

Dynamics of A Pathogen-Immune Interaction Model

by

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Abstract

A new mathematical model is proposed to describe the interaction between the virus and the immune cells in an HIV infected host. For this new model, we study the existence of non-negative equilibria, bifurcation of equilibria, and stability of equilibria. We also carry out numerical simulations to illustrate all possible dynamics. In addition, we numerically explore drug therapy treatment strategies to find the right regimes for the strengths of the therapy and the duration of the treatment so that sustained immunity can be established.

Dedication

I dedicate this report to my parents, my brothers and sisters who are always there to encourage me with their love, support and prayers.

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Chapter 1

Introduction

An estimated 35 million people are currently infected with the human immunodeficiency virus (HIV), and it has caused 15 million deaths since acquired immunodeficiency syndrome (AIDS) was first recognized in 1981. The human immune response of HIV is a complex and dynamic system, making testing and evolution treatment method challenging. In this report, I study the dynamics of mathematical model of the interaction between the pathogen and the immune system including the effect of treatment. I present an analysis of the existence and stability of equilibria of the model and discuss the effectiveness of treatment at controlling and clearing infections.

A virus is a small parasite that is not capable of reproduction by itself, but must infect a host cell in order to reproduce. An infected host cell can be damaged either by the virus or by the body's immune responses to the virus. The viral load is an important measurement of the severity of a viral

infection and is also an important determinant of the outcome of infection. For example, in HIV-1, virus load is correlated with pathogenicity, disease stages, and progression of disease.

One major component of the human immune system are the lymphocytes. These are a type of large white-blood cell generated by the immune system to defend the body against any foreign and harmful substances such as pathogens or cancerous cells. Lymphocytes normally circulate in the blood, but can be found concentrated in the spleen, tonsils, and lymph nodes [12]. There are three major types of lymphocytes: T-cells, B-cells, and natural killer (NK) cells. Natural killer cells, also known as NK-cells, K-cells, or killer cells, play a major role in defending the host against tumours and viruses. B-cells develop in the bone marrow and they are primarily responsible for humoral immunity. When B-cells are activated, they create antibodies that are specific to a single antigen. T-cells develop in the liver or bone marrow. T cells contain proteins called T-cell receptors. These receptors are able to recognize various types of antigen.

An antigen is foreign substance that is capable of stimulating an immune response, specifically activating lymphocytes. Antigens are often produced by cancer cells or viruses. There are two types of immune responses [14]: humoral immunity and cell mediated immunity. Humoral immunity focuses on identifying antigens prior to cell infection, while cell mediated immunity is an immune response that involves the activation of macrophages and natural killer (NK)-cells, the production of antigen-specific cytotoxic T-lymphocytes,

and the release of various cytokines in response to an antigen. Cytotoxic T lymphocytes (CTL) are another important components of the immune system. They protect against viral infections and some cancers by destroying cells that express foreign antigens on their surface. Most cytotoxic T cells express T-cell receptors (TCRs) that can recognize a specific antigen.

The HIV life cycle [4] proceeds as follows. Free virus in the body, binds to a specific type of CD4 receptor and a co-receptor on the surface of a host CD4 cell. This is similar to a key entering a lock. Once unlocked, HIV can fuse with the CD4 cell and release its genetic material into the cell. A special enzyme called reverse transcriptase changes the genetic material of the virus, so it can be integrated into the host DNA. This new genetic material enters the nucleus of the CD4 cell and uses an enzyme called integrase to integrate itself into own genetic material, where it may hide and stay inactive for several years. When the host cell becomes activated, the virus uses the enzymes to create more of its genetic material along with a more specialized genetic material which allows it make longer proteins. A special enzyme called protease cuts the longer HIV proteins into individual proteins. When these come together with the virus genetic material, a new virus has been assembled. In the final stage of the virus life cycle, known as budding, the virus pushes itself out of the host cell, taking with it part of the membrane of the cell. This part of the cell covers the virus and contains all of the structures necessary to bind to a new CD4 cell and receptors and begin the process again.

An HIV-infected person through three infectious stages [11]. During the first week after inoculation with the virus, large amounts of virus are being produced in the body. The patient develops high viral loads and shows symptoms of a viral infection. At the end of this primary phase, viral load falls again and the clinical symptoms disappear. After the primary phase of HIV infection, the patient enters the second phase which is called an asymptomatic HIV infection or chronic HIV infection. During this phase, HIV reproduces at very low rates, but the virus continues to replicate and the number of healthy cells continues to decline. The average length of the asymptotic period is 10 years. The end of this phase is marked by a rise in the viral load and a drop in the CD4 cell count. The final phase is generally taken to begin when the number of CD4 cells falls below 200 cells per cubic millimeter of blood. Patients in this stage are diagnosed as having AIDS. This stage of infection occurs when the immune system is badly damaged and the patient becomes vulnerable to opportunistic infections.

Mathematical models play a central role in gaining insight into HIV infection dynamics. They are essential to predict how an infection can be managed, reduced, or eradicated. Researchers modelling HIV include the dynamics of drug therapy in order to study how the drugs work to clear an infection.

An early model was proposed by Bonhoeffer [3] and Nowak and May [11] and is now the basis for mathematical studies of HIV dynamics. Their original

model consists of the following system of ordinary differential equations:

$$\frac{dx}{dt} = \lambda - dx - \beta xy, \quad (1.1a)$$

$$\frac{dx^*}{dt} = \beta xy - \delta x^*, \quad (1.1b)$$

$$\frac{dy}{dt} = N\delta x^* - cy. \quad (1.1c)$$

The variables x , x^* and y represent the concentration of healthy CD4⁺ cells, infected cells and free immunodeficiency virus (HIV) at time t , respectively. λ is the recruitment rate of healthy cell, d is the natural death rate of healthy cells, δ is the death rate of infected cells, β is the infection coefficient, N is the burst size, which is defined as the total number of free-virus particles release by each productively infected cell over its lifespan, and c is the clearance rate of free-virus particles. The model has two equilibria. One equilibrium corresponds to the uninfected state with no immune cells. The other equilibrium is an infected state with immune cells.

Since humoral immunity plays an important role in the adaptive immune response to an HIV infection, Kajiwara and Sasaki [7] and Murase *et al.* [10] added the effect of humoral immunity to system (1.1) to obtain the following

system:

$$\frac{dx}{dt} = \lambda - dx - \beta xy, \quad (1.2a)$$

$$\frac{dx^*}{dt} = \beta xy - \delta x^*, \quad (1.2b)$$

$$\frac{dy}{dt} = N\delta x^* - cy - pyz, \quad (1.2c)$$

$$\frac{dz}{dt} = ayz - bz. \quad (1.2d)$$

Here the variables x , x^* , y and parameters λ , d , δ , β , N , c are as before. The variable z represents the concentration of antibodies in humoral immune responses. The term pyz in Equation (1.2c) represents the loss rate of virus under attack by CTLs, and bz represents the natural clearance rate of antibodies. Humoral immunity is stimulated by virus in HIV infection. Therefore, the production rate of antibodies is modelled as ayz .

The model has three equilibria. One equilibrium is the uninfected state., with no immune cells. Another equilibrium is an infected state with immune cells absent. The last equilibrium is an infected state with immune cells present. In November 2011, the laboratory of Nobel laureate Balazs and David Baltimore published encouraging results from humanized mouse studies of an approach to HIV prevention they have named vectored immunoprophylaxis (VIP) [2]. The strategy involves the use of adeno-associated virus (AAV) as a vector to deliver genes that make broadly neutralizing antibodies against HIV after delivery into muscle tissue. Balazs discovered in his experiment that without vectored VIP the antibody response induced by HIV in mice is

so weak that it cannot protect mice from infection at all. Balazs also discovered that full protection from HIV infection in mice results from the effect of immunity induced by VIP. Therefore, in [18] the authors considered the case where the immunity by VIP is much stronger than the humoral immunity induced by HIV. Since the main focus in [18] is studying the effect of antibodies produced by VIP, the immune responses from the CTL immunity produced by infected cell are neglected. The production rate of antibodies ayz in Equation (1.2d) can be removed because the antibodies bind to specific antigen forming cell groups and are then swallowed by phagocytes. Thus, a loss of antibodies at a rate qyz in Equation (1.2d) is included. These changes lead to the following system of differential equations:

$$\frac{dx}{dt} = \lambda - dx - \beta xy, \quad (1.3a)$$

$$\frac{dx^*}{dt} = \beta xy - \delta x^*, \quad (1.3b)$$

$$\frac{dy}{dt} = N\delta x^* - cy - pyz, \quad (1.3c)$$

$$\frac{dz}{dt} = \mu - bz - qyz. \quad (1.3d)$$

It is shown in [18] that the introduction of vectored immunoprophylaxis gives rise to a backward bifurcation, and that ignoring antibodies loss due to their involvement with virus may result in the loss of the backward bifurcation. The model has four equilibria. Three of the equilibria are similar to the previous models. Another occurs with immune cells and no infection. This gives rise to a possible bistability which we will discuss later.

Gilchrist and Sasaki proposed a simpler model [6] which focuses on the interaction between the pathogen and the immune response, but replaces the dynamics of the host cell with a single recruitment term in the pathogen equation.

$$\frac{dy}{dt} = ay - pyz, \quad (1.4a)$$

$$\frac{dz}{dt} = cyz. \quad (1.4b)$$

Here the variables y and z represent the pathogen load and the immune response (lymphocyte density) respectively. The parameter a is the pathogen replication rate. The immune cells proliferate proportionally to the pathogen load (with proportionally constant c). The term pyz describes the loss rate of pathogen under attack of antibodies and p is the killing rate. The solution of $y(t)$ initially increases to a maximum and then declines to zero, while $z(t)$ increases to an asymptotic level.

Andre and Gandon [1] simplified system (1.4) by assuming that the proliferation rate of immune cell is independent of the pathogen load to obtain the following system :

$$\frac{dy}{dt} = ay - pyz, \quad (1.5a)$$

$$\frac{dz}{dt} = \rho z. \quad (1.5b)$$

The solution of $y(t)$ is similar to the previous model, while $z(t)$ grows to

infinity. Andre and Gandon assumed that the growth of the lymphocyte population is exponential at rate ρ . The difference between this model and other models [5, 6] is that Andre and Gandon assumed that the immune response is independent of pathogen density. The assumption comes from the fact that encounters between the immune cells and the antigens stimulate immune cells to proliferate and differentiate into effector cells. Effector cells are engaged actively in making effector B-cells secrete antibody and effector T-cells kill infected cells or help other cells to fight the infection.

Mohtashemi and Levins [9] added the spontaneous productions of specific cell and the decay rate of specific cells. They assumed that immune cells are produced by another compartment proportionally to the pathogen load and they obtain the following system:

$$\frac{dy}{dt} = ay - pyz, \quad (1.6a)$$

$$\frac{dz}{dt} = ky - bz + \mu. \quad (1.6b)$$

Mohtashemi and Levins considered an uninfected individual. Thus, $y(t) = 0$ and $z(t)$ will approach the equilibrium value $\frac{\mu}{b}$. Since Mohtashemi and Levins considered the dynamics within individual infected at time t , then the initial condition for system (1.6) are $z(0) = \frac{\mu}{b}$, $y(0) = y_0 > 0$, where y_0 is the inoculum size. If the threshold condition $a > \frac{p\mu}{b}$ is satisfied, the pathogen free equilibrium $(0, \frac{\mu}{b})$ is unstable and pathogen load will initially increase, then $(y(t), z(t))$ will converge to the positive equilibrium $(\frac{ba}{p} - \mu)^{\frac{1}{k}}$ which

is globally stable. If $a \leq \frac{2\mu}{b}$, then the pathogen load immediately starts decreasing and the infection is completely cleared.

Kostova [8] considered another immune response model that included virus load and effector T cells and memory T cells. Kostova was interested in studying the effect of persistence of viral infection at the population level. Kostova showed that the viral infection can persist even if the population has isolated individuals who are able to clear the virus completely.

