

A state-dependent Riccati equation-based estimator approach for HIV feedback control

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SUMMARY

We consider optimal dynamic multidrug therapies for human immunodeficiency virus (HIV) type 1 infection. In this context, we describe an optimal tracking problem attempting to drive the states of the system to a stationary state in which the viral load is low and the immune response is strong. We consider optimal feedback control with full-state as well as with partial-state measurements. In the case of partial-state measurement, a state estimator is constructed based on viral load and T-cell count measurements. We demonstrate by numerical simulations that by anticipation of and response to the disease progression, the dynamic multidrug strategy reduces the viral load, increases the CD4+ T-cell count and improves the immune response. Copyright © 2006 John Wiley & Sons, Ltd.

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1. INTRODUCTION

During the last two decades, medical treatment for human immunodeficiency virus (HIV) has greatly improved. Typically, therapy can prolong time to onset of acquired immune deficiency syndrome (AIDS) for tens of years. The prevailing medical practice is to prescribe highly active antiretroviral therapy (HAART) which can reduce viral load and maintain high CD4+ T-cell

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counts. This therapy involves combinations of three or more drugs that are called 'cocktails'. However, in spite of the success of HAART, some patients develop resistance to one or more of the drugs in long-term use. In these cases, it is necessary to change the composition of HAART. In addition, there may be severe side effects from the medication. Moreover, in developing countries, the expense of HAART is often prohibitively high. Motivated by these and other reasons, the search for alternative treatments is very active. In this paper, we study dynamic multidrug therapies that can lead to long-term control of HIV by the immune response system *after* discontinuation of drug treatment.

HIV infects CD4⁺ T-cells (a fundamental component of the human immune response system) and other target cells, hijacking their replication mechanisms. The infected cells then produce a large number of copies of the virus. Currently, the two most important categories of anti-HIV drugs are reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). A typical HAART cocktail consists of one or more RTIs and a PI. The RTIs prevent HIV from infecting cells by blocking the integration of the viral code into the target cells. PIs interfere with the replication of viruses by infected cells. Virions may still be produced, but they are generally noninfectious; that is, they are not capable of infecting new target cells. In practice, RTIs cannot completely block the virus integration of the DNA in target cells. Also, some infectious virions are produced under PI medication. Every drug has a maximum efficacy which depends on many factors such as, for example, viral strains present. One might expect that the effectiveness of HIV therapy could be improved by developing dynamic multidrug strategies, where the combination of drugs given to HIV patients changes over time in response to the individual's disease progression.

A number of different mathematical models based on systems of differential equations have been developed, see for example Reference [1]. Some of these models used to design dynamical drug treatments are presented in References [1–7]. In the long-term pathogenesis of HIV an immune response can play an important role. However, the models in References [1, 4] do not contain immune response while the authors in References [2, 3, 5–7] do consider the immune response. Since immune mechanisms responding to HIV are not yet very well understood, various immune response models have been proposed in the literature. In this study, we employ a model based on the models considered in Reference [2, 8] which contain an immune effector component.

Optimal treatment of HIV infection using a control theoretic approach is the subject of substantial research activity. The papers [2, 9–13] consider only RTI medication while the papers [14, 15] consider only PIs. In References [16–18], all effects of a HAART medication are combined and represented by one control variable in the model. In References [8, 19–22], dynamical multidrug therapies based on RTIs and PIs are designed. In these proposed therapies the dosage of both medications can change independently of each other and can either be continuous or on–off types. Studies of continuously varying medical therapies have been more common, see, e.g., References [2, 6, 9–12, 14, 15, 19, 20, 22–24]. More recently, the on–off type of treatment, which is also known as a structured treatment interruption (STI), has attracted a lot of attention in the medical literature (see for example References [2, 8, 25] and the references therein). A primary argument for use of STI therapy instead of continuously varying dosage is that one might lower the risk of HIV mutating to strains which are resistant to the current medication regimen. However, STI strategy is not without risk to the immune system. Among the main risks are the potential for viral-mediated CD4⁺ T-cells loss and the mutation by the virus against the reinitiated treatment [26]. Recent results on STI schedules including optimal

treatments are presented in References [2, 8, 17, 18, 21]. In this paper, we consider optimal feedback treatment of HIV infection by continuously varying dosages of RTIs and PIs in a nonlinear model including an immune response.

There are a number of control techniques that can be utilized to design dynamical therapies for HIV. Open-loop control has been employed in References [2, 8, 10–14, 21, 22, 24] and feedback control has been used in References [9, 13, 16–19, 23]. The papers [9, 16, 23] consider the feedback control based on partial measurements. An estimator is employed to construct the control in Reference [9] while in Reference [16] this possibility is only briefly mentioned. A linear quadratic regulator (LQR) control based on Riccati equations is studied in Reference [19].

For linear systems, LQR is a well-known and accepted methodology for the synthesis of control laws. However, most mathematical models for biological systems, including the HIV dynamics with immune response as studied in this paper, are nonlinear. One of the promising and emerging methodologies for designing nonlinear controllers is the state-dependent Riccati equation (SDRE) approach in the context of nonlinear regulator problems (see for example, References [27–30]). In essence, the SDRE method is a systematic way of designing nonlinear feedback controllers by factoring the state-dependent nonlinearity of the state equations as a product of a state-dependent matrix with the state vector. That is, by using direct parameterization the nonlinear system is brought to a linear structure with state-dependent coefficient matrices. This parametrization is however not unique and thus some flexibility in design is permissible. The state feedback control law is then given in terms of the solution of an SDRE. As shown in Reference [28], the SDRE method is a powerful approach that is readily applicable to the nonlinear tracking and nonlinear state estimation problems, since it is closely related to the algebraic Riccati equation-based method used to find the feedback controls in the linear cases.

While the SDRE method has been applied earlier to mostly engineering-type problems such as flight dynamics simulation [28] and chemical vapour deposition [31], the idea of *using SDRE for combined drug/immune response control of HIV infection* as presented here is new. In addition, we propose, in this paper, a more systematic approach to parametrization of the nonlinear system as a linear structure with state-dependent coefficient matrices. In our approach, the state-dependent matrix is the Jacobian of the nonlinear system dynamics. Our parametrization choice together with the proposed time discretization method imply that the state-dependent coefficient matrix is in fact the exact local linearization of the nonlinear state-dependent system dynamics at the current state of the system.

The outline of the paper is as follows. We begin in Section 2 with a description of a rather complex HIV model. An optimal quadratic tracking problem is formulated in Section 3 to drive the state of the system to a stationary state which we call the ‘healthy’ state (it has low viral load and high CD4+ T-cell count). Section 4 contains a direct factorization of the nonlinear system into a linear form with state-dependent coefficient matrices. By then mimicking standard LQR formulation for linear systems, a suboptimal feedback control is derived in Section 5. Sections 6 and 7 present the formulation of the state estimator for more realistic control problems where only partial state measurements are available for feedback. In Sections 8 and 9, we summarize the numerical procedure for the synthesis of the suboptimal feedback controls. Numerical simulation results are summarized in Section 10 and concluding remarks are presented in Section 11.

2. HIV MODEL

A modification of the mathematical model as presented in References [2, 8] for the pathogenesis of HIV is adopted for this paper. We include an additional state variable for noninfectious virus [1, 32]. The model is essentially based on the two target model proposed by Callaway and Perelson [32] without making distinction between short and long lived infected target cells. In addition, it contains an immune response component similar to the one described by Bonhoeffer *et al.* [3] with a Michaelis–Menten-type saturation nonlinearity. Our model captures many of the observed behavioural properties of HIV dynamics [3, 32] and, furthermore, its mathematical properties are well-suited for designing multidrug therapies using control theoretic approaches [2, 8]. The purpose of adding non infectious virus to the model is to reflect what is actually being measured in clinical data. The viral load measurements cannot differentiate between infectious and noninfectious virus, detecting only the total amount of virus. Hence, in order to construct a state estimator (for developing dynamic multidrug therapy based on the disease progression) using such measurements, we need to model also the noninfectious virus population. It should be noted that the inclusion of this additional state does not effect the dynamics of the other state variables.

The dynamics of our HIV model are described by the set of ordinary differential equations:

$$\begin{aligned}
 \dot{T}_1 &= \lambda_1 - d_1 T_1 - (1 - \varepsilon_1) k_1 V_1 T_1 \\
 \dot{T}_2 &= \lambda_2 - d_2 T_2 - (1 - f \varepsilon_1) k_2 V_1 T_2 \\
 \dot{T}_1^* &= (1 - \varepsilon_1) k_1 V_1 T_1 - \delta T_1^* - m_1 E T_1^* \\
 \dot{T}_2^* &= (1 - f \varepsilon_1) k_2 V_1 T_2 - \delta T_2^* - m_2 E T_2^* \\
 \dot{V}_1 &= (1 - \varepsilon_2) N_T \delta (T_1^* + T_2^*) - [c + (1 - \varepsilon_1) \rho_1 k_1 T_1 + (1 - f \varepsilon_1) \rho_2 k_2 T_2] V_1 \\
 \dot{V}_{\text{NI}} &= \varepsilon_2 N_T \delta (T_1^* + T_2^*) - c V_{\text{NI}} \\
 \dot{E} &= \lambda_E + b_E \frac{T_1^* + T_2^*}{T_1^* + T_2^* + K_b} E - d_E \frac{T_1^* + T_2^*}{T_1^* + T_2^* + K_d} E - \delta_E E
 \end{aligned} \tag{1}$$

In model (1), the state variables are: T_1 , the uninfected CD4+ T-cells; T_2 , the uninfected target cells of second kind; T_1^* , the infected T-cells; T_2^* , the infected target cells of second kind; V_1 , the infectious virus; V_{NI} , the noninfectious virus; and E , the immune effectors. The controllers ε_1 and ε_2 represent the RTI and PI ‘efficacies’, respectively. We do not give precise biological definitions for the target cells of second kind and the immune effectors. They could, for example, be related to macrophages and cytotoxic T-lymphocytes, respectively. For a more detailed description of the variables and rationale for model (1) we refer the reader to the articles [2, 8]. Table I contains the values of parameters, which are the same as those used in References [2, 8]. The only difference is that we use cubic millimeter as our unit volume instead of milliliter.

