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Design of Optimal Linear Feedback Controller for HIV Treatment

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ABSTRACT

The design of optimal linear feedback controllers for HIV treatment is a multidisciplinary endeavor that combines principles from control theory, systems biology, and medical science. The goal is to create adaptive treatment strategies that can effectively manage the dynamics of HIV infection and optimize patient outcomes. Given the rapid advancements in control methods and the growing use of modern computers in recent years, these tools have also been applied in the field of medical processes. In this paper, after reviewing the model presented for HIV, a suitable model to describe the disease dynamics is selected. Then, using the linear feedback control method and considering the effect of antiretroviral drugs, an attempt is made to properly treat HIV. The six-variable HIV virus infection model is the basis of this study. Furthermore, considering the effect of RTIs and PIs drugs as control inputs, it is observed that the system is a nonlinear, multi-input, multi-output system. The stability of the system's internal dynamics is examined, and an optimal control method is used to optimize the dosage of injectable drugs for the patient, aiming to reduce side effects while effectively controlling the disease.

1. INTRODUCTION

AIDS, or acquired immunodeficiency syndrome, is a disease caused by the Human Immunodeficiency Virus (HIV) that affects the immune system. The disease caused by the HIV virus has three main stages. In the first stage (acute infection), the individual may experience flu-like symptoms for a short period. For this reason, the disease often goes unnoticed for an extended period without symptoms, which is referred to as the latent period. The disease enters the third stage, or AIDS, when the number of cells (a type of white blood cell in the blood) drops below 200 cells per microliter [1]. Genetic research indicates that HIV emerged in West Africa in the early 20th century [2]. Since its discovery until 2009, AIDS has caused the death of 30 million people. By 2010, approximately 34 million people had been infected with AIDS. The usual management of HIV includes the use of antiretroviral drugs to control the HIV infection. Currently, there is no effective treatment or vaccine for HIV. Many treatment methods have been developed to improve the disease and prevent its progression, and these methods have been somewhat

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successful in controlling the disease. The most prominent of these methods is known as "Highly Active Antiretroviral Therapy (HAART)," which has significantly reduced the progression of the disease and increased the patient's life expectancy [3].

Current HAART options are a combination of at least three drugs, usually selected from two different categories. The most widely used antiretroviral drugs are classified into two main categories [4]:

- Reverse Transcriptase Inhibitors (RTIs)

These drugs act during the reverse transcription phase, preventing the conversion of viral RNA into DNA. Drugs in this category include Zidovudine, Lamivudine, Abacavir, Tenofovir, Efavirenz, and Nevirapine.

- Protease Inhibitors (PIs)

Unlike RTIs, drugs in this category act after the cell has been infected and the viral genome has integrated with the host cell chromosome. The primary goal of these drugs is to prevent the proper replication of new viruses by inhibiting viral proteases. Drugs in this category include Saquinavir, Ritonavir, and Indinavir.

2. REVIEW OF PAST WORK

Mathematical modeling based on nonlinear differential equations has had a significant impact on understanding the dynamics of HIV disease. various mathematical models have been proposed, most of which describe the interaction between the HIV virus and $CD4^{+}T$ immune cells (a type of white blood cell present in the blood) [9-13].

By understanding the dynamics of HIV, different treatment strategies can be employed to reduce the HIV virus and increase healthy white blood cells in the body. For example, optimal control [14-17], model-based predictive control [18-20], nonlinear control [21-23], and fuzzy control [24-27] have been used in many previous studies. Below is a summary of some of the past works:

In [11], precise linearization algorithms in continuous space and then in discrete space were used, taking into account the observer and the dynamics of the drug Zidovudine in the body, to obtain a suitable scenario for drug administration to the patient in order to reach standard health conditions. In [12], researchers obtained treatment strategies using optimal control based on a multi-objective function. They presented open-loop and closed-loop results and considered the effects of RTIs class drugs. They also proposed a control method based on the effects of RTI drugs to design therapeutic algorithms with minimal side effects using a suitable objective function.

In [13], a precise input-output linearization control method was used. In this paper, the researchers used pharmacokinetic and pharmacodynamic models for Zidovudine, an RTI drug, and based on that, they designed a drug regimen based on dosage. They also designed an appropriate drug regimen using an impulsive control strategy and precise input-output linearization based on pharmacokinetic and pharmacodynamic models for Zidovudine [14]. In [8], initially, a nonlinear predictive control method based on the model and a Kalman filter was used to present a treatment strategy based on the effects of two classes of drugs, RTIs and PIs.

In [9], the control law was designed based on singular perturbation approximation, considering the effects of RTI drugs. In [5], a control strategy based on linearizing the nonlinear model around the equilibrium point was proposed, and the input of the system was considered as the effect of the two drug classes, RTIs and PIs.

In [15], sliding mode control was used, considering the effects of RTI drugs, to control HIV disease. In [10], researchers proposed an $\boldsymbol{H}_{\infty}$ fuzzy controller based on the effects of two classes of drugs, RTIs and PIs, for controlling HIV infection.

3. DYNAMIC MODELING OF HIV DISEASE

Although HIV is a complex disease involving multiple interactions between viruses and the body's immune system, the main characteristics of this disease can be expressed using simple equations. In previous works, various models have been proposed to describe the dynamics of the HIV disease. For example, models with three state variables [10][33-34], four [16], five [7], and six [6] state variables have been considered. To accurately define and

predict the dynamic behavior of the disease, it is necessary to obtain the parameters used in the dynamic model through rich data.

In 2012, Lou and his colleagues were the first to identify model parameters using rich data. They placed 12 patients under organized treatment interruptions, allowing them to stimulate the disease dynamics 3 to 5 times in different patients by prescribing and discontinuing medication at different time intervals. At different times (every 3 days), they measured the viral concentration of each patient an average of 69 to 114 times, and based on this data, they were able to identify the parameter values. In addition to the accurate estimation of parameters from rich data, they also modeled the hidden resources' resistance in the patient's body.

Increasing the number of state variables allows for a more detailed and accurate description of the dynamic behavior of HIV patients. Therefore, in this study, a model with six state variables will be used to describe the HIV disease so that the behavior of the disease can be modeled with greater accuracy [17]. The dynamic model with six state variables, first presented by Wodarz and Nowak in [18], is as follows:

$$\begin{cases} \dot{x} = \lambda - dx - rxv \\ \dot{y} = rxv - ay - pyz \\ \dot{w} = cxyw - cqyw - bw \\ \dot{z} = cqyw - hz \\ \dot{v} = k(1 - \mu_p f_p)y - uv \\ \dot{r} = r_0(1 - \mu_T f_T) \end{cases} \quad (1)$$

In Model (1), the first equation describes the dynamics of the concentration of healthy $CD4^+$ cells (x). The constant parameter λ represents the production rate of new $CD4^+$cells. The second equation characterizes the dynamics of the concentration of infected $CD4^+$cells (y). The third equation describes the dynamics of CTL_e (w), which is responsible for enhancing immune memory.

