# Ordinary and Delay Differential Equation Models of Viral Infection With Application to HIV and Hepatitis C Virus

by

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# DEDICATION

This thesis is dedicated to the memory of my grandfather, Bagher Aavani, who passed away a few days before my defense.

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# ABSTRACT

Human adaptive immune response consists of three major types of cells, namely, CD4 T cells, CTL (Cytotoxic T Lymphocytes), and antibodies. CTL attack and kill cells that are infected by viruses. Antibodies are capable of identifying and neutralizing viruses. In the presence of virus infection, CD4 T Cells stimulate the proliferation of CTL. Also the proliferation of antibodies becomes stimulated by viruses. These ideas are used to introduce a new ordinary differential equation model for exploring the dynamics of infection.

Production of viruses by infectious CD4 T cells are not instantaneous and they require time to occur. Thus, explaining the dynamics of infections more accurately in the model, it is important to consider a time gap, which is known as delay. The new delay differential equation model, which considers a delay in the production of viruses, is also analyzed in this thesis.

Both models are useful to be applied for HIV and hepatitis C infections, because in these models target cells are CD4 T cells, infectious agents are viruses, and the biological implications of the mathematical results are similar to the stages of the infections.

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# CHAPTER I
# INTRODUCTION

In the area of mathematical immunology, many virus-cell models have been developed with ordinary differential equations or with delay differential equations. These models, known as virus dynamic models, describe the infections caused by viruses when they enter specific target cells. In this chapter, I will give a brief introduction to immunology and virology (Section 1.1), familiarize the reader with related works, pertinent to our models in virus dynamics (Section 1.2), and state the organization of the thesis (Section 1.3).

## 1.1 Introduction to Immunology and Virology

The immune system consists of lymphoid organs (bone marrow, thymus, lymph nodes, spleen, and often lymphoid tissues in the body) and cells that protect the body from harmful antigens. Antigens are alien substances such as viruses, fungi, or bacteria, capable of inducing a reaction of the immune system. This reaction recognizes and defends the body against antigens and is called the immune response. These cellular responses of the immune system are known as the adaptive immune response. There are three major types of cells in the adaptive immune response [24]:

1. Antibodies, produced by B cells, are capable of identifying and neutralizing viruses. B cells are produced in the bone marrow.

2. CTL (Cytotoxic T Lymphocytes, CD8 T cells or Killer T Cells) attack and kill cells that are infected by viruses. CTL are produced in the thymus. CTL have a protein CD8 on their surface, called a receptor, since it can bind itself to other molecules [18]. This receptor can recognize antigens on infected cells. After the process of recognition, CTL produce substances that can kill infected cells [24].

3. CD4 T cells, that are also produced in the thymus, cannot themselves kill viruses but they regulate and assist the immune response. Their participation in regulation of the immune response is to activate antibody producing B cells and CTL so that these cells can defend the body against foreign antigens.

When CD4 T cells encounter antigens, they release substances called cytokines. These cytokines stimulate CTL and direct their proliferation [24]. In the absence of these cells, the immune system loses one of its main branches and other branches of immune system do not work properly to clear the infection.

### 1.1.1 Virus

Viruses are small infectious agents that are not capable of reproducing themselves. They can only reproduce inside living cells. Virus particles, known as virions, consist of two main parts: the genetic material generally made from DNA or RNA, and a protein that protects these genes. The genome of the virus can be either DNA or RNA. After entering the cell, the virus directs the cell to reproduce its viral proteins and copies of its genome [18]. The reproduced viral protein then attaches to a new genome, forms new virus particles, and leaves the cell. The cell may eventually die after devoting all of its resources to producing virions.

### 1.1.2 HIV

Human immunodeficiency virus (HIV) is the causative agent of acquired immunodeficiency syndrome (AIDS), a disease that causes progressive failure of the immune system. HIV is an RNA retrovirus. That is, to enter a cell, HIV translates its RNA to DNA with a viral enzyme called reverse transcriptase [24]. The target cell of HIV is CD4 T cells. A healthy human body has about $1000/mm^3$ of CD4 T cells [19]. When the CD4 T cells of a patient decline to $200/mm^3$ or below, then that person is classified as having AIDS [19]. When the CD4 T cells decline, they cannot mount a strong response. This results in weak responses from CTL and antibodies which cannot clear the infection.

There are three states for HIV infection [18]:

1. The primary infection occurs within a few weeks of acquiring the virus and is the first stage. Usually the virus load increases during this stage. This stage is similar to the symptoms of flu. The number of CD4 T cells significantly decrease and then return to almost normal level.

2. The chronic stage of asymptomatic infection in which there are no considerable symptoms of disease is the second stage. The immune system is active. This

stage lasts an average of 10 years.

3. The acute stage in which there are symptoms of the disease is the final stage, leading to AIDS. The immune system can no longer defend the body and one or more other infections occur. Eventually a patient dies from these other infections.

### 1.1.3 HCV

Hepatitis C virus (HCV) is another RNA virus, but it is not a retrovirus. It is the causative agent of hepatitis C infection in humans. HCV primarily infects liver cells and the main target cells of this virus are CD4 T cells, the same target cells as HIV. The virus infects the helper cells and manipulates them to reproduce more virions, without killing them. The infection is often asymptomatic and the virus can continue replicating in the body on the average of 10 to 20 years [24].

## 1.2 Mathematical Models on Virus Dynamics

In this section I present a brief survey of ordinary differential equation (ODE) models that have been applied to virus dynamics. Then we continue by introducing some delay differential equation (DDE) models.

### 1.2.1 ODE Models

Early models in virus dynamics focused on the infection of CD4 T cells because most of these models related to understanding the dynamics of HIV infections. One well-known model of this type has the following form [6, 18]:

$$\begin{aligned} \frac{dC}{dt} &= \lambda - dC - \beta CV \\ \frac{dI}{dt} &= \beta CV - \rho I \\ \frac{dV}{dt} &= aI - kV. \end{aligned} \tag{1.1}$$

In the preceding model, $C$, $I$, and $V$ represent the density of uninfected or healthy CD4 T cells, infected T cells, and free virions. Parameter $\beta$ is the rate at which healthy CD4 T cells become infected, and the parameter $\lambda$ is the growth rate of the

uninfected T cells. Parameters $d, \rho$ and $k$ are the death rates of the uninfected T cells, the infected T cells, and virions, respectively. Korobeinikov [12] analyzed model (1.1), applying Lyapunov functions to prove global asymptotic stability of the equilibria.

More complex models also considered the body's immune response. Some of these models only introduce the CTL response. De Boer and Perelson (p.26, [6]), and Nowak and Bangham (p.76, [17]) suggested the following equation for the CTL response ($z$):

$$\frac{dz}{dt} = \alpha z I - bz. \tag{1.2}$$

where $\alpha$ and $b$ are the rates of neutralizing infected cells and the decay rate of CTL. Li et al. [8] proposed a similar model for HTLV-I. The human T-lymphotropic virus type I (HTLV-I) is a human RNA retrovirus that is a causative agent for a type of cancer, known as adult T-cell leukemia/lymphoma and HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP). HTLV-I infects primarily CD4 T cells. They proposed following equation for the CTL response

$$\frac{dz}{dt} = \alpha \frac{zI}{z+K} - bz \tag{1.3}$$

that CTL expansion saturates as the number of CTL increases.

Wodarz proposed models with more complex stimulation of CTL by helper cells C, replacing $\alpha z I$ in equation (1.3) with

$$\frac{\gamma C V^2 z}{1+\eta C V} \quad \text{or} \quad \frac{(c\epsilon C + k) V z}{1+\epsilon C + k} + \frac{\gamma C V^2 z}{1+\eta C V} \tag{1.4}$$

(see pp. 62, 64, [24].) No analyses were presented for those models. Our new model is similar to this second form but without density-dependence in the denominator.

Some other complex models just focused on the antibody response as an immune control. Marchuk (p.108, [15]) suggested the following equation as the antibody response for his general model of infectious disease, which was also studied by Asachenkov et al. [3]:

$$\frac{dF}{dt} = \rho C - (\mu_f + \eta\gamma V) F. \tag{1.5}$$

Parameter $\rho$ is the rate of production of antibodies, $\mu_f$ is the rate of decay of anti-

bodies due to aging, $\eta$ is the rate of decay of antibodies due to neutralizing antigens and $\gamma$ is the probability that one antibody particle encounters one virus particle.

Other models with an immune response for HIV and HCV include two differential equations, one for CTL and one for the antibody response, as a reaction of immune system to infections. Wodarz (p.1744, [23]) suggested the following equations for antibody ($w$) and CTL response ($z$):

$$\begin{aligned} \frac{dw}{dt} &= gwV - hw \\ \frac{dz}{dt} &= \alpha zI - bz. \end{aligned} \tag{1.6}$$

Parameter $g$ is the growth rate of antibody cells via stimulation from virus particles and $h$ is the decay rate of those cells. Similarly, $\alpha$ is the growth rate of CTL via infected cells and $b$ is the decay rate of those cells. The model (1.1) and (1.6) was mathematically analyzed by Yousfi et al. [25], using Lyapunov functions to prove global asymptotic stability of various equilibria.

### 1.2.2 DDE Models

In immunology, production of antigens, activation of the immune response, neutralization of antigens, and other processes are not instantaneous, they require time to occur. Thus, explaining the dynamics of infections more accurately in our models, it is important to consider this time gap, which is known as delay. The ODE models that consider delays are called delay differential equation models, DDE.

Most of the DDE models in virus dynamics concentrate on delay in production of virions or delay in becoming infected cells. In comparison with ODE, there are not too many models in DDE that consider the delay in activation of the immune response.

Ruan et al. [5] proposed a similar ODE model to model (1.1) for HIV. In their delay model, they introduced the following equation with a time delay

$$\frac{dI(t)}{dt} = \beta C(t-\tau)V(t-\tau). \tag{1.7}$$

In the above equation $\tau$ describes the time between the infection of CD4 T cell

and becoming productively infected cell. Note that the delay in the argument of $C(t-\tau)V(t-\tau)$ is called discrete delay.

Nelson and Perelson (p. 10, [16]) proposed a general model, which mathematically analyzed by Wang et. al [14], with intracellular delays and a combination drug therapy. The delay equations are as follows

$$\frac{dI(t)}{dt} = (1-n_{rt})k\int_0^\infty G_1(\tau)T(t-\tau)V(t-\tau)\,\mathrm{d}\tau - \delta I(t) \tag{1.8}$$

$$\frac{dV(t)}{dt} = (1-n_p)N\delta\int_0^\infty G_2(\tau)I(t-\tau)\,\mathrm{d}\tau - cV(t) \tag{1.9}$$

where T, I, and V are the concentration of uninfected target cells, productively infected cells, and virus, respectively. Parameter $\delta$ is the death rate of infected cells, $(1-n_p)N\delta$ is the production rate of the virus, c is the rate at which virus is cleared, and $(1-n_{rt})k$ is the infection rate.

The delay differential equations (1.8) and (1.9) are said to have distributed delays since they reflect a weighted average of delays $T(t-\tau)V(t-\tau)$ and $I(t-\tau)$ [21]. The distributed delay are more realistic but also more difficult to work with. The delay in (1.8) has a similar description to the delay in (1.7). In (1.9), delay describes a time needed for the production of new virus particles from productively infectious cells.