Table I. The values of the parameters in the HIV model.

Parameter	Value	Unit	Parameter	Value	Unit
λ_1	10.0	cells/mm ³ day	λ_2	31.98×10^{-3}	cells/mm ³ day
d_1	0.01	1/day	d_2	0.01	1/day
k_1	8.0×10^{-4}	mm ³ /virions day	k_2	0.1	mm ³ /virions day
m_1	0.01	mm ³ /cells day	m_2	0.01	mm ³ /cells day
ρ_1	1	virions/cells	ρ_2	1	virions/cells
δ	0.7	1/day	c	13.0	1/day
f	0.34	dimensionless	N_T	100.0	virions/cells
λ_E	1.0×10^{-3}	cells/mm ³ day	δ_E	0.1	1/day
b_E	0.3	1/day	d_E	0.25	1/day
K_b	0.1	cells/mm ³	K_d	0.5	cells/mm ³

In order to simplify our subsequent discussions, we introduce the notation x and u to denote the state and control vectors, respectively. Thus we define

$$x = \begin{pmatrix} T_1 \\ T_2 \\ T_1^* \\ T_2^* \\ V_I \\ V_{NI} \\ E \end{pmatrix} \quad \text{and} \quad u = \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$$

With the above notation, the HIV model (1) can be expressed in the generic form

$$\dot{x} = f(x) + B(x)u \quad (2)$$

where the precise representation for $f(x)$ and $B(x)$ will be described later in Section 4.

For feedback control, we need current knowledge on the state of the system. In our effort here we assume that partial state observations ($T_1 + T_1^*$, $V_I + V_{NI}$) are available (see Reference [2] for a discussion on the clinical data). This is representative of the type of clinical data widely discussed in the literature (see for example, Reference [2]). Hence, the output or observation takes the form

$$z = \begin{pmatrix} z_1 \\ z_2 \end{pmatrix} = \begin{pmatrix} 1 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 & 0 \end{pmatrix} x = C_x \quad (3)$$

where z_1 and z_2 represent the total CD4+ counts and the total viral loads, respectively.

3. AN OPTIMAL TRACKING PROBLEM FORMULATION

With the parameters given in Table I and the assumption of no medication ($\varepsilon_1 = \varepsilon_2 = 0$), the model exhibits several steady states. These are described and analysed in Reference [2, 8] with the noninfectious virus V_{NI} state always being zero in these steady states. We are particularly interested in the so-called ‘healthy’ steady state given by

$$\begin{aligned} T_1 &= 967.839 \text{ cells/mm}^3, & T_2 &= 0.621 \text{ cells/mm}^3, \\ T_1^* &= 0.076 \text{ cells/mm}^3, & T_2^* &= 0.006 \text{ cells/mm}^3 \\ V_1 &= 0.415 \text{ virions/mm}^3, & V_{\text{NI}} &= 0.0 \text{ virions/mm}^3, & \text{and} & E = 353.108 \text{ cells/mm}^3 \end{aligned} \quad (4)$$

which was also shown to be locally asymptotically stable. This means that after a sufficiently small perturbation from (4), the trajectory of the state x returns to the stable equilibrium (4). It is noted that this stable equilibrium exhibits a strong immune response, low viral load and reasonably large target cell (T_1) counts.

HAART has proven to be very effective at reducing the viral load to below detectable levels. However, sustainable suppression has proven to be difficult using HAART because patients taking these drugs experience adverse side effects that make adherence to therapy very difficult. In this paper, we adopt a control theoretic approach to find a suboptimal treatment strategy that can lead to high immune effector levels and subsequent control of viral load without the need for further drug therapy.

We formulate the problem of finding an effective multidrug therapy as a tracking problem. To this end, we define the objective functional

$$J(x, u) = \frac{1}{2} \int_0^\infty \{ (V_1 - 0.415)^2 + 10(E - 353.108)^2 + (\varepsilon_1/\varepsilon_1^{\max})^2 + (\varepsilon_2/\varepsilon_2^{\max})^2 \} dt \quad (5)$$

where V_1 is the number of free virus and E represents the immune response. The control variable ε_1 , where $0 \leq \varepsilon_1 \leq \varepsilon_1^{\max}$, denotes the ‘efficacy’ of the RTI. Similarly, the control variable ε_2 , $0 \leq \varepsilon_2 \leq \varepsilon_2^{\max}$, represents the ‘efficacy’ of the PI. We note that throughout we use the somewhat nonstandard terminology ‘efficacy’ interchangeably with the control level for the two drugs. The weights in (5) have been determined *a priori* through a series of numerical experiments. The feedback control algorithm proposed in Section 5 is not particularly sensitive to the choice of these weights.

We denote the control vector u by

$$u = \begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix}$$

We also introduce the following two vectors:

$$\tilde{u} = \begin{pmatrix} 0 \\ 0 \end{pmatrix} \quad \text{and} \quad \hat{u} = \begin{pmatrix} \varepsilon_1^{\max} \\ \varepsilon_2^{\max} \end{pmatrix}$$

The optimal tracking control problem is to find a dynamic multidrug therapy $u(t)$ satisfying

$$\min_{\tilde{u} \leq u(t) \leq \bar{u}} J(x(t), u(t)) \quad (6)$$

subject to the state equation given by (2) with initial condition $x(0) = x_0$. We could, of course, consider the restricted class of scalar controllers u where $\varepsilon_i(t) = \hat{\varepsilon}_i u(t)$. While this is the more usual treatment protocol in clinical practice, we are interested in investigation here of the more flexible scenario where the RTI and PI levels can vary independently. We also note that although we formulate a continuous feedback, current clinical practice involves discrete observations and hence our approach, if implemented, would have to be approximated by some type of interpolated estimate of the observed states (see especially the computational examples below where impractical observation sampling is used).

We note that our mathematical model for HIV dynamics (2) is nonlinear. One of the highly promising and emerging techniques for designing nonlinear feedback controllers is the SDRE approach in the context of the nonlinear regulator problem. This technique essentially uses direct parametrization to rewrite the nonlinear state function $f(x)$ in (2) as a product of a state-dependent coefficient matrix with the state vector. This parametrization is, of course, not unique and one obvious factorization is given in terms of the local linearization of the state equation. Even though we did not perform sensitivity analysis of the results with respect to parameter uncertainty, the main benefit to using a feedback control (as opposed to an open loop control obtained by a straightforward optimization of the objective function (5)) is its robustness to measurement errors (see results in Section 10.2.2) and parameter uncertainty (see also Section 11 for another discussion).

4. A LOCAL LINEARIZATION OF THE STATE EQUATION

To design a nonlinear feedback controller using the SDRE methodology, one usually first rewrites the nonlinear dynamics (2) in the state-dependent coefficient form $f(x) = A(x)x$. Underlying this form is the tacit assumption that $f(0) = 0$. Our HIV model (1) does not satisfy this condition. For this reason we divide $f(x)$ into two parts

$$f(x) = a + \tilde{f}(x) \quad \text{and} \quad \tilde{f}(0) = 0$$

where a is chosen in such a way that $f(0) - a = 0$. The simplest choice is $a = f(0)$. However, instead of using this simple choice we let a depend on x and we denote this dependence by $a(x)$. The choice of $a(x)$ will become clear below (see (9)).

We thus rewrite the state equation (2) as

$$\dot{x} = A(x)x + a(x) + B(x)u \quad (7)$$

That is, $f(x)$ is parameterized as

$$f(x) = A(x)x + a(x) \quad (8)$$

It has been noted [28–30] that the choice of $A(x)$ in systems where $f(0) = 0$ is not unique and the same also holds for our generalized formulation. However, for this formulation a natural

choice of the matrix $A(x)$ is the Jacobian of $f(x)$. That is,

$$A(x) = \frac{\partial f(x)}{\partial x} \quad \text{and} \quad a(x) = f(x) - A(x)x \quad (9)$$

For our particular HIV model (1) the Jacobian is given by

$$A(x) = \begin{pmatrix} -d_1 - k_1 V_1 & 0 & 0 & 0 & -k_1 T_1 & 0 & 0 \\ 0 & -d_2 - k_2 V_1 & 0 & 0 & -k_2 T_2 & 0 & 0 \\ k_1 V_1 & 0 & -\delta - m_1 E & 0 & k_1 T_1 & 0 & -m_1 T_1^* \\ 0 & k_2 V_1 & 0 & -\delta - m_2 E & k_2 T_2 & 0 & -m_2 T_2^* \\ -\rho_1 k_1 V_1 & -\rho_2 k_2 V_1 & N_T \delta & N_T \delta & A_{55} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -c & 0 \\ 0 & 0 & A_{73} & A_{74} & 0 & 0 & A_{77} \end{pmatrix}$$

where

$$A_{55} = -c - \rho_1 k_1 T_1 - \rho_2 k_2 T_2$$

$$A_{73} = A_{74} = \frac{b_E K_b E}{(T_1^* + T_2^* + K_b)^2} - \frac{d_E K_d E}{(T_1^* + T_2^* + K_d)^2}$$

and

$$A_{77} = \left(\frac{b_E}{T_1^* + T_2^* + K_b} - \frac{d_E}{T_1^* + T_2^* + K_d} \right) (T_1^* + T_2^*) - \delta_E$$

Finally, the matrix $B(x)$ in (7) is given by

$$B(x) = \begin{pmatrix} k_1 V_1 T_1 & 0 \\ f k_2 V_1 T_2 & 0 \\ -k_1 V_1 T_1 & 0 \\ -f k_2 V_1 T_2 & 0 \\ \rho_1 k_1 V_1 T_1 + f \rho_2 k_2 V_1 T_2 & -N_T \delta (T_1^* + T_2^*) \\ 0 & N_T \delta (T_1^* + T_2^*) \\ 0 & 0 \end{pmatrix}$$

5. OPTIMAL FEEDBACK CONTROLLERS

In this section, we formally derive the nonlinear feedback controllers for the optimal tracking problem described in Section 3. We first will assume that all state variables are available for feedback. Our approach is to use the SDRE technique and mimic the standard LQR formulation for linear systems.

