Proceedings of the American Control Conference
Anchorage, AK May 8-10, 2002

Optimal control of HIV infection with a continuously-mutating viral population

Jason J. Kutch* and Pini Gurfil†
Department of Mechanical and Aerospace Engineering,
Princeton University, Princeton, NJ, 08544

Abstract

There has been much discussion in recent years devoted to determining the optimal methodology for administering anti-viral medication therapies to fight HIV infection. There are many reasons to seek such an optimal therapy, including the minimization of drug toxicity and monetary cost. However, there is increasing recognition that exposure to many anti-HIV medications produces extremely rapid changes in the viral population in an infected individual, from drug-sensitive to drug-insensitive viral strains. This paper investigates the reasons underlying the development of drug-insensitive HIV strains, and then, using numerical optimal control techniques, demonstrates that optimal drug administration may be useful in increasing patient health by delaying the emergence of drug-resistant mutant viral strains. **Key Words**: Optimal control; HIV; Mutation; Drug therapy

1 Introduction

Optimal control procedures have been used in the past to suggest optimal anti-HIV medication dosages as functions of time. Kirschner et al. [6] used the Maximum Principle to derive optimal drug dosages based on the dynamical model of Perelson et al. [10]. This dynamical system, through the judicious choice of constant parameters, did account for many peculiarities of HIV infection. However, it did not take into account the effects of viral population mutation over time in response to drug therapy; effects that can become significant in the case of long-term anti-HIV therapy.

Shifts in the viral population from "normal" to so-called "escape mutants" can occur without treatment [9] and with treatment [5]. A normal viral population is characterized by the ability of the immune system and anti-viral drugs to destroy such viruses. Escape mutants are insensitive to either immune control, drug control, or both. In this paper, we are primarily interested in escape mutants that develop in response to anti-viral medications.

Let us consider the mechanism by which a drug-resistant viral population can emerge from an originally drug-sensitive viral pool. HIV is a retrovirus; it therefore contains RNA as its genetic material which it converts to DNA as it infects a host cell. This conversion process is extraordinarily error-prone, however, as it lacks the "proofreading" mechanisms that our own cells have during a similar process where new DNA molecules are made from old ones. For an excellent overview of virus structure and life cycle, see reference [7].

A genetically-homogeneous viral population typically dominates primary infection [5]. However, approximately 10^{10} viruses are produced per day during infection, and Coffin [1] has estimated that every possible point mutation in the viral genetic code occurs between 10^4 and 10^5 times per day. This mutation rate leads to an extraordinary amount of genetic variation, no matter how minor, in the viral population.

Most of these mutations do not produce viruses that are any more fit to infect host cells and evade destruction by either the immune system or anti-viral drugs. Yet often enough, a minuscule proportion of the total viral population is indeed less susceptible to destruction. Imagine that the small proportion in fact can completely resist destruction by

*Research Assistant
†Research Associate and Lecturer

anti-viral drugs. Under heavy drug therapy, most of the susceptible virus particles will be destroyed. The remaining drug-resistant virus will reproduce, and will eventually comprise the majority of the viral population, rendering the drug therapy ineffective. We see that the optimal administration of anti-viral therapy is integral to HIV viral dynamics. We therefore ask the following question: is it possible to find an optimal drug treatment schedule (control) which can fight the HIV viral population effectively minimizing the emergence of mutant drug-insensitive viral strains? We will seek to answer this question in the remainder of this paper by developing a dynamical model, described in Section 2, and then applying numerical optimal control procedures, discussed in Section 3.

2 Dynamical system model

For the purposes of this investigation, we will expound on the model of Perelson et al. [10]. The model in its original form will be given first, so that the more complicated version shown later may be seen as a very simple extension.

2.1 Standard model

Let $x_1(t)$ denote the concentration of healthy CD4+ T cells at time t expressed in cells per μL. CD4+ T cells (cluster designation 4, "+" denoting the activated state) are helper T cells displaying the CD4+ protein on their surface that mediate the body's immune response to HIV infection, and are believed to be the primary target for HIV infection [7] ("T cell" will be understood to mean "CD4+ T cell" for the remainder of the paper). When these cells become infected, they enter a second state called latently-infected T cells, denoted $x_2(t)$. These cells have viral genetic material incorporated into their own genome, are thus infected, but are not actively producing new virus particles. At some point in time, these cells become actively infected, denoted by $x_3(t)$, and start producing new virus. Finally we need to define a fourth state, denoted $x_4(t)$, that represents the amount of infectious virus in the blood plasma ready to cause new infections. The equations that define the interplay between these four states are:

