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Integral Backstepping and Synergetic Control for Tracking of Infected Cells During Early Antiretroviral Therapy

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ABSTRACT Human Acquired Immune Deficiency Syndrome or Human Immunodeficiency Virus (HIV) Infection is a disease caused by a lentivirus known as the HIV virus. It alters the human immune system making him/her vulnerable to diseases and infections. The susceptibility worsens if the syndrome is not controlled through proper drug injection. In the literature, the researchers have proposed different control methodologies of drug injection so that the infected cells may reach the desired reference value. In this paper, nonlinear control algorithms based on the integral backstepping approach and synergetic control have been proposed to reduce steady-state error for robust tracking of infected helper T-cells to a set reference level for a deterministic model of HIV virus. The model is based on the mass balance of helper T-cells and viral load. System stability analysis has been proved with the help of a suitable Lyapunov-based theory. The viral load has been suppressed to zero. Both the numerical analysis and the simulations have been performed to validate the performance of proposed controllers. The proposed controllers have been compared with each other, with generic backstepping and backstepping embedded with sliding mode control techniques. They have been used to check the effect of efficiency of the drug on the control input. The simulations have been performed on MATLAB/Simulink.

INDEX TERMS Acquired immune deficiency syndrome (AIDS), human immunodeficiency virus (HIV), highly active antiretroviral therapy (HAART), synergetic control, generic backstepping, steady-state error, antiretroviral therapy.

I. INTRODUCTION

Control engineering has played a significant role in control of biomedical systems like optimum drug dose for bacterial infections, automated anaesthetic delivery during surgery, endoscopic surgery, chemotherapy and many more. HIV/AIDS is a contagious disease with a very fast replication cycle of virus. HIV virus mainly attacks the T-lymphocytes which have importance in adaptive immune system because they help in the activation of antiviral immune response. A person is said to have AIDS if count of T-lymphocytes is below 200 cells/mm^3 in the blood plasma [1]. This count is controlled by a natural process named as homeostatic process and is effected by HIV virus. Antiretroviral drugs are used to directly interrupt the life cycle of HIV virus to reduce the viral load and to help people in improving their quality of life.

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Mathematical models of HIV-1/AIDS are not rich in information as it is difficult to understand the immune system response of human body against HIV infection. Due to its nonlinear behavior, HIV antiretroviral drug therapy is a nonlinear control problem when the state of HIV-1 infection is perturbed with the injection of drug. These models are not very well defined like many other systems due to which it is difficult to design a perfect control for drug dosage. It has been observed that a control method which is best for one individual is a total failure for another one.

Based on the growth and concentration of viral load in blood plasma, HIV infection evolves three stages: acute infection, clinical latency, and symptomatic stage [11]. Control techniques have been developed to control HIV infection at these distinct stages. Some researchers have focused on long term non-progressive (LTNP) stage while some researchers focused on acute infection and asymptomatic periods of disease. Much insight about HIV-1 infection and its treatment

can be gained by comparing the results obtained from the patient to the results obtained from the deterministic models. Control techniques have been used to reduce viral load, find the best time to start the therapy and treatment interruptions according to controllability.

Advancements have been made in molecular biology instrumentation in recent years due to which it is quite possible to detect viral load levels in blood plasma with the help of electron microscopy and polymerase chain reaction (PCR) method. Health care schemes have been developed for individual patients to treat them in a way that matches their specific reaction to a disease or infection. These schemes show increasing interest in immunology and virology by providing experimental approach to mathematical models of infectious diseases [7]. Control techniques have been used to design treatment therapies for dynamical models of HIV infection in such a way that the manipulated variable is the drug control and output is the viral load. Control is designed to find a drug regimen and drug administration for reduction of viral load directly or by tracking the infected cells to a level which reduces the viral load below the threshold value, within a specific time-period.

Nonlinear feedback control based on the principle of exact linearization to cancel the nonlinearities present in HIV model has been proposed in [6]. The product of healthy cells and virus particles generates the nonlinear behavior and we can measure virus particles in blood plasma. A control law has been implemented to reduce the effect of nonlinearities in the system model. A nonlinear model predictive control (NMPC) has been used for multi-drug therapy design for HIV infection [7]. An Extended state Kalman filter has been used for state estimation as in NMPC which required the knowledge of state variables but the problem is that all state variables cannot be measured directly.

Synergetic control designed for HIV virus model [2], is an analytic design procedure in which macro-variables and their specifications are defined by the designer according to the control specifications. The number of these macro-variables depends on the number of control inputs to the system. Dynamic behavior of the controlled system can be explained with the assumption that state variables approach to zero exponentially under the control input. Asymptotic global stability of controlled system has been obtained with the help of a suitable Lyapunov candidate function. Synergetic controller is linear approximation of sliding mode controller and thus helps in overcoming the chattering problem [19]. So, the control law obtained with Synergetic control is chattering free [12]. Synergetic control is not only robust but has the advantages of finite time convergence, insensitive to internal and external disturbances and parametric uncertainties [17].

Integral control is among basic components of control in industry for systems having feedback control. This control action helps in making input adjustments faster and accurate by making corrective changes in proportion to the amount of error in input. Main purpose of integral control is to reduce constant steady state error in closed loop feedback systems but in practice it helps in improving the feedback response of controller, reducing the parametric variations and slowly time varying disturbances.