Gourley et al. [9] considered an equation with an additional stage of infection, a cell that has been infected but is not yet productive, denoted as $e$. Their models were applied to hepatitis B virus infection because the infectious virus has incubation period which varies between 45 to 180 days, according to their data. So they introduced a discrete delay to describe the time needed for infectious cells to become reproductive. Their model for $e$ and $I$ has the following form:

$$\frac{de}{dt} = -de(t) + \frac{\beta V(t)C(t)}{C(t)+I(t)+e(t)} - \frac{\beta e^{-d\tau}V(t-\tau)C(t-\tau)}{C(t-\tau)+I(t-\tau)+e(t-\tau)} \tag{1.10}$$

$$\frac{dI}{dt} = \frac{\beta e^{-d\tau}V(t-\tau)C(t-\tau)}{C(t-\tau)+I(t-\tau)+e(t-\tau)} - aI(t). \tag{1.11}$$

The term $e^{-d\tau}$ represents the rate that cells survive during the time gap $\tau$. They verified the global dynamics of a the model.

## 1.3 Organization of the Thesis

In Chapter II, a new ordinary differential equation (ODE) model for viral infection will be introduced. Nonnegativity, boundedness, and existence of the solutions to the model will be verified to show that the model is well posed (Section 2.1). Next, the disease-free steady-state (DFS) and the basic reproduction number ($R_0$) will be derived and the DFS will be shown to be globally asymptotically stable when $R_0 < 1$ (Section 2.2). Sufficient conditions will be given for existence and local asymptotic stability of the second steady-state and additional stronger conditions will be given to prove the global asymptotic stability of the second steady state. In addition, sufficient conditions for existence and global stability of the third steady-state will be given (Section 2.3). Finally, in Section 2.4 biological explanations for the mathematical results will be discussed.

In Chapter III, several new delay differential equations (DDE) will be presented as an extension of the ODE model in Chapter II. Only one of these DDE will be analyzed in detail, a model with a delay in the viral reproduction. For this DDE model, conditions will be given for local asymptotic stability for the DFS (the same equilibrium as the ODE) in terms of the delay. In addition, a second steady state will be derived $E_2(\tau)$, where the equilibrium depends on the delay. Conditions will be derived for local asymptotic stability of the equilibrium $E_2(\tau)$.

In Chapter IV, some numerical examples of ODE and DDE models will be presented. Their asymptotic behavior will illustrate the results in the preceding chapters.

# CHAPTER II
# ODE MODEL

The new model for virus dynamics consists of a system of four ordinary differential equations, including variables $C$, $I$, $F$ and $V$ that represent the density of uninfected or healthy CD4 T cells, infected CD4 T cells, immune cells and free virus particles, respectively, at time $t$. The new term in this model is represented by the immune cells $F$, which are chemical stimulants associated with the immune response. The ODE model has the following form:

$$\begin{aligned} \frac{dC}{dt} &= \lambda(C^* - C) - \beta CV \\ \frac{dI}{dt} &= \beta CV - aI - \rho FI \\ \frac{dF}{dt} &= FV(\omega + eC) - bF \\ \frac{dV}{dt} &= aNI - \gamma FV - kV \end{aligned} \tag{2.1}$$

with initial conditions satisfying $0 < C(0) < C^*$, $V(0) > 0$, $I(0) \geq 0$,$F(0) > 0$, and $C(0) + I(0) < C^*$. Parameter $\beta$ is the rate of the infection and $\omega$ is the growth rate of immune cells via antigen stimulation. The constant $\lambda C^*$ is the growth of the uninfected T cells. Parameters $\lambda$, $a, b$ and $k$ are the death rates of the uninfected T cells, the infected T cells, immune cells and virus particles. Parameters $\gamma$ and $\rho$ are the rates of neutralizing virus particles and infected cells by the immune system. Parameter $e$ is the stimulation of the immune cells in the presence of virus particles with the aid of the T cells. The immune cells are stimulated by the virus and the CD4 T cells. The immune cells are initially present in small concentrations and stimulated at a rate $V(\omega + eC)$. $N$ is total number of new virus particles produced by each infected cell during its lifetime (average lifetime is $1/a$). Therefore, $aN$ is the production rate of virus by infected cell. We assume that all the parameters are positive. Generally, it is the case that $a \geq \lambda$, the death rate of infected cells is greater than healthy cells. Thus, we make the assumption

$$a \geq \lambda.$$

## 2.1 Nonnegativity, Boundedness, and Existence

We show that solutions are bounded on any interval $[0, T)$, where $T > 0$. Then we can extend the solution to the entire interval $t \in [0, \infty)$.

Let $x(t) = (C(t), I(t), F(t), V(t))$ and $\dot{x} = f(t, x(t))$. It is easy to show for model (2.1) that there exists a unique solution in the region $\Delta$, $|t| \leq a$ and $\|x(t) - x(0)\| \leq b$ by applying an existence and uniqueness theorem [11, 20]. In the bounded region $\Delta$, each of the partial derivatives of the right side of (2.1) with respect to $C$, $I$, $F$ or $V$ are bounded in $\Delta$. The existence theorem states that there exists a unique solution on the interval, $|t| \leq \min\{a, b/M\}$, where $M = \sup_{\Delta} \|f(t, x)\|$ [11].

It is easy to show that solutions are nonnegative for initial conditions nonnegative. This can be verified by checking that the derivatives are greater than or equal to zero on the boundary of $\mathbb{R}^4_+$, i.e, if $C = 0$, then $dC/dt = \lambda C^* > 0$.

Next we show boundedness. Note

$$\begin{aligned} \frac{d(C+I)}{dt} &\leq \lambda C^* - \lambda C - aI \\ &\leq \lambda C^* - \min\{\lambda, a\}(C+I) = \lambda C^* - \lambda(C+I). \end{aligned}$$

Thus from the initial conditions and by comparison with the linear ODE of order one implies the solution $C+I$ is bounded for all time. In particular, for $0 < C(0)+I(0) < C^*$, $C(t) + I(t) \leq C^* + (C(0) + I(0) - C^*)e^{-\lambda t} < C^*,\ 0 \leq t < \infty$. Then

$$\frac{dV}{dt} \leq aNC^* - kV$$

Thus, $V(t) \leq aNC^*/k + (V(0) - aNC^*/k)e^{-kt}$ and $V(t)$ is bounded for $0 \leq t < \infty$. Then

$$\frac{dF}{dt} \leq \bar{F} = F[\bar{V}(\omega + eC^*) - b]$$

and $F(t) \leq F(0)\exp([\bar{V}(\omega + eC^*) - b]t)$ for $0 < t < T$. Solutions are bounded for finite time. Hence, solutions can be extended to $t \in [0, \infty)$. We summarize these results in the following theorem.

**Theorem 2.1.1.** *Solutions to (2.1) exist for $t \in [0, \infty)$. In addition, $C$, $I$, and $V$*

*are uniformly bounded for* $t \in [0, \infty)$,

$$0 \leq C(t) + I(t) \leq C^* \quad \textit{and} \quad 0 \leq V(t) \leq \bar{V}. \tag{2.2}$$

## 2.2 The Disease-Free Steady-State and $R_0$

The disease free steady state (DFS) denoted $E_1$ ,can be calculated from model (2.1) by setting $I = F = V = 0$ so that $C = C^*$. Then the DFS is $E_1 = (C_1, I_1, F_1, V_1) = (C^*, 0, 0, 0)$. The basic reproduction number, denoted $R_0$, is the average number of secondary infections produced in an uninfected cell population, by an infected cell or free virus particle [7]. We use the next-generation method of van den Driessche and Watmough [22], to find $R_0$ and verify stability of the DFS. We summarize some of the notation and results in [22], needed to define $R_0$.

**Definition 2.2.1.** *Let* $x = (x_1, ..., x_n)^t$ *such that each* $x_i \geqslant 0$ *be the number of individuals in each compartment. Let the first* $m$ *compartments correspond to infected cells or free virus particles, using the notation in [22], we define the following:*
*(1)* $\mathscr{F}_i(x)$ *be the rate of appearance of new infections in compartment* $i$.
*(2)* $\mathscr{V}_i(x)^+$ *be the rate of transfer of individuals into compartment* $i$.
*(3)* $\mathscr{V}_i(x)^-$ *be the rate of transfer of individuals out of compartment* $i$.

$$\frac{dx_i}{dt} = f_i(x) = \mathscr{F}_i(x) - \mathscr{V}_i(x) \qquad i = 1, ..., n \tag{2.3}$$

*where* $\mathscr{V}_i = \mathscr{V}_i^- - \mathscr{V}_i^+$.

To apply Theorem 2 in [22] which verifies local asymptotic stability of DFS, the following five assumptions must be verified for the DFS, denoted here as $x_0$. Let $m$ be the number of infective state out of $n$, $m < n$.

(A1) If $x \geqslant 0$, then $\mathscr{F}_i, \mathscr{V}_i^+, \mathscr{V}_i^- \geqslant 0$ for $i = 1, ..., n$.

(A2) If $x_i = 0$ then $\mathscr{V}_i^- = 0$ for $i = 1, ..., m$.

(A3) $\mathscr{F}_i = 0$ if $i > m$.

(A4) If $x_i = 0$ then $\mathscr{F}_i = 0$ and $\mathscr{V}_i^+ = 0$ for $i = 1, ..., m$.

(A5) If $\mathscr{F}(x)$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts, where $x_0$ is the disease free steady state.

**Theorem 2.2.1.** *[Theorem 2, p.33, [22]] Consider the disease transmission model given by (2.3) with f(x) satisfying conditions (A1) through (A5). Define*

$$F = \left(\frac{\partial \mathscr{F}_i}{\partial_j}(x_0)\right) \qquad V = \left(\frac{\partial \mathscr{V}_i}{\partial_j}(x_0)\right) \qquad 1 \leqslant i, j \leqslant m \tag{2.4}$$

*then $x_0$ is locally asymptotically stable if $R_0 < 1$, but unstable if $R_0 > 1$, where $R_0 = \rho(FV^{-1})$.*

Note that $\rho$ in the above theorem is defined to be a spectral radius of matrix $(FV^{-1})$. We show that Theorem 2.2.1 applies to our model (2.1) and state it as the following theorem.

**Theorem 2.2.2.** *Model (2.1) satisfies conditions (A1) to (A5) with*

$$R_0 = \sqrt{\frac{\beta C^* N}{k}}.$$

*Thus if $R_0 < 1$, the DFS is locally asymptotically stable and unstable if $R_0 > 1$.*

*Proof.* Let

$$\mathscr{F} = \begin{pmatrix} \beta CV \\ aNI \\ 0 \\ 0 \end{pmatrix}, \quad \mathscr{V} = \begin{pmatrix} aI + \rho FI \\ \gamma FV + kV \\ -(\lambda(C^* - C) - \beta CV) \\ -FV(\omega + eC) + bF \end{pmatrix} = \mathscr{V}^- - \mathscr{V}^+$$

such that

$$\mathscr{V}^+ = \begin{pmatrix} 0 \\ 0 \\ \lambda C^* + \alpha CV \\ FV(\omega + eC) \end{pmatrix}, \quad \mathscr{V}^- = \begin{pmatrix} aI + \rho FI \\ \gamma FV + kV \\ \lambda C + \beta CV \\ bF \end{pmatrix}$$

Calculating the Jacobian matrix and evaluating at $E_1$,

$$J = \begin{pmatrix} F - V & 0 \\ -J_3 & -J_4 \end{pmatrix}$$

where

$$F = \begin{pmatrix} 0 & \beta C_1 \\ aN & 0 \end{pmatrix} = \begin{pmatrix} 0 & \beta C^* \\ aN & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} a + \rho F_1 & 0 \\ 0 & \gamma F_1 + k \end{pmatrix} = \begin{pmatrix} a & 0 \\ 0 & k \end{pmatrix}, \quad \text{and} \quad J_4 = \begin{pmatrix} \lambda & 0 \\ 0 & b \end{pmatrix}.$$

Verification of (A1) to (A4) are straightforward. To verify (A5) note that $Df(x_0)$ has negative real eigenvalues $-\lambda$, $-b$, $-a$, and $-k$.