The fourth equation represents the dynamics of CTL_e, whose function is to eliminate infected cells and free viruses. The fifth equation models the concentration of free viruses (v), which are produced by infected cells at a rate of k. Finally, the sixth equation represents the viral invasion index (r). The values of the constant parameters in Model (1) are presented in Table 1.

Table 1: Values and definitions of the parameters of the HIV model with six state variables.

Value (unit)	Parameter	Definition
λ	Healthy CD4+T production	$\mathbf{7 cells \mu l^{-1} day^{-1}}$
d	Healthy CD4+T clearance	$\mathbf{7 \times 10^{-3} day^{-1}}$
a	Infected CD4+T clearance	$\mathbf{0.0999 day^{-1}}$
p	Infected CD4+T kill	$\mathbf{2 \mu l cells^{-1} day^{-1}}$
c	CTLp Proliferation	$\mathbf{5 \times 10^{-6} \mu l^2 cells^{-2} day^{-1}}$
q	CTLp differentiation	$\mathbf{120 cells \mu l^{-1}}$
b	CTLp clearance	$\mathbf{0.017 day^{-1}}$
h	CTLe clearance	$\mathbf{0.06 day^{-1}}$
k	Virus production	$\mathbf{300 copies ml^{-1} cells^{-1} \mu l day^{-1}}$
u	Virus clearance	$\mathbf{0.2 day^{-1}}$
r_0	Virulance growth	$\mathbf{1 \times 10^{-9} copies^{-1} ml day^{-2}}$
f_T/f_p	RTI effect/ PI effect	$\mathbf{0(untreated)/1(treated)}$
μ_T	RTI drug effectiveness	$\mathbf{9 \times 10^{-9}}$
μ_p	PI drug effectiveness	$\mathbf{0.7}$

Based on the state-space trajectories shown in Figure 1, it can be concluded that the system's equilibrium point is independent of the initial conditions. Additionally, for all state-space trajectories, the model exhibits similar behavior. Specifically, after periodic peaks in the state variables healthy $CD4^+$cells and viruses the system ultimately reaches equilibrium. According to the described dynamics, the presence of the first virus in the body leads to a decrease in the number of healthy $CD4^+T$ cells from their standard level, while the number of infected $CD4^+T$ cells and free viruses increase according to their respective dynamics.

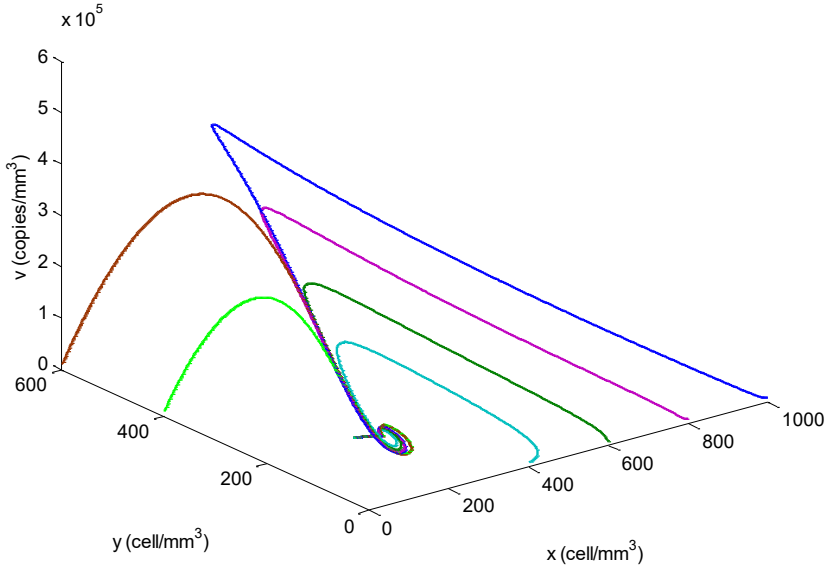

Fig. 1. State-space trajectories for the HIV model with six state variables, for different initial conditions.

4. FEEDBACK LINEARIZATION AND OPTIMAL CONTROL

Feedback linearization is a nonlinear control design method where the main idea is to transform the system's nonlinear dynamics (either partially or completely) into linear form, enabling the use of linear control methods. Feedback linearization methods can be considered a technique for transforming the system's original models into equivalent models in a simpler form. Therefore, they can also be used in the development of adaptive or robust nonlinear controllers.

4.1. Input-Output Linearization of MIMO Systems

First, the dynamic equations of the HIV system, as presented in Equation (1), are transformed into the form:

$$\dot{x} = f(x) + G(x)u, y = h(x)$$

$$\boldsymbol{f(x)} = \begin{bmatrix} \lambda - dx - rxv \\ xv - ay - pyz \\ cxyw - cqyw - bw \\ cqyw - hz \\ ky - uv \\ r_0 \end{bmatrix} = \begin{bmatrix} f_1 \\ f_2 \\ f_3 \\ f_4 \\ f_5 \\ f_6 \end{bmatrix} \boldsymbol{G(x)} = \begin{bmatrix} 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ -k\mu_p y & 0 \\ 0 & -\mu_T \end{bmatrix} \boldsymbol{x} = \begin{bmatrix} x \\ y \\ w \\ z \\ v \\ r \end{bmatrix} \quad (1)$$

By defining the state variables x (the concentration of healthy $CD4^+$cells) and v (the number of viruses) as the system outputs, we compute the system's relative degree.

$$\boldsymbol{y} = \boldsymbol{h(x)} = \begin{bmatrix} x \\ v \end{bmatrix} = \begin{bmatrix} y_1 \\ y_2 \end{bmatrix} \quad (2)$$

To establish an explicit relationship between the output y and the input u, the system output must be differentiated r times. The system is said to have a relative degree of r. It is important to note that this definition of relative degree r corresponds to the concept of relative degree in linear systems (i.e., the number of excess poles relative to zeros).

Furthermore, it can be formally demonstrated that in any control system of order n, at most n derivatives are required for each output to explicitly depend on the control input, meaning $r \leq n$.