Earlier integral action has been used in industry for linear controllers but recently, nonlinear controllers with integral action have been designed and implemented for industrial use [13]. This control action with adaptation has also been used in order to diminish slowly varying environmental forces [18]. Integral action has been used for position and path tracking problems in quadrotor [14], for control in SEPIC converter [15], for large signal stability of a boost converter [16] and for many other control problems. Integral control is used mostly for tracking based control techniques. Asymptotic tracking usually achieved with integral control means that output approaches to reference value as time approaches to infinity and for that error also approaches to zero. For further knowledge on the domain, the reader is referred to the research papers [20]–[22] and for detailed surveys to [23]–[25].

In this research work, two nonlinear controllers, synergetic control and integral backstepping control [26] have been proposed for HIV infection model. Proposed controllers work by tracking the infected cells to a reference level, so that the drug injection can be terminated due to reduced viral load. Controllers have been designed for tracking and to reduce the steady state error to zero. Based on robustness, stability, and steady state error, the proposed controllers have been compared with each other and with two conventional controllers i.e. generic backstepping and backstepping embedded with sliding mode control.

The paper is organized as follows: The nonlinear model of HIV virus has been explained in Section 2. Section 3.1 contains the design procedure for synergetic controller and the procedure of converting the model of HIV into the strict feedback form has been given in Section 3.2. Integral backstepping controller has been designed and the analysis of proving the asymptotic stability by using Lyapunov based theory has been discussed in Section 3.3. Simulation results have been detailed in Section 4, where a comparison of the proposed controller with generic backstepping controller and backstepping embedded with sliding mode control have also been given. Finally the conclusion has been given in Section 5.

II. DYNAMICAL MODEL OF HIV VIRUS

Mathematical models discussed in the literature for HIV infection which represent the behavior of system states over time, are dynamic in nature. Some of them are stochastic whereas some are deterministic. The model used in this research work describes the precise relationship between system states in the absence of random variations, is deterministic [1], [5], [8], [9]. It consists of first order nonlinear differential equations, given as:

$$\begin{cases} \dot{x}_1 = s - dx_1 - bx_1x_3 \\ \dot{x}_2 = bx_1x_3 - wx_2 \\ \dot{x}_3 = kx_2 - ex_3 - u(t) \end{cases} \tag{1}$$

TABLE 1. Values of parameters.

Parameter	Value
Production Rate of healthy CD4$^+$T-cells (s)	50 mgL^{-1}d^{-1}
Natural death rate of healthy CD4$^+$T-cells (d)	0.05d^{-1}
Infection coefficient (b)	5e^{-1}Lmg^{-1}d^{-1}
Natural death rate of infected cells (w)	0.4 d^{-1}
Number of virus copies produced from infected cells (k)	40 d^{-1}
Natural death rate of free virus (e)	9 d^{-1}
Efficiency of drug (a)	0.4

where x_1, x_2 and x_3 represent the concentration of healthy helper T-cells, infected helper T-cells and virus cells in mg/L in blood plasma. Other system parameters are s, d, w, e, b and k are constants. Parameter s represents the production rate of healthy helper T-cells and its value is taken as 50 mgL^{-1}d^{-1}. Parameters d, w and e represent the natural death rate of healthy helper T-cells, infected helper T-cells and virus cells respectively and their values are taken as 0.05d^{-1}, 0.4 d^{-1} and 9 d^{-1}. Infection coefficient is represented by b and its value is taken as 5e^{-4}Lmg^{-1}d^{-1}. Parameter k represents the growth rate of the viral copies from infected helper T-cells and its value is taken as 40 d^{-1}. System is nonlinear due to the presence of the term bx_1x_3 which represents the infection rate of healthy helper T-cells from virus cells. Reverse Transcriptase Inhibitors (RTIs) are used to reduce the infection rate of healthy cells from free viruses. These drugs interfere with reverse transcriptase enzyme and force the virus to use faulty building blocks for replication due to which virus is not able to change its viral RNA into viral DNA. These drugs are called the backbone of HIV treatment. Protease inhibitors (PIs) are used to reduce the viral copies growth of virus cells from infected cells (represented by kx_2 term in system model eq. (1)) by blocking the protease enzyme of HIV. These drugs are used during budding which is the last stage of HIV life cycle.

The concentration of Healthy cells in blood plasma can be increased indirectly by reducing the infection rate bx_1x_3 with the help of medical drug injection, which will in turn reduce the concentration of virus cells in the blood plasma. Virus population can also be reduced by reducing the term kx_2 and this will also increase the population of the healthy cells indirectly. Integral backstepping controller has been designed in a way to reduce the virus population by reducing the viral copies growth from infected cells and to make the system stable with zero steady state error.

III. CONTROL DESIGN

Backstepping control technique is a recursive method, used to design nonlinear controllers for the systems in strict feedback form. With the help of this technique, cancellation of useful nonlinearities can be avoided. This technique helps in investigating the stability and determining physical properties of the systems [3], [10]. In this control design, nonlinear generic backstepping controller has been modified by introducing the integral term in it so that the infected cells may be tracked to their reference level with zero steady state error. The proposed control technique can be used for continuous time, input-affine nonlinear system in strict feedback form [4]. Synergetic control has been designed in [2] for treatment of HIV by reducing the infection rate of healthy T-cells from free virus cells, with drug injection.

