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GLOBAL ANALYSIS OF CELL INFECTION AND VIRUS PRODUCTION ON HIV-1 DYNAMICS

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Abstract

More than one sub-type of HIVs have been identified. This raises an issue of co-infections by multiple strains of HIVs. In this thesis, we propose two mathematical models, one ignoring intracellular delay and the other incorporating the delay, to describe the interactions of the populations of $CD4^+$ cells and two HIV stains. By nature, the two strains compete for $CD4^+$ cells to invade for their own replications. By analyzing the two models, we find that the models demonstrate threshold dynamics: if the overall basic reproduction number $R_0 \leq 1$, then the infection free equilibrium is globally asymptotically stable; when $R_0 > 1$, then the competition exclusion principle generically holds in the sense that, except for the critical case $R_1 = R_2 > 1$ where R_i is the individual basic reproduction number for strain i, all biologically meaningful solutions will converge to the single infection equilibrium representing the winning of the strain that has greater individual basic reproduction number. Numerical simulations are also performed to illustrate the theoretical results. The results on the model with delay also show that the basic reproduction number will be over calculated if the cellular delay is ignored.

Keywords: HIV, basic reproduction number, global asymptotic stability, intracellular delays.

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Chapter 1

Introduction

Infectious diseases pose a complex and global threat to human populations. The numerous species of viruses, bacteria, and higher organisms that are able to infect humans have changed the course of history. Spread of the human immunodeficiency virus (HIV) has raised global concerns and a greater awareness of infectious diseases. Management of infection with HIV improved dramatically during the 1990s. The advent of high-performance quantitative HIV assay was one of the most important developments in HIV control. Understanding how the HIV works inside the human body will give scientists important clues about how to attack it. Mathematical models have been shown to be useful and helpful to the understanding of the complicated dynamics of the virus and immune cells. This chapter will provide some basic information about infection mechanism about how populations of viruses and populations of immune system cells interact in various circumstances.

1.1 Viruses

Viruses are of intense interest because they cause serious illness in humans or domestic animals, and some even damage crop plants. Among the striking examples is the HIV that has

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recently entered the human population and caused a plague of worldwide. As a consequence, AIDs killed 3 million people worldwide even in the single year of 2002 [6].

Viruses populate the world between the living and the non-living. The persistence of viruses is in part due to their ability to mutate rapidly and adapt to new situations. Viruses are sub-cellular and infectious agents that are obligate intracellular parasites. A mature, extracellular virus particle is called a virion. A virion contains a genome that may be DNA or RNA wrapped in a protein coat called a capsid or nucleocapsid. The nucleic acid genome of a virus contains the information needed by the virus to replicate and produce new virions after its introduction into a susceptible cell.

There are three broad classes of viruses recognized, which may have independent evolutionary origins. One class, which includes the poxviruses and herpesviruses among many others, contains DNA as the genome, with either a single stranded or double strandeds, and the DNA genome is replicated by direct DNA$\rightarrow$ DNA copying. A second class of viruses contains RNA as their genome and the RNA is replicated by direct RNA$\rightarrow$ RNA copying. The third class of viruses encodes the enzyme reverse transcriptase (RT), and these viruses have an RNA$\rightarrow$ DNA step in their life cycle. The genetic information encoded by these viruses thus alternates between being present in RNA and being present in DNA. Retroviruses (e.g.,HIV, family Retroviridae) contain the RNA phase in the virion, and they have a single-stranded RNA genome that is present in the virus particles in two copies. Thus, the replication of their genome occurs through a DNA intermediate (RNA$\rightarrow$ DNA$\rightarrow$ RNA). The hepadnaviruses(e.g.,hepatitis B virus, family Hepadnaviridae) contain the DNA phase as their genome, which is circular and largely double stranded. Thus their genome replicates through an RNA intermediate (DNA$\rightarrow$ RNA$\rightarrow$ DNA).

1.2 Human Immunodeficiency Virus

Human Immunodeficiency Virus (HIV) is currently grouped into two types: HIV-type 1 (HIV-1) and HIV-type2 (HIV-2), which are genetically related member of the lentiviruses genus of the Retroviridae family [6]. Both HIV-1 and HIV-2 may cause the well-known disease called AIDS (Acquired Immunodeficiency Syndrome), while HIV-2 is restricted to some regions of Western and Central Africa and is thus not as serious a pathogen as HIV-1. The latent period before disease develops is longer for HIV-2, the virus is not as easily transmissible, and it has not spread as extensively as has HIV-1. HIV-1 is responsible for the vast majority of AIDS in people.

The structure of HIV-1 is shown in 1.1. Each viral particle of HIV has a membrane similar in structure to that of the cell membrane. Inside, the viral particle there is nucleocapside, which contains two copies of HIV RNA combined with a nucleoprotein and enzymes reverse transcriptase, intergrase and protease [3].

There are three structural genes called *gag, pol* and *env* polyproteins [4]. The *gag* gene encodes for the protein p-24 and p-17. The *pol* gene encodes for the reverse transcriptase, the protease, and the integrase. The *env* proteins slices into two viral envelop protein called gp-41 and gp-120. Gp-41 is embedded in the membrane of the HIV particle,whereas gp-120 sits on the outside of the viral membrane attached to gp-41. Gp-120 is essential for the virus to enter its host cell [2].

1.3 The Life Cycle of HIV Infection

The HIV life-cycle is the story of how a single HIV virus particle infiltrates a cell and uses it to produce new HIV particles. Viruses cannot reproduce without the aid of a living cell. HIV needs to proliferate inside its target cells. The main target is an immune cell called a
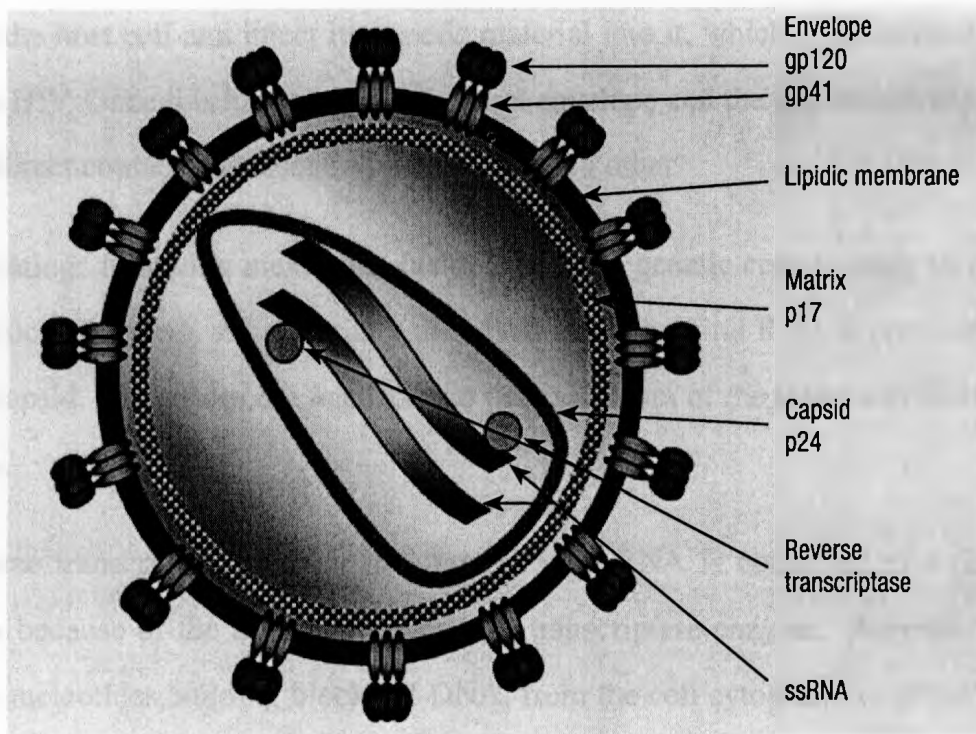
Figure 1.1: Structure of HIV-1 particle *source: [1]*

lymphocyte, more sepecifically a $CD4^+$ helper, a type of T-cell. T-cells are an important part of the immune system because they help facilitate the body's response to many common but potentially fatal infections. Without enough T-cells, the body's immune system is unable to defend itself against many infections. HIV's replication directly or indirectly causes a reduction in the number of T-cells in the body, eventually resulting in an increased risk of infections.

The steps by which HIV enters target cells and reproduce is commonly divided into six stages: the binding and entry phase, the uncoating phase, the reverse transcription phase, the provirus intergration phase, the virus protein synthesis and assembly phase and the budding phase [1], which are explained below.

- Binding and entry: once HIV comes into contact with a T-cell, the viral envelope protein gp-120 and gp-41 bind to a $CD4^+$ receptor and one of two co-receptors on the surface of a $CD4^+$ positive T-lymphocyte. In addition to binding a $CD4^+$ receptor, HIV must also bind either a CCR5 OR CXCR4 co-receptor protein to get into a cell. The virus then fuse

with the host cell and inject its genetic material into it, which is a blueprint for making more HIV. Once this has occurred, the viral envelope and the cell membrane are brought into direct contact and essentially melt into each other.

- Uncoating: following membrane fusion, the virus genetic core is ready to release. The nucleocapsid needs to be partially dissolved since the viral RNA is protected in the nucleocapsid. The virus core uncoats into the cytoplasm of the target cell freeing the viral RNA.

- Reverse transcription: the single-stranded viral RNA is converted to a double-strand DNA because of the action of the reverse transcriptase enzyme. Reverse transcriptase uses nucleotides,building blocks of DNA, from the cell cytoplasm to make this process possible.

- Integration: the newly formed HIV DNA inserts itself into the cell nucleus and facilitates its integration into the host genome. The integrated HIV DNA is called provirus. After successful integration of the viral DNA, the host cell is now latently infected with HIV. The provirus may remain inactive for several years, producing few or no new copies of HIV.

- Protein synthesis and viral assembly: Upon cell activation, transcription of proviral DNA into a messenger RNA occurs. Viral mRNA coding for long fragments migrates into the cytoplasm, where structural proteins of new virons are synthesized. Once the various viral subunits have been produced and processed, they must be separated for the final assembly into new virus. This separation, or cleavage, is accomplished by the viral protease enzyme.

- Budding: The genetic material enclosed in the nucleocapsid merges and migrates towards the cell surface. During the budding process, the virus acquire part of the cell's outer envelope as its new envelope, which is studded with protein/sugar combinations called HIV glycoproteins. The newly assembled virus pushes out from the host cell and

move on to infect other cells.

The following figure 1.2 shows the HIV infection life cycle.
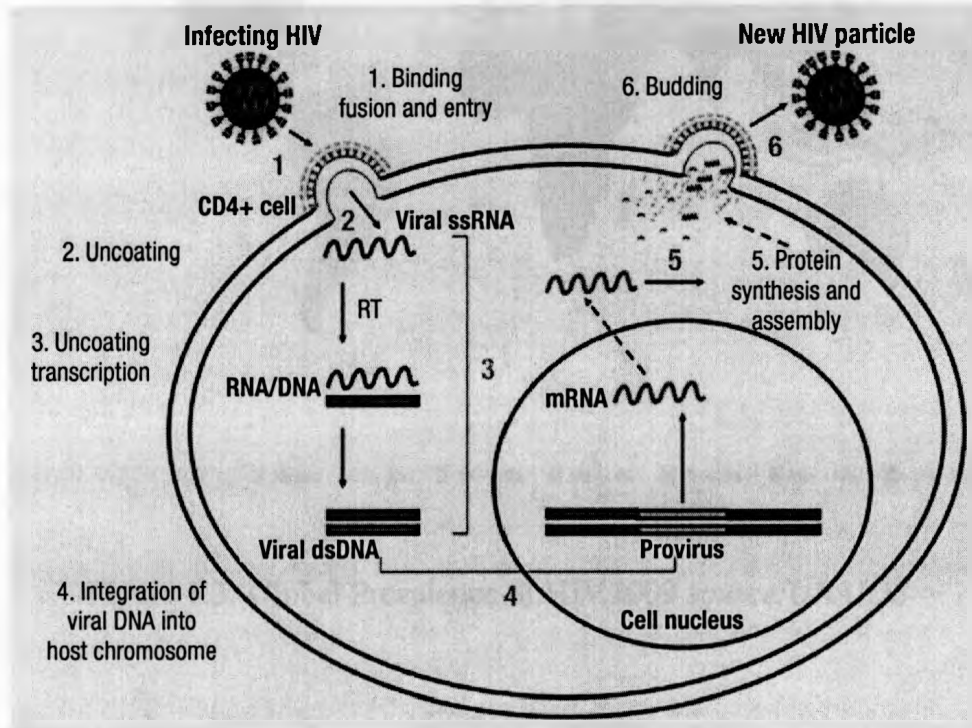
Figure 1.2: The life cycle of HIV infection. *source: [1]*

1.4 Epidemiology

In the begnning of the fourth decade of the AIDs epidemics, there are estimated 33.3 million people living with HIV worldwide. In 2009, there was an estimated 2.6 million people who became newly infected with HIV according to UNAIDS. The number of annual AIDS-related deaths worldwides is estimated 1.8 million in 2009. In North America, the HIV incidences increased from 1.2 million to 1.5 million and the newly infected with HIV rised from 66000 to 70000 between 2001 and 2009 [7].