Feedback linearization is categorized into state feedback linearization and input-output linearization. The system presented in this paper satisfies the conditions for input-output linearization, as will be demonstrated in the following section. The derivative of the output y, denoted as $\dot{y}$, is computed as follows:

$$L_f h(\boldsymbol{x}) = \frac{\partial h}{\partial \boldsymbol{x}} \boldsymbol{f}(\boldsymbol{x}) \text{ ، } \dot{y} = \frac{\partial h}{\partial \boldsymbol{x}} \dot{\boldsymbol{x}} = \frac{\partial h}{\partial \boldsymbol{x}} [\boldsymbol{f}(\boldsymbol{x}) + (\boldsymbol{x})] \stackrel{\text{def}}{=} L_f h(\boldsymbol{x}) + L_g h(\boldsymbol{x}) u \tag{3}$$

If for all $\boldsymbol{x} = \boldsymbol{x}_0$ in $L_g h(\boldsymbol{x}) = 0$, we can differentiate $\dot{y}$ and obtain the following relation:

$$\ddot{y} = L_f^2 h(\boldsymbol{x}) + L_g L_f h(\boldsymbol{x}) u \tag{4}$$

To calculate the first-order derivative of each output of the system separately, we proceed as follows:

$$\dot{y}_1 = \dot{x} = \lambda - dx - rxv \tag{5}$$

Given that $L_{g_1} L_f h_1(\boldsymbol{x}) = 0, L_{g_2} L_f h_1(\boldsymbol{x}) = 0$, in order for at least one of the inputs to appear, it is necessary to calculate the second-order derivative of y_1.

$$\begin{aligned} \ddot{y}_1 = -d\dot{x} - \dot{r}xv - r\dot{x}v - rx\dot{v} = -d(\lambda - dx - rxv) - xv(r_0 - \mu_T f_T) \\ -rv(\lambda - dx - rxv) - rx(k(1 - \mu_p f_p)y - uv) \end{aligned} \tag{6}$$

Therefore, the relative order of the system for the output y_1 is 2, i.e., $r_1 = 2$. The first-order derivative is calculated for the second output, y_2:

$$\dot{y}_2 = \dot{v} = k(1 - \mu_p f_p)y - uv \tag{7}$$

As can be observed, by taking the derivative once, the input f_p appears in the output. Therefore, the relative order of the system for the output y_2 is 1, i.e., $r_2 = 1$. Thus, the overall order of the system is $r = r_1 + r_2 = 3$. Consequently, only part of the system dynamics can be controlled, and it is necessary to analyze the stability of the internal dynamics of the system as well. Therefore, the following relations hold:

$$\begin{aligned} \ddot{y}_1 = L_f^2 h_1(\boldsymbol{x}) + L_{g_1} L_f h_1(\boldsymbol{x}) u_1 + L_{g_2} L_f h_1(\boldsymbol{x}) u_2 \\ \dot{y}_2 = L_f h_2(\boldsymbol{x}) + L_{g_1} h_2(\boldsymbol{x}) u_1 + L_{g_2} h_2(\boldsymbol{x}) u_2 \end{aligned} \tag{8}$$

By rearranging relation (8), the following equation can be obtained:

$$\begin{bmatrix} \ddot{y}_1 \\ \dot{y}_2 \end{bmatrix} = \begin{bmatrix} L_f^2 h_1(\boldsymbol{x}) \\ L_f h_2(\boldsymbol{x}) \end{bmatrix} + \underbrace{\begin{bmatrix} L_{g_1} L_f h_1(\boldsymbol{x}) & L_{g_2} L_f h_1(\boldsymbol{x}) \\ L_{g_1} h_2(\boldsymbol{x}) & L_{g_2} h_2(\boldsymbol{x}) \end{bmatrix}}_{\boldsymbol{C}(\boldsymbol{x})} \begin{bmatrix} u_1 \\ u_2 \end{bmatrix} \tag{9}$$

The control law for input-output linearization is as follows:

$$\begin{bmatrix} u_1 \\ u_2 \end{bmatrix} = \begin{bmatrix} L_{g_1} L_f h_1(\boldsymbol{x}) & L_{g_2} L_f h_1(\boldsymbol{x}) \\ L_{g_1} h_2(\boldsymbol{x}) & L_{g_2} h_2(\boldsymbol{x}) \end{bmatrix}^{-1} \begin{bmatrix} v_1 - L_f^2 h_1(\boldsymbol{x}) \\ v_2 - L_f h_2(\boldsymbol{x}) \end{bmatrix} \tag{10}$$

For the system under study, the characteristic matrix ***C(x)*** and the control law can be calculated as follows:

$$\boldsymbol{C}(\boldsymbol{x}) = \begin{bmatrix} kxyr\mu_p & xv\mu_T \\ -ky\mu_p & 0 \end{bmatrix} \tag{11}$$

$$\begin{bmatrix} f_p \\ f_T \end{bmatrix} = \begin{bmatrix} kxyr\mu_p & xv\mu_T \\ -ky\mu_p & 0 \end{bmatrix}^{-1} \begin{bmatrix} v_1 - L_f^2 h_1(\boldsymbol{x}) \\ v_2 - L_f h_2(\boldsymbol{x}) \end{bmatrix}$$

Where:

$$L_f^2 h_1(\boldsymbol{x}) = (d + vr)(dx - \lambda + xvr) - xr(ky - uv) - r_0 xv \tag{12}$$
$$L_f h_2(\boldsymbol{x}) = ky - uv$$

Applying the control law (10) results in the following two simplified equations:

$$\ddot{y}_1 = v_1 \tag{13}$$
$$\dot{y}_2 = v_2$$

Designing a tracking controller in this double integrator relationship is straightforward due to the availability of linear control methods. By using the pole placement method, the tracking error $e = y(t) - y_d(t)$ can be eliminated. Therefore, v1 and v2 in (13) are determined as follows:

$$v_1 = \ddot{y}_{d1} - k_1(\dot{y}_1 - \dot{y}_{d1}) - k_2(y_1 - y_{d1}) \tag{14}$$
$$v_2 = \dot{y}_{d2} - k_3(y_2 - y_{d2})$$

$$v_1 = \ddot{y}_{d1} - k_1(\lambda - dx - rxv - \dot{y}_{d1}) - k_2(x_1 - y_{d1}) \tag{15}$$
$$v_2 = \dot{y}_{d2} - k_3(x_5 - y_{d2})$$

Where k1, k2, and k3 are positive constants, the closed-loop tracking error is given by:

$$\ddot{e}_1 + k_1\dot{e}_1 + k_2 e_1 = 0 \tag{16}$$
$$\dot{e}_2 + k_3 e_2 = 0$$

With appropriate tuning of the control parameters, the tracking error can be rendered asymptotically stable.

