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HIV dynamics: Analysis and robust multirate MPC-based treatment schedules

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ABSTRACT

Analysis and control of human immunodeficiency virus (HIV) infection have attracted the interests of mathematicians and control engineers during the recent years. Several mathematical models exist and adequately explain the interaction of the HIV infection and the immune system up to the stage of clinical latency, as well as viral suppression and immune system recovery after treatment therapy. However, none of these models can completely exhibit all that is observed clinically and account the full course of infection. Besides model inaccuracies that HIV models suffer from, some disturbances/uncertainties from different sources may arise in the modelling. In this paper we study the basic properties of a 6-dimensional HIV model that describes the interaction of HIV with two target cells, $CD4^+$ T cells and macrophages. The disturbances are modelled in the HIV model as additive bounded disturbances. Highly Active AntiRetroviral Therapy (HAART) is used. The control input is defined to be dependent on the drug dose and drug efficiency. We developed treatment schedules for HIV infected patients by using robust multirate Model Predictive Control (MPC)-based method. The MPC is constructed on the basis of the approximate discrete-time model of the nominal model. We established a set of conditions, which guarantee that the multirate MPC practically stabilizes the exact discrete-time model with disturbances. The proposed method is applied to the stabilization of the uninfected steady state of the HIV model. The results of simulations show that, after initiation of HAART with a strong dosage, the viral load drops quickly and it can be kept under a suitable level with mild dosage of HAART. Moreover, the immune system is recovered with some fluctuations due to the presence of disturbances.

1. Introduction

Over the last decade a tremendous effort has been made in developing mathematical models of the immunology dynamics under the attack of the human immunodeficiency virus (HIV) and under the influence of antiretroviral therapies. HIV is responsible of acquired immunodeficiency syndrome (AIDS). HIV is a retrovirus which infects the $CD4^+$ T cells and macrophages which are the crucial immune responses and play important roles in phagocytosis. After infection, the $CD4^+$ T cells lose their function and become a virus factory, producing new virus particles until its death. Macrophages live longer than the $CD4^+$ T cell and it is an important source of virus after $CD4^+$ T cell depletion. When the number of $CD4^+$ T cell reaches below 200 cell/mm^3 of plasma, the HIV infected patient is regarded as an AIDS patient.

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The treatment of HIV infected patients is of major importance in today's social medicine. Currently, the most important categories of anti-HIV drugs are reverse transcriptase inhibitors (RTI) drugs and protease inhibitors (PI) drugs. Reverse transcriptase inhibitors prevent the HIV from infecting cells by blocking the integration of the HIV viral code into the host cell genome. Protease inhibitors prevent already infected host cells from producing infectious virus particles. Recently, Highly Active AntiRetroviral Therapies (HAART) which consist of one or more RTI and a PI, can suppress viral load below detectable levels and consequently prolong time to the onset of AIDS.

Optimal treatment scheduling of HIV infection using a control theoretic approach is the subject of substantial research activity. In [13,24,28,9,23,1,27,38], open-loop type optimal controllers are designed using the Pontryagin's Maximum Principle. A major drawback of open-loop optimal controllers is their lack of robustness against disturbances/model uncertainties. In fact, HIV dynamics are poorly known, this leads to model inaccuracies and parameter uncertainties. Also, another source of disturbances may arise from immune system fluctuating or immune effect of a coinfection, in addition to the measurements errors and estimation errors when using an observer to estimate the unmeasured states. Therefore, the design of optimal treatment schedules based on open loop optimal controller, may lead to undesired results. To overcome this problem, we have to design a feedback controller, that inherits a certain robustness to disturbances. Feedback control for HIV has been studied by [3,5,4].

In the last few years, model predictive control (MPC) method is developed for determining optimal treatment schedules for HIV patients [37,11,12,39,20,17]. The MPC method obtains the feedback control by solving a finite horizon optimal control problem at each time instant using the current state of the system as the initial state for the optimization and applying "the first part" of the optimal control. The study of stabilizing property of such schemes has been the subject of intensive research in recent years (see e.g. [15,2,29]).

In [39], the MPC is constructed on the basis of the discrete-time model where the sampling period is chosen to be seven days (i.e., $\tau = 7$). However, the authors did not consider the effect of the discretization of the differential equations on the stability analysis. Moreover, for large sampling periods, the viral load and the $CD4^+$ T cell count could not be kept within baseline ranges (see [25]). Alternatively, the optimal control problems can be solved by continuously varying drug levels in [37]. However, continuous-time variation of the dose seems hard to apply in the clinical treatment of patients. In [11] and [12], the HIV model is discretized with a suitable numerical method with short sampling period, and the MPC is designed on the basis of the approximate discrete-time model. For short sampling period, MPC is hard to apply to HIV model, because it requires the availability of blood measurements every sampling instants ($i\tau$, $i = 0, 1, \ldots$). A possible solution of this problem is to design a multirate version of MPC, where the measurements are needed every ℓ samplings ($i\tau\ell$, $i = 0, 1, \ldots$) (see [17] and [18]). In [37] and [39], it is shown only by simulation that the applied MPC have a certain degree of robustness to measurements and modelling errors.

The aim of the present paper is to develop treatment schedules for HIV infected patients by using robust multirate MPC. The disturbances are modelled in the HIV model as additive bounded disturbances. The construction of MPC is based on the approximate discrete-time model of the nominal model. We have shown that under suitable conditions, the multirate MPC practically stabilizes the exact discrete-time model with disturbances. These conditions have been verified for the HIV model. The importance of approximate discrete-time design is supported by a series of counter-examples (see e.g. [31,30] and [16]), which show that even for disturbance-free systems one can design a controller to stabilize the approximate model, but the original model is destabilized by the same controller. In [39], the MPC method is applied to an HIV model without verifying the stability conditions of the proposed method such as the asymptotic controllability of the system and the delectability condition.

The model of HIV infection we will use in this paper, considers the infection process of the HIV with two target cells, $CD4^+$ T cells and macrophages, which is a 6-dimensional nonlinear ODEs model. The importance of considering such model is due to the observation of Perleson el al., that after the rapid first phase of decay during the initial 1–2 weeks of antiretroviral treatment, plasma virus levels declined at a considerably slower rate [34]. This second phase of viral decay was attributed to the turnover of a longer-lived virus reservoir of infected cell population. Therefore, the two target cells model is more accurate than the one target cell model (see [35] and [7]). Models used in [37,11,12,39,17] do not capture the detailed viral dynamics the occur in macrophages. In our paper, we studied the basic properties of the 6-dimensional HIV model with additive disturbances. Note that these basic properties of the 6-dimensional HIV model are not well studied in the literature, compared with those of, say, the 4-dimensional model [33], and they are important for understanding the associated characteristics of the HIV dynamics. This also helps us to verify the stability conditions of the MPC method. The simulation results show that after initiating the HAART, the viral load drops dramatically and it can be kept under a suitable level by using a mild dosage of HAART. Moreover, the immune system returns near to the normal status with some fluctuations due to the presence of disturbances.

The layout of the paper is as follows: In Section 2, we introduce the HIV model and study its basic properties. In Section 3, we outline the robust multirate MPC design for sampled-data nonlinear systems and summarize the main results obtained in [16] and [10]. Application of robust MPC to the HIV model is given in Section 4. Section 5 presents the simulation results. The last section is the conclusion.

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2. HIV model

We shall use the mathematical model of HIV infection proposed by ([35] and [7]), incorporating to allow some disturbances. For simplicity we shall assume that the disturbances are model as additive which can model perturbed systems and a wide class of model mismatches. This model describes two co-circulation populations of target cells, potentially representing CD4$^+$ T cells and macrophages. The model can simulate differential drug penetration into target cell co-circulating in plasma, see [19]. After initiation of HAART which consists of RTI and PI drugs the model can be written as:

$$\dot{T} = s_1 - d_1 T - \beta_1 T V + w_1, \tag{1}$$

$$\dot{T}_1 = q_1 e^{-u_1} \beta_1 T V - k_1 T_1 - \mu_1 T_1 + w_2, \tag{2}$$

$$\dot{T}_2 = q_2 e^{-u_1} \beta_1 T V + k_1 T_1 - \mu_2 T_2 + w_3, \tag{3}$$

$$\dot{M} = s_2 - d_2 M - \beta_2 M V + w_4, \tag{4}$$

$$\dot{M}_1 = q_M e^{-u_1} \beta_2 M V - \delta M_1 + w_5, \tag{5}$$

$$\dot{V} = e^{-u_2} p_1 T_2 + e^{-u_2} p_2 M_1 - c V + w_6. \tag{6}$$

The state variables describes the plasma concentrations of: T, the uninfected CD4$^+$ T cells; T_1, the latently infected CD4$^+$ T cells; T_2, the actively infected CD4$^+$ T cells; M, the uninfected macrophages; M_1, the infected macrophages; and V, the free virus particles.

The populations of the uninfected CD4$^+$ T cells and macrophages are described by Eqs. (1) and (4), respectively, where s_1 and s_2 represent, respectively, the rates of which new CD4$^+$ T cell and macrophages are generated from sources within the body, d_1, d_2 are the death rate constants, and β_1, β_2 are the infection rate constants. Here, the law of mass action was used. Eq. (2) describes the population dynamics of the latently infected CD4$^+$ T cells and shows that they convert to actively produce virus with a rate constant k_1 and μ_1 is their death rate constant. Eq. (3), describes the population dynamics of the actively infected CD4$^+$ T cells and shows that they die with rate constant μ_2. Constants q_1 and q_2 are the probabilities that upon infection a CD4$^+$ T cell become either latent or actively producing virus. In Eq. (5), q_M is the probability of successfull infection, δ is the death rate constant of the infected macrophages. The virus particles are produced by the actively infected CD4$^+$ T cells and infected macrophages with rate constants p_1 and p_2, respectively, and are cleared from plasma with rate constant c. We emphasize that all the parameters of the model are positive and they differ from one patient to another. For the estimation of HIV model parameters, we refer the reader to the following papers [40,41,22,42]. The effect of the RTI and PI drugs are represented by the chemotherapy functions $e^{-\psi_1 m_1(t)}$ and $e^{-\psi_2 m_2(t)}$ where ψ_1 and ψ_2 are the efficiencies of RTI and PI drugs, respectively, and $m_1(t)$ and $m_2(t)$ are the drug dose at time t (see [6]). We shall consider the control input as $u_i(t) = \psi_i m_i(t)$, $i = 1, 2$.

