

Switching Strategies to Mitigate HIV Mutation

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Abstract—HIV mutates rapidly and may develop resistance to specific drug therapies. There is no general agreement on how to optimally schedule the available treatments for mitigating the effects of mutations. With a switched positive linear system, we examined different control strategies applied to a higher order nonlinear mutation model. Simulation results suggest that model predictive control could outperform the common clinical treatment recommendations. This brief is a step forward to develop further tools for helping the practitioners to find the optimal treatment schedule.

Index Terms—HIV, model predictive control (MPC), mutation, positive systems.

I. INTRODUCTION

HIGHLY active antiretroviral therapies (HAARTs), generally consisting of three different drugs, are the most important treatment for HIV-infected patients [1]. Unfortunately, HAART is not always successful. Many patients have long-term complications, whereas others experience virological failure: inability to maintain HIV RNA levels less than 200 copies/mL [1]. In most cases, viral rebound is associated with the emergence of resistance-conferring mutations within the viral genome, resulting in virus with reduced susceptibility to one or more of the drugs. This is caused by the reverse transcription process of viral RNA into DNA, which is susceptible to errors, introducing on average one base-pair mutation for each viral genome transcribed [2].

In this environment, one clinical goal is to delay the time until patients exhibit strains resistant to all existing regimens. There is therefore a crucial tradeoff between switching therapies. On the one hand, early switching risks poor adherence to a new drug regimen and prematurely exhausting the limited number of remaining salvage therapies. On the other hand, switching drugs too late allows the accumulation of mutations that leads to multidrug resistance [3].

Antiretroviral guidelines (AIDSinfo) [1] revealed that practitioners have not achieved consensus on the optimal time to change therapy in response to virological failure. The most acceptable strategy has been allowing detectable viremia up

to a higher level (1000–500 copies/mL). The latter approach we term as switch on virologic failure treatment.

In the same spirit as [4], we are concerned with a class of switched systems, where the continuous control is absent and only the switching signal must be determined [5]. In this brief, no constraints or penalties are imposed on switching. Under a particular symmetric assumption on the matrices, Hernandez-Vargas *et al.* [6] provided necessary conditions for optimality over a finite horizon, for which the optimal states and costates lie on a sliding surface.

For autonomous switched linear systems, the optimal control yields a two-point boundary value problem, which cannot be solved using regular techniques. Therefore, a general solution for the optimal control problem is difficult to reach either analytically or numerically [7].

One option for reducing the computational complexity of a complete optimal control problem is to perform optimal control decisions over a short receding horizon, this is a model predictive control (MPC) approach. Alternatively, while retaining a full horizon for the decisions, but relaxing the demand of optimality, piecewise copositive Lyapunov functions may be used to obtain suboptimal switching rules with a guaranteed level of performance [4].

Previous works in [4], [7], and [8] suggest that suboptimal controllers based on a switched linear reduction have superior performance to commonly used strategies in clinical practice. These studies were designed and applied on switched linear systems, which can approximate HIV dynamics when the patient is under treatment. However, it is very important to verify the effectiveness of these strategies in a more realistic scenario.

In this brief, we design a state observer and base control decisions on state estimates, rather than the nonlinear simulation model. Our simulation results suggest that a switched system observer coupled with MPC may give a very effective method for treatment scheduling in HIV infection.

II. SWITCHING TREATMENT TO MITIGATE HIV

The process of reverse transcription is extremely error prone and it is during this step that mutations can occur. In the absence of on-going viral replication, the generation of new variants is also arrested [2]. Therefore, Mellors *et al.* [9] noted that stronger suppression of viral replication reduces the chance that a resistant mutant will emerge. Hernandez-Vargas *et al.* [4] suggest that a strong suppression of the total viral load (V_T) increase the probability of viral extinction. Therefore, control strategies should penalize the total viral load

$$V_T := \sum_{i=1}^n V_i \quad (1)$$

Manuscript received February 24, 2012; accepted August 24, 2013. Manuscript received in final form September 4, 2013. This work was supported in part by SFI Ireland through the awards 07/RPR/1177 and 07/IN/11838 and in part by BMBF (GerontoShield). Recommended by Associate Editor M. Guay.

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Digital Object Identifier 10.1109/TCST.2013.2280920

where V_i is the concentration of the i th genotype and n is the total number of genotypes.