4.2. Optimal Control

The objective of an optimal control system is to determine the control signals in such a way that they satisfy physical constraints or limitations, while also minimizing or maximizing a specific performance criterion.

As mentioned, by employing feedback linearization, the system dynamics can be decomposed into two parts: linear dynamics and unobservable dynamics. Therefore, linear control methods can be used for the linearized part. Consequently, optimization techniques such as the Linear Quadratic Regulator (LQR) can be utilized for the design of an optimal controller. In this paper, we intend to use the second Lyapunov method to address the optimal control problem.

$$K = T^{-1}(T^T)^{-1}B^T P = R^{-1}B^T P \tag{17}$$

Equation (17) yields the optimal gain matrix *K*. The matrix *P* satisfies the following equation:

$$A^T P + PA - PBR^{-1}B^T P + Q = 0 \tag{18}$$

Equation (18) is referred to as the Riccati matrix equation. If the matrix A−BK is stable, the above method will always yield the correct solution. It should be noted that, for the design of the optimal controller, the Riccati equation will be solved using the command available in MATLAB, and the weighting matrices (R,Q) will be computed.

Consider the given linear control system with the following state-space equations:

$$\dot{\boldsymbol{x}}(t) = \boldsymbol{A}\boldsymbol{x}(t) + \boldsymbol{B}u(t) \tag{19}$$

Based on the system dynamics and the performed linearization, the matrices A and B are obtained in the following form:

$$A = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix}, B = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$$

Additionally, the weighting matrices Q and R in the design of the optimal controller are determined as follows to achieve a trade-off between the accuracy in tracking the desired output and the magnitude of the control signal.

$$\boldsymbol{Q} = \begin{bmatrix} 15 & 0 \\ 0 & 8 \end{bmatrix}, R = 0.05$$

Where Q is a positive definite (or semi-definite) real symmetric matrix and R is a positive definite and symmetric matrix. These two matrices are determined by a trial-and-error method. By substituting the above values into the Riccati equation, the matrix P and subsequently the gain matrix will be computed.

$$A^T P + PA - PBR^{-1}B^T P + Q = 0 \tag{20}$$

$$K = R^{-1}B^T P \tag{21}$$

Thus, considering the matrix P as follows:

$$P = \begin{bmatrix} P_{11} & P_{12} \\ P_{21} & P_{22} \end{bmatrix} \tag{22}$$

Substituting the aforementioned matrices (A,B,P) into Equation (20), the matrix P is obtained. Furthermore, by substituting P into Equation (21), the gain matrix K is derived in the following form.

$$K = [36.51 \quad 37.5 \quad 0.006] \tag{23}$$

5. SYSTEM SIMULATION AND RESULTS

In this section, the simulation results of the controller design using the feedback linearization method for the HIV disease system are presented. Before simulating the overall system with the controller, the dynamic response and initial conditions of the system are analyzed. The initial conditions of the system in this case are provided in Table 2.

Figures 2 to 4 illustrate the system's behavior over a 36-month period following the onset of the disease for three different patient types, each characterized by distinct parameters b and h as specified below. Figure 2 depicts the response of the system's dynamic model in the absence of external input stimulation (i.e., without medication).

$$\boldsymbol{A}: \boldsymbol{b} = \mathbf{0.01}(\mathbf{1}/\boldsymbol{day}), \boldsymbol{h} = \mathbf{0.08}(\mathbf{1}/\boldsymbol{day});$$
$$\boldsymbol{B}: \boldsymbol{b} = \mathbf{0.007}(\mathbf{1}/\boldsymbol{day}), \boldsymbol{h} = \mathbf{0.06}(\mathbf{1}/\boldsymbol{day});$$
$$\boldsymbol{C}: \boldsymbol{b} = \mathbf{0.006}(\mathbf{1}/\boldsymbol{day}), \boldsymbol{h} = \mathbf{0.05}(\mathbf{1}/\boldsymbol{day});$$

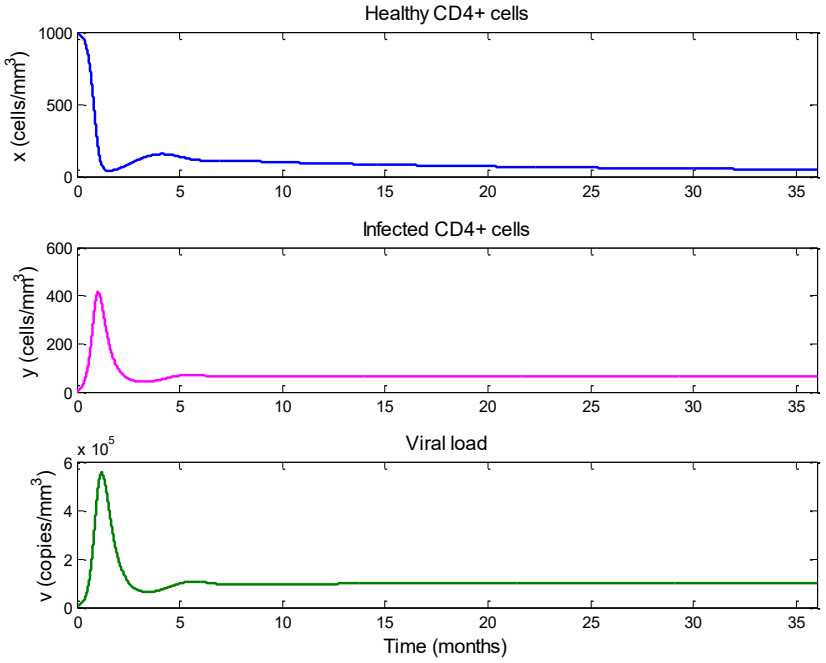

Fig. 2. Time Response of the HIV System with Six State Variables Without Input Consideration

Based on the state-space trajectories in Figure 2, it can be concluded that the system's equilibrium point is independent of its initial conditions. Furthermore, for all state-space trajectories, the model exhibits similar behavior. Specifically, after experiencing periodic peaks in the state variables, including healthy $CD4^+$ cells and viruses, the system ultimately converges to an equilibrium state.

According to the described dynamics, upon the introduction of the first virus into the body, the number of healthy $CD4^+$ cells begins to decline from its standard level, while the number of infected $CD4^+$ cells and free viruses increases according to their respective dynamics.

