Dynamic Multidrug Therapies for HIV: Optimal and STI Control Approaches

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Dynamic Multidrug Therapies for HIV: Optimal and STI Control Approaches

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Abstract

We formulate a dynamic mathematical model that describes the interaction of the immune system with the human immunodeficiency virus (HIV) and that permits drug "cocktail" therapies. We derive HIV therapeutic strategies by formulating and analyzing an optimal control problem using two types of dynamic treatments representing reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). Continuous optimal therapies are found by solving the corresponding optimality systems. In addition, using ideas from dynamic programming, we formulate and derive suboptimal structured treatment interruptions (STI) in antiviral therapy that include drug-free periods of immune-mediated control of HIV. Our numerical results support a scenario in which STI therapies can lead to long term control of HIV by the immune response system after discontinuation of therapy.

1 Introduction

Significant progress has been made in the treatment of human immunodeficiency virus (HIV) infected patients, resulting in improved quality of life and greater longevity. Due to advances in available drug treatments and their combination in "drug cocktails," many patients successfully maintain low viral load and safely high T-cell counts for months or even years.

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There are more than twenty FDA-approved anti-HIV drugs currently available, most falling into one of two categories: reverse transcriptase (RT) inhibitors and protease inhibitors (PIs). Hijacking a $CD4^+$ target cell is a crucial part of the viral life cycle, as HIV uses a host cell to replicate itself and thus proliferate. RT inhibitors prevent HIV RNA from being converted into DNA, thus blocking integration of the viral code into the target cell. On the other hand, protease inhibitors affect the viral assembly process in the final stage of the viral life cycle, preventing the proper cutting and structuring of the viral proteins before their release from the host cell. Protease inhibitors therefore effectively reduce the number of infectious virus particles released by an infected cell. While anti-retroviral treatment regimens are sometimes augmented by other types of drugs that enhance the effect of anti-HIV treatment, bolster the immune system, or reduce side effects, our current effort focuses on representatives of the two main classes – RTIs and PIs.

The most prevalent treatment strategy for acutely infected HIV patients is highly active anti-retroviral therapy (HAART) which utilizes two or more drugs. Typically these drug cocktails consist of one or more RT inhibitors as well as a protease inhibitor. Despite the great success of these multi-drug regimens in reducing and maintaining viral load below the limit of detection in many patients, their long-term use comes with substantial complications. Patients taking these drugs experience many common and some grave pharmaceutical side effects, which sometimes lead to poor adherence. Typically HIV (a retrovirus) mutates and produces resistant strains that are no longer sensitive to drug therapy, resulting in the need to change drug or even the inability to find pharmaceuticals that provide effective treatment. In addition, high drug cost and complicated pill regimens make effective HAART use burdensome for some patients and impossible for others who have limited access to anti-HIV drugs.

Concerns about the long-term use of anti-retroviral therapy strongly motivate the consideration of optimal schemes for its use. There is also evidence that cytotoxic T-lymphocytes (CD8 immune effector cells) and other immune responders are key players in determination of viral load set-points. Their prevalence and strength are also believed to be correlated to the rate of disease progression, thus further motivating investigation of treatment strategies that aim to boost adaptive cellular immune responses [21, 26]. One such strategy is structured treatment interruption (STI), a regimen in which patients are cycled on and off therapy [4, 13, 17]. An STI offers the patient relief from arduous drug therapy. During treatment interruptions, viral load typically rebounds to a high level, consequently stimulating or reactivating an adaptive immune response. In some remarkable cases, repeated stimulation in this manner has even enabled patients to maintain immune control of virus in the absence of treatment [18].

A number of studies have been conducted to explore the benefits of STIs, but the protocols used and results vary widely. For a concise summary of clinical STI studies, including protocols and results, we refer the reader to [3], in which the authors use a mathematical model to understand these varied outcomes by exploring different treatment schedules and initiation times as well as host factors including strength of immune responses. Some STI studies have used a fixed length, prescribed interruption schedule,

while others used viral load and T-cell measurements from patients to decide when to interrupt or resume therapy (see, e.g., [24, 17]). There is currently no consensus on which treatment strategies or interruption schemes are optimal. One way to explore optimal schemes is in the context of a mathematical model for HIV infection. In our efforts we investigate such optimal therapy strategies using a system of ordinary differential equations (ODEs) which model HIV infection dynamics, in conjunction with both continuous and discrete control theory. Among our results, we demonstrate that with this model we can determine and simulate optimal treatment schemes in which a patient moves from a virus dominant to an immune dominant state.

The paper is organized as follows. In Section 2, we describe the mathematical model we use. Our formulation of the control problem and the corresponding optimality system that characterizes the (continuous) optimal control solution is described in Section 3. Numerical results obtained from using a gradient method to solve the optimality system are presented in Section 4. However, our optimal control problem makes two unrealistic demands on the controllers. First, we assume that treatment protocol can be changed in a continuous manner, whereas in practice treatment alterations can only be made periodically (e.g., weekly). Secondly, as discussed previously, continuous therapy is difficult to maintain for long periods due to unintended side effects and possible emergence of drug resistance associated with suboptimal adherence. The complications resulting from life-long and continuous treatment emphasize the need for alternatives. In Section 5, we formulate and derive optimal STI treatments to control HIV and limit drug exposure. Numerical results illustrating the effectiveness of this dynamic and discrete therapeutic strategy are given.

2   Optimal Multidrug Therapies: Model Formulation

There is a wide variety of mathematical models that have been proposed to study various aspects of HIV dynamics as well as effects of anti-HIV therapeutic agents. For example, Callaway and Perelson [7] examined several models to gain insight into the mechanisms responsible for sustained low viral loads. Wein *et al.* [25] developed a model to track the dynamics of uninfected and infected $CD4^+$ T-cells and viral loads while allowing for virus mutations. Agur [2] focused on the tradeoff between the toxicity and efficacy of chemotherapy through cell cycle drug protocols. The paper by Bajaria *et al.* [3] presented numerical simulations of STI based on a mathematical model representing $CD4^+$ T-cell counts and viral loads in two physiological compartments: blood and lymph tissues. Kirschner and Webb [15] developed a model to study timing, frequency and intensity in the chemotherapy of AIDS.

The model we use to demonstrate the optimal treatment of HIV infection is adapted from the model used in [1], where the authors investigated single drug (RT inhibitor only) control. The system of ODEs describing the compartmental infection dynamics is given by

$$
\begin{array}{lll}
\text{Type 1 target:} & \dot{T}_1 = \lambda_1 - d_1 T_1 - (1 - \epsilon_1)k_1 V T_1 & \\[4pt]
\text{Type 2 target:} & \dot{T}_2 = \lambda_2 - d_2 T_2 - (1 - f\epsilon_1)k_2 V T_2 & \\[4pt]
\text{Type 1 infected:} & \dot{T}_1^* = (1 - \epsilon_1)k_1 V T_1 - \delta T_1^* - m_1 E T_1^* & \\[4pt]
\text{Type 2 infected:} & \dot{T}_2^* = (1 - f\epsilon_1)k_2 V T_2 - \delta T_2^* - m_2 E T_2^* & (2.1) \\[4pt]
\text{Virus:} & \dot{V} = (1 - \epsilon_2)N_T \delta(T_1^* + T_2^*) - cV & \\[4pt]
& \qquad\quad - [(1 - \epsilon_1)\rho_1 k_1 T_1 + (1 - f\epsilon_1)\rho_2 k_2 T_2]V & \\[4pt]
\text{Immune effectors:} & \dot{E} = \lambda_E + \dfrac{b_E(T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b}E - \dfrac{d_E(T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d}E - \delta_E E, &
\end{array}
$$

with specified initial values for T_1, T_2, T_1^*, T_2^*, V and E at time $t = t_0$. This model includes the key compartments observed in clinical data sets available to us: target cells (uninfected T_i and infected T_i^*, *cells/ml*), free virus (V, *copies/ml*), and immune response (CTL E, *cells/ml*). The model describes two co-circulating populations of target cells, potentially representing $CD4^+$ T-lymphocytes (T_1) and macrophages (T_2). We omit explanation of the source and death rates for these cell populations and rather focus our discussion on the interactions particularly relevant to drug treatment and STI scenarios. We discuss the model in the context of its representations of three methods for controlling infection: (1) reverse transcriptase inhibitors, (2) protease inhibitors, and (3) host adaptive immune responses. For a more detailed discussion of this model, see [7, 1].

