AUT Journal of Modeling and Simulation

AUT J. Model. Simul., 49(1)(2017)33-42
DOI: 10.22060/miscj.2016.839

PDC Control of Time Delay Fuzzy T-S modeled HIV-1 System through Drug Dosage

R. Abbasi[1], M. T. Hamidi Beheshti[2*]

[1] Department of ElectricalEengineering, Islamic Azad University, Tehran, Iran
[2] Department of Electrical & Computer, Tarbiat Modares University, Tehran, Iran

ABSTRACT: This paper proposes a Time Delay nonlinear dynamic model of HIV-1(Human Immunodeficiency Virus type 1), introducing the drug consumption efficiencies as the controlling input for the model. The paper also represents the fuzzy T-S representation and the corresponding Fuzzy T-S controller. The controller parameters are tuned using LMIs (Linear Matrix Inequalities). The main focus is on the stabilization problem for the resulting T-S fuzzy system with time-delay. In particular, it aims to present delay-dependent design of state feedback stabilizing fuzzy controller for the mentioned T-S fuzzy system with state delay. The design of the controller is based on the parallel distributed compensation.

Review History:
Received: 30 November 2015
Revised: 17 February 2016
Accepted: 21 May 2016
Available Online: 25 May 2016

Keywords:
Fuzzy T-S
HIV-1
LMI
Control
Time Delay

1- Introduction

Mathematical modeling of HIV-1 infection has proven to be instrumental for the modern understanding basis of the AIDS pathogenesis since it offers the unique means to adequately pose hypotheses concerning AIDS dynamics and treatment protocols [1].

On the one hand, fuzzy logic provides a simple and straightforward way to decompose the task of modeling and control design into a group of local tasks, which tend to be easier to handle. Fuzzy logic also provides the mechanism to blend these local tasks together to deliver the overall model and control design. On the other hand, advances in modern control have made available a large number of powerful design tools. This is especially true in the case of linear control designs. These tools for linear systems range from elegant state space optimal control to the more recent robust control paradigms. By employing the Takagi-Sugeno fuzzy model which utilizes local linear system description for each rule, we devise a control methodology to fully take advantage of the advances in modern control theory [2].

It is well known that time-delays can cause poor performance or instability. Therefore, the problem of delay-dependent stability and stabilization for T–S fuzzy systems with time-delays has been received great efforts by many researchers in recent years because delay-dependent approaches are generally less conservative than delay-independent ones when the sizes of time-delays are small [3].

Great efforts have been made in modeling HIV-1 and its interaction with the host immune system as a dynamic system, among which [4-19] have seen the dynamics as ordinary nonlinear differential equations and estimated the associated parameters. The effect of saturation in cell population has been investigated in [20,21]. The drug consumption coefficients are added to the model in [22-29] . Drug resistance feature of HIV-1 is also addressed in [30-32]. An integration of HIV-1 related cofactors such as cell apoptosis, population saturation, drug consumption and resistance is presented in [33-35]. Moreover, there has always been a tendency to employ rare innovative methods in modeling the dynamics, such as the works presented in [36-40]. The authors of [41-57] have considered time delay as a part of the model.

The problem of analyzing HIV-1 dynamics has been studied extensively in the literature. In this regard, the stability analysis is investigated in [13,14,22,23,25 and 27], and a variety of control strategies is applied to HIV-1. For instance, feedback control in [5-6 and 17], nonlinear theory based control in [11-12 and 26], model predictive control in [15, 24], optimal control in [7,19,28,29 and 33] and intelligent control in [56-60] can be noticed.

Model identification and parameter estimation are also widely recognized. It is worth mentioning the works carried out in [9,10, 16 and 18].

Time delay models have been the target of different controller design approaches, such as the ones presented in [42, 44-48]. Although a great deal of effort has been made in modeling HIV-1 and its interaction with the host immune system as a dynamic system, the aforementioned works do not encompass the overall challenges that a practical model must consider in view of the number of variables included in the model and hence the model comprehensiveness and compatibility with biologic texts and also the analysis approach and therefore rational relation between the model and control system theory. Hence, the main motivation of the present work is: a)to develop a novel model for HIV-1 dynamics considering the time delay as the integral part of most biologic models;

Corresponding author, E–mail: mbehesht@modares.ac.ir

b)to introduce control inputs namely drug consumption efficiencies to the model which improves the model proposed in the previous works of the authors [61] into a new one by considering the undeniable role of drugs in HIV-1 dynamics and smoothening the pathway into controller design which is equivalent to the treatment of patients, c)to infer a fuzzy T-S model out of the novel nonlinear model; and d)to design a fuzzy T-S controller for the model. The main focus of controller design approach is on the stabilization problem for the T-S fuzzy system with time-delay. In particular, it aims to present a delay-dependent design of state feedback stabilizing fuzzy controller for the T-S fuzzy system with the state delay. The design of the controller is based on the parallel distributed compensation.

To be clearer, as a solution to the open problem of HIV-1 infection chemotherapy from the aspect of health improvement and also the side effect reduction, this work proposes a dynamic model and a controller (namely drug dosage uptake by time) for the model of HIV-1.

In fact, this work aims to resolve the open problem of HIV-1 infection chemotherapy and introduce a replacement for the present HAART (Highly Active Anti Retroviral Therapy) in which the drug adherence is a major concern due to the side effects of such a therapy. A drug regimen which is able to control the drug consumption and also the viral load can improve the adherence and health of the patient. The paper is organized as follows: section 1 describes the model in detail; section 2 is a brief overview of the target fuzzy model and the corresponding controller. The simulation results are presented in section 3, and section 4 concludes the paper. Appendix A includes the tables and figures describing the model and Appendix B is a brief introduction to Fuzzy rule extraction method employed.

2- Model of HIV-1

The equations (1-1) - (1-7) are selected from the nonlinear ODE model of HIV-1 published in the previous work of the authors [61] (it is worth mentioning that the original nonlinear model is not repeated in this work for brevity. The readers are referred to [61] to access the original 83 nonlinear ODEs). The following modifications are added in this work:

First, considering the drug efficiencies μ^{i}_{RTI},i=PB,CNS,LT as the control input added to the model. The efficiencies μ^{i}_{RTI},i=PB,CNS,LT represent the efficiency of RTIs (Reverse transcriptase inhibitors) in PB (peripheral blood), CNS (central nervous system) and LT (lymphoid tissue) which are known to be the three main replication compartments of HIV-1. The form of the entrance of drug efficiencies in the model is in agreement with [22-29]. RTIs are the type of drugs preventing the process of reverse transcription; that is the process of copying viral genomic RNA into DNA. If the reverse transcription does not occur, the virus cannot integrate into the host genome and the cell cannot become infected. The RTIs can affect the process of changing eclipse infected cells into productively infected ones [62].

Second, considering the drug efficiencies μ^{i}_{RTI},i=PB,CNS,LT as the control input added to the model. The efficiencies μ^{i}_{RTI},i=PB,CNS,LT represent the efficiency of PIs (Protease inhibitors) which are known as the type of drugs inhibiting the protease enzyme resulting in prevention of functional viral particles generation and thus preventing the infection of target cells [62]. The form of the entrance of drug efficiencies in the case of PIs is also in agreement with [22-29].

