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Double Integral Sliding Mode Control Approach for the Treatment of HIV/AIDS under Antiretroviral Therapy

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Abstract

Human Immunodeficiency Virus (HIV) is a lentivirus that badly affects the immune system and becomes the cause of lethal disease called Acquired Immune Deficiency Syndrome (AIDS). This virus mainly destroys the healthy CD4 cells in the immune system and makes it vulnerable to other fatal infections and diseases. Antiretroviral therapy is the most common type of treatment in which we normally use the amount of drug doses to eradicate infected CD4 cells and viral load. In this paper, three nonlinear controllers namely Sliding Mode Controller (SMC), Integral Sliding Mode Controller (ISMC) and Double Integral Sliding Mode Controller (DISMC) have been designed using updated nonlinear mathematical model of HIV/AIDS under the effect of Antiretroviral drug doses. The main purpose of the design of controllers is to destroy the maximum number of infected CD4 cells and viral load while increasing as many healthy CD4 cells as possible. HIV-antigen specific cytotoxic T-lymphocytes play a defensive role together with the drug doses to destroy the number of infected CD4 cells and free viruses in a short time span. Lyapunov based theory has been used to analyze the global stability of the system. The simulations of all three proposed controllers have been done using MATLAB/Simulink and their results have been compared with each other based on the convergence of states to their desired reference values and steady state errors.

Keywords: HIV/AIDS, Antiretroviral Therapy, SMC, ISMC, DISMC, Nonlinear Control

Introduction

HIV directly targets the CD4 cells or T-helper cells in the immune system. CD4 cells are an integral part of the immune system which play a significant role in the defense against many other diseases. After the attack of HIV, CD4 cells start producing free virions due to the infection in them caused by the disease [1]. A normal human body without HIV infection has CD4+T count between 600 to 1200 cells/mm3 in blood plasma. If the CD4+T count of a person drops below 200 cells/mm3, then that person suffers from AIDS which is called the worst stage of HIV infection [2]. Many life-threatening cancers or infections such as malaria and tuberculosis take the advantage of weak immune system by HIV infection to badly affect the human body [2]. A contagious disease HIV replicates itself [3] after targeting the normal CD4 cells and hence decrease the large concentration of healthy CD4 cells of human body. HIV infection mainly occurs by tissue transplant, transfer of human blood, semen and breast milk [4] etc.

The three stages of HIV infection include acute infection, clinical latency or chronicle latency and AIDS. People may experience a flu-like illness after the attack of HIV. In acute infection, a patient has a large amount of virus in his/her blood plasma. Many people are often unaware of this deadly disease at this initial stage. If this stage is not treated properly then a person starts suffering from second stage which is clinical latency or sometimes called asymptomatic HIV infection. If the patient is treated properly under Antiretroviral Therapy, then he/she may be in this stage for several decades. The person0s CD4+T count begins to go down at the end of this stage. The last stage of HIV infection is AIDS and is known as the worst stage in which the patient has badly damaged immune system which makes him suffer from several cancers or deadly infections [5].

As we know that HIV/AIDS is not curable but can be controlled through drug doses under the effect of Antiretroviral Therapy to boost up the immune system to fight against other infections and diseases [6]. Antiretroviral Therapy is the most common treatment of HIV/AIDS in which the drug doses directly attack the replication cycle of free virus in blood plasma and affect the growth of HIV.

The dynamic behavior of many mathematical models of HIV/AIDS have been analyzed in the literature [7], [8], [9],[10] and stability analysis of HIV infection has also been discussed [11], [12]. Optimal control techniques under the effect of Antiretroviral Therapy have been applied to eradicate the HIV infection to some safe limit or to increase the life expectancy of HIV/AIDS infected patients [2], [4], [6], [13], [14], [15]. Control Lyapunov Function (CLF) approach has also been discussed to control the behavior of nonlinear uncertain HIV-1 model [16].

The life cycle of HIV completes in different stages and we know that the Antiretroviral drugs directly attack the virus cells and interrupt the life cycle of HIV at different stages. These drugs are normally used in a combination of two or three drugs to affect the growth rate of the virus as each drug has a specific

action and belongs to a specific class. The combination of Antiretroviral drugs is usually known as HIV regimen which may contain three drugs from at least two different classes of drugs. The different classes/types of drugs include fusion inhibitors, pharmacokinetic enhancers, nucle-oside reverse transcriptase inhibitors, non-Nucleoside reverse transcriptase inhibitors, integrase inhibitors, entry inhibitors and protease inhibitors. The drugs are used on daily basis to achieve the goal of reducing HIV drug resistance and increase the patient0s adherence to the drugs [17], [18].

SMC is a robust control technique that is used to design the discontinuous control law which is being used for driving the system trajectories on a sliding surface. This phase is called the reaching phase and then the system trajectories move along the sliding surface towards the origin with desired performance. Sliding mode is insensitive to parametric variations and dis-turbances once we are on the sliding surface [19]. It is a slight modification of Synergetic control technique. SMC has an advantage to track more than one states of the system as compared to other nonlinear controllers like Backstepping or Integral Backstepping controller. Addition of an integral action in SMC makes it Integral Sliding mode controller (ISMC). As we know that the maximum effort mainly occurs at the beginning of the reaching phase in case of SMC. ISMC has no reaching phase which makes it more robust as compared to simple SMC technique [20]. DISMC involves the addition of double integral action in simple SMC for fast convergence and further reduction of steady state errors of the system [21]. DISMC technique has been applied for MPPT of a PV system [22], brushless DC motor speed control [23] and for MPPT of a stand-alone PV system [24]. ISMC has been designed for nonlinear systems with matched and unmatched perturbations

[25] SMC has been designed for a linear focusing actuator in digital video cameras [26]. SMC and DISMC have been applied on four quadrant Quasi-Z-source converter [21]. In this paper, three nonlinear controllers namely SMC, ISMC and DISMC have been designed to track the first three states of mathematical model for maximizing the number of healthy cells to desired reference by decreasing maximum number of uninfected cells and free viruses under the effect of Antiretro-viral drugs.

