Time-constrained MPC approach for switched nonlinear systems with applications to biomedical problems

J. E. Sereno, A. D'Jorge, A. Ferramosca, E.A. Hernandez-Vargas, A. H. González

***Abstract*— Switched systems are important for modeling biomedical control problems, where the control action can be considered to be a switching signal to select the active mode (e.g., a drug therapy or intervention). Practical implementations impose constraints not only on the variable magnitudes, but also on each mode's active and inactive times (AT and IT). To address this, a model predictive control strategy is proposed using an enlarged model with integer state variables to track past AT/IT for each mode. Two biomedical applications were selected to demonstrate the controller's effectiveness through simulations. The results highlight that our approach is suitable for biomedical applications with intricate temporal requirements.**

***Index Terms*— Biomedical application, model predictive control, switched nonlinear systems, temporal constraints.**

I. Introduction

IN A SWITCHED system the dynamics commute between different modes (or subsystems) according to a switching signal, making it a type of hybrid model [1]. Mathematically, switching is considered a discrete behavior which selects one subsystem among a finite collection such that only one of them is active at a time [2]. In this work we focus on switched nonlinear autonomous systems. This means the switching signal is the unique decision variable that externally manipulates the system to achieve the control objective [3], [4]. Switched systems are particularly important for biomedical applications, *e.g.*, cyclic drug schedules for cancer treatment [5] and the modeling and control of different within-host infection diseases [6].

The most widely used temporal constraint in switched systems is one that allows only one mode to be active at a time. However, to improve the accuracy of the problem description and expand its applicability, explicit consideration of limits on active and inactive times is needed. Virtually all biomedical applications have some limitations in either the min-max AT or the min-max IT of each mode. Indeed, previous work shows the importance of handling temporal constraints in biomedical problems [7], [8]. Furthermore, other work addressed the problem of optimal control of switched systems considering dwell-time constraints [9], [10]. Other studies on the stability of switched systems can be found in [11]–[13].

From a control perspective, the explicit fulfillment of AT/IT limits is far from trivial. Indeed, although this work does not focus on this particular problem, such limitations modify the basic concept of equilibria. In a switched system to be controlled, the equilibria (or invariant sets) of a particular sub-model may no longer be equilibria of the whole system because of the existence of maximal AT constraints. Similarly, maximal IT constraints also indirectly alter, the system equilibria/invariance, since they limit the AT of the current active mode. Previous work in [14] and [8] focused on the characterization and computation of so called "Permanence Regions" for switched systems. These regions are extensions of the "Control Invariant Sets" in the sense that they only contain a subset such that, if the system starts there, it can remain in the region by using a feasible switching signal.

In [7], an MPC for drug scheduling in viral infections was based on a switched system with AT constraints. The authors define lower and upper limits for each drug therapy (i.e., for each mode or subsystem) according to their effectiveness and toxicity, while the control objective minimizes drug resistance. Other applications of switched systems considering – even implicitly – the AT limits can be central for the scheduling of evolutionary therapies [15], tailoring public health policies [16], and the eradication of drug-resistant infections [17].

The objective of this work is to propose a general representation of AT/IT dynamics by introducing an extended model that is then explicitly used in an MPC formulation. We propose a binary representation of the switching signal to incorporate two new state variables (denoted active and inactive memories) that account for the AT/IT history. Then, in the MPC optimization problem (which is a mixed-integer optimization problem), Min-Max bounds are imposed on the new states. Although no feasibility guarantees are given in this preliminary study, the resulting controller was tested through the simulation of two examples: a within-host infection and a between-host infection problem. In both simulation scenarios, the controller seems to properly achieve the objective while

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fulfilling AT/IT limits.

II. Background and Problem Formulation

Consider a discrete-time, switched nonlinear system given by

$$x(k+1) \quad = \quad f_{\sigma(k)}\left(x(k)\right), \tag{1}$$

where $x(k) \in \mathcal{X} \subset \mathbb{R}^{n_x}$ represents the system state at time $k \in \mathbb{I}_{\geq 0}$, with $\mathcal{X}$ being a closed set. The switching signal $\sigma : [0, \infty) \to \mathcal{P}$ determines which subsystem governs the system dynamics at each time step. Here, $\mathcal{P} := \{1, 2, \ldots, n_s\}$ denotes the set of available subsystems (or modes), with n_s being the total number of switching modes (SM). The function $f : \mathcal{X} \times \mathcal{P} \to \mathcal{X}$ is a known switched nonlinear mapping that determines the next state $x(k+1)$ based on the current state $x(k)$ and the active subsystem $\sigma(k)$. Each mode $\ell \in \mathcal{P}$ corresponds to a specific realization of the switching signal, $\sigma(k) = \ell$, and the system dynamics are governed by:

$$x(k+1) \quad = \quad F_\ell\left(x(k)\right), \tag{2}$$

where $F_\ell : \mathcal{X} \to \mathcal{X}$ is the autonomous dynamics of mode ℓ. The switching signal $\sigma(k)$ is the sole control action, allowing external manipulation to achieve a desired control objective.

