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Continuous-time optimal control for switched positive systems with application to mitigating viral escape ⋆

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Abstract: The optimal control problem for a particular class of switched systems is addressed in this paper. Using a linear co–positive cost function, a necessary and sufficient condition for optimal control is derived. Optimal states and costates can lie on a sliding surface, and this corresponds to a chattering switching law. Due to the complexity of exact solution of the general optimal control problem, we introduce a suboptimal, guaranteed cost algorithm, associated with the optimal problem. These results are then applied to a simplified model of HIV viral mutation dynamics, which under simplifying assumptions can be viewed as a positive switched linear system. Simulations compare the optimal switching control law with the sub-optimal guaranteed cost approach.

Keywords: Switched positive systems; optimal control; viral mutation ; HIV

1. INTRODUCTION

The problem of determining optimal switching trajectories in hybrid systems has been widely investigated, both from theoretical and from computational point of view [1], [2], [3] and [4]. For continuous-time switched systems, several prior works present necessary and/or sufficient conditions for a trajectory to be optimal, with the introduction of the minimum principle [5] and [6]. However, there is not a general solution for the problem.

Motivated by the problems of HIV (human immunodeficiency virus) infection, we examine a simplified model proposed by [9]; in this paper, positive switched systems allows the design of switching strategies to delay the emergence of highly resistant mutant viruses. Drug regimens offer more potent, less toxic and more durable choices. Combination antiretroviral therapy (ART) prevents immune deterioration, reduced morbidity and mortality, and prolongs the life expectancy of people infected with HIV [7]. Unfortunately, current therapies are only capable of partially and temporarily halting the replication of HIV. One of the main problems in 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 [7]. However, even this ART sequencing will fail in a proportion of patients in the presence highly resistant mutants, that is, mutants resistant to all know drug combinations.

This paper addresses the optimal control problem for a class of switched systems. The problem of drug combination in virus treatment as an application is given. The paper is organized as follows. Theorems for stability and guaranteed cost control of switched positive systems are introduced in Section 2. The importance of switched positive systems is shown with an application to virus treatment in Section 3. A complete characterization of the optimal switching rule is provided for a particular case. Numerical examples are provided in Section 4. Finally, Section 5 concludes the paper.

Throughout, $\mathbb{R}$ 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 number. A matrix is said to be *Metzler* if all its off-diagonal entries are non-negative. We write A' for the transpose of A, and $exp(A)$ for the usual matrix exponential of A. The symbol $\mathcal{S}_{gn}$ denotes the sign function, that takes value 1 when its argument is positive and -1 when its argument is negative. Finally $co(X_1, X_2, \cdots, X_N)$ denotes a convex combination of the matrices X_i.

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2. OPTIMAL CONTROL

Consider the following positive switched linear system on a finite time interval,

$$\dot{x}(t) = A_{\sigma(t)}x(t), \quad x(0) = x_0, \tag{1}$$

where $t \geq 0$, $x(t) \in \mathbb{R}^n_+$ is the state variable vector, $\sigma(t)$ is the switching signal, $x_0 \in \mathbb{R}^n_+$ is the initial condition and A_i belongs to a set of Metzler matrices $\{A_1, \ldots, A_N\}$. The cost functional to be minimized over all admissible switching sequences is given by

$$J(x_0, x, \sigma) = \int_0^T q'_{\sigma(\tau)}x(t)dt + c'x(T) \tag{2}$$

where $x(t)$ is a solution of (1) with the switching signal $\sigma(t)$. Vectors q_i, $i + 1, 2, \cdots, N$ are assumed to have nonnegative entries and c is assumed to have all positive entries. The optimal switching signal, the corresponding trajectory and the optimal cost functional will be denoted as $\sigma^o(t, x_0)$, $x^o(t)$ and $J(x_0, x^o, \sigma^o)$ respectively. The Hamiltonian function relative to system (1) and cost functional (2) is given by

$$H(x, \sigma, p) = q'_\sigma x + \pi' A_\sigma x \tag{3}$$

Theorem 1. Let $\sigma^o(t, x_0) : [0, T] \times \mathbb{R}^n_+ \to \mathcal{I} = \{1, \ldots, N\}$ be an admissible switching signal relative to x_0 and $x^o(t)$ be the corresponding trajectory. Let $\pi^o(t)$ denote a positive vector solution of the system of differential equations

