Sub-optimal switching with dwell time constraints for control of viral mutation

Esteban A. Hernandez-Vargas, Patrizio Colaneri, Richard H. Middleton

Abstract— **Regulation of mutant viri is important in many disease including HIV infection. Under current multi-drug Anti-Retroviral Therapies for HIV treatment, resistant mutations and failure to regulate viral load is typically observed after approximately 6 years. When this occurs, the current therapy must be abandoned and a new therapy initiated. An alternate approach is to treat this as a switching control problem, wherein therapy may be alternated well before virological failure is observed. In this paper we extend previous work on suboptimal control of a simplified model of HIV infection with mutations. The particular extension here is to include a 'dwell time' constraint on the switching actions, that is, impose a strict minimum time between altering therapy.**

I. Introduction

In this paper, motivated by the problem of treatment scheduling to mitigate HIV mutation, we consider the problem of therapy scheduling for mutating pathogens. According to [1], there continues to be a growth in the number of people living with HIV infection, although new HIV infection rates and AIDS related mortality are down. These results are largely due to the success of Highly Active Antiretroviral Therapy (HAART). HAART is composed of at least three different types of drugs, that interfere with different key mechanisms of the HIV infection cycle. There are 20 approved antiretroviral drugs in 6 mechanistic classes to design combination regimens [2].

However, the process of reverse transcription during viral infection is very error-prone, and the resulting genetic mutations may cause drug resistance or allow the virus to evade the immune system. The resultant genetic diversity is a result of both a rapid replication cycle (with the generation of up to 10^{10} viri every day in untreated HIV infection), coupled with a high mutation rate of approximately 3×10^{-5} per nucleotide base per cycle of replication [3]. Therefore, HAART may not eliminate the virus and continual therapy is essential. In addition, because of the emergence of resistant mutations, in almost all patients, the therapy used must be altered over time to prevent viral rebound and progression to AIDS (e.g. [4]).

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A natural question that can be posed is what is the best protocol for deciding when and how to switch to a new therapy in the treatment of HIV infection? This question has been an argumentative issue in the panel of anti-retroviral guidelines for adults and adolescents with HIV in USA [2]. This body only makes recommendations with the agreement of two-thirds of the panel members. Such agreement has not been reached in the 2011 version of the manual [2].

The most aggressive approach proposed for clinical practice would be to change for any repeated detectable viremia (HIV RNA $>$ 50 copies/ml after suppression). Other approaches allow detectable viremia up to a higher level (1000-500 copies/ml). However, ongoing viral replication in the presence of antiretroviral drugs promotes the selection of drug resistance mutations and may limit future treatment options [5]. Promising results were obtained in a preliminary evaluation of proactive switching between HAART regimens in a clinical trial called SWATCH (SWitching Antiretroviral Therapy Combinations against HIV-1) performed by [12]. In this initial trial alternating regimens outperformed virological failure based treatment. Nevertheless, the appropriate time to switch between treatments remains unclear.

In this paper, we follow line of research taking a systems and control approach to the design of protocols in HIV infection [6], [7], [8]. There are a number of possible models for HIV and mutation dynamics that may be used. One of the well known models is that in [9], or related works in [6]. With some simplifying assumptions, we have pursued analysis of a mathematical model in the form of a switched positive linear system (see for example [8], [10]). This has lead to a number of results aimed at optimal and suboptimal therapy schedules to combat mutant HIV (see for example [11], and preliminary clinical trials in [12]). Amongst the various approaches to this problem, sub-optimal (or guaranteed cost) approaches are attractive from a computational point of view (e.g. [8]). However, there are a number of limitations in these earlier works. One of these limitations is the lack of realistic constraints on the minimum time between decisions. In fact, in some cases, at least in an ideal setting, optimal controls can be shown to be sliding mode, and therefore switch infinitely fast [10]. This leads us to consider application of results on switching control with a 'dwell time' constraint following lines such as [13]. We extend these early results on infinite time dwell time constrained switching to finite time results for application to a model of HIV mutation dynamics.

The paper is organized as follows. A general nonlinear model and a more specialised positive linear switched system approximation are introduced in Section II. The control problem and some earlier results are reviewed in Section III. The main result of guaranteed cost with dwell time is presented in Section IV. Simulations results are discussed in Section V. The paper is finalized in Section VI.