The basic reproduction number is the spectral radius of the next-generation matrix,

$$FV^{-1} = \begin{pmatrix} 0 & \beta C^* \\ aN & 0 \end{pmatrix} \begin{pmatrix} 1/a & 0 \\ 0 & 1/k \end{pmatrix} = \begin{pmatrix} 0 & \dfrac{\beta C^*}{k} \\ N & 0 \end{pmatrix}. \tag{2.5}$$

Thus,

$$R_0 = \rho(FV^{-1}) = \sqrt{\frac{\beta C^* N}{k}}. \tag{2.6}$$

□

Often the basic reproduction number is defined as

$$\hat{R}_0 = \frac{\beta C^* N}{k} = R_0^2 \tag{2.7}$$

(see references [18],[19]). The expression in (2.7) can be obtained if one considers a type reproduction number as defined by Heesterbeek and Roberts [10] when trying to control the virus. From the next generation matrix

$$M = FV^{-1} = (m_{ij}) = \begin{pmatrix} 0 & \dfrac{\beta C^*}{k} \\ N & 0 \end{pmatrix}$$

the type reproduction for controlling the virus is

$$T_V = m_{22} + \frac{m_{12} m_{21}}{1 - m_{11}} = \frac{\beta C^* N}{k} = \hat{R}_0$$

(see [2]). The type reproduction number for controlling infected cells is similarly defined,

$$T_I = m_{11} + \frac{m_{12}m_{21}}{1 - m_{22}} = T_V = \hat{R}_0.$$

Next, we show that the DFS is globally asymptotically stable if $R_0 < 1$.

**Theorem 2.2.3.** *Steady-state $E_1 = (C^*, 0, 0, 0)$ is globally asymptotically stable if $R_0 < 1$.*

*Proof.* Consider

$$\begin{aligned} \frac{dI}{dt} &\leq \beta C^* V - aI \\ \frac{dV}{dt} &\leq aNI - kV \end{aligned} \tag{2.8}$$

where $\frac{d\vec{X}}{dt} \leq A\vec{X}$, $\vec{X} = (I, V)^t$ and

$$A = \begin{pmatrix} -a & \beta C^* \\ aN & -k \end{pmatrix}.$$

Since the off-diagonal elements of $A$ are positive, the solutions $\vec{X}(t)$ can be compared to $\frac{d\vec{Y}(t)}{dt} = A\vec{Y}(t)$. If $R_0 < 1$, the eigenvalues of $A$ have negative real part. Hence, by comparison of the solution $\vec{Y}(t)$ with $\vec{X}(t)$ it follows that $\lim_{t\to\infty}(I(t), V(t)) = (0, 0)$ [13].

There exists time $t^*$ and $\epsilon > 0$ such that $t \geq t^*$, $V(t)(\omega + eC^*) < b - \epsilon$. This implies $\frac{dF}{dt} < -\epsilon F$. It follows that $\lim_{t\to\infty} F(t) = 0$.

There also exists time $t^*$ and $\epsilon > 0$ such that $t \geq t^*$, $\frac{dC}{dt} \geq \lambda(C^* - C) - \lambda\epsilon C$. Then $\frac{dC}{dt} \geq \lambda(C^* - (1 + \epsilon)C)$ and it follows that $\liminf_{t\to\infty} C(t) \geq \frac{C^*}{1+\epsilon}$. Since $\epsilon$ is arbitrary and $C^* \geq C(t)$, then $\lim_{t\to\infty} C(t) = C^*$. So we conclude that $\lim_{t\to\infty}(C(t), I(t), F(t), V(t)) = E_1$. □

## 2.3 Other Steady-States

There exists a second immune-free steady-state if $R_0 > 1$. We call this steady-state the "acute stage" steady-state.

**Theorem 2.3.1.** *If $R_0 > 1$, there exists a second steady-state $E_2 = (C_2, I_2, F_2, V_2)$, where*

$$\begin{aligned} C_2 &= \frac{k}{\beta N} \\ I_2 &= \lambda \frac{\beta N C^* - k}{\beta a N} = \frac{\lambda}{a}(C^* - C_2) \\ F_2 &= 0 \\ V_2 &= \lambda \frac{\beta N C^* - k}{k\beta} = \frac{\lambda}{\beta C_2}(C^* - C_2) = \frac{a}{\beta C_2} I_2. \end{aligned} \tag{2.9}$$

*Equilibrium $E_2$ is locally asymptotically stable if $R_0 > 1$ and $V_2(\omega + eC_2) < b$.*

Note for existence of a positive equilibrium $E_2$ with $I_2 > 0$ and $V_2 > 0$ requires $C_2 < C^*$. That is, the healthy T cells are reduced below the DFS at $E_2$.

*Proof.* Since the components of $E_2$ must be positive, the condition for existence of $E_2$ is $R_0 > 1$.

To verify the conditions for local asymptotic stability of $E_2$, we need to linearize the system (2.1) about $E_2$. Therefore, the Jacobian matrix of the system (2.1) is

$$J = \begin{pmatrix} -\lambda - \beta V & 0 & 0 & -\beta C \\ \beta V & -(a + \rho F) & -\rho I & \beta C \\ FVe & 0 & V(\omega + eC) - b & F(\omega + eC) \\ 0 & aN & -\gamma V & -\gamma F - k \end{pmatrix}$$

Evaluating the Jacobian matrix J at $E_2$ leads to

$$J(E_2) = \begin{pmatrix} -\dfrac{\lambda C^*}{C_2} & 0 & 0 & -\beta C_2 \\ \beta V_2 & -a & -\rho I_2 & \beta C_2 \\ 0 & 0 & V_2(\omega + eC_2) - b & 0 \\ 0 & aN & -\gamma V_2 & -k \end{pmatrix}$$

with characteristic equation:

$$(V_2(\omega + eC_2) - b - x)(x^3 + a_1x^2 + a_2x + a_3) = 0$$

where

$$\begin{aligned} a_1 &= a + \lambda + k + \frac{\lambda}{k}(C^*\beta N - k) \\ a_2 &= \lambda C^*\beta N \frac{(a+k)}{k} \\ a_3 &= \lambda a(C^*\beta N - k) \end{aligned}$$

If $V_2(\omega + eC_2) < b$ by Routh-Hurwitz stability criterion [1], $E_2$ is locally asymptotically stable if the following three conditions are satisfied:

$$\begin{aligned} &(1) \quad a_1 > 0 \\ &(2) \quad a_3 > 0 \\ &(3) \quad a_1a_2 - a_3 > 0 \end{aligned} \tag{2.10}$$

Condition (1) and (2) clearly hold if $R_0 > 1$. Condition (3) can be simplified and written in the form:

$$a_1a_2 - a_3 = \frac{\lambda}{k^2}\left[C^*\beta N(a+k)(ak + \lambda C^*\beta N) + k^3(a + C^*\beta N)\right].$$

Thus conditions (1), (2), (3) hold together with the assumptions $R_0 > 1$ and $V_2(\omega + eC_2) < b$ imply local asymptotic stability of $E_2$. □

We need a stronger assumption to prove global asymptotic stability of $E_2$.

**Theorem 2.3.2.** *If $R_0 > 1$ and*

$$V_2(\omega + eC^*) + \frac{\rho I_2 N}{\gamma}(\omega + eC^*) < b, \tag{2.11}$$

*then the second steady-state $E_2 = (C_2, I_2, F_2, V_2)$, is globally asymptotically stable.*

Note if $\rho = 0$ or $\gamma \to \infty$, then condition (2.11) is close to the conditions in Theorem 2.3.1 for local asymptotic stability(except $C^*$ is in place of $C_2$).

*Proof.* Consider the following Lyapunov function

$$\begin{aligned} L(C,I,F,V) &= C_2\left(\frac{C}{C_2}-\ln\frac{C}{C_2}-1\right)+I_2\left(\frac{I}{I_2}-\ln\frac{I}{I_2}-1\right) \\ &+ \frac{1}{N}V_2\left(\frac{V}{V_2}-\ln\frac{V}{V_2}-1\right)+DF, \end{aligned} \tag{2.12}$$

where $D$ is a suitably chosen positive constant. A similar Lyapunov function without the '$DF$' term was used by Korobeinikov [12].

First, it is important to note that $L(C_2,I_2,F_2,V_2)=0$ and that $E_2$ is a unique minimum in the region $\mathbf{R}^4_+$; $L(C,I,F,V)>0$ except at $E_2$. Second, choose $D$ such that

$$\frac{\gamma V_2}{N}+\rho I_2 < Db < \frac{\gamma b}{N(\omega+eC^*)}. \tag{2.13}$$

This can be done because of the inequality (2.11).

Differentiating $L$ along solution trajectories of (2.1) leads to

$$\begin{aligned} \dot{L} &= -\lambda C+\lambda C^*+\lambda C_2-\frac{\lambda C_2C^*}{C}+aI_2-\frac{\beta I_2CV}{I} \\ &- \frac{aV_2I}{V}+\frac{kV_2}{N}+\frac{\gamma V_2F}{N}-bDF+DeCFV \\ &+ D\omega FV-\rho FI+\rho FI_2-\frac{\gamma FV}{N}. \end{aligned} \tag{2.14}$$

We apply the following identities from (2.9):

$$\begin{aligned} \lambda C^* &= aI_2+\lambda C_2 \\ \beta I_2 &= \frac{aI_2^2}{C_2V_2} \\ \frac{k}{N}V_2 &= aI_2. \end{aligned} \tag{2.15}$$

Therefore, using (2.15), we can write the expression in (2.14) as follows:

$$\begin{aligned} \dot{L} &= \lambda C_2\left(2-\frac{C}{C_2}-\frac{C_2}{C}\right)+aI_2\left(3-\frac{C_2}{C}-\frac{CVI_2}{C_2V_2I}-\frac{IV_2}{I_2V}\right) \\ &+ \frac{\gamma V_2F}{N}-bDF+DeCFV+D\omega FV-\rho FI+\rho FI_2-\frac{\gamma FV}{N}. \end{aligned}$$

Applying $C(t) \leq C^*$ and dropping the term $-\rho FI$, we have the following inequality

$$\begin{aligned} \dot{L} &\leq \lambda C_2 \left(2 - \frac{C}{C_2} - \frac{C_2}{C}\right) + aI_2 \left(3 - \frac{C_2}{C} - \frac{CVI_2}{C_2V_2I} - \frac{IV_2}{I_2V}\right) \\ &+ FV\left(DeC^* + D\omega - \frac{\gamma}{N}\right) + F\left(\frac{\gamma V_2}{N} + \rho I_2 - bD\right). \end{aligned} \tag{2.16}$$

Using (2.13), it follows that

$$\begin{aligned} DeC^* + D\omega - \frac{\gamma}{N} < 0 \\ \frac{\gamma V_2}{N} + \rho I_2 - bD < 0. \end{aligned} \tag{2.17}$$

Using the arithmetic-geometric inequality and (2.17), if $R_0 > 1$, then the positive definite function $L(C, I, F, V)$ has a negative derivative if $(C, I, F, V) \neq E_2$. By Lyapunov's stability theorem, the equilibrium $E_2$ is globally asymptotically stable [11]. □

There is a third steady-state where the immune response is positive and we call it "chronic stage" steady-state. This steady-state is computed in the next theorem.

