

Bilinear Robust H_∞ Controller to Minimize HIV Concentration in Blood Plasma

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Manuscript submitted August 1, 2019; accepted November 3, 2019.

doi: 10.17706/ijapm.2020.10.2.57-64

Abstract: Human Immunodeficiency Virus (HIV) is a type of virus which attacks $CD4^+T$ cells. Insufficient numbers of $CD4^+$ T cells will affect the performance of immunity systems so that someone become riskier to have AIDS or other diseases. HIV phenomenon is modelled as nonlinear system with disturbance, but there is no exact method to solve problems that related with analyzing nonlinear systems with control treatment. Thus, the nonlinear system is approximated into a bilinear system by using Carleman bilinearization method. A robust H_∞ -controller is designed as a control input to accomodate the disturbances in the dynamic system. Generally, the treatment for HIV is merely to obstruct the replication process. Therefore, the robust control input is described as the chemotherapy of hypothetical drugs which aimed to clear off the HIV concentration in blood plasma. Robust H_∞ -control is designed with the coefficient matrix of the bilinear system. The simulation result is analyzed by comparing the effect of the robust control toward bilinear and nonlinear system. From numerical simulations, an individual will experience heavy symptom if the hypothetical drugs chemotherapy is not given. This finding is strengthening the urgency of robust control as a chemotherapy with a waiting time. Based on the numerical simulation with robust H_∞ -control input, bilinear system has trends that give similar interpretation with the trends of nonlinear system. Besides that, robust H_∞ -control on bilinear system has demolishing speed of HIV concentration and infected $CD4^+T$ cells concentration which approximately equal to the demolishing speed from nonlinear system. Therefore, we can conclude that the performances of H_∞ -control on bilinear system is nearly same as the performances of nonlinear system.

Key words: Human immunodeficiency virus, chemotherapy, bilinear systems, carleman bilinearization, robust H_∞ -control.

1. Introduction

HIV is a virus that causes Acquired Immune Deficiency Syndrome (AIDS). HIV affects human's immune systems by infecting the $CD4^+T$ cells in blood plasma [1]. $CD4^+T$ cell is a type of lymphocyte which also called by helper T cells. $CD4^+T$ cells are divided into memory T cells to remember antigen's genetic code and suppressor T cells to respond cytotoxic T cells. Someone with a weak immune system is not only susceptible for AIDS, but also susceptible for other diseases e.g. pneumonia and meningitis [2]. The concentrations of $CD4^+T$ cells in a healthy person are in the range of 500 to 1000 cells mm^{-3} . A person with HIV is considered whenever the concentrations of $CD4^+T$ cells are between 200 to 500 cells mm^{-3} [2], [3].

The HIV replication cycle is divided into six stages [2], [4]. The stages are binding and entry, uncoating, reverse transcription, provirus integration, virus protein and assembly, and budding. In each stage of the HIV replication cycle, antiretroviral therapy is given as the efforts to decrease the concentration of HIV particles. Zidovudine (AZT) is the first registered drug which declared effective to fight HIV. The best condition that a person with HIV could have is having a treatment with the combinations of drugs. The combinations must be able to resist at least two out of six stages of the HIV replication.

Some mathematical works have been done in modelling this HIV replication in blood plasma. Tuckwell and Wan firstly constructed the dynamic system based on the phenomena [5]. Aguilar-Lopez developed the model by adding the control input and disturbance [1]. The constructed model is a nonlinear model which has weakness in the analysis method. Compared to linear or bilinear systems, nonlinear systems have no specific method to analyze the behavior of the system's state. The state feedback for the nonlinear system has studied in [6]. The other approach, the nonlinear system is approximated by a bilinear system in order to be able to analyze the performance [7], [8]. This method uses a specific mapping to produce the output's behaviour which similar to that of bilinear systems [8]. The control input that used in the model is a H_∞ -robust controller. The H_∞ -robust controller is constructed by using the components of the bilinear systems. The same control will be applied both in the nonlinear and bilinear systems, then the effects toward both systems will be compared. The numerical calculations will be used to show the successful performance of the methodology in minimize HIV concentration in blood plasma.