$$
\begin{aligned}
P(t) &= 1 - [x_1(t) + x_2(t) + x_3(t)]/T_m \\
\dot{x}_1(t) &= s/[1 + x_4(t)] - \mu_T x_1(t) + r x_1(t) P(t) - \\
&\qquad k_1 x_4(t) x_1(t) && (1) \\
\dot{x}_2(t) &= k_1 x_4(t) x_1(t) - \mu_T x_2(t) - k_2 x_2(t) && (2) \\
\dot{x}_3(t) &= k_2 x_2(t) - \mu_B x_3(t) && (3) \\
\dot{x}_4(t) &= N \mu_B x_3(t) - k_1 x_4(t) x_1(t) - \mu_V x_4(t) && (4)
\end{aligned}
$$

$\dot{x}(t)$ denotes the time derivative of $x(t)$. Perelson et al. [10] note that relatively small changes in parameter values can cause significant bifurcations in this model, and Stafford et al. [12] showed, using a similar model to fit actual plasma virus concentration data from ten HIV patients during primary infection, that small parameter variation could account for much of the qualitative difference between patients. Thus, even though these parameters were chosen with care to represent a typical individual, it should be noted that parameter variation is important and could effect how optimal control is used for this problem.

The first term in Eq.1 represents the source of new uninfected T cells. The dependence of this first term on the concentration of free virus is designed to mimic infection of T-cell precursors by virus, and was found to improve the performance of the model [6] ($s = 10$ μL^{-1} day^{-1}). The second term in this equation represents the death of uninfected T cells ($\mu_T = 0.02$ day^{-1}). The third term is logistic-like and models the reproduction of existing T cells, bounded above by T_m ($r = 0.03$ day^{-1},$T_m = 1500$ cells mL^{-1}). The fourth term models the infection of uninfected T cells by HIV ($k_1 = 2.4\times10^{-5}\mu\text{L}$ day^{-1}).

The first term in Eq.2 represents the production of new latently-infected T cells. The second term represents the natural death of these cells, and the third term models their conversion into actively-infected cells ($k_2 = 3\times10^{-3}$ day^{-1}). The first term in Eq.3 represents the other end of the latently-infected to actively-infected conversion, and the second term models the death of actively-infected cells, at which point large quantities of new virus particles are released ($\mu_B = 0.24$ day^{-1}).

Eq.4 models viral dynamics and the first term quantifies how many new viruses are produced per death of an actively-infected T cell ($N = 1200$). The second term models the loss of free virus as a

result of viruses infecting (and thus entering) uninfected T cells. Finally, the last term represents the destruction of free virus, thereby modelling the immune system's response as constant ($\mu_V = 2.4$ day^{-1}).

Eqs.1-4 represent a class of HIV dynamical models called "target cell limited." This designation means that the process of infection is limited by the number of cells available to infect, rather than active immunological control by the body (this latter type would be referred to as "immune control"). While the vast majority of HIV models have been of the target cell limited type, there has been much discussion surrounding which model class is more accurate. de Boer and Perelson [2] undertook a comparison of these model classes and found that, in the theoretical sense, they behave the same. However, Stafford et al. [12] showed that while a target cell limited model could account quite well for early infection in their HIV-infected patients, a more immune control-like model was necessary for later infection.

In summary, model parameter variation and model class are very important in determining model behavior. We will use the adapted target cell limited model of the Section 2.3, and will show that optimal control performed on this model can yield interesting and perhaps counter-intuitive observations.

2.2 Pharmacological control

Before we derive the optimal control, we must define how drugs will interact with the dynamical system given by Eqs.1-4. There are approximately nine anti-HIV drugs available today, and these are administered in many different combinations of three or four drugs [3]. These drugs fall into two main categories: reverse transcriptase inhibitors (RTI) and protease inhibitors (PI). RTIs prevent new HIV infections by disrupting the conversion of viral RNA into DNA that can be incorporated into the host cell's genome. Thus, RTI's will change the infection rate k_1. If we let $u_{RTI}(t)$ represent the normalized RTI dosage as a function of time, then k_1 of Eqs.1-4 will be modified to become $k_1'[u_{RTI}(t)]$ by the transformation

$$k_1'[u_{RTI}(t)] = (1 - \beta u_{RTI}(t))k_1 \tag{5}$$

The parameter β models drug efficacy, and is meant to take into account the effectiveness of the delivery. Although much more detailed models of the drug delivery process are needed, the constant β is meant to consider the fact that even though a pill may be taken with a highly potent anti-viral drug, the medication may have trouble finding the entire corpus of infected cells before it is cleared by the body. For this study, we will take $\beta = 0.5$