**Theorem 2.3.3.** *The chronic stage steady-state $E_3 = (C_3, I_3, F_3, V_3)$, where*

$$C_3 = \frac{\lambda C^*}{\lambda + \beta V_3} \tag{2.18}$$

$$I_3 = \frac{\beta C_3 V_3}{a + \rho F_3} \tag{2.19}$$

$$F_3 = \frac{-(\gamma a + k\rho) + \sqrt{(\gamma a + k\rho)^2 + 4\gamma\rho(aN\beta C_3 - ka)}}{2\gamma\rho} \tag{2.20}$$

$$V_3 = \frac{-(\omega\lambda + e\lambda C^* - \beta b) + \sqrt{(\omega\lambda + e\lambda C^* - \beta b)^2 + 4\omega\beta b\lambda}}{2\omega\beta} \tag{2.21}$$

*exists if* $R_1 = \dfrac{\beta N C_3}{k} > 1$.

Notice that $C_3 < C^*$. Thus, if $R_1 > 1$, it follows that $\hat{R}_0 > 1$ and $R_0 > 1$.

*Proof.* From the third and the first equations of (2.1), we have:

$$V_3 = \frac{b}{\omega + eC_3} \tag{2.22}$$

$$C_3 = \frac{\lambda C^*}{\lambda + \beta V_3}. \tag{2.23}$$

Therefore by (2.22) and (2.23) we derive the following quadratic equation for $V_3$,

$$\omega\beta V_3^2 + V_3(\omega\lambda + e\lambda C^* - \beta b) - b\lambda = 0. \tag{2.24}$$

The positive solution of (2.24) can be obtained from the quadratic formula as follows:

$$V_3 = \frac{-(\omega\lambda + e\lambda C^* - \beta b) + \sqrt{(\omega\lambda + e\lambda C^* - \beta b)^2 + 4\omega\beta b\lambda}}{2\omega\beta}. \tag{2.25}$$

Now from the second and the last equations of (2.1), we obtain

$$I_3 = \frac{\beta C_3 V_3}{a + \rho F_3} \tag{2.26}$$

$$aNI_3 = V_3(\gamma F_3 + k). \tag{2.27}$$

Finally when $\beta N C_3 > k$, applying (2.26) and (2.27), there is only one positive solution to the following quadratic equation:

$$\gamma\rho F_3^2 + F_3(\gamma a + k\rho) + (ka - aN\beta C_3) = 0$$

which is

$$F_3 = \frac{-(\gamma a + k\rho) + \sqrt{(\gamma a + k\rho)^2 + 4\gamma\rho(aN\beta C_3 - ka)}}{2\gamma\rho}.$$

□

The relationship between the acute and chronic stage steady-states, $E_2$ and $E_3$, is verified in the following theorem.

**Theorem 2.3.4.** *If $E_2$ and $E_3$ are positive steady states, then their respective com-*

*ponents satisfy the following inequalities:*

$$C_2 < C_3,\ I_2 > I_3, \text{ and } V_2 > V_3. \tag{2.28}$$

*Proof.* From (2.18) and the last equation of system (2.1), we obtain

$$\beta C_3 V_3 = (a + \rho F_3) I_3$$
$$aN I_3 = (\gamma F_3 + k) V_3.$$

So

$$I_3 = \frac{\beta C_3}{(a + \rho F_3)} \left( \frac{aN}{\gamma F_3 + k} \right) I_3.$$

Then

$$C_3 = \frac{(a + \rho F_3)(k + \gamma F_3)}{\beta a N} > \frac{k}{\beta N} = C_2.$$

Therefore, $C^* > C_3 > C_2$.

Now we prove $I_3 < I_2$ and $V_3 < V_2$. If we add the first and the second equations of (2.1) at $E_3$, we get

$$\lambda(C^* - C_3) - aI_3 - \rho F_3 I_3 = 0.$$

Therefore

$$I_3(a + \rho F_3) = \lambda(C^* - C_3) < \lambda(C^* - C_2)$$

and

$$I_3 < \frac{\lambda(C^* - C_2)}{a + \rho F_3} < \frac{\lambda(C^* - C_2)}{a} = I_2.$$

Finally

$$V_3 = \frac{aN I_3}{\gamma F_3 + k} < \frac{aN I_2}{k} = V_2.$$

□

In the next theorem we give sufficient conditions for global asymptotic stability of the steady state $E_3$.

**Theorem 2.3.5.** *If* $R_1 = \dfrac{\beta N C_3}{k} > 1$ *and*

$$\max\left\{\frac{\beta C_3 N-k}{NF_3\omega},\frac{\rho I_3+\frac{\gamma V_3}{N}}{b}\right\}$$
$$<\min\left\{\frac{\gamma}{N(\omega+eC^*)},\frac{2aI_3+\lambda C_3-\lambda C^*-\frac{kV_3}{N}}{F_3}\right\} \tag{2.29}$$

*then the steady-state $E_3$ is globally asymptotically stable.*

*Proof.* We consider the following Lyapunov function

$$\begin{aligned} L(C,I,F,V) &= C_3\left(\frac{C}{C_3}-\ln\frac{C}{C_3}-1\right)+I_3\left(\frac{I}{I_3}-\ln\frac{I}{I_3}-1\right) \\ &+ AV_3\left(\frac{V}{V_3}-\ln\frac{V}{V_3}-1\right)+BF_3\left(\frac{F}{F_3}-\ln\frac{F}{F_3}-1\right). \end{aligned} \tag{2.30}$$

Note that $L(C_3,I_3,F_3,V_3)=0$ and that $E_3$ is a unique minimum in the region $\mathbf{R}^4_+$; $L(C,I,F,V)>0$ except at $E_3$.

Differentiating $L$ in (2.30) along solution trajectories of (2.1) leads to

$$\begin{aligned} \dot{L} &= \dot{C}\left(1-\frac{C_3}{C}\right)+\dot{I}\left(1-\frac{I_3}{I}\right)+A\dot{V}\left(1-\frac{V_3}{V}\right)+B\dot{F}\left(1-\frac{F_3}{F}\right) \\ &= (\lambda C^*-\lambda C-\beta CV)\left(1-\frac{C_3}{C}\right)+(\beta CV-aI-\rho FI)\left(1-\frac{I_3}{I}\right) \\ &+ A(aNI-\gamma FV-kV)\left(1-\frac{V_3}{V}\right)+B(FV(\gamma+eC)-bF)\left(1-\frac{F_3}{F}\right). \end{aligned}$$

Let $A=\frac{1}{N}$ and we will choose $B>0$ such that $\dot{L}\leq 0$. Then

$$\begin{aligned} \dot{L} &= \lambda C^*-\lambda C-\frac{\lambda C^*C_3}{C}+\lambda C_3+\beta VC_3-\rho FI \\ &- \frac{\beta CVI_3}{I}+aI_3+\rho FI_3-\frac{\gamma}{N}FV-\frac{k}{N}V-a\frac{IV_3}{V} \\ &+ \frac{\gamma}{N}FV_3+\frac{k}{N}V_3+B(FV(\omega+eC)-bF)\left(1-\frac{F_3}{F}\right) \end{aligned}$$

We use the following identities from the third equilibrium

$$\beta C_3 V_3 = (a + \rho F_3) I_3 \quad \text{and} \quad \lambda C^* = \lambda C_3 + \beta C_3 V_3$$

Then

$$\begin{aligned}
\lambda C^* &= \lambda C_3 + a I_3 + \rho F I_3 \\
\frac{\lambda C^* C_3}{C} &= \frac{\lambda C_3^2}{C} + \frac{\beta C_3^2 V_3}{C} \\
\frac{\beta C_3^2 V_3}{C} &= \frac{a I_3 C_3 + \rho I_3 F_3}{C} \\
\frac{\beta C V I_3}{I} &= \beta C_3 V_3 \left( \frac{C V I_3}{C_3 V_3 I} \right) = (a I_3 + \rho F_3 I_3) \left( \frac{C V I_3}{C_3 V_3 I} \right)
\end{aligned}$$

Substituting the preceding identities into $\dot{L}$ and simplifying leads to

$$\begin{aligned}
\dot{L} &= \lambda C_3 \left( 2 - \frac{C}{C_3} - \frac{C_3}{C} \right) + a I_3 \left( 3 - \frac{C_3}{C} - \frac{C V I_3}{C_3 V_3 I} - \frac{I V_3}{I_3 V} \right) - a I_3 + \rho I_3 F_3 \\
&+ \beta C_3 V - \rho F I - \rho I_3 F_3 \left( \frac{C V I_3}{C_3 V_3 I} \right) + \rho F I_3 - \frac{\gamma F V}{N} - \frac{k V}{N} + \frac{\gamma F V_3}{N} \\
&+ \frac{k V_3}{N} + B F V (\omega + e C) - B F_3 V (\omega + e C) - B b F - B b F_3 - \frac{\rho I_3 F_3 C_3}{C}
\end{aligned}$$

After factoring out some terms and eliminating some negative terms,

$$-\rho F I - \rho I_3 F_3 \left( \frac{C V I_3}{C_3 V_3 I} \right) - e B F_3 V C - \frac{\rho I_3 F_3 C_3}{C},$$

we obtain

$$\begin{aligned}
\dot{L} &\leq \lambda C_3\left(2-\frac{C}{C_3}-\frac{C_3}{C}\right)+aI_3\left(3-\frac{C_3}{C}-\frac{CVI_3}{C_3V_3I}-\frac{IV_3}{I_3V}\right)\\
&+ \left(-aI_3+\rho I_3F_3+\frac{kV_3}{N}+BbF_3\right)\\
&+ \left(\beta C_3V-\frac{kV}{N}-BF_3\omega V\right)\\
&+ \left(\rho FI_3+\frac{\gamma FV_3}{N}-BbF\right)\\
&+ \left(BFV(\omega+eC)-\frac{\gamma FV}{N}\right).
\end{aligned}$$

The first two expressions in parentheses are negative by the arithmetic-geometric inequality. Therefore, if

$$-aI_3+\rho I_3F_3+\frac{kV_3}{N}+BbF_3<0 \tag{2.31}$$

$$\beta C_3-\frac{k}{N}-BF_3\omega<0 \tag{2.32}$$

$$\rho I_3+\frac{\gamma V_3}{N}-Bb<0 \tag{2.33}$$

$$B(\omega+eC)-\frac{\gamma}{N}<B(\omega+eC^*)-\frac{\gamma}{N} \tag{2.34}$$

then $\dot{L}<0$. Applying the identity

$$\rho I_3F_3=\beta C_3V_3-aI_3=\lambda(C^*-C_3)-aI_3$$

for (2.31), we get

$$-aI_3+\rho I_3F_3+\frac{kV_3}{N}+BbF_3=-2aI_3-\lambda C_3+\lambda C^*+\frac{kV_3}{N}+BbF_3.$$

Finally if the inequalities (2.29) hold, then all of the inequalities (2.31)-(2.34) are satisfied. Then we can conclude that $\dot{L}<0$. By Lyapunov's stability theorem, the equilibrium $E_3$ is globally asymptotically stable [11]. □

In the following theorem we prove that when the chronic and acute steady-states

are positive, then the acute stage steady-state is unstable.