A. Active and Inactive Time Constraints

In practical applications, particularly in biomedical systems, it is essential to impose constraints not only on the state variables but also on the active time and inactive time of each mode. These constraints are defined as follows:

- **Active Time (AT)**: The period of time each mode ℓ remains active. It is bounded by a minimum activation period $L^\ell_{\mathcal{A}}$ and a maximum activation period $U^\ell_{\mathcal{A}}$.
- **Inactive Time (IT)**: the period of time each mode ℓ remains inactive. It is bounded by a minimum inactive period $L^\ell_{\mathcal{I}}$ and a maximum inactive period $U^\ell_{\mathcal{I}}$.

It is worth mentioning that, usually, in the switching system literature, the concept of waiting time refers only to AT; thus, the definitions above are necessary to differentiate this approach from prior work.

Remark 1: *By setting $L^\ell_{\mathcal{A}} = 0$, and $U^\ell_{\mathcal{A}} = \infty$, or $L^\ell_{\mathcal{I}} = 0$, and $U^\ell_{\mathcal{I}} = \infty$, the constraints on AT or IT can be relaxed, allowing for greater flexibility in the control design as long as for each $\ell \in \mathcal{P}$ the following conditions are satisfied:*

$$L^\ell_{\mathcal{A}} \leq U^\ell_{\mathcal{A}}, \;\; L^\ell_{\mathcal{I}} \leq U^\ell_{\mathcal{I}}. \tag{3}$$

III. AT/IT Dynamics Representation

There are several ways to express the switching signal. To set AT/IT constraints on an MPC formulation, a binary representation is suggested to define discrete-time variables that account for the history of each mode.

Definition 1 (Binary Representation): *To incorporate AT/IT constraints into the MPC framework, the switching signal $\sigma(k)$ is represented in a Binary Representation (BR) vector form $\mathbf{v}(k) := [v^1(k), \; v^2(k), \ldots, \; v^{n_s}(k)]^T$, where each element $v^\ell(k) \in \{0, 1\}$ indicates whether mode ℓ is active ($v^\ell(k) = 1$) or inactive ($v^\ell(k) = 0$) at time k, for each $\ell \in \mathcal{P}$.*

This way, $\mathbf{v}(k)$ is a vector of dimension n_s consisting of a set of binary decision variables, satisfying the following condition:

$$\sum_{\ell=1}^{n_s} v^\ell(k) = 1. \tag{4}$$

Condition (4) is necessary to guarantee that only one mode is active at each time instant. To extend this concept to a more generalized form, we introduce the notion of an active mutually exclusive set as follows:

Definition 2 (Active Mutually Exclusive Set): *Consider a vector $\mathbf{u}$ containing a set of variables u^ℓ, with $\ell \in \mathcal{P}$, given by $\mathbf{u} = [u^1, \; u^2, \ldots, \; u^{n_s}]$. Then vector $\mathbf{u}$ is called an Active Mutually Exclusive Set (A-MES), if and only if exactly one variable u^ℓ is active (i.e., takes a nonzero value) while all others remain inactive (i.e., equal to zero).*

To track AT history of each mode, the concept of active memory is defined below.

Definition 3 (Active Memory): *Consider the switched system (1) with a BR of $\sigma(k)$ that satisfies condition (4). The active memory of the system is then defined as the discrete-time variable given by*

$$\mathbf{m}_{\mathcal{A}}(k+1) = (\mathbf{m}_{\mathcal{A}}(k) + \mathbf{v}(k)) \odot \mathbf{v}(k), \tag{5}$$

where $\mathbf{m}_{\mathcal{A}}(k) \in \mathbb{I}^{n_s}$ is a vector that contain the information of the activation period for the currently active SM-ℓ at each time interval. The operator $\odot$ stand for the Hadamard product [18]. That is, for a pair of vectors $\mathbf{A} = [a_1, a_2, \ldots, a_{n_s}]$ and $\mathbf{V} = [v_1, v_2, \ldots, v_{n_s}]$, the vector $\mathbf{W} = \mathbf{A} \odot \mathbf{V}$ is defined as $\mathbf{W} = [w_1, w_2, \ldots, w_{n_s}]$, where

$$w_i = a_i v_i, \quad \text{for } i = 1, 2, \ldots, n_s,$$

represent the element-wise product between vectors $\mathbf{A}$ and $\mathbf{V}$.

