

Solving an optimal control problem of hepatitis B virus dynamics: Efficacy of fuzzy logic strategy

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Abstract

This work aims at using fuzzy logic strategy to solve a hepatitis B virus (HBV) optimal control problem. To test the efficacy of this numerical method, we compare numerical results with those obtained using direct method. We consider a patient under treatment during 12 months where the two drugs are taken as controls. The results are rather satisfactory. In particular, the reaction of HBV to drugs can be modeled and a feedback can be approximated by the solution of a linear quadratic problem. The drugs reduce the risk of HBV. Furthermore, results of both numerical methods are in good agreement with experimental data and this justifies the efficacy of fuzzy logic strategy in solving optimal control problems.

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1. Introduction

Hepatitis B is one of diseases transmitted through contact either with blood or bodily fluids from an individual infected with the hepatitis B virus (HBV). It attacks an important organ of human body, the liver. Therefore, it called liver infection since the virus mainly affects liver function by invading the liver cells (hepatocytes) and uses the cells' machinery to replicate within it. HBV results in different and serious liver diseases such as chronic hepatic insufficiency, hepatocellular carcinoma, cirrhosis and can be a potential cause of the liver cancer. According to The World

Health Organisation (WHO), HBV is in two possible phases [21]: Acute hepatitis B infection that lasts less than six months and chronic hepatitis B infection which lasts six months or longer. There are more than 350 million people living with hepatitis B virus infection, most of which resulted in more than 0.8 million deaths per year due to HBV-related liver disease and liver cancer. The age can be considered to be a factor of developing a chronic infection in the sense that, children less than 6 years of age who become infected with the HBV are the most likely to develop chronic infection [22].

To date, the way to eliminate HBV transmission is to immunise susceptible individuals, especially newborns. Although process of immunisation brings to success, the prevalence prediction of long term in HBV remains challenge to provide useful information for public health decision-making. The mathematical model use is one feasible method to predict the prevalence of infectious disease including HBV [24]. These models can be one useful tools in controlling hepatitis B virus in order to put down the infection from the population.

The transmission dynamics model or the compartmental model is an important theoretical epidemiology method used to study the transmission dynamics of infectious diseases. The transmission dynamics model was first used in the early 1980s to study the transmission dynamics of hepatitis B and the effectiveness of control [13]. Some of these mathematical models address questions concerning the impact of vaccination and others have given a quantitative basis for making optimal decisions in public health policy regarding HBV transmission [6]. Anderson and May used a simple mathematical model to illustrate the effects of carriers on the transmission of HBV [1]. The mathematical model developed by Pang et al. [16] allowed them to explore the impact of vaccination and other controlling measures of HBV infection while Bhattacharyya and Ghosh [2], Kar and Batabyal [8], and Kar and Jana [9] proposed optimal control of infectious diseases. The optimal control theory has found wide-ranging applications in biological and ecological problems [12]. The use of this theory has been designed using model predictive control (MPC) method [5].

Motivated by the works mentioned above, we present in this work the method of using fuzzy logic strategy [14] to solve an optimal control problem of an uninfected Hepatitis B virus dynamics. To test its efficacy, we compare the solutions from this strategy with one obtained using direct method. It could be possible that one can use the same method to solve the similar problem that is related to different type of hepatitis such as A or C [15]. The contribution of this

paper comes in the formulation of HBV dynamics and control strategies and solving the resulting optimal problem for Hepatitis B virus. The other sections of this paper are organized as follows. The section 2 presents the methods and material. The mathematical model equations, optimal control problem, and fuzzy logic strategy as well as direct method are presented this this section. The section 3 deals with discretization of optimal control problem using fuzzy logic strategy and direct method. The numerical tests from simulations are presented in section 4. Finally, the section 5 deals with concluding remarks.

2. Methods and material

2.1. Governing equations

The mathematical model describing HBV dynamics is formulated as a system of three ordinary differential equations [5]. The dependent variables are T , I and V . At time t , T denotes the concentration of uninfected hepatocytes, I is the concentration of infected hepatocytes and V represents the concentration of free virions. The governing equations read

$$\frac{dT}{dt} = s - qT + aT \left[1 - \frac{T}{T_{\max}} \right] - \beta e^{-u_1} \frac{TV}{1+bV}, \quad (1)$$

