, discrete equations, stochastic differential equations or integrodifference equations [80]. In this dissertation, our dynamical system in Chapters 2 and 3 is a system of coupled ordinary and partial differential equations and in Chapter 4, our dynamical system is a system of ordinary differential equations. Thus, the formulation of optimal control problem requires the following: a mathematical description or model of the process to be controlled; a specification of the cost function (or performance index) ; a statement of initial and/or boundary conditions and the constraints on controls and/or state system [90].

### 1.3.1 Optimal Control of Ordinary Differential Equations

At the Steklov Institute in Moscow, discussions between engineers and mathematicians, motivated by the interest of Soviet engineers in optimal transients (nonlinearities, saturation effects and bounds on controls), led to the discovery of the "maximum principle" for optimal trajectories of a system by Lev Pontryagin [48]. Thus, the theory of optimal control of ordinary diffrential equations was developed by Lev Pontryagin and his collaborators in about 1950 [99]. Pontryagin introduced the idea of *adjoint* functions to append differential equations to the objective functional. This idea is similar to Lagrange multipliers in multivariate calculus, which attaches constraints to a function of several variables to be extremized. The adjoint function is sometimes called the *shadow price*, and interpreted as the marginal variation in the value of the objective functional with respect to the associated state variable at time $t$. The Hamiltonian, $H$, which combines the objective functional with the adjoint function and the state differential equation, converts the problem of maximizing (or minimizing) the objective functional subject to the dynamic system to the problem of maximizing (or minimizing) the Hamiltonian with respect to the control, $u(t)$. Given the existence of an optimal control and corresponding optimal states, Pontryagin's Maximum Principle gives existence of adjoint functions and their corresponding differential equations and terminal boundary conditions. Maximazing the Hamiltonian with respect to the control gives a characterization of an optimal control.

### 1.3.2 Optimal Control of Partial Differential Equations

The foundation of optimal control of partial differential equations was developed by J. L. Lions [83]. However, despite progress made in the late sixties and early seventies with the extension of the linear-quadratic regulatory theory to systems governed by partial differential equations, it was established in the French School that there is no complete generalization of Pontryagin's Maximun Principle for optimal control of partial differential equations [48]. The ideas of Pontryagin's Maximum Principle can be used as an aid in characterizing optimal control of PDEs. See the book by Li and Yong [82] for specific examples of second order partial differential equations with Pontryagin's Maximum Principle type results. There are some counterexamples to the generalization of Pontryagin's Maximum Principle in infinite dimensional systems.

After formulating an optimal control problem for partial differential equations in an appropriate weak solution space, one can usually use regularity and compactness results for second order PDEs to obtain existence of an optimal control. In order to characterize the optimal control, the objective functional for the problem is differentiated with respect to the controls. However, since the objective functional is a function of the state functions, the derivative of the control-to-state map is also needed. The derivative of a state with respect to control is called *sensitivity*. *A priori* estimates of the norms of the states in the solution space are necessary to justify convergence of difference quotients to sensitivities. The sensitivities solve the linearized version of the state system. In an appropriate weak sense, a relationship between sensitivity operator (obtained from the sensitivity system) and adjoint operator is established. The adjoint operator is introduced with appropriate final time conditions, and the right-hand side of the adjoint system has derivatives of the integrand of the objective functional with respect to each state variable.

Due to less regularity of solutions of first-order partial differential equations, existence and uniqueness results of the optimal control are obtained with the aid of Ekeland's variational principle [38].

**Theorem 1.1.** *(**Ekeland's Variational Principle** [38]) Let $(X, d)$ be a complete metric space and $f : X \to (-\infty, \infty]$ be a lower semicontinuous function, bounded from below and not identically $+\infty$. Let $\varepsilon > 0$ and $u \in X$ be such that $f(u) \leq \inf\{f(x)|x \in X\} + \varepsilon$. Then for any $\lambda > 0$, there exists $u_\varepsilon \in X$ such that*

$$(i) f(u_\varepsilon) \leq f(u) \quad (ii) d(u, u_\varepsilon) \leq \lambda \quad (iii) f(u_\varepsilon) < f(x) + \varepsilon\lambda^{-1} d(u_\varepsilon, x), \quad \forall x \in X \backslash \{u_\varepsilon\}.$$

In addition, if $X$ is a Banach space and $f : X \to (-\infty, \infty]$ is Gâteaux differentiable, then Ekeland's variational principle guarantees the existence of a minimizing sequence for the function $f$.

### 1.3.3 Optimal Control in Coupled Within-host and Between-host Models

Despite enormous work that has been done in the fields of mathematical immunology and mathematical epidemiology, the outbreak of some diseases cannot still be predicted today. To biuld more useful models, we move away from the ususal approaches, which are mostly restricted to immunological or epidemiological formulations, while making decoupling assumptions.

In this dissertation, we explicitly link immunological and epidemiological models of HIV, and set a framework for optimal control of immuno-epidemiological modeling, presenting novel optimal control results for such models. For the sake of illustration, we use a simple within-host model of HIV (human immunodeficiency virus), and an SI-type epidemiological model, structured by chronological time and age-since-infection. Our within-host model is a system of ordinary differential equations with classes depicting healthy $CD4^+$ T-cells, infected $CD4^+$ T-cells and free virus. In our within-host model, we explicitly incorporate the loss of virus due to binding to healthy cells. On the other hand, the epidemiological (or between-host) model is a system of coupled ordinary and partial differential equations, linked to the within-host model via transmission rate, disease-induced mortality and age-since-infection variable. In formulating our coupled model, we use the nesting approach, motivated by the work of Gilchrist and Sasaki [51]. We derive an explicit expression for the basic reproduction number of our coupled model, obtain equilibrium solutions and investigate the stability of equilibria.

In order to curtail the proliferation of virions at the within-host level, we incorporate controls through transmission and virion production suppressing drugs, and formulate an objective functional that seeks to minimize the virus at the within-host level, infectious individuals at the between-host level and the cost of implementing the control. An optimality system for our problem is obtained, and existence, characterization and uniqueness of optimal control pair is established. A semi-implicit finite-difference scheme for the optimality system implemented within a forward-backward sweep numerical method [80] is used for some illustrative numerical simulations.

### 1.3.4 Optimal Control in Multi-group Coupled Within-host and Between-host Models

In Chapter 3, we formulate a multi-group model at both the within-host and between-host levels. These models take into account the assumption that upon infection, individuals in the population exhibit different immunological characteristics. Our within-host model for two groups is a system of six ordinary differential equations and the between-host model consists of an ordinary differential equation coupled with two first-order partial differential equations. In this dissertation, we investigate stabilty analysis, well-posedness and optimal drug treatment in a multi-group within-host model coupled with an epidemiological model.

### 1.3.5 Optimal Harvesting and Biocontrol in a Predator-Prey Model

Sub-Antarctic islands are vital breeding sites for seabirds, but the presence of feral cats in Sub-Antarctic ecosystems have caused devastating effects on native seabird species [69, 98]. Generally, the domestic cat was introduced on some islands with the aim of controlling the population of alien rodents (*Rattus rattus*) and rabbits, but due to the generalist nature of cats, they prey largely on seabirds. Thus, eradicating cats from these islands is necessary to allow for recovery of seabird populations [98].

In this dissertation, we formulate two eco-epidemiological models of cats and birds. In the first model, we investigate stability analysis and optimal harvesting, and in the the second model, we incorporate disease-induced control, by trapping and infecting susceptible cats in the population. Our optimal control problem seeks to choose the initial number of infected cats, harvesting and the disease-related control to increase the number of bird population and to decrease the cat population. In our analysis, an optimality system for our problem is obtained, and existence, characterization and uniqueness of optimal control pair(s) are established. We use the fourth order Runge-Kutta method [68] to obtain approximate solutions to the optimality system, and a forward-backward sweep numerical method [80] is used for some illustrative numerical simulations.

## 1.4 Numerical Approximations

In Chapters 2, 3 and 4, we approximate solutions to the optimality system, consisting of the state system, adjoint system and control characterization, iteratively. For systems of ODEs coupled with PDEs in Chapters 2 and 3, we use a semi-implicit finite-difference approximation, and for a system of ODEs, we use the fourth order Runge-Kutta method [68] to obtain approximate solutions to the optimality system. The Trapezoidal Rule is used to handle integral terms contained in the optimality systems of Chapters 2 and 3. Since we have initial conditions for state equations and final time conditions for adjoint equations, a forward-backward sweep method [80] is used to fully implement our numerical scheme. This method is outlined as follows:

1. Establish an initial guess for the control.
2. Given the initial conditions for the states and surmised control, solve the state equations forward in time using a Runge-Kutta or finite-difference forward sweep method.
3. Given the transversality conditions and approximate solutions from step 2, solve the adjoint equations backward in time using a Runge-Kutta or finite-difference backward sweep method.
4. Evaluate the control characterization using approximate solutions of states and adjoints functions, and update the control with a convex combination of previous and current values of the control characterization.
5. Repeat previous steps until consecutive iterates of controls, states and adjoints are sufficiently close. If $u_c$ is the value of the control at the current iteration and $u_p$ is the value of the control at the previous iteration, then $u_c$ and $u_p$ are sufficiently close if

$$\frac{\|u_c - u_p\|}{\|u_c\|} \leq \varepsilon,$$

where $\varepsilon$ is the accepted tolerence and $\|u\|$ is the 1-norm of $u$ (sum of all absolute values of all components over time and space). The convergence of the forward-backward sweep method is based on the work by Hackbusch [55].

# Chapter 2

# Optimal Control in Coupled Within-host and Between-host Models

## 2.1 Introduction

There is continuous threat of outbreak of infectious disease despite ongoing advancements in drug therapies and vaccines [61]. Thus, it is necessary to develop better ways of understanding the spread of disease. To this effect, immunological and epidemiological models have been proposed with the aim of controlling the outbreak of infectious diseases.

Mathematical immunology is concerned with the study of disease dynamics in an infected host, where an infectious agent is spread from cell to cell within one patient [61]. The study of the interaction between a pathogen and the immune system gives an insight into the mechanism of disease proliferation. In mathematical epidemiology, the spread of disease in a population of hosts is examined with the goal of examining and tracing factors that contribute to the propagation of pathogens [61]. Epidemiological or between-host models are often structured to capture discrete immune status, such as susceptible, exposed, infectious, recovered (immune), vaccinated, time-since-infection to account for variable infectivity (pathogen load) and time-since-recovery to account for gradual loss of immunity. However, most epidemiological models ignore pathogen load and dependence of transmissibility on pathogen load, and detailed account of the immune status during infection [85].

We will investigate linking within-host models with epidemiological models, and as our motivating scenario, we use the human immunodeficiency virus (HIV), which is a retrovirus. In the future, we shall consider other scenarios such as Johne's disease and Toxoplasma gondii, but we concentrate on HIV for this introduction to our approach. HIV is generally a slow but progressive disease in which the virus is present throughout the body at all stages of the disease, and it is transmitted from one person to another through specific body fluids such as blood, semen, genital fluids, and breast milk. The life cycle of HIV infection consists of six stages; namely, binding and fusion, reverse transcription, integration, transcription, assembly and budding. Several mathematical epidemiology models of HIV [66, 71, 75, 76, 108] and mathematical immunology models of HIV [78, 96] have been formulated and analyzed.

The two key features in infectious diseases are the transmission between hosts and the immunological process at the individual host level. Understanding how the two features influence each other can be assisted through modeling. Linking components of the immune system with the compartments of the epidemic model leads to a two-scale model. Much of the work on such "linked" models deal with the two levels separately, making "decoupling" assumptions [3].

Despite advancements made with the study of epidemiological, within-host and immunological models, the outbreak of some diseases cannot still be predicted. This dilemma may be attributed to the fact that most modeling approaches are either restricted to epidemiological or immunological formulations, while making decoupling assumptions [61]. Current research focuses on the comprehensive modeling approach, called immuno-epidemiological modeling, which investigates the influence of population immunity on epidemiological patterns, translates individual characteristics such as immune status and pathogen load to population level and traces their epidemiological significance [33, 63, 85]. Several immuno-epidemiological models have been used to study the relationship between transmission and virulence [8, 42, 43, 49, 50, 51]. Some of these models deal with the two processes separately by making decoupling assumptions. Gilchrist and Sasaki [50] used the nested approach to model host-parasite coevolution in which the within-host model is independent of the between-host but the between-host model is expressed in terms of dependent variables of the within-host model. Also, Feng et al. [42] investigated a coupled within-host and between-host model of Toxoplasma gondii linked via the environment.

Our goals are to use a within-host model coupled with epidemiology model to capture the impact on the epidemic of giving treatment to individuals, and investigate mathematically such a coupled ODE/PDE system (well-posedness and optimal control).

Our general approach in immuno-epidemiological modeling involves three steps. The first step involves formulating a within-host model within an infected host. Secondly, construct an epidemiological model to describe the dynamics of host birth and death rates, and transmission of infection within the host population. Finally, nest the within-host model within the epidemiological model by linking the dynamics of the within-host model to the additional host mortality, recovery and transmission rates of the infection. The within-host and between-host models could be linked via a structural variable and through coefficients. In the latter case, coefficients of the epidemiological model are expressed as functions of the dependent variables of the within-host model. For example, transmission rate is proportional to within-host viral load and disease-induced death rate is proportional to parasite load and immune response, while in the former case, the independent variable of the within-host model is the age-since-infection variable of the between-host model [51, 85].

This work will have the first results on formulating this two-scale model in a careful mathematical framework and the first results on optimal control of such a model. We emphasize the novelty of mathematical results, as well as the importance of the epidemiological and immunological results. To curtail the proliferation of free virus at the within-host level, we introduce two functions, representing transmission and virion production suppressing drugs. Our goal is to use optimal control techniques in the coupled model to minimize free virus at the within-host level and infectious individuals at the population level, while minimizing the cost of implementing the controls (this may include toxicity effects). Optimal control of first-order partial differential equations is done differently than optimal control of parabolic PDEs due to the lack of regularity of solutions to the first-order PDEs. The steps in justifying the optimal control results are quite different and we use Ekeland's Principle [38] to get the existence of an optimal control.

In section 2.2, we present our within-host and between-host models. The within-host model is independent of the between-host model, but the between-host model is linked to the within-host via coefficients and a structural variable. In section 2.3, we prove the boundedness of state solutions to the within-host model, and existence and uniqueness of solutions to the between-host model is established. In section 2.3.2, an explicit expression for the basic reproduction number of the epidemiological model is derived, steady solutions calculated and stability analysis of equilibrium points is studied. We formulate and analyze an optimal control problem in section 2.4, and carry out numerical simulations in section 2.5.

## 2.2 Within-host and Between-host Models

In this section, we formulate a simple within-host model of HIV and a between-host model of HIV with age structure. In the within-host model, the independent variable is the time-since-infection $\tau$ and for the between-host model, the independent variables are chronological time $t$ and age-since-infection $\tau$. Our within-host model is given by the following system of ordinary differential equations:

$$\frac{dx}{d\tau} = r - \beta_1 V(\tau)x(\tau) - \mu x(\tau) \quad (2.1)$$

$$\frac{dy}{d\tau} = \beta_1 V(\tau)x(\tau) - d_1 y(\tau) \quad (2.2)$$

$$\frac{dV}{d\tau} = \nu_1 d_1 y(\tau) - (\delta_1 + s_1)V(\tau) - \hat{\beta}_1 V(\tau)x(\tau) \quad (2.3)$$

with initial conditions

$$x(0) = x^0, \quad y(0) = y^0 \quad and \quad V(0) = V^0, \quad (2.4)$$

where $x$ is the number of healthy cells (uninfected $CD4^+$ T cells), $y$ is the density of infected $CD4^+$ T cells, $V$ is the density of free (infectious) virus, $r$ is the recruitment

**Table 2.1:** Within-Host Model Parameters

| Quantity | Description | Units |
|---|---|---|
| $x$ | Density of healthy CD4$^+$ T-cells | cell/mm$^3$ |
| $y$ | Density of infected CD4$^+$ T-cells | cell/mm$^3$ |
| $V$ | Density of free virus | virion/mm$^3$ |
| $\tau$ | Time since start of infection | days |
| $r$ | Source term for healthy cells (CD4$^+$ T-cells) | cell mm$^{-3}$ day$^{-1}$ |
| $\mu$ | Natural death rate of healthy cells | day$^{-1}$ |
| $\beta_1$ | T cells infection rate by virus | mm$^3$ virion$^{-1}$ day$^{-1}$ |
| $\hat{\beta}_1$ | Binding rate of free virus to uninfected $CD4^+$ T cells | mm$^3$ cell$^{-1}$ day$^{-1}$ |
| $d_1$ | Death rate of infected cells | day$^{-1}$ |
| $\nu_1$ | Virion production rate | virion cell$^{-1}$ |
| $\delta_1$ | Death rate of free virus | day$^{-1}$ |
| $s_1$ | Shedding rate of free virus | day$^{-1}$ |

rate of healthy cells, $\mu$ is the death rate of healthy cells, $d_1$ is the death rate of infected cells, $\beta_1$ is the transmission rate, $\hat{\beta}_1$ is the binding rate of free virus to uninfected $CD4^+$ T cells, $\nu_1$ is the number of virions produced at bursting, $\delta_1$ is the death rate of virus, and $s_1$ is the shedding rate of virus. See Table 2.1 for a summary of parameters and units of the within-host model.

Our between-host SI (susceptible, infected) model assumes that the infected class is related to the within-host behavior of a particular individual, and individuals in this class are structured by both chronological time t and age of infection (age-since-infection), $\tau$. Thus, our between-host model is:

$$\frac{dS}{dt} = \Lambda - \frac{S(t)}{N(t)} \int_0^A c_1 s_1 V(\tau) i(\tau,t) d\tau - m_0 S(t) \quad in\ (0,T) \tag{2.5}$$

$$\frac{\partial i(\tau,t)}{\partial t} + \frac{\partial i(\tau,t)}{\partial \tau} = -m(V(\tau)) i(\tau,t) \quad in\ (0,T) \times (0,A) \tag{2.6}$$

$$i(0,t) = \frac{S(t)}{N(t)} \int_0^A c_1 s_1 V(\tau) i(\tau,t) d\tau, \quad for \quad t \in (0,T) \tag{2.7}$$

$$S(0) = S_0, \quad i(\tau,0) = i^0(\tau) \quad for \quad \tau \in (0,A),\ t = 0, \tag{2.8}$$

where S(t) is the number of susceptible individuals at time $t$, $i(\tau,t)$ is the density of infected individuals at time $t$ and age-since-infection $\tau$, $m(V(\tau))$ is the death rate of infected hosts (a function of viral load), $\Lambda$ is the recruitment rate of susceptible individuals, and $m_0$ is the death rate of susceptible individuals. The transmission rate is assumed to be proportional to the viral load of the infected individuals, calculated by integrating with respect to $\tau$, $\int_0^A c_1 s_1 V(\tau) i(\tau,t) d\tau$, where $c_1$ is the contact rate between susceptible and infected individuals. Thus, the new infectious process of the population at time $t$, denoted by $i(0,t)$, depends on the age distribution of the population at time $t$, as determined by the integral of $i(\tau,t)$ over all ages, weighted with the specific transmission rate $\beta(\tau) = c_1 s_1 V(\tau)$. The number of susceptible and infectious individuals in the population at time $t = 0$ are given by $S(0) = S_0 > 0$ and $i(\tau,0) = i^0(\tau)$, respectively. Thus, $i(\tau,0)$ is the initial age distribution of infectious

**Table 2.2:** Between-Host Model Parameters

| Quantity | Description | Units |
|---|---|---|
| $\tau$ | Age-since-infection | days |
| $t$ | Chronological time | years |
| $A$ | Maximal age-since-infection | years |
| $S(t)$ | Susceptible individuals at time $t$ | humans |
| $i(\tau, t)$ | Infected individuals of age $\tau$ and time $t$ | humans |
| $S(0)$ | Initial population of susceptible individuals | humans |
| $i(\tau, 0)$ | Initial population of infectious individuals of age-since-infection $\tau$ | humans |
| $i(0, t)$ | Newborns at time $t$ | humans |
| $\Lambda$ | Recruitment rate of susceptible humans | humans year$^{-1}$ |
| $m_0$ | Natural death rate of susceptible humans | year$^{-1}$ |
| $m(V)$ | Death rate of infectious humans | year$^{-1}$ |
| $c_1$ | Contact rate between susceptible and infectious humans | mm$^3$ virion$^{-1}$ year$^{-1}$ |

individuals in the population, with $i^0$ being a known nonnegative function of age-since-infection, $\tau$. The total population of infectious individuals from birth to maximal age-since-infection, $A$, is defined as

$$I(t) = \int_0^A i(\tau, t) d\tau,$$

and the total population size of individuals in the population is $N(t) = S(t) + I(t)$. For the sake of introduction to our method, we assume the simplest form for the mortality function [22], $m(V)$, as

$$m(V(\tau)) = m_0 + \mu_1 V(\tau),$$

so that in the absence of the virus, individuals die naturally at rate $m_0$. The term $\mu_1 V(\tau)$ gives the additional host mortality due to the virus. See Coombs et al. [22] for other forms of mortality functions.

## 2.3 Mathematical Analysis

### 2.3.1 Boundedness and Existence of Solutions

We show that for positive initial data, the state variables of the within-host model stay positive for all time, and use notions of differential inequalities [39] to establish boundedness of state solutions. The positivity and boundedness of state solutions of the within-host model will be used in the proof of existence of solutions to the between-host system and global stability of disease-free equilibrium of the epidemiological model. Now, using the method of integrating factors, we have the following representation of solution to the within-host model:

$$x(\tau) = x^0 e^{-(\mu\tau + \int_0^\tau \beta_1 V(\omega)d\omega)} + \int_0^\tau r e^{-(\mu(\tau-s) + \int_s^\tau \beta_1 V(\omega)d\omega)} ds \tag{2.9}$$

$$y(\tau) = y^0 e^{-d_1\tau} + \int_0^\tau \beta_1 e^{-d_1(\tau-s)} V(s)x(s)ds \tag{2.10}$$

$$V(\tau) = V^0 e^{-\int_0^\tau (\delta_1 + s_1 + \hat{\beta}_1 x(\omega))d\omega} + \int_0^\tau \nu_1 d_1 y(s) e^{-((\delta_1+s_1)(\tau-s) + \int_s^\tau \hat{\beta}_1 x(\omega)d\omega)} ds \tag{2.11}$$

**Theorem 2.1.** *Given the state equations (2.1) – (2.3), with positive initial conditions (2.4), there exist constants $\hat{C}, \tilde{C}, C > 0$ such that $0 < x(\tau) \leq \hat{C}$, $0 < y(\tau) \leq \tilde{C}$ and $0 < V(\tau) \leq C$, for all $\tau > 0$.*

*Proof.* Assume $x^0 > 0$ and $r > 0$, then from equation (2.9), $x(\tau) > 0$ for all $\tau > 0$. Further, assume $y^0 > 0$, $V^0 > 0$, and that there is a $\tau_1 > 0$ such that $y(\tau) > 0$ and $V(\tau) > 0$ on $[0, \tau_1)$. Here, $\tau_1$ is the first time any of the state variables hits 0. Now, if $y(\tau_1) = 0$ then from equation (2.10), there exists an interval $(t_1, t_2) \subset [0, \tau_1)$ with $t_1 \neq t_2$ such that $V(s) < 0$, for $s \in (t_1, t_2)$, which is a contradiction. Thus, $y(\tau) > 0$

in $[0, \tau_1]$. Finally, if $V(\tau_1) = 0$, then from equation (2.11), there exists an interval $(t_1, t_2) \subset [0, \tau_1)$ with $t_1 \neq t_2$ such that $y(s) < 0$, for $s \in (t_1, t_2)$, which is again a contradiction. Thus, $V(\tau) > 0$ in $[0, \tau_1]$. Hence, for $\tau > 0$, the state variables $x(\tau)$, $y(\tau)$ and $V(\tau)$ are positive.

To prove that $x$, $y$ and $V$ are bounded above, we use the notions of differential inequalities. Now, since $x$ and $V$ are positive, considering the equation that represents the density of healthy CD4$^+$ T-cells in the population, we have the following differential inequality

$$\frac{dx}{d\tau} \leq r - \mu x. \tag{2.12}$$

The solution of the differential inequality (2.12) satisfies

$$x(\tau) \leq x^0 e^{-\mu\tau} + \int_0^{\tau} r e^{-\mu(\tau - s)} ds,$$

which leads to the inequality $x(\tau) \leq \frac{r}{\mu} + x^0$, for all $\tau > 0$. Thus, with positive initial data, $x^0 > 0$, the density of healthy cells is bounded. Next, adding equations (2.1) and (2.2), we obtain

$$\frac{d(x + y)}{d\tau} = r - \mu x - dy \leq r - k(x + y),$$

where $k = \min\{\mu, d\}$. The solution to this differential inequality leads to
$x(\tau) + y(\tau) \leq \frac{r}{k} + x^0 + y^0$, for all $\tau > 0$. This shows that $y$ is bounded; that is, $y(\tau) \leq \tilde{C}$, for all $\tau > 0$. Finally, for the boundedness of the density of viral load, we have

$$\begin{aligned} \frac{dV}{d\tau} &= \nu_1 d_1 y - (\delta_1 + s_1)V - \hat{\beta}_1 V x \\ &\leq \nu_1 d_1 \tilde{C} - (\delta_1 + s_1)V, \end{aligned}$$

so that $V(\tau) \leq \frac{\nu_1 d_1 \tilde{C}}{\delta_1 + s_1} + V^0$, for all $\tau > 0$. Hence, the state solutions of the within-host model are positive and bounded above. □

We develop a representation formula for the solution (if it exists) to the epidemiological model determined by the methods of integrating factor and characteristics [12, 110], and prove the existence and uniqueness of the solution. We use the method of integrating factor to represent the solution of the first-order ordinary differential equation that models the population of susceptible individuals and the method of characteristics for the first-order partial differential equations representing infectious individuals in the population [67, 86]. A typical approach towards proving well-posedness of a differential equation problem is to write the problem in integral form. To do this, we integrate the differential equation (2.6) along the characteristic line $\tau - t = constant$ and consider cases where $\tau > t$ and $\tau < t$, which gives our representation formula for the solution to the epidemiological model:

$$\begin{aligned} S(t) &= S_0 e^{-(m_0+\alpha)t} + \frac{\Lambda}{m_0+\alpha}(1 - e^{-(m_0+\alpha)t}) \\ &\quad + \int_0^t e^{-(m_0+\alpha)(t-s)} S(s) \left( \alpha - \frac{1}{N(s)} \int_0^A c_1 s_1 V(\tau) i(\tau, s) d\tau \right) ds \quad (2.13) \\ i(\tau, t) &= \begin{cases} \frac{S(t-\tau)}{N(t-\tau)} e^{-\int_0^\tau m(V(s))ds} \int_0^A c_1 s_1 V(r) i(r, t-\tau) dr, & \tau < t \\ i^0(\tau - t) e^{-\int_0^t m(V(\tau - t + s))ds}, & \tau > t, \end{cases} \end{aligned}$$

where $S(t)$ in (2.13) is a representation formula for the solution to the differential equation

$$\frac{dS}{dt} + \alpha S(t) = \Lambda + \alpha S(t) - \frac{S(t)}{N(t)} \int_0^A c_1 s_1 V(\tau) i(\tau, t) d\tau - m_0 S(t),$$

with $\alpha \geq c_1 s_1 C > 0$. This differential equation is equivalent to equation (2.5).

To prove the existence and uniqueness of solution, we define our state solution space as

$$\begin{aligned} X &= \{(S, i) \in L^\infty(0, T) \times L^\infty(0, T; L^1(0, A)) | S(t) \geq \varepsilon > 0, \ \ i(\tau, t) \geq 0, \ \ \sup_t S(t) < \infty \\ &\quad and \ \sup_t \int_0^A i(\tau, t) d\tau < \infty \ a.e. \ t\}, \end{aligned}$$

where $L^\infty(0,A)$ is the space of all essentially bounded functions on $(0,A)$, and $\varepsilon = \min\left\{S_0, \frac{\Lambda}{m_0+\alpha}\right\}$. We define a map

$$\mathcal{L} : X \to X, \quad \mathcal{L}(S,i) = (L_1(S,i), L_2(S,i)),$$

where

$$\begin{aligned} L_1(S,i)(t) &= S_0 e^{-(m_0+\alpha)t} + \frac{\Lambda}{m_0+\alpha}(1-e^{-(m_0+\alpha)t}) + \alpha\int_0^t e^{-(m_0+\alpha)(t-s)}S(s)ds \\ &\quad - c_1 s_1 \int_0^t \int_0^A \frac{V(\tau)i(\tau,s)S(s)}{N(s)} e^{-(m_0+\alpha)(t-s)} d\tau ds, \end{aligned} \tag{2.14}$$

and

$$L_2(S,i)(\tau,t) = \begin{cases} \frac{S(t-\tau)}{N(t-\tau)} e^{-\int_0^\tau m(V(s))ds} \int_0^A c_1 s_1 V(r) i(r,t-\tau)dr, & \tau < t \\ i^0(\tau-t)e^{-\int_0^t m(V(\tau-t+s))ds}, & \tau > t \end{cases} \tag{2.15}$$

The following assumptions will be useful in establishing a Lipschitz property for the within-host and between-host state solutions in terms of control functions (See section 2.4), and in proving existence and uniqueness of solution to the epidemiological model:

- $S_0$, $m_0$, $\Lambda$, $c_1$ and $s_1$ are positive constants,
- $V$ is given, such that $0 < V(\tau) \le C$ for all $\tau > 0$
- $m(s)$ is non-negative and Lipschitz continuous,
- $i^0(\tau)$ is non-negative for all $\tau \in (0,A)$,
- $\int_0^A i^0(\tau)d\tau \le M$ and $0 < S_0 \le M$.

**Theorem 2.2.** *For $T < \infty$, there exists a unique non-negative solution $(S,i)$ to the epidemiological system (2.5) – (2.7).*

*Proof.* First, we show that the map $\mathcal{L}$ maps $X$ into itself. Indeed,

$$
\begin{aligned}
|L_1(S,i)|(t) &\leq |S_0e^{-(m_0+\alpha)t} + \frac{\Lambda}{m_0+\alpha}(1-e^{-(m_0+\alpha)t})| + \left|\alpha\int_0^t S(s)e^{-(m_0+\alpha)(t-s)}ds\right| \\
&\quad + \left|\int_0^t e^{-(m_0+\alpha)(t-s)}\frac{S(s)}{N(s)}\int_0^A c_1s_1V(\tau)i(\tau,s)d\tau ds\right| \\
&\leq M + |\frac{\Lambda}{m_0+\alpha}(1-e^{-(m_0+\alpha)T})| + \frac{\alpha}{m_0+\alpha}\sup_s S(s) \\
&\quad + \frac{K_1}{m_0+\alpha}\left(\sup_s \int_0^A i(\tau,s)d\tau\right) < \infty,
\end{aligned}
$$

where $K_1$ depends on the contact rate between susceptible and infectious individuals, shedding rate of free virus and the bound on the population of free virus. Next, we estimate the second component.

$$
\begin{aligned}
\int_0^A |L_2(S,i)|(\tau,t)d\tau &= \int_0^t \left|\frac{S(t-\tau)}{N(t-\tau)}e^{-\int_0^\tau m(V(\omega))d\omega}\int_0^A c_1s_1V(r)i(r,t-\tau)dr\right| d\tau \\
&\quad + \int_t^A \left|i_1^0(\tau-t)e^{-\int_0^t m(V_2(\tau-t+s))ds}\right| d\tau \\
&\leq \int_0^t \left|\int_0^A c_1s_1V(r)i(r,t-\tau)dr\right| d\tau + \int_0^A i^0(\tau)d\tau \\
&\leq K_2T\left(\sup_\xi \int_0^A i(\hat{r},\xi)d\hat{r}\right) + M < \infty,
\end{aligned}
$$

where $\hat{r} = r$, $\xi = t-\tau$, $K_2$ depends on the contact rate between susceptible and infectious individuals, shedding rate of free virus and the bound on the population of free virus. Finally, we show that $L_1(S,i)(t) \geq \varepsilon$ and $L_2(S,i)(\tau,t) \geq 0$, for all $\tau > 0$ and $t > 0$. Now, from Theorem 2.1, we obtain

$$
\begin{aligned}
L_1(S,i)(t) &\geq S_0e^{-(m_0+\alpha)t} + \frac{\Lambda}{m_0+\alpha}(1-e^{-(m_0+\alpha)t}) + \int_0^t e^{-(m_0+\alpha)(t-s)}S(s)(\alpha - c_1s_1C)ds \\
&\geq S_0e^{-(m_0+\alpha)t} + \frac{\Lambda}{m_0+\alpha}(1-e^{-(m_0+\alpha)t}) \geq \varepsilon > 0,
\end{aligned}
$$

due to the convex combination of $S_0$ and $\frac{\Lambda}{m_0+\alpha}$. Also, $L_2(S,i)(\tau,t) \geq 0$ since $S(t) \geq \varepsilon > 0$ and $i(\tau,t) \geq 0$. Hence, $\mathcal{L}$ maps $X$ to $X$.

Next, we show that the operator $\mathcal{L}$ admits a unique fixed point. To do this, we define an iterative sequence [86]

$$(S^{(n+1)}(t), i^{(n+1)}(\tau,t)) = (L_1(S^{(n)}(t), i^{(n)}(\tau,t)), L_2(S^{(n)}(t), i^{(n)}(\tau,t))), \tag{2.16}$$

where

$$\begin{aligned} S^{(n+1)}(t) &= S_0 e^{-(m_0+\alpha)t} + \frac{\Lambda}{m_0+\alpha}(1-e^{-(m_0+\alpha)t}) \\ &+ \int_0^t e^{-(m_0+\alpha)(t-s)} S^{(n)}(s) \left( \alpha - \frac{1}{N^{(n)}(s)} \int_0^A c_1 s_1 V(\tau) i^{(n)}(\tau,s) d\tau \right) ds \end{aligned}$$

and

$$i^{(n+1)}(\tau,t) = \begin{cases} \frac{S^{(n)}(t-\tau)}{N^{(n)}(t-\tau)} e^{-\int_0^\tau m(V(s))ds} \int_0^A c_1 s_1 V(s) i^{(n)}(s,t-\tau)ds, & \tau < t \\ i^0(\tau-t) e^{-\int_0^t m(V(\tau-t+s))ds}, & \tau > t. \end{cases}$$

We set $S^{(0)}(t) = 0$, $i^{(0)}(\tau,t) = 0$, and

$$\begin{aligned} S^{(1)}(t) &= S_0 e^{-(m_0+\alpha)t} + \frac{\Lambda}{m_0+\alpha}(1-e^{-(m_0+\alpha)t}) \\ i^{(1)}(\tau,t) &= \begin{cases} 0, & \tau < t \\ i^0(\tau-t) e^{-\int_0^t m(V(\tau-t+s))ds}, & \tau > t, \end{cases} \end{aligned}$$

and define a sequence for the total population as

$$N^{(n)}(t) = S^{(n)}(t) + \int_0^A i^{(n)}(\tau,t) d\tau.$$

To show that the sequence of functions $\{(S^{(n)}(t), i^{(n)}(\tau,t))\}$ converges for all $n \geq 0$, we introduce the notation

$$\begin{aligned} \mathbb{F}_n(t) &= |S^{(n+1)}(t) - S^{(n)}(t)| \\ \mathbb{I}_n(t) &= \int_0^A |i^{(n+1)}(\tau,t) - i^{(n)}(\tau,t)| d\tau, \end{aligned} \tag{2.17}$$

so that $\mathbb{N}_n(t) = \mathbb{F}_n(t) + \mathbb{I}_n(t)$. Now,

$$\mathbb{F}_0 = S_0 e^{-(m_0+\alpha)t} + \frac{\Lambda}{m_0+\alpha}(1 - e^{-(m_0+\alpha)t}) \leq \max\left\{S_0, \frac{\Lambda}{m_0+\alpha}\right\}$$

and $\mathbb{I}_0 = \int_0^A i^0(\tau)d\tau$, so that $\mathbb{N}_0 = \max\left\{S_0, \frac{\Lambda}{m_0+\alpha}\right\} + \int_0^A i^0(\tau)d\tau$. Next, for $n = 1$, we get

$$\begin{aligned}
\mathbb{F}_1 &= \left|\int_0^t e^{-(m_0+\alpha)(t-s)} S^{(1)}(s)\left(\alpha - \frac{1}{N^{(1)}(s)}\int_0^A c_1 s_1 V(\tau) i^{(1)}(\tau, s)d\tau\right) ds\right| \\
&\leq \max\left\{S_0, \frac{\Lambda}{m_0+\alpha}\right\} \frac{\alpha + c_1 s_1 C}{\alpha + m_0}, \qquad (2.18)
\end{aligned}$$

and

$$\begin{aligned}
\mathbb{I}_1(t) &= \int_0^t \frac{S^{(1)}(t-\tau)}{N^{(1)}(t-\tau)} e^{-\int_0^\tau m(V(s))ds} \int_t^A c_1 s_1 V(s) i^0(s+\tau-t) \frac{\pi(\tau)}{\pi(\tau - s)} ds d\tau \\
&\leq \frac{c_1 s_1 C}{m_0} \int_0^A i^0(\xi) d\xi, \qquad (2.19)
\end{aligned}$$

where $\xi = s + \tau - t$ and $\pi(\tau) = e^{-\int_0^\tau m(V(s))ds}$. Thus, combining equations (2.18) and (2.19), we have $\mathbb{N}_1(t) \leq \hat{C}\mathbb{N}_0$, for all $t$. Next, we consider the equations for $S$ and $i$, and use induction. First,

$$\begin{aligned}
\mathbb{F}_n(t) &= |S^{(n+1)}(t) - S^{(n)}(t)| \\
&\leq \alpha \int_0^t e^{-(m_0+\alpha)(t-\xi)} |S^{(n)}(\xi) - S^{(n-1)}(\xi)| d\xi \\
&\quad + \int_0^t \left|\int_0^A c_1 s_1 V(\tau)\left(\frac{S^{(n)}(\xi) i^{(n)}(\tau,\xi)}{N^{(n)}(\xi)} - \frac{S^{(n-1)}(\xi) i^{(n-1)}(\tau,\xi)}{N^{(n-1)}(\xi)}\right) d\tau\right| d\xi \\
&\leq \alpha \int_0^t |S^{(n)}(\xi) - S^{(n-1)}(\xi)| d\xi + \int_0^t \int_0^A c_1 s_1 V(\tau) \left|G(\tau,\xi)\right| d\tau d\xi, \qquad (2.20)
\end{aligned}$$

where

$$G(\tau, \xi) = \frac{S^{(n)}(\xi) i^{(n)}(\tau,\xi)}{N^{(n)}(\xi)} - \frac{S^{(n-1)}(\xi) i^{(n-1)}(\tau,\xi)}{N^{(n-1)}(\xi)}$$

$$
\begin{aligned}
&= \frac{S^{(n)}(\xi)}{N^{(n)}(\xi)}\left(i^{(n)}(\tau,\xi) - i^{(n-1)}(\tau,\xi)\right) + \frac{i^{(n-1)}(\tau,\xi)}{N^{(n-1)}(\xi)}\left(S^{(n)}(\xi) - S^{(n-1)}(\xi)\right) \quad (2.21)\\
&\quad + \frac{i^{(n-1)}(\tau,\xi)S^{(n)}(\xi)}{N^{(n)}(\xi)} - \frac{i^{(n-1)}(\tau,\xi)S^{(n)}(\xi)}{N^{(n-1)}(\xi)}\\
&= \frac{S^{(n)}(\xi)}{N^{(n)}(\xi)}\left(i^{(n)}(\tau,\xi) - i^{(n-1)}(\tau,\xi)\right) + \frac{i^{(n-1)}(\tau,\xi)}{N^{(n-1)}(\xi)}\left(S^{(n)}(\xi) - S^{(n-1)}(\xi)\right)\\
&\quad + \frac{i^{(n-1)}(\tau,\xi)}{N^{(n-1)}(\xi)}\frac{S^{(n)}(\xi)}{N^{(n)}(\xi)}\left(S^{(n-1)}(\xi) - S^{(n)}(\xi)\right) \quad (2.22)\\
&\quad + \frac{i^{(n-1)}(\tau,\xi)}{N^{(n-1)}(\xi)}\frac{S^{(n)}(\xi)}{N^{(n)}(\xi)}\int_0^A (i^{(n-1)}(\sigma,\xi) - i^{(n)}(\sigma,\xi))d\sigma.
\end{aligned}
$$

Since $0 < V(\tau) \leq C$, inequality (2.20) gives

$$
\begin{aligned}
|S^{(n+1)}(t) - S^{(n)}(t)| &\leq (\alpha + 2c_1 s_1 C)\int_0^t |S^{(n)}(\xi) - S^{(n-1)}(\xi)|d\xi\\
&\quad + 2c_1 s_1 C \int_0^t \int_0^A |i^{(n)}(\tau,\xi) - i^{(n-1)}(\tau,\xi)|d\tau d\xi\\
&= (\alpha + 2c_1 s_1 C)\int_0^t \mathbb{F}_{n-1}(\xi)d\xi + 2c_1 s_1 C \int_0^t \mathbb{I}_{n-1}(\xi)d\xi \quad (2.23)
\end{aligned}
$$

Thus,

$$
\mathbb{F}_n(t) \leq K_3 \int_0^t (\mathbb{F}_{n-1}(\xi) + \mathbb{I}_{n-1}(\xi))d\xi, \quad (2.24)
$$

where $K_3$ depends on the contact rate between susceptible and infectious individuals, shedding rate of free virus and the bound on the population of free virus. Next, we consider the second component.

$$
\begin{aligned}
\mathbb{I}_n(t) &= \int_0^A |i^{(n+1)}(\tau,t) - i^{(n)}(\tau,t)|d\tau\\
&\leq \int_0^t \int_0^A c_1 s_1 V(\sigma)\left|\frac{S^{(n)}(t-\tau)i^{(n)}(\sigma,t-\tau)}{N^{(n)}(t-\tau)} - \frac{S^{(n-1)}(t-\tau)i^{(n-1)}(\sigma,t-\tau)}{N^{(n-1)}(t-\tau)}\right| d\sigma d\tau\\
&\leq K_4 \int_0^t \mathbb{F}_{n-1}(\xi)d\xi + K_4 \int_0^t \mathbb{I}_{n-1}(\xi)d\xi, \quad (2.25)
\end{aligned}
$$

where we have mimicked equations (2.20) and (2.23), and used the substitution

$\xi = t - \tau$. Since $\mathbb{N}_n(t) = \mathbb{F}_n(t) + \mathbb{I}_n(t)$, combining inequalities (2.24) and (2.25), we see that $\mathbb{N}_n(t)$ satisfies the recurrence relation

$$\mathbb{N}_n(t) \leq K \int_0^t \mathbb{N}_{n-1}(\xi) d\xi, \quad with \quad \mathbb{N}_1(t) \leq \hat{C}\mathbb{N}_0,$$

where $K = K_3 + K_4$. Notice that

$$\mathbb{N}_2(t) \leq K \int_0^t \mathbb{N}_1(\xi) d\xi \leq K\hat{C}\mathbb{N}_0 t$$

and

$$\mathbb{N}_3(t) \leq K \int_0^t K\hat{C}\mathbb{N}_0 \xi d\xi = \hat{C}\mathbb{N}_0 \frac{K^2 t^2}{2}.$$

Thus, by induction, it follows that

$$\mathbb{N}_n(t) \leq \hat{C}\mathbb{N}_0 \frac{K^{n-1} t^{n-1}}{(n-1)!} \leq \hat{C}\mathbb{N}_0 \frac{K^{n-1} T^{n-1}}{(n-1)!}.$$

Now, the remainder term of the sequence $\{S^{(n)}(t)\}$ is such that

$$|S^{(n+m)}(t) - S^{(n)}(t)| \leq \sum_{j=n+1}^{n+m} \mathbb{N}_j(t) \leq \hat{C}\mathbb{N}_0 \sum_{j=n+1}^{\infty} \frac{K^{j-1} T^{j-1}}{(j-1)!} \to 0, \quad as \quad n \to \infty.$$

Also, using the notation in (2.17) and the definition of $\mathbb{N}_n(t)$, we have

$$\begin{aligned} \int_0^A |i^{(n+m)}(\tau, t) - i^{(n)}(\tau, t)| d\tau \;&\leq\; \sum_{j=n+1}^{n+m} \int_0^A |i^{(j)}(\tau, t) - i^{(j-1)}(\tau, t)| d\tau \\ &\leq\; \sum_{j=n+1}^{n+m} \mathbb{N}_j(t) \leq \hat{C}\mathbb{N}_0 \sum_{j=n+1}^{\infty} \frac{K^{j-1} T^{j-1}}{(j-1)!} \to 0 \; as \; n \to \infty. \end{aligned}$$

Thus, the sequence $\{(S^{(n)}(t), i^{(n)}(\tau, t))\}$ generated by the iterative sequence (2.16) is a Cauchy sequence in $X$, and is therefore convergent, since $X$ is complete. Thus, there exists $(S(t), i(\tau, t))$ in $X$ which is the limit of the given sequence. From the iterative sequence (2.16) and definition of the operator $\mathcal{L}$,

$$\mathcal{L}(S(t), i(\tau, t)) = (S(t), i(\tau, t));$$

it follows that the limit $(S(t), i(\tau, t))$ is a fixed point of the operator $\mathcal{L}$. This establishes the existence of solution to the epidemiological model for all $T < \infty$.

We prove uniqueness by assuming the existence of two solutions $(S(t), i(\tau, t))$ and $(\bar{S}(t), \bar{i}(\tau, t))$ for which

$$(S(t), i(\tau, t)) = (L_1(S(t), i(\tau, t)), L_2(S(t), i(\tau, t)))$$

and

$$(\bar{S}(t), \bar{i}(\tau, t)) = (L_1(\bar{S}(t), \bar{i}(\tau, t)), L_2(\bar{S}(t), \bar{i}(\tau, t))).$$

We substitute $(S(t), i(\tau, t))$ and $(\bar{S}(t), \bar{i}(\tau, t))$ in place of $(S^{(n)}(t), i^n(\tau, t))$ and $(S^{(n-1)}(t), i^{(n-1)}(\tau, t))$, respectively, in the proof of existence of solution above, and set

$$\hat{\mathbb{F}}(t) = |S(t) - \bar{S}(t)|, \quad \textit{and} \quad \hat{\mathbb{I}}(t) = \int_0^A |i(\tau, t) - \bar{i}(\tau, t)| d\tau.$$

This gives $\hat{\mathbb{N}}(t) \leq K \int_0^t \hat{\mathbb{N}}(\xi) d\xi$, so that by Gronwall's inequality in integral form, $\hat{\mathbb{N}}(t) \equiv 0$. Thus, $\hat{\mathbb{F}}(t) + \hat{\mathbb{I}}(t) = 0, \quad \forall t > 0$. Since $\hat{\mathbb{F}}(t) \geq 0$, and $\hat{\mathbb{I}}(t) \geq 0$, with $\hat{\mathbb{F}}(t) + \hat{\mathbb{I}}(t) = 0$, it follows that $\hat{\mathbb{F}}(t) = \hat{\mathbb{I}}(t) = 0$, for all $t > 0$. Hence, the solution, $(S(t), i(\tau, t))$, to the epidemiological model is unique. □

### 2.3.2 Basic Reproduction Number and Equilibria

In this subsection, we derive an explicit expression for the basic reproduction number of the epidemiological model, calculate steady state solutions and study stability of equilibrium points.

The basic reproduction number was originally developed for the study of demographics (Sharp and Lotka 1911 [106], Dublin and Lotka 1925 [37]) but was independently studied for vector-borne diseases such as malaria (Ross 1911 [103], MacDonald 1952 [35]) and directly transmitted human infections (Kermack and McKendrick 1927 [74]). It is now widely used for the study of infectious diseases.

The basic reproduction number, $\mathcal{R}_0$, is defined as the number of secondary infections that result from the introduction of a single infectious individual into a completely susceptible population during its entire period of infectiousness [21, 36, 59, 60, 61]. It provides an invasion criterion for the initial spread of the infection in a susceptible population. Also, it measures the transmissibility of a pathogen and determines the magnitude of public health intervention necessary to control epidemics [21, 62]. If $\mathcal{R}_0 < 1$, then on average, an infected individual produces less than one new infected individual over the course of its infectious period, and the infection cannot spread [36, 73, 89]. On the other hand, if $\mathcal{R}_0 > 1$, then each infected individual produces, on average, more than one new infection, and the disease can invade the population.

The basic reproduction number can be determined through the study and computation of eigenvalues of the Jacobian matrix of the system, evaluated at the disease-free equilibrium. A method for calculating these eigenvalues in a simpler way in a disease model, called the *next generation operator approach*, was introduced by Diekmann *et al.* [28, 29, 30, 31, 32] and elaborated on by van den Driessche and Watmough [36]. For age-structured models, we use the notions of *survival functions or probabilities* in the computation of the basic reproduction number, $\mathcal{R}_0$. Now, let $\mathcal{F}(\tau)$ be the probability that a newly infected individual remains infected until time-since-infection $\tau$, and $\widehat{\beta}(\tau)$ denote the average number of newly infected individuals that an infectious individual will produce per unit time when infected for a total time $\tau$, then the basic reproduction number is given by [62]

$$\mathcal{R}_0 = \int_0^A \widehat{\beta}(\tau)\mathcal{F}(\tau)d\tau.$$

In order to derive an explicit expression for the basic reproduction number, $\mathcal{R}_0$, of the age-structured epidemiological model, we compute the disease-free equilibrium, linearize the system around the disease-free equilibrium and determine conditions for its stability. Now, the disease-free equilibrium is $(S^*, i^*(\tau)) = (\frac{\Lambda}{m_0}, 0)$. We consider solutions nearby $(S^*, i^*(\tau))$ by setting $x(t) = S(t) - S^* \quad and \quad i(\tau, t) = z(\tau, t)$. Since at the disease-free equilibrium, $\Lambda - m_0 S^* = 0$, equation (2.5) becomes

$$\begin{aligned}\frac{dx}{dt} &= \Lambda - \frac{S^* + x(t)}{S^*\left(1 + \frac{n(t)}{S^*}\right)} \int_0^A c_1 s_1 V(\tau) z(\tau, t) d\tau - m_0(S^* + x(t)) \\ &= -\left(1 + \frac{x(t)}{S^*}\right)\left(1 - \frac{n(t)}{S^*} + h.o.t\right) \int_0^A c_1 s_1 V(\tau) z(\tau, t) d\tau - m_0 x(t) \\ &\approx -\int_0^A c_1 s_1 V(\tau) z(\tau, t) d\tau - m_0 x(t),\end{aligned}$$

where the higher order terms (h.o.t) are neglected to get the linearized approximation. The $i$ partial differential equation is linear in $i$, and the $\frac{S}{N}$ term in the boundary condition at $\tau = 0$, can be handled like above; the linearized system is:

$$\frac{dx}{dt} = -\int_0^A c_1 s_1 V(\tau) z(\tau, t) d\tau - m_0 x(t) \tag{2.26}$$

$$\frac{\partial z(\tau, t)}{\partial t} + \frac{\partial z(\tau, t)}{\partial \tau} = -m(V(\tau)) z(\tau, t) \tag{2.27}$$

$$z(0, t) = \int_0^A c_1 s_1 V(\tau) z(\tau, t) d\tau. \tag{2.28}$$

We seek a solution to equation (2.27) of the form $z(\tau, t) = \bar{z}(\tau) e^{\lambda t}$, where $\lambda$ is either a real or complex number. Substituting this solution into equations (2.27) – (2.28), we have the following eigenvalue problem

$$\frac{d\bar{z}(\tau)}{d\tau} = -(\lambda + m(V(\tau)))\bar{z}(\tau) \tag{2.29}$$

$$\bar{z}(0) = \int_0^A c_1 s_1 V(\tau) \bar{z}(\tau) d\tau. \tag{2.30}$$

The explicit solution to the differential equation gives

$$\bar{z}(0) = \int_0^A c_1 s_1 V(\tau)\bar{z}(0)e^{-\lambda\tau}e^{-\int_0^\tau m(V(s))ds}d\tau \tag{2.31}$$

Dividing both sides of equation (2.31) by $z(0)$, we obtain the characteristic equation $G(\lambda) = 1$, where

$$G(\lambda) = \int_0^A c_1 s_1 V(\tau)e^{-\lambda\tau}e^{-\int_0^\tau m(V(s))ds}d\tau. \tag{2.32}$$

This characteristic equation will be used to study stability of the disease-free equilibrium. Now, we define the basic reproduction number, $\mathcal{R}_0$, of the epidemiological model as $\mathcal{R}_0 = G(0)$ [18, 81, 100, 107], so that

$$\mathcal{R}_0 = \int_0^A c_1 s_1 V(\tau)e^{-\int_0^\tau m(V(s))ds}d\tau, \tag{2.33}$$

where the quantity $\pi(\tau) = e^{-\int_0^\tau m(V(s))ds}$ is the probability of survival in the infected class from onset of infection to age-since-infection $\tau$.

**Theorem 2.3.** *The epidemiological model has a unique endemic equilibrium,* $(S^*, i^*(\tau))$, *if* $\mathcal{R}_0 > 1$.

*Proof.* The equilibria of the epidemiological model are obtained by setting the time derivatives of the model to zero:

$$0 = \Lambda - \frac{S}{N}\int_0^A c_1 s_1 V(\tau)i(\tau)d\tau - m_0 S \tag{2.34}$$

$$\frac{di(\tau)}{d\tau} = -m(V(\tau))i(\tau) \tag{2.35}$$

$$i(0) = \frac{S}{N}\int_0^A c_1 s_1 V(\tau)i(\tau)d\tau. \tag{2.36}$$

The endemic equilibrium is obtained as follows. First, we solve the differential equation (2.35) to have

$$i^*(\tau) = i^*(0)e^{-\int_0^\tau m(V(s))ds}. \tag{2.37}$$

Next, we substitute the expression for $i^*$ into equation (2.34):

$$0 = \Lambda - \frac{S^*}{N} \int_0^A c_1 s_1 V(\tau) i^*(0) e^{-\int_0^\tau m(V(s))ds} d\tau - m_0 S^*. \tag{2.38}$$

Thus, from equations (2.36), (2.37) and (2.38), we obtain $i^*(0)$ as follows:

$$\begin{aligned} i^*(0) &= \frac{S^*}{N} \int_0^A c_1 s_1 V(\tau) i^*(0) e^{-\int_0^\tau m(V(s))ds} d\tau \\ &= \Lambda - m_0 S^*. \end{aligned} \tag{2.39}$$

From equations (2.36) and (2.37), and the total population at equilibrium $N^* = S^* + \int_0^A i^*(\tau) d\tau$, we obtain

$$\frac{S^*}{N^*} = \frac{1}{\mathcal{R}_0} \quad \text{and} \quad \frac{i^*(0)}{N^*} = \frac{\mathcal{R}_0 - 1}{\xi \mathcal{R}_0}, \tag{2.40}$$

where $\xi = \int_0^A e^{-\int_0^\tau m(V(s))ds} d\tau$. Also, from equations (2.39) and (2.40), we obtain $N^* = \frac{\Lambda \xi \mathcal{R}_0}{\mathcal{R}_0 - 1 + m_0 \xi}$. Finally, from equations (2.37) and (2.40), we obtain the endemic equilibrium point $(S^*, i^*(\tau))$, where

$$(S^*, i^*(\tau)) = \left( \frac{\Lambda \int_0^A e^{-\int_0^\tau m(V(s))ds} d\tau}{\mathcal{R}_0 - 1 + m_0 \int_0^A e^{-\int_0^\tau m(V(s))ds} d\tau}, \frac{\Lambda(\mathcal{R}_0 - 1) e^{-\int_0^\tau m(V(s))ds}}{\mathcal{R}_0 - 1 + m_0 \int_0^A e^{-\int_0^\tau m(V(s))ds} d\tau} \right),$$

which is biologically feasible if $\mathcal{R}_0 > 1$. □

### 2.3.3 Stability Analysis

To study the local stability of equilibria, we linearize the model around each of the equilibrium points, and consider an exponential solution to the linearized system.

**Theorem 2.4.** *The disease-free equilibrium is locally asymptotically stable if* $\mathcal{R}_0 < 1$ *and unstable if* $\mathcal{R}_0 > 1$.

*Proof.* If $\lambda \in \Re$, then from equation (2.32),

$$G'(\lambda) = -\int_0^A c_1 s_1 V(\tau)\tau e^{-\lambda\tau} e^{-\int_0^\tau m(V(s))ds} d\tau < 0,$$

since $V$ is nonnegative and bounded. Thus, $G$ is a decreasing function of $\lambda$, with $\lim_{\lambda\to\infty} G(\lambda) = 0$. Therefore, when $\mathcal{R}_0 = G(0) > 1$, there exists a unique positive real solution to the equation $G(\lambda) = 1$. Hence, the disease-free equilibrium is unstable when $\mathcal{R}_0 > 1$ [81, 100, 107].