Gandolfi and Pugliese [15] proposed a model consisting of two differential equations, one for the pathogen, and another for an index of specific immunity. The model has several different types of behaviours: (i) the specific immune response immediately clears the pathogen, (ii) an acute infection occurs because of the clearance of pathogen through specific immune response, (iii) uncontrolled infection, (iv) acute infection followed by convergence to a stable state of chronic infection, or (v) periodic solution with irregular acute infection.

$$\frac{dy}{dt} = ay - \frac{n_s y}{1 + a_s y} z - \frac{c_u y}{1 + r_u y} M, \quad (1.7a)$$

$$\frac{dz}{dt} = \frac{cy}{1 + \gamma y} z - bz + \mu. \quad (1.7b)$$

Gandolfi and Pugliese assumed that the growth rate of the virus population is proportional to the viral load and that predation of immune cells on pathogens follows a Holling function of the 2nd type [17, page 31]. A similar action is performed by aspecific cells, whose density is a constant M .

They kept the constant recruitment rate and the decay of specific immune cells as in (1.6b). However, they assumed in (1.7) that the self replication of specific immune cells is stimulated by pathogen load, but with a maximum replication rate. They assumed that the growth rate of the virus population saturates when the virus population reaches a very high level.

We will present our new model in the next chapter and study the existence of nonnegative equilibria in Chapter 3. Stability of these equilibria is investigated in Chapter 4. In Chapter 5 we present some numerical simulations to illustrate our results and numerically explore drug therapy strategies to establish sustained immunity. We summarize and discuss our work in the last chapter.

Chapter 2

The Model

Let y denote the virus population size, and z the population size of immune cells. Note that in those aforementioned models (1.4), (1.5), (1.6) and (1.7), the growth rate of the virus is assumed to be proportional to the virus population. In this work, we assume this is true only when the virus population is low. When the virus population becomes large, the growth rate is assumed to saturate. More precisely, we will use the function $\frac{ay}{1+\gamma y}$ to denote the growth rate of the virus. Immune cells are assumed to kill or destroy the virus at the rate pyz . We also assume that the level of immune response, stimulated by pathogen load, is simply proportional to both the viral load and the immune response when the virus load is low, but that the immune response saturates when the virus load is sufficiently high such that there is a maximum replication rate. This is modeled by the function $\frac{cyz}{1+\epsilon y}$. Immune cells are assumed to be inhibited by the virus at a rate qyz . Moreover, we

assume that there is a constant recruitment for immune cells, which can be varied during the drug therapy treatment. These assumptions leads to the following system of ordinary differential equations:

$$\frac{dy}{dt} = \frac{ay}{1 + \gamma y} - pyz, \quad (2.1a)$$

$$\frac{dz}{dt} = \frac{czy}{1 + \epsilon y} - qyz - bz + \mu, \quad (2.1b)$$

with the associated initial condition $(y(0), z(0)) \in \mathbb{R}_+^2$. Here the constants $a, \gamma, p, c, \epsilon, q, b, \mu$ are all positive. Since the partial derivatives of all terms on the right hand sides exist and are continuous for $y > \max\{\frac{-1}{\gamma}, \frac{-1}{\epsilon}\}$ and all z , existence and uniqueness of the solution to System (2.1) for $y(0) \geq 0$ and $z(0) \geq 0$, follows from standard theory of differential equations [13]. Noting that $y(0) = 0, z = z(0)e^{-bt} + \frac{\mu}{b}(1 - e^{-bt})$ is a solution to System (2.1), it follows that if $y(0) > 0$ then $y(t) > 0$ for all t . Since $\frac{dz}{dt} |_{z=0} = \mu > 0$, it follows that if $z(0) > 0$ then $z(t) > t$ for all t .

We use the scale of the time in days, the scale of the the pathgoen and the immune cells as (particles/mL). We also use the following scales of the parameters: $\gamma = (\text{particles/mL})$; $\epsilon = (\text{particles/mL})$; $q, p, c = (\text{particles/mL})^{-1}(\text{day})^{-1}$; $a, b = (\text{day})^{-1}$; and $\mu = (\text{particles/mL})(\text{day})^{-1}$

Chapter 3

Existence of Equilibria

An equilibrium solution for System (2.1) is a constant solution, (y^*, z^*) . Since the solution is constant, $\frac{dy}{dt} = \frac{dz}{dt} = 0$, so

$$\frac{ay}{1 + \gamma y} - pyz = 0, \quad (3.1a)$$

$$\frac{cyz}{1 + \epsilon y} - qyz - bz + \mu = 0. \quad (3.1b)$$

It follows from Equation (3.1a) that either $y = 0$ or $\frac{a}{1 + \gamma y} - pz = 0$. If $y = 0$, then there is a trivial equilibrium $E_0 = (0, \mu/b)$, which is called the pathogen free equilibrium.

If $\frac{a}{1 + \gamma y} - pz = 0$, then

$$z = \frac{a}{p(1 + \gamma y)}. \quad (3.2)$$

Substituting (3.2) into Equation (3.1b) gives

$$F_1(y) = F_2(y), \quad (3.3)$$

where

$$F_1(y) := \frac{\alpha cy}{1 + \epsilon y} \quad (3.4)$$

and

$$F_2(y) := a_0 + b_0 y \quad (3.5)$$

with $\alpha = \frac{a}{p}$, $a_0 = \alpha b - \mu$, $b_0 = \alpha q - \mu\gamma$.

Note that (3.3) yields a quadratic equation of y , which can be solved using the quadratic formula. However, it is rather difficult to determine if the roots of the quadratic equation are nonnegative or not. The graph of $F_1(y)$ is increasing and has a horizontal asymptote, and the graph of $F_2(y)$ is a straight line. We can examine the intersection points of these two curves in the first quadrant, which will give nonnegative roots of (3.3) and thus determine the nonnegative equilibria of (2.1). We have 6 cases to consider depending on the signs of a_0 and b_0 .

Case 1: $a_0 > 0$ and $b_0 > 0$.

Note that $F_1(0) = 0 < a_0 = F_2(0)$ and $\lim_{y \rightarrow \infty} F_1(y) = \frac{\alpha c}{\epsilon} < \lim_{y \rightarrow \infty} F_2(y) = \infty$. Therefore, System (3.1) has exactly one root if and only if the straight line given by $w = F_2(y)$ intersects the curve given by $w = F_1(y)$ tangentially.

This requires (3.3) be satisfied and $F_1'(y) = F_2'(y)$. That is,

$$\frac{\alpha cy}{1 + \epsilon y} = a_0 + b_0 y \quad (3.6)$$

and

$$\frac{\alpha c}{(1 + \epsilon y)^2} = b_0. \quad (3.7)$$

Solving (3.6) and (3.7) for y gives

$$y = \sqrt{\frac{b_0}{\epsilon a_0}} := y^*,$$

which, together with (3.7), yields

$$c = \frac{b_0}{\alpha} \left(1 + \epsilon \sqrt{\frac{b_0}{\epsilon a_0}} \right)^2 := c_0. \quad (3.8)$$

This shows that when $c = c_0$, System (2.1) has 2 equilibria: in addition to the pathogen free equilibrium, there is a unique positive equilibrium, (y^*, z^*) with $y^* = \sqrt{\frac{b_0}{\epsilon a_0}}$ and $z^* = \frac{\alpha}{1 + \gamma y^*}$. If $c > c_0$, then $F_1(y) = \frac{\alpha cy}{1 + \epsilon y} > \frac{\alpha c_0 y}{1 + \epsilon y}$, and hence the line $w = F_2(y)$ and the curve $w = F_1(y)$ have two intersection points. This implies that System (2.1) has 3 equilibria: in addition to the pathogen free equilibrium, there are two positive equilibria, (y_1^*, z_1^*) and (y_2^*, z_2^*) , where

$$y_1^* = \frac{-(b_0 + \epsilon a_0 - \alpha c) + \sqrt{(b_0 + \epsilon a_0 - \alpha c)^2 - 4a_0 b_0 \epsilon}}{2b_0 \epsilon}, \quad (3.9a)$$

$$y_2^* = \frac{-(b_0 + \epsilon a_0 - \alpha c) - \sqrt{(b_0 + \epsilon a_0 - \alpha c)^2 - 4a_0 b_0 \epsilon}}{2b_0 \epsilon}, \quad (3.9b)$$

$$z_i^* = \frac{\alpha}{1 + \gamma y_i^*}, \quad i = 1, 2. \quad (3.9c)$$

If $c < c_0$, then System (2.1) has only one equilibrium which is the pathogen free equilibrium.

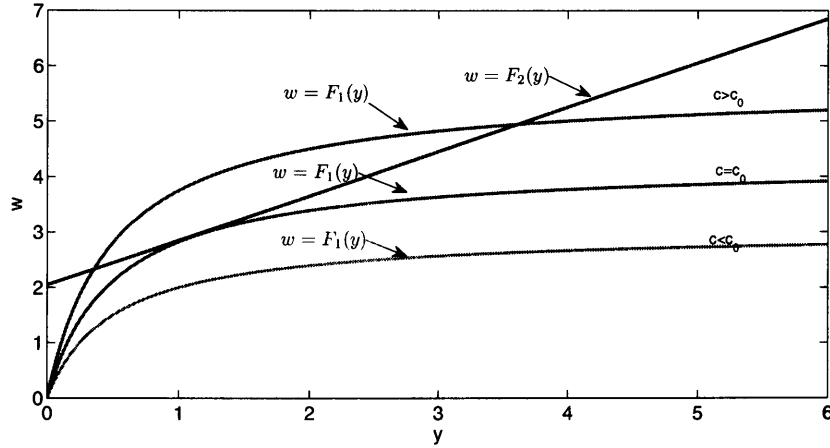


Figure 3.1: The graphs of F_1 and F_2 and the determination of the equilibria of System (2.1) in the case of $a_0 > 0$ and $b_0 > 0$. Parameter values are: $a = 3, b = \frac{3}{10}, \gamma = 1, p = \frac{2}{5}, q = 1, \mu = \frac{1}{5}, \epsilon = 2, c = \frac{3}{2}, \frac{4}{5}, a_0 = \frac{41}{20}, b_0 = \frac{73}{10}$

We can sketch the bifurcation curve in the c - ϵ space. It follows from (3.8) that

$$c = g(\epsilon) = \frac{b_0}{\alpha} \left(1 + \epsilon \sqrt{\frac{b_0}{\epsilon a_0}} \right)^2. \quad (3.10)$$

Equation (3.10) defines the bifurcation curve (see Figure 3.2) on which saddle-node bifurcations occur [16].

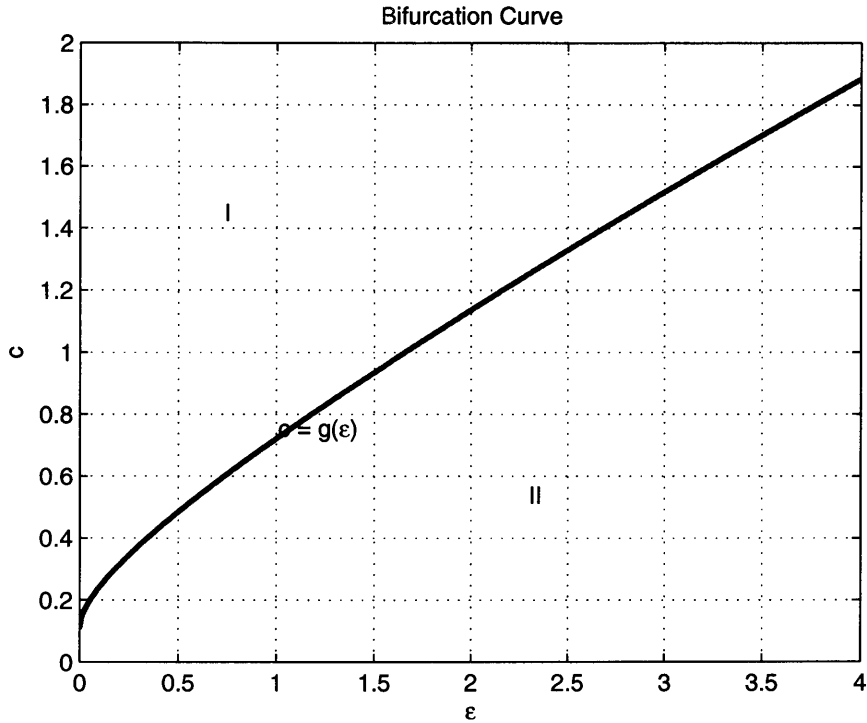


Figure 3.2: The bifurcation curve: In region I (above the curve), System (2.1) has 3 equilibria. In region II (under the curve), System (2.1) has one equilibrium. On the curve given by $c = g(\epsilon)$, System (2.1) has two equilibria. Parameter values are: $a = 3, b = \frac{3}{10}, \gamma = \frac{7}{2}, p = \frac{2}{5}, q = \frac{1}{5}, \mu = \frac{1}{5}$.

