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USING FUZZY LOGIC STRATEGY FOR SOLVING A THERAPEUTIC OPTIMAL CONTROL PROBLEM OF AN HIV DYNAMICAL INFECTION

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Abstract

This paper aims at the development of an approach integrating the fuzzy logic strategy for an HIV therapeutic dynamical optimal control problem. To test the efficiency of this strategy, the authors propose a numerical comparison with the indirect method. The results are in good agreement with experimental data.

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1. Introduction

AIDS - Acquired Immunity Defficiency Syndrome is the disease that has affected the whole world in the 25 years since it was first detected. It is caused by Human Immunodefficiency Virus (HIV). Of great concern today is the treatment of patients infected with HIV. It currently mobilizes many researchers, who do not spare any effort for all that can contribute to the improvement of the health for the people living with the disease. One of the possible way is to use the multidrug therapies. In this case, several drugs can be considered. They are identical or different classes (RTIs, PI, AZT, DDI, DDC, and D4T). The availability of the strongly active antiretroviral multidrug therapies (HAART: Highly Active Antiretroviral Therapy) in the countries with high incomes allowed remarkable falls of the deaths related to the AIDS. But the multidrug therapies presents certain disadvantages, in particular:

- Anti-HIV treatment does not cure an infection.
- The HIV can gradually acquire resistance to the drugs.

Several authors were interested in mathematical modelling of therapeutic control of the HIV [2]. These controls consist of strategies defined by the experts [1]. These strategies are more or less acceptable, but they present unverifiable side effects. The objective of this paper is to find adapted therapeutic controls, which minimize an objective function to stabilize the parameters. We consider the described mathematical model in [1], where a dynamic mathematical model justifies the interaction of the immune system with HIV and permits drug “cocktail” therapies. Here, an optimal control problem permits to derive optimal structured treatment interruption (STI) to control HIV and limit drug exposure. Taking into account nonlinearity of the differential equations, which model the dynamics of the infection in the human organism, the determination of solution is a problem, which can appear to be difficult. In this work, we propose a strategy of calculation based on fuzzy logic to determine a protocol of optimal treatment.

This paper is organized as follows. Section 2 is interested in methods. Thus, it presents the optimal control problem. Moreover, a short description of strategy approach of fuzzy logic for solving optimal control problems is discussed in this section. The Section 3 describes resolution approches to solve a problem of optimal control for HIV dynamical infection. We present the indirect approach and the approach integrating the fuzzy logic. The numerical simulation is presented in Section 4. Finally, we give concluding remarks in Section 5.

2. Methods

2.1. Model description

There are many mathematical models for dynamical infection of HIV in human organism [6], [7], [10], and [11]. Simple models describe the interaction between the immune system and the HIV [10], [11]. In this paper, we consider a mathematical model, which describes the interaction between the $CD4^+$ cells, the HIV, and the immune system. Such model has been elaborated by Perelson and Callaway [4] that considered six compartments. To complete this model, Bonhoeffer added the compartment permitting to describe the dynamics of the immune response [3]. In presence of a treatment, the model of dynamical infection is based on the compartmental diagram presented in the Figure 1.

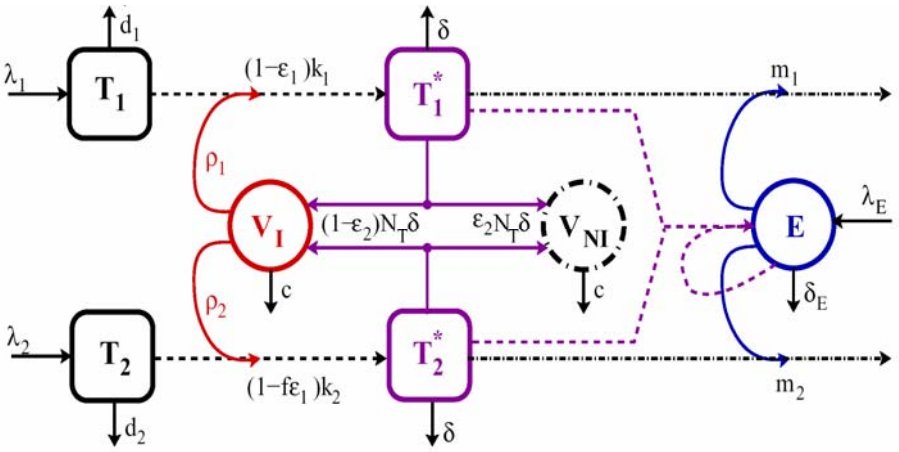

Figure 1. Compartmental diagram describing the dynamics of HIV infection in vivo.

If we note $\epsilon_1(t) = u_1(t)$ and $\epsilon_2(t) = u_2(t)$, the model proposed consists of the following differential equations [2]:

$$\begin{cases} \dfrac{dT_1}{dt} = \lambda_1 - d_1 T_1 - (1 - u_1(t))k_1 V_I T_1, \\ \dfrac{dT_2}{dt} = \lambda_2 - d_2 T_2 - (1 - fu_1(t))k_2 V_I T_2, \\ \dfrac{dT_1^*}{dt} = (1 - u_1(t))k_1 V_I T_1 - \delta T_1^* - m_1 E T_1^*, \\ \dfrac{dT_2^*}{dt} = (1 - fu_1(t))k_2 V_I T_2 - \delta T_2^* - m_2 E T_2^*, \quad f \in [0, 1], \\ \dfrac{dV_I}{dt} = (1 - u_2(t))10^3 N_T \delta (T_1^* + T_2^*) - cV_I \\ \qquad - (1 - u_1(t))\rho_1 10^3 k_1 V_I T_1 - (1 - fu_1(t))\rho_2 10^3 k_2 V_I T_2, \\ \dfrac{dV_{NI}}{dt} = u_2(t)10^3 N_T \delta (T_1^* + T_2^*) - cV_{NI}, \\ \dfrac{dE}{dt} = \lambda_E + \dfrac{b_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b} E - \dfrac{d_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d} E - \delta_E E. \end{cases} \tag{1}$$

The state variables are: T_1 (type 1 target cells, e.g., $CD4^+$ T-cells), T_2 (type 2 target cells, e.g., macrophages), V_I (infectious free virus), V_{NI} (non-infectious free virus), and E (cytotoxic T-lymphocytes). A superscript asterisk $(^*)$ denotes infected cells.

The natural infection rate $k_i (i = 1, 2)$ may differ between two populations, which could account for suspected differences in activation rates between lymphocytes and macrophages. The treatment factor $u_1(t)$, described further below, represents a reverse transcriptase inhibitor (RTI) that blocks new infections, and is potentially more effective in population $1 (T_1, T_1^*)$ than in population $2 (T_2, T_2^*)$, where the efficacy is fu_1 with $f \in [0, 1]$. The uninfected populations target cells T_1 and T_2 may have different source rates λ_i and natural death rates $d_i (i = 1, 2)$.

