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DYNAMICS OF HBV INFECTION MODEL WITH DNA-CONTAINING CAPSIDS, LOGISTIC HEPATOCYTE GROWTH AND ADAPTIVE IMMUNE RESPONSE

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Abstract. In this paper, the model describes the interactions between the hepatocytes, the free hepatitis B virus (HBV) with DNA-containing capsids, and the adaptive immune response represented by the cytotoxic T lymphocytes (CTL) cells and the anti-bodies with a delay-differential equation and logistic hepatocyte growth. We show the existence, positivity and boundedness of solution and we analyse the existence and the stability of the disease free equilibrium and the endemic equilibrium points. Also, the existence of the optimal control pair is established and Pontryagin's minimum principle is used to characterize the efficiency of drug treatment in inhibiting viral production and preventing new infections. The obtained results are discussed numerically to show that the optimal treatment strategies reduce the viral load and then increase the uninfected hepatocytes, this improves the patient's quality of life.

Keywords: hepatitis B viral infection; logistic hepatocyte growth; adaptive immune response; optimal control; Pontryagin's minimum principle; viral infection.

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1. INTRODUCTION

Hepatitis B virus (HBV) is a major cause of liver disease with more than 5 million deaths annually [1]. This severe disease can be transmitted easily through contact with any infected body fluids [2] and it is, for example, 100 times more infectious than HIV (human immunodeficiency virus) [4, 8]. In the last decades, several mathematical models have been developed to describe and understand the dynamics of HBV infection [9, 10, 12]. During the HBV infection, the adaptive immune response, which has two main responses plays an important role in the pathogenesis of this disease. The first of responses presents the cellular immune response, called cytotoxic T-lymphocyte (CTL) response which is responsible for attacking and killing the infected cells, while the second presents the humoral immune response, which is based on the antibodies that are produced by the B cells and are programmed to attack and neutralize the viruses [13, 14]. The mathematical analysis of HBV viral infection with HBV DNA-containing capsids was determined [3,5–7]. Several papers have developed some mathematical models that explain how these two immune responses are important in curing the viral infection [15–20,22]. Recently, the model describing a delayed differential-equations HBV infection with linear birth rate is studied in [21]. The dynamics of this model are governed by the following nonlinear system of differential equations:

$$
\begin{cases}
\dfrac{dH}{dt} = \lambda - dH(t) - \beta(1-u_1(t))V(t)H(t), \\
\dfrac{dI}{dt} = \beta e^{-k\tau}(1-u_1(t))V(t-\tau)H(t-\tau) - aI(t) - pI(t)Z(t), \\
\dfrac{dV}{dt} = (1-u_2(t))aNI(t) - \delta V(t) - qV(t)W(t), \\
\dfrac{dW}{dt} = gV(t)W(t) - hW(t), \\
\dfrac{dZ}{dt} = cI(t)z(t) - bZ(t).
\end{cases} \tag{1.1}
$$

In the model (1.1) the healthy hepatocytes are recruited at a constant rate λ from the source within the body, such as the bone marrow, and have a naturel life expectancy of $\frac{1}{d}$ days.

However, it is well established that liver recovery following injury is facilitated by widespread hepatocytes proliferation. To correct this problem, we introduce a logistic function for healthy hepatocytes growth and the mass action term $\beta V(t)H(t)$ is replaced by $K\frac{V(t)H(t)}{T(t)}$ where $T(t) = H(t) + I(t)$ is the total number of liver cells, So the equation becomes as follows $\frac{dH}{dt} = rH(t)\left(1 - \frac{T(t)}{T_m}\right) - K\frac{V(t)H(t)}{T(t)}$, [23–26] and this model (1.1) becomes

$$
\begin{cases}
\dfrac{dH}{dt} = rH(t)\left(1 - \dfrac{T(t)}{T_m}\right) - K(1-u_1(t))\dfrac{V(t)H(t)}{T(t)}, \\
\dfrac{dI}{dt} = Ke^{-k\tau}(1-u_1(t))\dfrac{V(t-\tau)H(t-\tau)}{T(t-\tau)} - \delta I(t) - pI(t)Z(t), \\
\dfrac{dD}{dt} = (1-u_2(t))aI(t) - \beta D(t) - \delta D(t), \\
\dfrac{dV}{dt} = \beta D(t) - uV(t) - qV(t)W(t), \\
\dfrac{dW}{dt} = gV(t)W(t) - hW(t), \\
\dfrac{dZ}{dt} = cI(t)Z(t) - bZ(t).
\end{cases}
\tag{1.2}
$$