Figure 3 illustrates the temporal variations of x, y, and v in the scenario where a single virus per unit volume (RNA copies/mm³) is present in the blood. Subsequently, the dynamic behavior of the six-state-variable model is analyzed under the condition where no treatment is applied, i.e., $f_p = f_t = 0$.

As expected, in the absence of treatment, Patient A exhibits the most rapid disease progression, whereas Patient C shows the slowest rate of disease progression, with Patient B displaying an intermediate behavior. Next, the system's behavior under treatment conditions will be examined.

As evident from the figure above, the administration of medication two months after the onset of the disease significantly halts disease progression. Drug administration leads to a notable increase in the concentration of healthy $CD4^+$ cells (x) and a reduction in the number of free viruses (v).

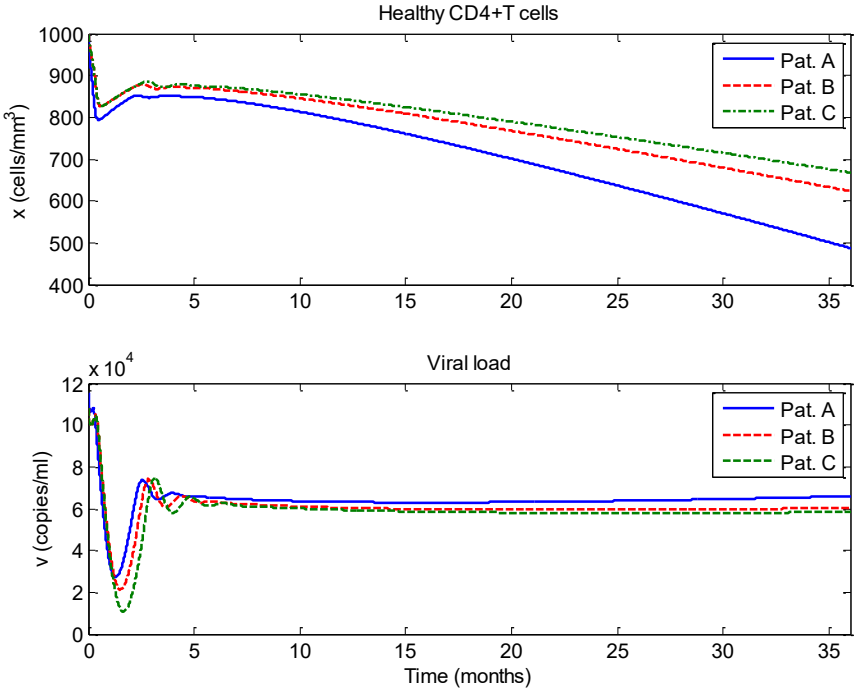

Fig. 3. Time Response of the HIV System in the Absence of Treatment

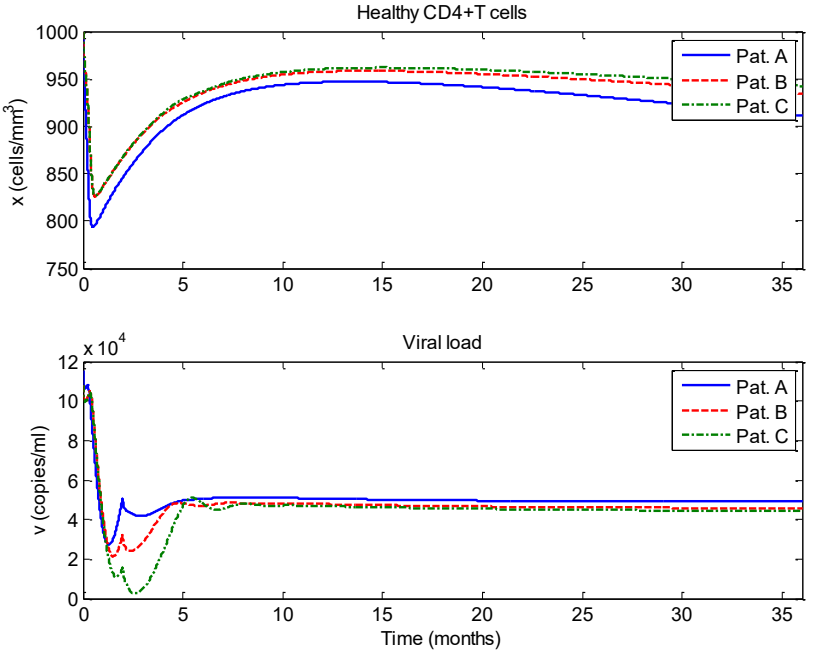

Fig. 4. Time Response of the HIV System Under Treatment

Subsequent simulations incorporate a control strategy after 12 months from the onset of the disease, regulating the administration of RTIs and PIs to maintain the concentration of healthy $CD4^+$ cells (x) and the viral load (v) at desirable levels. The objective of the controller design is to administer medication appropriately over a three-year period to prevent disease progression, ensuring that the concentration of healthy $CD4^+$ cells (x) remains close to the target value while minimizing the viral load (v) as much as possible. The results are presented in the following figures.

It is noteworthy that k1, k2, and k3 have been tuned using the LQR optimization method. The initial conditions of the system are considered as outlined in Table 5-1 [17]. The simulations have been conducted for two case studies.

Table 2. Initial Conditions of the System

Mode	$x(0)$	$y(0)$	$w(0)$	$z(0)$	$v(0)$	$r(0)$
Initial value	10^3 $cells\mu l^{-1}$	0 $cells\mu l^{-1}$	10^{-3} $cellsml^{-1}$	10^{-7} $cells\mu l^{-1}$	10^4 $copiesml^{-1}$	$\mathbf{4 \times 10^{-7}}$ $\boldsymbol{mlcopies^{-1}day^{-1}}$