We begin by rewriting the objective functional in (5) in the generic form

$$J(x, u) = \frac{1}{2} \int_0^\infty [(x - y)^T Q(x - y) + u^T R u] dt$$

where the dynamic tracking variable y represents the stable equilibrium state (4).

The Hamiltonian for our optimal control problem is given by

$$\begin{aligned} \mathcal{H}(x, u, p) = & \frac{1}{2}(x - y)^T Q(x - y) + \frac{1}{2}u^T R u + p^T(A(x)x + a(x) + B(x)u) \\ & - \check{w}^T(u - \check{u}) - \hat{w}^T(\hat{u} - u) \end{aligned}$$

where the penalty multiplier vectors \check{w} and \hat{w} , are introduced to account for the constraints on the control variable u , are nonnegative and satisfy the conditions

$$\check{w}^T(u - \check{u}) = \hat{w}^T(\hat{u} - u) = 0$$

at the optimal control. From the Hamiltonian, the necessary conditions for optimality are found to be

$$\begin{aligned} \dot{x} &= A(x)x + a(x) + B(x)u = \frac{\partial \mathcal{H}}{\partial p} \\ \dot{p} &= -Q(x - y) - \left[\frac{d(A(x)x)}{dx} \right]^T p - \left[\frac{d(a(x))}{dx} \right]^T p - \left[\frac{d(B(x)u)}{dx} \right]^T p = -\frac{\partial \mathcal{H}}{\partial x} \\ 0 &= Ru + B^T(x)p - \check{w} + \hat{w} = \frac{\partial \mathcal{H}}{\partial u} \end{aligned} \quad (10)$$

Let A_i : denote the i th row of $A(x)$ and B_i : denote the i th row of $B(x)$. Then

$$\frac{d(A(x)x)}{dx} = A(x) + \frac{d(A(x))}{dx}x = A(x) + \begin{bmatrix} \frac{dA_{1:}}{dx_1}x & \cdots & \frac{dA_{1:}}{dx_n}x \\ \vdots & \ddots & \vdots \\ \frac{dA_{n:}}{dx_1}x & \cdots & \frac{dA_{n:}}{dx_n}x \end{bmatrix} \quad (11)$$

and

$$\frac{d(B(x)u)}{dx} = \begin{bmatrix} \frac{dB_{1:}}{dx_1}u & \cdots & \frac{dB_{1:}}{dx_n}u \\ \vdots & \ddots & \vdots \\ \frac{dB_{n:}}{dx_1}u & \cdots & \frac{dB_{n:}}{dx_n}u \end{bmatrix} \quad (12)$$

The last equation of (10) leads to the optimal control

$$u = -R^{-1}(B^T(x)p - \check{w} + \hat{w})$$

Mimicking the tracking problem for linear systems, we assume that the adjoint state has the form

$$p = \Pi(x)x + b(x) \quad (13)$$

where Π is a matrix, b is a vector and both are state dependent. To find $\Pi(x)$ and $b(x)$, we differentiate (13) with respect to time along a trajectory and substitute the optimality condition (10) for \dot{p} to obtain

$$-Q(x - y) - \left[\frac{d(A(x)x)}{dx} \right]^T p - \left[\frac{d(a(x))}{dx} \right]^T p - \left[\frac{d(B(x)u)}{dx} \right]^T p = \dot{\Pi}x + \Pi\dot{x} + \dot{b} \quad (14)$$

where we use the notation

$$\dot{\Pi}(x) = \sum_{i=1}^n \Pi_{xi}(x)\dot{x}_i(t)$$

A similar definition also holds for \dot{b} . Substituting the expressions for p , \dot{x} , and u and rearranging terms, we find

$$\begin{aligned} & \left[\left(\dot{\Pi}(x) + \left[\frac{d(A(x))}{dx} x \right]^T \Pi(x) + \left[\frac{d(B(x)u)}{dx} \right]^T \Pi(x) + \left[\frac{d(a(x))}{dx} \right]^T \Pi(x) \right) \right. \\ & \quad \left. + (\Pi(x)A(x) + A^T(x)\Pi(x) - \Pi(x)B(x)R^{-1}B^T(x)\Pi(x) + Q) \right] x \\ & \quad + \dot{b} - Qy + \Pi(x)a(x) - \Pi(x)B(x)R^{-1}(-\check{w} + \hat{w}) \\ & \quad + \left(A^T(x) - \Pi(x)B(x)R^{-1}B^T(x) + \left[\frac{d(A(x))}{dx} x \right]^T + \left[\frac{d(B(x)u)}{dx} \right]^T + \left[\frac{d(a(x))}{dx} \right]^T \right) b = 0 \quad (15) \end{aligned}$$

If we approximate (see Reference [28]) by assuming that the derivative terms

$$\frac{d(A(x))}{dx}, \quad \frac{d(B(x)u)}{dx}, \quad \frac{d(a(x))}{dx}$$

are small as well as that Π and b are stationary, it follows that the suboptimal solution to the optimal tracking problem is given by

$$u = \min (\max(\tilde{u}, \hat{u}), \hat{u}) \quad (16)$$

where minimum and maximum are taken component wise and

$$\tilde{u} = -R^{-1} B^T(x)(\Pi(x)x + \tilde{b}(x)) \quad (17)$$

It should be emphasized that the above approximate feedback law for dynamic multidrug treatment is only suboptimal since the formula is only valid if both controls do not violate the constraints or violate the constraint simultaneously. However, our numerical studies suggest that the feedback law works reasonably well even when these conditions are not met. The state dependent function $\tilde{b}(x)$ is given by the expression

$$\tilde{b} = (A^T(x) - \Pi(x)B(x)R^{-1}B^T(x))^{-1}(Qy - \Pi(x)a(x))$$

where $\Pi(x)$ satisfies the SDRE

$$A^T(x)\Pi(x) + \Pi(x)A(x) - \Pi(x)B(x)R^{-1}B^T(x)\Pi(x) + Q = 0$$

One approach involves obtaining the solution to SDRE is by use of symbolic software packages such as Macsyma or Mathematica. However, once the nonlinear dynamics of the system become complex, one has to rely on numerical approximation techniques to obtain its solution. In Sections 8 and 9, we will discuss the numerical procedure that we used to obtain the solution of the SDRE.

6. COMPENSATOR DESIGN

For the synthesis of the nonlinear feedback control law derived in Section 5, full knowledge of all the state variables is required. However, in many problems of practical interest, only partial measurements of the state are available. In this section, we consider the problem of designing a state estimator (or Luenberger observer) to be used in conjunction with the nonlinear feedback control laws described earlier. We recall that the dynamical system and the observation are given by

$$\dot{x} = f(x) + B(x)u$$

$$z = Cx$$

where the output matrix C is defined by (3).

As in the linear problem, we design the state estimator to be of the form

$$\dot{x}_e = f_e(x_e) + F(Cx, x_e)$$

where the functions f_e and F are to be specified later. It should be emphasized that the rationale behind the state estimator is that it is indeed the state estimator x_e (and not the state x) that is to be used in the nonlinear feedback control laws given by Equations (16) and (17). Defining the error function between the state and the state estimator as $e = x - x_e$ and taking its derivative, we obtain

$$\dot{e} = f(x) + B(x)u - f_e(x_e) - F(Cx, x_e)$$

If we choose $f_e(x_e) = f(x_e) + B(x_e)u - F(Cx_e, x_e)$, the equation for the derivative of the error function becomes

$$\dot{e} = (f(x) + B(x)u - F(Cx, x_e)) - (f(x_e) + B(x_e)u - F(Cx_e, x_e))$$

We next parameterize the nonlinear function $f(x)$ as

$$f(x) = A(x)x + a(x)$$

and we choose F to be the product

$$F(Cx, x_e) = L(x_e)Cx$$

The derivative of the error then becomes

$$\begin{aligned} \dot{e} &= (A(x)x + a(x) + B(x)u - L(x_e)Cx) - (A(x_e)x_e + a(x_e) + B(x_e)u - L(x_e)Cx_e) \\ &= (A(x_e) - L(x_e)C)e + (B(x) - B(x_e))u + A(x)x - A(x_e)x + a(x) - a(x_e) \\ &= (A(x_e) - L(x_e)C)e + \left(\sum_i \frac{\partial B_{.i}(x_e)}{\partial x} u_i \right) e + \mathcal{O}(\|e\|^2) + f(x) - f(x_e) - A(x_e)e \\ &= \left(A(x_e) + \sum_i \frac{\partial B_{.i}(x_e)}{\partial x_e} u_i - L(x_e)C \right) e + \mathcal{O}(\|e\|^2) \end{aligned} \quad (18)$$

where we have used the Taylor series

$$B(x)u = B(x_e)u + \left(\sum_i \frac{\partial B_{.i}(x_e)}{\partial x_e} u_i \right) e + \mathcal{O}(\|e\|^2)$$

and

$$f(x) = f(x_e) + A(x_e)e + \mathcal{O}(\|e\|^2)$$

The subscript $\cdot i$ refers to the i th column of the associated matrix. In order to simplify the notation, we define

$$\hat{A}(x_e) = A(x_e) + \sum_i \frac{\partial B_{\cdot i}(x_e)}{\partial x_e} u_i \quad (19)$$

Since the goal of designing a state estimator is that it approximates the true state of the system closely, the error e should be small. Therefore, from Equation (18), the term $(\hat{A}(x_e) - L(x_e)C)e$ dominates $\mathcal{O}(\|e\|^2)$. For this reason we neglect the term $\mathcal{O}(\|e\|^2)$ from the rest of our discussion. Now, if we choose $L(x_e)$ so that the eigenvalues of $\hat{A}(x_e) - L(x_e)C$ have negative real parts, the estimation error e will converge to zero asymptotically as $t \rightarrow \infty$ (hence, x_e will approach x). In fact, if the parameterization pair $(\hat{A}(x), C)$ is detectable and $\hat{A}(x)$ is locally Lipschitz, then the estimate state x_e will converge locally asymptotically to the state x (see Reference [27]). Since $\hat{A}(x_e) - L(x_e)C$ and $\hat{A}^T(x_e) - C^T L^T(x_e)$ have the same eigenvalues, we can design the compensator gain $L(x_e)$ the same way that we design the feedback gain for the nonlinear feedback control problem. In particular, the compensator gain is given by

$$L^T(x_e) = N^{-1} C \Sigma(x_e)$$

or equivalently

$$L(x_e) = \Sigma(x_e) C^T N^{-1}$$

where $\Sigma(x_e)$ satisfies the state estimator-dependent Riccati equation

$$\Sigma(x_e) \hat{A}^T(x_e) + \hat{A}(x_e) \Sigma(x_e) - \Sigma(x_e) C^T N^{-1} C \Sigma(x_e) + M = 0 \quad (20)$$

Here M is a symmetric positive semidefinite matrix and N is a symmetric positive definite matrix. They are to be chosen so as to achieve a balance between desired convergence properties and compensator gain.

