Int. J. Open Problems Compt. Math., Vol. 12, No. 3, September 2019
ISSN 1998-6262;
www.i-csrs.org

Optimal control of a delayed hepatitis B viral infection infection model with DNA-containing capsids, the adaptive immune response and cure rate

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Received 14 May 2019; Accepted 20 July 2019

(Communicated by Tareq M. Hamadneh**)**

Abstract

We present in this paper a delay-differential equation model that describes the interactions between hepatitis B virus (HBV) with DNA-containing capsids, the liver cells (hepatocytes), the antibodies and the cytotoxic T-lymphocyte (CTL) cells. Both two treatments, the intracellular delay and the cure rate of infected cells are incorporated into the model. The first treatment represents the efficiency of drug treatment in preventing new infections, whereas the second stands for the efficiency of drug treatment in inhibiting viral production. Existence for the optimal control pair is established, Pontryagin's maximum principle is used to characterize these two optimal controls. The optimality system is derived and solved numerically using the forward and backward difference approximation. Finally, numerical simulations are established to show the role of optimal therapy in controlling viral replication.

Keywords: *HBV infection. abaptive immune response. Delay. Optimal control. Numerical simulation.*

2019 Mathematics Subject Classification: 03F55, 46S40.

1 Introduction

Hepatitis B virus (HBV) can engender liver disease, leading to the infection of the healthy hypatocytes cells [1]. Contracting this life-threatening pathology stems from body fluid contact. In the last couple of decades, a number of mathematical models describing HBV dynamics were elaborated [2–4]. Other HBV infection models, including HBV DNA-containing capsids effects, have been advanced and studied in recent works [5–7]. It is known that HBV DNA-containing capsids are released from the infected cells under the mature virions form after being enveloped by cellular membrane lipids and viral envelope proteins [8, 9]. All these studies cited above are based on HIV models which omitted the cure of infected cells. A part of these infected cells return to the uninfected state [23–25]. More recently, [11, 26] conducted research studies on the optimal control of HBV viral infection through combining both pegylated interferon (PEG IFN) and lamivudine (LMV) therapies. This present work aims at determining an optimal control of HBV infection through administering both PEG IFN and LMV drugs. The optimal control of HBV infection including HBV DNA-containing capsids and CTL immune response was studied [10]. In this paper, we are interested in the same problem, but we will introduce antibodies into this model and during therapy, a part of infected cells may also revert to the uninfected state at a rate r. This work is motivated by the role of antibodies in reducing the viral infection severity [27, 28]. For this purpose, we will consider the following nonlinear differential equations:

$$\begin{cases} \dfrac{dH}{dt} = s - \mu H(t) - (1-u_1)kH(t)V(t) + rI(t), \\ \dfrac{dI}{dt} = ke^{-\lambda\tau}(1-u_1)H(t-\tau)V(t-\tau) - (\delta + r)I(t), \\ \dfrac{dD}{dt} = (1-u_2)aI(t) - \beta D(t) - \delta D(t), \\ \dfrac{dV}{dt} = \beta D(t) - uV(t), \\ \dfrac{dW}{dt} = gV(t)W(t) - hW(t), \\ \dfrac{dZ}{dt} = cI(t)Z(t) - bZ(t). \end{cases} \tag{1}$$

Susceptible host cells (H) are produced at a rate s, die at a rate μ, and become infected by virus at a rate k. Infected cells (I) die at a rate δ and killed by the CTLs response at a rate p. In addition, through therapy, a part of infected cells may also revert to the uninfected state uninfected state a rate r [23]. The constant λ is assumed to be the death rate of infected but not yet virus-producing cells. The intracellular delay, τ, represents the time needed for infected cells to produce virions after viral entry. The term $e^{-\lambda\tau}$ is the probability of surviving

from time $t-\tau$ to time t. The intracellular HBV DNA-containing capsids (D) are produced at a rate a, they are transmitted to blood at a rate β and die at a rate δ. The virions (V) grow in blood at a rate β, decay at a rate u and is neutralized by antibodies at a rate q. Antibodies (W) expand in response to free virus with a rate g and decay at a rate h. CTLs (Z) develop in response to viral antigen derived from infected cells with a rate c and decay in the absence of antigenic stimulation with a rate b. Finally, u_1 and u_2 denote the efficiency of PEG IFN and LMV drugs respectively [10, 11]. It is noteworthy to mention the role of PEG IFN drug is to block the new infections of the healthy hepatocytes in the liver so that infection rate in the presence of drug is $(1-u_1)k$, while the prime function of the second drug (LMV) is to inhibit viral production such that the virion production rate under therapy is $(1-u_2)a$.

The paper is organized as follows. The next section is devoted to the optimization analysis of the viral infection model. In Section 3, we construct an appropriate numerical algorithm and give some numerical simulations. Finally, we conclude in the last section.

