MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **9**, Number **4**, October **2012**

doi:10.3934/mbe.2012.9.899

pp. **899–914**

HYBRID OPTIMAL CONTROL FOR HIV MULTI-DRUG THERAPIES: A FINITE SET CONTROL TRANSCRIPTION APPROACH

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(Communicated by Denise Kirschner)

Abstract. In this study, the treatment of Human Immunodeficiency Virus (HIV) infection is investigated through an optimal structured treatment interruption (STI) schedule of two classes of antiretroviral drugs, mainly, reverse transcriptase inhibitors and protease inhibitors. An STI treatment strategy may be beneficial in lowering the risk of HIV mutating to drug-resistant strains, and could provide patients with respite from toxic side effects of HAART. A shorter treatment period is considered compared to previous studies and the solution to the HIV STI problem is obtained via the Finite Set Control Transcription (FSCT) formulation. The FSCT formulation offers a unique approach for handling multiple independent decision variables simultaneously, and, as is shown by the results of this study, is well-suited for an effective treatment of the optimal STI problem. The results obtained in the present investigation demonstrate that immune boosting and subsequent natural suppression of the viral load are possible even when a reduced STI therapy treatment duration is in consideration.

1. **Introduction.** The treatment for patients infected by Human Immunodeficiency Virus (HIV) consists of a "cocktail" of two or more drugs and is known as Highly Active AntiRetroviral Therapy (HAART).[22, 2, 7] Typically, the HAART cocktail is a combination of two or more Reverse Transcriptase Inhibitors (RTIs) and one Protease Inhibitors (PIs),[22, 2, 7, 30, 19] both potent antiretroviral drugs that are administered in liquid, tablet, capsule, and injectable forms. The multi-drug regimens are very effective in controlling viral load, but have several shortfalls associated with long-term use. With extended usage, patients experience increased severity in side effects and may develop resistance to drugs.[22, 2, 7, 1] When this occurs, it becomes necessary to change the composition of the medication. However, in some cases it might be impossible to find alternative drugs that provide effective treatment. Furthermore, patients might be deterred from adherence due to the complexity of the drug regime and the high monetary costs of the treatment.

2000 *Mathematics Subject Classification.* Primary: 49J15, 92C50; Secondary: 65K05, 65K10.

Key words and phrases. Hybrid optimal control, drug therapy, structured treatment interruption.

Dynamic multidrug therapies, where drug combinations change in response to disease progression, may provide increased effectiveness of HIV therapy.[30] The studies by Caetano et al.,[7] Kutch et al.,[19] and Wein et al.[30] address dynamic multidrug approaches where RTI and PI drug dosages are continuously varying control variables that can change independently of each other.[22] An alternative strategy, known as a drug holiday or structured treatment interruption (STI), cycles the patient on and off therapy.[2, 1, 6, 18] In this approach, the control variable is treated as a binary variable, indicated to be either 'on' or 'off' at a given time. An STI treatment strategy may be beneficial in lowering the risk of HIV mutating to drug-resistant strains,[22] and could provide patients with respite from toxic side effects of HAART.

The present investigation considers the STI therapy design in the context of a nonlinear hybrid optimal control problem. A hybrid system may be described as having states that are governed by differential equations of motion, and controlled through some form of discrete or decision based logic. The on-off profile of the STI multidrug therapy fits well into this category. The control problem of optimal treatment interruption is posed as: determine the optimal STI treatment strategy in order to minimize the HIV strains and systemic costs of the drug treatments (undesirable side effects and treatment cost) while steering the immune response to a nominal (healthy) state.[2, 1, 22, 21] In this study, solutions to the HIV STI problem are explored via the Finite Set Control Transcription (FSCT) method.

The FSCT method considers the hybrid optimal control problem in the context of a transcribed parameter optimization problem.[17, 4, 5] Solutions are identified using standard Nonlinear Programming (NLP) algorithms such as SNOPT. Similar efforts in the published literature[23, 26, 15, 16, 13, 14, 10, 12, 3, 20, 29] address a subset of the present problem from the perspective of mixed integer optimization often using NLP algorithms. However, these methods do not adequately address problems involving multiple independently switching decision variables. The drawback in these cases is a formulation that does not minimize the dimensionality of a generally large and complex problem. This renders many of these techniques impractical in the analysis of complex hybrid systems such as in the case of (HIV) STI therapy problem.

Although optimal treatments have been previously explored specifically for the STI problem using a variety of methods [2, 1, 22, 21, 31], the same limitation is identified in these studies. That is, in the proposed studies, a single decision variable controls the on or off time of both RTI and PI drugs, despite the fact that the two drugs have different transient effects[31]. However, this approach might limit the effectiveness of dynamic multidrug therapy, which can be fully explored only if the drug dosages are allowed to change independently of each other. A significant advantage of the FSCT method is that it is capable of treating problems with multiple independent control variables (in this case RTIs and PIs) with ease. An immediate advantage of the proposed approach is a significant reduction in computational overhead during the numerical solution process. Furthermore, shorter interruption periods are more easily incorporated into the optimal solution via FSCT, a feature that is compromised in existing methodologies[2] in order to reduce the inherently large dimensionality of the STI problem. Indeed, by allowing frequent interruptions, the effectiveness of a relatively shorter treatment period compared to existing numerical studies in literature can be explored. In the present

investigation, a relatively short treatment period of 400 days is considered compared to existing numerical studies in literature where typically $700 - 750$ days of treatment are considered[2, 22, 31]. The treatment therapy designed in the present research shows that drug free management of HIV is feasible even after reduced treatment durations, thus reducing the systemic costs on the body associated with prolonged HIV drug therapy.