$$\frac{dI}{dt} = \beta e^{-u_1} \frac{TV}{1+bV} - \delta I, \quad (2)$$

$$\frac{dV}{dt} = p e^{-u_2} I - cV, \quad (3)$$

where s and qT are constant rate of production and death rate of uninfected hepatocyte, respectively. T_{\max} (cells/dl) is the T concentration at which proliferation shuts off. The constant a stands for the maximum proliferation rate of uninfected hepatocyte cells. This proliferation is modeled using logistic function [4] such that the maximum concentration of uninfected hepatocyte cells shuts off. The rate of infection is given by saturation functional response $\beta e^{-u_1} TV/(1+bV)$, where β denotes the constant infection rate which characterizes the infection efficiency and where b is a positive constant. The term δI denotes death rate of infected hepatocytes. The free virions are produced from infected hepatocytes at the rate of $p e^{-u_2} I$ with cV taken as clearance rate of viral particles. The mathematical model (1)-(3) shows the role of therapy. Furthermore, the first type of drug is described by chemotherapy

functions e^{-u_1} . It helps to prevent the virus from infecting the cell and the second denoted by the function e^{-u_2} facilitates the prevention of the infected cells from producing the new viruses. The values of initial conditions of the mathematical model (1)-(3) are presented in section numerical test below.

2.2. Optimal control problem

To formulate optimal control problem, let $E = (T, I, V)^t$ be a state vector and $E_0 = (T_0, 0, 0)^t$ denotes an uninfected steady state vector for healthy human. The constant T_0 stands for concentration at which uninfected hepatocyte cells are found out. According to physiological theory of HBV the cost functional can be formulated as follows [3],

$$J(u_1, u_2) = \int_0^{T_f} q_T (T - T_0)^2 + q_{u_1} u_1(t)^2 + q_{u_2} u_2(t)^2 \quad (4)$$

The positive scalar coefficients q_T , q_{u_1} and q_{u_2} are weights attached to each cost component term whereas T_f denotes the maximum time of prescription drug. The purpose is to minimize this objective function subject to the system (1)-(3).

2.3. Fuzzy logic strategy

We are interested in describing briefly an approach for solving mathematical problem developed in 1985 by Takagi-Sugeno [19], [20]. This approach uses a following general discrete optimization problem we want to be interested in. Furthermore, we want to find $U_k^* \in R^N$, $k = 0, \dots, N - 1$ that minimizes

$$J(U_0, \dots, U_{N-1}) = \sum_{k=0}^{N-1} (x_k^T R x_k + U_k^T Q U_k), \quad (5)$$

subject to

$$\begin{cases} x_{k+1} = f_k(x_k, U_k) \\ x_k \in R^N, U_k \in R^N, k = 0, \dots, N - 1 \end{cases} \quad (6)$$

where R and Q are positive defined matrices, x_k is state element and $f_k: R^N \times R^N \rightarrow R^N$ denotes a discrete function. This problem can also be solved using the dynamic programming method. However, the rate of convergence of this method is quadratic and solution is often represented as

a state of control feedback [16] and this solution which in some cases is not optimal depends on the choice of the initial trajectory. The mathematical problem is carried out to find fuzzy linearization regions in the state [17]. Taking these fuzzy regions as basis, non linear system is decomposed in a structured multi models of several independent linear models [10]. The linearization is made around an operating point contained in these regions.

Let $x_i, i = 1, \dots, S$ be operating point among total S points and $NL(x)$ stands for a nonlinear term of a mathematical model. There are two kinds of estimates of $NL(x)$:

$$NL(x) \approx NL_0(x) = NL(x_i), \quad (7)$$

and

$$NL(x) \approx NL_1(x) = NL(x_i) + \left(\frac{dNL(x)}{dx} \right) (x - x_i). \quad (8)$$

To minimize the error between the non linear function and the fuzzy approximation, Takagi-Sugeno introduced factor of the consequence for fuzzy [19]. Let ε denotes this factor, the approximation (8) can be formulated as follows:

$$\begin{aligned} NL(x) &\approx (1 - \beta)NL_0(x) + \varepsilon NL_1(x) \\ &\approx NL(x_i) + \beta \left(\frac{dNL(x)}{dx} \right)_{x_i}^T (x - x_i), \quad \text{with } 0 \leq \beta \leq 1. \end{aligned} \quad (9)$$

Hence, the linearization around x_i of (6) x_i lead to

$$x_{k+1} = A_{i,k}x_k + B_{i,k}U_k + C_{i,k}, \quad i = 1, \dots, S; \quad k = 0, \dots, N - 1 \quad (10)$$

where $A_{i,k}$ and $B_{i,k}$ are square matrices of $N \times N$ order and $C_{i,k}$ a matrix of $N \times 1$ order. Therefore, the optimal control problem (5)-(6) becomes a linear quadratic problem. The feedback control solution is given by the following expression [19]:

$$U_{i,k} = -K_i x_k, \quad i = 1, \dots, S; \quad k = 0, \dots, N - 1, \quad (11)$$

where

$$K_i = (Q + B_i^T E_i B_i)^{-1} B_i^T E_i A_i, \quad (12)$$

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

$$E_i - Q - A_i^T E_i A_i + A_i^T E_i B_i (R + B_i^T E_i B_i)^{-1} B_i^T E_i A_i = 0. \quad (13)$$

