

A Control Theoretic Approach to HIV/AIDS
Drug Dosage Design
and
Timing the Initiation of Therapy

by

Annah Mandu Jeffrey

Submitted in partial fulfillment of the requirements for the degree

Philosophae Doctoral (Electronic Engineering)

in the

Faculty of Engineering, the Built Environment and Information Technology

UNIVERSITY OF PRETORIA

July 2006

A Control Theoretic Approach to HIV/AIDS Drug Dosage Design and Timing the Initiation of Therapy

by

Annah Mandu Jeffrey

Promoter : Prof. Xiaohua Xia
Co-promoter : Prof. Ian K. Craig
Department : Electrical, Electronic and Computer Engineering
Degree : Philosophae Doctoral (Electronic Engineering)

Abstract

Current research on HIV therapy is diverse and multi-disciplinary. Engineers however, were late in joining the research movement and as such, engineering literature related to HIV chemotherapy is limited. Control engineers in particular, should have risen to the challenge, as it is apparent that HIV chemotherapy and control engineering have a lot in common. From a control theoretic point of view, HIV chemotherapy is control of a time varying nonlinear dynamical system with constrained controls. Once a suitable model has been developed or identified, control system theoretical concepts and design principles can be applied. The adopted control approach or strategy depends primarily on the control objectives, performance specifications and the control constraints. In principle, the designed control system can then be validated with clinical data. Obtaining measurements of the controlled variables however, has the potential to hinder effective control.

The first part of this research focuses on the application of control system analytical tools to HIV/AIDS models. The intention is to gain some insights into the HIV infection dynamics from a control theoretic perspective. The issues that need to be addressed are: Persistent virus replication under potent HAART, variability in response to therapy between individuals on the same regimen, transient rebounds of plasma viremia after periods of suppression, the attainment, or lack thereof, of maximal and durable suppression of the viral load. Such insights can help explain why an individual on antiretroviral therapy responds the way they do, as well as give the individual or practitioner the ability to preempt future responses.

The questions to answer are: When are the above mentioned observed responses from individuals on antiretroviral therapy most likely to occur as the HIV infection progresses, and does attaining one necessarily imply the other? Furthermore, the prognostic markers of virologic success, the possibility of individualizing therapy and timing the initiation

of antiretroviral therapy such that the benefits of therapy are maximized, are matters that will also be investigated.

The primary objective of this thesis is to analyze models for the eventual control of the HIV infection. HIV chemotherapy has multiple and often conflicting objectives, and these objectives had to be prioritized. The intention of the proposed control strategy is to produce practical solutions to the current antiretroviral problems. The scenario is such that, given the observed responses from individuals on antiretroviral therapy and the toxicity problems associated with this therapy, what can possibly be done to alleviate these problems? A solution should then be prescribed. The next question will then be, is such a solution implementable? The answer to this last question should be in the affirmative - Yes.

To this end, the second part of the research focuses on the addressing the HIV/AIDS control issues of sampling for effective control given the invasive nature of drawing blood from a patient and the derivation of drug dosage sequences to strike a balance between maximal suppression and toxicity reduction, when multiple drugs are concomitantly used to treat the infection.

Keywords: HIV/AIDS models, HIV immunology, HIV/AIDS model analysis, Initiate HIV therapy, Drug dosage design, Structured treatment interruption, Protocol design, Immune based therapy, Model predictive control, Control engineering in medicine, Biomedical engineering.

...

2 Corinthians 12:9

But he said to me,
“My grace is sufficient for you,
for my power is made perfect in weakness”.

Therefore,
I will boast all the more gladly about my weakness,
so that Christ’s power may rest on me.

Phillipians 4:13

I can do everything through him who gives me strength.

Acknowledgements

I would like to thank Professor Xiaohua Xia and Professor Ian K. Craig, my supervisors, for their guidance, patience and the many windows of opportunity that they have opened for me. I truly feel enlightened and empowered by the knowledge and skills that they have imparted to me. Let there be many more such occasions in our future collaborative research.

Thanks to the University of Botswana for financially supporting my studies (in full recognition of the stumbling blocks management frequently put in my way!). But I do appreciate the study leave I was given.

And to Jeff, for showing me that as futile as some of life's pursuits may turn out to be, self actualization is a must.