Free virus is produced by types of infected cells. We assume that they produce the virus at the same rate. In this model, virus may leave the V_I compartment due to natural death at rate c or via infecting a target cell (at rate $k_i T_i$) $(i = 1, 2)$. The action of a protease inhibitor (PI),

which causes infected cells to produce non-infectious virus V_{NI} is modelled by u_2. Therefore, u_1, u_2 are the controls and represent RTI and PI "efficacies", respectively. Tracking non-infectious virus is important because the clinically-measured viral load data for patients includes total free virus (sum of infectious V_I and non-infectious V_{NI}). The immune effectors E (cytotoxic T-lymphocytes) are produced in response to the presence of infected cells and existing immune effectors. The cytotoxic T-lymphocytes remove infected cells from the system in the equations for $\frac{dT_1^*}{dt}$ and $\frac{dT_2^*}{dt}$ at rates m_1 and m_2, respectively. N_T designates the productivity rate of virus by the infected $CD4^+$ cells and infected macrophages cells. $CD4^+$ T-cells and the macrophages cells have a finite life-span and die at a rate of δ per cell. ρ_1 (respectively, ρ_2) characterizes the capacity of antiretroviral that prevents the multiplication of the infected $CD4^+$ cells (respectively, infected macrophages cells). λ_E is the rate of natural production for the cells that play a crucial role in immune system. b_E designates the production rate of cells, which compose the immune system. d_E represents the elimination rate of cells, which constitute the immune response, δ_E is the natural death rate of the cells. K_b (respectively, K_d) represents the saturation constant for the immunized birth (respectively, death).

2.2. Setting of problem

Let us consider

$$F_1 = \lambda_1 - d_1 T_1 - (1 - u_1(t))k_1 V_I T_1;$$

$$F_2 = \lambda_2 - d_2 T_2 - (1 - fu_1(t))k_2 V_I T_2;$$

$$F_3 = (1 - u_1(t))k_1 V_I T_1 - \delta T_1^* - m_1 E T_1^*;$$

$$F_4 = (1 - fu_1(t))k_2 V_I T_2 - \delta T_2^* - m_2 E T_2^*;$$

$$F_5 = (1 - u_2(t))10^3 N_T \delta(T_1^* + T_2^*) - cV_I$$

$$- (1 - u_1(t))\rho_1 10^3 k_1 V_I T_1 - (1 - f u_1(t))\rho_2 10^3 k_2 V_I T_2;$$

$$F_6 = u_2(t) 10^3 N_T \delta (T_1^* + T_2^*) - c V_{NI};$$

$$F_7 = \lambda_E + \frac{b_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b} E - \frac{d_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d} E - \delta_E E, \tag{2}$$

and

$$F(t, X) = (F_1(t, X), F_2(t, X), F_3(t, X), F_4(t, X), F_5(t, X), F_6(t, X), F_7(t, X))^T, \tag{3}$$

the state system can be written as the following compact form:

$$\begin{cases} \dfrac{dX}{dt} = F(X(t); \mu(t)), \\ X(0) = X_0. \end{cases} \tag{4}$$

To determine the equilibrium state, we consider the state vector

$$X = (T_1, T_2, T_1^*, T_2^*, V_I, V_{NI}, E)^T,$$

the initial state vector

$$X_0 = (T_{1,0}, T_{2,0}, T_{1,0}^*, T_{2,0}^*, V_{I,0}, V_{NI,0}, E_0)^T,$$

the desired equilibrium state vector

$$X^e = (T_1^e, T_2^e, T_1^{*,e}, T_2^{*,e}, V_I^e, V_{NI}^e, E^e)^T,$$

and the control vector $\mu = (u_1, u_2)^T$. Moreover, we suppose the case, where the patient does not take any treatment. Then, it follows that

$$\mu(t) = 0, \quad \forall t \in [0, T_{\max}].$$

The equilibrium states are determined, if we take $F(X^e; 0) = 0$, and we consider that every fixed V_I^e corresponds to one and only one equilibrium state. Therefore, the equilibrium state is given by the following parameters

$$T_1^e = \frac{\lambda_1}{d_1 + k_1 V_I^e}, \quad T_2^e = \frac{\lambda_2}{d_2 + k_2 V_I^e}; \tag{5}$$

$$T_1^{*,e} = \frac{k_1 T_1^e}{\delta + m_1 E^e} V_I^e, \quad T_2^{*,e} = \frac{k_2 T_2^e}{\delta + m_2 E^e} V_I^e; \tag{6}$$

$$E^e = -\frac{\lambda_E}{\frac{b_E (T_1^{*,e} + T_2^{*,e})}{(T_1^{*,e} + T_2^{*,e}) + K_b} - \frac{d_E (T_1^{*,e} + T_2^{*,e})}{(T_1^{*,e} + T_2^{*,e}) + K_d} - \delta_E}; \tag{7}$$

$$V_{NI}^e = 0. \tag{8}$$

The numerical value is determined by using the symbolic calculation. The implementation in MATLAB permits to obtain the results given in the Table 1.

Table 1. The equilibrium points of the system (1), if $u_1(t_0)$ and $u_2(t_0)$ are zero

Equilibrium parameter	First equilibrium point (EQ_1)	Second equilibrium point (EQ_2)
T_1^e(cells / μl)	1096	814.6232
T_2^e(cells / μl)	4.5678	0.1238
$T_1^{e,*}$(cells / μl)	0	1.4799
$T_2^{e,*}$(cells / μl)	0	0.5213
V_I^e(copies / ml)	0	1463.7949
V_{NI}^e(copies / ml)	0	0
E^e(cells / μl)	0.1409	0.1487
	non infection	already tainted

The main idea of the problem is to permit the system to reach a equilibrium state from its initial state. In this case, the control parameter must stabilize the system to equilibrium point. For a patient who takes the treatment, the controls u_1 and u_2 influence the $CD4^+$ T-cells, macrophages and the immune response. The result of this influence is that the $CD4^+$ T-cells, the infected $CD4^+$ T-cells, the macrophages, the infected macrophages, the infectious free virus, the non-infectious free virus, and the cytotoxic T-lymphocytes stabilize around their respective equilibrium values T_1, T_1^*, T_2, T_2^*, V_I^e, V_{NI}^e, and E^e. We adopt a theoretical control approach, that is, we want to find a suboptimal treatment strategy that can lead to high immune response and subsequent control of viral load without the need for further drug therapy.

We formulate the problem of effective multidrug therapies as a tracking problem. Therefore, the optimal control problem can be formulated as follows.

Find (u_1^*, u_2^*) solution of

$$\begin{aligned}\min_{(u_1,u_2)} J(u_1, u_2) = \int_0^{T\max} \Big[&\beta_1(T_1 - T_1^e)^2 + \beta_2(T_2 - T_2^e)^2 + \beta_3(T_1^* - T_1^{*,e})^2 \\ &+ \beta_4(T_2^* - T_2^{*,e})^2 + \beta_5(V_I - V_I^e)^2 + \beta_6(V_{NI} - V_{NI}^e)^2 \\ &+ \beta_7(E - E^e)^2 + (\eta_1 u_1^2 + \eta_2 u_2^2)\Big] dt, \end{aligned} \tag{9}$$

subject the system (1). The parameters β_1, β_2, β_3, β_4, β_5, β_6, β_7, η_1, and η_2 are the weight positive real constants.

2.3. Description of fuzzy logic strategy approach

Let us consider the following problem.

