49th IEEE Conference on Decision and Control
December 15-17, 2010
Hilton Atlanta Hotel, Atlanta, GA, USA

Dynamic Optimization Algorithms to mitigate HIV escape

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Abstract— **More than 25 years since HIV was discovered, a cure for infection remains to be found. One main concern in treating HIV infection is the emergence of resistant genotypes, causing the patient to proceed to AIDS. In this paper, we consider a specific simplified switched system model of HIV mutation dynamics with four genotypes under two different treatments. We address the optimal control problem for a general class of switched systems to find the drug sequence that minimizes the viral load. This gives a two point boundary value problem, that is difficult to solve due to the switched system nature. Alternatively, exhaustive search approaches may be used but are computationally prohibitive. To avoid these problems we propose several algorithms based on linear programming to reduce the computational burden whilst still computing the optimal sequence.**

I. Introduction

The last update of UNAIDS in 2009, showed a worldwide increase of people living with HIV (human immunodeficiency virus). Approximately 33.4 million people (adults and children) are living with HIV and the estimated number of people newly infected with HIV was 2.7 million in 2008, 20% higher than the number in 2000. At present, there is no known method to eradicate the virus. In addition, long term treatment to control the replication often fails, causing patients infected with HIV to progress to AIDS (Acquired Immune Deficiency Syndrome). The estimation of deaths due to AIDS in 2008 was 2 million people.

For this reason, much research has been conducted for the last 27 years in order to find a possible solution to stop the infection. The major effort has been done in drug design in order to attack different stages of the HIV life cycle. Combination antiretroviral therapy (ART) prevents immune deterioration, reduces morbidity and mortality, and prolongs the life expectancy of people infected with HIV [1]. The concentration of virus in the blood is reduced by at least five orders of magnitude. However therapies are only capable of partially and temporarily halting the replication of HIV. One of the main concerns with HIV infection is that resistant mutations have been described for all antiretroviral drugs currently in use. This has led to the conclusion that switching therapeutic options will be required lifelong in order to prevent HIV disease progression [1]. However, even this ART sequencing will fail in a proportion of patients in the presence of highly resistant mutants, that is, mutants resistant to all known drug combinations.

Motivated by these problems with HIV infection, some authors have examined viral mutation from a mathematical perspective. Several models have been presented in recent years; [2], [3], and [4]. Most of these models present a basic relation between CD4+T cells, infected CD4+T cells, macrophages and virus. Other authors have studied the drug scheduling problem [5], [6], [7], and [8]. A treatment model proposed by [9] shows how system theory allows the design of switching strategies to delay the emergence of highly resistant mutant viruses. Using symmetric replication rate values in two genotypes, it was proved in [10] that the optimal switching rule is given by the Filippov trajectory along the plane of these genotypes. However, it is unrealistic to expect complete symmetry in the viral response to alternate treatments.

Switched systems present interesting theoretical challenges and are important in many real-world problems [12]. The problem of determining optimal switching trajectories in hybrid systems has been widely investigated, both from theoretical and from computational point of view [15], and [18].

For continuous-time switched systems, several prior works present necessary and/or sufficient conditions for a trajectory to be optimal, by utilising of the minimum principle [16] and [17]. However, as yet there is no general solution for this optimal control problem. Numerical algorithms have been proposed to determine optimal trajectories. Iterative solutions based on Pontryagin's maximum principle have been proposed, for example [14], but without any guarantee of convergence. On the other hand, dynamic programming is good for problems of reasonable dimension [14]. Here, based on the specific problem considered, we proposed algorithms based on linear programming (LP) in order to reduce the computational burden and simulation time.

The paper is organized as follows. The optimal control problem is reviewed in Section III. Algorithms for the computation of optimal trajectories are proposed in Section IV. The application to the mitigation of viral escape is introduced in Section V. Simulations results are presented in Section VI. The paper is finalized in Section VII.

This work was supported by Science Foundation of Ireland 07/RPR/I177 and 07/PI/I1838.