On the other hand, $\lim_{\lambda\to-\infty} G(\lambda) = +\infty$. Thus, when $\mathcal{R}_0 = G(0) < 1$, there exists a unique real and negative solution to the equation $G(\lambda) = 1$. Next, we assume that $\lambda$ is complex and let $\lambda = \xi + i\eta$ be an arbitrary complex solution to the characteristic equation $G(\lambda) = 1$. Then

$$\begin{aligned} 1 &= |G(\xi + i\eta)| \\ &\leq \int_0^A c_1 s_1 V(\tau) e^{-\xi\tau} |e^{-i\eta\tau}| e^{-\int_0^\tau m(V(s))ds} d\tau \\ &= \int_0^A c_1 s_1 V(\tau) e^{-\xi\tau} e^{-\int_0^\tau m(V(s))ds} d\tau =: G(Re(\lambda)). \end{aligned}$$

If $Re(\lambda) \geq 0$, then

$$1 = |G(\lambda)| \leq G(Re(\lambda)) \leq G(0) = \mathcal{R}_0 < 1,$$

which is absurd. Thus, all roots of the equation $G(\lambda) = 1$ are either real and negative or complex with negative real parts when $\mathcal{R}_0 < 1$. Hence the disease-free equilibrium is locally asymptotically stable when $\mathcal{R}_0 < 1$. □

**Theorem 2.5.** *The disease-free equilibrium is globally stable if* $\mathcal{R}_0 < 1$.

*Proof.* The general approach in showing global stability of the disease-free equilibrium is to view the boundary condition as a function of time, solve the PDE along characteristic lines and substitute the solution into the expression for the boundary condition to obtain an integral equation. Now, let

$$g(t) = \frac{S(t)}{N(t)} K(t),$$

where

$$K(t) = \int_0^A c_1 s_1 V(\tau) i(\tau, t) d\tau. \tag{2.41}$$

We derive an integral equation for $K(t)$ by using the following solution to the partial differential equation (2.6):

$$i(\tau, t) \quad = \quad \begin{cases} \dfrac{S(t-\tau)}{N(t-\tau)} e^{-\int_0^\tau m(V(s))ds} \displaystyle\int_0^A c_1 s_1 V(r) i(r, t-\tau) dr, & \tau < t \\ i^0(\tau - t) e^{-\int_0^t m(V(\tau - t + s))ds}, & \tau > t. \end{cases}$$

Substituting the expression for $i(\tau, t)$ in $K(t)$, we obtain

$$\begin{aligned} K(t) \quad &= \quad \int_0^t c_1 s_1 K(t-\tau) V(\tau) \frac{S(t-\tau)}{N(t-\tau)} e^{-\int_0^\tau m(V(s))ds} d\tau \\ &\quad + \int_t^A c_1 s_1 V(\tau) i^0(\tau - t) e^{-\int_0^t m(V(\tau - t + s))ds} d\tau \\ &\leq \quad \int_0^t c_1 s_1 K(t-\tau) V(\tau) e^{-\int_0^\tau m(V(s))ds} d\tau + \int_t^A c_1 s_1 V(\tau) i^0(\tau - t) d\tau. \end{aligned} \tag{2.42}$$

Since for all $\tau \in (0, A)$, $0 < V(\tau) \leq C$, it follows from the definition of (2.41) that

$$\limsup_t K(t) \leq c_1 s_1 C \limsup_t \int_0^A i(\tau, t) d\tau < \infty.$$

Thus, taking the lim sup of both sides of equation (2.42) as $t \to \infty$, we have

$$\limsup_{t\to\infty} K(t) \leq \mathcal{R}_0 \limsup_{t\to\infty} K(t),$$

which holds only if $\limsup_{t\to\infty} K(t) = 0$. This gives $\limsup_{t\to\infty} i(\tau, t) = 0$ for every fixed $\tau$. The solution to the equation that models susceptible individuals in the population is

$$S(t) = -\int_0^t e^{-m_0(t-s)} \frac{S(s)}{N(s)} \int_0^A c_1 s_1 V(\tau) i(\tau, s) d\tau ds + S_0 e^{-m_0 t} + \frac{\Lambda}{m_0}(1 - e^{-m_0 t}) \to \frac{\Lambda}{m_0} \quad as \quad t \to \infty.$$

Hence the disease-free equilibrium is globally stable when $\mathcal{R}_0 < 1$. □

**Theorem 2.6.** *The endemic equilibrium $(S^*, i^*(\tau))$ is locally asymptotically stable if $\mathcal{R}_0 > 1$ and the maximal age of infection, $A$, is sufficiently large.*

*Proof.* We consider solutions near the endemic equilibrium by setting

$$x(t) = S(t) - S^*, \quad z(\tau, t) = i(\tau, t) - i^*(\tau)$$

so that the total population is $N(t) = N^* + n(t)$. Substituting the perturbed solutions into equations (2.5) – (2.7), we have the following linearized system:

$$\frac{dx}{dt} = -\frac{x}{N^*}\int_0^A c_1 s_1 V(\tau) i^*(\tau) d\tau + \frac{S^*}{N^*}\frac{n}{N^*}\int_0^A c_1 s_1 V(\tau) i^*(\tau) d\tau - \frac{S^*}{N^*}\int_0^A c_1 s_1 V(\tau) z(\tau, t) d\tau - m_0 x \tag{2.43}$$

$$\frac{\partial z(\tau, t)}{\partial t} + \frac{\partial z(\tau, t)}{\partial t} = -m(V(\tau)) z(\tau, t) \tag{2.44}$$

$$z(0, t) = \frac{x}{N^*}\int_0^A c_1 s_1 V(\tau) i^*(\tau) d\tau - \frac{S^*}{N^*}\frac{n}{N^*}\int_0^A c_1 s_1 V(\tau) i^*(\tau) d\tau + \frac{S^*}{N^*}\int_0^A c_1 s_1 V(\tau) z(\tau, t) d\tau. \tag{2.45}$$

We seek for solutions to equations (2.43) – (2.45) of the form

$$x(t) = \bar{x} e^{\lambda t} \quad \text{and} \quad z(\tau, t) = \bar{z}(\tau) e^{\lambda t},$$

where $\bar{x}$ and $\bar{z}(\tau)$ are to be determined. This gives

$$\begin{aligned}
\lambda\bar{x} &= -\frac{\bar{x}}{N^*}\int_0^A c_1 s_1 V(\tau) i^*(\tau) d\tau + \frac{S^*}{N^*}\frac{\bar{n}}{N^*}\int_0^A c_1 s_1 V(\tau) i^*(\tau) d\tau \\
&\quad -\frac{S^*}{N^*}\int_0^A c_1 s_1 V(\tau)\bar{z}(\tau) d\tau - m_0\bar{x} && (2.46) \\
\frac{d\bar{z}(\tau)}{d\tau} &= -(\lambda + m(V(\tau)))\bar{z}(\tau) && (2.47) \\
\bar{z}(0) &= \frac{\bar{x}}{N^*}\int_0^A c_1 s_1 V(\tau) i^*(\tau) d\tau - \frac{S^*}{N^*}\frac{\bar{n}}{N^*}\int_0^A c_1 s_1 V(\tau) i^*(\tau) d\tau \\
&\quad +\frac{S^*}{N^*}\int_0^A c_1 s_1 V(\tau)\bar{z}(\tau) d\tau, && (2.48)
\end{aligned}$$

where $\bar{n} = \bar{x} + \int_0^A \bar{z}(\tau)d\tau$. Solving the differential equation (2.47), we obtain

$$\bar{z}(\tau) = \bar{z}(0)e^{-\lambda\tau}e^{-\int_0^\tau m(V(s))ds}.$$

From equations (2.46) and (2.48),

$$\bar{z}(0) = -(\lambda + m_0)\bar{x}. \tag{2.49}$$

Using the definitions of $\bar{n}$, $\bar{z}(\tau)$ and $\bar{z}(0)$, and setting $\tilde{\alpha} = \int_0^A c_1 s_1 V(\tau) i^*(\tau) d\tau$ in equation (2.46), we obtain the characteristic equation

$$1 = \frac{\tilde{\alpha}}{N^*(\lambda + m_0)}\left(\frac{S^*}{N^*} - 1\right) + \frac{S^*}{N^*}\int_0^A c_1 s_1 V(\tau) e^{-\lambda\tau}\pi(\tau) d\tau - \frac{\tilde{\alpha}}{N^*}\frac{S^*}{N^*}\int_0^A e^{-\lambda\tau}\pi(\tau) d\tau. \tag{2.50}$$

Using $m(V(\tau)) = m_0 + \mu_1 V(\tau)$ and integration by parts, we obtain

$$\begin{aligned}
&\int_0^A c_1 s_1 V(\tau) e^{-\lambda\tau}\pi(\tau) d\tau \\
&= \frac{c_1 s_1}{\mu_1}\int_0^A \mu_1 V(\tau) e^{-\lambda\tau} e^{-m_0\tau} e^{-\mu_1\int_0^\tau V(s)ds} d\tau \\
&= \frac{c_1 s_1}{\mu_1}\left(1 - e^{-(\lambda+m_0)A} e^{-\mu_1\int_0^A V(s)ds} - (\lambda + m_0)\int_0^A e^{-\lambda\tau}\pi(\tau) d\tau\right).
\end{aligned}$$

Thus,

$$\mu_1 \int_0^A V(\tau)e^{-\lambda\tau}\pi(\tau)d\tau + (\lambda + m_0)\int_0^A e^{-\lambda\tau}\pi(\tau)d\tau = 1 - e^{-(\lambda+m_0)A}e^{-\mu_1\int_0^A V(s)ds}. \tag{2.51}$$

From equation (2.51), the characteristic equation (2.50) becomes

$1 + \frac{\tilde{\alpha}}{N^*(\lambda+m_0)}$

$$= \frac{1}{\mathcal{R}_0}\left(\frac{\tilde{\alpha}}{N^*(\lambda+m_0)}\frac{\mu_1}{c_1s_1} + 1\right)\int_0^A c_1s_1V(\tau)e^{-\lambda\tau}\pi(\tau)d\tau + \frac{1}{\mathcal{R}_0}\frac{\tilde{\alpha}}{N^*(\lambda+m_0)}e^{-\lambda A}\pi(A),$$

so that

$$\mathcal{L}(\lambda) = \frac{\lambda + m_0 + \frac{\tilde{\alpha}}{N^*}}{\lambda + m_0 + \frac{\tilde{\alpha}}{N^*}\frac{\mu_1}{c_1s_1}}, \tag{2.52}$$

where

$$\mathcal{L}(\lambda) = \frac{1}{\mathcal{R}_0}\int_0^A c_1s_1V(\tau)e^{-\lambda\tau}\pi(\tau)d\tau + \frac{\frac{1}{\mathcal{R}_0}\frac{\tilde{\alpha}}{N^*(\lambda+m_0)}}{\frac{\tilde{\alpha}}{N^*(\lambda+m_0)}\frac{\mu_1}{c_1s_1} + 1}e^{-\lambda A}\pi(A).$$

When $\lambda = 0$ in equation (2.51), we obtain

$$\mu_1\int_0^A V(\tau)\pi(\tau)d\tau = 1 - \pi(A) - m_0\int_0^A \pi(\tau)d\tau,$$

so that $\mu_1\int_0^A V(\tau)\pi(\tau)d\tau < 1$. Since $\mathcal{R}_0 > 1$, it follows that $\frac{c_1s_1}{\mu_1} > 1$. Now, let $\lambda = a + ib$ be an arbitrary complex solution (if it exists) of the characteristic equation (2.52). If $\Re(\lambda) > 0$, then

$$\left|\frac{\lambda + m_0 + \frac{\tilde{\alpha}}{N^*}}{\lambda + m_0 + \frac{\tilde{\alpha}}{N^*}\frac{\mu_1}{c_1s_1}}\right| > 1 \quad \textit{and} \quad |\mathcal{L}(\lambda)| < 1$$

if, and only if, $A$ is sufficiently large. Thus, the case $\Re(\lambda) > 0$ gives a contradiction. If $\Re(\lambda) = 0$ ($a = 0$), we rewrite the characteristic equation (2.52) as

$$ib+m_0+\frac{\tilde{\alpha}}{N^*} = \frac{1}{\mathcal{R}_0}\left(\frac{\tilde{\alpha}}{N^*}\frac{\mu_1}{c_1 s_1}+m_0+ib\right)\int_0^A c_1 s_1 V(\tau)e^{-ib\tau}\pi(\tau)d\tau+\frac{1}{\mathcal{R}_0}\frac{\tilde{\alpha}}{N^*}e^{-ibA}\pi(A). \tag{2.53}$$

Equating imaginary parts of equation (2.53), we obtain

$$\begin{aligned} b\left(\mathcal{R}_0 - \int_0^A c_1 s_1 V(\tau)\cos(b\tau)\pi(\tau)d\tau\right) &= -\left(\frac{\tilde{\alpha}}{N^*}\frac{\mu_1}{c_1 s_1}+m_0\right)\int_0^A c_1 s_1 V(\tau)\sin(b\tau)\pi(\tau)d\tau \\ &\quad -\frac{\tilde{\alpha}}{N^*}\sin(bA)\pi(A). \end{aligned} \tag{2.54}$$

Now, using the expression for the basic reproduction number (2.33),

$$\begin{aligned} \mathcal{R}_0 - \int_0^A c_1 s_1 V(\tau)\cos(b\tau)\pi(\tau)d\tau &= 2\int_0^A c_1 s_1 V(\tau)\sin^2\left(\frac{b\tau}{2}\right)\pi(\tau)d\tau) \\ &> 2c_1 s_1 \varepsilon' \pi(\alpha_2)\int_{\alpha_1}^{\alpha_2}\sin^2\left(\frac{b\tau}{2}\right)d\tau \\ &= \tilde{K}_1\pi(\alpha_2) > 0, \quad for \quad (\alpha_1,\alpha_2)\subset[0,A], \end{aligned}$$

where $\varepsilon'$ is a lower bound on $V(\tau)$ for $\tau \in [0, A]$. Now, choose $B^*$ such that

$$B^*\tilde{K}_1\pi(\alpha_2) > \left(\frac{\tilde{\alpha}}{N^*}\frac{\mu_1}{c_1 s_1}+m_0\right)\int_0^A c_1 s_1 V(\tau)\pi(\tau)d\tau + \frac{\tilde{\alpha}}{N^*}\pi(A),$$

then for $b > B^*$, equation (2.54) is untenable. For $b < B^*$, the right-hand side of equation (2.52) gives

$$\left|\frac{m_0+\frac{\tilde{\alpha}}{N^*}+ib}{\frac{\tilde{\alpha}}{N^*}\frac{\mu_1}{c_1 s_1}+m_0+ib}\right| = \frac{\sqrt{(m_0+\frac{\tilde{\alpha}}{N^*})^2+b^2}}{\sqrt{(\frac{\tilde{\alpha}}{N^*}\frac{\mu_1}{c_1 s_1}+m_0)^2+b^2}} > \frac{\sqrt{(m_0+\frac{\tilde{\alpha}}{N^*})^2+B^{*2}}}{\sqrt{(\frac{\tilde{\alpha}}{N^*}\frac{\mu_1}{c_1 s_1}+m_0)^2+B^{*2}}} > 1,$$

and the left-hand side of equation (2.52) gives

$$|\mathcal{L}(\lambda)| \leq 1 + \frac{1}{\mathcal{R}_0}\frac{\tilde{\alpha}}{N^*}\left(\frac{\pi(A)}{|\frac{\tilde{\alpha}}{N^*}\frac{\mu_1}{c_1 s_1}+m_0+ib|}\right)$$

$$\leq \quad 1 + \frac{1}{\mathcal{R}_0} \frac{\tilde{\alpha}}{N^*} \left( \frac{e^{-m_0 A}}{\frac{\tilde{\alpha}}{N^*} \frac{\mu_1}{c_1 s_1} + m_0} \right) < \frac{\sqrt{(m_0 + \frac{\tilde{\alpha}}{N^*})^2 + {B^*}^2}}{\sqrt{(\frac{\tilde{\alpha}}{N^*} \frac{\mu_1}{c_1 s_1} + m_0)^2 + {B^*}^2}},$$

if $A$ is sufficiently large. Also, the case $\Re(\lambda) = 0$ gives a contradiction. Thus, all solutions of the characteristic equation (2.52) have negative real parts. Hence, the endemic equilibrium, $(S^*, i^*(\tau))$, is locally asymptotically stable when $\mathcal{R}_0 > 1$. □

**Remark:** We can also establish the local asymptotic stability of the endemic equilibrium when the maximal age-of-infection, $A$, is sufficiently small. To do this, we consider scenarios where solutions to the characteristic equation (2.50) are either real or complex.

For non-negative real solutions to equation (2.50), and using the expression for the basic reproduction number, $\mathcal{R}_0$, given in equation (2.33), we arrive at a contradiction. Next, we assume complex solutions to equation (2.50) and equate real and imaginary parts. If the real parts of our complex solutions are assumed to be positive, and if the maximal age-of-infection is sufficiently small with $\mathcal{R}_0 > 1$, we also arrive at a contradiction. We conclude that the solutions to our characteristic equation (2.50) are real and negative or complex roots with negative real parts whenever $\mathcal{R}_0 > 1$ and $A$ is sufficiently small.

## 2.4 Optimal Control Formulation and Analysis

Optimal control theory can be used to design intervention strategies for the control of infectious diseases and has been applied in decoupled immunological and epidemiological models of HIV [46, 70, 71, 72]. In this section, we apply optimal control theory in a coupled within-host and between-host model of HIV with age (age-since-infection) structure.

The theory of age-structured models abound in the literature [6, 110]. In 1974, Gurtin and MacCamy [54] introduced the first model of nonlinear continuous age-dependent population dynamics.

Optimal control of first-order PDEs coming from age-structured models requires more analysis for justification than optimal control of parabolic PDE or differential equations. There has been only a small amount of work on specific applications of optimal control to age-structure equations. Brokate [15] developed maximum principles for an optimal harvesting problem and a problem of optimal birth control. Barbu and Iannelli [13, 12] considered and optimal control problem for a Gurtin-MacCamy [110] type system, describing the evolution of an age-structured population. Anita [6, 5] investigated an optimal control problem for a nonlinear age-dependent population dynamics. Murphy and Smith [88] studied the optimal harvesting of an age-structured population, where the McKendrick model of population dynamics was used. These authors considered age-structured population models for a single population. Fister and Lenhart [44], on the other hand, considered optimal harvesting control for a competitive age-structured model, comprising two first-order partial differential equations. Also, Fister and Lenhart [45] investigated an optimal harvesting control in a predator-prey model in which the prey population is represented by a first-order partial differential equation with age-structure and the predator is represented by an ordinary differential equation in time. A key tool for the existence and uniqueness of optimal solution is Ekeland's variational principle [38].

In our coupled model, we incorporate two controls which aim at curtailing the transmission rate and virion production. Thus, our within-host model with control is:

$$\frac{dx}{d\tau} = r - \beta_1(1-u_1(\tau))V(\tau)x(\tau) - \mu x(\tau) \tag{2.55}$$

$$\frac{dy}{d\tau} = \beta_1(1-u_1(\tau))V(\tau)x(\tau) - d_1 y(\tau) \tag{2.56}$$

$$\frac{dV}{d\tau} = \nu_1(1-u_2(\tau))d_1 y(\tau) - (\delta_1 + s_1)V(\tau) - \hat{\beta}_1(1-u_1(\tau))V(\tau)x(\tau), \tag{2.57}$$

where the parameters are as defined in Table 2.1. The control functions $u_1$ and

$u_2$ are bounded Lebesgue measurable functions and represent the transmission and viral production suppressing drugs, respectively. The transmission suppressing drug works as an inhibitor of fusion of the free virus onto CD4$^+$ T lymphocytes. On the other hand, the virion production suppressing drug works as reverse transcriptase and protease inhibitors. Thus, the coefficient, $1 - u_1(t)$, represents the drug effect that reduces transmission of healthy cells to infected cells as a result of interaction with the virus, while the coefficient $1 - u_2(t)$ gives the effect of another drug that reduces the production of virions. The upper bounds on the controls give the efficacy of the transmission and virion production suppressing drugs. If $u_1 = 0$ and $u_2 = 0$ there is no inhibition of transmission and virion production.

### 2.4.1 Sensitivity and Adjoint Systems

Below, we formulate an objective functional for our coupled system, with the goal of minimizing free virus and infected individuals:

$$\begin{aligned} J(u_1, u_2) &= \int_0^T \int_0^A A_1 i(\tau, t) V(\tau) d\tau dt \qquad (2.58)\\ &+ \int_0^T \int_0^A i(\tau, t)(A_2 u_1(\tau) + A_3 u_2(\tau)) d\tau dt + \int_0^A (B_1 u_1(\tau)^2 + B_2 u_2(\tau)^2) d\tau, \end{aligned}$$

where $A_1$, $A_2$, $A_3$, $B_1$ and $B_2$ are positive constants that balance the relative importance for the terms in $J$. In our objective functional, the first term with $A_1$ represents the total of the infected individuals over time and the other two terms represents costs of implementing the controls. The optimal control formulation with equations (2.55) – (2.57), (2.4) and (2.5) – (2.8) is: Find $(u_1^*, u_2^*) \in \mathcal{U}$ such that

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

where the control set $\mathcal{U}$ is

$$\mathcal{U} = \{(u_1, u_2) \in (L^\infty(0, A))^2 | u_1 : (0, A) \to [0, \tilde{u}_1],\ u_2 : (0, A) \to [0, \tilde{u}_2]\}.$$

We formulate a Lipschitz property for state variables in our model in terms of the control functions $u_1$ and $u_2$. This property will be used to prove the existence of sensitivities and optimal control, and the uniqueness of optimal control.

**Theorem 2.7.** *The map* $(u_1, u_2) \to (x, y, V, S, i) = (x, y, V, S, i)(u_1, u_2)$ *is Lipschitz in the following ways:*

$$
\begin{aligned}
(i) \qquad & \int_0^A (|x-\bar{x}| + |y-\bar{y}| + |V-\bar{V}|)d\tau + \int_0^T |S-\bar{S}|dt + \int_Q |i-\bar{i}|d\tau dt \\
\leq \;& C_{A,T}\int_0^A (|u_1-\bar{u}_1| + |u_2-\bar{u}_2|)d\tau \\
(ii) \qquad & ||x-\bar{x}||_{L^\infty(\Omega)} + ||y-\bar{y}||_{L^\infty(\Omega)} + ||V-\bar{V}||_{L^\infty(\Omega)} + ||S-\bar{S}||_{L^\infty(0,T)} \\
& + ||i-\bar{i}||_{L^\infty(0,T;L^1(0,A))} \leq \hat{C}_{A,T}(||u_1-\bar{u}_1||_{L^\infty(\Omega)} + ||u_2-\bar{u}_2||_{L^\infty(\Omega)}),
\end{aligned}
$$

*where* $\Omega = (0, A)$ *and* $Q = \Omega \times (0, T)$.

*Proof.* (i) First, considering equation (2.55), we have

$$
\begin{aligned}
\frac{d}{d\tau}(x-\bar{x}) &= -\beta_1((1-u_1)Vx - (1-\bar{u}_1)\bar{V}\bar{x}) - \mu(x-\bar{x}) \qquad (2.59)\\
&= -\beta_1(\bar{u}_1-u_1)Vx - \beta_1(1-\bar{u}_1)(Vx-\bar{V}\bar{x}) - \mu(x-\bar{x}) \\
&= -\beta_1(\bar{u}_1-u_1)Vx - \beta_1(1-\bar{u}_1)(x(V-\bar{V}) + \bar{V}(x-\bar{x})) \\
&\quad -\mu(x-\bar{x}). \qquad (2.60)
\end{aligned}
$$

Integrating from 0 to $\tau$, noting that $x$ and $\bar{x}$ agree at $\tau = 0$, we have

$$
\begin{aligned}
x(\tau) - \bar{x}(\tau) &= -\int_0^\tau (\beta_1(\bar{u}_1(s)-u_1(s))V(s)x(s) + \mu(x(s)-\bar{x}(s)))ds \\
&\quad -\int_0^\tau \beta_1(1-\bar{u}_1(s))(x(s)(V(s)-\bar{V}(s)) + V(s)(x(s)-\bar{x}(s)))ds,
\end{aligned}
$$

so that

$$\begin{aligned}|x-\bar{x}|(\tau) &\leq \int_0^\tau (\beta_1|\bar{u}_1(s)-u_1(s)||V(s)||x(s)|+\mu|x(s)-\bar{x}(s)|)ds \\ &\quad +\int_0^\tau \beta_1|1-\bar{u}_1(s)|(|x(s)||V(s)-\bar{V}(s)|+|V(s)||x(s)-\bar{x}(s)|)ds \\ &\leq \int_0^\tau (C_1|u_1-\bar{u}_1|+C_2(|x-\bar{x}|+|V-\bar{V}|))ds,\end{aligned}$$

since $x$ and $V$ are bounded (See Theorem 2.1). Thus,

$$|x-\bar{x}|(\tau) \leq C_1\int_0^A |u_1-\bar{u}_1|ds + C_2\int_0^\tau (|x-\bar{x}|+|y-\bar{y}|+|V-\bar{V}|)ds. \quad (2.61)$$

Secondly, we consider equation (2.56), and write

$$\frac{d}{d\tau}(y-\bar{y}) = \beta_1((1-u_1)Vx-(1-\bar{u}_1)\bar{V}\bar{x})-d_1(y-\bar{y}).$$

It follows from equations (2.59) and (2.61) that

$$|y-\bar{y}|(\tau) \leq C_1\int_0^A |u_1-\bar{u}_1|ds + C_2\int_0^\tau (|x-\bar{x}|+|y-\bar{y}|+|V-\bar{V}|)ds. \quad (2.62)$$

Thirdly, we consider equation (2.57) and write

$$\begin{aligned}\frac{d}{d\tau}(V-\bar{V}) &= d_1\nu_1((1-u_2)y-(1-\bar{u}_2)\bar{y})-(\delta_1+s_1)(V-\bar{V}) \\ &\quad -\hat{\beta}_1((1-u_1)Vx-(1-\bar{u}_1)\bar{V}\bar{x}) \\ &= d_1\nu_1(y-\bar{y})+d_1\nu_1 y(\bar{u}_2-u_2)+d_1\nu_1\bar{u}_2(\bar{y}-y)-(\delta_1+s_1)(V-\bar{V}) \\ &\quad -\hat{\beta}_1 Vx(\bar{u}_1-u_1)-\hat{\beta}(1-\bar{u}_1)(x(V-\bar{V})+\bar{V}(x-\bar{x})).\end{aligned}$$

Integrating from 0 to $\tau$, noting that $V$ and $\bar{V}$ agree at $\tau=0$, we have

$$
\begin{aligned}
V(\tau)-\bar{V}(\tau) &= \int_0^\tau d_1\nu_1[(y(s)-\bar{y}(s))+y(s)(\bar{u}_2(s)-u_2(s))+\bar{u}_2(s)(\bar{y}(s)-y(s))]ds \\
&\quad -\int_0^\tau [(\delta_1+s_1)(V(s)-\bar{V}(s))+\hat{\beta}_1 V(s)x(s)(\bar{u}_1(s)-u_1(s))]ds \\
&\quad -\int_0^\tau [\hat{\beta}(1-\bar{u}_1(s))(x(s)(V(s)-\bar{V}(s))+\bar{V}(s)(x(s)-\bar{x}(s)))]ds.
\end{aligned}
$$

Therefore,

$$
\begin{aligned}
|V-\bar{V}|(\tau) &\leq \int_0^\tau (C_4|y-\bar{y}|+C_5|u_2-\bar{u}_2|+C_6|u_1-\bar{u}_1|+C_7(|x-\bar{x}|+|V-\bar{V}|))ds \\
&\leq C_8\int_0^A (|u_1-\bar{u}_1|+|u_2-\bar{u}_2|)ds+C_9\int_0^\tau (|x-\bar{x}|+|y-\bar{y}|+|V-\bar{V}|)ds.
\end{aligned}
\tag{2.63}
$$

Since $y$ is bounded. Combining equations (2.61), (2.62) and (2.63), we have

$$
\begin{aligned}
(|x-\bar{x}|+|y-\bar{y}|+|V-\bar{V}|)(\tau) &\leq C_{10}\int_0^A (|u_1-\bar{u}_1|+|u_2-\bar{u}_2|)ds \\
&\quad +C_{11}\int_0^\tau (|x-\bar{x}|+|y-\bar{y}|+|V-\bar{V}|)(s)ds.
\end{aligned}
$$

By Gronwall's inequality in integral form, we have

$$
\begin{aligned}
(|x-\bar{x}|+|y-\bar{y}|+|V-\bar{V}|)(\tau) &\leq C_{10}(1+C_{11}\tau e^{C_{11}\tau})\int_0^A (|u_1-\bar{u}_1|+|u_2-\bar{u}_2|)ds \\
&\leq C_{10}(1+C_{11}Ae^{C_{11}A})\int_0^A (|u_1-\bar{u}_1|+|u_2-\bar{u}_2|)ds,
\end{aligned}
$$

so that integrating both sides of the inequality above from $\tau=0$ to $\tau=A$, we obtain

$$
\int_0^A (|x-\bar{x}|+|y-\bar{y}|+|V-\bar{V}|)d\tau \leq C_{10}A(1+C_{11}Ae^{C_{11}A})\int_0^A (|u_1-\bar{u}_1|+|u_2-\bar{u}_2|)ds.
\tag{2.64}
$$

Now, using an equivalent expression for $S$, and mimicking equation (2.22), we obtain

$$\begin{aligned}
|S(t)-\bar{S}(t)| &= \left|c_1 s_1 \int_0^t e^{-m_0(t-\xi)} \int_0^A \left(\frac{S(\xi)V(\tau)i(\tau,\xi)}{N(\xi)} - \frac{\bar{S}(\xi)\bar{V}(\tau)\bar{i}(\tau,\xi)}{\bar{N}(\xi)}\right) d\tau d\xi\right| \\
&\leq \int_0^t \int_0^A c_1 s_1 \left|\frac{S(\xi)V(\tau)i(\tau,\xi)}{N(\xi)} - \frac{\bar{S}(\xi)\bar{V}(\tau)\bar{i}(\tau,\xi)}{\bar{N}(\xi)}\right| d\tau d\xi.
\end{aligned}$$

Similar to equation (2.22), we have

$$\begin{aligned}
&\tfrac{S(\xi)V(\tau)i(\tau,\xi)}{N(\xi)} - \tfrac{\bar{S}(\xi)\bar{V}(\tau)\bar{i}(\tau,\xi)}{\bar{N}(\xi)} \\
&= \frac{V(\tau)i(\tau,\xi)}{N(\xi)}(S(\xi)-\bar{S}(\xi)) + \frac{\bar{S}(\xi)\bar{V}(\tau)}{\bar{N}(\xi)}(i(\tau,\xi)-\bar{i}(\tau,\xi)) \\
&\quad + \frac{i(\tau,\xi)\bar{S}(\xi)}{N(\xi)}(V(\tau)-\bar{V}(\tau)) + \frac{i(\tau,\xi)\bar{S}(\xi)\bar{V}(\tau)}{\bar{N}(\xi)N(\xi)}(\bar{S}(\xi)-S(\xi)) \\
&\quad + \frac{i(\tau,\xi)\bar{S}(\xi)\bar{V}(\tau)}{\bar{N}(\xi)N(\xi)} \int_\Omega (\bar{i}(\tau,t)-i(\tau,t))d\tau. \qquad (2.65)
\end{aligned}$$

Now,

$$\begin{aligned}
&|S-\bar{S}|(t) \\
\leq\ & c_1 s_1 \int_0^t \int_0^A \left|\frac{V(\tau)i(\tau,\xi)}{N(\xi)}(S(\xi)-\bar{S}(\xi)) + \frac{\bar{S}(\xi)\bar{V}(\tau)}{\bar{N}(\xi)}(i(\tau,\xi)-\bar{i}(\tau,\xi))\right| d\tau d\xi \\
& + c_1 s_1 \int_0^t \int_0^A \left|\frac{i(\tau,\xi)\bar{S}(\xi)}{N(\xi)}(V(\tau)-\bar{V}(\tau)) + \frac{i(\tau,\xi)\bar{S}(\xi)\bar{V}(\tau)}{N(\xi)\bar{N}(\xi)}(\bar{S}(\xi)-S(\xi))\right| d\tau d\xi \\
& + c_1 s_1 \int_0^t \int_0^A \left|\frac{i(\tau,\xi)\bar{S}(\xi)\bar{V}(\tau)}{N(\xi)\bar{N}(\xi)} \int_0^A (\bar{i}(r,\xi)-i(r,\xi))dr\right| d\tau d\xi \\
\leq\ & c_1 s_1 \int_0^t \int_0^A \left(\left|\frac{i(\tau,\xi)}{N(\xi)}\right| |V(\tau)| \left|S(\xi)-\bar{S}(\xi)\right| + \left|\frac{\bar{S}(\xi)(\tau)}{\bar{N}(\xi)}\right| \left|\bar{V}(\tau)\right| \left|i(\tau,\xi)-\bar{i}(\tau,\xi)\right|\right) d\tau d\xi \\
& + c_1 s_1 \int_0^t \int_0^A \left|\frac{i(\tau,\xi)}{N(\xi)}\right| \left(\left|\bar{S}(\xi)\right| \left|V(\tau)-\bar{V}(\tau)\right| + \left|\frac{\bar{S}(\xi)}{\bar{N}(\xi)}\right| \left|\bar{V}(\tau)\right| \left|(S(\xi)-\bar{S}(\xi))\right|\right) d\tau d\xi \\
& + c_1 s_1 \int_0^t \int_0^A \left|\frac{i(\tau,\xi)}{N(\xi)}\right| \left|\frac{\bar{S}(\xi)}{\bar{N}(\xi)}\right| \left|\bar{V}_1(\tau)\right| \int_0^A |i(r,\xi)-\bar{i}(r,\xi)|\, dr d\tau d\xi \\
\leq\ & 2C_{12} \int_0^t |S-\bar{S}| d\xi + c_1 s_1 T \sup_{0\leq\xi\leq T} \left(|\bar{S}(\xi)| \int_0^A \left|\frac{i(\tau,\xi)}{N(\xi)}\right| |V(\tau)-\bar{V}(\tau)| d\tau\right) \\
& + 2C_{12} \int_0^t \int_0^A |i-\bar{i}| d\tau d\xi
\end{aligned}$$

$$
\leq \quad 2C_{12}\int_0^t |S-\bar{S}|d\xi + 2c_1 s_1 MT\int_0^A \left|\left|\frac{i}{N}\right|\right|_{L^\infty(0,T;L^1(0,A))} |V-\bar{V}|(\tau)d\tau
$$

$$
+2C_{12}\int_0^t\int_0^A |i-\bar{i}|d\tau d\xi.
$$

Thus,

$|S-\bar{S}|(t)$

$$
\leq 2C_{12}\int_0^t \left(|S-\bar{S}|(\xi)ds + \int_0^A |i-\bar{i}|(\tau,\xi)d\tau\right) d\xi + C_{13}T\int_0^A |V(\tau)-\bar{V}(\tau)|d\tau. \tag{2.66}
$$

Finally, we consider the equation for $i$ given in (2.13). Now, for $t<\tau<A$,

$$
\begin{aligned}
\int_t^A |i-\bar{i}|d\tau &= \int_t^A \left|i^0(\tau-t)e^{-\int_0^t m(V(\tau-t+s))ds} - i^0(\tau-t)e^{-\int_0^t m(\bar{V}(\tau-t+s))ds}\right| d\tau \\
&= \int_t^A \left|i^0(\tau-t)\right| \left|e^{-\int_0^t m(V(\tau-t+s))ds} - e^{-\int_0^t m(\bar{V}(\tau-t+s))ds}\right| d\tau \\
&\leq \int_t^A \left|i^0(\tau-t)\right| \left|\int_0^t m(V(\tau-t+s))ds - \int_0^t m(\bar{V}(\tau-t+s))ds\right| d\tau \\
&\leq K_1\int_t^A \left|i^0(\tau-t)\right| \int_0^t \left|V(\tau-t+s)-\bar{V}(\tau-t+s)\right| ds d\tau \\
&\leq K_1\int_0^A \left|i^0(\hat{\tau}-t)\right| \int_0^A \left|V(\hat{r})-\bar{V}(\hat{r})\right| d\hat{r}d\hat{\tau} \\
&\leq K_1 M\int_0^A |V-\bar{V}|d\hat{\tau},
\end{aligned} \tag{2.67}
$$

where $\hat{r}=\tau-t+s$, $\hat{\tau}=\tau$, $\hat{s}=s$ and $K_1$ is a Lipschitz constant for the function $m$. Also, we have used the fact that

$$
\left|e^{-\int_0^t m(V(\tau-t+s))ds} - e^{-\int_0^t m(\bar{V}(\tau-t+s))ds}\right| \leq \int_0^t |m(V(\tau-t+s)) - m(\bar{V}(\tau-t+s))|ds.
$$

Lastly, for $\tau<t<T$, we have

$\int_0^t |i_1 - \bar{i}_1| d\tau dt$

$$
\begin{aligned}
&= \int_0^t |\frac{S(t-\tau)}{N(t-\tau)} e^{-\int_0^\tau m(V(s))ds} \int_0^A c_1 s_1 V(r) i_1(r, t-\tau) dr \\
&\quad - \frac{\bar{S}(t-\tau)}{\bar{N}(t-\tau)} e^{-\int_0^\tau m(\bar{V}(s))ds} \int_0^A c_1 s_1 \bar{V}(r) \bar{i}_1(r, t-\tau) dr | d\tau \\
&= \int_0^t c_1 s_1 \left| \frac{S(t-\tau)}{N(t-\tau)} \pi(V)(\tau) K(i_1, V)(t-\tau) - \frac{\bar{S}(t-\tau)}{\bar{N}(t-\tau)} \pi(\bar{V})(\tau) K(\bar{i}_1, \bar{V})(t-\tau) \right| d\tau,
\end{aligned}
$$

where $\pi(\tau) = e^{-\int_0^\tau m(V(s))ds}$ and $K(t-\tau) = \int_0^A V(r) i(r, t-\tau) dr$. Similar to equation (2.65), we have

$\frac{S(t-\tau)}{N(t-\tau)} \pi(\tau) K(t-\tau) - \frac{\bar{S}(t-\tau)}{\bar{N}(t-\tau)} \bar{\pi}(\tau) \bar{K}(t-\tau)$

$$
\begin{aligned}
&= \frac{\pi(\tau) K(t-\tau)}{N(t-\tau)} (S(t-\tau) - \bar{S}(t-\tau)) + \frac{\bar{S}(t-\tau) \bar{\pi}(\tau)}{\bar{N}(t-\tau)} (K(t-\tau) - \bar{K}(t-\tau)) \\
&\quad + \bar{S}(t-\tau) \frac{K(t-\tau)}{N(t-\tau)} (\pi(\tau) - \bar{\pi}(\tau)) \\
&\quad + \frac{\bar{S}(t-\tau)}{\bar{N}(t-\tau)} \frac{K(t-\tau)}{N(t-\tau)} \bar{\pi}(\tau) [\bar{S}(t-\tau) - S(t-\tau) + \int_0^A (\bar{i}(h, t-\tau) - i(h, t-\tau)) dh].
\end{aligned}
$$

Using the expressions for $\pi(\tau)$ and $K(t-\tau)$, we have

$\frac{S(t-\tau)}{N(t-\tau)} \pi(\tau) K(t-\tau) - \frac{\bar{S}(t-\tau)}{\bar{N}(t-\tau)} \bar{\pi}(\tau) \bar{K}(t-\tau)$

$$
\begin{aligned}
&= \frac{1}{N(t-\tau)} e^{-\int_0^\tau m(V(s))ds} [S(t-\tau) - \bar{S}(t-\tau)] \int_0^A V(r) i(r, t-\tau) dr \\
&\quad + \frac{\bar{S}(t-\tau)}{\bar{N}(t-\tau)} e^{-\int_0^\tau m(\bar{V}(s))ds} \int_0^A (V(r) i(r, t-\tau) - \bar{V}(r) \bar{i}(r, t-\tau) dr \\
&\quad + \bar{S}(t-\tau) \frac{1}{N(t-\tau)} (e^{-\int_0^\tau m(V(s))ds} - e^{-\int_0^\tau m(\bar{V}(s))ds}) \int_0^A V(r) i(r, t-\tau)) dr \\
&\quad + \frac{\bar{S}(t-\tau)}{\bar{N}(t-\tau)} \frac{1}{N(t-\tau)} (S(t-\tau) - \bar{S}(t-\tau)) e^{-\int_0^\tau m(\bar{V}(s))ds} \int_0^A V(r) i(r, t-\tau) dr \\
&\quad + \frac{\bar{S}(t-\tau)}{\bar{N}(t-\tau)} \frac{e^{-\int_0^\tau m(\bar{V}(s))ds}}{N(t-\tau)} \int_0^A V(r) i(r, t-\tau) dr \int_0^A (\bar{i}(h, t-\tau) - i(h, t-\tau)) dh
\end{aligned}
$$

$$
\begin{aligned}
&\leq \hat{C}|S(t-\tau)-\bar{S}(t-\tau)|\int_0^A \frac{i(r,t-\tau)}{N(t-\tau)}dr \\
&\quad +\int_0^A i(r,t-\tau)|V(r)-\bar{V}(r)|dr+\int_0^A \bar{V}(r)|i(r,t-\tau)-\bar{i}(r,t-\tau)|dr \\
&\quad +\hat{C}\bar{S}(t-\tau)|e^{-\int_0^\tau m(V(s))ds}-e^{-\int_0^\tau m(\bar{V}(s))ds}|\int_0^A \frac{i(r,t-\tau)}{N(t-\tau)}dr \\
&\quad +\hat{C}|S(t-\tau)-\bar{S}(t-\tau)|\int_0^A \frac{i(r,t-\tau)}{N(t-\tau)}dr \\
&\quad +\hat{C}\int_0^A \frac{i(r,t-\tau)}{N(t-\tau)}dr\int_0^A |\bar{i}(h,t-\tau)-i(h,t-\tau)|dh \\
&\leq 2\hat{C}|S(t-\tau)-\bar{S}(t-\tau)|+\int_0^A i(r,t-\tau)|V(r)-\bar{V}(r)|dr \\
&\quad +2\hat{C}\int_0^A |i(r,t-\tau)-\bar{i}(r,t-\tau)|dr+\hat{C}\bar{S}(t-\tau)|e^{-\int_0^\tau m(V(s))ds}-e^{-\int_0^\tau m(\bar{V}(s))ds}|,
\end{aligned}
$$

since $0 < V(\tau) \leq \hat{C}$ for all $\tau > 0$, by Theorem 2.1 and $\int_0^A i(\tau,t)d\tau \leq N(t)$ a.e. $t$. Therefore,

$\int_0^t |i-\bar{i}|d\tau$

$$
\begin{aligned}
&\leq 2C_{12}\int_0^t |S(t-\tau)-\bar{S}(t-\tau)|d\tau+\int_0^t\int_0^A c_1s_1|i(r,t-\tau)||V(r)-\bar{V}(r)|drd\tau \\
&\quad +2C_{12}\int_0^t\int_0^A |i(r,t-\tau)-\bar{i}(r,t-\tau)|drd\tau \\
&\quad +C_{12}K_1\int_0^t |\bar{S}(t-\tau)|\int_0^A |V(r)-\bar{V}(r)|drd\tau \qquad (2.68) \\
&\leq 2C_{12}\int_0^t |S(\xi)-\bar{S}(\xi)|d\xi+c_1s_1T||i||_{L^\infty(0,T;L^1(0,A))}\int_0^A |V(\hat{r})-\bar{V}(\hat{r})|d\hat{r} \\
&\quad +2C_{12}\int_0^t\int_0^A |i(\hat{r},\xi)-\bar{i}(\hat{r},\xi)|d\hat{r}+C_{12}K_1T\sup_{0\leq\xi\leq T}|S(\xi)|\int_0^A |V(\hat{r})-\bar{V}(\hat{r})|d\hat{r},
\end{aligned}
$$

where $\xi = t-\tau$ and $\hat{r} = r$. Therefore,

$$
\int_0^t |i-\bar{i}|(\tau,t)d\tau \leq 2C_{12}\int_0^t \left(|S-\bar{S}|(\xi)+\int_0^A |i-\bar{i}|(\hat{r},\xi)d\hat{r}\right)d\xi+C_{14}T\int_0^A |V-\bar{V}|(\hat{r})d\hat{r}. \qquad (2.69)
$$

Combining inequalities (2.67) and (2.69), we have

$$\begin{aligned}\int_0^A |i-\bar{i}|(\tau,t)d\tau &= \int_0^t |i-\bar{i}|(\tau,t)d\tau + \int_t^A |i-\bar{i}|(\tau,t)d\tau \\ &\leq (K_1M + C_{14}T)\int_0^A |V-\bar{V}|(\hat{r})d\hat{r} \\ &\quad +2C_{12}\int_0^t \left(|S-\bar{S}|(\xi) + \int_0^A |i-\bar{i}|(\hat{r},\xi)d\hat{r}\right)d\xi. \quad (2.70)\end{aligned}$$

Next, we combine inequalities (2.66) and (2.70). This gives

$$\begin{aligned}|S-\bar{S}|(t) + \int_0^A |i-\bar{i}|(\tau,t)d\tau &\leq (K_1M + (C_{13}+C_{14})T)\int_0^A |V-\bar{V}|(\hat{r})d\hat{r} \\ &\quad +4C_{12}\int_0^t \left(|S-\bar{S}|(\xi) + \int_0^A |i-\bar{i}|(\hat{r},\xi)d\hat{r}\right)d\xi \\ &\leq C(A,T)\int_0^A \left(|u_1-\bar{u}_1| + |u_2-\bar{u}_2|\right)(\xi)d\xi \\ &\quad +4C_{12}\int_0^t \left(|S-\bar{S}|(\xi) + \int_0^A |i-\bar{i}|(\hat{r},\xi)d\hat{r}\right)d\xi,\end{aligned}$$

where $C(A,T) = C_{10}(1 + C_{11}Ae^{C_{11}A})(K_1M + (C_{13}+C_{14})T)$, by inequality (2.64). Thus, by Gronwall's inequality in integral form, we obtain
$|S-\bar{S}|(t) + \int_0^A |i-\bar{i}|(\tau,t)d\tau$

$$\begin{aligned}&\leq C(A,T)(1+4C_{12}te^{4C_{12}t})\int_0^A \left(|u_1-\bar{u}_1| + |u_2-\bar{u}_2|\right)d\tau \\ &\leq C(A,T)(1+4C_{12}Te^{4C_{12}T})\int_0^A \left(|u_1-\bar{u}_1| + |u_2-\bar{u}_2|\right)d\tau. \quad (2.71)\end{aligned}$$

Integrating both sides of inequality (2.71) from $t=0$ to $t=T$ gives

$\int_0^T |S-\bar{S}|(t)dt + \int_0^T\int_0^A |i-\bar{i}|(\tau,t)d\tau dt$

$$\leq C(A,T)(1+4C_{12}Te^{4C_{12}T})T\int_0^A \left(|u_1-\bar{u}_1| + |u_2-\bar{u}_2|\right)d\tau. \quad (2.72)$$

Finally, we combine equations (2.64) and (2.72), to have

$$\begin{aligned}
&\int_0^A (|x-\bar{x}|+|y-\bar{y}|+|V-\bar{V}|)(\tau)d\tau + \int_0^T |S-\bar{S}|(t)dt + \int_Q |i-\bar{i}|(\tau,t)d\tau dt \\
&\leq C_{A,T}\int_0^A (|u_1-\bar{u}_1|+|u_2-\bar{u}_2|)(\tau)d\tau
\end{aligned}$$

where $C(A,T) = C_{10}A(1+C_{11}Ae^{C_{11}A}) + C(A,T)(1+4C_{12}Te^{4C_{12}T})T$.

(ii) We find $L^\infty$ estimates of the state solutions by considering absolute values of $x-\bar{x}$, $y-\bar{y}$, $V-\bar{V}$ and $S-\bar{S}$, and $L^1$ estimate of $|i-\bar{i}|$. From equations (2.61), (2.62) and (2.63), we have

$$\begin{aligned}
|x-\bar{x}|(\tau) &\leq C_1\int_0^A |u_1-\bar{u}_1|ds + C_2\int_0^A (|x-\bar{x}|+|y-\bar{y}|+|V-\bar{V}|)ds \\
&\leq C_1\int_0^A |u_1-\bar{u}_1|ds + C_2C_{10}A(1+C_{11}Ae^{C_{11}A})\int_0^A (|u_1-\bar{u}_1|+|u_2-\bar{u}_2|)ds
\end{aligned}$$

Similarly,

$$\begin{aligned}
|y-\bar{y}|(\tau) &\leq C_1\int_0^A |u_1-\bar{u}_1|ds + C_3C_{10}A(1+C_{11}Ae^{C_{11}A})\int_0^A (|u_1-\bar{u}_1|+|u_2-\bar{u}_2|)ds \\
|V-\bar{V}|(\tau) &\leq (C_8+C_9C_{10}A(1+C_{11}Ae^{C_{11}A}))\int_0^A (|u_1-\bar{u}_1|+|u_2-\bar{u}_2|)ds,
\end{aligned}$$

by inequality (2.64). Taking the essential supremum over all $\tau \in [0,A]$, we have

$$\begin{aligned}
||x-\bar{x}||_{L^\infty(0,A)} &\leq A(C_1+C_2C(A))(||u_1-\bar{u}_1||_{L^\infty(0,A)} + ||u_2-\bar{u}_2||_{L^\infty(0,A)}) \\
||y-\bar{y}||_{L^\infty(0,A)} &\leq A(C_1+C_3C(A))(||u_1-\bar{u}_1||_{L^\infty(0,A)} + ||u_2-\bar{u}_2||_{L^\infty(0,A)}) \qquad (2.73) \\
||V-\bar{V}||_{L^\infty(0,A)} &\leq A(C_8+C_9C(A))(||u_1-\bar{u}_1||_{L^\infty(0,A)} + ||u_2-\bar{u}_2||_{L^\infty(0,A)}),
\end{aligned}$$

where $C(A) = C_{10}A(1+C_{11}Ae^{C_{11}A})$. Thus

$$||x-\bar{x}||_{L^\infty(0,A)}+||y-\bar{y}||_{L^\infty(0,A)}+||V-\bar{V}||_{L^\infty(0,A)}$$

$$\leq C_A(||u_1-\bar{u}_1||_{L^\infty(0,A)}+||u_2-\bar{u}_2||_{L^\infty(0,A)}), \tag{2.74}$$

where $C_A = A(2C_1 + C_8 + (C_2 + C_3 + C_9)C(A))$. Considering inequality (2.66), we have

$$\begin{aligned} |S-\bar{S}|(t) &\leq C_{12}\int_0^T \left(|S-\bar{S}|(\xi)+\int_0^A |i-\bar{i}|(\tau,\xi)d\tau\right)d\xi + C_{13}T\int_0^A |V(\tau)-\bar{V}(\tau)|d\tau \\ &\leq C_1(A,T)\int_0^A (|u_1-\bar{u}_1|+|u_2-\bar{u}_2|)d\tau, \end{aligned} \tag{2.75}$$

by inequalities (2.64) and (2.72), where

$C_1(A,T) = 2C_{12}C(A,T)T(1+4C_{12}e^{4C_{12}T})T + C_{13}C_{10}AT(1+C_{11}Ae^{C_{11}A})$. We take the essential supremum of both sides of Inequality (2.75) over all $t \in [0,T]$. This gives

$$||S-\bar{S}||_{L^\infty(0,T)} \leq AC_1(A,T)(||u_1-\bar{u}_1||_{L^\infty(0,A)}+||u_2-\bar{u}_2||_{L^\infty(0,A)}). \tag{2.76}$$

Lastly, to find $L^\infty$ estimate of $|i-\bar{i}|$, we start with the $L^1$ estimate of $|i-\bar{i}|$ over $\tau \in [0,A]$. Now, from equations (2.67) and (2.68), we have

$$\begin{aligned} &\textstyle\int_0^A |i-\bar{i}|d\tau = \int_0^t |i-\bar{i}|d\tau + \int_t^A |i-\bar{i}|d\tau \\ \leq\ & 2C_{12}\int_0^t |S(t-\tau)-\bar{S}(t-\tau)|d\tau + \int_0^t\int_0^A c_1s_1|i(r,t-\tau)||V(r)-\bar{V}(r)|drd\tau \\ &+2C_{12}\int_0^t\int_0^A |i(r,t-\tau)-\bar{i}(r,t-\tau)|drd\tau \\ &+C_{12}K_1\int_0^t |\bar{S}(t-\tau)|\int_0^A |V(s)-\bar{V}(s)|dsd\tau + K_1M\int_0^A |V(s)-\bar{V}(s)|ds \\ \leq\ & 2MT(c_1s_1+C_{12}K_1A)+K_1AM)||V-\bar{V}||_{L^\infty(0,A)} \\ &+2C_{12}\int_0^T\left(|S-\bar{S}|(\xi)+\int_0^A |i(\hat{r},\xi)-\bar{i}(\hat{r},\xi)|d\hat{r}\right)d\xi \end{aligned}$$

$$\leq C_2(A,T)(2MT(c_1 s_1 + C_{12}K_1 A) + K_1 AM)(||u_1 - \bar{u}_1||_{L^\infty(0,A)} + ||u_2 - \bar{u}_2||_{L^\infty(0,A)})$$
$$+2C_{12}C(A,T)AT(1 + 4C_{12}Te^{4C_{12}T})(||u_1 - \bar{u}_1||_{L^\infty(0,A)} + ||u_2 - \bar{u}_2||_{L^\infty(0,A)})$$
$$= C_3(A,T)(||u_1 - \bar{u}_1||_{L^\infty(0,A)} + ||u_2 - \bar{u}_2||_{L^\infty(0,A)}),$$

by inequalities (2.72) and (2.73), where $C_2(A,T) = A(C_8 + C_9 C_{10} A(1 + C_{11} A e^{C_{11} A}))$. Taking the essential supremum over all $t \in [0,T]$ , we obtain

$$\|i\|_{L^\infty(0,T;L^1(0,A))} \leq C_3(A,T)(||u_1 - \bar{u}_1||_{L^\infty(0,A)} + ||u_2 - \bar{u}_2||_{L^\infty(0,A)}). \tag{2.77}$$

Combining inequalities (2.74), (2.76) and (2.77), we obtain the desired result. □

In order to characterize the optimal control pair, we differentiate the objective functional with respect to the controls. Since the objective functional is defined in terms of the state functions, we first differentiate the control-to-state map, $(u_1, u_2) \rightarrow (x, y, V, S, i)$. The derivative of the control-to-state map is called sensitivity.

**Theorem 2.8.** *The map $(u_1, u_2) \rightarrow (x, y, V, S, i) = (x, y, V, S, i)(u_1, u_2)$ is differentiable in the following sense:*

$$\frac{(x, y, V, S, i)(u_1 + \varepsilon l_1, u_2 + \varepsilon l_2) - (x, y, V, S, i)(u_1, u_2)}{\varepsilon} \rightarrow (\psi, \varphi, \phi, \theta, \omega)$$

*in $(L^\infty(\Omega))^3 \times L^\infty(0,T) \times L^\infty(0,T;L^1(\Omega))$, as $\varepsilon \rightarrow 0$ with $(u_1 + \varepsilon l_1, u_2 + \varepsilon l_2)$, $(u_1, u_2)$ $\in \mathcal{U}$ and $l_1, l_2 \in L^\infty(\Omega)$. Furthermore, the sensitivity functions satisfy*

$$\frac{d\psi}{d\tau} = -\beta_1(1-u_1)V\psi - \beta_1(1-u_1)x\phi - \mu\psi + \beta_1 l_1 V x \tag{2.78}$$

$$\frac{d\varphi}{d\tau} = \beta_1(1-u_1)V\psi - d_1\varphi + \beta_1(1-u_1)x\phi - \beta_1 l_1 V x \tag{2.79}$$

$$\begin{aligned}\frac{d\phi}{d\tau} &= -\hat{\beta}_1(1-u_1)V\psi + \nu_1(1-u_2)d_1\varphi - (\delta_1 + s_1 + \hat{\beta}_1(1-u_1)x)\phi \\ &\quad + \hat{\beta}_1 l_1 V x - \nu_1 d_1 l_2 y \end{aligned} \tag{2.80}$$

$$\begin{aligned}\frac{d\theta}{dt} &= -m_0\theta - \frac{c_1 s_1}{N}\left(1 - \frac{S}{N}\right)\theta\int_\Omega i(\tau,t)V(\tau)d\tau - \frac{c_1 s_1 S}{N}\int_\Omega V(\tau)\omega(\tau,t)d\tau \\ &\quad - \frac{c_1 s_1 S}{N}\int_\Omega i(\tau,t)\phi(\tau)d\tau + \frac{c_1 s_1 S}{N^2}\int_\Omega\int_\Omega i(\tau,t)V(\tau)\omega(h,t)dhd\tau \end{aligned} \tag{2.81}$$

$$\frac{\partial\omega}{\partial t} + \frac{\partial\omega}{\partial\tau} = -m(V)\omega - m'(V)\phi i \quad in \quad \Omega\times(0,T), \tag{2.82}$$

*with initial and boundary conditions*

$$\psi(0)=0, \quad \varphi(0)=0, \quad \phi(0)=0, \quad \theta(0)=0, \quad \omega(\tau,0)=0, \ \forall\tau\in\Omega=(0,A) \tag{2.83}$$

*and*

$$\begin{aligned}\omega(0,t) &= \frac{c_1 s_1}{N(t)}\left(1 - \frac{S(t)}{N(t)}\right)\theta(t)\int_\Omega i(\tau,t)V(\tau)d\tau + \frac{c_1 s_1 S(t)}{N(t)}\int_\Omega V(\tau)\omega(\tau,t)d\tau \\ &+ \frac{c_1 s_1 S(t)}{N(t)}\int_\Omega i(\tau,t)\phi(\tau)d\tau - \frac{c_1 s_1 S(t)}{N(t)^2}\int_\Omega\int_\Omega i(\tau,t)V(\tau)\omega(h,t)dhd\tau \end{aligned} \tag{2.84}$$

*Proof.* Since the map $(u_1,u_2)\to(x,y,V,S,i)$ is Lipschitz in $L^\infty$, we have the existence of the Gâteaux derivatives (or sensitivities) $\psi$, $\varphi$, $\phi$, $\theta$ and $\omega$ by Barbu [12, p. 17] and Fister *et al.* [45, 44]. Now, given control functions $u_1$ and $u_2$, we consider other controls $u_1^\varepsilon = u_1 + \varepsilon l_1$ and $u_2^\varepsilon = u_2 + \varepsilon l_2$, where $l_1$ and $l_2$ are variation functions, with $\varepsilon > 0$. Let

$$(u_1,u_2)\in\mathcal{U}\to(x,y,V,S,i) = (x,y,V,S,i)(u_1,u_2)$$

and

$$(x^\varepsilon, y^\varepsilon, V^\varepsilon, S^\varepsilon, i^\varepsilon) = (x,y,V,S,i)(u_1+\varepsilon l_1, u_2+\varepsilon l_2).$$

Then the equations corresponding to controls $u_1$, $u_2$, $u_1^\varepsilon$ and $u_2^\varepsilon$ are (2.5) – (2.6) , (2.55) – (2.57), and the following:

$$\begin{aligned}
\frac{dx^\varepsilon}{d\tau} &= r - \beta_1(1-u_1^\varepsilon)V^\varepsilon x^\varepsilon - \mu x^\varepsilon \\
\frac{dy^\varepsilon}{d\tau} &= \beta_1(1-u_1^\varepsilon)V^\varepsilon x^\varepsilon - d_1 y^\varepsilon \\
\frac{dV^\varepsilon}{d\tau} &= \nu_1(1-u_2^\varepsilon)d_1 y^\varepsilon - (\delta_1+s_1)V^\varepsilon - \hat{\beta}_1(1-u_1^\varepsilon)V^\varepsilon x^\varepsilon \\
\frac{dS^\varepsilon}{dt} &= \Lambda - \frac{S^\varepsilon}{N^\varepsilon}\int_\Omega c_1 s_1 V^\varepsilon(\tau) i^\varepsilon(\tau,t)d\tau - m_0 S^\varepsilon \\
\frac{\partial i^\varepsilon(\tau,t)}{\partial t} + \frac{\partial i^\varepsilon(\tau,t)}{\partial \tau} &= -m(V^\varepsilon)i^\varepsilon(\tau,t).
\end{aligned}$$

The equations satisfied by the difference quotients $\frac{x^\varepsilon - x}{\varepsilon}$, $\frac{y^\varepsilon - y}{\varepsilon}$, $\frac{V^\varepsilon - V}{\varepsilon}$, $\frac{S^\varepsilon - S}{\varepsilon}$ and $\frac{i^\varepsilon - i}{\varepsilon}$ are:

$$\begin{aligned}
\frac{d}{d\tau}\left(\frac{x^\varepsilon - x}{\varepsilon}\right) &= -\beta_1\left(\frac{V^\varepsilon x^\varepsilon - Vx}{\varepsilon}\right) + \beta_1\left(\frac{u_1^\varepsilon V^\varepsilon x^\varepsilon - u_1 Vx}{\varepsilon}\right) - \mu\left(\frac{x^\varepsilon - x}{\varepsilon}\right) \\
\frac{d}{d\tau}\left(\frac{y^\varepsilon - y}{\varepsilon}\right) &= \beta_1\left(\frac{V^\varepsilon x^\varepsilon - Vx}{\varepsilon}\right) - \beta_1\left(\frac{u_1^\varepsilon V^\varepsilon x^\varepsilon - u_1 Vx}{\varepsilon}\right) - d_1\left(\frac{y^\varepsilon - y}{\varepsilon}\right) \\
\frac{d}{d\tau}\left(\frac{V^\varepsilon - V}{\varepsilon}\right) &= \nu_1 d_1\left(\frac{y^\varepsilon - y}{\varepsilon}\right) - \nu_1 d_1\left(\frac{u_2^\varepsilon y^\varepsilon - u_2 y}{\varepsilon}\right) - (\delta_1+s_1)\left(\frac{V^\varepsilon - V}{\varepsilon}\right) \\
&\quad -\hat{\beta}_1\left(\frac{V^\varepsilon x^\varepsilon - Vx}{\varepsilon}\right) + \hat{\beta}_1\left(\frac{u_1^\varepsilon V^\varepsilon x^\varepsilon - u_1 Vx}{\varepsilon}\right) \\
\frac{d}{dt}\left(\frac{S^\varepsilon - S}{\varepsilon}\right) &= -c_1 s_1\int_\Omega\left(\frac{S^\varepsilon(t)V^\varepsilon(\tau)i^\varepsilon(\tau,t)}{\varepsilon N^\varepsilon(t)} - \frac{S(t)V(\tau)i(\tau,t)}{\varepsilon N(t)}\right)d\tau - m_0\left(\frac{S^\varepsilon - S}{\varepsilon}\right) \\
\frac{\partial}{\partial t}\left(\frac{i^\varepsilon - i}{\varepsilon}\right) &= -\left(\frac{m(V^\varepsilon)i^\varepsilon - m(V)i}{\varepsilon}\right) - \frac{\partial}{\partial \tau}\left(\frac{i^\varepsilon - i}{\varepsilon}\right).
\end{aligned}$$

We derive expressions for some terms that appear in the equations above. First, the term $\frac{V^\varepsilon x^\varepsilon - Vx}{\varepsilon} = V^\varepsilon\left(\frac{x^\varepsilon - x}{\varepsilon}\right) + x\left(\frac{V^\varepsilon - V}{\varepsilon}\right)$. Secondly,

$$\begin{aligned}
\frac{u_1^\varepsilon V^\varepsilon x^\varepsilon - u_1 Vx}{\varepsilon} &= u_1\left(\frac{V^\varepsilon x^\varepsilon - Vx}{\varepsilon}\right) + l_1 V^\varepsilon x^\varepsilon \\
&= u_1 V^\varepsilon\left(\frac{x^\varepsilon - x}{\varepsilon}\right) + u_1 x\left(\frac{V^\varepsilon - V}{\varepsilon}\right) + l_1 V^\varepsilon x^\varepsilon.
\end{aligned}$$

Thirdly,

$$\begin{aligned}\frac{m(V^\varepsilon)i^\varepsilon - m(V)i}{\varepsilon} &= m(V^\varepsilon)\left(\frac{i^\varepsilon - i}{\varepsilon}\right) + i\left(\frac{m(V^\varepsilon) - m(V)}{\varepsilon}\right) \\ &= m(V^\varepsilon)\left(\frac{i^\varepsilon - i}{\varepsilon}\right) + i\left(\frac{m(V^\varepsilon) - m(V)}{V^\varepsilon - V}\right)\left(\frac{V^\varepsilon - V}{\varepsilon}\right).\end{aligned}$$

In Theorem 2.8, we showed that as $\varepsilon \to 0$,

$$\frac{(x,y,V,S,i)(u_1+\varepsilon l_1, u_2+\varepsilon l_2) - (x,y,V,S,i)(u_1,u_2)}{\varepsilon} \to (\psi,\varphi,\phi,\theta,\omega)$$

in $(L^\infty(\Omega))^3 \times L^\infty(0,T) \times L^\infty(0,T;L^1(\Omega))$. Thus, passing to limit in the representation of the difference quotients, and using equation (2.65), we have the sensitivity equations (2.78) – (2.82). From equations (2.4) and (2.7) – (2.8), the initial and boundary conditions satisfied by the difference quotients $\frac{x^\varepsilon - x}{\varepsilon}$, $\frac{y^\varepsilon - y}{\varepsilon}$, $\frac{V^\varepsilon - V}{\varepsilon}$, $\frac{S^\varepsilon - S}{\varepsilon}$ and $\frac{i^\varepsilon - i}{\varepsilon}$ are:

$$\left(\frac{x^\varepsilon - x}{\varepsilon}\right)(0) = 0, \quad \left(\frac{y^\varepsilon - y}{\varepsilon}\right)(0) = 0, \quad \left(\frac{V^\varepsilon - V}{\varepsilon}\right)(0) = 0, \quad \left(\frac{S^\varepsilon - S}{\varepsilon}\right)(0) = 0,$$

$$\left(\frac{i^\varepsilon - i}{\varepsilon}\right)(\tau,0) = 0, \quad \text{and}$$

$$\left(\frac{i^\varepsilon - i}{\varepsilon}\right)(0,t) = c_1 s_1 \int_\Omega \left(\frac{S^\varepsilon(t)V^\varepsilon(\tau)i^\varepsilon(\tau,t)}{\varepsilon N^\varepsilon(t)} - \frac{S(t)V(\tau)i(\tau,t)}{\varepsilon N(t)}\right) d\tau$$