It is obvious to realise that the linearization around every operating point gives the system for which the equations have the form (10). Since there is S operating points, we obtain S systems. Consequently, we have S controls calculated using (11). To get only one system and only one control U_k , we use defuzzyfication method [20]. Therefore, using (10) this transformation gives the following equation

$$x_{k+1} = Ax_k + BU_k + C, \quad k = 0, \dots, N - 1, \quad (14)$$

$$U_k = -Kx_k, \quad k = 0, \dots, N, \quad (15)$$

where

$$A = \frac{\sum_{i=1}^S \omega_i(x_i)A_{i,k}}{\sum_{i=1}^S \omega_i(x_i)}, \quad B = \frac{\sum_{i=1}^S \omega_i(x_i)B_{i,k}}{\sum_{i=1}^S \omega_i(x_i)}, \quad C = \frac{\sum_{i=1}^S \omega_i(x_i)C_{i,k}}{\sum_{i=1}^S \omega_i(x_i)}, \quad \text{and } K = \frac{\sum_{i=1}^S \omega_i(x_i)K_{i,k}}{\sum_{i=1}^S \omega_i(x_i)}, \quad (16)$$

and $w_i(x_i)$ denotes membership degree corresponding to the operating point x_i .

3. Discretization optimal control problem

We use two different methods to approximate the optimal control problem (4), (1)-(3): Fuzzy logic strategy and direct method. The purpose is two compare the numerical solution in order to conclude from the evidence the efficacy of fuzzy logic strategy.

3.1. Fuzzy logic strategy use

Setting

$$X = (T - T_0, I, V)^t \quad \text{and} \quad U = (u_1(t), u_2(t))^t. \quad (17)$$

the system (1)-(3) becomes

$$\begin{cases} \frac{dX_1}{dt} = s - q(X_1 + T_0) + a(X_1 + T_0) \left[1 - \frac{X_1 + T_0}{T_{\max}} \right] - \beta e^{-u_1} \frac{(X_1 + T_0)X_3}{1 + bX_3}, \\ \frac{dX_2}{dt} = \beta e^{-u_1} \frac{(X_1 + T_0)X_3}{1 + bX_3} - cX_2, \\ \frac{dX_3}{dt} = p e^{-u_2} X_2 - cX_3. \end{cases}$$

For $k=0, \dots, N$, using forward explicit Euler scheme to approximate the mathematical model (1)-(3), we obtain

$$\begin{cases} X_{1,k+1} = (1 + ha - hq)X_{1,k} + h(s - qT_0) + ha \left[-X_{1,k} \frac{(X_{1,k} + T_0)}{T_{\max}} + T_0 \left(1 - \frac{(X_{1,k} + T_0)}{T_{\max}} \right) \right] \\ \quad + \beta h \left(\frac{(X_{1,k} + T_0)X_{3,k}}{1 + bX_{3,k}} \right) U_1 - \beta h \frac{(X_{1,k} + T_0)X_{3,k}}{1 + bX_{3,k}}, \\ X_{2,k+1} = (1 - h\delta)X_{2,k} - h\beta \left(\frac{(X_{1,k} + T_0)X_{3,k}}{1 + bX_{3,k}} \right) U_1 + h\beta \frac{(X_{1,k} + T_0)X_{3,k}}{1 + bX_{3,k}}, \\ X_{3,k+1} = (1 - hc)X_{3,k} - hpX_{2,k}U_2 + hpX_{2,k}, \end{cases} \quad (18)$$

where $h = \frac{T_N}{N}$, $X_k = X(t_k)$ and we have set $e^z \approx 1 + z$, $\forall z \in R$.

Let T_i , I_i and V_i , $i = 1, 2, 3$ be the first, second and third operating points that take values in the labels centers of a universe of discourse X . Then (18) can be rewritten as follows

$$\begin{cases} X_{1,k+1} = (1 + ha - hq)X_{1,k} + h(s - qT_0) + ha \left[-T_i \frac{(T_i + T_0)}{T_{\max}} + T_0 \left(1 - \frac{(T_i + T_0)}{T_{\max}} \right) \right] \\ \quad + \beta h \left(\frac{(T_i + T_0)V_i}{1 + bV_i} \right) U_1 - \beta h \frac{(T_i + T_0)V_i}{1 + bV_i} \\ X_{2,k+1} = (1 - h\delta)I_i - h\beta \left(\frac{(T_i + T_0)V_i}{1 + bV_i} \right) U_1 + h\beta \frac{(T_i + T_0)V_i}{1 + bV_i} \\ X_{3,k+1} = (1 - hc)V_i - hpI_iU_2 + hpI_i \end{cases}, \quad i = 1, 2, 3 \quad (19)$$

