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Robust adaptive Lyapunov-based control of hepatitis B infection

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Omid Aghajanzadeh[1], Mojtaba Sharifi[2] ✉, Shabnam Tashakori[1], Hassan Zohoor[1]

[1]*Department of Mechanical Engineering, Sharif University of Technology, Tehran 11155-9567, Iran*
[2]*Department of Mechanical Engineering, Shiraz University, Shiraz 71936, Iran*
✉ *E-mail: m.sharifi@shirazu.ac.ir*

Abstract: A new robust adaptive controller is developed for the control of the hepatitis B virus (HBV) infection inside the body. The non-linear HBV model has three state variables: uninfected cells, infected cells and free viruses. A control law is designed for the antiviral therapy such that the volume of infected cells and the volume of free viruses are decreased to their desired values which are zero. One control input represents the efficiency of drug therapy in inhibiting viral production and the other control input represents the efficiency of drug therapy in blocking new infection. The proposed controller ensures the stability and robust performance in the presence of parametric and non-parametric uncertainties (and/or bounded disturbances). The global stability and tracking convergence of the process are investigated by employing the Lyapunov theorem. The performance of the proposed controller is evaluated using simulations by considering different levels of uncertainties. Based on the obtained results, the proposed strategy can achieve its desired objectives with different cases of uncertainties.

1 Introduction

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus. It is a major global health problem that can cause chronic infection and puts people at high risk of death from cirrhosis and liver cancer. An estimated 240 million people are chronically infected with hepatitis B (defined as hepatitis B surface antigen positive for at least 6 months). More than 686,000 people die every year due to complications of hepatitis B, including cirrhosis and liver cancer [1].

Available drugs cannot clear the hepatitis B virus (HBV) infection; however, they stop replication of virus and prevent liver damage. Accordingly, among the dynamic models that have been proposed for monitoring the HBV changes during the drug therapy, the virus infection model introduced by Nowak *et al.* [2] was widely used and validated in studies on the virus infection dynamics. This model was obtained by performing various experimental tests on different patients.

Some other experimental studies were performed on the animals' HBV-infected models by Ganem [3] and Feitelson and Larkin [4]. However, some human features make it extremely difficult to extend the animal models to the human HBV [4].

Different methods [5–7] exist in the literature for antiviral therapy problem of infectious diseases. Sharomi and Malik [8] reviewed the available literature on mathematical models that use optimal control theory to deduce the optimal strategies aimed at curtailing the spread of an infectious disease. Moradi *et al.* [9] used an adaptive control strategy to manipulate the drug usage and consequently decrease the tumour volume in the cancer chemotherapy. Three mathematical cell-kill models including log-kill, Norton–Simon and $E_{\max}$ hypotheses are considered in the presence of uncertainties [9]. Anelone and Spurgeon [10] employed a model of HIV infection together with an associated reachability analysis which considers the action of antiretroviral drugs to formulate the containment condition of HIV infection on the desirable manifold.

Hernandez-Vargas and Middleton [11] proposed a mathematical model for the HIV infection. Their model represented the whole trajectory in HIV infection and its progression to AIDS with three stages: primary infection, asymptomatic and symptomatic periods. Also, Rivadeneira *et al.* [12] explained different studies on the HIV dynamics and proposed optimal control methods for its drug therapy. Different model predictive control methods [13, 14] were suggested for optimal drug scheduling in HIV treatment.

In particular, some control strategies have been applied for the HBV treatment. For instance, Ntaganda and Gahamanyi [15] employed a fuzzy logic for optimal control of the HBV. Su and Sun [7] compared the HBV treatment process using two different therapies (traditional Chinese and Western medicines) by employing an optimal method. Laarabi *et al.* [16] applied another optimal control strategy in order to minimise the treatment costs and maximise the volume of healthy cells. However, not enough appropriate control methods were presented for the non-linear HBV dynamics with analysis of the process stability.

In this work, a robust adaptive Lyapunov-based control strategy is developed for the HBV treatment. The objectives of this control strategy are decreasing the number of infected cells and the number of hepatitis B viruses. As a result of achievement to these objectives, the uninfected cells will increase. For this purpose, two applicable control inputs (the antiviral drug usage) are used to track the descending desired values of infected cells and viruses. These control inputs represent the efficiency of drug therapy in blocking new infection and inhibiting viral production [17]. This means that a control input affects the healthy and sick cells dynamics and the other one affects the hepatitis virus dynamics. The stability of process and tracking convergence are guaranteed using the presented Lyapunov analysis.

In summary, the proposed controller has the following characteristics in comparison with the previously suggested controllers for the HBV [7, 15, 16]: (i) being robust to the parametric uncertainties of the process using the adaptive control theory [18], and (ii) robustness against bounded unstructured modelling (non-parametric) uncertainties and/or disturbances in the process by employing the sliding-mode control theory [19]. Accordingly, in this paper, by combining the non-linear adaptive control [18] and sliding-mode control [19], a new robust adaptive Lyapunov-based controller is presented for the HBV infection.

