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Dynamics of a fractional optimal control HBV infection model with capsids and CTL immune response

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This paper deals with a fractional optimal control problem model that describes the interactions between hepatitis B virus (HBV) with HBV DNA-containing capsids, liver cells (hepatocytes), and the cytotoxic T-cell immune response. Optimal controls represent the effectiveness of drug therapy in inhibiting viral production and preventing new infections. The optimality system is derived and solved numerically. Our results also show that optimal treatment strategies reduce viral load and increase the number of uninfected cells, which improves the patient's quality of life.

Keywords: *fractional derivative; HBV infection; optimal control; CTL response; numerical simulations.*

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1. Introduction

Hepatitis B is a major public health problem: a third of the world's population has been in contact with the virus and 350 million people suffer from chronic infection. Mortality related to this virus is also important, with one million deaths per year related to cirrhosis and hepatocellular cancer.

Acute "simple" hepatitis B is not treatable. Fulminant hepatitis requires transplantation. The goal of treatment for chronic hepatitis B is to suppress viral replication, if possible, before the stage of cirrhosis is reached. Therefore, only the replicative phase deserves special therapy.

Furthermore, in the case of chronic HBV infection, the treatment can include antiviral drugs, e.g. interferon (IFN). It has two modes of action: on the one hand, by an antiviral and antiproliferative action by inhibiting viral replication, on the other hand, it strengthens the host's immune response. Lamivudine is a nucleoside analog that directly inhibits HBV DNA polymerase. Its advantage is that it can be administered even in cases of decompensated cirrhosis. Adefovir, which blocks HBV DNA synthesis. Entecavir, which is more effective than lamivudine or adefovir, reduces the viral load in 90% of cases. However, despite all these drugs, none of them can totally eliminate the infection, they can only stop the reproduction of the virus and prevent any damage to the liver. In addition, the long treatment period can be difficult because of side effects, compliance and costs [1]. Thus, to get the most out of the use of drugs, it is necessary to establish strategies and guidelines regarding treatment and its duration.

Optimal control theory, which is a very useful tool for developing optimal therapeutic strategies in many epidemic situations, has been applied in HBV infection models. Ribeiro et al. studied the effect of treatment on HBV infection using a basic model of HBV infection with 3 compartments of uninfected cells, infected cells, and free HBV virus [2]. Using the same model, Hattaf et al. [3] discussed an effective numerical method based on optimal control to identify the best treatment strategy for viral hepatitis B (VHB) to block new infections and prevent viral production using drug therapy with minimal side effects. In [4], Elaiw et al. studied the optimal treatment with the same three compartments and with

a saturated functional infection. To study the dynamics of HBV infection when therapy is initiated at an early stage and to investigate the effect of delay in the infection process, Allali et al. [5] constructed a model of HBV with optimal control. In [6, 7], the optimal control strategy to reduce HBV viral replication was investigated by considering other components.

Fractional optimal control problems (FOCPs) are the generalization of classical optimal control problems (OCPs), in which the differential equations are fractional differential equations (FDEs) representing generalizations of the ordinary differential equations (ODEs) and which have become one of the appropriate mathematical tools to describe the dynamics of phenomena with memory that exists in most biological systems systems [8–15].

In this paper, we study an optimal control problem for HBV infection with capsids containing HBV DNA and a CTL immune response which represents an extension of our work presented in [16] that improved and generalized the mathematical models formulated by ordinary differential equations (ODEs) in [17,18] and also the FDE models introduced in [19–21] by considering the Hattaf's incidence rate [22] that includes the common types such as the bilinear incidence rate, the saturated incidence rate and the Beddington–DeAnglis functional response [23, 24]. For this purpose, we will consider the following nonlinear system of fractional differential equations:

$$\begin{cases} {}_0^C D_t^\alpha H(t) = s - \mu H - (1-u_1) f(H,V) V, \\ {}_0^C D_t^\alpha I(t) = (1-u_1) f(H,V) V - \delta I - pIZ, \\ {}_0^C D_t^\alpha C(t) = (1-u_2) aI - (\beta+\delta) C, \\ {}_0^C D_t^\alpha V(t) = \beta C - cV, \\ {}_0^C D_t^\alpha Z(t) = qIZ - bZ, \end{cases} \tag{1}$$

with initial conditions:

$$H(0) = H_0 \geqslant 0, \quad I(0) = I_0 \geqslant 0, \quad C(0) = C_0 \geqslant 0, \quad V(0) = V_0 \geqslant 0, \quad Z(0) = Z_0 \geqslant 0, \tag{2}$$

where $H(t)$, $I(t)$, $C(t)$, $V(t)$ and $Z(t)$ represent the concentrations of uninfected hepatocytes, infected hepatocytes, HBV DNA-containing capsids, virions and CTL cells at time t, respectively. The uninfected hepatocytes are produced from a source at a constant rate s, die at rate μH and become infected by virions at rate $f(H,V)V$. The parameter δ is the death rate for infected hepatocytes and capsids. The parameters a, β and c are, respectively, the production rate of capsids from infected hepatocytes, the rate at which the capsids are transmitted to blood which gets converted to virions, and the clearance rate of virions. The infected hepatocytes are killed by CTL cells at rate p while q and b denote CTL responsiveness rate and decay rate of CTL cells in absence of antigenic stimulation, respectively. In system (1), the infection transmission is modeled by Hattaf–Yousfi functional response [22] of the form $f(H,V) = \frac{kH}{\alpha_0+\alpha_1 H+\alpha_2 V+\alpha_3 HV}$, where α_0, α_1, α_2, $\alpha_3 \geqslant 0$ are the saturation factors measuring the inhibitory or psychological effect and k is a positive constant rate describing the infection process. u_1 and u_2 denote the efficiency of PEG IFN and LMV drugs, respectively. It is noteworthy to mention that the role of the PEG IFN drug is to block the new infections of the healthy hepatocytes in the liver, whereas the prime function of the second drug (LMV) is to inhibit viral production. Finally, ${}_0^C D_t^\alpha$ is the Caputo fractional derivative and α is a parameter that describes the order of the fractional time-derivative with $\alpha \in (0, 1]$.

The rest of this paper is outlined as follows. The following Section is devoted to the optimization analysis of the viral infection model. We construct an appropriate numerical algorithm and give some numerical simulations in Section 3. Finally, the conclusions are summarized in Section 4.

2. The optimal control problems

The problem is to maximize the objective functional

$$J(u_1,u_2) = \left\{ \int_0^{t_f} H(t) + Z(t) - \left[\tfrac{A_1}{2} u_1^2(t) + \tfrac{A_2}{2} u_2^2(t) \right] \right\} dt, \tag{3}$$

where t_f is the period of treatment and the positive constants A_1 and A_2 are based on the benefit-cost of the treatment u_1 and u_2, respectively. The two control functions, i.e. $u_1(t)$ and $u_2(t)$, are assumed

to be bounded and Lebesgue integrable. Our target is to maximize the objective functional defined in Equation (3) by increasing the number of the uninfected cells, maximizing the CTLs immune responses, decreasing the viral load, and minimizing the cost of treatment. In other words, we are seeking optimal control pair (u_1^*, u_2^*) such that

$$J(u_1^*, u_2^*) = \max\{J(u_1, u_2)\colon (u_1, u_2) \in U\}, \tag{4}$$

where U is the control set defined by

$$U = \{(u_1, u_2)\colon u_i \text{ measurable}, \ 0 \leqslant u_i \leqslant 1, \ t \in [0, t_f], \ i = 1, 2\}.$$