and setting $X_k = (X_{1,k}, X_{2,k}, X_{3,k})^t$ its compact form becomes

$$X_{k+1,i} = A_i X_{k,i} + B_i U_{k,i} + C_i, \quad i = 1, 2, 3, \quad (20)$$

where

$$A_i = \begin{pmatrix} 1 + ha - hq & 0 & 0 \\ 0 & 1 - h\delta & 0 \\ 0 & 0 & 1 - ch \end{pmatrix}, \quad (21)$$

$$B_i = h \begin{pmatrix} \beta \frac{(T_i + T_0)V_i}{1 + bV_i} & 0 \\ -\beta \frac{(T_i + T_0)V_i}{1 + bV_i} & 0 \\ 0 & -pI_i \end{pmatrix}, \quad i = 1, 2, 3$$

$$(22)$$

and

$$C_i = h \begin{pmatrix} -aT_i \frac{(T_i + T_0)}{T_{\max}} + aT_0 \left[1 - \frac{(T_i + T_0)}{T_{\max}} \right] - \beta \frac{(T_i + T_0)V_i}{1 + bV_i} + (s - qT_0), \\ \beta \frac{(T_i + T_0)V_i}{1 + bV_i}, \\ pI_i, \end{pmatrix}, i = 1, 2, 3. \quad (23)$$

Using the rectangular rule, the cost functional (4) gives the following form

$$J^N(X, U) = \sum_{k=0}^{N-1} (X_k^T R_1 X_k + U_k^T R_2 U_k) h, \quad (24)$$

where for elements a_1, a_2 and a_3 and b_1, b_2 R_1 and R_2 are matrices defined as follows

$$R_1 = \begin{pmatrix} a_1 & 0 & 0 \\ 0 & a_2 & 0 \\ 0 & 0 & a_3 \end{pmatrix}, \quad R_2 = \begin{pmatrix} b_1 & 0 \\ 0 & b_2 \end{pmatrix}, \quad (25)$$

where a_1, a_2, a_3 and b_1, b_2 are constant elements of corresponding matrix.

Therefore, the solution of optimal control problem (4), (1)-(3) using fuzzy logic is obtained by determining $U^* = (U_0^*, \dots, U_{N-1}^*)^T$ solution of (24) subject to (20). This problem is a linear quadratic (LQ) of three linear state systems whose solution leads to three feedback controls of the form

$$U_k = K_i X_k, \quad i = 1, 2, 3; \quad k = 0, \dots, N, \quad (26)$$

where K_i is a gain feedback.

After this discretization of the optimal control problem (4), (1)-(3) using fuzzy logic strategy, we focus now on its approximation that uses direct approach.

3.2. Direct approach use

Let $B^N = \{\psi_j^N, j = 1, \dots, N\}$ be a set of linear B-splines basis functions on the uniform grid

$$\Omega_N = \left\{ t_k = \frac{kT_N}{N}, \{k = 0, \dots, N\} \right\}. \quad (27)$$

The direct method consists of determining the discrete form of state equations (1)-(3) and the cost functional (4) using linear B-splines functions B^N . The function ψ_i^N are defined such that $\psi_i^N(t_k) = \delta_{ik}$,

where δ_{ik} denotes Kronecker symbol. Let W^N be a vector space whose the basis is B^N satisfying

$$\dim W^N = N \quad \text{and} \quad W^N \subset W^{N+1}.$$

We consider $W=C^0(0, T_N)$ and we take the interpolation operator

$$\begin{aligned} \Pi^N &: W \rightarrow W^N \\ \varphi &\mapsto \Pi^N \varphi \end{aligned} \quad (28)$$

satisfying

$$\Pi^N \varphi(t_k) = \varphi(t_k), \quad k = 1, \dots, N.$$

Therefore, system (1)-(3) is approximated using Π^N in W^N to the following form

$$\frac{dT^N}{dt} = s - qT^N + aT^N \left[1 - \frac{T^N}{T_{max}} \right] - \beta^{-u_1} \frac{T^N V^N}{1+bV^N} \quad (30)$$

$$\frac{dI^N}{dt} = \beta e^{-u_1} \frac{T^N V^N}{1+bV^N} - \delta I^N, \quad (31)$$

$$\frac{dV^N}{dt} = p e^{-u_2} I^N - cV^N. \quad (32)$$

$$T^N(0) = T^{N,0}, \quad I^N(0) = I^{N,0}, \quad V^N(0) = V^{N,0}. \quad (33)$$

Setting $\lambda = (u_1, u_2)^t$ and $q = (q_{u_1}, q_{u_2})^t$, the discretization of the cost functional (4) is