The terms involving $k_i T_i V$ represent the infection process wherein infected cells T_i^* result from encounters between uninfected target cells T_i and free virus V. The key difference between the two cell populations is in the infectivity rates k_1 and k_2, which could represent the difference in activation requirements for these types of cells. The model admits the possibility of multiple (ρ_i) virions infecting each target cell. In the infectivity terms, the drug efficacy $\epsilon_1(t)$ models an RT inhibitor that blocks new infections and is potentially more effective in population 1, (T_1, T_1^*), than in population 2, (T_2, T_2^*), where the efficacy is $f\epsilon_1(t)$. We consider $0 \le a_1 \le \epsilon_1(t) \le b_1 < 1$, so a_1 and b_1 represent minimal and maximal drug efficacy, respectively, and $f \in [0, 1]$.

Both types of infected cells produce free virus particles. We assume that the two types produce the same number, N_T, of free viral particles during a typical T_i cell life span. The control term $\epsilon_2(t)$ represents the efficacy of protease inhibitors. Thus, the productivity, N_T, is reduced to $(1 - \epsilon_2)N_T$ where $0 \le a_2 \le \epsilon_2(t) \le b_2 < 1$. We do not add a compartment to explicitly model the production of virus rendered non-infectious by the PIs.

Finally, infected cells T_i^* may be cleared via the action of immune effector cells (cytotoxic T-lymphocytes – CTLs), denoted by E. While the majority of the model is adapted from [7], the dynamics $\dot{E}$ for the immune response are as suggested by Bonhoeffer, *et al.* [4]. The joint presence of infected cells and existing immune effector cells stimulates the proliferation of additional effector cells. In addition, the third term in the $\dot{E}$ equation

represents immune impairment at high virus load. CTL detect and lyse infected cells, thus killing them, so their action is represented by the terms $m_i E T_i^*$ (infected cells die at rate $m_i E$, dependent on the density of immune effectors). Inclusion of immune effectors reflects the belief that they have a crucial role in the context of STIs and we will later show treatment strategies that boost them to the point of immune control.

The mathematical model (2.1) contains numerous parameters that must be assigned before numerical simulations can be carried out. In specifying model parameters, to the greatest extent possible we employ values similar to those reported or justified in the literature. The definitions and numerical values for the parameters are summarized in Table 2, which are principally extracted from the Callaway-Perelson [7] and Bonhoeffer, *et al.* [4] papers.

parameter	value	units	description
λ_1	10,000	$\frac{cells}{mL \cdot day}$	target cell type 1 production (source) rate
d_1	0.01**	$\frac{1}{day}$	target cell type 1 death rate
ϵ_1	$\in [0,1)$	–	efficacy of reverse transcriptase inhibitor
ϵ_2	$\in [0,1)$	–	efficacy of protease inhibitor
k_1	8.0×10^{-7}	$\frac{mL}{virions \cdot day}$	population 1 infection rate
λ_2	31.98	$\frac{cells}{mL \cdot day}$	target cell type 2 production (source) rate
d_2	0.01**	$\frac{1}{day}$	target cell type 2 death rate
f	0.34 ($\in [0,1]$)	–	treatment efficacy reduction in population 2
k_2	1×10^{-4}	$\frac{mL}{virions \cdot day}$	population 2 infection rate
δ	0.7*	$\frac{1}{day}$	infected cell death rate
m_1	1.0×10^{-5}	$\frac{mL}{cells \cdot day}$	immune-induced clearance rate for population 1
m_2	1.0×10^{-5}	$\frac{mL}{cells \cdot day}$	immune-induced clearance rate for population 2
N_T	100*	$\frac{virions}{cell}$	virions produced per infected cell
c	13*	$\frac{1}{day}$	virus natural death rate
ρ_1	1	$\frac{virions}{cell}$	average number virions infecting a type 1 cell
ρ_2	1	$\frac{virions}{cell}$	average number virions infecting a type 2 cell
λ_E	1	$\frac{cells}{mL \cdot day}$	immune effector production (source) rate
b_E	0.3	$\frac{1}{day}$	maximum birth rate for immune effectors
K_b	100	$\frac{cells}{mL}$	saturation constant for immune effector birth
d_E	0.25	$\frac{1}{day}$	maximum death rate for immune effectors
K_d	500	$\frac{cells}{mL}$	saturation constant for immune effector death
δ_E	0.1*	$\frac{1}{day}$	natural death rate for immune effectors

Table 1: Parameters used in model (2.1). Those in the top section of the table are taken directly from Callaway and Perelson. Parameters in the bottom section of the table are adapted from those in Bonhoeffer, *et al.*. The superscripts * denote parameters the authors indicated were estimated from human data and ** denote those estimated from macaque data.

Our model choice is in part motivated by its admission of multiple stable steady states or equilibrium points. This qualitative feature enables us to more accurately

model patients such as the "Berlin Patient" [18], who interrupted treatment twice and then controlled viral infection without further need for drugs, or some of those referenced by the extensive STI literature summary offered by Bajaria, *et al.* [3], which points to examples in which some patients have developed immune responses sufficient to control infection whereas in others the virus rebounded and again decimated the immune system. For example, in a study of HAART discontinuation [22], three of six patients successfully suppressed plasma virus for four to more than twenty-four months after stopping treatment. These patients exhibited comprehensive and strong HIV-specific immune responses, which are believed responsible for containment of the infection. Other patients failed to contain virus at all. Rosenberg, *et al.* reported on eight subjects in an interruption study [23]. Five of the eight subjects remained off therapy, maintaining viral load less than 500 copies/mL for five to nine months. These subjects exhibited increased CTL and T-helper cell responses. When studying the STI scenario, it is crucial that the mathematical model for HIV infection used be able to represent these different outcomes.

Other authors have considered similar mathematical models with the use of STI to transfer the system between locally stable equilibria or steady states representing "unhealthy" (high viral setpoint, small immune responses) versus "healthy" endpoints for the patient. Bonhoeffer, *et al.* [4] explore a model including uninfected target cells, actively and latently infected target cells, and immune response. They provide qualitative analysis including conditions on the model equilibria that will produce each of the two possible outcomes. Wodarz and Nowak [26] analyze a model with compartments for uninfected and infected T cells and cytotoxic T lymphocyte precursors (memory) and effector immune cells. They include analytic expressions for the possible model steady states as well as analytic conditions on the model parameters that indicate which of the equilibria will be stable.

A general analytical analysis of our model (2.1)'s steady states and their local stability is challenging due to the form and number of the nonlinearities. However we are still interested in the ability of the model to exhibit multiple locally asymptotically stable steady states, so we calculate the steady states and perform a standard linearization and eigenvalue analysis of the model, given the numerical values of the parameters specified above.

Letting $x = (T_1, T_2, T_1^*, T_2^*, V, E)$ denote the vector of model states, we may represent the model (2.1) as

$$\frac{dx(t)}{dt} = f(t, x; q), \tag{2.2}$$

where $f(t, x; q)$ is the right side of the ODE system and q is the vector of model parameters listed in Table 1. Given the parameter values in Table 1, we invoke Maple to solve $f(t, x; q) = 0$ for the steady states (equilibria) $\bar{x}_k$. We next calculate the jacobian matrix (matrix of partial derivatives of the right sides of the differential equations with respect to the state variables):

$$\frac{\partial f(t, x; q)}{\partial x} = \left[\frac{\partial f_i(t, x; q)}{\partial x_j} \right]$$

of the ODE system. We set $\epsilon_1 = \epsilon_2 = 0$, since we are interested in stability for the

6

off-treatment steady state values. The jacobian matrix is:

$$
\begin{bmatrix}
-d_1 - k_1 V & 0 & 0 & 0 & -k_1 T_1 & 0 \\
0 & -d_2 - k_2 V & 0 & 0 & -k_2 T_2 & 0 \\
k_1 V & 0 & -\delta - m_1 E & 0 & k_1 T_1 & -m_1 T_1^* \\
0 & k_2 V & 0 & -\delta - m_2 E & k_2 T_2 & -m_2 T_2^* \\
-\rho_1 k_1 V & -\rho_2 k_2 V & N_T \delta & N_T \delta & -c - \rho_1 k_1 T_1 - \rho_2 k_2 T_2 & 0 \\
0 & 0 & A_{6,3} & A_{6,4} & 0 & A_{6,6}
\end{bmatrix},
$$

where

$$
A_{6,3} = A_{6,4} = \frac{b_E K_b E}{(T_1^* + T_2^* + K_b)^2} - \frac{d_E K_d E}{(T_1^* + T_2^* + K_d)^2},
$$

and

$$
A_{6,6} = \left(\frac{b_E}{T_1^* + T_2^* + K_b} - \frac{d_E}{T_1^* + T_2^* + K_d} \right)(T_1^* + T_2^*) - \delta_E.
$$

Substituting a computed steady state $\bar{x}_k$ for x in this jacobian matrix, we obtain the ODE system dynamics linearized about the equilibrium $\bar{x}_k$. Linear ODE theory guarantees that if the eigenvalues of this matrix all have negative real parts, the equilibrium $\bar{x}_k$ is locally asymptotically stable.

