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Nonlinear adaptive control method for treatment of uncertain hepatitis B virus infection

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ABSTRACT

In this paper, a nonlinear adaptive control method is presented for the treatment of the Hepatitis B Virus (HBV) infection. Nonlinear dynamics of the HBV, modeling uncertainties and three state variables (the numbers of uninfected and infected cells and free viruses) are taken into account. The proposed control law is designed for the antiviral drug input such that the number of free viruses and consequently the number of infected cells decrease to the desired values. An adaptation law is also presented to overcome modeling uncertainties by updating estimations of the system parameters during the treatment period. The stability of the process and convergence to desired state values are investigated by utilizing the Lyapunov theorem. The performance of the proposed adaptive control strategy is evaluated via comprehensive simulations employing the nonlinear HBV model with different levels of uncertainty. The consideration of modeling uncertainties is in accordance with the reality where the HBV has different characteristics in different bodies. According to the obtained results, the proposed strategy can achieve the desired control objectives (reduction of viruses and infected cells) by adjusting the drug usage.

1. Introduction

More than 2 billion people alive (nearly 1 out of 3 people) have been infected by the Hepatitis B virus (HBV) [1]. The population of HBV carriers is nearly 400 million and 75% of them are in the Asia. Accordingly, the HBV causes about 1 million deaths each year in the world. Only in China, 15 million newly infected people are detected in each year. Among them, more than 30 million infections are chronic, and more than 350 thousand die annually from HCC and cirrhosis [2].

Mathematical modeling is an appropriate tool to investigate the behavior of the HBV infection. Mathematical models have been also used to study other viral infection dynamics such as the human immunodeficiency virus (HIV) infection [3] and the hepatitis C virus (HCV) infection [4]. In these models, the system's biology has been taken into account as some differential equations represent the dynamics of the virus, immune system and host cells [5].

It should be mentioned that the available drugs are not able to clear the HBV infection; however, they stop the virus replication and prevent it from damaging the liver [2]. Therefore, some dynamic models have been developed for predicting the HBV changes during the antiviral therapy [2,6]. Among these models, the virus infection model suggested by Nowak et al. [6] is more general and has been used and validated in previous studies on the HBV infection dynamics.

Some control methods have been used for the antiviral therapy of infectious diseases such as optimal closed-loop control [7] and model predictive control [8] for the HIV infection. Sheikhan and Ghoreishi [5] have investigated a fuzzy controller using five optimization algorithms for the treatment of a basic HBV infection. Moreover, they have designed and compared three optimal controllers [9] for the HBV by employing a covariance matrix adaptation-evolution strategy.

Different optimal control techniques have been suggested for the chemotherapy of the cancer disease by adjusting the drug usage based on mathematical models [10–12]. The optimal therapy [13] has also been used for the HBV infection resulting in a logistic hepatocyte growth. Ntaganda and Gahamanyi [14] have utilized a fuzzy logic approach to find an optimal solution for the HBV antiviral therapy. Su and Sun [15] have studied an optimal control strategy for anti-HBV infection by the combination of traditional Chinese therapy and Western medicine methods. In addition, a multi-rate model predictive control (MPC) method [16] has been used to find an optimal treatment schedule for the HBV infected patients.

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However, the realistic behavior of a disease may be different from the response of its mathematical model due to the presence of uncertainties. These dynamic uncertainties are usually different in various bodies and conditions (e.g., age, life style and local climate). Therefore, the modeling uncertainties should be taken into account for designing a treatment strategy using a drug delivery controller. For this purpose, Moradi et al. [17] have suggested an adaptive control method for the drug usage in order to reduce the cancer tumors' volume using an uncertain chemotherapy model. Betechuoh et al. [18] have proposed a method based on the neural networks to control the HIV infection. Some other adaptive control strategies [19–21] have been designed for the HIV dynamics having modeling uncertainties.

A control method has not yet been developed for the hepatitis type B virus infection in the presence of modeling uncertainties. Accordingly, in this study, a nonlinear adaptive control strategy is designed for the treatment of the HBV infection with uncertain nonlinear dynamics for the first time. Note that the parameters values of the original nonlinear HBV model and their uncertainties influence the performance of the previous model-based controllers. However, completely uncertain parameters of the HBV dynamic model are considered for designing the proposed nonlinear adaptive controller. Note that the magnitudes of uncertainties do not affect the controller's structure. Moreover, unlike the previous controllers (e.g., [16]) that required a linearization of the nonlinear HBV model around an operating point, the proposed nonlinear control scheme can achieve its objective for the treatment without using any linearization.

