DRUG-RESISTANT MUTATIONS IN MODELS OF HIV PATHOGENESIS

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Abstract

Over the past quarter-century, considerable work has been invested in the study of the Human Immunodeficiency Virus (HIV). Within the mathematical arena, numerous models have been developed to reflect various phenomena associated with the virus. We construct a new ordinary differential equation model for the evolution of the $CD4^+$ T cell population — the white blood cells principally targetted by the virus — in the presence of HIV, incorporating mutation of the wild-type virus and virus response to imperfect drug therapy. In so doing, we make the investigation of the model more tractable by eliminating an explicit reference to the virus population itself. We analyse this model both from a dynamical systems perspective and via numerical simulation, and show that the only possible long-term behaviours are the elimination of both forms of the virus, the elimination of the wild-type virus only, or the co-existence of both virus strains with the uninfected T cell population. We generalise this model to investigate the presence of multiple

mutations, and demonstrate that the behaviour of this augmented model reduces naturally to the single-mutant case. Finally, we consider the possibility of imperfect adherence to drug therapy by the patient, by introducing impulsive differential equations into the original model. We determine the impulsive periodic orbits of this model and inspect it numerically. Finally, we use this impulsive model to consider different frequencies and patterns of non-adherence on the part of the HIV sufferer. We determine that as interruptions to drug therapy occur more closely together, they become less harmful to the patient with regard to the progression of the virus.

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Dedication

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Chapter 1

Introduction to the Immune System and HIV

One of the greatest health crises of the modern era has been the outbreak of the Human Immunodeficiency Virus (HIV). Amongst the various weapons brought to bear against HIV has been the mathematical model. In this work, we shall introduce several novel models for studying HIV. But before we can introduce the analytical tools which will drive these endeavours, it is first essential that we acquaint ourselves with the two key real-world mechanisms that will contribute to our models: on one side, the human immune system, and on the other, the HIV pathogen.

In this chapter, we shall give a thorough overview of all the biological considerations of this work, illuminating in real terms how the immune system functions, and how HIV attacks the host by targetting components of the very immune system designed to safeguard it.

1.1 The Immune System

In the macroscopic world, human armies are incredibly complex entities, comprised of numerous divisions dedicated to different tasks, and consisting of a dizzying array of soldiers, each class having its own set of characteristics and duties. The human immune system is no different — it defends the body from foreign attack not through a single monolithic mechanism, but via multiple routes, making use of a variety of cells, working both together and singly, in its effort to rout invading matter. In the following, we shall summarise the essential functions of the immune system, particularly those which are important in the body's response to viral infection. See [1–3] for details.

Broadly speaking, the immune system exhibits two types of responses. The **innate** (or non-specific) response is the body's generic reaction to infection or body trauma; it is not tailored to the presence of any specific form of foreign agent or

tissue damage and represents a "one size fits all" approach to dealing with harm to the host. The **acquired** (also known as the adaptive or specific) response, on the other hand, involves cells which can identify foreign interlopers — be they mutated host cells, invading virions, or other "non-self" microorganisms — and coordinate a suitable retaliation. The cells which play the most crucial role in both the innate and specific responses are collectively known as the white blood cells, or **leukocytes**.

As we shall see in more detail, some leukocytes can interact directly with foreign material via receptors on their surface. Foreign molecules which can bind to leukocytes in this manner are called **antigens**. Technically, not all antigens will excite an immune response on their own; some can only do so once they have bound to other antigens. These are termed **haptens**, and are of no interest to this work. Those antigens which do provoke an immune response directly are properly called **immunogens**. (However, it is customary in the literature to ignore the distinction between immunogens and antigens, and to give preference to the latter term; we shall adhere to this practise.) Antigens can be found, for instance, on the surface of a **pathogen** — a non-self microorganism harmful to the host.

We are concerned with the specific case where the non-self presence takes the form of a pathogen known as the Human Immunodeficiency Virus, which will itself

be discussed in greater detail later in this chapter. HIV excites both the innate and acquired responses; indeed, it directly targets cells involved in the latter, and hence leads to the development of the Acquired Immunodeficiency Syndrome (AIDS), so named because of the deleterious effect of the virus on the acquired response. Although the mathematical models of HIV infection we shall consider will not explicitly incorporate every facet of the immune system's efforts to eradicate the pathogen, it is instructive to detail both those elements which are specifically included in the models, and those which are omitted, and to furthermore justify these omissions.

1.1.1 The Innate Response: The Complement System

The first prominent agent of the immune system typically activated following the intromission of non-self microorganisms is the **complement** system. Complement is a collection of proteins flowing freely in the bloodstream which are normally in an inactive state. The first component protein of the complement system can be alerted to the presence of antigenic material in the body in several different ways. In particular, it can bond directly to the surface of a pathogen, or to certain proteins produced in the early stages of infection which themselves bind to the surface of non-self material. Alternatively, the first component protein can be activated via

bonding with an **immune complex**, in which an antigen is itself bonded to a glycoprotein (a macromolecule composed of amino acids and sugars) known as an **antibody** or **immunoglobulin**. (Antibodies are produced by B lymphocytes, cells which play a key role in the acquired response, and exhibit several different immunological functions; they will be discussed in more detail later. The complement system therefore represents a link between the immune and acquired responses.)

The activation of the first component protein produces a cascade of chemical reactions in which the other proteins of the complement system become activated themselves (through one of three possible pathways). In particular, several of the complement proteins generate the membrane attack complex, which attacks foreign microorganisms directly. This results in the **lysis** of such cells (that is, their death by bursting, usually via the dissolution of the cell membrane).

Unfortunately, the complement system is highly toxic to the body. The membrane attack complex, for example, can attack indiscriminately, lysing not just the non-self material but host cells as well. As a result, complement excitation is typically virulent only in cases of extreme infection by foreign material, and the activation of complement is regulated by the body in order to limit possible damage to the body.

Additionally, the role of complement is not limited to **cytotoxicity** (that is, the

direct killing of cells). Byproducts resulting from the complement cascade serve to chemically attract more advanced components of the immune system (called **chemotaxis**), cause inflammation which also stimulates other immunological cells, and make the non-self material more easily or aggressively digested by certain structures in the immune system (a process known as **opsonisation**).

1.1.2 The Innate Response: Phagocytosis

The other prominent mechanism in the innate immunological response is **phagocytosis** — literally, "eating of cells". Whereas cell lysis involves the destruction of cells by compromising the integrity of their cellular membranes, in phagocytosis the target cell is consumed by an attacking cell. The principal types of phagocyte are the polymorphonuclear neutrophils, the monocytes/macrophages, and the dendritic cells.

The polymorphonuclear leukocytes encompass several types of white blood cells, characterised by the presence of granules in their cytoplasm (the extranuclear material which makes up much of the volume of a cell). Consequently, they are also known as **granulocytes**. The vast majority of polymorphonuclear leukocytes are **neutrophils**; although these are not the only phagocytic granulocytes, they are the most aggressively so. Neutrophils are attracted to the site of an infection via

chemotaxis and through the action of endothelial adhesion molecules.

Monocytes are phagocytic cells found in the blood; when they migrate to the tissues, they evolve (or **differentiate**) into **macrophages**. Although polymorphonuclear neutrophils devour non-self material more efficiently — and respond to the site of infection more rapidly — than monocytes and macrophages, the latter are significantly larger (and therefore have a greater capacity for the consumption of other cells) and are also much longer-lived. Furthermore, the macrophages are capable of **antigen presentation**, a critical component of the acquired response which will be discussed below.

Immature **dendritic cells** dwell in the blood and in the body's tissues, particularly those which come into contact with the environment, such as the skin, lungs and intestines. Dendritic cells are characterised by the small strands of cytoplasm (called **dendrites**) they are capable of forming. Like the macrophages, dendritic cells exhibit antigen presentation, and therefore play a key role in the immune system beyond phagocytosis.

Regardless of the type of phagocyte, however, the process of cell "eating" is essentially the same. Having identified a microorganism as being non-self, the phagocyte then attaches itself to the foreign material, a process which can be enhanced via opsonisation. The consumption of the foreign material then takes

place, with the phagocyte extruding pseudopodia to surround its target, eventually encasing it in a vesicle known as a **phagosome**. The phagosome is then transported within the phagocyte, where the non-self microorganism is finally digested. (Recent research suggests that dendritic cells may instead exhibit a similar faculty called **pinocytosis** — literally, "drinking of cells" — which involves the uptake of soluble material.)

1.1.3 The Innate Response: Other Mechanisms

Although the complement system and phagocytosis are the predominant elements of the innate response, they are not the only mechanisms available to the immune system's non-specific defense against the intromission of foreign material. Inflammation, for example, activates **mast cells** and polymorphonuclear leukocytes such as **basophils**. Early signs of infection are inhibited by chemicals known as **interferons** (usually in the presence of viruses) and **acute-phase proteins** (typically in response to bacteria). The **large granular lymphocytes**, such as **natural killer** (NK) cells, hunt for host cells which have been altered (such as by the actions of a virus or due to the development of tumours) and induce **apoptosis**, a form of cell death in which the cell shrinks and ultimately fragments, to then be phagocytosed.

1.1.4 The Acquired Response: Antigen Presentation

Although it would be convenient to think of the immune system's acquired response as separate from the innate response, the distinction is really far more blurry. Indeed, the functionality of the acquired response is largely dependent upon cells typically associated with the innate response, via a mechanism known as **antigenic presentation**.

Antigens are present not only on viruses and other intruders to a host's system, but indeed on all cells of the body; these are known as **human (histocompatibility-linked) leukocyte antigens**. Evidently, the immune system must be capable of recognising that antigens produced by the host are "self" and should not provoke an immune response. This is performed via the coding of a group of genes known as the **major histocompatibility complex** (MHC). "Histocompatibility" literally means "tissue compatibility", and is indicative of the fact that material in a host which is not coded in a manner consistent with the host's MHC will be rejected by the body.

The genes which make up the MHC can be divided into three classes. Of these, Class I and Class II are of particular importance to the acquired response. Class III genes also produce some of the elements necessary for the acquired response to be effective and play a role in other aspects of the immune system, such as providing

the genetic code for the complement system previously discussed.

When a macrophage or a dendritic cell phagocytoses an antigen, Class II molecules (that is, molecules coded by MHC Class II genes) act on the microorganism, binding proteins and then migrating to the surface of the macrophage or dendritic cell where the antigenic material is expressed. For this reason, macrophages and dendritic cells are known as **(professional) antigen-presenting cells**. MHC Class I molecules, on the other hand, can be expressed on the surface of any nucleated cell. Note that the MHC class depends on the type of antigen which was phagocytosed: MHC Class II molecules are associated with antigens arising directly from foreign microorganisms (**exogenous** antigens) while MHC Class I molecules are associated with antigens produced by host cells which are infected by viruses or are cancerous (**endogenous** antigens).

Once an antigenic fragment is expressed upon the surface of a macrophage or a dendritic cell, it matures and becomes less able to undertake further phagocytosis, but more efficient at antigen expression. The cell is also induced through chemotaxis to travel to the location of more advanced cells which can identify the antigen; these typically reside in the **lymph nodes**. Once there, the macrophage or dendritic cell will **present** its MHC Class II molecules to the receptor on the surface of a **$CD4^+$ T cell**. Similarly, **$CD8^+$ T cells** are receptive to the presentation of MHC

Class I molecules.

1.1.5 The Acquired Response: T Cells

The most crucial type of cell in this work is the $CD4^+$ T cell. It is not only an essential component of the body's immune system but, as we shall see, it is also the specific target of the human immunodeficiency virus and hence will become the fundamental component of our mathematical models of HIV.

One of the major classes of white blood cells is the **lymphocyte**. Although we have already noted two members of this class — the NK and K cells, both large granular lymphocytes — these are essentially minor members of the lymphocyte family. Lymphocytes originate as stem cells in the bone marrow. Some of these lymphoid progenitor cells continue to develop in the bone marrow, while others migrate to different parts of the lymphatic system, most notably the thymus. Those cells which mature in the thymus become **T lymphocytes**, more commonly simply referred to as **T cells**. Once developed, they depart the thymus and proliferate throughout the host.

The most significant characteristic of T cells is that they each possess receptors on their surface. As with other types of leukocytes, these receptors enable the T cell to bind to antigens. However, unlike the white blood cells involved in the

innate response, T cell antigen receptors are specific to a particular type of antigen; antigens of a type other than that for which the given T cell is coded cannot undergo binding to the receptor.

In addition to being subdivided according to the type of antigen which will cause the excitation of the T cell, they can also be classified according to the type of response they provide. This is determined by the antigen receptors, which will be associated with different glycoprotein molecules depending on the function the given T cell is to play in the immune system. These molecules are classified according to the **cluster determinant system**, and are therefore identified as molecules CD1, CD2, and so forth. In particular, the two molecules which are used to classify the major types of T cell are molecules CD4 and CD8; T cells which exhibit these are known as **$CD4^+$ T cells** and **$CD8^+$ T cells**. (Here the + simply denotes that these T cells express the indicated molecule; consequently, they are also known as $CD4^+8^-$ T cells and $CD4^-8^+$ T cells, respectively.)

The $CD4^+$ T cells are also known as **helper T cells**, and are activated by the presentation of antigen associated with MHC Class II molecules. Once excited, helper T cells proliferate quickly and begin to produce chemicals known as **cytokines**, most notably **interleukin 2** (IL-2), whose principal effect is to stimulate the production of additional T cells and other members of the immune system.

Further cytokines enhance phagocytosis, and perform other functions to aid in the elimination of non-self matter. Although they are chiefly regarded as facilitating the ability of other cells to attack invading microorganisms, it appears that some $CD4^+$ T cells are also cytotoxic themselves, helping to regulate and suppress the immune system in the event that discernment between self and non-self molecules fails.

However, cytotoxicity is not the major role of helper T cells; this is the purview of the $CD8^+$ T cells, known as **killer T cells** for this very reason. The $CD8^+$ T cells bind to antigens associated with MHC Class I molecules, and act to lyse the cells expressing such antigens.

An alternative way to classify T cells is according to their longevity. Nascent T cells which have yet to encounter antigen are known as **naïve** T cells. T cells which are produced in response to the presence of antigenic material in the host are called **effector** T cells. These are typically short-lived and highly excited, produced specifically for the purpose of effecting an immune response.

Finally, T cells which have been exposed to an antigen but subsequently returned to dormancy are known as **memory** T cells. Memory cells can enable the immune system to respond more quickly and effectively should the same antigen be recognised in the host again in the future; for instance, memory T cells will pro-

liferate far more rapidly in response to antigenic stimulation than do naïve T cells. Both $CD4^+$ and $CD8^+$ T cells can develop into memory cells.

1.1.6 The Acquired Response: B Cells

Lymphocytes which remain in the bone marrow during their maturation are known as **B lymphocytes**, or merely **B cells**. Like T cells, they also possess antigen receptors on their surface; however, the behaviour of B cells following antigenic presentation can differ greatly from T cells.

First, binding to antigen is not sufficient to completely stimulate a B cell. The B cells require cytokines secreted by helper T cells in order to become fully excited; however, B cells can act as antigen-presenting cells themselves in order to activate $CD4^+$ T cells. Those B cells which have encountered no antigens are known as **virgin** B cells.

Once fully excited, a B cell may differentiate into a memory cell, much in the same manner as T cells. However, the key immune response for B cells is to evolve into **plasma cells**. These are capable of producing different varieties of the glycoproteins known as antibodies or immunoglobulin, as previously discussed; these antibodies will be keyed to cells displaying the same type of antigen which originally stimulated the B cell.

In addition to provoking the activity of the complement system, as already noted, antibodies play a number of roles in the immune system. They can impede the ability of non-self microorganisms to bind to host cells and thereby infect or damage them; they can cause opsonisation by coating non-self material and facilitating phagocytosis; they can bind to antigens present on the surface of infected cells and lyse these cells; each antibody can adhere to two different microorganisms simultaneously, so that by working together, they can create a large clump of foreign matter which can more easily be cleared from the host (a phenomenon known as **agglutination**); and exhibit still other functions.

1.2 The Human Immunodeficiency Virus

Although the preceding discussion of the immune system applies generally to the reaction of the body to the presence of any non-self microorganisms, the chief concern of this work is the response of the immune system to pathogens, and to one pathogen in particular.

In the early 1980s, American scientists became alarmed by a marked rise in the occurrence of illnesses related to the suppression of the body's immune system. It soon became clear that some new malady was inhibiting the function of the immune

system, resulting in a disease which came to be known as the **Acquired Immune Deficiency Syndrome**. The pathogen which resulted in AIDS was initially called the Human T-Lymphotropic Virus-III or the Lymphadenopathy-Associated Virus, but these terms have been supplanted by the name **Human Immunodeficiency Virus** [4], [5], [6].

It is believed that the predominant strain of the virus, denoted HIV-1, likely arose first in the African nation of Cameroon, migrating from wild chimpanzees to humans; it has since spread globally. (A second strain, HIV-2, is less virulent than HIV-1 and remains principally confined to western Africa.) HIV is typically contracted either via the transmission of sexual secretions (genitally, orally or rectally) or the injection of infected blood (such as from transfusions or unsterilised syringes). HIV can also be passed from mother to child *in utero*, during childbirth or through breastfeeding.

HIV is so devastating to the immune system because its targets are the very $CD4^+$ helper T cells whose function is to coordinate the body's resistance to any invasion. A protein on the surface of the virion binds with the $CD4^+$ receptor on the surface of the lymphocyte, as well as to secondary receptors, which are typically associated with **chemokines** (chemotactic cytokines) secreted by the T cell. The viral and T cell membranes then fuse, permitting the contents of the virion to enter

the lymphocyte. (HIV can also affect macrophages and dendritic cells in much the same manner.)

The next step in the pathogenesis of HIV is unusual compared to that of most other viruses. Typically, a virion carries a copy of its DNA which it will insert into a victim cell. HIV, however, is a **retrovirus** (specifically, a **lentivirus**, characterised by its lengthy incubation within an infected cell before causing disease in a host). This means that each virion carries a copy of its RNA — the genetic precursor to DNA — which is injected into the target cell's cytoplasm. (In fact, retroviruses carry not one but two identical copies of their RNA genome, a phenomenon known as **diploidy**.)

The virion then employs a protein enzyme known as **reverse transcriptase** to transcribe the RNA into DNA. This process is not always perfect: the reverse transcriptase does not simply act on one of the RNA copies but moves back and forth between them. The resulting DNA is therefore essentially the synthesis which would arise naturally from the RNA molecules, but the reverse transcriptase sometimes errs in its replication of the RNA sequence. This is the most common cause of mutation of HIV, and the large number of mutant virions produced during the course of HIV infection is an important component of its pathogenesis.

Once the viral RNA has been converted into DNA, it is suitable for insertion

into the DNA of the lymphocyte. This is accomplished using a second enzyme known as **integrase**; the resulting integrated DNA is called an integrated **provirus**. The provirus lies dormant within the infected T cell until it is activated.

The cruel irony of HIV then becomes apparent, as the very act of inducing the helper T cell to replicate itself in order to aid in fighting the HIV infection incites the transcription of the viral DNA into the building blocks of new virions. Many of the elements needed for these virions are created in the form of an immature polypeptide chain; this is cleaved into individual proteins by a third enzyme called **protease**.

Once the new virions are fully assembled, they bud from the surface of the infected T cell. In some cases, this budding may transpire slowly such that the host cell continues to survive the infection; in other instances, the new HIV virions burst from the T cell, killing it.

HIV therefore has a calamitous effect on the helper T cell population: not only does bursting cause the death of T cells, but the infected $CD4^+$ T cells become targets for the killer $CD8^+$ T cells as well. Furthermore, infected T cells undergo increased rates of apoptosis.

The pathogenesis of HIV typically falls into three stages. The initial phase — which usually lasts for a period of weeks — involves an acute drop in $CD4^+$

T cell levels (which are normally around 1000 cells per μL of blood). Despite the deleterious effects on the overall immune response caused by the loss of so many helper T cells, the immune system is not crippled: cytotoxic T cells, antibodies produced by B cells, uninfected helper T cells, and other elements of the immune system continue to respond to the assault the pathogen. This stage — known as the **primary** (or acute) phase — often manifests with influenza-like symptoms in the host.

By the end of the primary phase of infection, the $CD4^+$ T cell count typically rebounds and roughly stabilises at a level known as the **set point**. The host usually displays no symptoms during this period, which is therefore known as the **chronic** (or latent, or asymptomatic) phase. Depending on the individual, it may last anywhere from a few short months to many years. It appears that, during this time, the immune system is essentially fighting a losing battle against the pathogen, slowing but never arresting the rate of infection.

Over the course of the chronic phase, the host's $CD4^+$ T cell count gradually decays until, finally, it becomes critically low. The onset of the final stage of infection — AIDS itself — is defined to occur when the $CD4^+$ T cell count drops below 200 cells per μL. At this stage, the loss of such a huge proportion of the helper T cell population has impaired the functioning of the acquired immune response to

such an extent that it is unable to combat opportunistic infections and tumours such as tuberculosis, pneumonia, shingles caused by the Varicella zoster virus, Kaposi's sarcoma, and other maladies which a healthy immune system would normally be able to eliminate. Death then, inevitably, results.

Chapter 2

Mathematical Background

Having explored the immunological background of HIV, we now wish to encapsulate many of the phenomena associated with its pathogenesis within a mathematical model. It is therefore essential that we first provide the mathematical underpinnings of such a task.

We shall begin by introducing key terminology and theory related to systems of ordinary differential equations and dynamical systems. We shall then go on to introduce the more sophisticated idea of differential equations with impulsive moments, which will ultimately enable us to consider discontinuous phenomena within the context of our model.

2.1 Systems of Differential Equations

To avoid devolving this text to an overtly elementary stage, we shall assume that the reader is familiar with the basic terminology associated with scalar ordinary differential equations (ODEs). For additional review, we refer the reader to suitable reference works in differential equations and dynamical systems, such as [7–12].

Consider a system consisting of ordinary differential equations involving n unknown functions $x_1(t), \ldots, x_n(t)$. Taking I to be an open interval, we let $x_i : I \to \mathbb{R}$ for all i. In this work we will be interested only in models which make no explicit reference to time, because we will avoid making any *a priori* chronological assumptions. As such, we can now consider an autonomous system of n ordinary differential equations in these n unknown functions, of the form

$$\begin{aligned}
\dot{x}_1(t) &= f_1(x_1(t), x_2(t), \ldots, x_n(t)) \\
\dot{x}_2(t) &= f_2(x_1(t), x_2(t), \ldots, x_n(t)) \\
&\vdots \\
\dot{x}_n(t) &= f_n(x_1(t), x_2(t), \ldots, x_n(t)).
\end{aligned}$$

Here, and throughout this work, we use the notation $\frac{dx}{dt} = \dot{x}(t)$ to represent the time-derivative of x with respect to t.

To simplify our notation further still, consider the vector $\mathbf{x} = (x_1, x_2, \ldots, x_n)^T$ — so that $\dot{\mathbf{x}} = (\dot{x}_1, \dot{x}_2, \ldots, \dot{x}_n)^T$ — and the vector-valued function $\mathbf{f} = (f_1, f_2, \ldots, f_n)^T$. Then we can write the system of ODEs more compactly as

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}(t)). \tag{2.1}$$

We are not interested in systems of differential equations in isolation, but rather in the context of initial value problems (IVPs) in which such a system is paired with an appropriate initial condition, of the form $\mathbf{x}(t_0) = \mathbf{x}^0$ where $\mathbf{x}^0 = (x_1^0, x_2^0, \ldots, x_n^0)^T$. (Note that there is typically a discrepancy in the notation between scalar values such as t and vector values such as $\mathbf{x}$. In the context of vectors, subscripts differentiate between the components of a given vector, while superscripts differentiate between individual vectors. In the context of scalars, we use subscripts to distinguish between scalars.) Note that there is no necessity that $t_0 = 0$, although it is often convenient to make this assumption. Indeed, because we are interested only in autonomous differential equations, we can always translate the independent variable — or, more formally, define a new function $X(t) \equiv x(t + t_0)$ — which satisfies both the same ODE and the same initial condition at $t = 0$ rather than at $t = t_0$.

An initial value problem thus takes the form

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}(t)), \quad \mathbf{x}(t_0) = \mathbf{x}^0 \tag{2.2}$$

while a solution to this IVP is given by $\phi(t, \mathbf{x}^0)$, for which $\phi(0, \mathbf{x}^0) = \mathbf{x}^0$.

Let the set of all continuous vector-valued functions $\mathbf{f} : \mathbf{U} \to \mathbb{R}$, where $\mathbf{U}$ is a subset of $\mathbb{R}^n$, be denoted by $C^0(\mathbf{U}, \mathbb{R})$. Similarly, let the set of all differentiable functions $\mathbf{f} : \mathbf{U} \to \mathbb{R}$ with continuous first derivatives be denoted by $C^1(\mathbf{U}, \mathbb{R})$. We will suppress the notation of the domain and range when there is no ambiguity, simply referring to C^0 and C^1 functions as appropriate.

We now have the following two theorems.

Theorem 1: Existence of Solutions

Let $f \in C^0(\mathbb{R}^n, \mathbb{R})$. Then for any $\mathbf{x}^0 \in \mathbb{R}^n$ there exists an interval $I_{\mathbf{x}^0} \equiv (\alpha_{\mathbf{x}_0}, \beta_{\mathbf{x}_0})$, not necessarily finite, containing $t_0 = 0$, and there exists a solution $\phi(t, \mathbf{x}^0)$ of Equation (2.2) defined for all $t \in I_{\mathbf{x}^0}$ such that $\phi(0, \mathbf{x}^0) = \mathbf{x}^0$. In addition, if $\alpha_{\mathbf{x}^0}$ is finite then

$$\lim_{t \to \alpha^+_{\mathbf{x}^0}} |\phi(t, \mathbf{x}^0)| = \infty.$$

Similarly, if $\beta_{\mathbf{x}^0}$ is finite then

$$\lim_{t \to \beta^-_{\mathbf{x}^0}} |\phi(t, \mathbf{x}^0)| = \infty.$$

The largest possible interval $I_{\mathbf{x}^0}$ described in Theorem 1 is called the **maximal interval of existence** of the solution $\phi(t, \mathbf{x}^0)$.

Theorem 2: Uniqueness of Solutions

If $f \in C^1(\mathbb{R}^n, \mathbb{R})$ then, for any $\mathbf{x}^0 \in \mathbb{R}^n$, $\phi(t, \mathbf{x}^0)$ is unique on $I_{\mathbf{x}^0}$ and $\phi(t, \mathbf{x}^0)$ is itself a C^1 function.

Theorems 1 and 2 can easily be generalised to functions whose domain is not the whole of $\mathbb{R}^n$. In particular, if $\mathbf{f} \in C^1(\mathbf{U}, \mathbb{R})$ for some open, bounded subset $\mathbf{U}$ of $\mathbb{R}^n$, then Theorem 2 remains unchanged and Theorem 1 must be amended only to reflect the fact that, if $\alpha_{\mathbf{x}^0}$ or $\beta_{\mathbf{x}^0}$ is finite, then the limit points as $t \to \alpha^+_{\mathbf{x}^0}$ or $t \to \beta^-_{\mathbf{x}^0}$ must lie on the boundary of $\mathbf{U}$.

It is generally difficult or impossible to find an exact solution of a given ODE. Consequently, the solution curves or **trajectories** in $(n + 1)$-dimensional space, passing through the initial condition $\mathbf{x}^0$, can typically be drawn only by numerical means. Although we will certainly make use of this approach, more information can often be drawn by investigating the differential equation through other methods.

Definition 1

A point $\overline{\mathbf{x}} \in \mathbb{R}$ is called an **equilibrium point** of Equation (2.1) if $f(\overline{\mathbf{x}}) = \mathbf{0}$.

In the literature, equilibrium points are also known as fixed points or steady state points. Graphically, an equilibrium point is such that if a trajectory starts at $\mathbf{x} = \bar{\mathbf{x}}$ then it will remain at $\mathbf{x} = \bar{\mathbf{x}}$ for all t.

Equilibria are of enormous utility, because they can be used to characterise how trajectories behave if their initial condition is sufficiently close to the equilibrium point: this is the **local stability** of the ODE.

Definition 2

An equilibrium point of Equation (2.1) is said to be **stable** if, for any $\epsilon > 0$, there exists a $\delta(\epsilon) > 0$ such that for every $\mathbf{x}^0$ for which $\|\mathbf{x}^0 - \bar{\mathbf{x}}\| < \delta$, the solution $\phi(t, \mathbf{x}^0)$ of Equation (2.1) satisfies $\|\phi(t, \mathbf{x}^0) - \bar{\mathbf{x}}\| < \epsilon$ for all $t \geq 0$.

Here, $\|\cdot\|$ denotes a norm. Observe that we have made explicit the dependence of δ on the choice of ϵ in this definition. Graphically, a stable equilibrium point is such that if a trajectory starts near $\mathbf{x} = \bar{\mathbf{x}}$, then it will remain near $\mathbf{x} = \bar{\mathbf{x}}$ as $t \to \infty$.

One form of stability is particularly important.

Definition 3

An equilibrium point $\bar{\mathbf{x}}$ is said to be **asymptotically stable** if it is both stable and there exists an $r > 0$ such that, for all $\mathbf{x}^0$ satisfying $\|\mathbf{x}^0 - \bar{\mathbf{x}}\| < r$,

$$\|\phi(t, \mathbf{x}^0 - \bar{\mathbf{x}})\| \to 0$$

as $t \to \infty$.

If an equilibrium point is asymptotically stable, then any trajectory that starts near $\mathbf{x} = \bar{\mathbf{x}}$ will become infinitesimally close to $\mathbf{x} = \bar{\mathbf{x}}$ as $t \to \infty$.

Definition 4

An equilibrium point $\bar{\mathbf{x}}$ which is not stable is said to be **unstable**. That is, there exists an $\eta > 0$ such that, for any $\delta > 0$, there exists an $\mathbf{x}^0$ for which $\|\mathbf{x}^0 - \bar{\mathbf{x}}\| < \delta$ and $t_{\mathbf{x}^0} > 0$ such that $\|\phi(t_{\mathbf{x}^0}, \mathbf{x}^0) - \bar{\mathbf{x}}\| = \eta$.

