UNIVERSIDADE FEDERAL DE PERNAMBUCO
PROGRAMA DE PÓS-GRADUAÇÃO EM ENGENHARIA DE PRODUÇÃO

OPTIMAL CONTROL IN BIOLOGICAL SYSTEMS AS A SUPPORT FOR CLINICAL DECISIONS

THIAGO MAGALHÃES AMARAL

Orientador: Fernando Menezes Campello de Souza, PhD.

RECIFE, NOVEMBRO/2009

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PARA OBTENÇÃO DO GRAU DE MESTRE

POR

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THIAGO MAGALHÃES AMARAL

"OPTIMAL CONTROL IN BIOLOGICAL SYSTEMS AS A SUPPORT FOR CLINICAL DECISIONS"

ÁREA DE CONCENTRAÇÃO: PESQUISA OPERACIONAL

A comissão examinadora, composta pelos professores abaixo, sob a presidência do(a) primeiro(a), considera o candidato THIAGO MAGALHÃES AMARAL **APROVADO COM DISTINÇÃO.**

Recife, 06 de novembro de 2009.

Prof. FERNANDO MENEZES CAMPELLO DE SOUZA, PhD (UFPE)

Prof. LUCIANO NADLER LINS, Doutor (UFPE)

Profa. PATRÍCIA SILVA LESSA, Doutor (UFPE)

"I have deeply regretted that I did not proceed far enough at least to understand something of the great leading principles of mathematics; for men thus endowed seem to have an extra sense." ***Charles Darwin***

"Dedico esta dissertação a minha família e amigos por toda a compreensão e apoio."

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RESUMO

O controle ótimo no mundo biológico tem uma vasta aplicação em incontáveis sistemas os quais influenciam enormemente nossas vidas. Objetiva-se a aplicação desta ferramenta em dois sistemas. O primeiro diz respeito ao controle ótimo de dosagem de drogas no tratamento de pacientes infectados pelo vírus HIV. O modelo de Campello de Souza (1999) é usado para estimar a dosagem de drogas onde a função objetivo é minimizada. Esta função representa um balanço entre os benefícios do tratamento e os efeitos colaterais. A técnica de controle ótimo usada é o Princípio do Máximo de Pontryagin, a qual é simulada através do *PROPT-TOMLAB — Matlab Optimal Control System Software* em uma versão de demonstração. As simulações objetivam a análise de três diferentes pacientes em dois diferentes cenários. Estes cenários têm como objetivo forçar as variáveis de estado a atingirem valores "normais" a fim de estabilizar a carga viral próximo a uma taxa que seja insignificante e elevar o nível de CD4 do paciente. São simulados tratamentos cedos e tardios. As simulações computacionais compararam diferentes cenários para investigar os parâmetros de incerteza da dinâmica entre o vírus HIV e os linfócitos $CD4$ e $CD8$. Os resultados mostram que o controle ótimo permite uma melhor administração entre os efeitos positivos da terapia e os efeitos colaterais, ao invés de se usar dosagens constantes de drogas como na atual prática médica. O segundo sistema descreve a aplicação do controle ótimo, também através do Princípio Máximo de Pontryagin, para controlar o nível de glicose em indivíduos diabéticos usando o modelo matemático desenvolvido por Bergman (1971, 1981). Correlacionam-se dados reais da literatura com o modelo teórico para analisar a robustez do modelo. É também estudada a minimização do funcional objetivo para diminuir os efeitos colaterais e consequentemente melhorar o estado de saúde do paciente. Os resultados mostram os benefícios de se utilizar o controle ótimo para regular a taxa de glicose em pacientes diabéticos.

Palavras Chaves: Engenharia Biomédica, Otimização de Sistemas, Bioestatística, Controle Ótimo, Diabetes e SIDA.

ABSTRACT

The use of optimal control in the biological world has extensive application in numerous systems. This dissertation discusses the application of this tool in two main systems. The first concerns the optimal control of drug dosages, the variable u, in the treatment of patients infected with the HIV virus. The mathematical model developed by Campello de Souza (1999) is used to estimate the drug dosage under which the objective function is minimized. This objective function sets out to represent a balance between the benefits of the treatment and its side effects. The optimal control technique used is Pontryagin's Maximum Principle which is simulated by PROPT-TOMLAB — Matlab Optimal Control Software in a demo version. The simulations are analyzed in three different patients under two different scenarios. The 1^{st} and 2^{nd} scenarios consider, respectively the cases when the patient undergoes treatment early and later, pushing up the variables to the "normal" values to stabilize the virus load close to its being at an insignificant rate. The computer simulation compared different scenarios so as to investigate the parameters of uncertainties of the dynamics of HIV and $CD4$ and $CD8$ lymphocytes. The results showed that the optimal control led to better administration between the therapeutic effects and side effects even for constant drug dosages. The second system describes the application of the optimal control, also by Pontryagin's Maximum Principle, to control glucose levels in diabetic individuals using the mathematical model developed by Bergman (1971 and 1981). Real data from the literature are correlated to the theoretical model so as to analyze the robustness of the model. A study is also conducted of minimizing the objective function so as to diminish the side effects and consequentially to improve the patient's state of health. The results showed the benefits of using the optimal control to regulate the glucose rate in diabetic patients.

Keywords: Biomedical Engineering, System Optimization, Biostatistics, Optimal Control, Diabetes and AIDS.

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List of Abbreviations

HIV	Human Immunodeficiency Virus
AIDS	Acquired Immune Deficiency Syndrome
$CD4$ or $CD4^+T$	Cluster of Differentiation 4
$CD8$ or $CD8^+T$	Cluster of Differentiation 8
UNAIDS	United Nations Programme on HIV/AIDS
WHO	World Heath Organization
IDF	International Diabetes Federation
AFR	Africa
EMME	Eastern Mediterranean and Middle East
EUR	Europe
NA	North America
SACA	South and Central America
SEA	South East Asia
WP	Western Pacific
RHD	Regional Health Directorate
RNA	Ribonucleic Acid
DNA	Deoxyribonucleic Acid
HAART	Highly Active Antiretroviral Therapy
LQR	Linear Quadratic Regulator
ARE	Algebraic Riccati Equation
TPBVP	Two-Point Boundary Value Problem
DAE	Differential Algebraic Equations
ODE	Ordinary Differential Equations
BG	Blood Glucose
ICU	Intensive Care Unit
HCV	Hepatitis C Virus

List of Symbols

V	Virus Population
U/u	Drug Dosage
$x(t)$	State Variable
$u(t)$	Control Variable
$\dot{x}(t)$	Movement Equation
$J(u)$	Functional
$H(x, u, y, t)$	Hamiltonian
α	Alpha Cells
β	Beta Cells
$CD4N$ or x_{1N}	The equilibrium value produced by natural homeostasis of CD4
$CD8N$ or x_{2N}	The equilibrium value produced by natural homeostasis of CD8
$x_1(0)$	Initial value of CD4
$x_2(0)$	Initial value of CD8
$x_3(0)$	Initial value of virus load
a	Natural regulation rate of CD4
b	Rate of infection of CD4 by HIV
c	Natural regulation rate of CD8
d	Rate of elimination of HIV by CD8
e	Rate of replication of HIV by CD4
f	Rate of elimination of HIV by CD8
z_1	Plasma glucose concentration above basal value
z_2	"Activity" of insulin in the interstitial tissue
z_3	Plasma insulin concentration above basal value
z_{1b}	Basal value of glucose concentration
z_{3b}	Basal value of insulin concentration
V_1	Distribution volume of insulin
n	Fractional disappearance rate of insulin
g	Factor of proportion

1 Introduction

> "When health is absent, wisdom cannot reveal itself, art cannot manifest, strength cannot fight, wealth becomes useless, and intelligence cannot be applied."
>
> **Herophilus**

> "He who has health has hope; and he who has hope has everything."
>
> **Arabic Proverb**

The application of mathematics to the study of biological systems, and more specifically of diseases, appears to have been initiated by Bernoulli (1760). He used a mathematical method to evaluate the effectiveness of the techniques of variolation against smallpox, with a view to influencing public health policy.

There are many applications of mathematical techniques, frequently used in systems engineering, the two main ones being: control systems theory and optimal control, which can be applied to biomedical experimentation, biological control systems, diagnosis, and biomedical engineering.

The application of mathematical and engineering techniques to biological systems appears, at first sights, to be an unwarranted leap into the unknown, until we consider how these systems are represented or described. Biological systems are often described as a set of ordinary differential equations, which are frequently the core of system engineering, as well. Because of this underlying similarity, many traditional engineering techniques are helping "systems researchers" gain further insight into biological systems. (Zannella, 2009).

Studying the mathematical models that describe an organism (system) can, as a consequence, show how the real biological world works and this can give support, for example, to medical decisions when the systems studied are diseases. In some cases, the models analyzed can control a specific system or create a new artificial system, one that responds differently from any natural biological system. Diseases, for example, can be manipulated through simulations which analyze the therapeutic effects and side effects.

The modeling of the structures of biological process confronts the analysis with a high order model and a complex structure. In this study, the technique of optimal control is used to study the behavior of biological systems to give support for clinical decisions. However, as the biological world consists of an infinite number of systems, in this dissertation only two main biological systems will be discussed. The first describes the behavior of the dynamic between HIV-1 with the lymphocytes CD4 and CD8 and the second, the dynamics of glucose and insulin. Both systems endeavor to formulate solutions for modeling and controlling diseases.

1.1 Justification

1.1.1 Reason for Studying the HIV-AIDS Control

AIDS — Acquired Immunodeficiency Syndrome — has desolated and devastated many families, communities and also some African countries. It has stigmatized groups that are closest to the margins of society. All these problems have, as a consequence, the fact of HIV having become a major international epidemic, easily crossing oceans and borders and affecting all sectors of society, from children to the elderly.

To date, more than 25 million people around the world have died of AIDS-related diseases. As per Table 1.1, in 2007, around 2.0 million men, women and children lost their lives. It is estimated 33 million people around the world are now living with and suffering from HIV, and most of these are likely to die over the next decade or so. The most recent research done by UNAIDS/WHO (2009), shows that, in 2007 alone, 2.7 million people were newly infected with HIV. It is disappointing that the global numbers of people infected with HIV continue to rise, despite the fact that effective prevention strategies and health programs to combat HIV-AIDS already exist. The survey also sounds an alarm about children's health, as it records 270 thousand child deaths from AIDS in 2007.

Figure 1.1 shows a global estimate for adults and children living with HIV in 2007 UNAIDS/WHO (2009) in all contries. Globally, around 11% of HIV infections are among babies who acquire the virus from their mothers; 10% result from injecting drugs; $5-10\%$ arise in male homosexual relationships; and $5-10\%$ occur in health care settings.

Table 1.1: Global HIV/AIDS estimates, end of 2007.

	Estimate	Range
People living with HIV/AIDS in 2007	33.0 million	30.3-36.1 million
Adults living with HIV/AIDS in 2007	30.8 million	28.2-34.0 million
Women living with HIV/AIDS in 2007	15.5 million	14.2-16.9 million
Children living with HIV/AIDS in 2007	2.0 million	1.9-2.3 million
People newly infected with HIV in 2007	2.7 million	2.2-3.2 million
Children newly infected with HIV/AIDS in 2007	0.37 million	0.33-0.41 million
AIDS deaths in 2007	2.0 million	1.8-2.3 million
Child AIDS deaths in 2007	0.27 million	0.25-0.29 million

Source: UNAIDS/WHO, 2009.

Heterosexual activity accounts for the remaining proportion — around two thirds of new infections. These data show AIDS is not just a problem for a unique sector of society (namely, it is not a problem related to homosexuality), as was thought in the $80's$, but rather affects all humanity.

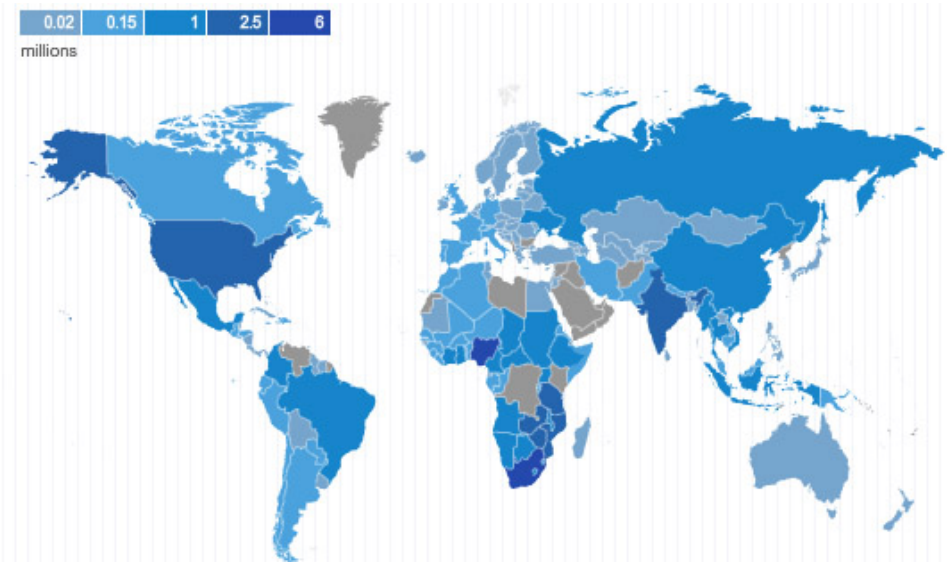


Figure 1.1: Estimated number of adults and children with HIV in 2007. Source UNAIDS/WHO, 2009.

In addition, UNAIDS/WHO (2009) has shown that Brazil had an adult HIV prevalence rate of 0.6% at the end of 2007, but, because of its large overall population, it accounts for nearly half of all people living with HIV in Latin America. It is estimated that 730,000 Brazilians are living with HIV/AIDS and approximately 15,000 people died due to AIDS in 2007.

The analysis of deaths in the years following 1996, for Brazil as a whole, shows a significant drop in mortality among men which has not been followed equally by women due to drugs distribution and despite prevention campaigns. Even so, mortality among men remains higher when compared to the female mortality rate (2005 rate: 8.06/100,000 and 3.97/100,000 respectively)(UNAIDS/WHO, 2009).

There are many alarmist facts about the research conducted by UNAIDS/WHO (2009). Some of them are as per AVERT (2009):

- Africa has 11.6 million AIDS orphans;
- At the end of 2007, women accounted for 50% of all adults living with HIV worldwide, and for 59% in sub-Saharan Africa;
- Young people (under 25 years old) account for half of all new HIV infections worldwide;
- In developing countries, 9.7 million people are in immediate need of life-saving AIDS drugs; of these, only 2.99 million (31%) are receiving the drugs;
- The number of people living with HIV has risen from around 8 million in 1990 to 33 million today, and is still growing. Around 67% of people living with HIV are in sub-Saharan Africa

Table 1.2 shows the average AIDS incidence rate per 100,000 inhabitants from 1994 to 2005 in the 5 different regions that constitute Brazil. From Table 1.2 it can be seen the percentage variation for the North and North–East at the AIDS has risen by, respectively, 58.9% and 36.3%. On the other hand, the survey shows a promising change with in the South and South–East when the percentage decline was -5.9% and -5.2% during the same period (considering the variation between 1999-2003 vs 2004-2005). (UNGASS, 2008).

Since 1983, the year of the first recorded case in Pernambuco, until 2008, the Regional Health Directorate (RHD) has notified 14,308 cases of the disease. The study shows that 4,754 are women, that means approximately 33%. With regard to the cities with highest rates, Recife leads the list with 5,982 cases. Jaboatão dos Guararapes and Olinda are

Table 1.2: Average AIDS incidence rate per 100,000 inhabitants and variation per period. Brazil and Regions, 1994 - 2005.

Regions	**1994-1998**	**1999-2003**	**Variation% (99-03 vs 94-98)**	**2004-2005**	**Variation % (04-05 vs 99-03)**
Brazil	15.6	18.3	17.0	18.8	3.0
North	4.4	8.4	90.3	13.4	58.9
North-East	4.8	7.7	60.8	10.5	36.3
South-East	24.7	24.5	-0.7	23.2	-5.2
South	17.3	26.7	54.3	25.2	-5.9
Midwest	12.4	15.4	24.2	17.7	15.5

Source: UNGASS, 2008.

ranked 2^{nd} and 3^{rd} with 1,629 and 1,205 notifications, respectively. The metropolitan region of Recife concentrates nearly 78.9% of all AIDS notifications in Pernambuco. (SHSP, 2009).

1.1.2 Reason for Studying the Glucose Control

The epidemiological evidence demonstrates that, without effective prevention but also control programmes, diabetes will probably continue to increase globally causing millions of deaths and bringing suffering to millions of people who suffer from it. It is estimated by the International Diabetes Federation (IDF, 2009) that approximately 246 million people, or 5.9%, in the age group 20-79 years, had diabetes worldwide in 2007. More than 70% live in developing countries and in most cases, in a state of poverty without the minimum of sanitary and food conditions. The worldwide estimate is expected to increase to around 380 million, or 7.3% of the adult population, by 2025 (Table 1.3). The largest increases will be in the so called economically emergent nations such as Brazil.

Table 1.3: Estimates of population and number of people with diabetes by International Diabetes Federation.

Population	**2007**	**2025**
Total world population (billions)	6.6	7.9
Adult population (age 20-79, billions)	4.1	5.2
Diabetes (20-79 age group)	—	—
Comparative prevalence (%)	6.0	7.3
Number of people with diabetes (millions)	246	380

Source: IDF, 2009.

The research done by IDF estimated the prevalence of diabetes mellitus for each country for the years 2007 and 2025, and it used data provided from 215 countries and territories, which were gathered on in different geographical basis, in a total of the seven IDF regions: Africa (AFR), Eastern Mediterranean and Middle East (EMME), Europe (EUR), North America (NA), South and Central America (SACA), South-East Asia (SEA), and the Western Pacific (WP). Figure 1.2 shows one of the results of the survey: the WP Region will have the highest number of people with diabetes, approximately 100 million, representing approximately an increase of 50% when compared with 2007. This demonstrates that diabetes is not a problem just for developing countries, but a health problem for all humanity. On the other hand, AFR has the smallest number of people with diabetes, but the expectation is growth of slightly more than 70%. Figure 1.3 shows a best estimate for each country in the world in 2025. (IDF, 2009).

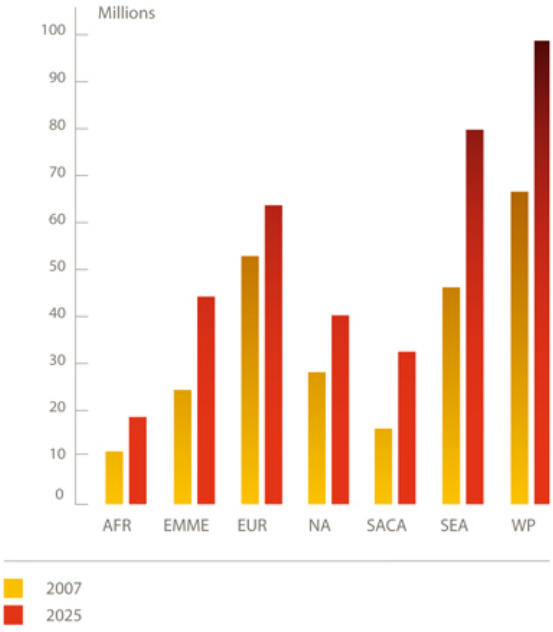


Figure 1.2: Number of people with diabetes (20 – 79 age group) by region, 2007 and 2025. IDF 2009.