with

$$T(t) = H(t) + I(t).$$

where $H(t)$,$I(t)$, $D(t)$, $V(t)$, $W(t)$ and $Z(t)$ denote the concentrations of uninfected cells, infected cells, intracellular HBV DNA-containing capsids, virus, Antibodies and cytotoxic T lymphocytes (CTLs), respectively. The uninfected hepatocytes grow at a rate that depends on the liver size, T_m, at a maximum per capita proliferation rate r. The healthy hepatocytes become infected by the virus at a rate $K\frac{VH}{T}$, where K is the mass action constant. Infected cells (I) die at a rate δ and killed by the CTLs response at a rate p. The constant λ is assumed to be the death rate for 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 $e^{-k\tau}$ 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 [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 $K(1-u_1)$, 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 existence, positivity and boundedness of solutions, followed in Section 3 by the optimization analysis of the viral infection model. In Section 4, we construct an appropriate numerical algorithm and give some numerical simulations. Finally, we conclude in the last section.

2. Positivity and Boundedness of Solutions

The model (1.2) presents a system of delayed differential equations. For such problem, initial functions need to be stated and the functional framework needs to be specified. 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 $\|\varphi\| = \sup_{-\tau\leq t\leq 0} \varphi(t)$. We assume that the initial functions verify

$$(H(t),I(t),D(t),V(t),W(t),Z(t)) \in X. \tag{2.1}$$

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

$$H(t)\geq 0, I(t)\geq 0, D(t)\geq 0, V(t)\geq 0, W(t)\geq 0, Z(t)\geq 0, \text{ for } t\in[-\tau,0]. \tag{2.2}$$

$$T_m \geq T(t) = H(t)+I(t) > 0, \text{ for } t\in[-\tau,0]. \tag{2.3}$$

For the solutions of (1.2) with initial functions satisfying (2.1), (2.2), and (2.3), we have the following

Theorem 2.1. *For any initial conditions* $(H(t),I(t),D(t),V(t),W(t),Z(t))$ *satisfying* (2.1)*,* (2.2)*, and* (2.3)*, the system* (1.2) *has a unique solution; in addition, this solution is non-negative and bounded for all* $t\geq 0$*.*

Proof. Notice that system (1.2) is locally Lipschitzian at $t = 0$. Hence the solution of system (1.2), subject to (2.3), exists and is unique on $[0,b)$ where b is the maximal existence time for solution of system (1.2). Observe that if $H(0) = 0$, then $H(t) \equiv 0$ for all $t > 0$. Hence we assume below that $H(0) > 0$. Notice also that if $I(0) = 0$ then $I(0) = ke^{-k\tau}\frac{V(-\tau)x(-\tau)}{T(-\tau)} \geq 0$ this from (2.2), which implies that for small $t > 0$, we have $I(t) > 0$. Of same that if $D(0) = 0$ then $D'(0) = aI(0) > 0$, which implies that for small $t > 0$, we have $D(t) > 0$, and if $V(0) = 0$ then $V'(0) = \beta D(0) > 0$, which implies that for small $t > 0$, we have $V(t) > 0$, and if $W(0) = 0, Z(0) = 0$, then $W(t) \equiv 0, Z(t) \equiv 0$ for all $t > 0$. Hence we assume below that $W(0) > 0, Z(0) > 0$.

Assume first that there is a $b > t_1 > 0$ such that $H(t_1) = 0$ and $H(t) > 0$, $I(t) > 0$, D(t)¿0, $V(t) > 0$, for $t \in [0,t_1]$. Observe that

$$\frac{dH(t)}{dt} = rH(t)(1 - \frac{T(t)}{T_m}) - K(1 - u_1(t))\frac{V(t)H(t)}{T(t)}.$$

It is easy to show that $0 < T(t) < T_m$ for $t \in [0,t_1]$, we can see that $\frac{dH(t)}{dt} \geq -KL(1 - u_1(t))\frac{V(t)H(t)}{T(t)}$, clearly $I(t) < T(t)$, for $t \in [0,t_1]$, these observation imply that for $t \in [0,t_1]$, we have $\frac{dH(t)}{dt} \geq -K(1 - u_1(t))\frac{V(t)H(t)}{I(t)}$.

Hence

$$H(t_1) \geq H(0)e^{-\int_0^{t_1} \frac{K(1-u_1(s))V(s)}{Y(s)}ds} > 0,$$

a contradiction.

Assume first that there is a $b > t_1 > 0$ such that $I(t_1) = 0$ and $H(t) > 0$, $I(t) > 0$, $D(t) > 0$, $V(t) > 0$, $W(t) > 0$, $Z(t) > 0$ for $t \in [0,t_1]$.