The critical tool to be used in the determination of the equilibrium points of Equation (2.1) is the **Jacobian matrix** of $\mathbf{f}$, given by

$$J(\mathbf{x}) = \begin{bmatrix} \frac{\partial f_1}{\partial x_1}(\mathbf{x}) & \frac{\partial f_1}{\partial x_2}(\mathbf{x}) & \cdots & \frac{\partial f_1}{\partial x_n}(\mathbf{x}) \\ \frac{\partial f_2}{\partial x_1}(\mathbf{x}) & \frac{\partial f_2}{\partial x_2}(\mathbf{x}) & \cdots & \frac{\partial f_2}{\partial x_n}(\mathbf{x}) \\ \vdots & \vdots & & \vdots \\ \frac{\partial f_n}{\partial x_1}(\mathbf{x}) & \frac{\partial f_n}{\partial x_2}(\mathbf{x}) & \cdots & \frac{\partial f_n}{\partial x_n}(\mathbf{x}) \end{bmatrix}.$$

Definition 5

If $\bar{\mathbf{x}}$ is an equilibrium point of Equation (2.1) then the system of differential equations

$$\dot{\mathbf{x}} = J(\bar{\mathbf{x}})\bar{\mathbf{x}}$$

is called the **linearisation** of $\mathbf{f}$ at $\bar{\mathbf{x}}$ (or the linear variational equation).

It is, in fact, this linearised version of Equation (2.1) which can be used to determine the local stability of an equilibrium point in many cases.

Theorem 3

Suppose that $\mathbf{f}$ is a C^1 function and $\bar{\mathbf{x}}$ is an equilibrium point of Equation (2.1). Then $\bar{\mathbf{x}}$ is asymptotically stable if all the eigenvalues of the Jacobian matrix $J(\bar{\mathbf{x}})$ have negative real parts, and $\bar{\mathbf{x}}$ is unstable if at least one of the eigenvalues of $J(\bar{\mathbf{x}})$ has a positive real part.

2.2 Transcritical Bifurcations

AS AN ALTERNATIVE, WE CAN VIEW Equation (2.1) as being of the form

$$\dot{\mathbf{x}} = \mathbf{f}(\mu, \mathbf{x}(t)), \tag{2.3}$$

where $\mu \in \mathbf{R}^m$ represents the parameters of the system. From experience, we know that, as any parameter changes, the overall behaviour of the system may

also change: equilibria may appear or be annihilated, and their stability may be altered. Points at which these fundamental modifications to the characteristics of the solutions occur are known as **local bifurcation points**.

To more precisely define the concept of a bifurcation point, we require some topological considerations.

Definition 6

If $\phi(t, \mathbf{x}^0)$ is a solution of Equation (2.2) defined for all $t \in I_{\mathbf{x}^0}$ such that $\phi(0, \mathbf{x}^0) = \mathbf{x}^0$, then the **orbit** $\gamma(x_0)$ of $\mathbf{x}^0$ is the subset of $\mathbb{R}^n$ defined by

$$\gamma(\mathbf{x}^0) = \bigcup_{t \in I_{\mathbf{x}^0}} \phi(t, \mathbf{x}^0).$$

For the next two definition, let $\Upsilon^k(\mathcal{D})$ be the space of C^k vector fields ($k \geq 1$) defined on a compact subset $\mathcal{D}$ of $\mathbb{R}^n$ and pointing inwards at the boundary points of $\mathcal{D}$.

Definition 7

Two differential equations $\dot{\mathbf{x}}(t) = \mathbf{f}(\mathbf{x})$ and $\dot{\mathbf{x}} = \mathbf{g}(\mathbf{x})$ defined on $\mathcal{D}$ are said to be **topologically equivalent** if there exists a homeomorphism $\mathbf{h} : \mathcal{D} \to \mathcal{D}$ such that $\mathbf{h}$ maps the orbits of the vector field $\mathbf{f}$ onto the orbits of $\mathbf{g}$ and preserves the sense of direction of time.

Note that by "homeomorphism" we mean that **h** is continuous and possesses a continuous inverse.

Definition 8

A vector field $\mathbf{f} \in \Upsilon^k(\mathcal{D})$, $k \geq 1$, is **structurally stable** if there exists a neighbourhood N_f of $\mathbf{f}$ in $\Upsilon^k(\mathcal{D})$ such that any $\mathbf{g} \in N_f$ is topologically equivalent to $\mathbf{f}$.

Finally, then, we have the following [7].

Definition 9

A parameter value of Equation (2.3) for which $\mathbf{f}$ is not structurally stable is called a bifurcation value, and the system is said to be at a (local) bifurcation point.

In general, a bifurcation point occurs when an eigenvalue of the Jacobian matrix of $\mathbf{f}$ at a fixed point $\mathbf{x}$ possesses a zero real part: the transitional state between stability and instability.

There are many different kinds of bifurcations, depending on the exact nature of the change to the qualitative behaviour of the system. One means of classifying them is according to their **codimension**, which — at the risk of oversimplifying the topological significance of the term — describes the number of conditions on

the parameters which give rise to the bifurcation. Hence a bifurcation will be of codimension 1 if it occurs when (some or all of) the m parameters meet just a single condition.

In this work, we are interested only in the **transcritical bifurcation**, which is a codimension-1 bifurcation. No equilibria are created or destroyed at a transcritical bifurcation, but an exchange of stability does occur, with an asymptotically stable fixed point becoming unstable, and an unstable fixed point becoming asymptotically stable. Geometrically, when $\mu = \overline{\mu}$, the two equilibria pass through each other at a point $\mathbf{x} = \overline{\mathbf{x}}$, exchanging stability as they do so.

More rigorously, for $\mu \in \mathbb{R}$ we may define a transcritical bifurcation in the following manner. [8, 10]

Theorem 4

Let $\dot{\mathbf{x}} = \mathbf{f}(\mu, \mathbf{x}(t))$ be a system of differential equations in $\mathbb{R}^n$ depending on the parameter μ. Suppose that $J(\mathbf{x})$ at $(\mu, \mathbf{x}) = (\overline{\mu}, \overline{\mathbf{x}})$ has a simple eigenvalue $\lambda = 0$ such that the corresponding eigenvector of $J(\mathbf{x})$ is $\mathbf{v}$ and the corresponding eigenvector of $[J(\mathbf{x})]^T$ is $\mathbf{w}$. Then a transcritical bifurcation occurs at $\mu = \overline{\mu}$ and $\mathbf{x} = \overline{\mathbf{x}}$ if each of the following conditions hold:

(a) $\mathbf{w}^T \dfrac{\partial \mathbf{f}}{\partial \mu}(\overline{\mu}, \overline{\mathbf{x}}) = 0,$

(b) $\mathbf{w}^T [J_\mu(\overline{\mu}, \overline{\mathbf{x}})\mathbf{v}] \neq 0,$

(c) $\mathbf{w}^T [J^2(\overline{\mu}, \overline{\mathbf{x}})(\mathbf{v}, \mathbf{v})] \neq 0.$

In the theorem, J_μ denotes the Jacobian matrix of $\frac{\partial \mathbf{f}}{\partial \mu}$, while J^2 is the **Hessian matrix**,

$$J^2(\mathbf{x}) = \begin{bmatrix} \frac{\partial^2 f_1}{\partial x_1^2}(\mathbf{x}) & \frac{\partial^2 f_1}{\partial x_2 \partial x_1}(\mathbf{x}) & \cdots & \frac{\partial^2 f_1}{\partial x_n \partial x_1}(\mathbf{x}) \\ \frac{\partial^2 f_2}{\partial x_1 \partial x_2}(\mathbf{x}) & \frac{\partial^2 f_2}{\partial x_2^2}(\mathbf{x}) & \cdots & \frac{\partial^2 f_2}{\partial x_n \partial x_2}(\mathbf{x}) \\ \vdots & \vdots & & \vdots \\ \frac{\partial^2 f_n}{\partial x_1 \partial x_n}(\mathbf{x}) & \frac{\partial^2 f_n}{\partial x_2 \partial x_n}(\mathbf{x}) & \cdots & \frac{\partial^2 f_n}{\partial x_n^2}(\mathbf{x}) \end{bmatrix}.$$

Finally, for vectors $\mathbf{y}$ and $\mathbf{z}$,

$$J^2(\overline{\mu}, \overline{\mathbf{x}})(\mathbf{y}, \mathbf{z}) = \sum_{i,j=1}^{n} \frac{\partial^2 \mathbf{f}(\overline{\mathbf{x}})}{\partial x_i \partial x_j} y_i z_j.$$

As we shall demonstrate in Chapter 4, the mathematical model developed in this work does not possess any other form of bifurcation. In particular, it exhibits no codimension-2 bifurcations, which are of significantly greater mathematical complexity than the relatively straightforward class of codimension-1 bifurcations.

2.3 An Introduction to Differential Equations with Impulses

Having developed and explored an ordinary differential equation model for HIV, we shall then introduce the notion of **moments of impulse** into our model in order to reflect the discontinuous nature of drug therapy in a patient suffering from HIV. In reality, drugs do not follow a constant or even continuous level of dosage, but pursue a trajectory that can be assumed to shift instantaneously when a new round of treatment occurs. In the next two sections, we will offer an overview of the basic terminology and theory behind differential equations with impulses [13–15].

We consider a system of differential equations

$$\dot{\mathbf{x}} = f(t, \mathbf{x}(t)), \tag{2.4}$$

where $t \in \mathbb{R}$ (and, in most cases, represents time) and $\mathbf{x}(t)$ is an n-dimensional column vector. We will let Ω be the phase space such that $\mathbf{x}(t) \in \Omega$ and $f : \mathbb{R}\times\Omega \to \mathbb{R}^n$.

We introduce the sets M_t and $N_t \in \mathbb{R}\times\Omega$ and an operator $A_t : M_t \to N_t$, for each $t \in \mathbb{R}$, as follows. If P_t is a point in the $(n+1)$-dimensional extended phase space $\mathbb{R}\times\Omega$, we assume that it begins at an initial point $(t_0, \mathbf{x}_0)$ and originally moves along the curve $(t, \mathbf{x}(t))$ defined by a solution $\mathbf{x}(t)$ of Equation (2.4) with initial condition $\mathbf{x}(t_0) = \mathbf{x}_0$. This continues until the moment $\tau_1 > t_0$ when P_t intersects the set M_t. At $t = \tau_1$, the operator A_{τ_1} discontinuously shifts P_t from the point $P_{\tau_1} = (\tau_1, \mathbf{x}(\tau_1))$ to the point $P^+_{\tau_1} \in N_{\tau_1}$. If we let $\mathbf{x}^+_1 = A_{\tau_1}\mathbf{x}(\tau_1))$ then $P^+_{\tau_1} = (\tau_1, \mathbf{x}^+_1)$. Thereafter, P_t moves along the curve $(t, \mathbf{x}(t))$ defined by a solution $\mathbf{x}(t))$ of Equation (2.4) with initial condition $\mathbf{x}(\tau_1) = \mathbf{x}^+_1$ until it again intersects with the set M_t. This process continues analogously for all such encounters.

Equation (2.4), together with the descriptions of the sets M_t and N_t and the operator A_t, define a system of differential equations with impulse effect or, more conveniently, a **system of impulsive differential equations** (IDEs). The times τ_k are called the **moments** (or instants) of the impulse effect. Observe that the solution

$\mathbf{x}(t)$ of an IDE is assumed to be left-continuous, that is,

$$\lim_{t \to \tau_k^-} \mathbf{x}(t) = \mathbf{x}(\tau_k) \neq \mathbf{x}_k^+ = \lim_{t \to \tau_k^+} \mathbf{x}(t).$$

For simplicity, we will often write

$$\Delta \mathbf{x}_k = \mathbf{x}_k^+ - \mathbf{x}(\tau_k).$$

Several classes of impulsive differential equations arise from this definition, depending on the way in which the moments of the impulse effect occur. For instance, the IDE could be autonomous (in that the occurrence of the impulses is not based upon the passage of time), although this type of IDE is of no value to the current work.

We shall assume that the set M_t is defined by the solutions of some equation $\phi(t, \mathbf{x}(t)) = 0$. Then the IDE can be written in the form

$$\begin{aligned} \dot{\mathbf{x}}(t) &= f(t, \mathbf{x}(t)), \qquad \text{if } \phi(t, \mathbf{x}(t)) \neq 0, \\ \Delta \mathbf{x} &= I(t, \mathbf{x}(t)), \qquad \text{if } \phi(t, \mathbf{x}(t)) = 0, \end{aligned} \tag{2.5}$$

where $I : \mathbb{R} \times \Omega \to \Omega$. In this case,

$$M_t = \{(t, \mathbf{x}(t)) \in \mathbb{R} \times \Omega \,|\, \phi(t, \mathbf{x}(t)) = 0\},$$

so that $t = \tau_k$ is a moment of the impulse effect if $\phi(\tau_k, \mathbf{x}(\tau_k)) = 0$. Furthermore, $N_t = \mathbb{R} \times \Omega$, while the operator A_t is defined by the mapping

$$(t, \mathbf{x}(t)) \mapsto (t, \mathbf{x}(t) + I(t, \mathbf{x}(t))).$$

The first class of IDE under consideration shall be those for which the moments of impulse are fixed. In this case, the set $M_t = \{\tau_k\}$ and is monotonically increasing. The resulting system is

$$\begin{aligned} \dot{\mathbf{x}}(t) &= f(t, \mathbf{x}(t)), \qquad \text{if } t \neq \tau_k, \\ \Delta\mathbf{x} &= I_k(\mathbf{x}(t)), \qquad \text{if } t = \tau_k. \end{aligned} \tag{2.6}$$

In this simplest case, the solution $\mathbf{x}(t)$ of the IDE satisfies the ordinary differential equation for $t \in (\tau_k, \tau_{k+1}]$ as well as the limit

$$\lim_{t \to \tau_k^+} \mathbf{x}(t) = \mathbf{x}(\tau_k) + I_k(\mathbf{x}(\tau_k)) \equiv \psi_k(\mathbf{x}(\tau_k)),$$

where $\psi_k : \Omega \to \Omega$. Note that we can therefore rewrite the system as

$$\begin{aligned} \dot{\mathbf{x}}(t) &= f(t, \mathbf{x}(t)), \qquad \text{if } t \neq \tau_k, \\ \lim_{t \to \tau_k^+} \mathbf{x}(t) &= \psi_k(\mathbf{x}(\tau_k)). \end{aligned} \tag{2.7}$$

The other major class of IDE in which we may be interested is that for which the moments of the impulse effects are not fixed — in other words, they will occur when the system has attained a given state. In this case, the system can be written in a form similar to Equation (2.6):

$$\dot{\mathbf{x}}(t) = f(t, \mathbf{x}(t)), \qquad \text{if } t \neq \tau_k(\mathbf{x}(t)), \tag{2.8a}$$

$$\Delta\mathbf{x} = I_k(\mathbf{x}(t)), \qquad \text{if } t = \tau_k(\mathbf{x}(t)). \tag{2.8b}$$

Here, $\tau_k : \Omega \to \mathbb{R}$. As before, however, we assume that $\{\tau_k(\mathbf{x}(t))\}$ is a monotonically increasing sequence.

Note that, in general, the solutions to impulsive differential equations are piecewise continuous. Only in the cases for which the trajectory P_t either fails to encounter the set M_t, or does so at fixed points of the operator A_t, can the solutions be continuous. In the case of Equation (2.6), all solutions will possess discontinuities at the same points in time (namely the moments of the impulse effect, τ_k), whereas this will not be true, in general, for solutions to Equation (2.8).

2.4 Existence and Uniqueness of Solutions to Differential Equations with Impulses

In this work, we shall concentrate on IDEs which assume the form of Equation (2.6). In general, however, we are interested in developing theory associated with Equation (2.8), since Equation (2.6) is effectively a special case of this equation.

First, we shall formally define what we mean by the solution of a system of impulsive differential equations as given by Equation (2.8). We shall place additional restrictions on τ_k in addition to the assumption that $\{\tau_k(\mathbf{x}(t))\}$ is monotonically in-

creasing for all $x(t)$. Namely, we shall assume that $\tau_k : \Omega \to [0, \infty)$, and that τ_k is continuous for all k.

Let I be an arbitrary interval with endpoints α and β (where $\alpha < \beta$). For convenience, we shall denote $D = \mathbb{R} \times \Omega$. Then we have the following definition [13].

Definition 10

The function $\phi : I \to \mathbb{R}^n$ is said to be a solution of the system given by Equation (2.8) if

(a) $(t, \phi(t)) \in D$ for $t \in I$,

(b) $\phi(t)$ is differentiable and $\dot{\phi}(t) = f(t, \phi(t))$ for all $t \in I$, $t \neq \tau_k(\phi(t))$,

(c) $\phi(t)$ is left-continuous in I and

$$\lim_{t \to \tau_k(\phi(t))^+} = \phi(t) + I_k(\phi(t)),$$

if $\tau_k(\phi(t)) \neq \beta$.

Definition 11

If $I = (t_0, \beta)$ and $\phi(t)$ is a solution of Equation (2.8), defined in I, such that

$$\lim_{t \to t_0^+} \phi(t) = \mathbf{x}_0$$

then $\phi(t)$ is said to be a solution of the initial value problem for Equation (2.8) with initial condition $(t_0, \mathbf{x}_0)$.

As noted above, if a solution to an IDE exists then it will be piecewise continuous in general. We denote each "piece" of the solution by D_k, that is,

$$D_k = \{(t, \mathbf{x}(t)) \in D \mid \tau_{k-1}(\mathbf{x}(t)) < t \leq \tau_k(\mathbf{x}(t))\}.$$

It will also be useful to consider each of these pieces with the point of discontinuity deleted; we call such a set D_k', defined analogously by

$$D_k' = \{(t, \mathbf{x}(t)) \in D \mid \tau_{k-1}(\mathbf{x}(t)) < t < \tau_k(\mathbf{x}(t))\}.$$

We can establish the existence of a solution to Equation (2.8) via the following theorem [13]. Here, σ_k denotes the hypersurfaces formed by $t = \tau_k(\mathbf{x}(t))$.

Theorem 5

Assume that $f : D \to \mathbb{R}^n$ is continuous in D_k and, for any k and any $(t_0, \mathbf{x}_0) \in D \cap \sigma_k$, there exists some $\beta > t_0$ and a solution $\phi(t)$ of the initial value problem for Equation (2.8a) such that $(t, \phi(t)) \in D_{k+1}$ for $t \in (t_0, \beta)$. Then there exists a solution to the initial value problem for Equation (2.8) for any $(t_0, \mathbf{x}_0) \in D$.

The uniqueness of a solution to Equation (2.8) is given by the following theorem [13].

Theorem 6

Under the assumptions of the previous theorem, together with the requirement that f be locally Lipschitz continuous with respect to $\mathbf{x}(t)$, then if $\phi(t)$ and $\psi(t)$ are solutions to Equation (2.8), $\phi(t) = \psi(t)$ for all t in the intersection of their respective domains.

Chapter 3

Survey of Models of HIV Pathogenesis

3.1 Introduction

THE BODY OF MATHEMATICAL LITERATURE surrounding the study of HIV infection has grown in leaps and bounds over the past two decades. Spurred in part by the enormous public awareness of HIV, and in part by the unique biomedical questions raised by its pathogenesis, mathematicians have developed a remarkable array of models in an attempt to capture the behaviour of infection by HIV and its response to various forms of treatment.

In this chapter, we examine some of the fundamental models of HIV infection, concentrating initially on those models which employ a traditional ordinary differential equation approach. We shall begin with ODE models which seek only to model HIV proliferation and the inherent immune response. Next we shall consider models which incorporate drug therapy to combat the HIV infection. And finally, we shall examine models in which the virus responds to the presence of drugs by developing resistant strains. Lastly, we shall deviate from our strict observation of ODE models, expanding our interest to models which include impulsive differential equations as well.

There is no standardised notation for mathematical models of HIV. We shall therefore seek to clarify the relationship between the various models discussed by applying a uniform notation throughout this chapter, often eschewing the notation which may have been used in the original references.

3.2 The One-Dimensional Model

Let $V(t)$ be the concentration of HIV virions in the host (such that it is expressed in units of particles per volume). We assume that new virus is produced at a rate P, while virions are cleared by the immune system at a rate

c. Here P is in units of particles per volume per time, while c is simply in units of per-time. The clearance rate c is a broadly-defined constant incorporating the action of cytotoxic T cells, macrophages, antibodies, and so forth, which assumes that the rate at which the immune system extinguishes the virus is proportional to the amount of virus present.

The simplest possible model for HIV infection [5] is thus as follows:

$$\dot{V}(t) = P - cV(t).$$

This model can straightforwardly be solved to obtain the solution

$$V(t) = \frac{P}{c} + C_1 e^{-ct},$$

for some constant C_1. In theory, then, if some drug treatment were completely effective and caused the production of new virus to cease (rendering $P = 0$), the rate of change of the virus concentration in the host would obey the elementary differential equation

$$\dot{V}(t) = -cV(t),$$

with an exponential solution

$$V(t) = V_0 e^{-ct},$$

where the constant V_0 represents the virus population prior to therapy.

This suggests a way of estimating the clearance rate c experimentally. Furthermore, if the host had entered the chronic phase of the infection before the treatment took place (and this will be a common assumption in investigating any model of HIV), we expect that the virus concentration is in a quasi-steady state such that $\dot{V}(t) = 0$ and therefore $P = cV_0$. This provides a way to estimate the HIV production rate.

However, this approach — while elementary and therefore a useful building block — is inexact in several respects. First, as we shall discuss in more detail later, the notion of therapy which perfectly inhibits virus production, while attractive, is not realistic; consequently, the value of c arrived at through this approach will be a lower bound at best. Additionally, experimental studies indicate that the exponential progression suggested by this model is overly simplistic, and lacks the finer detail necessary to genuinely encapsulate the progression of the disease. Finally, although this model provides some idea of the evolution of the virions, in immunological terms we are more interested in the dynamics of the $CD4^+$ T cell population. Consequently, a simple one-dimensional model cannot suffice for our needs.

3.3 The Basic Three-Dimensional Model

In addition to the virus concentration $V(t)$, we will now incorporate the concentration of uninfected helper T cells $T(t)$ and the concentration of infected helper T cells $U(t)$ into the model; analogously to $V(t)$, these terms are in units of cells per volume.

To be precise, $T(t)$ and $U(t)$ should refer exclusively to concentrations of HIV-specific $CD4^+$ T cells — that is, to those T cells which are stimulated by the presence of HIV — rather than to the entire population of helper T cells. However, presumably due to the difficulty in experimentally measuring levels of HIV-specific $CD4^+$ T cells as compared to the overall $CD4^+$ T cell count, many HIV models suppress this distinction. At any rate, the form of the models is unaffected.

To begin, we assume that in a healthy body, new $CD4^+$ T cells are produced at a constant rate s (in units of cells per volume per time), with a constant per-cell death rate of d (in units of per-time). This latter parameter also implies that the average lifespan of a helper T cell is $\frac{1}{d}$. Hence, in an uninfected individual, the $CD4^+$ T cell population would be governed by the differential equation

$$\dot{T}(t) = s - dT(t).$$

Next we assume that the body is infected with HIV virions, denoted by $V(t)$

as before. Infection by the virus creates a new population of helper T cells, $U(t)$, denoting the concentration of infected T cells. We assume that the rate at which uninfected T cells become infected is proportional to size of both the T cell and virus populations (thus representing the infection via a **mass-action** term, which both depletes the uninfected T cell population and augments the infected T cell population). We denote the constant of proportionality by k; this parameter therefore represents the rate of infection, and is in units of per (virus) particle per time.

As with their uninfected brethren, we assume that the natural death rate of an infected T cell is a constant, but we allow for the likelihood that the death rates of the uninfected and infected T cells may differ. Hence we represent the death rate of the infected helper T cells by δ (also in units of per-time). Again, we may observe that this suggests that the average lifespan of an infected T cell is $\frac{1}{\delta}$.

Finally, we must incorporate the production of new virus into the model. Previously, we had

$$\dot{V}(t) = P - cV(t).$$

Since the source of new virions is the infected T cells $U(t)$, however, it is reasonable to infer that P is proportional to the infected T cell population. Thus we assume that, on average, N virions will be produced from an infected T cell (such that N is in units of particles per cell) over the course of its lifespan. Since, as previously noted,

the average lifespan is $\frac{1}{\delta}$, we have that the average number of virions produced per infected T cell per unit of time is

$$\frac{N}{\frac{1}{\delta}} = N\delta.$$

Under this set of assumptions, we arrive at the system [4,5,16]

$$\dot{T}(t) = s - dT(t) - kV(t)T(t) \tag{3.1a}$$

$$\dot{U}(t) = kV(t)T(t) - \delta U(t) \tag{3.1b}$$

$$\dot{V}(t) = N\delta U(t) - cV(t) \tag{3.1c}$$

where, as before, c is the clearance rate of the virus from the system (in units of per-time). Note that the fine detail of the immune response, such as the activity of $CD8^+$ T cells, B cells, and other leukocytes, is not addressed in this basic model. Rather, all of these mechanisms are aggregated into the single clearance parameter c.

Some straightforward modifications to this basic model (before the incorporation of more significant phenomena, such as drug treatment, which will be addressed in subsequent sections) can also be found in the literature. For instance, Equation (3.1) neglects the proliferation of T cells caused by existing T cells (although the literature generally suggests that such a term has a negligible effect

on model dynamics). Perelson and Nelson [5] deal with this by replacing Equation (3.1a) with

$$\dot{T}(t) = s + pT(t)\left(1 - \frac{T(t)}{T_{max}}\right) - dT(t) - kV(t)T(t). \tag{3.2}$$

The idea behind the extra logistic term is that T cells will proliferate at a maximal rate p (in units of per-time) until such time as a density T_{max} (measured in cells per volume) is achieved. Note that that population must therefore decline should it ever reach T_{max}. Consequently, the rate of T cell production s must be less than the rate of death of this largest possible concentration, that is, we must require

$$dT_{max} > s.$$

Strictly speaking, this maximal number of $CD4^+$ T cells should be independent of the existence of infected T cells — in other words, T_{max} should be the maximum total T cell population, including both infectives and non-infectives. This yields

$$\dot{T}(t) = s + pT(t)\left(1 - \frac{T(t) + U(t)}{T_{max}}\right) - dT(t) - kV(t)T(t) \tag{3.3}$$

but Perelson and Nelson [5] suggest that because in reality $U(t) \ll T(t)$, this is an unnecessary complication.

Kirschner [17] also incorporates the proliferation of T cells due to the existing T cell population. However, she observes that because the only T cells which

ought to be under consideration in the model are HIV-specific T cells, they will be stimulated to different rates of proliferation depending upon the amount of virus present (while acknowledging that the nascent T cells thereby produced will not necessarily be HIV-specific). To account for this, Kirschner not only includes a dependence on $V(t)$ in her proliferation term (in contrast to Perelson and Nelson) but also formulates it using a saturation approach. She therefore replaces Equation (3.1a) with

$$\dot{T}(t) = s + p\frac{T(t)V(t)}{C + V(t)} - dT(t) - kV(t)T(t). \tag{3.4}$$

Here, p again represents the rate of proliferation while C (in units of particles per volume) is the half-saturation constant.

In addition, Kirschner observes that the stimulation of infected $CD4^+$ T cells to proliferate will result in their demise through bursting due to the ejection of the virions. Thus the concentration of infected T cells will be reduced at a rate analogous to the proliferation of T cells developed above. In Kirschner's model [17], then, the rate of change of the infected T cell population becomes

$$\dot{U}(t) = kV(t)T(t) - \delta U(t) - p\frac{U(t)V(t)}{C + V(t)}. \tag{3.5}$$

Finally, Kirschner's third modification to the basic model addresses both natural virus death and virus production from secondary sources — that is, host cells

which are susceptible to HIV infection other than $CD4^+$ T cells, such as infected macrophages. Again using a saturation-type term, Kirschner [17] replaces Equation (3.1c) with

$$\dot{V}(t) = Np\frac{U(t)V(t)}{C + V(t)} - c_T V(t)T(t) + g\frac{V(t)}{b + V(t)}. \tag{3.6}$$

Here, g is the rate of free virus production from secondary sources (in units of per-time) while b (in units of particles per volume) is the half-saturation constant. Note also that Equation (3.6) incorporates a modified version of the first term of Equation (3.1c). This reflects the assumption that all virion production from infected T cells will come about as a result of the bursting of stimulated T cells, and therefore accounts for the rate of bursting developed as part of Equation (3.5).

Müller and Bonhoeffer [16] incorporate the possibility that not all infected cells will survive to virus production. Under their scheme, Equation (3.1b) becomes

$$\dot{U}(t) = fkV(t)T(t) - \delta U(t), \tag{3.7}$$

where the dimensionless parameter $f \in [0, 1]$ represents the likelihood of the infected T cell progressing to such a state.

Perelson and Nelson [5] observe that the process of creating an infected T cell actually kills the virion responsible. Hence Equation (3.1c) — or, similarly, Equa-

tion (3.6) — could be modified to become

$$\dot{V}(t) = N\delta U(t) - cV(t) - kV(t)T(t), \tag{3.8}$$

with the mass-action term reflecting the growth in the infected helper T cell population also now accounting for the corresponding decrease in the free virus concentration.

Finally, note that the source term s, found in Equation (3.1a) and its variations, is not necessarily constant, although it is often assumed to be such. Kirschner [17] does in fact treat it as a saturating function of the viral load $V(t)$, of the form

$$s(t) = 0.5s + \frac{5s}{1 + V(t)}$$

for some constant s. This is intended to reflect the fact that HIV can progress to the thymus, and therefore will infect members of the T cell reservoir before they can migrate to the bloodstream. The new virus produced by these infectives would then be accounted for by the secondary source term in Equation (3.6).

3.4 The Two-Dimensional Model

Ironically, although we began by developing a one-dimensional model which accounted only for the HIV virus concentration, this is perhaps the least important of the three populations in the model. Practically, we are far more interested

in the uninfected and infected T cell counts. It would therefore be of benefit to eliminate the third equation, and $V(t)$, from the model altogether.

This approach is of particular benefit when considering more than one strain of HIV, as we shall do later in this chapter. Each new strain adds at least two equations to Equation (3.1) or any of its variations (one for the corresponding virus population, one for T cells infected by the given strain), making the analysis of the model significantly more difficult. Furthermore, even in the presence of two strains, a model which does not explicitly include any virus populations will remain a three-dimensional system, and hence can still straightforwardly be visually represented.

This is not a brand-new idea, but other references which take this approach [4,16] do so by inferring that $V(t)$ exists at a quasi-steady state. They then set $\dot{V}(t) = 0$ and solve for $V(t)$ in terms of $U(t)$. However, since this shows $V(t)$ to be proportional to $U(t)$, and $\dot{U}(t)$ is not zero, this justification appears spurious. Nonetheless, the proportional relationship between $V(t)$ and $U(t)$ arrived at by this method is, in and of itself, a reasonable assumption to make, given that we are already assuming an average number of virions produced by each infected T cell, as well as a constant clearance rate of the HIV virus.

