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Discrete-time control for switched positive systems with application to mitigating viral escape

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SUMMARY

This paper has been motivated by the problem of viral mutation in HIV infection. Under simplifying assumptions, viral mutation treatment dynamics can be viewed as a positive switched linear system. Using linear co-positive Lyapunov functions, results for the synthesis of stabilizing, guaranteed performance and optimal control laws for switched linear systems are presented. These results are then applied to a simplified human immunodeficiency viral mutation model. The optimal switching control law is compared with the law obtained through an easily computable guaranteed cost function. Simulation results show the effectiveness of these methods. Copyright © 2010 John Wiley & Sons, Ltd.

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1. INTRODUCTION

Many systems encountered in practice involve a coupling between continuous dynamics and discrete events. Hybrid systems constitute a relatively new and very active area of current research. Switched systems are a class of hybrid systems where the discrete events take a particular simplified form. They present interesting theoretical challenges and are important in many real-world problems [1]. Stability of these systems is not a trivial problem. Switching between individually stable subsystems may cause instability and conversely, switching between unstable subsystems may yield a stable switched system. This kind of phenomena justifies the recent interest in the area of switched systems. In particular, stability analysis of continuous time switched linear systems has been addressed in [2–6]. Moreover, there have been advances in discrete-time switched systems, for example, [7–10] provide excellent overviews. The problem of determining optimal switching trajectories in hybrid systems has been widely investigated as well, both from theoretical and from computational points of view [11–14]. For continuous-time switched systems, several prior works present necessary and/or sufficient conditions for a trajectory to be optimal, using Pontryagin's minimum principle [15, 16].

Positive systems [17], have a peculiar and important property that any nonnegative input and nonnegative initial state generates a nonnegative state trajectory and output for all future times.

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Common examples of positive systems include, chemical processes (reactors, heat exchangers, distillation columns, storage systems), stochastic models where states represent probabilities, and many other models used in biology, economics and sociology. While both nonlinear and linear positive systems have been studied, much recent attention has focused on both time-varying systems and time-invariant linear positive systems and on the Metzler matrices that characterize the properties of such systems. Stabilization of positive systems has been studied since it is problematic to fulfill the positivity constraint on the input variables [18–20]. A few recent works in switched positive systems [21, 22] study the stability problem using co-positive Lyapunov functions.

In this work we are particularly interested in a problem motivated by the treatment of human immunodeficiency virus (HIV) infection. At the end of 2007, approximately 33.2 million people were living with HIV, and more than 29 million people have died of the complications occurring in late stage HIV infection [23]. Drug regimens offer a range of options for controlling the progression of the infection. Combination antiretroviral therapy (ART) prevents immune deterioration, reduces morbidity and mortality, and prolongs the life expectancy of people infected with HIV [24–27]. 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 to prevent HIV disease progression [27]. 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 the problems of HIV mutation, we examine in simulation studies a simplified model of HIV mutation. In these examples, the switched positive systems theory allows the design of switching strategies to delay the emergence of highly resistant mutant viruses. For the purpose of comparison, we also simulate the strategy proposed in [28], based on the concept of reproductive capacity, that represents in mathematical terms the overall proliferation ability of a distribution of viral genotypes.

This paper aims to extend results on the stability and stabilization of continuous-time switched linear positive system [29], to discrete-time. In addition, this paper addresses the optimal control problem for this class of systems. The problem of drug combination in virus treatment as an application is given. The paper is organized as follows. In Section 3, theorems for stability and guaranteed cost control of switched positive systems in discrete-time are introduced. Next, in Section 4, optimal control using the discrete time form of the Hamilton–Jacobi–Bellman equations is addressed. The importance of the developed theory is shown with an application to virus treatment in Section 5. Section 6 concludes the paper.

2. NOTATION

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 numbers. For x in $\mathbb{R}^n$, x_i denotes the ith component of x, and the notation $x\succeq 0$ means that $x_i\geqslant 0$ for $1\leqslant i\leqslant n$. $\mathbb{R}^n_+=\{x\in\mathbb{R}^n : x\succeq 0\}$ 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.

3. DISCRETE STATE-SWITCHING CONTROL

Consider a discrete time switched system of the following general form

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

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defined for all $k \in \mathbb{N}$ where $x \in \mathbb{R}^n$ is the state, $\sigma(k)$ is the switching sequence, and $x(0)=x_0$ is the initial condition. For (1) to be a positive system for any switching sequence, A_i, $i=1,\ldots,N$ must be nonnegative matrices, that its entries are $a^i_{lj} \geqslant 0$, $\forall(l,j)$, $l \neq j$, $i=1,2,\ldots,N$. For each $k \in \mathbb{N}$,

$$\sigma(k) \in \{1,2,\ldots,N\} \tag{2}$$

Clearly, (2) constrains $A_{\sigma(k)}$ to jump among the N vertices of the matrix polytope $A_1,\ldots,A_N$. We assume that the full state vector is available and the control law is a state feedback

$$\sigma(k) = u(x(k)) \tag{3}$$

The control will be a function $u(\bullet)$: $\mathbb{R}^N \to \{1,\ldots,N\}$. Consider the simplex

$$\Lambda := \left\{ \lambda \in \mathbb{R}^N : \sum_{i=1}^{N} \lambda_i = 1, \lambda_i \succeq 0 \right\} \tag{4}$$

which allows us to introduce the following piecewise co-positive Lyapunov function:

$$\upsilon(x(k)) := \min_{i=1,\ldots N} \alpha_i' x(k) = \min_{\lambda \in \Lambda} \sum_{i=1}^{N} \lambda_i \alpha_i' x(k) \tag{5}$$

Now let us define a class of matrices, that we will denote by $\mathscr{M}$, consisting of all matrices $\Pi \in \mathbb{R}^{N \times N}$ with elements π_{ij}, such that

$$\pi_{ij} \geqslant 0, \quad \forall i \neq j, \quad \sum_{i=1}^{N} \pi_{ij} = 0, \quad \forall j \tag{6}$$

The following result provides a sufficient condition for the existence of a switching rule that asymptotically stabilizes the system.

Theorem 1
Assume that there exist a set of positive vectors $\alpha_1,\ldots,\alpha_N$, $\alpha_i \in \mathbb{R}^n_+$, and $\pi \in \mathscr{M}$, satisfying the coupled co-positive Lyapunov inequalities:

$$(A_i - I)'\alpha_i + \sum_{j=1}^{N} \pi_{ji}\alpha_j \prec 0 \tag{7}$$

The state-switching control with

$$u(x(k)) = \arg \min_{i=1,\ldots,N} \alpha_i' x(k) \tag{8}$$

makes the equilibrium solution $x=0$ of the system (1) globally asymptotically stable (in the positive orthant), with Lyapunov function $\upsilon(x(k))$ given by (5).