2 Mathematical model of HBV

The employed HBV dynamic model in this work is obtained from some clinical studies [2] on 50 patients for 24 weeks of the treatment. This non-linear hepatitis B virus dynamics is given by the following system of differential equations [17]:

Table 1 Parameter definitions for HBV model (1)–(3)

Parameter	Definition
d	death rate of target cells
δ	death rate of infected cells
c	clearance rate of free virions
p	production rate of virions per infected cell
β	infection rate of new target cells
λ	production rate of new target cells

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \lambda - \mathrm{d}x - (1-u_1)\beta xv \tag{1}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = (1-u_1)\beta xv - \delta y \tag{2}$$

$$\frac{\mathrm{d}v}{\mathrm{d}t} = (1-u_2)py - cv \tag{3}$$

These dynamics are structured such that the constant parameters were separated from the varying measurable states: numbers of infected cells (y), uninfected cells (x) and free viruses (v). Initial conditions of this dynamics $x(0)=x_0$, $y(0)=y_0$ and $v(0)=v_0$ are given and the definitions of above model parameters are listed in Table 1. Note that the number of healthy cells (x) has a maximum saturation population in the unit of human blood volume. This saturation level is obtained as $\lambda/d = 6.645\times10^7$ in Section 4 by employing the proposed controller.

In this model (1)–(3), $u_1(t)$ and $u_2(t)$ are the control inputs to achieve the desired objectives, which are reducing the amounts of infected cells y and viruses v in the patient's body. Based on [20], the time unit of the model is in day and all the parameters are given in day as well. This time unit (day) has also been used in other similar HBV models [2, 17, 21].

3 Robust adaptive controller design

In this section, the robust adaptive sliding mode control strategy is developed for the non-linear HBV model. For this purpose, the rates of drug usage $u_1(t)$ and $u_2(t)$ are controlled to track the descending desired values (y_d and v_d) for the numbers of infected hepatocytes (y) and free viruses (v). Moreover, using the proposed controller, the tracking performance is achieved in the presence of parametric and non-parametric uncertainties of the non-linear HBV model. The employed HBV dynamics is obtained from [2] in which numerous experimental tests were implemented to propose this model (1)–(3). These dynamics were structured such that the constant parameters are separated from the varying states (infected and uninfected cells and viruses). The values of these parameters were obtained from some experiments in [2] that are also represented in [22].

In this paper, different levels of uncertainty in the estimation of HBV model parameters have been considered. Another type of uncertainty considered in this work is the non-parametric or unstructured uncertainty. This type of uncertainty comes from some aspects of the process which are not taken into account in the developed model. These uncertainties can originate from measurement limitations and/or errors during the initial experiments, as well as the probable differences (such as age, genetic diversity and life style) among HBV patients.

Accordingly, two arbitrary disturbance functions D_1 and D_2 are taken into account as unstructured uncertainties of the HBV model. Therefore, (1)–(3) are modified to the following form:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \lambda - \mathrm{d}x - (1-u_1)\beta xv - D_1\beta xv \tag{4}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = (1-u_1)\beta xv - \delta y + D_1\beta xv \tag{5}$$

$$\frac{\mathrm{d}v}{\mathrm{d}t} = (1-u_2)py - cv + D_2py \tag{6}$$

The dynamics of the HBV model for the infected cells y and viruses v (5) and (6) can be rearranged as follows:

$$u_1(t) = -\frac{\dot{y}}{\beta xv} - \frac{\delta y}{\beta xv} + 1 + D_1 \tag{7}$$

$$u_2(t) = -\frac{\dot{v}}{py} - \frac{cv}{py} + 1 + D_2 \tag{8}$$

Then, the regressor matrices $\boldsymbol{Z}_1$ and $\boldsymbol{Z}_2$ in terms of certain functions of the variables ϕ_1, ϕ_2, x, y and v, and the vectors $\boldsymbol{\theta}_1$ and $\boldsymbol{\theta}_2$ in terms of the unknown parameters of the HBV dynamics (7) and (8) are defined as

$$\boldsymbol{Z}_1 = \left[-\frac{\phi_1}{vx}, \quad -\frac{y}{vx}\right] \tag{9}$$

$$\boldsymbol{Z}_2 = \left[-\frac{\phi_2}{y}, \quad -\frac{v}{y}\right] \tag{10}$$

$$\boldsymbol{\theta}_1 = \left[\frac{1}{\beta}, \quad \frac{\delta}{\beta}\right]^\mathrm{T} \tag{11}$$

$$\boldsymbol{\theta}_2 = \left[\frac{1}{p}, \quad \frac{c}{p}\right]^\mathrm{T} \tag{12}$$

such that (7) and (8) can be reformulated using $\phi_1 = \dot{y}$ and $\phi_2 = \dot{v}$ [23], as

$$-\frac{\phi_1}{\beta xv} - \frac{\delta y}{\beta xv} + 1 + D_1 = \boldsymbol{Z}_1(\phi_1, x, y, v)\boldsymbol{\theta}_1 + 1 + D_1 \tag{13}$$

$$-\frac{\phi_2}{py} - \frac{cv}{py} + 1 + D_2 = \boldsymbol{Z}_2(\phi_2, v, y)\boldsymbol{\theta}_1 + 1 + D_2 \tag{14}$$