Given the specified parameters, the model (2.1) exhibits three physical steady states and several non-physical steady states (omitted here) where one or more state variables are negative. There is a locally unstable equilibrium

$$
T_1 = 1000000,\ T_2 = 3198,\ T_1^* = 0,\ T_2^* = 0,\ V = 0,\ E = 10,
$$

which represents an uninfected patient, as well as two locally stable equilibria for an infected patient in the absence of treatment. These stable steady states are:

"unhealthy": $T_1 = 163573,\ T_2 = 5,\ T_1^* = 11945,\ T_2^* = 46,\ V = 63919,\ E = 24;$

"healthy": $T_1 = 967839,\ T_2 = 621,\ T_1^* = 76,\ T_2^* = 6,\ V = 415,\ E = 353108.$

Here the "unhealthy" steady state corresponds to a dangerously high viral set point, depleted T-cells, and minimal immune response, whereas the "healthy" steady state represents immune control of the viral infection and restoration of T-cell help. Our current work includes consideration of optimal strategies for effecting a transfer between these steady states.

The existence and local stability of these equilibria (and indeed the size of their domains of attraction) of course depend on the values of the parameters chosen. Across a population, the parameter values will vary to represent different host factors and host-virus interaction rates. For example, the infectivity rates k_1 and k_2 are crucial determinants of the viral load set point. If they are reduced to 10% of their values in the table, the only stable equilibria are those corresponding to the uninfected scenario (i.e., clearance of the virus) and one nonphysical steady state. If host immune responsiveness to infection is increased only by setting $b_E = 0.4$, the lone stable steady state is

$$
T1 = 983080,\ T2 = 1015,\ T1s = 38,\ T2s = 5,\ V = 215,\ E = 377553,
$$

and the immune system controls the persistent viral infection without further treatment. Lori, *et al.* [19] describe variation across patients in length of time until and strength of viral rebound when studying patients with STI. The dependence of the model behavior on crucial parameters and their subsequent estimation for individuals may help us predict not only these variations and those in the studies cited above, but also the expected responses to a specific treatment protocol.

In summary, the discussions above and subsequent results in this paper provide support for the following plausible scenario (depicted in Figure 1) with respect to the response (and its variability across patients) of HIV patients to treatment protocols. Patients may possess multiple locally
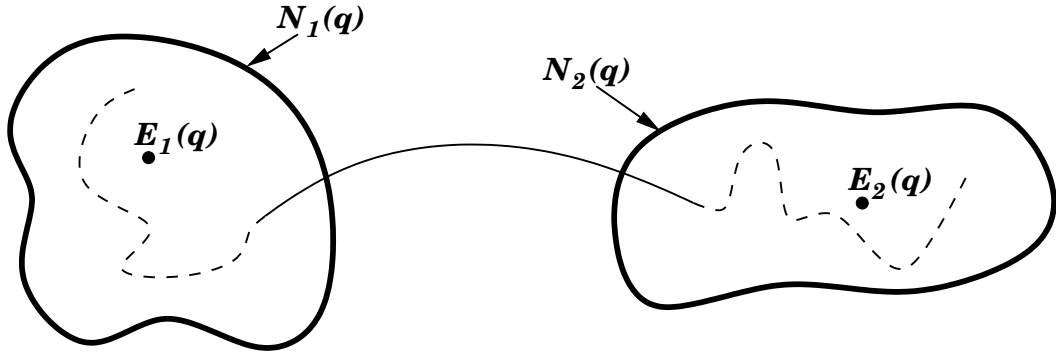

Figure 1: $E_1(q)$: "unhealthy" locally asymptotically stable equilibrium point with its domain of attraction $N_1(q)$; $E_2(q)$: "healthy" locally asymptotically stable equilibrium point with its domain of attraction $N_2(q)$; (- - -) uncontrolled trajectory; (—) controlled trajectory.

asymptotically stable equilibrium states $E_i(q)$ which depend on individual patient parameter values q. The corresponding regions or domains of attraction $N_i(q)$ for these equilibria also depend on the individual patient's parameter values. When undergoing treatment (HAART), whether continuous or STI, the patient's system may be moved from one domain of attraction to another. Since the regions of attraction (as well as the rates of attraction) vary across populations (the inter-individual variability mentioned above for existence and stability of equilibria), the same treatment protocol may very well produce different outcomes (e.g., strength of and length of time until viral rebound after treatment discontinuation) in different patients. A type of intra-individual variability (perhaps a misnomer here) may also play a role since the equilibria (and their regions of attraction) may depend on latent or unmodeled parameters that change within the patient with respect to time or state of health. This may manifest itself in the perceived variability of both critical time for initiation of HAART and patient response to discontinuation. Model simulations as well as analytical studies can assist in conceptual understanding of such phenomena where clinical and experimental investigations exploring these issues are often difficult if not impossible to pursue.

3 Control Formulation

Together with the mathematical model described by equation (2.1) for HIV dynamics, we consider a control problem with the objective function given by

$$J(\epsilon_1, \epsilon_2) = \int_{t_0}^{t_1} [QV(t) + R_1\epsilon_1^2 + R_2\epsilon_2^2 - SE(t)]\, dt, \tag{3.1}$$

where ϵ_1 and ϵ_2 are the control variables representing RTIs and PIs, respectively. The parameters Q, R_1, R_2 and S are weight constants for the virus, controls inputs, and immune effectors, respectively. The second and third terms in (3.1) represent systemic costs of the drug treatments (i.e., severity of unintended side effects as well as treatment cost). The case when $\epsilon_1(t) = b_1$ represents maximal use of RT inhibitors and $\epsilon_2(t) = b_2$ represents maximal use of protease inhibitors. The objective function (3.1) expresses our goal to minimize both the HIV population and systemic costs to body while maximizing immune response. Therefore, we seek an optimal control pair $(\epsilon_1^*, \epsilon_2^*)$ such that

$$J(\epsilon_1^*, \epsilon_2^*) = \min\{J(\epsilon_1, \epsilon_2) | (\epsilon_1, \epsilon_2) \in U\}$$

subject to the system of ODEs (2.1) and where $U = \{(\epsilon_1, \epsilon_2) | \epsilon_i$ is measurable, $a_i \leq \epsilon_i \leq b_i, t \in [t_0, t_1]$, for $i = 1, 2\}$ is the control set.

A number of researchers have used a control theoretic approach to formulate and study dynamic drug therapies for HIV-infected individuals. However, these investigators based their studies on other types of mathematical models for HIV dynamics and/or different objective functionals. For example, the studies in [6, 8, 14] for optimal control of the chemotherapy of HIV used an objective function based on a combination of maximizing $CD4^+T$ cell counts while minimizing the systemic cost of chemotherapy. H.R. Joshi [11] considered two different treatment strategies (controls) in a mathematical model consisting of only two states: uninfected $CD4^+T$ cells and viral loads. His controls represent immune boosting and viral suppressing drugs. Another deterministic control problem, proposed by Wein *et al.* [25], is based on a finite number of virus strains and allows mutations from one strain to another. Due to the high dimensionality of the control problem, the authors resort to an approximate method, which employs perturbation methods in conjunction with ideas from dynamic programming to derive a closed form dynamic therapeutic policy. Using numerical simulations, they demonstrated a dynamic strategy that reduces the total free virus, increases the uninfected $CD4^+$ count, and delays the emergence of drug-resistant strains. A similar study by J.J. Kutch and P. Gurfil [16] involves optimal control of HIV infection to derive an optimal drug administration scheme that may be useful in increasing patient health by delaying the emergence of drug-resistant mutant viral strains. Feedback control in HIV-1 populations is explored in [5]. There the authors considered several methods of stable control of the HIV population using an external feedback control term that is analogous to the introduction of a therapeutic drug regimen. The feedback control, based on periodic sampling of viral load and lymphocyte counts, uses a target tracking approach. Using this regimen design they showed that once the virus is controlled to very low levels the drug dosage can be

reduced proportionately. Under such circumstances it is suggested that side effects of therapy will also be mitigated.

Here we use an open loop control formulation to treat both continuous and STI control of the system (2.1) with the cost functional (3.1).