This paper has been divided into following sections: Mathe-matical model has been discussed in section II. The design procedure of SMC, ISMC and DISMC is given in section III. Section IV describes the simulation results and conclusion is given in section V.

Mathematical Model

The nonlinear dynamic mathematical model considered in this paper, has been proposed by Nowak and Bangham [13]. The model consists of four first order nonlinear differential equations and is given as:

$$\frac{dx1}{dt} = dx1 \quad „t"x1\ x3 \qquad (1a)$$

$$\frac{dx2}{dt} = „t"x1\ x3 \quad ax2 \quad px2\ x4 \qquad (1b)$$

$$\frac{dx3}{dt} = k\ x2 \quad ux3 \qquad (1c)$$

$$\frac{dx4}{dt} = cx2\ x4 \quad bx4 \qquad (1d)$$

- x1: Concentration of healthy or uninfected CD4 cells
- x2: Concentration of infected CD4 cells
- x3: Concentration of free virus cells
- x4: Concentration of HIV-antigen specific cytotoxic T-lymphocytes (CTL)

The parameters, k and c represent the production rate of healthy or uninfected cells, free viruses and cytotoxic T-lymphocytes respectively. Whereas, the parameters d, a, u and b represent the rate of natural decline of healthy CD4 cells, infected cells, free viruses and cytotoxic T-lymphocytes respectively. Represents the infection rate of healthy cells by HIV and p represents the death rate of infected cells respectively.

The number of healthy cells can be reproduced to a fixed rate which is represented by parameter in eq(1a), but the second term -dx1 describes that this reproduction rate decreases after the attack of virus produced by other CD4 cells. The third term -x1 x3 describes that the reproduction rate which was decreased by -dx1, further decreases after free viruses interact with those cells.

The number of infected cells depends upon the total number of cells in the human body that are ready to be infected by the free viruses. So, the total number of infected cells are proportional to the amount of healthy cells and viral load by factor represented by term x1 x3 in eq.(1b). The third term px2 x4 represents the killing of infected cells by cytotoxic T-lymphocytes. Whereas, the infected cells that are killed in the end are represented by second term ax2.

The production rate of free viruses is represented by the first term k x2 in eq.(1c) which shows that the free viruses increase with the increase in the number of infected cells. Whereas, the second term ux3 represents the destruction of free viruses by cytotoxic T-lymphocytes.

The term cx2 x4 in eq.(1d) represents the production of cyto-toxic T-lymphocytes. This production depends on the antigenic characteristics of virus and infected cells. bx4 in eq.(1d) represents the natural death of cytotoxic T-lymphocytes.

Several mathematical models of HIV/AIDS have been pro-posed in different papers in which many linear and nonlinear techniques have been applied, but these models lack the immune response of the human body in which the major role is played by cytotoxic T-lymphocytes. The model considered in this paper includes the state of HIV-antigen specific cytotoxic T-lymphocytes which play a defensive role together with drug doses to destroy the large number of infected CD4 cells and free viruses in a short time span.

As discussed in paper [13], we have two values of „t" which are „t" = = 1 for no treatment and „t" = e m„t" for the design of a controller. Where m„t" can be defined as a drug dose at time t. So, the eq(1a) and eq(1b) can be rewritten as:

$$\frac{dx_1}{dt} = dx_1 \quad e^{m_{\text{„}}t''} x_1 x_3 \qquad (2a)$$

$$\frac{dx_2}{dt} = e^{m_{\text{„}}t''} x_1 x_3 \quad ax_2 \quad px_2 x_4 \qquad (2b)$$

Controller Design

The block diagram for the control of HIV has been shown in **Fig.1.**

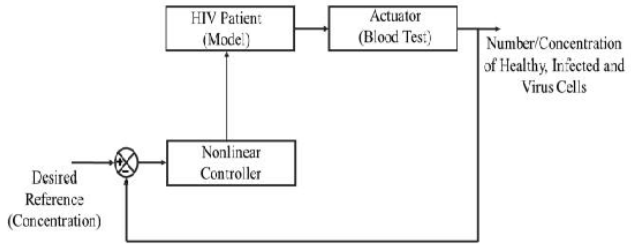

Figure 1: Control of HIV.

The design procedure of three nonlinear controllers namely SMC, ISMC and DISMC has been described in this section using the mathematical model of HIV/AIDS in order to track the first three states to their desired references.

Sliding Mode Controller Design

Firstly, we define the errors e1, e2 and e3 to track the first three states to their reference values as:

$$e1 = x1 \quad x_{1ref} \qquad (3a)$$

$$e2 = x2 \quad x_{2ref} \qquad (3b)$$

$$e3 = x3 \quad x_{3ref} \qquad (3c)$$

where e1 describes the error difference between the concentration of healthy or uninfected cells and the tracking reference value x1re f . The error e2 is the difference between the concentration of infected cells and their desired value x2re f . And similarly, the error e3 is the difference between the concentration of free viruses and their desired reference value x3re f.