$$J^N(\lambda^M) \approx \sum_{k=1}^{M-1} \left(q_T (T^N(t_k) - T_0)^2 + \sum_{j=1}^2 q_j (\lambda_{j,k}^M)^2 \right) h, \quad \text{with } h = \frac{T_{max}}{M} \quad (34)$$

which can be rewritten in compact form as follows

$$J^N(\lambda^M) \approx h \left((Y^T R Y) + (\lambda^M)^T B \lambda^M \right), \quad (35)$$

where $\underline{\lambda}^M$ is an $(M + 1) \times 2$ matrix whose elements $\lambda_{j,k}^M$ are components of λ_j^N in the set B^N , Y represents the matrix whose k^{th} component $T^N(t_k) - T_0$ is associated to $\lambda = \lambda^N$

$$= \begin{pmatrix} u_1^N & u_2^N \\ 0 & 0 \end{pmatrix}, R \text{ and } B \text{ are matrix defined by } R = \begin{pmatrix} q_T & 0 \\ 0 & q_T \end{pmatrix}, \quad B = \begin{pmatrix} q_{u_1} & 0 \\ 0 & q_{u_2} \end{pmatrix}.$$

Finally, using direct method we find $\lambda^{*,M} \in R^{(M+1)} \times R^{(M+1)}$ that minimizes (35) subject to (30)-(33).

4. Numerical test

The role of therapy prescribed for HBV is to remove all infected hepatocytes and virions in the body of patient to allow uninfected hepatocytes to be the equilibrium value T_0 . We consider a healthy subject with $T_0 = 1000$ cells/dl, $I = 0$ cells/dl and $V = 0$ cells/dl [12]. To use fuzzy logic strategy, we consider the universe of discourse X with three linguistic variables: uninfected hepatocytes (UH), infected hepatocytes (IH) and free virions (FV), respectively. According to physiology [7], [18], we consider $T \in [200,1500]$, $I \in [0,300]$ and $V \in [0,500]$. Each variable has three states: low, middle and high. It is taken as low, middle and high if its value is less than the lower bound of interval, in the interval and greater than upper bound of interval, respectively. Then, LUH (Low uninfected hepatocytes), NUH (Normal uninfected hepatocytes) and GUH (the highest uninfected hepatocytes) are terms (fuzzy sets) of the linguistic variable UH. Similarly, LIH, NIH and GUH (respectively LFV, NFV and GFV) are used as terms of the variable linguistic IH (respectively FV). From the relation (17), we have $X_1 \in [-800,500]$, $X_2 \in [0,300]$ and $X_3 \in [0,500]$. In the universe of discourse X the status of linguistic variables is understood in such way that we consider the labels centered respectively at -800 , -150 and 500 for UH; at 0 , 150 and 300 for IH and at $0,250$ and 500 for FV. Hence we suppose that these centers constitute the operating points values of the system (18). Below Table1 shows operating points associated to those linguistic variables whereas membership functions associated to this labeling are represented in the Figure 1, 2 and 3, respectively.

Variable	Operating Points
T	[-800;150;500]
I	[0;150;300]
V	[0;250;500]