Consequently, let us indeed assume that

$$V(t) = bU(t),$$

for some constant b (in units of particles per cell). The basic model given by Equation (3.1) is reduced from a system of three differential questions to a system of only two:

$$\dot{T}(t) = s - dT(t) - \tilde{k}T(t)U(t) \tag{3.9a}$$

$$\dot{U}(t) = \tilde{k}T(t)U(t) - \delta U(t) \tag{3.9b}$$

where $\tilde{k} = bk$ represents the overall virulence of the infection; it is in units of per cell per time.

3.5 Models with Drug Therapy

When discussing drug therapy of patients with HIV, two forms of treatment are principally considered. The first involves a class of drugs called reverse transcriptase (RT) inhibitors, which prevent the virus from transcribing its RNA into DNA and thereby infecting a target T cell. The second treatment is in the form of protease inhibitors, which cause noninfectious virions to arise from infected cells. Simply put, then, RT inhibitors prevent the migration from population $T(t)$ to population $U(t)$, while protease inhibitors dampen the growth of the population $V(t)$ of active virions (by causing the development of a second population of noninfectious free virus).

Sadly, no drug is perfect, and the model must (in principle) reflect the nonideal effectiveness of the therapy. As in [5], to model the influence of RT inhibitors we can replace Equation (3.1b) with

$$\dot{U}(t) = (1 - \eta_{RT})kV(t)T(t) - \delta U(t) \tag{3.10}$$

where $\eta_{RT} \in [0, 1]$ represents the effectiveness of the RT inhibition therapy. In the ideal case where the drug completely inhibits the reverse transcription (so that $\eta_{RT} = 1$), this equation simply becomes

$$\dot{U}(t) = -\delta U(t), \tag{3.11}$$

implying that the infected T cell population will decay exponentially.

The effects of protease inhibitors are more complicated to model, because the treatment leads to a new population, namely noninfectious virions. If we now assume that $V(t)$ is the population of strictly infectious virions, whereas $V_N(t)$ accounts for their noninfectious counterparts, we must replace Equation (3.1c) with two equations:

$$\begin{aligned} \dot{V}(t) &= (1 - \eta_P)N\delta U(t) - cV(t) \\ \dot{V}_N(t) &= \eta_P N\delta U(t) - cV_N(t) \end{aligned} \tag{3.12}$$

where $\eta_P \in [0, 1]$ represents the effectiveness of the protease inhibitor. In the case

where the treatment is completely effective ($\eta_P = 1$) these equations reduce to

$$\begin{aligned} \dot{V}(t) &= -cV(t) \\ \dot{V}_N(t) &= N\delta U(t) - cV_N(t) \end{aligned} \tag{3.13}$$

so that the number of effective virions declines exponentially. Note that due to the decoupled nature of the differential equation for $V_N(t)$, this equation could be suppressed unless an understanding of the dynamics of this population is of specific interest. (Indeed, even in the absence of drug therapy, HIV produces malfunctioning virus due to transcription errors, so there always exists a population comparable to $V_N(t)$ which is typically neglected.)

Of course, in practise, most patients receive a drug cocktail combining both RT and protease inhibitors, due to the serious problem of fast-evolving drug immunity exhibited by HIV (which will be considered in the next section). To model this so-called combination therapy, we can incorporate both Equations (3.10) and (3.12) into the basic model given by Equation (3.1) to obtain

$$\begin{aligned} \dot{T}(t) &= s - dT(t) - kV(t)T(t) \\ \dot{U}(t) &= (1 - \eta_{RT})kV(t)T(t) - \delta U(t) \\ \dot{V}(t) &= (1 - \eta_P)N\delta U(t) - cV(t) \\ \dot{V}_N(t) &= \eta_P N\delta U(t) - cV_N(t). \end{aligned} \tag{3.14}$$

If the RT and protease inhibitors are all 100% effective, this model reduces to

$$\begin{aligned} \dot{T}(t) &= s - dT(t) - kV(t)T(t) \\ \dot{U}(t) &= -\delta U(t) \\ \dot{V}(t) &= -cV(t) \\ \dot{V}_N(t) &= N\delta U(t) - cV_N(t), \end{aligned} \tag{3.15}$$

suggesting the elimination of the virus over time. Again, the equation for $V_N(t)$ could be neglected altogether.

Other possible extensions to the basic model found in [5] include those accounting for long-lived (noninfected and infected) cells $M(t)$ and $M_U(t)$, for latently infected cells $L(t)$, or indeed for both long-lived and latently infected cells.

3.6 Models with Drug Resistance

One of the major obstacles to the effective treatment of HIV is its ability to respond efficiently to the debilitating influence of drugs. The original HIV strain, called the **wild-type**, can undergo mutations which result in the emergence of additional drug-resistant strains. Having considered models which incorporate drug therapy into the progression of the virus, it is imperative that we now survey models which exhibit the evolution of HIV in response to drugs. To avoid the

proliferation of the model to five dimensions or more (incorporating wild-type infectives and free virus, and mutant infectives and free virus, in addition to the uninfected T cells), it is convenient to make use of the two-dimensional basic model given by Equation (3.9).

Müller and Bonhoeffer [16] consider the question of modelling the mutation between a wild-type virus population and a drug-resistant virus population. Let $\mu \in [0,1]$ be the mutation rate between the two variants (where $\mu = 0$ would indicate no mutation and $\mu = 1$ would indicate universal mutation), and assume that the two strains differ only in their overall infection rate, so that $U(t)$ remains the population of cells infected with wild-type virus (with infection rate $\tilde{k}$) and $U_M(t)$ is the population of cells infected with mutant virus (with infection rate $\tilde{k}_M$). Then Equation (3.9) now becomes

$$\begin{aligned} \dot{T}(t) &= s - dT(t) - \tilde{k}T(t)U(t) - \tilde{k}_M T(t)U_M(t) \\ \dot{U}(t) &= (1-\mu)\tilde{k}T(t)U(t) + \mu\tilde{k}_M T(t)U_M(t) - \delta U(t) \\ \dot{U}_M(t) &= \mu\tilde{k}T(t)U(t) + (1-\mu)\tilde{k}_M T(t)U_M(t) - \delta U_M(t). \end{aligned} \tag{3.16}$$

Nowak and May [4] exhibit a similar model, but neglect the possibility of back-mutation from the resistant strain to the wild-type virus. However, they do not eliminate either virus population from their model, resulting in the five-

dimensional system

$$\begin{aligned}
\dot{T}(t) &= s - dT(t) - kT(t)U(t) - k_M T(t)U_M(t) \\
\dot{U}(t) &= (1-\mu)kT(t)U(t) - \delta U(t) \\
\dot{V}(t) &= N\delta U(t) - cV(t) \\
\dot{U}_M(t) &= \mu kT(t)U(t) + k_M T(t)U_M(t) - \delta U_M(t) \\
\dot{V}_M(t) &= N_M \delta U_M(t) - cV_M(t).
\end{aligned} \tag{3.17}$$

Here N_M is the average number of virions produced by a T cell infected by the mutant strain.

We can easily reduce Nowak and May's system to its corresponding three-dimensional version:

$$\dot{T}(t) = s - dT(t) - \tilde{k}T(t)U(t) - \tilde{k}_M T(t)U_M(t) \tag{3.18a}$$

$$\dot{U}(t) = (1-\mu)\tilde{k}T(t)U(t) - \delta U(t) \tag{3.18b}$$

$$\dot{U}_M(t) = \mu\tilde{k}T(t)U(t) + \tilde{k}_M T(t)U_M(t) - \delta U_M(t). \tag{3.18c}$$

Nowak and May separately concern themselves not with how a drug-resistant mutant arises from the wild type, but rather with the response of both virus strains under the effects of drug therapy (effectively, this model assumes the preexistence of a resistant strain, but ignores the possibility of further mutation from the wild-type). In this case, Nowak and May eliminate the virus terms in the manner of

Equation (3.9) and assume that the production of new T cells infected by the wild-type strain has been inhibited with an effectiveness η (while the production of new T cells infected by the mutant form is not curtailed in this manner at all). Then Equation (3.9) can be rewritten as

$$\dot{T}(t) = s - dT(t) - (1-\eta)\tilde{k}T(t)U(t) - \tilde{k}_M T(t)U_M(t) \tag{3.19a}$$

$$\dot{U}(t) = (1-\eta)\tilde{k}T(t)U(t) - \delta U(t) \tag{3.19b}$$

$$\dot{U}_M(t) = \tilde{k}_M T(t)U_M(t) - \delta U_M(t). \tag{3.19c}$$

Note that there is an underlying assumption in this model that only RT inhibitors are being employed. In order to model protease inhibition, we would replace Equation (3.19a) with the equation

$$\dot{T}(t) = s - dT(t) - \tilde{k}T(t)U(t) - \tilde{k}_M T(t)U_M(t).$$

To model both RT and protease inhibition, we would instead replace Equation (3.19b) with

$$\dot{U}(t) = (1-\eta_P)(1-\eta)\tilde{k}T(t)U(t) - \delta U(t).$$

3.7 Models with Impulses

To date, the principal use of impulsive effects in models of HIV pathogenesis has been in a series of papers by Smith? and Wahl [18,19], Smith? alone [20], and Krakovska and Wahl [21]. (Note that Smith? does employ a question mark in his surname.) In these, the authors present two models. The first considers the effects of both protease and reverse transcriptase inhibitors in mitigating infection by a wild-type HIV strain. The second does not make a distinction between types of treatment but does incorporate the existence of a resistant strain of the virus into the model. Both involve large systems of differential equations, together with the impulsive effect.

The first of these [18] consists of ten differential equations together with two impulses. One impulse reflects treatment with a reverse transcriptase inhibitor $R(t)$, and the other indicates treatment with a protease inhibitor $P(t)$. Smith? and Wahl consider six populations of $CD4^+$ T cells: the uninfected population, $T(t)$, the infected population, $U(t)$, uninfected cells which have absorbed the reverse transcriptase inhibitor only, $T_R(t)$, uninfected cells which have absorbed the protease inhibitor only, $T_P(t)$, uninfected cells which have absorbed both the reverse transcriptase and protease inhibitors, $T_{RP}(t)$, and infected cells which have absorbed the

protease inhibitor, $U_P(t)$. They include two virus populations explicitly in their system: the infections virions, $V(t)$, and non-infectious virions produced by infected T cells that are either defective or have absorbed the protease inhibitor, $V_N(t)$. The novel parameters of Smith? and Wahl's system include ω (the fraction of virions produced by an infected T cell which are themselves infectious), η_R (the rate at which the reverse transcriptase inhibitor inhabits the intracellular compartment of the T cells), η_P (the rate at which the protease inhibitor inhabits the intracellular compartment), m_R (the rate at which the reverse transcriptase inhibitor is cleared from the intracellular compartment), and m_P (the rate at which the protease inhibitor is cleared from the intracellular compartment).

The system is then

$$
\begin{aligned}
\dot{T}(t) &= s - dT(t) - kV(t)T(t) - \eta_R T(t)R(t) - \eta_P T(t)P(t) + m_R T_R(t) + m_P T_P(t) \\
\dot{T}_R(t) &= \eta_R T(t)R(t) - dT_R(t) + m_P T_{RP}(t) - m_R T_R(t) - \eta_P T_R(t)P(t) \\
\dot{T}_P(t) &= \eta_P T(t)P(t) - dT_P(t) - kV(t)T_P(t) - \eta_R T_P(t)R(t) - m_P T_P(t) + m_R T_{RP}(t) \\
\dot{T}_{RP}(t) &= \eta_R T_P(t)R(t) - dT_{RP}(t) - m_P T_{RP}(t) - m_R T_{RP}(t) + \eta_P T_R(t)P(t) \\
\dot{U}(t) &= kV(t)T(t) - \delta U(t) - \eta_P U(t)P(t) + m_P U_P(t) \\
\dot{U}_P(t) &= kV(t)T_P(t) - \delta U_P(t) + \eta_P U(t)P(t) - m_P U_P(t) \\
\dot{V}(t) &= N\delta\omega U(t) - cV(t) - kV(t)T(t) - k\dot{V}(t)T_P(t) \\
\dot{V}_N(t) &= N\delta U_P(t) + N\delta(1-\omega)U(t) - cV_N(t) \\
\dot{R}(t) &= -d_R R(t), \quad t \neq t_k \\
\dot{P}(t) &= -d_P P(t), \quad t \neq s_k \\
\Delta R &= R^i, \quad t = t_k \\
\Delta P &= P^i, \quad t = s_k.
\end{aligned}
\tag{3.20}
$$

Smith? and Wahl analyse this model by considering extreme cases of dosage schedules (four cases, wherein the treatment frequencies of each of the two inhibitors is made either very large or very small) and find that it is the reverse transcriptase inhibitor which holds the greatest effect on T cell levels *in vivo*, to the point of (theoretically) maintaining the uninfected count close to that of levels

pre-infection.

Of greater relevance to our current work is Smith? and Wahl's second model [19, 20]. As in the author's model, Smith? and Wahl here dispense with the distinction between reverse transcriptase and protease inhibitors (although they maintain the virus population as an explicit inclusion in the model) and consider the emergence of a mutant, resistant strain from the wild-type virus. However, they do not consider an ongoing mutation rate from the wild-type to the mutant virus, and hence confine themselves to the case where the mutant virus population is pre-existing.

Rather than establishing a uniform model which is independent of the drug levels, Smith? and Wahl instead alter the formulation of their model according to a range of values of the drug concentration, $D(t)$. For $D(t)$ at low levels, it is assumed that there is a negligible chance of an uninfected T cell absorbing sufficient quantities of the drug to prevent infection by either form of the virus. For $D(t)$ at intermediate levels, it is assumed that there is a negligible chance of an uninfected T cell absorbing sufficient quantities of the drug to prevent infection by the mutant virions, but that the chance of infection by the wild-type virus being inhibited grows monotonically with $D(t)$. Finally, for $D(t)$ at high levels, it is assumed that there is a chance of an uninfected T cell preventing infection by either form of the

virus, with a greater likelihood in the case of the wild-type virus.

Each variant of Smith? and Wahl's model consists of nine differential equations, as well as an impulsive condition. In addition to the uninfected $CD4^+$ T cell population $T(t)$, the population of T cells infected by the wild-type virus $U(t)$, and the population of T cells infected by the mutant virus $U_M(t)$, Smith? and Wahl further include the population of uninfected T cells which have absorbed sufficient quantities of the drug so that infection by the wild-type virus is inhibited $T_W(t)$, and the population of uninfected T cells which have absorbed sufficient quantities of the drug so that infection by both forms of virus is inhibited $T_M(t)$. The wild-type and mutant virus populations are $V(t)$ and $V_M(t)$, respectively. New parameters in this case are m_W and m_M, the rates at which the drug is cleared from the intracellular compartment in cases of intermediate and high concentrations, respectively. The rate at which the drug is cleared from the body is denoted by m.

At low levels of drug concentration, the model takes the form

$$\dot{T}(t) = s - dT(t) - kV(t)T(t) - k_M V_M(t)T(t) + m_W T_W(t) \tag{3.21a}$$

$$\dot{T}_W(t) = -k_M V_M(t)T_W(t) - (d + m_W)T_W(t) + m_M T_M(t) \tag{3.21b}$$

$$\dot{T}_M(t) = -(d + m_M)T_M(t) \tag{3.21c}$$

$$\dot{U}(t) = kV(t)T(t) - \delta T(t) \tag{3.21d}$$

$$\dot{U}_M(t) = k_M V_M(t)T(t) + k_M V_M(t)T_W(t) - \delta U_M(t) \tag{3.21e}$$

$$\dot{V}(t) = N\delta\omega U(t) - cV(t) - kV(t)T(t) \tag{3.21f}$$

$$\dot{V}_M(t) = N\delta\omega U_M(t) - cV_M(t) - k_M V_M(t)T(t) - k_M V_M(t)T_W(t) \tag{3.21g}$$

$$\dot{V}_N(t) = k\delta(1 - \omega)[U(t) + U_M(t)] - \delta V_N(t) \tag{3.21h}$$

$$\dot{D}(t) = -mD(t), \quad t \neq t_k \tag{3.21i}$$

$$\Delta D = D^i, \quad t = t_k. \tag{3.21j}$$

At intermediate levels of drug concentration, the following equations are replaced:

$$\dot{T}(t) = s - dT(t) - kV(t)T(t) - k_M V_M(t)T(t) + m_W T_W(t) - \eta_W T(t)R(t) \tag{3.22a}$$

$$\dot{T}_W(t) = -k_M V_M(t)T_W(t) - (d + m_W)T_W(t) + m_M T_M(t) + \eta_W T(t)R(t), \tag{3.22b}$$

where η_W is the rate at which the intermediate-level drug concentrations inhibit the wild-type virus.

At high levels of drug concentration, the deviations from the original model are as follows:

$$\dot{T}(t) = s - dT(t) - kV(t)T(t) - k_M V_M(t)T(t) + m_W T_W(t) - \eta_{WM} T(t)R(t) \quad (3.23a)$$

$$\dot{T}_W(t) = -k_M V_M(t)T_W(t) - (d + m_W)T_W(t) + m_M T_M(t) \quad (3.23b)$$

$$+ \quad \eta_{WM} T(t)R(t) - \eta_M T_W(t)R(t)$$

$$\dot{T}_M(t) = -(d + m_M)T_M(t) + \eta_M T_W(t)R(t) \quad (3.23c)$$

where η_{WM} and η_M are the rates at which the high drug concentrations inhibit the wild-type and mutant virions, respectively.

Under Smith? and Wahl's model, at low drug levels the wild-type virus dominates, with the mutant form becoming extinct. At intermediate drug levels, both virus variants coexist. At high drug levels, the two virus strains may again coexist, or they may both become extinct. Smith? and Wahl also noted that, while the total T cell counts at low and intermediate drug concentrations were considerably less than in the disease-free state, these rebounded under high drug concentrations to survive at very near the drug-free tally.

In Chapter 5, we will detail the analytical methods used by Smith? and Wahl and employ it in the investigation of our own model incorporating impulsive effects.

Chapter 4

A New Model

The author's ultimate goal in developing a new model was to devise a more refined formulation for the progression of HIV under the influence of drug therapy. In particular, it was thought to be important to include in such a model the mutation of wild-type HIV. As discussed in Chapter 1, mutation appears to be a critical phenomenon in explaining why HIV is so difficult to control pharmacologically, and so it was felt that to ignore this mechanism would be to introduce a fundamental oversimplification into the model.

4.1 The Author's Model, Initial Version

While careful consideration was given to each term which would be incorporated into the model, it was also acknowledged that it would be, at best, inefficient to "reinvent the wheel." As detailed in the preceding chapter, popular models already exist to account for drug therapy in HIV pathogenesis, as do variant approaches to the inclusion of mutant virions in the analysis. In particular, then, the ensuing discussion owes much to models of Müller and Bonhoeffer, and of Nowak and May, given in Chapter 3 as Equations (3.16), (3.18) and (3.19).

Also playing a role in the formulation of the model was a desire to ensure that it be susceptible to a dynamical systems-type analysis, rather than being suitable only for investigation via numerical simulation — albeit, of course, without compromising the integrity of the model by making gratuitous oversimplifications purely to keep the system as "small" as possible. Consequently, it was decided to build the model on the basic two-dimensional system given in Equation (3.9). This greatly enhances the mathematical tractability of the system, especially when virus mutations are introduced. (For example, the two-mutant model to be studied in Chapter 5 is reduced to four dimensions rather than the seven which explicit inclusion of the virus would necessitate.) Furthermore, the removal of the virus

term does not impede the determination of the relative fitness of HIV under various scenarios (drug therapy, drug resistance, etc), a role which the infected T cell populations fill without loss of adequacy.

Since it is fundamental to the rest of the work in this chapter, we will repeat the basic two-dimensional model here for clarity:

$$\dot{T}(t) = s - dT(t) - \tilde{k}T(t)U(t) \tag{4.1a}$$

$$\dot{U}(t) = \tilde{k}T(t)U(t) - \delta U(t). \tag{4.1b}$$

The variables in this system are $T(t)$, the population of uninfected HIV-specific $CD4^+$ T cells, and $U(t)$, the population of HIV-specific $CD4^+$ T cells infected with HIV. The parameters are the T cell production term, s; the respective death rates of the uninfected and infected T cells, d and δ; and the virulence of the infection, $\tilde{k}$.

We assume that drug therapy has been initiated, such that the effectiveness of the treatment is η; as discussed in Chapter 3, we will henceforth assume that this therapy takes the form of RT inhibitors. Thus the model becomes

$$\begin{aligned} \dot{T}(t) &= s - dT(t) - (1-\eta)\tilde{k}T(t)U(t) \\ \dot{U}(t) &= (1-\eta)\tilde{k}T(t)U(t) - \delta U(t). \end{aligned} \tag{4.2}$$

We will assume that the wild-type virus mutates at a constant rate μ, the result being helper T cells infected with mutant virus, $U_M(t)$. As in Chapter 3, we assume

that the death rate of T cells infected by the mutant strain is δ, the same as the death rate of T cells infected by the wild-type strain. However, we will draw no such parallels in relation to the other two descriptive parameters: that is, we will assume that the mutant virus possesses a virulence $\tilde{k}_M$ and is resistant to the drug therapy such that its efficacy is η_M. We would typically expect a mutant to exhibit $\tilde{k}_M \leq \tilde{k}$ and $\eta_M \leq \eta$ (that is, that the mutant strain be less virulent but also less susceptible to therapy), but we shall make no overt assumptions in this regard, thus allowing for the possibility of retrograde mutations.

Unlike Müller and Bonhoeffer, but in accordance with Nowak and May, we shall neglect the possibility of back-mutation (that is, the reversion of the mutant virus to wild-type virus). Note, however, that we have deviated from Nowak and May in making no assertion that the mutant virus is completely resistant to the drug therapy, as in their model described in Equation (3.19). Consequently, our model is the following:

$$\begin{aligned}
\dot{T}(t) &= s - dT(t) - (1-\eta)\tilde{k}T(t)U(t) - (1-\eta_M)\tilde{k}_M T(t)U_M(t) \\
\dot{U}(t) &= (1-\mu)(1-\eta)\tilde{k}T(t)U(t) - \delta U(t) \\
\dot{U}_M(t) &= \mu(1-\eta)\tilde{k}T(t)U(t) + (1-\eta_M)\tilde{k}_M T(t)U_M(t) - \delta U_M(t).
\end{aligned} \tag{4.3}$$

In Chapter 5, we will extend this model by considering the possibility that a second mutant strain might be present. In Chapter 6, we will augment it by in-

troducing the notion of impulsive differential equations. First, though, we shall analyse Equation (4.3) by investigating its fixed points and its eigenvalues. In so doing, we will explain these results in both mathematical and biological terms, thereby demonstrating that the model is valid not only mathematically, but also with regards to the phenomena it represents. Finally, we will investigate Equation (4.3) numerically, illustrating the various kinds of behaviour which may arise from this system.

We first acknowledge, however, that following the completion of this step of our work, Rong, Feng and Perelson [22] published a model with much the same goal of considering both drug therapy and mutation of the virus. Their system is

$$\begin{aligned}
\dot{T}(t) &= s - dT(t) - k(1-\eta_{RT})T(t)V(t) - k_M(1-\eta_{RT}^M)T(t)V_M(t)\\
\dot{U}(t) &= (1-\mu)k(1-\eta_{RT})T(t)V(t) - \delta U(t)\\
\dot{V}(t) &= N(1-\eta_P)\delta U(t) - cV(t)\\
\dot{U}_M(t) &= \mu k(1-\eta_{RT})T(t)V(t) + k_M(1-\eta_{RT}^M)T(t)V_M(t) - \delta U_M(t)\\
\dot{V}_M(t) &= N_M(1-\eta_P^M)\delta U_M(t) - cV_M(t).
\end{aligned} \tag{4.4}$$

Here, η_{RT} and η_{RT}^M are the effectiveness of treatment with an RT inhibitor on the wild-type and mutant strains, respectively, while η_P and η_P^M are the effectiveness of treatment with a protease inhibitor on these two forms of the virus. However, a rigorous analysis of this system is provided only in the case where no drug resistance

is present (that is, $\eta_{RT} = \eta_{RT}^M = \eta_P = \eta_P^M = 0$). Consideration is also not given to this model from the perspective of the orbit structure of the solutions. Finally, although Rong, Feng and Perelson do deal with issues of drug non-adherence which we shall also tackle later in this work, the methods they employ differ greatly from those we shall use.

4.2 The Fixed Points

To begin, we first determine the fixed points of model. We begin by rewriting Equation (4.3) in a slightly simplified form in order to facilitate the analysis. Let

$$\alpha = (1 - \eta)\tilde{k} \quad \text{and} \quad \alpha_M = (1 - \eta_M)\tilde{k}_M.$$

As the product of the virulence and resistance to drug therapy of each strain of the virus, these new parameters essentially represent the "quality" of the wild-type and mutant viruses, respectively. In other words, an HIV strain which is both highly virulent and acutely resistant to therapy is of a very high "quality." On the other hand, a strain which is quite virulent but poorly resistant (or vice versa) may be less successful than one which is both moderately virulent and moderately resistant, and therefore could be viewed as being of lower relative "quality." With

these substitutions, the model becomes

$$\begin{aligned}\dot{T}(t) &= s - dT(t) - \alpha T(t)U(t) - \alpha_M T(t)U_M(t)\\ \dot{U}(t) &= (1-\mu)\alpha T(t)U(t) - \delta U(t)\\ \dot{U}_M(t) &= \mu\alpha T(t)U(t) + \alpha_M T(t)U_M(t) - \delta U_M(t).\end{aligned} \tag{4.5}$$

Where convenient, we will also set

$$\beta = \frac{d\delta}{s}.$$

This system exhibits three fixed points. In this chapter and the sequel, we shall use $\overline{X}$ to denote a steady-state value of a variable X. Note that we have not gone so far as to nondimensionalise the model, because we wish to examine the biological significance of each result.

The first, and simplest, fixed point is

$$\overline{T} = \frac{s}{d}, \quad \overline{U} = \overline{U}_M = 0. \tag{4.6}$$

Clearly, this represents the case where HIV is eradicated, and only the uninfected T cells survive.

Secondly, we have

$$\overline{T} = \frac{\delta}{\alpha_M}, \quad \overline{U} = 0, \quad \overline{U}_M = \frac{s(\alpha_M - \beta)}{\delta\alpha_M}. \tag{4.7}$$

In this instance, the T cells infected with the wild-type strain perish, leaving only the uninfected T cells and the T cells infected by the mutant variant.

The final fixed point is

$$\overline{T} = \frac{\delta}{(1-\mu)\alpha}, \quad \overline{U} = \frac{[(1-\mu)\alpha - \alpha_M]\xi}{\alpha}, \quad \overline{U}_M = \mu\xi \tag{4.8}$$

where

$$\xi = \frac{s[(1-\mu)\alpha - \beta]}{\delta(1-\mu)(\alpha - \alpha_M)}.$$

This reflects the scenario in which all three T cell populations survive.

We might anticipate that there would be a fourth fixed point, in which the T cells infected by the mutant virus vanish (in the case of a "low-quality", retrograde mutation), leaving only the uninfected T cells and those infected by the wild-type virus. However, it should be noted that the model assumes that mutation occurs at a constant rate, and is not an isolated event. Consequently, new mutant virus will always be produced from the wild-type and therefore $U_M(t)$ must endure (albeit perhaps at very low levels) as long as any HIV remains.

More obviously, there is no fixed point at which the population of uninfected T cells vanishes. This is because $T(t)$ is a factor in all of the non-constant terms in the equation for the rate of change of $T(t)$, and consequently as $T(t) \to 0$, these become negligible. In this case, the rate of change of $T(t)$ will be dominated by the constant production term s, ensuring that the T cell levels are constantly replenished — possibly at low levels depending on the size of the infected T cell populations.

4.3 Non-negativity of Fixed Points

Since the system is intended to model biological phenomena, it is imperative that no stable fixed point exists which involves negative values of $\overline{T}$, $\overline{U}$ or $\overline{U}_M$ for feasible values of the parameters. Otherwise, a negative attractor would exist which would have no interpretation in reality, thereby undermining the validity of the model. Thus we will begin our analysis by deriving the conditions under which each fixed point is non-negative. We will subsequently assess their stability.

Recall that s, d, δ, $\tilde{k}$ and $\tilde{k}_M$ are all positive parameters, while μ, η and η_M are defined in the interval $[0,1]$ (although we operate under the implicit assumption that $\mu > 0$ here, since we are uninterested in the case where no mutation occurs). Note that this means that α, α_M and β are also positive quantities.

The first fixed point is clearly non-negative for all parameter values, since $\overline{U}$ and $\overline{U}_M$ are zero and $\overline{T}$ is simply the quotient of two positive quantities.

A similar assertion applies to the value of $\overline{T}$ for the second fixed point while, again, $\overline{U} = 0$. For the equilibrium value of $\overline{U}_M$ to be non-negative, we require

$$\alpha_M \geq \beta. \tag{4.9}$$

In other words, the quality of the mutant strain must be sufficiently strong in order for this fixed point to be biologically feasible. In this case, not only are the T cells

infected with the mutant strain viable enough to survive, but indeed they may be so preferable that the population of T cells infected by the wild-type form are eradicated.

The analysis of the third fixed point is more complicated. First, $\overline{T}$ is, again, clearly non-negative, exactly as in the cases already considered. To investigate the non-negativity of $\overline{U}$ and $\overline{U}_M$, we will have to examine several cases. There are three quantities of interest here: the signs of both $\overline{U}$ and $\overline{U}_M$ will be affected by the positivity or negativity of $(1-\mu)\alpha - \beta$ and $\alpha - \alpha_M$, while the sign of $\overline{U}$ is also dependent upon the positivity or negativity of $(1-\mu)\alpha - \alpha_M$.

