Control Strategies for HIV Infected systems

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1 Introduction

HIV (Human Immunodeficiency Virus) attacks certain types of cells in human body, particularly the CD4+ T helper 1 (Th1) lymphocytes. Th1 has a central role in adaptive immune response by helping the function of other immune cells. For example, Th1 helps activate the antigen-specific CD8+ cytotoxic T lymphocytes (CTL). HIV infection causes a decline in Th1 activity which eventually leads to symptomatic stage of infection known as AIDS (Acquired Immunodeficiency Syndrome). Center for Disease Control and Prevention (CDC) reported that by the end of 2012 in the United States, 1,194,039 people have been diagnosed with AIDS with a cumulative death toll reaching 658,507 [1]. AIDS patients have an increased risk of common and opportunistic infections which rarely affects people with normal, working immune system. Therefore, HIV infection is a major health problem which necessitates the development of effective treatment strategies.

Recently, HAART (Highly Active Antiretroviral Therapy) has been successful in reducing AIDS-related death and complications. HAART consists of multiple drugs that act on different viral targets. Treating a newly infected person using HAART can rapidly reduce the initial burst of virus replication and preserve TH1 cell population. However, it can also lessen the intensity of the CTL response, thus creating an incomplete immune response. Some researchers have proposed the notion of interrupted drug treatment during primary (acute) infection[2]. This strategy is based on the idea that periodic and transient increases in the viral load might re-stimulate the waning HIV-specific CTL response. Supposing this method of treatment is successful, it also promises considerable decreases in medication costs over more regular treatment protocols. In this work, we consider treatment of both the interrupted and continuous type and weigh their merits. For each treatment variation, we propose a control strategy $u(t)$ to drive the system into a healthy state with a safe number of healthy T cells and minimal viral load.

2 Interrupted treatment control

In order to investigate the effectiveness of the structured treatment interruption (STI) method, we consider the coupled ODE model proposed by [3]:

$$\begin{aligned}
\dot{\mathbf{x}} &= \lambda - d\mathbf{x} - \beta(1-\eta u)\mathbf{xy} \\
\dot{\mathbf{y}} &= \beta(1-\eta u)\mathbf{xy} - a\mathbf{y} - p_1\mathbf{z_1 y} - p_2\mathbf{z_2 y} \\
\dot{\mathbf{z_1}} &= c_1\mathbf{z_1 y} - b_1\mathbf{z_1} \\
\dot{\mathbf{w}} &= c_2\mathbf{xyw} - c_2 q\mathbf{yw} - b_2\mathbf{w} \\
\dot{\mathbf{z_2}} &= c_2 q\mathbf{yw} - h\mathbf{z_2}.
\end{aligned}$$

Where $\mathbf{x}$ = healthy Th1 cells, $\mathbf{y}$ = infected Th1 cells, $\mathbf{z_1}$ = helper-independent CTL, $\mathbf{w}$ = CTL precursors, $\mathbf{z_2}$ = helper-dependent CTL, u is equal to 1 when we treatment takes place and 0 in the absence of treatment.

The control problem can be rephrased as a minimization of finite horizon objective function

$$V(X_k, U) = \sum_{i=k}^{k+N-1} l(X_i, u_i) + F(X_{k+N})$$

where $l(X_i, u_i) = \alpha_1(x_i - \hat{x})^2 + \alpha_2(w_i - \hat{w})^2 + \alpha_3|u_i|$, $F(X_k) = \alpha_1(x_k - \hat{x})^2 + \alpha_2(w_k - \hat{w})^2$, and the α_i are constants.

In order to best simulate an interrupted treatment protocol, we allow only $u = 0$ (no treatment) or $u = 1$ (full treatment). Every seven days, exhaustive search is used to find the set of U that minimizes the cost function for the next 6 weeks. In a dynamic fashion, we permit treatment for one week, and then propose a new strategy for the following week according to our objective. Results for simulation of a deterministic system are shown in FIG.1a. Integration is done using Adams-Bashforth 2 method. For the system $\dot{\vec{x}} = F(\vec{x})$, the scheme is $\vec{x}_{n+1} = \vec{x}_n + (1.5F(\vec{x}_n) - 0.5F(\vec{x}_{n-1}))\Delta t$.