7. STATE EQUATIONS AND STATE ESTIMATOR

The system of differential equations for the state x and the state estimator x_e are given by

$$\begin{aligned} \dot{x} &= f(x) + B(x)u + w_s(t) \\ \dot{x}_e &= f(x_e) + B(x_e)u + L(x_e)(Cx + w_m(t) - Cx_e) \end{aligned} \quad (21)$$

The equations for x and x_e are indeed coupled due to the term $B(x)u$ in the first equation of (21) and the term $L(x_e)Cx$ in the second equation of (21). Therefore, it is necessary to solve both equations together. In the following we use the notation

$$\mathbf{x} = \begin{pmatrix} x \\ x_e \end{pmatrix} \quad \text{and} \quad \mathbf{G}(\mathbf{x}) = \begin{pmatrix} f(x) + B(x)u + w_s(t) \\ f(x_e) + B(x_e)u + L(x_e)(Cx + w_m(t) - Cx_e) \end{pmatrix}$$

With this notation, the system of differential equations (21) can be expressed as

$$\dot{\mathbf{x}} = \mathbf{G}(\mathbf{x})$$

8. DISCRETIZATION METHOD

We perform the time discretization using backward differentiation formulas (BDF) [33] with a uniform time step Δt . The solution at time $k\Delta t$ is denoted by \mathbf{x}^k . Then the discrete form of (21) using BDF formulas is given by

$$\mathbf{x}^{k+1} = \alpha \Delta t \mathbf{G}(\mathbf{x}^{k+1}) + \sum_{i=0}^{q-1} \beta_i \mathbf{x}^{k-i}$$

where q is the degree of the BDF and α and β_i are constants that depend on q . The first-order BDF is the implicit Euler method defined by

$$q = 2, \quad \alpha = 1 \quad \text{and} \quad \beta_1 = 1$$

The second-order BDF is denoted by BDF2 and is given by

$$q = 2, \quad \alpha = \frac{2}{3}, \quad \beta_1 = \frac{4}{3} \quad \text{and} \quad \beta_2 = -\frac{1}{3}$$

With the BDF2 method it is necessary to perform the first step of integration using some other numerical method, since it requires the solutions at two previous time steps. A common choice is to use the implicit Euler method for the first time step. It can be shown that this does not reduce the order of accuracy. It is well known that the implicit Euler method and BDF2 have good stability properties [33].

Finally, we note that, at each time step, the implicit Euler method and the BDF2 method require the solution of system of nonlinear equations

$$\mathbf{x}^{k+1} - \alpha \Delta t \mathbf{G}(\mathbf{x}^{k+1}) = \sum_{i=0}^{q-1} \beta_i \mathbf{x}^{k-i}$$

for \mathbf{x}^{k+1} in terms of solutions at previous time steps, \mathbf{x}^k , \mathbf{x}^{k-1} , etc.

9. SOLUTION TO THE DISCRETE NONLINEAR EQUATIONS

The implicit time discretization requires us to solve nonlinear equations of the form

$$\mathbf{g}(\mathbf{x}) = \mathbf{x} - \alpha \Delta t \mathbf{G}(\mathbf{x}) - \sum_{i=0}^{p-1} \beta_i \mathbf{x}^{k-i} = 0 \quad (22)$$

In the calculations reported on here, Newton's iterative method [34] was used to obtain the solution of (22). Let the i th iterate be denoted by $\mathbf{x}^{(i)}$. Then Newton's method solves for the $(i + 1)$ th iterate in terms of the i th iterate by

$$\mathbf{x}^{(i+1)} = \mathbf{x}^{(i)} - (\mathbf{I} - \alpha \Delta t \mathbf{J})^{-1} \mathbf{g}(\mathbf{x}^{(i)})$$

where \mathbf{J} is the Jacobian matrix of \mathbf{G} .

In the above formula, we need to evaluate \mathbf{G} at \mathbf{x} . That is, we must calculate

$$\mathbf{G}(\mathbf{x}) = \begin{pmatrix} A(x)x + a(x) + B(x)u + w_s(t) \\ A(x_e)x_e + a(x_e) + B(x_e)u + L(x_e)(Cx + w_m(t) - Cx_e) \end{pmatrix}$$

where the control is given by

$$u = \min(\max(\tilde{u}, \check{u}), \hat{u})$$

with

$$\tilde{u} = -R^{-1}B^T(x_e)(\Pi(x_e)x_e + \tilde{b}(x_e))$$

In order to do this we need to solve the SDRE

$$\Pi(x_e)A(x_e) + A^T(x_e)\Pi(x_e) - \Pi(x_e)S(x_e)\Pi(x_e) + Q = 0$$

where we have used the notation $S(x_e) = B(x_e)R^{-1}B^T(x_e)$. In addition, the vector function $\tilde{b}(x_e)$ given by

$$\tilde{b}(x_e) = (A^T(x_e) - \Pi(x_e)S(x_e))^{-1}(Qy - \Pi(x_e)a(x_e))$$

also must be computed. Finally, to evaluate the compensator gain $L(x_e)$, which is given by

$$L(x_e) = \Sigma(x_e)C^T N^{-1}$$

the dual SDRE

$$\Sigma(x_e)\hat{A}^T(x_e) + \hat{A}(x_e)\Sigma(x_e) - \Sigma(x_e)C^T N^{-1}C\Sigma(x_e) + M = 0$$

with $\hat{A}(x_e)$ given by (19) also must be solved.

To obtain the Jacobian \mathbf{J} of \mathbf{G} , one can derive analytical formulas for \mathbf{J} which are rather cumbersome. In practice, it is more convenient to use a finite difference approximation of the Jacobian \mathbf{J} . For our application, the forward difference approximation that we employed is sufficiently accurate and of low computational cost.

10. SIMULATION RESULTS

The time period for simulations is 500 days. Unless otherwise stated we have used the time step $\Delta t = 1/96$, which corresponds to 15 min. The discretization was performed with the second-order BDF using the implicit Euler method to compute the first time step.

10.1. Full-state feedback control

We first present simulation results where we assumed that full-state observations are available for feedback.

10.1.1. Optimal treatment in the acute state. In our first example, we assume that medication starts immediately after HIV infection (an unrealistic assumption in practice—see further comments below). In this case, the initial values for the state variables are given by the acute state

$$\begin{aligned} T_1 &= 1000 \text{ cells/mm}^3, & T_2 &= 3.198 \text{ cells/mm}^3, & T_1^* &= 0.0 \text{ cells/mm}^3, & T_2^* &= 0.0 \text{ cells/mm}^3 \\ V_1 &= 0.001 \text{ virions/mm}^3, & V_{\text{NI}} &= 0.0 \text{ virions/mm}^3, & \text{and} & E &= 0.01 \text{ cells/mm}^3 \end{aligned} \quad (23)$$

In this example we also assume that the maximum ‘efficacies’ to be $e_1^{\max} = 0.7$ and $e_2^{\max} = 0.3$.

Figure 1 depicts the dynamics of the suboptimal RTI control e_1 and the PI control e_2 . The corresponding state progressions are shown in Figure 2. After approximately 325 days the state variables have reached near equilibrium and start to oscillate in the neighbourhood of the stable ‘healthy’ steady state (4). It is noted that the oscillations are not numerical artefacts but are likely consequences of the interaction (product) terms that appear in the mathematical model (1).

After 325 days the feedback control-based treatment calls for many cycles of on and off therapy, each with a short duration of few hours. This type of protocol is difficult for the patients to follow since, for example, many pills need to be taken together with food. Therefore,

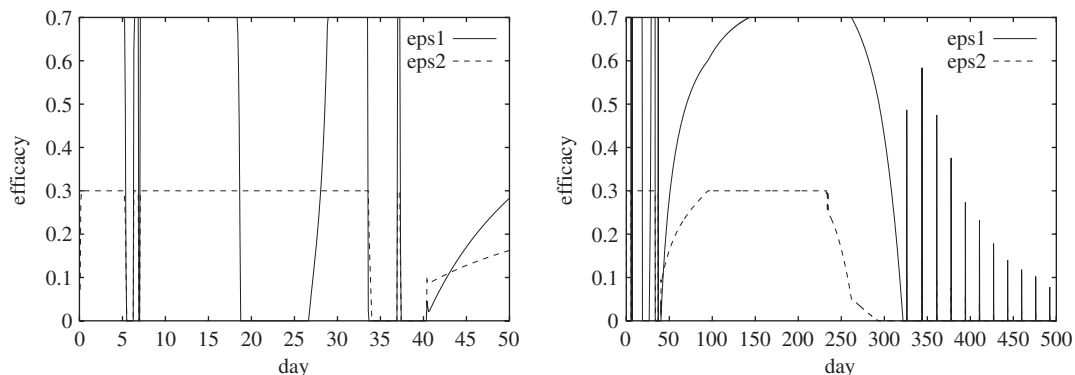


Figure 1. Multidrug therapy starting from the acute state.

