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Modeling and Control Of HIV Antiretroviral Therapy

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Modeling and Control of HIV

Antiretroviral Therapy

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In Computer Science

by

Phillip Thomas Deutsch

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ABSTRACT OF THE THESIS

Modeling and Control

Of HIV Antiretroviral Therapy

By

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Master of Science in Computer Science

University of California, Los Angeles, 2014

Professor Joseph DiStefano III, Chair

We review the literature on HIV infection and treatment from a mathematical modeler’s perspective. We examine dynamical ODE models of HIV infection, including target-cell limited immune-controlled models. We investigate various control theoretic approaches to the determination of optimal treatment from these models. Finally, we examine the application of insights gained from modeling experience to two questions arising in clinical practice: when to initiate therapy and whether to consider treatment interruption.
The thesis of Phillip Thomas Deutsch is approved.

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2014
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Introduction

The treatment of HIV infection has received a great deal of attention from the mathematical modeling community in the past 20 years, owing to the severity of the global AIDS pandemic. Early studies (Ho et al., 1995) provided a simple model of disease progression that described the chronic phase of HIV infection and informed pharmacokinetic studies of antiretroviral agents. Once this was accomplished, many authors proposed that the methodology of control theory could be used to develop treatment schedules for antiretrovirals which, in theory, would be superior to the existing system of fixed dosages by dynamically adjusting to the particulars of each patient’s disease. While no such method has been adopted clinically, insights from the modeling process may inform clinical practice on outstanding questions such as the debate over when to initiate treatment.

Finding an optimal treatment schedule for HIV is a two-part problem. The first part of the problem is creating a sufficiently accurate model of the evolution of HIV infection over time and how antiretroviral agents act to hinder or reverse the infection. The second part of the problem is to find a suitable algorithm for controller synthesis, which will take the model and use it to determine the optimal schedule of antiretroviral drugs with which to treat the disease. This review will investigate both topics in order, and conclude with a discussion of the applicability of modeling efforts to two practical questions that arise in clinical HIV treatment: when to initiate treatment, and whether it is reasonable to consider a strategy of “structured treatment interruption” where treatment is temporarily discontinued during “treatment holidays” and restarted at a later time.
Model

In order to be useful, a mathematical model of disease must be complex enough to capture all relevant features of the disease while remaining identifiable and tractable to simulation. There are many aspects of HIV infection relevant to modelers, some shared with other chronic infections such as cytomegalovirus and hepatitis C, and some unique to HIV. Like other chronic infections, HIV infection can be broken into multiple distinct phases, including an acute phase where viral load rapidly increases, until the infection is brought under immune control, followed by a chronic phase where disease progression is slow or nonexistent. Interventional studies (Ho et al., 1995; Perelson et al., 1996) have shown that the chronic phase cannot be attributed to a slow rate of viral production, but is instead a result of a quasi-steady state balance between production and death of the infected cells. The existence of a nonzero quasi-steady state indicates that a nonlinear model is necessary to describe HIV infection. Where HIV differs from other diseases is in the dynamics of its terminal phase, AIDS, caused by the depletion of CD4+ T-helper lymphocytes that are essential for the proper activation of cellular immunity. As the disease progresses to AIDS, cellular immunity is lost, creating a positive feedback where disease progress reinforces itself, allowing a renewed surge in HIV viral load as well as opening the door to opportunistic infections. HIV is an evasive disease: even the most aggressive antiviral therapies do not succeed in clearing the disease due to its ability to “hide” in latent reservoirs such as quiescent infected CD4+ lymphocytes (Finzi et al., 1997). Finally, like other viral infections HIV evolves over time due to selective pressure exerted by the immune system favoring strains that can escape immune response.

Fundamentally, models of HIV infection can be classified as predator-prey models (Wodarz, 2006). Viewed ecologically, the HIV-host system is a food chain with three levels. At the
bottom lie “target cells” such as CD4+ lymphocytes and macrophages that HIV can productively infect. Target cells are preyed upon by HIV, and immune effectors such as CD8+ lymphocytes destroy infected target cells. While immune effectors do not “eat” infected cells, the activation of the immune response is commonly modeled as being dependent on the density of both effector and infected cells, inducing a relationship mathematically indistinguishable from predation.