2. **HIV model description.** A wide variety of mathematical models describing short and long term progression of HIV have been proposed. A survey article of mathematical models that have been used to describe the pathogenesis of HIV infection is provided by Callaway, et al.[8] Although the surveyed studies describe the virus evolution by deterministic models, some available models consider the stochastic nature of early HIV infection based on the high variability and rapid response of HIV to changes in system parameters.[9, 27, 28]

The model implemented for this study is a system of ordinary differential equations developed by Adams et. al[1] and employed in several studies [2, 21, 22]. The selected six-state nonlinear dynamical model captures long-term target cell decay rate along with immune response. The pathogenesis is described by

$$\begin{aligned}
\dot{T}_1 &= \lambda_1 - d_1 T_1 - (1-\epsilon_1) k_1 V T_1 \\
\dot{T}_2 &= \lambda_2 - d_2 T_2 - (1-f\epsilon_1) k_2 V T_2 \\
\dot{T}_1^* &= (1-\epsilon_1) k_1 V T_1 - \delta T_1^* - m_1 E T_1^* \\
\dot{T}_2^* &= (1-f\epsilon_1) k_2 V T_2 - \delta T_2^* - m_2 E T_2^* \\
\dot{V} &= (1-\epsilon_2) N_T \delta (T_1^* + T_2^*) - cV \\
&\quad - \left[(1-\epsilon_1)\, \rho_1 k_1 T_1 + (1-f\epsilon_1) \rho_2 k_2 T_2 \right] V \\
\dot{E} &= \lambda_E + \frac{b_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b)} E - \frac{d_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d)} E - \delta_E E,
\end{aligned} \tag{1}$$

where state variables T_1 and T_2 denote uninfected target cells, T_1^* and T_2^* describe infected target cells, V describes free viruses, and E describes the immune response. The virus state V is measured in *copies/ml* while all other states are measured in *cells/ml*. A detailed description of each state as well as its biological significance is provided in [2, 1]. The variables $\epsilon_1(t)$ and $\epsilon_2(t)$, where, $0 \leq \epsilon_i \leq \epsilon_{i,max} < 1$ for $i = 1,\ 2$, are control terms given as efficacies of the RTI and PI anti-retroviral medication, respectively. The unity upper bound on both control variables indicates that drug therapy is less than 100% effective, an assumption based on multiple patient-specific factors such as drug absorption rates, adherence, and complications due to adverse effects. Furthermore, for an infected individual, a control history may be obtained to suppress the viral load to a minimum value but cannot fully eradicate the virus from the body. The assumption is consistent with clinical studies since no known cure for HIV has been established. Thus, for the HIV specific problem, the maximum efficacy of drug therapy is given as $\epsilon_{1,max} = 0.7$, and $\epsilon_{2,max} = 0.3$.[2] The parameters in the model stated in Equation (1) are summarized in Table 2 and described in [1].

The HIV dynamical model in Equation (1) has the following form,

$$\dot{\boldsymbol{y}} = \boldsymbol{f}(\boldsymbol{y}, \boldsymbol{u}), \tag{2}$$

TABLE 1. Parameter Values for the HIV Model

	value	units		value	units
λ_1	$10,000$	$\frac{cells}{ml \cdot day}$	d_1	0.01	$\frac{1}{day}$
k_1	8×10^{-7}	$\frac{ml}{virions \cdot day}$	m_1	1×10^{-5}	$\frac{ml}{cells \cdot day}$
ρ_1	1.0	$\frac{virions}{cell}$	δ	0.7	$\frac{1}{day}$
f	0.34	-	λ_E	1.0	$\frac{cells}{ml \cdot day}$
b_E	0.3	$\frac{1}{day}$	K_b	100	$\frac{cells}{ml}$
λ_2	31.98	$\frac{cells}{ml \cdot day}$	d_2	0.01	$\frac{1}{day}$
k_2	1×10^{-4}	$\frac{ml}{virions \cdot day}$	m_2	1×10^{-5}	$\frac{ml}{cells \cdot day}$
ρ_2	1.0	$\frac{virions}{cell}$	c	13	$\frac{1}{day}$
N_T	100.0	$\frac{virions}{cell}$	δ_E	0.1	$\frac{1}{day}$
d_E	0.25	$\frac{1}{day}$	K_d	500	$\frac{cells}{ml}$

where $\boldsymbol{y} = [T_1,\ T_2,\ T_1^*,\ T_2^*,\ V,\ E]^T$ and $\boldsymbol{u} = [\epsilon_1,\ \epsilon_2]^T$. The model exhibits several uncontrolled ($\boldsymbol{u} = \boldsymbol{0}$) equilibrium or steady-states. Of these, three are of special interest and are summarized in Table 2 [2]. A viral load greater than $30,000$ $copies/ml$

TABLE 2. Physical (Non-Negative) Equilibrium States

	$\boldsymbol{y}_u$	$\boldsymbol{y}_0$	$\boldsymbol{y}_h$
T_1	163573	10^6	967839
T_2	49	3198	621
T_1^*	11945	0	76
T_2^*	46	0	6
V	63919	0	415
E	24	10	353108
	(Unhealthy)	(Uninfected)	(Healthy)

is generally considered unsafe and requires treatment to bring the copies below a level that is detectable by current laboratory tests. Note that $\boldsymbol{y}_u$ displays high viral loads and very low immune effectors which are both indicators of ill health of the patient. The equilibrium condition of $\boldsymbol{y}_0$ corresponds to a nominal uninfected state, while $\boldsymbol{y}_h$ are each associated with a "healthy", immune-dominated patient condition with low viral load and high immune response.