PIs function by preventing the assembly of key viral proteins after they have been mistakenly produced by the infected host cell. PIs will therefore reduce the number of virus particles produced by an actively-infected T cell. If we let $u_{PI}(t)$ be the normalized PI dosage, then the parameter N from Eqs.1-4 will be modified to become $N'[u_{PI}(t)]$ by the transformation

$$N'[u_{PI}(t)] = (1 - \beta u_{PI}(t))N \tag{6}$$

2.3 Modelling continuous mutation

Richman [11] describes the emergence of mutant viral strains under anti-viral therapy, and shows a hypothetical curve of probability of mutant strain emergence versus anti-viral drug activity. As drug activity increases from 0%, probability of emergence increases from 0, and then plateaus. As drug activity increases to 100%, probability of mutant emergence decreases until it reaches 0 at 100%. The increase in emergence probability comes from increased selective pressure. The decrease results from the increase drug effectiveness against all strains. We can quantitatively model selective pressure and the emergence of mutant strains by adding differential equations to our model.

In the dynamical system of Eqs.1-4, Eqs.2-4 describe how the system interacts with normal virus. Suppose that we add two more sets of three differential equations, the first set describing infection by viruses immune to RTIs and the second set describing infection by viruses immune to PIs. The equation for uninfected T cells will then be modified to account for the presence of new virus. The

resulting set of equations is therefore:

$$P'(t) = 1 - [x_1(t) + x_2(t) + x_3(t) + x_5(t) + x_6(t) + x_8(t) + x_9(t)]/T_m$$

$$\dot{x}_1(t) = s/[1 + x_4(t) + x_7(t) + x_{10}(t)] - \mu_T x_1(t) + r x_1(t) P'(t) - k'_1[u_{RTI}(t)] x_4(t) x_1(t) - k_1 x_1(t) x_7(t) - k'_1[u_{RTI}(t)] x_1(t) x_{10}(t) \quad (7)$$

$$\dot{x}_2(t) = k'_1[u_{RTI}(t)] x_4(t) x_1(t) - \mu_T x_2(t) - k_2 x_2(t) \quad (8)$$

$$\dot{x}_3(t) = k_2 x_2(t) - \mu_B x_3(t) \quad (9)$$

$$\dot{x}_4(t) = N'[u_{PI}(t)] \mu_B x_3(t) - k_1 x_4(t) x_1(t) - \mu_V x_4(t) \quad (10)$$

$$\dot{x}_5(t) = k_1 x_7(t) x_1(t) - \mu_T x_5(t) - k_2 x_5(t) \quad (11)$$

$$\dot{x}_6(t) = k_2 x_5(t) - \mu_B x_6(t) \quad (12)$$

$$\dot{x}_7(t) = N'[u_{PI}(t)] \mu_B x_6(t) - k_1 x_7(t) x_1(t) - \mu_V x_7(t) \quad (13)$$

$$\dot{x}_8(t) = k'_1[u_{RTI}(t)] x_{10}(t) x_1(t) - \mu_T x_8(t) - k_2 x_8(t) \quad (14)$$

$$\dot{x}_9(t) = k_2 x_8(t) - \mu_B x_9(t) \quad (15)$$

$$\dot{x}_{10}(t) = N \mu_B x_9(t) - k_1 x_{10}(t) x_1(t) - \mu_V x_{10}(t) \quad (16)$$

Eq. 7 models the uninfected T-cell population modified for the presence of new viral strains. Eqs. 8-10 model the same quantities as Eqs. 2-4, except the equations are modified to represent the susceptibility of normal viruses to RTIs and PIs. Eq.11 models T cells latently infected by an RTI-resistant viral strain, Eq. 12 models T cells actively infected with this strain, and Eq. 13 models the amount of free RTI-resistant virus in blood plasma. Eqs. 14-16 perform similar modelling for a PI-resistant strain. This modelling works by allowing other virus states that have roughly the same dynamics, although they are less affected by drug administration. When we perform numerical simulations of the system, the initial viral population will be almost entirely normal, with only a very small amount of RTI-resistant and PI-resistant virus present. In the absence of drug therapy, the viral population will grow, but will remain predominantly normal. If we introduce medication, we find that the viral population will shift to almost exclusively mutant virus, which is exactly the result we expect. This method of modelling mutation is qualitatively similar to that of Wein et al. [14], but the ability optimal control to decrease viral population mutation has not yet been considered.

