

**Control of infection dynamics,
with applications to the HIV disease**

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Abstract

The human immunodeficiency virus (HIV) infection, that causes acquired immune deficiency syndrome (AIDS), is a dynamic process that can be modeled via differential equations. The primary goal of this thesis is to show how to drive any initial state into an equilibrium, called the long-term nonprogressor, in which the infected patient does not develop symptoms of AIDS. We first propose three control methods for HIV treatment. These methods are designed for antiretroviral drug therapy and are based on the understanding of the system dynamics. We apply these control strategies to several HIV dynamic models as well as a general disease dynamic model. Then we derive a new output feedback control scheme from one of the proposed methods. To show the feasibility of the output feedback control, the HIV model is studied analytically. This control method guarantees that the immune state is enhanced to a certain level, which is enough for a typical patient to be driven into the long-term nonprogressor. We also investigate methods to estimate approximately the state of the immune system based on the available outputs of the HIV model. The feasibility and effectiveness of the control strategies and estimation ideas are demonstrated by computer simulations.

Key Words. HIV dynamic model, AIDS, output feedback control, drug scheduling, biological system analysis.

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Chapter 1

Introduction

The human immunodeficiency virus (HIV) causes acquired immune deficiency syndrome (AIDS). The first cases of AIDS were reported in 1981, and two years later the HIV was identified as the virus that causes AIDS [3]. After the initial HIV infection, the virus resides in the blood of the HIV-positive patient, where it infects CD4 T-cells, which are essential components¹ of the human immune system [34]. An infected CD4 T-cell cannot fulfil its function in the immune system, and becomes a virus factory, making multiple HIV copies. This process decreases the number of CD4 T-cells in the HIV-infected patient. With a low level of CD4 T-cells, the immune system of a patient cannot function properly, thus the patient is vulnerable to other infections [62]. In modern clinical immunology a HIV patient is said to have AIDS when the patient has less than 200 CD4 T-cells in each mm³ of blood [54]. In 2006, the estimated number of people infected by HIV worldwide was 39.5 million and more than three-million people died of AIDS [70].

1.1 Survey of the literature

The HIV infection process involves interactions among the virus, the immune system and anti-retroviral drugs². This process can be modeled mathematically (See [5, 11, 46,

¹The cellular immune response in the human body employs T-cells to destroy body cells that have been infected by the virus, and T-helper cells influence the activation of other T-cells. Therefore T-helper cells are key components of the immune system.

²Since highly active anti-retroviral therapy (HAART) was developed in the late 1990s, it has succeeded in reducing and maintaining virus load below detection level in many patients. However, about 25% of

54, 55, 59] for specific models and [8] for general disease dynamic models). While the study of the HIV infection is not a traditional control application, the control theory literature provides some results concerning HIV treatment [22, 29]. Model-based optimal drug dosage problems in HIV treatment are studied in [32, 47, 48]. The drug-scheduling method suggested in [72] relies on open-loop optimal control to maximize the inhibition of HIV on the basis of measurements of the virus load. Finite-horizon open-loop control is applied to a HIV chemotherapy model in [44], while continuous-time feedback control schemes are used in [13, 33] for a dynamic model of HIV and lymphocytes, such as CD4 T-cells and CD8 T-cells. In [30] open-loop optimal control tools are applied to a simplified model obtained from [75].

Although HIV-infected patients are expected to develop AIDS, the possibility of a long-term nonprogressor (LTNP) is reported with clinical data [9, 50, 56], and studied by means of mathematical models³ describing the progress of the HIV infection [1, 73, 75, 76]. LTNP is the status of a patient who has HIV, but also a sufficient number of CD4 T-cells to fight off HIV and other infections. The mathematical model in [1, 73, 75, 76] with no drug input has at least two asymptotically stable equilibria, one of which corresponds to the AIDS status while the other corresponds to the LTNP status. Unfortunately, with few exceptions, the parameters of the human body are such that the state of a HIV-positive patient is located in the region of attraction of the equilibrium corresponding to the AIDS status, rather than the LTNP status. Accordingly, patients without medication normally progress to AIDS. It is obviously desirable that the state of the patient be driven into the LTNP region of attraction, where the patient does not progress to AIDS and drug treatment can be stopped.

This thesis focuses on the design of drug therapy to drive a patient to the LTNP status. Structured treatment interruption (STI) which switches between zero and maximal medication has been suggested to solve this problem [73, 75, 76]. However, STI scheduling depends on the values of the model parameters, and thus is vulnerable to parametric uncertainty. In addition the results of [73, 75, 76] indicate the possibility of attaining the LTNP status, but do not provide systematic drug-scheduling methods for driving the patient to the LTNP status.

patients stop therapy within the first year on HAART because of side effects [38].

³A number of HIV models are available, but the LTNP phenomenon is described by only a few HIV models in which the HIV specific immune modeling is sophisticated.

In [82, 83] model predictive control (MPC) tools have been applied to the model in [73] to determine when a full dose, or no medication, induce the LTNP status. This problem has been studied with optimal control methods in [1, 2, 10]. Moreover, in [67–69], optimal control theory has been applied to the disease dynamic model of [8]. A variation of the scheme used in [82, 83], as well as the effect of using a continuous function of drug efficiency, is considered in [65]. Although all these works show that the state of a patient can be successfully driven into the LTNP region of attraction, these control methods rely on the accurate and timely measurement of all of the model states, and thus are unrealistic. In addition these works use various dynamic models with diverse properties and rely heavily on the existence of optimal control laws, thus provide little understanding of the immune response.

1.2 Contribution of the thesis

The primary goal of this thesis is to steer the state of the system describing a HIV infected patient to the LTNP status. This is achieved by means of new methods of treatment.

The first method is based on an approximation of higher order dynamics by a reduced order model. For the approximation we divide the HIV infection model into two subsystems and modify one of the subsystems to emulate the whole system. With the modification we relieve the difficulties associated with the high order model, such as state observation and parameter estimation.

The second control method is known as gradual reduction of drug dose. By this scheme it is possible to steer the state of any patient to the LTNP status if the model parameters belong to certain parameter intervals. In order to justify the claim, we first analyze the stability and the bifurcation properties of a HIV model and show that there exists an equilibria curve towards the LTNP, which is locally stable for almost every fixed constant input.

The third control method is derived from a new control philosophy which aims at boosting the response of the immune system by means of drug scheduling. The control strategy is implemented by controlled drug scheduling based on the understanding of the immune boosting mechanism. The feasibility of the control methodology is illustrated via simulations on a general disease model and on three HIV dynamic models, one of

which is a tristable HIV dynamic model.

This control perspective yields an output feedback method to control the immune response. The suggested output feedback control idea guarantees that the immune state is enhanced to a certain level, which is enough for a typical patient to be driven into the long-term nonprogressor. To justify the control methodology the resulting controlled HIV dynamic model is studied analytically.

Finally we investigate methods to estimate approximately the state of the immune system on the basis of available outputs of the HIV model. We suggest two state estimation methods, denoted as state inferences.

Experimental verification by clinical data is out of the scope of the thesis: we concentrate on model-based study as well as computer simulations to verify the feasibility of the theoretical approach.

1.3 Organisation of the thesis

The thesis is organised as follows. In Chapter 2, Section 2.1 reviews some HIV models as well as general models of disease dynamics. Section 2.2 surveys measurement methods for the states of the HIV models, and discusses the relation between available measurements and the states of the HIV models.

Chapter 3 is organised as follows. In Section 3.1 the problem considered in the chapter is formulated, and in Section 3.2 the HIV model is modified to yield a reduced-order model. Section 3.3 introduces a new control strategy for the modified model and contains some simulation results. An improved control method with adapting reduced-order model parameters is presented in Section 3.4. This chapter concludes with a discussion of the results in Section 3.5.

Chapter 4 is organised as follows. In Section 4.1 and Section 4.2 we present the bifurcation analysis of the HIV model in [40] to prepare for an application of gradual reduction of drug dose. An example of gradual reduction of drug dose to the model is discussed in Section 4.3. Section 4.4 summarises the result of the chapter.

Chapter 5 is organised as follows. In Section 5.1 we analyze the immune system, develop a new strategy for drug dosage, and evaluate such a strategy by means of simulations. The proposed strategy is then applied to the HIV model in [1] in Section 5.2, and to the model of a general class of diseases in Section 5.3. In Section 5.4 we evaluate

the control idea on an alternative HIV dynamic system, which possesses a tristability property. Then Section 5.5 provides a summary and further remarks.

Chapter 6 is organised as follows. In Section 6.1 we describe the output feedback control idea and its performances are demonstrated by means of computer simulations. In Section 6.2 we analyze the controlled HIV model to show the control mechanism of the output feedback strategy. Section 6.3 provides summary and conclusions.

Chapter 7 is organised as follows. Section 7.1 proposes a state approximation method based on continuous output injection, and the method is illustrated by means of computer simulations. In Section 7.2 we suggest an alternative method to monitor the immune status of the HIV infected patient taking into account implementation issues. Section 7.3 describes further remarks.

We conclude this work in Chapter 8 with a summary of the main contributions of the thesis in Section 8.1 as well as a discussion on future work in Section 8.2.

1.4 Published material

The works in Section 2.2 and Chapter 3 are included in [22] and [15]. The results in Chapter 4 are presented in [17]. The results in Chapter 5 are published in [21], [16], [19], and [18]. The works in Chapter 6 and Chapter 7 are included in [23] and [20] respectively.

In addition, the preliminary work for Chapter 4 is published in [27], and its applications are included in [25], [26], and [24]. The formal analysis and proofs for the work of Chapter 4 are shown in [66] as well as [64].

Chapter 2

Background material

This chapter provides an introduction to HIV models and to a general model of disease dynamics, which are used throughout the thesis. In addition, some basic informations on HIV measurements are given and discussed.

2.1 Introduction to HIV dynamic models

The interactions between HIV and immunocytes in the human body can be described by means of several mathematical models. For a comprehensive explanation of HIV infection modeling see [54] or [59].

Throughout the thesis the states of the models describe concentrations of specific cells in a unit volume of blood and therefore are meaningful only when positive. The model parameters which are used throughout the thesis are normalized so the state variables do not represent actual data. For actual parameters in different HIV models see [37, 59]. Moreover each patient practically has different system parameters. For parameter estimation techniques in HIV models see [78].

2.1.1 HIV model with CTL-mediated immune response

In this section we recall the HIV infection model of [73], which allows to describe the LTNP equilibrium. In particular the model describes the cytotoxic T lymphocyte (CTL) response needed for the existence of the LTNP equilibrium. The model is described by

the equations

$$\dot{x} = \lambda - dx - \eta\beta xy, \quad (2.1)$$

$$\dot{y} = \eta\beta xy - ay - p_1 z_1 y - p_2 z_2 y, \quad (2.2)$$

$$\dot{z}_1 = c_1 z_1 y - b_1 z_1, \quad (2.3)$$

$$\dot{w} = c_2 xyw - c_2 qyw - b_2 w, \quad (2.4)$$

$$\dot{z}_2 = c_2 qyw - h z_2. \quad (2.5)$$

As indicated in Table 2.1, x is the concentration of uninfected CD4 T-cells, y is the concentration of infected CD4 T-cells, z_1 is the concentration of helper-independent CTLs, w is the concentration of CTL precursors, and z_2 is the concentration of helper-dependent CTLs.

State variable	Clinical meaning
x	Concentration of uninfected CD4 T-cell
y	Concentration of infected CD4 T-cell
z_1	Concentration of helper-independent CTL
w	Concentration of CTL precursor
z_2	Concentration of helper-dependent CTL

Table 2.1: Clinical meaning of the state variables of the HIV model (2.1)-(2.5).

The population of healthy (uninfected) CD4 T-cells increases at a rate λ (since the cells are produced by the thymus), and decreases in the absence of HIV at a rate dx (since the cells die naturally), which is proportional to the population of x . Uninfected CD4 T-cells are infected at a rate that is proportional to the product of x and y because the CD4 T-cell x is a target of HIV and the infected CD4 T-cells y produce new virus. The infected cell y dies out at a rate ay . In addition, the model describes the adaptive cell-mediated immune system. This system consists of the precursor CTL w , which provides long-term memory for a specific antigen, HIV in this case, as well as the effector CTL z_2 , which has the role of destroying the infected cell y at the rate $p_2 z_2 y$. The cell w differentiates into the cell z_2 at the rate $c_2 qyw$. In other words, the model implies that large populations of the infected cells y and of the precursor CTL w make the population of z_2 increase more rapidly. The term $c_2 xyw$ in (2.4) implies that the precursor CTL

w is generated at a rate proportional to the concentrations of x , y , and w . The helper-independent component of the CTL response is represented in this model by z_1 . These cells proliferate without CD4 T-cell help at the rate $c_1 z_1 y$, and destroy infected cells at the rate $p_1 z_1 y$. For a detailed explanation of the model see [73, 75].

The population of HIV is not explicitly shown in models (2.1)-(2.5) and the y state corresponds to infected CD4 T-cell in this model. The state y can be regarded proportional to the HIV load [12, 31, 73], because the turnover of HIV is much faster than that of y [60]. That is to say, we accept the approximation $v = C_p y$, where v is the virus level and C_p is a proportional parameter.

The quantity η , which varies between 0 and 1, describes the effect of the drug. In the presence of a control input η can be written as

$$\eta = 1 - \epsilon^* u, \quad (2.6)$$

where ϵ^* is the maximal effect of the drug. For example, $\epsilon^* = 0.98$ indicates that the maximal effect of the drug is 98%. From a control perspective, the input u , which has values between 0 and 1, represents the drug dose of highly active anti-retroviral therapy (HAART). If $u = 1$, a patient receives the maximal HAART therapy, while $u = 0$ means no medication.

Note that, with the exception of Chapter 4 in the thesis, the drug input u is restricted to be either 0 or 1 because the use of partially suppressive therapy (i.e., $0 < u < 1$) is difficult to achieve in practice [83]. In addition drug therapy at less than full dosage must not be applied because of the high probability of emergence of drug-resistant strains of HIV [83]. Consequently, equation (2.1) becomes $\dot{x} = \lambda - dx - \beta xy$ when $u = 0$, or $\dot{x} = \lambda - dx - (1 - \epsilon^*)\beta xy$ when $u = 1$.

The remaining parameters λ , d , β , a , p_1 , p_2 , c_1 , c_2 , q , b_1 , b_2 , and h are positive constants. The population of HIV is not explicitly modeled because it can be approximated by y .

2.1.2 HIV model with immune response strongly dependant on target cells

In this section we recall the model in [40]. The model is described by the equations

$$\dot{x} = \lambda - dx - \sum_{i=1}^n \beta_i y_i x, \quad (2.7)$$

$$\dot{y}_i = (\beta_i x - a_i - p_i z_i) y_i, \quad i = 1, 2, 3, \dots, n, \quad (2.8)$$

$$\dot{z}_i = (c_i y_i x^2 - b_i) z_i, \quad i = 1, 2, 3, \dots, n. \quad (2.9)$$

The clinical meaning of each state is given in Table 2.2. For a detailed explanation of the model (2.7)-(2.9) see [40].

Assume that only one viral strain exists (i.e., $n = 1$ in model (2.7)-(2.9)) and introduce a control term η , yielding the model

$$\dot{x} = \lambda - dx - \eta \beta y x, \quad (2.10)$$

$$\dot{y} = (\eta \beta x - a - pz)y, \quad (2.11)$$

$$\dot{z} = (cyx^2 - b)z. \quad (2.12)$$

The quantity η describes the effect of the drug, and can be written as

$$\eta = 1 - \epsilon^* u, \quad (2.13)$$

where ϵ^* is the maximum effect of the drug. From a control perspective, the input u represents the drug dose, which has values between 0 and 1. The remaining parameters λ , d , β , a , p , c , and b are positive constants.

State variable	Clinical meaning
x	Concentration of uninfected CD4 T-cell
y_i	Concentration of infected CD4 T-cell by viral strain i
z_i	Concentration of immune reaction cell specific to viral strain i

Table 2.2: Clinical meaning of the state variables of the HIV model (2.7)-(2.9).

2.1.3 HIV model with two target cell types

In this section we discuss the HIV model proposed in [1, 2, 10], which is described by the equations

$$\dot{x}_1 = \lambda_1 - d_1 x_1 - (1 - \epsilon_1 u_1) k_1 v x_1, \quad (2.14)$$

$$\dot{x}_2 = \lambda_2 - d_2 x_2 - (1 - f \epsilon_1 u_1) k_2 v x_2, \quad (2.15)$$

$$\dot{y}_1 = (1 - \epsilon_1 u_1) k_1 v x_1 - \delta y_1 - m_1 z y_1, \quad (2.16)$$

$$\dot{y}_2 = (1 - f \epsilon_1 u_1) k_2 v x_2 - \delta y_2 - m_2 z y_2, \quad (2.17)$$

$$\dot{v} = (1 - \epsilon_2 u_2) N_T \delta (y_1 + y_2) - c v - A_1(x_1, x_2, u_1) v, \quad (2.18)$$

$$\dot{z} = \lambda_E + \frac{b_E(y_1 + y_2)}{(y_1 + y_2) + K_b} z - \frac{d_E(y_1 + y_2)}{(y_1 + y_2) + K_d} z - \delta_E z, \quad (2.19)$$

where $A_1(x_1, x_2, u_1) = (1 - \epsilon_1 u_1) \rho_1 k_1 x_1 + (1 - f \epsilon_1 u_1) \rho_2 k_2 x_2$.

As indicated in Table 2.3, x_1 describes the uninfected CD4+ T-cell, x_2 the uninfected macrophage, y_1 the infected CD4+ T-cell, y_2 the infected macrophage, v the free virus, and z the CTL effector.

State variable	Clinical meaning
x_1	Concentration of uninfected CD4+ T-cell
x_2	Concentration of uninfected macrophage
y_1	Concentration of infected CD4+ T-cell
y_2	Concentration of infected macrophage
v	Concentration of free virus
z	Concentration of CTL effector

Table 2.3: Clinical meaning of the state variables of the HIV model (2.14)-(2.18).

The input terms u_1 and u_2 represent the antiviral effects from reverse transcriptase inhibitors (RTI) and protease inhibitors (PI), respectively. For a comprehensive explanation of the model see [1, 2, 10] and for further detail see [12, 14].

2.1.4 HIV model with two immune response types

In this section we recall the model in [6]. The model describes the interaction between infected and uninfected CD4 T-cells in the human body, including lytic and non-lytic

components of the immune response to HIV infection. The model is described by the equations

$$\dot{x} = \lambda - d_x x - \eta \beta y x N, \quad (2.20)$$

$$\dot{x}_1 = \lambda_H + \frac{\alpha y x_1}{\gamma_1 + y} - \epsilon x_1^2 - \eta \beta_H y x_1 N, \quad (2.21)$$

$$\dot{x}_2 = \lambda_H + \frac{\alpha y x_2}{\gamma_2 + y} - \epsilon x_2^2 - \eta \beta_H y x_2 N, \quad (2.22)$$

$$\dot{y} = \eta y [\beta x + \beta_H x_1 + \beta_H x_2] N - d_y y - K y, \quad (2.23)$$

where $\gamma_2 > \gamma_1$, $K = K(x_1, x_2) = k_1 x_1 + k_2 x_2$, and

$$N = N(x_1, x_2) = \frac{1}{1 + n_1 x_1 + n_2 x_2}.$$

As indicated in Table 2.4, x describes the concentration of uninfected CD4 T-cells which do not play a role in the HIV-specific immune response, and y the concentration of infected CD4 T-cells. x_1 and x_2 correspond to the concentrations of uninfected CD4 T-cells which participate in the HIV-specific immune response.

State	Clinical meaning
x	Concentration of uninfected CD4 T-cell unrelated to the HIV-specific immune response
y	Concentration of infected CD4 T-cell
x_1	Concentration of uninfected CD4 T-cell related to the HIV-specific immune response, type 1
x_2	Concentration of uninfected CD4 T-cell related to the HIV-specific immune response, type 2

Table 2.4: Clinical meaning of the state variables of the HIV model (2.20)-(2.23).

To deal with drug dosage as control input, we introduce the η term into the model. The quantity η describes the effect of the drug. In view of the presence of a control input, η can be written as

$$\eta(t) = 1 - \epsilon^* u(t),$$

where ϵ^* is the maximum effect of the drug. From a control perspective the input u represents the drug dose, which takes values between zero and one. Note that u is

restricted to be either 0 or 1 as explained in Subsection 2.1.1. The remaining parameters λ , λ_H , d_x , d_y , α , β , β_H , γ_1 , γ_2 , ϵ , k_1 , k_2 , n_1 , and n_2 are positive. For a detailed explanation of the model see [6].

2.1.5 Disease dynamic model

In this section we describe a general disease dynamic model. In particular, we consider the disease dynamic model given in [8, 67, 69] and described by the equations

$$\dot{x}_1 = (a_{11} - a_{12}x_3)x_1 + b_1u_1, \quad (2.24)$$

$$\dot{x}_2 = a_{21}(x_4)a_{22}x_1(t - \tau)x_3(t - \tau) - a_{23}(x_2 - x_2^*) + b_2u_2, \quad (2.25)$$

$$\dot{x}_3 = a_{31}x_2 - (a_{32} + a_{33}x_1)x_3 + b_3u_3, \quad (2.26)$$

$$\dot{x}_4 = a_{41}x_1 - a_{42}x_4 + b_4u_4, \quad (2.27)$$

where the states x_1 , x_2 , x_3 describe concentrations of specific cells in a unit volume of blood and therefore are meaningful only when positive.

As indicated in Table 2.5, x_1 describes the pathogenic antigen, x_2 the plasma cells, x_3 the antibody, and x_4 the relative characteristic of a damaged organ, where $x_4 = 0$ indicates a healthy organ and $x_4 = 1$ a dead organ.

State variable	Clinical meaning
x_1	Concentration of pathogenic antigen
x_2	Concentration of plasma cells
x_3	Concentration of antibody
x_4	Concentration of relative characteristic of a damaged organ

Table 2.5: Clinical meaning of the state variables of the disease model (2.24)-(2.27).

This model is a modification of the mathematical model from [8], obtained by adding therapeutic control inputs. Note that the model of [8] does not include any therapy effects. The inputs are introduced for the model in [67, 69] and they are the pathogen killer u_1 , the plasma cell enhancer u_2 , the antibody enhancer u_3 , and the organ healing factor u_4 . Accordingly $b_1 < 0$, $b_2 > 0$, $b_3 > 0$, and $b_4 < 0$ [67, 69]. τ and x_2^* in (2.25) are parameters which describe a pure time delay and a steady-state concentration of plasma cells, respectively. For further detail on the model see [8, 67, 69].

2.2 HIV measurements

HIV measurements are needed to monitor the status of a HIV-infected patient. In this section we summarize the status of measurements related to HIV infection dynamics. Several types of antibody tests, such as enzyme-linked immunosorbent assay (ELISA) or western blot, are not discussed because these tests cannot give quantitative data on the amount of the antibody. For additional information about HIV antibody testing see [58].

2.2.1 Viral load tests

Viral load tests, which return the level of the y state in model (2.1)-(2.5), are also known as viral load assays, polymerase chain reaction (PCR) tests, or branched deoxyribonucleic acid (bDNA) tests [3]. These tests work by looking for HIV genetic material, the ribonucleic acid (RNA). Each test has a threshold viral level, below which it cannot reliably detect HIV genetic material. This limit for clinical technology is currently 50 copies/ml [61], although some advanced experiments can detect HIV down to 5 copies/ml [52]. Each test is highly reliable and repeatable, and thus is used with a CD4 T-cell count to monitor the progress of a HIV-infected patient.

2.2.2 Flow cytometry and CD4 T-cell count

Examination of lymphocyte populations is possible because their cell surface markers are uniquely expressed. Monoclonal antibodies are used to identify T lymphocytes in human blood [28]. These antibodies are labeled with fluorescent markers [62]. A flow cytometer is designed to automate the analysis and separation of cells stained with fluorescent antibodies. The flow cytometer uses a laser beam and a light detector to count single intact cells in suspension (see Figure 2.1). Every time a cell with a fluorescent antibody passes the laser beam, the cell is excited by the laser and emits light, which is deflected and recorded by a detector. This instrument can sort populations of cells into various containers according to their fluorescence.

In HIV treatment, the measurement of T-cell subpopulations, such as a subpopulation of CD4 T-cells, is a key indicator of the prognosis of AIDS and it is routinely performed by flow cytometric analysis. Although trained users of a flow cytometer can obtain accurate results quickly and easily, this measurement method has limitations be-

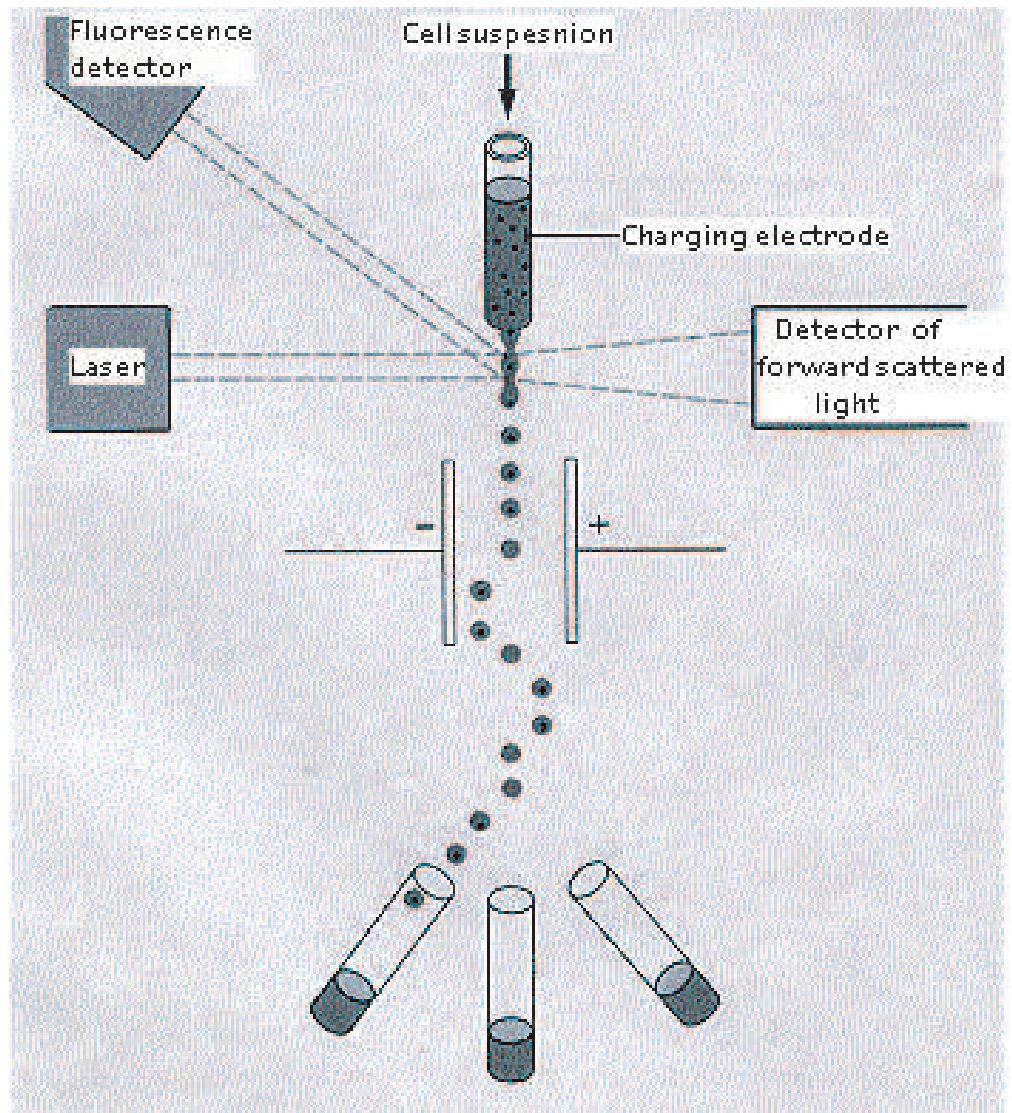


Figure 2.1: Basic flow cytometer [43]. A flow cytometer is designed to automate the analysis and separation of cells stained with fluorescent antibody. The flow cytometer uses a laser beam and light detectors to count single intact cells in suspension. Each time a cell with a fluorescent antibody passes the laser beam, the cell is excited by the laser and emits light, which is deflected and recorded by detectors.

cause measuring specific cells requires the corresponding fluorescent antibody to stain the target cells. For example, to measure unusual cells, the required antibody may be costly or difficult to obtain [36].

2.2.3 Discussion on HIV measurements

Although a flow cytometer is a highly precise instrument, variability in the CD4 T-cell count can be a significant problem [62]. For example, CD4 T-cell counts normally undergo diurnal variation with fluctuation by as much as 150 to 300 copies/mm³, while refrigeration of blood samples elevates the CD4 T-cell count. In addition, the CD4 T-cell count increases as samples wait for processing. These variations make it difficult to assess the real change in the CD4 T-cell population.

Meanwhile, since each viral load test has particular characteristics, results from different tests may not be comparable [3]. In particular, a pair of tests carried out on the same sample of blood may vary significantly. Therefore, in clinical treatment the viral load trend is more important than the individual viral load measurement.

Now consider the HIV model (2.1)-(2.5). In [22] we have assumed that the states x and y are clinically measurable by means of polymerase chain reaction (PCR) test and flow cytometry. PCR returns the level of HIV loads while a flow cytometer counts the level of CD4 T-cells (see [39, 53] for more information on PCR). The population of HIV is not explicitly shown in the HIV model (2.1)-(2.5)¹, and the y state corresponds to infected CD4 T-cell in model (2.1)-(2.5). The state y is approximately considered as proportional to the HIV load [12, 73], because the turnover of HIV is much faster than that of y [60].

Although we have assumed that x corresponds to the CD4 T-cells measured by a flow cytometer in [22], different assumptions are claimed in [1] because the result from flow cytometer could include the number of infected CD4 T-cells as well as uninfected CD4 T-cells. Nevertheless we can measure the number of infected CD4 T-cell y with the help of PCR.

To this end, firstly we must separate white blood cells from blood sample of the HIV patient by Ficoll-Hypaque method [49]. The PCR measures the number of HIV genome [3], and an infected CD4 T-cell has the HIV genome in its cellular DNA. Consequently, if

¹See Subsection 2.1.3 or [76] for HIV models including the population of HIV.

PCR is performed with the separated white blood cells, then only the number of infected CD4 T-cells y can be counted and the number of healthy CD4 T-cells x can be obtained by subtracting y from the CD4 count (i.e., $x + y$) of flow cytometry.

Chapter 3

Control method based on a reduced order model

This chapter describes a drug scheduling method based on a reduced-order model of the HIV infection, which does not require estimates of all of the parameters and states of the full-order model. We divide the full-order model into two subsystems, one of which is modified to approximate the full-order model. We show that the suggested method succeeds in driving the HIV patient state into the LTNP region of attraction. The works in this chapter are included in [22] and [15].

3.1 Problem formulation

Consider the HIV model (2.1)-(2.5), introduced in Section 2.1.1, namely

$$\dot{x} = \lambda - dx - \eta\beta xy, \quad (3.1)$$

$$\dot{y} = \eta\beta xy - ay - p_1 z_1 y - p_2 z_2 y, \quad (3.2)$$

$$\dot{z}_1 = c_1 z_1 y - b_1 z_1, \quad (3.3)$$

$$\dot{w} = c_2 xyw - c_2 qyw - b_2 w, \quad (3.4)$$

$$\dot{z}_2 = c_2 qyw - h z_2. \quad (3.5)$$

When a patient is treated it is desired that the drug be eventually terminated. To investigate this possibility we determine the five equilibrium points of the model (3.1)-(3.5) in Table 3.1. The stability properties of these equilibria are evaluated with the parameter set of [73, 82, 83] given in Table 3.2. Under the assumption that $\eta = 1$, which

corresponds to the case of no medication, the interpretation of each equilibrium is as follows. Point A indicates the status of a person who does not have HIV. With the parameters of Table 3.2 this equilibrium is unstable, which explains why it is difficult to revert a patient, once infected, back to the HIV-free status when the medication is stopped. Points C and E are locally exponentially stable. Point C is the status of a patient for whom HIV dominates. Point E is for a HIV-positive patient who does not progress to AIDS. For this reason this status is referred to as LTNP. With the parameters of Table 3.2, the number $y^{(E)}$ of infected cells is low, while the number $w^{(E)}$ of CTL precursors is large, which is desired. The control goal is to drive the state near this equilibrium from any initial state. Note that the HIV patient state cannot be induced to the LTNP status if full dose of HAART medication is applied everyday [25, 27, 65, 73, 75, 82, 83]. Points B and D, which are unstable for the parameters of Table 3.2, are not of interest for this discussion.

Point A (Healthy)	$x^{(A)} = \frac{\lambda}{d}, \quad y^{(A)} = 0,$ $z_1^{(A)} = 0, \quad w^{(A)} = 0, \quad z_2^{(A)} = 0.$	Unstable
Point B	$x^{(B)} = \frac{a}{\eta\beta}, \quad y^{(B)} = \frac{\lambda\eta\beta - da}{a\eta\beta},$ $z_1^{(B)} = 0, \quad w^{(B)} = 0, \quad z_2^{(B)} = 0.$	Unstable
Point C (AIDS)	$x^{(C)} = \frac{\lambda c_1}{dc_1 + b_1\eta\beta}, \quad y^{(C)} = \frac{b_1}{c_1},$ $z_1^{(C)} = \frac{\eta\beta x^{(C)} - a}{p_1}, \quad w^{(C)} = 0, \quad z_2^{(C)} = 0.$	LES
Point D	$x^{(D)} = \frac{\lambda}{d + \eta\beta y^{(D)}}, \quad y^{(D)} = \frac{[c_2(\lambda - dq) - b_2\eta\beta] + \sqrt{[c_2(\lambda - dq) - b_2\eta\beta]^2 - 4\eta\beta c_2 q db_2}}{2\eta\beta c_2 q},$ $z_1^{(D)} = 0, \quad w^{(D)} = \frac{hz_2^{(D)}}{c_2 q y^{(D)}}, \quad z_2^{(D)} = \frac{y^{(D)}(c_2\eta\beta q - c_2 a) + b_2\eta\beta}{c_2 p_2 y^{(D)}}.$	Unstable
Point E (LTNP)	$x^{(E)} = \frac{\lambda}{d + \eta\beta y^{(E)}}, \quad y^{(E)} = \frac{[c_2(\lambda - dq) - b_2\eta\beta] - \sqrt{[c_2(\lambda - dq) - b_2\eta\beta]^2 - 4\eta\beta c_2 q db_2}}{2\eta\beta c_2 q},$ $z_1^{(E)} = 0, \quad w^{(E)} = \frac{hz_2^{(E)}}{c_2 q y^{(E)}}, \quad z_2^{(E)} = \frac{y^{(E)}(c_2\eta\beta q - c_2 a) + b_2\eta\beta}{c_2 p_2 y^{(E)}}.$	LES

Table 3.1: Equilibrium points of the model (3.1)-(3.5) [25]. All stability properties are based on the typical parameter set of Table 3.2.

