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Brief paper

Optimal therapy scheduling for a simplified HIV infection model☆

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ABSTRACT

This work is motivated by the drug therapy scheduling problem in HIV infection. Using simplified switched linear system models of HIV mutation and treatment with certain class of symmetry and finite horizon cost functions, we demonstrate that the optimal state and costate trajectories lie on a sliding surface where infinitely fast switching may occur. Results suggest that in the absence of other practical constraints, switching rapidly between therapies is relevant. Simulations show the potential benefits of a proactive switching strategy to minimize viral load and delay the emergence of resistant mutant viruses.

1. Introduction

Highly active antiretroviral therapies (HAARTs) provide a rapid drop in plasma viral load with a large reduction of infected cells in patients with HIV infection. Even though long periods of HAART are provided, latently infected cells are still detectable. Therefore, cellular reservoirs may contribute to HIV persistence promoting the emergence of resistant mutants (Eisele & Siliciano, 2012).

In the recent treatment guidelines for HIV infection (AIDSinfo, 2011), clinicians did not achieve a consensus on the optimal time to change therapy in the event of virological failure (inability to maintain HIV RNA levels less than 50 copies/ml under HAART treatment). A widely accepted strategy (which we refer to as "switch on virological failure") is to continue the current therapy until the viral load exceeds a fixed level (*e.g.* 1000–500 copies/ml). Using a mathematical approach D'Amato, DAquila, and Wein (1998) proposed that alternating between therapies may delay the emergence of resistant mutant viruses. A preliminary clinical evaluation of proactive switching was performed in Martinez-Cajas and Wainberg (2008). In this initial trial alternating regimens appeared to outperform virological failure based treatment. Therefore switching between treatments may be crucial to minimize the risk of resistance (Craig & Xia, 2005; Luo, Piovoso, Martinez-Picado, & Zurakowski, 2011; Ouattara, Mhawej, & Moog, 2008). Under several simplifying assumptions, Hernandez-Vargas, Colaneri, Middleton, and Blanchini (2010) expressed the drug treatment scheduling problem of HIV infection as an optimal control application for a specific class of autonomous positive switched systems of the following form:

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

where $\sigma : R^n_+ \to \mathcal{I} = \{1, \ldots, N\}$ denotes the treatment selection and A_σ is a family of $n \times n$ matrices. The system (1) is positive if the non-negative orthant is positively invariant for any switching signal. Positivity is well known to be equivalent to all matrices A_σ being Metzler, that is, $a_{ij} \geq 0$ for any $i \neq j$ (Farina & Rinaldi, 2000).

Optimal control of hybrid systems has been widely studied (Cassandras, Pepyne, & Wardi, 2001; Dmitruk & Kaganovich, 2008, 2011; Spinelli, Bolzern, & Colaneri, 2006). The problem studied in this paper is closely related to the variational approach to the stability of switched systems previous developed by Boscain (2002), Margaliot (2006) and Rapoport (1996). We provide an analytic solution for a particular class of switched systems using sufficient conditions via the necessary conditions based on the Pontryagin principle. For simplicity no constraints or penalty terms are imposed on the switching. The cost functional is in the following form:

$$J := c'x(t_f) \tag{2}$$

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where c is a strictly positive vector. Note that this final time penalty is motivated by the observation that frequently the final viral escape is at an exponential rate that is largely independent of the treatment selection. Thus, the terminal cost (2) is a surrogate for delaying the escape time.

The paper is organized as follows: optimal control for switched systems is reviewed in Section 2. We apply these results to mutating HIV infection models under drug therapy in Section 3. Simulations are given in Section 4 followed by conclusions and future work in Section 5.

2. Optimal control problem

Consider the switched system (1) of dimension n, with $\sigma(t) \in \{1, 2, \ldots, N\}$ and the cost (2). When dealing with switched systems we can encounter sliding trajectories, i.e. infinite frequency switching of $\sigma(t)$. To include sliding trajectories, we embed the switched system in the larger class described by

$$\dot{x}(t) = \sum_{i=1}^{N} u_i(t) A_i x(t) \tag{3}$$

with $u(t) \in \mathcal{U} := \left\{ u : u_i \geq 0, \forall i; \sum_{i=1}^{N} u_i = 1 \right\}$ the unit simplex.

Remark 1. Clearly by construction the system (3) includes the system (1). It may be that for some t, $u(t)$ is not a vertex of the simplex, and there is no directly equivalent $\sigma(t)$. However (for example Bai & Yang, 2007), note that the set of possible trajectories of (1) are dense in the set of trajectories generated by (3). Therefore, extending the concept of valid switching signals to sliding modes based on the appropriate differential inclusions, we consider optimal control of the system (3). For further details of the related viscous solutions of differential equations and optimal control of differential inclusions see Bardi and Capuzzo-Dolcetta (2008) and Brandi and Salvadori (1998), respectively. The role of sliding modes (singular control) in optimization problems in terms of finite time convergence to the sliding surface is emphasized in McDonald (2008). □

Definition 1. A triple $u^o(t) : [0, t_f] \times \mathcal{U}, x^o(t), \pi^o(t)$, that satisfies (for almost all t) the system of equations:

$$\dot{x}^o(t) = \sum_{i=1}^{N} u_i^o(t) A_i x^o(t) \tag{4}$$

$$-\dot{\pi^o}(t) = \sum_{i=1}^{N} u_i^o(t) A_i' \pi^o(t) \tag{5}$$

$$u^o(t) \in \underset{u \in \mathcal{U}}{\operatorname{argmin}} \left\{ \pi^{o\prime}(t) \sum_{i=1}^{N} u_i A_i x^o(t) \right\} \tag{6}$$

with the boundary conditions $x^o(0) = x_0$ and $\pi^o(t_f) = c$, is called a Pontryagin solution for the optimal control problem.

