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**Research Article**

# An Adaptive Lyapunov-Based Controller for HIV Treatment

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**Abstract.** In view of the tremendous importance of patients' stability in medical sciences, this paper addresses the application of a sliding mode control in medical devices. In doing so, we consider a nonlinear dynamic system that shows the mathematical model of the human immunodeficiency virus. This nonlinear model has three variable states: healthy cells, infected cells, and free viruses. The proposed controller displays the effect of medication on preventing the production of the virus and blocking the new infection. This controller ensures the stability of this dynamic system provided for HIV in the event of a bounded disturbance. The stability and convergence of this process are proved by the Lyapunov theorem. Finally, a numerical example is given to demonstrate the efficiency of the proposed method.

**Keywords.** HIV, Mathematical modeling of HIV, Sliding mode control, Lyapunov stability.

**MSC.** 90C34; 90C40.

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## 1 Introduction

These viruses are mainly transmitted through infected blood, unprotected sex, and from the mother to the child during pregnancy, childbirth, or even breastfeeding [10]. In 1983, two separate research groups led by Robert Gallo and Luc Montagnier independently declared that a new retrovirus had infected AIDS patients [5]. Gallo claimed that the virus his group had isolated from an AIDS patient for research was quite similar in shape to other human T-Lymphotropic viruses (HTLV) that the group had initially isolated. The Gallo group called it (HTLV-III). At the same time, the Montagnier group isolated a virus from a patient with cervical lymph node swelling and physical weakness, two classic AIDS symptoms. Contradictions in the reports of the Gallo and Montagniergroups showed that the nuclei of the proteins of this virus were immunologically quite different from HTLV-I. The Montagnier group named the virus they had isolated, put the virus associated with Lymphadenopathy [1].

Since it transpired in 1986 that both viruses were the same, (HTLV-III) and (LAV) were renamed as HIV [7]. Currently, the prevalence of this disease is remarkably wide, and no treatment or vaccine has been developed for it [14]. Medical care mainly consists of taking actions to prevent the return of the virus and slow its progression. As AIDS is a highly fatal epidemic, the importance of stemming the growth of HIV, which ultimately develops into AIDS, cannot be over-emphasized [8].

Against this backdrop, by combining non-linear adaptive control and sliding-mode control, we present a new robust adaptive Lyapunov-based controller for HIV infection. The purpose of designing this adaptive control is not only to reduce the number of infected cells and viruses so that it converges to zero but also to help the number of healthy cells converge to the desired value.

## 2 The Mathematical Model of HIV

Optimal treatment or control of HIV infection using control theory has always been a popular research topic. Various mathematical models have been proposed in recent decades. The basic model that is considered as the mathematical model of HIV has three state variables, each of which indicates the number of cells per cubic millimeter of blood as follows [9]:

$$\begin{aligned} \dot{T} &= S - dT - \beta T V, \\ \dot{I} &= \beta T V - \mu I, \\ \dot{V} &= KI - CV, \end{aligned} \tag{1}$$

where $T$ represents healthy cells, $I$ represents the number of infected cells, and the variable $V$ represents free viruses in an infected person.

Free viruses infect healthy cells at a relative rate of $\beta TV$. The infected cells also cause free viruses to grow at a relative rate of $KI$ in the patient's body and disappear at a relative speed as $CV$. On the other hand, healthy cells are produced at a constant rate of $S$ and destroyed at a relative rate of $dT$.

Then, we convert the above dynamic device to the following control device, where $u_1(t)$ and $u_2(t)$ are the control inputs to achieve the desired values. In reality, $u(t) = (u_1(t), u_2(t))$ and $0 \leq u_i(t) \leq 1$. The expression $u_i(t) = 1$ indicates that we have completely cured the patient, and $u_i(t) = 0$ indicates the treatment [4].

$$\begin{aligned} \dot{T} &= S - dT - \beta TV(1-u_1), \\ \dot{I} &= (1-u_1)\beta TV - \mu I, \\ \dot{V} &= (1-u_2)KI - CV. \end{aligned} \tag{2}$$

The definitions of the above model parameters are listed in Table 1.