HIV infection can be transmitted in the following ways: [3]
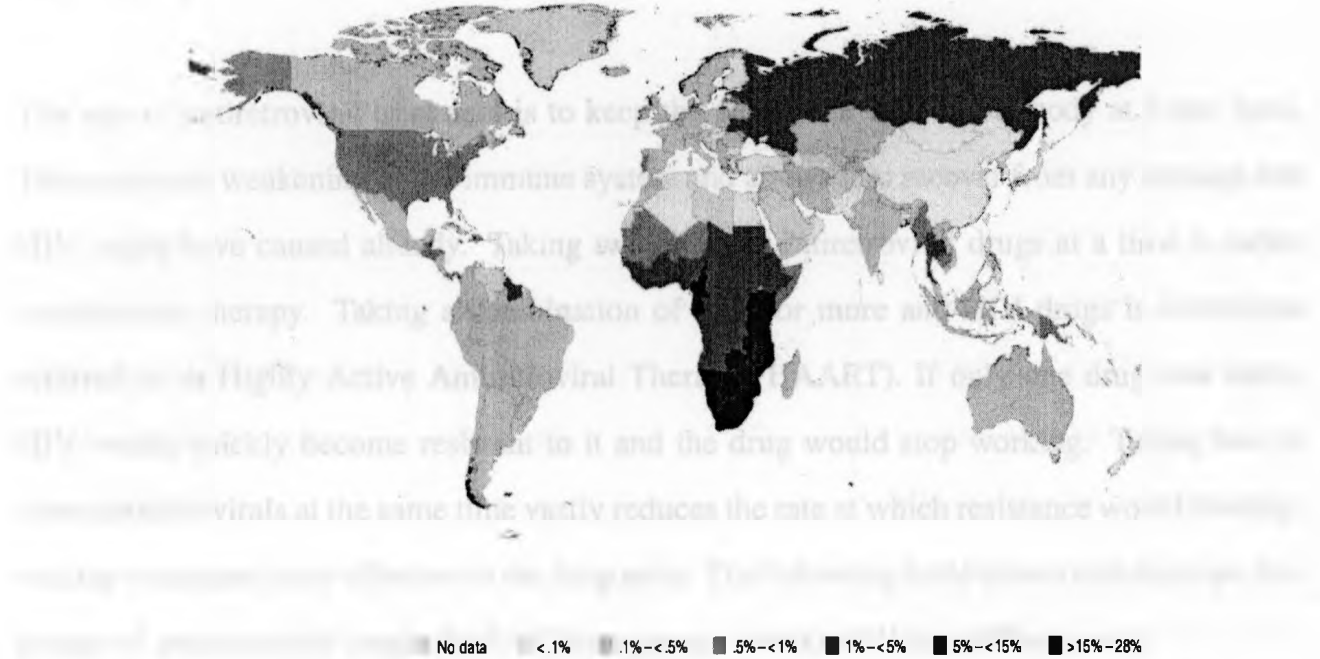
Figure 1.3: Global Prevalence of HIV,2009 *source:UNAIDS*

- Sexual transmission:

  - heterosexual transmission

  - homosexual transmission:

    * man-to-man transmission

    * woman-to-woman transmission

- Vertical transmission

- Blood transmission:

  - sharing infected injection equipment

  - infected blood products

  - needle-stick injuries

1.5 Treatment of HIV/AIDS

The aim of antiretroviral treatment is to keep the amount of HIV in the body at a low level. This stops any weakening of the immune system and allows it to recover from any damage that HIV might have caused already. Taking two or more antiretroviral drugs at a time is called combination therapy. Taking a combination of three or more anti-HIV drugs is sometimes referred to as Highly Active Antiretroviral Therapy (HAART). If only one drug was taken, HIV would quickly become resistant to it and the drug would stop working. Taking two or more antiretrovirals at the same time vastly reduces the rate at which resistance would develop, making treatment more effective in the long term. The following table shows that there are five groups of antiretroviral drugs. Each of these groups attacks HIV in a different way.

1.6 This thesis

The application of mathematical models to infectious disease has consisted of describing their spread throug human populations. Mathematical models present clear concepts and guideline for collection and analysis of data [5]. In Chapter 2, our 5-dimensional nonlinear ODEs model is introduced to describe the interation of the two competitive strains of viruses within host cells and global stability analysis is performed. Based on reality, intracellular delays are added to our previous mathematical model in Chapter 3. We investigate the global properties of our modified mathematical model which is determinded with similar consequences found for the model in Chapter 2. In chapter 4, we obtain our conclusion that the dynamics of both differential mathematical models are determined by the basic reproductive number and disccuss our future work.

Antiretroviral drug class	Abbreviation	First approach to treat HIV	How they attack HIV
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors	NRTIs, nucleoside analogues, nukes	1987	NRTIs interfere with the action of an HIV protein called reverse transcriptase, which the virus needs to make new copies of itself.
Non-Nucleoside Reverse Transcriptase Inhibitors	NNRTIs, non-nucleosides, non-nukes	1997	NNRTIs also stop HIV from replicating within cells by inhibiting the reverse transcriptase protein.
Protease Inhibitors	PIs	1995	PIs inhibit protease, which is another protein involved in the HIV replication process.
Fusion or Entry Inhibitors		2003	Fusion or entry inhibitors prevent HIV from binding to or entering human immune cells.
Integrase Inhibitors		2007	Integrase inhibitors interfere with the integrase enzyme, which HIV needs to insert its genetic material into human cells.

Table 1.1: Antiretroviral drug table

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Chapter 2

Global Properties of the HIV Infection Model with two competitive viruses

2.1 Introduction

Infection with human immunodeficiency virus (HIV) results in a chronic infection with ultimate fatal outcome. Studies on HIV virology and pathogenesis address the complex mechanisms that lead to the HIV infection of the cell and destruction of the immune system. A detailed understanding of HIV dynamics and how it establishes infection and causes AIDS are crucial for refining strategies for scientists to attack AIDS and control HIV spreading in population.

When HIV enters the body, it invades CD4+ T-cells, the main driver of the immune response. Through infection and eventual killing of these cells, HIV weakens the body's immune function and may cause Acquired Immune Deficiency Syndrome(AIDS), making the body susceptible to opportunistic infections.

Many epidemic models about multiple infections with different diseases have been inves-

tigated. For example, coinfection with AIDS and tuberculosis are studied in [17, 22], and coninfection with Hepatitis C and HIV is explored in [23]. Recent studies have demonstrated that multiple infections of cells by different strains of a pathogen occur far more frequently than single infection in vivo [6], which is significant shift from the prevalent paradigm of HIV infection that individual target cells are generally infected by a single strain HIV virions [14]. Therefore, considering two types of HIV virus which are competitive within host cells is more accurate than considering one type HIV only invading host cells models. Even there are lots of drug resistance [18, 19] and general in-host models with the single strain infection [8, 14] in theliterature, but the global properties of the two strains HIV infection models with loose conditions are not well studied. Of great interest, therefore, are investigating the mechanisms that underlie the high incidenc of two-strain competitive infection of cells by HIV and understanding their implication for HIV evolution and therapy. Studying such properties is important for understanding the associated characteristics of the HIV dynamics, and helps to determine the suitable drug dosages required to stabilize the system around the desired steady state [4, 20].

Our primary goal in this chapter is to investigate analytically the mechanisms underlying the emergence of two-strain viral loads during HIV infection. We calculate the basic reproduction number and analyze global properties of the two-strain HIV model. Our two-strain model is a 5-dimensional system of nonlinear ODEs that describes the interation of the two competitive viruses within host cells. The global stability of these equilibria is analyzed by constructing Lyapunov functions, which are extensions and modifications of the Lyapunov function given by Korobeinikov [8]. We prove that the global dynamics of our model is determined by the basic reproduction number R_0. If $R_0 \leq 1$, the infection-free equilibrium is globally asymptotically stable, and both strains of viruses are cleared. If $R_0 > 1$, the infection-free equilibrium loss its stability and the single-infection by the virus that has the greater basic reproduction number persists and the single-infection equilibrium is globally asymptotically stable. We provide numerical results of the model which support our analytical results.

2.2 A Two-Strain HIV Model

Most existing mathematical models for HIV virus dynamics are by systems of ordinary differential equations . A standard and classic differential equation model for HIV infection is the following system of ODEs [14, 13, 15]:

$$\dot{T} = \lambda - dT - kTV,$$
$$\dot{T^*} = kTV - \mu T^*, \tag{2.1}$$
$$\dot{V} = pT^* - cV,$$

where $T(t), T^*(t)$ and $V(t)$ are the population sizes of uninfected target cells, infected cells and the free virus particles, respectively, at time t. The assumption is that uninfected cells are generated at a constant rate, λ, and die at a rate d. Free virus particles infect uninfected target cells at a rate proportional to the product of their abundances, kTV. The rate constant, k, describes the efficacy of this process. Infected cells produce free virus particles at a rate proportional to their abundance, pT^*. Infected cells die at a rate μT^* either due to the natural death or the action of the virus and free virus particles are removed from the system at rate cV by the immune system or natural decay. Therefore, the average life-time of an infected cell, a free virus particle and an uninfected cell are $\frac{1}{\mu}, \frac{1}{c}$ and $\frac{1}{d}$ respectively. The model well predicts the primary phase of HIV infection, showing that during the first weeks of infection there is a peak in viral load with a subsequent decline to a relatively stable steady-state.

The model presented in this chapter adopts a similar structure as that in (2.1). We introduce another subtype of virus which competes with the original virus for host cell resource, but we ignore super infection. As the main purpose of this model is to look at the interaction between two subtype viruses, we propose our two-strain model given by the following system of ordinary differential equations:

$$\dot{T} = \lambda - dT - k_1 T V_1 - k_2 T V_2,$$

$$\dot{T}_1 = k_1 T V_1 - \mu_1 T_1,$$

$$\dot{T}_2 = k_2 T V_2 - \mu_2 T_2, \qquad\qquad (2.2)$$

$$\dot{V}_1 = p_1 T_1 - c_1 V_1,$$

$$\dot{V}_2 = p_2 T_2 - c_2 V_2,$$

where $T_1(t)$ denotes the population size of cells productively infected by strain-1 virus, whereas $T_2(t)$ denotes the population size of cells productively infected by strain-2 virus at time t; $V_1(t)$ and $V_2(t)$ represent the respective population sizes of subtype-1 and subtype-2 viruses; k_1 and k_2 represent the rate constants at which uninfected target cells are infected by subtype-1 and subtype-2 viruses, respectively. The two subtypes of infected cells are assumed to have two different death rate μ_1 and μ_2. Once uninfected target cells are infected by subtype-1 (subtype-2) viruses, new subtype-1 (subtype-2) virus particles are produced with constant rate p_1 (p_2). The new subtypes of virus have the respective clearance rate c_1 and c_2. All the parameters of the model are assumed to be positive. Here we omit the super-infection in host cells.

2.2.1   Well-posedness

The system (2.2) is biologically acceptable in the sense that no population goes negative. One expects that starting from non-negative initial values, all variables in the corresponding solution remain non-negative.

Theorem 2.2.1 *The compact set* $\Gamma = \{(T, T_1, T_2, V_1, V_2) \in \Re^5 : 0 \le T \le \frac{\lambda}{d}, 0 \le T + T_1 + T_2 \le \frac{\lambda}{\bar{r}}, 0 \le V_1 \le \frac{p_1 \lambda}{c_1 \bar{r}}, 0 \le V_2 \le \frac{p_2 \lambda}{c_2 \bar{r}}\}$ *is positively invariant.*

Proof First, we prove that $T(t)$ is positive for all $t \ge 0$. Assuming the opposite, let $t_1 > 0$ be the first time such that $T(t_1) = 0$, which means $T(t) > 0$ as $t \in [0, t_1)$. Since

$$\dot{T} = \lambda - dT - k_1 T V_1 - k_2 T V_2,$$

we get $\dot{T}(t_1) = \lambda > 0$, and hence $\dot{T}(t) < 0$ for $t \in (t_1 - \epsilon, t_1)$ where $\epsilon > 0$ is sufficiently small. This contradicts $T(t) > 0$ for $t \in [0, t_1)$. It follows that $T(t) > 0$ for $t > 0$.

Next, we show $V_1(t) \geq 0$ for all $t \geq 0$. Assume the opposite, and let $t_2 > 0$ be the first time such that $V_1(t_2) = 0$. Since

$$\dot{V}_1 = p_1 T_1 - c_1 V_1,$$

we have $\dot{V}_1(t_2) = p_1 T_1(t_2)$. On the other hand, solving $T_1(t)$ by the second equation of (2.2) gives

$$T_1(t_2) = (T_1(0) + \int_0^{t_2} k_1 T(\theta) V_1(\theta) e^{\mu_1 \theta} d\theta) e^{-\mu_1 t_2} > 0.$$

Hence $\dot{V}_1(t_2) = p_1 T_1(t_2) > 0$, implying $V_1(t)$ is positive for all $t \geq 0$.

The positiveness of $T(t)$ and $V_1(t)$ and the following formula

$$T_1(t) = (T_1(0) + \int_0^t k_1 T(\theta) V_1(\theta) e^{\mu_1 \theta} d\theta) e^{-\mu_1 t}$$

in turn leads to the positiveness of $T_1(t)$ for all $t \geq 0$. Similarly, we can show that $V_2(t)$ and $T_2(t)$ are positive for $t \geq 0$ under positive initial conditions.

From the first equation of (2.2), we obtain $\dot{T} \leq \lambda - dT$. Hence $limsup_{t \to \infty} T(t) \leq \frac{\lambda}{d}$. Adding the first three equations of (2.2), it follows

$$(T(t) + T_1(t) + T_2(t))' = \lambda - dT(t) - \mu_1 T_1(t) - \mu_2 T_2(t)$$

$$\leq \lambda - \bar{r}(T(t) + T_1(t) + T_2(t)),$$

where $\bar{r} = min\{d, \mu_1, \mu_2\}$. Thus, $limsup_{t \to \infty}(T(t) + T_1(t) + T_2(t)) \leq \frac{\lambda}{\bar{r}}$. For any $\epsilon > 0, \exists t^* > 0$, such that $T(t) + T_1(t) + T_2(t) \leq \frac{\lambda}{\bar{r}} + \epsilon$ for all $t \geq t^*$. The fourth equation of (2.2) implies

$$\dot{V_1} = p_1 T_1 - c_1 V_1 \le p_1(\frac{\lambda}{\tilde{r}} + \epsilon) - c_1 V_1(t), t \ge t^*.$$

This implies $limsup_{t\to\infty} V_1 \le \frac{p_1}{c_1}(\frac{\lambda}{\tilde{r}} + \epsilon)$. Since $\epsilon > 0$ is arbitrary, we attain $limsup_{t\to\infty} V_1(t) \le \frac{p_1\lambda}{c_1\tilde{r}}$.