**Theorem 2.3.6.** *If $\hat{R}_0 > R_1 > 1$, then $E_2$ is unstable.*

*Proof.* To prove, it is enough to show that if $R_1 > 1$, then $V_2(\omega + eC_2) - b > 0$. From (2.1), (2.18), and the last equation of (2.9) we obtain:

$$\begin{aligned} V_3(\omega + eC_3) &= 0 \\ \beta C_3 V_3 &= \lambda C^* - \lambda C_3 \\ \beta C_2 V_2 &= \lambda C^* - \lambda C_2. \end{aligned}$$

Since $C_2 < C_3$, then we have

$$C_2 V_2 = \frac{\lambda C^* - \lambda C_2}{\beta} > \frac{\lambda C^* - \lambda C_3}{\beta}.$$

Therefore, $C_2 V_2 > C_3 V_3$. Since $V_2 > V_3$ then

$$V_2(\omega + eC_2) - b > V_3(\omega + eC_3) - b = 0.$$

Thus $V_2(\omega + eC_2) - b > 0$. □

In the following theorem we prove that when the acute stage steady-state is asymptotically stable, then the chronic stage steady-state cannot exist.

**Theorem 2.3.7.** *Steady-state $E_2$ exists and $V_2(\omega + eC_2) < b$ if and only if $R_0 > 1 > R_1$.*

*Proof.* Assume $E_2$ exists and $V_2(\omega + eC_2) < b$. Then $R_0 > 1$ and $E_2$ is locally asymptotically stable by Theorem 2.3.1. We prove $R_1 < 1$ by contradiction. Assume $R_1 \geq 1$. In case $R_1 > 1$, by applying Theorem 2.3.6 we conclude that $E_2$ is unstable which is a contradiction. In case $R_1 = 1$, then $C_2 = C_3$, $V_2 = V_3$, and $V_2(\omega + eC_2) = V_3(\omega + eC_3) = b$ which is again a contradiction. Therefore, $R_1 < 1$.

Now we want to show that if $R_0 > 1 > R_1$, then $V_2(\omega + eC_2) - b < 0$. If $R_1 < 1$, then $C_3 < \frac{k}{\beta N} = C_2$. From (2.18) and (2.9) we obtain

$$C_3 V_3 = \frac{\lambda C^* - \lambda C_3}{\beta} > \frac{\lambda C^* - \lambda C_2}{\beta}.$$

Therefore, $C_3V_3 > C_2V_2$. Since $R_1 < 1$, from (2.18) we get

$$\frac{\beta N C_3}{k} = \frac{\beta N \lambda C^*}{k(\lambda + \beta V_3)} < 1.$$

Then

$$V_3 > \lambda \left( \frac{\beta N C^* - k}{\beta k} \right) = V_2$$

and $V_3 > V_2$. Therefore, $0 = V_3(\omega + eC_3) - b > V_2(\omega + eC_2) - b$. □

Finally, a conjecture is made concerning the global stability of $E_3$.

**Conjecture.** *If $\hat{R}_0 > R_1 > 1$, then $E_3$ is globally asymptotically stable.*

## 2.4 Summary

In this section, we will discuss some of the immunological implications of our mathematical results that were verified in the previous three sections.

The basic reproduction number, $R_0$, shows whether HIV or HCV infections can be established. If $R_0 < 1$, no infections can occur. So the ideal control strategy suggests the reduction of $R_0$ to a value below 1 in order for the infection to be cleared. However, when $R_0 > 1$, then HIV or HCV infection is possible, and whether the stage of infection is acute or chronic, depends on the threshold value $R_1$. If $\hat{R}_0 > R_1 > 1$, then the patient enters the chronic stage of HIV or HCV infection and remains there until $R_1$ becomes less than 1. In this chronic stage, the immune response is strong enough to control the infection and the density of viruses and infectious cells cannot become too high. But viruses continue to replicate themselves from the infectious cells. Since for HIV infection there is no complete cure, the best control strategy for this infection may be to achieve $R_1 > 1$. Finally, when $R_0 > 1 > R_1$ a patient leaves the chronic stage and enters the acute stage of the infection. For HIV we call this stage AIDS. Generally, the patient dies after six months. Because $R_1 < 1$ implies $V_2(\omega + eC_2) - b < 0$ (Theorem 2.3.6), the immune response becomes weaker over time and the density of immune cells, antibodies and CTL, decrease until they reach zero. In this case there is no immune response that can kill viruses or infectious cells.

# CHAPTER III
# THE DELAY MODEL

We consider several models where delays are included in the model (2.1) to account for steps in the process that are not instantaneous. Delay in the production of virus particles from infectious cells is a time needed for virus particles to be reproduced. This delay can also be caused by drug therapy. The model has the form:

$$\begin{aligned}
\frac{dC(t)}{dt} &= \lambda(C^* - C(t)) - \beta C(t)V(t) \\
\frac{dI(t)}{dt} &= \beta C(t)V(t) - aI(t) - \rho F(t)I(t) \\
\frac{dF(t)}{dt} &= F(t)V(t)(\omega + eC(t)) - bF(t) \\
\frac{dV(t)}{dt} &= aNI(t-\tau)e^{-a\tau-\rho\int_0^\tau F(u)\,du} - \gamma F(t)V(t) - kV(t)
\end{aligned} \tag{3.1}$$

The delayed term must account for the additional deaths that occur during the delay $\tau > 0$. The term $e^{-a\tau-\rho\int_0^\tau F(u)\,du}$ accounts for deaths of infected cells prior to reproduction of new virions. A delay on the cytotoxic T lymphocytes (CTL) response is a time needed for CTL activation prior to its affect on infectious cells. The model has the form:

$$\begin{aligned}
\frac{dC(t)}{dt} &= \lambda(C^* - C(t)) - \beta C(t)V(t) \\
\frac{dI(t)}{dt} &= \beta C(t)V(t) - aI(t) - \rho F(t-\tau_1)I(t-\tau_1)e^{-b\tau_1} \\
\frac{dF(t)}{dt} &= F(t)V(t)(\omega + eC(t)) - bF(t) \\
\frac{dV(t)}{dt} &= aNI(t) - \gamma F(t)V(t) - kV(t)
\end{aligned} \tag{3.2}$$

A delay on the antibodies response is a time needed for an antibody activation prior to its affect on virus particles. The model has the form:

$$\begin{aligned}
\frac{dC(t)}{dt} &= \lambda(C^* - C(t)) + \beta C(t)V(t) \\
\frac{dI(t)}{dt} &= \beta C(t)V(t) - aI(t) - \rho F(t)I(t) \\
\frac{dF(t)}{dt} &= F(t)V(t)(\omega + eC(t)) - bF(t) \\
\frac{dV(t)}{dt} &= aNI(t) - \gamma F(t-\tau_2)V(t-\tau_2)e^{-b\tau_2} - kV(t)
\end{aligned} \tag{3.3}$$

Finally, a model with two simultaneous delays in the immune response has the form:

$$\begin{aligned}
\frac{dC(t)}{dt} &= \lambda(C^* - C(t)) + \beta C(t)V(t) \\
\frac{dI(t)}{dt} &= \beta C(t)V(t) - aI(t) - \rho F(t-\tau_1)I(t-\tau_1)e^{-b\tau_1} \\
\frac{dF(t)}{dt} &= F(t)V(t)(\omega + eC(t)) - bF(t) \\
\frac{dV(t)}{dt} &= aNI(t) - \gamma F(t-\tau_2)V(t-\tau_2)e^{-b\tau_2} - kV(t)
\end{aligned} \tag{3.4}$$

The disease free steady-state for models (3.1)-(3.4) is the same as the model (2.1). Because the delay occurs in the nonlinear terms in models (3.2)-(3.4), that do not involve healthy T cells, local stability of the DFS $E_1 = (C^*, 0, 0, 0)$ for models (3.2)-(3.4) is the same as the nondelay model (2.1). However, local stability of the DFS for model (3.1) differs from the other delay models.

We simplify the delay model (3.1) and consider the following model with a discrete delay:

$$\begin{aligned}
\frac{dC(t)}{dt} &= \lambda(C^* - C(t)) - \beta C(t)V(t) \\
\frac{dI(t)}{dt} &= \beta C(t)V(t) - aI(t) - \rho F(t)I(t) \\
\frac{dF(t)}{dt} &= F(t)V(t)(\omega + eC(t)) - bF(t) \\
\frac{dV(t)}{dt} &= aNI(t-\tau)e^{-a\tau} - \gamma F(t)V(t) - kV(t)
\end{aligned} \tag{3.5}$$

with the nonnegative initial conditions

$$\begin{aligned} &0 < C(0) < C^* \\ &V(0) > 0 \\ &I(t) = \varphi(t), -\tau \leq t \leq 0 \\ &F(0) > 0. \end{aligned} \tag{3.6}$$

If $\rho$ is small, model (3.5) may be a reasonable approximation to model (3.1). In the remainder of this thesis, we will analyze model (3.5).

## 3.1 Nonnegativity, Boundedness, and Existence

We want to show that solutions exist, are bounded, and remain nonnegative on any interval $[-\tau, T)$, where $T > 0$. Then we can extend the solution to the entire interval $t \in [-\tau, \infty)$.

Let $x(t) = (C(t), I(t), F(t), V(t))$ and $y(t) = (C(t-\tau), I(t-\tau), F(t-\tau), V(t-\tau))$ and denote the differential equation (3.5) as

$$\frac{dx}{dt} = f(t, x, y) \tag{3.7}$$

with nonnegative and continuous initial condition $x(t) = \phi(t)$, $-\tau \leq t \leq 0$. The following theorems extend the existence and uniqueness theory from ordinary differential equations to ordinary delay differential equations. The theorems are stated for general delay differential equation (3.7) with $x \in \mathbf{R}^n$, $y \in \mathbf{R}^n$ and $\phi \in \mathbf{R}^n$ [21].

**Theorem 3.1.1.** *[Theorem 3.1, p. 26 and Remark 3.3, p. 27 [21]] Let $f(t, x, y)$ and the partial derivatives of $f_i$ with respect to $x_j$ be continuous on $\mathbf{R}^n$, and let $\phi : [-\tau, 0] \to \mathbf{R}^n$ be continuous. Then there exists $\sigma > 0$ and a unique solution of the initial-value problem on $[-\tau, \sigma]$.*

**Theorem 3.1.2.** *[Theorem 3.2, p. 26, and Remark 3.3, p. 27 [21]]. Let $f$ satisfy the hypothesis of Theorem 3.1.1 and let $x : [-\tau, \sigma) \to \mathbf{R}^n$ be noncontinuable solution of the initial-value problem. If $\sigma < \infty$ then*

$$\lim_{t \to \sigma^-} \|x(t)\| = \infty. \tag{3.8}$$

**Theorem 3.1.3.** *[Theorem 3.4, p. 27, [21]]. Suppose that* $f : \mathbf{R} \times \mathbf{R}^n_+ \times \mathbf{R}^n_+ \to \mathbf{R}^n$ *satisfies the hypothesis of Theorem 3.1.1 and*

$$\forall i, t, \forall x, y \in \mathbf{R}^n_+ : x_i = 0 \Rightarrow f_i(t, x, y) \geq 0. \tag{3.9}$$

*If the initial data* $\phi$ *satisfy* $\phi \geq 0$*, then the corresponding solution* $x(t)$ *satisfies* $x(t) \geq 0$ *for all* $t \geq 0$ *where it is defined.*

Note that Theorem 3.1.1 is stronger than needed for existence but can be directly applied to our system. Theorems 3.1.1, 3.1.2, and 3.1.3 are applied to system (3.5)-(3.6) to verify existence, uniqueness, and nonnegativity of solutions on $[-\tau, \infty)$.

