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A model predictive control based scheduling method for HIV therapy ☆

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Abstract

Recently developed models of the interaction of the human immune system and the human immunodeficiency virus (HIV) suggest the possibility of using interruptions of highly active anti-retroviral therapy (HAART) to simulate a therapeutic vaccine and induce cytotoxic lymphocyte (CTL) mediated control of HIV infection. We have developed a model predictive control (MPC) based method for determining optimal treatment interruption schedules for this purpose. This method provides a clinically implementable framework for calculating interruption schedules that are robust to errors due to measurement and patient variations. In this paper, we discuss the medical motivation for this work, introduce the MPC-based method, show simulation results, and discuss future work necessary to implement the method.

Keywords: Viral dynamics; Antiretroviral therapy; Nonlinear control

1. Introduction

In the majority of cases of untreated human immunodeficiency virus (HIV) infection, the patient undergoes a short (2–10 weeks) period of acute infection, which may be accompanied by symptoms similar to those found in most viral infections. During this period, there is a sharp drop in the concentration of circulating helper-T cells, and a large spike in the level of circulating free virus (to an average of 10^7/ml). During this period, a humoral (antibody) response and a cellular (cytotoxic-T cell) response are established (Koup et al., 1994). After this period, the level of circulating helper-T cells returns to near-normal (1000 cells/ml), and the viral load drops dramatically (to an average of about 50 000/ml). During the next phase of infection, which can last as long as 10 years, the patient remains asymptomatic, but the level of circulating helper-T cells slowly declines. When the number of helper-T cells drops below a critical threshold (200/ml), the patients adaptive immune system is no longer able to control infections, and a number of so-called opportunistic infections cause a rapid deterioration of health and a total collapse of the adaptive immune system. The slow rate of helper-T cell decline during the long, asymptomatic chronic infection phase once led people to believe that the virus was relatively inactive during this period, but it is now known that vigorous viral replication and helper-T cell turnover occurs during this time (Ho et al., 1995; Perelson et al., 1996; Perelson and Nelson, 1999). In fact, the total viral production during this phase is on the order of 10^{10} virions per day, and the turnover rate of helper-T cells on the order of 2×10^9 cells per day. The dynamics of HIV infection are

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obviously quite fast, but the immune response is able to maintain a near-homeostasis for a number of years.

1.1. Long-term non-progressors

While the majority of untreated HIV-infected patients exhibit the pattern of disease progression described above, a small number of untreated patients show no progressive decline in helper-T cell counts, and never develop AIDS. These patients are termed long-term non-progressors (LTNP). These patients exhibit extremely low viral loads, frequently below the threshold for measurement. Compared to patients with progressive infections, these patients exhibit strong HIV-specific helper-T cell responses (Rosenberg et al., 1997,1999; Rosenberg and Walker, 1998; Gloster et al., 2004; Moss et al., 2000). Levels of HIV-specific cytotoxic-T cells are similar in both cases (Rodes et al., 2004), but in the case of LTNPs, their HIV-specific cytotoxic-T cell counts are maintained at low levels of viral load (Harrer et al., 1996a,b; Migueles et al., 2002), where patients with progressive infections see corresponding decreases in the level of HIV-specific cytotoxic-T cell activity if the viral load is suppressed by therapy (McMichael and Rowland-Jones, 2001; Mollet et al., 2000; Kalams et al., 1999b; Appay et al., 2002). This is also seen in animal model experiments such as Schmitz et al. (1999) and Jin et al. (1999). Longitudinal studies of LTNPs have shown that the control of the virus sometimes fails (Rodes et al., 2004), probably due to mutational escape (Yang et al., 2003). Also, even in patients with exceptionally broad specificity in their CTL response to HIV, escape due to super-infection has been shown to occur (Altfeld et al., 2002a). Long-term non-progressors are widely studied as a model for potential therapeutic vaccines, as they apparently have naturally developed an immune response that successfully contains the virus.

1.2. Highly-active anti-retroviral therapy

Prior to 1995, anti-retroviral drugs were applied one or two at a time. Work done by Ho and colleagues (Ho et al., 1995) showed that the replication and mutation rates of HIV in vivo were so high as to make the emergence of strains resistant to any one drug inevitable. The solution was to use three or more drugs that target separate components of the HIV replication cycle. This multi-drug therapy regime is known as highly active anti-retroviral therapy (HAART). This technique is highly effective at reducing viral load and restoring immune function (Gray et al., 2000), and its use has drastically reduced AIDS-related deaths in the United States and other first-world nations. However, it is not without its drawbacks. HAART is expensive, costing as much as $10 000 per patient per year, and it must be continued for the life of the patient. Even though it can suppress the viral load below the measurement threshold, various viral reservoirs cause re-emergence of the virus upon cessation of therapy, even after many years of suppression (Finzi et al., 1999). Finally, the drugs used in HAART cause a number of adverse side effects in almost all patients, ranging from the mild to life-threatening (Gegeny, 2000; Manegold et al., 2001). While HAART is an effective therapy that prolongs the life of HIV-infected individuals, the associated costs keep us searching for a better solution. An excellent review of the available drugs, their usage, and their side effects can be found in Hoffmann and Kamps (2003).

1.3. Treatment interruptions

A significant amount of effort has been put into the use of interrupted schedules of HAART (Gulick, 2002). Interrupting HAART has been done for a number of reasons, usually to manage side effects or allow treatment of a secondary infection with which the drugs in HAART would interfere, such as hepatitis-A (Montaner, 2001; Dybul et al., 2001; Fischer et al., 2003). However the case of the "Berlin patient" began a series of investigations into the use of treatment interruptions as a way of boosting the immune response to HIV, and potentially controlling the virus (Autran and Carcelain, 2000). In the case of the Berlin patient, HAART was begun during acute infection, discontinued due to poor adherence, re-initiated, discontinued again due to hepatitis-A infection, re-initiated, then discontinued permanently, following which there was no measurable viral rebound (Lisziewicz et al., 1999). Follow-up with this patient showed measurable virus in the lymph nodes, but no viral rebound for several years after discontinuation of therapy. Obviously, the treatment schedule had somehow induced an immune response capable of controlling the HIV infection.