Table 1: Variables and their operating points

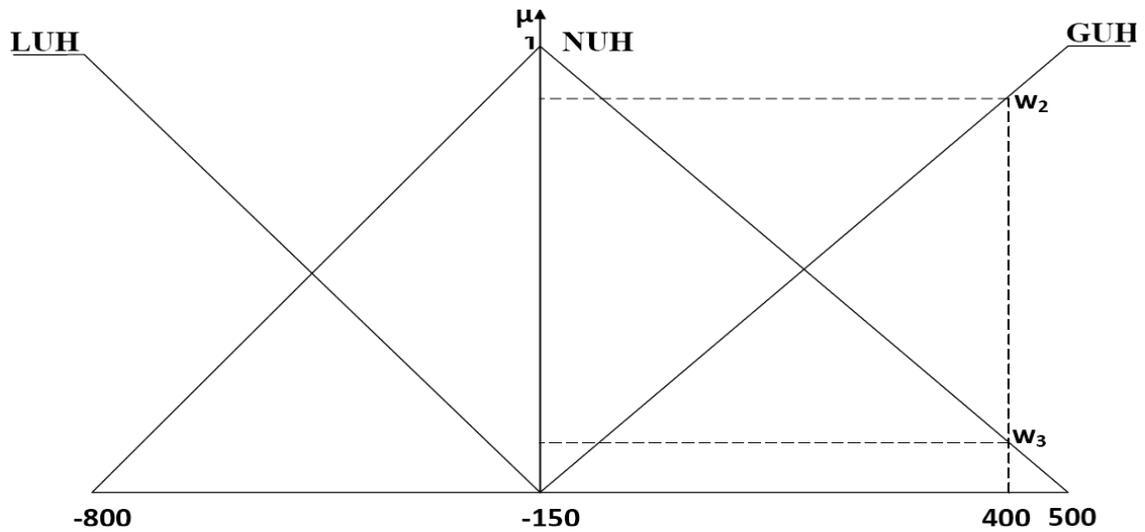


Figure 1: Membership function for uninfected hepatocytes

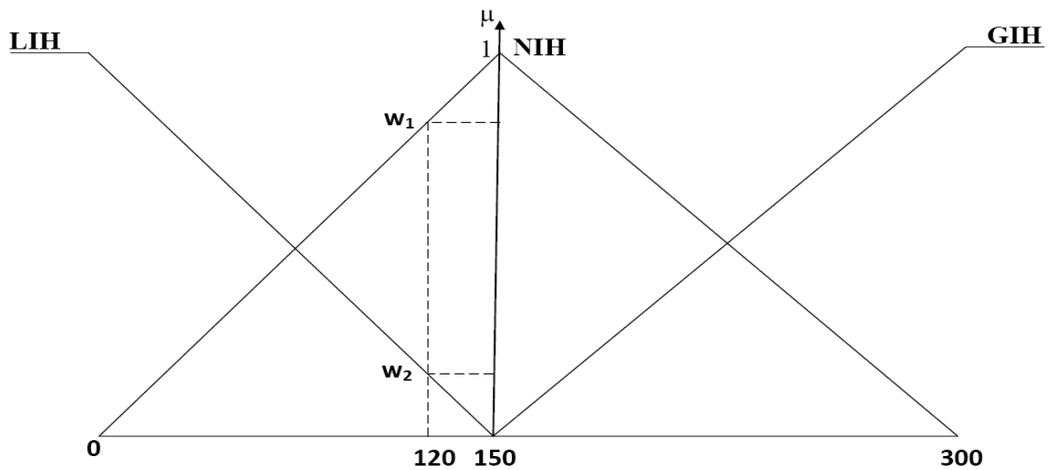


Figure 2: Membership function for infected hepatocytes

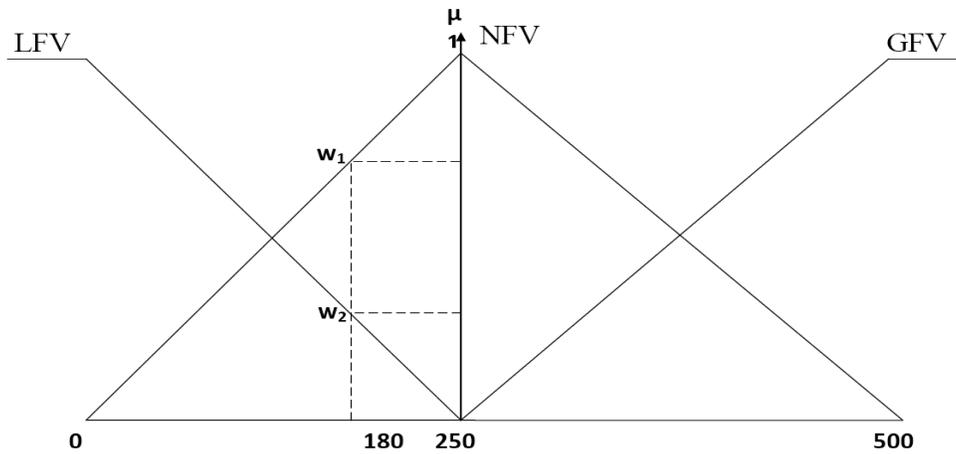


Figure 3: Membership function for free virions

The values of parameters used in numerical simulation are presented in Table 2 [12].

Parameter	a	q	s	β	c	p	b	δ	Tmax
Value	0.108	0.072	36	0.001	3	5	0.01	0.5	1500

Table 2: Parameters used in numerical simulation

Using values $N = 100$ and $TN=12$ (We consider also a patient under treatment during $TN=12$ months) the relations (21), (22) and (23) give after calculations the following matrices

$$A_i = \begin{pmatrix} 1.0036 & 0 & 0 \\ 0 & 0.95 & 0 \\ 0 & 0 & 0.7 \end{pmatrix}, i = 1,2,3$$

$$B_1 = \begin{pmatrix} 0 & 0 \\ 0 & 0 \\ 0 & 0 \end{pmatrix}, B_2 = \begin{pmatrix} 6.0714 & 0 \\ -6.0714 & 0 \\ 0 & -75 \end{pmatrix}, B_3 = \begin{pmatrix} 12.5 & 0 \\ -12.5 & 0 \\ 0 & -150 \end{pmatrix},$$

$$C_1 = \begin{pmatrix} 6.9120 \\ 0 \\ 0 \end{pmatrix}, C_2 = \begin{pmatrix} -4.0734 \\ 6.0714 \\ 75 \end{pmatrix}, C_3 = \begin{pmatrix} -21.5 \\ 12.5 \\ 150 \end{pmatrix}.$$

