

Exploring the EBV-MS Link Through A Mathematical Model of Immune Response Dynamics

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Abstract

While the exact etiology of multiple sclerosis (MS) remains elusive, it is believed to involve a complex interplay between genetic and environmental factors. Among these, Epstein-Barr Virus (EBV) has been implicated as a central contributing factor. This thesis explores the role of EBV in the pathogenesis of MS through an adapted mathematical model. The model examines the dynamics of EBV within the host, focusing on the viral life cycle between latent and lytic phases and its interaction with the host's immune response, particularly the role of cytotoxic T lymphocytes and B cells. The model investigates how CTL exhaustion rates might influence EBV reactivation and contribute to MS progression. We also assess the association of contracting EBV at a later age and developing MS due to less efficient cross-reactive immune responses. Moreover, through this study, we sought not only to validate existing hypotheses about the linkage between EBV and MS but also to generate new hypotheses that can be empirically tested through experimental studies.

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Chapter 1

Introduction

1.1 Multiple Sclerosis

Multiple Sclerosis is a chronic autoimmune disorder that primarily affects the central nervous system, leading to a wide range of neurological symptoms. It is characterised by the immune system's attack on the protective covering of neurons, the myelin sheath. This attack results in communication disruptions between the brain and the rest of the body, manifesting in symptoms such as fatigue, mobility issues, pain, cognitive impairment, and visual disturbances. The exact cause of MS remains unknown – current theories suggest a combination of genetic susceptibility and environmental factors that contribute to its development. However, several critical questions remain unsolved in MS research. These include the precise mechanisms driving its onset and progression, why some individuals develop MS while others do not, and the variability in the severity and course of the disease among patients.

1.2 Epstein-Barr Virus

1.2.1 EBV Epidemiology

Epstein-Barr Virus, a member of the herpesvirus family, is one of the most common human viruses globally. It is estimated that EBV infects about 95% of adults worldwide, typically acquired during childhood or early adulthood.[\[1\]](#)

The most common route of EBV transmission is through contact with saliva from an infected individual. Although less common, EBV can also be transmitted through other bodily fluids, such as blood and semen. This can occur during blood transfusions, organ transplants, or through sexual contact.[\[2\]](#)

1.2.2 EBV Life Cycle

Within a host, EBV can exist in both latent and lytic states. It infects two major cell types, B cells and epithelial cells. This dual tropism plays a crucial role in the virus's lifecycle, influencing both its maintenance within the host and its transmission to new hosts. [3]

The infection of B cells is central to the virus's strategy for long-term persistence. In its latent phase, EBV primarily infects B cells. Once inside these cells, the virus integrates its DNA into the host cell's genome, effectively hiding from the host's immune system. During latency, EBV expresses a limited set of its genes, known as latent genes. These genes are crucial for maintaining the viral genome within the host cell, altering cellular pathways to prevent apoptosis, and promoting cell proliferation. The latent genes include Epstein-Barr nuclear antigens (EBNA), latent membrane proteins (LMPs), and EBV-encoded RNAs (EBERs). These gene products help in maintaining the viral genome as an episome, promoting the survival and proliferation of the infected B cells, and evading the immune response. The latency phase is typically asymptomatic but is crucial for the long-term persistence of the virus in the host.[4]

The lytic phase of EBV is characterized by the active production of new virus particles. This phase can be triggered by various factors, including immune suppression or certain environmental stimuli. During lytic replication, the virus expresses a different set of genes, known as lytic genes, which are involved in DNA replication, capsid formation, and release of new virions.[4]

While B cells are crucial for latency, epithelial cells—particularly those in the oropharynx—play a vital role in the virus's reproductive cycle. The lytic infection of epithelial cells is critical for amplifying the viral population, enhancing the virus's ability to spread to new hosts through salivary exchange.

The switch from latency to the lytic cycle involves the expression of the immediate-early gene BZLF1. This protein acts as a transcriptional activator of lytic gene expression, initiating a cascade of lytic gene activation. The lytic cycle leads to the destruction of the host cell and the release of new virus particles, which can infect other cells or be transmitted to new hosts. [5]

sectionInfectious Mononucleosis

Most EBV infections are asymptomatic. However, primary EBV infection can manifest as infectious mononucleosis (IM) in some individuals, especially when the infection occurs during adolescence or young adulthood. Symptoms of infectious mononucleosis include fever, sore throat, swollen lymph nodes, and fatigue. [6]

The pathogenesis of infectious mononucleosis begins when EBV infects epithelial cells in the oropharynx and then spreads to B lymphocytes. In B cells, the virus typ-

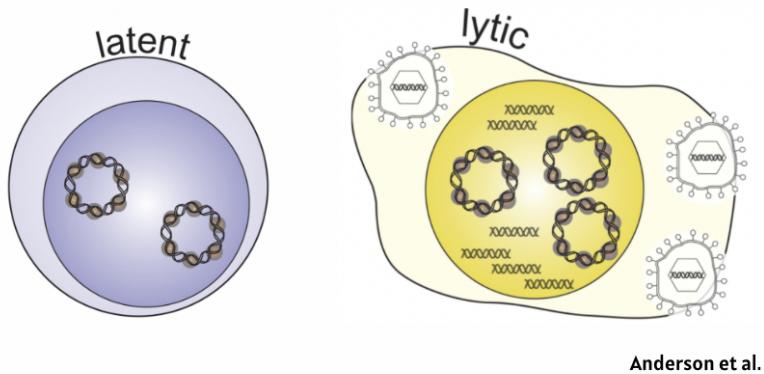


Figure 1.1: EBV Latent and Lytic Phase.

ically establishes a latent infection. However, during acute infectious mononucleosis, a significant number of these infected B cells enter the lytic cycle, producing new virions that further infect other B cells. The immune system reacts to the infection with a pronounced response from cytotoxic T lymphocytes. These immune cells target and kill infected B cells, which is a key driver of the symptomatic phase of the disease. The intense immune response contributes to the enlarged lymph nodes and spleen, typical hallmarks of mono. [4]

Beyond mononucleosis, EBV has also been associated with several other diseases. It is a known risk factor for certain types of cancers, such as Hodgkin's lymphoma, Burkitt's lymphoma and Nasopharyngeal Carcinoma. [4]

1.3 The Role of the Immune System

The immune system is broadly classified into two components: the innate immune system and the adaptive immune system. When a pathogen invades the body, it triggers a series of immune responses orchestrated by both the innate and adaptive immune systems.

The innate immune system is the body's first line of defense and responds to pathogens in a generic but rapid manner. It includes physical barriers such as the skin and mucous membranes, as well as immune cells like macrophages and neutrophils. These cells are equipped with pattern recognition receptors that detect common motifs on pathogens, triggering an immediate response.

The adaptive immune system is of interest to our study. The adaptive immune system is highly specific to the pathogens it encounters, having the ability to learn from an encounter with a pathogen and mount a stronger attack in subsequent expo-

sures.

T cells are a main component of adaptive immunity, divided into Helper T cells and Cytotoxic T Cells . Helper T cells secrete cytokines that activate Cytotoxic T cells and B cells; the former destroys virus-infected or cancerous cells by triggering apoptosis. Regulatory T cells maintain immune tolerance and prevent autoimmune responses by suppressing other immune cells.

B cells are another crucial component of the adaptive immune response. They are unique in their ability to produce antibodies, which are proteins that specifically bind to antigens on pathogens. This binding can neutralize the pathogen or mark it for destruction by other cells of the immune system. When B cells encounter their specific antigen, they are activated and rapidly proliferate into plasma cells and memory B cells. Plasma cells are short-lived and produce large volumes of antibodies to combat the current infection, whereas memory B cells remain in the body for the long term, ready to respond more rapidly and robustly should the same pathogen invade again. [7]

Memory T cells arise from T cells that were activated during previous infections. These cells persist after the pathogen is cleared and are vital for the immune system's ability to remember and quickly respond to specific pathogens. Memory T cells include central memory T cells, which reside in lymph nodes and provide a long-term reservoir of antigen-specific T cells, and effector memory T cells, which circulate in the blood and tissues ready to respond swiftly to re-infection.

The process of the immune response involves the initial recognition of the pathogen by innate immune defenses, which then control its spread until the adaptive immune response can be fully activated. This activation occurs when antigen-presenting cells like dendritic cells process the pathogen and present its antigens to T cells in the lymph nodes. This leads to the clonal expansion of antigen-specific T and B cells, which then differentiate into effector and memory cells. The effector cells carry out the pathogen's destruction, and the memory cells remain in the body to enhance the response to subsequent infections. [7]

1.4 EBV Association in MS

Several studies have indicated that MS is a rare complication of EBV infection. A longitudinal study of over 10 million US military personnel demonstrated that the risk of MS is minimal in individuals not infected with EBV and increases 32-fold following EBV infection. Moreover, studies have identified heightened immune responses to EBV within the CNS of individuals with MS. A critical marker of this response is the presence of EBV-reactive oligoclonal bands in the cerebrospinal fluid. Oligoclonal

bands are proteins that indicate an immune response within the CNS. The reactivity to EBV in these bands suggests that the immune system in MS patients is actively responding to EBV-related antigens within the CNS.