As $\varepsilon \to 0$, we have the initial and boundary conditions (2.83) and (2.84). □

We divide the sensitivity equations in Theorem 2.8 into three operators, depending on the independent variables on five components. These operators will be used in deriving a characterization for the controls $u_1$ and $u_2$. The three sensitivity operators, $\mathcal{L}_1$, $\mathcal{L}_2$ and $\mathcal{L}_3$, and the corresponding sensitivity equations are:

$$\mathcal{L}_1\begin{bmatrix}\psi\\ \varphi\\ \phi\end{bmatrix} = \begin{bmatrix}\beta_1 l_1 V x\\ -\beta_1 l_1 V x\\ \hat{\beta}_1 l_1 V x - \nu_1 d_1 l_2 y\end{bmatrix}, \quad \mathcal{L}\begin{bmatrix}\theta\\ \omega\end{bmatrix} \equiv \begin{bmatrix}\mathcal{L}_2\theta\\ \mathcal{L}_3\omega\end{bmatrix} = \begin{bmatrix}0\\ 0\end{bmatrix}, \qquad (2.85)$$

where

$$
\begin{aligned}
\mathcal{L}_1 \begin{bmatrix} \psi \\ \varphi \\ \phi \end{bmatrix} &= \begin{bmatrix} L_1\psi \\ L_1\varphi \\ L_1\phi \end{bmatrix} + M \begin{bmatrix} \psi \\ \varphi \\ \phi \end{bmatrix}, \quad \begin{bmatrix} L_1\psi \\ L_1\varphi \\ L_1\phi \end{bmatrix} = \begin{bmatrix} \frac{d\psi}{d\tau} \\ \frac{d\varphi}{d\tau} \\ \frac{d\phi}{d\tau} \end{bmatrix} \\
\mathcal{L} \begin{bmatrix} \theta \\ \omega \end{bmatrix} &= \begin{bmatrix} L_2\theta \\ L_3\omega \end{bmatrix} + N \begin{bmatrix} \theta \\ \omega \end{bmatrix}, \quad \begin{bmatrix} L_2\theta \\ L_3\omega \end{bmatrix} = \begin{bmatrix} \frac{d\theta}{dt} \\ \frac{\partial\omega}{\partial t} + \frac{\partial\omega}{\partial\tau} \end{bmatrix} \\
M &= \begin{pmatrix} \beta_1(1-u_1)V + \mu & 0 & \beta_1(1-u_1)x \\ -\beta_1(1-u_1)V & d_1 & -\beta_1(1-u_1)x \\ \hat{\beta}_1(1-u_1)V & -d_1\nu_1(1-u_2) & \delta_1 + s_1 + \hat{\beta}_1(1-u_1)x \end{pmatrix} \\
N \begin{bmatrix} \theta \\ \omega \end{bmatrix} &= \begin{pmatrix} B(\phi,\theta,\omega) + C(\omega) + m_0\theta \\ m'(V)\phi + m(V_1)\omega \end{pmatrix}, \\
B(\phi,\theta,\omega) &= \frac{c_1 s_1}{N}\left(1 - \frac{S}{N}\right)\theta \int_\Omega i(\tau,t)V(\tau)d\tau + \frac{c_1 s_1 S}{N}\int_\Omega V(\tau)\omega(\tau,t)d\tau \\
&\quad + \frac{c_1 s_1 S}{N}\int_\Omega i(\tau,t)\phi(\tau)d\tau, \\
C(\omega) &= -\frac{c_1 s_1 S}{N^2}\int_\Omega\int_\Omega i(\tau,t)V(\tau)\omega(h,t)dhd\tau.
\end{aligned}
$$

We derive the adjoint system from the sensitivity equations. Thus, if $\lambda$, $\xi$, $\eta$, $p$, and $q$ are adjoint variables, then we find adjoint operators $\mathcal{L}_j^*$, for $j = 1,2,3$ such that

$$
\begin{aligned}
&\textstyle\int_\Omega (\lambda,\xi,\eta)\mathcal{L}_1(\psi,\varphi,\phi)d\tau + \int_0^T p\mathcal{L}_2\theta dt + \int_Q q_1\mathcal{L}_3\omega d\tau dt \\
&\quad = \int_\Omega (\psi,\varphi,\phi)\mathcal{L}_1^*(\lambda,\xi,\eta)d\tau + \int_0^T \theta\mathcal{L}_2^* p dt + \int_Q \omega\mathcal{L}_3^* q d\tau dt
\end{aligned} \tag{2.86}
$$

with adjoint equations (in the weak sense defined below)

$$
\mathcal{L}_1^* \begin{bmatrix} \lambda \\ \xi \\ \eta \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ \int_0^T A_1 i(\tau,t)dt \end{bmatrix}, \quad \mathcal{L}^* \begin{bmatrix} p \\ q \end{bmatrix} = \begin{bmatrix} 0 \\ A_1V + A_2u_1 + A_3u_2 \end{bmatrix}, \tag{2.87}
$$

and

$$\mathcal{L}^* \begin{bmatrix} p \\ q \end{bmatrix} \equiv \begin{bmatrix} \mathcal{L}_2^* p \\ \mathcal{L}_3^* q \end{bmatrix}.$$

The right-hand side of the adjoint equations (2.87) are obtained by differentiating the integrand of the objective functional (2.58) with respect to each state variable. The transversality conditions associated with the adjoint variables are:

$$\lambda(A) = 0, \quad \xi(A) = 0, \quad \eta(A) = 0, \quad p(T) = 0 \tag{2.88}$$

$$q(\tau, T) = 0, \quad for \quad \tau \in \Omega \tag{2.89}$$

$$q(A, t) = 0, \quad for \quad t \in (0, T). \tag{2.90}$$

From the sensitivity system in Theorem 2.8 and the relationship between the sensitivity and adjoint operators given by equation (2.86), we use integration by parts to throw the derivatives in the differential operators in the sensitivity functions $\psi$, $\varphi$, $\phi$, $\theta$, and $\omega$ onto the adjoint functions $\lambda$, $\xi$, $\eta$, $p$ and $q$ to form the adjoint operator $\mathcal{L}_1^*$. Now,

$$\begin{aligned} \int_\Omega (\lambda, \xi, \eta) \mathcal{L}_1 \begin{pmatrix} \psi \\ \varphi \\ \phi \end{pmatrix} d\tau &= \int_\Omega (\lambda, \xi, \eta) \left[ \begin{pmatrix} L_1 \psi \\ L_1 \varphi \\ L_1 \phi \end{pmatrix} + M \begin{pmatrix} \psi \\ \varphi \\ \phi \end{pmatrix} \right] d\tau \\ &= \int_\Omega (\psi, \varphi, \phi) \begin{pmatrix} -\frac{d\lambda}{d\tau} \\ -\frac{d\xi}{d\tau} \\ -\frac{d\eta}{d\tau} \end{pmatrix} d\tau + \int_\Omega (\psi, \varphi, \phi) M^T \begin{pmatrix} \lambda \\ \xi \\ \eta \end{pmatrix} d\tau, \end{aligned}$$

where we have used the initial conditions (2.83) and transversality conditions (2.88). Thus,

$$\int_\Omega (\lambda,\xi,\eta)\mathcal{L}_1 \begin{pmatrix} \psi \\ \varphi \\ \phi \end{pmatrix} d\tau$$

$$\begin{aligned}
&= \int_\Omega \left(-\frac{d\lambda}{d\tau} + (\beta_1(1-u_1)V+\mu)\lambda - \beta_1(1-u_1)V\xi + \hat{\beta}_1(1-u_1)V\eta\right)\psi d\tau \\
&\quad + \int_\Omega \left(\frac{-d\xi}{d\tau} + d_1\xi - d_1\nu_1(1-u_2)\eta\right)\varphi d\tau \qquad (2.91)\\
&\quad + \int_\Omega \left(-\frac{d\eta}{d\tau} + \beta_1(1-u_1)x\lambda - \beta_1(1-u_1)x\xi + (\delta_1+s_1+\hat{\beta}_1(1-u_1)x)\eta\right)\phi d\tau.
\end{aligned}$$

Next,

$$\begin{aligned}
\int_0^T p(t)\mathcal{L}_2\theta dt &= \int_0^T p(t)\left(\frac{d\theta}{dt} + B(\phi,\theta,\omega) + C(\omega) + m_0\theta\right)dt \\
&= \int_0^T \left(-\frac{dp}{dt}\theta(t) + B(\phi,\theta,\omega)p(t) + C(\omega)p(t) + m_0 p(t)\theta(t)\right)dt \\
&= \int_0^T (-\frac{dp}{dt} + m_0 p(t))\theta(t)dt + \int_0^T c_1 s_1 p(t)\int_\Omega \frac{S(t)V(\tau)}{N(t)}\omega(\tau,t)d\tau dt \\
&\quad - \int_0^T c_1 s_1 p(t)\int_\Omega \frac{S(t)i(\tau,t)V(\tau)}{N^2(t)}\int_\Omega \omega(h,t)dh d\tau dt \\
&\quad + \int_0^T c_1 s_1 p(t)\int_\Omega \left[\frac{i(\tau,t)V(\tau)}{N(t)}(1-\frac{S(t)}{N(t)})\theta(t) + \frac{S(t)i(\tau,t)}{N(t)}\phi(\tau)\right]d\tau dt \\
&= \int_\Omega\int_0^T c_1 s_1 p(t)\frac{i(\tau,t)S(t)}{N(t)}\phi(\tau)dt d\tau + \int_0^T \left(\frac{-dp}{dt} + m_0 p(t)\right)\theta(t)dt \\
&\quad + c_1 s_1 \int_0^T \left(\frac{p(t)}{N(t)}\left(1-\frac{S(t)}{N(t)}\right)\int_\Omega i(\tau,t)V(\tau)d\tau\right)\theta(t)dt \qquad (2.92)\\
&\quad + \int_0^T\int_\Omega c_1 s_1 p(t)\left(\frac{S(t)V(\tau)}{N(t)} - \frac{S(t)}{N^2(t)}\int_\Omega i(h,t)V(h)dh\right)\omega(\tau,t)d\tau dt.
\end{aligned}$$

Finally, we consider the sensitivity operator $\mathcal{L}_3$, and use integration by parts in two dimensions to throw the derivatives in the differential operator in the sensitivity function $\omega$ onto the adjoint function $q$ to form the adjoint operator $\mathcal{L}_3^*$. Also, we apply the initial conditions given in equation (2.84), and the final time conditions (2.89) and (2.90):

$\int_0^T \int_\Omega q\mathcal{L}_3 \omega d\tau dt$

$$\begin{aligned}
&= \int_0^T \int_\Omega q\left(\frac{\partial \omega}{\partial t} + \frac{\partial \omega}{\partial \tau} + m'(V)\phi i(\tau,t) + m(V)\omega(\tau,t)\right) d\tau dt \\
&= \int_0^T \int_\Omega \left(-\frac{\partial q}{\partial t}\omega(\tau,t) - \frac{\partial q}{\partial \tau}\omega(\tau,t) + m'(V)\phi(\tau)i(\tau,t)q(\tau,t)\right) d\tau dt \\
&\quad + \int_0^T \int_\Omega m(V)\omega(\tau,t)q(\tau,t)d\tau dt - \int_0^T q(0,t)\omega(0,t)dt,
\end{aligned}$$

where

$\int_0^T q(0,t)\omega(0,t)dt$

$$\begin{aligned}
&= \int_0^T c_1 s_1 q(0,t) \int_\Omega \frac{i(\tau,t)V(\tau)}{N(t)} \left(1 - \frac{S(t)}{N(t)}\right) \theta(t) d\tau dt \\
&\quad + \int_0^T c_1 s_1 q(0,t) \int_\Omega \frac{S(t)V(\tau)}{N(t)}\omega(\tau,t)d\tau dt + \int_0^T c_1 s_1 q(0,t) \int_\Omega \frac{i(\tau,t)S(t)}{N(t)}\phi(\tau)d\tau dt \\
&\quad - \int_0^T c_1 s_1 q(0,t) \int_\Omega \frac{S(t)i(\tau,t)V(\tau)}{N(t)^2} \int_\Omega \omega(h,t)dh d\tau dt.
\end{aligned}$$

Thus,

$\int_0^T \int_\Omega q\mathcal{L}_3 \omega d\tau dt$

$$\begin{aligned}
&= \int_\Omega \int_0^T \left((m'(V)i(\tau,t)q(\tau,t) - c_1 s_1 q(0,t)\frac{i(\tau,t)S(t)}{N(t)})\right) dt \phi(\tau) d\tau \\
&\quad - \int_0^T \left(c_1 s_1 \frac{q(0,t)}{N(t)} \left(1 - \frac{S(t)}{N(t)}\right) \int_\Omega i(\tau,t)V(\tau)d\tau\right) \theta(t)dt \\
&\quad + \int_0^T \int_\Omega \left(-\frac{\partial q}{\partial t} - \frac{\partial q}{\partial \tau} + m(V)q(\tau,t)\right) \omega(\tau,t) d\tau dt \qquad (2.93) \\
&\quad - \int_0^T \int_\Omega c_1 s_1 q(0,t) \left(\frac{i(\tau,t)S(t)}{N(t)} - \frac{S(t)}{N(t)^2} \int_\Omega i(h,t)V(h)dh\right) \omega(\tau,t) d\tau dt.
\end{aligned}$$

Combining equations (2.91), (3.89) and (2.93), and using equation (2.86) , we have the following adjoint system corresponding to controls $(u_1, u_2)$ and states

$(x, y, V, S, i) = (x, y, V, S, i)(u_1, u_2)$:

$$\begin{aligned}
-\frac{d\lambda}{d\tau} &= -(\beta_1(1-u_1)V + \mu)\lambda + \beta_1(1-u_1)V\xi - \hat{\beta}_1(1-u_1)V\eta & (2.94)\\
-\frac{d\xi}{d\tau} &= -d_1\xi + \nu_1(1-u_2)d_1\eta & (2.95)\\
-\frac{d\eta}{d\tau} &= -\beta_1(1-u_1)x\lambda + \beta_1(1-u_1)\xi - (\delta_1 + s_1 + \hat{\beta}_1(1-u_1)x)\eta \\
&\quad -c_1 s_1 \int_0^T \frac{S(t)i(\tau,t)}{N(t)}(p(t) - q(0,t))dt - m'(V)\int_0^T i(\tau,t)q(\tau,t)dt \\
&\quad + \int_0^T A_1 i(\tau,t)dt & (2.96)\\
-\frac{dp}{dt} &= -m_0 p - \frac{c_1 s_1}{N}(p - q(0,t))\left(1 - \frac{S}{N}\right)\int_0^A V(\tau)i(\tau,t)d\tau & (2.97)\\
-\frac{\partial q}{\partial t} - \frac{\partial q}{\partial \tau} &= -m(V)q + \frac{c_1 s_1 S}{N^2}(p - q(0,t))\int_0^A V(\tau)i(\tau,t)d\tau & (2.98)\\
&\quad -c_1 s_1 (p - q(0,t))\frac{SV}{N} + A_1 V + A_2 u_1 + A_3 u_2, & (2.99)
\end{aligned}$$

with final time conditions (2.88) – (2.90). Given the sensitivity and adjoint equations, we state a theorem that characterizes the weak solution to our problem.

**Theorem 2.9.** *(**Weak Solution**) The weak solution of the adjoint system satisfies*

$$\int_\Omega \left(\lambda\alpha_1 + \xi\alpha_2 + \eta\alpha_3 - g\int_0^T A_1 i(\tau,t)dt\right)d\tau - \int_0^T \int_0^A (A_1 V + (A_2 u_1 + A_3 u_2))n\,d\tau dt = 0,$$

*where $\alpha_1, \alpha_2, \alpha_3$ are $L^\infty(0, A)$ functions obtained from test functions $z$, $f$ and $g$, and $r$ and $n$ satisfy equations (2.97) and (2.99) such that*

$$\frac{dz}{d\tau} + \beta_1(1-u_1)Vz + \beta_1(1-u_1)xg + \mu z = \alpha_1 \tag{2.100}$$
$$\frac{df}{d\tau} - \beta_1(1-u_1)Vz - \beta_1(1-u_1)xg + d_1 f = \alpha_2 \tag{2.101}$$
$$\frac{dg}{d\tau} + \hat{\beta}_1(1-u_1)Vz - \nu_1(1-u_2)d_1 f + (\delta_1 + s_1 + \hat{\beta}_1(1-u_1)x)g = \alpha_3 \tag{2.102}$$
$$\frac{dr}{dt} + m_0 r + \frac{c_1 s_1}{N}\left(1 - \frac{S}{N}\right) r \int_0^A i(\tau,t)V(\tau)d\tau + \frac{c_1 s_1 S}{N}\int_0^A V(\tau)n(\tau,t)d\tau$$
$$+\frac{c_1 s_1 S}{N}\int_0^A g(\tau)i(\tau,t)d\tau - \frac{c_1 s_1 S}{N^2}\int_0^A\int_0^A i(\tau,t)V(\tau)n(h,t)dhd\tau = 0 \tag{2.103}$$
$$\frac{\partial n(\tau,t)}{\partial t} + \frac{\partial n(\tau,t)}{\partial \tau} + m(V)n + m'(V)gi = 0 \quad in \quad Q \tag{2.104}$$

*with initial and boundary conditions*

$$z(0) = 0, \quad f(0) = 0, \quad g(0) = 0, \quad r(0) = 0, \quad n(\tau,0) = 0 \quad for \quad \tau \in (0, A) \tag{2.105}$$

*and*

$$n(0,t) = \frac{c_1 s_1}{N}\left(1 - \frac{S}{N}\right) r \int_0^A i(\tau,t)V(\tau)d\tau + \frac{c_1 s_1 S}{N}\int_0^A V(\tau)n(\tau,t)d\tau \tag{2.106}$$
$$+\frac{c_1 s_1 S}{N}\int_0^A g(\tau)i(\tau,t)d\tau - \frac{c_1 s_1 S}{N^2}\int_0^A\int_0^A i(\tau,t)V(\tau)n(h,t)dhd\tau.$$

*Proof.* Follows from the sensitivity equations and adjoint system, with $\alpha_1 = \beta_1 l_1 V x$, $\alpha_2 = -\beta_1 l_1 V x$ and $\alpha_3 = \hat{\beta}_1 l_1 V x - \nu_1 d_1 l_2 y$. □

We establish the existence of solution to the adjoint system via the existence of solution $(z, f, g, r, n)$ to system (2.100)−(2.106) (see Barbu [12], Fister and Lenhart [45, 44]). The solution of the adjoint system satisfies a Lipschitz property analogous to Theorem 2.7. This property will be used in proving uniqueness of an optimal control pair.

**Theorem 2.10.** *For* $(u_1, u_2) \in \mathcal{U}$*, the adjoint system (2.94)–(2.99) has a weak solution* $(\lambda, \xi, \eta, p, q)$ *in* $(L^\infty(0,A))^3 \times L^\infty(0,T) \times L^\infty(0,T,L^1(0,A))$ *such that*

$$\begin{aligned}&||\lambda - \bar{\lambda}||_{L^\infty(\Omega)} + ||\xi - \bar{\xi}||_{L^\infty(\Omega)} + ||\eta - \bar{\eta}||_{L^\infty(\Omega)} + ||p - \bar{p}||_{L^\infty(0,T)} + ||q - \bar{q}||_{L^\infty(Q)} \\ &\leq \tilde{C}_{A,T}(||u_1 - \bar{u}_1||_{L^\infty(\Omega)} + ||u_2 - \bar{u}_2||_{L^\infty(\Omega)}).\end{aligned}$$

*Proof.* Follows like in Theorem 2.7, part (ii). □

### 2.4.2 Characterization of Optimal Control

We use the Ekeland's Principle [6, 38] to characterize optimal control of first-order PDEs. To do this, we embed the objective functional $J$ in the space $L^1(\Omega) \times L^1(Q)$ by defining [13, 45, 44]

$$\mathcal{J}(u_1, u_2) = \begin{cases} J(u_1, u_2) & \text{if } (u_1, u_2) \in \mathcal{U} \\ +\infty & \text{if } (u_1, u_2) \notin \mathcal{U}. \end{cases} \tag{2.107}$$

In order to characterize the optimal control pair, we differentiate the objective functional with respect to the controls. However, since the objective functional is a function of the state functions, we must differentiate the state functions with respect to the controls.

**Theorem 2.11.** *If* $(u_1^*, u_2^*) \in \mathcal{U}$ *is an optimal control pair minimizing (3.102), and* $(x^*, y^*, V^*, S^*, i^*)$ *and* $(\lambda, \xi, \eta, p, q)$ *are the corresponding state and adjoint solutions, then*

$$u_1^*(\tau) = \mathcal{F}_1\left(\frac{\beta_1 V^* x^*(\xi - \lambda) - \hat{\beta}_1 V^* x^* \eta - A_2 \int_0^T i^*(\tau,t)dt}{2B_1}\right) \tag{2.108}$$

$$u_2^*(\tau) = \mathcal{F}_2\left(\frac{\nu_1 d_1 \eta y^* - A_3 \int_0^T i^*(\tau,t)dt}{2B_2}\right) \quad \text{a.e. in } L^1(\Omega), \tag{2.109}$$

*where*

$$\mathcal{F}_j(x) = \begin{cases} 0, & x < 0 \\ x, & 0 \leq x \leq \tilde{u}_j \qquad for \quad j = 1, 2. \\ \tilde{u}_j, & x > \tilde{u}_j \end{cases}$$

*Proof.* Since $(u_1^*, u_2^*)$ is an optimal control pair and we seek to minimize our functional, we have

$$\begin{aligned}
0 &\leq \lim_{\varepsilon \to 0^+} \frac{\mathcal{J}(u_1^* + \varepsilon l_1, u_2^* + \varepsilon l_2) - \mathcal{J}(u_1^*, u_2^*)}{\varepsilon} \\
&= \lim_{\varepsilon \to 0^+} \int_0^T \int_0^A \left( A_1 V^\varepsilon \left( \frac{i^\varepsilon - i^*}{\varepsilon} \right) + A_1 i^* \left( \frac{V^\varepsilon - V^*}{\varepsilon} \right) + \frac{A_2 \left( i^\varepsilon u_1^\varepsilon - i^* u_1^* \right)}{\varepsilon} \right) d\tau dt \\
&\quad + \lim_{\varepsilon \to 0^+} \int_0^T \int_0^A \left( \frac{A_3 \left( i^\varepsilon u_2^\varepsilon - i^* u_2^* \right)}{\varepsilon} \right) + \lim_{\varepsilon \to 0^+} \int_0^A B_1 \left( \frac{(u_1^\varepsilon)^2 - (u_1^*)^2}{\varepsilon} \right) d\tau \\
&\quad + \lim_{\varepsilon \to 0^+} \int_0^A B_2 \left( \frac{(u_2^\varepsilon)^2 - (u_2^*)^2}{\varepsilon} \right) d\tau \\
&= \int_0^A (\psi, \varphi, \phi) \begin{pmatrix} 0 \\ 0 \\ \int_0^T A_1 i^*(\tau, t) dt \end{pmatrix} d\tau + \int_0^T \theta.0 dt + 2 \int_0^A (B_1 l_1 u_1^* + B_2 l_2 u_2^*) d\tau \\
&\quad + \int_0^T \int_0^A \omega (A_1 V^* + A_2 u_1^* + A_3 u_2^* + l_1 A_2 i^* + l_2 A_3 i^*) d\tau dt \\
&= \int_\Omega (\psi, \varphi, \phi) \mathcal{L}_1^* \begin{pmatrix} \lambda_1 \\ \xi \\ \eta \end{pmatrix} d\tau + \int_0^T \theta \mathcal{L}_2^* p dt + 2 \int_0^A (B_1 l_1 u_1^* + B_2 l_2 u_2^*) d\tau \\
&\quad + \int_0^T \int_0^A (\omega \mathcal{L}_3^* q + l_1 A_2 i^* + l_2 A_3 i^*) d\tau dt \\
&= \int_\Omega (\lambda, \xi, \eta) \mathcal{L}_1 \begin{pmatrix} \psi \\ \varphi \\ \phi \end{pmatrix} d\tau + \int_0^T p \mathcal{L}_2 \theta dt + 2 \int_0^A (B_1 l_1 u_1^* + B_2 l_2 u_2^*) d\tau \\
&\quad + \int_0^T \int_0^A (q \mathcal{L}_3 \omega + l_1 A_2 i^* + l_2 A_3 i^*) d\tau dt,
\end{aligned}$$

in an appropriate weak sense. Using the sensitivity operators, we have

$$0 \leq \int_0^A ((\lambda, \xi, \eta) \begin{pmatrix} \beta_1 l_1 V^* x^* \\ -\beta_1 l_1 V^* x^* \\ \hat{\beta}_1 l_1 V^* x^* - \nu_1 d_1 l_2 y^* \end{pmatrix} + 2B(l_1 u_1^* + l_2 u_2^*)) d\tau$$

$$+ \int_0^T \int_0^A (A_2 l_1 i^*(\tau, t) + A_3 l_2 i^*(\tau, t)) d\tau dt$$

$$= \int_0^A l_1(\beta_1 V^* x^* (\lambda - \xi) + \hat{\beta}_1 V^* x^* \eta + 2B_1 u_1^* + A_2 \int_0^T i^*(\tau, t) dt) d\tau$$

$$+ \int_0^A l_2(2B_2 u_2^* - \nu_1 d_1 y^* \eta + A_3 \int_0^T i^*(\tau, t) dt) d\tau. \qquad (2.110)$$

For $B_1 > 0$, we characterize the controls $u_1^*$ and $u_2^*$ by considering the following cases:

• On the set $\{\tau \in \Omega | u_1^*(\tau) = 0\}$, we choose a nonnegative $l_1$ with support on this set. Thus, $\beta_1 V^* x^* (\lambda - \xi) + \hat{\beta}_1 V^* x^* \eta + A_2 \int_0^T (i^*(\tau, t) dt \geq 0$ so that

$$\frac{1}{2B_1}(\beta_1 V^* x^* (\xi - \lambda) - \hat{\beta}_1 V^* x^* \eta - A_2 \int_0^T i^*(\tau, t) dt) \leq 0.$$

• On the set $\{\tau \in \Omega | u_1^*(\tau) = \tilde{u}_1\}$, we choose a nonpositive $l_1$ with support on this set. Thus,

$$\frac{1}{2B_1}(\beta_1 V^* x^* (\xi - \lambda) - \hat{\beta}_1 V^* x^* \eta - A_2 \int_0^T i^*(\tau, t) dt) \geq \tilde{u}_1.$$

• Finally, on the set $\{\tau \in \Omega | 0 < u_1^*(\tau) < \tilde{u}_1\}$, we choose $l_1$ with arbitrary sign and support on this set. Thus,

$$u_1^*(\tau) = \frac{1}{2B_1}(\beta_1 V^* x^* (\xi - \lambda) - \hat{\beta}_1 V^* x^* \eta - A_2 \int_0^T i^*(\tau, t) dt).$$

Combining these cases, we have the characterization defined in equation (2.108). On the other hand, considering cases on the sets $\{\tau \in \Omega | u_2^*(\tau) = 0\}$, $\{\tau \in \Omega | u_2^*(\tau) = \tilde{u}_2\}$ and $\{\tau \in \Omega | 0 < u_2^*(\tau) < \tilde{u}_2\}$, we obtain the characterization given in equation (2.109). □

### 2.4.3 Existence of Optimal Control Pair

The lower semicontinuity of the functional, $\mathcal{J}$, defined in equation (3.102) with respect to $L^1$ convergence is needed to prove the existence of optimal control pair. Since solutions of first-order partial differential equations are known for nonsmoothness, the objective functional is not weakly lower semicontinuous with respect to $L^1$. Thus, existence results for an optimal control are not guaranteed [38]. Therefore, we circumvent this by applying the following Ekeland's Variational Principle, which guarantees the existence of a minimizing sequence: For $\varepsilon > 0$, there exist $(u_1^\varepsilon, u_2^\varepsilon) \in L^1(0, A) \times L^1(0, A)$ such that

$$
\begin{aligned}
(i) \quad \mathcal{J}(u_1^\varepsilon, u_2^\varepsilon) &\leq \inf_{(u_1,u_2)\in\mathcal{U}} \mathcal{J}(u_1, u_2) + \varepsilon \\
(ii) \quad \mathcal{J}(u_1^\varepsilon, u_2^\varepsilon) &= \min_{(u_1,u_2)\in\mathcal{U}} \mathcal{J}_\varepsilon(u_1, u_2), \\
where\ \mathcal{J}_\varepsilon(u_1, u_2) &= \mathcal{J}(u_1, u_2) + \sqrt{\varepsilon}(||u_1^\varepsilon - u_1||_{L^1(0,A)} + ||u_2^\varepsilon - u_2||_{L^1(0,A)}).
\end{aligned}
$$

We shall show that the minimizer, $(u_1^\varepsilon, u_2^\varepsilon)$, of the approximate functional converges to the optimal controls $(u_1^*, u_2^*)$ in $L^\infty(0, A) \times L^\infty(0, A)$. We start by proving the lower semicontinuity of the functional $\mathcal{J}$.

**Theorem 2.12.** ***(Lower semicontinuity)***
*The functional $\mathcal{J} : L^1(\Omega) \times L^1(\Omega) \to (-\infty, +\infty]$ is lower semicontinuous*

*Proof.* Let $(u_1^n, u_2^n) \to (u_1, u_2) \quad in \quad L^1(0, A)\times L^1(0, A)$, and assume that $(x, y, V, S, i)$ is the state solution corresponding to $(u_1, u_2)$ and $(x^n, y^n, V^n, S^n, i^n)$ is the state solution corresponding to $(u_1^n, u_2^n)$, then by Theorem 2.7, part (i), we have

$$x^n \to x, \quad y^n \to y, \quad V^n \to V \quad in \quad L^1(0, A)$$

$$S^n \to S \quad in \quad L^1(0, T), \quad and \quad i^n \to i \quad in \quad L^1((0, A) \times (0, T)).$$

Thus, on a subsequence, denoted by itself, we have

$u_1^n \to u_1,\ u_2^n \to u_2,\ x^n \to x,\ y^n \to y,\ V^n \to V a.e.\ in\ (0, A), \quad S^n \to S\ a.e.\ in\ (0, T),$

and $i^n \to i$ $a.e.$ $in$ $(0,A)\times(0,T)$, by Theorem 5, p. 21 [40]. Hence, on a subsequence, we have $(u_1^n)^2 \to (u_1)^2$ and $(u_2^n)^2 \to (u_2)^2$ $a.e.$ $in$ $(0,A)$, and

$$A_1 i^n V^n + i^n(A_2 u_1^n + A_3 u_2^n) \to A_1 i V + \gamma_1 i(A_2 u_1 + A_3 u_2) \quad in \quad (0,A)\times(0,T),$$

by Lemma 3.4.3, p. 100 [6]. Using Fatou's Lemma [40], we have that on a subsequence,

$$\begin{aligned}
&\textstyle\int_0^T \int_0^A (A_1 i(\tau,t)V(\tau) + i(\tau,t)(A_2 u_1 + A_3 u_2))d\tau dt \\
&\qquad = \int_0^T \int_0^A \liminf_{n\to\infty} (A_1 i^n V^n + i^n(A_2 u_1^n + A_3 u_2^n))d\tau dt \\
&\qquad \le \liminf_{n\to\infty} \int_0^T \int_0^A (A_1 i^n V^n + i^n(A_2 u_1^n + A_3 u_2^n))d\tau dt, \qquad (2.111)
\end{aligned}$$

and

$$\begin{aligned}
\int_0^A (B_1(u_1)^2 + B_2(u_2)^2)d\tau &= \int_0^A \liminf_{n\to\infty} (B_1(u_1^n)^2 + B_2(u_2^n)^2)d\tau \\
&\le \liminf_{n\to\infty} \int_0^A (B_1(u_1^n)^2 + B_2(u_2^n)^2)d\tau. \qquad (2.112)
\end{aligned}$$

Combining equations (2.111) and (2.112), we have

$\mathcal{J}(u_1,u_2)$

$$\begin{aligned}
&= \int_0^T \int_0^A (A_1 i V + i(A_2 u_1 + A_3 u_2))d\tau dt + \int_0^A (B_1(u_1)^2 + B_2(u_2)^2)d\tau \\
&\le \liminf_{n\to\infty} \int_0^T \int_0^A (A_1 i^n V^n + i^n(A_2 u_1^n + A_3 u_2^n))d\tau dt \\
&\quad + \liminf_{n\to\infty} \int_0^A (B_1(u_1^n)^2 + B_2(u_2^n)^2)d\tau \\
&\le \liminf_{n\to\infty} \left( \int_0^T \int_0^A (A_1 i^n V^n + i^n(A_2 u_1^n + A_3 u_2^n))d\tau dt + \int_0^A (B_1(u_1^n)^2 + B_2(u_2^n)^2)d\tau \right) \\
&= \liminf_{n\to\infty} \mathcal{J}(u_1^n, u_2^n).
\end{aligned}$$

Hence, the functional $\mathcal{J}$ is lower semicontinuous. □

**Theorem 2.13.** *If $(u_1^\varepsilon, u_2^\varepsilon)$ is an optimal control pair minimizing the approximate functional, $\mathcal{J}_\varepsilon$, then*
$(u_1^\varepsilon, u_1^\varepsilon)$

$$= \mathcal{F}\left(\frac{\beta_1 V^\varepsilon x^\varepsilon(\xi^\varepsilon - \lambda^\varepsilon) - \hat{\beta}_1 V^\varepsilon x^\varepsilon \eta^\varepsilon - A_2 K^\varepsilon(\tau) - \sqrt{\varepsilon}\kappa_1^\varepsilon}{2B_1}, \frac{\nu_1 d_1 \eta y^\varepsilon - A_3 K^\varepsilon(\tau) - \sqrt{\varepsilon}\kappa_2^\varepsilon}{2B_2}\right),$$

*where $K^\varepsilon(\tau) = \int_0^T i^\varepsilon(\tau, t)dt$, and the functions $\kappa_1, \kappa_2 \in L^\infty(0, A)$, with $|\kappa_1(\tau)| = 1$ and $|\kappa_2(\tau)| = 1$, for all $\tau \in (0, A)$.*

*Proof.* Since $(u_1^\varepsilon, u_2^\varepsilon)$ is an optimal control pair minimizing the approximate functional $\mathcal{J}_\varepsilon$,

$$\begin{aligned}
0 &\leq \lim_{\alpha\to 0^+} \frac{\mathcal{J}_\varepsilon(u_1^\varepsilon + \alpha l_1^\varepsilon, u_2^\varepsilon + \alpha l_2^\varepsilon) - \mathcal{J}_\varepsilon(u_1^\varepsilon, u_2^\varepsilon)}{\alpha} \\
&= \lim_{\alpha\to 0^+} \frac{\mathcal{J}(u_1^\varepsilon + \alpha l_1^\varepsilon, u_2^\varepsilon + \alpha l_2^\varepsilon) - \mathcal{J}(u_1^\varepsilon, u_2^\varepsilon)}{\alpha} + \sqrt{\varepsilon}(||l_1^\varepsilon||_{L^1(0,A)} + ||l_2^\varepsilon||_{L^1(0,A)}) \\
&= \int_0^A l_1^\varepsilon \left(\beta_1 V^\varepsilon x^\varepsilon(\lambda^\varepsilon - \xi^\varepsilon) + \hat{\beta}_1 V^\varepsilon x^\varepsilon \eta^\varepsilon + 2B_1 u_1^\varepsilon + A_2 \int_0^T i^\varepsilon(\tau, t)dt + \sqrt{\varepsilon}\frac{|l_1^\varepsilon|}{l_1^\varepsilon}\right) d\tau \\
&\quad + \int_0^A l_2^\varepsilon \left(2B_2 u_2^\varepsilon - \nu_1 d_1 y^\varepsilon \eta^\varepsilon + A_3 \int_0^T i^\varepsilon(\tau, t)dt + \sqrt{\varepsilon}\frac{|l_2^\varepsilon|}{l_2^\varepsilon}\right) d\tau \\
&= \int_0^A l_1^\varepsilon \left(\beta_1 V^\varepsilon x^\varepsilon(\lambda^\varepsilon - \xi^\varepsilon) + \hat{\beta}_1 V^\varepsilon x^\varepsilon \eta^\varepsilon + 2B_1 u_1^\varepsilon + A_2 \int_0^T i^\varepsilon(\tau, t)dt + \sqrt{\varepsilon}\kappa_1^\varepsilon\right) d\tau \\
&\quad + \int_0^A l_2^\varepsilon \left(2B_2 u_2^\varepsilon - \nu_1 d_1 y^\varepsilon \eta^\varepsilon + A_3 \int_0^T i^\varepsilon(\tau, t)dt + \sqrt{\varepsilon}\kappa_2^\varepsilon\right) d\tau,
\end{aligned}$$

where $\kappa_j^\varepsilon = \frac{|l_j^\varepsilon|}{l_j^\varepsilon} \in L^\infty(0, A)$ for $j = 1, 2$, with $|\kappa_j^\varepsilon| = 1$, and using equation (2.110) in Theorem 3.10. By standard optimal control arguments (see Theorem 3.10), we have the desired result. □

### 2.4.4 Uniqueness of Optimal Control Pair

In this subsection, we establish uniqueness of optimal control pair, by using the Lipschitz properties of the state and adjoint solutions given in Theorems 2.7 and 2.10, respectively, as well as the minimizing sequence obtained from the Ekeland's

Variational Principle. Finally, we shall show that the minimizer, $(u_1^\varepsilon, u_2^\varepsilon)$, of the approximate functional, $\mathcal{J}_\varepsilon$, converges to the optimal control, $(u_1^*, u_2^*)$.

**Theorem 2.14.** *(**Uniqueness**) If $\frac{\bar{C}_{A,T}}{2}\left(\frac{1}{B_1}+\frac{1}{B_2}\right)$ is sufficiently small, then there exists a unique optimal control pair $(u_1^*, u_2^*) \in \mathcal{U}$ minimizing the objective functional $\mathcal{J}$.*

*Proof.* Let $\mathcal{F}(x,y) = (\mathcal{F}_1(x), \mathcal{F}_2(y))$ and define $L : \mathcal{U} \to \mathcal{U}$, such that

$$L(u_1,u_2) = \mathcal{F}\left(\frac{\beta_1 V x(\xi-\lambda) - \hat{\beta}_1 V x\eta - A_2 K(\tau)}{2B_1}, \frac{\nu_1 d_1 \eta y - A_3 K(\tau)}{2B_2}\right),$$

where $K(\tau) = \int_0^T i(\tau,t)dt$, and $(x,y,V,S,i)$ and $(\lambda,\xi,\eta,p,q)$ are the state and adjoint solutions corresponding to the control pair $(u_1,u_2)$. Using the Lipschitz properties of the state and adjoint systems in Theorems 2.7 and 2.10, respectively, we have

$$||L(u_1,u_2) - L(\bar{u}_1,\bar{u}_2)|| \equiv ||\mathcal{F}_1(u_1) - \mathcal{F}_1(\bar{u}_1)||_{L^\infty(0,A)} + ||\mathcal{F}_2(u_2) - \mathcal{F}_2(\bar{u}_2)||_{L^\infty(0,A)}$$

$$\begin{aligned}
\le\ & \left|\left|\frac{\beta_1 V x(\xi-\lambda) - \hat{\beta}_1 V x\eta - A_2 K(\tau)}{2B_1} - \frac{\beta_1 \bar{V}\bar{x}(\bar{\xi}-\bar{\lambda}) - \hat{\beta}_1 \bar{V}\bar{x}\bar{\eta} - A_2 \bar{K}(\tau)}{2B_1}\right|\right|_{L^\infty(0,A)} \\
& + \left|\left|\frac{\nu_1 d_1 \eta y - A_3 \int_0^T i(\tau,t)dt}{2B_2} - \frac{\nu_1 d_1 \bar{\eta}\bar{y} - A_3 \int_0^T \bar{i}(\tau,t)dt}{2B_2}\right|\right|_{L^\infty(0,A)} \\
\le\ & \frac{1}{2B_1}||\beta_1(Vx(\xi-\lambda) - \bar{V}\bar{x}(\bar{\xi}-\bar{\lambda})) - A_2\int_0^T (i-\bar{i})(\tau,t)dt||_{L^\infty(0,A)} \\
& + \frac{1}{2B_1}||\hat{\beta}_1(Vx\eta - \bar{V}\bar{x}\bar{\eta})||_{L^\infty(0,A)} \\
& + \frac{1}{2B_2}||d_1\nu_1(\eta y - \bar{\eta}\bar{y}) - A_3\int_0^T (i-\bar{i})(\tau,t)dt||_{L^\infty(0,A)}.
\end{aligned}$$

Whence,

$$||L(u_1,u_2) - L(\bar{u}_1,\bar{u}_2)|| \le \frac{\bar{C}_{A,T}}{2}\left(\frac{1}{B_1}+\frac{1}{B_2}\right)(||u_1-\bar{u}_1||_{L^\infty(0,A)} + ||u_2-\bar{u}_2||_{L^\infty(0,A)}). \tag{2.113}$$

If $\frac{\bar{C}_{A,T}}{2}(\frac{1}{B_1}+\frac{1}{B_2})<1$, then the map $L$ admits a unique fixed point $(u_1^*,u_2^*)$, by the Banach Contraction Theorem. Next, we show that this fixed point is an optimal control pair, by using the minimizers, $(u_1^\varepsilon,u_2^\varepsilon)$, from Ekeland's Principle. To do this, we use the states $(x^\varepsilon,y^\varepsilon,V^\varepsilon,S^\varepsilon,i^\varepsilon)$ and adjoints $(\lambda^\varepsilon,\xi^\varepsilon,\eta^\varepsilon,p^\varepsilon,q^\varepsilon)$ corresponding to the minimizer $(u_1^\varepsilon,u_2^\varepsilon)$. Now, for $K^\varepsilon(\tau)=\int_0^T i^\varepsilon(\tau,t)dt$, $a^\varepsilon(\tau)=\beta_1 V^\varepsilon(\tau)x^\varepsilon(\tau)(\xi^\varepsilon(\tau)-\lambda^\varepsilon(\tau))-\hat{\beta}_1 V^\varepsilon(\tau)x^\varepsilon(\tau)\eta^\varepsilon(\tau)$ and $b^\varepsilon(\tau)=\nu_1 d_1\eta^\varepsilon(\tau)y^\varepsilon(\tau)$, we have

$$\left\|L(u_1^\varepsilon,u_2^\varepsilon)-\mathcal{F}\left(\tfrac{a^\varepsilon-A_2K^\varepsilon-\sqrt{\varepsilon}\kappa_1^\varepsilon}{2B_1},\tfrac{b^\varepsilon-A_3K^\varepsilon-\sqrt{\varepsilon}\kappa_2^\varepsilon}{2B_2}\right)\right\|_{(L^\infty(0,A))^2}$$

$$\begin{aligned}
&= \left\|\mathcal{F}\left(\frac{a^\varepsilon-A_2K^\varepsilon}{2B_1},\frac{b^\varepsilon-A_3K^\varepsilon}{2B_2}\right)-\mathcal{F}\left(\frac{a^\varepsilon-A_2K^\varepsilon-\sqrt{\varepsilon}\kappa_1^\varepsilon}{2B_1},\frac{b^\varepsilon-A_3K^\varepsilon-\sqrt{\varepsilon}\kappa_2^\varepsilon}{2B_2}\right)\right\| \\
&\le \left\|\frac{\sqrt{\varepsilon}\kappa_1^\varepsilon}{2B_1}\right\|_{L^\infty(0,A)}+\left\|\frac{\sqrt{\varepsilon}\kappa_2^\varepsilon}{2B_2}\right\|_{L^\infty(0,A)}=\frac{\sqrt{\varepsilon}}{2}\left(\frac{1}{B_1}+\frac{1}{B_2}\right).
\end{aligned} \tag{2.114}$$

Now, we show that

$$(u_1^\varepsilon,u_2^\varepsilon)\to(u_1^*,u_2^*)\quad in\quad L^\infty(0,A)\times L^\infty(0,A).$$

For $K^*(\tau)=\int_0^T i^*(\tau,t)dt$ and $K^\varepsilon(\tau)=\int_0^T i^\varepsilon(\tau,t)dt$, we have

$$\|(u_1^*,u_2^*)-(u_1^\varepsilon,u_2^\varepsilon)\|_{(L^\infty(0,A))^2}$$

$$\begin{aligned}
&= \|u_1^*-u_1^\varepsilon\|_{L^\infty(0,A)}+||u_2^*-u_2^\varepsilon\|_{L^\infty(0,A)} \\
&= \left\|\mathcal{F}_1\left(\frac{\beta_1V^*x^*(\xi-\lambda)-\beta_1V^*x^*\eta-A_2K^*}{2B_1}\right)-\mathcal{F}_1\left(\frac{a^\varepsilon-A_2K^\varepsilon-\sqrt{\varepsilon}\kappa_1^*}{2B_1}\right)\right\|_{L^\infty(0,A)} \\
&\quad+\left\|\mathcal{F}_2\left(\frac{\nu_1d_1y^*\eta-A_3K^*}{2B_2}\right)-\mathcal{F}_2\left(\frac{\nu_1d_1y^\varepsilon\eta^\varepsilon-A_3K^\varepsilon-\sqrt{\varepsilon}\kappa_2^\varepsilon}{2B_2}\right)\right\|_{L^\infty(0,A)} \\
&\le \|L(u_1^*,u_2^*)-L(u_1^\varepsilon,u_2^\varepsilon)\|_{L^\infty(0,A)} \\
&\quad+\left\|L(u_1^\varepsilon,u_2^\varepsilon)-\mathcal{F}\left(\frac{a^\varepsilon-A_2K^\varepsilon-\sqrt{\varepsilon}\kappa_1^\varepsilon}{2B_1},\frac{\nu_1d_1\eta^\varepsilon y^\varepsilon-A_3K^\varepsilon-\sqrt{\varepsilon}\kappa_2^\varepsilon}{2B_2}\right)\right\|_{L^\infty(0,A)} \\
&\le \frac{\bar{C}_{A,T}}{2}\left(\frac{1}{B_1}+\frac{1}{B_2}\right)\left(||u_1^*-u_1^\varepsilon\|_{L^\infty(0,A)}+\|u_2^*-u_2^\varepsilon\|_{L^\infty(0,A)}\right)+\frac{\sqrt{\varepsilon}}{2}\left(\frac{1}{B_1}+\frac{1}{B_2}\right),
\end{aligned}$$

from equations (4.47) and (4.48). Thus,

$$\|u_1^* - u_1^\varepsilon\|_{L^\infty(0,A)} + \|u_2^* - u_2^\varepsilon\|_{L^\infty(0,A)}$$

$$\leq \frac{\bar{C}_{A,T}}{2}\left(\frac{1}{B_1}+\frac{1}{B_2}\right)(\|u_1^* - u_1^\varepsilon\|_{L^\infty(0,A)} + \|u_2^* - u_2^\varepsilon\|_{L^\infty(0,A)}) + \frac{\sqrt{\varepsilon}}{2}\left(\frac{1}{B_1}+\frac{1}{B_2}\right).$$

Whence,

$$\|u_1^* - u_1^\varepsilon\|_{L^\infty(0,A)} + \|u_2^* - u_2^\varepsilon\|_{L^\infty(0,A)} \leq \frac{\frac{\sqrt{\varepsilon}}{2}\left(\frac{1}{B_1}+\frac{1}{B_2}\right)}{1-\frac{\bar{C}_{A,T}}{2}\left(\frac{1}{B_1}+\frac{1}{B_2}\right)},$$

for $\frac{\bar{C}_{A,T}}{2}\left(\frac{1}{B_1}+\frac{1}{B_2}\right)$ sufficiently small. Equivalently,

$$\|(u_1^*, u_2^*) - (u_1^\varepsilon, u_2^\varepsilon)\|_{L^\infty(0,A)\times L^\infty(0,A)} \leq \frac{\frac{\sqrt{\varepsilon}}{2}\left(\frac{1}{B_1}+\frac{1}{B_2}\right)}{1-\frac{\bar{C}_{A,T}}{2}\left(\frac{1}{B_1}+\frac{1}{B_2}\right)} \to 0 \quad as \quad \varepsilon \to 0^+.$$

Thus,

$$(u_1^\varepsilon, u_2^\varepsilon) \to (u_1^*, u_2^*) \quad in \quad L^\infty(0,A)\times L^\infty(0,A).$$

Finally, we show that $(u_1^*, u_2^*)$ is the minimizer of the functional, $\mathcal{J}$. Now, as the functional, $\mathcal{J}$, is lower semicontinuous, using Ekeland's Principle, we have $\mathcal{J}(u_1^\varepsilon, u_2^\varepsilon) \leq \inf_{(u_1,u_2)\in\mathcal{U}} \mathcal{J}(u_1, u_2) + \varepsilon$. Since $(u_1^\varepsilon, u_2^\varepsilon) \to (u_1^*, u_2^*)$ as $\varepsilon \to 0^+$, it follows that $\mathcal{J}(u_1^*, u_2^*) \leq \inf_{(u_1,u_2)\in\mathcal{U}} \mathcal{J}(u_1, u_2)$. □

## 2.5 Numerical Simulations

We present a numerical scheme for the within-host model (2.1) – (2.4) and between-host model (2.5) – (2.7) based on semi-implicit finite-difference schemes for ordinary differential equations [52, 58] and partial differential equations [7, 109]. Let $\Delta\tau = h > 0$ be the discretization step for the interval $[0, A]$, with $h = \frac{A}{M}$, where $M$ is the total number of subintervals in age (age-since-infection), and $\Delta t = k > 0$ be the discretization step for the interval $[0, T]$, with $k = \frac{T}{N}$, where $N$ is the total number of subintervals in time. We discretize the intervals $[0, A]$ and $[0, T]$ at the points $\tau_j = j\Delta\tau$ $(j = 0, 1, ..., M)$ and $t_n = n\Delta t$ $(n = 0, 1, ..., N)$, respectively. Next, we define the state and adjoint functions $x$, $y$, $V$, $S$, $\omega$ ( where $\omega \equiv i$), $\lambda$, $\xi$, $\eta$, $p$, $q$, and controls $u_1$ and $u_2$ in terms of nodal points $x^j$, $y^j$, $V^j$, $S^n$, $w_j^n$, $\lambda^j$, $\xi^j$, $\eta^j$, $p^n$, $q_j^n$, $u_1^j$ and $u_2^j$. Since $\omega_j^n$ is an approximation to the solution of the equation that models infectious individuals at time level $t_n$ and grid point $\tau_j$, we approximate the directional derivatives $\frac{\partial\omega(\tau,t)}{\partial t}$ and $\frac{\partial\omega(\tau,t)}{\partial\tau}$ by

$$\frac{\partial\omega(\tau_j, t_n)}{\partial t} \approx \frac{\omega_j^n - \omega_j^{n-1}}{\Delta t} \quad and \quad \frac{\partial\omega(\tau_j, t_n)}{\partial\tau} \approx \frac{\omega_j^{n-1} - \omega_{j-1}^{n-1}}{\Delta\tau}.$$

Age of individuals changes at the same speed as chronological time, and therefore we assume that $\Delta t = \Delta\tau$, so that

$$\frac{\partial\omega(\tau_j, t_n)}{\partial t} + \frac{\partial\omega(\tau_j, t_n)}{\partial\tau} \approx \frac{\omega_j^n - \omega_{j-1}^{n-1}}{\Delta t}.$$

Since initial conditions are given for the state system, we use the forward finite-difference approximation to obtain a semi-implicit scheme for the state system. Similarly, since final time conditions of the adjoint system are given, we approximate the time-since-start of infection, chronological time and age-since-infection derivatives of the adjoint functions by their first-order semi-implicit backward finite-difference approximations. To fully implement our numerical scheme for the coupled model, we use the parameter values of the within-host and epidemiological model of HIV given in Table 2.3, and the forward-backward sweep method, whereby solutions to the state system are obtained using a finite difference forward sweep method and solutions to the adjoint system are obtained using a finite difference backward sweep method [80]. We now illustrate numerical simulations of the optimal control and corresponding states for one sample set of parameters. For this set of parameters without control, we have $\mathcal{R}_0 = 4.3$.

**Table 2.3:** Within-Host Model Parameter Values

| Parameter | Value | Source |
|---|---|---|
| $r$ | 10 cells $mm^{-3}$day$^{-1}$ | [46, 58, 77, 96, 113] |
| $\mu$ | 0.02 day$^{-1}$ | [58, 96, 113] |
| $\beta_1$ | 2.4 $\times 10^{-5}$mm$^3$day$^{-1}$ | [58, 46, 77, 96, 113] |
| $\hat{\beta}_1$ | 2.4 $\times 10^{-5}$mm$^3$day$^{-1}$ | [58, 46, 77, 96, 113] |
| $d_1$ | 0.5 day$^{-1}$ | [58, 46, 77, 96] |
| $\nu_1$ | 1200 virions cell$^{-1}$ | [46] |
| $\delta_1$ | 3 day$^{-1}$ | [46, 96] |
| $s_1$ | 1.4 day$^{-1}$ | assumed |
| $c_1$ | $4 \times 10^{-5}$ mm$^3$virion$^{-1}$year$^{-1}$ | assumed |
| $\mu_1$ | $2 \times 10^{-7}$ virion$^{-1}$year$^{-1}$ | assumed |
| $m_0$ | 0.012 mm$^3$ year$^{-1}$ | assumed |
| $\Lambda$ | 2750 humans | assumed |

In Figure 2.1, we have trajectories representing healthy CD4$^+$ T cells, infected CD4$^+$ T cells and free virus in the absence/presence of transmission and virion production suppressing drugs for a total of 100 days. In the absence of drugs and starting with 600 healthy CD4$^+$ T cells per mm$^3$ of blood, the number of heathy cells decreases greatly within the first 20 days of infection. Between 20 – 100 days, the count of CD4$^+$ healthy cells lies below 200. With no infected CD4$^+$ T cells in the population at the beginning of the infection, the number of infected cells increases significantly between 10 – 30 days, with a maximum count of about 190 infected cells, and decreases thereof. Starting with 0.005 virions per mm$^3$ of blood, an acute phase is observed between 10 – 30 days since start-of-infection with a maximum count of about $2.5 \times 10^4$ virions, followed by a latent period.

Figures 2.2 and 2.3 represent the between-host dynamics in the absence of transmission and virion production transmission suppressing drugs. In the absence of drugs, trajectories for susceptible individuals suggest a steady decrease in the

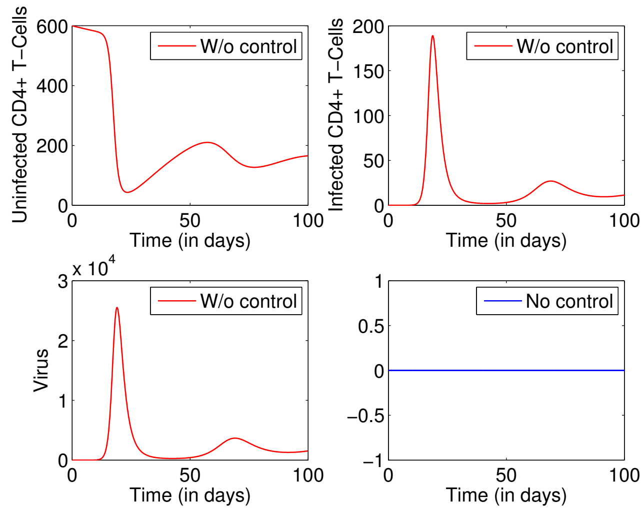


**Figure 2.1:** Healthy CD4$^+$ T Cells, Infected CD4$^+$ T Cells, Free Virus in the Absence of Control when $x^0 = 600$ cells mm$^{-3}$, $y^0 = 0$ cell mm$^{-3}$, $V^0 = 0.005$ virions mm$^{-3}$ and A=100 days.

population of susceptible individuals at the epidemiological level as the result of the proliferation of free virus at the within-host level. Also, with the assumption that at time $t = 0$, the initial age distribution of infectious individuals is modeled by $i(\tau, 0) = 100 \sin(\frac{\pi\tau}{25})$, we observe an oscillatory increase in the number of infectious individuals in the population as time evolves.

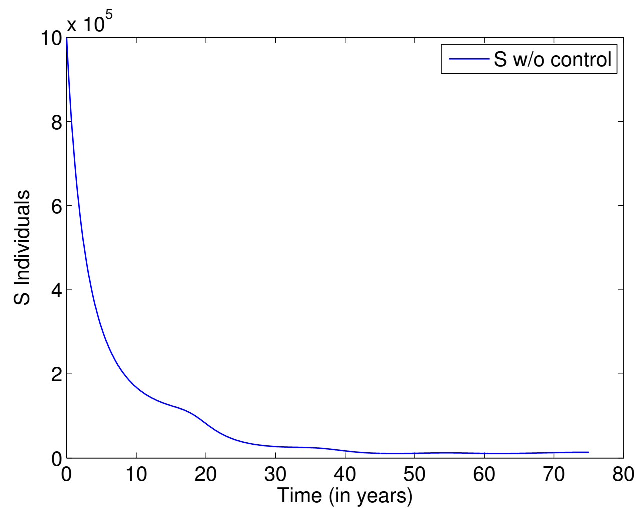


**Figure 2.2:** Susceptible Individuals in the Absence of Control.

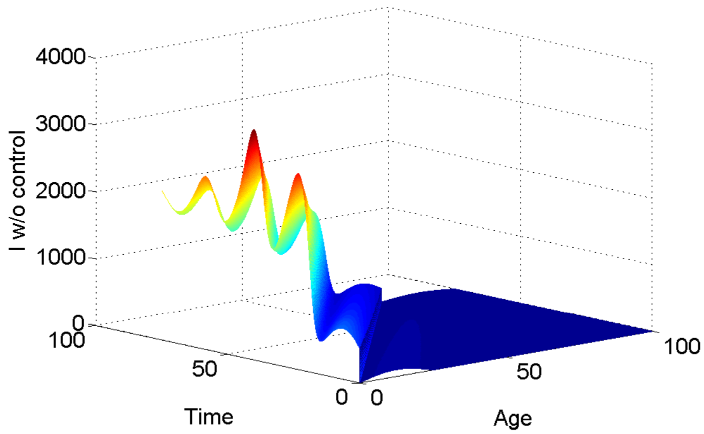


**Figure 2.3:** Infectious Individuals in the Absence of Control, with Initial Age Distribution $i(\tau, 0) = 100\sin(\frac{\pi\tau}{25})$.

In the presence of transmission and virion production suppressing drugs, trajectories indicate an increase in the number of healthy CD4$^+$ T cells, and a decrease in infected CD4$^+$ T cells and free virus in Figure 2.4. Also, the acute phase observed in the virus population within 10 – 30 days occurs with lower severity, and the viral

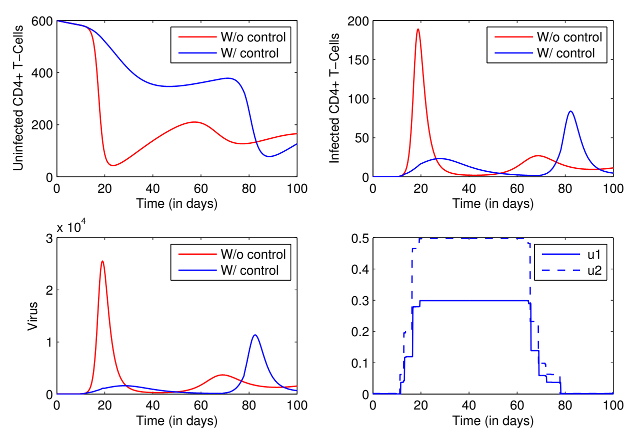


**Figure 2.4:** Healthy CD4$^+$ T Cells, Infected CD4$^+$ T Cells, Free Virus with and without Control when $x^0 = 600$ cells mm$^{-3}$, $y^0 = 0$ cell mm$^{-3}$, $V^0 = 0.005$ virions mm$^{-3}$, $A_1 = 1$, $A_2 = 0.7$, $A_3 = 0.7$, A=100 days, $B_1 = 5 \times 10^6$ and $B_2 = 1$.

relapse phase in the absence of control occurs sooner than in the presence of control. Similarly, the acute phase observed in the population of infected $CD4^+$ T-cells within

10 – 30 days occurs with lower severity. The control program suggests full treatment between 10 – 80 days since start-of-infection.

In the presence of transmission and virion production suppressing dugs, there are more susceptible individuals in the popuation, and a lower prevalence rate as delineated in Figure 2.5.