To obtain the necessary optimality conditions for our fractional optimal control problem, we convert (1), (3) and (4) into a problem of maximizing an Hamiltonian, H, pointwisely with respect to u_1 and u_2:

$$H = H(t) + Z(t) - \left[\tfrac{A_1}{2}u_1^2(t) + \tfrac{A_2}{2}u_2^2(t)\right] + \sum_{i=3}^{5}\lambda_i f_i$$

where f_i is the right hand side of the differential equation of i-th state variable. By applying Theorem 4.1 and Lemma 4.2 [25], the necessary conditions for the optimality of (4) are

$$\begin{cases} {}_0^C D_t^\alpha H(t) = s - \mu H - (1-u_1) f(H,V) V, \\ {}_0^C D_t^\alpha I(t) = (1-u_1) f(H,V) V - \delta I - pIZ, \\ {}_0^C D_t^\alpha C(t) = (1-u_2) aI - (\beta + \delta) C, \\ {}_0^C D_t^\alpha V(t) = \beta C - cV, \\ {}_0^C D_t^\alpha Z(t) = qIZ - bZ, \end{cases} \tag{5}$$

and

$$\begin{cases} {}_0^C D_t^\alpha \lambda_1(t') = 1 - \mu\lambda_1 + (1-u_1)\frac{\partial f}{\partial H} V(t)\left[\lambda_2(t) - \lambda_1(t)\right], \\ {}_0^C D_t^\alpha \lambda_2(t') = -\left(\delta + pZ(t)\right)\lambda_2(t) + (1-u_2)a\lambda_3(t) + c\lambda_5(t)Z(t), \\ {}_0^C D_t^\alpha \lambda_3(t') = -(\beta+\delta)\lambda_3(t) + \beta\lambda_4(t), \\ {}_0^C D_t^\alpha \lambda_4(t') = -(1-u_1)\left[\frac{\partial f}{\partial V} V(t) + f(H,V)\right] + \lambda_2(t)(1-u_2)\frac{\partial f}{\partial V} - c\lambda_4(t), \\ {}_0^C D_t^\alpha \lambda_5(t') = 1 - pI(t)\lambda_2(t) + \left(qI(t) - bZ\right)\lambda_5(t), \end{cases} \tag{6}$$

where $t' = t_f - t$ with the terminal conditions

$$H(0) = H_0 \geqslant 0, \quad I(0) = I_0 \geqslant 0, \quad C(0) = C_0 \geqslant 0, \quad V(0) = V_0 \geqslant 0, \quad Z(0) = Z_0 \geqslant 0, \tag{7}$$

and $\lambda_1(t_f) = \lambda_2(t_f) = \lambda_3(t_f) = \lambda_4(t_f) = \lambda_5(t_f) = 0$.

Furthermore, the optimal controls u_1^* and u_2^* are given by

$$u_1^* = \min\left(1, \max\left(0, \tfrac{(\lambda_1 - \lambda_2)}{A_1} f(H,V)\right)\right), \quad u_2^* = \min\left(1, \max\left(0, \tfrac{\lambda_3 a}{A_2} I\right)\right).$$

3. Numerical simulations

We give a numerical method to solve the optimality system (1) and present the results. To solve our FOCPs, we use the predict-evaluate-correct-evaluate (PECE) method of Adams–Basforth–Moulton [25]. First, we choose $s = 2.6 \times 10^7$, $\mu = 0.01$, $k = 1.67 \times 10^{-6}$, $\delta = 0.0053$, $p = 0.01$, $a = 150$, $\beta = 0.87$, $c = 3.8$, $q = 0.03$, $b = 0.2$, $\alpha = 0.6$, $\alpha_0 = 1$, $\alpha_1 = 0.1$, $\alpha_2 = 0.0001$, $\alpha_3 = 0.000001$, $A_1 = 5000$ and $A_2 = 5000$.

The figures from the numerical simulation of the model, allows us to compare the number of healthy and infected cells and the viral load before and after the treatment.

In the first figure (Fig. 1), we see that the number of healthy cells after treatment increases significantly, which leads to an improvement in the patient's quality of life.