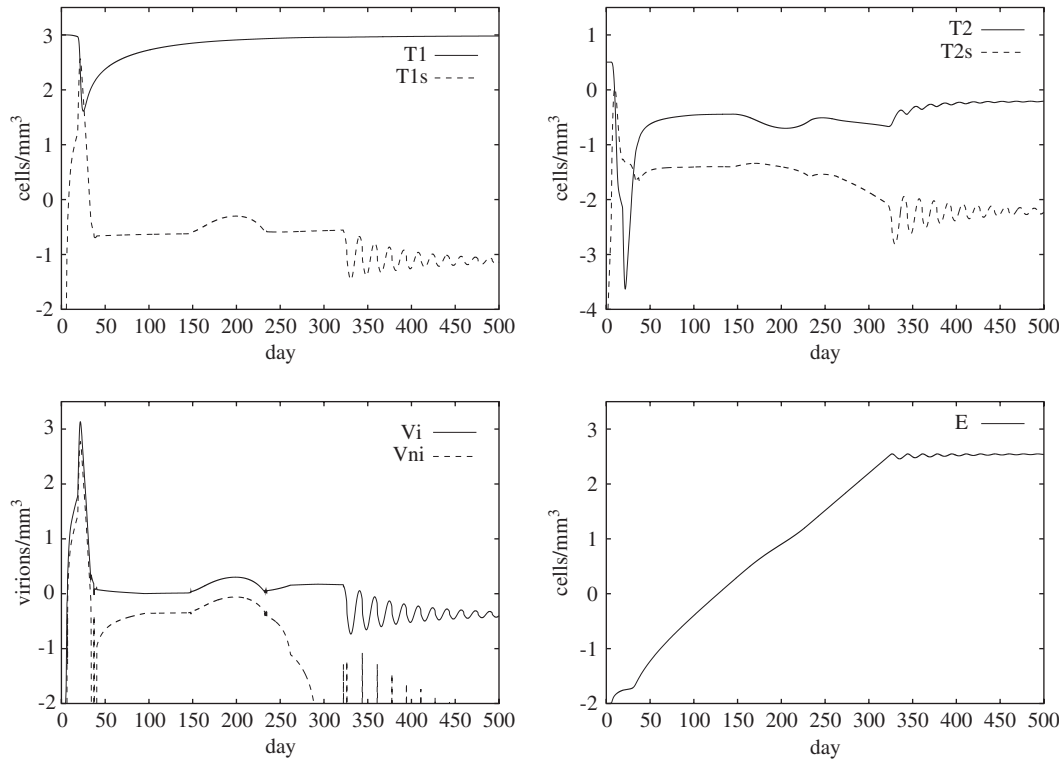


Figure 2. Plots of the state variables with the y-axis in \log_{10} -scale.

to avoid this type of treatment schedule in the long term we propose to terminate the medication when the viral load has reached a sufficiently low level. Thus the medication will be administered only when the condition

$$V_I + V_{NI} > 1.0 \text{ virions/mm}^3 \quad (24)$$

is satisfied. Figure 3 presents the resulting treatment regimen and Figure 4 depicts the corresponding state variables. In this case, even though it does take longer for the state to settle down to the 'healthy' equilibrium state, the results confirm that once the system reaches the stable equilibrium state, medication is no longer required. We remark that because of condition (24) we also do not give any medication during the first 2 days after the infection, since during this time the viral load is below our limit. In practice, the first treatment would be even further delayed since one would almost never be aware of the infection early on or even when the lower load level in (24) is first exceeded.

So far in our numerical studies discussed above, we used the maximum efficacies $\varepsilon_1^{\max} = 0.7$ and $\varepsilon_2^{\max} = 0.3$. An important and interesting question is how low these efficacies can be in order for state of the system to be able to reach the 'healthy' equilibrium state. In our previous work [8], the analysis revealed that without any medication the state will converge to the unhealthy

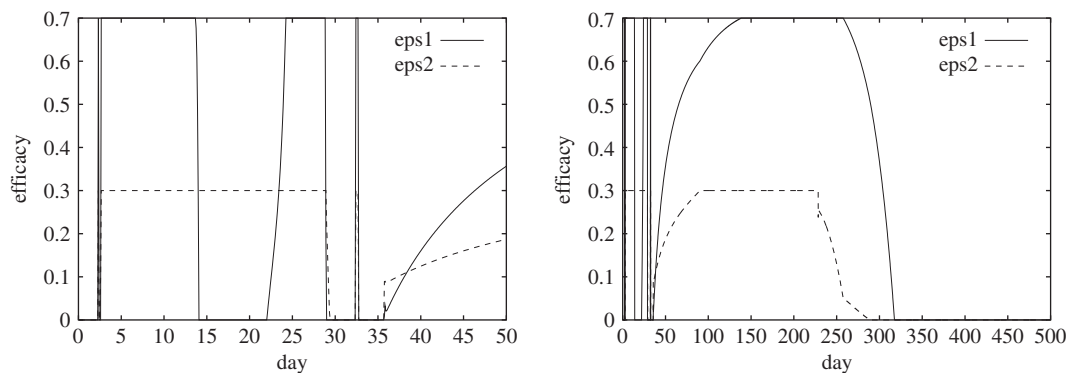


Figure 3. The medication levels starting from the acute state using the stopping criterion based on the viral load.

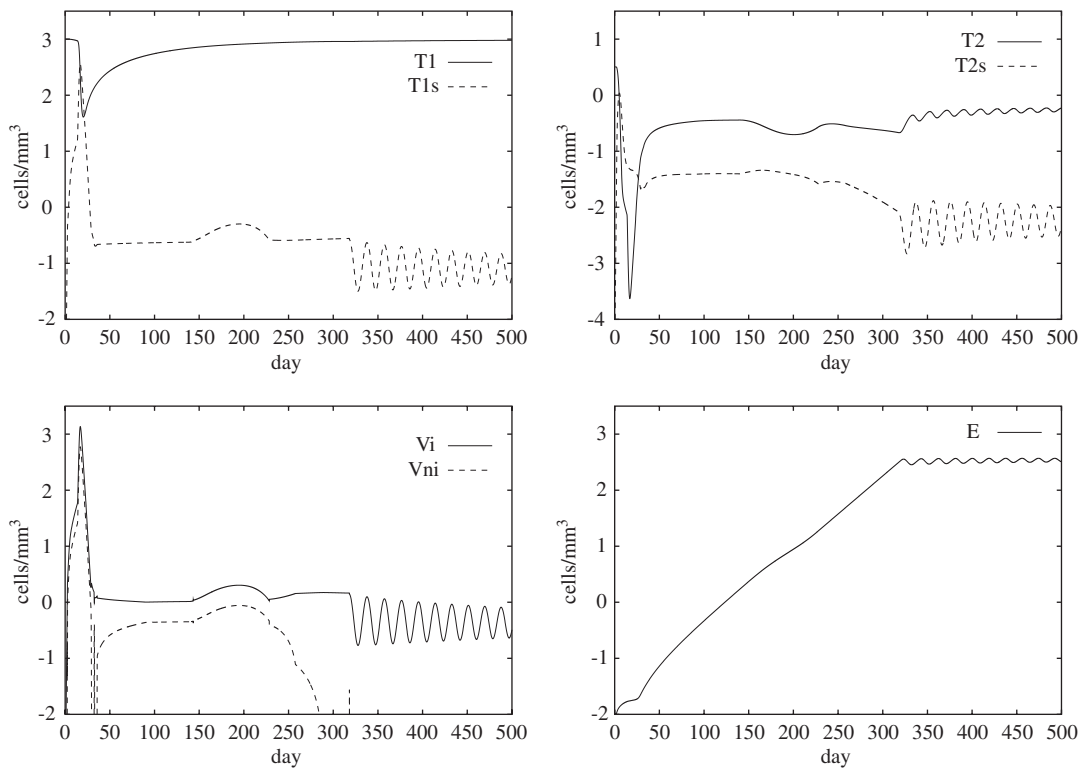


Figure 4. Plots of the state variables using the stopping criterion based on the viral load with the y -axis in \log_{10} -scale.

steady state (25) given below. Thus, there should be a threshold boundary in the $(\epsilon_1^{\max}, \epsilon_2^{\max})$ efficacy plane which indicates whether it is possible or not to reach the ‘healthy’ equilibrium state with any admissible drug therapy.

We investigated the influence of the maximum efficacies by varying both of them from zero to one and carrying out a series of numerical simulations with the nonlinear feedback controls for each of these combinations of bounds. Figure 5 depicts the number of days required for the immune effector E to reach the ‘healthy’ steady state level 350 cells/mm^3 as a function of maximum efficacies.

Finally, from Figure 5 we can observe a slight apparent lack of robustness of the proposed nonlinear feedback control law. This is probably a consequence of the local linearization of the nonlinear dynamics or the suboptimal nature of the approximate nonlinear controller. For example, when the maximum efficacies are $\varepsilon_1^{\max} = 0.8$ and $\varepsilon_2^{\max} = 0.0$, the ‘healthy’ equilibrium state is reachable. However, when the maximum efficacy ε_1^{\max} is increased by 0.025 , the ‘healthy’ equilibrium state is no longer reachable.

