IMMUNE RESPONSE MODELS OF HIV INFECTION AND TREATMENT

By

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To my father, for believing I could do anything, and my mother, for reminding me that what I do does not define me

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Immune Response Models of HIV Infection and Treatment

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Abstract

The role of the natural host immunity (sometimes called the *immune response*) to HIV infection has received much attention in recent years. It is clear that some patients progress to AIDS much more rapidly than others, and the specific immune response to HIV has been shown to be an important determinant of the rate of disease progression (or non-progression). In this thesis, we examine control theoretic mathematical models of HIV and its interaction with the immune system. We derive a system of ordinary differential equations that specifically incorporates patient immunity as a dynamic variable and introduce a control function to reflect the level of treatment intervention. We establish existence and continuity of an optimal control, characterise it, and show uniqueness of the optimality system. Numerical simulations of the optimality system are examined so as to determine the qualitative aspects of optimal treatment schemes, and the behaviour of the immune system under such an optimal regime. Extensions to the model are examined, and results are compared with those obtained from models not including immunity. Finally, a new model incorporating the nutritional status of the patient and its interaction with drug therapy and the immune system is considered.

Chapter 1

Introduction

In the past two decades, over 200,000 journal articles pertaining to AIDS and/or the human immunodeficiency virus (HIV) have been published. Among these are hundreds of mathematical and statistical models of various aspects of the disease.

Epidemiologists attempt to qualitatively assess the spread of an infection throughout a population using quantitative and theoretical means. Many of the early models of HIV/AIDS were developed to predict how the disease would spread outward from its original risk groups. Many epidemic models have been studied, and are still being studied. They model heterosexual and homosexual spread of virus, spread within prisons, vertical (mother-to-child) transmission, and many more aspects of this complex disease. Mathematical epidemiologists are able not only to predict with a certain degree of accuracy where an infection will go next, but also to determine using models just how much of an initial innoculum is needed for a disease to establish a persistent presence in the population under consideration. Also, using epidemic models, it is possible to simulate treatment and/or vaccination schedules in a persistently infected population, and, therefore, determine how and if it is possible to eliminate or at least significantly reduce the contagion.

Another aspect of mathematical modelling that is coming to the forefront of current research is immunological modelling. It is similar to epidemic modelling in that we are simulating populations of infected and healthy individuals, but in this case the individuals are cells and viral particles. Immunological modelling of HIV is a popular subject, due in part to the large volume of experimental evidence available, but more importantly, with the technology that we now have to determine how a pathogen behaves on a cellular level, we

can accurately describe its evolution in time using mathematical models.

Another reason HIV is a popular subject for modelling is its long latent period. A good model can predict what will happen in the long term very accurately and, with this, we can describe the progression to disease of a pathogen that does not immediately cause any noticeable effects and whose behaviour as a consequence is hard to predict.

In this thesis, we will examine HIV from the perspective of its interaction with the immune system. We will be investigating the role of the cytotoxic immunity to infection. But most importantly, we will be examining the qualitative effect of various treatment strategies on the components of the immune system that are most actively involved in responding to the virus. To that end, in the following section we briefly describe biologically how the immune system reacts to infection with HIV.

1.1   The Immune System and HIV

To accurately model any physical process, we must first understand how it works on its basic level. As its name indicates, the *human immunodeficiency virus* targets cells in the immune system.

Our "immune system" refers to a collection of cells and organs that work together synergistically. In its broadest sense, any part of our body that helps to keep us healthy is a component of the immune system. For the purposes of this thesis we consider the immune system as it consists of *lymphocytes* (white blood cells) and their sources. (See [31] for more background on the immune system.)

One class of white blood cells is the collection of *T-cells*, so called because they mature in the *thymus*, after originating in the bone marrow. The types of T-cells with which we shall be concerned are the CD4+ (*helper*) T-cells, and the cytotoxic lymphocytes ("CTL"s), which are activated CD8+ cells.

When an infectious agent enters the body, memory cells recognise this infection as *non-self* (that is, not a natural occurrence within the host's body). Helper T-cells are cells that can be considered as "messengers", or command centres of the immune system — they send a signal to other immune cells that an invader is to be fought. These other cells include, as the case may be, CTLs and macrophages (which destroy the invader) and B cells (which produce antibodies against the present invader and the possibility that this invader

may again enter. In this thesis, we will refer as "CTLs" those cells whose function it is to destroy infected CD4+ cells, and retain memory of this function.

If the immune system is functioning optimally, all of these components work together in an efficient manner and an infection is eliminated in short order, causing only temporary discomfort to the host. However, there are many ways in which the immune system may malfunction. In stressed or malnourished individuals, both types of T-cell response may be weakened and simple infections cannot be fought off. In autoimmune diseases, the body no longer differentiates between *self* and *non-self*, and immune cells are confused into attacking normal parts of the host. (This is similar to what happens in an allergic reaction.)

In the case of HIV, the specific concern lies with the helper T-cells. These cells (among others, including macrophages) express a CD4+ protein on their surface. HIV contains a CD4+ receptor and hence binds to these cells and infects them. Over time, it is able to deplete the population of CD4+ cells. The exact mechanism by which this occurs remains unknown, but several models have been suggested. See Kirschner, Webb and Cloyd [39].

Clearly this is a problem, since without the "immune messengers", none of the disease-fighting cells are aware that an invader is to be attacked. Therefore, infections that would be eliminated easily in a healthy individual eventually wear the patient down and cause death.

Pioneering mathematical models considered the eventual effect of HIV upon the population of CD4+ cells and early simulation of treatment considered how to maximise levels of these cells, and sometimes reduce virus levels. A classical and much-cited model is that of Perelson, Kirschner and deBoer [57] in 1993, which considered four populations of cells, each represented by a variable dependent upon time: healthy CD4+ cells, latently and actively infected CD4+ cells, and free virus. The evolution in time of each population is represented by a differential equation. Early treatment models ([35], [37], [73]) considered the effects of AZT and similar drugs, which reduce the infectivity of infected cells by halting the process of reverse transcription (a key part of HIV's replication process, whereby the genetic material is transcribed from RNA to DNA). Later, with the advent of protease inhibitors, researchers were able to investigate mathematically the effect of a drug that reduces the production rate of free virus (see [74], [76], [6], [36]). In Chapter 2, we will explain this concept further, and provide mathematical illustration.

Many early models did not include any specific expression for immunity to HIV, as

it was assumed to be constant over time. By "immunity", we mean (in this thesis) the ability of killer cells to actually recognise *and* eliminate the invader, as measured by actual numbers of these cells, their fitness, or both. These cells are the *cytotoxic lymphocytes* — or CTLs, the term we will henceforth use in this thesis.

However, it has been noted clinically for some time (see Gray et. al. [24], Arnaout, Nowak and Wodarz [2], Ogg et. al. [54], Wein at. al. [73], and references cited therein) that individuals who maintain a high level of CTLs remain healthy longer, in spite of the fact that HIV does not target these cells directly.

With these complexities in mind, and considering that the treatment strategy of "hit hard, hit early" that was so popular in the early days of combination drug therapy is now seen as potentially harmful, due to concerns of toxicity, expense, and the sheer burden of adherence to some of the strict protocols enforced upon individuals who choose to undergo therapy, it is obvious that optimal drug treatments schemes may not be so straightforward.

Certain strategies have been suggested to help deal with these problems. One is to allow periodic intervals of no treatment to allow the population of CTLs to rebuild to pre-treatment levels. Antigenic boosts to the immune system — in which a small amount of antigen is introduced into the host to fool the immune system into believing a new infection has occurred, and therefore mount a substantial response — is another. Non-monotonic levels of drugs, and delaying treatment until CD4+ levels are quite low and/or virus levels are quite high, are among the other options available.

1.2 How Models can Help

Given so many different possible regimes, and so much uncertainty as to which is best, we need a way to help narrow our options. One tool that can assist is an accurate mathematical model. We shall consider systems of differential equations in this thesis, although other types of models exist (stochastic models, which account for random effects, or computer models to deal with very large systems not tractable "by hand", are two examples). Differential equations model the evolution in time of populations of cells, and thus may help to track the long-term progression of infection, and determine when and if an equilibrium is reached, and whether it is stable. In general, it is desirable for an equilibrium point to be stable. We shall see systems in which there is a "healthy" equilibrium (no infection present)

and an "endemically infected" equilibrium (both healthy and infected cells co-exist). Usually, it is unrealistic to expect the healthy equilibrium to be stable once infection has been introduced into a system. The most that we can hope for in this case is stability of the infected equilibrium, so that healthy cells do not crash to zero.

Interesting — and most often undesirable — behaviour occurs when an infected equilibrium is driven unstable. There are many ways in which this can happen, including restabilisation of the healthy equilibrium. The real problem occurs when an equilibrium is driven unstable and periodic solutions are born. We shall see instances in which the presence of a time delay causes this to occur. Biologically, this means that our cell populations are oscillating, which can cause real problems if either infection peaks at too high a level, or healthy cells "trough out" at too low a level. In this case, it would be desirable to figure out if and how it is possible to restabilise the equilibrium.

A good model will predict with some accuracy the long-term course of infection. We seek steady states (equilibria), at which the cell populations remain relatively unchanged for some time. Including treatment in models can be done in several ways. A new "forcing" function can be introduced, or a parameter that mimics the effect of the drug can be inserted into the model.

In this thesis, we use two methods of modelling therapy. We compare treatment as approximated by a constant parameter with treatment as represented by a control. In the latter case, we use the tools of *optimal control theory* to determine treatment strategies. We let our drug be represented by a function that satisfies certain restrictions, and use *Pontryagin's Maximum Principle* to characterise the optimal control and derive the optimality system, which describes mathematically how the system representing the infected immune system behaves subject to optimal treatment. More background to optimal control theory will be given as it is needed. We refer to the excellent text by Fleming and Rishel [22] for further background to optimal control theory.

We shall examine various models of HIV infection. The two primary models are a model with and a model without an explicit compartment modelling immune response. The reason for doing this is so that we can compare the behaviour of the models, both untreated and subject to therapy. This will help provide a theoretical answer to the question: How important is specific immune response in the progression of HIV infection?

In the models that we will examine in this thesis, we assume that infection is spread directly from cell to cell is an important mode of HIV spread. There is precedent for studying cell-to-cell spread of HIV, since the virus is present in high concentrations in compartments such as the brain, bone marrow, and lymph tissue. See, for example, Chun et al. [10], Haase et al. [26], [27], Pantaleo et al. [55], Schacker et al. [61], Spouge et al. [66]. In such cases, it is highly probable that the close proximity of cells and the absence of blood plasma would render cell-to-cell spread the dominant transmission method. Additionally, we find that the dynamical behaviour of the models assuming cell-to-cell spread is qualitatively similar to that of those assuming a separate compartment for free virus. We further justify this assumption by noting that viral load is proportional to levels of infected cells (see [2]), and that we may thus estimate total body virus load from levels of infected cells.

In summary, the following are questions that, ideally, we would like to answer in this thesis:

- The role of immunity cells appears to be important in the progress of infection. Given this fact, how does the immune system react to HIV?

- What sort of drug treatment schemes are optimal in order to maintain a high level of immunity to HIV?

- Does the intracellular "latent" period affect the stability of the untreated models? If so, how do we treat? Will optimal treatments be very different from the case in which delay is not considered?

- How different should treatment be when we do consider immunity than when we do not?

- How do we deal with the intimate interplay between the nutritional status of the patient and their drug therapy? Specifically, what can we do to deal with the fact that medication has a negative effect on nutritional status, which is important for proper immune function?

This thesis shall be structured as follows:

- In Chapter 2, we will review four already-published models of HIV treatment. Three are control-theoretic in nature, but do not include immune response. The fourth does include immunity but is solved numerically.

- In Chapter 3, we will present an ODE model that is a modification of Wodarz and Nowak's [76] immunity model. We analyse stability of the ODE model and then introduce treatment via a control which we characterise completely, as well as presenting existence and regularity results for the optimal control, as well as uniqueness results for, and numerical simulations of the optimality system. We will observe the shape of the curve representing treatment so that we can determine the *qualitative* aspects of optimal treatment, in terms of strength of treatment as a function of time.

- In Chapter 4, we modify Chapter 3's immunity model. There is a biological time delay in the intercellular infection process, and we examine this via a delay-differential equation system. We present results on stability and bifurcation using the general characteristic equation for such a system, and apply these results to our specific system.

- In Chapter 5, we examine treatment of the delayed systems in Chapter 4 in two ways. First, we assume that treatment can be approximated by a parameter that suppresses the intercellular infection rate. We find that this parameter actually restabilises a system that has been destabilised by delay. We also approach treatment from a control theoretic perspective, deriving an optimal control and an optimality system for both discrete and distributed delayed cases. While it is possible to derive an optimality system in the case that we have a discrete delay, it is not generally possible to analyse the optimality system to the extent that we would like. The best we can usually hope for is to determine when and if delay-induced bifurcation occurs. A much more tractable method is to use a distributed delay and then apply the linear chain trick to transform our three-dimensional delay differential equation system into a four-dimensional ODE system. The problem then becomes one of controlling a four-dimensional system of ODEs.

- In Chapter 6, we consider a model of cell-to-cell spread of HIV that does *not* include immunity. We wish to completely analyse the model in the presence and absence of treatment. We first consider stability of the ODE model and then consider how treatment approximated by a constant parameter affects this. In the following section, we include the effect of delay and determine that delay-induced bifurcation does occur, under realistic parameter ranges. This is, as in Chapter 5, offset by "high

enough" treatment levels, as we find that the region of absolute stability for the interior equilibrium is directly proportional to the value of the treatment approximation parameter. Also, we consider theoretical aspects of optimal control of the delayed system.

- In Chapter 7, we present a model of HIV treatment that incorporates the patient's nutritional status as a variable. This is done because it is clinically evident that the higher the patient's nutritional status, the better the patient fares in terms of both clinical and surrogate markers. However, large doses of drugs cause rapid elimination and poor absorption of nutrient in the patient. We model this interplay and attempt to determine what, if any, restrictions we must place upon treatment in order to minimise these negative effects. We conclude by proposing an optimal control model for this problem.

- In Chapter 8, we present our conclusions and suggest possible extensions to the models presented.

As a final note before we proceed, we would like to point out that this is primarily a mathematical thesis. However, we approach it from the perspective of attempting to answer biological questions using mathematics. Effort will be taken to explain biological relevance wherever possible, but in some cases a mathematical result may be presented because it is of interest for its own sake.

Chapter 2

Review of Some Earlier Models

To date, many mathematical models of drug treatment of the human immunodeficiency virus (HIV) have been developed. Some models in the mid-1990s focused on modelling AZT treatment (see, for example, Kirschner and Webb [37], or Kirschner and Perelson [35]). However, as our understanding of HIV's dynamics has changed, so too have treatment strategies. Drug treatment has evolved and is becoming ever more sophisticated. Multiple-drug therapy has become the standard of care.

There are many different possible regimes for drug treatment of HIV, and ideas as to which is best have varied over the twenty-plus year history of AIDS. When AZT was introduced in 1987 there was hope of its being a "magic bullet", and patients swarmed to their doctors and pharmacists to get their prescriptions. However, the Concorde Trial [63], still one of the largest-scale and longest-term clinical studies of anti-HIV medication, showed no benefit to early AZT treatment. Indeed, by the early 1990s, it was apparent that many patients were not deriving the benefit from AZT they had hoped.

AZT (*azidothymidine*) is one of a class of medications referred to as *nucleoside analogue reverse transcriptase inhibitors* (NRTIs). Reverse transcriptase is an enzyme contained in HIV that transcribes its RNA to DNA, thus enabling replication of the virus. AZT and other NRTIs work by interrupting this process in the following way: RNA and DNA are composed of chains of the nucleotides adenosine, cytosine, guanine, and thymidine, each of which has two links. One is on either "end" of the nucleotide, so they can link together much like a train. AZT is an analogue of the nucleotide thymidine ("T"), but it contains only one link. Therefore, it attaches onto another nucleotide in the chain in the place where

thymidine is *meant* to be, and its free "end" contains no link for any other nucleotides to attach. This is how it interrupts the production of DNA chains, and hence prevents viral replication at this point. Other NRTIs such as ddI (Zerit) and ddC work similarly.

In the years to follow AZT's approval by the FDA, several other reverse transcriptase inhibitors were approved, some of which are NRTIs and others that are not. These drugs have met with varying degrees of success and patient tolerance, but it was not until the advent of protease inhibitors in the late 1990s that any sort of sustained hopefulness arose.

Protease inhibitors are not a new concept — they have been used for years to treat diseases such as hypertension and arthritis, among others. In the case of HIV, they work by inhibiting HIV's aspartyl protease, which is needed to cleave bonds between nine different proteins during HIV's reproductive cycle. In essence, they render any newly created viral particles non-infectious.

Mathematically, an RTI has classically been represented by a function (a parameter or a control) multiplying the infection rate and a protease inhibitor by a function reducing the production rate of new viral particles. (See Perelson and Nelson [58] for more information on using mathematics to describe the different ways of modelling drug treatment.) In a model of cell-to-cell infection such as we will see, a parameter reducing infectivity may be used to model the effect of either drug, given the assumption that viral load is proportional to infected cells (see Arnaout et. al. [2]).

In this chapter, we consider some models of HIV treatment that have already been published, and describe how our models introduce something new.

Several different means have been used to model treatment. Some authors have published mathematical models of HIV treatment using control theory (see Kirschner, Lenhart and Serbin [36], Wein, Zenios and Nowak [73], and Fister, Lenhart and McNally [21]). However, none of these papers has included immunity as a specific compartment. In 1999, Wodarz and Nowak [76] published a four-dimensional ordinary differential equation (ODE) model of the interactions between T-4 cells, viral load and immunity (both precursor or "memory" cells and effector immunity cells). They assumed that treatment negatively affects the population of immunity cells and modelled treatment numerically by running simulations of their ODE model with a parameter that reduces viral infectivity to represent treatment. Their conclusions were that interruption of therapy (to allow the immunity to rebuild after being suppressed by chemotherapy), or antigenic boosts to the immune system,

would be beneficial to the long-term clinical outcome of the patient.

In this chapter, we shall review the four models mentioned above and their conclusions. In the remainder of this thesis, we shall modify the models. Bearing in mind that this is primarily a mathematical thesis, our goals nevertheless include deriving some conclusions as to how we can best maintain optimal levels of cells we want (healthy $CD4^+$ cells and immunity cells), given the nature of chemotherapy available.

Now, we shall introduce some of the models that have been established in the literature.

2.1 Model 1

In 1996, Kirschner, Lenhart and Serbin [36] published a modification to the original HIV-dynamics model published by Perelson, Kirschner and deBoer [57], which modelled the interactions between healthy $CD4^+$ cells ($T(t)$), latently and productively infected $CD4^+$ cells ($T^*(t)$ and $T^{**}(t)$ respectively) and free virus ($V(t)$). Healthy T cells are produced at a rate s, die at a rate μ_T, grow at a rate r to a carrying capacity of T_{max} and are lost to infection at a rate k_1. Latently infected cells are produced from free virus at a rate k_1, decay at a rate μ_T and become productively infected at a rate k_2. Productively infected cells die by bursting (lysis) at a rate μ_b, and each bursting particle releases an average of N virions, so this is the source term for free virus. Free virus is lost by infecting T cells at a rate k_1 and dies at a rate μ_V.

In the absence of treatment, the model has two equilibria of interest: a healthy equilibrium with maximal levels of healthy T cells and zero levels of all other populations of cells, and an "endemically infected" equilibrium, with all populations at positive levels. It was shown in [57] that N, the average number of infectious virions produced, is a bifurcation parameter. If N is below a critical value N_{crit}, persistent infection cannot be established and the healthy equilibrium is stable, whereas if $N < N_{crit}$, the infected equilibrium becomes stable. Therefore, the goal of a mathematically modelled treatment should logically be to reduce N by as much as we can. Indeed, we shall see that this is how the problem is formulated.

Chemotherapy is introduced into an infected immune system, and an optimal chemotherapy strategy is solved for in terms of a control representing the percentage of effect the chemotherapy has on viral production.

Treatment is modeled by a drug reducing viral production. The optimal control problem is given by:

$$\max J(u) = \int_{t_{start}}^{t_{final}} [T(t) - \frac{1}{2}B(1 - u(t))^2]dt \qquad (2.1.1)$$

subject to the state system:

$$\frac{dT}{dt} = s - \mu_T T + rT(1 - \frac{T + T^* + T^{**}}{T_{max}}) - k_1 VT \qquad (2.1.2)$$

$$\frac{dT^*}{dt} = k_1 VT - \mu_T T^* - k_2 T^* \qquad (2.1.3)$$

$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_b T^{**} \qquad (2.1.4)$$

$$\frac{dV}{dt} = u(t)N\mu_b T^{**} - k_1 VT - \mu_V V. \qquad (2.1.5)$$

So the control $u(t)$ is the multiplier for the parameter N representing viral production. The objective functional has the effect of maximising retention of T-4 cell levels while minimising the cost in the sense that high concentrations of drugs can lead to resistance, because the body has "grown used to" the drug. In some cases prolonged treatment can even cause the drugs to become toxic to the system. Both of these effects are to be avoided, so the authors of [36] control those as well.

$(1 - u)^2$ represents the cost and B is the weight on the benefit and cost. The authors of [36] applied the Pontryagin Maximum Principle to the constrained control problem in order to determine the optimal u^* which maximises $J(u)$. They found the optimal control to be:

$$u^*(t) = \left(\frac{\lambda_4 N\mu_b T^{**} + \omega_1 - \omega_2 + B}{B}\right)^+,$$

where $a^+ = \max(a, 0)$.

Simulations performed by the authors of [36], in addition to analysis of the analytical results reproduced above, reveal the optimality of earliest treatment, coupled with a dynamic treatment where the initial dosages are strong and lessen over the course of treatment. This is one way in which a control — rather than simply a parameter that remains

constant for a fixed time period — is advantageous. Mathematically speaking, optimal treatments were, in general, monotone decreasing over the time interval of treatment. In the case where treatment was initiated 800 days after infection, there was a small peak in the drug level very shortly after initiation, after which the control was monotone decreasing. In both other scenarios (1000 and 1200 days after infection), the optimal control was monotone decreasing. Balancing effects to T-4 cell counts with drug cost, the earliest treatment is best, and furthermore, is always best no matter the length of treatment interval.

2.2 Model 2

In 1999, Fister, Lenhart and McNally [21] proposed a controlled model similar to that of Kirschner, Lenhart and Serbin (our "Model 1"), with a few differences. First, their drug multiplied the infectivity rate, a formulation that may be more appropriate for describing a reverse transcriptase inhibitor than a protease inhibitor (see [58] for further background on how to model different anti-HIV drugs). Also, they established more theoretical mathematical results, including existence of an optimal control and uniqueness of the optimality system. They sought to maximize T cells and minimise cost and as such their problem was formulated as:

$$\max J[u] = \int_0^T (T(t) - \frac{Bu(t)^2}{2})dt$$

subject to the state system:

$$\frac{dT}{dt} = s - \mu_T T + rT(1 - \frac{T + T^* + T^{**}}{T_{max}}) - (1 - u(t))k_1 VT \qquad (2.2.6)$$

$$\frac{dT^*}{dt} = (1 - u(t))k_1 VT - \mu_T T^* - k_2 T^* \qquad (2.2.7)$$

$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_b T^{**} \qquad (2.2.8)$$

$$\frac{dV}{dt} = N\mu_b T^{**} - k_1 VT - \mu_V V. \qquad (2.2.9)$$

In addition to establishing existence, they completely characterised their optimal control as:

$$u^*(t) = \min(1, \frac{k_1 V T (\lambda_1 - \lambda_2)^+}{B}).$$

(Note that $\lambda_{1,2}$ are the adjoint variables.)

They also performed numerical simulations indicating that strength of treatment should balance with duration (that is, the longer the treatment length, the smaller the dose should be). As well, optimal treatment schemes are monotone decreasing.

2.3 Model 3

In 1998, Wein, Zenios and Nowak [73] constructed a model which allowed for viral mutation and the ability for the clinician to choose, at any time point during treatment, to change treatment (hence the term "dynamic"). Their model assumed treatment that corresponds to different combinations of reverse transcriptase inhibitors.

The model itself is of high dimension, allowing for I different strains of virus and hence $2I + 1$ equations (I each for virus and infected cells, plus one for healthy cells). Assuming J different possible drugs, their control variables satisfied:

$$\sum_{j=1}^{J} d_j(t) \leq 1$$

$$d_j(t) = 0, 1,$$

where a value of 1 means the drug is applied at time t and 0 means that it is not. $x(t)$ represents healthy T-cells, $y_i(t)$ are cells infected by virus strain i and $v_i(t)$ is virus strain i. They also included efficacy of drug j on virus strain i by the parameter p_{ij}, and infectivity of the strain, represented by β_i. As well, q_{ij} represents mutation rate, or the fraction of reverse transcriptions of strain i resulting in a cell infected by strain j. π_i is the replication rate of strain i. Other parameters include λ, the source of healthy T-cells, μ, the natural death rate of healthy T cells, α_i, the death rate of cells infected by strain i, and k_i, the death rate for virus strain i.

Finally, the treatment is modelled as follows. The objective functional sought to be minimised represents the amount of virus in the system and hence the problem is formulated

as:

$$\min J = \int_0^T \sum_{i=1}^I v_i(t)\,dt$$

subject to the state system:

$$\frac{dx}{dt} = \lambda - \left(\mu + \sum_{i=1}^I \beta_i v_i(t)\left[1 - \sum_{j=1}^J p_{ij}d_j(t)\right]\right)x(t)$$

$$\frac{dy_i(t)}{dt} = \left(\sum_{k=1}^I q_{ki}\beta_k v_k(t)\left[1 - \sum_{j=1}^J p_{jk}d_j(t)\right]\right)x(t) - \alpha_i y_i(t)$$

$$\frac{dv_i(t)}{dt} = \pi_i y_i(t) - [k_i + \beta_i x(t)]v_i(t).$$

Clearly, such a complex and high-dimensional model does not readily admit a closed-form solution, and the authors do not use standard control techniques such as Pontryagin's Maximum Principle. Instead, they use a "perturbation technique", to arrive at the conclusion that dynamic treatment protocols, in which the clinician may decide at any point in time what treatment to initiate or stop, are far preferable to static protocols. Obviously, this is not *entirely* realistic, since no patient is available for monitoring continuously, but nevertheless is a helpful approximation, illuminating the fact that developing any drug treatment regimen for HIV is no simple matter.

The model we will introduce in Chapter 3 is similar to this model but without multiple strains and including immunity. It is stated in their paper that the authors "implicitly assume that the strength of the immunity remains constant over the time horizon under study".

2.4 Model 4

The final model we present is in some sense the inspiration for much of this thesis. It is a model that incorporates the specific immunity to HIV into the model mathematically.

The first model that Wodarz and Nowak [76] presented is:

$$\frac{dx}{dt} = \lambda - dx - \beta xy \qquad (2.4.10)$$

$$\frac{dy}{dt} = \beta xy - ay - pyz \qquad (2.4.11)$$

$$\frac{dw}{dt} = cxyw - cqyw - bw \qquad (2.4.12)$$

$$\frac{dz}{dt} = cqyw - hz. \qquad (2.4.13)$$

This is the untreated model; our "Model 4" refers to the treated model as represented by (2.4.14–2.4.17).

The variables and parameters are explained as follows:

$x(t)$ represents healthy $CD4^+$ cells, $y(t)$ is sort of a catchall term representing infectious cells and viral load (since there is no specific expression for viral evolution, the authors assume the dominance of cell-to-cell transmission, and measure viral load as levels of $y(t)$), $w(t)$ represents the population of CTL precursors and $z(t)$ the population of CTL effectors (the ones who actually do the killing). λ is the rate (assumed here to be constant) at which uninfected $CD4^+$ T cells are produced, d is their death rate, and β is the rate at which they become infected. Infected cells decay at a rate a and are killed by CTL effectors (z) at a rate p. CTL precursors proliferate at a rate c and differentiate into CTL effectors at a rate cq. Precursors have a natural decay rate b, and effectors a rate of h.

This model is stated to have two equilibria:

$$E_1 = \left(\frac{a}{\beta}, \frac{\lambda}{a} - \frac{d}{\beta}, 0, 0 \right)$$

and

$$E_2 = \left(\bar{x}, \frac{b}{c(\bar{x} - q)}, \frac{h\bar{z}}{cq\bar{y}}, \frac{\beta\bar{x} - a}{p} \right),$$

where

$$\bar{x} = \frac{c(\lambda + dq) - b\beta + \sqrt{[c(\lambda + dq) - b\beta]^2 - 4c^2\lambda qd}}{2cd}.$$

E_1 represents the case in which the pathogen replicates freely with no immunity. Obviously

this is not desirable. E_2, on the other hand, means that a persistent immunity has been established. If

$$c(\frac{\lambda}{a} - \frac{d}{\beta})(\frac{a}{\beta} - q) > 0,$$

then E_1 is unstable and E_2 is stable provided it actually exists and is not complex.