Remark 1: Even during long periods of viral suppression under HAART, latently infected cells are still present. Therefore, viral eradication may be impossible. Cellular reservoirs may contribute to HIV persistence promoting the emergence of resistant mutants [10]. Given the wide diversity of resistant mutants, the underlying HIV treatment problem might not be stabilizable [4].

A. HIV Mutation Model

There are many different mechanisms potentially involved in HIV infection, limited measurement capability, significant time variations, and nonlinearities. Therefore, modeling HIV infection is not a trivial problem [11], [12]. In contrast to the majority of the existing models, Hernandez-Vargas and Middleton [13] proposed a mathematical model that represents the three key clinical phases observed in untreated HIV infection: 1) an early peak in the acute infection; 2) a long asymptomatic period; and 3) a final increase in viral load with simultaneous collapse in healthy CD4+T cell counts. Moreover, the model proposed in [13] retains its ability to describe the three stages of the infection even under moderately large full parameter variations.

With the model [13], we consider a nonlinear model with the viral genotype i under a treatment σ using the following populations: uninfected CD4+T cells (T), infected CD4+T cells (T^*), uninfected macrophages (M), and infected macrophages (M^*). The model is as follows:

$$\begin{aligned} \dot{T} &= s_T + \frac{\rho_T}{C_T + V_T} T V_T - \sum_{i=1}^n k_{T,\sigma}^i T V_i - \delta_T T \\ \dot{M} &= s_M + \frac{\rho_M}{C_M + V_T} M V_T - \sum_{i=1}^n k_{M,\sigma}^i M V_i - \delta_M M \\ \dot{T}^* &= k_{T,\sigma}^i T V_i + \sum_{j=1}^n \mu m_{i,j} V_j T - \delta_{T^*} T_i^* \\ \dot{M}^* &= k_{M,\sigma}^i M V_i + \sum_{j=1}^n \mu m_{i,j} V_j M - \delta_{M^*} M_i^* \\ \dot{V}_i &= p_{T,\sigma}^i T_i^* + p_{M,\sigma}^i M_i^* - \delta_V V_i. \end{aligned} \quad (2)$$

The infection rate constant for the i th strain is written as $k_{T,\sigma}^i$ for CD4+T cells and $k_{M,\sigma}^i$ for macrophages. Viral proliferation is achieved in infected activated CD4+T cells and infected macrophages, this with rate constants $p_{T,\sigma}^i$ and $p_{M,\sigma}^i$, respectively. These parameters depend on the fitness of the genotype and the therapy that is used. The mutation rate is expressed by μ , and $m_{i,j} \in \{0, 1\}$ represents the genetic connections between genotypes. The death rates for the relevant species are δ_T , δ_{T^*} , δ_M , δ_{M^*} , and δ_V . A further explanation of the biological mechanisms and parameters involved in (2) can be found in [13].

Theoretically, at least three new mutations are needed to cause resistance to one treatment. Therefore, it is reasonable to assume for numerical purposes, a 16-variant two-treatment combination model. The viral mutation graph is simplified to

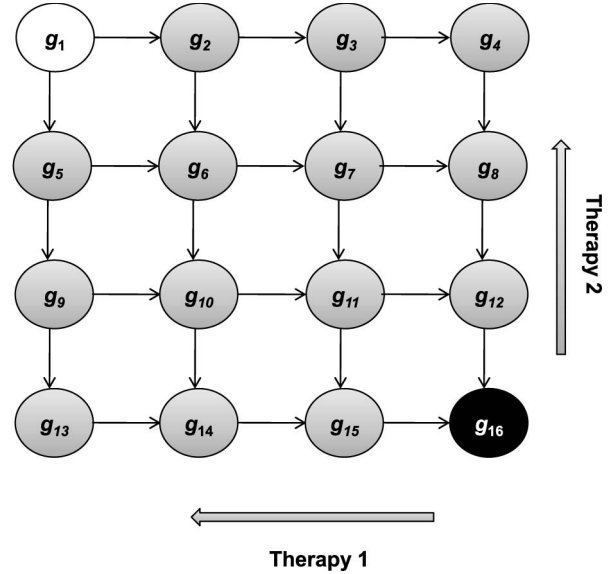


Fig. 1. Sixteen genotypes and two drug combination. The direction of the arrows represents the strength of the therapy. That is, therapy 1 has the greatest influence on strains g_1 , g_5 , g_9 , and g_{13} . Meanwhile, therapy 2 has the greatest impact on g_1 , g_2 , g_3 , and g_4 .

be a square grid, as shown in Fig. 1. The wild type genotype (g_1) would be the most prolific variant in the absence of any drugs. However, it is also the variant that all the drug combinations have been designed to combat, and therefore is susceptible to all the therapies. After several mutations, the highly resistant mutant (g_{16}) is a genotype with low proliferation rate, but resistant to all the drug therapies.