To analyze the model (3.1)-(3.5), let $X := [x, y, z_1, w, z_2]^T$ and let $\mathcal{U}$ be the set of measurable functions on $[0, \infty)$ with values between 0 and 1. Note that the input $\eta(\cdot)$ of interest is in $\mathcal{U}$. Also, let $\mathcal{P} = [0, \infty)^5$.

Theorem 1 *Consider the system (3.1)-(3.5). For every input function $\eta(\cdot) \in \mathcal{U}$, finite-time escape cannot occur, and the set $\mathcal{P}$ is positively invariant. In other words, for every $\eta(\cdot) \in \mathcal{U}$ and initial condition $X(0) \in \mathcal{P}$, the solution $X(t)$ of (3.1)-(3.5) exists for all*

λ	d	β	a	p_1	p_2	c_1	c_2	q
1	0.1	1	0.2	1	1	0.03	0.06	0.5
b_1	b_2	h	ϵ^*	$x(0)$	$y(0)$	$z_1(0)$	$w(0)$	$z_2(0)$
0.1	0.01	0.1	0.9799	0.2913	3.3333	0.0913	0.0100	0.0100

Table 3.2: Parameters and initial conditions for model (3.1)-(3.5). All simulations in this chapter use these typical parameters, which are taken from [73, 82, 83].

$t \geq 0$, and is contained in $\mathcal{P}$ for all $t \geq 0$.

Proof: Let $X(0) \in \mathcal{P}$ and assume that some component of $X(t)$ escapes at the finite time $T > 0$. Since (3.2), (3.3), and (3.4) have the linear form $\dot{y}(t) = f_y(t)y(t)$, $\dot{z}_1(t) = f_{z_1}(t)z_1(t)$, and $\dot{w}(t) = f_w(t)w(t)$, where $f_y(t)$, $f_{z_1}(t)$, and $f_w(t)$ are continuous on $[0, T)$, the states $y(t)$, $z_1(t)$, and $w(t)$ remain positive for $0 \leq t < T$. During this time interval the states $x(t)$ and $z_2(t)$ also remain positive since $y(t)$ and $w(t)$ are continuous and positive, $\dot{x} > 0$, and $\dot{z}_2 \geq 0$ by (3.1) and (3.5) for $x = 0$ and $z_2 = 0$, respectively. Hence $X(t) \in \mathcal{P}$ for $0 \leq t < T$. Now define $V(t) := x(t) + y(t)$, which is positive for all $t \in [0, T)$. Then

$$\begin{aligned}
\dot{V} &= \lambda - dx - ay - p_1 z_1 y - p_2 z_2 y \\
&\leq \lambda - k(x + y) \\
&= \lambda - kV,
\end{aligned}$$

where $k = \min\{d, a\}$. Thus $V(t)$ (and hence, $x(t)$ and $y(t)$) is bounded on the interval $0 \leq t < T$. Indeed, for $0 \leq t < T$, the functions $f_{z_1}(t) = c_1 y(t) - b_1$ and $f_w(t) = c_2 x(t)y(t) - c_2 q y(t) - b_2$ are bounded. Therefore, $z_1(t)$ and $w(t)$ do not diverge to infinity by boundedness of $f_{z_1}(t)$ and $f_w(t)$. Then, by (3.5), $z_2(t)$ is also bounded. Hence finite escape does not occur and $\mathcal{P}$ is positively invariant $\square$

3.2 Modification of the model

3.2.1 Separation of the model

We consider the full-order model (3.1)-(3.5) as the interconnection of two subsystems: the infection dynamics and the immune system. The infection dynamics are modeled by

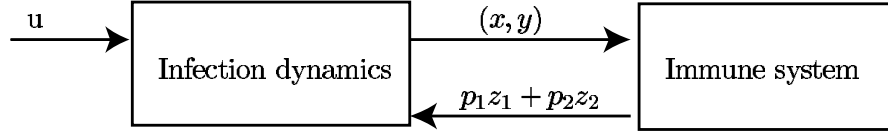


Figure 3.1: Interconnection between the infection dynamics and the immune system.

means of the two-dimensional nonlinear system

$$\dot{x} = \lambda - dx - \beta(1 - \epsilon^*u)xy, \quad (3.6)$$

$$\dot{y} = \beta(1 - \epsilon^*u)xy - ay - (p_1z_1 + p_2z_2)y, \quad (3.7)$$

with inputs u and $p_1z_1 + p_2z_2$, and outputs x and y .

The immune system is modeled by the three-dimensional nonlinear system

$$\dot{z}_1 = c_1z_1y - b_1z_1, \quad (3.8)$$

$$\dot{w} = c_2xyw - c_2qyw - b_2w, \quad (3.9)$$

$$\dot{z}_2 = c_2qyw - hz_2, \quad (3.10)$$

with inputs x and y , and output $p_1z_1 + p_2z_2$. The interconnection of these subsystems is shown in Figure 3.1.

We consider the full-order model (3.1)-(3.5) as the interconnection of two nonlinear systems for several reasons. Firstly, it is currently not possible to measure all the states of the full-order model (3.1)-(3.5) with high accuracy [83]. In particular, as discussed in Section 2.2, we can assume that the CD4 T-cells x and the HIV loads y are measured accurately. Therefore the system (3.6), (3.7) includes the states that can be measured reliably, whereas the system (3.8)-(3.10) has unmeasured states.

Secondly, it might be impossible to estimate the parameters of the immune system due to the lack of measurements of the immune system states. Even if estimation were possible, it may be impractical to estimate these parameters for each HIV patient. For additional information about parameter estimation in HIV dynamic models, see [77, 78].

Thirdly, although the full-order model (3.1)-(3.5) describes the human immune system with both helper-dependent CTL and helper-independent CTL, the immune system is only approximately modeled by a low-order system of differential equations. Therefore we separate the well-modeled part (3.6), (3.7) from the poorly¹ modeled part (3.8)-(3.10).

¹The model in [12] has an alternative immune system, which is different from (3.8)-(3.10).

In the infection dynamics (3.6), (3.7), we can regard the effect on the virus load from the immune system (3.8)-(3.10) as the positive function $\phi(z_1, z_2) = p_1 z_1 + p_2 z_2$ acting on (3.7). The system (3.6), (3.7) consists of the model used in [54] as well as the function ϕ , which corresponds to the control effect of the virus load produced by the system (3.8)-(3.10). By appending ϕ , the virus dynamic model of [54] becomes the system (3.6), (3.7).

For these reasons we seek a control method that depends only on (3.6), (3.7). To realize such a method, we note that (3.7) includes the states z_1 and z_2 , while (3.6) has only the states x and y . Our goal is thus to modify (3.7) so that the modified system exhibits dynamic behaviour similar to that of the full-order model (3.1)-(3.5) over short time intervals.

3.2.2 Construction of the reduced-order model

The full-order model (3.1)-(3.5) has two asymptotically stable equilibria with the typical parameter set. Therefore, when $u = 0$, the modified infection dynamics must have analogous equilibria for these parameters. Thus, as a candidate² for the modified infection dynamics we consider the reduced-order model

$$\dot{x} = \lambda - dx - \beta(1 - \epsilon^* u)xy, \quad (3.11)$$

$$\dot{y} = -\beta\epsilon^* uxy + A + By + Cy^2 + Dy^3, \quad (3.12)$$

where A , B , C , and D are real numbers with D nonzero. When $u = 0$, (3.11), (3.12) becomes

$$\dot{x} = \lambda - dx - \beta xy, \quad (3.13)$$

$$\dot{y} = A + By + Cy^2 + Dy^3. \quad (3.14)$$

The equilibria of (3.14) are determined by solving

$$A + By + Cy^2 + Dy^3 = 0. \quad (3.15)$$

The full-order model (3.1)-(3.5) has two asymptotically stable equilibrium points when $u = 0$. In order for the reduced order model (3.11), (3.12) to have two stable equilibria

²This is a possible candidate which has been found through a number of trials. Another candidate can exist for the approach of this chapter.

with $u = 0$, (3.15) must have three real solutions, namely, K_1 , K_2 , and K_3 , where $K_1 < K_2 < K_3$. Then A , B , and C are such that

$$\begin{aligned} A &= -DK_1K_2K_3, \\ B &= D(K_1K_2 + K_2K_3 + K_3K_1), \\ C &= -D(K_1 + K_2 + K_3). \end{aligned}$$

If $D > 0$ then K_2 is an asymptotically stable equilibrium of (3.14) whereas K_1 and K_3 are unstable. If $D < 0$ then K_1 and K_3 are asymptotically stable equilibria of (3.14) whereas K_2 is unstable (see Figure 3.2). Therefore D must be negative. In addition $K_1 > 0$ guarantees the existence of two asymptotically stable equilibria with positive y . Consequently the values $\frac{\lambda}{d+\beta K_1}$ and $\frac{\lambda}{d+\beta K_3}$ of x for the two equilibria are also positive since K_1 , K_3 , and parameters are positive. Note that $D < 0$ implies existence and boundedness of all trajectories of the model (3.13), (3.14).

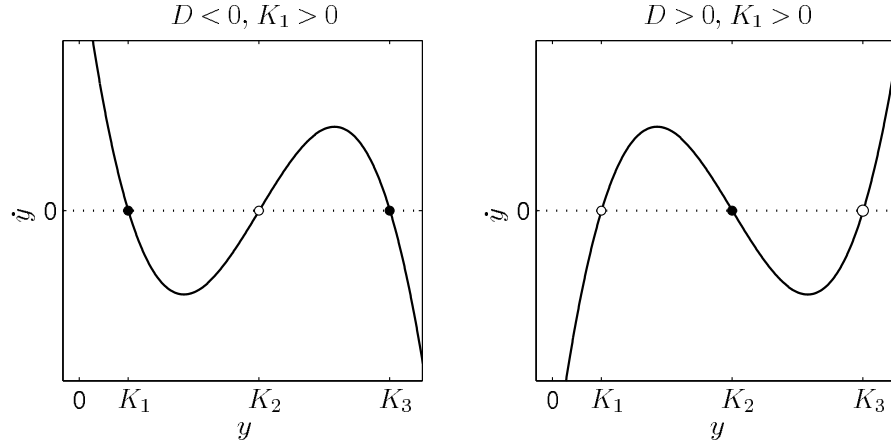


Figure 3.2: Graphs of y and $\dot{y}$ in equation (3.14). The left and the right graphs correspond to the cases with $D < 0$ and $D > 0$, respectively. It is assumed that $0 < K_1 < K_2 < K_3$. The dark dot in the graphs implies asymptotic stability of the equilibrium point whereas the white dot indicates instability of the point.

If the initial value of y is between 0 and K_2 , then $y(t)$ tends to K_1 . Then $x(t)$ tends to $\frac{\lambda}{d+\beta K_1}$ according to (3.13). If an initial state has a value of y greater than K_2 , then $y(t)$ tends to K_3 , and $x(t)$ tends to $\frac{\lambda}{d+\beta K_3}$. Therefore, the two-dimensional region of attraction for the equilibrium $(\frac{\lambda}{d+\beta K_1}, K_1)$ is $0 < y < K_2$ while the two-dimensional region of attraction for the equilibrium $(\frac{\lambda}{d+\beta K_3}, K_3)$ is $y > K_2$.

With the typical parameter set and $u = 0$, the full-order model (3.1)-(3.5) has five

equilibria, namely, $(10, 0, 0, 0, 0)$, $(0.2, 4.9, 0, 0, 0)$, $(0.2913, 3.3333, 0.0913, 0, 0)$, $(0.6079, 1.5451, 0, 0.8799, 0.4079)$, and $(8.2255, 0.0216, 0, 1240, 8.0255)$. Only the third and the fifth equilibria are asymptotically stable. Thus the y component 3.3333 of the third equilibrium is chosen as K_3 while the y component 0.0216 of the fifth is chosen as K_1 . Consequently, for $u = 0$, the reduced-order model (3.11), (3.12) has two asymptotically stable equilibria, namely, $(0.2913, 3.3333)$ and $(8.2255, 0.0216)$. Note that the modified reduced-order model will emulate the full-order system in a short period to present the effect of the immune system in those equilibria.

D and K_2 remain undetermined. At this point, we know only that $K_1 < K_2 < K_3$, $D < 0$, and $|D|$ must be sufficiently small. If $|D|$ is large and $u = 1$, then, with the typical parameters, the dynamics of (3.11), (3.12) do not vary dramatically whereas those of the full-order model (3.1)-(3.5) do. In the next section it is assumed that D and K_2 are fixed and a control methodology is presented.

3.3 Control strategy with constant parameters

In this section we assume that D and K_2 are constant and design a control strategy denoted as CSCP. With the above assumption all the parameters of (3.11), (3.12) are determined. The basic concept of the control strategy is that the low-order system (3.11), (3.12) for the modified infection dynamics is used as an emulator of a high-order system, the HIV patient.

The idea of using the reduced-order model (3.11), (3.12) in HIV treatment is as follows. We assume that the patient has HIV measurement tests at the beginning of a period of length T . Within the period T the reduced-order model (3.11), (3.12) exhibits dynamic behaviour similar to that of the high-order system. From HIV measurements (see Section 2.2), the CD4 T-cell count and viral load can be thought of as the values of the states x and y , respectively. Therefore we set these levels as the initial values for (3.11), (3.12) at the beginning of the period. During the period we consider (3.11), (3.12) as an emulator of the patient. Then we estimate the CD4 T-cell count and viral load of the patient by referring to the states x and y of (3.11), (3.12), respectively. The HIV measurements of the patient are available only once in each period, whereas the states x and y of the reduced-order model (3.11), (3.12) are available as desired by means of numerical integration. See Figure 3.3 for the configuration of the controlled system.

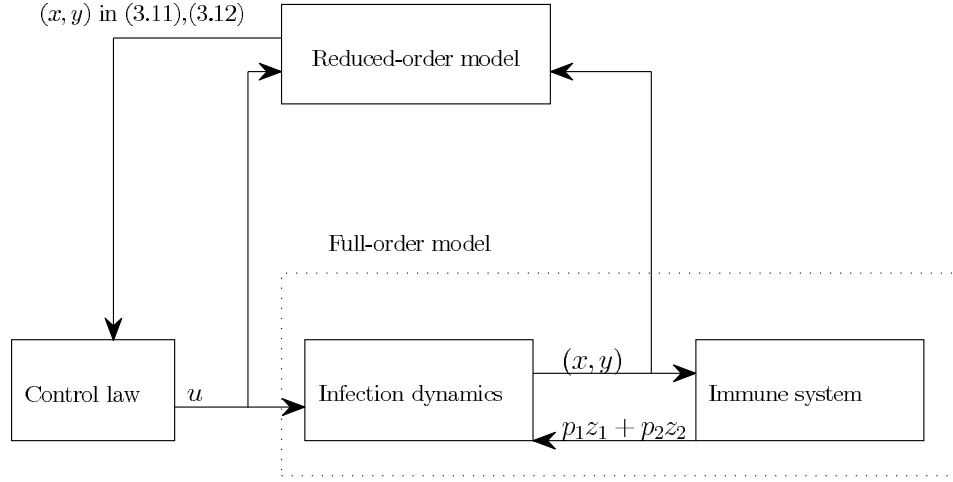


Figure 3.3: Diagram describing the configuration of the controlled system with reduced-order model. Note that (x, y) of full-order model is considered as discrete time input to reduced-order model.

Using (3.11), (3.12) we decide whether the anti-HIV therapy is taken each day. In other words the states x and y of the reduced-order model (3.11), (3.12) are available at the beginning of each day by means of numerical integration. This decision depends only on the value of y because $y = K_2$ is the boundary of the LTNP region of attraction in the reduced-order model (3.11), (3.12). If the state y of the reduced-order model (3.11), (3.12) is lower than K_2 at the beginning of the day, the anti-HIV medication is not administered to the patient for the day. Otherwise the medication is administered to the patient.

3.3.1 Control steps of CSCP

The idea of CSCP is realized by the following steps. Note that time is measured in days.

Initialization. Three positive numbers T , N , and K_2 , a negative number D , and a function $u_D(t)$ ($0 \leq t \leq 1$ day) of daily drug effect are chosen. T denotes the time period between each set of HIV measurements, while N denotes the total number of HIV measurements during medication. Therefore the period of total medication is NT days. Let n_T denote the number of days after the last HIV measurement and let n_N denote the number of HIV measurements after the beginning of the medication. Therefore, with the initialization $n_T = 0$ and $n_N = 0$, a generic day of the treatment can be denoted as the $(n_N T + n_T)$ th day.

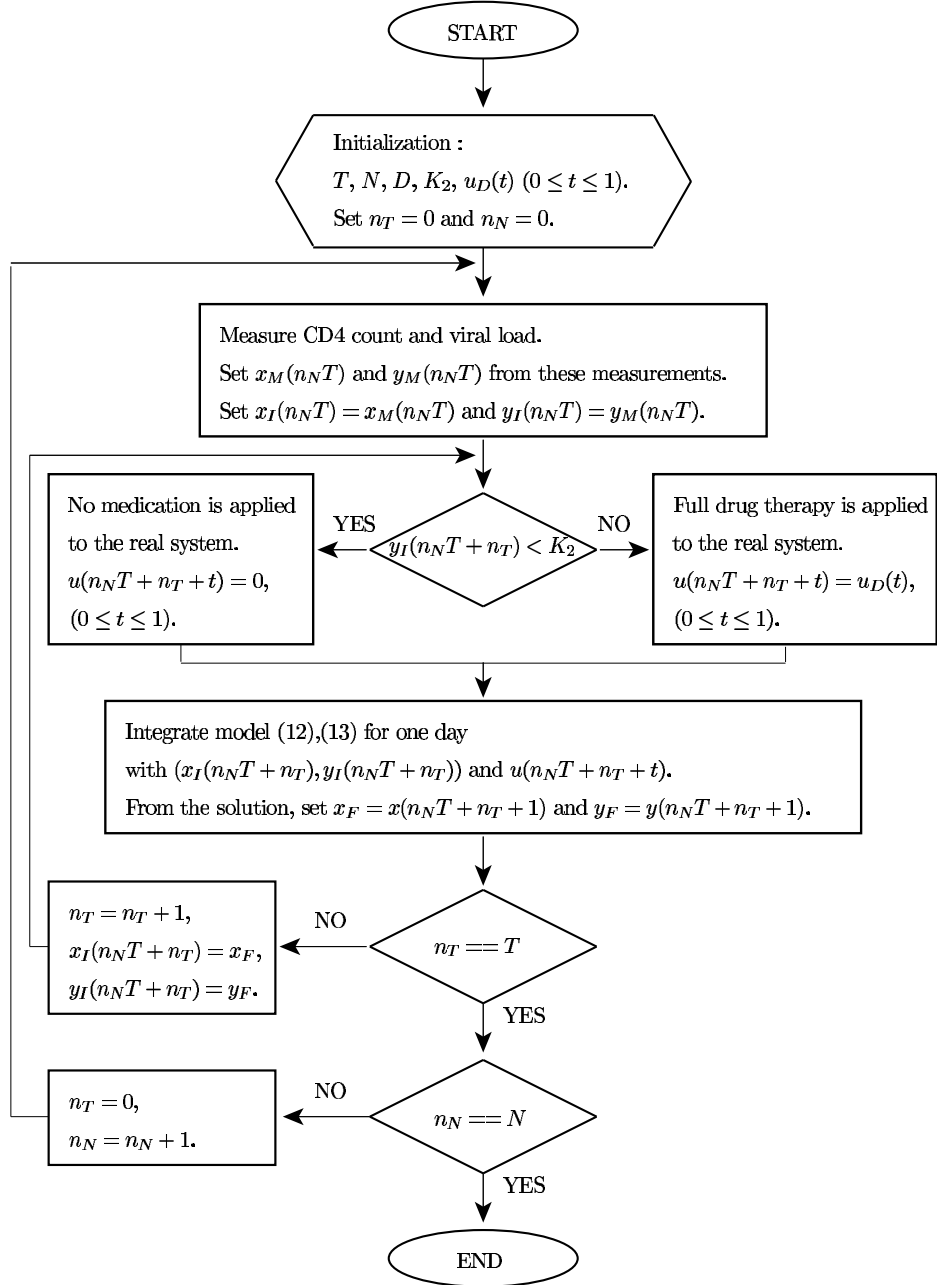


Figure 3.4: Control strategy with constant parameters (CSCP) D and K_2 .

STEP 1. The present CD4 T-cell count and viral load are measured and $x_M(n_NT)$ and $y_M(n_NT)$ are set from these measurements. The subscript M indicates that the values are obtained from measurements. Set $x_I(n_NT) = x_M(n_NT)$ and $y_I(n_NT) = y_M(n_NT)$. The subscript I indicates the initial value for the reduced-order model (3.11), (3.12) for each day.

STEP 2. At the beginning of each day, if $y_I(n_NT + n_T) \geq K_2$, then full drug therapy is applied to the HIV patient and the input $u(n_NT + n_T + t) = u_D(t)$ ($0 \leq t \leq 1$ day) applied to the reduced-order model (3.11), (3.12). Otherwise no medication is applied and the input $u(n_NT + n_T + t) = 0$ ($0 \leq t \leq 1$ day) is applied to the reduced-order model (3.11), (3.12).

STEP 3. Integrate the reduced-order model (3.11), (3.12) for one day with the initial point $(x_I(n_NT + n_T), y_I(n_NT + n_T))$ and the input $u(n_NT + n_T + t)$. Set $x_F = x(n_NT + n_T + 1)$ and $y_F = y(n_NT + n_T + 1)$, where the subscript F indicates the final value of the state of the reduced-order model (3.11), (3.12).

STEP 4. If $n_T = T$ then go to STEP 5. Otherwise increase n_T by one, set $x_I(n_NT + n_T) = x_F$, $y_I(n_NT + n_T) = y_F$, and go to STEP 2.

STEP 5. If $n_N = N$ then terminate this routine. Otherwise set $n_T = 0$, increase n_N by one, and go to STEP 1.

A flow chart illustrating these control steps is given in Figure 3.4.

3.3.2 Simulations of CSCP

In this subsection two computer simulations of the CSCP are presented. We regard the full-order model (3.1)-(3.5) as the HIV patient in the simulations. All simulations use the typical parameters of [73, 82, 83] and one of the initial conditions of [82, 83], as indicated in Table 3.2. Note that the initial point is in the vicinity of Point C when $u = 0$, which corresponds to a seriously progressed HIV infection. The design variables are defined as $K_1 = 0.0216$, $K_2 = 1.5451$, $K_3 = 3.3333$, $D = -0.6$, $N = 600$, $T = 4$ for the first simulation, and $T = 7$ for the second simulation. K_1 and K_3 are determined as discussed in the previous section.

The value $K_2 = 1.5451$ is selected according to Table 3.1 as the only equilibrium value of y such that $K_1 < K_2 < K_3$. We assume that the daily drug treatment implies a square-wave profile of u during the day because HAART drugs are usually taken orally

at fixed doses and the drug absorption dynamics cannot be manipulated arbitrarily. In particular the function of the one-day drug effect $u_D(t)$ ($0 \leq t \leq 1$ day) is assumed to be given by

$$u_D(t) = \begin{cases} 1, & \text{if } 0 \leq t \leq 0.6 \text{ day,} \\ 0, & \text{if } 0.6 < t \leq 1 \text{ day.} \end{cases}$$

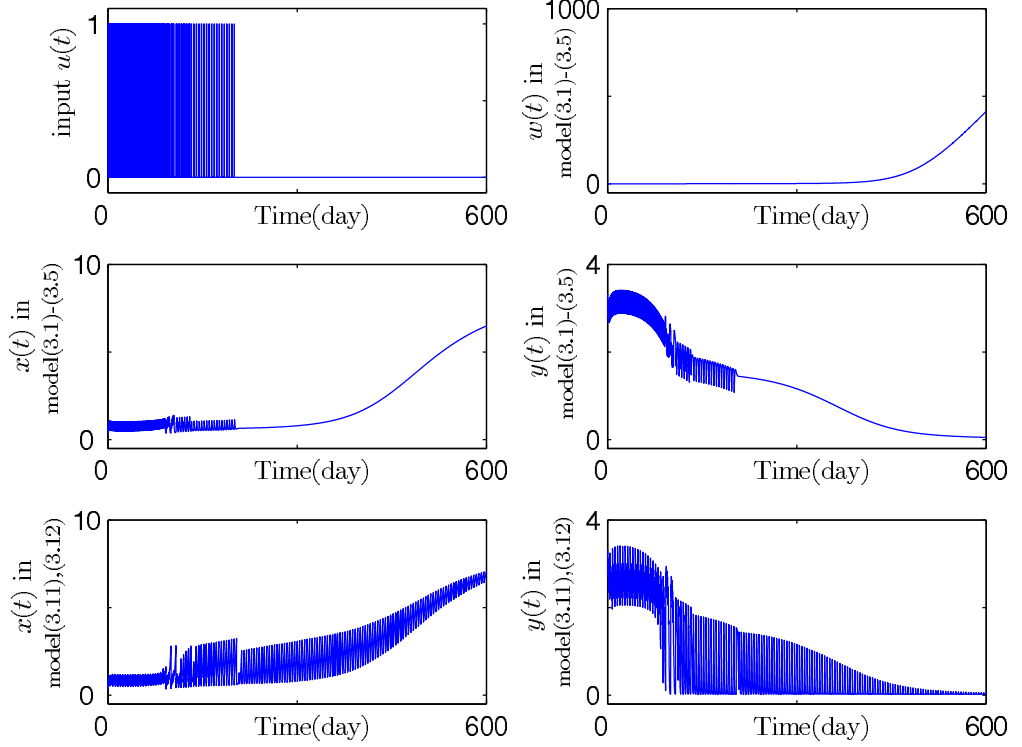


Figure 3.5: Simulation result of the control strategy with constant parameters D and K_2 , and with $T = 4$. The unit of x and y is (100copies/ μ l).

In the first simulation of this strategy (Figure 3.5), the drug therapy is terminated around the 200th day by the suggested control routine. After the termination of the therapy, $x(t)$ and $w(t)$ increase slowly, and $y(t)$ decreases slowly in the full-order model (3.1)-(3.5). The state in the full-order model (3.1)-(3.5) is successfully driven to the LTNP status³ because T is sufficiently small that the reduced-order model (3.11), (3.12) emulates the behaviour of the full-order model (3.1)-(3.5), although the reduced-order model (3.11), (3.12) uses constant values of D and K_2 .

³For recent data of treatment interruption in HIV therapy, see [7] where ‘STACCATO’ trials have been reported with physical experiments. The treatment decision making method used in ‘STACCATO’ trials is based on the level of CD4 T cell. A comparison study of the theoretical approach of this thesis and the clinical data provided by experimental works such as [7] should be carried out in the future.

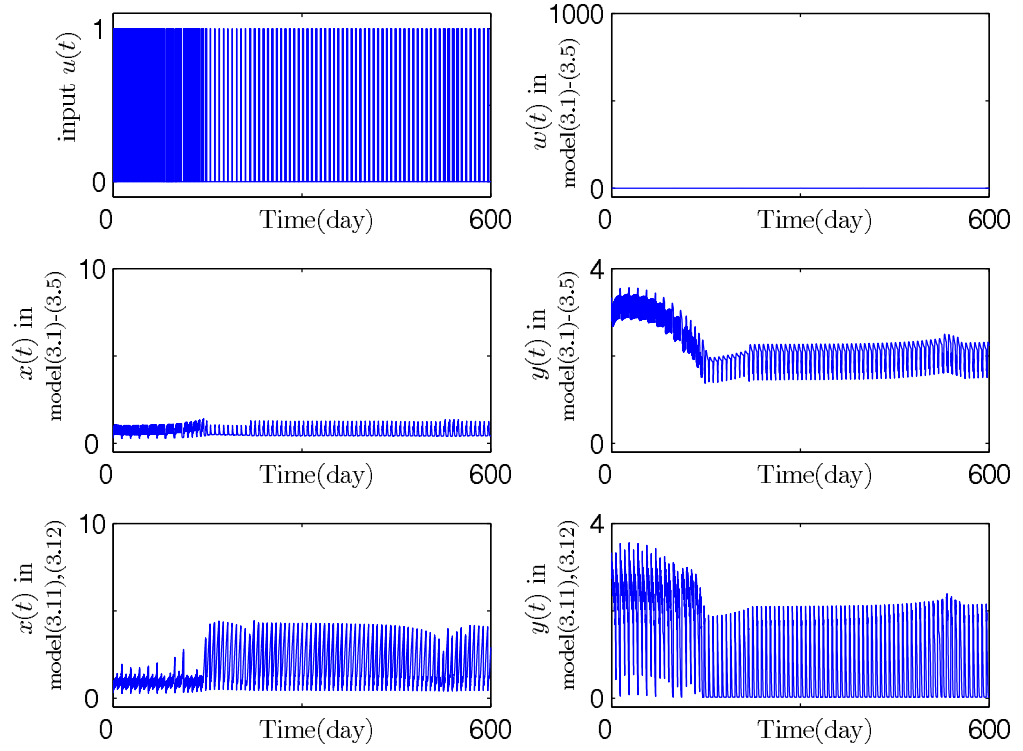


Figure 3.6: Simulation result of the control strategy with constant parameters D and K_2 , and with $T = 7$. The unit of x and y is (100copies/ μ l).

However, in the second simulation of the strategy (Figure 3.6), the drug treatment does not end within the length of the simulation. The strategy fails to bring the HIV patient to the LTNP status because T is too large for (3.11), (3.12) to emulate (3.1)-(3.5) effectively with fixed D and K_2 .

3.4 Control strategy with time-varying parameters

Figure 3.6 shows a recurring pattern in the simulation. This pattern implies that CSCP fails to drive the state into the LTNP region of attraction. To break this pattern we modify the values of D and K_2 during the medication and design a control strategy with varying parameters (CSVP). If we adjust D and K_2 once every period T , the occurrence of this pattern can be prevented. In this section a method for adjusting D and K_2 is described and illustrated.

At the beginning of a new period, let $t = n_N T$. From the previous period we know the initial point $(x_M(n_N T - T), y_M(n_N T - T))$ of the reduced-order model (3.11), (3.12),

the final point (x_F, y_F) of the reduced-order model (3.11), (3.12), the values of D and K_2 , and the history of the input $u(t)$, where $n_NT - T \leq t \leq n_NT$. In addition we can find the current levels of the CD4 T-cell count and viral load $(x_M(n_NT), y_M(n_NT))$ from measurements on the HIV patient. Although particular values of D and K_2 are used for the previous period, there may exist alternative values of D and K_2 that reduce the error between the reduced-order model (3.11), (3.12) and the patient, i.e., model (3.1)-(3.5). We define the difference $\varepsilon = y_F - y_M(n_NT)$ between y_F and $y_M(n_NT)$ as the error between the reduced-order model (3.11), (3.12) and the patient. Figure 3.7 shows a conceptual representation of the initial point of the reduced-order model (3.11), (3.12) for the previous period, the final point of the reduced-order model (3.11), (3.12), the current HIV measurements (CD4 T-cell count and viral load) of the HIV patient, and the error.

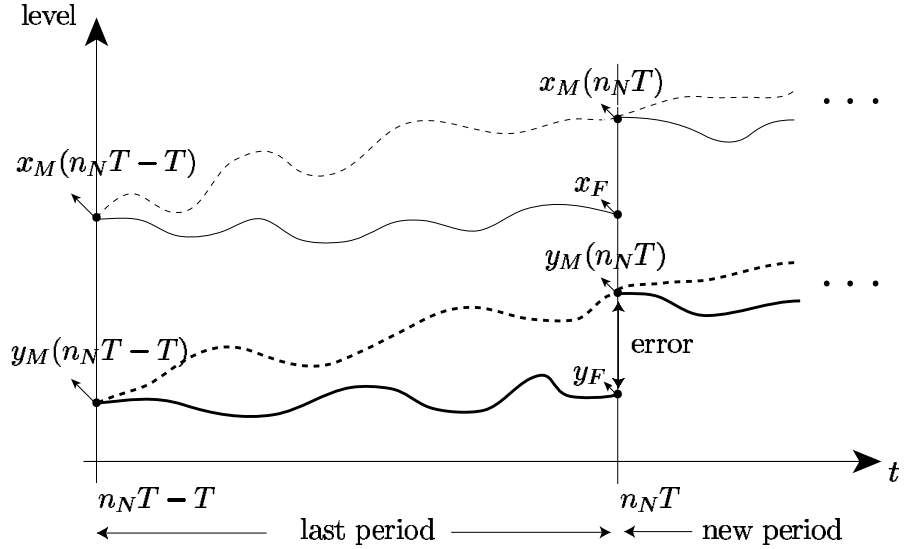


Figure 3.7: A conceptual figure depicting the state trajectories of the real system and of the reduced-order model (3.11), (3.12).

To find such values of D and K_2 we consider a rectangular region in the vicinity of the previous values of D and K_2 , and solve an optimization problem to minimize ε^2 within the rectangular region.

3.4.1 Control steps of CSVP

To realize the CSVP we use the steps of the CSCP with modifications to Initialization and STEP 5, called Initialization' and STEP 5', respectively. Initialization' for the CSVP

consists of Initialization used in the CSCP together with the selection of the positive numbers δD and δK_2 . STEP 5' for CSVP is as follows.

STEP 5'. If $n_N = N$, terminate this routine. Otherwise set $n_T = 0$ and increase n_N by one. The present CD4 T-cell count and viral load are measured and $x_M(n_NT)$ and $y_M(n_NT)$ are set from these measurements. Let D^* and K_2^* be the current values of D and K_2 , respectively. Find new D and K_2 satisfying

$$\min_{\substack{D \in [D^* - \delta D, D^* + \delta D] \\ K_2 \in [K_2^* - \delta K_2, K_2^* + \delta K_2]}} (y^*(n_NT) - y_M(n_NT))^2, \quad (3.16)$$

where $y^*(n_NT)$ is the y component of the solution of the reduced-order model (3.11), (3.12) for the initial point $(x_M(n_NT - T), y_M(n_NT - T))$ and the input function $u(n_NT - T + t)$, where $0 \leq t \leq T$. Set $x_I(n_NT) = x_M(n_NT)$, $y_I(n_NT) = y_M(n_NT)$, and go to STEP 2.

A flow chart for the CSVP is shown in Figure 3.8.

3.4.2 Simulation of CSVP

All system parameters, the initial point, and the design variables except D and K_2 are as in the simulation in which the HIV patient does not reach the LTNP status if the CSCP is used. The initial values of D and K_2 are set as -0.6 and 1.5451 , respectively. Also, both δD and δK_2 are defined as 0.1 . To solve the minimization problem numerically we use the Optimization Toolbox of MATLAB.

For the first 7 days all the trajectories in Figure 3.9 are the same as those of the simulation shown in Figure 3.6. Thereafter, once every period, the control method adjusts the parameters D and K_2 used by the reduced-order model (3.11), (3.12) to emulate the behaviour of the full-order model (3.1)-(3.5). Although T is the same as in the simulation shown in Figure 3.6, the patient state is induced to the LTNP status in this case. Moreover the state in Figure 3.9 converges faster than the state in Figure 3.5.