A. Notation

In 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), that is $A \succ 0$ and $A \succeq 0$, where 0 is the zero-matrix of the appropriate dimension. The transpose of A is represented by A', and e^A is the matrix exponential of A.

II. HIV Mutation Model

We consider the mathematical model proposed in [14]. This model contains several of the key biological factors known to be present in HIV infection. It also matches reasonably well all three stages of typical HIV infection. These three stages are: (i) an early peak in the acute infection; (ii) a long asymptomatic period; and, (iii) a final increase in viral load with simultaneous collapse in healthy CD4+T cell counts. Furthermore, this model maintains its qualitative behaviour, that is the three key stages of the infection, despite moderately parameter variations of any of the key dynamic parameters.

Therefore, based on the proposed model [14] we derived a non-linear model with mutations using the following populations: uninfected CD4+T cells (T), infected CD4+T cells (T^*), uninfected macrophages (M), infected macrophages (M^*), and HIV population (V). The model is as follows:

$$\begin{aligned}
\dot{T} &= s_T + \frac{\rho_T}{C_T+V_T}TV_T - \sum_{i=1}^{n} k^i_{T,\sigma}TV_i - \delta_T T \\
\dot{M} &= s_M + \frac{\rho_M}{C_M+V_T}MV_T - \sum_{i=1}^{n} k^i_{M,\sigma}MV_i - \delta_M M \\
\dot{T}^*_i &= k^i_{T,\sigma}TV_i + \sum_{j=1}^{n} \mu m_{i,j}V_jT - \delta_{T^*}T^*_i \qquad (1)\\
\dot{M}^*_i &= k^i_{M,\sigma}MV_i + \sum_{j=1}^{n} \mu m_{i,j}V_jM - \delta_{M^*}M^*_i \\
\dot{V}_i &= p^i_{T,\sigma}T^*_i + p^i_{M,\sigma}M^*_i - \delta_V V_i
\end{aligned}$$

where $V_T = \sum_{i=1}^{n} V_i$. Further explanation of the biological mechanisms and parameters involved in (1) can be found in [14].

As a simple motivating example of HIV mutation, we consider a model with 4 genetic variants, that is $n = 4$, and 2 possible drug therapies, $D = 2$. Note that a more accurate model would take into account detailed mutation graphs and proliferation rates as, for example, available at [15]. The wild type (g_1) is the most prolific variant in the absence of any drugs, however, it is also the variant that all drug combinations have been designed to combat, and therefore is susceptible to all therapies. After mutations the highly resistant genotype (HR) is a genotype with low proliferation rate, but resistant to all drug therapies [10].

$$\begin{array}{ccc}
(1:WT) & \Leftrightarrow & (2) \\
\Updownarrow & & \Updownarrow \\
(3) & \Leftrightarrow & (4:HR)
\end{array}$$

Fig. 1: Mutation Tree

Based on the guidelines for the use of antiretroviral agents [2], we consider therapies that are composed of reverse transcriptase inhibitors and protease inhibitors, which are modelled as follows;

$$\begin{aligned}
k^i_{T,\sigma} &= k_T f_i \eta^T_{\sigma,i} \qquad & k^i_{M,\sigma} &= k_M f_i \eta^M_{\sigma,i} \\
p^i_{T,\sigma} &= p_T f_i \theta^T_{\sigma,i} \qquad & p^i_{M,\sigma} &= p_M f_i \theta^M_{\sigma,i}
\end{aligned}$$

where $\eta_{\sigma,i}$ represents the infection efficiency for genotype i under treatment σ, and $\theta_{\sigma,i}$ expresses the viral production efficiency for the genotype i under treatment σ.

We assume that in the absence of treatment, mutation reduces the fitness of the genotype. For simplicity, we use linearly decreasing factors f_i, which represents the fitness of the genotype i. We assume that therapy 1 is effective against genotypes 1 and 2, whilst 3 and 4 are resistant to therapy 1. Conversely, therapy 2 is effective against genotypes 1 and 3 but not 2 and 4. Based on clinical evidence [16], protease inhibitors are more effective in CD4+T cells than in macrophages, which is represented by $\eta^T_{\sigma,i} > \eta^M_{\sigma,i}$ and $\theta^T_{\sigma,i} > \theta^M_{\sigma,i}$.

