Model Predictive Control for Optimal Anti-HIV Drug Administration

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Abstract

In this paper, model predictive control (MPC) strategies are applied to the control of human immunodeficiency virus infection, with the final goal of implementing optimal continuous therapy and optimal structured treatment interruptions protocol. The MPC algorithms proposed in this paper use a system of differential equations including a model for an immune response. The multidrug therapies use the commonly used drugs in highly active antiretroviral therapy (HAART), i.e., reverse transcriptase inhibitor and protease inhibitor anti-HIV drugs. The medical protocols designed by the proposed algorithms induce immune control of the virus without the need for continued treatment, as suggested by the models. Simulation studies show that the proposed methods provide a clinically implementable framework for calculating interruption schedules that are robust to errors due to measurement and patient variations.

Key Words and Phrases:Antiretroviral therapy, human immunodeficiency virus control, model predictive control (MPC), therapy optimization.

1 Introduction

Human Immunodeficiency Virus (HIV) infects CD4+ T-cells, which are an important part of the human immune system, and other target cells. The infected cells produce a large number of viruses. Medical treatments for HIV have greatly improved during the last two decades. Highly active antiretroviral therapy (HAART) allows for the effective suppression of HIV-infected individuals and prolongs the time before the onset of Acquired Immune Deficiency Syndrome (AIDS) for years or even decades and increases life expectancy and quality to the patient but eradication of HIV infection does not seem possible with currently available antiretroviral drugs. This is due primarily to the establishment of a pool of latently infected T-cells and sites within the body where drugs may not achieve effective levels [1-3]. HAART contains two major types of anti-HIV drugs, reverse transcriptase inhibitors (RTI) and protease inhibitors (PI). Reverse transcriptase inhibitors prevent HIV from infecting cells by blocking the integration of the HIV viral code into the host cell genome. Protease inhibitors prevent infected cells from replication of infectious virus particles, and can reduce and maintain viral load below the limit of detection in many patients. Moreover, treatment with either type of drug can also increase the CD4+ T-cell count that are target cells for HIV. Many of the host-pathogen interaction mechanisms during HIV infection and progression to AIDS are still unknown.

Mathematical modeling of HIV infection is of interest to the medical community as no adequate animal models exist in which to test efficacy of drug regimes. These models can test different assumptions and provide new insights into questions that are difficult to answer by clinical or experimental studies. A wide variety of mathematical models have been proposed to describe various aspects of in-host HIV infection dynamics [4]. The basic model of HIV infection is presented by Perelson et al. [5] that contains three state variables healthy CD4+ T-cells, infected CD4+ T-cells and concentration of free virus. In addition, the documented importance of the immune system

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in responding to HIV infection (and especially its apparent crucial role during structured treatment interruptions) strongly motivates the inclusion of at least one model compartment representing immune response to the pathogen. Thus, a number of models including some measure of cytotoxic T-lymphocyte (CTL) response to HIV infection have been proposed. For instance, a widely used six-dimensional HIV model that includes a compartment representing an immune response measure has been introduced in [6]. Moreover, in [7] the population of CTLs was divided into precursors and effectors and a model was proposed, by incorporating these compartments to the basic model of HIV infection, and the proposed model offers important theoretical insights into immune control of the virus based on treatment strategies while maintaining a simple structure. Furthermore, this modified model was developed to describe the natural evolution of HIV infection, as qualitatively described in several clinical studies [8].

Some authors have used mathematical model for HIV infection in conjunction with control theory to achieve appropriate goals, by incorporating the effects of therapy on an HIV-infected individual. For example, these goals may include maximizing the level of healthy CD4+ T-cells and minimizing the cost of treatment [9-15], maximizing immune response and minimizing both the cost of treatment and viral load [16-18], maximizing both the level of healthy CD4+ T-cells and immune response and minimizing the cost of treatment [19-21], maximizing both the level of healthy CD4+ T-cells and immune response and minimizing the cost of treatment [22], Maximizing the level of healthy CD4+ T-cells while minimizing both the side effects and drug resistance [23], Maximizing the level of healthy CD4+ T-cells while minimizing both the cost of treatment and viral load [24-26], and maximizing survival time of patient subject to drug cost [27], [28].

The papers [9, 14, 22, 24, 27, 29] consider only RTI medication while the papers [15], [16] consider only PIs. In [7], [19-21] all effects of a HAART medication are combined to one control variable in the model. In [8,11-13,16-18,25,26,28,30] dynamical multidrug therapies based on RTIs and PIs are designed. In the considered control approaches the amount of medications can be either continuous or on-off type. This treatment is also known as structured treatment interruption (STI). STI has received considerable attentions as it might reduce the risk of HIV mutating to strains which are resistant to current medication regimens. STI approach might also reduce possible long-term toxicity of the drugs. A concise summary of clinical STI studies, including protocols and results, is presented in [31].

The papers [18,25,26] are devoted to optimize STI medications using the evolutionary optimization approaches while the medications in piecewise constant level are obtained in [25,28] ,by using a method based on measure theoretical approach. In [6,9-12,15,17,22,24,25], open-loop type optimal controllers are designed using the Pontryagins 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 [16,29]. Among possible control strategies model predictive control (MPC) appears to be suitable for an optimal application of STI, due to its intrinsic robustness to disturbances and model uncertainties, and most importantly it allows us to fine-tune the treatment using medically intuitive notions of cost. Finally, the long time-scales of the model allow us to overcome the computation time issues which normally plague MPC-based methods. In the last few years, model predictive control (MPC) method is developed for determining optimal treatment schedules for HIV patients [13,19-21,25,30]. 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. [32-34]).

This paper designs MPC-based continuously varying medications and STI antiviral multidrug therapies for HIV using a tracking problem .

The paper is organized as follows: In section 2, the underlying HIV mathematical model is presented. In Section 3, two methods for defining optimal drug therapy protocols based on MPC

techniques are presented. In Section 4, simulation results are presented and discussed. The last section is the conclusion.