Similarly, we can obtain $limsup_{t\to\infty} V_2 \le \frac{p_2\lambda}{c_2\tilde{r}}$. The above have also shown that the set

$$\Gamma = \{(T, T_1, T_2, V_1, V_2) \in \Re^5 : 0 \le T \le \frac{\lambda}{d}, 0 \le T + T_1 + T_2 \le \frac{\lambda}{\tilde{r}}, 0 \le V_1 \le \frac{p_1\lambda}{c_1\tilde{r}}, 0 \le V_2 \le \frac{p_2\lambda}{c_2\tilde{r}}\}$$

is positively invariant and it also attracts all non-negative solution. The proof is completed.

2.2.2   Equilibria and basic reproduction numbers

A crucial mathematical threshold parameter for model (2.2) is the basic reproduction number R_0, which is defined as the number of newly infected cells that arise from any one infected cell when almost all cells are uninfected [2]. We apply the technique from [3] to calculate the basic reproduction number R_0 by using the next generation matrix.

The model always has the infection free equilibrium $E_0 = \left(\frac{\lambda}{d}, 0, 0, 0, 0\right)$. The next generation matrix of (2.2) denoted by FV^{-1}, is related to the linearization of (2.2) at E_0. Following [3], we can calculate F and V as

$$F = \begin{pmatrix} 0 & 0 & k_1\frac{\lambda}{d} & 0 \\ 0 & 0 & 0 & k_2\frac{\lambda}{d} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, and\ V = \begin{pmatrix} \mu_1 & 0 & 0 & 0 \\ 0 & \mu_1 & 0 & 0 \\ -p_1 & 0 & c_1 & 0 \\ 0 & -p_1 & 0 & c_2 \end{pmatrix},$$

giving the next generation matrix

$$FV^{-1} = \begin{pmatrix} \frac{k_1\lambda p_1}{d\mu_1 c_1} & 0 & \frac{k_1\lambda}{dc_1} & 0 \\ 0 & \frac{k_2\lambda p_2}{d\mu_2 c_2} & 0 & \frac{k_2\lambda}{dc_2} \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

The basic reproduction number is given by the spectrum radius of FV^{-1}, which is

$$R_0 = \rho(FV^{-1}) = max \left\{ \frac{k_1\lambda p_1}{d\mu_1 c_1}, \frac{k_2\lambda p_2}{d\mu_2 c_2} \right\}. \tag{2.3}$$

We define the respective basic reprodution number for subtype-1 virus strain and subtype-2 virus strain by

$$R_1 = \frac{k_1\lambda p_1}{d\mu_1 c_1}, and \ R_2 = \frac{k_2\lambda p_2}{d\mu_2 c_2}. \tag{2.4}$$

From (2.3), we obtain $R_0 = max \{R_1, R_2\}$.

There are two possible single-infection equilibria $E_1 = (\bar{T}, \bar{T}_1, 0, \bar{V}_1, 0)$ and $E_2 = (\tilde{T}, 0, \tilde{T}_2, 0, \tilde{V}_2)$, where

$$\bar{T} = \frac{\lambda}{d}\frac{1}{R_1}, \quad \bar{T}_1 = \frac{dc_1}{k_1 p_1}(R_1 - 1), \quad \bar{V}_1 = \frac{d}{k_1}(R_1 - 1). \tag{2.5}$$

and

$$\tilde{T} = \frac{\lambda}{d}\frac{1}{R_2}, \quad \tilde{T}_2 = \frac{dc_2}{k_2 p_2}(R_2 - 1), \quad \tilde{V}_2 = \frac{d}{k_2}(R_2 - 1). \tag{2.6}$$

It turns out that the values of R_1 and R_2 determine the existence of the single-infection equilibria: E_1 exists if and only if $R_1 > 1$, and E_2 exists if and only if $R_2 > 1$. Obviously, E_1 and E_2 are biologically meaningful under the conditions.

It is also possible for our model (2.2) to have a double infection equilibrium which is an equilibrium with all components being positive. Denote such a possible equilibrium by $E_3 = (T^*, T_1^*, T_2^*, V_1^*, V_2^*)$. Then calculation shows that the components in E_3 must satisfy

$$T^* = \frac{\mu_1 c_1}{k_1 p_1}(i.e. \frac{d}{\lambda R_1}) = \frac{\mu_2 c_2}{k_2 p_2}(i.e. \frac{d}{\lambda R_2}),$$

$$T_1^* = \frac{c_1 V_1^*}{p_1},$$

$$T_2^* = \frac{c_2 V_2^*}{p_2}, \tag{2.7}$$

$$d(R_1 - 1) = k_1 V_1^* + k_2 V_2^*,$$

$$d(R_2 - 1) = k_1 V_1^* + k_2 V_2^*.$$

By the last two equation in (2.7), it is clear that E_3 exists if and only if

$$R_1 = R_2 > 1. \tag{2.8}$$

If (2.8) holds, there are actually infinitely many co-existence equilibria.

Summerizing the above results, we have the following conclusion. When $R_0 \le 1$, E_0 is the only equilibrium; when $R_1 > 1, R_2 \le 1$, there are E_0 and E_1; when $R_2 > 1, R_1 \le 1$, there are E_0 and E_2; when $R_1 > 1, R_2 > 1$, in addition to E_0, E_1 and E_2, there are infinitely many co-exitence equilibria if $R_1 = R_2 > 1$. Considering the fact that there are ten model parameters in R_1 and R_2, the identity $R_1 = R_2$ is unlikely to hold in reality (or infeasible), and thus, this case will not be disscussed.

2.3   Global Stability of Equilibria

In this section we study the global stability of equilibria by using the Lyapunov functions.

From Theorem 2 of [3], it follows that the DFE, E_0, is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$. Before we prove the global stability of E_0, we introduce a useful function used recently by [8, 9, 5, 16]:

$$g(x) = x - \ln(x) - 1.$$

This function attains the global minimum at $x = 1$ with $g(1) = 0$, and remains positive for all other postitive values of x. Our Lyapunov function takes advantage of these properties of $g(x)$.

Theorem 2.3.1 *If $R_0 \leq 1$, the infection free-equilibrium E_0 is globally asymptotically stable.*

Proof Let $T_0 = \frac{\lambda}{d}$ and consider the Lyapunov function

$$V(T, T_1, T_2, V_1, V_1) = T_0 g(T/T_0) + T_1 + T_2 + \frac{\mu_1}{p_1} V_1 + \frac{\mu_2}{p_2} V_2.$$

From our previous disscusion, $V(T, T_1, T_2, V_1, V_1)$ is non-negative in the positive cone R_+^5 and attains zero at E_0. We will show that the derivative of V along the trajectories of our model (2.2) is negatively definite. Indeed,

$$
\begin{aligned}
\dot{V} = \quad & \dot{T} - \frac{T_0}{T}\dot{T} + \dot{T}_1 + \dot{T}_2 + \frac{\mu_1}{p_1}\dot{V}_1 + \frac{\mu_2}{p_2}\dot{V}_2 \\[2mm]
= \quad & \lambda - dT - k_1 T V_1 - k_2 T V_2 - \frac{T_0}{T}(\lambda - dT - k_1 T V_1 - k_2 T V_2) \\[2mm]
& + k_1 T V_1 - \mu_1 T_1 + k_2 T V_2 - \mu_2 T_2 \\[2mm]
& + \frac{\mu_1}{p_1}(p_1 T_1 - c_1 V_1) + \frac{\mu_2}{p_2}(p_2 T_2 - c_2 V_2).
\end{aligned}
$$

Some terms in the above can cancel out. After cancelling terms, using $T_0 = \frac{\lambda}{d}$ and rearranging terms, we obtain

$$
\begin{aligned}
\dot{V} = \quad & \lambda - dT - \frac{T_0}{T}\lambda + dT_0 \\[2mm]
& (k_1 T_0 - \frac{c_1 \mu_1}{p_1})V_1 + (k_2 T_0 - \frac{c_2 \mu_2}{p_2})V_2 \\[2mm]
= \quad & \lambda(2 - \frac{T}{T_0} - \frac{T_0}{T}) \\[2mm]
& + \frac{\mu_1 c_1}{p_1}(R_1 - 1)V_1 + \frac{\mu_2 c_2}{p_2}(R_2 - 1)V_2.
\end{aligned}
$$

Since the arithmetic mean is greater than or equal to the geometric mean and $R_0 = max\{R_1, R_2\} \leq$ 1, each of the three terms on the right hand side is non-positive. Hence $V(T, T_1, \dot{T}_2, V_1, V_1) \leq 0$ with the equality holding only at E_0. By the Lyapunov-LaSalle Theorem [10], E_0 is globally asymptotically stable if $R_0 \leq 1$.

When $R_0 > 1$, then E_0 becomes unstable and at least one of the E_1 and E_2 exists. We now investigate the global stability of these two possible single-strain equilibria.

Theorem 2.3.2 *Assume that E_1 exists (i.e. $R_1 > 1$). If $R_2 < R_1$, then, E_1 is globally asymptotically stable.*

Proof Consider the following Lyapunov function

$$V(T, T_1, T_2, V_1, V_1) = \bar{T}g(\frac{T}{\bar{T}}) + \bar{T}_1 g(\frac{T_1}{\bar{T}_1}) + T_2 + \frac{\mu_1}{p_1}\bar{V}_1 g(\frac{V_1}{\bar{V}_1}) + \frac{\mu_2}{p_2}V_2.$$

By the properties of $g(x)$, the Lyapunov function $V(T, T_1, T_2, V_1, V_1)$ is non-negative in the positive cone R_+^5 and attains zero at E_1. In order to show $\dot{V}$ is negatively definite, we differetiate $V(T, T_1, T_2, V_1, V_1)$ along the trajectories of (2.2) to get

$$\begin{aligned}
\dot{V} = & \quad (1 - \frac{\bar{T}}{T})\dot{T} + (1 - \frac{\bar{T}_1}{T_1})\dot{T}_1 + \dot{T}_2 + \frac{\mu_1}{p_1}(1 - \frac{\bar{V}_1}{V_1})\dot{V}_1 + \frac{\mu_2}{p_2}\dot{V}_2 \\
= & \quad (1 - \frac{\bar{T}}{T})(\lambda - dT - k_1 T V_1 - k_2 T V_2) + (1 - \frac{\bar{T}_1}{T_1})(k_1 T V_1 - \mu_1 T_1) \\
& + k_2 T V_2 - \mu_2 T_2 + \frac{\mu_1}{p_1}(1 - \frac{\bar{V}_1}{V_1})(p_1 T_1 - c_1 V_1) \\
& + \frac{\mu_2}{p_2}(p_2 T_2 - c_2 V_2).
\end{aligned}$$

Expanding the above equation, using the value of (2.5) and rearranging the terms, we obtain

$$\dot{V} = \quad (\lambda - dT - k_1 TV_1 - k_2 TV_2) - \frac{\bar{T}}{T}\lambda + d\bar{T} + k_1 \bar{T}V_1 + k_2 \bar{T}V_2$$

$$(k_1 TV_1 - \mu_1 T_1) - \frac{\bar{T}_1}{T_1}(k_1 TV_1 - \mu_1 T_1) + k_2 TV_2 - \mu_2 T_2$$

$$+\frac{\mu_1}{p_1}(p_1 T_1 - c_1 V_1) - \frac{\mu_1}{p_1}\frac{\bar{V}_1}{V_1}(p_1 T_1 - c_1 V_1) + p_2 T_2 - c_2 V_2$$

$$= \quad \lambda - dT - \frac{\bar{T}}{T}\lambda + d\bar{T} + k_2 \bar{T}V_2 - \frac{\bar{T}_1}{T_1}k_1 TV_1 + \bar{T}_1\mu_1$$

$$-\mu_1 T_1\frac{\bar{V}_1}{V_1} + \frac{\mu_1 c_1 \bar{V}_1}{p_1} - \frac{\mu_2 c_2 v_2}{p_2}$$

$$= \quad \lambda - dT - \frac{\bar{T}}{T}\lambda + d\bar{T} + \frac{k_2 c_1 \mu_1}{k_1 p_1}V_2 - \mu_1 \bar{T}_1\frac{k_1 TV_1}{\mu_1 T_1}$$

$$-\mu_1 \bar{T}_1\frac{\bar{T}_1}{\bar{T}_1}\frac{\bar{V}_1}{V_1} + \mu_1 \bar{T}_1 - \frac{\mu_2 c_2 v_2}{p_2}$$

$$= \quad d\bar{T}(2 - \frac{T}{\bar{T}} - \frac{\bar{T}}{T}) + \mu_1 \bar{T}_1(3 - \frac{\bar{T}}{T} - \frac{TV_1\bar{T}_1}{\bar{T}\bar{V}_1 T_1} - \frac{T_1\bar{V}_1}{\bar{T}_1 V_1})$$

$$+(\frac{k_2 c_1 \mu_1}{k_1 p_1} - \frac{\mu_2 c_2}{p_2})V_2$$

$$= \quad d\bar{T}(2 - \frac{T}{\bar{T}} - \frac{\bar{T}}{T}) + \mu_1 \bar{T}_1(3 - \frac{\bar{T}}{T} - \frac{TV_1\bar{T}_1}{\bar{T}\bar{V}_1 T_1} - \frac{T_1\bar{V}_1}{\bar{T}_1 V_1})$$

$$+\frac{\lambda}{d}k_2(\frac{1}{R_1} - \frac{1}{R_2})V_2.$$

Again by the relation of geometric mean and arithmetical mean as well as the assumption $R_2 < R_1$, we obtain that $\dot{V} \leq 0$. The equlity holds only at the equilibrium E_1. By the Lyapunov-LaSalle Theorem [10], we conclude that E_1 is globally stable in R_+^5.