2. Bilinear Robust H_∞ -Control Design

The mathematical model for the early infection phase of HIV particles and CD4⁺T cells originally developed by Tuckwell and Wan [5] and improved by Aguilar-Lopez *et al.* [1]. The model has the nonlinear form as follows

$$\begin{aligned} \dot{x}_1 &= k_1 - k_2x_1 - k_3x_1x_3, \\ \dot{x}_2 &= k_3x_1x_3 - k_4x_2, \\ \dot{x}_3 &= k_5x_2 - k_6x_3 + u + d, \end{aligned} \tag{1}$$

with x_1 is the amount of concentrations for uninfected CD4⁺T cells, x_2 is the amount of concentrations for infected cells, and x_3 is the amount of concentrations for HIV particles in blood plasma.

The equation (1) can be written in the form

$$\begin{aligned} \dot{x} &= f(x) + g(x)u(t) + k(x)d(t), \\ y(t) &= h(x) = Cx(t), \end{aligned} \tag{2}$$

with $x = [x_1 \ x_2 \ x_3]^T \in \mathbb{R}^3$ is the state variable, $u \in \mathbb{R}$ is the control input variable, $y \in \mathbb{R}$ is the output variable, $f(x) = [k_1 - k_2x_1 - k_3x_1x_3 \ k_3x_1x_3 - k_4x_2 \ k_5x_2 - k_6x_3]^T$, $g(x) = [0 \ 0 \ 1]^T$, $C = [0 \ 0 \ 1]$, and $d \in \mathbb{R}$ is the disturbance.

Theorem 1 [6] Consider the state-space representation as in equation (2) for a nonlinear system with disturbance. For any $\gamma > 0$, there exist a function $V(x) \geq 0$ satisfy the following Hamilton-Jacobi equation

$$\frac{\partial V(x)}{\partial x} f(x) + \frac{1}{2} \frac{\partial V(x)}{\partial x} M(x) \frac{\partial^T V(x)}{\partial x} + \frac{1}{2} h^T(x)h(x) = 0, \tag{3}$$

or satisfy the following Hamilton-Jacobi inequality

$$\frac{\partial V(x)}{\partial x} f(x) + \frac{1}{2} \frac{\partial V(x)}{\partial x} M(x) \frac{\partial^T V(x)}{\partial x} + \frac{1}{2} h^T(x)h(x) \leq 0, \tag{4}$$

with $M(x) = \left[\frac{1}{\gamma^2} k(x)k^T(x) - g(x)g^T(x) \right]$. A closed-loop system has L_2 -gain from d into $\begin{bmatrix} y \\ u \end{bmatrix}$ less than or equal to γ for a state-feedback input

$$u = -g^T(x) \frac{\partial^T V(x)}{\partial x}, \tag{5}$$

The robust H_∞ -control input is constructed by using the matrices component of the bilinear system. By using Theorem 1, a $\gamma > 0$ and $\tilde{V}(x) \geq 0$ must be chosen to satisfy equation (3) or inequality (4). Therefore, for a state-feedback input as in equation (5), system has L_2 -gain from d into $\begin{bmatrix} y \\ u \end{bmatrix}$ less than or equal to γ . $P(\tilde{x})$ is defined as $P(\tilde{x}) := \frac{\partial V(\tilde{x})}{\partial \tilde{x}} f(\tilde{x})$. $V(\tilde{x})$, with $\gamma = 0.5$, is chosen as follow

$$V(\tilde{x}) = g_0(\tilde{x}_1 + \tilde{x}_2) + g_1 \sqrt{1 + \tilde{x}_3^2} \tag{6}$$