I am grateful to my children for their understanding. I acknowledge your sacrifice and that you had to mother yourselves while I pursued my studies.

And last but not least, to Leatile and Tsaone as we tarried on together and their friendly encouragement.

Pretoria, South Africa
July, 2006

Annah Mandu Jeffrey

...

To Afentse, Kagiso, Anwar, Nefertari and Atang.

In memory of my Father, Ben Gasennelwe, whose idea it was that I become an engineer.

Contents

| | | |
|----------|--|-----------|
| 1 | Introduction | 1 |
| 1.1 | Motivation | 3 |
| 1.2 | HIV/AIDS Therapy: A Control Engineering Problem | 4 |
| 1.3 | Thesis Objectives and Scope | 7 |
| 1.4 | Contribution | 8 |
| 1.5 | Organization of Thesis | 8 |
| 2 | Background | 10 |
| 2.1 | HIV and the Immune System | 10 |
| 2.1.1 | Virus Replication | 10 |
| 2.1.2 | The Immune System | 12 |
| 2.1.3 | Compromised Immune Response | 15 |
| 2.1.4 | HIV Compartmentalization | 19 |
| 2.2 | Drugs Used to Treat HIV Infection | 20 |
| 2.2.1 | Replication Cycle Based Antiretroviral Therapies | 20 |
| 2.2.2 | The Development of Drug Resistance | 22 |
| 2.2.3 | Immune Based Therapies | 24 |
| 2.3 | Guidelines on the Use of Antiretroviral Agents | 25 |
| 2.3.1 | Recommended Regimens | 27 |
| 2.3.2 | The Need to Individualize Antiretroviral Therapy | 27 |
| 2.4 | Treatment Interruption | 30 |
| 2.4.1 | Reasons for Interrupting Therapy | 30 |
| 2.4.2 | Structured Treatment Interruption Protocols | 31 |
| 2.5 | Chapter Summary | 34 |
| 3 | HIV/AIDS Models | 36 |
| 3.1 | The Latently Infected Cell Model | 36 |
| 3.2 | Time Delay Models | 40 |
| 3.3 | Immune Response Models | 41 |

| | | |
|----------|--|-----------|
| 3.4 | The Chronically Infected Cell Model | 42 |
| 3.5 | The Extended Model | 43 |
| 3.6 | The External Virus Source Model | 44 |
| 3.7 | The Composite Long Lived Cell Model | 46 |
| 3.8 | Stochastic Models | 47 |
| 3.9 | Models Adopted in this Thesis | 47 |
| 3.9.1 | Validity: Limitations and Adequacy of Models | 47 |
| 3.9.2 | Parameter Estimates | 50 |
| 3.10 | Model Parameters Affected by Therapy | 50 |
| 3.11 | Chapter Summary | 53 |
| 4 | Model Analysis | 54 |
| 4.1 | Steady State Analysis | 54 |
| 4.1.1 | Analysis with Replication Cycle Based HAART | 55 |
| 4.1.2 | Analysis with Immune Based Therapies | 59 |
| 4.1.3 | Combining HAART with Immune Based Therapies | 63 |
| 4.1.4 | Conclusions | 63 |
| 4.2 | Transient Response Analysis | 65 |
| 4.2.1 | Analysis with the Latently Infected Cell Model | 65 |
| 4.2.2 | Analysis with the Extended Model | 69 |
| 4.2.3 | On Attaining Maximal and Durable Suppression of the Viral Load | 70 |
| 4.2.4 | Conclusions | 72 |
| 4.3 | Interruption of Highly Active Antiretroviral Therapy | 73 |
| 4.3.1 | Anti-CD4 Therapy as Adjuvant to HAART Interruption | 73 |
| 4.3.2 | HAART Interruption with the Latently Infected Cell Model | 74 |
| 4.3.3 | Conclusions | 77 |
| 4.4 | Controllability Analysis | 77 |
| 4.4.1 | Controllability | 78 |
| 4.4.2 | Analysis with Replication Cycle Based HAART | 79 |
| 4.4.3 | Analysis with Immune Based Therapies | 82 |
| 4.4.4 | Singular Value Decomposition | 83 |
| 4.4.5 | Controllability to the Advanced Stage | 86 |
| 4.4.6 | Conclusions | 89 |
| 4.5 | Identifiability Analysis | 89 |
| 4.5.1 | The Need for Parameter Estimates | 90 |
| 4.5.2 | Identifiability Properties of the Latently Infected Cell Model | 91 |