$$\dot{x}^o(t) = A_{\sigma^o(t,x_0)}x^o(t) \tag{4}$$

$$-\dot{\pi}^o(t) = A'_{\sigma^o(t,x_0)}\pi^o(t) + q_{\sigma^o(t,x_0)} \tag{5}$$

$$\sigma^o(t, x_0) = \arg\min_{i\in\mathcal{I}}\{\pi^{o\prime}(t)A_i x^o(t) + q'_i x^o(t)\} \tag{6}$$

with the boundary conditions $x^o(0) = x_0$ and $\pi^o(T) = c$. Then $\sigma^o(t, x_0)$ is an optimal switching signal relative to x_0 and the value of the optimal cost functional is

$$J(x_0, x^o, \sigma^o) = \pi'^o(0)x_0 \tag{7}$$

Proof The scalar function

$$v(x, t) = \pi^o(t)'x \tag{8}$$

is a generalized solution of the Hamilton-Jacobi

$$0 = \frac{\partial v}{\partial t}(x, t) + H\left(x(t), \sigma^o(t, x_0), \frac{\partial v}{\partial x}(x, t)'\right) \tag{9}$$

where

$$H(x, \sigma, p) = q'_\sigma x + \pi' A_\sigma x \tag{10}$$

Notice that the triple (x^o, π^o, σ^o) satisfies the necessary conditions of the Pontryagin principle, since

$$H(x^o, \sigma^o, \pi^o) \leq H(x^o, \sigma, \pi^o), \quad \sigma = 1, 2$$

Moreover,

$$\frac{\partial v}{\partial x}(x, t) = \pi(t)' \tag{11}$$

$$\frac{\partial v}{\partial t}(x, t) = \dot{\pi}(t)'x \tag{12}$$

so that, for almost all $t \in [0, T]$

$$\dot{\pi}^o(t)'x^o(t) + q'_{\sigma^o(t,x_0)}x^o(t) + \pi^o(t)'A_{\sigma^o(t,x_0)}x^o(t) \tag{13}$$

Moreover it satisfies the boundary condition

$$v(x^o(T), T) = \pi^o(T)'x^o(T) = c'x^o(T) \tag{14}$$

This completes the proof. ■

Notice that computation of the optimal control law as discussed in Theorem 1 is quite demanding, this is due to the two point boundary value problem.

2.1 Guaranteed cost

Due to the complexity of exact solution of the general optimal control problem as in Theorem 1, in this section we introduce a suboptimal, guaranteed cost algorithm associated with the optimal control problem. To this end, define the simplex

$$\Lambda := \left\{\lambda \in \mathbb{R}^N : \sum_{i=1}^N \lambda_i = 1,\ \lambda_i \geq 0\right\} \tag{15}$$

which allows us to introduce the following piecewise copositive Lyapunov function:

$$v(x) := \min_{i=1,\ldots,N} \alpha'_i x = \min_{\lambda\in\Lambda}\left(\sum_{i=1}^N \lambda_i \alpha'_i x\right) \tag{16}$$

The Lyapunov function in (16) is not differentiable everywhere. In particular, let us define the set $I(x) = \{i : v(x) = \alpha'_i x\}$. Then $v(x)$ fails to be differentiable precisely for those $x \in \mathcal{R}^n_+$ such that $I(x)$ is composed of more than one element, that is in the conjunction points of the individual Lyapunov functions $\alpha'_i x$. Now we will denote by $\mathcal{M}$ the subclass of Metzler matrices with zero column sum, that is all matrices $P \in \mathbb{R}^{N\times N}$ with elements p_{ji}, such that

$$p_{ji} \geq 0\ \forall j \neq i, \quad \sum_{j=1}^N p_{ji} = 0\ \forall j. \tag{17}$$

As a consequence, any $P \in \mathcal{M}$ has an eigenvalue at zero since $c'P = 0$, where $c' = [1 \cdots 1]$. We are now ready to formulate the main result on the guaranteed cost control of the system (1).

Theorem 2. Consider the linear positive switched system (1) and let the nonnegative vectors q_i be given. Moreover, take any $P \in \mathcal{M}$, and let $\{\alpha_1, \ldots, \alpha_N\}$, $\alpha_i \in \mathbb{R}^n_+$ the positive solutions of the differential equations

$$\dot{\alpha}_i + A'_i\alpha_i + \sum_{j=1}^N p_{ji}\alpha_j + q_i \preceq 0, \quad i = 1, \ldots, N \tag{18}$$

with final condition $\alpha_i(t) = c$, $\forall i$. Then, state-switching rule

$$\sigma(x(t)) = \arg\min_{i=1,\ldots,N} \alpha'_i(t)x(t) \tag{19}$$

is such that

$$\int_0^T q'_{\sigma(\tau)}x(t)dt + x(T)'c \leq \min_{i=1,\ldots,N} \alpha'_i(0)x_0 \tag{20}$$