In order to simplify their models, early modelers typically chose to model HIV infection with approximations that contain only two levels of the HIV ecosystem. A great advantage of this approach is that two-species chains are guaranteed to have relatively simple dynamics, whereas predator-prey models with three or more predators may lead to large amplitude oscillations, multiple bifurcations, and chaos (Klebanoff and Hastings, 1994). In principle, there are two classes of such simplified models. The first type consist of immune limited models where target cell populations are not modeled and HIV replication rate is independent of target cell population, thus control of HIV infection is entirely due to clearance of HIV infected cells by CD8+ lymphocytes. A simple example is given by the following system of ordinary differential equations

\begin{align*}
\dot{I} &= \beta V - \mu IZ \\
\dot{V} &= cI - \rho V \\
\dot{Z} &= gIZ - mZ
\end{align*}

where \( I \) represents the population of cells productively infected with HIV, \( V \) the population of free virus and \( Z \) the population of effectors. While this system consists of three state variables, only \( I \) and \( Z \) participate in the food chain directly, whereas \( V \) has simpler linear dynamics, hence the simple dynamics of the two species chain are applicable. While such a
system may be fitted to acute and latent phase patient data with similar performance to other models of the same complexity (De Boer and Perelson, 1998), it will fail in conditions where the target cell limitation is significant, such as immunosuppression, where this model will erroneously predict unbounded viral growth. Purely immune limited models have not gained traction in the literature, where authors prefer more complex systems that include both immune and target cell limitations.

In contrast to immune limited models, purely target cell limited models were and remain a popular form of simplified viral model (Gregio et al., 2009; Jang et al., 2011; Radisavljevic-Gajic, 2009). A typical example is below

\textbf{Equation 2}

\[ \dot{T} = s - dT - \beta TV \]
\[ \dot{I} = \beta TV - \mu I \]
\[ \dot{V} = cI - \rho V \]

where \( T \) is the concentration of uninfected target cells, \( I \) is the concentration of infected target cells, and \( V \) is the concentration of free virus. Like the immune-limited model, it possesses dynamics that are simple and structurally stable, and all parameters are known to be globally identifiable (Hongyu et al., 2011). Target cell limited models have been found adequate in modeling infection during the latent phase of infection over short time periods. As a result, target cell limited models have been frequently used in pharmacodynamic studies of HIV antivirals (Ho et al., 1995; Perelson et al., 1996). Target cell limited models can discriminate between two different types of antiviral drug types: drugs that inhibit infection, such as reverse transcriptase inhibitors and entry inhibitors which are modeled by decreasing the infectivity parameter \( \beta \), and drugs that inhibit replication, such as protease inhibitors, which are modeled by
reducing the viral production rate $c$. The model successfully predicts the rapid turnover of free virus in the bloodstream, in contrast to earlier beliefs regarding the progression of the disease. For reasonable parameter choices this model has two equilibria: one unstable equilibrium corresponding to an uninfected patient, and one stable fixed point attractor corresponding to an infection that cannot be cleared but also does not progress. This class of model is adequate for modeling latent HIV infection over a short period of time, but cannot model the acute infection because fitting the model to data containing variation of such large magnitude would require unreasonable parameter choices. Additionally because all trajectories are attracted to a stable fixed point, the simple target-cell limited model cannot capture the progression to AIDS without further augmentation, and thus is not adequate for assessing treatment effects over the long term.

In order to overcome the limits of target cell limited models, a number of models include additional state variables that model the host’s HIV specific immune response. The simplest of these models generalize the target cell limited model into a three species food chain by adding the immune response as a predator of HIV. Host immune response to HIV consists of both humoral and cellular immunity, but modelers have focused primarily on cell mediated immunity believed to be primarily responsible for control of HIV infection. The dynamics of immune activation are complex, and there are a variety of modeling strategies. Some authors, such as Culshaw (Culshaw et al., 2004) and Nowak and Bangham (Nowak and Bangham, 1996), simply combine the target cell limited and immune limited models, by adding a single immune state variable $Z$, to the target cell limited model, giving the system

\begin{align*}
\dot{T} &= s - dT - \beta TV \\
\dot{I} &= \beta TV - \mu I - fZ I \\
\end{align*}

Equation 3
Compared to the two species models, this model has much more complicated dynamics, and it is not clear that parameters can be identified for experimental data alone without further assumptions. For reasonable parameter choices, this model has at least two equilibria corresponding to an infected patient, one corresponding to an activate immune response and another to zero response. This fact has led several authors to propose a “phase change” approach to HIV treatment, in which patients who control HIV poorly are pushed by drug treatment into the high functioning equilibrium (Wodarz, 2001; Zurakowski and Teel, 2006), but there is little experimental validation of this approach.