In principle, this gives us eight possibilities but we can simplify matters slightly by observing that $\alpha - \alpha_M \geq (1-\mu)\alpha - \alpha_M$, since $\mu \in [0,1]$. Hence, if $(1-\mu)\alpha \geq \alpha_M$ then $\alpha \geq \alpha_M$. Similarly, if $\alpha \leq \alpha_M$ then $(1-\mu)\alpha \leq \alpha_M$. Thus we effectively have only six cases to consider:

1. if $(1-\mu)\alpha \geq \alpha_M$ and $(1-\mu)\alpha \geq \beta$ then both $\overline{U}$ and $\overline{U}_M$ will be non-negative;

2. if $(1-\mu)\alpha \geq \alpha_M$ and $(1-\mu)\alpha \leq \beta$ then both $\overline{U}$ and $\overline{U}_M$ will be non-positive;

3. if $\alpha \geq \alpha_M$ but $\alpha(1-\mu) \leq \alpha_M$ and $\alpha(1-\mu) \geq \beta$ then $\overline{U}$ will be non-positive while $\overline{U}_M$ will be non-negative;

4. if $\alpha \geq \alpha_M$ but $\alpha(1-\mu) \leq \alpha_M$ and $(1-\mu)\alpha \leq \beta$ then $\overline{U}$ will be non-negative

while $\overline{U}_M$ will be non-positive;

5. if $\alpha \leq \alpha_M$ and $(1-\mu)\alpha \geq \beta$ then $\overline{U}$ will be non-negative, but $\overline{U}_M$ will be non-positive;

6. if $\alpha \leq \alpha_M$ and $(1-\mu)\alpha \leq \beta$ then $\overline{U}$ will be non-positive, but $\overline{U}_M$ will be non-negative.

Only the first of these six cases results in non-negative equilibrium values, so we can conclude that the third fixed point of the system is non-negative only if

$$(1-\mu)\alpha \geq \alpha_M \quad \text{and} \quad (1-\mu)\alpha \geq \beta. \tag{4.10}$$

In other words, this fixed point is non-negative only if the mutation rate is adequately low and/or the quality of the wild-type virus is sufficiently strong, while the quality of the mutant strain is correspondingly weak — a set of conditions which make sense of the co-existence of the two types of infected T cells.

4.4 Eigenvalues and Stability

HAVING ESTABLISHED THE CONDITIONS under which each of the three equilibrium points is non-negative, we now determine their stability. This serves a twofold purpose. First, if a fixed point is stable for a set of parameter values which

allow it to be negative then this would suggest a fundamental flaw in the construction of the model. Second, the conditions for stability enable us to understand how changing parameter values affect the overall behaviour of the system.

The Jacobian matrix for this system is

$$J = \begin{bmatrix} -d - \alpha U - \alpha_M U_M & -\alpha T & -\alpha_M T \\ (1-\mu)\alpha U & (1-\mu)\alpha T - \delta & 0 \\ \mu\alpha U + \alpha_M U_M & \mu\alpha T & \alpha_M T - \delta \end{bmatrix}.$$

For each of the fixed points, we wish to determine the conditions under which all the eigenvalues of J are negative, so that the corresponding fixed point is asymptotically stable.

For the first fixed point, the eigenvalues of the Jacobian matrix are

$$\lambda_1 = -d, \quad \lambda_2 = \frac{s(\alpha_M - \beta)}{d}, \quad \lambda_3 = \frac{s[(1-\mu)\alpha - \beta]}{d}. \tag{4.11}$$

While clearly $\lambda_1 < 0$ always, note that λ_2 and λ_3 are negative only if

$$\beta > \alpha_M \quad \text{and} \quad \beta > (1-\mu)\alpha. \tag{4.12}$$

The first of these conditions implies that the second fixed point of the system is non-positive, per Equation (4.9), while the latter denies the first condition for the non-negativity of the third type of equilibrium (and the combination of these two

conditions contradicts the second condition), as given in Equation (4.10). Hence this fixed point is stable only when there are no other non-negative fixed points.

Now we turn our attention to the second fixed point. The eigenvalues of J now become

$$\begin{aligned} \lambda_1 &= \frac{\delta[(1-\mu)\alpha - \alpha_M]}{\alpha_M}, \\ \lambda_{2,3} &= \frac{1}{2\delta}\left\{-s\alpha_M \pm \sqrt{s^2\alpha_M^2 - 4\delta^2 s(\alpha_M - \beta)}\right\}. \end{aligned} \tag{4.13}$$

Observe that $\lambda_1 < 0$ if

$$\alpha_M > (1-\mu)\alpha.$$

The other two eigenvalues λ_2 and λ_3 are less straightforward to analyse, but they are tractable. Note first that the term outside the square root is negative. Under the condition cited for the non-negativity of this equilibrium point, Equation (4.9), the second term under the square root must be non-negative. Hence these eigenvalues are of the form

$$-|x| \pm \sqrt{x^2 - y^2}$$

and therefore they will be either negative real quantities, or complex quantities with a negative real part. Either way, we have established that this equilibrium will be asymptotically stable if

$$\alpha_M > \beta \quad \text{and} \quad \alpha_M > (1-\mu)\alpha. \tag{4.14}$$

These inequalities make sense in light of the preceding discussion: the first condition coincides with the condition that this equilibrium be non-negative, while the second indicates that the third fixed point is non-positive, as shown by Equation (4.10).

Additionally, it is instructive to investigate the conditions under which λ_2 and λ_3 are complex. This will occur when

$$\frac{2\delta^2}{s}\left[1-\sqrt{1-\frac{d}{\delta}}\right] < \alpha_M < \frac{2\delta^2}{s}\left[1+\sqrt{1-\frac{d}{\delta}}\right]. \tag{4.15}$$

Note that we assume that $d > \delta$, and hence all terms in this inequality are themselves real.

Finally, we examine the eigenvalues which arise in connection with the third fixed point:

$$\begin{aligned} \lambda_1 &= \frac{\delta[\alpha_M-(1-\mu)\alpha]}{(1-\mu)\alpha}, \\ \lambda_{2,3} &= \frac{1}{2\delta}\left\{-s(1-\mu)\alpha \pm \sqrt{s^2(1-\mu)^2\alpha^2-4\delta^2 s[(1-\mu)\alpha-\beta]}\right\}. \end{aligned} \tag{4.16}$$

Again the condition for $\lambda_1 < 0$ is obvious:

$$(1-\mu)\alpha > \alpha_M,$$

which is precisely the reverse of the condition found when analysing the corresponding eigenvalue for the second fixed point.

The analysis of the remaining eigenvalues, λ_2 and λ_3, is analogous to that of the second and third eigenvalues for the second fixed point. The term outside the square root is again negative. Under the second condition cited for the non-negativity of this fixed point, the second term under the square root must be non-negative. Again, then, these will be either negative real eigenvalues, or complex eigenvalues with a negative real part. Regardless, we have established that this equilibrium will be asymptotically stable if

$$(1-\mu)\alpha > \beta \quad \text{and} \quad (1-\mu)\alpha > \alpha_M. \tag{4.17}$$

These are precisely the two conditions which guarantee the non-negativity of this equilibrium point, as given by Equation (4.10).

Finally, we shall again determine when these two eigenvalues will be complex. The relevant condition is

$$\frac{2\delta^2}{s}\left[1-\sqrt{1-\frac{d}{\delta}}\right] < (1-\mu)\alpha < \frac{2\delta^2}{s}\left[1+\sqrt{1-\frac{d}{\delta}}\right], \tag{4.18}$$

which resembles the corresponding condition found for the eigenvalues of the second fixed point.

4.5 Behaviour of the System

We can now establish four regimes of behaviour for the system given by Equation (4.3). They are as follows:

1. $\beta > (1-\mu)\alpha$ and $\beta > \alpha_M$: the first fixed point is positive and stable; the second and third fixed points are negative and unstable (both wild-type and mutant strains are of poor quality),

2. $\alpha_M > \beta$ and $\alpha_M > (1-\mu)\alpha$: the first fixed point is positive and unstable; the second fixed point is positive and stable; the third fixed point is negative and unstable (the mutant strain is of sufficiently higher quality than the wild-type virus, or the wild-type virus experiences a high level of mutation, regardless of the level of quality of the wild-type strain),

3. $(1-\mu)\alpha > \beta > \alpha_M$: the first fixed point is positive and unstable; the second fixed point is negative and unstable; the third fixed point is positive and stable (the wild-type virus is of good quality and/or experiences low mutation, while the mutant strain is of poor quality),

4. $(1-\mu)\alpha > \alpha_M > \beta$: the first and second fixed points are positive and unstable; the third fixed point is positive and stable (the wild-type and mutant strains

are of good quality, but the wild-type virus is of appreciably better quality or undergoes a small rate of mutation).

4.5.1 Numerical Simulations: Parameter Values

To illustrate each regime, we must choose suitable parameter values. Although HIV has been studied extensively over the past quarter of a century, considerable uncertainty remains with regards to some quantities associated with its pathogenesis. Consequently, while every effort has been made to establish parameter values from reputable sources in the literature, it must be acknowledged that there exists an implicit uncertainty in many of these quantities.

Table 4.1: Parameter values for Equation (4.3).

Parameter	Symbol	Quantity	References
production of new T cells	s	$20\text{d}^{-1}\text{mm}^{-3}$	[4,23]
death rate of healthy T cells	d	0.02d^{-1}	[23]
death rate of infected T cells	δ	0.5d^{-1}	[17,23]
virulence of wild-type	$\tilde{k}$	$0.0038\text{mm}^3\text{d}^{-1}$	[4,16,17,23]
mutation rate from wild-type	μ	3×10^{-5}	[4,24,25]

Values for most of the parameters used in Equation (4.3) are given, with ref-

erences, in Table 4.1. Of particular note is the provenance of $\tilde{k}$. Both Nowak and May [4] and Müller and Bonhoeffer suggest that an appropriate form for the constant of proportionality b between the virus population $V(t)$ and the population of T cells infected with the wild-type virus is given by

$$b = \frac{N\delta}{c}.$$

Using the value of δ provided in Table 4.1, together with $N = 100$ and $c = 0.3\text{d}^{-1}$ as suggested by [17,23], we obtain the approximation

$$b \approx 160.$$

Furthermore, Kirschner [17] indicates that

$$k = 2.4 \times 10^{-5}\text{mm}^3\text{d}^{-1}$$

is a suitable parameter value for the rate of infectivity of the wild-type virus. Hence, using the relation $\tilde{k} = bk$, we derive the value of $\tilde{k}$ given in Table 4.1.

It is also worth noting that the literature exhibits a fair degree of variance in the value of s, the production term for naïve T cells. In [23], for example, $s = 10\text{d}^{-1}\text{mm}^{-3}$ while in [4] it is a full order of magnitude larger, with $s = 100\text{d}^{-1}\text{mm}^{-3}$. We have chosen a value of $s = 20\text{d}^{-1}\text{mm}^{-3}$ to ensure that the disease-free fixed point is such that the population of uninfected T cells comes to equilibrium at $\overline{T} = 1000\text{mm}^{-3}$, as

suggested by [4,17,23]. Note that, with these parameters values, we have fixed

$$\beta = 5 \times 10^{-4} \text{mm}^3\text{d}^{-1}.$$

Less clear-cut are the choices of values for $\tilde{k}_M$, η_M and η, which suggests that we should vary each of these in order to situate the system within the four regimes described above. Our general approach is to begin by varying η_M as our chief bifurcation parameter, since the effectiveness of the drug therapy relative to an individual mutation is not predictive, being dependent upon both the nature of the mutation and the type of therapy employed. If this is insufficient, we shall next vary η, since different forms of treatment will affect even the wild-type virus in different ways [25]. Our baseline assumption, however, will be that the drug inhibits 70% of the virus replication (that is, $\eta = 0.7$). Finally, if the need still persists, we shall adjust our choice of $\tilde{k}_M$ since there is also no certitude as to how virulent a mutant strain might be. However, as suggested by Nowak and May [4], we will typically assume $\tilde{k}_M$ to be approximately 80% of $\tilde{k}$, and hence set $\tilde{k}_M = 0.003$.

4.5.2 Numerical Simulations: The Disease-Free Equilibrium

First we illustrate the most trivial of the four regimes described above, namely that in which the disease-free equilibrium is the only stable fixed point. In this case,

our chosen parameter values are insufficient because the second condition for this regime is violated. In this instance, then, we set $\eta = 0.9$ (that is, the drug is more effective than our standard assumption) so that

$$(1 - \mu)\alpha \approx 3.8 \times 10^{-4} < \beta.$$

Furthermore, we set $\eta_M = 0.85$ (meaning that the drug is remarkably effective against both the wild-type and mutant strains of the virus) which gives

$$\alpha_M = 4.5 \times 10^{-3} < \beta.$$

The conditions for this regime are now satisfied.

The initial conditions used to generate a time series graph for this case, as well as the subsequent time series graphs depicted in this chapter, are given in Table 4.2. The initial condition for $T(t)$ is $T_0 = 500\text{mm}^{-3}$, a 50% reduction from the expected healthy T cell count of 1000mm^{-3}, reflecting the assumption that HIV infection is not novel. There is no special significance to this particular choice of T cell depletion. Rather, it was selected with consideration given to ensuring that the uninfected T cell count (i) exhibits a significant loss from healthy levels, and (ii) is not so extraordinarily depleted as to indicate that HIV infection has given way to full-blown AIDS. Recall that this system exhibits only one stable fixed point for any given set of parameter values so, operating under the assumption that these

dynamics are globally applicable (and a variety of numerical experiments suggest that there are no occurrences of phenomena such as chaos or periodic orbits), we are free to choose any initial conditions. The initial conditions for $U(t)$ and $U_M(t)$ depict the relatively shallow levels of infected T cells as compared to uninfected T cells [4, 17]. In particular, the initial condition for $U_M(t)$ is chosen to be an order of magnitude smaller than that for $U(t)$ to reflect the assumption that the mutant strain is of recent genesis. The phase portraits depicted in this chapter utilise this set of initial conditions, along with several other (comparable) initial conditions selected in order to fully illustrate the dynamical phenomena.

Table 4.2: Initial conditions for time series plots of Equation (4.3).

Population	**Variable**	**Initial Quantity**
Uninfected T cells	$T(t)$	500mm^{-3}
T cells infected with wild-type virus	$U(t)$	100mm^{-3}
T cells infected with mutant virus	$U_M(t)$	10mm^{-3}

The time series generated by these initial conditions when $\eta_M = 0.85$ and $\eta = 0.9$ is given in Figure 4.1. As expected, the two virus populations tend towards extinction while the population of uninfected T cells returns to its pre-infection level of 1000mm^{-3}. The corresponding phase portrait is given in Figure 4.2, which

illustrates the presence of an asymptotically stable node in this case.

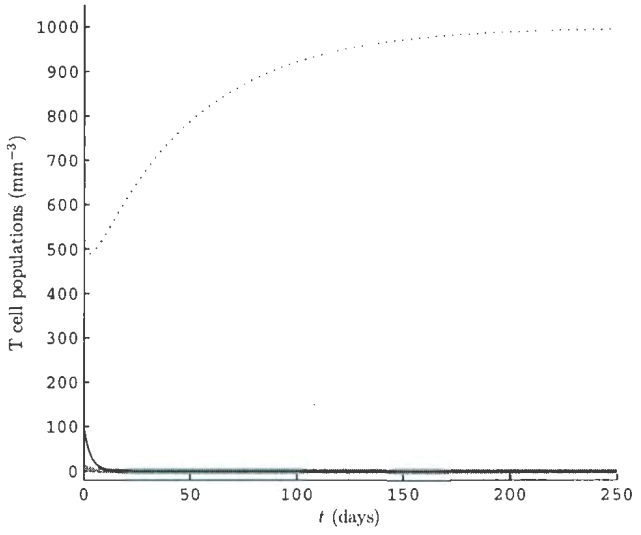

Figure 4.1: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\eta_M = 0.85$ and $\eta = 0.9$.

Obviously, this is the optimal situation for a patient suffering from HIV. However, the situation described in which the drug is extremely effective against both the wild-type strain and the mutant strain is not very feasible. In reality, the virus would mutate to produce a more strongly-resistant form. As such, while this fixed point is of some mathematical interest, it does not reflect a reasonable choice of parameter values.

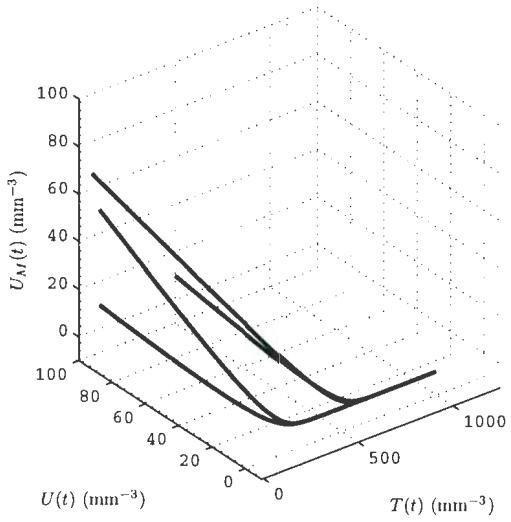

Figure 4.2: Phase portrait for Equation (4.3) with $\eta_M = 0.85$ and $\eta = 0.9$.

4.5.3 Numerical Simulations: The Mutant-dominant Equilibrium

For the second regime, in which the population of T cells infected with the wild-type virus dies out, we choose $\eta_M = 0.2$ so

$$\alpha_M = 0.0024 > \beta \quad \text{and} \quad (1-\mu)\alpha = 0.00114 < \alpha_M.$$

The time series plot is given in Figure 4.3. Again, the graph bears out our analytical expectations: the population of uninfected T cells attains an equilibrium state well below its disease-free levels, while the T cells infected with the mutant virus are selectively advantageous compared to those infected with the wild-type virus, which vanish.

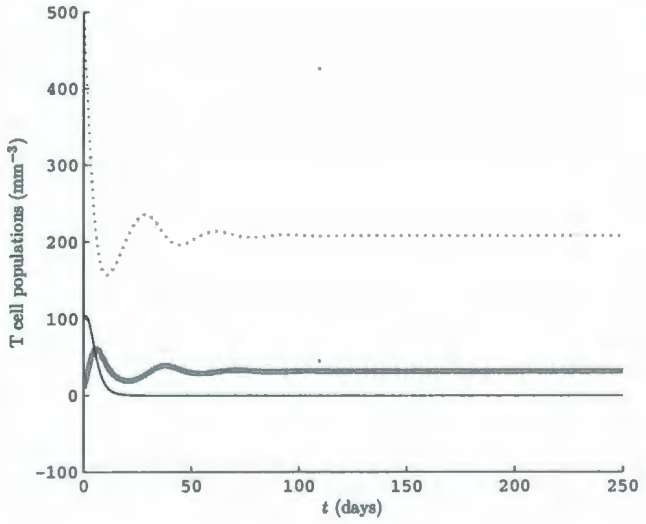

Figure 4.3: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\eta_M = 0.2$.

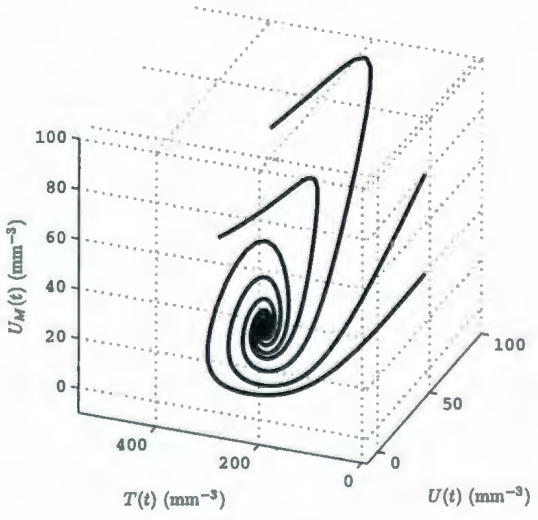

Figure 4.4: Phase portrait for Equation (4.3) with $\eta_M = 0.2$.

Of note, there is an evident oscillation present in both $T(t)$ and $U_M(t)$. This is borne out by the phase portrait, given in Figure 4.4, which confirms the presence of an asymptotically stable spiral-node, with the spiral existing in the (T, U_M)-plane. This is because the condition given by Equation (4.15) is satisfied:

$$\frac{2\delta^2}{s}\left[1-\sqrt{1-\frac{d}{\delta}}\right] \approx 5.1\times 10^{-4} < \alpha_M < \frac{2\delta^2}{s}\left[1+\sqrt{1-\frac{d}{\delta}}\right] \approx 0.049.$$

What about parameter values in this regime which give rise to an asymptotically stable node, absent of spiral phenomena? We first examine the case where

$$\alpha_M < \frac{2\delta^2}{s}\left[1-\sqrt{1-\frac{d}{\delta}}\right].$$

Observe that

$$\beta < \frac{2\delta^2}{s}\left[1-\sqrt{1-\frac{d}{\delta}}\right].$$

This result is not merely true for the values of s, d and δ that we have selected, but is in fact independent of parameter values. To see this, assume again that $\delta > d$.

Then we have

$$\begin{aligned}
1-\frac{d}{\delta} &< 1-\frac{d}{\delta}+\frac{d^2}{2\delta^2} \\
&< \left(1-\frac{d}{2\delta}\right)^2 \\
\sqrt{1-\frac{d}{\delta}} &< 1-\frac{d}{2\delta} \\
\frac{d}{2\delta} &< 1-\sqrt{1-\frac{d}{\delta}} \\
\frac{d\delta}{s} &< \frac{2\delta^2}{s}\left[1-\sqrt{1-\frac{d}{\delta}}\right] \\
\beta &< \frac{2\delta^2}{s}\left[1-\sqrt{1-\frac{d}{\delta}}\right].
\end{aligned}$$

Thus, one way that the system could lie in this second regime but exhibit only nodal behaviour is if

$$\beta < \alpha_M < \frac{2\delta^2}{s}\left[1-\sqrt{1-\frac{d}{\delta}}\right].$$

However, the range of possible values of α_M which satisfy this inequality is extremely small. By expanding as a Maclaurin series, we obtain the approximation

$$\frac{2\delta^2}{s}\left[1-\sqrt{1-\frac{d}{\delta}}\right] \approx \frac{2\delta^2}{s}\left[1-\left(1-\frac{d}{2\delta}-\frac{d^2}{8\delta^2}\right)\right] = \frac{d\delta}{s}+\frac{d^2}{4s} = \beta+\frac{d^2}{4s}.$$

Hence the length of the interval of α_M values which exhibit the desired behaviour is

$$\frac{2\delta^2}{s}\left[1-\sqrt{1-\frac{d}{\delta}}\right]-\beta \approx \frac{d^2}{4s} = 5\times 10^{-6}$$

for the given parameter values. As such, the system is very close to the first regime, and both the time series and phase portrait are nearly indistinguishable from those depicted in Figures 4.1 and 4.2.

For instance, if we once again set $\eta = 0.9$, but now let $\eta_M = 0.832$, then

$$\alpha_M = 5.04 \times 10^{-4} > \beta$$

and

$$(1 - \mu)\alpha \approx 3.8 \times 10^{-4} < \alpha_M,$$

so the system does indeed lie in the second regime. However, in this case,

$$\frac{2\delta^2}{s}\left[1 - \sqrt{1 - \frac{d}{\delta}}\right] > \alpha_M,$$

so the system will not exhibit a spiral-node. However, the parameter values are so close to those for the first regime that the steady-state values of $T(t)$ and $U_M(t)$ are

$$\overline{T} \approx 992.1 \quad \text{and} \quad \overline{U}_M \approx 0.32.$$

We therefore omit the time series and phase portrait for this case.

Let us now turn our attention to the remaining possibility, in which

$$\alpha_M > \frac{2\delta^2}{s}\left[1 + \sqrt{1 - \frac{d}{\delta}}\right].$$

In order for this inequality to be satisfied without changing the values of parameters which do not directly relate to the mutant strain, the mutant would have to

be a "supermutant," exhibiting significantly greater virulence than the wild-type virus, probably (though, if the virulence is sufficiently increased, not necessarily) combined with the better resistance to drug therapy we expect of HIV mutations. The time series for such a "supermutant" is given in Figure 4.5. In this case, we have set $\tilde{k}_M = 0.1$, two orders of magnitude larger than our standard value (and than the value of $\tilde{k}$)! Here, then,

$$\alpha_M = 0.08 > \frac{2\delta^2}{s}\left[1 + \sqrt{1 - \frac{d}{\delta}}\right].$$

Note that the catastrophic effects such a "supermutant" has on the population of uninfected T cells is such that the patient has certainly progressed to full-blown AIDS over the course this simulation, and so the model no longer truly applies. The corresponding phase portrait can be found in Figure 4.6, and illustrates the presence of an asymptotically stable node in this case, absent of a spiral-type phenomenon.

Observe that the transition from spiral-node behaviour to purely nodal behaviour, and vice versa, in this second regime does not constitute a bifurcation of the system. Although the change in the nature of the model is of intrinsic interest, the two cases remain topologically equivalent. We will discuss the true bifurcations of the system later in this section.

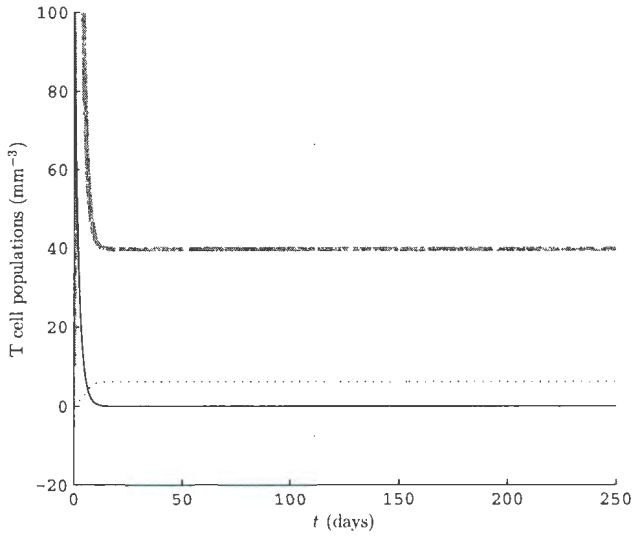

Figure 4.5: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\eta_M = 0.2$ and $\tilde{k}_M = 0.1$.

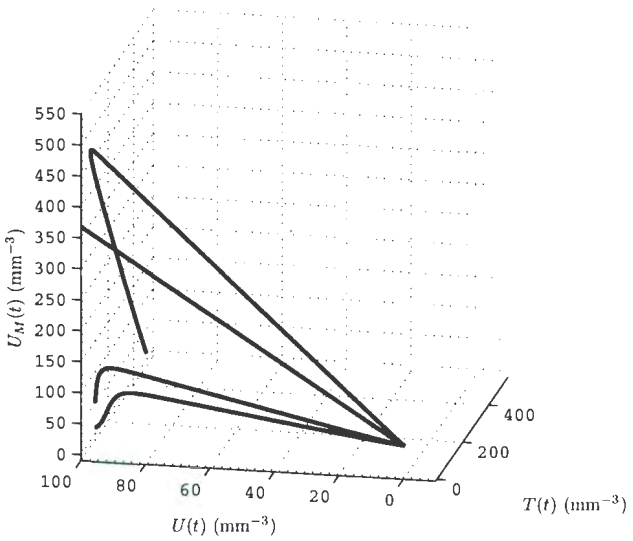

Figure 4.6: Phase portrait for Equation (4.3) with $\eta_M = 0.85$ and $\eta = 0.9$.

4.5.4 Numerical Simulations: The Coexistence Equilibrium

For the third regime, we immediately have the first condition satisfied, since

$$(1 - \mu)\alpha \approx 0.00114 > \beta.$$

It is possible to choose values of η_M and η which place us in this regime, but only in a narrow range (for example, $\eta_M = 0.8$ and $\eta = 0.85$) in which both virus populations are largely suppressed. A better illustration of this regime can be found by maintaining the values of the respective drug efficacies at $\eta_M = 0.2$ and our baseline assumption of $\eta = 0.7$, as we originally used in considering the second regime. Instead, we will assume in this case that the virulence of the mutant strain

is an order of magnitude less than our typical assumption: $\tilde{k}_M = 3.0\times10^{-4}\text{mm}^{-3}\text{d}^{-1}$. We now have

$$\alpha_M = 2.4 \times 10^{-4} < \beta,$$

as required.

The resulting time series can be found in Figure 4.7. Note that although it appears that the population of T cells infected with the mutant virus is becoming extinct, it is in fact merely subsisting at a very low level. As discussed earlier, the constant rate of mutation from the wild type makes it impossible for the mutant population to die out completely. In this case, $\overline{U}_M \approx 8.5 \times 10^{-4}\text{mm}^{-3}$. Hence all three T cell populations coexist in this case, although the wild-type virus is predominating over the mutant strain.

From the phase portrait given in Figure 4.8, we observe that the equilibrium point for these parameter values is an asymptotically stable spiral-node, with the spiral existing in the (T, U)-plane this time.

As with the second regime, let us turn our attention to the possibility that the equilibrium point is purely nodal, beginning with the case where

$$(1-\mu)\alpha < \frac{2\delta^2}{s}\left[1 - \sqrt{1 - \frac{d}{\delta}}\right].$$

Again, from the preceding discussion we are assured of a narrow range of param-

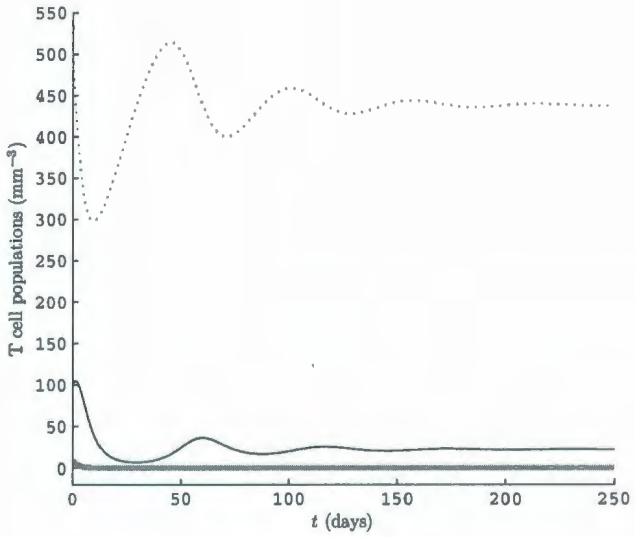

Figure 4.7: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\eta_M = 0.2$ and $\tilde{k}_M = 3.0 \times 10^{-4}\text{mm}^{-3}$.