In the meantime, as shown in Figure 3.9, the behaviour of the reduced-order model (3.11), (3.12) approaches that of the full-order model (3.1)-(3.5) at each period with a steady series of square-wave inputs $u(t)$. On the contrary, from the 100th day to the 350th day, where the input $u(t)$ switches twice in each period T , the full- and reduced-order models do not show similar behaviour.

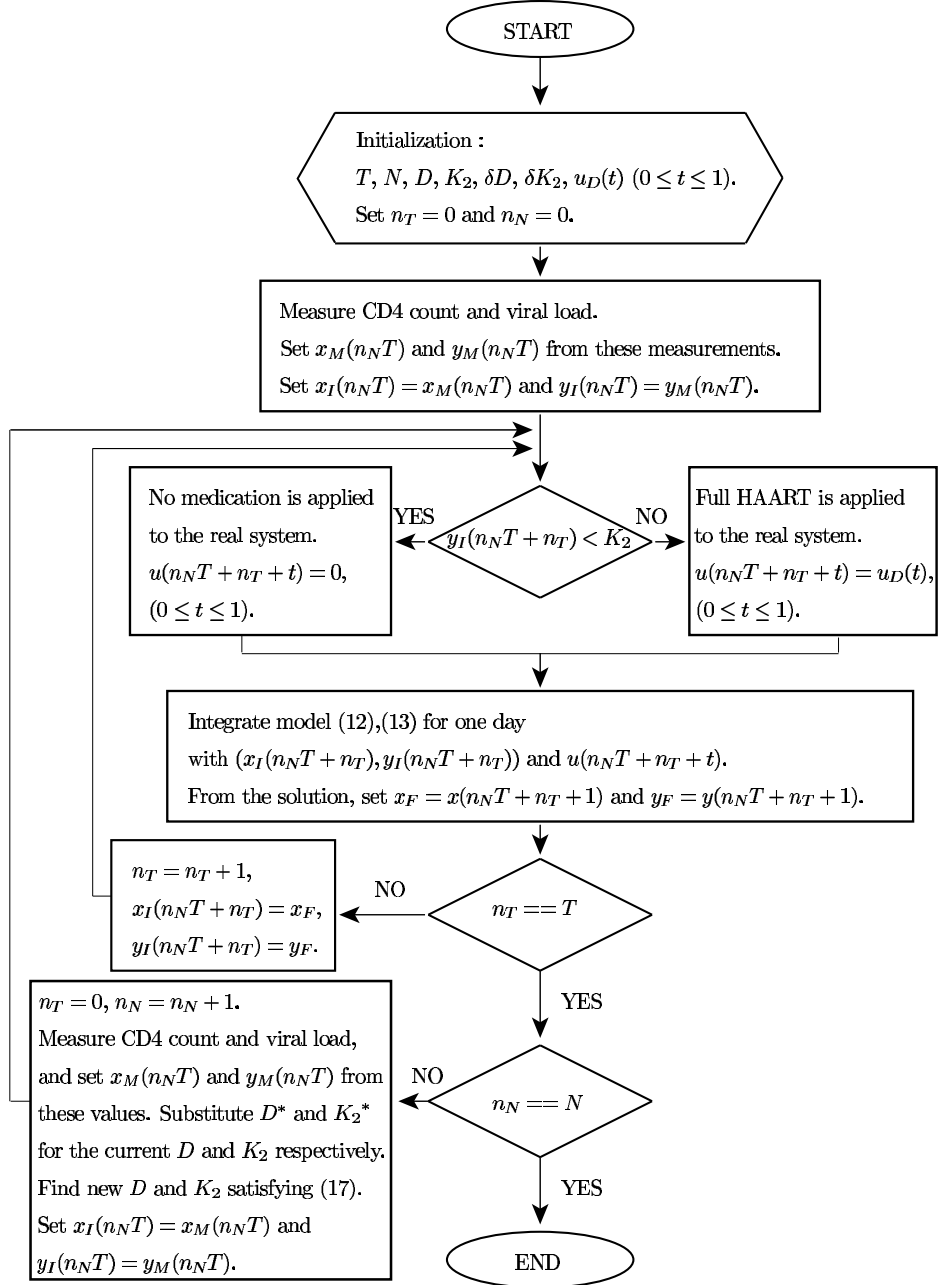


Figure 3.8: Control strategy with time-varying parameters (CSVP) D and K_2 .

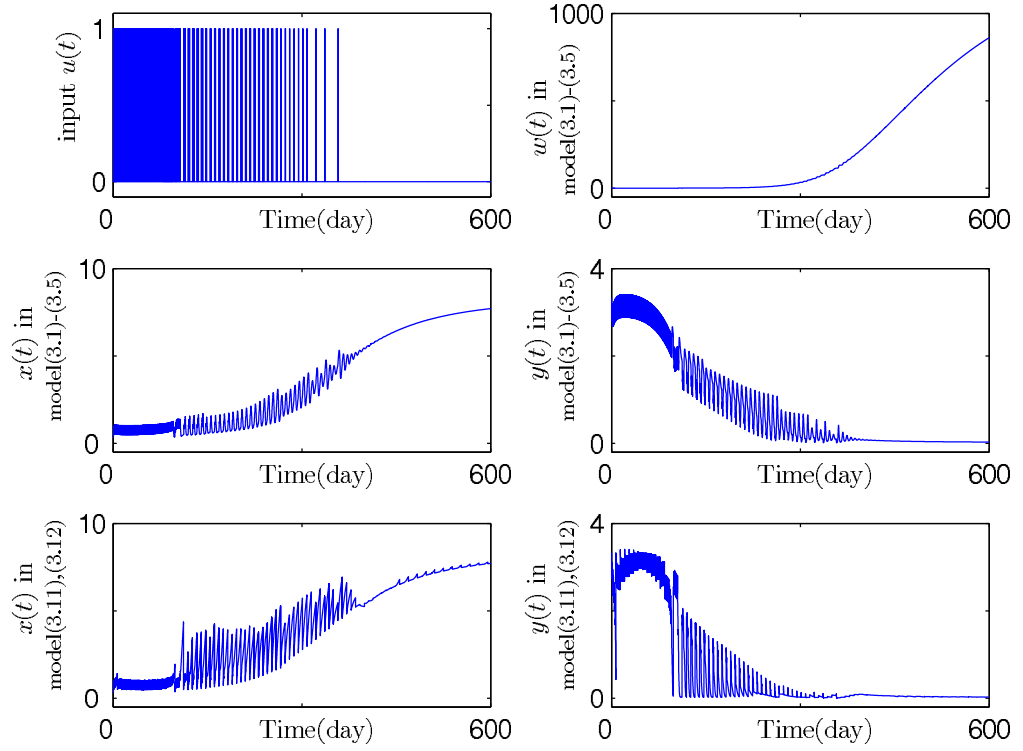


Figure 3.9: Simulation result of the control strategy with varying parameters D and K_2 when $T = 7$. The unit of x and y is (100copies/ μl).

3.5 Conclusions

In this chapter we have shown how the suggested control strategies can drive the HIV patient's state to the LTNP status. The works in this chapter are presented in [22] and [15]. All the results in the chapter are based on the HIV dynamics model (3.1)-(3.5). Thus more research is needed for other HIV models. In the next chapter we will discuss on a HIV model and analyse a bifurcation property in order for a continuous drug variation to be applied.

We now comment on the assumptions that are made in the simulations, and also discuss an idea for improving the given results.

1. It is assumed that the full-order model (3.1)-(3.5) accurately describes the dynamics of the HIV patient. Hence the two-dimensional system (3.11), (3.12) can emulate the five-dimensional system (3.1)-(3.5). However this fact does not mean that the control method is guaranteed to work clinically. It is necessary to consider more detailed models of the real system and to work with clinicians. For example

the model in [47] is a ten-dimensional model including a continuously mutating viral population but does not contain dynamics relating to the human immune system.

2. Although viral load test results are obtained in practice within ten days to two weeks [3], this measurement delay is not considered in the simulations in this chapter. Hence some modifications of the simulations and a more involved control scheme are required.
3. We assume that $u_D(t)$ is a square wave of amplitude 1 with 1-day time period and 60% width. However the dynamics of drug effect in the human body cannot be assumed to be a square wave. Further modeling of the drug delivery dynamics must be included in the full-order model (3.1)-(3.5).
4. In this chapter, the behaviour of the reduced-order model (3.11), (3.12) approaches that of the full-order model (5.1)-(5.5) at each period with a steady series of square-wave inputs $u(t)$, as shown in Figure 3.9. On the contrary, from the 100th day to the 350th day, where the input $u(t)$ switches twice in each period T , the full- and reduced-order models do not show similar behaviour. To increase the similarity between the behaviour of the full-order model (5.1)-(5.5) and that of the reduced-order model (3.11), (3.12), we can use the reduced-order model (3.11), (3.12) when $u(t) = 0$ and an alternative model when $u(t) = 1$. Currently, the reduced-order model (3.11), (3.12) is used for both $u(t) = 0$ and $u(t) = 1$, but this model is designed to emulate the full-order model (5.1)-(5.5) only when $u(t) = 0$.

Chapter 4

Control method by gradual reduction of drug dose

Recently a control strategy based on gradual reduction of drug dose (GRDD) has been proposed to induce CTL mediated control and to achieve the LTNP status [27, 66]. In this chapter we apply this drug scheduling scheme to a HIV model with immune system which strongly depends on the HIV target cells. By means of this method the HIV patient is steered to the LTNP status. The results in this chapter are presented in [17].

In addition, the preliminary work for this chapter is published in [27], and its applications are included in [25], [26], and [24]. The formal analysis and proofs for the work of the chapter are shown in [66] as well as [64].

4.1 Gradual reduction of drug dose and HIV model with immune response strongly dependant on target cells

GRDD, also known as gradual dose reduction (GDR), is a drug prescription scheme to taper off the drug medication level. This drug scheduling scheme is now considered in some clinical cases, such as long-term uses of neuroleptic, antidepressant or benzodiazepine for chronic patients [51, 71, 80]. In [27] GRDD has been introduced for HIV treatment to induce the patient state to the LTNP, see also [24–26]. A mathematical analysis of GRDD for the model in [75] has been performed in [66].

The scheme of GRDD is based on the bifurcation properties of the HIV model. In this chapter we consider the model (2.10)-(2.12), discussed in Section 2.1.2. We recall

Point F	$x^{(F)} = \frac{\lambda}{d}, \quad y^{(F)} = 0, \quad z^{(F)} = 0.$
Point G	$x^{(G)} = \frac{a}{\eta\beta}, \quad y^{(G)} = \frac{\lambda\eta\beta - ad}{a\eta\beta}, \quad z^{(G)} = 0.$
Point H	$x^{(H)} = \frac{\lambda c + \sqrt{\lambda^2 c^2 - 4bcd\eta\beta}}{2cd}, \quad y^{(H)} = \frac{b}{c(x^{(H)})^2}, \quad z^{(H)} = \frac{\eta\beta x^{(H)} - a}{p}.$
Point I	$x^{(I)} = \frac{\lambda c - \sqrt{\lambda^2 c^2 - 4bcd\eta\beta}}{2cd}, \quad y^{(I)} = \frac{b}{c(x^{(I)})^2}, \quad z^{(I)} = \frac{\eta\beta x^{(I)} - a}{p}.$

Table 4.1: Equilibrium points of the model (4.1)-(4.3).

the model here for convenience:

$$\dot{x} = \lambda - dx - \eta\beta yx, \quad (4.1)$$

$$\dot{y} = (\eta\beta x - a - pz)y, \quad (4.2)$$

$$\dot{z} = (cyx^2 - b)z. \quad (4.3)$$

The model has four equilibrium points: Point F, Point G, Point H, and Point I (see Table 4.1). Without any medication (i.e., $\eta = 1$), Point G and Point H are asymptotically stable [40].

We stress that Point G corresponds to the status of a patient for whom HIV dominates, whereas Point H corresponds to the status of a patient who does not progress to AIDS, i.e., the LTNP status.

4.2 Preliminary analysis of gradual reduction of drug dose

Let $X := [x, y, z]^T$ and let $\mathcal{U}$ be the set of measurable functions whose values are between 0 and 1. Therefore, the input $\eta(\cdot)$ of interest is in $\mathcal{U}$. Also, let $\mathcal{P} = \mathbb{R}_+^3 = [0, \infty)^3$.

Theorem 2 *Consider the system (4.1)-(4.3). For any $\eta(\cdot) \in \mathcal{U}$, no finite escape time phenomenon occurs and the set $\mathcal{P}$ is positively invariant. In other words, for any initial condition $X(0) \in \mathcal{P}$, the solution $X(t)$ of model (4.1)-(4.3) exists for all $t \geq 0$ and is contained in $\mathcal{P}$ for all $t \geq 0$.*

Proof: Suppose that $X(0) \in \mathcal{P}$ and that some components of $X(t)$ shows finite escape time phenomenon at a finite time $T > 0$. Since (4.2) and (4.3) have the linear form $\dot{y}(t) = f_y(t)y(t)$ and $\dot{z}(t) = f_z(t)z(t)$, where f_y and f_z may be regarded as continuous functions of time whose values exist for $0 \leq t < T$, the states $y(t)$ and $z(t)$ remain positive for $0 \leq t < T$. (Note that $\dot{y}$ and $\dot{z}$ go to zero when y and z approach to zero,

respectively, and also $\dot{y} = 0$ and $\dot{z} = 0$ when $y = 0$ and $z = 0$, respectively.) Since (4.1) has the form $\dot{x}(t) = \lambda + f_x(t)x(t)$, where f_x may be regarded as a continuous function of t for $0 \leq t < T$, it can be seen by means of a comparison lemma [42] that the state $x(t)$ also remains positive in this time interval. This implies that $X(t) \in \mathcal{P}$ for $0 \leq t < T$, regardless of $\eta(\cdot)$. Now let $V(t) := x(t) + y(t)$, which is positive for all $t \in [0, T)$. Then, let $k = \min\{d, a\}$ and note that

$$\dot{V} = \lambda - dx - ay - pzy \leq \lambda - k(x + y) = \lambda - kV.$$

Thus $V(t)$ (as well as $x(t)$ and $y(t)$) is bounded in the interval $0 \leq t < T$. This in turn implies that finite escape does not occur. Indeed, for $0 \leq t < T$, the function $f_z(t) = (cy(t)x(t)^2 - b)$ is bounded, and therefore, $z(t)$ is bounded. So we conclude that T equals infinity. $\square$

Assumption 1 *The parameters of model (4.1)-(4.3) are such that*

$$d < a, \tag{4.4}$$

$$2ad < \lambda\beta, \tag{4.5}$$

$$\frac{4d\beta}{\lambda^2} < \frac{c}{b}, \tag{4.6}$$

$$\frac{\beta^3}{a(\lambda\beta - ad)} > \frac{c}{b}. \tag{4.7}$$

Although Assumption 1 is technically designed to subsequent analysis of this chapter and the model parameters are normalized so the state variables do not represent actual data, Assumption 1 can be justified by previous works in the literature on HIV dynamics such as [54, 75], as seen in what follows.

Inequality (4.4) implies that the decay rate of the uninfected cells is smaller than that of the infected cells [54]. Inequality (4.5) implies the basic reproductive ratio [54] is larger than 2. For small basic reproductive ratio, the virus is automatically eradicated and the patient needs not be treated. However this is apparently not the case for most AIDS patients.

Regarding inequality (4.6), it is noted that if the immune responsiveness c lies below a threshold, treatment cannot result in the establishment of CTL memory [75]. While any formula for such a threshold is not presented in the literature, the condition (4.6) might be understood as a possible lower bound for the immune responsiveness.

Inequality (4.7) limits the size of β . In [75], it is mentioned that ‘If the rate of viral replication β is below a threshold..., an effective CTL response is always established.’ This means that, for too small β , LTNP is automatically achieved so that the patients need not be treated at all (note that this is not the case for most AIDS patients in the real world), hence β should be lower-bounded. The HIV literature has not presented any quantitative criterion regarding this, but the conditions (4.7) could be understood for such bound.

Lemma 1 *Suppose Assumption 1 holds.*

1. *The quantity inside the square-root term of Point H and Point I (see Table 4.1) is positive for all values of $0 < \eta \leq 1$ (therefore the system has four real equilibrium points for all η).*
2. *Point F and Point G coincide when*

$$\eta = \bar{\eta}_{FG} = \frac{ad}{\lambda\beta}.$$

Moreover $0 < \bar{\eta}_{FG} < \frac{1}{2}$.

3. *Point G and Point H coincide when $\eta = \bar{\eta}_{GH}$, where the solutions of*

$$Y(\eta) = b\beta^3\eta^3 - ac\lambda\beta\eta + a^2cd = 0 \tag{4.8}$$

are η_1^* , $\bar{\eta}_{GH}$ and η_3^* ($\eta_1^* < \bar{\eta}_{GH} < \eta_3^*$). Moreover $\bar{\eta}_{FG} < \bar{\eta}_{GH} < 1$.

4. *$z^{(H)} > 0$ when $\bar{\eta}_{GH} < \eta \leq 1$.*

Proof:

1. The term under the square-root of Point H and Point I is $\lambda^2c^2 - 4bcd\eta\beta$. When $\eta = 1$ this term achieves its minimum, namely $\lambda^2c^2 - 4bcd\beta$, which is positive by (4.6). Therefore all four points are real for any η .
2. By solving the equations $x^{(F)} = x^{(G)}$ and $y^{(F)} = y^{(G)}$ we obtain that Point G = $(\frac{\lambda}{d}, 0, 0)$ if and only if $\eta = \frac{ad}{\lambda\beta}$. Also $\frac{ad}{\lambda\beta}$ is positive and less than $\frac{1}{2}$ by (4.5).

3. $y^{(G)} = y^{(H)}$ and $z^{(G)} = z^{(H)}$ imply $Y(\eta) = 0$. By (4.5) and (4.7)

$$Y(-\infty) < 0,$$

$$Y(0) = a^2cd > 0,$$

$$Y(\bar{\eta}_{FG}) = b\beta^3 \frac{a^3d^3}{\lambda^3\beta^3} - ac\lambda\beta \frac{ad}{\lambda\beta} + a^2cd = b \frac{a^3d^3}{\lambda^3} > 0,$$

$$Y(2\bar{\eta}_{FG}) = b\beta^3 \left(\frac{2ad}{\lambda\beta} \right)^3 - ac\lambda\beta \frac{2ad}{\lambda\beta} + a^2cd < a^2bd \left(\frac{4d(\lambda\beta)}{\lambda^3} - \frac{c}{b} \right) < 0,$$

$$Y(1) = b\beta^3 - ac\lambda\beta + a^2cd = ba(\lambda\beta - ad) \left(\frac{\beta^3}{a(\lambda\beta - ad)} - \frac{c}{b} \right) > 0.$$

Thus the third-order algebraic equation $Y(\eta) = 0$ has three real solutions η_1^* , $\bar{\eta}_{GH}$, and η_3^* such that $\eta_1^* < \bar{\eta}_{GH} < \eta_3^*$ with $\eta_1^* < 0$ and $\bar{\eta}_{FG} < \bar{\eta}_{GH} < 2\bar{\eta}_{FG} < \eta_3^* < 1$. From $x^{(G)} = x^{(H)}$

$$\sqrt{\lambda^2c^2 - 4bcd\eta\beta} = \frac{2acd}{\beta\eta} - \lambda c. \quad (4.9)$$

Setting $\eta = \eta_1^*$ or $\eta = \eta_3^*$, the right-hand term of (4.9) is negative. Thus $x^{(G)} \neq x^{(H)}$ when $\eta = \eta_1^*$ or $\eta = \eta_3^*$. From $Y(\bar{\eta}_{GH}) = 0$ and $0 < \bar{\eta}_{GH} < 2\frac{ad}{\lambda\beta}$,

$$\begin{aligned} b\beta^3\bar{\eta}_{GH}^3 - ac\lambda\beta\bar{\eta}_{GH} + a^2cd &= 0 \\ \Downarrow \\ \lambda^2c^2 - 4bcd\beta\bar{\eta}_{GH} &= \frac{4a^2c^2d^2}{\beta^2\bar{\eta}_{GH}^2} - 4acd\lambda c + \lambda^2c^2 \\ \Downarrow \\ \sqrt{\lambda^2c^2 - 4bcd\beta\bar{\eta}_{GH}} &= \frac{2acd}{\beta\bar{\eta}_{GH}} - \lambda c. \end{aligned}$$

Thus, when $\eta = \bar{\eta}_{GH}$, $(x^{(G)}, y^{(G)}, z^{(G)}) = (x^{(H)}, y^{(H)}, z^{(H)})$ and $\bar{\eta}_{FG} < \bar{\eta}_{GH} < 1$.

4. Note that

$$x^{(H)} - \frac{a}{\eta\beta} = \frac{c(\lambda\eta\beta - 2ad) + \eta\beta\sqrt{\lambda^2c^2 - 4bcd\eta\beta}}{2cd\eta\beta}.$$

When $\eta \geq \frac{2ad}{\lambda\beta} = 2\bar{\eta}_{FG}$, $x^{(H)} > \frac{a}{\eta\beta}$ by (4.6). When $\bar{\eta}_{GH} < \eta < 2\bar{\eta}_{FG}$, $Y(\eta) < 0$ since this is a continuous function of η . Then,

$$\begin{aligned} -b\beta^3\eta^3 + ac\lambda\beta\eta - a^2cd &> 0 \\ \Downarrow \\ \eta^2\beta^2(\lambda^2c^2 - 4bcd\eta\beta) &> (2acd - \lambda c\eta\beta)^2 \\ \Downarrow \\ x^{(H)} &> \frac{a}{\eta\beta}. \end{aligned}$$

Thus $z^{(H)} > 0$ when $\bar{\eta}_{GH} < \eta \leq 1$.

□

In what follows, let $I_F = [0, \bar{\eta}_{FG})$, $I_{G1} = (\bar{\eta}_{FG}, \bar{\eta}_{GH})$, $I_{G2} = (\eta_3^*, 1]$, and $I_H = (\bar{\eta}_{GH}, 1]$.

Theorem 3 *Suppose Assumption 1 holds.*

1. *Point F is locally exponentially stable for $\eta \in I_F$.*
2. *Point G is locally exponentially stable for $\eta \in I_{G1} \cup I_{G2}$.*
3. *Point H is locally exponentially stable for $\eta \in I_H$.*

Proof:

1. The Jacobian matrix of system (4.1)-(4.3) at the Point F is

$$\begin{bmatrix} -d & -\eta\beta\frac{\lambda}{d} & 0 \\ 0 & \eta\beta\frac{\lambda}{d} - a & 0 \\ 0 & 0 & -b \end{bmatrix},$$

hence the stability is determined by the sign of the term $\eta\beta\frac{\lambda}{d} - a$, which is negative when $\eta \in I_F$, hence the claim holds.

2. The Jacobian matrix of system (4.1)-(4.3) at the Point G is

$$\begin{bmatrix} -\eta\beta\frac{\lambda}{a} & -a & 0 \\ \frac{\lambda\beta\eta - ad}{a} & 0 & -p\frac{\lambda\beta\eta - ad}{a\eta\beta} \\ 0 & 0 & -\frac{Y(\eta)}{\eta^3\beta^3} \end{bmatrix},$$

where $Y(\eta)$ is given in (4.8). Then the characteristic equation is $s^3 + G_1s^2 + G_2s + G_3 = 0$ with

$$\begin{aligned} G_1 &= \eta\beta\frac{\lambda}{a} + \frac{Y(\eta)}{\eta^3\beta^3}, \\ G_2 &= (\lambda\beta\eta - ad) + \frac{Y(\eta)}{\eta^2\beta^2}\frac{\lambda}{a}, \\ G_3 &= (\lambda\beta\eta - ad)\frac{Y(\eta)}{\eta^3\beta^3}. \end{aligned}$$

From the proof of Lemma 1, $Y(\eta) = 0$ when $\eta = \bar{\eta}_{GH}$ or $\eta = \eta_3^*$, and $Y(\eta) > 0$ when $\bar{\eta}_{FG} \leq \eta < \bar{\eta}_{GH}$ or $\eta_3^* < \eta \leq 1$.

Hence if $\eta \in I_{G1} \cup I_{G2}$, G_1 and G_3 are positive, and

$$G_1 G_2 - G_3 = \eta \beta \frac{\lambda}{a} \left(\lambda \beta \eta - ad + \frac{Y(\eta)}{\eta^2 \beta^2} \frac{\lambda}{a} + \frac{Y(\eta)^2}{\eta^3 \beta^3} \right) > 0.$$

Thus, when $\eta \in I_{G1} \cup I_{G2}$, Point G is locally exponentially stable by Routh-Hurwitz criterion.

3. The Jacobian matrix of system (4.1)-(4.3) at the Point H is

$$\begin{bmatrix} -d - \eta \beta y^{(H)} & -\eta \beta x^{(H)} & 0 \\ \eta \beta y^{(H)} & 0 & -p y^{(H)} \\ 2c x^{(H)} y^{(H)} z^{(H)} & c x^{(H)^2} z^{(H)} & 0 \end{bmatrix},$$

where $x^{(H)}$, $y^{(H)}$ and $z^{(H)}$ are from Table 4.1. Then the characteristic equation is $s^3 + H_1 s^2 + H_2 s + H_3 = 0$, with

$$\begin{aligned} H_1 &= \frac{\lambda}{x^{(H)}}, \\ H_2 &= (\eta \beta x^{(H)} - a)b + \eta \beta (\lambda - d x^{(H)}), \\ H_3 &= \frac{b\lambda}{x^{(H)}} (\eta \beta x^{(H)} - a) - 2pb\eta \beta y^{(H)} z^{(H)}. \end{aligned}$$

For $\eta \in I_H$, H_1 is positive and

$$H_3 = \frac{b\lambda}{x^{(H)}} (\eta \beta x^{(H)} - a) - 2pb\eta \beta y^{(H)} z^{(H)} = \frac{pbz^{(H)}}{x^{(H)}} (2dx^{(H)} - \lambda) > 0,$$

because $x^{(H)} = \frac{\lambda c + \sqrt{\lambda^2 c^2 - 4bcd\eta\beta}}{2cd} > \frac{\lambda}{2d}$. Moreover, in this interval

$$H_1 H_2 - H_3 = \frac{\lambda}{x^{(H)}} \eta \beta (\lambda - d x^{(H)}) + 2pb\eta \beta y^{(H)} z^{(H)} > 0,$$

since

$$x^{(H)} - \frac{\lambda}{d} = \frac{-\lambda c + \sqrt{\lambda^2 c^2 - 4bcd\eta\beta}}{2cd} < 0.$$

Therefore, when $\eta \in I_H$, Point H is locally exponentially stable by Routh-Hurwitz criterion.

□

4.3 Treatment by gradual reduction of drug dose

Assumption 2 *The drug is so effective that*

$$\frac{(1 - \epsilon^*)\lambda\beta}{da} < 1. \quad (4.10)$$

Theorem 4 *Consider the system (4.1)-(4.3) and assume Assumptions 1 and 2 hold. Then all trajectories $X(t)$ with $u = 1$ converge to Point F.*

Proof: As in the proof of Theorem 2, let $V(t) = x(t) + y(t)$. Then, by (4.4), $\dot{V}(t) = \lambda - dx - ay - pzy \leq \lambda - d(x + y) - (a - d)y \leq \lambda - d(x + y) = \lambda - dV(t)$, which holds for all $t \geq 0$ due to the positive invariance of $\mathcal{P}$.

If $y(t)$ converges to zero, then the claim holds because of (4.1), (4.2), and (4.3).

Otherwise, $V(t)$ becomes less than λ/d eventually since $\dot{V}(t) < \lambda - dV(t)$. This in turn implies that $x(t) < \lambda/d$ in a finite time. Then equation (4.2) becomes

$$\dot{y} = y(\eta\beta x - a - pz) \leq -\delta y, \quad (4.11)$$

for some $\delta > 0$, because $\eta < (da)/(\lambda\beta)$. Hence $y(t)$ converges to zero, which is contradiction.

Since $y(t)$ goes to zero, $x(t)$ converges to λ/d by (4.1) and $z(t)$ goes to zero by (4.3).

□

Now we state the treatment idea which is based on [42, Lemma 9.8] and consists of two steps. In the first step we use full dosage (i.e., $u = 1$). Thus η is in the interval I_F , and by Theorem 4 the state $X(t)$ converges to Point F. In the second step, we slowly reduce the dosage, so that the state $X(t)$ follows the exponentially stable equilibrium, Point G and then Point H. This may drive the state near Point H when η becomes 1 (i.e., $u = 0$).

Using Table 4.1 we define the exponentially stable points line (ESPL) $\chi(\eta)$ as

$$\chi(\eta) = \begin{cases} \text{Point F,} & \eta \in I_F, \\ \text{Point G,} & \eta \in I_{G1}, \\ \text{Point H,} & \eta \in I_H. \end{cases} \quad (4.12)$$

Note that Point G and H are functions of η whereas Point F is not. We regard the ESPL not defined at $\eta = \bar{\eta}_{FG}$ and $\eta = \bar{\eta}_{GH}$ since we do not have proven exponential stability of

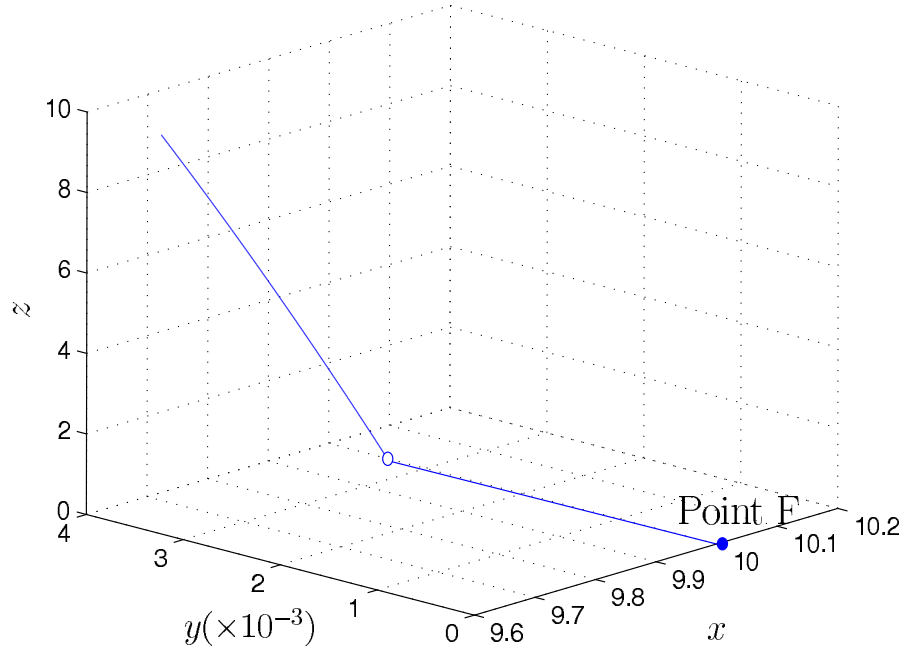


Figure 4.1: 3 dimensional plot of the exponentially stable points line (ESPL) given in (4.12). The case of $\eta \in I_F$ corresponds to Point F, (10,0,0).

λ	d	β	a	p	c	b	$x(0)$	$y(0)$	$z(0)$
1	0.1	1	0.2	1	0.03	0.01	0.2	4.9	10^{-4}

Table 4.2: Parameters and initial conditions for model (4.1)-(4.3).

any equilibrium point for these values of η . For additional analysis of the case $\eta = \bar{\eta}_{FG}$ and $\eta = \bar{\eta}_{GH}$, see [66].

Figure 4.1 shows the ESPL with the parameters of Table 4.2. Figure 4.2 displays the result of the application of the GRDD with $\epsilon^* = 0.99$ and the initial condition which corresponds to a serious status of AIDS, as presented in Table 4.2. The first and second step take 50 days and 450 days, respectively. Figure 4.3 is a 3 dimensional plot based on Figure 4.1 and Figure 4.2. The thick line and the thin line correspond to the ESPL and the state trajectory, respectively. Note that the scale is not as in Figure 4.1. Figure 4.3 shows that the patient is driven to the LTNP status.

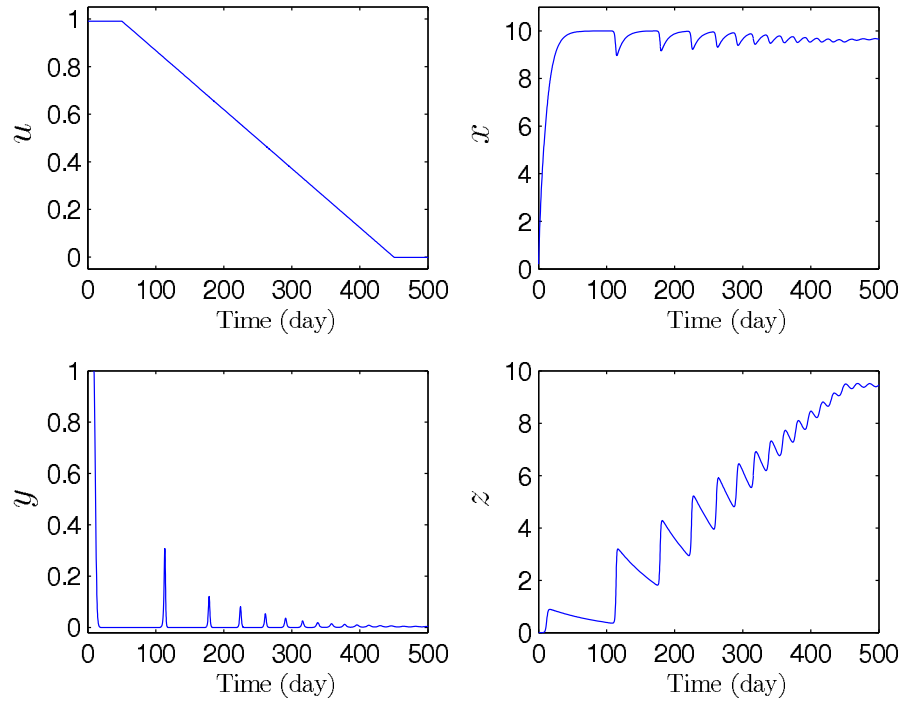


Figure 4.2: Result of the application of the gradual reduction of drug dose (GRDD). The unit of x and y is (100copies/ μ l).