In the second figure (Fig. 2), we can clearly see that the number of infected cells at the end of the treatment (50 days) is equal to 1.049, while without treatment it is 11.18, which gives a pharmacotherapeutic efficiency of 94% in blocking new infections.

The third figure (Fig. 3) shows that the number of capsids with treatment decreases from the first days, but without treatment always remains at a positive level.

The fourth figure (Fig. 4) shows that after the introduction of the treatment, the viral load decreases and the number of free virions at time t_f equals 2049, while without treatment it is 1.275×10^4.

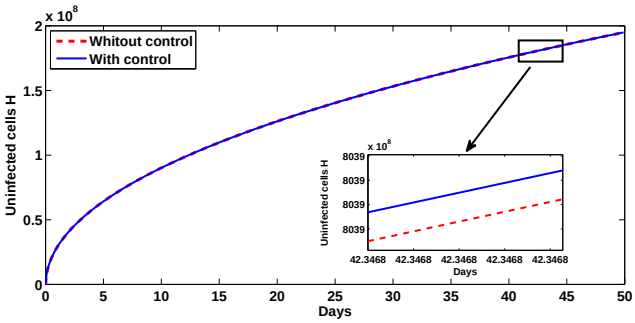

Fig. 1. Uninfected cells H with and without control.

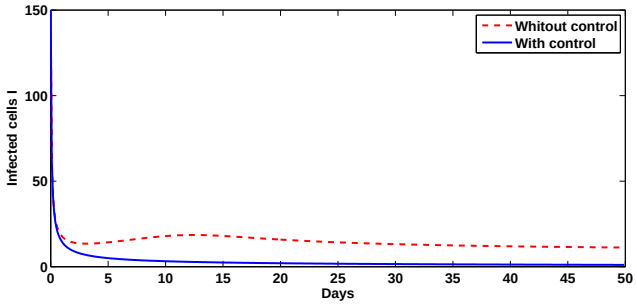

Fig. 2. Infected cells I with and without control.

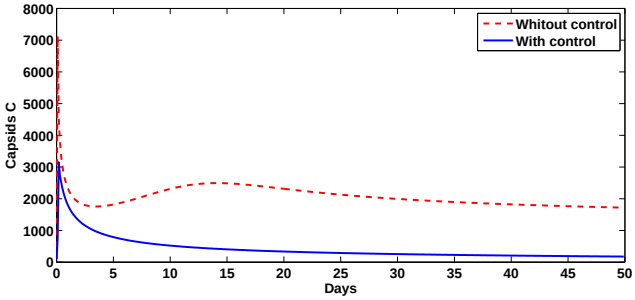

Fig. 3. Capsids C with and without control.

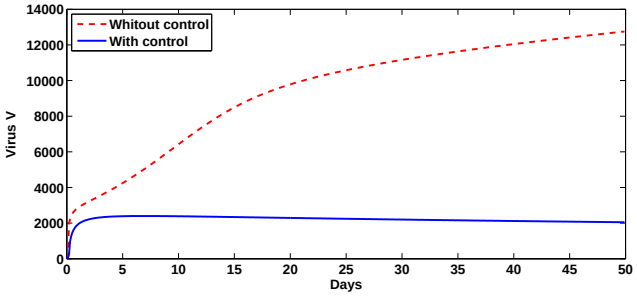

Fig. 4. Virus V with and without control.

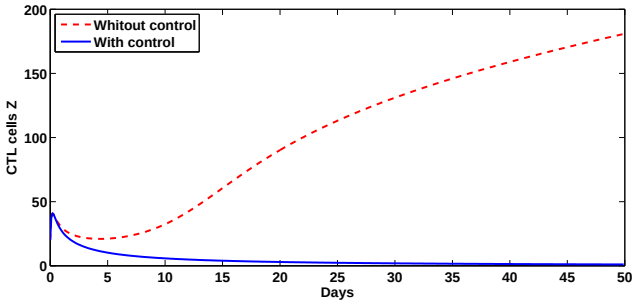

Fig. 5. CTL cells Z with and without control.