Proof Consider the Lyapunov function

$$v(x,t) = \min_{i=1,\ldots,N} \alpha_i'(t)x(t) \tag{21}$$

and let $i = \arg\min_l \alpha_l'(t)x(t)$. Then,

$$\begin{aligned} D^+(v(x),t) &= \min_k \left(\dot\alpha_k(t) + \alpha_k'(t)A_i x\right) \le \dot\alpha_i + \alpha_i'(t)A_i x \\ &\le -p_{ii}\alpha_i'(t)x - \sum_{j\neq i} p_{ji}\alpha_j'(t)x - q_i'x \le \\ &\le -p_{ii}\alpha_i'(t)x - \sum_{j\neq i} p_{ji}\alpha_i'(t)x - q_i'x = -q_i'x \end{aligned}$$

Hence, for all $\sigma(t)$,

$$D^+(v(x)) \le -q_{\sigma(t)}'x(t) \tag{22}$$

which, after integration, gives

$$\begin{aligned} v(x(T)) - v(0) &= \int_0^T D^+v(x(\tau))d\tau \\ &\le -\int_0^T q_{\sigma(\tau)}'x(\tau)d\tau. \end{aligned} \tag{23}$$

Therefore,

$$\int_0^T q_{\sigma(\tau)}'x(\tau)d\tau + c'x(T) \le v(0) = \min_{i=1,\ldots,N} \alpha_i'(0)x_0. \tag{24}$$

This concludes the proof. ∎

Notice that (18) requires the preliminary choice of the parameters p_{ij}. In particular, the search for p_{ij} and α_i that satisfy Theorem 2 is a bilinear matrix inequality. We can, at the cost of some conservatism in the upper bound, reduce these parameters to a single one, say γ, so allowing an easy search the best γ as far as the upper bound is concerned.

Corollary 1. Let $q \in \mathcal{R}_+^n$ and $c \in \mathcal{R}_+^n$ be given, and let the positive vectors $\{\alpha_1,\ldots,\alpha_N\}$, $\alpha_i \in \mathcal{R}_+^n$ satisfy for some $\gamma > 0$ the modified coupled co-positive Lyapunov equations:

$$\dot\alpha_i + A_i'\alpha_i + \gamma(\alpha_j - \alpha_i) + q_i \preceq 0 \qquad i \neq j = 1,\ldots,N. \tag{25}$$

with final condition $\alpha_i(T) = c$, $\forall i$. Then the state-switching control given by (19) is such that

$$\int_0^T q_{\sigma(\tau)}'x(t)dt + c'x(t) \le \min_{i=1,\ldots,N} \alpha_i'(0)x_0 \tag{26}$$

∎

3. VIRUS MUTATION TREATMENT MODEL

HIV is responsible for AIDS with tens of millions of people infected worldwide. Mutation is a key problem that limits the effectiveness of current treatment regimes and may lead to viral escape wherein despite long periods of effective viral control using ART, HIV may mutate to a form with high resistance to the ART used. In this case, viral loads may rebound to high levels which in turn result in immune system suppression and the complications associated with AIDS.

Variant	Therapy 1	Therapy 2
Wild type (x_1)	$\lambda_1 = -0.19$	$\lambda_1 = -0.19$
Genotype 1 (x_2)	$\lambda_{2,1} = 0.16$	$\lambda_{2,2} = -0.19$
Genotype 2 (x_3)	$\lambda_{3,1} = -0.19$	$\lambda_{3,2} = 0.16$
HR Genotype (x_4)	$\lambda_4 = 0.06$	$\lambda_4 = 0.06$

Table 1. Replication rates for viral variants and therapy combinations for a symmetric case

3.1 A 4 variant, 2 drug combination, linear model

A simplified model for mutation dynamics was described in [9]. Here we follow a similar philosophy, of seeking detailed mathematical results and insights based on a simplified model. The key species involved are: T: healthy (i.e. uninfected) CD4+ T cells, and $V_i : i = 1, 2, \ldots n$, virus strain i. In a similar way to [9], the key assumptions in our model are: constant CD4+T cell counts, scalar dynamics for each mutant, mutation rate independent of treatment and mutant, deterministic model. As a simple motivating example, recall the model from [9], we consider $n = 4$ genetic strains, and $N = 2$ possible drug therapies. The viral strains are described as:

- Wild type genotype (WTG): In the absence of therapy, this strain is the most prolific, however, it is also the strain susceptible to both therapies.
- Genotype 1 (G1): A strain that is resistant to therapy 1, but is susceptible to therapy 2.
- Genotype 2 (G2): A strain that is resistant to therapy 2, but is susceptible to therapy 1.
- Highly resistant genotype (HRG): A genotype, with relatively low proliferation rate, but that is resistant to both drug therapies.