(We would like to note that this model actually has a third equilibrium that was not mentioned in [76]. It is given by $E_0 = (\frac{\lambda}{d}, 0, 0, 0)$, and represents maximal levels of healthy cells and no infection or specific immunity. It is stable for $\beta\lambda < ad$, a not terribly likely situation.)

The authors then modelled treatment by a new parameter s which mimics a drug that reduces the viral replication rate, and as such s multiplies the term βxy.

$$\frac{dx}{dt} = \lambda - dx - s\beta xy \qquad (2.4.14)$$

$$\frac{dy}{dt} = s\beta xy - ay - pyz \qquad (2.4.15)$$

$$\frac{dw}{dt} = cxyw - cqyw - bw \qquad (2.4.16)$$

$$\frac{dz}{dt} = cqyw - hz. \qquad (2.4.17)$$

$s = 1$ represents no therapy, whereas $s = 0$ means that therapy is 100% effective. Computer simulations indicated that antigenic boosts to the immune system, coupled with, or instead of, intermittent drug therapy, would have the most positive effect on maintaining the immunity as measured in terms of precursor and effector cytotoxic T lymphocytes.

We have provided a brief summary of some of the work that has been done in this arena. In chapter 3, we present the results of a controlled ODE model incorporating immunity.

Chapter 3

A Controlled ODE Model With Immune Response

In this chapter, we will:

- Introduce the untreated system modelling the interaction of HIV and immunity, and completely determine its stability properties.

- Define the optimal control problem for this system.

- Establish existence of the optimal control and characterise it completely.

- Show regularity (continuity) of the optimal control.

- Derive the optimality system and show its uniqueness over "suitably small" time intervals.

- Determine the qualitative behaviour of the optimality system via numerical simulations.

3.1   The ODE Model

Here we introduce the ordinary differential equations modelling the immune dynamics of an HIV-infected immune system. Please bear in mind that these equations model an *untreated* individual. Treatment will be introduced in the next section via an optimal control.

The system is defined as follows:

$$\frac{dx}{dt} = \lambda - \delta x - \beta xy \tag{3.1.1}$$

$$\frac{dy}{dt} = \beta' xy - ay - \rho yz \tag{3.1.2}$$

$$\frac{dz}{dt} = cxyz - hz. \tag{3.1.3}$$

Variables are defined as follows: $x(t)$ and $y(t)$ are populations of uninfected and infected CD4$^+$ cells at time t, respectively. We consider viral load as proportional to levels of infected cells, since according to Arnaout et. al. [2], "free virus is thought to be short lived relative to infected cells". $z(t)$ is the population of immunity cells at time t. In this model, to reduce the dimension, we consider a single pool of immunity cells rather than separating them into precursor and effector cells as in [76] (that is, we are measuring the combined levels of both types of CTLs). We feel fairly confident in doing so, since the stability analysis we perform in the following section indicates that our system behaves qualitatively very much the same as that in [76].

Our parameters are explained as follows: λ is the source term for healthy CD4$^+$s, δ is their death rate and β is the rate at which they are infected by virus (in this case, we consider the viral source to be directly from infected cells). β'/β is the proportion of infected cells that survive the cellular incubation period (the time between infection and infectiousness). Throughout the remainder of this section, we shall assume that $\beta = \beta'$ for simplicity. a is the death rate of infected cells by means other than killing by CTLs, and ρ is the rate at which they are killed by CTLs. c is a generation constant for the CTL pool. Since it is an immunity specific to HIV, clearly it is proportional to $y(t)$, the term representing infection level. It is also dependent upon healthy CD4+ help (particularly the immune "memory" portion of the pool of CTLs), and levels of CTLs themselves, hence the cubic term. Finally, h is the death rate for CTLs. Parameter ranges used in simulations, as well as their references, are in Table 3.1 at the end of this chapter. Following the analysis in [2] and clinically cited viral load ranges for HIV-positive individuals, we assume that viral load is $\approx 10^6 - 10^9 y(t)$.

3.1.1 Stability of the ODE Model

We find that this system has three equilibria. They are:

$$E_0 = (\frac{\lambda}{\delta}, 0, 0)$$

$$E_1 = (\frac{a}{\beta'}, \frac{\lambda\beta'}{a\beta} - \frac{\delta}{\beta}, 0)$$

$$\overline{E} = (\frac{\lambda c - \beta h}{c\delta}, \frac{h\delta}{\lambda c - \beta h}, \frac{\beta'(\lambda c - \beta h)}{\rho c\delta} - \frac{a}{\rho}).$$

The first is an uninfected equilibrium corresponding to maximal levels of healthy $CD4^+$s and no infected cells or immunity. While at first glance the lack of immunity may seem alarming, we note that the immune response we are modelling here is that which is *specific to HIV*; therefore, in the absence of infection, we should expect no specific immune response.

The second equilibrium E_1 corresponds to positive levels of both healthy and infected cells, but no immunity. Clearly this is not desirable.

The interior equilibrium, $\overline{E}$, corresponds to positive levels of all three components— healthy and infected $CD4^+$ cells, and immune response (i.e. cytotoxic lymphocytes, or CTLs, as we shall refer to them). Notice that in this situation only the population of CTLs is affected by the ratio of β' to β.

Recall that an equilibrium is stable if all of the eigenvalues of its Jacobian matrix have negative real parts. This amounts to finding the roots of the characteristic equation, defined as

$$|vI - J(E)| = 0, \tag{3.1.4}$$

where I refers to the identity matrix, i.e. the $n \times n$ matrix with 1's along the diagonal and 0's elsewhere. $J(E)$ is the Jacobian matrix evaluated at the equilibrium E. The general Jacobian is determined as follows. Suppose we have the following nonlinear system of differential equations:

$$\frac{dx_1}{dt} = f_1(x_1, x_2, ..., x_n)$$

$$\frac{dx_2}{dt} = f_2(x_1, x_2, ..., x_n)$$

$$.....$$

$$\frac{dx_n}{dt} = f_2(x_1, x_2, ..., x_n).$$

Its Jacobian is given by:

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

Given the complicated nature of the coefficients of this equation in higher- dimensional systems, and their dependence upon parameters, we must apply the *Routh-Hurwitz criteria*. For a three-dimensional system, they state that for a characteristic equation:

$$v^3 + a_1 v^2 + a_2 v + a_3 = 0, \tag{3.1.5}$$

all roots have negative real part if and only if all of the following are satisfied:

$$a_1 > 0$$

$$a_3 > 0$$

$$a_1 a_2 - a_3 > 0.$$

We find that the general Jacobian is:

$$J = \begin{bmatrix} -\delta - \beta y^* & -\beta x^* & 0 \\ \beta' y^* & \beta' x^* - a - \rho z^* & -\rho y^* \\ cy^* z^* & cx^* z^* & cx^* y^* - h \end{bmatrix}.$$

Analysis of the Jacobian matrix evaluated at E_0, the healthy equilibrium, reveals that it is

stable if $\beta' < \frac{a\delta}{\chi}$, or that the fraction of infected cells surviving incubation is quite low.

Analysis of the Jacobian reveals at the interior equilibrium $\overline{E}$ reveals that it is stable exactly when the equilibrium E_1 is unstable, and vice-versa. In other words, a transcritical bifurcation occurs whereby the stability of the two equilibria switch. Specifically, $\overline{E}$ is stable so long as it is feasible and the following condition holds:

$$\beta' > \frac{ac\delta}{\lambda c - \beta h}.$$

Note that this is the feasibility condition for the interior equilibrium. When this inequality is reversed, $\overline{E}$ is unstable and E_1 is stable. However, under most realistic parameter ranges we find $\overline{E}$ to be the stable equilibrium. See Table 3.1 at the end of this chapter for a complete listing of parameter rages used and their references. Also, $\overline{E}$ is in fact a spiral point, as $J(\overline{E})$ has one real and two complex conjugate eigenvalues.

We summarise the above in the following proposition:

Proposition 3.1.1 *The uninfected equilibrium E_0 of the system (3.1.1)–(3.1.3) is stable for $\beta' < \frac{a\delta}{\chi}$. When this inequality is reversed, either E_1 or $\overline{E}$ is stable, depending upon parameters. Specifically, for $\beta' < \frac{ac\delta}{\lambda c - \beta h}$, E_1 is stable and $\overline{E}$ is unfeasible. When this inequality is reversed, E_1 loses stability and $\overline{E}$ becomes a locally asymptotically stable spiral point.*

3.1.2 Numerical Simulations

We can see that the equilibrium is stable under "reasonable" parameter ranges. (Again we refer to Table 3.1 at the end of this chapter for parameter ranges used and their references.)

Numerical simulations were run using the XPP package for phase-plane analysis of systems of differential equations. XPP was developed by Dr. Bard Ermentrout and further information on this package can be found at [16].

We show a plot of x versus time and see that it quickly settles toward a steady state value:
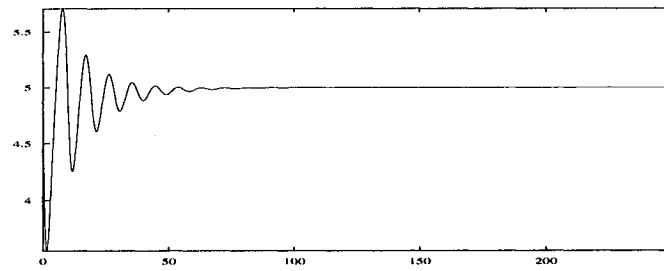
Figure 3.1.1: Healthy cells converge to equilibrium.

We see also that y and z quickly converge to their steady state values: (see Figures 3.1.2 and 3.1.3).
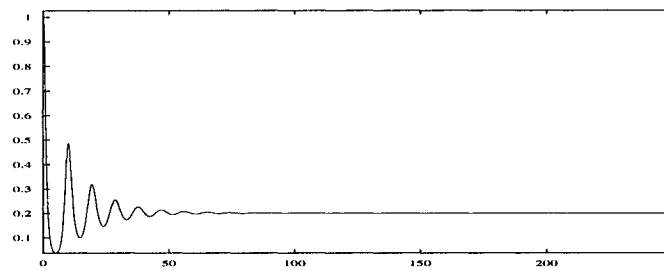
Figure 3.1.2: The population of infected cells converges to its steady state value.
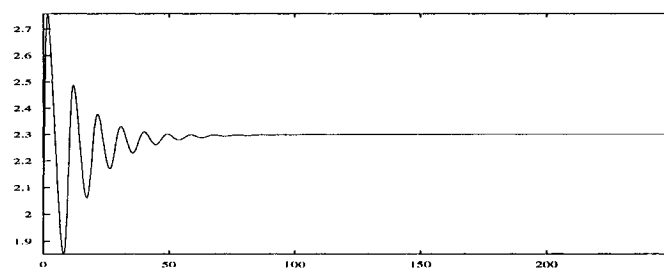
Figure 3.1.3: The population of immunity cells converges to an equilibrium.

3.1.3 Model Rationale

There are two considerations we would like to address here. The first is the choice of infection source, which is the infected CD4$^+$ cells. Cell-to-cell spread is an important method of HIV spread, since it is believed that the vast majority of viral activity occurs in compartments such as lymph nodes and the brain as well as other tissues, with only a small proportion actually happening in the peripheral blood (see Chun et. al. [10], Embretson et. al. [15], Haase et. al. [26] and [27], Pantaleo [55], Spouge et. al. [66], Schacker et. al. [61], Zack et. al. [79], Zhang et. al. [80], and [62]). Drug treatments such as abacavir, or ziagen, have the ability to penetrate the blood-brain barrier (see [40] for this and other information on effects of anti-HIV drugs), and most drug treatments, particularly nucleoside analogues, affect bone marrow and glandular tissue, rendering the assumption that drug treatment may affect such a system a fairly realistic one.

Also, due to the structure of the model, and the fact that we consider infected cells and viral load to be proportional, we are really modelling a drug that affects viral production in any compartment.

We would like also to briefly note the reason we consider only a single source/growth term λ. Primarily, it is a simplicity consideration. We consider a model incorporating a specific growth term for healthy CD4$^+$ cells as follows:

$$\frac{dx}{dt} = \lambda + rx\left(1 - \frac{x+y}{M}\right) - \delta x - \beta xy \qquad (3.1.6)$$

$$\frac{dy}{dt} = \beta' xy - ay - \rho yz \qquad (3.1.7)$$

$$\frac{dz}{dt} = cxyz - hz. \qquad (3.1.8)$$

We find essentially the same qualitative behaviour in this system as we do in the system (3.1.1)–(3.1.3) — a healthy equilibrium with no infection and no specific immunity, an equilibrium with positive levels of healthy cells, high levels of infected cells, and no specific immunity, and an interior equilibrium with all quantities at positive levels, which is stable in most realistic situations.

Also, the cubic term in the equation for $\frac{dz}{dt}$ could be given by a quadratic term dependent only on infected cells $y(t)$ and immunity effectors $z(t)$. The behaviour of the system, again,

is quite similar, except that our interior equilibrium is represented by lower levels of healthy cells and higher levels of infected cells, and is stable when it exists.

Another possibility for the CTL gain term would be a differential equation for z of the form $\frac{dz}{dt} = cy - hz$. Such a model has been analysed in [2], and could well be considered as an option for an optimal control problem.

3.2 The Optimal Control Problem

We would like to maximise levels of healthy CD4$^+$ cells, as well as levels of CTLs (immunity cells). Also, we want to keep cost—as measured in terms of chemotherapy strength, a combination of duration and intensity—as low as possible. Our control is a function $u(t)$ between 0 and 1, where $u(t) = 1$ represents totally effective chemotherapy and $u(t) = 0$ represents no treatment. We choose as our control class:

$U := \{u(t) : u$ is Lebesgue-measurable with values between 0 and 1$\}$.

Mathematically, the problem is formulated as:

$$\max J[u] = \int_0^T (x + z - \frac{Bu^2}{2})dt \qquad (3.2.9)$$

subject to the state system:

$$\frac{dx}{dt} = \lambda - \delta x - (1-u)\beta xy \qquad (3.2.10)$$

$$\frac{dy}{dt} = (1-u)\beta' xy - ay - \rho yz \qquad (3.2.11)$$

$$\frac{dz}{dt} = cxyz - hz. \qquad (3.2.12)$$

Since the control reduces the viral replication rate, we multiply our infectivity terms βxy and $\beta' xy$ by $(1-u)$. In this case, both our cellular infection rate and our viral (infection) production rate are represented by the same term, β, so the drug may represent either a protease or a reverse transcriptase inhibitor drug.

Prior to determining the mathematical formulation of our control, we must establish that it actually exists.

3.2.1 Existence of Optimal Control

Theorem 3.2.1 *An optimal control* $u^*(t) \in U$ *exists maximising the objective functional (3.2.9) subject to the state system (3.2.10)–(3.2.12).*

Proof: We establish existence of the optimal pair (x^*, u^*) satisfying (3.2.9)–(3.2.12) using the following result from Fleming and Rishel [22].

Lemma 3.2.2 *Consider the problem*

$$\max J(x_0, u) = \int_{t_0}^{t_1} L(t, x(t), u(t)) dt$$

subject to the state system:

$$\frac{dx}{dt} = f(t, x(t), u(t)), t_0 \leq t \leq t_1.$$

If f is continuous and satisfies the following inequalities:

(1) $|f(t, x, u)| < C_1(1 + |x| + |u|),$

(2) $|f(t, x', u) - f(t, x, u)| \leq C_2|x' - x|(1 + |u|)|$ *for positive* $C_1, C_2,$

and if the following conditions hold:

(a) $F' =$ *the class of all initial conditions* x_0 *such that u is Lebesgue-integrable on* $[t_0, t_1]$ *with values in the admissible control set U and such that the state system is satisfied is not empty;*

(b) U is closed and convex;

(c) The right hand side of the state system is continuous, bounded above by a sum of the bounded control and the state, and can be written as a linear function of u with coefficients depending on time and the state variables;

(d) The integrand of the objective functional, $L(t, x, u)$, *is concave in u and can be bounded above by* $c_1 - c_2|u|^\alpha$, *where* $c_1 > 0, \alpha > 1;$

then there exists (x_0^*, u^*) *maximising* $J(x_0, u)$ *on* F'.

Proof Sketch of Lemma 3.3:

We require that the following notation be observed:

$S:=$ the set to which the end (boundary) conditions e belong. S is compact by definition; here it is $[t_0, t_1]$. (We are letting $0 = t_0$ and $T = t_1$.)

x^*, u^*, e^*, x_0^* are optimal solutions to the state system, the optimal control, and corresponding end and initial conditions, respectively. The end conditions are framed in terms of the initial and final times and the values of the state at those times in the following way: $e = (t_0, t_1, x(t_0), x(t_1))$.

We will show that the assumptions in Lemma 3.3 ensure the existence of an optimal pair (x_0^*, u^*) maximising J on F'. Then we shall use this result to establish existence of the optimal control for our specific system.

Define $\mu = \sup_{F'} J(x_0, u)$. A sequence $(x_0^r, u^r) \in F'$ is a *maximising sequence* if

$$\mu = \lim_{r \to \infty} J(x_0^r, u^r).$$

Such a sequence $(x_0^r, u^r) \in F'$ yields a corresponding sequence u^r defined on $[t_0^r, t_1^r]$. The corresponding end conditions are $e^r = (t_0^r, t_1^r, x_0^r, x_1^r)$, where $x_i, i = 1, 2$ are the state values evaluated at t_j.

By Lemma 5.3 in [22], such a sequence always exists. Here we provide a brief example of such a maximising sequence:

Consider the problem $\max J[u] = \int_0^1 -tu^2 dt$ *subject to the one-dimensional state system:* $dx/dt = u, x(0) = 1, x(1) = 0$. *We can see that on the interval* $[0, 1]$, $J[u] \leq 0$ *always. A maximising sequence for* $x(t)$ *is* $x^r(t) = 1 - t^{1/r}$, *which satisfies the endpoint conditions and maximises* $J[u]$ *in the following way: Take* $u^r = dx^r/dt$ *and integrate to obtain* $J[u^r] = -1/2r \to 0$ *as* $r \to \infty$. *Since* $J \leq 0$ *on the interval with which we are concerned,* (x^r, u^r) *maximises* $J[u]$.

Now we choose some maximising sequence $(\overline{x_0}^j, \overline{u}^j)$, with $\overline{x}^j$ being the corresponding solution of the state system. Since S is compact the set of end conditions $\overline{e}^j$ is bounded. Now, application of Ascoli's theorem yields a subsequence $j_1, j_2, \ldots$ such that $\overline{x}^{jr} = x^r \to x^*$ uniformly on $[t_0, t_1]$, and $\lim_{r \to \infty} \overline{e}^{jr} = e^*$. By boundedness of x^r (satisfaction of condition (c) in Lemma 3.3), x^* is also bounded. Thus: $\lim_{r \to \infty} t_i^r = t_i^*$ and $\lim_{r \to \infty} x^r(t_i^r) = x^*(t_i^*)$.

So we know that $x^r \to x^*$ and $e^r \to e^*$. It can also be shown that x^* is in fact absolutely continuous.

We now define a new sequence: $Z^r(t) := \int_{t_0}^t L(s, x^r(s), u^r(s)) ds$. The sequences above can be chosen so that $\lim_{r \to \infty} Z^r(t) = Z^*(t)$ for every $t \in [t_0, t_1]$, and so that $Z^*(t) + ct$ is monotone on the interval $[t_0, t_1]$.

Now, if we let $\bar{x}^r = (x^r, Z^r)$ and $\bar{x}^* = (x^*, Z^*)$, we find that the derivative of $\bar{x}^*$ is an element of $\overline{F}(t, x^*(t))$ for each $t \in [t_0, t_1]$, so long as this derivative exists. Also, we obtain the existence of an integrable u^* and a measurable v^* such that: (a) $\frac{dx^*}{dt} = f(t, x^*(t), u^*(t))$ and (b) $\frac{dZ^*}{dt} = L(t, x^*(t), u^*(t)) + v^*$ almost everywhere in $[t_0, t_1]$.

These conditions above are used to show that as we approach the limit in r (that is, when we let r become a very large number), after some calculations we obtain:

$$\lim_{r \to \infty} [Z^r(t_1^r) - Z^r(t_0^r)] \le \int_{t_0}^{t_1} L(t, x^*, u^*) dt - c[(t_1^* - t_1) + (t_0^* - t_0)].$$

But the left hand side above is simply the value μ defined above, and the integral on the right hand side is the objective functional $J(x_0^*, u^*)$ as we defined it perviously, minus a quantity that is fast approaching zero. So we have shown:

$$\mu \le J(x_0^*, u^*).$$

In other words, the optimal pair (x^*, u^*) maximises J.

We proceed with the proof of Theorem 3.2.

Note that the preliminary conditions (1) and (2) of Lemma 3.3 are simply growth and Lipschitz conditions on the RHS of the state system. These are trivially satisfied in our case because the RHS, f, is differentiable in all state variables.

For the satisfaction of condition (a), we require continuity of the right hand side of the state with respect to the state variables, measurability of u, and boundedness of the right hand side in the time interval $[0, T]$. With these, we may apply Caratheodory's Theorem (see [41], Theorem 9.2.1). Our control class consists of Lebesgue-measurable functions, and the RHS is clearly continuous with respect to the state variables, so it remains only to show boundedness.

Define $\hat{x}, \hat{y}, \hat{z}$ as the supersolutions of x, y, z respectively.

First note that $x \le \frac{\lambda}{\delta}$ over *any* time horizon. This is because $\frac{dx}{dt} \le \lambda - \delta x$, and separation of variables yields $x(t) = \frac{\lambda}{\delta} - \alpha e^{-\delta t}$ where α is an arbitrary positive real number. Clearly, as $t \to \infty$ we have $x \to \frac{\lambda}{\delta}$. This yields $\hat{x} = \frac{\lambda}{\delta} = M_1$. Therefore, $\frac{d\hat{y}}{dt} = \beta M_1 \hat{y}$, and the supersolution $\hat{y}$ on a fixed time interval will be $\hat{y} = M_2 < \infty$. Thus, $\frac{d\hat{z}}{dt} = cM_1 M_2 \hat{z}$. In matrix form:

$$\begin{bmatrix} \frac{d\hat{y}}{dt} \\ \frac{d\hat{z}}{dt} \end{bmatrix} = \begin{bmatrix} \beta M_1 & 0 \\ 0 & cM_1 M_2 \end{bmatrix} \begin{bmatrix} \hat{y} \\ \hat{z} \end{bmatrix}$$

This is a linear system in finite time with bounded coefficients, so the supersolutions are uniformly bounded. Application of Caratheodory's Theorem yields the desired result; that is, the satisfaction of condition (a).

We move on to condition (b). The admissible control set U is closed and convex by definition. This condition is needed because we require $u^r \in U$ for each u^r such that $u^r \to u^*$. (That is, the components of the maximising sequence must be contained in the admissible control set.)

To establish condition (c)'s satisfaction, we note that by the result established to assist with the proof of (a), we know that the right hand side of the state system is indeed bounded above by a sum of the bounded control and the state. It is clear that the RHS is already written as a linear function of u as desired.

Finally, we verify condition (d), which is needed because if it does not hold, $J[u]$ may never achieve its maximum. The integrand of our objective functional $J[u]$ is given by:

$$x + z - \frac{Bu^2}{2}.$$

Clearly, this is a concave function in u given that it is a negative quadratic. Since $x < M\lambda$ and $z < \hat{z} = C$ for some constant C, we say that $c_1 = \frac{B}{2}$, $c_2 = M\lambda + C$, and $\alpha = 2$:

$$(x + z) - \frac{Bu^2}{2} < M\lambda + C - \frac{B|u|^2}{2} = c_1 - c_2 |u|^\alpha.$$

So the four existence conditions are established and Theorem 3.2 is proven.

This method shall be referred to in subsequent chapters whenever we wish to establish existence results.

3.2.2 Characterisation of an Optimal Control

We invoke Pontryagin's Maximum Principle to determine the precise formulation of our optimal control $u^*(t)$. To do this, we note that our Hamiltonian is given by:

$$H = x + z - \frac{Bu^2}{2} + \lambda w_1 - dxw_1 - (1-u)\beta xyw_1 + (1-u)\beta' xyw_2$$

$$-ayw_2 - \rho yzw_2 + cxyzw_3 - hzw_3 + v_1(t)u(t) + v_2(t)(1 - u(t)).$$

Note that $v_1(t)$ and $v_2(t)$ are penalty multipliers ensuring that $u(t)$ remains bounded between 0 and 1. We have that $v_1(t)u(t) = 0$ and $v_2(t)(1 - u(t)) = 0$ at the optimal u^*.

The w_js are our adjoint variables; they determine the adjoint system which, together with our state system, helps to determine our optimality system.

We shall consider all possible values for the control, including those on the boundary ($u = 0$ and $u = 1$).

Consider the set $\{t : 0 < u(t) < 1\}$.

Note that Pontryagin's Maximum Principle states that the unconstrained optimal control u^* satisfies:

$$\frac{\partial H}{\partial u^*} = 0.$$

So we find $\frac{\partial H}{\partial u}$ and solve for u^* by setting our partial derivative of H equal to zero. Thus:

$$\frac{\partial H}{\partial u^*} = -Bu + \beta xyw_1 - \beta' xyw_2 + v_1 - v_2 = 0$$

$$\Rightarrow Bu = \beta xyw_1 - \beta' xyw_2 + v_1 - v_2$$

$$\Rightarrow u^*(t) = \frac{\beta xyw_1 - \beta' xyw_2 + v_1 - v_2}{B}.$$

So we find that in this case, where $v_1(t) = v_2(t) = 0$, our optimal control is characterised as:

$$u^*(t) = \frac{\beta xyw_1 - \beta' xyw_2}{B}.$$

To completely characterise $u^*(t)$, we must consider the boundary cases $u^* = 0$ and $u^* = 1$ as well as the non-boundary cases. We have:

Consider the set $\{t : u(t) = 0\}$. In this case, $v_2 = 0$. Thus, from the definition of the optimal control above, we have:

$$0 = \frac{\beta xyw_1 - \beta' xyw_2 + v_1}{B}.$$

Since (by definition) $v_1 \geq 0$, we see that the above implies that

$$\beta xyw_1 - \beta' xyw_2 \leq 0,$$

so to ensure that u^* is not negative, we must define a new function:

$$s^+ = \max\{s, 0\}.$$

Therefore, on this set,

$$u^*(t) = \frac{\beta xyw_1 - \beta' xyw_2}{B}^+.$$

Now consider the set $\{t : u(t) = 1\}$. In this case, $v_1 = 0$. Thus:

$$1 = \frac{\beta xyw_1 - \beta' xyw_2 - v_2}{B}.$$

This tells us that $0 \leq v_2(t) = \beta xyw_1 - \beta' xyw_2 - B$, or, more precisely:

$$\frac{\beta xyw_1 - \beta' xyw_2}{B} \geq 1 = u^*.$$

So, on this set, we must choose

$$u^*(t) = \min\left\{\frac{\beta xyw_1 - \beta' xyw_2}{B}, 1\right\}.$$

To conclude, we take all three cases together and we find that we can completely characterise $u^*(t)$ as follows:

$$u^*(t) = \min\left\{1, \frac{\beta xyw_1 - \beta' xyw_2}{B}^+\right\}.$$

We summarise the above results in the following proposition:

Proposition 3.2.3 *An optimal control for the optimal control problem (3.2.9)–(3.2.12) is completely characterised by*

$$u^*(t) = \min\left\{1, \frac{\beta xyw_1 - \beta'xyw_2}{B}^+\right\}.$$

So, we can see that the control is described in terms of levels of circulating healthy and infected cells as well as their related adjoint/dual variables.

The optimality system is an important part of this problem. It describes mathematically how the system behaves under application of the control. Therefore, we may find how the different populations of cells grow or decay when the individual is treated with optimal therapy as characterised in section 3.2.

The optimality system is defined as the state system together with the adjoint system and the optimal control u^*. The adjoint system is given by:

$$\frac{dw_1}{dt} = -\frac{\partial H}{\partial x}$$
$$\frac{dw_2}{dt} = -\frac{\partial H}{\partial y}$$
$$\frac{dw_3}{dt} = -\frac{\partial H}{\partial z}.$$

The final component in the optimality system is the set of *transversality conditions*. They are a consequence of the following result.

Given the maximisation problem $\max J[u] = F(x(T)) + \int_0^T f_0(x,u)dt$, subject to the state system $dx/dt = f(t,x,u)$ and such that $x(T)$ belongs to some *target set* $g(x(T))$, we have the following transversality conditions on the adjoint variables:

$$w_i(T) = \nabla F(x(T)) + \sum_{i=1}^{k} c_i g_i(x(T)). \tag{3.2.13}$$

Note that the function F is known as the *terminal cost*.