10.1.2. Optimal treatment in the unhealthy steady state. In our second set of examples, we consider a patient who has not taken medication after HIV infection and the disease progression is proceeding towards the unhealthy steady state

$$\begin{aligned} T_1 &= 163.573 \text{ cells/mm}^3, & T_2 &= 0.005 \text{ cells/mm}^3, \\ T_1^* &= 11.945 \text{ cells/mm}^3, & T_2^* &= 0.046 \text{ cells/mm}^3 \\ V_I &= 63.919 \text{ virions/mm}^3, & V_{NI} &= 0.0 \text{ virions/mm}^3 \quad \text{and} \quad E = 0.024 \text{ cells/mm}^3 \end{aligned} \quad (25)$$

Again the question is whether our suboptimal approximate nonlinear feedback controller can transfer the system from the unhealthy state (25) to the ‘healthy’ equilibrium state (4) in finite time. We begin by letting the maximum efficacies be $\varepsilon_1^{\max} = 0.7$ and $\varepsilon_2^{\max} = 0.3$. The dynamics of

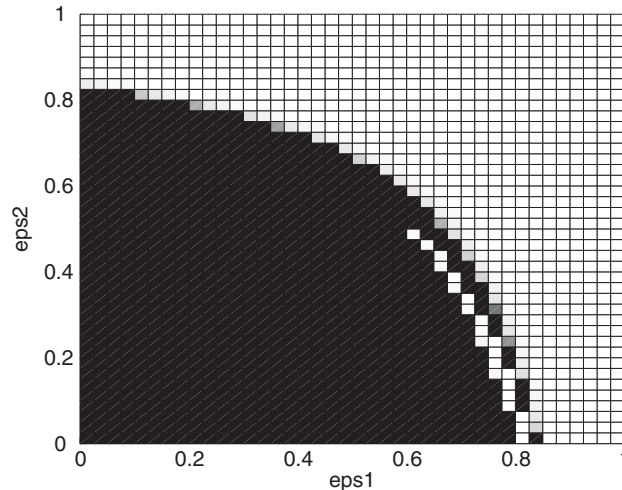


Figure 5. The number of days it takes the immune effector E to reach the ‘healthy’ steady-state level 350 cells/mm^3 starting from the acute state with varying maximum efficacies. White corresponds to about 292 days, the shades of grey vary between 300 and 1400 days, and black is never.

the suboptimal treatment strategy proposed by the nonlinear feedback control are shown in Figure 6 and the corresponding state variables are plotted in Figure 7. Clearly, in this case the ‘healthy’ equilibrium state is not reachable.

Next we increase the maximum efficacy e_1^{\max} of the RTI to be 0.75. The resulting optimal therapy regimen is depicted in Figure 8. The therapy does bring the system to the ‘healthy’ equilibrium state as can be seen in Figure 9. It is noted that we discontinued the medication using the viral load condition (24) as proposed earlier.

As in the earlier example for acute infection, we investigated the combination of the maximum efficacies e_1^{\max} and e_2^{\max} so that ‘healthy’ equilibrium state is reachable. Figure 10 depicts the number of days required for the immune effector E to reach the ‘healthy’ steady-state level 350 cells/mm³ as a function of maximum efficacies.

Figure 10 demonstrates that slightly smaller maximum efficacies are required than for the acute state in Figure 5. This again suggests a slight lack of robustness in the nonlinear feedback control for the acute state. It is most likely that the approximations are not sufficiently accurate for the highly nonlinear transient period observed after the infection in the acute-state case.

10.2. Feedback control and state estimation

In this section, we consider the design and synthesis of nonlinear feedback control-based treatments in which one only has partial state observations.

10.2.1. Inaccurate initial condition for the state estimator. We consider first the acute infection case where the initial value for the state x is given by (23). We disturbed the initial value of the state estimator x_e by 20% so that $x_e = 0.8x$. As in our earlier computational experiment, the maximum efficacies are $e_1^{\max} = 0.7$ and $e_2^{\max} = 0.3$. For the computation of the estimator, the weighting matrices in (20) are chosen to be

$$M = 0.01I_{7 \times 7} \quad \text{and} \quad N = I_{2 \times 2}$$

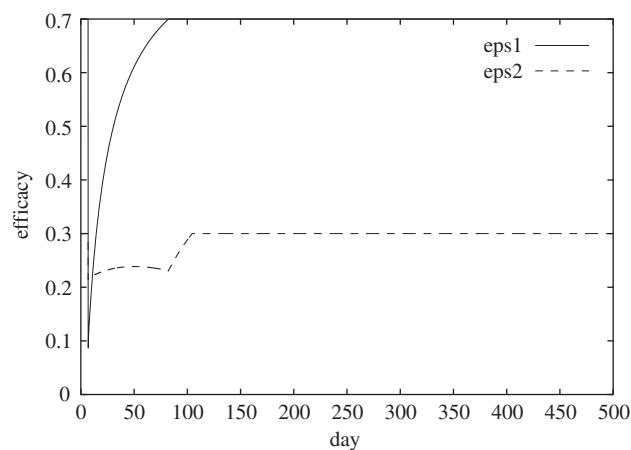
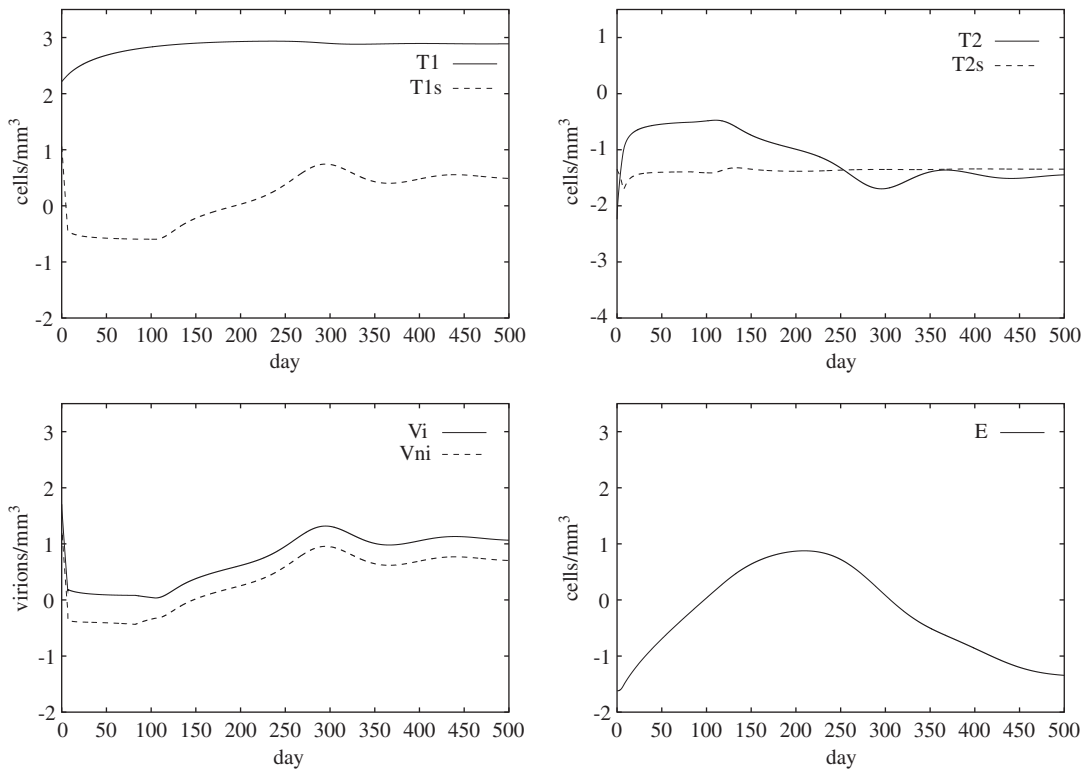
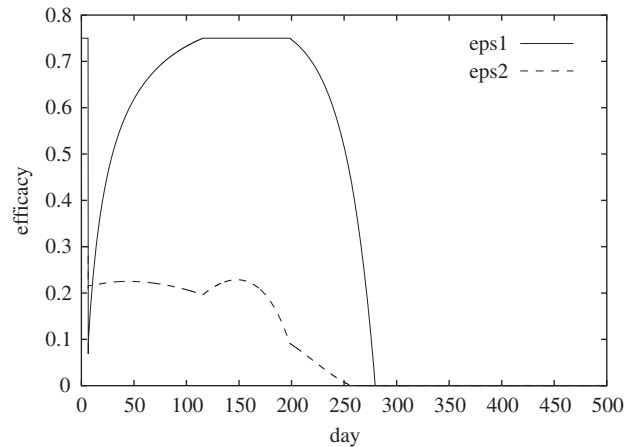


Figure 6. The suboptimal HIV treatment starting from the unhealthy steady state when $e_1^{\max} = 0.7$.

Figure 7. Plots of the state variables with the y -axis in \log_{10} -scale.Figure 8. The medication levels starting from the unhealthy steady state when $\epsilon_1^{\max} = 0.75$.

where $I_{l,l}$ denotes the $l \times l$ identity matrix. During the 100 first days in the simulation the estimator x_e has tendency to have negative components which is not feasible. In such a case, we project the negative components to be zero.