A. SYNERGETIC CONTROL DESIGN

This subsection contains the design of synergetic controller to reduce the viral load by reducing the growth of the viral copies from infected cells in blood plasma. Only one macro-variable will be defined in design procedure as the mathematical model of HIV virus given by eq. (1) has only one control input. This macro-variable is defined as:

$$\sigma = C_1(x_1 - x_{1ref}) + C_2(x_2 - x_{2ref}) + C_3(x_3 - x_{3ref}) \tag{2}$$

where C_1, C_2 and C_3 are real positive constants. Purpose of this control design is to track the state variables at their reference values with an exponential rate under the control input. For this, dynamic evolution is presented as:

$$T\dot{\sigma} + \sigma = 0 \tag{3}$$

where T represents the convergence rate of state variables to $\sigma = 0$. Its value should be greater than zero to satisfy the eq. (3). By taking the time derivative of eq. (2), we get

$$\dot{\sigma} = C_1\dot{x}_1 + C_2\dot{x}_2 + C_3\dot{x}_3 \tag{4}$$

because our desired reference levels x_{1ref}, x_{2ref} and x_{3ref} are constant. By placing the values of $\dot{x}_1$, $\dot{x}_2$ and $\dot{x}_3$ from system of equations (1) into eq. (4), we get

$$\begin{aligned}\dot{\sigma} = {} & C_1(s - dx_1 - bx_1x_3) + C_2(bx_1x_3 - wx_2) \\ & + C_3(kx_2 - ex_3 - u(t))\end{aligned} \tag{5}$$

Then using the eq. (2) and eq. (5) in eq. (3) and solving for control input $u(t)$, the control law is obtained as:

$$\begin{aligned}u(t) = {} & \frac{1}{TC_3}\left(T(C_1\dot{x}_1 + C_2\dot{x}_2) + TC_3(kx_2 - ex_3)\right) \\ & + \frac{1}{TC_3}\left(C_1(x_1 - x_{1ref}) + C_2(x_2 - x_{2ref})\right) \\ & + \frac{1}{T}\left(x_3 - x_{3ref}\right)\end{aligned} \tag{6}$$

To prove the asymptotic stability of the system, Lyapunov candidate function can be taken as:

$$V = \frac{1}{2}\sigma^2 \tag{7}$$

By taking the time derivative of this Lyapunov candidate function we get:

$$\dot{V} = \sigma\dot{\sigma} \tag{8}$$

From eq. (3), we can write

$$\dot{\sigma} = -\sigma/T \tag{9}$$

so, eq. (8) takes the form

$$\dot{V} = -\frac{1}{T}\sigma^2 \tag{10}$$

Thus the dynamical system is stable at desired equilibrium point and all states converge to the equilibrium point as time goes to infinity.

B. STRICT FEEDBACK FORM OF HIV SYSTEM

Mathematical model of HIV eq. (1) can be written in following general form as:

$$\begin{aligned} \dot{x} &= f(x) + g(x)u(t) \\ y &= h(x) \end{aligned} \tag{11}$$

where state vector is represented by x, y represents output of the system and control input is represented by $u(t)$. Control is designed to reduce the viral load x_3 with the help of drug injection. To apply integral backstepping, the model is required to be in strict feedback form. So, the model is first converted into the said form with the help of diffeomorphism process. For this we take

$$y = h(x) = x_3 \tag{12}$$

By taking the time derivative of eq. (12), we get:

$$\dot{y} = \dot{h}(x) = \dot{x}_3 \tag{13}$$

By placing the value of $\dot{x}_3$ from system (1) in eq. (13), we get:

$$\dot{h}(x) = kx_2 - ex_3 - u(t) \tag{14}$$

Relative degree of the system is one as eq. (14) has control input $u(t)$. For diffeomorphism we take:

$$\eta_1 = x_1 + x_2 \tag{15}$$

$$\eta_2 = x_2 \tag{16}$$

$$\zeta = x_3 \tag{17}$$

By taking the time derivatives of η_1, η_2 and ζ, we get:

$$\dot{\eta}_1 = \dot{x}_1 + \dot{x}_2 \tag{18}$$

$$\dot{\eta}_2 = \dot{x}_2 \tag{19}$$

$$\dot{\zeta} = \dot{x}_3 \tag{20}$$

Now by taking the values of $\dot{x}_1$, $\dot{x}_2$ and $\dot{x}_3$ from system of equations (1) and placing them in eq. (18), eq. (19) and eq.(20), we get our desired strict feedback form as follows:

$$\begin{cases} \dot{\eta}_1 = s - d\eta_1 + (d - w)\eta_2 \\ \dot{\eta}_2 = b\zeta(\eta_1 - \eta_2) - w\eta_2 \\ \dot{\zeta} = k\eta_2 - e\zeta - u(t) \end{cases} \tag{21}$$

C. INTEGRAL BACKSTEPPING CONTROL DESIGN

For this type of control design, the first step is to set a reference value for the infected cells. To track the infected cells on desired trajectory, we define the error equation given as

$$\varepsilon_1 = \eta_2 - \eta_{2ref} \tag{22}$$

where ε_1 is the error between infected cells η_2 and the desired reference point for infected cells η_{2ref}. Taking the time derivative of eq. (22), gives the dynamics of error ε_1 as follows:

$$\dot{\varepsilon}_1 = \dot{\eta}_2 - \dot{\eta}_{2ref} \tag{23}$$

By putting the value of $\dot{\eta}_2$ from system of equations (21), we get

$$\dot{\varepsilon}_1 = b\zeta(\eta_1 - \eta_2) - w\eta_2 - \dot{\eta}_{2ref} \tag{24}$$