We can also sketch the bifurcation curve in the μ - q space. It is difficult to solve for q in terms of μ from Equation (3.8). In order to obtain the bifurcation curve in the μ - q space, we find parametric expressions for μ and

q in terms of y and other parameters. By solving (3.6) and (3.7), we obtain

$$\mu = \alpha b - \frac{\alpha c \epsilon y^2}{(1 + \epsilon y)^2}, \quad (3.11)$$

$$q = \frac{c(1 - \gamma \epsilon y^2)}{(1 + \epsilon y)^2} + \gamma b. \quad (3.12)$$

Together, (3.11) and (3.12) define the bifurcation curve shown in Figure 3.3.

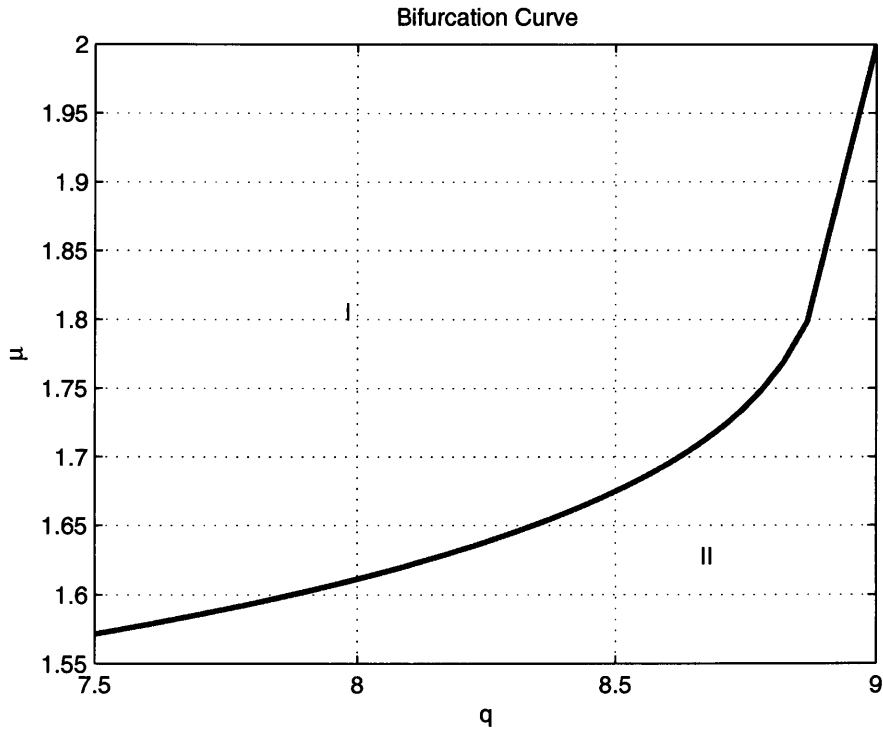


Figure 3.3: The bifurcation curve in the μ - q space: In region I (above the curve), System (2.1) has one equilibrium point. On the curve, System (2.1) has two equilibria. In region II (under the curve), System (2.1) has 3 equilibria. Parameter values are: $a = 4, b = 1, \gamma = 1, \epsilon = \frac{1}{50}, p = 2, c = 8$.

Case 2: $a_0 = 0$ and $b_0 > 0$.

In this case, there is a possibility for the straight line given by $w = F_2(y)$ to intersect the curve given by $w = F_1(y)$ tangentially at $y = 0$. In order for the line to be tangent to the curve, we require

$$\left. \frac{\alpha c}{(1 + \epsilon y)^2} \right|_{y=0} = b_0,$$

i.e

$$\alpha c = b_0$$

Let $b_0^* = \alpha c$, then we have 2 possibilities (see Figure 3.4): (i) If $b_0 \geq b_0^*$, then $F_2(y) = b_0 y > b_0^* y$, and hence the line $w = F_2(y)$ and the curve $w = F_1(y)$ do not intersect. This implies that the pathogen free equilibrium is the only equilibrium of System (2.1). (ii) If $0 < b_0 < b_0^*$, then $F_2(y) = b_0 y < b_0^* y$, and hence the line $w = F_2(y)$ and the curve $w = F_1(y)$ have one intersection point. This implies that System (2.1) has 2 equilibria. In addition to the pathogen free equilibrium, there is a unique positive equilibrium with $y^* = \frac{\alpha c - b_0}{\epsilon b_0}$ and $z^* = \frac{\alpha}{1 + \gamma y^*}$.

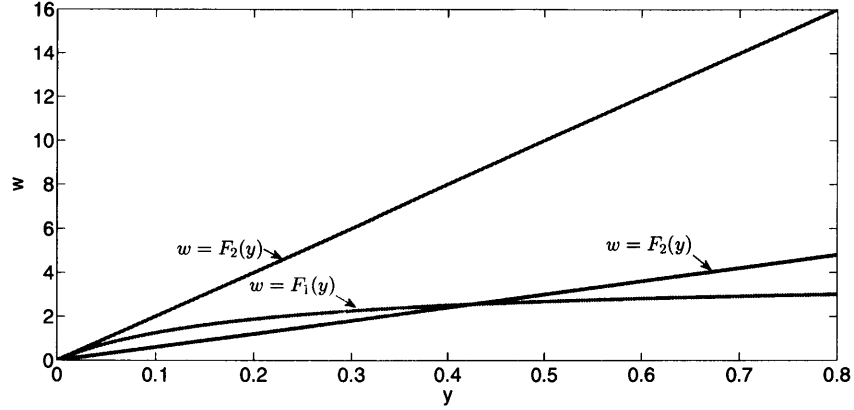


Figure 3.4: The graphs of F_1 and F_2 and the determination of the equilibria of System (2.1) in the case of $a_0 = 0$ and $b_0 > 0$. Parameter values are: $a = 3, b = 1, \gamma = 1, p = 1, q = 1, \mu = 3, q = 2, a_0 = 0, b_0 = 3$.

Case 3: $a_0 < 0$ and $b_0 > 0$.

We need the following lemma in order to prove the existence of the unique positive equilibrium.

Lemma 3.0.1. *Let $G(y) = F_1(y) - F_2(y)$.*

(i) *If $\frac{\alpha c}{b_0} > 1$, then $G(y)$ is increasing for $y \in (0, \bar{y})$ and is decreasing for $y \in (\bar{y}, \infty)$, where $\bar{y} = \frac{1}{\epsilon}(\sqrt{\frac{\alpha c}{b_0}} - 1) > 0$.*

(ii) *If $\frac{\alpha c}{b_0} \leq 1$, then $G(y)$ is decreasing for $y > 0$.*

Proof. Note that $G'(y) = F_1'(y) - F_2'(y) = \frac{\alpha c}{(1+\epsilon y)^2} - b_0$. If $\frac{\alpha c}{b_0} > 1$, then $\bar{y} > 0$ satisfying $G'(\bar{y}) = 0$. Moreover, $G'(y) > 0$ for $y \in (0, \bar{y})$, and $G'(y) < 0$ for $y \in (\bar{y}, \infty)$. If $\frac{\alpha c}{b_0} \leq 1$, then $G'(y) < G'(0) = \alpha c - b_0 \leq 0$ and hence $G(y)$ is decreasing for $y \in (0, \infty)$ and there exists a $y^* \in (0, \bar{y})$ such that $G(y^*) = 0$.

■

In this case, there is a unique positive $y^* \in \{y_1^*, y_2^*\}$ with $y_i^*, i = 1, 2$ given in (3.9a) and (3.9b) (see Figure 3.5). Note that $(b_0 + \epsilon a_0 - \alpha c)^2 - 4a_0 b_0 \epsilon > 0$.

If $b_0 + \epsilon a_0 - \alpha c > 0$, then

$$y^* = \frac{-(b_0 + \epsilon a_0 - \alpha c) + \sqrt{(b_0 + \epsilon a_0 - \alpha c)^2 - 4a_0 b_0 \epsilon}}{2b_0 \epsilon},$$

and

$$z^* = \frac{\alpha}{1 + \gamma y^*}.$$

Similarly if $b_0 + \epsilon a_0 - \alpha c \leq 0$, then clearly

$$y^* = \frac{-(b_0 + \epsilon a_0 - \alpha c) + \sqrt{(b_0 + \epsilon a_0 - \alpha c)^2 - 4a_0 b_0 \epsilon}}{2b_0 \epsilon},$$

and

$$z^* = \frac{\alpha}{1 + \gamma y^*}.$$

Case 4: $a_0 > 0$ and $b_0 = 0$.

In this case, the line given by the graph of $F_2(y)$ is horizontal. There are two possibilities (see Figure 3.6): (i) If $a_0 \geq a_0^* = \frac{\alpha c}{\epsilon}$, then $F_2(y) = a_0 \geq a_0^*$, and hence the line $w = F_2(y)$ and the curve $w = F_1(y)$ have no intersection. This implies that System (2.1) has only one equilibrium, which is the pathogen free equilibrium. (ii) If $0 < a_0 < a_0^*$, then $F_2(y) = a_0 < a_0^*$, and hence the line $w = F_2(y)$ and the curve $w = F_1(y)$ have one intersection point. This implies that System (2.1) has two equilibria: in addition to the pathogen free equilibrium, there is a unique positive solution (y^*, z^*) with $y^* = \frac{a_0}{\epsilon(a_0^* - a_0)}$ and

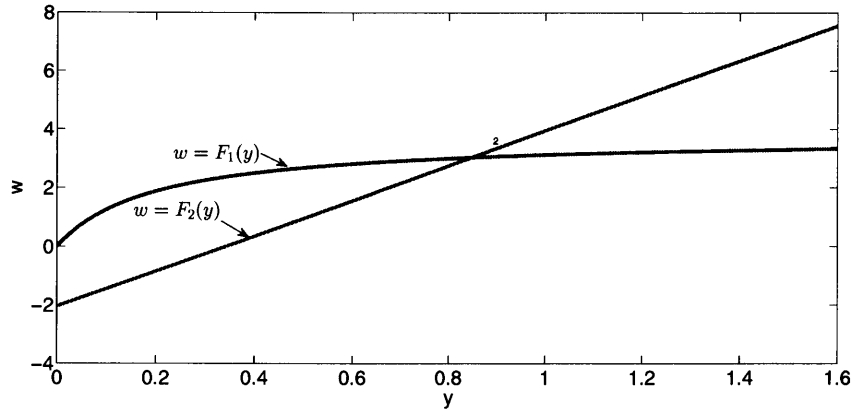


Figure 3.5: The graphs of F_1 and F_2 and the determination of the equilibria of System (2.1) in the case of $a_0 < 0$ and $b_0 > 0$. Parameter values are: $a = 1, b = \frac{1}{3}, \gamma = \frac{15}{2}, p = 2, q = 3, \mu = \frac{1}{5}, a_0 = \frac{-1}{30}, b_0 = \frac{13}{10}$.

$$z^* = \frac{\alpha}{1 + \gamma y^*}.$$

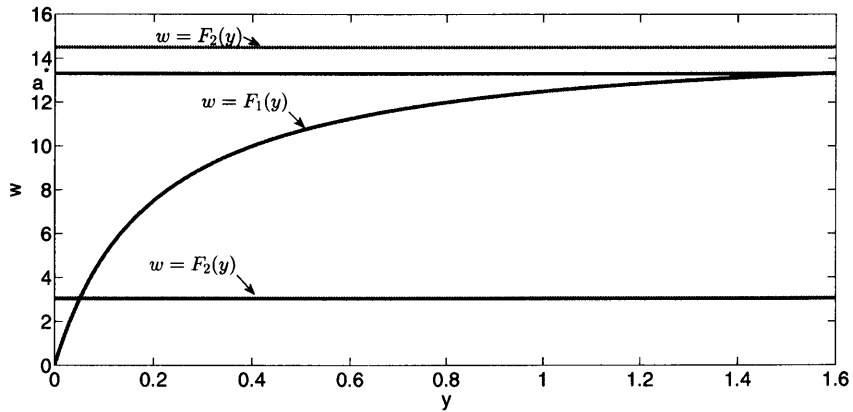


Figure 3.6: The graphs of F_1 and F_2 and the determination of the equilibria of System (2.1) in the case of $a_0 > 0$ and $b_0 = 0$. Parameter values are: $a = 3, p = \frac{141}{125}, c = \frac{5}{2}, \mu = \frac{1}{4}, \epsilon = 5, a_0 = \frac{319}{2000}, b_0 = 0$.