AIDSinfo [1] usually suggests two nucleotide analogs and either protease inhibitors or nucleotide reverse transcriptase inhibitors. The combination of these classes is crucial in controlling the development of resistance. Therefore, we consider therapies that are composed of reverse transcriptase inhibitors (that alter the infection constants, k_T and k_M) and protease inhibitors (that affect the viral production constants, p_T and p_M), which are modeled as follows:

$$\begin{aligned} k_{T,\sigma}^i &= k_T f_i \eta_{\sigma,i}^T \\ k_{M,\sigma}^i &= k_M f_i \eta_{\sigma,i}^M \\ p_{T,\sigma}^i &= p_T f_i \theta_{\sigma,i}^T \\ p_{M,\sigma}^i &= p_M f_i \theta_{\sigma,i}^M \end{aligned}$$

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

We assume that in the absence of treatment, mutation reduces the fitness of the genotype. For simplicity, we use linearly decreasing factors f_i , which represent the fitness of the genotype i . The directional effect of the two drug combinations is shown in Fig. 1, where the arrows show the efficiency of the drug. Clinical evidence [14] suggests that antiretrovirals are more effective in CD4+T cells than in macrophages, which is represented by $\eta_{\sigma,i}^T > \eta_{\sigma,i}^M$ and $\theta_{\sigma,i}^T > \theta_{\sigma,i}^M$.

B. Switched Linear Approximation

Two-target cell models are more accurate than single-target cell models. Perelson *et al.* [15] noted that after the first rapid phase of decay during the initial one to two weeks of antiretroviral treatment, plasma virus load declined at a considerably slower rate. This second phase of viral decay was attributed to the turnover of a longer lived viral reservoir. However, the design of switching strategies for the full-order nonlinear model (2) can be very demanding. Under normal treatment circumstances, typical clinical data suggest that the macrophage and CD4+T cell counts are approximately constant [15]. This assumption allows us to approximate the dynamics by a switched linear system

$$\begin{aligned}\dot{T}_i^* &= k_{T,\sigma}^i T V_i - \delta_{T^*} T_i^* + \sum_{j=1}^n \mu m_{i,j} V_j T \\ \dot{M}_i^* &= k_{M,\sigma}^i M V_i - \delta_{M^*} M_i^* + \sum_{j=1}^n \mu m_{i,j} V_j M \\ \dot{V}_i &= p_{T,\sigma}^i T_i^* + p_{M,\sigma}^i M_i^* - \delta_V V_i\end{aligned}\quad (3)$$

where T and M are treated as approximately constant. System (3) can be rewritten as follows:

$$\dot{x} = \begin{bmatrix} \Lambda_{1,\sigma} & 0 & \dots & 0 \\ 0 & \Lambda_{2,\sigma} & \dots & 0 \\ \vdots & & \ddots & \vdots \\ 0 & 0 & \dots & \Lambda_{n,\sigma} \end{bmatrix} x + \mu M_u x \quad (4)$$

where $x' = [T_1^*, M_1^*, V_1, \dots, T_n^*, M_n^*, V_n]$, $\Lambda_{j,\sigma}$ is given by

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

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

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

With the previous discussion, we consider the total viral load V_T as our cost function, this can be rewritten as follows:

$$J := c'x(t_f) \quad (5)$$

where $c = [0, 0, 1, \dots, 0, 0, 1]$ and t_f is an appropriate final time. We choose the final time because our observation is that the final escape of the highly resistant mutant is at an exponential rate, largely independent of treatment selection. Therefore, the total viral load at a far distant time is taken as an indirect indicator for the duration of viral suppression.

