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Antiretroviral therapy of HIV infection using a novel optimal type-2 fuzzy control strategy

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Abstract The human immunodeficiency virus (HIV), as one of the most hazardous viruses, causes destructive effects on the human bodies' immune system. Hence, an immense body of research has focused on developing antiretroviral therapies for HIV infection. In the current study, we propose a new control technique for a fractional-order HIV infection model. Firstly, a fractional model of the HIV model is investigated, and the importance of the fractional-order derivative in the modeling of the system is shown. Afterward, a type-2 fuzzy logic controller is proposed for antiretroviral therapy of HIV infection. The developed control scheme consists of two individual controllers and an aggregator. The optimal aggregator modifies the output of each individual controller. Simulations for two different strategies are conducted. In the first strategy, only reverse transcriptase inhibitor (RTI) is used, and the superiority of the proposed controller over a conventional fuzzy controller is

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demonstrated. Lastly, in the second strategy, both RTI and protease inhibitors (PI) are used simultaneously. In this case, an optimal type-2 fuzzy aggregator is also proposed to modify the output of the individual controllers based on optimal rules. Simulations results demonstrate the appropriate performance of the designed control scheme for the uncertain system.

1. Introduction

Nowadays, the treatment of patients infected with HIV has attracted a lot of attention. According to the statistic studies, during the last decades, the population of people who struggle with this virus has been increased at an alarming rate [1–3]. HIV, which is known as a pool of viral genotypes, is one of the most hazardous threats to human being's health. The propagation of this virus is very fast. In the early step, the virus will occupy T-cells. Then, after a short period of time, HIV viruses which previously cannot replicate by itself, build a virus factory and begin reproducing. At the last stage, HIV debilitates the human immune system and causes acquired immune deficiency syndrome (AIDS) [4].

Antiretroviral therapy, which involves taking a combination of HIV medicines every day, is recommended for all people living with HIV, regardless of how long they have had the virus or how healthy they are; i.e., everyone who has HIV must start taking HIV medicines as soon as possible after diagnosis [5]. Antiretroviral therapy cannot completely cure HIV, but it slows the progression of HIV and helps infected people live longer. In addition, it is demonstrated that antiretroviral therapy decreases the risk of HIV transmission. Starting Antiretroviral therapy slows the progression of HIV and can keep a person healthy for many years [6].

So far, various research studies have been carried out to find a proper prediction of disease dynamics through mathematical modeling [7]. In this regard, the mathematical model of different diseases, including Malaria, Tuberculosis, Cancers, and human immunodeficiency virus, have been presented [8–12]. Mathematical modeling of diseases could play an inevitable role in the understanding of the system. In fact, finding an accurate model of diseases could pave the way for the long and short-term prediction of disease as well as designing antiretroviral therapies. In [13] for the first time, the dynamical modeling of diseases was proposed, which was a breakthrough in this field of study. After that, dynamic modeling has been used for a wide variety of diseases [14–17]. Statistic studies clearly show that theoretical epidemiology has resulted in brilliant conceptual and technical developments. Studies in this field not only aims to analyze and anticipate the dynamics of the disease but also the goal of this field is to find effective policies for control of [18–20].

The fractional-order calculus refers to equations with fractional or any other derivative order [21–23]. Due to the fact that fractional calculus is an excellent tool for the description of hereditary properties and memory of systems, the fractional-order differential equation has been widely pursued in different fields, including engineering [24], economic [25,26], and biology [27–30]. Up to now, several numerical methods and approaches including, Atangana–Baleanu and Abdon-Baleanu-Caputo, have been proposed for solving various fractional equations [31–34].

Several studies have modeled HIV using fractional models. For example, Ding and Ye have proposed a fractional-order model of HIV infection and analyzed the stability of the system [35]. Fractional-order models of HIV infection of CD4 + T cells and the dynamics of the tumor-immune system have been studied by Rihan [36]. In [37], HIV epidemic model based on a fractional calculus perspective and drug-resistance has been proposed. In [38], a multi-patch fractional-order HIV/AIDS epidemic model has been proposed, and dynamics of the system, such as the relationship between the spread of the epidemic among patches and human movement with detailed analysis, have been studied.

Optimal control theory, which has numerous applications in both engineering and science, is a branch of mathematical optimization that aims to find a control engineering for a given system over in a way that an objective function is optimized [39]. So far, various approaches are applied to optimizing the design of control systems [40]. Most of these approaches are classified under two main categories: 1) calculus-based methods and 2) enumerative schemes. Although the calculus-based methods are extensively utilized, they have some drawbacks, such as locality in scope, and dependency on the existence of either derivatives or some function evaluation scheme. Hence, calculus-based techniques are not robust over a broad spectrum of optimization functions. Numerous enumerative schemes have been proposed to overcome disadvantages of calculus-based techniques [41]. The genetic algorithm, which is on the basis of search procedures in the mechanics of natural genetics, is global and robust over a wide variety of problems [42].

During the past several years, various control strategies have been applied to HIV-immune systems, including feedback control [43,44], and optimal control [45–51]. Among these methods, the fuzzy controllers have several benefits, such as robustness against uncertainties and computational simplicity [52–54]. Also, recently, some research works suggested type-2 fuzzy control [55–57]. Disturbance observers based on type-2 fuzzy logic possess several benefits, including their robustness and fault tolerance, which result in better performance in dealing with complex systems comparing with the conventional type-1 fuzzy [58–60]. On the other hand, optimal controls have attracted a lot of attention because of their ability to consider various aspects of the system in the optimization function. Thus, numerous studies have been carried out on the application of optimal controls for treatment strategies [61–63].

