Chapter 6

Conclusions and Future Work

6.1 Summary

The first chapter presented an overview of the problem at hand. The problems with antiretroviral therapy, the advances so far made in this area, and hence the motivation for conducting this research was presented. The case for HIV/AIDS therapy as a control engineering problem was made, and the role that Control Engineers have played, continue to play and should play in helping to combat the infection was made apparent.

As a foundation, Chapter 2 presented a brief background on immunology, virus replication mechanism and the events that lead to the immune system being compromised. The chapter presented replication cycle based HAART and immune based therapies - IBT, as drugs that are used to treat the infection. The guidelines perspective and advice on the treatment of HIV/AIDS infection then followed, and the case for the need to individualize antiretroviral therapy was presented. Issues relating to the interruption of HAART were discussed.

In Chapter 3, an over view of some HIV/AIDS mathematical models in the literature and the aspects of the immune system that each model illustrates were discussed. Justification for the choice of models that were adopted for this thesis was made. Issues of antiretroviral drug efficacy were discussed and the model parameters that are affected by therapy were presented.

Extensive analysis of the selected models, with and without therapy was carried out in Chapter 4. Therapy in this context, entailed the exclusive or concomitant use of replication cycle based antiretroviral and immune based therapies. This analysis endeavoured to find explanations, from a control theoretic perspective, to some clinically observed responses of individuals on antiretroviral therapy, as well as gain some insight into the following HIV/AIDS therapy issues:

- Variability in response to therapy between individuals on the same regimen.

- Transient rebounds of plasma viremia after periods of suppression.
- The attainment of maximal and durable suppression of the viral load.
- The prognostic markers of virologic success.
- Timing the initiation of antiretroviral therapy such that the benefits of therapy are maximized.
- The possibility of individualizing therapy.

The analysis started with the latently infected cell model and was where necessary, extended to the higher order extended model. At the end of the analysis, the usefulness of the analysis was made apparent as explanations to the above mentioned HIV/AIDS issues were made.

The models were analyzed for the eventual control of the HIV infection. To this end, Chapter 5, after presenting the control problem, also presented antiretroviral drugs as control inputs. Sampling issues, therapeutic range estimation, prioritization of objectives and Model Predictive Control as a control strategy of choice, were discussed.

A sequential perturbation dosage scheme that attained maximal suppression of the viral load with minimal drug exposure, for the treatment naïve individual in the asymptomatic stage of the infection, when replication cycle based HAART was used, was implemented. Once viral load suppression to below detectable levels was attained and maintained, a structured treatment interruption dosage schedule to further reduce total drug intake was implemented, when both replication cycle based HAART and immune based therapies were used. The designed control strategies were assessed for practicality and ease of implementation.

6.2 Conclusions

The following are the conclusions that were drawn from this research and are presented according to the problem that had to be addressed:

Variable response to therapy:

- The treatment steady state is drug efficacy and parameter dependent, but is independent of when, during the course of the infection, therapy in initiated. This exclusive dependence of the treatment steady state on the model parameters confirms previous observations that for a fixed drug efficacy, the variability in response to therapy between individuals is primarily due to inter-individual variations in parameters.

- From a viral load point to point controllability perspective, some stages of the HIV infection are more controllable than others. The transition pattern from the pre-treatment state to the treatment steady state will therefore depend on when therapy was initiated. This suggests that an individual can have variable response to therapy depending on when therapy is initiated.

Rebounds of plasma viremia after periods of suppression:

- For a fixed drug efficacy, the transition from the pre-treatment viral load to the treatment steady state is generally oscillatory and the viral load will transiently oscillate about the treatment steady state before settling. Viral load rebounds are therefore, from a treatment steady state perspective, all transient.
- The magnitude and frequency of the viral load rebounds about the treatment steady state depend on when during the course of the infection, therapy was initiated.
- For an individual, if the drug efficacy is such that the treatment steady state is above a value that is considered indicative of virologic failure, then the viral 'blip' will, in the clinical context, also be indicative of virologic failure. On the other hand, if the drug efficacy is such that the treatment steady state is below detectable levels, then the viral blip will be, again in the clinical context, transient.