Proof
Recalling that (6) is valid for $\Pi \in \mathscr{M}$ and that $\alpha_j' x(k) \geqslant \alpha_{\sigma(k)}' x(k)$ for all $j=i=1,\ldots,N$, we have

$$\begin{aligned} \Delta\upsilon(k) = \upsilon(x(k+1)) - \upsilon(x(k)) &= \min_{j=1,\ldots,N} \{\alpha_j' x(k+1)\} - \min_{j=1,\ldots,N} \{\alpha_j' x(k)\} \\ &= \min_{j=1,\ldots,N} \{\alpha_j' A_{\sigma(k)} x(k)\} - \min_{j=1,\ldots,N} \{\alpha_j' x(k)\} \end{aligned}$$

By definition of $\sigma(k)$ we have $\min_{j=1,\ldots,N}\{\alpha_j' x(k)\} = \alpha_{\sigma(k)}' x(k)$ and therefore

$$\begin{aligned} \Delta\upsilon(k) &\leqslant \alpha_{\sigma(k)}' A_{\sigma(k)} x(k) - \alpha_{\sigma(k)}' x(k) \\ &\leqslant \alpha_{\sigma(k)}' (A_{\sigma(k)} - I) x(k) \end{aligned}$$

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From (7), with $x(k)\neq 0$, it follows

$$\begin{aligned}\Delta v(k) &< -\sum_{j=1}^{N}\pi_{j\sigma(k)}\alpha_j' x(k)\\ &\leqslant -\sum_{j=1}^{N}\pi_{j\sigma(k)}\alpha_{\sigma(k)}' x(k)\\ &= 0\end{aligned}$$

□

Remark 1
Notice that (7) is the mean square stability condition for the positive system subject to Markovian switching with the discrete-time transition rate matrix $\Pi+I$. See [30] for the continuous-time case. So, this result is deeply connected to the theory of linear jump systems, see [31]. When the transition matrix Π is fixed, the provided conditions are linear, so that it allows the incorporation of additional state constraints, see, for example, the linear programming approach in [32].

In a similar vein, it is possible to assure an upper bound on an optimal cost function. Let q_i be positive vectors, $i=1,2,\ldots,N$, and consider the cost function;

$$J=\sum_{k=0}^{\infty} q_{\sigma(k)}' x(k) \tag{9}$$

then, the following result provides an upper bound on the optimal value J^o of J.

Lemma 1
Let $q_i\in\mathbb{R}_+^n$ be given. Assume that there exist a set of positive vectors $\{\alpha_1,\ldots\alpha_N\}$, $\alpha_i\in\mathbb{R}_+^n$ and $\pi\in\mathscr{M}$, satisfying the coupled co-positive Lyapunov inequalities;

$$(A_i-I)'\alpha_i+\sum_{j=1}^{N}\pi_{ji}\alpha_j+q_i\prec 0,\forall i \tag{10}$$

The state-switching control given by (8) makes the equilibrium solution $x=0$ of the system (1) globally asymptotically stable and

$$J^o\leqslant\sum_{k=0}^{\infty} q_{\sigma(k)}' x(k)\leqslant\min_{i=1,\ldots,N}\alpha_i' x_0 \tag{11}$$

Proof
If (10) holds, then (7) holds as well, then we can say that the equilibrium point $x=0$ for system (1) is globally asymptotically stable. In addition, by mimicking the proof of Theorem 1, we can prove that

$$\begin{aligned}\Delta v(x(k)) &= v(x(k+1))-v(x(k))\\ &\leqslant -q_{\sigma(k)}' x(k)\end{aligned}$$

Hence

$$\sum_{k=0}^{\infty}\Delta v(x(k))\leqslant -\sum_{k=0}^{\infty} q_{\sigma(k)}' x(k)$$

$$\sum_{k=0}^{\infty} q_{\sigma(k)}' x(k)\leqslant v(x(0))-v(x(\infty))$$

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therefore

$$\sum_{k=0}^{\infty} q'_{\sigma(k)} x(k) \leqslant \min_{i=1,\ldots,N} \alpha_i' x_0 \qquad \square$$

Remark 2
For fixed π_{ji} in order to improve the upper bound provided by Lemma 1, one can minimize $\min_i \alpha_i' x_0$ over all possible solutions of the linear inequalities (10).

Coupled co-positive Lyapunov functions can also be used to compute a lower bound to the optimal cost.

Lemma 2
Assume that there exist a set of positive vectors $\alpha_1, \ldots, \alpha_N$, $\alpha_i \in \mathbb{R}_+^n$ and $\Pi \in \mathscr{M}$, satisfying the coupled co-positive inequalities:

$$(A_j - I)' \alpha_i + \sum_{m=1}^{N} \pi_{mi} \alpha_m + q_i \succeq 0, \quad \forall i, j \tag{12}$$

Then, for any state trajectory such that $x(k) \to 0$,

$$\sum_{k=0}^{\infty} q'_{\sigma(k)} x(k) \succeq \max_{i=1,\ldots,N} \alpha_i' x_0 \tag{13}$$

Proof
Let

$$\upsilon(x(k)) = \max_i \alpha_i' x(k) \tag{14}$$

then

$$\begin{aligned}
\upsilon(x(k+1)) &= \max_{i=1,\ldots,N} \{\alpha_i' x(k+1)\} \\
&= \max_{i=1,\ldots,N} \{\alpha_i' A_{\sigma(k)} x(k)\} \\
&\geqslant \left(\alpha'_{\sigma(k)} - \sum_{m=1}^{N} \pi_{m\sigma(k)} \alpha'_m \right) x(k) - q'_{\sigma(k)} x(k) \\
&\geqslant \left(\alpha'_{\sigma(k)} - \pi_{\sigma(k)\sigma(k)} \alpha'_{\sigma(k)} - \sum_{m \neq \sigma(k)}^{N} \pi_{m\sigma(k)} \alpha'_m \right) x(k) - q'_{\sigma(k)} x(k) \\
&\geqslant \left(\alpha'_{\sigma(k)} - \pi_{\sigma(k)\sigma(k)} \alpha'_{\sigma(k)} - \sum_{m \neq \sigma(k)}^{N} \pi_{m\sigma(k)} \alpha'_{\sigma(k)} \right) x(k) - q'_{\sigma(k)} x(k) \\
&\geqslant \alpha'_{\sigma(k)} x(k) - q'_{\sigma(k)} x(k)
\end{aligned}$$

which implies

$$\upsilon(x(k+1)) - \upsilon(x(k)) \geqslant -q'_{\sigma(k)} x(k) \tag{15}$$

so that

$$\sum_{k=0}^{\infty} q'_{\sigma(k)} x(k) \geqslant \max_{i=1,\ldots,N} \alpha_i' x_0 \tag{16}$$

$\square$

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Remark 3
Notice that inequalities (7) are not LMI, since the unknown parameters π_{ji} multiply the unknown vectors α_j. If all matrices A_i are Schur matrices, $i=1,2,\cdots,N$, then a possible choice is $\pi_{ji}=0$, $i,j=1,2,\cdots,N$, so that inequalities (7) are satisfied by $\alpha_i=(I-A_i)^{-1}\bar{q}_i$, where $\bar{q}_i \succ q_i$.