Further studies on patients who initiated HAART during acute infection, followed by a pattern of structured treatment interruptions (STI), showed varying degrees of success in inducing at least a transient control of viral replication in the absence of continued therapy (Lori et al., 2000; Ortiz et al., 1999; Papasavvas et al., 2000; Ruiz et al., 2001; Rosenberg et al., 2000). In all of the successful cases, viral control was associated with increased HIV-specific helper-T responses and strong HIV-specific CTL responses that were maintained even at low viral load, which suggested an immune response profile similar to that seen in LTNPs. However, a follow-up study that tracked some of those patients that successfully controlled the virus in the absence of continued therapy showed a disappointing lack of durability in the immune response; among 14 patients who successfully controlled viral replication for up to 3 years following cessation of therapy, all except

one eventually experienced viral rebound (Kaufmann et al., 2004).

Studies involving STI during chronic HIV infection were also done, but with much less success at inducing even a transient control of infection (Haslett et al., 2000; Davey et al., 1999; Frost et al., 2002; Garcia et al., 2001; Oxenius et al., 2002; D'Offizi et al., 2002; Ortiz et al., 2001; Ruiz et al., 2000; Carcelain et al., 2001; Blankson et al., 2002; Fagard et al., 2003; Hatano et al., 2000). Although most of the patients in these studies experienced transient increases in their HIV-specific cytotoxic-T cell responses (Altfeld et al., 2002b), and some reported increases in HIV-specific helper-T responses as well (Blankson et al., 2002), this did not result in any long-term reduction in viral load. This might be explained by the fact that HIV preferentially infects HIV-specific helper-T cells (Douek et al., 2002), and HIV-specific helper-T function may be eliminated or severely impaired early during untreated HIV infection (Altfeld et al., 2001; Palmer et al., 2002; Pitcher et al., 1999; Ostrowski et al., 2001; Kaufmann and Rosenberg, 2003; Kalams et al., 1999a; Betts et al., 2001).

The use of STIs to induce efficient immune-mediated control of HIV is currently a matter of debate (Havlir, 2002). The studies mentioned above indicate that there is some significant success if therapy was initiated early in HIV infection, but little to no success if therapy was initiated during chronic infection (Lori and Lisziewicz, 2001). The durability of the induced control is disappointing, and the overall benefit of a short period of immune control is questionable (Kaufmann et al., 2004; Abbas and Mellors, 2002). There is concern that the use of interruptions might encourage the emergence of multi-drug resistant strains of HIV (Ananworanich et al., 2003; Abbas and Mellors, 2002; Dorman et al., 2000; Martinez-Picado et al., 2002; Schweighardt et al., 2002; Tremblay et al., 2003) but many experimental studies have not shown evidence of this (Ruiz et al., 2000; Bonhoeffer et al., 2000; Bucy and Kilby, 2001; Frost, 2002; Frost et al., 2002; Neumann et al., 1999; Papasavvas et al., 2003). In order for this to be a viable treatment option, techniques that provide better success rates will need to be developed, and methods of delaying or avoiding the mutational escape of the virus from immune control will need to be explored.

The possibility of inducing immune-mediated control is exciting for a number of reasons. While HAART is highly effective at suppressing viral load, it does not eradicate the disease, so treatment must be continued for the life of the patient (Finzi et al., 1999). While the widespread use of HAART in the United States has resulted in a significant drop in deaths due to opportunistic infections, it has at the same time revealed a number of problematic side effects (Gegeny, 2000). These range from the relatively benign, such as lipodystrophy, to the life-threatening, such as hepatitis co-infection. Liver failure is now the leading cause of death among HIV positive patients in the United States, and HAART has been implicated as one of the factors (Manegold et al., 2001). Also, for HAART to be effective at suppressing HIV infection, exact adherence to a complicated treatment schedule must be maintained, a task which becomes increasingly difficult over the course of the infection. Although STI-induced immune control has shown disappointing durability on its own, it could still be used in conjunction with a reduced-dosage HAART to attain similar levels of viral suppression with fewer side effects. Assuming that the immune response affects different targets from the HAART, this regimen should also be more durable than HAART alone.

According to the model by Wodarz et al., the treatment schedules which lead to immune-mediated control can be complicated and non-intuitive, requiring multiple, precisely timed treatment interruptions. We have developed a model predictive control (MPC) based method for finding these schedules. This method is well-suited to the problem for a number of reasons: It is easily adaptable, which will allow for various improved models to be integrated as they are developed. It inherits from the MPC framework a certain robustness to disturbances and model inaccuracies which is important, since the model in question is known to suffer from these. 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.

This paper is organized as follows: in Section 2, we introduce the modified Wodarz–Nowak model of HIV infection. In Section 3, we develop the MPC-based technique for determining treatment schedules. In Section 4, we show and discuss various simulation results. In Section 5, we discuss various open questions and future work necessary for implementation of this method. In Section 6, we summarize and evaluate the promise of this method in HIV treatment.

2. Modified Wodarz–Nowak model

The model of HIV infection we will use in this paper was introduced in Wodarz and Nowak (1999), and further developed in Wodarz, 2001. This is a five state nonlinear ordinary differential equation model focusing on the cytotoxic lymphocyte (CTL) response to HIV infection, as mediated by helper-T cells. It is a reduced model, developed from a more extensive model which considers interactions between populations of many different species, including antigen-presenting cells and free virus, and various activation pathways. Under certain conditions, described in detail in Wodarz (2001),

the model reduces to the one below. The model is

$$\dot{\mathbf{x}} = \lambda - d\mathbf{x} - \beta(1-\eta\mathbf{u})\mathbf{x}\mathbf{y},$$

$$\dot{\mathbf{y}} = \beta(1-\eta\mathbf{u})\mathbf{x}\mathbf{y} - a\mathbf{y} - p_1\mathbf{z_1}\mathbf{y} - p_2\mathbf{z_2}\mathbf{y},$$

$$\dot{\mathbf{z}}_\mathbf{1} = c_1\mathbf{z_1}\mathbf{y} - b_1\mathbf{z_1},$$

$$\dot{\mathbf{w}} = c_2\mathbf{x}\mathbf{y}\mathbf{w} - c_2q\mathbf{y}\mathbf{w} - b_2\mathbf{w},$$

$$\dot{\mathbf{z}}_\mathbf{2} = c_2q\mathbf{y}\mathbf{w} - h\mathbf{z_2} \quad (1)$$