In Brazil, according to VIGITEL 2007 (System of Monitoring of Risk and Protection for Non-Transmissible Chronic Diseases), the mean occurrence of diabetes in the adult population (over 18 years) is 5.2%, which means 6,399,187 people confirmed as diabetic. Prevalence increases with age: diabetes reaches 18.6% of the population over 65 years old

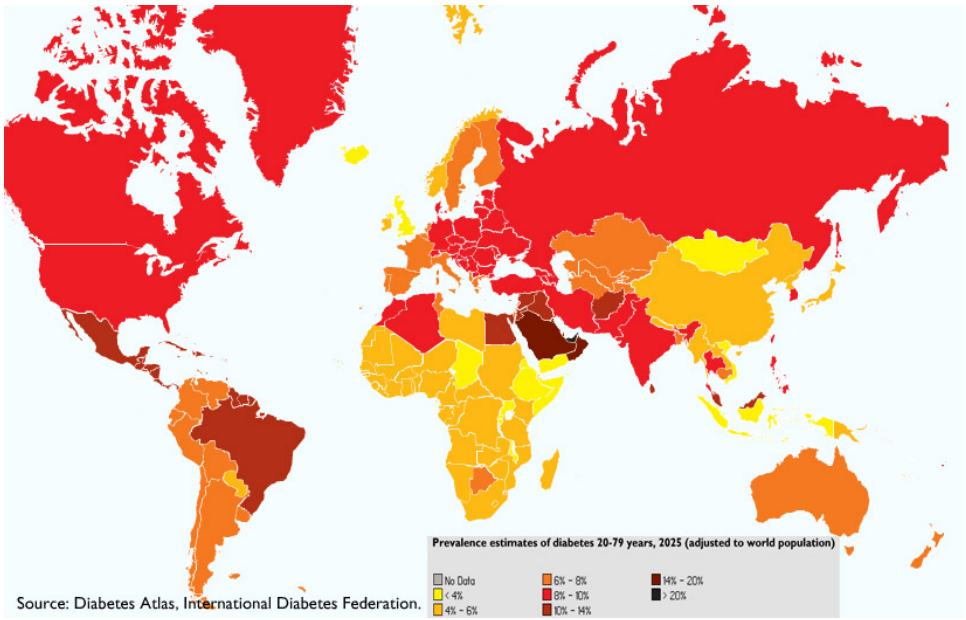
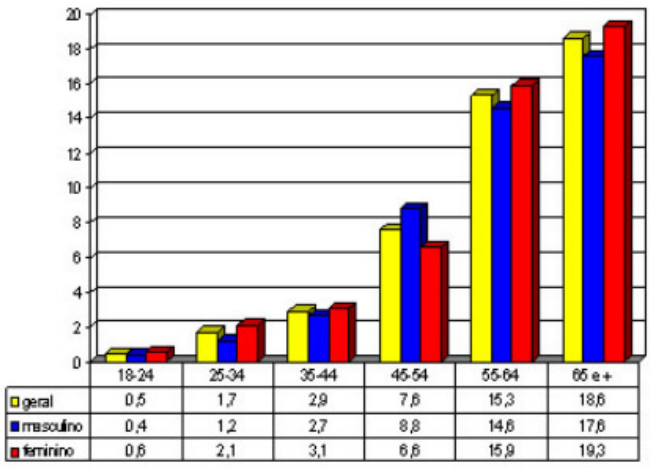


Figure 1.3: Estimate of prevalence of of diabetes $20-90$ *years in 2025. IDF 2009.*

(MS, 2009). Figure 1.4 shows the proportion of diabetes mellitus patients by age group in Brazil. Figure 1.5 shows the number of diabetes mellitus sufferers.



	18-24	25-34	35-44	45-54	55-64	65 e +
geral	0,5	1,7	2,9	7,6	15,3	18,6
masculino	0,4	1,2	2,7	8,8	14,6	17,6
feminino	0,6	2,1	3,1	6,6	15,9	19,3

Figure 1.4: Percentage of Diabetes Mellitus. Estimate by age group. Brazil, VIGITEL, 2007. In yellow, the mean percentage per age group, in blue, the male population and in red, the female population.

Table 1.4 shows the Epidemiology of Diabetes in Pernambuco. It demonstrates the predominance of diabetes in different areas in Pernambuco from Jan/2002 to Aug/2009. The Metropolitan Region of Recife is the region with most cases of type 1 and 2 diabetes

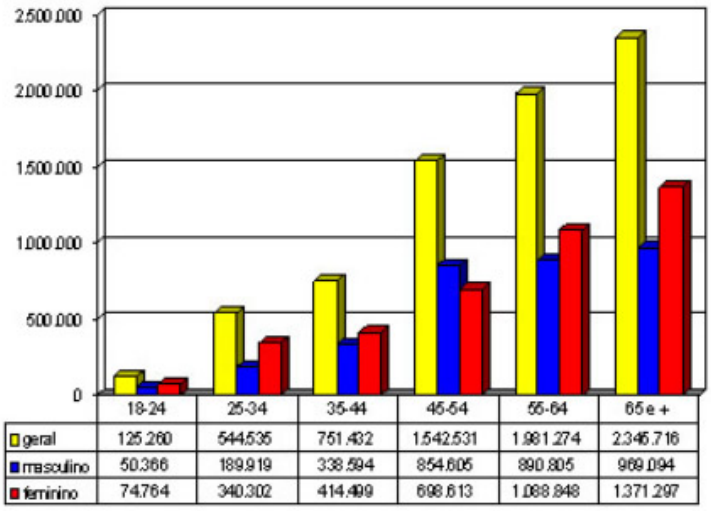


Figure 1.5: Number of People with Diabetes Mellitus. Estimate by age group. Brazil, VIGITEL, 2007. In yellow, absolute value per age group, in blue, the male population and in red, the female population.

and of hypertension with diabetes - 32.75%, 40.95% and 40.33% respectively. The 2^{nd} and 3^{rd} ranked regions with most cases are the RHD of Caruaru and Limoeiro. (DATASUS, 2009).

Table 1.4: Epidemiology of Diabetes in Pernambuco.

HSD	**Type 1 Diabetes**	**Type 2 Diabetes**	**Hypertension and Diabetes**
Recife	788	3,166	25,843
Limoeiro	326	925	7,863
Palmares	266	717	5,557
Caruaru	422	1,445	11,511
Garanhuns	164	419	3,852
Arcoverde	50	219	1,864
Salgueiro	21	43	689
Petrolina	152	429	2,608
Ouricuri	53	91	807
Afogados da Ingazeira	95	144	1,582
Serra Talhada	72	123	1,901
TOTAL	**2,409**	**7,731**	**64,077**

Source: DATASUS, 2009.

1.2 The Alliance between Mathematics and Biology

As described in Campello de Souza et al. (2002), mathematics is a logical indispensable tool for scientific activity. Its limitations are overcome when supplanted by its huge

potential, though this is not well exploited, and applied to all fields of science. A mathematical representation is a strong instrument that gives support to human thought as it explains intensities such as logical relations. It is not possible to engage in science without mathematics.

May (2004) expresses in his article the importance of relating mathematic and biology. He shows why mathematics has become so pervasive in biology and takes different forms in its applications, such as in biostatistics, bioinformatics, modeling diseases, drug development, etc.

Currently, mathematics is being applied to explore models of biological systems. Normally such activity consists of representing evidence-based assumptions as the starting point for a complicated and usually nonlinear dynamic system, followed by assigning particular parameters and then letting this complicated system produce its figures. This represents a revolutionary change in such theoretical studies.

One important application of mathematics in biological models is associated with ecology, such as when Lotka and Volterra explored interactions among species in their study. Today we can use mathematics to model bioprocesses and to optimize systems and costs. The future of bio-mathematics will be to improve the development of other fields such as bioinformatics, bionanotechology, genetics, population modeling, etc.

The mathematics in this dissertation is based on models reported in Phillips (1996), Grégio (2005), Caetano & Yoneyama (2002), Hardt (2007), Campello de Souza (1999), etc., for the case of HIV/AIDS. For the diabetes studies, other authors like Bergman & Urquhart (1971), Bergman et al. (1981), Doyle III et al. (1995), Natal (2004), Kovacs et al. (2008) and Dua et al. (2006) have had an important influence. More details are given in sections 2.3 and 7.3.1.

1.3 Objectives

1.3.1 General Objectives

To characterize biological states in terms of parameters obtained from dynamic systems, in order to be able to optimally control them, in a diagnostic and therapy decision support set up.

1.3.2 Specific Objectives

1. To study the application of mathematical and engineering techniques to biological systems in order to improve support to clinical decision making;

2. To model and simulate the dynamics of HIV-1 with CD4 and CD8 lymphocytes using optimal control of drug administration by Pontryagin's Maximum Principle;

3. To model and simulate the dynamics of diabetes using the optimal control of insulin.

1.4 Basic Methodology

There are infinite number of biological systems and some of them are of major importance in our lives. For this study two of the most important diseases were chosen that affect millions of people in the world: HIV/AIDS and diabetes. Special attention is paid in the research undertaken to understand the behavior of HIV/AIDS and glucose through mathematical models, in particular, when the benefits of the therapy and the side effects are analyzed together.

In the case of HIV/AIDS, the model developed by Campello de Souza (1999) was applied. This model uses three differential equations that represent the interaction between CD4 and CD8 lymphocytes and the HIV-1 virus. The technique of Pontriagin's Maximum Principle is used to minimize the objective function so as to optimize the drugs applied to control this disease. The direct method employed is the Linear Quadratic Regulator (LQR) because of its simplicity and robustness.

The optimization methods applied in this study require simulations with different scenarios that describe different patients, in different stages of the progression of the disease. For each patient, the control is made differently with the objective of adjusting the best dosage during early and late treatment. The software chosen to simulate and solve the complex system formed by six differential equations was PROPT-TOMLAB due to its good performance in this kind of problem.

In the case of diabetes, the same methodology is applied. The goal of this research was to describe a closed-loop control system that mimics the functionality of the pancreas in

providing regulation of the glucose rate in diabetic patients. The model chosen to analyze the dynamic between glucose and insulin was that developed by Bergman & Urquhart (1971) and Bergman *et al.* (1981) and cited in more modern studies. The representation used was recently improved by Dua *et al.* (2006) using the minimum number of compartments to describe it. The model is also called "Bergman's Minimal Model" and it consists of a set of three differential equations, similar to the model developed by Campello de Souza (1999) to study the case of HIV/AIDS.

More references in general will be presented throughout the text.

1.5 Organization of Work

This chapter sets out the justification, the objectives and the main academic approach that includes the discussion of methodology and a brief review of literature.

Chapter 2 presents some concepts concerning the biology of HIV and a synthesis of the mathematical model that will be used in this study. The notion of medicines to fight the HIV/AIDS will be introduced and how the optimal variable will be applied subsequently.

The third chapter presents the fundamentals of optimal control theory and the formulation of the HIV problem. In the first section there is a short introduction to Optimal Control Theory and notions about the virus clearance procedure. Subsequently the HIV problem applying Optimal Control Theory, in particular Pontryagin's Maximum Principle will be introduced.

Chapter 4 shows the linearization of the model and the solution of Riccati's equation to be applied the LQR. First, LQR control in general is studied and then applied to the model discussed.

Chapter 5 shows the optimization problem when the functional is minimized, and consequently when the optimal drug dosage is used to fight HIV. The method and the software to simulate different scenarios, patients and treatments are presented.

Chapter 6 presents concepts on the biology of diabetes with a synthesis of the dynamics between insulin and glucose. In the last section, type 1 and 2 diabetes will be described.

The seventh chapter shows first the importance of controlling the amount of glucose in the bloodstream. It also discusses concepts on closed loop control using insulin pumps.

A description is given of the groups of mathematical models in the literature focused on Bergman's Minimal Model. Finally, the chapter formulates the optimal therapy via Pontryagin's Maximum Principle, followed by linearization to facilitate the calculus and simulation.

Chapters 8 present conclusions and suggestions for future studies.

The text mixes the languages of biology and engineering, but in a predominantly hypothetical-deductive epistemology.

2 Concepts and Mathematical Model - HIV

> "The human immunodeficiency virus (HIV) epidemic has spawned a scientific effort unprecedented in the history of infectious disease research. This effort has merged aspects of clinical research, basic molecular biology, immunology, cell biology, epidemiology, and mathematical modeling in ways that have not been seen before. The ever unfolding discoveries of novel aspects of HIV-host interaction have been accompanied by (and often have resulted from) novel interactions among researchers in the disparate disciplines."
>
> **John Coffin**

2.1 Introduction

This chapter presents some concepts on the biology of HIV and a synthesis of the mathematical model that will be used in this study. The notion about medicines to fight the HIV/AIDS will be introduced and how the optimal variable will be applied subsequently.

2.2 The Biology of HIV

AIDS was discovered in the late 1970s when young homosexual men fell ill and began to die in United States from a unknown disease with the same symptoms as rare cancers and infectious diseases such as pneumonia. Although the causative virus, Human Immunodeficiency Virus (HIV), was identified in 1983, there is still no cure for AIDS.

Before analyzing the mathematical modeling in different components of the system, it is necessary to understand the interaction of HIV with the immunological system and also to know about a class of lymphocytes which has the ability to adapt and to interact with specific antigens. One reason why HIV is a particularly serious infection is that it attacks and destroys cells of the immune system — called T-cells — and more specifically the CD4 lymphocytes. Lymphocytes are white blood cells that secrete antibodies to specific antigens. The B cells are a subclass that counteract antigens circulating in the blood

stream, while T cells form antibodies for antigens inside or associated with normal cells. (Haefner, 2005)

Virus activity starts once HIV penetrates these cells. It takes over their machinery (or reprograms the cell) so that it begins to replicate itself from one cell. Another reason why HIV is a strong infection is that it has the ability to mutate itself rapidly. This makes it especially difficult to find appropriate treatment and vaccines to fight it.

There are two main types of HIV: HIV-1 and HIV-2. The first is responsible for the vast majority of infection and cases of AIDS in the world. The second is the more common type in West Africa and has a slower course than HIV-1. There are many variations of HIV that are not focused on this work.

As described in Haefner (2005), AIDS, itself, is clinically defined to be the condition of a patient having fewer than 200 CD4 white blood cells per milliliter of blood and testing positive for HIV antibodies. AIDS is advanced HIV-infection, that means, it is the late stage of infection when the immune system has been weakened. The individual at this level becomes more susceptible to a variety of infections which are called opportunistic infections and other conditions, e.g., cancer. Some examples of opportunistic infections include chronic cryptosporida diarrhea, cytomegalovirus eye infection, mycobacterium avium complex, pneumocystis pneumonia, and toxoplasmosis. Other AIDS-associated conditions include invasive cervical cancer, Kaposi's sarcoma, and lymphoma.

One important point to be aware of is nobody dies from AIDS or HIV (a common misapprehension); rather, a person with AIDS dies from an infection or condition that his weakened immune system can no longer fight off.

Figure 2.1 represents the virus action in the $CD4$ lymphocyte. The phases are enumerated and represent each phase of infection. The HIV enters the host through the fluids that get past the non-specific mechanical barriers (skin, mucous). These pathways are well known: sexual transmission and blood transfusions or contamination (by shared intervenous needles for example). Once inside, HIV enters the blood stream and from there attacks the lymphocytes. HIV is a retrovirus, which means it contains only RNA, no DNA, while in normal eukaryotic cells, segments of DNA transcribe themselves into

single stranded forms called RNA messenger, which leaves the nucleus and interacts with ribosomes to form proteins.

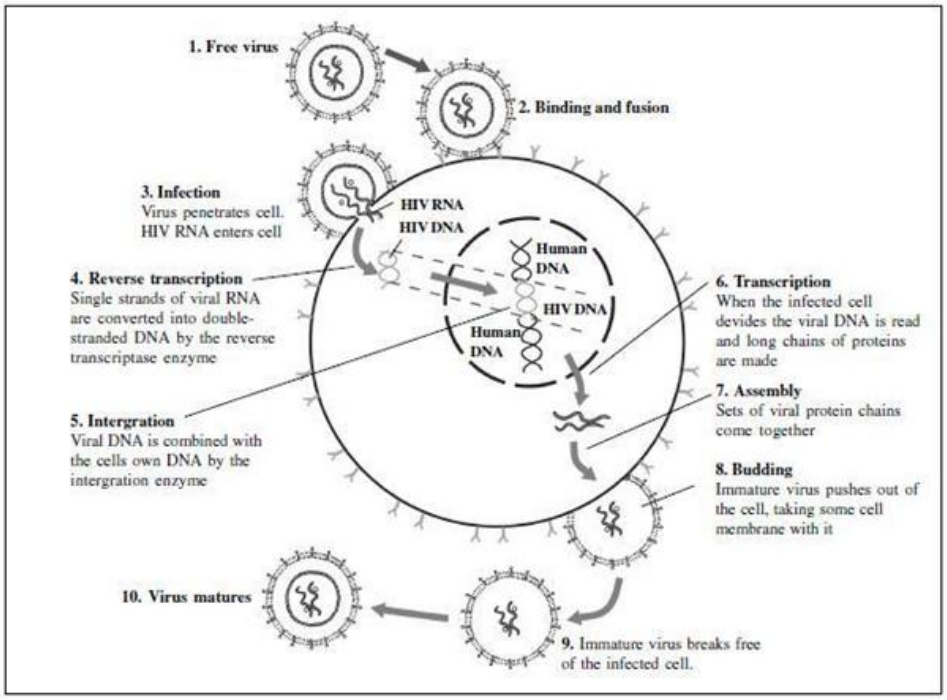


Figure 2.1: Biology of HIV - Synthesis. Source: Haefner, 2005.

During mitosis, double-stranded DNA makes two copies of itself by the process of transcription. So, in this mode, DNA (not RNA) is required for cellular reproduction. HIV, having only RNA, requires the host cell to provide the DNA machinery for its replication. HIV accomplishes this by binding to the cell, injecting its RNA into the cytoplasm, and subsequently using a viral enzyme called reverse transcriptase to form double-stranded DNA. This viral DNA is ultimately incorporated into the DNA host cell and is replicated along with host DNA during normal mitosis.

This process does not, itself, produce new HIV cells, only more copies of the DNA required for new virus cells. Over time (many months to years), poorly understood events in the infected host cells cause the viral DNA to produce viruses that bud out through the membranes of the infected host cells and enter the blood stream where it can infect new cells. This can happen repeatedly for each infected cell.

This continues over 1-10 years, resulting in the gradual diminution of the $CD4^{+}T$ cell population from a healthy level of about 1000-1200 cells per milliliter of blood to the

stage of clinical AIDS, that means 200 $CD4^{+}T$ cells per ml of blood. Once the immune system has been degraded to this level, the host organism is susceptible to attacks from other antigens and the patient usually dies from these extraneous attacks or opportunist diseases already listed. (Haefner, 2005)

It has been observed that the timing of this process varies greatly from patient to patient. Over the course of 10 years or so, most infected individuals advance to AIDS, but some patients are diagnosed within two years of infection, and others avoid AIDS for 15 years or more. Also, it has been reported in Campello de Souza (1999) that some people have been exposed to HIV-1 but did not develop AIDS.

In the last 10 years, many models appeared to represent the replication of the HIV. These models explored only the relation between the lymphocytes cells, in particular $CD4^{+}T$ and the virus. In this dissertation, the relation with three variables: CD4, CD8 and the free virus will be explored. The model chosen for this work, is the one presented by Campello de Souza (1999), with the parameters described by medical publication through the application of the optimal control to analyze the behavior of these variables.

2.3 Dynamic Model of HIV-1

A number of mathematical models have been proposed in the field of immunology, which can be found in Wick (1999), Behrens *et al.* (1999), Tan & Wiang (1999), Nowark *et al.* (1997), Huang *et al.* (2003), Craig & Xia (2005), Wodarz & Hamer (2007) among other works. There are in the literature some models proposed for a better comprehension of the evolution of AIDS in humans, attention is drawn to the models proposed by Phillips (1996), Tan & Wu (1998) and Grégio (2005). There are works about the control application to the models on HIV replication. These models are described by Perelson & Nelson (1999), Caetano & Yoneyama (2002), Snedecor (2003), Perelson *et al.* (2004), Wang & Li (2006) and Hardt (2007).

The model developed by Campello de Souza (1999) was applied in this work. This model uses three differential equations that represent the interaction between the CD4 and CD8 lymphocytes and the free HIV-1. The dynamic is described by the set of differential

equations 2.3.1:

$$\begin{aligned}\frac{dx_1}{dt} &= -ax_1 - bx_1x_3 + ax_{1N} \\ \frac{dx_2}{dt} &= -cx_2 + dx_2x_3 + cx_{2N} \\ \frac{dx_3}{dt} &= ex_1x_3 - fx_2x_3 - u \\ &= (ex_1 - fx_2)x_3 - u\end{aligned} \tag{2.3.1}$$

Where the variables x_1, x_{1N}, x_2, x_{2N}, x_3 and u represent respectively:

$$\begin{aligned}x_1 &= CD4 \\ x_{1N} &= CD4N \\ x_2 &= CD8 \\ x_{2N} &= CD8N \\ x_3 &= V \\ u &= U\end{aligned} \tag{2.3.2}$$

The interactions in this set of differential equation mean:

- The growth rate of CD4 diminishes when the HIV-1 population grows;
- The growth rate of HIV-1 increases with the increase in the population of HIV-1 and CD4;
- The growth rate of HIV-1 decreases with the increase in the CD8 population and with application of drugs.

In addition, the parameters mean:

- CD4N and CD8N are the equilibrium values of the CD4 and CD8 populations, respectively. They are produced by the normal homeostasis;
- U corresponds to the dosage of the drug or other therapies used in the treatment of AIDS (this is the control variable) and it is considered to be any and all that diminish the rate of HIV-1;

- CD4, CD8, and V are state variables. The HIV-1 population (i.e., the viral load) will be denoted by V (this will correspond to 10^7 times the viral load measured in copies/ml);

- And a, b, c, d, e, and f are the parameters of the system. The value of "a" is correlated with the normal rate of production and death of CD4 while "c" is correlated with CD8. "b" represents the rate which a virus finds a CD4 and "d" between a CD8 and the virus. "e" is linked to rate of increasing of the virus load while the "f" with the decreasing of virus. The third equation does not have own dynamics.