Remark 4
Theorem 1 can be used to guarantee an upper bound to the finite-time optimal control law

$$J_{FT}=c'x(T) \tag{17}$$

where T is the finite time and $c\succeq 0$ is a weight on the final state $x(T)$. Assume that inequalities (7) are feasible. Hence, thanks to linearity of (7) in α, it is possible to find $\alpha_i \succeq 0$ such that (7) are satisfied along with the additional constraint $c \preceq \alpha_i$, $\forall i$. Then, $c'x(T)\leqslant \min_i \alpha_i'x(T)=\upsilon(x(T))\leqslant\upsilon(x(0))=\min_i \alpha_i'x(0)$.

The theorems and lemmas presented above refer to a cost function over an infinite time horizon (also recall Remark 3). However, it is possible to slightly modify the relevant inequalities to account for finite time horizon functionals. To be precise, consider the system (1), the cost function

$$J=c'x(T)+\sum_{k=0}^{T-1} q'_{\sigma(k)}x(k) \tag{18}$$

and the difference equations, for $i=1,2,\ldots,N$

$$\alpha_i(k)=A_i'\alpha_i(k+1)+\sum_{j=1}^{N}\pi_{ji}\alpha_j(k)+q_i, \quad \alpha_i(T)=c \tag{19}$$

The following result holds.

Theorem 2
Let $q_i\in\mathbb{R}^n_+, i=1\ldots N$ be given. Let $\{\alpha_1(k),\ldots\alpha_N(k)\}$, $\alpha_i(k)\in\mathbb{R}^n_+$ be a set of nonnegative vectors satisfying (19) where $\pi\in\mathscr{M}$. The state-switching control

$$\sigma(k)=\arg\min_{i=1,\ldots,N}\ \alpha_i'(k)x(k) \tag{20}$$

is such that

$$c'x(T)+\sum_{k=0}^{T-1} q'_{\sigma(k)}x(k)\leqslant \min_{i=1,\ldots,N}\alpha_i'(0)x_0 \tag{21}$$

Proof
Let $V(x(k),k)=\min_i\{x(k)'\alpha_i(k)\}$. Then

$$\begin{aligned}
V(x(k+1),k+1)&=\min_i\{x(k+1)'\alpha_i(k+1)\}=\min_i\{x(k)'A'_{\sigma(k)}\alpha_i(k+1)\}\\
&\leqslant x(k)'A'_{\sigma(k)}\alpha_{\sigma(k)}(k+1)\\
&\leqslant V(x(k),k)-x(k)'q_{\sigma(k)}-x(k)'\sum_{r=1}^{N}\pi_{r\sigma(k)}\alpha_r(k)\\
&\leqslant V(x(k),k)-x(k)'q_{\sigma(k)}-x(k)'\alpha_{\sigma(k)}(k)\sum_{r=1}^{N}\pi_{r\sigma(k)}\\
&\leqslant V(x(k),k)-x(k)'q_{\sigma(k)}
\end{aligned}$$

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so that

$$\begin{aligned} J &= c'x(T) + \sum_{k=0}^{T-1} q'_{\sigma(k)}x(k) \\ &\leqslant c'x(T) - \sum_{k=0}^{T-1} V(x(k+1),k+1) - V(x(k),k) \\ &\leqslant c'x(T) - V(x(T),T)) + V(x_0,0) \\ &\leqslant \min_i \{x'_0\alpha_i(0)\} \end{aligned}$$ □

Remark 5
Note that in the infinite horizon case, the conditions required, (12), may be infeasible. However, in the finite horizon case, (19), the equations are always feasible (for example, taking $\pi_{ji}=0$), and for any fixed T can be solved by the reversed time difference Equation (19). If A_i are Schur matrices, then in the limit and with $\pi_{ji}=0$, $\lim_{T\to\infty}\alpha_i(0)=(I-A_i)^{-1}q_i$.

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 equations:

$$\alpha_i(k)=A'_i\alpha_i(k+1)+\zeta(\alpha_j(k)-\alpha_i(k))+q_i, \quad i\neq j=1,\ldots,N. \tag{22}$$

with final condition $\alpha_i(T)=c$, $\forall i$. Then, the state-switching control given by (20) is such that

$$c'x(T)+\sum_{k=0}^{T-1} q'_{\sigma(k)}x(k)\leqslant \min_{i=1,\ldots,N} \alpha'_i(0)x_0 \tag{23}$$

Proof
Consider any matrix Π chosen such that $\pi_{ii}=-\zeta$, therefore

$$\zeta^{-1}\sum_{j\neq i=1}^{N}\pi_{ji}=1 \quad \forall i=1,\ldots,N \tag{24}$$

Using (24), Equations (22) and (19) are equivalent, hence the upper bound of Theorem 2 holds. □

4. DISCRETE-TIME OPTIMAL CONTROL

In the previous section, we introduced both finite-time and infinite-time horizon upper bounds on the performance of the optimal feedback strategy. In many applications, it may be important to compute the optimal control law for a finite horizon cost function. In this section we introduce finite time optimal control for positive switched systems. In classical control theory, global sufficient conditions for optimality have been developed as a strengthening of the necessary conditions. Sufficient conditions introduce certain assumptions about regularity of the system and the behavior of the cost function, which must satisfy the Hamilton–Jacobi–Bellman equation [33]. Consider a cost function to be minimized over all admissible switching sequences given by:

$$J=c'x(T)+\sum_{k=0}^{T-1} q'_{\sigma(k)}x(k) \tag{25}$$

where $x(k)$ is a solution of (1) with the switching signal $\sigma(k)$. The vectors c and q_i, $i=1,2,\ldots,N$, are assumed to be positive. The optimal switching signal, the corresponding trajectory and the

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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;

$$V(x,k)=\min_{u\in U}\{q(k,x,u)+V(x(k+1),k+1)\} \tag{26}$$

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

$$V(x(k),k)=p(k)'x(k) \tag{27}$$

Using Equations (1) and (25)–(27), we obtain the following system

$$\begin{aligned} &x^o(k+1)=A_{\sigma^o(k)}x^o(k), x(0)=x_0\\ &p^o(k)=A'_{\sigma^o(k)}p^o(k+1)+q_{\sigma^o(k)}, p(T)=c\\ &\sigma^o(k)=\arg\min_s\{p^o(k+1)'A_sx^o(k)+q_sx^o(k)\} \end{aligned} \tag{28}$$

Notice that Equations (28) 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 cannot be solved using regular iteration techniques. A dynamic programming technique will be discussed next.

4.1. Exact solution of the optimal finite-horizon problem

In this section we first establish an important property of the optimal value function V (see (26)). Then, we give a procedure to compute the optimal solution. Finally, we show how to determine a lower bound for the cost that is useful in all cases in which the exact determination is too computationally demanding.

Lemma 3
For any k, the function $V(x,k)$ is concave and positively homogeneous, as a function of x.