2 The optimal control analysis

2.1 Non-Negativity and Boundedness of Solutions

In order to study the system of delayed differential equations (1), the initial functions need to be first stated and the functional framework needs to be specified. First, let $X = C([-\tau, 0]; \mathbb{R}^6)$ be the Banach space of continuous mapping from $[-\tau, 0]$ to $\mathbb{R}^6$ equipped with the sup-norm $\|\varphi\| = \sup_{-\tau \le t \le 0} \varphi(t)$. Assume that the initial functions verify

$$(H(t), I(t), D(t), V(t), W(t), Z(t) \in X). \tag{2}$$

As usual, for biological reasons, these initial functions $H(t)$, $I(t)$, $D(t)$, $V(t)$, $W(t)$ and $Z(t)$ have to be non-negative:

$$H(t) \ge 0, I(t) \ge 0, D(t) \ge 0, V(t) \ge 0, W(t) \ge 0, Z(t) \ge 0, \text{ for } t \in [-\tau, 0]. \tag{3}$$

We have the following result about the boundedness and the positivity of any solutions of the system (1):

Theorem 2.1. *For any initial conditions* $(H(t), I(t), D(t), V(t), W(t), Z(t))$ *satisfying* (2) *and* (3)*, the system* (1) *has a unique solution, moreover, this solution is non-negative and bounded for all* $t \ge 0$.

2.2 The optimization problem

In order to state the optimization problem, we first consider that u_1 and u_2 vary with time. The problem (1) becomes

$$\begin{cases} \dfrac{dH}{dt} = s - \mu H(t) - (1-u_1(t))kH(t)V(t) + rI(t), \\ \dfrac{dI}{dt} = ke^{-\lambda\tau}(1-u_1(t))H(t-\tau)V(t-\tau) - (\delta+r)I(t), \\ \dfrac{dD}{dt} = (1-u_2(t))aI(t) - \beta D(t) - \delta D(t), \\ \dfrac{dV}{dt} = \beta D(t) - uV(t), \\ \dfrac{dW}{dt} = gV(t)W(t) - hW(t), \\ \dfrac{dZ}{dt} = cI(t)Z(t) - bZ(t), \end{cases} \tag{4}$$

For this problem, we have the following result

Theorem 2.2. *For any initial conditions* $(H(t), I(t), D(t), V(t), W(t), Z(t))$ *satisfying* (2) *and* (3)*, the system* (4) *has a unique solution, in addition, this solution is non-negative and bounded for all* $t \geq 0$*.*

The optimization problem that we consider is to maximize the following objective functional

$$J(u_1, u_2) = \int_0^{t_f} \Big\{ H(t) + W(t) + Z(t) - \Big[\frac{A_1}{2} u_1^2(t) + \frac{A_2}{2} u_2^2(t) \Big] \Big\} dt, \tag{5}$$

where t_f is the period of treatment and the positive constants A_1 and A_2 are based on the benefits and costs of the treatment u_1, u_2, respectively. The two control functions, $u_1(t)$ and $u_2(t)$ are assumed to be bounded and Lebesgue integrable. Our target is to maximize the objective functional defined in equation (17) by increasing the number of the uninfected cells, 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

$$J(u_1^*, u_2^*) = max\{J(u_1, u_2) : (u_1, u_2) \in U\}, \tag{6}$$

where U is the control set defined by

$$U = \{(u_1(t), u_2(t)) : u_i(t) \text{ measurable}, 0 \leq u_i(t) \leq 1, t \in [0, t_f], i = 1, 2\}. \tag{7}$$

2.3 Existence of an optimal control pair

The existence of the optimal control pair can be directly obtained using the results in [13, 14]. More precisely, we have the following theorem

Theorem 2.3. *There exists an optimal control pair* $(u_1^*, u_2^*) \in U$ *such that*

$$J(u_1^*, u_2^*) = \max_{(u_1,u_2)\in U} J(u_1, u_2). \tag{8}$$

Proof. To use the existence result in [13], we must check the following properties:

(P_1) The set of controls and corresponding state variables is nonempty.

(P_2) The control U set is convex and closed.

(P_3) The right hand side of the state system is bounded by a linear function in the state and control variables.

(P_4) The integrand of the objective functional is concave on U.

(P_5) There exists constants $c_1, c_2 > 0$, and $\alpha > 1$ such that the integrand $L(H, u_1, u_2)$ of the objective functional satisfies

$$L(H, W, Z, u_1, u_2) \leq c_2 - c_1(\mid u_1 \mid^2 + \mid u_2 \mid^2)^{\frac{\alpha}{2}}. \tag{9}$$

Where

$$L(H, W, Z, u_1, u_2) = H(t) + W(t) + Z(t) - \Big[\frac{A_1}{2}u_1^2(t) + \frac{A_2}{2}u_2^2(t)\Big]. \tag{10}$$