Now, the sliding surface containing all the errors is given as

$$s = a1e1 + a2e2 + a3e3 \qquad (4)$$

By taking the derivative of eq.(4) w.r.t. time, we get

$$s\hat{U} = a1e\hat{U}1 + a2e\hat{U}2 + a3e\hat{U}3 \qquad (5)$$

The time derivatives of errors e1, e2 and e3 from eq.(3a), eq.(3b) and eq.(3c) are given as

$$e\hat{U}1 = x\hat{U}1 \quad x\hat{U}1re\ f \qquad (6a)$$

$$e2 = x2 \quad x_{2re\ f} \qquad (6b)$$
$$\hat{U} \quad \hat{U}$$

$$e\hat{U}3 = x\hat{U}3 \quad x\hat{U}_{3re\ f} \qquad (6c)$$

Since x1re f , x2re f , and x3re f are all constants so their derivatives w.r.t. time will be zero.

Now, we place the values of the errors eÛ1, eÛ2 and eÛ3 from eq.(6a), eq.(6b) and eq.(6c) in eq.(5).

$$s\hat{U} = a1\,x\hat{U}1 + a2\,x\hat{U}2 + a3\,x\hat{U}3 \qquad (7)$$

For sÛ to be negative definite, we write

$$s\hat{U} = a1\,x\hat{U}1 + a2\,x\hat{U}2 + a3\,x\hat{U}3 = ki\,jsj\,sign_{\text{„}}\frac{s}{\text{„}} \qquad (8)$$

Where ki is a positive number and is called design co-efficient. can be any number between 0 and 1 and is a small number which plays an important role for the removal of chattering. System convergence to the sliding surface increases with the distance which is ensured by jsj. By inserting the values of xÛ1, xÛ2 and xÛ3 from eq(2a), eq(2b) and eq(1c) in eq(8), we obtain

$$ki\,jsj\,sign_{\text{„}}\frac{s}{\text{„}} = a1_{\text{„}}\ dx1 \quad e^{m_{\text{„}}t''} x1\ x3'' +$$
$$a2_{\text{„}}e^{m_{\text{„}}t''} x1\ x3 \quad ax2 \quad px2\ x4'' + a3_{\text{„}}k\ x2 \quad ux3'' \qquad (9)$$

After rearranging eq.(9), we get

$$e^{m_{\text{„}}t''} = \frac{1}{{}_{\text{„}}a2 \quad a1''x1\,x3}\ {}_{\text{„}}\,ki\,jsj\,sign_{\text{„}}\frac{s}{\text{„}}\ a1_{\text{„}}\ dx1'' +$$
$$a2_{\text{„}}ax2 + px2\ x4'' \quad a3_{\text{„}}k\ x2 \quad ux3''' \qquad (10)$$

We now use a Taylor expansion of $e^{m_{\text{„}}t''}$ which is given as follows:

$$e^{m_{\text{„}}t''} = 1 \quad \frac{m\,t}{\text{„}''} + \frac{m_{\text{„}}t''^2}{2} \quad \frac{m_{\text{„}}t''^3}{3!} + :::$$

By neglecting the higher order terms of eq.(11), we get

$$e^{m_{\text{„}}t''} = 1 \quad \frac{m\,t}{\text{„}''} \qquad (12)$$

After rearranging eq.(12) and placing value of $e^{m_{\text{„}}t''}$ from eq.(10), we have

$$m_{\text{„}}t'' = \frac{1}{{}_{\text{„}}a2 \quad a1''x1\ x3}\ {}_{\text{„}}\,ki\,jsj\,sign_{\text{„}}\frac{s}{\text{„}}\ a1_{\text{„}}\ dx1'' +$$
$$a2_{\text{„}}ax2 + px2\ x4'' \quad a3_{\text{„}}k\ x2 \quad ux3''' \qquad (13)$$

which is the desired control law for SMC.

The Lyapunov candidate function to prove asymptotic stability of the system is given as

$$V = \frac{1}{2} \quad (14)$$

Now, taking the derivative of eq.(14) with respect to time gives

$$\dot{V} = s\dot{s} \quad (15)$$

Now, by inserting the value of $\dot{s}$ from eq.(8) in eq.(15), we obtain

$$\dot{V} = s \, k_i \, j_{si} \, sign \quad (16)$$

Eq.(16) clearly shows that $\dot{V}$ is negative definite which ensures that the system is asymptotically stable.

Integral Sliding Mode Controller Design

When we add integral terms of all the errors in simple SMC, then it will become ISMC. The errors e1, e2 and e3 of ISMC for the tracking of healthy cells, infected cells and viral load to their desired reference values have been defined in eq.(3a), eq.(3b) and eq.(3c) respectively. The integral action of errors is given as

$$e_4 = \int_0^t (x_1 - x_{1ref})\,dt \quad (17a)$$

$$e_5 = \int_0^t (x_2 - x_{2ref})\,dt \quad (17b)$$

$$e_6 = \int_0^t (x_3 - x_{3ref})\,dt \quad (17c)$$

We now define a sliding surface as:

$$s = a_1e_1 + a_2e_2 + a_3e_3 + a_4e_4 + a_5e_5 + a_6e_6 \quad (18)$$

By taking the derivative of eq.(18) with respect to time, we get

$$\dot{s} = a_1\dot{e}_1 + a_2\dot{e}_2 + a_3\dot{e}_3 + a_4\dot{e}_4 + a_5\dot{e}_5 + a_6\dot{e}_6 \quad (19)$$