and the states used describe concentrations of: $\mathbf{x}$, healthy helper-T lymphocytes, $\mathbf{y}$, HIV-infected helper-T lymphocytes, $\mathbf{z}_1$, helper-independent CTL, $\mathbf{w}$, CTL precursors (memory CTL), and $\mathbf{z}_2$, helper-dependent CTL. The variable $\mathbf{u}$ represents our control input, the application of HAART therapy, and η is the therapy's effectiveness. We only consider the region where all states are positive, since only this region has physical meaning. This region is also forward invariant. The model recognizes the dependence of the CTL immune response on the helper-T system, and distinguishes between the helper-T mediated CTL response, which establishes a long-lived CTL population and persists even at low antigen levels, and the shorter-lived helper-T independent response, which dies out at low antigen levels. The control input recognizes the actual effect of HAART, which does not directly facilitate viral clearance, but rather shuts down viral replication, preventing new infection. Although reverse-transcriptase inhibitors (RTI) and protease inhibitors (PI), the two principal components of HAART, behave in different ways with transiently different effects, we propose to use them together, and the differing effects (primarily a transient production of non-infectious virus following introduction of PI therapy) become insignificant on the long time-scales for which we use the model. In theory, the value of $\mathbf{u}$ can vary between 0 (no treatment), and 1 (full treatment). However, the use of partially suppressive therapy ($0<\mathbf{u}<1$) is problematic. While the increased replication rate in the absence of suppression increases the mutation rate, and consequently the rate at which drug-resistant mutants are generated, the competitive advantage of the wild-type causes it to out-compete the resistant mutants and minimizes the chance of persistent colonies emerging. In the case of full suppression, the resistant strains have a strong competitive advantage, but the low replication rate ensures a low mutation rate and a small probability of generating resistant mutants. Partial suppression allows larger numbers of resistant mutants to be generated in an environment where they enjoy a competitive advantage. The danger of this can be seen in studies which showed a significant increase in the emergence of resistance in patients previously subjected to mono- or dual-therapy as compared to treatment-naive patients when started HAART (Phillips et al., 2002; Mocroft et al., 2003). Mono- and dual-therapies differ in two ways from HAART; the suppression of the virus is less complete, and the probability of resistant mutants emerging is higher, since fewer nucleotide changes are needed to confer resistance. Partially suppressive HAART would mimic at least one of these factors, so we avoid this by restricting $\mathbf{u}(t)$ to be either 0 (no treatment) or 1 (full treatment).

Healthy CD4+ helper-T cells ($\mathbf{x}$) are generated at a rate λ and die, of apoptosis and other natural means, at a rate $d\mathbf{x}$, which leads to a virus-free steady-state population of λ/d. Mass action reasoning tells us that healthy helper-T cells are infected by the HIV virus at a rate proportional to the product of their concentration and that of the free virus. The high rate of production of free virus by infected cells coupled with the short half life of HIV cause the population of free virus to track proportionally the population of infected cells. The model represents the rate of infection of healthy helper-T cells in the term $\beta\mathbf{x}\mathbf{y}$. The inhibition of this infection by the application of HAART is represented by multiplying this term by $(1-\eta\mathbf{u})$. The development of a HIV-specific memory T cell population is dependent on the simultaneous interaction of HIV-specific CD8+ CTL precursors and HIV-specific CD4+ helper-T cells with antigen presenting cells (APCs) displaying HIV peptides. Assuming a relatively constant population of APCs, and assuming that the population of HIV-presenting APCs is proportional to the population of HIV-infected helper-T cells, mass-action reasoning tells us the expansion of the HIV-specific memory CTL population will be proportional to the product of the concentrations of healthy helper-T cells ($\mathbf{x}$), infected helper-T cells ($\mathbf{y}$), and naive CTL precursors ($\mathbf{w}$), $c_2\mathbf{x}\mathbf{y}\mathbf{w}$. The differentiation of these activated cells into CTL effectors ($\mathbf{z}_2$), does not require additional CD4+ help, and is proportional to the interaction of memory T cells and HIV-presenting APCs described by the term $c_2q\mathbf{y}\mathbf{w}$. The CTL effectors ($\mathbf{z}_2$) kill infected helper-T cells at a rate $p_2\mathbf{y}\mathbf{z}_2$ and undergo apoptosis at a rate $h\mathbf{z_2}$. There may be a helper-independent component to the CTL response, represented in this model by the term $\mathbf{z_1}$. These cells expand without CD4+ help at a rate $c_1\mathbf{z_1}\mathbf{y}$, undergo apoptosis at a rate $b_1\mathbf{z_1}$ and kill infected cells at a rate $p_1\mathbf{z_1}\mathbf{y}$. For a more complete description of the states and their interaction, please see Wodarz and Nowak (1999) and Wodarz (2001).

The steady-state behavior of this model has many possible bifurcations due to parameter changes, which are discussed in Wodarz (2001). In this paper, however, we consider only the case where the parameters are such that the model has, in the absence of treatment ($\mathbf{u}=0$), two stable steady states: one describing a progressive infection leading to AIDS and one describing the establishment of a successful immune response. The steady-state values corresponding to the successful

immune response are

$$\mathbf{x_o} = \frac{\lambda}{d + \beta \mathbf{y_o}},$$

$$\mathbf{y_o} = \frac{[c_2(\lambda - dq) - b_2\beta] - \sqrt{[c_2(\lambda - dq) - b_2\beta]^2 - 4\beta c_2 q d b_2}}{2\beta c_2 q},$$

$$\mathbf{z_{1o}} = 0,$$

$$\mathbf{w_o} = \frac{h\mathbf{z_{2o}}}{c_2 q \mathbf{y_o}},$$

$$\mathbf{z_{2o}} = \frac{\mathbf{y_o} c_2(\beta q - a) + b_2\beta}{c_2 p_2 \mathbf{y_o}}. \tag{2}$$

As we can see, this steady state only exists when the quantity $[c_2(\lambda - dq) - b_2\beta]^2 - 4\beta c_2 q d b_2$ is not negative (otherwise the steady state takes imaginary values). If the infectivity of the virus is small such that

$$\beta < \frac{c_1[c_2 b_1(\lambda - qd) - b_2 c_1 d]}{b_1(c_2 b_1 q + b_2 c_1)},$$

this steady state is always established. This describes the system while HAART is being applied ($\mathbf{u} = 1$) with sufficiently high effectiveness (η close to 1).