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II. Notation

Throughout this paper, $\mathbb{R}$ denotes the field of real number, $\mathbb{R}^n$ stands for the vector space of all n-tuples of real numbers, $\mathbb{R}^{n\times n}$ is the space of $n\times n$ matrices with real entries, and $\mathbb{N}$ denotes the set of natural numbers. For x in $\mathbb{R}^n$, x_i denotes the i^{th} component of x, and the notation $x \succeq 0$ means that $x_i \geq 0$ for $1 \leq i \leq n$. $\mathbb{R}^n_+ = \{x \in \mathbb{R}^n : x \succeq 0\}$ denotes the non-negative orthant in $\mathbb{R}^n$. Matrices or vectors are said to be positive (non-negative) if all their entries are positive (non-negative); this is written as $A \succ 0$ and $A \succeq 0$, where 0 is the zero-matrix of the appropriate dimension. We write A' for the transpose of A, and $exp(A)$ for the matrix exponential of A.

III. Optimal Control Problem Review

Consider a discrete time switched system of the following general form

$$x(k+1) = A_{\sigma(k)}x(k) \tag{1}$$

defined for all $k \in \mathbb{N}$ where $x \in \mathbb{R}^n$ is the state, $\sigma(k)$ is the switching sequence $\sigma(k) \in \{1,2,...,N\}$, and $x(0) = x_0$ is the initial condition. For (1) to be a positive system for any switching sequence, A_i, $i \in \{1,...,N\}$ must be nonnegative matrices, that is $A_i \succeq 0$. Clearly, $\sigma(k)$ constrains $A_{\sigma(k)}$ to jump among the N vertices of the matrix polytope $A_1,...,A_N$. We assume that the full state vector is available and the control law is a memoryless state feedback

$$\sigma(k) = u(x(k)) \tag{2}$$

The cost functional to be minimized over all admissible switching sequences is given by

$$J = c'x(T) + \sum_{k=0}^{T-1} q'_{\sigma(k)}x(k) \tag{3}$$

where $x(k)$ is a solution of (1) with the switching signal $\sigma(k)$. The vectors c and q_i, $i = 1,2,\cdots,N$, are assumed to be positive. The optimal switching signal, the corresponding trajectory and the optimal cost functional will be denoted as $\sigma^o(k)$, $x^o(k)$ and $J(x_0,x^0,\sigma^0)$ respectively. Letting $u = \sigma(k)$, $q(k,x,u) = q_{\sigma(k)}$, and using the Hamilton-Jacobi-Bellman equation for the discrete case, we have;

$$V(x,k) = \min_{u\in U}\{q(k,x,u) + V(k+1,x(k+1))\} \tag{4}$$

where denoting the costate vector by $p(k)$, the general solution for this system is

$$V(x(k),k) = p(k)'x(k) \tag{5}$$

Using equations (1), (3), (4) and (5), we obtain the following system

$$\begin{aligned} x^o(k+1) &= A_{\sigma^o(k)}x^o(k) \\ p^o(k) &= A'_{\sigma^o(k)}p^o(k+1) + q_{\sigma^o(k)} \\ \sigma^o(k) &= \operatorname*{argmin}_s\{p^o(k+1)'A_sx^o(k) + q'_sx^o(k)\} \end{aligned} \tag{6}$$

with boundary conditions $x(0) = x_0$ and $p(T) = c$. Notice that equations (6) are inherently nonlinear. The state equations must be integrated forward whereas the co-state equation must be integrated backward, both according to the coupling condition given by the switching rule. As a result, the problem is a two point boundary value problem, and can not be solved using regular integration techniques.

IV. Algorithms for Computing Optimal Switching Trajectories

For the application to be presented in the next section, we consider only a penalty on the final state, that is,

$$J = c'x(T) \tag{7}$$

Given the initial condition $x(0)$ the optimal control problem can be written as

$$\min_{i_T,i_{T-1},...,i_1\in\{1,...,N\}} c'\ A_{i_T}\ A_{i_{T-1}}\ \dots\ A_{i_1}x(0) \tag{8}$$

Let us recursively define the sequence of matrices

$$\begin{aligned} \Omega_T &= c \\ \Omega_{k-1} &= [A'_1\Omega_k\ A'_2\Omega_k\ \dots\ A'_N\Omega_k] \end{aligned}$$