Integral action (ψ) is added into error term ε_1 to get the error e_1 as:

$$e_1 = \varepsilon_1 + \psi \tag{25}$$

where ψ is given as:

$$\psi = \int_0^t (\eta_2 - \eta_{2ref})dt \tag{26}$$

The error ε_1 must approach to zero exponentially to assure the convergence of η_2 to η_{2ref}. For this purpose, a positive definite Lyapunov candidate function is taken as:

$$V_1 = \frac{1}{2}{\varepsilon_1}^2 + \frac{\kappa}{2}\psi^2 \tag{27}$$

where κ is a positive definite number. For asymptotic stability, derivative of V_1 must be negative definite. By taking the time derivative of eq. (27), we get:

$$\dot{V}_1 = \varepsilon_1\dot{\varepsilon}_1 + \kappa\psi\dot{\psi} \tag{28}$$

By taking the time derivative of eq. (26), we get:

$$\dot{\psi} = \eta_2 - \eta_{2ref} = \varepsilon_1 \tag{29}$$

By putting the value of $\dot{\varepsilon}_1$ and $\dot{\psi}$ in eq. (28), we get:

$$\dot{V}_1 = \varepsilon_1(b\zeta(\eta_1 - \eta_2) - w\eta_2 - \dot{\eta}_{2ref}) + \kappa\varepsilon_1\psi \tag{30}$$

Simplifying the eq. (30), we get:

$$\dot{V}_1 = \varepsilon_1(b\zeta(\eta_1 - \eta_2) - w\eta_2 - \dot{\eta}_{2ref} + \kappa\psi) \tag{31}$$

For $\dot{V}_1$ to be negative definite, let

$$(b\zeta(\eta_1 - \eta_2) - w\eta_2 - \dot{\eta}_{2ref} + \kappa\psi) = -c_1\varepsilon_1 \tag{32}$$

so that $\dot{V}_1$ becomes

$$\dot{V}_1 = -c_1{\varepsilon_1}^2 \tag{33}$$

where c_1 is control design parameter. Virtual control for viral load, also called desired trajectory (reference value) for virus load, is derived by using eq. (32) as.

$$\zeta = \frac{1}{b\eta_1 - b\eta_2}(w\eta_2 + \dot{\eta}_{2ref} - c_1\varepsilon_1 - \kappa\psi) \tag{34}$$

Now in order to include the next state in the controller (as we normally do in backstepping controller design), we take the virtual control ζ as $\zeta = \alpha$. So, the desired reference for viral load is given by:

$$\alpha = \frac{1}{b\eta_1 - b\eta_2}(w\eta_2 + \dot{\eta}_{2ref} - c_1\varepsilon_1 - \kappa\psi) \tag{35}$$

This α is that value of virtual control ζ which actually stabilizes the dynamics of η_1 and η_2.

In next step, we need to design a controller which can stabilize the whole system (21). The virtual control α is used

as reference point for the viral load and for tracking; the error equation may be written as

$$\varepsilon_2 = \zeta - \alpha \tag{36}$$

Updating the eq. (24) with ζ value from eq. (36), we get:

$$\dot{\varepsilon}_1 = b(\varepsilon_2 + \alpha)(\eta_1 - \eta_2) - w\eta_2 - \dot{\eta}_{2ref} \tag{37}$$

By placing the value of α from eq. (35) into eq. (37) and after simplification, we get:

$$\dot{\varepsilon}_1 = -c_1\varepsilon_1 + b\varepsilon_2(\eta_1 - \eta_2) - \kappa\psi \tag{38}$$

By placing the value of $\dot{\varepsilon}_1$ from eq. (38) into eq. (28), $\dot{V}_1$ will become

$$\dot{V}_1 = -c_1{\varepsilon_1}^2 + b\varepsilon_1\varepsilon_2(\eta_1 - \eta_2) \tag{39}$$

For $\dot{V}_1$ to be negative definite, both terms on R.H.S of eq. (39) must be negative definite. First term is negative definite but we are not sure about second term.

In the next step we will take the time derivative of eq. (36) to get:

$$\dot{\varepsilon}_2 = \dot{\zeta} - \dot{\alpha} \tag{40}$$

$\dot{\alpha}$ is calculated by taking the time derivative of eq. (35) as

$$\dot{\alpha} = \frac{1}{b(\eta_1 - \eta_2)^2}\left[\dot{\gamma}(\eta_1 - \eta_2) - \gamma(\dot{\eta}_1 - \dot{\eta}_2)\right] \tag{41}$$

where

$$\gamma = w\eta_2 + \dot{\eta}_{2ref} - c_1\varepsilon_1 - \kappa\psi \tag{42}$$

By placing the value of $\dot{\zeta}$ in eq. (40), we get:

$$\dot{\varepsilon}_2 = k\eta_2 - e\zeta - u(t) - \dot{\alpha} \tag{43}$$

Now there is the need of a composite Lyapunov candidate function V_2, to ensure the convergence of both ε_1 and ε_2 to zero. This function can be taken as:

$$V_2 = V_1 + \frac{1}{2}\varepsilon_2^2 \tag{44}$$

For convergence of both errors ε_1 and ε_2 to zero, $\dot{V}_2$ must be negative definite. This will ensure that η_2 will track η_{2ref} and ζ will track α. By taking the time derivative of eq. (44), we get:

$$\dot{V}_2 = \dot{V}_1 + \varepsilon_2\dot{\varepsilon}_2 \tag{45}$$

Putting the value of $\dot{V}_1$ from eq. (39), we get:

$$\dot{V}_2 = -c_1{\varepsilon_1}^2 + b\varepsilon_1\varepsilon_2(\eta_1 - \eta_2) + \varepsilon_2\dot{\varepsilon}_2 \tag{46}$$

Re-arranging the above eq. (46), we can write

$$\dot{V}_2 = -c_1{\varepsilon_1}^2 + \varepsilon_2(b\varepsilon_1(\eta_1 - \eta_2) + \dot{\varepsilon}_2) \tag{47}$$