A. Switched Linear System Approximation

The design of switching strategies, particularly optimal strategies, for the non-linear model (1) can be very demanding. Under normal treatment circumstances typical clinical data suggest that macrophages and CD4+T cell counts are approximately constant [11], [17]. This assumption allows us to simplify the dynamics to a switched linear system:

$$\begin{aligned}
\dot{T}^*_i &= k^i_{T,\sigma}TV_i - \delta_{T^*}T^*_i + \sum_{j=1}^{n} \mu m_{i,j}V_jT \\
\dot{M}^*_i &= k^i_{M,\sigma}MV_i - \delta_{M^*}M^*_i + \sum_{j=1}^{n} \mu m_{i,j}V_jM \qquad (2)\\
\dot{V}_i &= p^i_{T,\sigma}T^*_i + p^i_{M,\sigma}M^*_i - \delta_V V_i
\end{aligned}$$

where T and M are treated as approximately constant. The infection rate is expressed as $k^i_{T,\sigma}$ for CD4+T cells and

$k^i_{M,\sigma}$ for macrophages. Viral proliferation is achieved in infected activated CD4+T cells and infected macrophages, this is represented by $p^i_{T,\sigma}$ and $p^i_{M,\sigma}$ respectively. These parameters depend on the fitness of the genotype and the therapy that is being using. The mutation rate is expressed by μ, and $m_{i,j} \in \{0,1\}$ represents the genetic connections between genotypes:

$$[m_{ij}] = \begin{bmatrix} 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \end{bmatrix}$$

The death rates for the relevant species are δ_{T^*}, δ_{M^*}, δ_V. The system (2) can be rewritten as follows

$$\dot{x} = \begin{bmatrix} \Lambda_{1,\sigma} & 0 & \dots & 0 \\ 0 & \Lambda_{2,\sigma} & \dots & 0 \\ \vdots & & \ddots & \vdots \\ 0 & 0 & \dots & \Lambda_{n,\sigma} \end{bmatrix} x + \mu M_u x \tag{3}$$

where $x' = [T^*_1, M^*_1, V_1, \dots, T^*_n, M^*_n, V_n]$, $\Lambda_{j,\sigma}$ is given by

$$\Lambda_{j,\sigma} = \begin{bmatrix} -\delta_{T^*} & 0 & k^i_{T,\sigma} T \\ 0 & -\delta_{M^*} & k^i_{M,\sigma} M \\ p^i_{T,\sigma} & p^i_{M,\sigma} & -\delta_V \end{bmatrix}$$

and the mutation matrix has the following form (where $\otimes$ denotes the Kronecker product):

$$M_u = [m_{i,j}] \otimes \begin{bmatrix} 0 & 0 & T \\ 0 & 0 & M \\ 0 & 0 & 0 \end{bmatrix}.$$

III. Control Problem Review

The switched positive linear system (3) can be expressed in the following form:

$$\Sigma_A : \dot{x}(t) = A_{\sigma(t)} x(t), \quad x(0) = x_0, \tag{4}$$

where $A_{\sigma(t)}$ switches between some given finite collection (in the example above, $N = 2$) of matrices A_1,..., A_N, $t \geq 0$, $x(t) \in \mathbb{R}^n_+$ is the state variable vector, $x_0 \in \mathbb{R}^+_n$, $\sigma(t)$ is the piecewise constant switching signal. This function σ is assumed to have a finite number of discontinuities, which we call the switching times. These switching times are assumed to be bounded in number on every bounded time interval and $\sigma(t)$ takes a constant value on every interval between two consecutive switching times.

The system (4) is said to be positive if and only if the matrices A_i are Metzler, that is, their non-diagonal elements are non-negative. Then, for every non-negative initial state and every non-negative input its state and output are non-negative.