From the seconde equation of the system (1.2), we deduce that $\frac{dI(t)}{dt} \geq -\delta I(t) - pI(t)Z(t)$ for $t \in [0,t_1]$ which yields $I(t_1) \geq I(0)e^{-\int_0^{t_1}(\delta + pZ(s))ds} > 0$, also a contradiction.

Assume first that there is a $b > t_1 > 0$ such that $D(t_1) = 0$ and $H(t) > 0$, $I(t) > 0$, $D(t) > 0$, $V(t) > 0$, $W(t) > 0$, $Z(t) > 0$ for $t \in [0,t_1]$.

From the seconde equation of the system (1.2), we deduce that $\frac{dD(t)}{dt} \geq -(\beta + \delta)D(t)$ for $t \in [0,t_1]$ which yields $D(t_1) \geq D(0)e^{-(\beta+\delta)} > 0$, also a contradiction.

Assume first that there is a $b > t_1 > 0$ such that $V(t_1) = 0$ and $H(t) > 0$, $I(t) > 0$, $D(t) > 0$, $V(t) > 0$, $W(t) > 0$, $Z(t) > 0$ for $t \in [0,t_1]$.

From the third equation of the system (1.2), we deduce that $\frac{dV(t)}{dt} \geq -(u+qW(t))V(t)$ for $t \in [0,t_1]$ which yields $V(t_1) \geq V(0)e^{-\int_0^{t_1}(u+qW(s))ds} > 0$, also a contradiction.

Assume first that there is a $b > t_1 > 0$ such that $W(t_1) = 0$ and $H(t) > 0$, $I(t) > 0$, $D(t) > 0$, $V(t) > 0$, $W(t) > 0$, $Z(t) > 0$ for $t \in [0,t_1]$.

From the fourth equation of the system (1.2), we deduce that $\frac{dW(t)}{dt} \geq -hW(t)$ for $t \in [0,t_1]$ which yields $W(t_1) \geq W(0)e^{-ht_1} > 0$, also a contradiction.

Assume first that there is a $b > t_1 > 0$ such that $Z(t_1) = 0$ and $H(t) > 0$, $I(t) > 0$, $D(t) > 0$, $V(t) > 0$, $W(t) > 0$, $Z(t) > 0$ for $t \in [0,t_1]$.

From the fifth equation of the system (1.2), we deduce that $\frac{dZ(t)}{dt} \geq -bZ(t)$ for $t \in [0,t_1]$ which yields $Z(t_1) \geq W(0)e^{-bt_1} > 0$, also a contradiction.

For the boundedness of the solutions, we consider the following function:

$$F(t) = cge^{-k\tau}H(t) + cgI(t+\tau) + cg\delta D(t+\tau) + cg\delta V(t+\tau) + cq\delta W(t+\tau) + gpZ(t+\tau).$$

From (1.2), we have

$$\begin{aligned}\frac{dF(t)}{dt} =& cge^{-k\tau}\left(rH(t) - rH(t)\frac{T(t)}{T_m} - K(1-u_1)\frac{V(t)H(t)}{T(t)}\right)\\ &+ cg\left(Ke^{-k\tau}(1-u_1)\frac{V(t)H(t)}{T(t)} - \delta I(t+\tau) - pI(t+\tau)Z(t+\tau)\right)\\ &+ \delta cg\left((1-u_2)aI(t+\tau) - uV(t+\tau) - qV(t+\tau)W(t+\tau)\right)\\ &+ \delta cq\left(gV(t+\tau)W(t+\tau) - hW(t+\tau)\right) + gp\left(cI(t+\tau)Z(t+\tau) - bZ(t+\tau)\right).\end{aligned}$$

Since $u_2 \in [0,1]$, we have $1-u_2 \leq 1$, and $0 < T(t) < T_m$, $H(t) < T_m$, $-H(t)T(t) < -H(t)$ for $t > 0$ it follows that

$$\begin{aligned}\frac{dF(t)}{dt} \leq& cge^{-k\tau}rT_m - cge^{-k\tau}\frac{r}{T_m}H(t) - \delta cgI(t+\tau) - (\delta)^2 cg + D(t+\tau) -\\ &ucg\delta V(t+\tau) - hcq\delta W(t+\tau) - gpbZ(t+\tau).\end{aligned}$$

If we set, $\rho = min(\frac{r}{T_m}, \delta, u, h, b)$, we will have

$$\frac{dF(t)}{dt} \leq cge^{-k\tau} - \rho F(t).$$

This proves, by virtue of Gronwall's Lemma, that $F(t)$ is bounded, and so are the functions $H(t)$,I(t), $D(t)$, $V(t)$, $W(t)$ and $Z(t)$. Therefore, every local solution can be prolonged up to any time $t_m > 0$, which means that the solution exists globally.