In our problem, there is no terminal cost, so $F(x(T)) = 0$. We also do not have a target set for our state variables — we have a desired end result, of course, but the final state is in

fact free, so the summation term is also zero.

Therefore, the transversality conditions for the adjoint variables are:

$$w_i(T) = 0, i = 1, 2, 3. \tag{3.2.14}$$

Therefore, taking the state system together with the adjoint system, the optimal control, and the transversality conditions, we have the following optimality system:

$$\frac{dx}{dt} = \lambda - dx - (1-u)\beta xy$$

$$\frac{dy}{dt} = (1-u)\beta' xy - ay - \rho yz$$

$$\frac{dz}{dt} = cxyz - hz$$

$$\frac{dw_1}{dt} = -1 + dw_1 + (1-u)y(\beta w_1 - \beta' w_2) - cyzw_3$$

$$\frac{dw_2}{dt} = (1-u)x(\beta w_1 - \beta' w_2) + aw_2 + \rho zw_2 - cxzw_3$$

$$\frac{dw_3}{dt} = -1 + \rho yw_2 - cxyw_3 + hw_3$$

$$u^*(t) = \min\left\{1, \frac{xy(\beta w_1 - \beta' w_2)^+}{B}\right\}$$

$$w_i(T) = 0, i = 1, 2, 3.$$

3.2.3 Continuity Properties of the Optimal Control

We find that not only is our optimal u^* Lebesgue-measurable, it is in fact far better than that: it is continuous. To prove continuity, we employ a result from Fleming and Rishel [22] (Theorem 6.2).

Theorem 3.2.4 *An optimal control $u^*(t)$ for the problem (3.2.9)-(3.2.12) is continuous on the interval $[0, T]$.*

Proof: To prove the above result, we apply the following lemma:

Lemma 3.2.5 *Consider the optimal control problem:*

$$\max J[u] = \int_0^T L(t, x(t), u(t)) dt$$

subject to:

$$\frac{dx}{dt} = f(t, x(t), u(t)).$$

If there exists an absolutely continuous vector function $P = (P_1, ..., P_n)$ *defined on* $[0, T]$ *such that, for almost all* $t \in [0, T]$:

(1) $\frac{dP(t)'}{dt} = -P(t)' f_x(t, x^*(t), u^*(t)) - L_x(t, x^*(t), u^*(t))$

(2) $H(t, u) \geq H(t, u^*(t)), \forall u \in U$, *where*

$H(t, u) = P(t)' f(t, x^*(t), u) + L(t, x^*(t), u),$

and if the following conditions hold:

(3) L satisfies Lemma 3.3 (e)

(4) $-H(t,)$ *is strictly convex on* U,

then u^* *is continuous on* $[0, T]$.

Clearly, condition (3) is satisfied, since it was necessary for the previous existence result. We shall examine the remaining three conditions.

Condition (1): The component functions of the vector P are the antiderivatives of the adjoint variables w_j. We can see this as follows. Condition (1) is equivalent to saying:

$$\left[\begin{array}{ccc} \frac{dP_1(t)'}{dt} & \frac{dP_2(t)'}{dt} & \frac{dP_3(t)'}{dt} \end{array} \right]$$

$$= - \left[\begin{array}{ccc} P_1(t)' & P_2(t)' & P_3(t)' \end{array} \right] \left[\begin{array}{ccc} -\delta - (1-u)\beta y^* & -(1-u)\beta x^* & 0 \\ (1-u)\beta' y^* & (1-u)\beta' x^* - a - \rho z^* & -\rho y^* \\ cy^* z^* & cx^* z^* & cx^* y^* - h \end{array} \right] + \left[\begin{array}{c} -1 \\ 0 \\ -1 \end{array} \right]$$

Matrix multiplication yields the following system:

$$\frac{dP_1(t)'}{dt} = (\delta + (1-u)\beta\bar{y})P_1(t)' - (1-u)\beta\bar{y}P_2(t)' - c\overline{yz}P_3(t)' - 1$$

$$\frac{dP_2(t)'}{dt} = (1-u)\beta\bar{x}P_1(t)' - ((1-u)\beta\bar{x} - a - \rho\bar{z})P_2(t)' - c\overline{xz}P_3(t)'$$

$$\frac{dP_3(t)'}{dt} = \rho\bar{y}P_2(t)' - (c\overline{xy} - h)P_3(t)' - 1.$$

This is exactly the adjoint system that we derived in Section 3.2.2. Thus, the functions $P_i(t)' = w_i(t)$, are the adjoint variables. Since the adjoint variables are continuous, their integrals must be absolutely continuous. The components $P_i(t)$ of the vector P are simply the integrals of the P_i', or w_is. Thus such a vector of absolutely continuous functions exists.

Note also that the function H in (2) is simply the Hamiltonian. Recall also that the Hamiltonian was formulated as

$H = -Bu^2/2 +$ terms linear in $u+$ terms without u.

Taking its negative, we obtain:

$$-H = Bu^2/2 + \alpha u + \gamma.$$

This is a quadratic function, a parabola in fact, since its coefficients do not depend on u, so we can see that it is convex in u. By Pontryagin's Maximum Principle, $H(t,u) \geq H(t,u^*)$.

Therefore, all conditions in Lemma 3. are satisfied and an optimal control for (3.2.9)-(3.2.12) is continuous.

Now we return to the analysis of the optimality system. Our goals are as follows:

• Establish uniqueness of solution to the optimality system over suitably small time intervals.

• Perform numerical simulations to determine the precise qualitative behaviour of the optimality system, and of the optimal control itself, over fixed time intervals.

This system has the following interior equilibrium:

$$(\bar{x}, \bar{y}, \bar{z}, \overline{w_1}, \overline{w_2}, \overline{w_3}) = \left(\frac{c\lambda - (1-u^*)\beta h}{cd}, \frac{dh}{c\lambda - (1-u^*)\beta h}, \frac{(1-u^*)\beta'(c\lambda - (1-u^*)\beta h)}{c\rho} - \frac{a}{\rho}, \right.$$

$$\left. \frac{\rho(x+z)+a}{\rho xd}, \frac{(1-u^*)(c\lambda-(1-u^*)\beta h)}{\rho dh}, \frac{\beta'[\rho(x+z)+a]}{cd\rho xz} \right).$$

3.2.4 Uniqueness of the Optimality System

Before we analyse our optimality system (3.2.9)–(3.2.12), we shall establish uniqueness of its solutions over suitably small time intervals. To do this, we must use the results about boundedness that we established in Section 3.2.1. This method is based upon results in Fister et. al. [21].

Proposition 3.2.6 *For T sufficiently small, the solution to the optimality system is unique.*

Proof: We shall proceed by assuming that there are two solutions to the optimality system, and show that they must be equal. Let the two solutions be (x,y,z,w_1,w_2,w_3) and $(\bar{x},\bar{y},\bar{z},\overline{w_1},\overline{w_2},\overline{w_3})$. We choose solutions as follows: $x = e^{\alpha t}p, y = e^{\alpha t}p^*, z = e^{\alpha t}q, w_1 = e^{-\alpha t}r, w_2 = e^{-\alpha t}s, w_3 = e^{-\alpha t}v$. Similarly we define $\bar{x} = e^{\alpha t}\bar{p}, \bar{y} = e^{\alpha t}\bar{p}^*, \bar{z} = e^{\alpha t}\bar{q}, \overline{w_1} = e^{-\alpha t}\bar{r}, \overline{w_2} = e^{-\alpha t}\bar{s}, \overline{w_3} = e^{-\alpha t}\bar{v}$.

Thus we have that:

$$u = \min\left\{1, \frac{\beta e^{\alpha t}(r-s)pp^{*+}}{B}\right\}$$

and

$$\bar{u} = \min\left\{1, \frac{\beta e^{\alpha t}(\bar{r}-\bar{s})\bar{p}\bar{p}^{*+}}{B}\right\}.$$

The next step is to substitute the expressions for $x, y, z, \ldots$ into the state system differential equations. We begin with $x = e^{\alpha t}p$; the first equation in our system becomes (after dividing through by $e^{\alpha t}$):

$$\frac{dp}{dt} + \alpha p = \lambda e^{-\alpha t} - dp - \left(1 - \min\left\{1, \frac{\beta e^{\alpha t}(\bar{r}-\bar{s})\beta e^{\alpha t}pp^{*+}}{B}\right\}\right)\beta e^{\alpha t}pp^*.$$

Similarly, we proceed with the other five equations in our system. (The equations for our "second" solutions are virtually identical, except that in place of p we have $\bar{p}$, and so forth.

So I will only be reproducing the equations for the "originals".)

$$\frac{dp^*}{dt} + \alpha p^* = \left(1 - \min\left\{1, \frac{\beta e^{\alpha t}(\bar{r}-\bar{s})\beta e^{\alpha t}pp^{*+}}{B}\right\}\right)\beta e^{\alpha t}pp^* - ap - \rho e^{\alpha t}p^*q$$

$$\frac{dq}{dt} + \alpha q = ce^{2\alpha t}pp^*q - hq$$

$$-\frac{dr}{dt} + \alpha r = e^{\alpha t} - dr - \left(1 - \min\left\{1, \frac{\beta e^{\alpha t}(\bar{r}-\bar{s})\beta e^{\alpha t}pp^{*+}}{B}\right\}\right)e^{\alpha t}p^*(r-s) + ce^{2\alpha t}p^*qr$$

$$-\frac{ds}{dt} + \alpha s = -\left(1 - \min\left\{1, \frac{\beta e^{\alpha t}(\bar{r}-\bar{s})\beta e^{\alpha t}pp^{*+}}{B}\right\}\right)e^{\alpha t}\beta p(r-s) - ar - \rho e^{\alpha t}qs + ce^{2\alpha t}pqv$$

$$-\frac{dv}{dt} + \alpha v = e^{\alpha t} - \rho e^{\alpha t}p^*s + ce^{2\alpha t}pp^*v - hv.$$

Similarly, we calculate approximations for $\bar{x}, \bar{y}, \bar{z}, \overline{w_1}, \overline{w_2}, \overline{w_3}$. Then, the equations for x and $\bar{x}$, for y and $\bar{y}$, for z and $\bar{z}$, for w_1 and $\overline{w_1}$, w_2 and $\overline{w_2}$, and for w_3 and $\overline{w_3}$ are subtracted. Then, each equation is multiplied by an appropriate function and integrated from 0 to T.

Our integral equations are given by:

$$\frac{1}{2}[p(T) - \bar{p}(T)]^2 + \alpha \int_0^T (p - \bar{p})^2 dt = -d \int_0^T (p - \bar{p})^2 dt$$

$$+\beta \int_0^T e^{\alpha t}(pp^*u - \overline{pp^*u})(p - \bar{p})dt - \beta \int_0^T e^{\alpha t}(pp^* - \overline{pp^*})(p - \bar{p})dt.$$

$$\frac{1}{2}[p^*(T) - \bar{p}^*(T)]^2 + \alpha \int_0^T (p^* - \bar{p}^*)^2 dt = -a \int_0^T (p^* - \bar{p}^*)^2 dt + \beta \int_0^T e^{\alpha t}(pp^* - \overline{pp^*})(p^* - \bar{p}^*)dt$$

$$-\beta \int_0^T e^{\alpha t}(pp^*u - \overline{pp^*u})(p^* - \bar{p}^*)dt - \rho \int_0^T e^{\alpha t}(p^*q - \overline{p^*q})(p^* - \bar{p}^*)dt.$$

$$\frac{1}{2}[q(T) - \bar{q}(T)]^2 + \alpha \int_0^T (q - \bar{q})^2 dt = c \int_0^T e^{2\alpha t}(pp^*q - \overline{pp^*q})(q - \bar{q})dt$$

$$-c \int_0^T e^{2\alpha t}(pp^*qu - \overline{pp^*qu})(q - \bar{q})dt - h \int_0^T (q - \bar{q})^2 dt.$$

$$\frac{1}{2}[r(T) - \bar{r}(T)]^2 + \alpha \int_0^T (r - \bar{r})^2 dt = \int_0^T e^{\alpha t} dt - d \int_0^T (r - \bar{r})^2 dt$$

$$-\beta \int_0^T e^{\alpha t}(p^* r - \overline{p^* r})(r - \bar{r})dt + \beta \int_0^T e^{\alpha t}(p^* s - \overline{p^* s})(r - \bar{r})dt$$

$$+\beta \int_0^T e^{\alpha t}(p^* ru - \overline{p^* ru})(r - \bar{r})dt - \beta \int_0^T e^{\alpha t}(p^* su - \overline{p^* su})(r - \bar{r})dt$$

$$+c \int_0^T e^{2\alpha t}(p^* qv - \overline{p^* qv})(r - \bar{r})dt - c \int_0^T e^{2\alpha t}(p^* qvu - \overline{p^* qvu})(r - \bar{r})dt.$$

$$\frac{1}{2}[s(T) - \bar{s}(T)]^2 + \alpha \int_0^T (s - \bar{s})^2 dt = -a \int_0^T (s - \bar{s})^2 dt - \beta \int_0^T e^{\alpha t}(pr - \overline{pr})(s - \bar{s})dt$$

$$+\beta \int_0^T e^{\alpha t}(ps - \overline{ps})(s - \bar{s})dt + \beta \int_0^T e^{\alpha t}(pru - \overline{pru})(s - \bar{s})dt - \beta \int_0^T e^{\alpha t}(psu - \overline{psu})(s - \bar{s})dt$$

$$-\rho \int_0^T e^{\alpha t}(qs - \overline{qs})(s - \bar{s})dt + c \int_0^T e^{\alpha t}(p^* qr - \overline{p^* qr})(s - \bar{s})dt - c \int_0^T e^{\alpha t}(p^* qru - \overline{p^* qru})(s - \bar{s})dt.$$

$$\frac{1}{2}[v(T) - \bar{v}(T)]^2 + \alpha \int_0^T (v - \bar{v})^2 dt = -\rho \int_0^T e^{\alpha t}(p^* s - \overline{p^* s})(v - \bar{v})dt$$

$$+c \int_0^T e^{2\alpha t}(pp^* v - \overline{pp^* v})(v - \bar{v})dt - c \int_0^T e^{2\alpha t}(pp^* vu - \overline{pp^* vu})(v - \bar{v})dt - h \int_0^T (v - \bar{v})^2 dt.$$

Further, we can make estimates, bounding all these integral equations above by new integral equations. We obtain:

$$\frac{1}{2}[p(T) - \bar{p}(T)]^2 + \alpha \int_0^T (p - \bar{p})^2 dt \leq$$

$$d \int_0^T (p - \overline{p})^2 dt + C_1 e^{4\alpha T} \int_0^T [(p - \overline{p})^2 + (p^* - \overline{p}^*)^2 + (r - \overline{r})^2 + (s - \overline{s})^2] dt.$$

$$\frac{1}{2}[p^*(T) - \overline{p}^*(T)]^2 + \alpha \int_0^T (p^* - \overline{p}^*)^2 dt \leq$$

$$a \int_0^T (p^* - \overline{p}^*)^2 dt + C_2 e^{\alpha T} \int_0^T [(p - \overline{p})^2 + (p^* - \overline{p}^*)^2 + (q - \overline{q})^2] dt$$

$$+ C_3 e^{4\alpha T} \int_0^T [(p - \overline{p})^2 + (p^* - \overline{p}^*)^2 + (r - \overline{r})^2 + (s - \overline{s})^2] dt.$$

$$\frac{1}{2}[q(T) - \overline{q}(T)]^2 + \alpha \int_0^T (q - \overline{q})^2 dt \leq$$

$$h \int_0^T (q - \overline{q})^2 dt + C_4 e^{3\alpha T} \int_0^T [(p - \overline{p})^2 + (p^* - \overline{p}^*)^2 + (q - \overline{q})^2] dt.$$

$$\frac{1}{2}[r(T) - \overline{r}(T)]^2 + \alpha \int_0^T (r - \overline{r})^2 dt \leq$$

$$d \int_0^T (r - \overline{r})^2 dt + C_5 e^{\alpha T} \int_0^T [(p^* - \overline{p}^*)^2 + (r - \overline{r})^2 + (s - \overline{s})^2] dt$$

$$+ C_6 e^{3\alpha T} \int_0^T [(p^* - \overline{p}^*)^2 + (q - \overline{q})^2 + (r - \overline{r})^2] dt$$

$$+ C_7 e^{4\alpha T} \int_0^T [(p - \overline{p})^2 + (p^* - \overline{p}^*)^2 + (r - \overline{r})^2 + (s - \overline{s})^2] dt.$$

$$\frac{1}{2}[s(T) - \overline{s}(T)]^2 + \alpha \int_0^T (s - \overline{s})^2 dt \leq$$

$$a \int_0^T (s - \overline{s})^2 dt + C_8 e^{\alpha T} \int_0^T [(p - \overline{p})^2 + (q - \overline{q})^2 + (r - \overline{r})^2 + (s - \overline{s})^2] dt$$

$$+C_9 e^{4\alpha T} \int_0^T [(p-\bar{p})^2 + (p^* - \bar{p}^*)^2 + (r-\bar{r})^2 + (s-\bar{s})^2]dt.$$

$$\frac{1}{2}[v(T) - \bar{v}(T)]^2 + \alpha \int_0^T (v-\bar{v})^2 dt \le$$

$$h \int_0^T (v-\bar{v})^2 dt + C_{10} e^{\alpha T} \int_0^T [(p-\bar{p})^2 + (p^* - \bar{p}^*)^2 + (s-\bar{s})^2 + (v-\bar{v})^2]dt.$$

Finally, we add these together, which enables us to make the following estimate:

$$\frac{1}{2}[p(T) - \bar{p}(T)]^2 + \frac{1}{2}[p^*(T) - \bar{p}^*(T)]^2 + \frac{1}{2}[q(T) - \bar{q}(T)]^2$$

$$+\frac{1}{2}[r(T) - \bar{r}(T)]^2 + \frac{1}{2}[s(T) - \bar{s}(T)]^2 + \frac{1}{2}[v(T) - \bar{v}(T)]^2$$

$$+C_1 \int_0^T [(p-\bar{p})^2 + (p^* - \bar{p}^*)^2 + (q-\bar{q})^2]dt$$

$$+C_2 \int_0^T [(r-\bar{r})^2 + (s-\bar{s})^2 + (v-\bar{v})^2]dt \le$$

$$C_3 e^{4\alpha T} \int_0^T [(p-\bar{p})^2 + (p^* - \bar{p}^*)^2 + (q-\bar{q})^2 + (r-\bar{r})^2 + (s-\bar{s})^2 + (v-\bar{v})^2]dt$$

$$+C_4 \int_0^T [(p-\bar{p})^2 + (p^* - \bar{p}^*)^2 + (q-\bar{q})^2 + (r-\bar{r})^2 + (s-\bar{s})^2 + (v-\bar{v})^2]dt.$$

Thus taking everything to the LHS, we have:

$$(\alpha - c_1 - c_2 e^{4\alpha T}) \int_0^T [(p-\bar{p})^2 + (p^* - \bar{p}^*)^2 + (q-\bar{q})^2 + (r-\bar{r})^2 + (s-\bar{s})^2 + (v-\bar{v})^2]dt \le 0.$$

However, note that for

$$\alpha \geq c_1 + c_2$$

and

$$T \leq \frac{1}{4\alpha} \log(\frac{\alpha - c_1}{c_2}),$$

we must have $p = \bar{p}, p^* = \bar{p}^*, q = \bar{q}, r = \bar{r}, s = \bar{s}, v = \bar{v}$. In other words, over the time interval bounded as above, the solution of the optimality system is unique.

3.3 Numerical Results

Several methods of solving the optimality system were attempted before a correct, working method was found.

First, we attempted to use the boundary value solver in XPP. However, because the Jacobian of the system is not invertible, it is not possible to solve the system with the transversality (end) conditions on the adjoint variables. The best we can do in this case is to assume a free final time, but the solution will likely be quite different and not applicable in practice.

We also attempted to solve the system using a Runge-Kutta four scheme (programmed in Fortran), solving the state equations forward and the adjoint equations backward in time. However, the nonlinearity of the system rendered it highly sensitive to the initial guess that was made for the adjoint variables. Thus, the problem could not converge — the end conditions were not satisfied for any initial guess that was made.

Finally, the correct method was determined. As mentioned, because of the problem's nonlinearity and resultant sensitivity to the initial guess, the time scale of the problem caused difficulties. The problem first had to be rescaled, so that the time interval of $[0, 100]$ appears to be $[0, 1]$. This is simply a result of rescaling — on the graphs, $t = 0.1$ actually means $t = 10$ days.

The boundary value problem was then solved by implementing a Fortran program in which the initial guess was produced based upon known initial values, and the system was solved by analytic continuation. Essentially, the solution was determined first on a very small interval, and each step of the program "continued" that solution, extending it

onto longer and longer intervals, until ultimately a convergent solution was found for the entire interval. Recall in Section 3.2.3, in the proof sketch of Lemma 3.3, we discussed the construction of a maximising sequence — a sequence of approximations to the solution of the state system and the optimal control (x^r, u^r) that maximised the performance index J over the interval $[0, T]$. This numerical method employed essentially the same idea, constructing approximations to the control and the solution of the state that ultimately converged to the optimal pair.

The following graphs were generated for the control and the state variables in the case of a small weight factor $B = 1$. Note that a final time of $T = 100$ was chosen (partly due to the difficulty of programming over longer time periods); a longer time schedule could have been chosen, but the asymptotic behaviour of the variables does not change much after this point. If B were larger, we would expect that the second peak in u would be lower, and the drug would begin to drop off earlier. We shall see later that this is true.
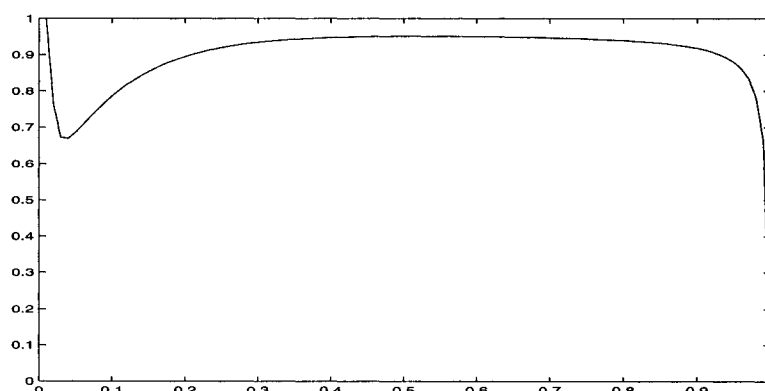
Figure 3.3.4: The optimal control versus time.

Note that the control starts out at its boundary value of $u = 1$, no matter the initial guess for u. It then drops to $u \approx 0.67$ before increasing again to remain between $u = 0.9 - 0.95$, from $t \approx 20$ to $t \approx 90$, at which point it drops sharply and reaches zero at the final time.
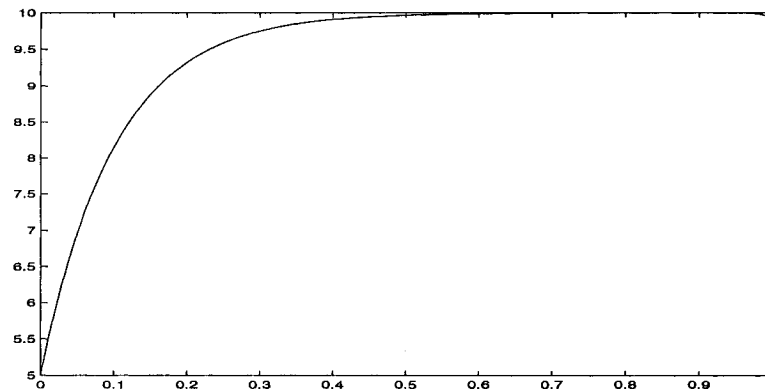
Figure 3.3.5: The healthy cell population versus time.

We can see that the optimal chemotherapy scheme has a very desirable effect upon the population of healthy cells. They increase to near their maximal level for almost the entire length of treatment. The sharp drop off at the end is because of the fact that the drug is stopped.
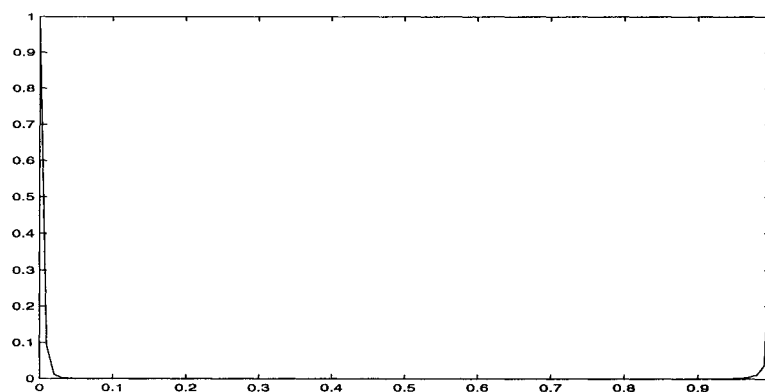
Figure 3.3.6: The infected cell population versus time.

The infection level actually drops to near zero for most of the treatment interval. It then increases somewhat when treatment is stopped. The infection level actually does not *reach* zero (although it appears to in the graph!), but rather a very small value, equivalent to a viral load from about $10^0 - 10^3$ (please refer to the section on parameter values at the end of this chapter for further explanation). So although infection is held at very low levels,

it is not eradicated. We must consider why this is true, from both a mathematical and a biological perspective.

Mathematically, the reason that optimal therapy is not succesful at eradicating infection is that no optimal solution has a drug that is given at 100% strength for the duration of the course of therapy. This is due to the formulation of the objective functional $J[u]$; specifically, the fact that we are *balancing* benefit and cost. We cannot afford to ignore drug toxicity or cost and therefore the fact that we are not only maximising healthy cells and CTLs but also minimising the square of the treatment function ensures that it would be far from optimal to administer full strength drug therapy continually.

Biologically, it is unrealistic to assume that any drug could be totally effective for long enough to reduce the system to its uninfected state, and this is reflected in our model. It is significant to note that infected cells are not eradicated, because many people believe that the class of latently infected cells is the reason antiviral therapy cannot be totally effective at eradicating infection [57]. Our model indicates that even without eradication, infection can be controlled and healthy cells maintained despite this fact.
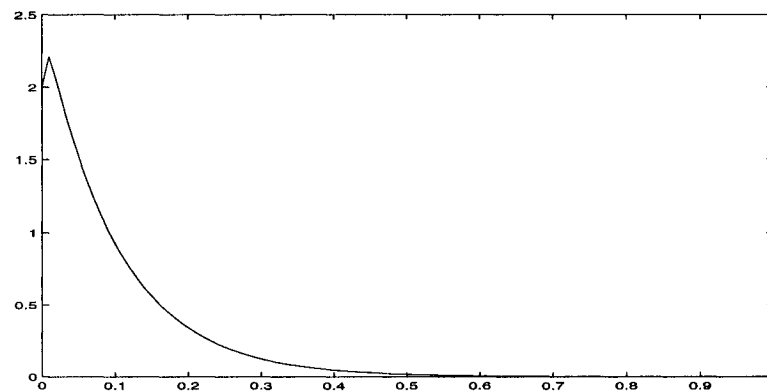
Figure 3.3.7: The immunity population versus time.

We can see that at the end of treatment, the immunity population has been reduced to a value very close to zero. As in the case of infected cells, we note that this never actually reaches zero. There is always a small pool of immunity cells, even at the final time. However, we can also see that there is an initial "spike" in the population of immunity cells. Looking back at the graph of infection versus time, we can see that this spike occurs in response to

the peak in infection level. We expect that after the final peak in infection level (the one occurring at $t = 100$), the immunity would then rise again. Although these results may seem less than optimal, given that we had initially defined the problem in terms of maximising immunity as well as healthy cells, we could also look at it another way. The drug has so effectively suppressed infection that the immunity is not needed. But we should also consider the possibility of separating immunity into memory and effector CTLs, rather than a generalised pool describing both, to determine whether it is possible to maintain memory CTLs at positive levels. This also shows that although the asymptotic properties of the ODE models are the same, the properties of the controlled models may not be.

We also note that the higher weight factor B, the lower is the second peak in the control. In all cases, we start out with treatment at full strength, but as the weight on cost grows, the amount of drug we give is lowered.