The dynamics of the model are described as follows

$$\dot x(t) = \left(\Lambda_{\sigma(t)} + \mu M\right)x(t) \tag{27}$$

where $x(t) \in \mathbb{R}_+^n$ is the vector of viral loads, Λ_σ is a diagonal matrix with elements $\{\lambda_1, \lambda_{2,\sigma}, \lambda_{3,\sigma}, \lambda_4\}$, μ is the mutation rate constant and M is the matrix describing the graph of feasible mutations. Typical viral mutation rates are of the order of $\mu = 1 \times 10^{-4}$ and replication rates are describe in the Table 1. We take a mutation graph that is symmetric and circular, that is:

$$M = \begin{bmatrix} 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \end{bmatrix} \tag{28}$$

3.2 Cost Function

For medical reasons, the objective of ART has been defined as maintaining viral suppression. In particular, this means keeping the total virus load as small as possible over the assigned horizon

$$J := c'x(T) \tag{29}$$

where c is the column vector with all ones. This cost should be minimized under the action of the switching rule, details about the cost function can be found in [9].

3.3 Optimal control for HIV virus mitigation

Considering the 4 variant, 2 drug combination model (27), this leads to the positive switched system

$$\dot{x} = A_\sigma x, \quad \sigma = \{1, 2\}$$

where

$$A_\sigma = \begin{bmatrix} \lambda_1 & 0 & 0 & 0 \\ 0 & \lambda_{2\sigma} & 0 & 0 \\ 0 & 0 & \lambda_{3\sigma} & 0 \\ 0 & 0 & 0 & \lambda_4 \end{bmatrix} + \mu \begin{bmatrix} 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \end{bmatrix}$$

Using symmetric replications rates, we can assume that

Assumption 1.

$$\lambda_{21} > 0, \quad \lambda_{22} < 0, \quad \lambda_{31} < 0, \quad \lambda_{32} > 0$$

Assumption 2.

$$\lambda_{21} - \lambda_{22} + \lambda_{31} - \lambda_{32} = 0$$

Using Assumption 1, note that

$$J = A_1 - A_2 = (\lambda_{21} - \lambda_{22}) \begin{bmatrix} 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix} = (\lambda_{21} - \lambda_{22})\bar{J}$$

Since $\lambda_{21} - \lambda_{22} > 0$, we can define the decision function $\gamma(t) = \pi(t)'\bar{J}x(t)$ that takes the form

$$\gamma(t) = \pi_2(t)[x_2(t) - x_3(t)] + x_3(t)[\pi_2(t) - \pi_3(t)] \quad (30)$$

Moreover, from the structure of A_1 and A_2 it is possible to conclude that

$$\begin{aligned} \dot{\gamma}(t) = & [\pi_2(t) - \pi_3(t)][x_1(t) + x_4(t)] \\ & -[x_2(t) - x_3(t)][\pi_1(t) + \pi_4(t)] \end{aligned} \quad (31)$$

The following lemma, which can be proven directly from (30) and Assumption 1 is useful to characterize the optimal solution.

Lemma 1. Under Assumption 1 the following conditions hold:

$$\begin{aligned} |\mathcal{S}_{gn}[x_2(t) - x_3(t)] + \mathcal{S}_{gn}[\pi_2(t) - \pi_3(t)]| = 2 \\ \implies \mathcal{S}_{gn}[\gamma(t)] = \mathcal{S}_{gn}[x_2(t) - x_3(t)] \\ \mathcal{S}_{gn}[x_2(t) - x_3(t)] + \mathcal{S}_{gn}[\pi_2(t) - \pi_3(t)] = 0, \\ \implies \mathcal{S}_{gn}[\dot{\gamma}(t)] = \mathcal{S}_{gn}[\pi_2(t) - \pi_3(t)] \\ \mathcal{S}_{gn}[\dot{x}_2(t) - \dot{x}_3(t)] = \mathcal{S}_{gn}[1.5 - \sigma(t)] \\ \mathcal{S}_{gn}[\dot{\pi}_2(t) - \dot{\pi}_3(t)] = \mathcal{S}_{gn}[\sigma(t) - 1.5] \end{aligned}$$