Find $U_k \in \mathbb{R}^N$, $k = 0, \ldots, N-1$ that minimizes

$$J(U_0, \ldots, U_{N-1}) = \sum_{k=0}^{N-1} (x_k^T R x_k + U_k^T Q U_k), \tag{10}$$

subject

$$\begin{cases} x_{k+1} = f_k(x_k, U_k) \\ x_k \in \mathbb{R}^n, U_k \in \mathbb{R}^m \end{cases}, \; k = 0, \ldots, N-1, \tag{11}$$

where R and Q are positive defined matrices.

The problems (10)-(11) can be solved by the dynamic programming method. This method has a fast convergence, its convergence rate is quadratic and the optimal solution is often represented as a state of control feedback [?]. However, the solution is determined by this method depends on the choice of the initial trajectory and in some cases, this solution is not optimal. It is for this reason that, the integration of the fuzzy logic [8] can permit to determine quickly the optimal solution. We develop a linearization strategy of the subject system by an approach based on the fuzzy logic. This approach had been developed by Takagi-Sugeno [13], [14]. The model that has been introduced in 1985 by Takagi-Sugeno permits to get some fuzzy linearization regions in the state space [9]. While taking these fuzzy regions as basis, non linear system is decomposed in a structure multi models, which is composed of several independent linear models [5]. The linearization is made around an operating point contained in these regions.

Let's consider the set of operating point X_i, $i = 1, \ldots, S$. Different fuzzy approximations of the nonlinear term $NL(x)$ can be considered.

1. The approximation of order zero gives:

$$NL(x) \approx NL_0(x) = NL(x_i). \tag{12}$$

2. Using the first order of Taylor expansion series, we obtain:

$$NL(x) \approx NL_1(x) = NL(x_i) + \left(\frac{dNL(x)}{dx}\right)_{x_i}^T (x - x_i). \tag{13}$$

To ameliorate this approximation, we introduce the factor of the consequence for fuzzy Takagi-Sugeno system. This factor permits to minimize the error between the non linear function and the fuzzy approximation. If ϵ designates this factor, the approximation (13) can be formulated as the following for me:

$$NL(x) \approx (1-\beta)NL_0(x) + \epsilon NL_1(x)$$

$$\approx NL(x_i) + \beta\left(\frac{dNL(x)}{dx}\right)_{x_i}^{T}(x - x_i), \quad \text{with } 0 \le \beta \le 1. \tag{14}$$

If one replaces the term NL by its value approached in (11), the linearization around x_i leads to

$$x_{k+1} = A_{i,k}x_k + B_{i,k}U_k + C_{i,k},\ i = 1, \ldots, S; \quad k = 0, \ldots, N-1, \tag{15}$$

where $A_{i,k}$ and $B_{i,k}$ are square matrix, which has $N \times N$ order and $C_{i,k}$ matrix with $N \times 1$ order.

Therefore, the optimal control problems (10)-(11) becomes a linear quadratic problem, which the feedback control is given by the following expression [?], [15]:

$$U_{i,k} = -K_i x_k,\ i = 1, \ldots, S; \quad k = 0, \ldots, N-1, \tag{16}$$

where

$$K_i = (Q + B_i^T E_i B_i)^{-1} B_i^T E_i A_i, \tag{17}$$

is the feedback gain matrix, and E_i discrete Riccati equation solution of the following form:

$$E_i - Q - A_i^T E_i A_i + A_i^T E_i B_i (R + B_i^T E_i B_i)^{-1} B_i^T E_i A_i = 0. \tag{18}$$

It is obvious that, the linearization around every operating point gives the system for which the equations have the form (15). Because, there are S operating points, we have S systems which have this form. Therefore, according to the relation (16), S controls are determined. The defuzzyfication method [14] permits to determine only one system and only one control U_k.

Then, this transformation gives the following equation:

$$x_{k+1} = Ax_k + BU_k + C, \quad k = 0, \ldots, N-1, \tag{19}$$

$$U_k = -Kx_k,\ k = 0, \ldots, N, \tag{20}$$

where

$$A = \frac{\sum_{i=1}^{S} \omega_i(x_i) A_{i,k}}{\sum_{i=1}^{S} \omega_i(x_i)},\ B = \frac{\sum_{i=1}^{S} \omega_i(x_i) B_{i,k}}{\sum_{i=1}^{S} \omega_i(x_i)},\ C = \frac{\sum_{i=1}^{S} \omega_i(x_i) C_{i,k}}{\sum_{i=1}^{S} \omega_i(x_i)}, \text{ and}$$

$$K = \frac{\sum_{i=1}^{S} \omega_i(x_i) K_{i,k}}{\sum_{i=1}^{S} \omega_i(x_i)}, \tag{21}$$

and where $\omega_i(x_i)$ designates membership degree partner to the operating point x_i.

3. Resolution Approaches

In this part, we are interested in the application of fuzzy logic strategy and indirect approach to solve the problems (1)-(9).

3.1. Fuzzy logic strategy

Let us consider the uniform grid

$$\Omega_N = \left\{ t_j = \frac{jT_{\max}}{N},\ j = 0, \ldots, N \right\}. \tag{22}$$

If we set

$$Y = X - X^e, \tag{23}$$

and $h = \frac{T_{\max}}{N}$, the first order explicit Euler's scheme on Ω_N permits to approach the system (4) as following

$$\begin{cases} Y_i^{j+1} = Y_i^j + hF(Y_i^j;\ \mu(t)),\ i = 1, \ldots, 7, \\ Y_i^0 = Y_0, \end{cases} \tag{24}$$

where Y_i^j denotes $Y_i(t_j)$, $i = 1, \ldots, 7$.

Let us consider

$\Delta t = t_{k+1} - t_k$, $k = 0, \ldots, N-1$, and $Y^j = \left(Y_1^j, Y_2^j, Y_3^j, Y_4^j, Y_5^j, Y_6^j, Y_7^j\right)^T$.

Using the method of the rectangles, we can approach the objective function (9) by the following form:

$$J^N(\mu) = \sum_{j=0}^{N-1} \left(\left(Y^j\right)^T R\left(Y_i^j\right) + \mu_j^T P \mu_j \right) h, \tag{25}$$

where $\mu_j = \mu(t_j)$, R denotes a matrix, whose elements are defined by

$$R_{i,l} = \begin{cases} \beta_i, & \text{if } i = l \\ 0, & \text{elsewhere} \end{cases}, i, l = 1, \ldots, 7,$$

and P the matrix, which has the following form

$$P = \begin{pmatrix} \eta_1 & 0 \\ 0 & \eta_2 \end{pmatrix}.$$

Fuzzy logic strategy idea is based on the linearization of every nonlinear term for the system (1). This strategy permits to obtain the Takagi-Sugeno's fuzzy system.

Let Y be a universe of discourse, whose linguistic variables are:

1. The $CD4^+$ T-cells (CD4NI);
2. The macrophages (CMNI);
3. The infected $CD4^+$ T-cells (CD4I);
4. The infected macrophages (CMI);
5. The infectious virus (VRI);
6. The non-infectious virus (VRNI);
7. The immune response (CSIM).