We consider that R_1 and R_2 are identity matrices and using (26) we obtain

$$K_1 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, K_2 = \begin{pmatrix} 0.0815 & -0.0772 & 0 \\ 0 & 0 & -0.0093 \end{pmatrix}$$

$$K_3 = \begin{pmatrix} 0.0400 & -0.0379 & 0 \\ 0 & 0 & -0.0047 \end{pmatrix}.$$

The defuzzification transformation concerns rows of matrixes A_i , B_i , C_i and K_i , $i = 1,2,3$ using the relation (16). Furthermore, we consider ω_i , $i = 1,2,3$ degree of membership for each membership function. Let 400 cells/dl, 120 cells/dl and 180 cells/dl be entry of uninfected hepatocytes, infected hepatocytes and free virions respectively. After calculations of degrees of membership of each linguistic T, I and V that is the values of w_1 , w_2 and w_3 from the membership functions illustrated in the Figures 1, 3 and 3, the results are shown in the Table 3.

Variable	w_1	w_2	w_3
T	0	0.85	0.15
I	0.8	0.2	0
V	0.72	0.28	0

Table 3: Variables and their corresponding degrees of membership

Hence the following matrices are calculated using defuzzification transformations, that is the formula (16).

$$A = \begin{pmatrix} 1.0036 & 0 & 0 \\ 0 & 0.95 & 0 \\ 0 & 0 & 0.7 \end{pmatrix}, B = \begin{pmatrix} 7.0357 & 0 \\ -1.2143 & 0 \\ 0 & -21 \end{pmatrix} C = \begin{pmatrix} -6.6874 \\ 1.2143 \\ 21 \end{pmatrix}$$

$$K = \begin{pmatrix} 0.0753 & -0.0753 & 0 \\ 0 & 0 & -0.0019 \end{pmatrix}.$$

Below, Figures 4 and 5 show the results from the numerical simulations of a patient suffering from HBV under treatment prescribed during a period of 12 months.

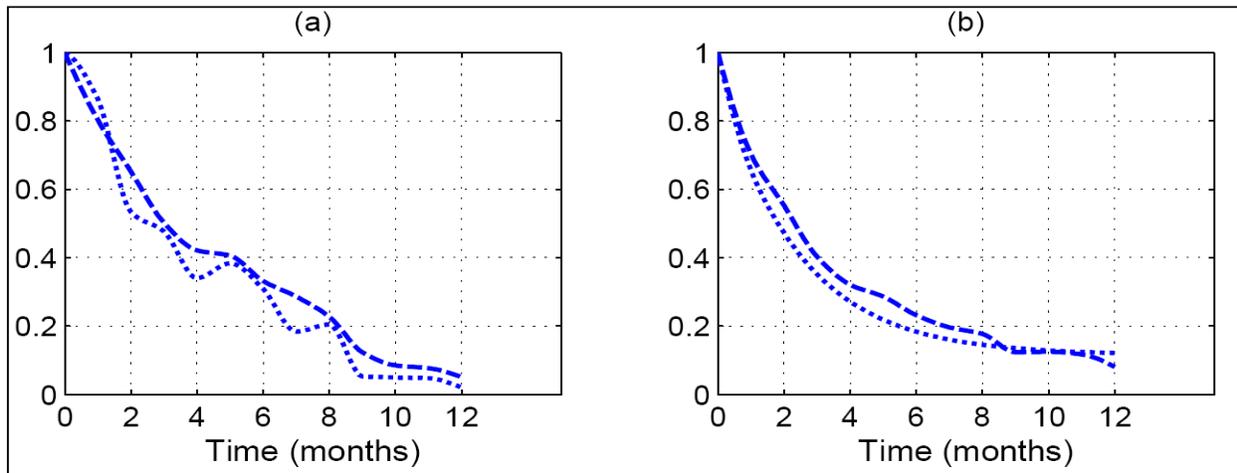


Figure 4: Variation of drugs (control) u_1 (a) and u_2 (b).

In this figure, the curves in dotted line represent the parameter using direct approach whereas the curves in dashed line show the parameter using fuzzy logic strategy. Figure 4 illustrates both chemotherapy u_1 and u_2 prescribed for a patient suffering from HBV. The control u_1 is imposed to prevent the virus to infect the hepatocytes cells whereas the role of control u_2 is to prevent infected hepatocytes cells to produce the new viruses. We consider that the number 1 stands for absence of treatment and 0 means the patient is at the end of this treatment (maximal use of therapy). This assumption is used in numerical simulation and we realize that the Figure 4 shows a decrease of controls in number from 1 to be closer to the lower value 0. This means that patient is not suffering from the effects of HBV while he/she is under treatment.

