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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. 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. Besides model inaccuracies that HIV models suffer from, some disturbances/uncertainties from different sources may arise in the modelling. 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 a 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 drop 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.

Keywords: Robust MPC, HIV/AIDS, Feedback stabilization, Sampled-data systems

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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/mm³ of plasma, the HIV infected patient is regarded as an AIDS patient.

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 ([12], [22], [26], [8], [21], [1], [25] and [36]), 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 sources 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]].

In the last few years, model predictive control (MPC) method is developed for determining optimal treatment schedules for HIV patients ([35], [10], [11], [37], [18], and [15]). 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. [13], [2] and [27]).

In [37], 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 [23]). Alternatively, the optimal control problems can be solved by continuously varying drug levels in [35]. However, continuous-time variation of the dose seems hard to apply in the clinical treatment of patients. In [10] and [11], 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 ($i\tau$, $i = 0, 1, \dots$). A possible solution of this problem is to design a multirate version of MPC, where the measurements is needed every τ samplings ($i\tau$), $i = 0, 1, \dots$) (see [15] and [16]). In [35] and [37], it is shown only by simulation that the applied MPC have a certain degree of robustness to measurements and modeling errors.

The aim of the present paper is to develop a 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 a 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. [29], [28] and [14]), 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 [37], 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 detectability 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 et 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 [32]. 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 [33] and [7]). Models used in ([35], [10], [11], [37] and [15]) 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 [31], 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 drop 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 [14] and [9]. 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.

2. HIV model:

We shall use the mathematical model of HIV infection proposed by ([33] and [7]), incorporating to allow some additive disturbances. This model describes two co-circulation population 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 [17]. After initiation of HAART which consists of RTI and PI drugs the model can be written as:

$$\dot{T} = s_1 - d_1 T - \beta_1 TV + w_1 \quad (1)$$

$$\dot{T}_1 = q_1 e^{-u_1} \beta_1 TV - k_1 T_1 - \mu_1 T_1 + w_2 \quad (2)$$

$$\dot{T}_2 = q_2 e^{-u_1} \beta_1 TV + k_1 T_1 - \mu_2 T_2 + w_3 \quad (3)$$

$$\dot{M} = s_2 - d_2 M - \beta_2 MV + w_4 \quad (4)$$

$$\dot{M}_1 = q_M e^{-u_1} \beta_2 MV - \delta M_1 + w_5 \quad (5)$$

$$\dot{V} = e^{-u_2} p_1 T_2 + e^{-u_2} p_2 M_1 - cV + w_6 \quad (6)$$

The state variables describes the plasma concentrations of: T_1 , 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 articles.

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. Equation (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. Equation (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 equation (5), q_M is the probability of successful 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 ([38], [39], [20] and [40]). The effect of the RTI and PI drugs are represented by the chemotherapy functions $e^{-\alpha_1 m_1(t)}$ and $e^{-\alpha_2 m_2(t)}$ where α_1 and α_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 $u_i(t) = \alpha_i m_i(t)$, $i = 1, 2$.

In equations (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

$$\|w_i(t)\| \leq \varepsilon_i, \quad i = 1, \dots, 6$$

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

2.1. Positive Invariance:

Now we show that under which conditions the nonnegative orthant R_+^6 is positively invariant for (1)-6):

$$\begin{aligned} \dot{T} \Big|_{(T=0)} = s_1 + w_1 \geq 0 & \quad \text{if} \quad w_1 \geq -s_1, \\ \dot{T}_1 \Big|_{(T_1=0)} = q_1 e^{-u_1} \beta_1 TV + w_2 \geq 0 & \quad \text{if} \quad w_2 \geq -q_1 e^{-u_1} \beta_1 TV, \\ \dot{T}_2 \Big|_{(T_2=0)} = q_2 e^{-u_1} \beta_1 TV + k_1 T_1 + w_3 \geq 0 & \quad \text{if} \quad w_3 \geq -q_2 e^{-u_1} \beta_1 TV - k_1 T_1, \\ \dot{M} \Big|_{(M=0)} = s_2 + w_4 \geq 0 & \quad \text{if} \quad w_4 \geq -s_2, \\ \dot{M}_1 \Big|_{(M_1=0)} = q_2 e^{-u_1} \beta_2 MV + w_5 \geq 0 & \quad \text{if} \quad w_5 \geq -q_2 e^{-u_1} \beta_2 MV, \\ \dot{V} \Big|_{(V=0)} = e^{-u_2} p_1 T_2 + e^{-u_2} p_2 M_1 + w_6 \geq 0 & \quad \text{if} \quad w_6 \geq -e^{-u_2} p_1 T_2 - e^{-u_2} p_2 M_1, \end{aligned} \quad (7)$$

with $(T, T_1, T_2, M, M_1, V) \geq 0$. This means that under the above conditions the nonnegative orthant R_+^6 is positively invariant, namely, if a trajectory starts in the nonnegative orthant, it remains there. We note that, the lower bound of the disturbances has to satisfy the conditions in (7) only at the the boundary of R_+^6 .

Proposition 1 If $q_1 + q_2 \leq 1$ and $q_M \leq 1$, then there exists such positive numbers L_1, L_2

and L_3 that the compact set

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

is positively invariant.

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

$$\dot{T}_{tot} = s_1 + w_1 + w_2 + w_3 - d_1 T - \mu_1 T_1 - \mu_2 T_2$$

$$\leq s_1 + \varepsilon_1 + \varepsilon_2 + \varepsilon_3 - \sigma_1 T_{tot},$$

$$\dot{M}_{tot} = s_2 + w_4 + w_5 - d_2 M - \delta M_1$$

$$\leq s_2 + \varepsilon_4 + \varepsilon_5 - \sigma_2 M_{tot},$$

where $\sigma_1 = \min\{d_1, \mu_1, \mu_2\}$ and $\sigma_2 = \min\{d_2, \delta\}$. Hence $0 \leq T_{tot}(t) \leq L_1$ for all $t \geq 0$ if $T_{tot}(0) \leq L_1$, and $0 \leq M_{tot}(t) \leq L_2$ for all $M_{tot}(0) \leq L_2$, where $L_1 = (s_1 + \varepsilon_1 + \varepsilon_2 + \varepsilon_3) / \sigma_1$, $L_2 = (s_2 + \varepsilon_4 + \varepsilon_5) / \sigma_2$. It follows that $0 \leq T(t), T_1(t), T_2(t) \leq L_1$ and $0 \leq M(t), M_1(t) \leq L_2$ for all $t \geq 0$ if $T(0), T_1(0), T_2(0) \leq L_1$ and $M(0), M_1(0) \leq L_2$. On the other hand,

$$\dot{V}(t) \leq p_1 L_1 + p_2 L_2 - cV(t) + \varepsilon_6,$$

then $0 \leq V(t) \leq L_3$ for all $t \geq 0$ if $V(0) \leq L_3$ where $L_3 = (p_1 L_1 + p_2 L_2 + \varepsilon_6) / c$.

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 $w_i(t) = 0$, $i = 1, 2, \dots, 6$, $t \geq 0$.