We ran simulations of the optimality system for various weighting factors ranging from $B = 0.1$ tp $B = 10$ and found the following results. First we can see that for $B = 0.1$, the medication scheme is not much different than it is for $B = 1$:
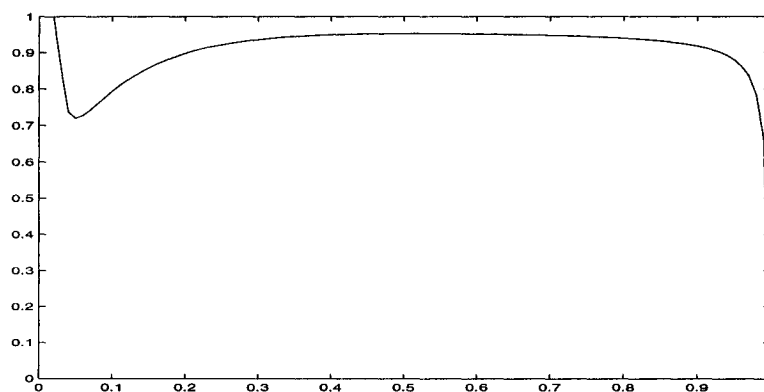
Figure 3.3.8: The control for $B = 0.1$.

But when we increase the weighting factor we can see that the drug scheme is slightly different. Observe the following graphs for the control $u(t)$ for weighting factors of $B = 5$ and $B = 10$:
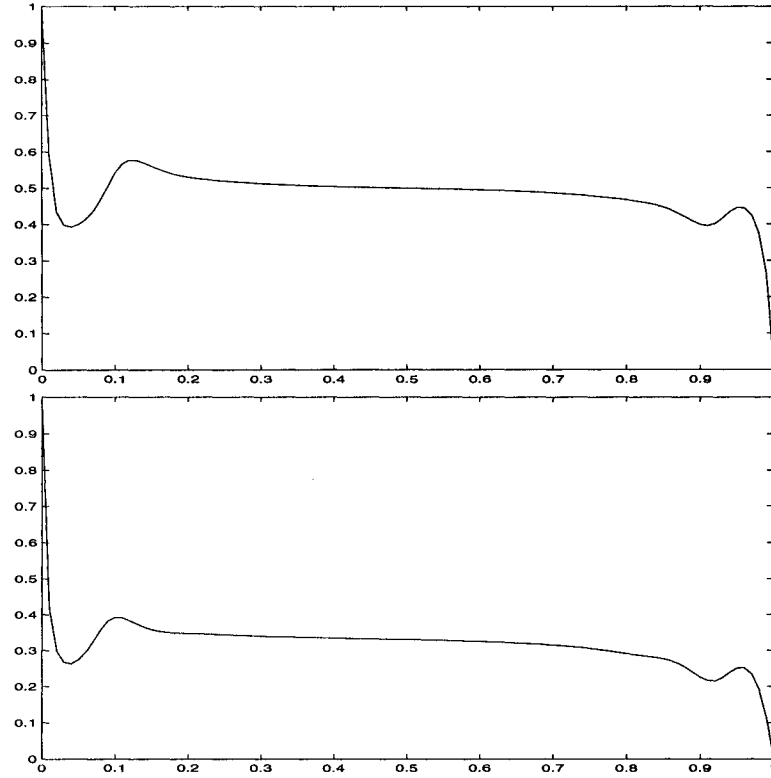
Figure 3.3.9: The control for higher weights on cost.

Alternatively, we could consider giving the drug for a shorter time as the weight is increased.

Comparing our results with those established in [36] and [21], we find that our control does behave somewhat differently from drugs used to control systems not explicitly modelling immunity. In [36], the control was either monotone decreasing from its maximum value, or it peaked slightly right near the initiation of treatment and then dropped off. However, we actually observe that our control *decreases* soon after initiation of treatment, only to rise again, remain close to constant, and drop rapidly near the end. We believe that this drop is directly dependent upon the action of the immunity, which occurs shortly after treatment initiation in response to the high infection level.

Table 3.1: **Variables and Parameter Ranges for Immune Response**

	Parameters and Variables	*Values*
	Dependent Variables	
$x(t)$	uninfected T-4 cell population size	
$y(t)$	infected T-4 cell population size/viral load	
$z(t)$	immunity cell population size	
	Parameters and Constants	
λ	source rate of T-4 cells	$1 - 10$ cells/day
δ	decay rate of healthy cells	$0.007 - 0.1$ cells/day
β	rate T-4 cells become infected	$0.00025 - 0.5$ cells/day
$\beta' : \beta$	proportion of infected cells surviving incubation	≈ 1
a	death rate infected T-4 cells, not by CTL killing	$0.2 - 0.3$ cells/day
ρ	rate at which infected cells are killed by CTLs	1/day
c	immunity activation rate	$0.1 - 1$/day
h	death rate of CTLs	$0.1 - 0.15$/day

Parameter ranges used for numerical simulations of Model 1 are given in Table 3.1 above. All parameter ranges for $\lambda, \delta, \beta, a$ were used in references [2], [73], [76], [57], [66], [38]. (Not all parameter values were used in all of these references.) However, the ranges for ρ, c, h were found in [2] and [76]. A wide range of possible parameter values has been suggested for HIV modelling. Part of the reason for this is that it is so difficult to assign one set of parameters to individuals showing such dramatically different clinical outcomes. Add to this the belief by some researchers that "with HIV, not many parameters are known... except for the half-life of infected cells" (Dominik Wodarz, personal communication, [78]).

However, the parameters are generally given in units of cells mm^{-3} day^{-1}. We must be somewhat careful, however. For example, assuming that λ lies in the range of $5 - 10$, $c = \rho = 1$, $\beta = 0.5$, $h = 0.1$ and $\delta = 0.02$, we obtain healthy cells at a level of $\approx 250 - 500$ mm^{-3}, consistent with an HIV-infected individual. We also obtain a CD4+:CTL ratio of about $2 : 1$. (No matter the value we use for infection rate, CTLs remain proportional with CD4+s.) Assuming viral load to be proportional to infected cells and that it is $\approx 10^6 - 10^9 \times y(t)$, we obtain a viral load in the $1,000 - 100,000$ range. This is not unreasonable, considering the nature of the viral load test — "viral load" is an approximation based upon PCR (as opposed to "viral burden", the actual number of viral particles per millilitre of plasma, a much harder to measure quantity).

In the simulations reproduced in this and Chapters Four and Five, we use parameters from [76] to display the qualitative behaviour of the systems in parameter space, but we note that the stability properties of the models are retained using most values from the ranges given in Table 3.1.

As a final note, we point out that the goals of this thesis are mathematical and qualitative in nature. Much larger, more quantitatively sophisticated models are needed to determine *precise* treatment regimes in terms of days on therapy, exact drug quantities, and so forth. Such models are a logical extension of the model presented here.

Chapter 4

A Delay-Differential Equation Model of HIV Including Immune Response

In this chapter, we analyse the qualitative behaviour of model (3.1.1)–(3.1.3) in the case where we incorporate a time lag. As will be the case in Chapter Six as well, the delay represents the time lag between when a cell becomes infected and when it is actually infectious (i.e. begins producing virus). Our objectives are to:

- Derive *general* conditions for delay-induced bifurcation for a three-dimensional system.

- Apply these to our specific problem to determine when and if delay-induced bifurcation occurs.

- Determine what the significance of our results are. So we ask: does the system behave "better" when nonconstant HIV-specific immunity is considered? In this case that would amount to delay-induced bifurcation either not occurring at all, or occurring only under unrealistic parameter ranges. We shall see in Chapter Six that when nonconstant immunity is not considered, instability results under realistic parameter ranges.

4.1 Biological Background

The reasons for considering delays are not only mathematically but biologically important. First of all, there is a time lag after a cell becomes infected with HIV, but before it begins to infect others, that has been estimated to be anywhere from six hours to two days (see for example Mittler at al. [46] or Nelson et al. [50], amd references cited therein for estimates of the intracellular latent period). Therefore, incorporating this delay into the models mathematically renders the systems in some sense more "continuous", as we are no longer ingoring a block of time that should be accounted for.

In this chapter and the two that follow, we shall be specifically concerned with whether the models incorporating delay are capable of exhibiting delay-induced or Hopf bifurcation for realistic values of the delay. This question has been addressed in a model including free virus, see Culshaw and Ruan [13]. We do this because the existence of stable steady states is very important biologically. For example, in Model (3.1.1)–(3.1.3), the interior equilibrium is stable in the absence of delay. This is desirable, as it indicates that the host remains healthy in all probability. However, if the incorporation of a time delay allows for a Hopf bifurcation to occur for realistic parameter values, we must consider the possibility that in life, the patient could easily be perturbed out of a steady state into instability, which will likely result in destruction of the host.

We will be examining the possibility of Hopf bifurcation occurring in our models. A Hopf bifurcation occurs when a pair of complex conjugate roots of the characteristic equation switch from having negative real parts (indicating asymptotic stability of the system) to having positive real parts (indicating a bifurcation occurs and the system is rendered unstable). When this occurs, a stable spiral point becomes a family of periodic orbits, indicating a fundamental instability in the patient's condition and likely destruction of the host.

4.2 Analysis of the General Characteristic Equation

To analyse the stability of the system and determine whether the delay may render it unstable, we must consider the characteristic equation. As in ODE systems, a delay system is asymptotically stable if and only if all roots of the characteristic equation have negative real parts. The characteristic equation is derived from the linearised system which is expressed

as

$$\frac{dx(t)}{dt} = Ax(t) + Bx(t - \tau),$$

where A and B are matrices with constant coefficients. Below we show how this linearised system is derived from the original nonlinear system, and how the characteristic equation is obtained.

Consider a system describing the change over time of n interacting populations. Now, assume that some of these populations are dependent upon events that are not occurring at time t, but rather τ time units ago. Mathematically such a system would be expressed as:

$$\frac{dx}{dt} = f(x(t)) + g(x(t - \tau)),$$

where x, f and g are vector-valued functions. In this case, the vectors are three-dimensional, consisting of three space variables, all dependent upon time.

The model is analysed by linearising the system about its interior equilibrium $(\bar{x}, \bar{y}, \bar{z})$ so that we can express a system in the following form:

$$\frac{d}{dt} \begin{bmatrix} x \\ y \\ z \end{bmatrix}(t) = A \begin{bmatrix} x \\ y \\ z \end{bmatrix}(t) + B \begin{bmatrix} x \\ y \\ z \end{bmatrix}(t - \tau),$$

where A and B are coefficient matrices. We assume a solution of the form $x(t) = e^{wt}$ and by substituting into the above expansion we obtain:

$$ve^{wt} = Ae^{wt} + Be^{w(t-\tau)} \Rightarrow |wI - A - Be^{-w\tau}| = 0.$$

In both cases our characteristic equation is of the form:

$$w^3 + a_1 w^2 + a_2 w + (a_3 w^2 + a_4 w + a_5)e^{-w\tau} + a_6 = 0. \tag{4.2.1}$$

Since we are interested in when and if delay-induced bifurcation occurs, we wish to determine if (4.1.1) may exhibit purely imaginary roots. We note that there are in fact two possibilities:

(a) Under certain assumptions on the coefficients of equation (4.1.1), all roots have

negative real part, for all values of the delay $\tau \geq 0$.

(b) If the assumptions in (a) are not satisfied, there is a critical value τ_0, such that when the delay $\tau < \tau_0$, the real parts of all roots remain negative. When $\tau = \tau_0$, there is a pair of purely imaginary roots and all other roots have negative real parts. When $\tau > \tau_0$, there is at least one eigenvalue with a positive real part.

We shall study the distribution of the roots of this polynomial, following the analysis in Ruan and Wei [60].

To begin with, note that roots of (4.1.1) will be complex of the form:

$$w = \alpha + i\omega,$$

where ω may be zero (if they are real).

For delay-induced bifurcation, we want to see if roots of the form $w = i\omega$ are possible. This is because in the case of delay-induced bifurcation, it occurs as a stable spiral point becomes unstable as the real part goes from negative to positive, passing through a pure imaginary value. What happens at this point is a family of periodic solutions bifurcates from the equilibrium when the eigenvalue is purely imaginary.

Substitution of $w = i\omega$ into equation (4.1.1) yields:

$$-i\omega^3 - a_1\omega^2 + ia_2\omega + (-a_3\omega^2 + ia_4\omega + a_5)(\cos(\omega\tau) - i\sin(\omega\tau)) + a_6 = 0.$$

(Note that the trigonometric forms come from the use of Euler's formula.)

We separate real and imaginary parts to obtain:

$$a_1\omega^2 - a_6 = -(a_3\omega^2 - a_5)\cos(\omega\tau) + a_4\omega\sin(\omega\tau)$$
$$\omega^3 - a_2\omega = (a_3\omega^2 - a_5)\sin(\omega\tau) + a_4\omega\cos(\omega\tau).$$

Squaring both sides and adding, we obtain:

$$\omega^6 + (a_1^2 - a_3^2 - 2a_2)\omega^4 + (a_2^2 - 2a_1a_6 + 2a_3a_5 - a_4^2)\omega^2 + a_6^2 - a_5^2 = 0. \qquad (4.2.2)$$

For purely imaginary roots of (4.1.1), we require that the above exhibit *positive* roots. To make our analysis easier, we employ the following notation:

$$
\begin{aligned}
v &= \omega^2 \\
p &= a_1^2 - a_3^2 - 2a_2 \\
q &= a_2^2 - 2a_1a_6 + 2a_3a_5 - a_4^2 \\
r &= a_6^2 - a_5^2.
\end{aligned}
$$

Equation (4.1.2) becomes:

$$
h(v) = v^3 + pv^2 + qv + r = 0. \tag{4.2.3}
$$

Claim 1: If $r < 0$, then equation (4.1.2) has at least one positive root.

Proof: Let

$$
h(v) = v^3 + pv^2 + qv + r.
$$

It is obvious that $h(0) = r$, and since $\lim_{v \to \infty} h(v) = \infty$, we can see that there is some $v_0 \in (0, \infty)$ such that $h(v_0) = 0$.

Claim 2: Suppose that $r > 0$. Then, for equation (4.1.2) to have positive real roots, we require that $p^2 - 3q \geq 0$.

Proof: Differentiating $h(v)$ with respect to v yields:

$$
\frac{dh(v)}{dv} = 3v^2 + 2pv + q.
$$

The roots of the above equation, which correspond to the extrema of (4.1.2), are:

$$
v_{1,2} = \frac{-p \pm \sqrt{p^2 - 3q}}{3}
$$

Clearly, if $p^2 - 3q < 0$, dh/dv does not have real roots, and the function $h(v)$ would thus be monotone increasing in v. Together with the assumption that $r > 0$, there must be no

positive real roots of $h(v)$. Therefore, for positive real roots of (4.1.2), it is necessary that $p^2 - 3q > 0$.

Note that, if $p^2 - 3q > 0$, $v_1 = \frac{-p + \sqrt{p^2 - 3q}}{3}$ is the local minimum of $h(v)$. This yields:

Claim: If $r \geq 0$, then equation (4.1.2) has positive roots if and only if $v_1 > 0$ and $h(v_1) \leq 0$.

Proof: Since sufficiency is obvious, we prove necessity by contradiction. Suppose that either $v_1 \leq 0$ *or* that both $v_1 > 0$ and $h(v_1) > 0$. In the first case, if $v_1 \leq 0$, since $h(v)$ is increasing for $v > v_1$ and $h(0) = r \geq 0$, there must be no positive real roots. In the second case, if both $v_1 > 0$ and $h(v_1) > 0$ hold, then since $v_2 = \frac{-p - \sqrt{p^2 - 3q}}{3}$ is the local maximum, $h(v_1) < h(v_2)$. So since $h(0) \geq 0$, $h(v)$ must have no positive real roots. Therefore, necessity is proven.

We summarise the above analysis in the following Lemma:

Lemma 4.2.1 *Suppose that $v_1 = \frac{-p + \sqrt{p^2 - 3q}}{3}$.*
  (a) If $r < 0 \Rightarrow$ (4.1.2) has at least one positive root.
  (b) If $r \geq 0$ and $p^2 - 3q < 0 \Rightarrow$ (4.1.2) has no positive root.
  (c) If $r \geq 0 \Rightarrow$ (4.1.2) has positive roots if and only if $v_1 = \frac{1}{3}(-p + \sqrt{p^2 - 3q}) > 0$ and $h(v_1) \leq 0$.

We note that at the bifurcation value τ_0,

$$w = \omega(\tau_0) = \omega_0.$$

So:

$$\omega(\tau_0) = \omega_0$$
$$\alpha(\tau_0) = 0.$$

So the real part of the characteristic equation equals zero and the imaginary part equals ω_0:

$$a_1\omega_0^2 - a_6 + (a_3\omega_0^2 - a_5)\cos(\omega_0\tau) - a_4\omega_0\sin(\omega_0\tau) = 0$$

$$\omega_0^3 - a_2\omega_0 - (a_3\omega_0^2 - a_5)\sin(\omega_0\tau) - a_4\omega_0\cos(\omega_0\tau) = 0.$$

We multiply the first equation by $(a_3\omega_0^2 - a_5)$ and the second by $-a_4\omega_0$, and add them together to cancel the sine terms. Thus:

$$\tau_0 = \frac{1}{\omega_0}\arccos\left\{\frac{(a_4 - a_1a_3)\omega_0^4 + (a_1a_5 + a_3a_6 - a_2a_4 - a_4)\omega_0^2 - a_5a_6}{(a_3\omega_0^2 - a_5)^2 + a_4\omega_0^2}\right\} + \frac{2j\pi}{\omega_0}, j = 0, 1, 2, \ldots.$$

$$(4.2.4)$$

Lemma 4.2.2 *Suppose that $a_1 > 0$, $a_5 + a_6 > 0$, $a_1a_2 - a_5 - a_6 > 0$.*

(a) If $r \geq 0$ and $p^2 - 3q < 0 \Rightarrow$ all roots of (4.1.1) have negative real part for all $\tau \geq 0$.

(b) If $r < 0$ or $r \geq 0$, $v_1 > 0$ and $h(v_1) \leq 0 \Rightarrow$ all roots have negative real parts for $\tau \in [0, \tau_0)$.

Proof: When $\tau = 0$, (4.1.1) becomes:

$$w^3 + a_1w^2 + a_2w + a_5 + a_6.$$

By the Routh-Hurwitz criteria, all roots of the above have negative real part if and only if $a_1 > 0, a_5 + a_6 > 0$ and $a_1a_2 - a_5 - a_6 > 0$. If $r \geq 0$ and $p^2 - 3q < 0$, we have shown already that (4.1.1) has no roots with zero real part for any $\tau \geq 0$. Otherwise, if $\tau \neq \tau_0$, (4.1.1) has no roots with zero real part, and τ_0 is the minimum value of τ so that (4.1.1) has purely imaginary roots. Application of Lemma 1.1 from [60], this concludes the proof.

Finally, from Ruan and Wei [60], we have the following transversality condition:

$$\frac{d}{d\tau}\alpha(\tau)|_{\tau=\tau_0} > 0.$$

This means that the real part of our root w is increasing as the delay increases.
We summarise the above results in the following proposition:

Proposition 4.2.3 *Let ω_0, τ_0 and $w(\tau)$ be defined as above, and let $v_0 = \omega_0^2$. Suppose also that $a_1 > 0$, $a_5 + a_6 > 0$, $a_1a_2 - a_5 - a_6 > 0$.*

(i) If $r \geq 0$ and $p^2 - 3q < 0$, all roots of (4.1.1) have negative real part for all $\tau \geq 0$.

(ii) If $r < 0$ or $r \geq 0$, $v_1 > 0$ and $h(v_1) < 0$ then all roots of (4.1.1) have negative real parts when $\tau \in [0, \tau_0)$.

(iii) If the conditions in (ii) are satisfied, $\tau = \tau_0$ and $h'(v_0) \neq 0$, then $\pm i\omega_0$ is a pair of simple purely imaginary roots of (4.1.1) and all other roots have negative real parts. As well, $(d/d\tau)Rew(\tau_0) > 0$.

4.3 Analysis of a Model with Delay in Infection Rate

We wish to examine how system (3.1.1)–(3.1.3) behaves when we have a delay in infection rate. That is, infected cells do not begin producing virus or infecting other cells until τ time units have elapsed. So the cells remain "latent" and the current behaviour of the system depends upon the behaviour of some of its components now, and that of some others τ time units ago.

Mathematically we express the system as:

$$\frac{dx(t)}{dt} = \lambda - \delta x(t) - \beta x(t)y(t) \tag{4.3.5}$$

$$\frac{dy(t)}{dt} = \beta' x(t-\tau)y(t-\tau) - ay(t) - \rho y(t)z(t) \tag{4.3.6}$$

$$\frac{dz(t)}{dt} = cx(t)y(t)z(t) - hz(t). \tag{4.3.7}$$

In this case, τ is the length of the delay. To employ the methods we developed in the previous section, we must linearise about the interior equilibrium, which is the same as before. So we define new variables:

$$u = x - \bar{x}$$
$$v = y - \bar{y}$$
$$w = z - \bar{z}.$$

We transform the interior equilibrium to zero and drop the nonlinear terms. Replacing our

dummy variables u, v, w by x, y, z again, we obtain the following linear system:

$$\frac{dx(t)}{dt} = -\frac{\lambda c\delta}{\lambda c - \beta h}x(t) - \frac{\beta(\lambda c - \beta h)}{c\delta}y(t)$$

$$\frac{dy(t)}{dt} = \frac{\beta'\delta h}{\lambda c - \beta h}x(t-\tau) + \frac{\beta'(\lambda c - \beta h)}{c\delta}y(t-\tau) - \frac{\beta'(\lambda c - \beta h)}{c\delta}y(t) - \frac{\rho\delta h}{\lambda c - \beta h}z(t)$$

$$\frac{dz(t)}{dt} = \left(\frac{\beta'h}{\rho} - \frac{ac\delta h}{\rho(\lambda c - \beta h)}\right)x(t) + \frac{\lambda c - \beta h}{\delta\rho}\left(\frac{\beta'(\lambda c - \beta h)}{c\delta} - a\right)y(t).$$

In matrix form:

$$\frac{dx(t)}{dt} = Ax(t) + Bx(t-\tau),$$

where

$$A = \begin{bmatrix} -\frac{\lambda c\delta}{\lambda c - \beta h} & -\frac{\beta(\lambda c - \beta h)}{c\delta} & 0 \\ 0 & -\frac{\beta'(\lambda c - \beta h)}{c\delta} & -\frac{\rho\delta h}{\lambda c - \beta h} \\ \frac{\beta'h}{\rho} - \frac{ac\delta h}{\rho(\lambda c - \beta h)} & \frac{\lambda c - \beta h}{\delta\rho}\left(\frac{\beta'(\lambda c - \beta h)}{c\delta} - a\right) & 0 \end{bmatrix}$$

and

$$B = \begin{bmatrix} 0 & 0 & 0 \\ \frac{\beta'\delta h}{\lambda c - \beta h} & \frac{\beta'(\lambda c - \beta h)}{c\delta} & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

Now we are all set to analyse our characteristic equation, which is the determinant:

$$\begin{vmatrix} v + \frac{\lambda c\delta}{\lambda c - \beta h} & \frac{\beta'(\lambda c - \beta h)}{c\delta} & 0 \\ -\frac{\beta'\delta h}{\lambda c - \beta h}e^{-v\tau} & v + \frac{\beta'(\lambda c - \beta h)}{c\delta}(1 - e^{-v\tau}) & \frac{\rho\delta h}{\lambda c - \beta h} \\ \frac{ac\delta h}{\rho(\lambda c - \beta h)} - \frac{\beta'h}{\rho} & \frac{\lambda c - \beta h}{\delta\rho}\left(a - \frac{\beta'(\lambda c - \beta h)}{c\delta}\right) & v \end{vmatrix} = 0,$$

which is of the form (4.1.1) with:

$$a_1 = \frac{\lambda c \delta}{\lambda c - \beta h} + \frac{\beta'(\lambda c - \beta h)}{c \delta}$$

$$a_2 = \frac{\beta' h(\lambda c - \beta h)}{c \delta} - ah$$

$$a_3 = -\frac{\beta'(\lambda c - \beta h)}{c \delta}$$

$$a_4 = \frac{\beta \beta' h}{c}$$

$$a_5 = 0$$

$$a_6 = \frac{\beta' h(\lambda c - \beta h)}{c} - adh.$$

Recall that the first condition for bifurcation was that:

$$r = a_6^2 - a_5^2 < 0.$$

However, $a_5 = 0$, and $a_6^2 \geq 0$ always, so this condition will never hold. So we'll check the second condition.

Notice that, with parameter values given in [76], $v_1 \approx 1/30$ and $h(v_1) \approx -0.037255$. The bifurcation value is $\tau_0 \approx 8.7$.

We would like to note that, for simplicity, simulations were run using parameter values from [76], but for any parameters given in Table 1 (Chapter Three), we do not find bifurcations occurring for any value of $\tau < 8$.

4.3.1 Numerical Simulations

Numerical simulations of the delayed system, using XPP, are quite instructive. We can see that for values of the delay $\tau = 1$, the system behaves exactly as the ODE system, with all components converging to their steady state values.
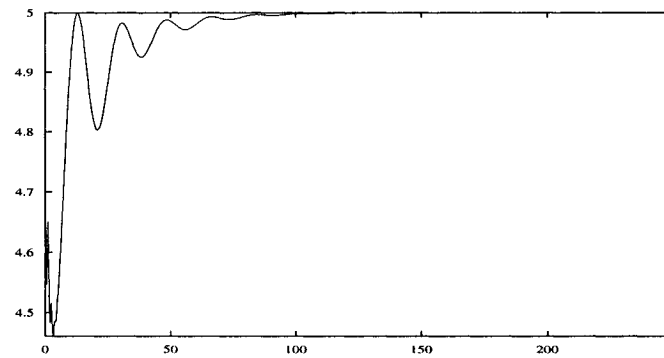
Here we can see x, y, z versus time:

Figure 4.3.1: The population of healthy cells converges to equilibrium for $\tau = 1$.
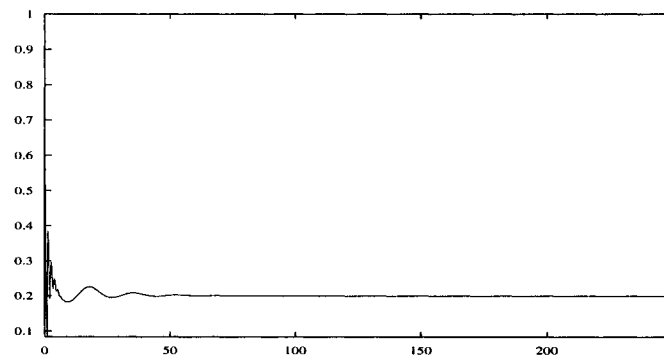

Figure 4.3.2: Infected cells converge to equilibrium for $\tau = 1$
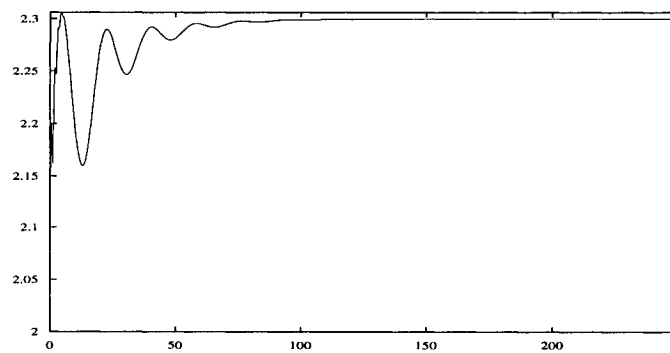

Figure 4.3.3: Immune response cells converge to equilibrium for $\tau = 1$

As well, we can see that when we plot the phase portrait of any two components, they spiral in to an equilibrium.