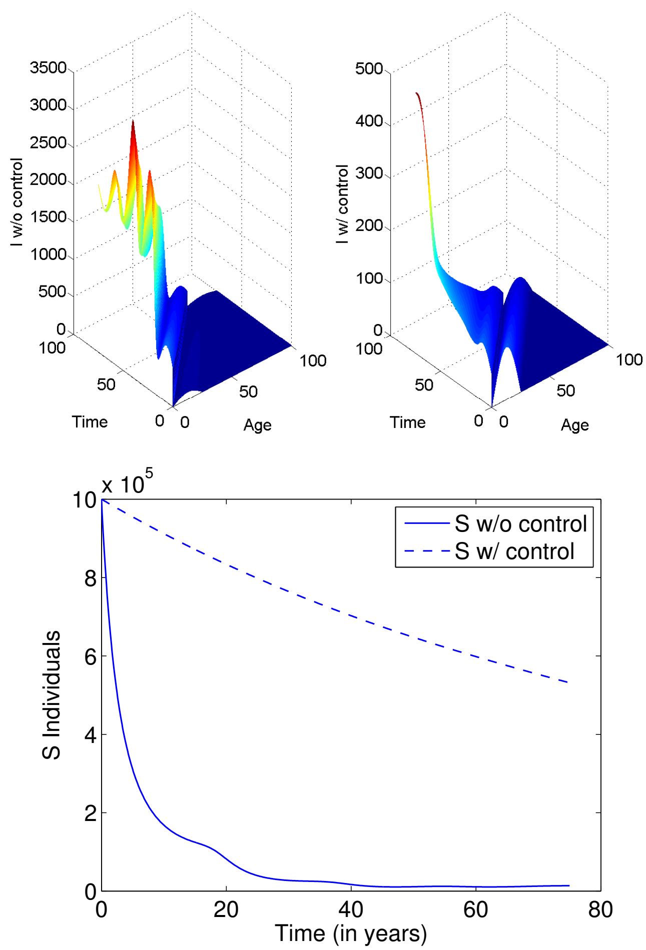


**Figure 2.5:** Susceptible and Infectious Individuals with and without Control, and Initial Age Distribution $i(\tau, 0) = 100 \sin(\frac{\pi\tau}{25})$ when $\Lambda = 2750$, $x^0 = 600$ cells per mm$^3$, $y^0 = 0$ cell per mm$^3$ and $V^0 = 0.005$ virions per mm$^3$.

A small value of $B_1$ ($B_1 = 1$) requires a maximum effort in the transmission suppressing drug between 20 – 80 days and close to 100 days since start of the infection. This result is shown in Figure 2.6.

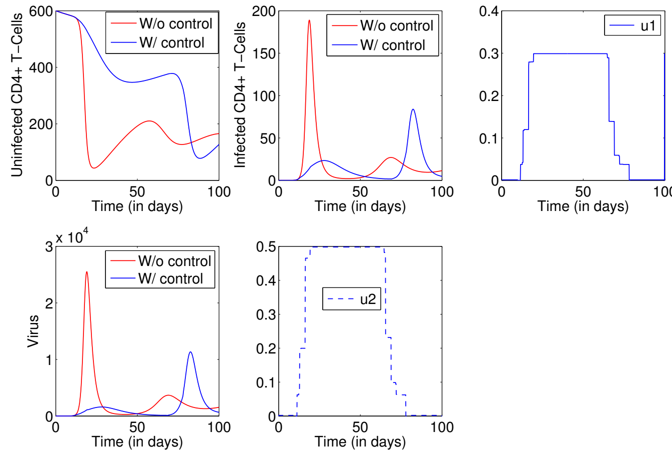


Figure 2.6: Healthy CD4$^+$ T Cells, Infected CD4$^+$ T Cells, Free Virus in the Presence/Absence of Control when $B_1 = 1$ and $B_2 = 1$.

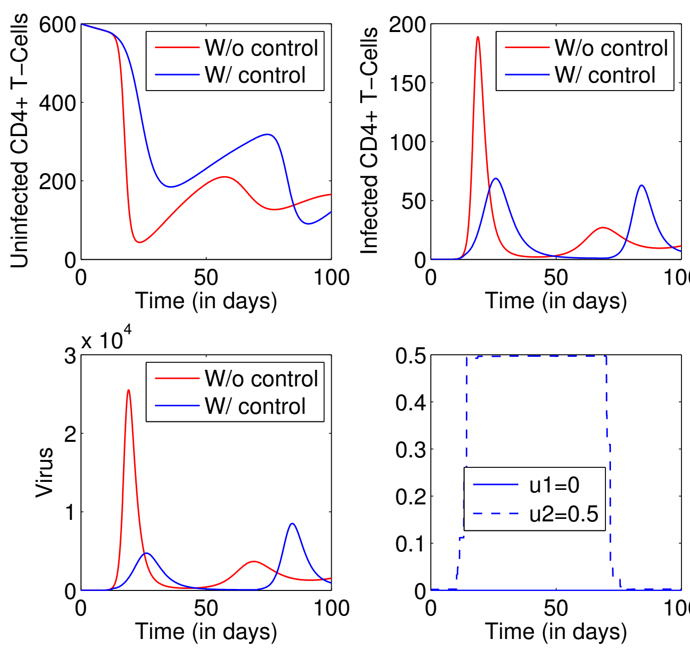


Figure 2.7: Healthy CD4$^+$ T Cells, Infected CD4$^+$ T Cells, Free Virus in the Presence/Absence of Control when $B_1 = 1$ and $B_2 = 1$.

Figure 2.7 depicts the within-host population in the absence of the transmission suppressing drug ($\tilde{u}_1 \equiv 0$), but in the presence of the virion production suppressing drug ($\tilde{u}_2 \equiv 0.5$). When $\tilde{u}_1 \equiv 0$, the trajectory for healthy cells indicates a decrease in the number of healthy cells compared to the number of healthy cells in the presence of the transmission suppressing drug. An acute phase in virion production and growth of infected cells which occurs between 10 – 40 days since start-of-infection as shown in Figure 2.7. As shown in Figure 2.8, the infectious population also experiences in incease in the number of infectious individuals compared to the infectious population in the presence of both drugs, and trajectories for susceptible individuals are as shown in Figure 2.9.

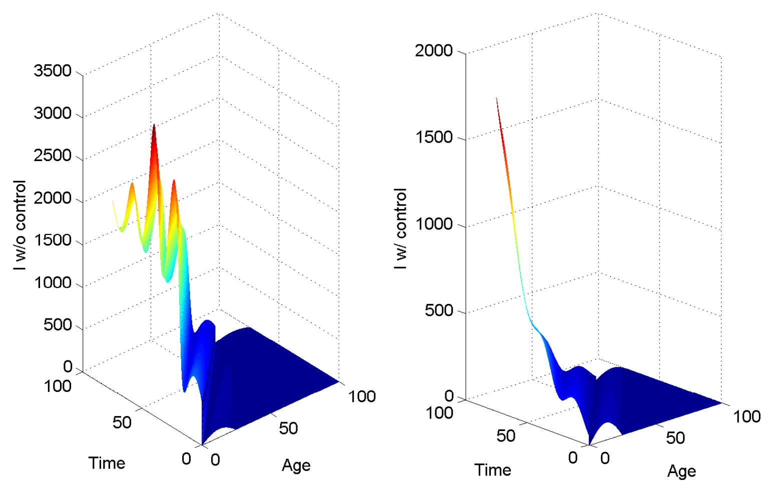


**Figure 2.8:** Infectious Individuals with and without Control when $\tilde{u}_1 = 0$, $\tilde{u}_2 = 0.5$, $B_1 = 1$ and $B_2 = 1$.

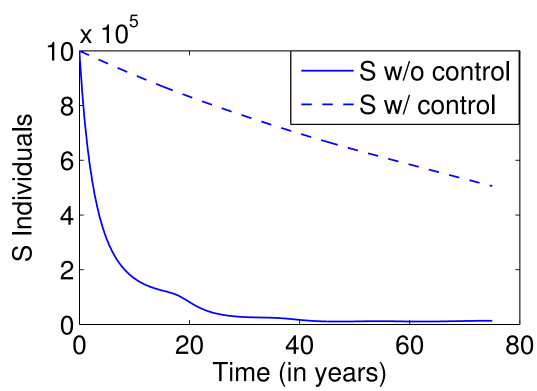


**Figure 2.9:** Susceptible Individuals in the Presence/Absence of Control.

In the absence of control, and at the population level, increasing the initial number of infectious individuals within an initial age distribution from $i(\tau,0) = 100\sin(\frac{\pi\tau}{25})$ to $i(\tau,0) = 500\sin(\frac{\pi\tau}{25})$, results in an oscillatory increase/decrease in the number of infectious individuals, sandwiched by an acute phase in prevalence. In the presence of control, and at the population level, there is a delay in prevalence, followed by an acute phase, but with lower severity and no oscillations. These results are represented in Figure 2.10.

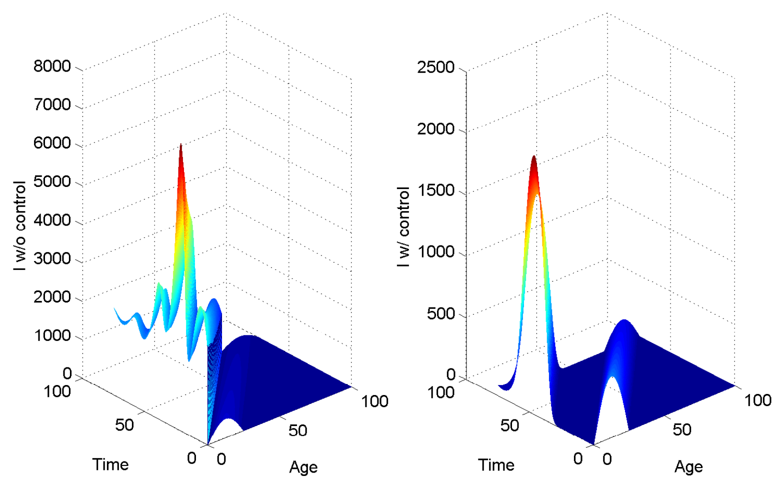


**Figure 2.10:** Infectious Individuals in the Presence/Absence of Control with Initial Age Distribution $i(\tau,0) = 500\sin(\frac{\pi\tau}{25})$.

Due to an increase in the number of infectious individuals at time $t = 0$, trajectories suggest more healthy cells in the population during the first fifty days as shown in Figure 2.11, as opposed to more healthycells within the first eighty days when fewer infectious cases were introduced as shown in Figure 2.4. The acute phase of virion production is delayed until fifty days since start-of-infection and with lower severity. The delay in virion production results in a corresponding delay in the growth rate of infectious cells as delineated in Figure 2.11. The optimal treatment strategies suggest a maximal treatment level in transmission and virion production suppressing drug efforts within the first fifty days, followed by a low virion production suppressing drug effort afterwards and a high transmission suppressing drug effort close to 100 days.

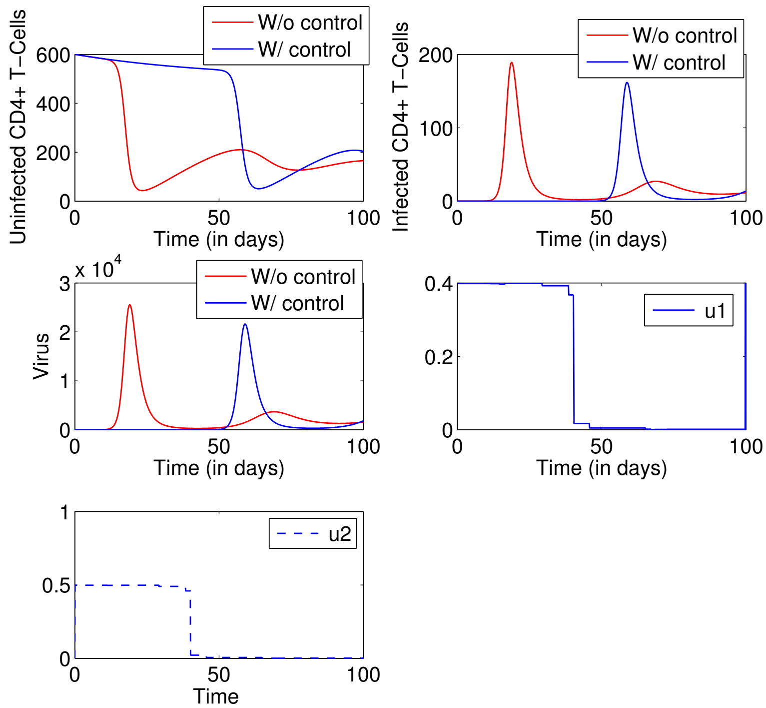


**Figure 2.11:** Healthy Cells, Infected Cells and Free Virius Populations in the Presence/Absence of Control when $B_1 = 1$ and $B_2 = 1$.

Starting with fewer infectious individuals at time $t = 0$, our numerical results suggest that at the within-host level, the acute phase of infection observed within $2-4$ weeks occurs with lower severity, followed by a latent phase between $4-10$ weeks. During week 11, the virus proliferates, with a less severe effect relative to the population of free virus in the absence of control. Moreover, when transmission and virion production suppressing drugs are administered, the susceptible population experiences an increase while the infectious population experiences a significant decrease in prevalence. With a higher number of individuals at time $t = 0$, our numerical results suggest a maximal treatment effort initially, resulting in a delay in the acute phase of virion production.

## 2.6 Conclusions

We formulated, in a careful way, a within-host model linked with an epidemiological model through a structural variable and coefficients. Existence and uniqueness results of the epidemiological model are established. Then we derived an explicit expression for the basic reproduction number of the epidemiological model, using the next generation method and examined conditions for existence of an endemic equilibrium. We showed that the disease-free equilibrium is locally asymptotically when $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$. Also, when $\mathcal{R}_0 < 1$, the disease-free equilibrium is globally stable. If $\mathcal{R}_0 > 1$, we showed that there exists an endemic equilibrium which is locally asymptotically stable when the maximal age of infection, $A$, is large enough. We constructed a solution space for our problem, and using a representation formula for the solution to our problem, we constructed an iterative sequence which was used to prove existence and uniqueness of solution to our problem. A key tool in obtaining these results is the Banach Fixed Point Theorem.

We formulated an optimal control problem which aims at minimizing infectious individuals, free virus and the cost of implementing the control. In order to curtail the proliferation of the virus at the within-host level, we incorporated transmission and virion production suppressing drugs into the within-host model. We establish a Lipschitz property for the within-host and between-host state solutions in terms of functions representing transmission and virion production suppressing drugs, which was used to establish the existence of sensitivities. The sensitivity equations were used in deriving an adjoint system. We obtained an optimal control characterization for the control pair and established the existence of optimal control using Ekeland's Principle. Using a minimizing sequence obtained via Ekeland's Principle, we proved uniqueness of our optimal control pairs.

A semi-implicit finite-difference scheme for our optimality system was implemented within a forward-backward sweep numerical method. In the absence of control in the population, numerical simulations indicate a decrease in the number of healthy

$CD4^+$ cells, and an increase in the number of infected cells and free virus within the first few days of infection at the within-host level. At the between-host level, there is a sustained decrease in the number of susceptible individuals and an oscillatory increase in the number of infectious cases. In the presence of transmission and virion production suppressing drugs, more healthy cells were observed with fewer infected cells and free virus at the within-host level. Also, fewer infectious cases were observed with a significant increase in the population of susceptible humans in the presence of transmission and virion production suppressing drugs. Investigation of numerical results when varying other parameters should be considered in the future.

We developed novel optimal control results for our linked system. Our analysis and control techniques give a new tool for investigating immuno-epidemiological models for other diseases. A paper with the results from this chapter has been accepted in the journal of *Mathematical Modelling of Natural Phenomena.* This work was done in collaboration with Drs. Souvik Bhattacharya, Maia Martcheva and Suzanne Lenhart.

# Chapter 3

# Optimal Control in Multi-group Coupled Within-host and Between-host Models

## 3.1 Introduction

In our multi-group within-host and between-host model of infectious diseases, we assume that all individuals in the population exhibit different immunological dynamics upon infection. Since individuals with stronger immune systems respond better to treatment in the case of antiretroviral therapy for the human immunodeficiency virus (HIV), and the optimum viral load required for shedding depends on the strength of the cytotoxic T lymphocyte (CTL) response of the particular host, we focus only on two classes of individuals with different immunological characteristics and viral load. Thus, the within-host dynamics of pathogen for each individual of group $j$ is

$$\frac{dx_j}{d\tau} = r - \beta_j v_j(\tau) x_j(\tau) - \mu x_j(\tau), \quad x_j(0) = x_j^0 \tag{3.1}$$

$$\frac{dy_j}{d\tau} = \beta_j v_j(\tau) x_j(\tau) - d_j y_j(\tau), \quad y_j(0) = y_j^0, \quad j = 1, 2 \tag{3.2}$$

$$\frac{dv_j}{d\tau} = \gamma_j d_j y_j(\tau) - (\delta_j + s_j) v_j(\tau) - \hat{\beta}_j v_j(\tau) x_j(\tau), \quad v_j(0) = v_j^0, \tag{3.3}$$

where $j = 1, 2$ defines the two classes of individuals with different immunological characteristics and viral load. In the model, $x_j$ defines the number of healthy cells in the $jth$ immunological class which is being produced at a constant rate $r$ and die at rate $\mu$. The growth and death rates of healthy cells are assumed to be the same for all individuals in all immunological classes. These healthy cells come in contact with free virus $v_j$ at rate $\beta_j$ and become infected cells $y_j$, with $\hat{\beta}_j$ being the binding rate of the virus to healthy cells. The infected cells in the $jth$ group die at rate $d_j$ and each produce $\gamma_j$ virions at bursting. The clearance and shedding rates of the virus are $\delta_j$ and $s_j$, respectively.

The epidemiological model is divided into two classes; individuals in each epidemiological class exhibits different immunological characteristics. We denote the number susceptible individuals at time $t$ by $S(t)$, and the density of infected individual structured by chronological time $t$ and age-since-infection $\tau$ by $i_j(\tau, t)$, where $j = 1, 2$. Individuals in each group exhibit the same immunological characteristics, but individuals in different groups exhibit different immunological characteristics and viral load. Our multi-group epidemiological (or between-host) model is:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \frac{S}{N}\sum_{j=1}^{2}\int_0^A c_j s_j v_j(\tau) i_j(\tau,t)d\tau - m_0 S \quad in \quad (0,T) && (3.4)\\
\frac{\partial i_1}{\partial t} + \frac{\partial i_1}{\partial \tau} &= -m(v_1(\tau)) i_1(\tau,t) \quad in \quad (0,A)\times(0,T) && (3.5)\\
i_1(0,t) &= p_1\frac{S}{N}\int_0^A c_1 s_1 v_1(\tau) i_1(\tau,t)d\tau + p_1\frac{S}{N}\int_0^A c_2 s_2 v_2(\tau) i_2(\tau,t)d\tau && (3.6)\\
\frac{\partial i_2}{\partial t} + \frac{\partial i_2}{\partial \tau} &= -m(v_2(\tau)) i_2(\tau,t) \quad in \quad (0,A)\times(0,T) && (3.7)\\
i_2(0,t) &= p_2\frac{S}{N}\int_0^A c_1 s_1 v_1(\tau) i_1(\tau,t)d\tau + p_2\frac{S}{N}\int_0^A c_2 s_2 v_2(\tau) i_2(\tau,t)d\tau && (3.8)\\
i_1(\tau,0) &= i_1^0(\tau), \quad i_2(\tau,0) = i_2^0(\tau) \quad in \quad (0,A)\times\{t=0\}. && (3.9)
\end{aligned}$$

In the epidemiological model, $m(v_j(\tau))$ is the death rate of infected hosts (a function of viral load) in the $jth$ class, $\Lambda$ is the recruitment rate of susceptible individuals, $m_0 = m(0)$ is the death rate of susceptible individuals and $p_j$ is the probability that an individual who is infected has immunological behavior similar to individuals in the $jth$ class. The transmission rate is assumed to be proportional to the viral load of infected individuals in the $jth$ group, calculated by integrating with respect to $\tau$, $\int_0^A (c_1 s_1 v_1(\tau) i_1(\tau,t) + c_2 s_2 v_2(\tau) i_2(\tau,t)) d\tau$, where $c_j$ is the contact rate between susceptible and infected individuals. Thus, the new infectious process of the population in group $j$ at time $t$, denoted by $i_j(0,t)$, depends on the age distribution of the population at time $t$, as determined by the integral of $i_j(\tau,t)$ over all ages, weighted with the specific transmission rate $\tilde{\beta}_j(\tau) = c_j s_j v_j(\tau)$. The number of susceptible and infectious individuals in the population at time $t = 0$ are given by $S(0) = S_0 > 0$ and $i_j(\tau,0) = i_j^0(\tau)$, respectively. Thus, $i_j(\tau,0)$ is the initial age distribution of infectious individuals in group $j$, with $i_j^0$ being a known nonnegative function of age-since-infection, $\tau$. The total population of infectious individuals from birth to maximal age-since-infection, $A$, is defined as

$$I(t) = \int_0^A i_1(\tau,t)d\tau + \int_0^A i_2(\tau,t)d\tau,$$

and the total population size of individuals in the population is $N(t) = S(t) + I(t)$. For the sake of introduction to our method, we assume the simplest form for the mortality function [22], $m(v_j)$, as

$$m(v_j(\tau)) = m_0 + \mu_j v_j(\tau),$$

so that in the absence of the virus, individuals die naturally at rate $m_0$. The term $\mu_j v_j(\tau)$ gives the additional host mortality in group $j$ due to the virus.

The the remainder of this section is arranged as follows: In section 3.2, we establish well-posedness of solution to the epidemiological model, and investigate stability of equilibrium points of the epidemiological model. In section 3.3, we formulate an optimal control problem and investigate existence, characterization and uniqueness results. Numerical simulations based on the semi-implicit finite difference schemes and the forward-backward sweep iterative method will be studied in section 3.4.

## 3.2 Existence of Solution, Equilibria and Stability Analysis of the Epidemiological Model

### 3.2.1 Existence of Solution

Integrating the differential equations (3.5) and (3.7) along the characteristic line $\tau - t = constant$ and considering cases where $\tau > t$ and $\tau < t$, we obtain the following representation formula for the solution to the epidemiological model:

$$\begin{aligned} S(t) &= S_0 e^{-(m_0+\tilde{\alpha})t} + \frac{\Lambda}{m_0+\tilde{\alpha}}(1 - e^{-(m_0+\tilde{\alpha})t}) \\ &\quad + \int_0^t e^{-(m_0+\tilde{\alpha})(t-s)} S(s) \left( \tilde{\alpha} - \frac{1}{N(s)} \sum_{j=1}^{2} \int_0^A c_j s_j v_j(\tau) i_j(\tau, s) d\tau \right) ds \end{aligned} \tag{3.10}$$

$$i_1(\tau,t) = \begin{cases} p_1 \frac{S(t-\tau)}{N(t-\tau)} e^{-\int_0^\tau m(v_1(s))ds} \sum_{j=1}^{2} \int_0^A c_j s_j v_j(s) i_j(s, t-\tau) ds, & \tau < t \\ i_1^0(\tau - t) e^{-\int_0^t m(v_1(\tau - t + s))ds}, & \tau > t \end{cases} \tag{3.11}$$

$$i_2(\tau,t) = \begin{cases} p_2 \frac{S(t-\tau)}{N(t-\tau)} e^{-\int_0^\tau m(V_2(s))ds} \sum_{j=1}^{2} \int_0^A c_j s_j v_j(s) i_j(s, t-\tau) ds, & \tau < t \\ i_2^0(\tau - t) e^{-\int_0^t m(v_2(\tau - t + s))ds}, & \tau > t. \end{cases} \tag{3.12}$$

where $S(t)$ in (3.10) is a representation formula for the solution to the differential equation

$$\frac{dS}{dt} + \tilde{\alpha} S(t) = \Lambda + \tilde{\alpha} S(t) - \frac{S(t)}{N(t)} \sum_{j=1}^{2} \int_0^A c_j s_j v_j(\tau) i_j(\tau, t) d\tau - m_0 S(t),$$

with $\tilde{\alpha} \geq C(c_1 s_1 + c_2 s_2) > 0$. This differential equation is equivalent to equation (3.4) and $C$ is a bound for $v_j$.

To prove the existence and uniqueness of solution, we define our state solution space as

$$X = \{(S, i_1, i_2) \in L^\infty(0,T) \times (L^\infty(0,T; L^1(0,A)))^2 | S(t) \geq \varepsilon > 0,\ i_1(\tau,t) \geq 0,$$
$$i_2(\tau,t) \geq 0,\ \sup_t S(t) < \infty,\ \sup_t \int_0^A i_1(\tau,t)d\tau < \infty \text{ and } \sup_t \int_0^A i_2(\tau,t)d\tau < \infty\ a.e.\ t\},$$

where $L^\infty(0,A)$ is the space of all essentially bounded functions on $(0,A)$, and $\varepsilon = \min\left\{S_0, \frac{\Lambda}{m_0+\tilde{\alpha}}\right\}$. We define a map

$$\mathcal{L} : X \to X, \quad \mathcal{L}(S, i_1, i_2) = (L_1(S, i_1, i_2), L_2(S, i_1, i_2), L_3(S, i_1, i_2)),$$

where

$$\begin{aligned} L_1(S,i)(t) &= S_0 e^{(m_0+\tilde{\alpha})t} + \frac{\Lambda}{m_0+\tilde{\alpha}}(1 - e^{-(m_0+\tilde{\alpha})t}) \\ &\quad + \int_0^t e^{-(m_0+\tilde{\alpha})(t-s)} S(s) \left( \tilde{\alpha} - \frac{1}{N(s)} \sum_{j=1}^2 \int_0^A c_j s_j v_j(\tau) i_j(\tau,s) d\tau \right) ds \end{aligned} \tag{3.13}$$

$$L_2(S,i)(\tau,t) = \begin{cases} p_1 \frac{S(t-\tau)}{N(t-\tau)} e^{-\int_0^\tau m(v_1(s))ds} \sum_{j=1}^2 \int_0^A c_j s_j v_j(s) i_j(s, t-\tau) ds, & \tau < t \\ i_1^0(\tau - t) e^{-\int_0^t m(v_1(\tau - t + s))ds}, & \tau > t \end{cases} \tag{3.14}$$

$$L_3(S,i)(\tau,t) = \begin{cases} p_2 \frac{S(t-\tau)}{N(t-\tau)} e^{-\int_0^\tau m(v_2(s))ds} \sum_{j=1}^2 \int_0^A c_j s_j v_j(s) i_j(s, t-\tau) ds, & \tau < t \\ i_2^0(\tau - t) e^{-\int_0^t m(v_2(\tau - t + s))ds}, & \tau > t. \end{cases} \tag{3.15}$$

The following assumptions will be useful in establishing a Lipschitz property for the within-host and between-host state solutions in terms of control functions:

- $S_0$, $m_0$, $\Lambda$, $c_j$ and $s_j$ are positive constants,
- $m(s)$ is non-negative and Lipschitz continuous,
- $i_j^0(\tau)$ is non-negative for all $\tau \in (0,A)$,
- $\int_0^A i_j^0(\tau)d\tau \leq M$ and $0 < S_0 \leq M$.

**Theorem 3.1.** *For $T < \infty$, there exists a unique solution $(S, i_1, i_2)$ to the epidemiological system (3.4) – (3.9).*

*Proof.* First, we show that the map $\mathcal{L}$ maps $X$ into itself. Indeed,

$$\begin{aligned}
|L_1(S,i_1,i_2)|(t) &\le |S_0 e^{-(m_0+\tilde{\alpha})t} + \frac{\Lambda}{m_0+\tilde{\alpha}}(1-e^{-(m_0+\tilde{\alpha})t})| \\
&\quad + \left| \int_0^t e^{-(m_0+\tilde{\alpha})(t-s)} S(s) \left( \tilde{\alpha} - \frac{1}{N(s)} \sum_{j=1}^{2} \int_0^A c_j s_j v_j(\tau) i_j(\tau,s) d\tau \right) ds \right| \\
&\le S_0 + \frac{\Lambda}{m_0+\tilde{\alpha}}(1-e^{-(m_0+\tilde{\alpha})t}) + \frac{\tilde{\alpha}}{m_0+\tilde{\alpha}} \sup_s S(s)(1-e^{-(m_0+\tilde{\alpha})t}) \\
&\quad + \frac{C}{m_0+\tilde{\alpha}} \sum_{j=1}^{2} c_j s_j \left( \sup_s \int_0^A i_j(\tau,s) d\tau \right) \\
&\le M + \frac{\Lambda}{m_0+\tilde{\alpha}}(1-e^{-(m_0+\tilde{\alpha})T}) + \frac{\tilde{\alpha}}{m_0+\tilde{\alpha}} \sup_s S(s) \\
&\quad + \frac{K_1}{m_0+\tilde{\alpha}} \sum_{j=1}^{2} \sup_s \int_0^A i_j(\tau,s) d\tau < \infty,
\end{aligned}$$

where $K_1$ depends on the contact rate between susceptible and infectious individuals, shedding rate of free virus and the bound on the population of free virus. Next, we estimate the second component.

$$\begin{aligned}
\int_0^A |L_2(S,i_1,i_2)|(\tau,t) d\tau &= \int_0^t |L_2(S,i_1,i_2)|(\tau,t) d\tau + \int_t^A |L_2(S,i_1,i_2)|(\tau,t) d\tau \\
&= \int_0^t \left| p_1 \frac{S(t-\tau)}{N(t-\tau)} e^{-\int_0^\tau m(v_1(\omega))d\omega} \sum_{j=1}^{2} \int_0^A c_j s_j v_j(r) i_j(r,t-\tau) dr \right| d\tau \\
&\quad + \int_t^A \left| i_1^0(\tau-t) e^{-\int_0^t m(v_1(\tau-t+s))ds} \right| d\tau \\
&\le p_1 \int_0^t e^{-m_0\tau} \sum_{j=1}^{2} \int_0^A c_j s_j v_j(r) i_j(r,t-\tau) dr d\tau + \int_0^A i_1^0(\tau) d\tau \\
&\le \frac{p_1 K_1}{m_0} \sum_{j=1}^{2} \left( \sup_\xi \int_0^A i_j(\hat{r},\xi) d\hat{r} \right) + M < \infty,
\end{aligned}$$

where we have used the substitution $\hat{r} = r$ and $\xi = t - \tau$. Similarly,

$$\int_0^A |L_3(S,i_1,i_2)|(\tau,t)d\tau \;\; \le \;\; \frac{p_2K_1}{m_0}\sum_{j=1}^{2}\left(\sup_{\xi}\int_0^A i_j(\hat{r},\xi)d\hat{r}\right)+M<\infty.$$

Finally, we establish the non-negativity of our solution. Indeed,

$$\begin{aligned} L_1(S,i_1,i_2)(t) &\ge S_0e^{-(m_0+\tilde{\alpha})t} \\ &\quad +\frac{\Lambda}{m_0+\tilde{\alpha}}(1-e^{-(m_0+\tilde{\alpha})t})+\int_0^t e^{-(m_0+\tilde{\alpha})(t-s)}S(s)\left(\tilde{\alpha}-C\sum_{j=1}^{2}c_js_j\right)ds \\ &\ge S_0e^{-(m_0+\tilde{\alpha})t}+\frac{\Lambda}{m_0+\tilde{\alpha}}(1-e^{-(m_0+\tilde{\alpha})t})\ge\varepsilon>0. \end{aligned}$$

Since $S(t)\ge\varepsilon>0$, $i_1(\tau,t)\ge 0$ and $i_2(\tau,t)\ge 0$, it follows that $L_2(S,i_1,i_2)(\tau,t)$ and $L_3(S,i_1,i_2)(\tau,t)$ are non-negative. Thus, $\mathcal{L}$ maps X to X ( or $\mathcal{L}$ is well-defined).

Next, we show that the operator $\mathcal{L}$ admits a unique fixed point. To do this, we define an iterative sequence [86]

$$(S^{(n+1)},i_1^{(n+1)},i_2^{(n+1)}) \;=\; (L_1(S^{(n)},i_1^{(n)},i_2^{(n)}),L_2(S^{(n)},i_1^{(n)},i_2^{(n)}),L_3(S^{(n)},i_1^{(n)},i_2^{(n)})), \tag{3.16}$$

where

$$\begin{aligned} S^{(n+1)}(t) &= S_0e^{-(m_0+\tilde{\alpha})t}+\frac{\Lambda}{m_0+\tilde{\alpha}}(1-e^{-(m_0+\tilde{\alpha})t}) \\ &\quad +\int_0^t e^{-(m_0+\tilde{\alpha})(t-s)}S^{(n)}(s)\left(\tilde{\alpha}-\frac{1}{N^{(n)}(s)}\sum_{j=1}^{2}\int_0^A c_js_jv_j(\tau)i_j^{(n)}(\tau,s)d\tau\right)ds \\ i_1^{(n+1)}(\tau,t) &= \begin{cases} p_1\frac{S^{(n)}(t-\tau)}{N^{(n)}(t-\tau)}e^{-\int_0^\tau m(v_1(s))ds}\sum_{j=1}^{2}\int_0^A c_js_jv_j(s)i_j^{(n)}(s,t-\tau)ds, & \tau<t \\ i_1^0(\tau-t)e^{-\int_0^t m(v_1(\tau-t+s))ds}, & \tau>t \end{cases} \end{aligned}$$

$$i_2^{(n+1)}(\tau,t) = \begin{cases} p_2 \frac{S^{(n)}(t-\tau)}{N^{(n)}(t-\tau)} e^{-\int_0^\tau m(v_2(s))ds} \sum_{j=1}^{2} \int_0^A c_j s_j v_j(s) i_j^{(n)}(s,t-\tau)ds, & \tau < t \\ i_2^0(\tau - t) e^{-\int_0^t m(v_2(\tau-t+s))ds}, & \tau > t. \end{cases}$$

We set $S^{(0)}(t) = 0$, $i_1^{(0)}(\tau,t) = 0$, $i_2^{(0)}(\tau,t) = 0$, and

$$\begin{aligned} S^{(1)}(t) &= S_0 e^{-(m_0+\tilde{\alpha})t} + \frac{\Lambda}{m_0+\alpha}(1 - e^{-(m_0+\tilde{\alpha})t}) \\ i_1^{(1)}(\tau,t) &= \begin{cases} 0, & \tau < t \\ i_1^0(\tau - t)e^{-\int_0^t m(v_1(\tau-t+s))ds}, & \tau > t, \end{cases} \\ i_2^{(1)}(\tau,t) &= \begin{cases} 0, & \tau < t \\ i_2^0(\tau - t)e^{-\int_0^t m(v_2(\tau-t+s))ds}, & \tau > t, \end{cases} \end{aligned}$$

and define a sequence for the total population as

$$N^{(n)}(t) = S^{(n)}(t) + \int_0^A i_1^{(n)}(\tau,t)d\tau + \int_0^A i_2^{(n)}(\tau,t)d\tau.$$

To show that the sequence of functions $\{(S^{(n)}(t), i_1^{(n)}(\tau,t), i_2^{(n)}(\tau,t))\}$ converges for all $n \geq 0$, we introduce the notation

$$\mathbb{F}_n(t) = |S^{(n+1)}(t) - S^{(n)}(t)| \tag{3.17}$$

$$\mathbb{I}_n(t) = \int_0^A |i_1^{(n+1)}(\tau,t) - i_1^{(n)}(\tau,t)|d\tau \tag{3.18}$$

$$\mathbb{J}_n(t) = \int_0^A |i_2^{(n+1)}(\tau,t) - i_2^{(n)}(\tau,t)|d\tau, \tag{3.19}$$

so that $\mathbb{N}_n(t) = \mathbb{F}_n(t) + \mathbb{I}_n(t) + \mathbb{J}_n(t)$. Now,

$$\mathbb{F}_0 = S_0 e^{-(m_0+\tilde{\alpha})t} + \frac{\Lambda}{m_0+\tilde{\alpha}}(1 - e^{-(m_0+\tilde{\alpha})t}) \leq \max\left\{S_0, \frac{\Lambda}{m_0+\tilde{\alpha}}\right\},$$

$\mathbb{I}_0 = \int_0^A i_1^0(\tau)d\tau$ and $\mathbb{J}_0 = \int_0^A i_2^0(\tau)d\tau$, so that

$$\mathbb{N}_0 = \max\left\{S_0, \frac{\Lambda}{m_0+\tilde{\alpha}}\right\} + \int_0^A i_1^0(\tau)d\tau + \int_0^A i_2^0(\tau)d\tau.$$

Next, for $n = 1$, we get

$$\begin{aligned}
\mathbb{F}_1(t) &= \left|\int_0^t e^{-(m_0+\tilde{\alpha})(t-s)} S^{(1)}(s)\left(\tilde{\alpha} - \frac{1}{N^{(1)}(s)}\sum_{j=1}^{2}\int_0^A c_j s_j v_j(\tau) i_j^{(1)}(\tau,s)d\tau\right)ds\right| \\
&\leq \max\left\{S_0, \frac{\Lambda}{m_0+\tilde{\alpha}}\right\}\frac{\tilde{\alpha}+C(c_1s_1+c_2s_2)}{\tilde{\alpha}+m_0}. \qquad (3.20)
\end{aligned}$$

Next

$$\begin{aligned}
\mathbb{I}_1(t) &= \int_0^A |i_1^{(2)}(\tau,t) - i_1^{(1)}(\tau,t)|d\tau \\
&= \int_0^t \frac{S^{(1)}(t-\tau)}{N^{(1)}(t-\tau)} e^{-\int_0^\tau m(v_1(s))ds}\sum_{j=1}^{2}\int_t^A c_j s_j v_j(s) i_j^0(s+\tau-t)\frac{\pi_1(\tau)}{\pi_1(\tau-s)}dsd\tau \\
&\leq \frac{C(c_1s_1+c_2s_2)}{m_0}\sum_{j=1}^{2}\int_0^A i_j^0(\xi)d\xi, \qquad (3.21)
\end{aligned}$$

where $\hat{\tau} = \tau$, $\xi = s+\tau-t$ and $\pi_1(\tau) = e^{-\int_0^\tau m(v_1(s))ds}$. Similarly,

$$\mathbb{J}_1(t) = \int_0^A |i_2^{(2)}(\tau,t) - i_2^{(1)}(\tau,t)|d\tau \leq \frac{C(c_1s_1+c_2s_2)}{m_0}\sum_{j=1}^{2}\int_0^A i_j^0(\xi)d\xi. \qquad (3.22)$$

Thus, combining equations (3.20), (3.21) and (3.22), we obtain $\mathbb{N}_1(t) \leq \hat{C}\mathbb{N}_0$, for all $t$, with $\hat{C} = \max\left\{\frac{\tilde{\alpha}+C(c_1s_1+c_2s_2)}{\tilde{\alpha}+m_0}, \frac{2C(c_1s_1+c_2s_2)}{m_0}\right\}$. Next, we consider the equations for $S$, $i_1$ and $i_2$, and use induction. First,

$$\begin{aligned}
\mathbb{F}_n(t) &\leq \tilde{\alpha}\int_0^t e^{-(m_0+\tilde{\alpha})(t-s)}|S^{(n)}(\xi) - S^{(n-1)}(\xi)|d\xi \\
&\quad + \int_0^t \sum_{j=1}^{2} c_j s_j \left|\int_0^A v_j(\tau)\left(\frac{S^{(n)}(\xi) i_j^{(n)}(\tau,\xi)}{N^{(n)}(\xi)} - \frac{S^{(n-1)}(\xi) i_j^{(n-1)}(\tau,\xi)}{N^{(n-1)}(\xi)}\right)d\tau\right|d\xi \\
&\leq \tilde{\alpha}\int_0^t |S^{(n)}(\xi) - S^{(n-1)}(\xi)|d\xi + C\sum_{j=1}^{2} c_j s_j \int_0^t\int_0^A |G_j(\tau,\xi)|\, d\tau d\xi, \qquad (3.23)
\end{aligned}$$

where

$$
\begin{aligned}
G_j(\tau,\xi) &\equiv \frac{S^{(n)}(\xi) i_j^{(n)}(\tau,\xi)}{N^{(n)}(\xi)} - \frac{S^{(n-1)}(\xi) i_j^{(n-1)}(\tau,\xi)}{N^{(n-1)}(\xi)} \\
&= \frac{S^{(n)}(\xi)}{N^{(n)}(\xi)} \left( i_j^{(n)}(\tau,\xi) - i_j^{(n-1)}(\tau,\xi) \right) + \frac{i_j^{(n-1)}(\tau,\xi)}{N^{(n-1)}(\xi)} \left( S^{(n)}(\xi) - S^{(n-1)}(\xi) \right) \\
&\quad + \frac{i_j^{(n-1)}(\tau,\xi)}{N^{(n-1)}(\xi)} \frac{S^{(n)}(\xi)}{N^{(n)}(\xi)} \left( S^{(n-1)}(\xi) - S^{(n)}(\xi) \right) \\
&\quad + \frac{i_j^{(n-1)}(\tau,\xi)}{N^{(n-1)}(\xi)} \frac{S^{(n)}(\xi)}{N^{(n)}(\xi)} \sum_{\ell=1}^{2} \int_0^A (i_\ell^{(n-1)}(\sigma,\xi) - i_\ell^{(n)}(\sigma,\xi)) d\sigma.
\end{aligned} \tag{3.24}
$$

Since $0 < v_j(\tau) \leq C$, inequality (3.23) gives

$$
\begin{aligned}
|S^{(n+1)}(t) - S^{(n)}(t)| &\leq \left( \tilde{\alpha} + 2C \sum_{j=1}^{2} c_j s_j \right) \int_0^t |S^{(n)}(\xi) - S^{(n-1)}(\xi)| d\xi \\
&\quad + C \sum_{j=1}^{2} c_j s_j \int_0^t \int_0^A |i_j^{(n)}(\tau,\xi) - i_j^{(n-1)}(\tau,\xi)| d\tau d\xi \\
&\quad + C \sum_{j=1}^{2} c_j s_j \int_0^t \sum_{\ell=1}^{2} \int_0^A |i_\ell^{(n)}(\sigma,\xi) - i_\ell^{(n-1)}(\sigma,\xi)| d\sigma d\xi \\
&\leq \hat{C}_1 \int_0^t \mathbb{F}_{n-1}(\xi) d\xi + \hat{C}_2 \int_0^t \mathbb{I}_{n-1}(\xi) d\xi + \hat{C}_3 \int_0^t \mathbb{J}_{n-1}(\xi) d\xi,
\end{aligned}
$$

where $\hat{C}_1$, $\hat{C}_2$, $\hat{C}_3$ depend on the contact rate between susceptible and infectious individuals, and shedding rate of free virus. Thus,

$$
\mathbb{F}_n(t) \leq C_1 \int_0^t (\mathbb{F}_{n-1}(\xi) + \mathbb{I}_{n-1}(\xi) + \mathbb{J}_{n-1}(\xi)) d\xi, \tag{3.25}
$$

where $C_1 = \max\{\hat{C}_1, \hat{C}_2, \hat{C}_3\}$. Next, we consider the second component.

$$
\mathbb{I}_n(t) = \int_0^A |i_1^{(n+1)}(\tau,t) - i_1^{(n)}(\tau,t)| d\tau
$$

$$
\begin{aligned}
&\leq \; p_1 \int_0^t \sum_{j=1}^{2} c_j s_j \int_0^A v_j(\xi) \left| \frac{S^{(n)}(t-\tau) i_j^{(n)}(\xi, t-\tau)}{N^{(n)}(t-\tau)} - \frac{S^{(n-1)}(t-\tau) i_j^{(n-1)}(\xi, t-\tau)}{N^{(n-1)}(t-\tau)} \right| d\xi d\tau \\
&\leq \; \hat{C}_1 p_1 \int_0^t \mathbb{F}_{n-1}(t-\tau) d\tau + \hat{C}_2 p_1 \int_0^t \mathbb{I}_{n-1}(t-\tau) d\tau + \hat{C}_3 p_1 \int_0^t \mathbb{J}_{n-1}(t-\tau) d\tau \\
&= \; \hat{C}_1 p_1 \int_0^t \mathbb{F}_{n-1}(\xi) d\xi + \hat{C}_2 p_1 \int_0^t \mathbb{I}_{n-1}(\xi) d\xi + \hat{C}_3 p_1 \int_0^t \mathbb{J}_{n-1}(\xi) d\xi,
\end{aligned}
$$

where we have mimicked equations (3.23), (3.24) and (3.25), and used the substitution $\xi = t - \tau$. Thus,

$$
\mathbb{I}_n(t) \leq C_2 \int_0^t (\mathbb{F}_{n-1}(\xi) + \mathbb{I}_{n-1}(\xi) + \mathbb{J}_{n-1}(\xi)) d\xi, \tag{3.26}
$$

where $C_2 = p_1 C_1$. Similarly,

$$
\mathbb{J}_n(t) \leq C_3 \int_0^t (\mathbb{F}_{n-1}(\xi) + \mathbb{I}_{n-1}(\xi) + \mathbb{J}_{n-1}(\xi)) d\xi. \tag{3.27}
$$

Since $\mathbb{N}_n(t) = \mathbb{F}_n(t) + \mathbb{I}_n(t) + \mathbb{J}_n(t)$, combining inequalities (3.25), (3.26) and (3.27), we see that $\mathbb{N}_n(t)$ satisfies the recurrence relation

$$
\mathbb{N}_n(t) \leq K \int_0^t \mathbb{N}_{n-1}(\xi) d\xi, \quad \textit{with} \quad \mathbb{N}_1(t) \leq \hat{C} \mathbb{N}_0,
$$

where $K = C_1 + C_2 + C_3$. Notice that

$$
\mathbb{N}_2(t) \leq K \int_0^t \mathbb{N}_1(\xi) d\xi \leq \hat{C} \mathbb{N}_0 K t
$$

and

$$
\mathbb{N}_3(t) \leq K \int_0^t K \hat{C} \mathbb{N}_0 \xi d\xi = \hat{C} N_0 \frac{K^2 t^2}{2}.
$$

Thus, by induction, it follows that

$$
\mathbb{N}_n(t) \leq \hat{C} \mathbb{N}_0 \frac{K^{n-1} t^{n-1}}{(n-1)!} \leq \hat{C} \mathbb{N}_0 \frac{K^{n-1} T^{n-1}}{(n-1)!}.
$$

Now, the remainder term of the sequence $\{S^{(n)}(t)\}$ is

$$|S^{(n+m)}(t) - S^{(n)}(t)| \leq \sum_{j=n+1}^{n+m} \mathbb{N}_j(t) \leq \hat{C}\mathbb{N}_0 \sum_{j=n+1}^{\infty} \frac{K^{j-1}T^{j-1}}{(j-1)!} \to 0, \quad as \quad n \to \infty.$$

Also, using the notation in ( 3.18) and definition of $\mathbb{N}_n(t)$, we have

$$\begin{aligned}\int_0^A |i_1^{(n+m)}(\tau,t) - i_1^{(n)}(\tau,t)|d\tau &\leq \sum_{j=n+1}^{n+m} \int_0^A |i_1^{(j)}(\tau,t) - i_1^{(j-1)}(\tau,t)|d\tau \\ &\leq \sum_{j=n+1}^{n+m} \mathbb{N}_j(t) \\ &\leq \hat{C}\mathbb{N}_0 \sum_{j=n+1}^{\infty} \frac{K^{j-1}T^{j-1}}{(j-1)!} \to 0 \quad as \quad n \to \infty.\end{aligned}$$

Similar result holds for the sequence $\{i_2^{(n)}(\tau,t)\}$. Thus, the sequence $\{(S^{(n)}(t), i_1^{(n)}(\tau,t), i_2^{(n)}(\tau,t))\}$ generated by the iterative sequence (3.16) is a Cauchy sequence in $X$, and is therefore convergent, since $X$ is complete. Thus, there exists $(S(t), i_1(\tau,t), i_2(\tau,t))$ in $X$ which is the limit of the given sequence. Thus, from the iterative sequence (3.16) and definition of the operator $\mathcal{L}$,

$$\mathcal{L}(S(t), i_1(\tau,t), i_2(\tau,t)) = (S(t), i_1(\tau,t), i_2(\tau,t)),$$

so that the limit $(S(t), i_1(\tau,t), i_2(\tau,t))$ is a fixed point of the operator $\mathcal{L}$. This establishes the existence of solution to the epidemiological model for all $T < \infty$.

We assume the existence of two solutions $(S(t), i_1(\tau,t), i_2(\tau,t))$ and $(\bar{S}(t), \bar{i}_1(\tau,t), \bar{i}_2(\tau,t))$ for which

$$(S, i_1, i_2) = (L_1(S, i_1, i_2), L_2(S, i_1, i_2), L_3(S, i_1, i_2)$$

and

$$(\bar{S}, \bar{i}_1, \bar{i}_2) = (L_1(\bar{S}, \bar{i}_1, \bar{i}_2), L_2(\bar{S}, \bar{i}_1, \bar{i}_2), L_3(\bar{S}, \bar{i}_1, \bar{i}_2).$$

We substitute $(S(t), i_1(\tau,t), i_2(\tau,t))$ and $(\bar{S}(t), \bar{i}_1(\tau,t), \bar{i}_2(\tau,t))$ in place of

$(S^{(n)}(t), i_1^{(n)}(\tau,t), i_2^{(n)}(\tau,t))$ and $(S^{(n-1)}(t), i_1^{(n-1)}(\tau,t), i_2^{(n-1)}(\tau,t))$, respectively, in the proof of existence of solution above, and set

$$\hat{\mathbb{F}}(t) = |S(t) - \bar{S}(t)|, \quad \hat{\mathbb{I}}(t) = \int_0^A |i_1(\tau,t) - \bar{i}_1(\tau,t)| d\tau \text{ and } \hat{\mathbb{J}}(t) = \int_0^A |i_2(\tau,t) - \bar{i}_2(\tau,t)| d\tau.$$

This gives $\hat{\mathbb{N}}(t) \leq K \int_0^t \hat{\mathbb{N}}(\xi) d\xi$, so that by Gronwall's lemma in integral form, $\hat{\mathbb{N}}(t) \equiv 0$. Thus, $\hat{\mathbb{F}}(t) + \hat{\mathbb{I}}(t) + \hat{\mathbb{J}}(t) = 0, \quad \forall t > 0$. Since $\hat{\mathbb{F}}(t) \geq 0$, $\hat{\mathbb{I}}(t) \geq 0$ and $\hat{\mathbb{J}}(t) \geq 0$, with $\hat{\mathbb{F}}(t) + \hat{\mathbb{I}}(t) + \hat{\mathbb{J}}(t) = 0$, it follows that $\hat{\mathbb{F}}(t) = \hat{\mathbb{I}}(t) = \hat{\mathbb{J}}(t) = 0$, for all $t > 0$. Hence, the solution to the epidemiological model is unique. □

### 3.2.2 Basic Reproduction Number and Equilibria

Analogous to the single population model [92], we derive the basic reproduction number for our model. In deriving the basic reproduction number, $\mathcal{R}_0$, we compute the disease-free equilibrium, linearize the system around the disease-free equilibrium and determine conditions for its stability. Now, we consider solutions near the disease-free equilibrium $(S^*, i_1^*(\tau), i_2^*(\tau)) = (\frac{\Lambda}{m_0}, 0, 0)$ by setting

$$x(t) = S(t) - S^*, y_1(\tau,t) = i_1(\tau,t), \text{ and } \quad y_2(\tau,t) = i_2(\tau,t).$$

Substituting the perturbed solutions into equations (3.4) – (3.9), we obtain the following linearized system:

$$\frac{dx}{dt} = -\sum_{j=1}^{2} \int_0^A c_j s_j v_j(\tau) y_j(\tau,t) d\tau - m_0 x(t) \tag{3.28}$$

$$\frac{\partial y_1}{\partial t} + \frac{\partial y_1}{\partial \tau} = -m(v_1(\tau)) y_1(\tau,t) \tag{3.29}$$

$$y_1(0,t) = p_1 \left( \int_0^A c_1 s_1 v_1(\tau) y_1(\tau,t) d\tau + \int_0^A c_2 s_2 v_2(\tau) y_2(\tau,t) d\tau \right) \tag{3.30}$$

$$\frac{\partial y_2}{\partial t} + \frac{\partial y_2}{\partial \tau} = -m(v_2(\tau)) y_2(\tau,t) \tag{3.31}$$

$$y_2(0,t) = p_2 \left( \int_0^A c_1 s_1 v_1(\tau) y_1(\tau,t) d\tau + \int_0^A c_2 s_2 v_2(\tau) y_2(\tau,t) d\tau \right). \tag{3.32}$$

We seek solutions to the firt-order partial differential equations (3.29) and (3.31) of the form

$$y_1(\tau,t) = \bar{y}_1(\tau)e^{\lambda t} \quad \textit{and} \quad y_2(\tau,t) = \bar{y}_2(\tau)e^{\lambda t},$$

where $\lambda$ is either a real or complex number. Substituting these solutions into equations (3.29) – (3.32), we have the following eigenvalue problem

$$\frac{d\bar{y}_1(\tau)}{d\tau} = -(\lambda + m(v_1(\tau)))\bar{y}_1(\tau) \tag{3.33}$$

$$\bar{y}_1(0) = p_1\left(\int_0^A c_1s_1v_1(\tau)\bar{y}_1(\tau)d\tau + \int_0^A c_2s_2v_2(\tau)\bar{y}_2(\tau)d\tau\right) \tag{3.34}$$

$$\frac{d\bar{y}_2(\tau)}{d\tau} = -(\lambda + m(v_2(\tau)))\bar{y}_2(\tau) \tag{3.35}$$

$$\bar{y}_2(0) = p_2\left(\int_0^A c_1s_1v_1(\tau)\bar{y}_1(\tau)d\tau + \int_0^A c_2s_2v_2(\tau)\bar{y}_2(\tau)d\tau\right). \tag{3.36}$$

The solutions to equations (3.33) and (3.35) are

$$\bar{y}_1(\tau) = \bar{y}_1(0)e^{-\lambda\tau}e^{-\int_0^\tau m(v_1(s))ds} \quad \textit{and} \quad \bar{y}_2(\tau) = \bar{y}_2(0)e^{-\lambda\tau}e^{-\int_0^\tau m(v_2(s))ds},$$

so that the initial conditions (3.34) and (3.36) become

$$\begin{cases} \bar{y}_1(0) = p_1\displaystyle\sum_{j=1}^{2} c_js_j\bar{y}_j(0)\int_0^A v_j(\tau)e^{-\lambda\tau}e^{-\int_0^\tau m(v_j(s))ds}d\tau \\ \bar{y}_2(0) = p_2\displaystyle\sum_{j=1}^{2} c_js_j\bar{y}_j(0)\int_0^A v_j(\tau)e^{-\lambda\tau}e^{-\int_0^\tau m(v_j(s))ds}d\tau. \end{cases}$$

The eigenvalue problem (3.33) – (3.36) has a non-trivial solution if, and only if,

$$(p_1J_1 - 1)(p_2J_2 - 1) - p_1p_2J_1J_1 = 0,$$

where $J_\ell = c_\ell s_\ell \int_0^A v_\ell(\tau)e^{-\lambda\tau}e^{-\int_0^\tau m(v_\ell(s))ds}d\tau$. This gives

$$1 = p_1J_1 + p_2J_2 \equiv \sum_{j=1}^{2}\int_0^A p_jc_js_jv_j(\tau)e^{-\lambda\tau}e^{-\int_0^\tau m(v_j(s))ds}d\tau. \tag{3.37}$$

The right-hand side of equation (3.37) is a function of $\lambda$, which we denote by $G(\lambda)$, where

$$G(\lambda) = \sum_{j=1}^{2} \int_0^A p_j c_j s_j v_j(\tau) e^{-\lambda\tau} e^{-\int_0^\tau m(v_j(s))ds} d\tau, \tag{3.38}$$

so that $G(\lambda) = 1$ is a characteristic equation that will be used to study stability of the disease-free equilibrium. We define the basic reproduction number, $\mathcal{R}_0$, of the epidemiological (or linked) model as $\mathcal{R}_0 = G(0)$ so that

$$\mathcal{R}_0 = \sum_{j=1}^{2} \int_0^A p_j c_j s_j v_j(\tau) e^{-\int_0^\tau m(v_j(s))ds} d\tau, \tag{3.39}$$

where $\pi_j(\tau) = e^{-\int_0^\tau m(v_j(s))ds}$ is the probability of survival in the infected class of group $j$ from onset of infection to age-since-infection, $\tau$.

**Theorem 3.2.** *The epidemiological model has a unique endemic equilibrium,* $(S^*, i_1^*(\tau), i_2^*(\tau))$, *if* $\mathcal{R}_0 > 1$.

*Proof.* We set the time derivatives of the epidemiological model to zero. This gives:

$$0 = \Lambda - \frac{S}{N} \sum_{j=1}^{2} \int_0^A c_j s_j v_j(\tau) i_j(\tau) d\tau - m_0 S \tag{3.40}$$

$$\frac{di_j(\tau)}{d\tau} = -m(v_j(\tau)) i_j(\tau) \tag{3.41}$$

$$i_j(0) = p_j \frac{S}{N} \sum_{k=1}^{2} \int_0^A c_k s_k v_k(\tau) i_k(\tau) d\tau. \tag{3.42}$$

In order to derive the endemic equilibrium, we solve the differential equation (3.41) to have

$$i_j^*(\tau) = i_j^*(0) e^{-\int_0^\tau m(v_j(s))ds}. \tag{3.43}$$

Next, substituting the expression for $i_j^*(\tau)$ into equation (3.40) yields

$$0 = \Lambda - \frac{S^*}{N^*} \sum_{j=1}^{2} \int_0^A c_j s_j v_j(\tau) i_j^*(0) e^{-\int_0^\tau m(v_j(s))ds} d\tau - m_0 S^*. \tag{3.44}$$

From equations (3.42), (3.43) and (3.44), we obtain $i_j^*(0)$ as

$$i_j^*(0) = p_j(\Lambda - m_0 S^*).$$

Since the total population at equilibrium is $N^* = S^* + \int_0^A i_1^*(\tau)d\tau + \int_0^A i_2^*(\tau)d\tau$, we obtain $N^* = \Lambda\xi + (1-m_0\xi)S^*$, where $\xi = p_1 \int_0^A e^{-\int_0^\tau m(v_1(s))ds}d\tau + p_2 \int_0^A e^{-\int_0^\tau m(v_2(s))ds}d\tau$. Now, from equation (3.40), we have

$$\frac{S^*}{N^*} = \frac{i_j^*(0)}{p_j(\Lambda - m_0 S^*)\mathcal{R}_0} = \frac{1}{\mathcal{R}_0},$$

so that

$$S^* = \frac{\Lambda\xi}{\mathcal{R}_0 - 1 + m_0\xi} \quad \text{and} \quad i_j^*(\tau) = \frac{p_j\Lambda(\mathcal{R}_0 - 1)e^{-\int_0^\tau m(v_j(s))ds}}{\mathcal{R}_0 - 1 + m_0\xi}.$$

Hence, the endemic equilibrium is $(S^*, i_1^*(\tau), i_2^*(\tau))$, where

$$\begin{aligned}&(S^*, i_1^*(\tau), i_2^*(\tau))\\ &= \left(\frac{\Lambda\xi}{\mathcal{R}_0 - 1 + m_0\xi}, \frac{p_1\Lambda(\mathcal{R}_0 - 1)e^{-\int_0^\tau m(v_1(s))ds}}{\mathcal{R}_0 - 1 + m_0\xi}, \frac{p_2\Lambda(\mathcal{R}_0 - 1)e^{-\int_0^\tau m(v_2(s))ds}}{\mathcal{R}_0 - 1 + m_0\xi}\right),\end{aligned}$$

which exists if $\mathcal{R}_0 > 1$. □

### 3.2.3 Stability Analysis

To study the local stability of equilibria, we linearize the model around each of the equilibrium points, and consider an exponential solution to the linearized system.

**Theorem 3.3.** *The disease-free equilibrium is locally asymptotically stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.*

*Proof.* If $\lambda \in \mathbb{R}$, then from equation (3.38), $G'(\lambda) < 0$, since $v_j$ is non-negative and bounded. Thus, $G$ is a decreasing function of $\lambda$. Therefore, there exists a unique positive solution to the characteristic equation $G(\lambda) = 1$ when $\mathcal{R}_0 = G(0) > 1$, since $G(\lambda) \to 0$ as $\lambda \to \infty$. Hence, the disease-free equilibrium is unstable when $\mathcal{R}_0 > 1$.