The net effect of both types of drugs is the same. They prevent the spread of the virus to other host cells, but the cells infected before the entrance of drug remain alive and infected. Typical drug regimens are a combination of three drugs, two types of RTIs and a PI which is taken two or three times a day and prevent the therapy failure because of drug resistance. This therapy is called HAART. The drug adherence is a major concern because of the side effects of such a therapy. A drug regimen, which is able to control the drug consumption and also the viral load, can improve the adherence and health of the patient [62]. The drug efficiencies (μ) and the control inputs (drug dosages (u)) are related as follows as in [24,25]:

$$\mu_i^j = 1 - \mu_i^{j*} u_i^j, \quad i = RTI, PI,\ j = PB, LT, CNS \quad 0 < \mu_i^{j*} u_i^j < 1$$

It is important to note that the drug concentration and hence the ARV (antiretroviral) agent efficiency in CNS (μ^{CNS}_{RTI} and μ^{CNS}_{PI}) is dependent on its concentration in PB (μ^{PB}_{RTI} and μ^{PB}_{PI} respectively). The type of dependence is variable for various types of antiretroviral agents. The precise values are inferable from Table A-1 which indicates the molecular weight, percentage of protein binding, the range of plasma (peripheral blood) and CNS concentration of antiretroviral agents. The situation is the same in lymphoid tissue, the other compartment of HIV-1 infection. Figure 1-1 illustrates the median concentration difference between lymphoid tissue (lymph nodes (LN)) and that of peripheral blood for different kinds of antiretroviral agents.

As mentioned above, the model is originally presented in [61] and seven equations of it are modified in (1-1)-(1-7). The equations (1-8) -(1-10) are added to the model as a result of the introduction of mentioned inputs to the model in this work. The reason is that consumption of PI drugs by the patient, results in a fraction of generated viral particles to be nonfunctional which is known as noninfectious viral load [62]. These particles are taken as three new state variables and the dynamics of them is extracted from other equations as it is usual in the literature, such as [62]. Accordingly, equations (1-8) - (1-10) describe the dynamics of V^{i}_{N},i=LT,PB,CNS which are in fact the free noninfectious viral load of three compartments of the host body, including PB, LT, and CNS.

The description of state variables and parameters is summarized inTables A-2, A-3, A-4 and A-5 of Appendix A.

$$\dot{E}^{PB}_{EI} = k_{ev1} E^{PB} V^{PB} + k_{ee1} E^{PB} E^{PB}_{PI} + k_{ec1} E^{PB} C^{PB}_{PI} - (1 - \mu^{PB}_{RTI}) E^{PB}(t - \tau_{\bar{V},\bar{E}}) (k_{ev1} V^{PB}(t - \tau_{\bar{V},\bar{E}}) + k_{ee1} E^{PB}_{PI} + k_{ec1} C^{PB}_{PI}(t - \tau_{\bar{V},\bar{E}})) \quad (1\text{-}1)$$

$$\dot{E}^{PB}_{PI} = r^{PB}_{\hat{E}} \left| E^{LT}_{PI} \right| \frac{y(72)}{((y(69)+y(70)) f^{LT}_{ss})_{pot}} + (1 - \mu^{PB}_{RTI}) E^{PB}(t - \tau_{\bar{V},\bar{E}}) (k_{ev1} V^{PB}(t - \tau_{\bar{V},\bar{E}}) + k_{ee1} E^{PB}_{PI} + k_{ec1} C^{PB}_{PI}(t - \tau_{\bar{V},\bar{E}})) - k_{\hat{E},rev} E^{PB}_{PI} - E^{PB}_{PI}(d_{\hat{E},\bar{V}}(V^{PB} + V^{PB}_{N}) + d_{\hat{E},\hat{E}} E^{PB}_{PI} + d_{E,\hat{E}}(E^{PB} + E^{PB}_{EI}) + d_{\hat{E},M} M^{PB}_{PI} + d_{\hat{E},m}(M^{PB} + M^{PB}_{EI}) + d_{\hat{E},++}(f^{ss}_{++} C^{PB} + C^{PB}_{EI}) + d_{\hat{C},\hat{E}} C^{PB}_{PI} + d_{\hat{E},Q} Q^{PB} + a_{\hat{E},cross}) - dlE^{PB}_{PI} - d_{\hat{E},CTL} E^{PB}_{CTL} E^{PB}_{PI} C^{PB}(1 + \frac{a_{12,CTL} i^{PB}_{12}}{i^{PB}_{12} + i_{12}}) - d_{\hat{E},tat} E^{PB}_{PI} - r^{CNS}_{\hat{E}} E^{PB}_{PI}(1 + \frac{i^{CNS}_{\gamma}}{i^{CNS}_{\gamma} + i_{rec_{\gamma}}}) \frac{y(71)}{(y(69)+y(70)) f^{PB}_{ss}} \quad (1\text{-}2)$$

$$\dot{V}^{PB} = f_{b,lt}(1 - I_{fdc}) \frac{V^{LT} - V^{PB}}{v_{PB}} + (1 - \mu^{PB}_{PI}) Fusf^{PB}(n_{\hat{E}} E^{PB}_{PI} + n_{\hat{C}} C^{PB}_{PI} + n_{\hat{M}} M^{PB}_{PI}) - \frac{f_{b,lt}}{v_{PB}} V^{PB} I_{fdc} - d_{\bar{V}} V^{PB} - V^{PB}(c_{vc,Q} k_{qv1} Q^{PB} + c_{vc,E} k_{ev1}(E^{PB} + E^{PB}_{EI} + E^{PB}_{PI}) + c_{vc,M} k_{m-v1}(M^{PB} + M^{PB}_{EI} + M^{PB}_{PI}) + c_{vc,C} k_{cv1}(f^{ss}_{++} C^{PB} + C^{PB}_{EI} + C^{PB}_{PI}) + c_{vc,x} k_{mv1}(x^{PB} + x^{PB}_{I}) - h_{v}(V^{PB} - V^{CNS}) \quad (1\text{-}3)$$

$$\dot{V}^{LT} = (1-\mu_{PI}^{LT})Fusf^{LT}(n_{\hat{E}}E_{PI}^{LT} + n_{\hat{C}}C_{PI}^{LT} + n_{\hat{M}}M_{PI}^{LT} + n_{\bar{m}}\bar{m}^{LT}) + \frac{f_{b,LT}}{v_{LT}}V^{PB} - d_{\dot{V}}V^{LT}$$
$$-c_{\bar{V},m}m^{LT}V^{LT} - V^{LT}(c_{vc,Q} - k_{qv2}Q^{LT} + c_{vc,E}k_{ev2}(E^{LT} + E_{EI}^{LT} + E_{PI}^{LT}) + c_{vc,M}k_{mv2}(M^{LT}$$
$$+M_{EI}^{LT} + M_{PI}^{LT}) + c_{vc,C}k_{cv2}(\frac{f_{++}^{ss}}{2}x^{CNS} + C_{EI}^{LT} + C_{PI}^{LT}) + c_{vc,m}k_{mv2}(m^{LT} + \bar{m}^{LT}) + c_{vc,x}k_{mv2}(x^{LT}$$
$$+x_I^{LT})) - f_{b,lt}(1-I_{fdc})\frac{V^{LT}}{v_{LT}} \quad (1\text{-}4)$$

$$\dot{E}_{EI}^{CNS} = E^{CNS}(k_{ev3}V^{CNS} + k_{ee3}E_{PI}^{CNS} + k_{em3}\bar{m}^{CNS} + k_{ec3}C_{PI}^{CNS}) - (1-\mu_{RTI}^{CNS})E^{CNS}(t-\tau_{\bar{V},\bar{E}})$$
$$(k_{ev3}V^{CNS}(t-\tau_{\bar{V},\bar{E}}) + k_{ee3}E_{PI}^{CNS}(t-\tau_{\bar{V},\bar{E}}) + k_{em3}\bar{m}^{CNS}(t-\tau_{\bar{V},\bar{E}}) + k_{ec3}C_{PI}^{CNS}(t-\tau_{\bar{V},\bar{E}})) \quad (1\text{-}5)$$