| | | |
|----------|--|------------|
| 4.5.3 | Identifiability Properties of the Extended Model | 93 |
| 4.5.4 | When to Take Measurements | 100 |
| 4.5.5 | Identifiability With the Use of Antiretroviral Agents | 100 |
| 4.5.6 | Conclusions | 101 |
| 4.6 | Model Reduction | 102 |
| 4.6.1 | Residualization of the Latently Infected Cell Model | 103 |
| 4.6.2 | Response Time Estimation with Reduced Model | 105 |
| 4.6.3 | Conclusions | 111 |
| 4.7 | Chapter Summary | 112 |
| 4.7.1 | Persistent Virus Replication under HAART | 112 |
| 4.7.2 | Variable Response to Therapy | 112 |
| 4.7.3 | Transient Viral Load Rebounds or Virologic Failure? | 113 |
| 4.7.4 | Indicators of Virologic and Immunologic Success | 114 |
| 4.7.5 | When Best to Initiate Antiretroviral Therapy?: Clarifying the Confusion | 115 |
| 4.7.6 | The Possibility of Individualizing Antiretroviral Therapy | 116 |
| 5 | Drug Dosage Design | 117 |
| 5.1 | The Dynamical System to be Controlled | 118 |
| 5.2 | Modelling Antiretroviral Drugs As Control Inputs | 119 |
| 5.2.1 | Drug Pharmacology | 120 |
| 5.2.2 | Therapeutic Range | 124 |
| 5.3 | Prioritization of Objectives of Therapy | 125 |
| 5.4 | Model Predictive Control | 126 |
| 5.4.1 | Overview | 126 |
| 5.4.2 | Suitability for HIV/AIDS Drug Dosage Design | 129 |
| 5.5 | Sampling | 129 |
| 5.6 | A Sequential Perturbation Approach to Dosage Design | 131 |
| 5.6.1 | Strategy | 131 |
| 5.6.2 | Objective Function and Constraints | 131 |
| 5.6.3 | Dosage Sequence Design | 134 |
| 5.6.4 | Results | 135 |
| 5.6.5 | Effect of Inadequate Sampling | 144 |
| 5.6.6 | Conclusions | 144 |
| 5.7 | Interruptible Drug Dosage Design | 147 |
| 5.7.1 | Bottlenecks and Advances in STI Protocol Design | 148 |

| | | |
|----------|---|------------|
| 5.7.2 | Strategy | 150 |
| 5.7.3 | Off/On HAART: Getting the Timing Right | 150 |
| 5.7.4 | Off/On HAART: Results | 153 |
| 5.7.5 | Including Protease Inhibitors in the STI Regimen | 158 |
| 5.7.6 | Immune Based Therapy to Augment HAART Interruptions | 159 |
| 5.7.7 | Conclusions | 161 |
| 5.8 | Chapter Summary | 163 |
| 6 | Conclusions and Future Work | 165 |
| 6.1 | Summary | 165 |
| 6.2 | Conclusions | 166 |
| 6.3 | Recommendations and Future Work | 170 |
| A | Parameter Estimates | 190 |

Abbreviations

| | |
|-------|---|
| AIDS | Acquired Immunodeficiency Syndrome |
| CD4 | Cluster Designation 4 |
| CD8 | Cluster Designation 8 |
| DNA | Deoxyribonucleic Acid |
| gp120 | glycoprotein 120 |
| FDC | Follicular Dendritic Cell |
| HAART | Highly Active Antiretroviral Therapy |
| HIV | Human Immunodeficiency Virus |
| IBT | Immune Based Therapy |
| LTNP | Long Term Non Progressor |
| SIT | Structured/Supervised/Scheduled Intermittent Therapy |
| STI | Structured/Supervised/Scheduled Treatment Interruptions |
| RNA | Ribonucleic Acid |
| RTI | Reverse Transcriptase Inhibitor |
| PI | Protease Inhibitor |