In order to verify these conditions, we use a result by Lukes in [14] to give the existence of solutions of system (1), which gives condition (P_1). The control set is convex and closed by definition, which gives condition (P_2). Since our state system is bilinear in u_1, u_2, the right hand side of system (1) satisfies condition (P_3), using the boundedness of the solutions. Note that we have the Hessian matrix of L in (u_1, u_2) is

$$Hess(u_1, u_2) = \begin{pmatrix} -A_1 & 0 \\ 0 & -A_2 \end{pmatrix}, \tag{11}$$

then,

$$det(Hess(u_1, u_2)) = A_1A_2 \geq 0, \qquad \forall (u_1, u_2) \in U,$$

So, that the integrand of our objective functional is concave. Also, we have the last needed condition

$$L(H, W, Z, u_1, u_2) \leq c_2 - c_1(\mid u_1 \mid^2 + \mid u_2 \mid^2), \tag{12}$$

where c_2 depends on the upper bound on H and $c_1 = min\left(\frac{A_1}{2}, \frac{A_2}{2}\right) > 0$. We conclude that there exists an optimal control pair $(u_1^*, u_2^*) \in U$ such that

$$J(u_1^*, u_2^*) = \max_{(u_1,u_2)\in U} J(u_1, u_2).$$

□

2.4 Optimality system

Pontryagin's Minimum Principle given in [15] provides necessary conditions for an optimal control problem. This principle converts (1), (17) and (18) into a problem of maximizing an Hamiltonian, T, pointwisely with respect to u_1 and u_2:

$$T(t, H, I, D, V, W, Z, H_\tau, v_\tau, u_1, u_2, \lambda) = \frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2 - H - W - Z + \sum_{i=0}^{6} \lambda_i f_i$$

with

$$\begin{cases} f_1 = s - \mu H(t) - (1-u_1)kH(t)V(t) + rI(t), \\ f_2 = ke^{-\lambda\tau}(1-u_1)H(t-\tau)V(t-\tau) - pI(t)Z(t) - (\delta + r)I(t), \\ f_3 = (1-u_2)aI(t) - \beta D(t) - \delta D(t), \\ f_4 = \beta D(t) - uV(t) - qV(t)W(t), \\ f_5 = gV(t)W(t) - hW(t), \\ f_6 = cI(t)Z(t) - bZ(t). \end{cases} \tag{13}$$

By applying Pontryagin's minimum principle with delay in state [15], we obtain the following theorem

Theorem 2.4. *For any optimal controls u_1^*, u_2^*, and solutions H^*, I^*, D^*, V^*, W^* and Z^* of the corresponding state system (1), there exists adjoint variables, λ_1, λ_2, λ_3, λ_4, λ_5 and λ_6 satisfying the equations*

$$\begin{cases} \lambda_1'(t) &= 1 + \lambda_1(t)\big[\mu + \big(1 - u_1^*(t)\big)kV^*(t)\big] \\ &\quad + \chi_{[0,t_f-\tau]}(t)\lambda_2\big(t+\tau\big)\big(u_1^*\big(t+\tau\big) - 1\big)ke^{-\lambda\tau}V^*(t), \\ \lambda_2'(t) &= \lambda_2(t)[(\delta + r)pZ^*] - \lambda_3(t)\big(1 - u_2^*(t)\big)a - \lambda_6(t)cZ^* - \lambda_1 r, \\ \lambda_3'(t) &= \lambda_3(t)\big(\delta + \beta\big) - \beta\lambda_4(t) \\ \lambda_4'(t) &= \lambda_1(t)\big[k(1-u_1^*(t))H^*(t)\big] + \lambda_4(t)\big(u + qW^*(t)\big) \\ &\quad + \chi_{[0,t_f-\tau]}(t)\lambda_2(t+\tau)\big[ke^{-\lambda\tau}(u_1^*(t+\tau) - 1)H^*(t)\big] \\ \lambda_5'(t) &= 1 + \lambda_4(t)qV^*(t) + \lambda_5(t)\big[h - cV^*(t)\big] \\ \lambda_6'(t) &= 1 + \lambda_2(t)pI^*(t) + \lambda_6(t)\big[b - cI^*(t)\big] \end{cases} \tag{14}$$

with the transversality conditions

$$\lambda_i(t_f) = 0, i = 1, ..., 6. \tag{15}$$

Moreover, the optimal control is given by

$$\begin{aligned} u_1^* =& min\left(1, max\left(0, \frac{k}{A_1}\left[\lambda_2(t)e^{-\lambda\tau}V_\tau^* H_\tau^* - \lambda_1(t)V^*(t)H^*(t)\right]\right)\right) \\ u_2^* =& min\left(1, max\left(0, \frac{1}{A_2}\lambda_3(t)aI^*(t)\right)\right). \end{aligned} \tag{16}$$

Proof. The adjoint equations and transversality conditions can be obtained by using Pontryagin's minimum principle with delay in state [15], such that

$$\begin{cases} \lambda_1'(t) = -\frac{\partial T}{\partial H}(t) - \chi_{[0,t_f-\tau]}(t)\frac{\partial T}{\partial H_\tau}(t+\tau), & \lambda_1(t_f) = 0, \\ \lambda_2'(t) = -\frac{\partial T}{\partial I}(t), & \lambda_2(t_f) = 0, \\ \lambda_3'(t) = -\frac{\partial T}{\partial D}(t), & \lambda_3(t_f) = 0, \\ \lambda_4'(t) = -\frac{\partial T}{\partial V}(t) - \chi_{[0,t_f-\tau]}(t)\frac{\partial T}{\partial V_\tau}(t+\tau), & \lambda_4(t_f) = 0, \\ \lambda_5'(t) = -\frac{\partial T}{\partial W}(t), & \lambda_5(t_f) = 0, \\ \lambda_6'(t) = -\frac{\partial T}{\partial Z}(t), & \lambda_6(t_f) = 0, \end{cases} \tag{17}$$