Another aspect of the immune response in MS patients is the presence of antibodies in their blood that bind to EBV proteins, such as the EBV Nuclear Antigen 1(EBNA1) in the brain. This binding pattern is indicative of an abnormal immune response to EBV in MS patients, further linking the virus to the pathogenesis of the disease. [8]

Further evidence comes from the observed cross-reactivity of antibodies. In people with MS, antibodies that are formed against EBV antigens have been found to also react with self-antigens in the body. This cross-reactivity implies that the immune response to EBV may attack the body's own myelin sheath. Lastly, the success of B cell depletion therapies in treating MS underscores the role of B cells, and by extension, EBV, in the disease's progression. [8]

In healthy individuals, EBV lytic cycle reactivation is a common and often asymptomatic process. CD8+ T cells effectively regulate this reactivation, maintaining a balance that prevents disease manifestation. However, aberrant lytic activity of the virus is linked with MS. Despite the presence of an increased number of EBV-specific CD8+ T cells in MS patients — ostensibly a sign of a robust immune response — these cells demonstrate an impaired functionality. This suggests a state of 'exhaustion' in these immune cells. This exhaustion, characterised by reduced cytokine polyfunctionality, might be a factor in the inadequate control of EBV reactivation, allowing for the accumulation of EBV-infected autoreactive B cells in the brain. These B cells, especially during phases of active disease, exhibit increased lytic gene expression. [9]

Chapter 2

Mathematical Modelling of Epstein-Barr Virus

Basic mathematical models of virus dynamics have been built and modified to study viral infections. These models describe the population dynamics of viral infection within an infected host, tracking three state variables: uninfected susceptible cells, infected cells, and free virus particles. Models have also been extended to track the number of latently and lytically infected cells to study the T cell response to a persistent virus infection. However, these models assume that lytically infected cells can produce virus without going through latent stages of infection, which does not reflect the biology of EBV infection.

This thesis presents an adapted mathematical model based on the framework established by Giao T. Huynh [10], to investigate the within-host dynamics of Epstein-Barr Virus infection, with a focus on the implications for multiple sclerosis.

Specifically, we use the model to investigate whether the Pender hypothesis is supported mathematically. The Pender hypothesis proposes that individuals with MS have an inadequate immune response, particularly due to exhausted CD8+ T cells, which are essential for controlling EBV-infected B cells. This deficiency allows EBV-infected autoreactive B cells to accumulate in the CNS. These B cells are capable not only of producing antibodies but also of presenting antigens in a manner that could initiate an autoimmune response against the CNS's own components, specifically the myelin sheath that insulates nerve fibers. This process potentially leads to the characteristic autoimmune attacks observed in MS.

Therefore, by extending the model from Giao T. Huynh, we aim to characterize the trajectory of EBV infection and explore how CTL exhaustion rate could potentially modulate EBV reactivation, influencing MS progression. We also delve into exploring how acute infectious mononucleosis may influence the development and progression of Multiple Sclerosis. Furthermore, we generate a new hypothesis using the model

that can be empirically tested through experimental studies.

2.1 Model Overview

The model captures the progression and control of EBV through a network of interactions involving B cells in various states (naive, latently infected, memory, and lytically infected), uninfected and lytically infected epithelial cells, and cytotoxic T lymphocytes divided into two groups targeting latently infected B cells and lytically infected cells, respectively (Fig. 2.2).

The model's framework is constructed upon a system of eleven ordinary differential equations, each representing the evolution of the population of cells or viruses over time. These equations account for the rates of infection, proliferation, and death of cells, as well as the production and clearance of viruses. Cytotoxic T lymphocytes are modeled to undergo activation and proliferation in response to EBV antigens, with their dynamics governed by saturating functions reflective of the biological limitations on activation and proliferation.

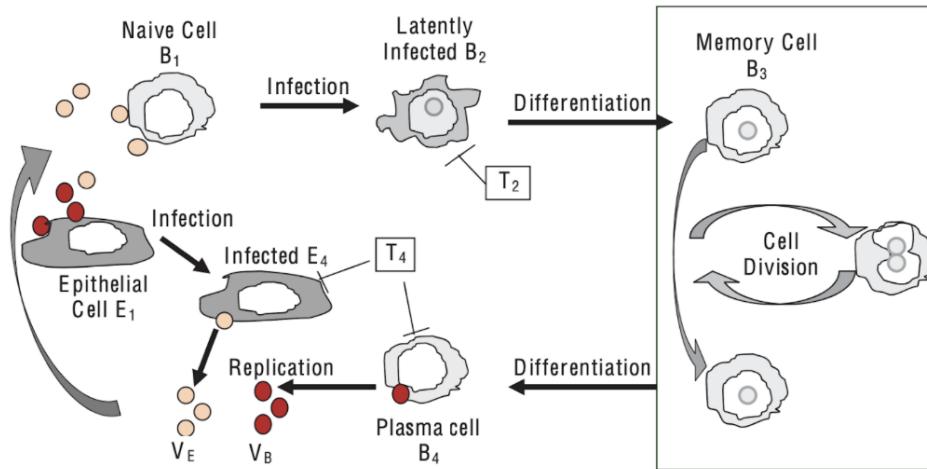


Figure 2.1: Compartments of EBV infection of B cells and Epithelial cells. [10]

2.2 Model Equations

$$\begin{aligned}
\frac{dB_1}{dt} &= d_1(B_0 - B_1) - \mu_{EB}V_E B_1 - \mu_{VB}V_B B_1 \\
\frac{dB_2}{dt} &= \rho(\mu_{EB}V_E B_1 + \mu_{VB}V_B B_1) - (d_2 + c)B_2 - k_2 B_2 T_2 \\
\frac{dB_3}{dt} &= cB_2 + rB_3 - srB_3 \\
\frac{dB_4}{dt} &= rB_3 - d_4 B_4 - k_4 B_4 T_4 \\
\frac{dE_1}{dt} &= d_e(E_0 - E_1) - \mu_{EB}V_E E_1 - \mu_{VE}V_E E_1 \\
\frac{dE_4}{dt} &= \mu_{EB}V_E E_1 + \mu_{VE}V_E E_1 - (d_e + \gamma)E_4 - k_4 E_4 T_4 \\
\frac{dV_B}{dt} &= nd_4 B_4 - d_v V_B \\
\frac{dV_E}{dt} &= n\gamma E_4 - d_v V_E \\
\frac{dT_2}{dt} &= \phi_2 T_1 w(B_2) + \theta_2 T_2 w(B_2) - \delta T_2 \\
\frac{dT_4}{dt} &= \phi_4 T_1 w(B_4 + E_4) + \theta_4 T_4 w(B_4 + E_4) - \delta T_4 - e T_4 \\
\frac{dT_{4exh}}{dt} &= e T_4 - \delta_{exh} T_{4exh}
\end{aligned}$$

$\frac{dB_1}{dt}$: describes the rate of change over time naive B cells B_1 . (2.1)

- $d_1(B_0 - B_1)$: represents the recruitment of new naive B cells. B_0 is the source or initial population of naive B cells, and d_1 is the rate at which naive B cells are supplied from this source. Assumes that the production of naive B cells is a regulated process that tries to maintain the number of naive B cells at a certain level B_0 . If B_1 is less than B_0 , is positive, indicating that new naive B cells are being produced. If B_1 is equal to B_0 , no new naive B cells are produced.
- $\mu_{EB}V_E B_1$: represents the loss of naive B cells due to infection by the epithelial-cell-derived virus V_E . μ_{EB} is the rate at which the epithelial-cell-derived virus infects naive B cells. As the product $V_E B_1$ increases, more naive B cells are lost to infection, leading to a decrease in the B_1 population.
- $\mu_{VB}V_B B_1$: represents the loss of naive B cells due to infection by the B-cell-derived virus V_B . μ_{VB} is the infection rate of the B-cell-derived virus. Again, as the product $V_B B_1$ increases, more naive B cells are lost to infection.

$$\frac{dB_2}{dt} : \text{describes the rate of change over time of latently infected B cells } B_2. \quad (2.2)$$

- $\rho(\mu_{EB}V_{EB}B_1 + \mu_{BB}V_{BB}B_1)$: accounts for the production of latently infected B cells. The infection of naive B cells B_1 by both epithelial-cell-derived virus V_{EB} and B-cell-derived virus V_B contributes to this. The parameters μ_{EB} and μ_{BB} represent the infection rates by the respective viruses, and ρ is the proliferation factor that converts the infected naive B cells into the latently infected B cells B_2 .
- $(d_2 + c)B_2$: represents the loss of latently infected B cells through natural death or transition to another state. d_2 is the rate at which these cells die naturally, and c is the rate at which latently infected B cells transition to the memory state B_3 due to the EBV gene expression switching off.
- $k_2B_2T_2$: captures the immune response against latently infected B cells. T_2 are the cytotoxic T lymphocytes that target latently infected B cells B_2 . The constant k_2 is the rate at which these immune cells kill the latently infected B cells.

$$\frac{dB_3}{dt} : \text{describes the rate of change over time of Latently Infected Memory B cells } B_3. \quad (2.3)$$