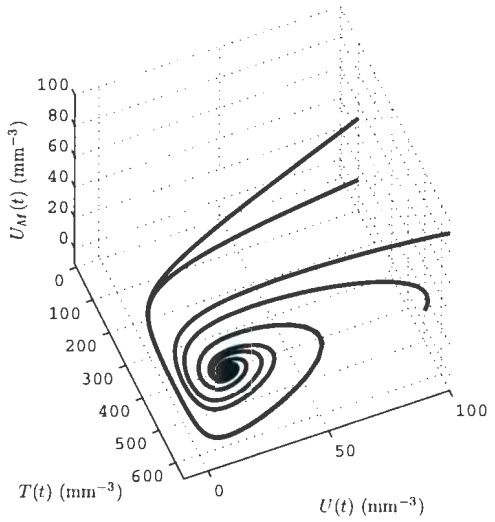

Figure 4.8: Phase portrait for Equation (4.3) with $\eta_M = 0.2$ and $\tilde{k}_M = 3.0\times10^{-4}\text{mm}^{-3}$.

eter values in which this is satisfied; the only modification we must make to our earlier analysis is to acknowledge that it is now $(1-\mu)\alpha$ which needs to fall within a narrow interval of length approximately $\frac{d^2}{4s}$. Keeping $\eta_M = 0.2$ and $\tilde{k}_M = 3\times10^{-4}$, we can situate the model within this interval while remaining in the third regime, by setting $\eta = 0.868$.

Again, however, the proximity of these parameter values to those which would place the system in the first regime results in behaviour similar to that depicted in Figures 4.1 and 4.2. Here, for instance, we find that

$$\overline{T} \approx 996.8\text{mm}^{-3}, \quad \overline{U} \approx 0.13\text{mm}^{-3}, \quad \overline{U}_M \approx 7.28\times10^{-6}\text{mm}^{-3}.$$

As with the regime-two analogue of this situation, we shall omit the corresponding time series and phase portrait.

The other possibility, that

$$(1-\mu)\alpha > \frac{2\delta^2}{s}\left[1+\sqrt{1-\frac{d}{\delta}}\right],$$

cannot be achieved under the parameter values established in Table 4.1. We have

$$\frac{2\delta^2}{s}\left[1+\sqrt{1-\frac{d}{\delta}}\right] \approx 0.049,$$

while

$$(1-\mu)\alpha = (1-\mu)(1-\eta)\tilde{k} \leq \tilde{k} = 0.0038.$$

Biologically speaking, it is probably not of any real-world interest. Nonetheless, if we relax our restrictions on these parameter values for the sake of providing a comprehensive mathematical overview of the model, we could achieve this behaviour by returning to the same parameter values used to generate Figures 4.7 and 4.8 (namely $\eta_M = 0.2$, $\eta = 0.7$, $\tilde{k}_M = 3\times10^{-4}\text{mm}^{-3}$), and compound this with the further modification that the virulence of the wild-type strain is in fact much greater than previously assumed: $\tilde{k} = 0.2\text{mm}^{-3}$. We now have

$$(1-\mu)\alpha \approx 0.06 > \frac{2\delta^2}{s}\left[1+\sqrt{1-\frac{d}{\delta}}\right].$$

The time series for this scenario can be found in Figure 4.9. Observe that, in this case, the incredible potency of the virus has a significantly deleterious effect

on the population of uninfected T cells, implying the onset of full-blown AIDS. Again, then, the situation described really falls outside the bounds of the model. As with Figure 4.7, it is worth emphasising that the population of T cells infected with the mutant virus is in fact at a very small, yet positive, steady state here: $\overline{U}_M \approx 0.0012\text{mm}^{-3}$.

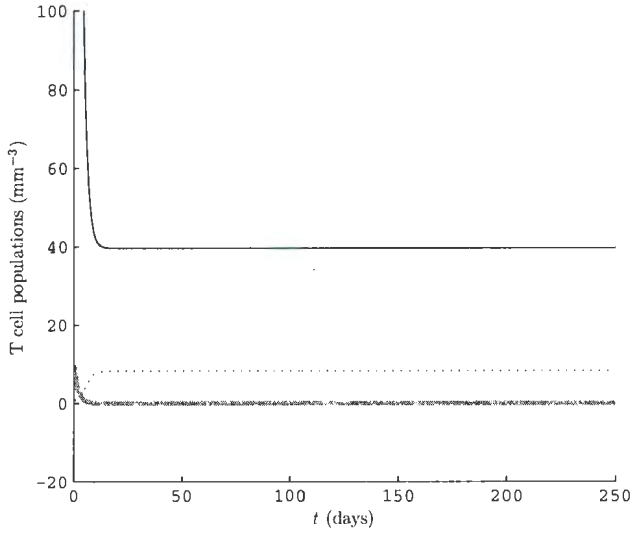

Figure 4.9: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\eta_M = 0.2$, $\tilde{k}_M = 3.0 \times 10^{-4}\text{mm}^{-3}$ and $\tilde{k} = 0.1\text{mm}^{-3}$.

The phase portrait for this set of parameter values may be found in Figure 4.10. Observe that the fixed point is now a node, with no spiral behaviour in evidence.

Finally, we come to the fourth regime. The only distinction between these final

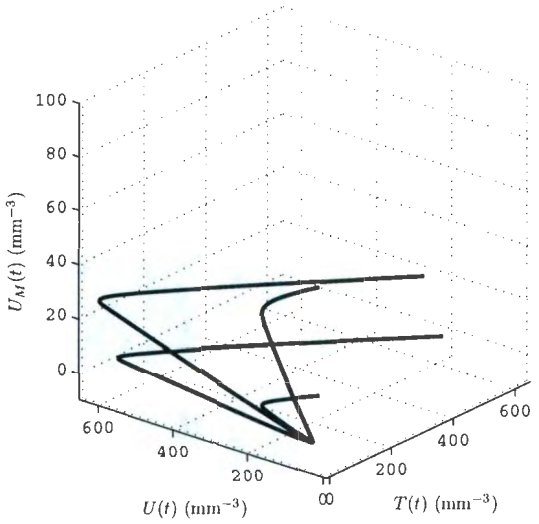

Figure 4.10: Phase portrait for Equation (4.3) with $\eta_M = 0.2$, $\tilde{k}_M = 3.0 \times 10^{-4}\text{mm}^{-3}$ amd $\tilde{k} = 0.1\text{mm}^{-3}$.

two regimes is the non-negativity of the second fixed point. However, because this point is unstable in both cases, we do not expect the overall dynamics to differ between them. This is clear from the time series given in Figure 4.11, which is similar in terms of behaviour to that of Figure 4.7. This is confirmed by the phase portrait, depicted in Figure 4.12, which exhibits an asymptotically stable spiral-node — with a very tight spiral in the (T, U)-plane — exactly as with Figure 4.8. The parameter values used to generate these plots are $\eta_M = 0.2$ and $\eta = 0.3$, that is, the wild-type virus is nearly as resistant to the drug therapy as the mutant strain. Note that, as expected,

$$\alpha_M \approx 0.0024 > \beta$$

and

$$(1 - \mu)\alpha \approx 0.0027 > \alpha_M.$$

Finally, let us again consider the ways in which the equilibrium point can be a pure node in the fourth regime, starting with the possibility that

$$(1 - \mu)\alpha < \frac{2\delta^2}{s}\left[1 - \sqrt{1 - \frac{d}{\delta}}\right].$$

As before, there is a small range of values of $(1 - \mu)\alpha$ in which this must occur; this can be achieved, for example, with $\eta_M = 0.833$ and $\eta = 0.868$. By now, we should not be surprised to discover that such a system behaves almost identically

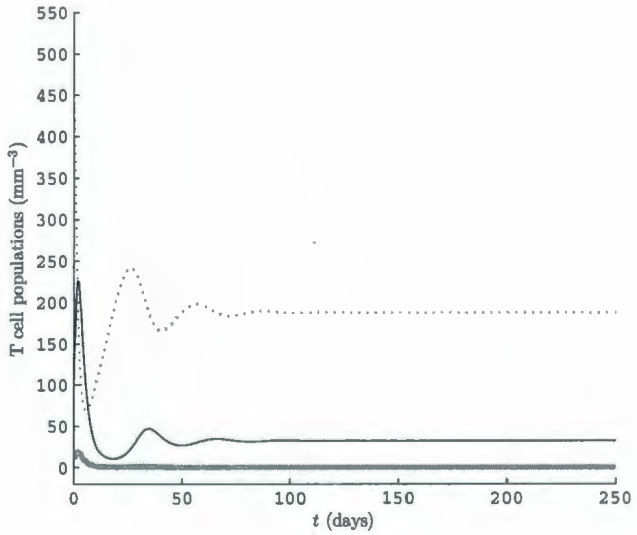

Figure 4.11: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\eta_M = 0.2$ and $\eta = 0.3$.

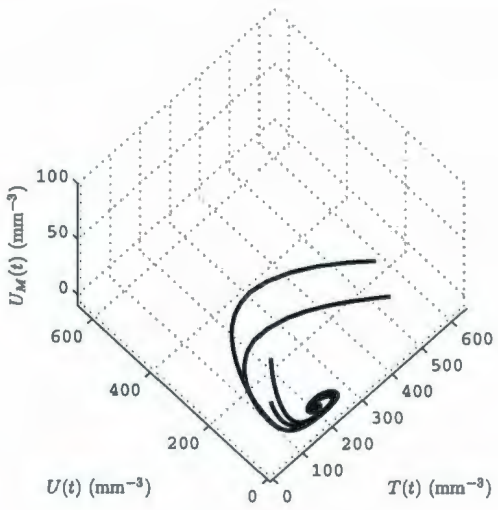

Figure 4.12: Phase portrait for Equation (4.3) with $\eta_M = 0.2$ and $\eta = 0.3$.

to the basic disease-free case of the first regime, as depicted in Figure 4.1 and 4.2. Here, for instance, the steady-state values are $\overline{T} \approx 996.8\text{mm}^{-3}$, $\overline{U} \approx 0.12\text{mm}^{-3}$ and $\overline{U}_M \approx 0.0032\text{mm}^{-1}$. Again, we suppress the relevant plots.

So, lastly, let us turn our attention to the case where

$$(1-\mu)\alpha > \frac{2\delta^2}{s}\left[1+\sqrt{1-\frac{d}{\delta}}\right].$$

As with the analysis of this possibility in the third regime, we must alter our chosen value of $\tilde{k}$ in order to satisfy this condition while still remaining within the fourth regime. For instance, if we choose $\eta_M = 0.2$, $\eta = 0.3$ and $\tilde{k} = 0.08\text{mm}^{-3}\text{d}^{-1}$ then we

have

$$(1-\mu)\alpha \approx 0.056 > \frac{2\delta^2}{s}\left[1+\sqrt{1-\frac{d}{\delta}}\right].$$

The results, however, are essentially identical to that depicted in Figures 4.9 and 4.10, and so we avoid repeating them here.

The overall conclusion that we can draw is that, as expected, there is no fundamental change in behaviour between the third and fourth regimes. As long as the wild-type virus exhibits a selective advantage as compared to the mutant strain, it does not matter if the mutation is qualitatively "good" or "bad." This is in accordance with our mathematical expectations, namely that the change of a fixed point from negative to positive does not produce an appreciable change in the dynamics of the system.

4.5.5 Bifurcations

Finally, these graphs demonstrate that the system may undergo three different bifurcations; each of these is a transcritical bifurcation, witnessing an exchange of stability but no creation or elimination of fixed points. These bifurcations are as follows:

1. if $\beta > (1-\mu)\alpha$, a bifurcation from the first (disease free) fixed point to the second (mutant strain dominant) fixed point occurs when $\beta = \alpha_M$,

2. if $\beta > \alpha_M$, a bifurcation from the first (disease free) fixed point to the third (coexistent) fixed point occurs when $\beta = (1-\mu)\alpha$,

3. if $\alpha_M > \beta$, a bifurcation from the second (mutant strain dominant) fixed point to the third (coexistent) fixed point occurs when $\alpha_M = (1-\mu)\alpha$.

Of course, each of these bifurcations is reversible.

To demonstrate these bifurcations more rigorously, let's consider them in the order given above, in conjunction with Theorem 4. For the first bifurcation when $\beta = \alpha_M$, both the first and second fixed points assume the steady-state values

$$\overline{T} = \frac{s}{d}, \quad \overline{U} = \overline{U}_M = 0.$$

The Jacobian has a zero eigenvalue, for which the corresponding eigenvectors of J and J^T are, respectively,

$$\mathbf{v} = \begin{bmatrix} -\frac{\delta}{d} \\ 0 \\ 1 \end{bmatrix} \quad \text{and} \quad \mathbf{w} = \begin{bmatrix} 0 \\ 1 \\ \frac{\beta - (1-\mu)\alpha}{\alpha\mu} \end{bmatrix}.$$

Then for $\beta > (1-\mu)\alpha$ we have that

$$\mathbf{w}^T \frac{\partial \mathbf{f}}{\partial \alpha_M} = 0$$
$$\mathbf{w}^T[J_{\alpha_M}\mathbf{v}] = \frac{[\beta-(1-\mu)\alpha]s}{\alpha d\mu} \neq 0$$
$$\mathbf{w}^T[J^2(\mathbf{v},\mathbf{v})] = \frac{-2\beta\delta[\beta-(1-\mu)\alpha]}{\alpha\mu d} \neq 0.$$

Hence this is a transcritical bifurcation.

For the second bifurcation, when $\beta = (1-\mu)\alpha$, observe that both the first and third fixed points become simply

$$\overline{T} = \frac{s}{d}, \quad \overline{U} = \overline{U}_M = 0.$$

The Jacobian has a zero eigenvalue, and the corresponding eigenvectors of J and J^T are, respectively,

$$\mathbf{v} = \begin{bmatrix} \frac{s[(1-\mu)\alpha_M-\beta]}{d^2\mu} \\ \frac{(1-\mu)(\beta-\alpha_M)}{\mu\beta} \\ 1 \end{bmatrix} \quad \text{and} \quad \mathbf{w} = \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix}.$$

Then we have that for $\beta > \alpha_M$,

$$\mathbf{w}^T \frac{\partial \mathbf{f}}{\partial \alpha} = 0$$
$$\mathbf{w}^T[J_\alpha \mathbf{v}] = \frac{(1-mu)s(\beta-\alpha_M)}{d\mu\alpha} \neq 0$$
$$\mathbf{w}^T[J^2(\mathbf{v},\mathbf{v})] = \frac{2s(1-\mu)(\beta-\alpha_M)[(1-\mu)\alpha_M-\beta]}{d^2\mu^2} \neq 0.$$

Note that, since $\beta > \alpha_M$, then $\beta > (1-\mu)\alpha_M$ as well, ensuring the third condition. Again, this is a transcritical bifurcation.

In the case of the third bifurcation, when $\alpha_M = (1-\mu)\alpha$, note that both the second and third fixed points can be rewritten as

$$\overline{T} = \frac{\delta}{\alpha_M}, \quad \overline{U} = 0, \quad \overline{U}_M = \frac{s[\alpha_M - \beta]}{\alpha_M \delta}.$$

The Jacobian has a zero eigenvalue with corresponding eigenvectors

$$\mathbf{v} = \begin{bmatrix} 1 \\ \dfrac{s(1-\mu)[\beta - \alpha_M]}{\delta^2 \mu} \\ \dfrac{s[\alpha_M(1-\mu) - \beta]}{\delta^2 \mu} \end{bmatrix} \quad \text{and} \quad \mathbf{w} = \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix}$$

of J and J^T, respectively. Then we have that for $\alpha_M > \beta$,

$$\begin{aligned} \mathbf{w}^T \frac{\partial \mathbf{f}}{\partial \alpha_M} &= 0 \\ \mathbf{w}^T [J_\alpha \mathbf{v}] &= \frac{s(1-\mu)(\beta - \alpha_M)}{\alpha \delta \mu} \neq 0 \\ \mathbf{w}^T [J^2(\mathbf{v}, \mathbf{v})] &= \frac{2s\alpha_M(1-\mu)(\beta - \alpha_M)}{\delta^2 \mu} \neq 0. \end{aligned}$$

This is therefore also a transcritical bifurcation.

Chapter 5

A Model with Two Mutants

Although the model given by Equation (4.3) appears to give a good description of HIV pathogenesis in the presence of a mutant strain of the virus, a critical question which naturally follows concerns the basic assumption that only one mutation is present at a given time. If the existence of more than two kinds of HIV at any one time produces fundamentally different behaviour than that observed in our investigation of Equation (4.3), then the robustness of this model must be called into question.

In this chapter we shall extend the model to incorporate two mutant strains, in addition to the wild-type form of the virus. We shall analyse this augmented model in a similar manner to our approach in Chapter 4. Finally, we shall again

demonstrate these results by providing some illustrative numerical examples.

5.1 The Author's Model, Two-Mutant Version

We consider a model with exactly two mutant strains, because if we can show that the types of behaviour exhibited by this model reduce to the phenomena exhibited by the one-mutant model then we can reasonably deduce that the same will be true of a model incorporating any number of mutations.

We assume that each mutation individually functions in the same manner as the single mutant of Equation (4.3). In other words, we conjecture that each mutant is produced from the wild-type strain at a constant rate μ_1 and μ_2, respectively. This results in two strains of T cells infected by mutant virions, which we now denote $U_1(t)$ and $U_2(t)$. We continue to assume that T cells infected by the mutant forms of the virus die at the same rate, δ, as T cells infected by the wild-type virus. In this case, the first mutation is characterised by virulence $\tilde{k}_1$ and susceptibility to drug therapy η_1, while the second mutant similarly exhibits virulence $\tilde{k}_2$ and susceptibility η_2. Again, we typically expect (but do not enforce) the restrictions $\tilde{k}_1 \leq \tilde{k}, \tilde{k}_2 \leq \tilde{k}, \eta_1 \leq \eta, \eta_2 \leq \eta$, where $\tilde{k}$ and η are the virulence and resistance to drug therapy, respectively, of the wild-type virus.

The resulting model is as follows:

$$\begin{aligned}
\dot{T}(t) &= s - dT(t) - (1-\eta)\tilde{k}T(t)U(t) \\
&\quad - (1-\eta_1)\tilde{k}_1 T(t)U_1(t) - (1-\eta_2)\tilde{k}_2 T(t)U_2(t) \\
\dot{U}(t) &= (1-\mu_1-\mu_2)(1-\eta)\tilde{k}T(t)U(t) - \delta U(t) \\
\dot{U}_1(t) &= \mu_1(1-\eta)\tilde{k}T(t)U(t) + (1-\eta_1)\tilde{k}_1 T(t)U_1(t) - \delta U_1(t) \\
\dot{U}_2(t) &= \mu_2(1-\eta)\tilde{k}T(t)U(t) + (1-\eta_2)\tilde{k}_2 T(t)U_2(t) - \delta U_2(t).
\end{aligned} \tag{5.1}$$

In addition to our preceding assumption that we could neglect back-mutation from the mutant virus to the wild-type virus, we similarly exclude the possibility of cross-mutation from one mutant strain to the other.

5.2 The Fixed Points

As with our investigation of the one-mutant model given by Equation (4.3), our analysis of Equation (5.1) will be greatly aided by rewriting it in a simplified form. We will follow a similar approach to the transformation of Equation (4.3) into Equation (4.5), by letting

$$\alpha = \tilde{k}(1-\eta) \quad \text{and} \quad \beta = \frac{d\delta}{s}$$

as before, and now setting

$$\alpha_1 = \tilde{k}_1(1-\eta_1) \quad \text{and} \quad \alpha_2 = \tilde{k}_2(1-\eta_2).$$

As with the quantity α_M discussed in Chapter 4, α_1 and α_2 can be viewed as a measure of the overall "quality" of the two mutants – the balance of the selective advantage provided by increased resistance to the drug therapy versus the disadvantage of decreased virulence.

The simplified model is given by

$$\begin{aligned}
\dot{T}(t) &= s - dT(t) - \alpha T(t)U(t) - \alpha_1 T(t)U_1(t) - \alpha_2 T(t)U_2(t) \\
\dot{U}(t) &= (1 - \mu_1 - \mu_2)\alpha T(t)U(t) - \delta U(t) \\
\dot{U}_1(t) &= \mu_1 \alpha T(t)U(t) + \alpha_1 T(t)U_1(t) - \delta U_1(t) \\
\dot{U}_2(t) &= \mu_2 \alpha T(t)U(t) + \alpha_2 T(t)U_2(t) - \delta U_2(t).
\end{aligned} \tag{5.2}$$

The first fixed point is effectively the same as the first fixed point of Equation (4.5):

$$\overline{T} = \frac{s}{d}, \quad \overline{U} = \overline{U}_1 = \overline{U}_2 = 0. \tag{5.3}$$

Again, this is the disease-free case in which all forms of HIV are eliminated, leaving only the population of uninfected T cells.

The second fixed point of Equation (5.2) is

$$\overline{T} = \frac{\delta}{\alpha_1}, \quad \overline{U} = \overline{U}_2 = 0, \quad \overline{U}_1 = \frac{s(\alpha_1 - \beta)}{\delta \alpha_1} \tag{5.4}$$

while the third fixed point is

$$\overline{T} = \frac{\delta}{\alpha_2}, \quad \overline{U} = \overline{U}_1 = 0, \quad \overline{U}_2 = \frac{s(\alpha_2 - \beta)}{\delta \alpha_2}. \tag{5.5}$$

These analogous equilibria reflect the two cases in which one population of T cells infected by a mutant strain survives, while the other perishes along with the T cells infected by the wild-type virus. In both instances, the form of this fixed point is reminiscent of the second fixed point of Equation (4.5).

The last fixed point of Equation (5.2) is

$$\begin{gathered}\overline{T} = \frac{\delta}{(1-\mu_1-\mu_2)\alpha}, \quad \overline{U} = \frac{[(1-\mu_1-\mu_2)\alpha-\alpha_1][(1-\mu_1-\mu_2)\alpha-\alpha_2]\zeta}{\alpha}, \\ \overline{U}_1 = \mu_1[\alpha_2-\alpha(1-\mu_1-\mu_2)]\zeta, \quad \overline{U}_2 = \mu_2[\alpha_1-\alpha(1-\mu_1-\mu_2)]\zeta\end{gathered} \tag{5.6}$$

where

$$\zeta = \frac{s[(1-\mu_1-\mu_2)\alpha-\beta]}{\delta(1-\mu_1-\mu_2)[(\alpha-\alpha_1)(\alpha-\alpha_2)-\mu_1\alpha(\alpha-\alpha_1)-\mu_2\alpha(\alpha-\alpha_2)]}.$$

As with the final fixed point of Equation (4.5), this is the case in which all the T cell populations survive. However, as we discovered at the end of Chapter 4, for realistic parameter values this really indicates that the wild-type strain dominates the mutant viruses, which are maintained (at an extremely low level) only by the assumption of a constant mutation rate from the wild-type. As we shall show later in this chapter, the same applies to this fourth fixed point of Equation (5.2).

Not every conceivable behaviour is reflected by these equilibria. For instance, there is no fixed point in which both mutant strains survive while the wild-type strain is eradicated, nor any case where more than one form of the virus is maintained at a significant level.

5.3 Non-negativity of Fixed Points

Once again, it is important to consider the conditions under which the fixed points of Equation (5.2) are non-negative, with the ultimate goal of ensuring that none of the equilibria is stable at negative values. As in Chapter 4, note that s, d, δ, $\tilde{k}$, $\tilde{k}_1$ and $\tilde{k}_2$ are all positive parameters, while μ_1, μ_2, η, η_1 and η_2 are defined in the interval $[0, 1]$. Hence α, α_1, α_2 and β are positive quantities as well.

As we might anticipate, the disease-free equilibrium is non-negative regardless of parameter values, since the only non-zero value is $\overline{T}$, which is a quotient of positive quantities.

Since their forms are analogous, we may consider the second and third fixed points together. In both cases, $\overline{T}$ is a quotient of positive parameters, while two of the infected T cell populations have a zero equilibrium value. The second fixed point, then, will be non-negative as long as

$$\alpha_1 \geq \beta \tag{5.7}$$

while the third fixed point will be non-negative if

$$\alpha_2 \geq \beta. \tag{5.8}$$

In both cases, as we observed in Chapter 4, β represents a minimum level of quality a mutant strain must exhibit in order to be biologically feasible.

Unfortunately, the fourth fixed point is sufficiently complicated to be intractable under this form of analysis, and we are unable to derive conditions for its non-negativity. Unlike Equation (4.5), in which the solution of such conditions was made easier by the symmetrical construction of each of the three equations, Equation (5.2) necessarily loses some of this symmetry because the equation for $\dot{U}(t)$ contains a term involving $\mu_1 + \mu_2$ whereas the equations for $\dot{U}_1(t)$ and $\dot{U}_2(t)$ include terms involving either μ_1 alone or μ_2 alone.

However, we can observe that when $\zeta = 0$, $\overline{U} = \overline{U}_1 = \overline{U}_2 = 0$. Furthermore, this can only happen if

$$(1 - \mu_1 - \mu_2)\alpha = \beta,$$

so

$$\overline{T} = \frac{\delta}{\beta} = \frac{s}{d}.$$

In other words, for $\zeta = 0$, the final fixed point coincides with the disease-free fixed point. Hence, by the continuity of the solutions, this fixed point cannot become negative without undergoing an exchange of stability with the first point.

5.4 Eigenvalues and Stability

The Jacobian matrix corresponding to Equation (5.2) is

$$J = \begin{bmatrix} -d - \alpha U - \alpha_1 U_1 - \alpha_2 U_2 & -\alpha T & -\alpha_1 U_1 & -\alpha_2 U_2 \\ (1-\mu_1-\mu_2)\alpha U & (1-\mu_1-\mu_2)\alpha T - \delta & 0 & 0 \\ \mu_1 \alpha U + \alpha_1 U_1 & \mu_1 \alpha T & \alpha_1 T - \delta & 0 \\ \mu_2 \alpha U + \alpha_2 U_2 & \mu_2 \alpha T & 0 & \alpha_2 T - \delta \end{bmatrix}.$$

For the disease-free fixed point, the Jacobian matrix has eigenvalues

$$\lambda_1 = -d, \quad \lambda_2 = \frac{s[(1-\mu_1-\mu_2)\alpha - \beta]}{d}, \quad \lambda_3 = \frac{s(\alpha_1 - \beta)}{d}, \quad \lambda_4 = \frac{s(\alpha_2 - \beta)}{d}. \tag{5.9}$$

We have $\lambda_1 < 0$ since d is a positive parameter, while the remaining eigenvalues are negative only for

$$\beta > \alpha_1, \quad \beta > \alpha_2, \quad \beta > (1-\mu_1-\mu_2)\alpha. \tag{5.10}$$

Observe that these conditions are similar to those for the first fixed point of Equation (4.5), given by Equation (4.12). The first two conditions also coincide with those under which the second and third equilibria fail to be non-negative, as indicated by Equations (5.7) and (5.8).

As we might expect given their analogous construction, the second and third fixed points produce very similar eigenvalues of J. For the second fixed point,

these are

$$\lambda_1 = \frac{\delta[(1-\mu_1-\mu_2)\alpha-\alpha_1]}{\alpha_1}, \quad \lambda_2 = \frac{\delta(\alpha_2-\alpha_1)}{\alpha_1}, \\ \lambda_{3,4} = \frac{1}{2\delta}\left\{-s\alpha_1 \pm \sqrt{s^2\alpha_1^2 - 4\delta^2 s(\alpha_1-\beta)}\right\}. \tag{5.11}$$

For the third fixed point, these are

$$\lambda_1 = \frac{\delta[(1-\mu_1-\mu_2)\alpha-\alpha_2]}{\alpha_2}, \quad \lambda_2 = \frac{\delta(\alpha_1-\alpha_2)}{\alpha_2}, \\ \lambda_{3,4} = \frac{1}{2\delta}\left\{-s\alpha_2 \pm \sqrt{s^2\alpha_2^2 - 4\delta^2 s(\alpha_2-\beta)}\right\}. \tag{5.12}$$

Let's consider the eigenvalues of the second equilibrium point; the analysis of the eigenvalues of the third equilibrium point will follow in exactly the same manner. We immediately see that λ_1 will be negative if

$$\alpha_1 > (1-\mu_1-\mu_2)\alpha,$$

which is virtually the same as the first condition of Equation (4.14) for the second fixed point of Equation (4.5). Furthermore, λ_2 will be negative if

$$\alpha_1 > \alpha_2.$$

Finally, making an argument similar to that presented in our consideration of the second equilibrium point of Equation (4.5), we see that as long as this fixed point is non-negative, λ_3 and λ_4 will either be negative real eigenvalues or complex conjugate eigenvalues with negative real parts. Either way, the second fixed point will be asymptotically stable under the conditions

$$\alpha_1 > \beta, \quad \alpha_1 > \alpha_2, \quad \alpha_1 > (1-\mu_1-\mu_2)\alpha. \tag{5.13}$$

The corresponding conditions for the third fixed point are

$$\alpha_2 > \beta, \quad \alpha_2 > \alpha_1, \quad \alpha_2 > (1 - \mu_1 - \mu_2)\alpha. \tag{5.14}$$

Unfortunately, it was not possible to derive the conditions for the stability of the final fixed point.

5.5 Behaviour of the System

Despite the fact that the final equilibrium point of Equation (5.2) proved intractable, our results about the first three fixed points suggest that there is a great deal of commonality between the behaviour of this model and that given by Equation (4.5). We can establish further evidence for this conclusion by examining some representative parameter values.

To this end, we shall use those parameter values employed to illustrate Equation (4.5), as given in Table 4.1. Because the mutation rate is relatively insignificant in comparison to the virulence or resistance to therapy of each virus strain, we set $\mu_1 = \mu_2 = \mu$. Furthermore, we shall typically adopt a familiar value for the drug resistance of the wild-type virus, $\eta = 0.7$. For the virulence of the mutant strains, we shall assume that the first strain is more virulent, with $\tilde{k}_1 = 0.003$ (which, again, is about 80% of $\tilde{k}$) and $\tilde{k}_2 = 0.0027$ (which is about 70% of $\tilde{k}$). We shall vary η_1 and

η_2. Our choice of initial conditions will echo those of Table 4.2, and is provided in Table 5.1. As in Chapter 4, the phase portraits will be supplemented by comparable initial conditions in order to better illustrate the dynamical phenomena.

Table 5.1: Initial conditions for time series plots of Equation (5.1).

Population	**Variable**	**Initial Quantity**
Uninfected T cells	$T(t)$	500mm^{-3}
T cells infected with wild-type virus	$U(t)$	100mm^{-3}
T cells infected with first mutant virus	$U_1(t)$	10mm^{-3}
T cells infected with second mutant virus	$U_2(t)$	10mm^{-3}

To situate the model within the disease-free regime, we follow the practise indicated in Chapter 4 and assume that all of the virus species are extremely susceptible to the drug therapy. We set $\eta = 0.9$, $\eta_1 = 0.85$ and $\eta_2 = 0.8$, and thus obtain the time series given in Figure 5.1. Evidently, for this four-dimensional model we cannot depict the full phase portrait. Since we are most interested in the two mutant strains here, we will instead depict the projection onto the (T, U_1, U_2) phase subspace. The asymptotically stable node corresponding to this case is illustrated in Figure 5.2.