The above contradictions together show that components of the solution of system (1.2) and and (2.3), are nonnegative for all $t \in [0,b)$. This together with the uniform boundedness of $T(t),D(t),V(t),W(t)$ and $Z(t)$ on [0,b) imply that $b = \infty$. This completes the proof of the theorem. □

3. THE OPTIMAL CONTROL ANALYSIS

In this section, we try to discuss the optimal control problem, to find the pair and to give the characterisation of this optimality.

3.1. The optimization problem. In order to state the optimization problem, we first consider that u_1 and u_2 vary with time. The problem (1.2) becomes

$$\begin{cases} \dfrac{dH}{dt} = rH(t)\left(1-\dfrac{T(t)}{T_m}\right) - K(1-u_1(t))\dfrac{V(t)H(t)}{T(t)}, \\ \dfrac{dI}{dt} = Ke^{-k\tau}(1-u_1(t))\dfrac{V(t-\tau)H(t-\tau)}{T(t-\tau)} - \delta I(t) - pI(t)Z(t), \\ \dfrac{dD}{dt} = (1-u_2(t))aI(t) - \beta D(t) - \delta D(t), \\ \dfrac{dV}{dt} = \beta D(t) - uV(t) - qV(t)W(t), \\ \dfrac{dW}{dt} = gV(t)W(t) - hW(t), \\ \dfrac{dZ}{dt} = cI(t)Z(t) - bZ(t). \end{cases} \tag{3.1}$$

For this problem, we have the following result.

Theorem 3.1. *For any initial conditions* $(H(t,I(t),D(t),V(t),Z(t),W(t))$ *satisfying* (2.1),(2.2) *and* (2.3)*, the system* (3.1) *has a unique solution; in addition, this solution is non-negative and bounded for all* $t \geq 0$.

Proof. First, the proof of the positivity of solutions is similar to the previous Theorem 3.3.

For boundedness, we will prove that the solutions remain bounded in each interval $[n\tau,(n+1)\tau]$ with $n \in \mathbb{N}$. It is known that $0 < T(t) < T_m$ for $t > 0$ with $T(t) = H(t) + I(t)$, thus $H(t)$

and I(t) are bounded as. We will start with $n = 0$. Let $t \in [0, \tau]$, From the third equation of the system (3.1) and $(1 - u_2(t)) \leq 1$ we have

$$\frac{dD}{dt} \leq aI(t) - (\beta + \delta)D(t).$$

Thus

$$D(t) \leq D(0)e^{-(\beta+\delta)t} + \int_0^t aI(\xi)e^{-(\beta+\delta)(\xi-t)}d\xi.$$

From the boundedness of I, we deduce that D is also bounded.

From the fourth equation of the system (3.1) we have

$$\frac{dV}{dt} \leq \beta D(t) - uD(t).$$

Thus

$$V(t) \leq V(0)e^{-ut} + \int_0^t \beta D(\xi)e^{-u(\xi-t)}d\xi.$$

From the boundedness of D, we deduce that V is also bounded.

From the fourth and the fifth equation of the system (3.1), we have

$$\frac{dW}{dt} + hW(t) = gV(t)W(t) = \frac{g}{q}\left(\beta D(t) - uV(t) - \dot{V}\right).$$

Thus

$$\frac{dW}{dt} + hW(t) \leq \frac{g}{q}\left(\beta D(t)\right),$$

$$W(t) \leq W(0)e^{-ht} + \frac{g\beta}{q}\left(\int_0^t (D(\xi)e^{h(\xi-t)}d\xi\right).$$

From the boundedness of D, we deduce that W is also bounded.

From the second and the sixth equation of the system (3.1), we have

$$\frac{dZ}{dt} + bZ(t) = cI(t)Z(t) = \frac{c}{p}\left(Ke^{-k\tau}(1 - u_1(t))\frac{V(t-\tau)H(t-\tau)}{T(t-\tau)} - \delta I(t) - \dot{I}\right).$$

Thus

$$Z(t) \leq Z(0)e^{-bt} + \frac{c}{p}\left(\int_0^t K\frac{V(\xi-\tau)H(\xi-\tau)}{T(\xi-\tau)} + (b-\delta)I(\xi))e^{b(\xi-t)}d\xi - I(t) + I(0)e^{-bt}\right).$$