2.4 Medication and the Control Variable

The control in this model is inserted in the variable u. There are basically four strategies to control the virus action with medicines. The first control is to utilize the fusion inhibitors which do not allow HIV to bind to CD4 cell surface molecules. One commercial example is Enfuvirtide. The second kind of control is to use reverse transcriptase inhibitors that do not permit the HIV to undergo reverse transcriptase, which means, to transform copies of genomic RNA into DNA. Examples are: Delavirdine, Nevirapine and Efavirenz.

The third type of control is to utilize integrase inhibitors to block the action of integrase, a viral enzyme that inserts the viral genome into the DNA of the host cell. This group includes, for example: Zidovudine, Stayudine and Abacavir. These are the protease inhibitors which blocks viral maturation. In other words, these inhibitors do not allow the amino acid chains to be severed by a specific viral protease before new viral particles become active. Examples are: Indinavir, Ritonavir and Amprenavir.

The different kinds of medicines are often used together (in combination) to reduce the amount of HIV in the body. One of the most common treatment schemes is HAART (Highly Active Antiretroviral Therapy) which uses an association of reverse transcriptase inhibitors and protease inhibitors.

One of the main concerns about using chemical treatment, is that, after several months, some patients develop side effects such as abdominal girth, abdominal fullness, disten-

tion or bloating (Mittler *et al.* , 1998). Other patients reported adverse effects such as headache, malaise, nausea, vomiting, nasal problems and musculoskeletal pain.

The effectiveness of a particular treatment scheme must be measured in an objective manner. This can be done by constructing a cost function that accounts for the number of CD4 and CD8 cells, and the rate of HIV-1 and the administered doses of drugs. The rates of CD4 and HIV-1 indicate the effectiveness of the treatment. On the other hand, the dosages of the administered drugs reflect the intensity of the side effects. Currently, specialists use the rates of CD4 and HIV-1 to evaluate the patients' health state.

The objective in this dissertation is to use a computer simulation for the application of the optimal control to minimize the side effects. Analysis can be conducted using LQR (Linear Quadratic Regulator) theory and applying the optimal control by Pontryagin's Maximum Principle. The target is to find a u^* that is correlated with the patient's state to minimize these side effects, to reduce expenditure on medicines during treatment and to reduce the amount of virus in the body and to keep the lymphocytes at a normal level. It is important to emphasize that the focus here is not to discover what is the drug with the best results.

3 The Optimal Control Problem

"We have to curb an epidemic that affects us all, as its impact is not restricted to the biological dimension: it goes further, placing us face to face with social and behavioral issues, such as prejudice, stigma and abandonment"

José Gomes Temporão – Minister of Health

3.1 Introduction

This chapter presents the fundamentals of optimal control theory and the formulation of the HIV problem. The first section gives a short introduction to Optimal Control Theory and notions on the virus clearance procedure. Subsequently the HIV problem applying Optimal Control Theory, in special Pontryagin's Maximum Principle is introduced.

3.2 Optimal Control Theory

Optimal control has found applications in many different fields, including biomedical engineering, production engineering, environmental issues, epidemiology, robotics, economics, and management science, and it continues to be an active research area within control theory.

Optimal control theory, an extension of the calculus of variations, is a mathematical optimization method for deriving control policies. The method is largely due to the work of Lev Pontryagin and his collaborators in the Soviet Union and Richard Bellman in the United States.

The formulation, via optimal control, of the problem of dynamic optimization focuses on one or more variables that serve as instruments of optimization. Unlike, however, the calculus of variations, where the objective is to find the optimal temporary direction to a variable state Y, the main goal of the theory of optimal control is to determine the optimal direction for the variable of control u. Certainly, as soon as the direction of optimal control, $u^*(t)$, is found, it can also find the corresponding direction of optimal state, $x^*(t)$. In fact, the directions $u^*(t)$ and $x^*(t)$ are usually found in the same process.

But the presence of a control variable as the central stage changes the basic orientation of the problem of dynamic optimization (Chiang, 1992).

An optimal control is a set of differential equations describing the paths of the control variables that minimize the cost functional. The optimal control can be derived using Pontryagin's Maximum Principle (a necessary condition), or by solving the Hamilton-Jacobi-Bellman equation (a sufficient condition).

In general in Santiago (2008), the technique implies choosing a trajectory of certain variables of control from an admissible set, in order to obtain, via a set of differential equations (movement equations) a trajectory of the variables of state that describe the system, thus maximizing a determined functional objective. The mathematical formulation of the problem is:

$$\max_{\{\mathrm{u}(t)\}} \quad J = J\{\mathrm{u}(t)\} = \int_{t_0}^{t_1} I(\mathrm{x}(t), \mathrm{u}(t), t)dt + F(\mathrm{x}_1, t_1) \tag{3.2.1}$$

subject to :

$$\dot{\mathrm{x}}(t) = \mathrm{f}(\mathrm{x}(t), \mathrm{u}(t), t) \tag{3.2.2}$$

$$t_0 \quad \text{and} \quad \mathrm{x}(t_0) = \mathrm{x}_0 \quad \text{given} \tag{3.2.3}$$

$$(\mathrm{x}(t), t) \quad \in \quad T \quad \text{where} \quad t = t_1 \tag{3.2.4}$$

$$\{\mathrm{u}(t)\} \in U \tag{3.2.5}$$

The most important terms are:

- State variable $x(t)$: a continuous function of time that characterizes the state of the system at any instant t within the specified interval $[t_0, t_1]$;
- Trajectory of state: $\{x\} = [x : -\infty, +\infty] \rightarrow R^n$. geometrically can be interpreted as a direction of points at E^n, starting from the initial state $\mathbf{x}(t_0) = \mathbf{x}_0$ and ending

at terminal state $\mathbf{x}(t_1) = \mathbf{x}_1$;

- Control variables $u(t)$: They are values that characterize the choices (decisions) made at any time t during specified interval;
- Control Set U: this is the set of all admissible control trajectories. Any optimal trajectory of control must belong to this set;
- Trajectory of control : $\{\mathbf{u}(t)\} = \{\mathbf{u}(t) \in E^n \mid t_0 \leq t \leq t_1\}$. Geometrically represents a direction of points at E^r;
- Movement equations $\dot{\mathbf{x}}(t)$: a set of n differential equations that, by supplying the rate of change at the time of each state variable as a function of the other state variables, control and time variables, characterizes the trajectory of the state $\{\mathbf{x}(t)\}$;
- Terminal time , t_1: $(\mathbf{x}(t), t) \in T$ in $t = t_1$ where T is a given sub-set of E^{n+1}, deemed the terminal surface;
- Functional Objective, Equation 3.2.1: this is the map that shows the control trajectories to points in the real line. The value that must be maximized, where I is the so-called intermediate function that must characterize the dependence of the functional at the time interval in relation to the state and control variables and the time itself. The second function F, called the final function, relates the functional to the state and the terminal time.

3.2.1 Pontryagin's Maximum Principle

Generally speaking, there are two different approaches to considering dynamic optimization problems. The first approach can be seen as a generalization of the usual maximization problem from calculus and it is inseparably connected with the work of Pontryagin et al. (1962). In the second approach the dynamic structure is used. In this case the theory of dynamic programming (introduced by Bellman) provides the theory that underpins attempts to solve the optimization problem.

This approach can be seen as a generalization of the necessary conditions provided by the calculus for maximizing functions or the calculus of variations for maximizing

functionals. Pontryagin's Maximum Principle provides the necessary conditions that an optimal solution has to satisfy, i.e., given that an optimal solution exists, it has to satisfy the conditions of the Maximum Principle.

The target is to maximize (or minimize, depending on the point of view):

$$\mathrm{J}(u) = c_t(x(t_f)) + \int_t^{t_f} c_c(x(\tau), u(\tau), \tau) d\tau \tag{3.2.6}$$

Subject to constraints and the terminal constraints:

$$\dot{\mathrm{x}}(t) = \mathrm{f}(\mathrm{x}(t), \mathrm{u}(t), t) \tag{3.2.7}$$

$$\mathrm{x}(t_0) = \mathrm{x}_0 \tag{3.2.8}$$

$$\mathrm{x}(t_f) = \mathrm{x}_f \tag{3.2.9}$$

The Hamiltonian is given by

$$H(x, u, y, t) = C_c(x, u, t) + y^T f(x, u, t) \tag{3.2.10}$$

If u^* is the optimal control by Pontryagin's Maximum Principle, then

$$H(x^*, u, y^*, t) \leq H(x^*, u^*, y^*, t) \qquad \forall t, u \in U$$

where $x^*(t)$ and $y^*(t)$ satisfy the case with terminal constraints and $y(t)$ is defined as the adjoint variable.

$$\frac{dx(t)^*}{dt} = H_y(x^*, u^*, y^*, t) \tag{3.2.11}$$

$$x^*(t_0) = x_0 \tag{3.2.12}$$

$$\frac{dy(t)^*}{dt} = -H_x(x^*, u^*, y^*, t) \tag{3.2.13}$$

$$y(t_f) = C_c x(x^*(t_f)) \tag{3.2.14}$$

3.3 The Equilibrium Points

When equation 2.3.1 is resolved, one of the equilibrium points of this dynamical system can be found, that will be:

$$x_{1e} = x_{1N} \tag{3.3.1}$$

$$x_{2e} = x_{2N} \tag{3.3.2}$$

$$x_{3e} = 0 \tag{3.3.3}$$

If, $ex_{1e} > fx_{2e}$, then, $\forall x_3(0) > 0$, the system will move away from the origin and will go to the other equilibrium point: (Campello de Souza, 1999)

$$x_{1e} = \frac{ax_{1N}}{a + bx_{3e}} \tag{3.3.4}$$

$$x_{2e} = \frac{cx_{2N}}{c - dx_{3e}} \tag{3.3.5}$$

or

$$x_{1e} = \frac{fbcx_{2N} + eadx_{1N}}{e(ad + bc)} \tag{3.3.6}$$

$$x_{2e} = \frac{fbcx_{2N} + eadx_{1N}}{f(ad + bc)} \tag{3.3.7}$$

$$x_{3e} = \frac{(ex_{1N} - fx_{2N})ac}{fbcx_{2N} + eadx_{1N}} \tag{3.3.8}$$

In the equilibrium,

$$\frac{x_{1e}}{x_{2e}} = \frac{f}{e}.$$

If all parameters are maintained constant all parameters and letting $a \to \infty$, one gets:

$$x_{1e} \to x_{1N} \tag{3.3.9}$$

$$x_{2e} \to x_{1N}\left(\frac{e}{f}\right) \tag{3.3.10}$$

$$x_{3e} \to \left(1 - \frac{fx_{2N}}{ex_{1N}}\right)\left(\frac{c}{d}\right) \tag{3.3.11}$$

Also,

$$c \ll d \Rightarrow x_{3e} > 0 \text{ very small; it does not vanish completely.}$$

In order to eliminate HIV, that is, to make $x_3 = 0$, one should have the condition:

$$ex_{1N} - fx_{2N} < 0$$

3.4 Virus Clearance Procedure

As was described by Ramratnam & Bonhoeffer (1999), in chronic HIV-1 infection a dynamic equilibrium exists between viral production and clearance. In this case, the important point is to focus on the control variable u, namely to monitor closely the effect of medicines during treatment.

$$U = gV \tag{3.4.1}$$

$$u = gx_3 \tag{3.4.2}$$

When g is a factor of proportion. Following Campello de Souza (1999), if HIV were an avid binder, that is, if it tries to make b increase, represented by $b \nearrow$, as much as possible, one would have

$$x_{1e} \approx x_{2N}\left(\frac{f}{e}\right).$$

That is,

$$b \nearrow \Rightarrow x_{1e} \approx x_{2N}\left(\frac{f}{e}\right).$$

Thus, if $f < e$ (typically $f \ll e$), the patient dies, and this would be a Pyrrhic's victory for the virus.

If the virus were intelligent, it would try to keep b as small as possible, in order to be able to keep the smallest possible equilibrium population.

The virus wants a large e (unless it is willing to commit suicide). One would then have the increase represented by:

$$e \nearrow \Rightarrow x_{3e} \to \frac{c}{d}.$$

Therefore the viral load is bounded by the parameters of the x_2 internal dynamics.

One has

$$\begin{aligned} x_{1e} + x_{2e} &= \frac{\frac{f}{e} + 1}{\frac{ad}{bc} + 1} x_{2N} + \frac{1 + \frac{e}{f}}{1 + \frac{bc}{ad}} x_{1N} \\ &= \frac{f+e}{ad+bc} \cdot \frac{bc}{e} x_{2N} + \frac{f+e}{ad+bc} \cdot \frac{ad}{f} x_{1N}. \end{aligned}$$

Then, if

$$ead = fbc,$$

one will have

$$x_{1e} + x_{2e} = x_{1N} + x_{2N}.$$

This is the condition for the system to maintain the total number of lymphocytes.

The target is to introduce a feedback control to decrease the growth rate of the virus population by the use of drugs. When $U = gV$, Equation 2.3.1 becomes:

$$\begin{aligned} \frac{dx_3}{dt} &= ex_1x_3 - fx_2x_3 - U \\ &= (ex_1 - fx_2)x_3 - gx_3 \\ &= (ex_1 - fx_2 - g)x_3 \end{aligned}$$

and the new equilibrium for the virus population, x_{3e}, is given by:

$$x_{3e} = \frac{-x + \sqrt{x^2 + y}}{2gdb} \tag{3.4.3}$$

where $x = (g - ex_{1N})ad - (fx_{2N} + g)bc$, and $y = 4abcd(fx_{2N} + g - ex_{1N})g$. (The equilibrium population of V cannot be negative. Thus, only the plus sign of the square root should be considered). In this case, x_{3e} will be zero when $fx_{2N} + g - ex_{1N} = 0$; that

is, when $g = ex_{1N} - fx_{2N}$. Note that if an individual has parameters e and f such that $ex_{1N} - fx_{2N} \leq 0$, then that person will be naturally immune to HIV-1 attack. That is, this immunity will occur when:

$$\frac{e}{f} \leq \frac{x_{2N}}{x_{1N}}$$

If a drug could be developed to increase f in such a way that this condition could be achieved, then clearance of the HIV-1 population in the body would also occur. An increase in the value of d would result in a decrease in x_{3e}, but not in the extinction of the HIV-1 population.

3.5 A Formulation of an Optimal Therapy via Pontryagin's Maximum Principle

It was chosen to utilize Pontryagin's Maximum Principle in this dissertation with the dynamic model presented in section 2.3. the case will be adopted where t_f is specified to get the optimal control, that means to find the u^*.

The problem will be how to minimize the cost function:

$$\underset{u}{\text{Max}} \int -(x_3^2 + \alpha u^2)dt \quad \text{subject to the system dynamic equations.} \tag{3.5.1}$$

One could also consider the objective functional:

$$\int_{t_0}^{t_1} -\left[x_3^2 + (x_1 - x_{1N})^2 + \alpha u^2\right] dt.$$

The Hamiltonian will be given by:

$$H = -(x_3^2 + \alpha u^2) + y_1(-ax_1 - bx_1x_3 - ax_{1N}) + y_2(-cx_2 + dx_2x_3 + cx_{2N}) + \\ + y_3[(ex_1 - fx_2)x_3 - u],$$

where the y_i's are the co-state variables.

For an interior solution:

$$\frac{\partial H}{\partial u} = -2\alpha u - y_3 = 0 \ \therefore \ u = -\frac{y_3}{2\alpha}.$$

The co-state variables dynamics will be described by:

$$\frac{dy_1}{dt} = -\frac{\partial H}{\partial x_1} = ay_1 - y_1 bx_3 - ex_3 y_3 \tag{3.5.2}$$
$$\frac{dy_2}{dt} = -\frac{\partial H}{\partial x_2} = cy_2 - dx_3 y_2 - fx_3 y_3 \tag{3.5.3}$$
$$\frac{dy_3}{dt} = -\frac{\partial H}{\partial x_3} = 2x_3 + bx_1 y_1 - dx_2 y_2 - (ex_1 - fx_2)y_3. \tag{3.5.4}$$

By rearranging:

$$\frac{dy_1}{dt} = (a + bx_3)y_1 - ex_3 y_3 \tag{3.5.5}$$
$$\frac{dy_2}{dt} = (c - dx_3)y_2 - fx_3 y_3 \tag{3.5.6}$$
$$\frac{dy_3}{dt} = 2x_3 + bx_1 y_1 - dx_2 y_2 - (ex_1 - fx_2)y_3. \tag{3.5.7}$$

One will have the following system of six differential equations:

$$\frac{dx_1}{dt} = -(a + bx_3)x_1 + ax_{1N} \tag{3.5.8}$$
$$\frac{dx_2}{dt} = (-c + dx_3)x_2 + cx_{2N} \tag{3.5.9}$$
$$\frac{dx_3}{dt} = (ex_1 - fx_2)x_3 - \frac{y_3}{\alpha} \tag{3.5.10}$$
$$\frac{dy_1}{dt} = (a + bx_3)y_1 - ex_3 y_3 \tag{3.5.11}$$
$$\frac{dy_2}{dt} = (c - dx_3)y_2 - fx_3 y_3 \tag{3.5.12}$$
$$\frac{dy_3}{dt} = 2x_3 + bx_1 y_1 - dx_2 y_2 - (ex_1 - fx_2)y_3. \tag{3.5.13}$$

There is no easy analytical solution for this set of differential equations. Another way to deal with the optimal control problem would be to linearize the system first.

Optimal control problems can be solved by indirect or direct methods. In the solution using an indirect method, one is required to solve a boundary value problem with 2n equations corresponding to n state and n adjoint variables if Pontryagin's Maximum Principle is invoked or to solve a partial differential equation if Dynamic Programming is used Kirk (1970) and Lewis (1986). One direct method is to analyze the behavior of the Linear Quadratic Regulator (LQR).

4 The Linear Quadratic Regulator

"All models are wrong, but some are useful."

George Box

4.1 Introduction

This chapter shows the linearization of the model and the solution of Riccati's equation to be applied to the LQR. First, LQR control in general is studied and then applied to the model discussed.

4.2 The Linearization of the Model

Data was adapted from the clinical literature which will be used as parameters for the linearized model (Perelson et al. 1993) and (Campello de Souza, 1999). The values are shown in Table 4.1.

Table 4.1: Parameters of the system for HIV-Lymphocytes.

Parameters	Value	Biological Interpretation
x_{1N}	1000	The equilibrium value produced by natural homeostasis of CD4
x_{2N}	550	The equilibrium value produced by natural homeostasis of CD8
$x_1(0)$	1000	Initial value of CD4
$x_2(0)$	550	Initial value of CD8
$x_3(0)$	0.0001	Initial value of viral load
a	0.25	Natural regulation rate of CD4
b	50	Infection of CD4 by HIV rate
c	0.25	Natural regulation rate of CD8
d	10	Elimination of HIV by CD8 rate
e	0.01	Rate of replication of HIV by CD4
f	0.0045	Rate of elimination of HIV by CD8

The graph in Figure 4.1 shows the values determined by a simulation that described the dynamics among the CD4 and CD8 lymphocytes and the HIV-1. It was plotted for a $t(0) = 0$ to $t(1) = 10$ years and the time scale was adjusted by multiplying the rate of virus by 1000. The graph indicates the oscillations of the CD4 and CD8 populations and HIV nature. The HIV-1 has a pulse-like shape that indicates the virus was growing

fast. This occurs in the first year when HIV disseminates itself throughout the body. Consequently, there is a decrease of CD4 and an increase of CD8 to attack the virus. The first pulse corresponds to a very high level of viral load $772.7\,copies/ml$ and 288.6 and $710.4\,cells/mm^3$ for the CD4 and CD8 respectively. There is a strong correlation between CD4, CD8 and the viral load, which can sometimes be positive and sometimes negative. More details in (Campello de Souza, 1999).

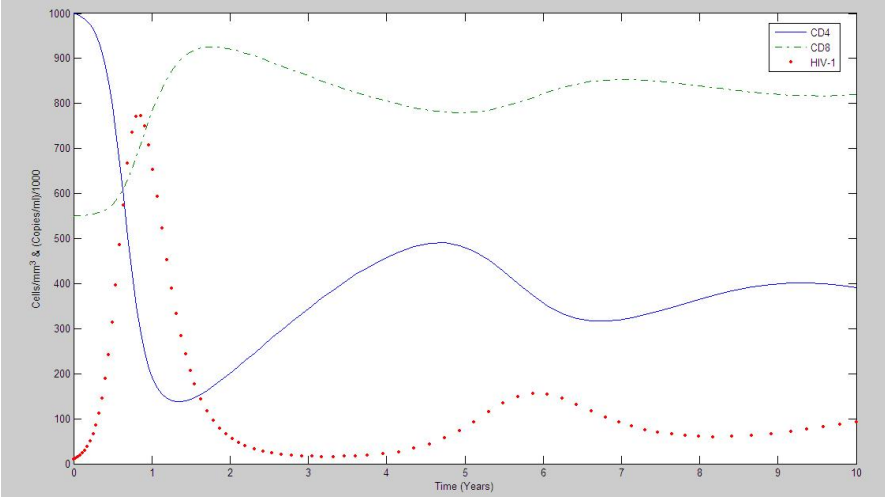


Figure 4.1: Simulation of non-linearized equations.