Prognostic indicators of virologic success:

- The maximality of viral load suppression and the durability of such suppression once attained, depend on the infection stage at which therapy is initiated. As such, the viral load and cell count at the start of therapy are more prognostic indicators of virologic response, than they are of virologic success. This study therefore, partially lends support to some clinical study findings that have suggested that the virologic and immunologic conditions at the start of therapy, determine the outcome.
- The real determinant of virologic success on an individual basis, is the combination of the virus and host cells' parameters and the end point efficacy of the drugs used. This finding, fully supports the reported cases where virologic failure has been attributed to the regimen used.
- It has been argued before that the basic reproductive ratio R_o, is one of the prognostic indicators of virologic success. Given that R_o is exclusively determined by the individuals virus and host cells' parameters, which are in turn co-determinants of virologic success, then the argument is justified.

The possibility of individualizing antiretroviral therapy:

- This study has indicated that it could be possible to obtain the full parameter estimate set for the HIV/AIDS models considered in this thesis, with appropriate system measurements, and that this parameter estimate set can be reduced if need be. This affirms that it is possible to individualize antiretroviral therapy.

The best time to initiate antiretroviral therapy:

- From a maximal viral load suppression perspective, it is best to initiate antiretroviral therapy during the early-acute infection stages. Failing which, then therapy should be initiated during the asymptomatic stage.
- Maximal viral load suppression generally implies durable suppression. From a durable viral load suppression perspective then, it is best to initiate therapy also during the early acute infection stages. For a truly durable suppression of the viral load however, a drug efficacy that is high enough to attain a treatment steady state that is below levels of detection should be used.
- Some stages of the HIV infection are more controllable than others, and the degree of viral load controllability is highest during the mid-acute infection stage. From a viral load point to point controllability perspective then, is the best time to initiate therapy during this stage. Failing which, then therapy should be initiated during the early asymptomatic stage.

Modelling antiretroviral drugs as control inputs:

- The instantaneous inhibitory effect of virus replication has been modelled as an oscillatory function of time. If however, the interval between dosing, or the release mechanism of the drug is such that the variation between the peak drug concentration and the minimum concentration is minimal, then the drug efficacy can be assumed to be constant.

Sampling for effective control:

- The sampling interval has been determined from the viral load transient response analysis and corresponds to the minimum sampling rate to prevent aliasing. This sampling interval is parameter dependent and will vary between individuals.

The rational sequencing of drugs:

This study has provided some potentially interesting insights on the way antiretroviral agents could be administered.

- Firstly, the study suggests that the initial dosage efficacy and the selection of

both the starting and subsequent regimens will depend on the frequency at which the viral load is sampled. The prescribed regimen is more inclined towards a fixed dosage regimen as the sampling interval increases and there is an associated increase in drug intake. This puts emphasis on the need for sampling to be more frequent than as recommended by the guidelines.

- Secondly, for mono class therapy, the eventual protease inhibitor efficacy is lower than that of the reverse transcriptase inhibitors. This suggests that protease inhibitors are better than reverse transcriptase inhibitors at suppressing the infectious viral load.
- When both drug options are available for therapy, there is a distinct switch from one class of antiretroviral agent to the other during treatment. Protease inhibitors were preferred for the eventual suppression of the viral load, even thought the initial regimen was more inclined towards the use of reverse transcriptase inhibitors. The underlying dynamics, or criteria for switching the regimen basis from one class to the other, and the possible elimination of one antiretroviral class from the regimen, requires further investigation.
- Results from this study suggest that a logical way to minimize cumulative toxicities is to start therapy with a low dosage (take advantage of the transient undershoot when dynamics are perturbed) and sequentially increase the dosage to further suppress and eventually maintain the viral load below detectable levels. This results in a sequential perturbation approach to therapy.
- The eventual dosage required to keep the viral load below detectable levels will be high.

