FEEDBACK CONTROL AND STATE ESTIMATION OF AN HIV MODEL

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ABSTRACT

We consider optimal dynamic multidrug therapies for human immunodeficiency virus(HIV) type 1 infection. We describe an optimal tracking problem attempting 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). We consider 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. In addition, the state estimation based on a moving horizon type approach is introduced.

INTRODUCTION

A number of researchers have used a control theoretic approach to derive optimal drug administration scheme of HIV infection. Open loop control have been discussed in [1,2] and feedback control has been studied in [3,5]. Moreover, the way that derive a optimal on-off type of treatment, which is also known as s structured treatment interruption (STI), has presented in [1,2]. Optimal feedback control based on the state dependent Riccati equation (SDRE) approach for HIV infection is considered in [3]. The authors in [3] do also consider the problems of designing a state estimator to be used with the nonlinear feedback control laws since only partial measurements of the state are available in many practical problems. However, the measurement time step is too short, e.g. 15 second. It does not make sense in real problems. So we do consider feedback control problem when measurements are a few months apart.

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 [6]. Some of these models used to design dynamical drug treatments are presented in [1,4,6]. In the long term pathogenesis of HIV an immune response can play an important role. However, the models in [6] 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

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:

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

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 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.

FEEDBACK CONTROL AND STATE ESTIMATION

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

$$x = (T_1\ T_2\ T_1^*\ T_2^*\ V_I\ V_{NI}\ E)^T, \quad u = (\epsilon_1\ \epsilon_2)^T$$

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

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

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. This is representative of the type of clinical data widely discussed in the literature (see for example, [1]).

Hence, the output or observation takes the form

$$z = \begin{pmatrix} z_1 \\ z_2 \end{pmatrix} = \begin{pmatrix} 1\ 0\ 1\ 0\ 0\ 0\ 0 \\ 0\ 0\ 0\ 0\ 1\ 1\ 0 \end{pmatrix} x = Cx, \tag{3}$$

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

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

$$J(x,u) = \frac{1}{2}\int_0^\infty \{(V_I - 0.415)^2 + 10(E - 353.108)^2 + (\epsilon_1/\epsilon_1^{\max})^2 + (\epsilon_2/\epsilon_2^{\max})^2\}dt, \tag{4}$$

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

$$\min_{\check{u}\le u(t)\le \hat{u}} J(x(t), u(t)) \tag{5}$$

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

We note that our mathematical model for HIV dynamics is nonlinear. One of the highly promising techniques for designing nonlinear feedback controllers is the state-dependent Riccati equation(SDRE) approach. To derive the optimal feedback controller, full knowledge of all the state variables is required. However, in many real problems, only partial measurements of the state are available. So we need to consider the problem of designing a state estimator. 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. We will discuss how to choose f_e and F in order to x_e approach x as $t \to \infty$.

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