Theorem 1. *Assume that there exists a unique Pontryagin solution (u^o, x^o, π^o) for the optimal control defined by system (3) and cost (2). Then $u^o(t)$ is an optimal control signal relative to x_0 and the value of the optimal cost functional is $\pi^{o\prime}(0)x_0$.*

Proof. Write the Hamiltonian function

$$H(x, u, \pi) = \pi(t)' \sum_{i=1}^{N} u_i A_i x(t)$$

and notice that $\dot{\pi}(t) = -\left(\frac{\partial H}{\partial x}\right)' = -\sum_{i=1}^{N} u_i(t) A_i' \pi(t)$, $\dot{x}(t) = \left(\frac{\partial H}{\partial \pi}\right)' = \sum_{i=1}^{N} u_i(t) A_i x(t)$. Moreover, the transversal conditions are satisfied and for all $u \in \mathcal{U}$:

$$H(x^o, u^o, \pi^o) \leq H(x^o, u, \pi^o).$$

Hence, in view of the Pontryagin principle, the triple (x^o, π^o, u^o) satisfies the necessary conditions for optimality. Optimality follows from the assumed uniqueness of the Pontryagin triple, see e.g. Bressan and Piccoli (2007, Theorem 7.1.1). □

Remark 2. For almost all t, the scalar function $v(x, t) = \pi^o(t)'x$ satisfies:

$$0 = \frac{\partial v}{\partial t}(x^o(t), t) + \min_u H\left(x^o(t), u, \frac{\partial v}{\partial x}(x^o(t), t)'\right)$$

with the boundary condition

$$v(x^o(t_f), t_f) = \pi^o(t_f)' x^o(t_f) = c' x^o(t_f).$$

This is however not enough to guarantee that any Pontryagin solution is also optimal, even though no counterexample for switched linear positive systems with positive linear cost has been worked out in the literature. Besides uniqueness, another sufficient condition ensuring optimality of a Pontryagin solution is the convexity of the functional $c'x(t_f)$ with respect to $u \in \mathcal{U}$. These topics will be the subject of future work. □

Note that if $u^o(t)$ lies at a vertex of $\mathcal{U}$, then an *admissible switching signals* (i.e. signals $\sigma(t) \in \{1, 2, \ldots, N\}$ for almost all t), $\sigma^o(t)$ can be constructed, see Spinelli et al. (2006), as follows:

$$\dot{x}^o(t) = A_{\sigma^o(t, x_0)} x^o(t)$$
$$-\dot{\pi^o}(t) = A'_{\sigma^o(t, x_0)} \pi^o(t)$$
$$\sigma^o(t, x_0) = \arg\min_{i \in \mathcal{I}} \{\pi^{o\prime}(t) A_i x^o(t)\}$$

with the boundary conditions $x^o(0) = x_0$, $\pi^o(t_f) = c$, and $J(x_0, x^o, \sigma^o) = \pi^{o\prime}(0)x_0$.

3. Optimal therapy scheduling: special cases

Simulations and clinical data suggest that once the patient is using HAART and until virological failure, macrophage and CD4+T cell counts are approximately constant (Perelson & Nelson, 1999). Under this assumption, most nonlinear HIV models (Hernandez-Vargas & Middleton, 2013) are rendered linear. For simplicity, we use the linear model proposed in Middleton, Colaneri, Hernandez-Vargas, and Blanchini (2010) that includes n different viral genotypes, with viral populations, $x_i : i = 1, \ldots, n$; and N different possible drug therapies that can be administered, represented by $\sigma(t) \in \{1, \ldots, N\}$. The viral dynamics are represented by the following simplified equation:

$$\dot{x}(t) = \left(R_{\sigma(t)} - \delta_V I\right) x(t) + \mu M_u x(t) \tag{7}$$

where $M_u := [m_{ij}]$ and $R_{\sigma(t)} := \operatorname{diag}\{\rho_{i,\sigma(t)}\}$. $\rho_{i,\sigma(t)}$ is the replication rate for viral genotype (i) and therapy combination σ, μ represents the mutation rate, δ_V is the viral clearance and $m_{i,j} \in \{0, 1\}$ represents the genetic connections between genotypes, that is, $m_{i,j} = 1$ if and only if it is possible for genotype j to mutate into genotype i.

Motivated by the HIV treatment application, we provide solutions based on the Pontryagin principle for particular subclasses of the model (7). These subclasses are restrict to $N = 2$, that means there are only two available treatments. In this case, the optimal control (6) may be a sliding mode when the decision variable $\gamma(t)$ vanishes on a non-trivial interval, where:

$$\gamma(t) := \pi'(t)(A_1 - A_2)x(t). \tag{8}$$

3.1. Invariant subspaces

One problem of interest is when x and π evolve on a particular invariant subspace as in the lemma below.

Lemma 1. *Consider the dynamic system (1) with initial condition $x(0) = x_0$, $N = 2$ and cost function $J = c'x(t_f)$. Suppose there exist $A_\alpha := \alpha A_1 + (1-\alpha)A_2$ $(\alpha \in (0,1))$; and tall matrices $v_x, w_x, v_\pi, w_\pi \in \mathbb{R}^{n\times m}$ (for any $m \le n$) such that:*

i. *v_x' is a left invariant of A_α;*
ii. *$v_x'x_0 = 0$;*
iii. *v_π is a right invariant of A_α;*
iv. *$c'v_\pi = 0$; and*
v. *$A_1 - A_2 = w_x v_x' + v_\pi w_\pi'$.*

Then there exists a Pontryagin solution over $t \in [0, t_f]$ that is a sliding mode.

Proof. Our claim is that:

$$x(t) = e^{A_\alpha t}x_0;$$
$$\pi(t) = e^{A_\alpha'(t_f - t)}c'$$

with the equivalent control $u_1(t) = \alpha$, $u_2(t) = (1-\alpha)$, satisfies the requirements of Definition 1. Clearly this is a valid solution to the state and costate equations and it remains to show that it satisfies the restrictions on $\gamma(t)$. However, because of the invariant subspace assumptions, it is always true that the state lives in the invariant subspace $v_x'x(t) = 0$. Similarly, the costate always evolves within the invariant subspace $\pi(t)'v_\pi = 0$. From condition (v) and (8), $\gamma(t) = 0 : \forall t \in [0, t_f]$. □

3.2. Generalized symmetry

An important case where the invariant subspace assumptions of Lemma 1 applies is when a particular kind of symmetry holds. In fact, the result applies also to a certain generalization of this symmetry as we shall see below. To this end, we first introduce a (generalized) transposition assumption.