3.1 The Optimality System

We begin this section by noting that the existence of an optimal control pair can be obtained using a result from Fleming and Rishel [9]. That is, it is rather straightforward to show that the right sides of the equation (2.1) are bounded by a linear function of the state and control variables and that the integrand of the objective function (3.1) is concave on U and is bounded below. These bounds give one the compactness needed to establish existence of the optimal controls using standard arguments given in [9].

We now proceed to compute candidates for optimal controls. To this end, we apply the Pontryagin Minimum Principle and begin by defining the Lagrangian (which is the Hamiltonian augmented with penalty terms for the constraints) to be:

$$
\begin{aligned}
L&(T_1, T_2, T_1^*, T_2^*, V, E, \epsilon_1, \epsilon_2, \xi_1, \xi_2, \xi_3, \xi_4, \xi_5, \xi_6) \\
&= QV + R_1\epsilon_1^2 + R_2\epsilon_2^2 - SE + \xi_1\Big(\lambda_1 - d_1T_1 - (1-\epsilon_1)k_1VT_1\Big) \\
&\quad +\xi_2\Big(\lambda_2 - d_2T_2 - (1-f\epsilon_1)k_2VT_2\Big) \\
&\quad +\xi_3\Big((1-\epsilon_1)k_1VT_1 - \delta T_1^* - m_1ET_1^*\Big) \\
&\quad +\xi_4\Big((1-f\epsilon_1)k_2VT_2 - \delta T_2^* - m_2ET_2^*\Big) \\
&\quad +\xi_5\Big((1-\epsilon_2)N_T\delta(T_1^* + T_2^*) - cV \\
&\qquad\qquad -[(1-\epsilon_1)\rho_1k_1T_1 + (1-f\epsilon_1)\rho_2k_2T_2]V\Big) \\
&\quad +\xi_6\Big(\lambda_E + \frac{b_E(T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b}E - \frac{d_E(T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d}E - \delta_E E\Big) \\
&\quad -w_{11}(\epsilon_1 - a_1) - w_{12}(b_1 - \epsilon_1) \\
&\quad -w_{21}(\epsilon_2 - a_2) - w_{22}(b_2 - \epsilon_2),
\end{aligned}
\tag{3.2}
$$

where $w_{ij}(t) \geq 0$ are the penalty multipliers satisfying

$$
w_{11}(t)(\epsilon_1(t) - a_1) = w_{12}(t)(b_1 - \epsilon_1(t)) = 0 \quad \text{at } \epsilon_1 = \epsilon_1^*
$$

and

$$
w_{21}(t)(\epsilon_2(t) - a_2) = w_{22}(t)(b_2 - \epsilon_2(t)) = 0 \quad \text{at } \epsilon_2 = \epsilon_2^*.
$$

Here $(\epsilon_1^*, \epsilon_2^*)$ is the optimal control pair yet to be found. Differentiating the Lagrangian with respect to state variables, T_1, T_2, T_1^*, T_2^*, V, and E, respectively, we obtain the following equations for the adjoint variables ξ_i :

$$
\dot{\xi}_1 = -\frac{\partial L}{\partial T_1}, \quad \dot{\xi}_2 = -\frac{\partial L}{\partial T_2}, \quad \dot{\xi}_3 = -\frac{\partial L}{\partial T_1^*}, \quad \dot{\xi}_4 = -\frac{\partial L}{\partial T_2^*}, \quad \dot{\xi}_5 = -\frac{\partial L}{\partial V} \quad \text{and} \quad \dot{\xi}_6 = -\frac{\partial L}{\partial E}.
$$

Using the Lagrangian expression (3.2), we can obtain in a rather straightforward manner the adjoint differential equations

$$
\begin{cases}
\dot{\xi}_1 = -\Big\{\xi_1[-d_1 - (1-\epsilon_1)k_1 V] + \xi_3(1-\epsilon_1)k_1 V - \xi_5(1-\epsilon_1)\rho_1 k_1 V\Big\} \\[4pt]
\dot{\xi}_2 = -\Big\{\xi_2[-d_2 - (1-f\epsilon_1)k_2 V] + \xi_4(1-f\epsilon_1)k_2 V - \xi_5(1-f\epsilon_1)\rho_2 k_2 V\Big\} \\[4pt]
\dot{\xi}_3 = -\Big\{\xi_3(-\delta - m_1 E) + \xi_5(1-\epsilon_2)N_T \delta \\[2pt]
\qquad\quad + \xi_6\Big(\dfrac{b_E E K_b}{(T_1^* + T_2^* + K_b)^2} - \dfrac{d_E E K_d}{(T_1^* + T_2^* + K_d)^2}\Big)\Big\} \\[8pt]
\dot{\xi}_4 = -\Big\{\xi_4(-\delta - m_2 E) + \xi_5(1-\epsilon_2)N_T \delta \\[2pt]
\qquad\quad + \xi_6\Big(\dfrac{b_E E K_b}{(T_1^* + T_2^* + K_b)^2} - \dfrac{d_E E K_d}{(T_1^* + T_2^* + K_d)^2}\Big)\Big\} \\[8pt]
\dot{\xi}_5 = -\Big\{Q - \xi_1(1-\epsilon_1)k_1 T_1 - \xi_2(1-f\epsilon_1)k_2 T_2 + \xi_3(1-\epsilon_1)k_1 T_1 \\[2pt]
\qquad\quad + \xi_4(1-f\epsilon_1)k_2 T_2 + \xi_5\Big(-c - (1-\epsilon_1)\rho_1 k_1 T_1 - (1-f\epsilon_1)\rho_2 k_2 T_2\Big)\Big\} \\[8pt]
\dot{\xi}_6 = -\Big\{-S - \xi_3 m_1 T_1^* - \xi_4 m_2 T_2^* \\[2pt]
\qquad\quad + \xi_6\Big(\dfrac{b_E(T_1^* + T_2^*)}{T_1^* + T_2^* + K_b} - \dfrac{d_E(T_1^* + T_2^*)}{T_1^* + T_2^* + K_d} - \delta_E\Big)\Big\} \\[8pt]
\text{and}\quad \xi_i(t_1) = 0 \quad\text{for } i = 1,\cdots,6.
\end{cases}
\tag{3.3}
$$

Next, we may differentiate the Lagrangian L with respect to ϵ_1 to obtain

$$
\frac{\partial L}{\partial \epsilon_1} = 2R_1 \epsilon_1 + (\xi_1 - \xi_3 + \rho_1\xi_5)k_1 V T_1 + (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2 V T_2 - w_{11} + w_{12} = 0.
$$

Solving for the optimal control we obtain

$$
\epsilon_1^* = \frac{-(\xi_1 - \xi_3 + \rho_1\xi_5)k_1 V T_1 - (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2 V T_2 + w_{11} - w_{12}}{2R_1}.
$$

To determine an explicit expression for the optimal control without w_{11} and w_{12}, we consider the following three cases:

(i) On the set $\{t\,|\,a_1 < \epsilon_1^*(t) < b_1\}$, we have $w_{11}(t) = w_{12}(t) = 0$. Hence the optimal control is

$$
\epsilon_1^* = \frac{-(\xi_1 - \xi_3 + \rho_1\xi_5)k_1 V T_1 - (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2 V T_2}{2R_1}.
$$

(ii) On the set $\{t\,|\,\epsilon_1^*(t) = b_1\}$, we have $w_{11}(t) = 0$. Hence

$$
b_1 = \epsilon_1^* = \frac{-(\xi_1 - \xi_3 + \rho_1\xi_5)k_1 V T_1 - (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2 V T_2 - w_{12}}{2R_1},
$$

which implies that

$$
\frac{-(\xi_1 - \xi_3 + \rho_1\xi_5)k_1 V T_1 - (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2 V T_2}{2R_1} \geq b_1
$$

since $w_{12}(t) \geq 0$.

(iii) On the set $\{t \mid \epsilon_1^*(t) = a_1\}$, we have $w_{12}(t) = 0$. Hence

$$a_1 = \epsilon_1^* = \frac{-(\xi_1 - \xi_3 + \rho_1\xi_5)k_1 V T_1 - (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2 V T_2 + w_{11}}{2R_1},$$

which implies that

$$\frac{-(\xi_1 - \xi_3 + \rho_1\xi_5)k_1 V T_1 - (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2 V T_2}{2R_1} \leq a_1$$

since $w_{11}(t) \geq 0$.

