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Two Mathematical Models Describing Human Immunodeficiency Virus and Epstein-Barr Virus

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Abstract

In this MQP, a mathematical model is created for two viruses' effects on the human immune system. These viruses are Human Immunodeficiency Virus (HIV) and Epstein-Barr Virus (EBV). First, two systems of ordinary differential equations were analyzed using information from papers written by Nowak and May (HIV), and Huynh and Adler (EBV), respectively. Then, MATLAB was used to solve each of the systems and find steady states and eigenvalues of the Jacobian evaluated at the steady states for the EBV model. The EBV model, a system of ten equations, was scaled and a series of steps were taken to reduce the model to a system of three equations. This system was solved numerically using MATLAB and shown to be consistent with the original model by Huynh and Adler.

Executive Summary

The first part of this project concerns Human-Immunodeficiency Virus (HIV) and its antigenic variation. A model developed by Nowak and May is examined, which is a system of 2n+1 ordinary differential equations. The variable n represents the number of mutations of the viral organism. The system was solved using MATLAB, and the solutions were plotted. Three different cases were examined, for when the parameter values satisfy certain inequalities. The three cases represent an acute illness, a chronic illness, and a typical illness, where the virus goes through an initial infection, lies dormant for several years, then reemerges.

The second part examines Epstein-Barr Virus (EBV). A model developed by Huynh and Adler is examined, which is a system of ten ordinary differential equations. In a similar fashion to the HIV model, the EBV model is solved using MATLAB. Information about Epstein-Barr virus infection is inferred from the mathematical model. The model is then scaled and explicit solutions are obtained for some of the equations in the system, using a steady state assumption for two of the equations. This reduces the system of ten equations to a system of three, which must be solved numerically.

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Chapter 1

Introduction

The viral organism is one which has had a profound effect on the human population of the world as a whole. Diverse antigenic variation is one of a virus' most offensive tactics, and consequently one of the reasons such viruses are so elusive to the human immune system. Viruses can cause some devastating and deadly diseases and infections. One in particular, HIV, has been sweeping across the world over the past 30-40 years. Another, Epstein-Barr virus, has had a profound, but somewhat more unknown effect on the world's population.

HIV first gained attention when a group of gay men in California died of a fungal infection, followed by a group that were diagnosed with Kaposi's sarcoma, which was usually only seen in elderly men (Ranga, 2009). Many other unusual cases like this in the gay community in California led to an investigation, where HIV was discovered as being the etiological source of a syndrome that is now called AIDS (Dorota, 2008).

Today, AIDS is classified as a pandemic, a syndrome that affects people across the world. However, of the 34 million people reportedly carrying the disease, 24 million live in Sub-Saharan Africa. It is estimated that 40 percent of 15 year olds living in this region will die of AIDS. However, an increasing number of countries in Africa (Zambia, Tanzania, Kenya, etc.) are now reporting stabilization of the virus (Schwartlander et al., 2000). As of 2008, there were an estimated 1.1 million people living with AIDS in the United States, 20 percent of which undiagnosed, and an estimated 617,025 people died that year from the infection (CDC, 2011). The US Center for Disease Control estimates that there are 50,000 people newly infected with the virus each year. Overall, though, there is no region of the world unaffected by HIV.

There are approximately 38.6 million humans living with HIV worldwide, with 25 million that have already died. Although the virus originally seemed to only infect young homosexual men, it became clear that was not the case. More recently, heterosexual transmission has become more common and accounts for about 85 percent of all HIV infections. Outside of Sub-Saharan Africa, about a third of all transmissions of the virus are due to use of dirty needles for injection drugs, especially in Eastern Europe and Southeast Asia (Simon et al., 2006). Needle exchange programs (NEP's) are being implemented to help prevent this method of transmission. In

the United States, NEP's have decreased HIV infection from needle exchanges by 33 percent (Vlahov, 1998).

Currently neither HIV nor AIDS can be cured, and there is no vaccine for HIV (CDC, 2011). A lot of research being conducted that will work toward finding a vaccine or cure. Medications are available that will slow down the progression or reduce the transmission of the virus, allowing those infected to live a better quality of life for a longer period of time (CDC, 2011).

There have been many mathematical models which have contributed to the scientific community's understanding of HIV. For review of HIV models, see the paper 'Mathematical and Statistical Studies of the Epidemiology of HIV' by R. M. Anderson. Major areas that have emerged from mathematical research from HIV over the years include: transmission demographics of the virus in particular at-risk groups (for example, San Francisco gay population); short-term prediction of temporal trends that cause AIDS; the different ways disease and infection progress with infected patients; and how HIV has affected developing countries demographically (Anderson, 1989).

Mathematical models have also revealed many things previously unknown about HIV and AIDS. One revolutionary finding is that although AIDS is a disease that occurs for a time period of about 10 years, it is made up of several 'sub-processes', some of which can take hours or days, and others which can take weeks or months (Perelson & Nelson, 1999). In addition, the minimum duration of the HIV-1 life cycle on average is 1.2 days, while the average time for HIV-1 to mutate and generate a new form of the virus is 2.6 days (Perelson et al., 1996).

Epstein-Barr virus was first discovered by Michael Anthony Epstein and Yvonne Barr in 1964 with tissue taken from a lymphoma. The virus causes a very wide spectrum of diseases, depending on the age range of the person infected. The rate of infection is higher in developing countries than developed countries. Over 90 percent of the human population worldwide is infected, with most developing the disease during early childhood. This is usually an asymptomatic case, but may be the cause of common childhood problems. During adolescence, the virus causes infectious mononucleosis (mono) 35-50 percent of the time. Infectious mononucleosis is considered the virus's prototype disease (NCID, 2006).

Epstein-Barr Virus also has been connected with other human malignancies, such as Hodgkin Disease, Burkitt Lymphoma, and Nasopharyngeal Carcinoma. In addition, it appears to affect a variety of other tumors, such as Carcinoma of the salivary glands (Callan, 2004). Pharmacological and immunotherapeutic approaches are being developed to treat EBV-associated tumors. In one study, 23 out of 31 adults with chronic illness and fatigue had persisting EB virus infection (Straus et al., 1985). Considering what mathematical modeling has done for progress on understanding HIV, further studies and mathematical modeling on Epstein-Barr Virus may also lead to further insight on the virus and the conditions it causes.

This first part of this MQP attempts to model the natural interplay between viral antigenic variation and the human immune response in an effort to better determine when, during the infection, HIV-I will progress to AIDS. The second half will present a method for simplification of a model for Epstein-Barr virus and its interactions with the human immune system.

Chapter 2

Antigenic Variation of HIV Model

The model implemented in MATLAB in this portion of the project shows the effects of HIV on the cellular level. It was created from a previously established mathematical model with some adjustments made in an effort to more realistically model HIV's interactions with the immune system. First we will go over the necessary biological background on HIV in order to better understand the model.

2.1 Background

HIV (Human Immunodeficiency Virus) is a virus that causes worldwide devastation. The reasons that HIV causes so much damage stem from its biological functions and how it interacts with the human immune system. Its host cells are CD4+ T-cells, which are part of the immune system component that signals to the rest of the immune system that infection is present. Unfortunately, this means that a full HIV infection means the downfall of the immune system, making the infected person susceptible to other, usually harmless, infections. This state of an ineffective immune system is called AIDS: Acquired Immune Deficiency Syndrome. Often the first sign of an HIV infection is this last stage, when the individual contracts an illness that does not usually present itself in healthy individuals.

When HIV is first contracted, the individual may have a short period of fever where the body is fighting off the infection, followed by a long asymptomatic stage, which often lasts several years. HIV presents itself as AIDS in the final stages of infection. There can therefore be three different types of infection. The first of these goes through all stages of infection, from the short initial fever stage, through the asymptomatic stage, and ending in the final immune system deficiency stage, this is referred to as a typical infection. The second situation is one where, after the short initial infection, the body keep is able to the virus from reemerging, thereby staying in a chronic, asymptomatic stage. Subsequently, this is called a chronic infection. The final situation in one in which the body does not survive the first initial infection stage, and

this is referred to as an acute infection. (Nowak et al., 1990).

The first case (an initial infection, followed by the asymptomatic phase, ending in AIDS) is the one that usually presents itself. One theory on how this operates is the theory of antigenic variation. The immune system takes time to create new antibodies through a trial and error process to fit specific protein structures on the antigen that it targets, so as each new strain is produced a new antibody is produced. Often, an antibody targets a protein that is not changed through all or some of the mutations, that this antibody can target multiple strains of the virus. However, if the virus is creating enough mutations quick enough, it can outrun the immune system's ability to counteract the new strains. This, combined with the death of CD4+ T-cells can explain why HIV is so virulent (Nowak et al., 1990). But what makes HIV go through enough mutations to act in this way, when other viruses do not?