A local stability analysis of the uncontrolled system dynamics performed in [2] shows that $\boldsymbol{y}_0$ is unstable, while $\boldsymbol{y}_u$ and $\boldsymbol{y}_h$ are each stable equilibrium conditions. In the subsequent sections, continuous and STI optimal control histories are obtained for systems described by the acute infection stage. This state is characterized by the introduction of a single virus particle to the uninfected steady state. Hence, the perturbed initial condition is given by

$$\boldsymbol{y}_i = \left[10^6,\ 3198,\ 0,\ 0,\ 1,\ 10\right]. \tag{3}$$

The natural, control-free ($\boldsymbol{u} = \boldsymbol{0}$) evolution of the acute infection stage is depicted in Figure 1 for a duration of 400 days. It is evident that without drug therapy, the virus will multiply unchecked before converging on the viral dominant (unhealthy) steady-state, $\boldsymbol{y}_u$. The objective of the control formulations in the subsequent sections is to

drive the system away from the unhealthy equilibrium to the healthy equilibrium condition identified above as $\boldsymbol{y}_h$.

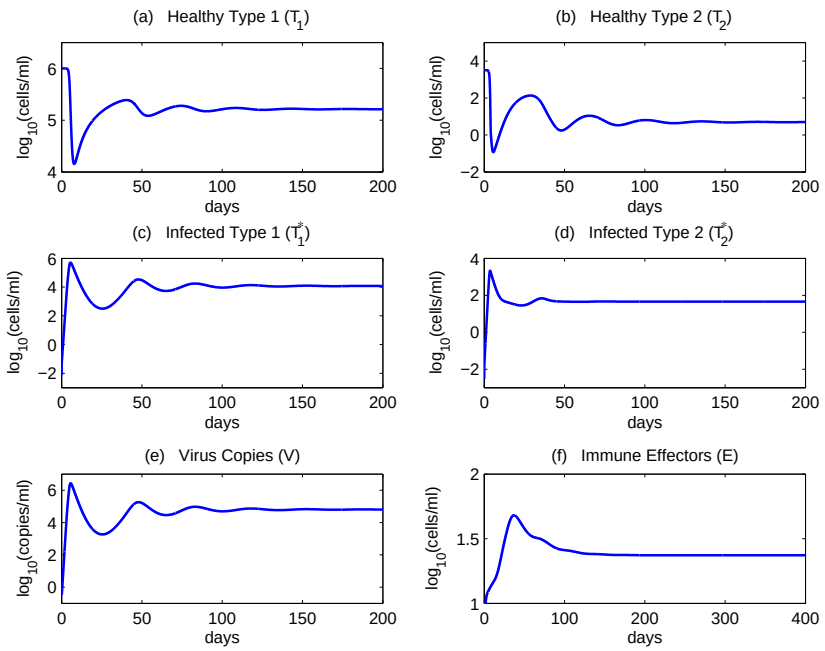

FIGURE 1. Time Evolution of Uncontrolled Acute Infection Stage.

3. **Structured treatment interruption therapy.** In the previous sections, the dynamics of HIV are described using a continuous nonlinear dynamical model consisting of a system of nonlinear ordinary differential equations. However, if a HIV drug treatment strategy consisting of RTI and PI is prescribed with treatment interruptions, the control variable is treated as a binary variable, indicated to be either 'on' or 'off' at a given time. Thus, the HIV system exhibits both continuously-varying state variables and discretely-chosen control components, and is appropriately referred to as a hybrid system. The resulting hybrid optimal control problem is solved by using an efficient transcription algorithm known as Finite Set Control Transcription.[24]

The FSCT method effectively formulates the hybrid optimal control problem as a parameter optimization problem using collocation that can be solved using a standard Nonlinear Programming (NLP) algorithm. In contrast to previous methods for solving the STI problem (for example, Adams et al.,[2]), FSCT works by assuming the control values and optimizing the elapsed time between when the drug is on or off. This allows for shorter time segments to be more easily incorporated into the optimal solution. Furthermore, the asynchronous optimal switching schedule allows for each drug schedule to be treated independent of the others, thereby offering the

greatest flexibility in the solution process. A brief overview of the FSCT method is provided in the next section.

3.1. **FSCT method overview.** In this section, a brief overview of the FSCT formulation is provided for a reader with a general background in optimal control theory. A complete development of the methodology may be found in Stanton and Marchand, 2010[24]. The general system of interest for this transcription method is described by

$$\dot{\boldsymbol{y}} = \boldsymbol{f}(t, \boldsymbol{y}, \boldsymbol{u}), \tag{4}$$

where $\boldsymbol{y} \in \mathbb{R}^{n_y}$ represents the continuous states, and $\boldsymbol{u} \in \mathbb{R}^{n_u}$ are the discrete control variables that may take-on values limited to a finite set, $\mathbb{U}_i$. Therefore, if u_i denotes the i^{th} control variable, for $i = 1, \ldots, n_u$, then $u_i \in \mathbb{U}_i$ where

$$\mathbb{U}_i = \{\tilde{u}_{i,1}, \ldots, \tilde{u}_{i,m_i}\}. \tag{5}$$

The FSCT formulation seeks to solve an optimal control problem described as,

$$\text{Minimize } \mathcal{J} = \phi(t_0, \boldsymbol{y}_0, t_f, \boldsymbol{y}_f) + \int_{t_0}^{t_f} L(t, \boldsymbol{y}, \boldsymbol{u})\, dt, \tag{6}$$

subject to constraints

$$\begin{aligned} \boldsymbol{0} &= \boldsymbol{\psi}_0(t_0, \boldsymbol{y}_0), \\ \boldsymbol{0} &= \boldsymbol{\psi}_f(t_f, \boldsymbol{y}_f), \\ \boldsymbol{0} &= \boldsymbol{\beta}(t, \boldsymbol{y}, \boldsymbol{u}), \end{aligned} \tag{7}$$

