Iranian Journal of Fuzzy Systems

Volume 18, Number 5, (2021), pp. 69-85

Original paper

University of Sistan and Baluchestan

A fuzzy generalized predictive controller to optimal drug dosage therapy of mathematical modeling of HIV

A. Vafamand[1], A. Fatehi[2] and S. M. Emad Oliaee[3]

[1,2,3] *Faculty of Electrical Engineering, K.N.Toosi University of Technology, Tehran, Iran.*

E-mails: a.vafamand@email.kntu.ac.ir, Fatehi@kntu.ac.ir, Emad.oliaee@ee.kntu.ac.ir

Abstract

This paper proposes a fuzzy-GPC based on a mathematical model of human immunodeficiency virus (HIV) to determine the drug dosage and control the progression of the illness. For this purpose, a Takagi-Sugeno (TS) fuzzy model is generated to identify the nonlinear behavior of HIV. The parameters of HIV are estimated by the least square error (LSE) estimation method. Moreover, three scenarios are proposed to control HIV. In scenario 1, according to TS fuzzy model, generalized Predictive Control (GPC) is designed for a daily base drug therapy. Scenario 2 and 3 are more practical. In scenario 2, since the biological behavior of patients are different, the variation in the patients biology is taken into account by generating data according to a group of patients with varying parameters in their mathematical model. In senario3, since daily diagnosis of patients health is costly, it is assumed that a patient information is available every month, and drug dosage is determined each month. As a result of which, the sample time of the measurement increases to 30 make it a multi-rate system. The result shows that the TS fuzzy models the mathematical model of HIV very well, and in all scenarios, the proposed controller has a good performance and the number of healthy cells are controlled in acceptable amount.

Keywords: Human immunodeficiency virus(HIV), drug dosage, TS fuzzy model, Fuzzy-General Predictive Control(GPC), varying parameters, increasing sample time.

1 Introduction

HIV or human immunodeficiency virus attacks immune system after enters to the body. As it is known, the immune system preserves the body from any type of infections and illnesses. What made this virus so dangerous is that the virus attacks immune system and destroys cluster of differentiation 4 (CD4) cells, which are ones of the crucial components of the immune system. As a result, the number of CD4 cells reduces, and the functionality of the immune system dramatically decreases [19] . Over time, the patient's immune system becomes too weak and even cannot defend the body against simple infections. If the number of CD4 cells falls below 200 per cubic millimeter of blood, the patient gets Acquired Immune Deficiency Syndrome (AIDS). AIDS is a critical stage, in which the patient may die in a year [23]. Unfortunately, still there is no specific cure for treatment. Researches show that unlike other viruses, the patient's body cannot get rid of the virus entirely even after treatment. So, these days, scholars try to control the virus instead of destroying it. If a proper treatment is administered, the virus can be controlled, and the patient can live as long as other healthy people. This fact illustrates the necessity of developing advanced treatments to capture the behavior of the HIV infection disease and controlling the virus.

In order to control the illness and plan a drug dosage, a mathematical model is an effective tool to describe the behavior of spreading HIV in a body. Different models have been proposed to describe the nonlinear and complex behavior of HIV. For instance, a three state model is introduced in [6, 18], which is a basic model and can describe the two first stages of the illness. Since the first two stages of the illness are crucial in designing drug therapy, a three-state model can be helpful effectively in treatment. Also, five and six states models are presented in [18]. The third stage of the

Corresponding Author: S. M. Emad Oliaee

Received: September 2019; Revised: September 2020; Accepted: April 2021.

illness, AIDS, and analyzing of parameters are obtained in [13]. A seven-state nonlinear model is established with antiretroviral therapy (ART) in [21]. Also, in [7, 27, 32, 38, 39], the estimation of the parameters is discussed.
For the purpose of controlling the illness and planning the drug dosage, different controllers have been designed. A Takagi-Sugeno (TS) fuzzy model is obtained in [3] and by using linear matrix inequality (LMI) technique, a robust H_∞ fuzzy controller was designed. By using a multi-objective function in [12] , two strategies are considered, and the drug therapy is planning according to the solutions in Pareto front. The cost functions are defined based on minimizing the drug dosage and maximizing the number of the healthy cells. In [22], four laws are established based on the close loop strategy in[12]. Firstly, the most effective parameters are identified and based on a Kalman filter, they are estimated. Then, by using non-dominated sorting genetic algorithm-II (NSGA-II), optimal structured treatment interruption (STI) strategies are extracted. A control input based on the Hamiltonian method and three-state model is suggested in [2]. In addition, optimal control is obtained for different mathematical models in [1, 16, 24, 28, 31].
Besides these efforts to control the HIV, model predictive control (MPC) is one of the control strategies, which is important in both academic and industrial communities for decades. It is one of the most powerful strategies due to its robustness against disturbance and uncertainties [40, 41]. Also, it can deal with physical constraints and time delays. Reference [30] is an appropriate paper in designing of MPC in field of HIV treatment. In this paper, the cost function is defined based on the concentration of healthy cells and drug dosage. The sample time is selected one day, and the drug dosage is determined for each day. Also, in [43], it is assumed that the value of healthy cells and viruses are available every week, and the MPC determines the drug dosage every week. Since the number of healthy cells and viruses are determined according to the blood test, the sampling time in [30] and [43] is not practical. Hence, a multi-rate MPC is applied in [25]. In the paper, the drug dosage is determined weekly while the number of healthy cells and viruses are measured each month. However, the controllers in [25, 30, 43] are designed based on a linear model. On the other hand, the HIV phenomenon has nonlinear dynamic. So, if a nonlinear model is deployed, the prediction of the behavior of the disease can be obtained more accurately. Meanwhile, the prediction procedure based on nonlinear model results is a more reliable control technique against uncertainties than the linear one. TS fuzzy models can approximate a large class of complex nonlinear systems as well and is an effective method to be incorporated with linear predictive controllers to obtain an overall nonlinear MPC [34].
The aim of this paper is using TS fuzzy model and generalized predictive controller (GPC) to design the controller based on a nonlinear model of HIV instead of a linear model. Since testing the blood and measuring the concentration of virus in the blood are highly costly and, it is not available in all hospitals and institutes, it is assumed that the concentration of healthy cells is only available. This is in contrast with [5, 8, 15, 16, 22, 24, 36], where the control input is determined by the number of both healthy cells and viruses. The required data to build the TS fuzzy model is generated by applying an Amplitude Pseudo Random Signal (APRBS) to the nonlinear mathematical model of HIV virus spreading in the body. According to this data, a TS fuzzy model is produced to identify HIV behavior. The parameters of the conclusion part in the fuzzy model are estimated by using Least Square (LS). In the design of GPC, a cost function is determined according to the concentration of healthy cells and drug dosage. Furthermore, the data is divided into past and future information based on the control horizon and Diophantine equation. As a result, the drug strategy is determined, and the number of healthy cells keeps above the 900 required thresholds.
The structure of this paper is organized as follows: In section II, the mathematical model of HIV, which is used to describe the behavior of the disease in the patients body is introduced. In section III, GPC and the formulation are considered. In section IV, a fuzzy-GPC is explained, and the controller design formulations are presented. In Section V, simulation results base on three scenarios are provided. Finally, in Section VI conclusion remarks of this paper are given.