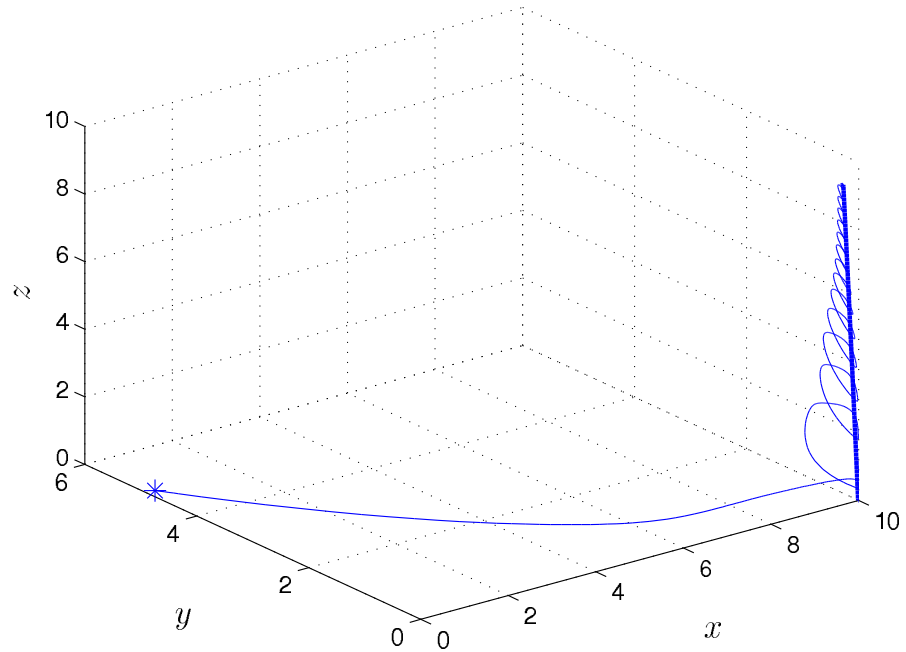


Figure 4.3: 3 dimensional plot of the result of gradual reduction of drug dose (GRDD). The thick line is the ESPL and the thin line is the state trajectory, which starts at the point (0.2000, 4.9000, 0.0001) marked with *.

4.4 Conclusion

In this chapter we have applied a new treatment scheme, known as GRDD, to the HIV infection model in [40] exploiting the positivity property of the system and a bifurcation analysis. It has been shown that, for any initial state, the state of the patient can be steered to the LTNP status by the proposed treatment if the model parameters satisfy specific assumptions. The results in this chapter are presented in [17].

In addition, the preliminary work for this chapter is published in [27], and its applications are included in [25], [26], and [24]. The formal analysis and proofs for the work of the chapter are shown in [66] as well as [64].

Chapter 5

Control method by activation of the immune response

The purpose of this chapter is to derive a new drug scheduling methodology for HIV patients on the basis of the properties of the immune system. The main idea stems from a simple graphical analysis. In this chapter we do not provide a formal treatment of the properties of the controlled system, but focus on the methodological and conceptual aspects of the design. The results in this chapter are published in [21], [16], [19], and [18].

5.1 Analysis and control of HIV model with CTL-mediated immune response

In this section we consider the model (2.1)-(2.5), namely

$$\dot{x} = \lambda - dx - \eta\beta xy, \quad (5.1)$$

$$\dot{y} = \eta\beta xy - ay - p_1 z_1 y - p_2 z_2 y, \quad (5.2)$$

$$\dot{z}_1 = c_1 z_1 y - b_1 z_1, \quad (5.3)$$

$$\dot{w} = c_2 xyw - c_2 qyw - b_2 w, \quad (5.4)$$

$$\dot{z}_2 = c_2 qyw - h z_2. \quad (5.5)$$

For the clinical meaning of the states, see Table 2.1. The model (5.1)-(5.5) has five equilibrium points, three of which are recalled here from Table 3.1:

Point A:

$$x^{(A)} = \frac{\lambda}{d}, \quad y^{(A)} = 0, \quad z_1^{(A)} = 0, \quad w^{(A)} = 0, \quad z_2^{(A)} = 0;$$

Point C:

$$x^{(C)} = \frac{\lambda c_1}{dc_1 + b_1 \eta \beta}, \quad y^{(C)} = \frac{b_1}{c_1}, \quad z_1^{(C)} = \frac{\eta \beta x^{(C)} - a}{p_1}, \quad w^{(C)} = 0, \quad z_2^{(C)} = 0;$$

Point E:

$$y^{(E)} = \frac{c_2(\lambda - dq) - b_2 \eta \beta - \sqrt{[c_2(\lambda - dq) - b_2 \eta \beta]^2 - 4\eta \beta c_2 q d b_2}}{2\eta \beta c_2 q}, \quad x^{(E)} = \frac{\lambda}{d + \eta \beta y^{(E)}},$$

$$z_1^{(E)} = 0, \quad w^{(E)} = \frac{h z_2^{(E)}}{c_2 q y^{(E)}}, \quad z_2^{(E)} = \frac{y^{(E)}(c_2 \eta \beta q - c_2 a) + b_2 \eta \beta}{c_2 p_2 y^{(E)}};$$

Table 5.1: Equilibrium points of the model (5.1)-(5.5)

In this section we use the same system parameters of Chapter 3 (see Table 3.2), whereas we use a different initial point. The initial point is one of those used in [82] as indicated in Table 5.2. This point is in the vicinity of Point A, which represents a newly infected patient¹.

$x(0)$	$y(0)$	$z_1(0)$	$w(0)$	$z_2(0)$
10	0.01	0.01	0.01	0.01

Table 5.2: Initial condition for model (5.1)-(5.5). This initial condition is given in [82].

From the discussion in Section 3.2, we can regard model (5.1)-(5.5) as the interconnection of two subsystems: the infection dynamics and the immune system [15, 22]. The goal of the control in this chapter is to enhance immunity and this is equivalent to boosting z_1 , w , and z_2 . Particularly, helper-dependent responses (i.e., w and z_2) must be enhanced in order to lead a HIV patient to the LTNP status (Point E), because the w and z_2 components of Point C are zero and those of Point E are positive and large. In addition, since z_2 depends upon w (see equation (5.5)), if w is increased, then z_2 is also increased.

Equation (5.4) can be written as $\dot{w} = K(x, y)w$ where $K(x, y) = c_2 xy - c_2 qy - b_2$.

¹This point is also regarded as the status of a HIV patient that has been treated with HAART for a long time [82].

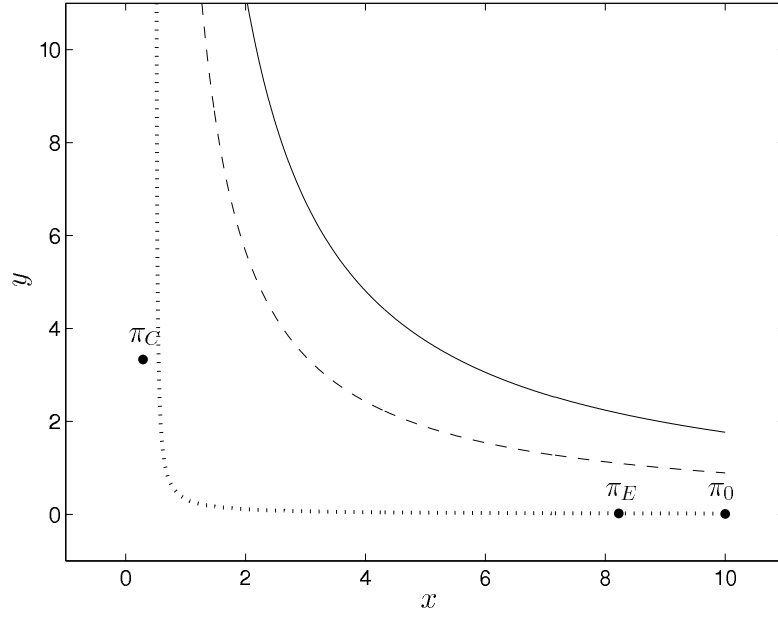


Figure 5.1: Graphical properties of the immune system enhancement in model (5.1)-(5.5).

Note that $K(x, y)$ depends upon the variables x and y of the infection dynamics, and also note that the infection dynamics is directly affected by the drug. Accordingly we can control $\dot{w}$ indirectly via the input u .

Figure 5.1 shows some geometric properties of the function $K(x, y)$ for the given parameters in the (x, y) positive quadrant. The dotted line describes the set $K(x, y) = 0$. Since $K(x, y) > 0$ above this line the immune term w increases when (x, y) belongs to this region. The dashed line and the solid line describe the sets $K(x, y) = 0.5$ and $K(x, y) = 1$, respectively. π_E and π_C correspond to the projection into the (x, y) -plane of Point E and Point C, respectively. π_0 indicates the projection into the (x, y) -plane of the initial state.

The basic control idea is to force the patient state to be such that $\dot{w}(t) > 0$ as long as possible. In the case of model (5.1)-(5.5) this idea can be implemented by means of the following control procedure.

5.1.1 The control procedure

Initialization: Select a positive number T_s . T_s denotes the sampling time for the computation of the control input. Let w denote the immune term, $K = c_2xy - c_2qy - b_2$

the immune increasing factor, and the set $K(x, y) \geq 0$ in the (x, y) positive orthant the immune increasing region. X_I is the initial condition of model (5.1)-(5.5).

STEP 1: Integrate model (5.1)-(5.5) with initial condition X_I for T_s time instants with full medication and with no medication. Let $X_{F, fm}$ and $X_{F, nm}$ be the values of the state of the model (5.1)-(5.5) at the end of the integration period with full medication and with no medication, respectively. Let $\pi_{F, fm}$ and $\pi_{F, nm}$ be the projections of $X_{F, fm}$ and $X_{F, nm}$, respectively, on the (x, y) plane.

STEP 2: If $\pi_{F, fm}$ is not in the immune increasing region, then set $u = 0$.

If $\pi_{F, fm}$ is in the immune increasing region and $\pi_{F, nm}$ is not in the immune increasing region, then set $u = 1$.

If both $\pi_{F, nm}$ and $\pi_{F, fm}$ are in the immune increasing region and the immune term of $X_{F, nm}$ is not smaller than that of $X_{F, fm}$, then set $u = 0$.

If both $\pi_{F, nm}$ and $\pi_{F, fm}$ are in the immune increasing region and the immune term of $X_{F, fm}$ is greater than that of $X_{F, nm}$, then set $u = 1$.

STEP 3: The input determined in STEP 2 is applied to the model (5.1)-(5.5) with initial point X_I for T_s time instants. Let X_F be the values of the state at the end of the integration period.

STEP 4: Set $X_I = X_F$ and go to STEP 1.

Consider the set Ω of the positive orthant such that all initial conditions in Ω are driven to the LTNP status by the proposed control procedure. The shape and size of the set Ω depend upon the system's parameters and the value of T_s . A simple estimate of Ω will be computed in Subsection 5.1.2. For initial conditions outside Ω to be driven inside Ω , it is necessary to apply a preliminary control action, for example full medication over a sufficiently long period (which will be considered in the next chapters). Note that the initial condition in Table 5.2, associated to a patient treated by long time HAART therapy, belongs to the set Ω , as shown in Figure 5.2 and Figure 5.3.

Figure 5.2 shows the results of the application of the proposed control procedure with $T_s = 1$ (day)². The control input becomes eventually zero³ and the patient state converges to the LTNP status, namely to Point E which is (8.2255, 0.0216, 0, 1240,

²This assumes that HIV measurements are carried out from day to day. If we choose smaller T_s , then the state trajectory can be controlled more minutely. This issue will be considered in the next chapters.

³19 days are required for the control signal to reach zero in Figure 5.2.

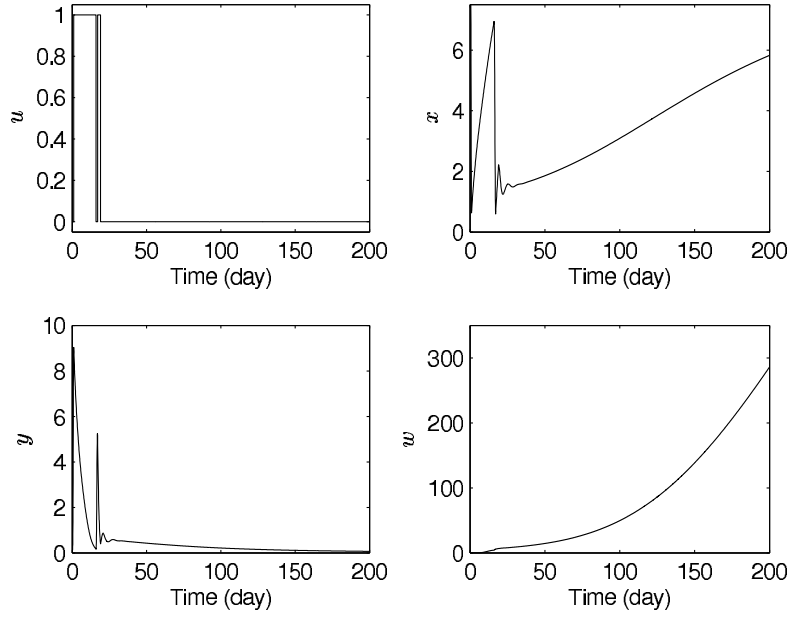


Figure 5.2: Results of the application of the control procedure in Section 5.1.1 to model (5.1)-(5.5) with $T_s = 1$ (day). The unit of x and y is (100copies/ μ l).

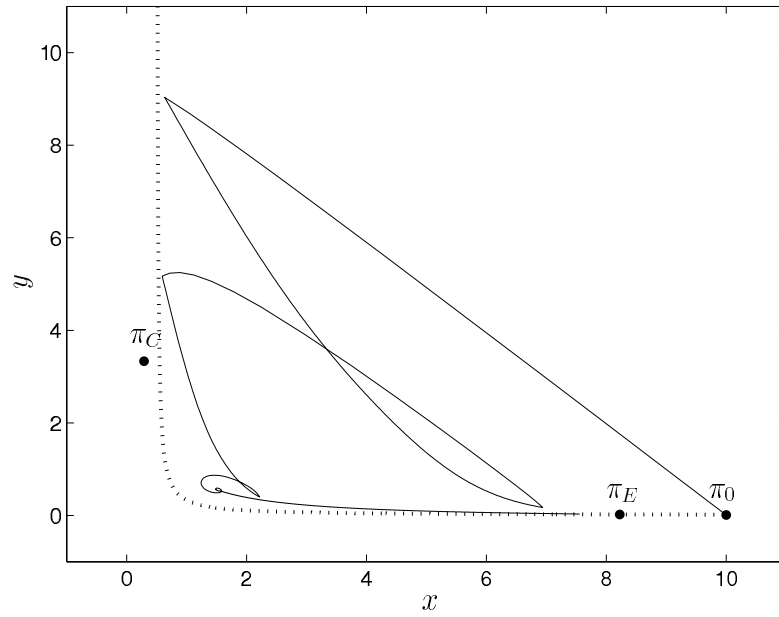


Figure 5.3: The (x, y) trajectory resulting from the proposed control strategy. The dotted line indicates the set $K(x, y) = 0$ and the solid line indicates the (x, y) trajectory. The (x, y) trajectory stays within the immune increasing region, $c_2xy - c_2qy - b_2 \geq 0$, and converges to Point E.

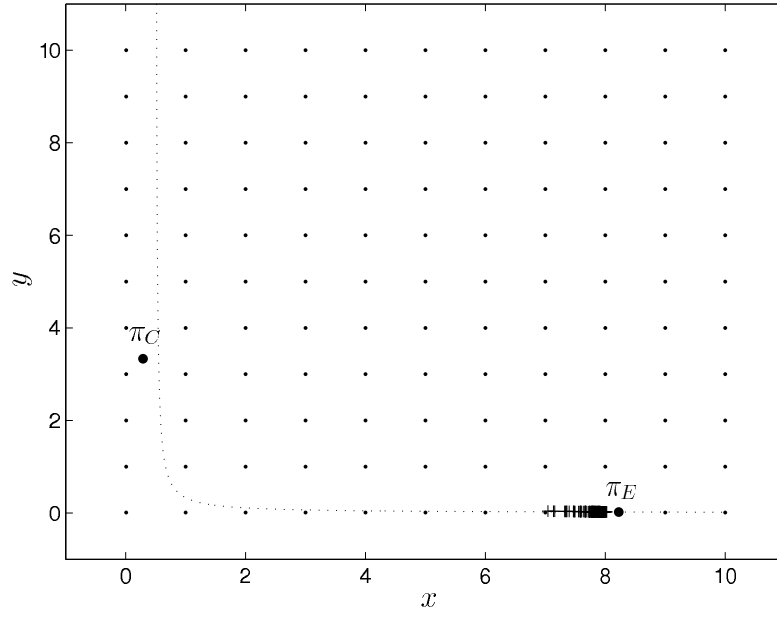


Figure 5.4: Estimation of the set Ω with $z_1 = 0.01$, $w = 0.01$, and $z_2 = 0.01$. The “.” and the “+” marks denote the projections of the initial points and of the final points in the (x, y) plane, respectively.

8.0255) for the given parameters. The (x, y) trajectory is shown in Figure 5.3, which shows that the (x, y) trajectory stays within the immune increasing region $c_2xy - c_2qy - b_2 \geq 0$ for all $t \geq 0$.

The proposed control strategy relies on the knowledge of the immune increasing region, which depends upon system’s parameters. Note however that it is sufficient to use a conservative estimate of the immune increasing region, hence rendering the control strategy robust.

5.1.2 The set Ω

To estimate the set Ω we use computer simulations. In these simulations it is assumed that $z_1(0) = 0.01$, $w(0) = 0.01$ and $z_2(0) = 0.01$, which means that the immune system is hardly boosted. We simulate with pairs of initial points $(x(0), y(0))$ with $x(0)$ and $y(0)$ taking values in the set $\{0.01, 1, 2, 3, \dots, 10\}$. All other conditions are as in the previous subsection.

In Figure 5.4, the initial points are indicated with “.” marks in (x, y) plane. The “+” marks denote the (x, y) states after the control process for 400 days. Figure 5.5

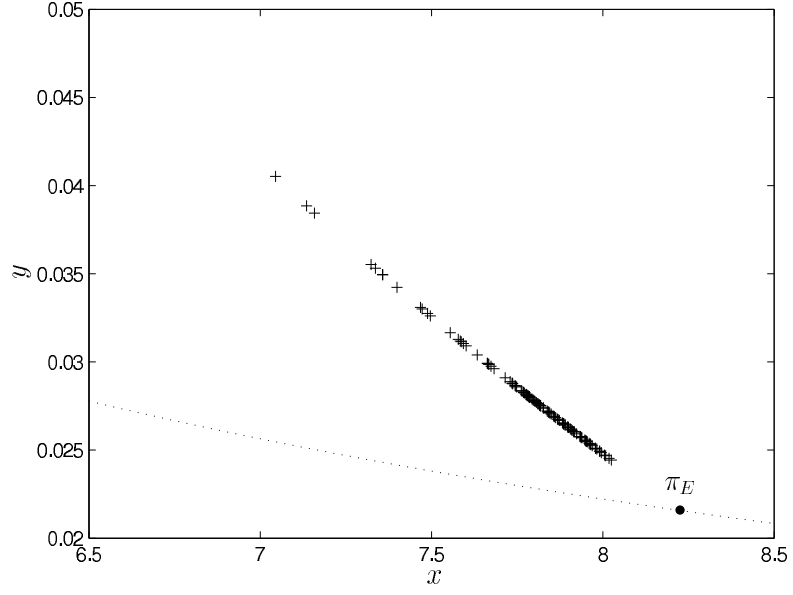


Figure 5.5: Zoomed in version of Figure 5.4. All “+” marks from Figure 5.4 are shown in this graph. The “+” marks belong to the region of attraction of Point E and belong to the immune increasing region.

shows a zoomed in version of Figure 5.4. All considered initial states yield trajectories which converge to the LTNP state, π_E . Particularly the trajectory with $x(0) = 10$ and $y(0) = 0.01$ is displayed in Figure 5.2 and Figure 5.3. The suggested control idea works for all considered initial points.

5.2 Analysis and control of HIV model with two target cell types

In this section we consider model (2.14)-(2.19) of Section 2.1.3, namely

$$\dot{x}_1 = \lambda_1 - d_1 x_1 - (1 - \epsilon_1 u_1) k_1 v x_1, \quad (5.6)$$

$$\dot{x}_2 = \lambda_2 - d_2 x_2 - (1 - f \epsilon_1 u_1) k_2 v x_2, \quad (5.7)$$

$$\dot{y}_1 = (1 - \epsilon_1 u_1) k_1 v x_1 - \delta y_1 - m_1 z y_1, \quad (5.8)$$

$$\dot{y}_2 = (1 - f \epsilon_1 u_1) k_2 v x_2 - \delta y_2 - m_2 z y_2, \quad (5.9)$$

$$\dot{v} = (1 - \epsilon_2 u_2) N_T \delta (y_1 + y_2) - c v - A_1(x_1, x_2, u_1) v, \quad (5.10)$$

$$\dot{z} = \lambda_E + \frac{b_E(y_1 + y_2)}{(y_1 + y_2) + K_b} z - \frac{d_E(y_1 + y_2)}{(y_1 + y_2) + K_d} z - \delta_E z, \quad (5.11)$$

with $A_1(x_1, x_2, u_1) = (1 - \epsilon_1 u_1) \rho_1 k_1 x_1 + (1 - f \epsilon_1 u_1) \rho_2 k_2 x_2$.

We use the same system parameters and an initial point of [10], as indicated in Table 5.3. The model (5.6)-(5.11) with the given parameters has at least⁴ two asymptotically stable equilibrium points, which correspond to the AIDS status and the LTNP status [1, 10]. The initial point represents a patient immediately after the HIV infection.

λ_1	d_1	ϵ_1	k_1	λ_2	d_2	f	k_2	δ
10	0.01	0.7	8.0×10^{-4}	31.98×10^{-3}	0.01	0.34	0.1	0.7
m_1	m_2	ϵ_2	N_T	c	ρ_1	ρ_2	λ_E	b_E
0.01	0.01	0.3	100	13	1	1	1.0×10^{-3}	0.3
K_b	d_E	K_d	δ_E	$T_1(0)$	$T_2(0)$	$T_1^*(0), T_2^*(0)$	$V(0)$	$E(0)$
0.1	0.25	0.5	0.1	1000	3.198	0.0	0.001	0.01

Table 5.3: Parameters and initial conditions for model (5.6)-(5.10).

The dynamics of the CTL effector z (given in equation (5.11)) are explained in [12]. Equation (5.11) can be written as $\dot{z} = \lambda_E + K(y)z$, where

$$K(y) = \frac{b_E y}{y + K_b} - \frac{d_E y}{y + K_d} - \delta_E,$$

with $y = y_1 + y_2$. The states y_1 and y_2 are determined by equations (5.8) and (5.9), respectively and these two equations include the RTI therapy input term, u_1 . Consequently $\dot{z}$ is affected by the input u_1 . Figure 5.6 shows the graph of $K = K(y)$ as a function of y for the given system parameters. If $K(y)$ is non-negative and λ_E is a positive constant, then $\dot{z} > 0$. Therefore the condition $K(y) \geq 0$ implies that the patient's state is inside the immune increasing region. With the given parameters, $K(y) = 0$ when y is either 0.0821 or 1.2178. Hence if $y \in [0.0821, 1.2178]$ the immune system is boosted.

To apply the control methodology from Section 5.1 to model (5.6)-(5.10) we assume that $u_1 = u_2 = u$ because drug therapy with only one category⁵ of anti-HIV drugs can cause the emergence of drug-resistant strains of HIV [83]. The state z is regarded as the immune term and $K(y)$ is regarded as the immune increasing factor. With this definition it is possible to apply directly the control steps proposed in Section 5.1. Similarly to

⁴In [1, 10], it is only shown that two of the equilibria of model (5.6)-(5.11) are asymptotically stable with the parameters of Table 5.3. Note that we do not need the stability of any other equilibrium points for the discussion in this thesis.

⁵Note that the input terms u_1 and u_2 represent the antiviral effects from reverse transcriptase inhibitors (RTI) and protease inhibitors (PI), respectively.

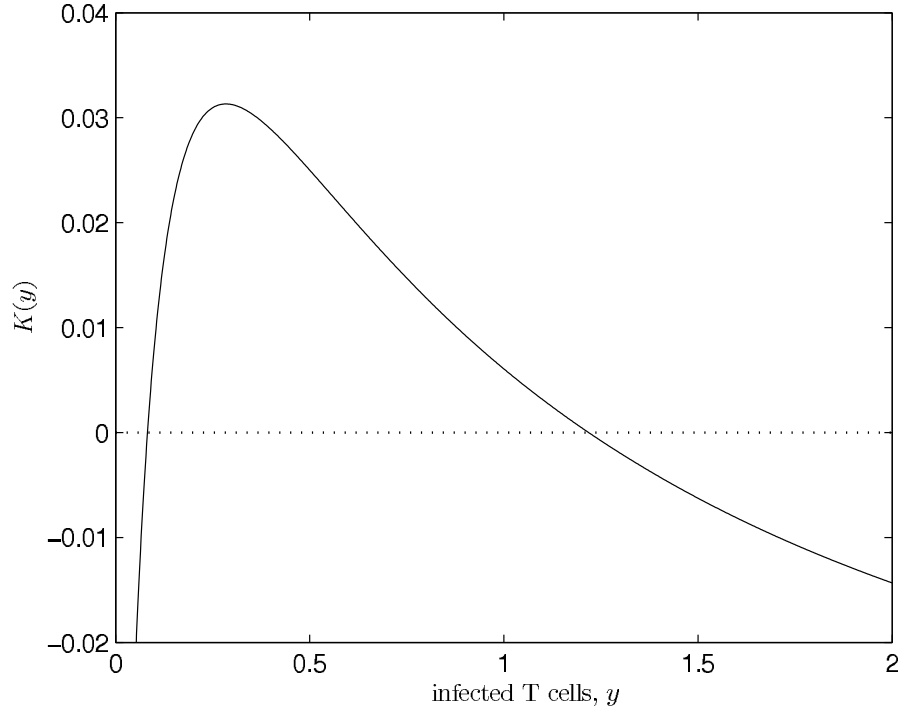


Figure 5.6: Graph of the function $K(y)$. The function derived from (5.11) is $K(y) = \frac{b_E y}{y + K_b} - \frac{d_E y}{y + K_d} - \delta_E$ with $y = y_1 + y_2$. The dotted line represents the set $K(y) = 0$. With the given parameters, $K(y) = 0$ when y is either 0.0821 or 1.2178.

what discussed in Section 5.1 it is possible to estimate a subset such that all initial conditions in this subset are driven to the LTNP state by the proposed control strategy.

Figure 5.7 shows the results of the application of the control procedure with $T_s = 1$. The control input converges to zero and the patient states converges to the LTNP status, given by (967.839, 0.621, 0.076, 0.006, 0.415, 353.108) [10]. The (x, y) trajectory is displayed in the top graph of Figure 5.8, where $x = x_1 + x_2$. π_0 in the graph represents the initial point in the (x, y) plane, and π_{LTNP} and π_{AIDS} denote the LTNP status and the AIDS status in the (x, y) plane, respectively. These two points are locally asymptotically stable [10]. π_{FM} indicates the point which is asymptotically stable when $u = 1$.

The bottom graph of Figure 5.8, which is a zoomed version of the top graph, provides an explanation of the control mechanism. In particular the shaded region is the region where the immune term z is enhanced. In the first two days of simulation the control input is zero because the patient state cannot enter the shaded area regardless of the input. As a result the patient state converges to π_{AIDS} (which is outside the area of

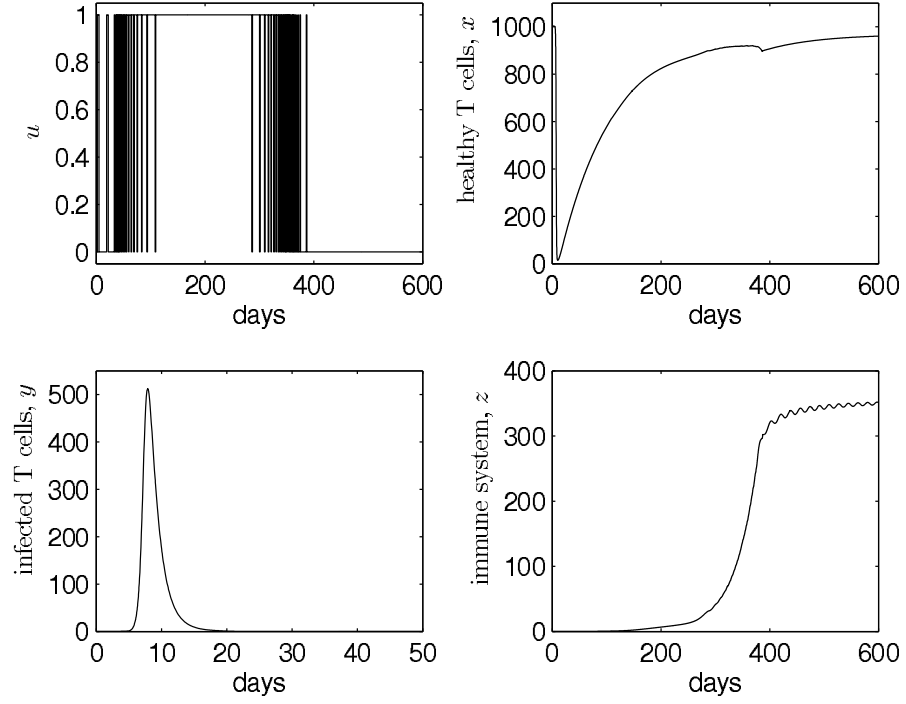


Figure 5.7: The results of the control procedure applied to model (5.6)-(5.10) with $T_s = 1$. The unit of x and y is (copies/ μ l). (Note the different time axis in the bottom left graph.)

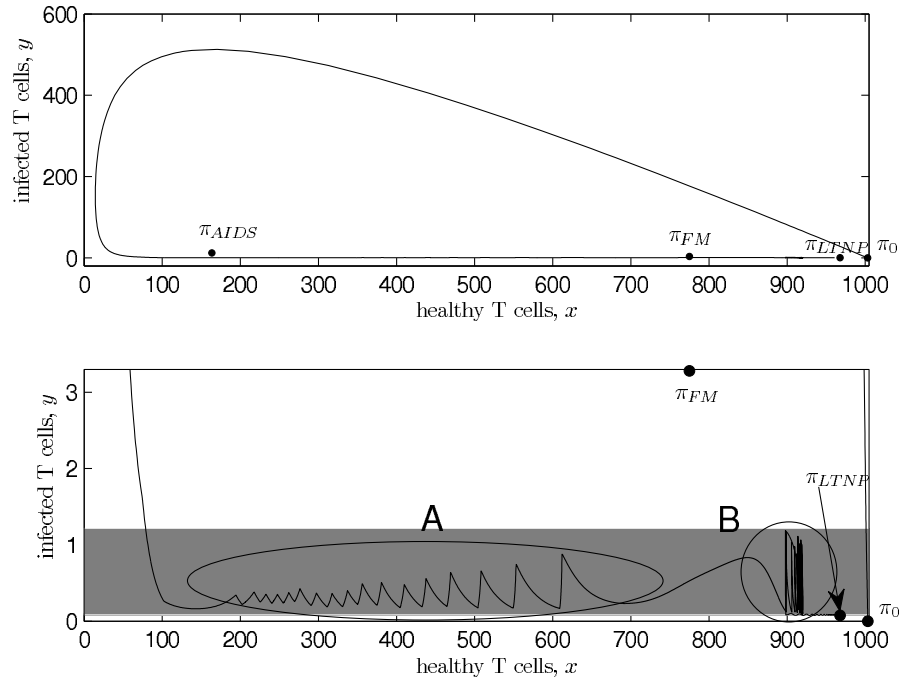


Figure 5.8: (x, y) graphs from Figure 5.7.

the bottom graph) and penetrates into the shaded area only in the third day. When the initial state is in the shaded area and $u = 0$, the resulting trajectory is a counterclockwise spiral converging to π_{AIDS} . On the other hand if $u = 1$ and the state is in region A, then the trajectory is a counterclockwise spiral converging to π_{FM} , whereas if $u = 1$ and the state is in region B, then the trajectory is a clockwise spiral and converges to π_{FM} . This implies that if the trajectory reaches the shaded area, where the immune term is enhanced, then there is a switching input sequence which forces the state to remain in the shaded area, provided T_s is sufficiently small. This behaviour is clearly illustrated in the bottom graph of Figure 5.8.

5.3 Analysis and control of disease dynamic model

In this section we show that the control methodology proposed in Section 5.1 is applicable to the model (2.24)-(2.27) discussed in Section 2.1.5, namely

$$\dot{x}_1 = (a_{11} - a_{12}x_3)x_1 + b_1u_1, \quad (5.12)$$

$$\dot{x}_2 = a_{21}(x_4)a_{22}x_1(t - \tau)x_3(t - \tau) - a_{23}(x_2 - x_2^*) + b_2u_2, \quad (5.13)$$

$$\dot{x}_3 = a_{31}x_2 - (a_{32} + a_{33}x_1)x_3 + b_3u_3, \quad (5.14)$$

$$\dot{x}_4 = a_{41}x_1 - a_{42}x_4 + b_4u_4. \quad (5.15)$$

We use the same system parameters and one of the initial conditions of [67, 69], as indicated in Table 5.4. The initial condition corresponds to a patient who would be led to fatal damage of the body without treatment.

a_{11}	a_{12}	a_{22}	a_{23}	a_{31}	a_{32}	a_{33}	a_{41}	a_{42}	b_1
1	1	3	1	1	1.5	0.5	0.5	1	-1
b_2	b_3	b_4	τ	x_2^*	$x_1(0)$	$x_2(0)$	$x_3(0)$	$x_4(0)$	
1	1	-1	0	2	3	2	4/3	0	

Table 5.4: Parameters and initial conditions for model (5.12)-(5.15).

The function $a_{21}(x_4)$, which describes the immune deficiency effect caused by the damage of the organ, is selected as in [69], namely

$$a_{21}(x_4) = \begin{cases} \cos \pi x_4, & \text{if } 0 \leq x_4 \leq 0.5, \\ 0, & \text{if } 0.5 < x_4. \end{cases} \quad (5.16)$$

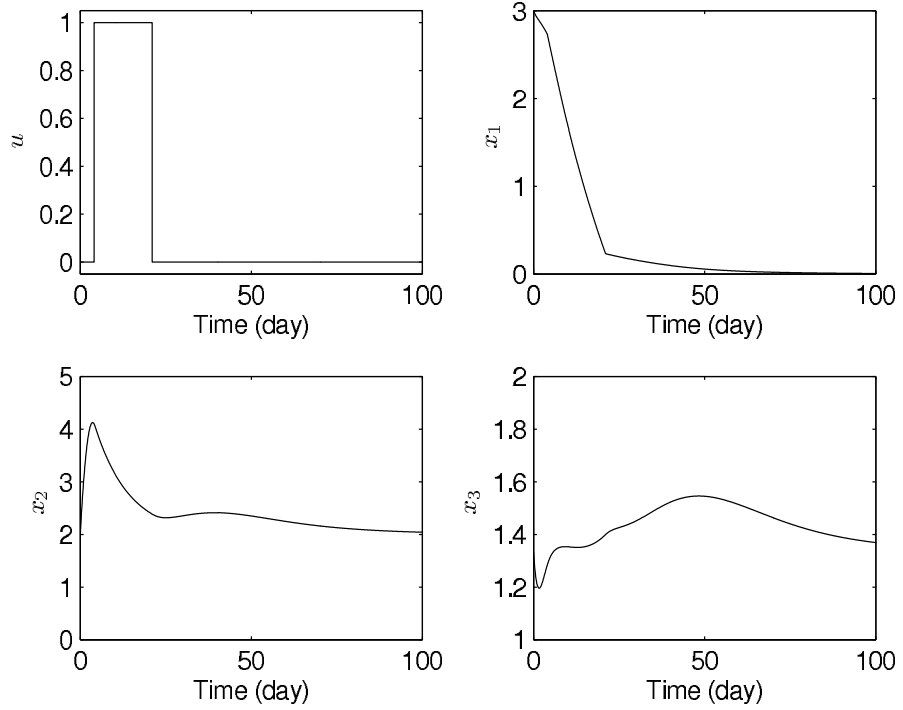


Figure 5.9: The results of the application of the control procedure to model (5.12)-(5.15) for 100 days with $T_s = 0.1$. The control method successfully suppresses the pathogen x_1 in a short period.