by transcribing into a nonlinear-programming problem (NLP) of the form,

$$\text{Minimize } F(\boldsymbol{x}) \tag{8}$$

subject to

$$\boldsymbol{c}(\boldsymbol{x}) = \left[\boldsymbol{c}_{\psi_0}^T(\boldsymbol{x})\ \boldsymbol{c}_{\psi_f}^T(\boldsymbol{x})\ \boldsymbol{c}_{\beta}^T(\boldsymbol{x})\ \boldsymbol{c}_{\dot{y}}^T(\boldsymbol{x})\right]^T = \boldsymbol{0}, \tag{9}$$

and subsequently utilizing a standard NLP optimizer such as SNOPT to obtain a solution for the parameter vector, $\boldsymbol{x}$. In the above NLP definition, the constraints are stated as equalities without loss of generality since inequality constraints may be easily converted to equality constraints through the Lagrange Multiplier method. Thus, $\boldsymbol{x}$ contains all the necessary information necessary to express $\boldsymbol{y}(t)$ and $\boldsymbol{u}(t)$ for $t \in [t_0, t_f]$.

The vector, $\boldsymbol{x}$, contains parameters that represent states $y_{i,j,k}$, and times $\Delta t_{i,k}$, t_0, t_f as is shown below

$$\boldsymbol{x} = [\cdots\ y_{i,j,k}\ \cdots\cdots\ \Delta t_k\ \cdots t_0\ t_f]^T. \tag{10}$$

The parameterization is a unique departure from traditional collocation and direct shooting methods that directly represent control variables. However, since the control variables are discrete in nature, their omission from the parameter vector permits the treatment of the problem as a nonlinear programming problem. Furthermore, as is demonstrated below, a control history is exactly determined by the time elements in the parameter vector.

Define n_s as the number of contiguous segments that comprise a trajectory from initial time, t_0, to final time, t_f. The interior segment boundaries are termed knots, and are characterized as points in time where one member of the control vector switches from one feasible value to another. If a control variable is allowed n_k

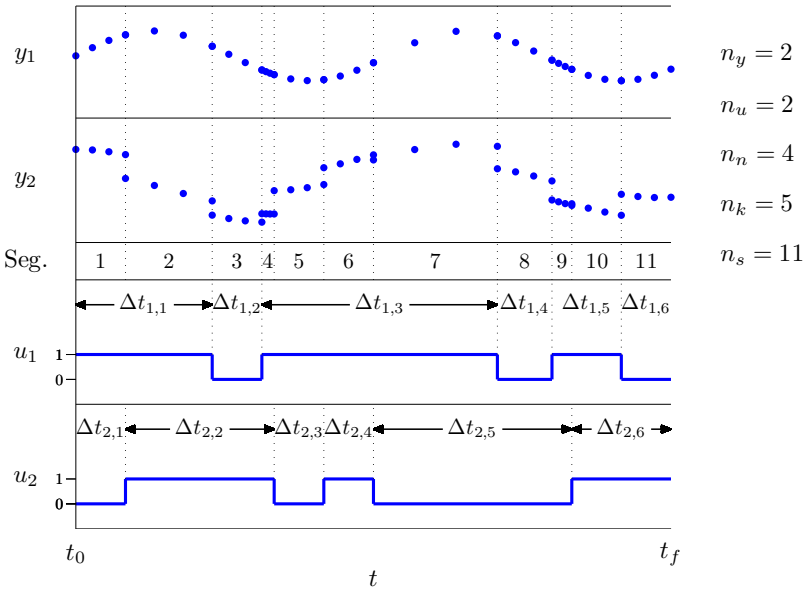

FIGURE 2. The Parameters of $\boldsymbol{x}$

switches during (t_0, t_f), then the trajectory is composed of $n_s = n_u n_k + 1$ segments. During each segment, the i^{th} control variable maintains a constant value.

Each segment is discretized into a set of n_n equally spaced points in time, called nodes. Specifically, a node is a point in time at which the values of the state variables are captured by the parameter vector. Thus, element $y_{i,j,k}$ in Equation (10) denotes the i^{th} state at the j^{th} node of the k^{th} segment. A total number of $n_y n_n n_s$ elements corresponding to all the state variables is contained in the parameter vector. The element $\Delta t_{i,k}$ in Equation (10) indicates the time elapsed between control switches at $(k-1)^{th}$ and k_{th} knot for the i^{th} control variable.

It is noted earlier that the control variables do not appear explicitly in $\boldsymbol{x}$. Instead, the values for each u_i are *prescribed* between each switching point. That is, $u^*_{i,k}$ denotes the pre-specified feasible value of the i^{th} control variable during $\Delta t_{i,k}$. Thus, with the control values prescribed, the optimizer determines the "best" values for $\Delta t_{i,k}$.

A pictorial explanation of the FSCT optimization method is provided in Figure 2. Consider a hybrid control problem with $n_y = 2$ states and $n_u = 2$ controls, where $\mathbb{U}_1 = \{0, 1\}$ and $\mathbb{U}_2 = \{0, 1\}$. The conceptual control variables are similar to the control inputs described earlier in the HIV treatment interruption problem in which the drug efficacies are limited to the finite set of values 1 (on) and 0 (off). Next, assume the transcription is selected such that $n_n = 4$ nodes per segment and $n_k = 5$ switching points per control variable. Thus, the number of segments is $n_s = (2)(5) + 1 = 11$ segments.

