Lyapunov based nonlinear controllers for the treatment of HIV/AIDS

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Abstract

Human Immunodeficiency Virus (HIV) is a form of virus responsible for destroying or weakening the immune system and causes Acquired Immune Deficiency Syndrome (AIDS). Immune system finds it difficult to fight against life threatening infections and diseases after the attack of this virus. Researchers have proposed many control algorithms of drug injection under antiretroviral therapy for the treatment of HIV/AIDS. In this paper, an updated mathematical nonlinear model of HIV/AIDS has been considered and four Lyapunov based nonlinear controllers namely; Synergetic, Generic Backstepping, Integral Backstepping and Lyapunov Redesign controllers have been designed. The main purpose of proposing the controllers is to regulate the amount of drug, so that the cells may track their desired reference value. Antiretroviral drug doses together with antigen- specific cytotoxic T-lymphocytes play an active role to eradicate HIV/AIDS by destroying infected CD4 cells and free virus and increasing maximum number of uninfected CD4 cells to an adequate level. The proposed nonlinear controllers can reduce maximum amount of steady state error and have fast convergence time. Lyapunov based theory has been used for the analysis of system global stability. Proposed controllers have been simulated under MATLAB/Simulink and detailed comparative analysis of these controllers has been given to study their behavior.

Keywords: Terms-HIV/AIDS, Drug doses, Synergetic control, Integral backstepping, Backstepping, Lyapunov redesign control, Nonlinear control

Introduction

Human Immunodeficiency Virus (HIV) is a deadly disease that badly affects the T-helper cells or white blood cells in the immune system and is the main cause of Acquired Immune Deficiency Syndrome (AIDS) [1]. Immune system is the defense or protection system of a human body that is made up of proteins, organs, tissues and cells which play a major role for its regulation [2]. After attacking the white blood cells in the immune system, HIV replicates itself, decreases the number of healthy cells below a certain limit and makes the immune system vulnerable to life threatening infections and cancers [1,3]. The virus is mainly caused by blood transfusion, tissue transplant, semen and vaginal breast milk [3,4].

After acute infection and clinical latency, AIDS is the third or worst stage of HIV which occurs if CD4+T lymphocytes or white blood cells fall below 200 cells/mm3 [5]. Even if CD4+T lymphocytes rise above 200 cells/mm3, that person will still be considered to have AIDS which means that there is no cure for this disease, but it can be controlled by eradicating the large number of infected cells through medication using certain automated control techniques [1].

One of the most common type of treatment of HIV/AIDS is antiretroviral therapy in which drug doses are being used to minimize the rapidly growing infected cells. Many control techniques have been applied for the control of this disease, but uninfected or healthy cells are usually being killed at the same time which is the major drawback. Nonlinear controllers are efficient for dealing with uncertain parameters of the system that have been ignored in the linear control techniques and are helpful to obtain fast convergence of states to their desired references and improve the steady state accuracy.

Many mathematical models have been considered to analyze the dynamic behavior of HIV/AIDS [6-9]. Optimal control is the most common control technique that has been applied on different models of HIV/AIDS for reduction of viral load in blood plasma. Lyapunov function for the control of HIV and stability analysis of HIV model have also been discussed in the literature. HIV completes its life cycle in different stages and the drugs used to directly attack the virus cells and interrupt the life cycle of virus at different stages are known as anti-retroviral drugs. These drugs are used in a combination of two or three drugs to target the specific stage of HIV virus as each drug has a specific action and belongs to a specific class. Combination of drugs is known as HIV regimen and may contain three drugs from at least two different classes of drugs. The various classes/types of drugs include protease inhibitors, entry inhibitors, fusion inhibitors, integrase inhibitors, pharmacokinetic enhancers, nucleoside reverse transcriptase inhibitors and Non-nucleoside reverse transcriptase inhibitors. The drugs help in stopping the replication cycle of virus, reduces infection of healthy cells from free virus and increase the effectiveness of drugs to suppress the HIV virus below detectable limits. The drugs are used on daily basis to achieve the goal of reducing HIV drug resistance and increase the patients adherence to drugs.

Synergetic control is a robust and chattering free technique, which has finite time convergence, ensures global asymptotic stability, is insensitive to internal and external disturbances and parametric uncertainties. It is a linear approximation of sliding mode control technique which has been applied for stabilizing Medium Voltage DC (MVDC) micro-grids. Backstepping is a recursive control method based on Lyapunov stability theory which designs controller for stabilizing each sub-system and step back from each sub system recursively, for finding the external control input. This technique has been applied for MPPT in PV system. The addition of integral action in Generic Backstepping makes it Integral Backstepping controller which reduces steady state error more as compared to that reduced by Backstepping controller. The controller also improves feedback response and reduces parametric variations. Integral Backstepping control technique has been applied for MPPT of PV system with Buck-boast converter and for the control of web winding system. Lyapunov Redesign is another nonlinear technique used for the controller design and has a simple structure according to which the states of the system reach the equilibrium point if the energy of the system dissipates along the trajectory of the system thus ensuring the asymptotic stability of the system.