2 HIV dynamics

There are different models presented to describe the progress of HIV and polynomial differential questions can describe the complex behavior of the illness. Among the existing models, the three-state model, the basic model, can effectively represent the two first stages of the behavior, which are important for planning a therapy [39].

$$\begin{aligned} \dot{x_1} &= \lambda - qx_1 - \beta\,(1-\eta u)\,x_1 x_3, \\ \dot{x_2} &= \beta\,(1-\eta u)\,x_1 x_3 - ax_2, \\ \dot{x_3} &= kx_2 - \gamma x_3. \end{aligned} \tag{1}$$

where x_1, x_2, and x_3 are the number of healthy cells or uninfected cells, infected cells, and free virus copies, respectively, and u is the drug dosage or the control input of the system. The definitions and values of the parameters are given in

Table 1 [39]. The behavior of dynamics of the mathematical model (1) is depicted in Figure 1. The schematic shows

Table 1: The definitions and values of the HIV dynamic parameters [39]

Parameters	***Definition***	***Value***
λ	production rate of the uninfected cells from the thymus	7
q	death rate of healthy cells	0.007
β	rate of the infection	4.2×10^{-7}
a	death rate of the y-cells	0.0999
k	viral copies per unit of time	90.67
γ	death rate of virus	0.2
η	Control therapeutic coefficient	0.9

that the healthy cells produce at the rate of λ and death at the rate of qx_1. When the virus enters a body, it attacks healthy cells and infects them at rate of $\beta x_1 x_3$. The infected cells can produce virus at rate of kx_2. Also, γx_3 and ax_2 are the death rate of the virus and infected cells, respectively [37].

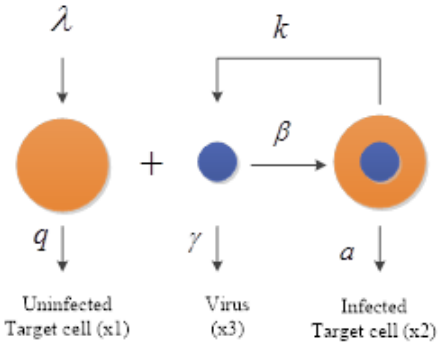

Figure 1: The schematic of mathematical model (1) when u=0 [37]

The initial values are $x_1(0) = 1000$,$x_2(0) = 0$, $x_3(0) = 10000$, which denotes a healthy body. The behavior of the system states with the defined initial conditions toward the stable point are depicted in Figure 2 for a patient.

3 General predictive control

GPC is developed by Clarke in 1987 [32]. It is one of the most popular predictive algorithms, which is used in the industrial process because of its good performance and robustness. The formulation is as follows. Most single-input and single-output (SISO) plants can be linearized around a particular set point. Thus, it can be described by the controlled auto-regressive integrated moving average (CARIMA) model (2) [10, 20].

$$A\left(z^{-1}\right)y(t) = z^{-d}B\left(z^{-1}\right)u(t-1) + C\left(z^{-1}\right)\frac{e(t)}{\Delta}. \tag{2}$$

$u(t)$ and $y(t)$ are input and output of the system. $e(t)$ is a white noise with zero mean. A, B, C are polynomials, which are defined as follows:

$$\begin{aligned} A\left(z^{-1}\right) &= 1 + a_1 z^{-1} + a_2 z^{-2} + \cdots + a_{na} z^{-na}, \\ B\left(z^{-1}\right) &= b_0 + b_1 z^{-1} + b_2 z^{-2} + \cdots + b_{nb} z^{-nb}, \\ C\left(z^{-1}\right) &= 1 + c_1 z^{-1} + c_2 z^{-2} + \cdots + c_{nc} z^{-nc}. \end{aligned} \tag{3}$$

parameter d is the delay time of the system and n_a, n_b and n_c are the maximum delay of the output, input, and noise, respectively. Operator Δ is defined in (4).

$$\Delta = 1 - z^{-1}. \tag{4}$$

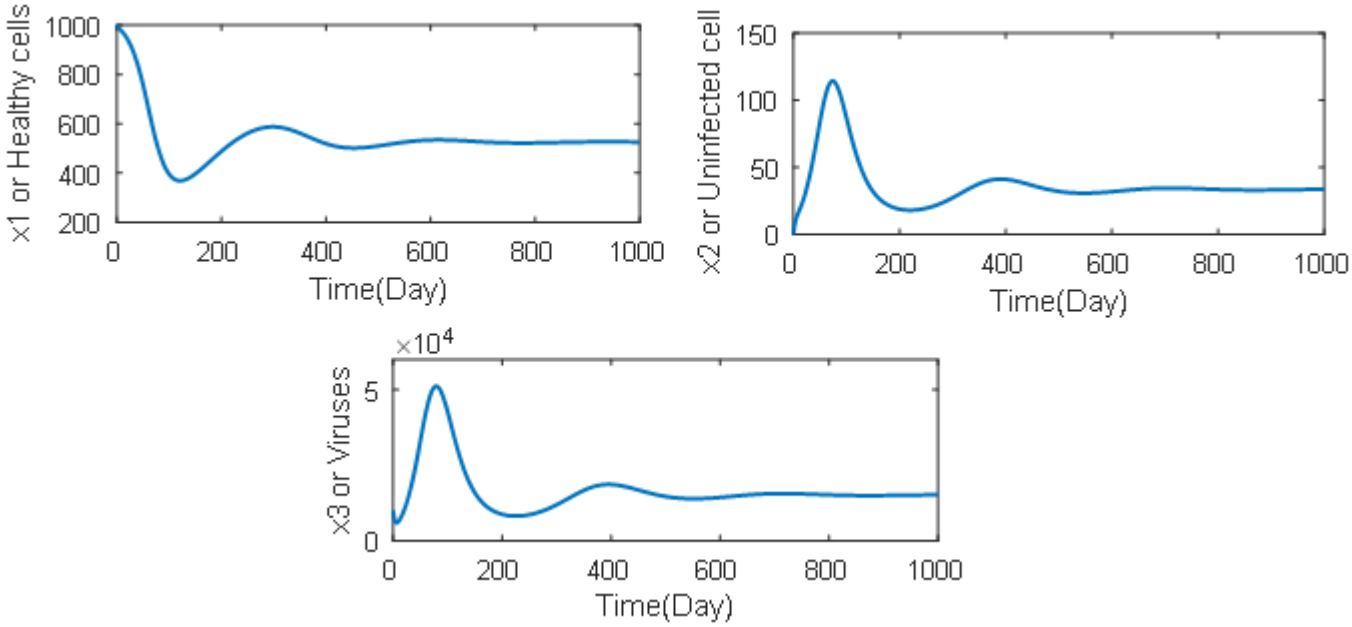

Figure 2: The state evolutions of the un-treatment HIV infection model

In GPC algorithm, the future control inputs are calculated to minimize a cost function, which is defined according to each problem. In (5) the cost function J is defined according to the error between the prediction of output $(\hat{y}\,(t+j \mid t))$ and future reference trajectory$(w\,(t+j))$, and the control variables [10, 20].

$$J\,(N_1, N_2, N_u) \;=\; \sum_{j=N_1}^{N_2} \delta\,(j)\,[\hat{y}\,(t+j \mid t) - w\,(t+j)]^2 + \sum_{j=1}^{N_u} \mu\,(j)\,[\Delta u\,(t+j-1)]^2. \tag{5}$$

$\delta\,(j)$ and $\mu\,(j)$ are weighting sequences, $N_1$and N_2 are the minimum and maximum costing horizon, and N_u is the maximum control horizon. The goal is that the future value of the control signal is calculated according to which the predicted output of the system is driven to the future reference trajectory. In order to minimize the cost function, Diophantine equation in (6) is used to separate the future and past information.

$$\begin{aligned} 1 &= E_j\left(z^{-1}\right)\tilde{A}\left(z^{-1}\right) + z^{-j}F_j\left(z^{-1}\right), \\ \tilde{A}\left(z^{-1}\right) &= \Delta A(z^{-1}). \end{aligned} \tag{6}$$

The polynomials E_j and F_j are obtained by dividing 1 by $\tilde{A}\left(z^{-1}\right)$. If (2) is multiplied by ΔE_j:

$$\tilde{A}\left(z^{-1}\right) E_j\left(z^{-1}\right) y\,(t+j) = E_j\left(z^{-1}\right) B\left(z^{-1}\right) \Delta u\,(t+j-d-1) + E_j(z^{-1})e(t+j). \tag{7}$$