HIV is a classified as a retrovirus, which are enveloped RNA viruses. These viruses use an enzyme called reverse transcriptase to turn their RNA into DNA, which is then integrated into the host's DNA to go through transcription and translation along with the host DNA. Because of this extra step of reverse transcription, there is a higher incidence of mutation in the viral lifecycle than with the usual central dogma of DNA $\rightarrow$ RNA $\rightarrow$Proteins. As HIV replicates, the chance that a mutation will produce a new strain increases, as much as one base pair per genome every time reverse transcription is executed. This creates more chance for mutations than a virus that follows the central dogma, and thus allows HIV to outrun the immune system (Nowak et al., 1990).

2.2 Nowak's Mathematical Model

The mathematical model used originates from a paper by M. A. Nowak, R. M. May, and R. M. Anderson written in 1990 entitled 'The Evolutionary Dynamics of HIV-1 Quasispecies and the Development of Immunodeficiency Disease' (Nowak & May, 2000). The model outlined in this source and in chapter 12 of Nowak's book, Virus Dynamics: Mathematical Principles of Immunology and Virology is described below.

There are five main assumptions that are used in the model:

1. The virus kills CD4+ T-helper cells
2. The virus mutates to evade the immune system and the immune system in turn creates new antibodies against the virus
3. The CD4+ T-helper cells direct the attack against the virus
4. Each mutant strain can kill any CD4+ T-helper cell
5. Immune responses can be characterized by responses to specific strains and response to all strains

HIV and two elements of the immune system are represented in this model: specific antibodies and non-specific antibodies. The populations of HIV are split into different strains that are represented in the body, with new strains being created through mutation. Each strain has a specific antibody that works against it. The non-specific antibodies target all strains of HIV. We therefore have a system of $2n + 1$ equations, where n is the number of strains of HIV. Although HIV does not specifically target antibodies, it does target the cells that tell the immune system that the antibodies are needed, and so a large HIV population will affect the numbers of antibodies. Each strain of HIV and each antibody is assumed to have the same growth and decay rates. The resulting system is as follows:

$$\begin{aligned} \dot{v}_i &= v_i(r - px_i - qz) \\ \dot{x}_i &= cv_i - bx_i - uvx_i \\ \dot{z} &= kv - bz - uvz \qquad i = 1...n \end{aligned} \tag{2.1}$$

v_i represents the population of each viral strain, x_i is the population of each specific antibody strain, z is the population of the non-specific antibodies, and v and x are the total populations of virus and specific antibodies, respectively. The number of viral strains is n. The parameter r represents the average replication rate of the virus, and the parameters p and q represent the neutralizing of the virus by specific and non-specific antibodies, respectively. The parameters c and k represent the rates at which the specific and non-specific antibodies are created in response to the presence of virus, and b is the decay rate of the immune responses at an absence of virus. The final parameter, u, denotes how well the virus can lessen immune responses by destroying CD4+ T-helper cells.

The antigenic variation model shows the mutations the virus undergoes. At certain intervals, the number of viral strains increases, thereby increasing the number of types of specific antibodies. The probability of a new viable strain can be determined by $P * dt$, where P is the rate of mutation and dt is the time elapsed since the previous mutation.

From this system, we can formulate an equation that describes the rate at which the entire virus population changes.

$$\dot{v} = \frac{v}{b + uv}(rb + ruv - pcD - qkv) \tag{2.2}$$

$$\text{where} \qquad D = \sum_{i=1}^{n} \frac{v_i^2}{v^2} \tag{2.3}$$

It is important to note here that D represents the Simpson index and $\frac{1}{n} \leq D \leq 1$. In the case of this model, D represents the inverse population of the virus. By the Cauchy-Schwarz inequality, it may be stated that

$$v^2 = \left(\sum_{i=1}^{n} v_i\right)^2 \leq \sum_{i=1}^{n} v_i^2 \sum_{i=1}^{n} 1^2 \leq n \sum_{i=1}^{n} v_i^2 \,, \tag{2.4}$$

Therefore,

$$\frac{1}{n} \leq \frac{\sum_{i=1}^{n} v_i^2}{v^2} = D \,.$$

To see that D is less than 1, we note that since $v_i \geq 0$, we have

$$\sum_{i=1}^{n} v_i^2 \leq \left(\sum_{i=1}^{n} v_i \right)^2$$

so that $D \leq 1$. We assume that the second and third equations in (2.1) operate in a faster time-scale and have reached equilibrium sooner than the virus. Using those two equations to solve for x_i and z in terms of v_i and the substituting the results into the first equation, we have

$$\begin{aligned} \dot{v}_i &= v_i \left(r - p\left(\frac{cv_i}{b+uv}\right) - q\left(\frac{kv}{b+uv}\right)\right) \\ &= \frac{v_i}{b+uv}\left(rb + ruv - pcv_i - qkv\right) \\ &= \frac{v^2}{b+uv}\left(\frac{rbv_i}{v^2} + \frac{ruv_i}{v} - \frac{pcv_i^2}{v^2} - \frac{qkv_i}{v}\right) \end{aligned}$$

Taking the sum from $i = 1...n$:

$$\dot{v} = \frac{v^2}{b+uv}\left(\frac{rb}{v} + ru - pc\sum_{i}^{n}\frac{v_i^2}{v^2} - qk\right) \tag{2.5}$$

$$\tag{2.6}$$

$$= \frac{v}{b+uv}(rb + ruv - pcvD - qkv) \tag{2.7}$$

Setting the derivative to zero in the last equation and solving, the optimal value v^* is obtained.

$$v^* = \frac{rb}{kq + cpD - ru} \tag{2.8}$$

Thus, increasing the genetic diversity (decreasing D), will result in higher virus level v^*.

This model lends itself to three cases, depending on the parameters provided. In the first case, the virus levels immediately rise to a high state and stay there:

$$ru > kq + cp \tag{2.9}$$

This represents death after an acute infection in the organism (Figure 3.1). In the second case, the virus population increases then falls to low levels:

$$kq > ru \tag{2.10}$$

This case describes a chronic infection in which the virus is not having an effect on the organism (Figure 3.2). This last case illustrates the viral population increasing, decreasing, and finally increasing once more:

$$kq + cp > ru > kq \tag{2.11}$$

This case represents a typical, chronic infection of HIV. It goes unnoticed for some time and later increases, resulting in disease and eventual death (Figure 3.3).

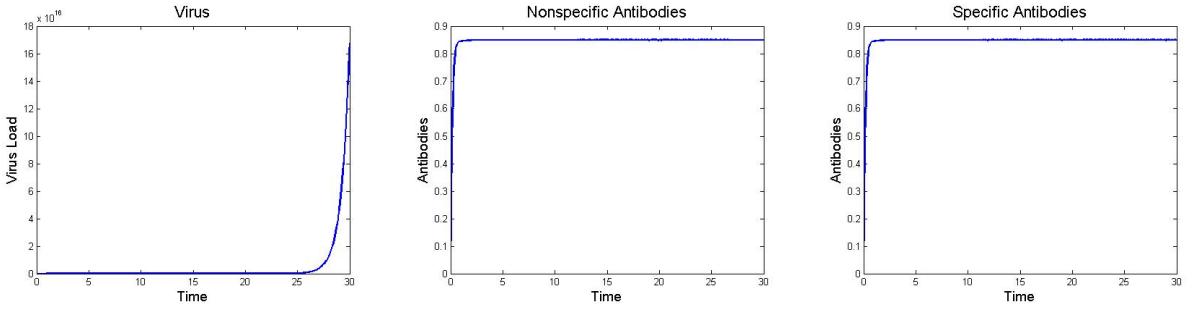


Figure 2.1: Death after acute infection with HIV, Condition (2.9)

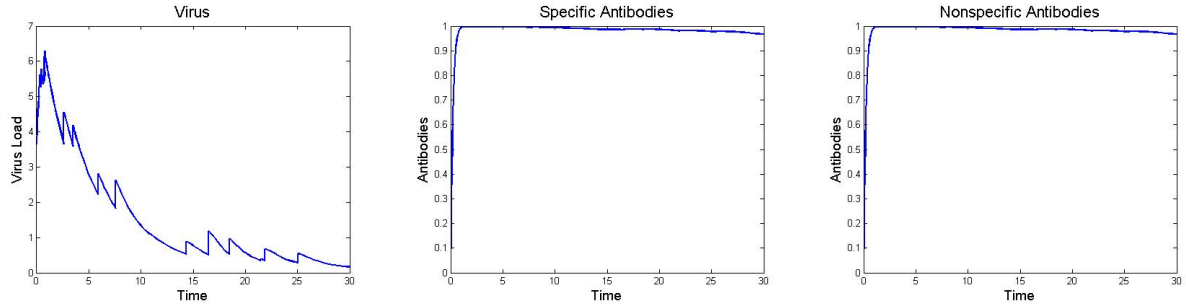


Figure 2.2: Asymptomatic chronic infection, Condition (2.10)