Accordingly, the non-linear control strategy for the amount of medication $u(t) = (u_1(t), u_2(t))$ is defined as

$$u_1(t) = \boldsymbol{Z}_1\hat{\boldsymbol{\theta}}_1 + 1 + \frac{\gamma_1\mathrm{sgn}(\tilde{y})}{vx} \tag{15}$$

$$u_2(t) = \boldsymbol{Z}_2\hat{\boldsymbol{\theta}}_2 + 1 + \frac{\gamma_2\mathrm{sgn}(\tilde{v})}{y} \tag{16}$$

The sign ^ is used to specify estimated values of the uncertain system parameters that are updated using adaptation laws. In other words, $\hat{\boldsymbol{\theta}}_1$ and $\hat{\boldsymbol{\theta}}_2$ are the estimations of $\boldsymbol{\theta}_1$ and $\boldsymbol{\theta}_2$ (introduced in (11) and (12)). The regressor matrices $\boldsymbol{Z}_1$ and $\boldsymbol{Z}_2$ in the control laws (15) and (16) are defined in (9) and (10) in terms of ϕ_1, ϕ_2, x, y and v. Based on (15) and (16), the controller is updated according to the patient's infected cells y, viruses v and uninfected cells x. The variables ϕ_1, ϕ_2 in (13) and (14) are also defined separately as

$$\phi_1 = \dot{y}_\mathrm{d} - \eta_1(y - y_\mathrm{d}) \tag{17}$$

$$\phi_2 = \dot{v}_\mathrm{d} - \eta_2(v - v_\mathrm{d}) \tag{18}$$

where η_1 and η_2 are positive parameters. The terms $\gamma_1\mathrm{sgn}(\tilde{y})/vx$ and $\gamma_2\mathrm{sgn}(\tilde{v})/y$ in (15) and (16) provide the robustness of the controller against the bounded model mismatches and/or disturbances (D_1 and D_2 in (4)–(6)). In these terms, γ_1 and γ_2 are positive gains, and $\tilde{y}$ and $\tilde{v}$ are defined as tracking errors of infected cells and viruses with respect to their desired values (y_d and v_d):

$$\tilde{y} = y - y_\mathrm{d} \tag{19}$$

$$\tilde{v} = v - v_\mathrm{d} \tag{20}$$

Note that the proposed controller (15)–(16) requires the measurements of infected cells (y), uninfected cells (x) and viruses (v) populations per unit volume of the blood. Some methods in multiplicity of infection are currently employed for quantification of viruses and infected cells per unit volume of liquids [24]. Consequently, similar to the previous studies on the modelling [2, 25] and control [7, 15, 16, 26] of the HBV infection, it is considered that the viruses and cells measurements are possible for implementation of the proposed strategy. Also, the non-linear HBV model originated from [2] in which the state variables (x, y and v) were measured to obtain the dynamic structure (1)–(3) and identify its parameters.

Now, the adaptation laws for updating the estimated parameters of the system ($\hat{\boldsymbol{\theta}}_1$ and $\hat{\boldsymbol{\theta}}_2$) are defined as

$$\dot{\hat{\boldsymbol{\theta}}}_1 = \boldsymbol{\Gamma}_1^{\mathrm{T}} \mathbf{Z}_1^{\mathrm{T}} x\, v\, \tilde{y} \tag{21}$$

$$\dot{\hat{\boldsymbol{\theta}}}_2 = \boldsymbol{\Gamma}_2^{\mathrm{T}} \mathbf{Z}_2^{\mathrm{T}} y \tilde{v} \tag{22}$$

where $\boldsymbol{\Gamma}_1$ and $\boldsymbol{\Gamma}_2$ are constant positive definite matrices.

In the next section, using the Lyapunov stability theorem, it will be proved that the proposed robust adaptive controller ensures the stability and convergence of the HBV therapy process in the presence of parametric and non-parametric uncertainties.

