Available online at www.sciencedirect.com

ScienceDirect

IFAC PapersOnline CONFERENCE PAPER ARCHIVE

IFAC PapersOnLine 53-2 (2020) 16043–16048

Discrete-time switching MPC with applications to mitigate resistance in viral infections

Alejandro Anderson * **Alejandro H. González** * **Antonio Ferramosca** ** **Esteban A. Hernandez-Vargas** ***

* *Institute of Technological Development for the Chemical Industry (INTEC), CONICET-Universidad Nacional del Litoral (UNL). Güemes 3450, (3000) Santa Fe, Argentina.*

** *CONICET - Universidad Tecnológica Nacional (UTN). Facultad Regional de Reconquista. Reconquista, Santa Fe, Argentina.*

*** *Instituto de Matemáticas, UNAM, Unidad Juriquilla, Mexico.*

Abstract: Many engineering applications can be described as switched linear systems, in which the manipulated control action is the time-dependent switching signal. In such a case, the control strategy must select a linear autonomous system at each time step, among a finite number of them. Even when this selection can be done by solving a Dynamic Programming (DP) problem, the implementation of such a solution is often difficult and state/control constraints cannot be explicitly accounted for. In this paper, a new set-based Model Predictive Control (MPC) strategy is presented to handle switched linear systems in a tractable form. The optimization problem at the core of the MPC formulation consists of an easy-to-solve mixed-integer optimization problem, whose solution is applied in a receding horizon way. The medical application of viral mutation and its respective drug resistance is addressed to acute and chronic infections. The objective is to attenuate the effect of mutations on the total viral load, and the numerical results suggested that the proposed strategy outperforms the schedule for available treatments.

Keywords: Model Predictive Control, Switched System, Viral Treatment, Resistance.

1. INTRODUCTION

Switched systems are dynamical systems composed by a collection of different state dynamics switching among them according to a discrete signal formed by a finite set of modes (Liberzon [2003]), the so-called switching law. The interest in switched systems relies in the fact that they have shown to be useful for modeling complex behaviors of physical systems, such as mechanical systems, automotive systems, power systems, aircrafts, traffic control systems, and biomedical systems. (Chapman et al. [2018], Hernandez-Vargas [2019]).

An interesting application of switched systems is the problem of scheduling therapies to mitigate mutation in viral infections. A convenient way to model the mitigation viral escape problem seems to be by means of a switched linear system (Hernandez-Vargas [2019]). This model helps us to understand how the viruses can mutate and develop resistance to specific drug therapies (Clavel and J Hance [2004]).

In Hernandez-Vargas [2019] different control strategies have been considered for the problem of viral mutations in order to investigate the potential benefits of a switching strategy to the problem of minimizing viral load and delaying the emergence of highly resistant mutant viruses. The main clinical goal is to delay the time until the appearance of strains resistant to the existing regimens (Martinez-Cajas and Wainberg [2008]). However, some care should be taken into account when a switching strategy is applied: an early switching carries the risk of poor adherence to new drug regimens and depletes the remaining therapies; a late switching produces the accumulates different mutations that leads to resistance. (Molla et. al. [1996]).

All the previous suggests that Model Predictive Control (MPC) may tackle - by taking advantage of its flexibility and anticipatory properties - all these clinical recommendations. The MPC is one of the most employed advanced control technique due to its ability to handle, easily and effectively, control and states constraints (Mayne et al. [2000], Rawlings et al. [2017]). Moreover, this technique is capable to provide stability, robustness, and tractable computation for linear and nonlinear systems (Rawlings and Mayne [2009]). Set invariance theory, which is closely related to Lyapunov stability theory (Blanchini and Miani [2015]), has also shown to be a useful tool for analyzing dynamical systems, which makes the set-based MPC an appropriate strategy to undertake the control problem (Anderson et al. [2018]).

The interest in MPC is growing also in the field of switched systems, due to the particular nature of the control problem. The switching law is in fact either considered as a perturbation (Sun and Ge [2011]) or as part of the control inputs. In this last case, conditions for stabilizability have been provided by using a min-switching policy (Liberzon [2003]), and Lyapunov–Metzler inequalities (C. Geromel and Colaneri [2006]). In this context, stability analysis of switched systems is neither intuitive nor trivial: for instance, switching between unstable subsystems may yield a stable system, and vice versa. (Liberzon [2003]). Because of its easy implementation and its anticipatory nature, MPC seems an appropriate strategy for computing switching laws, since it may anticipate the activation of possible switching. Moreover, set-theory has been recently

⋆ This work was supported by CONACYT, UNAM, and by PICT 3613 Herramientas para la optimización del desempeño económico de controladores predictivos en la industria de refinación de petroleo.