Combining these three cases, the optimal control ϵ_1 is characterized as

$$\epsilon_1^* = \max\left(a_1, \min\left(b_1, \frac{-(\xi_1 - \xi_3 + \rho_1\xi_5)k_1 V T_1 - (\xi_2 - \xi_4 + \rho_2\xi_5)fk_2 V T_2}{2R_1}\right)\right). \quad (3.4)$$

Using similar arguments, we also obtain the following expression for the second optimal control function

$$\epsilon_2^* = \max\left(a_2, \min\left(b_2, \frac{\xi_5 N_T \delta(T_1^* + T_2^*)}{2R_2}\right)\right). \quad (3.5)$$

The optimality system consists of the state system (2.1) coupled with the adjoint system (3.3) with the initial conditions and terminal conditions together with the expressions (3.4) and (3.5) for the control functions.

4 Numerical Results: Continuous Optimal Therapy

We point out that (as is standard in such formulations) initial conditions are specified for the state system (2.1), whereas terminal conditions are specified for the adjoint system (3.3). Therefore the optimality system is a two-point boundary value problem, which we solve numerically using a gradient method. The state system with initial conditions is solved forward in time using initial guesses for the controls and then the adjoint system with terminal conditions is solved backward in time. The controls are updated in each iteration using the formulas (3.4) and (3.5) for optimal controls. The iterations continue until convergence is achieved. For further discussion of this iterative method we refer the interested reader to [10]. The parameters used in solving the optimality system are those summarized in Table 1. Treatment was simulated for 400 days.

We simulate early infection by perturbing the "uninfected" unstable steady state, introducing one virus particle per ml of blood plasma and very low levels of infected T-cells. That is, we take initial conditions $T_1(0) = 10^6$, $T_2(0) = 3198$, $T_1^*(0) = 10^{-4}$, $T_2^*(0) = 10^{-4}$, $V(0) = 1$ and $E(0) = 10$. We bound drug efficacies by $a_1 = 0$, $a_2 = 0$, $b_1 = 0.7$ and $b_2 = 0.3$. Since the magnitudes of the virus population, drug treatment functions, and immune effector population in the objective function (3.1) are on different scales, we balance them by choosing weighting values $Q = 0.1$, $R_1 = 20000$, $R_2 = 20000$, and $S = 1000$.
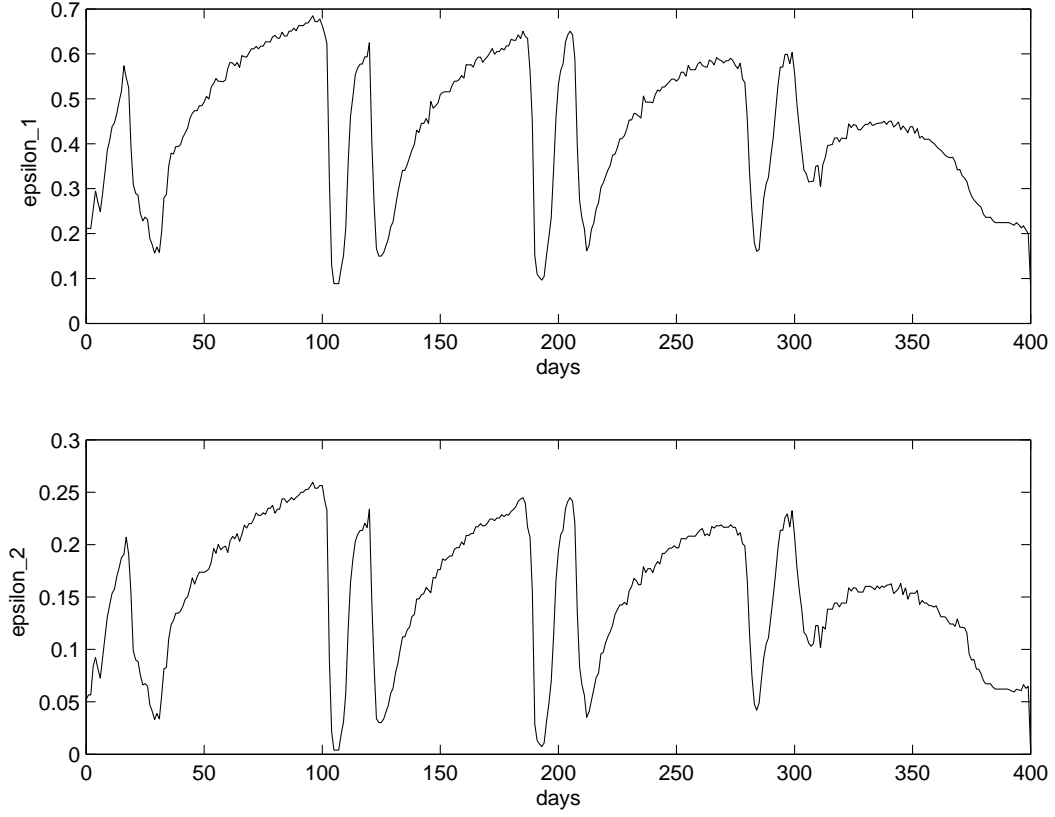
Figure 2: Optimal control pair with $Q = 0.1$, $R_1 = 20000$, $R_2 = 20000$ and $S = 1000$. The label ϵ_1 represents RT inhibitors and ϵ_2 represents protease inhibitors.

The optimal control function pair is depicted in Figure 2. We then determine the system behavior under this regimen by simulating the state equations (2.1). These optimal solutions together with non-optimal solutions corresponding to no drug treatments (i.e., $\epsilon_1 = \epsilon_2 \equiv 0$) and with fully efficacious persistent treatment using both RT inhibitors and protease inhibitors (i.e., $\epsilon_1 \equiv 0.7$ and $\epsilon_2 \equiv 0.3$) are presented in Figure 3 for comparison.

As depicted in Figure 2 the shapes of the two control functions are nearly identical. Perhaps the most intriguing observation from this figure is the STI-like characteristics of the optimal dynamic therapies. In particular, both drugs are tapered off around the 30th, 100th, 200th and 300th days. Consequently, the virus (V) and infected target cells (T_1^* and T_2^*) counts are relatively high around those days (Figure 3). This high virus load, in turn, stimulates the immune effectors (E) in order to boost immune responses.

From Figure 3, we observe that the population of uninfected T_1 cells corresponding to the optimal control pair approaches the population of uninfected T_1 cells with full treatment of both drugs at the end of the time period. Moreover, the virus load with the optimal control pair is maintained at low levels except at the 100th, 200th and 300th
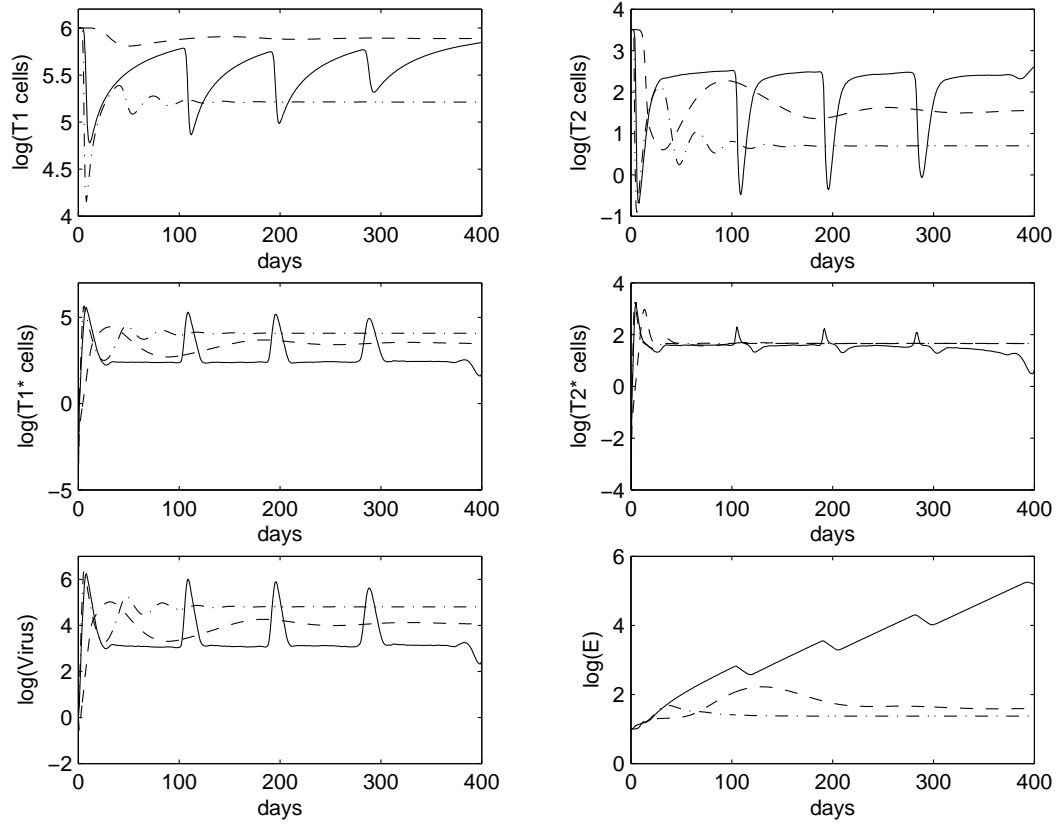
Figure 3: Optimal solutions $(-)$; solutions $(--)$ with fully efficacious treatment of both drugs (i.e., $\epsilon_1 \equiv 0.7$ and $\epsilon_2 \equiv 0.3$); and solutions $(-\cdot)$ with no treatments of both drugs (i.e., $\epsilon_1 = \epsilon_2 \equiv 0$) of early infection: $Q = 0.1$, $R_1 = 20000$, $R_2 = 20000$ and $S = 1000$.

days and is even smaller at the 400th day due to the high immune effectors (E). This happens even though both optimal control functions are very close to zero at the 400th day.