For $\dot{V}_2$ to be negative definite, $\dot{\varepsilon}_2$ in eq. (47) may be taken as

$$\dot{\varepsilon}_2 = -c_2\varepsilon_2 - b\varepsilon_1(\eta_1 - \eta_2) \tag{48}$$

So that $\dot{V}_2$ will become

$$\dot{V}_2 = -c_1{\varepsilon_1}^2 - c_2{\varepsilon_2}^2 \tag{49}$$

By comparing eq. (43) and eq. (48), control law $u(t)$ can be obtained as:

$$u(t) = k\eta_2 - e\zeta - \dot{\alpha} + c_2\varepsilon_2 + b\varepsilon_1(\eta_1 - \eta_2) \tag{50}$$

All the errors must approach to zero for tracking and exponential stability of system states. Control law with the efficiency of drug will be as follows:

$$u(t) = (1 - a)k\eta_2 - e\zeta - \dot{\alpha} + c_2\varepsilon_2 + b\varepsilon_1(\eta_1 - \eta_2) \tag{51}$$

where a is greater than or equal to zero but less than or equal to 1. As c_1 and c_2 are the control design parameters and have positive values, so $\dot{V}_2$ will always be negative definite and system states will be asymptotically stable at the desired equilibrium point.

The generic/simple backstepping controller would not contain the term $b\varepsilon_1(\eta_1 - \eta_2)$, so we have $u(t)$ for this case as:

$$u(t) = (1 - a)k\eta_2 - e\zeta - \dot{\alpha} + c_2\varepsilon_2 \tag{52}$$

Whereas backstepping embedded with SMC with signum function replaced by saturation function would have the term $-c_3\ sat(S/\beta)$, so that the expression for this case would be:

$$u(t) = k\eta_2 - e\zeta - \dot{\alpha} + c_2\varepsilon_2 - c_3 sat(S/\beta) \tag{53}$$

where c_3 is the switching gain, β represents the thickness of boundary layer and S is the sliding surface.

IV. SIMULATIONS & RESULTS

Simulations have been performed on MATLAB/Simulink for the proposed controllers given by eqs. (50) and (51) for primary infection stage of HIV virus for sampling period of one week. Initial conditions for healthy helper T-cells, infected helper T-cells and virus load are 350 mgL^{-1}, 125 mgL^{-1} and 75 mgL^{-1} respectively [1]. The values of the design parameter for the proposed controller are selected on hit and trial basis as there is no systematic method to design these values. For the designed control parameters, system should be stable and system states must have a positive value and an acceptable and realistic behavior. So, we select those values at which we get our desired response.

This section is divided into five subsections. First subsection analyzes and compares the performance of proposed controllers with each other. In subsection 4.2, integral backstepping controller has been compared with backstepping embedded with sliding mode controller (53), while the subsection 4.3 contains comparison of integral backstepping controller with generic backstepping controller (52). Proposed synergetic controller has been compared with generic backstepping controller and backstepping embedded with sliding mode controller (53) in subsections 4.4 and 4.5 respectively.

A. SIMULATION RESULTS FOR INTEGRAL BACKSTEPPING CONTROLLER WITH SYNERGETIC CONTROLLER

Values of design parameters c_1, c_2 and κ are taken as 0.8, 1 and 0.8, respectively, for integral backstepping controller whereas, for synergetic controller C_1, C_2, C_3 and T are taken

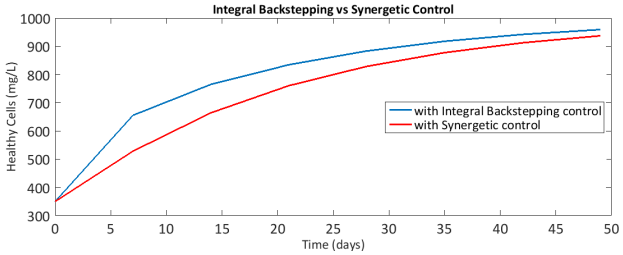

FIGURE 1. Behavior of healthy cells.

as 0.5, 0.5, 100 and 1 respectively. Behavior of healthy T-cells for the proposed controllers is shown in Fig.1 which shows the rapid increase in concentration of healthy cells in blood plasma. Fig.1 shows that the concentration of the healthy cells in blood plasma grows faster by using integral backstepping controller (52) as compared to synergetic controller. Tracking time of infected cells to their reference level is almost same by both the controllers (shown in Fig.2). The advantage of integral backstepping controller is zero steady state error which is not negligible with synergetic controller (shown by zoomed portion in Fig.2).

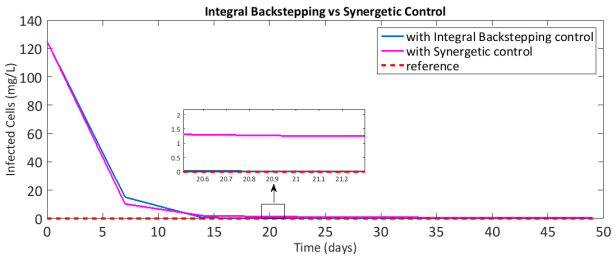

FIGURE 2. Tracking of infected cells.

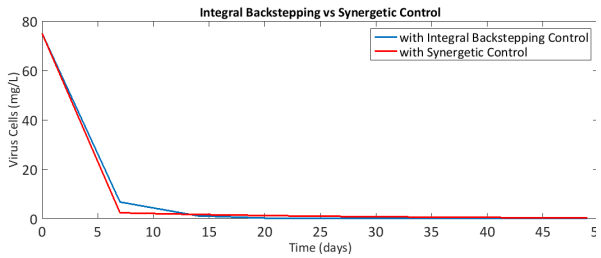

FIGURE 3. Behavior of virus cells.