III. SWITCHED LINEAR CONTROL

The following positive switched linear system on a finite time interval is considered:

$$\dot{x}(t) = A_{\sigma(t)}x(t), \quad x(0) = x_0 \quad (6)$$

where $t \geq 0$, R_+^n is the set of nonnegative real numbers, $x(t) \in R_+^n$ is the state variable vector, $\sigma(t)$ is the switching

signal, $x_0 \in R_+^n$ is the initial condition, and A_i belongs to a set of Metzler matrices $\{A_1, \dots, A_N\}$. The cost functional to be minimized over all admissible switching sequences is given by

$$J(x_0, x, \sigma) = \int_0^{t_f} q'_{\sigma(\tau)}x(\tau)d\tau + c'x(t_f) \quad (7)$$

where $x(t)$ is a solution of (6) with the switching signal $\sigma(t)$. Vectors q_i , $i = 1, 2, \dots, N$ are assumed to have nonnegative entries. The optimal switching signal, the corresponding trajectory, and the optimal cost functional will be denoted by $\sigma^o(t, x_0)$, $x^o(t)$, and $J(x_0, x^o, \sigma^o)$, respectively. The Hamiltonian function relative to (6) with cost functional (7) is given by

$$H(x, \sigma, \pi) = q'_{\sigma(t)}x(t) + \pi(t)'A_{\sigma(t)}x(t). \quad (8)$$

The optimal system for (6) and cost (7) was addressed in [7] and calls for extremal (optimal candidates) solving the Pontryagin equations

$$\begin{aligned}\dot{x}^o(t) &= A_{\sigma^o(t, x_0)}x^o(t) \\ -\dot{\pi}^o(t) &= A'_{\sigma^o(t, x_0)}\pi^o(t) + q_{\sigma^o(t, x_0)} \\ \sigma^o(t, x_0) &= \arg \min_{i=1, \dots, N} \{\pi^{o'}(t)A_i x^o(t) + q'_i x^o(t)\}\end{aligned}\quad (9)$$

with the boundary conditions $x^o(0) = x_0$ and $\pi^o(t_f) = c$. Note that the system (9) is a two-point boundary value problem and cannot be solved using regular integration techniques.

A simpler computable switching rule (11) is able to give an upper bound on the cost function (7). The strategy is as follows:

Corollary 1: Let $q \in R_+^n$ and $c \in R_+^n$ be given, and let the positive vectors $\{\alpha_1, \dots, \alpha_N\}$, $\alpha_i \in R_+^n$ satisfy for some $\zeta > 0$, the modified coupled copositive Lyapunov differential inequalities

$$\dot{\alpha}_i + A'_i \alpha_i + \zeta(\alpha_j - \alpha_i) + q_i, \leq 0 \quad i \neq j = 1, \dots, N \quad (10)$$

with final condition $\alpha_i(t_f) = c$, $\forall i$. Then, the switching rule

$$\sigma(x(t)) = \arg \min_{i=1, \dots, N} \alpha'_i(t)x(t) \quad (11)$$

is such that

$$\int_0^{t_f} q'_{\sigma(\tau)}x(\tau)d\tau + c'x(t) \leq \min_{i=1, \dots, N} \alpha'_i(0)x_0. \quad (12)$$

Proof: The proof can be found in [7]. ■

The parameter ζ can be easily optimized yielding in advance a quantitative evaluation of the possibility of viral mitigation through intelligent switching.

A. MPC

MPC involves solving an online finite horizon open-loop optimal control problem controls [16], [17]. MPC is based on the measurements obtained at time t . The controller then predicts the future dynamic behavior of the system over a prediction horizon T_p and computes an open-loop optimal control problem with control horizon T_c , to generate both current and future predicted control signals. Due to disturbances, measurement noise and model-plant mismatch, the true system behavior is different from the predicted one. To incorporate a feedback mechanism, only the first step

of the optimal control sequence is implemented. When the next measurement becomes available the whole procedure—prediction and optimization—is repeated to find a new input function with the control and prediction horizons moving forward. Further details of MPC for switched systems can be found in [18] and [19].

IV. SIMULATION RESULTS

For simulation purposes, we consider the recommendations provided by AIDSinfo [1], which suggests altering therapy with virologic failure as follows.

- 1) *Switch on Virologic Failure*: Introduce a new regimen if there is detectable viremia (HIV RNA >1000 copies/mL) and drug-resistant genotype identified.