If we consider the study made on a certain number of patient in Massachussets General Hospital [2], each parameter admits the limits. Then, the variation intervals of the parameters are given in Table 2.

Applying the change of variable that is using the formula (23) and considering the equilibrium values (EQ_2) according to the Table 1, it is easy to determine the components of the variable Y and their variation intervals. According to the theory of fuzzy logic, we can then consider that the linguistic variables of the universe of discourse admit the labels centered in values of operating points given in Table 3.

Considering operating points values, the Figures 2, 3, 4, and 5 illustrate the triangular membership functions associated to the considered labelling. These figures also show the linguistic terms for linguistic variables.

Table 2. Parameter and variation interval for a patient in "Massachussets General Hospital"

Parameter	Interval
T_1(cells / µl)	[200, 1000]
T_2(cells / µl)	[3, 18]
T_1^*(cells / µl)	[0, 2400]
T_2^*(cells / µl)	[0, 3]
V_I(copies / ml)	[0, 122000]
V_{NI}(copies / ml)	[0, 8000]
E (cells / µl)	[0, 1]

Table 3. Operating point values for the linguistic variables of universe of discourse

Linguistic variable	Operating point values
CD4NI	–614.6232, –214.6226, and 185.3780
CMNI	2.8762, 10.3762, and 17.8762
CD4I	–1.4799, 1198.5201, and 2398.5201
CMI	–0.5213, 0.9787, and 2.4787
VRI	–1463.7949, 59536.2056, and 120536.2060
VRNI	0, 4000 et 8000
CSIM	–0.1487, 0.3513, and 0.8513

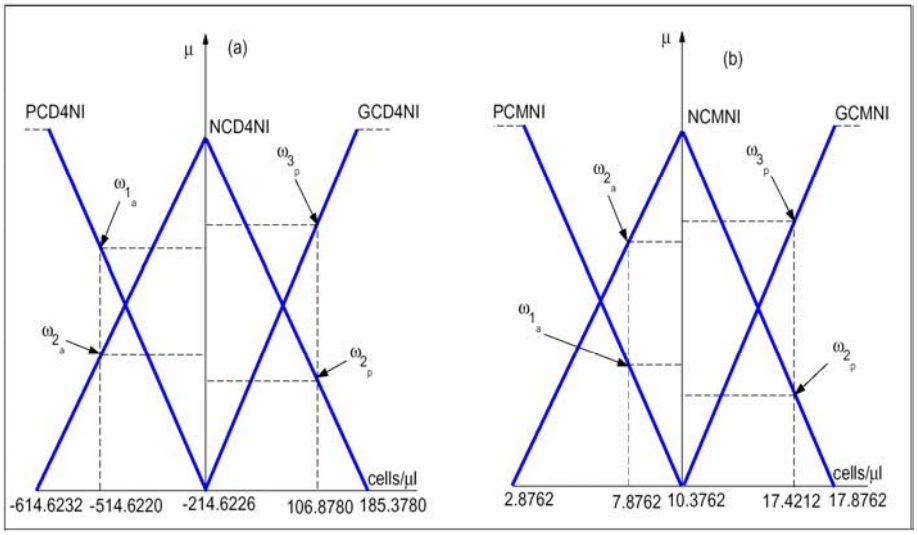

Figure 2. The triangular membership functions for the linguistic variables "$CD4^+$ *T*-cells" (a), and "macrophages" (b).

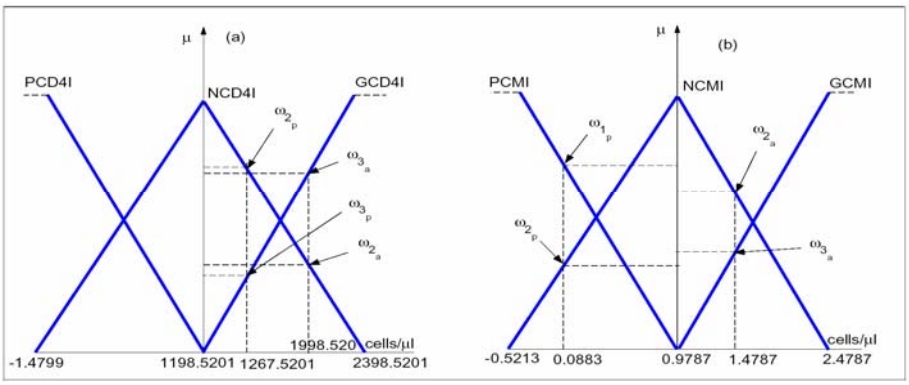

Figure 3. The triangular membership functions for the linguistic variables "infected $CD4^+$ *T*-cells" (a), and "infected macrophages" (b).

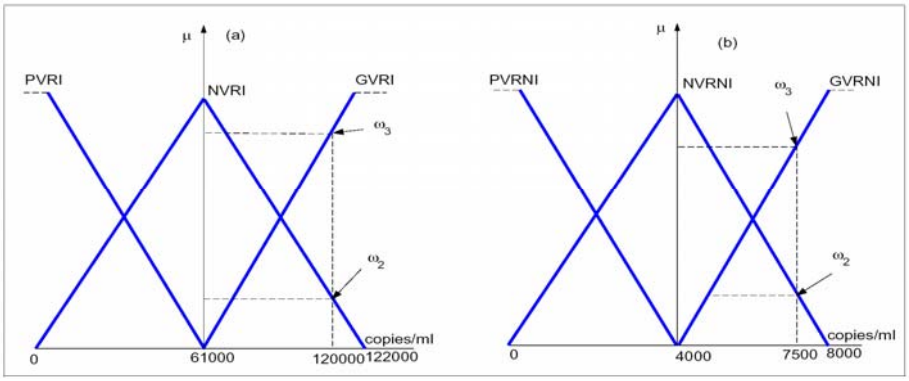

Figure 4. The triangular membership functions for the linguistic variables "infected virus" (a), and "non infections virus" (b).

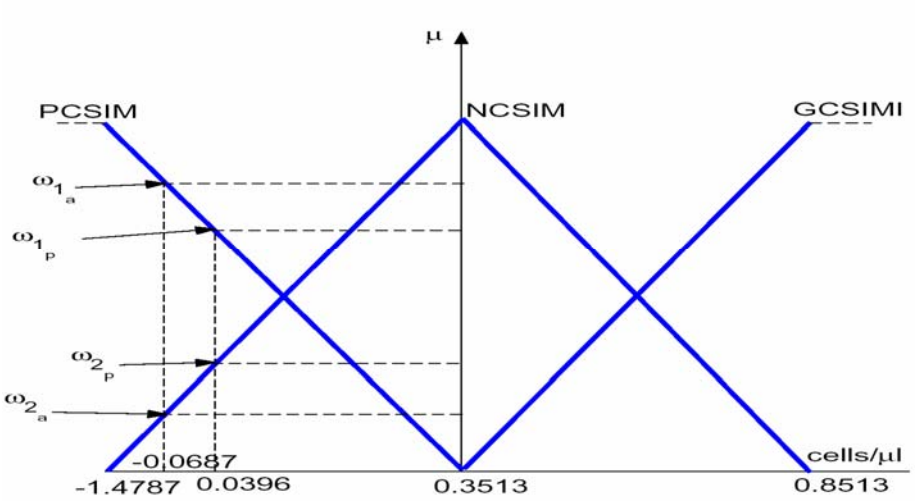

Figure 5. The triangular membership functions for linguistic variable "immune response".

