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A two-loop robust controller fyor HIV infection models in the presence of parameter uncertainties

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ABSTRACT

A two-loop robust nonlinear controller is proposed to deal with uncertain model parameters in HIV infection models, which are described by nonlinear differential equations of three state variables and antiretroviral drugs. The treatment goal is to suppress the concentration of infected CD4+ T cells to a target value using only the measurement of total CD4+ T cell concentration. The outer-loop controller is designed to achieve the treatment goal for the nominal HIV infection model, while a nonlinear disturbance observer (DOB) controller is employed in the inner-loop to compensate for parameter uncertainties. In the nonlinear DOB controller, a disturbance signal, equivalent to the parameter variation in terms of effect on the output, is canceled by its estimate. Numerical simulations verify that the proposed controller achieves robust performance for reducing the concentration of infected CD4+ T cells even in the presence of parameter uncertainties.

1. Introduction

Since the proposal of several mathematical models by Perelson and Nelson [1] and Nowak and May [2] to represent the interaction of HIV with CD4+ T cells, a variety of research has been actively conducted by means of the control theory to develop drug therapies for HIV-infected patients. A control method based on Jacobian linearization was employed to reduce the viral load [3]. Using the backstepping method, a nonlinear controller was designed for better control performance [4]. However, the backstepping method usually suffers from the problem of "explosion of terms" due to the repetitive differentiation of the virtual input [5]. Treatment scheduling based on model predictive control (MPC) was also developed for the immune system to suppress the virus [6]. An output feedback MPC approach was then presented to handle cases where the measurements of all state variables are not available [7]. In contrast to the two works based on the standard MPC framework [6,7], an offset-free MPC algorithm was developed to cope with model errors using the state augmentation approach [8]. Although simulation showed that the treatment goal was achieved through the MPC algorithm, the stability is not theoretically guaranteed in the presence of model errors. Feedback linearization has been employed to control the viral load [9,10], but this approach generally does not work properly in the presence of model errors, as it relies on the exact cancelation of nonlinear terms. A system theoretic approach was presented to treat HIV-infected patients via analysis of bifurcation and stability [11]. Thymic recovery in HIV patients was also studied using an optimal control approach [12].

The parameter values of an HIV-infection model depend on the patient's infection condition [13,14]. That is, parameter uncertainties (or parameter variations) may exist in the model. In the aforementioned references, excluding [8], however, various treatment algorithms have been proposed without considering any robustifying control term. As a result, they are unlikely to achieve the treatment goal in the presence of large uncertainties although they may work well for small uncertainties. Besides, many of the reported methods [3,4,6,9,10,12] require the measurements of all state variables to implement the control law, while such measurements are not feasible in real clinical situations. Therefore, it would be worthwhile to find the drug efficacy for the treatment of HIV infections in the presence of parameter uncertainties without having to measure all state variables.

In this paper, a two-loop robust nonlinear controller is proposed for HIV infection models with parameter uncertainties, even when not all state variables are available for feedback. Many references [7,8,13–16] employed the total concentration of CD4+ T cells and the viral load as measurable state variables. As will be seen later, on the other hand, the proposed controller requires only the measurement of the total concentration of CD4+ T cells. Thus, the treatment goal of this paper is to suppress the concentration

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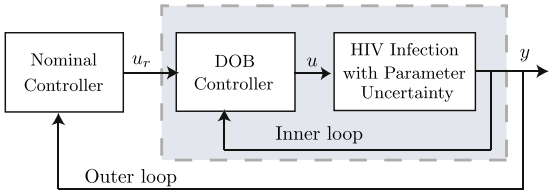

Fig. 1. Two-loop structure of the proposed controller. The inner-loop controller makes the shaded block behave as if it were the nominal HIV infection model. Here, u, y, and u_r represent the drug (RTI) efficacy, the total concentration of CD+4 T cells, and the output signal of the nominal controller, respectively.

of infected CD4+ T cells to the target value using only the total concentration of CD4+ T cells. To achieve the treatment goal in the presence of parameter uncertainties, a nonlinear controller with a two-loop structure is proposed, as shown in Fig. 1. The outer-loop controller is designed such that the treatment goal can be achieved for the nominal HIV infection model. That is, parameter uncertainties are not taken into account in the design of the outer-loop controller. In this regard, the outer-loop controller is also referred to as the nominal controller. The inner-loop controller, on the other hand, is in charge of compensating for parameter uncertainties. The nonlinear disturbance observer (DOB) controller [17] is adopted as the inner-loop controller. In the nonlinear DOB controller, a disturbance signal, equivalent to the parameter variation in terms of effect on the output, is canceled by its estimate. As a result, the shaded block in Fig. 1 becomes approximately equivalent to the nominal HIV infection model. Therefore, even in the presence of parameter uncertainties, the proposed two-loop controller achieves almost similar treatment performance as that of the nominal closed-loop system.