A popular extension of this simple three species model is the model of Wodarz and Nowak (Wodarz et al., 2000), who add an additional state variable $W$ to represent immune memory coupled to target cell density to capture immune degradation caused by CD4+ depletion.

\[ \dot{V} = cI - \rho V \]
\[ \dot{Z} = gZI - mZ \]

Equation 4
\[ \dot{T} = s - dT - \beta TV \]
\[ \dot{I} = \beta TV - \mu I - fZI \]
\[ \dot{V} = cI - \rho V \]
\[ \dot{Z} = gIW - mZ \]
\[ \dot{W} = fTIW - gIW - kW \]
This model is widely used in control studies because it can better capture the effect of immune memory, which is relevant when considering treatment strategies that employ treatment interruptions.

Another important class of HIV model that treats immunity are evolutionary models, in which multiple HIV epitopes compete in order to evade the immune system. These models replace the single state variables for infected cells and immune responses with an indexed set of responses, as below:

\[ \begin{align*}
\dot{T} &= s - dT - \sum_j \beta_j TV_j \\
\dot{I}_j &= \beta_j TV_j - \mu I_j - f Z_j I_j \\
\dot{V}_j &= c I - \rho V_j \\
\dot{Z}_j &= g Z_j I_j - m Z_j
\end{align*} \]

where \( T \) is the population of target cells and \( I, V, \) and \( Z \) are the populations of infected cells free virus and immune effector for each epitope \( j \). These models can be used to make predictions about HIV’s adaptation to a changing host environment, including the coevolutionary arms between HIV and the host immune system and, crucially, HIV’s evolution of resistance to antiviral drugs, which cannot be captured in simpler models (Altes et al., 2002; Lee et al., 2008). The key measure that is tracked in these models is an index of viral diversity: a greater diversity indicates a greater capacity to overcome challenges such as immunity and drugs. Most
simulation studies have shown a linear relationship between diversity and viral replication rate (Nowak and Bangham, 1996; Regoes et al., 1998), but clinical studies shown a decrease in diversity over time (Nowak and Bangham, 1996). As with the single epitope models discussed earlier, there is a minimal threshold of immune activity needed to sustain the immune response, leading to a bifurcation of the single stable infection equilibrium point of simpler models into multiple equilibria with different levels of immune activation.

While the above models can successfully capture HIV behavior during the latent and sometimes acute phases of infection, in all of them the state trajectories of the disease are ultimately attracted to a stable equilibrium point for biologically relevant parameter values. Hence, none of them can capture the ultimate progression of the disease to immunosuppression and AIDS. To rectify this issue, authors such as Perelson (De Boer and Perelson, 1998) and Pannochia modify the systems by replacing a constant parameter with a time-varying parameter, forcing the diseases to progress over time. Typically, this parameter is chosen to be $\beta$, the infectivity rate, although alternatives include immune parameters such as the immune activation rate. For the simpler target cell limited model an arbitrary time dependence can be identified from experimental data, while more complex immune models must typically fit assume a functional form such as linear time dependence (Hongyu et al., 2011).

**Controller**

Once a disease model has been chosen, a dosage schedule for HIV antivirals can be calculated using the methods of optimal control. In addition to the model, the control engineer must add two additional ingredients. The first ingredient is a cost functional, which assigns to the result of a given treatment schedule an overall score that can be compared with alternative
schedules. The optimal treatment is the treatment schedule whose cost functional is best. The second ingredient is the synthesis paradigm, which determines which classes of functions will be considered as potential treatments and consequently which algorithms are suitable for finding the optimal treatment.