$$\dot{E}_{PI}^{CNS} = r_{\hat{E}}^{CNS}E_{PI}^{PB}(1+\frac{I_\gamma^{CNS}}{I_\gamma^{CNS}+i_{rec_\gamma}^{I}})\frac{y(71)}{(y(69)+y(70))f_{ss}^{PB}} + (1-\mu_{RTI}^{CNS})E^{CNS}(t-\tau_{\bar{V},\bar{E}})(k_{ev3}V^{CNS}(t-\tau_{\bar{V},\bar{E}})$$
$$+k_{ee3}E_{PI}^{CNS}(t-\tau_{\bar{V},\bar{E}}) + k_{em3}\bar{m}^{CNS}(t-\tau_{\bar{V},\bar{E}}) + k_{ec3}C_{PI}^{CNS}(t-\tau_{\bar{V},\bar{E}})) + 2^{c_M}a_m k_{mm3}\bar{m}^{CNS}(t-\tau_M^{1st})\frac{I_2^{CNS}(t-\tau_M^{1st})}{I_2^{CNS}(t-\tau_M^{1st})+i_2^M}$$
$$+2^{c_M}a_{\bar{m}}^{CNS}M_{PI}^{CNS}(t-\tau_M^{1st})\frac{I_2^{CNS}(t-\tau_M^{1st})}{I_2^{CNS}(t-\tau_M^{1st})+i_2^M} - k_{\hat{E},rev}E_{PI}^{CNS} - E_{PI}^{CNS}(d_{\hat{E},\bar{V}}(V^{CNS}+V_N^{CNS}) + d_{\hat{E},\hat{E}}E_{PI}^{CNS}$$
$$+d_{\hat{E},\hat{E}}(E^{CNS}+E_{EI}^{CNS}) + d_{\hat{E},\hat{M}}M_{PI}^{CNS} + d_{\hat{E},M}(M^{CNS}+M_{EI}^{LT}) + d_{M,\hat{E}}m^{CNS} + d_{\hat{E},\bar{m}}\bar{m}^{CNS} + d_{\hat{E},++}(f_{++}^{ss}C^{CNS}+C_{EI}^{CNS})$$
$$+d_{\hat{C},\hat{E}}C_{PI}^{CNS} + a_{\hat{E},cross}) - dI.E_{PI}^{CNS} - d_{\hat{E},CTL}E_{CTL}E_{PI}^{CNS}C^{CNS}(1+\frac{a_{12,CTL}I_{12}^{CNS}}{I_{12}^{CNS}+i_{12}}) - d_{\hat{E},tot}E_{PI}^{CNS} \quad (1\text{-}6)$$

$$\dot{V}^{CNS} = h_v(V^{PB} - V^{CNS}) + (1-\mu_{PI}^{CNS})Fusf^{CNS}(n_{\hat{E}}E_{PI}^{CNS} + n_{\hat{C}}C_{PI}^{CNS} + n_{\hat{M}}M_{PI}^{CNS} + n_{\bar{m}}\bar{m}^{CNS}) - d_{\dot{V}}V^{CNS}$$
$$-c_{\bar{V},m}m^{CNS}V^{CNS} - V^{CNS}(c_{vc,E}k_{ev3}(E^{CNS}+E_{EI}^{CNS}+E_{PI}^{CNS}) + c_{vc,M}k_{m-v3}(M^{CNS}+M_{EI}^{CNS}+M_{PI}^{CNS})$$
$$+c_{vc,C}k_{cv3}(f_{++}^{ss}C^{CNS} + C_{EI}^{CNS} + C_{PI}^{CNS}) + c_{vc,m}k_{mv3}(m^{CNS}+\bar{m}^{CNS}) + c_{vc,x}k_{mv3}(x^{CNS}+x_I^{CNS}) \quad (1\text{-}7)$$

$$\dot{V}_N^{CNS} = \mu_{PI}^{CNS}Fusf^{CNS}(n_{\hat{E}}E_{PI}^{CNS} + n_{\hat{C}}C_{PI}^{CNS} + n_{\hat{M}}M_{PI}^{CNS} + n_{\bar{m}}\bar{m}^{CNS}) \quad (1\text{-}8)$$

$$\dot{V}_N^{LT} = \mu_{PI}^{LT}Fusf^{LT}(n_{\hat{E}}E_{PI}^{LT} + n_{\hat{C}}C_{PI}^{LT} + n_{\hat{M}}M_{PI}^{LT} + n_{\bar{m}}\bar{m}^{LT}) \quad (1\text{-}9)$$

$$\dot{V}_N^{PB} = \mu_{PI}^{PB}Fusf^{PB}(n_{\hat{E}}E_{PI}^{PB} + n_{\hat{C}}C_{PI}^{PB} + n_{\hat{M}}M_{PI}^{PB}) \quad (1\text{-}10)$$

3- The target fuzzy model and the control strategy [63]

A brief introduction to fuzzy T-S systems with state time delay is represented here. One can construct a T-S model if local description of the dynamic system to be controlled is available in terms of local linear models:

$$\dot{x} = A_i.x(t) + B_{ui}.u(t) + A_{\tau i}.x(t-\tau), i = 1,2,...,r \quad (2\text{-}1)$$

Where the state vector $x(t)\in R^n$, the delayed state vector $x(t-\tau)\in R^n$, the control input $u(t)\in R^m$, and the matrices A_i, B_{ui} and $A_{\tau i}$ are of appropriate dimensions. The above information is then fused with the available IF–THEN rules where the th rule can have the form:

Plant Rule i: IF θ_1 is μ_{i1} and … and θ_p is μ_{ip} THEN

$$\dot{x}(t) = A_i x(t) + D_i x(t-\tau_i(t)) + B_i u(t) + E_i u(t-\tau_i(t)),$$
$$x(t) = \phi(t), \quad t\in[-\tau, 0], \quad (2\text{-}2)$$

Where $x\in R^n$ and $u\in R^m$ are the state and control input, respectively; A_i, D_i and B_i are constant real matrices with appropriate dimensions; r is the number of plant rules; $\theta_j(x)$ and $\mu_{ij}(i=1,...,r\ ,\ j=1,...,p)$ are respectively the premise variables (which are the functions of state variables) and the fuzzy sets.

The design of state feedback stabilizing fuzzy controllers for the fuzzy system (2-2) is based on the parallel distributed compensation. The aim is to determine the local feedback gains F_i such that the closed-loop system is asymptotically stable.

Regulator Rule i: IF θ_j is μ_{i1} and … and θ_p is μ_{ip} THEN

$$u(t) = -F_i x(t), \quad i = 1,2,....,r \quad (2\text{-}3)$$

Theorem 2-1[63]. There exists a fuzzy control law such that the closed-loop fuzzy system (2-2) is asymptotically stable if there exist matrices $Q>0$, $U_i>0$, $V_i>0$, $W_i>0$, $S_i>0$ and Y_i, $i=1,2,...,r$ such that the following LMI's hold:

$$\Theta_{ij} + \Theta_{ji} < 0, \quad (2\text{-}4)$$

$$\begin{bmatrix} -Q & QA_k^T - Y_l^T B_k^T \\ A_k Q - B_k Y_l & -U_i \end{bmatrix} \le 0, \quad (2\text{-}5)$$

$$\begin{bmatrix} -Q & QD_k^T \\ D_k Q & -V_i \end{bmatrix} \le 0, \quad (2\text{-}6)$$

$$\begin{bmatrix} -Q & Y_l^T E_k^T \\ E_k Y_l & -W_i \end{bmatrix} \le 0, \quad (2\text{-}7)$$

$$\begin{bmatrix} -Q & Y_l^T \\ Y_l & -S_i \end{bmatrix} \le 0, \quad (2\text{-}8)$$

For i,k,l=1,2,...,r and $i \le j$, where

$$\Theta_{ij} = (A_i + D_i)Q + Q(A_i + D_i)^T - B_i Y_j - Y_j^T B_i^T + E_i S_i E_i^T$$
$$+\tau D_i(U_j + V_j + W_j)D_i^T + (3\tau + 1)Q, \quad (2\text{-}9)$$

If this is the case, the local feedback gains F_i are given by

$$F_i = Y_i Q^{-1}, \quad i = 1,2,...,r. \quad (2\text{-}10)$$

The readers are referred to [63] for the proof of the Theorem. local linear models of the system are obtained using LOLIMOT (Local Linear Model Trees) which is a Matlab toolbox mainly used for the identification and inversion of models [64]. The simulation is carried out using local linear models, namely fuzzy T-S rules. A brief introduction to LOLIMOT is stated in Appendix B.