Note that the time unit of this model is in a day and all the parameters are given in a day as well. Assuming $(\dot{V} = 0, \dot{I} = 0, \dot{T} = 0)$, the equilibrium point of the above dynamic is obtained as $(T \;\; V \;\; I) = (\frac{S}{d} \;\; 0 \;\; 0)$.

**Table 1:** Parameter definition for the HIV model (1).

| parameter | definition |
|---|---|
| $d$ | death rate of the target cells |
| $\mu$ | death rate of the infected cells |
| $C$ | clearance rate of the free viruses |
| $k$ | production rate of the viruses per infected cell |
| $\beta$ | infection rate of the new target cells |
| $S$ | production rate of the new target cells |

## 3 Robust Adaptive Controller Design

In this section, the robust adaptive sliding mode control strategy is developed for the non-linear HIV model. First, $T$ and $I$ are simply added together. In this case, the regular form of the mathematical model of AIDS control is written as follows:

$$\begin{aligned} \dot{T} &= S - dT - \beta TV(1-u_1), \\ \dot{T} + \dot{I} &= S - dT - \mu I, \\ \dot{V} &= (1-u_2)KI - CV. \end{aligned} \tag{3}$$

Now by assuming $x_1 = -T + \frac{S}{d}$, $x_2 = T + I - \frac{S}{d}$ and $x_3 = V$, the above dynamics change to

$$\begin{aligned} \dot{x}_1 &= -dx_1 + \beta\left(\frac{S}{d} - x_1\right)x_3(1-u_1), \\ \dot{x}_2 &= dx_1 - \mu(x_1 + x_2), \\ \dot{x}_3 &= (1-u_2)K(x_1+x_2) - Cx_3. \end{aligned} \tag{4}$$

For the dynamic system (4), the sliding surface is defined as:

$$S(x) = -x_1 + \alpha((d-\mu)x_2 + Kx_3) = 0,$$

or

$$x_1 = \alpha((d-\mu)x_2 + Kx_3),$$

where $\alpha$ is an adequate positive number.

The non-linear dynamic system is placed on the sliding surface using adaptive control and, then, reaches the origin.

The rates of drug usage $u_1(t)$ and $u_2(t)$ are controlled to track the descending and ascending desired values ($x_{1d}$ and $x_{3d}$) respectively for the number of uninfected cells $x_{1d}$ and free viruses $x_{3d}$. As stated earlier, our goal here is to increase the volume of the healthy cells and reduce the volume of viruses; that explains why we chose $x_{1d}$ and $x_{3d}$. Moreover, using the proposed controller, the tracking performance is achieved in the presence of the parametric and non-parametric uncertainties of the non-linear HIV model. Thereafter, two arbitrary disturbance functions $D_1$ and $D_2$ are taken into account as unstructured uncertainties of the HIV model [2].

$$\begin{aligned} \dot{x}_1 &= -dx_1 + \beta\left(\frac{S}{d} - x_1\right)x_3(1-u_1) - D_1\beta x_3\left(\frac{S}{d} - x_1\right), \\ \dot{x}_2 &= dx_1 - \mu(x_1 + x_2), \\ \dot{x}_3 &= (1-u_2)K(x_1+x_2) - Cx_3 - D_2K(x_1+x_2). \end{aligned} \tag{5}$$

Regarding the dynamics of the HIV model for the healthy cells $T$ and viruses $V$, the first and third relationships above can be rearranged as follows:

$$\begin{cases} u_1(t) = -\dfrac{\dot{x}_1}{\beta(x_3\frac{S}{d} - x_3x_1)} - \dfrac{dx_1}{\beta(x_3\frac{S}{d} - x_3x_1)} + 1 - D_1, \\ u_2(t) = -\dfrac{\dot{x}_3}{K(x_1+x_2)} - \dfrac{Cx_3}{K(x_1+x_2)} + 1 - D_2. \end{cases} \tag{6}$$