From the boundedness of H, I and V, it follows that Z is bounded. Following the same reasoning as before, for each interval $[n\tau, (n+1)\tau]$ with $n \geq 1$, we conclude that the solutions are bounded for all $t \geq 0$. Similarly to the Theorem 3.3, we deduce the global existence of solutions. □

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

$$J(u_1,u_2)=\int_0^{t_f}\Big\{H(t)+Z(t)+W(t)-\Big[\frac{A_1}{2}u_1^2(t)+\frac{A_2}{2}u_2^2(t)\Big]\Big\}dt, \tag{3.2}$$

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. 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 (3.2) by increasing the number of the uninfected cells, maximizing the CTLs and antibody 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

$$J(u_1^*,u_2^*)=max\{J(u_1,u_2):(u_1,u_2)\in U\}, \tag{3.3}$$

where U is the control set defined by

$$U=\{(u_1(t),u_2(t)):u_i(t)\quad \text{measurable},0\le u_i(t)\le 1,t\in[0,t_f],i=1,2\}. \tag{3.4}$$

3.2. Existence of an optimal control pair. The existence of the optimal control pair can be directly obtained using the results in [30, 31]. More precisely, we have the following theorem.

Theorem 3.2. *There exists an optimal control pair $(u_1^*,u_2^*)\in U$ such that*

$$J(u_1^*,u_2^*)=\max_{(u_1,u_2)\in U}J(u_1,u_2). \tag{3.5}$$

Proof. To use the existence result in [30], 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 $\beta>1$ such that the integrand $L(H,Z,W,u_1,u_2)$ of the objective functional satisfies

$$L(H,Z,W,u_1,u_2)\le c_2-c_1(\mid u_1\mid^2+\mid u_2\mid^2)^{\frac{\beta}{2}}. \tag{3.6}$$

In order to verify these conditions, we use a result by Lukes in [31] to give the existence of solutions of system (1.2), 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 (1.2) satisfies condition (P_3), using the boundedness of the solutions. Note that the integrand of our objective functional is concave. Also, we have the last needed condition

$$L(h,Z,W,u_1,u_2) \leq c_2 - c_1(\mid u_1 \mid^2 + \mid u_2 \mid^2), \tag{3.7}$$

where c_2 depends on the upper bound on H, Z, W, and $c_1 > 0$ since $A_1 > 0$ and $A_2 > 0$. We conclude that there exists an optimal control pair $(u_1^*, u_2^*) \in U$ such that

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

□

3.3. Characterization of the Optimal Control. Pontryagin's Minimum Principle given in [32] provides necessary conditions for an optimal control problem. This principle converts (1.2), (3.2) and (3.3) into a problem of maximizing an Hamiltonian, M, pointwisely with respect to u_1 and u_2:

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

with

$$\begin{cases} f_1 = rH(t)\left(1 - \dfrac{T(t)}{T_m}\right) - K(1-u_1(t))\dfrac{V(t)H(t)}{T(t)}, \\ f_2 = Ke^{-k\tau}(1-u_1(t))\dfrac{V(t-\tau)H(t-\tau)}{T(t-\tau)} - \delta I(t) - pI(t)Z(t), \\ f_3 = (1-u_2(t))aI(t) - \beta D(t) - \delta D(t), \\ f_4 = \beta D(t) - uV(t) - qV(t)W(t), \\ f_5 = gV(t)W(t) - hW(t), \\ f_6 = cI(t)Z(t) - bZ(t). \end{cases} \tag{3.8}$$

$\lambda_i, i = 1,2,3,4,5,6$ are the adjoint functions to be determined suitably.

By applying Pontryagin's minimum principle with delay in state [32], we obtain the following theorem.

Theorem 3.3. *Given optimal controls u_1^*, u_2^*, and solutions H^*, I^*, D^*, V^*, W^* and Z^* of the corresponding state system (1.2), there exists adjoint variables, $\lambda_1, \lambda_2, \lambda_3, \lambda_4, \lambda_5$ and λ_6 satisfying the equations*