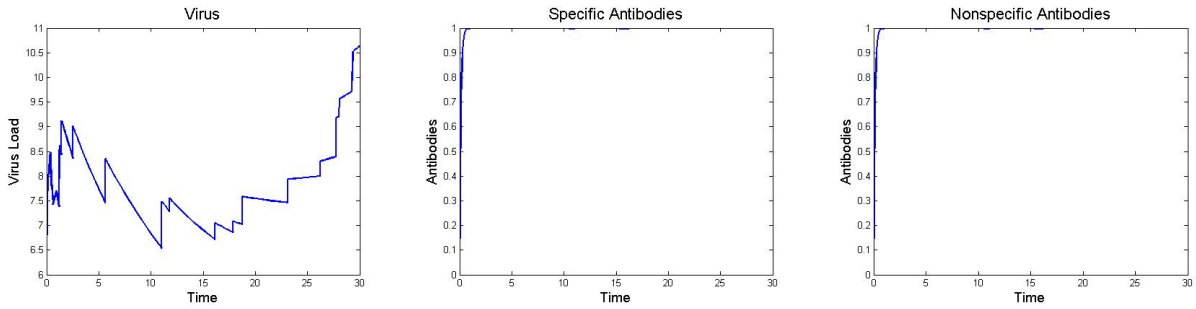


Figure 2.3: Typical progression of HIV, Condition (2.11)

Chapter 3

EBV Model

Biological systems are very complex and not well understood. This makes models of biological systems very complex. Although the complexity of the model may make results more realistic, it also does make these models very difficult to analyze. There must therefore be a balance between making biological systems realistic and making them possible to analyze mathematically so results and insight can be obtained.

Epstein-Barr virus is a virus that affects several systems in the body, therefore yielding complex models. The one focused on in this chapter on is a system of 10 differential equations, proposed by Giao Huynh and Frederick Adler in the paper 'Alternating Host Cell Tropism Shapes the Persistence, Evolution, and Coexistence of Epstein-Barr Virus Infections in Human' (Huynh & Adler, 2011).

In this chapter, we will be making modifications to this model with the goal of simplifying the model to one which can be used for mathematical analysis while still yielding biologically realistic numerical results. This chapter is organized as follows: section 3.1 explains the biological background necessary to understand this model, section 3.2 describes the model presented by Huynh and Adler (2011), and section 3.3 describes the steps used to simplify and solve Huynh and Adler's model .

3.1 Background

Epstein-Barr virus is a double-stranded DNA virus, in the Gamma Herpes family (Callan, 2004). Its genome comprises approximately 172,000 base pairs. There are two distinct types of the virus, appropriately termed EBV-1 and EBV-2, which share between 70-85 percent sequence homology. It is usually transmitted through oral contact with saliva, although in rare cases it can be transmitted through blood transfusion.

The virus works usually by infecting B lymphocytes through the binding of the major viral

envelope glycoprotein gp350 to the CD21 receptor on the surface of B-cell antibodies. Although it can infect other cell types (commonly epithelial cells), this is much less efficient, and occurs through separate, poorly defined pathways. The virus can permanently change B cells into permanent, latently infect lymphoblastoid cell lines (lcl's), which creates an in vitro system that has proved invaluable in studying the virus, although it is incomplete. To contrast, the virus infecting epithelial cells in vitro does not activate its full growth transformation (Kutok, 2006).

In the case of infectious mononucleosis, the virus's prototype disease, it works first by infecting epithelial cells in the pharynx (which will cause pharyngitis) and will later infect the B cells. The immune system will respond with its cytotoxic (CD8+) T cells against infected B-lymphocytes resulting in enlarged lymphocytes. Another virus, the Murine Gamma Herpes virus 68, can cause a condition comparable to infectious mononucleosis (Kutok, 2006).

Lab animals have also been used as models to study Epstein-Barr Virus. In a study of transgenic mice, three lineages were infected with the latent membrane protein 1 (LMP1) of EB virus. B-cell Lymphoma was detected in all three lineages, with the incidence increasing significantly with the age of the mouse (Kulwichit et al., 1998).

In latently infected cells, the virus is known to possess at least 14 distinct microRNA's (miRNA's). These are used by EB virus, among other viruses, to prevent infected cells and other cells from mounting appropriate antiviral responses. Seven of these 14 miRNA's have been conserved across over 13 million years of divergent evolution (Cai et al., 2006).

3.2 Huynh and Adler's Model

The model described by Huynh and Adler (2011) is displayed in System (3.1). The model describes interactions between four main classes of cells: B cells, epithelial cells, T cells, and free virus. One of the goals of this model is to show an observed behavior of Epstein-Barr virus. This behavior involves a conformational change in the free virus as it is released from different types of cells, thus affecting the infectivity of the free virus. When a B-cell lyses and releases free virus, those viruses can more easily infect epithelial cells, and vice versa. Thus, two of the equations below represent these two different behaviors of virus, V_B and V_E. There are four equations representing different types of B cells, the first being naive B cells (B_1), and the following three being different stages of infected B cells (B_2, B_3, and B_4). There is an equation for naive epithelial cells (E_1), and one for infected epithelial cells (E_2). The final two equations are for two types of T cells (T_2 and T_4), each of which target different types of infected cells. A table describing the parameters used in the model and their approximate values are given in Table (A.1) in Appendix A. Following System (3.1), we explain how each equation in the system is derived.

$$
\begin{aligned}
\dot{B}_1 &= d_1(B_0 - B_1) - \mu_{Eb} V_E B_1 - \mu_{Bb} V_B B_1 \\
\dot{B}_2 &= \rho(\mu_{Eb} V_E B_1 + \mu_{Bb} V_B B_1) - (d_2 + c) B_2 - k_2 B_2 T_2 \\
\dot{B}_3 &= c B_2 + r B_3 - r s B_3 \\
\dot{B}_4 &= r B_3 - d_4 B_4 - k_4 B_4 T_4 \\
\dot{E}_1 &= d_e(E_0 - E_1) - \mu_{Be} V_B E_1 - \mu_{Ee} V_E E_1 \\
\dot{E}_4 &= \mu_{Be} V_B E_1 + \mu_{Ee} V_E E_1 - (d_e + \gamma) E_4 - k_4 E_4 T_4 \\
\dot{V}_B &= n d_4 B_4 - d_v V_B \\
\dot{V}_E &= n \gamma E_4 - d_v V_E \\
\dot{T}_2 &= \phi_2 T_1 \omega(B_2) + \theta_2 T_2 \omega(B_2) - \delta T_2 \\
\dot{T}_4 &= \phi_4 T_1 [\omega(B_4 + E_4)] + \theta_4 T_4 [\omega(B_4 + E_4)] - \delta T_4
\end{aligned}
\tag{3.1}
$$

- In System (3.1), B_1 are the naive B cells and E_1 are the naive epithelial cells.
  - These cells begin with an initial population, B_0 and E_0, with turnover rates of d_1 and d_e, respectively.
  - Each of the naive cells, B_1 and E_1, are infected by virus at rates of μ_{Eb}, μ_{Bb}, μ_{Ee}, and μ_{Be} and become infected B cells and epithelial cells, B_2 and E_2, respectively. We employ the following notation. The first subletter in the infection rate stands for the type of virus that is infecting, the second stands for the type of cell that is being infected.
- In System (3.1), B_2 are the latently infected B cells, B_3 are the latently infected memory B cells, and B_4 are the lytically infected B cells.
  - The newly infected B cells become latently infected, and are represented by B_2, which have a proliferation rate of ρ, a natural death rate of d_2, become latently infected memory B cells, B_3, at a rate of c, and are killed by latently infected cell targeting T cells, T_2, at a rate of k_2.
  - The levels of latently infected memory B cells, B_3, are regulated at a rate of rs and have a division rate of r, where, on average, one enters the lytic stage, B_4, and one stays latent.
  - Lytically infected B cells, B_4, come about at a rate of r, lyse and release virus at a rate of d_4, and are killed off by lytically infected cell targeting T cells, T_4, at a rate of k_4.
- The infected epithelial cells, E_4, die at a natural death rate of d_e, due to lysis at a rate of γ, and by lytically infected cell targeting T cells, T_4, at a rate of k_4.
- For the Virus equations, V_B are the virus that come from B cells bursting and V_E are the virus that come from epithelial cells bursting.

  - The virus that are released by B_4 are represented by V_B and are released at a rate of nd_4, where n is the viral burst size, and die at a natural death rate of d_v.
  - The virus that are released by the lytically infected epithelial cells, E_4, are represented by V_E and are released at a rate of $n\gamma$, where, again, n is the viral burst size, and also die at a natural death rate of d_v.