Then we have that $V(x,0) = \min_i \Omega'_{0,i}x$, where $\Omega_{0,i}$ is the ith column of Ω_0 and in general

$$V(x,k) = \min_i \Omega'_{k,i}x(k) \tag{9}$$

At each step of the evolution the feedback strategy can be computed as

$$u(x(k)) = \operatorname*{argmin}_i \Omega'_{k,i}x(k) \tag{10}$$

namely selecting the smallest component of the vector $\Omega'_kx(k)$. The implementation of this strategy that we call "brute force" requires storing the columns of $\Omega'_kx(k)$ whose number would be $1,N,N^2,N^3,\dots,N^T$. This exponential growth could be too computationally demanding. Fortunately, it can be seen that, in general, many of the columns of the matrices Ω_k may be redundant and can be removed. This can be done by applying established dynamic programming methods as follows (see [13] for details).

A. Algorithm 1: Reverse Time Solution

Given $\Omega_{k,i}$ solve the LP problem

$$\mu_{k,i} = \min_{x:\ \Omega'_{k,\bar{i}}\ x\ \geq\bar{1}} \Omega'_{k,i}x \tag{11}$$

where $\bar{1} = [1\ 1\ \dots\ 1]'$ and $\Omega_{k,\bar{i}}$ the matrix obtained from Ω_k by deleting the $i-th$ column. Then if $\mu_{k,i} \geq 1$ the column $\Omega_{k,i}$ is redundant (and it should be eliminated from Ω_k). This means that for each Ω_k we can generate a "cleaned" version $\widehat{\Omega}_k$ of Ω_k in which all the redundant columns are removed. We point out that this elimination can be done while constructing the matrices Ω_k. Indeed any redundant column of Ω_k necessarily produces only redundant columns

in Ω_{k-1}. Then the procedure for the generation of a reduced representation $\Omega_k^{(1)}$ is achieved by performing the procedure described above as follows;

Algorithm

1) For a finite steps number T, suppose we know initial condition for the state x_0 and the final costate condition $p(T) = c$
2) Define $\Omega_T^{(1)} = c$ and set $k = 1$
3) Compute the next matrix

$$\widehat{\Omega}_k = [A_1'\Omega_{k+1}^{(1)}\ A_2'\Omega_{k+1}^{(1)}\ \ldots\ A_N'\Omega_{k+1}^{(1)}]$$

4) For each column i of $\widehat{\Omega}_k$
   i) Solve the LP (11) with Ω_k set to $\widehat{\Omega}_k$
   ii) If $\mu_{k,i} \geq 1$ then delete column i from $\widehat{\Omega}_k$
5) After examining all the columns, we have a reduced $\widehat{\Omega}_k$, set $\Omega_k^{(1)} = \widehat{\Omega}_k$, set $k = k-1$.
6) If $k \geq 0$ return to (3), otherwise continue
7) The optimal sequence will be given by,

$$\sigma(k) = \text{argmin}_i\, \Omega_{k,i}'^{(1)} x_0$$

■

Therefore, although the exact solution in general is of exponential complexity, it may be computationally tractable for problems of reasonable dimension in terms of horizon and number of matrices.

Remark 1. Note that the algorithm described above generates a control law that can be implemented for any initial condition.

■

Remark 2. A dual version of the above algorithm, may be constructed by taking the forward iterations

$$\begin{aligned}\Theta_0^{(1)} &= x(0)\\ \widehat{\Theta}_{k+1}^{(1)} &= [A_1\Theta_k^{(1)}\ A_2\Theta_k^{(1)}\ \ldots\ A_N\Theta_k^{(1)}]\end{aligned}$$

Then we have that the optimal feedback strategy can be computed as

$$\sigma(k) = \underset{i}{\text{argmin}}\, \Theta_{N-k,i}' c$$

so that one can solve the LP problem

$$\nu_{k,i} = \min_{\pi:\ \Theta_{k,\bar{i}}'\pi\ \geq \bar{1}} \Theta_{k,i}'\pi$$

where $\Theta_{k,\bar{i}}$ is the matrix obtained from Θ_k by deleting the $i-th$ column. In this case, if $\nu_{k,i} \geq 1$, then column i of Θ_k is redundant and may be removed.