- cB_2 : represents the rate at which latently infected B cells B_2 switch to the memory cell state B_3 . The parameter c is the rate of this conversion process. It indicates that a certain proportion of the B_2 cells will become memory cells, thus increasing the B_3 population.
- rB_3 : accounts for the proliferation or growth of the existing memory B cell population. The parameter r is the rate at which memory B cells divide. contributes to the increase of B_3 cells as they replicate.
- srB_3 : represents the homeostatic death of memory B cells. In the context of the model, s is the homeostatic regulation factor, which controls the size of the memory B cell population. The product srB_3 thus gives the rate at which memory B cells are lost due to homeostatic mechanisms that keep the population in check.

$$\frac{dB_4}{dt} : \text{describes the rate of change over time of lytically infected B cells } B_4. \quad (2.4)$$

- rB_3 : indicates the rate at which memory B cells B_3 become lytically infected, thereby transitioning into plasma cells B_4 . The parameter r here represents the rate of reactivation of the virus from the latently infected memory B cells to the lytic phase, which is when the virus begins to actively replicate and produce new viral particles, converting memory B cells into plasma cells.
- d_4B_4 : accounts for the natural death rate of the plasma cells B_4 . The parameter d_4 is the rate at which these cells die off naturally, which reduces the B_4 population.
- $k_4B_4T_4$: describes the killing of lytically infected B cells B_4 by the cytotoxic T lymphocytes that specifically target these infected cells T_4 . The constant k_4 is the rate at which this immune-mediated killing occurs, which also decreases the B_4 population.

$$\frac{dV_B}{dt} : \text{describes the rate of change over time of B-cell-derived virus .} \quad (2.5)$$

- nd_4B_4 : represents the production of new virus particles by the lytically infected B cells B_4 . Here, n stands for the average burst size, or the number of new viruses produced per lytically infected B cell when it bursts. The parameter d_4 is the rate at which these cells die and release new virus particles. So, the product nd_4B_4 gives the rate of new virus production.
- d_vV_B : accounts for the loss of B-cell-derived virus particles due to natural decay or clearance by the immune system. The parameter d_v is the decay rate of the virus, representing how quickly the virus particles are removed from circulation.

$$\frac{dV_E}{dt} : \text{describes the rate of change over time of epithelial-cell-derived virus.} \quad (2.6)$$

- $n\gamma E_4$: represents the production of new V_E viruses from lytically infected epithelial cells E_4 . The rate at which these cells release new viruses is denoted by γ , so the product $n\gamma E_4$ gives the total rate of virus production.
- d_vV_E : accounts for the natural decay or clearance of the virus (V_E) from the system. The parameter d_v is the rate at which the virus is cleared or dies out.

$$\frac{dE_1}{dt} : \text{describes the rate of change over time of epithelial cells within the host.} \quad (2.7)$$

- $d_e(E_0 - E_1)$: represents the turnover of uninfected epithelial cells. d_e is the turnover rate, E_0 is the initial population of uninfected epithelial cells, and E_1 is the current population of uninfected epithelial cells. This difference $E_0 - E_1$ indicates that the population of uninfected cells will increase or decrease towards a homeostatic level E_0 at a rate determined by d_e .
- $\mu_{EB}V_B E_1$: represents the rate at which uninfected epithelial cells E_1 become infected by the B-cell-derived virus V_B . μ_{EB} is the infection rate by V_B , indicating that a higher viral load or a higher number of susceptible cells will result in more infections.
- $\mu_{EV}V_E E_1$: This represents the rate at which uninfected epithelial cells E_1 become infected by the epithelial-cell-derived virus V_E . μ_{EV} is the infection rate by V_E , and it also implies that more infections occur with a higher viral load or more susceptible cells.

$$\frac{dE_4}{dt} : \text{describes the rate of change over time of lytically infected epithelial cells within the host.} \quad (2.8)$$

- $\mu_{BE}V_E E_1$: represents the rate at which uninfected epithelial cells E_1 become lytically infected due to the epithelial-cell-derived virus V_E . The μ_{BE} is the infection rate constant, dictating how quickly the infection spreads from the virus to the epithelial cell.
- $\mu_{EE}E_1$: is the rate of lytic infection of epithelial cells by the virus V_E , with μ_{EE} being the specific infection rate constant.
- $(d_e + \gamma)E_4$: accounts for the natural death rate d_e of the lytically infected epithelial cells and their death due to virus bursting out γ .
- $k_4 E_4 T_4$: This represents the rate at which lytically infected epithelial cells E_4 are killed by the effector T cells T_4 . The constant k_4 is the rate of immune-mediated killing.

$$\frac{dT_2}{dt} : \text{describes the rate of change over time of effector cytotoxic T cells targeting latently infected B cells} \quad (2.9)$$

- $\phi_2 \tau_1 w(B_2)$: represents the activation of naive CTLs T_1 into effector CTLs T_2 that target latently infected B cells. ϕ_2 is the rate at which this activation happens when stimulated by viral antigens from latently infected cells, τ_1 is the total naive CTL population, and $w(B_2)$ is a saturating function that depends on the number of latently infected B cells B_2 .

- $\theta_2\tau_2w(B_2)$: denotes the proliferation of already activated CTLs T_2 . θ_2 is the rate at which the effector cells proliferate upon stimulation by viral antigens from latently infected cells, τ_2 represents the effector CTL population, and $w(B_2)$ again is the saturating function of the infected cell population.
- δT_2 : This represents the death rate of the effector CTLs (T_2), with δ being the constant death rate.

$$\frac{dT_4}{dt} : \text{describes the rate of change over time of effector cytotoxic T cells targeting lytically infected B cells.} \quad (2.10)$$

- $\phi_4\tau_1w(B_4 + E_4)$: represents the activation of naive CTLs into effector CTLs that target lytically infected cells T_4 . ϕ_4 is the activation rate, τ_1 is the naive CTL population, and $w(B_4 + E_4)$ is the saturating function dependent on the number of lytically infected B cells B_4 and epithelial cells E_4 .
- $\theta_4\tau_4w(B_4 + E_4)$: represents the proliferation of activated effector CTLs T_4 in response to lytically infected cells. θ_4 is the proliferation rate, τ_4 is the effector CTL population, and $w(B_4 + E_4)$ is the saturating function of the infected cell population.
- δT_4 : This is the death rate of the effector CTLs (T_4), with δ as the constant death rate.

$$w(B_j) = \frac{B_j}{K + B_j} : \text{describes a saturating function for T cells.} \quad (2.11)$$

- Ensures that the activation and proliferation of CTLs cannot increase indefinitely and will plateau as the number of infected cells increases, where K is the number of infected cells at which the CTL activation or proliferation is half maximal.

$$\frac{dT_{4\text{exh}}}{dt} : \text{describes the exhaustion of effector T cells targeting lytically infected B cells.} \quad (2.12)$$

- $e_{T_4}T_4$ This is the rate at which T_4 cells become exhausted, with e_{T_4} as the constant exhaustion rate.
- $\delta_{exh}T_{4\text{exh}}$ This is the death rate of the effector CTLs T_4 , with δ_{exh} as the constant death rate.

Table 2.1: Parameters Values [10]

Parameter	Description	Value	Unit
d_1	Turnover rate of naive B cells	1/6000	min^{-1}
μ_{Eb}	B cell infection rate per epithelial-cell virus	3.3×10^{-10}	$\text{min}^{-1}\text{virus}^{-1}$
μ_{Bb}	B cell infection rate per B-cell virus	$\mu_{Eb}/100$	$\text{min}^{-1}\text{virus}^{-1}$
ρ	Proliferation factor	2	(no unit)
d_2	Death rate of latently infected B cells	1/11520	min^{-1}
c	Rate of latently infected cells going into memory stage	0.001	min^{-1}
k_2	Rate of latently infected B cells killed by T cells	3.8×10^{-8}	$\text{min}^{-1}\text{cell}^{-1}$
r	Rate of reactivation of lytic infection from latent infection	8.3×10^{-5}	min^{-1}
s	Regulation factor of memory B cells	2	(no unit)
d_4	Death rate of lytically infected cells due to viruses bursting out	1/4320	min^{-1}
k_4	Rate of lytically infected B cells killed by T cells	7.6×10^{-8}	$\text{min}^{-1}\text{cell}^{-1}$
d_e	Turn-over rate of epithelial cells	1/6000	min^{-1}
μ_{Be}	Epithelial cell infection rate per B-cell virus	3×10^{-11}	$\text{min}^{-1}\text{virus}^{-1}$
μ_{Ee}	Epithelial cell infection rate per epithelial-cell virus	$\mu_{Be}/5$	$\text{min}^{-1}\text{virus}^{-1}$
γ	Death rate of infected epithelial cells due to viruses bursting out	1/6000	min^{-1}
n	Viral burst size	1000	virus-cell^{-1}
d_v	Death rate of virus	1/2160	min^{-1}
ϕ_2	Rate of T cell activation against latent infection	1.95×10^{-5}	min^{-1}
ϕ_4	Rate of T cell activation against lytic infection	4.48×10^{-5}	min^{-1}
θ_2	Rate of T cell proliferation against latent infection	3.25×10^{-5}	min^{-1}
θ_4	Rate of T cell proliferation against lytic infection	3.25×10^{-5}	min^{-1}
K	Number of infected cells when T cell activation is half maximal	10^5	cell
δ	Death rate of T cells	1/156000	min^{-1}
δ_{exh}	Death rate of exhausted T cells	1/156000	min^{-1}

2.3 Model Assumptions

1. The production and death of free viruses are modeled using linear terms, which may not fully capture the nonlinear dynamics of viral replication and clearance.
2. B cells are naive and equally susceptible to EBV infection. This simplification overlooks the fact that EBV primarily targets B cells expressing CD21 receptors, whose presence varies among individuals and B cell subtypes. Additionally, different B cell subtypes exhibit varying susceptibility to EBV, influenced by their differentiation stage.
3. CD8+ cells, once exhausted, lose all functional capacity to combat EBV infection.
4. Rates of infection, cell turnover, proliferation and death to be constants with time.
5. All interactions between cells and viruses are equally likely, spatial organization of tissues and compartments within the host are ignored.
6. Only the role of cytotoxic T lymphocytes has been considered in eliminating EBV infection.