A steady state (T, T_1, T_2, M, M_1, V) satisfies

$$s_1 - d_1 T - \beta_1 TV + w_1 = 0, \tag{8}$$

$$q_1 e^{-\bar{u}_1} \beta_1 TV - k_1 T_1 - \mu_1 T_1 + w_2 = 0, \tag{9}$$

$$q_2 e^{-\bar{u}_1} \beta_1 TV + k_1 T_1 - \mu_2 T_2 + w_3 = 0, \tag{10}$$

$$s_2 - d_2 M - \beta_2 MV + w_4 = 0, \tag{11}$$

$$q_M e^{-\bar{u}_1} \beta_2 MV - \delta M_1 + w_5 = 0, \tag{12}$$

$$e^{-\bar{u}_2} p_1 T_2 + e^{-\bar{u}_2} p_2 M_1 - cV + w_6 = 0. \tag{13}$$

Solving T_1, T_2 and M_1 from equations (9), (10) and (12) in terms of TV and/or MV and inserting them into (13) we obtain

$$(a_4 T + a_5 M - c)V = 0 \tag{14}$$

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

The first solution of (14) is $V = 0$. Then substituting it in (8)-(12), we obtain the uninfected steady state $E_0 = (T_0, 0, 0, M_0, 0, 0)$ where $T_0 = s_1/d_1$ and $M_0 = s_2/d_2$. If $V \neq 0$, then

$$a_4T + a_5M - c = 0 \quad (15)$$

and by eliminating V from equations (8) and (10) we obtain

$$a_3T - a_2TM - a_1M = 0 \quad (16)$$

where $a_1 = s_1\beta_2$, $a_2 = \beta_1d_2 - \beta_2d_1$, $a_3 = s_2\beta_1$.

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.

If $a_2 = 0$ then the solutions of (15) and (16) are given by

$$T_0^* = \frac{a_1c}{a_1a_4 + a_3a_5}, \quad M_0^* = \frac{a_3c}{a_1a_4 + a_3a_5}.$$

If $a_2 \neq 0$, there are two possible solutions for (15) and (16)

$$T_+^* = \frac{-(a_1a_4 + a_3a_5 - a_2c) + \sqrt{(a_1a_4 + a_3a_5 - a_2c)^2 + 4a_1a_2a_4c}}{2a_2a_4},$$

$$M_+^* = \frac{1}{a_5}(c - a_4T_+^*),$$

$$T_-^* = \frac{-(a_1a_4 + a_3a_5 - a_2c) - \sqrt{(a_1a_4 + a_3a_5 - a_2c)^2 + 4a_1a_2a_4c}}{2a_2a_4},$$

$$M_-^* = \frac{1}{a_5}(c - a_4T_-^*).$$

Now we have to determine the positive solutions. First, we show that the discriminate

$\Delta = (a_1a_4 + a_3a_5 - a_2c)^2 + 4a_1a_2a_4c$, is positive

if $a_2 > 0$, $\Delta = (a_1a_4 + a_3a_5 - a_2c)^2 + 4a_1a_2a_4c > 0$,

if $a_2 < 0$, $\Delta = (a_1a_4 + a_3a_5 + a_2c)^2 - 4a_2a_3a_5c > 0$,

it follows that if $a_2 > 0$, then

$$T_+^* = \frac{-(a_1a_4 + a_3a_5 - a_2c) + \sqrt{(a_1a_4 + a_3a_5 - a_2c)^2 + 4a_1a_2a_4c}}{2a_2a_4} > 0,$$

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

$$T_+^* = \frac{(a_1a_4 + a_3a_5 + \bar{a}_2c) - \sqrt{(a_1a_4 + a_3a_5 + \bar{a}_2c)^2 - 4a_1\bar{a}_2a_4c}}{2\bar{a}_2a_4} > 0,$$

Similarity, it is easy to see that

$$\begin{aligned}
 a_2 > 0 &\Rightarrow T_+^* > 0, \text{ and } M_+^* > 0, \\
 a_2 < 0 &\Rightarrow T_+^* > 0, \text{ and } M_+^* > 0, \\
 a_2 > 0 &\Rightarrow T_-^* < 0, \text{ and } M_-^* > 0, \\
 a_2 < 0 &\Rightarrow T_-^* > 0, \text{ and } M_-^* < 0.
 \end{aligned}$$

Then, the only positive solutions are $T^* = T_+^*$ and $M^* = M_+^*$. Substituting them in Eqs. (8)-(12), we obtain the infected steady state which is given by $E_1 = (T^*, T_1^*, T_2^*, M^*, M_1^*, V^*)$ where

$$\begin{aligned}
 T^* &= \begin{cases} T_0^*, & \text{if } a_2 = 0 \\ T_+^*, & \text{if } a_2 \neq 0 \end{cases}, & M^* &= \begin{cases} M_0^*, & \text{if } a_2 = 0 \\ M_+^*, & \text{if } a_2 \neq 0 \end{cases}, \\
 T_1^* &= \frac{q_1 e^{-\bar{u}_1} d_1}{k_1 + \mu_1} \left(\frac{T_0}{T^*} - 1 \right) T^*, & T_2^* &= \frac{\bar{q} e^{-\bar{u}_1} d_1}{\mu_2 (k_1 + \mu_1)} \left(\frac{T_0}{T^*} - 1 \right) T^*, \\
 M_1^* &= \frac{q_M e^{-\bar{u}_1} d_2}{\delta} \left(\frac{M_0}{M^*} - 1 \right) M^*, & V^* &= \frac{d_1}{\beta_1} \left(\frac{T_0}{T^*} - 1 \right)
 \end{aligned} \tag{17}$$

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

Let us define

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

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

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

$$T^* = \frac{A_1}{R_0^c} - B_1 + \sqrt{\left(B_1 - \frac{A_1}{R_0^c} \right)^2 + \frac{2a_1 A_1}{a_2 R_0^c}}, \text{ if } a_2 > 0, \tag{18}$$

$$T^* = \frac{A_1}{R_0^c} + \bar{B}_1 - \sqrt{\left(\bar{B}_1 + \frac{A_1}{R_0^c} \right)^2 - \frac{2a_1 A_1}{\bar{a}_2 R_0^c}}, \text{ if } a_2 < 0, \tag{19}$$

$$T^* = \frac{T_0}{R_0^c} \text{ if } a_2 = 0, \tag{20}$$

$$M^* = \frac{A_2}{R_0^c} + B_2 - \sqrt{\left(\frac{A_2}{R_0^c} + B_2 \right)^2 - \frac{2a_3 A_2}{a_2 R_0^c}}, \text{ if } a_2 > 0, \tag{21}$$

$$M^* = \frac{A_2}{R_0^c} - \bar{B}_2 + \sqrt{\left(\bar{B}_2 - \frac{A_2}{R_0^c}\right)^2 + \frac{2a_3 A_2}{\bar{a}_2 R_0^c}}, \quad \text{if } a_2 < 0, \quad (22)$$

$$M^* = \frac{M_0}{R_0^c} \quad \text{if } a_2 = 0, \quad (23)$$

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

$$A_1 = \frac{1}{2}T_0 + \frac{p_2\beta_2 M_0 q_M (k_1 + \mu_1)\mu_2}{2p_1\delta\beta_1\bar{q}}, \quad B_1 = \frac{\beta_2}{2a_2} \left[T_0 d_1 + \frac{p_2 M_0 q_M d_2 (k_1 + \mu_1)\mu_2}{p_1\delta\bar{q}} \right],$$

$$A_2 = \frac{1}{2}M_0 + \frac{p_1\beta_1 T_0 \delta\bar{q}}{2p_2\beta_2 q_M (k_1 + \mu_1)\mu_2}, \quad B_2 = \frac{\beta_1}{2a_2} \left[M_0 d_2 + \frac{p_1 d_1 T_0 \delta\bar{q}}{p_2 q_M (k_1 + \mu_1)\mu_2} \right].$$