Lemma 1: *$\mathbf{m}_{\mathcal{A}}(k)$ is an A-MES, for all $k \in \mathbb{I}_{\geq 0}$.*

Proof: Let $\mathbf{V} = [v_1, v_2, \ldots, v_{n_s}]$ be a BR vector of n_s elements satisfying condition (4), i.e., there exists a unique index j for which $v_j = 1$, while all other elements satisfy $v_i = 0$ for $i \neq j$. Let $\mathbf{A} = [a_1, a_2, \ldots, a_{n_s}]$ be another vector of n_s elements. Then, the Hadamard product $\mathbf{W} = \mathbf{A} \odot \mathbf{V}$ results in a vector where all entries are zero except for $w_j = a_j$.

Now, considering the active memory equation (5), it follows that $\mathbf{m}_{\mathcal{A}}(k+1)$ has the same structure as $\mathbf{W}$ with $\mathbf{A} = \mathbf{m}_{\mathcal{A}}(k) + \mathbf{v}(k) = [a_1, a_2, \ldots, a_{n_s}]$, where each a_i represents the corresponding component of the sum. Since $\mathbf{W}$ was shown to have only one nonzero entry, $\mathbf{m}_{\mathcal{A}}(k+1)$ inherits this property. Therefore, by definition, $\mathbf{m}_{\mathcal{A}}(k+1)$ is an A-MES for all $k \in \mathbb{I}^{n_s}$. ■

Now, let us define the complementary vector form of the BR as $\bar{\mathbf{v}}(k) = 1 - \mathbf{v}(k)$. Thus, $\bar{\mathbf{v}}(k) \in \mathbb{B}^{n_s}$ represents the modes

that remain inactive at each time step. Since $\mathbf{v}(k)$ satisfy (4), then vector $\bar{\mathbf{v}}$ satisfies the following condition:

$$\sum_{\ell=1}^{n_s} \bar{v}^{\ell}(k) = n_s - 1. \tag{6}$$

By construction, $\bar{\mathbf{v}}(k)$ has exactly one zero entry, while all others are non-zero. To generalize this idea, we introduce the notion of an inactive mutually exclusive set as follows:

Definition 4 (Inactive Mutually Exclusive Set): *Consider a vector* $\mathbf{u}$ *containing a set of variables* u^{ℓ}*, with* $\ell \in \mathcal{P}$*, given by* $\mathbf{u} = [u^1,\ u^2, \ldots,\ u^{n_s}]$*. The vector* $\mathbf{u}$ *is called an Inactive Mutually Exclusive Set (I-MES) if and only if exactly one variable* u^{ℓ} *is inactive (i.e., equal to zero) while all others remain active (i.e., take a nonzero value).*

Similarly, to track the IT history of each mode, the concept of inactive memory is defined below.

Definition 5 (Inactive Memory): *Consider the switched system* (1)*, with a BR of* $\sigma(k)$ *that satisfies condition* (4)*. The inactive memory of the system is defined as the discrete-time variable given by*

$$\mathbf{m}_{\mathcal{I}}(k+1) = (\mathbf{m}_{\mathcal{I}}(k) + \bar{\mathbf{v}}(k)) \odot \bar{\mathbf{v}}(k), \tag{7}$$

where $\mathbf{m}_{\mathcal{I}}(k) \in \mathbb{I}^{n_s}$ *is a vector that contains the information of the inactive periods for all the SM-*ℓ *that remain inactive at each time interval.*

Lemma 2: $\mathbf{m}_{\mathcal{I}}(k)$ *is I-MES, for all* $k \in \mathbb{I}_{\geq 0}$.

Proof: Similar to the steps in the proof of Lemma 1, it can be seen that quation (7) has the same structure as $\mathbf{W}$ with $\mathbf{A} = (\mathbf{m}_{\mathcal{I}}(k) + \bar{\mathbf{v}}(k))$. Let $\bar{\mathbf{V}}$ be a complementary BR vector of n_s elements satisfying condition (6). Then, it can be shown that for this case $\mathbf{W}$ has only one entry equal to zero; hence, $\mathbf{m}_{\mathcal{I}}(k+1)$ inherits this property. Therefore, by definition, $\mathbf{m}_{\mathcal{I}}(k+1)$ is an I-MES for all $k \in \mathbb{I}^{n_s}$. ■