■

Remark 1. Theorem 1 does not consider the possible existence of sliding modes, i.e. infinite frequency switching of $\sigma(t)$. However, the optimal state and costate variables x^o, π^o can lie on a sliding surface, and this corresponds to a chattering switching law. This leads to the notion of extended (Filippov) trajectories satisfying a differential inclusion. To be precise, the optimal control is characterized by

$$\dot{x}^o(t) \in co\{A_1 x^o(t), A_2 x^o(t), \cdots, A_N x^o(t)\} \quad (32)$$

$$-\dot{\pi}^o(t) \in co\{A_1'\pi^o(t) + q_1, \cdots, A_N'\pi^o(t) + q_N\} \quad (33)$$

$$\pi'^o(t) A_i x^o(t) = constant, \forall i \quad (34)$$

In order to characterize the sliding modes, we look for a compatible linear combination of the matrices

$$\bar{A} = \alpha A_1 + (1 - \alpha) A_2$$

with $\alpha \in [0, 1]$.

Lemma 2. Under Assumption 2, the trajectories

$$x_2(t) = x_3(t), \quad \pi_2(t) = \pi_3(t)$$

satisfy

$$\begin{aligned} \dot{x}(t) &= (\alpha A_1 + (1 - \alpha) A_2) x(t), \\ \dot{\pi}(t) &= -(\alpha A_1 + (1 - \alpha) A_2) \pi(t) \end{aligned}$$

with

$$\alpha = \frac{\lambda_{32} - \lambda_{22}}{\lambda_{32} - \lambda_{22} + \lambda_{21} - \lambda_{31}}$$

and are such that

$$\gamma(t) \equiv 0$$

Proof It is enough to show that the variables $x_2(t) - x_3(t)$ and $\pi_2(t) - \pi_3(t)$ obey autonomous differential equations. Indeed,

$$\dot{x}_2(t) - \dot{x}_3(t) = \alpha(\lambda_{21} - \lambda_{31}) x_2(t) + (1 - \alpha)(\lambda_{22} - \lambda_{32}) x_3(t)$$

where

$$\alpha(\lambda_{21} - \lambda_{31}) = (1 - \alpha)(\lambda_{22} - \lambda_{32})$$

so that

$$\dot{x}_2(t) - \dot{x}_3(t) = r(x_2(t) - x_3(t))$$

Analogously

$$\dot{\pi}_2(t) - \dot{\pi}_3(t) = -r(\pi_2(t) - \pi_3(t))$$

where

$$r = \frac{\lambda_{21}\lambda_{32} - \lambda_{22}\lambda_{31}}{\lambda_{32} - \lambda_{22} + \lambda_{21} - \lambda_{31}}$$

■

Now, let

$$\begin{aligned} k_1 &= \text{argmin}\{x_2(0), x_3(0)\} \\ k_2 &= \text{argmin}\{c_2, c_3\} \end{aligned}$$

and

$$\begin{aligned} T_1^\star &= \min_{t \geq 0} : [0\ 1\ -1\ 0] e^{A_{k_1} t} x(0) = 0, \\ T_2^\star &= \min_{t \leq T} : [0\ 1\ -1\ 0] e^{-A_{k_2}(t - T)} c = 0. \end{aligned}$$

Notice that, thanks to the definition of k_1, k_2 and the monotonicity conditions of $x_2(t) - x_3(t)$, $\pi_2(t) - \pi_3(t)$, the time instants $T_1^\star$ and $T_2^\star$ are well defined and unique. Clearly, by definition $x_2(T_1^\star) = x_3(T_1^\star)$ and $\pi(T_2^\star) = \pi_3(T_2^\star)$. We are now in the position to provide the main result of this section.

Theorem 3. Let Assumptions 1, 2 be met with and assume that $T_1^\star \leq T_2^\star$. Then, the optimal control associated with the initial state $x(0)$ and cost $c'x(T)$ is given by $\sigma(t) = k_1, \quad t \in [0, T_1^\star]$ and $\sigma(t) = k_2, \quad t \in [T_2^\star, T]$. For $t \in [T_1^\star, T_2^\star]$, the optimal control is given by the Filippov trajectory along the plane $x_2 = x_3$, with dynamical matrix $A = \alpha A_1 + (1 - \alpha) A_2$.