The optimal control problem for positive switched systems with application to the scheduling treatment for HIV infection was formulated in [10], for which the terminal cost functional to be minimized over all admissible switching sequences is represented by

$$J := c' x(t_f) \tag{5}$$

where $x(t)$ is a solution of (4) with the switching signal $\sigma(t)$, $c = [0,0,1,...,0,0,1] \in \mathbb{R}^n$, and t_f is an appropriate final time. Here we use a final time cost, since the typical course of infection under treatment, exhibits a long period of suppression of the virus, followed by exponential growth of the highly resistant mutant. If the rate of final exponential growth is approximately independent of the treatment, then the total viral load at the terminal time is a surrogate for the duration of viral suppression to low levels. This duration is an important clinical parameter. For example, [18] showed that in the absence of ongoing viral replication, the generation of new variants is also arrested.

The optimal switching signal, the corresponding trajectory and the optimal cost functional will be denoted by $\sigma^o(t,x_0)$, $x^o(t)$ and $J(x_0, x^o, \sigma^o)$ respectively. The Hamiltonian function relative to (4) with the cost functional (5) is given by

$$H(x,\sigma,\pi) = \pi'(t) A_\sigma x(t) \tag{6}$$

If $\sigma^o(t,x_0) : [0,t_f] \times \mathbb{R}^n_+ \to \mathscr{I} = \{1,\dots,N\}$ be an admissible switching signal relative to x_0 and $x^o(t)$ be the corresponding trajectory. Then the optimal system can be formulated as follows:

$$\dot{x}^o(t) = A_{\sigma^o(t,x_0)} x^o(t) \tag{7}$$

$$-\dot{\pi}^o(t) = A'_{\sigma^o(t,x_0)} \pi^o(t) \tag{8}$$

$$\sigma^o(t,x_0) = \arg\min_{i \in \mathscr{I}} \{\pi^{o\prime}(t) A_i x^o(t)\} \tag{9}$$

where $\pi^o(t)$ denote a positive vector solution of the system of differential equations with the boundary conditions $x^o(0) = x_0$ and $\pi^o(t_f) = c$. Notice that computation of the optimal control law as discussed in (9) is quite demanding, this is due to the two point boundary value problem: the states must be integrated forward whereas the co-state must be integrated backwards, both with the coupling condition of the switching rule (9).

A. Guaranteed Cost Control

Due to the complexity of either analytical or numerical solution to the optimal control problem, a suboptimal (that is, guaranteed cost) algorithm associated with the optimal control problem was introduced in [10]. Let us define

$$\Lambda := \left\{ \lambda \in \mathbb{R}^N : \sum_{i=1}^N \lambda_i = 1,\ \lambda_i \geq 0 \right\} \tag{10}$$

which yields the following piecewise linear co-positive Lyapunov function:

$$v(x) := \min_{i=1,\dots,N} \alpha_i' x = \min_{\lambda \in \Lambda} \left(\sum_{i=1}^N \lambda_i \alpha_i' x \right) \tag{11}$$

The Lyapunov function in (11) is not differentiable everywhere. Given the set $I(x) = \{i : v(x) = \alpha_i' x\}$, $v(x)$ fails to be differentiable precisely for those $x \in \mathbb{R}^n_+$ such that $I(x)$ is composed of more than one element, that is in the conjunction points of the individual Lyapunov functions $\alpha_i' x$. One way of designing a switching control scheme is via the guaranteed cost approach. For example, with a finite time horizon, in [10], we proved the following result:

Lemma 1: Consider the positive switched linear system (4). Suppose that we can find $p_{ij} \geq 0; i \neq j = 1,...N$ and positive solutions $\alpha_i(t) : i = 1,...N$ over $t \in [0, t_f]$ of the coupled differential equations:

$$\frac{d}{dt}\alpha_i(t) + A_i^{'}\alpha_i(t) + \sum_{j \neq i}^{N} p_{ij}(\alpha_j - \alpha_i) = 0 \qquad (12)$$

with final condition, $\alpha_i(t_f) = c; i = 1,...N$;

Then, the switching law,

$$\sigma(t) = \arg\min_{i=1,...N} \alpha_i'(t)x(t) \qquad (13)$$

guarantees that

$$c'x(t_f) \leq \min_{i=1,...N} \alpha_i'(0)x_0 \qquad (14)$$

Notice that (12) requires the preliminary choice of the parameters p_{ij}. In particular, the search for p_{ij} and α_i that satisfy Lemma 1 is a bilinear matrix inequality. At the cost of some conservatism in the upper bound, these bilinear parameters can be reduced to a single one, say ζ, so allowing an easy search for the best ζ as far as the upper bound is concerned.