It is apparent from Figure 2 that each control variable may take up to $n_k + 1 = 6$ different values over the trajectory duration. The control values are arbitrarily

prescribed from the set of feasible values before the optimization run. During the optimization procedure, if a control value is deemed unnecessary or non-optimal, then the duration of the corresponding time segment is essentially reduced to zero. However, such a process also runs the risk of arbitrarily reducing a given time segment to small but non-zero values. This may not be desirable or even practical in certain problems in which control switches can only occur at a certain rate. For instance, in the HIV STI problem, minimum segment durations may be driven entirely by drug absorption and elimination rates. Hence, it may become necessary to constrain the lower bound of $\Delta t_{i,k}$.

Figure 2 further illustrates that the node distribution is not necessarily uniform over the interval $[t_0\ t_f]$. The duration of each segment is dictated by the current values of $\Delta t_{i,k}$. The $n_n = 4$ nodes per segment are evenly distributed over a segment, but for shorter segments, this means a closer spacing between nodes. Thus, the state values contained in $\boldsymbol{x}$ may pertain to dense or sparse regions, depending on the time parameters in $\boldsymbol{x}$.

It is also important to note that two nodes are associated with a given knot: the terminal node from the preceding segment and the initial node from the following segment. Therefore, in this parameterization, two sets of state values are contained in $\boldsymbol{x}$ for the times at each knot. For a feasible solution, continuous state variables exhibit identical values at simultaneous nodes. Constraints in $\boldsymbol{c}(\boldsymbol{x})$ are included to enforce continuity across segments. Of course, these constraints are not always satisfied on intermediate iterations of the solution process. For example, in Figure 2, the continuity constraints for y_2 are not all met. Subsequently, this $\boldsymbol{x}$ does not represent a feasible solution. During the FSCT optimization process, elements of $\boldsymbol{x}$ are updated to ensure that, upon completion, the continuity constraints are satisfied.

Additional constraints are included in $\boldsymbol{c}(\boldsymbol{x})$ to ensure that

$$0 = t_f - t_0 - \sum_{k=1}^{n_k+1} \Delta t_{i,k},\ i = 1, \ldots, n_u.$$

Also, at all times, $\Delta t_{i,k} \geq 0$ so that there are no negative time intervals.

By pre-specifying the control values, a collocation transcription results in which control switching times are optimized to indicate an optimal control history over all of the feasible control values. Multiple control variables are easily managed and treated independently. The control variables for a given segment subsequently affect the hybrid system dynamics, and they are included in appropriate constraint equations for that segment. As the optimizer searches for a feasible and locally optimal set of parameters, the state values are modified at each node so that, upon completion, the state and control histories represent a matching, feasible trajectory.

The total number of feasible values for a control variable, m_i, significantly affects the choice of n_k, the number of switching points allowed over the trajectory. Clearly, when $n_k \gg \max(m_i)$, it is possible to pre-specify each control value over several time durations, allowing more flexibility in the resulting NLP problem and a greater likelihood to converge on a small local minimum. However, as n_k gets larger, the sizes of $\boldsymbol{x}$ and $\boldsymbol{c}(\boldsymbol{x})$ also increase, a feature that may complicate or slow down the optimization process. This characteristic indicates the primary limitation of the FSCT method. In order to perform an optimization, a user must specify n_k, thus limiting the number of control switches to some maximum value.

In practice, it is useful to overparameterize a problem by setting n_k to an arbitrarily high value, allowing for more control switches than are ultimately necessary. Overparameterizing allows the optimizer to demonstrate the optimal number of switches (less than the parameterized number) by driving to zero the duration of superfluous control values. The overparameterization also allows the user additional flexibility to arbitrarily pre-specify control values, knowing that non-optimal control values are ultimately eliminated in the final solution. Indeed, in the treatment of the STI problem that follows, the concept of overparameterization is employed. Consequently, ensuing solutions may display features that are ultimately artifacts of the parameterization. For example, two knots may occur simultaneously, appearing as though the control switches from one value to another and then instantaneously to a third. In the parameterization, zero-duration segments are present, indicating that particular pre-specified control values are effectively eliminated from the solution.

3.2. **STI solution via FSCT.** The FSCT formulation is implemented in order to obtain an optimal STI treatment schedule. The cost function associated with this problem is originally proposed in [2] and stated as

$$\mathcal{J} = \int_{t_0}^{t_f} \left[QV(t) + R_1 u_1^2(t) + R_2 u_2^2(t) - SE(t) \right] \, dt, \tag{11}$$

where the weights are modified to $Q = 0.001$, $R_1 = R_2 = 20$, and $S = 1000$. Two control axes are present, each with the finite set of values

$$\mathcal{U}_i = \{0, \epsilon_{i,max}\}. \tag{12}$$

That is, each of the two drugs may have zero or full efficacy for each time segment considered. Thus, the optimal control problem considered in this investigation is given by the cost function described in Equation (11) subject to path constraints in Equation (1) with boundary constraints $\boldsymbol{y}_i$ given in Equation (3), $t_0 = 0$, $t_f = 400$ seconds, $\boldsymbol{y} \geq \boldsymbol{0}$, and discrete control variables that may take-on values limited to the finite set in Equation (12).