Now, the time derivatives of e_4, e_5 and e_6 are given as follows:

$$\dot{e}_4 = x_1 - x_{1ref} = e_1 \quad (20a)$$

$$\dot{e}_5 = x_1 - x_{2ref} = e_2 \quad (20b)$$

$$\dot{e}_6 = x_1 - x_{3ref} = e_3 \quad (20c)$$

Now, inserting the values of errors $\dot{e}_1$, $\dot{e}_2$ and $\dot{e}_3$ from eq.(6a), eq.(6b) and eq.(6c) and values of $\dot{e}_4$, $\dot{e}_5$ and $\dot{e}_6$ from eq.(20a), eq.(20b) and eq.(20c) in eq.(19), we have

$$\dot{s} = a_1\dot{x}_1 + a_2\dot{x}_2 + a_3\dot{x}_3 + a_4e_1 + a_5e_2 + a_6e_3 = k_i \, j_{si} \, sign \quad (21)$$

By inserting the values of $\dot{x}_1$, $\dot{x}_2$ and $\dot{x}_3$ from eq.(2a), eq.(2b) and eq.(1c) in eq.(21), we obtain

$$k_i \, j_{si} \, sign = a_1 \, dx_1 - e \, m_i t \, x_1 x_3 + a_2 e \, m_i t \, x_1 x_3 - ax_2 - px_2 x_4 + a_3 k \, x_2 - ux_3 + a_4e_1 + a_5e_2 + a_6e_3 \quad (22)$$

After rearranging eq.(22), we can write

$$e \, m_i t = \frac{1}{a_2 - a_1 x_1 x_3} \, k_i \, j_{si} \, sign - a_1 \, dx_1 + a_2 ax_2 + px_2 x_4 - a_3 k \, x_2 - ux_3 - a_4e_1 - a_5e_2 - a_6e_3 \quad (23)$$

From eq.(11) and eq.(23), we can write

$$m_i t = 1 \frac{1}{a_2 - a_1 x_1 x_3} \, k_i \, j_{si} \, sign - a_1 \, dx_1 + a_2 ax_2 + px_2 x_4 - a_3 k \, x_2 - ux_3 - a_4e_1 - a_5e_2 - a_6e_3 \quad (24)$$

which is the desired control law for HIV/AIDS treatment in case of ISMC. To analyze the asymptotic stability of the system, we insert the value of $\dot{s}$ from **eq.(21)** in **eq.(15),** so we obtain

$$\dot{V} = s \, k_i \, j_{si} \, sign \quad (25)$$

So, V is negative definite and the system is asymptotically stable as V! 0. Hence, all the errors approach zero and all the references have been tracked.

Double Integral Sliding Mode Controller Design

In DISMC, we add double integral terms of tracking errors e1, e2 and e3 to get

$$e_7 = \int_0^t \int_0^t (x_1 - x_{1ref})\,dt\,dt \quad (26a)$$

$$e_8 = \int_0^t \int_0^t (x_2 - x_{2ref})\,dt\,dt \quad (26b)$$

$$e_9 = \int_0^t \int_0^t (x_3 - x_{3ref})\,dt\,dt \quad (26c)$$

The sliding surface for the system to design the DISMC, can be defined as

$$s = a_1e_1 + a_2e_2 + a_3e_3 + a_4e_4 + a_5e_5 + a_6e_6 + a_7e_7 + a_8e_8 + a_9e_9 \quad (27)$$

Now, by taking the time derivatives of eq.(26a), eq.(26b) and eq.(26c), we have

$$eÛ7 = \int_0^t (x1 - x1ref)dt = e4 \quad (28a)$$

$$eÛ8 = \int_0^t (x2 - x2ref)dt = e5 \quad (28b)$$

$$eÛ9 = \int_0^t (x9 - x9ref)dt = e6 \quad (28c)$$

The derivative of s from eq.(27) w.r.t. time is given as:

$$sÛ = a1eÛ1 + a2eÛ2 + a3eÛ3 + a4eÛ4 + a5eÛ5 + a6eÛ6 + a7eÛ7 + a8eÛ8 + a9eÛ9 \quad (29)$$

By inserting the values of all errors eÛ1, eÛ2, eÛ3, eÛ4, eÛ5, eÛ6, eÛ7, eÛ8 and eÛ9 into eq.(29), we obtain

$$sÛ = a_1 xÛ_1 + a_2 xÛ_2 + a_3 xÛ_3 + a_4e_1 + a_5e_2 + a_6e_3 + a_7e_4 + a_8e_5 + a_9e_6 = k_i jsj sign(s) \quad (30)$$

Now, using eq.(2a), eq.(2b) and eq.(1c) in eq.(30), we get

$$sÛ = k_i jsj sign(s) = a_1 dx_1 - e^{-mt} x_1 x_3 + a_2 e^{-mt} x_1 x_3 - ax_2 + px_2 x_4 + a_3 k x_2 - ux_3 + a_4e_1 + a_5e_2 + a_6e_3 + a_7e_4 + a_8e_5 + a_9e_6 \quad (31)$$

After rearranging eq.(31)

$$e^{-mt} = \frac{1}{a_2 - a_1 x_1 x_3}\left[k_i jsj sign(s) - a_1 dx_1 + a_2 ax_2 + px_2 x_4 - a_3 k x_2 + ux_3 - a_4e_1 - a_5e_2 - a_6e_3 - a_7e_4 - a_8e_5 - a_9e_6\right] \quad (32)$$

From eq.(11) and eq.(32), we can write

$$mÛ = 1 - \frac{1}{a_2 - a_1 x_1 x_3}\left[k_i jsj sign(s) - a_1 dx_1 + a_2 ax_2 + px_2 x_4 - a_3 k x_2 + ux_3 - a_4e_1 - a_5e_2 - a_6e_3 - a_7e_4 - a_8e_5 - a_9e_6\right] \quad (33)$$

To analyze the asymptotic stability of the system, insert the value of sÛ from eq.(31) in eq.(15), we obtain

$$VÛ = -k_i jsj sign(s) \quad (34)$$

So, V is negative definite and all the states track their desired references accordingly as V! 0.