Since $\tilde{x}_i \geq 0$, then the condition $\tilde{V}(x) \geq 0$ is satisfied by choosing $g_0, g_1 \in \mathbb{R}^+$ appropriately. The first derivative of $V(\tilde{x})$ can be written as

$$\dot{V}(\tilde{x}) = \begin{bmatrix} g_0 & g_0 & \frac{g_1 \tilde{x}_3}{\sqrt{1 + \tilde{x}_3^2}} & 0 & \dots & 0 \end{bmatrix}. \tag{7}$$

$W(\tilde{x})$ is defined on the following equation

$$W(\tilde{x}) = P(\tilde{x}) + \frac{1}{2}M(\tilde{x}) + \frac{1}{2}h^T(\tilde{x})h(\tilde{x}), \tag{8}$$

then it is needed to show that $W(\tilde{x}) \leq 0$. $P(\tilde{x}), M(\tilde{x})$, and $W(\tilde{x})$ can be written by following equations

$$P(\tilde{x}) = g_0(k_1 - k_2\tilde{x}_1 - k_4\tilde{x}_2) + \frac{g_1 \tilde{x}_3}{\sqrt{1 + \tilde{x}_3^2}}(k_5\tilde{x}_2 - k_6\tilde{x}_3),$$

$$M(\tilde{x}) = \left(\frac{1}{\gamma^2} - 1 \right) \left(\frac{g_1 \tilde{x}_3}{\sqrt{1 + \tilde{x}_3^2}} \right)^2$$

$$W(\tilde{x}) = g_0(k_1 - k_2\tilde{x}_1 - k_4\tilde{x}_2) + \frac{g_1 \tilde{x}_3}{\sqrt{1 + \tilde{x}_3^2}}(k_5\tilde{x}_2 - k_6\tilde{x}_3) + \frac{1}{2} \left(\frac{1}{\gamma^2} - 1 \right) \left(\frac{g_1 \tilde{x}_3}{\sqrt{1 + \tilde{x}_3^2}} \right)^2 + \frac{1}{2} \tilde{x}_3^2. \tag{9}$$

The form $W(\tilde{x})$ on equation (9) can be rewritten into $W(\tilde{x}) = W_1(\tilde{x}) + W_2(\tilde{x})$ with

$$W_1(\tilde{x}) = g_0(k_1 - k_2\tilde{x}_1 - k_4\tilde{x}_2),$$

$$W_2(\tilde{x}) = \frac{g_1 \tilde{x}_3}{\sqrt{1 + \tilde{x}_3^2}}(k_5\tilde{x}_2 - k_6\tilde{x}_3) + \frac{1}{2} \left(\frac{1}{\gamma^2} - 1 \right) \left(\frac{g_1 \tilde{x}_3}{\sqrt{1 + \tilde{x}_3^2}} \right)^2 + \frac{1}{2} \tilde{x}_3^2$$

Aguilar-Lopez defined the coefficient for control as $g_1 = 1100d^{-1}$ [1], while $g_0 = 60000d^{-1}$ is determined from the simulation result. Since $\tilde{x}_i \geq 0$ for $i = 1, 2, 3$, then the condition $W_1(\tilde{x}) < 0$ and $W_2(\tilde{x}) > 0$ can be satisfied. In other words, condition $W_1(\tilde{x}) \leq -W_2(\tilde{x})$ always be satisfied for $t \in [0, T]$.

Since $W_1(\tilde{x}) \leq -W_2(\tilde{x})$, then inequality $W(\tilde{x}) \leq 0$ is satisfied.