If

$$\beta > \frac{c_1[c_2 b_1(\lambda - qd) - b_2 c_1 d]}{b_1(c_2 b_1 q + b_2 c_1)},$$

as is the case when $\mathbf{u} = 0$, there exists another stable steady state with values

$$\mathbf{x_a} = \frac{\lambda c_1}{d c_1 + b_1 \beta},$$

$$\mathbf{y_a} = \frac{b_1}{c_2},$$

$$\mathbf{z_{1a}} = \frac{\beta \mathbf{x_a} - a}{p_1},$$

$$\mathbf{w_a} = 0,$$

$$\mathbf{z_{2a}} = 0. \tag{3}$$

This steady state corresponds to a progressive infection leading to AIDS. Although only the first steady state (Eq. (2)) exists in the case where HAART is applied, it is worth noting that the location of the steady state described in Eq. (2) moves as a function of β (or, in the $\mathbf{u} = 1$ case, $\beta_{effective} = \beta(1 - \eta\mathbf{u})$), and its location in the applied treatment case lies outside the region of attraction of the same steady state in the no treatment case. That is, if treatment is applied for a sufficiently long time for the states to approach their steady-state values, and treatment is removed, the states will then converge to the steady state corresponding to progressive infection, not the steady state corresponding to a successful immune response. This would be the case even if a successful immune response had already been established. Establishing a successful immune response requires switching between the applied-treatment and no treatment cases, and using the transient behavior of these two cases to drive the states into the region of attraction of the first steady state. A more complete discussion of these behaviors can be found in Wodarz (2001).

This model is normalized, i.e. the values of the states have not been adjusted to correspond to any actual data. However, the basic features of the model (i.e. two steady states) have been verified through laboratory research on Simian immunodeficiency virus (SIV) infection in apes (Wodarz et al., 2000), and treatment interruptions in HIV patients have been associated with CTL control of the virus as well (Papasavvas et al., 2000; Davey et al., 1999; Ortiz et al., 1999; Rosenberg et al., 2000; Garcia et al., 2001). The success in using the model to plan schedules to induce immune control in SIV and the unscheduled successes in human patients lend hope to the possibility of using the model to design similar patterns of treatment for use in HIV-infected patients. Experimental measurements of some parameters were made by Frost (2002) and Ho et al. (1995), most notably the measurements of infected-cell half-lives by Ho et al. (1995). The robustness of the method developed in this paper, discussed in detail in Section 4.2 shows that precise values for the parameters are unnecessary, and the potential of this method will motivate experiments to obtain sufficiently accurate parameter estimates.

3. MPC treatment scheduling

Using control techniques to plan treatment applications for HIV is not a new idea (see for example Kirschner and Webb, 1997; de Souza, 1999; Brandt and Chen, 2001; Wein et al., 1997). In particular, Kirschner et al. use optimal control to argue for early initiation of treatment, a practice which has now become standard. However, the models used in these previous approaches do not accurately reflect the interactions between the helper-T and CTL systems, and consequently do not predict the possibility of induced immune control. Also, these previous approaches allow for continuous variation of the level of treatment, which is both difficult to achieve, given the dynamics of drug uptake, and potentially dangerous, as discussed in Section 2.

MPC is a technique in which the control is determined by solving, at each sampling period, a finite-horizon optimal control problem. For a discrete system of the form

$$\mathbf{X_{k+1}} = f(\mathbf{X_k}, \mathbf{u_k}) \tag{4}$$

and a current state $\mathbf{X_k}$ we find a length N sequence $\mathbf{U} = \{\mathbf{u_k}, \mathbf{u_{k+1}}, \ldots, \mathbf{u_{k+N-1}}\}$ which minimizes a cost function of the form

$$V(\mathbf{X_k}, \mathbf{U}) = \sum_{i=k}^{k+N-1} l(\mathbf{X_i}, \mathbf{u_i}) + F(\mathbf{X_{k+N}}), \tag{5}$$

where l is the stage cost and F is the terminal cost. The resulting optimal control sequence is applied, but only for one sampling period, since at the next sampling period a new optimal control is calculated. Under certain conditions, which depend on the specific implementation of MPC being applied, this procedure can guarantee both stability of a desired set point 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 Mayne et al. (2000).

This framework is uniquely well-suited for use in scheduling treatment interruptions for HAART for a number of reasons. The finite set of possible control values causes problems for many control design techniques, but it actually helps in MPC by making the optimization easier to solve. The stage and terminal costs flow in a natural way from the medical notions of treatment objectives and systemic cost. Finally, the application of MPC is frequently limited by the computational cost of the optimization; cost functions are restricted to those which lead to optimization problems which can be solved within the sampling time. In this application, however, the sampling times are measured in weeks, so computational time is not at a premium and the possibilities for cost functions are expanded.

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. We would like to achieve this while both maximizing the CTL response and minimizing the decrease in helper-T concentration. With this in mind, we choose our stage cost to be

$$l(\mathbf{X_i}, \mathbf{u_i}) = \alpha_1(\mathbf{x_i} - x_o)^2 + \alpha_2(\mathbf{w_i} - w_o)^2 + \alpha_3|\mathbf{u_i}| \tag{6}$$

where α_j are positive weighting constants and x_o, w_o, X_o are the steady-state values of their respective states at the desired equilibrium. If, for every $\mathbf{x} \in \mathscr{X}$ there exists a sequence $\mathbf{u} \in \mathscr{U}$ which drives the system to the desired steady state A,the work in Grimm et al. (2003) shows that a stage cost satisfying for all $\mathbf{x} \in \mathscr{R}^n$, $\mathbf{u} \in \mathscr{U}$ that $W(\mathbf{X_{i+1}}) - W(\mathbf{X_i}) \leqslant -\alpha_W(|\mathbf{X_i}|_A) + \gamma_W(l(\mathbf{X_i}, \mathbf{u_i}))$ for some $W : \mathscr{R}^n \to \mathscr{R}_{\geqslant 0}$ satisfying $W(\mathbf{X_i}) \leqslant \bar{\alpha}_W(|\mathbf{X_i}|_A)$ (for some $\alpha_W \in K_\infty$, $\gamma_W \in K_\infty$, $\bar{\alpha}_W : \mathscr{R}_{\geqslant 0} \to \mathscr{R}_{\geqslant 0}$ non-decreasing) is sufficient to ensure asymptotic stability, given a sufficiently long horizon N. Analytically verifying that l satisfies this detectability condition is difficult without explicitly defining the discretized version of the system. The local asymptotic stability of X_o guarantees that the detectability condition is satisfied at least locally, and the detectability properties of $|\mathbf{x}|_A$ through l on the continuous-time system encourage us to believe that these properties are satisfied globally. The robust performance exhibited in simulation further verifies this.

The MPC control algorithm we are using guarantees that the closed-loop system has a continuous Lyapunov function (it is formed via the value function and a function that demonstrates detectability). The existence of a continuous Lyapunov function implies some non-zero robustness to state and modeling errors. Non-zero robustness is classical when the right-hand side of the closed-loop is continuous. Our feedbacks are not continuous; robustness is guaranteed according to the main result in Kellett and Teel (2002), which says that stability is robust if and only if there exists a continuous Lyapunov function. While this result tells us that a non-zero margin of robustness exists, it does not tell us how large it is; we explore this experimentally in Section 4.