Next we can generate the case where the population of T cells infected by the

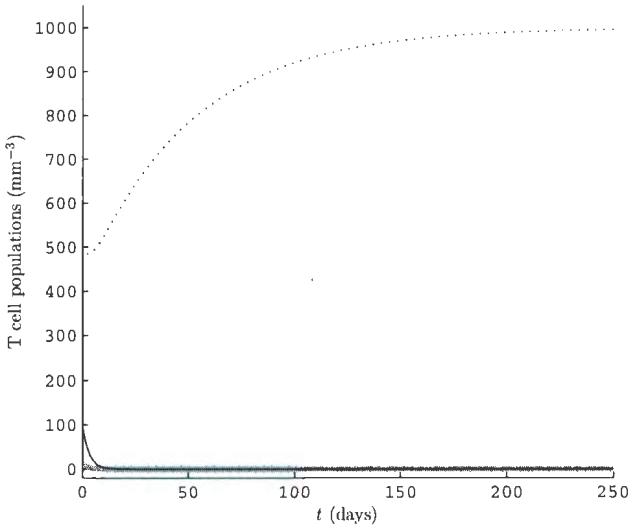

Figure 5.1: Time series for $T(t)$ (black dotted line), $U(t)$ (black line), $U_1(t)$ (grey line), $U_2(t)$ (grey dotted line) with $\eta = 0.9$, $\eta_1 = 0.85$ and $\eta_2 = 0.8$.

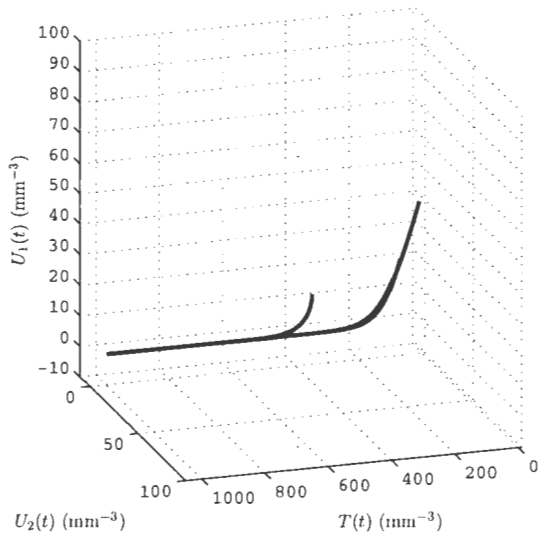

Figure 5.2: Phase portrait for Equation (5.1) with $\eta = 0.9$, $\eta_1 = 0.85$ and $\eta_2 = 0.8$.

first mutant strain is dominant while the remaining infected T cell population is eliminated. We choose $\eta_1 = 0.2$ and $\eta_2 = 0.15$, and obtain the time series given in Figure 5.3. Here we see that, although the second mutation exhibits stronger resistance to drug therapy, this is insufficient to compensate for its reduced virulence. The phase portrait projection demonstrates that these parameter values give rise to an asymptotically stable spiral-node, as shown in Figure 5.4.

The obverse case can be depicted by setting $\eta_1 = 0.25$ and $\eta_2 = 0.1$. The corresponding time series can be found in Figure 5.5. Now the discrepancy between the resistance of the two mutant strains is sufficient to lend the second strain the

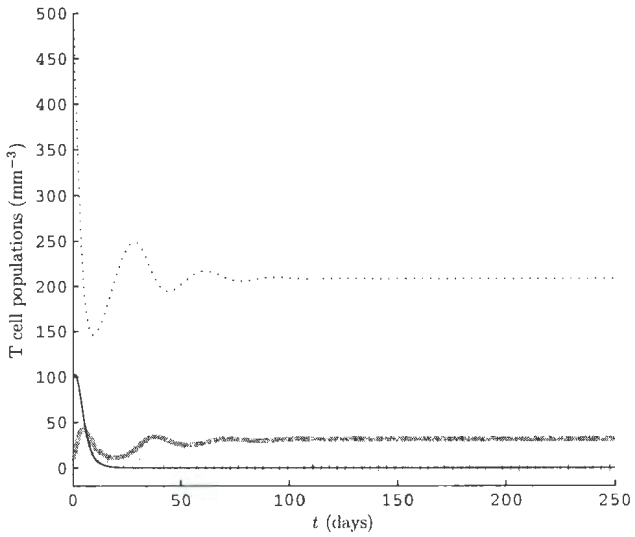

Figure 5.3: Time series for $T(t)$ (black dotted line), $U(t)$ (black line), $U_1(t)$ (grey line), $U_2(t)$ (grey dotted line) with $\eta_1 = 0.2$ and $\eta_2 = 0.15$.

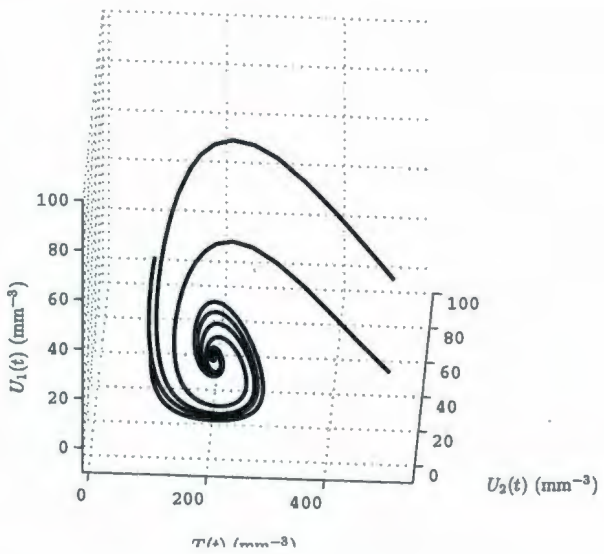

Figure 5.4: Phase portrait for Equation (5.1) with $\eta_1 = 0.2$ and $\eta_2 = 0.15$.

selective advantage. The phase portrait — again indicating that the fixed point is an asymptotically stable spiral-node — is depicted in Figure 5.6.

As with the second fixed point of Equation (4.5), it should be acknowledged that there are also parameter values for which no complex eigenvalues occur, and thus the dominance of the respective mutations is achieved via an asymptotically stable node, rather than an asymptotically stable spiral-node. We shall omit the illustration of these cases, however; their correspondence to Figures 5.3 and 5.5 is analogous to that described in Chapter 4.

Lastly, we consider the regime in which the final fixed point is asymptotically

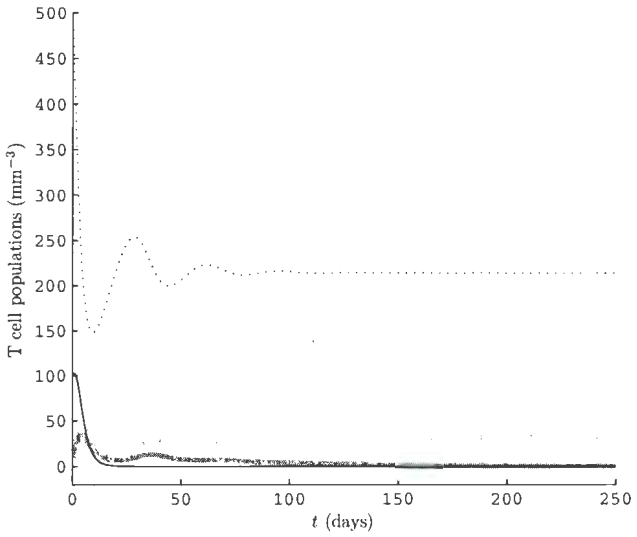

Figure 5.5: Time series for $T(t)$ (black dotted line), $U(t)$ (black line), $U_1(t)$ (grey line), $U_2(t)$ (grey dotted line) with $\eta_1 = 0.25$ and $\eta_2 = 0.1$.

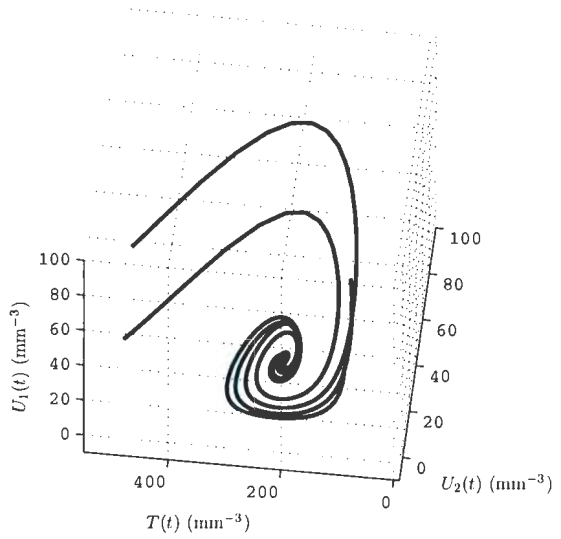

Figure 5.6: Phase portrait for Equation (5.1) with $\eta_1 = 0.25$ and $\eta_2 = 0.1$.

stable. Although this was not tractable analytically, it is easy to illustrate, as with $\eta = 0.3$, $\eta_1 = 0.2$, $\eta_2 = 0.15$. The time series is given in Figure 5.7. Again, as in our consideration of the final equilibrium point in Chapter 4, it should be noted that the populations of T cells infected by the mutant strains are not extinct in this case, but rather subsisting at a very low level.

Exhaustive numerical investigations indicate that, in fact, these are the only types of behaviour exhibited by Equation (5.1) for the standard parameter values given in Table 4.1. This evidence, combined with the apparent parallels between the fixed points, non-negativity conditions and stability conditions for both the one-

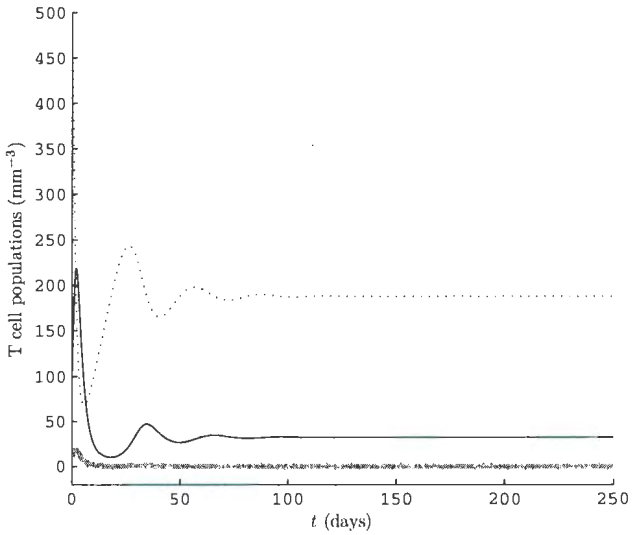

Figure 5.7: Time series for $T(t)$ (black dotted line), $U(t)$ (black line), $U_1(t)$ (grey line), $U_2(t)$ (grey dotted line) with $\eta = 0.3$, $\eta_1 = 0.2$ and $\eta_2 = 0.15$.

and two-mutant models suggests — even in the absence of a complete analysis of the final fixed point of Equation (5.1) — that, indeed, the two models behave analogously, exhibiting only transcritical bifurcations and regimes in which at most one population of infected T cells exists at a significant level.

Consequently, we conclude that for an ODE model of virus mutation, there is no need to consider the existence of more than one mutant species. One mutant strain will dominate all others on a short timescale (or all of them will diminish to insignificant levels, leaving the wild-type as the lone viable species) and so only this dominant mutant need be considered. As such, we can conclude that the model given by Equation (5.1) in fact simplifies to that given by Equation (4.3).

Chapter 6

A Model with Impulsive Moments

A KEY SIMPLIFICATION MADE IN THE construction of the ordinary differential equation model given by Equation (4.3) is the assumption that the level of drug in the system is constant. Of course, this does not reflect reality: dosages are taken only periodically, and therefore the amount of drug in the system increases abruptly at these moments of time, and decays thereafter until the next dosage. No simple continuous function obviously simulates this kind of behaviour, and even if one did present itself, its use would still only approximate the true behaviour of the drug, since the amount in the system should change discontinuously at the instant in which a new dosage is taken [26].

In this chapter, we shall detail the construction of a new version of the model

which incorporates impulsive differential equations. We shall conduct an analysis of the dynamical behaviour of this model comparable to that performed for the ODE version, and examine the similarities and differences which arise from the two models. The use of impulses provides us with an opportunity to model phenomena which could not be incorporated into Equation (4.3). For instance, it is common for HIV patients to adhere imperfectly to the drug therapy. Unlike continuous models, models with impulses provide a natural way to include various patterns of non-adherence into the HIV pathogenesis, and to otherwise alter the drug treatment regimen. We shall consider the effects of increasing or decreasing the dosing frequency, and examine the ramifications of various schedules of imperfect adherence.

6.1 The Author's Model, Impulsive Version

Since the introduction of an impulse into Equation (4.3) is directly tied to the drug concentration $D(t)$, we must address the connection between this quantity and the parameters η and η_M, used previously to denote the efficacy of the (constant) drug concentration. Per Wahl and Nowak [27] we can instead write

$$\eta = \frac{D(t)}{D(t) + \theta} \quad \text{and} \quad \eta_M = \frac{D(t)}{D(t) + \theta_M},$$

where θ and θ_M are the concentrations of drug which would inhibit by 50% the reproduction of the wild-type and mutant strains.

We can now represent the dynamics of the drug concentration via a fourth equation,

$$\dot{D}(t) = -mD(t), \tag{6.1}$$

where m is the rate of clearance of the drug. We will assert that this equation is valid at all times $t \neq t_k$, where t_k are the moments of the impulsive differential equation — that is, the instants at which the amount of drug is replenished. The accompanying impulsive condition is

$$\Delta D = D^i \tag{6.2}$$

such that

$$\lim_{t \to t_k^+} D(t) = D^i + \lim_{t \to t_k^-} D(t).$$

In other words, the concentration of drug in the host jumps by D^i at each moment $t = t_k$.

The single-mutant model now becomes

$$\begin{aligned}
\dot{T}(t) &= s - dT(t) - \left(1 - \frac{D(t)}{D(t)+\theta}\right)\tilde{k}T(t)U(t) - \left(1 - \frac{D(t)}{D(t)+\theta_M}\right)\tilde{k}_M T(t)U_M(t) \\
\dot{U}(t) &= (1-\mu)\left(1 - \frac{D(t)}{D(t)+\theta}\right)\tilde{k}T(t)U(t) - \delta U(t) \\
\dot{U}_M(t) &= \mu\left(1 - \frac{D(t)}{D(t)+\theta}\right)\tilde{k}T(t)U(t) + \left(1 - \frac{D(t)}{D(t)+\theta_M}\right)\tilde{k}_M T(t)U_M(t) - \delta U_M(t) \qquad (6.3) \\
\dot{D}(t) &= -mD(t), \quad t \neq t_k \\
\Delta D &= D^i, \quad t = t_k.
\end{aligned}$$

6.2 The Fixed Points and Impulsive Periodic Orbits

Note that the differential equation for $D(t)$ does not depend on the other quantities $T(t)$, $U(t)$ or $U_M(t)$, so we can easily integrate and solve for $D(t)$ explicitly on each interval $t_k < t \leq t_{k+1}$:

$$D(t) = D_0 e^{-m(t-t_k)} \qquad (6.4)$$

where

$$D_0 = \lim_{t \to t_k^+} D(t).$$

Although this expression tends towards zero over time, the impulsive condition indicates that $D(t)$ will be forced away from zero at each moment of the IDE. Note

that the cumulative effect of the impulse can be expressed via the recurrence relation

$$\lim_{t\to t_k^+} D(t) = \lim_{t\to t_k^-} D(t) + D^i.$$

If we assume that the impulsive moments t_k are evenly spaced, let $\tau = t_{k+1} - t_k$.

Then

$$\lim_{t\to t_k^-} D(t) = \left[\lim_{t\to t_{k-1}^+} D(t)\right] e^{-m\tau}$$

and so

$$\begin{aligned}\lim_{t\to t_k^+} D(t) &= \left[\lim_{t\to t_{k-1}^+} D(t)\right] e^{-m\tau} + D^i \\ &= \left[\lim_{t\to t_{k-1}^-} D(t) + D^i\right] e^{-m\tau} + D^i \\ &= \left[\lim_{t\to t_{k-1}^-} D(t)\right] e^{-m\tau} + D^i(1 + e^{-m\tau}).\end{aligned}$$

Hence, repeating this process k times, we have that

$$\lim_{t\to t_k^+} D(t) = D^i e^{-km\tau} + D^i \sum_{n=0}^{k} e^{-nm\tau}.$$

Note, however, that as $k \to \infty$ we can use the result

$$\lim_{k\to\infty} \sum_{n=0}^{k} e^{-nm\tau} = \frac{1}{1 - e^{-m\tau}}$$

to obtain that

$$\lim_{t\to t_k^+} D(t) \to \frac{D^i}{1 - e^{-m\tau}}.$$

Furthermore, if

$$\lim_{t \to t_k^+} D(t) = \frac{D^i}{1 - e^{-m\tau}}$$

then

$$\lim_{t \to t_{k+1}^-} D(t) = \frac{D^i}{1 - e^{-m\tau}} e^{-m\tau}.$$

We can conclude, then, that if the impulsive moments are evenly spaced, each new dosage will tend towards an impulsive periodic orbit with endpoints

$$\frac{D^i}{1 - e^{-m\tau}} \quad \text{and} \quad \frac{D^i}{1 - e^{-m\tau}} e^{-m\tau}.$$

We label this impulsive periodic orbit D^*; we shall use similar notation throughout this chapter to denote other periodic orbits. As before, we shall use the notation $\overline{X}$ to indicate a fixed point.

Depending on the parameter values, we shall now show that the fixed points we computed for $T(t)$, $U(t)$ and $U_M(t)$ in examining the ODE model may persist in the IDE model, or they may be replaced by impulsive periodic orbits. As suggested by Smith? and Wahl [18], in the latter case we can characterise these periodic orbits (and analyse the tendency of solutions to move towards or away from them) in terms of D^*. It should be noted that, in general, systems exhibiting periodic solutions cannot be analysed in the manner of an ODE system; however, the framework of IDEs permits an analogous approach [13–15, 19].

As in the case of the ODE model, our analysis can be simplified by introducing new parameters. Much like the introduction of the parameters α and α_M to obtain Equation (4.5), we will set

$$\omega = \theta\tilde{k} \quad \text{and} \quad \omega_M = \theta_M\tilde{k}_M.$$

Observe that θ and θ_M play a similar role in the IDE model to $1-\eta$ and $1-\eta_M$ in the ODE model. Equation (6.3) now becomes

$$\begin{aligned}
\dot{T}(t) &= s - dT(t) - \frac{\omega}{D(t)+\theta}T(t)U(t) - \frac{\omega_M}{D(t)+\theta_M}T(t)U_M(t) \\
\dot{U}(t) &= (1-\mu)\frac{\omega}{D(t)+\theta}T(t)U(t) - \delta U(t) \\
\dot{U}_M(t) &= \mu\frac{\omega}{D(t)+\theta}T(t)U(t) + \frac{\omega_M}{D(t)+\theta_M}T(t)U_M(t) - \delta U_M(t).
\end{aligned} \tag{6.5}$$

Here we have suppressed the equation and condition on $D(t)$, since we have already solved it analytically. As in the case of our investigation of Equation (4.5), we will make the substitution

$$\beta = \frac{d\delta}{s}$$

when suitable.

Recall that the ODE model exhibited three fixed points: a disease-free fixed point, a fixed point at which the wild-type HIV strain was eradicated, and a fixed point at which the wild-type and mutants viruses coexisted. For the model with impulses, we again set $\dot{T}(t)$, $\dot{U}(t)$ and $\dot{U}_M(t)$ equal to 0, and solve in terms of the

impulsive periodic orbit D^*. We find that three solutions — which variously consist of either fixed point values or additional periodic orbits — now arise, and can be classified in a similar manner.

First, the disease-free fixed point of Equation (4.5)

$$\overline{T} = \frac{s}{d}, \quad \overline{U} = \overline{U}_M = 0 \tag{6.6}$$

is a fixed point of Equation (6.5). In other words, if the parameters are such that HIV will actually be eradicated then the long-term behaviour is independent of the treatment schedule: after sufficient time has passed, there is no virus remaining to be affected by the drug.

The second solution is actually one in which only $U(t)$ reaches an equilibrium value, while $T(t)$ and $U_M(t)$ follow impulsive periodic orbits proportional to D^*. Specifically, these are

$$T^* = \frac{\delta}{\omega_M}(D^* + \theta_M), \quad \overline{U} = 0, \quad U_M^* = \frac{s[\omega_M - \beta(D^* + \theta_M)]}{\delta\omega_M}. \tag{6.7}$$

In this instance, the wild-type virus is annihilated in favour of the mutant strain. However, the populations of both the uninfected T cells and the T cells infected by the mutant virus continue to vary as the drug level varies — with, as we would expect, the population of uninfected T cells increasing as the amount of drug in the system increases, and the population of infected T cells decreasing.

The final solution is one in which each of $T(t)$, $U(t)$ and $U_M(t)$ follows an impulsive periodic orbit. Unlike the previous case, however, the dependence of $U(t)$ and $U_M(t)$ is no longer a simple matter of direct proportionality to D^*. The periodic orbits are now given by

$$\begin{aligned} T^* &= \frac{\delta}{(1-\mu)\omega}(D^* + \theta), \\ U^* = \frac{[(1-\mu)\omega(D^* + \theta_M) - \omega_M(D^* + \theta)]\xi^*}{\omega}, &\quad U_M^* = \mu(D^* + \theta_M)\xi^* \end{aligned} \tag{6.8}$$

where

$$\xi^* = \frac{s[(1-\mu)\omega - \beta(D^* + \theta)]}{\delta(1-\mu)[\omega(D^* + \theta_M) - \omega_M(D^* + \theta)]}.$$

6.3 Non-negativity of Fixed Points and Impulsive Periodic Orbits

Once again, it is important to consider the conditions we must place upon the parameters to ensure that each fixed point or impulsive periodic orbit remains positive. Observe that, as can be seen from Equation (6.4), $D(t) > 0$ for all t, and hence $D^* > 0$ as well. In addition, note that ω, ω_M and β are positive quantities.

As with the ODE model, the fixed point given by Equation (6.6) is non-negative for all parameter values, since both s and d are positive (guaranteeing the positivity of $\overline{T}$) while $\overline{U} = \overline{U}_M = 0$.

In the case of the impulsive periodic orbit given by Equation (6.7), we have $\overline{U} = 0$. T^* is a quotient of positive parameters multiplying the positive periodic orbit D^*, so $T^* > 0$ as well. More interesting is U_M^*. It will be non-negative as long as

$$\omega_M \geq \beta(D^* + \theta_M), \tag{6.9}$$

which is analogous in form to the condition for non-negativity derived for the second fixed point of the ODE model, Equation (4.9).

This condition can perhaps more usefully be written in an impulsive context as

$$\frac{\omega_M}{\beta} \geq D^* + \theta_M. \tag{6.10}$$

Recall that D^* is not a fixed value, but rather a periodic trajectory driven by the impulsive moments. This means that the condition given by Equation (6.10) may not be satisfied for the entire period of D^*, but may be satisfied for a subinterval of that period. In other words, U_M^* may be negative for part of the orbit of D^*, and non-negative for the remainder of the orbit. Obviously, this is behaviour not seen in the ODE version of the model, where a condition such as Equation (4.9) guarantees the non-negativity of the corresponding equilibrium point for all t.

Finally, we come to the impulsive periodic orbit given by Equation (6.8). Once again, T^* is a positive multiple of D^*, so it must be non-negative. By performing

an analysis analogous to that given for the third fixed point of Equation (4.5), we conclude that U^* and U_M^* will be non-negative as long as

$$(1-\mu)\omega(D^*+\theta_M) \geq \omega(D^*+\theta) \quad \text{and} \quad \omega(1-\mu) \geq \beta(D^*+\theta). \tag{6.11}$$

As with the preceding, there are clear similarities to the corresponding condition given in Equation (4.10), but this time it is more useful to rewrite the condition in the form

$$\frac{(1-\mu)\omega}{\omega_M} \geq \frac{D^*+\theta}{D^*+\theta_M} \quad \text{and} \quad \frac{(1-\mu)\omega}{\beta} \geq D^*+\theta. \tag{6.12}$$

Again, we note the possibility that these conditions may be satisfied for some, but not all, of the periodic orbit D^*.

6.4 Eigenvalues and Stability

In the previous section, we drew a number of parallels between the conditions under which the fixed points or impulsive periodic orbits of the impulsive model are non-negative, and the conditions under which the fixed points of the ODE model are non-negative. We shall make similar comparisons in studying the eigenvalues, and hence the stability, of these fixed points and impulsive periodic orbits, observing again that the key difference in the case of Equation (6.5) is the

dependence upon the state of the impulsive periodic orbit D^* describing the *in vivo* drug levels.

The Jacobian matrix of Equation (6.5) is given by

$$J = \begin{bmatrix} -d - \frac{\omega}{D+\theta}U - \frac{\omega_M}{D+\theta_M}U_M & -\frac{\omega}{D+\theta}T & -\frac{\omega_M}{D+\theta_M}T \\ \frac{(1-\mu)\omega}{D+\theta}U & \frac{(1-\mu)\omega}{D+\theta}T - \delta & 0 \\ \frac{\mu\omega}{D+\theta}U + \frac{\omega_M}{D+\theta_M}U_M & \frac{\mu\omega}{D+\theta}T & \frac{\omega_M}{D+\theta_M}T - \delta \end{bmatrix}.$$

As in Chapter 4, we shall determine the conditions under which each of the fixed points and impulsive periodic orbits is stable, that is, under which J possesses only negative eigenvalues.

For the disease-free fixed point, the eigenvalues of the Jacobian matrix are

$$\lambda_1 = -d, \quad \lambda_2 = \frac{s[\omega_M - \beta(D^* + \theta_M)]}{d(D^* + \theta_M)}, \quad \lambda_3 = \frac{s[(1-\mu)\omega - \beta(D^* + \theta)]}{d(D^* + \theta)}. \tag{6.13}$$

Evidently, $\lambda_1 < 0$ for all feasible values of d, while λ_2 and λ_3 are negative only if

$$\beta(D^* + \theta_M) > \omega_M \quad \text{and} \quad \beta(D^* + \theta) > (1-\mu)\omega. \tag{6.14}$$

These conditions can be compared to those for the first fixed point of Equation (4.5), given by Equation (4.12). In this case, they can more usefully be written as

$$D^* + \theta_M > \frac{\omega_M}{\beta} \quad \text{and} \quad D^* + \theta > \frac{(1-\mu)\omega}{\beta}. \tag{6.15}$$

The first of these conditions coincides with the condition under which the impulsive periodic orbit given by Equation (6.7) becomes negative, as indicated by

Equation (6.10). The other condition implies that the impulsive periodic orbit given by Equation (6.8) is also negative, as given by Equation (6.12). Hence, exactly as in the ODE case, the disease-free fixed point is asymptotically stable only when the system possesses no other non-negative fixed points.

For the impulsive periodic orbit given by Equation (6.7), in which the T cells infected with the wild-type virus are driven to extinction in favour of the mutant strain, the eigenvalues of the Jacobian matrix are

$$\begin{aligned} \lambda_1 &= \frac{\delta[(1-\mu)\omega(D^* + \theta_M) - \omega_M(D^* + \theta)]}{\omega_M(D^* + \theta)}, \\ \lambda_{2,3} &= \frac{-s\omega_M \pm \sqrt{s^2\omega_M^2 - 4\delta^2 s(D^* + \theta_M)[\omega_M - \beta(D^* + \theta_M)]}}{2\delta(D^* + \theta)}. \end{aligned} \tag{6.16}$$

Considering λ_1 first, we immediately see that this eigenvalue will be negative if

$$\omega_M(D^* + \theta) > (1-\mu)\omega(D^* + \theta_M).$$

We can subject $\lambda_{2,3}$ to the same analysis employed for the eigenvalues of the corresponding fixed points of the ODE model. Thus we conclude that, when this impulsive periodic orbit is positive, as fulfilled by the condition

$$\omega_M > \beta(D^* + \theta_M)$$

as given in Equation (6.10), $\lambda_{2,3}$ will possess a negative real part (although it may be a real or complex number). Thus these three eigenvalues will all possess negative

real parts as long as they fulfill the joint conditions

$$\omega_M > \beta(D^* + \theta_M) \quad \text{and} \quad \omega_M(D^* + \theta) > (1 - \mu)\omega(D^* + \theta_M),$$

which is similar to Equation (4.14) in the ODE case. In this context, we more usefully write these conditions in the form

$$\frac{\omega_M}{\beta} > D^* + \theta_M \quad \text{and} \quad \frac{\omega_M}{(1-\mu)\omega} > \frac{D^* + \theta_M}{D^* + \theta}. \tag{6.17}$$

The impulsive periodic orbit given by Equation (6.8) yields the following eigenvalues of J:

$$\lambda_1 = \frac{\delta[\omega_M(D^* + \theta) - (1-\mu)\omega(D^* + \theta_M]}{(1-\mu)\omega(D^* + \theta_M)},$$
$$\lambda_{2,3} = \frac{1}{2\delta(D^* + \theta)}\left\{-s(1-\mu)\omega \pm \sqrt{s^2(1-\mu)^2\omega^2 - 4\delta^2 s(D^* + \theta)[(1-\mu)\omega - \beta(D^* + \theta)]}\right\}. \tag{6.18}$$

In order for λ_1 to be negative, we require

$$(1-\mu)\omega(D^* + \theta_M) > \omega_M(D^* + \theta).$$

As with the corresponding condition for the third fixed point of the ODE system, this is the antithesis of the condition found for λ_1 of the impulsive periodic orbit given by Equation (6.7). Also as in the ODE case, we can pursue an analysis similar to that of the second and third eigenvalues of the preceding impulsive periodic orbit. We find that, as long as the impulsive periodic orbit given by Equation (6.8)

is positive, $\lambda_{2,3}$ must possess a negative real part. In other words, the desired condition is

$$(1-\mu)\omega > \beta(D^* + \theta),$$

although the eigenvalues may be real or may form a complex conjugate pair. Thus the eigenvalues of this impulsive periodic orbit will all be negative as long as the dual conditions

$$(1-\mu)\omega(D^* + \theta_M) > \omega_M(D^* + \theta) \quad \text{and} \quad (1-\mu)\omega > \beta(D^* + \theta)$$

are satisfied. Note the similarity to Equation (4.17). We can rewrite these conditions as

$$\frac{(1-\mu)\omega}{\omega_M} > \frac{D^* + \theta}{D^* + \theta_M} \quad \text{and} \quad \frac{(1-\mu)\omega}{\beta} > D^* + \theta. \tag{6.19}$$

6.5 Behaviour of the System

As with the ordinary differential equation model given by Equation (4.5), we can establish four regimes of behaviour for the system of Equation (6.5). These parallel the four regimes described for Equation (4.5), but are intrinsically dependent upon the impulsive periodic orbit D^*. Consequently, as the amount of drug in the body changes, the positivity and stability of the other fixed points and impulsive periodic orbits can also change, even if all the parameters of the system

remain constant. Hence it makes the most sense to characterise these regimes in terms of the drug concentration wherever possible. The regimes of behaviour are as follows:

1. $D^* + \theta_M > \frac{\omega_M}{\beta}$ and $D^* + \theta > \frac{(1-\mu)\omega}{\beta}$: the fixed point given by Equation (6.6) is positive and stable; the impulsive periodic orbits given by Equations (6.7) and (6.8) are negative and unstable (there is enough drug in the system to suppress both the wild-type and mutant virus strains),

2. $\frac{\omega_M}{\beta} > D^* + \theta_M$ and $\frac{\omega_M}{(1-\mu)\omega} > \frac{D^* + \theta_M}{D^* + \theta}$: the fixed point given by Equation (6.6) is positive and unstable; the impulsive periodic orbit given by Equation (6.7) is positive and stable; the impulsive periodic orbit given by Equation (6.8) is negative and unstable (the mutant strain is sufficiently resistant to the drug, whereas the wild-type virus is not),

3. $\frac{(1-\mu)\omega}{D^* + \theta} > \beta > \frac{\omega_M}{D^* + \theta_M}$: the fixed point given by Equation (6.6) is positive and unstable; the impulsive periodic orbit given by Equation (6.7) is negative and unstable; the impulsive periodic orbit given by Equation (6.8) is positive and stable (the mutant strain is severely inhibited by the drug, but the wild-type virus successfully resists it),

4. $\frac{(1-\mu)\omega}{D^* + \theta} > \frac{\omega_M}{D^* + \theta_M} > \beta$: the fixed point given by Equation (6.6) and the

impulsive periodic orbit given by Equation (6.7) are positive and unstable; the impulsive periodic orbit given by Equation (6.8) is positive and stable (the drug concentration is insufficient to inhibit either virus variant).