Chapter 3

Analysis & Implications of the EBV Model in MS

3.1 Healthy Immune Response

In order to test the validity of the mathematical model, we simulate the model for a healthy immune response by setting the T cell exhaustion rate parameter e_T to zero. We integrate our ODE system using Scipy.

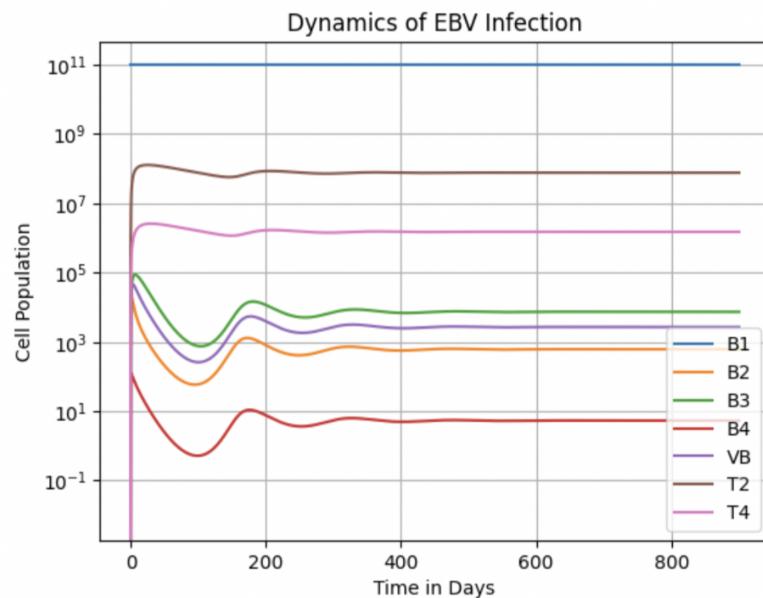


Figure 3.1: EBV Dynamics for a Healthy Immune Response.

The model's results align with the well-documented biological phases of EBV infection and immune modulation, characterized by several distinct patterns.

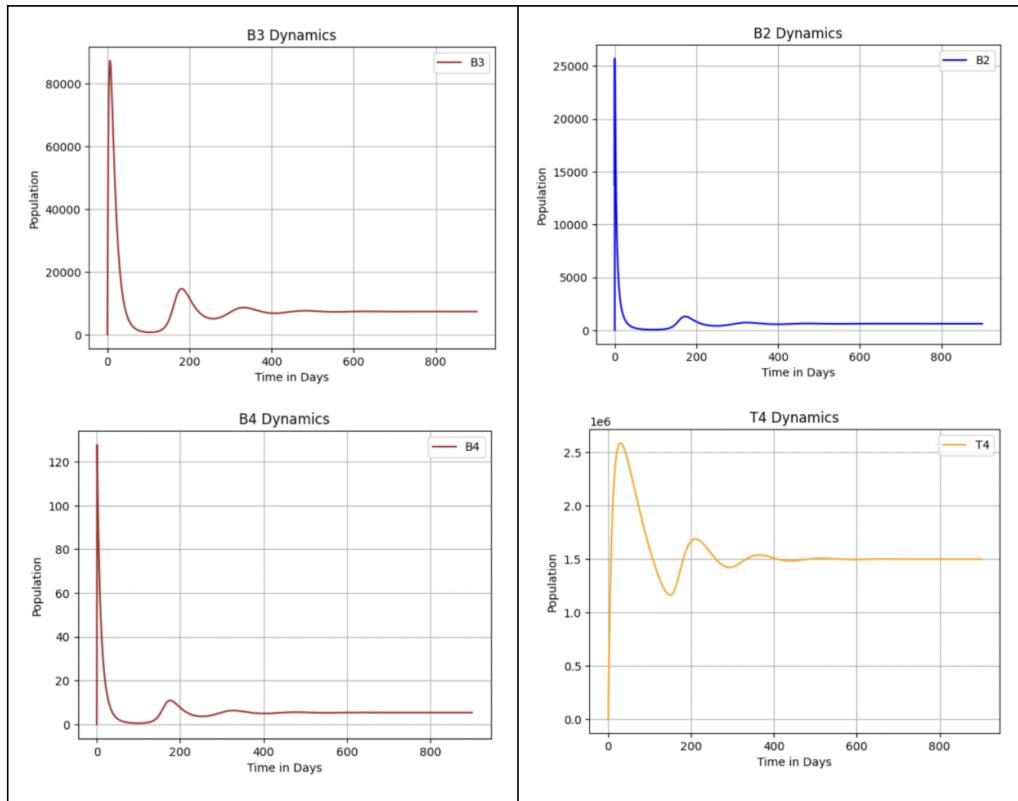


Figure 3.2: EBV Dynamics for Individual Compartments.

Upon introduction of the virus, the model exhibits a rapid escalation in the populations of both latently and lytically infected cells. This phase corresponds to the initial viral invasion and its subsequent replication before the immune response is fully activated.

Consequent to the initial viral proliferation, there is a significant induction of cytotoxic T lymphocytes (CTLs). The model predicts an inverse correlation between the burgeoning CTL populations and the declining numbers of infected cells, illustrating the CTLs' pivotal role in curtailing the infection.

As the acute phase subsides under the pressure of the immune response, the model demonstrates a reduction in lytically infected cells alongside the stabilization of latently infected and memory B cells. This phase mirrors the virus's strategy to evade immune detection by entering a latent state within host cells.

Over time, our model stabilizes into a dynamic equilibrium where the virus persists in a latent form with periodic reactivation. This equilibrium is maintained by a

balance between the immune surveillance mechanisms and the latent viral reservoir, punctuated by low-level oscillations in the populations of CTLs and latently infected cells due to episodic viral reactivation.

The model occasionally predicts spikes in lytic activity, indicative of the viral reactivation events that are clinically observed as intermittent episodes of viral shedding or symptomatic resurgence. The lytic activity is also effectively controlled by the T cell response and brought back down to low concentrations.

3.2 T Cell Exhaustion

T cell exhaustion is a state of T cell dysfunction that arises during chronic viral infections, characterized by the progressive loss of T cell effector functions. T cell exhaustion typically develops under conditions of persistent antigen exposure, as seen in chronic viral infections. Continuous exposure to antigens without effective clearance leads to T cell receptor signaling alterations that promote exhaustion. [11]

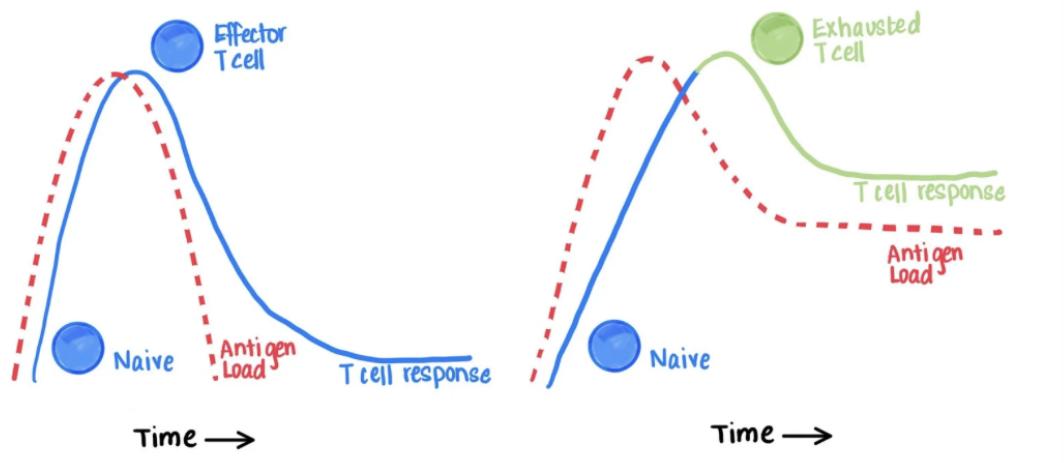


Figure 3.3: Chronic exposure to infections leads to exhaustion of T Cells.

This study attempts to assess the impact of exhaustion of CD8+ T cells on the rate of lytic EBV reactivation in MS patient B cells. To do so, we model and analyze the dynamics between the functional status of CD8+ T cells and the activity of lytically infected EBV cells. Specifically, we delineate how varying the rate of T cell exhaustion influences the concentration of lytically infected B cells, causing MS progression.