With Definitions 3 and 5, and Lemmas 1 and 2 previously introduced, we are now able to consider AT/IT constraints. Formally, given an switched system (1) with a BR of $\sigma(k)$ fulfilling condition (4), its active and inactive memory variables provide an AT/IT representation of the system, as defined in Definitions 3 and 5, respectively. Moreover, these variables adhere to the constraints given in equation (3) for each SM-ℓ, allowing the active and inactive time constraints representation of the switched system (1) as follows:

$$\mathbf{L}_{\mathcal{A}} \ \leq\ \mathbf{m}_{\mathcal{A}}(k) \ \leq\ \mathbf{U}_{\mathcal{A}},\ \mathbf{L}_{\mathcal{I}} \ \leq\ \mathbf{m}_{\mathcal{I}}(k) \ \leq\ \mathbf{U}_{\mathcal{I}}, \tag{8}$$

for $k \in \mathbb{I}_{\geq 0}$, where the vectors $\mathbf{L}_{\mathcal{A}} = \left[L^1_{\mathcal{A}}, L^2_{\mathcal{A}}, \ldots, L^{n_s}_{\mathcal{A}}\right]^T$ and $\mathbf{U}_{\mathcal{A}} = \left[U^1_{\mathcal{A}}, U^2_{\mathcal{A}}, \ldots, U^{n_s}_{\mathcal{A}}\right]^T$ define the AT bounds, while the vectors $\mathbf{L}_{\mathcal{I}} = \left[L^1_{\mathcal{I}}, L^2_{\mathcal{I}}, \ldots, L^{n_s}_{\mathcal{I}}\right]^T$ and $\mathbf{U}_{\mathcal{I}} = \left[U^1_{\mathcal{I}}, U^2_{\mathcal{I}}, \ldots, U^{n_s}_{\mathcal{I}}\right]^T$ define the IT bounds.

IV. Switching NMPC formulation

In this section, an NMPC formulation that considers (8) is presented. The objective is to minimize the following cost function at each time step k:

$$J_N(x; \mathbf{v}) = \sum_{j=0}^{N-1} V_t(x(j), \mathbf{v}(j)) + V_f(x(N)), \tag{9}$$

where N denotes the control horizon. The stage cost V_t and the final cost V_f are positive weighted functions. The system state at time k is represented by $x(k)$, while the predicted control sequence, which is subject to optimization, is given by $\mathbf{v}(j) = [v^1(j), v^2(j), \ldots, v^{n_s}(j)]$ with $j \in \mathbb{I}_{[0,N-1]}$ and $v^{\ell}(j) \in \mathbb{B}$, $\ell \in \mathcal{P}$. Then, for any current state x and vectors $\mathbf{v_0}$, $\mathbf{m}_{\mathcal{A}_0}$, and $\mathbf{m}_{\mathcal{I}_0}$ at time k, the optimization problem to be solved is formulated as follows: $\mathcal{P}_{MPC_{\mathcal{AI}}}(x, \mathbf{v_0}, \mathbf{m}_{\mathcal{A}_0}, \mathbf{m}_{\mathcal{I}_0}; \mathbf{v})$:

$$\begin{aligned}
\min_{\mathbf{v}} \quad & J_N(x; \mathbf{v}) \\
s.t. \quad & \\
& x(0) = x,\ \mathbf{v}(0) = \mathbf{v_0}, \bar{\mathbf{v}}(0) = 1 - \mathbf{v_0} \\
& \mathbf{m}_{\mathcal{A}}(0) = \mathbf{m}_{\mathcal{A}_0},\ \mathbf{m}_{\mathcal{I}}(0) = \mathbf{m}_{\mathcal{I}_0}, \\
& x(j+1) = F_{v^{\ell}(j)}(x(j)), \\
& x(j) \in \mathcal{X},\ v^{\ell}(j) \in \mathbb{B}^{n_s}, \\
& \mathbf{m}_{\mathcal{A}}(j+1) = (\mathbf{m}_{\mathcal{A}}(j) + \mathbf{v}(j)) \odot \mathbf{v}(j), \\
& \mathbf{m}_{\mathcal{I}}(j+1) = (\mathbf{m}_{\mathcal{I}}(j) + \bar{\mathbf{v}}(j)) \odot \bar{\mathbf{v}}(j), \\
& \mathbf{L}_{\mathcal{A}} \leq \mathbf{m}_{\mathcal{A}}(j) \leq \mathbf{U}_{\mathcal{A}}, \\
& \mathbf{L}_{\mathcal{I}} \leq \mathbf{m}_{\mathcal{I}}(j) \leq \mathbf{U}_{\mathcal{I}},
\end{aligned} \tag{10}$$

with $j \in \mathbb{I}_{[0,N-1]}$, and $\ell \in \mathcal{P}$. Once the optimal solution is computed, the first optimal control action $\mathbf{v}_0^*$ is applied to the system, the discrete time is shifted forward (i.e., $k \to k+1$), and the iteration continues with a new solution of the optimization problem, resulting in a receding horizon control policy.