In the Figure 2, 106.8780 and – 514.6220 (resp., 17.4212 and 7.8762) designate the entry values of linguistic variables "$CD4^+$ *T*-cells" (resp., "macrophages") in the case of the first and advanced phase of a patient having the HIV infection. PCD4NI, NCD4NI, and GCD4NI (resp., PCMNI, NCMNI, and GCMNI) represent the linguistic terms of "$CD4^+$ *T*-cells" (resp., "macrophages"). The below index *p* and *a* represent, respectively, the first phase and advanced phase. In the Figure 3, 1267.5201 and 1998.520 (resp., 0.0883 and 1.4787) designate the entry values of linguistic variables "infected $CD4^+$ *T*-cells" (resp., "infected macrophages"*M*) in the case of the first and advanced phase of a patient having the HIV infection. PCD4I, NCD4I, and GCD4I (resp., PCMI, NCMI, and GCMI) represent the linguistic terms of "infected $CD4^+$ *T*-cells" (resp., "infected macrophages"). The below index *p* and *a* represent, respectively, the first phase and advanced phase. In the Figure 4, 70386.20600 and 118536.2060 (resp., 4990.9 and 7500) designate the entry values of linguistic variables "infected virus" (resp., "non infections virus") in the case of the first and advanced phase of a patient having the

HIV infection. PVRI, NVRI, and GVRI (resp., PVRNI, NVRNI, and GVRNI) represent the linguistic terms of "infected virus" (resp., "non infections virus"). The below index p and a represent, respectively, the first phase and advanced phase. In the Figure 5, 0.0396 and –0.0687 designates, respectively, entry value of linguistic variable "the immune response" in the case of the first and advanced phase of a patient having the HIV infection. PCSIM, NCSIM, and GCSIM represent the linguistic terms of "the immune response". The below index p and a represent, respectively, the first phase and advanced phase.

Let us set $k = 1, 2, 3$ operating point number and $V_j = (D_j, G_j, K_j, M_j, N_j, S_j, Z_j)^T$, where $D_j, G_j, K_j, M_j, N_j, S_j,$ and Z_j designate, respectively, the operating point for linguistic variables CD4NI, CMNI, CD4I, CMI, VRI, VRNI, and CSIM. Taylor approximation of order zero for the first equation of system (24) gives:

$$Y^{j+1} = Y^j + h[F_L(Y^j; \mu(t)) + F_{NL}(V_j; \mu(t))],\ i = 1, \ldots, 7,$$

where F_L is linear term of F and F_{NL}, its nonlinear term in the system (24).

Therefore, optimal control problem (9) with subject the system (1) can be formulated as follows. Find $\mu^* = (\mu_0^*, \ldots, \mu_{N-1}^*)$ solution of

$$\min_{\mu} J(u) \approx \sum_{j=0}^{N-1} \left(\left(Y^j\right)^T R\left(Y^j\right) + \mu_j^T P \mu_j \right) h, \tag{26}$$

subject to

$$Y^{j+1} = A_k Y^j + B_k \mu_j + C_k,\ k = 1, 2, 3, \tag{27}$$

where A_k is a 7×7 matrix, whose non zero elements are

$$A_k^{(1,1)} = 1 - hd_1 - hV_I^e k_1; \qquad A_k^{(1,5)} = -hk_1 T_1^e;$$

$$A_k^{(2,2)} = 1 - hd_2 - hV_I^e k_2; \qquad A_k^{(2,5)} = -hk_2 T_2^e;$$

$$A_k^{(3,1)} = hV_I^e k_1; \qquad A_k^{(3,3)} = 1 - \delta h - m_1 hE^e;$$

$$A_k^{(3,5)} = hk_1 T_1^e; \qquad A_k^{(3,7)} = -hm_1 T_1^{*,e};$$

$$A_k^{(4,2)} = hV_I^e k_2; \qquad A_k^{(4,4)} = 1 - \delta h - m_2 hE^e;$$

$$A_k^{(4,5)} = hk_2 T_2^e; \qquad A_k^{(4,7)} = -hm_2 T_2^{*,e};$$

$$A_k^{(5,1)} = -h10^3 \rho_1 k_1 V_I^e; \qquad A_k^{(5,2)} = -h10^3 \rho_2 k_2 V_I^e;$$

$$A_k^{(5,3)} = h10^3 N_T \delta; \qquad A_k^{(5,4)} = h10^3 N_T \delta;$$

$$A_k^{(5,5)} = 1 - ch - h10^3(\rho_1 k_1 T_1^e + \rho_2 k_2 T_2^e); \qquad A_k^{(6,6)} = 1 - ch;$$

$$A_k^{(7,7)} = 1 - h\delta_E.$$

B_j is a 7×2 matrix, which non zero elements are:

$$B_k^{(1,1)} = hk_1(D_s N_s + D_s V_I^e + T_1^e N_s + V_I^e T_1^e);$$

$$B_k^{(2,1)} = hk_2 f(G_s N_s + G_s V_I^e + T_2^e N_s + V_I^e T_2^e);$$

$$B_k^{(3,1)} = -hk_1(D_s N_s + V_I^e D_s + T_1^e N_s + V_I^e T_1^e);$$

$$B_k^{(4,1)} = -hk_2 f(G_s N_s + V_I^e G_s + T_2^e N_s + V_I^e T_2^e);$$

$$B_k^{(5,1)} = h10^3[\rho_1 k_1(D_s N_s + V_I^e D_s + T_1^e N_s + V_I^e T_1^e) + f\rho_2 k_2(G_s N_s + V_I^e G_s + T_2^e N_s + V_I^e T_2^e)];$$

$$B_k^{(5,2)} = -h10^3 N_T \delta(K_s + M_s + T_1^{*,e} + T_2^{*,e});$$

$$B_k^{(6,2)} = h10^3 N_T \delta(K_s + M_s + T_1^{*,e} + T_2^{*,e}),$$

and

$$C_k = \begin{pmatrix} -hk_1 D_s N_s + h(\lambda_1 - d_1 T_1^e - k_1 V_I^e T_1^e) \\ -hk_2 G_s N_s + h(\lambda_2 - d_2 T_2^e - k_2 V_I^e T_2^e) \\ hk_1 D_s N_s - hm_1 K_s Z_s + h(k_1 V_I^e T_1^e - \delta T_1^{*,e} - m_1 E^e T_1^{*,e}) \\ hk_2 G_s N_s - hm_2 M_s Z_s + h(k_2 V_I^e T_2^e - \delta T_2^{*,e} - m_2 E^e T_2^{*,e}) \\ -h10^3 \rho_1 k_1 D_s N_s - h10^3 \rho_2 k_2 D_s N_s - hcV_I^e \\ +h10^3 N_T \delta(T_1^{*,e} + T_2^{*,e}) - h10^3 V_I^e(\rho_1 k_1 T_1^e + \rho_2 k_2 T_2^e) \\ -hcV_{NI}^e \\ \dfrac{hb_E(K_s + M_s + T_1^{*,e} + T_2^{*,e})}{(K_s + M_s + T_1^{*,e} + T_2^{*,e}) + K_b}(Z_s + E^e) + h(\lambda_E - \delta_E E^e) \\ -\dfrac{hd_E(K_s + M_s + T_1^{*,e} + T_2^{*,e})}{(K_s + M_s + T_1^{*,e} + T_2^{*,e}) + K_d}(Z_s + E^e) \end{pmatrix}.$$

For application, let us consider the parameters given in Table 4 [2].