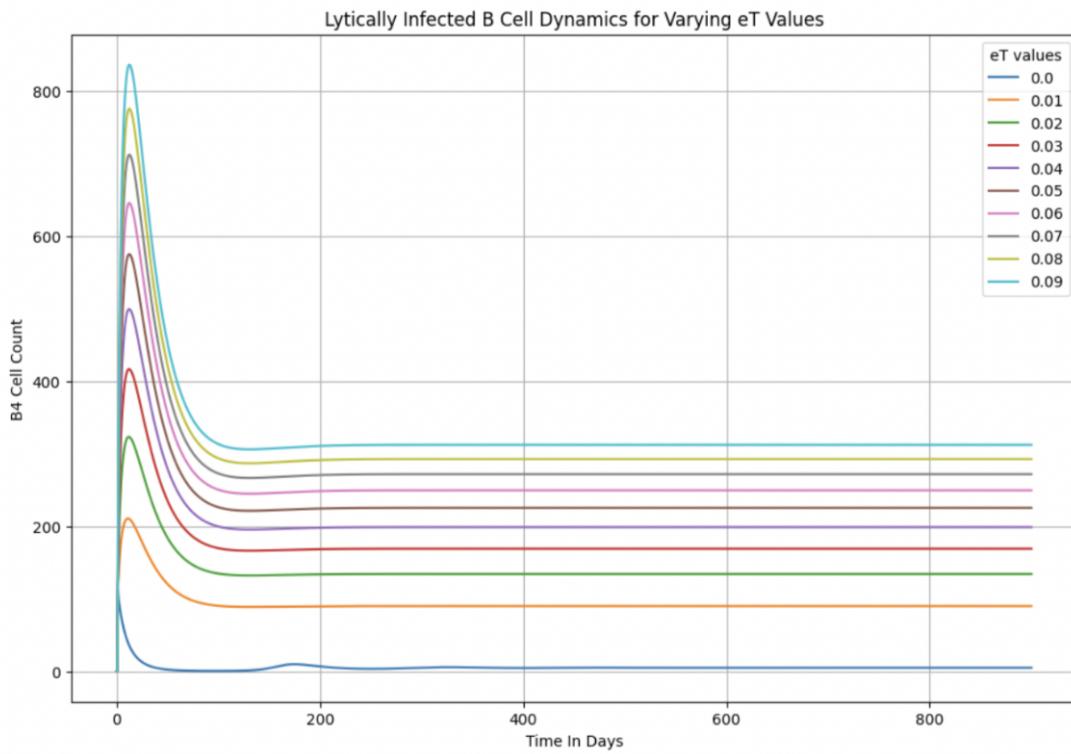


Figure 3.4: Lytic Infection Peaks for varying T Cell Exhaustion Rates

We vary the parameter value eT and observe the change in lytic infection in B cell. The immune response changes markedly in the presence of increasing T cell exhaustion. The model illustrates that when the functionality of T cells is compromised, there's a stabilization of lytically infected B cells at higher levels. This stabilization does not revert to the minimal levels observed in healthy individuals, suggesting a persistent and uncontrolled viral activity.

The differential exhaustion of T4 cells led to several distinct outcomes in the modeled host-virus interaction. The exhaustion of CTLs responsible for controlling lytically infected B cells resulted in these cells stabilizing at higher levels than typically observed with an intact immune response. This persistent elevation reflects an impaired ability of the immune system to clear lytic infections, thereby facilitating sustained viral activity and shedding.

Due to the higher levels of lytically infected cells, our model predicts prolonged periods of viral shedding. This increase in viral activity likely raises the risk of transmission and could contribute to more severe episodes of reactivation, characteristic of compromised lytic phase control.

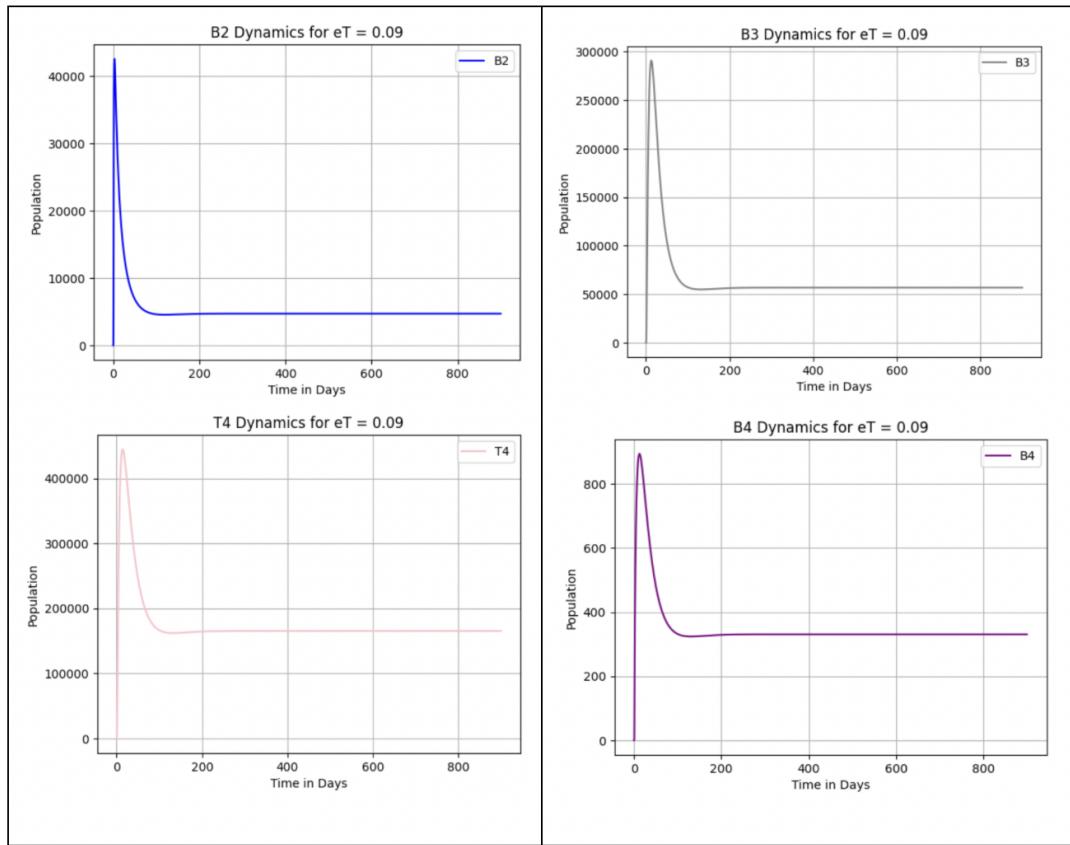


Figure 3.5: Individual Compartment Dynamics after T Cell Exhaustion

Although the exhaustion was restricted to CTLs against lytically infected cells, the increased burden of active viral replication might indirectly affect the overall efficacy of the immune system, including the function of CTLs targeting latent infections. In the immune system, resources such as cytokines and effector cells are often allocated based on the perceived threat. If CTLs targeting lytically infected cells are exhausted and unable to control the lytic phase effectively, this could lead to an overall increased viral load and immune system distraction, potentially reducing the effectiveness of the immune response against latently infected cells indirectly.

We can conclude that T Cell exhaustion gives rise to uncontrolled viral activity in the body. This uncontrolled viral activity can potentially cause EBV-infected autoreactive B cells to accumulate in the CNS which initiate an autoimmune response against the myelin sheath, contributing to the pathogenesis of MS.

3.3 Stability Analysis

Stability analysis in dynamical systems is a method used to determine the behavior of a system near its equilibrium points over time. We use this analysis for understanding how our system's long term behaviour responds to changes in parameter values, specifically change in rate of exhaustion of T cells.

To conduct stability analysis, we start by identifying fixed points of the system. Fixed points of an ODE are solutions where the system does not change. In the context of EBV dynamics, these points could represent disease-free states, endemic states, or other possible persistent states of the system. The first step is to solve for these points by setting the rate of change of all variables in the ODE system to zero and solving the resulting system of equations (i.e, the nullclines).

$$\begin{aligned}
 d_1(B_0 - B_1) - \mu_{EB}V_E B_1 - \mu_{VB}V_B B_1 &= 0 \\
 \rho(\mu_{EB}V_E B_1 + \mu_{VB}V_B B_1) - (d_2 + c)B_2 - k_2 B_2 T_2 &= 0 \\
 cB_2 + rB_3 - srB_3 &= 0 \\
 rB_3 - d_4 B_4 - k_4 B_4 T_4 &= 0 \\
 d_e(E_0 - E_1) - \mu_{EB}V_E E_1 - \mu_{VE}V_E E_1 &= 0 \\
 \mu_{EB}V_E E_1 + \mu_{VE}V_E E_1 - (d_e + \gamma)E_4 - k_4 E_4 T_4 &= 0 \\
 nd_4 B_4 - d_v V_B &= 0 \\
 n\gamma E_4 - d_v V_E &= 0 \\
 \phi_2 T_1 w(B_2) + \theta_2 T_2 w(B_2) - \delta T_2 &= 0 \\
 \phi_4 T_1 w(B_4 + E_4) + \theta_4 T_4 w(B_4 + E_4) - \delta T_4 - e T_4 &= 0 \\
 e T_4 - \delta_{exh} T_{4exh} &= 0
 \end{aligned}$$

B1: 99994986392.68452, B2: 593.8768998803637, B3: 7154.230178660359, B4: 4.973432346073526, E1: 999544.4023148816, E4: 0.6354827488876893, VB: 2486.6648804223905, VE: 228.76955517725483, T2: 74030368.21944639, T4: 1567936.0206942908,	B1: 99641529016.33757, B2: 4584.679233113551, B3: 55237.09919427245, B4: 312.0219358722804, E1: 968330.2638938098, E4: 356.75438121566526, VB: 15601.9679352992, VE: 1284.5772388899, T2: 68583862.53388, T4: 190289.08136063901,
i) Fixed points for a healthy immune response.	ii) Fixed points for exhausted T Cell Immune Response

Figure 3.6: Fixed points for each system.