In Eqs. (1)–(6), $w_i(t)$ describes model uncertainties/disturbances that may arise from different sources such as, modelling errors, immune system fluctuation, immune effect of a co-infection, measurement noise, estimation errors, and so on.

We assume that, the model uncertainties/disturbances satisfy the following bound

$$\left\| w_i(t) \right\| \leqslant \epsilon_i, \quad \epsilon_i \geqslant 0,\ i = 1, \ldots, 6. \tag{7}$$

We are now ready to present a study on the basic mathematical properties of the model.

2.1. Positive invariance

Now we show that the model (1)–(6) is biologically acceptable in the sense that no population goes negative. To do so, we show that under which conditions the nonnegative orthant $\mathbb{R}^6_+$ is positively invariant for (1)–(6):

$$\begin{aligned}
&\dot{T}|_{(T=0)} = s_1 + w_1 \geqslant 0 \quad \text{if } w_1 \geqslant -s_1,\\
&\dot{T}_1|_{(T_1=0)} = q_1 e^{-u_1} \beta_1 T V + w_2 \geqslant 0 \quad \text{if } w_2 \geqslant -q_1 e^{-u_1} \beta_1 T V,\\
&\dot{T}_2|_{(T_2=0)} = q_2 e^{-u_1} \beta_1 T V + k_1 T_1 + w_3 \geqslant 0 \quad \text{if } w_3 \geqslant -q_2 e^{-u_1} \beta_1 T V - k_1 T_1,\\
&\dot{M}|_{(M=0)} = s_2 + w_4 \geqslant 0 \quad \text{if } w_4 \geqslant -s_2,\\
&\dot{M}_1|_{(M_1=0)} = q_M e^{-u_1} \beta_2 M V + w_5 \geqslant 0 \quad \text{if } w_5 \geqslant -q_M \beta_2 e^{-u_1} M V,\\
&\dot{V}|_{(V=0)} = e^{-u_2} p_1 T_2 + e^{-u_2} p_2 M_1 + w_6 \geqslant 0 \quad \text{if } w_6 \geqslant -e^{-u_2} p_1 T_2 - e^{-u_2} p_2 M_1,
\end{aligned} \tag{8}$$

with $(T, T_1, T_2, M, M_1, V) \geqslant 0$. This means that under the above conditions the nonnegative orthant $\mathbb{R}^6_+$ is positively invariant, namely, if a trajectory starts in the nonnegative orthant, it remains there. We note that, the conditions in (8) give a lower bound of the disturbances only at the boundary of $\mathbb{R}^6_+$.

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Proposition 1. *Suppose that the disturbances satisfy the bound* (7) *and* q_1, q_2 *and* q_M *satisfy* $q_1 + q_2 \leqslant 1$ *and* $q_M \leqslant 1$, *then there exists such positive numbers* L_1, L_2 *and* L_3 *that the compact set*

$$\Omega = \{(T, T_1, T_2, M, M_1, V):\ 0 \leqslant T, T_1, T_2 \leqslant L_1,\ 0 \leqslant M, M_1 \leqslant L_2,\ 0 \leqslant V \leqslant L_3\}, \tag{9}$$

is positively invariant.

Proof. Let $T_{tot} = T + T_1 + T_2$, and $M_{tot} = M + M_1$. Then

$$\begin{aligned}
\dot{T}_{tot} &= \left(e^{-u_1}q_1 + e^{-u_1}q_2 - 1\right)\beta_1 TV + s_1 + w_1 + w_2 + w_3 - d_1 T - \mu_1 T_1 - \mu_2 T_2 \\
&\leqslant (q_1 + q_2 - 1)\beta_1 TV + s_1 + w_1 + w_2 + w_3 - d_1 T - \mu_1 T_1 - \mu_2 T_2 \\
&\leqslant s_1 + \epsilon_1 + \epsilon_2 + \epsilon_3 - \sigma_1 T_{tot}, \\
\dot{M}_{tot} &= \left(e^{-u_1}q_M - 1\right)\beta_2 MV + s_2 + w_4 + w_5 - d_2 M - \delta M_1 \\
&\leqslant (q_M - 1)\beta_2 MV + s_2 + w_4 + w_5 - d_2 M - \delta M_1 \\
&\leqslant s_2 + \epsilon_4 + \epsilon_5 - \sigma_2 M_{tot},
\end{aligned}$$

where $\sigma_1 = \min\{d_1, \mu_1, \mu_2\}$ and $\sigma_2 = \min\{d_2, \delta\}$. Hence $0 \leqslant T_{tot}(t) \leqslant \frac{s_1+\epsilon_1+\epsilon_2+\epsilon_3}{\sigma_1}$ for all $t \geqslant 0$ if $T_{tot}(0) \leqslant \frac{s_1+\epsilon_1+\epsilon_2+\epsilon_3}{\sigma_1}$, and $0 \leqslant M_{tot}(t) \leqslant \frac{s_2+\epsilon_4+\epsilon_5}{\sigma_2}$ for all $t \geqslant 0$ if $M_{tot}(0) \leqslant \frac{s_2+\epsilon_4+\epsilon_5}{\sigma_2}$. It follows that $0 \leqslant T(t), T_1(t), T_2(t) \leqslant L_1$ and $0 \leqslant M(t), M_1(t) \leqslant L_2$ for all $t \geqslant 0$ if $T(0), T_1(0), T_2(0) \leqslant L_1$, and $M(0), M_1(0) \leqslant L_2$, where $L_1 = \frac{s_1+\epsilon_1+\epsilon_2+\epsilon_3}{\sigma_1}$ and $L_2 = \frac{s_2+\epsilon_4+\epsilon_5}{\sigma_2}$. On the other hand,

$$\dot{V}(t) \leqslant e^{-u_2}p_1 L_1 + e^{-u_2}p_2 L_2 - cV + w_6 \leqslant p_1 L_1 + p_2 L_2 - cV + \epsilon_6,$$

then $0 \leqslant V(t) \leqslant L_3$ for all $t \geqslant 0$, if $V(0) \leqslant L_3$, where $L_3 = \frac{p_1 L_1 + p_2 L_2 + \epsilon_6}{c}$. □

Note that Ω contains all the biologically relevant states, thus we can restrict the state space of the system to the compact set Ω. Since the drug doses cannot be arbitrarily increased we may consider a compact control constraint set only.

2.2. Steady states

We shall compute the steady states of system (1)–(6) under constant controller in the absence of the disturbances, i.e., for $u_j(t) = \bar{u}_j$, $j = 1, 2$, and $w_i(t) = 0$, $i = 1, 2, \ldots, 6$, $t \geqslant 0$. A steady state (T, T_1, T_2, M, M_1, V) satisfies

$$s_1 - d_1 T - \beta_1 TV = 0, \tag{10}$$

$$q_1 e^{-\bar{u}_1}\beta_1 TV - k_1 T_1 - \mu_1 T_1 = 0, \tag{11}$$

$$q_2 e^{-\bar{u}_1}\beta_1 TV + k_1 T_1 - \mu_2 T_2 = 0, \tag{12}$$

$$s_2 - d_2 M - \beta_2 MV = 0, \tag{13}$$

$$q_M e^{-\bar{u}_1}\beta_2 MV - \delta M_1 = 0, \tag{14}$$

$$e^{-\bar{u}_2}p_1 T_2 + e^{-\bar{u}_2}p_2 M_1 - cV = 0. \tag{15}$$

Solving T_1, T_2 and M_1 from equations (11), (12) and (14) in terms of TV and/or MV and inserting them into (15) we obtain

$$(a_4 T + a_5 M - c)V = 0, \tag{16}$$

where

$$a_4 = \frac{p_1\beta_1[k_1 q_1 + (k_1 + \mu_1)q_2]e^{-(\bar{u}_1+\bar{u}_2)}}{\mu_2(k_1 + \mu_1)}, \qquad a_5 = \frac{p_2\beta_2 q_M e^{-(\bar{u}_1+\bar{u}_2)}}{\delta}.$$

The first solution of (16) is $V = 0$. Then substituting it in (10)–(14), we obtain the uninfected steady state $E_0 = (T_0, 0, 0, M_0, 0, 0)$ where $T_0 = \frac{s_1}{d_1}$, $M_0 = \frac{s_2}{d_2}$. If $V \neq 0$, then

$$a_4 T + a_5 M - c = 0, \tag{17}$$

and by eliminating V from Eqs. (10) and (13) we obtain

$$a_3 T - a_2 TM - a_1 M = 0, \tag{18}$$

where

$$a_1 = s_1\beta_2, \qquad a_2 = \beta_1 d_2 - \beta_2 d_1, \qquad a_3 = s_2\beta_1.$$

We note that the coefficients a_1, a_3, a_4 and a_5 are positive, while a_2 may be positive, or negative, or equal zero.