Figure 4.3.4: Healthy versus infected cells, $\tau = 1$
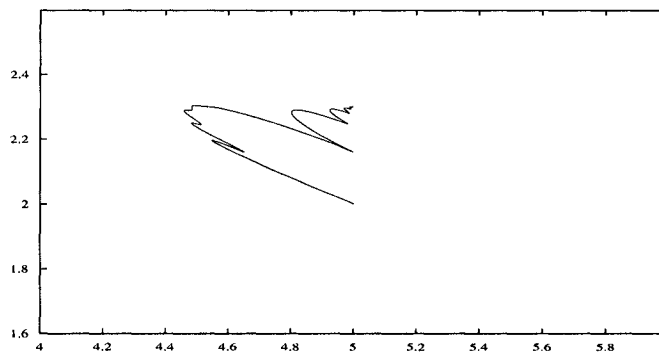
Figure 4.3.5: Healthy cells versus immunity, $\tau = 1$
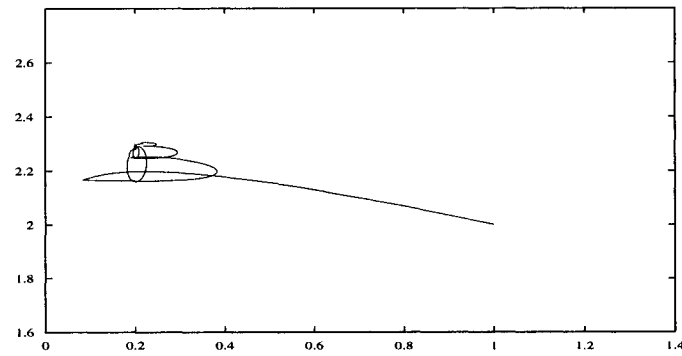
Figure 4.3.6: Infected cells versus immunity, $\tau = 1$

However, when we increase the delay we observe some periodicity in our components when they are plotted against time:
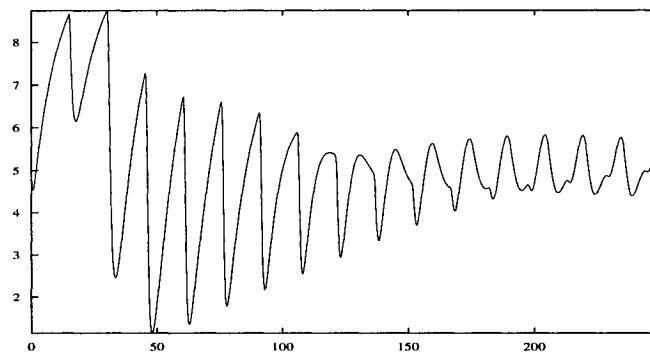
Figure 4.3.7: Healthy cells no longer tend to stability, $\tau = 10$
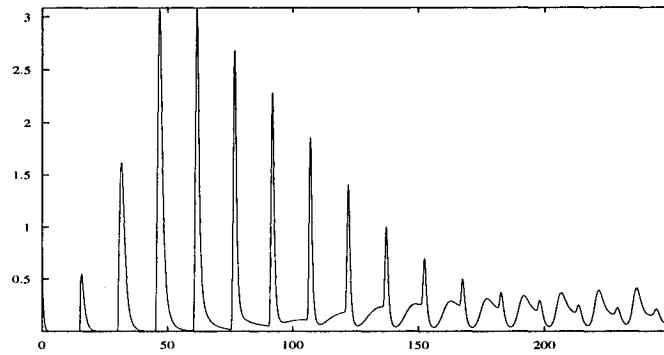
Figure 4.3.8: Infected cells oscillate, $\tau = 10$
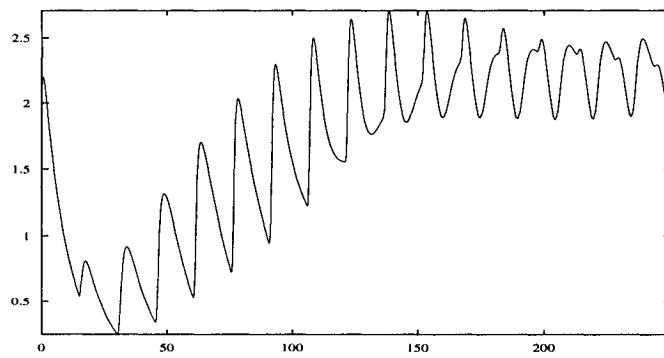
Figure 4.3.9: So does the immunity, $\tau = 10$

Also, we can see convergence to some sort of periodic orbit in the phase plane:
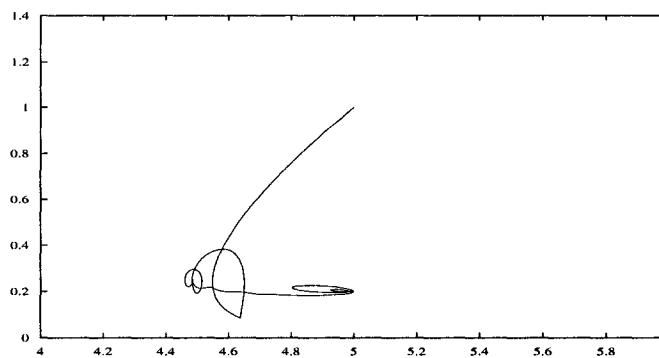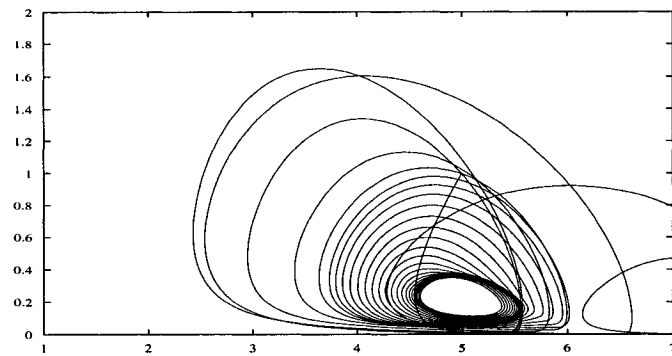
Figure 4.3.10: Healthy cells versus infected cells, $\tau = 10$
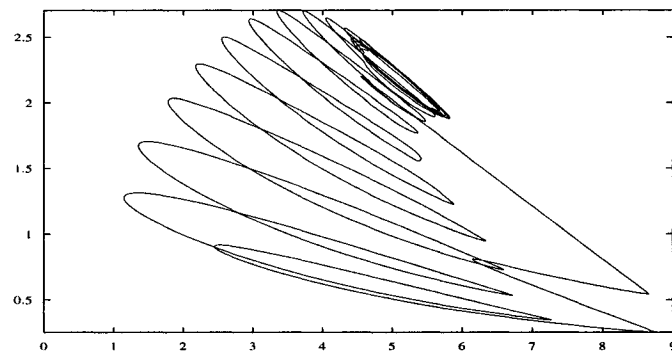
Figure 4.3.11: Healthy cells versus the immunity, $\tau = 10$
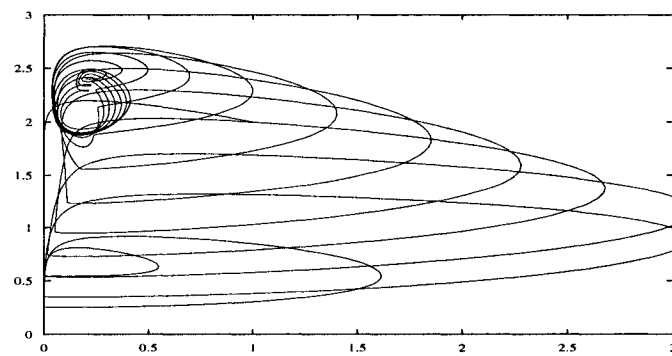
Figure 4.3.12: Infected cells versus immunity, $\tau = 10$

All simulations above are shown for $\beta' = \beta$. We note that if we assume only 70% of infected cells survive incubation, our oscillations appear slightly different:
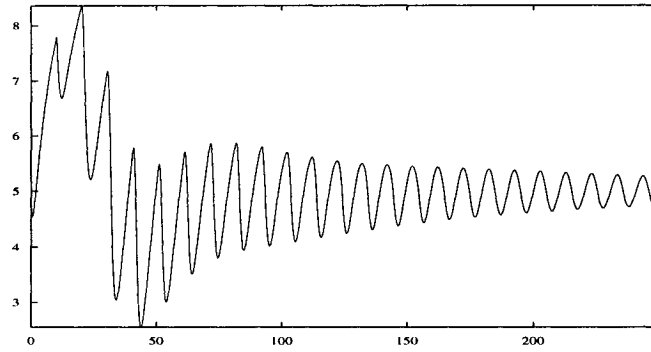
Figure 4.3.13: Healthy cells oscillate, $\beta = 0.35, \tau = 10$
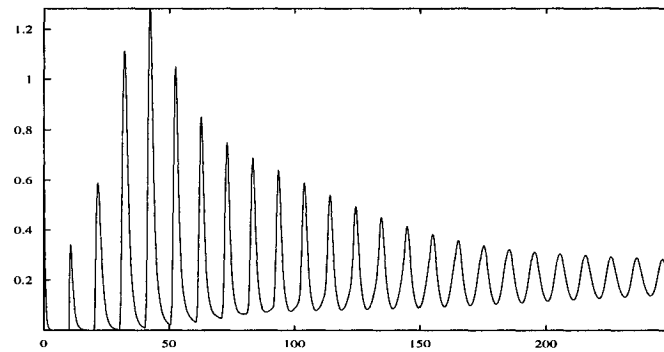
Figure 4.3.14: Infected cells oscillate, $\beta = 0.35, \tau = 10$
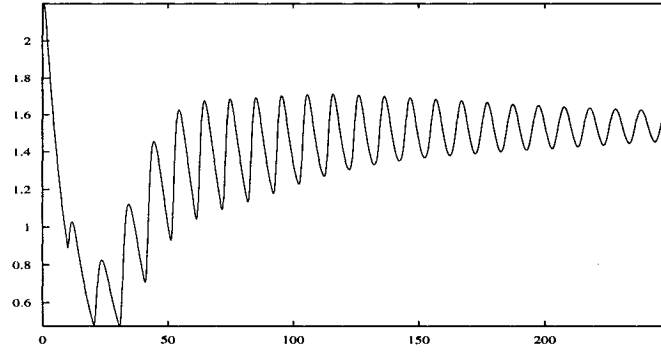
Figure 4.3.15: Immune response cells oscillate, $\beta = 0.35, \tau = 10$

We should note here that although this system does exhibit bifurcation behaviour, it does not occur for a realistic value of the delay, and hence our system is likely to remain stable and behave similarly to the ODE system (3.1.1)–(3.1.3).

4.3.2 Using a Distributed Delay

Another way to eliminate the appearance of $(t - \tau)$ from our differential equations is to use a distributed delay instead of a discrete delay. We then may apply the linear chain trick to transform our three-dimensional system into a four-dimensional system. This is useful because it will make the numerical analysis of our optimality system possible.

In this case the system would become:

$$\frac{dx}{dt} = \lambda - \delta x - \beta xy \tag{4.3.8}$$

$$\frac{dy}{dt} = \beta' \int_{-\infty}^{t} \alpha e^{-\alpha(t-w)} xy\, dw - ay - \rho yz \tag{4.3.9}$$

$$\frac{dz}{dt} = cxyz - hz. \tag{4.3.10}$$

We let

$$\Psi = \int_{-\infty}^{t} \alpha e^{-\alpha(t-w)} xy\, dw,$$

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whereby we obtain the relation $\frac{d\Psi}{dt} = \alpha xy - \alpha\Psi$. Thus the above system of functional differential equations is equivalent to the following system of ODEs:

$$\frac{dx}{dt} = \lambda - \delta x - \beta xy \qquad (4.3.11)$$

$$\frac{dy}{dt} = \beta'\Psi - ay - \rho yz \qquad (4.3.12)$$

$$\frac{dz}{dt} = cxyz - hz \qquad (4.3.13)$$

$$\frac{d\Psi}{dt} = \alpha xy - \alpha\Psi. \qquad (4.3.14)$$

It is simple to verify that this system exhibits instability under the same circumstances as does the system with discrete delay.

Our characteristic equation is:

$$v^4 + b_1 v^3 + b_2 v^2 + b_3 v + b_4 = 0. \qquad (4.3.15)$$

with

$$b_1 = \alpha + a + \delta + \beta'\bar{y} + \rho\bar{z}$$

$$b_2 = \alpha(a + \delta) + a\delta - \alpha\beta\delta\bar{x} + (h\rho + \alpha\beta' + \alpha\beta'a)\bar{y} + (\alpha\rho + \delta\rho + \alpha\beta'\rho\bar{y})\bar{z}$$

$$b_3 = \alpha a\delta - \alpha\beta\delta\bar{x} + (\alpha h\rho + \alpha a\beta' + \delta h\rho + \beta'h\rho\bar{y})\bar{y} + (\alpha\delta\rho + \alpha\beta'\rho\bar{y} - \beta h\rho\bar{y})\bar{z}$$

$$b_4 = \alpha h\rho\bar{y}(\delta + \beta c\bar{y} - \beta'\bar{z}).$$

We may apply the Routh-Hurwitz criteria, which state that for a four-dimensional system with characteristic equation (4.2.15), the interior equilibrium is stable for:

$$b_4 > 0, b_1 b_2 b_3 - b_1^2 b_4 - b_3^2 > 0.$$

A quick check of these conditions for the distributed delay model reveal that the system becomes unstable for $\alpha < 0.15$ or an average delay of about 9 days as in the system with discrete delay.

4.3.3 Biological Significance

Although our parameters were scaled, they are measured in time units of days (see [76]). We would like to call attention to the fact that the value of the delay after which instability occurs is about 8 days or so, which is far longer than the average delay in infectivity of 1-2 days. This indicates that in most situations, we should expect an individual with adequate immune response to HIV to remain stable unless some perturbation occurs (which most often does at some point in AIDS progression).

We shall contrast this result with the results of Chapter Six, in which we will examine a model of HIV spread that goes from cell to cell as does this one. However we will not assume any specific immunity to HIV in that model. Recall that that model quickly became unstable due to delay. One reason this might occur is that the immunity is important to keep the system stable — without it, the patient's condition is more likely to destabilise. Note, however, that we were not assuming that there was no immunity, but rather that it remains constant. When we consider variable immunity, our patient fares better. We conjecture that this is because even though the system is detrimentally affected by high levels of infection, if conditions are such that the immunity remains sustained (i.e. the interior equilibrium is stable), the patient will not destabilise due to the intracellular delay.

Chapter 5

Treatment of the Delay-Differential Equation Model

5.1 The Delayed Model with Suppression of Infection

We observed in the previous sections that our model with a delay in infection rate exhibited delay-induced bifurcation when τ was increased beyond its critical value, τ_0, which was close to nine days. Mathematically speaking, the interior equilibrium was conditionally stable and a Hopf bifurcation occurs at τ_0, whereby a periodic solution was born.

In this section, we ask: what is the effect of incorporating treatment into the delayed system? Ultimately, we would like to answer this using optimal control theory, so that we can maximise desirable quantities *at the same time as* we minimise cost. But we can also add the treatment as represented by a parameter and examine how this parameter affects the conditional stability of the equilibrium. That is, is the steady state still stable under the same circumstances as before?

Let u be a constant between 0 and 1, with $u = 1$ representing fully effective treatment and $u = 0$ representing no treatment. Our treated system with delay is represented by:

$$\frac{dx(t)}{dt} = \lambda - \delta x(t) - (1-u)\beta x(t)y(t) \tag{5.1.1}$$

$$\frac{dy(t)}{dt} = (1-u)\beta' x(t-\tau)y(t-\tau) - ay(t) - py(t)z(t) \tag{5.1.2}$$

$$\frac{dz(t)}{dt} = (1-u)cx(t)y(t)z(t) - hz(t). \tag{5.1.3}$$

Its interior equilibrium is given by:

$$\bar{E} = \left(\frac{\lambda c - (1-u)\beta h}{c\delta}, \frac{\delta h}{\lambda c - (1-u)\beta h}, \frac{(1-u)\beta'\lambda c - (1-u)^2\beta\beta' h}{cd\rho} - \frac{a}{\rho}\right).$$

We linearise about the interior equilibrium to obtain a system of the form:

$$\frac{dx(t)}{dt} = Ax(t) + Bx(t-\tau),$$

where

$$A = \begin{bmatrix} -\delta - \frac{\beta'\delta h}{\lambda c-(1-u)\beta h} & -\frac{\beta'(\lambda c-(1-u)\beta h)}{c\delta} & 0 \\ 0 & -\frac{\beta'(\lambda c-(1-u)\beta h)}{c\delta} & -\frac{\rho\delta h}{\lambda c-(1-u)\beta h} \\ \frac{\beta' h}{\rho} - \frac{ac\delta h}{\rho(\lambda c-(1-u)\beta h)} & \frac{\beta'(\lambda c-(1-u)\beta h)^2}{\rho c\delta} - \frac{a(\lambda c-(1-u)\beta h)}{c\delta} & 0 \end{bmatrix}$$

and

$$B = \begin{bmatrix} 0 & 0 & 0 \\ \frac{\beta'\delta h}{\lambda c-(1-u)\beta h} & \frac{\beta'(\lambda c-(1-u)\beta h)}{c\delta} & 0 \\ 0 & 0 & 0 \end{bmatrix}.$$

Our characteristic equation is again of the form:

$$v^3 + a_1 v^2 + a_2 v + (a_3 v^2 + a_4 v + a_5)e^{-v\tau} + a_6 = 0,$$

with the coefficient values:

$$a_1 = \frac{\beta'(\lambda c - (1-u)\beta h)}{c\delta}$$

$$a_2 = \frac{\beta'(\lambda c - (1-u)\beta h)}{c}(\frac{h}{c\delta} + 1) + \frac{\beta\beta'h(1-u)^2}{c} - \frac{ah}{c}$$

$$a_3 = -\frac{\beta'(\lambda c - (1-u)\beta h)}{c\delta}$$

$$a_4 = \frac{(1-u)^2\beta\beta'h}{c} - \frac{\beta'(\lambda c - (1-u)\beta h)}{c}$$

$$a_5 = 0$$

$$a_6 = \frac{\beta'(\lambda c - (1-u)\beta h)}{c^2} - \frac{a\delta h}{c} + \frac{(1-u)^2\beta\beta'h^2}{c}(\frac{1}{c} - 1).$$

Recall that we had two requirements for conditional stability, and they were that either:

$$a_6^2 - a_5^2 < 0,$$

which is clearly impossible in this case, or that:

$$v_1 = \frac{-(a_1^2 - a_3^2 - 2a_2) + \sqrt{(a_1^2 - a_3^2 - 2a_2)^2 + a_4^2 - a_2^2 + 2a_1a_6 - 2a_3a_5}}{3} > 0$$

and that

$$h(v_1) < 0,$$

where $h(v)$ is represented by equation (4.1.3) from Chapter Four.

It turns out that indeed this condition is satisfied for *any* value of u. We also note that the conditions for two purely imaginary roots of the characteristic equation (4.1.1) were checked and found not to be satisfied for any value of u. This means that there is only one switch in stability as τ varies.

What does this mean in practical terms? Well, we still have an interior equilibrium that is conditionally stable, but there is a dependence of our bifurcation parameter τ_0 upon u. That is, the higher u is, the higher τ_0 must be to induce bifurcation. What this means in terms of actual treatments is that if treatment is high enough, the destabilising effect of the

delay is eliminated.

We can observe some striking examples of this phenomenon when we observe the following numerical simulations.
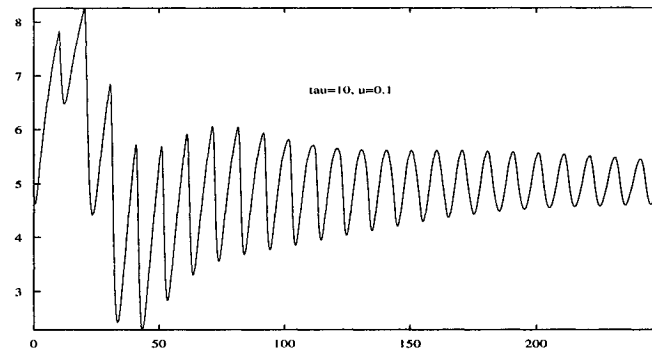
Figure 5.1.1: Healthy cells oscillate with time, $\tau = 10$, $u = 0.1$
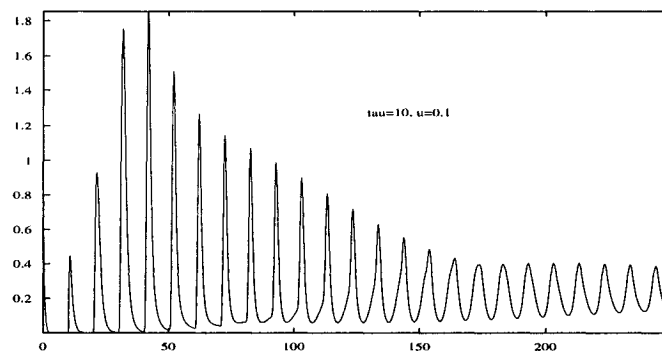
Figure 5.1.2: Infected cells oscillate with time, $\tau = 10$, $u = 0.1$
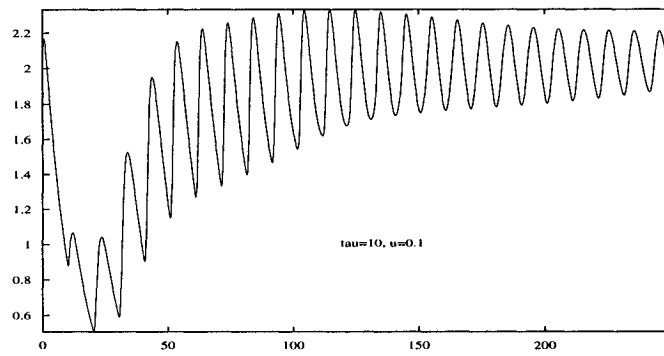
Figure 5.1.3: Immune response cells oscillate, $\tau = 10$, $u = 0.1$

We can see that the cells oscillate about a periodic orbit in the phase plane:
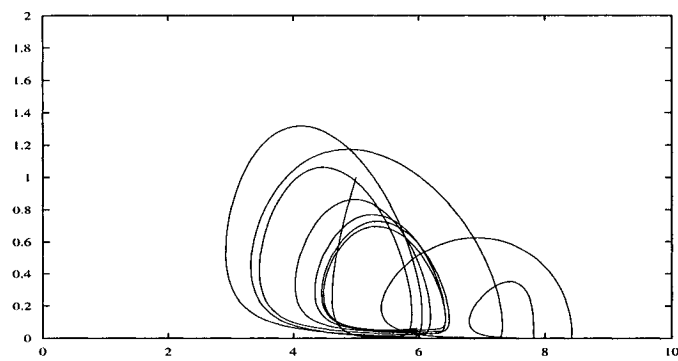
Figure 5.1.4: Healthy versus infected cells, $\tau = 10$, $u = 0.1$
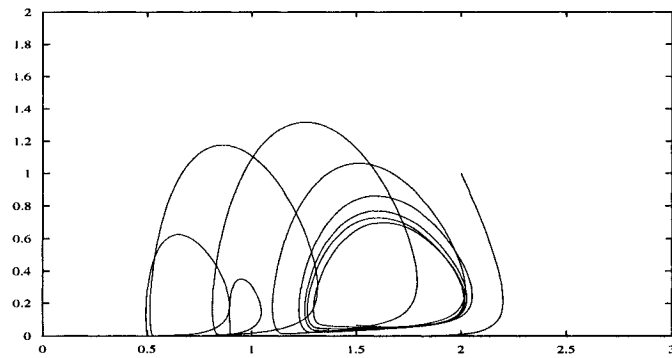
Figure 5.1.5: Infected cells versus the immunity, $\tau = 10$, $u = 0.1$

Now, observe what happens when u is increased:
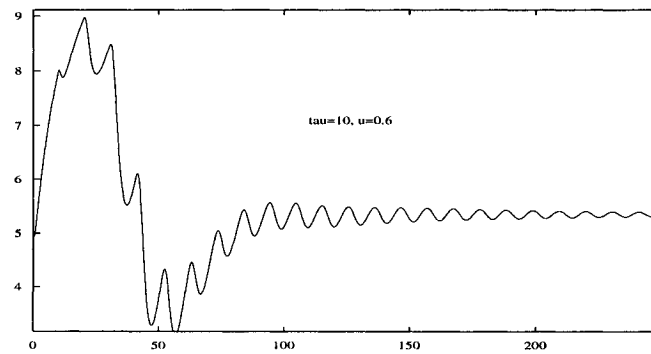
Figure 5.1.6: Healthy cells stabilise, $\tau = 10$, $u = 0.6$
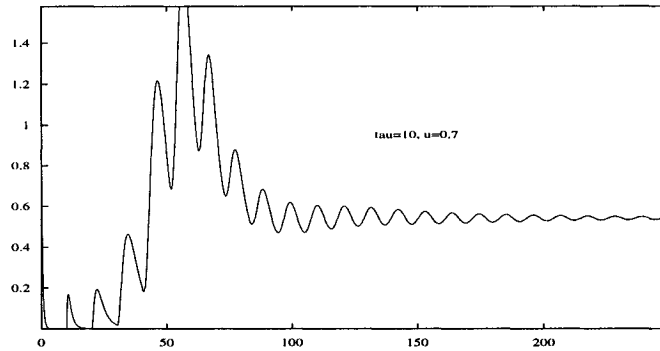
Figure 5.1.7: Infected cells stabilise, $\tau = 10$, $u = 0.6$
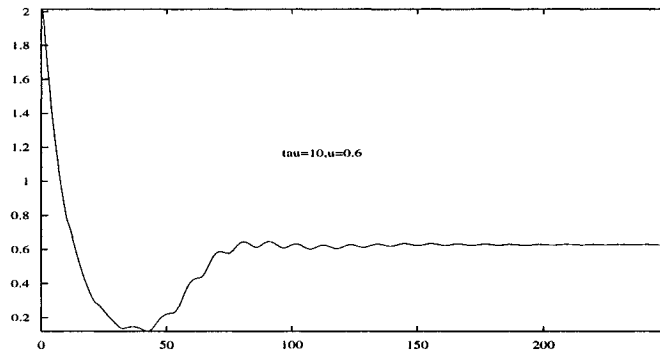
Figure 5.1.8: Immune response cells stabilise, $\tau = 10$, $u = 0.6$

It is clear from these images that if enough treatment is administered, the destabilising effect of the delay will be offset. Clearly maximal treatment will eliminate the infected cell population, but there is no treatment currently available that is in fact totally effective in this sense.

5.2 Theoretical Aspects of Optimal Control of the Delayed System

In this section, we would like to analyze how the delayed system behaves under application of our optimal control. Note that for systems with discrete delay, Pontryagin's Maximum

Principle still holds and the main difference will lie in time-dependence in our control and the optimality system, which will now contain delays in several terms.

We shall consider control of model (5.1.1-5.1.3).

Similar to the control problem for the ODE system, we find that we must:

$$\max J[u] = \int_0^T (x + z - \frac{Bu^2}{2})dt$$

subject to the state system:

$$\frac{dx(t)}{dt} = \lambda - \delta x(t) - (1 - u(t))\beta x(t)y(t) \tag{5.2.4}$$

$$\frac{dy(t)}{dt} = (1 - u(t))\beta' x(t - \tau)y(t - \tau) - ay(t) - \rho y(t)z(t) \tag{5.2.5}$$

$$\frac{dz(t)}{dt} = cx(t)y(t)z(t) - hz(t). \tag{5.2.6}$$

We find the Hamiltonian is:

$$H = x(t) + z(t) - \frac{Bu(t)^2}{2} + \lambda w_1(t) - \delta x(t)w_1(t) - (1 - u(t))\beta x(t)y(t)$$

$$+(1 - u(t))\beta' x(t - \tau)y(t - \tau) - ay(t)w_2(t) - \rho y(t)z(t)w_2(t)$$

$$+cx(t)y(t)z(t)w_3(t) - hz(t)w_3(t) + v_1(t)u(t) + v_2(t)(1 - u(t)).$$

Applying Pontryagin's Maximum Principle to this Hamiltonian we find that our optimal control is almost the same as before, but there is one notable difference:

$$u^*(t) = \min\left\{1, \max\left\{\frac{\beta x(t)y(t)w_1(t) - \beta' x(t - \tau)y(t - \tau)w_2(t)}{B}, 0\right\}\right\}. \tag{5.2.7}$$

Using the conditions for the adjoint variables we obtain an optimality system as follows:

$$\frac{dx(t)}{dt} = \lambda - \delta x(t) - (1 - u(t))\beta x(t)y(t)$$

$$\frac{dy(t)}{dt} = (1 - u(t))\beta' x(t - \tau)y(t - \tau) - ay(t) - \rho y(t)z(t)$$

$$\frac{dz(t)}{dt} = cx(t)y(t)z(t) - hz(t)$$

$$\frac{dw_1(t)}{dt} = -1 + dw_1(t) + (1 - u(t))\beta y(t)w_1(t)$$
$$- (1 - u(t))\beta' y(t - \tau)w_2(t) - cy(t)z(t)w_3(t)$$

$$\frac{dw_2(t)}{dt} = (1 - u(t))\beta x(t)w_1(t) - (1 - u(t))\beta' x(t - \tau)w_2(t)$$
$$+ aw_2(t) + \rho z(t)w_2(t) - cx(t)z(t)w_3(t)$$

$$\frac{dw_3(t)}{dt} = -1 + \rho y(t)w_2(t) - cx(t)y(t)w_3(t) + hw_3(t)$$

$$u^*(t) = \min\left\{1, \max\left\{\frac{\beta x(t)y(t)w_1(t) - \beta' x(t - \tau)y(t - \tau)w_2(t)}{B}, 0\right\}\right\}.$$

To properly analyze this delayed system, we must find and linearise about its interior equilibrium:

$$\bar{x} = \frac{\lambda c - (1 - u^*)\beta h}{c\delta}$$

$$\bar{y} = \frac{\delta h}{\lambda c - (1 - u^*)\beta h}$$

$$\bar{z} = \frac{(1 - u^*)\beta'(\lambda c - (1 - u^*)\beta h)}{\rho c\delta} - \frac{a}{\rho}$$

$$\overline{w_1} = \frac{\rho + \beta'}{\delta\rho}$$

$$\overline{w_2} = \frac{\lambda c - (1 - u^*)\beta h}{\delta h\rho}$$

$$\overline{w_3} = (1 - u^*)\left[\frac{\beta'(\rho + \beta')(\lambda c - (1 - u^*)\beta h)}{c\delta^2\rho} - 1\right] + \frac{ac\delta}{\beta'(\lambda c - (1 - u^*)\beta h)}$$
$$+ \frac{\lambda c - (1 - u^*)\beta h}{\delta h\rho}\left[\frac{\beta'(\lambda c - (1 - u^*)\beta h)}{c\delta} - a\right].$$

As usual, we linearise by setting:

$$
\begin{aligned}
u &= x - \bar{x} \\
v &= y - \bar{y} \\
w &= z - \bar{z} \\
\alpha_1 &= w_1 - \overline{w_1} \\
\alpha_2 &= w_2 - \overline{w_2} \\
\alpha_3 &= w_3 - \overline{w_3}.
\end{aligned}
$$

This yields a characteristic equation of the form:

$$
c(w) = \begin{vmatrix}
w - a_1 & -a_2 & 0 & 0 & 0 & 0 \\
-b_1 e^{-w\tau} & w - a_3 - b_2 e^{-w\tau} & -a_4 & 0 & 0 & 0 \\
-a_5 & -a_6 & w - a_7 & 0 & 0 & 0 \\
0 & -a_8 - b_3 e^{-w\tau} & -a_9 & w - a_{10} & -a_{11} & -a_{12} \\
-a_{13} - b_4 e^{-w\tau} & 0 & -a_{14} & -a_{15} & w - a_{16} & -a_{17} \\
-a_{17} & -a_{18} & 0 & 0 & -a_{19} & w - a_{20}
\end{vmatrix} = 0.
$$

This equation is of the form:

$$w^6 + c_1 w^5 + c_2 w^4 + c_3 w^3 + c_4 w^2 + c_5 w + c_6$$

$$+ (c_7 w^5 + c_8 w^4 + c_9 w^3 + c_{10} w^2 + c_{11} w + c_{12}) e^{-w\tau}.$$

This is a sixth-degree transcendental equation for our characteristic equation. Theoretically, it is possible to evaluate such an equation to determine whether it exhibits purely imaginary roots, but we follow the analysis as performed in section 1 of this chapter and find that this amounts to determining if and when a *twelfth-* degree polynomial exhibits positive roots. Clearly this is next to impossible in a general setting. So, we choose to analyse this equation using Maple. We find purely imaginary roots for $\tau \approx 5$.