4 Lyapunov analysis

The closed-loop dynamics of the system using the proposed non-linear robust adaptive controller is obtained by substituting the control laws (15) and (16) in the HBV model (7) and (8) and by adding and subtracting some terms:

$$\begin{aligned} -\frac{\dot{y}}{\beta x v} - \frac{\delta y}{\beta x v} + 1 + D_1 = & -\frac{\dot{y}_{\mathrm{d}} - \eta_1 (y - y_{\mathrm{d}})}{\hat{\beta} x v} \\ & -\frac{\hat{\delta} y}{\hat{\beta} x v} + 1 + \frac{\gamma_1 \mathrm{sgn}(\tilde{y})}{x v} \\ & -\frac{\dot{y}_{\mathrm{d}} - \eta_1 (y - y_{\mathrm{d}})}{\beta x v} - \frac{\delta y}{\beta x v} + 1 \\ & +\frac{\dot{y}_{\mathrm{d}} - \eta_1 (y - y_{\mathrm{d}})}{\beta x v} + \frac{\delta y}{\beta x v} - 1 \end{aligned} \tag{23}$$

$$\begin{aligned} -\frac{\dot{v}}{p y} - \frac{c v}{p y} + 1 + D_2 = & -\frac{\dot{v}_{\mathrm{d}} - \eta_2 (v - v_{\mathrm{d}})}{\hat{p} y} - \frac{\hat{c} v}{\hat{p} y} + 1 + \frac{\gamma_2 \mathrm{sgn}(\tilde{v})}{y} \\ & -\frac{\dot{v}_{\mathrm{d}} - \eta_2 (v - v_{\mathrm{d}})}{p y} - \frac{c v}{p y} + 1 \\ & +\frac{\dot{v}_{\mathrm{d}} - \eta_2 (v - v_{\mathrm{d}})}{p y} + \frac{c v}{p y} - 1 \end{aligned} \tag{24}$$

Using (9)–(14) in (23) and (24), the closed-loop dynamics of the controlled process is obtained as

$$-\frac{1}{\beta x v}\left(\dot{\tilde{y}} + \eta_1 \tilde{y}\right) + D_1 = \mathbf{Z}_1 \tilde{\boldsymbol{\theta}}_1 + \frac{\gamma_1 \mathrm{sgn}(\tilde{y})}{x v} \tag{25}$$

$$-\frac{1}{p y}\left(\dot{\tilde{v}} + \eta_2 \tilde{v}\right) + D_2 = \mathbf{Z}_2 \tilde{\boldsymbol{\theta}}_2 + \frac{\gamma_2 \mathrm{sgn}(\tilde{v})}{y} \tag{26}$$

where $\tilde{\boldsymbol{\theta}}_1 = \hat{\boldsymbol{\theta}}_1 - \boldsymbol{\theta}_1$ and $\tilde{\boldsymbol{\theta}}_2 = \hat{\boldsymbol{\theta}}_2 - \boldsymbol{\theta}_2$ are the vectors of parameter estimation errors. By simplifying (25) and (26), the closed-loop dynamics is finally expressed as

$$\dot{\tilde{y}} = -\eta_1 \tilde{y} - \beta x v \mathbf{Z}_1 \tilde{\boldsymbol{\theta}}_1 - \beta \gamma_1 \mathrm{sgn}(\tilde{y}) + \beta x v D_1 \tag{27}$$

$$\dot{\tilde{v}} = -\eta_2 \tilde{v} - p y \mathbf{Z}_2 \tilde{\boldsymbol{\theta}}_2 - \gamma_2 p \mathrm{sgn}(\tilde{v}) + p y D_2 \tag{28}$$

To prove the process stability and the tracking convergence using the proposed controller, a Lyapunov function candidate is used as

$$V = \frac{1}{2}\left(\tilde{v}^2 + \tilde{y}^2 + \beta \tilde{\boldsymbol{\theta}}_1^{\mathrm{T}} \boldsymbol{\Gamma}_1^{-1} \tilde{\boldsymbol{\theta}}_1 + p \tilde{\boldsymbol{\theta}}_2^{\mathrm{T}} \boldsymbol{\Gamma}_2^{-1} \tilde{\boldsymbol{\theta}}_2\right) \geq 0 \tag{29}$$

The time derivative of V is then obtained as

$$\dot{V} = \tilde{v}\dot{\tilde{v}} + \tilde{y}\dot{\tilde{y}} + \beta \dot{\hat{\boldsymbol{\theta}}}_1^{\mathrm{T}} \boldsymbol{\Gamma}_1^{-1} \tilde{\boldsymbol{\theta}}_1 + p \dot{\hat{\boldsymbol{\theta}}}_2^{\mathrm{T}} \boldsymbol{\Gamma}_2^{-1} \tilde{\boldsymbol{\theta}}_2 \tag{30}$$

where $\dot{\tilde{\boldsymbol{\theta}}}_i = \dot{\hat{\boldsymbol{\theta}}}_i$, because $\boldsymbol{\theta}_i$ is a constant vector and $\dot{\boldsymbol{\theta}}_i = 0$. By employing the non-linear closed-loop dynamics (27) and (28) in (30), we have