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If $a_2 = 0$, then the solutions of (17) and (18) are given by

$$T_0^* = \frac{a_1 c}{a_1 a_4 + a_3 a_5}, \qquad M_0^* = \frac{a_3 c}{a_1 a_4 + a_3 a_5}.$$

If $a_2 \neq 0$, there are two possible solutions for (17) and (18)

$$T_+^* = \frac{-(a_1 a_4 + a_3 a_5 - a_2 c) + \sqrt{(a_1 a_4 + a_3 a_5 - a_2 c)^2 + 4 a_1 a_2 a_4 c}}{2 a_2 a_4},$$
$$M_+^* = \frac{1}{a_5}\left(c - a_4 T_+^*\right),$$
$$T_-^* = \frac{-(a_1 a_4 + a_3 a_5 - a_2 c) - \sqrt{(a_1 a_4 + a_3 a_5 - a_2 c)^2 + 4 a_1 a_2 a_4 c}}{2 a_2 a_4},$$
$$M_-^* = \frac{1}{a_5}\left(c - a_4 T_-^*\right).$$

Now we have to determine the positive solutions. First, we show that the discriminate $\Delta = (a_1 a_4 + a_3 a_5 - a_2 c)^2 + 4 a_1 a_2 a_4 c$, is positive

$$\text{if } a_2 > 0, \quad \Delta = (a_1 a_4 + a_3 a_5 - a_2 c)^2 + 4 a_1 a_2 a_4 c > 0,$$
$$\text{if } a_2 < 0, \quad \Delta = (a_1 a_4 + a_3 a_5 + a_2 c)^2 - 4 a_2 a_3 a_5 c > 0,$$

it follows that if $a_2 > 0$ then

$$T_+^* = \frac{-(a_1 a_4 + a_3 a_5 - a_2 c) + \sqrt{(a_1 a_4 + a_3 a_5 - a_2 c)^2 + 4 a_1 a_2 a_4 c}}{2 a_2 a_4} > 0,$$

and if $a_2 < 0$, let $\bar{a}_2 = -a_2$ and then

$$T_+^* = \frac{(a_1 a_4 + a_3 a_5 + \bar{a}_2 c) - \sqrt{(a_1 a_4 + a_3 a_5 + \bar{a}_2 c)^2 - 4 a_1 \bar{a}_2 a_4 c}}{2 \bar{a}_2 a_4} > 0.$$

Similarly, it is easy to see that

$$a_2 > 0 \implies T_+^* > 0, \text{ and } M_+^* > 0,$$
$$a_2 < 0 \implies T_+^* > 0, \text{ and } M_+^* > 0,$$
$$a_2 > 0 \implies T_-^* < 0, \text{ and } M_-^* > 0,$$
$$a_2 < 0 \implies T_-^* > 0, \text{ and } M_-^* < 0.$$

Then, the only positive solutions are $T^* = T_+^*$ and $M^* = M_+^*$. Substituting them in Eqs. (10)–(14), we obtain the infected steady state which is given by $E_1 = (T^*, T_1^*, T_2^*, M^*, M_1^*, V^*)$ where

$$T^* = \begin{cases} T_0^*, & \text{if } a_2 = 0, \\ T_+^*, & \text{if } a_2 \neq 0, \end{cases} \qquad M^* = \begin{cases} M_0^*, & \text{if } a_2 = 0, \\ M_+^*, & \text{if } a_2 \neq 0, \end{cases}$$
$$T_1^* = \frac{q_1 e^{-\bar{u}_1} d_1}{k_1 + \mu_1}\left(\frac{T_0}{T^*} - 1\right)T^*, \qquad T_2^* = \frac{e^{-\bar{u}_1}\bar{q} d_1}{\mu_2 (k_1 + \mu_1)}\left(\frac{T_0}{T^*} - 1\right)T^*,$$
$$M_1^* = \frac{q_M e^{-\bar{u}_1} d_2}{\delta}\left(\frac{M_0}{M^*} - 1\right)M^*, \qquad V^* = \frac{d_1}{\beta_1}\left(\frac{T_0}{T^*} - 1\right), \tag{19}$$

where, $\bar{q} = k_1 q_1 + (k_1 + \mu_1) q_2$.

Let us define

$$R_0^c(\bar{u}_1, \bar{u}_2) = \frac{\{p_1 \beta_1 T_0 \delta \bar{q} + p_2 q_M \beta_2 M_0 (k_1 + \mu_1)\mu_2\} e^{-(\bar{u}_1 + \bar{u}_2)}}{c \delta (k_1 + \mu_1)\mu_2}.$$

Lemma 1. *The infected steady state E_1 exists if and only if $R_0^c > 1$.*

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Proof. Assume that $R_0^c > 1$, we have shown already that $T^* > 0$ and $M^* > 0$, we have to show the remaining components of E_1, i.e., T_1^*, T_2^*, M_1^*, V^*, are positive.

We can see that T^* and M^* can be written as follows

$$T^* = \frac{A_1}{R_0^c} - B_1 + \sqrt{\left(B_1 - \frac{A_1}{R_0^c}\right)^2 + \frac{2a_1A_1}{a_2R_0^c}}, \quad \text{if } a_2 > 0, \tag{20}$$

$$T^* = \frac{A_1}{R_0^c} + \overline{B}_1 - \sqrt{\left(\overline{B}_1 + \frac{A_1}{R_0^c}\right)^2 - \frac{2a_1A_1}{\bar{a}_2R_0^c}}, \quad \text{if } a_2 < 0, \tag{21}$$

$$T^* = \frac{T_0}{R_0^c}, \quad \text{if } a_2 = 0, \tag{22}$$

$$M^* = \frac{A_2}{R_0^c} + B_2 - \sqrt{\left(B_2 + \frac{A_2}{R_0^c}\right)^2 - \frac{2a_3A_2}{a_2R_0^c}}, \quad \text{if } a_2 > 0, \tag{23}$$

$$M^* = \frac{A_2}{R_0^c} - \overline{B}_2 + \sqrt{\left(\overline{B}_2 - \frac{A_2}{R_0^c}\right)^2 + \frac{2a_3A_2}{\bar{a}_2R_0^c}}, \quad \text{if } a_2 < 0, \tag{24}$$

$$M^* = \frac{M_0}{R_0^c}, \quad \text{if } a_2 = 0, \tag{25}$$

where, $\bar{a}_2 = -a_2$, $\overline{B}_1 = -B_1$, $\overline{B}_2 = -B_2$ and

$$A_1 = \frac{1}{2}T_0 + \frac{p_2q_M\beta_2M_0(k_1+\mu_1)\mu_2}{2p_1\beta_1\delta\bar{q}}, \qquad B_1 = \frac{\beta_2}{2a_2}\left[T_0d_1 + \frac{p_2q_MM_0d_2(k_1+\mu_1)\mu_2}{p_1\delta\bar{q}}\right],$$

$$A_2 = \frac{1}{2}M_0 + \frac{p_1T_0\beta_1\delta\bar{q}}{2p_2\beta_2q_M(k_1+\mu_1)\mu_2}, \qquad B_2 = \frac{\beta_1}{2a_2}\left[M_0d_2 + \frac{p_1T_0d_1\delta\bar{q}}{p_2q_M\mu_2(k_1+\mu_1)}\right].$$

From Eqs. (20)–(25), it can be seen that T^* and M^* are decreasing functions of R_0^c.

Now we show that if $R_0^c = 1$ then $T^* = T_0$ and $M^* = M_0$. Eqs. (20), (21), (23) and (24) can be simplified to the following

$$T^* = A_1 - B_1 + \sqrt{\left(\frac{T_0\beta_1d_2}{2a_2} + \frac{\beta_2^2d_1M_0p_2q_M(k_1+\mu_1)\mu_2}{2a_2\beta_1p_1\delta\bar{q}}\right)^2} = A_1 - B_1 + \sqrt{(B_1 + T_0 - A_1)^2} = T_0, \quad a_2 > 0,$$

$$T^* = A_1 + \overline{B}_1 - \sqrt{\left(\frac{T_0\beta_1d_2}{2\bar{a}_2} + \frac{\beta_2^2d_1M_0p_2q_M(k_1+\mu_1)\mu_2}{2\bar{a}_2\beta_1p_1\delta\bar{q}}\right)^2} = A_1 + \overline{B}_1 - \sqrt{(A_1 + \overline{B}_1 - T_0)^2} = T_0, \quad a_2 < 0,$$

$$M^* = A_2 + B_2 - \sqrt{\left(\frac{M_0\beta_2d_1}{2a_2} + \frac{\beta_1^2d_2T_0p_1\delta\bar{q}}{2a_2\beta_2p_2q_M\mu_2(k_1+\mu_1)}\right)^2} = A_2 + B_2 - \sqrt{(A_2 + B_2 - M_0)^2} = M_0, \quad a_2 > 0,$$

$$M^* = A_2 - \overline{B}_2 + \sqrt{\left(\frac{M_0\beta_2d_1}{2\bar{a}_2} + \frac{\beta_1^2d_2T_0p_1\delta\bar{q}}{2\bar{a}_2\beta_2p_2q_M\mu_2(k_1+\mu_1)}\right)^2} = A_2 - \overline{B}_2 + \sqrt{(\overline{B}_2 - A_2 + M_0)^2} = M_0, \quad a_2 < 0.$$

From the above analysis we obtain the following:

$$R_0^c = 1 \implies E_1 = E_0,$$

$$R_0^c > 1 \implies 0 < T^* < T_0,\ 0 < M^* < M_0, \text{ and } T_1^*, T_2^*, M_1^*, V^* > 0,$$

$$R_0^c < 1 \implies T^* > T_0,\ M^* > M_0, \text{ and } T_1^*, T_2^*, M_1^*, V^* < 0.$$

Now assume that the steady state E_1 exists then $T_1^*, T_2^*, M_1^*, V^* > 0$, and from (19) we obtain $T^* < T_0$, and $M^* < M_0$. It follows from (17) that $R_0^c > 1$. □

2.3. Local stability of E_0

Proposition 2. *If $R_0^c < 1$, then E_0 is locally asymptotically stable for the nominal system.*