2 Mathematical model of HIV

In this paper, the pathogenesis of HIV is modeled with a system of ordinary differential equations (ODEs) introduced in [6] and employed in [16-18]. This model captures many of the observed behavioral properties of long term HIV dynamics. The system of ODEs describing the model reads

$$\begin{aligned}
\dot{T}_1 &= \lambda_1 - d_1 T_1 - (1 - f_R\mu_R)k_1 V T_1,\\
\dot{T}_2 &= \lambda_2 - d_2 T_2 - (1 - f_R\kappa\mu_R)k_2 V T_2,\\
\dot{T}_1^* &= (1 - f_R\mu_R)k_1 V T_1 - \delta T_1^* - m_1 E T_1^*,\\
\dot{T}_2^* &= (1 - f_R\kappa\mu_R)k_2 V T_2 - \delta T_2^* - m_2 E T_2^*,\\
\dot{V} &= (1 - f_P\mu_P)N_T\delta(T_1^* + T_2^*) - cV - (1 - f_R\mu_R)\rho_1 k_1 T_1 V\\
&\quad -(1 - f_R\kappa\mu_R)\rho_2 k_2 T_2 V,\\
\dot{E} &= \lambda_E + b_E\frac{T_1^* + T_2^*}{T_1^* + T_2^* + K_b}E - d_E\frac{T_1^* + T_2^*}{T_1^* + T_2^* + K_d}E - \delta_E E. \qquad (1)
\end{aligned}$$

The state variables in the model (1) are: T_1 is uninfected CD4+ T-cells, T_2 is uninfected macrophages, T_1^* is infected T-cells, T_2^* is infected macrophages, V is viruses, and E is immune effectors. We use milliliter (ml) as a volume unit. Most of the terms in the model (1) have straightforward interpretations. The diagram in Figure 1 shows the interactions between the compartments. The positive terms λ_1, λ_2, and λ_E in the first, second, and last equation in (1) correspond to the production of new T-cells, macrophages, and immune effectors, respectively. For example, T-cells are produced by bone marrow. The negative terms containing coefficients d_1, d_2, δ, c, and δ_E present the death/clearance of cells/viruses. The terms involving $k_i V T_i$ represent the infection process wherein infected cells T_i^* result from encounters between uninfected target cells T_i and free virus V. Since RTI drugs blocks new infections, their effect has been included in model (1) by reducing the infection rate of uninfected target cells and this effect is potentially more in T_1 population than in T_2 population, where is given respectively by $f_R\mu_R$ and $f_R\kappa\mu_R$, with $\kappa \in [0, 1)$. PI drugs reduce the rate of virus production, and their effect is considered in model (4) by $f_P\mu_P$ which reduces the production of Viruses by infected cells in the dynamical equation. In model (1) f_P and f_R are the control inputs (i.e., the drugs uptake, normalized between 0 and 1) and the coefficients μ_R and μ_P indicate the maximum efficacies of RTI and PI drugs. In practice, an RTI medication cannot completely block the integration of the viral code into the target cells and a PI can only partially prevent the replication of viruses by infected cells. This means that μ_R and μ_P should be less than one. Moreover, the terms involving $m_i E T_i^*$ represent the clearance of infected cells via the action of immune effector cells (cytotoxic T-lymphocytes CTLs). The second term in the last equation in (1) presents the stimulation of immune effector production due to the presence of infected cells while the third term describes how a high amount of infected cells impairs the production. The concentration of infected cells has to be in a parameter dependent range for the production rate to be larger than the clearance rate, that is, to have a strengthening immune response. Thus, the anti-HIV therapy cannot be so strong that the amount of infected cells falls below the range in which an immune response occurs. On the other hand, if the medication is too inefficacious then the response is impaired by a high concentration of infected cells. Note it is assumed that both types of infected cells produce the same number, N_T , of free viral particles during a typical T_i cell life span and virus is lost through the terms $(1 - f_R\mu_R)\rho_1 k_1 T_1 V$ and $(1 - f_R\kappa\mu_R)\rho_2 k_2 T_2 V$, effectively accounting for the virus lost when infecting healthy CD4+ T-cells and macrophages, which do not produce any new virus, e.g., as a result of the infected cell's natural death or through the action of CTLs.

The mathematical model (1) contains numerous parameters that must be assigned before numerical simulations can be carried out. The definitions and numerical values for the parameters are summarized in Table 1, which are taken from [6].

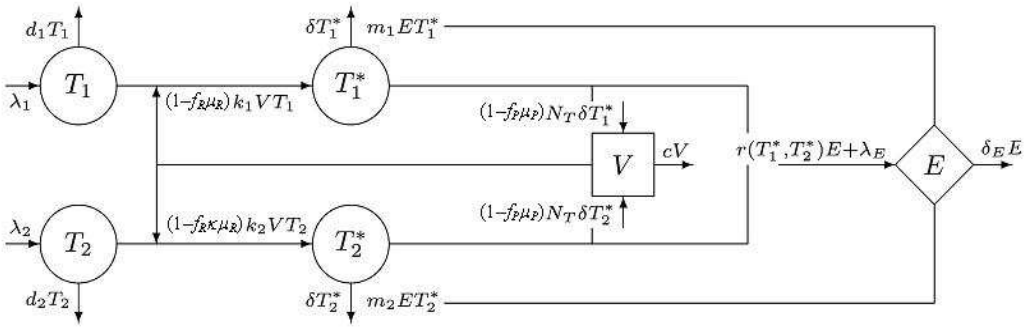

Figure 1: A diagram of the HIV model, where the function r is $r(T_1^*, T_2^*) = b_E(T_1^* + T_2^*)/(T_1^* + T_2^* + K_b) - d_E(T_1^* + T_2^*)/(T_1^* + T_2^* + K_d)$.

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When no medication is administrated ($f_P = f_R = 0$), the steady states of the model (1), that is, the states in which the time derivatives are zero, are described and analyzed in [6], [17]. A steady state of particular interest is the so-called "healthy" steady state given by

$$T_1 = 967839\frac{cells}{ml}, \quad T_2 = 621\frac{cells}{ml}, \quad T_1^* = 76\frac{cells}{ml},$$

$$T_2^* = 6\frac{cells}{ml}, \quad V = 415\frac{viruses}{ml}, \quad and \quad E = 353108\frac{cells}{ml}. \tag{2}$$

The value of T_1 in (2) is close to a thousand cells per milliliter, which corresponds to a person without HIV under the model (1) and given parameters. This is the reason for calling this state "healthy". Furthermore, the viral load V in (2) is fairly low. Following [6], [16-18], we have chosen the initial condition of (1) to be the acute infection

$$T_1 = 1,000,000\frac{cells}{ml}, \quad T_2 = 3,198\frac{cells}{ml}, \quad T_1^* = 0.0\frac{cells}{ml},$$

$$T_2^* = 0.0\frac{cells}{ml}, \quad V = 0.001\frac{viruses}{ml}, \quad and \quad E = 10\frac{cells}{ml}. \tag{3}$$

In the acute infection (3), the state variables have the same values as that of a healthy person except that there is a small quantity of HIV in the blood. A Highly Active Anti-Retroviral Therapy (HAART) can lead to a low viral load, but it cannot completely clear HIV; see [1-3], for example. Therefore, it is not a realistic goal to try to eradicate HIV using therapy. It can be claimed that a person infected with HIV can live in the healthy state (2) for a long time without medical problems due to HIV and without any medication for HIV. Hence, it would be highly desirable to design multidrug therapies which would steer the medical condition towards the healthy state. Once a neighborhood of this state is reached the therapy can be discontinued due to the local asymptotic stability of (2).