From equations (18)-(23), 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 $M^* = M_0$. Equations (18), (19), (21) and (22) can be simplified to the following

$$\begin{aligned} T^* &= A_1 - B_1 + \sqrt{\left(\frac{T_0\beta_1 d_2}{2a_2} + \frac{\beta_2^2 d_1 M_0 p_2 q_M (k_1 + \mu_1)\mu_2}{2a_2 p_1 \beta_1 \delta\bar{q}}\right)^2}, \\ &= A_1 - B_1 + \sqrt{(B_1 + T_0 - A_1)^2} = T_0 \quad a_2 > 0, \end{aligned}$$

$$\begin{aligned} T^* &= A_1 + \bar{B}_1 - \sqrt{\left(\frac{T_0\beta_1 d_2}{2\bar{a}_2} + \frac{\beta_2^2 d_1 M_0 p_2 q_M (k_1 + \mu_1)\mu_2}{2\bar{a}_2 p_1 \beta_1 \delta\bar{q}}\right)^2}, \\ &= A_1 + \bar{B}_1 - \sqrt{(A_1 + \bar{B}_1 - T_0)^2} = T_0 \quad a_2 < 0, \end{aligned}$$

$$\begin{aligned} M^* &= A_2 + B_2 - \sqrt{\left(\frac{M_0\beta_2 d_1}{2a_2} + \frac{\beta_1^2 d_2 T_0 p_1 \delta\bar{q}}{2a_2 p_2 \beta_2 q_M (k_1 + \mu_1)\mu_2}\right)^2}, \\ &= A_2 + B_2 - \sqrt{(A_2 + B_2 - M_0)^2} = M_0 \quad a_2 > 0, \end{aligned}$$

$$\begin{aligned} M^* &= A_2 - \bar{B}_2 + \sqrt{\left(\frac{M_0\beta_2 d_1}{2\bar{a}_2} + \frac{\beta_1^2 d_2 T_0 p_1 \delta\bar{q}}{2\bar{a}_2 p_2 \beta_2 q_M (k_1 + \mu_1)\mu_2}\right)^2}, \\ &= A_2 - \bar{B}_2 + \sqrt{(\bar{B}_2 - A_2 + M_0)^2} = M_0 \quad a_2 < 0. \end{aligned}$$

From the above analysis we obtain the following:

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

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

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

Now assume that the steady state E_1 exists then $T_1^*, T_2^*, M_1^*, V^* > 0$, from (17) we obtain $T^* < T_0$ and $M^* < M_0$. It follows from (18)-(23) that $R_0^c > 1$.

2.3. Local stability of E_0 :

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

Proof. Let us linearized the nominal system (1)-(6) with constant controllers around E_0 .

The coefficient matrix is

$$J = \begin{bmatrix} -d_1 & 0 & 0 & 0 & 0 & -T_0\beta_1 \\ 0 & -k_1 - \mu_1 & 0 & 0 & 0 & q_1 e^{-\bar{u}_1} T_0 \beta_1 \\ 0 & k_1 & -\mu_2 & 0 & 0 & q_2 e^{-\bar{u}_1} T_0 \beta_1 \\ 0 & 0 & 0 & -d_2 & 0 & -M_0 \beta_2 \\ 0 & 0 & 0 & 0 & -\delta & q_M e^{-\bar{u}_1} M_0 \beta_2 \\ 0 & 0 & p_1 e^{-\bar{u}_2} & 0 & p_2 e^{-\bar{u}_2} & -c \end{bmatrix}$$

The characteristic equation is given by:

$$\text{Det}(J - \lambda I) = (\lambda + d_1)(\lambda + d_2)(\lambda^4 + b_3\lambda^3 + b_2\lambda^2 + b_1\lambda + b_0) = 0,$$

where,

$$b_0 = -\{p_1\beta_1 T_0 \delta \bar{q} + p_2\beta_2 M_0 q_M (k_1 + \mu_1)\mu_2\} e^{-(\bar{u}_1 + \bar{u}_2)} + c\delta (k_1 + \mu_1)\mu_2 \\ = c\delta (k_1 + \mu_1)\mu_2 (1 - R_0^c),$$

$$b_1 = -\{p_1\beta_1 T_0 (\bar{q} + \delta q_2) + p_2\beta_2 M_0 q_M (k_1 + \mu_1 + \mu_2)\} e^{-(\bar{u}_1 + \bar{u}_2)} + c\delta (k_1 + \mu_1 + \mu_2) \\ + \mu_2 (c + \delta)(k_1 + \mu_1),$$

$$b_2 = -\{p_1\beta_1 T_0 q_2 + p_2\beta_2 M_0 q_M\} e^{-(\bar{u}_1 + \bar{u}_2)} + \delta (k_1 + \mu_1) + \mu_2 (\delta + k_1 + \mu_1) + c(\delta + k_1 + \mu_1 + \mu_2),$$

$$b_3 = c + \delta + k_1 + \mu_1 + \mu_2.$$

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

$$b_1 > \delta \mu_2 (k_1 + \mu_1) > 0$$

$$b_2 > \delta (k_1 + \mu_1) + \mu_2 (\delta + k_1 + \mu_1) + c(k_1 + \mu_1) > 0.$$

Moreover, the Routh-Hurwitz criteria holds. Then, E_0 is locally asymptotically stable.

Remark 1 For the parameters given in Table 2, we can see that, when there is no treatment, $R_0^c \Big|_{(\bar{u}_1 = \bar{u}_2 = 0)} = 2.46493$, 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 has a negative real part, this means that E_1 is locally asymptotically stable.

2.4. Global stability of E_0

Theorem 2 If $R_0^c \leq 1$, then E_0 globally asymptotically stable for the nominal system.

Proof By the method of Korobeinikov [24], we define a Lyapunov function for the nominal system

$$W(T, T_1, T_2, M, M_1, V) = \gamma_1 T_0 \left[\frac{T}{T_0} - \ln \left(\frac{T}{T_0} \right) - 1 \right] + \gamma_2 M_0 \left[\frac{M}{M_0} - \ln \left(\frac{M}{M_0} \right) - 1 \right] + \gamma_3 T_1 + \gamma_4 T_2 + \gamma_5 M_1 + \gamma_6 V$$

with,

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

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

$$\frac{dW}{dt} = \gamma_1 s_1 \left[2 - \frac{T}{T_0} - \frac{T_0}{T} \right] + \gamma_2 s_2 \left[2 - \frac{M}{M_0} - \frac{M_0}{M} \right] + \gamma_6 c (R_0^c - 1) V. \quad (24)$$

Since the arithmetical mean is greater than or equal to the geometrical mean, then the first two terms of (24) are less than or equal to zero. Therefore, if $R_0^c \leq 1$ then $dW/dt \leq 0$ for all $T, M, V > 0$.

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

$$R_0^c(\bar{u}_1, \bar{u}_2) = R_T^c + R_M^c, \\ R_T^c = \frac{p_1 \beta_1 s_1 \bar{q} e^{-(\bar{u}_1 + \bar{u}_2)}}{c d_1 (k_1 + \mu_1) \mu_2}, \quad R_M^c = \frac{p_2 \beta_2 s_2 q_M e^{-(\bar{u}_1 + \bar{u}_2)}}{c \delta d_2}.$$

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 consider only the four dimensional model (1)-(3) and (6) and design 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 2. The nominal system (1)-(6) is globally asymptotically controllable to E_0 with piecewise constant controllers.

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

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

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

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. $V_{\text{sup}} = 50$ copies mL^{-1}) is given by

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

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 [31]).