When $\mathcal{R}_0 = G(0) < 1$, there exists a unique negative solution to the characteristic equation $G(\lambda) = 1$, since $G(\lambda) \to +\infty$ as $\lambda \to -\infty$. Next, we assume that $\lambda$ is complex and let $\lambda = \xi + i\eta$ be an arbitrary complex solution (if it exists) to the characteristic equation $G(\lambda) = 1$. Then

$$\begin{aligned} 1 &= |G(\xi + i\eta)| \\ &\leq \sum_{j=1}^{2} \int_0^A p_j c_j s_j v_j(\tau) e^{-\xi\tau} e^{-\int_0^\tau m(v_j(s))ds} d\tau =: G(\Re(\lambda)). \end{aligned}$$

If $\Re(\lambda) \geq 0$, then $1 \leq G(\Re(\lambda)) \leq G(0) = \mathcal{R}_0 < 1$, which is absurd. Thus, all roots of $G(\lambda) = 1$ have negative real parts when $\mathcal{R}_0 < 1$. Hence the disease-free equilibrium is locally asymptotically stable when $\mathcal{R}_0 < 1$. □

**Theorem 3.4.** *The disease-free equilibrium is globally stable if $\mathcal{R}_0 < 1$.*

*Proof.* Follows as in Numfor et al. [92, Theorem 2.5]. □

**Theorem 3.5.** *The endemic equilibrium*
$(S^*, i_1^*(\tau), i_2^*(\tau))$

$$= \left( \frac{\Lambda\xi}{\mathcal{R}_0 - 1 + m_0\xi}, \frac{p_1\Lambda(\mathcal{R}_0 - 1)e^{-\int_0^\tau m(v_1(s))ds}}{\mathcal{R}_0 - 1 + m_0\xi}, \frac{p_2\Lambda(\mathcal{R}_0 - 1)e^{-\int_0^\tau m(v_2(s))ds}}{\mathcal{R}_0 - 1 + m_0\xi} \right)$$

*is locally asymptotically stable if $\mathcal{R}_0 > 1$ and the maximal age of infection, $A$, is sufficiently small or $A$ is sufficiently large with $\frac{c_1 s_1}{\mu_1} = \frac{c_2 s_2}{\mu_2}$.*

*Proof.* We consider solutions near the endemic equilibrium by setting

$$x(t) = S(t) - S^*, \quad y_1(\tau, t) = i_1(\tau, t) - i_1^*(\tau), \quad y_2(\tau, t) = i_2(\tau, t) - i_2^*(\tau),$$

so that the total population is $N(t) = N^* + n(t)$, where

$$n(t) = x(t) + \int_0^A y_1(\tau,t)d\tau + \int_0^A y_2(\tau,t)d\tau \text{ and } N^* = S^* + \int_0^A i_1^*(\tau)d\tau + \int_0^A i_2^*(\tau)d\tau.$$

Substituting the perturbed solutions into equations (3.4) – (3.9), we have the following linearized system:

$$\begin{aligned}
\frac{dx}{dt} &= -\frac{x(t)}{N^*}\int_0^A c_1s_1v_1(\tau)i_1^*(\tau)d\tau + \frac{S^*}{N^*}\frac{n(t)}{N^*}\int_0^A c_1s_1v_1(\tau)i_1^*(\tau)d\tau \\
&\quad -\frac{x(t)}{N^*}\int_0^A c_2s_2v_2(\tau)i_2^*(\tau)d\tau + \frac{S^*}{N^*}\frac{n(t)}{N^*}\int_0^A c_2s_2v_2(\tau)i_2^*(\tau)d\tau \qquad (3.45)\\
&\quad -\frac{S^*}{N^*}\int_0^A c_1s_1v_1(\tau)y_1(\tau,t)d\tau - \frac{S^*}{N^*}\int_0^A c_2s_2v_2(\tau)y_2(\tau,t)d\tau - m_0x \\
\frac{\partial y_1}{\partial t} + \frac{\partial y_1}{\partial \tau} &= -m(v_1(\tau))y_1(\tau,t) \qquad (3.46)\\
y_1(0,t) &= \frac{p_1x(t)}{N^*}\int_0^A c_1s_1v_1(\tau)i_1^*(\tau)d\tau - \frac{p_1S^*}{N^*}\frac{n(t)}{N^*}\int_0^A c_1s_1v_1(\tau)i_1^*(\tau)d\tau \qquad (3.47)\\
&\quad +\frac{p_1S^*}{N^*}\int_0^A c_1s_1v_1(\tau)y_1(\tau,t)d\tau + \frac{p_1S^*}{N^*}\int_0^A c_2s_2v_2(\tau)y_2(\tau,t)d\tau \qquad (3.48)\\
&\quad +\frac{p_1x(t)}{N^*}\int_0^A c_2s_2v_2(\tau)i_2^*(\tau)d\tau - \frac{p_1S^*}{N^*}\frac{n(t)}{N^*}\int_0^A c_2s_2v_2(\tau)i_2^*(\tau)d\tau \\
\frac{\partial y_2}{\partial t} + \frac{\partial y_2}{\partial \tau} &= -m(v_2(\tau))y_2(\tau,t) \qquad (3.49)\\
y_2(0,t) &= \frac{p_2x}{N^*}\int_0^A c_1s_1v_1(\tau)i_1^*(\tau)d\tau - \frac{p_2S^*}{N^*}\frac{n}{N^*}\int_0^A c_1s_1v_1(\tau)i_1^*(\tau)d\tau \\
&\quad +\frac{p_2S^*}{N^*}\int_0^A c_1s_1v_1(\tau)y_1(\tau,t)d\tau + \frac{p_2S^*}{N^*}\int_0^A c_2s_2v_2(\tau)y_2(\tau,t)d\tau \qquad (3.50)\\
&\quad +\frac{p_2x(t)}{N^*}\int_0^A c_2s_2v_2(\tau)i_2^*(\tau)d\tau - \frac{p_2S^*}{N^*}\frac{n(t)}{N^*}\int_0^A c_2s_2v_2(\tau)i_2^*(\tau)d\tau.
\end{aligned}$$

Next, we seek solutions to equations (3.45) – (3.50) of the form

$$x(t) = \bar{x}e^{\lambda t}, \quad y_1(\tau,t) = \bar{y}_1(\tau)e^{\lambda t} \quad \textit{and} \quad y_2(\tau,t) = \bar{y}_2(\tau)e^{\lambda t}.$$

This gives

$$
\begin{aligned}
\lambda\bar{x} &= -\frac{\bar{x}}{N^*}\int_0^A c_1s_1v_1(\tau)i_1^*(\tau)d\tau + \frac{S^*}{N^*}\frac{\bar{n}}{N^*}\int_0^A c_1s_1v_1(\tau)i_1^*(\tau)d\tau \\
&\quad -\frac{\bar{x}}{N^*}\int_0^A c_2s_2v_2(\tau)i_2^*(\tau)d\tau + \frac{S^*}{N^*}\frac{\bar{n}}{N^*}\int_0^A c_2s_2v_2(\tau)i_2^*(\tau)d\tau \qquad (3.51)\\
&\quad -\frac{S^*}{N^*}\int_0^A c_1s_1v_1(\tau)\bar{y}_1(\tau)d\tau - \frac{S^*}{N^*}\int_0^A c_2s_2v_2(\tau)\bar{y}_2(\tau)d\tau - m_0\bar{x} \\
\frac{d\bar{y}_1(\tau)}{d\tau} &= -(\lambda + m(v_1(\tau)))\bar{y}_1(\tau) \qquad (3.52)\\
\bar{y}_1(0) &= \frac{p_1\bar{x}}{N^*}\int_0^A c_1s_1v_1(\tau)i_1^*(\tau)d\tau - \frac{p_1S^*}{N^*}\frac{\bar{n}}{N^*}\int_0^A c_1s_1v_1(\tau)i_1^*(\tau)d\tau \\
&\quad +\frac{p_1\bar{x}}{N^*}\int_0^A c_2s_2v_2(\tau)i_2^*(\tau)d\tau - \frac{p_1S^*}{N^*}\frac{\bar{n}}{N^*}\int_0^A c_2s_2v_2(\tau)i_2^*(\tau)d\tau \qquad (3.53)\\
&\quad +\frac{p_1S^*}{N^*}\int_0^A c_1s_1v_1(\tau)\bar{y}_1(\tau)d\tau + \frac{p_1S^*}{N^*}\int_0^A c_2s_2v_2(\tau)\bar{y}_2(\tau)d\tau \\
\frac{d\bar{y}_2(\tau)}{d\tau} &= -(\lambda + m(v_2(\tau)))\bar{y}_2(\tau) \qquad (3.54)\\
\bar{y}_2(0) &= \frac{p_2\bar{x}}{N^*}\int_0^A c_1s_1v_1(\tau)i_1^*(\tau)d\tau - \frac{p_2S^*}{N^*}\frac{\bar{n}}{N^*}\int_0^A c_1s_1v_1(\tau)i_1^*(\tau)d\tau \\
&\quad +\frac{p_2\bar{x}}{N^*}\int_0^A c_2s_2v_2(\tau)i_2^*(\tau)d\tau - \frac{p_2S^*}{N^*}\frac{\bar{n}}{N^*}\int_0^A c_2s_2v_2(\tau)i_2^*(\tau)d\tau \qquad (3.55)\\
&\quad +\frac{p_2S^*}{N^*}\int_0^A c_1s_1v_1(\tau)\bar{y}_1(\tau)d\tau + \frac{p_2S^*}{N^*}\int_0^A c_2s_2v_2(\tau)\bar{y}_2(\tau)d\tau,
\end{aligned}
$$

where $\bar{n} = \bar{x} + \int_0^A \bar{y}_1(\tau)d\tau + \int_0^A \bar{y}_2(\tau)d\tau$. Solving the differential equations (3.52) and (3.54), we obtain

$$
\bar{y}_1(\tau) = \bar{y}_1(0)e^{-\lambda\tau}e^{-\int_0^\tau m(v_1(s))ds} \quad and \quad \bar{y}_2(\tau) = \bar{y}_2(0)e^{-\lambda\tau}e^{-\int_0^\tau m(v_2(s))ds}.
$$

From equations (3.51), (3.53) and (3.55), $(\lambda+m_0)\bar{x} = -\frac{\bar{y}_1(0)}{p_1}$ and $(\lambda+m_0)\bar{x} = -\frac{\bar{y}_2(0)}{p_2}$, so that

$$
\bar{y}_j(0) = -p_j(\lambda + m_0)\bar{x}. \qquad (3.56)
$$

Using the definitions of $\bar{n}$, $\bar{y}_1(\tau)$, $\bar{y}_2(\tau)$, $\bar{y}_j(0)$, and setting $\alpha_j = \int_0^A c_js_jv_j(\tau)i_j^*(\tau)d\tau$, equation (3.51) becomes

$$
\begin{aligned}
(\lambda+m_0)\bar{x} &= -\frac{\bar{x}\alpha_1}{N^*}+\frac{S^*}{N^*}\frac{\alpha_1}{N^*}\left(\bar{x}+\sum_{j=1}^{2}\bar{y}_j(0)\int_0^A e^{-\lambda\tau}e^{-\int_0^\tau m(v_j(s))ds}d\tau\right)\\
&\quad -\frac{\bar{x}\alpha_2}{N^*}+\frac{S^*}{N^*}\frac{\alpha_2}{N^*}\left(\bar{x}+\sum_{j=1}^{2}\bar{y}_j(0)\int_0^A e^{-\lambda\tau}e^{-\int_0^\tau m(v_j(s))ds}d\tau\right)\\
&\quad -\frac{S^*}{N^*}\sum_{j=1}^{2}\bar{y}_j(0)\int_0^A c_js_jv_j(\tau)e^{-\lambda\tau}e^{-\int_0^\tau m(v_j(s))ds}d\tau\\
&= \frac{(\alpha_1+\alpha_2)\bar{x}}{N^*}\left(\frac{S^*}{N^*}-1\right)+(\lambda+m_0)\bar{x}\frac{S^*}{N^*}\sum_{j=1}^{2}p_j\int_0^A c_js_jv_j(\tau)e^{-\lambda\tau}\pi_j(\tau)d\tau\\
&\quad -\frac{(\alpha_1+\alpha_2)}{N^*}\frac{S^*}{N^*}(\lambda+m_0)\bar{x}\sum_{j=1}^{2}p_j\int_0^A e^{-\lambda\tau}e^{-\int_0^\tau m(v_j(s))ds}d\tau, \qquad (3.57)
\end{aligned}
$$

due to $\bar{y}_j(0)$ defined in equation (3.56). Dividing both sides of equation (3.57) by $(\lambda+m_0)\bar{x}$, and substituting $\frac{S^*}{N^*}=\frac{1}{\mathcal{R}_0}$, we obtain the following characteristic equation

$$
1=\frac{\alpha_1+\alpha_2}{N^*\mathcal{R}_0}\left(\frac{1-\mathcal{R}_0}{\lambda+m_0}-\sum_{j=1}^{2}p_j\Gamma_j(\lambda)\right)+\frac{1}{\mathcal{R}_0}\sum_{j=1}^{2}p_j\int_0^A c_js_jv_j(\tau)e^{-\lambda\tau}\pi_j(\tau)d\tau, \quad (3.58)
$$

where

$$
\Gamma_j(\lambda)=\int_0^A e^{-\lambda\tau}\pi_j(\tau)d\tau \quad \text{and} \quad \pi_j(\tau)=e^{-\int_0^\tau m(v_j(s))ds}.
$$

**Case 1 (Small A):** If $\lambda=\theta$ is a non-negative real solution of the characteristic equation (3.58), then from the expression for the basic reproduction number in (3.39), the second term on the right-hand side of equation (3.58) is less than or equal to one and

$$
\frac{\alpha_1+\alpha_2}{N^*\mathcal{R}_0}\left(\frac{1-\mathcal{R}_0}{\theta+m_0}-\sum_{j=1}^{2}p_j\Gamma_j(\theta)\right)\geq 0,
$$

which is untenable, since $\mathcal{R}_0>1$, $\Gamma_j(\theta)>0$ and $N^*>0$. Thus, $\lambda$ is real and negative. Next, let $\lambda=a+ib$ be an arbitrary complex solution (if it exists) of equation (3.58). Since complex solutions exists in conjugate pairs, we assume $b>0$, so that

$$1 = \frac{\alpha_1+\alpha_2}{N^*\mathcal{R}_0}\left(\frac{(1-\mathcal{R}_0)(a+m_0-ib)}{(a+m_0)^2+b^2} - \sum_{j=1}^{2} p_j \int_0^A e^{-a\tau}(\cos(b\tau)-i\sin(b\tau))\pi_j(\tau)d\tau\right)$$
$$+\frac{1}{\mathcal{R}_0}\sum_{j=1}^{2}\int_0^A p_j c_j s_j v_j(\tau)e^{-a\tau}(\cos(b\tau)-i\sin(b\tau))\pi_j(\tau)d\tau. \tag{3.59}$$

Equating real and imaginary parts of equation (3.59), we obtain

$$1 = \frac{\alpha_1+\alpha_2}{N^*\mathcal{R}_0}\left(\frac{(1-\mathcal{R}_0)(a+m_0)}{(a+m_0)^2+b^2} - \sum_{j=1}^{2} p_j \int_0^A \cos(b\tau)e^{-a\tau}\pi_j(\tau)d\tau\right)$$
$$+\frac{1}{\mathcal{R}_0}\sum_{j=1}^{2}\int_0^A p_j c_j s_j v_j(\tau)\cos(b\tau)e^{-a\tau}\pi_j(\tau)d\tau.$$

If $\Re(\lambda) \geq 0$, and using the expression for the basic reproduction number, we obtain the inequality

$$\frac{\alpha_1+\alpha_2}{N^*\mathcal{R}_0}\left(\frac{(1-\mathcal{R}_0)(a+m_0)}{(a+m_0)^2+b^2} - \sum_{j=1}^{2} p_j \int_0^A \cos(b\tau)e^{-a\tau}\pi_j(\tau)\right) \geq 0,$$

which is untenable whenever $\Re(\lambda) = a \geq 0$ and $A$ is sufficiently small such that $\cos(b\tau) > 0$, $\tau \in (0, A)$. Thus, $\Re(\lambda) < 0$ and hence the endemic equilibrium is locally asymptotically stable when $\mathcal{R}_0 > 1$.

**Case 2 (Large A):** Now, using the mortality function, $m(v_j(\tau)) = m_0 + \mu_j v_j(\tau)$, and integration by parts, the term

$$\sum_{j=1}^{2} p_j \int_0^A c_j s_j v_j(\tau)e^{-\lambda\tau}\pi_j(\tau)d\tau = \sum_{j=1}^{2}\frac{p_j c_j s_j}{\mu_j}\int_0^A \mu_j v_j(\tau)e^{-(\lambda+m_0)\tau}e^{-\int_0^\tau \mu_j v_j(s)ds}d\tau$$
$$= \sum_{j=1}^{2}\frac{p_j c_j s_j}{\mu_j}\left(1-e^{-\lambda A}\pi_j(A)-(\lambda+m_0)\Gamma_j(\lambda)\right). \tag{3.60}$$

Thus, if $\lambda = 0$ in equation (3.60) and $\mathcal{R}_0 > 1$, then

$$1 < \mathcal{R}_0 = \sum_{j=1}^{2} \frac{p_j c_j s_j}{\mu_j}(1 - \pi_j(A)) - m_0 \sum_{j=1}^{2} \frac{p_j c_j s_j}{\mu_j}\Gamma_j(0).$$

Whence, $1 < \sum_{j=1}^{2} \frac{p_j c_j s_j}{\mu_j} \leq \max\left\{\frac{c_1 s_1}{\mu_1}, \frac{c_2 s_2}{\mu_2}\right\}$ due to the convex combination of $\frac{c_1 s_1}{\mu_1}$ and $\frac{c_2 s_2}{\mu_2}$. Now, using equation (3.60), equation ( 3.58) becomes

$$\begin{aligned}
1 + \frac{\alpha_1 + \alpha_2}{N^*(\lambda + m_0)} \quad &= \quad \frac{1}{\mathcal{R}_0}\frac{\alpha_1 + \alpha_2}{N^*(\lambda + m_0)} + \frac{1}{\mathcal{R}_0}\sum_{j=1}^{2}\int_0^A p_j c_j s_j v_j(\tau) e^{-\lambda\tau}\pi_j(\tau) d\tau \\
&\quad - \frac{\alpha_1 + \alpha_2}{N^*\mathcal{R}_0}\frac{1}{\lambda + m_0}\frac{\mu_1}{c_1 s_1}\sum_{j=1}^{2}\frac{p_j c_j s_j}{\mu_j}(1 - e^{-\lambda A}\pi_j(A)) \\
&\quad + \frac{\alpha_1 + \alpha_2}{N^*\mathcal{R}_0}\frac{p_2 c_2 s_2}{\mu_2}\frac{\mu_1}{c_1 s_1}\Gamma_2(\lambda) - \frac{\alpha_1 + \alpha_2}{N^*\mathcal{R}_0}p_2\Gamma_2(\lambda) \\
&\quad + \frac{\alpha_1 + \alpha_2}{N^*\mathcal{R}_0}\frac{\mu_1}{c_1 s_1}\frac{1}{\lambda + m_0}\sum_{j=1}^{2}\int_0^A p_j c_j s_j v_j(\tau) e^{-\lambda\tau}\pi_j(\tau) d\tau \\
&= \quad \frac{1}{\mathcal{R}_0}\left(1 + \frac{\alpha_1 + \alpha_2}{N^*(\lambda + m_0)}\frac{\mu_1}{c_1 s_1}\right)\sum_{j=1}^{2}\int_0^A p_j c_j s_j v_j(\tau) e^{-\lambda\tau}\pi_j(\tau) d\tau \\
&\quad + \frac{1}{\mathcal{R}_0}\frac{\alpha_1 + \alpha_2}{N^*(\lambda + m_0)}\left(1 - \frac{\mu_1}{c_1 s_1}\sum_{j=1}^{2}\frac{p_j c_j s_j}{\mu_j}(1 - e^{-\lambda A}\pi_j(A))\right) \\
&\quad - \frac{\alpha_1 + \alpha_2}{N^*\mathcal{R}_0}\left(1 - \frac{c_2 s_2}{\mu_2}\frac{\mu_1}{c_1 s_1}\right)p_2\Gamma_2(\lambda). \qquad (3.61)
\end{aligned}$$

This gives

$$\begin{aligned}
\frac{1 + \frac{\alpha_1 + \alpha_2}{N^*(\lambda + m_0)}}{1 + \frac{\alpha_1 + \alpha_2}{N^*(\lambda + m_0)}\frac{\mu_1}{c_1 s_1}} \quad &= \quad \frac{1}{\mathcal{R}_0}\sum_{j=1}^{2}\int_0^A p_j c_j s_j v_j(\tau) e^{-\lambda\tau}\pi_j(\tau) d\tau \\
&\quad + \frac{\frac{1}{\mathcal{R}_0}\frac{\alpha_1 + \alpha_2}{N^*(\lambda + m_0)}}{1 + \frac{\alpha_1 + \alpha_2}{N^*(\lambda + m_0)}\frac{\mu_1}{c_1 s_1}}\left(1 - \frac{\mu_1}{c_1 s_1}\sum_{j=1}^{2}\frac{p_j c_j s_j}{\mu_j} + \frac{\mu_1}{c_1 s_1}\sum_{j=1}^{2}\frac{p_j c_j s_j}{\mu_j}e^{-\lambda A}\pi_j(A)\right) \\
&\quad - \frac{\frac{\alpha_1 + \alpha_2}{N^*\mathcal{R}_0}}{1 + \frac{\alpha_1 + \alpha_2}{N^*(\lambda + m_0)}\frac{\mu_1}{c_1 s_1}}\left(1 - \frac{c_2 s_2}{\mu_2}\frac{\mu_1}{c_1 s_1}\right)p_2\Gamma_2(\lambda) =: \mathcal{L}(\lambda). \qquad (3.62)
\end{aligned}$$

Now, if $\frac{c_1 s_1}{\mu_1} = \frac{c_2 s_2}{\mu_2}$, we obtain $1 - \frac{c_2 s_2}{\mu_2}\frac{\mu_1}{c_1 s_1} = 0$ and $1 - \frac{\mu_1}{c_1 s_1}\sum_{j=1}^{2}\frac{p_j c_j s_j}{\mu_j} = 0$. Thus, if $\Re(\lambda) > 0$, then the left-hand side of equation (3.62) gives

$$\left| \frac{1 + \frac{\alpha_1+\alpha_2}{N^*(\lambda+m_0)}}{1 + \frac{\alpha_1+\alpha_2}{N^*(\lambda+m_0)}\frac{\mu_1}{c_1 s_1}} \right| > 1 \tag{3.63}$$

and the corresponding right-hand side gives

$$|\mathcal{L}(\lambda)| \leq \frac{1}{\mathcal{R}_0}\sum_{j=1}^{2}\int_0^A p_j c_j s_j v_j(\tau) e^{-\Re(\lambda)\tau}\pi_j(\tau)d\tau + \frac{1}{\mathcal{R}_0}\left| \frac{\frac{\alpha_1+\alpha_2}{N^*(\lambda+m_0)}}{1 + \frac{\alpha_1+\alpha_2}{N^*(\lambda+m_0)}\frac{\mu_1}{c_1 s_1}} \right| e^{-(\Re(\lambda)+m_0)A}.$$

Thus, $|\mathcal{L}(\lambda)| < 1$ if $A$ is sufficiently large. The case $\Re(\lambda) > 0$ gives a contradiction. If $\Re(\lambda) = 0$ ($a = 0$), we multiply both sides of the characteristic equation (3.61) by $m_0 + ib$. This gives

$$\begin{aligned} \frac{\alpha_1+\alpha_2}{N^*} + m_0 + ib &= \frac{1}{\mathcal{R}_0}\left(\frac{\alpha_1+\alpha_2}{N^*}\frac{\mu_1}{c_1 s_1} + m_0 + ib\right)\sum_{j=1}^{2}\int_0^A p_j c_j s_j v_j(\tau) e^{-ib\tau}\pi_j(\tau)d\tau \\ &+ \frac{1}{\mathcal{R}_0}\frac{\alpha_1+\alpha_2}{N^*}\left(1 - \frac{\mu_1}{c_1 s_1}\sum_{j=1}^{2}\frac{p_j c_j s_j}{\mu_j}(1 - e^{-ibA}\pi_j(A))\right) \\ &- \frac{(m_0+ib)(\alpha_1+\alpha_2)}{N^*\mathcal{R}_0}\left(1 - \frac{c_2 s_2}{\mu_2}\frac{\mu_1}{c_1 s_1}\right)p_2\Gamma_2(\lambda). \end{aligned} \tag{3.64}$$

Equating imaginary parts of equation (3.64), we obtain

$$\begin{aligned} & b\left(\mathcal{R}_0 - \sum_{j=1}^{2}\int_0^A p_j c_j s_j v_j(\tau)\cos(b\tau)\pi_j(\tau)d\tau\right) \\ = & -\left(\frac{\alpha_1+\alpha_2}{N^*}\frac{\mu_1}{c_1 s_1} + m_0\right)\sum_{j=1}^{2}\int_0^A p_j c_j s_j v_j(\tau)\sin(b\tau)\pi_j(\tau)d\tau \\ & -\frac{\alpha_1+\alpha_2}{N^*}\frac{\mu_1}{c_1 s_1}\sin(bA)\sum_{j=1}^{2}\frac{p_j c_j s_j}{\mu_j}\pi_j(A) - \frac{b(\alpha_1+\alpha_2)}{N^*}\left(1 - \frac{c_2 s_2}{\mu_2}\frac{\mu_1}{c_1 s_1}\right)p_2\Gamma_2(\lambda) \end{aligned} \tag{3.65}$$

Now, using the expression for the basic reproduction number (3.39), we have

$$\begin{aligned}
\mathcal{R}_0 - \sum_{j=1}^{2}\int_0^A p_j c_j s_j v_j(\tau)\cos(b\tau)\pi_j(\tau)d\tau &= \sum_{j=1}^{2}\int_0^A p_j c_j s_j v_j(\tau)(1-\cos(b\tau))\pi_j(\tau)d\tau \\
&= 2\sum_{j=1}^{2}\int_0^A p_j c_j s_j v_j(\tau)\sin^2\left(\frac{b\tau}{2}\right)\pi_j(\tau)d\tau \\
&> 2\sum_{j=1}^{2} p_j c_j s_j \varepsilon'_j \pi_j(\alpha_2)\int_{\alpha_1}^{\alpha_2}\sin^2\left(\frac{b\tau}{2}\right)d\tau \\
&= \tilde{K}_2\pi(\alpha_2) > 0,
\end{aligned}$$

where $\varepsilon'_j$ is the lower bound on $v_j(\tau)$ for $\tau \in [0, A]$ and $(\alpha_1, \alpha_2) \subset [0, A]$. Now, choose $B^*$ such that

$$\begin{aligned}
B^*\tilde{K}_2\pi(\alpha_2) &> \left(\frac{\alpha_1+\alpha_2}{N^*}\frac{\mu_1}{c_1 s_1} + m_0\right)\sum_{j=1}^{2}\int_0^A p_j c_j s_j v_j(\tau)\pi_j(\tau)d\tau \\
&\quad + \frac{\alpha_1+\alpha_2}{N^*}\frac{\mu_1}{c_1 s_1}\sum_{j=1}^{2}\frac{p_j c_j s_j}{\mu_j}\pi_j(A) + \frac{b(\alpha_1+\alpha_2)}{N^*}\left(1 - \frac{c_2 s_2}{\mu_2}\frac{\mu_1}{c_1 s_1}\right)p_2\Gamma_2(\lambda).
\end{aligned}$$

Then, for $b > B^*$, equation (3.65) is untenable. For $b < B^*$, the left-hand side of equation (3.62) gives

$$\left|\frac{\frac{\alpha_1+\alpha_2}{N^*} + m_0 + ib}{\frac{\alpha_1+\alpha_2}{N^*}\frac{\mu_1}{c_1 s_1} + m_0 + ib}\right| = \frac{\sqrt{\left(\frac{\alpha_1+\alpha_2}{N^*} + m_0\right)^2 + b^2}}{\sqrt{\left(\frac{\alpha_1+\alpha_2}{N^*}\frac{\mu_1}{c_1 s_1} + m_0\right)^2 + b^2}} > \frac{\sqrt{\left(\frac{\alpha_1+\alpha_2}{N^*} + m_0\right)^2 + B^{*2}}}{\sqrt{\left(\frac{\alpha_1+\alpha_2}{N^*}\frac{\mu_1}{c_1 s_1} + m_0\right)^2 + B^{*2}}} > 1,$$

and the right-hand side of equation (3.62), with $\frac{c_1 s_1}{\mu_1} = \frac{c_2 s_2}{\mu_2}$ and $\Re(\lambda) = 0$ gives

$$\begin{aligned}
|\mathcal{L}(\lambda)| &\leq 1 + \frac{\alpha_1+\alpha_2}{N^*\mathcal{R}_0}\frac{\sum_{j=1}^{2} p_j\pi_j(A)}{\left|\frac{\alpha_1+\alpha_2}{N^*}\frac{\mu_1}{c_1 s_1} + m_0 + ib\right|} \\
&\leq 1 + \frac{\alpha_1+\alpha_2}{N^*\mathcal{R}_0}\frac{e^{-m_0 A}}{\frac{\alpha_1+\alpha_2}{N^*}\frac{\mu_1}{c_1 s_1} + m_0} < \frac{\sqrt{\left(\frac{\alpha_1+\alpha_2}{N^*} + m_0\right)^2 + B^{*2}}}{\sqrt{\left(\frac{\alpha_1+\alpha_2}{N^*}\frac{\mu_1}{c_1 s_1} + m_0\right)^2 + B^{*2}}},
\end{aligned}$$

if $A$ is sufficiently large. The case $\Re(\lambda) = 0$ is also a contradiction. Thus, the real parts of $\lambda$ are non-positive, and hence, the endemic equilibrium is locally asymptotically stable if $\mathcal{R}_0 > 1$, $A$ is sufficiently large and $\frac{c_1 s_1}{\mu_1} = \frac{c_2 s_2}{\mu_2}$. $\square$

## 3.3 Optimal Control Formulation and Analysis

In order to reduce the proliferation of free virus at the within-host level, we introduce two control functions $u_1$ and $u_2$, representing transmission and virion production suppressing drugs, respectively. This leads to the following multi-group within-host model

$$\frac{dx_j}{d\tau} = r - \beta_j(1-u_1(\tau))v_j(\tau)x_j(\tau) - \mu x_j(\tau) \tag{3.66}$$

$$\frac{dy_j}{d\tau} = \beta_j(1-u_1(\tau))v_j(\tau)x_j(\tau) - d_j y_j(\tau), \quad j = 1,2 \tag{3.67}$$

$$\frac{dv_j}{d\tau} = \gamma_j(1-u_2(\tau))d_j y_j(\tau) - (\delta_j + s_j)v_j(\tau) - \hat{\beta}_j(1-u_1(\tau))v_j(\tau)x_j(\tau), \tag{3.68}$$

We develop Lipschitz properties for the solutions to the state system in terms of controls. These properties will be used in proving the existence of sensitivities, and the existence and uniqueness of optimal control pair.

**Theorem 3.6.** ***(Lipschitz Property)*** *The map*

$$(u_1, u_2) \to (x_1, x_2, y_1, y_2, v_1, v_2, S, i_1, i_2) = (x_1, x_2, y_1, y_2, v_1, v_2, S, i_1, i_2)(u_1, u_2)$$

*is Lipschitz in the following ways:*

$$(i) \quad \sum_{j=1}^{2}\int_\Omega (|x_j - \bar{x}_j| + |y_j - \bar{y}_j| + |v_j - \bar{v}_j|)d\tau + \int_0^T |S - \bar{S}|dt + \sum_{j=1}^{2}\int_Q |i_j - \bar{i}_j| d\tau dt$$
$$\leq C_{A,T}\int_\Omega (|u_1 - \bar{u}_1| + |u_2 - \bar{u}_2|)d\tau$$

$$
\begin{aligned}
(ii) \qquad & ||S - \bar{S}||_{L^\infty(0,T)} \\
& + \sum_{j=1}^{2} (||x_j - \bar{x}_j||_{L^\infty(\Omega)} + ||y_j - \bar{y}_j||_{L^\infty(\Omega)} + ||v_j - \bar{v}_j||_{L^\infty(\Omega)} + ||i_j - \bar{i}_j||_{L^\infty(Q)}) \\
\leq \; & \hat{C}_{A,T}(||u_1 - \bar{u}_1||_{L^\infty(\Omega)} + ||u_2 - \bar{u}_2||_{L^\infty(\Omega)}),
\end{aligned}
$$

*where* $\Omega = (0, A)$ *and* $Q = \Omega \times (0, T)$.

*Proof.* Follows as in Numfor et al.[92, Theorem 3.2]. □

### 3.3.1 The Optimality System

In this subsection, we derive a sensitivity system, an adjoint system and a control characterization. To derive a characterization of an optimal control, we define an objective functional, $J$, for our problem, where our objective is to minimize free virus, population of infectious individuals and the cost of implementing the control. Thus, we use the following objective functional

$$
\begin{aligned}
J(u_1, u_2) \;=\; & \int_0^T \int_0^A (A_1 i_1(\tau, t) v_1(\tau) + i_1(\tau, t)(A_2 u_1(\tau) + A_3 u_2(\tau))) d\tau dt \\
& + \int_0^T \int_0^A (A_4 i_2(\tau, t) v_2(\tau) + i_2(\tau, t)(A_2 u_1(\tau) + A_3 u_2(\tau))) d\tau dt \\
& + \int_0^A (B_1 u_1(\tau)^2 + B_2 u_2(\tau)^2) d\tau, \qquad (3.69)
\end{aligned}
$$

where $A_1$, $A_2$, $A_3$, $A_4$, $B_1$ and $B_2$ are positive constants that balance the relative importance for the terms in $J$. The term $\int_0^T \int_0^A (A_1 i_1(\tau, t) v_1(\tau) + A_4 i_2(\tau, t) v_2(\tau)) d\tau dt$ in the objective functional gives the total of infected individuals in the population over the time period $T$ and age-since-infection $A$ to be minimized. The terms $i_1(\tau, t) u_1(\tau)$ and $i_2(\tau, t) u_1(\tau)$ represent the number of infected individuals treated with the transmission suppressing drug respectively, and $A_2$ is the cost per individual treated with this drug. Thus, $\int_0^T \int_0^A (A_2 i_1(\tau, t) u_1(\tau) + A_2 i_2(\tau, t) u_1(\tau)) d\tau dt + \int_0^A B_1 u_1^2(\tau) d\tau$ gives the cost of implementing the control with the transmission suppressing drug for all infected individuals of age-since-infection, $A$. Here, we assume a nonlinear cost for treatment and chose the quadratic cost for illustration. By analogy, we define other terms in the objective functional.

The optimal control formulation for our problem is: Find $(u_1^*, u_2^*) \in \mathcal{U}$ such that

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

where the set of all admissible controls is

$$\mathcal{U} = \{(u_1, u_2) \in L^\infty(0, A) \times L^\infty(0, A) | u_1 : (0, A) \to [0, \tilde{u}_1],\ u_2 : (0, A) \to [0, \tilde{u}_2]\}.$$

The upper bounds on the controls give the efficacy of the transmission and virion production suppressing drugs while the lower bounds, $u_1 = 0$ and $u_2 = 0$, represent the case where there is no inhibition of transmission and virion production.

We take the Gâteaux derivatives of $J$ with respect to controls $(u_1, u_2) \in \mathcal{U}$. Since the objective functional is defined in term of the states, we start by finding the derivatives of the control-to-state map. These derivatives are called sensitivities.

**Theorem 3.7.** ***(Sensitivities)*** *The map*

$$(u_1, u_2) \to (x_1, x_2, y_1, y_2, v_1, v_2, S, i_1, i_2) = (x_1, x_2, y_1, y_2, v_1, v_2, S, i_1, i_2)(u_1, u_2)$$

*is differentiable in the following sense:*

$$\frac{\Phi(u_1 + \varepsilon l_1, u_2 + \varepsilon l_2) - \Phi(u_1, u_2)}{\varepsilon} \to (\psi_1, \psi_2, \varphi_1, \varphi_2, \phi_1, \phi_2, \theta, \omega_1, \omega_2)$$

*in* $(L^\infty(\Omega))^6 \times L^\infty(0, T) \times (L^\infty(0, T; L^1(\Omega)))^2$, *as* $\varepsilon \to 0$ *with* $(u_1+\varepsilon l_1, u_2+\varepsilon l_2)$, $(u_1, u_2) \in \mathcal{U}$ *and* $l_1, l_2 \in L^\infty(\Omega)$, *where* $\Phi = (x_1, x_2, y_1, y_2, v_1, v_2, S, i_1, i_2)$. *Furthermore, for* $j = 1, 2$, *the sensitivity functions satisfy*

$$\frac{d\psi_j}{d\tau} = -(\beta_j(1-u_1)v_j+\mu)\psi_j - \beta_j(1-u_1)x_j\phi_j + \beta_j l_1 v_j x_j \tag{3.70}$$

$$\frac{d\varphi_j}{d\tau} = \beta_j(1-u_1)v_j\psi_j - d_j\varphi_j + \beta_j(1-u_1)x_j\phi_j - \beta_j l_1 v_j x_j \tag{3.71}$$

$$\begin{aligned}\frac{d\phi_j}{d\tau} &= -\hat{\beta}_j(1-u_1)v_j\psi_j + \gamma_j(1-u_2)d_j\varphi_j - (\delta_j + s_j + \hat{\beta}_j(1-u_1)x_j)\phi_j \\ &\quad +\hat{\beta}_j l_1 v_j x_j - \gamma_j d_j l_2 y_j \end{aligned}\tag{3.72}$$

$$\begin{aligned}\frac{d\theta}{dt} &= -m_0\theta(t) - \frac{1}{N(t)}\left(1-\frac{S(t)}{N(t)}\right)\theta(t)\sum_{k=1}^{2} c_k s_k \int_\Omega i_k(\tau,t)v_k(\tau)d\tau \\ &\quad -\frac{S(t)}{N(t)}\sum_{k=1}^{2} c_k s_k \int_\Omega [v_k(\tau)\omega_k(\tau,t) + i_k(\tau,t)\phi_k(\tau)]d\tau \\ &\quad +\frac{S(t)}{N(t)^2}\int_\Omega(\omega_1(h,t)+\omega_2(h,t))dh\sum_{k=1}^{2} c_k s_k \int_\Omega i_k(\tau,t)v_k(\tau)d\tau \quad in \quad (0,T)\end{aligned}\tag{3.73}$$

$$\frac{\partial\omega_j}{\partial t} + \frac{\partial\omega_j}{\partial\tau} = -m(v_j(\tau))\omega_j(\tau,t) - \mu_j\phi_j(\tau)i_j(\tau,t) \quad in \quad \Omega\times(0,T) \tag{3.74}$$

*with initial and boundary conditions*

$$\psi_j(0)=0, \quad \varphi_j(0)=0, \quad \phi_j(0)=0, \quad \theta(0)=0, \omega_j(\tau,0)=0, \quad for \quad \tau\in\Omega=(0,A) \tag{3.75}$$

*and*

$$\begin{aligned}\omega_j(0,t) &= \frac{p_j}{N(t)}\left(1-\frac{S(t)}{N(t)}\right)\theta(t)\sum_{k=1}^{2} c_k s_k \int_\Omega i_k(\tau,t)v_k(\tau)d\tau \\ &\quad +p_j\frac{S(t)}{N(t)}\sum_{k=1}^{2} c_k s_k \int_\Omega [v_k(\tau)\omega_k(\tau,t)+i_k(\tau,t)\phi_k(\tau)]d\tau \\ &\quad -p_j\frac{S(t)}{N(t)^2}\int_\Omega(\omega_1(h,t)+\omega_2(h,t))dh\sum_{k=1}^{2} c_k s_k \int_\Omega i_k(\tau,t)v_k(\tau)d\tau.\end{aligned}\tag{3.76}$$

*Proof.* Follows as in Numfor et al. [92, Theorem 3.3]. □

To distinguish functions which are functions of $\tau$ only, $t$ only, and both $T$ and $\tau$, we divide the sensitivity equations in Theorem 3.7 into three operators. These operators will be used in the characterizing the optimal control pair. Now, the sensitivity operators, $\mathcal{L}_1$, $\mathcal{L}_2$ and $\mathcal{L}_3$, and the corresponding sensitivity equations are:

$$\mathcal{L}_1 \begin{bmatrix} \psi_1 \\ \psi_2 \\ \varphi_1 \\ \varphi_2 \\ \phi_1 \\ \phi_2 \end{bmatrix} = \begin{bmatrix} \beta_1 l_1 v_1 x_1 \\ \beta_2 l_1 v_2 x_2 \\ -\beta_1 l_1 v_1 x_1 \\ -\beta_2 l_1 v_2 x_2 \\ \hat{\beta}_1 l_1 v_1 x_1 - \gamma_1 d_1 l_2 y_1 \\ \hat{\beta}_2 l_1 v_2 x_2 - \gamma_2 d_2 l_2 y_2 \end{bmatrix}, \quad \mathcal{L}_2\theta = 0 \;\; and \;\; \mathcal{L}_3 \begin{bmatrix} \omega_1 \\ \omega_2 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}, \quad (3.77)$$

where

$$\begin{aligned} \mathcal{L}_1 \begin{bmatrix} \psi_1 \\ \psi_2 \\ \varphi_1 \\ \varphi_2 \\ \phi_1 \\ \phi_2 \end{bmatrix} &= \begin{bmatrix} \frac{d\psi_1}{d\tau} \\ \frac{d\psi_2}{d\tau} \\ \frac{d\varphi_1}{d\tau} \\ \frac{d\varphi_2}{d\tau} \\ \frac{d\phi_1}{d\tau} \\ \frac{d\phi_2}{d\tau} \end{bmatrix} + M \begin{bmatrix} \psi_1 \\ \psi_2 \\ \varphi_1 \\ \varphi_2 \\ \phi_1 \\ \phi_2 \end{bmatrix} \\ M &= \begin{pmatrix} b_1 v_1 + \mu & 0 & 0 & 0 & b_1 x_1 & 0 \\ 0 & b_2 v_2 + \mu & 0 & 0 & 0 & b_2 x_2 \\ -b_1 v_1 & 0 & d_1 & 0 & -b_1 x_1 & 0 \\ 0 & -b_2 v_2 & 0 & d_2 & 0 & -b_2 x_2 \\ \hat{\beta}_1(1-u_1)v_1 & 0 & -b_5 & 0 & b_3 & 0 \\ 0 & \hat{\beta}_2(1-u_1)v_2 & 0 & -b_6 & 0 & b_4 \end{pmatrix} \\ b_1 &= \beta_1(1-u_1), \quad b_3 = \delta_1 + s_1 + \hat{\beta}_1(1-u_1)x_1, \quad b_5 = d_1\gamma_1(1-u_2) \\ b_2 &= \beta_2(1-u_1), \quad b_4 = \delta_2 + s_2 + \hat{\beta}_2(1-u_1)x_2, \quad b_6 = d_2\gamma_2(1-u_2) \\ \mathcal{L}_2\theta &= \frac{d\theta}{dt} + B(\phi_j, \theta, \omega_j) + C(\omega_j) + m_0\theta \qquad (3.78) \end{aligned}$$

$$B(\phi_j,\theta,\omega_j) = \frac{1}{N}\left(1-\frac{S}{N}\right)\theta\sum_{k=1}^{2}c_k s_k\int_\Omega i_k(\tau,t)v_k(\tau)d\tau \tag{3.79}$$

$$+\frac{S}{N}\sum_{k=1}^{2}c_k s_k\int_\Omega(v_k(\tau)\omega_k(\tau,t)d\tau+i_k(\tau,t)\phi_k(\tau))d\tau, \tag{3.80}$$

$$C(\omega_j) = -\frac{S}{N^2}\int_\Omega(\omega_1(h,t)+\omega_2(h,t))dh\sum_{k=1}^{2}c_k s_k\int_\Omega i_k(\tau,t)v_k(\tau)d\tau, \tag{3.81}$$

$$\mathcal{L}_3\begin{bmatrix}\omega_1\\ \omega_2\end{bmatrix} = \begin{bmatrix}\frac{\partial\omega_1}{\partial t}+\frac{\partial\omega_1}{\partial\tau}\\ \frac{\partial\omega_2}{\partial t}+\frac{\partial\omega_2}{\partial\tau}\end{bmatrix}+\begin{bmatrix}m'(v_1)\phi_1 i_1+m(v_1)\omega_1\\ m'(v_2)\phi_2 i_2+m(v_2)\omega_2\end{bmatrix}. \tag{3.82}$$

Below, we derive the adjoint system from the sensitivity system. Thus, if $\lambda_1$,$\lambda_2$, $\xi_1$, $\xi_2$, $\eta_1$, $\eta_2$, $p$, $q_1$ and $q_2$ are adjoint functions, then we find adjoint operators $\mathcal{L}_j^*$, for $j=1,2,3$ such that

$$\int_\Omega(\lambda_1,\lambda_2,\xi_1,\xi_2,\eta_1,\eta_2)\mathcal{L}_1\begin{pmatrix}\psi_1\\ \psi_2\\ \varphi_1\\ \varphi_2\\ \phi_1\\ \phi_2\end{pmatrix}d\tau+\int_0^T p\mathcal{L}_2\theta dt+\int_Q(q_1,q_2)\mathcal{L}_3\begin{pmatrix}\omega_1\\ \omega_2\end{pmatrix}d\tau dt$$

$$= \int_\Omega(\psi_1,\psi_2,\varphi_1,\varphi_2,\phi_1,\phi_2)\mathcal{L}_1^*\begin{pmatrix}\lambda_1\\ \lambda_2\\ \xi_1\\ \xi_2\\ \eta_1\\ \eta_2\end{pmatrix}d\tau+\int_0^T\theta\mathcal{L}_2^* p dt+\int_Q(\omega_1,\omega_2)\mathcal{L}_3^*\begin{pmatrix}q_1\\ q_2\end{pmatrix}d\tau dt \tag{3.83}$$

with adjoint equations (in some appropriate weak sense), where

$$\mathcal{L}_1^* \begin{bmatrix} \lambda_1 \\ \lambda_2 \\ \xi_1 \\ \xi_2 \\ \eta_1 \\ \eta_2 \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \\ A_1 \int_0^T i_1(\tau,t)dt \\ A_4 \int_0^T i_2(\tau,t)dt \end{bmatrix}, \ \mathcal{L}_2^* p = 0, \ \mathcal{L}_3^* \begin{bmatrix} q_1 \\ q_2 \end{bmatrix} = \begin{bmatrix} A_1 v_1 + A_2 u_1 + A_3 u_2 \\ A_4 v_2 + A_2 u_1 + A_3 u_2 \end{bmatrix}. \tag{3.84}$$

The right-hand side of the adjoint operators (3.84) are obtained by differentiating the integrand of the objective functional (3.69) with respect to each state variable. The transversality conditions associated with the adjoint variables are:

$$\lambda_j(A) = 0, \quad \xi_j(A) = 0, \quad \eta_j(A) = 0, \quad p(T) = 0 \tag{3.85}$$

$$q_j(\tau, T) = 0, \quad for \quad \tau \in (0, A) \tag{3.86}$$

$$q_j(A, t) = 0, \quad for \quad t \in (0, T) \quad and \quad j = 1, 2. \tag{3.87}$$

From the sensitivity system in Theorem 3.7 and the relationship between the sensitivity and adjoint operators given by equation (3.83), we use integration by parts to throw the derivatives in the differential operators in the sensitivity functions $\psi_j$, $\varphi_j$, $\phi_j$, $\theta$, and $\omega_j$ onto the adjoint functions $\lambda_j$, $\xi_j$, $\eta_j$, $p$ and $q_j$ to form the adjoint operators. Now,

$\int_\Omega (\lambda_1, \lambda_2, \xi_1, \xi_2, \eta_1, \eta_2)\mathcal{L}_1(\psi_1, \psi_2, \varphi_1, \varphi_2, \phi_1, \phi_2)d\tau$

$$= \int_\Omega [(\lambda_1, \lambda_2, \xi_1, \xi_2, \eta_1, \eta_2)\begin{pmatrix} \frac{d\psi_1}{d\tau} \\ \frac{d\psi_2}{d\tau} \\ \frac{d\varphi_1}{d\tau} \\ \frac{d\varphi_2}{d\tau} \\ \frac{d\phi_1}{d\tau} \\ \frac{d\phi_2}{d\tau} \end{pmatrix} + (\lambda_1, \lambda_2, \xi_1, \xi_2, \eta_1, \eta_2)M \begin{pmatrix} \psi_1 \\ \psi_2 \\ \varphi_1 \\ \varphi_2 \\ \phi_1 \\ \phi_2 \end{pmatrix}]d\tau$$

$$= \int_\Omega (\psi_1, \psi_2, \varphi_1, \varphi_2, \phi_1, \phi_2)\begin{pmatrix} -\frac{d\lambda_1}{d\tau} \\ -\frac{d\lambda_2}{d\tau} \\ -\frac{d\xi_1}{d\tau} \\ -\frac{d\xi_2}{d\tau} \\ -\frac{d\eta_1}{d\tau} \\ -\frac{d\eta_2}{d\tau} \end{pmatrix} d\tau + \int_\Omega (\psi_1, \psi_2, \varphi_1, \varphi_2, \phi_1, \phi_2)M^T \begin{pmatrix} \lambda_1 \\ \lambda_2 \\ \xi_1 \\ \xi_2 \\ \eta_1 \\ \eta_2 \end{pmatrix} d\tau,$$

where we have used the initial conditions (3.75) and transversality conditions in (3.85). Thus,

$\int_\Omega (\lambda_1, \lambda_2, \xi_1, \xi_2, \eta_1, \eta_2)\mathcal{L}_1(\psi_1, \psi_2, \varphi_1, \varphi_2, \phi_1, \phi_2)d\tau$

$$\begin{aligned} = & \int_\Omega \left(-\frac{d\lambda_1}{d\tau} + (\beta_1(1-u_1)v_1 + \mu)\lambda_1 - \beta_1(1-u_1)v_1\xi_1 + \hat{\beta}_1(1-u_1)v_1\eta_1\right)\psi_1 d\tau \\ & + \int_\Omega \left(-\frac{d\lambda_2}{d\tau} + (\beta_2(1-u_1)v_2 + \mu)\lambda_2 - \beta_2(1-u_1)v_2\xi_2 + \hat{\beta}_2(1-u_1)v_2\eta_2\right)\psi_2 d\tau \\ & + \int_\Omega \left(\frac{-d\xi_1}{d\tau} + d_1\xi_1 - d_1\gamma_1(1-u_2)\eta_1\right)\varphi_1 d\tau \\ & + \int_\Omega \left(\frac{-d\xi_2}{d\tau} + d_2\xi_2 - d_2\gamma_2(1-u_2)\eta_2\right)\varphi_2 d\tau \\ & + \int_\Omega \left(-\frac{d\eta_1}{d\tau} + \beta_1(1-u_1)x_1\lambda_1 - \beta_1(1-u_1)x_1\xi_1 + (\delta_1 + s_1 + \hat{\beta}_1(1-u_1)x_1)\eta_1\right)\phi_1 d\tau \\ & + \int_\Omega \left(-\frac{d\eta_2}{d\tau} + \beta_2(1-u_1)x_2\lambda_2 - \beta_2(1-u_1)x_2\xi_2 + (\delta_2 + s_2 + \hat{\beta}_2(1-u_1)x_2)\eta_2\right)\phi_2 d\tau. \end{aligned} \tag{3.88}$$

Next, we consider the equation for the operator $\mathcal{L}_2$:

$\int_0^T p(t)\mathcal{L}_2\theta dt$

$$
\begin{aligned}
&= \int_0^T \left(-\frac{dp}{dt} + m_0 p(t) - \frac{p(t)}{N(t)}\left(1 - \frac{S(t)}{N(t)}\right)\sum_{k=1}^{2} c_k s_k \int_\Omega i_k(\tau,t) v_k(\tau) d\tau\right)\theta(t) dt \\
&\quad + \int_0^T \frac{p(t)S(t)}{N(t)} \sum_{k=1}^{2} c_k s_k \int_\Omega (v_k(\tau)\omega_k(\tau,t) + i_k(\tau,t)\phi_k(\tau)) d\tau dt \\
&\quad - \int_0^T \frac{p(t)S(t)}{N(t)^2} \sum_{k=1}^{2} c_k s_k \int_\Omega i_k(\tau,t) v_k(\tau) d\tau \int_0^A (\omega_1(h,t) + \omega_2(h,t)) dh dt \\
&= \int_0^T \int_0^A \frac{c_1 s_1 p(t) S(t) i_1(\tau,t)}{N(t)} \phi_1(\tau) d\tau dt + \int_0^T \int_0^A \frac{c_2 s_2 p(t) S(t) i_2(\tau,t)}{N(t)} \phi_2(\tau) d\tau dt \\
&\quad + \int_0^T \left(-\frac{dp}{dt} + m_0 p(t) - \frac{p(t)}{N(t)}\left(1 - \frac{S(t)}{N(t)}\right)\sum_{k=1}^{2} c_k s_k \int_\Omega i_k(\tau,t) v_k(\tau) d\tau\right)\theta(t) dt \\
&\quad + \int_0^T \int_0^A \left(\frac{c_1 s_1 p(t) S(t) v_1(t)}{N(t)} - \frac{p(t)S(t)}{N(t)^2}\sum_{k=1}^{2} c_k s_k \int_\Omega i_k(\tau,t) v_k(\tau) d\tau\right)\omega_1(h,t) dh dt \\
&\quad + \int_0^T \int_0^A \left(\frac{c_2 s_2 p(t) S(t) v_2(t)}{N(t)} - \frac{p(t)S(t)}{N(t)^2}\sum_{k=1}^{2} c_k s_k \int_\Omega i_k(\tau,t) v_k(\tau) d\tau\right)\omega_2(h,t) dh dt.
\end{aligned}
\tag{3.89}
$$

Finally, we consider the sensitivity operator $\mathcal{L}_3$, and use integration by parts in two dimensions to throw the derivatives in the differential operator in the sensitivity functions $\omega_1$ and $\omega_2$ onto the adjoint functions $q_1$ and $q_2$ to form the operator $\mathcal{L}_3^*$. Also, we apply the initial conditions given in equation (3.76), and the final time conditions (3.86) and (3.87):

$\int_0^T \int_0^A (q_1, q_2)\mathcal{L}_3 \begin{pmatrix} \omega_1 \\ \omega_2 \end{pmatrix} d\tau dt$

$$
\begin{aligned}
&= \int_0^T \int_\Omega q_1(\tau,t)\left(\frac{\partial\omega_1}{\partial t} + \frac{\partial\omega_1}{\partial\tau} + m'(v_1(\tau))\phi_1(\tau) i_1(\tau,t) + m(v_1(\tau))\omega_1(\tau,t)\right) d\tau dt \\
&\quad + \int_0^T \int_\Omega q_2(\tau,t)\left(\frac{\partial\omega_2}{\partial t} + \frac{\partial\omega_2}{\partial\tau} + m'(v_2(\tau))\phi_2(\tau) i_2(\tau,t) + m(v_2(\tau))\omega_2(\tau,t)\right) d\tau dt
\end{aligned}
$$

$$
\begin{aligned}
= \quad & \int_0^T \int_\Omega \left( -\frac{\partial q_1}{\partial t}\omega_1(\tau,t) - \frac{\partial q_1}{\partial \tau}\omega_1(\tau,t) + m'(v_1(\tau))\phi_1(\tau)i_1(\tau,t)q_1(\tau,t) \right) d\tau dt \\
& + \int_0^T \int_\Omega m(v_1(\tau))\omega_1(\tau,t)q_1(\tau,t)d\tau dt - \int_0^T q_1(0,t)\omega_1(0,t)dt \\
& + \int_0^T \int_\Omega \left( -\frac{\partial q_2}{\partial t}\omega_2(\tau,t) - \frac{\partial q_2}{\partial \tau}\omega_2(\tau,t) + m'(v_2(\tau))\phi_2(\tau)i_2(\tau,t)q_2(\tau,t) \right) d\tau dt \\
& + \int_0^T \int_\Omega m(v_2(\tau))\omega_2(\tau,t)q_2(\tau,t)d\tau dt - \int_0^T q_2(0,t)\omega_2(0,t)dt, \qquad (3.90)
\end{aligned}
$$

where for $j = 1, 2$, the boundary terms $\int_0^T q_j(0,t)\omega_j(0,t)dt$ are defined as:

$$
\begin{aligned}
& \textstyle\int_0^T q_j(0,t)\omega_j(0,t)dt \\
= \quad & \int_0^T \frac{p_j q_j(0,t)}{N(t)} \left(1 - \frac{S(t)}{N(t)}\right) \theta(t) \sum_{k=1}^{2} c_k s_k \int_\Omega i_k(\tau,t)v_k(\tau)d\tau dt \qquad (3.91) \\
& + \int_0^T \frac{p_j q_j(0,t)S(t)}{N(t)} \left( c_1 s_1 \int_0^A v_1(\tau)\omega_1(\tau,t) + c_2 s_2 \int_0^A v_2(\tau)\omega_2(\tau,t) \right) d\tau dt \\
& + \int_0^T \frac{p_j q_j(0,t)S(t)}{N(t)} \left( c_1 s_1 \int_0^A i_1(\tau,t)\phi_1(\tau,t) + c_2 s_2 \int_0^A i_2(\tau,t)\phi_2(\tau) \right) d\tau dt \\
& - \int_0^T \frac{p_j q_j(0,t)S(t)}{N(t)^2} \sum_{k=1}^{2} c_k s_k \int_0^A i_k(\tau,t)v_k(\tau)d\tau \int_0^A (\omega_1(h,t) + \omega_2(h,t))dhdt.
\end{aligned}
$$

Thus, from (3.91), equation (3.90) becomes

$$\int_0^T \int_0^A (q_1, q_2)\mathcal{L}_3 \begin{pmatrix} \omega_1 \\ \omega_2 \end{pmatrix} d\tau dt$$

$$\begin{aligned}
= & \int_0^T \int_0^A \Big( m'(v_1(\tau)) i_1(\tau,t) q_1(\tau,t) - c_1 s_1 p_1 q_1(0,t) \frac{S(t) i_1(\tau,t)}{N(t)} \\
& \qquad - c_1 s_1 p_2 q_2(0,t) \frac{S(t) i_1(\tau,t)}{N(t)} \Big) \phi_1(\tau) d\tau dt \\
& + \int_0^T \int_0^A \Big( m'(v_2(\tau)) i_2(\tau,t) q_2(\tau,t) - c_2 s_2 p_1 q_1(0,t) \frac{S(t) i_2(\tau,t)}{N(t)} \\
& \qquad - c_2 s_2 p_2 q_2(0,t) \frac{S(t) i_2(\tau,t)}{N(t)} \Big) \phi_2(\tau) d\tau dt \qquad (3.92) \\
& - \int_0^T \left( \frac{p_1 q_1(0,t) + p_2 q_2(0,t)}{N(t)} \left(1 - \frac{S(t)}{N(t)}\right) \sum_{k=1}^{2} c_k s_k \int_\Omega i_k(\tau,t) v_k(\tau) d\tau \right) \theta(t) dt \\
& + \int_Q \Big( -\frac{\partial q_1}{\partial t} - \frac{\partial q_1}{\partial \tau} + m(v_1(\tau)) q_1(\tau,t) - c_1 s_1 (p_1 q_1(0,t) + p_2 q_2(0,t)) \frac{S(t) v_1(\tau)}{N(t)} \\
& \qquad + (p_1 q_1(0,t) + p_2 q_2(0,t)) \frac{S(t)}{N(t)^2} \sum_{k=1}^{2} c_k s_k \int_0^A i_k(h,t) v_k(h) dh \Big) \omega_1(\tau,t) d\tau dt \\
& + \int_Q \Big( -\frac{\partial q_2}{\partial t} - \frac{\partial q_2}{\partial \tau} + m(v_2(\tau)) q_2(\tau,t) - c_2 s_2 (p_1 q_1(0,t) + p_2 q_2(0,t)) \frac{S(t) v_2(\tau)}{N(t)} \\
& \qquad + (p_1 q_1(0,t) + p_2 q_2(0,t)) \frac{S(t)}{N(t)^2} \sum_{k=1}^{2} c_k s_k \int_0^A i_k(h,t) v_k(h) dh \Big) \omega_2(\tau,t) d\tau dt.
\end{aligned}$$

Combining equations (3.88), (3.89) and (3.92), and using the relationship between the sensitivity and adjoint operators, we have the following system of adjoint equations corresponding to controls $(u_1, u_2)$, and states $(x_1, x_2, y_1, y_2, v_1, v_2, S, i_1, i_2) = (x_1, x_2, y_1, y_2, v_1, v_2, S, i_1, i_2)(u_1, u_2)$:

$$
\begin{aligned}
-\frac{d\lambda_1}{d\tau} &= -(\beta_1(1-u_1)v_1+\mu)\lambda_1+\beta_1(1-u_1)v_1\xi_1-\hat{\beta}_1(1-u_1)v_1\eta_1 && (3.93)\\
-\frac{d\lambda_2}{d\tau} &= -(\beta_2(1-u_1)v_2+\mu)\lambda_2+\beta_2(1-u_1)v_2\xi_2-\hat{\beta}_2(1-u_1)v_2\eta_2 && (3.94)\\
-\frac{d\xi_1}{d\tau} &= -d_1\xi_1+d_1\gamma_1(1-u_2)\eta_1 && (3.95)\\
-\frac{d\xi_2}{d\tau} &= -d_2\xi_2+d_2\gamma_2(1-u_2)\eta_2 && (3.96)\\
-\frac{d\eta_1}{d\tau} &= -\beta_1(1-u_1)x_1\lambda_1+\beta_1(1-u_1)x_1\xi_1-(\delta_1+s_1+\hat{\beta}_1(1-u_1)x_1)\eta_1\\
&\quad -c_1s_1\int_0^T\frac{S(t)i_1(\tau,t)}{N(t)}p(t)dt-m'(v_1(\tau))\int_0^T i_1(\tau,t)q_1(\tau,t)dt && (3.97)\\
&\quad +c_1s_1\int_0^T(p_1q_1(0,t)+p_2q_2(0,t))\frac{S(t)i_1(\tau,t)}{N(t)}dt+A_1\int_0^T i_1(\tau,t)dt\\
-\frac{d\eta_2}{d\tau} &= -\beta_2(1-u_1)x_2\lambda_2+\beta_2(1-u_1)x_2\xi_2-(\delta_2+s_2+\hat{\beta}_2(1-u_1)x_2)\eta_2\\
&\quad -c_2s_2\int_0^T\frac{S(t)i_2(\tau,t)}{N(t)}p(t)dt-m'(v_2(\tau))\int_0^T i_2(\tau,t)q_2(\tau,t)dt && (3.98)\\
&\quad +c_2s_2\int_0^T(p_1q_1(0,t)+p_2q_2(0,t))\frac{S(t)i_2(\tau,t)}{N(t)}dt+A_4\int_0^T i_2(\tau,t)dt\\
-\frac{dp}{dt} &= -m_0p-\frac{p}{N}\left(1-\frac{S}{N}\right)\sum_{j=1}^{2}c_js_j\int_0^A v_j(\tau)i_j(\tau,t)d\tau && (3.99)\\
&\quad +\frac{p_1q_1(0,t)+p_2q_2(0,t)}{N}\left(1-\frac{S}{N}\right)\sum_{j=1}^{2}c_js_j\int_0^A i_j(\tau,t)v_j(\tau)d\tau\\
-\frac{\partial q_1}{\partial t}-\frac{\partial q_1}{\partial \tau} &= -m(v_1)q_1-c_1s_1(p(t)-p_1q_1(0,t)-p_2q_2(0,t))\frac{Sv_1}{N}\\
&\quad +(p(t)-p_1q_1(0,t)-p_2q_2(0,t))\frac{S}{N^2}\sum_{j=1}^{2}c_js_j\int_0^A i_j(\tau,t)v_j(\tau)d\tau\\
&\quad +A_1v_1+A_2u_1+A_3u_2 && (3.100)\\
-\frac{\partial q_2}{\partial t}-\frac{\partial q_2}{\partial \tau} &= -m(v_2)q_2-c_2s_2(p(t)-p_1q_1(0,t)-p_2q_2(0,t))\frac{Sv_2}{N}\\
&\quad +(p(t)-p_1q_1(0,t)-p_2q_2(0,t))\frac{S}{N^2}\sum_{j=1}^{2}c_js_j\int_0^A i_j(\tau,t)v_j(\tau)d\tau\\
&\quad +A_4v_2+A_2u_1+A_3u_2, && (3.101)
\end{aligned}
$$

with final time conditions given in equations (3.85) – (3.87).