PID Controller Design

We have simulated the HIV model using the PID block in Matlab/Simulink and used the error and trial method to determine the values of design parameters Kp, Kd and Ki. Final values taken for proportional, integral and derivative constant can be seen in Fig.2.

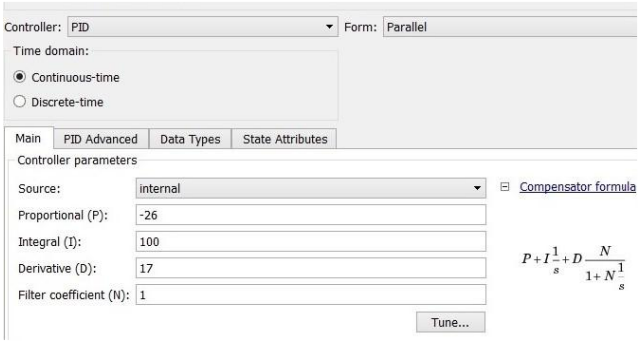

Figure 2: Values for PID.

Simulation Results and Analysis

This section presents the simulation results of proposed non-linear controllers using SMC, ISMC and DISMC techniques and linear PID controller. The comparative analysis of these controllers has also been discussed. The comparison shows the behavior of uninfected cells, infected cells, free virus, HIV-antigen cytotoxic T-lymphocytes and control input of the proposed nonlinear controllers and PID controller. All these controllers have been simulated using MATLAB/Simulink. The values of model parameters have been used from [13] and are given in Table.I. Whereas, the initial conditions are given as:

$$x_1(0) = 0.7\ mgL^{-1},\ x_2(0) = 0.2\ mgL^{-1},\ x_3(0) = 0.8\ mgL^{-1},\ x_4(0) = 0.03\ mgL^{-1},\ t_f = 10\ d$$

The tracking references for first three states of SMC, ISMC

Parameters	Values
	1.0 mgL 1 d 1
d	1.0d 1
a	0.8d 1
	1.0 Lmg 1 d 1 (no treatment)
p	0.05 Lmg 1 d 1
b	0.01 d 1
c	0.1 Lmg 1 d 1
u	0.01107 d 1
k	1.0d 1

Table 1: Values of Parameters.

and DISMC are given as:

$$x1ref = 1, x2ref = 0 \text{ and } x3ref = 0$$

The values of gains for SMC, ISMC and DISMC are given in Table.II, Table.III and Table.IV respectively. The controller gains have been obtained using trial and error method, in which we choose gains randomly and then check for the error value.

Fig.3 shows that the infected cells tend to increase in the absence of control input and then they show a decreasing behavior under the effect of SMC and PID controller.

Gains	Values
a1	103
a2	2 103
a3	5 10100
ki	00:07
	00:01
	00:01

Table 2: Values of Gains for SMC.

SMC vs PID

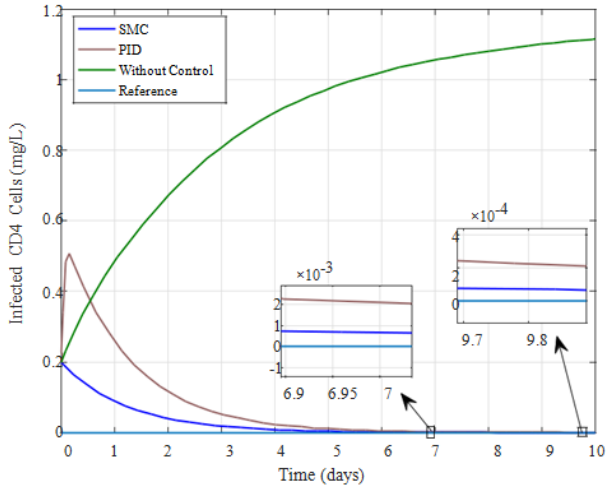

Figure 3: Infected CD4 Cells in Case of SMC and PID.

Gains	Values
a1	103
a2	2 103
a3	5 1010
a4	106
a5	5 104
a6	8 104
ki	0:065
1	
1	

Table 3: Values of Gains for ISMC.

Fig.4 shows the behavior of infected cells under the effect of SMC, ISMC, DISMC and PID controller. Upon analyzing the behavior of SMC and ISMC, it can clearly be seen that ISMC is better than SMC controller in terms of convergence of cells to zero and the steady state error. The better performance of ISMC is because of addition of integral term that improves the steady state error accuracy of the controller.

Gains	Values
a1	106
a2	2 102
a3	5 1010
a4	1013
a5	8 103
a6	5 10100
a7	103
a8	8 1060
a9	5 10100
ki	00:03
	00:01
	00:01

Table 4: Values of Gains for DISMC.

SMC vs ISMC vs DISMC vs PID

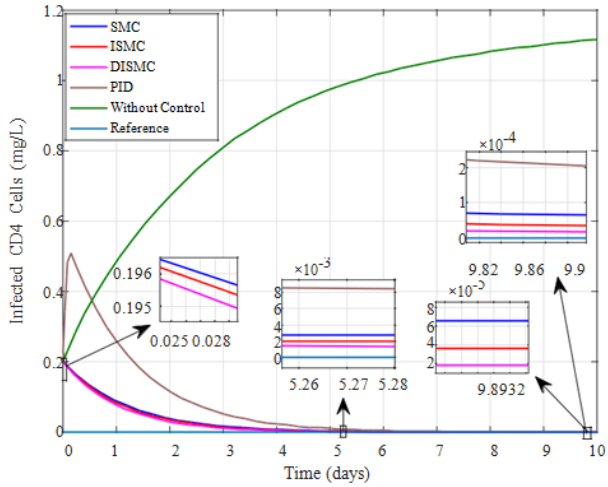

Figure 4: Comparison of Infected CD4 Cells.