Corollary 1: Let $q \in \mathbb{R}^n_+$ and $c \in \mathbb{R}^n_+$ be given, and let the positive vectors $\{\alpha_1, \ldots, \alpha_N\}$, $\alpha_i \in \mathbb{R}^n_+$ satisfy for some $\zeta > 0$ the modified coupled co-positive Lyapunov differential inequalities

$$\frac{d}{dt}\alpha_i(t) + A_i'\alpha_i + \zeta(\alpha_j - \alpha_i) \preceq 0 \qquad i \neq j = 1, \ldots, N. \quad (15)$$

with final condition $\alpha_i(t_f) = c$, $\forall i$. Then the state-switching control is such that

$$c'x(t) \leq \min_{i=1,...,N} \alpha_i'(0)x_0 \qquad (16)$$

■

IV. Dwell time constrained guaranteed cost switching

A switched system is stable if all individuals subsystems are stable and the switching is sufficiently slow to allow the transient effects to dissipate after each switch [19]. The introduction of the dwell time (T), see for example Fig. 2, has been very important in switched system theory.

Nevertheless, because of the nature of HIV infection, the system (1) may be unstable and in fact not stabilizable. Due to the existence of a highly resistant genotype, once this variant has "emerged" the population will explode after a period of time. This motivates our study of design strategies for a finite-time horizon (t_f).

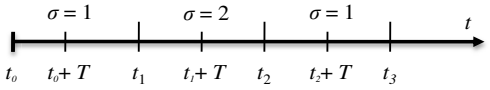


Fig. 2: Dwell-time Switching signal

Here we use the ideas espoused in [13] to incorporate dwell time constraints into this formulation. For our main result, Theorem 1, we need the following definition of the switching control law:

Definition 1: Given positive vector valued functions of time, $\alpha_i(t)$, we define a finite (or countable if $t_f = \infty$) set of switching times, $t_k : k = 0, 1, ...$, and switches, $\sigma(t)$, as follows:

$$\begin{aligned} t_0 : &= 0; \quad \sigma(0) = \arg\min_i \alpha_i(0)'x(0), && (17)\\ \kappa(t) : &= min_t \{k : t > t_k\} && (18)\\ \sigma_k : &= \arg\min_i \alpha_i(t_k)'x(t_k), && (19)\\ t_{k+1} : &= \arg\max_{t \geq t_k + T} \left\{\alpha_{\sigma_k}'x(t) \leq \alpha_j(t)'e^{A_j T}x(t)\right\} && (20)\\ \forall j &\neq \sigma_k \quad k = 0, 1, 2, ...\\ \sigma(t) &:= \sigma(t_{\kappa(t)}). && (21) \end{aligned}$$

We can now formulate the main result of this paper as follows:

Theorem 1: Consider the switched positive linear system (4). Suppose that we can find $p_{ij} \geq 0; i \neq j = 1,...N$ and positive solutions $\alpha_i(t) : i = 1,...N$ over $t \in [0, t_f]$ of the coupled differential equations:

$$\frac{d}{dt}\alpha_i(t) + A_i^{'}\alpha_i(t) + \sum_{j \neq i}^{N} p_{ij}(e^{A_j' T}\alpha_j - \alpha_i) = 0 \qquad (22)$$

with final conditions, $\alpha_i(t_f) = c; i = 1,...N$. Then, the switching law with dwell time T given in Definition 1 guarantees that

$$c'x(t_M) \leq \min_{i=1,...N} \alpha_i^{'}(0)x_0$$

where $M := \kappa(t_f)$.