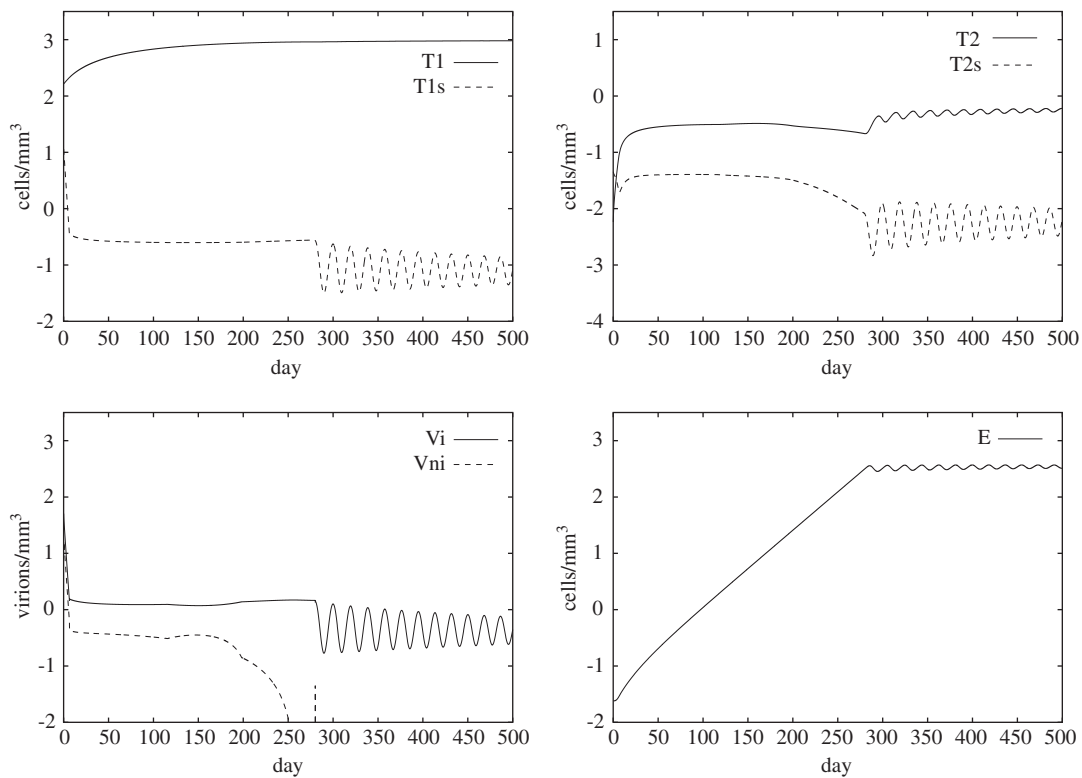


Figure 9. Plots of the state variables with the y-axis in \log_{10} -scale.

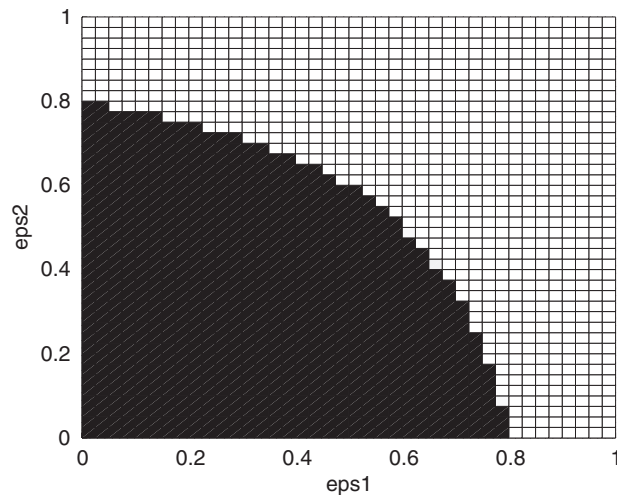


Figure 10. The number of days it takes the immune effector E to reach the 'healthy' steady-state level 350 cells/mm³ starting from the unhealthy state with varying maximum efficacies. White corresponds to about 283 days and black is never.

Figure 11 records the suboptimal treatment protocol obtained using the estimator x_e in the nonlinear feedback control laws. The therapy dynamics are fairly similar to the ones shown in Figure 3. Figure 12 depicts the Euclidean distance between the state and the estimator. This plot clearly indicates that the state estimator converges to the state asymptotically. In Figure 13, we plot the state variables and their estimators for the first 50 days. After 50 days it is difficult to discern the differences between the state and the estimator in such plots and they are omitted. It should be mentioned that our state estimator design is only suboptimal, and, therefore, it takes more than 50 days for the state estimator to track the original state of the system adequately.

10.2.2. Noisy measurements. We next consider the suboptimal feedback controller in the presence of noise in the observations. At the k th time step, we denote the measurement without noise and the noise by Cx^k and w_m^k , respectively. We assume the noise to be lognormally distributed without correlation between the components. Furthermore, we assume the noise has zero mean and the variance of the i th component is taken to be $\sigma_i^2(Cx^k)_i$. The assays measuring CD4 cell counts and viral loads typically have this type of measurement errors [35, 36]. Under these assumptions the i th component of the noise is given by

$$(w_m^k)_i = \exp(\mathcal{N}(\log(Cx^k)_i - \frac{1}{2}\log(\sigma_i^2 + 1), \log(\sigma_i^2 + 1))) - (Cx^k)_i$$

where $\mathcal{N}(\cdot, \cdot)$ is the normal distribution with the mean given by the first argument and the variance given by the second argument. In the following experiment, the parameter σ_i^2 is chosen as $\sigma_i^2 = (0.10)^2$. The measurements without the noise and with the noise are graphed in Figure 14 where the observation sampling time is 2 h.

Since our estimator-based feedback control design is only suboptimal, in order to make the estimator x_e sufficient for reasonable control (in the presence of measurement errors) it appears to be necessary to reduce the sampling time increments. For the next results, we used 15 s sampling time steps, that is, $\Delta t = 1/5760$. We used the same initial values as in the case without noise, that is, the state corresponds to the acute infection and the state estimator initial value is 20% off.

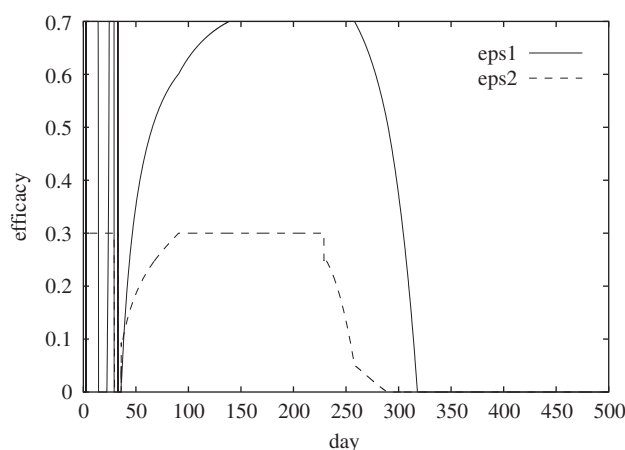


Figure 11. The suboptimal dynamics treatment based on the state estimator.

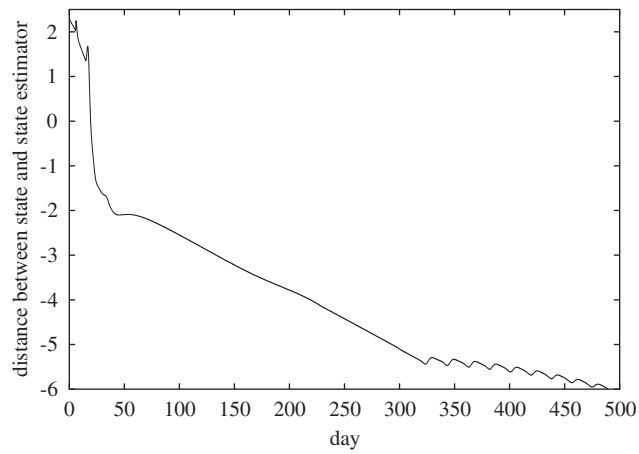


Figure 12. The Euclidean distance between the state and state estimator with the y -axis in \log_{10} -scale.

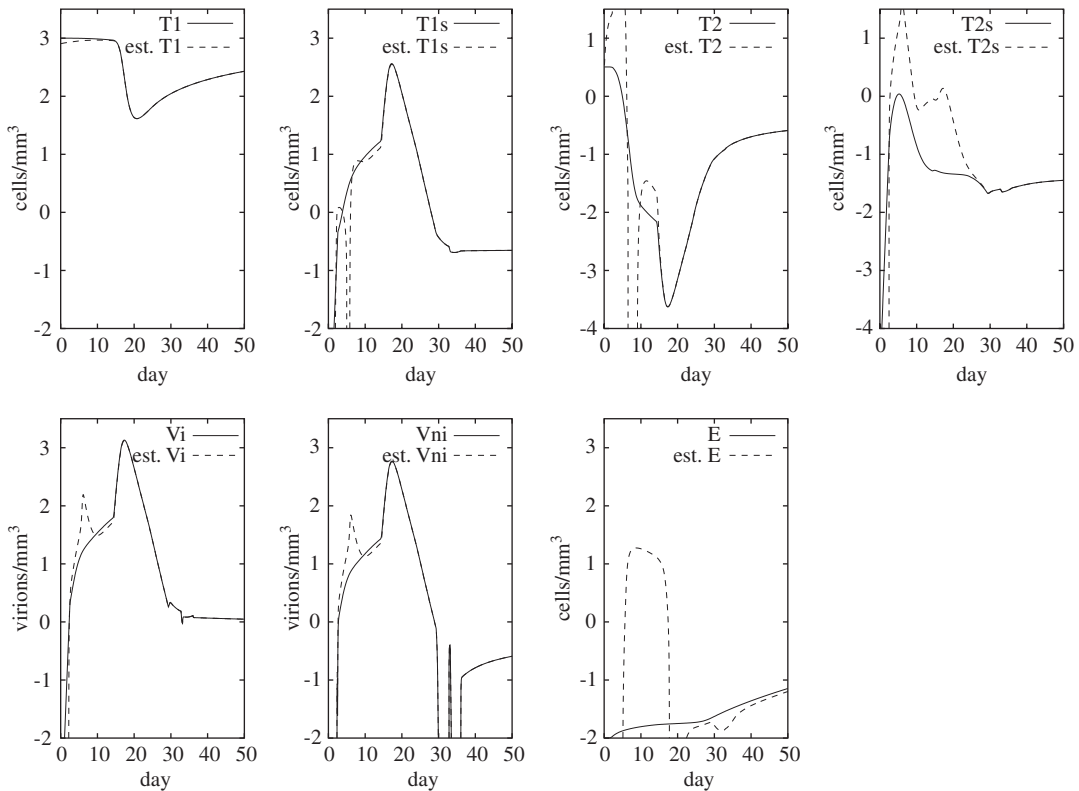


Figure 13. Plots of the state variables and corresponding estimators for the first 50 days with the y -axis in \log_{10} -scale.