As it is mentioned, fractional calculus is very beneficial to modeling the real word problems [64,65]. Motivated by this background, in the present study, we propose a fractional model of HIV, which could present more aspects of HIV infection. The recent demands of control of diseases are to increase

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safety and reliability. As it is evident, the existence of uncertainty is undeniable in the biological systems [66,67]. The type-2 fuzzy controller is a formidable tool in dealing with uncertain systems. To the best of our knowledge, no studies have been carried out on antiretroviral therapy for HIV using type-2 fuzzy controller. Thereby, using a type-2 fuzzy interval, a new control technique has been designed for the control of fractional-order HIV model. Also, taking advantage of optimization methods, the genetic algorithm has been applied to the control scheme to design the rules of the controller. There are a few studies in the literature that simultaneously consider both RTIs and PIs in designing control strategies for HIV. In the current study, using the optimal type-2 fuzzy controller, we consider both RTIs and PIs simultaneously and by considering the effectiveness of treatment and their costs, an effective control strategy is designed for the system.

The layout of the paper is as follows: Firstly, a model of HIV has been studied, and its equilibrium points are calculated then a fractional model for HIV is presented, and some numerical results have been illustrated in Section 2. After that, in Section 3, an optimal type-2 fuzzy controller for the fractional model of HIV is designed. Thereafter, in section 4, the simulation results of two different control strategies are demonstrated. Lastly, in section 5, conclusions have been presented.

2. Mathematical model of the system

In [68], the model of HIV infection is represented as follows:

$$\begin{aligned}\frac{dT}{dt} &= S - dT - (1-u_1)\beta TV,\\ \frac{dI}{dt} &= (1-u_1)\beta TV - \mu I,\\ \frac{dV}{dt} &= (1-u_2)KI - CV,\end{aligned} \tag{1}$$

where variables $T, I and V$ denote the amount of healthy CD4 + T cells in cells/mm3, the amount of HIV-infected CD4 + T cells in cells/mm3, and free particles of the virus in copies/mL. Parameter S denotes the rate at which the healthy CD4 + T cells are produced. Also, these cells normally die at a rate d. Parameter β represents the rate at which the healthy CD4 + T cells are infected. μ stands for the rate at which the infected CD4 + die. K indicates the rate at which HIV-infected CD4 + T cells produce new virions, and C denotes the death rate of virions. These biological rates are positive, which Table 1 demonstrate the numerical value of them. RTIs and PIs are significant categories of antiretroviral drugs to combat HIV. In this model, these antiretroviral drugs are represented by the functions $u_1(t)$and $u_2(t)$. These functions have values between 0 and 1 and show the effectiveness of both types of drugs.

To obtain equilibrium points of the model, the left side of Eq. (1), must be equal to zero. Then solving the obtained algebraic system of equations gives the equilibrium points which are named by disease-free equilibrium point and the endemic equilibrium point. Consequently, the equilibrium points of system (1) are as follows:

$$E_{df} = \begin{bmatrix}\frac{S}{d} & 0 & 0\end{bmatrix}, \tag{2}$$

whereE_{df} is the disease-free equilibrium point. Also, the endemic equilibrium point is as follow:

$$E_e = \begin{bmatrix}T^* & V^* & I^*\end{bmatrix}, \tag{3}$$

Table. 1 The value of the system's parameters [45].

Parameter	Value
S	10
d	0.02
β	2.4×10^5
μ	0.24
C	2.4
K	100

$$T^* = \frac{\mu C}{\beta K}, V^* = \frac{S}{\mu} - \frac{d\mu}{\beta K} and I^* = \frac{KS}{\mu C} - \frac{d}{\beta}$$

The linearization around the equilibrium points has the following state transition matrix and input matrix:

$$A = \begin{bmatrix}-d-\beta V^* & 0 & -\beta T^*\\ \beta V^* & \mu & \beta T^*\\ 0 & K & -C\end{bmatrix} B = \begin{bmatrix}\beta T^* V^* & 0\\ -\beta T^* V^* & 0\\ 0 & -KI^*\end{bmatrix}, \tag{4}$$

with the typical parameter values given in Table 1, at equilibrium point E_{df} (which is now (500,0,0)) we have the following transition and input matrix

$$A_{E_{df}} = \begin{bmatrix}-0.02 & 0 & -0.012\\ 0 & -0.24 & 0.012\\ 0 & 100 & -2.4\end{bmatrix}, B_{E_{df}} = \begin{bmatrix}0 & 0\\ 0 & 0\\ 0 & 0\end{bmatrix}, \tag{5}$$

The three eigenvalues of $A_{E_{df}}$ are (-0.02, 0.2183, −2.8583). Since around this equilibrium system has a positive eigenvalue, the system is not stable at this operating point E_{df}. At equilibrium point E_e (which is now (240.00, 21.67,902.78)) we have

$$A_{E_e} = \begin{bmatrix}-0.0417 & 0 & -0.0058\\ 0.0217 & -0.24 & 0.0058\\ 0 & 100 & -2.4\end{bmatrix}, B_{E_e} = \begin{bmatrix}5.2 & 0\\ -5.2 & 0\\ 0 & 0\end{bmatrix}, \tag{6}$$

and consequently, the three eigenvalues of A_{E_e} are (-0.0192 + 0.0658i, −0.0192–0.0658i, −2.6433 + 0.0000i). Since in this condition all eigenvalues have negative real parts, the system is stable at this equilibrium point. Actually, the operating point E_e corresponds to the asymptomatic stage of an HIV patient, and a typical control action (treatment) during this stage is needed to bring the viral load down to a lower level. Through proper treatment, we aim to increase healthy cells and reduce infected cells and viruses.

2.1. Fractional-order HIV model

Herein, we present a fractional model for HIV infection. In this study, the Caputo derivative is used. In [69], the definition of the Caputo derivative and integral is defined as follows.