Proof:

Taking $V(t) = x(t)'\alpha_{\sigma(t)}(t)$ - with $\sigma(t)$ given above, the proof follows in several steps. Firstly, note that at each instance $t = t_k$, there may be a discontinuity in $V(t)$. However, at each discontinuity, in view of (19), we have:

$$V(t_k^+) \leq V(t_k^-) \qquad (23)$$

Secondly, note that

$$\begin{aligned} V(t_k + T^-) &= \alpha_{\sigma_k}'x(t_k + T)\\ &= \alpha_{\sigma_k}'e^{A_{\sigma_k} T}x(t_k)\\ &\leq \alpha_{\sigma_{k-1}}'x(t_k) \text{ in view of (20)}\\ &= V(t_k^-) \end{aligned}$$

Thirdly, over the interval $t \in [t_k + T^-, t_{k+1}^-)$, (21) must be satisfied, and therefore we have:

$$\begin{aligned}
\dot{V}(t) &= \frac{d}{dt}\left(\alpha'_{\sigma_k}(t)x(t)\right) \\
&= \alpha'_{\sigma_k}(t)A_{\sigma_k}x(t) + \frac{d}{dt}\left(\alpha'_{\sigma_k}(t)x(t)\right) \\
&\leq -\sum_{j\neq\sigma_k}^{N} p_{j\sigma_k}(\alpha'_j e^{A_j T} - \alpha_{\sigma'_k})x(t) \text{ using (22)} \\
&\leq 0 \text{ in view of (20)}
\end{aligned}$$

It follows that

$$V(t_{k+1}^-) \leq V(t_k + T)$$

and therefore

$$V(t_{k+1}^-) \leq V(t_k^-)$$

so that $V(t_M) - V(0) \leq 0$. ■

In a similar way to Corollary 1, by further restricting the class of solutions, we can reduce the BMIs in Theorem 1, to LMIs with one bilinear term which admits ready solution via a line search.

Corollary 2: Consider the switched positive linear system (4). Suppose that we can find $\gamma \geq 0$ and positive $\alpha_i(t) : i = 1,...N$ over $t \in [0, t_f]$ of the coupled differential equations:

$$\frac{d}{dt}\alpha_i(t) + A_i'\alpha_i(t) + \gamma(e^{A_j'T}\alpha_j - \alpha_i) \preceq 0; \quad \forall j \neq i \qquad (24)$$

with final conditions, $\alpha_i(t_f) = c; i = 1,...N$. Then, the switching law with dwell time T given in Definition 1 guarantees that

$$c'x(t_M) \leq \min_{i=1,...N} \alpha_i'(0)x_0$$

where $M := \kappa(t_f)$.

■

V. Simulation results

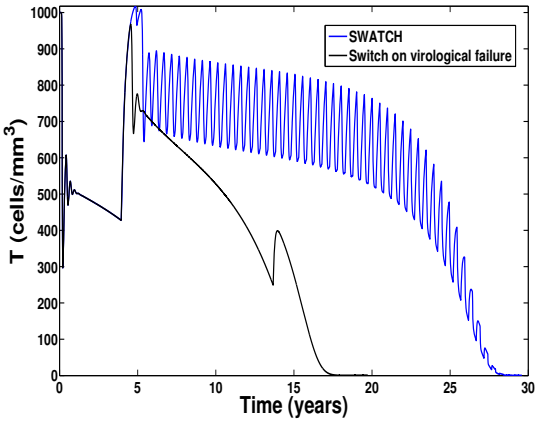
Control strategies had been designed on the switched linear systems (2) and applied to the non-linear model (1), which may represent adequately HIV dynamics when the patient is under treatment regimen [10]. For a somewhat realistic scenario to represent HIV infection dynamics, we consider that the patient is untreated during the initial 4 years of infection. Parameters values were taken from [14], linear decreasing fitness factors and treatment efficiencies are presented in Table I.