(3.9)
$$\begin{cases} \frac{d\lambda_1(t)}{dt} & = 1-\lambda_1(t)\big[r(1-\frac{T^*(t)}{T_m})-\frac{rH^*(t)}{T_m}-\big(1-u_1^*(t)\big)KV^*(t)\frac{I^*(t)}{T^{*2}}\big] \\ & -\chi_{[0,t_f-\tau]}(t)\lambda_2\big(t+\tau\big)\big(u_1^*\big(t+\tau\big)-1\big)Ke^{-k\tau}V^*(t)\frac{I(t)}{T^{*2}(t)}, \\ \frac{d\lambda_2(t)}{dt} & = \lambda_1(t)\big(\frac{rH^*(t)}{T_m}-(1-u_1^*(t))KV^*(t)\frac{H^*(t)}{T^{*2}}\big)+\lambda_2(t)\big(\delta+pZ\big)-\lambda_3(t)\big(1-u_2^*(t)\big)a \\ & -cZ^*(t)\lambda_6(t), \\ \frac{d\lambda_3(t)}{dt} & = \lambda_3(t)\big(\beta+\delta\big)-\lambda_4(t)\beta, \\ \frac{d\lambda_4(t)}{dt} & = \lambda_1(t)\big[K(1-u_1^*(t))\frac{H^*(t)}{T^*(t)}\big]+\lambda_4(t)\big(u+qW(t)\big)+\lambda_5(t)gW^*(t) \\ & +\chi_{[0,t_f-\tau]}(t)\lambda_2(t+\tau)\big[Ke^{-k\tau}(u_1^*(t+\tau)-1)\frac{H^*(t)}{T^*(t)}\big], \\ \frac{d\lambda_5(t)}{dt} & = 1+\lambda_4(t)qV^*(t)+\lambda_5(t)\big[h-gV^*(t)\big], \\ \frac{d\lambda_6(t)}{dt} & = 1+\lambda_2(t)pI^*(t)+\lambda_6(t)\big[b-cI^*(t)\big], \end{cases}$$

and

$$T^*(t) = H^*(t)+I^*(t)$$

with the transversality conditions

$$\lambda_i(t_f) = 0, i = 1,...,6. \tag{3.10}$$

Moreover, the optimal control is given by

$$\begin{aligned} u_1^* &= min\left(1, max\left(0, \frac{\beta}{A_1}\left[\lambda_2(t)e^{-k\tau}\frac{V_\tau^*H_\tau^*}{T_\tau^*}-\lambda_1(t)\frac{V^*(t)H^*(t)}{T^*}\right]\right)\right) \\ u_2^* &= min\left(1, max\left(0, \frac{1}{A_2}\lambda_3(t)aI^*(t)\right)\right). \end{aligned} \tag{3.11}$$

Proof. The adjoint equations and transversality conditions can be obtained by using Pontryagin's minimum principle with delay in state [32], such that

$$
\begin{cases}
\frac{d\lambda_1(t)}{dt} = -\frac{\partial M}{\partial H}(t) - \chi_{[0,t_f-\tau]}(t)\frac{\partial M}{\partial H_\tau}(t+\tau), & \lambda_1(t_f) = 0,\\
\frac{d\lambda_2(t)}{dt} = -\frac{\partial M}{\partial I}(t), & \lambda_2(t_f) = 0,\\
\frac{d\lambda_3(t)}{dt} = -\frac{\partial M}{\partial D}(t), & \lambda_3(t_f) = 0,\\
\frac{d\lambda_4(t)}{dt} = -\frac{\partial M}{\partial V}(t) - \chi_{[0,t_f-\tau]}(t)\frac{\partial M}{\partial V_\tau}(t+\tau), & \lambda_4(t_f) = 0,\\
\frac{d\lambda_5(t)}{dt} = -\frac{\partial M}{\partial W}(t), & \lambda_5(t_f) = 0,\\
\frac{d\lambda_6(t)}{dt} = -\frac{\partial M}{\partial Z}(t), & \lambda_6(t_f) = 0,
\end{cases} \tag{3.12}
$$

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

$$
\frac{\partial H}{\partial u_1}(t) = 0, \qquad \frac{\partial H}{\partial u_2}(t) = 0. \tag{3.13}
$$

That is,

$$
\begin{aligned}
\frac{\partial T}{\partial u_1}(t) =& A_1 u_1(t) + K\lambda_1(t)\frac{V(t)H(t)}{T(t)} - K\lambda_2(t)V_\tau H_\tau e^{-k\tau} = 0,\\
\frac{\partial T}{\partial u_2}(t) =& A_2 u_2(t) - a\lambda_3(t)I(t) = 0.
\end{aligned} \tag{3.14}
$$

By the boundedness of the two controls in U, it is easy to obtain u_1^* and u_2^* in the form of (3.11), respectively.

3.4. The Optimality System. The optimality system consists of the state system coupled with the adjoint system with the initial conditions, the transversality conditions, and the characterization of the optimal control.