Definition 1.. *Based on Caputo method, a fractional-order derivative of function $f(t) \in C^n([t_0, +\infty), R)$ is given by*

$$D^q f(t) = \frac{1}{\Gamma(n-q)} \int_{t_0}^{t} \frac{f^{(n)}(s)}{(t-s)^{q-n+1}} ds, \tag{7}$$

where$t \geq t_0$, $q$is a fractional-order and $q > 1$.Parameter n is an integer parameter which $n-1 \leq q < n$. Also, when $0 < q < 1$ the Caputo derivative can be calculated as:

$$D^q f(t) = \frac{1}{\Gamma(1-q)} \int_{t_0}^{t} \frac{f^{'}(s)}{(t-s)^q} ds. \tag{8}$$

Definition 2.. *The fractional integral of $f(t)$ is as follow*:

$$I^q f(t) = \frac{1}{\Gamma(q)} \int_{t_0}^{t} (t-\tau)^{q-1} f(s) ds, \tag{9}$$

where $t \geq t_0$ and $q > 0$. In addition, $\Gamma(q)$ denotes the Gamma function and is calculated by the following formula:

$$\Gamma(s) = \int_0^{\infty} t^{s-1} e^{-t} dt, \tag{10}$$

Now, we propose a fractional model of HIV with two control inputs as:

$$\begin{aligned} D^{q_1} T &= S - dT - (1-u_1)\beta TV, \\ D^{q_1} I &= (1-u_1)\beta TV - \mu I, \\ D^{q_1} V &= (1-u_2)KI - CV. \end{aligned} \tag{11}$$

In this mathematical model, the infected cells are produced with a frequency ratio of KI while free virus particles infect healthy cells based on their frequency ratio, βTV. The free virus particles are eliminated at a rate of CV. Moreover, at a rate of μI, the patient's T cells are destroyed.

A sufficient condition for the local asymptotic stability of the equilibrium points is that the eigenvalues λ_i of the Jacobian matrix fulfill the condition $|\arg \lambda_i| > \alpha \frac{\pi}{2}$. This confirms that fractional-order equations are, at least, as stable as their integer-order counterpart.

The numerical results of the proposed fractional system for different values of fractional-order derivatives are depicted in Figs. 1-3. The numbers of healthy CD4 + T cells, infected CD4 + T cells, and viruses without any treatment are illustrated by Figs. 1-3. The initial condition for this figure is considered as $[500, 0, 1]$. As it is shown in this figure, for instance, for $q_1 = 0.9$, the amount of infected CD4 + T cells reached up to 80, and after a short time, it decreased to about 21, while the number of healthy CD4 + T cells reduced to 240. This confirms the stability of the equilibrium point E_e. Also, the population of viruses increased more than 3450, and after almost 250 days, it reached 900 or so, which in this situation, the patient is diagnosed with AIDS. As it is shown, the aforementioned values are different for each fractional order.

Based on these figures, the value of fractional-order plays an important role in system behavior. Hence, using the fractional model, we could investigate the behavior of the system more precisely.

3. Optimal fuzzy type 2 controller

The antiretroviral treatment that provides a condition to regulate HIV infection is supposed to be control actions. The threshold of HIV virus number is 50 HIV RNA, and antiretroviral treatment keeps the number of HIV virus below this threshold; hence antiretroviral treatment is a successful tool for control of HIV infection [70]. Some basic definitions of type-2 fuzzy systems and details of the proposed control scheme have been described in the following.

3.1. Type-2 fuzzy system

A type-1 fuzzy system has four steps: fuzzification, rules evaluation, aggregation, and defuzzification which the output of a type-1 fuzzy engine is given by

$$y_f = \frac{\sum_{j=1}^{m} \theta_i \prod_{i=1}^{n} \mu_{A_i^j}(\chi_i)}{\sum_{j=1}^{m} \prod_{i=1}^{n} \mu_{A_i^j}(\chi_i)} = \sum_{i=1}^{m} \theta_i \xi_i(\chi) = \theta^T \xi(\chi), \tag{12}$$

$$\xi_i(\chi) = \frac{\theta_i \prod_{i=1}^{n} \mu_{A_i^j}(\chi_i)}{\sum_{j=1}^{m} \prod_{i=1}^{n} \mu_{A_i^j}(\chi_i)}, \tag{13}$$

where $\chi = [\chi_1, \chi_2, \cdots, \chi_n]^T$ and $\theta = \left[\theta_1, \theta_2, \hat{A} \cdot \hat{A} \cdot \hat{A} \cdot, \theta_m\right]^T$ denote the input vector for the fuzzy system and adjustable parameter vector, respectively. Parameter m indicates the number of fuzzy rules. Also, $\mu_{A_i^j}(\chi_i)$and $\xi_i(\chi)$respectively are the membership function and fuzzy basis function vector. A type-2 fuzzy engine is an extension of the type-1 fuzzy engine. In the type-2 fuzzy, the output processing block is used instead of defuzzifier block, which is

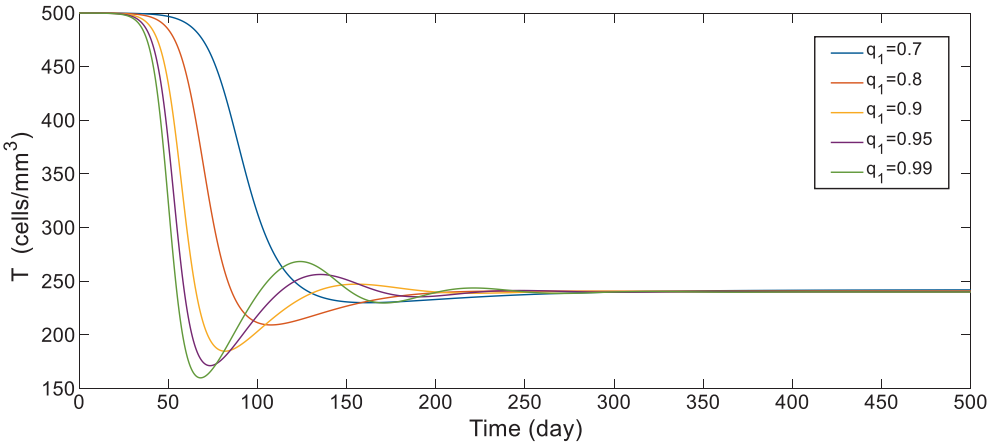

Fig. 1 The amount of healthy CD4 + T cells ($cells/mm^3$) without any treatment.