In response to this tracking, viral load also approaches to its minimum value i.e. viral load becomes zero, as shown in Fig.3. Behavior of virus cells (Fig.3) shows the sudden drop in viral load with synergetic controller, but this viral load reaches to exact zero value after about five weeks of therapy (shown by red line in Fig.3). With integral backstepping controller virus cells show a more realistic behavior and viral load becomes zero after two weeks of medication (shown by blue line in Fig.3).

Behavior of control input (drug injection) with and without efficiency of drug, for the proposed controllers is shown in Fig.4. This comparison shows that without including the

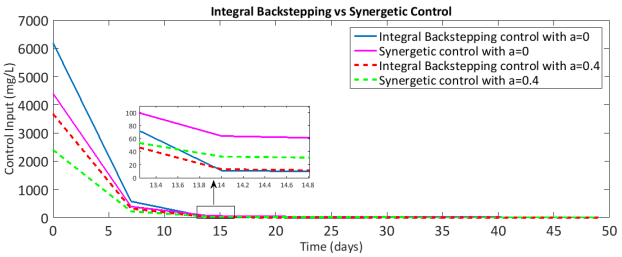

FIGURE 4. Control Comparison under varying efficiency of drug.

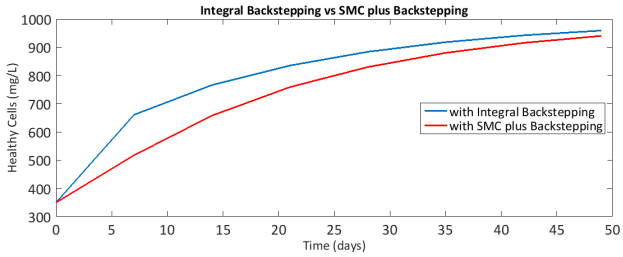

FIGURE 5. Comparison of behavior of healthy cells.

efficiency of used drug in control law, drug injection is high at start of therapy (shown by blue line in Fig.4) whereas, this drug dose is reduced to about half when efficiency of drug is incorporated in the control law (shown by red dotted line in Fig.4).

It has been observed that drug injection is terminated as soon as infected cells track their reference value. It has also been observed that by using integral backstepping controller the drug injection is high at start of therapy as compared to synergetic controller but drug injection is terminated earlier by using integral backstepping controller. Simulation results also show that efficiency of drug has no effect on concentration of healthy cells, infected cells and viral load.

B. COMPARISON OF INTEGRAL BACKSTEPPING WITH BACKSTEPPING EMBEDDED WITH SMC

Comparison behavior of healthy cells for the said controllers (shown in Fig.5) shows that healthy cells approach to their maximum level faster with integral backstepping controller. It has been observed that for tracking of infected cells to their reference value, both controllers (integral backstepping and (53) are good but integral backstepping controller has the advantage of zero steady state error as shown in Fig.6. Suppression of viral load to zero is shown in Fig.7 for the said controllers. Viral load approaches zero in almost two weeks of medication. Drug injection is also terminated after two weeks of medication (shown in Fig.8). There is just a slight difference in drug dose for both controllers which is shown in zoomed portion of Fig.8.

C. COMPARISON OF INTEGRAL BACKSTEPPING WITH GENERIC BACKSTEPPING CONTROL

Simulation results show that healthy T-cells reach their maximum value faster by using integral backstepping controller as

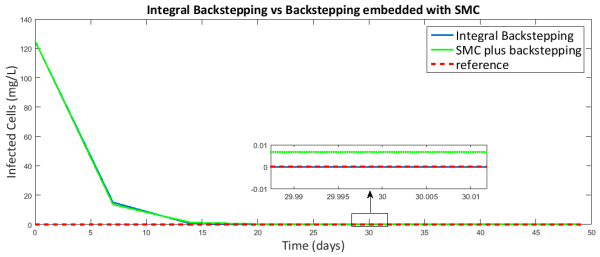

FIGURE 6. Comparison of tracking of infected cells.

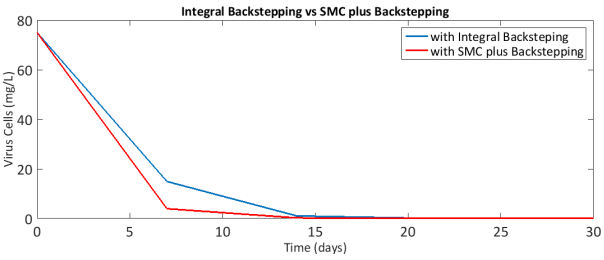

FIGURE 7. Comparison of behavior of virus cells.

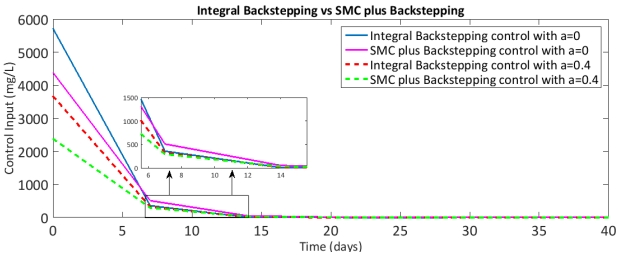

FIGURE 8. Control comparison under varying efficiency of drug.