Proof
The fact that the function $V(x,k)$ is positively homogeneous is obvious from (27). To prove concavity, consider two initial states x_A and x_B and take any convex combination $x=\alpha x_A+\beta x_B$, $\alpha,\beta\geqslant 0$ and $\alpha+\beta=1$. Let $\bar{\sigma}(k)$ be the optimal sequence associated with initial condition x achieving the optimal cost $\bar{J}$. Let $x_A(k)$ and $x_B(k)$ be the state sequences corresponding to $\bar{\sigma}(k)$ and the initial states $x_A(0)=x_A$ and $x_B(0)=x_B$. By linearity of the system we have

$$\bar{x}(k)=\alpha x_A(k)+\beta x_B(k)$$

Denote by J_A and J_B the (non-optimal) costs associated with these sequences and denote by $\bar{J}_A$ and $\bar{J}_B$ the optimal costs with initial conditions x_A and x_B. In view of the linearity of the cost we have

$$\bar{J}=\alpha J_A+\beta J_B\geqslant\alpha\bar{J}_A+\beta\bar{J}_B$$

This proves concavity of $V(x,0)$. The concavity for a generic k can be proved by dynamic programming arguments. □

Remark 6
Note that if we relax the assumption of positivity of the dynamics, then in general the optimal value function need not be either convex or concave [34].

The previous lemma has several implications including the fact that given any convex combination (in a general polytope) of initial conditions, the best cost is achieved on a vertex. This fact will be used later to determine a lower bound for the cost. Without loss of generality, consider the

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case where $q=0$, that is, there is a terminal cost only. Note that if this is not the case, we can introduce a new variable $y(k)$ having equation

$$y(k+1)=y(k)+q'x(k)$$

and initial condition $y(0)=0$, so that

$$J=c'x(T)+y(T).$$

In this way the original optimal control problem is reduced to a problem in which only the final cost $J=c'x(T)$ is considered.

Given the initial condition $x(0)$ the optimal control problem turns out to be

$$\min_{i_T,i_{T-1},\ldots,i_1} \quad c'A_{i_T}A_{i_{T-1}}\ldots A_{i_1}x(0)$$

Let us recursively define the sequence of matrices

$$\begin{aligned}
\Omega_0 &= c \\
\Omega_1 &= [A_1'\Omega_0 \;\; A_2'\Omega_0 \ldots A_N'\Omega_0] = [A_1'c \;\; A_2'c \ldots A_N'c] \\
&\vdots \\
\Omega_{k+1} &= [A_1'\Omega_k A_2'\Omega_k \ldots A_N'\Omega_k]
\end{aligned}$$

Then we have that $V(x,0)=\min_i \Omega_{T,i}'x$, where $\Omega_{T,i}$ is the ith column of Ω_T and, in general

$$V(x,k)=\min_i \Omega_{T-k,i}'x(k) \tag{29}$$

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

$$u(x(k))=\arg\min_i \Omega_{T-k,i}'x(k)$$

namely selecting the smallest component of the vector $\Omega_{T-k}'x(k)$. One consequence of this fact is formalized next.

Proposition 1
The function $V(x,T)$ is concave and piecewise co-positive.

The implementation of the strategy requires storing the columns of $\Omega_{T-k}'x(k)$ whose number would be $1+N+N^2+N^3+\cdots+N^{\mathrm{T}}$. This exponential growth could be too computationally demanding. 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 [35] for details). Given $\Omega_{k,i}$ solve the LP problem

$$\mu_{k,i}=\min_x \Omega_{k,i}'x \quad \text{s.t. } \Omega_{k\bar{i}}'x \geqslant \bar{1}$$

where $\bar{1}=[1 \;\; 1 \ldots 1]'$ and $\Omega_{k\bar{i}}$ denote the matrix obtained from Ω_k by deleting the ith column. Then, the column $\Omega_{k,i}$ is redundant (and it should be eliminated from Ω_k) iff $\mu_{k,i}\geqslant 1$. This means

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that for each Ω_k we can generate a 'cleaned' version $\bar{\Omega}_k$ 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 produces redundant columns in Ω_{k+1}. Then, the procedure for the generation of the minimal representation $\bar{\Omega}_{k+1}$ is achieved by performing the procedure described above as follows:

- Clean Ω_k and produce a minimal $\bar{\Omega}_k$
- Compute $\Omega_{k+1}=[\bar{\Omega}_k A_1 \bar{\Omega}_k A_2 \ldots \bar{\Omega}_k A_N]$

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. One way to further reduce the computational burden is to accompany the above algorithm (backward iteration) with its dual version (forward iteration). Indeed, consider the sequence of matrices

$$\begin{aligned}
\Theta_0 &= x(0)\\
\Theta_1 &= [A_1\Theta_0 A_2\Theta_0 \ldots A_N\Theta_0] = [A_1x(0)A_2x(0)\ \ldots A_Nx(0)]\\
&\vdots\\
\Theta_{k+1} &= [A_1\Theta_k\ A_2\Theta_k \ldots A_N\Theta_k]
\end{aligned}$$

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

$$u(x(k)) = \arg\min_i \Theta'_{k,i}\pi$$

so that one can solve the LP problem

$$v_{k,i} = \min_{\pi} \Theta'_{k,i}\pi, \quad \text{s.t.}\Theta'_{k\bar{i}}\pi \geqslant \bar{1}$$

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

Whenever the computation of the exact solution may be impractical, we may take advantage of the concavity to achieve a lower bound for the cost by solving off-line the problem for a finite number of initial conditions only. Assume that an optimization horizon T is given along with a family of initial conditions x_k grouped in a matrix

$$[x_1, x_2, \ldots x_p] = X$$

Let $\bar{J}_k = V(x_k, 0)$ the corresponding optimal costs. Assume also that the vectors of the canonical basis $[00\ldots1\ldots0]$ are included in the family. Then we have the following.

Proposition 2
For any $\gamma_i \geqslant 0$ and $x=\sum_{i=1}^{N}\gamma_i x_i$, the piecewise-linear function

$$\check{V}_T(x) = \sum_{k=0}^{N} \gamma_i \bar{J}_k \tag{30}$$

is defined over $\mathbb{R}^n_+$ and is a lower bound for the optimal cost: $\check{V}_T(x)\leqslant V(x,0)$. Furthermore, $\check{V}_T(x)$ is interpolating, that is, $\check{V}_T(x)$ is equal to the optimal cost for all vectors x aligned with the selected points: $\check{V}_T(\lambda x_k) = V(\lambda x_k, 0)$, for $\lambda > 0$.