Remark 2: *The optimization problem in* (10) *is posed as a nonconvex mixed-integer nonlinear optimization problem. This is more difficult to solve than a QP derived from traditional MPC. Despite this, our approach enables the integration of AT/IT dynamics variables into the optimal control problem. Here, an intuitive and standardized framework is provided for designing and implementing MPC in switching systems while accounting for AT/IT limits, independently of the programming language.*

Remark 3: *Incorporating time constraints in switched systems involves addressing potential feasibility issues within the MPC formulation. Although a detailed analysis of recursive feasibility is beyond the scope of this paper, it is worth mentioning that AT/IT bounds should fulfill two key conditions to avoid infeasibility. The first condition is:*

$$U^{\ell}_{\mathcal{A}} \geq L^{i}_{\mathcal{I}}, \quad \forall\ \ell, i \in \mathcal{P},\ i \neq \ell,$$

and it ensures that once the max AT is reached and the system can no longer remain in a given SM, there is another SM available for switching. The second condition is:

$$L^{\ell}_{\mathcal{A}} \leq U^{i}_{\mathcal{I}}, \quad \forall\ \ell, i \in \mathcal{P},\ i \neq \ell,$$

and it guarantees that the min AT is satisfied before any max IT constraint forces the system to return to a specific SM. Enforcing these conditions for all SM combinations is related to the controllability of the time-constrained switched system. Furthermore, the aforementioned conditions ensure the recursive feasibility of the MPC for the case $\mathcal{X} = R^n$*, or*

when the system is far from the boundary of $\mathcal{X}$. To establish necessary and sufficient conditions for recursive feasibility when $\mathcal{X}$ is bounded, control invariant sets for switched systems with AT/IT (imposing conditions on the behavior of F_ℓ, $\ell \in \mathcal{P}$, on the boundary of $\mathcal{X}$) should be defined and characterized.

V. Application to Biomedical Systems

The AT/IT dynamic representation is useful to propose MPC formulations for a broad spectrum of biomedical problems. The applicability is shown through two applications: in-host and between-host scenarios.

A. Scheduling Evolutionary Therapies

Consider the equations of a dynamical pathogen mutation model with n_x different pathogen strains, $x \in \mathbb{R}^{n_x}$, and with n_s possible drug therapies that can be administered, represented by $\sigma(t) \in \mathcal{P}$ [17].

$$\begin{aligned}\dot{x}_i(t) =& \rho_i^{\sigma(t)} x_i(t) \left(1 - \frac{\sum_{i=1}^{n_x} x_i(t)}{K}\right) - \delta x_i(t) \\ &+ \mu \sum_{j=1}^{n_x} m_{i,j}^{\sigma(t)} x_j(t),\end{aligned} \tag{11}$$

where each strain population is represented with x_i. The growth rate of the strain i under drug therapy $\sigma(t)$ is represented by $\rho_i^{\sigma(t)}$. The clearance and mutation rate are defined by the fixed parameters δ and μ, respectively, for all strains. The genetic connections between strains are represented by $m_{i,j} \in \mathbb{B}$, that is, $m_{i,j} = 1$ represents the mutation that occurs from strain j to i, $m_{i,j} = 0$ otherwise. We consider this mutation matrix change under different drug therapies, $m_{i,j}^{\sigma(t)}$.

Typically there are limiting factors for pathogen replication rate, which is considered in excess ($K \approx \infty$) [7], [17]. Therefore, the first nonlinear term in (11) can be simplified to obtain a linear model since $\left(1 - \frac{\sum_{i=1}^{n_x} x_i}{K} \approx 1\right)$. Here, we keep the nonlinear term to represent competition effects. The pathogen mutation model (11) could be directly represented in its switched system form described by (1), such that the switching signal σ changes a subset of parameters (ρ_i^σ and $m_{i,j}^\sigma$), to obtain a finite set of modes. The switch signal for drug therapy $\sigma(t)$ follows a BR, which means that each drug therapy can be represented by a binary variable $v^\ell(k)$, with $\ell \in \mathcal{P}$. By satisfying condition (4) for the BR vector, discrete-time memory variables can be established to characterize the active and inactive time dynamics of the pathogen mutation model (11). Thus, the NMPC formulation in (10) can be applied.

For numerical simulations, we consider the scenario of ten pathogen strains, $n_x = 10$, and five possible drug therapies, $n_s = 5$. All model parameters were taken from [17] in which the pathogen clearance rate is $\delta = 0.25$ day^{-1}, mutation rate is about 10^{-4}, and carrying capacity is $K = 10^6$. The initial state is set as $x_1(0) = 10^3$, and $x_6(0) = 10$, all other pathogens initialize to zero, as in [17]. Replication rates and mutation matrices under each therapy are set as in [17].