$$\begin{aligned} \dot{V} = & \tilde{v}\left(-\eta_2 \tilde{v} - p y \mathbf{Z}_2 \tilde{\boldsymbol{\theta}}_2 - \gamma_2 p \mathrm{sgn}(\tilde{v}) + p y D_2\right) \\ & +\tilde{y}\left(-\eta_1 \tilde{y} - \beta x v \mathbf{Z}_1 \tilde{\boldsymbol{\theta}}_1 - \beta \gamma_1 \mathrm{sgn}(\tilde{y}) + \beta x v D_1\right) \\ & +\beta \dot{\hat{\boldsymbol{\theta}}}_1^{T} \boldsymbol{\Gamma}_1^{-1} \tilde{\boldsymbol{\theta}}_1 + p \dot{\hat{\boldsymbol{\theta}}}_2^{T} \boldsymbol{\Gamma}_2^{-1} \tilde{\boldsymbol{\theta}}_2 \end{aligned} \tag{31}$$

Using the parameter adaptation laws (21) and (22), $\dot{V}$ in (31) is simplified to:

$$\begin{aligned} \dot{V} = & -\eta_2 \tilde{v}^2 + \tilde{v}(-p\gamma_2 \mathrm{sgn}(\tilde{v}) + p y D_2) \\ & -\eta_1 \tilde{y}^2 + \tilde{y}(-\beta \gamma_1 \mathrm{sgn}(\tilde{y}) + \beta x v D_1) \end{aligned} \tag{32}$$

The positive gains γ_1 and γ_2 in the robust controller (15) and (16) should be adjusted as large to overcome the upper bounds of non-parametric uncertainties (disturbances D_1 and D_2) by satisfying the following inequalities:

$$\gamma_1 \geq |x v D_1|, \quad \gamma_2 \geq |y D_2| \tag{33}$$

Employing (33) in the time derivative of Lyapunov function (32) results in:

$$\dot{V} \leq -\eta_1 \tilde{v}^2 - \eta_2 \tilde{y}^2 \tag{34}$$

Proposition: Based on the Lyapunov stability theorem [18], the proposed non-linear control method guarantees the stability and tracking convergence ($\tilde{y} \to 0$ and $\tilde{v} \to 0$ as $t \to \infty$). In other words, if the rate of antiviral drug usage $u(t) = (u_1(t), u_2(t))$ is adjusted based on the presented control laws (15) and (16), the populations of infective cells and free viruses converge to their desired values ($y \to y_{\mathrm{d}}$ and $v \to v_{\mathrm{d}}$).

Proof: According to (29), the Lyapunov function V is positive definite ($V \geq 0$) in terms of $\tilde{y}$, $\tilde{v}$, $\tilde{\boldsymbol{\theta}}_1$ and $\tilde{\boldsymbol{\theta}}_2$. Also, the time derivative of Lyapunov function is negative semi-definite ($\dot{V} \leq 0$) in (34). Thus, V is bounded and consequently $\tilde{y}$, $\tilde{v}$, $\tilde{\boldsymbol{\theta}}_1$ and $\tilde{\boldsymbol{\theta}}_2$ remain bounded. The desired number of infected cells (y_{d}) and the desired number of viruses (v_{d}) are defined bounded. Therefore, since $\tilde{y} = y - y_{\mathrm{d}}$ and $\tilde{v} = v - v_{\mathrm{d}}$, the state variables y and v are also bounded due to the boundedness of y_{d} and v_{d}. Moreover, by applying the Barbalat's lemma [18], it is concluded that $\dot{V} \to 0$ as $t \to \infty$. As a result and based on (34), the tracking errors of infected cells and viruses converge to zero ($\tilde{y} \to 0$ and $\tilde{v} \to 0$). Therefore, the objectives of proposed non-linear robust adaptive controller ($y \to y_d$ and $v \to v_d$) are achieved. However, the vectors of parameters estimation errors ($\tilde{\boldsymbol{\theta}}_1 = \hat{\boldsymbol{\theta}}_1 - \boldsymbol{\theta}_1$ and $\tilde{\boldsymbol{\theta}}_2 = \hat{\boldsymbol{\theta}}_2 - \boldsymbol{\theta}_2$) remain bounded.

Since the numbers of desired viruses and infected cells are designed to be descending and converge to zero ($y_{\mathrm{d}} \to 0$ and $v_{\mathrm{d}} \to 0$) during treatment, the numbers of actual viruses and infected cells also converge to zero as a result of the above-mentioned Lyapunov-based convergence proof ($y \to y_{\mathrm{d}} \to 0$ and

Table 2 Parameters and initial values of variables for the non-linear HBV dynamics (1)–(3) [22]

Parameter	Value
d	0.0038
β	1.981×10^{-13}
δ	0.0125
p	842.0948
c	0.67
$x(0)$	5.5556×10^7 cells/mL
$y(0)$	1.1111×10^7 cells/mL
$v(0)$	6.3096×10^9 copies/mL
λ	2.5251×10^5

Table 3 Percentages of parametric uncertainties and coefficients of non-parametric uncertainties (40) and (41)