Indeed, our initial numerical results are very promising. They show the potential to design optimal therapeutic options that minimize the total viral load, increase the uninfected $CD4^+$-T cell counts, and boost immune response while allowing patients very brief drug holidays. However, optimal continuous therapy is not practical since in a clinical setting treatment can only be altered at intervals. In the next section, we derive optimal HIV therapeutic strategies that provide clinical benefits similar to those of the continuous treatment while allowing for supervised, or structured, treatment interruption.

5 Optimal STI Therapies

In this section we consider optimal control of viral load through drug structured treatment interruptions (STIs). More precisely, we consider optimal STI control in order to determine the best schedules in which patients are put on and off therapy over predefined periods of time.

Here we assume the (time discretized) controls ϵ_1 and ϵ_2 have vector forms (i.e., are discrete resulting from being either on or off each day) and consist of only 0 or b_i in each component. If a component of a control vector is 0, it indicates drug treatment is off on that day and if it is b_i, it indicates full drug treatment is on. Since we consider a drug treatment strategy over 900 days, the size of each control vector is 1×900. The set of all such control vectors is denoted by Λ. The goal is to seek the optimal control vector pair $(\epsilon_1^*, \epsilon_2^*)$ satisfying

$$\min_{\epsilon_1, \epsilon_2 \in \Lambda} J(\epsilon_1, \epsilon_2) = J(\epsilon_1^*, \epsilon_2^*)$$

subject to the state system (2.1) and where $J(\epsilon_1, \epsilon_2)$ is defined by (3.1).

Since the number of elements of the set Λ is finite, the existence of an optimal control vector pair is guaranteed. We could use a crude direct search approach [1] involving simple comparisons to find the optimal STI control pair. That is, we could begin by selecting any pair from the set Λ and then solving the state system using this pair as controls. We would next select another pair from the set Λ and again solve the state system using the pair as controls. Upon comparing the values of objective functional, J, we select the control pair corresponding to the smaller cost functional value. If we iterate this strategy over all possible pairs from the set Λ, we obtain the optimal control vector pair, ϵ_1^* and ϵ_2^*. However, this strategy to obtain the optimal STI control pair leads to a large number of cost functional evaluations and hence a large number of solutions to the state system (2.1). In our example, the number of cost functional evaluations would be $(2^{900})^2$ since each control vector is a 1×900 vector. This makes this approach computationally infeasible.

We therefore seek to reduce the number of iterations, and consider several ideas to accomplish this goal. One is to consider 5 day segments instead of 1 day segments as above. This is more reasonable from a practical point of view since it is not clinically feasible for drug strategies to allow change with a daily frequency. For 5 day segments, the size of each control vector is reduced to 1×180 from 1×900. However the reduced number of iterations is $(2^{180})^2$ which is still quite large.

One approach to further alleviate this computational burden is to consider subperiods of the given period such as [0, 30], [0, 60], [0, 90], [0, 120], $\cdots$, [0, 900]. This approach, which is similar to the underlying idea for dynamic programming, is discussed and used in [1] where only single drug therapies are considered. We shall refer to this simply as the "subperiod method". In this method, we find an optimal STI control pair, $(\epsilon_{1,1}^*, \epsilon_{1,2}^*)$, over the first subperiod, [0, 30], using the reduced iteration technique (5 day segments) as above. Since the size of $\epsilon_{1,1}^*$ and $\epsilon_{1,2}^*$ is 1×6 (for 5 day segments over 30 days), optimal solutions can be obtained very quickly (with only $(2^6)^2 = 4096$ iterations). In the second

step, we consider our control vectors over the period $[0, 60]$ as follows:

$$\epsilon_{2,1} = [\epsilon_{1,1}^*, \star, \star, \star, \star, \star, \star] \quad \text{and} \quad \epsilon_{2,2} = [\epsilon_{1,2}^*, \star, \star, \star, \star, \star, \star]$$

where $\star$ is 0 or b_i. That is, we fix the $[0, 30]$ optimal STI pair, $\epsilon_{1,1}^*$ and $\epsilon_{1,2}^*$, as the first 6 elements of the controls, $\epsilon_{2,1}$ and $\epsilon_{2,2}$, respectively, and iterate $\epsilon_{2,1}$ and $\epsilon_{2,2}$ to find the last 6 elements of each control that make an "optimal" STI control pair, $(\epsilon_{2,1}^*, \epsilon_{2,2}^*)$, over the period $[0, 60]$. In this case, the number of iterations is also just $(2^6)^2 = 4096$ so we can obtain it quickly. We repeat this process to find an "optimal" STI control pair, $(\epsilon_{3,1}^*, \epsilon_{3,2}^*)$, over $[0, 90]$, $(\epsilon_{4,1}^*, \epsilon_{4,2}^*)$, over $[0, 120]$, and so on. The STI control pair obtained over the whole period $[0, 900]$ is $\epsilon_1^* = \epsilon_{30,1}^*$ and $\epsilon_2^* = \epsilon_{30,2}^*$. It should be emphasized that the STI control pair, ϵ_1^* and ϵ_2^* is now only *suboptimal*. However, we observed in [1], where only single drug therapies were considered, that this subperiod approach yielded a suboptimal STI therapy that produces results which are reasonable approximations to those for a fully efficacious continuous therapy as well as to those for an optimal STI therapy in some examples.