If we substitute u_1^* and u_2^* in the systems (1.2) and (3.9), we obtain the following optimality system:

$$
\begin{aligned}
\frac{dH^*}{dt} &= rH^*(t)(1 - \frac{T^*(t)}{T_m}) - K(1-u_1^*(t))\frac{V^*(t)H^*(t)}{T^*(t)},\\
\frac{dI^*}{dt} &= Ke^{-k\tau}(1-u_1^*(t))\frac{V^*(t-\tau)H^*(t-\tau)}{T^*(t-\tau)} - aH^*(t) - pH^*(t)Z^*(t),\\
\frac{dD^*}{dt} &= (1-u_2^*(t))aI^*(t) - \beta D^*(t) - \delta D^*(t),\\
\frac{dV^*}{dt} &= \beta D^*(t) - uV^*(t) - qV^*(t)W^*(t),\\
\frac{dW^*}{dt} &= gV^*(t)W^*(t) - hW^*(t),
\end{aligned}
$$

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

$$\frac{d\lambda_1(t)}{dt} = 1 - \lambda_1(t)\left[r(1-\frac{T^*(t)}{T_m}) - \frac{rH^*(t)}{T_m} - \big(1-u_1^*(t)\big)KV^*(t)\frac{I^*(t)}{T^{*2}(t)}\right] - \chi_{[0,t_f-\tau]}(t)\lambda_2\big(t+\tau\big)\big(u_1^*\big(t+\tau\big) - 1Ke^{-k\tau}V^*(t)\frac{I(t)}{T^{*2}(t)},$$

$$\frac{d\lambda_2(t)}{dt} = \lambda_1(t)\big(\frac{rH^*(t)}{T_m} - (1-u_1^*(t))KV^*(t)\frac{H^*(t)}{T^{*2}}\big) + \lambda_2(t)\big(a+pz\big) - \lambda_3(t)\big(1-u_2^*(t)\big)aN - cZ^*(t)\lambda_5(t) - \chi_{[0,t_f-\tau]}(t)\lambda_2\big(t+\tau\big)\big(u_1^*\big(t+\tau\big)-1\big)Ke^{-k\tau}v^*(t)\frac{H(t)}{T^{*2}(t)},$$

$$\frac{d\lambda_3(t)}{dt} = \lambda_3(t)\big(\beta+\delta\big) - \lambda_4(t)\beta,$$

$$\frac{d\lambda_4(t)}{dt} = \lambda_1(t)\big[K(1-u_1^*(t))\frac{H^*(t)}{T^*(t)}\big] + \lambda_4(t)\big(u+qW(t)\big) + \lambda_5(t)gW^*(t) + \chi_{[0,t_f-\tau]}(t)\lambda_2(t+\tau)\big[Ke^{-k\tau}(u_1^*(t+\tau)-1)\frac{H^*(t)}{T^*(t)}\big],$$

$$\frac{d\lambda_5(t)}{dt} = 1 + \lambda_4(t)qV^*(t) + \lambda_5(t)\big[h - gV^*(t)\big],$$

$$\frac{d\lambda_6(t)}{dt} = 1 + \lambda_2(t)pI^*(t) + \lambda_6(t)\big[b - cI^*(t)\big],$$

$$u_1^* = min\left(1, max\left(0, \frac{\beta}{A_1}\left[\lambda_2(t)e^{-k\tau}\frac{V_\tau^*H_\tau^*}{T_\tau^*} - \lambda_1(t)\frac{V^*(t)H^*(t)}{T^*(t)}\right]\right)\right)$$

$$u_2^* = min\left(1, max\left(0, \frac{1}{A_2}\lambda_3(t)aNI^*(t)\right)\right).$$

$$\lambda_i(t_f) = 0, i = 1, ..., 5$$

□

4. NUMERICAL SIMULATIONS

In order to solve our optimization system, we will use a numerical scheme based on forward and backward finite difference approximation. Hence, we will have the following numerical algorithm.The graphs fromsimulating the model, given below, help to compare the uninfected cells, the infected cells, the viral load and the immune response before and after the treatments with controls.

Step 1:

for $i = -m, ..., 0$, do:

$H_i = H_0$, $I_i = I_0$, $T_i = H_0 + I_0$, $D_i = D_0$, $V_i = V_0$, $W_i = W_0$, $Z_i = Z_0$,

$u_1^i = 0$, $u_2^i = 0$.