Corresponding: alejgon@santafe-conicet.gov.ar, esteban@im.unam.mx

10.1016/j.ifacol.2020.12.412

used in the context of stability of switching systems (Fiacchini and Jungers [2014]), suggesting that set-based MPC approach may be a promising tool for the analysis of stability, robustness and constraint satisfaction of this kind of systems.
This paper presents a novel set-based MPC formulation for discrete-time switched linear systems, which includes a study of invariant regions for the closed-loop, when the control action is the selection of a particular sub-system. The performance is assessed by simulating the aforementioned viral mutation problem, including results that prove the advantages of the new strategy.

1.1 Notation

$\mathbb{Z}$ denotes the set of integer numbers and $\mathbb{Z}_{\geq 0}$ the set of non-negative integers. Furthermore, $\mathbb{Z}_q = \{n \in \mathbb{Z} : 0 \leq n \leq q\}$ and $\mathbb{Z}_{l:q} = \{n \in \mathbb{Z} : l \leq n \leq q\}$. The Euclidean distance between two points $x,\ y$, in $\mathbb{R}^n$, is denoted as $d(x, y)$, while the distance from a point $x \in \mathbb{R}^n$ to a set $\Omega \subset \mathbb{R}^n$ is denoted as $d_\Omega(x) := \inf\{d(x, y) :\ y \in \Omega\}$.

2. OPTIMAL CONTROL FOR DISCRETE-TIME SWITCHED LINEAR SYSTEM

Consider the discrete-time switched linear system described by

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

where $x(k) \in \mathcal{X} \subset \mathbb{R}^n$ is the system state at the k–th sampling time, being $\mathcal{X}$ is closed. $\sigma(k) \in \Sigma := \{1, 2, \cdots, q\}$ is the switching signal that, at any instant k, selects a transition matrix $A_i \in \mathbb{R}^{n\times n}$ with $i \in \Sigma$. Hereafter, the signal $\sigma(\cdot)$ is considered as a control/manipulated variable.

In order to stabilize system (1) at the origin, we consider the cost function

$$J_N(x, \boldsymbol{\sigma}) = \sum_{k=0}^{N-1} c_{\sigma(k)}x(k) + cx(N) \tag{2}$$

where $x = x(0)$ is the current state; $x(j+1) = A_{\sigma(j)}x(j)$, for $j \in \mathbb{Z}_{N-1}$; $\boldsymbol{\sigma} = \{\sigma(0), \cdots, \sigma(N-1)\}$ is a switching discrete path, $c_{\sigma(j)}$ is a positive weight vector corresponding to signal $\sigma(j)$, and vector c is a positive final weight. The cost function (2) must satisfy the Hamilton–Jacobi–Bellman equation (Locatelli [2001]).

Let us define the optimal switching signal, the corresponding trajectory and the optimal cost functional as $\sigma^0(k)$, $x^0(k)$ and $J_N(x, \boldsymbol{\sigma}^0)$, respectively, where $\boldsymbol{\sigma}^0 := \{\sigma^0(0), \cdots, \sigma^0(N-1)\}$. Using the Hamilton–Jacobi–Bellman equation for discrete-time case, we have:

$$\mathcal{V}(x(k), k) = \min_{\sigma(k)\in\Sigma}\{c_{\sigma(k)} + \mathcal{V}(x(k+1), k+1)\},\ \text{for } k \in \mathbb{Z}_{0:N}$$

The general solution for this system can be given by

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

where $p(k)$ denote the costate vector, with $V(x(0), 0) = Nx(0)$. Therefore, the following nonlinear system is obtained:

$$\begin{aligned} &x^0(k+1) = A_{\sigma^0(k)}x^0(k),\ \ x(0) = x_0 \\ &p^0(k) = A'_{\sigma^0(k)}p^0(k+1) + c_{\sigma^0(k)},\ \ p(N) = c \\ &\sigma^0(k) = arg\ \min_s\{p^0(k+1)'A_s x^0(k) + c_s x^0(k).\} \end{aligned} \tag{3}$$

The state equation is solved forwards in time whereas the costate equation must be integrated backward.

However, to obtain the aforementioned solution could be difficult, if not impossible, because of the computational complexity. In the next section, a Receding Horizon (RHC) strategy will be presented that - although sub-optimal - reasonably approximates the optimal solution, at a significant smaller computational cost. Furthermore, the proposed strategy includes a complete cost function (penalizing the states all along a given horizon) and considers full state and input constraints.