4- Simulation Results

In order to describe the results, it is necessary to have a brief look at the process of HIV-1 infection and its interaction with the host body:

In the earliest stages of infection, after the virus has entered the host, we observe the acute phase. The viral load (V^{PB}) grows to high levels and immune responses rise. The immune responses reduce viral load to the lower levels but fail to clear the virus. The target cells count (such as X^{PB}) take a temporary dip before returning to normal levels. During this phase, infected individuals can experience symptoms typical of viral infections in general, such as fever, rash, and fatigue. Once the viral load has fallen to lower levels, these symptoms subside, and this marks the beginning of the asymptomatic or chronic phase of the infection. During this phase, viral load remains relatively low and the target cells count remain relatively high. The final stage of the infection is the development of AIDS. This is characterized by a fall in the target cells count, and a sharp rise in viral load. Because the body has a highly reduced target cells count, the immune system does not function anymore, and the patient dies from a variety of infections that would otherwise be cleared. Such infections are called opportunistic infections. The duration of the asymptomatic phase of infection is highly variable. On average, it takes between 5–10 years. However, some patients develop AIDS rapidly after only a few months, while so-called LTNPs (long term nonprogressors) do not develop any signs of AIDS for as long as 15–20 years after infection. Such patients are characterized by very low viral loads and high levels of immune responses. The reasons for the transition from the asymptomatic phase to the development of AIDS are unknown [62].

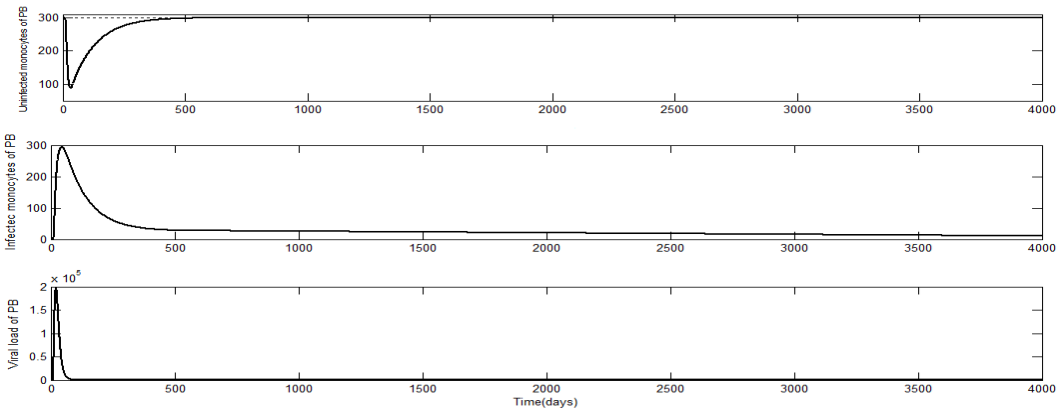

Fig. 3-1. controlled X^{PB}, X_i^{PB} and V^{PB}

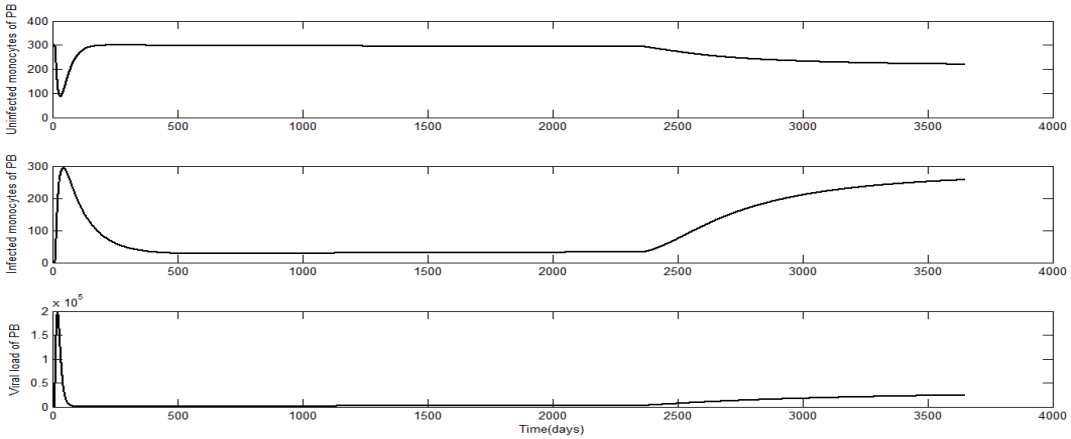

Fig. 3-2. uncontrolled X^{PB}, X_i^{PB} and V^{PB}

The full dimensional system is a new dynamic model of 86 ODE equations considering the 83 ones previously stated by the authors in [61] (seven of which is modified in (1-1) - (1-7)) plus three new equations stated in (1-8)-(1-10). The stability of the model is investigated using state variables being locally linearized. The results for variables mostly mentioned in literature is depicted in Figure 3-1 which illustrates three state variables, including Uninfected monocyte pool count (X^{PB}), Infected monocyte pool count (X_i^{PB}) and the viral load (V^{PB}) in peripheral blood as the integral part of most dynamic models of HIV-1 or even the whole model as in [6-11] and the asymptotic nature of them is easily seen. The mentioned state variables indicate the so-called LTNP which was described thoroughly above. Keeping the HIV-1 infected patients in LTNP is the target of HIV-1 treatment because it is obviously desirable that the state of the patient be driven into the LTNP, where the patient does not progress to AIDS and drug treatment can be stopped [23].

Figure 3-2 illustrates the uncontrolled state variables X^{PB}, X_i^{PB} and V^{PB} for comparison. It is seen that the open loop system states tend to an equilibrium point of AIDS or equivalently complete defeat of host body immune system.

5- Results and Future Work

This paper proposes a novel nonlinear model for the interaction of HIV-1 with host body. The novelty of the model lies in the addition of control inputs, namely drug consumption efficiencies and three new state variables (equations) into a nonlinear ODE model of HIV-1 dynamics which is proposed by the authors previously. The proposed model is unprecedented from the aspect of a number of state variables and also the biologic parameters it includes. This paper is also the pioneering work in adopting the Fuzzy T-S modeling and controlling method for such a model. The T-S fuzzy model is carried out through the procedure of inferring locally linearized models out of the original nonlinear ODE model. This is a breakthrough which provides the ability to use the Fuzzy T-S theory and numerical facilities it provides such as the delay dependent stabilization state feedback design based on Lyapunov-krasovskii functional used in this paper. This procedure summarizes the stabilization problem into LMI's solution. The stability of the closed loop system is proved toward the equilibrium point of LTNP. This achievement is comparable to open loop system which tends to an equilibrium point of AIDS or equivalently complete defeat of host body immune system.