**Theorem 3.1.4.** *A unique nonnegative solution exists to system (3.5)-(3.6) on the interval* $[-\tau, \infty)$.

*Proof.* First, it is easy to see that the partial derivatives with respect to $x_i$, $i = 1, 2, 3, 4$ of the right side of (3.5) are continuous on any bounded region and the initial condition is continuous. Thus Theorem 3.1.1 applies and there exists a unique solution for $t \in [-\tau, \sigma)$, $\sigma > 0$. Next, we show that on the interval of existence, solutions are nonnegative. In model (3.5), if $x, y \geq 0$ and $x_i = 0$ for some $i$, then it is easy to see that $f_i(t, x, y) \geq 0$. So Theorem 3.1.3 implies that $C(t), I(t), F(t), V(t) \geq 0$ for $0 \leq t < T$. To show boundedness of solutions, we use results from Chapter II to show that the nonnegative solutions $C(t)$, $I(t)$, and $F(t)$ are bounded for $t \leq T$ (proof of Theorem 2.1.1). Now, since $I(t)$ is bounded for $t \leq T$, $0 \leq I(t - \tau) \leq K < \infty$. Then

$$\frac{dV(t)}{dt} \leq aNK - kV(t) \tag{3.10}$$

Thus, V(t)$\leq$ $aNK/k + (V(0) - aNK/k)\, e^{-kt}$ which shows V (t) is also bounded. Theorem 3.1.2 can be applied; solutions do not blow up and they can be continued to $[0, \infty)$. □

## 3.2 Local Stability of the Disease-Free Steady-State

Let $\Re(z)$ denote the real part of a complex number $z = x + iy$, that is, $\Re(z) = x$. The following theorem was verified by Brauer [4] for the case that $p(z)$ and $q(z)$ do not depend on $\tau$ and the four conditions in the theorem are satisfied for all $\tau > 0$.

The proof of the theorem also applies to the case when $p(z)$ and $q(z)$ are functions of $\tau$ and the four conditions hold for $\tau > \bar{\tau}$, where $\bar{\tau} > 0$.

**Theorem 3.2.1** (Theorem 1, p. 187, [4]). *Let $p(z)$ and $q(z)$ be analytic functions in some open set containing $\Re(z) \geq 0$ and $z$ be a root of the following equation*

$$p(z) + q(z)e^{-\tau z} = 0, \tag{3.11}$$

*where $\tau$ is the delay parameter. Suppose for all $\tau > \bar{\tau} > 0$ the following four conditions hold:*

*(a)* $p(z) \neq 0$ *for* $\Re(z) \geq 0$.

*(b)* $\overline{p(-iy)} = p(iy)$ *and* $\overline{q(-iy)} = q(iy)$ *for* $0 \leq y < \infty$.

*(c)* $|q(iy)| < |p(iy)|$ *for* $0 \leq y < \infty$.

*(d)* $\lim\limits_{|z|\to\infty;\Re(z)\geq 0} \left|\dfrac{q(z)}{p(z)}\right| = 0$.

*Then $\Re(z) < 0$ for every root $z$ of equation (3.11) satisfying $\tau > \bar{\tau}$.*

Given a system of DDE,

$$\frac{d\vec{X}(t)}{dt} = F(\vec{X}(t), \vec{X}(t-\tau)),$$

such as (3.5), to linearize about an equilibrium $E_1$, let $\vec{Y}(t) = \vec{X}(t) - E_1$. Then $d\vec{Y}(t)/dt = d\vec{X}(t)/dt$. Linearization of $\vec{Y}(t)$ leads to $d\vec{Y}(t)/dt = A\vec{Y}(t) + B\vec{Y}(t-\tau)$. Matrices $A$ and $B$ are the Jacobian matrices with the terms that involve no delay or delays, respectively. This is a linear system, so to solve it, it is necessary to find the eigenvalues $x$ such that $\vec{Y}(t) = \vec{Y}_0 e^{xt}$. Substituting into the linearized equation:

$$x\vec{Y}(t) = A\vec{Y}(t) + B\vec{Y}(t)e^{-x\tau}$$

because $\vec{Y}(t-\tau) = \vec{Y}_0 e^{x(t-\tau)} = \vec{Y}(t)e^{-x\tau}$. If the origin of this linearized system is locally asymptotically stable (eigenvalues $x$ have negative real part), then the steady-state $E_1$ for the original nonlinear DDE system is locally asymptotically stable (The-

orem 4.8, p. 55 [21]). We use Theorem 3.2.1 to prove a stability result for equilibrium $E_1$ for model (3.5).

**Theorem 3.2.2.** *The disease-free steady-state $E_1$ of (3.5) is locally asymptotically stable if $\tau > (\ln R_0^2)/a > 0$. Otherwise, it is unstable.*

*Proof.* Linearization of the delay model (3.5) about an equilibrium yields the linearized system $\vec{Y}(t)x = A\vec{Y}(t) + B\vec{Y}(t)e^{-x\tau}$ where

$$\overrightarrow{Y}(t) = \overrightarrow{Y_0}e^{xt} \quad , \quad \overrightarrow{Y_0} = (y_0, y_1, y_2, y_3)^t,$$

$$A = \begin{pmatrix} -\lambda - \beta V & 0 & 0 & -\beta C \\ \beta V & -a - \rho F & -\rho I & \beta C \\ FVe & 0 & V(\omega + eC) - b & F(\omega + eC) \\ 0 & 0 & -\gamma V & -\gamma F - k \end{pmatrix} \tag{3.12}$$

$$B = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & -aNe^{-a\tau} & 0 & 0 \end{pmatrix} \tag{3.13}$$

and $x$ is a complex number. Thus, $(xI - A - Be^{-x\tau})\overrightarrow{Y} = \overrightarrow{0}$. We call $(xI - A - Be^{-x\tau})$, the characteristic matrix.

The characteristic equation is

$$\det(xI - A - Be^{-x\tau}) = 0.$$

If we substitute $E_1$ in (3.12) and (3.13) we obtain the following characteristic equation

$$(x + b)(x + \lambda)(x^2 + (a + k)x + ak - aC^*\beta Ne^{-a\tau - x\tau}) = 0.$$

Therefore, one of the eigenvalues is $-b$ and one is $-\lambda$. Consider the following equation

$$x^2 + (a + k)x + ak - aC^*\beta Ne^{-a\tau}e^{-x\tau} = 0$$

or

$$p(x) + q(x)e^{-x\tau} = 0$$

where

$$p(x) = x^2 + (a+k)x + ak, \quad q(x) = -aC^*\beta N e^{-a\tau}.$$

Using the Routh-Hurwitz criteria [1], if $p(x) = 0$, it follows that if $a + k > 0$ and $ak > 0$ then $\Re(x) < 0$. Here, (a) holds in Theorem 3.2.1.

Evaluating $p(x)$ at $x = iy$ for $0 \leq y < \infty$ yields

$$p(iy) = -y^2 + (a+k)iy + ak.$$

Thus,

$$\begin{aligned} |p(iy)|^2 &= (ak - y^2)^2 + y^2(a+k)^2 \\ &= (a^2 + y^2)(k^2 + y^2). \end{aligned}$$

Then

$$|p(iy)| \geq ak > aC^*\beta N e^{-a\tau} = |q(iy)|$$

provided $R_0^2 < e^{a\tau}$ or equivalently $\tau > (\ln R_0^2)/a$ and condition (b) is satisfied.

Finally, condition (d) holds since

$$\lim_{x\to\infty} \left|\frac{q(x)}{p(x)}\right| = \lim_{x\to\infty} \frac{aC^*\beta N e^{-a\tau}}{x^2 + (a+k)x + ak} = 0$$

□

## 3.3 The Stability of the Second Steady-State

There exists a second immune free steady state, $E_2(\tau)$, if $\tau < (\ln R_0^2)/a$. Note that this second steady-state $E_2(\tau)$ depends on the delay $\tau$.

**Theorem 3.3.1.** *If $R_0 > 1$ and $\tau < (\ln R_0^2)/a$, then there exists a second steady-state*

$E_2(\tau) = (C_2(\tau), I_2(\tau), F_2(\tau), V_2(\tau))$ *where*

$$\begin{aligned} C_2(\tau) &= \frac{ke^{a\tau}}{\beta N} \\ I_2(\tau) &= \lambda\frac{\beta N C^* - ke^{a\tau}}{\beta a N} \\ F_2(\tau) &= 0 \\ V_2(\tau) &= \lambda\frac{\beta N C^* - ke^{a\tau}}{k\beta e^{a\tau}}. \end{aligned} \tag{3.14}$$

*Proof.* From the third equation of (3.5), it is easy to see $F_2(\tau) = 0$. Also from the second and the last equations of (3.5) we obtain

$$I_2(\tau) = \frac{\beta C_2(\tau) V_2(\tau)}{a} = \frac{kV_2(\tau)e^{a\tau}}{aN}$$

and therefore, $C_2(\tau) = ke^{a\tau}/\beta N$. Then, from the first equation of (3.5), it is also easy to show

$$V_2(\tau) = \lambda\frac{\beta N C^* - ke^{a\tau}}{k\beta e^{a\tau}}.$$

Steady state $I_2(\tau)$ can be found by substituting $V_2(\tau)$ into (3.3). □

Note that the delay increases the healthy T cells at the steady state $C_2(\tau) > C_2$. Conditions are derived for local stability of the second steady-state $E_2(\tau)$ given in (3.14).

**Theorem 3.3.2.** *If $R_0 > 1$,*

$$\tau < (\ln R_0^2)/a \quad \textit{and} \quad V_2(\tau)(\omega + eC_2(\tau)) - b < 0, \tag{3.15}$$

*then the second steady-state $E_2(\tau)$ of model (3.5) is locally asymptotically stable.*

*Proof.* We first try to find the characteristic equation for the second steady-state, $E_2(\tau)$, and use Theorem 3.2.1 to verify the conditions for stability of that steady-state. If we enter the components of $E_2(\tau)$ in matrices (3.12) and (3.13), we get the

the following characteristic matrix

$$\begin{pmatrix} x+\lambda+\frac{e^{-a\tau}\Phi}{k} & 0 & 0 & \frac{e^{a\tau}k}{N} \\ -\frac{e^{-a\tau}\Phi}{k} & x+a & \frac{\rho\Phi}{aN\beta} & -\frac{e^{a\tau}k}{N} \\ 0 & 0 & x+b-\frac{e^{-a\tau}\lambda(\frac{eke^{a\tau}}{\beta N}+\omega)\Phi}{k\beta} & 0 \\ 0 & -ae^{(-a\tau-x\tau)}N & \frac{e^{-a\tau}\gamma\Phi}{k\beta} & x+k \end{pmatrix}, \quad (3.16)$$

where $\Phi = \lambda(-e^{a\tau}k + \beta NC^*)$.