Case 5: $a_0 > 0$ and $b_0 < 0$.

Note that $G'(y) = F_1'(y) - F_2'(y) = \frac{\alpha c}{(1 + \epsilon y)^2} - b_0$. Therefore, in this case,

$G'(y) > 0$ and $G(y)$ is increasing. On the one hand, we note that $G(0) = -a_0 < 0$. On the other hand, $\lim_{y \rightarrow \infty} G(y) = \infty$. Thus, there exists y^* such that $G(y^*) = 0$. That is, Equation (3.3) has a unique positive solution (see Figure 3.7). Note that $(b_0 + \epsilon a_0 - \alpha c)^2 - 4a_0 b_0 \epsilon > 0$. If $b_0 + \epsilon a_0 - \alpha c < 0$, then clearly

$$y^* = \frac{-(b_0 + \epsilon a_0 - \alpha c) - \sqrt{(b_0 + \epsilon a_0 - \alpha c)^2 - 4a_0 b_0 \epsilon}}{2b_0 \epsilon}.$$

Thus System (2.1) has a unique positive equilibrium given by (y^*, z^*) with

$$y^* = \frac{-(b_0 + \epsilon a_0 - \alpha c) - \sqrt{(b_0 + \epsilon a_0 - \alpha c)^2 - 4a_0 b_0 \epsilon}}{2b_0 \epsilon},$$

and

$$z^* = \frac{\alpha}{1 + \gamma y^*}.$$

Case 6: $a_0 \leq 0$ and $b_0 \leq 0$.

In this case, Equation (3.3) has no solution because there is no intersection point between the straight line given by $w = F_2(y)$ and the curve given by $w = F_1(y)$ (see Figures 3.8-3.10). This implies that System (2.1) has only one equilibrium, which is the pathogen free equilibrium.

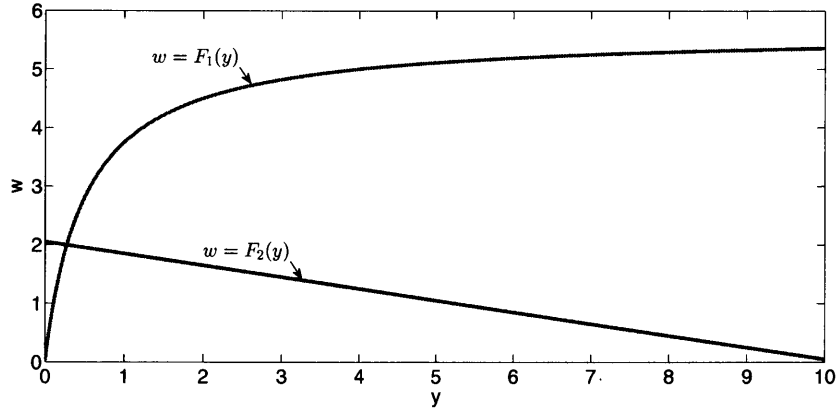


Figure 3.7: The graphs of F_1 and F_2 and the determination of the equilibria of System (2.1) in the case of $a_0 > 0$ and $b_0 < 0$. Parameter values are: $a = 3, b = 1, \gamma = 1, p = 1, q = \frac{1}{2}, \mu = 2, a_0 = 1, b_0 = -\frac{1}{2}$.

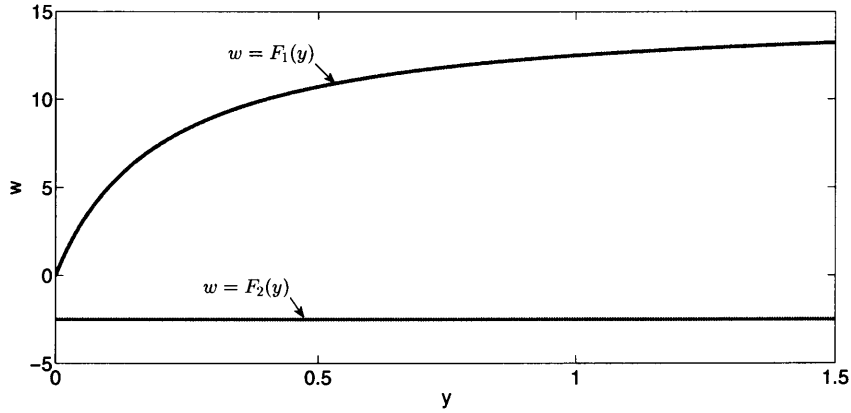


Figure 3.8: The graphs of F_1 and F_2 and the determination of the equilibria of System (2.1) in the case of $a_0 < 0$ and $b_0 = 0$. Parameter values are: $a = 3, b = 1, \gamma = 3, p = 1, q = 4, \mu = 4, a_0 = -1, b_0 = 0$.

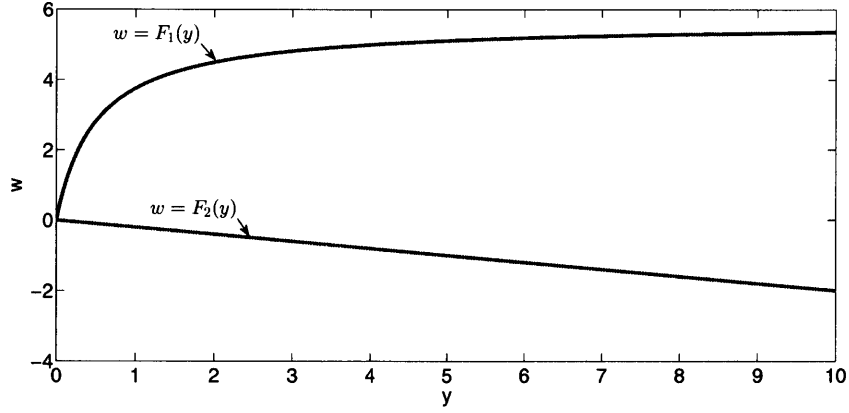


Figure 3.9: The graphs of F_1 and F_2 and the determination of the equilibria of System (2.1) in the case of $a_0 = 0$ and $b_0 < 0$. Parameter values are: $a = 3, b = \frac{1}{2}, \gamma = 1, p = 1, q = \frac{1}{5}, \mu = \frac{3}{2}, a_0 = 0, b_0 = \frac{-9}{10}$.

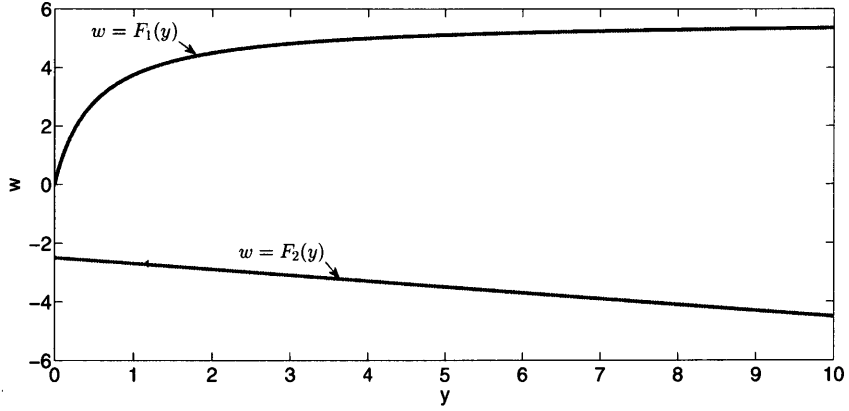


Figure 3.10: The graphs of F_1 and F_2 and the determination of the equilibria of System (2.1) in the case of $a_0 < 0$ and $b_0 < 0$. Parameter values are: $a = 3, \gamma = \frac{17}{2}, p = \frac{2}{5}, q = \frac{1}{5}, \mu = \frac{3}{2}, b = \frac{1}{15}, a_0 = \frac{-1}{4}, b_0 = \frac{-1}{5}$.

Summarizing the above 6 cases, we have our main result on the existence of equilibria for System (2.1).

Theorem 3.0.2. *Consider System (2.1). Let $a_0 = \alpha b - \mu$, $b_0 = q\alpha - \mu\gamma$ and $c_0 = \frac{b_0}{\alpha} \left(1 + \epsilon \sqrt{\frac{b_0}{\epsilon a_0}}\right)^2$. We have the following results:*

(i) *If $a_0 > 0$, $b_0 > 0$ and $c > c_0$, then System (2.1) has 3 equilibria. In addition to the pathogen free equilibrium, there are 2 positive equilibria $E_1^* = (y_1^*, z_1^*)$ and $E_2^* = (y_2^*, z_2^*)$, where*

$$y_1^* = \frac{-(b_0 + \epsilon a_0 - \alpha c) + \sqrt{(b_0 + \epsilon a_0 - \alpha c)^2 - 4a_0 b_0 \epsilon}}{2b_0 \epsilon},$$

$$y_2^* = \frac{-(b_0 + \epsilon a_0 - \alpha c) - \sqrt{(b_0 + \epsilon a_0 - \alpha c)^2 - 4a_0 b_0 \epsilon}}{2b_0 \epsilon},$$

$$z_1^* = \frac{\alpha}{1 + \gamma y_1^*}, \quad z_2^* = \frac{\alpha}{1 + \gamma y_2^*}.$$

(ii) *If $0 < a_0 < a_0^* = \frac{\alpha c}{\epsilon}$, $b_0 = 0$ or $a_0 = 0$, $0 < b_0 < b_0^* = \alpha c$, or $a_0 < 0$, $b_0 > 0$, or $a_0 > 0$, $b_0 < 0$, or $a_0 > 0$, $b_0 > 0$ and $c = c_0$ hold, then System (2.1) has two equilibria. In addition to the pathogen free equilibrium, there is a unique positive equilibrium.*

(iii) *The pathogen free equilibrium $E_0^* = (0, \frac{\mu}{b})$ is the only equilibrium of System (2.1) if $a_0 = 0$, $b_0 > b_0^* = \alpha c$ or $a_0 \geq a_0^* = \frac{\alpha c}{\epsilon}$, $b_0 = 0$, or $a_0 \leq 0$, $b_0 \leq 0$, or $a_0 > 0$, $b_0 > 0$ and $c < c_0$.*

Chapter 4

Stability Analysis

4.1 Local stability of equilibria

The Jacobian matrix of System (2.1) at a general point (y, z) is

$$J = \begin{pmatrix} \frac{a}{(1+\gamma y)^2} - pz & -py \\ \frac{cz}{(1+\epsilon y)^2} - qz & \frac{cy}{1+\epsilon y} - qy - b \end{pmatrix}.$$

At the pathogen free equilibrium $E_0^* = (0, \frac{\mu}{b})$, the Jacobian matrix is

$$J_0 = \begin{pmatrix} a - \frac{p\mu}{b} & 0 \\ \frac{\mu(c-q)}{b} & -b \end{pmatrix}.$$

The eigenvalues are $\lambda_1 = a - \frac{p\mu}{b}$ and $\lambda_2 = -b$. For the system to be locally stable, both eigenvalues must be negative numbers. Hence, we must have

the following conditions on the system parameters: $b > 0$ and $\mu p > ab$. This condition is often represented in terms of the basic reproduction number. The basic reproduction number R_0 [11] is the expected number of secondary cases produced by a single (typical) infection in a completely susceptible population. Computation of R_0 typically involve products of infection rate and duration of infection. In this case, the basic reproduction number is $R_0 = \frac{ab}{p\mu}$. This term can be interpreted as the product of the rate of infection, a , for a single infected individual, and the expected duration of infection period, $b/(p\mu)$. If $R_0 < 1$, then $\lambda_1 = ab(1 - \frac{1}{R_0}) < 0$. Therefore, the pathogen free equilibrium is locally asymptotically stable. If $R_0 > 1$, then $\lambda_1 = ab(1 - \frac{1}{R_0}) > 0$. The pathogen free equilibrium is a saddle point with one dimensional stable manifold and one dimensional unstable manifold.