We again simulate early infection by introducing one virus particle per ml of blood plasma, i.e., $T_1(0) = 10^6$, $T_2(0) = 3198$, $T_1^*(0) = 10^{-4}$, $T_2^*(0) = 10^{-4}$, $V(0) = 1$ and $E(0) = 10$. And we also use $a_1 = 0$, $a_2 = 0$, $b_1 = 0.7$ and $b_2 = 0.3$. Using the subperiod method, a suboptimal STI control pair and associated solutions are depicted in Figure 4 and Figure 5, respectively. We note that PI therapy is interrupted more than RT inhibitors, especially between the 300th day and the 500th day. Notable features include that the virus load remains less than 10^3 and the population of uninfected T_1 cells recovers from the effects of HIV after around the 600th day even though both drugs are discontinued at that time. This is due to a very strong immune response. We notice that both drugs are interrupted around the 50th and 300th days. These interruptions cause extremely high virus load in turn leads to more infected T_1^* and T_2^* cells at those times. Immune response is thus stimulated and augmented especially through these interruptions. This is a good example of moving a patient from an infected state to a healthy state.
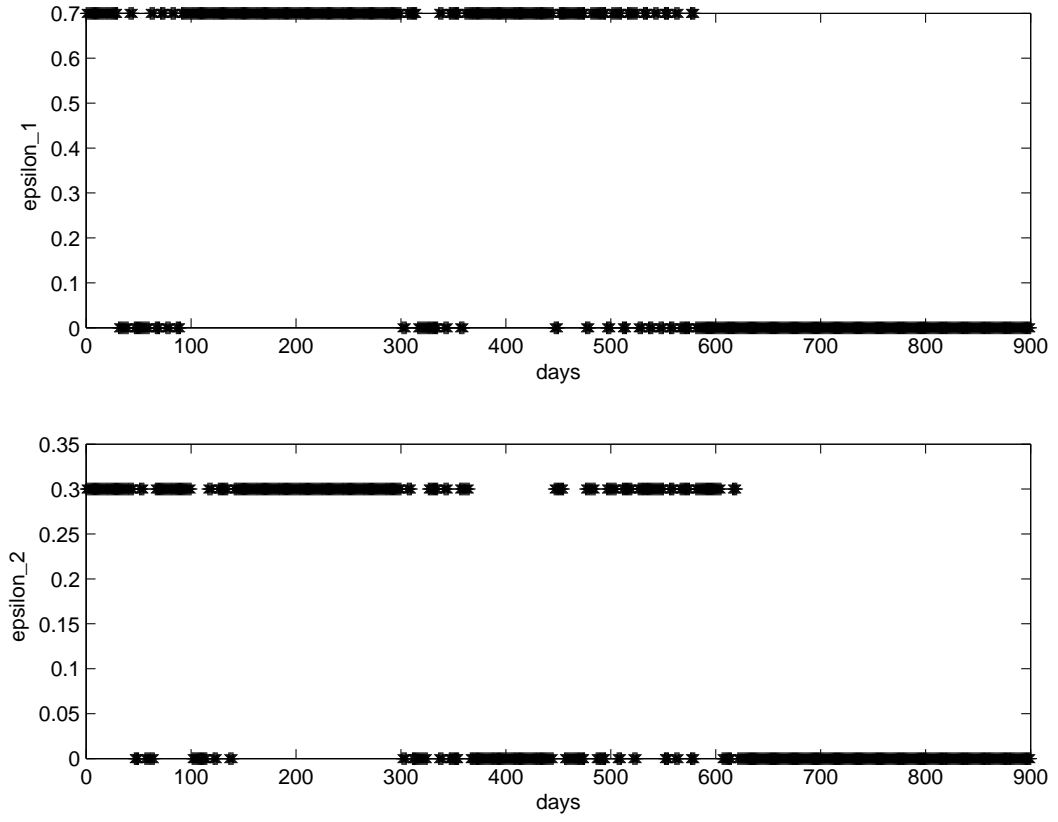
Figure 4: Optimal STI control pair in early infection. The label ϵ_1 represents RT inhibitors and ϵ_2 represents protease inhibitors.
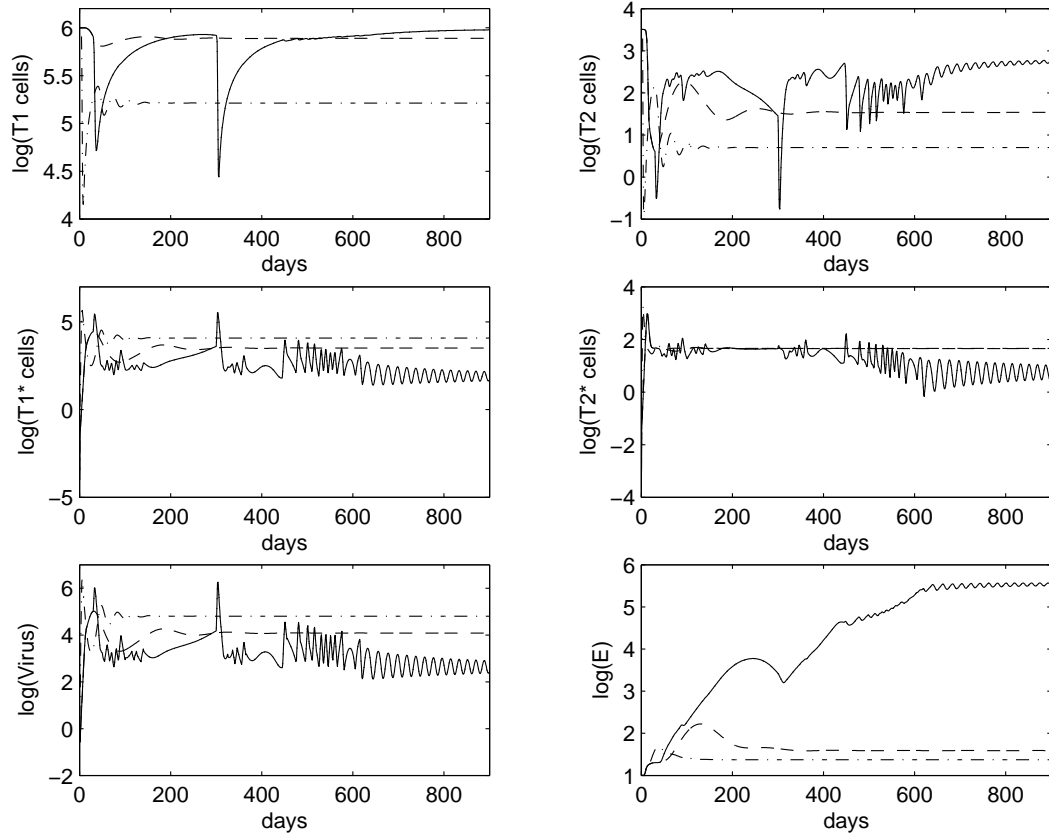
Figure 5: STI control solutions $(-)$, solutions $(-\cdot)$ with no treatments of both drugs $(\epsilon_1 = \epsilon_2 \equiv 0)$, solutions $(--)$ with fully efficacious treatment of both drugs $(\epsilon_1 \equiv 0.7$ and $\epsilon_2 \equiv 0.3)$ in early infection over the period $[0, 900]$. $Q = 0.1$, $R_1 = 20000$, $R_2 = 20000$ and $S = 1000$.

We turn next to an example of moving between the model's two stable equilibria as discussed in earlier sections. In other words, control functions can found that move an HIV-infected individual between the steady states, rather than from the infected initial condition. We consider using the "unhealthy" stable equilibrium as the initial condition for model (2.1) over the time interval $[0, 750]$, i.e., $T_1(0) = 163573$, $T_2(0) = 5$, $T_1^*(0) = 11945$, $T_2^*(0) = 46$, $V(0) = 63919$ and $E(0) = 24$ in order to demonstrate that an "unhealthy" stable equilibrium can be moved to a "healthy" stable equilibrium via a suboptimal STI. The suboptimal STI control pair and its associated solutions are depicted in Figure 6 and Figure 7, respectively. The phase plane diagram displaying virus versus immune effectors is shown in Figure 8. We see that the populations of virus and immune effectors are shifted from "unhealthy" which exhibits high virus and low immune effectors to "healthy" which has low virus and high immune effectors. Indeed using the control theory paradigm in a HIV therapeutic setting, our modeling efforts
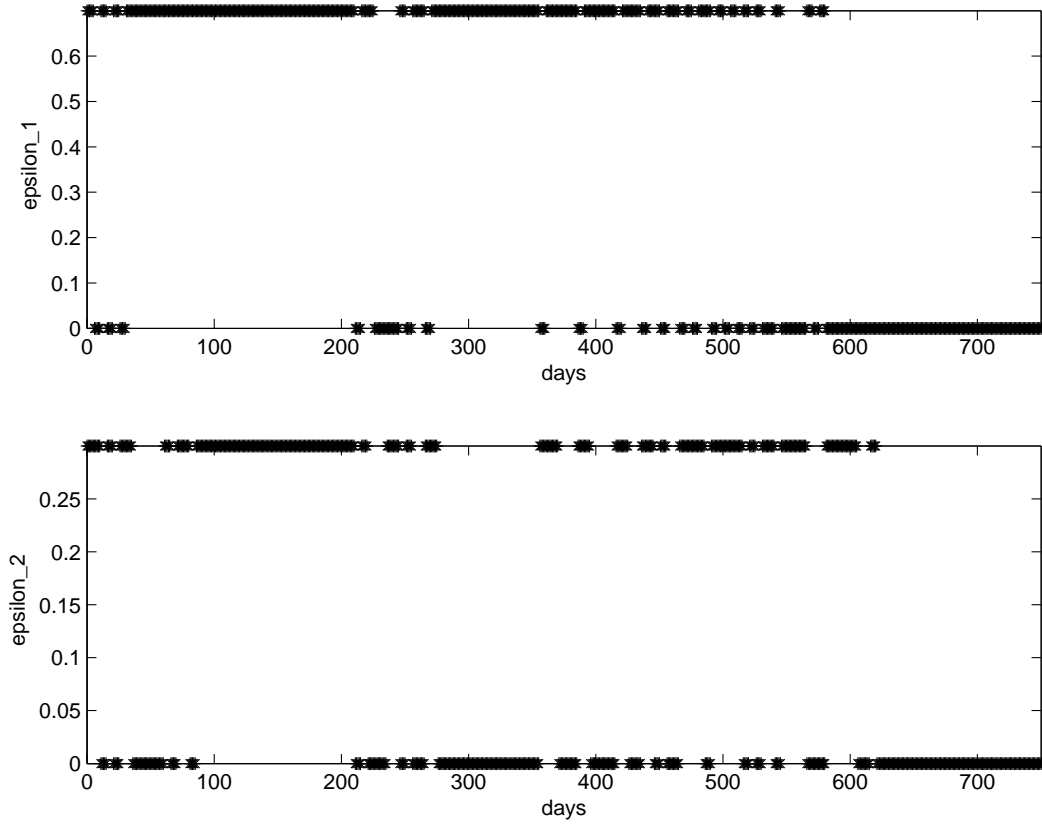

