MODELING THE EFFECTS OF DRUGS OF ABUSE ON HIV INFECTIONS WITH TWO VIRAL SPECIES

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MODELING THE EFFECTS OF DRUGS OF ABUSE ON HIV INFECTIONS WITH TWO VIRAL SPECIES

Peter Maurice Uhl, Candidate for the Master of Science Degree
University of Missouri-Kansas City, 2017

ABSTRACT

Injection drug use is one of the greatest risk factors associated with contracting human immunodeficiency virus (HIV), and drug abusers infected with HIV suffer from a higher viral load and rapid pathogenesis. Replication of HIV may result in a large number of mutant viruses that can escape recognition of the host’s immune response. Experimental results have shown that the presence of morphine can decrease the viral mutation rate and cellular immune responses. This thesis presents a mathematical model to determine if the decrease in mutation and cellular immune response in the presence of morphine can account for the increased viral load. Two viral species are considered: a wild-type and a mutant. The morphine-altered mutation rate and cellular immune response is shown to allow the wild-type virus to outcompete the mutant, resulting in a higher set point viral load. Calculation of the basic reproduction number for each species shows that the dominant species is determined by a threshold morphine concentration, with the mutant dominating below the threshold and the wild-type dominating above. Stability analysis is performed on the infection free and mutant only equilibria of the system and numerical simulations reflect the
increased viral load associated with morphine use.
The faculty listed below, appointed by the Dean of College of Arts and Science, have examined a thesis titled “Modeling the Effects of Drugs of Abuse on HIV Infections with Two Viral Species”, presented by Peter Maurice Uhl, candidate for the Master of Science degree, and certify that in their opinion it is worthy of acceptance.

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CHAPTER 1
INTRODUCTION

Human immunodeficiency virus (HIV) is a significant health concern in the United States and around the world, with some 56,000 new infections per year in the United States [1]. HIV is a blood borne pathogen and one of the most common forms of transmission is by the sharing of needles used for injecting cocaine or heroin between infected and non-infected persons. Drugs of abuse have been shown to have adverse effects on the progression of HIV infections, including a higher set point viral load and decreased amounts of CD4+ T cells [2]. Studies involving rhesus macaques and simian immunodeficiency virus (SIV) have shown that morphine causes a faster progression to AIDS and pathogenesis in morphine affected animals, and studies of HIV have also demonstrated a quicker progression to AIDS associated with opiate use [3]. It is therefore important to investigate the mechanisms by which morphine affects the progression of HIV infections.

Cytotoxic T-lymphocytes (CTLs) are an important component of the human immune system for combating viral infections, including HIV, by limiting viral reproduction and the infection of hosts target cells, therefore the production of CTLs plays a significant role in the progression of an infection [4]. However, HIV possesses a high genetic variability which results in the production of escape mutants that can avoid detection by CTLs [5]. Continuous infection of target cells also results in a large amount of newly infected cells and free virus particles [6]. As a result, the production
of mutant viruses is a significant barrier to the treatment of HIV by antiviral drugs or to the development of an effective vaccine [5].

Mathematical models have been very useful in understanding the dynamics of infectious diseases [6, 7]. A problem on which there has been little study is to determine the effects of morphine on the viral dynamics of HIV when multiple viral species are present, and the objective of this thesis is to present such a model. This thesis is organized as follow: Chapter 2 will introduce the relevant biological concepts and mathematical modeling of HIV dynamics, Chapter 3 will develop a novel mathematical model that incorporates immune escape and morphine effects into an HIV dynamics model, Chapter 4 will introduce the basic reproduction number and discuss the steady state solutions of the model, Chapter 5 will present some numerical simulations of the model and discuss short- and long-term viral dynamics, and Chapter 6 will be a discussion of the results and future works.
CHAPTER 2
BACKGROUND AND LITERATURE REVIEW

HIV Infections and Drugs of Abuse

The target cells of HIV are CD4+ T cells, which are a part of the immune system that signal other immune cells to attack foreign antigens when they are present [8, 9]. HIV virions attack CD4+ cells by attaching to receptors on the CD4+ cell surface and entering the interior of the cell, where the virions can begin reproducing [10]. Once the virus has entered a target cell, the target cell becomes infected and begins releasing new virions. The early stages of infection are characterized by a rapid production of a large number of virions and infected cells [11], making the early weeks of infection crucial in determining the long-term viral dynamics.

In the acute stage of the infection the host’s immune system responds by creating a large amount of virus specific CTLs. The CTLs perform actions to inhibit viral growth, for example producing cytokines that limit viral reproduction, reducing the amount of receptors available on target cells, and by destroying infected cells directly, but it is not clear which actions are the most important for combating acute HIV infections [12]. The high number of CTLs puts pressure on the virus to quickly mutate to a form that can evade the CTLs, this combined with the quick replication speed of HIV results in a large number of mutant viruses being produced [13, 14]. After the infection has progressed and the immune response by CTLs has been reduced it is possible for mutant viruses to revert back to the original wild-type strain.
Experimental studies have shown that opiates can increase viral replication by increasing CCR5 expression in target cells [15] and studies on rhesus macaques have shown similar levels of viral growth in the early stages of infection between morphine dependent and control animals, but higher set point viral loads associated with morphine use [2]. Morphine has also been shown to affect the amount of escape mutants that evolve, but the exact effect remains unclear [16]. Thus, it is desirable to develop a mathematical model that will include components for the hosts cellular immune response (CTLs), escape mutations, and morphine use.