■

Remark 3. For a given initial state x_0 and final cost vector c, we can combine both the reverse and forward time solutions to, a midpoint (e.g. $T/2$) and finding $\min_{i,j} \Omega_{T/2,i}'^{(1)} \Theta_{T/2,j}^{(1)}$.

■

B. Algorithm 2: Box Constraint Algorithm

The algorithm presented in the last section removes columns that are redundant for any x in $\mathbb{R}_n^+$. This can be improved if we derive tighter bounds on $x(k)$ which apply independent of the switching sequence. If $A_{LB} \preceq A_i \preceq A_{UB}$ for all i, where bounds can be chosen as $A_{LB} = \min A_i$ and $A_{UB} = \max A_i$, then it must be true that

$$A_{LB}^k x_0 \leq x(k) \leq A_{UB}^k x_0 \tag{12}$$

We can therefore replace (11) with the test:

$$\mu_{k,i} = \min_{x,\alpha:\ \alpha \geq 0,\ \Omega_{k,\bar{i}}\, x \geq \alpha \bar{1},\ \beta_k} \Omega_{k,i}' x - \alpha \tag{13}$$

where β_k represents the inequality (12). If $\mu_{k,i} \geq 0$ then $\Omega_{k,i}$ is redundant.

C. Algorithm 3: Joint Forward/Backward Box Constraint Algorithm

Using a box constraint the search space for Algorithm 1 is reduced. We can apply Remark 3 in order further improved the last algorithm. Instead of solving $T/2$ steps forwards and then $T/2$ steps backwards and then combining sequences to get the optimal, we can solve backwards-forwards step by step in order to make a tighter box constraint as follows:

Algorithm

1) Initialize $\Omega_T^{(3)} = c$ and $\Theta_0^{(3)} = x_0$, $s = 1$
   one step backward
2) Find

$$\widehat{\Omega}_{T-s}^{(3)} = [A_1'\Omega_{T-s+1}^{(3)}\ A_2'\Omega_{T-s+1}^{(3)}\ \ldots\ A_N'\Omega_{T-s+1}^{(3)}]$$

3) For every ℓ solve the LP given in (13) using the next tighter box constrained:

$$A_{LB}^{T-2s+1} x_{LB,s-1} \leq x_{T-2s+1} \leq A_{UB}^{T-2s+1} x_{UB,s-1}$$

   where $x_{LB,s-1} = \min_\ell \Theta_{s-1,\ell}$ and $x_{UB,s-1} = \max_\ell \Theta_{s-1,\ell}$
4) Delete column $\widehat{\Omega}_{T-s,\ell}$ if $\mu_{T-s,\ell} \geq \alpha$
5) After examining all the columns, set $\Omega_{T-s}^{(3)} = \widehat{\Omega}_{T-s}^{(3)}$
   one step forward
6) Find

$$\widehat{\Theta}_s^{(3)} = [A_1\Theta_{s-1}^{(3)}\ A_2\Theta_{s-1}^{(3)}\ \ldots\ A_N\Theta_{s-1}^{(3)}]$$

7) For every ℓ, remove the column $\Theta_{s,\ell}'$ and solve the LP given in (13) using the tighter box constrained:

$$A'^{T-2s}_{LB}\pi_{LB,T-s} \leq \pi_s \leq A'^{T-2s}_{UB}\pi_{UB,T-s}$$

   where $\pi_{LB,T-s} = \min_\ell \Omega_{T-s,\ell}$ and $\pi_{UB,T-s} = \max_\ell \Omega_{T-s,\ell}$.
8) Delete column $\Theta_{s,\ell}$ if $\mu_{s,\ell} \geq \alpha$
9) After examining all the columns, set $\Theta_s^{(3)} = \widehat{\Theta}_s^{(3)}$
10) Increment s. If $s \leq T/2$ return to (2). Otherwise continue
11) Find the optimal sequence from $\min_{i,j} \Omega_{T/2,i}'^{(3)} \Theta_{T/2,j}^{(3)}$

■

V. Application to a Mathematical Model of Virus Mutation Treatment

In this section, we study a particular application of the switched control in positive systems theory described in the previous sections. For this purpose, we focus on the problem of treatment scheduling to minimize the adverse effects of virus mutation in HIV infection. Viral mutation is problematic since it gives rise to drug resistance if a single drug or single drug combination is given. For this purpose we use a simple model proposed by [9], such model is simple enough to allow control analysis and optimization of treatment switching.