Definition 2. A matrix $T \in \mathbb{R}^{n\times n}$ is called a (generalized) transposition if there exists a matrix $v \in \mathbb{R}^{n\times m}$ such that:

$$T = I - vv'; \quad \text{and} \tag{9}$$
$$v'v = kI \quad \text{for some } k > 1. \tag{10}$$

Note, for example, that with $k = 2$ in Definition 2, T is precisely a transposition with $T^2 = I$.

Assumption 1. The matrix A_2 may be obtained as a (generalized) transposition of A_1, namely, there exists a transposition T such that:

$$A_2 = TA_1T. \tag{11}$$

The following lemma shows how this assumption may be used to construct an invariant subspace.

Lemma 2. *Under Assumption 1, v' is a basis for a left invariant subspace of $A_\alpha = \alpha A_1 + (1-\alpha)A_2$; in particular $v'A_\alpha = \alpha(v'A_1v)v'$ where $\alpha = \frac{k-1}{k}$.*

Proof. Using (11) we may rewrite A_α as

$$A_\alpha = \alpha A_1 + (1-\alpha)TA_1T.$$

Substituting (9) in A_α we obtain

$$A_\alpha = \alpha A_1 + (1-\alpha)(A_1 - A_1vv' - vv'A_1 + vv'A_1vv')$$

multiplying v' by the left, and using (10), we have

$$v'A_\alpha = \alpha v'A_1 + (1-\alpha)(k-1)(v'A_1vv' - v'A_1)$$

then using $\alpha = \frac{k-1}{k}$, we obtain

$$v'A_\alpha = \alpha(v'A_1v)v'. \quad \square$$

We now extend this result to show how it may be used to find optimal switching controls.

Theorem 2. *Under the following conditions:*

i. *Assumption 1;*
ii. *The initial conditions and cost satisfy $v'x_0 = 0$ and $v'c = 0$, with v as in Definition 2; and*
iii. *A_1 and A_2 are symmetric;*

Then a Pontryagin solution is given by the trajectory along the plane $v'x(t) = 0$ with dynamical matrix A_α.

Proof. The proof follows directly from Lemmas 1 and 2 and the fact that the left and right invariant subspaces are equivalent for the symmetric matrix A_α. Condition (v) of Lemma 1 can be established as follows:

$$\begin{aligned} A_1 - A_2 &= A_1 - (I - vv')A_1(I - vv') \\ &= v\left(v'A_1 - \frac{1}{2}v'A_1vv'\right) + \left(A_1v - \frac{1}{2}vv'A_1v\right)v' \\ &= vw' + wv' \end{aligned}$$

where $w = A_1v - \frac{1}{2}vv'A_1v$. □

Note that as well as the matrix version of symmetry, $A_1' = A_1$, there is also a permutation symmetry here. In particular, T is now idempotent, and the dynamics under the two treatment options are identical apart from relabelling of some of the state variables. Furthermore, the conditions that the initial conditions and costate start on the invariant subspace are equivalent to equal weighting and initial conditions on state variables that are transposed under T. We therefore see that certain kinds of symmetric problems generically admit Pontryagin solutions that are a sliding mode. Next we look at a specific class of systems for which this solution is optimal.

3.3. General solution for a 4 variant model

Consider a system with 4 states, and two treatment options, $N = 2$ of the following structure, see Middleton et al. (2010).

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

Remark 3. In reality, HIV treatments are a combination of multiple (usually 3 or more) individual drugs, each of which has independent susceptibility to viral mutation. Even if considering only 2 classes of treatment, a full order model for this would have up to $2^{(3\times 2)} = 64$ (or possibly more) viral strains. The 4 variant model is a significant simplification of complex mutation dynamics in real HIV behavior that is more amenable to analysis. □

Assumption 2. $\lambda_{21} > 0, \lambda_{22} < 0, \lambda_{31} < 0, \lambda_{32} > 0.$

In addition, we make the following symmetry assumption:

Assumption 3. $\lambda_{21} - \lambda_{22} + \lambda_{31} - \lambda_{32} = 0.$

Using Assumptions 2 and 3, $\Delta A = A_1 - A_2$ can be rewritten as follows

$$\Delta A = (\lambda_{21} - \lambda_{22})\bar{J}$$

where $\bar{J} = \text{diag}\,(0, 1, -1, 0)$. Since $\lambda_{21} - \lambda_{22} > 0$, we define the normalized decision function $\bar{\gamma}(t) = \pi(t)'\bar{J}x(t)$, that takes the form

$$\bar{\gamma}(t) = \pi_2(t)[x_2(t) - x_3(t)] + x_3(t)[\pi_2(t) - \pi_3(t)]. \tag{12}$$

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

$$\begin{aligned}\dot{\bar{\gamma}}(t) &= \mu[\pi_2(t) - \pi_3(t)][x_1(t) + x_4(t)] \\ &\quad - \mu[x_2(t) - x_3(t)][\pi_1(t) + \pi_4(t)].\end{aligned} \tag{13}$$

The following lemma, which can be proven directly from (12) and Assumption 2 is useful to characterize the optimal solution. In the following the sign function $\mathcal{S}_{gn}[\cdot]$ is introduced, i.e. $\mathcal{S}_{gn}[v] = 1$ if $v > 0$, $\mathcal{S}_{gn}[v] = -1$ if $v < 0$ and $\mathcal{S}_{gn}[v] = 0$ if $v = 0$.