To begin the optimization process, the number of knots are selected, indicating the total allowable control switches over the course of the trajectory. Considering the long propagation period and complicated dynamics of the HIV problem, a very large number of knots is necessary to solve the problem. However, since large n_k can slow down the optimization process, a discretized solution approach is implemented similar to that in [2, 1]. Specifically, smaller solution spaces are considered by breaking up the trajectory into seven partitions, p_1, p_2, ..., p_7, each of which is characterized by node and knot distribution in each of the $n_u = 2$ control axes as follows,

$$\begin{aligned}
p_1: &\quad t = [0, 50]\,,\ n_n = 10,\ n_k = 10 \\
p_2: &\quad t = [50, 100]\,,\ n_n = 10,\ n_k = 10 \\
p_3: &\quad t = [100, 200]\,,\ n_n = 10,\ n_k = 10 \\
p_4: &\quad t = [200, 250]\,,\ n_n = 10,\ n_k = 5 \\
p_5: &\quad t = [250, 300]\,,\ n_n = 10,\ n_k = 5 \\
p_6: &\quad t = [300, 350]\,,\ n_n = 10,\ n_k = 8 \\
p_7: &\quad t = [350, 400]\,,\ n_n = 10,\ n_k = 10.
\end{aligned} \tag{13}$$

Thus, each partition is characterized by 10 nodes per segment, while the total initial allowable control switches varies for each partition. The discretized approach permits overparameterization of each partition without slowing down the optimization process. While the result is optimal for each partition, the overall solution is considered near-optimal. The approach is outlined as follows:

1. Solve p_1 via FSCT with acute infection as the initial state.
2. Use the final state of the solved p_1 partition as the initial state for p_2.
3. Solve p_2 via FSCT.
4. Repeat the process from Step 2 until all partitions are solved.

For example, let $n_k = 10$ knots per control axis for an initial optimization for partition p_1. Let the control values be prescribed as

$$u_{i,k}^* = \epsilon_{i,max} \left| \cos\left(\frac{\pi}{2}(k-1)\right) \right|, \tag{14}$$

indicating that u_i begins at the value $\epsilon_{i,max}$ and alternates between 0 and $\epsilon_{i,max}$ over each segment of $n_k + 1 = 11$ segments per control axis. An initial guess is devised with $t_0 = 0$, $t_f = 50$ days, and all knot times are evenly distributed over the interval such that each segment duration is identical. The state parameters in $\boldsymbol{x}$ are constructed to create a linear progression in each state from its initial value to its final value. Initial, final, and knot condition constraints are satisfied by the $\boldsymbol{x}$ supplied to the optimizer before the first iteration, but continuity constraints are not immediately satisfied. During the optimization process, $\boldsymbol{x}$ is improved such that all constraints are satisfied. In addition, the final $\boldsymbol{x}$ minimizes the objective function in Equation (11). The final state of this optimization routine is then used to generate a solution for partition p_2, ..., p_7 is a similar manner.

The results of the FSCT implementation are illustrated in Figures 3 and 4. As shown in Figure 3, the drug therapy regime is characterized by frequent interruptions in both u_1 and u_2. Moreover, the control history exhibits a general trend of opposing interruption schedules for u_1 and u_2. That is, for the majority of the multidrug therapy, rather than interrupting both drug schedules at the same time, the optimal solution recommends prescribing one drug while the other is temporarily interrupted (turned-off). Furthermore, several instantaneous control switches are noticeable, for example at $t = 200$ and $t = 400$ days. At each of these times there exist time durations $\Delta t_{i,k}$ for turning-on or turning-off the drugs, and each has been optimized to be identically zero. The implication is that certain user-prescribed control switches were unnecessary or non-optimal and are therefore eliminated from the final solution by driving the corresponding control axis duration to zero.

The state history in Figure 4 indicates periods of viral load suppression followed by brief spikes in viral population near the 0, 100 and 200 day mark. The spikes are accompanied by dips in the healthy target cell population. However, following each of these spikes, immune effectors are stimulated, eventually gaining continued viral load suppression beyond the 250 day mark. The results demonstrate that STI therapy may enable immune boosting and viral load suppression even after a significantly shorter treatment period compared to previous studies. Indeed, at the conclusion of STI therapy, the final state of the system is found to be

$$T_{1f} = 94208,\ T_{2f} = 185,\ T_{1f}^* = 295,\ T_{2f}^* = 9,\ V_f = 1576,\ E_f = 285702, \tag{15}$$

which is identified as being in the neighborhood of the healthy equilibrium $\boldsymbol{y}_h$. Furthermore, allowing the state in Equation (15) to drift in an uncontrolled manner results in the system asymptotically converging to $\boldsymbol{y}_h$. The convergence to the

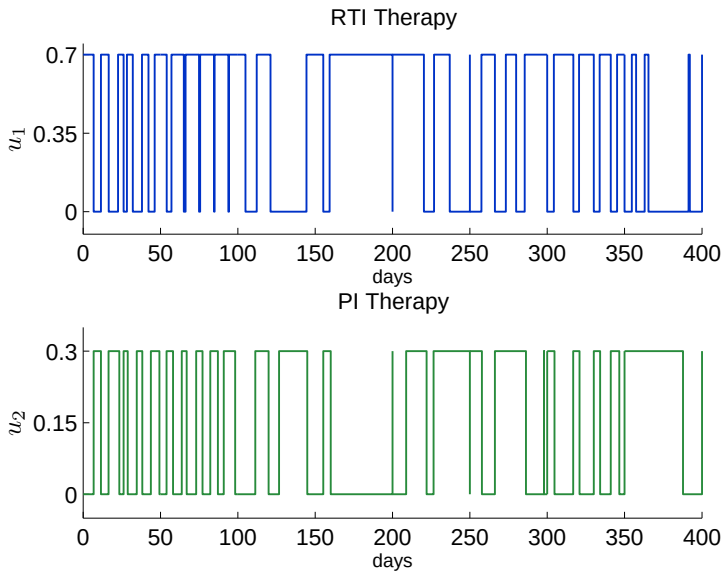

FIGURE 3. Optimal STI Therapy Obtained Using the FSCT Method. (Weighting Factors $Q = 0.001$, $R_1 = R_2 = 20$, and $S = 1000$.)

healthy equilibrium highlights the effectiveness of STI therapy in enabling natural, drug-free suppression of the viral load. The drift states are illustrated in Figure 5.