Parallel to Theorem 2.3.2, we have the following theorem for E_2

Theorem 2.3.3 *Assume that E_2 exists (i.e. $R_2 > 1$). If $R_1 < R_2$, then E_2 is globally asymptotically stable.*

Proof The proof of this theorem is symmetric to that of Theorem 2.3.2, by considering the Lyapunov function

$$V(T, T_1, T_2, V_1, V_1) = \tilde{T}g(\frac{T}{\tilde{T}}) + T_1 + \tilde{T}_2 g(\frac{T_2}{\tilde{T}_2}) + \frac{\mu_1}{p_1}V_1 + \frac{\mu_2}{p_2}\tilde{V}_2 g(\frac{V_2}{\tilde{V}_2}).$$

We omit the details of proof.

From the biological perspective, when $R_0 > 1$ and $R_1 \neq R_2$, the viral strain that has the greater reproductive number will dominate the virus population. That is, competition exclusion generically holds in this case. The diagram in Figure 2.1 summarizes the results in Theorems 2.3.1 - 2.3.3 in the $R_1 - R_2$ plane, where the equilibria in bold font is stable in that region, while the rest are unstable.
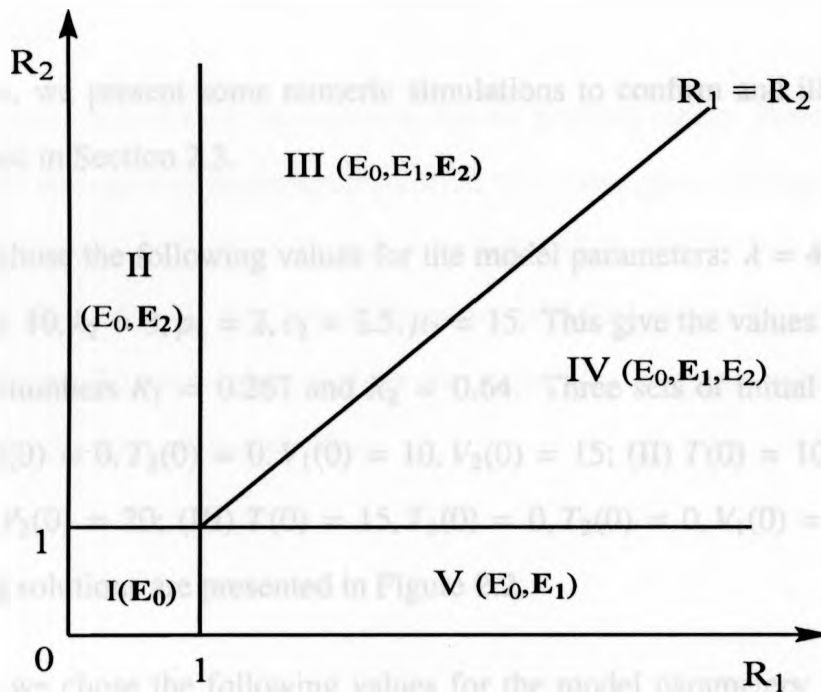
Figure 2.1: Global Stability of Equilibria

Remark A more general model with n strains was proposed and analysed in [11]. Competition exclusion result was also established for that model under the condition $1 < R_n \leq R_{n-1} \leq \dots \leq R_2 < R_1$. Our results for $n = 2$ case give a bit more information as explained below.

By [11], for $n = 2$, if $1 < R_2 < R_1$, then E_1 is globally asymptotically stable; if $1 < R_1 < R_2$, then E_2 is globally asymptotically stable. By our results, if $R_2 < R_1$ and $R_1 > 1$, then E_1 is

globally asymptotically stable, regardless of whether $R_2 \leq 1$ or $R_2 > 1$. Similarly if $R_1 < R_2$ and $R_2 > 1$, then E_2 is globally asymptotically stable, regardless of whether $R_1 \leq 1$ or $R_1 > 1$. Moreover, for case $R_1 = R_2 > 1$, there is no information on the dynamics of the model in [11]. However we have shown that in this critical case, there are infinitely many positive equilibria. And numerical simulations show that every positive solution converges to one of these positive equilibria.

2.4   Numerical Simulations

In this section, we present some numeric simulations to confirm and illustrate the theoretic results obtained in Section 2.3.

First, we chose the following values for the model parameters: $\lambda = 4, d = 1, k_1 = 2, p_1 = 1, c_1 = 3, \mu_1 = 10, k_2 = 3, p_2 = 2, c_2 = 2.5, \mu_2 = 15$. This give the values two individual basic reproduction numbers $R_1 = 0.267$ and $R_2 = 0.64$. Three sets of initial values are used: (I) $T(0) = 20, T_1(0) = 0, T_2(0) = 0, V_1(0) = 10, V_2(0) = 15$; (II) $T(0) = 10, T_1(0) = 0, T_2(0) = 0, V_1(0) = 8, V_2(0) = 20$; (III) $T(0) = 15, T_1(0) = 0, T_2(0) = 0, V_1(0) = 20, V_2(0) = 9$. The corresponding solutions are presented in Figure 2.2.

Secondly, we chose the following values for the model parameters: $\lambda = 4, d = 1, k_1 = 5, p_1 = 6, c_1 = 4, \mu_1 = 3, k_2 = 1, p_2 = 4, c_2 = 3, \mu_2 = 4$. This give the values two individual basic reproduction numbers $R_1 = 10$ and $R_2 = 1.33$. Three sets of initial values are used: (I) $T(0) = 20, T_1(0) = 0, T_2(0) = 0, V_1(0) = 6, V_2(0) = 18$; (II) $T(0) = 10, T_1(0) = 0, T_2(0) = 0, V_1(0) = 10, V_2(0) = 15$; (III) $T(0) = 15, T_1(0) = 0, T_2(0) = 0, V_1(0) = 20, V_2(0) = 10$. The corresponding solutions are presented in Figure 2.3.

Thirdly, we chose the following values for the model parameters: $\lambda = 10, d = 1, k_1 = 4, p_1 = 8, c_1 = 8, \mu_1 = 5, k_2 = 3, p_2 = 10, c_2 = 5, \mu_2 = 4$. This give the values two individual basic reproduction numbers $R_1 = 8$ and $R_2 = 15$. Three sets of initial values are used: (I)

$T(0) = 10, T_1(0) = 0, T_2(0) = 0, V_1(0) = 4, V_2(0) = 6$; (II) $T(0) = 20, T_1(0) = 0, T_2(0) =$ $0, V_1(0) = 7, V_2(0) = 15$; (III) $T(0) = 15, T_1(0) = 0, T_2(0) = 0, V_1(0) = 20, V_2(0) = 10$. The corresponding solutions are presented in Figure 2.4.

We mentioned that the case $R_1 = R_2 > 1$ is too sensitive in reality and thus, is practically not feassible. But mathematically, in this case there are infinitely many co-infection equilibria whose V_1 and V_2 component are given by the following linear equation with the non-negative restriction:

$$\begin{cases} k_1 V_1 + k_2 V_2 = d(R - 1), \\ V_1 \geq 0, V_2 \geq 0. \end{cases}$$

In such a case, no particular equilibrium can be globally stable. However, the simulations show that every biologically meaningful solution will converge to one equilibrium. To demonstrate this, we choose $\lambda = 4, d = 1, k_1 = 2, p_1 = 3, c_1 = 1, \mu_1 = 4, k_2 = 4, p_2 = 1.5, c_2 = 2, \mu_2 = 2$, giving $R_1 = R_2 = 6 > 1$. For two different set of initial values, the simulation results are presented in Figure 2.5 where the plottings are on the $V_1 - V_2$ plane, which clearly show that the convergence depends on initial values.
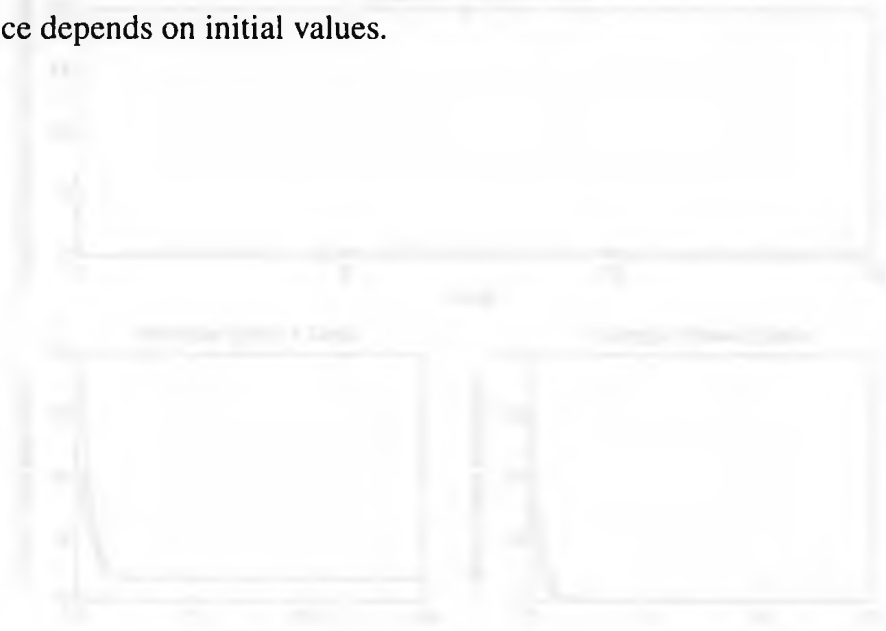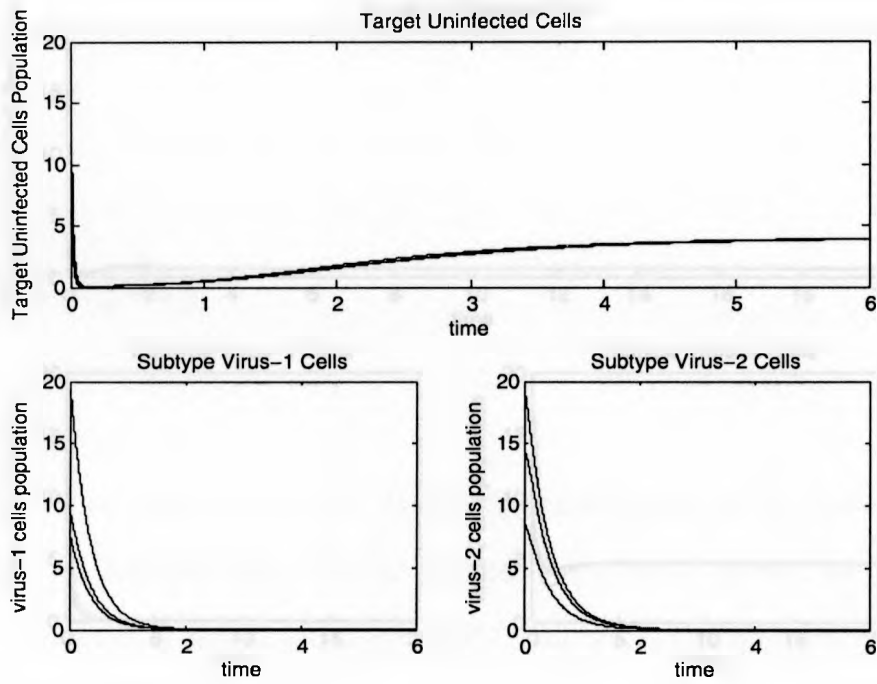
Figure 2.2: $R_1 < 1$ and $R_2 < 1$: viruses of both strains all die out.
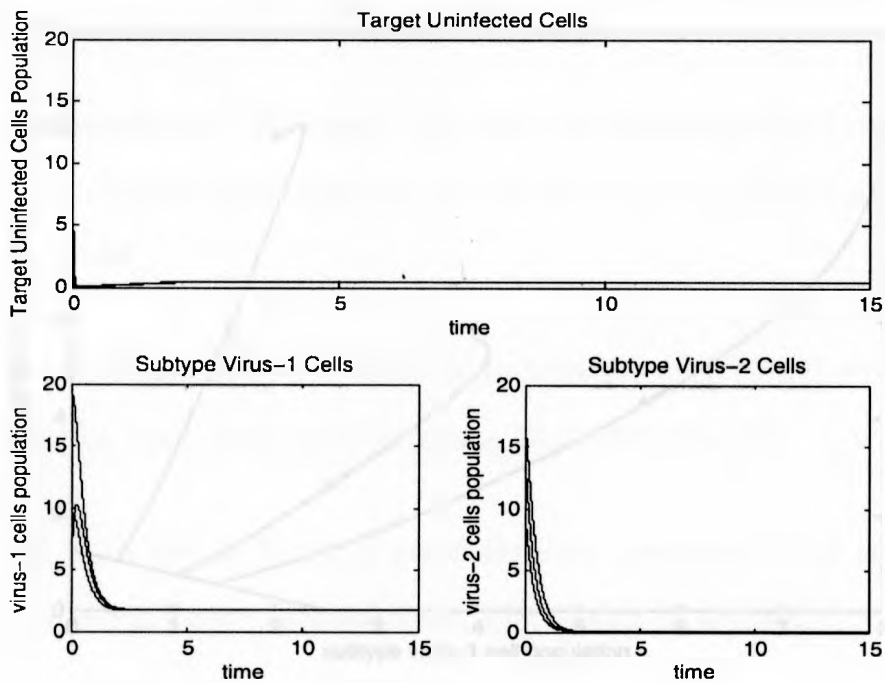
Figure 2.3: $R_1 > 1$ and $R_2 < R_1$: subtype-1 wins the competition.
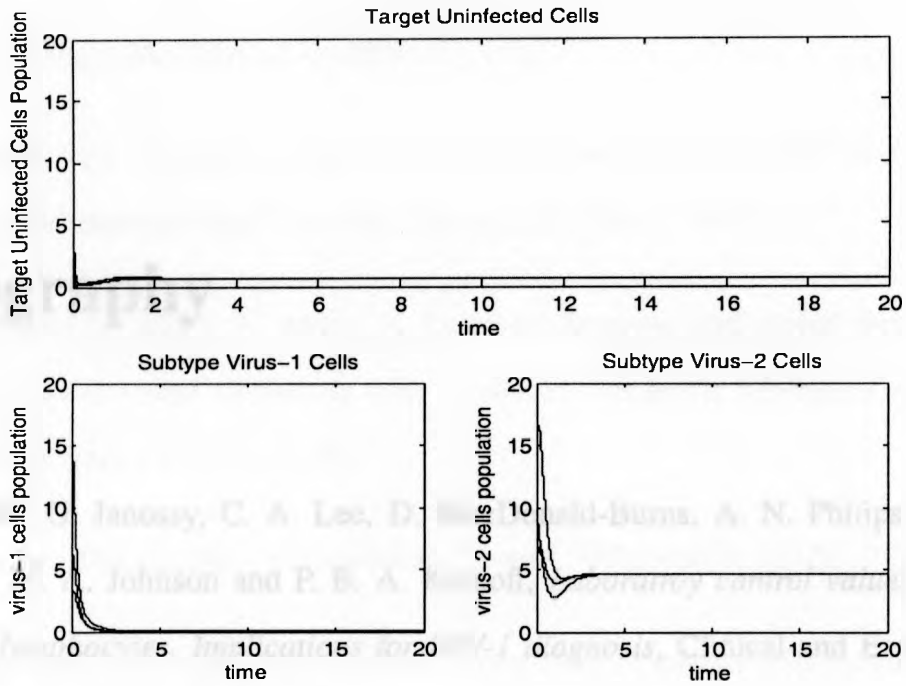
Figure 2.4: $R_2 > 1$ and $R_1 < R_2$: subtype-2 wins the competition.
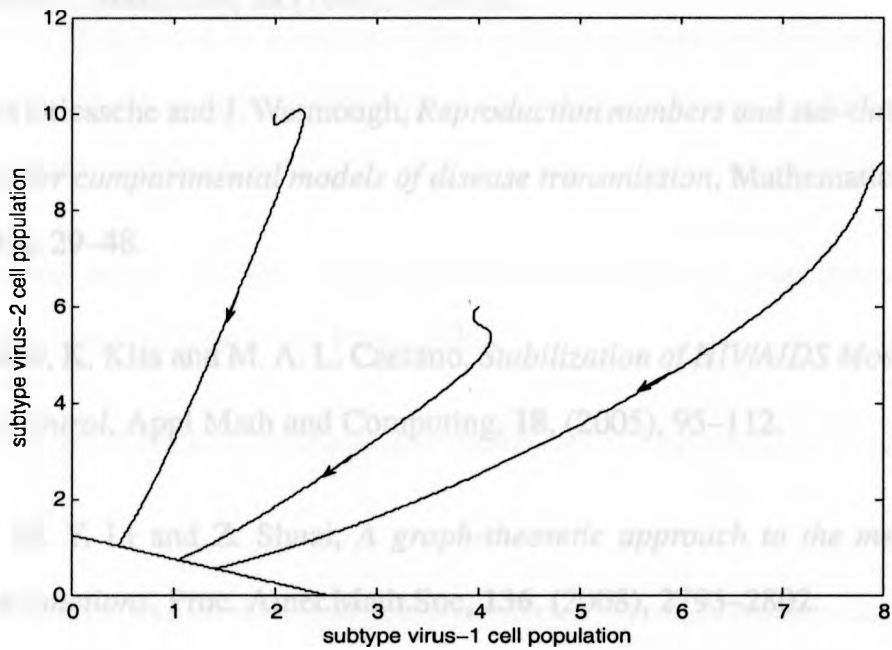
Figure 2.5: $R_1 = R_2 > 1$: co-infection occurs.