2.5 Sensitivity analysis of the infected steady state

As we have shown in Remark 1 that in the absence of treatment the infected steady state E_1 is stable. Our aim is to design a treatment schedule to steer the system state near to the uninfected steady state E_0 (i.e., to shift E_1 near to E_0). Therefore, it is desirable to predict how changes in the parameters will affect the infected steady state. Let x_i^* , $i = 1, \dots, 6$, denote the infected steady state, then the sensitivity of x_i^* to parameters r_k , $k = 1, 2, \dots, p$, is given by $\partial x_i^* / \partial r_k$. This is given in Table 1. For the parameters given in Table 2, we can see that the infected steady state is more sensitive to the parameters β_1, β_2, d_1 and d_2 while it is less sensitive to the parameters s_1 , and s_2 .

Table (1). Ranked sensitivety of infected steady state to parameters.

x_i^*	r_i	$\frac{\partial x_i^*}{\partial r_i}$	x_i^*	r_i	$\frac{\partial x_i^*}{\partial r_i}$	x_i^*	r_i	$\frac{\partial x_i^*}{\partial r_i}$
T^*	β_1	8.86×10^{12}	T^*	μ_1	7.22×10^4	M^*	k_1	894.8
V^*	β_1	4.79×10^{12}	T_1^*	d_1	5.7×10^4	T_2^*	k_1	806.18
V^*	β_2	5.03×10^{11}	M_1^*	d_1	4.9×10^4	V^*	p_2	539.84
M^*	β_2	4.38×10^{11}	V^*	k_1	3.93×10^4	M^*	q_M	429.94
T^*	β_2	3.69×10^{11}	M_1^*	δ	3.29×10^4	T_1^*	δ	396.2
M^*	β_1	1.09×10^{11}	T^*	k_1	2.89×10^4	T^*	p_2	396.2
T_2^*	β_1	9.81×10^{10}	T_1^*	μ_1	2.44×10^4	M_1^*	c	251.31
M_1^*	β_2	4.38×10^{10}	T_1^*	k_1	2.43×10^4	M_1^*	μ_1	223.7
T_1^*	β_1	1.27×10^{10}	M^*	μ_2	2.43×10^4	T_2^*	q_M	153.53
M_1^*	β_1	1.09×10^{10}	T_2^*	μ_2	2.19×10^4	V^*	s_2	125.96
T_2^*	β_2	4.08×10^9	M^*	q_2	2.19×10^4	T_1^*	c	115.8
T_1	β_2	5.27×10^8	T_2^*	q_2	1.98×10^4	T^*	s_2	92.45
V^*	d_1	2.15×10^7	V^*	q_M	1.89×10^4	M^*	s_2	90.23
V^*	d_2	1.76×10^6	M^*	q_1	1.57×10^4	M_1^*	k_1	89.48
T^*	d_2	1.29×10^6	T_2^*	d_2	1.43×10^4	V^*	s_1	53.33
M^*	d_2	1.26×10^6	T^*	q_3	1.39×10^4	M^*	p_1	50.57
V^*	μ_2	1.06×10^6	T_2^*	q_1	1.14×10^4	T_1^*	q_M	19.81
V^*	q_2	9.63×10^5	M^*	δ	8.6×10^3	T_2^*	p_1	18.06
T^*	μ_2	7.83×10^5	T_2^*	δ	3.07×10^3	M^*	p_2	12.3
T^*	q_2	7.07×10^5	M_1^*	μ_2	2.43×10^3	M_1^*	s_2	10.98
V^*	q_1	6.88×10^5	M^*	c	2.25×10^3	M_1^*	p_1	5.06
T^*	q_1	5.05×10^5	M^*	μ_1	2.24×10^3	T_2^*	p_2	4.39
T^*	d_1	5.02×10^5	V^*	p_1	2.22×10^3	T_1^*	p_1	2.33
M^*	d_1	4.9×10^5	M_1^*	q_2	2.19×10^3	T^*	s_1	1.42
T_2^*	d_1	4.42×10^5	T_2^*	μ_1	2.02×10^3	M_1^*	p_2	1.23
V^*	δ	3.78×10^5	T_1^*	d_2	1.84×10^3	M^*	s_1	1.21
T^*	δ	2.77×10^5	M_1^*	q_M	1.65×10^3	T_2^*	s_1	1.09
T_1^*	q_1	1.71×10^5	T^*	p_1	1.63×10^3	T_2^*	s_2	1.02
M_1^*	d_2	1.53×10^5	M_1^*	q_1	1.57×10^3	T_1^*	p_2	0.57
V^*	c	1.1×10^5	T_1^*	μ_2	1.12×10^3	T_1^*	s_1	0.14
V^*	μ_1	9.83×10^4	T_1^*	q_2	1.01×10^3	T_1^*	s_2	0.13
T^*	c	8.1×10^4	T_2^*	c	897.42	M_2	s_1	0.12

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 [14] and [9]. 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 can not 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 [9], when both the state space of the system and the control constraint set are restricted to compact sets.

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

$$\dot{z}(t) = f(z(t), u(t)) + w(t), \quad z(0) = z_0 \quad (25)$$

where $z(t) \in \mathbf{R}^n$, $u(t) \in U \subset \mathbf{R}^m$, $w(t) \in W \subset \mathbf{R}^p$ are the state, control input and disturbances, respectively, $f: \mathbf{R}^n \times U \rightarrow \mathbf{R}^n$ 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 $0 \in W$. In what follows, the notation $B_\Delta = \{z \in \mathbf{R}^l : \|z\| \leq \Delta\}$ will be used in \mathbf{R}^n , \mathbf{R}^m and \mathbf{R}^p and K, K_∞ and KL denote the usual class- K , class- K_∞ and class- KL functions (see e.g. [29]).

The control is taken to be a piecewise constant signal

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

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

We shall assume that state measurements can be performed at the time instants, $i\tau$, $i = 0, 1, \dots$,

$$y_i := z(i\tau), \quad i = 0, 1, \dots,$$

where $\} is an integer which is fixed.$

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

$$W_\mu = \{w \in L_{[0, \infty)}^\infty : w(t) \in W \text{ a.e. } t \in [0, \infty) \text{ with } \|w\|_\infty \leq \mu\},$$

$$W_\}^p = \{\mathbf{w}^{(i)} = \{w_\tau[i], \dots, w_\tau[(i+1)] - 1\}, w \in W_\mu, i = 0, 1, \dots\}.$$

We shall assume that there is a compact set $X \subset \mathbf{R}^n$ containing the origin, which is positively invariant with respect to system (25) for any $w(\cdot) \in W$ and any piecewise constant controller $\bar{u} \in U$. Let $t \in [0, \tau] \cap \Phi^E(t; z, \bar{u}, \bar{w}(\cdot))$ denote the solution of (25) with given \bar{u} , \bar{w} and $z = z(0)$. Then the exact discrete-time model can be defined as

$$z_{i+1} = \tilde{F}_\tau^E(z_i, u_i, w_\tau[i]), \quad (26)$$

where $\tilde{F}_\tau^E(z, u, w_\tau) := \Phi^E(\tau, z, u, w_\tau)$.

Let $\mathbf{u}^{(i)} = \{u_0^{(i)}, \dots, u_{\}-1^{(i)}\}$, $\mathbf{w}^{(i)} = \{w_\tau[i], \dots, w_\tau[(i+1)] - 1\}$ and $\bar{F}_\}^E(\xi, \mathbf{u}, \mathbf{w}) = \Phi^E(\tau, \xi, \mathbf{u}, \mathbf{w})$, then the exact $\}$ -step discrete-time model is given by

$$\xi_{i+1}^E = \bar{F}_\}^E(\xi_i^E, \mathbf{u}^{(i)}, \mathbf{w}^{(i)}), \quad \xi_0^E = z_0 \quad (27)$$

We note that the exact discrete-time models (26) and (27) describe, respectively, the behavior of the system at the time instants $i\tau$ and $i\tau\}$, $i = 0, 1, \dots$.