A. Mutation base model

The based model we consider has n different viral genotypes, with viral populations, $x_i : i = 1,...n$; and D different possible drug therapies that can be administered, represented by $\sigma(t) \in \{1,...D\}$, where σ is permitted to change with time, t. We represent the behavior by an ordinary differential equation:

$$\dot{x}_i(t) = \rho_{i,\sigma(t)} x_i(t) - \delta x_i(t) + \sum_{j \neq i} \mu m_{i,j} x_j(t) \qquad (14)$$

where μ is a small parameter representing the mutation rate, δ is the death or decay rate and $m_{i,j} \in \{0,1\}$ represents the genetic connections between genotypes, that is, $m_{i,j} = 1$ if and only if it is possible for genotype j to mutate into genotype i. Equation (14) can be rewritten in vector form as

$$\dot{x}(t) = \left(R_{\sigma(t)} - \delta I\right) x(t) + \mu M x(t) \qquad (15)$$

where $M := [m_{ij}]$ and $R_{\sigma(t)} := diag\{\rho_{i,\sigma(t)}\}$.

B. A 4 variant, 2 drug combination model

As simple motivating example, we take a model with 4 genetic variants, that is $n = 4$, and 2 possible drug therapies, $D = 2$. The viral variants (also called 'genotypes' or 'strains') are described as:

- Wild type genotype (WTG): In the absence of any drugs, this would be the most prolific variant. However, it is also the variant that both drug combinations have been designed to combat, and therefore is susceptible to both therapies.
- Genotype 1 (G1): A genotype that is resistant to therapy 1, but is susceptible to therapy 2.
- Genotype 2 (G2): A genotype that is resistant to therapy 2, but is susceptible to therapy 1.
- Highly resistant genotype (HRG): A genotype, with low proliferation rate, but that is resistant to all drug therapies.

We take parameters values from [9]; the viral clearance rate is $\delta = 0.24\ day^{-1}$ which corresponds to a half life of slightly less than 3 days and proliferation rates are shown in Table I. Typical viral mutation rates are of the order of $\mu = 10^{-4}$. We take a mutation graph that is symmetric and circular, see Fig.1. That is, we allow only the connections: $WT \leftrightarrow G1$, $G1 \leftrightarrow HRG$, $HRG \leftrightarrow G2$ and $G2 \leftrightarrow WTG$. Other connections would require double mutations and for simplicity, we consider these to be of negligible probability. This leads to the mutation matrix:

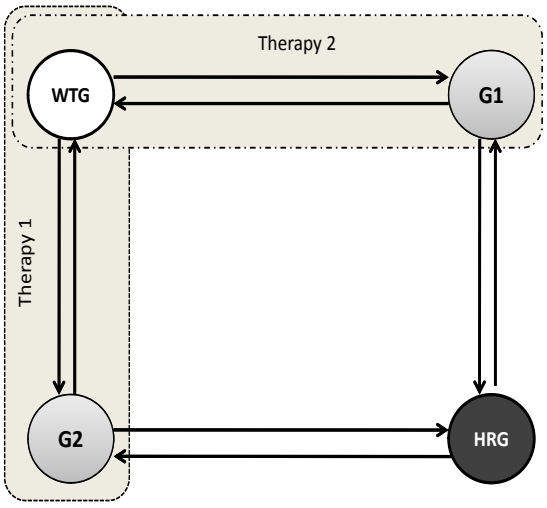

Fig. 1. Mutation Tree

Variant	Therapy 1	Therapy 2
Wild type (x_1)	$\rho_{1,1} = 0.05$	$\rho_{1,2} = 0.05$
Genotype 1 (x_2)	$\rho_{2,1} = 0.27$	$\rho_{2,2} = 0.15$
Genotype 2 (x_3)	$\rho_{3,1} = 0.01$	$\rho_{3,2} = 0.25$
HR Genotype (x_4)	$\rho_{4,1} = 0.27$	$\rho_{4,2} = 0.27$