Then the NMPC with AT/IT constraints, as given in (10), is designed to minimize

$$J_N(x; \mathbf{v}) = \sum_{j=0}^{N-1} \|x(j)\|_Q^2 + \|x(N)\|_P^2, \tag{12}$$

where $N = 3$, $Q = 10^{-6}$, $P = 10^{-2}$. We simulate a period of 400 days, for sake of comparison with respect to the results presented in [17], with a sampling time $T_s = 10$ days; thus, the predicted horizon N accounts for 30 days of prediction. Here, the switching modes are represented by $\ell \in \mathcal{P}$, with $\mathcal{P} = \{1, 2, 3, 4, 5\}$. The AT bounds are set as $\mathbf{L}_\mathcal{A}^\ell = 20$ days and $\mathbf{U}_\mathcal{A}^\ell = 60$ days for all $\ell \in \mathcal{P}$. Similarly, the IT bounds are defined as $\mathbf{L}_\mathcal{I}^\ell = 20$ days for all $\ell \in \mathcal{P}$. On the IT no upper limit is imposed, meaning that $U_\mathcal{I}^\ell = \infty$, for all $\ell \in \mathcal{P}$. In this way, each drug therapy must be administered for at least 20 days and no more than 2 months. If a drug therapy is interrupted, it cannot be used again for the next 20 days.

The temporal evolution of the total pathogen load under the drug therapies proposed by the NMPC is shown in Fig. 1 (top graph, solid lines). Black dots in the control sequence graphs represent the sampling instants, ensuring AT/IT limits compliance. A standard switching NMPC, which does not consider AT/IT, was also simulated, see the total pathogen load (top graph, dotted lines), and the control sequence (middle graph). As observed, total pathogen load exhibits a decreasing dynamic. This shows that our formulation is capable of achieving pathogen eradication, even when the scheduling of drug therapies must comply with AT/IT limits, ensuring that no treatment is applied for less than 20 days and no more than 2 month. The sequence of modes applied by NMPC formulation in (10) is shown in the bottom graph.

As expected, the MPC without AT/IT limits achieves lower total pathogen load. However, it presents rapid switching between modes, making it inadequate for real applications. Moreover, the decrease of the total pathogen population x_T through time presented no significant differences between both control strategies. Indeed, for both strategies x_T is lower than 10^{-1}. Thus, the MPC formulation in (10) maintains good performance even when AT/IT limits are considered.

In contrast to the results presented in [17], our proposal achieves similar performance regarding to maintain a lower total pathogen load. However, the sub-optimal switching type 1 and 2 presented in [17] does not have additional temporal constraints.

B. Designing Public Health Policies

Consider the case of a dynamical model of virus spread in which the earliest control action to reduce disease spread is by means of social distancing measures (SD). Thus, the following SIDARTHE compartmental epidemic model serves to explain the spread of the virus between the population,

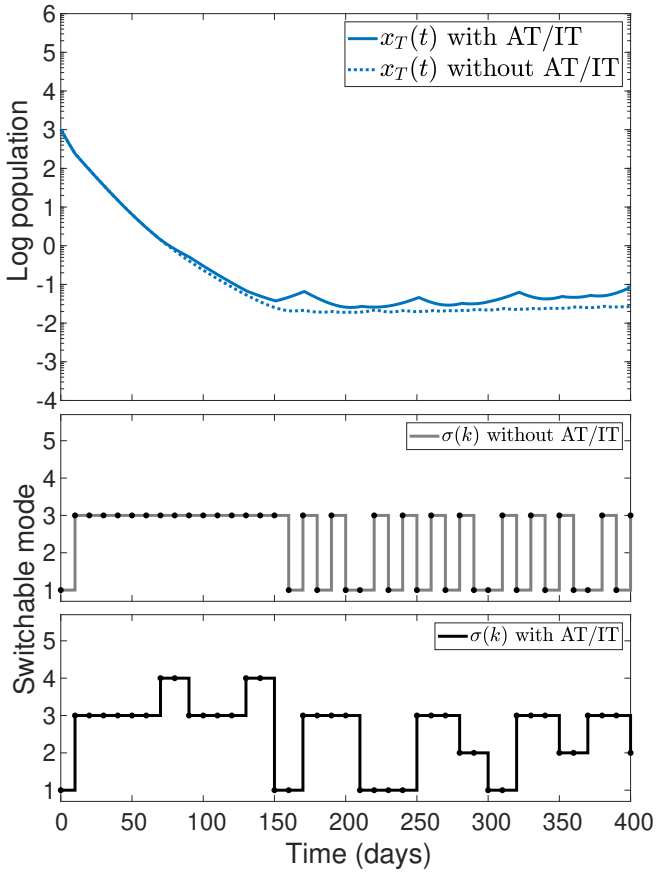

Fig. 1. NMPC (10) for pathogen mutation. Pathogen temporal dynamics (top), x_T stands for total pathogen population, dotted and solid lines represent the temporal evolution for the switching control sequence without AT/IT (middle) and with AT/IT (bottom), respectively.