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Proof. Let us linearized the nominal system (1)–(6) with constant controllers around E_0. The coefficient matrix is

$$J=\begin{bmatrix} -d_1 & 0 & 0 & 0 & 0 & -T_0\beta_1 \\ 0 & -k_1-\mu_1 & 0 & 0 & 0 & q_1e^{-\bar{u}_1}T_0\beta_1 \\ 0 & k_1 & -\mu_2 & 0 & 0 & q_2e^{-\bar{u}_1}T_0\beta_1 \\ 0 & 0 & 0 & -d_2 & 0 & -M_0\beta_2 \\ 0 & 0 & 0 & 0 & -\delta & q_Me^{-\bar{u}_1}M_0\beta_2 \\ 0 & 0 & p_1e^{-\bar{u}_2} & 0 & p_2e^{-\bar{u}_2} & -c \end{bmatrix}.$$

The characteristic equation is given by:

$$Det(J-\lambda I)=(\lambda+d_1)(\lambda+d_2)\big[\lambda^4+b_3\lambda^3+b_2\lambda^2+b_1\lambda+b_0\big]=0,$$

where

$$\begin{aligned} b_0&=-\big\{p_1\beta_1T_0\delta\bar{q}+p_2q_M\beta_2M_0(k_1+\mu_1)\mu_2\big\}e^{(-\bar{u}_1-\bar{u}_2)}+c\delta(k_1+\mu_1)\mu_2=c\delta(k_1+\mu_1)\mu_2\big(1-R_0^c\big),\\ b_1&=-\big\{p_1\beta_1T_0(\bar{q}+\delta q_2)+p_2q_M\beta_2M_0(k_1+\mu_1+\mu_2)\big\}e^{(-\bar{u}_1-\bar{u}_2)}+c\delta(\mu_1+\mu_2+k_1)+\mu_2(c+\delta)(\mu_1+k_1),\\ b_2&=-\{p_1T_0q_2\beta_1+p_2q_M\beta_2M_0\}e^{(-\bar{u}_1-\bar{u}_2)}+\delta(\mu_1+k_1)+\mu_2(\delta+\mu_1+k_1)+c(\mu_1+\mu_2+\delta+k_1),\\ b_3&=c+\mu_1+\mu_2+\delta+k_1. \end{aligned}$$

We note that b_1 and b_3 are positive, then by using the condition $R_0^c<1$ we can show the following:

$$\begin{aligned} &b_1>\mu_2\delta(\mu_1+k_1)>0,\\ &b_2>\delta(\mu_1+k_1)+\mu_2(\delta+\mu_1+k_1)+c(\mu_1+k_1)>0. \end{aligned}$$

Moreover, the Routh–Hurwitz criteria hold. Then, E_0 is locally asymptotically stable. □

Remark 1. For the parameters given in Table 1, we can see that, when there is no treatment, $R_0^c|_{(\bar{u}_1=\bar{u}_2=0)}=2.46493$, then E_0 is unstable. In contrast, when we linearized the nominal model around the infected steady state E_1, we found that all eigenvalues of the jacobian matrix have a negative real part, this means that E_1 is locally asymptotically stable.

2.4. Global stability of E_0

Proposition 3. *If $R_0^c(\bar{u}_1,\bar{u}_2)\leqslant 1$, then E_0 is globally asymptotically stable for the nominal system.*

Proof. By the method of Korobeinikov [26], we define a Lyapunov function for the nominal system

$$\begin{aligned} W(T,T_1,T_2,M,M_1,V)=\gamma_1T_0\left[\frac{T}{T_0}-\ln\left(\frac{T}{T_0}\right)-1\right]+\gamma_2M_0\left[\frac{M}{M_0}-\ln\left(\frac{M}{M_0}\right)-1\right]\\ +\gamma_3T_1+\gamma_4T_2+\gamma_5M_1+\gamma_6V \end{aligned}$$

with

$$\begin{aligned} &\gamma_1=e^{-\bar{u}_1-\bar{u}_2}p_1\delta\bar{q}, && \gamma_2=e^{-\bar{u}_1-\bar{u}_2}p_2q_M\mu_2(k_1+\mu_1),\\ &\gamma_3=e^{-\bar{u}_2}p_1k_1\delta, && \gamma_4=e^{-\bar{u}_2}p_1\delta(k_1+\mu_1),\\ &\gamma_5=e^{-\bar{u}_2}p_2\mu_2(k_1+\mu_1), && \gamma_6=\mu_2\delta(k_1+\mu_1). \end{aligned}$$

We note that W is defined, continuous and positive definite for all $(T,T_1,T_2,M,M_1,V)>0$. Also, the global minimum $W=0$ occurs at the uninfected steady state E_0. Further, it satisfies

$$\frac{dW}{dt}=s_1\gamma_1\left[2-\frac{T}{T_0}-\frac{T_0}{T}\right]+s_2\gamma_2\left[2-\frac{M}{M_0}-\frac{M_0}{M}\right]+\gamma_6c\big[R_0^c-1\big]V. \tag{26}$$

Since the arithmetical mean is greater than or equal to the geometrical mean, then the first two terms of (26) are less than or equal to zero. Therefore, if $R_0^c\leqslant 1$ then $\frac{dW}{dt}\leqslant 0$ for all $T,M,V>0$. □

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In fact, R_0^c can be written as a sum of two parameters R_T^c and R_M^c

$$R_0^c = R_T^c + R_M^c,$$
$$R_T^c = \frac{p_1\beta_1 s_1 \bar{q} e^{-(\bar{u}_1+\bar{u}_2)}}{cd_1(k_1+\mu_1)\mu_2},$$
$$R_M^c = \frac{p_2 q_M \beta_2 s_2 e^{-(\bar{u}_1+\bar{u}_2)}}{c\delta d_2}.$$

We observe that R_T^c and R_M^c are the basic reproduction ratio of each T-cell and macrophages dynamics separately. If $R_0^c < 1$ then it is sure that $R_T^c < 1$ and $R_M^c < 1$. But if one considers only the four-dimensional model (10)–(12) and (15) and designs a controller such that $R_T^c < 1$, then the whole system may be unstable around E_0, because $R_0^c > 1$. This shows the importance of considering the effect of the macrophages in the HIV dynamics.

Proposition 4. *The nominal system* (1)–(6) *is globally asymptotically controllable to* E_0 *with piecewise constant controllers.*

Proof. Let $u_1(t) = \widehat{u}_1$ and $u_2(t) = \widehat{u}_2$ with $\widehat{u}_1 + \widehat{u}_2 > u_c$, where

$$u_c = \ln\left(\frac{p_1\beta_1 T_0\delta\bar{q} + p_2 q_M\beta_2 M_0(k_1+\mu_1)\mu_2}{c\delta(k_1+\mu_1)\mu_2}\right).$$

Then $R_0^c(\widehat{u}_1, \widehat{u}_2) < 1$, therefore the corresponding trajectory will tend to E_0 as $t \to \infty$. □

Remark 2. We observe that u_c is the minimum controller required to obtain a treatment steady state viral load of zero. Also, by solving the equation for V^*, the minimum drug dose that is required to obtain a treatment steady state viral load below a specific value $V_{\sup}$ (e.g. $V_{\sup} = 50$ copies mL^{-1}) is given by

$$\widehat{u}_1 + \widehat{u}_2 > u_{\sup} = \ln\left(\frac{p_1\beta_1 T_0\bar{q}d_1}{c\mu_2(d_1 + V_{\sup}\beta_1)(k_1+\mu_1)} + \frac{p_2 q_M\beta_2 M_0 d_2}{\delta c(d_2 + V_{\sup}\beta_2)}\right).$$

Remark 3. If one does not take into account the effect of macrophages cells, then our stability results are also useful for the four-dimensional model T, T_1, T_2 and V, by putting $s_2 = d_2 = \beta_2 = \delta = p_2 = 0$ (see [33]).

3. Robust multirate MPC for sampled-data systems

In this section, we outline the multirate MPC design for sampled-data nonlinear systems in the presence of bounded disturbances and give a review on the results obtained in [16] and [10]. We have shown in the preceding section that, the HIV system states can be taken from a compact set. Moreover, since the drug dosage of HAART cannot arbitrarily increased, thus the controller can also be taken from a compact set. Therefore, we give only a short outline of the proof of the main results of [10], when both the state space of the system and the control constraint set are restricted to compact sets.

The set of real and natural numbers (including zero) are denoted, respectively, by $\mathbb{R}$ and $\mathbb{N}$. The notation $\mathbb{R}_{\geqslant 0}$ denote the set of real numbers in the interval $[0, \infty)$. A continuous function $\sigma : \mathbb{R}_{\geqslant 0} \to \mathbb{R}_{\geqslant 0}$ is of class-$\mathcal{K}$ if $\sigma(0) = 0$, $\sigma(s) > 0$ for all $s > 0$ and it is strictly increasing. It is of class-$\mathcal{K}_\infty$ if it is of class-$\mathcal{K}$ and $\sigma(s) \to \infty$ when $s \to \infty$. A continuous function $\beta : \mathbb{R}_{\geqslant 0} \times \mathbb{R}_{\geqslant 0} \to \mathbb{R}_{\geqslant 0}$ is of class-$\mathcal{KL}$ if $\beta(s, \tau)$ is of class-$\mathcal{K}$ in s for every $\tau \geqslant 0$, it is strictly decreasing in τ for every $s > 0$ and $\beta(s, \tau) \to 0$ when $\tau \to \infty$. In what follows, the notation $\mathcal{B}_\Delta = \{z \in \mathbb{R}^l : \|z\| \leqslant \Delta\}$ will be used in $\mathbb{R}^n$.