Therefore, the transfer function of bilinear system in L_2 -gain from d into $\begin{bmatrix} y \\ u \end{bmatrix}$ is less than or equal to γ . In other words, the constructed robust H_∞ -control can guarantee a robust stability condition in globally asymptotic stable.. And the robust H_∞ -control is

$$u = -1100 \frac{\tilde{x}_3}{\sqrt{1 + \tilde{x}_3^2}} \tag{10}$$

Control input as equation (10) is categorized as a control input for bilinear system with $V(\tilde{x})$ at equation (6). The bilinear system is an approximation for nonlinear system with the state variables are extended into 1092 dimensions. However, the effects of input control will only be compared between the performances of state variables \tilde{x}_1, \tilde{x}_2 , and \tilde{x}_3 of bilinear system and x_1, x_2 , and x_3 of nonlinear system. Since the bilinear system is the approximation of its nonlinear form, then it will be determined that the performance of bilinear systems will be similar or not to the performance of nonlinear system.

3. Numerical and Simulation Results

The values of parameters for the simulation are as indicated in Table 1.

Table 1. Research Parameter (Laurino *et al.*)

Parameters	Definition	Value	Units
k_1	Constant rate of CD4 ⁺ T cells regeneration	50	$mgL^{-1}d^{-1}$
k_2	Diminishment rate of uninfected cells per capita	0.05	d^{-1}
k_3	Infection rate of CD4 ⁺ T cells by virus	$5 \cdot 10^{-4}$	$Lmg^{-1}d^{-1}$
k_4	Diminishment rate of infected cells per capita	0.4	d^{-1}
k_5	Growth rate of HIV particles	40	d^{-1}
k_6	Diminishment rate of HIV particles per capita	9	d^{-1}

The first simulation is the simulation without using control input ($u(t) = 0$). The simulation result for nonlinear system and bilinear system is illustrated in Fig. 1.

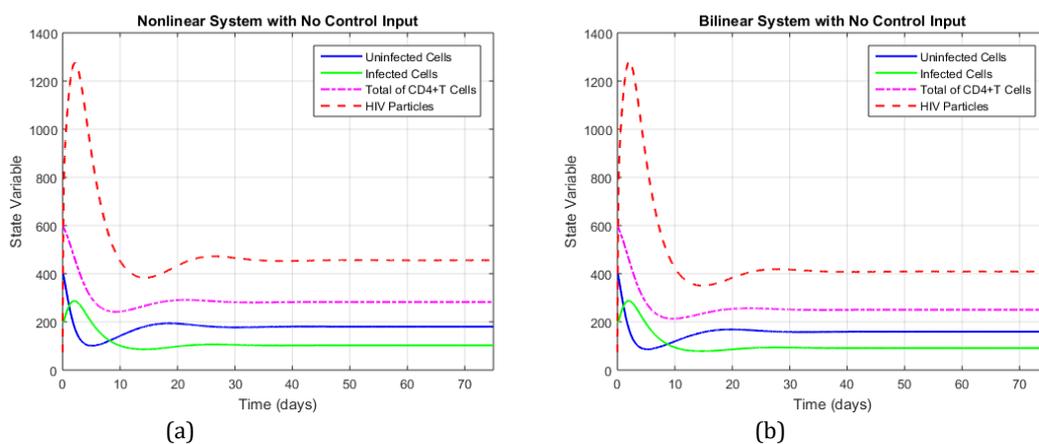


Fig. 1. Systems with No control input (a). Nonlinear (b) Bilinear.

The observation time for the first simulation is 75th days ($T = 75$). The first simulation for the nonlinear system give the result that the trajectories of state variables are convergent to the equilibrium point E_1 . For bilinear system, the first simulation shows that the final mass concentration of the CD4⁺T cells (\tilde{x}_1 and \tilde{x}_2) is $251.5 mgL^{-1}$. For nonlinear system, the first simulation shows that the final mass concentration of the

CD4⁺T cells (x_1 and x_2) is 282.5 mgL^{-1} . The result indicates that an individual is experiencing a heavy symptoms and susceptible towards illness that attacks weak immune system. Therefore, the control input as a hypothetical drugs chemotherapy is applied to minimize the HIV concentrations as well as keeping the CD4⁺T cells' condition in the normal shape.