We constrain our control to take either the value 0 or 1. To be consistent with application in a clinical setting, we simulate weekly visits, set our sampling time at one week, and do not take measurements nor change our control at intervals of faster than one week. Since our sampling time is so long, it is not necessary to create an explicit discretization of our differential equation; we use a numerical simulator to approximate our discretization. Also, a finite horizon and a finite control space mean that we have, for each horizon, a finite number of possible control sequences. We solve our optimizations by exhaustively searching this space.

Table 1
Parameter values

d	β	a	p_1	p_2	c_1	c_2	b_1	b_2
0.1	1	0.2	1	1	0.03	0.06	0.1	0.01
λ	q	η	N	α_1	α_2	α_3	MaxStep	
1	0.5	0.9799	6	1	1	1	0.1	

These are the parameter values used in our implementation of the MPC feedback algorithm.

4. Simulation results

We implemented the algorithm described in Section 3 in MATLAB. In this section, we show simulation results which illustrate the algorithm's performance over a variety of conditions. For simplicity and readability, we plot only the healthy helper-T cells, infected helper-T cells, CTL memory and control states ($\mathbf{x}$, $\mathbf{y}$, $\mathbf{w}$, and $\mathbf{u}$). In every case, $\mathbf{z_2}$ tracked $\mathbf{w}$, and $\mathbf{z_1}$ rapidly approaches zero as immune control is established, so this is a sufficient sampling to understand the results. $\mathbf{x}$, $\mathbf{y}$, and $\mathbf{w}$ are

plotted as solid, dashed, and dotted lines, respectively, and **u** is plotted as a shaded area. The algorithm used nominal parameters as described in Table 1, and, unless otherwise stated, the common initial condition is $\mathbf{x} = 10$, $\mathbf{y} = 0.1$, $\mathbf{z_1} = 0.1$, $\mathbf{w} = 0.1$, $\mathbf{z_2} = 0.1$. The algorithm provided robust stability in simulation from every initial condition. We show in Sections 4.1–4.3 that the method successfully stabilizes the desired steady state despite state measurement error and modeling error. In Section 4.4, we demonstrate the flexibility of the method through simulations in which we vary the cost function.

4.1. Robustness: measurement noise

The main benefits to using a closed-loop control method are noise rejection and robustness. Our MPC-based method grants us a certain degree of robustness to measurement and modeling errors, which we

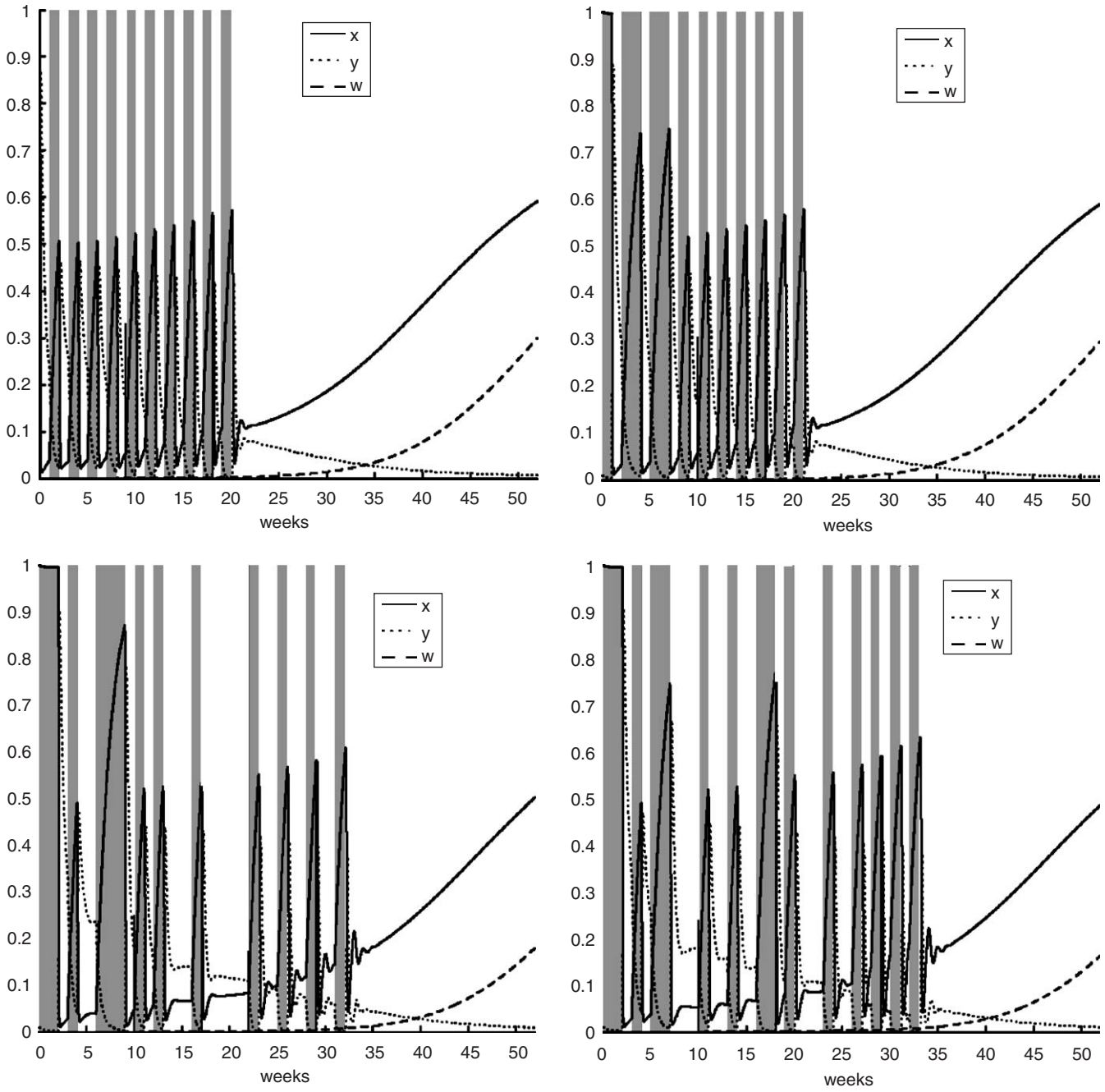

Fig. 1. Random measurement error. Noise of up to 100% of the value of each state was introduced into each measurement. The algorithm successfully stabilized the desired steady in every case, though the state took longer to converge. The plots above show representative outputs for up to 10%, 25%, 50% and 100% random measurement error, respectively.

demonstrate through simulation. We introduced into the state measurement a random noise signal, which would add or subtract from each state as much as 10% of the state value. The algorithm 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 25, 50 and 100% random error. The error caused the treatment scheduling algorithm to take significantly longer to stabilize the system, using many unnecessary treatment interruptions, but in every case the controller eventually induced a successful immune response. A sampling of these results can be seen in Fig. 1.