3 MPC treatment scheduling

Model predictive control (MPC) refers to a class of computer control algorithms that control the future behavior of a plant through the use of an explicit process model. At each control interval the MPC algorithm computes an open-loop sequence of manipulated variable adjustments in order to optimize future plant behavior. The first input in the optimal sequence is injected into the plant, and the entire optimization is repeated at subsequent control intervals. The control sequence is chosen in a way that an appropriate cost function, typically comprising a measure of the deviation of the future state sequence from reference target values and a measure of the control effort, is minimized while state and control constraints are fulfilled. MPC widely used in

Table 1: the parameters in the HIV model

Parameter	Value	Unit	Parameter	Value	Unit
λ_1	10000	$\frac{cells}{mlday}$	λ_2	31.98	$\frac{cells}{mlday}$
d_1	0.01	$\frac{1}{day}$	d_2	0.01	$\frac{1}{day}$
k_1	8.0×10^{-7}	$\frac{ml}{viruses\, day}$	k_2	1.0×10^{-4}	$\frac{ml}{viruses\, day}$
m_1	1.0×10^{-5}	$\frac{ml}{cells\, day}$	m_2	1.0×10^{-4}	$\frac{ml}{viruses\, day}$
ρ_1	1.0	$\frac{viruses}{cells}$	ρ_2	1	$\frac{viruses}{cells}$
δ	0.7	$\frac{1}{day}$	c	13	$\frac{1}{day}$
κ	0.34	–	N_T	100.0	$\frac{viruses}{cells}$
λ_E	1.0	$\frac{cells}{ml\, day}$	δ_E	0.1	$\frac{1}{day}$
b_E	0.3	$\frac{1}{day}$	d_E	0.25	$\frac{1}{day}$
K_b	100	$\frac{cells}{ml}$	K_d	500	$\frac{cells}{ml}$
μ_R	0.8	–	μ_R	0.4	–

many areas, especially in the process industries [35], for systems with a large number of controlled and manipulated variables, which interact significantly. In general, feedback control technologies, and MPC in particular, have started to gain significant attention in the biomedical area [13,19-21,25,30]. In order to give a formal description of the proposed MPC algorithms, some preliminary definitions are necessary. Let Δ be the sampling time, we denote with $X(i)$ the state of the system at time $t_i = i\Delta$, i.e.,

$$X(i) = [T_1(t_i) \quad T_2(t_i) \quad T_1^*(t_i) \quad T_2^*(t_i) \quad V(t_i) \quad E(t_i)]^T = \\ [T_1(i) \quad T_2(i) \quad T_1^*(i) \quad T_2^*(i) \quad V(i) \quad E(i)]^T.$$

Next, let $U(i) = [f_P(i) \quad f_R(i)]^T$ denote the vector of PI and RTI drugs taken in the time interval $[i\Delta, (i+1)\Delta]$, and rewrite the system model (4) in the integrated form

$$X(i+1) = F(X(i), U(i)),$$

where $F(\cdot)$ is a vector-value function obtained by numerical integration of (4) over the sampling Δ, assuming a constant drug uptake during the sampling time. With these definitions, it is now possible to state the following finite-horizon optimal control problem (FHOCP) to be solved at each discrete time i which we refer to it as MCP 1:

$$\min_{\mathbf{U}_k} \quad g(X(k+N)) + \sum_{i=k}^{k+N-1} \ell(X(i), U(i)).$$

subject to

$$X(k)\, given, X(i+1) = F(X(i), U(i)),\ i = k, ..., k+N-1$$
$$\begin{bmatrix} 0 \\ 0 \end{bmatrix} \leq U(i) \leq \begin{bmatrix} 1 \\ 1 \end{bmatrix}, i = k, ..., k+N-1$$
$$X(k+N) \in \Omega$$

in which N is an integer(control horizon), $\ell(\cdot, \cdot)$ is the stage cost, $g(\cdot)$ is the terminal cost, Ω is the terminal constraint, and $\mathbf{U}_k = [U(k) \quad U(k+1) \quad \cdots \quad U(k+N-1)]$ is the decision variable. From a therapeutic point of view, it may be unsafe to administrate drugs at a dose less than maximum because virus mutations may occur (see e.g., [21] and references therein for a more exhaustive discussion on this point). Therefore, standard HAART protocols require persistent drugs uptake at maximum value. However, a number of clinical and theoretical studies attempted STI protocols in which periods of therapy at maximum dosages are alternated with periods of treatment suspension [21]. The reasons for these attempts can be found in several side effects of

HAART, such as serious hepatic damages and the high cost of the therapy, but also in the evidence that appropriate suspension periods may enhance the immune response of the patient. The optimal control problem of MPC 1 is modified to obtain an STI protocol approach by restricting the PI and RTI doses to take values of either 0 or 1. Thus, the modified FHOCP, which defines algorithm MPC 2, is obtained from MPC 1 by modifying the control constraint as follows:

$$U(i) \in \{0,1\}^2, i = k, ..., k+N-1.$$

The objective of our treatment scheduling is to drive the patient to a state in which the immune system will suppress the virus without continued treatment while minimizing the overall administered dosage. With this in mind, we choose our stage cost to be

$$\ell(X(i), U(i)) = (X(i) - \widetilde{X})^T Q(X(i) - \widetilde{X}) + U(i)^T RU(i),$$

where Q and R are positive definite diagonal matrices and $\widetilde{X}$ is the healthy steady state given by (2). Let $\mathbf{U}_k^*$ be a minimizing control input sequence. The MPC law is defined as $\kappa_N(X(k)) = U^*(k)$, the first element of $\mathbf{U}_k^*$. Under certain conditions, which depend on the specific implementation of MPC being applied, the closed-loop system $X(i+1) = F(X(i), \kappa_N(X(i)))$ can guarantee both stability of a desired set point $\widetilde{X}$ and robustness to disturbances (details for our implementation follow). A thorough overview of the history of MPC and its various incarnations can be found in [34]. The following conditions that, if satisfied, ensure closed-loop asymptotic (exponential) stability if further minor assumptions are satisfied [34]:

1. There exist a feasible control law $\kappa(\cdot)$, such that $F(x, \kappa(x)) \in \Omega, \forall x \in \Omega$ (The terminal constraint Ω be positively invariant under $\kappa(\cdot)$).
2. $g(F(x, \kappa(x))) - g(x) \leq -\beta\ell(x, \kappa(x)), \forall x \in \Omega$ where $\beta \in (0, \infty)$(g is a local Lyapunov function).

We now briefly discuss why the HIV model satisfies the mentioned assumptions. The first assumption is reasonable for our system, as it is locally exponentially stable with zero control and asymptotically controllable to desired set point. Therefore, by choosing a sufficiently small neighborhood of $\widetilde{X}$ as Ω and setting $\kappa(\cdot) \equiv 0$ the first assumption is satisfied. To verify the second assumptions, we linearized the system (1) around the $\widetilde{X}$ in case of zero controllers. Let A be the coefficient matrix of the linearized system. Then the discrete-time model for the linearized system is given by:

$$X(k+1) = e^{A\Delta} X(k). \tag{4}$$

Because the neighborhood Ω is small enough, it is possible to set $F(x, \kappa(x)) \approx e^{A\Delta} x, \forall x \in \Omega$. We set $g(x) = \beta(x - \widetilde{X})^T P(x - \widetilde{X})$, where $g(\cdot)$ is a local quadratic Lyapunov function at the desired equilibrium and P is a positive definite symmetric matrix. It is easy to see that the second condition is satisfied if P and Q satisfy the Lyapunov equation for the discrete-time system (4)

$$A_\Delta^T P A_\Delta - P + Q = 0, \qquad A_\Delta = e^{A\Delta}. \tag{5}$$

Notice that in practice we choose a sufficiently large parameter β and in this way the obtained value $X(N+k)$ remains close to $\widetilde{X}$, given a sufficiently long horizon N. So, we do not consider an explicit terminal constraint. The removal of the terminal constraint makes the problem much easier to solve and the computational burden is reduced.

4 Simulation Results

We implement two therapy protocols based on the MPC algorithms described in Section 3 , and we show simulation results which illustrate the algorithms performance over a variety of conditions. All computations are carried out by MATLAB. We choose a sampling time of three days , $\Delta = 3$. Consequently, we do not worry about creating an explicit discretization of our differential equation; we simply use a numerical simulator to approximate our discretization. Moreover, we chose horizon length N to be $N = 8$. In particular, the MPC 1 algorithm is implemented by the *fmincon* code of the Optimization toolbox. Also, in the case of STI a finite horizon and a finite control space

mean that we have, for each horizon, a finite number of possible control sequences. We implement MPC 2 by using the Simulated Annealing (SA) metaheuristic combined with the Steepest Descent Explorer [36] for searching this space. The parameter β and the matrix Q has been chosen through a series of numerical experiments as $\beta = 10^{-3}$ and $Q = diag(2 \times 10^{-5}, 0, 0, 0, 0, 3 \times 10^{-5})$. This means that we are interested in both maximizing the CTL response and minimizing the decrease in helper-T concentration. Therefore, by solving the Lyapunov equation (5) we have

$$P = \begin{pmatrix} 0.0005 & 0.0175 & 0.0063 & 0.0063 & 0.0005 & -0.0003 \\ 0.0175 & 2.0420 & 2.7178 & 2.7178 & 0.1807 & -0.0383 \\ 0.0063 & 2.7178 & 160.1839 & 160.1839 & 9.6666 & 0.0048 \\ 0.0063 & 2.7178 & 160.1839 & 160.1839 & 9.6666 & 0.0048 \\ 0.0005 & 0.1807 & 9.6666 & 9.6666 & 0.5835 & -0.0001 \\ -0.0003 & -0.0383 & 0.0048 & 0.0048 & -0.0001 & 0.0009 \end{pmatrix}.$$

Moreover,unless otherwise stated, the matrix R have been chosen as $R = diag(10^{-4}, 10^{-4})$. In this section we demonstrate the flexibility of the method through simulations in which we vary the cost function. Moreover,we show that the method successfully stabilizes the desired steady state despite state measurement error and modeling error.

4.1 Nominal Simulation Results

We first analyze the performance of the MPC-based therapy optimization algorithms for the nominal case in which we assume that the algorithms use nominal parameters as described in Table 1. We present in Figures 2, the closed-loop response of the behavior of the state variables of the model over a period of 40 months from infection, and the upper plots in Figure 3 show the corresponding medications.As expected, both MPC algorithms accomplish the goal of stabilizing the desired steady state while reducing the drug dosage with respect to sustained HAART therapy at maximum dosage. The choice of the sampling time Δ, the horizon length N, the matrices Q and R and the parameter β all contribute to this satisfactory result. Since the MPC 2 only considers on/off therapy periods, the algorithm computes a stronger dosage than the MPC 1. Clearly, the medications given by both the MPC algorithms have clear apparent on and off periods. The medications given by the MPC 1 are discontinued after about 350 days, while the medication suggested by the MPC 2 requires more than 450 days. We note that, early termination of the medical treatment reduces undesired side effects and the possibility of mutations leading to drug-resistant HIV strains. Figure 2(a) shows that, the level of uninfected CD4+ T-cells achieved by MPC 1 is high at all times and it is slightly higher than the corresponding value obtained by MPC 2. Moreover, Figure 2(f) shows that the therapies given by the MPC 1 leads to an immune response which reached the healthy steady state level in about 300 days, while the therapy proposed by the MPC 2 required more than 450 days to reach the same level. Thus, in these senses the MPC 1 gives more effective medication than the MPC 2.