6.5.1 Numerical Simulations: Parameter Values

We will now illustrate each of these regimes for appropriate parameter values. Many of the quantities chosen for Table 4.1 remain suitable, but we now have additional parameters whose values must be substantiated. The updated list of parameter values is given in Table 6.1. Note that, as in Chapter 4, we have

$$\beta = 5 \times 10^{-4} \text{mm}^3 \text{d}^{-1}.$$

We do not seek to model the effects of any particular drug, and so we have chosen typical values for θ and m here. As with the ODE model, we have particular freedom to choose the value of θ_M, depending upon the strength of the resistance of the mutant strain that we wish to model.

Furthermore, we now require values to describe the impulse. We shall assume that the moments of impulse are evenly spaced, with a new dose of the drug therapy taken daily, so $t_k = k$ days. We shall additionally assume that the amount

Table 6.1: Parameter values for Equation (6.3).

Parameter	Symbol	Quantity	References
production of new T cells	s	$20\text{d}^{-1}\text{mm}^{-3}$	[4,23]
death rate of healthy T cells	d	0.02d^{-1}	[23]
death rate of infected T cells	δ	0.5d^{-1}	[17,23]
virulence of wild-type	$\tilde{k}$	$0.0038\text{mm}^3\text{d}^{-1}$	[4,16,17,23]
virulence of mutant	$\tilde{k}_M$	$0.003\text{mm}^3\text{d}^{-1}$	[4]
mutation rate from wild-type	μ	3×10^{-5}	[4,24,25]
drug concentration for 50% inhibition of wild-type	θ	$3 \times 10^{-8}\text{M}$	[27]
rate of drug clearance	m	12d^{-1}	[17,18]

of drug introduced at this point is

$$D^i = 6 \times 10^{-6} M,$$

which again reflects a typical value suggested by [17–19]. Finally, for convenience, we shall assume that our numerical simulations start precisely at an impulsive moment (that is, that treatment has just begun) so that $D_0 = D^i$. The augmented table of standard initial conditions, which otherwise resembles Table 4.2 for the ODE model, is given in Table 6.2.

Table 6.2: Initial conditions for time series plots of Equation (6.3).

Population	**Variable**	**Initial Quantity**
Uninfected T cells	$T(t)$	500mm^{-3}
T cells infected with wild-type virus	$U(t)$	100mm^{-3}
T cells infected with mutant virus	$U_M(t)$	10mm^{-3}
Drug concentration	$D(t)$	$6 \times 10^{-6}\text{M}$

A time series depicting the evolution of the drug concentration under the given parameter values with $t_k = k$ days is given in Figure 6.1. By way of comparison, a corresponding time series for the case where $t_k = 0.2k$ days is given in Figure 6.2.

We now proceed with our numerical investigation of Equation (6.5) in much the same way as we explored Equation (4.5) in Chapter 4. The impulsive system

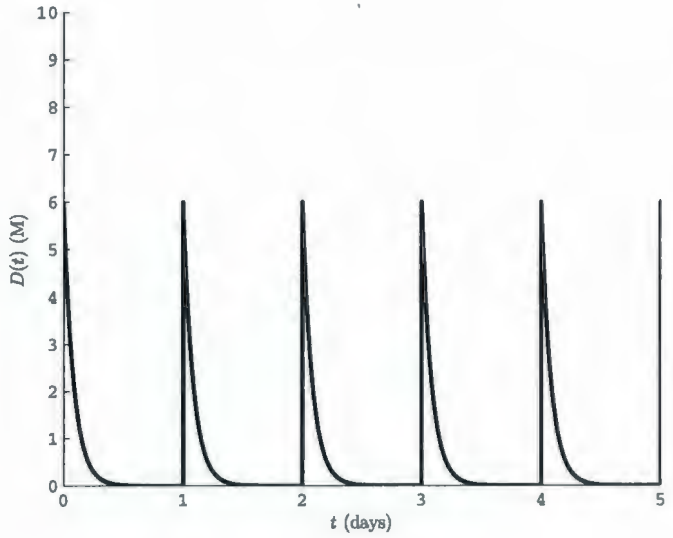

Figure 6.1: Time series for $D(t)$, with $t_k = k$ days.

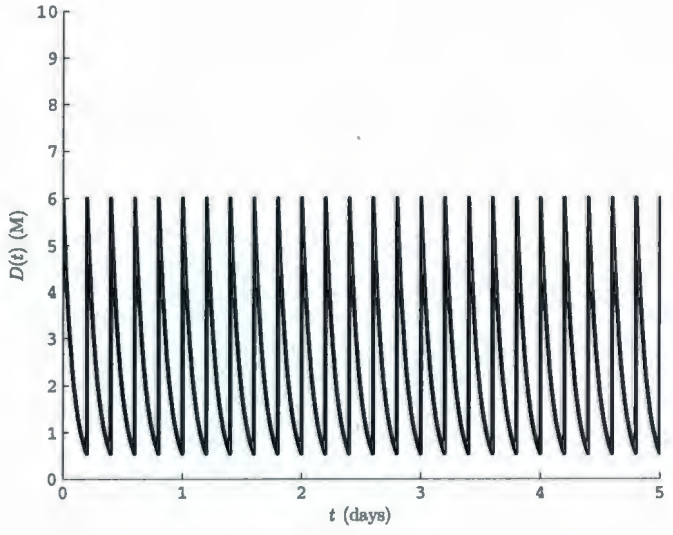

Figure 6.2: Time series for $D(t)$, with $t_k = 0.2k$ days.

permits us greater flexibility, because we can now manipulate elements such as the dosing period, and consider the possibility that the patient does not adhere completely to the treatment regimen. However, we shall defer these topics to later sections of this chapter; to obtain a basic understanding of the system given by Equation (6.3), we shall leave the period of the dosages unchanged, and instead manipulate the other parameters of the model.

To follow the methodology of the preceding chapter, it would appear that the parameter which could be most usefully treated as the principal bifurcation parameter is θ_M, with other values altered depending on the needs of each particular regime. However, because D^* now plays such a prominent role in the evolution of the model, it will frequently be the case that the system will shift from one regime to another within a single impulsive period. This is important behaviour that we will investigate later in this section, but for our initial observations we wish to keep the system within the same regime for all t. This is most usefully accomplished by considering a slower clearance rate of the drug, and so in these first numerical simulations we will in fact find ourselves adjusting the value of m quite often.

6.5.2 Numerical Simulations: The Disease-Free Equilibrium

To begin, we briefly consider the first regime, in which the disease-free equilibrium is asymptotically stable. We have shown analytically that this is identical to the corresponding result for the ODE model: there are no impulsive periodic orbits apart from D^* and so this is a true fixed point. Unlike Equation (4.3), it is more difficult to place the system in this regime due to the fact that the amount of drug is no longer assumed to be constant: as time progresses between dosages, the influence of the drug quickly subsides.

Under the given parameter values,

$$\frac{\omega_M}{\beta} = 2000\omega_M \approx 6\theta_M,$$

so in order for the first condition of this regime to be satisfied for all t, we must have $\min D(t) > 5\theta_M$. However, for the indicated parameter values,

$$D(1) = D_0 \exp -12 \approx (3.7 \times 10^{-5})D_0.$$

Since $D_0 = 6$ initially, and becomes $6 + D(1) \approx 6$ at subsequent impulsive moments, it is certainly true that $\min D(t) < 5\theta_M$. Hence, in order to illustrate this regime, we will consider a drug which is unrealistically robust, such that $m = 2\text{d}^{-1}$. We will also let the mutant be scarcely more resistant to treatment than the wild-type, with $\theta_M = 1.0 \times 10^{-7}\text{M}$.

The time series plot for this situation is given in Figure 6.3. As anticipated, there appears to be no periodic behaviour associated with this regime. In fact, the graph is virtually indistinguishable from the corresponding ODE case depicted in Figure 4.1, with both of the infected T cell populations tending towards extinction and the uninfected T cell population returning to its uninfected level of 1000mm^{-3}.

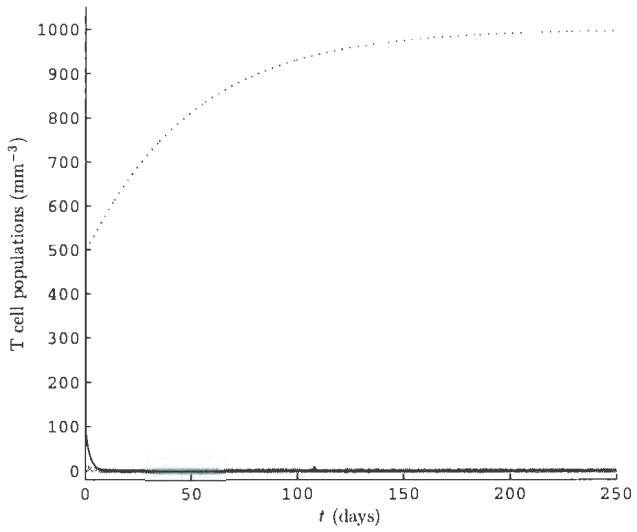

Figure 6.3: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 1.0 \times 10^{-7}\text{M}$ and $m = 2\text{d}^{-1}$.

6.5.3 Numerical Simulations: The Mutant-Dominant Impulsive Periodic Orbit

For the second regime, we expect the impulsive moments to force periodic oscillations in both $T(t)$ and $U_M(t)$. Again, complete subscription to this regime of behaviour is difficult to achieve simply by changing θ_M. We will assume that the mutant strain is more resistant to the drug, and that the drug is cleared at a rate slower than in the previous example, but still much faster than in our baseline assumption. Hence we let $\theta_M = 1.5 \times 10^{-6}$M and $m = 7\text{d}^{-1}$.

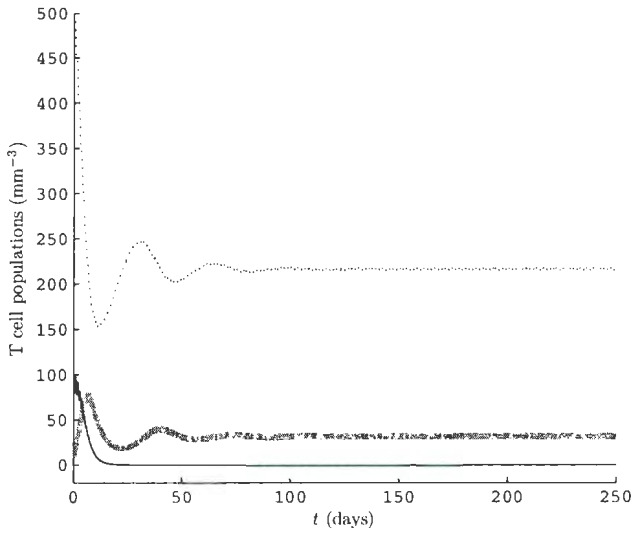

Figure 6.4: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 1.5 \times 10^{-6}$M and $m = 7\text{d}^{-1}$.

The resulting time series is given in Figure 6.4. As expected, the population of T cells infected by the wild-type virus vanishes under these parameter values, while those infected by the mutant strain thrive. This plot appears to be similar to Figure 4.3. However, consider Figure 6.5. This is a magnification of Figure 6.4 between $t = 175$d and $t = 200$d. Here we can see the persistent oscillations exhibited by $U_M(t)$ in response to the daily replenishment of the drug. Although not shown, similar behaviour can be observed in $T(t)$. On the other hand, $U(t)$ demonstrates no such oscillations: it simply tends towards extinction.

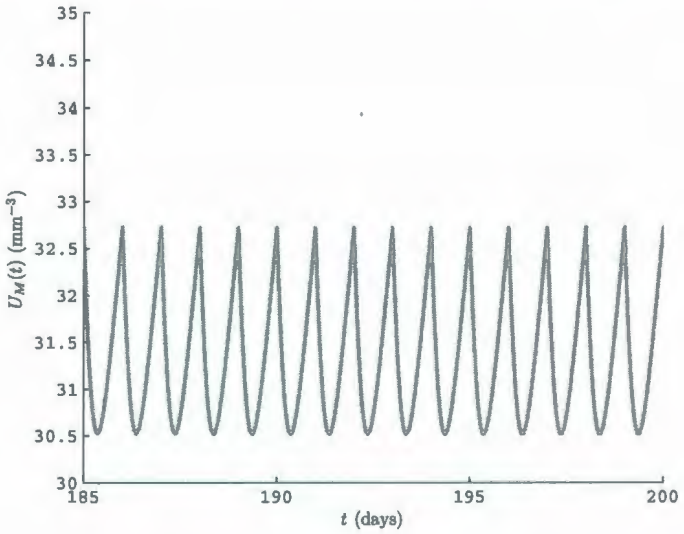

Figure 6.5: Magnified view of $U_M(t)$ in Figure 6.4.

6.5.4 Numerical Simulations: The Coexistence Impulsive Periodic Orbit

For the third regime, we seek values for which the wild-type virus will obtain a selective advantage over the mutant strain. This suggests that both forms of the virus should be strongly resistant to the drug, while the virulence of the mutant strain is significantly lower than its wild-type counterpart. We choose $\theta_M = 1.5 \times 10^{-6}$M, $\theta = 9.5 \times 10^{-7}$M, and $\tilde{k}_M = 3 \times 10^{-4}\text{mm}^3\text{d}^{-1}$. We can, however, let $m = 12\text{d}^{-1}$ as in our general assumptions.

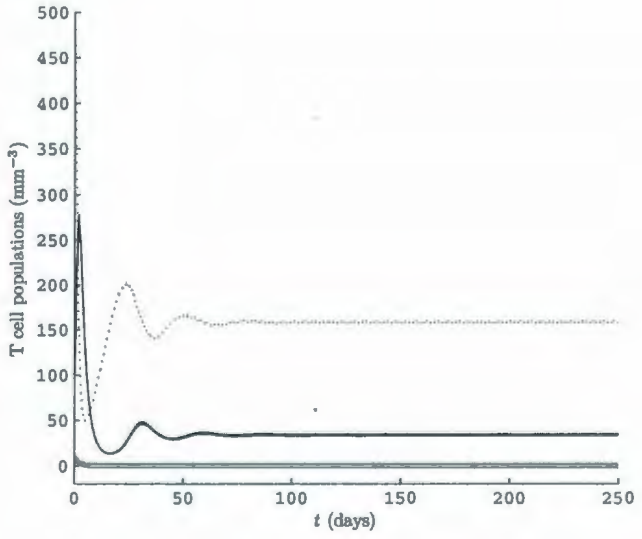

Figure 6.6: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 1.5 \times 10^{-6}$M, $\theta = 9.5 \times 10^{-7}$M, $\tilde{k}_M = 3 \times 10^{-4}\text{mm}^3\text{d}^{-1}$ and $m = 12\text{d}^{-1}$.

Figure 6.6 gives the corresponding time series. In this case, all of the T cell populations exhibit periodic oscillations, although they are difficult to perceive given the scale of the plot. Even $U_M(t)$, which appears to have converged to zero, is in fact oscillating at very small, yet positive, values. This can be seen from the magnified plot given in Figure 6.7.

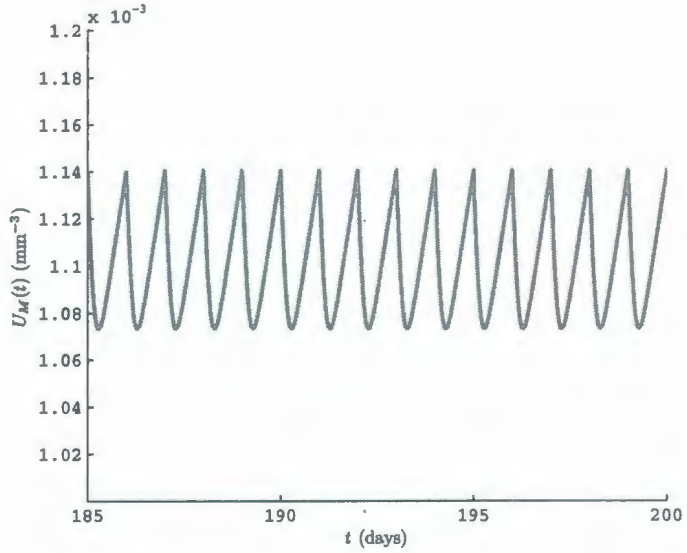

Figure 6.7: Magnified view of $U_M(t)$ in Figure 6.6.

From our study of the ODE model in Chapter 4, we expect the behaviour of Equation (6.3) in the fourth regime to be essentially the same as in the third regime. We illustrate this situation by using identical parameter values as for Figure 6.6, with the exception of restoring $\tilde{k}_M = 0.003$. The result is the time series depicted

in Figure 6.8 which does, indeed, vary only slightly from the previous plot (the population of T cells infected by the mutant virus is slightly elevated, for instance). Again, each of $T(t)$, $U(t)$ and $U_M(t)$ exhibits periodic oscillations.

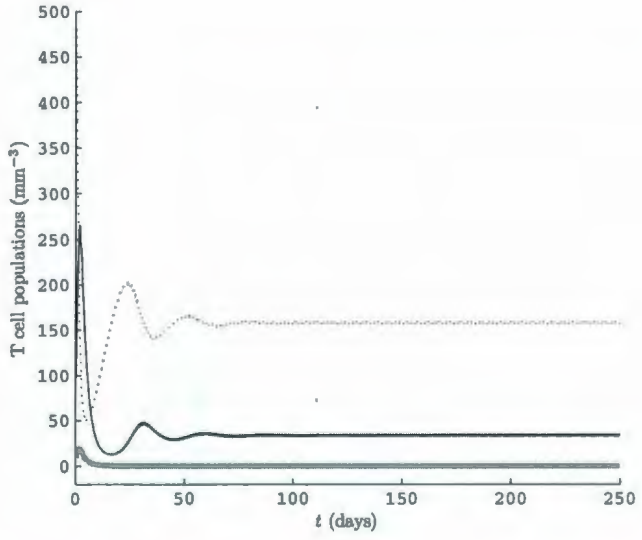

Figure 6.8: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 1.5 \times 10^{-6}$M, $\theta = 9.5 \times 10^{-7}$M and $m = 12\text{d}^{-1}$.

6.5.5 Numerical Simulations: Other Cases

The cases considered so far are highly specialised, however, because the parameter values have been carefully chosen so that the impulsive periodic orbit D^* does not pull the system into different regimes of behaviour at different times. It is because

of the specialised nature of these examples that we have not pursued the cases for the second, third and fourth regimes in which no complex eigenvalues arise, as we did for the ODE system in Chapter 4. It is far more likely that the basin of attraction will change as the drug concentration decreases between impulsive moments.

Consider, for example, the case where all the parameter values are as given in Table 6.1, and $\theta_M = 3.0 \times 10^{-7}$M (an order of magnitude greater than θ). Observe that

$$\lim_{t \to 1^-} D(t) \approx 3.7 \times 10^{-5} \ll D^i$$

so we can assume that, in general

$$\lim_{t \to t_k^+} D(t) \approx D^i = 6 \quad \text{and} \quad \lim_{t \to t_k^-} D(t) \approx 3.7 \times 10^{-5}.$$

Immediately upon the initiation of a new treatment period,

$$D^* + \theta_M \approx 6.3 > \frac{\omega_M}{\beta} = 1.8$$

and

$$D^* + \theta \approx 6.03 > \frac{(1-\mu)\omega}{\beta} \approx 0.23$$

so the system lies within the first regime. In other words, the drug concentration is initially powerful enough to inhibit both the wild-type and mutant forms of the virus.

As time passes, however, the strength of the drug's influence quickly wanes. For instance, at $t = t_k + 0.25$,

$$D^* + \theta_M \approx 0.60 < \frac{\omega_M}{\beta}$$

while

$$\frac{\omega_M}{(1-\mu)\omega} \approx 7.89 > \frac{D^* + \theta_M}{D^* + \theta} \approx 1.82.$$

This means that the system has now shifted to the second regime: the mutant strain is no longer controlled by the therapy, although the wild-type remains in check.

By the time $t = t_k + 0.55$, however, circumstances have changed again. Now we have

$$D^* + \theta_M \approx 0.31 < \frac{\omega_M}{\beta}$$

and

$$\frac{\omega_M}{(1-\mu)\omega} < \frac{D^* + \theta_M}{D^* + \theta} \approx 8.08.$$

The system now lies in the fourth regime, because the drug levels have reached sufficiently low levels so as to inhibit the spread of neither the wild-type nor the mutant virus. The system remains in the fourth regime until the drug level is replenished at $t = t_{k+1}$, at which point this cycle begins to repeat.

The time series plot for this situation is given in Figure 6.9. Observe that it is ultimately the second-regime-type behaviour which predominates: this makes

sense, because there is a substantial amount of time within each impulsive period during which the wild-type virus is inhibited and the mutant strain is not, and the virulence of the mutant virus is not drastically poor in comparison with that of the wild-type. That is, the difference between $\tilde{k}$ and $\tilde{k}_M$ is not sufficient to allow the wild-type form to "catch up." Nonetheless, the rise of the mutant strain is slow, with the crossover not occurring until $t \approx 81$ days.

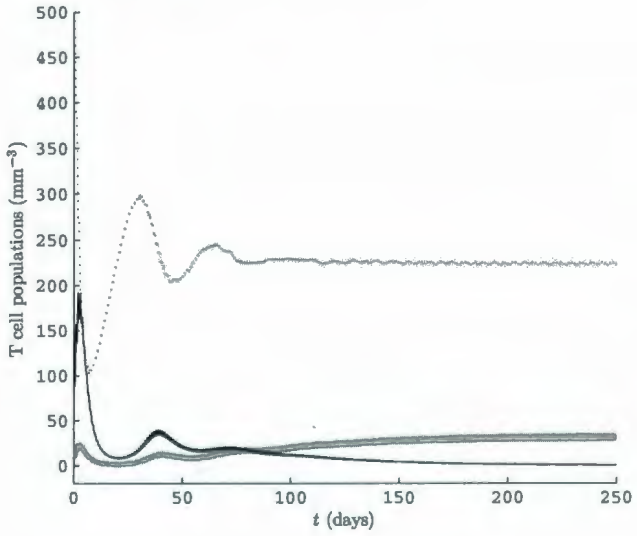

Figure 6.9: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 3.0 \times 10^{-7}$M.

This situation can be drawn out even further. The dominance of the mutant strain demands that its resistance to the drug be sufficiently great (compared to

the wild-type) so as to compensate for its reduced virulence. If the mutant is slightly less resistant to therapy than in the preceding example, it will take a much longer time to become the prevalent species of virus. Consider the system with $\theta_M = 2.0 \times 10^{-7}$M. On each impulsive period, the model follows the same evolution as described above, shifting from the first regime initially, to the second regime, and finally to the fourth regime. As shown in Figure 6.10, the overall behaviour of the system is much like that of Figure 6.9. However, in this case, the population of T cells infected by the mutant virus does not exceed the population of T cells infected by the wild-type virus until $t \approx 401$ days.

Ultimately, the resistance of the mutant strain can be lowered to such a degree that this form of the virus loses its selective advantage. At $\theta_M = 1.0 \times 10^{-7}$M, for instance, the system still goes through the same three stages already described, but now the growth of the mutant virus is sufficiently impaired that the more virulent wild-type remains dominant for all t, as shown in Figure 6.11.

Other paths through the regimes of behaviour are also possible. For instance, if the mutant virus is very resistant to the drug then it will never be controlled. If we let $\theta_M = 3.0 \times 10^{-6}$M, for example, the system begins in the second regime, since at $t = t_k$,

$$D^* + \theta_M \approx 9.0 < \frac{\omega_M}{\beta} = 18$$

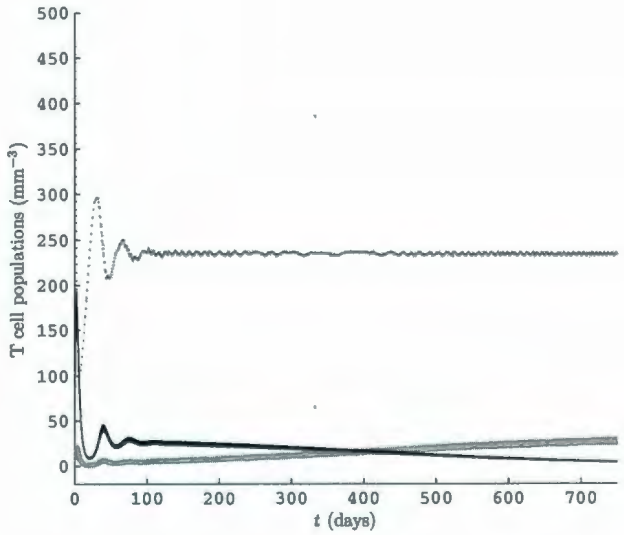

Figure 6.10: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 2.0 \times 10^{-7}$M.

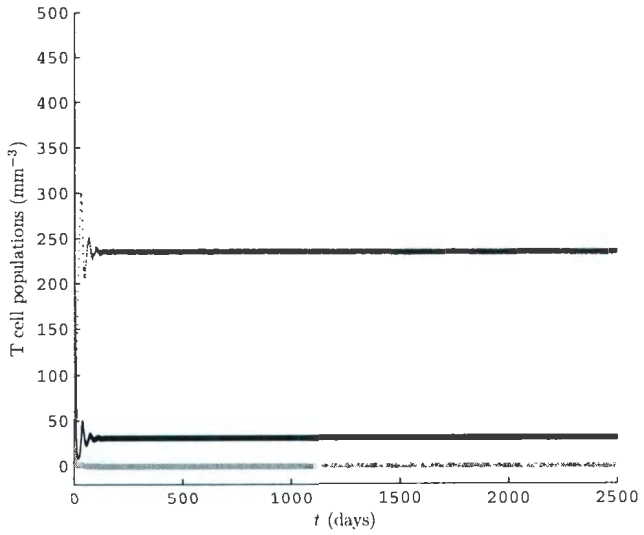

Figure 6.11: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 1.0 \times 10^{-7}$M.

and

$$\frac{D^* + \theta_M}{D^* + \theta} \approx 1.49 < \frac{\omega_M}{(1-\mu)\omega} \approx 78.9.$$

Subsequently, at $t = t_k + 0.6$, the first inequality is still obeyed, with

$$D^* + \theta_M \approx 3.0 < \frac{\omega_M}{\beta}$$

but now

$$\frac{D^* + \theta_M}{D^* + \theta} \approx 87.1 > \frac{\omega_M}{(1-\mu)\omega},$$

situating the system within the fourth regime. As a result, the mutant virus rises to prominence much more quickly than in the previous examples. This is shown in Figure 6.12.

The same routes could also be accomplished by varying $\tilde{k}$ instead. Allowing variation in the other parameters opens up still more potential behaviours for the system. We will not attempt to exhaustively catalogue the resulting variations here, but prefer to acknowledge their existence. Instead, we will now take advantage of the opportunities offered by the impulsive differential equation framework to investigate other phenomena associated with HIV and drug therapy.

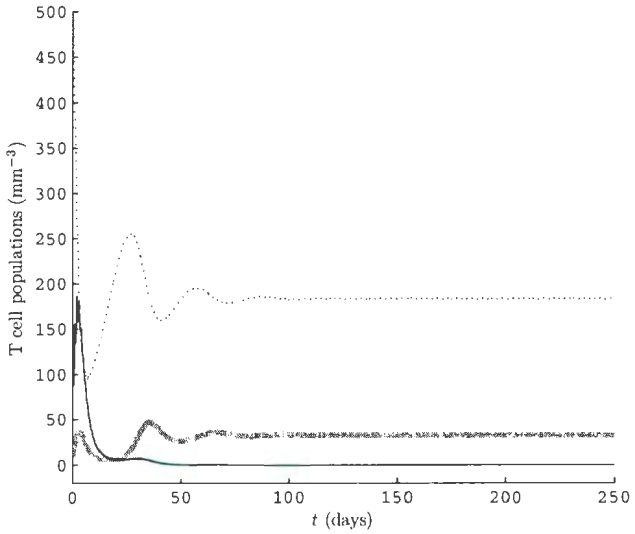

Figure 6.12: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 3.0 \times 10^{-6}$M.