Now if we calculate the determinant of (3.16) we obtain the following characteristic equation:

$$\left( x+b-\frac{e^{-a\tau}\lambda(\frac{eke^{a\tau}}{\beta N}+\omega)(-e^{a\tau}k+\beta NC^*)}{k\beta} \right) \left(p(x)+q(x)e^{-x\tau}\right) = 0 \quad (3.17)$$

where

$$\begin{aligned} p(x) &= \frac{e^{-a\tau}(a+x)(k+x)(e^{a\tau}kx+\beta N\lambda C^*)}{k} \\ q(x) &= (-akx-ak\lambda). \end{aligned} \quad (3.18)$$

By some easy simplifications, the first factor in the characteristic equation is

$$\left( x+b-\frac{e^{-a\tau}\lambda(\frac{eke^{a\tau}}{\beta N}+\omega)(-e^{a\tau}k+\beta NC^*)}{k\beta} \right) = x+b-V_2(\tau)(\omega+eC_2(\tau)).$$

Therefore by the assumption of the theorem, the first eigenvalue of the (3.17) is negative.

If $p(x) = 0$, then $\Re(x) < 0$. Here, (a) holds in Theorem 3.2.1. We try to prove

condition (c). Evaluating $p(x)$ and $q(x)$ at $x = iy$ for $0 \leq y < \infty$ yields

$$\begin{aligned} p(iy) &= -iy^3 + \frac{e^{-a\tau}y^2(-ae^{a\tau}k - e^{a\tau}k^2 - \beta N\lambda C^*)}{k} \\ &+ \frac{iye^{-a\tau}(ak^2e^{a\tau} + a\beta N\lambda C^* + k\beta N\lambda C^*)}{k} + a\beta N\lambda C^* e^{-a\tau} \\ q(iy) &= -aiky - ak\lambda. \end{aligned}$$

Thus,

$$\begin{aligned} |p(iy)|^2 &= \left(ae^{-a\tau}\beta N\lambda C^* + \frac{e^{-a\tau}y^2(-ae^{a\tau}k - e^{a\tau}k^2 - \beta N\lambda C^*}{k}\right)^2 \\ &+ \left(-y^3 + \frac{e^{-a\tau}y(ae^{a\tau}k^2 + a\beta N\lambda C^* + k\beta N\lambda C^*)}{k}\right)^2 \\ |q(iy)|^2 &= a^2k^2y^2 + a^2k^2\lambda^2. \end{aligned}$$

Then we have

$$|p(iy)|^2 - |q(iy)|^2 = y^6 + m_1y^4 + m_2y^2 + m_3 \tag{3.19}$$

where

$$\begin{aligned} m_1 &= \frac{e^{-2a\tau}(ae^{a\tau}k + e^{a\tau}k^2 + \beta N\lambda C^*)^2}{k^2} - \frac{2e^{-a\tau}(ae^{a\tau}k^2 + a\beta N\lambda C^* + k\beta N\lambda C^*)}{k} \\ m_2 &= -a^2k^2 - \frac{2ae^{-2a\tau}\beta N\lambda C^*(ae^{a\tau}k + e^{a\tau}k^2 + \beta N\lambda C^*)}{k} \\ &+ \frac{e^{-2a\tau}(ae^{a\tau}k^2 + a\beta N\lambda C^* + k\beta N\lambda C^*)^2}{k^2} \\ m_3 &= -a^2k^2\lambda^2 + a^2e^{-2a\tau}(\beta N\lambda C^*)^2. \end{aligned}$$

If all the coefficients of the polynomial (3.19) are greater than or equal to zero, then by Descartes' rule of signs the polynomial does not have any positive or negative root. This means that the range of the polynomial is the set of all positive real numbers for every value of $x$.

If we simplify $m_1$, then we obtain

$$m_1 = a^2 + k^2 + e^{-2a\tau}\frac{(\beta N\lambda C^*)^2}{k^2} > 0.$$

If we simplify $m_2$, then

$$m_2 = \frac{e^{-2a\tau}(a^2+k^2)(\beta N\lambda C^*)^2}{k^2} > 0.$$

Finally, if we simplify $m_3$,

$$m_3 = a^2\lambda^2k^2\left(\frac{e^{-2a\tau}(\beta NC^*)^2}{k^2} - 1\right) = a^2\lambda^2k^2\left(R_0^4e^{-2a\tau} - 1\right).$$

Therefore if $\ln(R_0^2)/a > \tau$, then $m_3$ is always positive.

Finally, we can obtain condition (d) as follow

$$\lim_{x\to\infty}\left|\frac{q(x)}{p(x)}\right| = \lim_{x\to\infty}\frac{(ak^2x + ak^2\lambda)}{e^{-a\tau}(a+x)(k+x)(e^{a\tau}kx + \beta N\lambda C^*)} = 0.$$

All of the conditions of Theorem 3.2.1 hold so that $E_2(\tau)$ is locally asymptotically stable. □

The last case of a steady-state with an immune response, steady-state $E_3(\tau)$, will be studied in future research.

## 3.4 Summary

In this section, we will discuss some of the immunological implications of our mathematical results that were verified in the previous sections for the DDE model (3.5).

The value of the delay, $\tau$, shows whether HIV or HCV infections can be established if there is a delay prior to viral reproduction. If $\tau > \ln(R_0^2)/a$, then the delay is sufficiently large so that production of the viruses is slow and does not lead to HIV or HCV infections. Therefore in this situation, the infection can be cleared. Therefore, the ideal control strategy is for the infection is to be completely cleared, to increase $\tau$ to a value greater than $(\ln R_0^2)/a$. However when $\tau < (\ln R_0^2)/a$, then the production of viruses is fast and if the immune response does not play a dominant role, the

infection persists. In this case if $V_2(\tau)(\omega + eC_2(\tau)) - b < 0$, the immune response is weak and the density of immune cells, antibodies and CTL decrease until they reach zero. In the absence of an immune response the infection reaches a high level which we call the acute stage.

# CHAPTER IV
# NUMERICAL EXAMPLES

In this chapter, we use numerical solutions to illustrate the theoretical results that were verified in Chapters II and III for models (2.1) and (3.5). Parameter values are hypothetical. The numerical values depend on the particular units that are chosen. Biological reasonable qualitative behavior of an infection is initiated when there is a large viral load, no infected cells and healthy cells are at a steady-state. We assume $k \geq a \geq \lambda$. The parameter values in all cases are:

$$\lambda = 0.1, \quad C^* = 10, \quad a = 0.2, \quad \rho = 0.01, \quad e = 0.0001, \quad k = 0.7, \tag{4.1}$$

$$b = 0.1, \quad N = 10, \quad \text{and} \quad \gamma = 0.01. \tag{4.2}$$

Only the two parameters $\beta$ and $\omega$ are varied in the examples. These two parameters represent the transmission rate and the stimulation rate of the immune response by the virus.

## 4.1 Simulations for the ODE Model

For numerical simulation of the ODE model (2.1) we use the initial conditions:

$$C(0) = C^*, \quad I(0) = 0, \quad F(0) = 2, \quad \text{and} \quad V(0) = 15. \tag{4.3}$$

Figure 4.1 shows the solution dynamics of model (2.1) when the reproduction numbers, $R_0$, and $R_1$, are less than one. In this case the only steady-state is the DFS $E_1$. According to Theorem 2.2.3, $E_1$ is globally asymptotically stable.

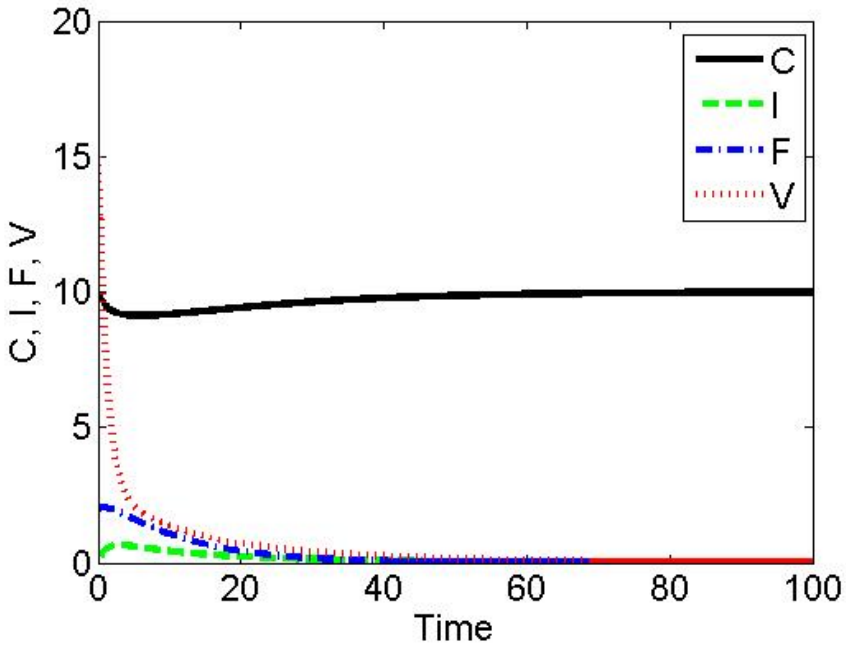


Figure 4.1: Numerical solution of model (2.1) when $R_0 < 1$. The density of infectious cells, immune cells, and viruses will eventually decrease to 0, but the density of CD4 T cells converges to $C^*$. In other words, the solutions converge to the disease free steady-state $E_1$, where the infection wipes out. Parameter values $\beta = 0.005$ and $\omega = 0.01$. The basic reproduction numbers are $R_0 = 0.845$ and $R_1 = 0.487$. The DFS is $E_1 = (10, 0, 0, 0)$.

If $R_0 > 1$, the DFS ,$E_1$, becomes unstable by Theorem 2.2.2 and by Theorem 2.3.1 the acute stage steady-state, $E_2$, exists. In addition, if $R_1 > 1$, by Theorem 2.3.6 the acute stage steady-state $E_2$ is unstable and the chronic steady-state, $E_3$, exists. In Figure 4.2, solutions converge to $E_3$ but not to $E_2$.

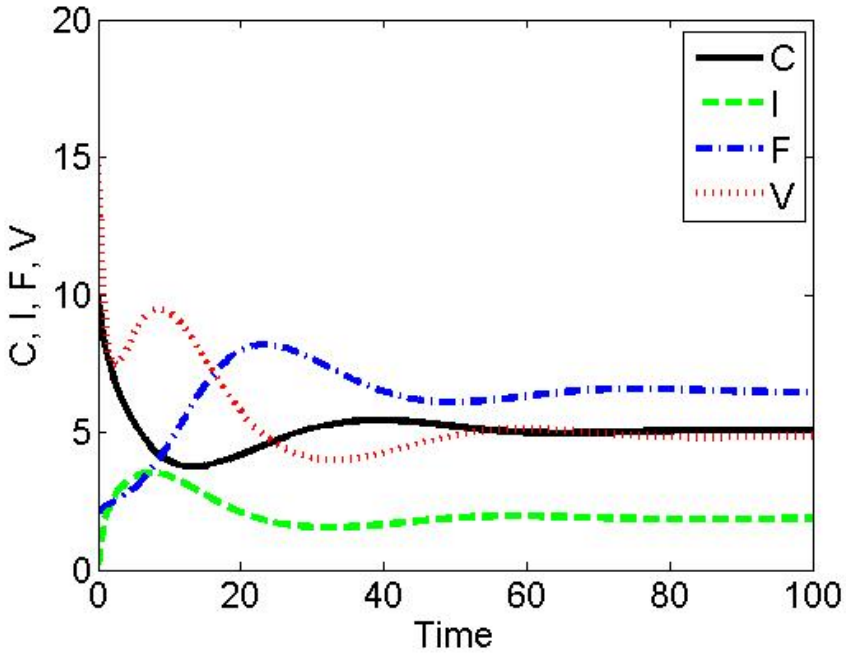


Figure 4.2: Numerical solution of model (2.1) when $R_1 > 1$. In the chronic stage, viruses continue to replicate, but the immune response is stronger and can control the infection. So the number of viruses and infectious cells cannot get exceedingly large. Also, at this stage there is a considerable amount of CD4 T cells that can stimulate the immune response to confront the infection. Parameter values $\beta = 0.02$ and $\omega = 0.02$. The basic reproduction numbers are $R_0 = 1.690$ and $R_1 = 1.446$ with $E_3 = (5.062, 1.865, 6.478, 4.877)$.