Lemma 3. *Under Assumption 2 the following conditions hold for any Pontryagin solution, $x(t)$, $\pi(t)$, $u(t)$:*

$$\begin{aligned}&\left\{\mathcal{S}_{gn}[x_2(t) - x_3(t)] = \mathcal{S}_{gn}[\pi_2(t) - \pi_3(t)]\right\} \\ &\quad\Longrightarrow \left\{\mathcal{S}_{gn}[\bar{\gamma}(t)] = \mathcal{S}_{gn}[x_2(t) - x_3(t)]\right\} \\ &\left\{\mathcal{S}_{gn}[x_2(t) - x_3(t)] = -\mathcal{S}_{gn}[\pi_2(t) - \pi_3(t)]\right\} \\ &\quad\Longrightarrow \left\{\mathcal{S}_{gn}[\dot{\bar{\gamma}}(t)] = \mathcal{S}_{gn}[\pi_2(t) - \pi_3(t)]\right\} \\ &\mathcal{S}_{gn}[\dot{x}_2(t) - \dot{x}_3(t)] = \mathcal{S}_{gn}[\alpha - u_1(t)] \\ &\mathcal{S}_{gn}[\dot{\pi}_2(t) - \dot{\pi}_3(t)] = \mathcal{S}_{gn}[u_1(t) - \alpha].\end{aligned}$$

To characterize the sliding modes, it is necessary to find a suitable convex combination of the matrices A_1, A_2 as follows:

Lemma 4. *Consider any time interval, $[t_1, t_2]$ and suppose that $x_2(t_1) = x_3(t_1)$, $\pi_2(t_2) = \pi_3(t_2)$. Under Assumption 3, there is a Pontryagin solution over $[t_1, t_2]$ such that $x_2(t) = x_3(t)$, $\pi_2(t) = \pi_3(t)$ with $\alpha = \frac{\lambda_{32} - \lambda_{22}}{\lambda_{32} - \lambda_{22} + \lambda_{21} - \lambda_{31}}$.*

Proof. Given the structure of $\bar{J}$, this can clearly be written as $\bar{J} = vw' + wv'$ where $w = \frac{1}{2}[0, 1, 1, 0]'$ and $v = [0, 1, -1, 0]'$. The remainder of the proof follows that of Lemma 1. □

For the future proof of optimality, we establish positive invariance of certain regions for any Pontryagin solutions to the optimal control problem.

Lemma 5. *With respect to any Pontryagin solution, and subject to Assumptions 2 and 3, the following regions are positively invariant:*

$$\begin{aligned}\mathcal{R}_{+1} &:= \{(x, \pi) : \bar{\gamma} > 0, x_2 - x_3 \le 0, \pi_2 - \pi_3 \ge 0\} \\ \mathcal{R}_{+2} &:= \{(x, \pi) : \bar{\gamma} < 0, x_2 - x_3 \ge 0, \pi_2 - \pi_3 \le 0\}.\end{aligned}$$

Proof. We prove this result for $\mathcal{R}_{+1}$ only as the other case follows similarly. Note that $\bar{\gamma} > 0$ implies that $u_1 = 0$ and therefore

$$\begin{aligned}\dot{x}_2 - \dot{x}_3 &= \lambda_{22}x_2 - \lambda_{32}x_3 < 0, \\ \dot{\pi}_2 - \dot{\pi}_3 &= -\lambda_{22}\pi_2 + \lambda_{32}\pi_3 > 0.\end{aligned}$$

Furthermore, from (13), in this region $\dot{\bar{\gamma}} \ge 0$. □

Now define $k_1 = \text{argmin}\{x_2(0), x_3(0)\}$, $k_2 = \text{argmin}\{c_2, c_3\}$, and

$$T_1 = \underset{t\ge 0}{\text{argmin}} : [0\ 1\ -1\ 0]e^{A_{k_1}t}x(0) = 0,$$

$$T_2 = \underset{t\le t_f}{\text{argmax}} : [0\ 1\ -1\ 0]e^{-A_{k_2}(t-t_f)}c = 0.$$

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 and T_2 are well defined and unique. Clearly, by definition $x_2(T_1) = x_3(T_1)$ and $\pi(T_2) = \pi_3(T_2)$. We are now in the position to provide the main result for the four variant model (recall that $\sigma = 1$ means $u_1 = 1$, $\sigma = 2$ means $u_1 = 0$ and a sliding mode corresponds to the singular arc associated with $u_1 = \alpha$).

Theorem 3 (*Long Horizon Case*). *Let Assumptions 2 and 3 be met, let $\mu > 0$ and assume that $T_1 \le T_2$. Then, the optimal control associated with the initial state $x(0)$ and cost $c'x(t_f)$ is given by $\sigma(t) = k_1$, $t \in [0, T_1]$ and $\sigma(t) = k_2$, $t \in [T_2, t_f]$. For $t \in [T_1, T_2]$, the optimal control is given by the trajectory along the plane $x_2 = x_3$, with dynamical matrix $A_\alpha = \alpha A_1 + (1-\alpha)A_2$ and α as given in Lemma 2.*

Proof. We first define our candidate optimal solution triple as follows:

$$\begin{aligned}&u_1(t) = k_1, \quad t \in [0, T_1] \\ &u_1(t) = \alpha, \quad t \in [T_1, T_2] \\ &u_1(t) = k_2, \quad t \in [T_2, t_f] \\ &x(t) = e^{A_{k_1}t}x(0), \quad t \in [0, T_1] \\ &x(t) = e^{A_\alpha(t-T_1)}x(T_1), \quad t \in [T_1, T_2] \\ &x(t) = e^{A_{k_2}(t-T_2)}x(T_2), \quad t \in [T_2, t_f] \\ &\pi(t) = e^{A_{k_2}(t_f - t)}c, \quad t \in [T_2, t_f] \\ &\pi(t) = e^{A_\alpha(T_2 - t)}\pi(T_2), \quad t \in [T_1, T_2] \\ &\pi(t) = e^{A_{k_1}(T_1 - t)}\pi(T_1), \quad t \in [0, T_1].\end{aligned}$$

Next, consider the time interval $t \in [T_1, T_2]$. By definition, $x_2(T_1) = x_3(T_1)$ and $\pi_2(T_2) = \pi_3(T_2)$. By Lemma 4, in the interval $[T_1, T_2]$ we have $x_2(t) = x_3(t)$ and $\pi_2(t) = \pi_3(t)$, and therefore the Pontryagin conditions are satisfied in this interval.