In [67–69] the time unit is not specified and simulations are carried for 10 time units. With the given initial state the patient’s organ becomes deadly damaged after 4 time units [67–69]. We assume that 1 time unit in model (5.12)-(5.15) is 10 days and we set $T_s = 0.1$, which corresponds to 1 day, to implement the control strategy of Section 5.1. Consequently we simulate model (5.12)-(5.15) for 100 days. Note that without treatment the disease would result in a fatally damaged organ after 40 days.

To apply the control methodology proposed in Section 5.1 to model (5.12)-(5.15) we assume $u_2 = u_3 = u_4 = 0$, hence u_1 is the only control input. This is motivated by the observation that the antiviral drug input in model (5.1)-(5.5) corresponds to the antigen killer u_1 in model (5.12)-(5.15). In addition we regard the state x_2 as the immune term and the function $a_{21}(x_4)a_{22}x_1(t - \tau)x_3(t - \tau)$ as the immune increasing factor K , which is a function of x_1 , x_3 , and $a_{21}(x_4)$, when $\tau = 0$. Thus $K(x_1, x_3, a_{21}(x_4)) \geq 0$ is the immune increasing space of the model⁶. With these assumptions it is possible to apply

⁶We call $K(x_1, x_3, a_{21}(x_4)) \geq 0$ the immune increasing space, instead of immune increasing region, because the immune increasing factor K is a function of three variables.

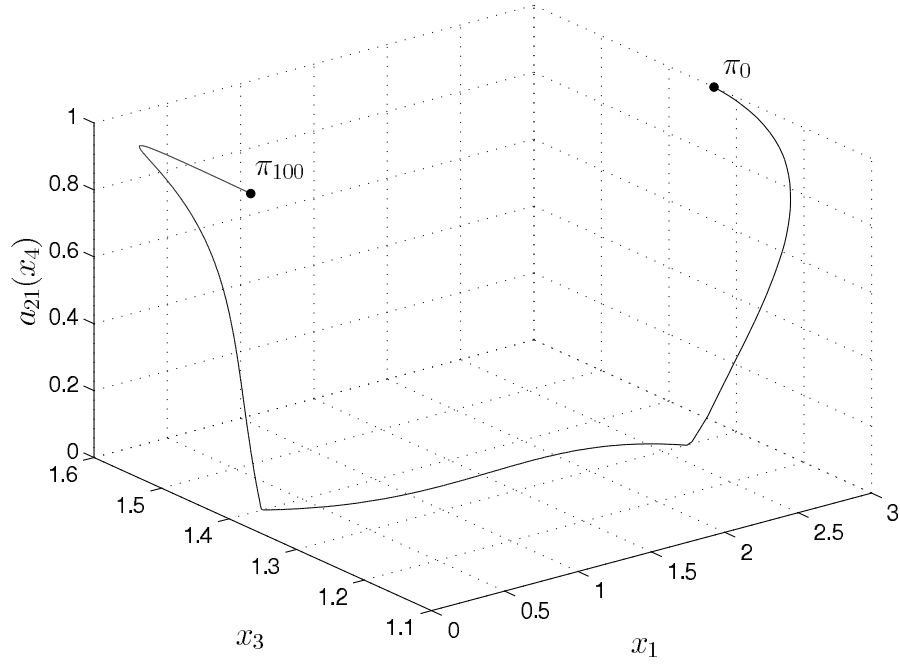


Figure 5.10: The $(x_1, x_3, a_{21}(x_4))$ trajectory from Figure 5.9. π_0 and π_{100} indicate the projections of the initial and final points into the $(x_1, x_3, a_{21}(x_4))$ space, respectively.

the control strategy developed for model (5.1)-(5.5) to the model (5.12)-(5.15).

Note, however that, as x_1 and x_3 are positive, $a_{22} = 3$, and $a_{21}(x_4)$ is non-negative, by (5.16), the trajectory always stays in the immune increasing space. As a result STEP 2 of the procedure has to be replaced by the following step.

STEP 2*: The control input is the one that maximizes x_2 at the end of the integration period.

Figure 5.9 shows the results of the application of the proposed control procedure for 100 days. The procedure, unlike what proposed in [67–69] (where optimal control tools are used), provides either full dosage or no dosage of medication for each day and successfully suppresses the pathogen x_1 in a short period. The $(x_1, x_3, a_{21}(x_4))$ trajectory obtained from the control procedure is displayed in Figure 5.10.

5.4 Analysis and control of HIV model with two immune response types

In this section we evaluate the control idea by applying it to an alternative HIV dynamic system, which shows a tristability property. To the best of our knowledge, this is the first

study on drug scheduling for a tristable HIV model. We consider the model (2.20)-(2.23) in Section 2.1.4, namely

$$\dot{x} = \lambda - d_x x - \eta \beta y x N, \quad (5.17)$$

$$\dot{x}_1 = \lambda_H + \frac{\alpha y x_1}{\gamma_1 + y} - \epsilon x_1^2 - \eta \beta_H y x_1 N, \quad (5.18)$$

$$\dot{x}_2 = \lambda_H + \frac{\alpha y x_2}{\gamma_2 + y} - \epsilon x_2^2 - \eta \beta_H y x_2 N, \quad (5.19)$$

$$\dot{y} = \eta y [\beta x + \beta_H x_1 + \beta_H x_2] N - d_y y - K y, \quad (5.20)$$

where $\gamma_2 > \gamma_1$, $K = K(x_1, x_2) = k_1 x_1 + k_2 x_2$, and

$$N = N(x_1, x_2) = \frac{1}{1 + n_1 x_1 + n_2 x_2}.$$

We use the same system parameters of [6], as indicated in Table 5.5.

λ	λ_H	d_x	d_y	α	β	β_H	γ_1	γ_2	ϵ
2	10^{-7}	0.05	0.2	0.3	0.03	0.03	2	6	0.05
k_1	k_2	n_1	n_2	ϵ^*	$x(0)$	$x_1(0)$	$x_2(0)$	$y(0)$	
0.1	0	0	2	0.8	6.6671	0.0001	0.0001	8.3327	

Table 5.5: Parameters and initial conditions for model (5.17)-(5.20).

With these parameters model (5.17)-(5.20) is a tristable system [6] when $u = 0$. To highlight this property three trajectories of the systems are displayed in Figure 5.11. The three initial conditions in Figure 5.11 are $(40, 5, 5, 1)$, $(0.01, 0.01, 0.01, 10)$, and $(10, 1, 0.01, 6)$. We integrate model (5.17)-(5.20) with $u = 0$ from these initial conditions for 1,000 days, and obtain the three points :

Point P : (30.5919, 2.0279, 0.7433, 1.2737),

Point Q : (6.6671, 0.0000, 0.0000, 8.3328),

Point R : (9.0522, 1.0225, 0.0000, 5.6985).

Figure 5.11 shows that each trajectory converges to one of these points. Point Q implies the status of a patient for whom HIV dominates, which is locally stable with the given parameters. Point P describes the LTNP, i.e. a patient who is infected with HIV but does not progress to AIDS. With the given parameters Point P is also locally stable. At Point P, the number of infected cells (the y component) is maintained very low, while the

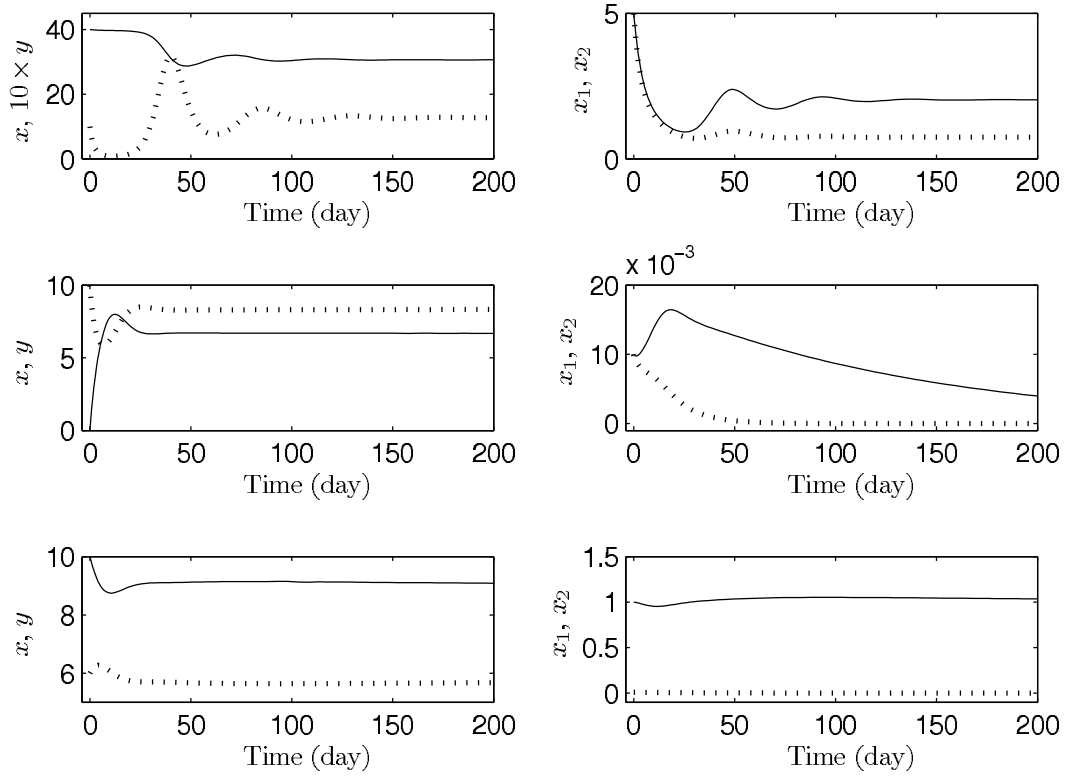


Figure 5.11: State histories of model (5.17)-(5.20) with input $u = 0$ from the initial state $(40, 5, 5, 1)$ (top graphs), $(0.01, 0.01, 0.01, 10)$ (middle graphs), $(10, 1, 0.01, 6)$ (bottom graphs). $x(t)$ and $x_1(t)$ are represented by solid lines while $y(t)$ and $x_2(t)$ are represented by dotted lines.

numbers of the HIV-specific CD4 T-cells (the x_1 and x_2 components) are large, which is desired. Finally Point R can be interpreted as a substitution status for the LTNP, which will be discussed in Sections 5.4.2. The main goal of controlled drug scheduling is to bring the state of a patient to within a small neighbourhood of the LTNP status, Point P.

The initial state considered in this section is shown in Table 5.5, which represents a patient with AIDS, in the vicinity of Point Q. Figure 5.12 shows the simulation result of the withdrawal of drugs after full-dosage treatment for 500 days with this initial point. Regardless of the treatment, the infected cells (y state) re-emerge to pre-treatment levels and the immune response (x_1 and x_2 states) are not excited after the cessation of drugs. Hence immunological control of the HIV in the absence of the drug is not achieved and a systematic drug scheduling is needed for the HIV patient to be driven into the region of attraction of the LTNP status.

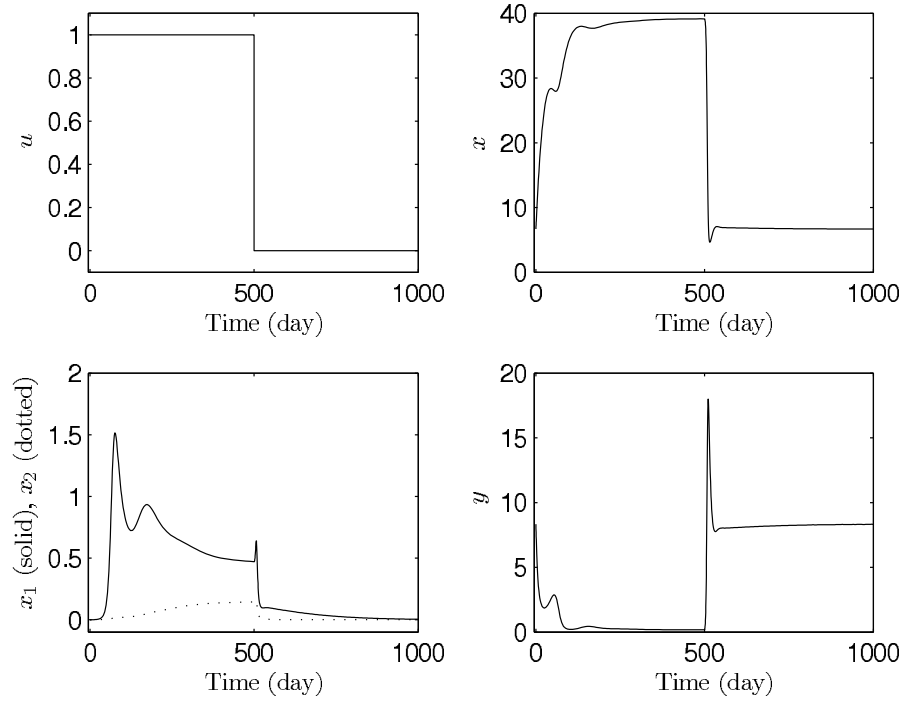


Figure 5.12: Result of the cessation of drugs after 500 days of treatment. Although the infected cells (y) seem to be eradicated during the treatment, they re-emerge to pre-treatment levels when the drugs are stopped.

5.4.1 Modification of the control procedure

Exploiting the ideas introduced in Chapter 3 we regard model (5.17)-(5.20) as the interconnection of two subsystems: the infection dynamics and the immune system (see Figure 5.13). The infection dynamics are described by equations (5.17) and (5.20), while the immune system is represented by equations (5.18) and (5.19). The goal of the control is to enhance immunity, and this is equivalent to boosting x_1 and x_2 . To lead a HIV patient to the LTNP status (Point P), the HIV specific immune response (i.e., x_1 and x_2) must be enhanced because the x_1 and x_2 components of Point Q are zero and those of Point P are positive and large. Therefore we must increase the x_1 and x_2 terms by controlled medication scheduling.

Equation (5.18) can be written as

$$\dot{x}_1 = \lambda_H + K_1(x_1, x_2, y, u)x_1,$$

where

$$K_1(x_1, x_2, y, u) = \frac{\alpha y}{\gamma_2 + y} - \epsilon x_1 - (1 - \epsilon^* u) \beta_H y N_1(x_1, x_2),$$

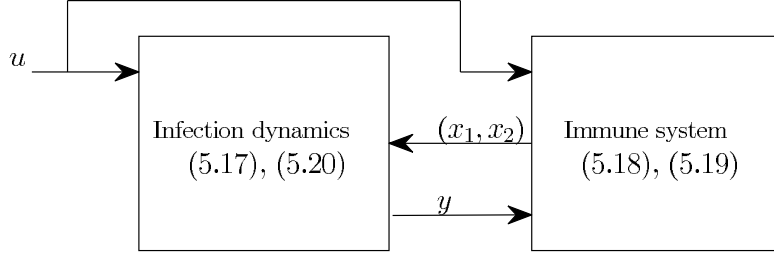


Figure 5.13: Interconnection between the infection dynamics and the immune system in model (5.17)-(5.20). Note that the input u is applied to both subsystems.

with $N_1(x_1, x_2) = \frac{1}{1+n_1x_1+n_2x_2}$. On the other hand equation (5.19) can be written as

$$\dot{x}_2 = \lambda_H + K_2(x_2, y, u)x_2,$$

where

$$K_2(x_2, y, u) = \frac{\alpha y}{\gamma_2 + y} - \epsilon x_2 - (1 - \epsilon^* u) \beta_H y N_2(x_2),$$

with $N_2(x_2) = \frac{1}{1+n_2x_2}$. In this section we consider the case⁷ with $n_1 = 0$ and $k_2 = 0$.

Figure 5.14 shows some geometric properties of the function $K_1(x_1, x_2, y, u)$ for the given parameters and for $x_2 = 0$, in the (x_1, y) positive orthant. The dotted lines describe the sets in which $K_1(x_1, 0, y, 0) = 0$, $K_1(x_1, 0, y, 0) = 0.02$, and $K_1(x_1, 0, y, 0) = 0.04$, respectively. The solid lines depict the sets in which $K_1(x_1, 0, y, 1) = 0$, $K_1(x_1, 0, y, 1) = 0.05$, and $K_1(x_1, 0, y, 1) = 0.1$, respectively. These graphs allow to conclude, for example, that if x_2 is sufficiently small and the point (x_1, y) is placed into the set in which $K_1(x_1, 0, y, 0) = 0$ and $x_1 > 0$, then the state x_1 increases when $u = 0$. $\tilde{\pi}_P$, $\tilde{\pi}_Q$, and $\tilde{\pi}_R$ correspond to the projection into the (x_1, y) -plane of Point P, Point Q, and Point R, respectively. Note that $\tilde{\pi}_Q$ and $\tilde{\pi}_R$ are located in the set in which $K_1(x_1, 0, y, 0) = 0$, while $\tilde{\pi}_P$ is not.

Figure 5.15 shows some geometric properties of the function $K_2(x_2, y, u)$ for the given parameters in the (x_2, y) positive quadrant. The dotted lines indicate the sets in which $K_2(x_2, y, 0) = 0$, $K_2(x_2, y, 0) = 0.02$, and $K_2(x_2, y, 0) = 0.04$, respectively. The solid lines represent the sets in which $K_2(x_2, y, 1) = 0$, $K_2(x_2, y, 1) = 0.05$, and $K_2(x_2, y, 1) = 0.1$, respectively. These graphs allow to conclude, for example, that if the point (x_2, y) is such that $K_2(x_2, y, 0) = 0$, then the state x_2 increases when $u = 0$ by

⁷In [6], this case is described as x_1 is lytic and x_2 is non-lytic. Lytic immune response kills infected cells, whereas nonlytic immune response inhibits viral replication via soluble mediators [74].

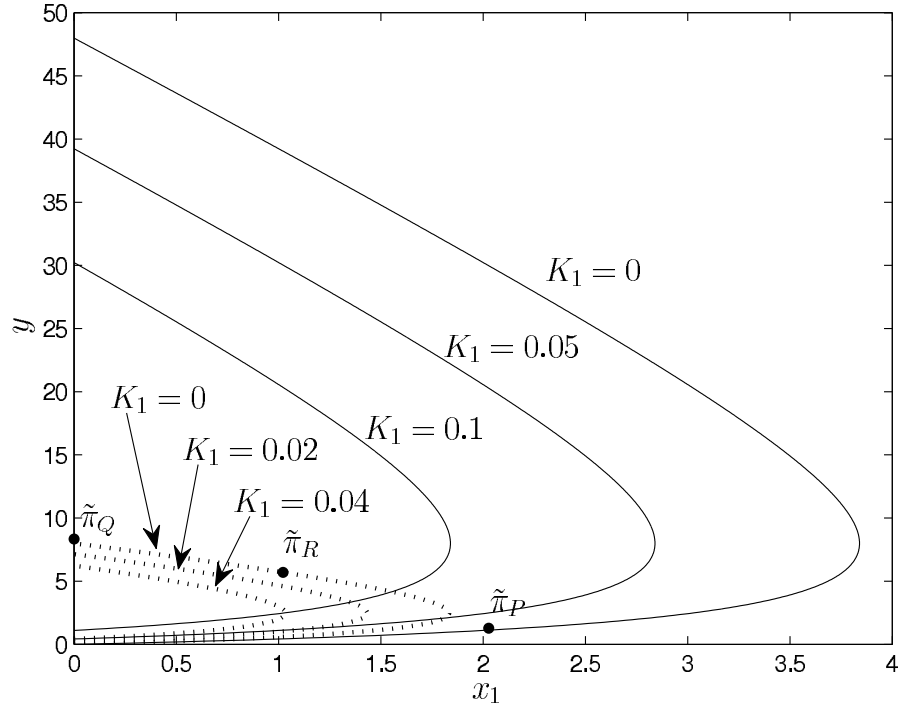


Figure 5.14: Properties of the function $K_1(x_1, x_2, y, u)$.

(5.19) and $\lambda_H > 0$. π_P , π_Q , and π_R correspond to the projection into the (x_2, y) -plane of Point P, Point Q, and Point R, respectively.

Note that only the Point P (i.e., the LTNP) has a positive x_2 component among the three steady states, and that $K_2(x_2, y, 0)$ depends upon the variables x_2 and y , which are directly affected by the drug from (5.19) and (5.20). Accordingly, we can control $\dot{x}_2$ indirectly via the input u . The basic control idea is therefore to force the state to be such that $K_2(x_2, y, u) \geq 0$ (which implies $\dot{x}_2(t) > 0$) as long as possible. In the case of model (5.17)-(5.20) this idea can be implemented by means of the following control procedure.

The control procedure

Initialisation: Select a positive number T_s . T_s denotes the sampling time for the computation of the control input. Let x_2 denote the immune term, $K_2(x_2, y, u)$ the immune increasing factor, the set in the (x_2, y) plane in which $K_2(x_2, y, 0) \geq 0$ the immune increasing region for $u = 0$, the set in the (x_2, y) plane in which $K_2(x_2, y, 1) \geq 0$ the immune increasing region for $u = 1$. X_I is the initial condition of model (5.17)-(5.20).

STEP 1: Integrate model (5.17)-(5.20) with initial condition X_I for T_s with full

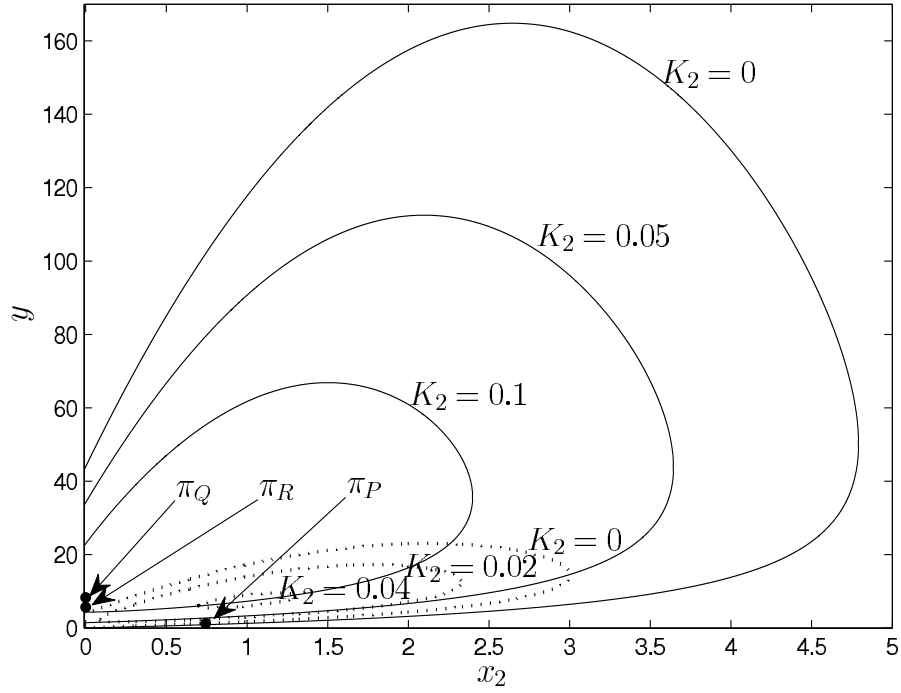


Figure 5.15: Properties of the function $K_2(x_2, y, u)$.

medication and with no medication. Let $X_{F,fm}$ and $X_{F,nm}$ be the values of the state of the model (5.17)-(5.20) at the end of the integration period with full medication and with no medication, respectively. Let $\pi_{F,fm}$ and $\pi_{F,nm}$ be the projections of $X_{F,fm}$ and $X_{F,nm}$, respectively, on the (x_2, y) plane.

STEP 2: If $\pi_{F,nm}$ is not in the immune increasing region for $u = 0$, then set $u = 1$. Otherwise set $u = 0$.

STEP 3: The input determined in STEP 2 is applied to the model (5.17)-(5.20) with initial point X_I for T_s . Let X_F be the value of the state at the end of the integration period.

STEP 4: Set $X_I = X_F$ and go to STEP 1.

5.4.2 Simulations and remarks

Figure 5.16 shows the results of the application of the proposed control procedure with $T_s = 1$ (day). The control input becomes eventually zero and the patient state converges to the LTNP status, namely to Point P. The resulting (x_2, y) trajectory is displayed in the top graph of Figure 5.18, which shows that the (x_2, y) trajectory stays within the

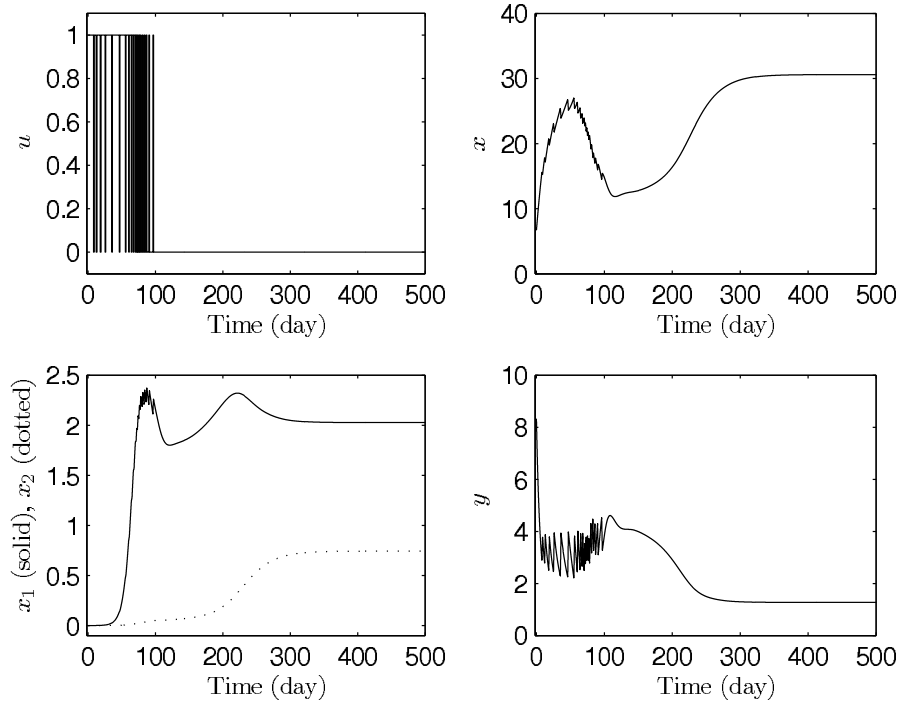


Figure 5.16: Results of the application of the control procedure in Subsection 5.4.1 to model (5.17)-(5.20) with $T_s = 1$ (day).

immune increasing region for $u = 0$.

While the given initial state X_I is successfully driven to the LTNP status we now investigate an alternative strategy by which X_I is driven to Point R (the importance of this alternative control goal will be discussed later in this section). To this end we consider the following step, which replaces STEP 2 of the control procedure.

STEP 2': If $\pi_{F, fm}$ is not in the immune increasing region for $u = 0$, then set $u = 1$. Otherwise set $u = 0$.

From the initial point X_I , full dosage (i.e., $u = 1$) forces the trajectories to move towards the lower-right of the (x_1, y) -plane and of the (x_2, y) -plane by (5.18), (5.19), and (5.20). No medication (i.e., $u = 0$) drives the trajectories towards the upper-left of those planes. Therefore the input decision in STEP 2' yields on-off switches of u without boosting the state x_2 . Note that on-off input switches enhance the state x_1 in the vicinity of Point Q, as we can see from Figure 5.14. Thus the control procedure with STEP 2' is such that the initial point X_I reaches Point R, while the control procedure

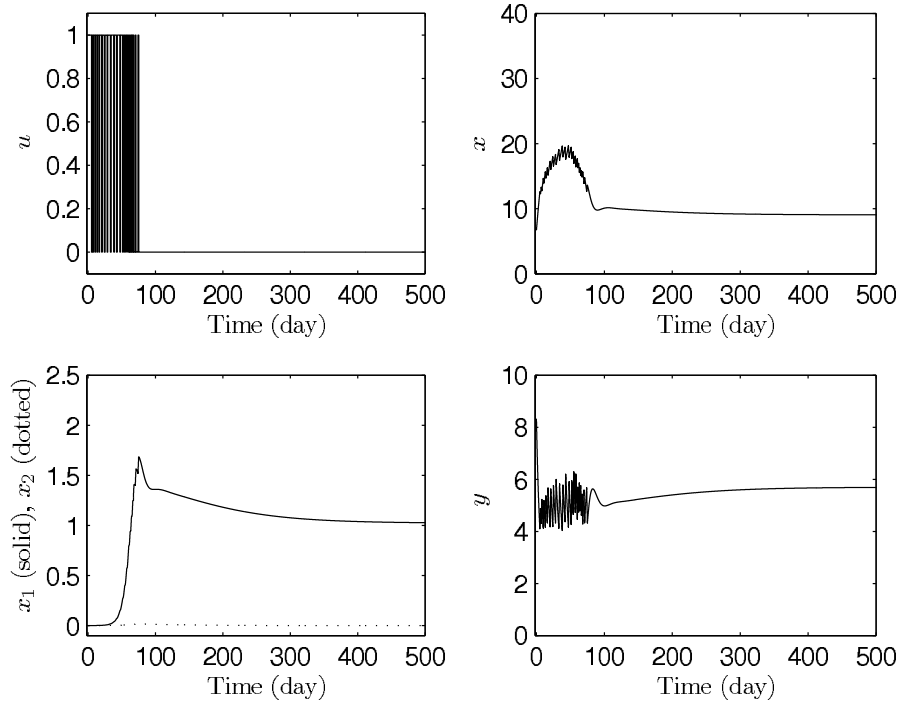


Figure 5.17: Results of the application of the alternative control procedure with STEP 2' to model (5.17)-(5.20) with $T_s = 1$ (day).

with STEP 2 drives the initial state to Point P by enhancing both x_1 and x_2 .

Figure 5.17 shows the results of the application of the alternative procedure with $T_s = 1$ (day). The control input becomes eventually zero and the patient state converges to Point R. The (x_2, y) trajectory is displayed in the bottom graph of Figure 5.18, which shows that the (x_2, y) trajectory stays outside the immune increasing region for $u = 0$.

In Figure 5.18 the dotted lines indicate the sets in which $K_2(x_2, y, 0) = 0$, $K_2(x_2, y, 0) = 0.02$, and $K_2(x_2, y, 0) = 0.04$, respectively. The solid lines describe the (x_2, y) trajectories. Note that the (x_2, y) trajectories starts from X_I , which is close to π_Q . The trajectory of the top graph converges towards π_P , while that of the bottom graph converges towards π_R .

We complete this section with some remarks.

1. One of the most difficult problems in HIV treatment is the emergence of HIV mutation [37]. If HIV mutates to escape from the LTNP status (Point P in this section) then this virus cannot be suppressed by the human immune response [79]. This is the reason why we investigate the control method of STEP 2'.

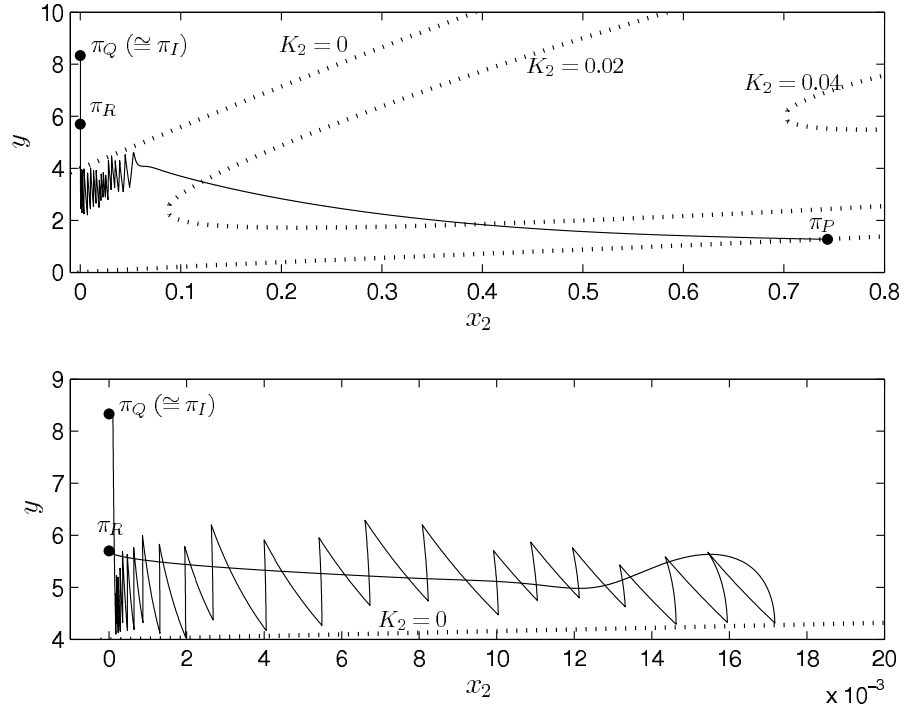


Figure 5.18: The (x_2, y) trajectories resulting from the proposed control strategies. In the top graph the (x_2, y) trajectory stays within the immune increasing region for $u = 0$, while we can see that the trajectory of the bottom graph stays outside the region. (Note the different scales.)

If we drive the state to Point R and again to Point P, then the emergence of HIV mutants against both x_1 and x_2 can be postponed as long as the state remains in the neighbourhood of Point R. This is because the level of x_2 is sufficiently low in the vicinity of Point R and the mutational escape of HIV from x_2 requires a certain level of x_2 [35]. Note that we deal with a model having three stable steady states, but the more complicated models with n steady-states in [4, 40] can be studied similarly.

2. To drive the patient status into the LTNP we can consider the GRDD scheduling scheme, introduced in Chapter 4. We have applied the GRDD scheme to model (5.17)-(5.20) with the initial state in Table 5.5. Figure 5.19 shows the result. We see that the state is successfully driven to the LTNP status, Point P. However the current scheme of GRDD cannot drive the state towards Point R.