Let us take $N = 100$ and $T_{\max} = 10$, after calculation, we obtain the following results:

Table 4. The values of the parameters in the HIV model

Parameter	Value	Unit	Parameter	Value	Unit
λ_1	1.096	$\frac{\text{cells}}{\text{mm}^3.\text{day}}$	λ_2	0.10099	$\frac{\text{cells}}{\text{mm}^3.\text{day}}$
d_1	10^{-3}	$\frac{1}{\text{day}}$	d_2	0.022109	$\frac{1}{\text{day}}$
k_1	2.407×10^{-7}	$\frac{\text{mm}^3}{\text{virions.day}}$	k_2	5.5290×10^{-4}	$\frac{\text{mm}^3}{\text{virions.day}}$
m_1	0.024385	$\frac{\text{mm}^3}{\text{cells.day}}$	m_2	0.013099	$\frac{\text{mm}^3}{\text{cells.day}}$
ρ_1	1	$\frac{\text{virions}}{\text{cells}}$	ρ_2	1	$\frac{\text{virions}}{\text{cells}}$
δ	0.18651	$\frac{1}{\text{day}}$	c	4.784	$\frac{1}{\text{day}}$
f	0.53915	–	N_T	19.41	$\frac{\text{virions}}{\text{cells}}$
λ_E	9.9085×10^{-3}	$\frac{\text{cells}}{\text{mm}^3.\text{day}}$	δ_E	0.070299	$\frac{1}{\text{day}}$
b_E	1.299×10^{-2}	$\frac{1}{\text{day}}$	d_E	0.010213	$\frac{1}{\text{day}}$
K_b	0.39087	$\frac{\text{cells}}{\text{mm}^3}$	K_d	0.83790	$\frac{\text{cells}}{\text{mm}^3}$

$$A_k = \begin{pmatrix} 0.9599 & 0 & 0 & 0 & -0.196 \times 10^{-6} & 0 & 0 \\ 0 & 0.9169 & 0 & 0 & -0.685 \times 10^{-7} & 0 & 0 \\ 0.352 \times 10^{-6} & 0 & 0.9810 & 0 & 0.196 \times 10^{-6} & 0 & 0 \\ 0 & 0.0809 & 0 & 0.9812 & 0.685 \times 10^{-7} & 0 & 0 \\ -0.0352 & -80.9332 & 362.0159 & 362.0159 & 0.4951 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0.5216 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0.9930 \end{pmatrix}.$$

$$B_1 = \begin{pmatrix} 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & -40.1918 \times 10^{-11} \\ 0 & 40.1918 \times 10^{-11} \\ 0 & 0 \end{pmatrix}, \quad B_2 = \begin{pmatrix} 0.8810 & 0 \\ 35.4132 & 0 \\ -0.8810 & 0 \\ -19.0931 & 0 \\ 19974.0141 & -434962.1159 \\ 0 & 434962.1159 \\ 0 & 0 \end{pmatrix},$$

$$B_3 = \begin{pmatrix} 2.9365 & 0 \\ 121.4168 & 0 \\ -2.9365 & 0 \\ -65.4619 & 0 \\ 68398.4333 & -869924.2317 \\ 0 & 869924.2317 \\ 0 & 0 \end{pmatrix},$$

$$C_1 = \begin{pmatrix} -0.0211 \\ 0.2330 \\ 0.0217 \\ 0.0001 \\ -51228.5573 \\ 0 \\ -0.0001 \end{pmatrix}, \quad C_2 = \begin{pmatrix} 0.3081 \\ -34.1557 \\ -1.3337 \\ 0.0146 \\ 705329.4993 \\ 0 \\ 0.0001 \end{pmatrix}, \text{ and } C_3 = \begin{pmatrix} -0.5373 \\ -119.1348 \\ -4.4407 \\ 0.0493 \\ -1237443.1301 \\ 0 \\ 0.0002 \end{pmatrix}.$$

It is obvious that the three state systems (27) permit to obtain three feedback controls, which have the following form:

$$\mu_j = -L_k Y_j, \quad k = 1, 2, 3; \quad j = 1, \ldots, N-1, \tag{28}$$

where L_k is a gain feedback matrix. L_k must be determined according to the relation (17). We suppose that R and P are, respectively, 7×7 and 2×2 identity matrices. After calculations, we obtain the following matrices:

$$L_1 = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0.0007 & -0.0019 & -0.0020 & -0.0021 & -0.0001 & 0 & 0.0012 \end{pmatrix},$$

$$L_2 = \begin{pmatrix} 1.1142 & 0.0002 & -0.0109 & 0.0001 & -0.0001 & 0.0001 & -0.0015 \\ 0.0467 & -0.0007 & -0.0019 & -0.0015 & -0.0001 & 0.0001 & 0.0001 \end{pmatrix},$$

$$L_3 = \begin{pmatrix} 0.3341 & 0.0001 & -0.0033 & 0.0001 & -0.0001 & 0.0001 & -0.0005 \\ 0.0242 & -0.0003 & -0.0010 & -0.0007 & -0.0001 & 0.0001 & 0.0001 \end{pmatrix}.$$

To transform three systems (27) in only one system, it is necessary to apply defuzzyfication technique [13] on matrices B_1, B_2, B_3, C_1, C_2, and C_3. This transformation depends on the degrees of membership given in Table 5.

Hence, the technique of defuzzyfication gives the following results:

First infection phase

$$B = \begin{pmatrix} 1.8585 & 0 \\ 99.5374 & 0 \\ -1.8585 & 0 \\ -53.6656 & 0 \\ 60031.3078 & -794768.2941 \\ 0 & 459972.4376 \\ 0 & 0 \end{pmatrix}, \quad C = \begin{pmatrix} -0.0939 \\ -97.5161 \\ -5.4161 \\ 0.0172 \\ -218539.1208 \\ 0 \\ 0.0001 \end{pmatrix}.$$

Table 5. Values of the membership degrees of linguistic variables CD4NI, CMNI, CD4I, CMI, VRI, VRNI, and CSIM according to data of the study made in "Massachussets General Hospital" on the alive patients with HIV