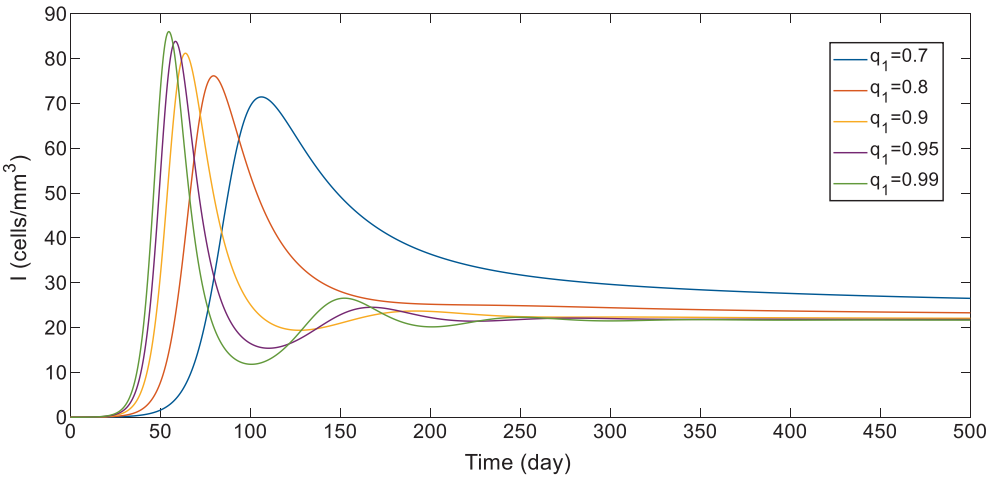

Fig. 2 The number of infected cells ($cells/mm^3$) without any treatment.

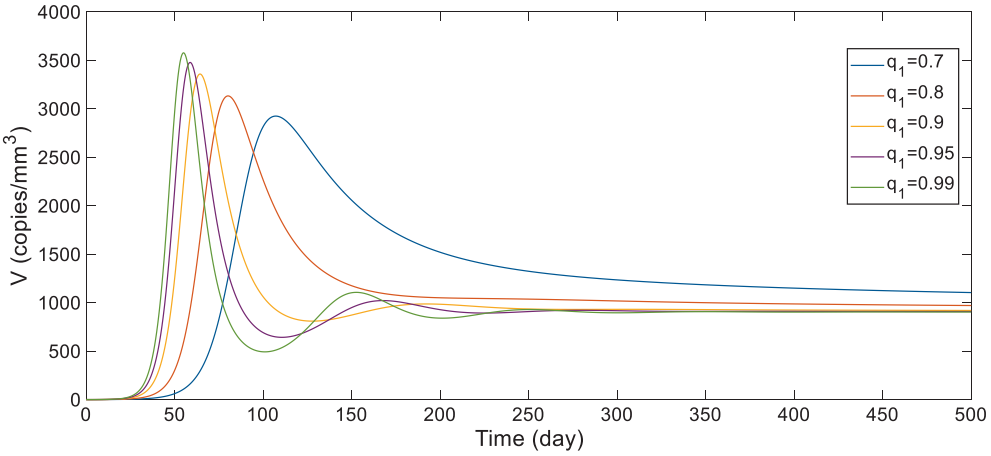

Fig. 3 The number of viruses ($copies/mm^3$) without any treatment.

the considerable difference between a type-2 and type-1 fuzzy engines. The important advantage of a type-2 system in comparison with a fuzzy type-1 is its robustness performance in dealing with uncertainties and disturbances [71,72]. A type-2 fuzzy logic system can be applied to systems when there are uncertain linguistic variables, dynamic uncertainties, and inaccurate information. A type-2 fuzzy set possesses an additional degree of freedom, which increases the ability of the system to deal with uncertainties [73,74]. A type-2 fuzzy sets (A_f) and interval type-2 fuzzy sets (A_{if}) are given by

$$A_f = \int_{\chi} \int_{u \in J_{\chi}} \frac{u_A(\chi,u)}{(\chi,u)}, \qquad A = \int_{\chi} \int_{u \in J_x} \frac{f_{\chi}(u)}{(\chi,u)} = \int_{\chi} \frac{\int_{u \in J_{\chi}} \frac{f_{\chi}(u)}{u}}{\chi}, \tag{14}$$

in which χ and $u \subseteq J_{\chi} \subseteq [0,1]$ respectively represents the primary and secondary variables. $u_A(\chi)$ stands for a type-2 membership function. $f_{\chi}(u)$ indicates the amplitude of secondary membership function which satisfies the following condition: $0 \le f_{\chi}(u) \le 1$. The framework of a type-2 fuzzy system with q inputs and Mrules is presented as:

Rule: If x_1 is F_1^i and x_2 is F_2^i .... and x_p is F_2^p THEN y is $y = y_i \; i = 1, 2, \cdots ..M$

where $F_j^i \; (j = 1, 2, ..., p)$indicates antecedent of type-2 fuzzy systems and $y_i = \left[y_i^s, y_i^v\right]$ represents consequent of type-2 fuzzy systems wherey_i^v and y_i^srespectively are model output comprising the lower and upper membership functions.