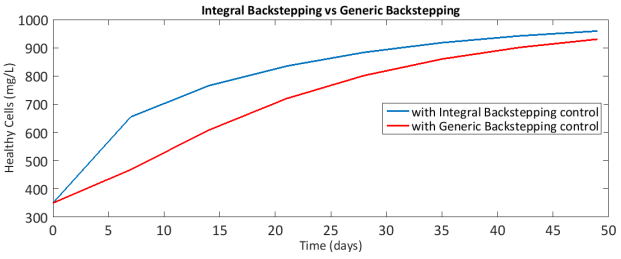

FIGURE 9. Comparison of behavior of healthy cells.

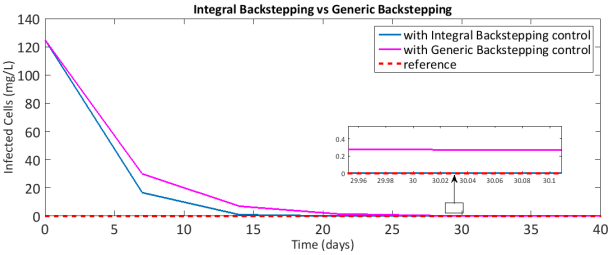

FIGURE 10. Comparison of tracking of infected cells.

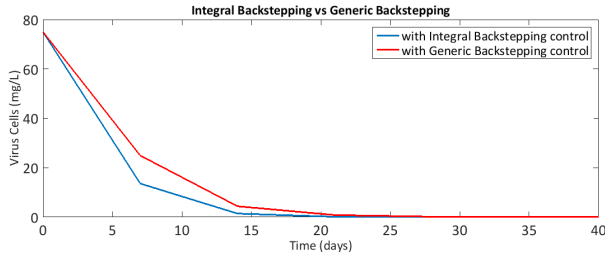

FIGURE 11. Comparison of behavior of virus cells.

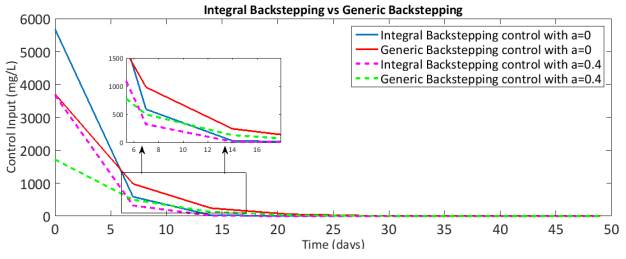

FIGURE 12. Control comparison under varying efficiency of drug.

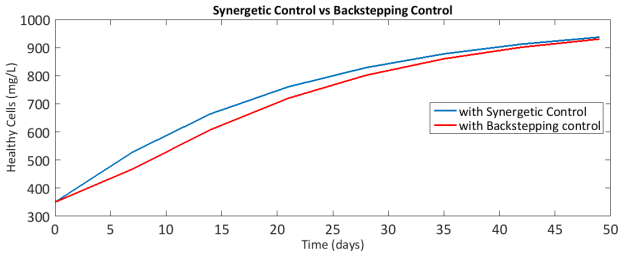

FIGURE 13. Comparison of behavior of healthy cells.

compared to (52) (as shown in Fig.9). Fig.10 shows the tracking of infected cells to the reference value. Steady state error is also reduced to zero with integral backstepping controller as shown by zoomed portion of Fig.10 whereas this error is almost 0.3 with generic backstepping controller (52).

Comparison behavior of virus cells (shown in Fig.11) shows that viral load approaches zero faster by using integral backstepping controller (shown by blue line in Fig.11). Fig.12 shows the comparison of drug injection for said controllers. Simulation result shows that therapy time is lesser by using integral backstepping controller whereas reduced drug injection is observed at start of therapy with (52) (shown by red and green line in Fig.12).

D. COMPARISON OF SYNERGETIC CONTROL WITH BACKSTEPPING CONTROL

Fig.13 shows the comparison behavior of healthy cells for synergetic controller and backstepping controller (52). This comparison shows the good tracking of synergetic controller because healthy cells reach to their maximum count faster with synergetic controller. Tracking behavior of infected cells for the said controllers is shown in Fig.14, which shows that tracking is good with synergetic controller but has the disadvantage of non-zero steady state error.

With backstepping controller steady state error is zero for that time period (shown by zoomed portion in Fig.14).

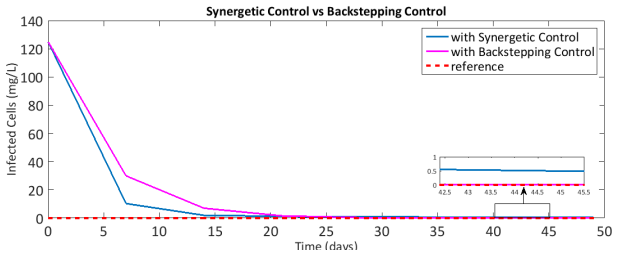

FIGURE 14. Comparison of tracking of infected cells.

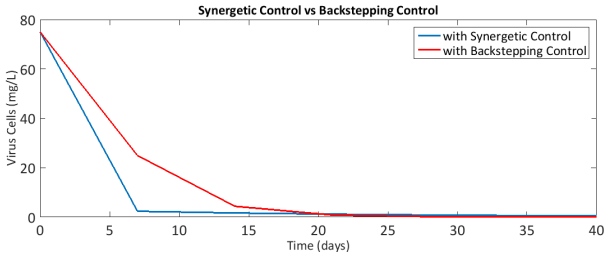

FIGURE 15. Comparison of behavior of virus cells.