The optimal control u_1^* and u_2^* can be solved from the optimality conditions,

$$\frac{\partial T}{\partial u_1}(t) = 0, \qquad \frac{\partial T}{\partial u_2}(t) = 0. \tag{18}$$

$$\begin{aligned} \frac{\partial T}{\partial u_1}(t) =& A_1 u_1(t) + k\lambda_1(t)v(t)H(t) - k\lambda_2(t)V_\tau H_\tau e^{-\lambda\tau} = 0, \\ \frac{\partial T}{\partial u_2}(t) =& A_2 u_2(t) - a\lambda_3(t)I(t) = 0. \end{aligned} \tag{19}$$

By the boundedness of the two controls in U, it is easy to obtain u_1^* and u_2^* in the form of (16), respectively.
If we substitute u_1^* and u_2^* in the systems (1), we obtain the following optimality system:

$$\begin{aligned} \frac{dH^*}{dt} &= s - dH^*(t) - k(1-u_1^*(t))V^*(t)H^*(t) + rI^*(t), \\ \frac{dI^*}{dt} &= ke^{-\lambda\tau}(1-u_1^*(t))V^*(t-\tau)H^*(t-\tau) - (\delta+r)I^*(t), \\ \frac{dD^*}{dt} &= (1-u_2^*(t))aI^*(t) - \delta D^*(t) - \beta D^*(t) \\ \frac{dV^*}{dt} &= \beta D^*(t) - uV^*(t), \end{aligned}$$

$$\frac{dW^*}{dt} = gV^*(t)W^*(t) - hW^*(t),$$

$$\frac{dZ^*}{dt} = cI^*(t)Z^*(t) - bZ^*(t),$$

then,

$$\begin{cases} \lambda_1'(t) &= 1 + \lambda_1(t)\big[\mu + \big(1 - u_1^*(t)\big)kV^*(t)\big] \\ & +\chi_{[0,t_f-\tau]}(t)\lambda_2\big(t+\tau\big)\big(u_1^*\big(t+\tau\big) - 1\big)ke^{-\lambda\tau}V^*(t), \\ \lambda_2'(t) &= \lambda_2(t)(\delta + r) - \lambda_3(t)\big(1 - u_2^*(t)\big)a - \lambda_1(t)r, \\ \lambda_3'(t) &= \lambda_3(t)\big(\delta + \beta\big) - \beta\lambda_4(t) \\ \lambda_4'(t) &= \lambda_1(t)\big[k(1 - u_1^*(t))H^*(t)\big] + \lambda_4(t)\big(u + qW^*(t)\big) \\ & +\chi_{[0,t_f-\tau]}(t)\lambda_2(t+\tau)\big[ke^{-\lambda\tau}(u_1^*(t+\tau) - 1)H^*(t)\big], \\ \lambda_5'(t) &= 1 + \lambda_4(t)qV^*(t) + \lambda_5(t)\big[h - cV^*(t)\big] \\ \lambda_6'(t) &= 1 + \lambda_2(t)pI^*(t) + \lambda_6(t)\big[b - cI^*(t)\big] \end{cases} \tag{20}$$

$$\begin{aligned} u_1^* =& min\left(1, max\left(0, \frac{k}{A_1}\left[\lambda_2(t)e^{-\lambda\tau}V_\tau^*H_\tau^* - \lambda_1(t)V^*(t)H^*(t)\right]\right)\right) \\ u_2^* =& min\left(1, max\left(0, \frac{1}{A_2}\lambda_3(t)aI^*(t)\right)\right). \end{aligned} \tag{21}$$

$$\lambda_i(t_f) = 0, i = 1, ..., 6. \tag{22}$$

□

3 Numerical simulations

In order to perform the numerical simulations, the optimization system will be solved numerically using a discretized scheme based on forward and backward finite difference approximation method [19–21]. Indeed, we will have the following numerical algorithm:

Step 1:
for $i = -m, ..., 0$, do:
$H_i = H_0$, $I_i = I_0$, $D_i = D_0$, $V_i = V_0$, $W_i = W_0$, $W_i = W_0$, $u_1^i = 0$, $u_2^i = 0$.
end for
for $i = n, ..., n+m$, do:
$\lambda_1^i = 0, \lambda_2^i = 0, \lambda_3^i = 0, \lambda_4^i = 0, \lambda_5^i = 0, \lambda_6^i = 0$.
end for
Step 2:
for $i = 0, ..., n-1$, do:

$$H_{i+1} = H_i + h[s - \mu H_i - k(1-u_1^i)V_i H_i + rI_i],$$
$$I_{i+1} = I_i + h[ke^{-\lambda\tau}(1-u_1^i)V_{i-m}H_{i-m} - (\delta + r)I_i],$$
$$D_{i+1} = D_i + h[(1-u_2^i)aI_i - \delta D_i - \beta D_i],$$
$$V_{i+1} = V_i + h[\beta D_i - uV_i],$$
$$W_{i+1} = W_i + h[gV_iW_i - hW_i],$$
$$Z_{i+1} = Z_i + h[cI_iZ_i - bZ_i],$$
$$\lambda_1^{n-i-1} = \lambda_1^{n-i} - h[1 + \lambda_1^{n-i}(\mu + (1-u_1^i)kV_{i+1})] + \chi_{[0,t_f-\tau]}(t_{n-i})\lambda_2^{n-i+m}(u_1^{i+m} - 1)ke^{-\lambda\tau}V_{i+1}],$$
$$\lambda_2^{n-i-1} = \lambda_2^{n-i} - h[\lambda_2^{n-i}(\delta + r) - \lambda_3^{n-i}(1-u_2^i)a - \lambda_1^{n-i}r],$$
$$\lambda_3^{n-i-1} = \lambda_3^{n-i} - h[\lambda_3^{n-i}(\delta + \beta) - \lambda_4^{n-i}\beta],$$
$$\lambda_4^{n-i-1} = \lambda_4^{n-i} - h[\lambda_1^{n-i}(1-u_1^i)kH_{i+1} + \lambda_4^{n-i}(u + qW_{i+1}) + \chi_{[0,t_f-\tau]}(t_{n-i})\lambda_2^{n-i+m}(u_1^{i+m} - 1)ke^{-\delta\tau}H_{i+1}],$$
$$\lambda_5^{n-i-1} = \lambda_5^{n-i} - h[1 + q\lambda_2^{n-i}V_{i+1} + \lambda_5^{n-i}(h - gV_{i+1})],$$
$$\lambda_6^{n-i-1} = \lambda_6^{n-i} - h[1 + p\lambda_2^{n-i}I_{i+1} + \lambda_6^{n-i}(b - cI_{i+1})],$$
$$R_1^{i+1} = (k/A_1)(\lambda_2^{n-i-1}e^{-\lambda\tau}V_{i-m+1}H_{i-m+1} - \lambda_1^{n-i-1}V_{i+1}H_{i+1})$$
$$R_2^{i+1} = (1/A_2)\lambda_3^{n-i-1}aI_{i+1},$$
$$u_1^{i+1} = min(1, max(R_1^{i+1}, 0)),$$
$$u_2^{i+1} = min(1, max(R_2^{i+1}, 0)),$$

end for
Step 3:
for $i = 1, ..., n$, write
$H^*(t_i) = H_i, I^*(t_i) = I_i, D^*(t_i) = D_i, V^*(t_i) = V_i, W^*(t_i) = W_i, Z^*(t_i) = Z_i, u_1^*(t_i) = u_1^i, u_2^*(t_i) = u_2^i$.
end for

The numerical algorithm.

The parameters of our numerical simulations are taken from [17, 18]; i.e. $s = 2.6\times10^7$, $k = 1.67\times10^{-12}$, $\mu = 0.01$, $\delta = 0.053$, $a = 150$, $\beta = 0.87$, $u = 3.8$, $\tau = 5$, $\lambda = 1.1 \times 10^{-2}$, $A_1 = 50000$ and $A_2 = 5000$. The role of these two last positive parameters A_1 and A_2 is to balance the terms size in the equations. The new parameter of our problem, the cure rate will be $r = 0.01$ [23].

Figure 1 shows the uninfected cells during the first weeks of observation. It can be seen, that after the treatments (with control), the uninfected cells

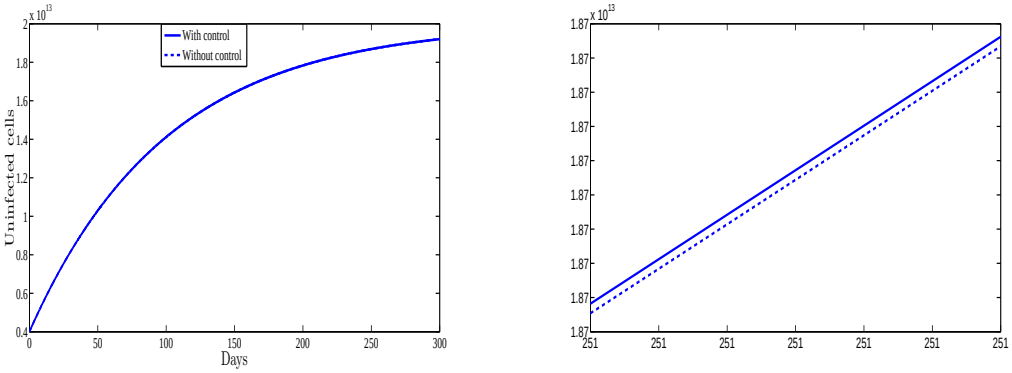

Figure 1: The uninfected cells (left) as function of time and a zoomed region (right).

population grows significantly comparing with the curve representing the no-treatment case.