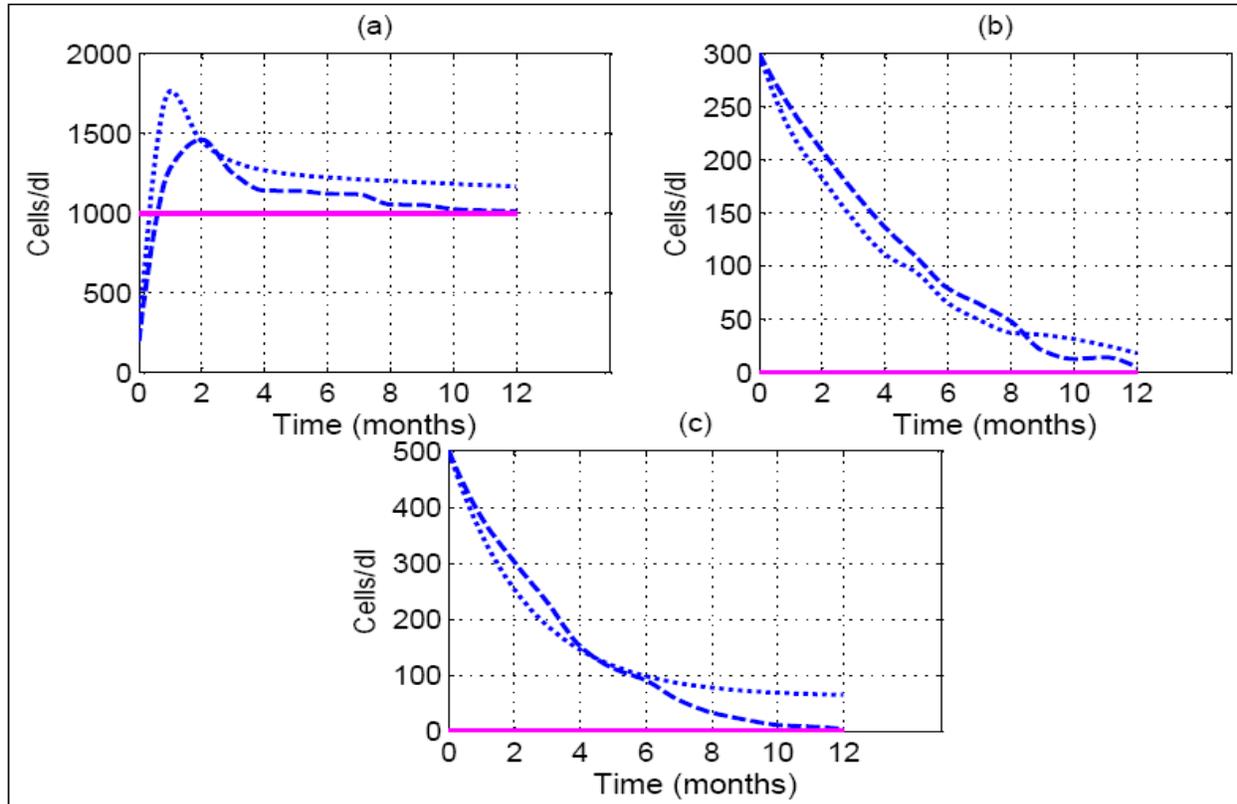


Figure 5: Variation of the concentration of uninfected hepatocytes **(a)**, infected hepatocytes **(b)** and free virions **(c)** for a patient suffering from HBV under treatment during a period 12 months. The curves in dotted line represent the parameter using direct approach whereas the curves in dashed line show the parameter using fuzzy logic strategy.

The Figure 5 shows the response of these controls to variation of the concentration of uninfected hepatocytes (Figure 5(a)), infected hepatocytes (Figure 5(b)) and free virions (Figure 5(c)) respectively. The Figure (a) shows an increase of uninfected hepatocytes to its higher value during the first month of treatment and they decrease to reach the equilibrium value for healthy subject. The Figures 5(b) and 5(c) illustrate that both infected hepatocytes and free virions decrease from starting time of taking therapeutic drugs to reach their equilibrium values for healthy subject.

5. Concluding remarks

In the current paper, an optimal control problem related to HBV dynamics has been exposed and solved with the use of two different numerical methods, i.e direct and fuzzy logic methods. In this context, we found the optimal trajectories of uninfected hepatocytes, infected hepatocytes

and free virions as response to two controls of hepatitis B virus. These controls are drugs prescribed for a patient suffering from HBV. The findings show that the results obtained using fuzzy logic strategy are satisfactory and provide the curves which are close to those given by numerical simulation using standard method known as direct method. Therefore, this justifies the efficacy of fuzzy logic strategy in solving optimal control problems.

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