We also consider SWITCH treatment [20], [21]. The rationale behind this strategy is that one could preempt virologic rebound and reduce accumulating drug-resistant genotypes by alternating treatments. This strategy is as follows.

- 1) *Switch*: Alternate between two regimens every three months while viral load is suppressed.

The outcome in [22] showed similar side effects between the switch on virologic failure and SWITCH strategies. Therefore, we assume there are no serious side effects due to rapid switching between multiple regimens. To simulate HIV dynamics, we consider the model (2), further details of the model and parameters values can be obtained in [13]. AIDSinfo [1] recommends antiretroviral therapy for patients with $CD4+T$ counts between 350 and 500 cells/mm³. Therefore, in our test scenario, we introduce treatment after four years postinfection.

Fig. 2 shows the performance of the switch on virologic failure and SWITCH strategies. On the one hand, switch on virologic failure provides a fast recovery in $CD4+T$ cells counts and a sharp drop in viral load to undetectable levels, consistent with clinical observations [1]. Before the first virologic failure, clinical markers satisfy the levels required for healthy immunological responses ($CD4+T \geq 500$ cells/mm³). Note in Fig. 2 how the first virologic failure is presented after 10 years. To avoid the collapse of $CD4+T$ cell counts, the introduction of the second therapy is necessary. However, the persistent low-level viremia and long-term reservoirs causes a second virologic failure after three years [23]. Therefore, the final time before the final viral escape is approximately 17 years after initial infection.

These results are consistent with the clinical observations in [23], Sungkanuparph *et al.* reported that the median time to failure was 68.4 months for patients with persistence low viremia (PLV; 51–1000 copies/mL for at least three months) and more than 72 months for patients without PLV. Sungkanuparph *et al.* [23] suggested that PLV is associated with virologic failure. That is, patients with a PLV >400 copies/mL and a history of HAART experience are more likely to experience virologic failure.

On the other hand, simulation results for the SWITCH strategy do not present virologic failure for approximately 37 years. In addition, Fig. 2 shows a normal range of $CD4+T$ cell counts (500–1500 cells/mm³) during SWITCH.

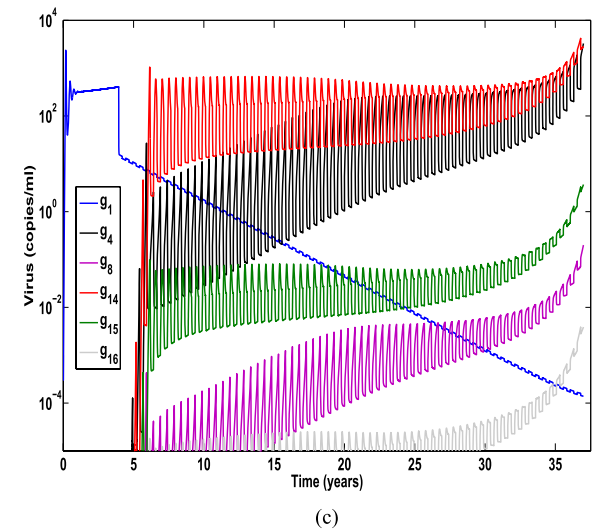
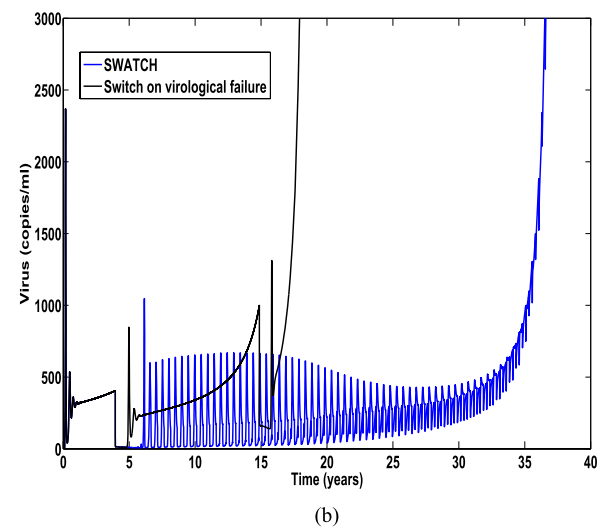
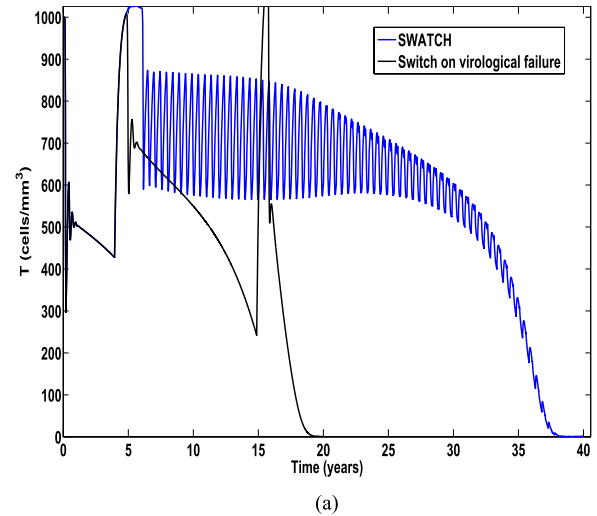