originally presented in [19],

$$\begin{aligned}
\dot{S} &= -S(\alpha I + \beta D + \gamma A + \beta R),\\
\dot{I} &= S(\alpha I + \beta D + \gamma A + \beta R) - (\epsilon + \zeta + \lambda)I,\\
\dot{D} &= \epsilon I - (\zeta + \lambda)D,\\
\dot{A} &= \zeta I - (\theta + \mu + \kappa)A,\\
\dot{R} &= \zeta D + \theta A - (\mu + \kappa)R,\\
\dot{T} &= \mu A + \mu R - (\sigma + \tau)T,\\
\dot{H} &= \lambda I + \lambda D + \kappa A + \kappa R + \sigma T,\\
\dot{E} &= \tau T,
\end{aligned} \tag{13}$$

where Susceptible (S), Infected (I), Diagnosed (D), Ailing (A), Recognized (R), Threatened (T), Healed (H), and Extinct (E) are the system state variables and represent the fraction of the population in each stage. A detailed model parameter description could be found in [19]. The reproduction number, $\mathcal{R}(t)$, of the SIDARTHE model is given by,

$$\mathcal{R}(\cdot) = \frac{1}{\zeta + \lambda}\left(\alpha(\cdot) + \frac{1}{\theta + \mu + \kappa}\left(\gamma(\cdot)\zeta + \frac{\beta\theta\zeta}{\mu + \kappa}\right)\right),$$

where parameters α and γ are the ones affected by SD measures. Instead of a continuous control action variable, real government social distancing measures are better represented by a finite set of SD, from the hardest one (lockdown), to more relaxed ones (face mask-wearing), to the complete absence of measures. Thus, to represent this control action characteristic as a switching signal, the reproduction number is expressed as

$$\mathcal{R}^{\sigma}(t) = \overline{\mathcal{R}} - \sigma(t)\Delta\mathcal{R}, \text{ with } \Delta\mathcal{R} = \frac{\overline{\mathcal{R}} - \underline{\mathcal{R}}}{n}, \tag{14}$$

where $\overline{\mathcal{R}} = 3.4$ and $\underline{\mathcal{R}} = 0.4$ represent the maximum $\mathcal{R}$ (reproduction number in the absence of interventions) and the minimum $\mathcal{R}$ (maximal effectiveness of SD measures, it is assumed greater than zero) respectively. The finite number of SD measures is represented by n, this way $\sigma(t) \in \mathbb{I}_{[0:n]}$. As one can see in (14), $\sigma = 0$ corresponds to no SD measures, while $\sigma = n$ corresponds to the hardest SD measure.

Virus spread model (13) can be represented in the switched system form as described in (1). In this framework, the switching signal σ modifies the parameters, α and γ, thereby adjusting the reproduction number and encoding a finite set of SD measures as a discrete set of values. This switching signal $\sigma(t)$ follows a BR, where each SD measure is represented by a binary variable $v^{\ell}(k)$, with $\ell \in \mathcal{P}$.

In this specific case, for $\ell = 1$, the variable $v^1(k)$ corresponds to the absence of SD measures ($\sigma = 0$) and the total number of modes is given by $n_s = n + 1$. Since $\mathbf{v}(k)$ satisfies condition (4) it is possible to establish the discrete-time memory variables to represent the AT/IT of the epidemic model (13). This enables the application of the NMPC formulation (10). For the numerical simulations, we consider a time period of 250 days, with a sampling time $T_s = 5$ days. The system parameters are taken from [20], where four different SD measures are modeled ($n = 4$), resulting in five different SM ($n_s = 5$).

In accordance with the epidemic control objectives presented in [21], the NMPC with AT/IT limits formulated as (10) aims to minimize:

$$\begin{aligned}
J_N(x;\mathbf{v}) = &\sum_{j=0}^{N-1} \|\mathbf{v}(j) - \mathbf{v}^*\|^2_{R_\mathbf{v}} + \|S(j) - S^*\|^2_Q\\
&+ \|S(N) - S^*\|^2_P,
\end{aligned} \tag{15}$$