Fig. 4 represents the interval type-2 fuzzy membership functions. Parameter μ stands for the mean of the membership function. In addition, the deviations of the upper and lower membership functions are respectively represented by σ_1 and σ_2,. The upper and lower memberships function are defined as:

$$\bar{\mu}_i^q = \exp\left(-\frac{1}{2}\left(\frac{x_q - \mu_i^q}{\bar{\sigma}_i^q}\right)^2\right), \qquad \check{\mu}_i^q = \exp\left(-\frac{1}{2}\left(\frac{x_q - \mu_i^q}{\check{\sigma}_i^q}\right)^2\right), \tag{15}$$

where $\sigma = \left[\check{\sigma}_i^q, \bar{\sigma}_i^q\right]$ and μ_i^qrespectively represent the uncertain widths and the mean of the ith lower and upper membership functions for the qth input. $\check{\mu}_i^q$ and $\bar{\mu}_i^q$ are the lower and upper types of the firing degrees, which are associated with *ith* lower and upper membership functions, respectively.

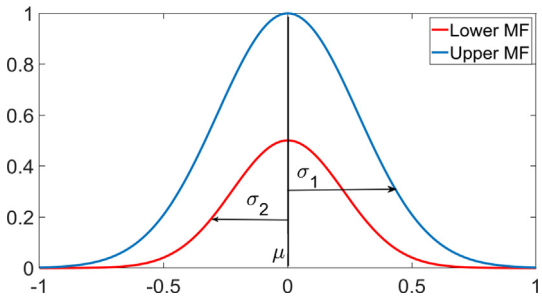

Fig. 4 Interval type-2 membership function.

Then, according to [75,76], the type-reduction procedure is calculated, and the outputs y_s and y_v are obtained. In the center-of-sets defuzzification approach, rule consequents are obtained by singleton positions as follows:

$$y_s = \frac{\sum_{i=1}^{L} \check{\chi}^i w_s^i + \sum_{i=L+1}^{M} \bar{\chi}^i w_s^i}{\sum_{i=1}^{L} \check{\chi}^i + \sum_{i=L+1}^{M} \bar{\chi}^i},$$
$$y_v = \frac{\sum_{i=1}^{L} \check{\chi}^i w_v^i + \sum_{i=L+1}^{M} \bar{\chi}^i w_v^i}{\sum_{i=1}^{L} \check{\chi}^i + \sum_{i=L+1}^{M} \bar{\chi}^i}, \tag{16}$$

where the consequent parameters for the lower and upper firing rules are shown by w_s^i and w_v^i, respectively. Based on Karnk–Mendel, the parameters L and R are utilized in the type reduction procedure. In addition, the weight strength of the rules ($\check{\chi}^i$and $\bar{\chi}^i$)are defined as follows:

$$\check{\chi}^i(x) = \check{\mu}_{F_1^i}^q(x_1) \times \check{\mu}_{F_2^i}^q(x_2) \ldots\ldots \times \check{\mu}_{F_q^i}^q(x_q),$$
$$\bar{\chi}^i(x) = \bar{\mu}_{F_1^i}^q(x_1) \times \bar{\mu}_{F_2^i}^q(x_2) \ldots\ldots \times \bar{\mu}_{F_q^i}^q(x_q). \tag{17}$$

where $\check{\mu}_{F_j^i}^q(x_1)$ and $\bar{\mu}_{F_1^i}^q(x_1)$ $(j = 1, 2, 3, \cdots, q) \in [0,1]$ respectively, denote the lower and upper grades of membership functions. $\check{\mu}_{F_j^i}^q(x_1)$ and $\bar{\mu}_{F_1^i}^q(x_1)$ are in scale of [0,1] and consequently $\check{\chi}^i(x)$ and $\bar{\chi}^i(x)$ are in scale of [0,1].

The average of y_l and $y_r$are utilized to defuzzify the interval set; this way, the output of the fuzzy system can be presented as follows [75,77]:

$$y_{f2} = \frac{1}{2}(y_s + y_v). \tag{18}$$

3.2. The proposed method for treatment using fuzzy type 2 controller

In antiretroviral therapies, we aim to increase the number of healthy cells as well as to reduce the number of infected cells and viruses. In the antiretroviral therapy for HIV infection, two types of drugs called RTIs and PIs (u_1 and u_2) have been utilized. Each type of these drugs could have different performance on the system according to the number of viruses and health conditions. Hence, we have a complex multi-input multi-output system. Thereby, using type-2 fuzzy controllers, we want to manage the complexity and uncertainties which exist in the system. The core idea in this approach is to divide a complicated problem into several simple problems. To this end, we design for each sub-system an individual controller, then the output of each control scheme feeds an aggregator. After that, the outputs of the aggregator are applied as a control input to the system [78]. Actually, when we want to apply both antiretroviral drugs RTI and PI, this method improves the effectiveness of the control technique.

In the proposed method, each individual controller is designed based on a type-2 fuzzy logic system. Then, the outputs of the individual controllers are combined using an aggregator. The proposed aggregator also utilizes a type-2 fuzzy controller. In order to achieve optimal rules, the rules of the aggregator are generated employing a genetic algorithm. The aggregator modifies and improves the values of control input for the system using the values of each individual controller. Since the rules for the type-2 fuzzy system in the aggregator are designed using a GA optimization, we will obtain the optimal control efforts. Actually, using the aggregator in the control scheme will help to provide the best combination of the information obtained by the individual controllers and result in the improvement of the performance of overall control. The architecture of the developed control technique is illustrated in Fig. 5.

Gaussian membership functions are utilized for all type-2 fuzzy controllers. In order to generate the longitudinal control, a fuzzy system with one input and one output is designed for PIs where in this fuzzy engine x_3 is input and is ($\widehat{u}_2$) output. For RTIs a type-2 fuzzy engine with two input (x_1 and x_3) and one output ($\widehat{u}_1$) is designed. Also, a type-2 fuzzy engine with two inputs and two outputs is designed as an aggregator.