Assuming $\varphi_1 = \dot{x}_1$, $\varphi_2 = \dot{x}_3$ and $D_1 = \dfrac{\gamma_1 sgn(\tilde{x}_1)}{x_3\frac{S}{d} - x_3x_1}$, $D_2 = \dfrac{\gamma_2 sgn(\tilde{x}_3)}{(x_1+x_2)}$ as well,

$$Z_1 = \left[ -\frac{\varphi_1}{(\frac{S}{d}x_3 - x_1x_3)}, -\frac{x_1}{(\frac{S}{d}x_3 - x_1x_3)} \right], \qquad Z_2 = \left[ -\frac{\varphi_2}{(x_2+x_1)}, -\frac{x_3}{(x_2+x_1)} \right],$$

and

$$\theta_1 = \left[ \frac{1}{\beta}, \frac{d}{\beta} \right]^T, \qquad \theta_2 = \left[ \frac{1}{K}, \frac{C}{K} \right]^T.$$

So (6) can be reformulated as [11],

$$\begin{cases} -\frac{\varphi_1}{\beta(x_3\frac{S}{d} - x_3x_1)} - \frac{dx_1}{\beta(x_3\frac{S}{d} - x_3x_1)} + 1 - D_1 = Z_1(\varphi_1, x_1, x_3)\theta_1 + 1 - D_1 \\ -\frac{\varphi_2}{K(x_2+x_1)}, -\frac{Cx_3}{K(x_2+x_1)} + 1 - D_2 = Z_2(\varphi_2, x_1, x_2, x_3)\theta_2 + 1 - D_2, \end{cases} \tag{7}$$

such that $Z_1$ and $Z_2$ are regressor matrices in terms of certain functions of the variables $\varphi_1$, $\varphi_2$, $x_1$, $x_2$ and $x_3$, so $\theta_1$ and $\theta_2$ are vectors of the unknown parameters of the HIV dynamics. The non-linear control for the amount of medication $u(t) = (u_1(t), u_2(t))$ is, accordingly, defined as

$$\begin{cases} -\frac{\varphi_1}{\beta(x_3\frac{S}{d} - x_3x_1)} - \frac{dx_1}{\beta(x_3\frac{S}{d} - x_3x_1)} + 1 - D_1 = Z_1\hat{\theta}_1 + 1 - \frac{\gamma_1 sgn(\tilde{x}_1)}{x_3\frac{S}{d} - x_3x_1}, \\ -\frac{\varphi_2}{K(x_2+x_1)} - \frac{Cx_3}{K(x_2+x_1)} + 1 - D_2 = Z_2\hat{\theta}_2 + 1 - \frac{\gamma_2 sgn(\tilde{x}_3)}{(x_1+x_2)}. \end{cases} \tag{8}$$

In these terms, $\gamma_1$ and $\gamma_2$ are positive gains, we have $\tilde{x}_1 = (x_1 - x_{1d})$, $\tilde{x}_3 = (x_3 - x_{3d})$. It should also be noted that the sign $\hat{}$ is used to specify the estimated values of the uncertain system parameters that are updated using adaptation laws; thus, $\hat{\theta}_i$ is the estimate of $\theta_i$.

## 4 Lyapunov Analysis

The convergence of the method is proved according to the adaptive controls that are introduced and using the appropriate Lyapunov function.

The expressions $\varphi_1$ and $\varphi_2$ can be considered as:

$$\varphi_1 = \dot{x}_{1d} - \eta_1(x_1 - x_{1d}),$$
$$\varphi_2 = \dot{x}_{3d} - \eta_2(x_3 - x_{3d}),$$

where $\eta_1$ and $\eta_2$ are positive parameters and are defined as

$$\tilde{x}_1 = x_1 - x_{1d}, \qquad \tilde{x}_3 = x_3 - x_{3d}.$$

Using the proposed non-linear robust adaptive controller, the closed-loop dynamics of the system is obtained by substituting the control laws in (8) as follows:

$$\begin{cases} u_1(t) = Z_1\hat{\theta}_1 + 1 - \dfrac{\gamma_1 sgn(\tilde{x}_1)}{x_3\frac{S}{d} - x_3x_1}, \\ u_2(t) = Z_2\hat{\theta}_2 + 1 - \dfrac{\gamma_2 sgn(\tilde{x}_3)}{(x_1+x_2)}. \end{cases} \tag{9}$$