By replacing from Diophantine equation (6) in (7):

$$(1 - z^{-j}F_j\left(z^{-1}\right))\, y\,(t+j) \;\; = E_j\left(z^{-1}\right) B\left(z^{-1}\right) \Delta u\,(t+j-d-1) + E_j\left(z^{-1}\right) e(t+j). \tag{8}$$

Finally, (8)can be rewritten as (9)

$$\hat{y}\,(t+j) = F_j\left(z^{-1}\right) y\,(t) + E_j\left(z^{-1}\right) B(z^{-1})\Delta u\,(t+j-d-1) + E_j\left(z^{-1}\right) e(t+j). \tag{9}$$

$e(t+j)$ indicates noise in the future. Therefore, the best estimation for it is its mean, which is zero. Equation 10 can predict the output in the future.

$$\hat{y}\,(t+j) = F_j\left(z^{-1}\right) y\,(t) + E_j\left(z^{-1}\right) B(z^{-1})\Delta u\,(t+j-d-1)\,. \tag{10}$$

By considering $G_j\left(z^{-1}\right)=E_j\left(z^{-1}\right)B(z^{-1})$, equation (10) can be rewritten as (11):

$$\hat{y}\left(t+j\right)=F_j\left(z^{-1}\right)y\left(t\right)+G_j\left(z^{-1}\right)\Delta u\left(t+j-d-1\right). \tag{11}$$

E_j and F_j are defined in the first two equation in (12), which are obtained by dividing 1 by $\tilde{A}\left(z^{-1}\right)$. Also, they can be expressed second two question in (12) as the [10]:

$$\begin{aligned} F_j\left(z^{-1}\right)&=f_{j,0}+f_{j,1}z^{-1}+\cdots+f_{j,n_a}z^{-n_a},\\ E_j\left(z^{-1}\right)&=e_{j,0}+e_{j,1}z^{-1}+\cdots+fe_{j,j-1}z^{-(j-1)},\\ E_{j+1}\left(z^{-1}\right)&=E_j\left(z^{-1}\right)+e_{j+1,j}z^{-j},\\ f_{j+1,i}\left(z^{-1}\right)&=f_{j,i+1}-f_{j,0}\tilde{a}_{i+1}\quad i=0,\ldots,n_a-1. \end{aligned} \tag{12}$$

Thus $G_j\left(z^{-1}\right)$ is calculated according to (13).

$$\begin{aligned} G_{j+1}&=G_j+f_{j,0}b_i\quad i=0,\ldots,\ n_b,\\ G_j\Delta u\left(t+j-d-1\right)&=g_{j,0}\Delta u\left(t+j-d-1\right)+g_{j,1}\Delta u\left(t+j-d-2\right)+\ldots \end{aligned} \tag{13}$$

Finally, the estimation of output is as follows. L is defined as the free response:

$$\hat{y}=GU+F\left(z^{-1}\right)y\left(t\right)+\acute{G}\left(z^{-1}\right)\Delta u\left(t-1\right)=GU+L. \tag{14}$$

Matrixes in (14) are defined in (15).

$$\begin{aligned} \hat{y}&=\begin{bmatrix} \hat{y}\left(t+d+1\mid t\right)\\ \hat{y}\left(t+d+2\mid t\right)\\ \cdots\\ \hat{y}\left(t+d+N\mid t\right) \end{bmatrix} \qquad U=\begin{bmatrix} \Delta u(t)\\ \Delta u(t+1)\\ \cdots\\ \Delta u(t+N-1) \end{bmatrix}\\ G&=\begin{bmatrix} g_0 & 0 & \ldots & 0\\ g_1 & g_0 & \ldots & 0\\ \ldots & \ldots & \ldots & \ldots\\ g_{N-1} & g_{N-2} & \ldots & g_0 \end{bmatrix} \qquad F\left(z^{-1}\right)=\begin{bmatrix} F_{d+1}(z^{-1})\\ F_{d+2}(z^{-1})\\ \cdots\\ F_{d+N}(z^{-1}) \end{bmatrix}\\ \acute{G}&=\begin{bmatrix} \left(G_{d+1}(z^{-1})-g_0\right)z\\ \left(G_{d+2}\left(z^{-1}\right)-g_0-g_1z^{-1}\right)z^2\\ \cdots\\ \left(G_{d+N}\left(z^{-1}\right)-g_0-g_1z^{-1}-g_{N-1}z^{-(N-1)}\right)z^N \end{bmatrix} \end{aligned} \tag{15}$$

Therefore, Equation (16) is obtained by replacing (14) in the cost function (5).

$$J=\left(GU+L-w\right)^T\left(GU+L-w\right)+\lambda u^Tu. \tag{16}$$

Equation (16) can be rewritten as in (17).

$$\begin{aligned} J&=\frac{1}{2}U^THU+b^TU+f_0,\\ H&=2\left(G^TG+\lambda I\right),\\ b^T&=2(L-w)^TG,\\ f_0&=(L-w)^T(L-w). \end{aligned} \tag{17}$$

Therefore, the vector of U is calculating in (18).

$$U=-H^{-1}b=\left(G^TG+\lambda I\right)^{-1}G^T(w-L). \tag{18}$$

Constrain on the input signal

One of the advantages of GPC is that the constraint can be considered explicitly in the optimization. One of the constraints is that the control input has minimum and maximum value as represents in (19). Therefore, the constraint can be expressed in (19). In order to design control input in the desired bound, both of linear equalities in (19) should be considered [10].

$$u_1 < u(t) < u_2$$

$$\begin{bmatrix} 1 & 0 & \dots & 0 \\ 1 & 1 & \dots & 0 \\ \dots & \dots & \dots & \dots \\ 1 & 1 & 1 & 1 \end{bmatrix} \begin{bmatrix} \Delta u(t) \\ \Delta u(t+1) \\ \dots \\ \Delta u(t+N_c+1) \end{bmatrix} \leq \begin{bmatrix} 1 \\ 1 \\ \dots \\ 1 \end{bmatrix} (u_2 - u(t-1))$$

$$\begin{bmatrix} -1 & 0 & \dots & 0 \\ -1 & -1 & \dots & 0 \\ \dots & \dots & \dots & \dots \\ -1 & -1 & -1 & -1 \end{bmatrix} \begin{bmatrix} \Delta u(t) \\ \Delta u(t+1) \\ \dots \\ \Delta u(t+N_c+1) \end{bmatrix} \leq \begin{bmatrix} 1 \\ 1 \\ \dots \\ 1 \end{bmatrix} (u(t-1) - u_1). \quad (19)$$

The optimization is solved according to liner constraint, which is shown in (19). If it has a feasible solution, so the control input will be in the band.

4 Fuzzy-GPC

Since a lot of plants are nonlinear with uncertainties, the conventional GPC should be extended to nonlinear systems. One way is combining the fuzzy techniques with the predictive control approach, which results in a low computational burden and precise control approach[17, 35]. The considered TS fuzzy-GPC is shown in Figure 3. The robustness of fuzzy-MPC is studied in [40, 41, 33, 42]. In (5), it is mentioned that the control input is optimized based on the error between predicted output and reference, and control variables. As the figure 3 shows, the vector of future outputs $(y - hat)$, which is obtained based on the fuzzy model, is used in the optimization to calculate the control input.

