Design of Therapies for HIV-1 Infection using Predictive Control Techniques

João Gonçalo Correia Vasconcelos Pinheiro

Dissertação para a Obtenção do Grau de Mestre em Engenharia Electrotécnica e de Computadores

Júri
Presidente: Prof. Carlos Jorge Ferreira Silvestre
Orientador: Prof. João Manuel Lage de Miranda Lemos
Co-Orientador: Prof. Susana de Almeida Mendes Vinga Martins
Vogal: Prof. António Pedro Aguiar

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Abstract

Although many papers address the issue of therapy design for HIV-1 infection based on control methods, the results available in the literature do not in general consider the fact that the manipulated variable is not continuous but a train of pulses. In addition, they are usually concerned only with the relation between drug effect (assumed to be manipulated) and virus dynamics. In order to improve the direct relation with actual clinical practice, the present work takes as manipulated variable a train of impulses that represent the pills taken by the patient and includes pharmacokinetics (PK) and pharmacodynamic (PD) drug models. In addition, patient adherence to treatment and their impact on virus drug resistance is also modeled. The problem of driving the viral load to a low specified value, while minimizing the amount of drugs administered to the patient, is thus addressed by nonlinear model predictive control (NMPC) with periodic inputs. Therefore, the dissertation contributions consist in the characterization of the results obtained with this type of control strategy in a HIV-1 infection model comprising drug PK and PD, development of virus resistance to drugs and virus dynamics. Furthermore, it is shown that various amounts of reverse transcriptase inhibitor (RTI) and protease inhibitor (PI) drugs can be given depending on the weights of the cost function minimized by periodic NMPC, while attaining the same control objective. It is proposed that these weights can be adjusted to minimize the toxicity of the drug cocktail administered.
Resumo

Apesar de diversos artigos abordarem o tópico de projecto de terapias para a infecção com o VIH através do uso de técnicas de controlo, os resultados disponíveis na literatura não consideram em geral o facto de a variável manipulada não ser contínua, mas sim uma sequência de impulsos. Além disto, estes caracterizam apenas a relação entre o efeito das medicações disponíveis, que se assumem possíveis de manipular directamente, e a dinâmica da infecção. Por forma a melhorar a relação directa com a prática clínica, o modelo considerado neste trabalho usa como variável de entrada uma sequência de impulsos, correspondendo aos comprimidos tomados pelo paciente, e incluindo modelos farmacocinéticos (PK) e farmacodinâmicos (PD) da infecção. São também modelados os efeitos de aderência ao tratamento e de resistência do vírus à medicação utilizada. O problema de baixar a concentração de vírus até um determinado valor, minimizando a quantidade total de medicação utilizada, é aqui abordado utilizando controlo preditivo não-linear, usando variáveis de controlo periódicas. As contribuições deste trabalho consistem portanto na caracterização dos resultados obtidos com este tipo de estratégia de controlo, em conjugação com um modelo da infecção por VIH que inclui a farmacocinética e a farmacodinâmica envolvidas, desenvolvimento de resistência a fármacos e efeito de aderência ao tratamento. É também mostrado que diversas quantidades relativas de inibidores de transcriptase (RTI) e de protease (PI) podem ser administradas, mantendo o objectivo de controlo cumprido, através da manipulação dos pesos usados na função de custo do controlo. É proposto que um ajuste destes pesos possa ser usado para minimizar o nível de toxicidade da combinação de fármacos administrada.
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<td>Acquired Immunodeficiency Syndrome</td>
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<tr>
<td>ARV</td>
<td>Antiretroviral</td>
</tr>
<tr>
<td>HAART</td>
<td>Highly Active Antiretroviral Therapy</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
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<tr>
<td>RNA</td>
<td>Ribonucleic Acid</td>
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Chapter 1

Introduction

1.1 Motivation

Since its discovery in 1981, the Acquired Immunodeficiency Syndrome (AIDS), caused by the Human Immunodeficiency Virus 1 (HIV-1) infection, has claimed more than 25 million human lives. HIV-1 infects now about 0.6% of the world population, with a disproportionate number of cases occurring in Sub-Saharan Africa, worsening the already delicate situation these countries live in. Despite the increasing awareness about the disease and the efforts done in prevention, an estimated 2.6 million people were newly infected in 2009 [32].

HIV-1 is a retrovirus, a Ribonucleic Acid (RNA) virus that is replicated in a host cell, via the enzyme reverse transcriptase, to produce Deoxyribonucleic Acid (DNA) from its RNA genome. The host cells are primarily CD4+ T (helper T cells) from the immune system, whose concentrations are led to low levels by the infection, either by direct viral killing, programmed cell death (apoptosis), or killing by lymphocytes that recognize the cell as being infected. As the CD4+ T levels become lower, cell mediated immunity is lost, making the organism very vulnerable to opportunistic infections. After a period of 10 years in average, the HIV-1 infection reaches a critical state, where the CD4+ T cell count is below 200 Cell/mm$^3$, and the patient is said to have developed AIDS.

The treatment options available have shown to significantly extend the life expectancy of people infected with HIV-1 and are done using anti-retroviral drugs, frequently administered in combinations of 3 or 4 different drugs, a treatment known as Highly Active Antiretroviral Therapy (HAART) [34]. The difficulty in selecting a regimen of the mentioned drugs is considerably high, when taking into account the possible side effects and the effectiveness in preventing viral resistance. If followed strictly, these treatments have shown to succeed in preventing that the patient develops AIDS. Even when the patient has already developed AIDS, the average survival time for a patient under treatment becomes 5 years [33].

Although the HAART results are encouraging, there are several concerns regarding this type of treatment. For approximately half of the people who are treated, the therapy fails to achieve its objectives. The main reasons behind therapy failure are low patient adherence or non-persistence, which can come from low availability of the medication, complexity of the regimen or withdrawal based on drug side-effects. This failure to follow the treatment plan closely can cause the development of resistant strains of the virus, which will not react to anti-retroviral drugs. Besides this, the drugs in question are still too expensive, and the majority of the infected people in the world do not have access to such treatments.

In the past decade, these challenges have generated a lot of work concerning the mathematical modeling of the HIV-1 infection, in hope of gaining a better knowledge of the virus dynamics...
and of the impact that certain therapies can have in containing the infection. These models have been supported by real patient data, that became increasingly available as more patients were followed in their treatments. Promising results were achieved, with a diversity of models being proposed spanning different levels of complexity, that could effectively reproduce the virus dynamics when compared with the data collected from real patients.

The success in the infection modeling motivated the question of understanding if it would be possible to use automatic control on these models, as a way of projecting therapies that would take into account the specific virus dynamics of each particular patient. This is in line with the recent tendency of Personalized Medicine. The control problem is formulated as to find a drug administration profile such that the viral load is driven to a value below a specified threshold, within a specified time interval. This allows for a lower amount of drugs to be used to contain the infection, having an important impact in reducing possible side-effects, as well as in reducing the costs involved in providing these therapies to such an alarming number of infected people. Furthermore, the therapy design can be done having into account which drugs have more severe side-effects, prioritizing the usage of the least harmful drugs for the patient. An improvement would then be achieved, not only in absolute quantities of drugs administered, but also in relative ones.

The practical application of the treatment recommendations, obtained through automatic control techniques, would heavily depend on the availability of an adequate measure of the patient state. Recent progresses in instrumentation made it possible to provide such measurements in the majority of hospitals, and the current tendency is that instruments become cheaper and more accurate in taking the relevant measurements for the infection treatment. This opens the applicability of eventual results in this line of research to a much broader group of people. However, even considering a widespread availability of this type of instrumentation, not all the model states are available for measurement, and their values are often necessary to achieve good control results, making it necessary to obtain the remaining ones through state estimation.

This method of therapy design also has to face the problem that there is a lot of parametric uncertainty in the models, resulting from imperfect parameter estimation, and non-parametric uncertainties as well, that result from un-modeled dynamics of the infection. These uncertainties make both control and state estimation less accurate, leading to less successful therapeutic results.

As stated before, one of the main causes of treatment failure is non-adherence to the treatment, resulting in the development of drug resistant strains of the virus, that do not respond to the drugs administered. This fact led to several proposals of ways to include these effects in the HIV-1 infection models used, thus being able to have them into account when projecting the treatment plans through the chosen control technique, which were shown to replicate the effects seen in the available patient data.

Promising as they are, the models and respective control that were devised were in general Pharmacodynamic (PD) models, meaning they merely focus on the effect the drugs used have on the virus dynamics. In order to realistically project therapies, the Pharmacokinetic (PK) of the drugs, that study the dynamics of the drug plasma concentrations, should also be considered. The combination of both models allows the design of therapies that consist of drug doses taken as pills, simulating their variation in concentration and consequently in their effect over the virus dynamics.

This work focuses on designing such therapies for a model of the HIV-1 infection that considers an Antiretroviral (ARV) treatment comprising two different drug classes, reverse transcriptase inhibitors (Reverse Transcriptase Inhibitor (RTI)) and protease inhibitors (Protease Inhibitor (PI)). The RTI, have the effect of avoiding the infection of healthy CD4+ T cells, while the
focus on preventing the replication of the virus particles in the host cells. The totality of the model includes one PK model for each drug and a three state non-linear PD model of the infection. Patient adherence and drug resistance effects are also included, which is done in a more realistic way than when considering exclusively a PD model, once the drug levels for which resistance starts developing can now be expressed in actual drug concentrations, and imperfect adherence can be modeled by the patient actually failing to take certain drug doses.

The need for state estimation in this type of problems has already been made clear, and is fulfilled in this work through an Extended Kalman Filter (EKF), which has shown good results when applied to non-linear problems such as this one. Although Decimated Moving Horizon Estimation [30] has an improved performance with respect to the Extended Kalman Filter (EKF), this last algorithm has a lower computational load and suits the purposes of this work.

The control approach chosen to address this problem was Non-Linear Model Predictive Control (NMPC) [14, 15], a technique based on non-linear model predictions, used to find the optimal set of inputs for which the model states are as close as possible to the state reference used. This choice is justified by the power and flexibility of this technique, that has shown good results before, when applied to non-linear systems of a similar complexity to the one considered here.

Besides the implementation of a solution for this control problem, an analysis of its potentialities is also set as an objective, through the adjustment of its parameters, namely concerning the control over the relative amount of each drug to be used. As mentioned before, this can have implications in finding treatments that incur in less side-effects for the patient. Additionally, it is relevant to understand how this type of control solution would react to situations of low adherence to the treatment, and consequent development of resistance to the drugs used. As discussed earlier, limitations exist concerning the patient measurement periodicity. Understanding how the infection control reacts to these same limitations then becomes an important objective to be achieved through the work developed in this dissertation. Another significant aspect is model uncertainty and its impact on control performance. As such, the effect of parameter estimation errors is evaluated in this respect.

1.2 Literature Review

The fields of theoretical immunology and virology, subject to an overview in [13], have witnessed a great development in the past decades, applying mathematical principles to these areas, with the objective of gaining insight about the biological processes studied. This idea is not new [12], but recent progresses in molecular biology instrumentation have boosted the interest in this field, by providing an experimental approach to the mathematical models.

Work on mathematical model analysis of the HIV-1 infection has been going on since the seminal paper [16] was published, where the pharmacodynamics of the infection were studied and a dynamic model was developed, pointing the attention to the importance of phenomena that take place in time scales of days and weeks, that are fast when compared with the time scale of AIDS. From that moment on, many works have been reported in the literature concerning both model development and analysis [17, 18], with more complex models being proposed, going from the initial third order model to models reaching 6 states. There was also a focus in patient adherence and drug resistance effects, that were considered in the models studied in [9, 10, 19]. In [11] a model of pharmacodynamics of antiretroviral drugs in HIV-1 infected patients that incorporates drug susceptibility and patient adherence is discussed.
Parameter identifiability and estimation have been addressed, with approaches proposed in \cite{8, 5, 6, 7}, through data available from clinical trials, showing the possibility of effectively characterizing the infection using these dynamic models.