Consider a continuous-time nonlinear control system with additive disturbances given by

$$\dot{z}(t) = f\big(z(t), u(t)\big) + w(t), \quad z(0) = z_0 \tag{27}$$

where $z(t) \in \mathbb{R}^n$, $u(t) \in U \subset \mathbb{R}^m$, $w(t) \in W \subset \mathbb{R}^p$ are the state, control input and disturbances, respectively, $f : \mathbb{R}^n \times U \to \mathbb{R}^n$ is continuous and Lipschitz continuous w.r.t z in any compact set and $f(0, 0) = 0$, U is compact and $0 \in U$, W is compact and $0 \in W$.

The control is taken to be a piecewise constant signal

$$u(t) = u(i\tau) =: u_i, \quad \text{for } t \in \big[i\tau, (i+1)\tau\big),\ i \in \mathbb{N},$$

where $\tau > 0$ is the control sampling period which is fixed.

In this paper we address the problem of state feedback stabilization of (27) under "low measurement rate". More precisely, we shall assume that state measurements can be performed at the time instants $j\tau^m$, $j = 0, 1, \ldots$:

$$y_j := z\big(j\tau^m\big), \quad j = 0, 1, \ldots,$$

where τ^m is the measurement sampling period. We assume that $\tau^m = \ell\tau$ for the integer $\ell > 0$ which is fixed.

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For a given function $w:\mathbb{R}_{\geqslant 0}\to\mathbb{R}^n$, we use the following notation: $w_\tau[i]:=\{w(t),\ t\in[i\tau,(i+1)\tau]\}$ where $i\in\mathbb{N}$. We denote the norm $\|w\|_\infty:=\operatorname{ess.sup}_{s\geqslant 0}\|w(s)\|$. We assume that there exists $\mu>0$ such that $W\subset\mathcal{B}_\mu$. Let us define

$$\mathcal{W}_\mu=\big\{w\in L^\infty_{[0,\infty)}:\ w(t)\in W \text{ a.e. } t\in[0,\infty) \text{ with } \|w\|_\infty\leqslant\mu\big\},$$
$$\mathcal{W}^\rho_\ell=\big\{\mathbf{w}^{(i)}=\big\{w_\tau[i\ell],\ldots,w_\tau\big[(i+1)\ell-1\big]\big\},\ w\in\mathcal{W}_\rho,\ i=0,1,\ldots\big\}.$$

We shall assume that there is a compact set $\mathcal{X}\subset\mathbb{R}^n$ containing the origin, that is positively invariant with respect to system (27) for any $w(.)\in W$ and any piecewise constant controller $\overline{u}\in U$. Let $t\mapsto\Phi^E(t,z,\overline{u},\overline{w}(.))$ denote the solution of (27) with given $\overline{u}$, $\overline{w}$ and $z=z(0)$. Then the exact discrete-time model can be defined as

$$z_{i+1}=\widetilde{F}^E_\tau\big(z_i,u_i,w_\tau[i]\big), \tag{28}$$

where $\widetilde{F}^E_\tau(z,u,w_\tau):=\Phi^E(\tau;z,u,w_\tau)$.

Let $\mathbf{u}^{(i)}=\{u^{(i)}_0,\ldots,u^{(i)}_{\ell-1}\}$, $\mathbf{w}^{(i)}=\{w_\tau[i\ell],\ldots,w_\tau[(i+1)\ell-1]\}$ and $\mathcal{F}^E_\ell(\xi,\mathbf{u},\mathbf{w}):=\Phi^E(\tau\ell,\xi,\mathbf{u},\mathbf{w})$, then the exact ℓ-step discrete-time model is given by

$$\xi^E_{i+1}=\mathcal{F}^E_\ell\big(\xi^E_i,\mathbf{u}^{(i)},\mathbf{w}^{(i)}\big),\qquad \xi^E_0=z_0. \tag{29}$$

We note that the exact discrete-time models (28) and (29) describe, respectively, the behavior of the system at the time instants $k\tau$ and $k\ell\tau$, $k=0,1,\ldots$.

In this work, the construction of multirate MPC is based on the nominal prediction and only small disturbances are allowed. The nominal system of (27) is given by

$$\dot{x}(t)=f\big(x(t),u(t)\big),\qquad x(0)=z(0), \tag{30}$$

and its exact discrete-time model is given by

$$x^E_{i+1}=F^E_\tau\big(x^E_i,u_i\big). \tag{31}$$

We note that, since f is typically nonlinear, F^E_τ in (31) is not known in most cases, therefore the controller design can be carried out by means of the nominal approximate discrete-time model

$$x^A_{i+1}=F^A_{\tau,h}\big(x^A_i,u_i\big), \tag{32}$$

where h is a modelling parameter, which is typically the step size of the underlying numerical method. The applied numerical scheme approximation has to ensure the closeness of the exact models in the following sense.

Assumption A1. There exists an $h^*>0$ such that

(i) $F^A_{\tau,h}(0,0)=0$, $F^A_{\tau,h}$ is continuous in both variables uniformly in $h\in(0,h^*]$, and Lipschitz continuous w.r.t x in any compact set, uniformly in small h,
(ii) there exists a $\gamma\in\mathcal{K}$ such that

$$\big\|F^E_\tau(x,u)-F^A_{\tau,h}(x,u)\big\|\leqslant\tau\gamma(h)$$

for all $x\in\mathcal{X}$, all $u\in U$, and $h\in(0,h^*]$.

Assumption A2. There exists an $h^*>0$ such that the nominal exact discrete-time model (31) is practically asymptotically controllable from $\mathcal{X}$ to the origin with piecewise constant controllers for all $h\in(0,h^*]$. (See e.g. [16] for the definition.)

For the solutions of (28), (31) and (32) with $\mathbf{u}=\{u_0,u_1,\ldots\}$, $\mathbf{w}=\{w_\tau[0],w_\tau[1],\ldots\}$ and x_0 we shall use the notations $\Phi^E_i(x_0,\mathbf{u},\mathbf{w})$, $\phi^E_i(x_0,\mathbf{u})$ and $\phi^A_i(x_0,\mathbf{u})$, respectively.

The following problem is to be solved: for given τ and ℓ find a control strategy

$$\mathbf{v}_h:\mathcal{X}\to\underbrace{U\times U\times\cdots\times U}_{\ell\text{ times}},\qquad \mathbf{v}_h(x)=\big\{u_0(x),\ldots,u_{\ell-1}(x)\big\},$$

using the nominal approximate discrete-time model (32), to practically stabilize the exact discrete-time system (28).

Let $N\in\mathbb{N}$ with $N\geqslant\ell$ be given. Let (32) be subject to the cost function

$$J_{\tau,h}(N,x,\mathbf{u})=\sum_{i=0}^{N-1}\tau l_h\big(x^A_i,u_i\big)+g\big(x^A_N\big), \tag{33}$$

where $\mathbf{u}=\{u_0,\ldots,u_{N-1}\}$, $x^A_i=\phi^A_i(x,\mathbf{u})$, $i=0,1,\ldots,N$, l_h and g are given functions, satisfying the following assumptions.

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Assumption A3. Let $\mathcal{X}_1 = \mathcal{X} + \mathcal{B}_1$,

(i) $g : \mathcal{X}_1 \to \mathbb{R}$ is continuous, positive definite radially unbounded and Lipschitz continuous in any compact set,
(ii) $l_h(x,u)$ is continuous with respect to x and u, uniformly in small h, and Lipschitz continuous in any compact set,
(iii) there exist an $h^* > 0$ and two class-$\mathcal{K}_\infty$ functions φ_1 and φ_2 such that the inequality

$$\varphi_1\big(\|x\|\big) \leqslant l_h(x,u) \leqslant \varphi_2\big(\|x\|\big) + \varphi_2\big(\|u\|\big),$$

holds for all $x \in \mathcal{X}_1$, $u \in U$ and $h \in (0, h^*]$.

Assumption A4. There exist $h^* > 0$ and $\eta > 0$ such that for all $x \in \mathcal{G}_\eta = \{x\colon\ g(x) \leqslant \eta\}$ there exists a $\kappa(x) \in U$ such that inequality

$$\tau l_h\big(x, \kappa(x)\big) + g\big(F^A_{\tau,h}\big(x, \kappa(x)\big)\big) \leqslant g(x) \tag{34}$$

holds true for all $h \in (0, h^*]$.

We define the value function, which represents the optimal value of (33) for a given initial condition, as

$$V_N(x) = \inf\big\{ J_{\tau,h}(N, x, \mathbf{u})\colon\ u_i \in U \big\}.$$

If this optimization problem has a solution denoted by $\mathbf{u}^* = \{u_0^*, \ldots, u_{N-1}^*\}$, then the first ℓ elements of $\mathbf{u}^*$ are applied at the state x, i.e.,

$$\mathbf{v}_h(x) = \big\{u_0^*(x), \ldots, u_{\ell-1}^*(x)\big\}.$$

Let h_0^* denote the minimum of the values h^* generated by Assumptions A1–A4. Let Δ_x and Δ_u be such numbers that $\|x\| \leqslant \Delta_x$, $\|u\| \leqslant \Delta_u$ if $x \in \mathcal{X}$, $u \in U$.

Theorem 1. *(See [16].) If Assumptions* A1–A4 *hold true, then*

(i) *there exist an h_1^* with $0 < h_1^* \leqslant h_0^*$, and a constant $V^A_{\max}$ independent of N, such that $V_N(x) \leqslant V^A_{\max}$ for all $x \in \mathcal{X}$, $h \in (0, h_1^*]$ and $N \in \mathbb{N}$,*
(ii) *there exist constants N^*, L_V and δ_V and functions $\sigma_1, \sigma_2 \in \mathcal{K}_\infty$ such that for all $x \in \mathcal{X}$, $N > N^*$, $h \in (0, h_1^*]$ and $i = 1, 2, \ldots, \ell$,*

$$\sigma_1\big(\|x\|\big) \leqslant V_N(x) \leqslant \sigma_2\big(\|x\|\big),$$
$$V_N\big(\phi_i^A\big(x, \mathbf{v}_h(x)\big)\big) - V_N(x) \leqslant -\tau\varphi_1\big(\|x\|\big).$$

Moreover, for all $x, y \in \mathcal{X}_1$ with $\|x - y\| \leqslant \delta_V$,

$$\big|V_N(x) - V_N(y)\big| \leqslant L_V \|x - y\|$$

for all $h \in (0, h_1^*]$.