**Cost Functional**

The cost functional chosen for the controller has a decisive impact on the ultimate computed treatment schedule. There are two families of functional forms for cost functionals that should be considered. The first is set-point control, where a particular value is chosen to be the ideal state and any deviation is penalized, encouraging control action to restore the system to the set-point. This form of objective functional is common in industrial control design, and many synthesis algorithms such as LQR require an objective of this form, but it does not accurately reflect the objectives of HIV treatment. Set-point controllers will punish deviation in any direction from the set-point, hence if a patient’s status improves, the controller will act to degrade it, which is counterproductive. An alternative approach is thresholding, where state values are punished only after they cross a threshold. In practice, this acts as a one-sided set point, avoiding the problem above. An advantage of set-point methods is that they are generally fairly insensitive to the choice of weights. A disadvantage of set-point type methods is that they may generate wild behavior when the set-point becomes infeasible due to the progression of the disease. The alternative to set-point methods are weight based methods which independently weight the benefits and costs of therapy. While this approach better captures the objectives of therapy, the treatment schedules produced as a consequence tend to be more unstable and require precise tuning of weights in order to produce reasonable results.
A simple family of control methods that has been applied to this problem is open-loop control. Open loop control is distinguished by its lack of state feedback: a treatment schedule is calculated once and never updated. The advantage of open-loop control is that it is easy to compute and prove useful properties of the solution such as robustness. A typical open loop approach makes use of variational methods, such as Pontryagin’s Maximum Principle, where a Hamiltonian function is constructed which characterizes the optimal control in terms of a system of differential equations. Hence, the optimization problem is reduced to a nonlinear boundary value problem which, though nontrivial, can be attacked using a number of well-studied approaches. For HIV control problems, successful approaches have included analytic continuation (Culshaw et al., 2004), iterative methods (Jang et al., 2011), and shooting methods (Banks et al., 2005). An alternative to continuous control that has been adopted recently is piecewise constant controls, where the dosage is changed only when new measurements are made and is constant otherwise. This functional form is more representative of treatment in practice. This approach makes standard variational techniques inapplicable due to the discontinuity of the controller, but instead allows the controller to be represented as a finite dimensional vector of dosages at specified treatment intervals. An optimal control can then be found using techniques of nonlinear optimization. As optimization scales poorly, this technique is best suited to finding controls over short time horizons. Unfortunately, the optimization problem is unlikely to be convex, preventing a guarantee of performance. Nonetheless, authors such as Zuratowski (Zurakowski, 2011) and David (David et al., 2011) have successfully used nonlinear solvers to obtain robust treatment schedules.

While open-loop methods possess desirable analytic properties, unfortunately, the problem of HIV control clearly requires state feedback. First, patient noncompliance with treatment is a
well-known difficulty in HIV treatment, and since compliance behavior cannot be predicted in advance, control methods must be able to incorporate deviations as they occur. Deviations can also be caused by unanticipated shifts in disease factors such as viral evolution. Finally, even using robust methods where small deviations lead to small errors, errors are magnified over time.

To address the shortcomings of open-loop methods some authors (Gregio et al., 2009; Radisavljevic-Gajic, 2009) have attempted to apply the well-known Linear-Quadratic Regulator framework for controller synthesis to HIV treatment, which combines a linear model with a quadratic cost functional. Because the disease model is not linear, this approach chooses a “set-point”, a desired state at which the patient is held via drug treatment, and the system is linearly approximated about the set-point. Unfortunately, this framework is a poor fit for this problem. First, the set-point formalization is not a good fit for this problem. The clinical objective in treating HIV is not to keep the patient’s health in a precisely defined state but instead to prevent patient health from deteriorating, and if possible to improve it. Since a functioning set-point control allows no change at all, it accomplishes the goal of preventing deterioration but thwarts the goal of improving health. Secondly, the linearization used in these methods is at best accurate only in a small neighborhood of the set-point, so it cannot be used to model patients far from the set point, as will be the case at the beginning of treatment and after any treatment interruption. Hence, these methods can at best be used to maintain a set-point, but cannot be used to bring patients to the set-point to begin with. To address this shortcoming, Radislavic-Gajic (Radisavljevic-Gajic, 2009) suggests a hybrid method where LQR is preceded by an open-loop method for bringing the system to the set-point, but it remains an open question how to handle the case when open-loop control fails to bring the system to the desired set-point. Finally, LQR methods are generally not robust to error, and the lack of robustness is amplified by the
increasing deviation from linearity as the system moves farther from the set-point. Given the interpatient variability observed in the progression of HIV disease, any practical application must assume that there will be non-trivial differences in patient characteristics, so robustness is very important, and hence the inherent LQR methods cannot be relied upon.