Proof
For $x=0$ we have $\check{V}_T(0)=V(0,0)$. So let $x\in\mathbb{R}^n_+$, $x\neq 0$, be given and $\gamma\geqslant 0$ any feasible solution of (30), so that $x=X\gamma$. Note that such a γ exists since we included the principal directions, and

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then $\check{V}_T$ is defined on $\mathbb{R}^n_+$. Denote by $\gamma_s = \sum_{k=1}^N \gamma_k > 0$. Then,

$$V(x,0) = V\left(\sum_{k=1}^N x_k \gamma_k, 0\right) = \gamma_s V\left(\sum_{k=1}^N \frac{\gamma_k}{\gamma_s} x_k, 0\right)$$

$$\geqslant \gamma_s \sum_{k=1}^N \frac{\gamma_k}{\gamma_s} V(x_k,0) = \sum_{k=1}^N \gamma_k \; J_k$$

Since the above inequality is valid for all feasible γ, it holds for the maximizer, so that

$$V(x,0) \geqslant \check{V}_T(x)$$

Now take $x = x_1$ and the feasible $\gamma = [1\ 0\ 0 \ldots\ 0]$. Then, by the definition of $\check{V}_T$

$$\check{V}_T(x_1) \geqslant J_1 = V(x_1,0)$$

so that $V_T(x_1) = V(x_1,0)$. The fact that function $V_T(x)$ is positively homogeneous as $V(x,0)$ implies that $V_N(\lambda x_1) = V(\lambda x_1, 0)$ for $\lambda \geqslant 0$. The same property holds for the remaining x_k and thus the proof is concluded. □

In the next section, we apply the techniques developed to a simplified mathematical model of treatment scheduling to ameliorate the effects of virus mutation in HIV infection.

5. 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. Viral mutation is problematic since it gives rise to drug resistance if a single drug or single drug combination is given, see Figure 1. Several mathematical models have been proposed to describe HIV dynamics since 1990. Most of the models present a basic relationship between immune system cells; $CD4^+$ T cells that are one of the main targets of the virus, macrophages cells that constitute an alternate target for HIV replication, infected cells and virus [36–40]. These models used different mechanisms to explain HIV infection dynamics; however, for this paper we are just interested in the virus mutation treatment problem. For this reason we proposed a model for mutation dynamics that is

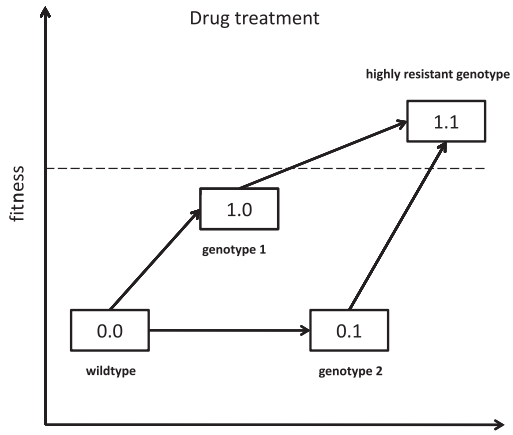

Figure 1. Drug treatment.

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simple enough to allow control analysis and optimization of treatment switching. Based on the model in [40], we make the following assumptions:

- Constant macrophage and $CD4^+$ T cell counts: The main nonlinearities in the more general model are bilinear, and all involve either the macrophage or healthy T-cell count. In addition, under normal treatment circumstances (that is after the initial infection stage, and until full progression to a dominant highly resistant mutant), typical simulations and/or clinical data suggest that the macrophage and T-cell counts are approximately constant. This assumption allows us to simplify the dynamics to being essentially linear.
- Scalar dynamics for each mutant: A more extensive model for HIV dynamics would include a set of states for each possible genotype such as: $V_i(t)$ (viral concentration); $T_i(t)$ (T cells infected by mutant i); $M_i(t)$ (macrophages infected by mutant i) etc. To simplify the model, we focus on the viral load, $V_i(t)$, only. If the dynamics of the 'group' (T_i, M_i, V_i, ...) is linear, many of the techniques here generalize in a straightforward way.
- Viral clearance rate independent of treatment and mutant: Although in some cases, particularly in view of the earlier assumption of representing the dynamics as scalar, viral clearance rate might well depend on one or more of the treatment regime, or the viral genetics; for simplicity, we take this as a constant.
- Mutation rate independent of treatment and mutant: In a similar vein, we assume that the mutation rate, between species with the same genetic distance, is constant. In practice, there will be some dependence of mutation rate on the replication rate, and therefore there will be some relationship between mutant, treatment and mutation rate.
- Deterministic model: In this paper we are interested in deriving control strategies with either optimal or 'verifiable' performance. To simplify the control design we base the design on a deterministic model. This is a significant limitation, though we note that under the assumption of linearity, the deterministic model does describe the expected behavior of a fuller stochastic model.

5.1. Mutation base model

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

$$\frac{\mathrm{d}}{\mathrm{d}t}\{x_i(t)\} = \rho_{i,\sigma(t)} x_i(t) - \delta x_i(t) + \sum_{j \neq i} \mu m_{ij} x_j(t) \tag{31}$$

where μ is a small parameter representing the mutation rate, δ is the death or decay rate and $m_{ij} \in \{0, 1\}$ represents the genetic connections between genotypes, that is, $m_{ij} = 1$ if and only if it is possible for genotype j to mutate into genotype i. Equation (31) can be rewritten in vector form as

$$\frac{\mathrm{d}}{\mathrm{d}t}\{x(t)\} = (R_{\sigma(t)} - \delta I)x(t) + \mu M x(t) \tag{32}$$

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

5.2. 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 (WT): 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.

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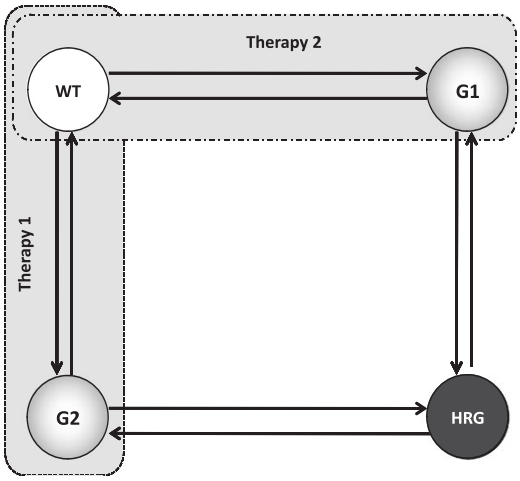

Figure 2. Mutation graph.

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

Variant	Therapy 1	Therapy 2
Wild type (x_1)	$\rho_{1,1}=0.05$	$\rho_{1,2}=0.05$
Genotype 1 (x_2)	$\rho_{2,1}=0.40$	$\rho_{2,2}=0.05$
Genotype 2 (x_3)	$\rho_{3,1}=0.05$	$\rho_{3,2}=0.40$
HR Genotype (x_4)	$\rho_{4,1}=0.30$	$\rho_{4,2}=0.30$

- 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 the viral clearance rate [41] as $\delta=0.24\,\text{day}^{-1}$ which corresponds to a half life of slightly less than 3 days. Typical viral mutation rates are of the order of $\mu=10^{-4}$. We take a mutation graph that is symmetric and circular, see Figure 2. That is we allow only the connections: $\text{WT}\leftrightarrow G1$, $G1\leftrightarrow\text{HRG}$, $\text{HRG}\leftrightarrow G2$ and $G2\leftrightarrow\text{WT}$. Other connections would require double mutations and for simplicity, we consider these to be of negligible probability. This leads to the mutation matrix:

$$M=\begin{bmatrix}0&1&1&0\\1&0&0&1\\1&0&0&1\\0&1&1&0\end{bmatrix} \tag{33}$$

We also describe the various replication rates in the Table I. These numbers are of course idealized, however, the general principles they are based on are:

- Symmetry: We do not expect a large difference in relative proliferation ability, although there will be some differences. Furthermore, a more detailed model would also include asymmetry in the genetic tree, which would usually have a much more complex structure than a simple cycle.
- Genetic distance from wild type reduces fitness: In the absence of effective drug treatments, we might expect that fitness (that is, reproduction rate) decreases with genetic distance from the wild type, which we expect to be most fit. This need not always be true, but is a useful starting point.