In order to investigate the robustness of this control technique, we introduce noise to the measured parameters each week and investigated the resulting number of weeks we need for the treatment. For each point, 100 iterations were performed, and the results are shown in Fig.1b.

We also consider a modified treatment interruption that allows 3 different possibilities for u: $\{0, 0.5, 1\}$. As can be seen in 1c. we find that we need slightly more time for the treatment, although each concentration of interest proceeds to the steady state in less time. We note that the same effect can be achieved by increasing the values of α_1 and α_2 in the cost function, which more harshly penalizes deviations from the desired steady-state.

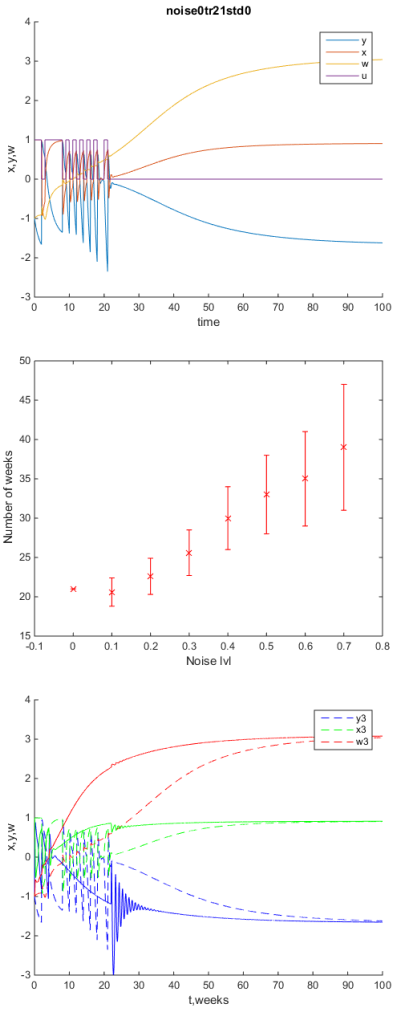

Figure 1: (a) Typical x, y, w vs time plot, (b) Number of weeks required for treatment versus noise level, (c) Comparison of 3-possibility treatment vs. 2-possibility treatment

Since the actual biological system is not actually a deterministic process, we also considered a stochastic approach to simulating the system. Propagation of the system forward in time is achieved through the Tau-leaping approximation to the Gillespie Algorithm. Dynamic control is performed in the same way as before, using a deterministic model to exhaustively search for the optimal control in the coming six weeks.

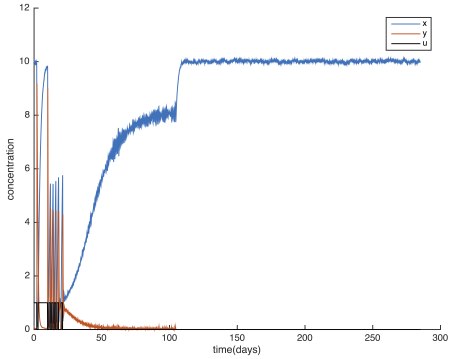

Figure 2: Eradication of virus can be achieved with treatment early in disease progression

In this analysis, we see that for large numbers of T cells and virus initially present, the system begins to approach the behavior of the deterministic system. However, for lower numbers of cells (both T cells and virus) in the system initially present ($\approx 10^6$ in total) we find that the system is often able to eradicate the virus as it fluctuates while approaching the desired steady state. Instead, a new steady state is reached, where the system is fully recovered and no virus remains as shown in Figure 2. Many researchers have argued that early application of HAART may have this effect, which is well demonstrated by the model[8].

While this is certainly is a promising result, it is important to notice that viral mutations and CTL loss can occur during this vacation of treatment, leading to troubling patient outcomes in practice [9]. However, to our knowledge an interrupted treatment regimen with as precise a control as used in our experiment has not been used, instead opting for switching between full and zero treatment every two to eight weeks.