**Viral Dynamics Modeling**

Deterministic differential equations are used extensively to model infectious disease, and a similar approach will be used here. The simplest HIV model is given by

\[
\begin{align*}
T' &= \lambda - \beta VT - \delta_T T \\
V' &= pI - \delta_V V \\
I' &= \beta VT - \delta_I I
\end{align*}
\]

Where \( T \), \( I \), and \( V \) are the populations of target cells, infected cells, and free virions, respectively, and a prime denotes the derivative with respect to time, in days. Target cells are produced at constant rate \( \lambda \) and die naturally at rate \( \delta_T \) per cell. Infected cells are produced via the mass action term \( \beta TV \) proportional to the number of target cells and free virions. Free virions are produced at rate \( pI \) proportional to the number of infected cells. Target cells, infected cells, and free virions die at rates \( \delta_T T \), \( \delta_I I \), and \( \delta_V V \), respectively [6, 20].
Vaidya et al. [21] developed a model that incorporates two separate target cell subpopulations based on the experimental observation that morphine can increase the co-receptor expression of certain target cells and make them more susceptible to infection and that individual cells can transition between these subpopulations [21]. The differential equations for this model are

\[
\begin{align*}
T'_l &= \lambda + qT_h - rT_l - \beta_l VT_l - \delta T_l \\
T'_h &= rT_l - qT_h - \beta_h VT_h - \delta T_h \\
V' &= pI - \delta V \\
I' &= \beta_l VT_l + \beta_h VT_h - \delta I
\end{align*}
\]

The two subpopulations of target cells are denoted \( T_l \) and \( T_h \) and have corresponding infection terms \( \beta_l VT_l \) and \( \beta_h VT_h \). The subpopulations are distinguished by their different susceptibilities to infection induced by morphine use, with \( T_l \) having lower susceptibility and \( T_h \) having higher susceptibility. Target cells transition between subpopulations at rates \( qT_h \) from \( T_h \) to \( T_l \) and \( rT_l \) from \( T_l \) to \( T_h \).

Konrad et al. [19] developed a model to study the effectiveness of a CTL based vaccine that included a wild-type virus \( V_w \), a mutant virus \( V_m \), and a cellular immune response in the form of CTLs. In their model, the total viral load is divided into subpopulations of wild-type and mutant virus with corresponding subpopulations of infected cells. This model accounts for immune response by including a population of CTLs, \( C \), the production of which is stimulated by the presence of infected cells and which kill infected cells at rates proportional to the populations of CTLs and infected cells.
CHAPTER 3
MATHEMATICAL MODELS

This chapter will develop a novel mathematical model that incorporates the effects of morphine on the viral mutation rate and the CTL proliferation rate into existing HIV models, then give a description of the parameters of the model.

Model Formulation

Modifying the model from Vaidya et al. [21] to include populations of wild-type viruses, mutant viruses, and CTLs results in the system

\[
\begin{align*}
T_l' &= \lambda + qT_h - rT_l - \beta_l V_w T_l - \hat{\beta}_l V_m T_l - \delta T_l \\
T_h' &= rT_l - qT_h - \beta_h V_w T_h - \hat{\beta}_h V_m T_h - \delta T_h \\
V_w' &= pI_w - \delta V_w \\
V_m' &= pI_m - \delta V_m \\
I_w' &= (1 - \epsilon)(\beta_l V_w T_l + \beta_h V_w T_h) - bI_w C - \delta I_w \\
I_m' &= \epsilon(\beta_l V_w T_l + \beta_h V_w T_h) + \hat{\beta}_l V_m T_l + \hat{\beta}_h V_m T_h \\
&\quad - \hat{b}I_m C - \delta I_m \\
C' &= \omega + \alpha(I_w + I_m)C - \delta C C
\end{align*}
\]

Target cells interact with free virions to produce actively infected cells via infection; target cells are divided into subpopulations $T_l$, which are less susceptible to infection due to lower co-receptor expression, and $T_h$ which are more susceptible to infection. Target cells transition from $T_h$ to $T_l$ at rate $qT_h$ and from $T_l$ to $T_h$ at rate
It is assumed that newly created target cells are all in the $T_l$ subpopulation and are produced at constant rate $\lambda$ [6, 21]. Wild-type virions infect $T_l$ target cells at rate $\beta_l V_w T_l$, where $\beta_l$ is the per capita infection rate of $T_l$ by the wild-type virus. Mutant virions infect $T_l$ target cells at rate $(1 - F)\beta_l V_m T_l$, where $F$ is the fitness cost of the mutant virus— a reduction in the mutant’s infection rate relative to the wild-type’s caused by mutation[26]. Similarly, $T_h$ cells are infected by wild-type and mutant viruses at rates $\beta_h V_w T_h$ and $(1 - F)\beta_h V_m T_h$, respectively, where $\beta_h$ is the per capita infection rate of $T_h$ by the wild-type virus [19]. Target cells die naturally at rates $\delta_{T_l} T_l$ and $\delta_{T_h} T_h$ corresponding to $T_l$ and $T_h$ [27, 19].