3. MPC FOR SWITCHED SYSTEM

In this section, the formal MPC for switched systems (SwMPC) is introduced. The control objective is to steer the system to a given invariant target set, as the natural generalization of a given equilibrium target point. First, the concept of invariant sets for switching systems is introduced.

3.1 Invariant sets for switched systems

Next, the concept of invariance for switched systems is presented.

Definition 1. (Switched Invariant Set). A set $\Omega \subset \mathcal{X}$ is a switched invariant set (SIS) for system (1) if for all $x \in \Omega$, there exists $\sigma \in \Sigma$ such that $A_\sigma x \in \Omega$.

Proposition 2. Let $I \subseteq \Sigma$ be a sub-index set such that A_i is non-singular for all $i \in I$, and let $\Omega \subset \mathcal{X}$ be a compact set such that

$$\Omega \subseteq \bigcup_{i\in I} A_i^{-1}\Omega. \tag{4}$$

Then, Ω is a SIS for system (1).

To see the above result, assume that $\Omega \subseteq \bigcup_{i\in I} A_i^{-1}\Omega$ and let $x \in \Omega$. Then, there exists $\hat{i} \in I$ such that $x \in A_{\hat{i}}^{-1}\Omega$, or, the same, $A_{\hat{i}}x \in \Omega$, which means that Ω is a SIS of system (1).

3.2 SwMPC formulation

Let us consider the following cost function

$$J_N(x; \boldsymbol{\sigma}) := \sum_{j=0}^{N-1} c_{\sigma(j)}d_\Omega(x(j)) + cd_\Omega(x(N)), \tag{5}$$

where $x = x(0)$ is the current state; $x(j+1) = A_{\sigma(j)}x(j)$, $j \in \mathbb{Z}_N$, with N being the control/prediction horizon, are the predicted system states; $\boldsymbol{\sigma} = \{\sigma(0), \cdots, \sigma(N-1)\}$ is a switching path; $c_{\sigma(j)}$ is a positive weight corresponding to signal $\sigma(j)$, and vector c is a positive final weight.

Let us consider also the binary variables $\alpha_i^j \in \{0, 1\}$, for all $i \in \Sigma$ and $j \in \mathbb{Z}_{N-1}$, such that:

- $\alpha_i^j = 1 \Rightarrow \sigma(j) = i$
- $\alpha_i^j = 0 \Rightarrow \sigma(j) \neq i.$

$\boldsymbol{\alpha} = \{\alpha_i^j,\ i \in \Sigma, j \in \mathbb{Z}_{N-1}\}$ is a set of integer optimization variables from which the sequence of signals $\boldsymbol{\sigma}$ can be obtained.

Let $\Omega \in \mathcal{X}$ be a SIS for system (1) and let x be the initial state at time k. Then, the MPC optimization problem is defined as:

$$\min_{\boldsymbol{\alpha}} \; J_N(x;\boldsymbol{\sigma}(\boldsymbol{\alpha})) \tag{6}$$

$$\text{s.t.} \quad x(0) = x, \tag{7}$$

$$x(j+1) = \sum_{i=1}^{q} \alpha_i^j A_{\sigma(j)} x(j), \quad j \in \mathbb{Z}_{N-1}, \tag{8}$$

$$\alpha_i^j \in \{0,1\}, \quad j \in \mathbb{Z}_{N-1}, \quad i \in \Sigma, \tag{9}$$

$$\sum_{i=1}^{q} \alpha_i^j = 1, \quad j \in \mathbb{Z}_{N-1}, \tag{10}$$

$$x(j) \in \mathcal{X}, \quad j \in \mathbb{Z}_{N-1} \tag{11}$$

$$\sigma(j) = \{i : \alpha_i^j = 1\}, \quad j \in \mathbb{Z}_{N-1} \tag{12}$$

$$x(N) \in \Omega. \tag{13}$$

where constraint (7) equals the first predicted state with the current system state x, which is an optimization parameter. Constraint (8) accounts for the switched system evolution, in terms of the optimization variable α_i^j, while $\alpha_i^j \in \{0,1\}$ are integer optimization variables. Constraint (10) implies that only one signal is applied at each step j. Constraint (12) relates signal $\sigma(j)$ with the optimization variable α_i^j, and constraint (13) is a terminal condition forcing the predicted state at time N to belong to the target set Ω (stability constraint).