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Chapter 3

Global Dynamics of A two-strain HIV Infection Model with Intracellular Delay

3.1   Introduction

It has been realized that mathematical modelling can provide valuable insight into HIV-1 pathogenesis. These mathematical models are formulated by using differential equations to explore the mechanisms and dynamical behaviors of the viral infection process [3, 8, 17, 18, 19]. Such understanding may offer guidance for developing efficient anti-viral drug therapies [14, 15, 10].

In the previous chapter, we studied the two-strain viruses competition for host resources during HIV infection by the following systems of ordinary differential equations:

$$\dot{T} = \lambda - dT - k_1 T V_1 - k_2 T V_2,$$

$$\dot{T}_1 = k_1 T V_1 - \mu_1 T_1,$$

$$\dot{T}_2 = k_2 T V_2 - \mu_2 T_2, \qquad (3.1)$$

30

$$\dot{V}_1 = p_1 T_1 - c_1 V_1,$$

$$\dot{V}_2 = p_2 T_2 - c_2 V_2,$$

where $T(t)$ is the population size of uninfected target cells, whereas $T_1(t)$ denotes the population size of cells productively infected by subtype-1 virus and $T_2(t)$ denotes the population size of cells productively infected by subtype-2 virus at time t. $V_1(t)$ and $V_2(t)$ represent the respective population sizes of subtype-1 and subtype-2 viruses. The positive constant λ is the rate at which new target cells are generated, d is their specific death rate, k_1 and k_2 represent the rate constants at which uninfected target cells are infected by subtype-1 and subtype-2 virus, respectively. The two subtypes of infected cells are assumed to have different death rate μ_1 and μ_2. Once uninfected target cells are infected either by subtype-1 (subtype-2) virus, new subtype-1 (subtype-2) virus particles are produced with constant rate p_1 (p_2), the two types have the respective clearance rate c_1 and c_2. An underlying assumption in such an ODE model is that infection of cells by virions is instantaneous and the production of new virions by infected cells is instantaneous as well.

However, in reality, there is a lag between the time target cells are contacted by virus particles and the time the contacted cells become actively affected meaning that the virions have enter cells and started producing new virions [23]. This can be explained by the initial phase of the virus life cycle, which include all stages from viral attachment until the time that the host cell contains the infectious viral particles in its cytoplasm. To account for this lag, models that include time delays have been developed and investigated [8, 15, 23]. One distinct feature of delay differential equation models is that a delay typically destabilize an stable equilibrium and cause sustained oscillation through Hopf bifurctions. By rigorously establishing the global dynamics of the two-strain competitive viral model with intracellular delays, we show that no sustained oscillations are possible in our model.

To incorporate the intracellular phase of the virus life-cycle, we assume that subtype-1 virus and subtype-2 virus production occur in average, τ_1 and τ_2 time units later, after the respective virus enter the host cells. The recruitment of subtype-1 virus producing cells at time t is given

by the number of cells that were newly infected by strain-1 at time $t - \tau_1$ and are still alive at

time t. In the same way, the recruitment of subtype-2 virus producing cells at time t is given by

the number of cells that were newly infected by strain-2 at time $t - \tau_2$ and are still alive at time

t. If we assume two constant death rates s_1 and s_2 for infected but not yet virus-producing cells

for subtype-1 and subtype-2, the probability of subtype-1 surviving the time period from $t - \tau_1$

to t is $e^{-s_1\tau_1}$, the probability of subtype-2 surviving the time period from $t - \tau_2$ to t is $e^{-s_2\tau_2}$.

The transfer diagram for the transmission of viral infection under such a scenario is shown in

Figure 3.1. Thus the following delay differential equations model is proposed:

$$\dot{T} = \lambda - dT(t) - k_1 T(t) V_1(t) - k_2 T(t) V_2(t),$$

$$\dot{T_1} = k_1 T(t - \tau_1) V_1(t - \tau_1) e^{-s_1\tau_1} - \mu_1 T_1(t),$$

$$\dot{T_2} = k_2 T(t - \tau_2) V_2(t - \tau_2) e^{-s_2\tau_2} - \mu_2 T_2(t), \tag{3.2}$$

$$\dot{V_1} = p_1 T_1(t) - c_1 V_1(t),$$

$$\dot{V_2} = p_2 T_2(t) - c_2 V_2(t),$$

Delays have been incorporated into virus dynamics models in [8, 23, 12], but only for single strain models. Here we consider two strains. Many previous in-host models also considered the effects of anti-viral drug therapies such as HAART [15, 1, 21], but only local stability were analysed in these works. We note that by renaming the coefficients due to the effect of reverse transcriptase inhibitors and protease inhibitors, the model in [15, 1, 21] can be transformed into the form of (3.2). Our results on the global dynamics of model (3.2) can apply to these models with anti-viral therapies, and hence can rule out the existence of periodic solutions. This shows novelty of this work and should benefit other researchers working on similar models.

In the present chapter we analyse model (3.2) including intracellular delays. We establish global asymptotic stability of the infected-free, and single-infected by constructing Lyapunov functionals. To this end, we first establishes the well-posedness of (3.2) in section 3.2. Then we discuss the existence of equilibria in the feasible region and derive the basic reproductive
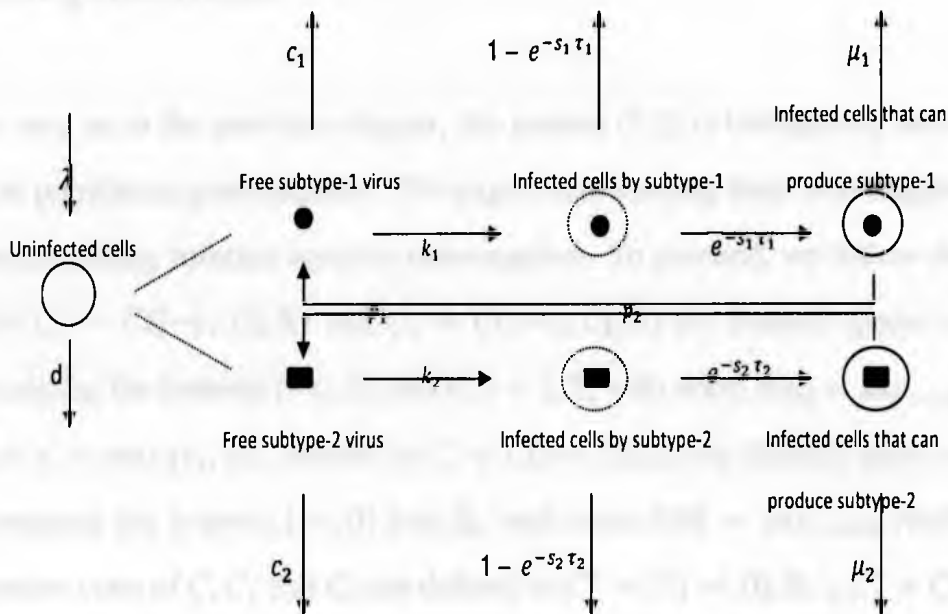
Figure 3.1: Transfer diagram for model (3.2)

number R_0. It turns out that R_1 is a decreasing function of the delay τ_1 and R_2 is a decreasing function of the delay τ_2. These imply that ignoring the intracellular delays will overestimate the basic reproduction number. We show that the basic reproductive number R_0 generically determines the global dynamics of model (3.2). More specifically, if $R_0 \leq 1$, the infection-free equilibrium E_0 is globally asymptotically stable, and two subtype viruses will be cleared; if $R_0 > 1$ and $R_1 \neq R_2$, the single-infected equilibrium arising from the greater basic reproduction number is globally asymptotically stable. The proof utilizes a global Lyapunov functional that is motivated by the work in [11, 12]. The global stability of single-infected equilibira rule out any possibility of sustained oscillations. In addition, numerical simulations are also conducted to demonstrate global dynamics of system (3.2).

3.2 Well-posedness

In the same way as in the previous chapter, the system (3.2) is biologically acceptable in the sense that no population goes negative. We expect that starting from non-negative initial values, the corresponding solution remains non-negative. To proceed, we follow the convention to denote by $C_1 = C([-\tau_1, 0], \mathbb{R})$ and $C_2 = C([-\tau_2, 0], \mathbb{R})$ the Banach spaces of continuous functions mapping the interval $[-\tau_i, 0]$ into $\mathbb{R}$, $i = 1, 2$, with norm $\|\Phi_i\| = sup_{-\tau_i \leq \theta \leq 0} |\Phi_i(\theta)|$ for $\Phi_i \in C_i$. Let $\tau = max\{\tau_1, \tau_2\}$, denote by $C = C([-\tau, 0], \mathbb{R})$ the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}$, with norm $\|\Phi\| = sup_{-\tau \leq \theta \leq 0} |\Phi(\theta)|$ for $\theta \in C$. The nonnegative cone of C, C_1 and C_2 are defined as $C^+ = C([-\tau, 0], \mathbb{R}_+), C_1^+ = C([-\tau_1, 0], \mathbb{R}_+)$ and $C_2^+ = C([-\tau_2, 0], \mathbb{R}_+)$. The initial conditions for system (3.2) are chosen at $t = 0$ as $\varphi \in C^+ \times \mathbb{R}_+ \times \mathbb{R}_+ \times C_1^+ \times C_2^+$. The well-posedness for our delay differential equation model (3.2) is established by the following theorem.