When target cells are infected by either the wild-type virus $V_w$ or the mutant virus $V_m$ they become actively infected cells $I_w$ and $I_m$, at which point there is no distinction based on levels of co-receptor expression. In the model developed by Konrad et al [19], a portion of target cells infected by the wild-type virus mutate and become mutant infected cells rather than wild-type infected cells based on the mutation parameter $\epsilon$. The parameters $\mu$ and $\eta$ are introduced to model the lowered mutation rate caused by morphine [16] so that the per capita mutation rate becomes $\frac{\epsilon}{\mu + \eta M}$, where $M$ is the concentration of morphine which, for simplicity, is assumed to be constant. Therefore, wild-type infected cells are produced at rate $(1 - \frac{\epsilon}{\mu + \eta M})(\beta_l V_w T_l + \beta_h V_w T_h)$, while the remainder $\frac{\epsilon}{\mu + \eta M}(\beta_l V_w T_l + \beta_h V_w T_h)$ are converted into mutant infected cells. Mutant infected cells are additionally produced by way of infection of target cells by mutant virions at the total rate of $(1 - F)(\beta_l V_m T_l + \beta_h V_m T_h)$. Infected cells die at rates $\delta_{I_w} I_w$ and $\delta_{I_m} I_m$. Wild-type and mutant infected cells produce free virions, $V_w$ and $V_m$, which are cleared at rates
\[ \delta_V V_w \text{ and } \delta_V V_m, \] respectively [27, 19].

Due to different epitope mutations, CTLs are assumed to be produced at constant rate \( \omega \) and also to reproduce in the presence of infected cells [19]. Konrad et al. denote \( \alpha \) as the rate of CTL production in response to the total amount of infected cells \( I_w + I_m \). The parameters \( \gamma \) and \( \xi \) are introduced to lower the CTL production rate [2], changing the CTL production rate to \( \frac{\alpha}{\gamma + \xi M} (I_w + I_m) C \). CTLs kill wild-type infected cells at rate \( b I_w C \), where \( b \) is the per capita wild-type clearance rate. Due to responses by epitope-specific CTLs there is some recognition of the mutant by the CTL response [19, 28], so the clearance rate of the mutant virus is assumed to be \( \frac{b}{B} I_m C \), where \( B \) represents the escape ratio - a reduction in the ability of CTLs to kill mutant infected cells. CTLs die at rate \( \delta_C C \). Since the viral species are distinguished only by the fitness cost of the mutant, \( F \), and the escape ratio, \( B \), it is only necessary to consider two populations of virus.

The model can be written as the following system of differential equations:

\[
\begin{align*}
T'_l & = \lambda + qT_h - rT_l - \beta_l V_w T_l - (1 - F) \beta_l V_m T_l - \delta_T T_l \\
T'_h & = rT_l - qT_h - \beta_h V_w T_h - (1 - F) \beta_h V_m T_h - \delta_T T_h \\
V'_w & = pI_w - \delta_V V_w \\
V'_m & = pI_m - \delta_V V_m \\
I'_w & = (1 - \frac{\epsilon}{\mu + \eta M})(\beta_l V_w T_l + \beta_h V_w T_h) - b I_w C - \delta_I I_w \\
I'_m & = \frac{\epsilon}{\mu + \eta M}(\beta_l V_w T_l + \beta_h V_w T_h) + (1 - F)(\beta_l V_m T_l + \beta_h V_m T_h) \\
& \quad - \frac{b}{B} I_m C - \delta_I I_m \\
C' & = \omega + \frac{\alpha}{\gamma + \xi M} (I_w + I_m) C - \delta_C C
\end{align*}
\]

For simplicity, the notation \( \hat{\beta}_l = (1 - F) \beta_l, \hat{\beta}_h = (1 - F) \beta_h, \hat{\epsilon} = \frac{\epsilon}{\mu + \eta M} \), and
\[ \hat{\alpha} = \frac{\alpha}{\gamma + \xi M} \] will sometimes be used.

**Parameter Descriptions**

Vaidya et al. [21] provides that there are approximately $10^6$ target cells initially per ml of blood, with about $40980/\text{ml}$ belonging in the $T_l$ population and the remaining $10^6 - 40980/\text{ml}$ in the $T_h$ population. They also estimate an initial viral load of 200 viral RNA copies per ml, which is here assumed to all belong to the wild-type population. Since there is initially no infection, $I_w$ , $I_m$, and $C$ are all initially zero. Additionally, they provide estimates for $\lambda$ of $3690/\text{ml}$ per day, $r = 0.16$ cells per day, and $q = 0.24$ cells per day when morphine is not present and $r = 0.55$ cells per day and $q = 1.02 \times 10^{-6}$ cells per day when morphine is present. The wild-type infection rate of $T_l$, $\beta_l$, is estimated to be on the order of $10^{-9}\text{ml}$ per day and the wild-type infection rate of $T_h$, $\beta_h$ approximately two orders of magnitude higher. Finally, they estimate the death rate of infected cells $\delta_I$ as between 0.31 and 0.78 cells per day and the common production rate of the viruses as $p = 2500$ virions per day. The infection rates of $T_l$ and $T_h$ by the mutant virus is calculated as a percentage of the corresponding infection rate of the wild-type virus, giving $(1 - F)\beta_l$ and $(1 - F)\beta_h$ where the fitness cost $F$ is a number between zero and one [6].

Ramratnam et al. [29] estimate the average virion clearance rate as 23 cells per day, giving $\delta_V = 23$ [29] and Stafford et al. [30] provide the average target cell life span as 100 days, giving $\delta_T = 0.01$ [30]. This model assumes that only forward mutation takes place, i.e., that mutant infected cells will not mutate back into the wild-type infected population. The forward mutation rate $\epsilon$ has been observed experimentally to be $3 \times 10^{-5}$ in [31], the parameters $\mu$ and $\eta$ that account for the effect of morphine
on $\epsilon$ will be varied. De Boer and Perelson [33] estimated the CTL proliferation rate as $\alpha = 6.7^{-5}ml$ per day, and as before the parameters $\gamma$ and $\xi$ accounting for the effect of morphine will vary. Konrad et al. [19] take $\delta_C$ on the order of $10^{-1}$ cells per day and the rate of killing of wild- type infected cells on the order of $10^{-2}$, the escape ratio $B$ will be varied.