In this work, the construction of multirate MPC is based on the nominal prediction and only small disturbances are allowed. The nominal system of (25) is given by

$$\dot{x}(t) = f(x(t), u(t)), \quad x(0) = z(0) \quad (28)$$

and its exact discrete-time model is given by

$$x_{i+1}^E = F_{\tau}^E(x_i^E, u_i), \quad (29)$$

We note that, since f is typically nonlinear, F_{τ}^E in (29) is not known in most cases, therefore the controller design can be carried out by means of the nominal approximate discrete-time model

$$x_{i+1}^A = F_{\tau,h}^A(x_i^A, u_i), \quad (30)$$

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) $F_{\tau,h}^A(0,0) = 0$, $F_{\tau,h}^A$ 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 $\gamma \in K$ such that

$$\|F_{\tau}^E(x, u) - F_{\tau,h}^A(x, u)\| \leq \tau\gamma(h),$$

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

Assumption A2 There exists an $h^* > 0$ such that the nominal exact discrete-time model (29) is practically asymptotically controllable from X to the origin with piecewise constant controllers for all $h \in (0, h^*]$ (See e.g. [14] for the definition).

For the solutions of (26), (29) and (30) with $\mathbf{u} = \{u_0, u_1, \dots\}$, $\mathbf{w} = \{w_{\tau}[0], w_{\tau}[1], \dots\}$, and x_0

we shall use the notations $\Phi^E(x_0, \mathbf{u}, \mathbf{w})$, $\phi_i^E(x_0, \mathbf{u})$ and $\phi_i^A(x_0, \mathbf{u})$, respectively.

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

$$\mathbf{v}_h : X \rightarrow \underbrace{U \times U \times \dots \times U}_{\text{ } \tau \text{ times}}, \quad \mathbf{v}_h(x) = \{u_0(x), \dots, u_{\tau-1}(x)\},$$

using the nominal approximate discrete-time model (30), to practically stabilize the exact discrete-time system (26).

Let $N \in \mathbf{N}$ with $N \geq \tau$ be given. Let (30) be subject to the cost function

$$J_{\tau,h}(N, x, \mathbf{u}) = \sum_{i=0}^{N-1} \tau l_h(x_i^A, u_i) + g(x_N^A), \quad (31)$$

$\mathbf{u} = \{u_0, \dots, u_{N-1}\}$, $x_i^A = \phi_i^A(x, \mathbf{u})$, $i = 0, 1, \dots, N$, l_h and g are given functions, satisfying the following assumptions.

Assumption A3 Let $X_1 = X + B_1$, (i) $g : X_1 \rightarrow \mathbf{R}$ is continous, 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- K_∞ functions ϕ_1 and ϕ_2 such that the inequality

$$\phi_1(\|x\|) \leq l_h(x, u) \leq \phi_2(\|x\|) + \phi_2(\|u\|),$$

holds for all $x \in X_1$, all $u \in U$ and $h \in (0, h^*]$.

Assumption A4 There exist $h^* > 0$ and $\eta > 0$ such that for all $x \in G_\eta = \{x : g(x) \leq \eta\}$ there exists a $\kappa(x) \in U$ such that inequality

$$\tau l_h(x, \kappa(x)) + g(F_{\tau, h}^A(x, \kappa(x))) \leq g(x) \quad (32)$$

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

We define the value function, which represents the optimal value of (31) for a given initial condition, as

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

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

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

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 $\|x\| \leq \Delta_x$, $\|u\| \leq \Delta_u$ if $x \in X$, $u \in U$.

Theorem 3 ([14]) If Assumptions A1-A4 hold true, then (i) there exist an h_1^* with $0 < h_1^* \leq h_0^*$, and a constant V_{\max}^A independent of N , such that $V_N(x) \leq V_{\max}^A$ for all $x \in X$, $h \in (0, h_1^*]$ and $N \in \mathbf{N}$,

(ii) there exist constants N^* , L_V and δ_V and functions $\sigma_1, \sigma_2 \in K_\infty$ such that for all $x \in X$, $N > N^*$, $h \in (0, h_1^*]$ and $i = 1, 2, \dots$,

$$\begin{aligned} \sigma_1(\|x\|) &\leq V_N(x) \leq \sigma_2(\|x\|) \\ V_N(\phi_i^A(x, \mathbf{v}_h(x))) - V_N(x) &\leq -\tau\phi_1(\|x\|), \end{aligned}$$

Moreover, for all $x, y \in X_1$ with $\|x - y\| \leq \delta_V$

$$|V_N(x) - V_N(y)| \leq L_V \|x - y\|,$$

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

Clearly $X \subset \{x : V_N(x) \leq V_{\max}^A\}$.

Theorem 4 Suppose that Assumptions A1-A4 are valid and N is chosen such that $N \geq N^*$. Then, there exist $\beta \in KL$, $\theta \in K_\infty$, $\mu^* > 0$ and for any $\delta > 0$ there exists an $h^* > 0$ such that for any $x_0 \in X$ and $h \in (0, h^*]$ the trajectory of the N -step exact discrete-time system

$$\xi_{i+1}^E = \bar{F}_\gamma^E(\xi_i^E, \mathbf{v}_h(\xi_i^E), \mathbf{w}^{(i)}), \quad \xi_0^E = x_0 \quad (33)$$

with the γ -step MPC \mathbf{v}_h and $\mathbf{w}^{(i)} \in W_\gamma^{\mu^*}$ satisfies

$$\|\xi_i^E\| \leq \beta(\|x_0\|, i)\tau + \theta(\mu^*) + \delta, \quad i \geq 0.$$

Proof. The proof can follow the same line as that of Theorem 2 in [9] and Theorem III.1 in [30] with small modifications due to the the global character of the statement (in the sense that the whole state space X belongs to the basin of attraction). Moreover, because of our assumptions of the positive invariance of X , we know that $\xi_i^E \in X$ if $\xi_0^E = x_0 \in X$. Thus, we give only a short outline of the proof. Let L_f 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

$$\|\Phi_i^E(x_0, \mathbf{v}_h, \mathbf{w}^{(0)}) - \phi_i^A(x_0, \mathbf{v}_h)\| \leq \bar{\gamma}(h) + L\mu, \quad i = 0, 1, \dots, \gamma,$$

for all $x_0 \in X$, $\mathbf{w}^{(0)} \in W_\gamma^\mu$ and $h \in (0, h_2^*]$, where, $\bar{\gamma}(h) = \tau\gamma(h) \frac{e^{L_f\tau} - 1}{e^{L_f\tau} - 1}$,

$L = \tau e^{L_f\tau} \frac{e^{L_f\tau} - 1}{e^{L_f\tau} - 1}$. Let $\nu > 0$ be an arbitrary number. Let σ_1 and σ_2 be given in Theorem 3 and let $\delta_1 = \sigma_2^{-1}(\nu/4)$ and $\hat{L} = 2LL_\nu$. Let $h_3^* > 0$ and μ_1 be such that inequalities

$$\bar{\gamma}(h) < \min\left\{\frac{\nu}{4L_\nu}, \frac{\tau\phi_1(\delta_1)}{4L_\nu}, \frac{\delta_\nu}{4}\right\}, \quad \mu_1 < \min\left\{\frac{\tau\phi_1(\delta_1)}{\hat{L}}, \frac{3\delta_\nu}{4}\right\}$$

hold true for all $h \in (0, h_3^*]$. Let $h^* = \min\{h_1^*, h_2^*, h_3^*\}$ and $\mu^* = \min\{\mu, \mu_1\}$ and choose $d = \hat{L}\mu^* + \nu$. Using Theorem 3 and the definition of d , one can show in the same way as in [9] that if $\xi_k^E \in X$ and either $V_N(\xi_{k+1}^E) \geq d/2$ or $V_N(\xi_k^E) \geq d$ hold true, then

$$V_N(\xi_{k+1}^E) - V_N(\xi_k^E) \leq -\frac{\tau}{4}\phi_1(\|\xi_k^E\|) \quad (34)$$

The construction of a suitable KL function is standard (see e.g. [29]).