In Figure 4.3, $R_0 > 1$ and $R_1 < 1$. In this case by Theorem 2.3.1, the acute stage steady-state is locally asymptotically stable since $V_2(\omega + eC_2) - b < 0$. It appears that steady-state $E_2$ is globally stable, even though the conditions of Theorem 2.3.2 do not hold.

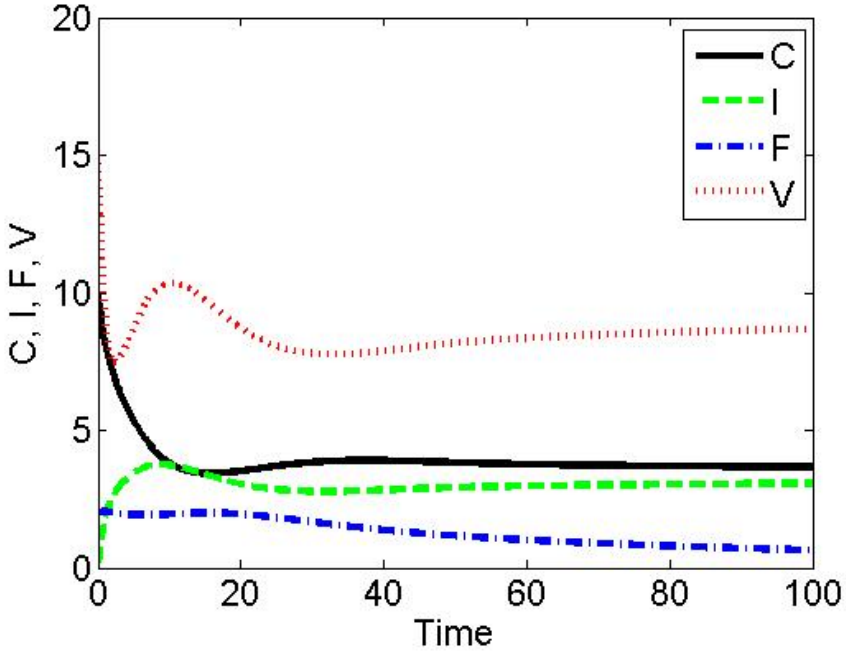


Figure 4.3: Numerical solution that converges to the acute steady-state $E_2$. If the acute stage steady state is locally asymptotically stable, the viral load becomes too high because the immune response is so weak that it cannot clear the infection. The parameter values are $\beta = 0.02$ and $\omega = 0.01$. Basic reproduction numbers are $R_0 = 1.690$ and $R_1 = 0.974$ with $V_2(\omega+eC_2)-b = -0.004$, and $E_2 = (3.500, 3.250, 0, 9.286)$.

Finally, we demonstrate an example where the global stability conditions for the acute stage steady-state hold in Theorem 2.3.2. See Figure 4.4.

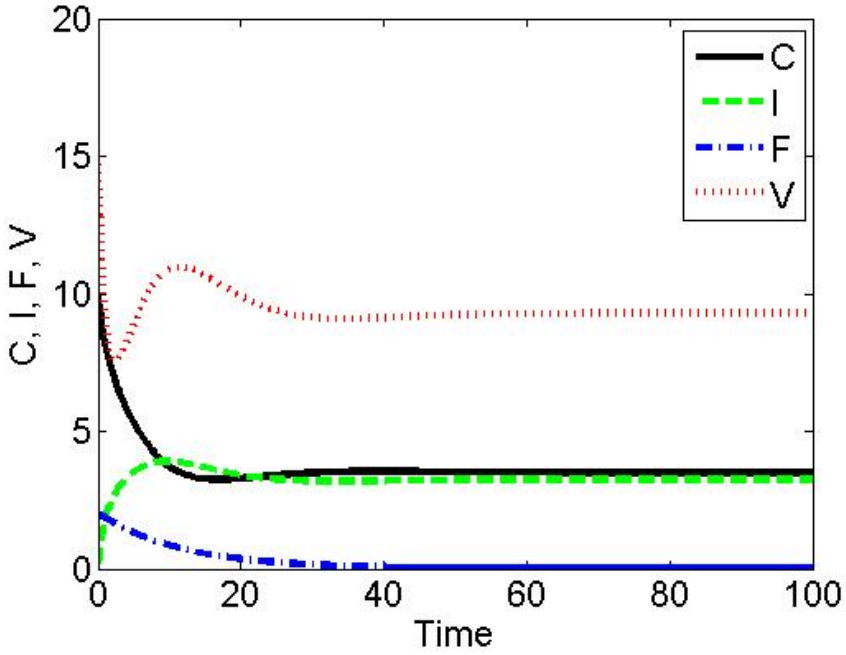


Figure 4.4: Numerical solution that converges to the acute stage steady-state $E_2$. In this example, the immune response eventually becomes deactivated and there is a high viral load. For this simulation, parameter values $\beta = 0.02$ and $\omega = 0.001$. Basic reproduction numbers are $R_0 = 1.690$, $R_1 = 0.143$, $V_2(\omega + eC_2) - b = -0.087$, $V_2(\omega + eC^*) + \frac{\rho I_2 N}{\gamma}(\omega + eC^*) - b = -0.016$, and $E_2 = (3.500, 3.250, 0, 9.286)$.

### 4.2 Simulations for the DDE Model

We present two numerical solutions for the DDE model (3.5). Initial conditions are the same as in the simulation of the ODE model, conditions (4.3). That is,

$$C(0) = C^*, \quad I(t) = 0, \quad F(0) = 0, \quad \text{and} \quad V(0) = 15, \quad -\tau \leq t \leq 0.$$

In addition, the parameter values are given in (4.1) and (4.2). In model (3.5), if $\tau > (\ln R_0^2)/a$, then the delay is large enough to decrease the speed of virus productions by infectious cells. In this case, the DFS is locally asymptotically stable even though $R_0 > 1$. The numerical example for this case is shown in Figure 4.5.

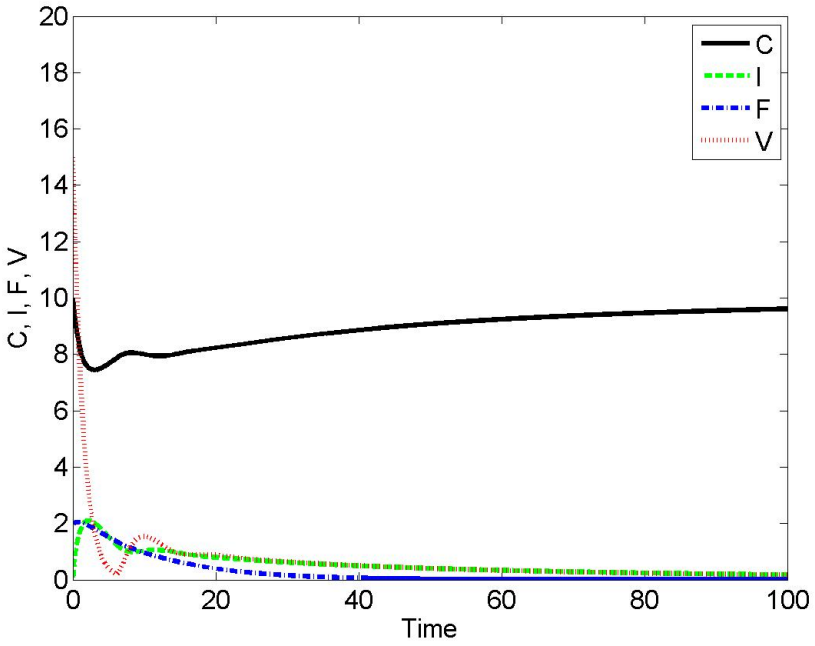


Figure 4.5: Numerical solution of model (3.5) when $\tau > (\ln R_0^2)/a > 1$. The density of infectious cells, immune cells, and viruses eventually decrease to zero, but the density of CD4 T cells stays close to $C^*$. Therefore, the DFS is locally asymptotically stable. For this simulation, parameters are $\tau = 6$, $(\ln R_0^2)/a = 5.249$, $\beta = 0.02$, and $\omega = 0.01$. The basic reproduction numbers are $R_0 = 1.690$ and $R_1 = 0.143$ with $E_1 = (10, 0, 0, 0)$.

Finally, in model (3.5) if $\tau < (\ln R_0^2)/a$ and $V_2(\tau)(\omega + eC_2(\tau)) - b < 0$, then $E_2(\tau)$ becomes locally asymptotically stable. In this situation, the delay is not large enough to decrease the speed of virus productions and the immune response becomes deactivated. There is high level of virus production and acute stage occurs. The computer simulation for this case is shown in Figure 4.6.

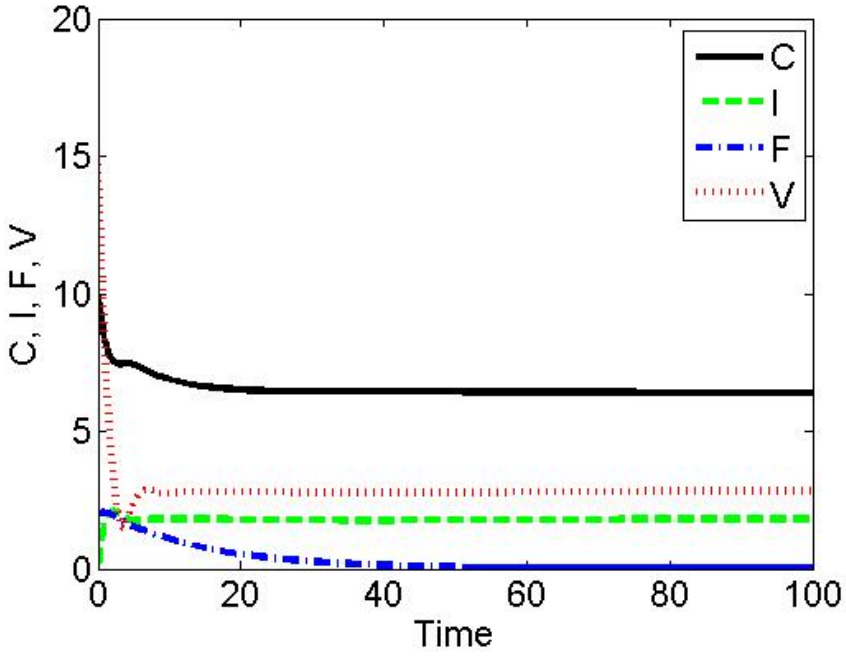


Figure 4.6: Numerical solution of model (3.5) with $\tau < (\ln R_0^2)/a > 1$ and $V_2(\tau)(\omega + eC_2(\tau)) - b < 0$. The second steady-state, $E_2(\tau)$, is locally asymptotically stable. Parameter values $\tau = 3$, $(\ln R_0^2)/a = 5.249$, $\beta = 0.02$, $\omega = 0.01$. The basic reproduction numbers are $R_0 = 1.690$ and $R_1 = 0.143$ with $E_2(\tau) = (6.3774, 1.8113, 0, 2.8402)$.

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