The next numerical simulations are the application of robust H_∞ -control as the control input for the dynamic systems. The purpose of this simulation is to determine the performance of each state variable after the control input is used. For the bilinear system, the robust H_∞ -control input is described in the equation (10). Since we want to compare the effect of robust H_∞ -control input on bilinear and nonlinear system, then the control input for nonlinear system takes the form as also in the equation (10). The difference only by changing the state variables \tilde{x} (on the bilinear system) with the state variables x (on the nonlinear system).

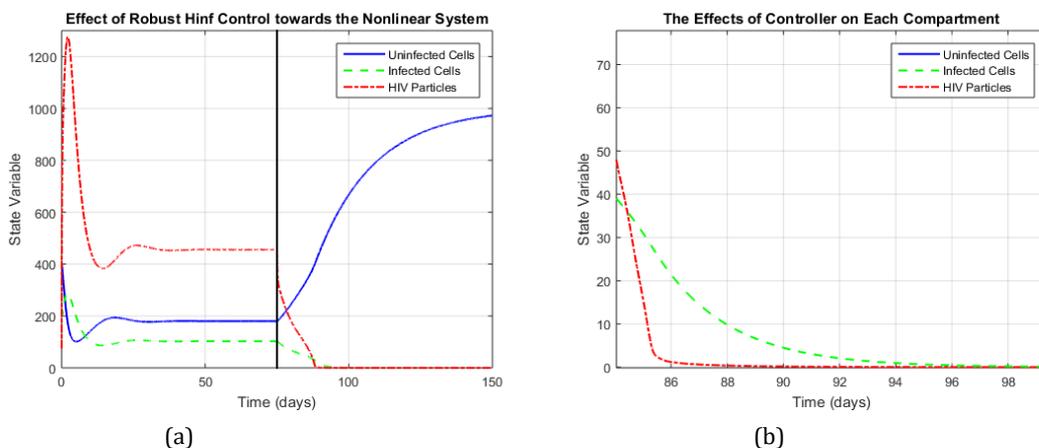


Fig. 2. (a) Effect of Robust H_∞ control towards nonlinear systems (b) effect of controller on each compartment.

The second simulation is the simulation for the nonlinear system with robust H_∞ -controller. The simulation result is illustrated in the Fig. 2a. It shows that x_3 , which defined the mass concentration of HIV particles, is convergent to the origin point since day 13 after the robust H_∞ -control input is given. In other words, it takes 88 days to totally diminish the HIV particles from the body. The diminishment happens because of the effect of hypothetical drugs chemotherapy that started at the 75th day. The diminishment process significantly affects the mass concentration of the infected CD4⁺T cells. It shows that x_2 , which defined the mass concentration of infected CD4⁺T cells, is convergent to the origin point since day 23 after the robust H_∞ -control input is given. In other words, it takes 98 days for the body to not contain any infected CD4⁺T cells. Fig. 2b illustrates the convergency of both infected cell's trajectory (x_2) and HIV particle's trajectory (x_3).

The third simulation is the simulation for bilinear system with robust H_∞ -controller. The simulation result is illustrated in the Fig. 3a. \tilde{x}_3 , which defined the mass concentration of HIV particles, is convergent to the origin point since day 12 after the control treatment is given. In other words, it takes 87 days to totally diminish the HIV particles from the body. The diminishment happens because of the effect of hypothetical drugs chemotherapy that started at the 75th day. As also happened in the nonlinear system, the diminishment of HIV particles also affects the mass concentration of infected CD4⁺T cells. \tilde{x}_2 , which defined the mass concentration of infected CD4⁺T cells, is convergent to the origin point since day 21 after the control treatment is given. In other words, it takes 96 days for the body to not contain any infected CD4⁺T cells. Fig. 3b illustrates the convergency of both infected cell's trajectory (\tilde{x}_2) and HIV particle's

trajectory \tilde{x}_3).