	ω_{1_p}	ω_{2_p}	ω_{3_p}	ω_{1_a}	ω_{2_a}	ω_{3_a}
μ_{CD4NI}	0	0.1962	0.8038	0.75	0.25	0
μ_{CMNI}	0	0.0607	0.9393	0.6667	0.3333	0
μ_{CD4I}	0	0.9425	0.0575	0	0.3333	0.6667
μ_{CMI}	0.5936	0.4064	0	0	0.6611	0.3389
μ_{VRI}	0	0.8221	0.1779	0	0.0328	0.9672
μ_{VRNI}	0	0.7523	0.2477	0	0.1250	0.8750
μ_{CSIM}	0.6234	0.3766	0	0.84	0.16	0

$$L = \begin{pmatrix} 0.7432 & 0.0001 & -0.0073 & 0.0001 & -0.0001 & 0.0001 & -0.0001 \\ 0.0360 & -0.0004 & -0.0015 & -0.0009 & -0.0001 & 0.0001 & 0.0005 \end{pmatrix}.$$

Advanced stage of infection

$$B = \begin{pmatrix} 0.8810 & 0 \\ 35.4132 & 0 \\ -0.8810 & 0 \\ -19.0931 & 0 \\ 19974.0141 & -434962.1159 \\ 0 & 653360.4007 \\ 0 & 0 \end{pmatrix}, \quad C = \begin{pmatrix} 0.3081 \\ -34.1557 \\ -1.3337 \\ 0.0146 \\ 705329.4993 \\ 0 \\ 0.0001 \end{pmatrix},$$

$$L = \begin{pmatrix} 1.1142 & 0.0002 & -0.0109 & 0.0001 & -0.0001 & 0.0001 & -0.0001 \\ 0.0467 & -0.0007 & -0.0019 & -0.0015 & -0.0001 & 0.0001 & 0.0005 \end{pmatrix}.$$

3.2. Indirect approach

In this part, the objective is to solve the optimal control problem (9) subject to the constraints (1) by an indirect approach. Let us note that this approach requires the necessary optimality conditions. We use the Pontryagin maximum principle [12], which relates the optimality of the control to minimize or maximize the Hamiltonian function.

Let us take $F = (F_1, F_2, F_3, F_4, F_5, F_6, F_7)^T$, the vector whose components are given by (2). The Hamiltonian function associated with the objective function for the optimal control problem (9), and to the state system (1) can be written as follows

$$H(t, X, p, \mu) = \sum_{i=1}^{7} (\beta_i (X_i - X_i^e)^2 + p_i F_i) + \sum_{j=1}^{2} \eta_j \mu_j^2, \tag{29}$$

where p_i is the component of adjoint vector.

Let us consider

$$G_1 = -2\beta_1 (X_1 - X_1^e) + p_1 (d_1 + (1 - u_1) k_1 X_5) - p_3 (1 - u_1) k_1 X_5 + p_5 (1 - u_1) \rho_1 10^3 k_1 X_5, \tag{30}$$

$$G_2 = -2\beta_2(X_2 - X_2^e) + p_2(d_2 + (1-u_1 f)k_2 X_5) - p_4(1-u_1 f)k_2 X_5 + p_5(1-u_1 f)\rho_2 10^3 k_2 X_5, \tag{31}$$

$$G_3 = -2\beta_3(X_3 - X_3^e) + p_3(\delta + m_1 X_7) - p_5(1-u_2)10^3 N_T \delta - p_6 u_2 10^3 N_T \delta + p_7 X_7\left(\frac{d_E K_d}{(X_3 + X_4 + K_d)^2} - \frac{b_E K_b}{(X_3 + X_4 + K_b)^2}\right), \tag{32}$$

$$G_4 = -2\beta_4(X_4 - X_4^e) + p_4(\delta + m_2 X_7) - p_5(1-u_2)10^3 N_T \delta - p_6 u_2 10^3 N_T \delta + p_7 X_7\left(\frac{d_E K_d}{(X_3 + X_4 + K_d)^2} - \frac{b_E K_b}{(X_3 + X_4 + K_b)^2}\right), \tag{33}$$

$$G_5 = -2\beta_5(X_5 - X_5^e) + p_1(1-u_1)k_1 X_1 + p_2(1-u_1 f)k_2 X_2 - p_3(1-u_1)k_1 X_1 - p_4(1-u_1 f)k_2 X_2 + p_5(c + (1-u_1)\rho_1 10^3 k_1 X_1 + (1-u_1 f)\rho_2 10^3 k_2 X_2), \tag{34}$$

$$G_6 = -2\beta_6(X_6 - X_6^e) + cp_6, \tag{35}$$

$$G_7 = -2\beta_7(X_3 - X_3^e) + p_3 m_1 X_3 + p_4 m_2 X_4 - p_7(X_3 + X_4)\left(\frac{b_E}{X_3 + X_4 + K_b} - \frac{d_E}{X_3 + X_4 + K_d} - \delta_E\right). \tag{36}$$

Therefore, the system of adjoint state is

$$\frac{dp_i}{dt} = G_i, \quad i = 1, \ldots, 7. \tag{37}$$

Finally, the optimal control is determined thanks to the resolution of the optimization problem, which we can formulate as follows.

Find μ^* solution of

$$\min_{\mu} H(t, X, p, \mu). \tag{38}$$

The determination of the solution for such problem can be made in several computer platforms. We consider the implementation by using MATLAB thanks to the function *f* solve.

4. Numerical Simulation

4.1. Results

Our objective is to stabilize the $CD4^+$ *T*-cells, macrophage cells, the infected $CD4^+$ T-cells, the infected macrophages, the infectious virus, the non-infectious virus, and immune system cells around their equilibrium values. This mechanism is possible thanks to the controls therapeutic u_1 and u_2, which can take the values at every moment in the interval [0, 1] [6], [10]. We consider that the patient takes antiretroviral drugs during six months $(T_{\max} = 180 \text{ days})$. The solutions of the optimal control problem (9) subject to the system (1), (26)-(27), and (38) can be determined in several computer platforms. The implementation of these solutions is made in MATLAB. If we consider that AHLF and AINDIR, which refer to the approach integrates the fuzzy logic strategy and the indirect approach, we obtain the Table 6.

Table 6. The minimal values of the objective function (J_{opt}) and the time of execution (*T*) of the main program (subroutine of MATLAB) for the resolution of the optimal control problem (9) subject to the system (1) by AHLF and AINDIR

		First phase	Advanced phase
AHLF	J_{opt}	124.5457	281.2508
	T (second)	11.5218	12.5341
AINDIR	J_{opt}	0.3590	1.9600
	T (second)	226.7570	221.4290

The Table 6 shows that, for two infection phases, the execution time of the program, which solve the problem of optimal control by AHLF is less than the one of main program providing a solution to the problem by AINDIR. This table also shows that, the value of the objective function obtained using AINDIR is less than the one given by the use of AHLF. This result is due to the fact that, the indirect approach is accurate compared to the approach integrating fuzzy logic that needs a method of discretization (finite difference explicit Euler first order). For the variation of the parameters, we are interested in the simulation results of the advanced phase. The numerical simulation of therapeutic control problem for a patient of HIV infection in the advanced phase gives the appearance of curves represented in the Figures 6, 7, and 8.