3.3. Genetic algorithm optimization for aggregator

Because of the side effects of drug consumption in HIV treatment strategies, using an optimal approach could significantly improve the results of the treatment. By increasing the value of the drugs, the number of healthy CD4 + T cells will be increased, and the number of HIV-infected CD4 + T cells and free particles of the virus will be decreased. However, as it is evident, drugs have several detrimental side effects. Hence, using an optimal strategy is crucial in setting a treatment strategy. Also, sometimes these drugs are immensely expensive. To take these factors into account in this study, we have applied the genetic algorithm with the type-2 fuzzy control. A genetic algorithm optimization is used to determine the rules of the type-2 fuzzy aggregator.

The genetic algorithm optimization enhances the immune response of the body by maximizing the healthy T + cells count during the treatment as well as minimizing the side effects by reducing the value of drug usage. The genetic algorithm's chromosome, which is used for obtaining optimal rules, is depicted in Fig. 6.

4. Numerical Simulations

In this section, using numerical simulation, the performance of the proposed control scheme is investigated. The uncertainties are considered for the parameter of the system. Parameters of the model are considered to change by the following pattern:

Parameter for simulation = actual value of the parameter$\times(1 + .5sin(.1t))$. (19)

In this case, when there are many uncertainties and unknown factors in the system, the developed control technique through the type-2 fuzzy systems can significantly improve the results of the treatment.

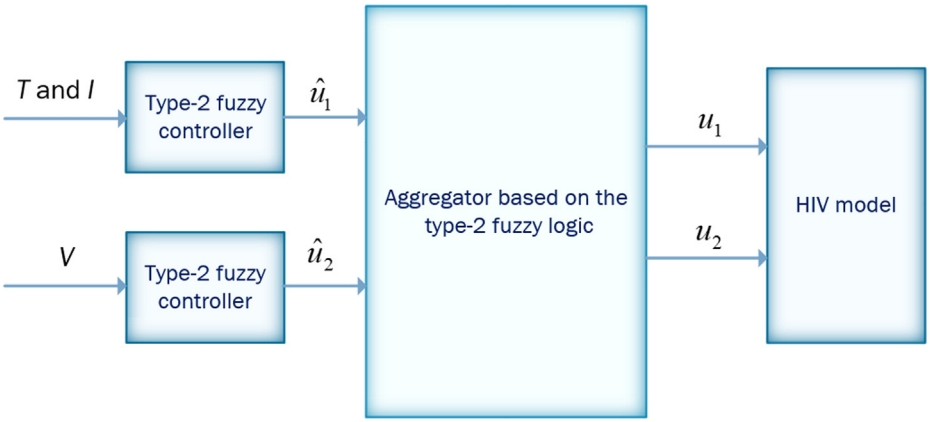

Fig. 5 The architecture of the proposed control scheme for HIV treatment.

Fig. 6 The chromosome which is used in genetic algorithm for obtaining optimal rules.

4.1. Strategy A: Antiretroviral therapy using RTI

In this strategy, only the RTIs (control input u_1) is used to control HIV infection. The numerical results when control u_1 is applied to the system are demonstrated by Fig. 7. The control input is turned on at $t = 45$days. It can be seen that as our aim at increasing healthy cells and reducing infected cells and viruses, using both controllers is well fulfilled, but the type-2 fuzzy controller shows better performance in comparison with the type-1 one. Under performance type-2 fuzzy controller, at $t = 100$ the amount of healthy CD4 + T cells ($cells/mm^3$), infected cells ($cells/mm^3$), and viruses (copies/mm3) are 438,

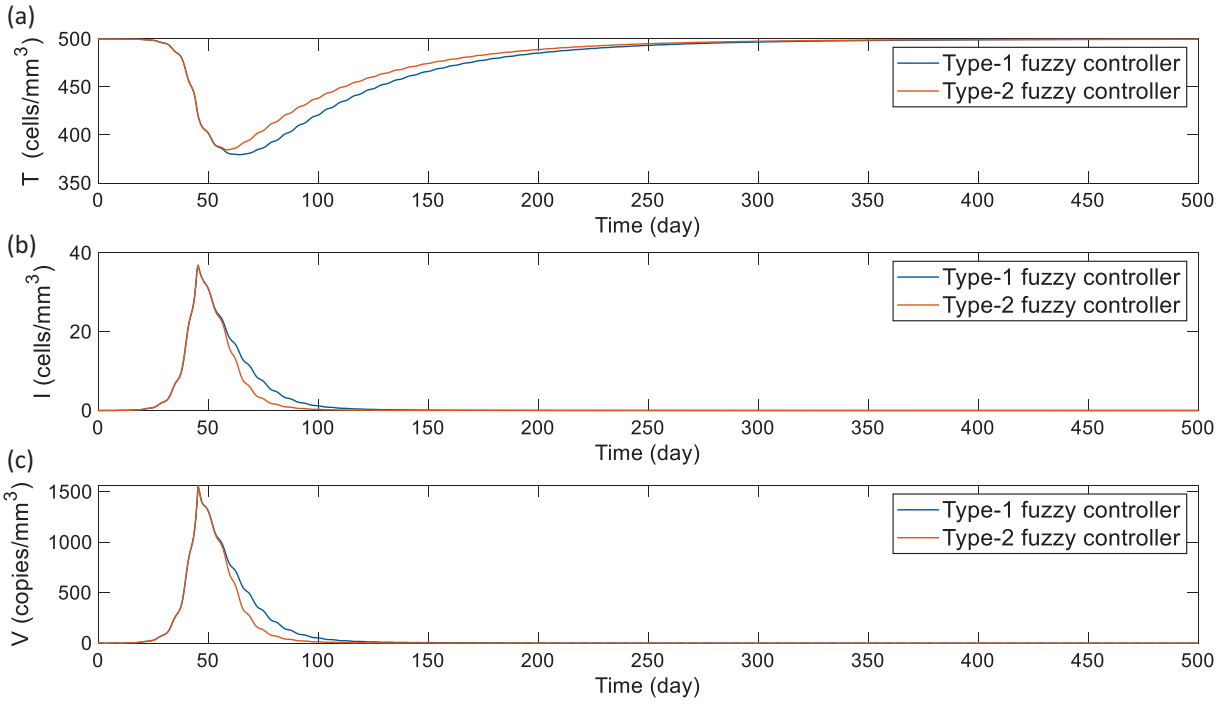

Fig. 7 The amount of (a) healthy CD4 + T cells ($cells/mm^3$) (b) infected cells ($cells/mm^3$) and (c) viruses (copies/mm3) under strategy A which includes RTIs (control input u_1).