- For the T cell equations, T_2 are the T cells that target latently infected cells, B_2, and T_4 are the T cells that target lytically infected cells, B_4 and E_4.
  - The T cells have a native population, T_1, which is regulated and become targeting cells as needed (in this case either targeting latently infected cells, T_2, or lytically infected cells, T_4). They do this at a rate of ϕ_2 and ϕ_4, respectively.
  - The function ω is a saturating function which is defined below in Equation (3.2), where K is the number of targeted cells when activation is at half maximum. Since T_2 targets the latently infected cells, B_2, this equation uses $\omega(B_2)$, and similarly, T_4 targets lytically infected cells, B_4 and E_4, and includes $\omega(B_4 + E_4)$.
  - Each T cell has a proliferation rate of θ_2, θ_4, respectively, and each have the same natural death rate δ.

$$\omega(B_j) = \frac{B_j}{K + B_j} \tag{3.2}$$

In order to compare this original model to our adjusted simplified models, steady state values, eigenvalues of the Jacobian evaluated at the steady-states, and graphs for solution this system were obtained using MATLAB. The graphs were obtained using the built-in MATLAB function, 'ode23s', which is used to solve stiff systems of ordinary differential equations. The time units are shown in minutes, starting at 0 minutes and ending at 5×10^5 minutes, or 0 to around 350 days. To solve for the steady states of the system, we used all zeros for initial conditions, except for the virus, which had 500 free virus for V_B and 11000 free virus for V_E as initial conditions. To find the steady-states, 'fsolve', another built-in MATLAB function used to solve systems of linear and nonlinear equations and systems of equations, was used on System (3.1). For initial guesses, the end values from 'ode23s' were used. The function fsolve also provided the Jacobian of System (3.1), and the eigenvalues of the Jacobian were found using the MATLAB function 'eig'. These eigenvalues gave information on the stability of the steady-states. The results are given in Table 3.1 and Figure 3.1.

To summarize the results of Huynh and Adler's model, first note that the real parts of each eigenvalue of the Jacobian are negative, meaning this set of steady-states is stable. The graphs of both naive cells, B cells (B_1) and epithelial cells (E_1) in Figure 3.1a, first oscillate a bit and then level off to a steady state. The latent (B_2), memory (B_3), and lytic B cells (B_4) in Figure 3.1b all achieve a sharp peak and then reach a steady state. The infected epithelial cells (E_4) in Figure 3.1c behave similarly, as does the free virus in Figure 3.1d. The T cells (T_2 and T_4) in

Cell Type	Steady-States	Eigenvalues
Naive B Cells	2.1939×10^5	-5.7912×10^{-3}
Latently Infected B Cells	8.7086×10^3	$-5.0687 \times 10^{-3} + 1.6685 \times 10^{-4}i$
Latently Infected Memory B Cells	1.0492×10^5	$-5.0687 \times 10^{-3} - 1.6684 \times 10^{-4}i$
Lytically Infected B Cells	1.7363×10^3	$-5.1556 \times 10^{-4} + 2.3384 \times 10^{-4}i$
Naive Epithelial Cells	1.7117×10^5	$-5.1556 \times 10^{-4} - 2.3384 \times 10^{-4}i$
Infected Epithelial Cells	9.3903×10^2	$-1.8597 \times 10^{-4} + 2.5185 \times 10^{-5}i$
Free Virus from B Cells	8.6817×10^5	$-1.8597 \times 10^{-4} - 2.5185 \times 10^{-5}i$
Free Virus from Epithelial Cells	3.3805×10^5	$-2.6590 \times 10^{-5} + 2.4421 \times 10^{-5}i$
T Cells for Latently Infected Cells	1.2312×10^5	$-2.6590 \times 10^{-5} - 2.4421 \times 10^{-5}i$
T Cells for Lytically Infected Cells	6.2947×10^4	-6.9733×10^{-6}

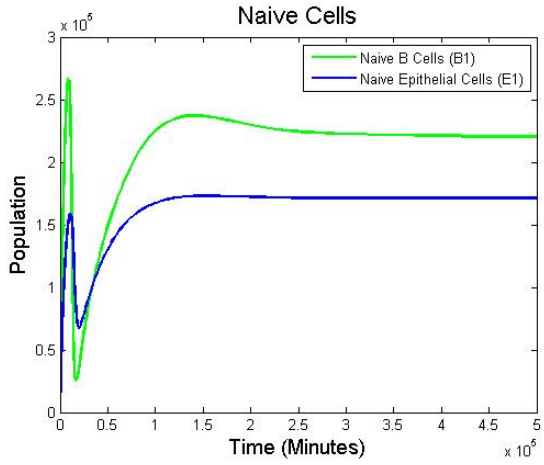
Table 3.1: Steady-states for System (3.1) and the eigenvalues of the Jacobian Matrix evalued at the steady-states

Figure 3.1e, conversely, are graphs which slowly increase and reach a steady state at a slower rate. The steady states in Table 3.1 achieved in the method described above are all biologically meaningful. If the initial guesses used in the "fsolve" function are all set equal to zero, the model achieves negative steady-states, which have no real biological meaning, therefore all zeroes must not be a steady state for the model. In addition, various other initial guesses were attempted, but many of them also produced negative steady-states, as well as positive eigenvalues for the Jacobian, which would suggest an unstable set of steady-states. Therefore, the steady-states found have a small domain of attraction.

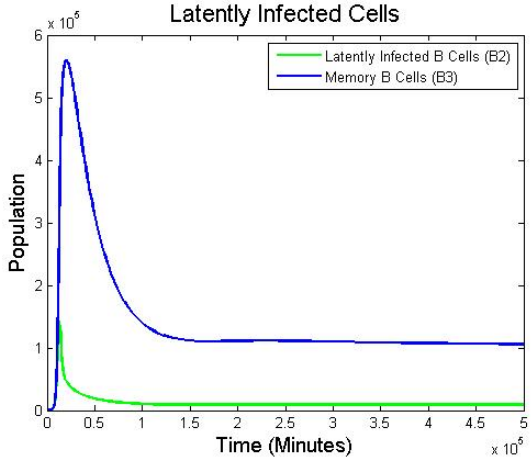
Biologically, this model behaves much like the biological system it is modeled after. When the virus (V_B and V_E) in Figure 3.1d initially infects the body, it has a short period of drastic increase. It is infecting cells without being stopped by the immune system, yielding many infected cells (B_2, B_3, B_4, and E_4), as seen in Figures 3.1b and 3.1c. Therefore, there is a period where there are much fewer naive cells (B_1 and E_1) than initially, which can be viewed in Figure 3.1a. The body then begins to fight back with the immune system through the T cells (T_2 and T_4) in Figure 3.1e. The T cells (T_2 and T_4) take some time to specialize to the cells infected with the virus, and slowly increase in the presence of infected cells. The T cells (T_2 and T_4) begin to target the latently infected cells (B_2) and lytically infected cells (B_4 and E_4) and kill them off. The infected cells (B_2, B_3, B_4, and E_4) and virus (V_B and V_E) then go through a period of decrease, until each population reaches an equilibrium. This is the way the model operates, and this is also the way the virus operates in the body.

Epstein-Barr virus sets itself apart from other viruses in that it causes a chronic asymptomatic infection following the illness caused by its initial infection. This model successfully captures that. There are no biologically meaningful steady-states that satisfy System (3.1) other than that in Table 3.1. In this set of steady-states, there is an equilibrium of all types of naive cells, virus, infected cells, and T cells, implying a chronic infection. There is no set of steady-states

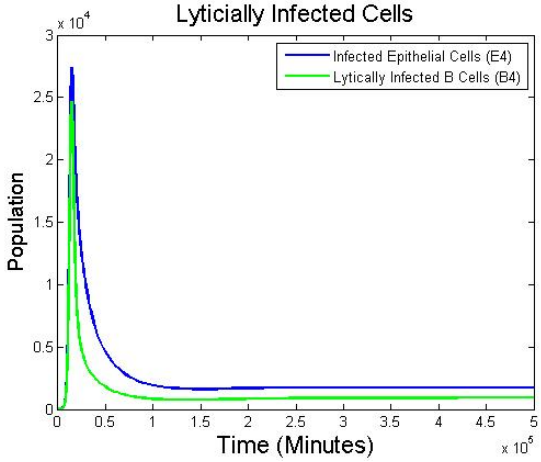
that captures the elimination of virus or that of the body succumbing to the virus. In this way, the model by Huynh and Adler successfully captures the mechanisms of the biological system.



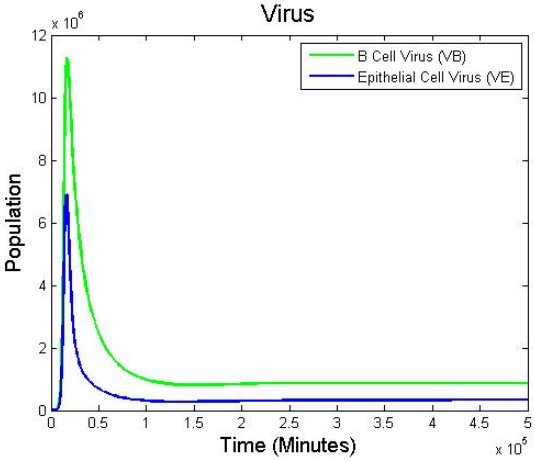
(a) Naive Cells



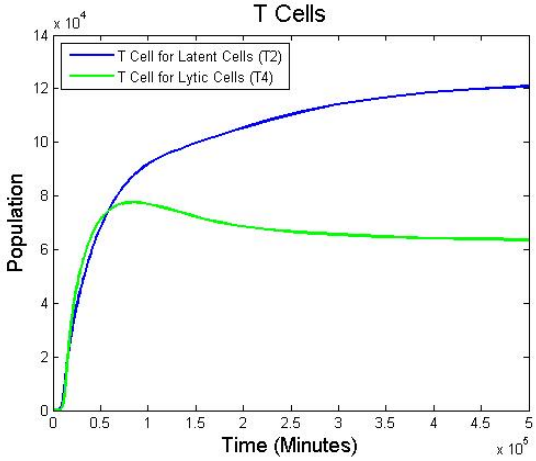
(b) Infected B Cells



(c) Infected Epithelial Cells



(d) Free Virus



(e) T Cells

Figure 3.1: Graphs of the solutions of System (3.1), grouped by cell type and behavior.