Theorem 3.2.1 *Under the above initial conditions, all solutions of system* (3.2) *are positive and ultimately bounded in* $C \times \mathbb{R} \times \mathbb{R} \times C_1 \times C_2$

Proof First, we prove that $T(t)$ is positive for all $t \geq 0$. Assuming the opposite, let $t_1 > 0$ be the first time such that $T(t_1) = 0$, which means $T(t) > 0$ as $t \in [0, t_1)$. Since

$$\dot{T} = \lambda - dT(t) - k_1 T(t) V_1(t) - k_2 T(t) V_2(t),$$

we get $\dot{T}(t_1) = \lambda > 0$, and hence $T(t) < 0$ for $t \in (t_1 - \epsilon, t_1)$ where $\epsilon > 0$ is sufficiently small. This contradicts $T(t) > 0$ for $t \in [0, t_1)$. It follows that $T(t) > 0$ for $t > 0$. Next, we show $V_1(t) \geq 0$ for all $t \geq 0$. Assume the opposite and let $t_2 > 0$ be the first time such that $V_1(t_2) = 0$. Since

$$\dot{V}_1(t) = p_1 T_1(t) - c_1 V_1(t),$$

we have $\dot{V}_1(t_2) = p_1 T_1(t_2)$. On the other hand, solving $T_1(t)$ by the second equation of (3.2) gives

$$T_1(t_2) = (T_1(0) + \int_0^{t_2} k_1 T(\theta - \tau_1) V_1(\theta - \tau_1) e^{-s_1 \tau_1} e^{\mu_1 \theta} d\theta) e^{-\mu_1 t_2} > 0$$

Hence $\dot{V}_1(t_2) = p_1 T_1(t_2) > 0$ implying $V_1(t)$ is positive for all $t \geq 0$.

The positiveness of $T(t)$ and $V_1(t)$ and the following formula

$$T_1(t) = (T_1(0) + \int_0^t k_1 T(\theta - \tau_1) V_1(\theta - \tau_1) e^{-s_1 \tau_1} e^{\mu_1 \theta} d\theta) e^{-\mu_1 t} > 0.$$

in turn leads to the positiveness of $T_1(t)$ for all $t \geq 0$. Similarly, we can show that $V_2(t)$ and $T_2(t)$ are positive for $t \geq 0$ under positive initial conditions.

From the first equation of (3.2), we obtain $\dot{T}(t) \leq \lambda - dT(t)$. Hence $limsup_{t\to\infty} T(t) \leq \frac{\lambda}{d}$. Adding the first three equations of (3.2), it follows

$$(T(t) + T_1(t + \tau_1) + T_2(t + \tau_2))' = \lambda - dT(t) - \mu_1 T_1(t + \tau_1) - \mu_2 T_2(t + \tau_2)$$

$$+ k_1 T(t) V_1(t)(e^{-s_1 \tau_1} - 1) + k_2 T(t) V_2(t)(e^{-s_2 \tau_2} - 1)$$

$$\leq \lambda - \bar{r}(T(t) + T_1(t + \tau_1) + T_2(t + \tau_2))$$

where $\bar{r} = min\{d, \mu_1, \mu_2\}$. Thus, $limsup_{t\to\infty}(T(t) + T_1(t + \tau_1) + T_2(t + \tau_2)) \leq \frac{\lambda}{\bar{r}}$. For any $\epsilon > 0, \exists t^* > 0$, such that $T(t) + T_1(t + \tau_1) + T_2(t + \tau_2) \leq \frac{\lambda}{\bar{r}} + \epsilon$ for all $t \geq t^*$. Thus, $T(t), T_1(t)$ and $T_2(t)$ are all ultimately bounded by $\frac{\lambda}{\bar{r}}$. The fourth equation of (3.2) implies

$$\dot{V}_1 = p_1 T_1(t) - c_1 V_1(t) \leq p_1(\frac{\lambda}{\bar{r}} + \epsilon) - c_1 V_1(t), t \geq t^*$$

This implies $limsup_{t\to\infty} V_1 \leq \frac{p_1}{c_1}(\frac{\lambda}{\bar{r}} + \epsilon)$. Since $\epsilon > 0$ is arbitrary, we attain $limsup_{t\to\infty} V_1(t) \leq \frac{p_1 \lambda}{c_1 \bar{r}}$. Similarly, we can obtain $limsup_{t\to\infty} V_2(t) \leq \frac{p_2 \lambda}{c_2 \bar{r}}$. Therefore, $T(t), T_1(t), T_2(t), V_1(t)$ and $V_2(t)$ are ultimately bounded in $C \times \mathbb{R} \times \mathbb{R} \times C_1 \times C_2$.

3.3   Equilibria and basic reproduction numbers

In system (3.2), without infection $(T_1, T_2, V_1, V_2) = (0, 0, 0, 0)$, uninfected target cells stabilizes at the equilibrium $T = \frac{\lambda}{d}$. The basic reproductive number R_1 for in-host models [17, 12, 16] measures the average number virus-producing target cells produced by an single subtype-1

virus-producing target cell during its entire infectious period in an entirely uninfected target-cell population. As illustrated in Figure 3.2, the basic reproduction number R_1 for strain-1 is given by

$$R_1 = \frac{p_1}{\mu_1} \cdot \frac{k_1 e^{-s_1 \tau_1}}{c_1} \cdot \frac{\lambda}{d}. \tag{3.3}$$

Similarly, the basic reproduction number R_2 for strain-2 which is the average number virus-producing target cells produced by an single subtype-2 virus producing target cell during its entire infectious period in an entirely uninfected target-cell population is obtained by

$$R_2 = \frac{p_2}{\mu_2} \cdot \frac{k_2 e^{-s_2 \tau_2}}{c_2} \cdot \frac{\lambda}{d}. \tag{3.4}$$

When no intracellular delay is considered, $\tau_1 = \tau_2 = 0$, our R_1 and R_2 reduce to the respective basic reproduction number for our previous model (3.1) (i.e. (2.21)). If $s > 0$, R_1 and R_2 is the decreasing functions of the delay τ_1 and τ_2. It shows that the intracellular delays decrease R_1 and R_2 if cells die during the delay periods. Thus, ignoring the intracellular delay in a viral model will overestimate the basic reproduction number.

From our system (3.2) and our result (3.3) (3.4), we define the system basic reproduction number $R_0 = max\{R_1, R_2\}$.

Model system (3.2) always has the infection-free equilibrium $E_0 = \left(\frac{\lambda}{d}, 0, 0, 0, 0\right)$. There are two possible single-infection equilibria $E_1 = \left(\bar{T}, \bar{T}_1, 0, \bar{V}_1, 0\right)$ and $E_2 = \left(\tilde{T}, 0, \tilde{T}_2, 0, \tilde{V}_2\right)$, where

$$\bar{T} = \frac{\lambda}{d}\frac{1}{R_1}, \quad \bar{T}_1 = \frac{dc_1}{k_1 p_1}(R_1 - 1), \quad \bar{V}_1 = \frac{d}{k_1}(R_1 - 1). \tag{3.5}$$

and

$$\tilde{T} = \frac{\lambda}{d}\frac{1}{R_2}, \quad \tilde{T}_2 = \frac{dc_2}{k_2 p_2}(R_2 - 1), \quad \tilde{V}_2 = \frac{d}{k_2}(R_2 - 1). \tag{3.6}$$

It turns out that the values of R_1 and R_2 determine the existence of the single-infection equilibria: E_1 exists if and only if $R_1 > 1$ and E_2 exists if and only if $R_2 > 1$. Obviously, E_1 and E_2

Burst size   Basic reproduction number

$$\frac{p_1}{\mu_1} \qquad R_1 = \frac{\lambda}{d} \cdot \frac{k_1 e^{-s_1 \tau_1}}{c_1} \cdot \frac{p_1}{\mu_1}$$
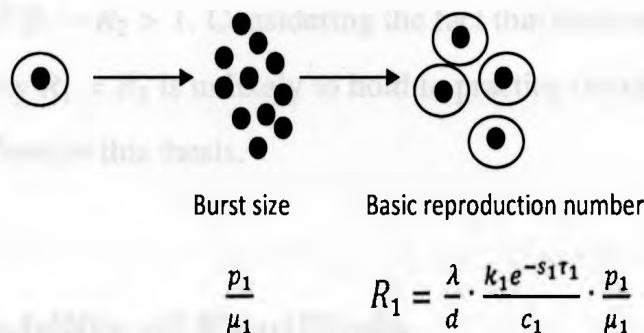
Figure 3.2: An illustration of the basic reproduction number in model(3.2)

are biologically meaningful under the conditions.

It is also possible for our model (3.2) to obtain the double-infection equilibrium which means a equilibrium with all components being positive. Denote such a possible equilibrium by $E_3 = \left(T^*, T_1^*, T_2^*, V_1^*, V_2^*\right)$, Then calculation shows that the components in E_3 must satisfy

$$T^* = \frac{\mu_1 c_1 e^{s_1 \tau_1}}{k_1 p_1} (i.e. \frac{d}{\lambda R_1}) = \frac{\mu_2 c_2 e^{s_2 \tau_2}}{k_2 p_2} (i.e. \frac{d}{\lambda R_2}),$$

$$T_1^* = \frac{c_1 V_1^*}{p_1},$$

$$T_2^* = \frac{c_2 V_2^*}{p_2}, \tag{3.7}$$

$$d(R_1 - 1) = k_1 V_1^* + k_2 V_2^*,$$

$$d(R_2 - 1) = k_1 V_1^* + k_2 V_2^*.$$

By the last two equation in (3.7), it is clear that E_3 exists if and only if

$$R_1 = R_2 > 1. \tag{3.8}$$

If (3.8) holds, there are actually infinitely many co-existence equilibria.

Summarizing the above results, we have the following conclusion. When $R_0 \leq 1$, E_0 is the only equilibrium; when $R_1 > 1, R_2 \leq 1$, there are E_0 and E_1; when $R_2 > 1, R_1 \leq 1$, there are E_0 and E_2; when $R_1 > 1$ and $R_2 > 1$, in addition to E_0, E_1 and E_2, there are infinitely many

co-exitence equilibria if $R_1 = R_2 > 1$. Considering the fact that there are ten model parameters in R_1 and R_2, the identity $R_1 = R_2$ is unlikely to hold in practice (or infeasible), and hence, E_3 will not be considered here in this thesis.

3.4   Global Stability of Equilibria

In this section we study the global stability of equilibria by using the Lyapunov functionals.

We apply Lyapunov functionals similar to those recently used by [11, 6, 20]. A useful function is used to construct our Lyapunov fuctionals:

$$g(x) = x - \ln(x) - 1.$$

This function attains the global minimum at $x = 1$, $g(1) = 0$, and remains positive for all other postitive values of x. Our Lyapunov functionals take advantage of these properties of $g(x)$. In the following theorems we show that the equilibria exhibit global stability under some threshold conditions.

Theorem 3.4.1 *If $R_0 \leq 1$, the infection free-equilibrium E_0 is globally asymptotically stable.*

Proof Let $T_0 = \frac{\lambda}{d}$ and consider the Lyapunov functional

$$
V(T, T_1, T_2, V_1, V_1) = \quad T_0 g(T(t)/T_0) + e^{s_1 \tau_1} T_1(t) + e^{s_2 \tau_2} T_2(t)
$$
$$
+ \frac{\mu_1}{p_1} e^{s_1 \tau_1} V_1(t) + \frac{\mu_2}{p_2} e^{s_2 \tau_2} V_2(t)
$$
$$
+ k_1 \int_{-\tau_1}^{0} T(t + \theta) V_1(t + \theta) \, d\theta + k_2 \int_{-\tau_2}^{0} T(t + \theta) V_2(t + \theta) \, d\theta.
$$

Obviously, $V(T, T_1, T_2, V_1, V_1)$ is non-negative in the positive cone $C^+ \times \mathbb{R}_+ \times \mathbb{R}_+ \times C_1^+ \times C_2^+$ and attains zero at E_0. We will show that the derivative of V along the trajectories of our model (3.2) is negatively defininte. Differentiation gives

$$\dot{V} = T(t) - \frac{T_0}{T(t)}\dot{T}(t) + e^{s_1\tau_1}\dot{T_1}(t) + e^{s_2\tau_2}\dot{T_2}(t) + \frac{\mu_1}{p_1}e^{s_1\tau_1}\dot{V_1}(t) + \frac{\mu_2}{p_2}e^{s_2\tau_2}\dot{V_2}(t)$$

$$+k_1T(t)V_1(t) - k_1T(t-\tau_1)V_1(t-\tau_1) + k_2T(t)V_2(t) - k_2T(t-\tau_2)V_2(t-\tau_2)$$

$$= \lambda - dT(t) - k_1T(t)V_1(t) - k_2T(t)V_2(t) - \frac{T_0}{T(t)}(\lambda - dT - k_1T(t)V_1(t) - k_2T(t)V_2(t))$$

$$+e^{s_1\tau_1}(k_1T(t-\tau_1)V_1(t-\tau_1)e^{-s_1\tau_1} - \mu_1T_1) + e^{s_2\tau_2}(k_2T(t-\tau_2)V_2(t-\tau_2)e^{-s_2\tau_2} - \mu_2T_2)$$

$$+\frac{\mu_1}{p_1}e^{s_1\tau_1}(p_1T_1(t) - c_1V_1(t)) + \frac{\mu_2}{p_2}e^{s_2\tau_2}(p_2T_2(t) - c_2V_2(t))$$

$$+k_1T(t)V_1(t) - k_1T(t-\tau_1)V_1(t-\tau_1) + k_2T(t)V_2(t) - k_2T(t-\tau_2)V_2(t-\tau_2)$$

After cancelling terms, using $T_0 = \frac{\lambda}{d}$ and rearranging terms, we get

$$\dot{V} = \lambda - dT(t) - \frac{T_0}{T(t)}\lambda + dT_0$$

$$(k_1T_0 - \frac{c_1\mu_1}{p_1}e^{s_1\tau_1})V_1(t) + (k_2T_0 - \frac{c_2\mu_2}{p_2}e^{s_2\tau_2})V_2(t)$$

$$= \lambda(2 - \frac{T(t)}{T_0} - \frac{T_0}{T(t)})$$

$$+\frac{c_1\mu_1}{p_1}e^{s_1\tau_1}(\frac{k_1p_1\lambda}{\mu_1c_1d}e^{s_1\tau_1} - 1)V_1(t) + \frac{c_2\mu_2}{p_2}e^{s_2\tau_2}(\frac{k_2p_2\lambda}{\mu_2c_2d}e^{s_2\tau_2} - 1)V_2(t)$$

$$= \lambda(2 - \frac{T(t)}{T_0} - \frac{T_0}{T(t)})$$

$$+\frac{\mu_1c_1}{p_1}e^{s_1\tau_1}(R_1 - 1)V_1(t) + \frac{\mu_2c_2}{p_2}e^{s_2\tau_2}(R_2 - 1)V_2(t).$$

Since the arithmetic mean is greater than or equal to the geometric mean, if $R_0 = max\{R_1, R_2\} \leq 1$, each of the three terms on the right hand side is non-positive. Hence $\dot{V}(T, T_1, T_2, V_1, V_1) \leq 0$, and $\dot{V} = 0$ if and only if $(T, T_1, T_2, V_1, V_1) = \left(\frac{\lambda}{d}, 0, 0, 0, 0\right) = E_0$ Therefore, the globally asymptotical stability of E_0 follows from the Lyaunov-LaSalle invariance principle by [7].