Proof We will verify that the control law satisfies the conditions given by the Hamilton-Jacobi equations in the intervals $[0, T_1^\star]$ and $[T_2^\star, T]$. Moreover, in the interval $[T_1^\star, T_2^\star]$ the optimal control state and costate variables slide along the trajectories $x_2(t) = x_3(t)$ and $\pi_2(t) = \pi_3(t)$. To this end, let $\sigma(t) = k_1$ for $t \in [0, T_1^\star]$, $\sigma(t) = k_2$ for $t \in [T_2^\star, T]$ and

$$\begin{aligned}
\pi(t) &= e^{A_{k_1}(T_1^\star - t)}\pi(T_1^\star), \quad t \in [0, T_1^\star] \\
\pi(t) &= e^{A(T_2^\star - t)}\pi(T_2^\star), \quad t \in [T_1^\star, T_2^\star] \\
\pi(t) &= e^{A_{k_2}(T-t)}c, \quad t \in [T_2^\star, T] \\
x(t) &= e^{A_{k_1}t}x(0), \quad t \in [0, T_1^\star] \\
x(t) &= e^{A(t-T_1^\star)}x(T_1^\star), \quad t \in [T_1^\star, T_2^\star] \\
x(t) &= e^{A_{k_2}(t-T_2^\star)}x(T_2^\star), \quad t \in [T_2^\star, T]
\end{aligned}$$

First of all notice that, by definition, $x_2(T_1^\star) = x_3(T_1^\star)$ and $\pi_2(T_2^\star) = \pi_3(T_2^\star)$. Thanks to Lemma 2, in the interval $[T_1^\star, T_2^\star]$ we have $x_2(t) = x_3(t)$ and $\pi_2(t) = \pi_3(t)$. In the intervals $[0, T_1^\star]$ and $[T_2^\star, T]$, consider the decision function and its derivative, given by (30), (31), respectively. Now, we have $\gamma(T_1^\star) = \gamma(T_2^\star) = 0$ and, for $t \in [0, T_1^\star]$, $t \in [T_2^\star, T]$:

$$\dot{x}_2(t) - \dot{x}_3(t) = \lambda_{2k_i}x_2(t) - \lambda_{3k_i}x_3(t) = \begin{cases} > 0 & k_i = 1 \\ < 0 & k_i = 2 \end{cases}$$

$$\dot{\pi}_2(t) - \dot{\pi}_3(t) = -\lambda_{2k_i}\pi_2(t) + \lambda_{3k_i}\pi_3(t) = \begin{cases} > 0 & k_i = 1 \\ < 0 & k_i = 2 \end{cases}$$

This means that, for $t \in [0, T_1^\star]$, $t \in [T_2^\star, T]$:

$$x_2(t) - x_3(t) = \begin{cases} < 0 & k_i = 1 \\ > 0 & k_i = 2 \end{cases}$$

$$\pi_2(t) - \pi_3(t) = \begin{cases} > 0 & k_i = 1 \\ < 0 & k_i = 2 \end{cases}$$

$$\dot{\gamma}(t) = \begin{cases} > 0 & k_i = 1 \\ < 0 & k_i = 2 \end{cases}$$

Since $\gamma(T_i^\star) = 0$ it follows

$$\gamma(0) = \pi(0)'\bar{J}x(0) = \begin{cases} < 0 & k_1 = 1 \\ > 0 & k_1 = 2 \end{cases}$$

$$\gamma(T) = \pi(T)'J\bar{x}(T) = \begin{cases} < 0 & k_2 = 1 \\ > 0 & k_2 = 2 \end{cases}$$

which confirms $\sigma(t) = \text{argmin}_i\ \pi(t)'A_i x(t) = k_1$, for $t \in [0, T_1^\star]$ and $\sigma(t) = \text{argmin}_i\ \pi(t)'A_i x(t) = k_2$, for $t \in [T_2^\star, T]$. ∎

Even though in practice the horizon length T may often be large enough to guarantee that $T_1^\star \leq T_2^\star$, for completeness, we wish to also consider the *small horizon* case.