Model predictive control is a technique popular in industrial control that blends open-loop and closed loop methodologies. MPC is an iterative multistep method. In each step, an open loop control is calculated using the currently measured model state, and the control is applied to the system for a specified amount of time. After this time is up, a new state is measured and the process is repeated. The incorporation of measured data provides state feedback, while allowing simpler open-loop controller algorithms to be used. MPC is significantly more computationally intensive than other methods, due to the large number of steps for which controls must be calculated, but since new controls must be calculated only one per measurement, this would not be a problem clinically. The robustness of MPC methods can be enhanced further by the use of estimators which attempt to adapt to errors in parameter estimates from data while the controller is running. Pannochia uses deadbeat estimators, an estimator that models deviation of the model from truth as a constant offset on the observed output variables. David (David et al., 2011) uses the Extended Kalman Filter, a modification of the traditional Kalman filter that allows for estimation of parameters of nonlinear functions. While proof of desirable properties such as optimality and consistency does not exist, MPC methods have shown impressive performance in simulations studies, displaying robustness in situations of moderate to high noise (Zurakowski, 2011), as well as robustness to variations in parameter values (David et al., 2011), a feat not equaled by alternative control paradigms.
Though optimal control in HIV treatment has been discussed for almost 15 years, it has not found its way into clinical practice, due to its complexity and the shortcomings discussed above. Despite this, it is not necessary that any of these methods be adopted in order to provide insight into clinical practice. One question that these methods can attempt to answer is when to initiate HIV therapy. Expert opinion is divided on when antiretroviral therapy should be initiated: some would only initiate therapy when CD4+ count drops below 350 cells/mm$^3$, others at 500, still others as soon as the disease is detected (Mauskopf et al., 2005). Models can, in principle, predict which course of action is superior, but in practice modelers are almost evenly divided on this issue. Mauskopf and others (Mauskopf et al., 2005), using simpler target-cell limited models argue for later intervention, while more sophisticated models (Kirschner et al., 1997) tend to favor earlier intervention, possibly because they place greater emphasis on promoting natural immunity which is not a factor in simple models.

Another question that can be addressed by the optimal control framework is the notion of structured treatment interruption (STI), planned interruption of treatment at advantageous times in the course of therapy. Proponents of STI have suggested numerous potential benefits: controlling HIV with a natural immune response, and mitigating the toxic side effects of antivirals. Skeptics of STI are concerned that interrupting treatment will allow drug resistant strains to multiply. Most modelers that have studied the STI question have been optimistic about the potential for successful intervention in certain circumstances. Unfortunately, clinical trials have uniformly been negative in assessment of STI (Bonhoeffer et al., 2000). If STI is to be viable in the future, better criteria must be developed for identifying when to time interruptions. The model based approach to STI centers on the assumption that there are two stable equilibria of disease state in an infected patient, one corresponding to a sicker patient and another
corresponding to a relatively healthier patient, and that a carefully chosen therapy can guide patients from a sicker to healthier state. Modelers have generally been optimistic about the potential of this approach, so the failure of STI in practice must cause them to question whether their models are a complete and accurate summary of the relevant immune dynamics. As modelers who have attacked this problem have made use of a variety of different models and control paradigms, from simple target cell limited models (Adams et al., 2004; Rosenberg et al., 2007; Zurakowski and Wodarz, 2008) to complex models with 10 or more variables (Wodarz and Nowak, 2002), it appears there is no single reason for the discrepancy between models and reality. Furthermore, modelers disagree on what effect STI should be anticipated to have on the development of drug resistance, with some believing that interruptions will inhibit the development of resistance due to the cessation of selection (Zurakowski and Wodarz, 2008) while others believe that they will cause resistance mutants to merge by allowing increased replication (Bonhoeffer et al., 2000; Rosenberg et al., 2007).

Conclusion

A great variety of models and control paradigms have been proposed for determining an optimal treatment for HIV. Simpler models of HIV are limited in applicability, and more complex models are not well understood and may not be identifiable. MPC appears to be the best control method for modeling treatment, and LQR methods should not be pursued due to their inherent weakness of nonrobustness, while open-loop methods seem insufficient to fully model treatment over a period of decades without incorporating feedback. Modelers do not agree on questions such as when to initiate therapy or STI, and as such further research is needed before anything of value could be contributed clinically. Future work should include further analysis of newer
methods such as model predictive control that appear to produce good results but are not well understood theoretically in the context of HIV control.
References