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 (25) with

$$f(z, u) = \begin{pmatrix} s_1 - d_1(z_1 + T_0) - \beta_1(z_1 + T_0)z_6 \\ q_1 e^{-\bar{u}_1} \beta_1(z_1 + T_0)z_6 - k_1 z_2 - \mu_1 z_2 \\ q_2 e^{-\bar{u}_1} \beta_1(z_1 + T_0)z_6 + k_1 z_2 - \mu_2 z_3 \\ s_2 - d_2 M - \beta_2(z_4 + M_0)z_6 \\ q_2 e^{-\bar{u}_1} \beta_2(z_4 + M_0)z_6 - \delta z_5 \\ e^{-\bar{u}_2} p_1 z_3 + e^{-\bar{u}_2} p_2 z_5 - c z_6 \end{pmatrix}, \quad (35)$$

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

Let the compact set X be defined as

$$X = \left\{ z \in \mathbf{R}^6 : -T_0 \leq z_1 \leq L_1 - T_0, 0 \leq z_2, z_3 \leq L_1, -M_0 \leq z_4 \leq L_2 - M_0, \right. \\ \left. 0 \leq z_5 \leq L_2, 0 \leq z_6 \leq L_3 \right\},$$

where L_1, L_2 and L_3 are in Proposition 1.

With this definition, f satisfies all regularity assumptions, and according to Proposition 1, X is positively invariant if $q_1 + q_2 \leq 1$ and $q_M \leq 1$. In what follows, we assume that $q_1 + q_2 \leq 1$ and $q_M \leq 1$. Moreover, we consider both the controller and disturbances are taken from compact sets.

To verify Assumptions A3 and A4, we linearized the nominal system (35) 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 2. 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:

$$x(k+1) = e^{A_c \tau} x(k) \quad (36)$$

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:

$$l_h(x, u) = 0.01 x' Q x + 1000(u_1 - u_c^{(1)})^2 + 2000(u_2 - u_c^{(2)})^2, \quad (37)$$

$$g(x) = x' P x, \quad (38)$$

where P is a positive definite diagonal matrix given by

$$P = \text{diag}(0.001, 1, 1, 0.01, 0.1, 0.001)$$

and Q is a positive definite symmetric matrix satisfying the Lyapunov equation for the discrete-time system (36)

$$Q = -(A'_\tau P A_\tau - P), \quad A_\tau = e^{A_c \tau}.$$

From (37)-(38), Assumption A3 is satisfied. It has been verified numerically by solving a constrained minimization problem with several starting points that Assumption A4 is satisfied over the whole set X . Assumption A2 follows from Proposition 2 and Assumption A1 holds also true if we choose a suitable numerical integration scheme

(e.g. the Runge-Kutta formula). Thus all Assumptions of the proposed method can be satisfied with suitable choice of the parameters of the MPC method.

5. Numerical results:

We perform simulation studies using the parameter values taken from ([22], [34], [7] and [3]). These values are listed in Table 2.

Table (2): The values of the paramters in the HIV model and the system states at the initiation of the therapy

Parameter	Value	Variable	Value
s_1	$10^4 \text{ mL}^{-1} \text{ day}^{-1}$	T^*	$4.0385 \times 10^5 \text{ mL}^{-1}$
d_1	0.01 day^{-1}	T_1^*	$8.5 \times 10^2 \text{ mL}^{-1}$
β_1	$4.5 \times 10^{-8} \text{ mL day}^{-1}$	T_2^*	$6.6 \times 10^3 \text{ mL}^{-1}$
q_1	0.005	M^*	$1.398 \times 10^4 \text{ mL}^{-1}$
q_2	0.55	M_1^*	$1.61 \times 10^3 \text{ mL}^{-1}$
μ_1	0.01 day^{-1}	V^*	$3.28 \times 10^5 \text{ mL}^{-1}$
k_1	0.025 day^{-1}		
μ_2	0.5 day^{-1}		
p_1	$240 \text{ cell}^{-1} \text{ day}^{-1}$		
c	5 day^{-1}		
β_2	$1.75 \times 10^{-8} \text{ mL day}^{-1}$		
δ	0.05 day^{-1}		
p_2	$35 \text{ cell}^{-1} \text{ day}^{-1}$		
q_M	1		
s_2	$150 \text{ mL}^{-1} \text{ day}^{-1}$		
d_2	0.005 day^{-1}		

We assume that the treatment is initiated during the asymptomatic stage of infection as suggested by [19] (when the system is in the infected steady state E_1 , see Table 2).

We assume that the state measurements are performed at the instants $j\tau$, $j = 0, 1, \dots$. 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 $\tau = 4$. The

disturbances are simulated by $w_i(t) \in [\eta_i, \varepsilon_i]$

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

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

$$\begin{aligned} \eta_1 &= \max\{-s_1, -\varepsilon_1\}, \\ \eta_2 &= \max\{-q_1 e^{-u_1} \beta_1 TV, -\varepsilon_2\}, \\ \eta_3 &= \max\{-q_2 e^{-u_1} \beta_1 TV - k_1 T_1, -\varepsilon_3\}, \\ \eta_4 &= \max\{-s_2, -\varepsilon_4\}, \\ \eta_5 &= \max\{-q_M e^{-u_1} \beta_2 MV, -\varepsilon_5\}, \\ \eta_6 &= \max\{-p_1 e^{-u_2} T_2 - p_2 e^{-u_2} M_1, -\varepsilon_6\}, \end{aligned}$$

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

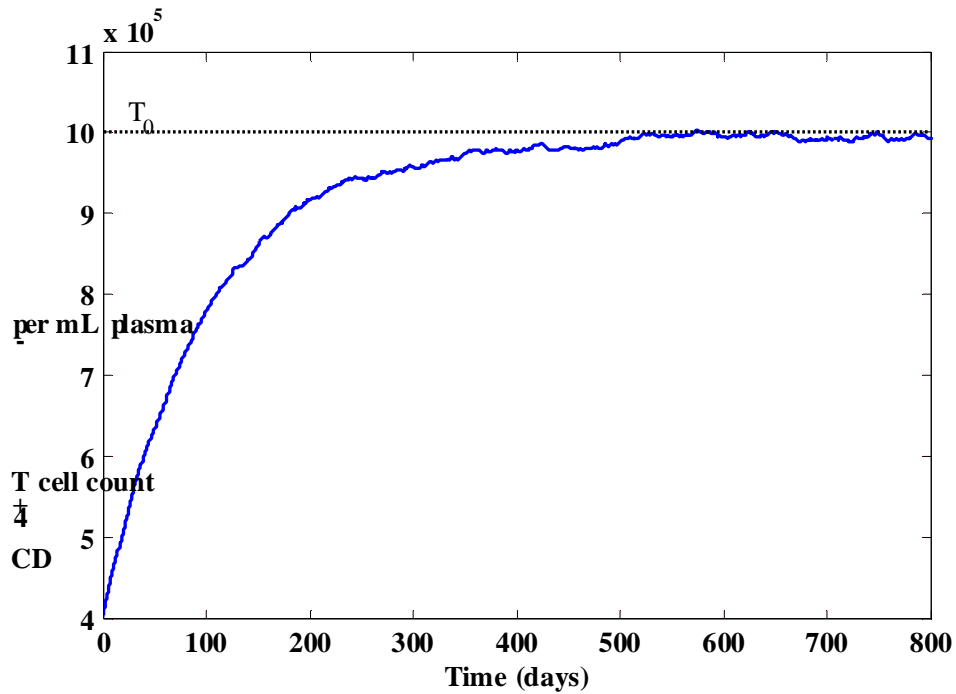
Simulations for the continuous-time system are carried out using ode45 program in MATLAB when $\varepsilon_1 = 2000$, $\varepsilon_2 = 10$, $\varepsilon_3 = 1$, $\varepsilon_4 = 100$, $\varepsilon_5 = 1$, $\varepsilon_6 = 5$.