3.3 A Simplified Model

A seris of steps were taken to reduce System (3.1) to a system with fewer equations. System (3.1) is first scaled to give results in the range of 0-10. A steady state assumption is then made for two of the species. This made several of the remaining equations in System (3.1) have explicit solutions. These equations are solved analytically and the remaining equations are solved numerically.

3.3.1 Scaling the Model

The first step taken in simplifying System (3.1) was to scale the model. In doing this, we make each species around the same order of magnitude, making the orders of magnitude of each term's coefficient easier to analyze. In order to do this, we divided each of the first three B cell equations (B_1, B_2, and B_3) by $10^{-1}B_0$, the naive epithelial cell equation (E_1) by $10^{-1}E_0$, each of the T cell equations (T_2 and T_4) by $10^{-1}T_1$, the latent cells (B_4 and E_4) by $10^{-2}B_0$ and $10^{-2}E_0$, respectively, and the two virus equations (V_B and V_E) by $10^3 n$ and $10^2 n$, respectively. This scales each species down by at least 10^3, the result being that each species has solutions in the range of $(1, 10)$, with the exception being the lytic cells (B_4 and E_4), which are in the range of $(0, 1)$. The resulting system is below in System (3.3).

$$\begin{aligned}
\dot{B_1} &= d_1(10 - B_1) - \mu_{Eb}10^2 nV_E B_1 - \mu_{Bb}10^3 nV_B B_1 \\
\dot{B_2} &= \rho(\mu_{Eb}10^2 nV_E B_1 + \mu_{Bb}10^3 nV_B B_1) - (d_2 + c)B_2 - k_2 B_2(10^{-1}T_1)T_2 \\
\dot{B_3} &= cB_2 + rB_3 - rsB_3 \\
\dot{B_4} &= r10B_3 - d_4 B_4 - k_4 B_4(10^{-1}T_1)T_4 \\
\dot{E_1} &= d_e(10 - E_1) - \mu_{Be}10^3 nV_B E_1 - \mu_{Ee}10^2 nV_E E_1 \\
\dot{E_4} &= \mu_{Be}10^3 nV_B(10)E_1 + \mu_{Ee}10^2 nV_E(10)E_1 - (d_e + \gamma)E_4 - k_4 E_4(10^{-1}T_1)T_4 \\
\dot{V_B} &= 10^{-5}d_4 B_0 B_4 - d_v V_B \\
\dot{V_E} &= 10^{-4}\gamma E_0 E_4 - d_v V_E \\
\dot{T_2} &= \phi_2 10\omega[(B_0 10^{-1})B_2] + \theta_2 T_2 \omega[(B_0 10^{-1})B_2] - \delta T_2 \\
\dot{T_4} &= \phi_4 10\omega[(B_0 10^{-2})B_4 + (E_0 10^{-2})E_4] + \theta_4 T_4 \omega[(B_0 10^{-2})B_4 + (E_0 10^{-2})E_4] - \delta T_4
\end{aligned} \tag{3.3}$$

At this point, the orders of magnitude of the coefficient of each term can be compared without too much thought about the orders of magnitude of the individual species. Table 3.2 is showing, for each equation, each term and the order of magnitude of its coefficient. If an equation is shown to have coefficients with very small orders of magnitude when compared to other equations, the rate of that species can be assumed to be zero, and the species can be represented by its steady state value.

Looking at the graphs in Figure 3.1, we can see that each of the lytic cells (B_4 and E_4) reach their steady state values relatively quickly when compared with the other species. We can therefore make a steady state assumption and assume constant values for each of the lytic cells.

Equation	Term	Coefficient Order of Magnitude
$\dot{B_1}$	$d_1(10 - B_1)$	1.6667×10^{-4}
$\dot{B_1}$	$\mu_{Eb}10^2 nV_E B_1$	3.3×10^{-5}
$\dot{B_1}$	$\mu_{Bb}10^3 nV_B B_1$	3.3×10^{-6}
$\dot{B_2}$	$\rho\mu_{Eb}10^2 nV_E B_1$	6.6×10^{-5}
$\dot{B_2}$	$\rho\mu_{Bb}10^3 nV_B B_1$	6.6×10^{-6}
$\dot{B_2}$	$(d_2 + c)$	1.1×10^{-3}
$\dot{B_2}$	$k_2 B_2(10^{-1}T_1)T_2$	1.1×10^{-3}
$\dot{B_3}$	cB_2	10^{-3}
$\dot{B_3}$	rB_3	8.3×10^{-5}
$\dot{B_3}$	rsB_3	1.66×10^{-4}
$\dot{B_4}$	$r10B_3$	8.3×10^{-4}
$\dot{B_4}$	$d_4 B_4$	2.3148×10^{-4}
$\dot{B_4}$	$k_4 B_4(10^{-1}T_1)T_4$	2.3×10^{-3}
$\dot{E_1}$	$d_e(10 - E_1)$	1.6667×10^{-4}
$\dot{E_1}$	$\mu_{Be}10^3 nV_B E_1$	3×10^{-5}
$\dot{E_1}$	$\mu_{Ee}10^2 nV_E E_1$	6×10^{-7}
$\dot{E_4}$	$\mu_{Be}10^3 nV_B(10)E_1$	3×10^{-4}
$\dot{E_4}$	$\mu_{Ee}10^2 nV_E(10)E_1$	6×10^{-6}
$\dot{E_4}$	$(d_e + \gamma)E_4$	3.3333×10^{-4}
$\dot{E_4}$	$k_4 E_4(10^{-1}T_1)T_4$	2.3×10^{-3}
$\dot{V_B}$	$10^{-5}d_4 B_0 B_4$	8.5648×10^{-4}
$\dot{V_B}$	$d_v V_E$	4.6296×10^{-4}
$\dot{V_E}$	$10^{-4}\gamma E_0 E_4$	3.3×10^{-3}
$\dot{V_E}$	$d_v V_E$	4.6296×10^{-4}
$\dot{T_2}$	$\phi_2 10\omega((B_0 10^{-1})B_2)$	1.9500×10^{-4}
$\dot{T_2}$	$\theta_2 T_2\omega((B_0 10^{-1})B_2)$	3.25×10^{-5}
$\dot{T_2}$	δT_2	6.4103×10^{-6}
$\dot{T_4}$	$\phi_4 10[\omega((B_0 10^{-2})B_4 + (E_0 10^{-2})E_4)]$	4.48×10^{-4}
$\dot{T_4}$	$\theta_4 T_4[\omega((B_0 10^{-2})B_4 + (E_0 10^{-2})E_4)]$	3.25×10^{-5}
$\dot{T_4}$	δT_4	6.4103×10^{-6}

Table 3.2: This table describes the orders of magnitude of the coefficients of all the terms in System (3.3). The first column gives the equation that the term occurs in, the second describes the entire term, including variables and coefficients, and the final column gives the order of magnitude of the coefficients of the term.