The models developed allowed for therapy design through control algorithms \cite{20, 21} that drove the modeled infection to a safe level, using control techniques such as nonlinear control \cite{22, 14, 23} and optimal control \cite{24, 25}. A recent paper \cite{31} addresses the application of periodic control to drug delivery, using a variation of a model for tolerance to the cardio-accelerating effect of nicotine.

Predictive control is currently receiving an increased attention in relation to HIV-1. In \cite{26} MPC is used to schedule interruptions in highly active anti-retroviral therapy (HAART) used to simulate a therapeutic vaccine. Treatment schedules based on robust multirate MPC are proposed in \cite{27}. In order to minimize drug consumption, \cite{28} proposes a MPC based algorithm in which the dose (given with a sampling time of one week) is restricted either to be zero or the maximum acceptable value.

1.3 Contributions

The dissertation contributions start with the characterization of the NMPC and EKF state estimation implementations devised, used to solve the HIV-1 model control problem considered. Control results are detailed for the PD model, where the NMPC control technique is shown to be more effective than Linear MPC. Results are also provided for the control of the complete PK+PD model of the infection, taking into account a range of different conditions such as parameter uncertainty, imperfect patient adherence and drug resistance effects. For the PK+PD control system, the effects of control parameter manipulation are explored, namely in determining the combination of PI and RTI drug doses that is used to achieve the control objective, that can be used to minimize treatment toxicity. A robustness analysis of this control system is also provided, with respect to parameter uncertainty, sparse measurements, imperfect adherence and drug resistance effects.

1.4 Dissertation Outline

A general description of the dissertation structure is given in this section, by means of the list of chapters provided below, where their general purpose is described.

- **Chapter 2** Provides a detailed explanation of the HIV-1 infection model used, as well as of the notation used throughout the dissertation.

- **Chapter 3** Details the EKF state estimation designed for this problem, also providing test results concerning its robustness.

- **Chapter 4** Describes the NMPC technique used and its implementation in this particular control problem, for the PD and PK+PD models.

- **Chapter 5** Presents and discusses the control results obtained, comparing NMPC and Linear MPC solutions for control of the PD model, and later addressing PK+PD model control results, considering a series of different conditions such as parameter uncertainty, imperfect patient adherence and drug resistance effects.
• **Chapter 6** Explores the potentialities of tuning control parameters in improving the control quality, and also in influencing the drug dose combinations used in the control, discussing its application to treatment toxicity minimization.

• **Chapter 7** Focuses on a robustness analysis of the control system with respect to several adverse conditions, such as parameter uncertainty, sparse measurements, imperfect adherence and drug resistance effects.
Chapter 2

HIV-1 Infection Model

This chapter focuses on describing the HIV-1 infection model considered in this work, starting with a general overview pointing out the main components, and then exploring each one of them in detail in the subsequent sections. A simplified notation for the whole model in discrete time is defined, that is essential for simplifying the comprehension of the chapters ahead, where state estimation and control are explained.

2.1 General Model Description

The general HIV-1 infection model considered in this work describes the infection dynamics taking as inputs a series of periodic drug doses administered to a given patient. The model has as outputs the total CD4+ T cell concentration (healthy and infected), as well as the concentration of virus particles present in the sample in question. The model structure is summarized by the diagram in Figure 2.1, where these two outputs are referred to as $y_1$ and $y_2$ respectively.

Figure 2.1: PK+PD model of HIV-1 infection including adherence and drug resistance models.

The infection treatment is made possible through two inputs, corresponding to two different drugs. These are the Reverse Transcriptase Inhibitors (RTI), that prevent healthy cells from
being infected by virus particles, and the Protease Inhibitors (PI), preventing new virus particles from being produced. The RTI doses administered are represented as $u_{PK1}$, while PI doses correspond to $u_{PK2}$. These are modeled as trains of square impulses with a narrow duration, corresponding to the pills taken by the patient.

It should be remarked that this is a simplification. There are other active principles and, furthermore, the action of the active principles may vary depending on the galenic formulation.

As shown on Figure 2.1, the model initially includes a model of patient adherence to the therapeutics, aiming to replicate the effect of a patient failing to take certain prescribed drug doses. The drug doses that are actually taken are represented as $u_{PK1}$ and $u_{PK2}$. This is followed by one PK model for each drug, that determine the plasma concentration of that same drug through time, for an administered drug dose at a certain instant. The plasma concentrations, referred to as $C_{p1}$ and $C_{p2}$, are then fed to the PD model. Here the concentrations are first converted into drug effects $u_1$ and $u_2$, including a model of the development of virus resistance to drugs, as a consequence of low adherence. Those drug effect values are then introduced into the virus dynamics model, determining their actual impact in containing the infection.

Being the general description of its structure complete, the next sections now focus on further detailing each part of the model.

### 2.2 PK Models

#### 2.2.1 PK Models Identification

As stated in the previous section, a PK model for a certain drug describes its plasma concentration variation for a certain discrete drug dose taken by the patient. The concentration behavior is likely to be different for each one of the drugs that can be administered, making it necessary to obtain a distinct model for each one of them. Having access to data on their pharmacokinetic behavior, it becomes possible to develop the two distinct models through identification.

A least-squares approach was selected to identify the models, which were selected to be Autoregressive Model with Exogenous Terms (ARX) models with the structure

$$PK(q) = \frac{B_{PK}(q)}{A_{PK}(q)} = \frac{b_1q^{-1} + b_2q^{-2} + b_3q^{-3}}{1 + a_1q^{-1} + a_2q^{-2} + a_3q^{-3}}$$

where $q^{-1}$ is the backward shift operator and $a_i$ and $b_i$ are parameters.

A delay of one sampling period was imposed in the model, as there must be a minimum degree of delay between the instant when the dosage is administered and the plasma concentration changes. As shown in (2.1), the model order chosen was 3 for both the numerator and denominator, once it proved to be the smallest order for which the identification results were acceptable. Least-squares identification was then performed yielding the two models below

$$C_{p1}(q) = \frac{B(q)}{A(q)} = \frac{0.01399q^{-1} - 0.03482q^{-2} + 0.03216q^{-3}}{1 - 2.176q^{-1} + 1.617q^{-2} - 0.415q^{-3}}$$

$$C_{p2}(q) = \frac{B(q)}{A(q)} = \frac{0.01825q^{-1} - 0.04469q^{-2} + 0.03363q^{-3}}{1 - 2.502q^{-1} + 2.159q^{-2} - 0.6433q^{-3}}$$

where $C_{p1}$ is the plasma concentration of the RTI drugs and $C_{p2}$ is the plasma concentration of the PI drugs. Their responses to a single dosage (impulse) are illustrated in Figure 2.2.
It is immediately visible from the impulse response that the concentration values rise and return to low values in a period of about one day in both cases, meaning that, for the drugs considered, achieving the goal of maintaining a stable concentration in the patient’s system will probably require at least daily drug doses to be administered.

Again an approximation is made here, since the shape of these responses may be affected by various factors, e.g. by taking the medication during meals.

### 2.2.2 State-Space Formulation

It is useful to define the PK models in (2.2) and (2.3) in a continuous time state-space formulation, for utilization in describing the state estimation and control designed in the next chapters. The models had to undergo a conversion to continuous time, using a ZOH approximation, before being transformed into a state-space formulation, yielding two models with three states each presented below

\[
\dot{C}_{s1} = \begin{bmatrix} \dot{C}_{s11} \\ \dot{C}_{s12} \\ \dot{C}_{s13} \end{bmatrix} = A_{PK1} C_{s1} + B_{PK1} u_{PK1} = \begin{bmatrix} -17.59 & 1 & 0 \\ -138.61 & 0 & 1 \\ -321.36 & 0 & 0 \end{bmatrix} \begin{bmatrix} C_{s11} \\ C_{s12} \\ C_{s13} \end{bmatrix} + \begin{bmatrix} 0.72 \\ -11.71 \\ 140.17 \end{bmatrix} u_{PK1}
\]

\[
C_{p1} = \begin{bmatrix} 1 & 0 & 0 \\ \end{bmatrix} \begin{bmatrix} C_{s11} \\ C_{s12} \\ C_{s13} \end{bmatrix}
\]

\[
\dot{C}_{s2} = \begin{bmatrix} \dot{C}_{s21} \\ \dot{C}_{s22} \\ \dot{C}_{s23} \end{bmatrix} = A_{PK2} C_{s2} + B_{PK2} u_{PK2} = \begin{bmatrix} -8.82 & 1 & 0 \\ -67.32 & 0 & 1 \\ -140.31 & 0 & 0 \end{bmatrix} \begin{bmatrix} C_{s21} \\ C_{s22} \\ C_{s23} \end{bmatrix} + \begin{bmatrix} 0.6437 \\ -7.8314 \\ 72.1560 \end{bmatrix} u_{PK2}
\]

\[
C_{p2} = \begin{bmatrix} 1 & 0 & 0 \\ \end{bmatrix} \begin{bmatrix} C_{s21} \\ C_{s22} \\ C_{s23} \end{bmatrix}
\]

(2.4)
where the variables $C_{p1}$ and $C_{p2}$ are the RTI and PI plasma concentrations. For matters of simplification, the model in (2.4) can be referred to as follows

$$
\dot{C}_{s1} = \gamma_1(C_{s1}(t), u_{PK1}(t))
$$

$$
\dot{C}_{s2} = \gamma_2(C_{s2}(t), u_{PK2}(t))
$$

$$
C_p(t) = \begin{bmatrix}
C_{p1} \\
C_{p2}
\end{bmatrix}(t) = h_{PK}C_s(t)
$$

(2.5)

where it can be seen that the output equations have been merged into one. This was done to facilitate the integration with the PD model in a posterior section of this chapter, by making the following assumptions

$$
h_{PK} = \begin{bmatrix}
1 & 0 & 0 \\
1 & 0 & 0
\end{bmatrix}
$$

$$
C_s = \begin{bmatrix}
C_{s1} \\
C_{s2}
\end{bmatrix}
$$

(2.6)

### 2.3 PD Model

#### 2.3.1 Hill Equation

The outputs of the model identified in the previous section are drug concentrations, while the non-linear virus dynamics model used has inputs corresponding to the effect of each available drug. It is thus required that an adequate conversion from drug concentrations to drug effects is devised, in order to bring the two models together. The method chosen to achieve this was to use the Hill equation

$$
\eta(C_p) = \frac{C_p}{C_{50} + C_p}
$$

(2.7)

where $C_p$ is the plasma concentration obtained as output of the PK model, and $C_{50}$ is the concentration at which the drug reaches an effect of 0.5. The behavior of this function is best understood by examining the graph in Figure 2.3 where the relationship between the drug concentration $C_p$ and its effect is depicted for varying values of $C_{50}$.

![Figure 2.3: Drug effect as a function of its concentration.](image)

The existence of two distinct drugs obviously calls for two different equations to be used, with values of $C_{50}$ that are specifically adapted to each one of them. The two equations used
are depicted below

\[ u_1(t) = \frac{C_{p_1}(t)}{C_{50} + C_{p_1}(t)} \]  \hspace{1cm} (2.8)

\[ u_2(t) = \frac{C_{p_2}(t)}{C_{50} + C_{p_2}(t)} \]  \hspace{1cm} (2.9)

where \( u_1 \) and \( u_2 \) correspond to the effects of [RTI] and [PI] drugs respectively, thus being limited between 0 and 1.

### 2.3.2 Virus Dynamics

The non-linear model describing the HIV-1 infection virus dynamics considered in this work is better described in \[ 1 \], and models the infection using the following three state variables:

- \( x_1 \), plasma concentration of healthy T-CD4+ cells;
- \( x_2 \), plasma concentration of infected T-CD4+ cells;
- \( x_3 \), plasma concentration of free virus particles (virions).