At a positive equilibrium (y, z) , the Jacobian matrix is

$$J_1 = \begin{pmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{pmatrix},$$

where

$$J_{11} = \frac{a}{(1 + \gamma y)^2} - \frac{p\alpha}{1 + \gamma y} = -\frac{a\gamma y}{(1 + \gamma y)^2},$$

since

$$z = \frac{\alpha}{1 + \gamma y},$$

$$J_{12} = -py,$$

$$J_{21} = \left(\frac{c}{(1 + \epsilon y)^2} - q \right) \frac{\alpha}{1 + \gamma y} = \frac{\alpha c}{(1 + \gamma y)(1 + \epsilon y)^2} - \frac{q\alpha}{1 + \gamma y},$$

and

$$J_{22} = \frac{cy}{1 + \epsilon y} - qy - b = \frac{-\mu}{z} = \frac{-\mu(1 + \gamma y)}{\alpha}.$$

The determinant of J_1 is given by

$$D(J_1) = J_{11}J_{22} - J_{12}J_{21} = \frac{py}{1 + \gamma y} \left[\mu\gamma - q\alpha + \frac{\alpha c}{(1 + \epsilon y)^2} \right]$$

and the trace of J_1 is given by

$$\text{tr}(J_1) = -\frac{a\gamma y}{(1 + \gamma y)^2} - \frac{\mu(1 + \gamma y)}{\alpha} < 0.$$

4.2 Case 1: $a_0 > 0$ and $b_0 > 0$

If $c = c_0$, then there exist 2 equilibria. In addition to the pathogen free equilibrium, there is a unique positive equilibrium (y^*, z^*) and $D_1(y^*) = 0$. In this case, $R_0 > 1$, which means that the pathogen free equilibrium is a saddle point.

If $c > c_0$, then there exist 3 equilibria. In addition to the pathogen free equilibrium, there are 2 positive equilibria $E_1^* = (y_1^*, z_1^*)$ and (y_2^*, z_2^*) with $y_1^* < y^* < y_2^*$. Therefore, $D(y_1^*) > 0$ and $D(y_2^*) < 0$. Thus, (y_1^*, z_1^*) is stable and (y_2^*, z_2^*) is a saddle point. In this case, $R_0 > 1$, which means that the pathogen free equilibrium is a saddle point.

If $c < c_0$, then the pathogen free equilibrium is the only equilibrium for System (2.1). In this case, $R_0 > 1$, which means that the pathogen free equilibrium is a saddle point.

4.3 Case 2: $a_0 = 0$ and $b_0 > 0$

If $0 < b_0 < b_0^* = \alpha c$, then there exist 2 equilibria. In addition to the pathogen free equilibrium, there is a unique positive equilibrium (y^*, z^*) with $y^* = \frac{\alpha c - b_0}{\epsilon b_0}$ and $z^* = \frac{\alpha}{1 + \gamma y^*}$.

Thus,

$$D(y^*) = \gamma\mu - \alpha q + \frac{\alpha c}{(1 + \epsilon y^*)^2} = \frac{b_0^2}{\alpha c} - b_0 = \frac{b_0}{\alpha c} (b_0 - \alpha c) < 0.$$

The trace is negative and the determinant is negative. Therefore, (y^*, z^*) is a saddle point. In this case, $R_0 = 1$, which means that the pathogen free equilibrium is neutrally stable.

If $b_0 \geq b_0^* = \alpha c$, then the pathogen free equilibrium is the only equilibrium point for System (2.1). In this case, $R_0 = 1$, which means that the pathogen free equilibrium is neutrally stable.

4.4 Case 3: $a_0 < 0$ and $b_0 > 0$

In addition to the pathogen free equilibrium, there is a unique positive equilibrium (y^*, z^*) with

$$y^* = \frac{-(b_0 + \epsilon a_0 - \alpha c) + \sqrt{(b_0 + \epsilon a_0 - \alpha c)^2 - 4a_0 b_0 \epsilon}}{2b_0 \epsilon}$$

and

$$z^* = \frac{\alpha}{1 + \gamma y^*}.$$

Thus,

$$D(y^*) = \frac{py^*}{1 + \gamma y^*} \left[\frac{\alpha c}{(1 + \epsilon y^*)^2} - b_0 \right] < 0$$

The trace is negative and the determinant is negative. Therefore, (y^*, z^*) is a saddle point. In this case, $R_0 < 1$, which means that the pathogen free equilibrium is stable.

4.5 Case 4: $a_0 > 0$ and $b_0 = 0$

If $0 < a_0 < a_0^* = \frac{\alpha c}{\epsilon}$, then there exist 2 equilibria. In addition to the pathogen free equilibrium, there is a unique positive equilibrium (y^*, z^*) with

$$y^* = \frac{a_0}{\epsilon(a_0^* - a_0)}, \quad z^* = \frac{\alpha}{1 + \gamma y^*}$$

Thus

$$D(y^*) = \frac{py}{1 + \gamma y^*} \left[\frac{\alpha c}{(1 + \epsilon y^*)^2} \right] > 0.$$

The trace is negative and the determinant is positive. Therefore, (y^*, z^*) is

stable. In this case, $R_0 > 1$, which means that the pathogen free equilibrium is a saddle point. If $a_0 \geq a_0^* = \frac{\alpha c}{\epsilon}$, then the pathogen free equilibrium is the only equilibrium point for System (2.1). In this case, $R_0 > 1$, which means that the pathogen free equilibrium is a saddle point.

4.6 Case 5: $a_0 > 0$ and $b_0 < 0$

In this case, there exist 2 equilibria. In addition to the pathogen free equilibrium, there is a unique positive equilibrium (y^*, z^*) with

$$y^* = \frac{-(b_0 + \epsilon a_0 - \alpha c) - \sqrt{(b_0 + \epsilon a_0 - \alpha c)^2 - 4a_0 b_0 \epsilon}}{2b_0 \epsilon},$$

$$z^* = \frac{\alpha}{1 + \gamma y^*}$$

and

$$D(y^*) = \frac{py}{1 + \gamma y^*} \left[\frac{\alpha c}{(1 + \epsilon y^*)^2} - b_0 \right] > 0.$$

The trace is negative and the determinant is positive. Therefore, (y^*, z^*) is stable. Note that $a_0 > 0$ is equivalent to that $R_0 > 1$. Thus that the pathogen free equilibrium is a saddle point.

4.7 Case 6: $a_0 \leq 0$ and $b_0 \leq 0$

In this case, the pathogen free equilibrium E_0^* is the only equilibrium point for System (2.1). Note that $a_0 \leq 0$ is equivalent to $R_0 \leq 1$. So the pathogen

free equilibrium is stable if $a_0 < 0$ and is neutrally stable if $a_0 = 0$.

4.8 Stability results

Summarizing the above analyses, we have the following results.

Theorem 4.8.1. *Consider System (2.1). Let $a_0 = \alpha b - \mu$ and $b_0 = q\alpha - \mu\gamma$, $c_0 = \frac{b_0}{\alpha} \left(1 + \epsilon \sqrt{\frac{b_0}{\epsilon a_0}}\right)^2$. We have the following results:*

a) *Assume that $a_0 > 0$ and $b_0 > 0$.*

(i) *If $c < c_0$, then the pathogen free equilibrium E_0^* is a saddle point.*

(ii) *If $c = c_0$, then the pathogen free equilibrium E_0^* is a saddle point and the unique positive equilibrium E_1^* is stable.*

(iii) *If $c > c_0$, then the pathogen free equilibrium E_0^* is a saddle point, while E_1^* is stable, and E_2^* is a saddle point.*

b) *Assume $a_0 = 0$ and $b_0 > 0$.*

(i) *If $b_0 \geq b_0^* = \alpha c$, then the pathogen free equilibrium E_0^* is neutrally stable.*

(ii) *If $0 < b_0 < b_0^* = \alpha c$, then the pathogen free equilibrium E_0^* is neutrally stable and the unique positive equilibrium E_1^* is a saddle point.*

c) *Assume $a_0 < 0$ and $b_0 > 0$, then the pathogen free equilibrium E_0^* is stable and the unique positive equilibrium E_1^* is a saddle point.*

d) Assume $a_0 > 0$ and $b_0 = 0$.

(i) If $a_0 \geq a_0^* = \frac{\alpha c}{\epsilon}$, then the pathogen free equilibrium E_0^* is a saddle point.

(ii) If $0 < a_0 < a_0^*$, then the pathogen free equilibrium is a saddle point and the unique positive equilibrium E_1^* is stable.

e) If $a_0 > 0$ and $b_0 < 0$, then the pathogen free equilibrium E_0^* is a saddle point and the unique positive equilibrium E_1^* is stable.

f) If $a_0 \leq 0$ and $b_0 \leq 0$, then the pathogen free equilibrium is either stable or neutrally stable (in the case that $a_0 = 0$).

Chapter 5

Numerical Simulations

In this chapter, we present some numerical simulations to demonstrate our analytical results. We choose different parameter values for each case and we plot the corresponding phase portrait. We will also give the biological interpretation for each case. In the case where the virus population keeps increasing and the population of immune cells keeps declining, we apply various drug therapy strategies to find the right regimes for establishing sustained immunity to control the growth of the virus.

5.1 Possible phase portraits of System (2.1)

We first take the parameter values: $a = 1$, $p = 1$, $\gamma = 2$, $\mu = 1$, $q = 3$, $b = 2$, $c = 8$, $\epsilon = 3$ and $c = 8$. For this set of parameter values, we obtain $a_0 = 1 > 0$, $b_0 = 1 > 0$, $c_0 = 7.41 < c$. Therefore, by Theorem 4.8.1, we know

that there exist three equilibria: $E_0^* = (0, \frac{1}{2})$, $E_1^* = (\frac{1}{3}, \frac{3}{5})$, and $E_2^* = (1, \frac{1}{3})$. Moreover, the pathogen free equilibrium E_0^* is a saddle point, while E_1^* is stable and E_2^* is a saddle point. The phase portrait is depicted in Figure 5.1.

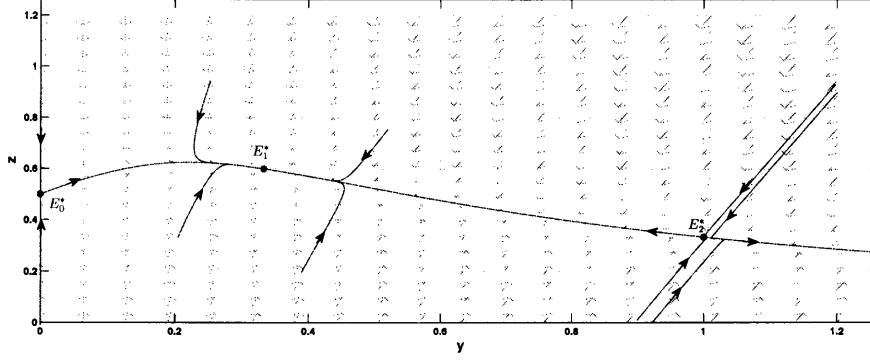


Figure 5.1: The phase portrait of System (2.1) with $a = 1$, $p = 1$, $\gamma = 2$, $\mu = 1$, $q = 3$, $b = 2$, $c = 8$ and $\epsilon = 3$.