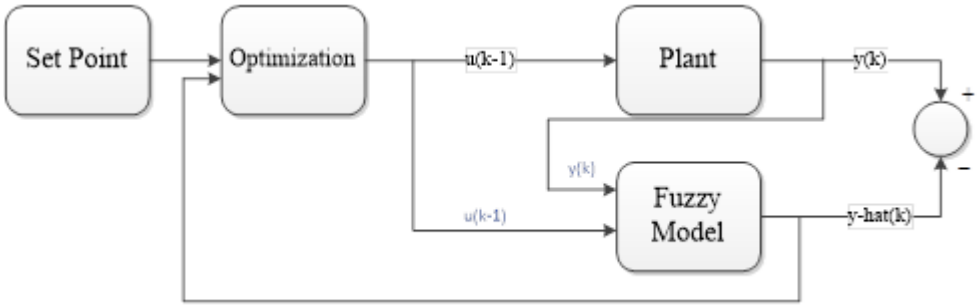

Figure 3: Fuzzy-GPC block diagram

A nonlinear system, can be represented as in (20) where NF denotes a nonlinear function [20].

$$y(k) = NF[y(k-1), y(k-2), \dots, y(k-n_y),\ u(k-d-1),\ \dots,\ u(k-d-n_u)]. \quad (20)$$

If the nonlinear system is estimated by TS fuzzy system, thus (20) can be written as in (21).

$$\begin{aligned} &Ri:\ \text{if } s_1(k) \text{ is } M_{i1}, \text{ and } \dots \text{ and } s_n(k) \text{ is } M_{in} \\ &\text{then } y_i(k) = a_i\left(z^{-1}\right)\ y(k-1) + b_i\left(z^{-1}\right)\ u(k-d-1) \text{ for } i = 1\ ,\ \dots,\ c, \end{aligned} \quad (21)$$

where s_l denotes the l_{th} input, R_i indicates the rule number i, M_{il} denotes l_{th} membership function of rule i , and c indicates the number of rules. $a_i\left(z^{-1}\right)$ and $b_i\left(z^{-1}\right)$ are defined in (22).

$$\begin{aligned} a_i\left(z^{-1}\right) &= a_{1i} + a_{2i}z^{-1} + \dots + a_{n_y i}z^{-(n_y-1)}, \\ b_i\left(z^{-1}\right) &= b_{1i} + b_{2i}z^{-1} + \dots + b_{n_u i}z^{-(n_u-1)}. \end{aligned} \quad (22)$$

The input vector of the TS fuzzy system is defined as x in (23) according to the past input and output.

$$s(k) = [\ s_1(k)\ ,\ \ldots,\ s_n(k)] = [y(k-1),\ \ldots,\ y(k-n_y),\ u(k-d-1\ ),\ \ldots,\ u(k-d-n_u)]. \tag{23}$$

Therefore, the output of the fuzzy system is estimated in (24).

$$\begin{aligned} y(k) &= \sum_{i=1}^{c} \omega_i [x(k)] \left(a_i\left(z^{-1}\right)\ y(k-1) + b_i\left(z^{-1}\right)\ u(k-d-1)\right) \\ &= \sum_{i=1}^{c} \omega_i [s(k)]\, s(k)\, \theta_i \\ &= \Psi(k)\Phi. \end{aligned} \tag{24}$$

$$\begin{aligned} \omega_i [s(k)] &= \frac{\prod_{j=1}^{n} A_{ij}(s_j)}{\sum_{i=1}^{c}\prod_{j=1}^{n} A_{ij}(s_j)} \\ \theta_i &= \left[\ a_{1i}, \ldots,\ a_{n_y i}, b_{1i},\ ..,\ b_{n_u i}\right]^T. \\ \Phi &= \left[\theta_1^T\ \theta_2^T\ \ldots\ \theta_c^T\right]^T, \\ \Psi(k) &= [\ \omega_1 [s(k)]\, s(k)\ \ \omega_2 [s(k)]\, s(k)\ \ \ldots.\ \omega_c [s(k)]\, s(k)]. \end{aligned}$$

It is assumed that the system is modeled as in (24). Thus, the CARIMA model can be rewritten as (25) [20].

$$\begin{aligned} \overline{a}\left(z^{-1}\right) y(k) &= \overline{b}\left(z^{-1}\right) u(k-d-1), \\ \overline{a}\left(z^{-1}\right) &= 1 - \overline{a}_1 z^{-1} - \cdots -\ \overline{a}_{ny} z^{-ny} \\ \overline{b}\left(z^{-1}\right) &= b_1 - \overline{b}_1 z^{-1} - \cdots -\ \overline{b}_{nu} z^{-(nu-1)}. \end{aligned} \tag{25}$$

where

$$\begin{aligned} \overline{a_l} &= \sum_{i=1}^{c} \omega_i [s(k)]\, a_{li} \quad l = 1\ ,\ldots.,\ n_y \\ \overline{b_m} &= \sum_{i=1}^{c} \omega_i [s(k)]\, b_{mi} \quad\ \ m = 1\ ,\ldots.,\ n_u. \end{aligned} \tag{26}$$

Equation (25) is similar to (2), but in (25) the parameters of CARIMA are changed according to each data.

5 Controlling HIV by fuzzy-GPC

In this section, three scenarios are considered. In the first one, the data from the identification is gathered daily from only one patient. In Scenarios 2 and 3 more realistic situations than the first one are considered. In Scenario 2, the data is gathered from multi patients, which results in a smaller period of data collection than that of Scenario 1. Also, in Scenario 3, a larger sampling time for both model identification and fuzzy-GPC than the first scenario is considered. In all of the scenarios, the parameters of consequent part of TS fuzzy are obtained according to LS, which is discussed in [26] .

5.1 Scenario 1

5.1.1 Identification

In order to maintain the organism as close as possible to the unstable healthy equilibrium point, drug dosage is considered an input for the open-loop state trajectory. Also, the concentration of healthy cells is considered as the output of the system, i.e. y.

Finding a proper input signal to fully excites the dynamics of the system is an important step to construct a TF fuzzy model for HIV infection. Thus, through the identification process, the parameters are determined. In [26], an Amplitude Pseudo-Random Binary Sequence (APRBS) is used. The suggested APRBS can effectively shows the behavior of HIV phenomena. The input signal is illustrated in Figure 4, and the output data is depicted in Figure 5. The gathered input-output data is divided into three parts: the train, validation, and test, which contain 70%, 20%, and 10% of all data, respectively. The train and validation data are used to estimate the parameters of the TS fuzzy model.

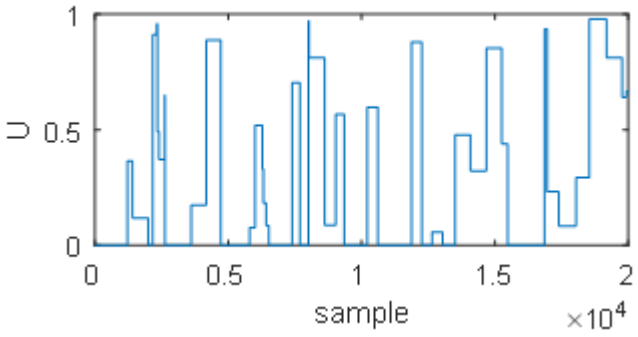

Figure 4: The APRBS signal

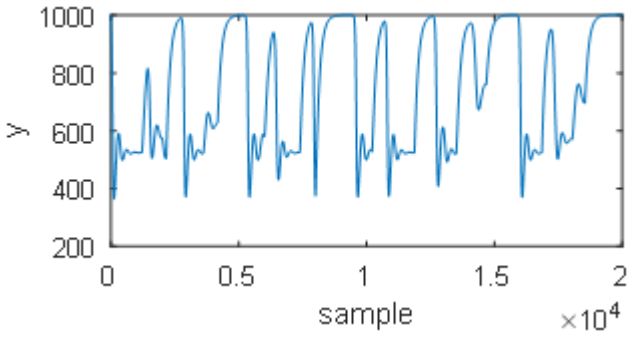

Figure 5: The output of system or the concentration of healthy cellsl

According to analyzing the data, the dynamic that is considered for the premise and conclusion parts are represented in (27) and (28), respectively.

$$u\,(k-1)\ \ ,\ \ y(k-15). \tag{27}$$

$$u\,(k-1)\ \ ,u\,(k-5)\,,\ \ y\,(k-15)\,,\ \ y(k-40). \tag{28}$$

The schematic of the TS fuzzy system which is considered to approximate the HIV model is represented in Figure 6.