0.25, and 15, respectively. At that time, those with the type-1 fuzzy controller are 421, 1.40, and 55, respectively.

It can be seen in Fig. 8 that control effort u_1 for the type-2 fuzzy controller is more. For both controllers, the rules are the same, but fuzzy type-2 has bigger control input as well as better performances in dealing with the uncertain system. As it is shown, this strategy (only use of RTIs) controls the behavior of the system.

4.2. Strategy B: Antiretroviral therapy using RTI and PI simultaneously.

In this section, the behavior of the system has been simulated for the case which both u_1 and u_2 are used to control HIV infection. To reduce the side effects and cost of the treatment, the following fitness function for the genetic algorithm optimization is considered as:

$$J = \eta_1 norme(u_1) + \eta_2 norme(u_2) + \eta_3 norme\left(x_1 - \frac{\mu C}{\beta K}\right), \qquad (20)$$

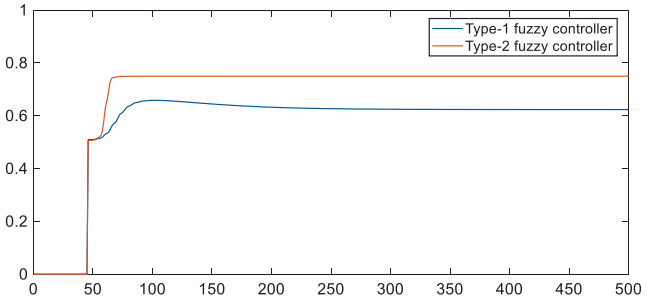

Fig. 8 Time history of the efforts u_1(RTIs).

where J is the fitness function for the genetic algorithm and $\eta_1 = 1$, $\eta_2 = 2$ and $\eta_3 = 10$ (Parameters η_1 and η_2 should be selected according to the cost of each drug). Terms $u_1$and u_2 and the distance of the healthy cells with the desired equilibrium point is considered in the fitness function. By justifying the parameter η_1, η_2 and η_3 we could change them between minimizing the systemic cost to the body and boosting the immune response. In this method, we consider each chromosome as a rule. Each gene has a value in the interval (1,2). Also, the population size is 30, the number of generations is considered 25, the crossover probability is 0.9, and the mutation probability is 0.05. Finally, the surface of the best fuzzy rules which are produced by the genetic algorithm is depicted in Fig. 9, where input 1 is $\widehat{u}_1$, input 2 is $\widehat{u}_2$, output 1 is u_1 , and output 2 is u_2.

Using the proposed aggregator, the output of each controller has been modified and optimized. Numerical results conspicuously show the effectiveness of the offered control method. Fig. 10 demonstrates that the number of healthy cells has been significantly increased. Also, based on this figure, the number of infected cells and viruses has been considerably decreased.

The control scheme is depicted in Fig. 11 is applied to the system. In obtaining these rules, several factors such as the cost of the drugs, side effects, and the importance of the speed of the treatment could be considered. Actually, these matters, which are a significant concern in the real applications, have been taken into account through the proposed method. Another benefit of the proposed method is the smooth behavior of the system in comparison with other methods. For instance, in [79], Nonlinear Feedback Control has been proposed for HIV treatment, in which the results of the Nonlinear Feedback Control have fluctuation, while for real applications, treatment strategies should be free from a lot of vibration.

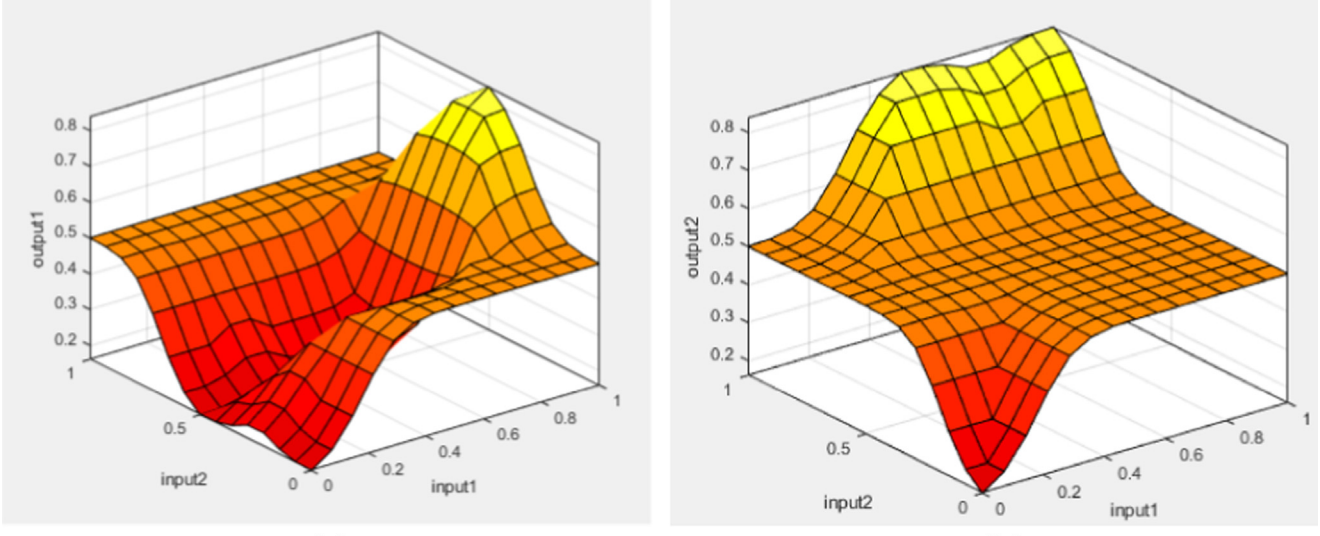

Fig. 9 The surface of type-2 fuzzy aggregator obtained by genetic algorithm optimization.