The future work includes an addition of observer to the model and controller design in the same way. The method also has the capability of being employed to more general models of HIV-1 with more dimensions and of course reflecting more biologic facts about the virus dynamics. The other pathway for future is consideration of physical characteristics of host body compartments, such as blood stream dynamics and blood-brain barrier properties in modeling HIV-1 employing ANSYS. The blood-brain barrier is known to be the main barrier for drug penetration into the CNS and hence the main reason for the invasion of viral load into PB and AIDS.

6- Appendix A: Complimentary Tables and figures for model description

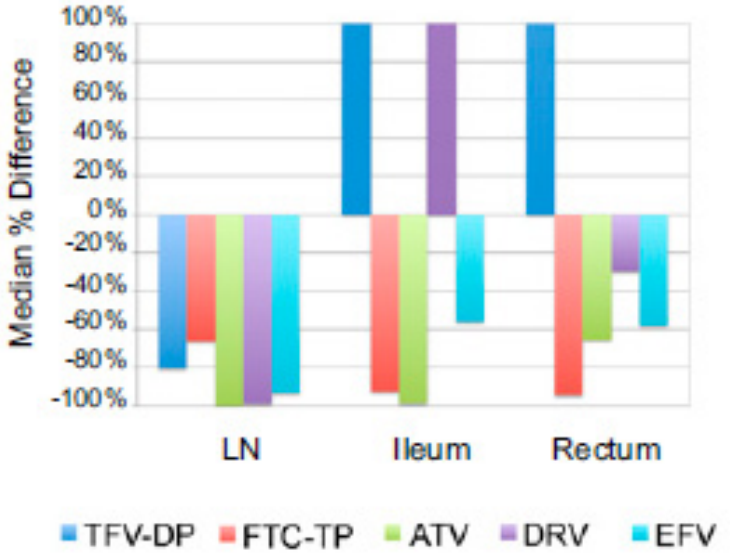

Fig. A-1. [65]:median difference of ARV concentration compared to PB [64] shown for tenofovir disoproxil fumarate-diphosphate (TDF-DP), emtricitabine–triphosphate (FTC-TP), efavirenz (EFV), atazanavir (ATV), ritonavir(RTV).

Table A-1. Properties of antiretroviral agents [66].

Antiretroviral	Molecular weight	Protein binding %	Plasma concentration	CNS concentration
Nucleos(t)ide reverse-transcriptase inhibitors				
Zidovudine (ZDV)	267.2	34-38	4.5-6.7 µmol/ml	0.12-0.41 µmol/ml
Lamivudine (3TC)	229.3	<36	4.3-8.7 µmol/ml	0.05-1.14 µmol/ml
Stavudine (D4T)	224.2	Negligible	3.3-6.4 µmol/ml	0.2-0.36 µmol/ml
Didanosine (DDI)	236.2	<5	2.12-11 µmol/ml	0.17-0.51 µmol/ml
Abacavir (ABC)	286.3	49	5.2-10.9 µmol/ml	0.5-1.8 µmol/ml
Tenofovir disoproxil –TDF (PMPA precursor of TDF)	519.4 289.2 (PMPA)	-(PMPA)		
Non-nucleosidic reverse-transcriptase inhibitors				
Nevirapine (NVP)	266.3	60	7.5-16.9 µmol/ml	1.3-10.9 µmol/ml
Efavirenz (EFV)	315.7	99.5	9.2-16.6 µmol/ml	0.006-0.09 µmol/ml
Etravirine (ETV)	435	99.9	0,6 µmol/ml	
Protease inhibitors				
Indinavir (IDV)	613.8	60	12.2-13.0 µmol/ml	0.03-0.66 µmol/ml
Ritonavir (RTV)	721	98-99	10.5-26 µmol/ml	Nd-0.32 µmol/ml
Nelfinavir (NFV)	567.8	>99	5.6-8.45 µmol/ml	Nd-0.012 µmol/ml
Saquinavir (SQV)	670.9	98	1.84-3.23 µmol/ml	Nd-0.008 µmol/ml
Amprenavir (APV)	505.6	90	10.6-19.2 µmol/ml	Nd-0.36 µmol/ml
Lopinavir (LPV)	628.8	98-99	67945 ± 4215 µg/l	16.75 ± 8.6 µg/l
Atazanavir (ATV)	704.9	++(+)	128–6200 ng/ml	Nd–40 ng/ml
Fosamprenavir - FPV(converted rapidly to APV)	585.6	+++		
Darunavir (DRV)	548	95	1800–12900 ng/ml	15.9–212.0 ng/ml

Table A-2 states the description of ODE state variables [61].

Table A-2. Description of ODE state variable [61].

Symbol	Description
x^j	Uninfected monocyte pool count in j (j= Peripheral blood (PB), Lymphoid tissue (LT) , Central nervous system (CNS))
x_I^j	Infected monocyte pool count in j (j=PB, LT, CNS)
m^j	Uninfected macrophage pool count in j (j= LT, CNS)
$\bar{m}^j$	Uninfected macrophage pool count in j (j= LT, CNS)
Q^j	Naïve CD4+T-cell pool count in j (j=PB, LT)
E^j	Uninfected eff ector CD4+T-cell count in j (j=PB, LT, CNS)
E_{EI}^j	Infected (eclipse phase) CD4+T-cell count in j (j=PB, LT, CNS)
E_{pI}^j	Productively infected CD4+T-cell count in j (j=PB, LT, CNS)
M^j	Uninfected memory CD4+T-cell pool count in j (j=PB, LT, CNS)
M_{EI}^j	Infected (eclipse phase) memory CD4+T-cell pool count in j (j=PB, LT, CNS)
M_{pI}^j	Productively infected memory CD4+T-cell pool count in j (j=PB, LT, CNS)
C^j	Uninfected CTL count in j (j=PB, LT, CNS)
C_{EI}^j	Infected (eclipse phase) CTL count in j (j=PB, LT, CNS)
C_{pI}^j	Productively infected CTL count in j (j=PB, LT, CNS)
V^j	Infectious free HIV-1 of j (j=PB, LT, CNS)
V_N^j	Noninfectious free HIV-1 of j (j=PB, LT, CNS)
I_2^j	IL-2 of j (j=PB, LT, CNS)
I_{12}^j	IL-12 of j (j=PB, LT, CNS)
I_γ^j	INF-g of j (j=PB, LT, CNS)
I_{fdc}	Delay (FDC function)
λ	Delay (Lambda function)

In which the parameters are outlined in Table A-5

Table A-5. Parameters of Infectivity coefficient[61].

fv	Ratio between viable and non-viable particles within an HIV-1 population	$5\times10^{-4}-10^{-2}$Dimensionless
h_{vc}	(constant) probability per unit time per virion of a successful collision with, and attachment to a target cell	$0.00027\ vol\times target\ cell^{-1}\times t^{-1}$
$\tilde{I}_{R5}^L, \tilde{I}_{R5}^M$	overall R5 HIV-1 normalized infectivity in [0,1] on CD4 T lymphocytes and monocyte–macrophage cell lineage, respectively	Dimensionless
$\tilde{I}_{X4}^L, \tilde{I}_{X4}^M$	overall X4 HIV-1 normalized infectivity in [0,1] on CD4 T lymphocytes and monocyte – macrophage cell lineage, respectively	Dimensionless
$\tilde{I}_{R5X4}^L, \tilde{I}_{R5X4}^M$	overall R5X4 HIV-1 normalized infectivity in [0,1] on CD4 T lymphocytes and monocyte–macrophage cell lineage, respectively	Dimensionless
$k_{m,v}$	infectivity coefficient for virus-to-cell transmission involving the monocyte–macrophage cell lineage	$vol\times target\ cell^{-1}\times t^{-1}$
V_{R5}	CCR5-using HIV-1 population fraction	Dimensionless
V_{x4}	CXCR4-using HIV-1 population fraction	Dimensionless
V_{R5x4}	CCR5 and CXCR4-using HIV-1 population fraction	Dimensionless

The parameter description and values are listed in Table A-3.