3 Continuous control

We also consider a more traditional approach to this treatment optimization problem by allowing the control parameter to take any value between 0 and 1. We perform this analysis on the an example system described in [4]:

$$\frac{dT}{dt} = \frac{s}{1+V} - \mu_T T + rT\left(1 - \frac{T+T^*+T^{**}}{T_{max}}\right) - k_1 VT$$

$$\frac{dT^*}{dt} = k_1 VT - \mu_T T^* - k_2 T^*$$

$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_b T^{**}$$

$$\frac{dV}{dt} = u(t) N \mu_b T^{**} - k_1 VT - \mu_V V$$

Where T = healthy T cells, T^* = latently infected T cells, T^{**} = actively infected T cells, and V = viral load. Here, we only consider a deterministic model, for

which we propose a single optimal control over a 500 day period using the objective function

$$J(u) = \int_0^{500} T(t) - \frac{1}{2}B(1-u(t))^2 dt$$

where $B = 100$ in our experiment. It is worth noting that we have now switched the meaning of our control parameter (i.e. u=1 now means no control).

Solving this constrained optimization problem requires the formulation of a Lagrangian from the integrand of the objective

$$\begin{aligned} L(T, T^*, T^{**}, V, u, \lambda_1, \lambda_2, \lambda_3, \lambda_4) &= T(t) - \frac{1}{2}B(1-u(t))^2 \\ &+ \lambda_1\left(\frac{s}{1+V} - \mu_T T + rT\left(1 - \frac{T+T^*+T^{**}}{T_{max}}\right) - k_1 VT\right) \\ &+ \lambda_2(k_1 VT - \mu_T T^* - k_2 T^*) + \lambda_3(k_2 T^* - \mu_b T^{**}) \\ &+ \lambda_4(u(t)N\mu_b T^{**} - k_1 VT - \mu_V V) + \omega_1 u(t) + \omega_2(1-u(t)). \end{aligned}$$

The variational problem can then be solved numerically using Pontryagin's maximum principle, along with the constraint that $\lambda_i(500) = 0$. The results are shown in Figure 3.

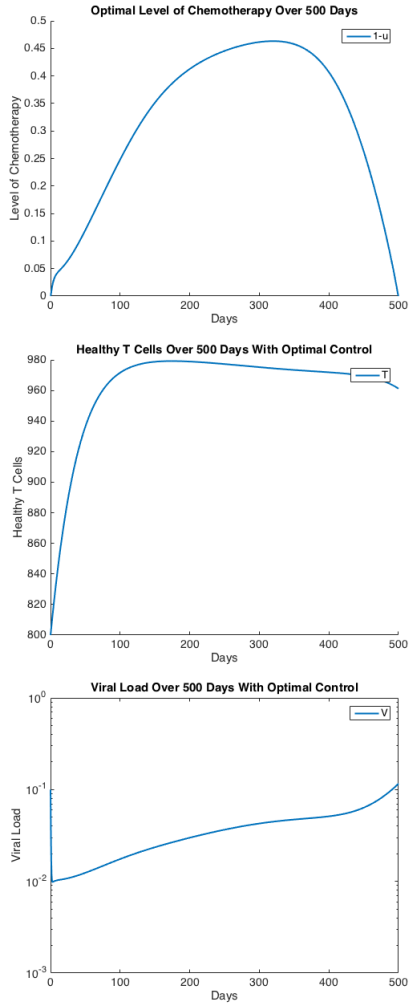

Figure 3: Optimal control (top) and resulting T cell (center) and virus concentrations (bottom)

In Figure 3, we see that considerable increase of T cell count and depletion of viral load is possible, although we do not approach a sustainable immune state. That is, unless the control parameter is less than $u_c \approx .65$, the healthy steady state is not stable. This indicates that continued treatment of patients will be necessary after 500 days. It is important to notice that our treatment strategy does not resemble the switch-like control of the interruption technique, indicating that such a strategy would be less successful at satisfying the objective over the treatment period.

4 Conclusion

In this work, continuous and discrete interrupted control techniques were investigated. It was shown that interrupted control technique is able to drive the system into the healthy steady-state sufficiently fast even in the presence of high noise in the measured parameters. The control technique with 3 different possibilities for treatment was compared to the conventional bang-bang control technique. A considerable finding was achieved using a stochastic model that indicates a potential technique for viral eradication if HAART is applied sufficiently early in the treatment period. However, the poor performance of the classic interrupted control strategy in practice indicates that the virus may be able to mutate during drug vacations, potentially adding additional complications not described by the model. The continuous control strategy brings a more realistic simulation, which indicates the necessity of a lifelong treatment. Nonetheless, this technique causes an immediate decline in viral load that can be sustained with continued treatment.

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