The optimal value of the cost function is given by

$$J_N^0(x) = J_N(x, \boldsymbol{\sigma}^0(x)), \tag{14}$$

where sequence $\boldsymbol{\sigma}^0$ is the solution to problem (6). The control law, derived from the application of a receding horizon control (RHC) policy, is given by $\kappa_{MPC}(x) = \sigma^0(0)$, where $\sigma^0(0)$ is the first element of the optimal solution sequence $\boldsymbol{\sigma}^0$. This way, the closed-loop system under the MPC law is given by:

$$x(k+1) = A_{\kappa_{MPC}(x(k))} x(k), \tag{15}$$

The domain of attraction of the SwMPC controller derived from problem in (6) (i.e., the set of states that can be feasibly controlled by the SwMPC) is given by $\mathcal{X}_N$, i.e., the controllable set, in N step, to the target set Ω.

Remark 3. Given that Ω is a SIS in $\mathcal{X}_N$, then the domain of attraction of problem in 6, $\mathcal{X}_N$, is nonempty.

Remark 4. Under mild assumptions, it can be shown that the closed-loop (15) is recursively feasible and stable.

3.3 SwMPC algorithm

The control algorithm executed at any k-th time instant is presenting in Algorithm 1.

Algorithm 1

Require: $N \in \mathbb{N}$, $\mathcal{X} \subset \mathbb{R}^n$ and $\Omega \subseteq \mathcal{X}$

1: Read $x(k)$
2: Solve (6) subject to (7)-(13)
3: Inject $\sigma^0(0)$ into the system.
4: $k \leftarrow k+1$
5: Go back to 1

The resulting optimization problem is a Mixed Integer Quadratic Programming (MIQP), which can be solved by specific solvers. For the simulations of the next sections, Algorithm 1 is implemented in YALMIP, a Toolbox for Modeling and Optimization in MATLAB (Löfberg [2004]). The selected optimizer is the Gurobi Optimizer (Version 8.1, Academic License), which in turn relies on a branch-and-bound algorithm to solve MIQP problems (Gurobi Optimization LLC [2019], Land and Doig [1960]).

4. APPLICATION TO VIRAL MUTATION PROBLEM

Here, we focus on the problem of treatment scheduling to minimize the adverse effects of virus mutation in acute and chronic infections. Acute infections are resolved by the immune system in a short period, while in chronic infections the pathogen persists. In both scenarios, a key issue is given by the rise to drug resistance. To focus in virus mutation treatment scenario we use the following model (Hernandez-Vargas et al. [2011]):

$$\dot{V}_i(t) = \rho_{i,\sigma(t)} V_i(t) - \delta V_i(t) + \sum_{i \neq j} \mu m_{i,j} V_j(t), \tag{16}$$

where parameter μ represents the mutation rate, δ is the decay rate of all genotypes, and $m_{i,j} \in \{0,1\}$ is the genetic connections between genotypes (only if $m_{i,j} = 1$ it is possible for genotype j mutates to genotype i). Equation (16) can be rewritten as

$$\dot{V}(t) = (R_{\sigma(t)} - \delta I) V(t) + \mu M V(t) \tag{17}$$

where $M := [m_{i,j}]$ and $R_{\sigma(t)} := diag\{\rho_{i,\sigma(t)}\}$, and every element of $V(t)$ is a particular genotype. For illustrative reasons, we take a model with four genetic variants and two possible drug therapies, as shown in Figure 1.

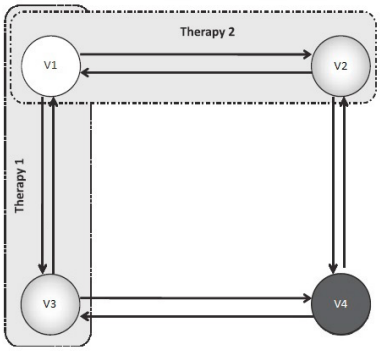

Fig. 1. The virus V_1 is susceptible to both therapies. V_2 is susceptible to therapy 2 while V_3 is susceptible to therapy 1. There is a highly resistant genotype (V_4) which is resistant to therapy 1 and 2.

Figure 1 shows a mutation graph that is symmetric and circular, only connections: $V_1(t) \leftrightarrow V_2(t)$, $V_2(t) \leftrightarrow V_4(t)$, $V_4(t) \leftrightarrow V_3(t)$, $V_3(t) \leftrightarrow V_1(t)$ are possible. This leads to the mutation matrix:

$$M = \begin{bmatrix} 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 \end{bmatrix} \tag{18}$$

4.1 Simulations results

For simulation comparisons, we will introduce the definitions of different therapeutic strategies that are recommended in clinics:

Scenario	V_1	V_2	V_3	V_4
1	$\rho_{1,1} = 0.05$	$\rho_{2,1} = 0.27$	$\rho_{3,1} = 0.05$	$\rho_{4,1} = 0.27$
	$\rho_{1,2} = 0.05$	$\rho_{2,2} = 0.05$	$\rho_{3,2} = 0.27$	$\rho_{4,2} = 0.27$
2	$\rho_{1,1} = 0.05$	$\rho_{2,1} = 0.28$	$\rho_{3,1} = 0.01$	$\rho_{4,1} = 0.27$
	$\rho_{1,2} = 0.05$	$\rho_{2,2} = 0.20$	$\rho_{3,2} = 0.25$	$\rho_{4,2} = 0.27$
3	$\rho_{1,1} = 0.05$	$\rho_{2,1} = 0.26$	$\rho_{3,1} = 0.01$	$\rho_{4,1} = 0.29$
	$\rho_{1,2} = 0.01$	$\rho_{2,2} = 0.15$	$\rho_{3,2} = 0.25$	$\rho_{4,2} = 0.27$
4	$\rho_{1,1} = 0.05$	$\rho_{2,1} = 0.40$	$\rho_{3,1} = 0.05$	$\rho_{4,1} = 0.23$
	$\rho_{1,2} = 0.05$	$\rho_{2,2} = 0.05$	$\rho_{3,2} = 0.40$	$\rho_{4,2} = 0.23$

Table 1. Replication rates (R_σ) different therapy combinations. Scenarios 1-3 represent chronic infections and Scenario 4 is an acute one.

i. The *switching on virologic failure* (VF) strategy, recommended by AIDSInfo [2013], suggest to introduce a new regimen when there is detectable viremia (HIV RNA $>$ 1000 $copies/ml$) and a drug-resistant genotype is identified.
ii. The SWATCH approach, recommended by Martinez-Cajas and Wainberg [2008], is based on the possibility of preempt virologic rebound; this strategy reduces the accumulating drug-resistant genotypes by alternating between the two regimes every three months while viral load is suppressed.

The viral mutation model (17) is described in discrete-time with a regular treatment interval $\tau = 28\ days$; during this time interval the treatment is considered to be fixed. If $k \in \mathbb{N}$ denotes the number of intervals, equation (17) can be described by the following discrete-time switched linear system (1), where $x(k) = x(k\tau)$ is the sampled state and $A_\sigma = e^{(R_\sigma - \delta I + \mu M)\tau}$. The state is constrained to $x(k) \in \mathcal{X} := \mathbb{R}^4_{\geq 0}$, and $\sigma(k) \in \{1, 2\}$ for all $k \in \mathbb{Z}_{\geq 0}$.

Viral mutation rates are about $\mu = 10^{-4}$ and the connection matrix by (18). We consider the initial condition

$$V_1(0) = 1000 \text{ copies/ml}, \quad V_2(0) = \mu V_1(0),$$
$$V_3(0) = \mu V_1(0), \quad V_4(0)) = \mu V_2(0) + \mu V_3(0), \tag{19}$$

and the viral clearance rate is $\delta = 0.24/day$, which corresponds to a half life less than 3 days. As we mentioned before, the decision time is $\tau = 28$ days, for a period of $T = 336$ days.

The rates of the viral replication under treatment σ, R_σ, can illustrate hypothetical infection scenarios, among them the chronic and the acute one. In Hernandez-Vargas [2019] three chronic scenarios for replication rates are presented (1-3 of Table 1). The first one is the ideal case and describes a complete symmetry between genotypes V_2 and V_3: therapy 1 inhibits V_3 with the same intensity as therapy 2 inhibits V_2. In general, a complete model should include asymmetry in the genetic tree and a complex structure instead of a simple cycle. Scenario two shows an asymmetry replication rate between genotype V_2 and V_3, and both therapies induce the same replication in genotypes V_1 and V_4. The third scenario is the more realistic one, since each genotype experience different dynamics to a new treatment. The three of them, however, represent chronic infections. In this work we present a fourth scenario corresponding to an acute infection (e.g. influenza), characterized by a rapid increase of the viral load, which however may be cleared in short time (see Table 1).

The *total viral load* at time instant k, $V_{total}(k)$, is defined by $V_{total}(k) = \sum_{i=1}^{4} V_i(k)$, where $V_i(k)$ is the viral load of the variant i at time instant k.

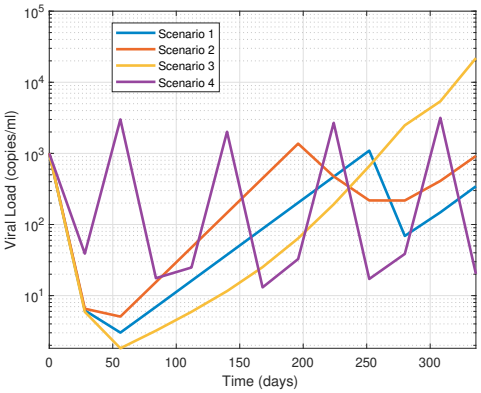

Fig. 2. Switching on virologic failure for Scenario 1 to 4.