Figure 4.2 shows the model linearized around the second point. This figure shows the exponential decrease in the time with CD4.

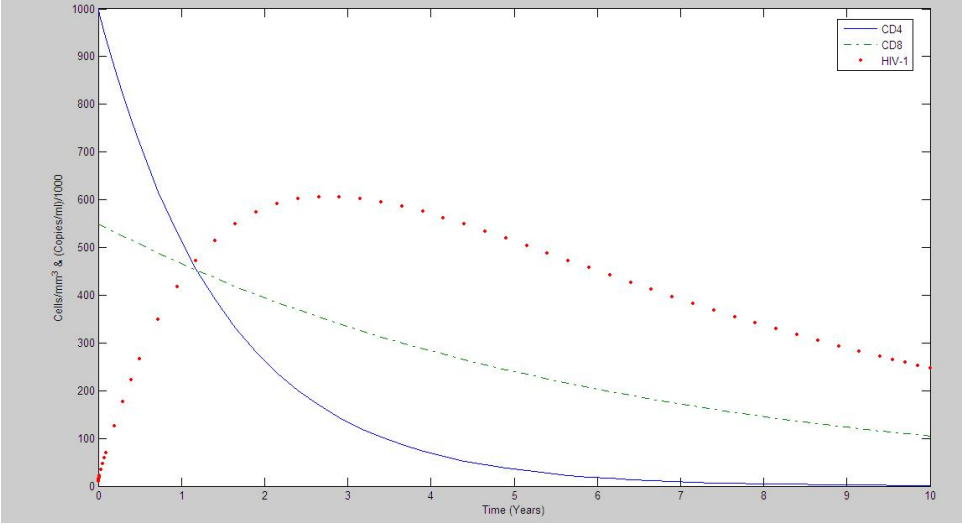


Figure 4.2: Simulation of linearized equations.

The critical points with the data from Table 1. are found to be:

$$\text{first point } x^* = (1000; 550; 0)$$
$$\text{second point } x^* = (991.66; 828.703; 0.008407)$$

The first point is the state of a patient free of HIV and the second one that of the patient who has just been infected by the virus, which means, there is no presence of AIDS because the value of CD4 is approximately around the normal state.

The idea of using a LQR scheme or applying the optimal control by Pontryagin's Maximum Principle is to keep the patient's state near the second critical point by using a feedback control, given that it is practically impossible to eliminate all the virus load from the body.

If using linearity is used, the possibilities can be easily sorted out. The system will be linearized around the second equilibrium point.

$$\frac{dx_1}{dt} = (-a - bx_3)\big|_{x_3=x_{3e}} x_1 \tag{4.2.1}$$
$$\frac{dx_2}{dt} = (-c + dx_3)\big|_{x_3=x_{3e}} x_2 \tag{4.2.2}$$
$$\frac{dx_3}{dt} = (ex_3)\big|_{x_3=x_{3e}} x_1 + (-fx_3)\big|_{x_3=x_{3e}} x_2 + (ex_1 - fx_2)\big|_{x_1=x_{1e};x_2=x_{2e}} x_3 \tag{4.2.3}$$

By substituting the values, one obtains:

$$\frac{dx_1}{dt} = \left[-a - b\frac{(ex_{1N} - fx_{2N})ac}{fbcx_{2N} + eadx_{1N}}\right] x_1 \tag{4.2.4}$$
$$\frac{dx_2}{dt} = \left[-c + d\frac{(ex_{1N} - fx_{2N})ac}{fbcx_{2N} + eadx_{1N}}\right] x_2 \tag{4.2.5}$$
$$\frac{dx_3}{dt} = \left[e\frac{(ex_{1N} - fx_{2N})ac}{fbcx_{2N} + eadx_{1N}}\right] x_1 + \left[-f\frac{(ex_{1N} - fx_{2N})ac}{fbcx_{2N} + eadx_{1N}}\right] x_2 + 0x_3 \tag{4.2.6}$$

Let the simplification be:

$$\lambda = \frac{(ex_{1N} - fx_{2N})ac}{fbcx_{2N} + eadx_{1N}},$$

Then one will have:

$$\begin{aligned}\frac{dx_1}{dt} &= (-a - b\lambda)\, x_1 \\ \frac{dx_2}{dt} &= (-c + d\lambda)\, x_2 \\ \frac{dx_3}{dt} &= e\lambda x_1 - f\lambda x_2 - u\end{aligned}$$

The result will be the linearized system given by Matrix of Dynamic System 4.2:

$$\begin{bmatrix}\dot{x_1} \\ \dot{x_2} \\ \dot{x_3}\end{bmatrix} = \begin{bmatrix}-a - b\lambda & 0 & 0 \\ 0 & -c + d\lambda & 0 \\ e\lambda & -f\lambda & 0\end{bmatrix} \begin{bmatrix}x_1 \\ x_2 \\ x_3\end{bmatrix} + \begin{bmatrix}0 \\ 0 \\ -1\end{bmatrix} u$$

$$x_1(0) > 0, \quad x_2(0) > 0, \quad x_3(0) > 0$$

By using the parameters in Table 1, one derives:

$$\begin{bmatrix}\dot{x_1} \\ \dot{x_2} \\ \dot{x_3}\end{bmatrix} = \begin{bmatrix}-0.6703910 & 0 & 0 \\ 0 & -0.16593 & 0 \\ 0.00008407 & -0.0000378315 & 0\end{bmatrix} \begin{bmatrix}x_1 \\ x_2 \\ x_3\end{bmatrix} + \begin{bmatrix}0 \\ 0 \\ -1\end{bmatrix} u$$

$$x_1(0) > 0, \quad x_2(0) > 0, \quad x_3(0) > 0$$

Assuming that only CD4 cells and the free virus are monitored, (in this case consideration was only given to simplifing CD4 because AIDS is strongly correlated with this variable in the literature), this becomes:

$$\begin{bmatrix}y_1 \\ y_2 \\ y_3\end{bmatrix} = \begin{bmatrix}1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1\end{bmatrix} \begin{bmatrix}x_1 \\ x_2 \\ x_3\end{bmatrix}$$

4.3 The Linear Quadratic Regulator

A most effective and widely used technique of linear control systems design is the optimal LQR because of its simplicity and its robust properties.

A brief description of LQR state feedback design is given below. More details are described by Lewis (2009).

Consider the linear time invariant system:

$$\dot{x} = Ax + Bu \tag{4.3.1}$$

$$y = Cx + Du \tag{4.3.2}$$

with state vector, $x(t) \in \mathbb{R}^n$, input vector, $u(t) \in \mathbb{R}^m$ and output vector $y(t) \in \mathbb{R}^l$. If all the states are measurable, the state feedback

$$u = -Kx \tag{4.3.3}$$

with state feedback gain matrix, $K \in \mathbb{R}^{mxn}$, can be applied to obtain the desirable closed loop (cl) dynamics

$$\dot{x} = (A - BK)x \tag{4.3.4}$$

$$= A_{cl}x \tag{4.3.5}$$

For LQR control, the following cost function is defined:

$$J = \frac{1}{2}\int_0^\infty [x(t)^T Q x(t) + u(t)^T R u(t)]dt \tag{4.3.6}$$

Substitution of Equation 4.3.3 into Equation 4.3.6 yields:

For LQR control the following cost function is defined:

$$J = \frac{1}{2}\int_0^\infty x(t)^T (Q + K^T R K)x(t)dt \tag{4.3.7}$$

The objective of the LQR control, is to find a state feedback gain matrix K, such that the cost function 4.3.7 is minimized. In Equation 4.3.7 the matrices $Q \in \mathbb{R}^{n\times n}$ and $R \in \mathbb{R}^{m\times m}$ are weighting matrices, which determine the closed-loop response of the system. The matrix Q is a weighting matrix for the states and matrix R is a weighting matrix for the input signals. A consideration between response time of the system and control effort can

be made by choosing Q and R. Q should be selected to be positive semi-definite and R to be positive definite.

To minimize the cost function, Equation 4.3.7 should be finite. Since Equation 4.3.7 is an infinite integral, convergence implies $x(t) \to 0$ and $u(t) \to 0$ as $t \to \infty$. This in turn guarantees stability of the closed-loop system Equation 4.3.4. To find the optimal feedback, K, it is assumed that

$$\frac{d}{dt}(x^T P x) = -x(Q + K^T R K)x \tag{4.3.8}$$

Substituting 4.3.8 into 4.3.7 results in

$$J = \frac{1}{2}\int_0^\infty \frac{d}{dt}(x^T P x)dt \tag{4.3.9}$$

$$= \frac{1}{2}x^T(0)Px(0) \tag{4.3.10}$$

Substituting the differentiated form of 4.3.8 into 4.3.4 yields:

$$x^T(A_{cl}^T P + P A_{cl} + Q + K^T R K) = 0 \tag{4.3.11}$$

Substitution of 4.3.4 into 4.3.11 yields

$$A_{cl}^T P + P A_{cl} + Q + K^T R K - K^T B^T P - P B K = 0 \tag{4.3.12}$$

Assuming that the following identity is selected

$$K = R^{-1} B^T P \tag{4.3.13}$$

the following result can be obtained.

$$A^T P + P A + Q - P B R^{-1} B^T P = 0 \tag{4.3.14}$$

This result is the Algebraic Riccati Equation (ARE). It is a matrix quadratic equation, which can be solved for P given A,B,Q and R, provided that (R, B) is controllable and

(Q, A) is observable. In this case 4.3.14 has two solutions. There is one positive definite and one negative definite solution. The positive definite solution has to be selected.

The same result can be obtained by analyzing Pontryagin's Maximum Principle:

The Hamiltonian from Equation 4.3.6 will be:

$$H = \frac{1}{2}\left(x^T D x + u^T R u\right) + y^T(Ax + Bu)$$

From the Pontryagin Maximum Principle, for an interior solution:

$$\frac{\partial H}{\partial u} = Ru + B^T y = 0 \ \therefore \ u^* = -R^{-1}B^T y \ \text{ (a linear function of the co-state variables).}$$

The solution of LQR problems is well known and can be found, for instance, in Lewis (1986) and Kirk (1970).

The canonical equations will be:

$$\begin{aligned} \dot{x} &= \frac{\partial H}{\partial y} = Ax + Bu = Ax - BR^{-1}B^T y, \quad x(t_0) = x_0 \\ \dot{y} &= -\frac{\partial H}{\partial x} = -Qx - Ay^T, \quad y(t_1) = F^T x_1. \end{aligned} \tag{4.3.15}$$

Assuming a linear solution of the form

$$y = P(t)x$$

where $P(t)$ is an $n \times n$ matrix, one obtains the Riccati equation:

$$\dot{y} = \dot{P}x + P\dot{x} = -Qx - A^T P x$$

$$\therefore \ \dot{P}x + P\left[Ax - BR^{-1}B^T P x\right] = -Qx - A^T P x$$

$$\therefore \ \left[\dot{P} + PA + A^T P - PBR^{-1}B^T P + Q\right] x = 0$$

$$PA + A^T P - PBR^{-1}B^T P + Q = 0 \quad \text{(Riccati's equation)}, \tag{4.3.16}$$

When the quadratic criteria is used, the selection of matrixes such as Q and R becomes a hard process to find. Usually, this selection consists of verifying after some simulations

of the project, which values in theses matrixes best satisfy certain criteria (like maximum control, stabilization time, etc). There is not a systematic method for selecting them. It is usual to adopt the diagonal shape to Q and R, because of this possibility that the components of state and control are individually analyzed. For this problem were adopted R as an identity matrix because there is no weighting for the drugs because they can be anything that reduces HIV-1, see the section on medicines in Chapter 2, and Q as a diagonal matrix with strong weighting to reduce the virus, which explains a value 10^{-3} for Q in x_3.

In this case, substituting the results from Table 1, the following problem is obtained:

$$\begin{bmatrix} -0.6703910 & 0 & 0.00008407 \\ 0 & -0.16593 & -0.0000378315 \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} P_1 & P_2 & P_3 \\ P_4 & P_5 & P_6 \\ P_7 & P_8 & P_9 \end{bmatrix}$$

$$+ \begin{bmatrix} P_1 & P_2 & P_3 \\ P_4 & P_5 & P_6 \\ P_7 & P_8 & P_9 \end{bmatrix} \begin{bmatrix} -0.6703910 & 0 & 0 \\ 0 & -0.16593 & 0 \\ 0.00008407 & -0.0000378315 & 0 \end{bmatrix}$$

$$- \begin{bmatrix} P_1 & P_2 & P_3 \\ P_4 & P_5 & P_6 \\ P_7 & P_8 & P_9 \end{bmatrix} \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix} \begin{bmatrix} 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} P_1 & P_2 & P_3 \\ P_4 & P_5 & P_6 \\ P_7 & P_8 & P_9 \end{bmatrix} + \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 0.001 \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

By resolving the Riccati equation and using Matlab, one finds that P is a real and symmetric matrix:

$$P = \begin{bmatrix} 0.74583301755078 & -0.00000000008864 & 0.00000039470179 \\ -0.00000000008864 & 3.01331886956256 & -0.00000070750545 \\ 0.00000039470179 & -0.00000070750545 & 0.00316227766017 \end{bmatrix}$$

The closed loop optimal control law will then be:

$$u^* = R^{-1}B^T P x, \tag{4.3.17}$$

where u^* can be obtained through the matrix R, B and P. The scheme of the system is represented by Figure 4.3:

$$u^* = \begin{bmatrix} 0.00000039470179 & -0.00000070750545 & 0.00316227766017 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix}$$

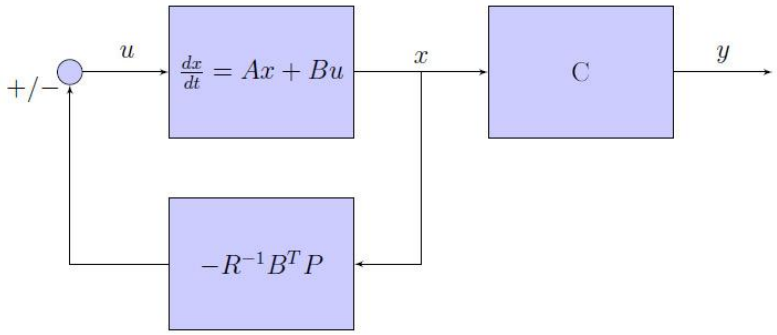


Figure 4.3: Representation of a LQR System.

Computer simulations were carried out using the model described by the System Matrix 4.2 and the parameters of Table 1. Numerical results were obtained for treatment schemes of constant and optimal doses by computer simulation. These simulations can be conducted using the *lqr* function on Matlab. This will give the optimal controller. The *lqr* function allows two parameters, R and Q, to be chosen which balance the relative importance of the input and state in the cost function that it is trying to optimize.

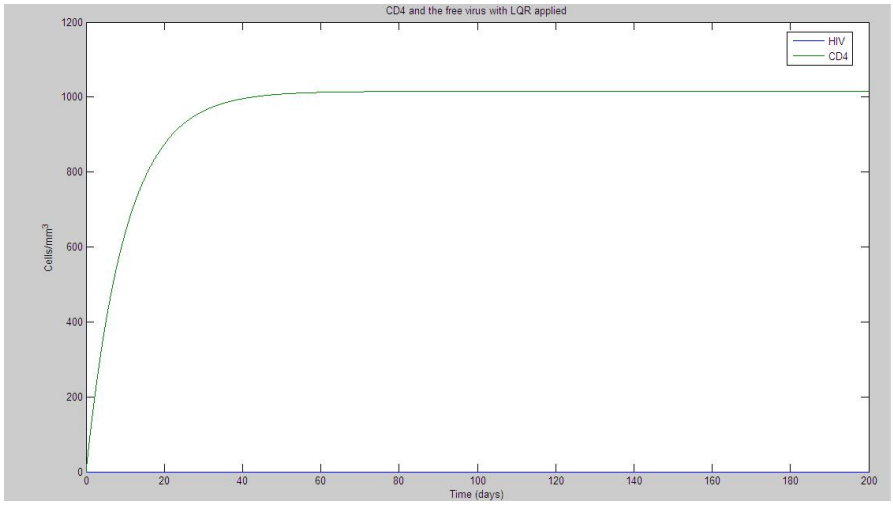


Figure 4.4: LQR applied to reestablish the CD4 state, the same can be obtained for the CD8.

Figure 4.4 shows how to use the LQR to reestablish the parameters of CD4, namely, feedback control is applied as shown in the controller representation. The simulations can be used to represent the patients' state and to help to analyze the activity of the virus load correlated with other variables, such as the lymphocytes.

5 Results: Simulations with the Model

> "System identification covers a very broad area, because modeling dynamical phenomena from observed data is applied in numerous fields that are as diverse as astronomy, microbiology, psychology, management, and so on. However, one common characteristic is that the development of more advanced methods goes hand in hand with the tremendous growth in computing power. This allows the modeling of very large data sets (for instance in biology and in finance and marketing) and the development of more advanced (nonlinear) models."
>
> **Christiaan Heij**

5.1 Introduction

This chapter shows the optimization problem when the functional is minimized, and consequently when the optimal drug dosage is used to fight HIV. The method and the software to simulate different scenarios, patients and treatments are presented.

5.2 The Optimization Problem

The goal of this dissertation is to find the minimum value of $J(x_1, x_2, x_3, u)$, to minimize the input functions $u(t)$, i.e., using less drugs, thus minimizing the virus load to near $x_3 = 0$ and consequently, improving the patients' state of health.

$$\underset{u}{\text{Max}} \; -\frac{1}{2}\int_{t_0}^{t_1} \left[(x_1^2 + x_2^2 + x_3^2) + u^2\right] dt$$

Using the Matrix of the Dynamic System 5.2.1:

$$\dot{x} = \begin{bmatrix} -a - b\lambda & 0 & 0 \\ 0 & -c + d\lambda & 0 \\ e\lambda & -f\lambda & 0 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ -1 \end{bmatrix} u \tag{5.2.1}$$

$$x_1(t_0) = x_1(0), \quad x_1(t_1) = 600$$

$$x_2(t_0) = x_2(0), \quad x_2(t_1) = 700$$

$$x_3(t_0) = x_3(0), \quad x_3(t_1) = 0.001$$

5.3 The Method and Software

In the first section the optimal control for the AIDS problem was formulated. Chapter 3 showed that it had a contour problem of TPBVP (Two Points Boundary Value Problem), when there are initial conditions for states and final conditions for the co-state variables which describe the dynamic system.

There are many algorithms to solve TPBVP problems such as Steepest Descent or Boundary Iterations and Quasi-linearization. These algorithms can be found in books like (Kirk, 1970) and (Lewis, 1986) for example. For this problem, Program PROPT - Matlab Optimal Control Software was used in a demo version with a special license granted generously by Marcus M. Edvall. PROPT is an engine that combines modeling, compilation and a solver so as to generate highly complex optimal control problems and was chosen on account of the history of good performance this model has.

PROPT uses a pseudospectral collocation method for solving optimal control problems. This means that the solution takes the form of a polynomial, and this polynomial satisfies Differential Algebraic Equations (DAE) or Ordinary Differential Equations and the path constraints at the collocation points. The default choice is to use Gauss points as collocation points, although any set of points can be specified and used.

To run the actual data, the parameter estimation was adapted, in particular the "e" value in the Matrix of Dynamic System 5.2.1, to simulate different kinds of patients and

scenarios. Computer simulations are necessary to elucidate the dynamic in biological systems with the objective of supporting medical decisions.

5.4 Simulation of Different Kinds of Patient

Some HIV medications lead to the development of drug-resistant HIV when patients take as few as two percent of their medications. For some other medications, resistance occurs only when patients take large dosages of drugs. These differences appear to be explained by the different levels of viral "fitness" of the drug-resistant HIV (Bangsberg, 2009).

Viral "fitness" refers to the inherent ability of a virus to replicate and cause disease. When patients do not complete a course of taking pills, this can cause HIV to mutate and become resistant to the effects of the medications, while the medications that were consumed, in turn, cause the newly resistant virus to become less fit (Bangsberg, 2009).

Another aspect to be considered here is not just the ability of the virus to become "fitter", but also the human ability to develop the virus. There are individuals who are more susceptible than others to developing AIDS during the infection period. In this case, more attention is given to represent how different individuals should deal with the HIV attack. For the set of simulations in this dissertation, initially the parameter "e" in the Dynamic System Matrix 5.2.1 was adapted in a series of attempts to discover the best behavior in this variable so as to describe the susceptibility of HIV in different patients.

The parameters chosen for three different patients were $e = 0.005$, $e = 0.01$ and $e = 0.02$. These simulations can be visualized in Figure 5.1, Figure 5.2 and Figure 5.3 all plotted for a period of 10 years.