The interactions between each state involved yield the non-linear state space model below:

\[
\begin{align*}
\dot{x}_1 &= s - dx_1 - (1 - u_1)\beta x_1 x_3 \\
\dot{x}_2 &= (1 - u_1)\beta x_1 x_3 - \mu x_2 \\
\dot{x}_3 &= (1 - u_2)kx_2 - cx_3 \\
y &= \begin{bmatrix} y_1 \\ y_2 \end{bmatrix} = \begin{bmatrix} 1 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}
\end{align*}
\]  \hspace{1cm} (2.10)

The first equation shows that the healthy cell concentration \( x_1 \) is proportional to their production rate \( s \), and inversely proportional to their death rate, corresponding to the product of their death rate coefficient \( d \) and \( x_1 \). The healthy cell concentration \( x_1 \) is also inversely proportional to the cell infection rate, described by the product between \( x_1 \), the concentration of virions \( x_3 \), and the infection rate coefficient \( \beta \). This rate can be changed by the influence of input variable \( u_1 \), corresponding to the [RTI] effect. This variable can take values from 0 to 1, corresponding to none and total efficiency in preventing cell infection.

The second equation has a first term representing the cell infection rate, identical to the one just described, while the second term represents the death rate of infected cells, proportional to parameter \( \mu \), their death rate coefficient, and to the infected cell concentration \( x_2 \).

The first term in the third model equation represents the free virus production rate, which is the product of the virus production rate coefficient \( k \), the concentration of infected cells \( x_2 \), and a parcel accounting for the effect of input variable \( u_2 \), representing the action of [PI] drugs, that prevent infected cells from producing virus particles. The second term represents the death rate of the virions, \( c \) being their death rate coefficient. These dynamics are more easily understood through the diagram in Figure 2.4.

The output equation shows that, as stated in the beginning of the chapter, the two measurable states are \( y_1 = x_1 + x_2 \), corresponding to the total concentration of cells, and \( y_2 = x_3 \).
Figure 2.4: Diagram of virus dynamics model.

that stands for the concentration of free virus particles. A summarized explanation of each parameter meaning, as well as their standard values used in the simulations throughout this work, are given in Table 2.1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>$s$</td>
<td>Healthy Cells Production Rate</td>
<td>10</td>
<td>$mm^{-3}day^{-1}$</td>
</tr>
<tr>
<td>$d$</td>
<td>Healthy Cells Death Rate Coefficient</td>
<td>0.02</td>
<td>$day^{-1}$</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Infection Rate Coefficient</td>
<td>$2.4 \times 10^{-5}$</td>
<td>$mm^3 day^{-1}$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Infected Cells Death Rate Coefficient</td>
<td>0.24</td>
<td>$day^{-1}$</td>
</tr>
<tr>
<td>$k$</td>
<td>Virus Production Rate Coefficient</td>
<td>100</td>
<td>$day^{-1}$</td>
</tr>
<tr>
<td>$c$</td>
<td>Virus Death Rate Coefficient</td>
<td>2.4</td>
<td>$day^{-1}$</td>
</tr>
</tbody>
</table>

Table 2.1: Virus dynamics model parameters.

A quick analysis of the equations in (2.10) shows that the model includes several non-linearities, which should make its control a challenging problem to overcome. For matters of simplification, the model in (2.10) can be referred to in the way shown below, where the Hill equations defined in the previous section were included in the notation.

$$\dot{x} = \phi(x(t), C_p(t))$$

$$y = h_{PD}(x(t), C_p(t))$$

(2.11)

2.3.3 Model Behavior Analysis

In order to provide a better understanding of the model described in the previous section, a study of its behavior is provided, as well as the corresponding interpretation in the context of this disease. The first step should be to observe the model behavior for a healthy person that has just contracted the infection. As proposed in [14], it is assumed that the patient in question has no infected cells, and has a virus concentration of only 1 copy/mm$^3$, yielding the following initial condition:

$$x = \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} = \begin{bmatrix} 500 \\ 0 \\ 1 \end{bmatrix}$$

(2.12)

It was also assumed that no type of medication was provided to the patient at this stage, meaning the manipulated variables in the model always took a value of zero. The model was
then run for the initial conditions stated, using three different model parameter combinations, and the resulting state variations are represented in Figure 2.5.

![Graphs](image)

(a) $x_1$

(b) $x_2$

(c) $x_3$

Figure 2.5: Virus dynamics model response for initial conditions in (2.12) and input values $u = [0\ 0]$.

The results show that, for the standard parameter values case, the concentration of free virus and infected CD4+T cells only starts to rise significantly after about 30 days. After this point those concentrations rise sharply, peaking around 50 days of infection, accompanied by a severe decrease in the concentration of healthy cells. The concentrations of infected cells and virions then decline, stabilizing after about 6 months at the values shown in (2.13).

$$
x_{eq} = \begin{bmatrix}
x_1 \\
x_2 \\
x_3
\end{bmatrix} = \begin{bmatrix}
240 \\
21.67 \\
902.78
\end{bmatrix}
$$

(2.13)

The figure also depicts the model response for situations where $k = 120$ and $\mu = 0.288$, representing a 20% increase in each one of these parameters. When $k = 120$, meaning that the virus production rate will be higher, the virion and infected cell concentrations peak and stabilize sooner and at higher values than before, reflecting the fact that a bigger amount of virus particles is now being produced. In the case where $\mu = 0.288$, the inverse happens. As the infected cell death rate is now higher, the organism tends to have less cells producing
virus particles, resulting in a behavior in which the virus concentrations peak and stabilize later in time, and at lower values than in the standard case.

In actual clinical situations this steady infection state is maintained for 2 to 10 years, after which the patient develops AIDS, resulting from a drastic decline in the number of healthy CD4+T cells. However, this stage is not covered by the model in question. When simulating the treatment of a given patient in this work, it will always be assumed that he already is in the steady infection state in (2.13).

As recommended in [4], the treatment objective will be to bring the concentration of free virus particles, corresponding to model state \( x_3 \), to a value below 100 copies/mm\(^3\) within eight weeks of treatment, and below 50 copies/mm\(^3\) before reaching 6 months of treatment. Succeeding in keeping the concentrations in these low levels prevents the patient from developing AIDS and entering the critical phase of the disease.

### 2.4 Model Discretization

The implementation of the controllers and estimation filters to be described in further sections was done in discrete time, which required a discretization of the HIV-1 infection model to be performed. A Zero Order Hold (ZOH) technique was used to approximate the derivatives in each part of the model.

Starting with the PK models, the ZOH approximation of their simplified notation shown in (2.6) yields

\[
\begin{align*}
C_{s_1}(k+1) &= C_{s_1}(k) + \Delta \gamma_1(C_{s_1}(k), u_{PK_1}(k)) \\
C_{s_2}(k+1) &= C_{s_2}(k) + \Delta \gamma_2(C_{s_2}(k), u_{PK_2}(k))
\end{align*}
\]

(2.14)

where \( \Delta \) is the sampling interval and the discrete time \( k \) stands for the continuous time \( k\Delta \).

The dynamics described in (2.14) can be rewritten as

\[
\begin{align*}
C_{s_1}(k+1) &= \Gamma_1(C_{s_1}(k), u_{PK_1}(k)) \\
C_{p_1}(k) &= h_{PK_1}(C_{s_1}(k)) \\
C_{s_2}(k+1) &= \Gamma_2(C_{s_2}(k), u_{PK_2}(k)) \\
C_{p_2}(k) &= h_{PK_2}(C_{s_2}(k))
\end{align*}
\]

(2.15)

with an obvious definition for \( \Gamma_1 \) and \( \Gamma_2 \).

In the PD model, the Hill equations do not require any approximation to be written in discrete form, being identical to their continuous versions:

\[
\begin{align*}
u_1(k) &= \frac{C_{p_1}(k)}{C_{50}^1 + C_{p_1}(k)} \\
u_2(k) &= \frac{C_{p_2}(k)}{C_{50}^2 + C_{p_2}(k)}
\end{align*}
\]

(2.16)

(2.17)

For the virus dynamics, and also using a simplified notation of the model in (2.11), the discretization of the virus dynamics model through ZOH has the result shown below

\[
x(k+1) = x(k) + \Delta \phi(x(k), C_p(k))
\]

(2.18)
where again $\Delta$ is the sampling interval and the discrete time $k$ stands for the continuous time $k\Delta$. The discrete dynamics in (2.18) can be rewritten including the Hill equations in (2.16), with an obvious definition for $\Phi$:

$$x(k + 1) = \Phi(x(k), C_p)$$
$$y(k) = h_{PD}(x(k), C_p) \tag{2.19}$$

For the purpose of facilitating the description of algorithms in the coming chapters of the dissertation, a notation for the total discretized HIV-1 infection model had to be devised. The first step towards that goal should be to define a new state vector:

$$z = \begin{bmatrix}
C_{s11} \\
C_{s12} \\
C_{s13} \\
C_{s21} \\
C_{s22} \\
C_{s23} \\
x_1 \\
x_2 \\
x_3
\end{bmatrix} = \begin{bmatrix}
C_{s1} \\
C_{s2} \\
x
\end{bmatrix} \tag{2.20}$$

Using this state vector, the total HIV-1 infection model can be defined as

$$z(k + 1) = f(z(k), u_{PK}(k))$$
$$y(k) = h(z(k)) \tag{2.21}$$

where $f$ and $h$ stand for:

$$f(z(k), u_{PK}(k)) = \begin{bmatrix}
\Gamma_1(C_{s1}(k), u_{PK1}(k)) \\
\Gamma_2(C_{s2}(k), u_{PK2}(k)) \\
\Phi(x(k), h_{PK}C_s(k))
\end{bmatrix}$$
$$h = \begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0
\end{bmatrix} \tag{2.22}$$

### 2.5 Adherence and Drug Resistance

#### 2.5.1 Adherence Model

The biggest cause of failure in HIV-1 infection treatment is low patient adherence, meaning that the patient fails to take all the doses prescribed, and thus disturbs the intended control of the virion concentration levels. The prevalence of this situation makes it relevant to include it in the model, to try and estimate the effects of low adherence in the success with which the infection is contained. In [10], adherence is defined as the function $A$, given by:

$$A = \begin{cases}
1, & \text{if all doses are taken during the assessment time} \\
R_k, & \text{if } R_k \text{100% doses are taken during assessment time}
\end{cases} \tag{2.23}$$
The definition above can be included in the infection control implementation already developed, by assigning to each dose a probability of $R_k$ that the patient actually takes it. For whatever simulation time chosen, by its end the patient will have taken approximately $R_k100\%$ of the doses prescribed.

### 2.5.2 Drug Resistance Model

In case the drug concentrations decrease below certain limit values during treatment, the patient can develop resistance to those drugs, meaning that an equal drug concentration has less effect than it had before. This decrease in effect is permanent, meaning that the degree of efficacy of a certain drug can not be recovered once its concentration rises over the mentioned limit again. This situation is better illustrated in the diagram in Figure 2.6, where the shaded area signals the instants when the drug concentration is causing resistance to develop.

![Figure 2.6: Graphic explanation of drug resistance effect.](image)

This effect can be added to the model described before by changing the $C_{50}$ values in the Hill equations accordingly. The variables $C_{50}^i$, $i = 1, 2$ are then redefined as

\[
C_{50}^1 = f_{R_1}(t)C_{50_{base}}^1 \\
C_{50}^2 = f_{R_2}(t)C_{50_{base}}^2
\]

where $f_{R_i}, i = 1, 2$ corresponds to:

\[
f_{R_1}(t) = 1 + K_{R_1} \int_0^t \max[0, L_{R_1} - C_{p_1}(\tau)] \, d\tau \\
f_{R_2}(t) = 1 + K_{R_2} \int_0^t \max[0, L_{R_2} - C_{p_2}(\tau)] \, d\tau
\]

The integral in (2.25) causes the variable $f_{R_i}$ to increase each time the drug concentration $C_p$ goes below a minimum threshold $L_{R_i}$. The resistance model just described is graphically detailed in Figure 2.7.

![Figure 2.7: Drug resistance model.](image)

Since the resistance the organism develops is definitive, so is the increase of $f_{R_i}$, meaning that its value will not decrease when the concentration is above the threshold value $L_{R_i}$. The
integral gain $K_R$, will define the rate at which this resistance is developed, and will help tune the influence of this effect in the model, bringing it as close as possible to what happens in actual patients.
Chapter 3

Non-Linear State Estimation with Extended Kalman Filter

This chapter details the non-linear state estimation devised for the HIV-1 infection model, done using a multi-rate implementation of an Extended Kalman Filter. An explanation is given of the selected filter tuning, which is then tested for robustness through a series of simulations that replicate the type of variations the model states should encounter when being controlled.