For the remaining two intervals $t \in [0, T_1]$ ($i = 1$) and $t \in [T_2, t_f]$ ($i = 2$), consider $\bar{\gamma}$ (12), and $\dot{\bar{\gamma}}$ (13). Now, $\bar{\gamma}(T_1) = \bar{\gamma}(T_2) = 0$ and, for $t \in [0, T_1]$ or $t \in [T_2, t_f]$:

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

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

This means that, for $t \in [0, T_1]$, or $t \in [T_2, t_f]$:

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

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

Therefore, within either time interval, the sign of $\dot{\bar{\gamma}}$ is uniform:

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

Since $\bar{\gamma}(T_i) = 0$ for $i = 1, 2$ it follows that the sign of $\bar{\gamma}$ is uniform within either time interval, and takes the required sign to satisfy the Pontryagin conditions.

We now have to show that the proposed Pontryagin solution, $u(t), x(t), \pi(t)$ is unique so that optimality follows. We do this by considering other candidate Pontryagin solutions and producing a contradiction, thereby establishing that the proposed solution is optimal.

To this end, consider Figs. 1 and 2, that correspond to the case $x_2(0) < x_3(0)$. The case $x_2(0) = x_3(0)$ can be understood in a simple way via the same figures with $T_1 = 0$, whereas the case $x_2(0) > x_3(0)$ can be obtained by symmetry. Consider also Fig. 5

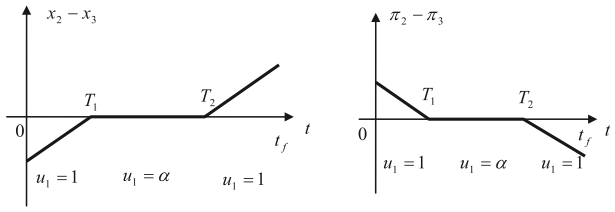

Fig. 1. Long horizon with $k_1 = k_2 = 1$.

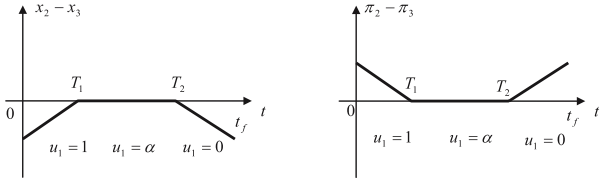

Fig. 2. Long horizon with $k_1 = 1, k_2 = 2$.

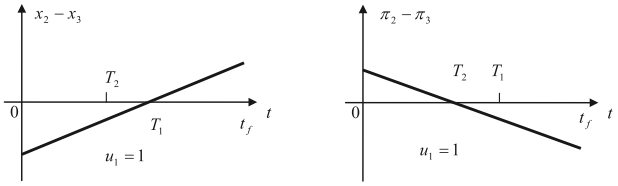

Fig. 3. Small horizon with $k_1 = k_2 = 1$.

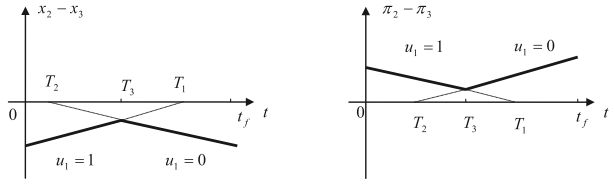

Fig. 4. Small horizon with $k_1 = 1, k_2 = 2$.

that shows the four orthants in the coordinates $x_2 - x_3$ and $\pi_2 - \pi_3$, labeled in $\bar{\gamma}$ and $\dot{\bar{\gamma}}$. Notice also that in the case $\mu \neq 0$ the only point for which $\bar{\gamma} = 0$ and $\dot{\bar{\gamma}} = 0$ is the origin, i.e. $x_2 = x_3$ and $\pi_2 = \pi_3$.

Case (a): $\pi_2(0) - \pi_3(0) \leq 0$. Since we have also assumed $x_2(0) < x_3(0)$ it follows that $\bar{\gamma}(0) < 0$ and $u_1(0) = 1$. Then initially, $x_2(t) - x_3(t)$ increases and $\pi_2(t) - \pi_3(t)$ decreases. Therefore, there is an initial time interval $[0, \tau_1]$ wherein $\bar{\gamma}(t) < 0$, $\dot{\pi}_2 < \dot{\pi}_3$, and therefore $\pi_2(t) < \pi_3(t)$. These conditions persist unless we reach $x_2 = x_3$. However, at this point we have entered the positively invariant region $\mathcal{R}_{+2}$. Therefore, in this case, we must have $\bar{\gamma} < 0$ and $\pi_2 < \pi_3$ over the entire time interval. However, this contradicts either: (i) $\pi_2(t_f) - \pi_3(t_f) = c_2 - c_3$ (if $c_2 > c_3$); or (ii) if $c_2 < c_3$ the long horizon assumption on the existence of T_2 which yields $\pi_2(T_2) = \pi_3(T_2)$.

Case (b): $\pi_2(0) - \pi_3(0) \geq 0$, $\bar{\gamma}(0) > 0$. In this case, we start in $\mathcal{R}_{+1}$ and therefore remain in this region. In a similar manner to case (a), this produces a contradiction with respect to either the final value of the costate, or the existence of T_2.