The membership functions for two inputs of TS fuzzy model, $u(.)$ and $\overline{y}(.)$ are defined evenly in each of the variable spaces, as plotted in Figure 7 [34].

The parameters of the fuzzy system are estimated by Least Square (LS) [34]. Since the parameters of conclusion part in the fuzzy model have the linear relationship with the output of fuzzy systems, therefore the parameters which estimated by LS in (Table 2 in [34]) are used in designing the controller.

5.1.2 Fuzzy-GPC

By estimating the parameters of the TS fuzzy and generating the model of HIV, fuzzy-GPC can be designed. Since the concentration of healthy cells in the body of a healthy person are more than 800 per cubic millimeter of blood, so the reference in the cost function is set to 900. As a result of which, the drug dosage will be determined to prevent the progression of the illness to AIDS. The parameters of GPC which are defined in (5) are shown in Table 2.

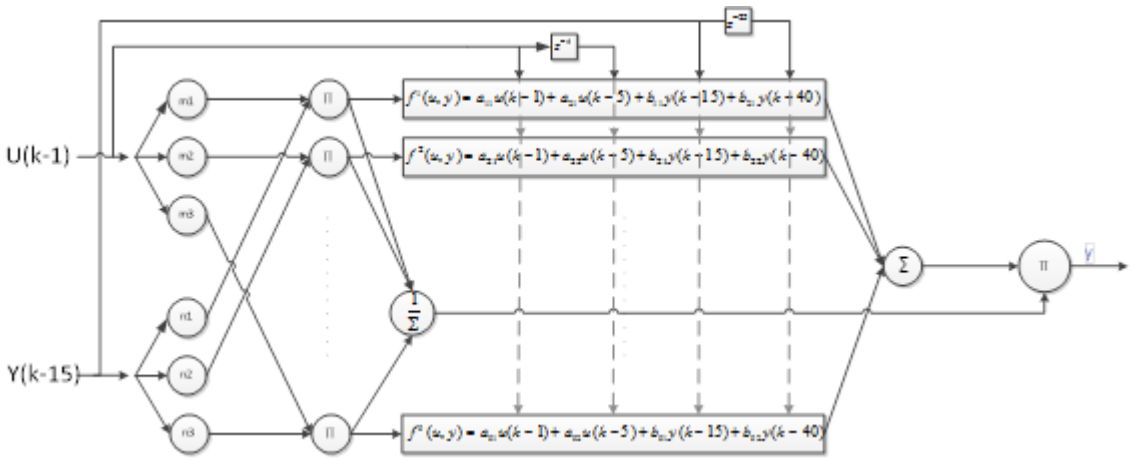

Figure 6: The schematic of TS fuzzy for HIV model

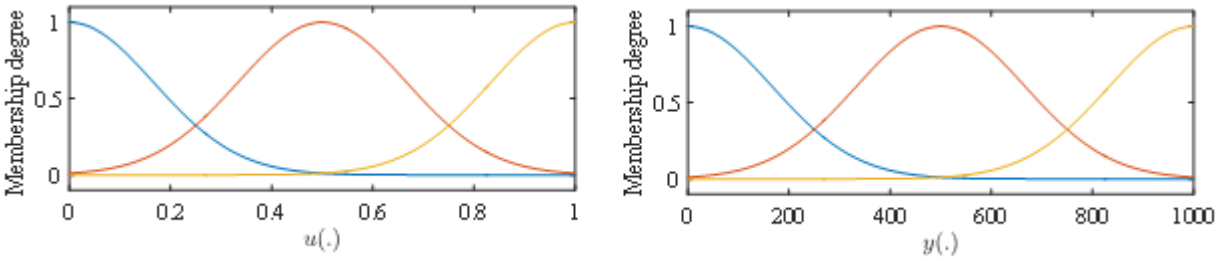

Figure 7: Membership functions of inputs of the TS fuzzy system (the input and output of the SISO HIV model)

Since the diagnose of HIV has a delay, which is about three weeks to three months after the entry of the virus to the body, most of the time doctors cannot start the treatment in a proper time. This fact is considered in the simulation, as a result of which the treatment is started in the 50^{th} day. In the mathematical model (1), the drug dosage or u should be in the range of zero to one. Therefore, the constraint on the control signal is considered in the optimization to be sure the amount of u is in the range. The results of simulation and parameters of the CARIMA are shown in Figure 8 and Figure 9, respectively. Also, to evaluate the results of Scenario 1 with the method in [22], the simulations are shown in Figure 8 and the results are reported in Table 5. Since the control input in [22] is designed to reach LTNP equilibrium and in our paper the goal is to reach the number of healthy cells to a determined value, the cost functions which are mentioned in [22] are changed to be suitable with our goal in the paper. According to laws 1 and 2 in [22], there are different points in Pareto front that are considered as the best solution. In this paper, the solution, which minimizes the error between the reference and the output is depicted in Figure 8 and Figure 13.

The number of the uninfected cells, infected cells, and viruses are shown in Figure 10 for the two cases of which the patient takes medicine and does not take it.

As Figure 8 and Figure 10 show, the number of healthy cells are controlled at 900. So, the amount of the infected cells and viruses are less than the amount of the case in which the patient does not take medicine. According to Figure 10, the amount of virus in a steady-state is not zero. This fact is compatible with reality, which researches indicate that the number of viruses in the body of a patient can be controlled and never can be eradicated completely [4, 9, 11].

Figure 11 indicates the number of healthy cells according to different initial values of viruses, which are 104, 1000 and 10000. As the figure shows, if the initial value is 104 or1000, the number of healthy cells in 50^{th} day are more than 900, as a result of which the controller can easier control the progression of the virus than the case which the amount of initial value is 10000.

The designed fuzzy-GPC in this scenario is proper according to the simulation term but it has some problems in terms of practical implementation. One of the drawbacks is that the volume of the required data to identify the model is large. So, generating all of the data according to just one model, means that it is expected that all of the data is gathered according to just one person, which is impractical. Another drawback is that the sample time of the system is one day, which means that the patient must be diagnosed every day. This is costly and impractical. Therefore,

Table 2: The definition and value of parameters in fuzzy-GPC

Parameters	***Definition***	***Value***
N_1	lower value of prediction horizon	7
N_2	higher value of prediction horizon	50
N_u	control horizon	50
δ	weighting factor for predicted error	1
μ	weighting factor for control increments	100
w	future reference trajectory	900

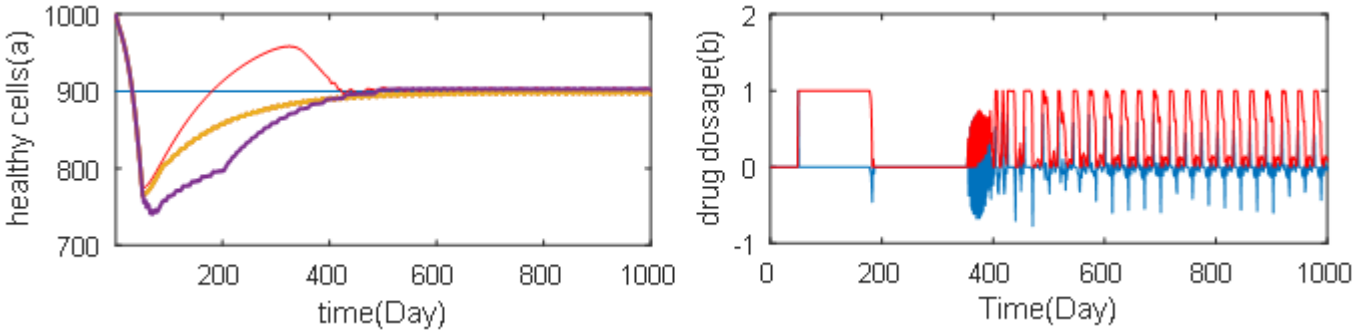

Figure 8: The output of fuzzy-GPC controller for Scenario 1 (red), reference (blue), law 1 (yellow), and law 2 (purple) in [22]. (b) drug dosage (red) and Δu (blue) for scenario 1

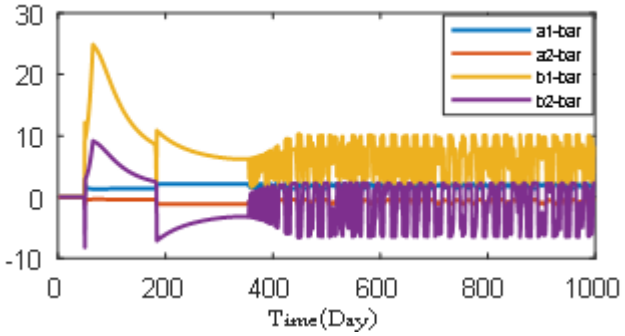

Figure 9: Parameters of CARIMA according to (25) and (26) for scenario 1

the implementation of the controller is impossible. Improving the proposed method to solve these two drawbacks are considered in the following two scenarios.