The therapeutic strategies that we are going to test are the switching on virologic failure (VF) and the SWATCH approach, both presented above. On the other hand, for all scenarios the optimal solution will be computed by the "brute force" approach, which analyzes the best numerical solution of all possible combinations for therapies 1 and 2 with decision time $\tau = 28\ days$ for a period of $T = 336\ days$. That is, $2^{T/\tau}$ possible treatment combinations are evaluated and the sequence of treatments that gives the least amount of total viral load over the whole period of time is chosen (i.e., the one that minimizes the cost (2)). Notice that this approach has more computational complexity as the period of time is incremented or the treatment interval is reduced, making it a not implementable optimization. Figure 2 shows the *switching on virologic failure* treatment for the 4 scenarios. The total viral load initially drops rapidly for chronic infections. However, the appearance of resistant genotype will drive a virologic failure after 200 days making a new therapy necessary. Scenarios 1 and 2 exhibit a second drop in viral population, not as pronounced as it was for therapy 1. For scenario 3, the viral escape is almost not affected by the new therapy, which is because the highly resistant genotype, V_4, is directing the dynamics of the system (see Figure 5). The acute infection has a very different behavior; unlike the other cases, the system can be stabilized, i.e. the total viral load can be driven to undetectable levels ($V_{total}(T) \leq 50$ copies/ml). However, since the therapy changes regimen by an exceeding of an upper bound, the total viral load does not reach its minimum values and shows an oscillating behavior. Figure 3 shows in more detail, where genotype 2 and 3 has an asymmetric behavior resulting in the oscillating of the total viral load.

The SWATCH strategy shows - as previously highlighted by Hernandez-Vargas et al. [2011] - a better performance than the switching on virologic failure. Figure 4 shows a lower concentration in the total viral load over the year for chronic infections, while the viral population is cleared in acute infection.

The optimal solution for chronic infections is given by "brute force" approach, in order to compare performance of the proposal with the best possible result. In chronic infection scenario there is always a viral escape, because the high resistance genotype rises with resistance for the two regimens. For scenario 3, the *total viral load* grows up to $V_{total}(T) = 83,14$ copies/ml by the final time $T = 336$ days, but if the final time is extending to $T = 420$ days the total viral load increases to $V_{total}(T) =$

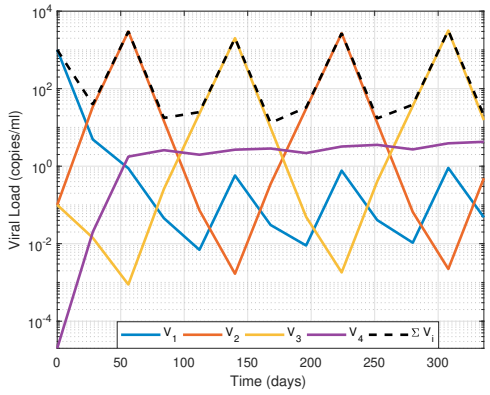

Fig. 3. Switching on virologic failure for acute infection.

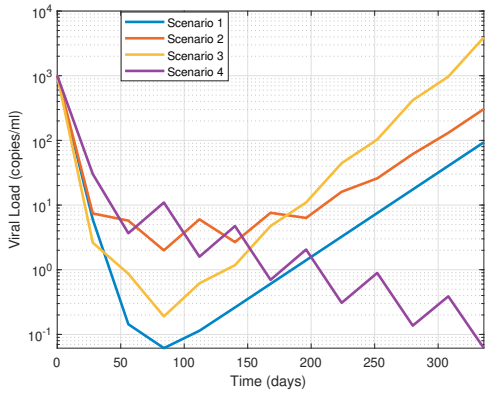

Fig. 4. SWATCH treatment for Scenario 1 to 4.

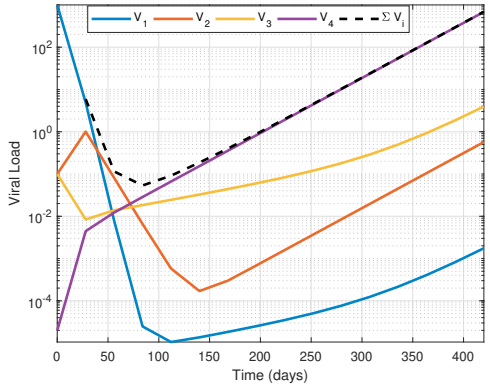

Fig. 5. Optimal solution for chronic infection of scenario 3 with period of $T = 420\ days$.