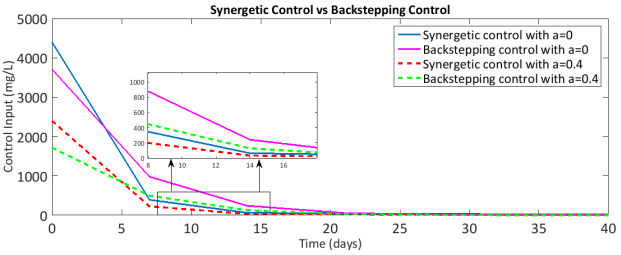

FIGURE 16. Control Comparison under varying efficiency of drug.

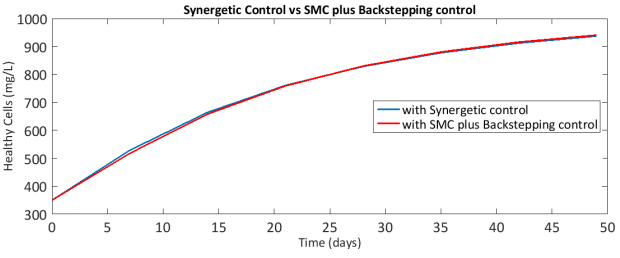

FIGURE 17. Comparison of behavior of healthy cells.

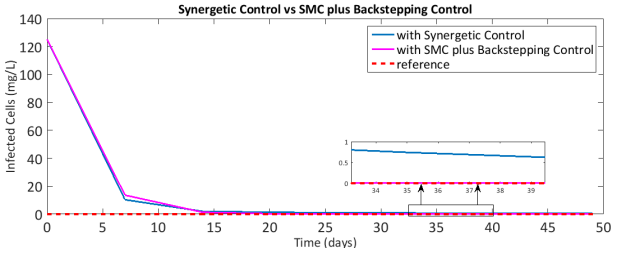

FIGURE 18. Comparison of tracking of infected cells.

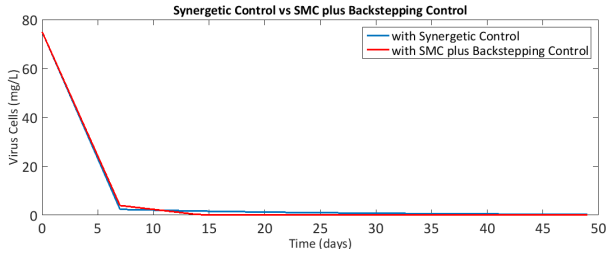

FIGURE 19. Comparison of behavior of virus cells.

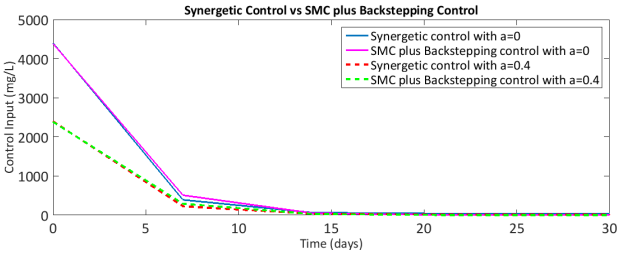

FIGURE 20. Control comparison under varying efficiency of drug.

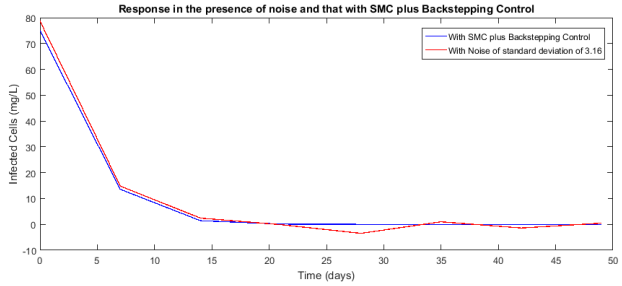

FIGURE 21. Comparison of response with noise vs controlled one.

Fig.15 shows the sudden drop in viral load with synergetic controller but viral load becomes zero after about four weeks of therapy. Drug injection is terminated earlier with synergetic controller although the drug dose is high at start of therapy as shown in Fig.16.

E. COMPARISON OF SYNERGETIC CONTROL WITH BACKSTEPPING EMBEDDED WITH SMC

Comparison behavior of healthy cells for the said controllers show that healthy cells approach to their maximum level at same time with the said controllers (shown in Fig.17). Fig.18 shows that both controllers are robust to track the infected cells to their reference level but (53) has the advantage of lesser steady state error, which is not negligible with synergetic controller.

Behavior of viral load is shown in Fig.19 which shows that viral load approaches to zero at almost the same time with both controllers. Drug injection at the start of therapy and drug termination time for therapy is also same for both controllers, as shown in Fig.20.

The zero mean noise with a standard deviation of 3.16 has been added in infected cells and the results have been presented in Fig.21. The response of the controller is very nice in this case as well.

V. CONCLUSION

In this paper, two nonlinear controllers based on integral backstepping technique and synergetic control techniques have been proposed for the suppression of viral load for HIV infection during primary infection stage. For this purpose, control laws have been designed in such a way that infected T-cells track the reference value and drug injection is terminated as soon as viral load approaches to zero. Proposed controllers have been compared with each other for tracking, zero steady state error and for lesser therapy time. They have also been compared with generic backstepping and backstepping embedded with sliding mode control to meet the same objectives.

The performance of the integral backstepping controller outclassed the conventional generic backstepping controller (52), synergetic controller and backstepping embedded with sliding mode controller (53) for reference tracking and for zero steady state error. Drug dosage is high at start of therapy with integral backstepping controller which is not recommended for patients with poor medical health. On the other hand, there is the reduced risk of patient's drug resistance capability and lesser time period for drug injection with the proposed controller. The work can be further extended by implementing the proposed controller for advanced stages of HIV infection and its experimental applications on real platforms.

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