TABLE I
Replication rates for viral variants and therapy combinations for an asymmetric case

$$M = \begin{bmatrix} 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \end{bmatrix} \qquad (16)$$

C. Cost Function Motivation

For biological reasons, if the total viral load is small enough during a finite time of treatment, then there is a significant probability that the total virus load becomes zero and stays at zero. Notice that in a more accurate stochastic model of viral dynamics, $x_i(t)$ is the expected value of the number of virus v_i. Therefore, from Markov's inequality, we can show that small $E[x]$ guarantees a high probability of viral extinction $(P(\sum_i v_i = 0) \geq 1 - E[\sum_i v_i] = 1 - \sum_i x_i)$. It is therefore logical to propose a cost

$$J := c' x(T) \qquad (17)$$

where c is the column vector with all ones, and T is an appropriate final time.

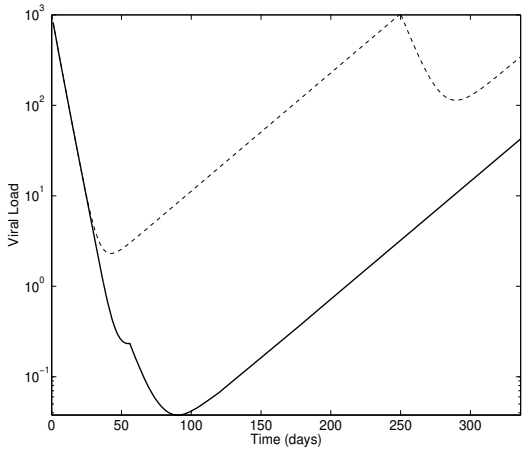

Fig. 2. Total virus load using optimal treatment in continuous line and using switch on failure in dashed line

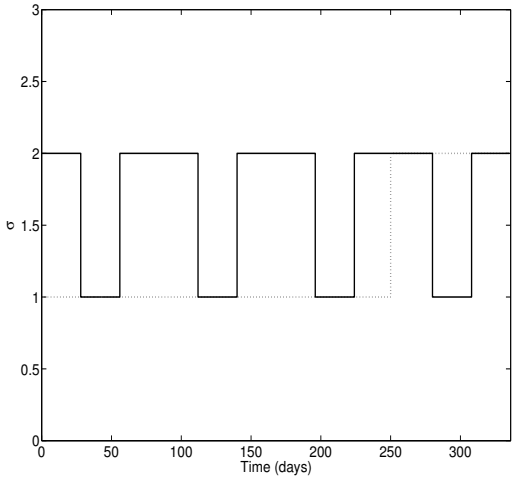

Fig. 3. Optimal switching rule in continuous line and switch on failure rule in dashed line

VI. Simulation results

The model for the treatment of viral mutation given in (14) is described in continuous time. In practice, measurements can only reasonably be made infrequently. For simplicity, we consider a regular treatment interval τ, during which treatment is fixed. If we use $k \in \mathbb{N}$ to denote the number of intervals since $t = 0$, then

$$x(k+1) = A_{\sigma(k)}x(k) \tag{18}$$

where $x(k) = x(k\tau)$ is the sampled state, $A_\sigma := exp(R_\sigma - \delta I + \mu M)\tau$ and σ is constant during the interval $t \in [k\tau, (k+1)\tau]$.

The decision time τ is fixed to 28 days, note that typically during the treatment of HIV, clinical visits have a frequency of once a month or less. Using the parameter values of

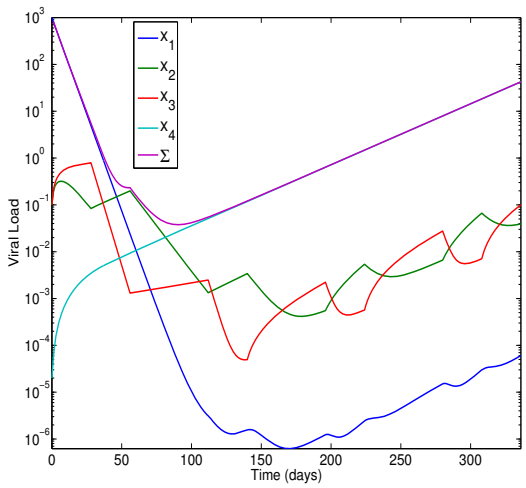

Fig. 4. Four genotypes dynamic under optimal treatment

TABLE II
Total viral load concentration at the end of treatment of 336 days using decision time of 28 days