The weak solution to our problem is characterized in Theorem 3.8. This solution is used in characterizing the solution to the adjoint system which satisfies a Lipschitz property analogous to Theorem 3.6. This property will be used in proving existence and uniqueness of an optimal control pair.

**Theorem 3.8.** *The weak solution of the adjoint system satisfies*

$$\begin{aligned} 0 &= \sum_{j=1}^{2}\int_0^A(\lambda_j\alpha_j+\xi_j\tilde{\alpha}_j+\eta_j\hat{\alpha}_j)d\tau-\int_0^T\int_0^A(A_1g_1(\tau)i_1(\tau,t)+A_4g_2(\tau)i_2(\tau,t))d\tau dt \\ &-\int_0^T\int_0^A(A_1v_1(\tau)+A_2u_1(\tau)+A_3u_2(\tau))n_1(\tau,t)d\tau dt \\ &-\int_0^T\int_0^A(A_4v_2(\tau)+A_2u_1(\tau)+A_3u_2(\tau))n_2(\tau,t)d\tau dt, \end{aligned}$$

*where for $j=1,2$, $\alpha_j$, $\tilde{\alpha}_j$, $\hat{\alpha}_j$ are $L^\infty(0,A)$ functions obtained from test functions $z_j$, $f_j$ and $g_j$, and $r$ and $n_j$ satisfy equations (3.99) – (3.101) such that*

$$\begin{aligned} &\frac{dz_j}{d\tau}+(\beta_j(1-u_1)v_j+\mu)z_j+\beta_j(1-u_1)x_jg_j=\alpha_j \\ &\frac{df_j}{d\tau}-\beta_j(1-u_1)v_jz_j+d_jf_j-\beta_j(1-u_1)x_jg_j=-\tilde{\alpha}_j \\ &\frac{dg_j}{d\tau}+\hat{\beta}_j(1-u_1)v_jz_j-\gamma_j(1-u_2)d_jf_j+(\delta_j+s_j+\hat{\beta}_j(1-u_1)x_j)z_j=\hat{\alpha}_j \\ &\frac{dr}{dt}+m_0r(t)+\frac{1}{N(t)}\left(1-\frac{S(t)}{N(t)}\right)r(t)\sum_{k=1}^{2}c_ks_k\int_\Omega i_k(\tau,t)v_k(\tau)d\tau \\ &+\frac{S(t)}{N(t)}\sum_{k=1}^{2}c_ks_k\int_\Omega[v_k(\tau)n_k(\tau,t)+i_k(\tau,t)z_k(\tau)]d\tau \\ &-\frac{S(t)}{N(t)^2}\sum_{k=1}^{2}c_ks_k\int_\Omega i_k(\tau,t)v_k(\tau)\int_\Omega(n_1(h,t)+n_2(h,t))dhd\tau=0 \quad in \quad (0,T) \\ &\frac{\partial n_j}{\partial t}+\frac{\partial n_j}{\partial\tau}+m(v_j(\tau))n_j(\tau,t)+m'(v_j(\tau))z_j(\tau)i_j(\tau,t)=0 \quad in \quad \Omega\times(0,T) \end{aligned}$$

*with boundary and initial conditions*

$$\begin{aligned} n_j(0,t) &= \frac{p_j}{N(t)}\left(1-\frac{S(t)}{N(t)}\right)r(t)\sum_{k=1}^{2}c_k s_k\int_\Omega i_k(\tau,t)v_k(\tau)d\tau \\ &+p_j\frac{S(t)}{N(t)}\sum_{k=1}^{2}c_k s_k\int_\Omega[v_k(\tau)n_k(\tau,t)+i_k(\tau,t)z_k(\tau)]d\tau \\ &-p_j\frac{S(t)}{N(t)^2}\sum_{k=1}^{2}c_k s_k\int_\Omega i_k(\tau,t)v_k(\tau)\int_\Omega(n_1(h,t)+n_2(h,t))dhd\tau, \end{aligned}$$

*and*

$$z_j(0)=0,\quad f_j(0)=0,\quad g_j(0)=0,\quad r(0)=0,\quad n_j(\tau,0)=0,\quad for\quad \tau\in\Omega.$$

*Proof.* Follows from the sensitivity equations and adjoint system, with $\alpha_j=\beta_j l_1 v_j x_j$, $\tilde{\alpha}_j=\beta_j l_1 v_j x_j$ and $\hat{\alpha}_j=\hat{\beta}_j l_1 v_j x_j-\gamma_j d_j l_2 y_j$. □

**Theorem 3.9.** *For* $(u_1,u_2)\in\mathcal{U}$*, the adjoint system (3.93) – (3.101) has a weak solution* $(\lambda_1,\lambda_2,\xi_1,\xi_2,\eta_1,\eta_2,p,q_1,q_2)$ *in* $(L^\infty(0,A))^6\times L^\infty(0,T)\times(L^\infty(0,T,L^1(0,A)))^2$ *such that*

$$\begin{aligned} &\sum_{j=1}^{2}\left(\|\lambda_j-\bar{\lambda}_j\|_{L^\infty(\Omega)}+\|\xi_j-\bar{\xi}_j\|_{L^\infty(\Omega)}+||\eta_j-\bar{\eta}_j||_{L^\infty(\Omega)})\right)+||p-\bar{p}||_{L^\infty(0,T)} \\ &+\sum_{j=1}^{2}\|q_j-\bar{q}_j\|_{L^\infty(Q)} \\ \leq\ &\tilde{C}_{A,T}(\|u_1-\bar{u}_1\|_{L^\infty(\Omega)}+\|u_2-\bar{u}_2\|_{L^\infty(\Omega)}). \end{aligned}$$

*Proof.* Follows like in Theorem 3.6, part (ii). □

We characterize the optimal control pair $(u_1^*,u_2^*)$ by differentiating the control-to-objective functional map. Since the solutions of first-order partial differential equations are less regular than the solutions of parabolic PDEs, the method used in characterizing optimal control of first-order PDEs is different from that of parabolic PDEs. We use the Ekeland's Principle [6, 38] to characterize optimal control of first-order PDEs. To do this, we embed the objective functional $J$ in the space $L^1(\Omega) \times L^1(Q)$ by defining [13, 45, 44]

$$\mathcal{J}(u_1, u_2) = \begin{cases} J(u_1, u_2) & \text{if } (u_1, u_2) \in \mathcal{U} \\ +\infty & \text{if } (u_1, u_2) \notin \mathcal{U}. \end{cases} \tag{3.102}$$

In order to characterize the optimal control pair, we differentiate the objective functional, $\mathcal{J}$, with respect to the controls. However, since the objective functional is a function of the state functions, we must differentiate the state functions with respect to the controls.

**Theorem 3.10.** *(**Characterization**) If $(u_1^*, u_2^*) \in \mathcal{U}$ is an optimal control pair minimizing (3.102), and $(x_1^*, x_2^*, y_1^*, y_2^*, v_1^*, v_2^*, S^*, i_1^*, i_2^*)$ and $(\lambda_1, \lambda_2, \xi_1, \xi_2, \eta_1, \eta_2, p, q_1, q_2)$ are the corresponding state and adjoint solutions, respectively, then*

$$u_1^*(\tau) = \mathcal{H}_1\left(\frac{a_1^*(\tau) + a_2^*(\tau) - A_2 \int_0^T (i_1^*(\tau,t) + i_2^*(\tau,t))dt}{2B_1}\right), \tag{3.103}$$

$$u_2^*(\tau) = \mathcal{H}_2\left(\frac{a_3^*(\tau) - A_3 \int_0^T (i_1^*(\tau,t) + i_2^*(\tau,t))dt}{2B_2}\right) \quad a.e. \text{ in } L^1(\Omega), \tag{3.104}$$

*where*

$$\begin{aligned} a_1^*(\tau) &= \beta_1 v_1^*(\tau) x_1^*(\tau)(\xi_1(\tau) - \lambda_1(\tau)) - \hat{\beta}_1 v_1^*(\tau) x_1^*(\tau) \eta_1(\tau) \\ a_2^*(\tau) &= \beta_2 v_2^*(\tau) x_2^*(\tau)(\xi_2(\tau) - \lambda_2(\tau)) - \hat{\beta}_2 v_2^*(\tau) x_2^*(\tau) \eta_2(\tau) \\ a_3^*(\tau) &= \gamma_1 d_1 \eta_1(\tau) y_1^*(\tau) + \gamma_2 d_2 \eta_2(\tau) y_2^*(\tau), \end{aligned} \tag{3.105}$$

*and $\mathcal{H}_j$ is defined as*

$$\mathcal{H}_j(x) = \begin{cases} 0, & x < 0 \\ x, & 0 \le x \le \tilde{u}_j, \qquad j = 1, 2 \\ \tilde{u}_j, & x > \tilde{u}_j \end{cases}$$

*Proof.* Since $(u_1^*, u_2^*)$ is an optimal control pair and we seek to minimize our functional, we have

$$\begin{aligned}
0 \;&\leq\; \lim_{\varepsilon\to 0^+} \frac{\mathcal{J}(u_1^*+\varepsilon l_1, u_2^*+\varepsilon l_2) - \mathcal{J}(u_1^*, u_2^*)}{\varepsilon} \\
&= \lim_{\varepsilon\to 0^+} \int_0^T \int_0^A \left( A_1 v_1^\varepsilon \left( \frac{i_1^\varepsilon - i_1^*}{\varepsilon} \right) + A_1 i_1^* \left( \frac{v_1^\varepsilon - v_1^*}{\varepsilon} \right) + \frac{A_2\left(i_1^\varepsilon u_1^\varepsilon - i_1^* u_1^*\right)}{\varepsilon} \right) d\tau dt \\
&\quad + \lim_{\varepsilon\to 0^+} \int_0^T \int_0^A \left( A_4 v_2^\varepsilon \left( \frac{i_2^\varepsilon - i_2^*}{\varepsilon} \right) + A_4 i_2^* \left( \frac{v_2^\varepsilon - v_2^*}{\varepsilon} \right) + \frac{A_2\left(i_2^\varepsilon u_1^\varepsilon - i_2^* u_1^*\right)}{\varepsilon} \right) d\tau dt \\
&\quad + \lim_{\varepsilon\to 0^+} \int_0^T \int_0^A \left( \frac{A_3\left(i_1^\varepsilon u_2^\varepsilon - i_1^* u_2^*\right)}{\varepsilon} + \frac{A_3\left(i_2^\varepsilon u_2^\varepsilon - i_2^* u_2^*\right)}{\varepsilon} \right) d\tau dt \\
&\quad + \lim_{\varepsilon\to 0^+} \int_0^A \left( \frac{B_1((u_1^\varepsilon)^2 - (u_1^*)^2)}{\varepsilon} + \frac{B_2((u_2^\varepsilon)^2 - (u_2^*)^2)}{\varepsilon} \right) d\tau \\
&= \int_0^T \int_0^A [(A_1 v_1^* \omega_1 + A_1 i_1^* \phi_1 + (A_2 u_1^* + A_3 u_2^*)\omega_1] d\tau dt \\
&\quad + \int_0^T \int_0^A [(A_4 v_2^* \omega_2 + A_4 i_2^* \phi_2 + (A_2 u_1^* + A_3 u_2^*)\omega_2] d\tau dt \\
&\quad + \int_0^T \int_0^A (A_2 l_1 (i_1^* + i_2^*) + A_3 l_2 (i_1^* + i_2^*)) d\tau dt + 2\int_0^A (B_1 l_1 u_1^* + B_2 l_2 u_2^*) d\tau \\
&= \int_0^A (\psi_1, \psi_2, \varphi_1, \varphi_2, \phi_1, \phi_2) \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ A_1 \int_0^T i_1^*(\tau,t)dt \\ A_4 \int_0^T i_2^*(\tau,t)dt \end{pmatrix} d\tau + \int_0^T \theta.0 dt \\
&\quad + \int_0^T \int_0^A (\omega_1, \omega_2) \begin{pmatrix} A_1 v_1 + A_2 u_1^* + A_3 u_2^* \\ A_4 v_2 + A_2 u_1^* + A_3 u_2^* \end{pmatrix} d\tau dt + 2\int_0^A (B_1 l_1 u_1^* + B_2 l_2 u_2^*) d\tau \\
&\quad + \int_0^T \int_0^A (A_2 l_1 (i_1^* + i_2^*) + A_3 l_2 (i_1^* + i_2^*)) d\tau dt
\end{aligned}$$

$$= \int_0^A (\psi_1, \psi_2, \varphi_1, \varphi_2, \phi_1, \phi_2)\mathcal{L}_1^* \begin{pmatrix} \lambda_1 \\ \lambda_2 \\ \xi_1 \\ \xi_2 \\ \eta_1 \\ \eta_2 \end{pmatrix} d\tau + \int_0^T \int_0^A (\omega_1, \omega_2)\mathcal{L}_3^* \begin{pmatrix} q_1 \\ q_2 \end{pmatrix} d\tau dt$$

$$+ \int_0^T \theta \mathcal{L}_2^* p dt + \int_0^T \int_0^A (A_2 l_1(i_1^* + i_2^*) + A_3 l_2(i_1^* + i_2^*)) d\tau dt$$

$$+2 \int_0^A (B_1 l_1 u_1^* + B_2 l_2 u_2^*) d\tau$$

$$= \int_0^A (\lambda_1, \lambda_2, \xi_1, \xi_2, \eta_1, \eta_2)\mathcal{L}_1 \begin{pmatrix} \psi_1 \\ \psi_2 \\ \varphi_1 \\ \varphi_2 \\ \phi_1 \\ \phi_2 \end{pmatrix} d\tau + \int_0^T \int_0^A (q_1, q_2)\mathcal{L}_3 \begin{pmatrix} \omega_1 \\ \omega_2 \end{pmatrix} d\tau dt$$

$$+ \int_0^T p \mathcal{L}_2 \theta dt + \int_0^T \int_0^A (A_2 l_1(i_1^* + i_2^*) + A_3 l_2(i_1^* + i_2^*)) d\tau dt$$

$$+2 \int_0^A (B_1 l_1 u_1^* + B_2 l_2 u_2^*) d\tau$$

$$= \int_0^A ((\lambda_1, \lambda_2, \xi_1, \xi_2, \eta_1, \eta_2) \begin{pmatrix} \beta_1 l_1 v_1^* x_1^* \\ \beta_2 l_1 v_2^* x_2^* \\ -\beta_1 l_1 v_1^* x_1^* \\ -\beta_2 l_1 v_2^* x_2^* \\ \hat{\beta}_1 l_1 v_1^* x_1^* - \gamma_1 d_1 l_2 y_1^* \\ \hat{\beta}_2 l_1 v_2^* x_2^* - \gamma_2 d_2 l_2 y_2^* \end{pmatrix} + 2B(l_1 u_1^* + l_2 u_2^*)) d\tau$$

$$+ \int_0^T \int_0^A (A_2 l_1(i_1^* + i_2^*) + A_3 l_2(i_1^* + i_2^*)) d\tau dt,$$

by equations (3.83) and (3.84), and using the sensitivity operators in equation (3.77). Thus,

$$
\begin{aligned}
0 \leq & \int_0^A l_1 \Big( \beta_1 v_1^* x_1^* (\lambda_1 - \xi_1) + \hat{\beta}_1 v_1^* x_1^* \eta_1 + \beta_2 v_2^* x_2^* (\lambda_2 - \xi_2) + \hat{\beta}_2 v_2^* x_2^* \eta_2 + 2B_1 u_1^* \\
& + A_2 \int_0^T (i_1^* + i_2^*) dt \Big) d\tau \\
& + \int_0^A l_2 \Big( 2B_2 u_2^* - \gamma_1 d_1 y_1^* \eta_1 - \gamma_2 d_2 y_2^* \eta_2 + A_3 \int_0^T (i_1^*(\tau, t) + i_2^*(\tau, t)) dt \Big) d\tau.
\end{aligned}
$$

Considering cases on the sets $\{\tau \in \Omega | u_j^*(\tau) = 0\}$, $\{\tau \in \Omega | u_j^*(\tau) = \tilde{u}_j\}$ and $\{\tau \in \Omega | 0 < u_j^*(\tau) < \tilde{u}_j\}$, for $j = 1, 2$, we obtain the desired characterization given in equations (3.103) and (3.104). $\square$

### 3.3.2 Existence of Optimal Control Pair

Existence results are obtained via Ekeland's Principle. In order to use Ekeland's Principle, we prove that our objective functional is lower semi-continuous with respect to $L^1$ convergence. On the other hand, uniqueness of optimal control pair is established by using the Lipschitz properties of the state and adjoint solutions given in Theorems 3.6 and 3.9, respectively, as well as the minimizing sequence obtained from the Ekeland's Variational Principle.

**Theorem 3.11.** ***(Lower semi-continuity)***
*The functional $\mathcal{J} : L^1(\Omega) \times L^1(\Omega) \to (-\infty, +\infty]$ is lower semi-continuous.*

Given a lower semi-continuous functional, $\mathcal{J}$, we have the following Ekeland's Principle which guarantees the existence of minimizers of an approximate functional, $\mathcal{J}_\varepsilon$:
For $\varepsilon > 0$, there exist $(u_1^\varepsilon, u_2^\varepsilon) \in L^1(0, A) \times L^1(0, A)$ such that

$$
\begin{aligned}
(i) \quad \mathcal{J}(u_1^\varepsilon, u_2^\varepsilon) &\leq \inf_{(u_1, u_2) \in \mathcal{U}} \mathcal{J}(u_1, u_2) + \varepsilon \\
(ii) \quad \mathcal{J}(u_1^\varepsilon, u_2^\varepsilon) &= \min_{(u_1, u_2) \in \mathcal{U}} \mathcal{J}_\varepsilon(u_1, u_2), \\
\text{where } \mathcal{J}_\varepsilon(u_1, u_2) &= \mathcal{J}(u_1, u_2) + \sqrt{\varepsilon}(||u_1^\varepsilon - u_1||_{L^1(0,A)} + ||u_2^\varepsilon - u_2||_{L^1(0,A)}).
\end{aligned}
$$

**Theorem 3.12.** *If $(u_1^\varepsilon, u_2^\varepsilon)$ is an optimal control pair minimizing the approximate functional, $\mathcal{J}_\varepsilon$, then*

$$(u_1^\varepsilon(\tau), u_2^\varepsilon(\tau)) \quad = \quad \mathcal{H}\left(\frac{e_1^\varepsilon(\tau) + e_2^\varepsilon(\tau) - A_2K^\varepsilon(\tau) - \sqrt{\varepsilon}\kappa_1^\varepsilon(\tau)}{2B_1}, \frac{e_3^\varepsilon(\tau) - A_3K^\varepsilon(\tau) - \sqrt{\varepsilon}\kappa_2^\varepsilon(\tau)}{2B_2}\right),$$

*where*

$$\begin{aligned}
e_1^\varepsilon(\tau) &= \beta_1 v_1^\varepsilon(\tau)x_1^\varepsilon(\tau)(\xi_1^\varepsilon(\tau) - \lambda_1^\varepsilon(\tau)) - \hat{\beta}_1 v_1^\varepsilon(\tau)x_1^\varepsilon(\tau)\eta_1^\varepsilon(\tau) \\
e_2^\varepsilon(\tau) &= \beta_2 v_2^\varepsilon(\tau)x_2^\varepsilon(\tau)(\xi_2^\varepsilon(\tau) - \lambda_2^\varepsilon(\tau)) - \hat{\beta}_2 v_2^\varepsilon(\tau)x_2^\varepsilon(\tau)\eta_2^\varepsilon(\tau) \qquad (3.106) \\
e_3^\varepsilon(\tau) &= \gamma_1 d_1 \eta_1(\tau) y_1^\varepsilon(\tau) + \gamma_2 d_2 y_2^\varepsilon(\tau)\eta_2^\varepsilon(\tau) \\
K^\varepsilon(\tau) &= \int_0^T (i_1^\varepsilon(\tau,t) + i_2^\varepsilon(\tau,t))dt,
\end{aligned}$$

*and the functions $\kappa_1, \kappa_2 \in L^\infty(0,A)$, with $|\kappa_1(\tau)| = 1$ and $|\kappa_2(\tau)| = 1$, for all $\tau \in (0,A)$.*

### 3.3.3 Uniqueness of Optimal Control Pair

Analogous to uniqueness results in Chapter 3, we state and prove the uniqueness result for multi-group coupled within-host and betwen-host models.

**Theorem 3.13.** *If $\frac{\bar{C}_{A,T}}{2}\left(\frac{1}{B_1} + \frac{1}{B_2}\right)$ is sufficiently small, then there exists a unique optimal control pair $(u_1^*, u_2^*) \in \mathcal{U}$ minimizing the objective functional $\mathcal{J}$.*

*Proof.* Let $\mathcal{H}(x,y) = (\mathcal{H}_1(x), \mathcal{H}_2(y))$ and define $L : \mathcal{U} \to \mathcal{U}$, such that

$$L(u_1, u_2) = \mathcal{H}\left(\frac{a_1 + a_2 - A_2K(\tau)}{2B_1}, \frac{\gamma_1 d_1 \eta_1 y_1 - A_3K(\tau)}{2B_2}\right),$$

where $a_j$, $j = 1, 2$ are defined in equation (3.105). Let $(x_1, x_2, y_1, y_2, v_1, v_2, S, i_1, i_2)$ and

$(\lambda_1, \lambda_2, \xi_1, \xi_2, \eta_1, \eta_2, p, q_1, q_2)$ be state and adjoint solutions corresponding to the control pair $(u_1, u_2)$.

$$||L(u_1,u_2)-L(\bar{u}_1,\bar{u}_2)||_{L^\infty(0,A)\times L^\infty(0,A)}$$

$$\begin{aligned}
&\equiv ||\mathcal{H}_1(u_1)-\mathcal{H}_1(\bar{u}_1)||_{L^\infty(0,A)}+||\mathcal{H}_2(u_2)-\mathcal{H}_2(\bar{u}_2)||_{L^\infty(0,A)}\\
&\le \left\|\frac{e_1+e_2-A_2K(\tau)}{2B_1}-\frac{\bar{e}_1+\bar{e}_2-A_2\bar{K}(\tau)}{2B_1}\right\|_{L^\infty(0,A)}\\
&\quad+\left\|\frac{e_3-A_3K(\tau)}{2B_2}-\frac{\bar{e}_3-A_3\bar{K}(\tau)}{2B_2}\right\|_{L^\infty(0,A)}\\
&\le \frac{1}{2B_1}\|e_1-\bar{e}_1\|_{L^\infty(0,A)}+\frac{1}{2B_1}\|e_2-\bar{e}_2\|_{L^\infty(0,A)}+\frac{1}{2B_2}\|e_3-\bar{e}_3\|_{L^\infty(0,A)}\\
&\quad+\frac{1}{2}\left(\frac{A_2}{B_1}+\frac{A_3}{B_2}\right)\|K-\bar{K}\|_{L^\infty(0,A)},
\end{aligned}$$

where for $j=1,2$

$$\begin{aligned}
e_j-\bar{e}_j &= \beta_j(v_jx_j(\xi_j-\lambda_j)-\bar{v}_j\bar{x}_j(\bar{\xi}_j-\bar{\lambda}_j))-\hat{\beta}_j(v_jx_j\eta_j-\bar{v}_j\bar{x}_j\bar{\eta}_j)\\
&= \beta_j(\xi_j\bar{v}_j(x_j-\bar{x}_j)+x_j\xi_j(v_j-\bar{v}_j)+\bar{v}_j\bar{x}_j(\xi_j-\bar{\xi}_j))\\
&\quad-\beta_j(\lambda_j\bar{v}_j(x_j-\bar{x}_j)+x_j\lambda_j(v_j-\bar{v}_j)+\bar{v}_j\bar{x}_j(\lambda_j-\bar{\lambda}_j))\\
&\quad-\hat{\beta}_j(\eta_j\bar{v}_j(x_j-\bar{x}_j)+x_j\eta_j(v_j-\bar{v}_j)+\bar{v}_j\bar{x}_j(\eta_j-\bar{\eta}_j))
\end{aligned}$$

and

$$e_3-\bar{e}_3=\gamma_1d_1\eta_1(y_1-\bar{y}_1)+\gamma_1d_1\bar{y}_1(\eta_1-\bar{\eta}_1)+\gamma_2d_2\eta_2(y_2-\bar{y}_2)+\gamma_2d_2\bar{y}_2(\eta_2-\bar{\eta}_2).$$

$$||L(u_1,u_2)-L(\bar{u}_1,\bar{u}_2)||_{L^\infty(0,A)\times L^\infty(0,A)}$$

$$\begin{aligned}
&\le \frac{C_4}{2B_1}(||x_1-\bar{x_1}||_{L^\infty(0,A)}+||x_2-\bar{x_2}||_{L^\infty(0,A)}+||v_1-\bar{v_1}||_{L^\infty(0,A)}+||v_2-\bar{v_2}||_{L^\infty(0,A)})\\
&\quad+\frac{C_4}{2B_1}(||\xi_1-\bar{\xi}_1||_{L^\infty(0,A)}+||\xi_2-\bar{\xi}_2||_{L^\infty(0,A)}+||\lambda_1-\bar{\lambda}_1||_{L^\infty(0,A)}+||\lambda_2-\bar{\lambda}_2||_{L^\infty(0,A)})\\
&\quad+\left(\frac{C_4}{2B_1}+\frac{C_5}{2B_2}\right)(||\eta_1-\bar{\eta}_1||_{L^\infty(0,A)}+||\eta_2-\bar{\eta}_2||_{L^\infty(0,A)})+\frac{C_6}{2B_2}\|y_1-\bar{y}_1\|_{L^\infty(0,A)}\\
&\quad+\frac{C_6}{2B_2}\|y_2-\bar{y}_2\|_{L^\infty(0,A)}+\frac{1}{2}\left(\frac{A_2}{B_1}+\frac{A_3}{B_2}\right)(||i_1-\bar{i_1}||_{L^\infty(Q)}+||i_2-\bar{i_2}||_{L^\infty(Q)}).
\end{aligned}$$

Using the Lipschitz properties of the state and adjoint systems in Theorems 3.6 and 3.9, respectively, we have

$$||L(u_1,u_2)-L(\bar{u}_1,\bar{u}_2)|| \leq \frac{\bar{C}_{A,T}}{2}\left(\frac{1}{B_1}+\frac{1}{B_2}\right)\left(||u_1-\bar{u}_1||_{L^\infty(0,A)}+||u_2-\bar{u}_2||_{L^\infty(0,A)}\right). \tag{3.107}$$

If $\frac{\bar{C}_{A,T}}{2}\left(\frac{1}{B_1}+\frac{1}{B_2}\right)<1$, then the map $L$ admits a unique fixed point $(u_1^*,u_2^*)$, by the Banach Contraction Theorem. Next, we show that this fixed point is an optimal control pair, by using the minimizers, $(u_1^\varepsilon,u_2^\varepsilon)$, from Ekeland's Principle. To do this, we use the states $(x_1^\varepsilon,x_2^\varepsilon,y_1^\varepsilon,y_2^\varepsilon,V_1^\varepsilon,V_2^\varepsilon,S^\varepsilon,i_1^\varepsilon,i_2^\varepsilon)$ and $(\lambda_1^\varepsilon,\lambda_2^\varepsilon,\xi_1^\varepsilon,\xi_2^\varepsilon,\eta_1^\varepsilon,\eta_2^\varepsilon,p^\varepsilon,q_1^\varepsilon,q_2^\varepsilon)$ corresponding to the minimizer $(u_1^\varepsilon,u_2^\varepsilon)$. Thus

$$\begin{aligned}
&\|L(u_1^\varepsilon,u_2^\varepsilon)-\mathcal{H}\left(\frac{e_1^\varepsilon+e_2^\varepsilon-A_2K^\varepsilon-\sqrt{\varepsilon}\kappa_1^\varepsilon}{2B_1},\frac{e_3^\varepsilon-A_3K^\varepsilon-\sqrt{\varepsilon}\kappa_1^\varepsilon}{2B_2}\right)\|_{(L^\infty(0,A))^2}\\
=\;&\|\mathcal{H}\left(\frac{e_1^\varepsilon+e_2^\varepsilon-A_2K^\varepsilon}{2B_1},\frac{e_3^\varepsilon-A_3K^\varepsilon}{2B_2}\right)\\
&-\mathcal{H}\left(\frac{e_1^\varepsilon+e_2^\varepsilon-A_2K^\varepsilon-\sqrt{\varepsilon}\kappa_1^\varepsilon}{2B_1},\frac{e_3^\varepsilon-A_3K^\varepsilon-\sqrt{\varepsilon}\kappa_1^\varepsilon}{2B_2}\right)\|_{(L^\infty(0,A))^2}\\
\leq\;&\left\|\frac{\sqrt{\varepsilon}\kappa_1^\varepsilon}{2B_1}\right\|_{L^\infty(0,A)}+\left\|\frac{\sqrt{\varepsilon}\kappa_2^\varepsilon}{2B_2}\right\|_{L^\infty(0,A)}=\frac{\sqrt{\varepsilon}}{2}\left(\frac{1}{B_1}+\frac{1}{B_2}\right).
\end{aligned} \tag{3.108}$$

Next, we show that $(u_1^\varepsilon,u_2^\varepsilon)\to(u_1^*,u_2^*)\quad in\quad L^\infty(0,A)\times L^\infty(0,A)$. Now,

$$\begin{aligned}
&\|(u_1^*,u_2^*)-(u_1^\varepsilon,u_2^\varepsilon)\|_{(L^\infty(0,A))^2}\\
=\;&\|u_1^*-u_1^\varepsilon\|_{L^\infty(0,A)}+||u_2^*-u_2^\varepsilon||_{L^\infty(0,A)}\\
=\;&\left\|\mathcal{H}_1\left(\frac{a_1^*+a_2^*-A_2K^*}{2B_1}\right)-\mathcal{F}_1\left(\frac{e_1^\varepsilon+e_2^\varepsilon-A_2K^\varepsilon-\sqrt{\varepsilon}\kappa_1^*}{2B_1}\right)\right\|_{L^\infty(0,A)}\\
&+\left\|\mathcal{H}_2\left(\frac{a_3^*-A_3K^*}{2B_2}\right)-\mathcal{F}_2\left(\frac{e_3^\varepsilon-A_3K^\varepsilon-\sqrt{\varepsilon}\kappa_2^\varepsilon}{2B_2}\right)\right\|_{L^\infty(0,A)}\\
=\;&\left\|L(u_1^*,u_2^*)-\mathcal{H}\left(\frac{e_1^\varepsilon+e_2^\varepsilon-A_2K^\varepsilon-\sqrt{\varepsilon}\kappa_1^\varepsilon}{2B_1},\frac{e_3^\varepsilon-A_3K^\varepsilon-\sqrt{\varepsilon}\kappa_1^\varepsilon}{2B_2}\right)\right\|_{(L^\infty(0,A))^2}
\end{aligned}$$

$$
\begin{aligned}
&\leq \|L(u_1^*, u_2^*) - L(u_1^\varepsilon, u_2^\varepsilon)\|_{L^\infty(0,A)} \\
&\quad + \left\| L(u_1^\varepsilon, u_2^\varepsilon) - \mathcal{H}\left( \frac{e_1^\varepsilon + e_2^\varepsilon - A_2 K^\varepsilon - \sqrt{\varepsilon}\kappa_1^\varepsilon}{2B_1}, \frac{e_3^\varepsilon - A_3 K^\varepsilon - \sqrt{\varepsilon}\kappa_1^\varepsilon}{2B_2} \right) \right\|_{L^\infty(0,A)} \\
&\leq \frac{\bar{C}_{A,T}}{2}\left(\frac{1}{B_1} + \frac{1}{B_2}\right)(||u_1^* - u_1^\varepsilon\|_{L^\infty(0,A)} + \|u_2^* - u_2^\varepsilon\|_{L^\infty(0,A)}) + \frac{\sqrt{\varepsilon}}{2}\left(\frac{1}{B_1} + \frac{1}{B_2}\right),
\end{aligned}
$$

from equations (3.107) and (3.108). Also, $a_j^*$ and $e_j^*$ are defined in equations (3.105) and (3.106), respectively. Thus,

$$
\begin{aligned}
&\|u_1^* - u_1^\varepsilon\|_{L^\infty(0,A)} + \|u_2^* - u_2^\varepsilon\|_{L^\infty(0,A)} \\
&\qquad \leq \frac{\bar{C}_{A,T}}{2}\left(\frac{1}{B_1} + \frac{1}{B_2}\right)(\|u_1^* - u_1^\varepsilon\|_{L^\infty(0,A)} + \|u_2^* - u_2^\varepsilon||_{L^\infty(0,A)}) \\
&\qquad\quad + \frac{\sqrt{\varepsilon}}{2}\left(\frac{1}{B_1} + \frac{1}{B_2}\right).
\end{aligned}
$$

Whence,

$$
\|u_1^* - u_1^\varepsilon\|_{L^\infty(0,A)} + ||u_2^* - u_2^\varepsilon\|_{L^\infty(0,A)} \leq \frac{\frac{\sqrt{\varepsilon}}{2}\left(\frac{1}{B_1} + \frac{1}{B_2}\right)}{1 - \frac{\bar{C}_{A,T}}{2}\left(\frac{1}{B_1} + \frac{1}{B_2}\right)},
$$

for $\frac{\bar{C}_{A,T}}{2}\left(\frac{1}{B_1} + \frac{1}{B_2}\right)$ sufficiently small. Equivalently,

$$
\|(u_1^*, u_2^*) - (u_1^\varepsilon, u_2^\varepsilon)\|_{L^\infty(0,A)\times L^\infty(0,A)} \leq \frac{\frac{\sqrt{\varepsilon}}{2}\left(\frac{1}{B_1} + \frac{1}{B_2}\right)}{1 - \frac{\bar{C}_{A,T}}{2}\left(\frac{1}{B_1} + \frac{1}{B_2}\right)} \to 0 \quad as \quad \varepsilon \to 0^+.
$$

Thus,

$$
(u_1^\varepsilon, u_2^\varepsilon) \to (u_1^*, u_2^*) \quad in \quad L^\infty(0,A) \times L^\infty(0,A).
$$

Lastly, we establish that $(u_1^*, u_2^*)$ is indeed a minimizer of the functional, $\mathcal{J}$. Now, using Ekeland's Principle, we have $\mathcal{J}(u_1^\varepsilon, u_2^\varepsilon) \leq \inf_{(u_1,u_2)\in\mathcal{U}} \mathcal{J}(u_1, u_2) + \varepsilon$. Since $(u_1^\varepsilon, u_2^\varepsilon) \to (u_1^*, u_2^*)$ as $\varepsilon \to 0^+$, it follows that $\mathcal{J}(u_1^*, u_2^*) \leq \inf_{(u_1,u_2)\in\mathcal{U}} \mathcal{J}(u_1, u_2)$. □

## 3.4 Numerical Simulations

Using a numerical procedure as in Chapter 2, and with parameter values for group one ($j = 1$) as in Chapter 2, together with similar values for group two ($j = 2$), we obtain sample figures for the within-host and between-host dynamics.

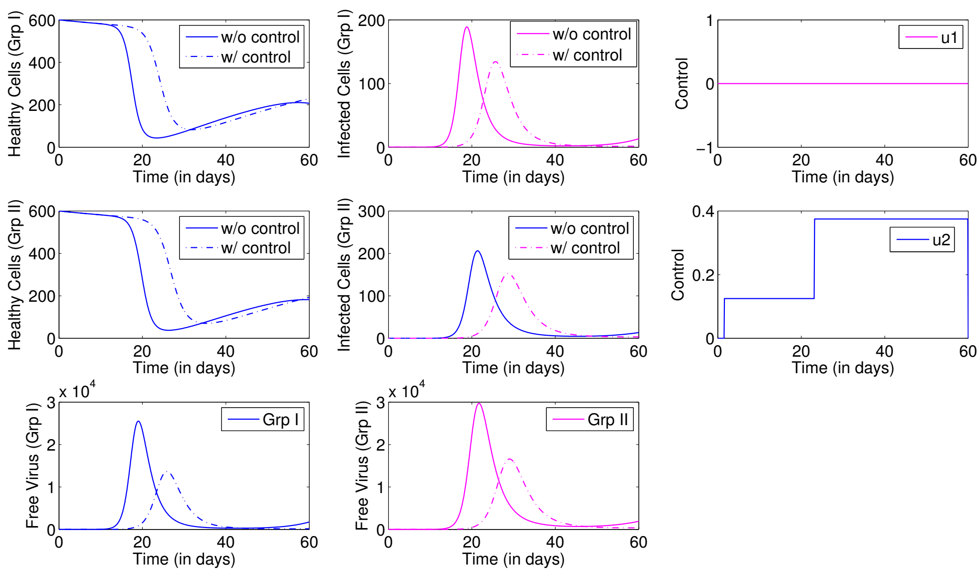


**Figure 3.1:** Infectious Individuals in the Presence/Absence of Control when $\Lambda = 2750$, $x_1^0 = x_2^0 = 600$ cells per mm$^3$, $y_1^0 = y_2^0 = 0$ cell per mm$^3$,$v_1^0 = v_2^0 = 0.005$ virions per mm$^3$, $\tilde{u}_1 = 0$ and $\tilde{u}_2 = 0.5$.

Figure 3.1 delineates the population of heathy cells, infected cells and free virus of both groups in the absence of transmission suppressing drug, but in the presence of the virion production suppressing drug. The acute phase observed in the free virus and infected cell populations within $10 - 30$ days since start-of-infection to $20 - 40$ days. At the population level, susceptible individuals experience a steady decrease in population within the first three years in the absence of control and a decrease within the first nine years in the presence of the virion production suppressing drug as shown in Figure 3.3. In the absence of control, a peak in prevalence is observed in both populations at the between-host level as depicted in Figure 3.2. In the presence of the virion production suppressing drug, trajectories for infectious populations indicate an oscillatory increase and decrease in prevalence.

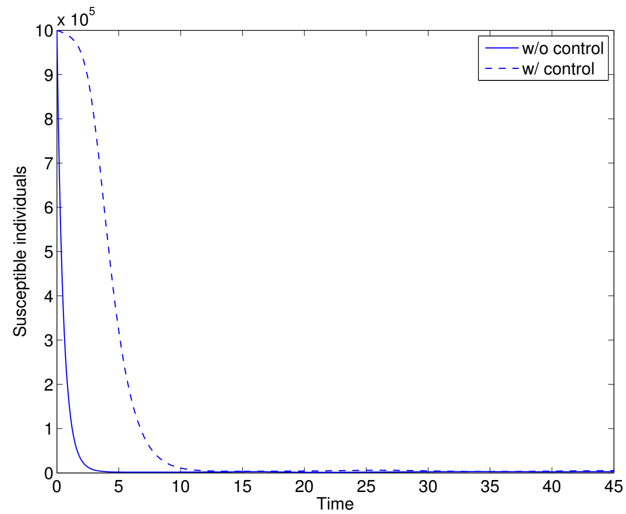


**Figure 3.2:** Susceptible Individuals in the Presence/Absence of Control when $\Lambda = 2750$, and $S_0 = 1 \times 10^6$.

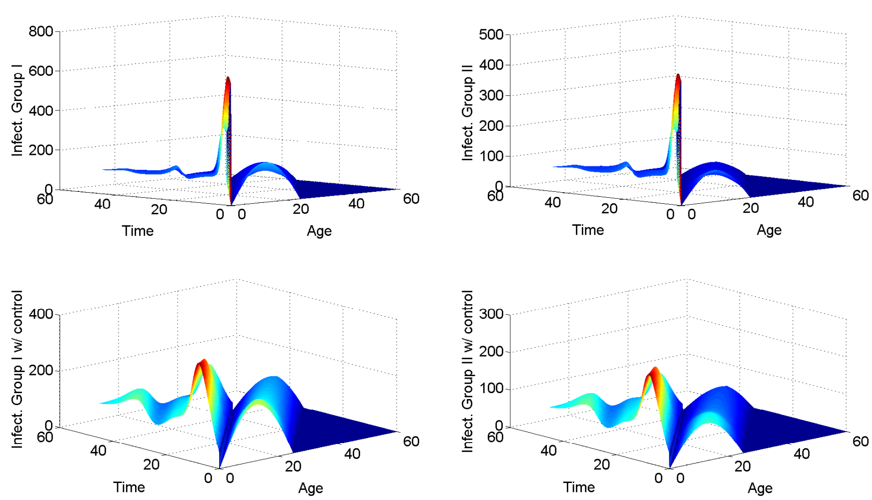


**Figure 3.3:** Infectious Individuals in the Presence/Absence of Control with Initial Age Distribution $i_1(\tau, 0) = 200 \sin(\frac{\pi\tau}{25})$, $i_2(\tau, 0) = 100 \sin(\frac{\pi\tau}{25})$.

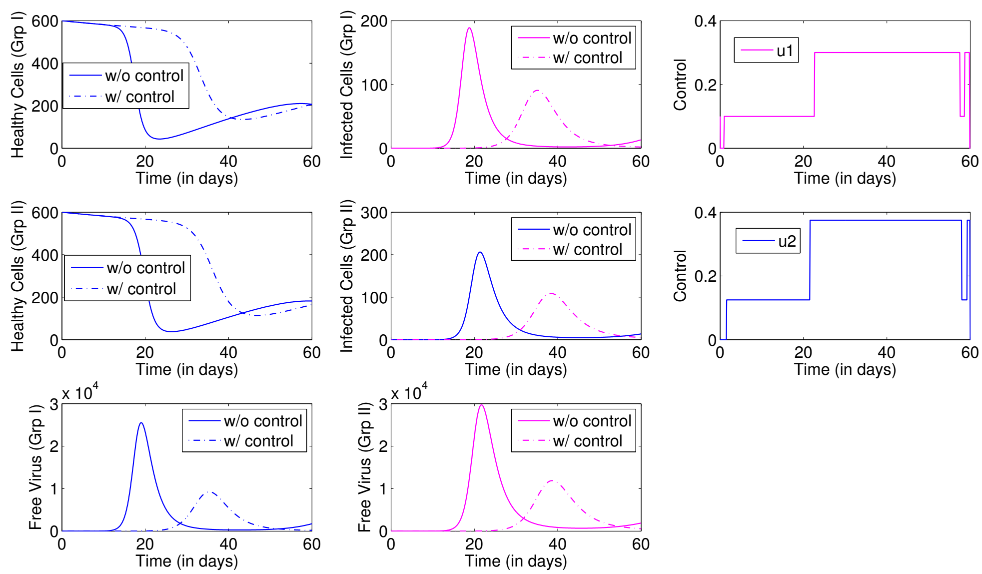


**Figure 3.4:** Infectious Individuals in the Presence/Absence of Control when $\Lambda = 2750$, $x_1^0 = x_2^0 = 600$ cells per mm$^3$, $y_1^0 = y_2^0 = 0$ cell per mm$^3$,$v_1^0 = v_2^0 = 0.005$ virions per mm$^3$, $\tilde{u}_1 = 0.4$ and $\tilde{u}_2 = 0.5$.

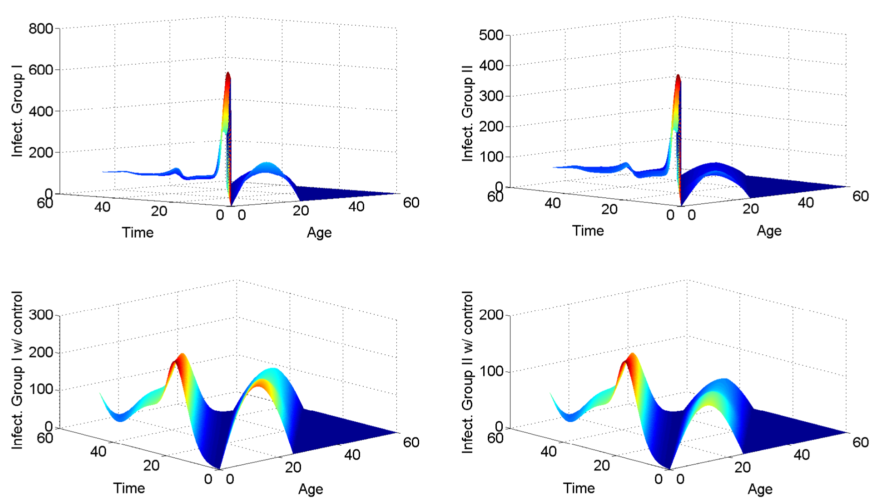


**Figure 3.5:** Infectious Individuals in the Presence/Absence of Control.

Figures 3.4 – 3.9 represent within-host and between-host populations in the presence of transmission and virion production suppresing drugs. In Figures 3.7 – 3.9, the death rate of free virus of groups one and two are $\delta_1 = 3$ and $\delta_2 = 1.5$, respectively.

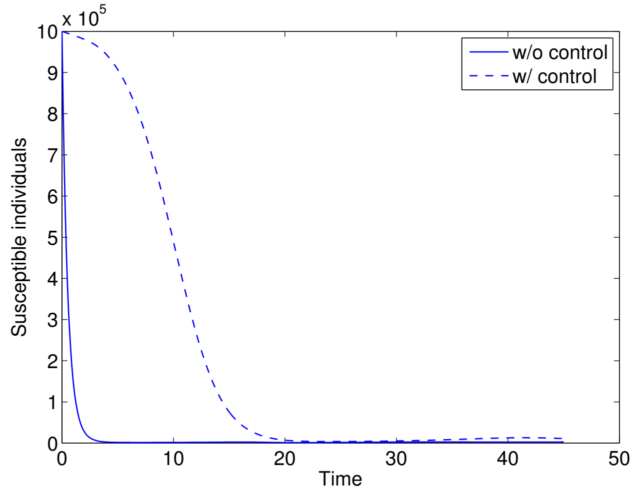


**Figure 3.6:** Susceptible Individuals in the Presence/Absence of Control.

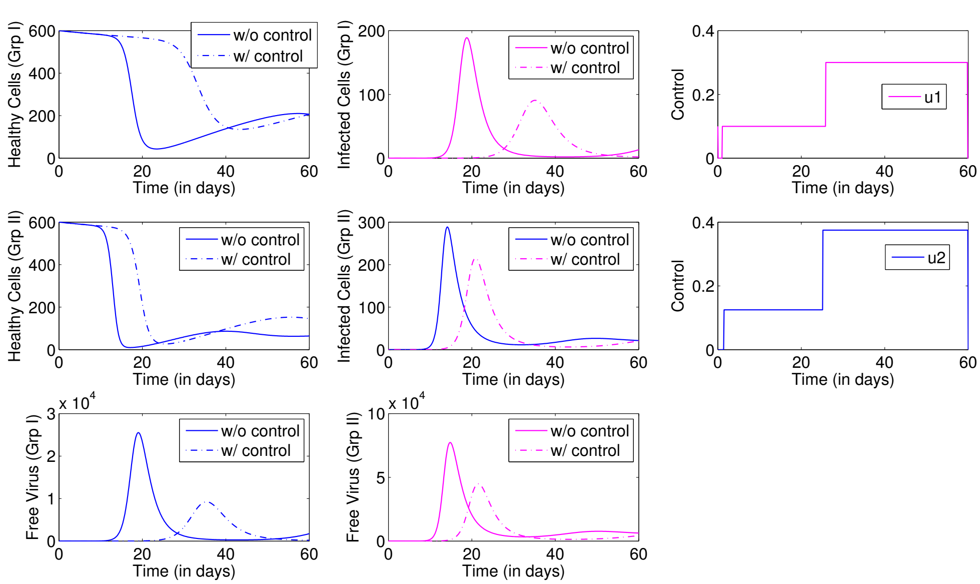


**Figure 3.7:** Infectious Individuals in the Presence/Absence of Control when $\Lambda = 2750$, $x_1^0 = x_2^0 = 600$ cells per mm$^3$, $y_1^0 = y_2^0 = 0$ cell per mm$^3$,$v_1^0 = v_2^0 = 0.005$ virions per mm$^3$, $\tilde{u}_1 = 0.4$, $\tilde{u}_2 = 0.5$, $\delta_1 = 3$ and $\delta_2 = 1.5$.

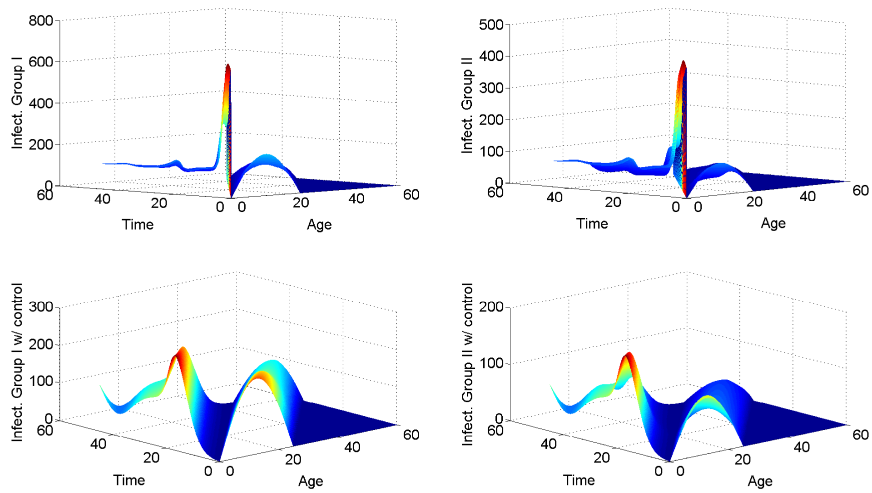


**Figure 3.8:** Infectious Individuals in the Presence/Absence of Control when $\delta_1 = 3$ and $\delta_2 = 1.5$.

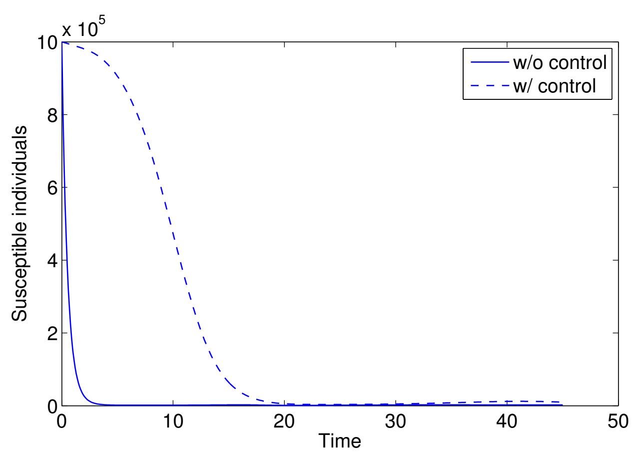


**Figure 3.9:** Susceptible Individuals in the Presence/Absence of Control when $\delta_1 = 3$ and $\delta_2 = 1.5$.

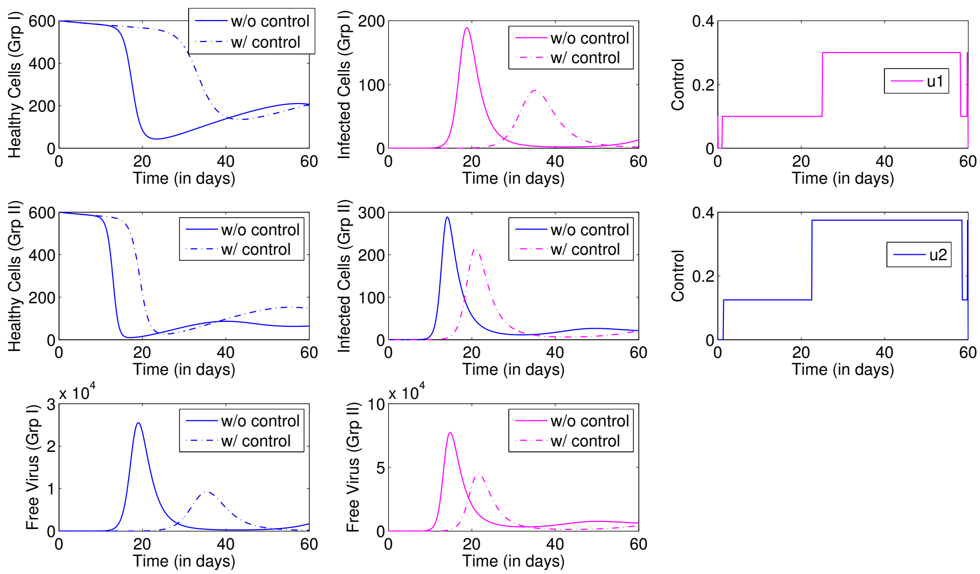


**Figure 3.10:** Infectious Individuals in the Presence/Absence of Control when $\Lambda = 2750$, $x_1^0 = x_2^0 = 600$ cells per mm$^3$, $y_1^0 = y_2^0 = 0$ cell per mm$^3$,$v_1^0 = v_2^0 = 0.005$ virions per mm$^3$, $\tilde{u}_1 = 0.4$ and $\tilde{u}_2 = 0.5$, $\delta_1 = 3$ and $\delta_2 = 1.5$.

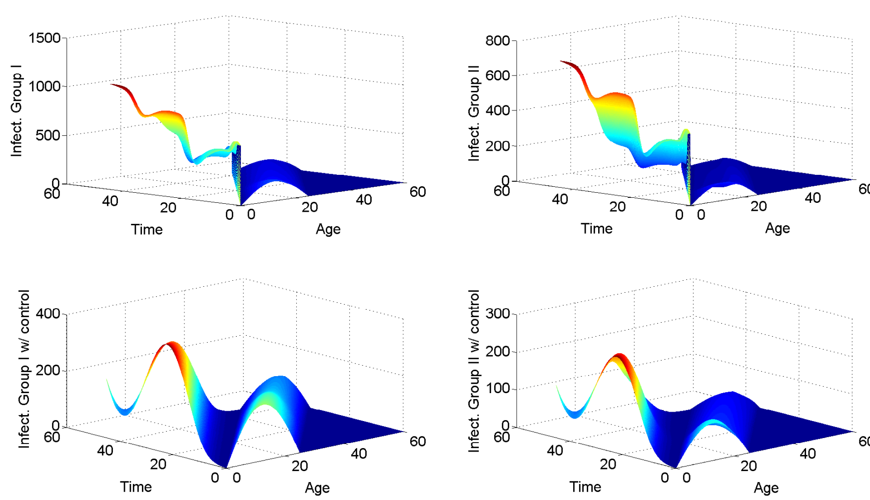


**Figure 3.11:** Infectious Individuals in the Presence/Absence of Control when $\delta_1 = 3$, $\delta_2 = 1.5$ and $\Lambda = 2750$ is changed to $\Lambda = 27500$.

Figures 3.10 – 3.12 represent trajectories for within-host and between-host populations when the clearance rate of free virus of groups one and two are $\delta_1 = 3$ and

$\delta_2 = 1.5$, respectively, with the recruitment rate of susceptible individuals changed from $\Lambda = 2750$ to $\Lambda = 27500$. Trajectories suggest an oscillatory increase in the populations of infectious indivuals in the absence of control and an oscillatory increase/decrease in the presence of control, but with lower severity in prevalence. Susceptible individuals in the presence of control experience an initial increase in population within the first 10 years, followed by a decrease from years $10 - 30$ and an increase afterwards.

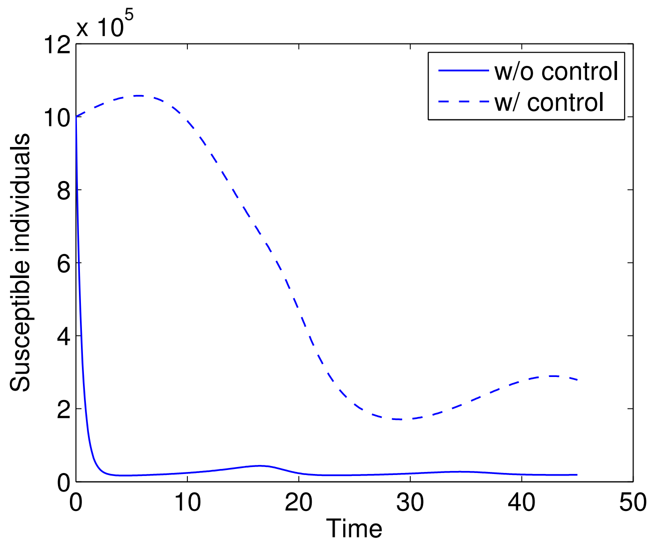


**Figure 3.12:** Susceptible Individuals in the Presence/Absence of Control when $\delta_1 = 3$, $\delta_2 = 1.5$ and $\Lambda = 2750$ is changed to $\Lambda = 27500$.

## 3.5 Conclusions

We formulated a coupled within-host model of ODEs and between-host model of ODE and PDEs with multiple immunology groups. Existence and uniquesness of solution, and stability of equilibria have been investigated. Local asymptotic and global stability results for the disease-free equilibrium are established when $\mathcal{R}_0 < 1$. When $\mathcal{R}_0 > 1$, local asymptotic stability result for the endemic equilibrium are obtained only if the maximal age-of-infection, $A$, is either small enough or sufficiently large.

Incorporating the same transmission and virion production suppressing drugs for both groups of individuals at the within-host level, illustrative numerical simulations for one set of parameter values are obtained. Simulations suggest an oscillatory increase/decrease in the number of infectious indiviuals but with lower severity in prevalence in the presence of control. Also, the susceptible population experiences an oscillatory increase/decrease in the number of susceptible individuals in the presence of control, and with a higher amplitude relative to the susceptible population in the absence of control. At the within-host level, simulations suggest a delay in the acute phase in virion production and proliferation of infected cells.

# Chapter 4

# Optimal Harvesting and Biocontrol in a Predator-Prey Model

## 4.1 Introduction

In the United States, cats are the most popular companion animal with more than 80 million living in our homes. The number of feral cats is unknown but estimated to range from 60 – 80 million [84]. The feral domestic cat is an opportunistic predator, eating what is most easily available, switching prey according to their relative spatial and temporal availability [47].

Among the most notorious and harmful introduced predators are feral cats (*Felis catus*). Cats have often been introduced on islands in attempts to control rats, which get to the shore from hitching a ride from sealing or whaling boats or from shipwrecks [41]. Feral cats are predatory invasive species with negative effect on wildlife and pose significant threat to tree and ground nesting birds, herpetofauna and small mammals they prey upon [84]. These introduced predators (cats) often attack native prey (birds) which have no anti-predation mechanisms, such as seabirds, which have to return to land to raise their young, after nesting on islands [41].

On remote oceanic islands, introduced feral cats pose devastating threats on the native fauna, particularly seabirds. For example, five cats introduced on Marion island in 1949 resulted in a population of more than 2000 cats some 25 years later, depleting some 500,000 common diving petrels and severely affecting hole-nesting petrels [94]. At this same time, five cats introduced on the Kerguelen islands grew to several tens of thousands and is now estimated to kill more than three million seabirds every year [94]. Controlling the population of cats in an attempt to conserve the population of seabirds on the Kerguelen islands is the motivation for our model. There has been some work on the control of the population of cats on remote islands, using Feline Immunodeficiency Virus (FIV) [24, 25, 26, 34, 94, 95]; see Robertson [102] for a review of feral cat control and Nogales et al. [91] for a review of feral cat eradication on islands.

We will construct appropriate models for predator-prey systems with disease in the predator population. Also, we will formulate optimal control problems with the objective of minimizing the predator population and maximizing the prey population via harvest and FIV infectivity. Thus, our goal is to investigate control strategies (harvest & disease-related) in a predator-prey model with induced disease in the predator population.

Our system of differential equations models the situation where FIV has already been introduced as a potential biological control agent to regulate the cats (predators) and therefore to conserve the birds (prey). Feline Immunodeficiency Virus is a retrovirus inducing Acquired Immunodeficiency Syndrome (AIDS) in cats and is thought to be transmitted by bites during fights for female monopolization or for territorial defense [95, 94]. Thus, FIV is dominant in the male cat. It is a host-specific virus with low virulence [65]. In the presence of FIV in the population, we divide the cat population into susceptible (S) and infectious (I) classes. As a first model, we concentrate on applying optimal control theory to harvest. Subsequently, we investigate a control strategy which incorporates time dependent controls and a scalar control simultaneously. The time dependent controls represent the harvest rate and the rate of trapping and infecting susceptible cats in the population, and the scalar control represents the initial number of infected predators.

For the remainder of the work in this chapter, we present our eco-epidemiological model in section 4.2, and establish the positivity and boundedness of state solutions. Also, we determine the basic and demographic reproduction numbers of cats, and investigate stability analysis of steady states. In section 4.3, we formulate an optimal control problem for our initial model with the objective of minimizing the predator population and cost of harvest, and maximizing the prey population. Necessary conditions, characterization and uniqueness results are established. In section 4.4, we analyze a predator-prey model which incorporates the initial number of infected cats as a scalar control, and time-dependent control functions of harvesting, and trapping and infecting susceptible cats in the population. In section 4.5, we carry out numerical simulations for our model, using a forward-backward numerical method, and present our conclusions in section 4.6.