3.1 Extended Kalman Filter

As shown in the HIV-1 infection model description, not all its states are accessible for measurement. In fact there is only access to the concentration of virus particles, that corresponds to the state \( x_3 \), and to the total concentration of CD4+ T cells, corresponding to the sum of the two remaining system states \( x_1 + x_2 \). An estimate of all the system states is then necessary, since those states are needed to perform the prediction within the model predictive control block. An effective way to estimate all the system states is to use an Extended Kalman Filter \([3]\), that allows the same kind of estimation done with the Kalman Filter to be performed in the non-linear case.

This type of state estimation is done in two steps: prediction and update. Firstly, a prediction of the system states for the next instant is computed using the discretized version of the HIV-1 infection non-linear model described in (2.16), as shown below:

\[
\hat{z}_{k|k-1} = f(\hat{z}_{k-1|k-1}, u_{PK_{k-1}})
\]  

(3.1)

The second part of this step consists in computing the estimated covariance matrix \( P_{k|k-1} \). The first value of the estimated covariance \( P_{k-1|k-1} \) is to be specified previously according to the problem to be addressed. This is done in the Kalman Filter by using the dynamics matrix of the system to propagate the covariance matrix, and summing the covariance matrix of the process noise \( Q_k \). The bigger the process noise we assume for a given state, the less we trust the model predictions of its value. In the Extended Kalman Filter case, the dynamics matrix of the linear system is replaced by a Jacobian matrix, corresponding to the linearization of the non-linear model around the previous system state:

\[
P_{k|k-1} = F_k P_{k-1|k-1} F_k^T + Q_k
\]

\[
F_{k-1} = \frac{\partial f}{\partial z} \hat{z}_{k-1|k-1}, u_{PK_{k-1}}
\]

(3.2)
In the case of the HIV-1 infection model, the Jacobian matrix for the linearized system is the one shown below:

\[ F_{k-1} = \begin{bmatrix}
-17.59 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
-138.61 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
-321.36 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & -8.82 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & -67.32 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & -140.31 & 0 & 0 & 0 & 0 & 0 \\
T_s x_1 x_3 \beta & 0 & 0 & 0 & 0 & 1 - T_s (d + U_1) \beta x_3 & 0 & -T_s U_1 \beta x_1 \\
-T_s x_1 x_3 \beta & 0 & 0 & 0 & 0 & T_s U_1 \beta x_3 & 1 - T_s \mu & T_s U_1 \beta x_1 \\
0 & 0 & 0 & -T_s k x_2 \beta & 0 & 0 & 0 & T_s U_2 k & 1 - T_s c \\
\end{bmatrix} \]

(3.3)

where \( U_1 = 1 - u_1 \) and \( U_2 = 1 - u_2 \), and \( T_s \) is the system sampling period, also assumed to be the sampling period of the model used in the predictions. It is then enough to replace the states in the matrix with the last known system state to obtain the desired linearization around the last operating point.

The update step starts with the computation of the innovation residual \( \tilde{y}_k \), done by subtracting the predicted outputs computed using the non-linear model of the system to the measured outputs \( y_k \):

\[ \tilde{y}_k = y_k - h(\hat{z}_{k|k-1}) \]

(3.4)

The residual covariance \( S_k \) is then computed by multiplying the current covariance matrix by the output matrix \( H_k \) of the system and summing the observation noise \( R_k \) as follows:

\[
S_k = H_k P_{k|k-1} H_k^T + R_k
\]

(3.5)

where the output matrix is a Jacobian corresponding to a linearization around the last state of the system. The bigger the observation noise, the less we trust the information obtained through the outputs of the system.

In this case there is no need to perform a linearization, once the output function of the system model is already linear:

\[
H_{k-1} = \begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\
\end{bmatrix}
\]

(3.6)

The state estimate is then updated proportionally to the Kalman gain \( K_k \), that is proportional to the estimate covariance, and inversely proportional to the residual covariance:

\[
K_k = P_{k|k-1} H_k^T S_k^{-1}
\]

\[
\hat{z}_{k|k} = \hat{z}_{k|k-1} + K_k \tilde{y}_k
\]

(3.7)

expressing thus less confidence in the model prediction as it takes higher values.

Finally the estimated covariance is updated, according to the Kalman gain used to adjust the state estimates:
The process is then repeated, once the next system measurement is taken.

### 3.2 Multi-Rate EKF

The EKF performance can be improved by implementing it in a multi-rate way, meaning that the filter will be allowed to perform several prediction steps between each measurement and corresponding update step.

The number of prediction steps performed between each update step is to be determined by a new parameter, the EKF prediction interval $T_{EKF}^p$, corresponding to the time interval between two predictions. For instance, if it takes a value of 0.25 days and the system sampling period $T_s$ is 1 day, 4 prediction steps will be performed before an update step takes place. This number of prediction steps can be defined as variable $N_p$ as shown below

$$N_p = \frac{T_s}{T_{EKF}^p}$$

When tuning the EKF parameters, it will be required to take into account the fact that the prediction step will now occur many more times than in the standard implementation. More specifically, it should be noted that $Q_k$ is now added several times in the covariance matrix $P_{k|k-1}$ propagation step depicted in (3.2), before the update step is performed and $R_k$ is taken into account.

It is thus expectable that an adequate tuning of the EKF will now require a reduction of the $Q_k$ values used in the standard case, or a corresponding increase in $R_k$. Otherwise, the process noise value will have more impact in the computation of the Kalman gain than intended, thereby deteriorating the estimation.

### 3.3 EKF Tuning

The Extended Kalman Filter has three tunable variables, whose values should be selected according to the specific problem to be addressed. These are the process noise $Q_k$, the observation noise $R_k$, and the initial estimation covariance $P_{k-1|k-1}$. These are chosen to be diagonal matrices, so that a single matrix entry exclusively affects the corresponding state in the $Q_k$ and $P_{k-1|k-1}$ cases, or a single model output in $R_k$. The matrices are defined as follows:

$$Q_k = \begin{bmatrix} q_{11} & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & q_{99} \end{bmatrix}, \quad R_k = \begin{bmatrix} r_{11} & 0 & 0 \\ 0 & r_{22} & \vdots \\ 0 & \vdots & r_{99} \end{bmatrix}, \quad P_{k-1|k-1} = \begin{bmatrix} p_{11} & \cdots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \cdots & p_{99} \end{bmatrix}$$

As explained earlier, the less we trust the values estimated by the model, the larger should the values in the matrix $Q_k$ be. In the case of $R_k$, the larger the values, the less we trust the measured outputs. The initial values of $P_{k-1|k-1}$ should be higher if we want the first measurements to have a big impact on the estimated value.

Since in this particular problem we measure the value of state $x_3$ directly as one of the system outputs, we should trust the measured values the most, meaning that we should have a high $q_{99}$ and a low $r_{22}$. The other system output is $x_1 + x_2$, where $x_1$ always takes much higher
values than $x_3$, making the latter harder to estimate. We should then rely more on the values predicted by the model than on the measured output when estimating $x_2$. This means that $r_{11}$ should be high, $q_{88}$ should be low and $q_{77}$ can take a higher value than $q_{88}$ since the measurements indicate the $x_1$ value more accurately.

Following the previous logic, considering the fact that a multi-rate implementation was used, and after some experimentation, the process and observation noise values yielding the best results were determined to be the ones presented in (3.11) below:

$$Q_k = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0.5 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0.001 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 50
\end{bmatrix} \quad (3.11)$$

$$R_k = \begin{bmatrix}
0.5 & 0 \\
0 & 0.0005
\end{bmatrix} \quad (3.12)$$

The initial estimation covariance $P_{k-1|k-1}$ should determine which state values are corrected the most using the innovation residual, each time a system measurement is taken. The fact that $x_3$ is measured directly suggests that this state should have a higher estimation covariance and thus follow the measurements closely, while for the two other virus dynamics states it should be lower, relying more on the predictions made, especially in the case of $x_2$, for the reasons explained earlier. The matrix values chosen are presented below:

$$P_{k-1|k-1} = \begin{bmatrix}
1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0.1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0.01 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1
\end{bmatrix} \quad (3.13)$$

### 3.4 EKF Robustness Evaluation

Once the EKF was implemented, it became important to understand the estimation quality that it could provide, as well as its robustness to sparser measurements, in other words to larger system sampling intervals. Tests showed that when the model parameters used in the estimation were accurate, the EKF showed great robustness, withstanding very large sampling times while still providing very good estimations of the system states, as can be seen in Figure 3.1.

The simulations were run respecting the parameter values stated in Table 3.1, where the input values chosen, as well as their periodicity, are within the values that are needed to address this particular control problem, as will be seen further ahead in the dissertation.
Despite being very encouraging, the results obtained do not account for any uncertainty in the model parameters, meaning that it is assumed that the model used to describe the infection for a given patient is completely accurate. This will obviously not happen in a real life situation, where the parameters will surely deviate in a certain amount from their ideal values. It is thus important to assess the robustness level of the state estimation in this type of situations.

<table>
<thead>
<tr>
<th>System Sampling Interval</th>
<th>30 day</th>
</tr>
</thead>
<tbody>
<tr>
<td>EKF Prediction Interval</td>
<td>0.05 day</td>
</tr>
<tr>
<td>Input Values</td>
<td>[400 600] mg</td>
</tr>
<tr>
<td>Input Periodicity</td>
<td>0.5 day</td>
</tr>
</tbody>
</table>

Table 3.1: EKF and simulation parameters.

That was done by repeating the simulations just described, while making the model parameter $k$ used in the estimation deviate 20% from the value in the model, to 120 $day^{-1}$. The simulation and estimation parameters kept the same values as in Table 3.1 except for the
sampling period $T_s$ which was reduced to 15 day, with the results depicted in Figure 3.2.

![Graphs](image)

(a) $x_1$
(b) $x_2$
(c) $x_3$
(d) $C_P$

Figure 3.2: Model and EKF responses with model parameter $k = 120 \text{ day}^{-1}$, using a sampling period of $T_s = 15 \text{ day}$ and remaining parameters in Table 3.1.

The results show an evident deviation of the estimations from the real values between measurements, when their values are corrected through the update step that is performed. This does not happen for the concentration estimations, once the parameter uncertainty concerns exclusively the virus dynamics model.

Results also suggest that the more severe the parameter uncertainty present, the more does the degree of estimation degradation depend on the sampling interval used. If the sampling interval is too large, estimations will deviate from the real state values due to the parameter uncertainty for a long time, creating large discrepancies between them. The degradation in the estimation quality that occurs as the system sampling interval $T_s$ increases is better understood by observing Figure 3.3, in which the average estimation error is plotted for several simulations identical to the one plotted in Figure 3.2 but varying the values of the system sampling interval for each of them.

Based on the results obtained, it is possible to conclude that the quality of the EKF estimation will depend on a compromise between model parameter uncertainty and the size of the system sampling interval. It can nevertheless be stated that, for a relatively small parameter
uncertainty, the patient can be sampled with a periodicity that may be considerably large without severely disturbing the quality of the state estimation. This fact makes it more plausible that conclusions based on these models may be applied to a real life situation.
Chapter 4

Non-Linear Model Predictive Control of HIV-1 Infection Model

The NMPC technique used to control the HIV-1 infection model is detailed in this chapter, starting with an overview of this approach and its potentialities, followed by a more extensive explanation of its structure. A complete description of the algorithms developed to implement the NMPC technique, for the control of the PD model and the total PK+PD model, is also made at this point.

4.1 Introduction to NMPC

Non-Linear Model Predictive Control is a technique that uses a system model to predict the future system behavior for a given set of inputs, as illustrated in Figure 4.1 and then uses that prediction to compute the best possible control so that certain specifications are met.