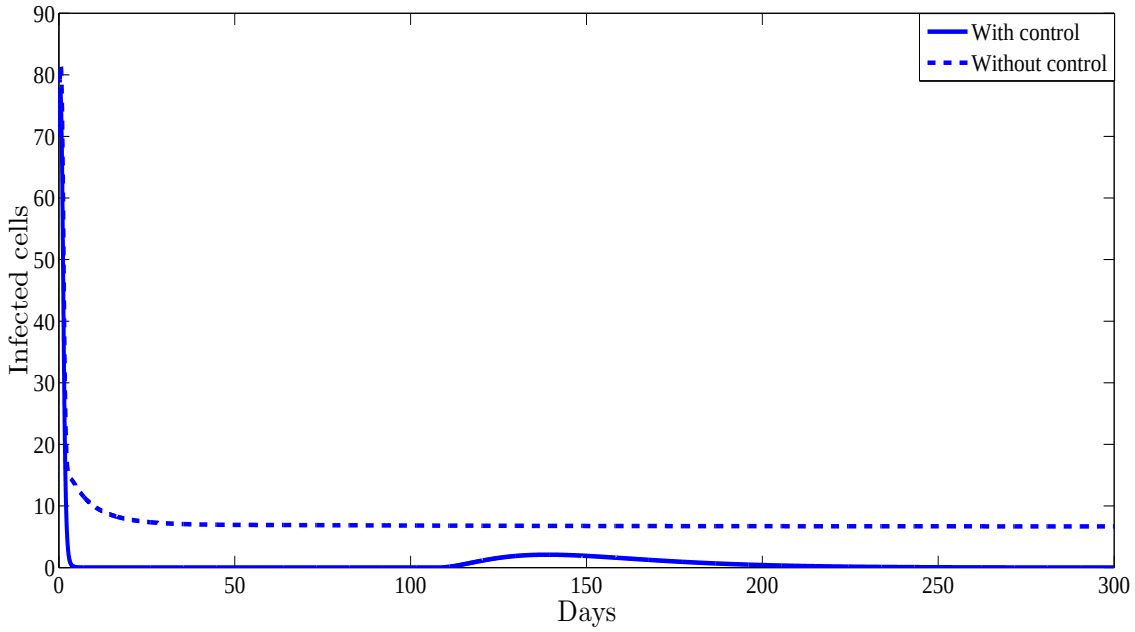

Figure 2: The infected cells as function of time.

From Figure.2, we clearly observe that the curve representing the infected cells under control converges toward 0.002, whereas, without control, it converges toward 7.729, which means that administrating the good therapy amounts can help the patient by the significant reduction of the infected cells number

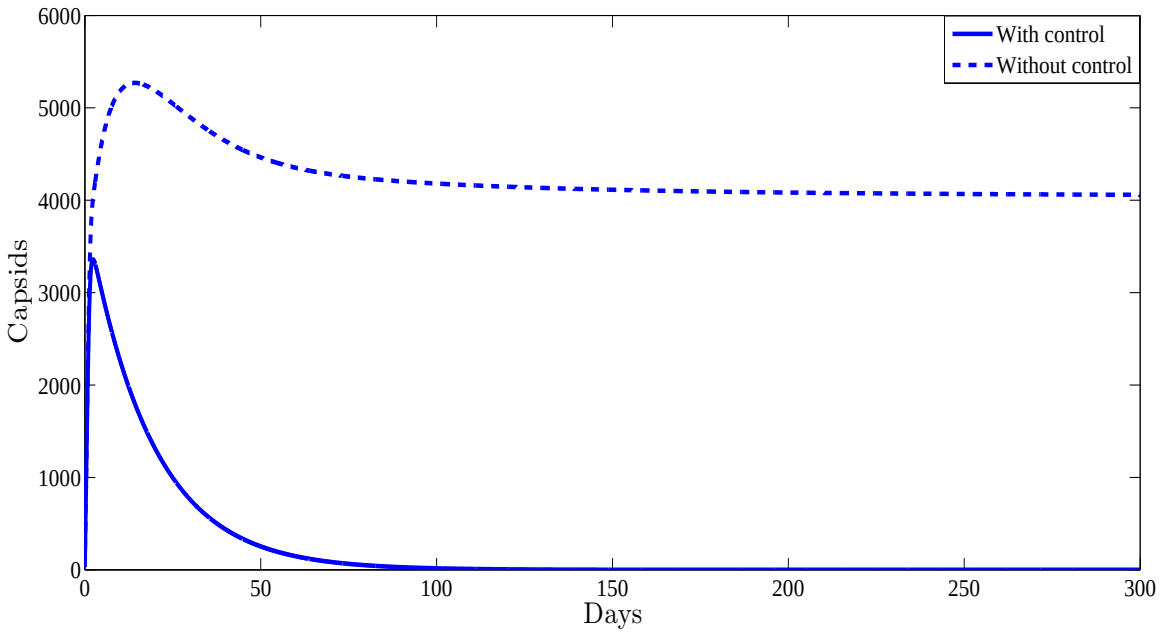

Figure 3: The capsids as function of time.

Figure 3 shows that after introducing good therapy, the number of capsids load declines towards 2.36×10^3. However, the number of capsids remains at a very high level in the case without any control strategy.

The role of therapy control is also observed in Figure 4. It was shown that with control, the number of HBV virions decreases significantly after the first weeks of therapy, while without control it stays equal to a high level. This indicates the impact of the administrated therapy in controlling viral replication.