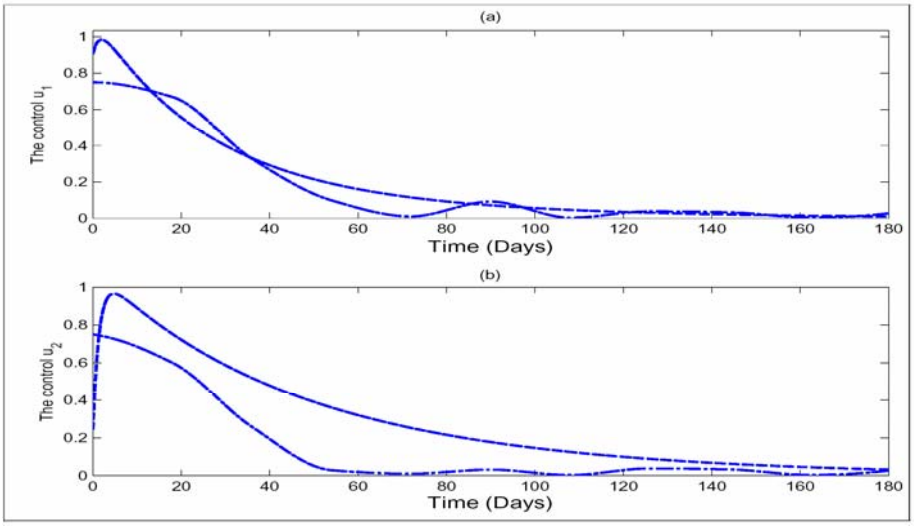

Figure 6. The optimal therapeutic control variation in the advanced phase case. The dashed line (respectively, the dashed-dot line) designates the optimal curve for the hybrid approach integrating the fuzzy logic strategy (respectively, the indirect approach).

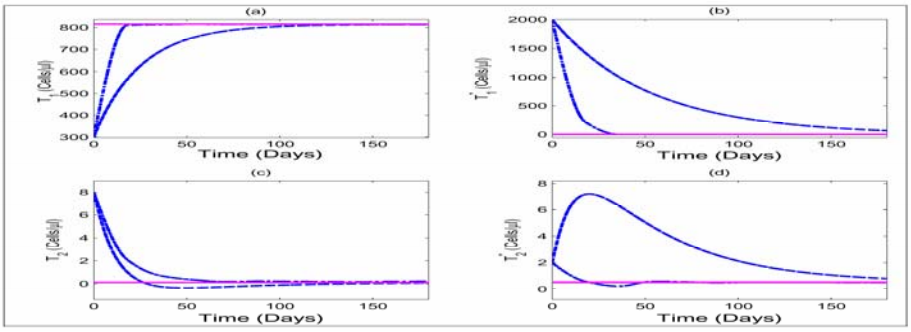

Figure 7. Variation of the $CD4^+$ cells non tainted (a), of the infected $CD4^+$ cells (b), of the macrophages cells (c), and of the infected macrophages cells (d) in relation to their equilibrium values of balance (solid line) in the advanced phase case. The dashed line (respectively, the dashed-dot line) designates the optimal curve for the hybrid approach integrating the fuzzy logic strategy (respectively, the indirect approach).

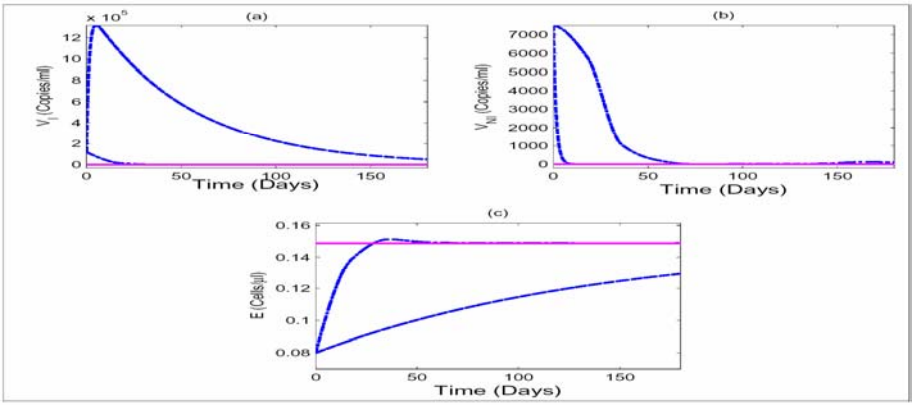

Figure 8. Variation of infectious virus (a), of the non infectious viruses (b), and of cells constituting the immune system (c) in relation to their equilibrium values (solid line) in the advanced phase case. The dashed line (respectively, the dashed-dot line) designates the optimal curve for the hybrid approach integrating the fuzzy logic strategy (respectively, the indirect approach).

4.2. Discussion

Figure 6 shows the comparison of therapeutic optimal control curves u_1 and u_2 by using fuzzy logic strategy and indirect approach. Using the indirect approach to solve the problem of optimal control (9) subject to the system (1), we get controls u_1 and u_2, which decrease gradually from the first day of the advanced phase to achieve their minimum value (zero), where they are stabilized. The u_1 stabilizes at 70th day of the early phase whereas u_2 becomes stable in 65th day. The Figure 7(a) (respectively 7(c)) shows that by using the approach integrating the fuzzy logic strategy approach, the $CD4^+$ cells (respectively, macrophages cells) increase (respectively, decrease) to reach their equilibrium values. The hybrid approach integrating fuzzy logic permits the stabilization to the equilibrium value of $CD4^+$ cells, and macrophages cells at 120th day after the onset of the advanced phase. These figures show that using the indirect approach, the plateaus of stabilization for the $CD4^+$ cells (respectively, macrophages cells) is reached after 20th (respectively, 70th) day after the onset of the advanced phase of infection. In the advanced phase, the variation of infected macrophages cells obtained by using the hybrid approach integrating fuzzy logic is illustrated by Figure 7(d). The first day of this phase, they increase to reach their maximal value at 30th day. Using the indirect approach, this figure shows that infected macrophages cells decrease from the first day of the advanced phase to stabilize at 50th day of the beginning of advanced phase. The allure of curves for non-infectious viruses represented in the Figure 8(b) show that by using two approaches, these viruses decreased at the beginning of the advanced phase of infection before to stabilize themselves. With the indirect approach, these viruses decreased to the equilibrium value and stabilized themselves after 65th day. At the 10th day after the onset of advanced phase is the day, when non-infectious virus stabilize to their equilibrium value by the strategy integrating fuzzy logic approach. Figure 8(c) shows that, the use of the indirect approach and the strategy integrating fuzzy logic approach to resolve the problem (9) subject to the system (1) permits the increase of cells that constitute the immune system to stabilize to their desired value. Using the indirect approach,

these cells stabilize to their equilibrium value at 50th day of the beginning of the advanced phase of infection. The cells that constitute the immune system increase to approach their equilibrium value, if we use the strategy integrating fuzzy logic approach.

5. Concluding Remarks

In this work, we have compared two approaches for solving the problem of therapeutic control of HIV infection. The resolution technique used provides interesting answers to the question, which consists of determinition of the best treatment by the presence of two controls that represent antiretroviral drug to the infection. Numerical simulations give rise to interesting conclusions. Considering these results, we note that the characteristics of hybrid approach integrating the fuzzy logic strategy are the benefits on the indirect approach. Therefore, it can be used to solve optimal control problems in the areas of relatively high dimension.

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