Fig. 2. Switch on virologic failure and SWITCH treatments. (a) $CD4+T$ cells. (b) Viral load. (c) Genotype profile for SWITCH.

Thus, with this example, simulation results suggest that proactive switching (SWITCH) could provide larger time scales to preserve normal $CD4+T$ cell levels in patients with HIV than the switch on virologic failure strategy.

In Fig. 2, we can observe the dynamics of the most representative genotypes during SWITCH. The wild type (g_1) is suppressed by both the therapies, yielding a strong reduction of this genotype. Remarkably, the final viral escape is not due to the highly resistant genotype (g_{16}) as would be expected. Instead, periodic oscillation promotes other fitter genotypes (g_4 and g_{14}) to escape earlier the effects of therapies.

A. Switched Linear Model-Based Strategies

Laboratory tests performed during patient visits can be used to stage HIV disease and assist in the selection of drug regimens [1], these are genotypic resistance testing, CD4 + T counts, and viral load. Note that genotypic resistance testing has helped physicians to optimize the management of patients infected with drug-resistant HIV [24]. Then, the output for the system (2) could be written in the following vector form:

$$y(t) = \begin{bmatrix} y_1(t) \\ y_2(t) \end{bmatrix} = \begin{bmatrix} T(t) \\ V_1(t) \dots V_n(t) \end{bmatrix}. \quad (13)$$

Drug treatments are introduced at fourth-year postinfection for a period of six years. We consider frequent patient visits to the hospital once a month, however, treatment regimens can be switched only every three months [22]. Macrophage counts are considered constant (700 cells/mm^3). CD4 + T cell counts serve to update the switched linear model (3).

Remark 2: The control strategies proposed in this section could be impractical due to common implementation issues in biomedical problems: incomplete state measurement, irregularity of measurements, noise in observations, questionable predictive power of models, and so on. To achieve a more realistic simulation, we use a Luenberger observer based on switched linear systems (3) to estimate the infected cells variables (T_i^* , M_i^*) from the nonlinear model (2). The switched observer is as follows:

$$\dot{\hat{x}}(t) = A_{\sigma(t)}\hat{x}(t) + K_{\sigma(t)}(y_2(t) - \hat{y}_2(t)) \quad (14)$$

where \hat{x} is the state estimated vector, $K_{\sigma(t)}$ are the observer gains, and $\hat{y}_2(t)$ is the estimated output vector for the genotype distribution. $K_{\sigma(t)}$ is an adaptation to positive systems based on the algorithms provided in [25]. CD4 + T cell counts serve for updating the switched linear system (3).

We show the applicability of the proposed strategies based on the following limitations: an observer based on the reduced model (3), constant counts of macrophages, and infrequent samples provided from the nonlinear model (2). Note that since real macrophage counts are varying significantly in the nonlinear model (2), we may assume that the proposed strategies provide certain robustness to incomplete measurements.

The following strategies based on the switched linear model (3) were implemented, as shown in Fig. 3.

- 1) *Costate Control:* Compute the switching trajectory for the interval $[0, t_f]$ with the optimal switched linear system (9). Then, using the trajectory of $\pi(t)$ and the estimations of the observer (14), we compute online the switching signal σ at time t .
- 2) *Guaranteed Cost Control:* Compute the switching trajectory with (10) for the interval $[0, t_f]$. Then, using the

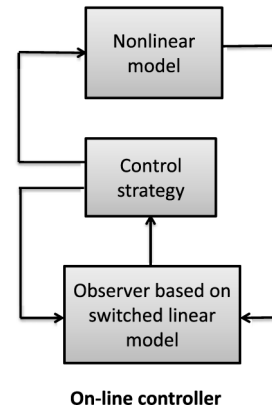


Fig. 3. Control scheme.