3.3.2 Solving System (3.3)

Now that B_4 and E_4 are assumed constant, this makes both viral equations first-order and linear, and an explicit solution can now be found for V_B and V_E, as well as T_4:

$$\begin{aligned} V_B(t) &= c_1 e^{-d_v t} + \frac{C_B}{d_v} \\ V_E(t) &= c_2 e^{-d_v t} + \frac{C_E}{d_v} \\ T_4(t) &= c_3 e^{(\theta_4 H - \delta)t} + \frac{10\phi_4 H}{-\theta_4 H + \delta} \end{aligned} \tag{3.4}$$

where:

$$\begin{aligned} c_1 &= 1.3455 - \frac{C_B}{d_v} \\ c_2 &= 4.0001 - \frac{C_E}{d_v} \\ H &= \frac{10^{-2}(B_0 B_4 + E_0 E_4)}{K + 10^{-2}(B_0 B_4 + E_0 E_4)} \\ c_3 &= 2.5828 + \frac{10\phi_4 H}{\theta_4 H - \delta} \\ C_B &= 10^{-5} d_4 B_0 B_4 \\ C_E &= 10^{-4} \gamma E_0 E_4 \end{aligned} \tag{3.5}$$

Since V_B and V_E both have an explicit solution, they can now be substituted into the equations for B_1 and E_1. Therefore, B_1 and E_1 can now be solved using the integrating factor method. Substituting in the solutions above gives:

$$\begin{aligned} \dot{E}_1 &= 10 d_e + E_1(\alpha_1 + \beta_1 e^{-d_v t}) \\ \dot{B}_1 &= 10 d_1 + B_1(\alpha_2 + \beta_2 e^{-d_v t}) \end{aligned} \tag{3.6}$$

where:

$$\begin{aligned} \alpha_1 &= -10 d_e - 10^3 n \mu_{Be} \frac{C_B}{d_v} - 10^2 n \mu_{Ee} \frac{C_E}{d_v} \\ \beta_1 &= -10^3 n \mu_{Be} c_1 - 10^2 n \mu_{Ee} c_2 \\ \alpha_2 &= -10 d_1 - 10^2 n \mu_{Eb} \frac{C_E}{d_v} - 10^3 n \mu_{Bb} \frac{C_B}{d_v} \\ \beta_2 &= -10^2 n \mu_{Eb} c_2 - 10^3 n \mu_{Bb} c_1 \end{aligned} \tag{3.7}$$

In both cases, the integrating factor μ is given by $\mu_{1,2} = \mathsf{exp}(-\int_0^t \alpha_{1,2} + \beta_{1,2}e^{-d_4 s}ds)$. The resulting solutions are:

$$\begin{aligned} E_1(t) &= \mathsf{exp}(-\Gamma_1(t))[E_1(0)e^{\Gamma_1(0)} + d_e 10 \int_0^t e^{\Gamma_1(s)}ds] \\ B_1(t) &= \mathsf{exp}(-\Gamma_2(t))[B_1(0)e^{\Gamma_2(0)} + d_1 10 \int_0^t e^{\Gamma_2(s)}ds] \end{aligned} \tag{3.8}$$

where:

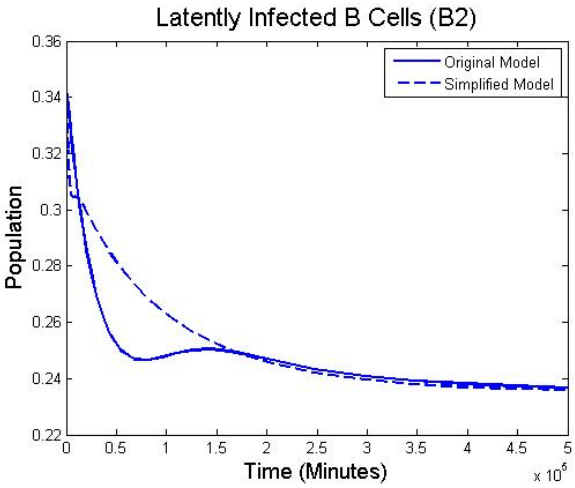
$$\begin{aligned} \Gamma_1(t) &= -\alpha_1 t + \frac{\beta_1}{d_v}e^{-d_v t} \\ \Gamma_2(t) &= -\alpha_2 t + \frac{\beta_2}{d_v}e^{-d_v t} \end{aligned} \tag{3.9}$$

$$\begin{aligned} \dot{B}_2 &= \rho(\mu_{Eb}10^2 n(c_1 e^{-d_v t} + \frac{C_B}{d_v})B_1 + \mu_{Bb}10^3 n(c_2 e^{-d_v t} + \frac{C_E}{d_v})B_1) \\ &\quad -(d_2 + c)B_2 - k_2 B_2(10^{-1}T_1)T_2 \\ \dot{B}_3 &= cB_2 + rB_3 - rsB_3 \\ \dot{T}_2 &= \phi_2 10\omega[(B_0 10^{-1})B_2] + \theta_2 T_2 \omega[(B_0 10^{-1})B_2] - \delta T_2 \end{aligned} \tag{3.10}$$

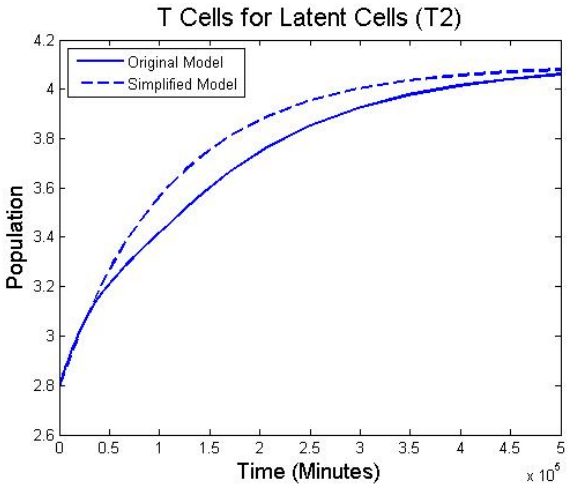
The integrals in both solutions above cannot be solved explicitly, and so they were solved numerically using the MATLAB function 'quadgk', which uses adaptive Gauss-Kronrod quadrature to numerically solve integrals.

The next step in solving System (3.1) would be to solve B_2 and T_2 together. However, these equations cannot be solved explicitly. Therefore, the last three equations, B_2, B_3, and T_2, were solved numerically. The graphs of the numeric solution are displayed in Figure 3.2. Each graph produced shows the solution beginning at a later time point. This time point is approximately where B_4 and B_4 reach their steady state, at approximately 7.5×10^4 minutes. As with the graphs of the original model solutions, the final time point is around 350 days.

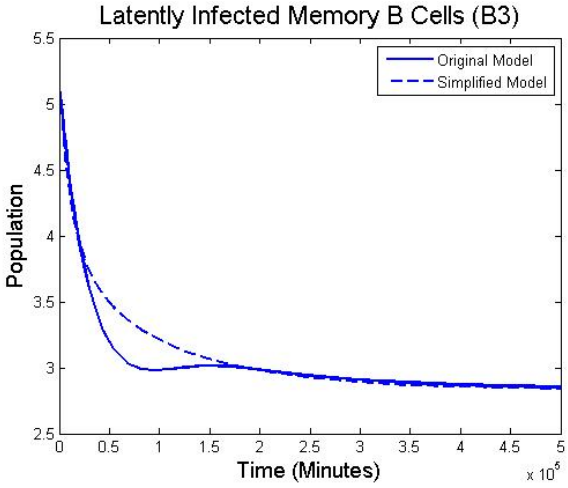
The graphs of the solutions (see Figure 3.2) of the final three equations represent good approximations of System (3.1). Therefore, the system of ten equations was successfully reduced to a system of three. This smaller system can be used to represent the larger in analysis that one may want to conduct. However, one cannot do phase plane analysis on this system, as the system includes equations with variable coefficients.



(a) Latently Infected B Cells



(b) T Cells for Latent Cells



(c) Latently Infected Memory B Cells

Figure 3.2: Graphs of the numerical solutions of the remaining species, B_2, B_3, and T_2. These graphs begin at a later time point than those in Figure 3.1, at approximately 7.5×10^4 minutes.

Chapter 4

Conclusion

In Chapter 2 we investigated an antigenic variation model of Human Immunodeficiency Virus and used MATLAB to produce results similar to those of Nowak's findings. We saw what conditions on the parameters cause the three different real-world cases. The first of these cases is that of an acute infection. In this case, the patient has the initial infection with HIV which causes fever symptoms, and the patient does not survive. The second case was that of chronic infection, where the patient has the initial infection with HIV, goes into the fever stage, then the virus is fought off by the immune system enough to allow the patient to be asymptomatic, and the virus then persists at this very low level. In the third case, the patient goes through these two stages of fever and an asymptomatic period, but the patient then begins to get sick again from other infections. In this stage of typical infection, the immune system is rendered nearly useless and the patient is very susceptible to infection, which eventually kills the patient. The prevalent theory behind how this works is antigenic variation, where the virus undergoes mutation to evade the adaptive immune system. Since a model using the theory of antigenic variation fits the behavior of the infection, we can conclude that this theory is supported.

In Chapter 3, we discussed Epstein-Barr Virus and described a model that includes two classes of cells that it infects: B cells and Epithelial cells. Because EBV infects various classes of cells, biological models can become very complex and building on the models or making further analysis would be very difficult.

We first scaled the model to make all the species the same or a similar order of magnitude. This made the model easier to analyze. After the model was scaled, it was then assumed that two equations in the model would equal zero, and therefore their solution would be constant. Therefore, the solutions to five more equations could be found, which allowed them to be examined in an analytical manner. For three of these equations, an exact working solution was found in terms of parameter values and standard mathematical functions. For the other two, part of the solution was a unsolvable integral with a double exponential. The integration was then done numerically to obtain a solution. After the said equations solutions' had been found, this reduced the original model to a system of three differential equations, which were then

solved numerically.