Note, since the underlying dynamics that govern the behavior of the uninfected target cell states, T_1 and T_2, are similar in nature, the time evolutions of the two states are expected to share a common trend. In fact, the same is true for the infected target cells, T_1^* and T_2^*, as is clearly illustrated in Figures 5(c)-(d). A zoomed in plot for Figure 5(a) is provided in Figure 6 to better illustrate the oscillatory nature of T_1 and verify its dynamic similarity to the T_2 state.

Recall that the optimal control trajectories illustrated in Figures 3 and 4 are obtained with control variables prescribed by Equation (14), where each control variable begins at $\epsilon_{i,max}$ (full-treatment). While it is possible to modify Equation (14) in a manner that enforces each control variable to begin at 0 (no-treatment), the modification, in effect, implies delaying the treatment until a later time. In fact, numerical studies performed with the same node and knot distribution as Equation (13) but with control variables prescribed to begin at zero did not yield a converged optimal result.

The FSCT based results demonstrate that STI may be an effective strategy in stimulating immune-response even when shorter treatment periods of 400 days are considered compared to $700-750$ days of treatment addressed in existing literature. Shorter treatment periods have several advantages including reducing the long term complications associated with extended drug usage. As stated earlier, the optimal solution illustrated in Figure 3 is characterized by high frequency interruptions. The smallest non-instantaneous control switch occurs in the RTI drug schedule following an approximate 8 hour rest (no-treatment) period. From a clinical perspective, a treatment interruption lasting only several hours may be considered less practical.

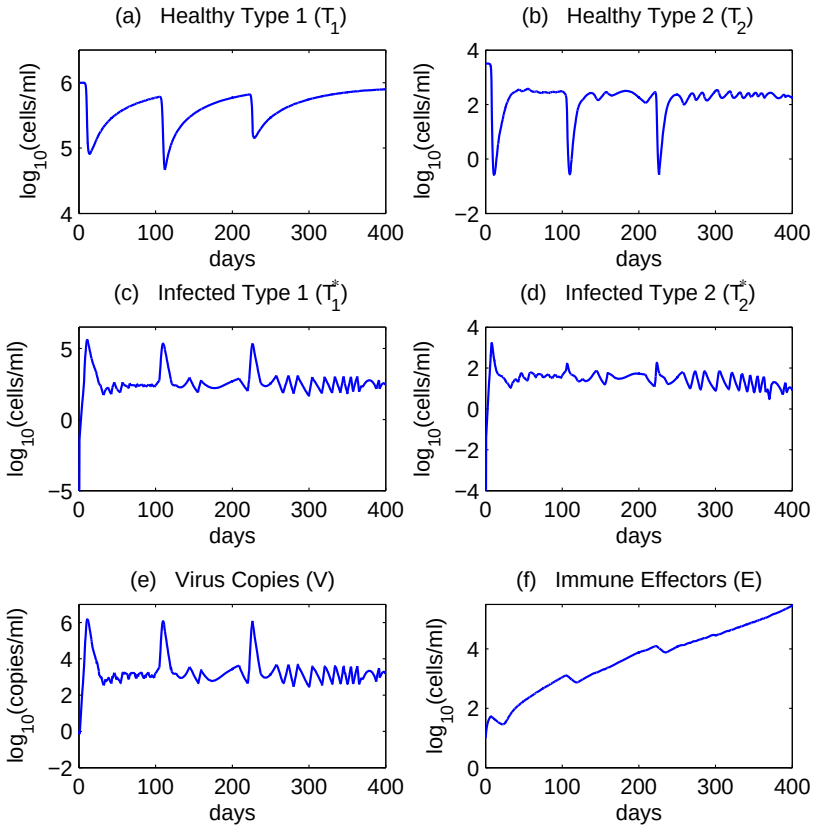

FIGURE 4. State History Corresponding to STI Control Strategy in Figure 3.

However, from a dynamical perspective, the FSCT solution indicates that a strong immune response and suppression of viral load is possible for a reduced treatment duration if frequent treatment interruptions are permitted. Furthermore, following the optimal treatment strategy, drug-free management of HIV becomes feasible as demonstrated in Figure 5 by the asymptotic convergence of the states to the healthy equilibrium.

Finally, it is observed that while the FSCT method is capable of producing optimal control histories for the STI problem, it does not provide optimal control laws for real-time implementation[24]. That is, the FSCT method is ultimately an open-loop control strategy, where the control solution is precomputed for the model described in Equation (1) and the parameters specifically prescribed in Table 1. A potential drawback of such an approach is that modeling errors, perturbations, and other unknowns may render the optimized treatment schedule ineffective. However, this limitation may be overcome by developing feedback control techniques for tracking an a priori computed FSCT solution[24]. For example, preliminary studies have considered FSCT together with Model Predictive Control (MPC) design for