Case of uncertainty	Parametric uncertainties		Non-parametric uncertainty	
	Uncertainty percentage for $\hat{\theta}_1(0)$	Uncertainty percentage for $\hat{\theta}_2(0)$	k_{1j} for $j = 1, 2, 3$	k_{2j} for $j = 1, 2, 3$
1	+50	+30	0.2	0.3
2	+30	−20	0.15	0.2
3	−30	−50	0.1	0.1

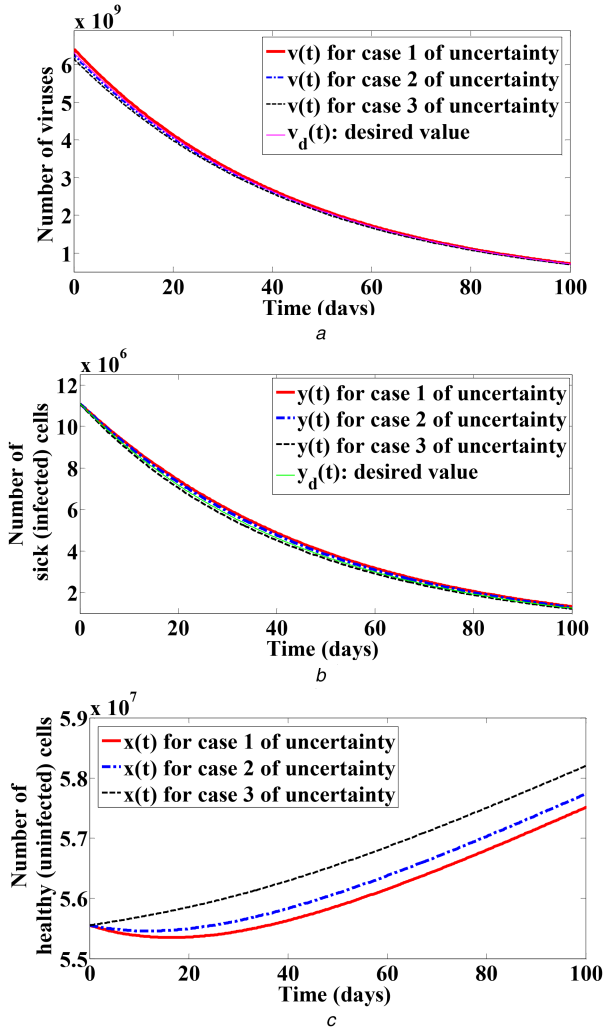

Fig. 1 *Controller performance*
(a) Decreasing the number of viruses, ***(b)*** Decreasing the number of infected cells, ***(c)*** Increasing the number of healthy (uninfected) cells, per ml of the blood volume

$v \to v_d \to 0$). Now, for evaluation of the uninfected cells (x) behaviour, (4) is rearranged as

$$\frac{dx}{dt} = \lambda - x(d + (1 - u_1)\beta v + D_1 \beta v) \tag{35}$$

Setting $y \to 0$ and $v \to 0$, we have:

$$(d + (1 - u_1)\beta v + D_1 \beta v) \to d \tag{36}$$

which means that:

$$\dot{x} \to \lambda - dx \tag{37}$$

Therefore, as the time tends to infinity, the number of healthy cells (x) will converge to its maximum steady-state value ($x \to \lambda/d$), which is 6.645×10^7 based on Table 2. □

5 Numerical results

The proposed robust adaptive sliding-mode control strategy is evaluated in this section by performing some simulations. For this purpose, the parameters and initial conditions of the hepatitis B virus infection with the non-linear model (1)–(3) are considered the same as ones presented in [22] for a patient. These values are listed in Table 2.

The desired descending amounts of infected cells and viruses in the blood that should be tracked using the proposed controller are assumed to be

$$y_d = (y_0 - y_f)e^{-s_1 t} + y_f \tag{38}$$

$$v_d = (v_0 - v_f)e^{-s_2 t} + v_f \tag{39}$$

where y_f and v_f are the final desired values of y and v, respectively. The constant parameters s_1 and s_2 are desired exponentially decreasing rates of infected cells and viruses during the treatment. For a treatment period of 100 days, these parameters are set on $s_1 = s_2 = 5.75$. It is worth mentioning that without loss of generality, other continuous decreasing functions for the desired values of y and v can be used instead of ones expressed in (38) and (39).

The unstructured uncertainties and/or disturbances (D_1 and D_2 in (4)–(6) are considered to be non-linear time varying; however, they can have any bounded functionality, without loss of generality. According to the progress of the HBV disease, D_1 and D_2 are assumed here to change daily, weekly and monthly due to the periods of human life, as

$$D_1 = k_{11}\sin(2\pi t) + k_{12}\sin\left(\frac{2\pi t}{7}\right) + k_{13}\sin\left(\frac{2\pi t}{30}\right) \tag{40}$$

$$D_2 = k_{21}\sin(2\pi t) + k_{22}\sin\left(\frac{2\pi t}{7}\right) + k_{23}\sin\left(\frac{2\pi t}{30}\right) \tag{41}$$

where k_{ij} are coefficients of time varying disturbances.