In the first part of the simulations, the desired values for the concentration of healthy cells x and the concentration of free viruses v in the blood are considered as follows:

$$x(desired) = 700 cells\mu l^{-1}$$

$$v(desired) = log(2.6 \times 10^3)$$

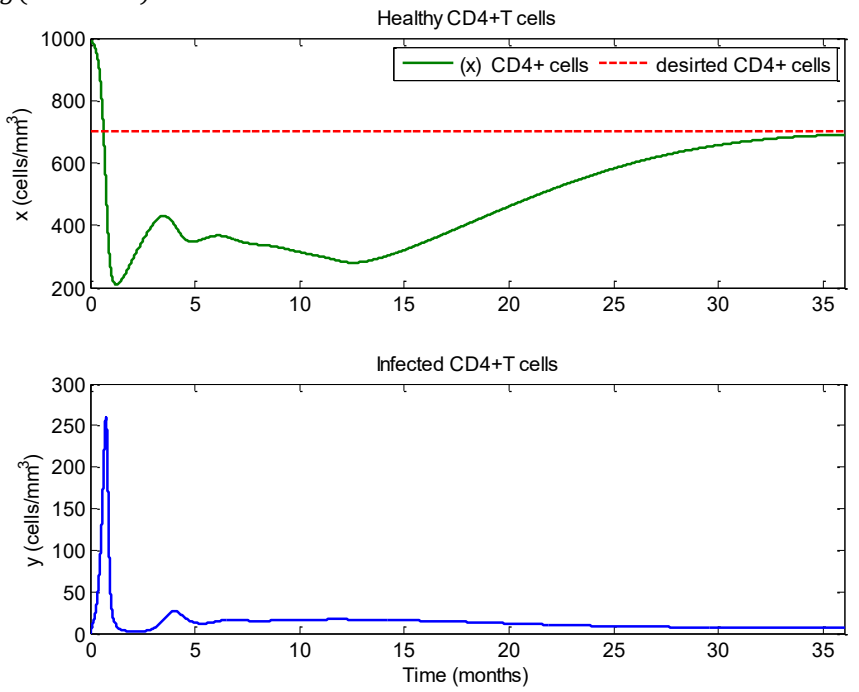

Fig. 5. The concentration of healthy cells (x) and the concentration of infected cells (y) after treatment.

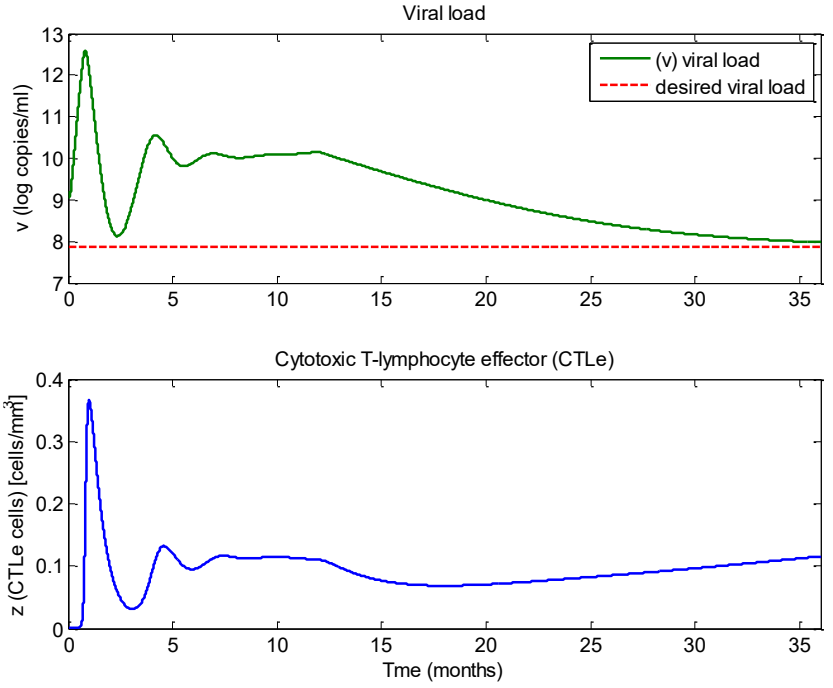

Fig. 6. The concentration of free viruses (v) and the dynamics of $\mathbf{CTL_e}$ after treatment.

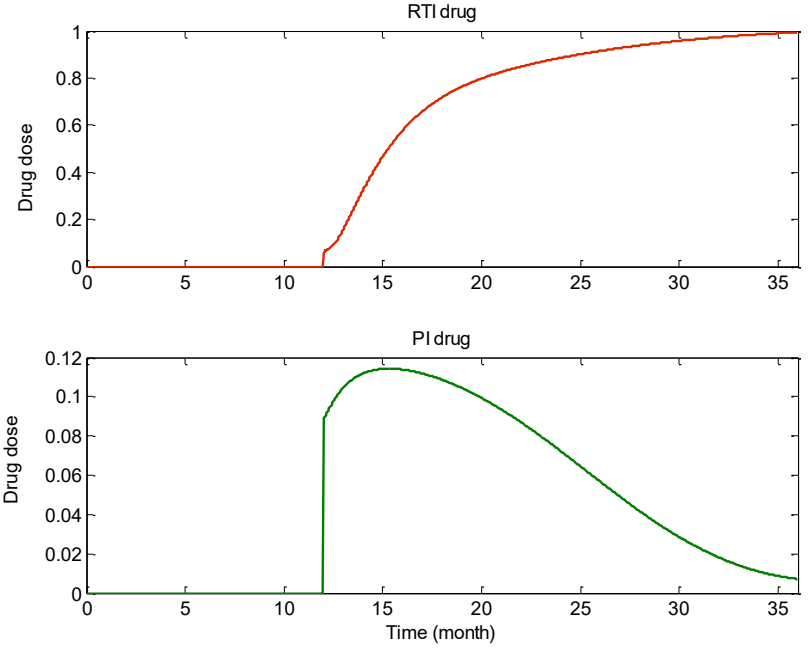

Fig. 7. Control inputs in the treatment state.

In the second part of the simulations, the desired values for the system outputs are considered as follows:

$$x(desired) = 900 cells\mu l^{-1}$$

$$v(desired) = log(2.1 \times 10^3)$$

The performance of the controller in bringing the system outputs to the desired values is then examined. The following figures demonstrate the system's behavior when the controller is used to control the disease. The

controller's task is to prevent disease progression by administering appropriate RTIs and PIs, while maintaining the concentration of healthy $CD4^+$ cells and viral load within the desired levels as specified by the physician.