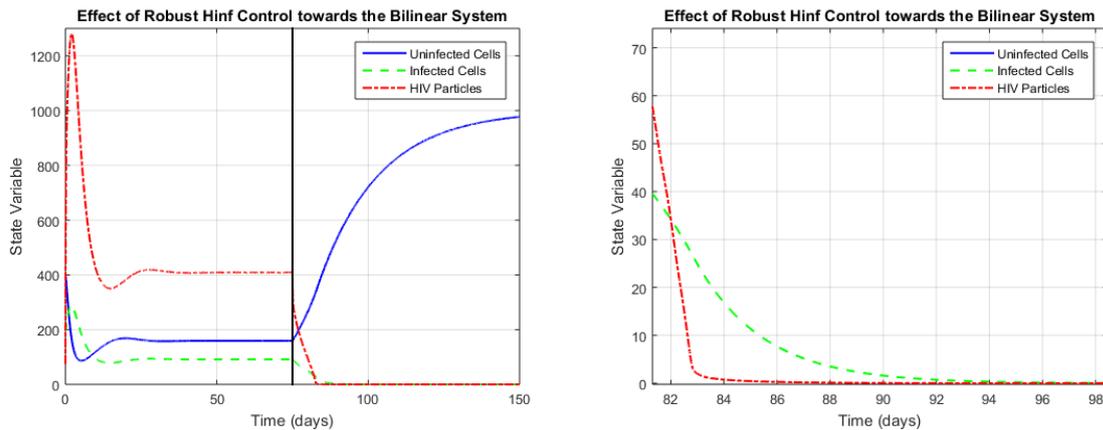


Fig. 3. (a) Effect of robust H_∞ control towards bilinear systems (b) effect of controller on each compartment.

Overall, the numerical simulations is divided into two types of observation i.e. observation of system with no control input and observation of system with robust H_∞ -control input. All simulations are interpreted towards the phenomena about HIV replication in the blood plasma. The first simulation shows that the mass concentrations of $CD4^+$ T cells (both infected and uninfected cells) are decreasing in both bilinear and nonlinear system. Table 2 below shows the decreasing mass concentrations of $CD4^+$ T cells up to 53% for nonlinear system and 58% for bilinear system. From the result on Table 2, it can be seen that the bilinear system's result gives a good approximation towards the nonlinear system's results.

Table 2. The Comparison of $CD4^+$ T Cells' Decreasing

Dynamical System	Initial Condition ($T = 0$)	Final Condition ($T = 75$)	Decreasing Percentage
Nonlinear System	600 mgL^{-1}	282 mgL^{-1}	53%
Bilinear System	600 mgL^{-1}	251.5 mgL^{-1}	58%

The next part that will be analyzed is the trajectory's trend of each system. Without no control input, the uninfected and infected $CD4^+$ T cells are decreasing and the HIV particles are increasing. This phenomena can be seen in both systems. An individual, whom in a good condition at the start of the observation, will experience heavy symptoms and have a weak immunity system at the end of the observation. Bilinear system is able to representatively approximate the performance of nonlinear system in observation with no control input.

The control input for this research is robust H_∞ -controller which defined as a hypothetical drugs chemotherapy. This hypothetical drugs chemotherapy is assumed to be able to fully diminish the HIV particles. The interpretation from Fig. 3a and Fig. 3b shows that all the trajectories are convergent to the equilibrium point E_0 . Besides that, it is clearly seen that the trend of all trajectories of bilinear system have the same trend as the trajectories of nonlinear system.

The convergency of all state variables after the implementation of robust H_∞ -controller proves the effectivity of the controller. It is known that the state variables converges to the HIV-free equilibrium point at the end of observation time. The convergency of x_2 and x_3 to the origin point means that the mass concentration of infected cells and HIV particles are fully diminished. Then, the convergency of x_1 to the condition $x_1 = 1000$ means that all $CD4^+$ T cells are the uninfected cells. Therefore, robust H_∞ -controller is successfully able to make the system is robustly stable.