The antibody immune response is clearly affected by the control. This is illustrated in Figure 5; indeed, with control, the curve of antibodies converges towards zero; however, without any control strategy it converges towards 39.05 which clearly indicates the importance of adding the antibody component to HBV viral dynamics. We also note that an increase of infected cells or viral load corresponds to an increase in immune response (antibody).

The CTL cells are clearly affected by the control. This is shown in Figure 6; indeed the curve of CTL cells converges towards zero with control, while without any control it converges towards 49.7×10^3 which reveals the importance of adding the CTL component to HBV viral dynamics.

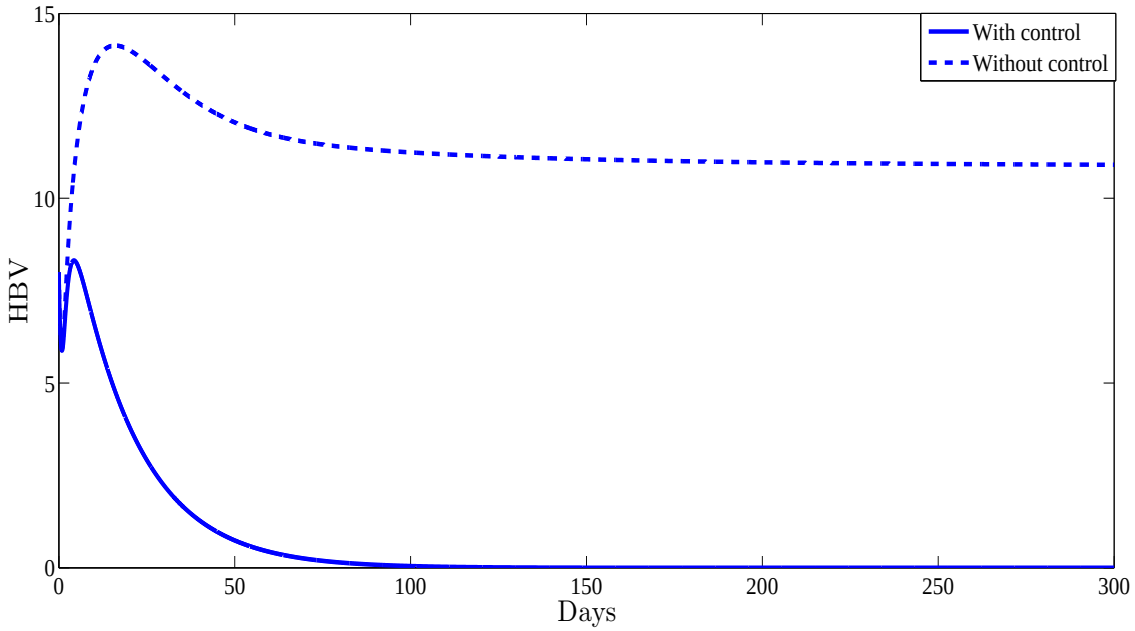

Figure 4: The virions as function of time.

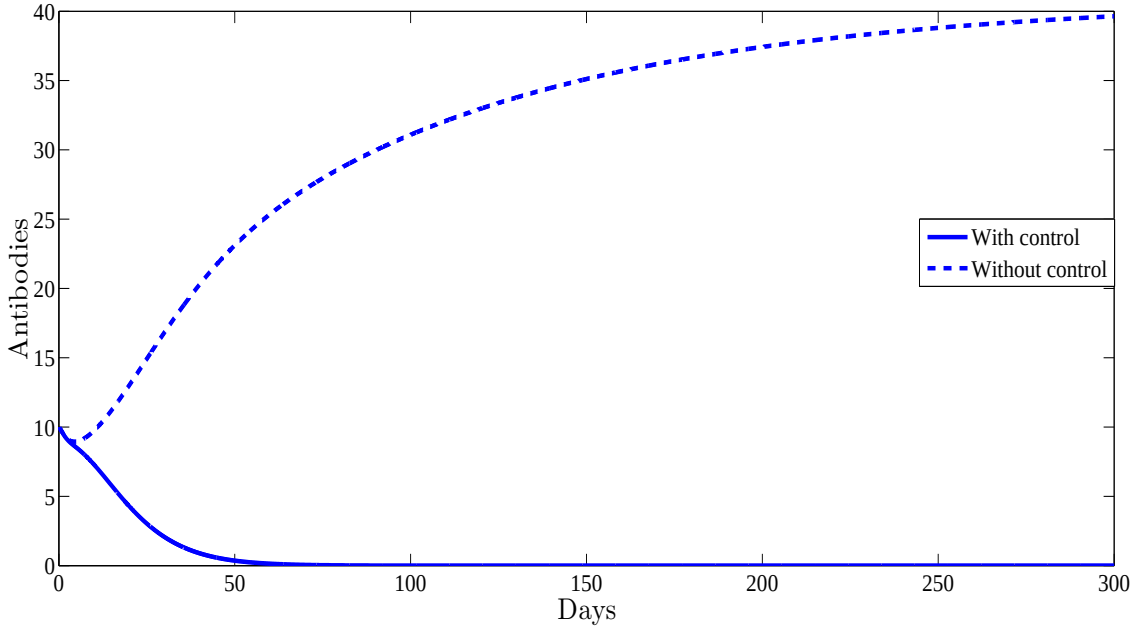

Figure 5: The evolution of antibodies as function of time.