Theorem 4. Let Assumption (1) be met and $0 < T_2^\star \leq T_1^\star < T$. Then, the optimal control associated with the initial state $x(0)$ and cost $c'x(T)$ is given as follows:

If $k_1 = k_2$, then

$$\sigma(t) = k_1, \quad t \in [0, T]$$

otherwise, if $k_1 \neq k_2$, then

$$\sigma(t) = \begin{Bmatrix} k_1 : t \in [0, T_3^\star] \\ k_2 : t \in [T_3^\star, T] \end{Bmatrix}$$

where $T_3^\star \in [T_2^\star, T_1^\star]$ is such that for $t = T_3^\star$

$$x(T_2^\star)'e^{A_{k_1}(t-T_2^\star)}\bar{J}e^{-A_{k_2}(t-T_1^\star)}\pi(T_1^\star) = 0$$

Proof Let first consider the case $k_1 = k_2$. Then, we will verify that the constant control law $\sigma(t) = k_1$ satisfies the sufficient condition given by the Hamilton-Jacobi equations, i.e.

$$\begin{aligned}
\sigma(t) &= \text{argmin}_i\ \pi(t)'A_i x(t), \\
\dot{\pi}(t) &= -A_{\sigma(t)}\pi(t), \quad \pi(T) = c
\end{aligned}$$

To this end, consider again the decision function $\gamma(t)$ and its derivative, given by (30) and (31), respectively. Consider

$$\begin{aligned}
\pi(t) &= e^{A_{k_1}(T-t)}c, \quad t \in [0, T] \\
x(t) &= e^{A_{k_1}t}x(0), \quad t \in [0, T]
\end{aligned}$$

Moreover let $\bar{k}_1 = 1$ if $k_1 = 2$ and viceversa. Since $T_2^\star \leq T_1^\star$, we conclude that

$$\mathcal{S}_{gn}[x_2(t) - x_3(t)] = \mathcal{S}_{gn}[\pi_2(t) - \pi_3(t)] = k_1 - \bar{k}_1,$$

in the interval $(T_2^\star, T_1^\star)$. This implies that $\mathcal{S}_{gn}[\gamma(t)] = k_1 - \bar{k}_1$ in the same interval. Moreover,

$$\mathcal{S}_{gn}[\dot{\gamma}(t)] = \mathcal{S}_{gn}[\pi_2(t) - \pi_3(t)]$$

in $t \in [0, T_2^\star)$ and $t \in (T_1^\star, T]$. This means that the sign of $\gamma(t)$ is constant in $[0, T]$ and equals $k_1 - \bar{k}_1$. The proof of the first part is concluded.

Consider now the case $k_1 \neq k_2$. By assumption,

$$\mathcal{S}_{gn}[x_2(t) - x_3(t)] = k_1 - \bar{k}_1, \quad t \in [0, T_2^\star)$$

and

$$\mathcal{S}_{gn}[\pi_2(t) - \pi_3(t)] = k_2 - \bar{k}_2, \quad t \in (T_1^\star, T]$$

Notice that, in any possible switching point in the interval $[T_2^\star, T_1^\star]$, the derivatives of $x_2(t) - x_3(t)$ and $\pi_2(t) - \pi_3(t)$ change sign at $t = T_3^\star$, so that $\mathcal{S}_{gn}[\dot{\gamma}(t)]$ is constant in $[0, T]$, and consequently, $\mathcal{S}_{gn}[x_2(t) - x_3(t)] = k_1 - \bar{k}_1$, $\mathcal{S}_{gn}[\pi_2(t) - \pi_3(t)] = k_2 - \bar{k}_2$ in $[0, T]$. We now have to prove that indeed there exists a $T_3^\star$. To this end, notice that

$$\mathcal{S}_{gn}[\gamma(T_2^\star)] = k_1 - \bar{k}_1, \quad \mathcal{S}_{gn}[\gamma(T_1^\star)] = k_2 - \bar{k}_2$$

This, together with $\mathcal{S}_{gn}[\dot{\gamma}(t)] = \mathcal{S}_{gn}[x_2(t) - x_3(t)]$ implies that there exists $T_3^\star \in (T_2^\star, T_1^\star)$ for which $\gamma(T_3^\star) = 0$. This value is the only point $t \in [T_2^\star, T_1^\star]$ satisfying $x(T_2^\star)'e^{A_{k_1}(t-T_2^\star)}\bar{J}e^{-A_{k_2}(t-T_1^\star)}\pi(T_1^\star) = 0$. ∎

4. SIMULATION RESULTS

To show numerically last results, we choose the initial condition vector $x = [10^3, 10^2, 0, 10^{-5}]$ and the cost function weighting as $c = [1, 50, 1, 1]'$. Firstly, we compute the time where the system will not switch $T_1^\star$, for this example is 16.792 days, after this time the control will be switching in the sliding surface $x_2 = x_3$ for the period from $T_1^\star$ to $T_2^\star$, where $T_2^\star$ is 11.17 days before the end of