Once fixed points are identified, we analyze their stability through linearization. We approximate the system near each fixed point using the Jacobian matrix of partial derivatives.

$$\begin{bmatrix} -VB\mu Bb - VE\mu Eb - d_1 & 0 & 0 & 0 \\ \rho(VB\mu Bb + VE\mu Eb) & -T_2 k_2 - c - d_2 & 0 & 0 \\ 0 & 0 & r & -rs + r \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -T_4 k_4 - d_4 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & d_{4n} \\ 0 & 0 & 0 & 0 \\ 0 & -\frac{1.0 \cdot 10^{-6} B_i T \phi_i}{(1.0 \cdot 10^{-6} B_i + 1)} - \frac{1.0 \cdot 10^{-6} B_i T \theta_i}{(1.0 \cdot 10^{-6} B_i + 1)} + \frac{T \phi_i}{B_i + 100000.0} + \frac{T \theta_i}{B_i + 100000.0} & 0 & 0 \\ 0 & 0 & -\frac{1.0 \cdot 10^{-6} T \phi_i (B_i + E_i)}{(1.0 \cdot 10^{-6} B_i + 1.0 \cdot 10^{-6} E_i + 1)} + \frac{T \phi_i}{B_i + E_i + 100000.0} - \frac{1.0 \cdot 10^{-6} T \theta_i (B_i + E_i)}{(1.0 \cdot 10^{-6} B_i + 1.0 \cdot 10^{-6} E_i + 1)} + \frac{T \theta_i}{B_i + E_i + 100000.0} & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

$$\begin{bmatrix} 0 & 0 & -B_1 \mu Bb & -B_1 \mu Eb & 0 & 0 \\ 0 & 0 & B_1 \mu Bb \rho & B_1 \mu Eb \rho & -B_2 k_2 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -E_1 \mu Be & -E_1 \mu Ee & 0 & -B_4 k_4 \\ 0 & 0 & E_1 \mu Be & E_1 \mu Ee & 0 & 0 \\ 0 & \gamma n & -dv & 0 & 0 & -E_4 k_4 \\ 0 & 0 & 0 & -dv & 0 & 0 \\ 0 & -\frac{1.0 \cdot 10^{-6} T \phi_i (B_i + E_i)}{(1.0 \cdot 10^{-6} B_i + 1.0 \cdot 10^{-6} E_i + 1)} + \frac{T \phi_i}{B_i + E_i + 100000.0} - \frac{1.0 \cdot 10^{-6} T \theta_i (B_i + E_i)}{(1.0 \cdot 10^{-6} B_i + 1.0 \cdot 10^{-6} E_i + 1)} + \frac{T \theta_i}{B_i + E_i + 100000.0} & 0 & B_i + 100000.0 - \delta \\ 0 & 0 & 0 & 0 & -\delta + \frac{\theta_i (B_i + E_i)}{eT} & 0 \\ 0 & 0 & 0 & 0 & 0 & -\delta_{exh} \end{bmatrix}$$

Figure 3.7: Jacobian Matrix for our Dynamical System.

Next, we calculate the eigenvalues of the Jacobian matrix evaluated at the fixed points. Based on the eigenvalue analysis, fixed points can be categorized into several types, which describe the behavior of the system around these points

$\{-2.8142344266319 - 1.74542628337312e-68*I: 1,$ $-0.119486840936789 - 6.28142303899835e-69*I: 1,$ $-0.119405954516285 - 4.53358248611309e-69*I: 1,$ $-0.000636712329157764 - 0.000433897795434614*I: 1,$ $-0.000636712329157764 + 0.000433897795434614*I: 1,$ $-0.000166672759851864 - 1.42492023893324e-8*I: 1,$ $-0.000166672759851864 + 1.42492023893324e-8*I: 1,$ $-0.00025234246699110: 1,$ $-6.84301169875584e-6: 1,$ $-1.55920155780961e-6: 1\}$	$\{-16.0410723449031: 1,$ $-0.0225756818567185: 1,$ $-0.0214504329776486: 1,$ $0.000434007134533756: 1,$ $-0.00204256766557453 - 0.000826077351839931*I: 1,$ $-0.00204256766557453 + 0.000826077351839931*I: 1,$ $-0.000438030953432003 - 0.00164551536604681*I: 1,$ $-0.000438030953432003 + 0.00164551536604681*I: 1,$ $0.000874493905277497 - 0.000860033363625866*I: 1,$ $0.000874493905277497 + 0.000860033363625866*I: 1,$ $-6.41025641025641e-6: 1\}$
Eigenvalues for healthy immune response.	Eigenvalues for exhausted T cell response.

Figure 3.8: Eigenvalues of Jacobian Matrix.

The Jacobian evaluated at fixed points for a healthy immune response showed predominantly negative complex eigenvalues, indicating that the system typically exhibits damped oscillations. This means infection tends to reactivate but is controlled effectively by the immune system. Moreover, under any perturbation, the system will tend to return back to those stable points (of low concentration of infection).

For an exhausted T cell response, we get a pair of positive complex eigenvalues, which means the system is unstable in those directions. Specifically, for around eT

0.01, we see a Hopf bifurcation has occurred when a pair of complex conjugate eigenvalues of the Jacobian matrix of the system crosses the imaginary axis from the left to the right as a parameter is varied, changing from having negative real parts (indicating stability) to positive real parts (indicating instability).

The occurrence of a Hopf bifurcation in the model under conditions of T cell exhaustion implies a critical shift in system behavior. For individuals with T cell exhaustion, any perturbation could potentially destabilize the equilibrium, leading to significant spikes in infection levels.

From this we generate a hypothesis that environmental or biological triggers can destabilise infection in people with T cell exhaustion and this instability and subsequent rise in infection levels can contribute to the pathogenesis of MS.

Chapter 4

Acute Infectious Mononucleosis, Age and MS

Epidemiology studies associate the development of MS with acute mononucleosis in adolescence or young adulthood. [12] A plausible theory could be that during IM, the immune system might erroneously recognize CNS components as viral elements similar to those of EBV, thus launching an inappropriate autoimmune response. [8] To explore this hypothesis further, we try to integrate the factor of age into our EBV model. This adjustment allows us to simulate the immune response typical of IM for increasing age and assess any emerging patterns that might link to the development of MS. Through this modeling approach, we aimed to uncover potential connections between the vigorous immune responses in IM and the pathogenesis of MS.

The diversity and complexity of the pre-existing memory B-cell and T-cell repertoire can evolve with age. Adolescents infected with EBV are likely to mobilize a significant number of cross-reactive memory B and T cells that were previously developed in response to other viral infections. These cross-reactive T-cell responses can be activated more rapidly, yet they might be less effective at managing the infection compared to the primary responses from naive T cells. [13]

In this section, we use Giao Hyunh's model incorporating critical immune system features relevant to infectious mononucleosis such as the dynamics of specific and cross-reactive responses from both antibodies and T cells. The model systematically tracks the populations of viruses, infected B cells, epithelial cells, specific CD8+ T cells, and cross-reactive CD8+ T cells as they interact during the course of infection. [10]

4.1 The Model

$$\begin{aligned}
\frac{dB_1}{dt} &= d_1(B_0 - B_1) - f(a)\mu_{EB}V_E B_1 - f(a)\mu_{VB}V_B B_1 \\
\frac{dB_2}{dt} &= \rho(f(a)\mu_{EB}V_E B_1 + f(a)\mu_{VB}V_B B_1) - (d_2 + c)B_2 - k_2 B_2 T_2 - \chi_2 k_2 B_2 T_{2c} \\
\frac{dB_3}{dt} &= cB_2 + rB_3 - srB_3 \\
\frac{dB_4}{dt} &= rB_3 - d_4 B_4 - k_4 B_4 T_4 - \chi_4 k_4 B_4 T_{4c} \\
\frac{dE_1}{dt} &= d_e(E_0 - E_1) - h(a)\mu_{EB}V_E E_1 - h(a)\mu_{VE}V_E E_1 \\
\frac{dE_4}{dt} &= h(a)\mu_{EB}V_E E_1 + h(a)\mu_{VE}V_E E_1 - (d_e + \gamma)E_4 - k_4 E_4 T_4 - \chi_4 k_4 E_4 T_{4c} \\
\frac{dV_B}{dt} &= nd_4 B_4 - d_v V_B \\
\frac{dV_E}{dt} &= n\gamma E_4 - d_v V_E \\
\frac{dT_2}{dt} &= (1 - \sigma_2)\phi_2 T_N w(B_2) + \theta_2 T_2 w(B_2) - \delta T_2 \\
\frac{dT_{2c}}{dt} &= \sigma_2 m \phi_2 T_M w(B_2) + m \theta_2 T_2 w(B_2) - m \delta T_2 \\
\frac{dT_4}{dt} &= (1 - \sigma_4)\phi_4 T_N w(B_4 + E_4) + \theta_4 T_4 w(B_4 + E_4) - \delta T_4 \\
\frac{dT_{4c}}{dt} &= \sigma_4 m \phi_4 T_M w(B_4 + E_4) + m \theta_4 T_4 w(B_4 + E_4) - m \delta T_4
\end{aligned} \tag{4.1}$$

In this model, χ_j (where $j = 2$ or 4) ranges from 0 to 1 and quantifies how effectively cross-reactive T cells can eliminate infected cells relative to specific T cells. Lower values of χ_j indicate that cross-reactive T cells are less effective at killing infected cells.