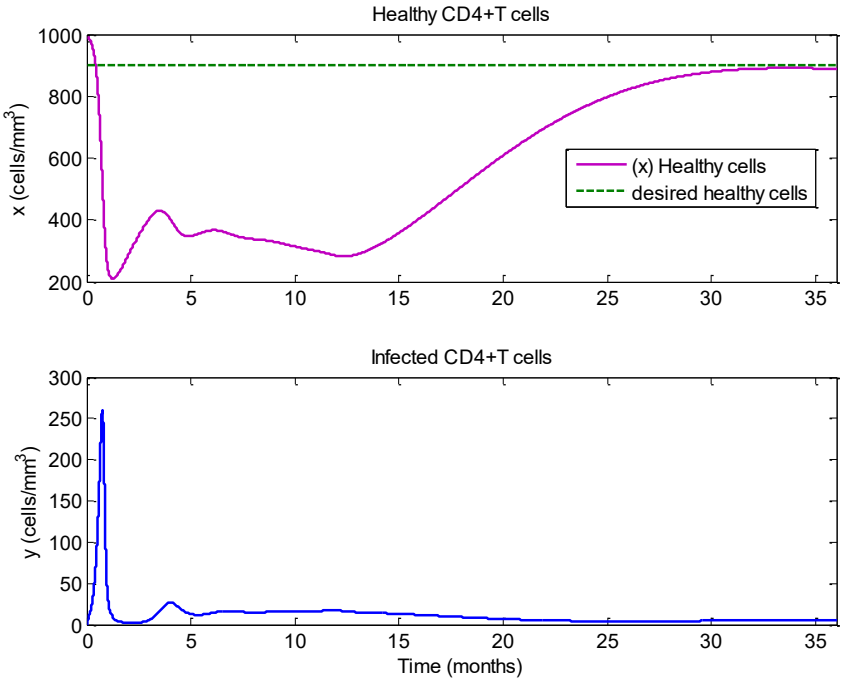

Fig. 8. Concentration of healthy cells (x) and concentration of infected cells (y) after treatment.

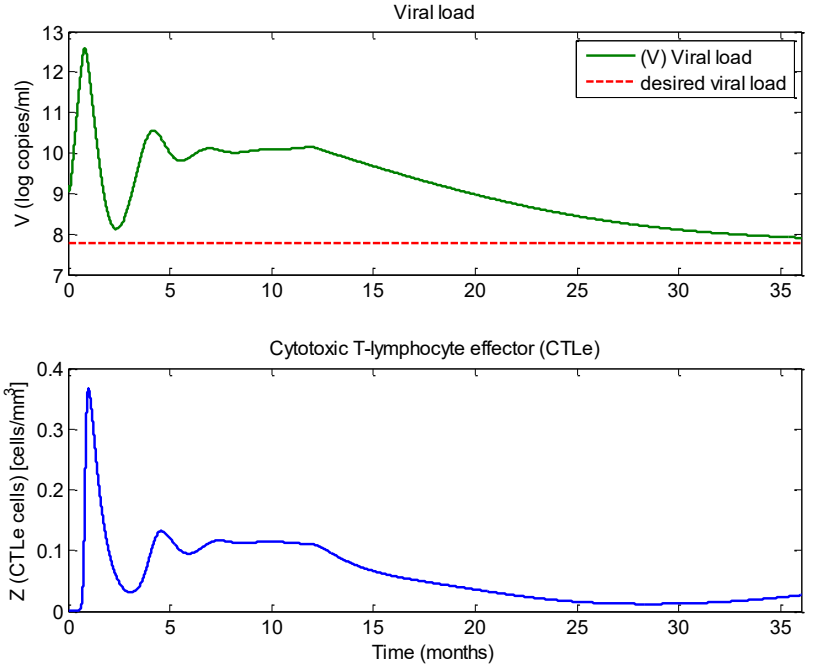

Fig. 9. Concentration of free viruses (v) and the dynamics of $\mathbf{CTL}_e$ after treatment.

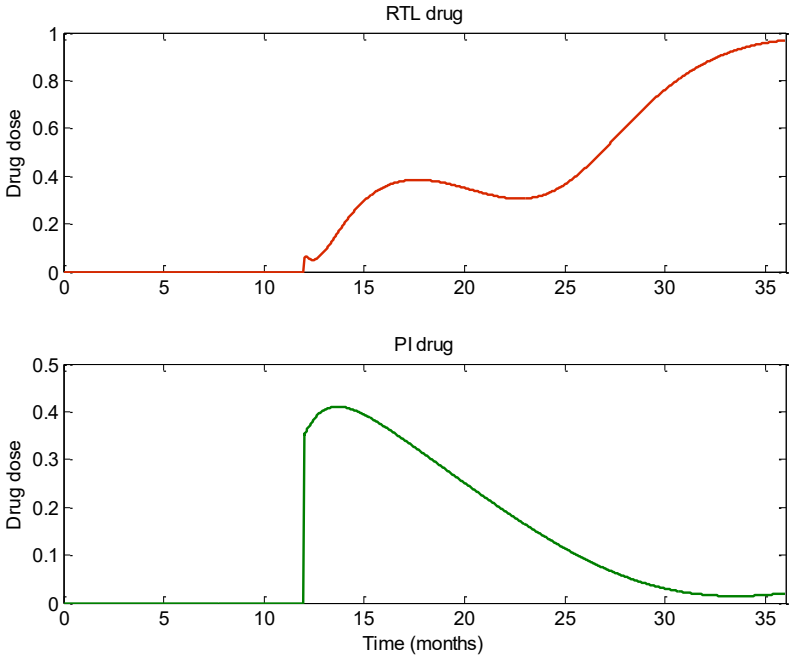

Fig. 10. Control inputs in the treatment state.

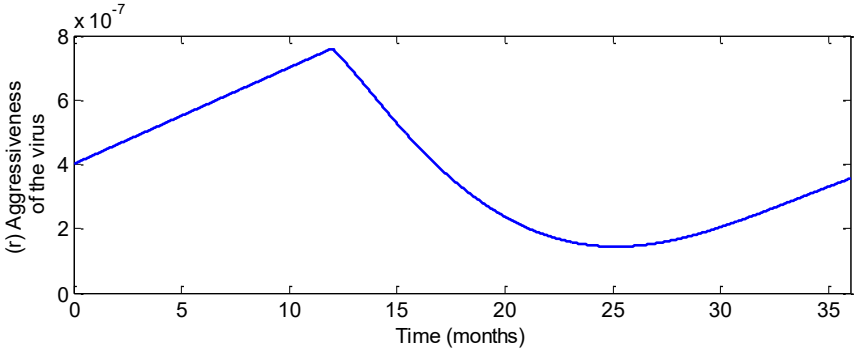

Fig. 11. Virus attack metric (r) in the treatment state.