where the first term encourages the removal of social distancing (SD) measures once S^* is achieved. The second and third terms aim to steer the susceptible population towards the herd immunity value $S^* = 1/\overline{\mathcal{R}}$. For this case $N = 10$, $R_\mathbf{v} = 10^{-6}$, $Q = 10^{-3}$, and $P = 10^{-2}$. Threatened individuals are constrained not to exceed $T_{\max} = 0.01$. The AT bounds are set as $L^{\ell}_{\mathcal{A}} = 15$ days and $U^{\ell}_{\mathcal{A}} = 30$ days for all $\ell \neq 1$, while for $\ell = 1$ (no SD measures case), the bounds are $L^1_{\mathcal{A}} = T_s$ and $U^1_{\mathcal{A}} = \infty$. For IT bounds, $L^{\ell}_{\mathcal{I}} = 5$ days for all $\ell \neq 5$, and for $\ell = 5$ (the hardest SD measure), it is considered $L^5_{\mathcal{I}} = 15$ days. The only max IT bound is $U^1_{\mathcal{I}} = 90$ days.

The temporal evolution of the virus spread model under the SD measures proposed by the NMPC (10) is shown in Fig. 2 (top graph, solid lines). Black dots in the control sequence graphs denote sampling instants, ensuring AT/IT limits compliance. A standard switching NMPC which does not consider AT/IT was also simulated, temporal evolution (top graph, dotted lines), and control sequence (middle graph). The NMPC achieves epidemic objectives by steering the susceptible population toward S^* while maintaining the threatened

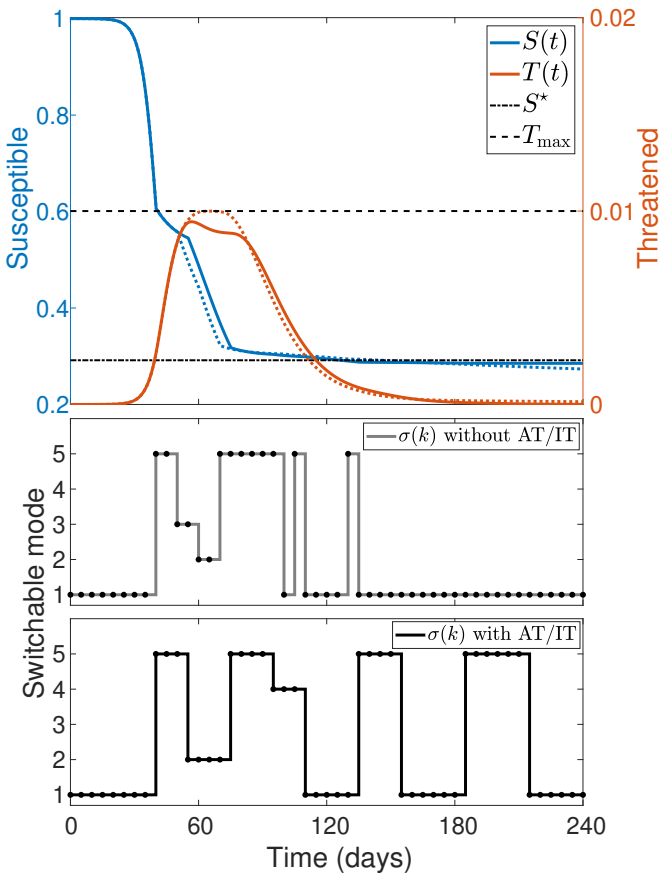

Fig. 2. NMPC (10) for viral spread between hosts. Susceptible (left y-axis) and Threatened population (right y-axis) (top), dotted and solid lines represent the temporal evolution for the switching control sequence without AT/IT (middle) and with AT/IT (bottom), respectively.

population below the predefined threshold. Fast commutations between the hardest SD measure and no SD measure mode are observed after 100 days for the standard switching NMPC, even though it meets the epidemic objectives. The sequence of SD measures proposed by the NMPC formulation in (10) is displayed in the bottom graph. As shown, the control objectives are achieved while satisfying the AT/IT limits. Specifically, each SD measure must be applied for no less than 15 days and no longer than 1 month. After the strictest SD measure ends, it cannot be reapplied for at least 15 days (due to $L_{\mathcal{I}}^5 = 15$). Within 3 months the control system must remove all SD measures and switch back to SM-1 (as $U_{\mathcal{I}}^1 = 90$).

VI. Conclusions

This paper introduces a model representation of AT/IT inherent to switched systems, enabling an MPC formulation capable of handling AT/IT limits. The proposal was successfully applied to two biomedical problems, with numerical results demonstrating its effectiveness and applicability. Further applications could find a place in tailoring therapies at different scales [22], and in artificial pancreas devices where temporal logic restrictions have been shown to prevent dysglycemia [23].

The developed technique opens a new paradigm in the MPC field, and offers transformative potential for long-term advances with wide-ranging applications in both theoretical and applied domains. Future work will focus on a formal analysis of recursive feasibility and asymptotic stability for this type of formulation.

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