The objective of this control strategy is reduction of the number of viruses per unit volume of the blood by converging to a desired value. As a result of achievement to this objective, the cells infected by the HBV will also decrease and the uninfected cells will increase to a steady state population. For this purpose, the antiviral drug usage is employed as the applicable control input for tracking the descending desired number of viruses. The stability of the controlled process and tracking convergence are proved using the Lyapunov method.

The rest of this paper is arranged as follows. Section 2 describes the nonlinear mathematical model of the HBV infection. The controller is designed and detailed in Section 3, and the Lyapunov stability analysis is presented in Section 4. The HBV model becomes dimensionless in Section 5 for the simulations that are presented in Section 6. Finally, the concluding remarks are summarized in Section 7.

2. Nonlinear mathematical model of HBV

At first, it is essential to choose an appropriate model in order to analyze the HBV behavior. The validated nonlinear HBV model is represented by the following set of differential equations [6]:

$$\frac{dx}{dt} = \lambda - dx - \beta vx \tag{1}$$

$$\frac{dy}{dt} = \beta vx - \delta y \tag{2}$$

$$\frac{dv}{dt} = py - cv \tag{3}$$

where the state variables are the numbers of uninfected (x) and infected (y) cells, and the number of free viruses (v) per unit volume of the blood. The definitions of constant parameters used in the above model are listed in Table 1 [5].

Now, by considering the factor of drug usage $1 - \mu u(t)$ in the hepatitis B virus dynamics, Eq. (3) is represented via the following form [5]:

$$\dot{v} = [1 - \mu u(t)]py - cv \tag{4}$$

Table 1
Parameter definitions [5].

Parameter	Definition
λ	Rate of production of new target cells
d	Death rate of target cells
β	Rate of infection of new target cells
δ	Death rate of infected cells
p	Rate of production of virions per infected cell
c	Clearance rate of free virions
μ	Efficacy of the drug coefficient

where $u(t)$ is the normalized rate of antiviral drug usage that should be in the range of [01]. In other words, the physiological constraint of this HBV treatment process is limitation of the drug rate: $0 \le u(t) \le 1$. The parameter μ also specifies the efficacy of drug therapy.

3. Design of the controller

In this section, the nonlinear adaptive control method is proposed for the mentioned HBV model (1)–(3). The objective of this adaptive control method is decreasing the number of viruses inside the body by the antiviral drug usage. By employing this drug delivery control method, the number of free viruses (v) decreases via tracking a descending desired value (vdes). After a limited time, the number of viruses decreases and converges to the zero and the magnitude of the term βvx in Eqs. (1) and (2) decreases to zero. As a result, it can be proved that the number of infected cells (y) reduces and the number of uninfected cells (x) increases after a bounded time based on their dynamics (1) and (2). Moreover, the proposed controller becomes robust against parametric uncertainties of the nonlinear HBV model via employing an adaptation law to appropriately update the parameters' estimation. Schematic diagram of the proposed nonlinear adaptive controller is shown in Fig. 1.

Now, the HBV virus dynamics (4) is reformulated as

$$-[1 - \mu u(t)]py = -cv - \dot{v} \tag{5}$$

The above equation can be rewritten in terms of $u(t)$ as

$$u(t) = -\frac{\dot{v}}{\mu py} + \frac{1}{\mu} - \frac{cv}{\mu py} \tag{6}$$

The right side of Eq. (6) is nonlinear in terms of the variables (v, $\dot{v}$ and y); however, one can parameterize (6) in terms of the model parameters. Accordingly, considering the arbitrary variable ϕ instead of $\dot{v}$, Eq. (6) can be represented as follows:

$$-\frac{\phi}{\mu py} - \frac{cv}{\mu py} + \frac{1}{\mu} = R(\phi, v, y)\theta \tag{7}$$

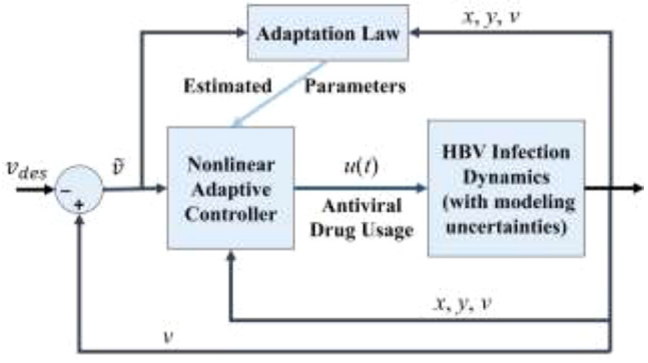

Fig. 1. Schematic diagram of the nonlinear adaptive control strategy for antiviral therapy of the HBV infection.