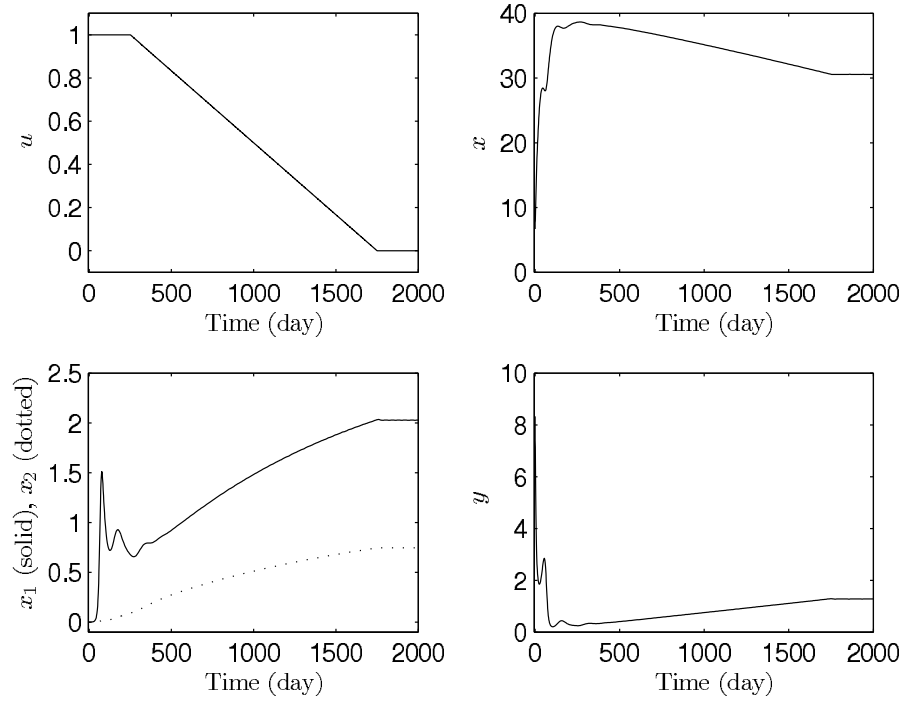


Figure 5.19: Result of GRDD application to model (5.17)-(5.20).

5.5 Conclusion

We have provided a unified control methodology for drug scheduling for disease dynamics and have shown its applicability, by means of computer simulations, for different disease models. The method relies on the intuitive idea that the control action has to boost the immune system and it is based on a simple graphical analysis of the immune system model. Our model-based study suggests that applying the proposed treatment in the real world could lead to an immune control of HIV if the model is close to the actual immune mechanism. Note that the proposed scheme serves as a guideline of drug planning rather than a ready-to-use clinical treatment.

The control method is appropriate for HIV/AIDS cases. Figure 5.20 shows the situation in HIV/AIDS treatment. The HIV antiviral drug produces an effect on the levels of uninfected and infected HIV target cells. HIV target cells are key component of the human immune system, and the dynamics of the immune system are related with the populations of uninfected and infected HIV target cells. Therefore we can control the drug dosage in order to maximize the action of the immune system in HIV/AIDS models via the levels of uninfected and infected HIV target cells.

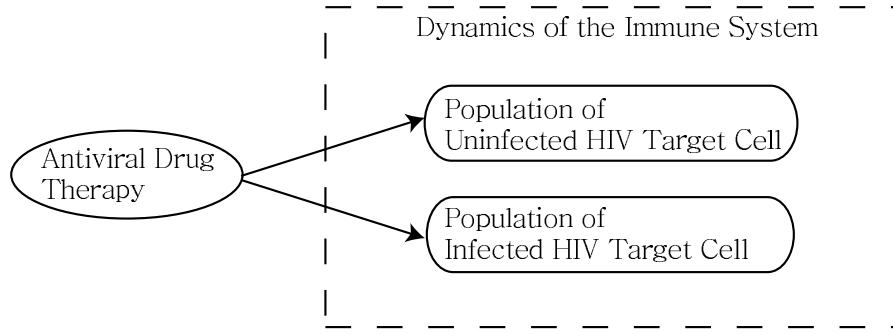


Figure 5.20: The relations between drug input, HIV target cell, and the immune system dynamics in HIV/AIDS treatment.

The results in this chapter are published in [21], [16], [19], and [18]. In conclusion we comment on further ideas which may be considered to advance the present results.

1. The simulations in Section 5.1 and Section 5.3 initiate drug therapy on the second and the fifth day, respectively, because no medication increases the immune response faster than full medication in the beginning of the treatment. In the simulation of Section 5.2 the medication initiates on the third day because we must wait the patient state to enter the immune increasing region. The long delay of treatment initiation in [47], where the medication initiates at ninth year, is due to the maximization of the efficacy of drug dose. For the problem of the decision of therapy initiation, a theoretic controllability analysis is given in [41].
2. The immune system's models in this chapter have different properties. For example, Figure 5.1 and Figure 5.8 show different shapes of the immune increasing regions in the plane identified by the levels of uninfected and infected HIV target cell. The boundary in Figure 5.1 is a curved line, whereas that in Figure 5.8 is composed of two straight lines. Accordingly the control results are not comparable because the control steps are dependent on the immune increasing region, hence on the model of the immune system.
3. In this chapter we use a constant T_s . However, a variable T_s can be used to enhance further the immune system. For example, if we use a sufficiently small T_s in Section 5.1, the (x, y) trajectory in Figure 5.3 would show smaller swings. In the meanwhile we can divide the HIV therapy into two stages, first we make the patient state enter the immune increasing region and then enhance the immune system as

much as possible in the second stage. In this case we can use a comparatively large constant T_s in the first stage and a variable T_s in the second stage.

Chapter 6

Output feedback control in HIV dynamics

The motivation of the research in this chapter comes from the drug scheduling methodology for HIV patients in Chapter 5. The main idea, which stems from a simple graphical analysis, has been conceptually introduced in Chapter 5, and in turn leads to the design of a feedback control strategy in this chapter. In this chapter we justify the idea from a mathematical perspective and provide some formal properties of the resulting controlled system. The works in this chapter are included in [23] and [18].

6.1 Description of output feedback control

Consider model (2.1)-(2.5) of Section 2.1.1, which is also discussed in Chapter 3 and Section 5.1, namely

$$\dot{x} = \lambda - dx - \eta\beta xy, \quad (6.1)$$

$$\dot{y} = \eta\beta xy - ay - p_1 z_1 y - p_2 z_2 y, \quad (6.2)$$

$$\dot{z}_1 = c_1 z_1 y - b_1 z_1, \quad (6.3)$$

$$\dot{w} = c_2 xyw - c_2 qyw - b_2 w, \quad (6.4)$$

$$\dot{z}_2 = c_2 qyw - h z_2. \quad (6.5)$$

In this chapter we use the same system parameters of Chapter 3 and Section 5.1 as nominal parameters (see Table 3.2). The model (6.1)-(6.5) has five equilibrium points,

three of which are recalled from Table 3.1, for convenience:

Point A:

$$x^{(A)} = \frac{\lambda}{d}, \quad y^{(A)} = 0, \quad z_1^{(A)} = 0, \quad w^{(A)} = 0, \quad z_2^{(A)} = 0;$$

Point C:

$$x^{(C)} = \frac{\lambda c_1}{dc_1 + b_1 \eta \beta}, \quad y^{(C)} = \frac{b_1}{c_1}, \quad z_1^{(C)} = \frac{\eta \beta x^{(C)} - a}{p_1}, \quad w^{(C)} = 0, \quad z_2^{(C)} = 0;$$

Point E:

$$y^{(E)} = \frac{\theta(\eta) - \sqrt{\theta(\eta)^2 - 4\eta\beta c_2 q d b_2}}{2\eta\beta c_2 q}, \quad x^{(E)} = \frac{\lambda}{d + \eta\beta y^{(E)}},$$

$$z_1^{(E)} = 0, \quad w^{(E)} = \frac{h z_2^{(E)}}{c_2 q y^{(E)}}, \quad z_2^{(E)} = \frac{y^{(E)}(c_2 \eta \beta q - c_2 a) + b_2 \eta \beta}{c_2 p_2 y^{(E)}};$$

where $\theta(\eta) = c_2(\lambda - dq) - b_2 \eta \beta$.

The initial point for the simulations in this chapter is identical to the initial point of Section 5.1, that is, $x(0) = 10$, $y(0) = 0.01$, $z_1(0) = 0.01$, $w(0) = 0.01$, and $z_2(0) = 0.01$ (see Table 5.2) unless it is explicitly indicated. From the discussion in Section 3.2, we can regard model (6.1)-(6.5) as the interconnection of two subsystems: the infection dynamics and the immune system. The infection dynamics are described by equations (6.1) and (6.2) and the immune system is described by equations (6.3)-(6.5). The goal of the control is to enhance immunity. Then we must increase w by controlled medication scheduling as discussed in Section 5.1, and we recall that equation (6.4) can be written as $\dot{w} = K(x, y)w$, where $K(x, y) = c_2 xy - c_2 qy - b_2$. Thus we can control the growth of w , indirectly, via the input u . For some geometric properties of the function $K(x, y)$ for the given parameters see Figure 5.1 in Section 5.1.

In this section we propose a control strategy that requires only partial state information. The states x and y are considered as output of the infection dynamics and input of the immune system. These states are also regarded as the measured¹ output of the model (6.1)-(6.5). Thus the output feedback controller uses the states x and y as controller input. A schematic diagram of the closed loop system is depicted in Figure

¹The states x and y are measurable with experimental environment as discussed in Section 2.2. In addition these states can be theoretically observed using Riccati equation-based estimator [10].

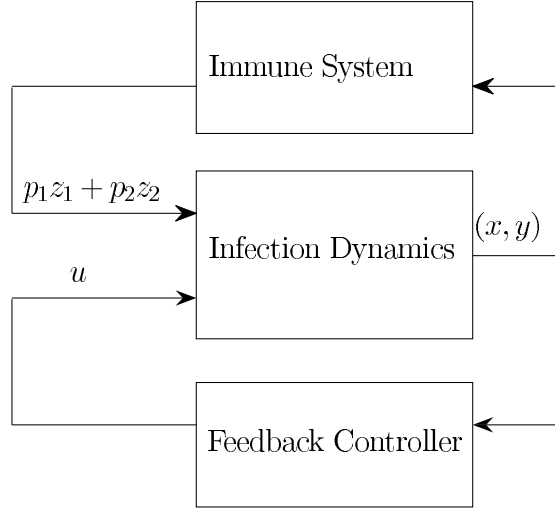


Figure 6.1: Diagram describing the interconnections of the infection dynamics, the immune system, and the controller.

6.1 and the control procedure is described in the following steps².

Initialization: Select a positive number T_i . T_i denotes the period of full medication preceding the application of the proposed control law and driving the state to Point A. Let $L_1 = L_1(x, y) = y - y_\kappa$ and $L_2 = L_2(x, y) = y - (x - q)$ where³ $y^{(E)} < y_\kappa \leq y^{(C)}$. X_I is the initial condition of model (6.1)-(6.5).

STEP 1: (Preliminary Control Action)

Apply $u = 1$ for T_i time instants.

STEP 2: (The Control Law)

If $L_1 < 0$ and $L_2 < 0$, then $u = 0$. Otherwise, $u = 1$ ⁴.

The preliminary control action is justified by the discussion in Section 5.5. The control law in STEP 2 corresponds to the control procedure of Section 5.1 for a sufficiently small T_s and a different immune increasing region given by the conditions $L_1 < 0$ and $L_2 < 0$.

Figure 6.2 shows the results of the application of the feedback control procedure with $y_\kappa = b_1/c_1$. In the simulation STEP 1 is unnecessary since the initial point $(x(0),$

²This control procedure stems from the discussion in Section 5.5.

³The property $y^{(E)} < y^{(C)}$ will be proven in Lemma 3.

⁴Note that the output feedback is only used to decide the timing of u , not the magnitude of the u .

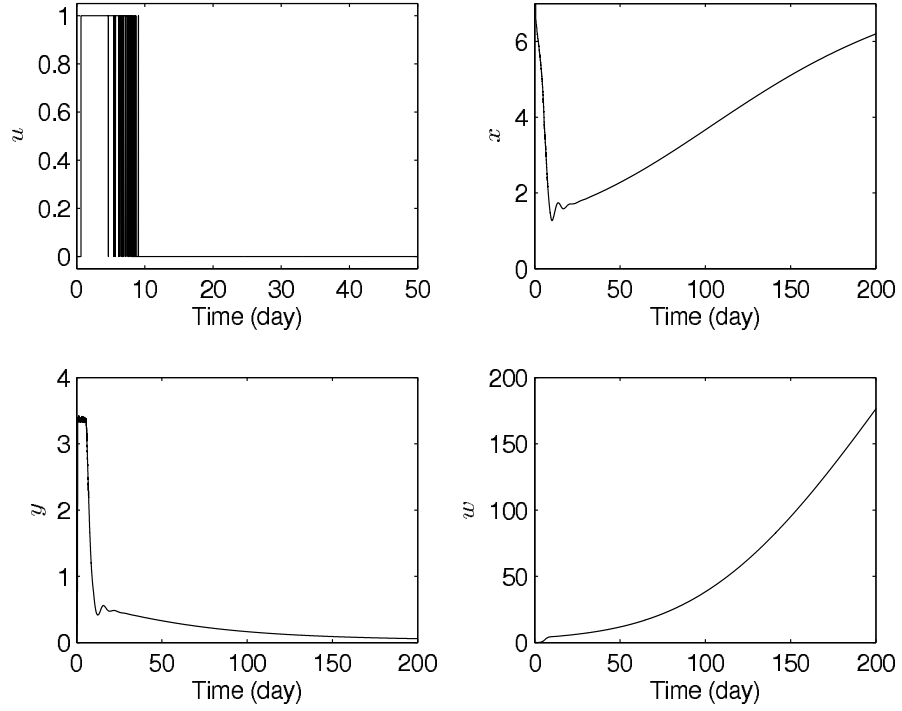


Figure 6.2: Results of the application of the output feedback control scheme to model (6.1)-(6.5) with $y_\kappa = b_1/c_1$. The unit of x and y is (100copies/ μ l). Note the different time scales.

$y(0), z_1(0), w(0), z_2(0)) = (10, 0.01, 0.01, 0.01, 0.01)$ is sufficiently close to Point A. The control input becomes eventually zero and the patient state converges to the LTNP status, i.e., to Point E. The resulting (x, y) trajectory is displayed in Figure 6.3, which shows that the (x, y) trajectory stays within the set defined by $L_1 < 0$ and $L_2 < 0$.

Note that the virus level (i.e., y) is restricted by the condition $L_1 < 0$. This condition prevents the state from progressing towards Point C. On the other hand the condition $L_2 < 0$ renders the increase of w *locally optimised*, see Subsection 6.2.5 for additional discussion.

6.1.1 Examples of applications of the output feedback control

In this subsection we discuss further examples of applications of the output feedback control, which will be discussed in Chapter 7. Particularly the initial point used in these examples is identical to one of those used in [83], as indicated in Table 6.1. This point is in the vicinity of Point A, which represents a newly infected patient.

Now we consider the *trapezoidal* set $\tau(y_\kappa)$ defined by the inequalities $y > 0, y < x - q$,

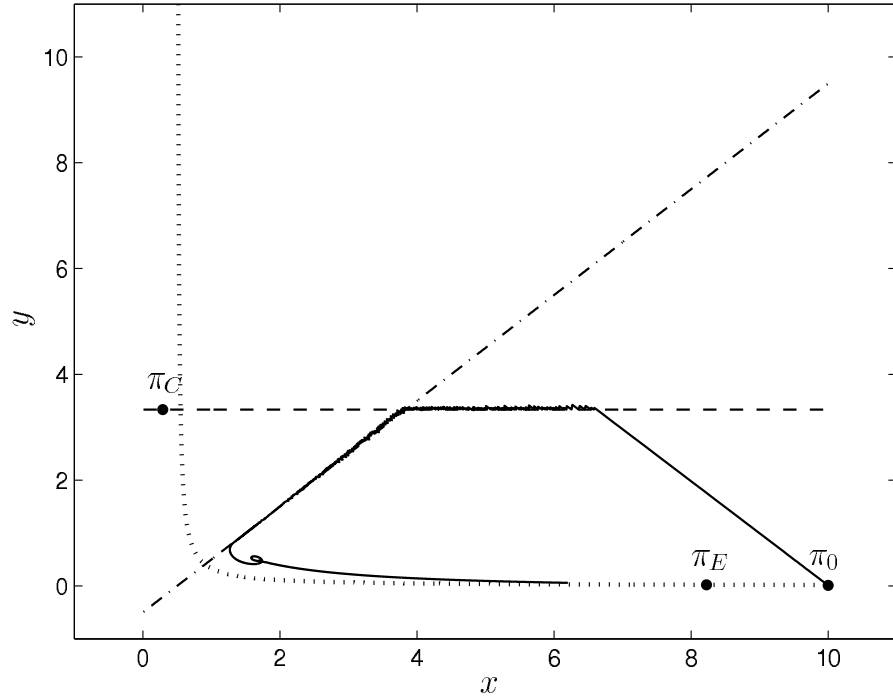


Figure 6.3: The (x, y) trajectory resulting from the output feedback control strategy. The dotted line and the solid line indicate the set $K(x, y) = 0$ and the (x, y) trajectory, respectively. The dashed line and the dash-dotted line represent the sets $L_1 = 0$ with $y_\kappa = b_1/c_1$ and $L_2 = 0$, respectively.

$x + y < \frac{\lambda}{d} + \epsilon$, and $y < y_\kappa$, where ϵ is any small positive number. The conditions $y^{(E)} < y_\kappa \leq y^{(C)}$ in the Initialization step guarantee that Point E and Point C are located inside and outside the set $\tau(y_\kappa)$, respectively.

$x(0)$	$y(0)$	$z_1(0)$	$w(0)$	$z_2(0)$
10	0.1	0.1	0.1	0.1

Table 6.1: Initial condition for model (6.1)-(6.5). This initial condition is given in [83].

Figure 6.4 shows the results of the application of the output feedback control with $y_\kappa = 0.5$ and $T_i = 20$. In STEP 1 the state moves sufficiently close to Point A and enters the set τ . The control input becomes eventually zero and the patient state converges to the LTNP status, i.e., to Point E. The top graph in Figure 6.4 shows that the (x, y) trajectory stays within the set τ , which is the area enclosed by the dotted line.

Figure 6.5 shows the result of the same control scheme applied using a sample-and-

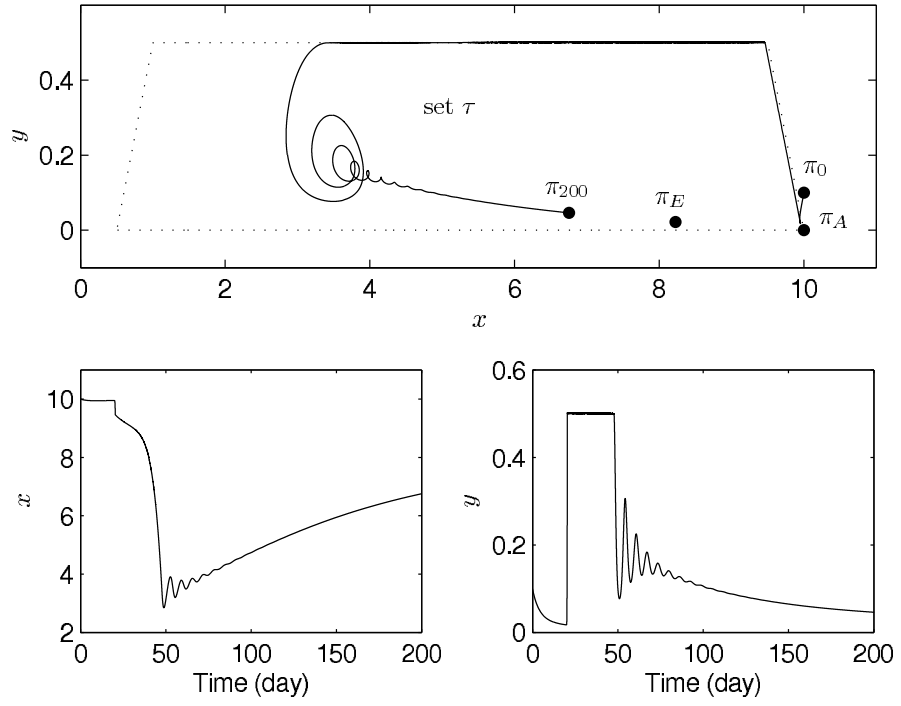


Figure 6.4: Results of the application of the control procedure of Section 6.1 to model (6.1)-(6.5).

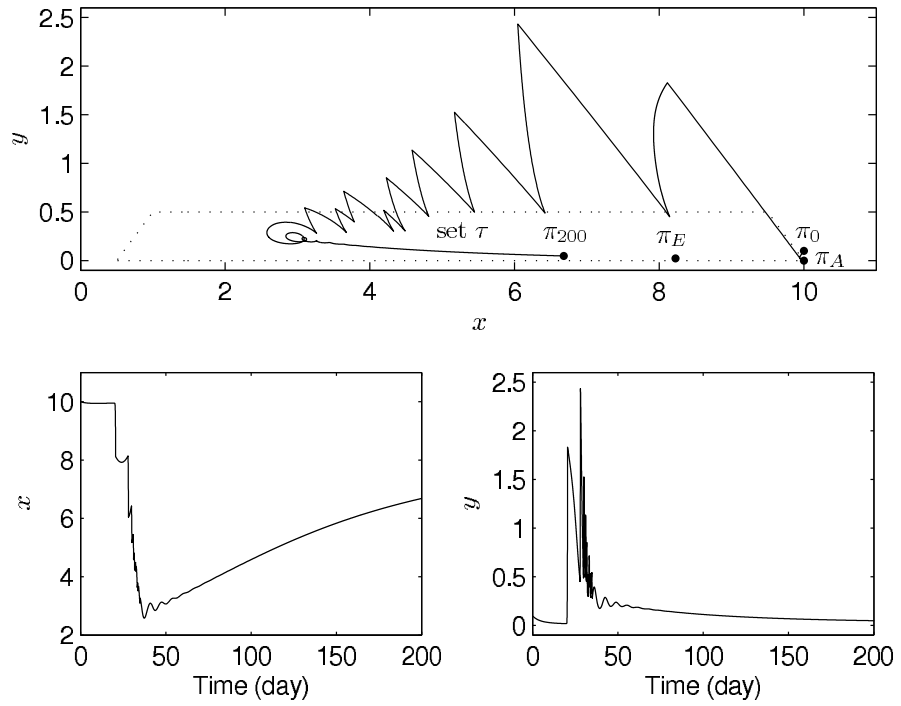


Figure 6.5: Results of the application of the control procedure of Section 6.1 with a sample-and-hold device of fixed sampling period. The sample period is 0.25 (day).

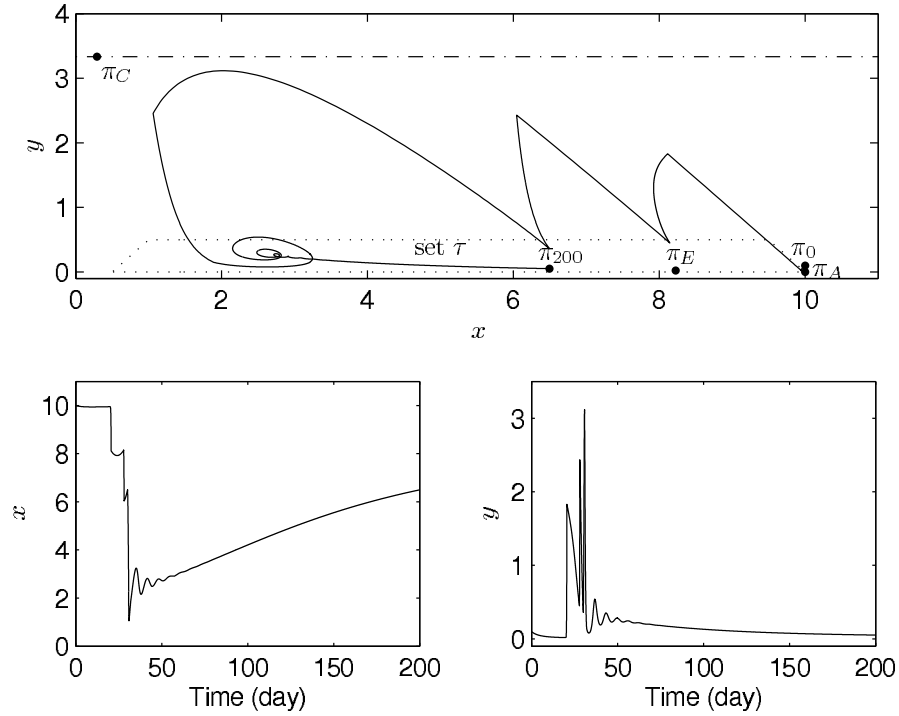


Figure 6.6: Results of the application of the control procedure of Section 6.1 with a sample-and-hold device with non constant sampling period. We assign 0.25 (day) sampling period in the interval $[20, 28)$, 1 (day) in the interval $[28, 35)$, and 7 (day) in the interval $[35, 200]$. In the top graph π_C corresponds to the projection into the (x, y) plane of Point C, and the dash-dotted line indicates the set $y = y^{(C)} = b_1/c_1$.

hold device. The sample period T_h is 0.25 (day). A sufficiently small T_h ⁵ guarantees that the (x, y) trajectory is such that $y(t) < \frac{b_1}{c_1}$ with $y_\kappa \leq \frac{b_1}{c_1}$ because the control method forces the state to stay inside the set τ (this fact will be proven in Subsection 6.2.3).

In clinical terms, the control example in Figure 6.5 implies four HIV measurements in a day, which means the patient's blood must be sampled every 6 hours. This is hard to achieve practically. However this frequent sampling is not needed in all the time interval $[20, 200]$. In other words we need a 0.25 (day) sampling period only for the first few days in order for the HIV patient to be driven into the region of attraction of the LTNP. For example, if we assign 0.25 (day) sampling period in the interval $[20, 28)$, 1 (day) in

⁵This T_h does not have the same meaning of the T_s in Section 5.1. In this section the control decision is made at the current moment and the decision is held for T_h , while in Section 5.1 the control decision is made by predicting in T_s . Nonetheless, the resulting control actions are essentially the same because these methods force the state to stay inside the set τ .

the interval $[28, 35)$, and 7 (day) in the interval $[35, 200]$, then the immune system of the patient is boosted enough to be in the region of attraction of LTNP. This result is presented in Figure 6.6.

6.2 Analysis of the controlled HIV model

6.2.1 Basic analysis of the HIV model

Let $X := [x, y, z_1, w, z_2]^T$ and let $\mathcal{U}$ denote the set of measurable functions with values in the set $[0, 1]$. Note that the input $\eta(\cdot)$ of interest belongs to $\mathcal{U}$. Finally let $\mathcal{P} = [0, \infty)^5$.

Assumption 3 *The parameters of the model (6.1)-(6.5) are positive and such that*

$$d < a, \tag{6.6}$$

$$\beta > \frac{a}{q}, \tag{6.7}$$

$$\lambda > aq, \tag{6.8}$$

$$\frac{b_1}{c_1} > \max \left\{ \frac{\lambda}{2\beta q}, \frac{1}{2} \left(\frac{\lambda}{a} - q \right) \right\}, \tag{6.9}$$

$$\frac{b_2}{c_2} < \min \left\{ \frac{(\sqrt{\lambda} - \sqrt{dq})^2}{\beta}, \frac{1}{4} \left(\frac{\lambda}{a} - q \right)^2, \left(\frac{a-d}{\beta} \right)^2 \right\}, \tag{6.10}$$

$$(1 - \epsilon^*)\beta < \min \left\{ \frac{ad}{\lambda}, \frac{(a-d)c_1}{2b_1} \right\}. \tag{6.11}$$

Although Assumption 3 is technically designed to subsequent analysis of this chapter and the model parameters are normalized so the state variables do not represent actual data, Assumption 3 can be justified by previous works in the literature on HIV dynamics such as [54, 75, 83], as seen in what follows.

Inequality (6.6) implies that the decay rate of the uninfected cells is smaller than that of the infected cells [54]. Inequality (6.7) gives a lower-bound for β . If the rate of viral replication β is below a threshold, then an effective CTL response is always established [75]. Hence, for very small β , the LTNP status is automatically achieved, and the patient needs not be treated. However this is apparently not the case for most AIDS patients. A quantitative lower-bound for β is not provided in [75]: the condition (6.7) could be regarded as such a bound.

Inequality (6.8) requires that the differentiation of CTL precursor into helper-dependent CTL occurs slowly. Combining (6.8) with (6.6) we obtain $\lambda > dq$, which is essential for

the existence of the LTNP equilibrium. To see this, suppose that $q \geq \frac{\lambda}{d}$. Then, because $x \leq \frac{\lambda}{d} + \epsilon$ after a certain time (see the proof of Theorem 5), it follows from (6.4) that

$$\dot{w} \leq c_2\left(\frac{\lambda}{d}\right)yw - c_2qyw - b_2w \leq -b_2w < 0,$$

for $w \neq 0$, which implies the extinction of CTL precursors and no treatment can induce the drug-free immune control of HIV.

In (6.9), b_1/c_1 is assumed to be lower-bounded. Note that $y^{(C)} = b_1/c_1$, i.e., the y level of the status of AIDS. Thus (6.9) implies that the disease status is seriously fatal to the human body, which is consistent with the current outbreak of AIDS.

Regarding inequality (6.10), it is noted that if the immune responsiveness c_2 lies below a threshold, treatment cannot result in the establishment of CTL memory [75]. While any formula for such a threshold is not presented in [75], the condition (6.10) might be understood as a possible lower bound for the immune responsiveness.

Inequality (6.11) means that highly effective drug treatment is available for HIV patients. In the thesis we do not consider the drug-resistant case associated to HIV evolution and we suppose that the virus level of the patient can be suppressed by drug treatment. Inequality (6.11) requires a strongly effective drug and the mathematical analysis in this chapter is based on this assumption. Note that the value of ϵ^* from [83] is such that inequality (6.11) does not hold. This value of ϵ^* is nevertheless used in simulations to highlight the robustness of the proposed methodology.

Lemma 2 *Consider the model (6.1)-(6.5). Suppose Assumption 3 holds. Then $y^{(E)}$ is well-defined and positive for $u = 0$.*

Proof: If $u = 0$, then $\eta = 1$ and

$$y^{(E)} = \frac{\theta(1) - \sqrt{\theta(1)^2 - 4\beta c_2 q d b_2}}{2\beta c_2 q},$$

where $\theta(\eta) = c_2(\lambda - dq) - b_2\eta\beta$. From (6.6), (6.10), and (6.8), $\theta(1)$ and $\theta(1)^2 - 4\beta c_2 q d b_2$ are positive. Also $\theta(1) - \sqrt{\theta(1)^2 - 4\beta c_2 q d b_2} > 0$ because all parameters are positive. Thus $y^{(E)}$ is well-defined and positive for $u = 0$. $\square$

Lemma 3 *Consider the model (6.1)-(6.5). Suppose Assumption 3 holds. Then $y^{(E)} < y^{(C)}$ for $u = 0$.*

Proof: From (6.9),

$$y^{(C)} = \frac{b_1}{c_1} > \frac{\lambda}{2\beta q} = \frac{c_2\lambda}{2\beta c_2 q} > \frac{\theta(1)}{2\beta c_2 q} > \frac{\theta(1) - \sqrt{\theta(1)^2 - 4\beta c_2 q d b_2}}{2\beta c_2 q} = y^{(E)},$$

where, as above, $\theta(\eta) = c_2(\lambda - dq) - b_2\eta\beta$. $\square$

Theorem 5 *Consider the model (6.1)-(6.5). Suppose Assumption 3 holds and $u(t) = 1$ for all $t \geq 0$. Then all trajectories with initial condition $X(0) \in \mathcal{P}$ converge to Point A.*

Proof: Let $V(t) = x(t) + y(t)$. By (6.6), $\dot{V}(t) = \lambda - dx - ay - p_1 z_1 y - p_2 z_2 y \leq \lambda - d(x + y) = \lambda - dV(t)$, which holds for all $t \geq 0$ due to the positive invariance of $\mathcal{P}$. Then $[0, \frac{\lambda}{d}]$ is an attractive region for $V(t)$. This implies that $\limsup_{t \rightarrow \infty} V(t) \leq \frac{\lambda}{d}$, which in turn implies that $x(t) \leq \frac{\lambda}{d} + \epsilon$ for all $\epsilon > 0$ and for all $t \geq t_\epsilon$ for some $t_\epsilon > 0$ (because $x(t)$ and $y(t)$ are both positive). Then equation (6.2) becomes

$$\dot{y} = y((1 - \epsilon^*)\beta x - a - p_1 z_1 - p_2 z_2) \leq -\delta y,$$

for some δ , which is positive by equation (6.11). Hence, it follows that $y(t)$ converges to zero. Since $y(t)$ goes to zero, $x(t)$ converges to λ/d by (6.1). Then all other states (z_1 , w , and z_2) go to zero by equations (6.3)-(6.5). $\square$

6.2.2 Properties of the immune increasing factor K

Now recall that $K(x, y)$, defined as $K(x, y) = c_2 xy - c_2 qy - b_2$, denotes the immune increasing factor and that the set $K(x, y) \geq 0$ of the (x, y) positive orthant denotes the immune increasing region (see Subsection 5.1.1). Note that $K(x^{(A)}, y^{(A)}) = -b_2 < 0$.

By Theorem 5, if $u(t) = 1$ the state of model (6.1)-(6.5) converges to Point A. Therefore, by continuity of $K(x, y)$ with respect to x and y , there is a finite time T such that $K(x(T), y(T)) < 0$ and the state of the system is in a neighbourhood of Point A.

Consider an initial condition close to Point A and described by $X_\delta = (\frac{\lambda}{d} - \delta_1, \delta_2, \delta_3, \delta_4, \delta_5)$. By the proof of Theorem 5, $\delta_1, \delta_2, \delta_3, \delta_4$, and δ_5 are positive and sufficiently small. Note, in addition, that

$$\dot{K} = c_2 y [\eta \beta x (x - q - y) + \lambda - dx - (x - q)(a + p_1 z_1 + p_2 z_2)]. \quad (6.12)$$

Then $\frac{\dot{K}(X_\delta)}{c_2\delta_2}$ for $u = 0$ is given by

$$\begin{aligned} & \beta \left(\frac{\lambda}{d} - \delta_1 \right) \left(\frac{\lambda}{d} - \delta_1 - q - \delta_2 \right) + \lambda - d \left(\frac{\lambda}{d} - \delta_1 \right) - \left(\frac{\lambda}{d} - \delta_1 - q \right) (a + p_1\delta_3 + p_2\delta_5) > \\ & \beta \left(\frac{\lambda}{d} - \delta_1 \right) \left(\frac{\lambda}{d} - \delta_1 - q - \delta_2 \right) - \left(\frac{\lambda}{d} - \delta_1 - q \right) (a + p_1\delta_3 + p_2\delta_5) > \\ & \left(\frac{\lambda}{d} - q - \delta_1 \right) \left(\beta \frac{\lambda}{d} - a - \beta\delta_1 - p_1\delta_3 - p_2\delta_5 \right) - \beta \frac{\lambda}{d} \delta_2. \end{aligned}$$

Since, by equations (6.6), (6.7), and (6.8), $(\frac{\lambda}{d} - q)$ and $(\beta \frac{\lambda}{d} - a)$ are positive then $\dot{K}(X_\delta) > 0$ for $u = 0$ and $\delta_1, \delta_2, \delta_3, \delta_4$ and δ_5 sufficiently small.