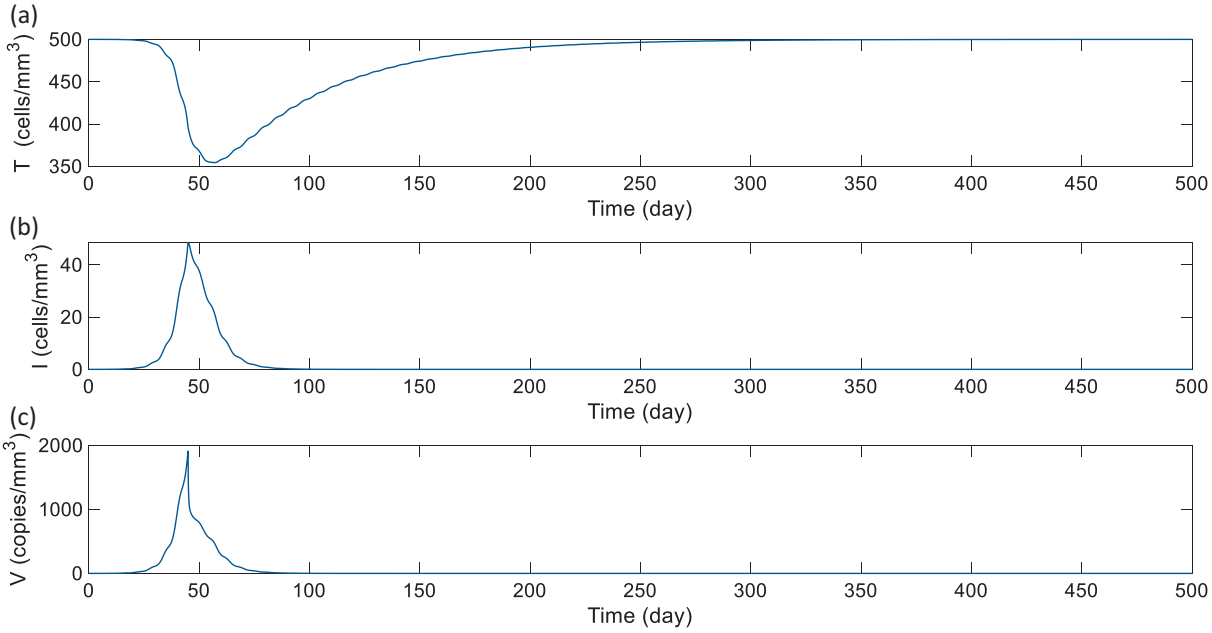

Fig. 10 The amount of (a) healthy CD4 + T cells (*cells*/mm^3) (b) infected cells (*cells*/mm^3) and (c) viruses (copies/mm3) under strategy C which includes RTIs (control input u_1) and PIs (control input u_2).

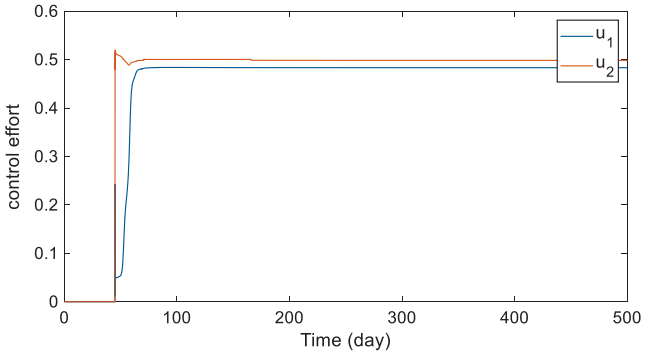

Fig. 11 Time history of the efforts u_1(RTIs) and u_2(PIs).

5. Conclusion

In this study, a fractional-order HIV model was studied. The behavior of the system and the effects of the fractional-order derivative in the results of the system were demonstrated. It was shown that the value of the fractional derivative could dramatically change the behavior of the model. Thereafter, a type-2 fuzzy logic controller was developed for antiretroviral therapy of HIV infection. The proposed controller consisted of two individual controllers and an aggregator. Using an optimal aggregator, the outputs of the individual controllers were modified. Based on the Caputo method, simulations for two strategies were performed. In the first strategy, only RTI was applied to the system. In this case, the results of the type-1 and type-2 fuzzy controller without the aggregator were compared. Through this comparison, it was demonstrated that the offered type-2 fuzzy controller results in more effective performances. Finally, in the second strategy, both RTI and PI were used simultaneously. For this strategy, in addition to the individual controllers, the optimal type-2 fuzzy aggregator was used to modify the output of the controller. By considering several factors, such as side effects of drugs, cost, and interaction between drugs, the proposed aggregator modified the value of the individual controllers. Actually, to reduce the side effects and cost of the treatment, their effects were considered in the optimal rules of the type-2 fuzzy aggregator. According to the simulation results, it can be confirmed that the offered optimal control technique is useful and effective in the control of the uncertain model of HIV infection. Future work could consider other optimization methods such as ant colony and particle swarm. Also, using an adaptive neural network-based method with the type-2 fuzzy controller can lead to better performances.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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