The functions f and h represent the modulating effects of antibodies on the infection dynamics of B cells and epithelial cells, respectively. These functions are integral parameters in the equations governing cell-specific infections. Observations suggest that antibodies against viral glycoproteins can impede the infection of B cells while facilitating the infection of epithelial cells.[\[14\]](#) In the absence of antibody effects, both f and h are set to 1. When antibody effects are present, f decreases to reflect reduced infection efficiency in B cells, while h increases, indicating enhanced infection efficiency in epithelial cells. The forms of $f(a)$ and $h(a)$ are modeled using Hill functions:

$$f(a) = 1 - \frac{a^2}{A^2 + a^2},$$

$$h(a) = 1 + \frac{\lambda a^2}{A^2 + a^2}.$$

where a quantifies the strength of the antibody, with λ representing the peak impact of antibodies on epithelial cell infection and A denoting the level of antibody effect that yields half-maximal infection efficiency changes. As a increases, $f(a)$ declines and $h(a)$ rises until reaching a saturation point, implying a threshold level of antibodies necessary for significant modulation of infection in both cell types. [14][15]

Regarding the CTL response, the model differentiates between specific responses to latent (T_2) and lytic (T_4) infections from naive T cells, and cross-reactive responses (T_{2c} and T_{4c}) from memory T cells. Both naïve and memory T cell populations, T_N and T_M , are assumed constant. Upon exposure to viral antigens, naïve T cells become effector cells targeting latent or lytic infections at rates $(1 - \sigma_2)\phi_2$ and $(1 - \sigma_4)\phi_4$, respectively, where σ_j denotes the proportion of the cross-reactive T cell response. These effector cells can proliferate at rates θ_2 and θ_4 when stimulated by antigens from infected cells.

Cross-reactive responses are initiated from the memory T cell pool at rates $\sigma_j\phi_j$, with $m \geq 1$ indicating a faster activation from memory compared to naive T cells. These cross-reactive T cells, while able to respond and proliferate swiftly, have a shorter lifespan (scaled by m), reflecting observations that memory cells exhibit rapid response but increased susceptibility to apoptosis. [16]

The remaining state variables and parameters are consistent with those described in the previous model.

4.2 Results

The results show that cross-reactive immune responses, though activated more rapidly, lack the specificity required to sustain effective viral suppression. This rapid activation fails to control the viral load efficiently, leading to heightened infection peaks.

The infection peaks, encompassing both latent and lytic phases, are significantly higher compared to those observed in models simulating a healthy immune response (Fig 4.1). This not only reflects the characteristic symptoms of infectious mononucleosis but also underscores the inadequacy of the cross-reactive immune response in controlling the infection.

The model also reveals that T cell concentrations stabilize at higher levels than typically observed in a healthy scenario (Fig 4.2). This stabilization at elevated levels, highlights the persistent struggle to control the infection effectively.

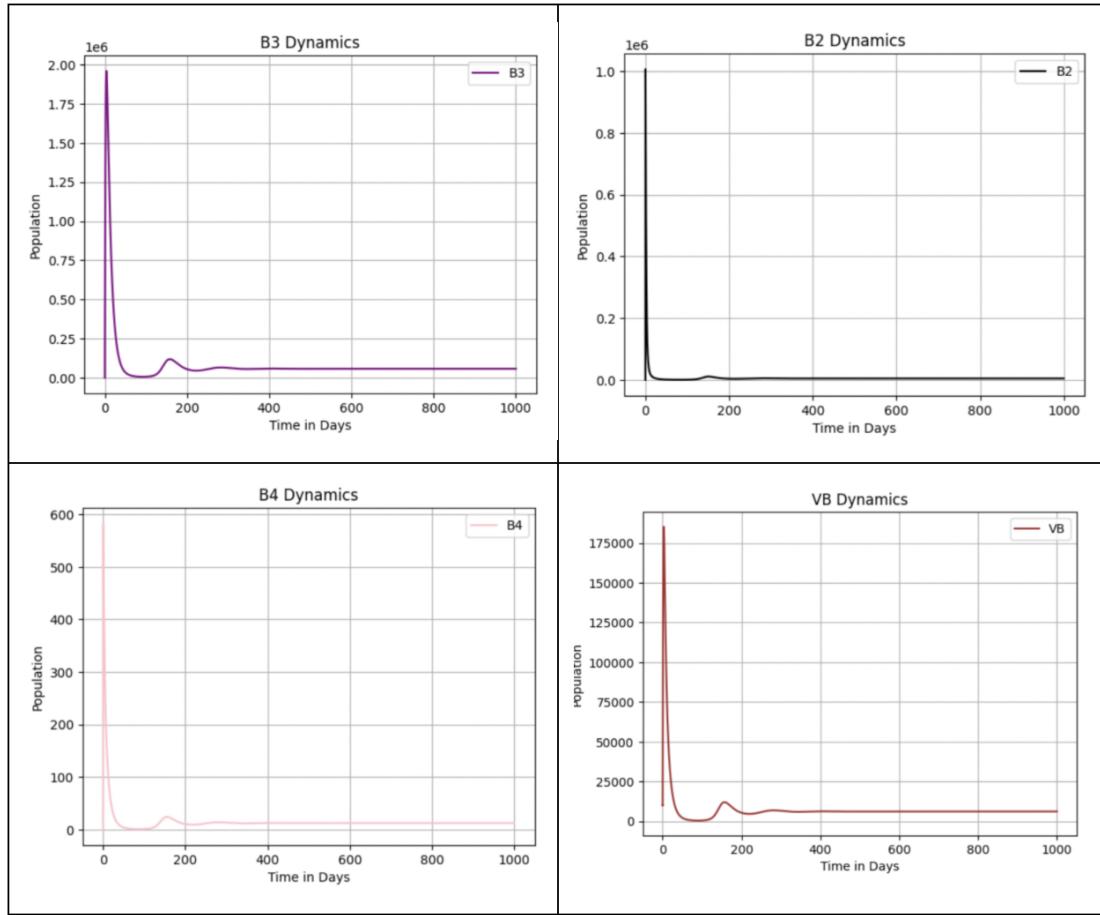


Figure 4.1: B Cell Response for $\sigma_j = 0.5$ and $\chi_j = 0.5$.

An increase in the effects of antibodies (Fig. 4.3) correlates with an escalation in infection peaks. This suggests that while antibodies are responsive, their influence may exacerbate the peak viral loads during acute phases of the infection.

As the parameter sigma (Fig. 4.4), which represents the strength of the cross-reactive T cell response, increases, we observe a corresponding rise in both latent and lytic infection peaks. This indicates that stronger cross-reactive responses, despite their swiftness, do not effectively manage the infection but rather contribute to its severity.

We find that during the course of IM, there is a pronounced immune response, particularly characterized by the activation of cytotoxic T cells in order to control the proliferation of B cells infected by the EBV. However, this intense immune activation may extend beyond the specific target of EBV, potentially leading to the recognition and destruction of similar antigens that are present in the central nervous