One of the most useful things about the MPC-based methods is the ability to fine-tune the performance of the system by adjusting the cost functions. To demonstrate this, we adjusted the weightings of the elements of the stage cost . We increased the weight on the term penalizing excess drug usage. This allowed us to change the relative importance of decreasing helper T-cells, drug usage and CTL growth, and the algorithm returned a schedule which converged to the desired equilibrium more slowly, using more anti-retroviral therapy overall. Figure 2(f)shows the immune response corresponding to the therapy schedules given by the MPC algorithms with two different weights on drug cost, and the corresponding drug dosages obtained by these algorithms are plotted in Figure 3. The therapies given by the MPC 1 and the MPC 2 with weight $R = diag(100, 100)$ lead to an immune response which reached the healthy steady state level in about 480 and 620 days, respectively. It should be note that changing the matrix Q leads to a different matrix P which is obtained by solving the corresponding Lyapunov equation (5), and we don't consider this case.

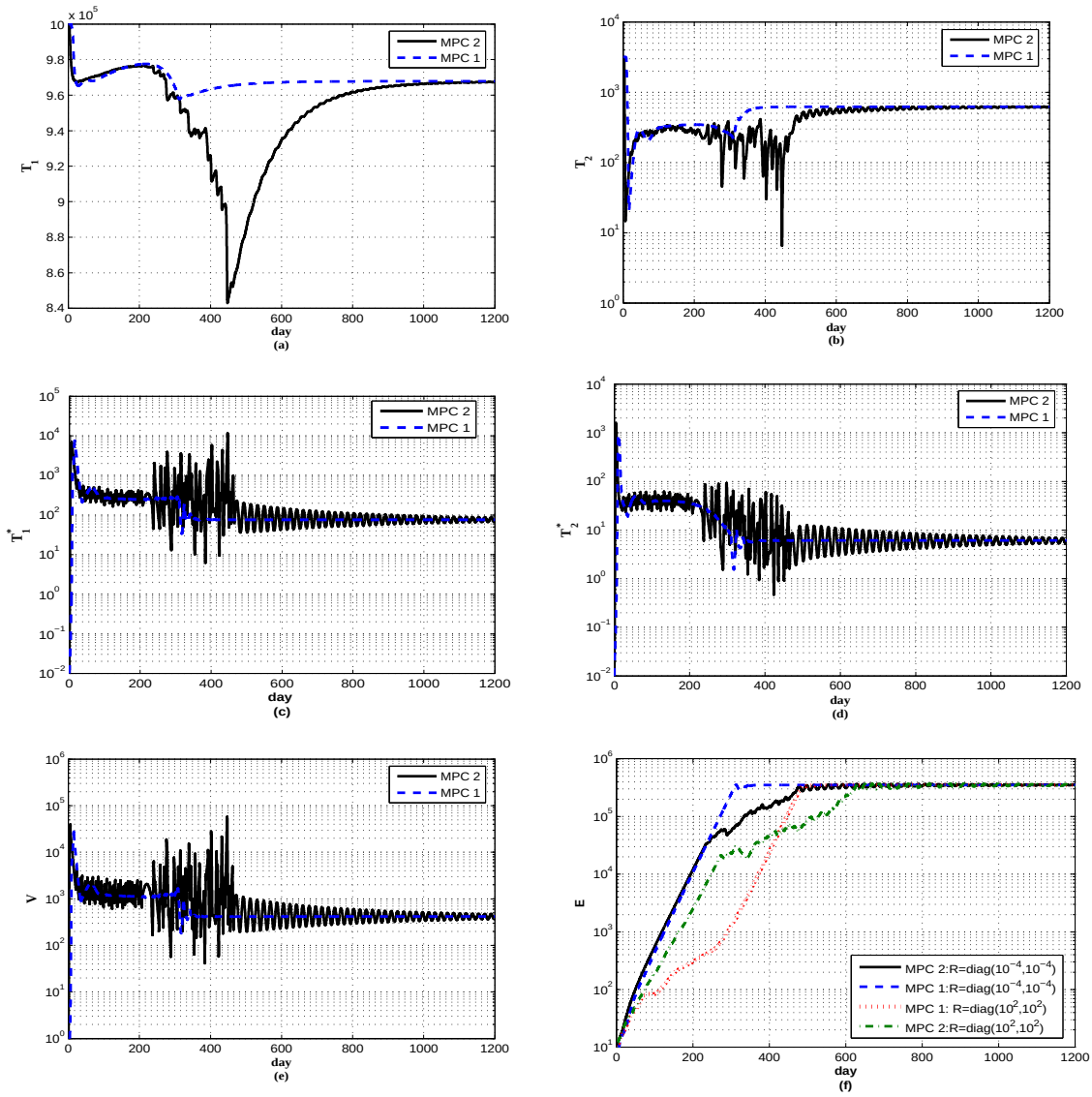

Figure 2: Closed-loop response of state variables using MPC 1 or MPC 2.

4.2 Robustness to Measurement Noise

We now present closed-loop simulation results obtained in the presence of measurement noise. Measurements of states are affected by random noise with a noise-to-signal ratio up to 5, 10 and 15%. For each case, 100 simulation experiments have been executed. Both MPC algorithms succeeded in stabilizing the desired steady state for each of 100 simulations. To further investigate this robustness, we ran 100 simulations each at up to 20, and 25% random error. For up to 20% error the MPC 1 failed to induce a successful immune response 32 times,while the MPC 2 succeeded in stabilizing the desired steady state every time. When we allowed up to 25% error, the MPC 2 failed to induce a successful immune response 23 times while the MPC 1 could never stabilize the desired steady state. Therefore, MPC 2 appears less sensitive to the presence of measurement noise than MPC 1. A sampling of these results can be seen in Figure 4. In Figure 5 only the control functions corresponding to 5 and 20% errors are plotted for brevity. Obviously, the error caused the MPC 2 to take significantly longer to stabilize the system, using many unnecessary treatment interruptions, and the error caused oscillations in the trend of control functions obtained by the MPC 1. It is important to remark that the sensitivity to noise is increased by neglecting the terminal cost i.e., setting $\beta = 0$.