The constant rate of CTL production $\omega$ is assumed to be 50 cells per day and to decay exponentially when morphine is present, therefore the parameter $\psi$ is introduced as the decay rate giving $\hat{\omega} = \omega e^{-\psi M}$ when morphine is present. Olkkola et al. [23] measured the kinetics and dynamics of morphine in children and observed initial concentrations of morphine between $28 - 325\mu l$ per kilogram of body weight, therefore $300\mu l/kg$ is taken as a reasonable morphine concentration.

The parameter descriptions are summarized in Table 1:
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Description</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda$</td>
<td>3690 $ml^{-1}day^{-1}$</td>
<td>Production rate of $T_I$ cells</td>
<td>Vaiyda et al.</td>
</tr>
<tr>
<td>$r$</td>
<td>0.16 $day^{-1}$</td>
<td>Conversion of $T_I$ to $T_H$</td>
<td>Vaiyda et al.</td>
</tr>
<tr>
<td>$q$</td>
<td>0.24 $day^{-1}$</td>
<td>Conversion of $T_H$ to $T_I$</td>
<td>Vaiyda et al.</td>
</tr>
<tr>
<td>$\beta_I$</td>
<td>$10^{-9} cells^{-1}ml day^{-1}$</td>
<td>Wild-type infection rate of $T_I$ cells</td>
<td>Vaiyda et al.</td>
</tr>
<tr>
<td>$\beta_H$</td>
<td>$10^{-7} cells^{-1}ml day^{-1}$</td>
<td>Wild-type infection rate of $T_H$ cells</td>
<td>Vaiyda et al.</td>
</tr>
<tr>
<td>$F$</td>
<td>0 – 1</td>
<td>Fitness cost of mutation</td>
<td>Varied</td>
</tr>
<tr>
<td>$p$</td>
<td>2500 $day^{-1}$</td>
<td>Production rate of virus</td>
<td>Vaiyda et al.</td>
</tr>
<tr>
<td>$b$</td>
<td>0.005 $cells^{-1}ml day^{-1}$</td>
<td>CTL killing rate of wild-type</td>
<td>Konrad et al.</td>
</tr>
<tr>
<td>$B$</td>
<td>1 – 100</td>
<td>Escape ratio</td>
<td>Varied</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>$6.7 \times 10^{-6} cells^{-1}ml day^{-1}$</td>
<td>CTL proliferation rate</td>
<td>De Boer et al.</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>0.4 – 1</td>
<td>Morphine parameter affecting $\alpha$</td>
<td>Varied</td>
</tr>
<tr>
<td>$\xi$</td>
<td>0.4 – 1</td>
<td>Morphine parameter affecting $\alpha$</td>
<td>Varied</td>
</tr>
<tr>
<td>$\omega$</td>
<td>50</td>
<td>CTL production rate</td>
<td>Varied</td>
</tr>
<tr>
<td>$\psi$</td>
<td>0.85</td>
<td>CTL production decay rate</td>
<td>Varied</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>$3 \times 10^{-5}$</td>
<td>Mutation rate</td>
<td>Mansky et al.</td>
</tr>
<tr>
<td>$\mu$</td>
<td>0.1667 – 1</td>
<td>Morphine parameter affecting $\epsilon$</td>
<td>Varied</td>
</tr>
<tr>
<td>$\eta$</td>
<td>0.1667 – 1</td>
<td>Morphine parameter affecting $\epsilon$</td>
<td>Varied</td>
</tr>
<tr>
<td>$\delta_T$</td>
<td>0.01 $day^{-1}$</td>
<td>Target cell death rate</td>
<td>Stafford et al.</td>
</tr>
<tr>
<td>$\delta_V$</td>
<td>23 $day^{-1}$</td>
<td>Virus clearance rate</td>
<td>Ramratnam et al.</td>
</tr>
<tr>
<td>$\delta_I$</td>
<td>0.3 $day^{-1}$</td>
<td>Infected cell death rate</td>
<td>Vaiyda et al.</td>
</tr>
<tr>
<td>$\delta_C$</td>
<td>0.63 $day^{-1}$</td>
<td>CTL death rate</td>
<td>Konrad et al.</td>
</tr>
<tr>
<td>$\xi$</td>
<td>$0 - 400 ml/kg$</td>
<td>Concentration of morphine</td>
<td>Olkkola et al.</td>
</tr>
</tbody>
</table>
CHAPTER 4
MODEL ANALYSIS

This chapter will discuss the stability of two equilibria of the model: the infection free equilibrium and the mutant only equilibrium, determine their local stability, and demonstrate that there is no biologically relevant wild-type only equilibrium. The local stability of the infection free equilibrium will be determined by calculating the basic reproduction number of the virus, the local stability of the mutant only equilibrium will be determined by calculating the eigenvalues of the Jacobian matrix of the model evaluated at the mutant only equilibrium.

**Basic Reproduction Number**

The basic reproduction number is an important quantity in the study of viral dynamics and is defined as the average number of secondary infections resulting from a single initial infection [22]. Determining the long-term behavior of infections involves studying the equilibria of differential equations, and models of viral dynamics generally have at least two equilibria: an infection free equilibrium and an infected equilibrium. The stability of the infection free equilibrium (IFE) can be described by the basic reproduction number, denoted \( R_0 \), with the IFE being locally asymptotically stable if \( R_0 < 1 \) and unstable if \( R_0 > 1 \) [22]. That is, if an initial infection on average results in less than one secondary infections the infection will die out. Since this model contains two viral species the basic reproduction number is a combination of the two quantities \( R_0^w \) and \( R_0^m \), the reproduction numbers corresponding to the
wild-type and mutant viruses, respectively.