It is not unusual for feedback-controlled systems to display impressive robustness to flat random (as shown here) or Gaussian random measurement noise. These types of noise do not change the average value of the measured signal, and, so long as the controller is not too aggressive, the disturbances introduced by the faulty measurements tend to decay. The absolute level of robustness to measurement noise, if we consider the possibility of colored noise and pathological cases, is

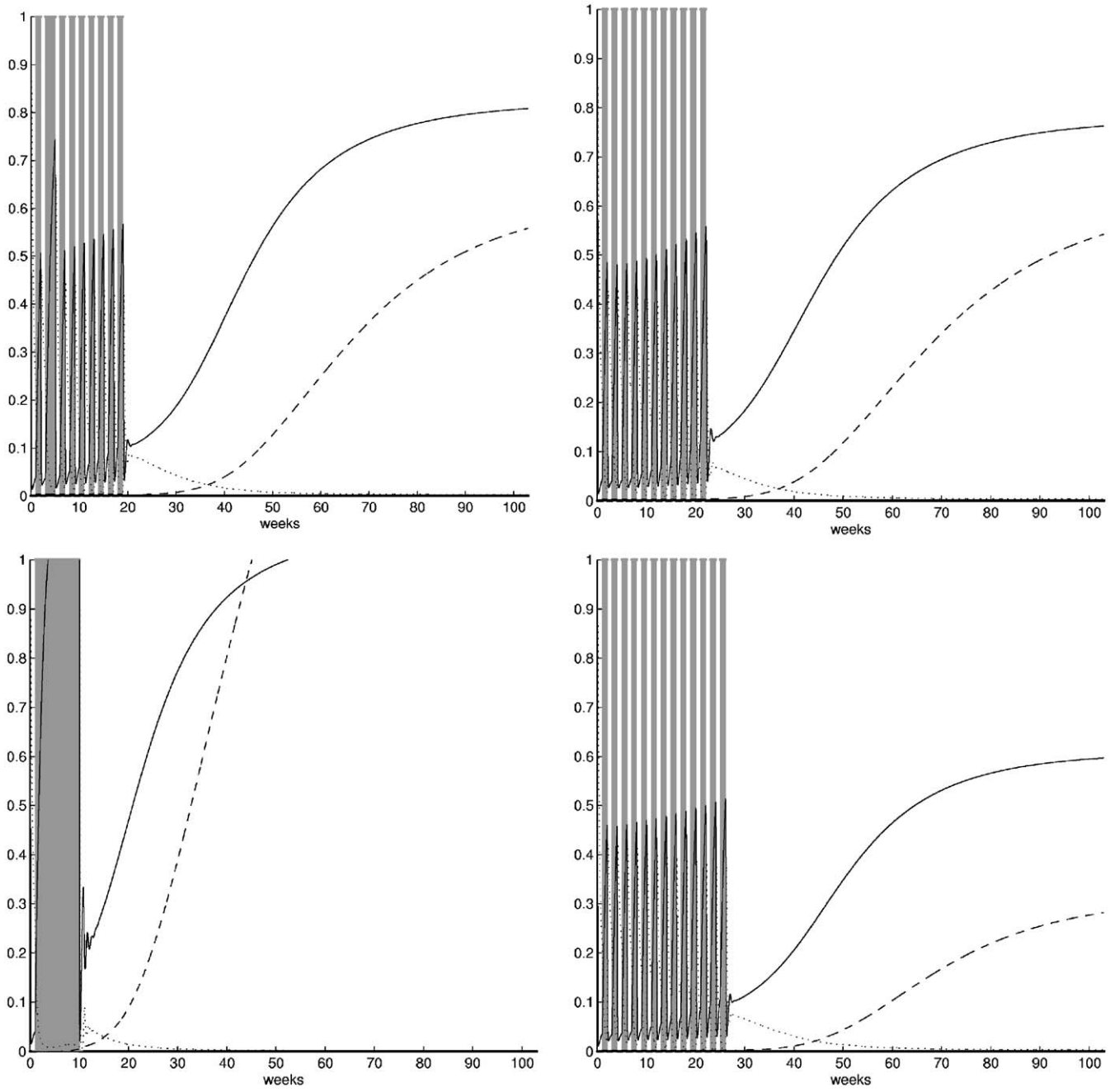

Fig. 2. Random modeling error. Random variations of up to 30% of the value of each parameter are introduced to the system, while the algorithm uses a nominal model. The above plots are representative for, from the upper left, the cases of 0%, 10%, 20% and 30% error, respectively.

likely much lower. However, flat random or Gaussian random error is likely the best model for measurements of the type used in this application, so we are likely to see this level of robustness in practice.

4.2. Robustness: modeling error

Implementing this algorithm requires that we first identify the parameters in the model, finding estimates of such parameters as the rate of generation of helper-T cells, the rate of death of infected cells, and the effectiveness of HAART at suppressing viral replication, among others. To explore the robustness of our technique to errors in these estimates, we introduced a random variation into every parameter in the model. The scheduling algorithm 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, 25 and 30% of each parameter value, allowing the algorithm up to 2 years to successfully stabilize the desired steady state. These simulations were carried out from the same common initial condition described in Section 4.1. For up to 15% error the scheduling algorithm induced a successful immune response every time. When we allowed up to 20% error, the scheduling algorithm failed to induce a successful immune response one time out of 140. The number of errors increased to two out of 100 at 25% error, and 12 out of 129 at 30% error. A representative sampling of these results can be seen in Fig. 2, and the results are summarized in Table 2. This is a worst-case scenario, as it is unlikely that we would be equally uncertain about every parameter. If we knew which parameters were the sources of uncertainty, we could likely show a much greater robustness. Nonetheless, the degree of robustness we do see certainly validates the use of feedback in treatment scheduling.

4.3. Robustness: combined errors

For ease of comparison, we analysed the scheduling algorithm's robustness to modeling and measurement error in isolation, starting from a common initial condition. However, the treatment scheduling algorithm is also robust to these errors when they occur simultaneously. To demonstrate this, we ran 100 simulations, starting from random initial conditions, in which we introduced random errors into both the model parameters and the state measurements of up to 10% of their respective values. A sampling of the results can be seen in Fig. 3. In every case, the treatment scheduling algorithm induced a successful immune response.