When $R_0 > 1$, then E_0 becomes unstable and at least one of the E_1 and E_2 exists. We now investigate the global stability of these two possible single-strain equilibria.

Theorem 3.4.2 *Assume that E_1 exists (i.e. $R_1 > 1$), if $R_2 < R_1$, then, E_1 is globally asymptotically stable.*

Proof Define a Lyapunov functional $V : C \times \mathbb{R} \times \mathbb{R} \times C_1 \times C_2 \to \mathbb{R}$ by

$$
\begin{aligned}
V(T, T_1, T_2, V_1, V_1) = \quad & \bar{T} g\left(\frac{T(t)}{\bar{T}}\right) + \bar{T}_1 e^{s_1 \tau_1} g\left(\frac{T_1(t)}{\bar{T}_1}\right) + e^{s_2 \tau_2} T_2(t) + \frac{\mu_1}{p_1} \bar{V}_1 e^{s_1 \tau_1} g\left(\frac{V_1(t)}{\bar{V}_1}\right) \\
& + \frac{\mu_2}{p_2} e^{s_2 \tau_2} V_2(t) + k_1 \bar{T} \bar{V}_1 \int_{-\tau_1}^{0} g\left(\frac{T(t+\theta) V_1(t+\theta)}{\bar{T} \bar{V}_1}\right) d\theta \\
& + k_2 \int_{-\tau_2}^{0} T(t+\theta) V_2(t+\theta) \, d\theta.
\end{aligned}
$$

By the properties of $g(x)$, the Lyapunov functional $V(T, T_1, T_2, V_1, V_1)$ is non-negative in the positive cone $C^+ \times \mathbb{R}_+ \times \mathbb{R}_+ \times C_1^+ \times C_2^+$ and attains zero at E_1. In order to show $\dot{V}$ is negatively definite, we differentiate $V(T, T_1, T_2, V_1, V_2)$ along the trajectories of (3.2) to get

$$
\begin{aligned}
\dot{V} = \quad & \dot{T}(t) + \frac{\bar{T}}{T(t)} \dot{T}(t) + e^{s_1 \tau_1} \dot{T}_1(t) - e^{s_1 \tau_1} \frac{\bar{T}_1}{T_1(t)} \dot{T}_1(t) + e^{s_2 \tau_2} \dot{T}_2(t) \\
& + \frac{\mu_1}{p_1} e^{s_1 \tau_1} \dot{V}_1(t) - \frac{\mu_1}{p_1} e^{s_1 \tau_1} \frac{\bar{V}_1}{V_1(t)} \dot{V}_1(t) + \frac{\mu_2}{p_2} e^{s_2 \tau_2} \dot{V}_2(t) \\
& + k_1 \bar{T} \bar{V}_1 \frac{d}{dt} \int_{-\tau_1}^{0} g\left(\frac{T(t+\theta) V_1(t+\theta)}{\bar{T} \bar{V}_1}\right) d\theta \\
& + k_2 T(t) V_2(t) - k_2 T(t - \tau_2) V_2(t - \tau_2). \quad\quad\quad\quad\quad\quad\quad\quad (3.9)
\end{aligned}
$$

Note that

$$k_1 \bar{T} \bar{V}_1 \frac{\mathrm{d}}{\mathrm{dt}} \int_{-\tau_1}^{0} g(\frac{T(t+\theta)V_1(t+\theta)}{\bar{T}\bar{V}_1}) d\theta$$

$$= \quad k_1 \bar{T} \bar{V}_1 \int_{-\tau_1}^{0} \frac{\mathrm{d}}{\mathrm{dt}} g(\frac{T(t+\theta)V_1(t+\theta)}{\bar{T}\bar{V}_1}) d\theta$$

$$= \quad k_1 \bar{T} \bar{V}_1 \int_{-\tau_1}^{0} \frac{\mathrm{d}}{\mathrm{d}\theta} g(\frac{T(t+\theta)V_1(t+\theta)}{\bar{T}\bar{V}_1}) d\theta$$

$$= \quad k_1 \bar{T} \bar{V}_1 (g(\frac{T(t)V_1(t)}{\bar{T}\bar{V}_1}) - g(\frac{T(t-\tau_1)V_1(t-\tau_1)}{\bar{T}\bar{V}_1}))$$

$$= \quad k_1 \bar{T} \bar{V}_1 (\frac{T(t)V_1(t)}{\bar{T}\bar{V}_1} - ln\frac{T(t)V_1(t)}{\bar{T}\bar{V}_1} - \frac{T(t-\tau_1)V_1(t-\tau_1)}{\bar{T}\bar{V}_1} + ln\frac{T(t-\tau_1)V_1(t-\tau_1))}{\bar{T}\bar{V}_1})$$

$$= \quad k_1 T(t)V_1(t) - k_1 \bar{T} \bar{V}_1 lnT(t)V_1(t) + k_1 \bar{T} \bar{V}_1 ln\bar{T}\bar{V}_1 - k_1 T(t-\tau_1)V_1(t-\tau_1)$$

$$\quad + k_1 \bar{T} \bar{V}_1 lnT(t-\tau_1)V_1(t-\tau_1) - k_1 \bar{T} \bar{V}_1 ln\bar{T}\bar{V}_1$$

$$= \quad k_1 T(t)V_1(t) - k_1 T(t-\tau_1)V_1(t-\tau_1)$$

$$\quad + k_1 \bar{T} \bar{V}_1 lnT(t-\tau_1)V_1(t-\tau_1) - k_1 \bar{T} \bar{V}_1 lnT(t)V_1(t) \quad (3.10)$$

Plugging (3.10) and system of (3.2) into equation (3.9), we obtain

$$\dot{V} = \quad \lambda - dT(t) - k_1 T(t)V_1(t) - k_2 T(t)V_2(t)$$

$$- \frac{\bar{T}}{T(t)}\lambda + d\bar{T} + k_1 \bar{T}V_1(t) + k_2 \bar{T}V_2(t)$$

$$+ k_1 T(t-\tau_1)V_1(t-\tau_1) - \mu_1 e^{s_1\tau_1}T_1(t)$$

$$- \bar{T}_1 \frac{k_1 T(t-\tau_1)V_1(t-\tau_1)}{T_1(t)} + e^{s_1\tau_1}\mu_1\bar{T}_1$$

$$+ k_2 T(t-\tau_2)V_2(t-\tau_2) - \mu_2 e^{s_2\tau_2}T_2(t)$$

$$+ \mu_1 e^{s_1\tau_1}T_1(t) - \frac{\mu_1 c_1}{p_1}e^{s_1\tau_1}V_1(t) \quad (3.11)$$

$$- \mu_1 e^{s_1\tau_1}\bar{V}_1 \frac{T_1(t)}{V_1(t)} + \frac{\mu_1 c_1}{p_1}e^{s_1\tau_1}\bar{V}_1$$

$$+ \mu_2 e^{s_2\tau_2}T_2(t) - \frac{\mu_2 c_2}{p_2}e^{s_2\tau_2}V_2(t)$$

$$+ k_1 T(t)V_1(t) - k_1 T(t-\tau_1)V_1(t-\tau_1)$$

$$- k_1 \bar{T}\bar{V}_1 lnT(t)V_1(t) + k_1 \bar{T}\bar{V}_1 lnT(t-\tau_1)V_1(t-\tau_1)$$

$$+ k_2 T(t)V_2(t) - k_2 T(t-\tau_2)V_2(t-\tau_2)$$

The components of E_1 are related by the equilibrium equation, i.e.,

$$\lambda = d\bar{T} + k_1 \bar{T} \bar{V}_1$$

$$k_1 \bar{T} \bar{V}_1 = \mu_1 \bar{T}_1 e^{s_1 \tau_1}$$

$$p_1 \bar{T}_1 = c_1 \bar{V}_1$$

$$k_1 \bar{T} = \frac{\mu_1 \bar{T}_1 e^{s_1 \tau_1}}{\bar{V}_1}$$

$$= \frac{\mu_1 \bar{T}_1 e^{s_1 \tau_1} c_1}{p_1 \bar{T}_1}$$

$$= \frac{\mu_1 c_1}{p_1} e^{s_1 \tau_1}.$$

Making use of these, we can rearrange and simplify the equation (3.11) as

$$
\begin{aligned}
\dot{V} = \quad & d\bar{T}\left(2 - \frac{Tt}{\bar{T}} - \frac{\bar{T}}{T(t)}\right) - \frac{k_1 \bar{T}^2 \bar{V}_1}{T(t)} \\
& + k_1 \bar{T} \bar{V}_1 + k_2 \bar{T} V_2(t) - k_1 \bar{T}_1 \frac{T(t-\tau_1)V_1(t-\tau_1)}{T_1(t)} \\
& + k_1 \bar{T} \bar{V}_1 - \frac{k_1 \bar{T} \bar{V}_1}{\bar{T}_1} \bar{V}_1 \frac{T_1(t)}{V_1(t)} \\
& + k_1 \bar{T} \bar{V}_1 - \frac{\mu_2 c_2}{p_2} e^{s_2 \tau_2} V_2(t) \\
& - k_1 \bar{T} \bar{V}_1 \ln T(t) V_1(t) + k_1 \bar{T} \bar{V}_1 \ln T(t-\tau_1)V_1(t-\tau_1) \\
= \quad & d\bar{T}\left(2 - \frac{Tt}{\bar{T}} - \frac{\bar{T}}{T(t)}\right) \\
& - k_1 \bar{T} \bar{V}_1 \left(g\left(\frac{\bar{T}_1 T(t-\tau_1)V_1(t-\tau_1)}{\bar{T} \bar{V}_1 T_1(t)}\right) - \ln\frac{\bar{T}_1 T(t-\tau_1)V_1(t-\tau_1)}{\bar{T} \bar{V}_1 T_1(t)}\right) \\
& - k_1 \bar{T} \bar{V}_1 \left(g\left(\frac{\bar{T}}{T(t)}\right) - \ln\frac{\bar{T}}{T(t)}\right) \\
& - k_1 \bar{T} \bar{V}_1 \left(g\left(\frac{\bar{V}_1 T_1(t)}{\bar{T}_1 V_1(t)}\right) - \ln\frac{\bar{V}_1 T_1(t)}{\bar{T}_1 V_1(t)}\right) \\
& - k_1 \bar{T} \bar{V}_1 \left(\ln T(t)V_1(t) - \ln T(t-\tau_1)V_1(t-\tau_1)\right) \\
& + \left(k_2 \bar{T} - \frac{\mu_2 c_2}{p_2} e^{s_2 \tau_2}\right)V_2(t)
\end{aligned}
$$

$$= dT\bar{T}(2 - \frac{Tt}{\bar{T}} - \frac{\bar{T}}{T(t)})$$

$$- k_1\bar{T}\bar{V}_1 g(\frac{\bar{T}_1 T(t-\tau_1)V_1(t-\tau_1)}{\bar{T}\bar{V}_1 T_1(t)})$$

$$- k_1\bar{T}\bar{V}_1 g(\frac{\bar{T}}{T(t)}) - k_1\bar{T}\bar{V}_1 g(\frac{\bar{V}_1 T_1(t)}{\bar{T}_1 V_1(t)})$$

$$+ \frac{k_2\lambda}{d}(\frac{1}{R_1} - \frac{1}{R_2})V_2(t).$$

Therefore, by our assumptions, $\dot{V} \le 0$ with equality holding only at E_1. From the Lyapunov-LaSalle inveriance principle [7], the equilibrium E_1 is globally asymptotically stable. The proof is completed.

Parallel to Theorem 3.4.2, we have the following theorem for E_2

Theorem 3.4.3 *Assume that E_2 exists (i.e. $R_2 > 1$), if $R_1 < R_2$, then E_2 is globally asymptotically stable.*

Proof The proof of this theorem is symmetric to that of Theorem 3.4.2 by considering the following Lyapunov functional: $V : C \times \mathbb{R} \times \mathbb{R} \times C_1 \times C_2 \to \mathbb{R}$

$$V(T, T_1, T_2, V_1, V_1) = \bar{T}g(\frac{T(t)}{\bar{T}}) + e^{s_1\tau_1}T_1(t) + \bar{T}_2 e^{s_2\tau_2}g(\frac{T_2(t)}{\bar{T}_2}) + \frac{\mu_1}{p_1}e^{s_1\tau_1}V_1(t)$$

$$+ \frac{\mu_2}{p_2}\tilde{V}_2 e^{s_2\tau_2}g(\frac{V_2(t)}{\tilde{V}_2}) + k_1\int_{-\tau_1}^{0} T(t+\theta)V_1(t+\theta)\,d\theta$$

$$k_2\bar{T}\tilde{V}_2\int_{-\tau_2}^{0} g(\frac{T(t+\theta)V_2(t+\theta)}{\bar{T}\tilde{V}_2})\,d\theta$$

We omit the details of the proof.