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- Therapy at best 90% effective: In the absence of drugs, from typical data, we might expect an overall viral proliferation rate (with high, constant T-cell count) of approximately $\rho = 0.5\,\text{day}^{-1}$. This would correspond to an exponential explosion rate, from near the uninfected equilibrium, with a doubling time of approximately 3 days. Under drug therapy, we drop the replication rate by a factor of 10. Genotype 1 replication rate is lower under drug therapy 1 (equivalently, no therapy) at $\rho = 0.4$, and the highly resistant genotype replication is lower again.

5.3. 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 ($P(\sum_i v_i = 0) \geqslant 1 - E[\sum_i v_i] = 1 - \sum_i x_i$). It is therefore logical to propose a cost

$$J := c' x(t_f) \tag{34}$$

where c is the column vector with all ones, and t_f is an appropriate final time. This cost should be minimized under the action of the switching rule. Another interesting interpretation of the cost relies on the theory of Markov jump linear systems. Indeed, notice that the state, Equation (31) can be written as follows:

$$\frac{\mathrm{d}}{\mathrm{d}t}\{x_i(t)\} = \eta_{i,u(t)} x_i(t) + \mu \sum_{j \neq i} \lambda_{ij} x_j(t) \tag{35}$$

where $\eta_{i,u(t)} = \rho_{i,u(t)} + 2\mu - \delta$ and $\lambda_{i,j} = m_{i,j}$, $i \neq j$, $\lambda_{i,i} = -2$. Notice that matrix: $\mu\Lambda$, where $\Lambda = \{\lambda_{i,j}\}$ is a stochastic matrix, which can be considered as the infinitesimal transition matrix of the Markov jump linear system

$$\dot{\xi} = 0.5\eta_{i,u(t)}\xi \tag{36}$$

Moreover, $\sum_{i=1}^{n} x_i(t) = E[\xi^2(t)]$. Minimizing $\sum_{i=1}^{n} x_i(t)$ is then equivalent to minimizing the variance of the stochastic process $\xi(t)$. Notice that if $\lim_{t\to\infty} E[\xi^2(t)] = 0$, then the system (36) is stable in the mean-square sense.

5.4. Simulation results

The model for the treatment of viral mutation given in (31) 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

$$x(k+1) = A_{\sigma(k)} x(k) \tag{37}$$

where $x(k) = x(k\tau)$ is the sampled state and $A_\sigma := \exp(R_\sigma - \delta I + \mu M)\tau$. Because the system (37) is frequently not stabilizable, we introduce exponential weighting to new coordinates $\tilde{x}(k+1) = \tilde{A}_{\sigma(k)}\tilde{x}(k)$ where $\tilde{A}_\sigma := A_\sigma - \beta I$, $\beta \geqslant 0$ is chosen to ensure stability, $\tilde{x}$ is the transformation given by $\tilde{x}(k) = \exp(-\beta k)x(k\tau)$, and σ is constant during the interval $t \in [k\tau, (k+1)\tau]$. Associated with the system (37), we consider the cost

$$J_\infty := \sum_{k=0}^{\infty} q' \tilde{x}(k) \tag{38}$$

where q is column vector with ones. Then, a guaranteed cost switching rule for the transformed system is:

$$\sigma(\tilde{x}(k)) := \arg\min_i \{\tilde{x}(k)'\alpha_i\} = \arg\min_i \{x(k)'\alpha_i\} \tag{39}$$

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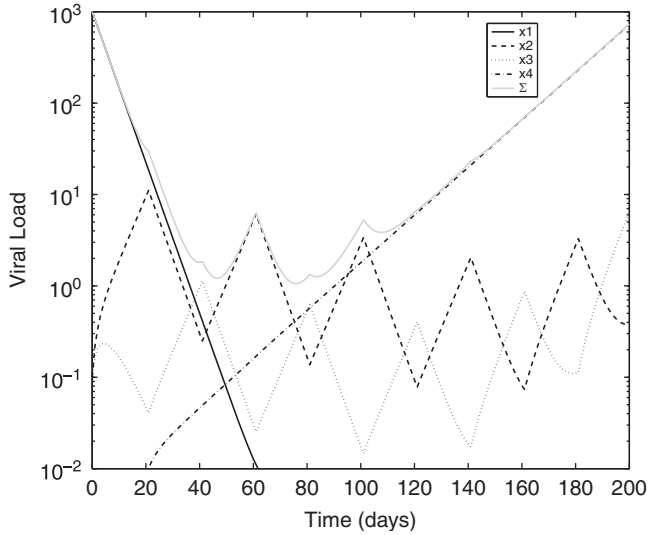

Figure 3. Performance of guaranteed cost control using (39).

where α_i is given by

$$\alpha_i := -(\tilde{A}_i' - I)^{-1} q \tag{40}$$

Notice that, since $\tilde{A}_i$ is a Schur matrix, $-\tilde{A}_i' + I$ is an M-matrix, whose inverse is a positive matrix, so that the vectors α_i in (39) are positive. The control rule (39) guarantees an upper bound on the cost function, i.e.

$$J_\infty < \min_i \tilde{x}_0' \alpha_i \tag{41}$$

Then we can write

$$J := \sum_0^\infty \exp(-\beta k) q' x(k\tau) < \min_i x_0' \alpha_i \tag{42}$$

We take the decision time τ equal to 20 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 Table I and the control rule in (39), we see in Figure 3 that for an initial period of time, the 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. The decision variables for this example, and the consequent control rule based on (29), are illustrated in Figure 4. For this important application, we are interested in comparing the performance of the control (39) with other strategies. If we use a guaranteed cost control over a finite period of time proposed in Theorem 2, the condition that all matrices A_i are Schur matrices can be removed, therefore $\beta = 0$. Using Corollary 1, the switching rule is given by

$$\sigma(x(k), k) := \arg\min_i \{x(k)' \alpha_i(k)\} \tag{43}$$

We need to solve backward in time the system (22) with final condition $\alpha(T) = c$. Both guaranteed cost controls have the same performance as can be seen in Table II, this is because the symmetry of the replication rates values, in Table I. We are also interested in the optimal control problem (28), where we take $q = 0$, that is

$$J := c' x(t_f) = c' \exp(\beta T) \tilde{x}(T), \quad t_f = \tau T \tag{44}$$

The system of Equations (28) 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

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Table II. Total viral load concentration for the symmetric case at the end of treatment of 200 days using decision time of 20 days.