Table A-3. Parameters of model (1-1)-(1-10) [61].

Symbol	Description	Value
$a_{j,cross}$	Cellular apoptosis rate of $j(j=\hat{E},\hat{M})$ induced by CD4–gp120 cross-linking	$[1;5\times10^{-4}]day^{-1}$
a_m	Antigenic stimulation coefficient for T-cells	$5\times10^{-8}day^{-1}$
$a_{12,CTL}$	Coefficient of the IFN-γ secretion by CTLs stimulated by IL-12	1
C_j	Number of mitotic cycles of j(j=Q,M,C) after antigenic stimulation	[7;8;10]
$C_{VC,j}$	Free virus required to infect a cell j(j=x,m,Q,E,M,C)	$2\times10^{-10}virus\ \ cell^{-1}$
$C_{\bar{v},m}$	Free HIV-1 phagocytosis rate by macrophages	$2\times10^{-10}ml\ \ cell^{-1}day^{-1}$
$d_{j,CTL}$	Cellular apoptosis rate of $j(j=y,\bar{m},\hat{E},\hat{C},\hat{M})$ induced by the CTL cytotoxic activity	$2\times10^{-9}ml\ \ cell^{-1}day^{-1}$
$d_{j,tat}$	Cellular apoptosis rate of $j(j=Q,E,\hat{E},M,\hat{M})$ induced by Tat	$[1\times10^{-9};1\times10^{-10};1\times10^{-4};1\times10^{-10};1\times10^{-4}]ml\ \ cell^{-1}day^{-1}$
$d_{j,j'}$	Cellular apoptosis rate of j induced by gp120 when interacting with the infected cell j' $([j,j']=[E,\bar{V}];[E,\hat{E}],[E,\hat{M}];[E,\hat{C}];[E,\bar{m}];$ $[\hat{E},\bar{V}];[\hat{E},Q];[\hat{E},\hat{E}];[\hat{E},\hat{M}];[\hat{E},m];[\hat{E},\bar{m}];[\hat{E},++];[\hat{C},\hat{E}];$ $[M,\bar{V}];[M,\hat{E}];[M,\hat{M}];[M,\hat{C}];[M,\bar{m}];$ $[\hat{M},\bar{V}];[m,\hat{M}];[\bar{m},\hat{M}];[\hat{M},++];[\hat{M},\hat{C}];[Q,\hat{C}])$	$1\times10^{-9}ml\ \ cell^{-1}day^{-1}$
dl	Cell death rate due to membrane lysis	$0.5\ \ day^{-1}$
$d\bar{v}$	Free virus death rate	$0.24\ \ day^{-1}$
$f_{b,lt}$	Blood volumetric flow rate from PB to LT	$50\ \ l\ \ day^{-1}$
f^{j}_{ss}	Fraction of the T-cell pool in j(j=PB,LT)	$[1.95\times10^{-2};9.8\times10^{-1};5\times10^{-4}]$
$f_{\bar{v}}$	Fraction of viable HIV-1 produced by an infected cell	10^{-2}
$f^{ss}{}_{++}$	Double positive CTL pool fraction in PB and CNS	$2.5*10^{-2}$
i^{j}_{2}	IL-2 concentration needs to promote 50% of maximum stimulation of j(j=Q,M,C)	$[30;18;30]U/ml$
n_j	Production rate of free HIV-1 by an infected cell $j(j=\bar{m},\hat{E},\hat{M},\hat{C})$	$[530;1000;850;850]virus\ \ ml^{-1}day^{-1}cell^{-1}$
r_j^{PB}	Steady-state recruitment rate of $j(j=E,\hat{E},M,\hat{M},C,\hat{C},I_2,I_{12},I_\gamma,L_{R5},U)$ from LT to PB	$[5,4\times10^{-6},5\times10^{-6},3,2\times10^{-4},3\times10^{-4},6\times10^{-5},10^{-6},5\times10^{-4},10^{-4},10^{-4},6\times10^{-4},6\times10^{-3}]day^{-1}$
r_j^{LT}	Steady-state recruitment rate of $j(j=x,Q,\breve{C})$ from PB to LT	$[3\times10^{-2};9.3\times10^{-3};3\times10^{-2}]day^{-1}$
r_j^{CNS}	Steady-state recruitment rate $j(j=x,y,E,\hat{E},M,\hat{M},C,\hat{C})$ of from PB to CNS	$[2\times10^{-4};9\times10^{-5};4.5\times10^{-5};10^{-5};1.48\times10^{-5};8\times10^{-6};5\times10^{-5};4.5\times10^{-5}]day^{-1}$
τ_j^{1st}	Time period of the first mitotic cycle $j(j=Q,M,C)$ of after stimulation	[3;1;3]days
$\tau_{\bar{v},j}$	Time period of the HIV-1 intracellular life cycle in	1 day

The infectivity coefficient in model (1-1) - (1-10) is as follows in Table A-4:

Table A-4. Infectivity coefficient.

Virus-to-cell infection	
Monocyte-Macrophage cells	$k_{m,v}(t)=f_v h_{vc}[V_{R5}\tilde{I}_{R5}{}^{M}(t)+V_{X4}\tilde{I}_{X4}{}^{M}(t)+V_{R5X4}\tilde{I}_{R5X4}{}^{M}(t)]$

7- Appendix B: Introduction to LOLIMOT [64]

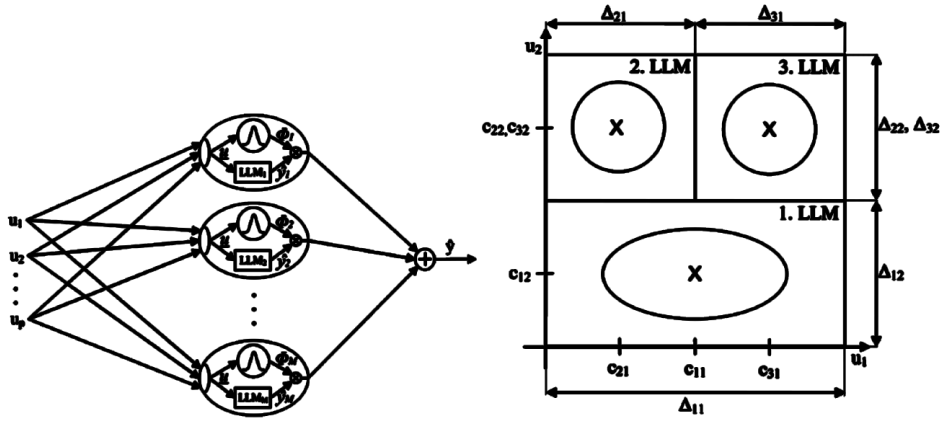

Fig. B1. Left: Network Structure of Local Linear Neuro-Fuzzy Model. Right: Partitioning of Input Space by Validity Functions

The Local Linear Model Trees (LOLIMOT) algorithm is based upon Neural-Fuzzy models of Takagi-Sugeno type to infer the local linear approximations of a model. During the execution of this algorithm, a "divide and conquer strategy" is applied to the modeling problem, so that the major problem is split into smaller ones. The basic network structure of a local linear neuro-fuzzy model is depicted in Figure B-1. Every neuron consists of a local linear model (LLM), and a validity function ϕ, which defines the validity of the LLM within the input space. The local linear model output is defined by:

$$\hat{y}_i = \omega_{i0} + \omega_{i1}u_1 + \omega_{i2}u_2 + \ldots + \omega_{ip}u_p \quad \text{(B-1)}$$