The other modification made to the original model was the redefinition of the parameter N as a function of time. This modification was suggested in Perelson et al. [10] as a way to model increased viral virulence over time. With the constant $N = 1200$, the uninfected T-cell count does not reach the extremely low levels observed in the latter stages of HIV disease. For the numerical simulations of the next sections, $N(t)$ will increase linearly from 1000 to 4000 over 10 years (3650 days). Without drug therapy, this $N(t)$ gives rise to a T-cell count of 200 per μL after 10 years. A T-cell count of 200 is generally associated with the development of AIDS [4]; the median time to development of AIDS is 10 years [7].

3 Optimal control

Optimal control methods have been applied to the derivation of optimal therapies for viral infections [6, 13]. These studies have applied the Maximum Principle in their derivation, and then used the procedure of gradient descent to numerically find the optimal control satisfying the design constraints. In this study, we adopt an alternative approach that involves converting the standard optimal control problem into a parameter optimization problem by discretizing the control input vector [8].

3.1 Parameter optimization

Generally speaking, the optimal control problem that we wish to solve is finding a control history $u(t)$ that maximizes a cost functional J given by

$$J = \phi[x(t_f), t_f] + \int_{t_0}^{t_f} L[x(t), u(t), t] dt, \quad (17)$$

subject to some dynamical constraints $\dot{x}(t) = f(x, u, t)$ and static constraints $u_{min} \leq \| u(t) \| \leq u_{max}$. Instead of working with a continuous control function $u(t)$ we define it in terms of nodal points $u_n : n = 0, 1, ..., N_p$, where u_0 is the control at time t_0 and u_{N_p} is the control at the final time t_f. We assume that the nodes are evenly spaced in the time interval $[t_0, t_f]$. The value of $u(t)$ may be computed at any point in the continuous time domain by interpolation.

The method for obtaining the optimal control is then as follows: make a random initial guess for the value of the nodal control points u_n, numerically integrate the state equations using linear interpolation to find the continuous value of the control, compute the value of the cost functional J, and then use existing optimization code to update the points u_n. The process is repeated until J achieves a maximum. To reduce the problem of local minima, optimization was performed using a deterministic crowding genetic algorithm.

The optimal control was found using the following following cost functional over the 10 year treatment period:

$$L[u(t)] = 10(1 - u_{RTI}(t))^2 + 10(1 - u_{PI}(t))^2 \tag{18}$$

$$\phi[x(t_f)] = 1000x_1(t_f) \tag{19}$$

3.2 Results

Preliminary optimizations using $N_p = 4$ and 5 indicated that the control inputs would be most effective during the last third of the treatment period. The optimal control for both RTI and PI drugs was $u^\star = [0, 0, 0, 1]^T$ for $N_p = 4$ and $u^\star = [0, 0, 0, 1, 1]^T$ for $N_p = 5$. Once this was determined, another optimization was performed for $N_p = 10$, varying only the last three components of each control u_{RTI} and u_{PI} and setting the other components to zero. This method allowed a feasible optimization over the region of greatest potential benefit from drug therapy.

Figure 1 shows the T-cell counts as functions of time for the dynamical system of Eqs.7-16 under maximal control, optimal control $[0, 0, 0, 0, 0, 0, 0, 0, 1, 1]^T$, and no control. We can see from Figure 1 that we can use the optimal control to obtain a T-cell count after 10 years of nearly 300 greater than the maximal control, at one-fourth the use of anti-viral medications. Also notice that the optimal T-cell count trajectory does not descend below the 200 cells per μL threshold to the development of AIDS, whereas the trajectory without control does.

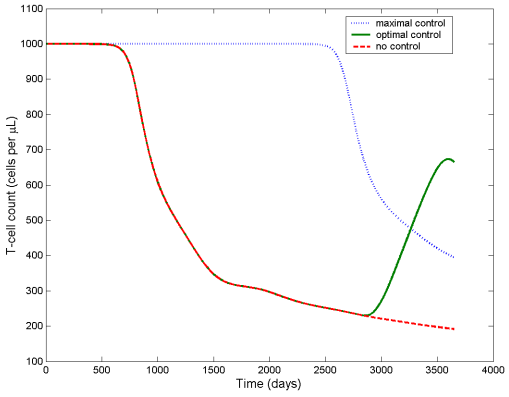

Figure 1: T-cell counts over time for maximal control, optimal control, and no control for minimum drug usage and maximum T-cell count after 10 years. The optimal control T-cell trajectory is shown for the optimal control $u^\star_{RTI} = u^\star_{PI} = [0, 0, 0, 0, 0, 0, 0, 0, 1, 1]^T$