We take the parameter values: $a = 1$, $p = 1$, $\gamma = 2$, $\mu = 1$, $q = 3$, $b = 2$, $\epsilon = 3$ and $c = 7$. For this set of parameter values, we obtain $a_0 = 1 > 0$, $b_0 = 1 > 0$, $c = 7 < c_0 = 7.41$. Therefore, by Theorem 4.8.1, we know that there exists one equilibrium which is the pathogen free equilibrium: $E_0^* = (0, \frac{1}{2})$. Moreover, the pathogen free equilibrium E_0^* is a saddle point. The phase portrait is depicted in Figure 5.2.

We take the parameter values: $a = 1$, $p = 1$, $\gamma = 2$, $\mu = 1$, $q = 3$, $b = 2$, $\epsilon = 3$ and $c = 7.46$. For this set of parameter values, we obtain $a_0 = 1 > 0$, $b_0 = 1 > 0$, $c = c_0 = 7.46$. Therefore, by Theorem 4.8.1, we know that there exist two equilibria: $E_0^* = (0, \frac{1}{2})$ and $E_1^* = (\frac{15}{26}, \frac{13}{28})$. Moreover, the pathogen

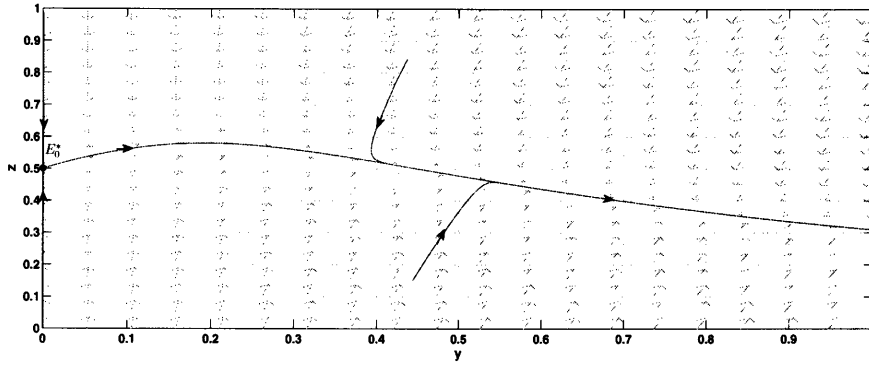


Figure 5.2: The phase portrait for System (2.1) with $a = 1$, $p = 1$, $\gamma = 2$, $\mu = 1$, $q = 3$, $b = 2$, $c = 7$, and $\epsilon = 3$.

free equilibrium E_0^* is a saddle point while E_1^* is stable. The phase portrait is depicted in Figure 5.3.

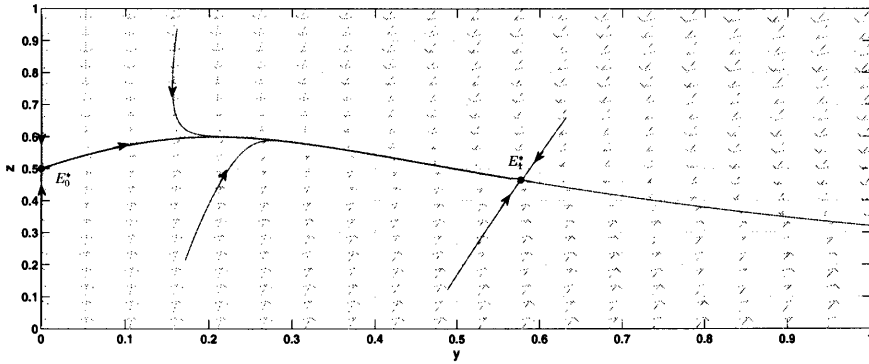


Figure 5.3: The phase portrait for System (2.1) with $a = 1$, $p = 1$, $\gamma = 2$, $\mu = 1$, $q = 3$, $b = 2$, $c = 7.46$, and $\epsilon = 3$.

We take the parameter values: $a = 1$, $p = \frac{2}{5}$, $\gamma = 1$, $\mu = \frac{3}{4}$, $q = 1$, $b = \frac{3}{10}$, $\epsilon = 3$ and $c = \frac{1}{2}$. For this set of parameter values, we obtain

$a_0 = 0, b_0 = \frac{7}{4} > b_0^* = \frac{5}{4}$. Therefore, by Theorem 4.8.1, we know that there exists one equilibrium which is the pathogen free equilibrium: $E_0^* = (0, \frac{5}{2})$. Moreover, the pathogen free equilibrium E_0^* is a saddle point. The phase portrait is depicted in Figure 5.4.

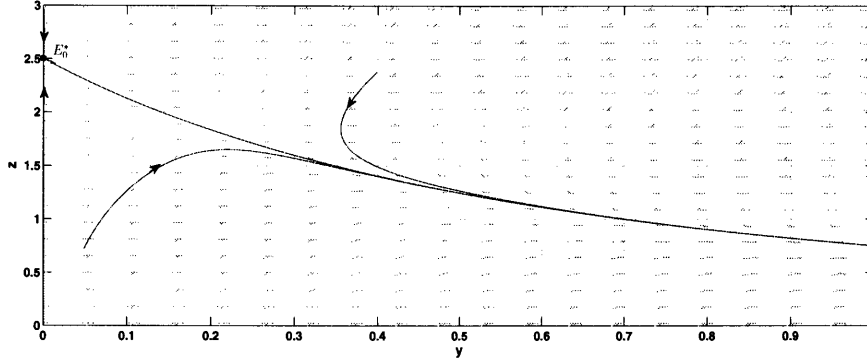


Figure 5.4: The phase portrait for System (2.1) with $a = 1, p = \frac{2}{5}, \gamma = 1, \mu = \frac{3}{4}, q = 1, b = \frac{3}{10}, c = \frac{1}{2}$, and $\epsilon = 3$.

We take the parameter values: $a = 1, p = \frac{2}{5}, \gamma = 1, \mu = \frac{3}{4}, q = 1, b = \frac{3}{10}, \epsilon = 3$ and $c = 1$. For this set of parameter values, we obtain $a_0 = 0, b_0 = \frac{7}{4} < b_0^* = \frac{10}{4}$. Therefore, by Theorem 4.8.1, we know that there exist two equilibria: $E_0^* = (0, \frac{5}{2})$ and $E_1^* = (\frac{1}{7}, \frac{35}{16})$. Moreover, the pathogen free equilibrium E_0^* is stable, while E_1^* is a saddle point. The phase portrait is depicted in Figure 5.5.

We take the parameter values: $a = 1, p = 2, \gamma = \frac{1}{2}, \mu = 4, q = 6, b = 3, \epsilon = 2$ and $c = 2$. For this set of parameter values, we obtain $a_0 = \frac{-5}{2} < 0$, and $b_0 = 1 > 0$. Therefore, by Theorem 4.8.1, we know that there exist

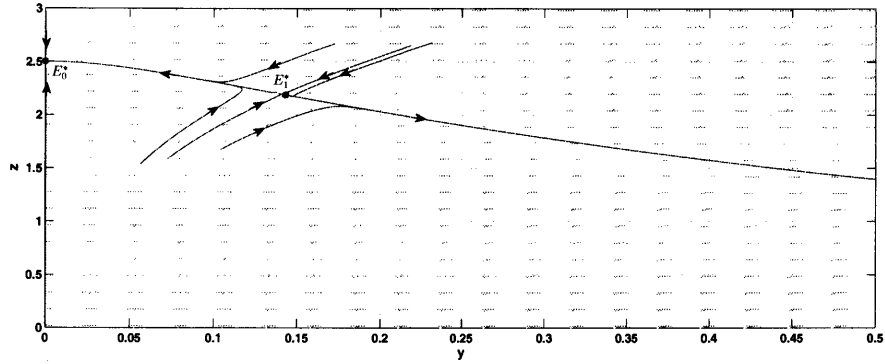


Figure 5.5: The phase portrait for System (2.1) with $a = 1$, $p = \frac{2}{5}$, $\gamma = 1$, $\mu = \frac{3}{4}$, $q = 1$, $b = \frac{3}{10}$, $c = 1$, and $\epsilon = 3$.

two equilibria: $E_0^* = (0, \frac{3}{4})$ and $E_1^* = (\frac{120}{41}, \frac{13}{64})$. Moreover, the pathogen free equilibrium E_0^* is stable while E_1^* is a saddle point. The phase portrait is depicted in Figure 5.6.

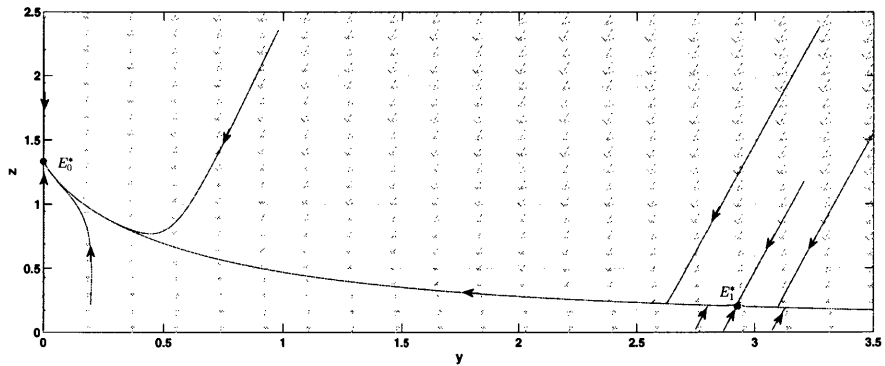


Figure 5.6: The phase portrait for System (2.1) with $a = 1$, $p = 2$, $\gamma = \frac{1}{2}$, $\mu = 4$, $q = 6$, $b = 3$, $c = 2$ and $\epsilon = 2$.

We take the parameter values: $a = 1$, $p = \frac{1}{2}$, $\gamma = 1$, $\mu = 2$, $q = 1$, $b = 3$,

$\epsilon = \frac{3}{10}$ and $c = \frac{1}{10}$. For this set of parameter values, we obtain $a_0 = 4 > a^* = \frac{2}{3}$, $b_0 = 0$. Therefore, by Theorem 4.8.1, we know that there exist one equilibrium which is the pathogen free equilibrium $E_0^* = (0, \frac{2}{3})$. Moreover, the pathogen free equilibrium E_0^* is a saddle point. The phase portrait is depicted in Figure 5.7.

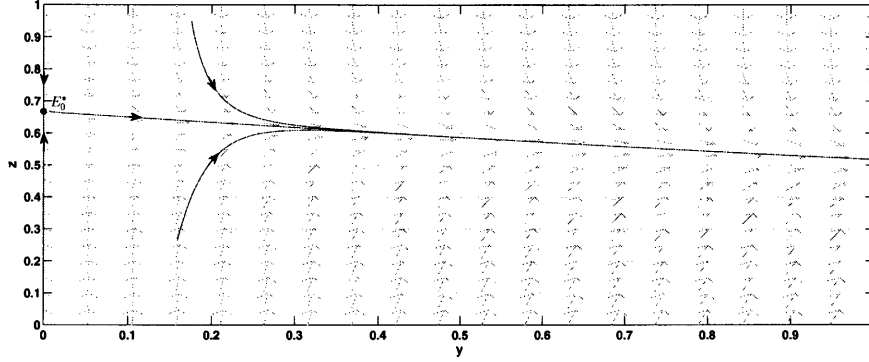


Figure 5.7: The phase portrait for System (2.1) with $a = 1$, $p = \frac{1}{2}$, $\gamma = 1$, $\mu = 2$, $q = 1$, $b = 3$, $c = \frac{1}{10}$ and $\epsilon = \frac{3}{10}$.