5.2 Scenario 2

The generated data in scenario 1, is according to the sample time of one day. As a result, if all the data is going to be acquired from one person, about 50 years data is needed, which is impossible. But the data can be organized by gathering the data of 10 people in 5 years instead of just one person in 50 years.

In this scenario, 10 patients are considered, and the APSBRS signal is divided into 10 parts. Then each part of the identifying input is applied to one patient. Thereby, the overall duration of collecting data is reduced 10 times, because the data is gathered in parallel. This method has another advantage to make the proposed method practically sound too. The biological of one person is different from another and a treatment developed according to only one patient cannot be used to properly treat other patients. When data of multiple patients are used to construct the nonlinear TS model, the model is more extensive and, so, the designed controller based on that, as the proposed treatment for the other patients, is more robust. The fuzzy-GPC can handle such uncertainty, as it is inherently robust against systems uncertainties. In [26], according to the clinical data, some researches were accomplished to find the range of each of

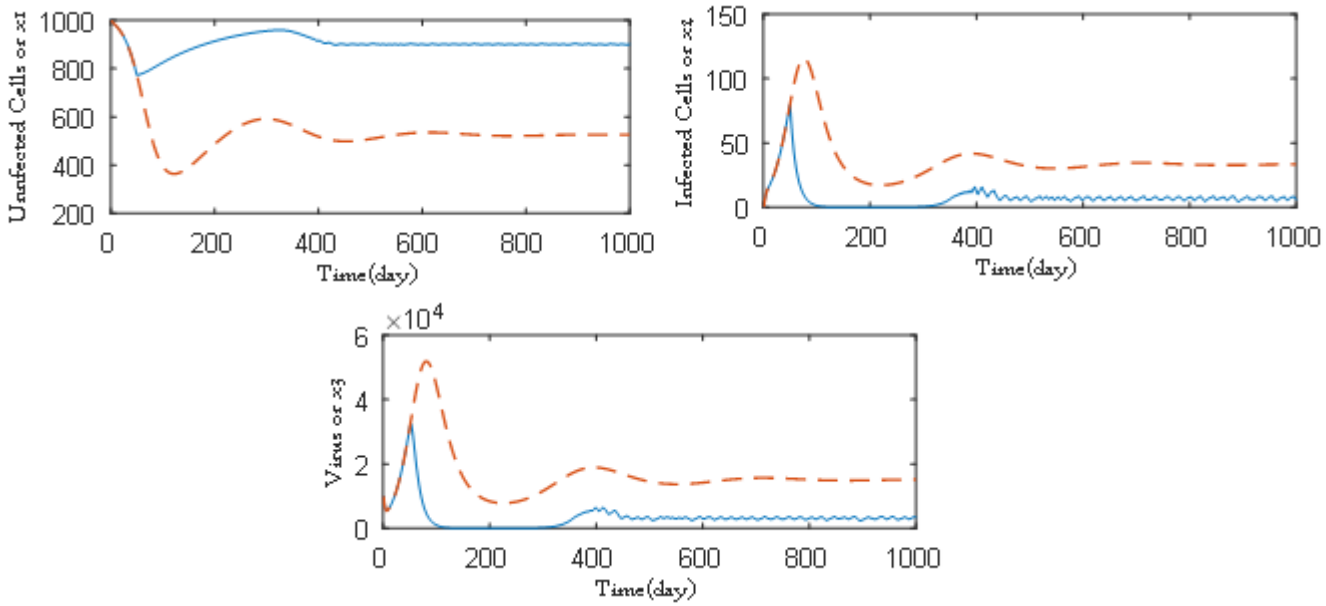

Figure 10: Comparing two cases in which a patient takes a treatment (blue) and dose not (red)

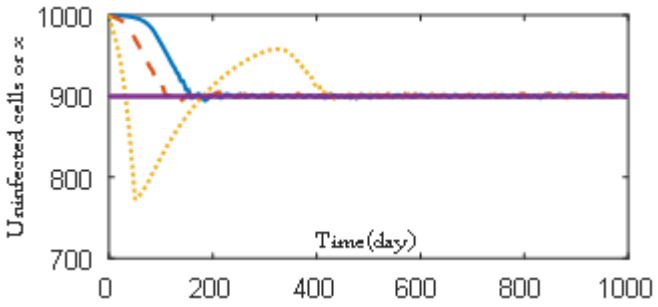

Figure 11: The output of fuzzy-GPC for different viruses' initial value (104 by solid blue line, 1000 by dash red line, 10000 by dotted orange line and reference by purple line)

the parameters of an HIV model. The results showed that a , γ, and d are almost same in individuals, while β , k, and λ are mainly different from one person to another. Inspired from [13] in which the ranges of the parameters are obtained according to varying one parameter and fixing other parameters, in this paper, the range of the parameters is computed as shown in Table 3.

Table 3: The range of varying parameters in mathematical model

Parameters	***Definition***	***Variation***
λ	production rate of the uninfected cells from the thymus	$(-20,\ 20)\%$
β	rate of the infection	$(-15,\ 7)\ \%$
k	viral copies per unit of time	$(-11,\ 16)\,\%$

Based on the results given in Table 3, ten random pairs for λ, β, and k are generated. The input data in Figure 4 is divided into ten portions, and each of them is applied to model (1) with corresponding random parameters. Then, the output data is generated by putting the data together in the series. As a result, 20000 sample data is generated according to ten different persons, which as stated above is more practical.

The same structure for TS fuzzy model as Scenario 1 is considered to estimate the HIV model with new data. The results are shown in Figure 12, which indicate that there are some small differences between the real data (the nonlinear model) and the estimated data at the TS fuzzy model. The parameters of the consequence part are provided in Table

4.