Therefore, by adding and subtracting a few expressions in (6), we obtain

$$\begin{aligned} &-\frac{\dot{x}_1}{\beta(x_3\frac{S}{d} - x_3x_1)} - \frac{dx_1}{\beta(x_3\frac{S}{d} - x_3x_1)} + 1 - D_1 = \\ &-\frac{\dot{x}_{1d} - \eta(x_1 - x_{1d})}{\hat{\beta}(x_3\frac{S}{d} - x_3x_1)} - \frac{d\hat{x}_1}{\hat{\beta}(x_3\frac{S}{d} - x_3x_1)} + 1 - \frac{\gamma_1 sgn(\tilde{x}_1)}{x_3\frac{S}{d} - x_3x_1} - \frac{\dot{x}_{1d} - \eta_1(x_1 - x_{1d})}{\beta(x_3\frac{S}{d} - x_3x_1)} - \\ &\frac{dx_1}{\beta(x_3\frac{S}{d} - x_3x_1)} + 1 + \frac{\dot{x}_{1d} - \eta_1(x_1 - x_{1d})}{\beta(x_3\frac{S}{d} - x_3x_1)} + \frac{dx_1}{\beta(x_3\frac{S}{d} - x_3x_1)} - 1, \end{aligned} \tag{10}$$

$$\begin{aligned} &-\frac{\dot{x}_3}{K(x_2+x_1)} - \frac{Cx_3}{K(x_2+x_1)} + 1 - D_2 = \\ &-\frac{\dot{x}_{3d} - \eta_2(x_3 - x_{3d})}{\hat{K}(x_1+x_2)} - \frac{\hat{C}x_3}{\hat{K}(x_1+x_2)} + 1 - \frac{\gamma_2 sgn(\tilde{x}_3)}{(x_1+x_2)} - \frac{\dot{x}_{3d} - \eta_2(x_3 - x_{3d})}{K(x_1+x_2)} - \\ &\frac{Cx_3}{K(x_1+x_2)} + 1 + \frac{\dot{x}_{3d} - \eta_2(x_3 - x_{3d})}{K(x_1+x_2)} - \frac{Cx_3}{K(x_1+x_2)} - 1. \end{aligned} \tag{11}$$

Using the relationships mentioned so far and placing them in terms (10) and (11) :

$$\begin{cases} \dfrac{-1}{\beta(x_3\frac{S}{d} - x_3x_1)}(\dot{\tilde{x}}_1 + \eta_1\tilde{x}_1) - D_1 = Z_1\tilde{\theta}_1 - \dfrac{\gamma_1 sgn(\tilde{x}_1)}{x_3\frac{S}{d} - x_3x_1}, \\ \dfrac{-1}{K(x_1+x_2)}(\dot{\tilde{x}}_3 + \eta_2\tilde{x}_3) - D_2 = Z_2\tilde{\theta}_2 - \dfrac{\gamma_2 sgn(\tilde{x}_3)}{(x_1+x_2)}. \end{cases} \tag{12}$$

Finally, by simplifying (11), the closed-loop dynamic is expressed as:

$$\begin{cases} \dot{\tilde{x}}_1 = -\eta_1\tilde{x}_1 - D_1\beta(x_3\frac{S}{d} - x_3x_1) - Z_1\tilde{\theta}_1(x_3x_1 - \beta\frac{S}{d}x_3) + \beta\gamma_1 sgn(\tilde{x}_1), \\ \dot{\tilde{x}}_3 = -\eta_2\tilde{x}_3 - D_2K(x_1+x_2) - Z_2\tilde{\theta}_2K(x_1+x_2) + K\gamma_2 sgn(\tilde{x}_3). \end{cases} \tag{13}$$

**Theorem 1.** If the adaptation laws are defined as:

$$\begin{cases} \dot{\hat{\theta}}_1 = \frac{1}{\beta}Z_1\Gamma_1^T(\beta x_1x_3 + \frac{S}{d}x_3)\tilde{x}_1, \\ \dot{\hat{\theta}}_2 = -Z_2\Gamma_2^T(x_1+x_2)\tilde{x}_3, \end{cases} \tag{14}$$

so that $t \to \infty$ then $x_1 \to x_{1d}$ and $x_3 \to x_{3d}$ on the condition that

$$\gamma_1 \geq \left|\tilde{x}_1 D_1\beta(x_3\frac{S}{d} - x_3x_1)\right|, \qquad \gamma_2 \geq \left|\tilde{x}_3 D_2K(x_1+x_2)\right|.$$