TABLE I
SIMULATION RESULTS AFTER SIX YEARS OF HAART

Strategy	Viral load	CD4+T cells
Switch on virologic failure	342	549
SWATCH	222	652
Costate control	179	701
Guaranteed Cost	234	696
MPC	7.5	857

trajectory of $\alpha(t)$ and the estimations of the observer (14), we compute σ at time t .

- 3) *MPC:* Compute the switching trajectory using the system (4) and update with the estimations of the observer (14) as it described in Section III-A, we consider a prediction horizon of one year.

Simulation results in Table I reveal not only that proactive switching strategies may outperform the switched on virologic failure, but also that the proposed switched strategies may provide better results than SWATCH treatment. Note that the costate control gives an optimal trajectory for the linear system, which does not guarantee optimality for the nonlinear case. MPC exhibits much less viral load (≤ 50 copies/mL) and the highest CD4 + T cell counts at the end of the treatment compared with the other strategies.

Proactive switching appears to be important, nevertheless this does not imply that therapies should alternate permanently, see Fig. 4. For this example, MPC suggests that therapy 1 should be maintained for one year, then alternation between treatments will promote undetectable levels in the viral load. This example provides the insight that the alternation of treatments should be design depending on the stage of the infection and genotype distribution. High frequency in the switching also minimizes somewhat the viral load, however, this could promote bad drug adherence and health risks in patients due to drug toxicity.

Observer estimations during MPC strategy are shown in Fig. 4. Even though only one measurement per month and constant counts for macrophages are considered, the observer (14) provided somewhat good estimations of infected cells. Fig. 4 also shows that MPC switching inhibits quickly those cells infected with the wild type (g_1), whereas the other genotypes are kept under very low levels ($\leq 0.1 \text{ cell/mm}^3$). As the therapy

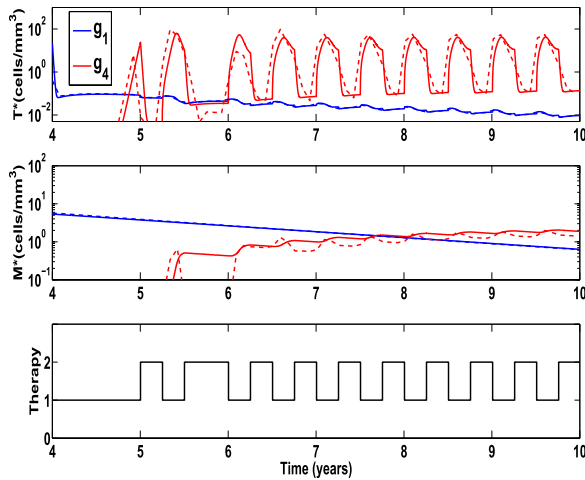


Fig. 4. Treatment scheduling based on MPC using the switched linear model (3) and observer estimations (14). Solid lines: the dynamics of the nonlinear model (2). Dashed lines: the respective estimations.

used was not changed for the first year, the appearance of the genotype resistant to therapy 1 (g_4) was observed promoting infection between $CD4+T$ cells and macrophages. However, MPC adequately controls the genotype (g_4) alternating almost periodically between regimens.

Model-based strategies may provide good result with undetectable levels of virus and high $CD4+T$ cell counts. These results suggest that alternating between treatments, genotypic resistance testing, and frequent visits with the practitioner may be clinically relevant to adequately extend the time to viral escape.

V. CONCLUSION

We applied different control strategies based on a switched linear system to a nonlinear mutation model. These results suggest that proactive switching may be important to extend the time to viral escape. The MPC technique showed the best performance.

Further work is needed to have more detailed models, to test the conclusions under a range of different parameter values and uncertainties, and for more realistic mutation graph models. Moreover, an assessment of the extra costs inherent in the strategy (for example, the additional measurements required) versus the potential benefits is needed.

This brief is a step forward to propose alternative strategies in HIV treatment and helps to explain what further improvements might be possible. The strategy of alternating therapy merits further investigation.

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