Structured treatment interruption protocol design:

- Immune based proliferation suppressors have been found, in this study, to have marginal effect on the viral load treatment steady state and no effect at all on the $CD4^+$ T cell steady state counts. Adding immunosuppressive hydroxyurea to replication cycle based HAART for the initial suppression of the viral load, as it has been done in some clinical trials, was therefore, an ill conceived idea. However, proliferation suppressors do have a transient effect on the viral load response and could be added to the STI regimen.
- In the absence of immune control of the virus, it takes longer to re-suppress the viral load after a HAART interruption, than it does for the viral to rebound during an interruption. This means that with the use of replication cycle based HAART, STI treatment schedules with equal Off/On periods, such as those that have been

used in some clinical trials were designed to fail.

- Setting lower viral load upper limits has been found to result in shorter Off/On cycles. The derived shorter Off/On cycles that result with lower viral load upper limits have a relatively higher percentage reduction in total drug intake, when compared with the longer Off/On cycles that resulted with higher viral load upper limits. As it appears, increasing the viral load cutoff limit is a case of increased risk of drug resistance with no reward.
- Intensifying the STI HAART regimen by adding immune based therapies to it results in even shorter Off/On cycles and further reduces HAART exposure. However, care should be taken not to make the already toxic HAART regimen more toxic. Conformation to pre-designed STI Off/On schedules can be attained by such intensification of the STI HAART regimen.

Practicality of implementation:
The issue is whether such a dosage scheme can be practically implemented. Given that an individual's model parameter estimates could be obtained, the results from this study indicate that if the sampling interval is reasonable, which it is in this case, then such a dosage scheme can be practically implemented. However, even though the models predict that any drug efficacy can result in some degree of viral load reduction, one needs to consider or investigate the clinical implications of under dosing, or more generally, the implications of not taking drugs as prescribed.

6.3 Recommendations and Future Work

A lot has been done in model development and a lot more still needs to be done. Model accuracy needs to be further improved, though this will ultimately make model analysis more difficult.

Issues of resistance, though not considered in this thesis, are real. This is especially so if dosage sequences with variable drug intake are considered. This area also needs to be addressed.

Items that still need to be properly formulated are:

1. Environmental and social factors that influence infection progression.
2. Organ health, as in quantifying the extent to which the immune system is repairable.

Besides facilitating the simulation of a more realistic infection progression, it can also

explain such cases of attaining virologic success with immunologic failure (durable viral load suppression to below detectable levels with suboptimal T cell gains). Being able to quantify organ health can also improve the determination of immune competence in chronically infected patients, and facilitate the development of tests that may then predict which patients will be the best candidates for STI. This should be one of the objectives of STI.

The HIV/AIDS models presented in this thesis are inherently nonlinear regarding the states and parameters are known to change over time. Even though results based on linear time-invariant system analysis are valid (at least locally), an in-depth nonlinear analysis of the system still has to be carried out. This could unveil some model characteristics or properties that were not made apparent or addressed in this thesis and give more insights into the disease dynamics and possible treatment strategies.

Explicitly modelling the immune response to the virus would make the HIV control problem more challenging for the control engineer. Modelling the immune response would actually increase in number, the equilibrium points of the system. Other challenges that the control engineer could take up are including the trafficking of virus particles between compartments. Macrophages residing in tissue in particular, are one of the obstacles of virus eradication.

The control strategy that has been presented in this thesis needs to be upgraded. There is much uncertainty in model parameters estimates and these estimates are known to change with time. Even though MPC has some degree of robustness to model inaccuracies, the controller's performance in the presence of disturbances and parameter changes has to be assessed and issues relating to the controller's stability have to be addressed. Adaptive strategies need to be explored.

For control purposes, the derived input drug sequences are specified from an end point drug efficacy perspective and this efficacy can be assumed to be constant for the interval that the dosage is fixed. However, determining the actual required dosage that corresponds to the derived input efficacy sequences will be problematic as it involves firstly, that the relationship between the two be defined for each individual and for each regimen that the individual uses. A lot of research work needs to be done in that area.

All the foregoing calls for collaborative research with immunologists and related medical practitioners in order to take the research work of control engineers further and make it more applicable and of use.