*Proof.* Consider Lyapunov's function as follows [11]:

$$V = \frac{1}{2}(\tilde{x}_3^2 + \tilde{x}_1^2 + \beta\tilde{\theta}_1^T\Gamma_1^{-1}\tilde{\theta}_1 + K\tilde{\theta}_2^T\Gamma_2^{-1}\tilde{\theta}_2) \geq 0, \tag{15}$$

where $\Gamma_i$ s are constant positive definite matrices. Accordingly, the above equation is positive definite ($V \geq 0$) in terms of $\tilde{\theta}_1$, $\tilde{\theta}_2$, $\tilde{x}_1^2$, $\tilde{x}_3^2$, the time derivative of $V$ is, then, obtained as

$$\dot{V} = \tilde{x}_3\dot{\tilde{x}}_3 + \tilde{x}_1\dot{\tilde{x}}_1 + \beta\dot{\hat{\theta}}_1^T\Gamma_1^{-1}\tilde{\theta}_1 + K\dot{\hat{\theta}}_2^T\Gamma_2^{-1}\tilde{\theta}_2. \tag{16}$$

Note that $\dot{\tilde{\theta}}_i = \dot{\hat{\theta}}_i$ because $\theta_i$ is a constant vector and $\dot{\theta}_i$.

By employing the non-linear closed-loop dynamics (13) in (16) and using the parameter adaptation laws, $\dot{V}$ is simplified to:

$$\begin{aligned}\dot{V} = &-\eta_2\tilde{x}_3^2 - \tilde{x}_3(\gamma_2 sgn(\tilde{x}_3) + D_2K(x_1 + x_2) - \eta_1\tilde{x}_1^2 \\ &- \tilde{x}_1(-\gamma_1 sgn(\tilde{x}_1) + D_1\beta(x_3\frac{S}{d} - x_3x_1)).\end{aligned} \tag{17}$$

By selecting the positive gains ($\gamma_1$ and $\gamma_2$), the robust controller (9) should be adjusted large enough to overcome the upper bounds of the non-parametric uncertainties ($D_1$ and $D_2$) by satisfying the following inequalities:

$$\gamma_1 \geq \left|\tilde{x}_1 D_1\beta(x_3\frac{S}{d} - x_3x_1)\right|, \qquad \gamma_2 \geq \left|\tilde{x}_3 D_2K(x_1 + x_2)\right|.$$

Now employing them in the time derivative of the Lyapunov function (17) results in:

$$\dot{V} \leq -\eta_2\tilde{x}_3^2 - \eta_1\tilde{x}_1^2 \leq 0. \tag{18}$$

Also, the time derivative of the Lyapunov function is negative semi-definite ($\dot{V} \leq 0$) in (18). Therefore, $V$ is bounded and consequently $\tilde{x}_1$, $\tilde{x}_3$, $\tilde{\theta}_1$, $\tilde{\theta}_2$ remain bounded, hence the vectors of the parameter estimation errors also remain bounded.

Based on the Lyapunov stability theorem and by applying Barbalat's lemma [15], we conclude that $\dot{V} \to 0$ as $t \to \infty$.

Consequently, according to the Lyapunov theorem, $x_1 \to x_{1d}$ and $x_3 \to x_{3d}$.

In fact, as the time tends to infinity, the number of infected cells ($I$) and free viruses ($V$) converge to zero ($I \to 0,\ V \to 0$), the number of healthy cells ($T$) converges to its maximum steady-state value ($T \to \frac{S}{d}$).