Guaranteed cost control				
Infinite-time	Finite-time	Optimal control	Existing control	Single therapy
664.99	664.99	664.99	870.80	3.05×10^{13}

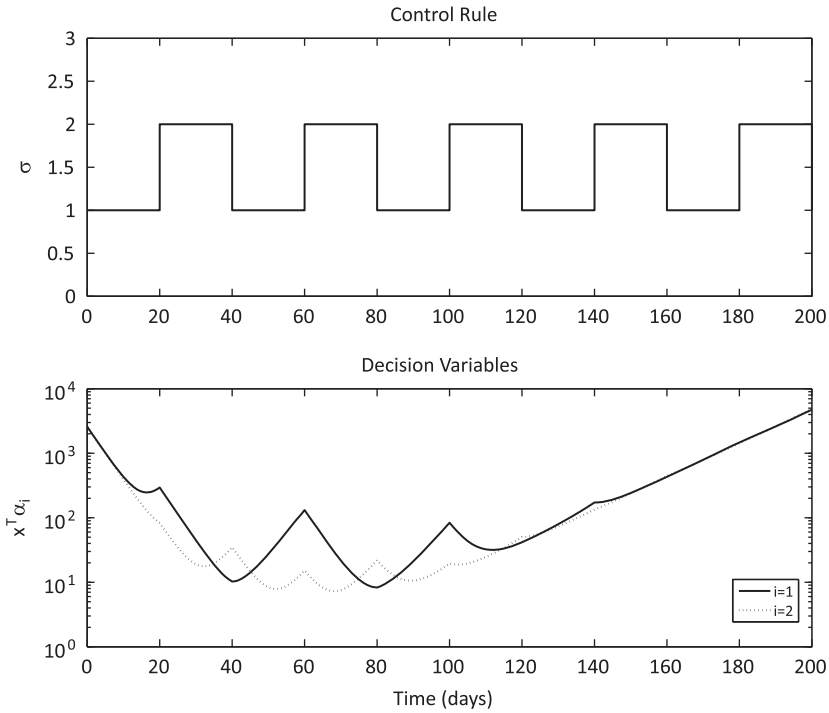

Figure 4. Switched control given by the rule in (39).

force' approach, which analyzes all possible combinations for therapies 1 and 2 with decision time $\tau = t_d$ for a period of T days, that is, we evaluate $2^{T/t_d}$ possible treatment combinations. For comparison purposes, we consider the total viral load at the end of the treatment. Thus, $J = \exp(\beta T)\tilde{x}(T)'c$ is computed in Table II for the guaranteed cost control. We can see in Figure 5 how the optimal control gives the same treatment as the guaranteed cost control, and these control strategies give the same total viral load at the end of the treatment as can be seen in Table II. Clearly, there is also a very dramatic difference compared to a non-switching approach to this problem. Furthermore, note that in this example guaranteed cost controls have slightly better performance at the end of the therapy than the control proposed by [28]. If we analyze the last results we notice that in this particular case guaranteed cost controls have the same performance as the optimal rule, even though different initial conditions are considered. However, at this point in time, we are not aware of any proof that there are circumstances under which the control given by (39) is the same as the optimal control. Simulation results show regular behavior in the control rule due to the symmetry of values in Table I. In practice, it is unrealistic to expect complete symmetry in the viral response to alternate treatments. As a further example, we consider an asymmetric configuration as is shown in Table III. Table IV displays the results for various switching rules; first, we note finite time guaranteed cost control gives superior performance to its infinite horizon counterpart. In addition, both guaranteed cost controls have a superior performance with respect to the control proposed by [28]. The guaranteed cost control over finite time horizon shows viral load concentration close to the optimal control and inferior to the other strategies.

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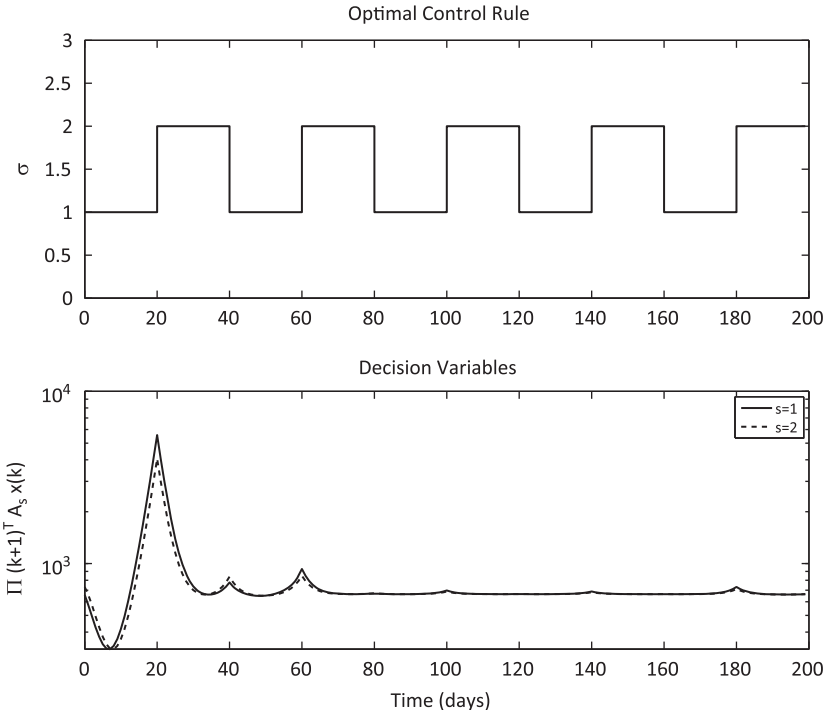

Figure 5. Control law and decision variables for optimal control.

Table III. Replication rates for viral variants and therapy combinations for an asymmetric case.

Variant	Therapy 1	Therapy 2
Wild type (x_1)	$\rho_{1,1}=0.05$	$\rho_{1,2}=0.1$
Genotype 1 (x_2)	$\rho_{2,1}=0.25$	$\rho_{2,2}=0.05$
Genotype 2 (x_3)	$\rho_{3,1}=0.10$	$\rho_{3,2}=0.30$
HR Genotype (x_4)	$\rho_{4,1}=0.30$	$\rho_{4,2}=0.30$

Table IV. Total viral load concentration for the asymmetric case at the end of treatment of 200 days using decision time of 20 days.

Guaranteed cost control				
Infinite-time	Finite-time	Optimal control	Existing control	Single therapy
185.95	159.30	152.59	197.04	9.96×10^4

6. CONCLUSIONS

We have introduced stability conditions for the switched positive systems in discrete-time. They have been used for the synthesis of the switching rules, for which a guaranteed cost function can be associated. In addition, the optimal control problem in discrete time for switched positive systems is addressed and the development of sufficient conditions for optimality are developed through Hamilton–Jacobi theory. These strategies are applied to a specific virus mutation problem. Numerical results show that in the specific symmetric example studied, guaranteed cost controls have the same performance as the optimal control. For the asymmetric example, the best performance is given by the guaranteed cost control over finite time horizon, which has a performance very close to the optimal rule. From these examples we see that using different drugs at the right moment is of great importance for patient treatment.