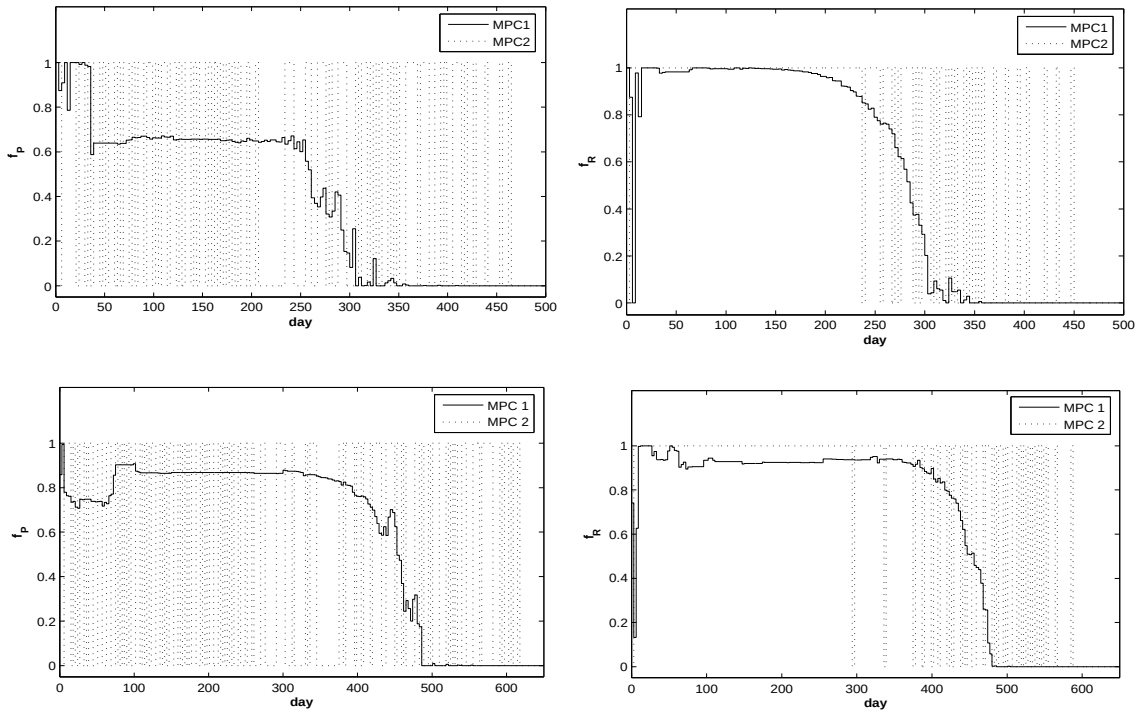

Figure 3: Continuous and STI drug dosage obtained by the MPC algorithms with different weights on control cost: $R = diag(10^{-4}, 10^{-4})$ (upper plots) and $R = diag(100, 100)$ (lower plots).

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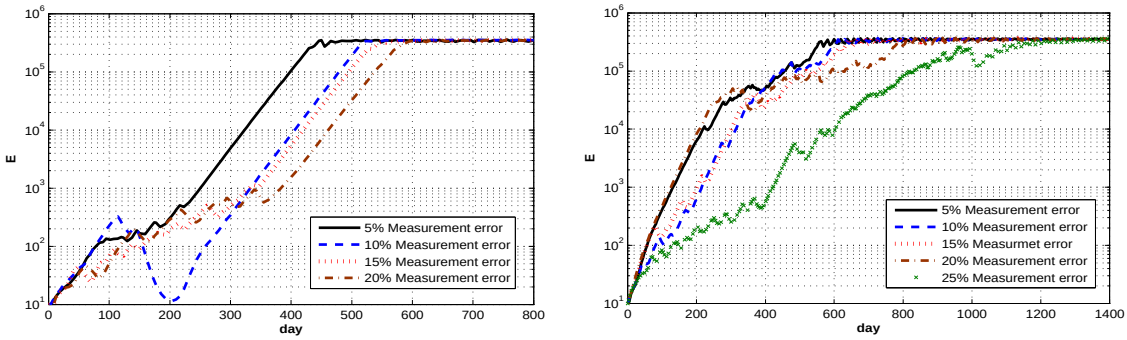

Figure 4: Closed-loop response of immune system with noisy measurements, using MPC 1 (left plots) and MPC 2 (right plots).

4.3 Robustness to Model Error

The study [37] fitting the parameters of the model (1) using clinical data shows that, for different patients, the maximum efficacies μ_R and μ_P essentially vary in the whole range from zero to one, with the average values close to 0.5. The paper [6] studying anti-HIV medications used the maximum RTI efficacy 0.8 while no PI medications were employed. The papers [17,18] used the values 0.7 and 0.3 for the maximum efficacies of RTI and PI, respectively. Numerical experiments in [16] show that a strong immune response allowing discontinuing medication at some point is possible when the total combined efficacy $1 - (1 - \mu_R)(1 - \mu_P)$ is higher than about 0.8. The maximum efficacies 0.7 and 0.3 approximately lead to this limiting value. The value 0.8 and 0.4 used in this paper lead to the combined total efficacy 0.88, which is closer to an average patient