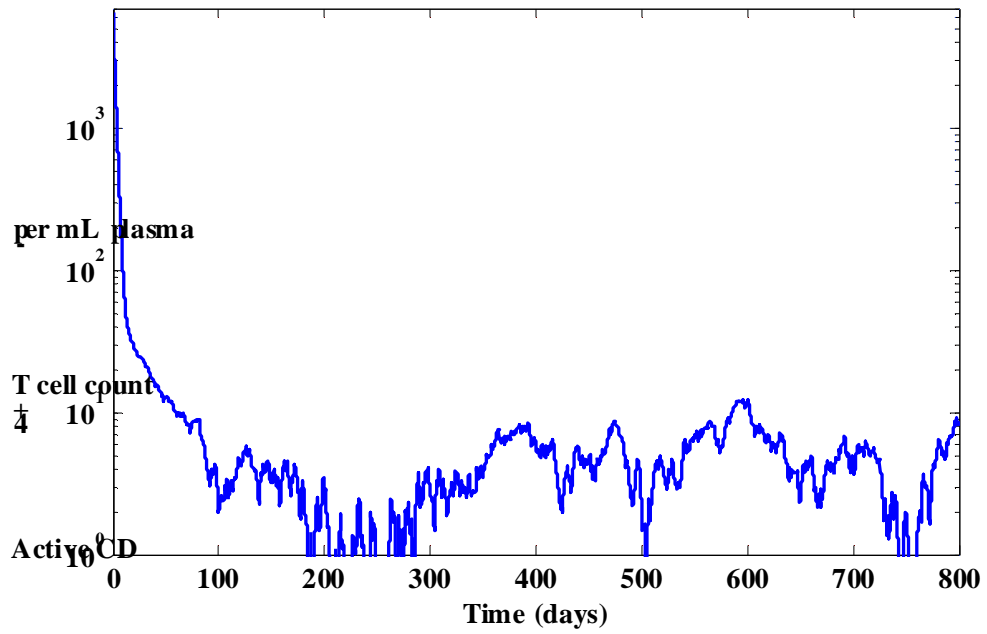
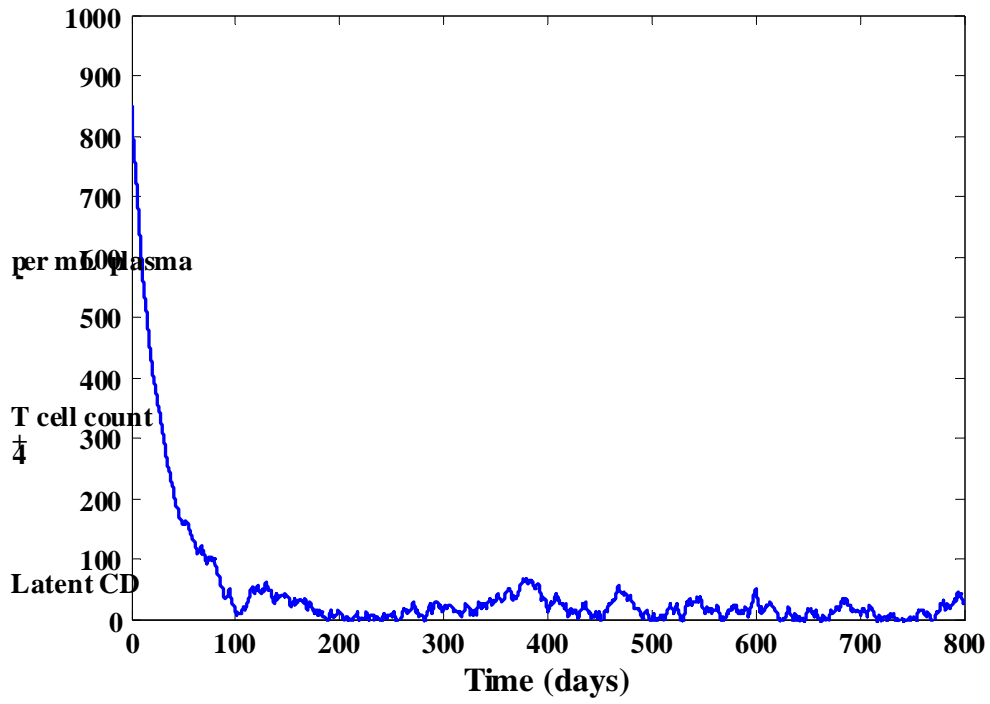
Figures 1-6 show the evolution of the HIV model variables under the application of multirate MPC strategy in the presence of disturbances. Figures 1 and 4 show that, when the MPC is applied, the number of uninfected $CD4^+$ T cells is increasing as well as the macrophages but with a slower rate than $CD4^+$ T cells. This means that, the HAART helps the immune system to recover with some fluctuations due to the presence of disturbances. From figure 2, 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. Figure 6 shows that, after initiation of HAART, the viral load drops quickly and it can be kept under a suitable level 130 copies/mL, with a small controller, corresponding to rather mild dosage of HAART. The model predictive controller as a function of the time is shown in figure 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). The size of this ball depends on the disturbances bound and the numerical errors.