The IFE of is the constant solution of the system in which there is no virus present, so it is of the form \((T^*_l, T^*_h, 0, 0, 0, C^*)\) and is obtained by solving the algebraic system

\[
\begin{align*}
0 &= \lambda + qT^*_h - rT^*_l - \delta_T T^*_l \\
0 &= rT_l - qT^*_h - \delta_T T^*_h \\
0 &= \omega - \delta_C C^*
\end{align*}
\]

which yields

\[
\begin{align*}
T^*_l &= \frac{\lambda(q+\delta_T)}{\delta_T(q+r+\delta_T)} \\
T^*_h &= \frac{\lambda r}{\delta_T(q+r+\delta_T)} \\
C^* &= \frac{\omega}{\delta_C}.
\end{align*}
\]

The method of calculating the basic reproduction number used here is by constructing the next-generation matrix of the model and calculating its spectral radius. The next-generation matrix is obtained from the infected subsystem of the model; the equations of the system that contain viruses and infected cells [34]. For this model, the infected subsystem is given by

\[
\begin{align*}
V'_w &= pI_w - \delta_V V_w \\
V'_m &= pI_m - \delta_V V_m \\
I'_w &= (1 - \hat{\epsilon})(\beta_l V_w T_l + \beta_h V_w T_h) - bI_w C - \delta_I I_w \\
I'_m &= \hat{\epsilon}(\beta_l V_w T_l + \beta_h V_w T_h) + (\beta_l V_m T_l + \beta_h V_m T_h) - \frac{b}{B} I_m C - \delta_I I_m
\end{align*}
\]

The next step is to calculate the Jacobian matrix of the infected subsystem
and decompose it into $\mathcal{F} - \mathcal{V}$, where $\mathcal{F}$ is the infection part of the system which describes newly infected components and $\mathcal{V}$ is the transition part, which describes transitions of infected components between populations of the model. For this model, $\mathcal{F}$ and $\mathcal{V}$ are given by

$$
\mathcal{F} = \begin{bmatrix}
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
(1 - \hat{\epsilon})(\beta_l T^*_l + \beta_h T^*_h) & 0 & 0 & 0 \\
\hat{\epsilon}(\beta_l T^*_l + \beta_h T^*_h) & \hat{\beta}_l T^*_l + \hat{\beta}_h T^*_h & 0 & 0
\end{bmatrix}
$$

and

$$
\mathcal{V} = \begin{bmatrix}
\delta_V & 0 & -p & 0 \\
0 & \delta_V & 0 & -p \\
0 & 0 & \delta_I + bC^* & 0 \\
0 & 0 & 0 & \delta_I + \frac{b}{\beta}C^*
\end{bmatrix}
$$

The next generation matrix is then given by $\mathcal{F}\mathcal{V}^{-1}$ and its spectral radius is the basic reproduction number of the system. The spectrum of $\mathcal{F}\mathcal{V}^{-1}$ was obtained using the computer algebra system in Maple and is shown below:
σ(FV⁻¹) = \begin{pmatrix} 0 \\ 0 \\ -\frac{p(T_h^* \beta_0 + T_l^* \beta_1 - T_h^* \beta_0 - T_l^* \beta_1)}{(\delta_T + bC^*)} δ_V \\ -\frac{pB(FT_h^* \beta_0 + FT_l^* \beta_1 - T_h^* \beta_0 - T_l^* \beta_1)}{B\delta_T + bC^*} δ_V \end{pmatrix}

where the third entry corresponds to $R_0^w$ and the fourth to $R_0^m$. The basic reproduction number is then $R_0 = \max(R_0^w, R_0^m)$ and the IFE is locally asymptotically stable provided $R_0^w < 1$ and $R_0^m < 1$ and unstable otherwise. Sensitivity analysis can be done on the parameters in order to identify those that have the greatest effect on the basic reproduction number. [32]. For a parameter $x$, the forward sensitivity index is given by [36, 35]

$$S_x = \frac{x R_0 \partial R_0}{R_0 \partial x}.$$ 

Using the parameter values in Table 1, the sensitivity indicies for $R_0^w$ and $R_0^m$ are given in Table 2. Based on Table 2, increasing $\lambda$ and $p$ increases both $R_0^w$ and $R_0^m$ significantly while increasing $\delta_V$, $\delta_I$, and $\delta_T$ decreases both $R_0^w$ and $R_0^m$ significantly.

**Dominant Viral Species**

In order to observe the effect of morphine on $R_0$, and therefore on the viral load, $R_0^w$ and $R_0^m$ are calculated for various concentrations of morphine, noting that if $R_0^w > R_0^m$ the wild-type virus will be the dominate viral species while if $R_0^w < R_0^m$ the mutant will dominate. Using the Parameter values in Table 1 and letting $M$ vary
### Table 2. Sensitivity Indices