Figure 15 depicts the optimal treatment strategy with imperfect measurements. Because of the noise the controls contain some oscillations from 250 to 320 days. The short interruptions in the medications during the 143th day and the 305th day are probably due to lack of robustness in

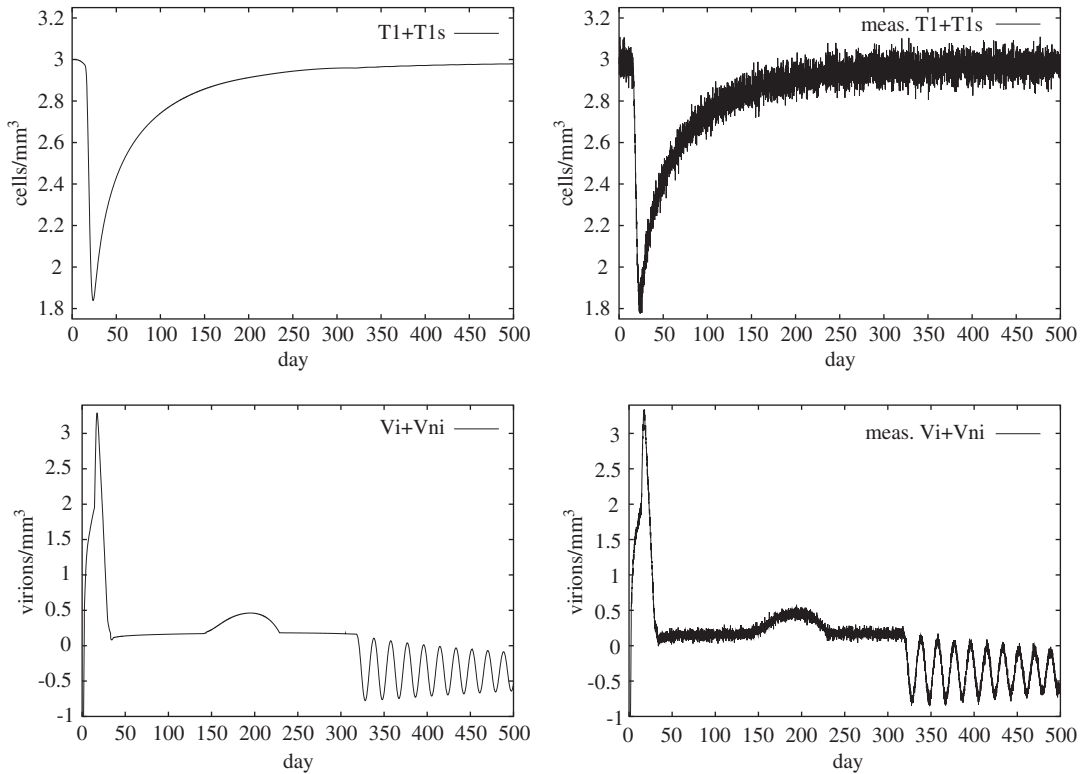


Figure 14. The measurements with the y-axis in \log_{10} -scale.

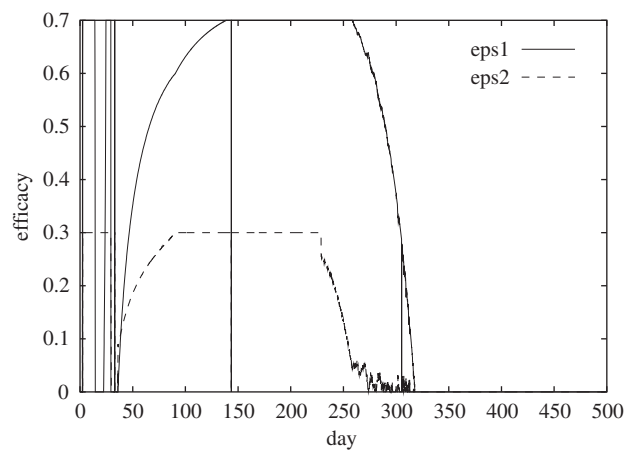


Figure 15. The optimal estimator-based treatment when there is noise in measurements.

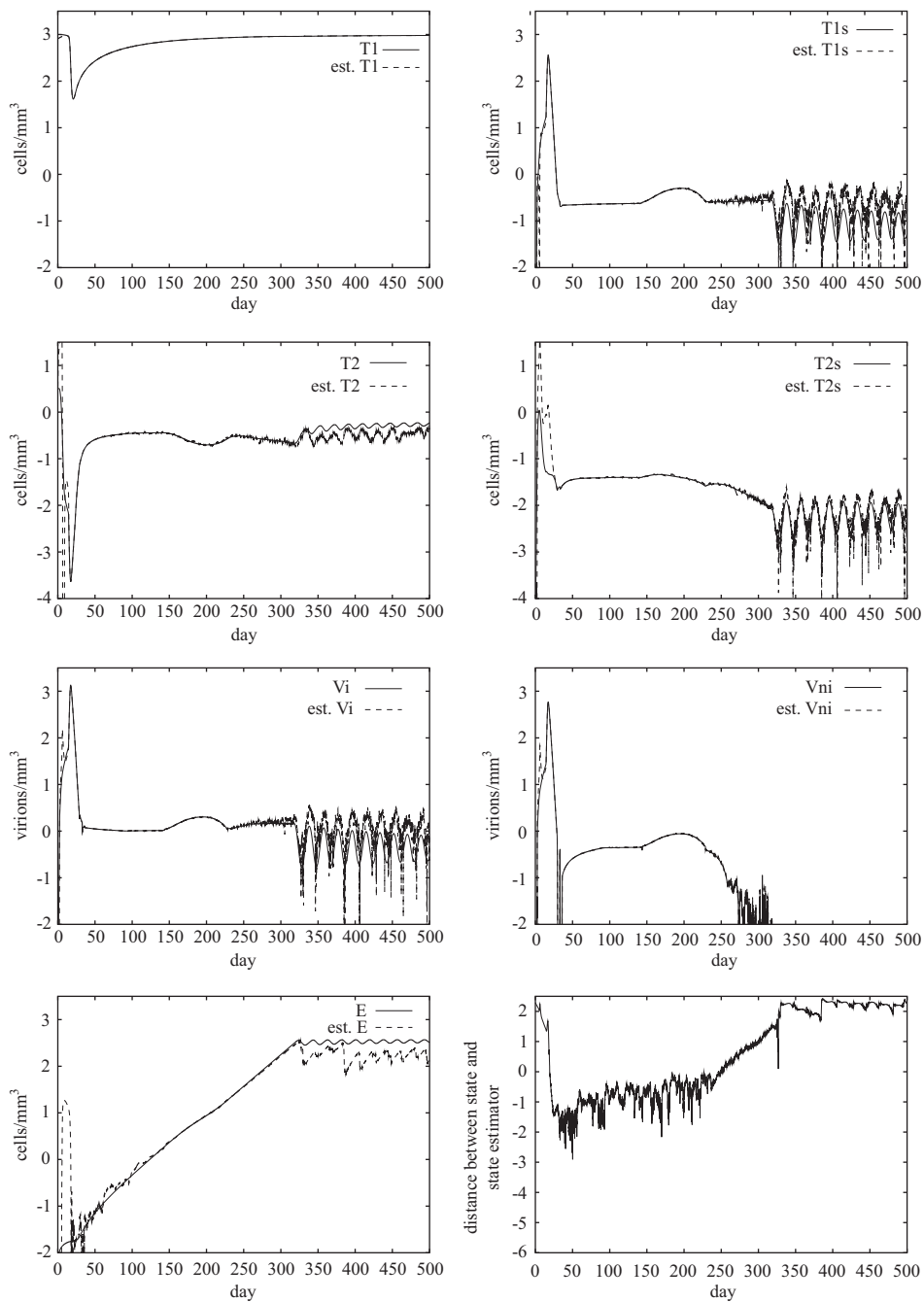


Figure 16. The states, their estimators and the Euclidean distance between them in the lower right corner with the y -axis in \log_{10} -scale.

our Newton solver and are thus an artefact of our computational schemes. In Figure 16, we plot the state variables and their estimators for the entire 500 days and the Euclidean distance between them. Note that the estimators approximate very well the true states of the system except at the beginning and the end of the simulations. Despite these discrepancies, the suboptimal dynamic multidrug therapy is still very similar to the one without noise in observations depicted in Figure 11.

11. CONCLUSIONS

We presented and used techniques and ideas from control theory to design and synthesize nonlinear feedback control-based treatment regimes for HIV. The mathematical model for HIV progression includes compartments for target cells, infected cells, virus, and immune response that are subjected to multiple (RTI- and PI-type) drug treatments as controllers. We have demonstrated through numerical simulations that by using a ‘target tracking’ approach, suboptimal feedback-based treatment strategies can be designed to move the state of the system from an ‘unhealthy’ state (high virus load and low immune response) to a ‘healthy’ one (with low viral load and high immune effector levels). An important advantage of this drug regimen design is that once the viral load is controlled to very low levels, the drug dosage can be reduced or completely terminated. Consequently, long-term pharmaceutical side effects could also be reduced. Thus, this approach suggests that by anticipating and responding to the disease progression, dynamic feedback strategies such as those designed in this paper could lead to long-term control of HIV after discontinuation of therapy.

The potential for SDRE-based estimator approach for HIV feedback control is exciting, but more work is necessary before it can be implemented in clinical conditions. First, while our treatment strategy suggests optimal dynamic multidrug therapies, whether the strategy will successfully maintain viral load at low levels for long periods remains to be seen experimentally. This is especially important because HIV grows out of the chronic infection stage into AIDS by developing mutations that allow immune escape. Therefore, more research is needed to incorporate the effects of drug resistance and mutation as well as more accurate models for the immune response still need to be developed. We have also assumed that the model parameters are fixed. This too is not the case because parameters do vary from patient to patient. In addition, there are also unmodelled dynamics that show up as parameter uncertainty or drift. In view of this, it should be stressed that further research must be carried out to determine whether our proposed optimal treatment protocol can provide sufficient robustness to these problems.

ACKNOWLEDGEMENTS

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