5.2.1 Numerical Results

Numerical simulations of the delayed optimality system were run using XPP. We assumed a free final time, since it is not possible to solve such a nonlinear delayed boundary value problem using this method. All initial values were set close to the calculated equilibrium values. The results obtained were as follows:

For $\tau = 1$, we find that the system tends toward its interior equilibrium as the ODE system does.

However, we notice that as the length of the delay is increased to a value of $\tau = 5$, periodicity begins to appear in all components. Notice the behaviour of x, y, z versus time now:
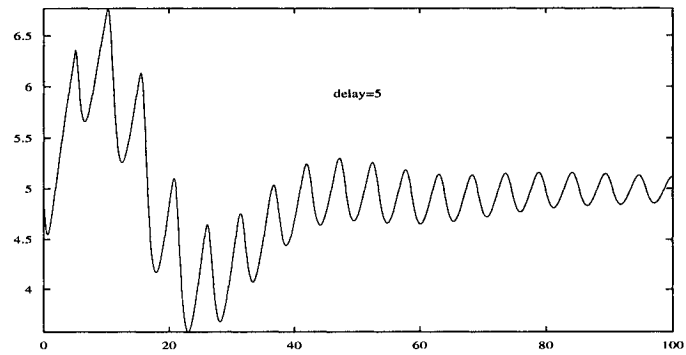
Figure 5.2.9: Healthy cells oscillate, $\tau = 5$
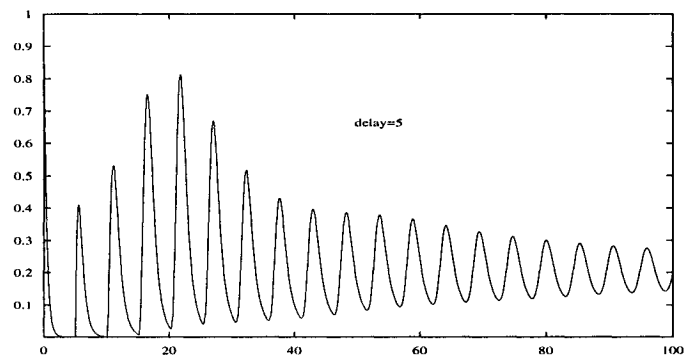
Figure 5.2.10: Infected cells exhibit periodicity, $\tau = 5$
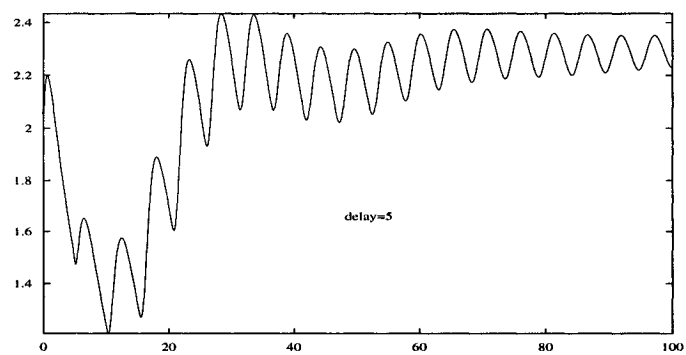
Figure 5.2.11: Immune response cells oscillate with time, $\tau = 5$

Also, plotting any two components against each other, we notice limit cycle behaviour. Observe the following phase portrait of y versus x:
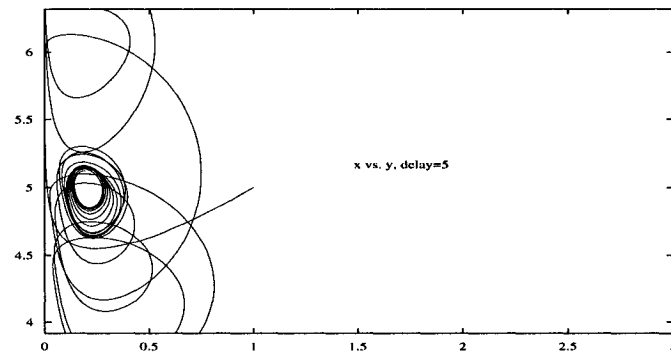
Figure 5.2.12: Infected versus healthy cells, $\tau = 5$

We do not consider optimal control of the system with distributed delay, since realistically, the system is unlikely to exhibit bifurcation in most realistic scenarios.

Chapter 6

A Treatment Model without Immune Response

In this chapter, we examine a model of cell-to-cell spread of HIV and its behaviour under treatment that reduces infection rate. This model was adapted from the paper by Spouge et. al. [66]. It assumes direct infection from infected to healthy cells, which is important to consider since a significant amount of HIV activity occurs in tissues such as lymph glands (see [62]). We shall begin by reviewing the qualitative behaviour of the ODE model as presented in [66], and then we shall modify it and investigate its behaviour in the following situations:

- We examine treatment of the ODE system with a parameter representing a drug that reduces the infectivity rate. We find that the higher the strength or efficacy of the treatment, the more infected cells that must survive to ensure stability of the interior (infected) equilibrium. Otherwise, the healthy equilibrium may regain stability.

- We incorporate a delay between the time of infection and the time that infected cells begin to produce virus. We discover that the interior equilibrium loses stability via a delay-induced bifurcation, so long as the number of infected cells surviving the incubation period is large enough. Moreover, we find that the higher the number of infected cells that survive, the smaller the critical value of the delay.

- We incorporate treatment into the delayed model. We find that since the critical delay depends upon the fraction of infected cells surviving incubation, which depends upon

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the treatment level, that treatment, if high enough, has the ability to restabilise the system after it has become unstable due to the delay.

6.1 The ODE Model

In this section, we discuss the ODE model

$$\frac{dC}{dt} = r_C C(t)\left(1 - \frac{C(t) + I(t)}{C_M}\right) - k_I C(t)I(t) \tag{6.1.1}$$

$$\frac{dI}{dt} = k'_I C(t)I(t) - \mu_I I(t). \tag{6.1.2}$$

Variables and parameters are explained as follows: $C(t)$ represents the concentration of healthy cells and $I(t)$ represents the concentration of infected cells. r_C is the effective reproductive rate of healthy cells (the term is the total reproductive rate for healthy cells, minus the death rate for healthy cells), C_M is the effective carrying capacity of the system, k_I represents the infection of healthy cells by the infected cells in a *well-mixed* system, $\frac{k'_I}{k_I}$ is the fraction of cells surviving the incubation period, μ_I is the death rate of the infected cells.

Notice that the system has the following three equilibria: the trivial equilibrium $E_0 = (0,0)$, the healthy equilibrium $E_1 = (C_M, 0)$, and the infected equilibrium $\overline{E} = (\overline{C}, \overline{I})$. Stability analysis of these three equilibria reveals two possible scenarios:

(i) When $C_M < \frac{\mu_I}{k'_I}$ (which, under parameter ranges given, usually is not the case), the healthy cells predominate and infected cells die exponentially. In this case E_0 is unstable, E_1 is asymptotically stable, and $\overline{E}$ is unstable. We note that the condition for E_1 to be stable is that $k_I < 1.5 \times 10^{-7}$, or that *less than* 7.5% of infected cells survive the incubation period to become infectious. In this case E_1 is asymptotically stable. We note, however, that in reality it is unlikely that so few cells would survive latency, and that the following case is more likely.

(ii) When $\frac{\mu_I}{k'_I} < C_M < \frac{r_C}{k_I}$, healthy cells and infected cells co-exist. This would correspond to the case where, in models representing cell-free viral spread, we have an endemically infected steady state. This means that infection is present but it does not grow out of bound, and levels of healthy cells do not crash to zero. In this case E_0 remains unstable, E_1

is now also unstable and $\overline{E}$ has become asymptotically stable. A transcritical bifurcation occurs at $C_M > \mu_I/k_I'$, corresponding to $k_I' = 1.5 \times 10^{-7}$. With parameter values given in Table 6.1 at the end of this chapter, numerical simulations show that the positive equilibrium $\overline{E}$ is asymptotically stable (see Figure 3.1).
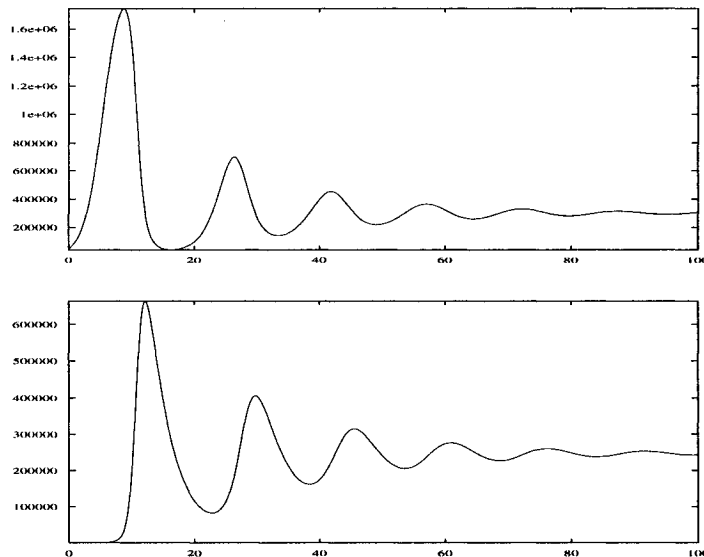
Figure 6.1.1: $C(t)$ and $I(t)$ converge to the steady state values.

In the (C, I)−plane, trajectories spiral towards the equilibrium (see Figure 6.1.2).
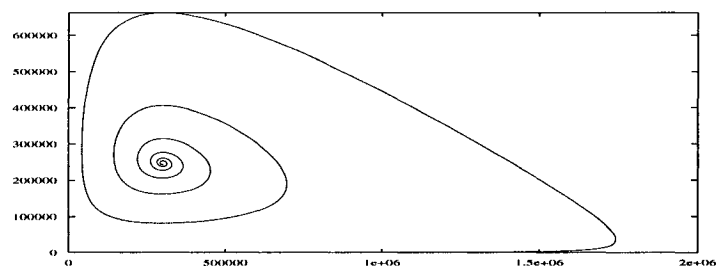
Figure 6.1.2: The infected equilibrium is asymptotically stable.

The equilibrium $\overline{E}$ is, in fact, globally stable for $\frac{\mu_I}{k_I'} < C_M < \frac{r_C}{C_M}$. We can see this by applying Liapunov's theorem. We choose the following Liapunov function:

$$V(C,I) = c_1\left(-\overline{C}\log\frac{C}{\overline{C}} + C - \overline{C}\right) + c_2\left(-\overline{I}\log\frac{I}{\overline{I}} + I - \overline{I}\right) \tag{6.1.3}$$

This function is clearly positive if we choose c_1, c_2 to be positive constants, and it equals zero for $E = \overline{E}$. We have

$$\begin{aligned}
\frac{dV}{dt} &= c_1\frac{dC/dt}{C}(C-\overline{C}) + c_2\frac{dI/dt}{I}(I-\overline{I}) \\
&= -c_1\frac{r_C}{C_M}(C-\overline{C})^2 + \left[c_2 k_I' - c_1\frac{(r_C - k_I C_M)}{C_M}\right](C-\overline{C})(I-\overline{I}).
\end{aligned}$$

Assume that $C_M < \frac{r_C}{k_I}$ and choose $c_1 = k_I'$, $c_2 = \frac{(r_C - k_I C_M)}{C_M} > 0$. We have

$$\frac{dV}{dt} = -\frac{k_I' r_C}{C_M}(C-\overline{C})^2 < 0,$$

which implies that the equilibrium $\overline{E}$ is globally asymptotically stable for $\frac{\mu_I}{k_I'} < C_M < \frac{r_C}{k_I}$. We thus have proved

Proposition 6.1.1 *If*

$$\frac{\mu_I}{k_I'} < C_M < \frac{r_C}{k_I}, \tag{6.1.4}$$

then the infected equilibrium $\overline{E}$ of the ODE model (6.1.1)–(6.1.2) is globally asymptotically stable.

6.2 The ODE Model With Suppression of Infection Rate

In this section, we examine the stability properties of system (6.1.1)–(6.1.2) under treatment by a drug that reduces the viral replication rate. We let treatment be represented by u, which is bounded below by zero (no treatment) and above by one (fully effective treatment). The system is now given by:

$$\frac{dC}{dt} = r_C C(t)\left(1 - \frac{C(t) + I(t)}{C_M}\right) - (1-u)k_I C(t)I(t) \tag{6.2.5}$$

$$\frac{dI}{dt} = (1-u)k_I' C(t)I(t) - \mu_I I(t). \tag{6.2.6}$$

Once again we observe three equilibria: a trivial equilibrium which remains an always unstable saddle point, a healthy equilbrium

$$E_1 = (C_M, 0)$$

and an interior equilibrium given by:

$$\overline{E} = \left(\frac{\mu_I}{(1-u)k_I'}, \frac{(1-u)r_Ck_I'C_M - r_C\mu_I}{(1-u)k_I'(r_C + (1-u)k_IC_M)} \right).$$

Analysis of the Jacobian matrix shows that the healthy equilibrium is stable for $k_I' < \frac{\mu_I}{(1-u)C_M}$. When k_I' passes through this value a transcritical bifurcation occurs whereby the healthy equilibrium loses stability and the infected equilibrium is asymptotically stable. However we note that this condition may also be stated in terms of the treatment u. That is, the healthy equilibrium is stable provided

$$u > 1 - \frac{\mu_I}{k_I'C_M},$$

and the infected equilibrium is stable if this inequality is reversed. For example, if 50% of infected cells survive incubation, we require a treatment level of $u > 0.85$ to drive the system back to health. If 75% of infected cells survive incubation, we require $u > 0.9$ to drive the system back to health.

We would like to note that giving such high treatment continuously is unrealistic given drug toxicity concerns, but examining the system's behaviour under these circumstances is useful in that it provides reassurance that it does indeed behave in a realistic way. In the following section we shall examine what happens when we use optimal control theory to determine a treatment that will minimise drug cost.

6.3 The Controlled ODE Model: A Theoretical Examination

We wish to examine what happens when we control treatment so as to maximise levels of healthy cells and minimise drug cost. In this case our treatment is a control $u(t)$ with values between zero and one; we assume that u is Lebesgue-measurable. Our optimal

control problem becomes:

$$\max J[u] = \int_0^T \left(C - \frac{Bu^2}{2} \right) dt \tag{6.3.7}$$

subject to the state system:

$$\frac{dC}{dt} = r_C C(t) \left(1 - \frac{C(t) + I(t)}{C_M} \right) - (1 - u)k_I C(t) I(t) \tag{6.3.8}$$

$$\frac{dI}{dt} = (1 - u)k_I' C(t) I(t) - \mu_I I(t). \tag{6.3.9}$$

We may use Pontryagin's Maximum Principle to find the optimal control from the Hamiltonian:

$$H = C - \frac{Bu^2}{2} + r_C C \lambda_1 - \frac{r_C C^2}{C_M} \lambda_1 - \frac{r_C CI}{C_M} \lambda_1 - (1 - u)k_I CI \lambda_1$$

$$+ (1 - u)k_I' CI \lambda_2 - \mu_I I \lambda_2 + v_1(t)u(t) + v_2(t)(1 - u(t)).$$

(Note that the λ_j are the adjoint or dual variables.)

As in chapter three, we find that

$$u^*(t) = \min \left\{ 1, \frac{CI(k_I \lambda_1 - k_I' \lambda_2)^+}{B} \right\}.$$

Our optimality system is the state system together with the optimal control $u^*(t)$ and the adjoint system as defined by:

$$\frac{d\lambda_1}{dt} = -1 - r_C \lambda_1 + \frac{2r_C C}{C_M} \lambda_1 + \frac{r_C I}{C_M} \lambda_1 + (1 - u)k_I I \lambda_1 - (1 - u)k_I' I \lambda_2 \tag{6.3.10}$$

$$\frac{d\lambda_2}{dt} = \frac{r_C C}{C_M} \lambda_1 + (1 - u)k_I C \lambda_1 - (1 - u)k_I' C \lambda_2 + \mu_I \lambda_2. \tag{6.3.11}$$

So the full optimality system is given by:

$$\frac{dC}{dt} = r_C C(t)\left(1 - \frac{C(t) + I(t)}{C_M}\right) - (1-u)k_I C(t)I(t) \tag{6.3.12}$$

$$\frac{dI}{dt} = (1-u)k_I' C(t)I(t) - \mu_I I(t) \tag{6.3.13}$$

$$\frac{d\lambda_1}{dt} = -1 - r_C\lambda_1 + \frac{2r_C C}{C_M}\lambda_1 + \frac{r_C I}{C_M}\lambda_1 + (1-u)k_I I\lambda_1 - (1-u)k_I' I\lambda_2 \tag{6.3.14}$$

$$\frac{d\lambda_2}{dt} = \frac{r_C C}{C_M}\lambda_1 + (1-u)k_I C\lambda_1 - (1-u)k_I' C\lambda_2 + \mu_I\lambda_2 \tag{6.3.15}$$

$$u^*(t) = \min\left\{1, \frac{CI(k_I\lambda_1 - k_I'\lambda_2)^+}{B}\right\}. \tag{6.3.16}$$

6.3.1 Stability Results

For the sake of mathematical completeness, we shall determine the stability properties of the optimality system. We can easily find the interior equilibrium of this system and determine its stability by finding the roots of the Jacobian matrix. The Jacobian is given by:

$$\begin{bmatrix} a_1 & a_2 & 0 & 0 \\ a_3 & 0 & 0 & 0 \\ a_4 & a_5 & -a_1 & -a_3 \\ a_5 & 0 & -a_2 & 0 \end{bmatrix}$$

where

$$a_1 = r_c - \frac{2r_C C}{C_M} - \frac{r_C I}{C_M} - (1-u^*)I$$

$$a_2 = -\frac{r_C C}{C_M} - (1-u)k_I C$$

$$a_3 = (1-u)k_I' I$$

$$a_4 = \frac{2r_C\lambda_1}{C_M}$$

$$a_5 = \frac{r_C\lambda_1}{C_M} + (1-u)k_I\lambda_1 - (1-u)k_I'\lambda_2.$$

This yields a characteristic equation in a highly tractable form; it is:

$$v^4 - (a_1^2 + 2a_2a_3)v^2 + a_2^2a_3^2 = 0, \tag{6.3.17}$$

or, setting $v^2 = z$:

$$z^2 - (a_1^2 + 2a_2a_3)z + a_2^2a_3^2 = 0, \tag{6.3.18}$$

which has repeated roots for:

$$v^2 = \frac{a_1^2 + 2a_2a_3 \pm a_1\sqrt{a_1^2 + 4a_2a_3}}{2}.$$

However, we note that there is no possibility of all roots having negative real part due to the repeated roots; therefore, the infected equilibrium of the optimality system will be unstable. We find that both values of v^2 are positive; this ensures no complex roots of the characteristic equation. So, the general optimal control problem with a "free" final time exhibits an interior equilibrium that is an unstable saddle point. This means that under therapy with the optimal control, we have $C(t)$ increasing and $I(t)$ decreasing. Examining the qualitative appearance of the control, we deduce that the optimal control is decreasing from its maximum to an end of $u = 0$, corresponding to no treatment at the final time (when one is implemented).

However, while of theoretical interest, we would not necessarily expect the infected equilibrium to be stable, since we are trying to drive the system back to health. More information can be gleaned from observing numerical simulations. We solve the optimality system numerically using a Runge-Kutta four scheme (forward and backward calculations for state and adjoint varibles). We start with a guess for the adjoint variables and the optimal control, and find that healthy cells increase linearly until they reach a saturation point about $6 - 7\%$ higher than their initial value, whereas infected cells drop quite rapidly to near zero. However, infection is never completely eradicated. We find that the control itself stays near its maximal value until almost the end of treatment (250 days in this case), at which point it drops off sharply to zero.

6.4 The Discrete Delay Model

In this section we consider the delay differential equation model with a discrete delay, namely:

$$\frac{dC}{dt} = r_C C(t)\left(1 - \frac{C(t) + I(t)}{C_M}\right) - k_I C(t) I(t) \tag{6.4.1}$$

$$\frac{dI}{dt} = k_I' C(t - \tau) I(t - \tau) - \mu_I I(t). \tag{6.4.2}$$

Notice that the model has the same equilibria given in section 2, $E_0 = (0,0)$, $E_1 = (C_M, 0)$, and $\overline{E} = (\overline{C}, \overline{I})$.

We are interested in the stability of the infected equilibrium $\overline{E}$. The characteristic equation of the linearized system is given by:

$$\Delta(\lambda) = \lambda^2 + p\lambda + r + (s\lambda + q)e^{-\lambda\tau} = 0, \tag{6.4.3}$$

where

$$p = \frac{\mu_I(k_I' C_M + r_C)}{k_I' C_M}$$

$$q = r_C \mu_I \frac{(k_I' C_M - 2\mu_I)}{k_I' C_M}$$

$$r = \frac{r_C \mu_I^2}{k_I' C_M}$$

$$s = -\mu_I.$$

Characteristic equations of this form have been extensively examined in [59]. Certain conditions on the coefficients p, q, r and s will ensure either all roots of the characteristic equation have negative real part or at least one root has positive real part. The results of interest to us are as follows:

Lemma 6.4.1 *Consider a characteristic equation of the form (6.4.3).*

(i) If $p + s > 0$ and $q + r > 0$, then all roots of the characteristic equation have negative real part in the absence of delay.

(ii) *If* $p + s > 0$, $q + r > 0$, *and either* $(s^2 - p^2 + 2r < 0$ *and* $r^2 - q^2 > 0)$ *or* $(s^2 - p^2 + 2r)^2 < 4(r^2 - q^2)$, *then all roots of the characteristic equation have negative real part for all delay values, that is, the equilibrium is absolutely stable.*

(iii) *If* $p + s > 0$, $q + r > 0$, *and either* $r^2 - q^2 < 0$ *or* $(s^2 - p^2 + 2r > 0$ *and* $(s^2 - p^2 + 2r)^2 = 4(r^2 - q^2))$, *then there is a critical value* τ_0 *defined by:*

$$\tau_0 = \frac{1}{\omega_+} \arccos \frac{q(\omega_+^2 - r) - ps\omega_+^2}{s^2\omega_+^2 + q^2}, \tag{6.4.4}$$

where ω_+ *satisfies*

$$2\omega_+^2 = (s^2 - p^2 + 2r) + \sqrt{(s^2 - p^2 + 2r)^2 - 4(r^2 - q^2)}, \tag{6.4.5}$$

when $\tau \in [0, \tau_0)$, *all roots of the characteristic equation have negative real part; when* $\tau = \tau_0$, *there is a pair of purely imaginary roots* $\pm i\omega_+$; *and when* $\tau > \tau_0$, *the characteristic equation has at least one root with positive real part.*

We will use the above results to analyze the stability of the infected equilibrium. Checking the first two conditions, we note that $p + s > 0$ holds if

$$\mu_I \left(\frac{k_I' C_M + r_C}{k_I' C_M} - 1 \right) > 0$$

which is obviously the case, since r_C is positive. The second condition, $q + r > 0$, holds whenever $k_I' > \mu_I / C_M$, which is exactly the condition for the feasibility of the interior equilibrium in the ODE model. This is not surprising, because the preceding two conditions are simply conditions for stability of the system in the absence of delay.

Consider the third condition for the characteristic equation to have only roots with negative real part. For this to be true, we require that *both* of the following conditions hold:

$$r^2 - q^2 > 0, \tag{6.4.6}$$

$$s^2 - p^2 + 2r < 0. \tag{6.4.7}$$

The second condition holds for all values of parameters. However, the first condition is somewhat more interesting. Notice that for $r^2 - q^2 > 0$, we require the following inequality

to be satisfied:

$$C_M^2 k_I'^2 - 4\mu_I C_M k_I' + 3\mu_I^2 < 0.$$

This is true when

$$\frac{\mu_I}{C_M} < k_I' < \frac{3\mu_I}{C_M}.$$

We summarize the conditions on stability as follows:

Proposition 6.4.2 *The positive equilibrium $\overline{E}$ of system (6.4.1)–(6.4.2) is asymptotically stable for all delay τ when*

$$\frac{\mu_I}{C_M} < k_I' < \frac{3\mu_I}{C_M}. \tag{6.4.8}$$

Thus, there is a region of absolute stability for the infected equilibrium. Notice that this region corresponds to only between 7.5% and 22.5% of infected cells surviving the latent period. The obvious question to ask is, what happens when more cells survive (which, in realistic situations, is likely)?

We note that for $k_I' > 3\mu_I/C_M$, $r^2 - q^2 < 0$, and delay-induced instability may occur because the characteristic equation has a root with positive real part. Define

$$A = \sqrt{((k_I'C_M)^2 - \mu_I)((k_I'C_M)^2 - 3\mu_I)}.$$

We summarize the conditions for bifurcation as follows:

Theorem 6.4.3 *Assume that*

$$k_I' > \frac{3\mu_I}{C_M}. \tag{6.4.9}$$

Then there is a critical value τ_0 given by

$$\tau_0 = \frac{1}{\omega_+} \arccos \frac{1}{k_I'C_M} \left[\frac{(k_I'C_M(r_C + \mu_I) - r_C\mu_I)A - 2r_C\mu_I k_I'C_M(k_I'C_M - 2\mu_I)}{\mu_I A + 2r_C(k_I'C_M - 2\mu_I)^2} \right],$$

where

$$\omega_+ = \frac{1}{2k_I'C_M} \sqrt{2r_C\mu_I(2A - r_C\mu_I)},$$

such that the infected equilibrium $\overline{E}$ of system (6.4.1)–(6.4.2) is asymptotically stable when $\tau \in [0, \tau_0)$ and unstable when $\tau > \tau_0$. A Hopf bifurcation occurs at $\overline{E}$ when $\tau = \tau_0$; that is, a family of periodic solutions bifurcates from $\overline{E}$ when τ passes through the critical value τ_0.

Notice that τ_0 depends on k_I'. In the following, we will see that for larger values of k_I', the critical value τ_0 gets smaller, whereas the periods and amplitudes of the oscillatory solutions get larger.

Using values of k_I' corresponding to $25\%, 50\%, 75\%$ of cells surviving incubation, we obtain the following results for the critical value of the delay.

Suppose that 25% of infected cells survive incubation. This corresponds to a value of $k_I' = 5 \times 10^{-7}$. In this case, using the formulas given above, we obtain a critical value of the delay to be $\tau_0 = 6.23$ days. Since the actual incubation period is one day, we do not expect this to be of biological significance. Numerical simulations show that both C and I are stable for realistic values of all other parameters, when $k_I' = 5 \times 10^{-7}$.