Clearly $\mathcal{X} \subset \{x\colon\ V_N(x) \leqslant V^A_{\max}\}$.

Theorem 2. *Suppose that Assumptions* A1–A4 *are valid and N is chosen such that $N \geqslant N^*$. Then, there exist $\beta \in \mathcal{KL}$, $\theta \in \mathcal{K}_\infty$, $\mu^* > 0$ and for any $\delta > 0$ there exists an $h^* > 0$ such that for any $x_0 \in \mathcal{X}$, and $h \in (0, h^*]$ the trajectory of the ℓ-step exact discrete-time system*

$$\xi^E_{i+1} = \mathcal{F}^E_\ell\big(\xi^E_i, \mathbf{v}_h\big(\xi^E_i\big), \mathbf{w}^{(i)}\big), \quad \xi^E_0 = x_0, \tag{35}$$

with the ℓ-step MPC $\mathbf{v}_h$ and $\mathbf{w}^{(i)} \in \mathcal{W}_\ell^{\mu^*}$ satisfies

$$\big\|\xi^E_i\big\| \leqslant \beta\big(\|x_0\|, i\ell\tau\big) + \theta\big(\mu^*\big) + \delta \quad \text{for all } i \geqslant 0.$$

Proof. The proof can follow the same line as that of Theorem 2 in [10] and Theorem III.1 in [32] with small modifications due to the global character of the statement (in the sense that the whole state space $\mathcal{X}$ belongs to the basin of attraction). Moreover, because of our assumptions of the positive invariance of $\mathcal{X}$, we know that $\xi^E_k \in \mathcal{X}$, if $\xi^E_0 = x_0 \in \mathcal{X}$. Thus, we give only a short outline of the proof. Let $L_f > 0$ be the Lipschitz constant of f. Using Assumption A1 and Gronwall's lemma, we can show that, there exists an $h_2^* > 0$ such that

$$\big\|\Phi^E_i\big(x_0, \mathbf{v}_h(x_0), \mathbf{w}^{(0)}\big) - \phi^A_i\big(x_0, \mathbf{v}_h(x_0)\big)\big\| \leqslant \overline{\gamma}(h) + L\mu, \quad i = 0, 1, \ldots, \ell$$

for all $x_0 \in \mathcal{X}$, $\mathbf{w}^{(0)} \in \mathcal{W}_\ell^\mu$ and all $h \in (0, h_2^*]$, where, $\overline{\gamma}(h) = \tau\gamma(h)\frac{e^{L_f\tau\ell}-1}{e^{L_f\tau}-1}$ and $L = \tau e^{L_f\tau}\frac{e^{L_f\tau\ell}-1}{e^{L_f\tau}-1}$. Let $\nu > 0$ be an arbitrary number. Let σ_1 and σ_2 be given in Theorem 1 and let $\delta_1 = \sigma_2^{-1}(\frac{\nu}{4})$ and $\widehat{L} = 2LL_V$. Let $h_3^* > 0$ and μ_1 be such that inequalities

$$\overline{\gamma}(h) < \min\left\{\frac{\nu}{4L_V}, \frac{\tau}{4L_V}\varphi_1(\delta_1), \frac{1}{4}\delta_V\right\}, \qquad \mu_1 < \min\left\{\frac{\tau}{\widehat{L}}\varphi_1(\delta_1), \frac{3}{4L}\delta_V\right\}$$

hold true for all $h \in (0, h_3^*]$. Let $h^* = \min\{h_2^*, h_3^*\}$ and $\mu^* = \min\{\mu, \mu_1\}$ and choose $d = \widehat{L}\mu^* + \nu$. Using Theorem 1 and the definition of d, one can show in the same way as in [10] that if $\xi_k^E \in \mathcal{X}$ and either $V_N(\xi_{k+1}^E) \geqslant \frac{d}{2}$ or $V_N(\xi_k^E) \geqslant d$ hold true, then

$$V_N\big(\xi_{k+1}^E\big) - V_N\big(\xi_k^E\big) \leqslant -\frac{\tau}{4}\varphi_1\big(\|\xi_k^E\|\big). \tag{36}$$

The construction of a suitable $\mathcal{KL}$ function is standard (see e.g. [31]). □

Remark 4. We note that it is not easy to calculate the maximum integration step size h^* as well as the maximum disturbance bound μ^* given in Theorem 2. Nevertheless, the result is of value, since it underpins that small integration step size and small additive disturbances can be tolerated.

4. Robust MPC for the HIV model

In this section we apply the robust multirate MPC method proposed in section 3 to the HIV model. We shall show that, with a suitable choice of N and functions g and l_h, the assumptions of the previous section can be satisfied. Introduce new variables by the definition $z_1 = T - T_0$, $z_2 = T_1$, $z_3 = T_2$, $z_4 = M - M_0$, $z_5 = M_1$, $z_6 = V$. In these new variables the model (1)–(6) takes the form of (27) with

$$f(z,u) = \begin{pmatrix} s_1 - d_1(z_1 + T_0) - \beta_1(z_1 + T_0)z_6 \\ q_1 e^{-u_1}\beta_1(z_1 + T_0)z_6 - k_1 z_2 - \mu_1 z_2 \\ q_2 e^{-u_1}\beta_1(z_1 + T_0)z_6 + k_1 z_2 - \mu_2 z_3 \\ s_2 - d_2(z_4 + M_0) - \beta_2(z_4 + M_0)z_6 \\ q_M\beta_2 e^{-u_1}(z_4 + M_0)z_6 - \delta z_5 \\ e^{-u_2}p_1 z_3 + e^{-u_2}p_2 z_5 - c z_6 \end{pmatrix}, \tag{37}$$

and $w = (w_1, w_2, w_3, w_4, w_5, w_6)'$.

Let the compact set $\mathcal{X}$ be defined as

$$\mathcal{X} = \big\{z \in \mathbb{R}^6 \colon -T_0 \leqslant z_1 \leqslant L_1 - T_0,\ 0 \leqslant z_2, z_3 \leqslant L_1,\ -M_0 \leqslant z_4 \leqslant L_2 - M_0,\ 0 \leqslant z_5 \leqslant L_2,\ 0 \leqslant z_6 \leqslant L_3\big\},$$

where L_1, L_2 and L_3 are as in Proposition 1.

With this definition, f satisfies all regularity assumptions, and according to Proposition 1, $\mathcal{X}$ is positively invariant if $q_1 + q_2 \leqslant 1$ and $q_M \leqslant 1$. In what follows, we assume that $q_1 + q_2 \leqslant 1$ and $q_M \leqslant 1$. Since the drug doses cannot be arbitrarily increased we can consider a compact control constraint set. The disturbance vector w is assumed to be bounded in a compact set containing the origin.

We note that, when applying the receding horizon algorithm, the cost function $J_{\tau,h}$ is redefined at each sampling instant, thus the applied control doesn't minimize it over any interval. The optimization of this cost is not the aim of the computations but it serves only as an aid for finding the desired stabilizing controller. Therefore the biological content doesn't play any role in its choice. Caetano and Yoneyama [6] proposed a cost function which has a biological meaning, but it is not suitable for our MPC approach. In the receding horizon control literature, there are several strategies for choosing the design parameters to satisfy stability conditions (see [8,14] and [18]). We call design parameters the data present in the open-loop optimal control problem that we are able to choose; these are the control horizon N, the running and terminal costs functions l_h and g and the terminal set $\mathcal{G}_\eta$. In what follows we show that under appropriate choice of the design parameters, the stability conditions can be verified.

To verify Assumptions A3 and A4, we linearized the nominal system (37) around the origin in case of constant controllers, i.e., $u_1(t) = \bar{u}_1 > u_c^{(1)}$, $u_2(t) = \bar{u}_2 > u_c^{(2)}$ with $u_c^{(1)} + u_c^{(2)} = u_c$, where u_c is given in Proposition 4. Let A_C be the coefficient matrix of the linearized system and $x = (T - T_0, T_1, T_2, M - M_0, M_1, V)'$. Then the discrete-time model for the linearized system is given by:

$$x(k+1) = e^{A_C\tau}x(k). \tag{38}$$

Let the sampling period be chosen to be $\tau = 1$ and, $\bar{u}_1 = \bar{u}_2 = 2$. The running cost and the terminal cost can be chosen as:

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Table 1
The values of the parameters in the HIV model and the system states at the initiation of the therapy.