Genetic studies Phair (1994), Paxton *et al.* (1996) and Fowke *et al.* (1996) have observed that many individuals with multiple exposure to HIV-1 remain seronegative, while some of those infected by HIV-1 progress at rates significantly slower or faster than the norm. Researchers have correlated these findings with some mutant genes in HIV co-receptors. Studies have found the presence of mutant alleles such as $D32$ and $m303$ of $CCR5$ suggesting resistance or protection against HIV in some individuals Dean *et al.* (1996), Samson *et al.* (1996) and Quillent *et al.* (1998). It seems that mutant alleles have

somehow changed the structure of the helper T cells in such a way that it is very difficult for the virus's receptor to connect to it. Hence, the virus stops replicating, and individuals show a resistance to HIV. Individuals with two mutant alleles seem to have full protection against HIV infection. Individuals with one mutant allele seem to have partial resistance and, if infected, progress more slowly than individuals without mutant alleles. For Hsu Schmitz *et al.* , these conclusions indicated the "existence of genetic heterogeneity with respect to susceptibility to HIV infection and to the rate of AIDS progression in general populations".

Figure 5.1 shows a simulation for a patient with a low replication rate for HIV. This patient can maintain the CD4 on a stable and healthy plateau, i.e., a CD4 with 570 $cells/mm^3$ and HIV with 50 $copies/ml$. The peak reaches a value of 161.7 $copies/ml$ for the virus load. This patient can live with the virus for a long time without developing AIDS. This fact happens in 1 percent of Caucasians who have the variant gene that lacks a section known as CCR5 that does not allow the virus to enter the cell (Valle *et al.* , 2004).

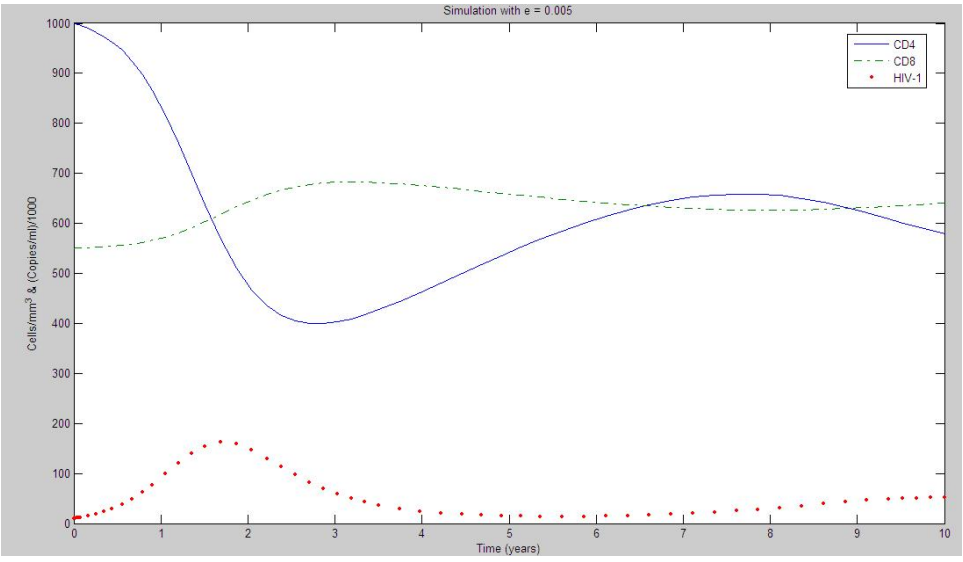


Figure 5.1: First Patient - Simulation for a patient with strong will to fight the HIV. This patient can normally live for years without developing AIDS. The parameter used was $e = 0.005$.

Figure 5.2 describes a "normal" patient who maintains CD4 around 400 $cells/mm^3$ and a virus load of around 82.4 $copies/ml$. The peak for HIV reached 770 $copies/ml$ in the first year because of dissemination of HIV throughout the body. This is the period for

the organism to recognize the virus and to start to fight it. This is the subject described in Campello de Souza (1999) and chosen as the "normal" patient in this work. This patient can remain in good health, despite having and without developing AIDS for years.

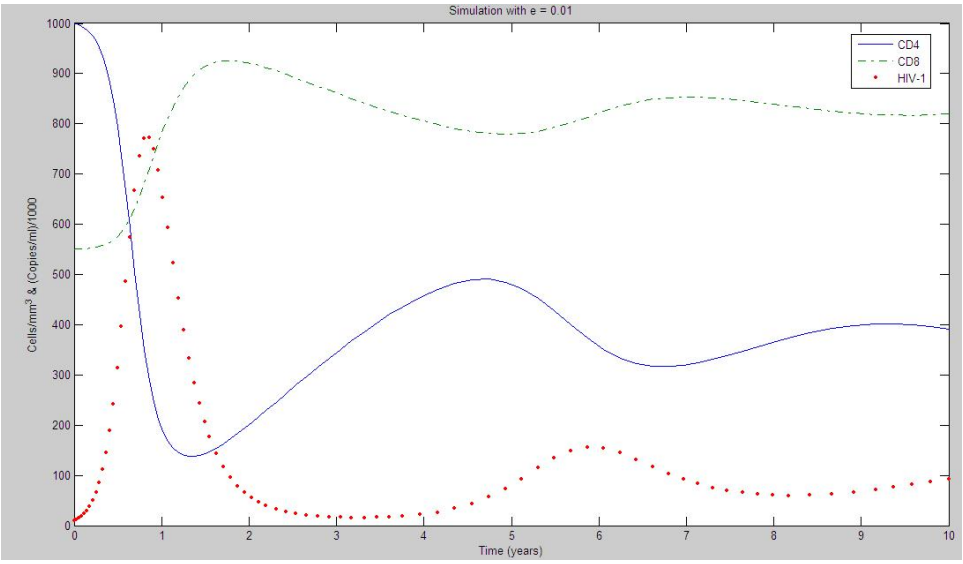


Figure 5.2: Second Patient - Simulation for a patient with the "normal" will to fight HIV. This patient normally can live for 5 to 12 years without developing AIDS. The parameter used was $e = 0.01$.

Figure 5.3 describes a patient who is more susceptible to having a low average life-span. In Africa, WHO (World Health Organization) reports that the average life-span, for example, is between 3 to 7 years after infection. But this condition depends not exclusively on the susceptibility to developing AIDS but also on the health treatment given by the government or on sanitary conditions, for example. In this case, the simulation was of a patient with a high pulse-like shape that indicates the virus was growing fast (reaching a maximum of 2336 $copies/ml$) and which diminishes drastically the CD4 value, i.e. around 266 $cells/mm^3$. A person can be considered to have AIDS when the CD4 count is less than 200 $cells/mm^3$, and consequently to have a greater chance of developing "opportunist infections".

To simulate different HIV/AIDS behaviors with this model two kinds of scenarios for the 3 patients described in the Figure 5.1, Figure 5.2 and Figure 5.3 were created to compare different treatments, with a constant and an optimal dosage of drugs.

The objective of the first and second scenarios is to force the system to reach the

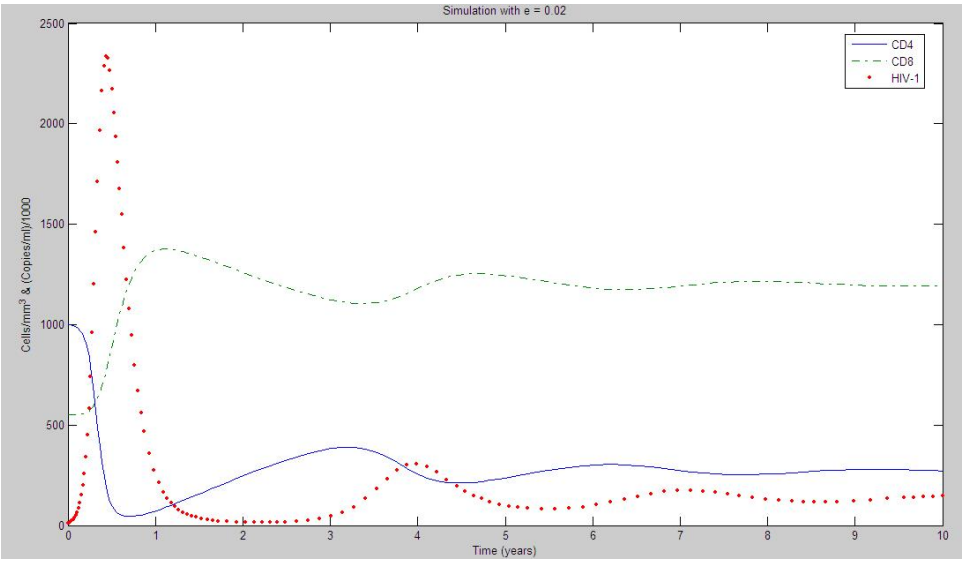


Figure 5.3: Third Patient - Simulation for a patient with a weak will to fight HIV. This patient normally develops AIDS rapidly, i.e., in 3 to 7 years. The parameter used was $e = 0.02$.

"good health" state, by pushing up the variable to a final condition which can give to the patient a better ability to stabilize the virus at acceptable values. A 2 year period was simulated. It is important to stress that a relative scale will be used to visualize both the lymphocytes and the virus load in the same way as in the other simulations.

5.5 1^{st} Scenario

The objective in this study is to stabilize the growing of HIV and to keep CD4 and CD8 at "healthy" levels. The target of the first scenario is to analyze the dynamic represented by the Dynamic System Matrix 5.5.1, where the early treatment was applied. In early treatment, the patient discovers in advance that he has HIV and he decides to undergo the optimal treatment approximately 6 months after infection. The final condition is adjusted to allow the patient to maintain CD4, CD8 and HIV at 600 $cells/mm^3$, 700 $cells/mm^3$ and 0.001 $copies/ml$ respectively in a "healthy state". It important to emphasize that it is impossible to eliminate all the virus load from the body. The initial and final parameters are summarized in Table 5.1.

$$\underset{u}{\text{Max}} \; -\frac{1}{2}\int_{t_0}^{t_1} \left[(x_1^2 + x_2^2 + x_3^2) + u^2\right] dt$$

$$\dot{x} = \begin{bmatrix} -a - b\lambda & 0 & 0 \\ 0 & -c + d\lambda & 0 \\ e\lambda & -f\lambda & 0 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ -1 \end{bmatrix} u \tag{5.5.1}$$

$$x_1(t_0) = x_1(0), \quad x_1(t_1) = 600$$

$$x_2(t_0) = x_2(0), \quad x_2(t_1) = 700$$

$$x_3(t_0) = x_3(0), \quad x_3(t_1) = 0.001$$

Table 5.1: Parameters for the 1^{st} Scenario.

Initial Conditions	**Values**	**Final Conditions**	**Values**
$CD4 = x_1(t_0)$	1000 $cell/mm^3$	$CD4 = x_1(t_1)$	600 $cell/mm^3$
$CD8 = x_2(t_0)$	550 $cell/mm^3$	$CD8 = x_2(t_1)$	700 $cell/mm^3$
$HIV = x_3(t_0)$	0.0001 $copies/ml$	$HIV = x_3(t_1)$	0.001 $copies/ml$

Figure 5.4 shows the behavior when the optimal control is used on the first patient. It is important to notice that there is just one peak of drug dosage (approximately 0.15 units of drug) around the first year to keep the viral load at the acceptable value. This forces the system to maintain the level of CD4 and CD8 at a stable level and the value of HIV nearly at the ideal one. Figure 5.4 also shows that a minimum quantity of drugs is necessary to combat the virus, because the patient's organism put CD8 in charge of eliminating the load virus by itself.

Figure 5.5 presents an important phenomenon in the second patient. Near the third month, there is the first and small peak of drug dosage, approximately 0.5 units of u, when immediately the viral load starts to grow and reaches a maximum of 552.3 $copies/ml$. At this moment, the controller applies a high dose of drug (2.357 units of u) to decrease the virus load to 0.001 $copies/ml$.

Figure 5.6 shows the critical patient's behavior to this scenario. It is easy to notice that for this patient there are more doses applied (7 in total), with a high peak around the second year (approximately 5 units of drug). The dosage needed to fight the virus is

higher due to his organism being more susceptible to developing AIDS.

5.6 2^{nd} Scenario

The dynamic represented by the Matrix of Dynamic System 5.5.1 was analyzed in the second scenario, where later treatment was applied. In later treatment, the patient discovers belatedly that he has HIV and he decides, in this case, to undergo optimal treatment, approximately 3-4 years after infection. The free virus reached a high level and, on the other hand, the CD4 rate a low rate. The final conditions are forced to provide a "healthy" state for the patient. The parameters are described in Table 5.2.

Table 5.2: Parameters for the 2^{nd} Scenario.

Initial Conditions	**Values**	**Final Conditions**	**Values**
$CD4 = x_1(t_0)$	500 $cell/mm^3$	$CD4 = x_1(t_1)$	600 $cell/mm^3$
$CD8 = x_2(t_0)$	600 $cell/mm^3$	$CD8 = x_2(t_1)$	700 $cell/mm^3$
$HIV = x_3(t_0)$	0.09 $copies/ml$	$HIV = x_3(t_1)$	0.001 $copies/ml$

Figure 5.7 shows the behavior for the first patient. 6 peaks can be seen during the optimal control of dosage. Doses of around 1 unit of drug were used at the end of the second year, a moment when the HIV dropped drastically to the normal value.

Figure 5.8 shows the decrease in HIV due to using the optimal drug dosage for two years for the second patient. 11 peaks were used to control HIV and to keep CD4 and CD8 at stable parameters. The maximum of drugs used was 0.5 unit of drug.

Figure 5.9 presents the critical patient in the second scenario. Frequently dosages of drug were administered during the period, (a total of 25 times), to reduce the growth of HIV. The maximum was slightly more than 0.5 units of u. 4 peak were needed to reduce drastically the rate of HIV after the first year.

5.7 Comparison with Real Treatment

For both scenarios, it is possible to realize control of the disease, by bringing the patient to a stable state during treatment. However, WHO adopts a treatment with a constant dosage during this period. Table 5.3 shows the comparison between the optimal

treatment and a treatment using a constant dosage. Different constant dosages were used for the patients because they have different ways to fight the virus.

The criteria used were to establish a value of one third of a maximum peak (in the optimal treatment) as a constant value. For example, in Figure 5.10 the dosage constant was 0.047 units of u for two years that correspond to one third of the peak in the first scenario (approximately 0.14 units of drug). This graph shows an important fact about using the optimal or the constant dosage when compared with Figure 5.4. It can be observed that the rate of HIV in the constant treatment reaches the maximum of $550\,copies/ml$ while the optimal treatment reaches a maximum of $100\,copies/ml$. This characteristic is directly correlated to the progress of the virus in the body.

From Table 5.3 the better values to the optimal treatment can be seen.

Table 5.3: Optimal Dosage vs Constant Dosage in units of drug (u).

	1^{st} **Scenario**		2^{nd} **Scenario**	
Patient	**Optimal Dosage**	**Constant Dosage**	**Optimal Dosage**	**Constant Dosage**
1^{st} Patient	$7.9\,10^{-3}$	$94\,10^{-3}$	$76.9\,10^{-3}$	$660\,10^{-3}$
2^{nd} Patient	$52.5\,10^{-3}$	$1334\,10^{-3}$	$112.3\,10^{-3}$	$344\,10^{-3}$
3^{rd} Patient	$173.7\,10^{-3}$	$2668\,10^{-3}$	$194.3\,10^{-3}$	$352\,10^{-3}$

5.8 Discussion

The use of therapies (that uses whatever u) has dramatically reduced the progress of disease among patients with HIV, but the optimal moment to begin therapy is still uncertain.

Before beginning the discussion about the results in this study, it is important to stress the research done by Kitahata *et al.* (2009) in the United States and Canada from 1996 to 2005. The survey showed one analysis conducted with 9,155 patients which met the inclusion criteria with a CD4 count of more than 500 cells per millimeter. Of these patients, 2,220 (24%) began antiretroviral therapy within 6 months after the first CD4 count was within the range of interest, and 6,935 (76%) deferred therapy. The main result of this survey has shown that among patients in the deferred-therapy group, there was an increase in the risk of death of 94% (relative risk, $1.94; 95\%\,CI$, $1.37\,to\,2.79$; $P < 0.001$) when compared with the patients who have undergone early therapy.

The effectiveness of the optimal control treatment scheme is measured in a cost function that takes into account the number of CD4 cells and the doses of drugs administered. The CD4 cells indicate the effectiveness of the treatment, while the doses of the administered drugs reflect the intensity of the side effects. In these results notice the lower dosage used to control the virus in the sense of minimizing a quadratic type performance index.

The results showed that the patients who most improved the HIV rate (and also with a higher CD4) using lesser quantities of drugs can be attributed to multiple factors:

- Earlier treatment control;
- Viral replication;
- The patient's immunological state.

The fact of using a lesser drug dosage means having less side effects, but in some cases it is correlated with the high risk of developing drug resistance. Noticed that the optimal control allows less antiretroviral during therapy, and consequently produces less toxic effects, such as peripheral neuropathy, anemia, and renal insufficiency.

It is also important to know, that the decision to initiate or defer the therapies could have been influenced by such factors, as described in Kitahata *et al.* (2009):

- Age;
- CD4 count and HIV RNA level;
- History of injection-drug use;
- Presence or absence of HCV (Hepatitis C Virus) infection.

In the next two chapters, the application of optimal control in the dynamics between the glucose and insulin will be studied.

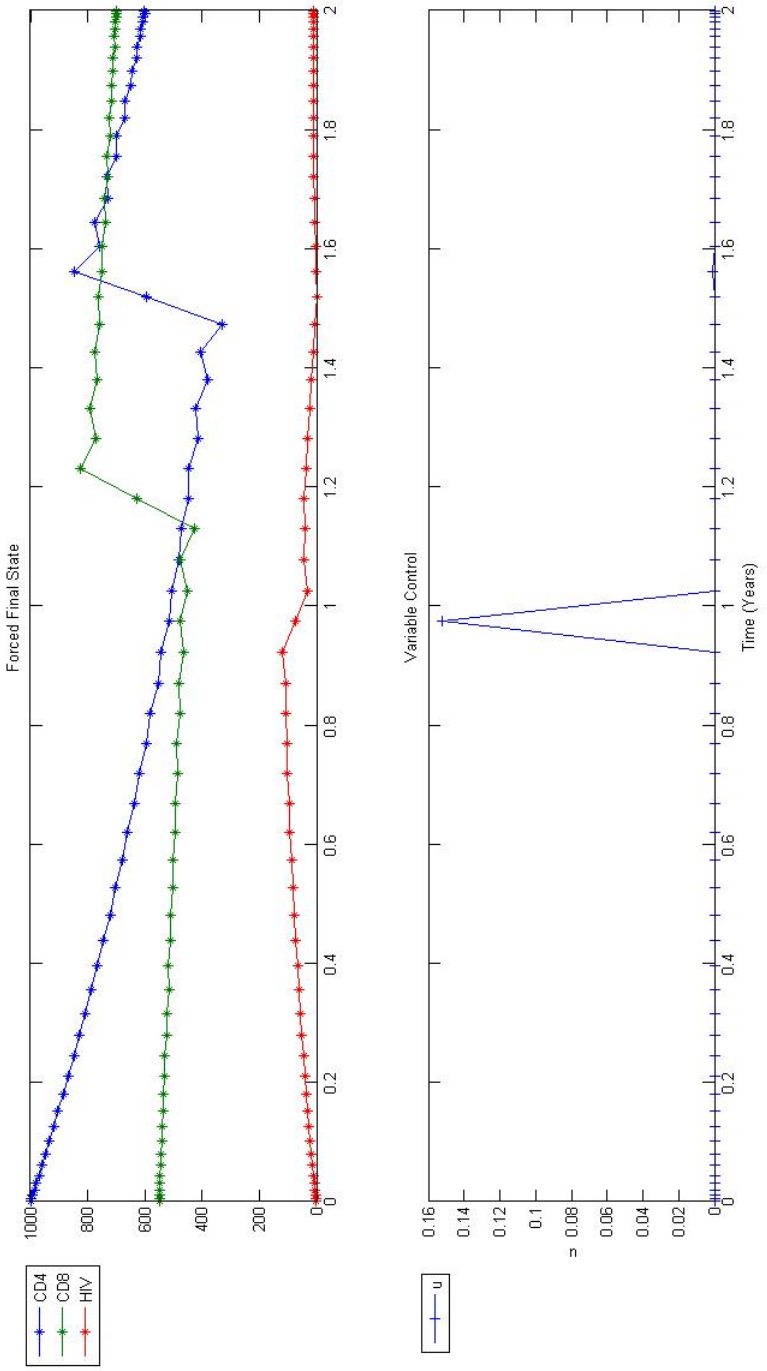


Figure 5.4: Simulation for the First Patient - 1st Scenario.