Table 3. The Comparison of Rate of Diminishment at Both Systems

Bilinear System	Nonlinear System
HIV particles are diminished with the rate 34.17 mgL^{-1} per day	HIV particles are diminished with the rate 35.04 mgL^{-1} per day
Infected cells are diminished with the rate 4.35 mgL^{-1} per day	Infected cells are diminished with the rate 4.46 mgL^{-1} per day

The last part to be discussed is the rate of diminishment of the infected cells and HIV particles of both bilinear and nonlinear system. The comparison results are shown at the Table 3. It can be seen that the state variables of bilinear system has rate of diminishment that approximate the rate of diminishment of the state variables of nonlinear systems. Since the bilinear system is generated as an approximation of nonlinear system, then this result clearly state the benefits of implementing robust H_{∞} system at the bilinear system.

It is known that a complex computational method is needed to analyze the nonlinear system. This complexity of the method leads to the needs of extra efforts to solve problems related with nonlinear systems. Besides that, there is no specific method to be able to accomodate all types of nonlinear systems. Therefore, the result about decreasing's percentage, trends of the trajectories, and rate of diminishment are sufficient enough to show the effectiveness of implementing bilinear system as the approximation of nonlinear system.

4. Conclusions

In this paper, phenomena about HIV replication in blood plasma is modelled into a nonlinear system. Due to the barriers to analyze nonlinear system, alternative way to approximate the nonlinear system by a bilinear system is used. The purpose of this research is to find a control input to solve the modelling problems. The robust H_{∞} -controller is used as the control input because the model contains disturbance. The robust H_{∞} -controller is constructed by the method developed by van der Schaft with the components of bilinear system. The result shows the effectiveness of robust H_{∞} -controller to minimize the HIV particles in blood plasma. Several findings from the comparison between bilinear and nonlinear system also strengthen the result that the bilinear system would representatively approximate the nonlinear system. By the end of the observation, blood plasma only contains the uninfected CD4⁺T cells.

Conflict of Interest

No conflict of interest.

Author Contributions

This paper is a part of the Thesis Magister of Jonathan Saputra who Roberd Saragih and Dewi Handayani are the supervisor of him.

Acknowledgment

The authors acknowledge Kemenristekdikti for its support.

References

- [1] Aguilar-Lopez, R., Gomez-Acata, R. V., Lara-Cisneros, G., & Femat, R. (2016). Nonlinear and robust control strategy based on chemotherapy to minimize the HIV concentration in blood plasma. *Journal of Control Science and Engineering*, 1-6.
- [2] Fanales-Belasio, E., Raimondo, M., Suligoj, B., & Butto, S. (2010). HIV virology and pathogenetic mechanisms of infection: A brief overview. *Annali Dell'Istituto Superiore Di Sanita*, 46, 5-14.
- [3] Vajpayee, M., Kaushik, S., Sreenivas, V., Wig., N., & Seth, P. (2005). CDC staging based on absolute CD4

count and CD4 percentage in an HIV-1-infected Indian population: Treatment implications. *Clinical and Experimental Immunology*, 141, 485.

- [4] Greene, W. C., Zebysy, Z., & Ikeda, Y. (2008). Novel targets for HIV therapy. *Antiviral Research*, 80, 251-265.
- [5] Tuckwell, H. C., & Wan, F. Y. M. (2004). On the behavior of solutions in viral dynamical models. *BioSystems*, 73, 157-161.
- [6] Schaft, A. (1992). L_2 –gain analysis of nonlinear systems and nonlinear H_∞ state feedback control. *IEEE Trans. Autom. Control*, 37, 770-784.
- [7] Bai, Z., & Skoogh, D. (2005). A projection method for model reduction of bilinear dynamical systems. *Linear Algebra and Its Applications*, 406-425.
- [8] Flagg, G. (2012). Interpolation methods for the model reduction of bilinear systems. PhD Thesis, Faculty of the Virginia Polytechnic Institute and State University.

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