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REFERENCES

1. Liberzon D. *Switching in Systems and Control*. Systems and Control Foundations and Applications. Birkhauser: Boston, 2003.
2. Branicky MS. Multiple Lyapunov functional and other analysis tools. *IEEE Transactions on Automatic Control* 1998; **43**:475–482.
3. Hespanha JP. Uniform stability of switched linear systems: extensions of LaSalle's principle. *IEEE Transactions on Automatic Control* 2004; **49**:470–482.
4. Hockerman-Frommer J, Kulkarni SR, Ramadge PJ. Controller switching based on output predictions errors. *IEEE Transactions Automatic Control* 1998; **43**:596–607.
5. Johansson M, Rantzer A. Computation of piecewise quadratic Lyapunov functions for hybrid systems. *IEEE Transactions on Automatic Control* 1998; **43**:555–559.
6. Liberzon D, Morse AS. Basic problems in stability and design of switched systems. *IEEE Control System Magazine* 1999; **19**:59–70.
7. Geromel JC, Colaneri P. Stability and stabilization of discrete-time switched systems. *International Journal of Control* 2006; **79**(7):719–728.
8. De Carlo RA, Branicky MS, Pettersson S, Lennartson B. Perspectives and results on the stability and stabilizity of hybrid systems. *Proceedings of the IEEE* 2000; **88**:1069–1082.
9. Daafouz J, Bernussou J. Parameter dependent Lyapunov functions for discrete-time systems with time varying parametric uncertainties. *Systems and Control Letters* 2001; **43**:355–359.
10. Xie GM, Wang L. Reachability realization and stabilizability of switched linear discrete-time systems. *Journal of Mathematical Analysis and Applications* 2003; **280**:209–220.
11. Spinelli W, Bolzern P, Colaneri P. A note on optimal control of autonomous switched systems on a finite time interval. *Proceedings of American Control Conference*, Minnesota, U.S.A., 2006.
12. Branicky M, Bokar V, Mitter S. A unified framework for hybrid control:model and optimal control theory. *IEEE Transactions on Automatic Control* 1998; **43**(1):31–45.
13. Cassandras C, Pepyne D, Wardi Y. Optimal control of a class of hybrid systems. *IEEE Transactions on Automatic Control* 2001; **46**(3):398–415.
14. Xu X, Antsaklis P. Optimal control of switched systems based on parameterization of the switched instants. *IEEE Transactions on Automatic Control* 2004; **49**(1):2–16.
15. Sussman H. A maximum principle for hybrid optimal control problems. *Proceedings of Conference Decision and Control*, Phoenix, U.S.A., 1999.
16. Piccoli B. Necessary conditions for hybrid optimization. *Proceedings of Conference Decision and Control*, Phoenix, U.S.A., 1999.
17. Farina L, Rinaldi S. *Positive Linear Systems*. Wiley-Interscience Series. Wiley: New York, 2000.
18. Rumchev VG, James DJ. Spectral characterization and pole assignment for positive linear discrete-time system. *International Journal Systems Science* 1995; **26**(2):295–312.
19. Kaczoreck T. Stabilization of positive linear systems. *Proceedings of Conference Decision and Control*, Florida, U.S.A., 1998.
20. Leenheer PD, Aeyels D. Stabilization of positive linear systems. *Systems and Control Letters* 2001; **44**(4):259–271.
21. Gurvits L, Shorten R, Mason O. On the stability of switched positive linear systems. *IEEE Transactions on Automatic Control* 2007; **52**(6):1099–1103.
22. Knorn F, Mason O, Shorten R. On linear co-positive Lyapunov functions for sets of linear positive systems. *Automatica* 2009; **45**(8):1943–1947.
23. UNAIDS/WHO, *AIDS Epidemic Update*, 2007.
24. Egger M, Hirschel B, Francioli P *et al.* Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: prospective multicentre study. *Swiss HIV Cohort Study* 1997; **315**(7117):1194–1199.
25. Hogg RS, Yip B, Kully C *et al.* Improved survival among HIV-infected patients after initiation of triple-drug antiretroviral regimens. *CMAL* 1999; **160**(5):659–665.
26. Murphy EL, Collier AC, Kalish LA *et al.* Highly active antiretroviral therapy decreases mortality and morbidity in patients with advanced HIV disease. *Annals of Internal Medicine* 2001; **135**(1):17–26.
27. Martinez-Cajas J, Wainberg MA. Antiretroviral therapy: optimal sequencing of therapy to avoid Resistance. *Drugs* 2008; **68**(1):43–72.
28. von Kleist M, Menz S, Huisinga W. A new HIV treatment paradigm: switching drugs before failure. *International Conference on Systems Biology*, Stanford, CA, U.S.A., 2009.
29. Zappavigna A, Colaneri P, Geromel J, Middleton R. Stabilization of continuous-time switched linear positive systems. *The American Control Conference*, Baltimore, U.S.A., 2010.
30. Ait Rami M, Shamma J. Hybrid positive systems subject to Markovian switching. *IFAC Conference on Analysis and Design of Hybrid System*, Zaragoza, Spain, 2009.
31. El Ghaoui L, Ait Rami M. Robust stabilization of jump linear systems using linear matrix inequalities. *International Journal of Robust and Nonlinear Control* 1996; **6**(9):1015–1022.

DOI: 10.1002/rnc

32. Ait Rami M, Tadeo F. Controller synthesis for positive linear systems with bounded controls. *IEEE Transactions on Circuits and Systems* 2007; **54**:151–155.
33. Locatelli A. *Optimal Control*: *An Introduction*. Birkhäuser: Basel, 2001.
34. Blanchini F, Savorgnan C. Stabilizability of switched linear systems does not imply the existence of convex Lyapunov functions. *Automatica* 2008; **44**(4):1166–1170.
35. Blanchini F, Miani S. *Set-theoretic Methods in Control*. Birkhauser: Basel, 2008.
36. Nowak M, May R. *Virus Dynamics*: *Mathematical Principles of Immunology and Virology*. Oxford University Press: New York, 2000.
37. Kirschner D. Using mathematics to understand HIV immune dynamics. *AMS* 1996; **43**:191–202.
38. Perelson A, Nelson P. Mathematical analysis of HIV-1 dynamics in vivo. *SIAM Review* 1999; **41**:3–44.
39. Xia X. Modeling of HIV infection: vaccine readiness, drug effectiveness and therapeutical failures. *Journal of Process Control* 2007; **17**:253–260.
40. Hadjiandreou M, Conejeros R, Vassiliadis V. Towards a long-term model construction for the dynamic simulation of HIV infection. *Mathematical Bioscience and Engineering* 2007; **4**:489–504.
41. Ferreira J, Middleton RH. A preliminary analysis of HIV infection dynamics. *Irish Signals and Systems Conference*, Galway, Ireland, 2008.

DOI: 10.1002/rnc