## 4.2 Eco-epidemiological Model

In order to formulate our eco-epidemiological model, we formulate two submodels; namely, one describing the predator-prey dynamics of cats and birds, and the other describing disease spread within the cat population, motivated by the work of Oliveira and Hilker [95, 94]. Let $N(t)$ denote he density of prey at time $t$ and $P(t)$ denote the density of predator at time $t$. We assume that in the absence of the predator, the prey population grows logistically with intrinsic growth rate $r > 0$ and environmental carrying capacity $K > 0$. In the presence of a virus (Feline Immunodeficiency Virus, FIV), we divide the predator population into susceptible and infectious individuals, and assume that susceptible predators become infectious when they come in contact with infectious predators. Let $S(t)$ and $I(t)$ denote the density of susceptible and infectious predators, respectively, at time $t$, so that $P(t) = S(t) + I(t)$ is the total population of predators at time $t$. FIV infection leads to life long carriers, and thus, there is no recovery or immunity to FIV [25]. Finally, we incorporate culling to obtain the following eco-epidemiological model:

$$\frac{dN}{dt} = rN(t)\left(1 - \frac{N(t)}{K}\right) - aN(t)(S(t) + I(t)) \tag{4.1}$$

$$\frac{dS}{dt} = (b + \varepsilon_1 aN(t))(S(t) + I(t)) - \frac{\Phi(P(t))S(t)I(t)}{P(t)} - (m + h(t))S(t) \tag{4.2}$$

$$\frac{dI}{dt} = \frac{\Phi(P(t))S(t)I(t)}{P(t)} - (m + h(t) + \mu)I(t), \tag{4.3}$$

with initial conditions

$$N(0) = N_0, \quad S(0) = S_0, \quad I(0) = I_0, \tag{4.4}$$

where $m$ is the natural death rate of predator, $h(t) \geq 0$ is the culling rate of predator at time $t$, $\varepsilon_1$ is the trophic conversion efficiency of susceptible predators (conversion rate of prey biomass into that of the predator), $a$ is the predation rate of predators and $\mu$ denotes the additional mortality rate of predator due to infection. The term $\Phi(P)$ is the transmission rate from susceptible predator to infectious predator, which could be density-dependent with $\Phi(P) = \beta_{dd}P$, if the contact rate between individuals increases linearly, or frequency-dependent with $\Phi(P) = \beta_{fd}$, if the contact rate between individuals is constant. Since cats have a high reproductive capacity and are sexually mature by $5 - 6$ months of age, so that with high mortality rates, cat numbers are sustained [93], we incorporate the birth rate of cats, $b$, in our model. If cats depend solely on birds, then $b = 0$, otherwise, $b > 0$. Table 4.1 gives a description of the parameters and their units of the eco-epidemiological model.

In a population of cats, if the contact rate increases linearly, transmission rate is assumed to follow the mass action law. This is suitable for populations in urban habitats with more 1000 individuals per $km^2$ or rural/suburban habitats with 10-100 individuals per $km^2$ [65]. On the other, if there is a constant number of contacts with bites, transmission is assumed to follow the standard incidence (also called

**Table 4.1:** Parameters of the eco-epidemioogical model

| Parameter | Description | Units |
|---|---|---|
| $r$ | Recruitment rate of birds | year$^{-1}$ |
| $a$ | Predation rate of cats on birds | cat$^{-1}$year$^{-1}$ |
| $\varepsilon_1$ | Trophic conversion efficiency | cat bird$^{-1}$ |
| $m$ | Natural death rate of cats | year$^{-1}$ |
| $\mu$ | Disease-induced mortality of cats | year$^{-1}$ |
| $b$ | Birth rate of cats | year$^{-1}$ |
| $h$ | Culling rate of cats | year$^{-1}$ |
| $\beta_{dd}$ | Density dependent transmission | cat$^{-1}$year$^{-1}$ |
| $\beta_{fd}$ | Frequency dependent transmission | year$^{-1}$ |
| $K$ | Carrying capacity of birds | birds |

proportionate mixing). This is suitable for populations in rural/suburban habitats with cat densities from 100-1000 per $km^2$ and smaller than 10 individuals per $km^2$ in non-anthropized areas [65].

### 4.2.1 Reproduction Numbers, Steady States and Stability Analysis

In this subsection, we assume $h(t) \equiv h$ and $\Phi(P) = \beta_{dd}P$. We change variables to nondimensionalize system (4.1) – (4.3), and to study the stability analysis of steady states. We introduce the following nondimensional variables and parameters:

$$\begin{aligned} x &= \frac{N}{K} \quad y = \frac{S}{S_0} \quad z = \frac{I}{S_0} \quad \tau = rt \quad \alpha = \frac{aS_0}{r} \\ \beta &= \frac{\beta_{dd}S_0}{r} \quad \delta = \frac{b}{r} \quad \xi = \frac{a\varepsilon K}{r} \quad e = \frac{m}{r} \quad \gamma = \frac{\mu}{r} \quad \theta = \frac{h}{r} \end{aligned}$$

This leads to the following nondimensionalized system:

$$\frac{dx}{d\tau} = x(1-x) - \alpha x(y+z) \tag{4.5}$$
$$\frac{dy}{d\tau} = \delta(y+z) + \xi x(y+z) - \beta yz - (e+\theta)y \tag{4.6}$$
$$\frac{dz}{d\tau} = \beta yz - (e+\theta+\gamma)z. \tag{4.7}$$

Oliveira and Hilker [94] investigated the equilibrium solutions and stability analysis of system (4.1) – (4.3) when $h(t) \equiv 0$ and $b = 0$. In this subsection, we study the model when $h(t) \equiv h > 0$ and $b > 0$ (due to sustainability of the population of cats [93]).

**Theorem 4.1.** *System (4.5 ) – (4.7) has five possible equilibria:*
*(i) the trivial equilibrium point* $(x_1^*, y_1^*, z_1^*) = (0, 0, 0)$,
*(ii) the cat-free steady state* $(x_2^*, y_2^*, z_2^*) = (1, 0, 0)$,
*(iii) the predator-prey coexistence steady state in the disease-free subsystem*

$$(x_3^*, y_3^*, z_3^*) = \left(\frac{e+\theta-\delta}{\xi}, \frac{\delta+\xi-e-\theta}{\alpha\xi}, 0\right),$$

*which is biologically feasible if* $\delta < e+\theta$ *and* $\delta+\xi > e+\theta$,
*(iv) the predator steady state in the prey-free subsystem*

$$(x_4^*, y_4^*, z_4^*) = \left(0, \frac{e+\theta+\gamma}{\beta}, \frac{(\delta-e-\theta)(e+\theta+\gamma)}{\beta(e+\theta+\gamma-\delta)}\right),$$

*which is biologically feasible if* $\delta > e+\theta$ *and* $e+\theta+\gamma > \delta$,
*(v) the predator-prey coexistence equilibrium* $(x_5^*, y_5^*, z_5^*)$, *where*

$$x_5^* = \frac{\xi+\gamma+e+\theta-\delta-\sqrt{D}}{2\xi}, \quad y_5^* = \frac{e+\theta+\gamma}{\beta}$$
$$z_5^* = \frac{\beta(\xi+\delta)-(e+\theta+\gamma)(\beta+2\alpha\xi)+\beta\sqrt{D}}{2\alpha\beta\xi},$$

*with* $D = (\delta + \xi - (e + \theta + \gamma))^2 + \frac{4\alpha\gamma\xi}{\beta}(e + \theta + \gamma) > 0$*;* $x_5^*$ *and* $z_5^*$ *are positive if* $(e + \theta + \gamma)\left(1 - \frac{\alpha\gamma}{\beta}\right) > \delta$ *and* $\beta(\xi + \delta) + \beta\sqrt{D} > (e + \theta + \gamma)(\beta + 2\alpha\xi)$*, respectively.*

*Proof.* The steady states $(x_j^*, y_j^*, z_j^*)$ for $j = 1, 2, ..., 5$ are obtained by solving the equations $\frac{dx}{d\tau} = 0$, $\frac{dy}{d\tau} = 0$ and $\frac{dz}{d\tau} = 0$. For $x_5^* > 0$, the numerator was simplified to the above condition. □

Using the next generation method [28, 29, 30, 31, 32, 36], we obtain the following demographic reproduction number, $\mathcal{R}_D$, and basic reproduction number, $\mathcal{R}_0$, of cats in the presence of culling, evaluated at the cat-free equilibrium and the predator-prey coexistence steady state in the disease-free subsystem, respectively:

$$\mathcal{R}_D = \frac{\delta + \xi}{e + \theta} \quad \text{and} \quad \mathcal{R}_0 = \frac{\beta(e + \theta)(\mathcal{R}_D - 1)}{\alpha\xi(e + \theta + \gamma)}. \tag{4.8}$$

The demographic reproduction number gives the expected number of offspring of a predator individual in its lifetime, with the assumption that the prey population is at carrying capacity. On the other hand, the basic reproduction number, $\mathcal{R}_0$, only makes sense if $\mathcal{R}_D > 1$. If $\mathcal{R}_D > 1$, predators are sustained by prey, while the disease establishes itself in the population if $\mathcal{R}_0 > 1$. These reproduction numbers give insight into the existence and stability of the cat-free steady state and the predator-prey coexistence equilibrium in the disease-free subsystem. Next, we proceed to examine the stability of these steady states.

**Theorem 4.2.** *(i) The trivial extinction point* $(0, 0, 0)$ *is unstable.*
*(ii) The cat-free steady state* $(1, 0, 0)$ *is stable if* $\mathcal{R}_D < 1$ *and unstable if* $\mathcal{R}_D > 1$*.*
*(iii) The predator-prey coexistence steady state in the disease-free subsystem* $(x_3^*, y_3^*, z_3^*)$ *exists if* $\mathcal{R}_D > 1$ *and is stable if* $\mathcal{R}_0 < 1$*.*
*(iv) The predator steady state in the prey-free subsystem* $(x_4^*, y_4^*, z_4^*)$ *exists if* $\mathcal{R}_D > 1$*, and is stable if*

$$\frac{\gamma(e + \theta)(\mathcal{R}_D - 1)}{\xi\mathcal{R}_0(e + \theta + \gamma - \delta)} > 1.$$

*Proof.* The stability analysis of the nondimensionalized model (4.5)−(4.7) is governed by the Jacobian matrix

$$J(x,y,z) = \begin{pmatrix} 1-2x-\alpha(y+z) & -\alpha x & -\alpha x \\ \xi(y+z) & \delta-e-\theta+\xi x-\beta z & \delta+\xi x-\beta y \\ 0 & \beta z & \beta y-(e+\theta+\gamma) \end{pmatrix}. \tag{4.9}$$

(i) At the trivial extinction point $(x_1^*, y_1^*, z_1^*) = (0,0,0)$, the Jacobian matrix (4.9) reduces to

$$J_1(0,0,0) = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \delta-e-\theta & \delta \\ 0 & 0 & -(e+\theta+\gamma) \end{pmatrix}.$$

Thus, the eigenvalues of $J_1$ are $\lambda_1 = 1 > 0$, $\lambda_2 = \delta - e - \theta$ and $\lambda_3 = -(e+\theta+\gamma) < 0$. Hence, the trivial steady state $(0,0,0)$ is unstable.

(ii) At the cat-free steady state $(x_2^*, y_2^*, z_2^*) = (1,0,0)$, the Jacobian matrix (4.9) reduces to

$$J_2(1,0,0) = \begin{pmatrix} -1 & -\alpha & -\alpha \\ 0 & \delta-e-\theta+\xi & \delta+\xi \\ 0 & 0 & -(e+\theta+\gamma) \end{pmatrix}.$$

Thus, the eigenvalues of $J_2$ are $\lambda_1 = -1 < 0$, $\lambda_2 = (e+\theta)(\mathcal{R}_D - 1)$ and $\lambda_3 = -(e+\theta+\gamma) < 0$. Hence, the cat-free steady state $(1,0,0)$ is stable if $\mathcal{R}_D < 1$, and unstable if $\mathcal{R}_D > 1$.

(iii) At the predator-prey coexistence steady state in the disease-free subsystem $(x_3^*, y_3^*, z_3^*) = \left(\frac{e+\theta-\delta}{\xi}, \frac{\delta+\xi-e-\theta}{\alpha\xi}, 0\right)$, the Jacobian matrix (4.9) reduces to

$$J_3(x_3^*, y_3^*, z_3^*) = \begin{pmatrix} \frac{\delta-e-\theta}{\xi} & \frac{-\alpha(e+\theta-\delta)}{\xi} & \frac{-\alpha(e+\theta-\delta)}{\xi} \\ \frac{\delta+\xi-e-\theta}{\alpha} & 0 & e+\theta-\frac{\beta(\delta+\xi-e-\theta)}{\alpha\xi} \\ 0 & 0 & \beta\left(\frac{\delta+\xi-e-\theta}{\alpha\xi}\right)-(e+\theta+\gamma) \end{pmatrix}.$$

One eigenvalue of $J_3$ satisfies

$$\lambda_1 = \beta\left(\frac{\delta+\xi-e-\theta}{\alpha\xi}\right) - (e+\theta+\gamma) \equiv (e+\theta+\gamma)(\mathcal{R}_0 - 1),$$

and the other two eigenvalues, $\lambda_{2,3}$, satisfy the quadratic equation

$$\lambda_{2,3}^2 - \left(\frac{\delta-e-\theta}{\xi}\right)\lambda_{2,3} + \frac{(e+\theta-\delta)(\delta+\xi-e-\theta)}{\xi} = 0.$$

This gives

$$\begin{aligned}\lambda_2 &= \frac{\delta-e-\theta}{2\xi} + \frac{1}{2}\sqrt{\left(\frac{\delta-e-\theta}{\xi}\right)^2 - \frac{4(e+\theta-\delta)(e+\theta)(\mathcal{R}_D-1)}{\xi}},\\ \lambda_3 &= \frac{\delta-e-\theta}{2\xi} - \frac{1}{2}\sqrt{\left(\frac{\delta-e-\theta}{\xi}\right)^2 - \frac{4(e+\theta-\delta)(e+\theta)(\mathcal{R}_D-1)}{\xi}}.\end{aligned}$$

Thus, $\lambda_2$ and $\lambda_3$ are real and negative roots or complex roots with negative real parts. Hence, the predator-prey coexistence steady state in the disease-free subsystem is stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$.

(iv) At the predator steady state in the prey-free subsystem $(x_4^*, y_4^*, z_4^*) = \left(0, \frac{e+\theta+\gamma}{\beta}, \frac{(\delta-e-\theta)(e+\theta+\gamma)}{\beta(e+\theta+\gamma-\delta)}\right)$, the Jacobian matrix reduces to

$$J_4(x_4^*, y_4^*, z_4^*) = \begin{pmatrix} 1 - \frac{\alpha(e+\theta+\gamma)}{\beta} - \frac{\alpha(\delta-e-\theta)(e+\theta+\gamma)}{\beta(e+\theta+\gamma-\delta)} & 0 & 0 \\ \frac{\xi(e+\theta+\gamma)}{\beta} + \frac{\xi(\delta-e-\theta)(e+\theta+\gamma)}{\beta(e+\theta+\gamma-\delta)} & \frac{\delta(e+\theta-\delta)}{e+\theta+\gamma-\delta} & \delta-(e+\theta+\gamma) \\ 0 & \frac{(\delta-e-\theta)(e+\theta+\gamma)}{e+\theta+\gamma-\delta} & 0 \end{pmatrix}.$$

One eigenvalue of $J_4$ satisfies

$$\begin{aligned}\lambda_1 &= 1 - \frac{\alpha(e+\theta+\gamma)}{\beta} - \frac{\alpha(\delta-e-\theta)(e+\theta+\gamma)}{\beta(e+\theta+\gamma-\delta)}\\ &= 1 - \frac{\gamma(e+\theta)(\mathcal{R}_D-1)}{\xi\mathcal{R}_0(e+\theta+\gamma-\delta)},\end{aligned}$$

and the other two eigenvalues, $\lambda_{2,3}$, satisfy the quadratic equation

$$\lambda_{2,3}^2 - \left(\frac{\delta(e+\theta-\delta)}{e+\theta+\gamma-\delta}\right)\lambda_{2,3} + (\delta-e-\theta)(e+\theta+\gamma) = 0.$$

This gives

$$\begin{aligned}\lambda_2 &= \frac{\delta(e+\theta-\delta)}{2(e+\theta+\gamma-\delta)} + \frac{1}{2}\sqrt{\left(\frac{\delta(e+\theta-\delta)}{e+\theta+\gamma-\delta}\right)^2 - 4(\delta-e-\theta)(e+\theta+\gamma)}\\ \lambda_3 &= \frac{\delta(e+\theta-\delta)}{2(e+\theta+\gamma-\delta)} - \frac{1}{2}\sqrt{\left(\frac{\delta(e+\theta-\delta)}{e+\theta+\gamma-\delta}\right)^2 - 4(\delta-e-\theta)(e+\theta+\gamma)}.\end{aligned}$$

Thus, $\lambda_2$ and $\lambda_3$ are real and negative roots or complex roots, with negative real parts. Hence, the steady state $(x_4^*, y_4^*, z_4^*)$ is stable if $\frac{\gamma(e+\theta)(\mathcal{R}_D-1)}{\xi\mathcal{R}_0(e+\theta+\gamma-\delta)} > 1$ and unstable if $\frac{\gamma(e+\theta)(\mathcal{R}_D-1)}{\xi\mathcal{R}_0(e+\theta+\gamma-\delta)} < 1$. □

Finally, we examine the stability of the predator-prey coexistence equilibrium, using the Routh-Hurwitz conditions [1, 79, 89].

**Theorem 4.3.** *If* $\frac{(\beta+\alpha\xi)\sqrt{D}}{\alpha\xi} > \xi+\gamma-e+\theta+\delta$, $2e\xi > (1+\xi)\delta$, $\xi < 1$ *and* $\frac{(\gamma+1)}{2\xi}(\delta+\xi-(e+\theta+\gamma)+\sqrt{D}) > 1+\frac{\alpha\gamma}{\beta}(e+\theta+\gamma)$, *then the predator-prey coexistence equilibrium,* $\left(x_5^*, \frac{e+\theta+\gamma}{\beta}, z_5^*\right)$, *is stable.*

*Proof.* The Jacobian matrix (4.9) at the point $\left(x_5^*, \frac{e+\theta+\gamma}{\beta}, z_5^*\right)$ is

$$J_5\left(x_5^*, \frac{e+\theta+\gamma}{\beta}, z_5^*\right)$$

$$= \begin{pmatrix} 1-\frac{\alpha(e+\theta+\gamma)}{\beta}-2x_5^*-\alpha z_5^* & -\alpha x_5^* & -\alpha x_5^* \\ \frac{\xi(e+\theta+\gamma)}{\beta}+\xi z_5^* & \delta-e+\xi x_5^*-\beta z_5^* & \delta-(e+\theta+\gamma)+\xi x_5^* \\ 0 & \beta z_5^* & 0 \end{pmatrix},$$

The eigenvalues of $J_5$ satisfy

$$\left(1-\tfrac{\alpha(e+\theta+\gamma)}{\beta}-2x_5^*-\alpha z_5^*-\lambda\right)\left(-\lambda(\delta-e+\xi x_5^*-\beta z_5^*-\lambda)-\beta z_5^*(\delta-(e+\theta+\gamma)+\xi x_5^*)\right)$$

$$-\alpha x_5^*\left(\frac{\xi(e+\theta+\gamma)}{\beta}+\xi z_5^*\right)\lambda-\alpha\beta x_5^* z_5^*\left(\frac{\xi(e+\theta+\gamma)}{\beta}+\xi z_5^*\right)=0.$$

This leads to the characteristic equation

$$\lambda^3+a_1\lambda^2+a_2\lambda+a_3=0, \tag{4.10}$$

where

$$\begin{aligned}
a_1 &= -\left(1-\frac{\alpha(e+\theta+\gamma)}{\beta}+\delta-e+(\xi-2)x_5^*-(\alpha+\beta)z_5^*\right),\\
a_2 &= \left(1-\frac{\alpha(e+\theta+\gamma)}{\beta}-2x_5^*-\alpha z_5^*\right)(\delta-e+\xi x_5^*-\beta z_5^*)\\
&\quad+\alpha x_5^*\left(\frac{\xi(e+\theta+\gamma)}{\beta}+\xi z_5^*\right)-\beta z_5^*(\delta-(e+\theta+\gamma)+\xi x_5^*)\\
a_3 &= \beta z_5^*(\delta-(e+\theta+\gamma)+\xi x_5^*)\left(1-\frac{\alpha(e+\theta+\gamma)}{\beta}-2x_5^*-\alpha z_5^*\right)\\
&\quad+\alpha\beta x_5^* z_5^*\left(\frac{\xi(e+\theta+\gamma)}{\beta}+\xi z_5^*\right).
\end{aligned}$$

The eigenvalues of equation (4.10) have negative real parts, if the following Routh-Hurwitz conditions hold: $a_1>0$, $a_3>0$ and $a_1a_2>a_3$. Now,
$1-\frac{\alpha(e+\theta+\gamma)}{\beta}-x_5^*-\alpha z_5^*$

$$\begin{aligned}
&= 1-\frac{\alpha(e+\theta+\gamma)}{\beta}-\frac{\xi+e+\theta+\gamma-\delta-\sqrt{D}}{2\xi}\\
&\quad+\frac{-\beta(\delta+\xi)+(e+\theta+\gamma)(\beta+2\alpha\xi)-\beta\sqrt{D}}{2\beta\xi}\\
&= 1-\frac{\xi+e+\theta+\gamma-\delta-\sqrt{D}}{2\xi}+\frac{e+\theta+\gamma-\delta-\xi-\sqrt{D}}{2\xi}\\
&= 0.
\end{aligned}$$

Thus,

$$
\begin{aligned}
a_1 &= -\left(1-\frac{\alpha(e+\theta+\gamma)}{\beta}+\delta-e+(\xi-2)x_5^*-(\alpha+\beta)z_5^*\right),\\
&= e-\delta+(1-\xi)x_5^*+\beta z_5^*\\
&= e-\delta+\frac{\beta(\delta+\xi)-(e+\theta+\gamma)(\beta+2\alpha\xi)+\beta\sqrt{D}}{2\alpha\xi}\\
&\quad -\frac{\xi+\gamma+e+\theta-\delta-\sqrt{D}}{2}+x_5^*\\
&= \frac{\beta(\delta+\xi)}{2\alpha\xi}-\frac{\beta}{2\alpha\xi}(e+\theta+\gamma)-(\theta+\gamma)+\frac{(\beta+\alpha\xi)\sqrt{D}}{2\alpha\xi}\\
&\quad -\frac{\xi+\gamma+e+\theta+\delta}{2}+x_5^*\\
&= \frac{\beta(\delta+\xi)}{2\alpha\xi}-\frac{(\beta+2\alpha\xi)(e+\theta+\gamma)}{2\alpha\xi}+e+\frac{(\beta+\alpha\xi)\sqrt{D}}{2\alpha\xi}-\frac{\xi+\gamma+e+\theta+\delta}{2}+x_5^*\\
&> \frac{(\beta+\alpha\xi)\sqrt{D}}{2\alpha\xi}-\frac{\xi+\gamma-e+\theta+\delta}{2}+x_5^*>0.
\end{aligned}
$$

Next,

$$
\begin{aligned}
a_3 &= -\beta x_5^*z_5^*(\delta-e-\theta-\gamma+\xi x_5^*)+\alpha\beta x_5^*z_5^*\left(\frac{\xi(e+\theta+\gamma)}{\beta}+\xi z_5^*\right)\\
&= \beta x_5^*z_5^*\left(e+\theta+\gamma-\delta-\xi x_5^*+\frac{\alpha\xi(e+\theta+\gamma)}{\beta}+\alpha\xi z_5^*\right)\\
&= \beta x_5^*z_5^*\left(e+\theta-\delta+\gamma-\frac{\xi+\gamma+e+\theta-\delta-\sqrt{D}}{2}\right)\\
&\quad +\beta x_5^*z_5^*\left(\frac{\alpha\xi(e+\theta+\gamma)}{\beta}+\frac{\beta(\delta+\xi)-(e+\theta+\gamma)(\beta+2\alpha\xi)+\beta\sqrt{D}}{2\beta}\right)\\
&= \beta x_5^*z_5^*\left(e+\theta-\delta+\frac{\gamma+\delta-\xi-e-\theta+\sqrt{D}}{2}+\frac{\delta+\xi-e-\theta-\gamma+\sqrt{D}}{2}\right)\\
&= \beta\sqrt{D}x_5^*z_5^*>0.
\end{aligned}
$$

Simplifying the expressions in $a_2$, we obtain

$$\begin{aligned}
a_2 &= -x_5^*(\delta - e + \xi x_5^* - \beta z_5^*) \\
&\quad +\alpha x_5^* \left( \frac{\xi(e+\theta+\gamma)}{\beta} + \xi z_5^* \right) - \beta z_5^*(\delta - (e+\theta+\gamma) + \xi x_5^*) \\
&= x_5^* \left( e - \delta - \xi x_5^* + \beta z_5^* + \frac{\alpha\xi(e+\theta+\gamma)}{\beta} + \alpha\xi z_5^* \right) + \beta z_5^*(e+\theta-\delta+\gamma-\xi x_5^*) \\
&= x_5^* \left( e - \delta - \frac{\xi+\gamma+e+\theta-\delta-\sqrt{D}}{2} + \beta z_5^* + \frac{\alpha\xi(e+\theta+\gamma)}{\beta} \right) \\
&\quad + \frac{\beta(\delta+\xi) - (e+\theta+\gamma)(\beta+2\alpha\xi) + \beta\sqrt{D}}{2\beta} x_5^* + \beta(e+\theta-\delta+\gamma) z_5^* - \beta\xi x_4^* z_5^* \\
&= (-\theta-\gamma+\sqrt{D}) x_5^* + \beta(e+\theta-\delta+\gamma) z_5^* + \beta(1-\xi) x_5^* z_5^*.
\end{aligned}$$

Therefore,

$a_1 a_2 - a_3$

$$\begin{aligned}
&= (e - \delta + (1-\xi)x_5^* + \beta z_5^*) \left( (-\theta-\gamma+\sqrt{D}) x_5^* + \beta(e+\theta-\delta+\gamma) z_5^* + \beta(1-\xi) x_5^* z_5^* \right) \\
&\quad -\beta\sqrt{D} x_5^* z_5^* \\
&= (e - \delta + (1-\xi)x_5^* + \beta z_5^*)(\sqrt{D} - \theta - \gamma) x_5^* - \beta\sqrt{D} x_5^* z_5^* \\
&\quad +(e - \delta + (1-\xi)x_5^* + \beta z_5^*)(\beta(e+\theta-\delta+\gamma) z_5^* + \beta(1-\xi) x_5^* z_5^*) \\
&= \sqrt{D} x_5^* (e - \delta + (1-\xi) x_5^*) \\
&\quad +(e - \delta + (1-\xi)x_5^* + \beta z_5^*)(\beta(e+\theta-\delta+\gamma) z_5^* + \beta(1-\xi) x_5^* z_5^* - (\theta+\gamma) x_5^*),
\end{aligned}$$

with

$$\begin{aligned}
&\sqrt{D} x_5^* (e - \delta + (1-\xi) x_5^*) \\
&\qquad = \sqrt{D} x_5^* \left( e - \delta + \frac{\xi+\gamma+e+\theta-\delta-\sqrt{D}}{2\xi} - \frac{\xi+\gamma+e+\theta-\delta-\sqrt{D}}{2} \right)
\end{aligned}$$

$$
\begin{aligned}
&= \sqrt{D}x_5^*\left(\frac{\xi+\gamma+e+\theta-\delta-\sqrt{D}}{2\xi}+\frac{e-\xi-\gamma-\theta-\delta+\sqrt{D}}{2}\right)\\
&= \frac{\sqrt{D}x_5^*}{2\xi}\left(\xi+\gamma+e+\theta-\delta-\sqrt{D}-\xi(\xi+\gamma+e+\theta+\delta-\sqrt{D})+2e\xi\right)\\
&= \frac{\sqrt{D}x_5^*}{2\xi}\left((1-\xi)(\xi+\gamma+e+\theta-\sqrt{D})+2e\xi-(1+\xi)\delta\right)>0,
\end{aligned}
$$

and

$$
\begin{aligned}
&\beta(e+\theta-\delta+\gamma)z_5^*+\beta(1-\xi)x_5^*z_5^*-(\theta+\gamma)x_5^*\\
&\qquad > \alpha\gamma(e+\theta+\gamma)z_5^*+\beta(1-\xi)x_5^*z_5^*-(\theta+\gamma)x_5^*\\
&\qquad = \alpha e\gamma z_5^*+(\theta+\gamma)(\alpha\gamma z_5^*-x_5^*)+\beta(1-\xi)x_5^*z_5^*,
\end{aligned}
$$

where

$$
\begin{aligned}
&\alpha\gamma z_5^*-x_5^*\\
&= \gamma\left(\frac{\beta(\delta+\xi)-(e+\theta+\gamma)(\beta+2\alpha\xi)+\beta\sqrt{D}}{2\beta\xi}-\frac{\xi+\gamma+e+\theta-\delta-\sqrt{D}}{2\xi}\right)\\
&= \frac{\gamma}{2\xi}\left(\delta+\xi-(e+\theta+\gamma)+\sqrt{D}\right)+\frac{1}{2\xi}(\delta+\xi-(e+\theta+\gamma)+\sqrt{D})\\
&\quad -1-\frac{\alpha\gamma}{\beta}(e+\theta+\gamma)\\
&= \frac{(\gamma+1)}{2\xi}\left(\delta+\xi-(e+\theta+\gamma)+\sqrt{D}\right)-1-\frac{\alpha\gamma}{\beta}(e+\theta+\gamma)>0.
\end{aligned}
$$

Thus, Routh Hurwitz conditions hold, and hence, the predator-prey coexistence equilibrium is stable. □

In a situation requiring control of the cat population, we formulate an optimal control problem and investigate harvesting and disease-related control strategies. We are finished with the nondimensionalized system and return to system (4.1) – (4.3).

### 4.2.2 Positivity and Boundedness of State Solutions

In order to prove the existence of an optimal control problem in section 4.3, we require the state functions of the eco-epidemiological model to be bounded. First, we show that, if $N_0 > 0$, $S_0 > 0$ and $I_0 > 0$, then the state functions are positive and bounded for all $t \in [0, t_1]$.

**Theorem 4.4.** *Given the state equations for $N$, $S$ and $I$ defined in equations (4.1) – (4.3), there exist constants $C_1$, $C_2$, $C_3 > 0$ such that $0 < N(t) \leq C_1$, $0 < S(t) \leq C_2$ and $0 < I(t) \leq C_3$, for all $t \in [0, t_1]$.*

*Proof.* We start by establishing positivity of state functions for all $t > 0$. Now, from equation (4.1), we have

$$\frac{dN}{dt} = [r\left(1 - \frac{N(t)}{K}\right) - aP(t)]N(t)$$

so that

$$N(t) = N_0 exp\left\{\int_0^t (r\left(1 - \frac{N(\xi)}{K}\right) - aP(\xi))d\xi\right\} > 0.$$

Next, from the equation (4.2), we have

$$\begin{aligned}\frac{dI(t)}{dt} &= \frac{\Phi(P(t))S(t)I(t)}{P(t)} - (m + h(t) + \mu)I(t)\\ &= \left(\frac{\Phi(P(t))S(t)}{P(t)} - (m + h(t) + \mu)\right)I(t),\end{aligned}$$

so that

$$I(t) = I_0\ exp\left\{\int_0^t \left(\frac{\Phi(P(\xi))S(\xi)}{P(\xi)} - m - h(\xi) - \mu\right)d\xi\right\} > 0.$$

Finally, we consider the equation (4.3):

$$\begin{aligned}\frac{dS(t)}{dt} &= (b + \varepsilon_1 aN(t))(S(t) + I(t)) - \frac{\Phi(P(t))S(t)I(t)}{P(t)} - (m + h(t))S(t)\\ &= \left(b + \varepsilon_1 aN(t) - \frac{\Phi(P(t))I(t)}{P(t)} - (m + h(t))\right)S(t) + (b + \varepsilon_1 aN(t))I(t).\end{aligned}$$

Using the method of integrating factors, we obtain

$$\begin{aligned} S(t) &= S_0\, exp\left\{\int_0^t \left(b+\varepsilon_1 aN(\xi)-\frac{\Phi(P(\xi))I(\xi)}{P(\xi)}-m-h(\xi)\right)d\xi\right\} \\ &+\int_0^t (b+\varepsilon_1 aN(s))I(s)exp\left\{\int_s^t (b+\varepsilon_1 aN(\xi))d\xi\right\}ds \\ &+\int_0^t (b+\varepsilon_1 aN(s))I(s)exp\left\{-\int_s^t \left(\frac{\Phi(P(\xi))I(\xi)}{P(\xi)}+m+h(\xi)\right)d\xi\right\}ds > 0. \end{aligned}$$

Thus, for positive initial data, state functions of the eco-epidemiological model are positive for all $t > 0$.

Lastly, we show that the state functions are bounded in finite time. Now,

$$\begin{aligned} \frac{dN(t)}{dt} &= rN(t)\left(1-\frac{N(t)}{K}\right)-aN(t)(S(t)+I(t)) \\ &\leq rN(t)\left(1-\frac{N(t)}{K}\right), \end{aligned} \tag{4.11}$$

since $N(t) > 0$ and $P(t) = S(t) + I(t) > 0$ for all $t > 0$. The differential inequality (4.11) satisfies

$$N(t) \leq \frac{KN_0}{N_0+(K-N_0)e^{-rt}}.$$

Thus, $\lim_{t\to\infty}\sup N(t) \leq K$. It follows that $N$ is bounded. Next, since $N(t) > 0$, $P(t) > 0$ and $h(t) \geq 0$, with positive parameters $m$, $\varepsilon$, $a$ and $b$, we have

$$\begin{aligned} \frac{dP(t)}{dt} &= (b+\varepsilon_1 aN(t))P(t)-(m+h(t))P(t)-\mu I(t) \\ &\leq (b+\varepsilon_1 aN(t))P(t) \\ &\leq (b+C_1\varepsilon_1 a)P(t). \end{aligned}$$

Thus, by Gronwall's inequality in differential form,

$$P(t) \leq P_0 e^{(b+C_1\varepsilon_1 a)t} \leq P_0 e^{(b+C_1\varepsilon_1 a)t_1},$$

for all $t \in (0, t_1]$. Therefore, $P$ is bounded for any finite time $t \in [0, t_1]$. Since $P$ is bounded and $S$ and $I$ are finite, it follows that $S$ and $I$ are bounded. Hence, the state functions of the eco-epidemiological model are bounded. □

## 4.3 Optimal Control Formulation and Analysis for Harvesting Only

We first concentrate on finding an optimal harvesting strategy to minimize the predator population and maximize the prey population, while minimizing the cost involved in our control. Thus, we consider the following objective functional

$$J(h) = \int_0^{t_1} (A_1(S(t) + I(t)) - A_2N(t) + ch(t)(S(t) + I(t)) + \varepsilon h^2(t))dt, \qquad (4.12)$$

where $A_1$, $A_2$ , $c$ and $\varepsilon$ are positive constants that balance the relative importance of terms in $J$. The terms $\int_0^{t_1}(A_1(S(t) + I(t))dt$ and $\int_0^{t_1} A_2N(t)dt$ in the objective functional give the respective numbers of cats and birds over the time period $t_1$ being modeled. Also, the term $h(S + I)$ represents the total number of cats harvested, where $h$ represents the rate of harvesting cats from the population, and $c$ is the cost per cat harvested. Thus, $\int_0^{t_1}(ch(t)(S(t)+I(t))+\varepsilon h^2(t))dt$ gives the cost of harvesting cats from the population. Due to difficulty in harvesting at high levels, the cost of harvesting is nonlinear. For the sake of simplicity, we chose a quadratic cost.

In order to formulate our optimal control problem, we define the set of all admissible controls. Now, let

$$\mathcal{U} = \{h : [0, t_1] \to [0, h_{\max}] | h \text{ is Lebesgue measurable}\}$$

be the set of all admissible controls, then the optimal control formulation is:
Find $h^* \in \mathcal{U}$ such that

$$J(h^*) = \inf_{h \in \mathcal{U}} J(h)$$

subject to the state system (4.1)−(4.3).

### 4.3.1 Existence of Harvesting Optimal Control

As the first step in analyzing the optimal control problem, we prove the existence of such optimal control. Using the Pontryagin's Maximum Principle [99], we derive necessary conditions that an optimal control, $h^* \in [0, h_{\max}]$ and its corresponding states $(N^*, S^*, I^*)$ must satisfy.

**Theorem 4.5.** *There exists an optimal control $h^* \in \mathcal{U}$ which minimizes the objective functional, $J$, subject to the state system (4.1)−(4.3).*

*Proof.* By the boundedness of states and control, the infimum is finite, and thus there exists a minimizing sequence $\{h_n\}_{n\geq 1}$, and let $N_n$, $S_n$ and $I_n$ be state trajectories corresponding to $h_n$. That is,

$$\lim_{n\to\infty} J(h_n) = \inf_{h\in\mathcal{U}} J(h).$$

In section 4.2.2, we showed that for all $t \in [0, t_1]$, the state variables $N$, $S$ and $I$ are bounded. Therefore, there exist constants $C_1$, $C_2$ and $C_3$ such that $|N_n(t)| \leq C_1$, $|S_n(t)| \leq C_2$ and $|I_n(t)| \leq C_3$, for all $n$ and all $t \in [0, t_1]$. Since $N_n$, $S_n$ and $I_n$ are bounded for all $n$ over the interval $[0, t_1]$ and from the structure of system (4.1)−(4.3), it follows that their derivatives $N_n'$, $S_n'$ and $I_n'$ are also bounded for all $n$ and all $t \in [0, t_1]$. Thus, there exist constants $C_4$, $C_5$ and $C_6$ such that $|N_n'(t)| \leq C_4$, $|S_n'(t)| \leq C_5$ and $|I_n'(t)| \leq C_6$, for all $n$ and all $t \in [0, t_1]$. It follows that $N_n$, $S_n$ and $I_n$ are Lipschitz continuous, since differentiable functions with bounded first derivatives are Lipschitz continuous. Thus, there exist Lipschitz constants $K_1$, $K_2$ and $K_3$ such that

$$|N_n(\tilde{t})-N_n(\hat{t})| \leq K_1|\tilde{t}-\hat{t}|, \quad |S_n(\tilde{t})-S_n(\hat{t})| \leq K_2|\tilde{t}-\hat{t}| \quad \textit{and} \quad |I_n(\tilde{t})-I_n(\hat{t})| \leq K_3|\tilde{t}-\hat{t}|$$

for all $\tilde{t}, \hat{t} \in [0, t_1]$. Let $K = \max\{K_1, K_2, K_3\}$, then $N_n$, $S_n$ and $I_n$ are Lipschitz continuous with the same Lipschitz constant $K$. Thus, the sequence $\{N_n, S_n, I_n\}$ is equicontinuous. Therefore, by Arzela-Ascoli theorem, there exists $(N^*, S^*, I^*)$ such that on a subsequence,

$$(N_n, S_n, I_n) \to (N^*, S^*, I^*) \quad \text{uniformly on} \ \ [0, t_1].$$

Also, the control sequence, $h_n$, is bounded for any $n$ and $t$. Precisely, $|h_n(t)| \leq h_{\max}$ for any $n$ and $t$ by definition of $\mathcal{U}$. Thus, $h_n(.)$ is uniformly bounded in $L^\infty([0, t_1])$, and hence uniformly bounded in $L^2([0, t_1])$. Since every bounded sequence in $L^2$ has a weakly convergent subsequence, there exists a subsequence $h_{n_k}$ and control $h^* \in \mathcal{U}$ such that

$$h_{n_k} \rightharpoonup h^* \quad \text{weakly in} \quad L^2([0, t_1]).$$

Using the lower-semicontinuity of $L^2$ norms with respect to weak convergence, we have

$$\int_0^{t_1} (h^*)^2 dt \leq \liminf_{n_k \to \infty} \int_0^{t_1} h_{n_k}^2 dt.$$

Therefore,

$$\begin{aligned} J(h^*) &= \int_0^{t_1} (A_1(S^*(t) + I^*(t)) - A_2 N^*(t) + c h^*(t)(S^*(t) + I^*(t)) + \varepsilon (h^*(t))^2) dt \\ &\leq \liminf_{n \to \infty} \int_0^{t_1} (A_1(S_n(t) + I_n(t)) - A_2 N_n(t) + c h_n(t)(S_n(t) + I_n(t)) + \varepsilon (h_n(t))^2) dt \\ &= \lim_{n \to \infty} J(h_n) \\ &= \inf_{h \in \mathcal{U}} J(h). \end{aligned}$$

Using the convergence of the sequences $(N_n)_{n \geq 1}$, $(S_n)_{n \geq 1}$ and $(I_n)_{n \geq 1}$ and passing to the limit in the ODE system, we have that $N^*$, $S^*$ and $I^*$ are the states corresponding to the control $h^*$. Note that the uniform convergence of states and the weak convergence of the controls are needed in terms like $h_n S_n$. Thus, we conclude that

$$J(h^*) = \min_{h \in \mathcal{U}} J(h),$$

meaning, $h^*$ is an optimal control. □

### 4.3.2 Characterization of Optimal Control

In this subsection, we construct the Hamiltonian, $H := H(t, N(t), S(t), I(t), h(t))$, for our problem using the integrand of the objective functional (4.12), adjoint functions, and the right-hand side of our state equations, and use Pontryagin's Maximum Principle to derive necessary conditions. Thus, the Hamiltonian is

$$\begin{aligned} H &= A_1(S(t)+I(t)) - A_2 N(t) + ch(t)(S(t)+I(t)) + \varepsilon h(t)^2 \\ &\quad + \lambda_N(t)(rN(t)\left(1 - \frac{N(t)}{K}\right) - aN(t)(S(t)+I(t))) \\ &\quad + \lambda_S(t)\left((b + \varepsilon_1 a N(t))(S(t)+I(t)) - \frac{\Phi(P(t))S(t)I(t)}{P(t)} - (m + h(t))S(t)\right) \\ &\quad + \lambda_I(t)\left(\frac{\Phi(P(t))S(t)I(t)}{P(t)} - (m + h(t) + \mu)I(t)\right), \end{aligned}$$

where $\lambda_N$, $\lambda_S$ and $\lambda_I$ are adjoint functions associated with the states $N$, $S$ and $I$, respectively.

**Theorem 4.6.** *For density-dependent transmission, and given an optimal control $h^*$, with corresponding states $N^*$, $S^*$ and $I^*$, there exist adjoint functions $\lambda_N$, $\lambda_S$ and $\lambda_I$ satisfying*

$$\begin{aligned}
\lambda_N'(t) &= (-r + \frac{2rN^*(t)}{K} + a(S^*(t) + I^*(t)))\lambda_N(t) - \varepsilon_1 a(S^*(t) + I^*(t))\lambda_S(t) \\
&\quad + A_2 && (4.13) \\
\lambda_S'(t) &= aN^*(t)\lambda_N(t) - ch^*(t) - A_1 \\
&\quad -(b + \varepsilon_1 aN^*(t) - \beta_{dd} I^*(t) - (m + h^*(t)))\lambda_S(t) - \beta_{dd} I^*(t)\lambda_I(t) && (4.14) \\
\lambda_I'(t) &= aN^*(t)\lambda_N(t) - ch^*(t) - A_1 && (4.15) \\
&\quad -(b + \varepsilon_1 aN^*(t) - \beta_{dd} S^*(t))\lambda_S(t) - (\beta_{dd} S^*(t) - (m + h^*(t) + \mu))\lambda_I(t) \\
\lambda_N(t_1) &= \lambda_S(t_1) = \lambda_I(t_1) = 0. && (4.16)
\end{aligned}$$

*Furthermore, the optimal control is characterized by*

$$h^*(t) = \min\left\{h_{\max}, \max\left\{0, \frac{S^*(t)\lambda_S(t) + I^*(t)\lambda_I(t) - c(S^*(t) + I^*(t))}{2\varepsilon}\right\}\right\}. \quad (4.17)$$

*Proof.* For density-dependent transmission, $\Phi(P) = \beta_{dd} P$, where $\beta_{dd}$ is the transmission rate. We find the derivatives of the adjoint functions by differentiating the Hamiltonian with respect to different state variables. That is,

$$\lambda_N'(t) = -\frac{\partial H}{\partial N}, \quad \lambda_S'(t) = -\frac{\partial H}{\partial S} \quad \text{and} \quad \lambda_I'(t) = -\frac{\partial H}{\partial I}.$$

The optimality equation for the problem is

$$\frac{\partial H}{\partial h} = c(S(t) + I(t)) + 2\varepsilon h(t) - S(t)\lambda_S(t) - I(t)\lambda_I(t). \quad (4.18)$$

- On the set $\{t | h^*(t) = 0\}$, $\frac{\partial H}{\partial h} \geq 0$, so that

$$c(S^*(t) + I^*(t)) - S^*(t)\lambda_S(t) - I^*(t)\lambda_I(t) \geq 0.$$

Dividing both sides of the last inequality by $-2\varepsilon(\varepsilon > 0)$, we have

$$\frac{S^*(t)\lambda_S(t) + I^*(t)\lambda_I(t) - c(S^*(t) + I^*(t))}{2\varepsilon} \leq 0.$$

Thus, on this set, the following characterization holds:

$$h^*(t) = \max\left(0, \frac{S^*(t)\lambda_S(t) + I^*(t)\lambda_I(t) - c(S^*(t) + I^*(t))}{2\varepsilon}\right). \tag{4.19}$$

• On the set $\{t|h^*(t) = h_{\max}\}$, $\frac{\partial H}{\partial h} \leq 0$, so that

$$c(S^*(t) + I^*(t)) + 2\varepsilon h_{max} - S^*(t)\lambda_S(t) - I^*(t)\lambda_I(t) \leq 0.$$

Thus,

$$\frac{S^*(t)\lambda_S(t) + I^*(t)\lambda_I(t) - c(S^*(t) + I^*(t))}{2\varepsilon} \geq h_{\max}.$$

Thus, on this set, the following characterization holds:

$$h^*(t) = \min\left(h_{\max}, \frac{S^*(t)\lambda_S(t) + I^*(t)\lambda_I(t) - c(S^*(t) + I^*(t))}{2\varepsilon}\right). \tag{4.20}$$

• On the set $\{t|0 < h^*(t) < h_{\max}\}$, $\frac{\partial H}{\partial h} = 0$. This yields $c(S^*(t) + I^*(t)) - S^*(t)\lambda_S(t) - I^*(t)\lambda_I(t) = 0$. Solving for the control function $h^*$, we have

$$h^*(t) = \frac{S^*(t)\lambda_S(t) + I^*(t)\lambda_I(t) - c(S^*(t) + I^*(t))}{2\varepsilon}. \tag{4.21}$$

Hence, we obtain the optimal control characterization given in equation (4.17), by combining equations (4.19) and (4.20). □

**Theorem 4.7.** *For frequency-dependent transmission, and given an optimal control $h^*$, with corresponding states $N^*$, $S^*$ and $I^*$, there exist adjoint functions $\lambda_N$, $\lambda_S$ and $\lambda_I$ satisfying the equations*

$$
\begin{aligned}
\lambda_N'(t) &= (-r + \frac{2rN^*(t)}{K} + a(S^*(t)+I^*(t)))\lambda_N(t) - \varepsilon_1 a(S^*(t)+I^*(t))\lambda_S(t) \\
&\quad + A_2 && (4.22) \\
\lambda_S'(t) &= aN^*(t)\lambda_N(t) - \left(b + \varepsilon_1 aN^*(t) - (m+h^*(t)) - \beta_{fd}\left(\frac{I^*(t)}{S^*(t)+I^*(t)}\right)^2\right)\lambda_S(t) \\
&\quad - \beta_{fd}\left(\frac{I^*(t)}{S^*(t)+I^*(t)}\right)^2 \lambda_I(t) - ch^*(t) - A_1 && (4.23) \\
\lambda_I'(t) &= aN^*(t)\lambda_N(t) - \left(b + \varepsilon_1 aN^*(t) - \beta_{fd}\left(\frac{S^*(t)}{S^*(t)+I^*(t)}\right)^2\right)\lambda_S(t) \\
&\quad - \left(\beta_{fd}\left(\frac{S^*(t)}{S^*(t)+I^*(t)}\right)^2 - (m+h^*(t)+\mu)\right)\lambda_I(t) - ch^*(t) - A_1 && (4.24) \\
\lambda_N(t_1) &= \lambda_S(t_1) = \lambda_I(t_1) = 0. && (4.25)
\end{aligned}
$$

*Furthermore, the optimal control is characterized by*

$$
h^*(t) = \min\left\{h_{\max}, \max\left\{0, \frac{S^*(t)\lambda_S(t) + I^*(t)\lambda_I(t) - c(S^*(t)+I^*(t))}{2\varepsilon}\right\}\right\}. \quad (4.26)
$$

*Proof.* Follows as in Theorem 4.6. □

**Remark:** The adjoint systems in Theorems 4.6 and 4.7 are linear in $\lambda_N$, $\lambda_S$ and $\lambda_I$. Since we have a linear system in finite time with bounded coefficients, it follows that $\lambda_N$, $\lambda_S$ and $\lambda_I$ are uniformly bounded.

### 4.3.3 Optimality System with Density-dependent Transmission

The optimality system consists of the state equations, initial conditions, adjoint equations, transversality conditions and optimal control characterization. For density-dependent transmission, the optimality system is:

$$\begin{aligned}
\frac{dN}{dt} &= rN(t)\left(1-\frac{N(t)}{K}\right) - aN(t)(S(t)+I(t)) && (4.27)\\
\frac{dS}{dt} &= (b+\varepsilon_1 aN(t))(S(t)+I(t)) - \beta_{dd}S(t)I(t) - (m+h(t))S(t) && (4.28)\\
\frac{dI}{dt} &= \beta_{dd}S(t)I(t) - (m+h(t)+\mu)I(t) && (4.29)\\
\lambda_N'(t) &= \left(-r+\frac{2rN(t)}{K}+a(S(t)+I(t))\right)\lambda_N(t) - \varepsilon_1 a(S(t)+I(t))\lambda_S(t) + A_2 && (4.30)\\
\lambda_S'(t) &= aN(t)\lambda_N(t) - (b+\varepsilon_1 aN(t) - \beta_{dd}I(t) - m - h(t))\lambda_S(t) - \beta_{dd}I(t)\lambda_I(t)\\
&\quad -ch(t) - A_1 && (4.31)\\
\lambda_I'(t) &= aN(t)\lambda_N(t) - (b+\varepsilon_1 aN(t) - \beta_{dd}S(t))\lambda_S(t) - (\beta_{dd}S(t) - m - h(t) - \mu)\lambda_I(t)\\
&\quad -ch(t) - A_1 && (4.32)\\
h(t) &= \min\left(h_{\max}, \max\left(0, \frac{S(t)\lambda_S(t)+I(t)\lambda_I(t)-c(S(t)+I(t))}{2\varepsilon}\right)\right), && (4.33)
\end{aligned}$$

with initial conditions (4.4) and final time conditions (4.16), where we have dropped the asterisks for notational simplicity.

### 4.3.4 Uniqueness of Optimality System

Using the boundedness of state and adjoint functions, we show that the solution of the optimality system is unique. The uniqueness of optimality system guarantees the uniqueness of the optimal control. In establishing the uniqueness property, we shall use the Lipschitz property of the function $h$, where $h(s) = \min\{\beta, \max\{\alpha, s\}\}$, for fixed constants $\alpha, \beta \in \Re^+$, with $\beta > \alpha$. Now, we state and prove an important property on the uniqueness of optimality system.

**Theorem 4.8.** *For $t_1$ sufficiently small, the optimality system (4.27) – (4.33) is unique.*

*Proof.* Assume $(N, S, I, \lambda_N, \lambda_S, \lambda_I)$ and $(\bar{N}, \bar{S}, \bar{I}, \bar{\lambda}_N, \bar{\lambda}_S, \bar{\lambda}_I)$ are solutions of the optimality system (4.27) – (4.33), and set

$$
\begin{array}{llll}
N(t) = e^{\xi t}x(t) & \bar{N}(t) = e^{\xi t}\bar{x}(t) & \lambda_N(t) = e^{-\xi t}u(t) & \bar{\lambda}_N(t) = e^{-\xi t}\bar{u}(t) \\
S(t) = e^{\xi t}y(t) & \bar{S}(t) = e^{\xi t}\bar{y}(t) & \lambda_S(t) = e^{-\xi t}u(t) & \bar{\lambda}_S(t) = e^{-\xi t}\bar{v}(t) \\
I(t) = e^{\xi t}z(t) & \bar{I}(t) = e^{\xi t}\bar{z}(t) & \lambda_I(t) = e^{-\xi t}w(t) & \bar{\lambda}_I(t) = e^{-\xi t}\bar{w}(t)
\end{array}
$$

with the following characterization of the optimal control:

$$
\begin{aligned}
h(t) &= min\left(h_{max}, max\left(0, \frac{S(t)\lambda_S(t) + I(t)\lambda_I(t) - c(S(t) + I(t))}{2\varepsilon}\right)\right) \\
\bar{h}(t) &= min\left(h_{max}, max\left(0, \frac{\bar{S}(t)\bar{\lambda}_S(t) + \bar{I}(t)\bar{\lambda}_I(t) - c(\bar{S}(t) + \bar{I}(t))}{2\varepsilon}\right)\right).
\end{aligned}
$$

Substituting the assumed form of solutions and optimal control characterization into the optimality system (4.27) – (4.33), we have

$$
\begin{aligned}
e^{\xi t}(x' + \xi x) &= re^{\xi t}x(1 - \frac{e^{\xi t}x}{K}) - ae^{2\xi t}x(y + z) && (4.34) \\
e^{\xi t}(y' + \xi y) &= be^{\xi t}(y + z) + \varepsilon_1 ae^{2\xi t}x(y + z) - \beta_{dd}e^{2\xi t}yz - (m + h)e^{\xi t}y && (4.35) \\
e^{\xi t}(z' + \xi z) &= \beta_{dd}e^{2\xi t}yz - (m + h + \mu)e^{\xi t}z && (4.36) \\
e^{-\xi t}(u' - \xi u) &= (-re^{-\xi t} + \frac{2rx}{K} + a(y + z))u - \varepsilon_1 a(y + z)v + A_2 && (4.37) \\
e^{-\xi t}(v' - \xi v) &= axu - (\varepsilon_1 ax - \beta_{dd}z + (b - m - h)e^{-\xi t})v - \beta_{dd}wz \\
&\quad -ch - A_1 && (4.38) \\
e^{-\xi t}(w' - \xi w) &= axu - (be^{-\xi t} + \varepsilon_1 ax - \beta_{dd}y)v - (\beta_{dd}y - (m + h + \mu)e^{-\xi t})w \\
&\quad -ch - A_1. && (4.39)
\end{aligned}
$$

and

$$
\begin{aligned}
e^{\xi t}(\bar{x}' + \xi \bar{x}) &= r e^{\xi t}\bar{x}(1 - \frac{e^{\xi t}\bar{x}}{K}) - a e^{2\xi t}\bar{x}(\bar{y} + \bar{z}) && (4.40)\\
e^{\xi t}(\bar{y}' + \xi \bar{y}) &= b e^{\xi t}(\bar{y} + \bar{z}) + \varepsilon_1 a e^{2\xi t}\bar{x}(\bar{y} + \bar{z}) - \beta_{dd} e^{2\xi t}\bar{y}\bar{z} - (m + \bar{h}) e^{\xi t}\bar{y} && (4.41)\\
e^{\xi t}(\bar{z}' + \xi \bar{z}) &= \beta_{dd} e^{2\xi t}\bar{y}\bar{z} - (m + \bar{h} + \mu) e^{\xi t}\bar{z} && (4.42)\\
e^{-\xi t}(\bar{u}' - \xi \bar{u}) &= (-r e^{-\xi t} + \frac{2r\bar{x}}{K} + a(\bar{y} + \bar{z}))\bar{u} - \varepsilon_1 a(\bar{y} + \bar{z})\bar{v} + A_2 && (4.43)\\
e^{-\xi t}(\bar{v}' - \xi \bar{v}) &= a\bar{x}\bar{u} - (\varepsilon_1 a\bar{x} - \beta_{dd}\bar{z} + (b - m - \bar{h})e^{-\xi t})\bar{v} - \beta_{dd}\bar{w}\bar{z} \\
&\quad - c\bar{h} - A_1 && (4.44)\\
e^{-\xi t}(\bar{w}' - \xi \bar{w}) &= a\bar{x}\bar{u} - (b e^{-\xi t} + \varepsilon_1 a\bar{x} - \beta_{dd}\bar{y})\bar{v} - (\beta_{dd}\bar{y} - (m + \bar{h} + \mu)e^{-\xi t})\bar{w} \\
&\quad - c\bar{h} - A_1. && (4.45)
\end{aligned}
$$

The initial and final time conditions stay the same:

$$
x(0) = N_0, \quad y(0) = S_0, \quad z(0) = I_0, \quad u(t_1) = 0, \quad v(t_1) = 0, \quad w(t_1) = 0. \qquad (4.46)
$$

Multiplying equations (4.34) – (4.36) and (4.40) – (4.42) by $e^{-\xi t}$ and subtracting corresponding equations, we have

$$
\begin{aligned}
x' - \bar{x}' + \xi(x - \bar{x}) &= r(x - \bar{x}) - \frac{r e^{\xi t}}{K}(x^2 - \bar{x}^2) - a e^{\xi t}(xy - \bar{x}\bar{y} + xz - \bar{x}\bar{z}) && (4.47)\\
y' - \bar{y}' + \xi(y - \bar{y}) &= \varepsilon_1 a r^{\xi t}(xy - \bar{x}\bar{y} + xz - \bar{x}\bar{z}) - \beta_{dd} e^{\xi t}(yz - \bar{y}\bar{z}) - m(y - \bar{y}) \\
&\quad + b(y - \bar{y} + z - \bar{z}) - (hy - \bar{h}\bar{y}) && (4.48)\\
z' - \bar{z}' + \xi(z - \bar{z}) &= \beta_{dd} e^{\xi t}(yz - \bar{y}\bar{z}) - (m + \mu)(z - \bar{z}) - (hz - \bar{h}\bar{z}) && (4.49)
\end{aligned}
$$

Similarly, we multiply equations (4.37) – (4.39) and (4.43) – (4.45) by $-e^{\xi t}$ and subtract corresponding equations to have

$$\begin{aligned}
-[u' - \bar{u}' - \xi(u - \bar{u})] &= -\frac{2r}{K}e^{\xi t}(xu - \bar{x}\bar{u}) \qquad (4.50)\\
&\quad -ae^{\xi t}(uy - \bar{u}\bar{y} + uz - \bar{u}\bar{z}) + \varepsilon_1 ae^{\xi t}(vy - \bar{v}\bar{y} + vz - \bar{v}\bar{z})\\
-[v' - \bar{v}' - \xi(v - \bar{v})] &= -ae^{\xi t}(ux - \bar{u}\bar{x}) + \varepsilon_1 ae^{\xi t}(vx - \bar{v}\bar{x}) - \beta_{dd}e^{\xi t}(vz - \bar{v}\bar{z})\\
&\quad -m(v - \bar{v}) + b(v - \bar{v}) - (hv - \bar{h}\bar{v}) + \beta_{dd}e^{\xi t}(wz - \bar{w}\bar{z})\\
&\quad +ce^{\xi t}(h - \bar{h}) \qquad (4.51)\\
-[w' - \bar{w}' - \xi(w - \bar{w})] &= -ae^{\xi t}(ux - \bar{u}\bar{x}) + \varepsilon_1 ae^{\xi t}(vx - \bar{v}\bar{x}) - \beta_{dd}e^{\xi t}(vy - \bar{v}\bar{y})\\
&\quad +ce^{\xi t}(h - \bar{h}) + b(v - \bar{v}) - (m + \mu)(w - \bar{w}) - (hw - \bar{h}\bar{w})\\
&\quad +\beta_{dd}e^{\xi t}(wy - \bar{w}\bar{y}). \qquad (4.52)
\end{aligned}$$

Multiply equations (4.47), (4.48) and (4.49) by $x - \bar{x}$, $y - \bar{y}$ and $z - \bar{z}$, respectively and integrate from $t = 0$ to $t = t_1$. Notice that $x$, $\bar{x}$; $y$, $\bar{y}$ and $z$, $\bar{z}$ agree at $t = 0$. Thus,

$\frac{1}{2}(x(t_1) - \bar{x}(t_1))^2 + \xi \int_0^{t_1}(x - \bar{x})^2 dt$

$$\begin{aligned}
&= r\int_0^{t_1}(x - \bar{x})^2 dt\\
&\quad -\frac{r}{K}\int_0^{t_1} e^{\xi t}(x^2 - \bar{x}^2)(x - \bar{x})dt - a\int_0^{t_1} e^{\xi t}(xy - \bar{x}\bar{y} + xz - \bar{x}\bar{z})(x - \bar{x})dt\\
&= r\int_0^{t_1}(x - \bar{x})^2 dt - a\int_0^{t_1} e^{\xi t}(y(x - \bar{x})^2 + \bar{x}(x - \bar{x})(y - \bar{y}))dt\\
&\quad -\frac{r}{K}\int_0^{t_1} e^{\xi t}(x + \bar{x})(x - \bar{x})^2 - a\int_0^{t_1} e^{\xi t}(z(x - \bar{x})^2 + \bar{x}(x - \bar{x})(z - \bar{z}))dt\\
&\leq r\int_0^{t_1}(x - \bar{x})^2 dt + (\frac{2C_1}{K} + C_2 a)\int_0^{t_1}(x - \bar{x})^2 dt + \frac{C_1 a}{2}\int_0^{t_1}((x - \bar{x})^2 + (y - \bar{y})^2)dt\\
&\quad +C_3 a\int_0^{t_1}(x - \bar{x})^2 dt + \frac{C_1 a}{2}\int_0^{t_1}((x - \bar{x})^2 + (z - \bar{z})^2)dt\\
&\leq C_7\int_0^{t_1}((x - \bar{x})^2 + (y - \bar{y})^2 + (z - \bar{z})^2)dt. \qquad (4.53)
\end{aligned}$$