Monotherapy	Switched on failure	Optimal Treatment
9.89×10^6	344.66	42.56

Table I we consider three different scenarios of treatment; one is using a single therapy without switching, which is called monotherapy. Then we consider a "switched on failure" treatment, based on the guidelines for the use of the antiretroviral agents in HIV-1 infected adults presented by the Department of Health and Human Services (DHHS) [11], which recommends to switch of treatment when HIV RNA is over 1000 copies/ml (treatment failure). To end, we want to compute the optimal switching rule in order to minimize the total viral load concentration at the end of the treatment.

We can observe in Table II, which presents simulated results after 336 days of treatment, that there is a significant difference in the total viral load between the monotherapy and switched on failure treatment. This is because treatment 2 is introduced around week 35, see Fig.2, then the proliferation rate of genotype 1 is affected, giving a decreased in the total viral load. However, using an optimal control approach, the viral load is decreased to undetectable levels ($\leq$ 50 copies/ml) introducing treatment 2 as is portrayed in Fig.3. This optimal switching rule was computed using the algorithms proposed in Section IV. Fig.4 shows how during a period of time the optimal switching rule, maintains a low wild type concentration and suppresses the concentrations of genotypes 1 and 2. However, the highly resistant genotype eventually grows since none of the therapies affect this genotype.

Using switched on failure treatment and the optimal one

in Fig.2, we conclude that prior treatment is important to suppress HIV RNA levels maximally and prevent further selection of resistant mutations. However, to find the optimal trajectories is difficult, because the system of equations (6) is a two point boundary value problem, with additional complexities arising from the discrete nature of the switching signal. One possible numerical solution is a "brute force" approach which analyzes all possible combinations for therapy 1 and 2 with decision time $\tau = t_d$ for a period of T days, that is, we evaluate $2^{\frac{T}{t_d}}$ possible treatment combinations.

To examine long simulation times, it is necessary to find faster algorithms. In Table III we test the algorithms for 15 steps of simulation; and it can be seen that "brute force" is extremely slow for this period of simulation, this is because we are analyzing 4096 columns. Using algorithm 1 we can get a faster simulation, removing redundant columns. At the end of the optimization 11 columns are remain; a reduction of 99.7% of columns respect to "brute force"' and computational time is reduced dramatically. Using the box constrained algorithm this problem can be solved in less time. Starting from initial and end points, Remark 3 can

TABLE III
COMPUTATIONAL RESOURCES

Method	Brute Force	Algorithm 1	Box Constraint
Time (sec)	555	4.44	3.88
Columns	4096	11	1

reduce computational time in last algorithms, that is for every step in both directions we keep less columns compare to a single direction algorithm.

Table IV shows that the box constraint algorithm using Remark 3 has a lower computation time than algorithm 1. Moreover, we obtain further improvement using algorithm 3; the process of removing columns is more effective than other algorithms due to the tighter box constraint. These results show that we can compute a treatment sequence in a short period of time. For example, 48 decision steps can be solved using algorithm 3 in 6.5 mins, something that is impossible with "brute force".

TABLE IV
COMPUTATIONAL RESOURCES USING REMARK 1.

Method	Algorithm 1	Box Constraint	Algorithm 3
Time (sec)	3.3	2.3	1.74
Forward Columns	7	3	1
Backward Columns	10	6	2

VII. CONCLUSIONS

The problem of optimal scheduling treatment to mitigate the viral escape in HIV has been addressed. Using a switched system for modeling HIV mutation treatment the optimal control is developed through Hamilton-Jacobi theory, resulting in a difficult two boundary condition problem. For this purpose we use a "brute force" algorithm in order to analyze every possible sequence. However, this approach results in an exponential growth in computational demands. To deal with this problem we design algorithms for a general class of switched systems using linear programming able to remove redundant columns based on dynamic programming methods. Simulation results show the effectiveness of these methods.

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