TABLE I: Fitness and parameter treatment efficiencies

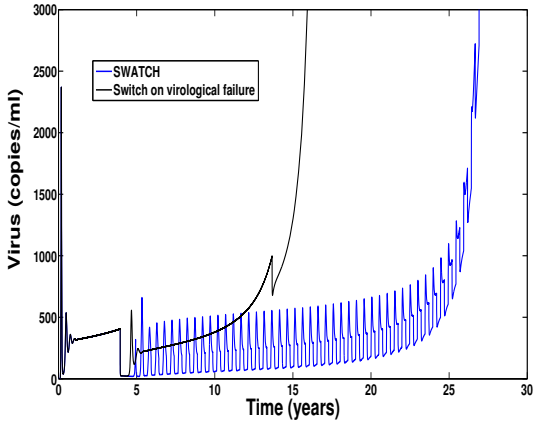
g_i	f_i	$\eta, \theta^T_{\sigma=1}$	$\eta, \theta^T_{\sigma=2}$	$\eta, \theta^M_{\sigma=1}$	$\eta, \theta^M_{\sigma=2}$
1	1	0.8	0.7	0.8	0.7
2	0.83	0.01	0.01	0.3	0.2
3	0.83	0.4	0.3	0.1	0.1
4	0.77	0	0	0.1	0.1

HAART treatment is introduced after the fourth year, a fast recovery in CD4+T cell counts accompanied by a sharp drop in viral load to undetectable levels are exhibited in Fig.3. Using the common clinical treatment, switch on virological failure, key markers of immune system health, namely healthy CD4+ T cell counts, can be maintained in acceptable ranges ($> 300\ cells/mm^3$) for approximately 14 years, that is when the first virological failure is presented. Therefore the second regimen is provided, nevertheless a virological failure occurs afterwards. This is consistent with clinical observations that suggest HIV reservoirs and the persistent low-level viremia may promote virological failure even though a patient is under HAART [18].

SWATCH treatment (alternating periodically between two regimens every three months) as suggested in [12] may delay the viral explosion; for the proposed example the virological failure is presented about the year 26. This is 10 years more in comparison to the switch on virological failure treatment, see Fig.3b. Moreover, Fig.3a reveals that CD4+T cells counts are maintained in good levels (over



(a) CD4+T cells



(b) Viral load

Fig. 3: Switch on virological failure and SWATCH treatments to the non-linear model

400 $cells/mm^3$) for longer period than the common medical treatment. These numerical results reveal the importance of proactive switching to extend healthy conditions.

To compare these strategies, we consider treatments from the year 4 and keep them for a period of 6 years. Due to cells are maintained almost constant in this period, switched linear systems (2) may be used to design switching regimens.

TABLE II: Simulation results during 6 years of treatment

Strategy	CD4+T cells	Viral Load
Switch on virological Failure	372	534
SWATCH	650	215
Guaranteed Cost	930	34
Guaranteed Cost with dwell time	931	33.5

Table II shows that alternation of antiretroviral regimens with drugs that have different resistance profiles might extend the overall long-term effectiveness of first- and second-line treatment options [12]. That is high levels of CD4+T cell counts (> 500 $cell/mm^3$) with undetectable virus levels (< 50 $copies/ml$). Based on clinical recommendations, we consider 3 months for the dwell time; both suboptimal strategies overperformed switch on virological failure and SWATCH strategies, providing slightly better results the introduction of dwell time constraint. Using Corollary 2 with $\gamma = 5 \times 10^{-5}$ we compute the sub-optimal switching signals, which are shown in Fig.4. Notice that depending on resistance profiles, periodic switching might not be required.

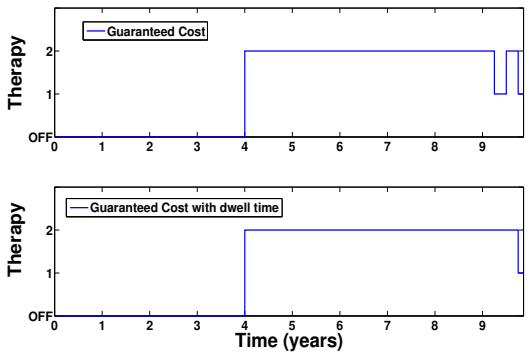


Fig. 4: Sub-optimal switching signals

VI. CONCLUSIONS

The incorporation of dwell time constraints into the formulation of guaranteed cost control was addressed in this paper. For the studied examples, the performance of this new strategy is similar than previous formulation of guaranteed cost control studies.

For the mitigation of mutation in HIV, numerical results showed that recycling drugs with different profiles could more effectively decrease accumulation of resistance mutations compared with changing the regimen after a virological failure is detected. Suboptimal strategies provided promising results for further studies in HIV treatment.

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