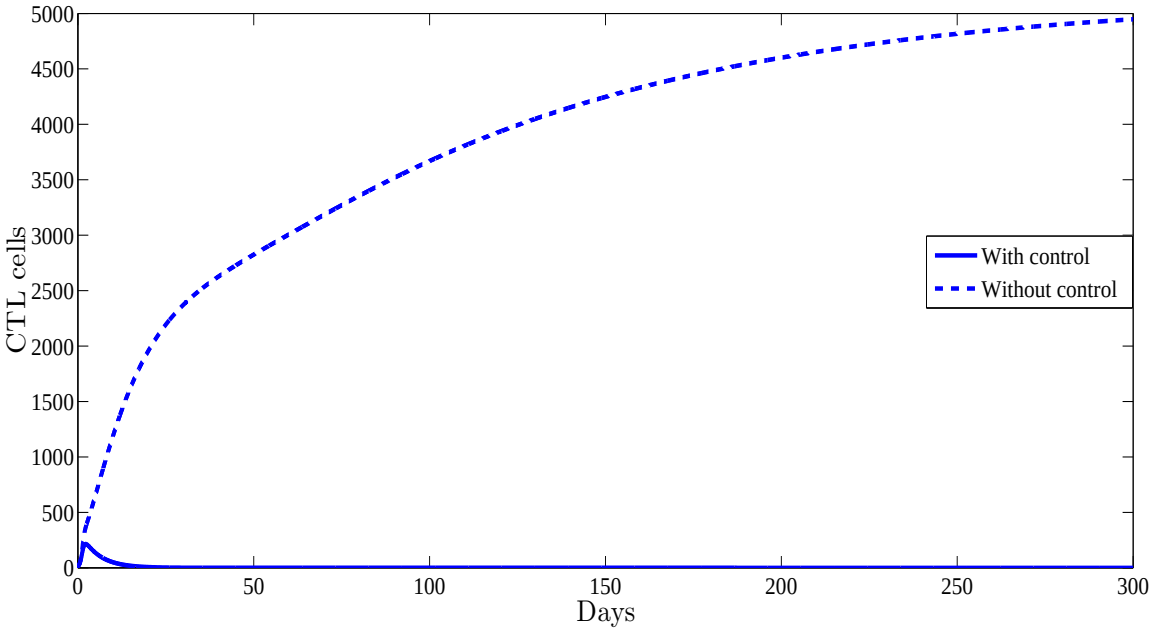

Figure 6: The CTL response as function of time.

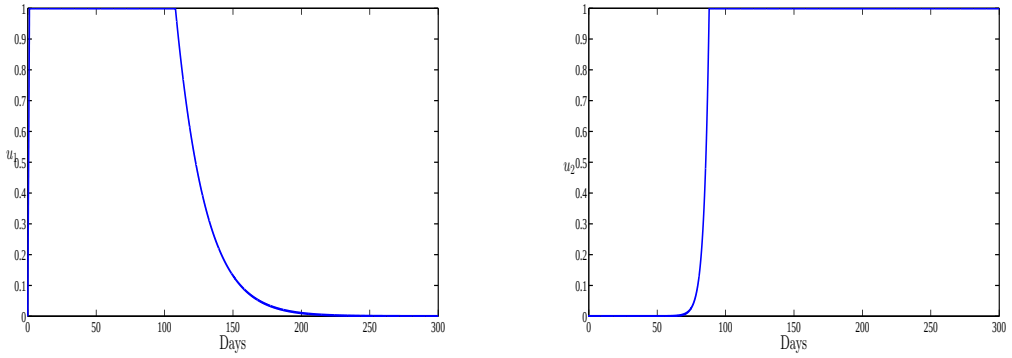

Figure 7: The optimal control u_1 (left) and the optimal control u_2 (right) versus time.

Finally, The two optimal controls u_1 and u_2, corresponding to blocking new infections and inhibiting viral production, are represented in Figure 6. The two curves present the drug administration schedule during the period of treatment. Both controls start from zero and oscillate between zero and one. When the first immune boosting drug is administered at full scale, the second drug is at its lowest and vice versa. In this case, the new infection is totally blocked

4 Conclusion

In this paper, we have studied an HBV infection model with intracellular HBV DNA-containing capsids in the presence of the adaptive immune response which is represented by the cytotoxic T lymphocytes (CTL) cells and the antibodies. The considered model includes six differential equations describing the interaction between the uninfected cells, infected cells, capsids, HBV virus, cytotoxic T-lymphocyte cells and antibody immune responses. An intracellular time delay, both the treatments and cure rate of infected cells are incorporated into the model. We have proved the existence and uniqueness of the optimal controls using Pontryagin's maximum principle. The problem was solved numerically using backward and forward finite-difference scheme. It was shown that, with the two optimal treatments, the number of the healthy hepatocytes increases remarkably, whereas the number of the infected hepatocytes decreases significantly. In addition, it was also observed that, with the control strategy, the viral load decreases considerably compared with the model without control, which can improve the patient's life quality.

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