<table>
<thead>
<tr>
<th></th>
<th>$R_0^w$</th>
<th>$R_0^o$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$x$</td>
<td>$S_x$</td>
<td>$S_x$</td>
</tr>
<tr>
<td>$\lambda$</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>$q$</td>
<td>0.5705966223</td>
<td>0.5705966226</td>
</tr>
<tr>
<td>$r$</td>
<td>0.01538461539</td>
<td>0.5943714821</td>
</tr>
<tr>
<td>$\beta_l$</td>
<td>0.01538461539</td>
<td>0.01538461538</td>
</tr>
<tr>
<td>$\beta_h$</td>
<td>0.9846153847</td>
<td>0.009846153846</td>
</tr>
<tr>
<td>$p$</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>$b$</td>
<td>$-4.046294658 \times 10^{-7}$</td>
<td>$-4.046246133 \times 10^{-8}$</td>
</tr>
<tr>
<td>$B$</td>
<td>NA</td>
<td>$3.939487339 \times 10^{-8}$</td>
</tr>
<tr>
<td>$\delta_T$</td>
<td>$-1.023774858$</td>
<td>$-1.023774859$</td>
</tr>
<tr>
<td>$\delta_V$</td>
<td>$-1$</td>
<td>$-1$</td>
</tr>
<tr>
<td>$\delta_I$</td>
<td>$-0.9999995953$</td>
<td>$-0.9999999598$</td>
</tr>
<tr>
<td>$\delta_C$</td>
<td>$4.051855513 \times 10^{-7}$</td>
<td>$1.057200164 \times 10^{-8}$</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>$-9.94476127 \times 10^{-7}$</td>
<td>NA</td>
</tr>
<tr>
<td>$\mu$</td>
<td>$5.494167551 \times 10^{-9}$</td>
<td>NA</td>
</tr>
<tr>
<td>$F$</td>
<td>NA</td>
<td>$-0.25$</td>
</tr>
</tbody>
</table>
Figure 1. Computed values of $R_w$ and $R_m$ for increasing $M$. A population switch occurs at approximately $M = 31$.

from 0 to 300 gives the results shown Figure 1.

Setting $M = 0$ results in $R_0^m = 3.7439$ and $R_0^w = 2.2812$, indicating that the mutant virus is dominate when there is no morphine and that the IFE is unstable. A population switch occurs at approximately $M = 31$ and the mutant becomes dominant for any higher morphine concentrations. In the next chapter, simulations of the steady state viral load will show that the dominance of the mutant virus contributes to the higher viral load when mophine is present.

**Mutant Only Equilibrium**

The mutant only equilibrium (MOE) is the equilibrium in which there is no wild-type virus present and is of the form $(T^*_l, T^*_h, 0, V^*_m, 0, I^*_m, C^*)$. Note that because
of the mutation term in the equation for $I_m$ some mutant virus is being produced whenever the wild-type virus is present and for this reason there is no positive wild-type only equilibrium. The mutant only equilibrium is calculated by solving the system

\[
\begin{align*}
0 &= \lambda + q T_h^* - r T_l^* - \hat{\beta}_l V_m^* T_l^* - \delta_T T_l^* \\
0 &= r T_l^* - q T_h^* - \hat{\beta}_h V_m^* T_h^* - \delta_T T_h^* \\
0 &= p I_m^* - \delta_V V_m^* \\
0 &= \hat{\beta}_h V_m^* T_l^* + \beta_h V_m^* T_h^* - \frac{b}{B} I_m^* C^* - \delta_I I_m^* \\
0 &= \omega + \hat{\alpha} I_m^* C^* - \delta_C C^*
\end{align*}
\]

which yields

\[
\begin{align*}
T_h^* &= \frac{\lambda}{(q + \hat{\beta}_h + \delta_T)(1 + \frac{\hat{\beta}_h V_m^*}{r})} \\
T_l^* &= T_h^* \cdot \frac{q + \beta_h V_m^* + \delta_T}{r} \\
I_m^* &= \frac{\delta_V V_m^*}{p} \\
C^* &= \frac{\omega}{\delta_C - \hat{\alpha} I_m^*}
\end{align*}
\]

where $V_m^*$ is the solution of

\[
0 = \hat{\beta}_l V_m^* [T_h^* \frac{q + \beta_h V_m^* + \delta_T}{r}] + \hat{\beta}_h V_m^* T_h^* \\
- \frac{b}{B} \left( \frac{\delta_V V_m^*}{p} \right) \left( \frac{\omega}{\delta_C - \hat{\alpha} V_m^*} \right) - \frac{\delta_T \delta_V V_m^*}{p}.
\]

Substituting $T_h^*$ and solving numerically gives a value for $V_m^*$. Several values of $V_m^*$ are plotted in Figure 2 for different values of $M$. Notably, increased values of $M$ cause an increase in $V_m^*$ and a decrease in $C^*$. For all values in Table 2, $F = 0.2$
Figure 2. Solutions of $V_m^*$ equation. The zero-intercept of each curve is the MOE value of $V_m$ for the particular value of $M$.

Table 3. Mutant Only Equilibrium

<table>
<thead>
<tr>
<th></th>
<th>$M = 0$</th>
<th>$M = 30$</th>
<th>$M = 300$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_m$</td>
<td>$8.058 \times 10^5$</td>
<td>$9.277 \times 10^5$</td>
<td>$9.64 \times 10^5$</td>
</tr>
<tr>
<td>$T_h$</td>
<td>$3.8685 \times 10^4$</td>
<td>$3.4817 \times 10^4$</td>
<td>$3.3809 \times 10^4$</td>
</tr>
<tr>
<td>$T_l$</td>
<td>$7.6032 \times 10^4$</td>
<td>$7.0551 \times 10^4$</td>
<td>$6.9123 \times 10^4$</td>
</tr>
<tr>
<td>$I_m$</td>
<td>$7.413 \times 10^3$</td>
<td>$8.5348 \times 10^3$</td>
<td>$8.868 \times 10^3$</td>
</tr>
<tr>
<td>$C$</td>
<td>$86.1578$</td>
<td>$17.7607$</td>
<td>$2.4286 \times 10^{-5}$</td>
</tr>
</tbody>
</table>

and $B = 10$.