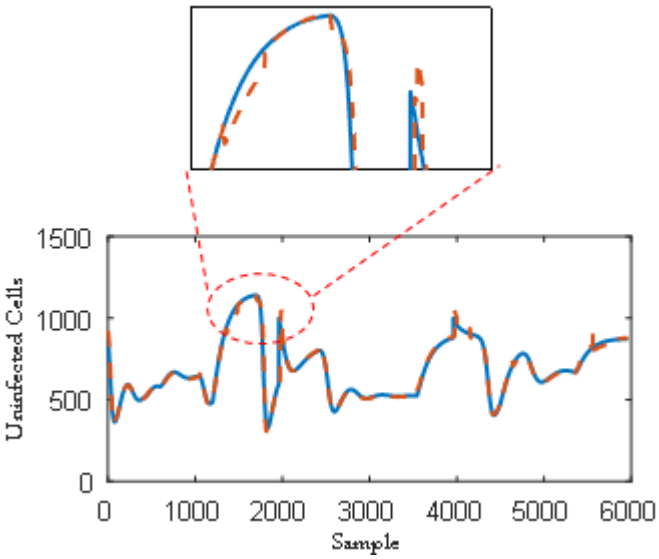

Figure 12: The real output and its estimation based on the identified TS fuzzy model for scenario 2 (Real output by the solid blue line, the estimated output dashed red line

Table 4: The conclusion parameters of fuzzy model for Scenario 2 based on LS

Rules	***Parameters of conclusion part***			
	a_1	a_2	b_1	b_2
***Rule* 1**	-1624	2227	3641	1.4536
***Rule* 2**	128	13	1.5852	-0.5910
***Rule* 3**	28	12	1.1444	-0.1537
***Rule* 4**	16066	5489	-260.9288	246.8179
***Rule* 5**	-11	5	1.9200	-0.9064
***Rule* 6**	51	3	0.9861	-0.0170
***Rule* 7**	3088	1741	108.7609	-108.3546
***Rule* 8**	46	11	0.8921	0.0782
***Rule* 9**	39	13	1.2065	-0.2548

The controller is designed according to the GPC parameters in Table 2 and the TS fuzzy model in Table 4. The results of scenario 2 and the method in [22] are depicted in Figure 13. As the figure shows, laws 1 and 2 in [14] cannot track the reference in the situation that λ is not a pre-defined value. Since in fuzzy-GPC method, the model is generated toward the data that they are based on different values of parameters, it is robust against the variation in the parameters. To compare the results of Scenarios 1 and 2 with laws 1 and 2 in [22], the final value of x_1, norm 2 error and the total amount of u, which indicates the total dosage of drug the patient takes, are reported in Table5 for 1000 days. The total amount of drugs is reported since the more the patient takes the drug, the more it costs and has more side effects. In addition, the possibility of being resistance to the drug increases.

5.3 Scenario 3

The sampling time of fuzzy-GPC in Scenarios 1 and 2 is one day that has two drawbacks. Firstly, it is hypothesized that the output of the system or the value of uninfected cells is measured every day. The value is determined by taking the blood test, so it is not possible to have it every day. Secondly, the dosage of a drug must be determined every day. Therefore, it is hard for the patient to get a new value of the dosage treatment and consume different amounts of drugs each day, also the human mistake may increase.
To solve these drawbacks, it is considered that the value of healthy cells is measured, and the drug dosage is determined monthly. So, this amount will be fixed in a month, and it is easier for the patients from treatment point of view.

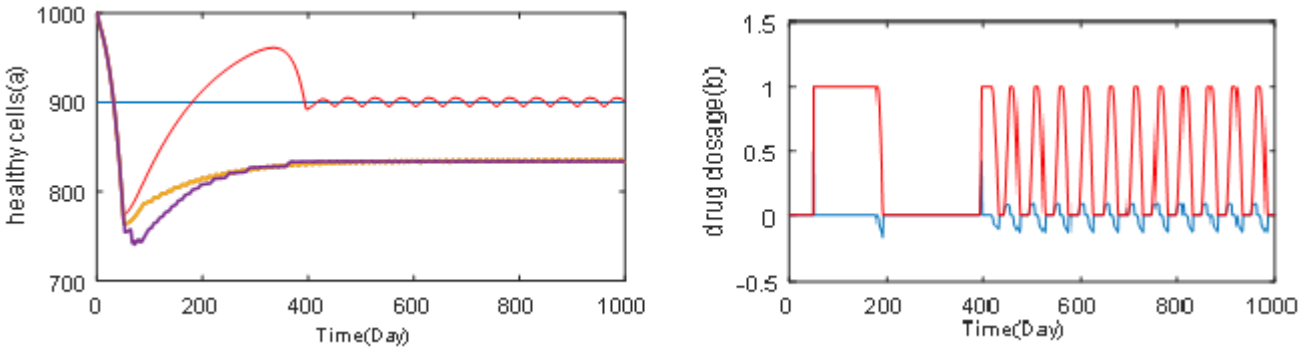

Figure 13: The out of fuzzy-GPC controller for Scenario 2 (red) and reference (blue) , law 1 (yellow) and law 2 (purple) in [22]. (b) drug dosage (red) and Δu (blue) for Scenario 2

Table 5: Performance comparison between fuzzy-GPC method and laws 1 and 2 in [22]

	Method	x_{1final}	$\|x_1 - x_{desire}\|_2$	$\sum u$
Scenario1	Fuzzy-GPC	901.51	1.13e+03	408.84
	Law 1	897.73	1.19e+03	444
	Law 2	902.45	1.80e+03	454
Scenario2	Fuzzy-GPC	901.20	1.15e+03	390.78
	Law 1	834.22	2.39e+03	406
	Law 2	833.78	2.54e+03	420

Therefore, the sampling time of applying input and measuring the output increases to 30 days. By increasing the sampling time from one to 30, the dynamics in (29) and (30) are used in premise and consequences of the TS fuzzy model.

$$u\,(k-30l)\ \ ,\ \ y(k-30l). \tag{29}$$

$$u\,(k-30l)\ \ ,u\,(k-60l)\,,\ y\,(k-30l)\,,\ y(k-60l). \tag{30}$$

where $u\,(k-30l)$ and $y(k-30l)$ stand for the input and output of the previous month and $u\,(k-60l)$ and $u\,(k-60l)$ denote the data of two months ago. The same TS fuzzy structure as Scenario 2 is considered, and the parameters are estimated by LS. Table 6 shows the parameters, and Figure 14 depicts the results of the identification. Since the sampling time increases, the accuracy of identification decreases. But, the model, in this case, has better performance in the stimulatory case.

Table 6: The conclusion parameters of fuzzy model for scenario 3 based on LS

Rules	***Parameters of conclusion part***			
	a_1	a_2	b_1	b_2
***Rule* 1**	-5836.72	6066.573	3.8786	-0.91685
***Rule* 2**	194.1494	-128.419	1.583427	-0.59849
***Rule* 3**	54.51514	12.01247	3.387466	-2.40238
***Rule* 4**	15422.13	31386.77	-207.649	214.7879
***Rule* 5**	83.19645	-20.1024	1.696424	-0.73659
***Rule* 6**	17.88064	4.767673	1.703883	-0.71657
***Rule* 7**	-14980.5	-1858.72	41.39104	-3.96044
***Rule* 8**	73.11412	0.703444	1.159047	-0.19852
***Rule* 9**	16.44531	-0.6702	1.695118	-0.71064

The parameters of the controller are determined according to Table 7. Note that in this table, the prediction horizon is $N_1 = 3$, which is equivalent to 90 days. The start of treatment is 62^{nd} day. The results are shown in Figure 15.

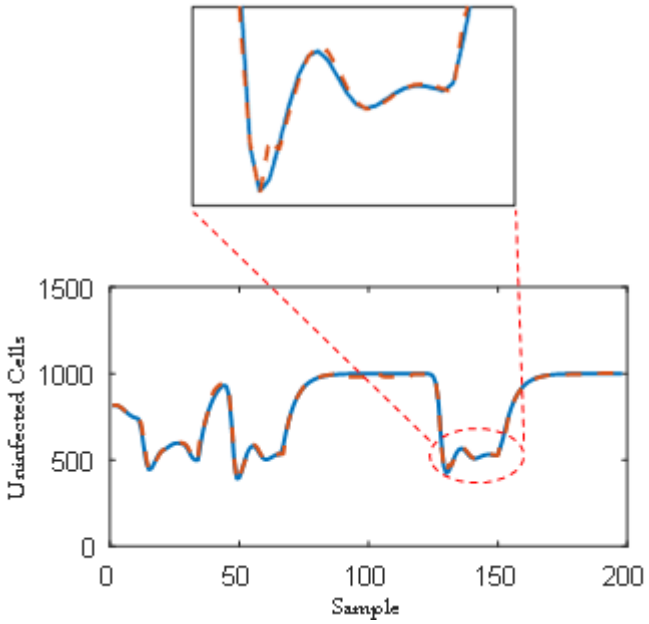

Figure 14: The real output and its estimation based on the identified TS fuzzy model for scenario 3 (Real output by the solid blue line, the estimated output dashed red line).