4 Discussion

We have presented an existing model for HIV infection and then expanded it to consider a mutating viral population. We then established how drug therapy would interact with the model, and applied a numerical optimal control procedure to find the normalized dosage of RTI and PI drugs as a function of time such that a maximum T-cell count would be obtained after 10 years with minimum drug use. We found that the T-cell count could be best improved by drug treatment only if treatment were witheld until the last third of the 10-year treatment period. This finding is consistent with the idea that medication against viral infection should not be administered when the immune system's natural defenses are combating the virus, as drug usage during this time would only lead to the development of escape mutants in the viral population.

Our analysis is specifically designed for a 10-year treatment period. Extending this analysis to a longer treatment period would be difficult because a more sophisticated function $N(t)$ would need to be developed. With the model in its present state, we would not be able to control the HIV infection for much longer as the drug efficacy begins to decrease as soon as medication is administered.

However, we have succeeded in controlling a virulent HIV infection for a period of 10 years with minimal drug therapy. Havlir and Richman [5] have suggested that after anti-viral drug efficacy has substantially decreased, the anti-HIV therapy can be

switched to another combination of RTI and PI drugs. This method may allow the development of a new optimal therapy over the next treatment period. However, the suggestion of these authors of using large drug dosages early during infection may not be prudent, in light of our numerical results, due to the tendency of this approach to foster the development of escape mutants.

Our preliminary results indicate that substantially more accurate models of HIV infection consider viral mutants that develop as a result not only of pharmacological control, but also immune control. Unfortunately, this modelling necessitates the use of a 16-dimensional dynamical model, which proved computationally prohibitive to control using the control procedure described above. We also desire a computationally tractable control procedure that can deal with the mismatch between our interest in the system's development over years and the day-scale operational time constants of the system. An improved method must be used which allows the control to change on the same time-scale as the virus. These two computational pitfalls necessitate further work.

We have explored a numerically-robust method of deriving optimal drug dosages to fight HIV infection. We have also demonstrated the potential of a control method to consider viral systems that mutate in response to drug administration.

5 References

1. Coffin, J.M., *Science* , 267: 483, 1995.

2. de Boer, R.J., Perelson, A.S., *Journal of Theoretical Biology,* 190: 201-214, 1998.

3. Finzi, D. et al., *Science,* 278: 1295-1300, 1997.

4. Flint, S.J, Enquist, L.W., Krug, R.M., Racaniello, V.R., Skalka, A.M. *Principles of Virology.* Washington: ASM Press, 2000.

5. Havlir, D.V., Richman, D.D., in *Immunopathogenesis of HIV infection,* Pantaleo, G. and A.S. Fauci, eds., Berlin: Springer-Verlag, 1997.

6. Kirschner, D., Lenhart, S., Serbin, S., *Journal of Mathematical Biology* , 35: 775-792, 1997.

7. How HIV Causes AIDS, *from the National Institute of Allergy and Infectious Disease* (NIAID), http://www.niaid.nih.gov/factsheets/howhiv.htm

8. Pandy, M.G., Anderson, F.C., Hull, D.G., *Journal of Biomechanical Engineering,* 114: 450-460, 1992.

9. Pantaleo, G., Graziosi, C., Fauci, A.S., in *Immunopathogenesis of HIV infection,* Pantaleo, G. and A.S. Fauci, eds., Berlin: Springer-Verlag, 1997.

10. Perelson, A.S., Kirschner, D.E., de Boer, R., Dynamics of HIV Infection of CD4+ T cells, *Mathematical Biosciences* , 114: 81-125, 1993.

11. Richman, D.D., The implication of drug resistance for strategies of combination antiviral chemotherapy, *Antiviral Research,* 29: 31-33, 1996.

12. Stafford, M.A., Corey, L., Cao, Y., Daar, E.S., Ho, D.D., Perelson, A.S., *Journal of Theoretical Biology,* 203: 285-301, 2000.

13. Stengel, R.F., Ghigliazza, R., Kulkarni, N., Laplace, O., *Proceedings of the 2001 American Control Conference* .

14. Wein, L.M., D'Amato, R.M., Perelson, A.S., *Journal of Theoretical Biology,* 192: 81-98, 1998.