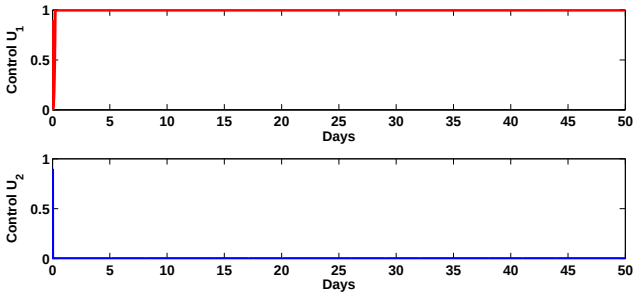

Fig. 6. The optimal controls u_1 and u_2.

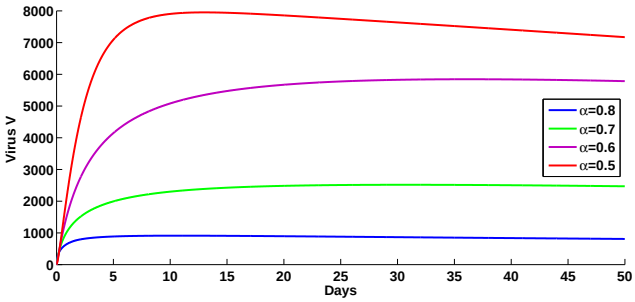

Fig. 7. The state variable V with control and the fractional derivative order α.

From the fifth figure (Fig. 5), it can be seen that CTL cells are also affected by the treatment. The number of these cells always remains positive and is never eliminated. A small increase in infection is directly followed by an increase in the immune response, and if the infection decreases this response also decreases. Figure 6 shows the optimal u_1 and u_2 controls to prevent re-infection and inhibit viral production. In this figure, we can see that after the first two days of treatment, u_1 is always equal to 1, which verifies the increase of CTL cells activity in the immune system, which also proves that the viral load is reduced from the first weeks. On the other hand, the second control, u_2 does not vary, this variation remaining zero.

This means that the treatment of people with hepatitis B virus infection who show replication (reproduction) of the hepatitis B virus with LMV is unnecessary. Finally, Figure 7 shows that the value of virion concentration decreases when α limits to 1. On the other hand, the memory effect characterized by the fractional derivative decreases when α limits to 1 ($0 < \alpha < 1$) [26]. Therefore, by decreasing the memory effect, the virus concentration decreases.

4. Conclusion

In this paper, we studied a model of HBV infection that includes five fractional differential equations describing the interaction between uninfected cells, infected cells, intracellular capsids containing HBV DNA, HBV virus and CTL response during therapy. We presented an optimal treatment to minimize the cost of treatment, reduce the viral load and improve the immune response. The problem was solved numerically using a forward and backward finite difference scheme. It was shown that with both optimal treatments, the number of healthy hepatocytes increases remarkably, while the number of infected hepatocytes decreases significantly. In addition, it was also observed that with the control strategy, the viral load decreases significantly compared to the no-control model, which can improve the patient's quality of life.

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Динаміка дробової моделі оптимального керування HBV-інфекцією з капсидами та імунною відповіддю CTL

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У цій статті розглядається дробова модель оптимального керування, яка описує взаємодію між вірусом гепатиту В (HBV) та капсидами, що містять ДНК HBV, клітинами печінки (гепатоцитами) та імунною відповіддю цитотоксичних Т-клітин. Оптимальне керування виявляє ефективність медикаментозної терапії в інгібуванні виробництва вірусів і запобіганні новим інфекціям. Система оптимальності виведена та розв'язана чисельно. Отримані результати також показують, що оптимальні стратегії лікування зменшують вірусне навантаження та збільшують кількість неінфікованих клітин, що покращує якість життя пацієнта.

Ключові слова: *дробова похідна; HBV-інфекція; оптимальне керування; CTL-реакція; чисельне моделювання.*