The results of Theorem 3.4.1 - 3.4.3 can also be visualized by Figure 2.1 in chapter 2, except that R_1 and R_2 are now defined by 3.3 and 3.4, instead of 2.4.

3.5   Numerical Simulations

In this section, we present some numeric simulations for the DDE model (3.2) to confirm and illustrate the theoretic results obtained in Section 3.4, which is not significantly different from those for the ODE model (2.2), except that some plottings are in logarithmic function for better and clearer displays.

First, we chose the following values for the model parameters: $\lambda = 6, d = 1, k_1 = 2, p_1 = 1, c_1 = 3, \mu_1 = 10, s_1 = 2, \tau_1 = 0.1, k_2 = 3, p_2 = 2, c_2 = 2.5, \mu_2 = 15, s_2 = 1.5, \tau_2 = 0.15$. This give the values two individual basic reproduction numbers $R_1 = 0.327$ and $R_2 = 0.767$. Three sets of initial values are used: (I) $T(0) = 80, T_1(0) = 50, T_2(0) = 40, V_1(0) = 45, V_2(0) = 35$; (II) $T(0) = 60, T_1(0) = 70, T_2(0) = 50, V_1(0) = 30, V_2(0) = 20$; (III) $T(0) = 50, T_1(0) = 60, T_2(0) = 30, V_1(0) = 20, V_2(0) = 45$. We used a base 10 logarithmic scale for target cells population. The corresponding solutions are presented in Figure 3.3.

Secondly, we chose the following values for the model parameters: $\lambda = 6, d = 1, k_1 = 5, p_1 = 6, c_1 = 4, \mu_1 = 3, s_1 = 2, \tau_1 = 0.1, k_2 = 1, p_2 = 4, c_2 = 3, \mu_2 = 4, s_2 = 1.5, \tau_2 = 0.15$. This give the values two individual basic reproduction numbers $R_1 = 12.28$ and $R_2 = 1.597$. Three sets of initial values are used: (I) $T(0) = 80, T_1(0) = 50, T_2(0) = 40, V_1(0) = 45, V_2(0) = 35$; (II) $T(0) = 60, T_1(0) = 70, T_2(0) = 50, V_1(0) = 30, V_2(0) = 20$; (III) $T(0) = 50, T_1(0) = 60, T_2(0) = 30, V_1(0) = 20, V_2(0) = 45$. A base 10 logarithmic scale for target cells population, subtype-1 infected cells and subtype-1 virus cells was employed in our figures. The corresponding solutions are presented in Figure 3.4.

Thirdly, we chose the following values for the model parameters: $\lambda = 6, d = 1, k_1 = 4, p_1 = 8, c_1 = 8, \mu_1 = 5, s_1 = 2, \tau_1 = 0.1, k_2 = 3, p_2 = 10, c_2 = 5, \mu_2 = 4, , s_2 = 1.5, \tau_2 = 0.15$. This give the values two individual basic reproduction numbers $R_1 = 3.93$ and $R_2 = 7.19$. Three sets of initial values are used: (I) $T(0) = 80, T_1(0) = 50, T_2(0) = 40, V_1(0) = 45, V_2(0) = 35$; (II) $T(0) = 60, T_1(0) = 70, T_2(0) = 50, V_1(0) = 30, V_2(0) = 20$; (III) $T(0) = 50, T_1(0) = 60, T_2(0) =$

$30, V_1(0) = 20, V_2(0) = 45$. A base 10 logarithmic scale for target cells population, subtype-2 infected cells and subtype-2 virus cells was employed in our figures. The corresponding solutions are presented in Figure 3.5.
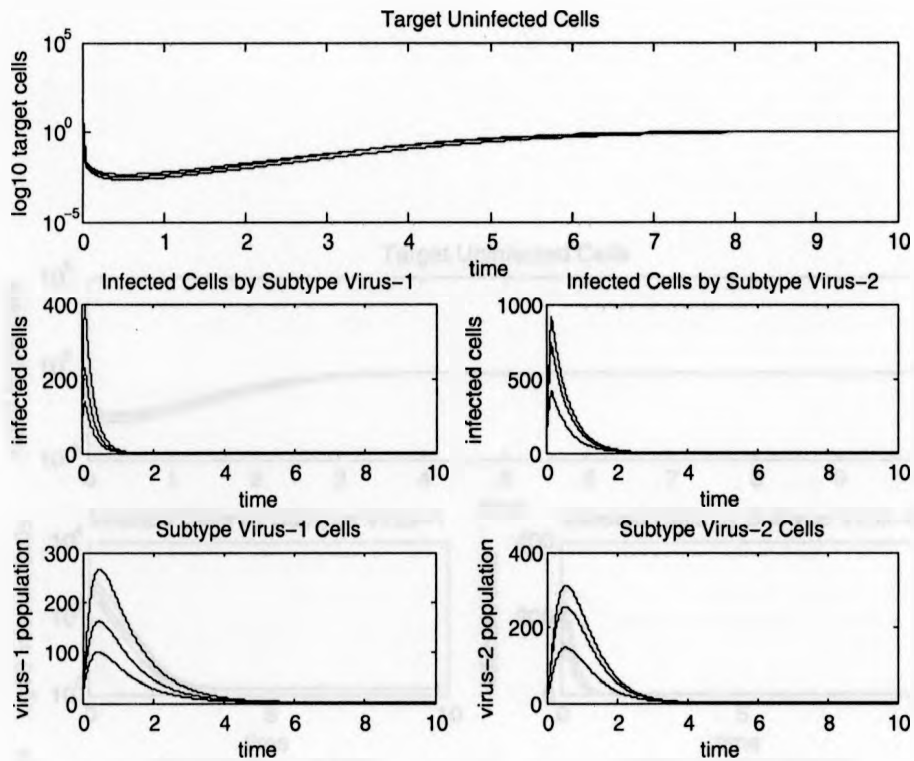

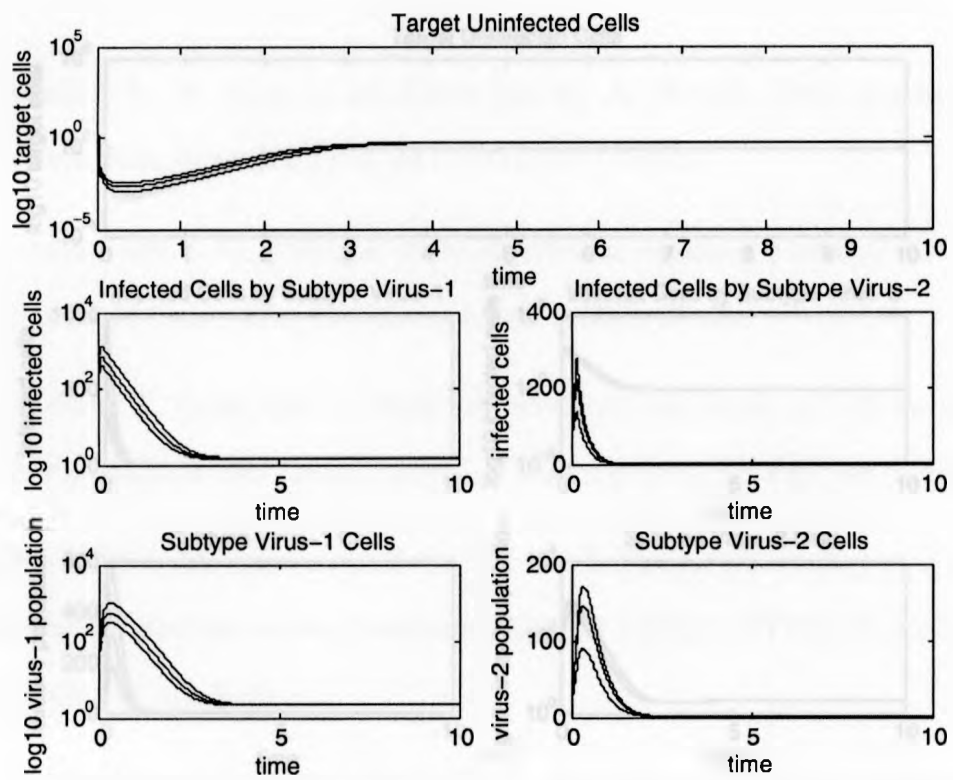Figure 3.3: $R_1 < 1$ and $R_2 < 1$: viruses of both strains all die out

Figure 3.4: $R_1 > 1$ and $R_2 < R_1$: subtype-1 wins the competition
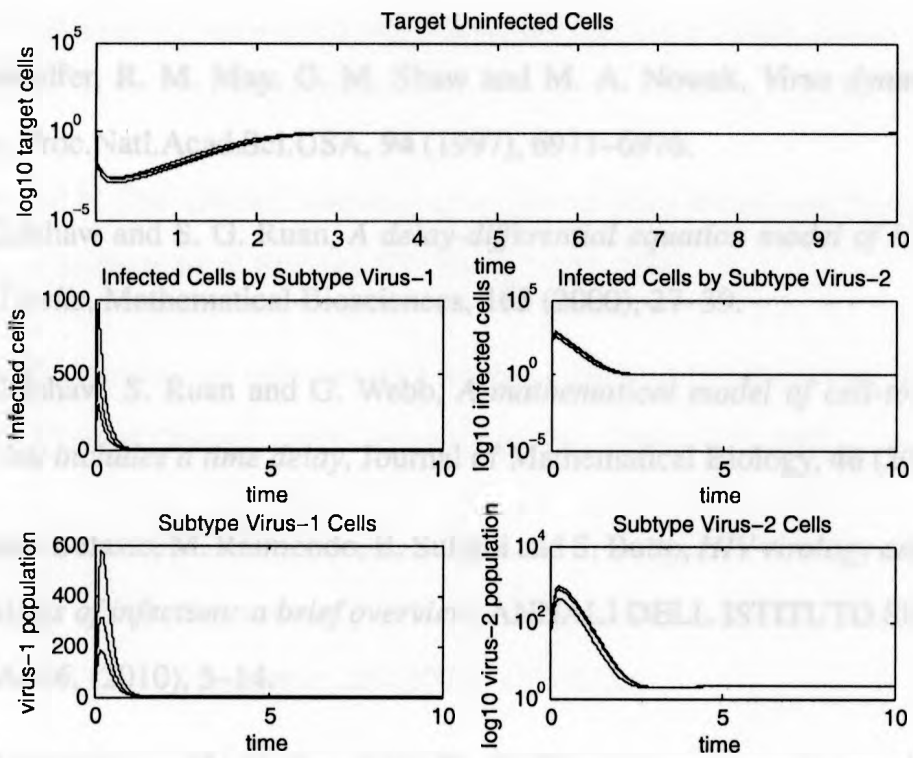
Figure 3.5: $R_2 > 1$ and $R_1 < R_2$: subtype-2 wins the competition

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Chapter 4
Conclusion and discussion

In this thesis, we have considered two mathematical models that describe the interaction of $CD4^+$ cells and the HIV virus of two different strains. The first one is a system of ordinary differential equations (ODE) and which is a result of ignoring the intracellular delays. The second one incorporate two intracellular delays resulting in a system of delay differential equations (DDE) which is essentially an infinitely dimensional system. We have verified the well-posedness of the two models. By analyzing the models, we have shown that both models demonstrate global threshold dynamics in terms of the individual and overall basic reproduction numbers. Indeed, we have identified the overall basic reproduction number $R_0 = max\{R_1, R_2\}$ where R_1 and R_2 are the respective basic reproduction numbers for strain-1 and strain-2. We have shown for both models that when $R_0 < 1$, then the infection free equilibrium is globally asymptotically stable meaning that the the virus of both strains will eventually be cleared out; when $R_0 > 1$ but $R_1 \neq R_2$, then all positive solutions approach the single infection equilibrium that corresponds to winning of the strain having the larger individual basic reproduction number. In other words, when $R_0 > 1$ but $R_1 \neq R_2$, the competition exclusion principle generically holds, implying that the co-infection can generically not be established. Even the more generous model was studied in [5] for ODE, we have to point out that our results came from looser conditions. The critical case $R_1 = R_2 > 1$ is too senstive to the pa-

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rameters because this identity invloves more than ten model paramters and thus, can seldom be satisfied in reality. If this does happen, numerical simulations show that every solution does converge to a co-infection equilibrium, but the convergence depends on the initial values.

Although both the ODE model and the DDE model demonstrate the same threshold dynamics, the results on the DDE model does reveal something important which can be explained by the formulas (3.3) and (3.4). These two formulas show that the individual basic reproduction numbers depend on the corresponding delays and hence the overall basic reproduction number depends on the two delays. Indeed they are decreasing in τ_1 and τ_2. An implication is that if the intracellular delays are ignored, the basic reproduction numbers will be overcalculated.

We pointed out that although we have only considered two strains, by the nature of competition, and by the mathematical theory on competitive systems, we believe that the results also hold for similar models with more than two strains, either with delay or without delay.

We remark that we do not consider the immune response in the models in this thesis. It is known that the immune reponse is an important factor HIV virus enters a host, and thus, should be incorporated into models for more precise predictions. For a single strain, there have been some models with immune responses, see, e.g., [9, 1, 2, 3, 4, 6, 7, 8]. It is very natural and interesting to extend those models to ones with two or more strains. We feel such models will be much harder to analyze since even the single strain ones are already harder than those without immune reponses. Very complicated dynamics can be expected, as has been shown in the single strain model in [8].

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