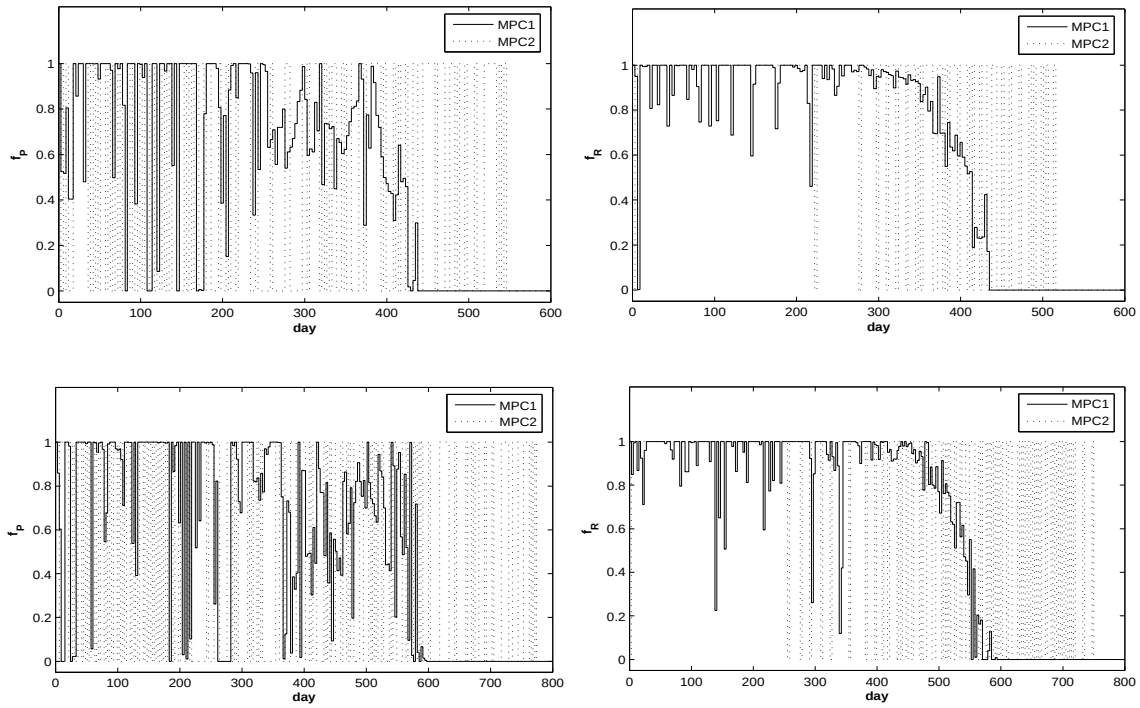

Figure 5: Continuous and STI drug dosage obtained by the MPC algorithms for up to 5 (upper plots) and 20% (lower plots) random measurement error.

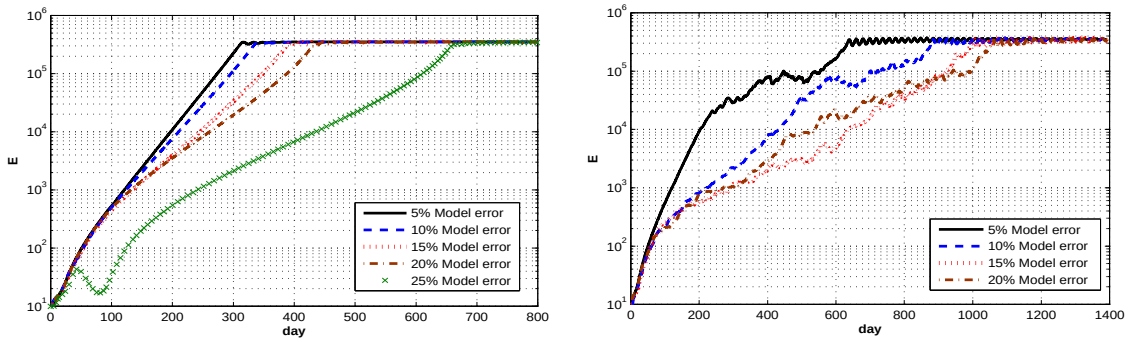

Figure 6: Closed-loop response of immune system with random modeling error, using MPC 1 (left plots) and MPC 2 (right plots).

susceptible to having a strong immune response according to the fitted parameters in [37]. To explore the robustness of our technique to errors in these estimates, we introduced a random variation into these parameters in the model. The scheduling algorithms continues to use the nominal, but now incorrect values to calculate its schedules. We ran at least 100 simulations each with this error randomly distributed at up to 5, 10 , 15, 20 and 25% of these parameter values, allowing the MPC algorithms up to 4 years to successfully stabilize the desired steady state. For up to 15% error both the MPC algorithms induced a successful immune response every time. When we allowed up to 20% error, the MPC 1 induced a successful immune response every times, while the MPC 2 failed to induce a successful immune response 37 times. When we allowed up to 25% error, the MPC 1 failed to induce a successful immune response 18 times while the MPC 2 could never stabilize the desired steady state, and therefore the MPC 1 is probably more robust to model

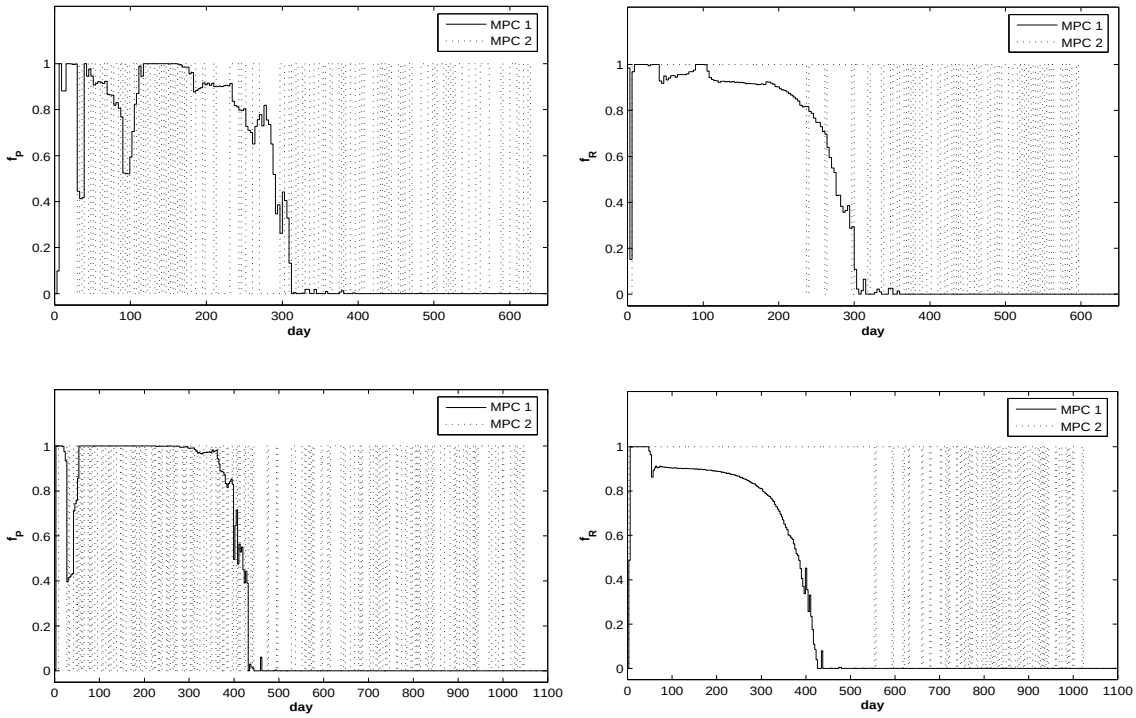

Figure 7: Continuous and STI drug dosage obtained by the MPC algorithms for up to 5 (upper plots) and 20% (lower plots) random modeling error.