In these simulations, three cases of uncertainty are considered in the HBV model for evaluation of the controller performance. The percentages of parametric uncertainties and the coefficients of disturbances and/or non-parametric uncertainties (40) and (41) in these three cases are listed in Table 3.

The controller gains in (15)–(18) and the adaptation gains in (21) and (22) are adjusted using a trial and error method to have appropriate tracking convergence: $\eta_1 = \eta_2 = 0.6$, $\gamma_1 = \gamma_2 = 0.1$, $\mathbf{\Gamma}_1 = \text{diag}(40, 10)$ and $\mathbf{\Gamma}_2 = \text{diag}(2, 25)$.

The performance of the proposed non-linear controller in exponential decreasing of the infected cells y and viruses v per ml of the blood volume is shown in Fig. 1, for three cases of uncertainties.

As seen in Fig. 1, the proposed controller provides the tracking of desired exponentially decreasing values (defined in (38) and

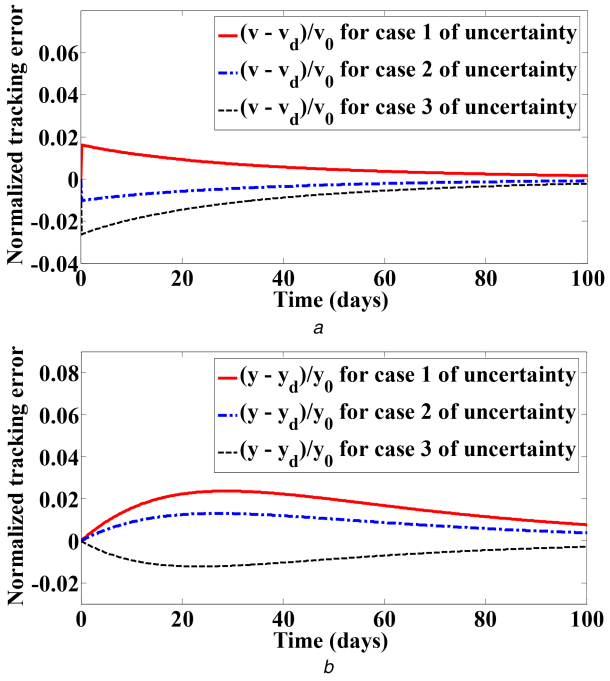

Fig. 2 *Normalised tracking errors*
(a) Number of viruses, ***(b)*** Number of infected cells, in comparison with their desired values

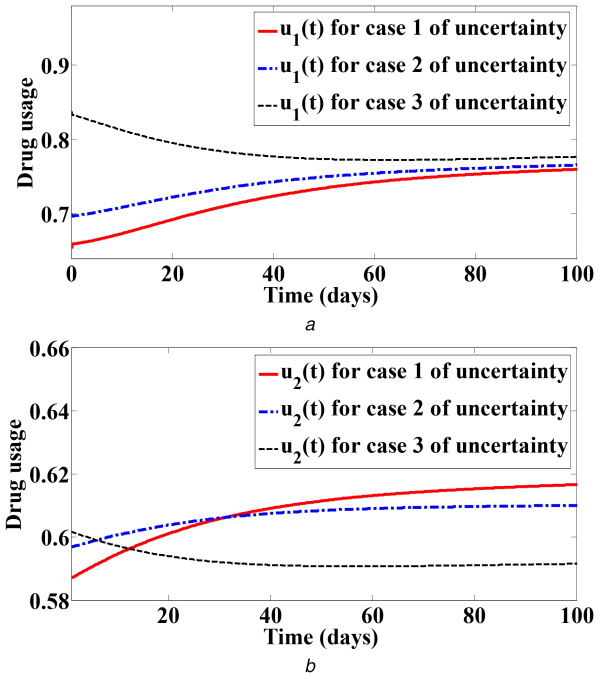

Fig. 3 *Drug usage*
(a) $u_1(t)$, ***(b)*** $u_2(t)$ for different cases of modelling uncertainty (introduced in Table 3)

(39) for the hepatitis B viruses and infected cells ($v \to v_d$ and $y \to y_d$). To better illustrate this convergence performance, the normalised tracking errors for the populations of virions and infected cells with respect to their desired values ($\tilde{v}/v_0 = (v - v_d)/v_0$ and $\tilde{y}/y_0 = (y - y_d)/y_0$) are shown in Fig. 2. It is observed that the tracking errors converge to zero ($\tilde{y} \to 0$ and $\tilde{v} \to 0$) in the presence of different uncertainty cases (introduced in Table 3), as proved in Section 4 (Lyapunov analysis).