A potential weakness of the models of Epstein-Barr Virus in this paper is mass-action kinetics. Since all of the systems of differential equations in this project use mass-action kinetics, they may be inaccurate, since the accuracy of mass-action kinetics is still an open problem in mathematical academia.

There are several open-ended questions about Epstein-Barr Virus, some of which include various cancers of B cells and Epithelial cells that EBV infection seems to have a correlation with. There is a model for Nasopharengyl Carcinoma (NPC) proposed by Giao Huynh (Huynh, 2010), which involves latently infected epithelial cells. It would be interesting to see how these latent and cancerous epithelial cells would play into the dynamics of the system that we discuss in Chapter 3. Using one of the simplified models that we propose, viewing the interactions between the cancerous cells, free virus, B cells, and immune system would be much more possible and less complex than if one were to use the original model, System (3.1).

Using the model with the cancerous latently infected epithelial cells, one could also investigate how various treatments would affect the dynamics of the entire system, and compare this to a typical EBV infection. For example, one treatment for NPC involves the induction of the lytic cycle in the latently infected NPC cells (Jurgens et al., 2006). In the tumor, large amounts of cells are latently infected with EBV. During a treatment as previously mentioned, these would enter the lytic cycle and burst, releasing larger amounts of virus at a time than a normal amount of infected epithelial cells would release. This could have a measureable effect on the infection of B cells. Building a model around this situation may be useful to investigate the repercussions of this type of treatment or possibly give some insight on how treatment should be approached.

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Appendix A

Parameter Table for Section 3.2

Parameter	Approximate Value	Biological Meaning
d_1	1.6667×10^{-4}	Turnover Rate of Naive B-Cells
μ_{Eb}	3.3×10^{-10}	B Cell infection rate per epithelial cell virus
μ_{Bb}	3.3×10^{-12}	B Cell infection rate per B cell virus
ρ	2	Proliferation of B cells
d_2	8.6806×10^{-5}	Death rate of latently infected B cells
c	10^{-3}	Rate of latently infected B cells going into memory stage (B_3)
k_2	3.8×10^{-8}	Rate of latently infected B cells killed by activated T cell
r	8.3×10^{-5}	Rate of reactivation of lytic infection from latent infection
s	2	Regulation factor for memory B cells
d_4	2.3148×10^{-4}	Death rate of lytically infected cell due to lysis
k_4	7.6×10^{-8}	Rate of lytically infected B cells killed by activated T cells
d_e	1.6667×10^{-4}	Turn-over rate of epithelial cells
μ_{Be}	3×10^{-11}	Epethelial cell infection rate per epithelial cell virus
μ_{Ee}	1.5×10^{-11}	Epethelial cell infection rate per epithelial cell virus
γ	1.6667×10^{-4}	Death rate of infected epithelial cells due to cell lysis
n	10^4	Viral burst size
d_v	4.6296 × 106−4	Death rate of virus
ϕ_2	1.95×10^{-5}	Rate of CTL activation against lytic infection
ϕ_4	4.48×10^{-5}	Rate of CTL activation against lytic infection
θ_2	3.25×10^{-5}	Rate of effector CTL proliferation against latent infection
θ_4	3.25×10^{-5}	Rate of effector CTL proliferation against lytic infection
K	10^5	Number of infected cells when T cell activation is at half maximum
δ	1.7857×10^{-5}	Death rate of T cells
B_0	3.7×10^5	Initial population of naive B cells
E_0	2×10^5	Initial population of naive epithelial cells
T_1	3×10^5	Naive population of T cells

Table A.1: Original Model Parameter Values

Appendix B

MATLAB Code

B.1 Code for Chapter 2

```
%HIV Antigenic Variation Model

function [t,y]=graphmodel(Y)
%This function graphs an antigenic variation model for HIV by running the
%ode solver ode45 until a mutation is made, when the number of virus
%strains is increased, and therefore number of specific antibodies
%increased.

close all; clc;
global r
global p
global q
global c
global b
global u
global k
global n
global y0
global P
global dt
global tstart
global T

%Values for global variables, parameters as defined in Virus Dynamics, c12
if Y==1 %Parameters for Chronic Infection Case
```

```
    r=2.3;
    p=2;
    q=2.4;
    c=1;
    k=1;
    u=1;
    b=.01;
    'Chronic Infection'
elseif Y==2 %Parameters for Typical Infection Case
    r=2.5;
    p=2;
    q=2.4;
    c=1;
    k=1;
    u=1;
    b=.01;
    'Typical Infection'
elseif Y==3 %Parameters for Acute Infection Case
    r=2.5;
    p=1.5;
    q=1.3;
    c=.85;
    k=.85;
    u=1;
    b=.1;
    'Acute Infection'
end


n=10;
P=0.1;
dt=0;
tstart=0;
T=30;

%matricies to accumulate the output: col vector of time steps, col vector
%of non specific antibodies at each time step, and matrices of virus and
%antibody of/for each strain at each time step
tend=zeros(1,1);
vend=zeros(1,n);
xend=zeros(1,n);
zend=zeros(1,1);
```

```
%generates initial values
y0=zeros(2*n+1,1);
for j=1:n
    y0(j,1)=rand;
    vend(1,j)=y0(j,1); %puts initial values in output
end

options=odeset('Events',@events);

%runs ode45, one iteration runs ode45 until stopped by event function, the
%output is accumulated, n is increased for new mutation, and initial times
%and values reset
while tstart<T
    [t,y]=ode23s(@model,[tstart T],y0,options);
    tstart=t(length(t));

    %accumulates output
    tend=vertcat(tend,t);
    vend=vertcat(vend,y(:,1:n));
    xend=vertcat(xend,y(:,n+1:2*n));
    zend=vertcat(zend,y(:,2*n+1));

    %Increases number of mutations
    n=n+1;

    %resets intial values to be ready for next iteration
    y0=zeros(2*n+1,1);
    for l=1:n-1
      y0(l,1)=y(length(t),l);
      y0(n+l,1)=y(length(t),(n-1)+l);
    end
    y0(2*n+1,1)=y(length(t),length(y(length(t),:)));
    y0(n,1)=rand;

    %adds strain and antibody for the output
    vend=horzcat(vend,zeros(length(vend),1));
    vend(n,1)=y0(n,1);
    xend=horzcat(xend,zeros(length(xend),1));
end

%Sums virus and antibodies at each time point
```

```
v=zeros(length(tend),1);
x=zeros(length(tend),1);

for i=1:length(v)
    if i<=length(tend)
        v(i,1)=sum(vend(i,1:n));
        x(i,1)=sum(xend(i,1:n));
    end
end

%Graph the solutions
plot(tend,v,'b','LineWidth',2)
xlabel('Time','fontsize',14);
ylabel('Virus Load','fontsize',14)
title('Virus','fontsize',16)
figure;
plot(tend,x,'b','LineWidth',2)
xlabel('Time','fontsize',14);
ylabel('Antibodies','fontsize',14)
title('Specific Antibodies','fontsize',16)
figure;
plot(tend,zend,'b','LineWidth',2)
xlabel('Time','fontsize',14);
ylabel('Antibodies','fontsize',14)
title('Nonspecific Antibodies','fontsize',16)

%Setting up the model
function dy = model(t,y)

global r
global p
global q
global c
global b
global u
global k
global n

%Defines the system of 2n+1 equations
dy=zeros(2*n+1,1);
for i=1:n
    dy(i) = y(i)*(r-p*y(n+i)-q*y(2*n+1));%viruses
```

```
    dy(n+i) = c*y(i)-b*y(n+i)-u*sum(y(1:n,1))*y(n+i);%specific antibodies
end
%nonspecific antibodies
dy(2*n+1,1) =-b*y(2*n+1)-u*sum(y(1:n,1))*y(2*n+1)+ k*sum(y(1:n,1));

%Defining the Event Function
function [value,isterminal,direction] = events(t,y)

global P
global dt
global tstart
dt=t(length(t))-tstart;

%P*dt is probability of new mutation, with P being mutation rate and dt
%being time since last mutation
if rand<P*dt
   value=0;
else
    value=1;
end

isterminal = 1;   % Stop the integration
direction = -1;   % Negative direction only
```