Case (c): $\pi_2(0) - \pi_3(0) > 0$, $\bar{\gamma}(0) \leq 0$. Note that if $\bar{\gamma}(0) = 0$ then at some small time later we are effectively in case (b) and the contradiction there holds. Therefore $\bar{\gamma}(t)$ remains negative until some $t = \tau_1 > 0$. Suppose $\tau_1 < T_1$, then by the definition of T_1, $x_2(\tau_1) < x_3(\tau_1)$, and therefore to satisfy $\bar{\gamma}(\tau_1) = 0$ we must have $\pi_2(\tau_1) > \pi_3(\tau_1)$. Then just after $t = \tau_1$ we enter $\mathcal{R}_{+1}$ and remain there, and as in cases (a), (b) this leads to a contradiction. Suppose instead that $\tau_1 > T_1$. Then for $t \in (T_1, \min\{\tau_1, T_2\})$, it must be true

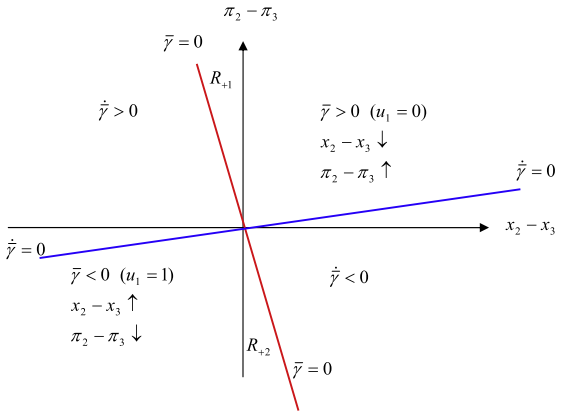

Fig. 5. Plane $x_2 - x_3, \pi_2 - \pi_3$.

that $x_2(t) > x_3(t)$ and $\bar{\gamma}(t) < 0$. This implies that $\pi_2(t) < \pi_3(t)$ and therefore we are in $\mathcal{R}_{+2}$ and a similar contradiction to before holds. Therefore, the only case that does not lead to a contradiction is that $\bar{\gamma}(t)$ reaches zero precisely at $t = T_1$, $x_2(T_1) = x_3(T_1)$ and $\pi_2(T_1) = \pi_3(T_1)$ as in the proposed solution.

By reversing the same logic, we can show that the final time interval must be of the form postulated, $x_2(T_2) = x_3(T_2)$ and $\pi_2(T_2) = \pi_3(T_2)$. Finally, as evident from Fig. 5, the only Pontryagin solution in the interval $[T_1, T_2]$ with $x_2(T_i) = x_3(T_i)$ and $\pi_2(T_i) = \pi_3(T_i)$ is $u_1(t) = \alpha$ (this means the origin of the plane in Fig. 5). □

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

Theorem 4 (*Small Horizon Case*)**.** *Let Assumption (2) be met, assume $\mu \neq 0$ and $0 < T_2 \leq T_1 < t_f$. Then, the optimal control associated with the initial state $x(0)$ and cost $c'x(t_f)$ is given as follows:*

(i) *If $k_1 = k_2$, then $\sigma(t) = k_1$, $t \in [0, t_f]$,*

(ii) *otherwise, if $k_1 \neq k_2$, then $\sigma(t) = \begin{Bmatrix} k_1 : & t \in [0, T_3] \\ k_2 : & t \in [T_3, t_f] \end{Bmatrix}$, where $T_3 \in [T_2, T_1]$ is such that for $t = T_3$*

$$g(t) := x(0)' e^{A_{k_1}(t)} \bar{J} e^{-A_{k_2}(t - t_f)} c = 0.$$

Proof (*Outline*)**.** The proof follows similar steps of Theorem 3 and we therefore abbreviate many of the details. We first verify that the proposed control law satisfies the Pontryagin conditions (3).

Consider case (i) $k_1 = k_2$ (see Fig. 3). Also take $k_1 = 1$, with the other case following by symmetry. Our candidate solutions are

$$\pi(t) = e^{A_1(t_f - t)} c, \quad t \in [0, t_f]$$
$$x(t) = e^{A_1 t} x(0), \quad t \in [0, t_f]$$

and for all t, $u_1(t) = 1$. It remains to confirm that this satisfies the decision condition, (6). Note that by definition of T_2, $x_2(t) - x_3(t)$ changes sign only at $t = T_2$. Similarly, $\pi_2(t) - \pi_3(t)$ changes sign only at $t = T_1$. For $t \in [\max\{0, T_2\}, \min\{T_1, t_f\}]$ both $x_2(t) - x_3(t)$ and $\pi_2(t) - \pi_3(t)$ are both negative, and therefore $\bar{\gamma}(t) < 0$ as required. A further two regions may need to be considered, $[0, T_2]$, $[T_1, t_f]$. In these regions we have $\dot{\bar{\gamma}}(t) > 0$, $\dot{\bar{\gamma}}(t) < 0$ respectively, and therefore $\bar{\gamma}(t) < 0$ for the entire interval $t \in [0, t_f]$.

Now consider case (ii), $k_1 \neq k_2$ (see Fig. 4). We discuss $k_1 = 1$, $k_2 = 2$ with the other case following similarly. We first show that T_3 exists. Note that $g(T_2)$ is negative and $g(T_1)$ is positive. Uniqueness follows since

$$g'(t) := x(0)' e^{A_1(t)} (A_1 \bar{J} - \bar{J} A_2) e^{-A_2(t - t_f)} c \geq 0$$

where the inequality follows since for our case, $(A_1\bar{J} - \bar{J}A_2)$ is diagonal and non-negative. Our candidate optimal solution is therefore

$$\pi(t) = e^{A_2(t_f - t)}c, \quad t \in [T_3, t_f]$$
$$\pi(t) = e^{A_1(T_3 - t)}e^{A_2(t_f - T_3)}c, \quad t \in [0, T_3]$$
$$x(t) = e^{A_1 t}x(0), \quad t \in [0, T_3]$$
$$x(t) = e^{A_2(t - T_3)}e^{A_1 T_3}x(0), \quad t \in [T_3, t_f]$$
$$u_1(t) = 1, \quad t \in [0, T_3)$$
$$u_1(t) = 2, \quad t \in (T_3, t_f].$$

From the definition of T_3, the candidate $\bar{\gamma}(t)$ swaps sign at $t = T_3$. We now have to show that the proposed Pontryagin triple is unique. Note that by the definitions of T_1 and T_2, for any Pontryagin solution $x_2(t) < x_3(t)$ for $t \in [0, T_1)$ and $\pi_2(t) > \pi_3(t)$ for $t \in (T_2, t_f]$.