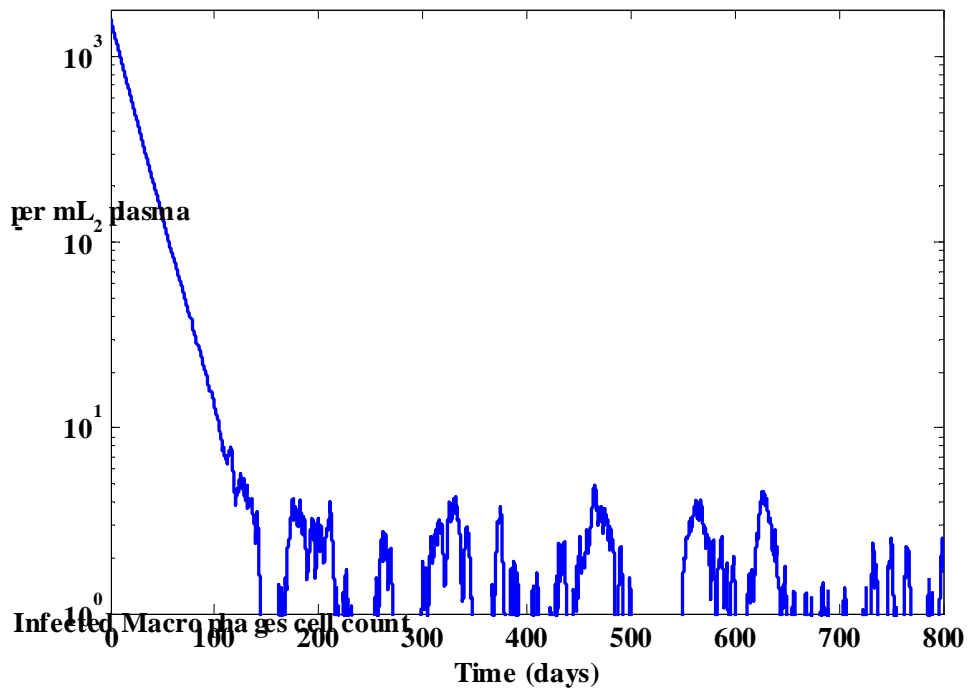
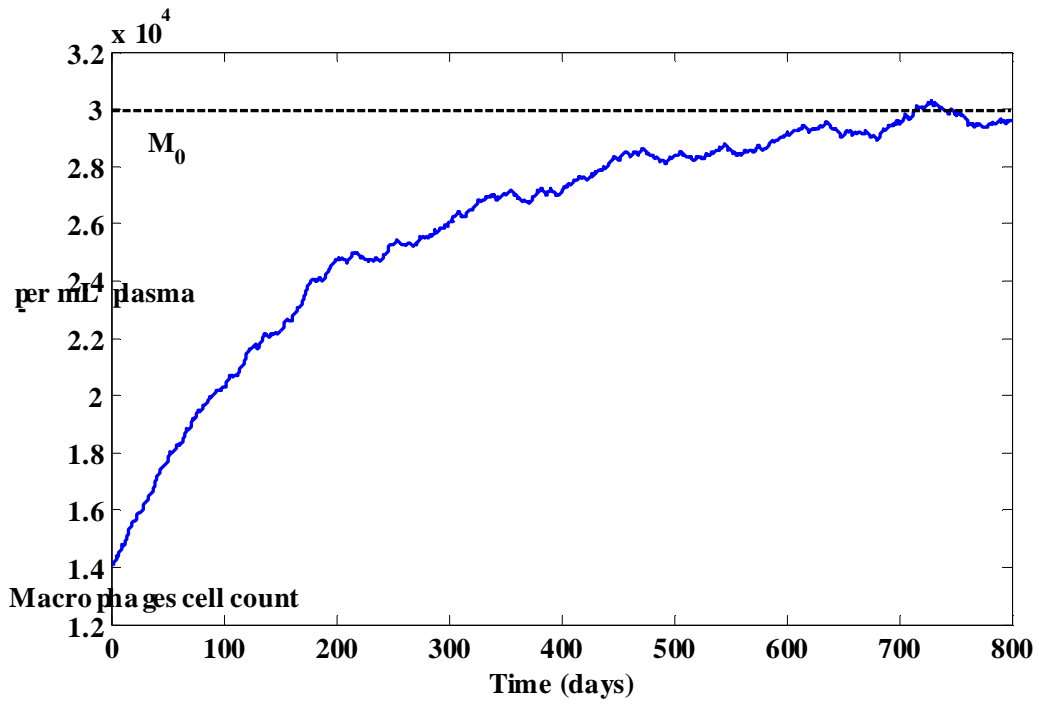
6. Conclusions:

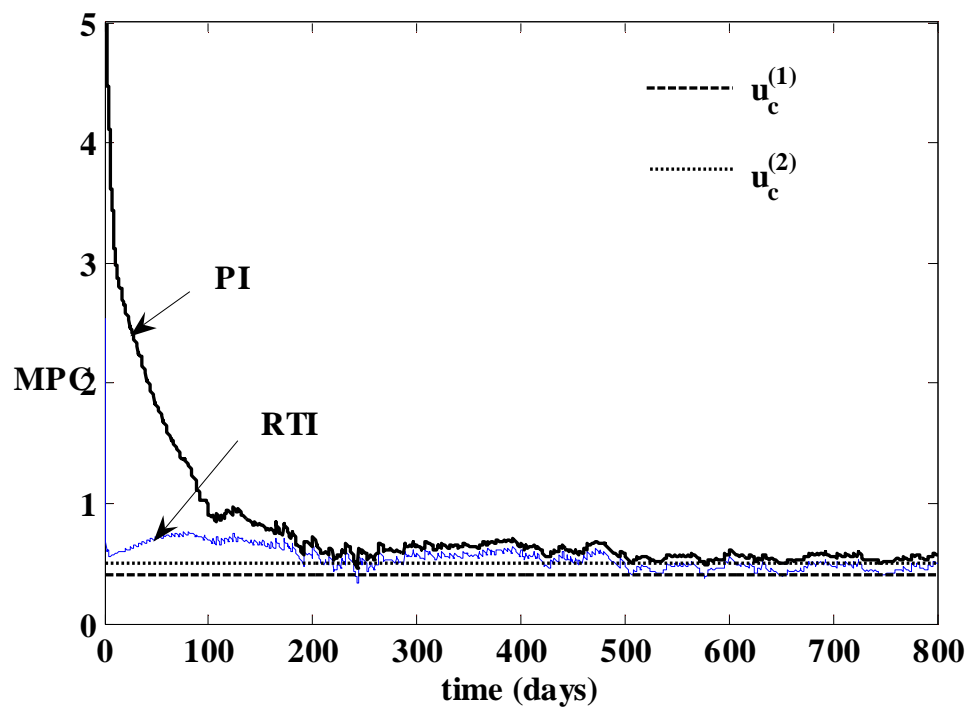
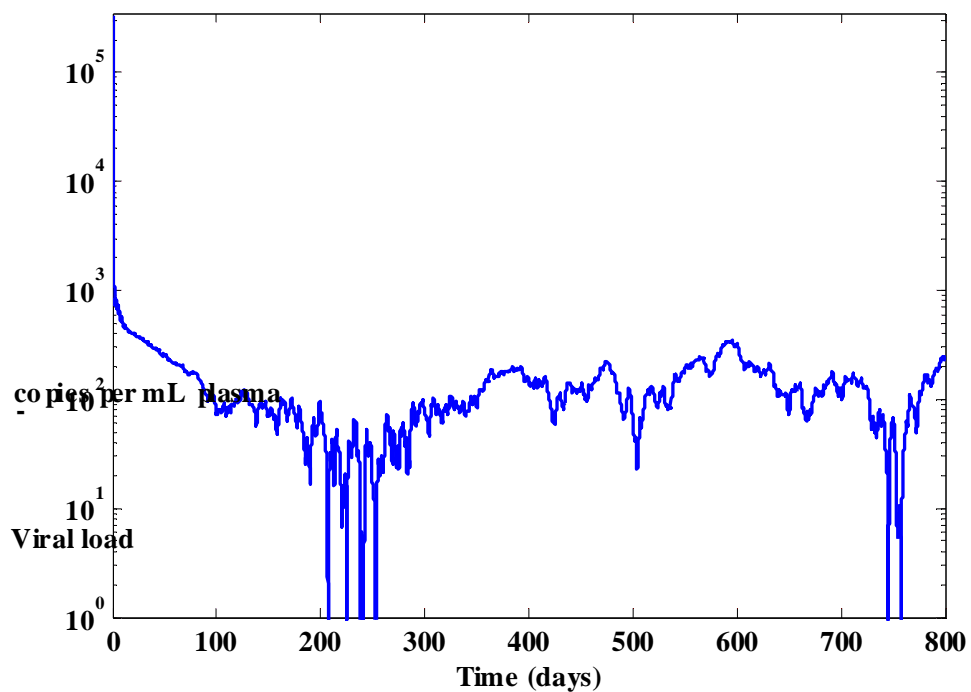
The basic properties of the 6-dimensional HIV model incorporating to allow some additive disturbances were studied. The stabilizing property of multirate MPC for nonlinear systems with additive disturbances via approximate discrete-time model of the nominal system was proven. Highly Active AntiRetroviral 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 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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