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.

Table 2
Robustness to modeling error

% Error	Success rate	# of samples
5	100%	100
10	100%	100
15	100%	115
20	99.4%	140
25	98%	100
30	90.7%	129

This table compares the degree of flat-random error in the parameter estimates with the success rate of the feedback algorithm in stabilizing the desired outcome.

4.4. Varying the cost function

One of the most useful things about 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 decreased helper-T concentration while decreasing the weight on the terms penalizing excess drug usage and rewarding CTL memory growth. This allowed us to change the relative importance of these goals, and the algorithm returned a schedule which converged to the desired equilibrium more slowly, using more anti-retroviral therapy overall, but did so while maintaining a higher average healthy helper-T cell concentration. A comparison of the performance of the adjusted cost function and the nominal cost function can be seen in Fig. 4.

5. Future work

The potential for MPC-based treatment scheduling for HIV infection is exciting, but a great deal more work is necessary before it can be implemented. The degree to which we can expect model uncertainty needs to be investigated and compared to the robustness of our method. We need to determine whether current measurement techniques can give us sufficiently accurate state measurements, and, if not, observer-based methods need to be explored. The model will need to be revised to better match measured patient data. The issues of drug resistance and mutation need to be considered. Finally, the cost functions and optimization objectives need to be refined to better achieve the medical aims of the treatment.

For the purposes of this study, we assumed that we were able to measure all the states in the model. In practice this is not the case. Indeed, we can measure

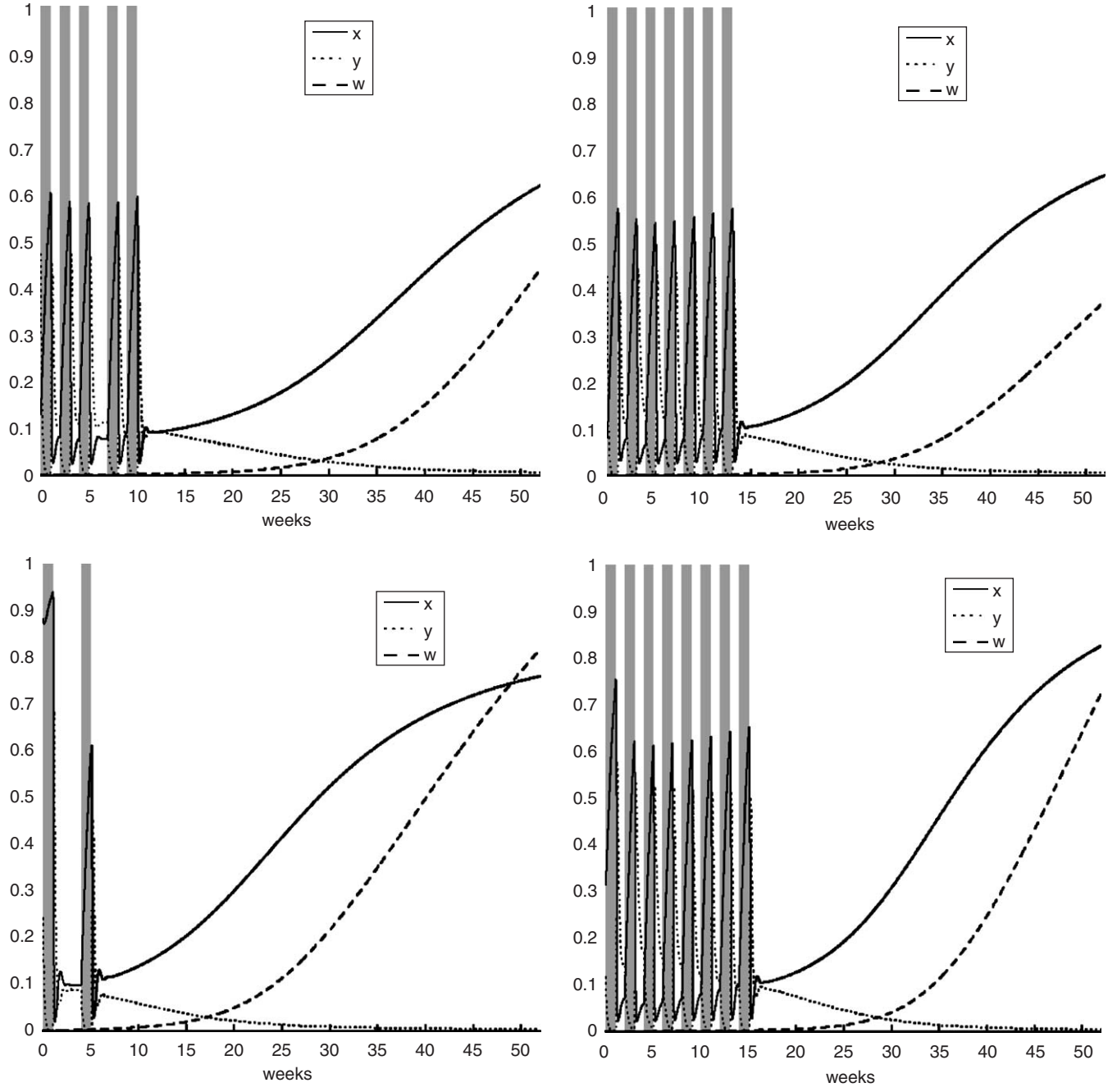

Fig. 3. Mixed random error. The values of the initial conditions are varied randomly. Random variations of up to 10% of the value of each parameter are introduced to the system as in Fig. 2. Random measurement noise of up to 10% of each state is added as in Fig. 1. The treatment scheduling algorithm successfully stabilized the desired steady state in every case.

accurately only a subset of the states of the HIV infection model, and the degree of accuracy with which these measurements can be made varies greatly from measurement to measurement. To use model predictive control in this case, we need to implement an observer. The use of observers in model predictive control is still an active area of research; recent results in Messina et al. (2004) verify that our specific implementation of MPC can be used with an observer. Given the varied levels of accuracy in the available measurements, it may be to our advantage to deliberately restrict our measurements to a more accurate subset, and substitute estimated values for measured values where the measurement is highly noisy. Accuracy analysis of existing measurements will be necessary to design a useful observer, and will require collaboration with clinical researchers.