Next,

$\frac{1}{2}(y(t_1)-\bar{y}(t_1))^2+\xi\int_0^{t_1}(y-\bar{y})^2dt$

$$\begin{aligned}
&= a\varepsilon_1\int_0^{t_1} e^{\xi t}(xy-\bar{x}\bar{y}+xz-\bar{x}\bar{z})(y-\bar{y})dt-\beta_{dd}\int_0^{t_1} e^{\xi t}(yz-\bar{y}\bar{z})(y-\bar{y})dt\\
&\quad -m\int_0^{t_1}(y-\bar{y})^2dt+b\int_0^{t_1}((y-\bar{y})+(z-\bar{z}))(y-\bar{y})dt-\int_0^{t_1}(hy-\bar{h}\bar{y})(y-\bar{y})dt\\
&= a\varepsilon_1\int_0^{t_1} e^{\xi t}(y(x-\bar{x})(y-\bar{y})+\bar{x}(y-\bar{y})^2+z(x-\bar{x})(y-\bar{y})+\bar{x}(z-\bar{z})(y-\bar{y}))dt\\
&\quad -\beta_{dd}\int_0^{t_1} e^{\xi t}(z(y-\bar{y})^2+\bar{y}(z-\bar{z})(y-\bar{y}))dt-\int_0^{t_1}(y(h-\bar{h})(y-\bar{y})+\bar{h}(y-\bar{y})^2)dt\\
&\quad +b\int_0^{t_1}(y-\bar{y})^2dt+b\int_0^{t_1}(y-\bar{y})(z-\bar{z})dt-m\int_0^{t_1}(y-\bar{y})^2dt\\
&\leq C_8\int_0^{t_1}((x-\bar{x})^2+(y-\bar{y})^2+(z-\bar{z})^2)dt+\frac{C_2}{2}\int_0^{t_1}(h-\bar{h})^2dt, \qquad (4.54)
\end{aligned}$$

since for two real numbers $a$ and $b$, $2ab\leq a^2+b^2$. Using the fact that for $a,b\in\Re$ with $b>a$, $\min(b,\max(a,s))$ is Lipschitz continuous in $s$, and $(a+b)^2\leq 2(a^2+b^2)$, we obtain

$\frac{C_2}{2}\int_0^{t_1}(h-\bar{h})^2dt$

$$\begin{aligned}
&\leq \frac{C_2}{8\varepsilon^2}\int_0^{t_1}(S\lambda_S-\bar{S}\bar{\lambda}_S+I\lambda_I-\bar{I}\bar{\lambda}_I-c(S-\bar{S}+I-\bar{I}))^2dt\\
&= \frac{C_2}{8\varepsilon^2}\int_0^{t_1}(vy-\bar{v}\bar{y}+wz-\bar{w}\bar{z}-ce^{\xi t}(y-\bar{y}+z-\bar{z}))^2dt\\
&\leq \frac{C_2}{4\varepsilon^2}\int_0^{t_1}((vy-\bar{v}\bar{y}+wz-\bar{w}\bar{z})^2+c^2e^{2\xi t}(y-\bar{y}+z-\bar{z})^2)dt\\
&\leq \frac{C_2}{2\varepsilon^2}\int_0^{t_1}((vy-\bar{v}\bar{y})^2+(wz-\bar{w}\bar{z})^2+c^2e^{2\xi t}((y-\bar{y})^2+(z-\bar{z})^2))dt\\
&= \frac{C_2}{2\varepsilon^2}\int_0^{t_1}(((v-\bar{v})y+\bar{v}(y-\bar{y}))^2+((w-\bar{w})z+\bar{w}(z-\bar{z}))^2)dt\\
&\quad +\frac{C_2c^2}{2\varepsilon^2}\int_0^{t_1} e^{2\xi t}((y-\bar{y})^2+(z-\bar{z})^2)dt\\
&\leq \frac{C_2}{\varepsilon^2}\int_0^{t_1}((y^2(v-\bar{v})^2+\bar{v}^2(y-\bar{y})^2)+(z^2(w-\bar{w})^2+\bar{w}^2(z-\bar{z})^2)dt\\
&\quad +\frac{C_2c^2}{2\varepsilon^2}\int_0^{t_1} e^{2\xi t}((y-\bar{y})^2+(z-\bar{z})^2)dt
\end{aligned}$$

$$\begin{aligned}
&\leq \frac{C_2^3}{\varepsilon^2}\int_0^{t_1}(v-\bar{v})^2dt+\frac{C_2C_9^2e^{2\xi t_1}}{\varepsilon^2}\int_0^{t_1}(y-\bar{y})^2dt+\frac{C_2C_3^2}{\varepsilon^2}\int_0^{t_1}(w-\bar{w})^2dt\\
&\quad+\frac{C_2C_{10}^2e^{2\xi t_1}}{\varepsilon^2}\int_0^{t_1}(z-\bar{z})^2dt+\frac{C_2c^2e^{2\xi t_1}}{2\varepsilon^2}\int_0^{t_1}((y-\bar{y})^2+(z-\bar{z})^2)dt\\
&\leq (C_{10}+C_{11}e^{2\xi t_1})\int_0^{t_1}((v-\bar{v})^2+(w-\bar{w})^2+(y-\bar{y})^2+(z-\bar{z})^2)dt.
\end{aligned}$$

Thus,

$$\frac{C_2}{2}\int_0^{t_1}(h-\bar{h})^2dt \leq (C_{10}+C_{11}e^{2\xi t_1})\int_0^{t_1}((v-\bar{v})^2+(w-\bar{w})^2+(y-\bar{y})^2+(z-\bar{z})^2)dt. \tag{4.55}$$

Combining equations (4.54) and (4.55), we have

$$\begin{aligned}
&\frac{1}{2}(y(t_1)-\bar{y}(t_1))^2+\xi\int_0^{t_1}(y-\bar{y})^2dt \qquad (4.56)\\
&\leq (C_{12}+C_{11}e^{2\xi t_1})\int_0^{t_1}((v-\bar{v})^2+(w-\bar{w})^2+(x-\bar{x})^2+(y-\bar{y})^2+(z-\bar{z})^2)dt.
\end{aligned}$$

Finally,

$\frac{1}{2}(z(t_1)-\bar{z}(t_1))^2+\xi\int_0^{t_1}(z-\bar{z})^2dt$

$$\begin{aligned}
&= \beta_{dd}\int_0^{t_1}e^{\xi t}(yz-\bar{y}\bar{z})(z-\bar{z})dt-(m+\mu)\int_0^{t_1}(z-\bar{z})^2dt-\int_0^{t_1}(hz-\bar{h}\bar{z})(z-\bar{z})dt\\
&= \beta_{dd}\int_0^{t_1}e^{\xi t}(z(y-\bar{y})(z-\bar{z})+\bar{y}(z-\bar{z})^2)dt-(m+\mu)\int_0^{t_1}(z-\bar{z})^2dt\\
&\quad-\int_0^{t_1}(z(h-\bar{h})(z-\bar{z})+\bar{h}(z-\bar{z})^2dt\\
&\leq C_{13}\int_0^{t_1}((y-\bar{y})^2+(z-\bar{z})^2)dt+\frac{C_3}{2}\int_0^{t_1}(h-\bar{h})^2dt\\
&\leq C_{13}\int_0^{t_1}((y-\bar{y})^2+(z-\bar{z})^2)dt\\
&\quad+(\tilde{C}_{10}+\tilde{C}_{11}e^{2\xi t_1})\int_0^{t_1}((v-\bar{v})^2+(w-\bar{w})^2+(y-\bar{y})^2+(z-\bar{z})^2)dt,
\end{aligned}$$

where $\tilde{C}_{10}=\frac{C3C_{10}}{C_2}$ and $\tilde{C}_{11}=\frac{C3C_{11}}{C_2}$. Thus,

$\frac{1}{2}(z(t_1)-\bar{z}(t_1))^2+\xi\int_0^{t_1}(z-\bar{z})^2dt$

$$\leq (C_{14}+\tilde{C}_{11}e^{2\xi t_1})\int_0^{t_1}((v-\bar{v})^2+(w-\bar{w})^2+(y-\bar{y})^2+(z-\bar{z})^2)dt. \qquad (4.57)$$

Similarly, we multiply equations (4.50), (4.51) and (4.52) by $u-\bar{u}$, $v-\bar{v}$ and $w-\bar{w}$, respectively and integrate from $t=0$ to $t=t_1$, noting that $u$, $\bar{u}$; $v$, $\bar{v}$ and $w$, $\bar{w}$ agree at $t=t_1$. This gives

$\frac{1}{2}(u(0)-\bar{u}(0))^2+\xi\int_0^{t_1}(u-\bar{u})^2dt$

$$\begin{aligned}
&= \frac{-2r}{K}\int_0^{t_1} e^{\xi t}(ux-\bar{u}\bar{x})(u-\bar{u})dt - a\int_0^{t_1} e^{\xi t}(uy-\bar{u}\bar{y}+uz-\bar{u}\bar{z})(u-\bar{u})dt \\
&\quad +\varepsilon_1 a\int_0^{t_1} e^{\xi t}(vy-\bar{v}\bar{y}+vz-\bar{v}\bar{z})(u-\bar{u})dt \\
&= \frac{-2r}{K}\int_0^{t_1} e^{\xi t}(x(u-\bar{u})^2+\bar{u}(u-\bar{u})(x-\bar{x}))dt + +\varepsilon_1 a\int_0^{t_1} e^{\xi t}\bar{z}(u-\bar{u})(v-\bar{v}))dt \\
&\quad -a\int_0^{t_1} e^{\xi t}(y(u-\bar{u})^2+\bar{u}(u-\bar{u})(y-\bar{y})+z(u-\bar{u})^2+\bar{u}(u-\bar{u})(z-\bar{z}))dt \\
&\quad +\varepsilon_1 a\int_0^{t_1} e^{\xi t}(v(u-\bar{u})(y-\bar{y})+\bar{y}(u-\bar{u})(v-\bar{v})+v(u-\bar{u})(z-\bar{z}))dt \\
&\leq (C_{15}+C_{16}e^{2\xi t_1})\int_0^{t_1}((u-\bar{u})^2+(v-\bar{v})^2+(x-\bar{x})^2+(y-\bar{y})^2+(z-\bar{z})^2)dt.
\end{aligned} \qquad (4.58)$$

Similarly, we have the following:

$\frac{1}{2}(v(0)-\bar{v}(0))^2+\xi\int_0^{t_1}(v-\bar{v})^2dt$

$$\leq (C_{17}+C_{18}e^{3\xi t_1})\int_0^{t_1}((u-\bar{u})^2+(v-\bar{v})^2+(w-\bar{w})^2+(x-\bar{x})^2+(y-\bar{y})^2+(z-\bar{z})^2)dt. \qquad (4.59)$$

and

$\frac{1}{2}(w(0)-\bar{w}(0))^2+\xi\int_0^{t_1}(w-\bar{w})^2dt$

$$\leq (C_{19}+C_{20}e^{3\xi t_1})\int_0^{t_1}((u-\bar{u})^2+(v-\bar{v})^2+(w-\bar{w})^2+(x-\bar{x})^2+(y-\bar{y})^2+(z-\bar{z})^2)dt. \qquad (4.60)$$

Combining equations (4.53), (4.56), (4.57), (4.58), (4.59) and (4.60), and setting

$$F(t) = (u(t) - \bar{u}(t))^2 + (v(t) - \bar{v}(t))^2 + (w(t) - \bar{w}(t))^2 \geq 0,$$

and

$$G(t) = (x(t) - \bar{x}(t))^2 + (y(t) - \bar{y}(t))^2 + (z(t) - \bar{z}(t))^2 \geq 0,$$

for all $t \in [0, t_1]$, we have

$$\begin{aligned}
&\tfrac{1}{2}(F(0) + G(t_1)) + \xi \textstyle\int_0^{t_1}(F(t) + G(t))dt \\
\leq\ & C_7 \int_0^{t_1} (F(t) + G(t))dt + (C_{12} + C_{11}e^{2\xi t_1}) \int_0^{t_1} (F(t) + G(t))dt \\
& +(C_{14} + \tilde{C}_{11}e^{2\xi t_1}) \int_0^{t_1} (F(t) + G(t))dt + (C_{15} + C_{16}e^{2\xi t_1}) \int_0^{t_1} (F(t) + G(t))dt \\
& +(C_{17} + C_{18}e^{3\xi t_1}) \int_0^{t_1} (F(t) + G(t))dt + (C_{19} + C_{20}e^{3\xi t_1}) \int_0^{t_1} (F(t) + G(t))dt \\
\leq\ & (\tilde{C} + \hat{C}e^{3\xi t_1}) \int_0^{t_1} (F(t) + G(t))dt,
\end{aligned}$$

where $\tilde{C} = C_7 + C_{12} + C_{14} + C_{15} + C_{17} + C_{19}$ and $\hat{C} = C_{11} + \tilde{C}_{11} + C_{16} + C_{18} + C_{20}$. Therefore,

$$\frac{1}{2}(F(0) + G(t_1)) + \xi \int_0^{t_1} (F(t) + G(t))dt \leq (\tilde{C} + \hat{C}e^{3\xi t_1}) \int_0^{t_1} (F(t) + G(t))dt.$$

Since $\frac{1}{2}(F(0) + G(t_1)) \geq 0$, it follows that

$$(\xi - \tilde{C} - \hat{C}e^{3\xi t_1}) \int_0^{t_1} (F(t) + G(t))dt \leq 0. \tag{4.61}$$

Now, we choose $\xi$ such that $\xi > \tilde{C} + \hat{C}$. If we choose $t_1$ such that $t_1 < \frac{1}{3\xi} ln(\frac{\xi - \tilde{C}}{\hat{C}})$, with $\frac{\xi - \tilde{C}}{\hat{C}} > 1$, then $\xi - \tilde{C} - \hat{C}e^{3\xi t_1} > 0$. Thus, equation (4.61) holds, if and only if, $x(t) = \bar{x}(t)$, $y(t) = \bar{y}(t)$, $z(t) = \bar{z}(t)$, $u(t) = \bar{u}(t)$, $v(t) = \bar{v}(t)$ and $w(t) = \bar{w}(t)$. In terms of the original variables, we have $N(t) = \bar{N}(t)$, $S(t) = \bar{S}(t)$, $I(t) = \bar{I}(t)$, $\lambda_N(t) = \bar{\lambda}_N(t)$,

$\lambda_S(t) = \bar{\lambda}_S(t)$ and $\lambda_I(t) = \bar{\lambda}_I(t)$. Hence, we have established uniquenesness of the optimality system for small time, $t_1$. □

Similarly, we obtain:

**Theorem 4.9.** *For $t_1$ sufficiently small, the optimality system comprising of the state system (4.1) – (4.4) ( with frequency-dependent transmission rate, $\Phi(P) = \beta_{fd}$), adjoint system and optimal control characterization given in Theorem 4.7 is unique.*

## 4.4 Optimal Harvest, Infectivity and Parameter Optimization

We incorporate FIV infectivity in the model by trapping and infecting a fraction of susceptible predators in the population. Thus, the control function, $u$, is the effort in trapping and infecting susceptible predators in the population, and the model below incorporates this control strategy:

$$\frac{dN}{dt} = rN(t)\left(1 - \frac{N(t)}{K}\right) - aN(t)(S(t) + I(t)) \tag{4.62}$$

$$\frac{dS}{dt} = (b + \varepsilon_1 aN(t))(S(t) + I(t)) - \frac{\Phi(P(t))S(t)I(t)}{P(t)} - (m + h(t))S(t) - u(t)S(t) \tag{4.63}$$

$$\frac{dI}{dt} = \frac{\Phi(P(t))S(t)I(t)}{P(t)} - (m + h(t) + \mu)I(t) + u(t)S(t), \tag{4.64}$$

with initial conditions

$$N(0) = N_0, \quad S(0) = S_0, \quad I(0) = I_0, \tag{4.65}$$

The term $uS$ represents the fraction of susceptible cats that are infected and reintroduced into the population. The scalar, $I_0$, is also taken as a control, meaning that the initial infected predator population is to be chosen. Therefore, we minimize the objective functional

$$J(I_0,h,u) = A_3 I_0^2 + \int_0^{t_1} (A_1(S(t)+I(t)) - A_2 N(t) + ch(t)(S(t)+I(t)) + \varepsilon h(t)^2)dt + \int_0^{t_1} (B_1 u(t) S(t) + B_2 u(t)^2) dt, \quad (4.66)$$

over time dependent controls $h(t)$ and $u(t)$, and scalar control $I(0) = I_0$. The coefficient $B_1$ converts the total number of susceptible cats trapped and infected with FIV to the cost of infecting susceptible cats, so that $B_1uS + B_2u^2$ represents the total cost of trapping and infecting susceptible cats in the population. The term $A_3 I_0^2$ represents a cost to have initial infected predator population, $I_0$. The cost of harvesting cats and infecting susceptible cats is nonlinear, due to difficulty in harvesting and infecting cats at high levels. The optimal control formulation for our problem involving harvesting, FIV infectivity and parameter optimization is: Find $(I_0^*, h^*, u^*) \in \tilde{\mathcal{U}}$ such that

$$J(I_0^*, h^*, u^*) = \min_{I_0} \left( \min_{h,u} J(I_0,h,u) \right) \quad (4.67)$$

subject to the state system defined in equations (4.62) – (4.65), where the objective functional is given by equation (4.66), and the set of all admissible controls is

$$\tilde{\mathcal{U}} = \{(I_0,h,u) \in M \times (L^\infty([0,t_1]))^2 | h : [0,t_1] \to [0,h_{max}],\ u : [0,t_1] \to [0,u_{max}]\},$$

with $M \subset \mathbb{N}$, the set of natural numbers.

One way to optimize a parameter and time dependent control(s) is to start with the time dependent control(s), and incorporate the parameter optimization afterwards. In finding $\min_{h,u} J(I_0,h,u)$, we use the Hamiltonian

$$
\begin{aligned}
\tilde{H} &= A_1(S(t)+I(t)) - A_2N(t) + ch(t)(S(t)+I(t)) + \varepsilon h(t)^2 + B_1u(t)S(t) + B_2u(t)^2 \\
&+\lambda_N(t)\left(rN(t)\left(1-\frac{N(t)}{K}\right) - aN(t)(S(t)+I(t))\right) \\
&+\lambda_S(t)\left((b+\varepsilon_1 aN(t))(S(t)+I(t)) - \frac{\Phi(P(t))S(t)I(t)}{P(t)} - (m+h(t)+u(t))S(t)\right) \\
&+\lambda_I(t)\left(\frac{\Phi(P(t))S(t)I(t)}{P(t)} - (m+h(t)+\mu)I(t) + u(t)S(t)\right).
\end{aligned}
$$

The following theorem characterizes the time dependent controls, and adjoint equations for system (4.62) – (4.64), when density- and frequency- dependent transmission rates are studied.

**Theorem 4.10.** *Given a fixed* $I_0$*:*

*a) For density-dependent transmission, and given optimal controls* $h^* = h^*(I_0)$ *and* $u^* = u^*(I_0)$*, with corresponding states* $N^*$*,* $S^*$ *and* $I^*$*, there exist adjoint functions* $\lambda_N$*,* $\lambda_S$ *and* $\lambda_I$ *satisfying the equations*

$$
\begin{aligned}
\lambda_N'(t) &= (-r + \frac{2rN(t)}{K} + a(S(t)+I(t)))\lambda_N(t) - \varepsilon_1 a(S(t)+I(t))\lambda_S(t) + A_2 \\
\lambda_S'(t) &= aN(t)\lambda_N(t) - (b + \varepsilon_1 aN(t) - \beta_{dd}I(t) - (m+h(t)+u(t)))\lambda_S(t) \\
&\quad -(\beta_{dd}I(t) + u(t))\lambda_I(t) - ch(t) - B_1u(t) - A_1 \\
\lambda_I'(t) &= aN(t)\lambda_N(t) - ch(t) - A_1 \\
&\quad -(b + \varepsilon_1 aN(t) - \beta_{dd}S(t))\lambda_S(t) - (\beta_{dd}S(t) - (m+h(t)+\mu))\lambda_I(t),
\end{aligned}
$$

*with final time conditions (4.25), where we have dropped the asterisks for notational simplicity.*

*b) The optimal control characterization for the time dependent controls* $h^*$ *and* $u^*$ *are*

$$
\begin{aligned}
h^*(t) &= \min\left\{h_{\max}, \max\left\{0, \frac{S^*(t)\lambda_S(t) + I^*(t)\lambda_I(t) - c(S^*(t)+I^*(t))}{2\varepsilon}\right\}\right\} \\
u^*(t) &= \min\left\{u_{\max}, \max\left\{0, \frac{S^*(t)(\lambda_S(t) - \lambda_I(t) - B_1)}{2B_2}\right\}\right\}.
\end{aligned}
$$

*c) For frequency-dependent transmission, and given optimal controls $h^*$ and $u^*$, with corresponding states $N^*$, $S^*$ and $I^*$, there exist adjoint functions $\lambda_N$, $\lambda_S$ and $\lambda_I$ satisfying the equations*

$$\begin{aligned}
\lambda_N'(t) &= (-r + \frac{2rN(t)}{K} + a(S(t)+I(t)))\lambda_N(t) - \varepsilon_1 a(S(t)+I(t))\lambda_S(t) + A_2 \\
\lambda_S'(t) &= aN(t)\lambda_N(t) - \left(b + \varepsilon_1 aN(t) - \beta_{fd}\left(\frac{I(t)}{S(t)+I(t)}\right)^2 - (m+h(t)+u(t))\right)\lambda_S(t) \\
&\quad -(\beta_{fd}\left(\frac{I(t)}{S(t)+I(t)}\right)^2 + u(t))\lambda_I(t) - ch(t) - B_1 u(t) - A_1 \\
\lambda_I'(t) &= aN(t)\lambda_N(t) - (b + \varepsilon_1 aN(t) - \beta_{fd}\left(\frac{S(t)}{S(t)+I(t)}\right)^2)\lambda_S(t) \\
&\quad -(\beta_{fd}\left(\frac{S(t)}{S(t)+I(t)}\right)^2 - (m+h(t)+\mu))\lambda_I(t) - ch(t) - A_1,
\end{aligned}$$

*Proof.* The proofs of (a) and (c) follow as in Theorems 4.6 and 4.7. To prove (b), we differentiate the Hamiltonian, $\tilde{H}$, with respect to the controls $h$ and $u$. This gives

$$\begin{aligned}
\frac{\partial \tilde{H}}{\partial h} &= c(S(t)+I(t)) + 2\varepsilon h(t) - S(t)\lambda_S(t) - I(t)\lambda_I(t) \\
\frac{\partial \tilde{H}}{\partial u} &= B_1 S(t) + 2B_2 u(t) - S(t)\lambda_S(t) + S(t)\lambda_I(t).
\end{aligned}$$

Using optimal control arguments analogous to the argument for characterizing control involving harvesting, we obtain optimal control characterizations for the time dependent controls defined in (b). □

## 4.5 Numerical Simulations

The optimality system is solved using an iterative scheme. A forward-backward sweep method [80], using the fourth order Runge-Kutta is used to solve for the state and adjoint equations. Starting with an initial condition for the state functions and an initial guess for the control, a forward sweep with fourth order Runge-Kutta is used to obtain an approximate solution to the state equations. Using this estimate and the final time conditions, the solution to the adjoint system is approximated using a backward sweep with fourth order Runge-Kutta method. The control is updated by using an average of its previous values and values from the control characterization [80]. Iterations continue until successive values of all variables from current and previous iterations are sufficiently close.

**Table 4.2:** Parameter values of the eco-epidemioogical model

| Parameter | Value | References |
|---|---|---|
| $r$ | 0.1 – 0.5 | [41, 94, 104] |
| $a$ | 0.00017 | calculation |
| $\varepsilon_1$ | 0.01 – 0.03 | [94, 97] |
| $m$ | 0.6 | [25, 41] |
| $\mu$ | 0.2 | [23] |
| $b$ | 0.61 | – |
| $h$ | 0 – 1 | vary |
| $\beta_{dd}$ | 0.0012 | calculation |
| $\beta_{fd}$ | 1.5 | [24] |
| $K$ | $2 \times 10^6$ | calculation |

The density-dependent transmission rate, $\beta_{dd}$, was approximated using $\beta_{dd} = \frac{\beta_{fd}}{S_0+I_0}$.

In Figure 4.1, we have trajectories for cats and birds in a situation where cats depend solely on birds for survival, that is when $b = 0$. As the population of cats increases, the population of birds decreases, and when the birds are at low densities, the cats become extinct. However, since cats are opportunistic predators, switching prey according to their spatial and temporal availability, we assume there is a birth term for cats, $b > 0$. Incorporating birth in the cat population, our numerical simulations suggest a steady decrease in bird population and an increase in cat population as shown in Figure 4.2. These simulations suggest that with fewer birds

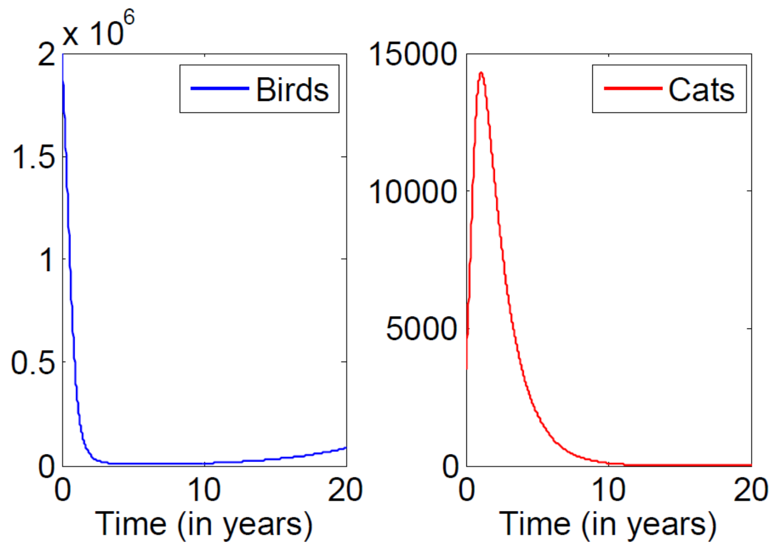


**Figure 4.1:** Predator and Prey when $N_0 = 2 \times 10^6$, $P_0 = 3500$, $b = 0$ and $h = 0$.

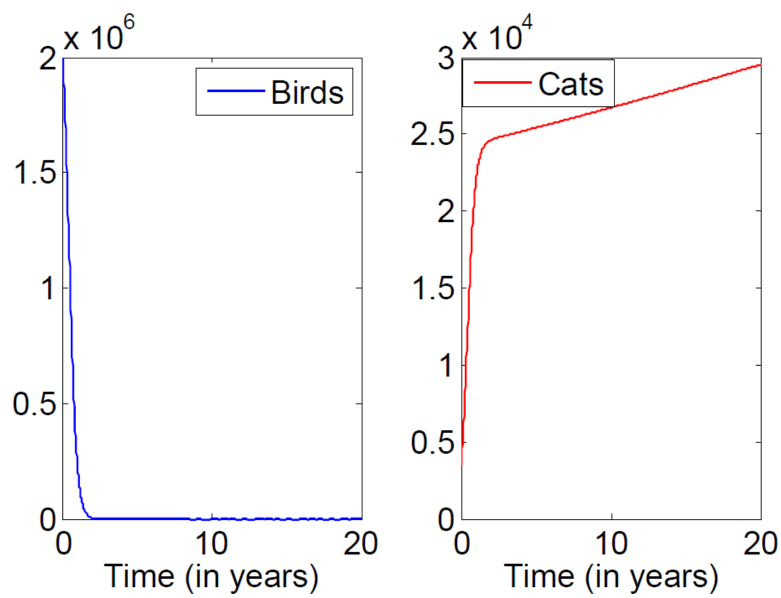


**Figure 4.2:** Predator and Prey when $N_0 = 2 \times 10^6$, $P_0 = 3500$, $b = 0.61$ and $h = 0$.

in the population, the cats switch prey and continue to increase in population, but with a lower amplitide. Therefore, the bird population becomes extinct when $b > m$, and both the birds and cats coexist if $b < m$ .

Using the equilibrium point of cats and birds in the absence of disease and culling as the initial population of birds and susceptible cats, and introducing a

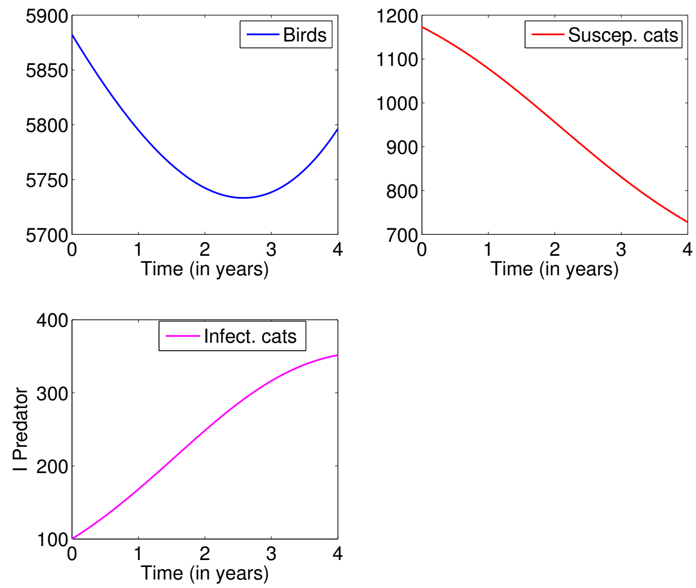


**Figure 4.3:** Prey, Susceptible and Infectious Predator with Density-dependent Transmission Rate when $N_0 = 5883$, $S_0 = 1173$, $I_0 = 100$, $m = 0.61$, $b = 0.60$ and $h_{\max} = 0$.

biological control agent, FIV (Feline Immunodeficiency Virus), but without harvest, the susceptible cat population decreases for the entire time period of 4 years, and the infectious cat population increases for the entire time period of 4 years as depicted in Figure 4.3. Similarly, the population of birds decreases in the first 2.5 years and increases afterwards. Thus, as a control strategy, we cull cats from the population at a constant rate as shown in Figure 4.4. Figure 4.4 represents predator-prey populations when predators are harvested at a constant rate of 0.3. This results in an increase in the population of birds, and a decrease in the susceptible cat population for the entire time period of 4 years. There is an initial increase in the population of infectious cats in the first year and a decrease afterwards. This suggests that harvesting could be used as a control strategy to destabilize the population of cats in an attempt to conserve the population of birds.

Turning to using optimal control of harvesting for 4 years, Figure 4.5 represents trajectories for birds, susceptible cats and infectious cats in the absence/presence of

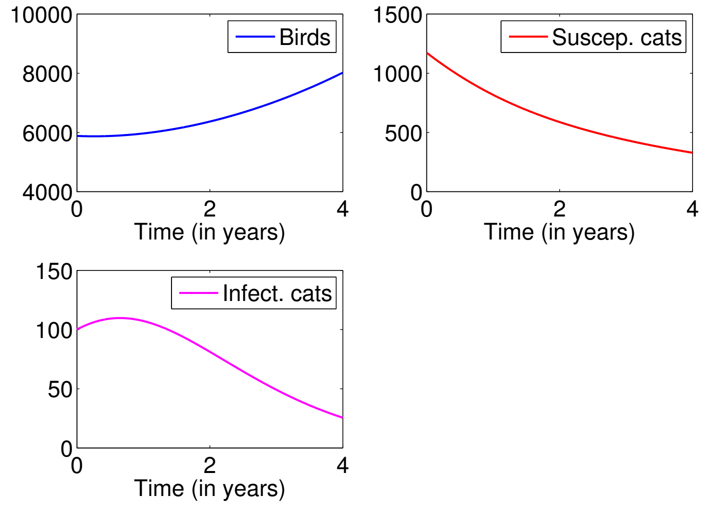


**Figure 4.4:** Prey, Susceptible and Infectious Predator with Density-dependent Transmission Rate when $N_0 = 5883$, $S_0 = 1173$, $I_0 = 100$, $m = 0.61$, $b = 0.60$ and $h_{\max} = 0.3$.

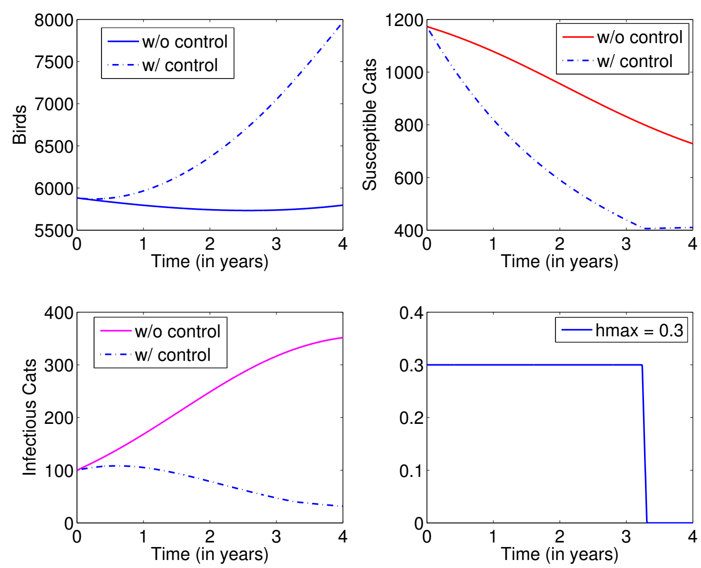


**Figure 4.5:** Prey, Susceptible and Infectious Predator with Density-dependent Transmission Rate when $N_0 = 5883$, $S_0 = 1173$, $I_0 = 100$, $m = 0.61$, $b = 0.60$, $h_{\max} = 0.3$, $A_1 = 1$, $A_2 = 1$, $c = 1$ and $\varepsilon = 100$.

harvesting (or culling). Trajectories for birds and infectious cats indicate an increase in bird population and a decrease in infectious cat population. However, susceptible cats experience a decrease in population within the first 3.4 years, followed by a constant population. The harvesting effort suggest maximum harvesting within the first 3.4 years, and harvesting at a very low level afterwards.

With optimal harvesting, susceptible cats remain a problem in the population. Thus, if the birth rate of cats is smaller than the background mortality of cats, then harvesting alone does not suffice as a control strategy in eradicating cats. Thus, we investigate the situation where the birth rate of cats is greater than their background mortality.

When cat birth rate is greater than their background mortality, we choose the initial population of birds as one-half their carrying capacity. The initial population of susceptible cats corresponds to the population of cats at the time when the population of birds is one-half their carrying capacity. In the presence of harvesting, trajectories suggest an initial increase in the population of susceptible cats within the first year, followed by a decrease for two years as shown in Figure 4.6. Between 3 – 4 years, the population of susceptible cats is at a constant level. Infectious cats are at a low level.

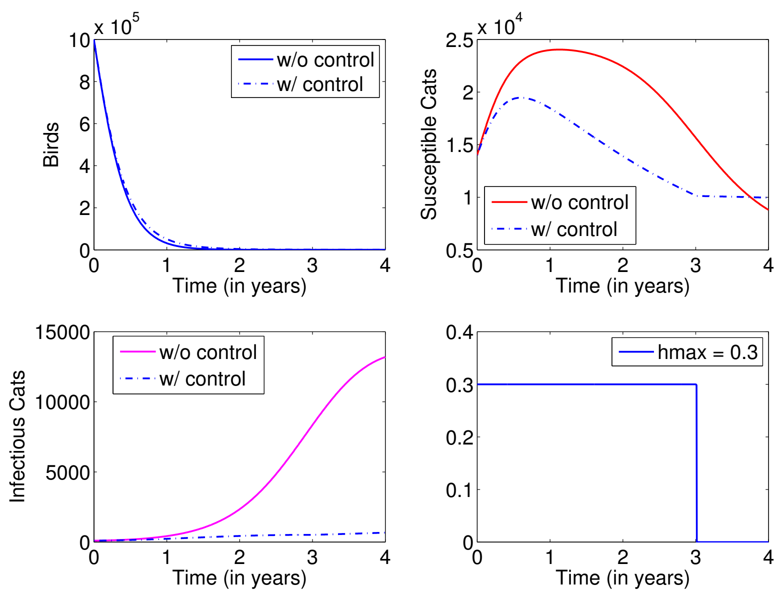


**Figure 4.6:** Prey, Susceptible and Infectious Predator with Density-dependent Transmission Rate when $N_0 = 1 \times 10^6$, $S_0 = 14000$, $I_0 = 100$, $K = 2 \times 10^6$, $h_{\max} = 0.3$, $\beta_{dd} = 0.0001$, $A_1 = 1$, $A_2 = 1$, $c = 1$ and $\varepsilon = 100$.

Figure 4.7 indicates trajectories for birds and cats in the presence/absence of control when the density-dependent transmission rate of cats is increased from $\beta_{dd} = 0.0001$ to $\beta_{dd} = 0.001$. Trajectories for susceptible and infectious cats indicate an initial increase in population, followed by a decrease in population.

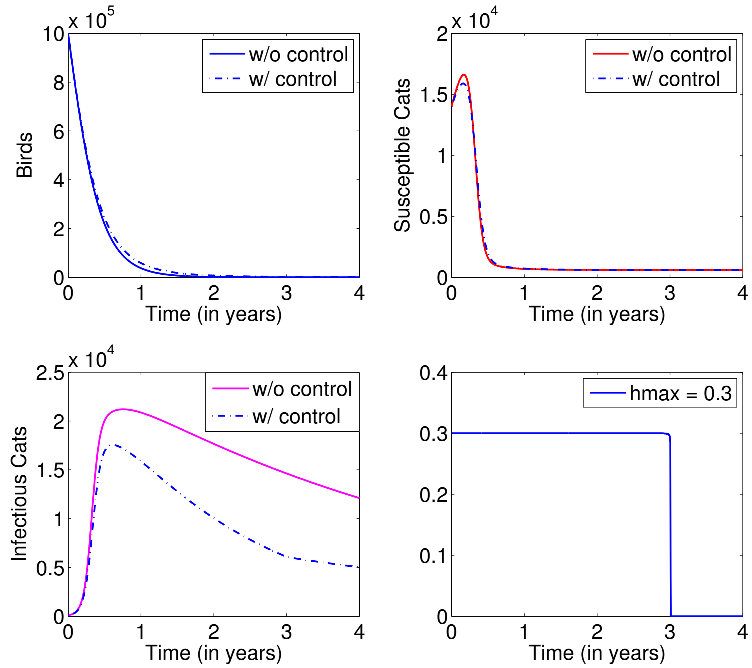


**Figure 4.7:** Density-dependent Transmission Rate is Increased from $\beta_{dd} = 0.0001$ to $\beta_{dd} = 0.001$, with $h_{max} = 0.3$, $A_1 = 1$, $A_2 = 1$, $c = 1$ and $\varepsilon = 100$.

At low levels of cats and birds, and in the presence of harvesting, trajectories indicate a decrease in susceptible and infectious cats. Also, trajectories indicate an increase in the bird population relative to the population of birds in the absence of harvesting. These results are depicted in Figure 4.8.

Despite harvesting and considering both high and low levels of cats and birds, both susceptible and infectious cat populations are endemic, and the population of birds are at a low level irrespective of the restrictions on the birth and mortality rates of cats. Thus, we combine harvesting with trapping susceptible cats, infecting them and reintroducing the cats in the population. Also, we incorporate the initial popuation of infectious cats as a scalar control.

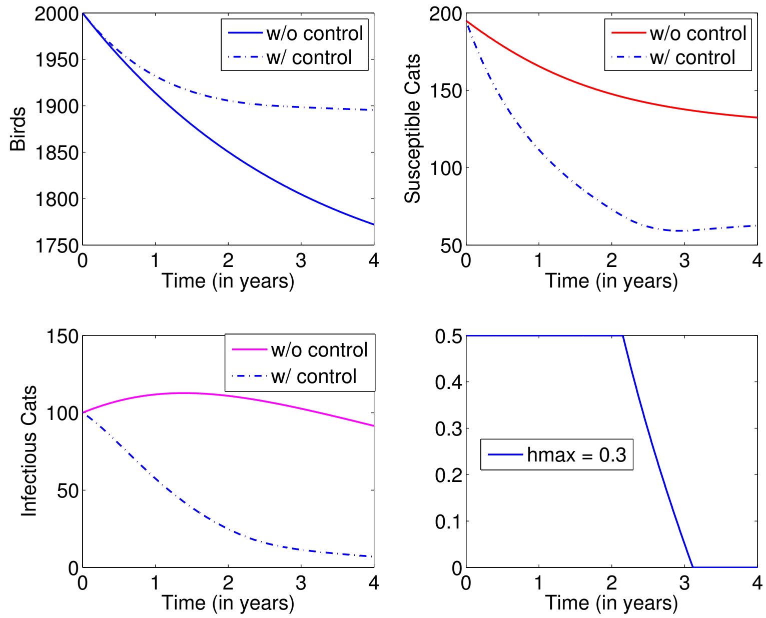


**Figure 4.8:** Prey, Susceptible and Infectious Predator with Density-dependent Transmission Rate when $N_0 = 2000$, $S_0 = 195$, $I_0 = 100$, $K = 2000$, $h_{\max} = 0.3$, $\beta_{dd} = 0.0051$, $A_1 = 1$, $A_2 = 1$, $c = 1$ and $\varepsilon = 100$.

To find the optimal parameter $I_0^*$, we find the $J$ values for each $I_0 \in M$, using the optimal harvest, $h^*(I_0)$, and optimal effort in trapping and infecting susceptible predators, $u^*(I_0)$, in the objective functional given in equation (4.66). Thus, we find $I_0^*$ such that

$$J(I_0^*, h^*(I_0^*), u^*(I_0^*)) = \min_{I_0 \in M} J(I_0, h^*(I_0), u^*(I_0)), \tag{4.68}$$

numerically. We illustrate this idea using

$$M = \{10, 20, 30, 50, 75, 100, 150, 200, 300, 400, 600, 1000\}.$$

Table 4.3 gives values of the objective functional evaluated at $h^*(I_0)$ for $I_0 \in M$, with no $u$ control involved.

**Table 4.3:** Parameter Optimization when $A_3 = 1$

| $I_0$ | Value of J for $t = 4$ yrs | Value of J for $t = 10$ yrs | $I_0$ | Value of J for $t = 4$ yrs | Value of J for $t = 10$ yrs |
|---|---|---|---|---|---|
| 10 | 36726.3 * | 67576.2 * | 150 | 59239.3 | 88676.6 |
| 20 | 37025.3 | 67738.7 | 200 | 76806.2 | 105886.4 |
| 30 | 37529.3 | 68118.3 | 300 | 126966.1 | 155471.8 |
| 50 | 39141.8 | 69500.3 | 400 | 197157.5 | 225218.8 |
| 75 | 42286.3 | 72381.9 | 600 | 397606.7 | 425031.8 |
| 100 | 46684.1 | 76540.8 | 1000 | 1038681.9 | 1065385.7 |

When "harvesting only" is considered with $A_3 = 1$, we obtain $I_0^* = 10$ infectious cats, where the asterisk indicates extremal value. Thus, in Figures 4.9, 4.10, 4.11 and 4.12, we use $I_0^* = 10$ infectious cats.

**Table 4.4:** Parameter Optimization when $A_3 = 0.1$

| $I_0$ | Value of J for $t = 4$ yrs | Value of J for $t = 10$ yrs | $I_0$ | Value of J for $t = 4$ yrs | Value of J for $t = 10$ yrs |
|---|---|---|---|---|---|
| 10 | 41668.0 | 79628.8 | 150 | 43555.0 | 79595.8 |
| 20 | 41661.6 * | 79442.2 | 200 | 45226.4 | 80778.9 |
| 30 | 41680.1 | 79292.8 | 300 | 50123.6 | 84884.6 |
| 50 | 41781.4 | 79079.8 | 400 | 57079.9 | 91223.7 |
| 75 | 42027.6 | 78967.2* | 600 | 77124.1 | 110359.4 |
| 100 | 42405.5 | 79019.2 | 1000 | 141556.1 | 173674.5 |

Tables 4.4 and 4.5 give values of the objective functional evaluated at $h^*(I_0)$ and $u^*(I_0)$, for $I_0 \in M \subset \mathbb{N}$, with $A_3 = 0.1$ and $A_3 = 0.01$, respectively. When a combination of harvesting, trapping and infecting susceptible cats is considered with $A_3 = 0.1$, the optimal parameter $I_0^* = 20$ infectious cats within a time horizon of 4 years and is $I_0^* = 75$ infectious cats within a time horizon of 10 years. When

**Table 4.5:** Parameter Optimization when $A_3 = 0.01$

| $I_0$ | Value of J for $t = 4$ yrs | Value of J for $t = 10$ yrs | $I_0$ | Value of J for $t = 4$ yrs | Value of J for $t = 10$ yrs |
|---|---|---|---|---|---|
| 10 | 41659.0 | 79619.8 | 150 | 41530.0 | 77570.8 |
| 20 | 41625.6 | 79406.2 | 200 | 41626.4 | 77178.9 |
| 30 | 41599.1 | 79211.8 | 300 | 42023.6 | 76784.6 * |
| 50 | 41556.4 | 78854.8 | 400 | 42679.9 | 76823.7 |
| 75 | 41521.3 | 78460.9 | 600 | 44724.1 | 77959.4 |
| 100 | 41505.5 * | 78119.2 | 1000 | 51556.1 | 83674.5 |

$A_3 = 0.01$, the optimal parameter is $I_0^* = 100$ infectious cats within a time horizon of 4 years and is $I_0^* = 300$ infectious cats within a time horizon of 10 years.

Using the optimal scalar as the initial number of infectious cats, trajectories in Figure 4.9 indicate an increase in the number of birds in the population, and the

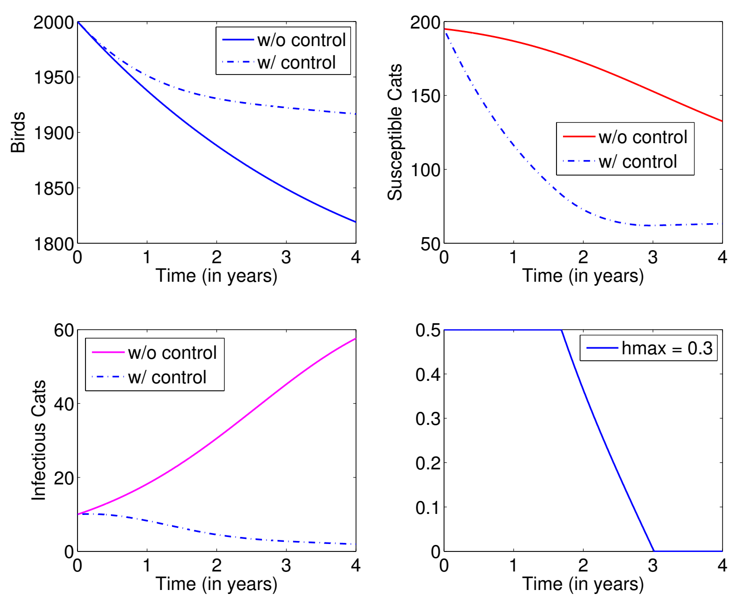


**Figure 4.9:** Prey, Susceptible and Infectious Predator with Density-dependent Transmission Rate when $N_0 = 2000$, $S_0 = 195$, $I_0^* = 10$, $K = 2000$, $h_{\max} = 0.3$, $\beta_{dd} = 0.0073$, $A_1 = 1$, $A_2 = 0.1$, $c = 1$ and $\varepsilon = 100$.

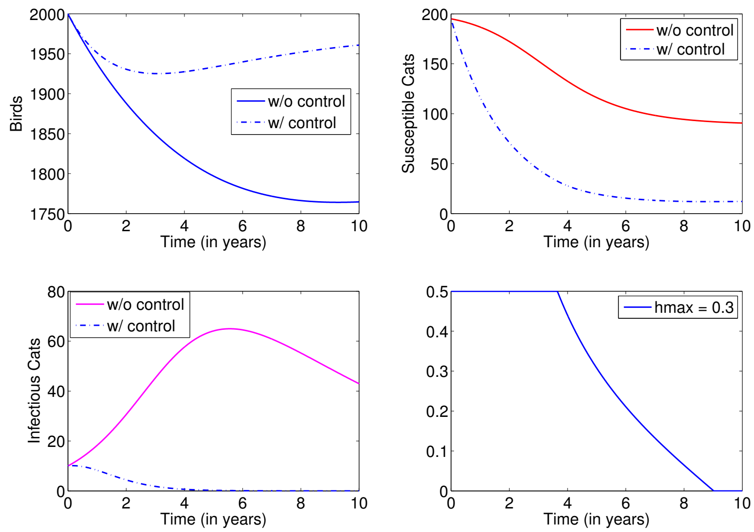


**Figure 4.10:** Time Horizon Increased from $t = 4$ years to $t = 10$ years when $h_{\max} = 0.3$.

optimal effort in harvesting is at its maximum level for a shorter period of time relative to the results obtained in Figure 4.8. In Figure 4.10, we considered a scenario for a time period of 10 years. Trajectories indicate a decrease in the population of susceptible and infectious cats, and an increase in the population of birds. The optimal effort in harvesting is at its maximum level for approximately 3.8 years, and decreases between 3.8 and 9 years.

Figures 4.11 and 4.12 indicate trajectories for birds, susceptible cats and infectious cats where the initial populations of birds and susceptible cats corresponds to the equilibrium point of birds and cats in the absence of disease and culling, and the optimal scalar, $I_0^* = 10$, is the initial number of infectious cats. Trajectories delineate a decrease in the populations of susceptible and infectious cats and an increase in the population of birds when a combination of harvesting and scalar optimization are investigated.

Incorporating harvesting, trapping and infecting susceptible cats and scalar optimization, trajectories in Figures 4.13 and 4.14 indicate a decrease in the population of susceptible and infectious cats within the entire time horizon. Also,

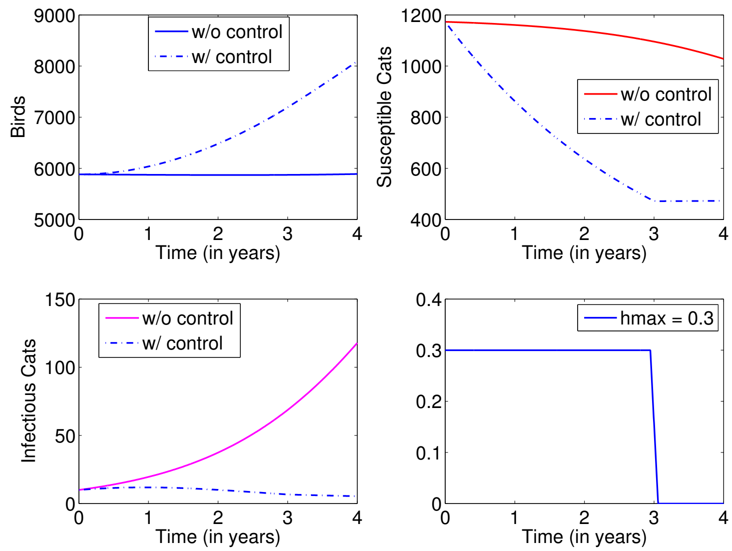


**Figure 4.11:** Prey, Susceptible and Infectious Predator with Density-dependent Transmission Rate when $N_0 = 5883$, $S_0 = 1173$, $I_0^* = 10$, $K = 2 \times 10^6$, $h_{\max} = 0.3$, $\beta_{dd} = 0.0013$, $A_1 = 1$, $A_2 = 0.1$, $A_3 = 1$, $c = 1$ and $\varepsilon = 100$.

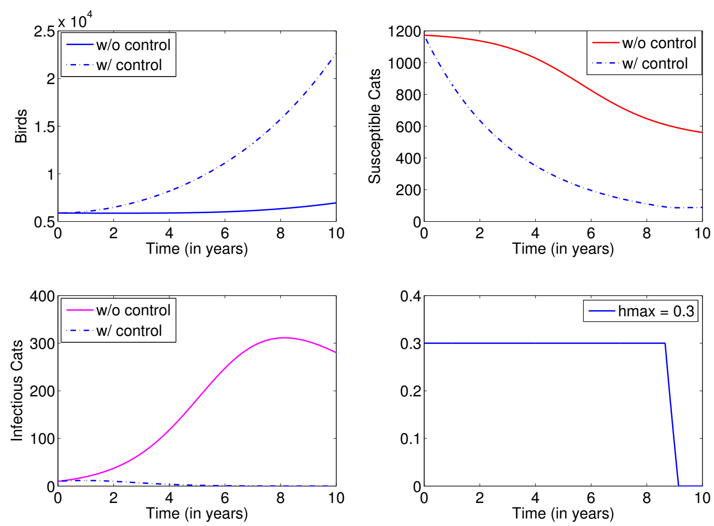


**Figure 4.12:** Time Horizon Increased from $t = 4$ years to $t = 10$ years.

more birds are conserved in the population as shown in Figure 4.14. The effort in harvesting last longer at its maximal level in relation to Figures 4.9 and 4.10 due to the infection and reintroduction of susceptible cats in the population.

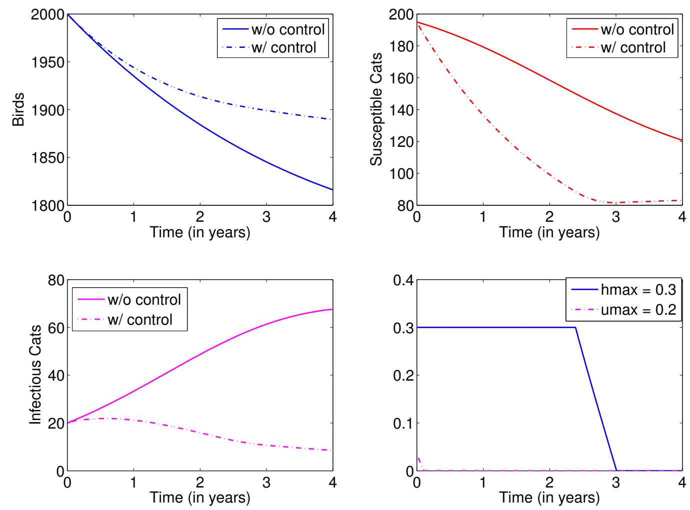


**Figure 4.13:** Prey, Susceptible and Infectious Predator with Density-dependent Transmission Rate when $N_0 = 2000$, $S_0 = 195$, $I_0^* = 20$, $K = 2000$, $h_{\max} = 0.3$, $u_{\max} = 0.2$, $\beta_{dd} = 0.007$, $A_1 = 1$, $A_2 = 0.1$, $A_3 = 0.1$, $B_1 = 1$, $B_2 = 200$, $c = 1$, and $\varepsilon = 100$.

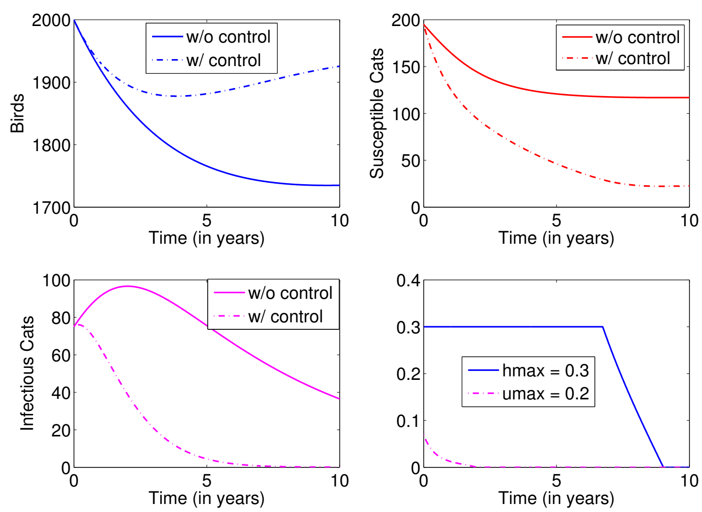


**Figure 4.14:** Time Horizon Increased from $t = 4$ years to $t = 10$ years when $h_{\max} = 0.3$, $u_{\max} = 0.2$ and $I_0^* = 75$.

The optimal effort in trapping and infecting susceptible cats may be difficult to implement at a high rate. Thus, we used a smaller number for the upper bound of $u$.

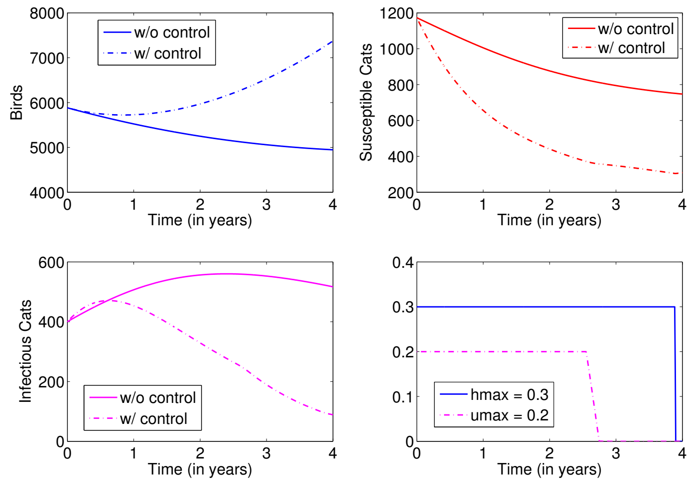


**Figure 4.15:** Prey, Susceptible and Infectious Predator with Density-dependent Transmission Rate when $N_0 = 5883$, $S_0 = 1173$, $I_0^* = 400$, $K = 2 \times 10^6$, $h_{\max} = 0.3$, $u_{\max} = 0.2$, $\beta_{dd} = 0.001$, $A_1 = 1$, $A_2 = 0.1$, $A_3 = 0.1$, $B_1 = 1$, $B_2 = 200$, $c = 1$, and $\varepsilon = 100$.

Figure 4.15 represents trajectories for cats and birds when the cost of introducing infected cats in the population is changed from a quadratic cost $(A_3 I_0^2)$ to a linear cost $(A_3 I_0)$. With a linear cost, the optimal parameter is $I_0^* = 400$ infectious cats. In Figure 4.15, trajectories suggest a decrease in the population of susceptible cats and an increase in the population of birds within the entire time horizon. The population of infectious cats experiences an initial increase followed by a decrease, due to infection of susceptible cats in the population.

**Remark:** Generally, a control strategy is applied for a short period of time and is re-evaluated to determine how to continue with the program/strategy or if an alternative approach is required. In our simulations, we used a time period of 4 years in investigating optimal harvesting only, optimal harvesting and scalar optimization, and a combination of optimal harvesting, trapping and infecting of susceptible cats and parameter optimization.

## 4.6 Conclusions

We formulated a predator-prey model and investigated harvesting and disease-related control, with the objective of controlling cat population and conserving the population of birds. We modified the standard predator-prey model by incorporating disease-induced mortality rate with the assumption that cats depend solely on births for survival. Numerical simulations depict a decrease in the population of cats in the absence of birds, which is not realistic, since cats are opportunistic predators, switching prey according to their spatial and temporal availabilty. Thus, we incorporated a birth term for the cats, and simulations suggest an increase in the population of cats in the absence of birds, though with a lower amplitude. Since the population of cats is sustained even in the absence of birds, we introduced a biological control agent, feline immunodeficiency virus, in the population of the cats.

We obtained the basic and demographic reproduction numbers for cats in the model and establish conditions for existence of steady states. Stability analysis of equilibria was studied. Also, we investigated a harvesting strategy by culling cats from the population. Our numerical simulations indicate that at high densities, harvesting alone is not sufficient to control the population of cats while conserving the population of birds within four years. However, at low densities, numerical results indicate a decrease in trajectories for susceptible and infectious cats, and an increase in the trajectories for birds. Thus, there is need for further investigation in order to completely eradicate cats from the population.

A combination of harvesting and disease-related control strategies suggest a decrease in cat population and an increase in the population of birds, compared to optimal harvesting alone. This tool could be used more effectively if realistic estimates of the cost of controls could be found.

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# Vita

Eric Numfor was born in the North West Province, Cameroon on June 25, 1977. After completing High School education at Cameroon College of Arts, Science and Technology, Bambili in 1996, he attended the University of Buea, Cameroon from 1996 – 1999. He graduated with a B.S. degree in Mathematics and minor in Management. In March 2000, he enrolled for a Master of Science Degree Program at the University of Buea. After obtaining his M.S. degree in Mathematics in 2002, Eric taught as an instructor at Christ the King College from 2003 – 2006, and as an Instructor/Assistant Lecturer at the University of Buea from 2003 – 2009 (January).

In January 2009, Eric joined the graduate program in mathematics at East Tennessee State University. His graduate program was supported by a graduate teaching assistantship. He obtained a M.S. degree in Mathematics in 2010.

In August 2010, Eric began his graduate career in the Department of Mathematics at the University of Tennessee, Knoxville. His graduate school was supported by graduate teaching/research assistantships. On his teaching assistantship, he taught Math for Life Sciences I, Calculus I, Pre-Calculus, College Algebra and Statistical Reasoning. His third year was supported by a graduate research assistantship from the National Institute for Mathematical and Biological Synthesis, and most of his summer terms were supported by graduate research assistantships from his PhD advisor, Dr. Suzanne Lenhart. Eric graduated with a PhD in Mathematics in August 2014. He continues his research career in mathematical biology and teaching as an Assistant Professor of Mathematics at Georgia Regents University.