With ω_{ij} as parameters of the neuron i.If the validity functions are chosen as normalized Gaussians, then:

$$\sum_{i=1}^{M}\Phi_i(\underline{u}) = 1 \quad and \quad \Phi_i = \frac{\mu_i(\underline{u})}{\sum_{j=1}^{M}\mu_j(\underline{u})} \quad \text{(B-2)}$$

Where the membership function μ is defined as:

$$\mu_i(\underline{u}) = \exp\left(-\frac{1}{2}\frac{(u_1 - c_{i1})^2}{\sigma_{i1}^2}\right) + \exp\left(-\frac{1}{2}\frac{(u_2 - c_{i2})^2}{\sigma_{i2}^2}\right) + \ldots + \exp\left(-\frac{1}{2}\frac{(u_p - c_{ip})^2}{\sigma_{ip}^2}\right) \quad \text{(B-3)}$$

The estimation of the linear equation parameters is done through an optimization by the local least squares method. The parameter vector for each i=1,...,M, the regression matrix, and the weight matrix are respectively:

$$\underline{\omega}_i = \begin{bmatrix}\omega_{i0}\\ \omega_{i1}\\ \vdots\\ \omega_{ip}\end{bmatrix}, \underline{X}_i = \begin{bmatrix}1 & u_1(1) & u_2(1) & \ldots & u_p(1)\\ 1 & u_1(1) & u_2(1) & \ldots & u_p(1)\\ \vdots & \vdots & \vdots & & \vdots\\ 1 & u_1(N) & u_2(N) & \ldots & u_p(N)\end{bmatrix} \quad \text{(B-4)}$$

$$and \quad \underline{Q}_i = \begin{bmatrix}\phi_i(\underline{u}(1)) & 0 & \ldots & 0\\ 0 & \phi_i(\underline{u}(2)) & \ldots & 0\\ \vdots & \vdots & \ddots & \vdots\\ 0 & 0 & \ldots & \phi_i(\underline{u}(N))\end{bmatrix}$$

The weighted least squares solution of the rule conclusion parameters is given by:

$$\hat{\underline{\omega}}_i = (\underline{X}_i^T\underline{Q}_i\underline{X}_i)\underline{X}_i^T\underline{Q}_i y \quad i = 1,\ldots,M \quad \text{(B-5)}$$

The local least squares method mentioned to estimate the rule conclusions is only applicable if the validity functions have been estimated first. The number of the validity functions and their parameters depicted in Fig. 2 define the partitioning of the input space. The functions divide input space into rectangle areas while C_{ij}, σ_{ij} indicate the centers of the rectangles, the standard deviations and $\sigma_{ij}=k_\sigma.\Delta_{ij}$ ($k_\sigma=1/3$ is proved to be optimal) respectively. The LOLIMOT is an incremental tree construction algorithm which divides the input space axes into an orthogonal way. By iterations, one new local linear model is added to the model. To do that, validity functions are calculated and the local linear models are adapted with the least squares method. A brief description of the LOLIMOT algorithm is as follows:

1. Start with an initial model.
2. Find the worst LLM.
3. Check all possible divisions.
4. Find the best division.
5. Check for convergence.

For more details please refer to [64].

References

[1] Joly, M., J. M. Pinto (2006). "Role of Mathematical Modeling on the Optimal Control of HIV-1 Pathogenesis", PROCESS SYSTEMS ENGINEERING 52(3).

[2] Tanaka, K., H. O. Wang (2001). "FUZZY CONTROL SYSTEMS DESIGN AND ANALYSIS", John Wiley & Sons.

[3] Kwon, O.M., et al. (2012). "Augmented Lyapunov–Krasovskii functional approaches to robust stability criteria for uncertain Takagi–Sugeno fuzzy systems with time-varying delays", Fuzzy Sets and Systems 201: 1–19.

[4] Caetano, M. A. L., et al. (2008, June). "Optimal medication in HIV seropositive patient treatment using fuzzy cost function." 2008 American Control Conference, Seattle, Washington, USA.

[5] Brandt, M. E., G. Chen (2001,July). "Feedback Control

of a Biodynamical Model of HIV-1." IEEE Transactions on Biomedical Engineering 48(7).

[6] Craig, I., X. Xia(2005,February). "Can HIV/AIDS Be Controlled? Applying control engineering concepts outside traditional fields." IEEE Control Systems Magazine.

[7] Costanza, V., et al. (2009). "A closed-loop approach to antiretroviral therapies for HIV infection. " Biomedical Signal Processing and Control 4: 139–148.

[8] Mhawej, M. J., et al. (2009). "Apoptosis characterizes immunological failure of HIV infected patients. " Control Engineering Practice17: 798–804.

[9] Xia, X., (2003). "Estimation of HIV/AIDS parameters . " Automatica 39: 1983 – 1988.

[10] Xia, X.,(2007). "Modeling of HIV infection: Vaccine readiness, drug effectiveness and therapeutical failures. " Journal of Process Control 17: 253–260.

[11] Biafore, F. L., C. E. D'Attellis (2005,September). "Exact Linearisation and Control of a HIV-1 Predator-Prey Model. " Proceedings of the 2005 IEEE Engineering in Medicine and Biology 27th Annual Conference , Shanghai, China.

[12] Ge, S. S., et al. (2005,March). "Nonlinear Control of a Dynamic Model of HIV-1. " IEEE Transactions on Biomedical Engineering 52(3).

[13] Jeffrey, A. M., X. Xia (2003,November). "When to Initiate HIV Therapy: A Control Theoretic Approach. " IEEE Transactions on Biomedical Engineering 50(11).

[14] Elaiw, A. M., (2010). "Global properties of a class of HIV models. " Nonlinear Analysis: Real World Applications 11: 2253_2263.

[15] Zurakowski, R., et al. (2004). "HIV treatment scheduling via robust nonlinear model predictive control. " IEEE 2004 5th Asian Control Conference.

[16] Chang, H., A. Astolfi (2007,July). "Control of the HIV Infection Dynamics with a Reduced Second Order Model." Proceedings of the 2007 American Control Conference, New York City, USA.

[17] Chang, H., A. Astolfi (2009). "Enhancement of the immune system in HIV dynamics by output feedback. " Automatica 45: 1765_1770.

[18] Chang, H.J., et al. (2004,December). "Control of Immune Response of HIV Infection Model by Gradual Reduction of Drug Dose. " 43rd IEEE Conference on Decision and Control.

[19] Yongqi, L., S. Zhendong (2010,July). "Backward Bifurcation in an HIV Model with Two Target Cells." Proceedings of the 29th Chinese Control Conference, Beijing, China.

[20] Chen, B. S., et al. (2010,July). "B. S. The Applications of Stochastic Regulation Control to HIV Therapy." Proceedings of the Ninth International Conference on Machine Learning and Cybernetics, Qingdao.

[21] Ledzewicz, U., H. Schattler (2002). "On optimal controls for a general mathematical model for chemotherapy of HIV. " IEEE.

[22] Ko, J. H., et al.(2006,March). "Optimized Structured Treatment Interruption for HIV Therapy and Its Performance Analysis on Controllability." IEEE Transactions on Biomedical Engineering 53(3).

[23] Chang, H., A. Astolfi (2008,April). "Control of HIV Infection Dynamics. " IEEE CONTROL SYSTEMS MAGAZINE.

[24] Pannocchia, G., et al. (2010,May). "A Model Predictive Control Strategy Toward Optimal Structured Treatment Interruptions in Anti-HIV Therapy. " IEEE Transactions on Biomedical Engineering 57(5).

[25] Mhawej, M. J., et al. (2010). "Control of the HIV infection and drug dosage. " Biomedical Signal Processing and Control 5: 45–52.