Now consider three cases. Case (a): $\pi_2(0) \leq \pi_3(0)$. This then leads to $\bar{\gamma} < 0$ and therefore $\pi_2 - \pi_3$ decreases. It can be shown that this situation persists and therefore there is a contradiction with the terminal condition, $\pi(t_f) = c$. Case (b): $\pi_2(0) > \pi_3(0)$ and $\bar{\gamma}(0) > 0$. This is part of the set $\mathcal{R}_{+1}$ which is positively invariant, and yields a valid solution only when $t_f < T_3 < T_1$. Case (c): $\pi_2(0) > \pi_3(0)$ and $\bar{\gamma}(0) < 0$. This yields $\dot{\bar{\gamma}}(0) > 0$ and the solution is as postulated wherein $T_3 < T_1 < t_f$.

Reversing the argument to work backwards from $t = t_f$, gives the solution postulated, including possible cases where T_3 exists, but is outside the range $(0, t_f)$. □

Remark 4. Theorem 4 implicitly includes cases where one or more of T_1, T_2 and T_3 are outside the range $(0, t_f)$. □

Remark 5. Suppose $\mu = 0$. Then, the matrices of the system commute, and existing results (e.g. see Agrachev and Liberzon (2001) and Margaliot (2007)) can be applied. In our case (diagonal matrices), it is possible to prove that an optimal control is described by a single switch of duration

$$T_s = \frac{1}{2(\lambda_{21} - \lambda_{22})} \ln \frac{x_3(t_f)^{\sigma=1}}{x_2(t_f)^{\sigma=1}}$$

where $x(t_f)^{\sigma=1}$ denotes the state vector at time t_f evaluated with $\sigma = 1$. This solution is non-unique, and for symmetric initial conditions, and under Assumptions 2 and 3, the sliding mode control, $u_1(t) = \alpha$ is also optimal. □

4. Simulation results

HIV treatments are designed to require the accumulation of three or more resistance mutations before the appearance of a fully resistant variant. This would give a complex scenario with a much higher degree of complexity. To illustrate the results of Section 3, we propose a 4 variant, 2 drug treatment model, with an initial condition vector $x = [10^3, 5, 0, 10^{-5}]$ and a symmetric cost function weighting as $c = [1, 1, 1, 1]'$. The viral clearance rate is $\delta_V = 0.24$ day^{-1}, which corresponds to a half life of less than 3 days (Perelson & Nelson, 1999). Notice that other authors (Huang, Wu, & Acosta, 2010; Luo, Piovoso, Martinez-Picado, & Zurakowski, 2012; Putter, Heisterkamp, Lange, & De Wolf, 2002) suggest a slightly faster clearance rate, approximately 1 per day. Viral mutation rates are of the order of $\mu = 10^{-4}$ (Mansky, 1996). The various replication rates are described in the Table 1, these numbers are of course idealized, however the general principles are based on Hernandez-Vargas et al. (2010). For an optimal treatment, using Theorem 3, therapy 2 is used for $t < T_1 = 12.2$ days, then therapies alternate with high frequency as illustrated in Fig. 6. The wild type virus is attenuated to undetectable levels (less than 50 copies/ml). The highly resistant genotype grows slowly which induces the final viral escape. Fig. 6(b) reveals how the costate dynamics are similar to the state, but in reverse time.

Table 1
Symmetric replication rates for viral variants.

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

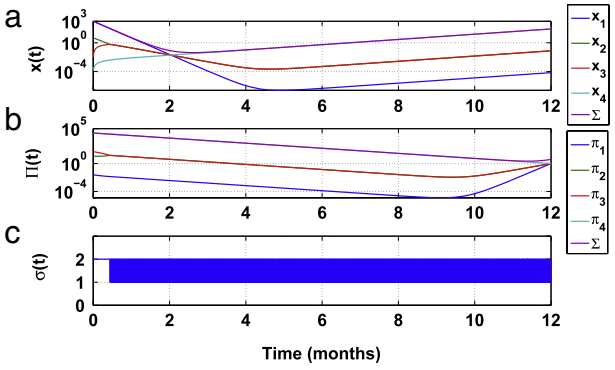

Fig. 6. Optimal trajectories (a) genotype dynamics (b) adjoint state variables (c) switching rules.

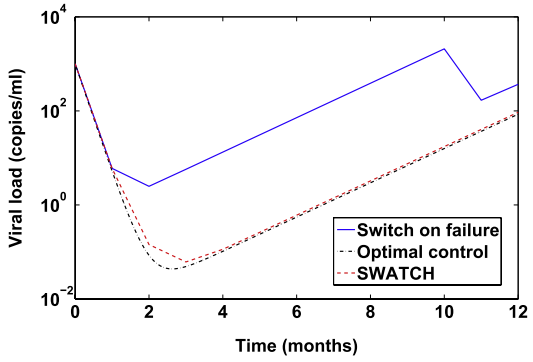

Fig. 7. Different treatment strategies to mitigate the viral escape.

Remark 6. Optimal trajectories are associated with chattering switching laws that are of course not realistically applicable for HIV treatment. However, this theoretical result provides an important insight since it clarifies when the therapies have to be switched more frequently in order to better control viral load. In order to accommodate the need for a lower bound on the commutation intervals, future works will address the problem of incorporating a dwell time constraint for the switching signal. □

Using a switch on virological failure strategy, the therapy is changed after 9 months (when viral load $\geq$1000 copies/ml). Therefore, the population of the resistant genotype is large enough that it that cannot be contained by the second therapy, see Fig. 7. In contrast, proactive switching may reduce viral load to very low levels during the whole treatment, 100 copies/ml, promoting a larger delay in the viral escape. Notice that an open loop alternating strategy and the optimal control present close performance for this example. This means that a periodic oscillating strategy might be effective in postponing viral escape without requiring a detailed model, high computational time and full state measurements.