To determine the stability of the MOE, the Jacobian matrix is calculated and evaluated at the MOE. The Jacobian matrix is
\[
J = \begin{bmatrix}
  J_{11} & J_{12} & J_{13} & J_{14} & 0 & 0 & 0 \\
  J_{21} & J_{22} & J_{23} & J_{24} & 0 & 0 & 0 \\
  0 & 0 & J_{33} & 0 & J_{35} & 0 & 0 \\
  0 & 0 & 0 & J_{44} & 0 & J_{46} & 0 \\
  J_{51} & J_{52} & J_{53} & 0 & J_{55} & 0 & J_{57} \\
  J_{61} & J_{62} & J_{63} & J_{64} & 0 & J_{66} & J_{67} \\
  0 & 0 & 0 & 0 & J_{75} & J_{76} & J_{77}
\end{bmatrix}
\]

where

\[
\begin{align*}
J_{11} &= -r - \beta_l V_w - \hat{\beta}_l V_m - \delta_T \\
J_{12} &= q \\
J_{13} &= -\beta_l T_l \\
J_{14} &= -\hat{\beta}_l T_l \\
J_{21} &= r \\
J_{22} &= -q - \beta_h V_w - \hat{\beta}_h V_m - \delta_T \\
J_{23} &= -\beta_h T_h - \hat{\beta}_h T_h \\
J_{24} &= -\hat{\beta}_h T_h \\
J_{33} &= -\delta_V \\
J_{35} &= p \\
J_{44} &= -\delta_V \\
J_{46} &= p \\
J_{51} &= (1 - \hat{\epsilon})\beta_l V_w \\
J_{52} &= (1 - \hat{\epsilon})\beta_h V_w
\end{align*}
\]
\[ \begin{align*}
J_{53} &= (1 - \hat{\epsilon})(\beta_l T_l + \beta_h T_h) \\
J_{55} &= -bC - \delta_I \\
J_{57} &= -bI_w \\
J_{61} &= \hat{\epsilon} \beta_l V_w + \hat{\beta}_l V_m \\
J_{62} &= \hat{\epsilon} \beta_h V_w + \hat{\beta}_h V_m \\
J_{63} &= \hat{\epsilon}(\beta_l T_l + \beta_h T_h) \\
J_{64} &= \hat{\beta}_l T_l + \hat{\beta}_h T_h \\
J_{66} &= -\frac{b}{B} C - \delta_I \\
J_{67} &= -\frac{b}{B} I_m \\
J_{75} &= \hat{\alpha} C \\
J_{76} &= \hat{\alpha} C \\
J_{77} &= \hat{\alpha}(I_w + I_m) - C.
\end{align*} \]

The MOE is locally asymptotically stable if the real parts of each eigenvalue of \( J \) is negative and unstable otherwise [24, 27]. For \( M = 0 \),

\[
\sigma(J((T_l^*, T_h^*, 0, V_m^*, 0, I_m^*, C^*))) = \{-23.3439, -0.0349 \pm 0.0894i, -0.5773, -0.4175, -23.4343, -0.2967\}
\]

and for \( M = 30 \)

\[
\sigma(J((T_l^*, T_h^*, 0, V_m^*, 0, I_m^*, C^*))) = \{-23.3099, -0.0351 \pm 0.0894i, -0.6281, -0.4238, -23.3832, -0.0026\}
\]
so the MOE is locally asymptotically stable for these values of $M$, but $M = 300$ results in

$$\sigma(J((T_{I}^{*}, T_{h}^{*}, 0, V_{m}^{*}, 0, I_{m}^{*}, C^{*}))) = \{-23.3010, -0.0357 \pm 0.0895i, -0.4255, -0.6298, -23.3738, 0.0738\}$$

indicating the MOE becomes unstable by $M = 300$. Assuming that the values of the MOE are constant around $M = 30$ and taking the real part maximal eigenvalue of $J$ as a function of $M$ shows that a bifurcation takes place at $M \approx 31$ (Figure 3). It is also of interest to examine the effects of $F$ and $B$ on the stability of the MOE. Since the MOE is stable for $M = 30$, this is an acceptable value of $M$ to investigate the effects of $F$ and $B$. Figure 4 shows a bifurcation at approximately $F = 0.21$ when $M = 30$, identifying $F$ as a bifurcation parameter. However, Figure 5 shows that the real part of the maximal eigenvalue of $J$ is negative for any $B \in [1, 100]$ at $M = 30$, indicating that $B$ is not a bifurcation parameter for this amount of morphine.
Figure 3. Effect of $M$ on the stability of the MOE. The MOE becomes unstable at approximately $M = 31$.

Figure 4. Effect of $F$ on the stability of the MOE, $M = 30$. The MOE becomes unstable at approximately $F = 0.21$. 
Figure 5. Effect of $B$ on the stability of the MOE, $M = 30$. The MOE remains stable for this range of $B$.

**Wild-type Only Equilibrium**

A wild-type only equilibrium is a nonnegative solution of the form $(T_l^*, T_h^*, V_w^*, 0, I_w^*, 0, C^*)$ to the system of equations

\[
\begin{align*}
0 &= \lambda + qT_h - rT_l - \beta_l V_w T_l - \delta T_l \\
0 &= rT_l - qT_h - \beta_h V_w T_h - \delta T_h \\
0 &= pI_w - \delta V_w \\
0 &= (1 - \hat{\epsilon})(\beta_l V_w T_l + \beta_h V_w T_h) - bI_w C - \delta I_w \\
0 &= \hat{\epsilon}(\beta_l V_w T_l + \beta_h V_w T_h) \\
0 &= \omega + \hat{\alpha} I_w C - \delta C C.
\end{align*}
\]
Solving the second equation for $T^*_h$ gives:

$$T^*_h = \frac{r}{q + \beta_h V^*_w + \delta_T} T^*_l$$

and the fifth equation is equivalent to

$$0 = \beta_l V_w T_l + \beta_h V_w T_h.$$ 

If $V^*_w = 0$ this system is exactly the IFE, so cancelling $V^*_w$ and substituting $T^*_h$ gives:

$$0 = T^*_l (\beta_l + \beta_h (\frac{r}{q + \beta_h V^*_w + \delta_T}))$$

so either $T^*_l = 0$ or $\beta_l + \beta_h (\frac{r}{q + \beta_h V^*_w + \delta_T}) = 0$. Substituting $T^*_l = 0$ into the first equation results in the negative solution $T^*_h = -\frac{\lambda}{q}$. Letting $\beta_l + \beta_h (\frac{r}{q + \beta_h V^*_w + \delta_T}) = 0$ is equivalent to

$$V^*_w = -\frac{1}{\beta_h} (\frac{\beta_l r}{\beta_l + q + \delta_T})$$

which is also a negative solution, so there is no nonnegative wild-type only equilibrium.
This chapter will provide simulations of the system for various levels of morphine. The long-term viral load will be calculated for varying concentrations of morphine.

**Short and Long Term Viral Dynamics**

Using the initial values and parameters given in Chapter 3 along with $F = 0.2$, $B = 10$, $\psi = 0.05$ and $\mu = \eta = \gamma = \xi = 1$ the model is solved using the ode15s function in MATLAB over a period of 200 days and the total viral load $V_w + V_m$ is plotted on a log10 scale.

Whether or not morphine is present, the viral load rapidly increases to approximately $7.5 \log_{10}$ before decreasing to a steady state of approximately $5.9 \log_{10}$ for $M = 0$ and $6 \log_{10}$ for $M = 300$ with a difference in viral load of approximately $2.18840 \times 10^5$ between the two cases (Figure 6). Decreasing $B$ from 10 to 1 (Figure 7) increase the difference in the steady state viral load to $7.27520 \times 10^5$, which is closer to results obtained experimentally [2].

As discussed in Chapter 4, a population switch occurs at $M \approx 31$ for the base parameter values. Therefore, it is of interest to observe the populations of the individual species in the cases where the wild-type dominates and in the case where the mutant dominates. Figure 8 separately shows the populations of the wild-type
Figure 6. Total viral load with base parameter values. The model reflects the higher viral load caused by morphine.

Figure 7. Total viral load with decreased escape ratio. Decreasing the escape ratio gives a difference in viral load closer to experimental results.
Figure 8. Individual virus populations, $M = 0$. When no morphine is present the mutant is the dominant species.

and mutant when $M = 0$. In this case, the logarithm of the wild-type virus becomes negative indicating that the wild-type population is approaching zero and the total viral load is essentially only the mutant population.

Figure 9 shows the individual populations for $M = 300$, a high enough morphine concentration for the wild-type to dominate. In this case the wild-type makes up the bulk of the viral load, however, due to mutation a small amount of mutant virus continues to be produced. These simulations are in agreement with the population switch discussed in Chapter 4.

Figure 10 shows the effect on the viral load at 200 days as a function of the
Figure 9. Individual virus populations, $M = 300$. For this amount of morphine the wild-type is the dominant species.

Figure 10. Viral load at 200 days as a function of $M$. 
morphine concentration. There is a roughly 0.5 log10 difference in viral load between the $M = 0$ and $M = 300$ cases and the viral load is most sensitive to changes in $M$ when $0 < M < 50$. 
CHAPTER 6
DISCUSSION AND FUTURE WORK

Discussion

This thesis presents a mathematical model to describe the within-host viral dynamics of an HIV infection which considers escape mutants, the use of morphine, and different populations of target cells based on susceptibility to infection. The model is primarily based on earlier models from [21, 19] and simulates the increase in viral load that results from the use of morphine by introducing terms that lower the mutation rate of the virus and host’s cellular immune response. Values of parameters in the model where taken both from earlier studies that provided estimates and from experimental data.

The basic reproduction number of each viral species is calculated by way of the next-generation matrix method. The basic reproduction number was taken as a function of the concentration of morphine present and it was observed that a population switch occurs for a sufficiently high morphine concentration. At higher concentrations of morphine the wild-type virus dominates the mutant, but the reduced cellular immune response still results in a higher set point viral load. The infection free equilibrium is unstable regardless of whether or not morphine is present. The mutant only equilibrium is also stable for a sufficiently low morphine concentration and fitness cost of the virus, but becomes unstable as these parameters increase.

Short- and long-term viral dynamics are simulated by solving the model nu-
merically. If there is sufficient morphine for the wild-type virus to dominate a small amount of the mutant will persist due to mutation. If the mutant is the dominant species then it will effectively make up the entirety of the viral load. Varying the morphine concentration causes changes in the set point viral load for low concentrations, but the viral load stabilizes once the morphine concentration exceeds approximately $100 \text{ml/kg}$.

One limitation of the model is the assumption that the morphine concentration $M$ is constant with respect to time. This assumption is made for simplicity in calculations and for providing an easy way to determine the morphine concentration necessary for the population switch to occur. Future work will focus on developing a method to incorporate a time-dependent morphine concentration and determining how this would affect the dynamics. It will also be of interest to investigate the sensitivity of the parameters introduced to model morphine effects, namely $\mu, \eta, \gamma$ and $\xi$, establish for them, and determining their effect on the stability of the equilibria of the model. Additionally, since it is possible for both the infection free and mutant only equilibria to be unstable it will be important to investigate any scenarios in which the wild-type and mutant coexist.
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VITA

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