B.2 Code for Chapter 3

B.2.1 Code to Graph the Solutions of System (3.1)

```
%This function solves the system of ODE's using ode23s and then
%produces graphs of the solutions

function [t,y] = modelgraph

%Solve the System
y0 = [0; 0; 0; 0; 0; 0; 500; 11000; 0; 0]; %Initial Conditions
tstart = 0; %Time Start
T = 500000; %Time End
[t,y] = ode23s(@model, [tstart, T], y0);

%Graph the Solution
plot(t,y(:,1),'g','LineWidth',2)
```

```
hold on
plot(t,y(:,5),'b','LineWidth',2)
hold on
xlabel('Time','fontsize',14)
ylabel('Population','fontsize',14)
title('Naive Cells','fontsize',16)
legend('Naive B Cells','Naive Epithelial Cells','Location','SouthEast')
figure;
plot(t,y(:,2),'g','LineWidth',2)
hold on
plot(t,y(:,3),'b','LineWidth',2)
hold on
plot(t,y(:,4),'c','LineWidth',2)
xlabel('Time','fontsize',14)
ylabel('Population','fontsize',14)
title('Infected B Cells','fontsize',16)
legend('Latently Infected B Cells','Memory B Cells','Lytically Infected B Cells')
figure;
plot(t,y(:,6),'g','LineWidth',2)
xlabel('Time','fontsize',16)
ylabel('Population','fontsize',14)
title('Infected Epithelial Cells','fontsize',16)
legend('Infected Epithelial Cells')
figure;
plot(t,y(:,7),'g','LineWidth',2)
hold on
plot(t,y(:,8),'b','LineWidth',2)
xlabel('Time','fontsize',14)
ylabel('Population','fontsize',14)
title('Virus','fontsize',16)
legend('B Cell Virus','Epithelial Cell Virus')
figure;
plot(t,y(:,9),'b','LineWidth',2)
hold on
plot(t,y(:,10),'g','LineWidth',2)
xlabel('Time','fontsize',14)
ylabel('Population','fontsize',14)
title('T Cells','fontsize',16)
legend('T Cell for Latent Cells','T Cell for Lytic Cells','Location','NorthWest')

%Function that sets up the system for ode23s
function dy = model(t,y)
```

```
%Parameter Values
d1=1/6000;
muEB=3.3*10^-10;
muBB=muEB/100;
rho=2;
d2=1/11520;
c=.001;
k2=3.8*10^-8;
r=8.3*10^-5;
s=2;
d4=1/4320;
k4=7.6*10^-8;
dE=1/6000;
muBE=3*10^-11;
muEE=muBE/5;
gamma=1/6000;
n=1000;
dV=1/2160;
phi2=1.95*10^-5;
phi4=4.48*10^-5;
theta2=3.25*10^-5;
theta4=3.25*10^-5;
K=10^5;
delta=1/156000;
T1=300000;
B0=370000;
E0=200000;

dy = zeros(10,1);
%The System
%The System
dy(1) = d1*(B0-y(1))-muEB*y(8)*y(1)-muBB*y(7)*y(1);
%Naive B Cells
dy(2) = rho*(muEB*y(8)*y(1)+muBB*y(7)*y(1))-(d2+c)*y(2)-k2*y(2)*y(9);
%Latently Infected B Cells
dy(3) = c*y(2)+r*y(3)-s*r*y(3);
%Latently Infected Memory B Cells
dy(4) = r*y(3)-d4*y(4)-k4*y(4)*y(10);
%Lytically Infected B Cells
dy(5) = dE*(E0-y(5))-muEE*y(8)*y(5)-muBE*y(7)*y(5);
%Naive Epithelial Cells
```

```
dy(6) = muEE*y(8)*y(5)+muBE*y(7)*y(5)-(dE+gamma)*y(6)-k4*y(6)*y(10);
%Infected Epithelial Cells
dy(7) = n*d4*y(4)-dV*y(7);
%Free Virus from B Cells
dy(8) = n*gamma*y(6)-dV*y(8);
%Free Virus from Epithelial Cells
dy(9) = phi2*T1*(y(2)/(K+y(2)))+theta2*y(9)*(y(2)/(K+y(2)))-delta*y(9);
%T Cells for Latent Cells
dy(10) = phi4*T1*((y(4)+y(6))/(K+(y(4)+y(6))))
    +theta4*y(10)*((y(4)+y(6))/(K+(y(4)+y(6))))-delta*y(10);
%T Cells for Lytic Cells
```

B.2.2 Code to Solve for Steady States and Eigenvalues of the Jacobian Matrix Evaluated at the Steady States

```
%This function finds the steady states and eigenvalues
%of the Jacobian evaluated at the steady states. It takes
%two functions as inputs, one used for ode23s (f1) and one used
%for fsolve (f2), and starting values (y0) for the fsolve function

function solvefun(f1,f2,y0)
%First, ode23s is used to get sarting values for fsolve
tstart = 0;
T = 500000;
[t,y] = ode23s(f1, [tstart, T], y0);
x0=transpose(y(length(y),:));

%fsolve is used to find states and the jacobian evaluated at
%the steady state, then eig was used to find the eigenvalues
%of the jacobian
[sstates,fval,exitflag,o,jac] = fsolve(f2,x0);
evals=eig(jac);
```

B.2.3 Code used for f1 Input in Section B.2.2

```
%This function is used for the MATLAB function ode23s
%in order to find initial values for fsolve, which is used to
%find steady states and the Jacobian of the system

function dy = modelode(t,y)
```

```
%Parameter Values
d1=1/6000;
muEB=3.3*10^-10;
rho=2;
d2=1/11520;
c=.001;
k2=3.8*10^-8;
r=8.3*10^-5;
s=2;
d4=1/4320;
k4=7.6*10^-8;
dE=1/6000;
muBE=3*10^-11;
gamma=1/6000;
n=1000;
dV=1/2160;
phi2=1.95*10^-5;
phi4=4.48*10^-5;
theta2=3.25*10^-5;
theta4=3.25*10^-5;
K=10^5;
delta=1/156000;
T1=300000;
B0=370000;
E0=200000;

dy = zeros(10,1);
%The System
dy(1) = d1*(B0-y(1))-muEB*y(8)*y(1)-muBB*y(7)*y(1);
%Naive B Cells
dy(2) = rho*(muEB*y(8)*y(1)+muBB*y(7)*y(1))-(d2+c)*y(2)-k2*y(2)*y(9);
%Latently Infected B Cells
dy(3) = c*y(2)+r*y(3)-s*r*y(3);
%Latently Infected Memory B Cells
dy(4) = r*y(3)-d4*y(4)-k4*y(4)*y(10);
%Lytically Infected B Cells
dy(5) = dE*(E0-y(5))-muEE*y(8)*y(5)-muBE*y(7)*y(5);
%Naive Epithelial Cells
dy(6) = muEE*y(8)*y(5)+muBE*y(7)*y(5)-(dE+gamma)*y(6)-k4*y(6)*y(10);
%Infected Epithelial Cells
dy(7) = n*d4*y(4)-dV*y(7);
%Free Virus from B Cells
```

```
dy(8) = n*gamma*y(6)-dV*y(8);
%Free Virus from Epithelial Cells
dy(9) = phi2*T1*(y(2)/(K+y(2)))+theta2*y(9)*(y(2)/(K+y(2)))-delta*y(9);
%T Cells for Latent Cells
dy(10) = phi4*T1*((y(4)+y(6))/(K+(y(4)+y(6))))
    +theta4*y(10)*((y(4)+y(6))/(K+(y(4)+y(6))))-delta*y(10);
%T Cells for Lytic Cells
```

B.2.4 Code used for f2 Input in Section B.2.2

```
%This function is used for the MATLAB function fsolve
%in order to find steady states and the Jacobian of the system

function z = modelfsolve(y)
%Parameter Values
d1=1/6000;
muEB=3.3*10^-10;
muBB=muEB/100;
rho=2;
d2=1/11520;
c=.001;
k2=3.8*10^-8;
r=8.3*10^-5;
s=2;
d4=1/4320;
k4=7.6*10^-8;
dE=1/6000;
muBE=3*10^-11;
muEE=muBE/5;
gamma=1/6000;
n=1000;
dV=1/2160;
phi2=1.95*10^-5;
phi4=4.48*10^-5;
theta2=3.25*10^-5;
theta4=3.25*10^-5;
K=10^5;
delta=1/156000;
T1=300000;
B0=370000;
E0=200000;
```

```
%The System
z = [d1*(B0-y(1))-muEB*y(8)*y(1)-muBB*y(7)*y(1);
    %Naive B Cells
    rho*(muEB*y(8)*y(1)+muBB*y(7)*y(1))-(d2+c)*y(2)-k2*y(2)*y(9);
    %Latently Infected B Cells
    c*y(2)+r*y(3)-s*r*y(3);
    %Latently Infected Memory B Cells
    r*y(3)-d4*y(4)-k4*y(4)*y(10);
    %Lytically Infected B Cells
    dE*(E0-y(5))-muBE*y(7)*y(5)-muEE*y(8)*y(5);
    %Naive Epithelial Cells
    muBE*y(7)*y(5)+muEE*y(8)*y(5)-(dE+gamma)*y(6)-k4*y(6)*y(10);
    %Infected Epithelial Cells
    n*d4*y(4)-dV*y(7);
    %Free Virus from B Cells
    n*gamma*y(6)-dV*y(8);
    %Free Virus from Epithelial Cells
    phi2*T1*(y(2)/(K+y(2)))+theta2*y(9)*(y(2)/(K+y(2)))-delta*y(9);
    %T Cells for Latent Cells
    phi4*T1*((y(4)+y(6))/(K+(y(4)+y(6))))
        +theta4*y(10)*((y(4)+y(6))/(K+(y(4)+y(6))))-delta*y(10)];
    %T Cells for Lytic Cells
```