In this paper, five nonlinear controllers have been proposed namely Synergetic, Backstepping, Integral Backstepping, and Lyapunov Redesign controllers for minimizing the infected cells and free viruses while maintaining as many healthy cells as possible. Synergetic controller has been designed to track healthy cells, infected cells and free virus to their desired reference values while Backstepping, Integral Backstepping and Lyapunov Redesign controllers have been designed to track healthy and infected cells to their reference values.

The paper has following subdivisions: Section II presents the nonlinear mathematical model of HIV/AIDS. Design pro-cedure of Synergetic, Integral Backstepping, and Lyapunov Redesign controllers has been given in Section III. Description of simulation results is given in Section IV and conclusion has been highlighted in Section V.

Mathematical Model

This paper considers four states mathematical model which has been proposed by Nowak and Bangham. The non-linear of linear model represents the dynamic behavior of HIV/AIDS under the effect of antiretroviral therapy. Nonlinear and other control techniques have been applied on many three states mathematical models of HIV, but these models lack the immune response of the human body in which major role is played by antigen-specific cytotoxic T-lymphocytes. These cells play a defensive role together with the drug dose by destroying free virus and infected cells in a short time span. The model considered in this paper consists of four states first order nonlinear differential equations namely healthy CD4 cells or uninfected cells, infected CD4 cells, free virus and HIV-antigen specific cytotoxic T-lymphocytes as follows.

Where states x1, x2, x3 and x4 represent the concentration of healthy CD4 cells, infected CD4 cells, free virus and antigen-specific cytotoxic T-lymphocytes in mg/L. The system parameters or constants are represented as the first parameter of eq. shows that number of healthy CD4 cells can be reproduced to a fixed rate, but this reproduction rate will decrease after the attack of virus produced by other CD4 cells namely - Dx1. The reproduction rate further decreases by the term – β x1 x3 after those cells interact with free virus.

The number of infected cells depends upon the total number of cells in the body. So, total number of infected cells are directly related to total number of healthy cells in the body by factor β represented by β x1 x3 in eq. The infected cells killed by cytotoxic T-lymphocytes are represented by term Px2 x4 whereas infected cells that are killed in the end are represented by the term Ax2.

Kx2 term in eq. represents the rate of production of free virus. So the number of free virus increases with the increase in the number of infected cells. The destruction of free virus by cytotoxic T-lymphocytes is represented by term Ux3.

The natural death of cytotoxic T-lymphocytes is represented by bx4 in eq. The production of cytotoxic T-lymphocytes is represented by Cx2, x4 and is dependent on the antigenic characteristics of virus and infected cells.

Controller Design

By using value of α from we obtain

Firstly, we define an error E1 between x2 and x2ref for tracking the infected cells to their reference value as.

Simulation Results

This section describes the simulation results of four nonlinear controllers namely Synergetic, Generic Backstepping, Integral Backstepping, Lyapunov Redesign Controller and one linear PID controller. Comparison of all controllers has also been discussed. The simulations have been performed by using MATLAB/Simulink with following parameters and initial conditions.

p and c are taken in Lmg-1d-1 whereas the values of d, a, b, u and k are taken in d-1 **(Figure 1)**.

For convergence of e1 and e2 to their respective references, we define positive definite Lyapunov candidate function V as:

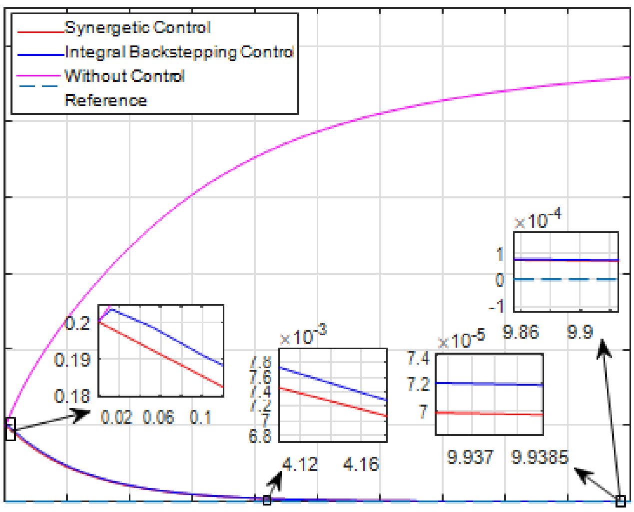

Figure 1: Comparison of Infected CD4 Cells.