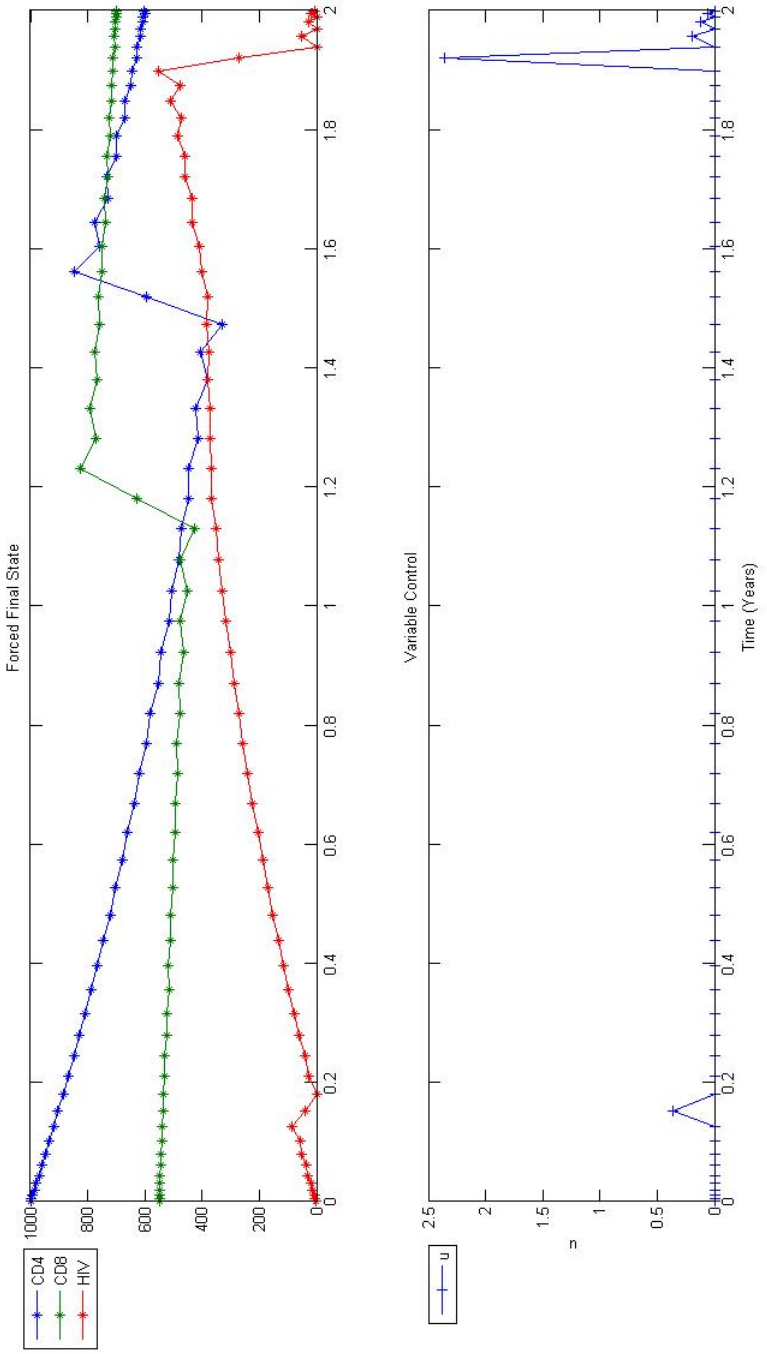


Figure 5.5: Simulation for the Second Patient - 1st Scenario.

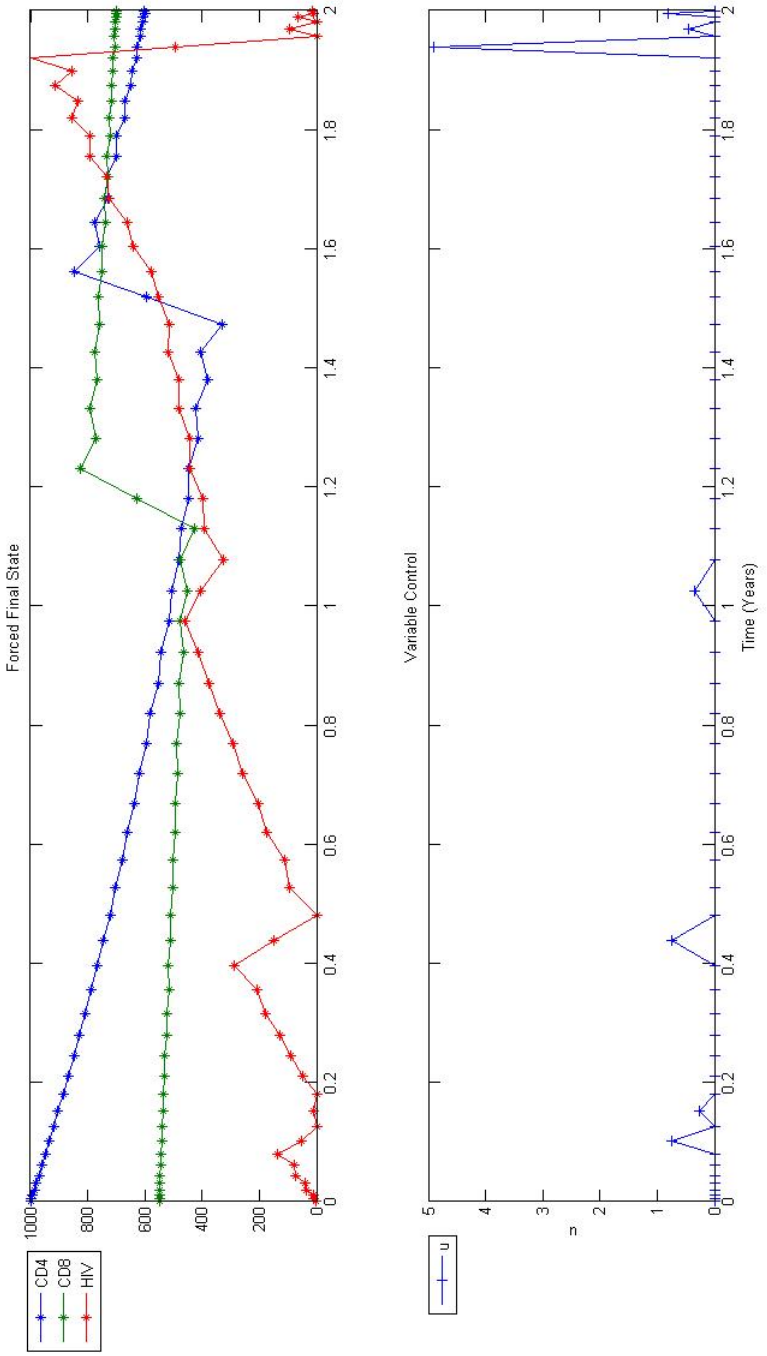


Figure 5.6: Simulation for the Third Patient - 1st Scenario.

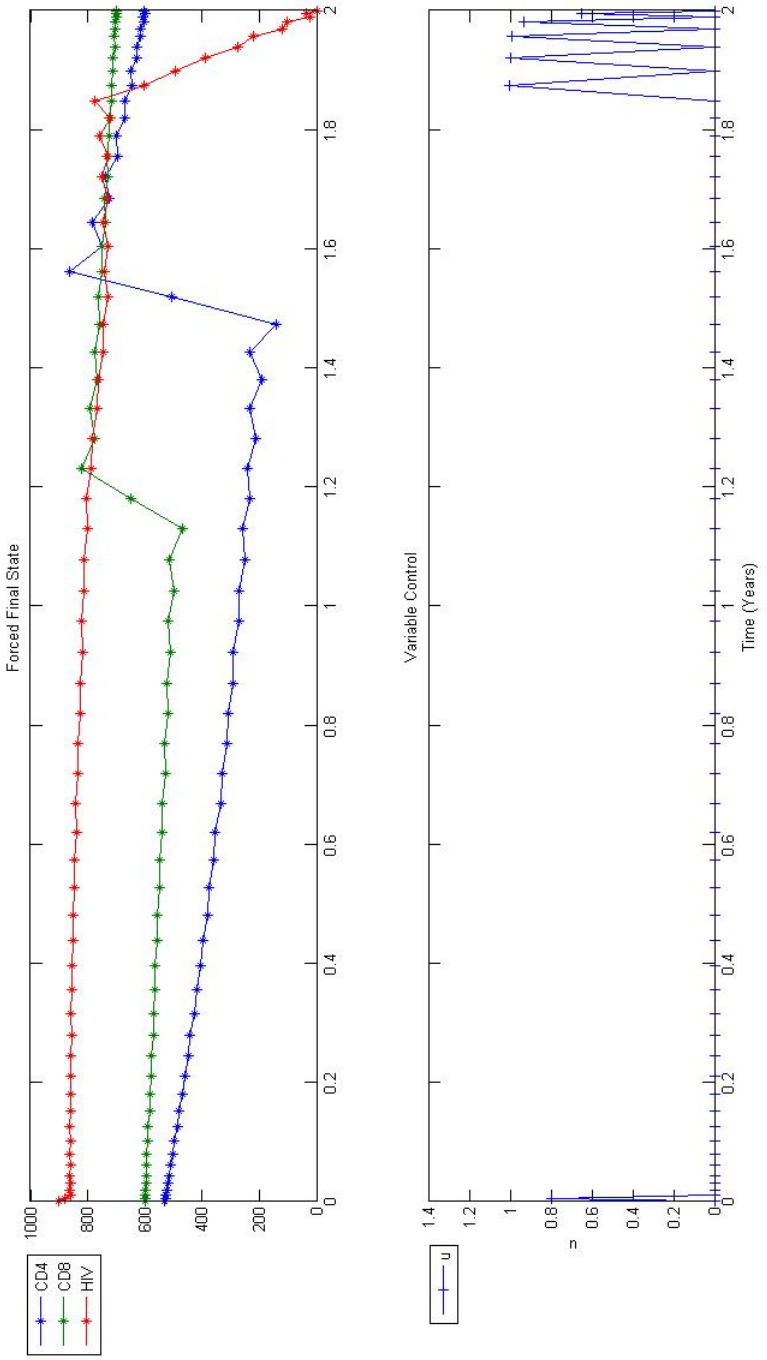


Figure 5.7: Simulation for the First Patient - 2nd Scenario.

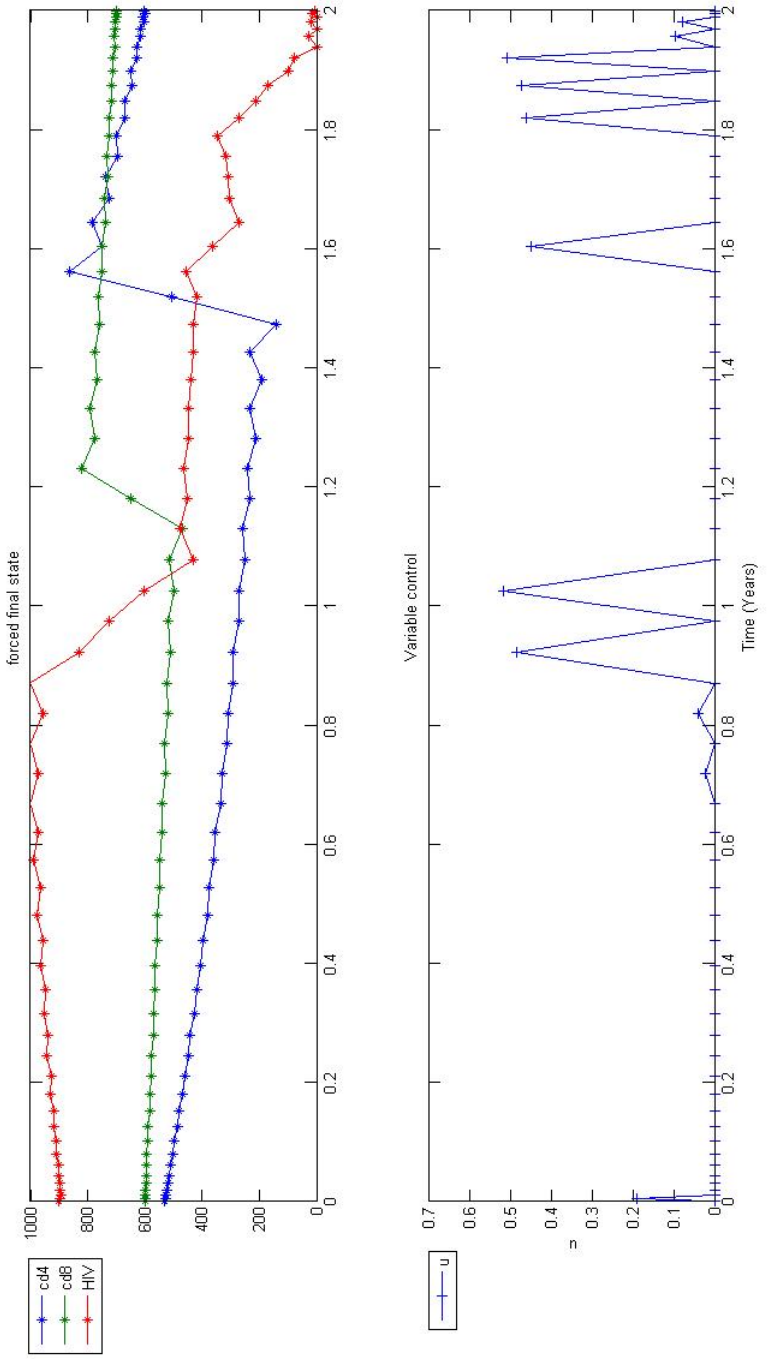


Figure 5.8: Simulation for the Second Patient - 2nd Scenario.

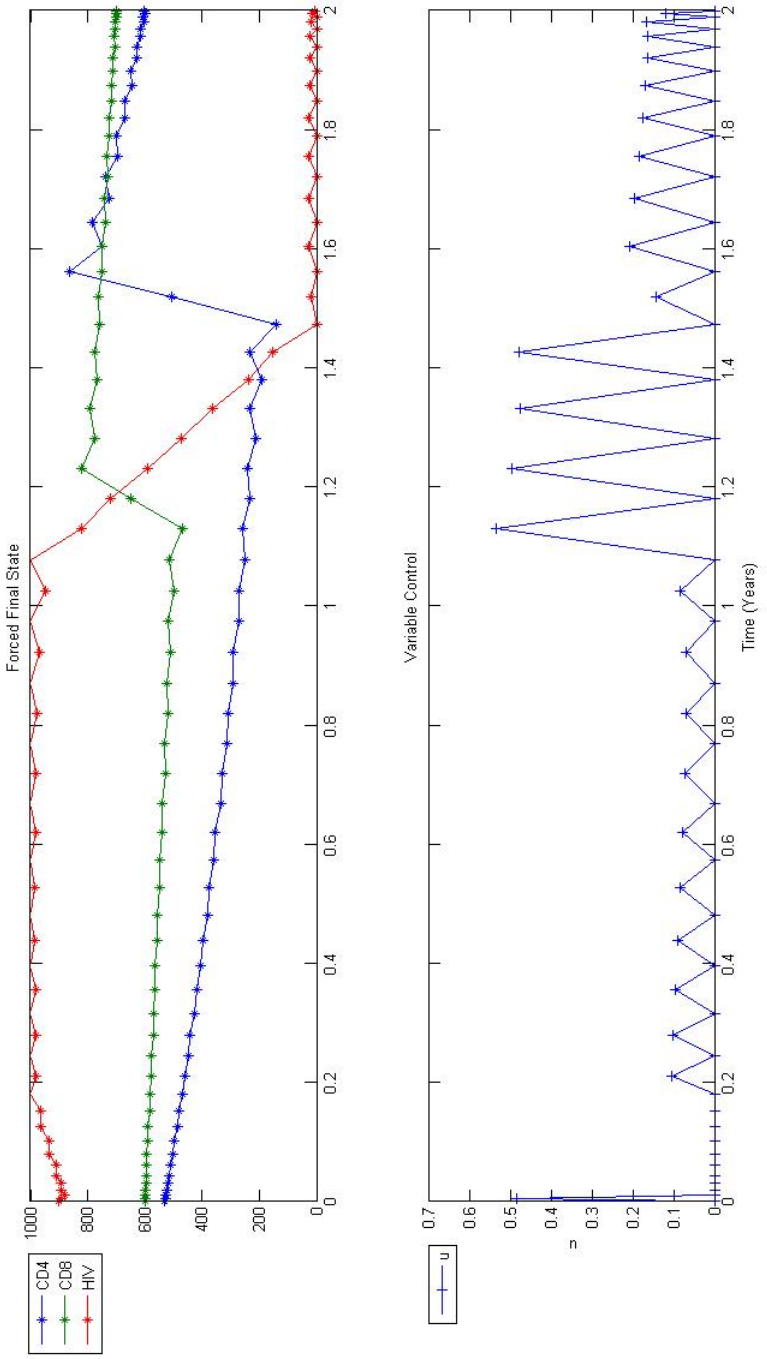


Figure 5.9: Simulation for the Third Patient - 2^{nd} Scenario.

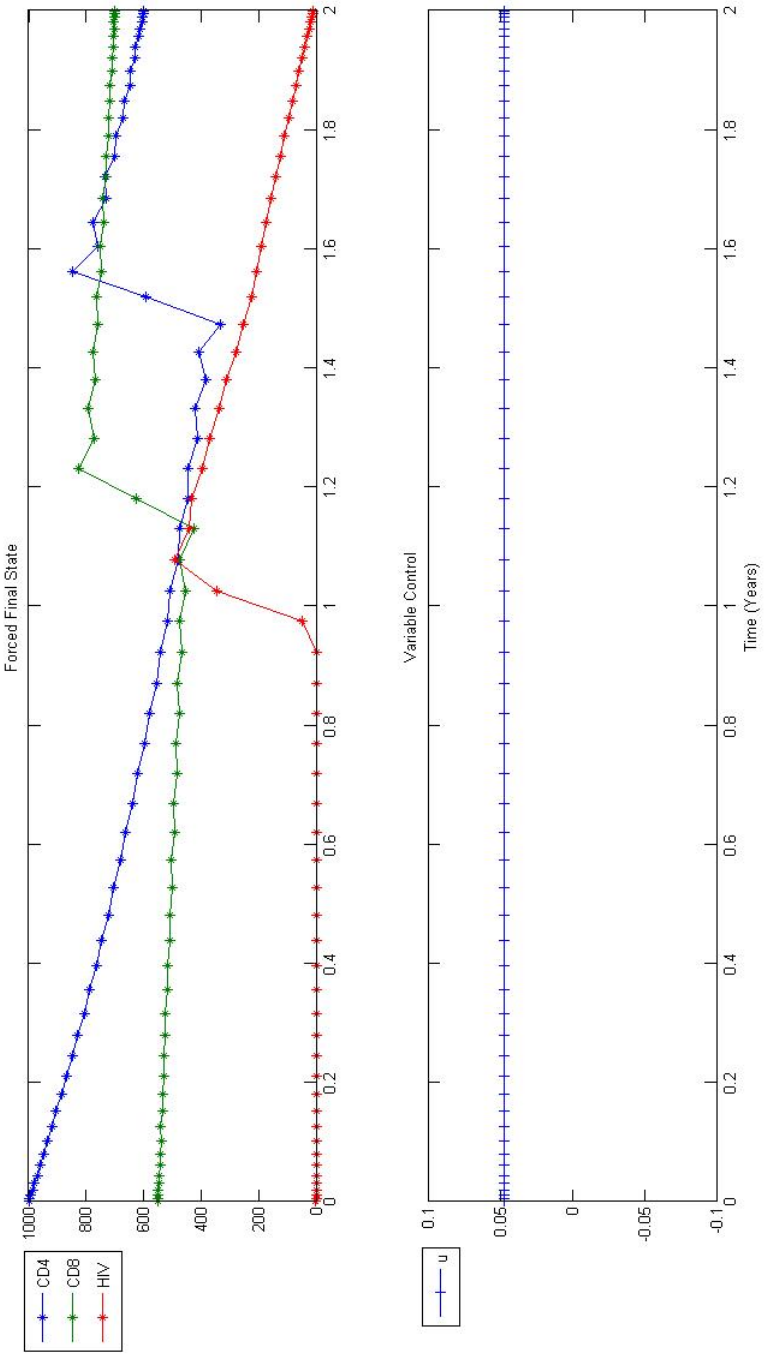


Figure 5.10: Simulation for the First Patient - 1^{st} Scenario - Constant Dosage.

6 Concepts about Diabetes

> "The word "diabetes" is a powerful one. It is unlike any other word, unique in its own ways and known to many languages. This word elicits numerous emotions running the gamut of angst and hope, defining not only a disease but also a deep and profound history of medical science and affecting individuals in all parts of the world."
>
> **Andrew Galmer**

6.1 Introduction

This chapter presents concepts on the biology of diabetes and synthesizes the dynamics between insulin and glucose. In the last section, type 1 and 2 diabetes will be described.