The proposed controller is designed as follows. First, a state feedback controller is designed using the nominal model under the assumption that all state variables are measurable. Second, a nonlinear state observer is designed based on the nominal model to obtain state estimates only from the measurement of total CD+4 T cell concentrations. An output feedback controller is then constructed by combining the state feedback controller and the nonlinear state observer. This output feedback controller plays the role of the outer-loop controller. Finally, the nonlinear DOB controller is designed to make the uncertain closed-loop system behave like the nominal system.

The paper is organized as follows. In Section 2, a mathematical model of HIV infection therapy is presented, and the treatment goal of the paper is stated. Under the assumption that all model parameters are known exactly, the nominal controller is designed in Section 3. In Section 4, the nonlinear DOB controller is designed to cope with uncertain model parameters. To illustrate the performance of the proposed controller, various simulation results are presented in Section 5. Finally, a conclusion is offered in Section 6

2. Mathematical model of HIV infection therapy

A deterministic model of HIV infection therapy can be expressed by the following differential equations [3,9,10,13,14,16]:

$$\begin{aligned}\dot{x}_1 &= s - dx_1 - \beta(1-u)x_1x_3\\ \dot{x}_2 &= \beta(1-u)x_1x_3 - \mu x_2\\ \dot{x}_3 &= k(1-u_P)x_2 - cx_3\end{aligned} \tag{1}$$

where x_1, x_2 and x_3 represent the concentrations of healthy CD4+ T cells, infected CD4+ T cells and free virus, respectively. Healthy cells are produced at the rate s, and die naturally at the rate d. They are infected at the rate β through interaction with the virus. The infected cells then die at the rate μ. Virus particles are created at the rate k, and are cleared at the rate of c per cell. The nominal values of model parameters for (1) are listed in Table 1. (Parameter values are quoted from reference [14], which are estimated from actual patients.)

Table 1
Nominal values of model parameters.

Parameter	Value	Unit
s	295	cells/(mm^3 × day)
d	0.182	1/day
β	3.89×10^{-6}	mL/(copy × day)
μ	1.02	1/day
k	5890	copies × mm^3/(cell × mL × day)
c	24	1/day

Two kinds of antiretroviral drugs are involved in the model equations to treat HIV infection: reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). The efficacies of these two drugs are denoted by u and u_P, which range between 0 (no medication) and 1 (full medication). As assumed in references [3,9,11], $u_P = 0$ is used in this paper. System (1) can then be rewritten as

$$\begin{aligned}\dot{x}_1 &= s - dx_1 - \beta(1-u)x_1x_3\\ \dot{x}_2 &= \beta(1-u)x_1x_3 - \mu x_2\\ \dot{x}_3 &= kx_2 - cx_3\end{aligned} \tag{2}$$

As mentioned previously, the model parameters may be uncertain during the entire treatment period. Therefore, it is assumed in this research that β, k and c are unknown constants, while the rest of the parameters (s, μ and d) are known. Under this assumption, the HIV infection model is modified as follows:

$$\begin{aligned}\dot{x}_1 &= s - dx_1 - \tilde{\beta}(1-u)x_1x_3\\ \dot{x}_2 &= \tilde{\beta}(1-u)x_1x_3 - \mu x_2\\ \dot{x}_3 &= \tilde{k}x_2 - \tilde{c}x_3\end{aligned} \tag{3}$$

Here, $\tilde{\beta}$, $\tilde{k}$ and $\tilde{c}$ are used instead of β, k and c to indicate that these parameters are unknown constants.

The equilibrium point of the nominal model is required in the design of the controller. For a given $r_0(>0)$, the equilibrium point $x^* = (x_1^*, x_2^*, x_3^*)$ should be computed such that $x_2^* = r_0$. For convenience sake, system (2) is rewritten as

$$\dot{x} = F(x, u) \tag{4}$$

where $x := [x_1, x_2, x_3]^T$. Solving $F(x^*, u_{ss}) = 0$ with $x_2^* = r_0$ results in

$$x_1^* = \frac{s - \mu r_0}{d}, \qquad x_3^* = \frac{k}{c}r_0 \tag{5}$$

$$u_{ss} = 1 - \frac{\mu dc}{\beta k(s - \mu r_0)} \tag{6}$$

If no drug treatment is performed, i.e. $u = 0$, the nominal model (2) has the following two equilibrium points:

$$\left(\frac{s}{d},\ 0,\ 0\right) =: X_h, \qquad \left(\frac{\mu c}{\beta k},\ \frac{s}{\mu} - \frac{dc}{\beta k},\ \frac{ks}{c\mu} - \frac{d}{\beta}\right) =: X_{inf}$$

Using the values of the model parameters in Table 1, we obtain

$$\begin{aligned}X_h &= [1621,\ 0,\ 0]^T,\\ X_{inf} &= [1068,\ 98.57,\ 24192]^T\end{aligned} \tag{7}$$

Obviously, X_h and X_{inf} correspond to healthy and infected persons, respectively. In simulation studies, X_{inf} will be used as the initial condition.

This paper aims to design a controller to reduce the viral load by 90% in eight weeks after treatment, and to suppress it