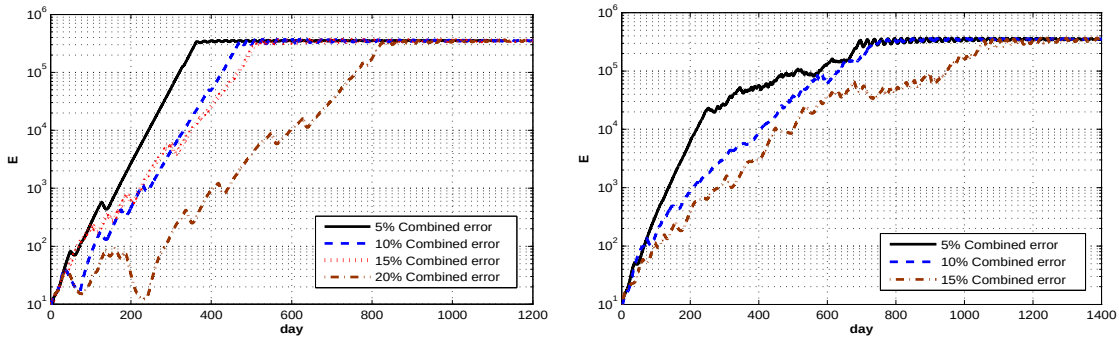

Figure 8: Closed-loop response of immune system with random combined error, using MPC 1 (left plots) and MPC 2 (right plots).

error than the MPC 2. A sampling of these results can be seen in Figure 6. In Figure 7 only the control functions corresponding to 5 and 20% errors are plotted for brevity.

4.4 Robustness to Combined Errors

We analyzed the robustness of scheduling algorithms to modeling and measurement errors when they occur simultaneously. To demonstrate this, we ran 100 simulations, each with random errors up to 5, 10, 15, and 20% into both the model parameters described in section 4.3 and the state measurements allowing the algorithm up to 4 years to successfully stabilize the desired steady state. For up to 5% error both the MPC algorithms induced a successful immune response every time. When the error increased up to 10%, the MPC 1 induced a successful immune response every times while the MPC 2 failed to induce stability 17 times. The total failures of the MPC 1 and the MPC

Table 2: Success rate of MPC algorithms (%)

		Error(%)				
		5	10	15	20	25
Measurement error	MPC 1	100	100	100	68	0
	MPC 2	100	100	100	100	77
Model error	MPC 1	100	100	100	100	82
	MPC 2	100	100	100	63	0
Combined error	MPC 1	100	100	87	42	–
	MPC 2	100	83	65	0	–

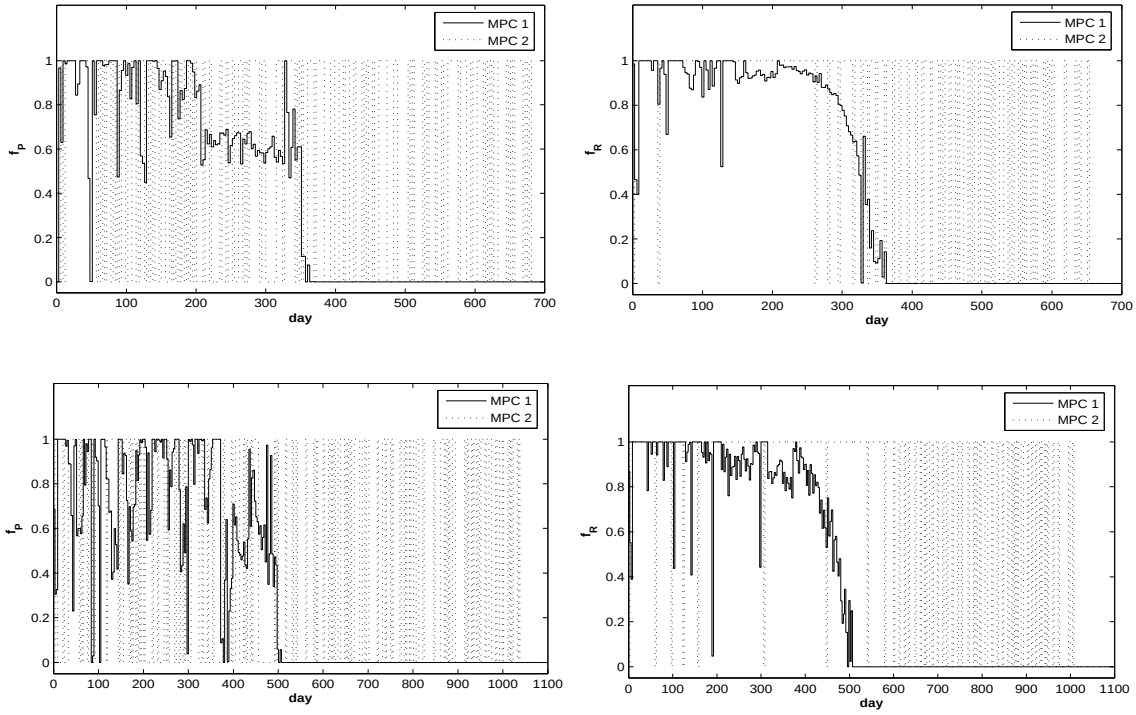

Figure 9: Continuous and STI drug dosage obtained by the MPC algorithms for up to 5 (upper plots) and 15% (lower plots) random combined error.

2 respectively increased to 13 and 35 times, in presence up to 15% error. Finally, when we allowed up to 20% error, the MPC 1 failed to induce a successful immune response 58 times while the MPC 2 could never stabilize the desired steady state. A sampling of these results can be seen in Figure 8. In Figure 9 only the control functions corresponding to 5 and 15% errors are plotted for brevity, and the success rate of the feedback algorithms in stabilizing the desired outcome for all cases are summarized in Table 2. The robust performance of the treatment scheduling algorithm under model and measurement uncertainty is very encouraging. It will take significant experimental work to verify that the robustness is sufficient for the application, but the results are promising.

5 Conclusion

In this paper, we presented two MPC algorithms for the determination of optimal therapy protocols for controlling HIV infection. The first algorithm computes at each sampling time (of three days), the optimal drug dose sequence over a horizon (of 24 days) that enhances the CTL immune response by optimally scheduling the drug treatment for HIV infected patients. The second algorithm

instead restricts the dose either to be zero or one (maximum dose), thus resulting in an optimal STI protocol. Simulation results show that the proposed MPC approach is able to stabilize the HIV system around the healthy steady state effectively, despite the possible presence of measurement noise and relevant model errors.

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