Parameter	Value	Variable	Value
s_1	10^4 mL^{-1}day^{-1}	$\overline{T}$	4.0385×10^5 mL^{-1}
d_1	0.01 day^{-1}	$\overline{T}_1$	8.5×10^2 mL^{-1}
β_1	4.5×10^{-8} mL day^{-1}	$\overline{T}_2$	6.6×10^3 mL^{-1}
q_1	0.005	$\overline{M}$	1.398×10^4 mL^{-1}
q_2	0.55	$\overline{M}_1$	1.61×10^3 mL^{-1}
μ_1	0.01 day^{-1}	$\overline{V}$	3.2798×10^5 mL^{-1}
k_1	0.025 day^{-1}		
μ_2	0.5 day^{-1}		
p_1	240 cell^{-1}day^{-1}		
c	5 day^{-1}		
β_2	1.75×10^{-8} mL day^{-1}		
δ	0.05 day^{-1}		
p_2	35 cell^{-1}day^{-1}		
q_M	1		
s_2	150 mL^{-1}day^{-1}		
d_2	0.005 day^{-1}		

$$l_h(x,u) = \alpha_1 x' Q x + \alpha_2 \big(u_1 - u_c^{(1)}\big)^2 + \alpha_3 \big(u_2 - u_c^{(2)}\big)^2, \tag{39}$$

$$g(x) = x' P x, \tag{40}$$

where α_i are positive weighting constants, P is a positive definite diagonal matrix and Q is a positive definite symmetric matrix satisfying the Lyapunov equation for the discrete-time system (38)

$$Q = -\big(A_\tau' P A_\tau - P\big), \qquad A_\tau = e^{A_C \tau}.$$

From (39)–(40), Assumption A3 is satisfied. Assumption A2 follows from Proposition 4 and Assumption A1 holds also true if we choose a suitable numerical integration scheme (e.g. the Runge–Kutta formula). To verify Assumption A4, the weights α_i and the matrix P have been chosen through a series of numerical experiments as $\alpha_1 = 0.01$, $\alpha_2 = 1000$, $\alpha_3 = 2000$ and $P = diag(0.001, 1, 1, 0.01, 0.1, 0.001)$. It has been verified numerically by solving a constrained minimization problem with several starting points that Assumption A4 is satisfied over the whole set $\mathcal{X}$. Thus all Assumptions of the proposed method can be satisfied with suitable choice of the parameters of the MPC method. We note that by adjusting the weights α_i as well as the matix P, the performance of the MPC can be fine-tuned. Similar case has been discussed in [39], therefore it will not be presented in our paper.

5. Numerical results

We perform simulation studies using the parameter values taken from [24,36,7,3]. These values are listed in Table 1.

According to the suggestion in [21], we assume that the system is in the infected steady state before initiating the treatment i.e. $E_1|_{(u_1=u_2=0)} = (\overline{T}, \overline{T}_1, \overline{T}_2, \overline{M}, \overline{M}_1, \overline{V})$, see Table 1.

We assume that the state measurements are performed at the instants $j\ell\tau$, $j = 0, 1, \ldots$. All computations are carried out by MATLAB. In particular, the optimal control sequence is computed by the fmincon code of the Optimization toolbox. To reduce the computational complexity we chose horizon length N to be $N = 8$ and $\ell = 4$. The disturbances are simulated by $w_i(t) \in [\eta_i, \epsilon_i]$,

$$w_i(t) = w_i(j) = \eta_i + (\epsilon_i - \eta_i) r(j), \quad t \in \big[j\tau, (j+1)\tau\big),\ i = 1, \ldots, 6,\ j = 0, 1, \ldots,$$

where the parameters $r(j)$ are uniformly distributed random numbers on $[0, 1]$, and $\eta_i = -\epsilon_i$ when the system states lie in the interior of the positive orthant $\mathbb{R}^6_+$. At the boundary of $\mathbb{R}^6_+$, the lower bound η_i has to be chosen as the following:

$$\begin{aligned}
\eta_1 &= \max\{-s_1, -\epsilon_1\},\\
\eta_2 &= \max\big\{-q_1 e^{-u_1} \beta_1 (z_1 + T_0) z_6, -\epsilon_2\big\},\\
\eta_3 &= \max\big\{-q_2 e^{-u_1} \beta_1 (z_1 + T_0) z_6 - k_1 z_2, -\epsilon_3\big\},\\
\eta_4 &= \max\{-s_2, -\epsilon_4\},\\
\eta_5 &= \max\big\{-q_M \beta_2 e^{-u_1} (z_4 + M_0) z_6, -\epsilon_5\big\},\\
\eta_6 &= \max\big\{-e^{-u_2} p_1 z_3 - e^{-u_2} p_2 z_5, -\epsilon_6\big\},
\end{aligned}$$

to guarantee that the positive orthant $\mathbb{R}^6_+$ is positively invariant.

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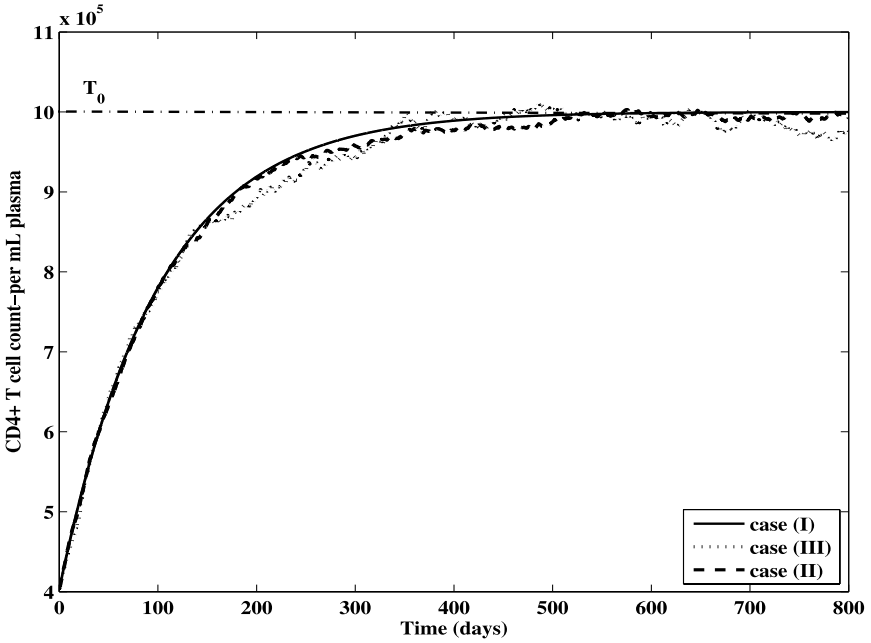

Fig. 1. The evolution of uninfected $CD4^+$ T cells under robust MPC for cases (I)–(III).

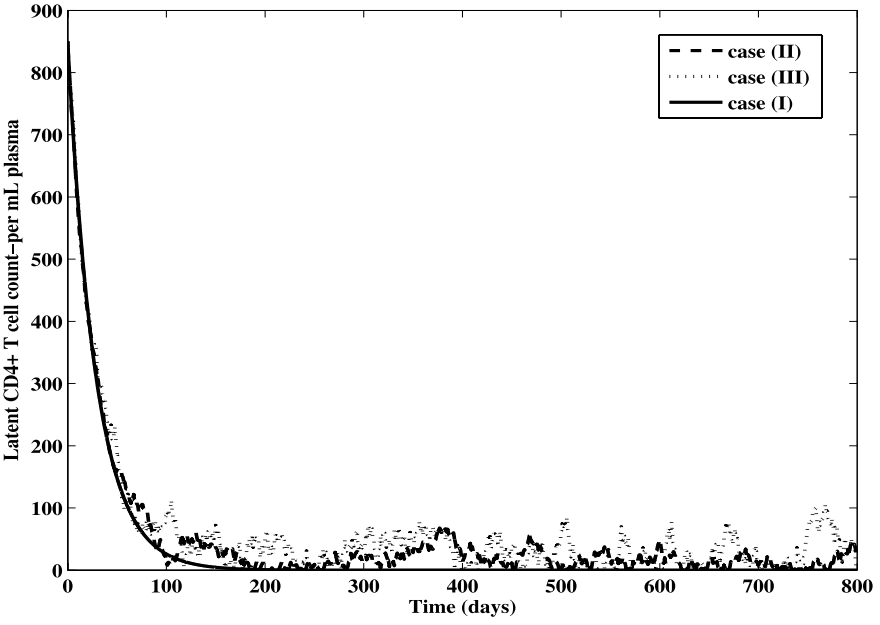

Fig. 2. The evolution of latently infected $CD4^+$ T cells under robust MPC for cases (I)–(III).

Simulations for the continuous-time system are carried out using `ode45` program in MATLAB for three cases:

(I) $w_i(t) = 0$;
(II) $\epsilon_1 = 2000$, $\epsilon_2 = 10$, $\epsilon_3 = 1$, $\epsilon_4 = 100$, $\epsilon_5 = 1$, $\epsilon_6 = 5$;
(III) $\epsilon_1 = 4000$, $\epsilon_2 = 20$, $\epsilon_3 = 2$, $\epsilon_4 = 200$, $\epsilon_5 = 2$, $\epsilon_6 = 10$.

Figs. 1–6 show the evolution of the HIV model variables under the application of multirate MPC strategy for the cases (I)–(III). Figs. 1 and 4 show that, when the MPC is applied, the number of uninfected $CD4^+$ T cells is increasing as well as the macrophages but with a slower rate than $CD4^+$ T cells. This means that, the HAART helps the immune system to

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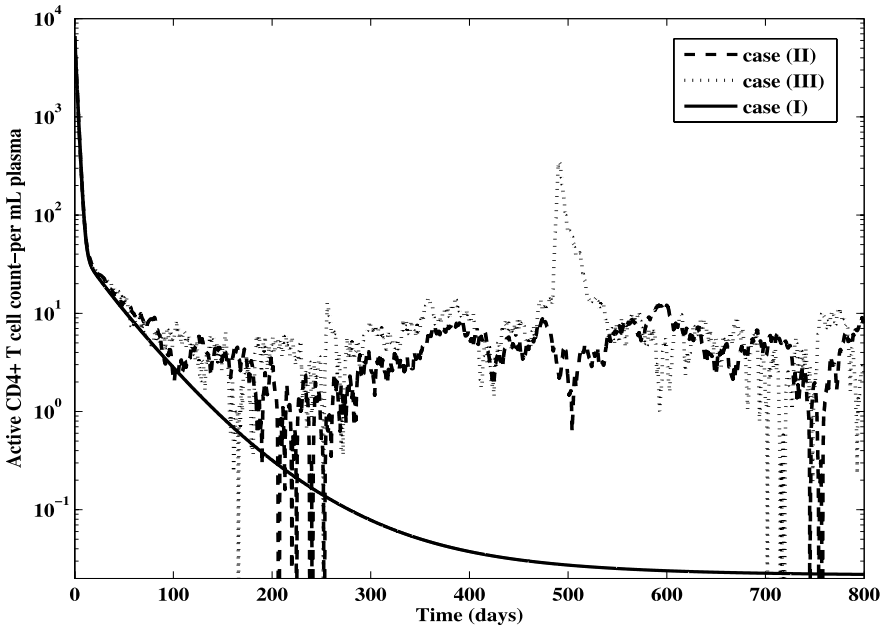

Fig. 3. The evolution of actively infected $CD4^+$ T cells under robust MPC for cases (I)–(III).