Figure 6: Optimal STI control pair over the time interval $[0, 750]$. The label ϵ_1 represents RT inhibitors and ϵ_2 represents protease inhibitors. Simulation results are obtained using the initial condition $T_1(0) = 163573$, $T_2(0) = 5$, $T_1^*(0) = 11945$, $T_2^*(0) = 46$, $V(0) = 63919$ and $E(0) = 24$.
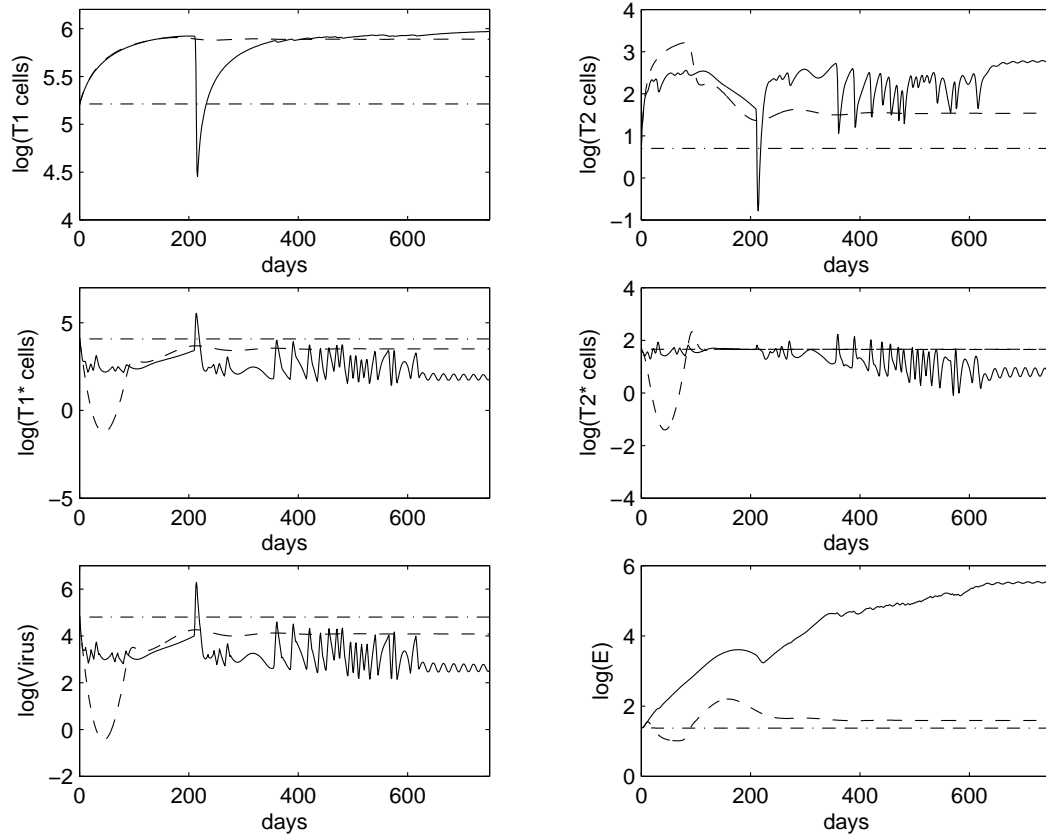
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Figure 7: STI control solutions $(-)$, solutions $(-\cdot)$ with no treatments of both drugs $(\epsilon_1 = \epsilon_2 \equiv 0)$, solutions $(--)$ with fully efficacious treatment of both drugs $(\epsilon_1 \equiv 0.7$ and $\epsilon_2 \equiv 0.3)$ over the period $[0, 750]$. The initial condition is $T_1(0) = 163573$, $T_2(0) = 5$, $T_1^*(0) = 11945$, $T_2^*(0) = 46$, $V(0) = 63919$ and $E(0) = 24$. $Q = 0.1$, $R_1 = 20000$, $R_2 = 20000$ and $S = 1000$.

clearly suggest the possibility that STI will lead to immune boosting and subsequent control of viral load without the need for drugs.
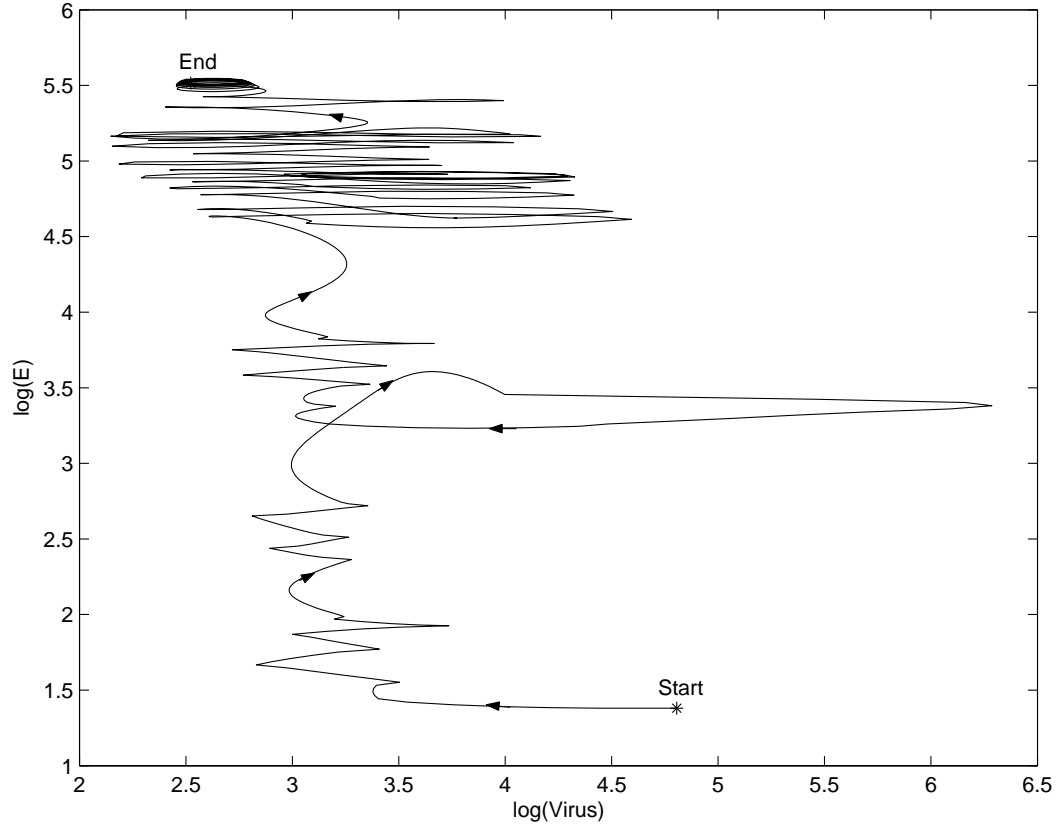
Figure 8: Phase plane for virus versus immune effectors with unhealthy steady states initial condition, i.e., $T_1(0) = 163573$, $T_2(0) = 5$, $T_1^*(0) = 11945$, $T_2^*(0) = 46$, $V(0) = 63919$ and $E(0) = 24$.

6 Concluding Remarks

In this paper we have formulated a dynamic model with compartments including target cells, infected cells, virus, and immune response that is subject to multiple (RTI- and PI-like) drug treatments as control inputs. For certain ranges of the parameters, the uncontrolled model possesses multiple locally asymptotically stable steady states. We then applied techniques and ideas from open loop control theory and dynamic programming to derive continuous and suboptimal STI therapy protocols. In particular, we use the "subperiod method" introduced in [1] for therapies involving a single drug to develop results for drug "cocktails". We demonstrate that one can use the resulting suboptimal STI strategies to move the model system from an "unhealthy" locally stable region of attraction to a similar "healthy" one in which the immune response is dominant in controlling the viral levels. This illustrates one possible scenario by which STI therapies could lead to long term control of HIV after discontinuation of therapy.

Acknowledgments

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