Using the above facts we provide some properties of model (6.1)-(6.5).

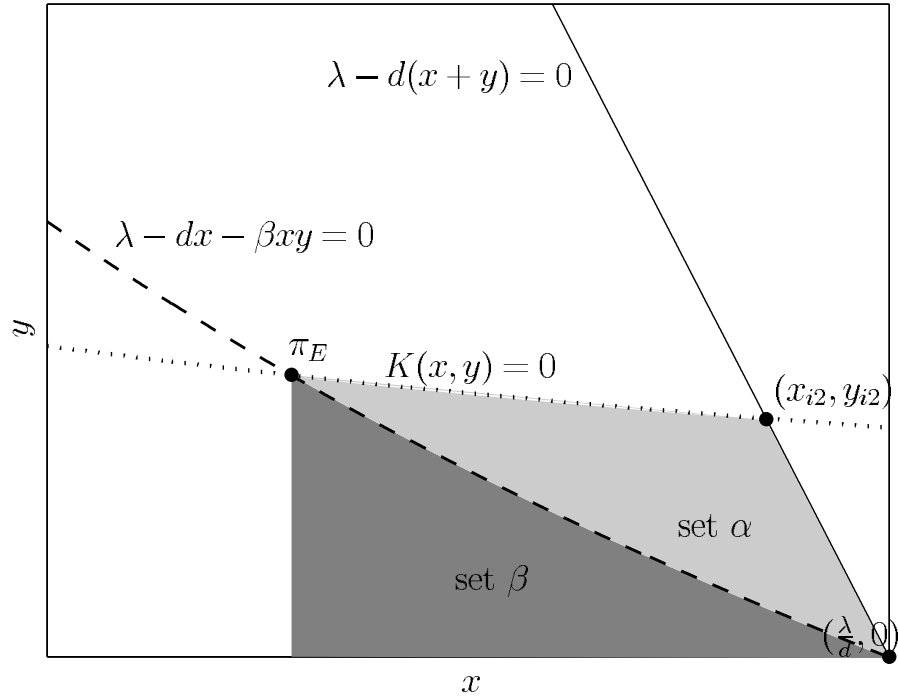


Figure 6.7: The curves $K(x, y) = c_2xy - c_2qy - b_2 = 0$ (dotted), $\dot{x} = \lambda - dx - \beta xy = 0$ (dashed), and $\lambda - dV = 0$ (solid), where $V = x + y$. The points (x_{i2}, y_{i2}) is defined as the intersection of $K = 0$ and $\lambda - dV = 0$ in the (x, y) plane.

Proposition 1 Consider the model (6.1)-(6.5) and a state $X(0) \in \mathcal{P}$ which is sufficiently close to Point A with $x(0) + y(0) \leq \frac{\lambda}{d}$. Suppose $u(t) = 0$ for $t \geq 0$, and let $X(t)$ be the corresponding trajectory. Then there exists $T > 0$ such that $X(T)$ belongs to the immune increasing region.

Proof: As in the proof of Theorem 5, let $V(t) = x(t) + y(t)$. Then $V(t) \leq \lambda/d$ for all $t \geq 0$ because we assume $x(0) + y(0) \leq \lambda/d$ (see the proof of Theorem 5). Consider now the set α and the set β , as depicted in Figure 6.7. Note that the x component is not less than $x^{(E)}$ and the y component is not greater than $y^{(E)}$ for any point in the set $\alpha \cup \beta$. Moreover, by assumption, the point $(x(0), y(0))$ is located in the set $\alpha \cup \beta$, and $z_1(0)$, $w(0)$ and $z_2(0)$ are sufficiently small.

Since $y^{(E)} < y^{(C)} = \frac{b_1}{c_1}$, $\dot{z}_1 < 0$ in the set $\alpha \cup \beta$, which implies that $z_1(t)$ goes to zero as long as the point (x, y) stays within the set $\alpha \cup \beta$. In addition $z_2(t)$ goes to zero as long as the point (x, y) stays within the set $\alpha \cup \beta$, since $\dot{w} < 0$ in the set $\alpha \cup \beta$. Now, in the set $\alpha \cup \beta$,

$$\dot{y} = y(\beta x - a - p_1 z_1 - p_2 z_2) \geq \delta y,$$

for some positive δ , since $x(t) > x^{(E)} > q > a/\beta$ in the set $\alpha \cup \beta$ by (6.7) (also see Figure 6.8).

For all $(x, y) \in \beta$, $\dot{x} > 0$ and $\dot{y} \geq \delta y$. Hence for any $(x(0), y(0)) \in \beta$, $(x(T_\beta), y(T_\beta))$ enters the set α in a finite time $T_\beta > 0$.

For all $(x, y) \in \alpha$, $\dot{x} < 0$ and $\dot{y} \geq \delta y$. Hence for any $(x(0), y(0)) \in \alpha$, $(x(T_\alpha), y(T_\alpha))$ enters the immune increasing region (the upper region of the set $K(x, y) = 0$) in a finite time $T_\alpha > 0$. Note that the point (x, y) in the set α cannot enter the set β because $\dot{y} \geq \delta y > 0$ on the set $\dot{x} = 0$ which is the boundary between the set α and the set β (part of the dashed line in Figure 6.7).

Hence the point (x, y) enters the immune increasing region in finite time. Moreover the point penetrates into the immune increasing region passing through $K(x, y) = 0$, $x \in (x^{(E)}, x_{i2})$. $\square$

Proposition 2 *Consider the model (6.1)-(6.5) and a state $X = (x, y, z_1, w, z_2)$. Assume there exists u such that*

$$x(x - q - y)\eta\beta + \lambda - dx \geq (x - q)(a + p_1 z_1 + p_2 z_2). \quad (6.13)$$

Then there is an input u which renders $\dot{K}(x, y)$ non-negative.

Proof: At the point (x, y) , we have, by (6.12),

$$\dot{K}(x, y) = c_2 y (\eta \beta x (x - q - y) + \lambda - dx - (x - q)(a + p_1 z_1 + p_2 z_2)).$$

Note now that c_2 and y are positive. Then, in order to render $\dot{K}(x, y)$ non-negative, we need

$$\eta\beta x(x - q - y) + \lambda - dx - (x - q)(a + p_1 z_1 + p_2 z_2) \geq 0.$$

Thus, if there is a value of u that renders inequality (6.13) true, then $\dot{K}(x, y)$ can be rendered non-negative. $\square$

The first term on the left-hand side of inequality (6.13) includes the input u via the term η , which is multiplied by $x(x - q - y)\beta$. Therefore, to maximise the left-hand side, u can be selected as

$$u = \begin{cases} 1, & \text{if } y > x - q, \\ 0, & \text{if } y < x - q. \end{cases} \quad (6.14)$$

Note that by equation (6.14), u is chosen to render $\dot{K} \geq 0$ whenever this is possible. However (6.14) locally maximises $\dot{w}$, as will be discussed in Subsection 6.2.5.

Proposition 2 is interpreted as follows. In the (x, y) plane, consider a state (x^*, y^*) . At this state, $K = c_2 x^* y^* - c_2 q y^* - b_2 = K^*$. The equation of the line $K = K^*$ in the plane is

$$y = \frac{K^* + b_2}{c_2} \frac{1}{x - q}.$$

Then the gradient of the line is

$$\frac{dy}{dx} = -\frac{K^* + b_2}{c_2} \frac{1}{(x - q)^2}.$$

The gradient of the line at the point (x^*, y^*) is

$$\begin{aligned} \frac{dy}{dx}(x^*, y^*) &= -\frac{(c_2 x^* y^* - c_2 q y^* - b_2) + b_2}{c_2} \frac{1}{(x^* - q)^2} \\ &= -y^*(x^* - q) \frac{1}{(x^* - q)^2} \\ &= -\frac{y^*}{x^* - q}. \end{aligned}$$

At the point (x^*, y^*) , the time derivatives of the states x and y from (6.1) and (6.2) are

$$\begin{aligned} V_x &:= \frac{dx}{dt}(x^*, y^*) = \lambda - dx^* - \eta\beta x^* y^*, \\ V_y &:= \frac{dy}{dt}(x^*, y^*) = (\eta\beta x^* - a - p_1 z_1^* - p_2 z_2^*) y^*. \end{aligned}$$

The state can be driven into the area $K \geq K^*$ if and only if

$$\begin{aligned} V_y &\geq -\frac{y^*}{x^* - q} V_x \\ \Leftrightarrow x^* \left(1 - \frac{y^*}{x^* - q} \right) \eta\beta + \frac{\lambda - dx^*}{x^* - q} - a &\geq p_1 z_1^* + p_2 z_2^*. \end{aligned}$$

Therefore, if there is a value of u that renders inequality (6.13) true with the selection (6.14), then the state can be driven to the area $K \geq K^*$ instantaneously.

6.2.3 The enhanced level of the immune system

Consider the set $\tau(y_\kappa)$ defined in Subsection 6.1.1 by the inequalities $y > 0$, $y < x - q$, $x + y < \frac{\lambda}{d} + \epsilon$, and $y < y_\kappa$, where ϵ is any small positive number. Assume⁶ $y_\kappa = y^{(C)} = b_1/c_1$ (Figure 6.8 depicts the set $\tau(y_\kappa)$, with $y_\kappa = b_1/c_1$).

Proposition 3 *Consider the model (6.1)-(6.5) with the input u selected as in STEP 1 of the output feedback control. Then all trajectories of the model enter the set $\tau(y_\kappa)$ in finite time.*

Proof: The state y is positive by Theorem 1. The state converges to Point A by Theorem 5 and also $x(t) + y(t) < \frac{\lambda}{d} + \epsilon$ for all $t \geq t_\epsilon$ for some $t_\epsilon > 0$, from the proof of Theorem 5, hence all trajectories of the model enter the set $\tau(y_\kappa)$ in finite time. $\square$

Proposition 4 *Consider the model (6.1)-(6.5) with the input u selected as in STEP 2 of the output feedback control. Then the set $\tau(y_\kappa)$ is positively invariant, i.e., all trajectories starting in $\tau(y_\kappa)$ remain in $\tau(y_\kappa)$ for all future time t .*

Proof: The state y is positive by Theorem 1, and also $x(t) + y(t) < \frac{\lambda}{d} + \epsilon$ for all $t \geq t_\epsilon$ for some $t_\epsilon > 0$ from the proof of Theorem 5. By condition (6.11), $\dot{y} < 0$ if $u = 1$ for $X \in \mathcal{P}$, from the proof of Theorem 5. To conclude the proof, $\dot{x}$ must be greater than $\dot{y}$ on the set $\left\{ (x, y) \mid y = x - q, x \in [q, q + \frac{b_1}{c_1}] \right\}$. Note that if $\lambda - dx - \eta\beta xy > y(\eta\beta x - a)$ with $u = 1$, then $\dot{x} > \dot{y}$ on this set. The above condition rewrites as

$$\lambda - dx - (1 - \epsilon^*)\beta xy > (1 - \epsilon^*)\beta xy - ay$$

which is equivalent to

$$\lambda - aq > x[2(1 - \epsilon^*)\beta x + d - a - 2q(1 - \epsilon^*)\beta],$$

hence it is true because the left-hand term is positive by (6.8) and the right-hand term is negative by condition (6.11). Hence all trajectories starting in $\tau(y_\kappa)$ remain in $\tau(y_\kappa)$ for all future time t with the input u selected as in STEP 2. $\square$

⁶A different selection for y_κ will be discussed in Subsection 6.2.4.

Note that Proposition 4 implies $\lim_{t \rightarrow \infty} z_1(t) = 0$ by equation (6.3), and this property will be useful in Chapter 7. Propositions 3 and 4 imply that the feedback control guarantees that the state of the model (6.1)-(6.5), with the input as in STEPS 1 and 2, does not converge to Point C (i.e. to the AIDS status). The set $\tau(y_\kappa)$ contains points

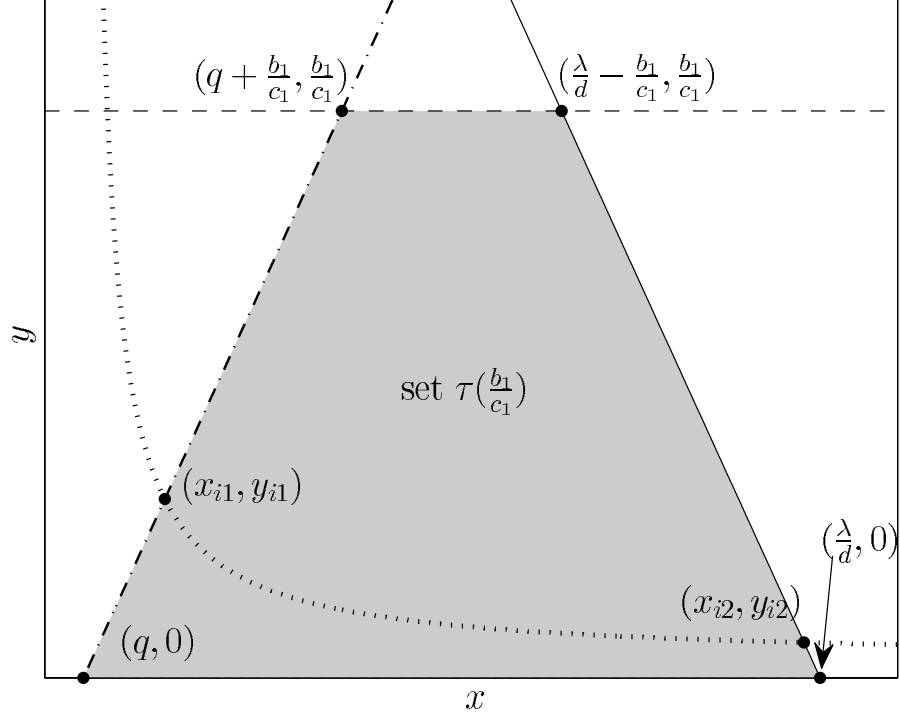


Figure 6.8: The trapezoidal set $\tau(y_\kappa)$ with $y_\kappa = y^{(C)} = \frac{b_1}{c_1}$ and $\epsilon = 0$. The dotted line and the dashed line indicate the sets $K(x, y) = 0$ and $y = y_\kappa$, respectively. The solid line and the dash-dotted line represent the sets $y + x = \frac{\lambda}{d}$ and $y = x - q$, respectively.

in which $K < 0$ (see Figure 6.8). At STEP 1 in the feedback method the state enters the set $K < 0$ in the set $\tau(y_\kappa)$, and at STEP 2 the state enters the set $K \geq 0$ in the set $\tau(y_\kappa)$. In the case of Figure 6.3 in Section 6.1, the states never returns to the set $K < 0$ in the set $\tau(y_\kappa)$. However, even if the state returns to the set $\tau(y_\kappa) \cap (K < 0)$, the feedback control method guarantees that the immune system (i.e., w and z_2) is boosted to a certain level, as discussed in the following statements.

Proposition 5 *Consider the model (6.1)-(6.5) with the input u selected as in STEP 2 after the preliminary control action in STEP 1. Suppose that the states $X = (x, y, z_1, w, z_2)$ is on the line $K(x, y) = 0$ at $t = T_1$ and T_2 and that $X(t)$ is in the set $K(x, y) < 0$, for $t \in [0, T_1)$, and $X(t)$ is in the set $K(x, y) > 0$ for $t \in (T_1, T_2)$. Assume that $\dot{K}$ is*

negative at $t = T_2$. Then $z_2(T_2) > z_{2m}(x(T_2))$ and $w(T_2) > w_m(x(T_2))$, where

$$z_{2m}(x) = \frac{1}{p_2} \left(x \left(1 - \frac{b_2}{c_2(x-q)^2} \right) \beta + \frac{\lambda - dx}{x-q} - a \right), \quad (6.15)$$

$$w_m(x) = \frac{hc_1}{c_2qb_1} z_{2m}(x). \quad (6.16)$$

Proof: Note that at $t = 0$, the state is sufficiently close to Point A by Theorem 5. From Proposition 2, at $t = T_2$,

$$x(T_2) \left(1 - \frac{y(T_2)}{x(T_2) - q} \right) \eta \beta + \frac{\lambda - dx(T_2)}{x(T_2) - q} - a < p_1 z_1(T_2) + p_2 z_2(T_2).$$

Moreover, by Proposition 4, $z_1(T_2)$ is negligible and $u = 0$ by the definition of the control law. Hence

$$z_2(T_2) > \frac{1}{p_2} \left(x(T_2) \left(1 - \frac{y(T_2)}{x(T_2) - q} \right) \beta + \frac{\lambda - dx(T_2)}{x(T_2) - q} - a \right).$$

By Proposition 4, for $0 \leq t \leq T_2$,

$$\dot{z}_2 = c_2 q y w - h z_2 < c_2 q \frac{b_1}{c_1} w - h z_2 \leq c_2 q \frac{b_1}{c_1} w_M - h z_2,$$

where w_M is the maximum of w in the time interval $0 \leq t \leq T_2$. Then $w_M = w(T_2)$ because $w(0)$ is sufficiently small and w monotonically increases to $w(T_2)$ in the interval $T_1 \leq t \leq T_2$ ⁷. By the comparison lemma (see [42, Lemma 3.4]), $z_2(T_2) < \frac{c_2 q b_1}{h c_1} w(T_2)$ since $z_2(0)$ is sufficiently small. Hence $z_2(T_2) > z_{2m}(x(T_2))$ and $w(T_2) > w_m(x(T_2))$. $\square$

To show that the level of immune system in Proposition 5 is enough for the states to be in the region of attraction of Point E for the model (6.1)-(6.5) with the given system parameters, we use computer simulations. In these simulations it is assumed that $z_1(0) = 0.0001$, $u = 0$ (note that the input is constant), $z_2(0) = z_{2m}(x(0))$, and $w(0) = \frac{hc_1}{c_2qb_1} z_2(0)$. We simulate with 50 pairs of initial points on the line $K(x(0), y(0)) = 0$ with $x(0)$ regularly spaced between x_{i3} and x_{i2} (see Figure 6.9)⁸.

The bottom graph of Figure 6.9 shows a zoomed-in version of the top graph. All considered initial states yield trajectories which converge to the LTNP state (π_E mark). The trajectory with $x(0) = x_{i3}$ is displayed with a dashed line in the top graph. This

⁷By the assumptions of Proposition 5, w_M is $w(0)$ or $w(T_2)$. If $w_M = w(0)$, then $z_2(T_2)$ goes to zero by (6.5). Hence $w_M = w(T_2)$ by contradiction.

⁸The point (x_{i3}, y_{i3}) is defined as the intersection of $y = x - q$ and $\lambda - dx - \beta xy = 0$. Note that $\dot{x} > 0$ regardless of u (either $u = 0$ or $u = 1$) in the region $\lambda - dx - \beta xy > 0$ in the set $\tau(y_\kappa)$. Therefore the state cannot reach $K(x, y) = 0$ for $x \in [x_{i1}, x_{i3}]$ in the set $\tau(y_\kappa)$.

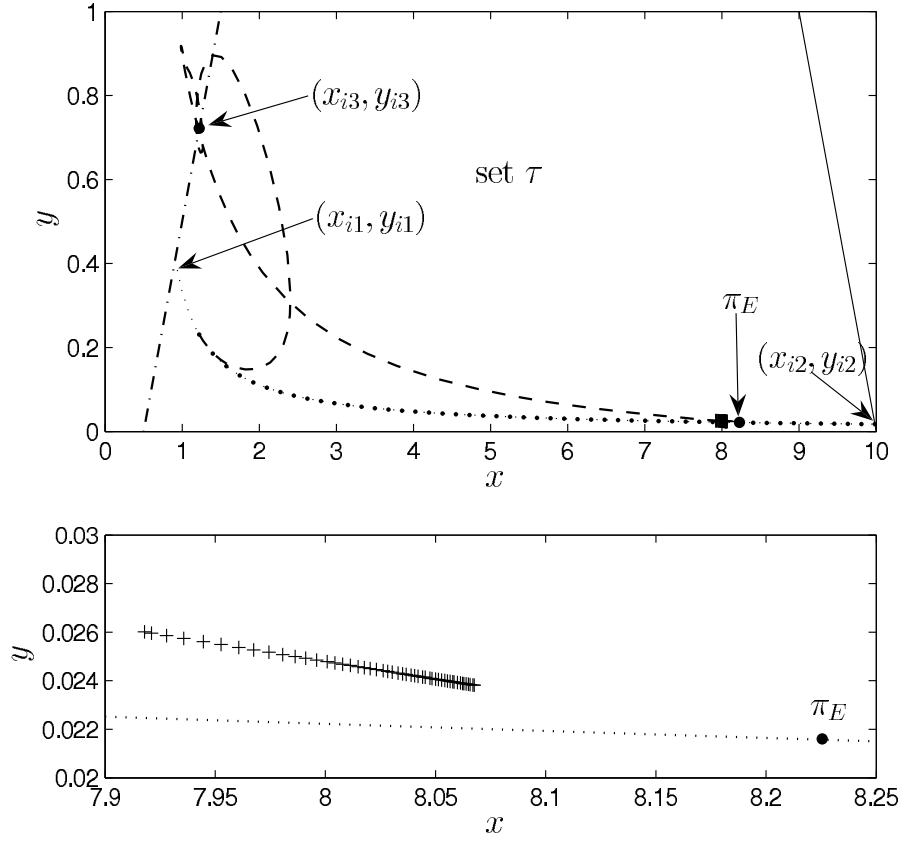


Figure 6.9: Simulations for 500 days with 50 initial points on the line $K(x, y) = 0$, ($x \in [x_{i3}, x_{i2}]$), the levels of $w(T_2)$ and $z_2(T_2)$ in Proposition 5, and the condition $u = 0$. (x_{i3}, y_{i3}) is the intersection of $y - (x - q) = 0$ and $\lambda - dx - \beta xy = 0$. The “.” and the “+” marks denote the projections on the (x, y) plane of the initial points and of the final points, respectively. The dashed line represents the (x, y) trajectory with the initial condition $x(0) = x_{i3}$ on the line $K(x, y) = 0$.

trajectory goes outside the set τ because we use a constant $u = 0$ instead of the output feedback controller in the simulation of Figure 6.9.

We now study if the (x, y) trajectory stays within the set $\tau(y_\kappa) \cap (K < 0)$ for a long time. To this end we provide a general property of the HIV dynamic model, by which we conclude that if the (x, y) state enters the set $\tau(y_\kappa) \cap (K < 0)$ during the output feedback control, then the state cannot remain there but has to return to the set $\tau(y_\kappa) \cap (K > 0)$.

Proposition 6 *Consider the model (6.1)-(6.5) and assume $X(t) \in \tau(y_\kappa) \cap (K < 0)$ with*

$u(t) = 0$ for $t \in (-T_3, 0]$ where T_3 is sufficiently large and positive⁹. Let $X(t)$ be the corresponding trajectory with $u(t) = 0$ for $t \geq 0$. Then there exists $T_4 \geq 0$ such that $X(T_4)$ belongs to the immune increasing region.

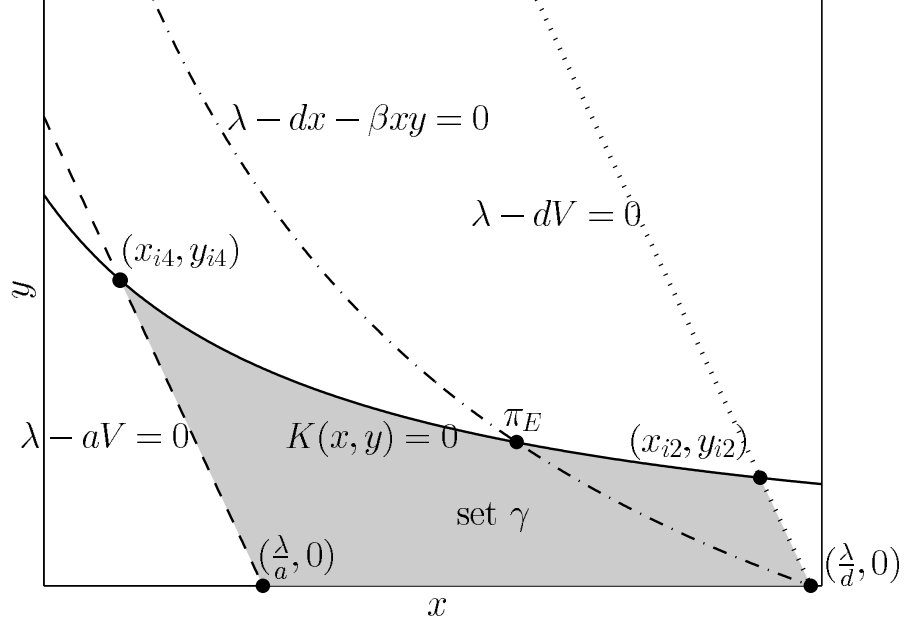


Figure 6.10: The lines $K(x, y) = 0$ (solid), $V = \lambda/a$ (dashed), and $V = \lambda/d + \epsilon$ (dotted) where $V = x + y$ and $\epsilon = 0$. The point (x_{i4}, y_{i4}) is the intersection of $K = 0$ and $\lambda - aV = 0$, while (x_{i2}, y_{i2}) is the intersection of $K = 0$ and $\lambda - dV = 0$.

Proof: Consider the set γ defined by the inequalities $K < 0$, $y > 0$, $V > \lambda/a$, and $V < \lambda/d + \epsilon$ where ϵ is any small positive number, as depicted in Figure 6.10. The points (x_{i1}, y_{i1}) and (x_{i2}, y_{i2}) are defined in Figure 6.8. As in the proof of Theorem 5, let $V(t) = x(t) + y(t)$. Then $V(t) < \frac{\lambda}{d} + \epsilon$ for all $t \geq t_\epsilon$ for some $t_\epsilon > 0$ (see the proof of Theorem 5). In addition $\dot{x} = \lambda - dx - \beta xy > \lambda - (d + \beta y_{i1})x$ in the set $\tau(y_\kappa) \cap (K < 0)$ with $u = 0$. Note that $d + \beta y_{i1} < a$ by (6.10), hence $x(0) > \frac{\lambda}{a}$ by assumption. Thus the point $(x(0), y(0))$ is located in the set γ .

⁹This assumption is established as the worst condition for enhancing w and z_2 . However this assumption implies that the uninfected CD4 T-cells (x) and the infected CD4 T-cells (y) stay in the vicinity of the curve $\lambda - dx - \beta xy = 0$ in the set $\tau(y_\kappa) \cap (K < 0)$, which is *ironically* a good clinical condition for a HIV patient (see Figure 6.10). Note that the immune response for HIV does not need to be boosted if this clinical condition is maintained.

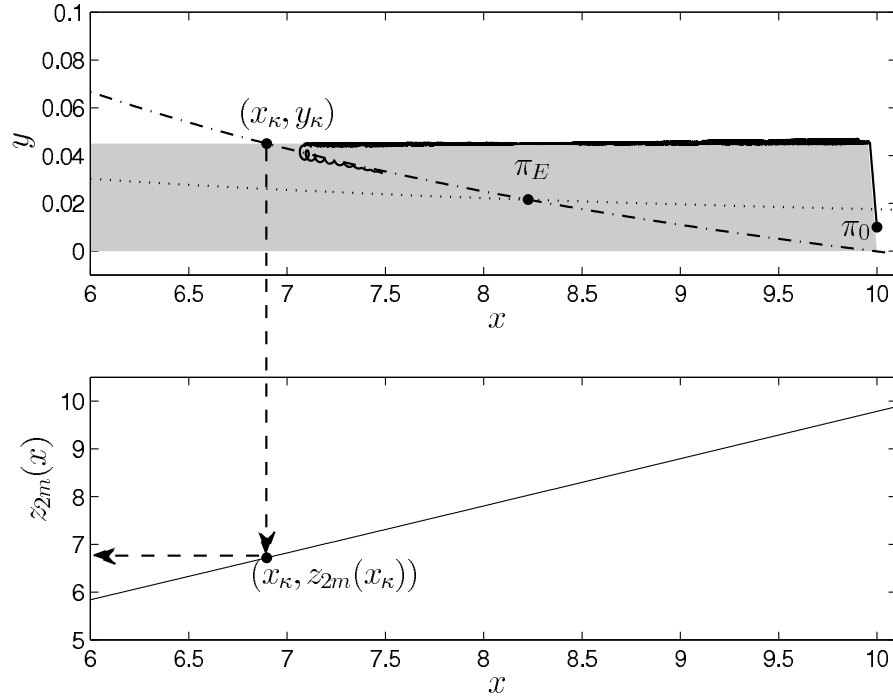


Figure 6.11: The grey region indicates the set $\tau(y_\kappa)$ where $y_\kappa = \frac{1}{75}y^{(C)}$. The dash-dotted line, the dotted line, and the solid line describe the sets $\lambda - dx - \beta xy = 0$, $K(x, y) = 0$, and the (x, y) trajectory, respectively (top graph). From y_κ , we obtain the corresponding x_κ from the top graph and z_{2m} of (6.15) from the bottom graph.

By assumption, $z_1(0)$ and $z_2(0)$ are sufficiently small. Note that $z_1(t)$ goes to zero ($\dot{z}_1 < 0$ by $y < y_{i4} < y^{(C)}$)¹⁰, and that $z_2(t)$ goes to zero by $\dot{w} < 0$ in the set γ . Then the states does not cross the line $\lambda - aV = 0$ because $\dot{V}(t) > \lambda - aV(t) - p_1 z_1 y - p_2 z_2 y > \lambda - aV(t) - p_1 z_1(0)y_{i4} - p_2 z_2(0)y_{i4}$. In addition

$$\dot{y} = y(\beta x - a - p_1 z_1 - p_2 z_2) \geq \delta y,$$

for some positive δ because $x_{i4} > q > \frac{a}{\beta}$ by (6.7) and $x(t) > x_{i4}$ in the set γ . Hence the state enters the immune increasing region through $K(x, y) = 0$, $x \in (x_{i4}, x_{i2})$. $\square$

6.2.4 The enhanced level of the immune system with a smaller y_κ

From Figure 6.9 we infer that the guaranteed levels of the immune system can be changed using a different value of y_κ . To this end we consider the set $\tau(y_\kappa)$ where $y_\kappa = \frac{1}{75}y^{(C)}$,

¹⁰ $K = 0$ and $\lambda + aV = 0$ have two intersections in the positive orthant if and only if $\frac{b_2}{c_2} < \frac{1}{4} \left(\frac{\lambda}{a} - q \right)^2$. In addition, if $\frac{b_1}{c_1} > \frac{1}{2} \left(\frac{\lambda}{a} - q \right)$, the smaller real part of the y components of the intersections becomes less than $\frac{b_1}{c_1}$. Therefore $y_{i4} < y^{(C)}$ by (6.9) and (6.10).

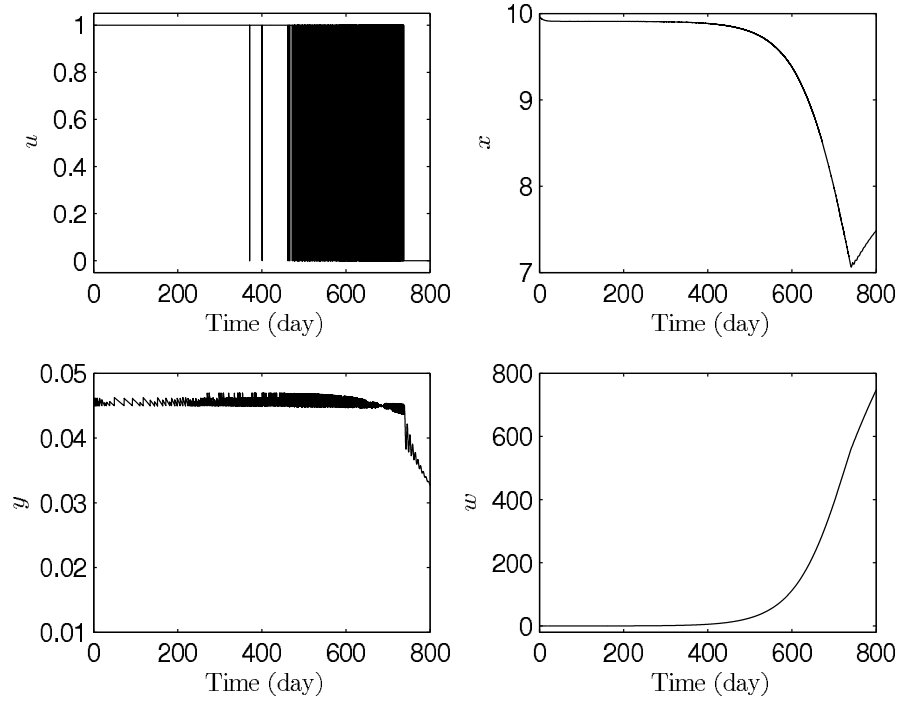


Figure 6.12: Results of the application of the output feedback control scheme to model (6.1)-(6.5) with the set $\tau(y_\kappa)$ where $y_\kappa = \frac{1}{75}y^{(C)}$. The unit of x and y is (100copies/ μ l).

as depicted in the top graph of Figure 6.11. Note that Propositions 3 and 4 still hold for this set $\tau(y_\kappa)$, and the inequalities $y^{(E)} < y_\kappa \leq y^{(C)}$ still hold in Figure 6.11. If we assign a smaller y_κ , a larger x_κ and a larger z_{2m} in (6.15) are obtained from the top graph and the bottom graph in Figure 6.11, respectively. The point (x_κ, y_κ) is the intersection of the boundary of the set $\tau(y_\kappa)$ and $\lambda - dx - \beta xy = 0$. Note that $x_\kappa = \frac{\lambda}{d + \beta y_\kappa}$ in this case, because the intersection is on the line $y = y_\kappa$.

We perform a simulation of the control procedure of Section 6.1 with the set $\tau(\frac{1}{75}y^{(C)})$ and the same initial conditions used in Section 6.1. Figure 6.12 shows the results. Compared with the case of the set $\tau(y^{(C)})$ in Section 6.1, the case of the set $\tau(\frac{1}{75}y^{(C)})$ requires longer control efforts (over 750 days) and shows slower enhancement of the immune system (compare Figure 6.2 and Figure 6.12), while it theoretically guarantees greater boosted level of the immune system from (6.15).