[26] Barao, M., J.M. Lemos (2007). "Nonlinear control of HIV-1 infection with a singular perturbation model." Biomedical Signal Processing and Control 2: 248–257.

[27] Gumel, A.B., S.M. Moghadas (2004). "HIV control in vivo: Dynamical analysis. " Communications in Nonlinear Science and Numerical Simulation 9: 561–568.

[28] Orellana, J. M. (2010). "Optimal drug scheduling for HIV therapy efficiency improvement . " Biomedical Signal Processing and Control.

[29] Wu, J., M. Zhang (2010,June) "A Game Theoretical Approach to Optimal Control of Dual Drug Delivery for HIV Infection Treatment. " IEEE Transactions on Systems, Man, and Cybernetics—Part B: Cybernetics 40(3).

[30] Velichenko, V. V., D. A. Pritykin (2006). "Numerical Methods of Optimal Control of the HIV-Infection Dynamics." Journal of Computer and Systems Sciences International 45(6): 894–905.

[31] Luo, R., et al. (2009,June). "A Generalized Multi-strain Model of HIV Evolution with Implications for Drug-resistance Management." 2009 American Control Conference Hyatt Regency Riverfront, St. Louis, MO, USA.

[32] Rong L., et al. (2007). "Modeling within-host HIV-1 dynamics and the evolution of drug resistance: Trade-offs between viral enzyme function and drug susceptibility . " Journal of Theoretical Biology 247: 804–818.

[33] Banks, H. T., et al. (2005). "An SDRE Based Estimator Approach for HIV Feedback Control. ".

[34] Adams, B.M., et al. (2005). "Model Fitting and Prediction with HIV Treatment Interruption Data.".

[35] Stan, G. B., et al. (2007). "Modelling the influence of activation-induced apoptosis of CD41 and CD81 T cells on the immune system response of a HIV-infected patient. " IET Systems Biology.

[36] Singh, G. B. "Computational Modeling and Prediction of the Human Immunodeficiency Virus (HIV) Strains. " IEEE.

[37] Shechter, S. M., et al. (2004). "MODELING THE PROGRESSION AND TREATMENT OF HIV." Proceedings of the IEEE 2004 Winter Simulation Conference.

[38] Spagnuolo, A. M., et al. (2004,September). "Modeling HIV-1 Dynamics and the Effects of Decreasing Activated Infected T-cell Count by Filtration." Proceedings of the 26th Annual International Conference of the IEEE EMBS, San Francisco, CA, USA.

[39] Marwala, T., B. Crossingham (2008). "Neuro-Rough Models for Modelling HIV." 2008 IEEE International Conference on Systems, Man and Cybernetics (SMC 2008).

[40] Ding, Y., H. Ye (2009). "A fractional-order differential equation model of HIV infection of CD4C T-cells." Mathematical and Computer Modeling 50: 386_392.

[41] Roy, P. K., et al. (2009,August). "HIV model with intracellular delay -a mathematical study." 5th Annual IEEE Conference on Automation Science and Engineering Bangalore, India.

[42] Banks, H.T., et al. (2007). "Time delay systems with distribution dependent dynamics." Annual Reviews in Control 31: 17–26.

[43] Banks, H.T., et al. (2003). "Incorporation of variability into the modeling of viral delays in HIV infection dynamics." Mathematical Biosciences 183: 63–91.

[44] Lv, C., Z. Yuan (2009). "Stability analysis of delay differential equation models of HIV-1 therapy for fighting a virus with another virus." Journal of Mathematical Analysis and Applications 352: 672–683.

[45] Xu, R., (2011). "Global dynamics of an HIV-1 infection model with distributed intracellular delays." Computers and Mathematics with Applications 61: 2799–2805.

[46] Jiang, X., et al. (2008). "Analysis of stability and Hopf bifurcation for a delay-differential equation model of HIV infection of CD4+ T-cells." Chaos, Solitons and Fractals 38: 447–460.

[47] Zhou, X., et al. (2008). "Analysis of stability and Hopf bifurcation for an HIV infection model with time delay ." Applied Mathematics and Computation 199: 23–38.

[48] Srivastava, P. Kr., P. Chandra, (2010). "Modeling the dynamics of HIV and CD4+T cells during primary infection." Nonlinear Analysis: Real World Applications 11: 612_618.

[49] Nelson, P. W., et al. (2000). "A model of HIV-1 pathogenesis that includes an intracellular delay." Mathematical Biosciences 163: 201-215.

[50] Wang, Y., et al. (2009). "Oscillatory viral dynamics in a delayed HIV pathogenesis model." Mathematical Biosciences 219: 104–112.

[51] Nelson, P. W., A. S. Perelson (2002). "Mathematical analysis of delay differential equation models of HIV-1 infection." Mathematical Biosciences 179: 73–94.

[52] Ouifki, R., G. Witten (2009). "Stability analysis of a model for HIV infection with RTI and three intracellular delays." BioSystems 95: 1–6.

[53] Li, D., W. Ma, (2007). "Asymptotic properties of a HIV-1 infection model with time delay." Journal of Mathematical Analysis and Applications 335: 683–691.

[54] Xu, R., (2011). "Global stability of an HIV-1 infection model with saturation infection and intracellular delay." Journal of Mathematical Analysis and Applications 375: 75–81.

[55] Culshaw, R. V., S. Ruan (2000). "A delay-differential equation model of HIV infection of CD4+T-cells." Mathematical Biosciences 165: 27-39.

[56] Guardiola, J., et al. (2003). "Simulating the Effect of Vaccine-Induced Immune Responses on HIV Infection ." Human Immunology 64: 840–851.

[57] Hu, Z., et al. (2010). "Analysis of the dynamics of a delayed HIV pathogenesis model." Journal of Computational and Applied Mathematics 234: 461_476.

[58] Betechuoh, B. L., et al. (2008). "Computational Intelligence for HIV Modelling." IEEE.

[59] Lin, F., et al. (2005,December). "Theory for a Control Architecture of Fuzzy Discrete Event Systems for Decision Making. " Proceedings of the 44th IEEE Conference on Decision and Control, and the European Control Conference 2005, Seville, Spain.

[60] Melgarejo, M. A., et al. (2006,July). "A Genetic-Fuzzy System Approach To Control a Model of the HIV Infection Dynamics. " 2006 IEEE International Conference on Fuzzy Systems, Vancouver, BC, Canada.

[61] Abbasi, R., M. T. H. Beheshti, (2015)"Modeling and stability analysis of HIV-1 as a Time Delay Fuzzy T-S system via LMI's." in press, Applied Mathematical Modeling 39(23–24): 7134-7154.

[62] Wodarz, D., (2007). "Killer cell dynamics: Mathematical and computational approaches to immunology." springer.

[63] Lin, C., et al. (2007). "LMI Approach to Analysis and Control of Takagi-Sugeno Fuzzy Systems with Time Delay." Springer.

[64] Nentwig, M., P. Mercorelli (2010). "A Matlab/Simulink Toolbox for Inversion of Local Linear Model Trees." IAENG International Journal of Computer Science, 37:1, IJCS_37_1_03.

[65] Fletcher, C. V., et al. (2014,February) "Persistent HIV-1 replication is associated with lower antiretroviral drug concentrations in lymphatic tissues ." PNAS 111(6):2307–2312.

[66] Ene, L., et al. (2011). "How much do antiretroviral drugs penetrate into the central nervous system?. " Journal of Medicine and Life 4(4): 432-439.

Please cite this article using:

R. Abbasi and M. T. Hamidi Beheshti,"PDC Control of Time Delay Fuzzy T-S modeled HIV-1 System through Drug Dosage", *AUT J. Model. Simul.*, 49(1)(2017)33-42.

DOI: 10.22060/miscj.2016.839