The comparison of DISMC and ISMC shows that DISMC is improved version of ISMC because of the further addition of an integral term that can decrease the steady state error and also improves the convergence time of the controller. It can be seen in the zoomed portions of the figure that the settling time in case of DISMC is less and the steady state error is also less as compared to that shown in SMC and ISMC. But there is a minimal difference in this case as we are considering a very small sample of the infected cells.

Fig. **5** shows the effect of proposed nonlinear controllers on increased concentration of infected cells. It can be seen from the figure that upon taking large sample of infected cells, the difference now is visible that results shown by DISMC is far better in terms of convergence rate and steady state error.

The comparison of PID and SMC controller in Fig.4 shows that PID has failed to track the desired reference and shows a high steady state error that can also be seen in the figure. While comparing the transient response of both the controllers, it can be seen that there is a sudden drastic increase in the concentration of infected cells initially and the convergence is also slow in case of PID controller. So, it shows that linear controller is not suitable as compared to SMC, ISMC and DISMC.

SMC vs **ISMC** vs **DISMC**

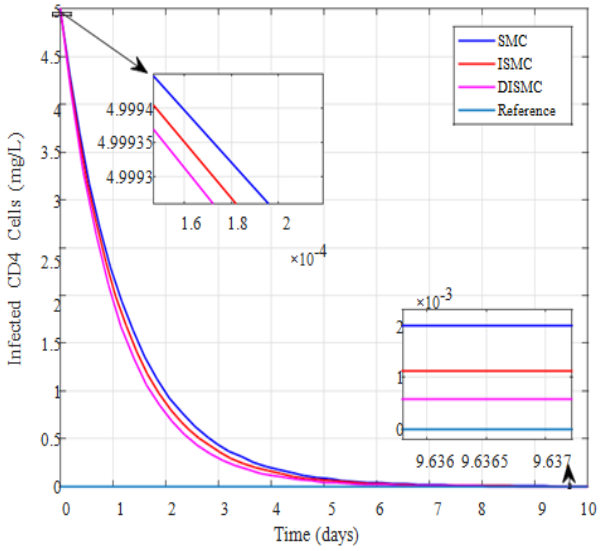

Figure 5: Comparison of Infected CD4 Cells with Different Value of Initial Condition.

Fig.6 shows the behavior of healthy cells under the effect of SMC and PID controller.

While comparing the behavior under SMC and its variants, it can clearly be seen in the zoomed parts that DISMC dominates ISMC and SMC controller on the basis of the convergence of uninfected cells to their desired reference and steady state error.

Since the difference between the results of SMC, ISMC and DISMC is too small so the curves for all three controllers are seen overlapping on each other.

The desired reference for the healthy cells has been set at 1mg/L and the initial condition is set at 0.7 mg/L and SMC and ISMC controller achieves the tracking with a less difference in their time of convergence and steady state error. The comparison of ISMC and DISMC show that

SMC vs **ISMC** vs **DISMC** vs **PID**

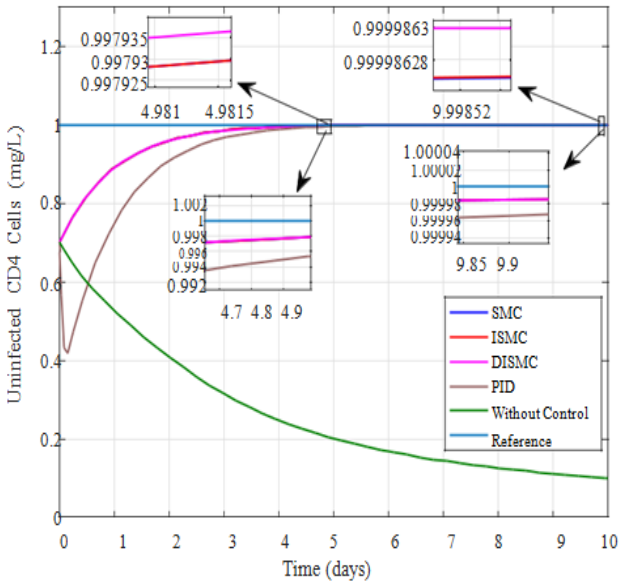

Figure 6: Comparison of Uninfected CD4 Cells.

the normal cells show an improvement in the tracking in case of DISMC. This is because the addition of an integral term ensures the fast convergence and improves steady state error accuracy. From the figure, it can clearly be seen that the transient response of DISMC is way better than that shown in SMC and ISMC on the basis of the settling time and fast convergence.

The steady state error in case of DISMC is closest to zero that affirms the better steady state accuracy of DISMC than SMC and ISMC.

The response of healthy cells under the effect of PID has also been shown and upon analyzing, it can clearly be seen that the cells initially decrease drastically and then track their reference with more steady state error as compared to that shown in SMC controllers.

The convergence of the cells can be seen by analyzing the transient response and it clearly shows that PID controller has more settling time and very slow convergence as compared to SMC which show that SMC is better than linear controller.

Fig.7 shows the behavior of uninfected cells with different initial conditions using DISMC controller. The values of the gains used in this case are the same and it clearly shows that DISMC is effective enough to track the healthy cells even with different values of initial condition. This result proves the robustness of the SMC.