We have briefly investigated robustness to modeling errors. We expect a certain amount of parameter

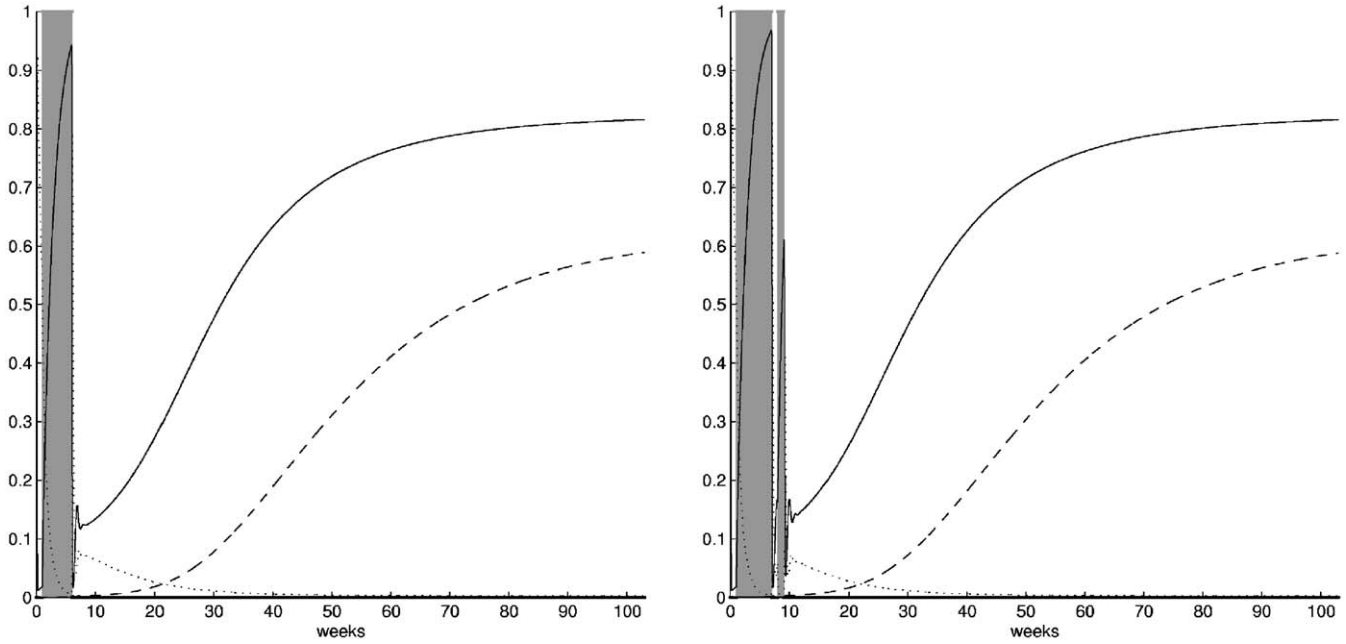

Fig. 4. Changed cost function. The stage cost in the first plot has weights with values $\alpha_1 = 1$, $\alpha_2 = 1$, $\alpha_3 = 1$, the second has weights with values $\alpha_1 = 100$, $\alpha_2 = 0.5$, $\alpha_3 = 0.1$. Initial condition is $\mathbf{x} = 10$, $\mathbf{y} = 0.01$, $\mathbf{z_1} = 0.01$, $\mathbf{w} = 0.01$, $\mathbf{z_2} = 0.01$. Both algorithms stabilize the desired steady state, but the second does so while maintaining a higher average level of healthy helper-T cells, at the cost of slower convergence and longer total anti-retroviral use.

variation from patient to patient, and while this might be resolved through the use of an identification scheme, there are also unmodeled dynamics, which will appear as parameter uncertainty or drift. The amount of variation and drift we can expect is unknown; in order to discover this, the model parameters need to be matched to patient data. More information about the degree of uncertainty in each parameter will allow us to determine whether our method can give us sufficient robustness to these problems.

Several variations on the model used in our method have been considered in Wodarz and Nowak (1999), Wodarz (2001), Wodarz et al. (2000), Altes et al. (2002) and Arnaout et al. (2000). We must determine whether the additional features modeled in these papers are useful or important in our application. In Wodarz (2001) and Altes et al. (2002), the authors model the dynamics of active and resting T cells. This is one variation likely to be useful in our application, since the sum of these two states more closely approximates what we can currently measure. Such a model would also let us account for the possibility of selective extinction of HIV-specific helper-T cells during periods of high viral activity. We are currently investigating expanded models which more accurately represent the dynamics of helper-T activation. Also, in Wodarz (2001), a state representing an alternate, resistant strain of the virus is introduced. It would be worth exploring under what conditions a treatment schedule could restore helper-T functionality and induce an effective CTL immune response in the presence of a HAART-resistant strain before the presence of the HAART selects the resistant strain to dominance and control is lost.

The possible correlation between treatment interruptions and the emergence of drug resistance must also be considered. There is still concern that the transient increases in viral load brought on by the treatment interruptions will increase the risk of drug resistant mutations occurring. It would be worth investigating a variation on the cost functions that penalizes treatment interruptions or viral rebound levels in such a way as to minimize the risk. Also, the possibility of escape mutants, which are resistant to an already established immune response, also needs to be considered.

Finally, we are working on refining the cost functions used in our method, using criteria gleaned from colleagues in immunology. A better understanding of the clinical goals and requirements will lead to more useful cost functions and a more realistic control design.

6. Summary

Enhancing the immune response to HIV through scheduled interruptions of HAART, leading to CTL-mediated control of the viral load, is an exciting prospect. Control techniques address best the complexities involved in finding an effective interruption

schedule. MPC is a uniquely appropriate framework for this problem. It provides needed stability and robustness, its structure accommodates the problem's specific implementation requirements, and its flexibility allows for an intuitive integration of the problem's objectives.

In this paper, we have implemented such an MPC-based treatment scheduling technique. We have simulated its performance while varying initial conditions, model parameters and cost functions. The results demonstrated the methods effectiveness as well as its flexibility.

The applicability of this technique is likely to be limited to those patients who begin therapy early in infection, preserving the HIV-specific responsiveness of their immune system. Though the durability of the induced response has been disappointing when used along, the technique proposed in this paper should result in a more reliable method of inducing successful immune responses, which could be used in conjunction with a reduced-dose schedule of HAART to achieve similar levels of suppression with greater durability and significantly reduced toxicity.

While the results so far are very promising for the future of MPC-based treatment scheduling, a great deal of work remains to be done. This will demand a great deal of collaboration across disciplines. We have sketched a few avenues of research we expect to be worthwhile, which we are pursuing together with colleagues in immunology.

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