We take the parameter values: $a = 1$, $p = \frac{1}{2}$, $\gamma = 1$, $\mu = 2$, $q = 1$, $b = 3$, $\epsilon = 1$ and $c = 4$. For this set of parameter values, we obtain $0 < a_0 = 4 < a^* = \frac{\alpha c}{\epsilon} = 8$ and $b_0 = 0$. Therefore, by Theorem 4.8.1, we know that there exist two equilibria: $E_0^* = (0, \frac{2}{3})$ and $E_1^* = (1, 1)$. Moreover, the pathogen free equilibrium E_0^* is a saddle point while E_1^* is stable. The phase portrait is depicted in Figure 5.8.

We take the parameter values: $a = 1$, $p = 1$, $\gamma = 4$, $\mu = 1$, $q = 2$, $b = 3$, $\epsilon = 1$ and $c = 2$. For this set of parameter values, we obtain $a_0 = 2 > 0$

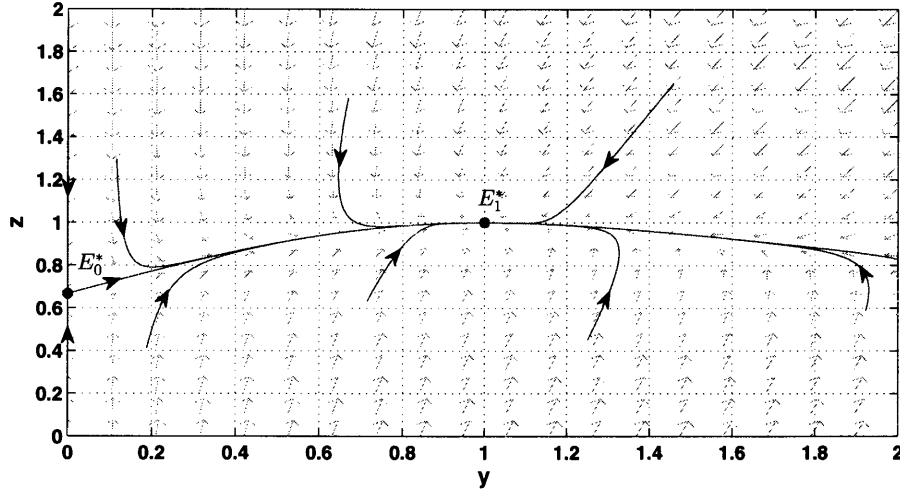


Figure 5.8: The phase portrait for for System (2.1) with $a = 1$, $p = \frac{1}{2}$, $\gamma = 1$, $\mu = 2$, $q = 1$, $b = 3$, $c = 4$ and $\epsilon = 1$.

and $b_0 = -2 < 0$. Therefore, by Theorem 4.8.1, we know that there exist two equilibria: $E_0^* = (0, \frac{1}{3})$ and $E_1^* = (\frac{21}{34}, \frac{17}{59})$. Moreover, the pathogen free equilibrium E_0^* is a saddle point while E_1^* is stable. The phase portrait is depicted in Figure 5.9.

We take the parameter values: $a = 1$, $p = 2$, $\gamma = 1$, $\mu = 2$, $q = 2$, $b = 2$, $\epsilon = 2$ and $c = 1$, For this set of parameter values, we obtain $a_0 = -1 < 0$ and $b_0 = -1 < 0$. Therefore, by Theorem 4.8.1, we know that there exist one equilibrium which is the pathogen free equilibrium $E_0^* = (0, \frac{2}{3})$. Moreover, the pathogen free equilibrium E_0^* is a saddle point. The phase portrait is depicted in Figure 5.10.

Our analytical analysis can be illustrated by Figure 5.11 in the a_0 - b_0 space.

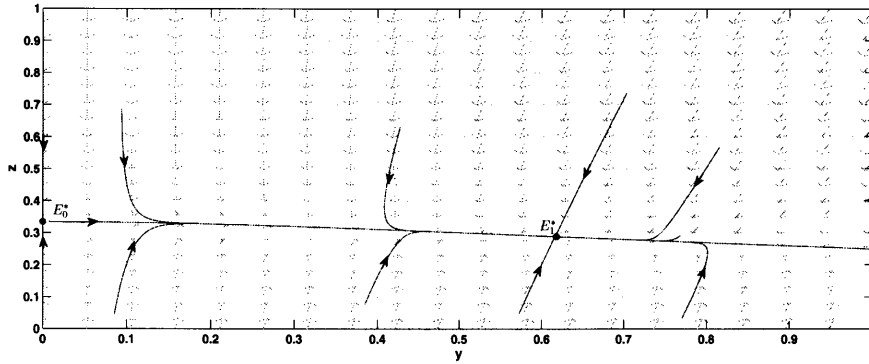


Figure 5.9: The phase portrait for for System (2.1) with $a = 1$, $p = 1$, $\gamma = 4$, $\mu = 1$, $q = 2$, $b = 3$, $c = 2$ and $\epsilon = 1$.

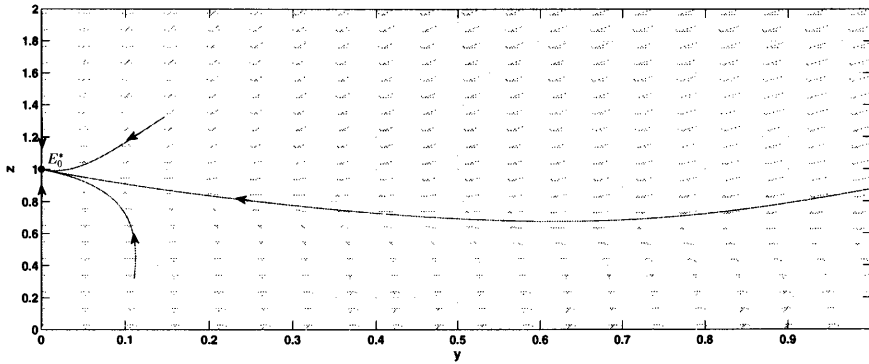


Figure 5.10: The phase portrait for for System (2.1) with $a = 1$, $p = 2$, $\gamma = 1$, $\mu = 2$, $q = 2$, $b = 2$, $c = 1$ and $\epsilon = 2$.

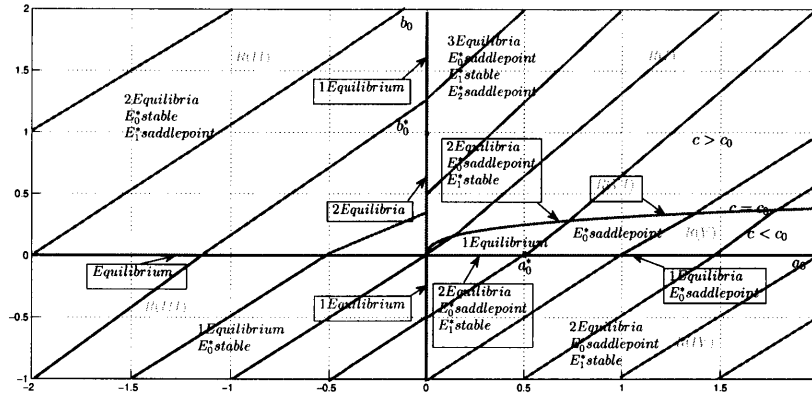


Figure 5.11: Stability diagram of System (2.1). In region R(I), there exist 3 equilibria: in addition to pathogen free equilibrium, there are two positive equilibria E_1^* and E_2^* . In region R(II): in addition to the pathogen free equilibrium, there exist a unique positive equilibrium E_1^* . The pathogen free equilibrium is stable and E_1^* is a saddle point. In region R(III), the pathogen free equilibrium is stable. In region R(IV), there exist 2 equilibria: the pathogen free equilibrium is a saddle point and the positive equilibrium E_1^* is stable. In region R(V), the pathogen free equilibrium is a saddle point. In region R(VI), there exist 2 equilibria: the pathogen free equilibrium is a saddle point and the positive equilibrium E_1^* is stable.

5.2 Drug therapy strategies

From the above numerical simulations and the obtained phase portraits, we know that there are three possible scenarios that drug therapy is needed: (i) System (2.1) admits only the pathogen free equilibrium, which is a saddle point; (ii) System (2.1) has two equilibria: the pathogen free equilibrium, which is stable, and a positive equilibrium, which is a saddle point; and (iii) System (2.1) has three equilibria: the pathogen free equilibrium, which is a saddle point, and two positive equilibria, one is a saddle point and the other is stable. In each of the three cases, for some initial concentrations of the virus and immune cells, the governed virus-immune cell interaction will lead to the decay of the immune cells and the unstoppable growth of the virus. One possible drug therapy is to increase the value of constant recruitment for immune cells, μ , during treatment and set its value back to the original value when the treatment stops. In the following, we will numerically explore the possible strategies.

For scenario (i), we take parameter values as $a = 1$, $p = \frac{2}{5}$, $\gamma = 1$, $\mu = \frac{3}{4}$, $q = 1$, $b = \frac{3}{10}$, $\epsilon = 3$ and $c = \frac{1}{2}$. As seen from Figure 5.4, the solutions approach the pathogen free equilibrium E_0^* , which indicates that the virus load is maintained at a constant level and there exists sustained immunity. Suppose the treatment starts at $t = 100$ and the treatment duration is denoted by T . Under the treatment strategy with $\mu = 2.50$, sustained immunity can be achieved if the treatment duration $T \geq 138$. Extensive simulations (30

simulations) suggest that if $\mu < 2.50$, then the treatment fails and life long therapy is required in order to stop the rapid growth of the virus, while in order for the therapy to be successful, μ should be large enough, in this case, $\mu = 2.50$ is required. Moreover, the larger μ value, the less treatment duration T . Figure 5.12 demonstrates the effects of various treatment strategies.

For scenario (ii), we take parameter values as $a = 1$, $p = \frac{2}{5}$, $\gamma = 1$, $\mu = \frac{3}{4}$, $q = 1$, $b = \frac{3}{10}$, $c = 1$, and $\epsilon = 3$. As seen from Figure 5.5, if the initial population densities of the virus and the immune cells are located on the left hand side of the saddle point E_1^* , then the solutions approach the pathogen free equilibrium E_0^* , which indicates that the virus load is maintained at a constant level and immunity is sustained. However, if the initial concentrations of the virus and the immune cells are located on the right hand side of the saddle point E_1^* , then the population of immune cells decays and the virus load keeps increasing. This suggests that the no sustained immunity will be established and the growth of virus cannot be stopped. Suppose the treatment starts at $t = 100$ and the treatment duration is denoted by T . Under the treatment strategy with $\mu = 1.35$, no sustained immunity can be achieved and life long treatment is needed; under the treatment strategy with $\mu = 2.48$, sustained immunity can be achieved if the treatment duration $T \geq 160$. Extensive simulations suggest that if $\mu < 2.48$, then the treatment fails and life long therapy is required in order to stop the rapid growth of the virus, while in order for the therapy to be successful, μ should be large