As explained in the figure, the time length of the input values series that is considered in the prediction is called the control horizon, referred to in this work as $T_{ch}$. The total length of the prediction is called the prediction horizon, to which the variable name $T_{ph}$ was assigned. These two parameters will naturally influence the quality of the control, as they determine how far into the future the control algorithm will look, allowing for a better decision of which input values to use. In control problems that have real-time constraints, the sizes of the two horizons can be an issue as they make the computations considerably heavier when they increase. As this particular control problem does not present very demanding constraints of
that type, the only issue should be to find the horizon values that yield satisfying results. For simplification purposes, the control horizon was always set throughout this work as being equal in size to the prediction horizon, and frequently only the prediction horizon is mentioned when tuning the control.

In a MIMO system such as this one, it can happen that there are fewer input variables than output states, which causes that not all of the states can be brought exactly to their setpoint values. Since generally some states have more importance than others, priorities can be assigned to each state so that the most important ones are assured to reach their reference values. If the system to be controlled has several available inputs, it is also possible to influence which of them is preferably used the most. This becomes very useful if the usage of a particular input is disadvantageous, for instance due to its side effects, as it is the case in this particular problem. This will be later exploited when optimizing the controller settings to comply with toxicity constraints.

4.2 NMPC Control Algorithm

The NMPC technique is explained in detail in [2] for the continuous case. However, this particular problem requires the control to be computed for specific discrete instants in time, corresponding to each drug dose that is taken. This requires the algorithm to be formulated in discrete time. As stated in the previous section, the control is computed by finding the inputs that yield the best predicted system response for a given reference. This is done by solving on-line the following cost functional optimization problem

$$\min_{\bar{u}_{PK}^{T_{ch}-1}} J(z(t), \bar{u}_{PK}^{T_{ch}}, T_{ch}, T_{ph}, T_u)$$

where $T_{ch}$ and $T_{ph}$ are the control and prediction horizons respectively, $T_{ph} \geq T_{ch}$, while $T_u$ is the control periodicity and $z(t)$ is the current state vector value, obtained as a direct measurement or a state estimation. The variable $\bar{u}_{PK}$ corresponds to the virtual control sequence used in the predictions, and is given by:

$$\bar{u}_{PK}^{T_{ch}+i} := [\bar{u}_{PK}(t) \ldots \bar{u}_{PK}(t + T_{ch} - 1)]^T$$

It is assumed that, for $i = 1, \ldots, T_{ph} - T_{ch}$

$$\bar{u}_{PK}(T_{ch} + i) = \bar{u}_{PK}(T_{ch})$$

meaning that if the control horizon is smaller than the prediction horizon, the last value in the virtual control sequence used in the predictions, and is given by:

$$J(z(t), \bar{u}_{PK}^{T_{ch}}, T_{ch}, T_{ph}, T_u) = T_{ph} \sum_{k=1}^{T_{ph}} L[\bar{z}(t + k), \bar{u}_{PK}(t + k - 1)]$$

where $L$ corresponds to a function called stage cost, and $\bar{z}$ represents the predicted state values for the sequence of virtual inputs $\bar{u}_{PK}$. This function specifies the control of the system states to be achieved, as well as the priority given to the usage of each input variable. Its standard quadratic form, which is adopted in this work, is the following

$$L(\bar{z}, \bar{u}_{PK}) = (\bar{z} - z_s)^T Q(\bar{z} - z_s) + \bar{u}_{PK}^T R \bar{u}_{PK}$$
where $Q$ and $R$ are symmetric, positive definite matrices, and the variable $z_s$ is the state reference value.

As stated before, this particular control problem consists in keeping the virion concentration $x_3$ below a value of 50 copies/mm$^3$, meaning that the controller should focus exclusively on making state $x_3$ follow its reference. The setpoint tracking focus is determined in the stage cost equation by matrix $Q$, that should thereby assign a weight factor exclusively to this state, making the other state values irrelevant to the final stage cost function value, as seen below:

$$Q = \begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 
\end{bmatrix}$$  \hspace{1cm} (4.6)

Concerning the input variables, there is interest in keeping control over which of them is used the most, for applications concerning treatment toxicity minimization, which will be explored further ahead. With this objective in mind, the matrix $R$ that defines their impact in the stage cost function was designed so that they were affected by an individual weight each. This translates into the following matrix:

$$R = \begin{bmatrix}
w_{u_1} & 0 \\
0 & w_{u_2} 
\end{bmatrix}$$  \hspace{1cm} (4.7)

Once the minimization problem in (1.1) is solved, and thus the optimal value of $\bar{u}_{PK}^{T_{th}}$ is found, the first pair of input variable values of this sequence is applied to the system. After a period of time corresponding to the treatment periodicity $T_u$, the controller updates the current state vector values $z(t)$, and uses them together with the current reference value to restart the algorithm.

### 4.3 NMPC Implementation

During the course of the work presented in this dissertation, two implementations of the algorithm described above were devised, one that controlled exclusively the PD model using drug effects $u = [u_1 \ u_2]^T$, and another one that controlled the totality of the HIV-1 infection model described, comprising the PD and PK models, using periodic drug doses $u_{PK} = [u_{PK1} \ u_{PK2}]^T$ as input variables for control.

Both implementations used the S-Function block in Simulink to run a function solving the NMPC optimization problem in (4.1), differing on the constraints and the cost functionals used. As shown in Figure 4.2a in the PD model control implementation the estimated state vector that the EKF outputs is $\hat{x}$, including solely the PD model states, and the input variable vector used to control the model is $u$, corresponding to the RTI and PI drug effects.

The PK+PD implementation is illustrated in Figure 4.2b where the estimated state vector is now $\hat{z}$, that includes the estimations of all the PK and PD model states. The input signal computed by the NMPC block, and then fed to the model and to the estimator, is now the discrete drug doses vector $u_{PK}$. 29
It should be noted that in both implementations the HIV-1 Model is in continuous time, while the estimation and control blocks run in discrete time. Different sampling times are assigned for each block, that should be multiples of each other.

### 4.3.1 PD Model

Since the PD model control is performed by manipulating the drug effects, the cost functional minimization should be done imposing the following the constraints on the input variables:

\[ 0 \leq u_1 \leq 1, \quad 0 \leq u_2 \leq 1 \quad (4.8) \]

The inclusion of these constraints over the set of inputs \( \bar{u} \) that minimizes the cost functional, is done as depicted below in (4.9), where the specific optimization problem for the PD model is detailed.

\[
\min_{\bar{u}} J(x(t), \bar{u}, T_{ch}, T_{ph}, T_u) \text{ such that } A\bar{u} \leq b
\]

\[
A = \begin{bmatrix}
-1 & 0 & \cdots & 0 \\
0 & \ddots & 0 \\
\vdots & 0 & \ddots & 0 \\
0 & \cdots & 0 & -1 \\
1 & 0 & \cdots & 0 \\
0 & \ddots & 0 & \vdots \\
\vdots & 0 & \ddots & 0 \\
0 & \cdots & 0 & 1
\end{bmatrix}, \quad b = \begin{bmatrix}
0 \\
\vdots \\
0 \\
\vdots \\
1 \\
\vdots \\
0 \\
1
\end{bmatrix}
\quad (4.9)
\]

It should be kept in mind that the set of input variables \( \bar{u} \) to optimize is of length \( l_{\bar{u}} \), reason why the dimensions of \( A \) are \( 2l_{\bar{u}} \times l_{\bar{u}} \), and for \( b \) they are \( 2l_{\bar{u}} \times 2 \).

The algorithm that implements the cost functional mentioned in (4.9) must then contain a prediction of the PD model states for a given set of inputs, and then a calculation of its value...
based on the stage cost equation in (4.5). The model used for the predictions is discretized using a sampling period corresponding to the control periodicity \( T_u \), a choice justified by the fact that the input value fed to the system remains constant during that time interval, as shown in Figure 4.3.

![Figure 4.3: Diagram of virtual and real input signal sequences for PD model NMPC.](image)

The detailed cost functional algorithm is presented below, where for simplification purposes it is assumed that a step equivalent to the one in (4.3) has already been performed, resizing \( \bar{u} \) if necessary. The variable \( x_{in} \) corresponds to the current estimated state vector, and \( r_{in} \) to the current reference value, which are both received as inputs in the controller block.

**Algorithm 1** NMPC Cost Functional Algorithm for PD Model

```plaintext
Require: \( \bar{u}, x_{in}, r_{in}, T_{ph}, T_u \)

\text{cost} \leftarrow 0
\bar{x}(1) \leftarrow x_{in}
\text{for } k = 1 \text{ to } T_{ph} \text{ do }
\bar{x}_1(k + 1) \leftarrow \bar{x}_1(k) + T_u[s - d \bar{x}_1(k) - (1 - \bar{u}_1(k)) \beta \bar{x}_1(k) \bar{x}_3(k)]
\bar{x}_2(k + 1) \leftarrow \bar{x}_2(k) + T_u[(1 - \bar{u}_1(k)) \beta \bar{x}_1(k) \bar{x}_3(k) - \mu \bar{x}_2(k)]
\bar{x}_3(k + 1) \leftarrow \bar{x}_3(k) + T_u[(1 - \bar{u}_2(k)) k \bar{x}_2(k) - c \bar{x}_3(k)]
y(k) \leftarrow \bar{C} \bar{x}(k)
\text{cost} \leftarrow \text{cost} + (\bar{x}(k) - r_{in})^T Q (\bar{x}(k) - r_{in}) + \bar{u}(k)^T R \bar{u}(k)
\text{end for}
\text{return } \text{cost}
```

As explained before, once the set of input variables is obtained by optimization of the cost functional, the first values in the set are applied to the system, and then the algorithm is repeated.

### 4.3.2 PK+PD Model

The inclusion of the PK model turns the inputs to optimize into discrete administered drug doses, a fact that poses different challenges on the optimization to be performed. First of all, the input variable values to obtain have now different constraints. As they represent drug dose values [\( mg \)], they have to be positive, and respect a maximum value to be determined as adequate for administration. That maximum value was assumed to be 1200\( mg \), the value chosen for the PK model identification, yielding the constraints expressed below:

\[
0 \leq u_{PK1} \leq 1200, \ 0 \leq u_{PK2} \leq 1200
\] (4.10)
The input sequence to optimize is now a sequence of discrete impulse values of length $l_u = T_{ch}/T_u$, corresponding to each one of the drug doses prescribed, which is represented by $\bar{u}_I$. Aside from the differences just stated, the optimization problem can be formulated in the same way as done in the previous section, as the number of input variable values to optimize has the same dependency on the $T_{ch}$ and $T_u$ values. The problem is stated as follows:

$$\min \bar{u} \ J(z(t), \bar{u}_I, T_{ch}, T_{ph}, T_u) \text{ such that } A\bar{u} \leq b$$

$$A = \begin{bmatrix}
-1 & 0 & \cdots & 0 \\
0 & \ddots & 0 & \vdots \\
\vdots & 0 & \ddots & 0 \\
0 & \cdots & 0 & -1 \\
1 & 0 & \cdots & 0 \\
0 & \ddots & 0 & \vdots \\
\vdots & 0 & \ddots & 0 \\
0 & \cdots & 0 & 1
\end{bmatrix} \quad b = \begin{bmatrix}
0 & 0 \\
\vdots & \vdots \\
0 & 0 \\
1200 & 1200 \\
\vdots & \vdots \\
1200 & 1200
\end{bmatrix} \quad (4.11)$$

In the previous implementation, the system response prediction made in the NMPC algorithm used a prediction interval of $T_u$, corresponding to the control periodicity. However, now that the inputs are impulses corresponding to discrete drug doses, making the same assumption would result in a prediction where the inputs used would not be seen as impulses, since the prediction interval would be too large for that to happen. For the prediction to be realistic, it should use a prediction interval that is smaller than the control periodicity $T_u$, so that there can be instants in the prediction where the inputs will take null values, replicating the fact that the inputs are fed to the real system as impulses. This prediction interval is called $T_p$, and its relationship with $T_u$ is better understood through the illustration in Figure 4.4.

Figure 4.4: Diagram of virtual and real input signal sequences for PK+PD model NMPC.

