

# An SDRE Based Estimator Approach for HIV Feedback Control

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## ABSTRACT

We present and use techniques and ideas from control theory to design and synthesize nonlinear feedback control-based treatment regimes for HIV. We demonstrate 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 work could lead to long-term control of HIV after discontinuation of therapy.

## 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 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 reverse transcriptase inhibitors prevent HIV from infecting cells by blocking the integration of the viral code into the target cells. Protease inhibitors interfere with the replication of viruses by infected cells. Virions may still be produced, but they are generally non infectious; 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 [9]. Some of these models used to design dynamical drug treatments are presented in [1,4,9]. In the long term pathogenesis of HIV an immune response can play an important role. However, the models in [9] do not contain immune response while the authors in [1,4] 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.

## HIV MODEL AND CONTROL

In this study, we employ a model based on the models considered in [1,2] which contain an immune effector component. The dynamics of our HIV model are described by the set of ordinary differential equations:

$$\begin{aligned}
\dot{T}_1 &= \lambda_1 - d_1 T_1 - (1 - \epsilon_1) k_1 V_I T_1 \\
\dot{T}_2 &= \lambda_2 - d_2 T_2 - (1 - f \epsilon_1) k_2 V_I T_2 \\
\dot{T}_1^* &= (1 - \epsilon_1) k_1 V_I T_1 - \delta T_1^* - m_1 E T_1^* \\
\dot{T}_2^* &= (1 - f \epsilon_1) k_2 V_I T_2 - \delta T_2^* - m_2 E T_2^* \\
\dot{V}_I &= (1 - \epsilon_2) N_T \delta (T_1^* + T_2^*) - [c + (1 - \epsilon_1) \rho_1 k_1 T_1 + (1 - f \epsilon_1) \rho_2 k_2 T_2] V_I \\
\dot{V}_{NI} &= \epsilon_2 N_T \delta (T_1^* + T_2^*) - c V_{NI} \\
\dot{E} &= \lambda_E + b_E \frac{T_1^* + T_2^*}{T_1^* + T_2^* + K_b} E - d_E \frac{T_1^* + T_2^*}{T_1^* + T_2^* + K_d} E - \delta_E E.
\end{aligned} \tag{1}$$

In the 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;  $V_I$ , the infectious virus;  $V_{NI}$ , the non infectious virus; and  $E$ , the immune effectors. The controllers  $\epsilon_1$  and  $\epsilon_2$  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 the model (1) we refer the reader to the articles [1,2]. Table 1 contains the values of parameters, which are the same as those used in [1,2]. The only difference is that we use  $\text{mm}^3$  (cubic millimeter) as our unit volume instead of ml (milliliter).

Optimal treatment of HIV infection using a control theoretic approach is the subject of substantial research activity. The papers [1,6] consider only RTI medication while the papers [8] consider only PIs. In [2] 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., [1,6,8]. More recently, the on-off type of treatment, which is also known as a structured treatment interruption (STI), has attracted a lot of attention

parameter	value	unit	parameter	value	unit
$\lambda_1$	10.0	$\frac{\text{cells}}{\text{mm}^3 \cdot \text{day}}$	$\lambda_2$	$31.98 \times 10^{-3}$	$\frac{\text{cells}}{\text{mm}^3 \cdot \text{day}}$
$d_1$	0.01	$\frac{1}{\text{day}}$	$d_2$	0.01	$\frac{1}{\text{day}}$
$k_1$	$8.0 \times 10^{-4}$	$\frac{\text{mm}^3}{\text{virions} \cdot \text{day}}$	$k_2$	0.1	$\frac{\text{mm}^3}{\text{virions} \cdot \text{day}}$
$m_1$	0.01	$\frac{\text{mm}^3}{\text{cells} \cdot \text{day}}$	$m_2$	0.01	$\frac{\text{mm}^3}{\text{cells} \cdot \text{day}}$
$\rho_1$	1	$\frac{\text{virions}}{\text{cells}}$	$\rho_2$	1	$\frac{\text{virions}}{\text{cells}}$
$\delta$	0.7	$\frac{1}{\text{day}}$	$c$	13.0	$\frac{1}{\text{day}}$
$f$	0.34	—	$N_T$	100.0	$\frac{\text{virions}}{\text{cells}}$
$\lambda_E$	$1.0 \times 10^{-3}$	$\frac{\text{cells}}{\text{mm}^3 \cdot \text{day}}$	$\delta_E$	0.1	$\frac{1}{\text{day}}$
$b_E$	0.3	$\frac{1}{\text{day}}$	$d_E$	0.25	$\frac{1}{\text{day}}$
$K_b$	0.1	$\frac{\text{cells}}{\text{mm}^3}$	$K_d$	0.5	$\frac{\text{cells}}{\text{mm}^3}$

Table 1 The values of the parameters in the HIV model.

in the medical literature (see for example, [1,2] 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. Recent results on structured treatment interruption schedules including optimal treatments are presented in [1,2]. 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 [1,2,6,7,?] and feedback control has been used in [5]. The papers [5] consider the feedback control based on partial measurements.

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

$$J(x, u) = \frac{1}{2} \int_0^\infty \{(V_I - 0.415)^2 + 10(E - 353.108)^2 + (\epsilon_1/\epsilon_1^{\max})^2 + (\epsilon_2/\epsilon_2^{\max})^2\} dt, \quad (2)$$

where  $V_I$  is the number of free virus and  $E$  represents the immune response. The optimal tracking control problem is to find a dynamic multidrug therapy  $u(t)$  satisfying

$$\min_{\tilde{u} \leq u(t) \leq \hat{u}} J(x(t), u(t)) \quad (3)$$

subject to the state equation given by (1) with initial condition  $x(0) = x_0$ .

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, [3]). 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 a state dependent Riccati equation. As shown in [3], 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 [3] and chemical vapor deposition, the idea of *using SDRE for combined drug/immune response control of HIV infection* as presented here is new. In addition, we propose 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.

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