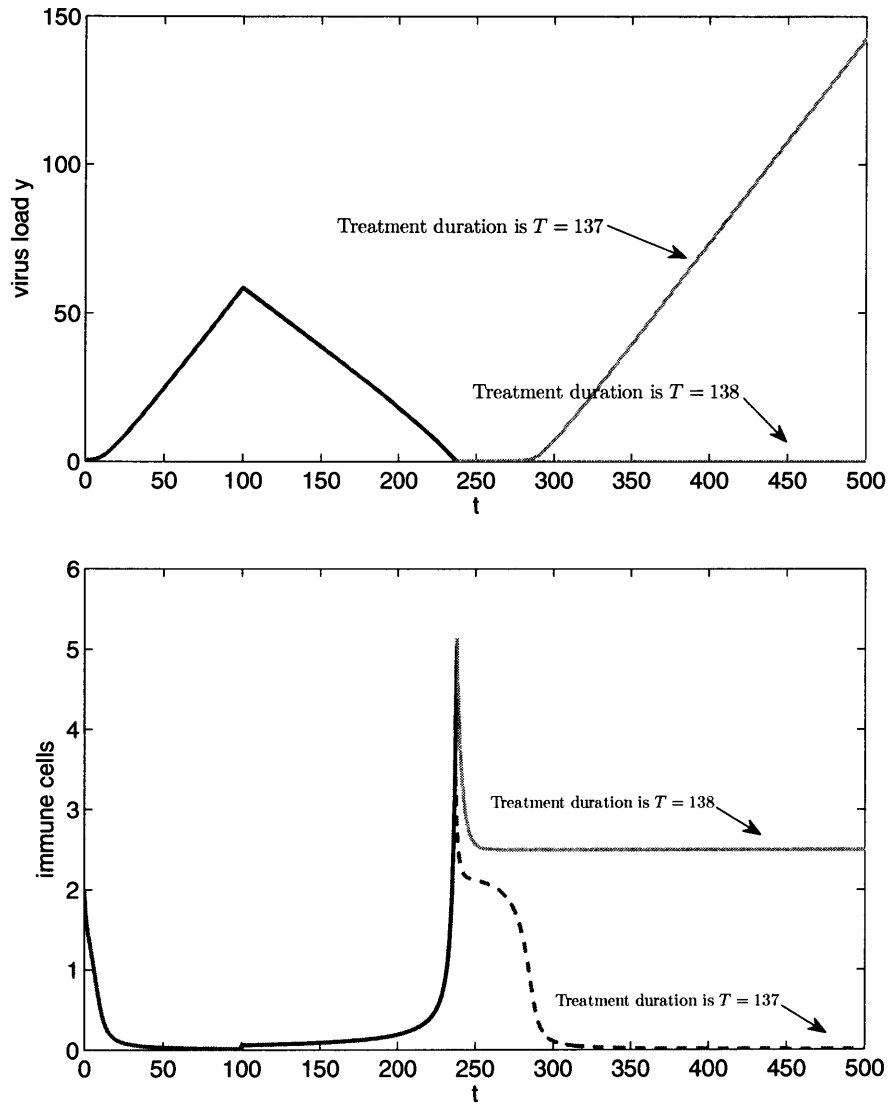


Figure 5.12: Top: the evolution of the virus load under different treatment strategies. Bottom: the evolution of the immune cells under different treatment strategies. Initial values are $y(0) = 0.5$ and $z(0) = 2$. If the treatment duration $T \geq 138$, then the sustained immunity can be achieved when $\mu = 2.50$.

enough, in this case, $\mu \geq 2.48$ is required. Moreover, the larger the value of μ , the lower the treatment duration T required for sustained immunity.

Figure 5.13 demonstrates the effects of various treatment strategies.

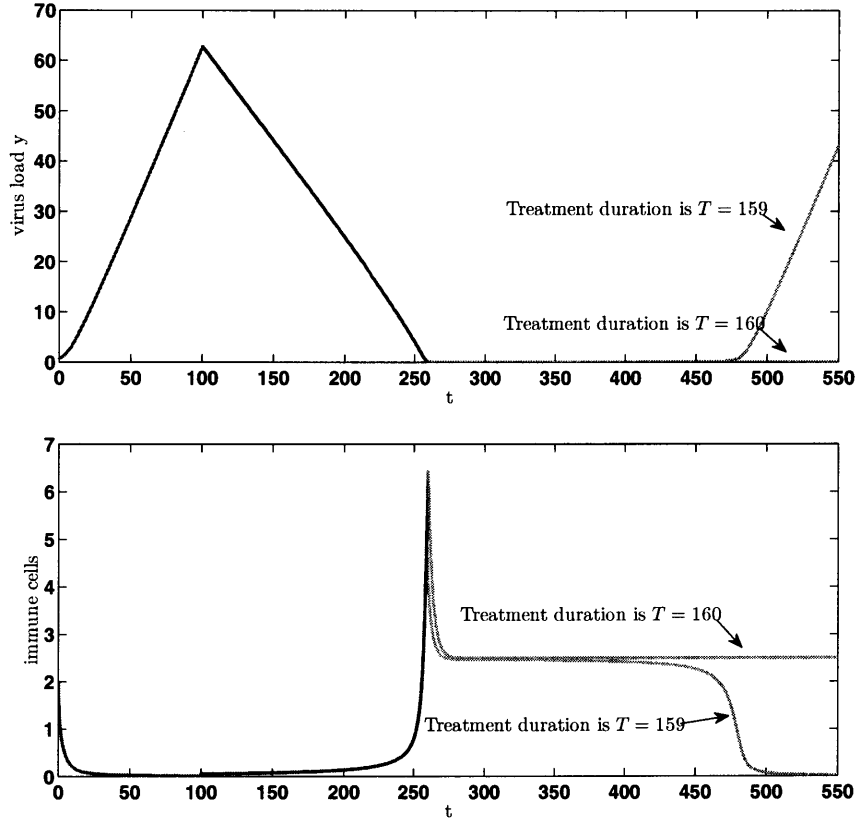


Figure 5.13: Top: the evolution of the virus load under different treatment strategies. Bottom: the evolution of the immune cells under different treatment strategies. Initial values are $y(0) = 0.9$ and $z(0) = 2$. Under the treatment strategy with $\mu = 2.48$, sustained immunity can be achieved if the treatment duration $T = 160$. If the treatment duration $T = 159$, then the sustained immunity cannot be achieved

For scenario (iii), we take parameter values as $a = 1$, $p = 1$, $\gamma = 2$, $\mu = 1$, $q = 3$, $b = 2$, $c = 8$ and $\epsilon = 3$. As seen from Figure 5.1, if the initial

population densities of the virus and the immune cells are located on the left hand side of the stable manifold of the saddle point E_2^* , then the solutions approach the positive equilibrium E_1^* , which indicates that the virus load is maintained at a constant level and immunity is sustained. However, if the initial concentrations of the virus and the immune cells are located on the right hand side of the stable manifold of the saddle point E_2^* , then the population of immune cells decays and the virus load keeps increasing. This suggests that the no sustained immunity will be established and the growth of virus cannot be stopped. Suppose the treatment starts at $t = 100$ and the treatment duration is denoted by T . Under the treatment strategy with $\mu = 1.35$, no sustained immunity can be achieved and life long treatment is needed; under the treatment strategy with $\mu = 1.40$, sustained immunity can be achieved if the treatment duration $T \geq 369$; if the value of μ is increased to $\mu = 1.45$ during the treatment, then the treatment duration can be shortened to $T = 169$. Extensive simulations suggest that if $\mu < 1.39$, then the treatment fails and life long therapy is required in order to stop the rapid growth of the virus, while in order for the therapy to be successful, μ should be large enough, in this case, $\mu \geq 1.39$ is required. Moreover, the larger the value of μ , the lower the treatment duration T required for sustained immunity. Figure 5.14 demonstrates the effects of various treatment strategies.

The above simulations suggest that in order to establish successful immunity keeping the virus load low or being cleared, the drug therapy, whose strength

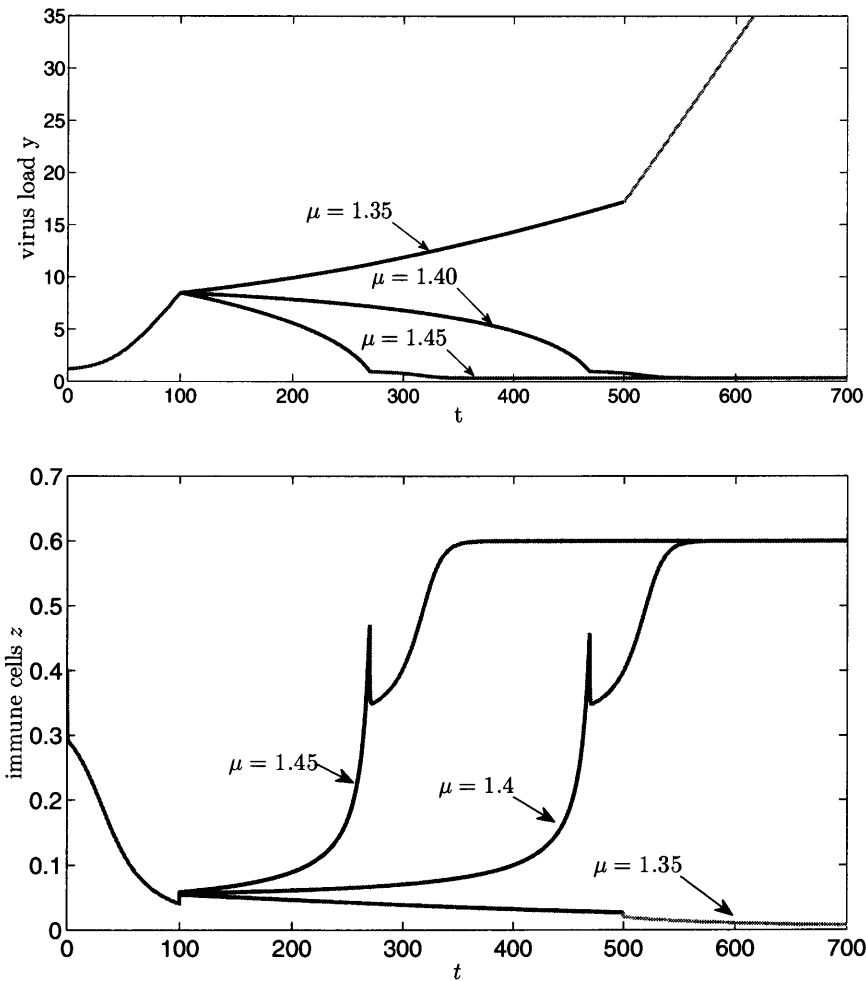


Figure 5.14: Top: the evolution of the virus load under different treatment strategies. Bottom: the evolution of the immune cells under different treatment strategies. Initial values are $y(0) = 1.2$ and $z(0) = 0.4$. Under the treatment strategy with $\mu = 1.35$, no sustained immunity can be achieved and life long treatment is needed; Under the treatment strategy with $\mu = 1.40$ and $\mu = 1.45$, sustained immunity can be achieved.

is characterized by the value of μ , should be strong enough, and with stronger therapy, a lower treatment duration T is required. If the therapy is too weak, then life-long treatment is needed.

Chapter 6

Summary and Conclusion

In this report, we have proposed a new model to study the pathogen-immune interaction dynamics. Our new model assumes that the growth rate of the virus population saturates when the virus population reaches a very high level. We also assume that the level of immune response is simply proportional to both the viral load and the immune response when the virus load is low, but that the immune response saturates when the virus load is sufficiently high. This is modeled by the function $\frac{cyz}{1+\epsilon y}$. Immune cells are assumed to kill or destroy the virus at the rate pyz , in the meantime they are inhibited by the virus at a rate qyz . Moreover, we assume that there is a constant recruitment for immune cells, which can be varied during the drug therapy treatment.

For this new model, we have investigated the existence of nonnegative equilibria and equilibrium bifurcations. More specifically, we derived the con-

ditions under which the model admits one equilibrium (the pathogen free equilibrium), or two or three equilibria (the pathogen free equilibrium and the positive equilibria), and the model undergoes a saddle node bifurcation. We have also carried out detailed stability analysis for these equilibria. If the pathogen free equilibrium is stable, then this indicates that the virus can be cleared from the patient, while if a positive equilibrium is stable, then this implies that the virus population will be maintained at a constant level in the host due to sustained immunity. If the immune cells keep decreasing and the virus population keeps increasing, then this suggests that the drug therapy treatment should be applied. During the treatment, the value of μ is increased, and the value is set back to the pretreatment value when the treatment stops. Our numerical simulations suggest that depending on the initial concentrations of the virus and the immune cells, to establish successful immunity keeping the virus load low or being cleared, there exists a threshold value $\mu_{threshold}$ for the strength of drug therapy. If $\mu < \mu_{threshold}$, then a life-long treatment is required. If $\mu \geq \mu_{threshold}$, then the therapy is successful and the treatment duration T depends on the values of μ and the initial concentrations of the virus and the immune cells, as well as the time to start the treatment. Our model can provide some insights on detecting if the virus in the host can be controlled at a relatively low level or if the virus's growth is unstoppable, which results in AIDS from HIV for HIV patients, and some general guidance on the applicability of the drug therapy. But still it is just a theoretical model, more complex mechanisms such as drug

resistance, the time lag in the immune cells' expansion should be taken into the consideration in our future work.

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