6.2 Biology of Diabetes

The first known historical mention of diabetes is in the Ebers Papyrus (a 110-page scroll, which is about 20 meters long, and contains some 700 formulas and remedies), which was written by the ancient Egyptians more than 3,500 years ago. The signs and symptoms were discussed in depth, which led to theories on first treatments and to an understanding of the prevention. Nations throughout time have been involved in a collaborative effort to understand diabetes through observations and experimentation with hopes of treating the disease. Examples of ancient diagnosis included tasting the urine of diabetics along with using ants to analyze specimens. Although crude in their methodology, early scientists helped to prepare a foundation on which future studies were conducted until the age of modern medicine.(Galmer, 2008)

Scientists such as Langerhans and Banting (Nobel Prize in 1923) conducted laboratory research that led to a better understanding of this disease. This era saw the development of insulin, oral medications, and blood monitoring devices or insulin pumps that changed the way the diabetes was managed.

Galmer also described diabetes as a serious medical condition that deals with abnormal control of sugars in the bloodstream that cause a variety of symptoms and serious associated complications. It is medically described as a collection of metabolic disorders that result in chronically elevated blood glucose levels. (Galmer, 2008)

Two main pancreatic endocrine hormones, insulin and glucagon, are responsible for regulating the blood glucose level. They form two feedback loops in controlling the blood sugar level that function inversely. According to (DCCT, 1993), blood glucose concentration should be controlled within the range of 60 to 120 mg/dL. If insulin is supplied in excess, the blood glucose concentration falls below the normal value ($< 60\,mg/dL$) and this state is known as hypoglycemia, whereas if insulin is not supplied sufficiently, the concentration rises above the normal value ($> 120\,mg/dL$) and this state is known as hyperglycemia. Both these situations can affect an individual's health, in very different ways. Hypoglycemia has short term effects which can lead to diabetic coma, neurological problems and possibly death, while hyperglycemia has a long term impact.

Diabetes is characterized in many different types, but in this study the focus will be on only Type 1 and Type 2 Diabetes. Both types of diabetes unfortunately result from morbid complications associated with hyperglycemia, leading to amputations, cardiac failure, peripheral vascular disease, stroke, diabetic neuropathy, eye problems, and kidney failure. Although there is no cure for diabetes as is the case with AIDS, it is possible to control and prevent the disease through medication by monitoring the blood sugars with portable meters, dieting, and physical exercise. This prevention has improved patients' state of health, increased life expectancy and reduced health costs.

6.2.1 Dynamics between insulin and glucose

The interplay between insulin and glucagon maintains the Blood Glucose (BG) concentration in the body at normal values by distributing the energy needed by the organs such as the brain, heart and others, to perform their functions. BG in non-diabetic humans is maintained within a precise concentration range and is the major stimulant that secretes the hormone insulin. Many factors affect the circulating levels of glucose such as phenotype, food intake, rate of digestion, excretion, exercises and psychological state

(Hadley, 1992). These influences can be harmful, individually or in combination, and constantly affect the physiological processes that regulate plasma glucose levels. The glucose level may drop momentarily due to muscular activity and especially if food intake is limited. The diminished level of blood glucose is recognized by certain cells in the pancreatic Islets of Langerhans called the alpha (α) cells.

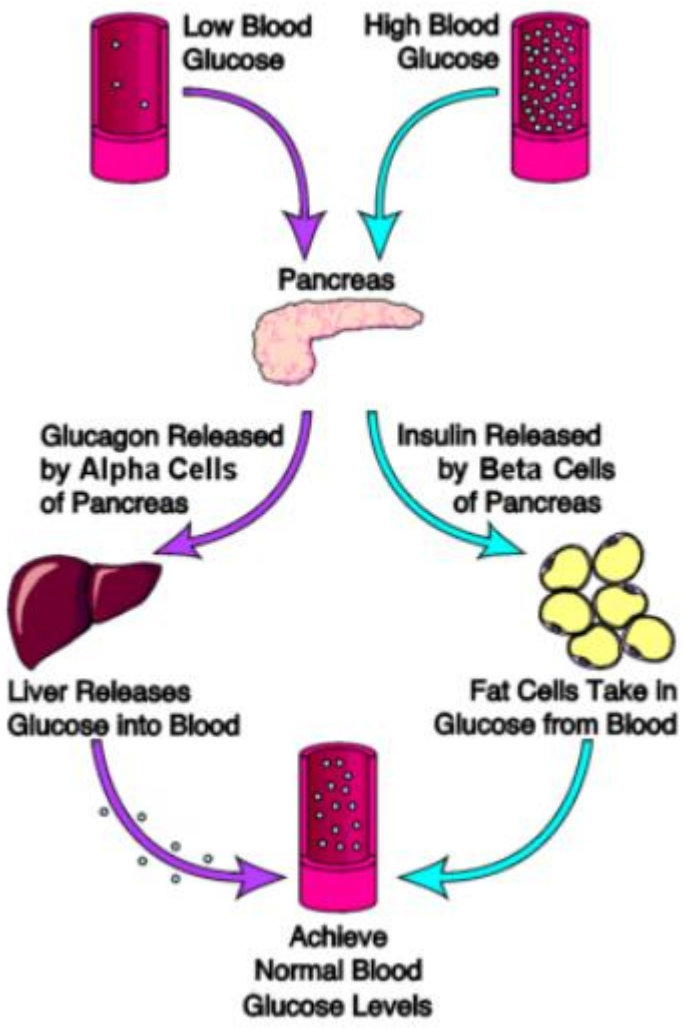


Figure 6.1: Insulin has an effect on a number of cells, including muscles, red blood cells, and fat cells. In response to insulin, these cells absorb glucose from the blood, having the net effect of decreasing high blood glucose levels to the normal range. On the other hand, the pancreas produces glucagon to release glucose into the bloodstream. Source: Norman, 2009.

These cells then release glucagon, a hormone that acts on the cells of the liver to induce the release of glucose when there are decreased amounts of glucose (for example, when a high quantity of energy is needed to do some physical exercise) in the bloodstream

(Masharani *et al.* , 2004). If, on the other hand, BG is high, as occurs after ingestion of a meal, other pancreatic islet cells, the so called beta (β) cells, release the hormone insulin. Insulin induces the uptake of glucose from the blood into the liver and other cells (such as muscle cells). When there is a high quantity of glucose in the blood, the insulin stocks the excess as "fat energy". Thus, the glucose level of the blood is lowered to the normal circulating concentration, as can be seen in Figure 6.1. Lack of insulin, therefore, results in a serious inability to lower BG, which results in abnormal quantities of glucose in the bloodstream and consequentially in the disease called diabetes mellitus.

The mechanisms that occur within the pancreas should be normal biological processes so as to produce a balanced quantity of energy controlled by feedback. The physiology of diabetes relates to principles of chemical transport and feedback mechanisms that depend on the presence or absence of certain hormones in the biological system. Exocrine functions of the islet cells of the pancreas can be manipulated through stimulation by glucose, direct and indirect control mechanisms. These control mechanisms can be improved by biomedical engineering with efficient devices which control the dynamic between glucose and insulin. Alteration in these mechanisms leads to poor control of blood glucose and causes secondary problems that can be associated with these defects. Pathology, or presence of disease, occurs when any of these functions are ineffective at performing proper physiological demands of the body. It is important to differentiate the types of diabetes so as to understand the behavior and dynamics in different patients.

6.3 Types of Diabetes

6.3.1 Type 1 Diabetes

As described in (Galmer, 2008), type 1 diabetes comprises 10 percent of the diabetic population and is commonly diagnosed in children who have a genetic predisposition to developing this autoimmunity. Although the disease can also occur in adulthood, a greater percentage of children, nearly 1 in 500 children, are diagnosed with type 1 diabetes. Type 1 diabetes was previously referred to describe juvenile diabetes or insulin-dependant diabetes. Nowadays, these names are outdated because they are poor generalizations and

do not describe the nature of the pathology. Therefore, a more accurate definition of type 1 diabetes represents the destruction of beta cells within the pancreas.

Destruction of these cells can be attributable to autoimmune response or idiopathic reasons. Combinations of environmental and genetic factors determine an individual's susceptibility to developing type 1 diabetes. It is not uncommon for beta cell destruction to begin months to years before the development of diabetic signs and symptoms. The complete destruction of beta cells in the pancreas makes these patients dependent on scheduled insulin injections to control their hyperglycemia and to prevent complications (Kahn *et al.* , 2004).

Studies show that there is a significant correlation between an individual who has a family history of diabetes and who develops type 1 diabetes. There is a 6 percent increase in risk if a parent or blood relation has type 1 diabetes. Likewise, this risk increases substantially if both groups show diabetic signs. Risk can also be accounted for by analyzing the effects of ethnicity on developing type 1 diabetes. In the United States, for example, Caucasians were found to have the highest correlation with type 1 diabetes. From a world survey, it can be seen that individuals from Finland and Sardinia have the highest rate of incidence. In contrast, Asians and Pacific Islanders were found to be the least effected groups. (Kahn *et al.* , 2004).

6.3.2 Type 2 Diabetes

Type 2 diabetes is the more prevalent type of diabetes, comprising about 90 percent of individuals diagnosed with diabetes. Type 2 diabetes was previously known as adult-onset diabetes and non-insulin-dependent diabetes, but these terms are also outdated. Individuals that are diagnosed with type 2 diabetes are commonly found to be over the age of forty with underlying obesity. Many of these diabetics are characterized as having a sedentary lifestyle and a poor diet. Although the majority of type 2 diabetics are over the age of forty, younger individuals are at risk because of the increased frequency of obesity among them and their sedentary lifestyle, and because they are part of the "fast food" generation. (Kahn *et al.* , 2004)

Type 2 diabetics are fully capable of producing sufficient amounts of insulin during the early stages of diagnosis. Although the exact mechanism has not yet been determined, it has been shown that the main problem of type 2 diabetics lies in the peripheral insulin receptors that have become resistant to the action of insulin. Insulin is not able to bind to these receptors and is rendered useless in delivering sufficient amounts of glucose to the cells, causing glucose levels to rise in the blood. In addition to binding problems, other mechanisms can cause the same effects. These mechanisms include biochemical processes that occur after insulin has bound to the receptors on the cellular membrane. (Kahn *et al.* , 2004)

One major difference between type 1 and type 2 diabetes is that type 2 diabetes patients are most commonly obese, with fat being distributed centrally (in midriff) while the arms and legs are usually spared (Masharani *et al.* , 2004).

7 Glucose Control

> "Diabetes costs hundreds of billions of dollars to treat each year. World treatment costs are growing more quickly than world population. However, the larger costs of diabetes arise from disability and loss of life caused by its preventable complications, including heart, kidney, eye and foot disease."
>
> **International Diabetes Federation**

7.1 Introduction

This chapter presents first the importance of controlling the quantity of glucose in the bloodstream. It also discusses concepts about closed loop control using insulin pumps. Groups of mathematical models found in the literature are described with the focus on Bergman's. Finally, the chapter formulates the optimal therapy via Pontryagin's Maximum Principle, followed by linearization to facilitate the calculus and simulation.

7.2 The Importance of Control Glucose in the Bloodstream

BG is a variable to be controlled in a patient and accordingly description in Chee & Fernando (2007) of some important factors to be kept within the normal range are:

1. A high glucose concentration exerts an osmotic pressure on extracellular fluid, and can cause cellular dehydration;

2. Too low a BG level carries the risk of hypoglycaemic coma. Glucose is the only source of energy that can be used by the brain. Prolonged and profound hypoglycaemia can produce severe brain damage;

3. Too high a glucose concentration ($> 11.1\ mmol/l$) can affect the healing of wounds and interfere with the human neutrophil function (Watts *et al.* , 1987);

4. Therapy that maintains BG level at below 11.9 $mmol/l$ has been shown to improve the long-term health of diabetic patients who have had acute myocardial infarction;

5. Findings from Van der Berghe *et al.* (2001) have shown that maintaining BG at a level that did not exceed 110 mg/dl (6.1 $mmol/l$) substantially reduced mortality and morbidity in critically-ill patients in the Intensive Care Unit (ICU). In addition, a pronounced hyperglycaemia in critically-ill patients, even those who have not previously had diabetes, may lead to complications in such patients.

7.3 Closed Loop Control

To better understand the control function of glucose, one needs to think of the patient as a "plant" to be controlled in the control system. This closed loop system would include a glucose sensor that can measure blood glucose concentration. This information would then be passed to a control system that would calculate the necessary insulin delivery rate to keep the patient under metabolic control. Then a signal will be sent to a mechanical pump by the controller, to deliver the desired amount of insulin. In general, using pumps is preferable to injections since this is more reliable in maintaining the correct level of sugar in the blood and is also closer to the normal pancreas (Kaveh & Shtessel, 2006). The process repeats continually by feedback. Figure 7.1 shows a simplification of automatic regulation.

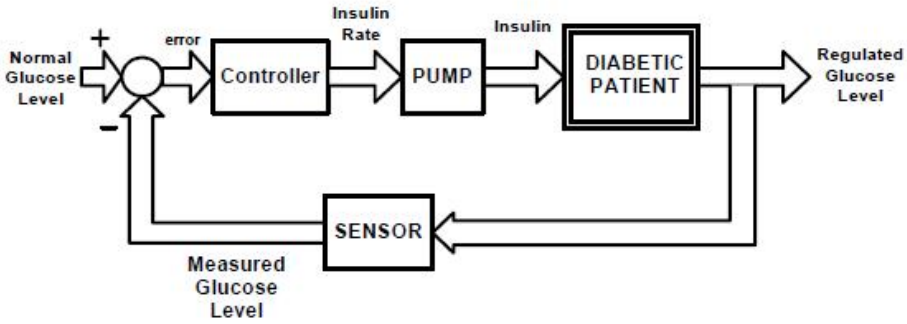


Figure 7.1: Closed loop control of diabetic patients using insulin pumps. Automatic regulation of a patient's BG level requires a minimum of three components, namely, a continuous the BG sensor, a controller that matches BG level with an appropriate insulin delivery rate, and an infusion pump to deliver the insulin to the subject. Source: Kaveh and Shtessel, 2006.

The controller is the component of the system that regulates the blood glucose levels in the patient. The formulation of the control rule depends on the knowledge we have about the sensor, the pump and the patient - and specifically, the BG measurement methods, the type (or preparation) of insulin used, the route of infusion, and the patient's characteristics. Various BG measurement techniques exist, and each has its unique characteristics.

Dua (2006) describes four major sites for invasive insulin delivery reported by Nalecz *et al.* (1987): subcutaneous, intramuscular, intravenous and intraperitoneal. While the subcutaneous site is the simplest and safest in the long term, the absorption of insulin from the subcutaneous tissue is delayed. The intramuscular site is usually preferred for people affected by fragile diabetes, who have a subcutaneous barrier to insulin absorption, but this may result in muscle fibrosis and disconnection of the cannula. The intravenous site on the other hand results in faster delivery of insulin and, therefore, is ideal for controlling the glucose concentration. The main problem with this mode comes from the presence of the intravenous lines which may not be appropriate for some patients. The most physiological mode of insulin delivery is achieved through the intraperitoneal site, though the major disadvantage is its difficult access.

Recent advances in technology have brought in noninvasive modes of insulin delivery such as transdermal, pulmonary and oral, Kennedy (1991) and Parker *et al.* (2004). These modes are not painful unlike the invasive modes, but they have problems such as low skin permeability in the transdermal mode, the patient not inhaling the accurate amount of insulin in the pulmonary mode and issues concerned with the oral bioavailability for the oral mode.

A small perturbation over a long period of time can cause irreversible brain or heart damage if glucose is not delivered appropriately. So the time required to achieve glucose regulation is of great importance. It is obvious that physical characteristics vary from person to person and so different patients have different responses to the same treatment, which in turn can cause parameter variations in the system. What must be taken into consideration is that a small change in some of the parameters can dramatically affect the closed loop performance and even result in the patient's death. Therefore, it is vital for

the patients that the controller used in designing the closed loop system be robust enough to counteract any kind of perturbations and disturbances.

7.3.1 Mathematical Model of Glucose Control

The goal of a closed-loop control system is to mimic the functionality of the pancreas in providing automatic regulation of blood glucose level in patients. To be precise, the closed-loop control systems should really answer the question: "How much insulin should be given such that the patient's blood glucose level is restored, as closely as possible, to that of a healthy individual?"

As the name implies, the model-based approach involves the use of a model in the control of the blood glucose level. This model is the human glucose-insulin interaction. If this complex interaction can be captured and described in terms of mathematics, then the glucose control problem becomes a mathematical problem, and a mathematical problem can be solved using various mathematical techniques. (Chee & Fernando, 2007)

The attempts to capture the glucose-insulin mechanism have resulted in the formulation of various glucose-insulin kinetic models. These models range from simple expressions that relate glucose and insulin, to very complete mathematical models. The three general groups of mathematical models are:

1. Linear (e.g. Bolie (1961), Gatewood *et al.* (1968), Ceresa *et al.* (1968) and Salzsieder *et al.* (1985))

2. Non-linear (e.g. Bergman & Urquhart (1971), Bergman *et al.* 1981, Toffolo *et al.* (1980), Doyle III *et al.* (1995), Fischer *et al.* (1987) and De Caetano & Arino (2000), Steil *et al.* (1993), Natal (2004), Kaveh & Shtessel (2006), Dua *et al.* (2006))

3. Comprehensive (e.g. Steil *et al.* (2005), Sorensen *et al.* (1982), Dalla Man *et al.* (2006), Hovorka *et al.* (2004), Hernandez *et al.* (2001), Guyton & Hall (1996) and Kovacs *et al.*(2008)).

The linear model has the disadvantage that it is a gross oversimplification of the glucose-insulin interaction in real humans (this is far more complex than the linear model).

Campello de Souza points out that "nothing" in nature is in fact linear, e.g., biological system dynamics are often non-linear in nature, and low-order models can conduct errors when describing a real process.

Non-linear model ranges from less complex ones to comprehensive ones. A comprehensive model attempts to expand the knowledge of metabolic regulations into a generally large, non-linear model of a high order, with a large number of model parameters. This includes the modeling of the distribution and metabolism of glucose and insulin, hepatic glucose balance (i.e. glucose production and disposal), renal excretion, glucose utilization, and insulin release and degradation, to describe the system thoroughly. Comprehensive models, in general, cannot be easily identified (Chee & Fernando, 2007).

7.3.2 Dynamic Model of Glucose/Insulin

The aim in this study is to undertake a theoretical analysis of the optimal control of glucose levels in diabetic individuals using the mathematical model of the dynamics of glucose and insulin interaction in the blood system developed by Bergman & Urquhart (1971) — Bergman *et al.* (1981) and still cited in more recent studies.

The schematic representation of this model is shown in Fig. 7.2. This representation also described in Dua *et al.* (2006) captures the glucose-insulin response of the patient by using the minimum number of compartments.

The model applied in this study is also called "Bergman's Minimal Model". There are many different versions and a new version will be used of Bergman's model adapted to the objectives of this dissertation. It consists of a set of Differential Equations 7.3.1:

$$\begin{aligned} \frac{dz_1}{dt} &= -p_1 z_1 - z_2(z_1 - z_{1b}) + D(t) \\ \frac{dz_2}{dt} &= -p_2 z_2 + p_3 z_3 \\ \frac{dz_3}{dt} &= -n(z_3 - z_{3b}) + \frac{U(t)}{V_1} \end{aligned} \tag{7.3.1}$$

The parameters of the system are described in Table 7.1:

The states in this model are $x_t = [z_1 \quad z_2 \quad z_3]^T$ and $u_t = U(t)$ is the control variable. Health subjects and diabetic patients have their p's values given by Table 7.2. The

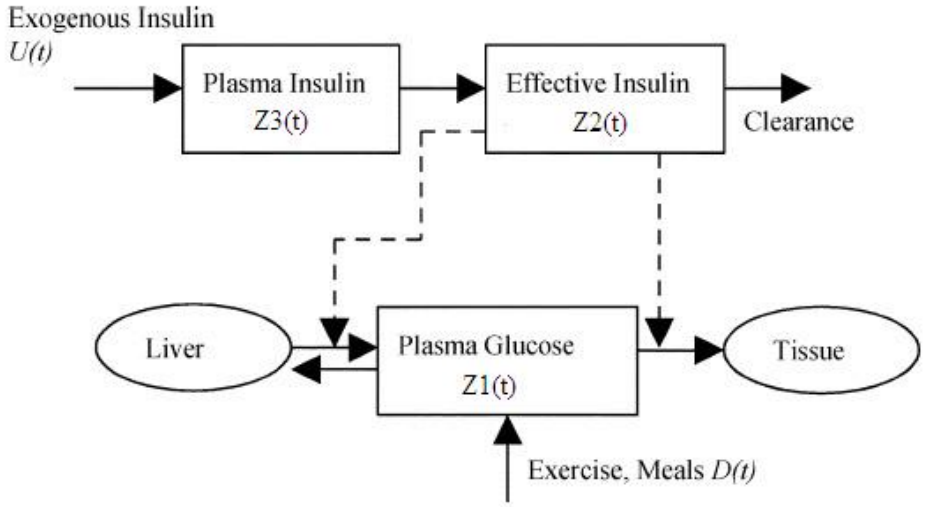


Figure 7.2: Schematic representation of Bergman's Minimal Model. Source: Dua et al, 2006.