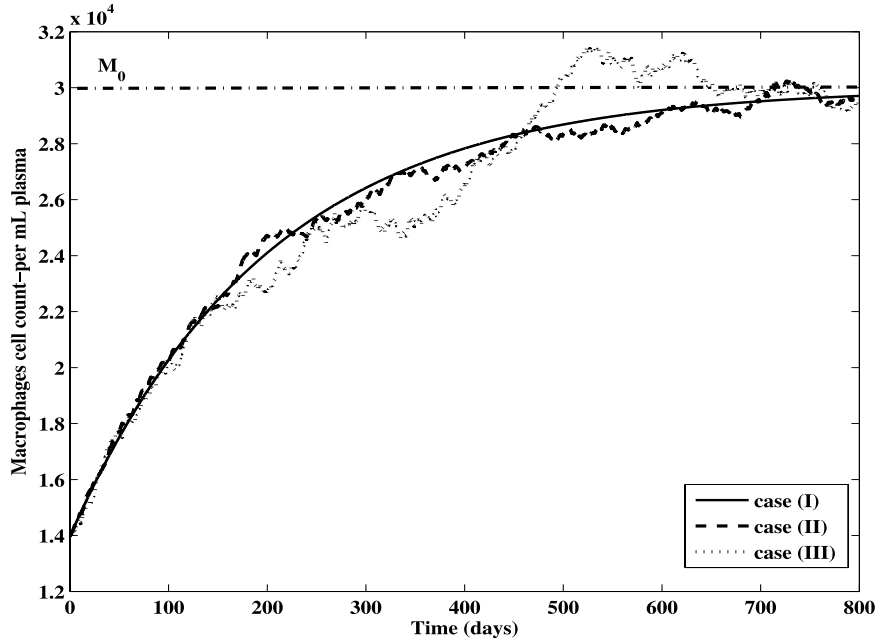

Fig. 4. The evolution of uninfected macrophages under robust MPC for cases (I)–(III).

recover with some fluctuations due to the presence of disturbances. From Fig. 3 and 5, we can see that the number of latently infected $CD4^+$ T cells, actively infected $CD4^+$ T cells, and infected macrophages are decaying during the treatment. Fig. 6 shows that, after initiation of HAART, the viral load drops quickly and it can be kept under a suitable level, with a small controller, corresponding to rather mild dosage of HAART. The model predictive controller as a function of the time for case (II) is shown in Fig. 7. It is observed that, the treatment is initiated with a stronger dosage of HAART, and sequentially decreasing over time. Thus we can say that, when the multirate MPC strategy is applied in the presence of bounded disturbances, the trajectory of the system tends to a ball around the uninfected steady state E_0 and remains there (i.e., practical stability). We observe that, for the disturbance-free (I), the size of the ball is very small due to small

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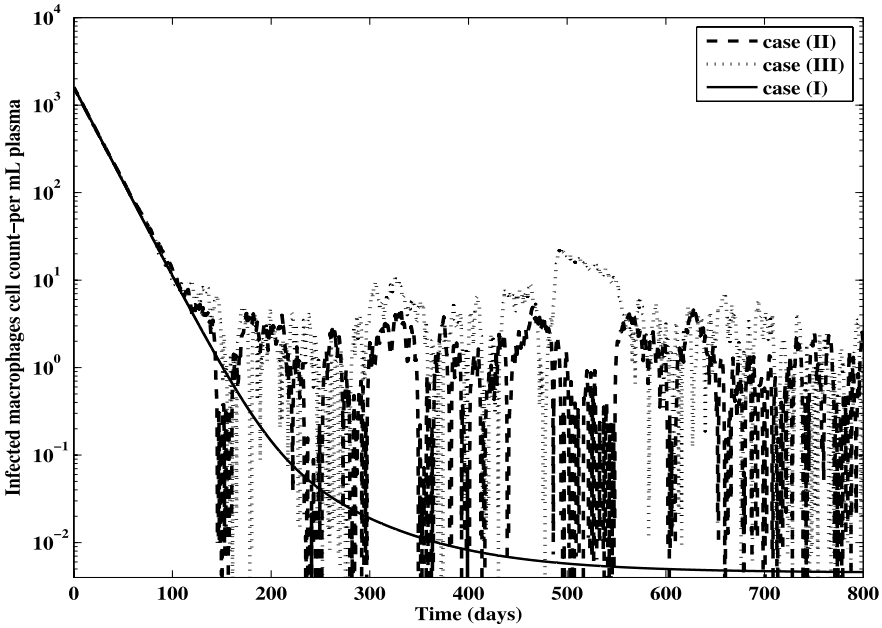

Fig. 5. The evolution of infected macrophages under robust MPC for cases (I)–(III).

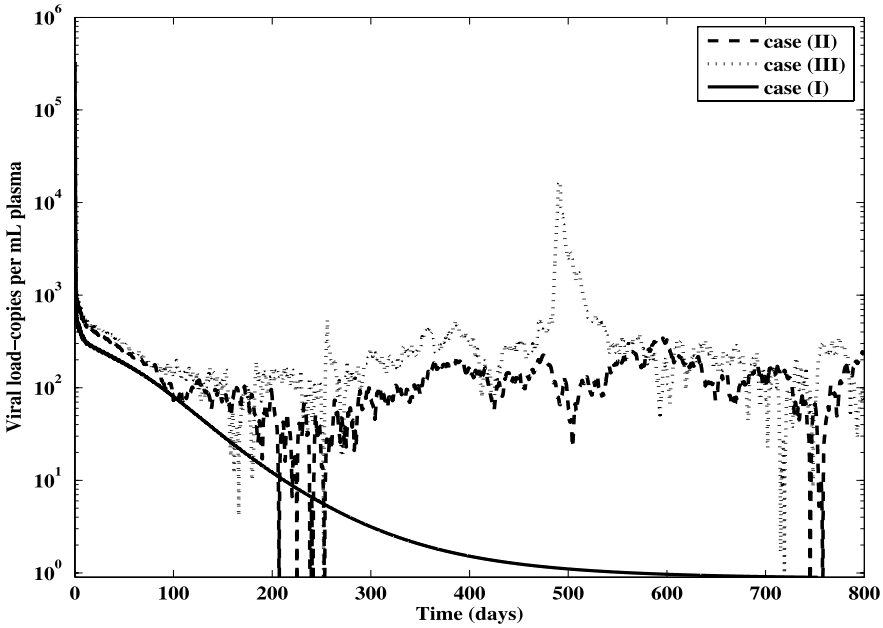

Fig. 6. The evolution of free viruses under robust MPC for cases (I)–(III).

numerical errors. For cases (II) and (III), the size of the ball becomes larger and larger by increasing the bounds of the disturbances.

6. Conclusion

The basic properties of the 6-dimensional HIV model incorporating to allow some additive disturbances were studied. The stabilizing property of multirate MPC for nonlinear systems with additive disturbances via approximate discrete-time model of the nominal system was proved. Highly Active AntiRetroviral Therapy (HAART) is used. The control input is defined to be dependent on the drug dose and drug efficiency. The proposed MPC method is applied for determining HAART

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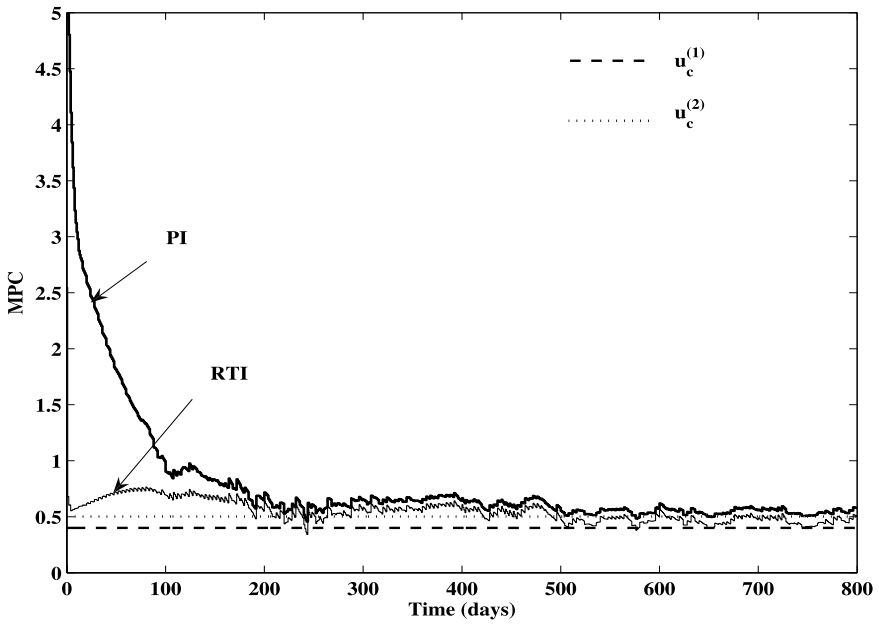

Fig. 7. Robust MPC for case (II).

schedules and stabilizing the HIV system around the uninfected steady state. The results of simulations show that the proposed method can effectively be applied to eliminate some drawbacks of the approaches previously published in the literature.

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