DISMC With Different Initial Conditions

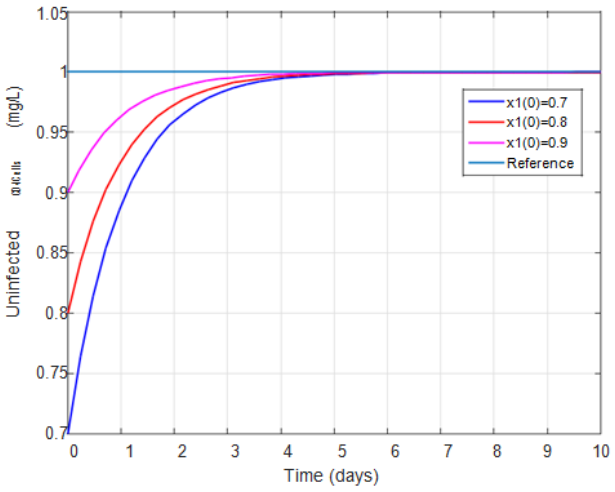

Figure 7: Uninfected CD4 Cells with Different Values of Initial Condition for DISMC.

Fig.8 describes the behavior of free virus cells for the proposed controllers and PID controller. The comparison of SMC and ISMC shows that there is a very less difference in the tracking capability, steady state error and convergence for both the controllers. However, a slight difference can be observed in the zoomed portion of figure and it shows that ISMC slightly dominates the SMC controller. The comparison of DISMC and other proposed controllers show that the concentration of free virus cells tracks efficiently in case of DISMC when analyzing in terms of settling time, steady state error and convergence time as seen in the zoomed part of the figure. The behavior of free virus cells using PID controller shows slow convergence and more steady state error when compared with the proposed controllers. The cells remain almost the same throughout the therapy and there is no significant decrease in the concentration of the cells. The behavior of cells in the absence of the therapy or control input can also be seen in the figure that increase drastically right from the initial time until the end of the therapy.

SMC vs **ISMC** vs **DISMC** vs **PID**

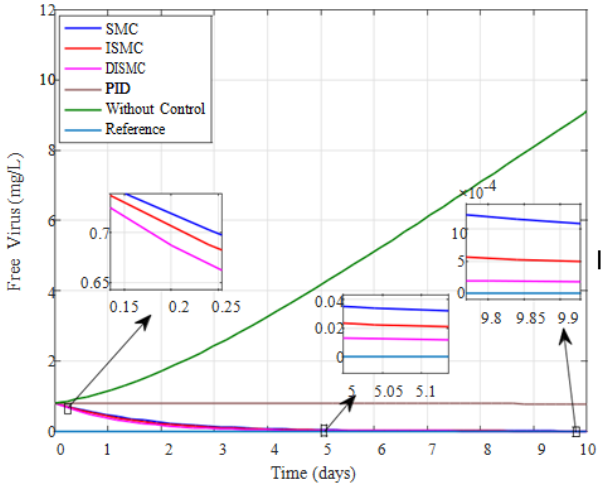

Figure 8: Comparison of Free Virus.

Fig.9 has been drawn for cytotoxic T-lymphocytes for all the controllers. These cells play an important role in the defense of the human body against the disease and are known to assist the therapy process as discussed earlier. Their behavior using SMC and ISMC show that cells used in the therapy process are more in case of ISMC and can be accounted for the better results in the decrease of infected cells and free virus cells. The comparison of DISMC and other proposed controllers shows that the cells at the end of the therapy are less in case of DISMC and this behavior can be explained by the better performance of the controller in terms of close to zero infected and free virus cells and relatively fast convergence of both the cells to their desired references. So, DISMC is better than SMC and ISMC. The behavior of the cells in the absence of control input has also been shown in the figure and it can be seen that the concentration of cytotoxic T-lymphocytes tends to increase. Upon analyzing the behavior of cytotoxic T-lymphocytes using linear PID controller and the proposed controllers, it can be seen that the cells at the end of the therapy are more in case of PID controller than all other controllers. This behavior can be accounted for the slow convergence of the other cells to their desired references and high steady state error as compared to SMC, ISMC and DISMC. It is also worth mentioning that the decrease in the number of cytotoxic T-lymphocytes has not any negative impact on the body as very less amount of cells are being reduced as compared to a huge decrease in the concentration of the infected and free virus cells that can increase the life expectancy of the patient.

SMC VS ISMC VS DISMC VS PID

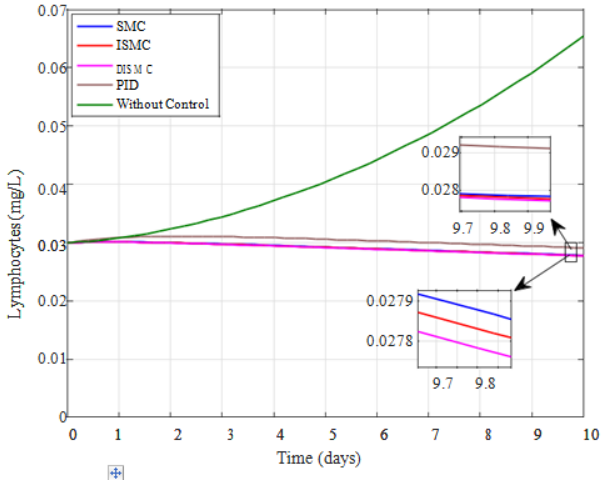

Figure 9: Comparison of Lymphocytes.