As can be observed, with the injection of medication, the concentration of healthy $CD4^+$ cells in the blood increases, and with the proper drug injection scenario, it can even be brought to the desired level. On the other hand, in addition to the increase in the concentration of healthy cells, the concentration of free viruses must also be reduced in the patient's blood to prevent the progression of the disease. The dynamic behavior of the state variables for the concentration of healthy cells and free viruses is shown in Figures 8 and 9. As mentioned earlier, the state variable r is a measure of the virus's attack on healthy cells. In the untreated state, this variable increases linearly with time. However, in the treatment state, with the injection of PIs and RTIs, as shown in Figure 10, the virus's attack on healthy cells decreases. As a result, the virus activity decreases, and consequently, the concentration of healthy cells in the blood increases.

6. CONCLUSION

The goal of this thesis was to design a feedback linearization controller for controlling the HIV disease. Initially, a brief introduction to the presented models was given, and a comparison was made between the existing models. It was observed that equations with more variables model the disease behavior with greater accuracy. Therefore, a dynamic model with six state variables in the state space was used in this thesis. One of the simplest and most

powerful methods in controlling dynamic systems is feedback linearization, and its principles and concepts were thoroughly explained. This control method was applied to the system, and satisfactory results were achieved. Later, optimal control was used to optimize the control input to reach the desired goals with the minimum dose of medication. Since the system under study is a multi-input, multi-output (MIMO) system, feedback linearization for MIMO systems was required. Given the definition of the system's outputs, it was observed that exact linearization of the system is not possible because the relative degree of the system is less than the number of state variables. In this case, in addition to designing the controller, the stability of the system's internal dynamics must be analyzed by examining the stability of the system's zero dynamics, all of which were completed in this thesis. One of the issues with the feedback linearization control method is that it is a model-based approach, meaning the controller's performance largely depends on the accuracy of the model used, and changes in system parameters can significantly degrade the controller's performance.

For future work, it is recommended to use robust methods such as H_∞ and other robust controllers for system control. Additionally, regarding the model used in this thesis, the system's control inputs are only the drug dose administered to the patient, which could be adjusted by modifying the dynamic model to consider the drug dose as the control input. This thesis assumed that all the system's state variables are measurable, but in practice, only some state variables may be observable. Therefore, linear or nonlinear observers could be used to estimate the system's state variables, bringing the applied method closer to reality.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Hadjiandreou, M. M., Conejeros, R., & Wilson, D. (2009). Planning of patient-specific drug-specific optimal HIV treatment strategies. Chemical Engineering Science, 64(18), 4024-4039. https://doi.org/10.1016/j.ces.2009.06.009

[2] Sharp, P. M., & Hahn, B. H. (2011). Origins of HIV and the AIDS pandemic. Cold Spring Harbor Perspectives in Medicine, 1. https://doi.org/10.1101/cshperspect.a006841

[3] Yarchoan, R., Tosate, G., & Little, R. F. (2005). Therapy insight: AIDS-related malignancies—the influence of antiviral therapy on pathogenesis and management. Nature Clinical Practice Oncology, 8, 406-415. https://doi.org/10.1038/ncponc0253

[4] World Health Organization. (2010). Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach.

[5] Radisavljevic, V. (2009). Optimal control of HIV-virus dynamics. Annals of Biomedical Engineering, 37(6), 1251-1261. https://doi.org/10.1007/s10439-009-9672-7

[6] Pannocchia, G., Laurino, M., & Landi, A. (2010). A model predictive control strategy toward optimal structured treatment interruptions in anti-HIV therapy. IEEE Transactions on Biomedical Engineering, 57(5), 1040-1050. https://doi.org/10.1109/TBME.2009.2039571

[7] Zurakowski, R., & Teel, A. R. (2006). A model predictive control-based scheduling method for HIV therapy. Journal of Theoretical Biology, 238, 368-382. https://doi.org/10.1016/j.jtbi.2005.05.004

[8] Pinheiro, J. V., & Lemos, J. M. (2011). Multi-drug therapy design for HIV-1 infection using nonlinear model predictive control. 19th Mediterranean Conference on Control and Automation, Aquis Corfu Holiday Palace, Corfu, Greece. https://doi.org/10.1109/MED.2011.5983037

[9] Barao, M., & Lemos, J. M. (2006). Nonlinear control of HIV-1 infection with a singular perturbation model. IFAC Proceedings Volumes, 39(18), 333-338. https://doi.org/10.3182/20060920-3-FR-2912.00061

[10] Assawinchaichote, W., & Junhom, S. (2011). H∞ fuzzy controller design for HIV/AIDS infection system with dual drug dosages via an LMI approach. International Journal of Energy, 5(2), 27-33.

[11] Hajizadeh, I., & Shahrokhi, M. (2015). Observer-based output feedback linearization control with application to HIV dynamics. Industrial & Engineering Chemistry Research, 54(10), 2697-2708. https://doi.org/10.1021/ie5022442

[12] Costanza, V., Rivadeneira, P. S., Biafore, F. L., & Attellis, C. E. (2010). Taking side effects into account for HIV medication. IEEE Transactions on Biomedical Engineering, 57(9). https://doi.org/10.1109/TBME.2010.2049845

[13] Mhawej, M. J., Moog, C. H., & Biafore, F. (2009). The HIV dynamics is a single input system. 13th International Conference on Biomedical Engineering (pp. 1263-1266). Berlin, Germany. https://doi.org/10.1007/978-3-540-92841-6_310

[14] Rivadeneira, P. S., & Moog, C. H. (2012). Impulsive control of single-input nonlinear systems with application to HIV dynamics. Applied Mathematics and Computation, 218(17), 8462-8474. https://doi.org/10.1016/j.amc.2012.01.071

[15] Zarrabi, M. R., Farahi, M. H., Effati, S., & Koshkouei, A. J. (2012). Using sliding mode control in stability treatment of HIV disease. Advanced Modeling and Optimization, 14(1), 165-173.

[16] Mhawej, M. J., & Moog, C. H. (2010). Control of the HIV infection and drug dosage. Biomedical Signal Processing and Control, 5(17), 45-52. https://doi.org/10.1016/j.bspc.2009.05.001

[17] Landi, A., Mazzoldi, A., Andreoni, C., Bianchi, M., Cavallini, A., Laurino, M., Ricotti, L., Iuliano, R., Matteoli, B., & Nelli, L. C. (2008). Modelling and control of HIV dynamics. Computer Methods and Programs in Biomedicine, 89(2), 162-168. https://doi.org/10.1016/j.cmpb.2007.08.003

[18] Wodarz, P. D., & Nowak, M. A. (2002). Mathematical models of HIV pathogenesis and treatment. BioEssays, 24, 1178-1187. https://doi.org/10.1002/bies.10196