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

by

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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.

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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.

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Pretoria, South Africa — Annah Mandu Jeffrey
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To Afentse, Kagiso, Anwar, Nefertari and Atang.

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

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Contents

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