Table 7: The definition and value of parameters in fuzzy-GPC for scenario 3

Parameters	***Definition***	***Value***
N_1	lower value of prediction horizon	1
N_2	higher value of prediction horizon	3
N_u	control horizon	3
δ	weighting factor for predicted error	1
μ	weighting factor for control increments	10000
w	future reference trajectory	900

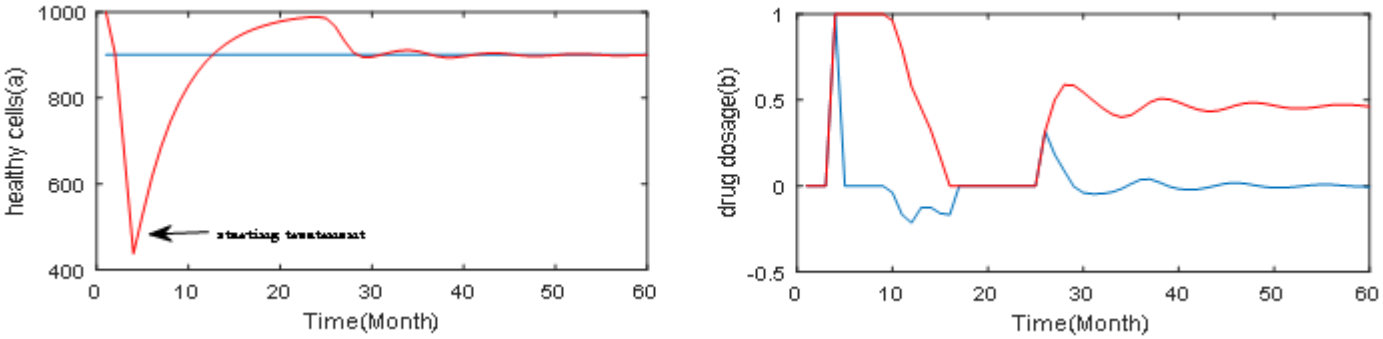

Figure 15: The out of fuzzy-GPC controller (red) and reference (blue). (b) drug dosage (red) and Δu for Scenario 3.

As can be seen in Figure 15, the fuzzy-GPC with sampling time 30 effectively handles the HIV virus. At the beginning of the treatment, the dosage is fully prescribed. When the number of healthy cells increases to beyond 900, the fuzzy-GPC suggests no dosage for some period and thereby, the number of healthy cells decreases. This treatment is equivalent to the STI treatment method [14, 29]. In this treatment, it is suggested that at first, the patient take fully drug. After partial recovery, it is suggested that the patient does not take any drug to remove its side effects from the body. After a few months of rest, again, the patient takes the drug. In the end, the controller of this scenario proposes the amount of 0.5 for drug dosage to keep the amount of the healthy cells about 900. To compare the results of different scenarios, the percentage of drug dosage in the treatment period, and the mean of three states of the nonlinear models

are reported in Table 8 for 1000 days of different treatment scenarios. x1 denotes the number of the healthy cells As the results show, scenario 1 has a good performance. While the number of healthy cells is measured every day and the parameters have the pre-defined value. As expected, in Scenario 3, the mean value of the healthy cells is smaller than others and the percentage of required drugs is higher. However, this scenario is more practical since the medical test to measure the number of healthy cells is taken every month, which is more realistic.

Table 8: Comparing the results of proposed scenarios

	Starting Treatment	Drug %	$\overline{x_1}$	$\overline{x_2}$	$\overline{x_3}$
Scenario 1	$51^{th}day$	43.03	902.23	7.75	3.55e+03
Scenario 2	$51^{th}day$	41.13	901.78	7.79	3.56e+03
Scenario 3	$61^{th}day$	44.65	873.01	9.75	4.45e+03
No treatment	-	0	538.70	36.74	1.66e+04
Full treatment	$51^{th}day$	100	959.08	2.87	1.35e+03

6 Conclusions

In this paper, a fuzzy-GPC is applied to a nonlinear mathematical model of HIV to determine the drug dosage and prevents the progression of HIV to AIDS. For this purpose, since a nonlinear model can estimate the behavior of the system better than a linear one, a TS fuzzy model was used to predicate the behavior of the system. Three scenarios were considered. Firstly, in Scenario 1, the fuzzy-GPC was designed to daily determine the drug dosage according to the TS fuzzy model. In Scenario 2, by varying the parameters of the mathematical model, the data was regenerated according to some patients with various biological behavior. In this case, the gathered data is within five-years of treatment which is more practical. In Scenario 3, since the amount of healthy cells which is needed to determine the condition of the disease is determined by blood test and on the other hand, the recording of the healthy cells and applying drug for every day is impossible, the sample time has increased to 30 day to be more practical. The experimental results show that the proposed method can accurately control the number of viruses and healthy cells in all scenarios. In scenario 2, the model can effectively predict the behavior of the system, so the designed drug dosage can control the number of healthy cells. Moreover, the results in scenario 3 show that the proposed treatment is efficient although the number of healthy cells are determined every month and the treatment is equivalent to the STI.

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Iranian Journal of Fuzzy Systems

Volume 18, Number 5 (2021), pp. 205

University of Sistan and Baluchestan

A fuzzy generalized predictive controller to optimal drug dosage therapy of mathematical modeling of HIV

A. Vafamand, A. Fatehi and S. M. Emad Oliaee

کنترل کننده فازی – پیش بین تعمیم یافته برای تعیین بهینه دوز دارویی براساس مدل ریاضی بیماری HIV

چکیده. در این مقاله، کنترل کننده fuzzy-GPC برای تعیین دوز دارویی و کنترل پیشرفت بیماری HIV براساس مدل ریاضی ارائه شده‌است. برای این منظور، یک مدل فازی تاکاگی–سوگنو (TS) برای شناسایی رفتار غیرخطی مدل HIV تولید شده‌است. پارامترهای مدل TS با استفاده از کمترین مربعات خطا تخمین زده می‌شوند. در این مقاله، سه سناریو برای کنترل بیماری HIV ارائه شده‌است. در سناریو اول، بر اساس مدل فازی تاکاگی–سوگنو، یک کنترل پیش‌بینی تعمیم یافته (GPC) برای تعیین دوز دارویی به صورت روزانه طراحی شده‌است. سناریو دوم و سوم به گونه‌ای طراحی شده‌اند که برای پیاده‌سازی عملی همخوانی بیشتری داشته باشند. در سناریو دوم، از آنجایی که پارامترای بیولوژیکی بیماران متفاوت است، تغییرات در پارامترهای بیولوژیکی در مدل‌سازی اعمال شده‌است. در این قسمت محدوده تغییرات پارامترهای ریاضی بدست آورده شده و این تغییرات در مدل ریاضی اعمال شده و در نهایت کنترل کننده پیاده‌سازی شده‌است. در سناریو سوم، از آنجایی که اندازه‌گیری مقدار سلول‌های سالم افراد بیمار به صورت روزانه پرهزینه است، فرض شده‌است که اطلاعات سلول‌های سالم بیماران به صورت ماهانه در دسترس است و بدین ترتیب دوز دارویی به صورت ماهانه تعیین می‌شود. بنابراین زمان نمونه برداری خروجی به ۳۰ افزایش یافته و یک سیستم چند نرخه خواهیم داشت. نتایج نشان می‌دهد که مدل فازی تاکاگی–سوگنو مدل ریاضی بیماری را به خوبی مدل‌سازی می‌کند و در همه سناریوها عملکرد کنترل کننده مناسب است و مقدار سلول‌های سالم بر روی میزان قابل قبولی کنترل شده‌است.