688, 29 copies/ml, which means that the viral escape does occur (see Figure 5).

4.2 MPC-based scheduling method

The same scenarios studied above will be tackled by the MPC proposed in this work. A prediction horizon of $N = 5$ is considered - equivalent to 5τ days - with the decision time $\tau = 28$ days for a period of $T = 336$ days. The objective of the controller is to drive the total viral load to undetectable levels ($V_{total}(T) < 50$ copies/ml). Since the objective can not be maintained over time for chronic infections due to

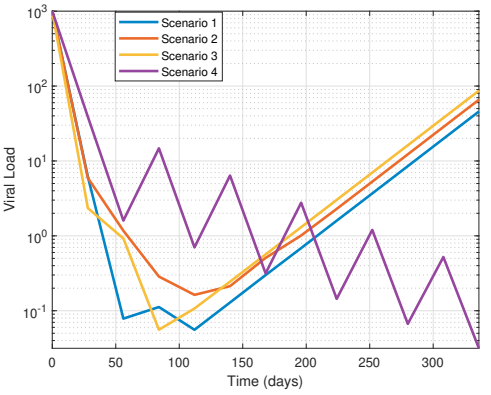

Fig. 6. SwMPC strategy for all scenarios.

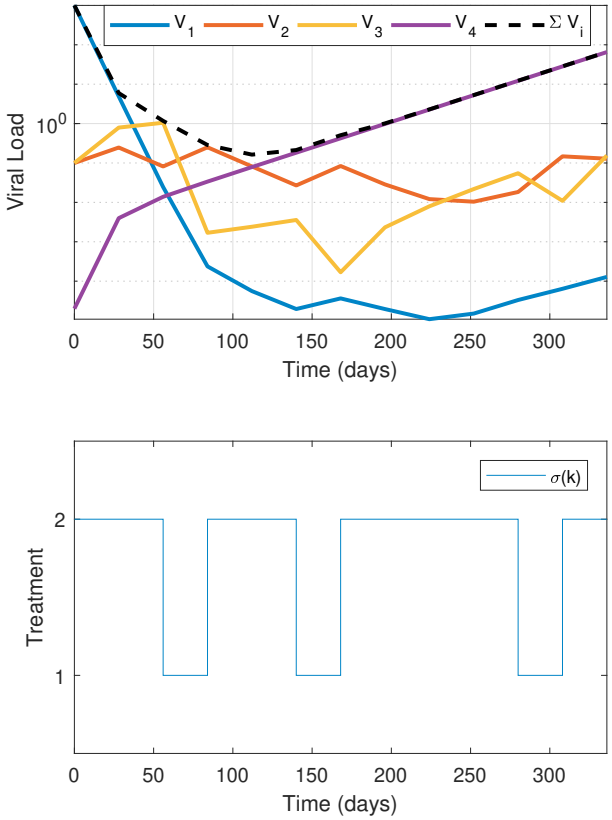

Fig. 7. Viral dynamics for Scenario 2 and treatment by the SwMPC.

the promoting persistence of high resistance genotypes it is expected that the proposed strategy delays the viral escape time. Figure 6 shows the four scenarios under the proposed SwMPC. As it can be seen, the controller suppresses the viral load, for all cases. In chronic infection scenarios the total viral load is maintained below to the virologic failure levels, while in acute infections it is completely cleared. Figure 7, on the other hand, shows the behavior of all genotypes only for Scenario 2, together with the switching sequence provided by the SwMPC. The sequence is not intuitive at all, since therapy 1 is used only three times throughout the year of treatment, in the third, sixth and eleventh month.

Scenario	SWATCH	VF	OPTIMAL	SwMPC
1	1175.6	3483.9	1086.0	1087.0
2	1587.1	5277.9	1108.4	1123.3
3	6478.6	3169.4	1104.2	1156.2
4	1175.6	12075.0	1067.4	1067.6

Table 2. Performance index $\mathcal{I}_T$ for all strategies.

Remark 5. It is important to highlight that in chronic infection scenarios, where the system cannot be stabilized, the viral escape cannot be avoided. However, the simulation results suggest that the proposed MPC delays the escape time, which is considerably beneficial in this context.