6.2.5 Interpretation of the condition $L_2(x, y) = 0$

In this subsection we discuss how to select $u(t)$ to locally (in time) maximise $w(t)$. This is realised by a numerical method. Consider model (6.1)-(6.5), i.e., $\dot{X}(t) = f(X(t), u(t))$

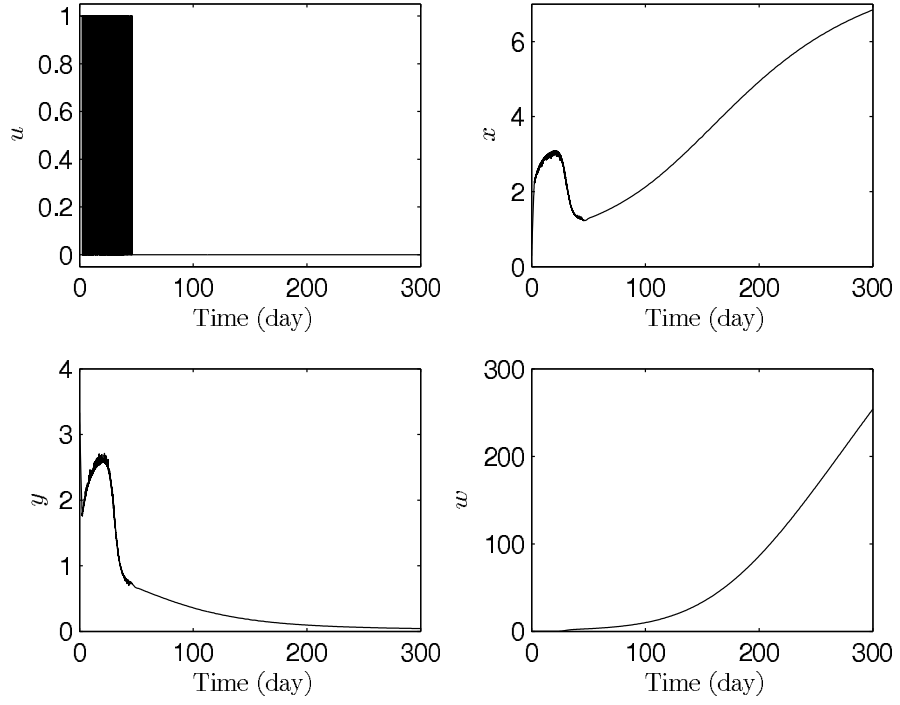


Figure 6.13: Results of the application of the on-line selection of u to maximise the increase of w , for model (6.1)-(6.5). The unit of x and y is (100copies/ μ l).

with $X = [x, y, z_1, w, z_2]^T$. With a sufficiently small δT and the current state value $X(t)$, we obtain an approximation of $X(t + \delta T)$ by the classical 4th order Runge-Kutta method [45], namely,

$$X(t + \delta T) = X(t) + \frac{1}{6}(k_1 + 2k_2 + 2k_3 + k_4), \quad (6.17)$$

where

$$\begin{aligned} k_1 &= \delta T f(X(t)), \\ k_2 &= \delta T f(X(t) + 0.5k_1), \\ k_3 &= \delta T f(X(t) + 0.5k_2), \\ k_4 &= \delta T f(X(t) + k_3). \end{aligned}$$

As a result, an approximation of $w(t + \delta T)$, calculated by (6.17), is a function of $u(t)$ and we can select $u(t)$ to locally maximise $w(t + \delta T)$. To implement this strategy, we find $u(t)$ satisfying

$$\max_{u(t) \in U_E} w(t + \delta T),$$

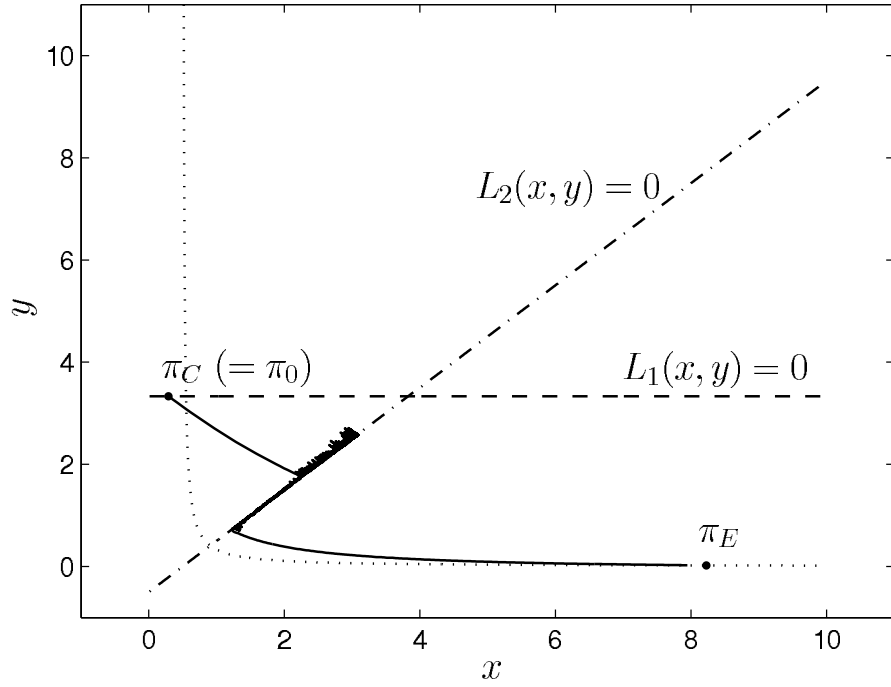


Figure 6.14: The (x, y) trajectory resulting from the on-line strategy. The dotted line and the solid line indicate the set $K(x, y) = 0$ and the (x, y) trajectory, respectively. The dashed line and the dash-dotted line represent the sets $L_1(x, y) = 0$ and $L_2(x, y) = 0$, respectively.

where, for example, $U_E = \{0.01, 0.02, \dots, 1\}$ and $\delta T = 0.00001$.

Figure 6.13 shows the results of the application of this method. The system parameters are as in the previous simulations, while the initial condition is $X(0) = (0.2913, 3.3333, 0.0913, 0.0001, 0.0001)$, sufficiently close to Point C. The resulting (x, y) trajectory is displayed in Figure 6.14, which shows that the (x, y) trajectory moves along the sets $L_2(x, y) = 0$ in the middle of the treatment.

Therefore the condition $L_2(x, y) = 0$ of the output feedback scheme in Section 6.1 implies local maximal growth of w .

6.3 Conclusion

We have provided an output feedback control method for HIV drug therapy. The immune boosting mechanism yielded by the control law has been discussed and supported by formal statements. We have also shown that the proposed idea guarantees a minimal activation of the immune system. The applicability of the method is demonstrated by

means of computer simulations. The works in this chapter are included in [23] and [18].

Chapter 7

Approximate estimation of immune states in HIV dynamics

Control methods based on the understanding of the boosting mechanism of the immune response have been proposed in Chapter 5 and Chapter 6. The purpose of this chapter is to provide approximate estimation methods for the states of the immune system of the HIV patient on the basis of available measurements. We show the applicability of these state inference ideas by means of numerical simulations. The results in this chapter are presented in the work of [20].

The methods in this chapter rely on approximations hence we use the terminology *state inference* rather than state observer. Note that the inference of the immune states is not used in feedback control loop in this chapter (see Figure 7.1). The purpose of this chapter is just to monitor the CTL response in HIV dynamics (2.1)-(2.5).

To begin with we recall model (2.1)-(2.5) of Section 2.1.1, namely

$$\dot{x} = \lambda - dx - \eta\beta xy, \quad (7.1)$$

$$\dot{y} = \eta\beta xy - ay - p_1 z_1 y - p_2 z_2 y, \quad (7.2)$$

$$\dot{z}_1 = c_1 z_1 y - b_1 z_1, \quad (7.3)$$

$$\dot{w} = c_2 xyw - c_2 qyw - b_2 w, \quad (7.4)$$

$$\dot{z}_2 = c_2 qyw - h z_2. \quad (7.5)$$

The model (7.1)-(7.5) with $u = 0$ has five equilibrium points, three of which are recalled from Table 3.1, for convenience, as given in what follows.

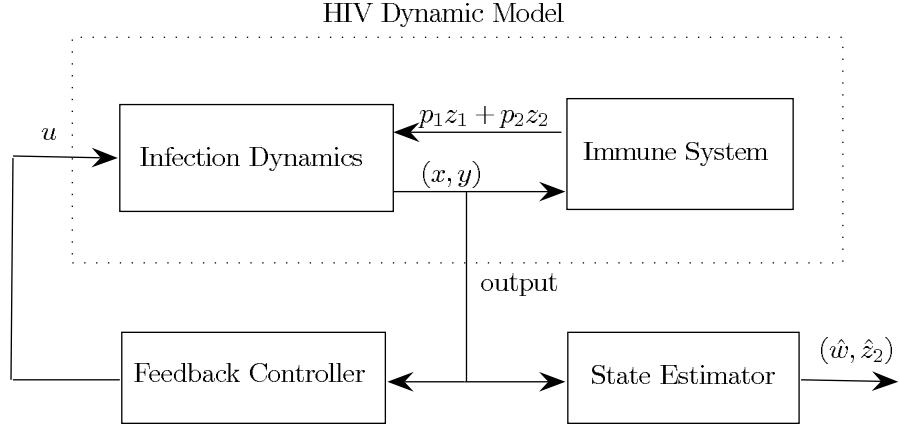


Figure 7.1: Diagram describing the connections of the HIV model, the controller, and the state estimator. The block inside the dotted-line indicates the HIV dynamics (7.1)-(7.5), which consist of two subsystems, the infection dynamics and the immune system.

Point A:

$$x^{(A)} = \frac{\lambda}{d}, \quad y^{(A)} = 0, \quad z_1^{(A)} = 0, \quad w^{(A)} = 0, \quad z_2^{(A)} = 0;$$

Point C:

$$x^{(C)} = \frac{\lambda c_1}{dc_1 + b_1 \eta \beta}, \quad y^{(C)} = \frac{b_1}{c_1}, \quad z_1^{(C)} = \frac{\eta \beta x^{(C)} - a}{p_1}, \quad w^{(C)} = 0, \quad z_2^{(C)} = 0;$$

Point E:

$$y^{(E)} = \frac{c_2(\lambda - dq) - b_2 \eta \beta - \sqrt{[c_2(\lambda - dq) - b_2 \eta \beta]^2 - 4 \eta \beta c_2 q d b_2}}{2 \eta \beta c_2 q}, \quad x^{(E)} = \frac{\lambda}{d + \eta \beta y^{(E)}},$$

$$z_1^{(E)} = 0, \quad w^{(E)} = \frac{h z_2^{(E)}}{c_2 q y^{(E)}}, \quad z_2^{(E)} = \frac{y^{(E)}(c_2 \eta \beta q - c_2 a) + b_2 \eta \beta}{c_2 p_2 y^{(E)}}.$$

In Chapter 6 we have shown that an output feedback can be designed to boost the immune response of the human body to steer the system to Point E, i.e. the LTNP status.

In this chapter we suggest state estimation methods for the state of the immune system of model (7.1)-(7.5). The methods are aimed to be used during the STEP 2, defined in Section 6.1. Note that we do not need any state estimation during STEP 1, defined in Section 6.1, because the state converges to Point A by Theorem 5. Also z_1 does not need to be estimated in STEP 2 because it converges towards 0, as shown in Proposition 4.

7.1 State inference of immune system via continuous output measurement

For model (7.1)-(7.5), assume the following.

1. $z_1(t)$ is zero.
2. x and y are the system outputs and are twice differentiable¹.

Consider now the functions

$$\gamma_{z_2}(x, \dot{x}, y, \dot{y}) = \frac{\lambda - dx - ay - \dot{x} - \dot{y}}{p_2 y}, \quad (7.6)$$

and

$$\gamma_w(x, \dot{x}, \ddot{x}, y, \dot{y}, \ddot{y}) = \frac{1}{c_2 q p_2 y^2} \left[\left(h - \frac{\dot{y}}{y} \right) (\lambda - dx - ay - \dot{x} - \dot{y}) - (d\dot{x} + a\dot{y} + \ddot{x} + \ddot{y}) \right]. \quad (7.7)$$

By (7.1), (7.2), and the assumption on $z_1(t)$, $\gamma_{z_2}(x, \dot{x}, y, \dot{y}) = z_2$. Then, by (7.5), the function $\gamma_w(x, \dot{x}, \ddot{x}, y, \dot{y}, \ddot{y})$ is such that

$$\begin{aligned} & \frac{1}{c_2 q p_2 y} \left[\frac{h}{y} (\lambda - dx - ay - \dot{x} - \dot{y}) - \left(\frac{\dot{y}}{y^2} (\lambda - dx - ay - \dot{x} - \dot{y}) + \frac{1}{y} (d\dot{x} + a\dot{y} + \ddot{x} + \ddot{y}) \right) \right] \\ &= \frac{1}{c_2 q p_2 y} \left[h \frac{1}{y} (\lambda - dx - ay - \dot{x} - \dot{y}) + \frac{d}{dt} \left(\frac{1}{y} (\lambda - dx - ay - \dot{x} - \dot{y}) \right) \right] \\ &= \frac{1}{c_2 q y} (h z_2 + \dot{z}_2) = w. \end{aligned}$$

Note that the assumption on $z_1(t)$ is acceptable during STEP 2 since $z_1(t)$ decreases *exponentially* by Proposition 5 and Proposition 4 during the drug treatment (see Section 6.1). Consequently, $z_1(t)$ becomes sufficiently small for all t in STEP 2 and negligible as time goes by. Also note that we obtain an approximation of a differentiator from the assumption on the continuous measurability of the state x and y . See Figure 7.2 for the implementation of an approximate differentiator with a transport delay.

As a result of the above discussion, approximations of w and z_2 are given by

$$\begin{aligned} z_2 &\cong \gamma_{z_2}(x, D(x, \delta_T), y, D(y, \delta_T)) \quad (= \hat{z}_2), \\ w &\cong \gamma_w(x, D(x, \delta_T), D(D(x, \delta_T), \delta_T), y, D(y, \delta_T), D(D(y, \delta_T), \delta_T)) \quad (= \hat{w}), \end{aligned}$$

¹This implies that x and y are *continuously* measurable.

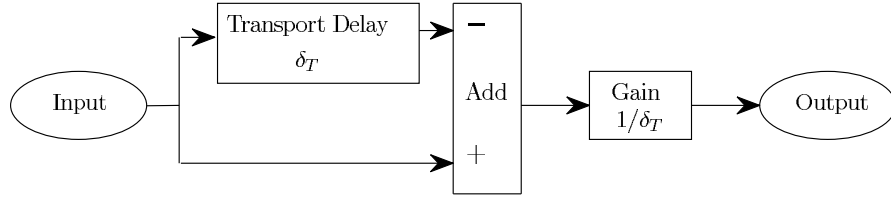


Figure 7.2: Diagram describing an implementation of approximate differentiator in Simulink using transport delay.

where $D(x, \delta_T) = (x(t) - x(t - \delta_T))/\delta_T$ (see Figure 7.2).

This state approximation idea is denoted as state inference via continuous output measurement (SIC). Two simulations of SIC have been carried out for the examples from Subsection 6.1.1. The time ranges of the graphs are selected to show the performance of SIC and we consider the errors

$$e_w = w - \hat{w},$$

$$e_{z_2} = z_2 - \hat{z}_2.$$

Figure 7.3 shows the result of SIC in the interval $[50, 100]$ for the case in Figure 6.4. The variables $w(t)$ and $z_2(t)$ of model (7.1)-(7.5) are depicted with dotted lines in the first and third graph, respectively. For $\hat{w}(t)$ and $\hat{z}_2(t)$, the parameter δ_T is 0.05.

From the assumption on double differentiability of the state x and y , SIC cannot guarantee good performance in the interval $[20, 50]$, because this interval includes too many switches between 0 and 1 of the input function $u(t)$. The switchings render $\dot{x}$ and $\dot{y}$ discontinuous, by equations (7.1) and (7.2), which implies that $\ddot{x}$ and $\ddot{y}$ are not defined for all t .

However we can apply SIC in the time interval $[20, 200]$ for the case in Figure 6.5, because this case has only a few input switching instants and we can use SIC piece by piece² for each period in which the input is constant. Note that a constant $u(t)$ implies twice differentiable system outputs, $x(t)$ and $y(t)$, by (7.1) and (7.2).

Figure 7.4 shows $\hat{w}$ and e_w , particularly in the interval $[26, 38]$. Note that the time range of the bottom graph is $[20, 200]$ although the time ranges of the top and middle graphs are $[26, 38]$. $w(t)$ and $\hat{w}(t)$ are depicted with the dotted line and the solid line,

²This implies that the inferences of z_2 and w do not exist for the first δ_T and $2\delta_T$ periods after each input switching, respectively (see the definition of $D(\cdot, \delta_T)$ and Figure 7.2). Note that $\hat{w}$ and e_w in Figure 7.4 are discontinuous at each input switching instant.

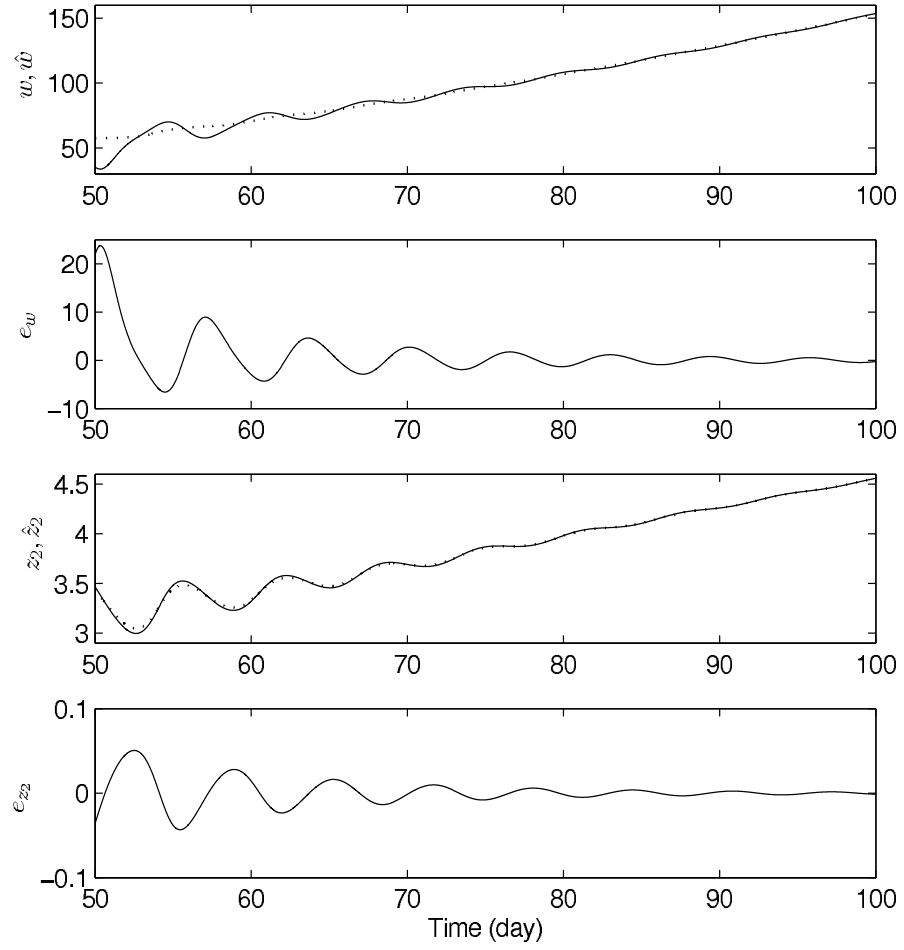


Figure 7.3: State histories of state inference via continuous output measurement for the example in Figure 6.4 for the time interval $[50, 100]$.

respectively, in the top graph. e_w is displayed with the solid line in the middle and bottom graphs. A rescaled $u(t)$ is plotted with dashed line as a square wave function in the middle graph. The third graph in the figure confirms the performance of SIC in the whole time period $[20, 200]$. $\hat{z}_2$ and e_{z_2} are not shown in the figure, and the parameter δ_T is selected equal to 0.01.

7.2 State inference of immune system via discrete output measurement

Although SIC is a good state approximation for the immune system, we consider an alternative state approximation method because the continuous output injection in SIC

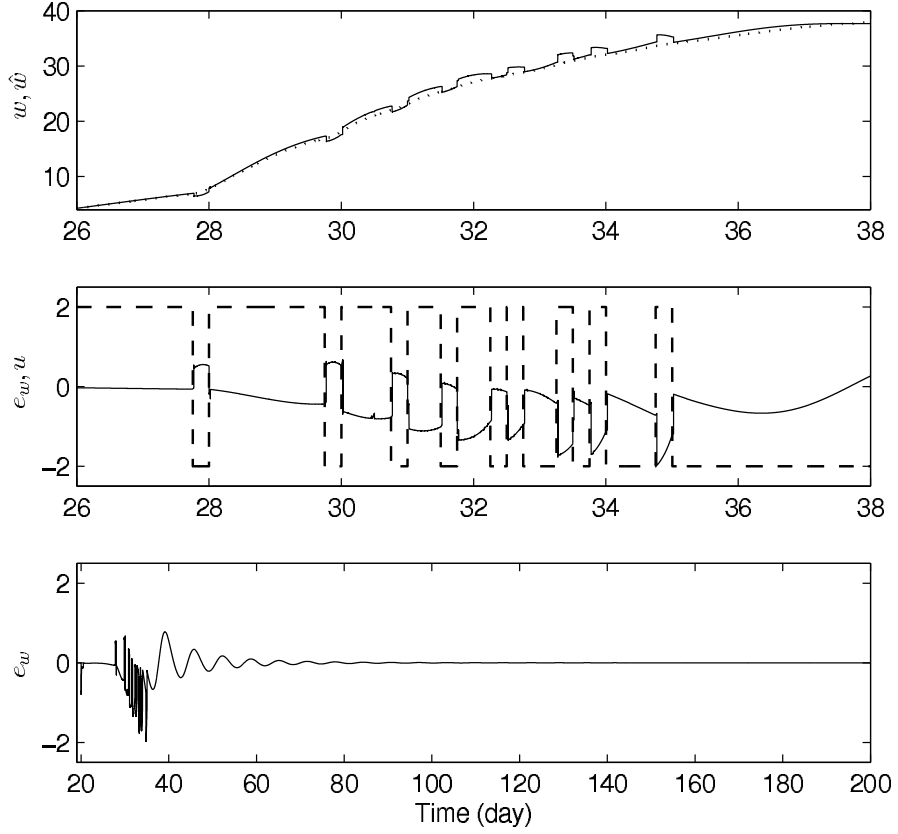


Figure 7.4: State histories of state inference via continuous output measurement and of the errors for the example in Figure 6.5. Note that $\hat{w}$ and e_w are discontinuous at each input switching instant.

is hardly implementable in practice. In fact the levels of x and y are measured at discrete time instants from patient's blood samples (see Section 2.2 for a discussion on HIV measurements). This implies that currently we cannot use SIC which requires continuous measurement of x and y . We denote the state approximation idea in this section as state inference via discrete output measurement (SID).

Firstly we infer $z_2(t)$ for the example in Figure 6.5, where x and y are measured every 0.25 day. The approximation idea stems from [57, Section III.A]. We can approximately calculate $\dot{x}$ and $\dot{y}$ from two samples of x and y , respectively. Also approximations of $\ddot{x}$ and $\ddot{y}$ can be obtained from three samples of x and y , respectively.

We assume that z_1 is sufficiently small because $y(t)$ is such that $y(t) < \frac{b_1}{c_1}$. Then, by (7.1) and (7.2),

$$z_2 = \frac{\lambda - dx - ay - \dot{x} - \dot{y}}{p_2 y},$$

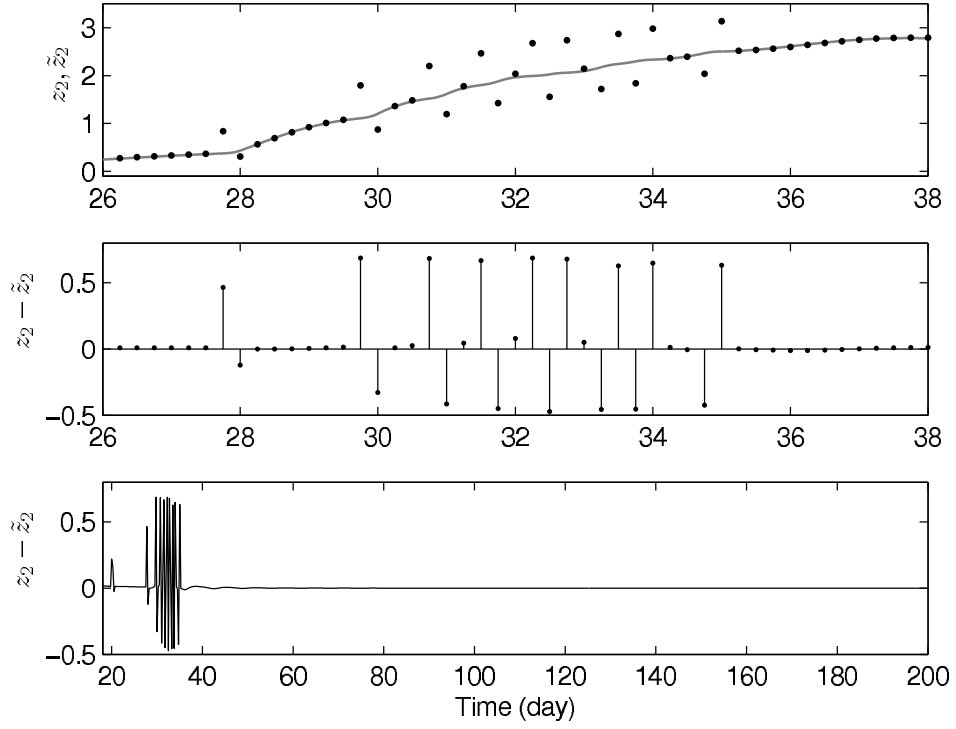


Figure 7.5: State inference via discrete output measurement of z_2 for the example in Figure 6.5 with 1 sample each 0.25 (day). In the top graph, $\tilde{z}_2$ is the state approximation of z_2 by state inference via discrete output measurement. $\tilde{z}_2$ is given by points each 0.25 (day), while z_2 is shown with the solid line.

and the SID of z_2 , denoted by $\tilde{z}_2$, is plotted in Figure 7.5. In the first graph the solid line corresponds to $z_2(t)$ from the model (7.1)-(7.5) and the points indicate $\tilde{z}_2$, every 0.25 (day) in the time interval $[26, 38]$. The second graph shows the error between z_2 and $\tilde{z}_2$ from the first graph. The last graph presents the overall performance of the SID of z_2 in the time interval $[20, 200]$. We see that discrete-time measurements of x and y can be used to estimate the level of z_2 .

The variable w is inferred using the same method. By equation (7.5)

$$w = \frac{1}{c_2 q} \left(\frac{\dot{z}_2 + h z_2}{y} \right),$$

and an approximation of $\dot{z}_2$ is obtained from $\tilde{z}_2$. However $\tilde{z}_2$ is oscillating in the interval $[26, 36]$, which makes the SID of w unreliable in this interval. This oscillation is caused by the switching of the input u between 0 and 1. If the input u is changed from 1 to 0 (or vice-versa) at a certain instant, then $\tilde{z}_2$ is not reliable by (7.1) and (7.2) because $\dot{x}$ and $\dot{y}$ are not continuous.

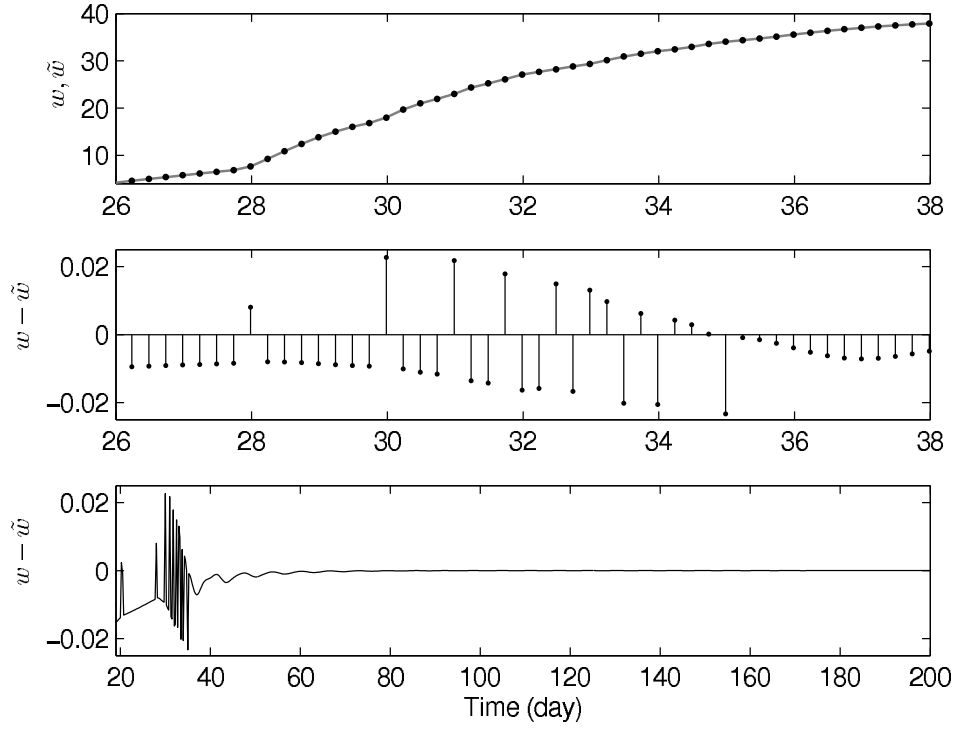


Figure 7.6: State inference via discrete output measurement of w for the example in Figure 6.5 with 4 samples each 0.25 (day). In the top graph $\tilde{w}$ is the state approximation of w by state inference via discrete output measurement. $\tilde{w}$ is given by points at each 0.25 (day), while w is shown with the solid line.

To overcome this problem in $\tilde{z}_2$, we apply the method used in the previous section. By multiple measurements in each period, where the input u is guaranteed to be constant, we reliably obtain not only $\tilde{z}_2$ but also $\tilde{w}$, the SID of w as shown in Figure 7.6. From the ideas in [57], three measurements of x and y are needed to approximate $\ddot{x}$ and $\ddot{y}$, respectively, although we use four measurements³ to infer w in Figure 7.6.

7.3 Conclusion

We have presented two state approximation methods to monitor the immune status in a HIV dynamic model. In the first method we suggest an approximate estimation (i.e.,

³Suppose that the four measurements are carried at T , $T + \delta$, $T + 2\delta$, and $T + 3\delta$. For example, we infer $z_2(T + \delta)$ based on the measurements at T and $T + 2\delta$. Similarly we infer $z_2(T + 2\delta)$ based on the measurements at $T + \delta$ and $T + 3\delta$. By these inferred $z_2(T + \delta)$ and $z_2(T + 2\delta)$ we approximately obtain $\dot{z}_2$ and also the inference of w .

SIC) which requires continuous output injection from the HIV dynamic system. The second method (i.e., SID) allows to infer the states of the immune system using only three (or four) measures of x and y if the system parameters are known. The works in this chapter are included in [20]. We complete this chapter with some remarks.

1. The function γ_w in Section 7.1 does not depend on the w dynamics (7.4) except for c_2 and q which are scaling factors. Thus we do not need any information on (7.4) in order to see the trend of w . This implies that we can use extremum seeking methods for the boosting of the immune term w regardless of (7.4). This will be the subject of future research.
2. While state inference methods show promising performance, measurement noise and model uncertainty problems should be researched in detail.

Chapter 8

Conclusion

The primary goal of this thesis is to steer the state of the system describing a HIV infected patient to the LTNP status. This is achieved by means of new methods of treatment.

The first method, described in Chapter 3, is based on an approximation of higher order dynamics by a reduced order model. For the approximation we divide the HIV infection model into two subsystems and modify one of the subsystems to emulate the whole system. With the modification we relieve the difficulties associated with the high order model, such as state observation and parameter estimation.

The second control method, discussed in Chapter 4, is known as gradual reduction of drug dose. By this scheme it is possible to steer the state of any patient to the LTNP status if the model parameters belong to certain parameter intervals. In order to justify the claim, we first analyze the stability and the bifurcation properties of a HIV model and show that there exists an equilibria curve towards the LTNP, which is locally stable for almost every fixed constant input.

The third control method, studied in Chapter 5, is derived from a new control philosophy which aims at boosting the response of the immune system by means of drug scheduling. The control strategy is implemented by controlled drug scheduling based on the understanding of the immune boosting mechanism. The feasibility of the control methodology is illustrated via simulations on a general disease model and on three HIV dynamic models, one of which is a tristable HIV dynamic model.

This control perspective yields an output feedback method to control the immune response in Chapter 6. The suggested output feedback control idea guarantees that

the immune state is enhanced to a certain level, which is enough for a typical patient to be driven into the long-term nonprogressor. To justify the control methodology the resulting controlled HIV dynamic model is studied analytically.

Finally, in Chapter 7, we investigate methods to approximate the state of the immune system on the basis of available outputs of the HIV model. To this end we suggest two state estimation methods, denoted as state inferences.

8.1 Main contribution

The main part of this research relies on a property of the immune system in a HIV model. The property is that excitement of a key component in the immune system depends on the infection dynamic states, which correspond to HIV infected cells and uninfected cells. Interestingly these two states can be measured by clinical methods and moreover they are directly affected by antiretroviral drugs, which are used in HIV antiviral-drug therapy. Therefore we propose control methods of drug scheduling to enhance the response of the immune system. The methods are based on the comprehension of the immune boosting mechanism, and also can be applied to various biological systems, which describe infection dynamics with drug input. Consequently this thesis provides guidelines for drug scheduling to strengthen the immune system of an infected patient.

8.2 Future work

1. In this work we assume the immune system is clearly modeled by differential equations but the human immune system is too complicated to be modeled with a few differential equations, thus unmodeled parts of the immune system must be considered. To overcome such a modeling-limitation problem, we can exploit adaptive control methods, such as extremum seeking and the method used in Section 3.4. Extremum seeking methods might be suitable to maximize the immune system without precise immune system modeling, and the method of Section 3.4 is available for partly modeled problem by means of parameter adaptation.
2. The input term used in this thesis is the idealized therapy effect to the human body. Although the input function obtained from the control procedure can drive the patient state into the region of attraction of the LTNP, the realization of the

function in the human body could be difficult, because the function is a square wave. Therefore further consideration for the drug delivering mechanisms must be researched. For example a modeling method to describe biobarriers between drugs and their target is used for cancer chemotherapy [63, 81].

3. The proposed control methods are simple and powerful to boost the immune system, as seen in the simulations. However alternative control laws can be investigated because the methods in this thesis do not consider the cost of drugs, side effects of HAART, the duration of the anti-HIV therapy, and noise in the HIV measurements. Finally constraints on the levels of HIV and CD4 T-cells must be considered during the medication.

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