Although there is a small difference between the results of 10 both the controllers, but Synergetic controller shows close to zero steady state error as compared to Integral Backstepping 8 controller. Moreover, Integral Backstepping controller shows slow convergence as compared to Synergetic controller shows **(Figure 2,3 and 4).**

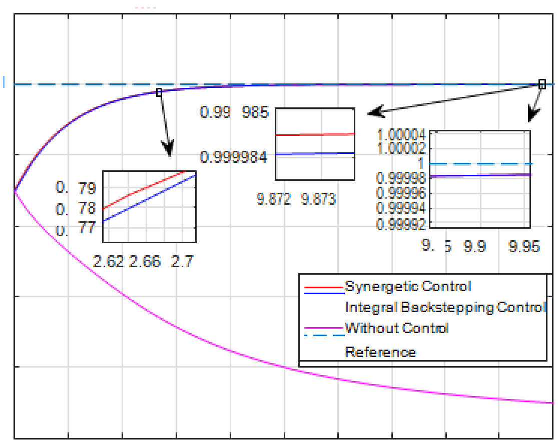

Figure 2: Comparison of Uninfected CD4 Cells.

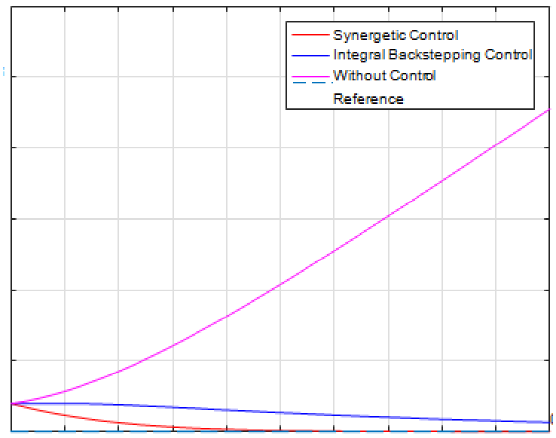

Figure 3: Uninfected CD4 Cells with Different Values of Initial Condition for Synergetic Control.

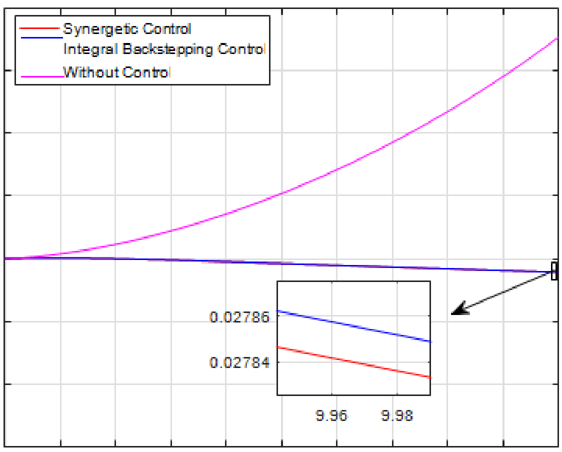

Figure 4: Comparison of Free Virus.

We can see in that cytotoxic T-lymphocytes for Synergetic controller have small terminal value as compared to that for Integral Backstepping controller at final time. The main reason for this behavior is that the infected cells and free virus fr Synergetic controller show fast convergence to their desired reference, achieve close to zero steady state error

and healthy cells on the other hand increase to an adequate level. So, more number of cytotoxic T-lymphocytes will be used along with the application of drug in case of Synergetic Controller as compared to those used in Integral Backstepping controller.

shows that the infected cells converge to zero faster in case of Backstepping controller as compared to Integral Backstepping controller. But steady state error in case of Backstepping controller is more as compared to that in Integral Backstepping and Synergetic controllers. So more infected cells retained at the end of time by applying Backstepping controller as compared to other two controllers.

Conclusion

Four nonlinear controllers namely Synergetic, Integral Backstepping, Backstepping, and Lyapunov Redesign controllers have been designed for the treatment of HIV/AIDS. They have been designed from four states nonlinear model of HIV/AIDS to destroy the maximum number of infected cells and viral load and increase the healthy CD4 cells to an adequate level with fast convergence and zero steady state error. Though drug doses minimize the HIV/AIDS in a small period, but they play more active role together with cytotoxic T-lymphocytes for fast convergence and zero steady state error. The results of PID controller have also been shown to understand the difference between the performances of linear and nonlinear controllers. Synergetic controller performs better than other controllers considering rate of convergence and steady state error and the amount of drug is also high at the start of therapy as compared to other controllers. 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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