The cost functional algorithm should take this into account, implying that it should create a new virtual input signal $\bar{u}_{PK}$, where the impulse values in $\bar{u}_I$ will be distributed according to $T_u$ and $T_p$ values. The signal $\bar{u}_{PK}$ is then used to compute the predictions and to calculate the cost functional value. In order to help describe this virtual input signal sequence, a few auxiliary variables should be defined, the first being the number of impulses $N_i$ included in the prediction horizon period of time

$$N_i = \frac{T_{ph}}{T_u} \quad (4.12)$$
obtained by dividing the prediction horizon by the time between impulses (control periodicity). It is also useful to define $N_s$ as the number of prediction steps between impulses, obtained dividing $T_u$ by the prediction interval $T_p$:

$$N_s = \frac{T_u}{T_p}$$  \hspace{1cm} (4.13)

For example, in the case shown in Figure 4.4, $N_s$ would have a value of 4. Finally, the total number of samples in the prediction is given by dividing the prediction horizon $T_{ph}$ by the prediction interval $T_p$, and is defined as $N_k$ below:

$$N_k = \frac{T_{ph}}{T_p}$$  \hspace{1cm} (4.14)

Once the sequence of virtual control is created, the cost functional algorithm needs to compute the sequence of state predictions corresponding to the PK and PD models, and then calculate the cost value by using its definition in (4.4). The complete implementation of the cost functional is shown in the algorithm below, where $\bar{u}_I$ is assumed to have undergone an adjustment equivalent to the one in (4.3), for simplification purposes.

**Algorithm 2** NMPC Cost Functional Algorithm for PK+PD Model

**Require:** $\bar{u}_I$, $z_{in}$, $r_{in}$, $T_{ph}$, $T_u$

1. $cost \leftarrow 0$
2. $\bar{z}(1) \leftarrow z_{in}$
3. for $k = 1$ to $N_k$
   1. $\bar{u}_PK(k) \leftarrow 0$
4. end for
5. for $k = 1$ to $N_i$
   1. $\bar{u}_{PK}(k,N_s) \leftarrow \bar{u}_I(k)$
6. end for
7. for $k = 1$ to $T_{ph}$
   1. $C_{s1}(k+1) \leftarrow \Gamma_1(C_{s1}(k), \bar{u}_{PK_1}(k))$
   2. $C_{s2}(k+1) \leftarrow \Gamma_2(C_{s2}(k), \bar{u}_{PK_2}(k))$
   3. $C_{p1}(k) \leftarrow [1 \ 0 \ 0]C_{s1}(k)$
   4. $C_{p2}(k) \leftarrow [1 \ 0 \ 0]C_{s2}(k)$
   5. $\bar{u}_1(k) \leftarrow C_{p1}(k)/(C_{p1}^1 + C_{p1}(k))$
   6. $\bar{u}_2(k) \leftarrow C_{p2}(k)/(C_{p2}^2 + C_{p2}(k))$
   7. $\bar{x}_1(k + 1) \leftarrow \bar{x}_1(k) + T_p[s - d\bar{x}_1(k) - (1 - \bar{u}_1(k))\beta\bar{x}_1(k)\bar{x}_3(k)]$
   8. $\bar{x}_2(k + 1) \leftarrow \bar{x}_2(k) + T_p[(1 - \bar{u}_1(k))\beta\bar{x}_1(k)\bar{x}_3(k) - \mu\bar{x}_2(k)]$
   9. $\bar{x}_3(k + 1) \leftarrow \bar{x}_3(k) + T_p[(1 - \bar{u}_2(k))k\bar{x}_2(k) - c\bar{x}_3(k)]$
   10. $y(k) \leftarrow C\bar{x}(k)$
   11. $cost \leftarrow cost + (\bar{z}(k) - r_{in})^TQ(\bar{z}(k) - r_{in}) + \bar{u}_{PK}(k)^TR\bar{u}_{PK}(k)$
7. end for
8. return $cost$

Variables $z_{in}$ and $r_{in}$ correspond again to the current estimated state vector and current reference value respectively. The two first cycles in the algorithm transform the sequence
of impulse input values $\bar{u}_I$ into $\bar{u}_{PK}$, that consists in converting the impulse train from a sampling period of $T_u$ to one of $T_p$, resulting in a signal similar to the one depicted in Figure 4.4.

Once the optimal cost value has been found through the optimization stated in (4.11), the first value of the corresponding sequence of virtual input variables $\bar{u}_I$ will be used as an input to the system. This input will take the form of an impulse that simulates a discrete drug dose taken by the patient. After a period of time corresponding to the control periodicity $T_u$ has passed, the controller will again take the state values from the estimator, and restart the whole optimization process to find the next drug doses to administer.
Chapter 5

Control Results

The control results obtained by using the control and estimation designed in the previous chapters are presented at this point. Initially, a comparison is made between the linear and non-linear variants of model predictive control, by analyzing the results obtained by each technique when controlling the PD model. Following this, a series of control results for the complete PK+PD HIV-1 infection model are displayed, covering cases that include model parameter uncertainty and low patient adherence.

5.1 Control Problem

The control problem consists in bringing the concentration of free virions, which corresponds to the state $x_3$, to a level of 100 copies/mm$^3$ in less than 8 weeks [4], corresponding to about 56 days, and below 50 copies/mm$^3$ within 6 months of treatment. Instead of choosing a step signal as reference, that would make the initial control phase considerably turbulent, the reference signal chosen to this effect was

$$r(t) = 50 + (902.8 - 50)e^{-\frac{t}{\tau_r}}$$  \hspace{1cm} (5.1)

which follows the treatment guidelines while posing less demanding objectives to the controller at the initial stages of the treatment.

The variable $\tau_r$ is the time constant that determines the speed at which the reference signal decreases towards the desired value of 50 copies/mm$^3$, and was used in the simulations in this report with a value of $\tau_r = 5$ days.

5.2 PD Model Control

The first stage of the work presented in this dissertation consisted in solving the control problem through linear MPC, which was known to have severe limitations concerning the performance it could achieve. Despite the fact that the main focus of this work is on the non-linear solution, it is still relevant to compare the potentialities of each technique in order to understand how much is gained by opting for the non-linear variant. This comparison only concerns the control of the PD model, as illustrated in Figure 4.2b.
5.2.1 Linear MPC

The linear MPC technique uses a linearization of the system dynamics, performed at the infection state (2.12), to compute the state predictions. A linear observer was used to estimate the model state values. Control results were obtained for a situation where the reference signal referred in (5.1) is applied to the system, being plotted in Figure 5.1. The controller parameters used are listed in Table 5.1.

<table>
<thead>
<tr>
<th>Control Periodicity</th>
<th>1 (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediction Horizon</td>
<td>6 (days)</td>
</tr>
<tr>
<td>Input Weights</td>
<td>$w_{u1}$ 5</td>
</tr>
<tr>
<td></td>
<td>$w_{u2}$ 10</td>
</tr>
</tbody>
</table>

Table 5.1: Controller parameters for Linear MPC simulations in Figure 5.1

An analysis of the linear MPC results shows that there is a clear difficulty in making the state $x_3$ follow the reference in an accurate way, with the virion concentration never being able to come close to the reference values. The input values vary inconsistently during the 100 days of the simulation, never reaching a state where the infection is controlled and the...
doses are only focused in maintaining the number of virions below the desired limit without need for sudden variations. The linear state estimation used also fails to estimate precisely the model state values, more significantly for state \( x_2 \) as expected, making the job of the controller even harder.

Controller parameter tuning proved to be unsuccessful in significantly improving this situation, either by increasing the prediction horizon used or manipulating the weights associated with each input variable. These weights did not prove capable of efficiently determining the average amount of each drug used in the control without severe consequences in the control quality. This situation leaves a lot of room for improvement using NMPC, concerning the control quality and the ability of achieving efficient control for different combinations of average drug doses administered.

5.2.2 Non-Linear MPC

The non-linear version of MPC (NMPC) was then applied to solve the same control problem, using the algorithm implementation described in Section 4.3.1. The state estimation was also replaced, now being performed by a multi-rate EKF, that has different potentialities from the linear estimation used before.

The input signal sequence computed by the controller initially showed a lot of vulnerability to noise, showing a lot of oscillations in its values. A low-pass filter was then placed after the control block, in order to stop those oscillations from happening. The filter is described by the transfer function

\[
F(s) = \frac{1}{\tau s + 1} \quad \tau = \frac{1}{2\pi f_c}
\]

and after an analysis of the signals to filter and some experimentation, a cutoff frequency of \( f_c = 0.01 \text{ days}^{-1} \) was selected. Simulations were run for the same reference signal as before, and using the parameter values in Table 5.2.

<table>
<thead>
<tr>
<th>System Sampling Interval</th>
<th>0.25 day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control Periodicity</td>
<td>1 day</td>
</tr>
<tr>
<td>Prediction Horizon</td>
<td>6 day</td>
</tr>
<tr>
<td>Input Weights</td>
<td>( w_{u1} = 5 \times 10^3 )</td>
</tr>
</tbody>
</table>

Table 5.2: Controller parameters for simulations in Figure 5.2.

The results of this simulation are plotted in Figure 5.3 where it can be seen that the control shows a lot more quality than it did in the Linear MPC case, with the state \( x_3 \) following the reference with good precision.

A small oscillation can be noticed before the state \( x_3 \) stabilizes around the desired reference. This is understandable, since the filtering is also making the control slower. In fact, if we use smaller cutoff frequencies, the oscillations tend to get bigger, meaning we have a trade-off here between how quick the desired reference can be reached, and how effectively the input variable oscillations in steady state are supressed.
5.3 PK+PD Model Control

The main set of results presented in this dissertation concerns the control of the total HIV-1 infection model, including both the PK and PD models. This was done by using the NMPC technique, which was shown to be far superior to its linear variant in the previous section, being the only one able to successfully address this particular problem.

5.3.1 NMPC Control

The first simulation scenario considered, using NMPC to control the total HIV-1 infection model, was one where the model parameters used in the estimation and control prediction are accurate, and no adherence or drug resistance effects are considered. The results obtained should provide an idea of what the ideal controller performance is, which can then be compared with the results achieved when the task is made harder by the parameter uncertainty, imperfect patient adherence and drug resistance effects. The control and estimation parameters used are listed in Table 5.3 below.

An analysis of the simulation results in Figure 5.2 shows that the control algorithm is suc-
### Controller Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>System Sampling Interval</td>
<td>1 day</td>
</tr>
<tr>
<td>EKF Prediction Interval</td>
<td>0.05 day</td>
</tr>
<tr>
<td>Control Periodicity</td>
<td>0.5 day</td>
</tr>
<tr>
<td>Controller Prediction Interval</td>
<td>0.25 day</td>
</tr>
<tr>
<td>Prediction Horizon</td>
<td>3 day</td>
</tr>
<tr>
<td>Input Weights ( w_{u1} )</td>
<td>( 1 \times 10^{-4} )</td>
</tr>
<tr>
<td>Input Weights ( w_{u2} )</td>
<td>( 3 \times 10^{-4} )</td>
</tr>
</tbody>
</table>

Table 5.3: Controller parameters for simulations in Figure 5.3.

---

**Figure 5.3:** Model response with NMPC and EKF state estimation, using the parameters in Table 5.3.

Successful in achieving the desired control specifications, with the number of virions tracking its reference value very closely. The input doses used are initially high, but once state \( x_3 \) begins to stabilize around 50 \( \text{copies/mm}^3 \), they stabilize at lower values while maintaining the control objective. The plasma concentrations of each drug expectedly behave similarly to their corresponding drug dose values, appearing in the graphs as bands once their concentrations are always varying within a certain interval between each time a dose is taken.
5.3.2 NMPC Results with Model Parameter Uncertainty

One of the most important limitations in this type of therapy design concerns the uncertainty in the model parameters, used in the state estimation and control prediction. The parameter estimation techniques have shown good results, but it is still expectable that a certain level of model parameter uncertainty should occur when estimating the model parameters based on patient data, and causing some degradation in the control quality.

It is then important to simulate this type of situations, helping to understand how the control system will react to the uncertainties it can encounter. This can be done by changing the value of a given parameter in the model to be controlled, while keeping it at its old value in the EKF estimator and NMPC block, thus creating the desired uncertainty.