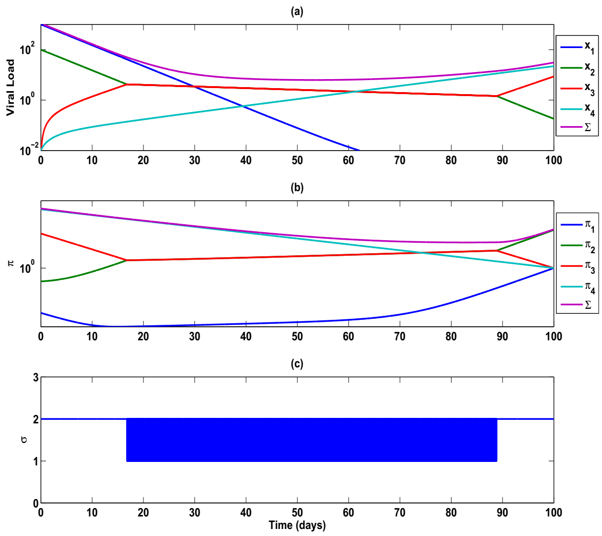

Fig. 1. Optimal Control (a) Genotype dynamics (b) Adjoint Variable (c) Control signal

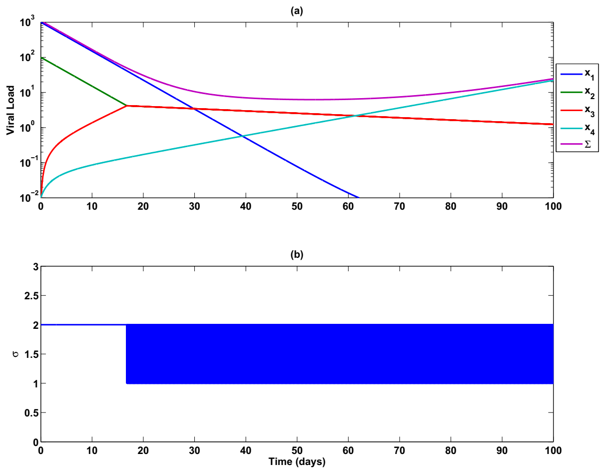

Fig. 2. Guaranteed Cost Control (a) Genotype dynamics (b) Control signal

the treatment. We can see in Fig. 1 the performance of the optimal control. Using a cost function weighting as $c = [1, 1, 1, 1]'$ and the guaranteed cost control, an upper bound can be computed, for such control a performance no worse than $\min_i(\alpha_i' x(0)) = 81.001$ will be obtain. The final cost for a simulation of 100 days is $J = 24.56$, which is exactly the the same as the optimal control.

These simulation results show that at least in some cases, guaranteed cost control capture's the possible sliding mode behavior of the optimal control law. Indeed, consider a matrix $P \in \mathcal{M}$ and its Frobenius eigenvector β, i.e. such that $P\beta = 0$. It is known that β is a nonnegative vector and it is possible to choose it in such a way that $\sum_{i=1}^{N} \beta_i = 1$. Now, it is easy to see that the solution of the differential equations (18) associated with the choice $\gamma\Pi \in \mathcal{M}$ are such that $\lim_{\gamma\to\infty} \alpha_i(t) = \bar{\alpha}(t), \forall i$. In order to characterize the limit function $\bar{\alpha}$, multiply each equation (18) by β_i and sum up all of them. Since $\sum_{i=1}^{N} \beta_i p_{ji} = 0$, and $\alpha_i(t) = \bar{\alpha}(t)$, it results:

$$-\dot{\bar{\alpha}}(t) = \left(\sum_{i=1}^{N} \beta_i A_i\right) \bar{\alpha}(t) + \sum_{i=1}^{N} \beta_i q_i$$

This equation is analogous to the equation of the costate time evolution along a sliding mode. Therefore, the guaranteed cost control is capable of generating the possible sliding behavior as exhibited by the optimal trajectories satisfying, in some time interval, the equation $\dot{\bar{x}}(t) = \left(\sum_{i=1}^{N} \beta_i A_i\right) \bar{x}(t)$.

5. CONCLUSIONS

The main result of this paper shows that the optimal control for this specific class of switched systems is given by the Filippov trajectory along the plane $x_2 = x_3$. Relaxing the demand for optimality, we introduce a suboptimal, guaranteed cost algorithm, associated with the optimal problem. Both strategies are applied to a specific virus mutation problem. Using simulations results we conclude that in this example, guaranteed cost control yields very similar performance to the optimal control.

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