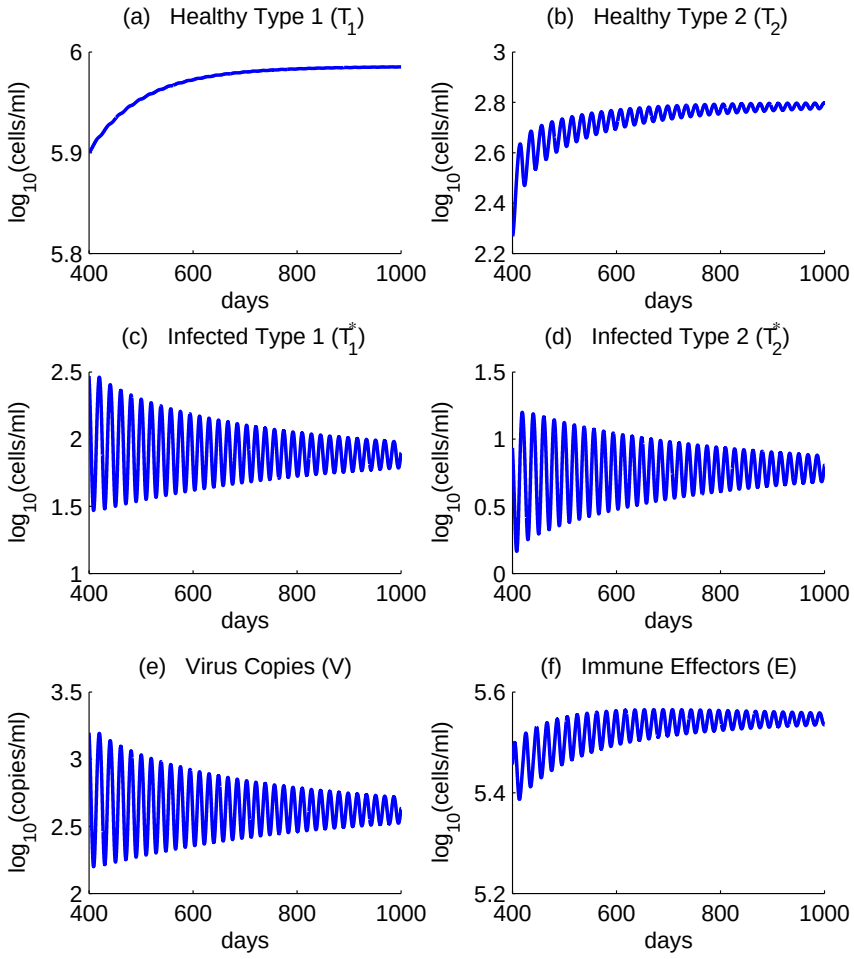

FIGURE 5. Control-Free Drift Following Conclusion of STI Therapy.

real-time implementation of problems encountered in the aerospace field[24, 25]. Specifically, the FSCT produced optimal state and control histories are used as reference trajectories for real-time tracking with an MPC control law. While further investigations are necessary in this regard, a similar approach may be used for the STI control problem so that optimized drug schedules can be realized in the presence of unmodeled effects or other unknowns such as missed doses by the patient.

4. **Conclusion.** Dynamic multidrug therapies, where drug combinations change in response to disease progression, may provide increased effectiveness of HIV treatment. However, complications may arise with long term usage of HIV drugs, including increased severity in side effects and drug resistance. Structured treatment

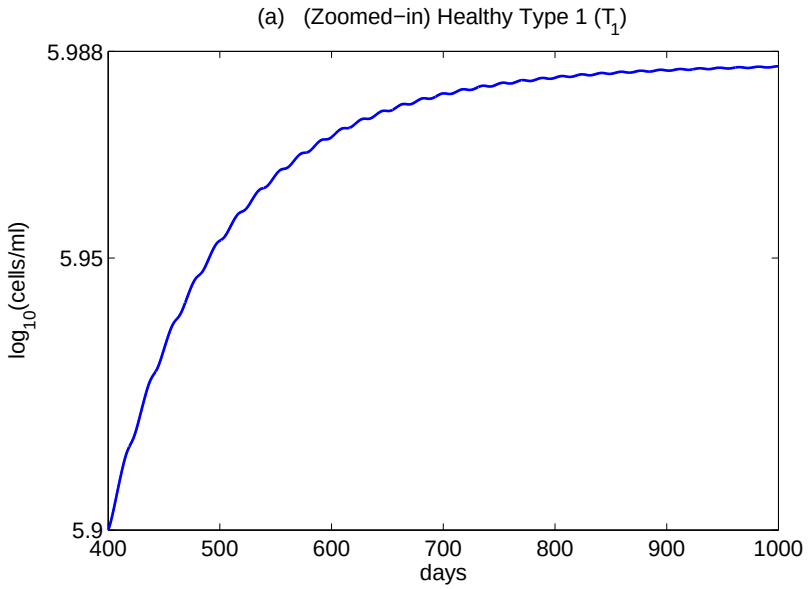

FIGURE 6. Zoomed-in Plot of T_1 State Control-Free Drift.

interruption, where patients are cycled on and off drugs, may lead to increased effectiveness of HIV therapy without the need of extended drug usage. In the presented research, the treatment of HIV infection is investigated through an optimal STI schedule of two drugs, RTIs and PIs. Specifically, STI therapy design is investigated in the context of a nonlinear hybrid optimal control problem and the optimal solution is determined through the novel FSCT method.

The FSCT method transcribes the hybrid optimal control problem into a NLP problem. The unique transcription method is able to handle multiple independent decision variables simultaneously, thereby providing an efficient optimization methodology for large scale problems such as optimal STI therapy design. With the control values limited to a finite set of zero (off-treatment) or maximum (on-treatment) efficacy, two independent switching schedules are obtained for the RTI and PI therapy. A relatively short treatment period of 400 days is considered compared to $700 - 750$ days in previous studies. Shorter treatment periods have several advantages, including reducing the long term complications associated with extended drug usage. The optimal solution obtained via FSCT demonstrates that high frequency treatment interruptions can lead to immune boosting and promote natural (drug-free) management of the viral load even when reduced treatment durations are in consideration.

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Received August 16, 2011; Accepted March 13, 2012.

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