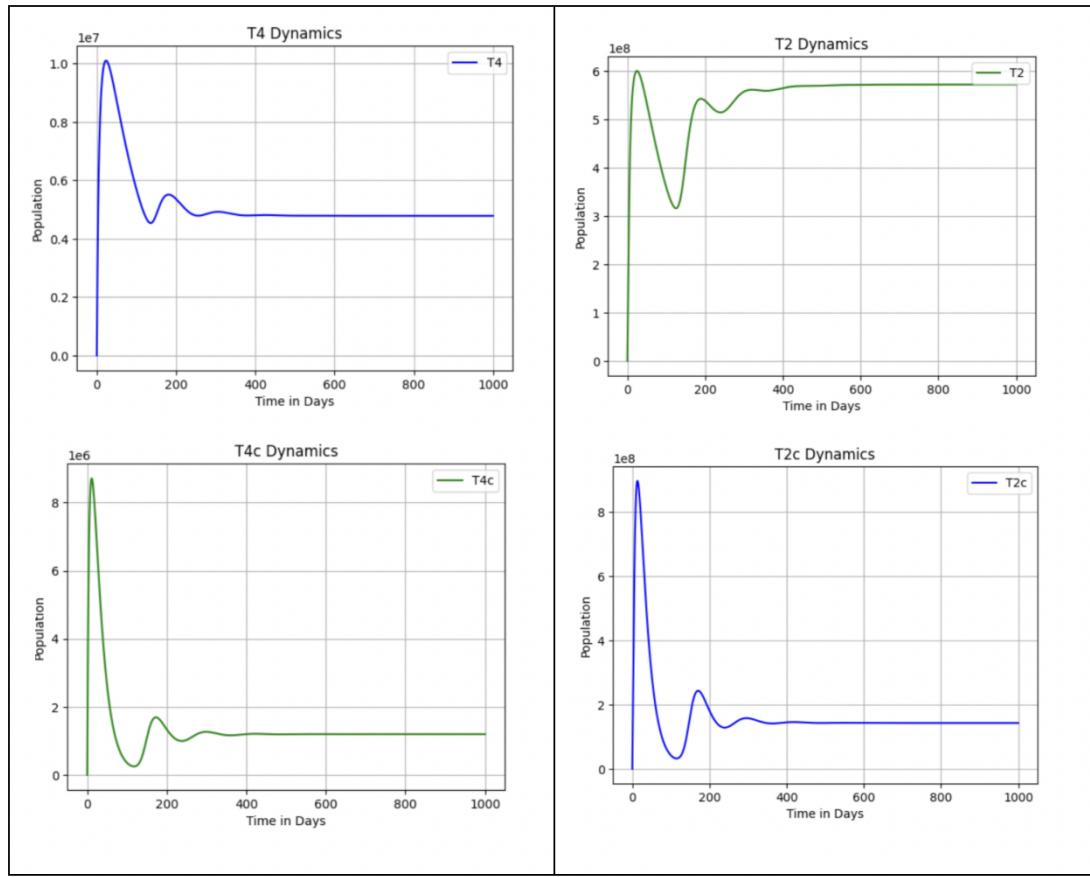


Figure 4.2: T Cell Response for $\sigma_j = 0.5$ and $\chi_j = 0.5$.

system. This phenomenon could inadvertently initiate autoimmune mechanisms that are characteristic of MS.

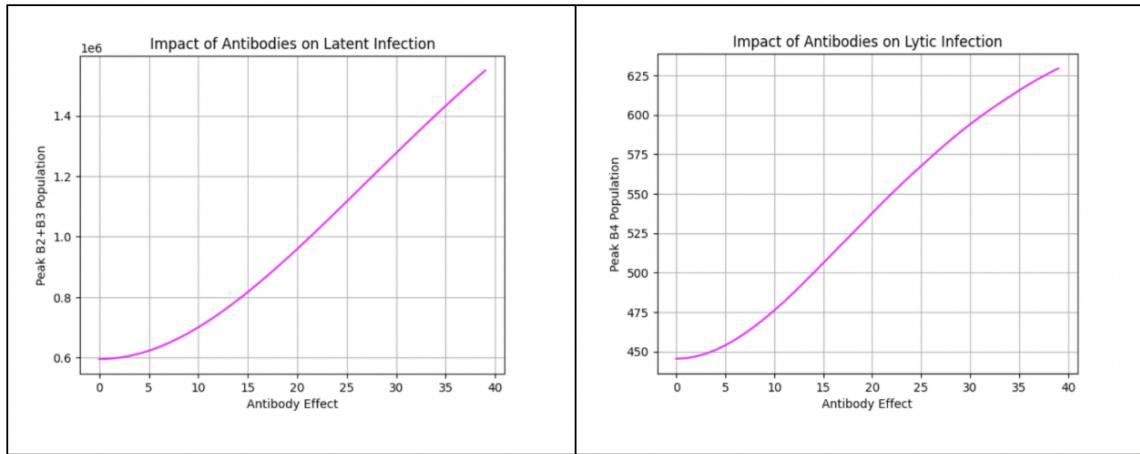


Figure 4.3: Antibody Effect on Infection Peak.

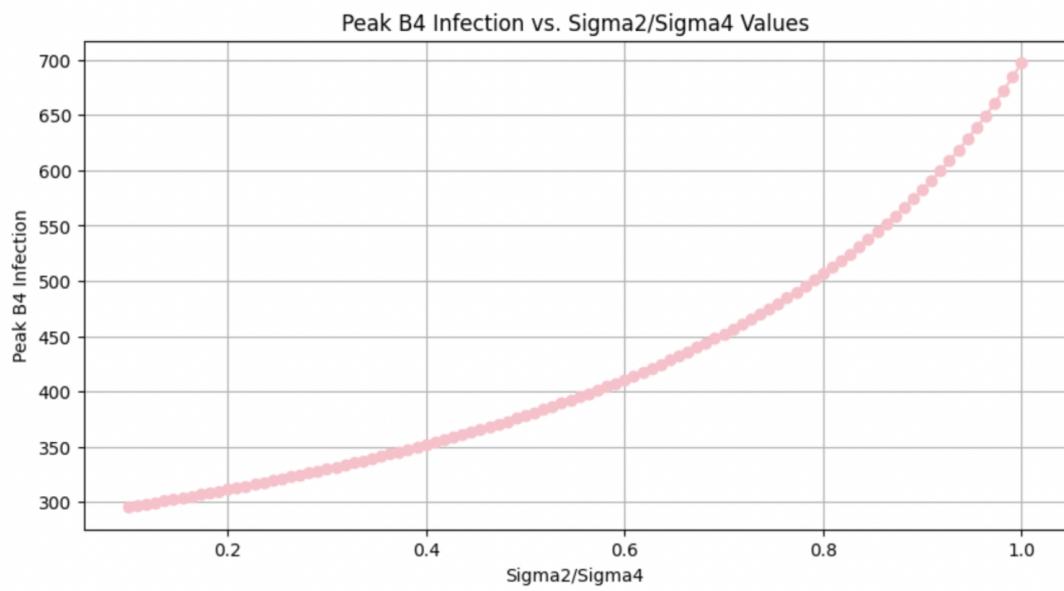


Figure 4.4: Cross Reactive T Cell Response on Infection Peak.

Chapter 5

Discussion

5.1 Conclusion

This thesis has critically explored the complex interactions between EBV infection and the immune system within the framework of a mathematical model, emphasizing the implications for MS development. The adapted model provided an in-depth analysis of the virus's lifecycle, distinguishing between latent and lytic phases, and examined how cytotoxic T lymphocytes and B cells respond to viral antigens.

We mathematically affirm the Pender hypothesis that T Cell exhaustion gives rise to uncontrolled viral activity in the body which can potentially cause EBV-infected autoreactive B cells to accumulate in the CNS and initiate an autoimmune response against the myelin sheath, contributing to the pathogenesis of MS.

Through conducting stability analysis, we generate the hypothesis that under conditions of T cell exhaustion, perturbations could lead to destabilization of the system, potentially leading to increased EBV activity and heightened MS risk. This hypothesis underscores the importance of the balance maintained by the immune system in controlling EBV, and how disruptions in this balance (due to biological or epigenetic triggers), specifically in case of impaired T cell functionality, could precipitate the onset of MS.

Moreover, we show that contracting EBV during adolescence or young adulthood, particularly manifesting as infectious mononucleosis, increases the risk of developing MS later in life. This risk is due to the diversity and complexity of the immune system's memory repertoire, which evolves with age. Specifically, the model highlights how cross-reactive memory T cells, although rapidly mobilized, are often less effective compared to primary responses from naive T cells. This inefficacy may lead to inadequate viral control, contributing to the higher prevalence of MS among those who experience infectious mononucleosis.

5.2 Limitations and Future Directions

One of the primary limitations of this study is the absence of quantitative data to validate the model's predictions. While the theoretical framework offers a conceptual understanding of the disease dynamics, empirical data are crucial for testing the accuracy and reliability of the model. Future research should focus on integrating data from longitudinal studies or controlled experiments. This integration would not only validate the model but also enhance its predictive power by allowing for the calibration of model parameters to reflect real-world dynamics more accurately.

Moreover, the parameters used in our model are based on average responses, which do not account for the significant biological variability between individuals. This variability can influence the progression and outcome of EBV infections and associated diseases. Future models could incorporate stochastic elements or parameter sensitivity analyses to predict a range of possible outcomes. To address inter-individual variability, developing personalized models that can simulate specific immune responses based on individual genetic, immunological, and environmental factors would be a significant advancement. This approach could lead to personalized treatment strategies, particularly for conditions like MS where patient responses to treatments vary widely.

The current model does not include spatial dynamics, which are important in understanding how the virus and immune responses interact within different tissues and compartments of the body. Expanding the model to include spatial dynamics would enable a more detailed examination of the infection at the tissue or organ level. Such models could elucidate how EBV navigates and establishes latency or reactivation within specific cellular microenvironments, offering insights into targeted drug delivery systems or localized treatment approaches.

Future models could also explore the interactions between EBV and environmental triggers, understanding how concurrent factors might influence EBV dynamics and disease outcomes.

Bridging the gap between theoretical models and clinical practice by developing simulation-based tools for clinical decision-making could pave the way for therapeutic interventions aimed at managing or preventing MS.

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