Now suppose that half the infected cells survive incubation. In this case, the critical value for τ_0 obtained analytically is 0.82 days, which *is* of biological significance. Numerical simulations show that for $k_I' = 10^{-6}$ and $\tau = 0.4 < \tau_0$, the components $C(t)$ and $I(t)$ are converging to the steady state values as time increases (see Figure 6.4.1).
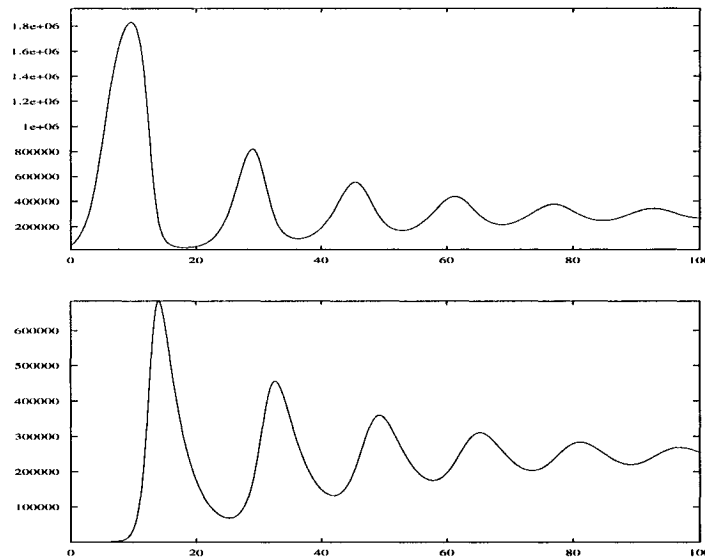
Figure 6.4.1: $C(t)$ and $I(t)$ converge to the steady state values when $\tau < \tau_0$, here $\tau = 0.4$.

In the (C, I)−plane, trajectories spiral towards the equilibrium (see Figure 6.4.2).

Figure 6.4.2: The infected equilibrium is asymptotically stable when $\tau = 0.4 < \tau_0$.

When the delay is increased to $\tau = 1 > \tau_0$, the components $C(t)$ and $I(t)$ oscillate with increasing time (see Figure 6.4.3).
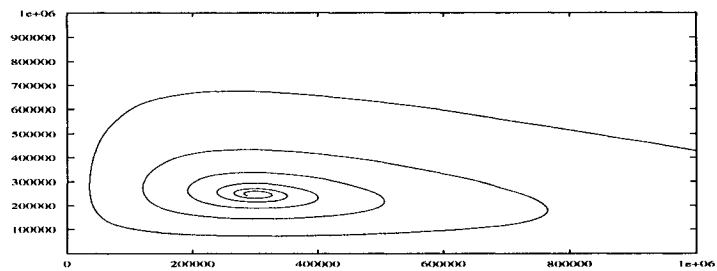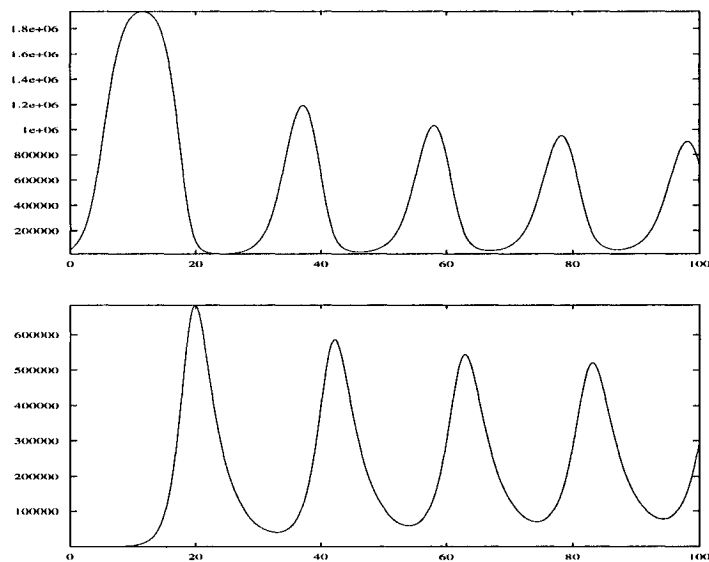

Figure 6.4.3: The oscillations of C and I vs. time, $\tau = 1$

In the (C, I)−plane, trajectories are approaching the periodic solution as the time increases (see Figure 6.4.4).
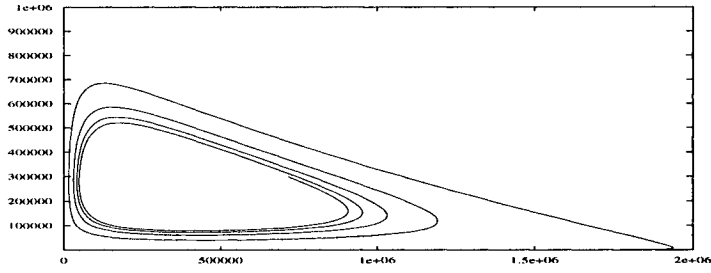
Figure 6.4.4: There is an orbitally asymptotically stable periodic solution when $\tau = 1 > \tau_0$.

If 75% of the infected cells survive, numerical analysis shows that when k_I' is smaller the oscillations are more frequent (i.e., the periods are shorter) and the amplitudes are smaller. Thus, increasing the value of k_I' will increase the periods and the amplitudes of the periodic solutions. There appears to be an interplay between the value of the delay and the fraction of infected cells surviving incubation. Specifically, the more cells survive incubation, the smaller the critical value of the delay must be to induce instability of the interior equilibrium.

Note that this system has been dealt with in the case in which the delay is distributed, see [14]. The asymptotic behaviour of the distributed delay system is both qualitatively and quantitatively (i.e. length of the critical delay) similar to that of the discrete delay case, so we shall only refer back to the distributed delay model in the section on optimal control.

6.5 The Delayed Model With Suppression of Infection Rate

In this section we will show that treatment, if strong enough, restabilises the system that has been driven unstable by the delay. This happens because of the dependence of τ_0 on k_I' as we saw in the previous section. The smaller the fraction of infected cells that survive incubation, the longer the critical value of the delay. However, the stronger the treatment is, the smaller will be the fraction of infected cells that actually will survive incubation, and hence a system that was previously unstable given realistic values of τ will be stable under sufficient treatment.

Consider the following treated model with discrete delay:

$$\frac{dC}{dt} = r_C C(t)\left(1 - \frac{C(t) + I(t)}{C_M}\right) - (1 - u)k_I C(t)I(t) \qquad (6.5.10)$$

$$\frac{dI}{dt} = (1 - u)k_I' C(t - \tau)I(t - \tau) - \mu_I I(t). \qquad (6.5.11)$$

Recall from section 6.2, describing the ODE model treated with a constant parameter, that the uninfected equilibrium was stable provided $u > 1 - \frac{\mu_I}{k_I' C_m}$, or that $k_I' < \frac{\mu_I}{(1-u)C_m}$. So we can see that there is a dependence on u of the number of infected cells surviving the incubation period. This makes sense from a biological perspective; we would expect a treatment reducing the infectivity rate to decrease the number of infected cells. But recall from the section in which we studied the effect of the delay on the untreated system that the bifurcation value τ_0 depended upon k_I' in the sense that the more infected cells surviving the incubation period, the shorter the delay needed to be to induce instability. So we might deduce that the stronger the treatment, the longer the delay needs to be to induce instability. This is in fact true! For example, consider the delayed system with a delay of one day. If we add in a treatment value of $u = 0.2$, we see that the system remains unstable, with periodic solutions bifurcating from the interior equilibrium. However, as we increase our treatment value to $u = 0.5$, we see these oscillations begin to die out and for $u = 0.8$, as treatment efficacy increases, the oscillations are gone entirely. We can see the dependence of τ_0 on u; for example, if we observe numerical simulations of the above system with $u = 0.5$ and $\tau = 1$, we can see the oscillations beginning to die out; but if we increase τ to 3 days, we see oscillations reappearing in both components.

In fact, we can refer back to the results on absolute and conditional stability of the interior equilibrium in the case without treatment. We find that the region of absolute stability can be framed in terms of u.

Proposition 6.5.1 *The interior equilibrium of (6.5.8–6.5.9) is absolutely stable for*

$$\frac{\mu_I}{C_M} < (1 - u)k_I' < \frac{3\mu_I}{C_M}.$$

Thus, if 50% of infected cells survive incubation, the equilibrium is absolutely stable for $0.55 < u < 0.85$. For 75% surviving, the range of absolute stability is smaller, from $0.7 < u < 0.9$. Observe the following numerical simulations:

First, we observe the behaviour of C versus time when only half the infected cells survive incubation and treatment is at a low level $u = 0.1$:
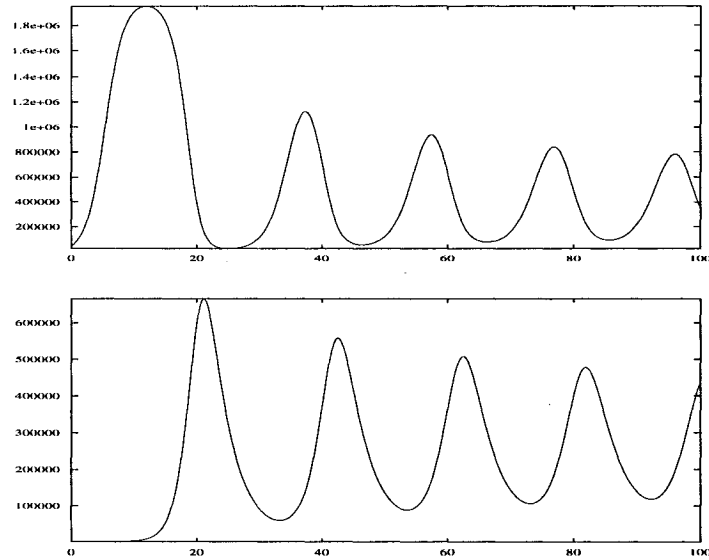
Figure 6.5.5: The oscillations of C and I vs. time, $\tau = 1$, $u = 0.1$

We can see that when we increase our treatment level to only $u = 0.6$, the oscillations damp out with time, and the system tends to a steady state:
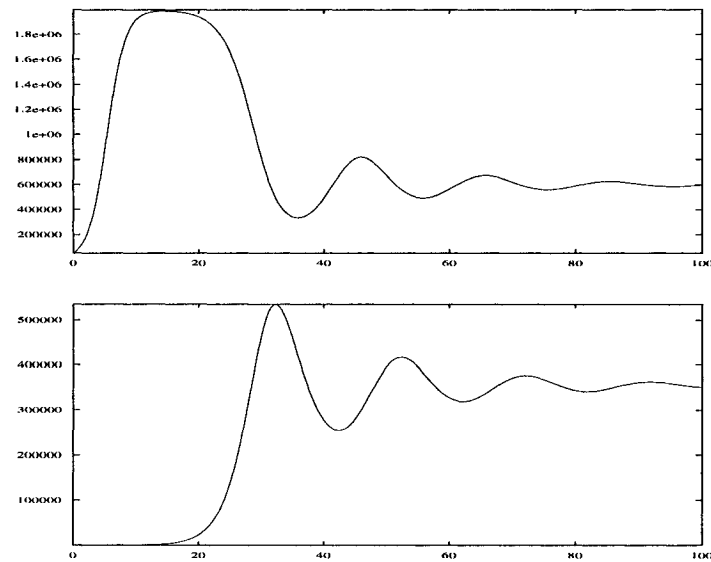
Figure 6.5.6: C and I converge to stability under sufficient treatment.

But we note that it takes more treatment to stabilise the system when 75% of infected cells survive incubation. We still observe oscillations if $u = 0.3$:
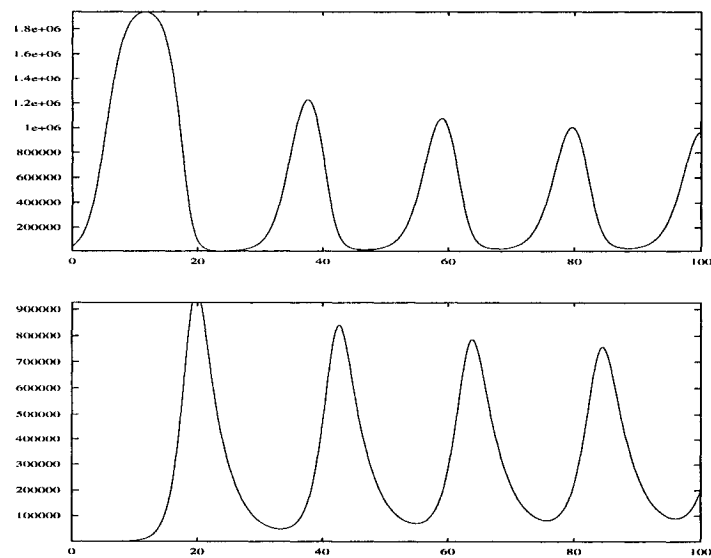
Figure 6.5.7: C and I oscillate for $u = 0.3$.

We must increase our treatment parameter to $u = 0.75$ to observe a decrease in oscillatory behaviour:
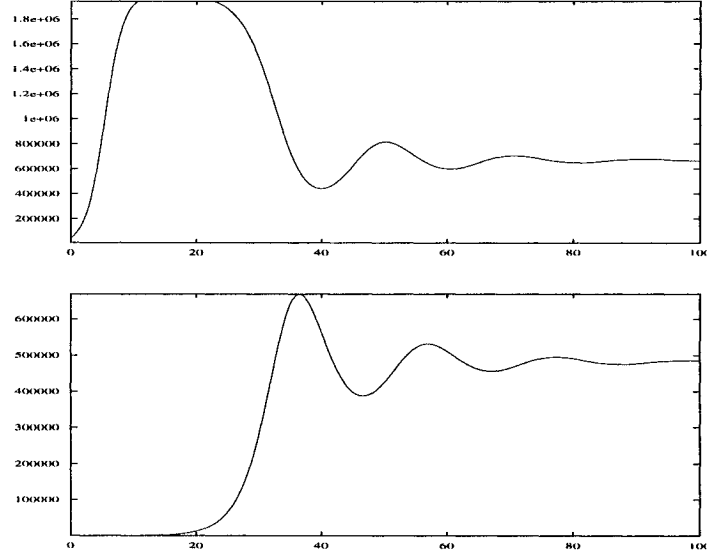
Figure 6.5.8: C and I converge to stability under sufficient treatment.

We carry out stability analysis exactly as in Section 6.4, noting that the interior equilibrium will be stable in the absence of delay so long as $k_I' > \frac{\mu_I}{(1-u)C_m}$. We can check the conditions for absolute and conditional stability, and we notice that $r^2 - q^2 < 0$ whenever $(1 - u)k_I' > \frac{3\mu_I}{C_M}$, and our equilibrium remains conditionally stable, but the bifurcation value τ_0 increases with increasing treatment u.

We would like to note, also, that when 75% of infected cells survive incubation, there is a higher level of infection at equilibrium (with treatment) than there is when only half of infected cells survive.

6.6 Theoretical Aspects of Optimal Control of the Delayed Model

We note before we begin that there are two ways we can analyse an optimal control problem for a delay-differential equation system. They are:

- We can use a discrete delay and apply Pontryagin's Maximum Principle which holds for delayed systems ([23]). The difficulty lies in analysing the optimality system, which will be a delay-differential equation system of twice the dimension of the state system. In this case, only limited numerical analysis to determine when and if bifurcation occurs is possible. While of theoretical interest, it does not help us to gain a deep understanding of the behaviour of the optimality system and the optimal control.

- We may use a distributed delay and then apply the linear chain trick to transform our n-dimensional delay system into a higher-dimensional ODE system. For simplicity, we assume the delay kernel to be the weak kernel so that we increase the dimension of our state system by only one and that of our optimality system by only two. Then we may proceed in exactly the same fashion as in the ODE case. We will provide more background on the use of distributed delay in Section 6.6.2. We would like to note that this system has proven very difficult to analyse numerically, and we include this section principally in the interest of possible future work.

6.6.1 The Discrete Delay Controlled Model

Again we assume that the control $u(t)$ is a Lebesgue-measurable function with values between zero and one, and that τ is the length of the delay in days. Assuming a discrete delay, the control problem becomes to:

$$\max J[u] = \int_0^T (C - \frac{Bu^2}{2}) dt$$

subject to the state system:

$$\frac{dC(t)}{dt} = r_C C(t) \left(1 - \frac{C(t) + I(t)}{C_M} \right) - (1 - u) k_I C(t) I(t), \qquad (6.6.12)$$

$$\frac{dI(t)}{dt} = (1 - u) k_I' C(t - \tau) I(t - \tau) - \mu_I I(t). \qquad (6.6.13)$$

The Hamiltonian is given by:

$$H = C(t) - \frac{Bu^2}{2} + r_C C(t)\lambda_1(t) - \frac{r_C C(t)^2}{C_M}\lambda_1(t) - \frac{r_C C(t)I(t)}{C_M}\lambda_1(t) - (1-u)k_I C(t)I(t)\lambda_1(t)$$

$$+(1-u)k_I' C(t-\tau)I(t-\tau)\lambda_2(t) - \mu_I I(t)\lambda_2(t) + v_1(t)u(t) + v_2(t)(1-u(t)).$$

As in chapter three, the v_j are penalty multipliers, ensuring that the control remains bounded between 0 and 1. Again we apply Pontryagin's maximum principle, and consider the boundary cases as in chapter three, to deduce that our optimal u^* is given by:

$$u^*(t) = \min\left\{1, \max\left(\frac{k_1 C(t)I(t)\lambda_1(t) - k_I' C(t-\tau)I(t-\tau)\lambda_2(t)}{B}, 0\right)\right\}.$$

Again we can determine the optimality system using the following definitions for the time-derivatives of the adjoint variables:

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial C}$$

$$\frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial I}.$$

Note that due to the fact that our partial derivatives are being taken with respect to the state variables and not to time, the delay only affects the system by its appearance in the differential equations for the adjoint variables.

The full optimality system is given by:

$$\frac{dC(t)}{dt} = r_C C(t)\left(1 - \frac{C(t)+I(t)}{C_M}\right) - (1-u)k_I C(t)I(t)$$

$$\frac{dI(t)}{dt} = (1-u)k'_I C(t-\tau)I(t-\tau) - \mu_I I(t)$$

$$\frac{d\lambda_1}{dt} = -1 - r_C C(t)\lambda_1(t) + \frac{2r_C C(t)}{C_M}\lambda_1(t) + \frac{r_C I(t)}{C_M}\lambda_1(t)$$

$$+ (1-u)k_I I(t)\lambda_1(t) - (1-u)k'_I I(t-\tau)\lambda_2(t)$$

$$\frac{d\lambda_2}{dt} = \frac{r_C C(t)}{C_M}\lambda_1(t) + (1-u)k_I C(t)\lambda_1(t) - (1-u)k'_I C(t-\tau)\lambda_2(t) + \mu_I \lambda_2(t)$$

$$u^*(t) = \min\left(1, \max\left(\frac{k_1 C(t)I(t)\lambda_1(t) - k'_I C(t-\tau)I(t-\tau)\lambda_2(t)}{B}, 0\right)\right).$$

6.6.2 Optimal Control of the System with Distributed Delay

Prior to introducing the optimal control model, we first present the distributed delay model.

Let $C(t)$ represent the concentration of healthy cells and $I(t)$ be the concentration of infected cells. We consider the following system modeling the interaction of the healthy and infected cells:

$$\frac{dC}{dt} = r_C C(t)\left(1 - \frac{C(t)+I(t)}{C_M}\right) - k_I C(t)I(t) \tag{6.6.14}$$

$$\frac{dI}{dt} = k'_I \int_{-\infty}^{t} C(u)I(u)F(t-u)du - \mu_I I(t). \tag{6.6.15}$$

The initial values of system (6.6.14)–(6.6.15) are

$$C(s) = \phi(s) \geq 0, \quad I(s) = \psi(s) \geq 0, \quad s \in (-\infty, 0],$$

where ϕ and ψ are continuous functions on $(-\infty, 0]$.

We assume that the cells, which are productively infectious at time t, were infected u time units ago, where u is distributed according to a probability distribution $F(u)$, called the *delay kernel*. We use the family of generic delay kernels of the form

$$F(u) = \frac{\alpha^{n+1}u^n}{n!}e^{-\alpha u},$$

where $\alpha > 0$ is a constant and $n \geq 0$ is an integer. According to MacDonald [43], n is called the *order* of the delay kernel and the *average delay* is defined by

$$\tau = \int_0^\infty uF(u)du = \frac{n+1}{\alpha}.$$

In the literature, the kernels with $n = 0$ and $n = 1$, i.e.,

$$F(u) = \alpha e^{-\alpha u} \quad \text{and} \quad F(u) = \alpha^2 u e^{-\alpha u},$$

are called the *weak* and *strong* kernels, respectively, and are frequently used in biological modeling.

We consider the distributed delay model with a weak kernel, that is:

$$\frac{dC}{dt} = r_C C(t)\left(1 - \frac{C(t) + I(t)}{C_M}\right) - k_I C(t) I(t) \tag{6.6.16}$$

$$\frac{dI}{dt} = k_I' \int_{-\infty}^t \alpha e^{-\alpha(t-u)} C(u) I(u) du - \mu_I I(t). \tag{6.6.17}$$

We study the stability of the infected equilibrium by letting:

$$X(t) = \int_{-\infty}^t \alpha e^{-\alpha(t-u)} C(u) I(u) du. \tag{6.6.18}$$

Then system (6.6.16)–(6.6.17) is equivalent to the following ODE system

$$\frac{dC(t)}{dt} = r_C C(t)\left(1 - \frac{C(t) + I(t)}{C_M}\right) - k_I C(t) I(t) \tag{6.6.19}$$

$$\frac{dI(t)}{dt} = k_I' X(t) - \mu_I I(t) \tag{6.6.20}$$

$$\frac{dX(t)}{dt} = \alpha C(t) I(t) - \alpha X(t). \tag{6.6.21}$$

The positive steady state of system (6.6.24)–(6.6.26) is given by $\overline{E} = (\overline{C}, \overline{I}, \overline{X})$, where $\overline{X} = \frac{\mu_I}{k_I'}\overline{I}$. Its stability properties are summarised in the following proposition:

Proposition 6.6.1 *If the conditions*

$$a_1(\alpha) > 0, \quad a_3(\alpha) > 0 \quad \text{and} \quad a_1(\alpha)a_2(\alpha) - a_3(\alpha) > 0 \qquad (6.6.22)$$

are satisfied, then the positive steady state $\overline{E}$ of system () is asymptotically stable. If there is a critical value $\alpha_0 > 0$ such that conditions

$$a_1(\alpha_0)a_2(\alpha_0) = a_3(\alpha_0), \qquad (6.6.23)$$

$$\left.\frac{d\text{Re}\lambda_{2,3}}{d\alpha}\right|_{\alpha=\alpha_0} \neq 0, \qquad (6.6.24)$$

and

$$\frac{d}{d\alpha}[a_1(\alpha)a_2(\alpha) - a_3(\alpha)]|_{\alpha=\alpha_0} \neq 0$$

are satisfied, then a Hopf bifurcation occurs at $\overline{E}$; that is, a family of periodic solutions bifurcates from $\overline{E}$ when α passes through the critical value α_0.

Notice that for the weak kernel $\alpha e^{-\alpha u}$, the average delay is defined as $\overline{\tau} = \frac{1}{\alpha}$. The above analysis demonstrates that when $\overline{\tau}$ is small (i.e. when α is large), the steady state is stable. When $\overline{\tau}$ is sufficiently large (i.e. as α becomes smaller), the steady state becomes unstable and a Hopf bifurcation occurs. That is, a periodic solution bifurcates from the steady state when α passes a critical value α_0.

With parameter values given in Table 6.1 and a value of $k'_I = 1.5 \times 10^{-6}$, $\alpha_0 \approx 1.95$. Numerical simulations show that the steady state $\overline{E} = (\overline{C}, \overline{I})$ is asymptotically stable when $\alpha > \alpha_0$ (i.e., $\overline{\tau} < \overline{\tau}_0$).

We note that we may use this system of ordinary differntial equations to help simplify our delayed control problem. The problem of controlling a two-dimensional system of delay differential equations becomes one of controlling a three-dimensional system of ordinary differntial equations. The optimal control problem becomes:

$$\max J[u] = \int_0^T (C - \frac{Bu^2}{2})dt \qquad (6.6.25)$$

subject to

$$\frac{dC(t)}{dt} = r_C C(t)\left(1 - \frac{C(t)+I(t)}{C_M}\right) - (1-u)k_I C(t)I(t) \qquad (6.6.26)$$

$$\frac{dI(t)}{dt} = (1-u)k'_I X(t) - \mu_I I(t) \qquad (6.6.27)$$

$$\frac{dX(t)}{dt} = \alpha C(t)I(t) - \alpha X(t). \qquad (6.6.28)$$

Before continuing, we would like to note that the observant reader might notice that this three-dimensional system is not unlike a system we might derive were we to consider a specific compartment for latently infected cells, $X(t)$, rather than modelling using a time delay.

Our Hamiltonian will be:

$$H = C(t) - \frac{Bu^2}{2} + r_C C(t)\lambda_1(t) - \frac{r_C C(t)^2}{C_M}\lambda_1(t) - \frac{r_C C(t)I(t)}{C_M}\lambda_1(t)$$

$$-(1-u)k_I C(t)I(t)\lambda_1(t) + (1-u)k'_I X(t)\lambda_2(t) - \mu_I I(t)\lambda_2(t)$$

$$+\alpha C(t)I(t)\lambda_3(t) - \alpha X(t)\lambda_3(t) + v_1(t)u(t) + v_2(t)(1-u(t)).$$

Again applying the maximum principle, we find that our optimal control takes on a slightly different form:

$$\frac{\partial H}{\partial u} = -Bu + k_I CI\lambda_1 - k'_I X\lambda_2$$

and therefore

$$u^*(t) = \min\left\{1, \max\{\frac{k_I CI\lambda_1 - k'_I X\lambda_2}{B}, 0\}\right\}. \qquad (6.6.29)$$

Our adjoint system is given by:

$$\frac{d\lambda_1}{dt} = -1 - r_C + \frac{2r_C C\lambda_1}{C_m} + \frac{r_C I\lambda_1}{C_m} + (1-u)k_I I\lambda_1 - \alpha I\lambda_3 \qquad (6.6.30)$$

$$\frac{d\lambda_2}{dt} = \frac{r_C C\lambda_1}{C_m} + (1-u)k_I C\lambda_1 + \mu_I \lambda_2 - \alpha C\lambda_3 \qquad (6.6.31)$$

$$\frac{d\lambda_3}{dt} = -(1-u)k_I'\lambda_2 + \alpha\lambda_3. \qquad (6.6.32)$$

We must ensure existence of an optimal control for this problem. Referring back to the conditions (a)–(d) of Lemma 3.3 in Chapter Three, we note that the only one we need be concerned with specifically are the boundedness results necessary for the satisfaction of conditions (a), (c). We'd like to check that the right-hand side of the state system does in fact exhibit at most linear growth. This is a fairly simple matter as we note that $C_m \geq C(t)$ and so we have that:

$$\overline{C} = C_m$$

$$\Rightarrow \frac{d\hat{I}}{dt} = k_I'\hat{X}$$

$$\frac{d\hat{X}}{dt} = C_m\hat{I}.$$

In matrix form:

$$\frac{d}{dt}\begin{bmatrix} \hat{I} \\ \hat{X} \end{bmatrix} = \begin{bmatrix} 0 & k_I' \\ C_M & 0 \end{bmatrix}\begin{bmatrix} \hat{I} \\ \hat{X} \end{bmatrix}.$$

So again, since this is a linear system in finite time with bounded coefficients and the other three conditions are satisfied by assumption, this system does have an optimal control as characterised by (6.6.34). This boundedness will also ensure uniqueness of the optimality system, following the same method as in chapter three.

6.7 Biological Significance

We would like to point out that in this system with no immunity considered, our system very easily tends to instability, which is bad for the patient. We hypothesise that if immunity

Table 6.1: **Variables and Parameters for Cell-to-Cell Spread**

Parameters and Variables		Values
	Dependent Variables	
C	concentration of healthy cells	$5 \times 10^5/mL$
I	concentration of infected cells	$500/mL$
	Parameters and Constants	
C_{max}	carrying capacity of healthy cells	$2 \times 10^6/mL$
k_I	rate constant for cell-to-cell spread	$2 \times 10^{-6}/(mL)(day)$
r	healthy cell reproductive rate constant	$0.7/day$
μ_C	death rate of healthy cells	$0.02/day$
μ_I	death rate of infected cells	$0.3/day$
	Derived Quantities	
C_M	effective carrying capacity of healthy cells	$2 \times 10^6/mL$
r_C	effective healthy cell reproductive rate constant	$0.68/day$

is considered, delay will induce instability in far fewer cases.