6.6 The Effect of Changing the Dosing Interval

Apart from the added realism offered by the impulsive differential equation model, we now have the versatility to keep the standard parameters of the system constant and observe what happens when we vary the impulsive effect itself, specifically by altering the instances of the drug replenishment.

The most basic way of going about this is to simply change how frequently a new dose is introduced. We expect that a shorter dosage period will result in the suppression of both infected T cell populations, with the uninfected T cell population becoming increasingly resilient. Although the mutant strain will be inhibited more than at longer dosage periods, it will be less negatively affected than the wild-type, and so will become the dominant virus species more quickly. On the other hand, less frequent replenishment of the drug will cause the mutant form to lose its selective advantage: with weaker inhibition of the virus strains, the fact that the mutant is less virulent than the wild-type will result in the latter becoming the foremost virus species. We also expect the uninfected T cell population to become smaller.

To see this, consider the parameter values used to generate Figure 6.9, with $\theta_M = 3 \times 10^{-7}$M and all other parameter values as given in Table 6.1. As already noted,

with daily doses the mutant strain becomes dominant at $t \approx 81$ days. Observe also that $T(t)$ experiences small oscillations with a mean value of approximately 223.8mm^{-3}.

We begin by shortening the interval between consecutive doses. If this is reduced to 0.75 days, we obtain the time series depicted in Figure 6.13. This reflects precisely the behaviour we anticipated. The mutant strain becomes dominant over the wild-type very quickly — at $t \approx 22.5$ days, even before the transient effects of the initial conditions have become negligible. The uninfected T cell population now subsists at roughly 251.7mm^{-3}.

These effects become even more pronounced if we make the drug replenishment twice as frequent as in our baseline assumption, occurring every 0.5 days. As shown in Figure 6.14, the mutant form of the virus almost instantly prevails over the wild-type strain, while the uninfected T cell population rises to a mean count of about 332.9mm^{-3}.

Despite the increase in the frequency of drug therapy in these two examples, the mutant virus still manages to eke out a substantial (if reduced) existence, and the uninfected T cell levels are significantly below the disease-free ideal. If we allow the doses to be extremely frequent — for instance, every 0.2 days — then the drug remains at sufficient levels to completely inhibit both strains of the virus in

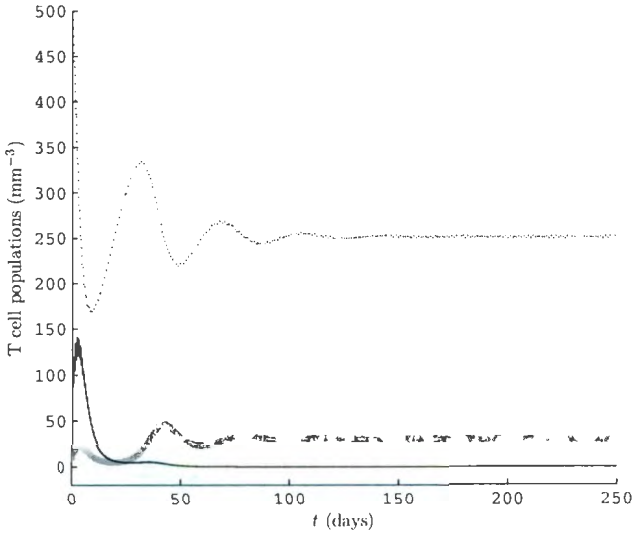

Figure 6.13: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 3 \times 10^{-7}$M and therapy occurring every 0.75 days.

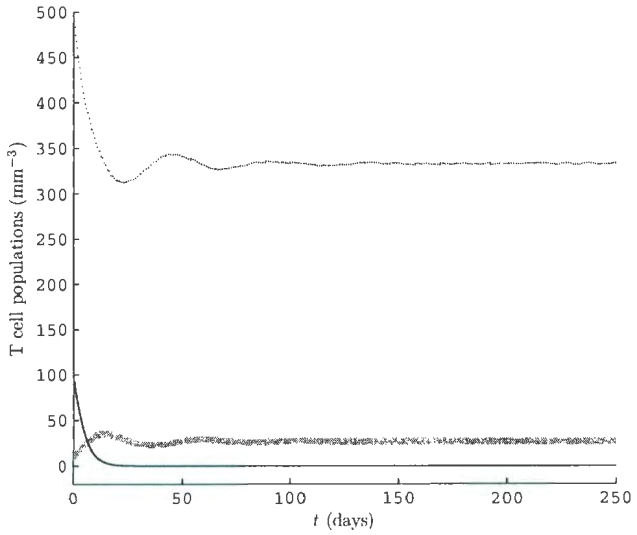

Figure 6.14: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 3 \times 10^{-7}$M and therapy occurring every 0.5 days.

the long-term. As seen in Figure 6.15, under these circumstances the uninfected T cell count slowly returns to pre-infection levels.

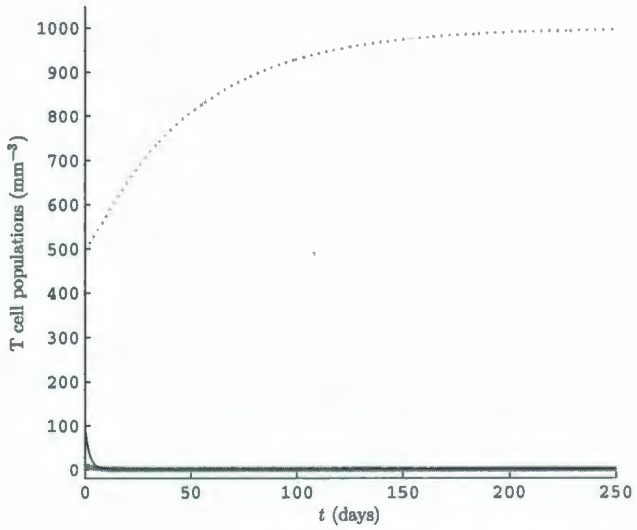

Figure 6.15: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 3 \times 10^{-7}$M and therapy occurring every 0.2 days.

Note that HIV drugs are often cytotoxic or induce other undesirable side effects in the sufferer that are not evident from the model. The idea of simply flooding the patient with these medications is therefore unrealistic.

These results are also sensitive to parameters such as the resistance of the mutant strain. For instance, if we repeat Figure 6.15 but with a much more resistant mutant ($\theta_M = 3 \times 10^{-6}$M) then we find that the mutant form again survives in

significant quantities, and the uninfected T cell count remains low. This is depicted in Figure 6.16.

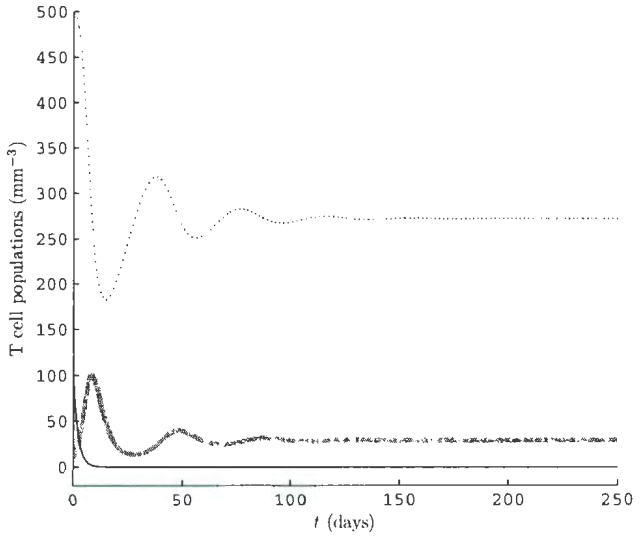

Figure 6.16: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 3 \times 10^{-6}$M and therapy occurring every 0.2 days.

Now consider some examples in which the replenishment of the drug becomes less frequent. In Figure 6.17, the period is prolonged by 5%, to 1.05 days. Observe the sensitivity of the dominance of the mutant strain to the dosage frequency: it now takes much longer for the level of the T cells infected by the mutant virus to exceed that of the T cells infected by the wild-type strain. This now occurs at $t \approx 128$ days. Less aggressively affected is the population of uninfected T cells. As

expected, its long-term mean value does fall, but only slightly, to approximately 221.3mm^{-3}.

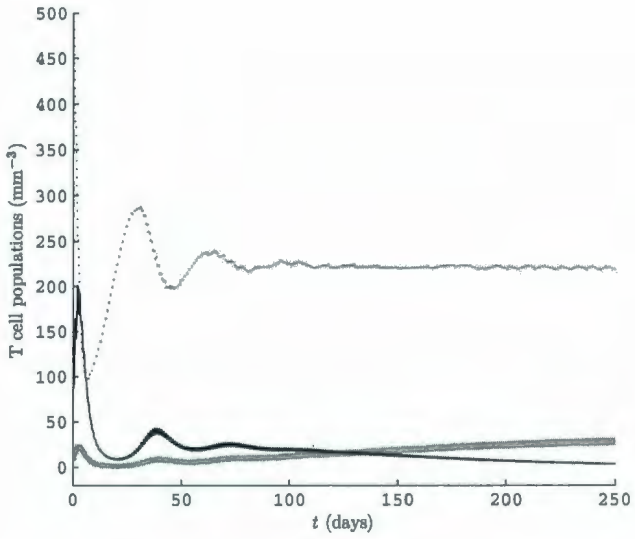

Figure 6.17: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 3 \times 10^{-7}$M and therapy occurring every 1.05 days.

Figure 6.18 depicts what happens when the period is 20% greater than our baseline value, 1.2 days. There is now sufficiently little drug introduced that the greater resistance of the mutant is no longer preferable, given its reduced virulence.

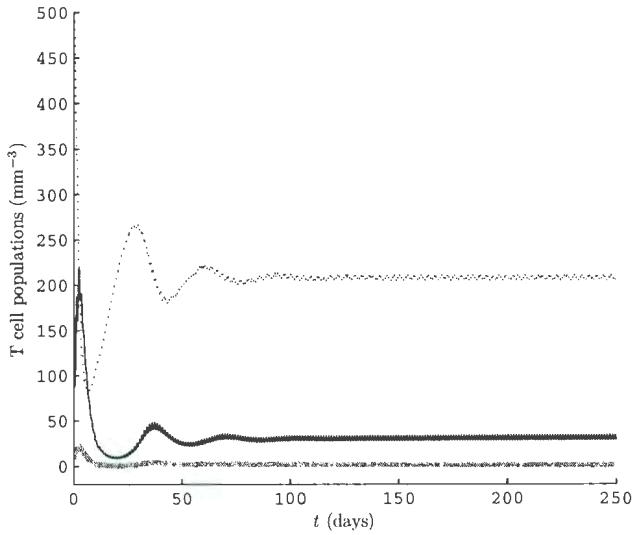

Figure 6.18: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 3 \times 10^{-7}$M and therapy occurring every 1.2 days.

6.7 Drug Holidays: The Effects of Non-Adherence to Treatment

In the preceding, we have assumed that the patient adheres perfectly to the assigned (periodic) course of drug therapy. In reality, however, there are many reasons why HIV sufferers do not follow treatment stringently — whether due to the toxic nature of the drug cocktails, the inconvenience of the regimen, or another reason. Some researchers have suggested that it is advantageous for a patient to take so-called "drug holidays" or **structured treatment interruptions**, with the principal argument for this course of action being that it stimulates the immune system to better fight the virus of its own accord [20, 22, 28–32].

Given that the framework of impulsive differential equations enforces no requirement that the impulsive moments be periodic in nature, Equation (6.3) represents a mechanism by which the effects of these drug holidays can be numerically investigated. Of particular interest is the effect of nonadherence on the population of uninfected T cells, and on the relative dominance of the two virus strains.

We will first explore what happens when z scheduled doses of the drug are missed within a given period of time. We shall conduct our investigations with the parameter data of Table 6.1 and $\theta_M = 3.0 \times 10^{-7}$M, so that Figure 6.9 represents

the "baseline" behaviour (that is, it represents the evolution of the system under perfect adherence). The most straightforward case to consider is that in which these doses are missed regularly.

First, consider what happens when $z = 20$ over a 500-day interval, such that treatment does not occur for $t = 25, 50, 75, \ldots$. This is depicted in Figure 6.19. Observe that the overall behaviour of the system does not change significantly: the population of T cells infected by the mutant strain of the virus eventually supersedes the population of T cells infected by the wild-type virus, while the population of uninfected T cells oscillates about some median value that is significantly lower than the disease-free ideal.

However, several differences in the details are apparent. First, the introduction of structured treatment interruptions causes more significant oscillations in each of the three populations. This is because the oscillations present in the perfect-adherence case still occur, but these are now superimposed upon the more substantial oscillations caused by the missed dose. The imperfect adherence shifts the system towards a different set of fixed points or impulsive periodic orbits, and once the patient returns to the established treatment schedule, the former behaviour begins to reassert itself, until the next missed dose moves it away again. This is illustrated in the magnified view of $T(t)$ provided in Figure 6.20.

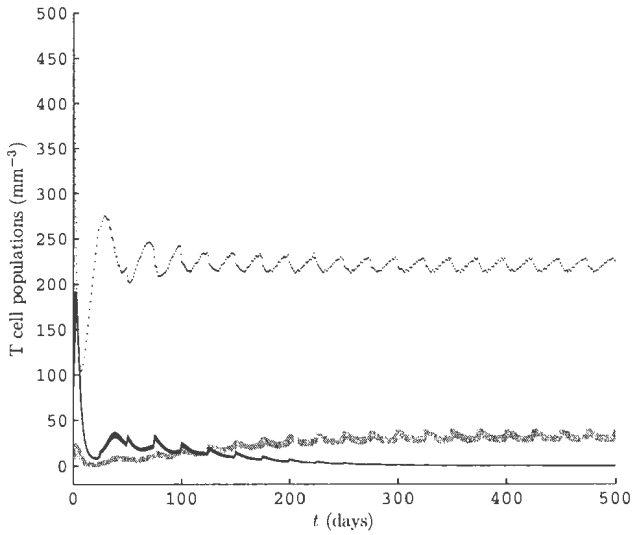

Figure 6.19: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 3 \times 10^{-7}$M and $z = 20$ missed treatments (evenly distributed).

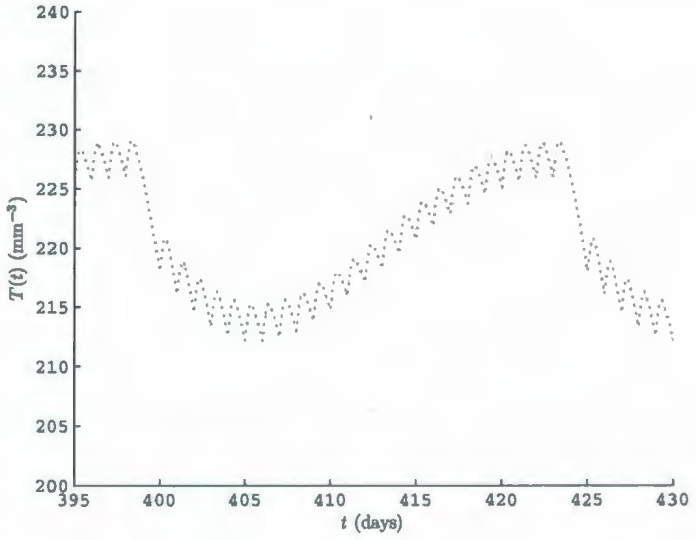

Figure 6.20: Magnified view of $T(t)$ in Figure 6.19.

The mean long-term value of the uninfected T cells becomes slightly lower as a result of the imperfect adherence, now standing at approximately 220.7mm^{-3}. Furthermore, the point at which the mutant strain of the virus comes to dominate the wild-type is much later, occurring at about $t = 114$ days. This makes sense, because there are now prolonged periods during which the mutant form loses its selective advantage.

A subsidiary question, then, is to ask how the average total population of infected T cells $U(t) + U_M(t)$ is affected by this jostling for position between the two virus strains. In Figure 6.9, the average count is 31.18mm^{-3}, while in Figure 6.19

it actually drops very slightly, to 31.12mm^{-3}. However, in Figure 6.9, the infected T cells account for 12.23% of the total T cell population; in Figure 6.19, they represent 12.36%. As we continue to investigate drug holidays, we shall return to these values as additional indicators of the success or failure of the treatment non-adherence: for example, it may be worth suffering a small drop in the uninfected T cell count in return for a significant drop in the total infected T cell population.

As a second illustration, consider the case where $z = 50$ misses over a 500-day interval. This is depicted in Figure 6.21. In this case, the shorter span of time between missed doses serves to tame the oscillatory behaviour observed in Figure 6.19: the system simply does not have enough time to (nearly) re-attain the perfect-adherence state before another missed dose occurs. The mean long-term value of the uninfected T cell population is now 216.7mm^{-3}, which again is smaller than in the preceding cases. The mutant strain does not become predominant until about $t = 350$ days. The mean long-term total number of infected T cells rises slightly to 31.40mm^{-3}, representing 12.67% of the total number of T cells.

Table 6.3 lists data for several values of z over a 500-day span. This illustrates the trend described above: as more doses are missed, the virulent wild-type plays an increasing role in the pathogenesis, and so the uninfected T cell levels drop while the total infected T cell counts ultimately rise.

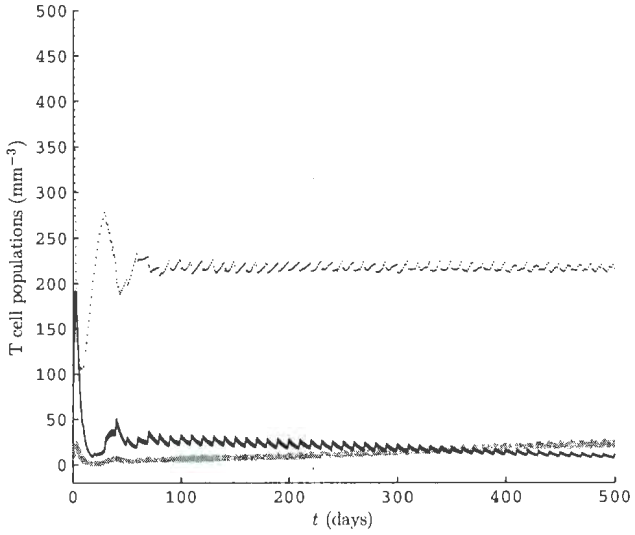

Figure 6.21: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 3 \times 10^{-7}$M and $z = 50$ missed treatments (evenly distributed).

Table 6.3: Effects of missing z evenly-spaced drug treatments over 500 days.

z	mean $T(t)$ (mm^{-3})	mean $U(t) + U_M(t)$ (mm^{-3})	% of inf. T cells
10	221.8	31.21	12.34
20	220.7	31.12	12.36
30	218.8	31.31	12.52
50	216.7	31.40	12.67
75	208.0	31.69	13.22

Of course, it is unreasonable to expect that an HIV sufferer would be so dogmatic in their non-adherence to the treatment regimen. The preceding experiments were therefore repeated, but with the missed doses assigned according to a random distribution. Figures 6.22 and 6.23 depict two different 500-day cycles, each with a different random distribution of $z = 20$ drug holidays.

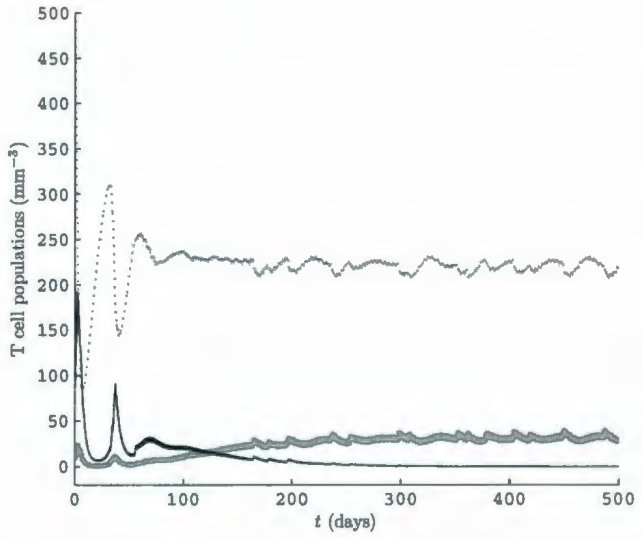

Figure 6.22: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 3 \times 10^{-7}$M and $z = 20$ missed treatments (randomly distributed).

This random distribution does, however, raise the possibility that a drug holiday might have a different effect on the overall behaviour of the system if it occurred very early in the 500-day interval, before transient phenomena arising from the

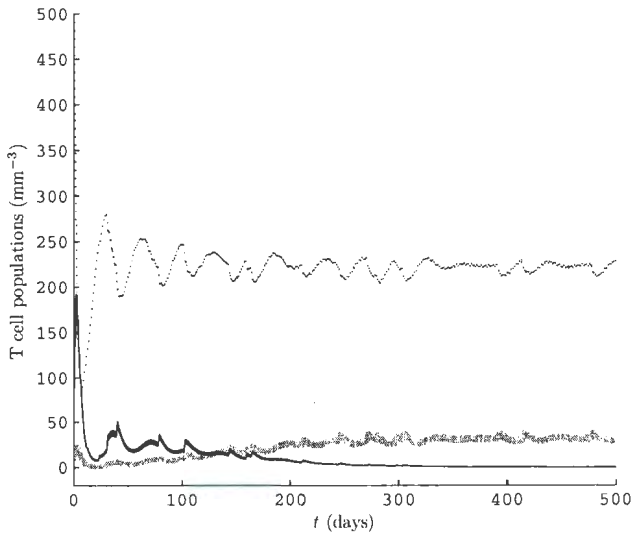

Figure 6.23: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 3\times10^{-7}$M and $z = 20$ missed treatments (randomly distributed, different from Figure 6.22).

Table 6.4: Effects of missing z randomly-distributed drug treatments over 500 days.

z	mean $T(t)$ (mm^{-3})	mean $U(t) + U_M(t)$ (mm^{-3})	% of inf. T cells
10	221.9	31.20	12.33
20	220.4	31.22	12.41
30	219.0	31.26	12.49
50	216.2	31.32	12.65
75	211.8	31.28	12.87

choice of initial conditions can still be felt. Of particular concern would be a scenario in which a number of drug holidays are clustered early in the integration. To guard against this, a randomly-distributed schedule of missed doses was fabricated. This identical schedule was then applied to several concatenated 500-day intervals (in which the final state of one cycle was used to provide the initial conditions for the next). In this manner, the effects of the original transient behaviour could be suppressed.

Table 6.4 shows the results of these numerical experiments, which are taken as the mean of a large number of trials. While the data do not deviate significantly from that of Table 6.3, note that the infected T cells uniformly represent a smaller percentage of the overall T cell count when the missed doses are randomised.

While this approach is more realistic than evenly spacing the drug holidays, it is still unsatisfactory, because drug holidays are not usually taken completely at random, either. In particular, rather than missed dosages occurring in isolation, it is likely that several consecutive dosages will be missed. As a final numerical experiment, we consider the extreme case in which all z instances of non-adherence occur sequentially, as shown in Figure 6.24. This graph indicates that having a sufficient number of treatment interruptions in succession can (temporarily) reverse the dominance of the mutant form of the virus.

Again, we wish to ensure that these results are not affected by the possibility that this grouped holiday might occur early in the given 500-day cycle. We follow the same procedure outlined above, concatenating several such intervals during which the grouped treatment interruption occurs at the same point of each iteration.

Table 6.5 shows the results of these trials. The raw numbers of uninfected and infected T cells do not demonstrate a significant change from the preceding tests. However, the infected T cells do represent a smaller percentage of the total T cell population than in cases where the drug holidays are randomly distributed. This is particularly apparent in comparing these results to the case where the drug holidays are evenly spaced.

We can now draw two conclusions from these numerical investigations of non-

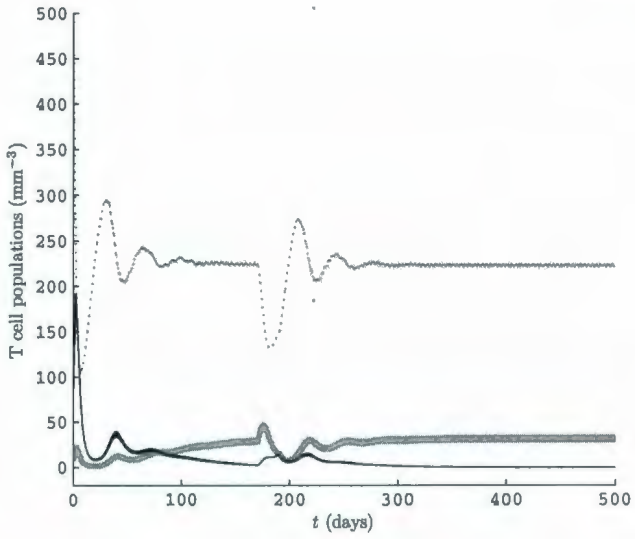

Figure 6.24: Time series for $T(t)$ (dotted line), $U(t)$ (black line), $U_M(t)$ (grey line) with $\theta_M = 3 \times 10^{-7}$M and $z = 20$ missed treatments (consecutive, beginning at $t = 171$ days).

Table 6.5: Effects of missing z consecutive drug treatments over 500 days.

z	mean $T(t)$ (mm^{-3})	mean $U(t) + U_M(t)$ (mm^{-3})	% of inf. T cells
10	222.5	31.10	12.26
20	221.9	31.14	12.31
30	221.1	31.19	12.36
50	218.8	31.26	12.50
75	217.9	31.27	12.55

adherence to therapy using the model represented by Equation (6.3). First, the effect of structured treatment interruptions is small in the context of the ramifications for the HIV pathogenesis. Second, as indicated by Tables 6.3, 6.4 and 6.5, drug holidays are less harmful if they occur closely together than if they are staggered.

Chapter 7

Concluding Remarks

In this work, we have presented three new models for HIV drug therapy in the presence of both the wild-type virus and a resistant mutant strain. In particular, the IDE model offers the opportunity to both analyse and numerically simulate different treatment regimens within a mathematical framework. We have gone to some length to investigate and explore these models from the perspectives of both dynamical systems and rigorous computation.

Inevitably — and, perhaps, encouragingly — many other avenues of research present themselves, both in terms of further study of the models constructed in this work, and of refining and augmenting these models to exhibit more sophisticated behaviour. In this final chapter, we enumerate some of these possible directions.

7.1 Global Dynamics of the ODE System

Although we have provided a thorough and rigorous stability analysis of the ordinary differential equation model given by Equation (4.3), these results possess certitude only on a local scale. What we were not able to accomplish in this work was an analysis of the global dynamics of the system. For example, we wish to establish that none of the functions $T(t)$, $U(t)$ or $U_M(t)$ become unboundedly large under any feasible parameter values. A global stability analysis — presumably using the standard framework of Lyapunov functions and the LaSalle Invariance Principle (as in, for example, Guo [33]) — is a desirable next step to enhance the sophistication of the mathematical understanding of Equation (4.3).

7.2 Delay Differential Equations

As briefly mentioned in Chapter 3, another powerful tool for modelling HIV pathogenesis is delay (or functional) differential equations, in which the differential equation involves both the current state of the variables as well as one or more past states. Delay differential equations can arise in HIV models in several ways: for instance, they could represent the pharmacological delay (that is, the fact that a drug will not affect the system immediately, but will take time to be absorbed

by the body) or the viral eclipse phase (the interval between the infection of a T cell by the virus and the production of nascent virions from the newly infected cell). These phenomena have been considered in various previous models [34–36] but the possibility of combining both a delay and an impulsive effect opens up a new realm of investigation.

7.3 Sophistication of Drug Therapy Non-Adherence Patterns

We were unable to find authoritative research on the pattern of behaviour amongst HIV sufferers who exhibit imperfect adherence to drug therapy. For instance, would such a patient typically miss just two consecutive doses? Or a full week? Or more than that? What is a reasonable interval between drug holidays, during which the patient remains adherent? Improved knowledge of these patterns — if, indeed, such patterns exist — would provide greater focus to the investigation of treatment interruptions using the impulsive differential equation model of Equation (6.3).

7.4 Generalisation of the Model to Encompass Other Classes of IDE

As noted in Chapter 2, the framework of the impulsive differential equation admits more general impulsive moments than those utilised here. In particular, rather than assigning the impulsive effect to occur at prescribed moments t_k, it is possible instead to stipulate that the impulse will occur when certain criteria are met. For example, this approach could be utilised to model the scenario wherein a new course of drugs is not taken according to a strict schedule, but is only begun when the T cell count falls below a given level. Comparison of the results of such an impulsive scheme with those of Equation (6.3) could offer considerable insight.

7.5 Further Analysis of the Model with Impulses

Although this work does provide some analysis of Equation (6.3), the rigorous study of impulsive differential equations (except under special circumstances, or through numerical simulations) remains a formidable challenge. The body of knowledge concerning IDEs is still at a fairly nascent stage, but the utility of the model presented here offers encouragement to advance the frontier

of knowledge of this subject. Certainly, additional analytical results would be invaluable in better understanding the role that the impulsive effect plays in the behaviour of the present model.

7.6 Incorporation of Additional Immunological Phenomena

As discussed in Chapter 3, there are many aspects of the immune system which are not dealt with (or which are dealt with in only a very homogenous way) in Equations (4.3) and (6.3). Components such as $CD8^+$ T cells, macrophages and other phagocytes, and long-lived lymphocytes arguably play a crucial role in the HIV pathogenesis, and therefore it may be important to incorporate their effects into the models in a more sophisticated manner. Similarly, the models could be augmented with the inclusion of other HIV-related phenomena, such as latently-infected cells.

7.7 Restoration of Explicit Virus Populations

Finally, we could revisit the simplifying assumption that the infected T cells and corresponding virus populations are proportional to each other. As previously indicated, this would complicate the analysis of the model: Equation (4.3) would grow to include five ODEs (because separate equations would be needed for both the wild-type virus and the mutant strain), while Equation (6.3) would involve at least six equations and potentially more, even exhibiting multiple impulsive effects if different types of inhibition were incorporated, as in [18]. However, the dismissal of a simplifying assumption always raises the possibility of lending added accuracy to the model, and from there offers even more opportunities for further study, possibly in conjunction with some of the other ideas discussed in this chapter.

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