It was mentioned earlier that x approaches to $\lambda/d(= 6.645 \times 10^7)$ as the time tends to infinity (by employing the proposed strategy, if $t \to \infty$ then $x \to \lambda/d$). However, since 100-day treatment period is not comparable to infinity, x does not converge to its maximum level in Fig. 1*c*. To show the final convergence value, the result of x should be plotted for more than

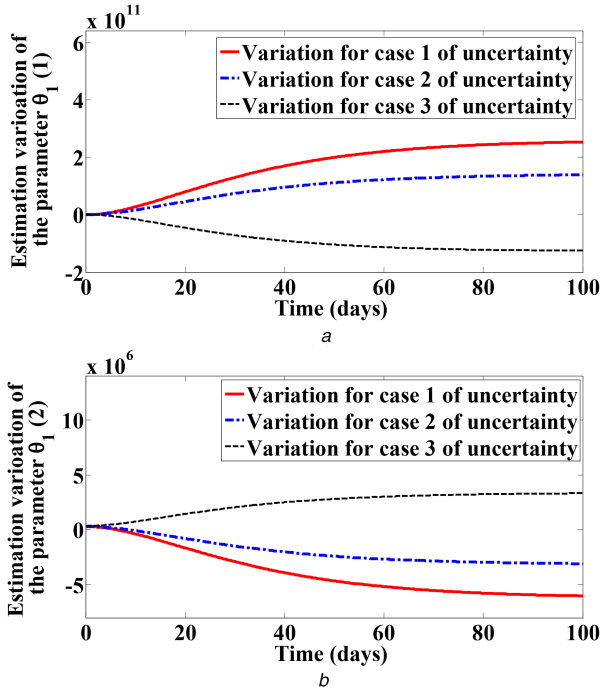

Fig. 4 *Adaptation performance for the parameters*
(a) $\hat{\boldsymbol{\theta}}_{1,1}$, ***(b)*** $\hat{\boldsymbol{\theta}}_{1,2}$ in different cases of uncertainty (in Table 3)

300 days of treatment time. However, since the first 100 days of treatment is the most important time for the reduction of viruses and infected cells and increasing the number of uninfected cells, the simulation results are presented for this time interval.

The aforementioned convergence to desired control objectives is the result of drug therapy based on the designed robust adaptive laws (15) and (16). This drug usage $\boldsymbol{u}(t) = (u_1(t), u_2(t))$ is shown in Fig. 3 for different cases of modelling uncertainty.

As seen, the controller could adapt to different uncertainties and adjust the drug inputs (Fig. 3) such that the desired descending numbers of viruses and infected cells are tracked (Figs. 1 and 2).

To demonstrate the parameter adaptation performance of the proposed strategy, the variations of parameters estimations with respect to their initial values are shown in Fig. 4 for two elements of $\hat{\boldsymbol{\theta}}_1(t) - \hat{\boldsymbol{\theta}}_1(0)$. The adaptation of $\hat{\boldsymbol{\theta}}_1(t)$ is obtained using the update rule (21), and the uncertainty percentages of the initial estimation $\hat{\boldsymbol{\theta}}_1(0)$ are mentioned in Table 3 for different cases. It is observed in Fig. 4 that the estimation of unknown parameters in $\hat{\boldsymbol{\theta}}_1(t)$ are bounded and consequently the error $\tilde{\boldsymbol{\theta}}_1 = \hat{\boldsymbol{\theta}}_1 - \boldsymbol{\theta}_1$ remains bounded as it was proved in Section 4. The results for $\hat{\boldsymbol{\theta}}_2(t)$ are similar and they are not illustrated for the sake of brevity.

6 Conclusion

A non-linear robust adaptive Lyapunov-based control strategy was designed in this paper for the antiviral drug therapy of the hepatitis B virus infection with different cases of uncertainty. The objectives of proposed robust adaptive controller are decreasing the populations of infected cells and viruses by tracking desired descending values, which result in increasing the healthy (uninfected) cells. The stability of controlled process together with the tracking convergence and the bounded parameter adaptation were proved using the Lyapunov analysis.

The controller performance in the presence of different cases of parametric and non-parametric uncertainties was investigated by some simulations. Due to the obtained results, the proposed non-linear control strategy is robust against a wide range of modelling uncertainties and bounded disturbances, and can rapidly adjust the antiviral drug usage to reduce hepatitis viruses and infected cells.

The proposed non-linear robust adaptive control strategy can be used in realistic health treatments of HBV patients, and can be redesigned for other diseases with different dynamic models in

future works. In future studies on the HBV treatment, a discontinuous (discrete) control law can be developed to be applicable in clinical implementations. This is because that a discontinuous state feedback (discontinuous measurement of patient's viruses and cells) is more feasible in realistic therapies. However, the stability analysis of a discrete controller for a continuous non-linear dynamic model of HBV may be mathematically challenging.

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