In this particular case, the model parameter $k$ was changed to $120 \text{ day}^{-1}$, a deviation of 20% from its original value. A similar simulation to the one in the last section was then run, now with a system sampling period $T_s = 7 \text{ day}$. The results obtained are plotted in Figure 5.4.

![Model response with NMPC and EKF state estimation](image)

Figure 5.4: Model response with NMPC and EKF state estimation, for a system sampling period $T_s = 7 \text{ day}$ and model parameter $k = 120 \text{ days}^{-1}$.

The results show the expected deviation in the state estimation and control for a situation with this much parameter uncertainty, with the estimation values and prescribed doses
changing substantially each time a new system measurement was taken, which is to say every 7 days. It should be noted that despite this difficulties, the controller managed to achieve the intended control objective, by succeeding in adapting the therapy each time it took a new system measurement into account, and thus showing a certain robustness to this kind of situations.

5.3.3 NMPC Results with Adherence and Resistance Effects

The patient adherence and resistance effects, considered non-existent in the results showed until now, are the two biggest obstacles to an efficient HIV-1 infection control. These two effects are interconnected once it is mainly low adherence that causes drug concentrations to drop to low values, and consequently allows the organism to develop resistance to those same drugs.

It is thus relevant to observe the control system behavior in this type of situation, which was done by running a similar simulation to the ones in previous sections, this time adding the adherence and drug resistance effects, using the parameters in Table 5.4. The results are plotted in Figure 5.5.

Figure 5.5: PK+PD model response with NMPC and EKF state estimation, using the parameters in Table 5.3 adherence of 95% and resistance with $K_r = 1 \times 10^{-4}$
Table 5.4: Adherence and resistance model parameters for simulations in Figure 5.5.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence</td>
<td>95%</td>
</tr>
<tr>
<td>Concentration Limit $L_r$</td>
<td>$70ng/mm^3$</td>
</tr>
<tr>
<td>Resistance Gain $K_r$</td>
<td>$1 \times 10^{-4}$</td>
</tr>
<tr>
<td>$C_{50base}$</td>
<td>$200ng/mm^3$</td>
</tr>
<tr>
<td>$C_{50base}$</td>
<td>$200ng/mm^3$</td>
</tr>
</tbody>
</table>

The results obtained show significant decreases in the plasma concentrations and consequently in the effects of each one of the drugs each time a drug dose is missed, resulting in a visible deterioration in the control. However, the controller proves able to readjust the input doses when that happens, so that the number of virions $x_3$ never deviates too much from the desired reference. This allows for good control results to be achieved despite the imperfect patient adherence and the consequent drug resistance developed, provided that these effects are not too severe, showing that there is room for devising therapies that achieve their treatment objectives while subject to this type of limitations.
Chapter 6

Parameter Effects in Controller Performance

The focus of this chapter is in studying the effect that the adjustment of certain controller parameters can have in the control results achieved, and how that can be explored to improve them. This was done for the prediction horizon values, for the control periodicity, and afterwards for the controller input weights, which prove able to adequately regulate the system. Finally, an application of the input weight properties is discussed, as a way to perform treatment toxicity minimization.

6.1 Prediction Horizon

There is an evident interest in understanding the effect of the prediction horizon value in the quality of the control achieved, since its increase should be able to improve the controller performance. The high computational cost of setting it to high values can be tolerated, but it should be kept to a minimum if not making an impact on improving control. It is useful to know up to what point does it make a difference to keep increasing its length, through a series of tests.

For this purpose, similar simulations to the ones in previous sections were run at this point, varying exclusively the prediction horizon values used. The cost and average error values obtained in each of them are plotted in Figure 6.1.

There is a clear decrease in the cost and average error values as the prediction horizon increases, showing that longer predictions have an important effect in improving the quality of the control obtained. The improvements are more profound for smaller horizons, with the cost and error values declining at a smaller rate when the horizon reaches values around 5 day. This leads to the conclusion that there is room for improvement by adjusting the prediction horizon, but that for certain values the improvements achieved start to be small, perhaps not justifying the added complexity in the computations that can lead to very long simulation times.

6.2 Control Periodicity

The control periodicity is a parameter that should heavily influence the control quality, and it is of special relevance once it relates directly to the real life limitations of the infection treatment, in this case concerning the amount of pills that should be taken in a certain
period of time by the patient in question. The PK models should be the main constraint to the control periodicity values that can yield satisfying control results, once the time interval between the administration of two drug doses must be short enough for the concentration not to drop to zero again. This way it will be possible to maintain the drug concentrations at high values and thus achieve an efficient control.

A series of simulations was then run, varying the control periodicity for each one of them, aiming to characterize the effect of this particular parameter. The cost and average error values for each one of them are plotted in Figure 6.2.

An analysis of the results in Figure 6.2 leads to the conclusion that there is in fact a deterioration of the control quality as the control periodicity increases, with error values reaching unsatisfying values for values bigger or equal to 2 day. This was expectable, since the PK models described in Chapter 2 assumed that the drug concentrations would wear off about 1 day after the pill was taken, thus turning that period of time into the maximum value of control periodicity that should be possible to use while achieving good control results.
6.3 Input Weight Variation

The main tuning knobs in this type of control technique are the input weights $w_{u1}$ and $w_{u2}$, whose role in the NMPC algorithm is to determine which input should be used preferably when attempting to control the system. Since some restrictions to the input values used might be imposed based on their toxicity levels, the ability to influence their relative amounts while maintaining an efficient control of the system is of great importance.

It is then useful to understand the effect that the weight values have in the system behavior, and how well is it possible to use them to determine the proportion of each drug that should be used. A series of simulations was run for this purpose, and aside from registering the cost and average error values for varying input weights, the average input values used throughout each simulation were also monitored.

The input weight chosen to be manipulated in the simulations was $w_{u1}$, while $w_{u2}$ was set to $3 \times 10^{-3}$ and the remaining parameter values in Table 5.3 were kept at the same values. The results obtained are shown in Figure 6.3, where in 6.3d, the average input values of $u_{PK1}$ and $u_{PK2}$ obtained for each simulation are plotted against each other, providing a better perception of the possible input combinations obtained.

![Graphs showing cost, error, and input values](image)

Figure 6.3: Cost, average error and average input values for varying input weight $w_{u1}$.

The main conclusion drawn from the simulation results is that this control technique does
provide a real control over which input to use the most, without compromising the control results too much, something impossible to achieve through linear control. It is clear from Figure 6.3 that when \( w_{u_1} \) increases, the average value of input \( u_{PK_1} \) used in the control decreases, being compensated by a bigger usage of \( u_{PK_2} \). The opposite happens when \( w_{u_2} \) increases, this time with a reduction in the usage of \( u_{PK_2} \), although it was chosen not to present the simulation results proving that fact to avoid being redundant.

### 6.4 Toxicity Minimization

The fact that the amount of each drug that is used to control the infection can be manipulated, through the use of parameters \( w_{u_1} \) and \( w_{u_2} \), opens the possibility of exploring that property to minimize the toxicity of the overall treatment. This naturally requires toxicity models of each drug to be known, making the computation of the total treatment toxicity possible.

Denoting by \( <u_{PK_i}> \) the average value of \( u_{PK_i} \) through the whole treatment, and by \( g_i \) the function that measures toxicity for drug \( i, i = 1, 2 \), the total toxicity is given by:

\[
T_x = g_1(<u_{PK_1}>) + g_2(<u_{PK_2}>)
\]  

(6.1)

In order to illustrate the type of toxicity functions that could be used in this situation, the functions \( g_1(<u_{PK_1}>) \) and \( g_2(<u_{PK_2}>) \) were defined as follows:

\[
g_1(<u_{PK_1}>) = e^{\frac{<u_{PK_1}> - 550}{50}}
\]

\[
g_2(<u_{PK_2}>) = e^{\frac{<u_{PK_2}> - 300}{50}}
\]  

(6.2)

The behavior of the two functions described above is best understood through their graphical representation, presented in Figure 6.3.

It should be remarked that quantifying toxicity is a very difficult task, that depends on several factors. The curves shown in Figure 6.4 are indicative, being used for exemplificative purposes. Another possibility would be to define an interval of acceptable toxicity levels. In this case, an interval for values of average dosage would be yielded.
The average input combinations obtained can be described by a function such as the one below:

\[ \langle u_{PK_2} \rangle = \varphi(\langle u_{PK_1} \rangle) \]  

(6.3)

whose graphical representation corresponds to the plot in Figure 6.3d. If \( \langle u_{PK_2} \rangle \) is replaced by \( \varphi(\langle u_{PK_1} \rangle) \) in (6.1), it is possible to plot the total toxicity \( T_x \) as a function of \( \langle u_{PK_1} \rangle \), which yields the graph displayed in Figure 6.3d.

![Graph showing total toxicity function \( T_x \) for corresponding average input values used.](image)

Figure 6.5: Total toxicity function \( T_x \) for corresponding average input values used.

The graph makes clear that the total toxicity function \( T_x \) has a minimum, that corresponds to a certain balance in the usage of each drug as expected. If a toxicity limit is well defined, it will be possible to define an interval of \( \langle u_{PK_1} \rangle \) values for which that limit is respected. Considering that the average drug dose \( \langle u_{PK_1} \rangle \) can be described as a function of the input weight values used, it then becomes possible to define the total toxicity function \( T_x \) as

\[ T_x(w_{u_1}) = g_1(\langle u_{PK_1} \rangle) + g_2(\varphi(\langle u_{PK_1} \rangle)) \]  

(6.4)

where it is assumed that

\[ \langle u_{PK_1} \rangle = \Psi(w_{u_1}) \]  

(6.5)

\( \Psi(w_{u_1}) \) being a function describing the relationship between the input weight and average input values, that was established by the results shown in Figure 6.3c. This allows for the optimization problem to be formulated as follows:

\[ \min_{w_{u_1}} T_x(w_{u_1}) \]  

(6.6)

yielding a weight value that minimizes treatment toxicity. This optimization is best illustrated by Figure 6.6 where the toxicity levels obtained for each value of input weight \( w_{u_1} \) used are plotted.

When presented on a logarithmic scale, the results also show that at intermediate weight values toxicity is lower, while for very high or very low values the toxicity values rise sharply, as happened in the toxicity plot in order to the average input values, shown in Figure 6.5. This was expected as the higher the weight value, the lower the average input value used.
The treatment plan to follow should in this case be the one obtained using input weight values of $w_{u1} = 1 \times 10^{-4}$ and $w_{u2} = 3 \times 10^{-3}$, since the $w_{u2}$ value was not altered in any of the simulations. The average input values used would be 150.9mg for the PI drugs, and 454.7mg for the RTI drugs.

More precision in this conclusion could be reached if a greater number of simulations varying the $w_{u1}$ value were run, resulting in a $T_x(w_{u1})$ plot with a higher number of data points. As the purpose here is to exemplify the minimization process, using toxicity models that are merely indicative, there is no need for a very high number of points to be used.
Chapter 7

Robustness Analysis

In this chapter, the control designed for the PK+PD model is tested for robustness with respect to several factors, that are likely to worsen the quality of the results achieved. First of all, the impact of model parameter uncertainty on the control quality is studied, followed by the influence of sparse measurements, which are likely to disturb the control through a deterioration in the state estimation obtained. The attention is then turned to the effect different values of patient adherence and levels of drug resistance development can have on the results.

7.1 Effect of Parameter Uncertainty

One of the most likely problems to arise when trying to draw conclusions based on these models, as mentioned before, is that the parameter values used in the prediction model do not exactly match the ones of the patient in question. Those uncertainties are modeled here by making the parameters of the model to be controlled different from the ones used for prediction in the NMPC and EKF blocks.

In this setting, several simulations were run for varying values of the model parameters, while maintaining the parameters in the estimation and prediction unaltered. The cost and average error values obtained were then registered for each case, making it possible to get an idea of how much deviation from the real parameters is needed to severely disturb the control.