Fig.10 describes the control input for the proposed controllers and PID controller. It can be seen that the amount of drug dosage is more in case of DISMC as compared to that shown in SMC and ISMC. The behavior can be explained by the presence of term „t" = e m„t " that clearly shows that high amount of drug m„t" can result in the decrease of infection in healthy cells. Hence, the drug injection is high at the start of the therapy for the proposed controllers and decrease with the passage of time due to successful tracking of healthy, infected and free virus cells to their desired references.

SMC VS ISMC VS DISMC VS PID

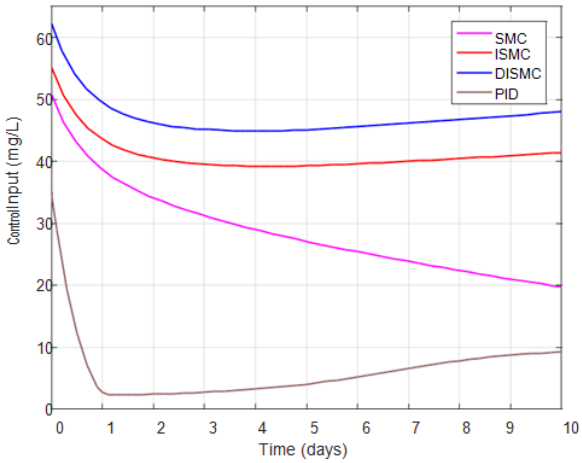

Figure 10: Comparison of Control Inputs.

Fig.11 shows the behavior of infected cells for all the controllers in the presence of Gaussian noise. Here, a Gaussian noise of mean= 0 and variance = 10 6 with sample time = 1 has been added in the infected cells of SMC, ISMC, DISMC and PID controller. The zoomed part in the figure shows that infected cells in case of PID controller are oscillating around the reference line. They lose their tracking ability on the zero reference. On the other hand, the perfect tracking of infected cells in the presence of external disturbance in case of sliding mode controller shows that it is robust and is invariant to external disturbances and parametric uncertainties. The graph of Gaussian noise is shown in Fig.12.

SMC VS ISMC VS DISMC VS PID

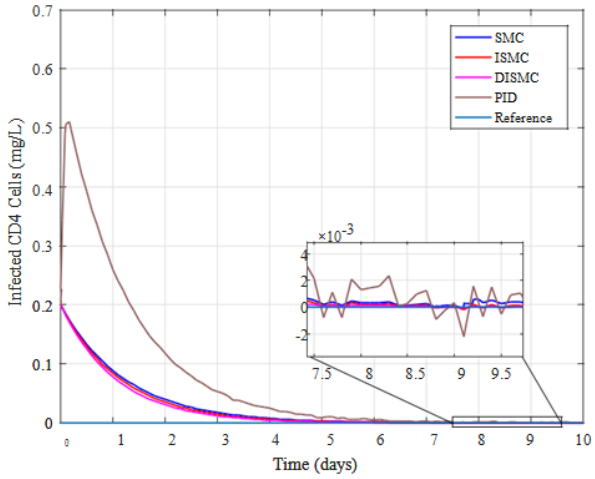

Figure 11: Behavior of Infected CD4 Cells in the presence of Noise.

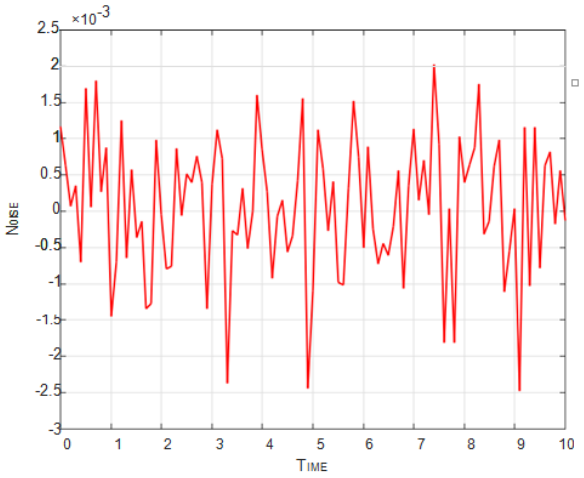

Figure 12: Gaussian Noise.

As clearly seen from the above all figures that PID controller shows poor performance than SMC, ISMC and DISMC. This shows that nonlinear controllers are more efficient as compared to linear PID controller as it works only on linear approximation of the system. The controller neglects the nonlinear terms of the system which is its main disadvantage. On the other hand, nonlinear robust controllers like SMC, ISMC and DISMC can achieve the global stability of the system.

Conclusion

Three nonlinear controllers namely Sliding Mode Con-troller, Integral Sliding Mode Controller and Double Integral Sliding Mode Controller have been designed in this paper for the control of HIV/AIDS under the effect of Antiretroviral drug doses. All three controllers have been designed by using an updated nonlinear four states mathematical model of HIV/AIDS to destroy the maximum number of infected cells and viral load in blood plasma while increasing as many healthy cells as possible. Cytotoxic T-lymphocytes together with drug doses also play an active role for the fast con-vergence of infected cells and free viruses to their desired reference values with steady state errors close to zero. The simulation results of linear PID controller have also been given to know the difference between the performances of linear and proposed nonlinear controllers. The comparison analysis of the results for all three controllers show that the Double Integral Sliding Mode Controller has better performance than Sliding Mode Controller, Integral Sliding Mode Controller and PID controller based on the convergence rate and steady state errors of the states. Although high drug dosage at start of therapy is not recommended for the patients with severe medical conditions but there is actually less risk of patient's drug resistance capability owing to the fact that less time period is required for the drug dosage.

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