4.3 Performance comparison

In chronic infections the virus persists, promoting an unavoidable viral escape. This fact makes the switched system that models the infection dynamic essentially non-stabilizable and, so, it will not be possible to drive the system to the undetectable virus zone and keep it there indefinitely. So, the following index is proposed to compare the presented strategies:

$$\mathcal{I}_T = \sum_{k=0}^{T} V_{total}(k), \tag{20}$$

where $V_{total}(k)$ is the *total viral load* at time instant k

The best performance is obtained by the optimal solution computed by "brute force" approach, according to Table 2. The indexes in Table 2 reveal that the proactive switching strategies may outperform the 'switched on virologic failure' strategy, as it was previously stated in Hernandez-Vargas et al. [2011]. Nevertheless, the proposed SwMPC provides better results than SWATCH treatment, and exhibits almost the same performance than the optimal solution, in all cases, which is a result to be highlighted considering that the MPC is an implementable strategy, which is robust to model-plant mismatches, explicitly considers constraints and has a low computational burden.

5. CONCLUSIONS

The proposed controller is applied to a simplified viral mutation model, proving that it can attenuate the effect of the viral mutation in several challenging scenarios, containing chronic and acute infection cases. The controller is compared with some basic viral mutation treatments and with the optimal solution of every posed scenario. In acute infections, the proposed controller cleared the total viral population in a short period, close to the optimal solution. In chronic infections, the results suggest that the proposed MPC significantly extends the time to viral escape.

REFERENCES

AIDSInfo. Panel of antiretroviral guidelines for adults and adolescents. *Department of Health and Human Services, Washington*, Guidelines for the use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents, 2013.

A. Anderson, A. H. González, A. Ferramosca, A. D'Jorge, and E. Kofman. Robust MPC suitable for closed-loop re-identification, based on probabilistic invariant sets. *Systems & Control Letters*, 118:84 –93, 2018.

F. Blanchini and S. Miani. *Set-Theoretic Methods in Control*. Systems & Control: Foundations & Applications. Springer International Publishing, 2015. ISBN 9783319179339.

J C. Geromel and P Colaneri. Stability and stabilization of discrete time switched systems. *International Journal of Control - INT J CONTR*, 79:719–728, 07 2006.

M. Chapman, E. Mazumdar, E. Langer, R. Sears, and C. Tomlin. On the analysis of cyclic drug schedules for cancer treatment using switched dynamical systems. pages 3503–3509, 12 2018. doi: 10.1109/CDC.2018.8619490.

F. Clavel and A. J Hance. HIV drug resistance. *The New England journal of medicine*, 350:1023–35, 04 2004.

M. Fiacchini and M. Jungers. Necessary and sufficient condition for stabilizability of discrete-time linear switched systems: A set-theory approach. *Automatica*, 50:75–83, 01 2014.

Gurobi Optimization LLC. Gurobi optimizer reference manual, 2019. URL `http://www.gurobi.com`.

E. A. Hernandez-Vargas. *Modeling and Control of Infectious Diseases in the Host: With MATLAB and R, Academic Press - ELSEVIER*. 2019.

E. A. Hernandez-Vargas, P. Colaneri, R. Middleton, and F. Blanchini. Discrete-time control for switched positive systems with application to mitigating viral escape. *International journal of robust and nonlinear control*, 21(10):1093–1111, 2011.

A. H. Land and A. G. Doig. An automatic method of solving discrete programming problems. *Econometrica*, 28(3):497–520, 1960.

D Liberzon. *Switching in System and Control*. 01 2003. ISBN 0-8176-4297-8.

Arturo Locatelli. *Optimal Control: An Introduction*, volume 55. 01 2001.

J. Löfberg. YALMIP : A Toolbox for Modeling and Optimization in MATLAB. In *In Proceedings of the CACSD Conference*, Taipei, Taiwan, 2004.

J. Martinez-Cajas and M. Wainberg. Antiretroviral therapy - optimal sequencing of therapy to avoid resistance. *Drugs*, 68:43–72, 02 2008.

D. Q. Mayne, J. B. Rawlings, C. V. Rao, and P. O. M. Scokaert. Constrained model predictive control: Stability and optimality. *Automatica*, 36:789–814, 2000.

A. Molla et. al. Ordered accumulation of mutations in hiv protease confers resistance to ritonavir. *Nature Medicine*, 2, 08 1996.

J. B. Rawlings and D. Q. Mayne. *Model Predictive Control: Theory and Design*. Nob-Hill Publishing, 1st edition, 2009.

J. B. Rawlings, D. Q. Mayne, and M. Diehl. *Model predictive control: theory, computation, and design*, volume 2. Nob Hill Publishing Madison, WI, 2017.

Z. Sun and S.S. Ge. *Stability Theory of Switched Dynamical Systems*, pages 1–253. 01 2011.