7.1.1 Parameter $k$

The first model parameter for which the sensitivity test was performed was $k$, corresponding to the virus production rate. Variations of multiples of 5% were imposed on this variable, exclusively in the HIV-1 infection model that is to be controlled, while in the NMPC and EKF blocks the predictions were always made using the standard value of $100 \text{ days}^{-1}$. The cost and average error values obtained were then registered for each case, making it possible to get an idea of how much deviation from the real parameters is needed to severely disturb the control.

An analysis of the results shows that there is a considerable deterioration of the control when the actual value of the parameter is superior than the one used in the prediction, with the cost and average error values increasing quickly to very high values. When the inverse happens, meaning that $k$ in the controlled model is smaller than the one used in the prediction, those values change a lot less, even reducing their value.

This makes sense if we recall that $k$ corresponds to the virus production rate, and that the control objective here is to reduce the virion concentration to very low values. If this value is actually smaller than in the NMPC and EKF predictions, there will probably be an excessive
use of the drugs, but nevertheless the virion concentration is going to drop to low values. It should be remarked that the excessive use of drugs results in a non-necessary increase of toxicity effects. If the predictions assume a smaller virus production rate than the real one, the medication is going to be insufficient and the concentration will spike, causing high error values to arise.

### 7.1.2 Parameter $\mu$

The deviations in value of parameter $\mu$ should have different results, since this coefficient influences the rate at which infected cells die. Similar simulations to the ones in Section 7.1.1 were run for parameter $\mu$, and the results obtained are plotted in Figure 7.2.

The plotted results show a considerable increase of the cost and average error values when the model value of $\mu$ is decreased, meaning the infected cells stay around longer producing virus particles and opposing the control of the system. When $\mu$ is increased in the controlled
model, those values vary less and in the opposite direction becoming smaller. This happens because the control is made easier, once the infected cells die quicker and do not have time to produce as much virions as they did before.

7.2 Effect of Sparse Measurements

If it is assumed that model measurements are taken with a larger period than the one used before, state estimation quality will degrade, and the control results should consequently get worse. It is then relevant to know how serious this degradation is, and for which values of the system sampling period $T_s$ this starts to happen. This is also a parameter for which important real life limitations exist, with patient measurements being expensive and impractical to perform with a very high periodicity. A compromise will then need to be found between the feasibility of a certain system sampling interval and the effect it can have in degrading the control.

For the purpose of understanding its impact in the quality of the control, simulations were run for increasing system sampling intervals, setting the model parameter $k = 120 \text{ day}^{-1}$ in the controlled model, while in the NMPC and EKF predictions it remained as $k = 100 \text{ day}^{-1}$. This aimed to induce the type of estimation degradation shown in Chapter 3, also making the control less precise through an added uncertainty in the controller predictions. The resulting cost and average error values for each simulation is plotted on Figure 7.3.

![Figure 7.3: Cost and average error values for varying system sampling intervals.](image)

An analysis of the results shows that the control suffers a gradual degradation as the system sampling interval is increased. This is expected, since the multi-rate implementation of the EKF used had already shown a certain robustness in Chapter 3 indicating that the control should not have a very sudden degradation. These results open the door to finding a good compromise between a feasible schedule of patient measurements and an efficient control of the HIV-1 infection.

7.3 Low Adherence Effect

While in Section 5.3.3 it was possible to witness the kind of impact that imperfect adherence had on the infection control, it is also relevant to understand what is the gradual degradation...
in the control as the adherence values decrease. With that in mind, several simulations were run for varying adherence values, while the cost and average error values for each one of them were recorded and plotted in Figure 7.4. The parameters used in the simulations, other than the adherence value, were the ones stated in Tables 5.3 and 5.4.

![Figure 7.4: Cost and average error values for varying patient adherence values.](image)

The results obtained show the expected degradation in the control as the adherence values decrease, indicating that for values lower than about 80% the control obtained may cease to be satisfactory. It is worth noting that these results are also influenced by the resistance parameters, meaning that if it is easier for the organism to develop resistance to the drugs, decreasing adherence should have a more significant impact in the control quality than the one seen in these results.

Given the heavy influence of the drug resistance effect in the results shown, it becomes important to understand how differently does that resistance develop for different adherence values. That goal was achieved by simulating the model control, while registering the $C_{50}$ values variation through time, for two cases with different patient adherences. The time variation of those $C_{50}$ values obtained is plotted in Figure 7.5.

![Figure 7.5: Time variation of $C_{50}$ values for adherence values of 80% and 95%.](image)
The results show very distinct variations in the $C_{50}$ values for patient adherence values of 80% and 95%, evident for both the RTI and PI drugs. The assumption that the drug effects would wear off faster for lower patient adherences is confirmed, since the rate at which the $C_{50}$ values increase for an adherence of 80% is much higher than for an adherence of 95%. This is a reflex of the longer periods of time drug concentrations spend below the stipulated limit when smaller adherence values occur, as a consequence of a higher number of missed drug administrations. The irreversibility of this process is also confirmed, as the $C_{50}$ values never decrease, reacting to the times when the drug concentrations are above the desired limit by keeping its value unchanged.

### 7.4 Drug Resistance Effect

The development of resistance to treatment can have a very serious impact on the control results achieved, which makes it relevant to study this influence through a series of tests. These tests focus on different parameters that determine how drug resistance is developed in the HIV-1 infection model considered.

The parameters that more directly influence the effect of a given drug are the $C_{50}$ values, which were both set in Section 5.3 simulations as being 200 ng/mm$^3$. A value increase of these parameters causes the corresponding drug concentration to have less effect in bringing the number of virions $x_3$ to the desired reference values in the virus dynamics model.

A series of simulations for varying $C_{50}$ values were then run, always set as being the same value for both drugs as a simplification, aiming to assess the impact of this parameter in the control quality, through the cost and average errors obtained for each simulation. For the situation to be more realistic, the $C_{50}$ values were only changed in the controlled model, and not in the models used for estimation or prediction. The remaining parameters were set as in the previous sections, and the results obtained are plotted in Figure 7.6.

![Figure 7.6: Cost and average error values for varying $C_{50}$ values.](image)

The results show a steady and very significant deterioration in the control as the $C_{50}$ values increase, showing that if the resistance developed is such that these values are driven to over about 350 ng/mm$^3$, it will probably not be possible to achieve the defined control objectives. The rate at which drug resistance is developed is altered by parameter $K_r$, once each one of the drug concentrations goes under its limit $L_r$ to be set accordingly. One should be aware...
of the impact this parameter can have, so that it can be adequately tuned and generate a reasonable amount of drug resistance development.

This is why the same type of simulations were run while varying the $K_r$ value, also assumed to be the same for RTI and PI drugs. The $C_{50}$ parameters were reset to their initial $200\text{mg/mm}^3$ value, while all the other parameters remained at their standard values. Figure 7.7 shows the results obtained for each simulation.

Figure 7.7: Cost and average error values for varying $K_r$ values.

The conclusion taken by analyzing the results is that the control quality is very sensible to $K_r$ variations, showing a very quick degradation as the parameter value increases. Efficient control only seems to be achieved for values below $1 \times 10^{-4}$, which was the value used in the simulations until this point. The adjustment of this parameter when trying to bring this model closer to reality should then be done with care, knowing that small variations in its value can make great damage in the quality of the control.
Chapter 8

Conclusions and Future Work

8.1 Conclusions

The first conclusion reached in this dissertation, through the simulation results presented, is that NMPC shows a significantly improved capability of controlling a system such as the PD model of the HIV-1 infection, when compared to the Linear MPC solution. This fully justifies its choice to develop a control solution for the complete PK+PD model introduced in this work. The improved results in the control achieved are accompanied by an increased flexibility and control over the amounts of each drug used.

Concerning the control of the complete PK+PD HIV-1 infection model, the NMPC and EKF state estimation designed proved able to deliver very satisfying results, keeping the infection in a safe level with a very efficient usage of the drugs available. The results were also positive when a certain uncertainty in the parameters was introduced, as well as imperfect adherence and drug resistance effects, with the controller being able to adapt its behavior so that the main control objective would not be compromised.

The control parameters were shown to have an important impact in shaping the control performed, affecting both its quality and the amount of each input used. Results indicated a clear influence of the prediction horizon size in the control quality, and a significant vulnerability of the control to increases in the control periodicity, a reaction that was expected and that is closely linked to the PK models used for each drug. The time a certain drug concentration takes to return to low levels after a drug dose, something which is determined by the PK model, will limit the control periodicities that can be used while achieving a good control of the infection.

Results also showed an important influence of the controller input weights, being able to determine the relative amount of each drug used in the control, a property that can be used to choose the drug combinations that present the lowest toxicity level to the patient. As discussed in Chapter 6, this can be done by using toxicity models of each drug and combining them with the possible input combinations, in order to find a function whose minimum corresponds to the optimal treatment, that presents the minimum possible toxicity.

Conclusions were also achieved on the robustness limits of the control system designed, with respect to several different adverse situations. It was shown that parameter uncertainty can cause excessive drug doses to be used in containing the infection, possibly reaching levels that present considerable toxicity to the patient, or cause the drug doses administered to be insufficient, letting the infection grow out of control. In both cases, the uncertainty values causing this type of damage were quantified, so as to provide a margin within which the control should be successful.
The sampling interval used, corresponding to the periodicity with which the patient is subject to virion concentration measurements, also represented an important constraint to have into account in this work. It has been stated here that the controller showed a capability of adapting itself to estimation errors due to parameter uncertainty, but that can only happen if measurements are taken with enough periodicity for the state estimation to be corrected and the control to be adapted in time. The tests performed showed a considerable robustness of the control as that period was increased, while considering some uncertainty in the parameters, reaching measurement periodicities that should be relatively feasible in a real life situation.

It was possible to infer, through the analysis of the patient adherence and drug resistance impact in control performance, that the margin for tolerated adherence values is heavily dependent on the speed with which drug resistance is developed, and that once developed this resistance has the potential to make the control of the infection impossible.

Overall, the main conclusion that can be drawn is that NMPC successfully projects optimal therapies for the HIV-1 infection, using periodic drug doses, showing the robustness and versatility to both withstand adverse conditions and constraints, and allowing the optimization of the treatment regarding its toxicity.

8.2 Future Work

The work presented in this dissertation still has a great margin for improvement, towards the goal of making it applicable in designing real therapies. These improvements cover multiple aspects, that are discussed in detail in this final section.

A possible improvement in adapting the control to real life situations is to use quantized drug doses, meaning that it would only be possible to administer doses that are multiples of a given base value. This obviously tries to replicate the fact that drugs are available as pills, in the sense that the patient can only take the drug amount corresponding to one or several pills.

There is also the possibility of using more complex PD models to describe the HIV-1 infection, and thus take into account more aspects of the virus dynamics that were not addressed by the model used in this dissertation. This should improve the accuracy of the control, that should be able to predict the behavior of the infection more precisely.

Concerning the drug PK models, there is space for improvement as well. The PK models used in this work took into account the general behavior of ARV drugs, but were not adapted to each drug in particular. The usage of PK models that are accurately adapted to each drug, based on clinical data for each one of them, is also an important step in making the model and control results more realistic.

The toxicity models used in toxicity minimization were also assumed as an example, thus failing to present an exact measure of the possible unwanted consequences of a given treatment. The inclusion of specific toxicity models for each drug, where the toxicity limits tolerated are well defined, would help achieve more accurate conclusions on which drug combination is the best for each person.

Currently the controller does not know when the patient missed a dose, merely reacting to the increase in virus particles that follows. If the control technique allowed for the controller to be informed about this fact, a better drug dose adjustment could be devised, taking this occurrence into account.

The limitations concerning patient measurement have already been pointed out throughout this work, and they remain as a very important aspect in bringing the conclusions reached to
real life, devising adequate and efficient therapies. Once the improvements enounced before are achieved, a goal should be set of reaching good control results using a patient sampling time of 3 months. An important aspect in this matter is state estimation, that needs to be robust enough to withstand such sparse measurements.

As can be seen, there is a considerable amount of work to be done towards the final goal of improving the treatment of the HIV-1 infection, by using these models to project the therapies. Nevertheless, the basis set in this work opens good possibilities for improvement, making it expectable that interesting results can be achieved in the near future.
Bibliography