5. Conclusions

For the proposed models of treatment in HIV and simplifying assumptions in the proliferation rate and the mutation graph, we show that the optimal control for a class of positive switched systems is given by the trajectory along the plane $v'x(t) = 0$ with dynamical matrix A_α. Such behavior suggests that in the absence of other practical constraints, switching rapidly between therapies may be desirable. This work provides the speculative possibility that therapy alternation may sustain viral suppression to very low levels inhibiting the emergence of resistant mutant viruses. Further research will include more realistic models and cost functions that penalize the switching.

References

Agrachev, A. A., & Liberzon, D. (2001). Lie-algebraic stability criteria for switched systems. *SIAM Journal on Control and Optimization*, *40*(1), 253–269.

AIDSinfo (2011). Panel of antiretroviral guidelines for adults and adolescents, "guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents, 2011". http://www.aidsinfo.nih.gov.

Bai, X., & Yang, X. S. (2007). A new proof of a theorem on optimal control of switched systems. *Journal of Mathematical Analysis and Applications*, *331*(2), 895–901.

Bardi, M., & Capuzzo-Dolcetta, I. (2008). *Optimal control and viscosity solutions of Hamilton–Jacobi–Bellman equations*. Boston: Birkhäuser.

Boscain, U. (2002). Stability of planar switched systems: the linear single input case. *SIAM Journal on Control and Optimization*, *41*(1), 89–112.

Brandi, P., & Salvadori, A. (1998). On measure differential inclusions in optimal control theory. *Rendiconti del Seminario Matematico*, [ISSN: 0373-1243] *56*(4), 69–86.

Bressan, A., & Piccoli, B. (2007). *Introduction to mathematical control theory, 2007*. In AIMS series on applied mathematics, Philadelphia.

Cassandras, C. G., Pepyne, D. L., & Wardi, Y. (2001). Optimal control of a class of hybrid systems. *IEEE Transactions on Automatic Control*, *46*(3), 398–415.

Craig, I., & Xia, X. (2005). Can HIV/AIDS be controlled? Applying control engineering concepts outside traditional fields. *IEEE Control Systems Magazine*, *25*(1), 80–83.

D'Amato, R. M., DAquila, R. T., & Wein, L. M. (1998). Management of antiretroviral therapy for HIV infection: modelling when to change therapy. *Antiviral Therapy*, *3*, 147–158.

Dmitruk, A. V., & Kaganovich, A. M. (2008). The hybrid maximum principle is a consequence of Pontryagin maximum principle. *Systems & Control Letters*, *57*(11), 964–970.

Dmitruk, A. V., & Kaganovich, A. M. (2011). Maximum principle for optimal control problems with intermediate constraints. *Computational Mathematics and Modeling*, *22*(2), 180–215.

Eisele, E., & Siliciano, R. (2012). Redefining the viral reservoirs that prevent HIV-1 eradication. *Immunity*, *37*(3), 377–388.

Farina, L., & Rinaldi, S. (2000). *Positive linear systems: theory and applications*. New York: Wiley.

Hernandez-Vargas, E., Colaneri, P., Middleton, R., & Blanchini, F. (2010). Discrete-time control for switched positive systems with application to mitigating viral escape. *International Journal of Robust and Nonlinear Control*, *21*(10), 1093–1111.

Hernandez-Vargas, E., & Middleton, R. (2013). Modeling the three stages in HIV infection. *Journal of Theoretical Biology*, *320*, 33–40.

Huang, Y., Wu, H., & Acosta, E. P. (2010). Hierarchical Bayesian inference for HIV dynamic differential equation models incorporating multiple treatment factors. *Biometrical Journal*, *52*(4), 470–486.

Luo, R., Piovoso, M. J., Martinez-Picado, J., & Zurakowski, R. (2011). Optimal antiviral switching to minimize resistance risk in HIV therapy. *PloS One*, *6*(11), e27047.

Luo, R., Piovoso, M. J., Martinez-Picado, J., & Zurakowski, R. (2012). HIV model parameter estimates from interruption trial data including drug efficacy and reservoir dynamics. *PloS One*, *7*(7), e40198.

Mansky, L. M. (1996). Forward mutation rate of human immunodeficiency virus type 1 in a t lymphoid cell line*. *AIDS Research and Human Retroviruses*, *12*(4), 307–314.

Margaliot, M. (2006). Stability analysis of switched systems using variational principles: an introduction. *Automatica*, *42*(12), 2059–2077.

Margaliot, M. (2007). A counterexample to a conjecture of Gurvits on switched systems. *IEEE Transactions on Automatic Control*, *52*(6), 1123–1126.

Martinez-Cajas, J., & Wainberg, M. A. (2008). Antiretroviral therapy: optimal sequencing of therapy to avoid resistance. *Drugs*, *68*(1), 43–72.

McDonald, D. B. (2008). Lyapunov optimizing sliding mode control for linear systems with bounded disturbance. *Applied Mathematical Sciences*, *2*(19), 901–918.

Middleton, R. H., Colaneri, P., Hernandez-Vargas, E., & Blanchini, F. (2010). Continuous-time optimal control for switched positive systems with application to mitigating viral escape. In *Proceedings of the 8th IFAC symposium on nonlinear control systems* (pp. 266–271).

Ouattara, D. A., Mhawej, M. J., & Moog, C. H. (2008). Clinical tests of therapeutical failures based on mathematical modeling of the HIV infection. *IEEE Transactions on Automatic Control*, *53*, 230–241. (Special Issue).

Perelson, A. S., & Nelson, P. W. (1999). Mathematical analysis of HIV-1 dynamics in vivo. *SIAM Review*, *41*(1), 3–44.

Putter, H., Heisterkamp, S. H., Lange, J. M. A., & De Wolf, F. (2002). A Bayesian approach to parameter estimation in HIV dynamical models. *Statistics in Medicine*, *21*(15), 2199–2214.

Rapoport, L. (1996). Asymptotic stability and periodic motions of selector-linear differential inclusions. *Robust Control via Variable Structure and Lyapunov Techniques*, 269–285.

Spinelli, W., Bolzern, P., & Colaneri, P. (2006). A note on optimal control of autonomous switched systems on a finite time interval. In *American control conference* (p. 6). IEEE.

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