Table 7.1: Parameters of the system.

Parameters	**Values**	**Units**	**Biological Interpretation**
z_1	—	mg/dL	Plasma glucose concentration above basal value
z_2	—	min^{-1}	"Activity" of insulin in the interstitial tissue
z_3	—	mU/L	Plasma insulin concentration above the basal value
D	$D(t) = 0.5e^{-0.05t}$	$mg/dLmin^{-1}$	Meal glucose disturbance normally $t = 6\,min$ is used
U	—	mU/min	Exogenous insulin infusion rate
z_{1b}	81	mg/dL	Basal value of glucose concentration
z_{3b}	15	mU/L	Basal value of insulin concentration
V_1	12	L	Volume of insulin distribution
n	5/54	min^{-1}	Fractional disappearance rate of insulin

available clinical data indicate that for patients with diabetes the value of p_1 is well below the normal value and is difficult to quantify; as a theoretical case $p_1 = 0$ is adopted (Fisher, 1991).

Table 7.2: Parameters for health and diabetic subjects.

p	**Health Subjects**	**Diabetic Subjects**
p_1	0.028	0
p_2	0.025	0.025
p_3	0.000013	0.000013

7.3.3 The Equilibrium Points

Once the set of equations in 7.3.1 are resolved the equilibrium points of the minimal model can be found, considering $u(t) = 0$ and that there is no meal uptake: The first equilibrium point given:

$$z_{1e} = 0 \tag{7.3.2}$$

$$z_{2e} = 0 \tag{7.3.3}$$

$$z_{3e} = 0 \tag{7.3.4}$$

$$\tag{7.3.5}$$

The second equilibrium point:

$$z_{1e} = \frac{z_{2e} z_{1b}}{(p_1 + z_2 e)} \tag{7.3.6}$$

$$z_{2e} = \frac{p_3 z_{3e}}{p_2} \tag{7.3.7}$$

$$z_{3e} = z_{3b} \tag{7.3.8}$$

$$\tag{7.3.9}$$

or

$$z_{1e} = \frac{p_3 z_{3b} z_{1b}}{(p_2 p_1 + p_3 z_{3b})} \tag{7.3.10}$$

$$z_{2e} = \frac{p_3 z_{3b}}{p_2} \tag{7.3.11}$$

$$x_{3e} = z_{3b} \tag{7.3.12}$$

$$\tag{7.3.13}$$

7.3.4 A Formulation of an Optimal Therapy via Pontryagin's Maximum Principle

Pontryagin's Maximum Principle was also chosen as an optimization techniques to calculate the optimal insulin infusion for the correction of hyperglycemia based on Bergman's theoretical model as was done for the HIV-1 problem.

Thus, the problem will be to minimize the objective function, i.e., to diminish to the maximum the glucose level and the quantity of exogen insulin. The case where t_f is specified to get the optimal control will be also adopted, i.e., to find the u.

$$\underset{u}{\text{Max}} \int -((z_1 - z_{1b})^2 + u^2)dt \tag{7.3.14}$$

The Hamiltonian will be given by:

$$H = -((z_1 - z_{1b})^2 + u^2) + y_1[-p_1 z_1 - z_2(z_1 - z_{1b}) + D] + y_2(-p_2 z_2 + p_3 z_3) + \\ + y_3\left[-n(z_3 - z_{3b}) + \frac{u(t)}{V_1}\right],$$

where the y_i's are the co-state variables. For an interior solution:

$$\frac{\partial H}{\partial u} = -2u + \frac{y_3}{V_1} = 0 \ \therefore \ u = \frac{y_3}{2V_1}.$$

The co-state variables dynamics will be described by:

$$\frac{dy_1}{dt} = -\frac{\partial H}{\partial z_1} = 2(z_1 - z_{1b}) + y_1 p_1 + y_1 z_2 \tag{7.3.15}$$

$$\frac{dy_2}{dt} = -\frac{\partial H}{\partial z_2} = y_1(z_1 - z_{1b}) + y_2 p_2 \tag{7.3.16}$$

$$\frac{dy_3}{dt} = -\frac{\partial H}{\partial z_3} = -y_2 p_3 + n y_3. \tag{7.3.17}$$

One will have the following system of six differential equations:

$$\frac{dz_1}{dt} = -p_1 z_1 - z_2(z_1 - z_{1b}) + D(t) \tag{7.3.18}$$
$$\frac{dz_2}{dt} = -p_2 z_2 + p_3 z_3 \tag{7.3.19}$$
$$\frac{dz_3}{dt} = -n(z_3 - z_{3b}) + \frac{y_3}{2{V_1}^2} \tag{7.3.20}$$
$$\frac{dy_1}{dt} = 2(z_1 - z_{1b}) + y_1 p_1 + y_1 z_2 \tag{7.3.21}$$
$$\frac{dy_2}{dt} = y_1(z_1 - z_{1b}) + y_2 p_2 \tag{7.3.22}$$
$$\frac{dy_3}{dt} = -y_2 p_3 + n y_3. \tag{7.3.23}$$

7.3.5 Linearization of Bergman's Minimal Model

For non-linear systems such as Bergman's Minimal Model (Equations 7.3.1), the models are linearized to reduce the number of parameters of being determined and they have the advantage to be available for use mathematically as in the linear models.

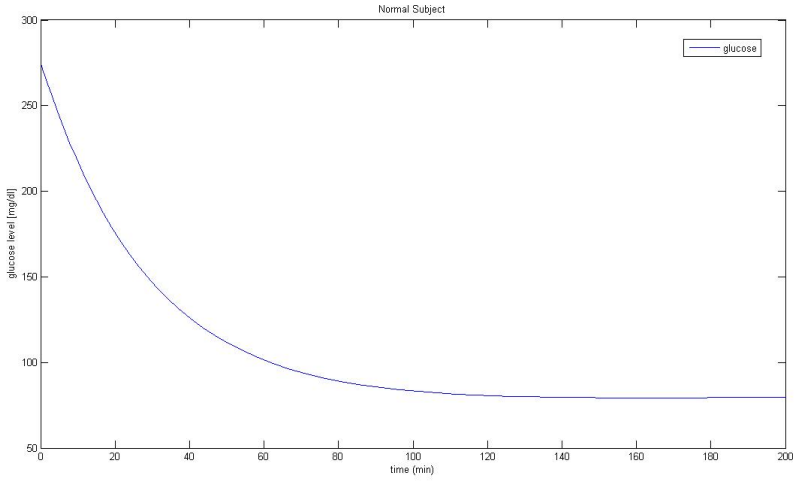


Figure 7.3: Simulation of non linearized equations describing the glucose behavior for a health subject.

Linearizing around the second equilibrium point means to find the followed matrix, where f is the equation described in 7.3.1.

$$\frac{\partial f}{\partial z}\Big|_{z=z_e} = \begin{bmatrix} -p_1 - z_{2e} & -z_{1e} - z_{1b} & 0 \\ 0 & -p_2 & p_3 \\ 0 & 0 & -n \end{bmatrix}$$

Substituting the values of the parameters for a diabetic subject:

$$\begin{bmatrix} \dot{z_1} \\ \dot{z_2} \\ \dot{z_3} \end{bmatrix} = \begin{bmatrix} -0.0078 & 0 & 0 \\ 0 & -0.025 & 0.000013 \\ 0 & 0 & -0.09259 \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \\ z_3 \end{bmatrix} + \begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix} D + \begin{bmatrix} 0 \\ 0 \\ 0.08333 \end{bmatrix} u$$

$$z_1(0) > 0, \quad z_2(0) > 0, \quad z_3(0) > 0$$

Assuming that only glucose and insulin are being monitored, because $\frac{dz_2}{dt}$ is not a physiological state variable, thus it becomes:

$$\begin{bmatrix} y_1 \\ y_2 \\ y_3 \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix} \begin{bmatrix} z_1 \\ z_2 \\ z_3 \end{bmatrix}$$

7.3.6 Riccati's Equation

Section 4.3 shows how to get the Riccati's Equation:

$$PA + A^T P - PBR^{-1}B^T P + Q = 0 \quad \text{(Riccati's equation)}, \tag{7.3.24}$$

As already explained, Q and R are difficult to find, and usually the diagonal shape Q and R (identity) is adopted.

$$\begin{bmatrix} P_1 & P_2 & P_3 \\ P_4 & P_5 & P_6 \\ P_7 & P_8 & P_9 \end{bmatrix} \begin{bmatrix} -0.0078 & 0 & 0 \\ 0 & -0.025 & 0.000013 \\ 0 & 0 & -0.09259 \end{bmatrix}$$

$$+\begin{bmatrix} -0.0078 & 0 & 0 \\ 0 & -0.025 & 0 \\ 0 & 0.000013 & -0.09259 \end{bmatrix}\begin{bmatrix} P_1 & P_2 & P_3 \\ P_4 & P_5 & P_6 \\ P_7 & P_8 & P_9 \end{bmatrix}$$

$$-\begin{bmatrix} P_1 & P_2 & P_3 \\ P_4 & P_5 & P_6 \\ P_7 & P_8 & P_9 \end{bmatrix}\begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}\begin{bmatrix} 0 & 0 & 1 \end{bmatrix}\begin{bmatrix} P_1 & P_2 & P_3 \\ P_4 & P_5 & P_6 \\ P_7 & P_8 & P_9 \end{bmatrix}+\begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 5 \end{bmatrix}=\begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}$$

Resolving the Riccati's equation with Matlab, one finds that P is a real and symmetric matrix.

$$P=\begin{bmatrix} 64.1026 & 0 & 0 \\ 0 & 20.000 & 0.0001 \\ 0 & 0.0001 & 2.1454 \end{bmatrix}$$

The closed loop control law will be:

$$u^* = R^{-1}B^T P z. \tag{7.3.25}$$

u^* can be obtained through the matrix R, B and P:

$$u^*=\begin{bmatrix} 0 & 0.0001 & 2.1454 \end{bmatrix}\begin{bmatrix} z_1 \\ z_2 \\ z_3 \end{bmatrix}$$

7.3.7 Simulations

The blood sample described in Tillil *et al.* (1988) and more recently in Hucking *et al.* (2008) shows "real" glucose and insulin data. This sample was taken from a fasting subject during a period of time and adapted for this study. Figure 7.4 shows a typical response from a normal subject after ingesting some food sampled discretely over time.

To summarize the behavior of Figure 7.4, notice that the glucose starts at 170 mg/dl and reaches a peak of 175 mg/dl, dropping gradually to the basal level, around 80 mg/dl. Insulin has a similar behavior, following the trajectory of glucose after a small time delay.

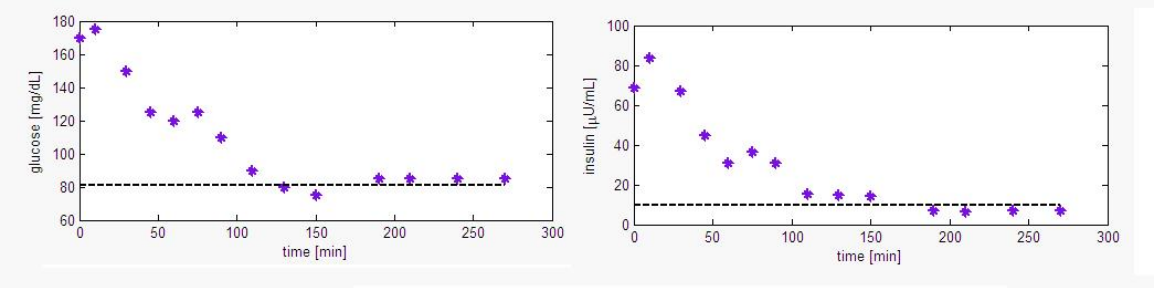


Figure 7.4: Data from a normal subject adapted from Hucking et al., 2008.

The insulin in the plasma rapidly rises to a peak, approximately 85 $\mu U/ml$, and then gradually drops to the basal level, around 15 $\mu U/ml$. Different subjects have different responses in this kind of graph.

The objective of this part of the study is to demonstrate an implementation of Matlab to simulate insulin and glucose levels during a real test and determines how the control can be applied to regulate the dosages for diabetic patients when the system described by Equation 7.3.1 is considered.

The code used with Matlab was based on the ode-solvers (ode45), and with the Euler method for the integration. Adaptation was made from Natal (2004) to find the plasma insulin concentration input by interpolation of time-insulin values (considering the sample described in Figure 7.4). When a variable step solver is used, the interpolated input value has to be calculated in each simulation step, given the new time sample selected by the solver.

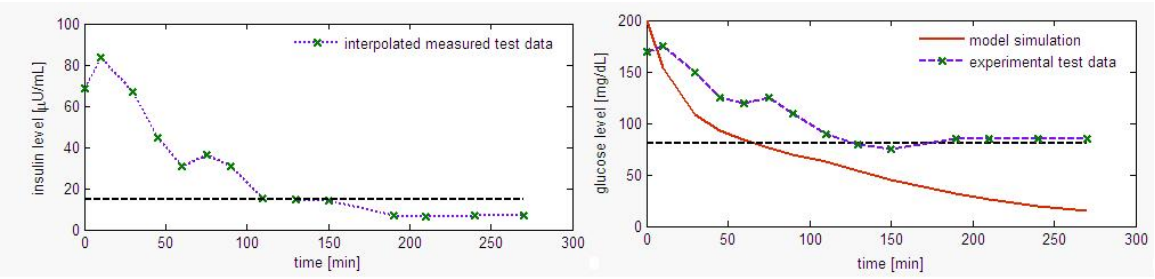


Figure 7.5: Simulation of the minimal model when insulin is considered as input.

Figure 7.5 represents a simulation when the input signal is the plasma insulin. It shows the interpolated measured data test and the model simulation, in this case for the glucose.

The model has a rough approximation with real data and the curve has an exponential shape.

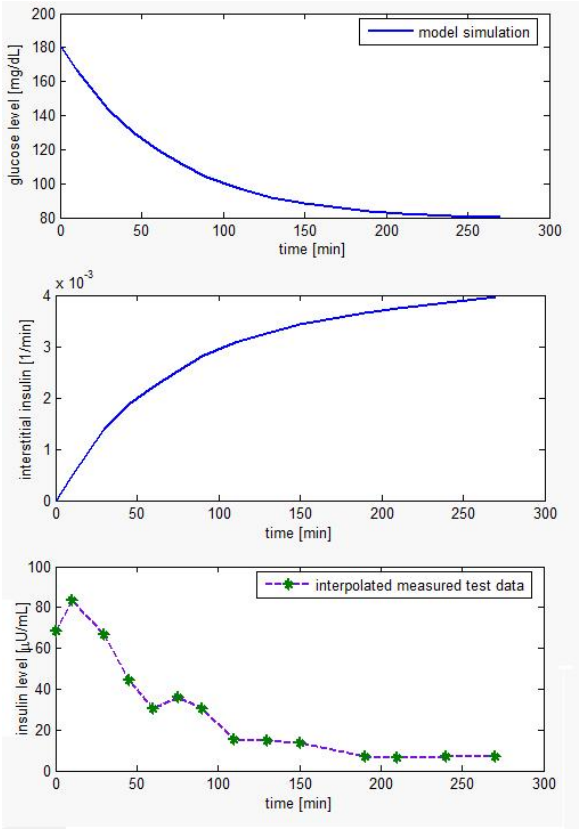


Figure 7.6: Simulation of the minimal model when glucose is considered as input.

Figure 7.6 shows an estimate of plasma glucose. The parameters were adapted from Natal (2004) to minimize the difference between the measured time (Figure 7.4) of glucose and the model described by the set of differential equations in 7.3.1. The routine *lsqnonlin* is also used from Optimization Toolbox. Figure 7.6 shows the minimal model for insulin kinetics. In this case, glucose, $z_1(t)$ is the input. It is also important to emphasize that the $z_2(t)$ is considered as interstitial insulin activity, and it is not a physiological parameter, but a representation that mimics an effective insulin activity (Natal, 2004).

7.4 Discussion

In this part of study, an approach was described to relate the dynamic between glucose and insulin. The kinetics of glucose and insulin were analyzed, and how the real data can

be interpolated to give the result throughout the model. The present study also demonstrates that the minimal model can be applied to study the behavior of the hormones that constitute the endocrinal system, and permit the construction and formulation of considerations for the clinical glycemic control problem. In particular they study the diversity of non-linearities in the dynamics system described by Equations 7.3.1.

The simulations showed how the feedback can regulate blood glucose level in response to glucose and insulin as input. The first simulation, Figure 7.5, shows a considerable correlation between the simple model and the data on patients.

This study has been limited because the "real" data were adapted from other articles and could therefore be conduct with a simple acquisition protocol. Chase *et al.* (2006) has described some limitations of the Minimal Model: It does not account for saturation of glucose removal by insulin, saturation of insulin transport, the dynamics of insulin receptors and their mass. However, these characteristics were not the main objective of this study.

8 Conclusions

"Do not worry about your difficulties in Mathematics. I can assure you mine are still greater."

Albert Einstein

- Mathematical modeling can help form a better understanding of the biological world in quantitative terms and it is becoming an increasingly important aid in the field of improving the diagnosis, and prognosis of diseases and in the planning of therapy. The models help us to understand the nonlinear dynamics of the real world by applying software to simulate the set of dynamics equations. The complexity of biological systems is particularly well suited to the application of models because they facilitate identifying the natural laws of these systems;

- The major aim of this study was to create signs to improve the understanding of how optimal control could be used in biological systems, and consequently, by modeling and simulating functions of the subsystems, for example those which constitute a disease, in an attempt to reduce the uncertainty present in nature. These applications can be used in clinical routines to improve physicians' decisions. It was shown that numerical optimization methods based on mathematical models can be of value in providing drug administration schemes that lead to a good compromise between therapeutic and side effects;

- Controlling the HIV/AIDS pandemic is likely be one of the greatest challenges to public health in the 21^{st} century. This will lead to changes in social relationships and global inequalities. Moreover, it will allow us to overcome the stigma that belongs to us all;

- This study showed that the optimal treatment given by simulations, using the model developed by Campello de Souza (1999), reaches better indices than the application of a constant drug dosage in the case of HIV/AIDS. However, it is also understood that these studies need to be simulated using more clinical data and need to be biostatically controlled. When studies are conducted with human data it is also

necessary to protect AIDS sufferers by forming an ethics council on AIDS. These kinds of studies would be fundamental to compare different forms of treatment;

- It was proved that it is important to fight the virus earlier to diminish the side effects produced by high dosages. The results showed that the patients who showed most improvement in reducing the HIV rate used fewer quantities of drugs. This characteristic can be attributed to multiple factors such as: starting the treatment control earlier, to the capacity to have more or less virus replication and to the patient's immunological state;

- It was shown that using less drug dosage by optimal control means having less side effects, but in some cases in the literature this fact is correlated to the high risk of developing drug resistance. Notice that the optimal control allows the use of fewer drugs during therapy, and consequently produces fewer toxic effects;

- Diabetes has a significant impact on patient mortality, outcome and the cost of healthcare. We can say that this disease kills slowly and brings suffering to millions of people. Tight regulation can reduce negative outcomes significantly and as in the case studied of HIV/AIDS can reduce the side effects. This dissertation has examined Bergman's Minimal Model to control the hyperglycemia by applying Pontryagin's Maximum Principle. The goal of such control would be to apply this model to automate treatment in order to achieve good outcomes with minimal clinical efforts for the patient;

- More simulations and tests are required to better define the relationships between measurable data and the patient's state of health to enable a better comparison of results and to determine an optimal treatment for each patient. Other important aspects, for using simulations, are that they allow testing of the control algorithm to be performed without involving real patients;

- Continuous control systems for disease treatment are potentially bloodless, painless and result in more precise therapies. They have a powerful application when simulated and implemented with biomedical devices, such as insulin pumps. This

allows microsystems with reliable sensors and with embedded control algorithms to be created. Modeling and computer simulation assist the integration of sensing, actuating and controlling components and the evaluation of their interaction with the process or medical situation;

- This dissertation showed a limited application in the world of the biological systems. This methodology should be explored in future studies that cover different diseases, ecological systems, physiologies, etc, since all of them can be modeled by differential equations.

8.1 Suggestions for Future Studies

"Estudar dói; Estudar dói muito; Estudar dói muito e por muito tempo."

Fernando Campello de Souza

Given the limitations present in this work, suggestion for future works are:

- To apply this methodology to other biological systems;
- To focus on experimental identification in real patients and to conduct validation of the model used as controller, and consequently to allow a complete clinical validation of the results;
- To use other forms of control for the models;
- To use more variables to characterize other physiological parameters in the case of diabetes or HIV/AIDS;
- The optimal control by Pontryagin's Maximum Principle should be applied to study the regulation during prolonged disturbances such as physical exercise which may require the extension of the physiological model for simulation and analysis in the case of diabetes;
- To use other models, for example, stochastic ones, to obtain the optimal response, by studying the phenomena of resistance to the virus HIV, for example;

- To improve the models so that they are more objective in the way the drugs are applied, for example, using protease or transcriptase inhibitors as control variables.

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