It means that according to the first equation from (2):

$$(S - dT - \beta TV(1 - u_1)) \to S - dT,$$

which means that:

$$\dot{T} \to S - dT \qquad \xrightarrow{\dot{T}\to 0} \qquad T \to \frac{S}{d}.$$

□

## 5 Simulation

In this section, we evaluate the proposed robust adaptive sliding mode control strategy through some simulations. To this end, consider the following data, which are related to a patient and selected from [16]:

$$C = 2, \quad d = 0.007, \quad K = 40.60, \quad S = 7, \quad \mu = 0.0888, \quad \beta = 4.2163 * 10^{-7},$$
$$\hat{\theta}_1(0) = [2 \times 10^6, 15 \times 10^3]^T, \quad \hat{\theta}_2(0) = [0.02, 0.05]^T, \quad I_d = e^{-t},$$
$$T_d = \frac{S}{d} + e^{-t}, \quad V_d = 0.1e^{-t}.$$

By replacing control values $(u_1(t), u_2(t))$ of (9), in equations (4) and solving the system of differential equations (4) and (14), the values $x_1$, $x_2$, $x_3$, $\hat{\theta}_1$ and $\hat{\theta}_2$ are obtained, and according to the relations $x_1 = -T + \frac{S}{d}$, $x_2 = T + I - \frac{S}{d}$ and $x_3 = V$, the values $(V, I, T)$ are achieved. The results of the process described in this article are shown in Figures 1 and 2.

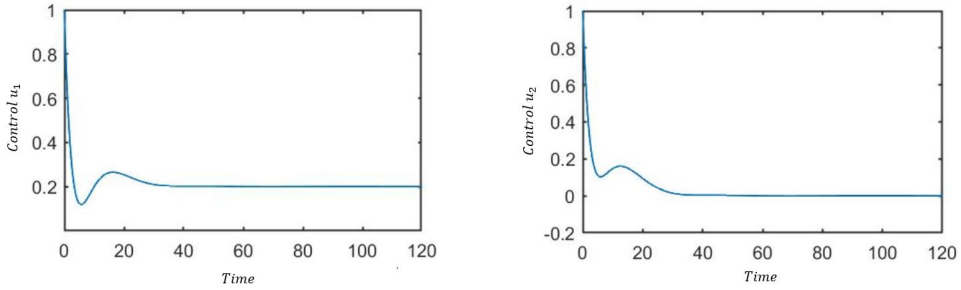


**Figure 1:** The action of drug dosage using the adaptive control method.

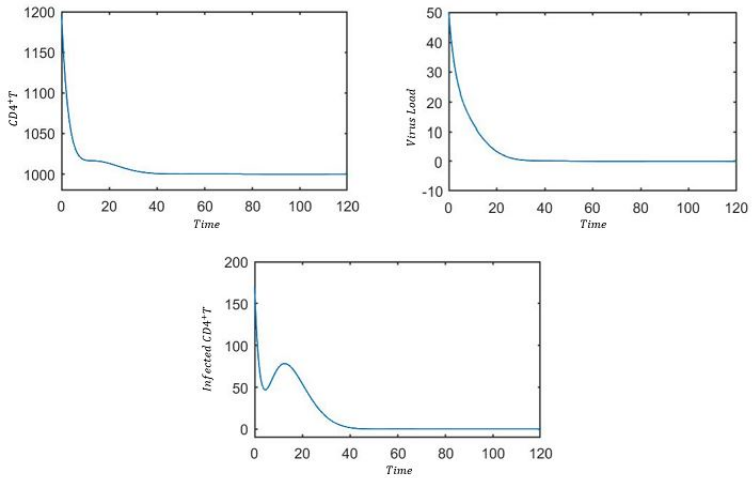


**Figure 2:** Status of the healthy and infectious cells, the free viruses, as well as the drug dosage using the adaptive control method.

## 6 Conclusion

A non-linear robust adaptive Lyapunov-based control strategy was designed in this paper for HIV treatment. The proposed robust adaptive controller aims to decrease values, causing an increase in the number of healthy cells. The stability of the controlled process, tracking convergence, and bounded parameter adaption was proved using the Lyapunov analysis, and the controller performance in the face of various uncertainties was investigated using some simulations. If the obtained results are anything to go by, we can argue that the proposed non-linear control strategy is robust against a wide range of modeling uncertainties and bounded disturbances and can rapidly adjust the antiviral drug levels to the reduced HIV viruses and infected cells. This controller can be redesigned and used to treat HIV patients and other patients if different dynamic models are developed in future works.

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