All parameters in this table are from [66].

Chapter 7

Incorporating Nutritional Status of the Patient

It has been common knowledge since its advent that AIDS has a detrimental effect upon the bodyweight of an infected individual. In fact, since 1987, this condition, known as "HIV-associated wasting syndrome", has been on the Centre for Disease Control's list of AIDS-defining illnesses ([9]).

However, the problem is even more involved than this. Not only does HIV negatively affect the patient's weight, but the nutrient intake of the patient has a strong effect upon the patient's overall health. This is true even for individuals with uncompromised immune systems. Malnutrition is one of the leading causes of immune deficiency worldwide. It is clear that adequate nutritional intake can only benefit the HIV-positive individual.

Additionally, there are studies indicating that nutrients such as zinc, thiamin and others have a direct impact on the HIV-immune system dynamics (see Baum et. al., [5], [4], Fields-Gardner et.al. [19], Kim et. al. [33], Macallan et. al. [42], as well as references cited therein). Sufficient intake of macronutrients (proteins, carbohydrates and fats) and certain micronutrients such as vitamins A, E, B, K, and minerals zinc and selenium, is strongly associated with:

- reduced infectivity on the cellular level, and

- increased production of helper and killer lymphocytes.

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To add to the complexity of the issue, we note that most (if not all) anti-HIV drugs have a negative effect on the nutritional status of a patient, creating an unfortunate feedback loop wherein the treatments used to enhance immune function suppress a key contributor to immune function itself! A quick look at the 2001 Lippincott's Nursing Drug Guide ([40]) reveals that the reverse transcriptase inhibitors abacavir, delavirdine mesylate, didanosine (ddI), efavirenz (Sustiva), lamivudine (3TC), nevapirine and zidovudine (AZT), as well as the protease inhibitors saquinavir, ritonavir (Norvir), nelfinavir mesylate (Viracept) and indinavir sulfate (Crixivan) all have commonly occurring adverse effects on the gastrointestinal system. Virtually *all* of these drugs list nausea, diarrhea, vomiting and anorexia as adverse effects, with diarrhea listed as "common" in *all* cases; the others are "common" side effects of most of the aforementioned drugs. Add to this the difficulty of eating properly on such regimens, and it becomes obvious that the patient's nutritional status will be compromised by drug therapy.

So what can we do?

We attempt to determine a drug treatment strategy that will address these problems. We examine a very simple model to begin with, which shows the interactions between healthy and infected $CD4^+$ cells and the nutrient status of the patient. Treatment is approximated by a parameter that has a detrimental effect on the nutrient status, which in turn has a positive effect on generation of healthy cells. We examine the stability properties of this model to determine what sort of restrictions should be imposed upon treatment in order to maintain a high nutritional status.

We would like also to note that extensions to this system may be useful for understanding alternative AIDS treatments in third-world countries where malnutrition is a very real factor and drugs are not readily available due to cost.

Finally, we note that this model is extremely preliminary and as such, relatively primitive as a mathematical biology model representing the interaction between nutrition and the immune system. In the future, there will doubtless be models that are formulated far better than is this one. Even if this proves to be the case, we feel that this model is of value both for the effort it represents to model an important medical problem, and as a model that can stand on its own for applied mathematical analysis.

7.1 The System

We shall start off very simply, assuming that the treatment u' is constant. The reason we use u' rather than u is because in this system a value of $u' = 0$ will correspond to totally effective treatment whereas $u' = 1$ will mean the absence of treatment. Please be careful to distinguish this u' from u from previous chapters — in this case, $u' = 0$ means totally effective treatment, *not* no treatment. This is done because it renders the analysis far simpler. We assume that nutrient status, as modelled by the variable $n(t)$, enhances the production of CD4+ lymphocytes. In future work, we shall expand the model and assume that it also enhances the immunity. But for now, we shall consider only healthy cells as represented by $x(t)$, infection level as modelled by $y(t)$, and nutrient status, $n(t)$. Our model is represented by the following equations:

$$\frac{dx(t)}{dt} = \lambda n(t) - \delta x(t) - u'\beta x(t)y(t) \qquad (7.1.1)$$

$$\frac{dy(t)}{dt} = u'\beta x(t)y(t) - ay(t) \qquad (7.1.2)$$

$$\frac{dn(t)}{dt} = su' - ky(t). \qquad (7.1.3)$$

The model equations are explained as follows: We see that the source λ for healthy cells is enhanced by $n(t)$. They are lost to decay at a rate of δ and to infection at a rate of β. We see that u' multiplies the infectivity rate and so if $u' = 1$ the system behaves as if there were no treatment, whereas if $u' = 0$, treatment will be totally effective. Infection is gained at the rate at which healthy cells are lost, and decays at a rate of a. Finally, nutrient status is dependent upon treatment level in the following way: if treatment is fully effective, there is no source for nutrient. This assumes two things: first, it is implicit that u' shall never actually *reach* zero, or full effectiveness. This is not unrealistic, as no therapy has yet managed to cure HIV infection. Also, it assumes that the closer we are to no treatment, the more likely we are to have a constant source of nutrition (the parameter s). But as $u' \to 0$, the source for nutrient becomes more and more suppressed. Also, we assume that infection has a detrimental effect upon nutrient status, so that $n(t)$ is lost at a rate proportional to $ky(t)$.

Note that in the absence of infection $(y(t) = 0)$, any equilibrium will correspond to

$su' = 0$, in which case we would assume that nutrient status is constant. This is realistic, subject to the normal (presumably minor) fluctuations in the average healthy person's diet. This "reduces" the system to the differential equations for $x(t)$ and $y(t)$, where $x(t)$ is proportional to n_0, the constant value for the healthy person's nutrient status.

But the interesting things happen when we try to model the effect of drugs and nutrition on an infected individual. Assuming that infection level is nonzero, we solve for equilibria and note that:

$$\bar{x} = \frac{a}{\beta u'}$$

$$\bar{y} = \frac{su'}{k}$$

$$\bar{n} = \frac{a\delta}{\lambda\beta u'} + \frac{asu'}{\lambda k}.$$

Let's just take a look at these values and see what they mean. First, as $u' \to 0$ (its maximal value), x grows very large and if there is no treatment then $\bar{x} = \frac{a}{\beta}$. $y(t)$, on the other hand, is directly proportional to treatment so that if $u' \to 0$, then we also have $y(t) \to 0$. The equilibrium value for $n(t)$ is proportional to both u' and its inverse.

In the next section, we study the local stability of the equilibrium $\bar{E} = (\bar{x}, \bar{y}, \bar{z})$.

7.2 Stability Analysis

The general Jacobian matrix for this system is given by:

$$J = \begin{bmatrix} -\delta - u'\beta\bar{y} & -u'\beta\bar{x} & \lambda \\ u'\beta\bar{y} & u'\beta\bar{x} - a & 0 \\ 0 & -k & 0 \end{bmatrix}.$$

Evaluated at this interior equilibrium and taking the characteristic equation $|vI - J(\bar{E})|$, we obtain:

$$c(v) = v^3 + a_1 v^2 + a_2 v + a_3 = 0, \tag{7.2.4}$$

where:

$$a_1 = \delta + \frac{u'^2 s\beta}{k}$$

$$a_2 = \frac{u'^2 sa\beta}{k}$$

$$a_3 = u'^2 s\beta\lambda.$$

Recall that the Routh-Hurwitz criteria require that the conditions

$$a_1 > 0, a_3 > 0, a_1 a_2 > a_3$$

be satisfied for stability. Clearly for positive parameter values, the first two hold so we need only check the last condition. This yields the following necessary condition:

$$a(\delta k + u'^2 \beta) > \lambda k,$$

which is equivalent to the restriction on u' that:

$$u'^2 > \frac{k(\lambda - \delta)}{s\beta}.$$

Clearly, taking only the positive root makes sense, and we find that for stability of the equilibrium $\overline{E}$, we require:

$$u' > \sqrt{\frac{k(\lambda - \delta)}{s\beta}}.$$

7.3 Numerical Results

Simulations were run in XPP, using parameter values of $\beta = 0.2$, $k = 0.05$, $s = 1$ and all other parameter values from [76]. First, we observe that under these parameter values we find that $u' > 0.25$ (approximately) for stability. (Recall that this means that treatment must actually be *below* a certain level of strength.)

First, let's see how things look for $u = 0.2$ (a value too small for stability, theoretically):
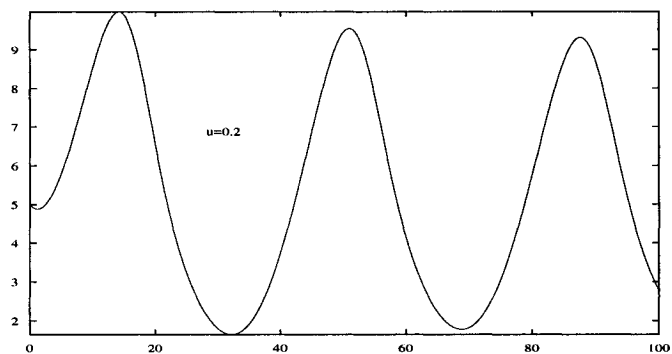
Figure 7.3.1: The healthy cell population is unstable.
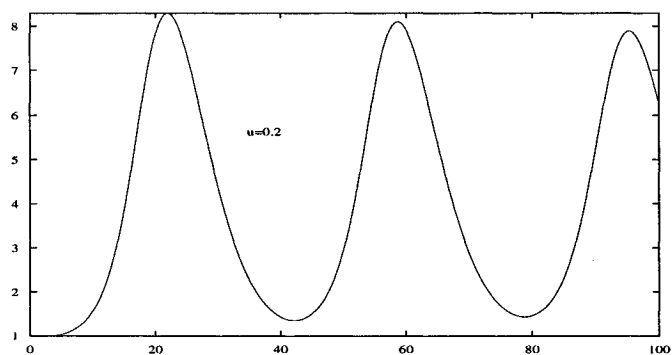
Figure 7.3.2: The infection level is unstable.
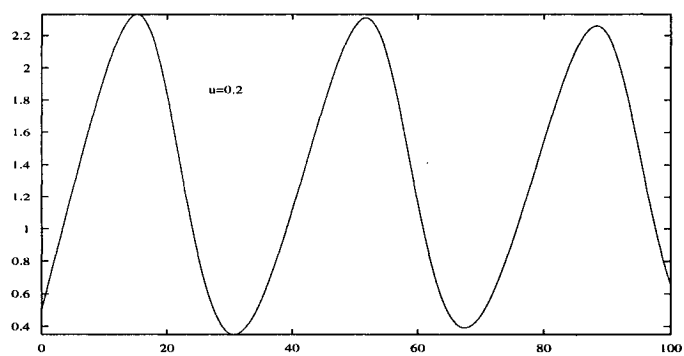
Figure 7.3.3: The nutrient level is unstable.

Note that $u' = 0.2$ corresponds to a fairly strong level of treatment. Now, consider the case in which we administer a "medium" amount of treatment, so that $u' = 0.5$. We can see the populations all converging to equilibrium.
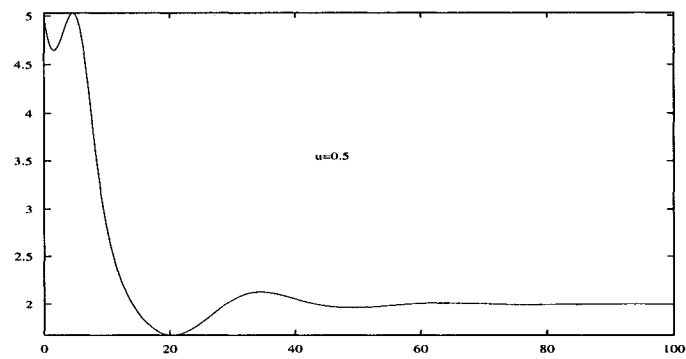
Figure 7.3.4: The healthy cell population converges to equilibrium.
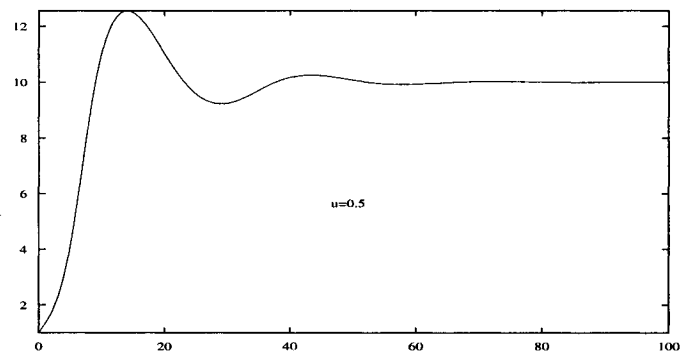
Figure 7.3.5: The infection level is stable.
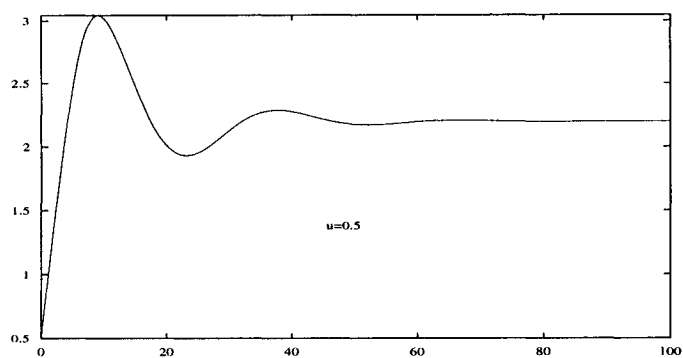
Figure 7.3.6: The nutrient level is stable.

Finally, consider what happens if we let $u' = 0.75$. (Recall that this corresponds to less treatment than the previous two cases.)
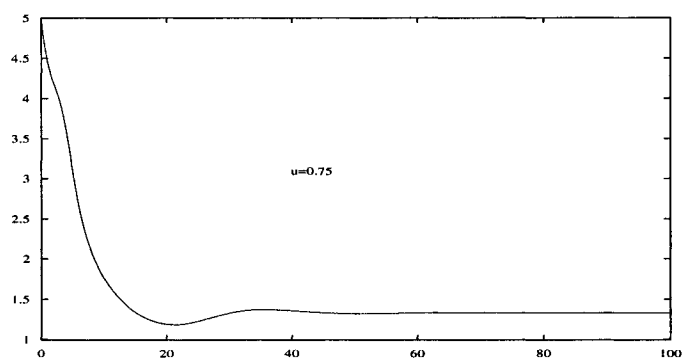
Figure 7.3.7: The healthy cell population converges to equilibrium.
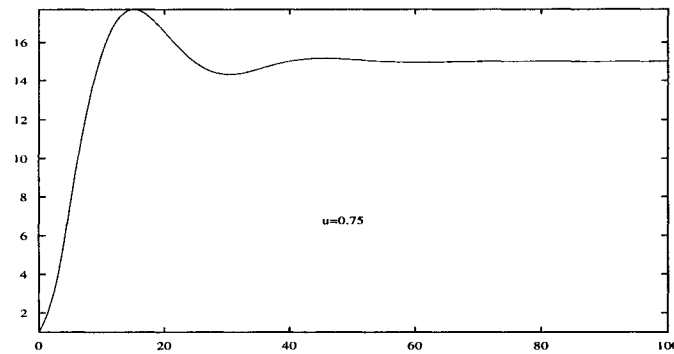
Figure 7.3.8: The infection level is stable.
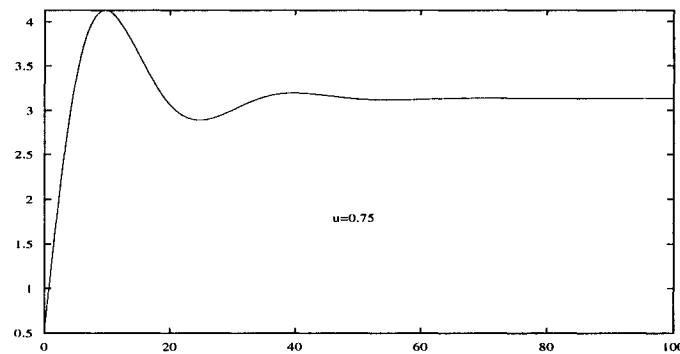
Figure 7.3.9: The nutrient level is stable.

We can see that the level of healthy cells is lower than it would be with stronger treatment, whereas the level of infection is higher. The level of nutrient status, however, decreases with increasing treatment (u' lower). Observe also that, though the system is stable for low treatment values, the infection level is high and the healthy cell population is low. Therefore, the goal should be to provide a "medium" or "medium-strong" level of treatment. It must be low enough that stability is not lost, but not so low that infection is very high. Therefore a balance between benefit and cost is required, thus rendering this model an ideal candidate for an optimal control problem.

If we let $u' = 1$, and consider only the untreated system, we find that stability depends upon s being high enough (sufficient nutrient source), or k being low enough (nutrient is

not cleared too quickly by infection).

However, an integral part of this study was the assumption that treatment has a detrimental effect upon nutrient status. Nutrient status, on the other hand, also has a positive effect upon health as measured in terms of the supply rate of healthy CD4+s. The model shows that u' has a destabilising effect upon the equilibrium $\bar{E}$. In practical terms, this means that if treatment is above a certain level of strength, stability will be lost, and presumably, the patient's condition will deteriorate. This fits with the assumptions of the model.

We would like to point out that though this is a very preliminary model, its behaviour appears realistic and we are examining extensions to this model, including immunity as well as other factors.

7.4 Optimal Control Aimed at Maintenance of High Nutritional Status

Finally, we propose a model that seeks the drug treatment that would be optimal in terms of maintaining the patient's nutrient status at a fairly high level as well as controlling infection. We note that we can approach this as a maximisation or a minimisation problem, and the results will probably be similar. This is because the qualitative behaviour of the ODE system indicates that high healthy CD4+ cells correlate with low infection levels. Therefore, we shall propose the following possible model.

The problem is to

$$\max J[u] = \int_0^T (x(t) + n(t) - (1 - u'(t))^2)dt \qquad (7.4.5)$$

subject to the state system:

$$\frac{dx(t)}{dt} = \lambda n(t) - \delta x(t) - u'(t)\beta x(t)y(t) \qquad (7.4.6)$$

$$\frac{dy(t)}{dt} = u'(t)\beta x(t)y(t) - ay(t) \qquad (7.4.7)$$

$$\frac{dn(t)}{dt} = su'(t) - ky(t). \qquad (7.4.8)$$

Note that here we have chosen to maximise healthy CD4+s and nutrient status, while minimising drug cost. Cost is represented by $(1 - u'(t))^2$ because, in this case, $u'(t) = 0$ actually represents *highest* treatment. We are currently working on establishing the behaviour of this optimal system.

Chapter 8

Conclusions and Future Work

In this chapter, we discuss the results that we have derived in this thesis, and refer back to the goals with which we started. We discuss how we answered the questions we posed in the beginning, and if we were not able to answer them, we explain why, and how we might tackle them in the future. Also, we suggest some possible modifications to the primary model (3.1.1–3.1.3), which may make it more realistic.

8.1 Discussion and Conclusions

We have considered several models of the HIV-immune system interaction. To discuss our results, it is natural to look back at the questions posed in the Introduction. We shall reproduce these questions and answer them one at a time.

- The role of immunity cells appears to be important in the progress of infection. Given this fact, how does the immune system react to HIV?

Mathematically, we find that an immune system infected with HIV will either establish a persistent specific immunity or it will not. The establishment of such an immunity depends upon host and viral parameters. When it exists, immunity equilibrates at a level proportional to healthy CD4+ cells.

- What sort of drug treatment schemes are optimal in order to maintain a high level of immunity to HIV?

We sought to determine optimal treatment strategies that would maximise not only healthy cells but immunity cells as well. In addition to the mathematical results of existence and uniqueness of control and optimality system, we found that optimal treatments begin at full strength. After an initial decrease, the optimal treatment grows high again and drops sharply to zero at the final time. Healthy cells are able to be maintained at close to maximum levels for most of the duration of therapy. Infection level decreases to very low levels, but is never eradicated. However, at the end of the treatment schedule, when the drug is no longer given, the infection level begins to rise again. When the infection is low, so too is the specific immune response. We should note that the specific immunity is always maintained at a positive level — it is never eliminated. Also, note that an increase in infection is followed by a corresponding increase in the immunity, which then serves to suppress infection (by killing off infected cells). Once the infection is low, the immunity is not needed at such high levels and this is why it too drops off. We note the initial decrease in the control with interest. This occurs at roughly the same time as the immunity is high, indicating that during periods of effective immune responsiveness, less medication is needed to control infection. We suggest that this may indicate that high/low or on/off drug treatment schemes may work well to keep infection under control, provided we can maintain a sufficient immunity. As well, implementing treatments that enhance a patient's natural immunity may be beneficial as an alternative to quite such high levels of drug therapy.

- Does the intracellular "latent" period affect the stability of the untreated models? If so, how do we treat? Will optimal treatments be very different from the case in which delay is not considered?

The intracellular "latent" period can cause delay-induced bifurcation in our model, but for all parameter ranges considered, we find that the bifurcation value of the delay is significantly lower than the $1 - 2$ day latent period documented in the literature (see [66] and references cited therein). As well, the amplitude of the oscillations is not very large. So, although the results are of mathematical interest, in most situations the delay is unlikely to affect stability. Very roughly contrasting this with a model not incorporating immunity as a variable, we can see that in the situation with only constant immune responsiveness, we may see delay-induced instability more often and this may indicate the importance of the immune response in controlling infection.

Stability and bifurcation analysis of the delayed systems with constant-valued treatment indicated that the treatment widens the range of parameter values for which the delayed systems are absolutely stable — that is, stable no matter the value of the delay. This means that if high enough, treatment has the ability to restabilise a system that has been driven unstable by delay.

Optimal control of the delayed system was also considered. It is difficult to proceed beyond the characterisation of an optimal control and the establishment of the optimality system when we have a fixed final time due to the lack of software available to deal with such delayed nonlinear boundary value problems. We may assume a free final time and consider when bifurcation occurs, but this is of limited *practical* interest since it does not help with determining optimal strategies. In this case, applying the linear chain trick and converting an n-dimensional system of delay differential equations into an $(n + k)$-dimensional system of ordinary differential equations enables us to analyse the optimality system. In general, from the analytic properties of the system and the control, optimal treatment strategies are not dramatically different than they are in the non-delayed case. They are generally decreasing over the time interval of treatment $[0, T]$. Together with the results about constant-valued treatment, we may wish to consider maintaining maximal treatment for a longer initial time period in order to help restabilise the system.

The numerical analysis of delayed optimality systems is an important one and, together with a numerical analyst, we are working on constructing a code that will solve such systems, in particular with application to biological problems.

- How different should treatment be when we do consider immunity than when we do not?

Contrasting our optimal strategies from those derived in [36] and [21], we can see that the main difference is that our optimal treatment actually lowers for a period of time while the immunity of the host takes over. Other than that, all optimal strategies are "essentially" decreasing. (Ours are simply non-monotone, whereas those in [21] are monotonically decreasing.)

- How do we deal with the intimate interplay between the nutritional status of the patient and their drug therapy? Specifically, what can we do to deal with the fact that

medication has a negative effect on nutritional status, which is important for proper immune function?

Finally, our very simple model incorporating nutritional status of the patient indicates that in order to maintain health and stability of the patient, we must be careful not to over-treat. Extensions of this model, including the incorporation of the immunity and treatment as a control problem to maximise health and nutrient status, are currently being considered.

8.2 Possible Extensions to the Model and Future Work

8.2.1 A Model Incorporating Age Structure

We note that some HIV chemotherapies no longer have an effect after the maximum age at which reverse transcription occurs. Therefore, in the case where we model a RT-inhibitor drug, we may wish to include age structure in the model, so that we can include the fact that treatment only affects cells of less than a certain age.

Age-structured models of HIV infection have been considered before; see Kirschner and Webb [37]. Similarly to the inclusion of delays in HIV models, the incorporation of cellular age structure renders the models more realistic as it reflects the clinical fact that cells older than a certain age likely remain unaffected by drug therapy. The model that we propose below is a direct modification of that of Kirschner and Webb.

We let the parameter a denote the age of infection (how long a cell has been infected). We then let $y(t,a)$ be the density of infected cells having age of infection a at time t and note that the total population of infected cells is given by:

$$\int_0^{a_{max}} y(t,a)da.$$

With that in mind, the model we suggest is:

$$\frac{dx}{dt} = \lambda - dx - \beta xy \tag{8.2.1}$$

$$y(t,0) = \beta xy \tag{8.2.2}$$

$$\frac{\partial y}{\partial t} + \frac{\partial y}{\partial a} = -ay - \rho yz \tag{8.2.3}$$

$$\frac{dz}{dt} = cxz \int_0^{a_{max}} y(t,a)da - hz. \tag{8.2.4}$$

We can integrate the equation for y with respect to age to obtain:

$$\frac{dy}{dt} + y(a + \rho z) = \beta xy. \tag{8.2.5}$$

We then substitute in the equilibrium value (which is the same as for (3.1.1–3.1.3)) and the value for $y(t,0)$ to obtain an expression for y as a function of age:

$$y = -\frac{\beta h}{c}a + k, \tag{8.2.6}$$

where k is an arbitrary real-valued constant.

We can model treatment by solving the problem:

$$\max \int_0^T \int_0^{a_{max}} (x + z - \frac{Bu^2}{2})dadt$$

subject to

$$\frac{dx}{dt} = \lambda - dx - \beta xy + \int_0^{a_{max}} u(t,a)y(t,a)da \tag{8.2.7}$$

$$y(t,0) = \beta xy \tag{8.2.8}$$

$$\frac{\partial y}{\partial t} + \frac{\partial y}{\partial a} = -ay - \rho yz - \int_0^{a_{max}} u(t,a)y(t,a)da \tag{8.2.9}$$

$$\frac{dz}{dt} = cxz \int_0^{a_{max}} y(t,a)da - hz. \tag{8.2.10}$$

We assume that $u(t,a)$ has an effect only in the first a_{max} units of time after infection.

8.2.2 Including Diffusion Effects

We may account for the diffusion of healthy and infected cells in the context of cell-to-cell spread. First we examine the combined effects of delay and diffusion upon the system from chapter four:

$$\frac{\partial C(t)}{\partial t} = d\Delta C(t) + r_C\left(1 - \frac{C(t) + I(t)}{C_M}\right) - k_I C(t)I(t) \tag{8.2.11}$$

$$\frac{\partial I(t)}{\partial t} = \Delta I(t) + k_I' C(t-\tau)I(t-\tau) - \mu_I I(t). \tag{8.2.12}$$

(Note that the case of diffusion without delay was examined in [74], and no diffusion-induced instability occurred.)

Or, we may wish to consider diffusive effects in the model with immune response:

$$\frac{\partial x(t)}{\partial t} = d\Delta x(t) + \lambda - \delta x(t) - \beta x(t)y(t) \tag{8.2.13}$$

$$\frac{\partial y(t)}{\partial t} = \Delta y(t) + \beta' y(t-\tau)x(t-\tau) - ay(t) - \rho y(t)z(t) \tag{8.2.14}$$

$$\frac{\partial z(t)}{\partial t} = cx(t)y(t)z(t) - hz(t), \tag{8.2.15}$$

where τ may equal zero.

8.2.3 Including Viral Evolution

None of the models analysed in this thesis specifically accounted for viral evolution, as viral load was presumed to be proportional to infected cell levels. We might wish to include a specific compartment for viral evolution, which might look something like:

$$\frac{dx(t)}{dt} = \lambda - \delta x(t) - \beta x(t)v(t) \qquad (8.2.16)$$

$$\frac{dy(t)}{dt} = \beta' x(t)v(t) - ay(t) - \rho y(t)z(t) \qquad (8.2.17)$$

$$\frac{dv(t)}{dt} = Nay(t) - \beta x(t)v(t) - \mu v(t) - \rho' v(t)z(t) \qquad (8.2.18)$$

$$\frac{dz(t)}{dt} = cx(t)y(t)z(t) - hz(t), \qquad (8.2.19)$$

8.2.4   A Minimisation Problem

In our analysis of the original immunity model from Chapter Three, we conisdered our optimal pair to be one that maximised the objective functional — that is, we considered which quantities we wished to keep *high*. However, it is also reasonable and a biologically important problem to consider the minimisation of total viral load as represented by (a quantity proportional to) $y(t)$. In this case, our state system would remain the same as in Chapter Three, but our control problem would be:

$$\min J[u] = \int_0^T (y(t) + \frac{Bu^2}{2})dt$$

subject to the state system (3.2.10)–(3.2.12).

However, we conjecture that since, in the untreated ODE system, infection is inversely proportional to healthy cells, the optimal solution will be very similar qualitatively to that which we derived in Chapter Three.

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