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:

$$H_{i+1} = H_i + h[rH_i(1 - \tfrac{T_i}{T_m}) - \beta(1-u_1^i)\tfrac{V_i H_i}{T_i}],$$

$$I_{i+1} = I_i + h[\beta e^{-k\tau}(1-u_1^i)V_{i-m}\tfrac{H_{i-m}}{T_{i-m}} - aI_i - pI_iZ_i],$$

$$D_{i+1} = D_i + h[(1-u_2^i)aI_i - \beta D_i - \delta D_i],$$

$$V_{i+1} = V_i + h[\beta D_i - uV_i - qV_iW_i],$$

$$W_{i+1} = W_i + h[gV_iW_i - hW_i],$$

$$Z_{i+1} = Z_i + h[cI_iZ_i - bZ_i],$$

$$T_{i+1} = H_{i+1} + I_{i+1},$$

$$\lambda_1^{n-i-1} = \lambda_1^{n-i} - h[1 - \lambda_1^{n-i}(r(1-\tfrac{T_{i+1}}{T_m}) - r\tfrac{H_{i+1}}{T_m} - (1-u_1^i)\beta V_{i+1}\tfrac{I_{i+1}}{T_{i+1}}) - \chi_{[0,t_f-\tau]}(t_{n-i})\lambda_2^{n-i+m}(u_1^{i+m}-1)Ke^{-k\tau}V_{i+1}\tfrac{I_{i+1}}{T_{i+1}^2}],$$

$$\lambda_2^{n-i-1} = \lambda_2^{n-i} - h[\lambda_1^{n-i}(r\tfrac{H_{i+1}}{T_m} - (1-u_1^i)KV_{i+1}\tfrac{H_{i+1}}{T_{i+1}^2}) + \lambda_2^{n-i}(a+pZ_{i+1}) - \lambda_3^{n-i}(1-u_2^i)aN - cZ_{i+1}\lambda_5^{n-i}] - \chi_{[0,t_f-\tau]}(t_{n-i})\lambda_2^{n-i+m}(u_1^{i+m}-1)Ke^{-k\tau}V_{i+1}\tfrac{H_{i+1}}{T_{i+1}^2}],$$

$$\lambda_3^{n-i-1} = \lambda_3^{n-i} - h\big[\lambda_1^{n-i}(1-u_1^i)K\tfrac{H_{i+1}}{T_{i+1}} + \lambda_3^{n-i}(\delta + qW_{i+1}) - \lambda_4^{n-i}gW_{i+1} + \chi_{[0,t_f-\tau]}(t_{n-i})\lambda_2^{n-i+m}(u_1^{i+m}-1)Ke^{-k\tau}\tfrac{H_{i+1}}{T_{i+1}}\big],$$

$$\lambda_4^{n-i-1} = \lambda_4^{n-i} - h[1 + q\lambda_3^{n-i}V_{i+1} + \lambda_4^{n-i}(h - gV_{i+1})],$$

$$\lambda_5^{n-i-1} = \lambda_4^{n-i} - h[1 + p\lambda_2^{n-i}I_{i+1} + \lambda_5^{n-i}(b - cI_{i+1})],$$

$$R_1^{i+1} = (\beta/A_1)(\lambda_2^{n-i-1}e^{-k\tau}v_{i-m+1}\tfrac{x_{i-m+1}}{T_{i-m+1}} - \lambda_1^{n-i-1}V_{i+1}\tfrac{H_{i+1}}{T_{i+1}})$$

$$R_2^{i+1} = (1/A_2)\lambda_3^{n-i-1}aNI_{i+1},$$

$$u_1^{i+1} = min(1, max(R_1^{i+1}, 0)),$$

$$u_2^{i+1} = min(1, max(R_2^{i+1}, 0)),$$

end for

Step 3:

for i = 1, ... , n, write

$H^*(t_i) = H_i, I^*(t_i) = I_i, T^*(t_i) = T_i, D^*(t_i) = D_i, V^*(t_i) = V_i, Z^*(t_i) = Z_i, W^*(t_i) = W_i, u_1^*(t_i) = u_1^i, u_2^*(t_i) = u_2^i$. end for

FIGURE 1. The numerical algorithm.

The parameters of our numerical simulations are inspired from [33,34]; i.e. $r = 1$, $T_m = 2 \times 10^{11}$, $K = 0.0018$, $K = 1.1 \times 10^{-2}$, $\tau = 1$, $a = 0.0693$, $N = 480$, $u = 0.693$, $\delta = 0.053$, $\beta = 0.87$, $p = 0.001$, $c = 0.00000044$, $b = 0.5$, $q = 0.01$, $g = 10^{-8}$, $h = 0.1$, $A_1 = 250$, $A_2 = 2500$.

Figure 1 and Figure 2 shows a significant difference in the mass of healthy hepatocytes with and without control from the very beginning of treatment (in the first three days), and after that, it resumes the stable state.

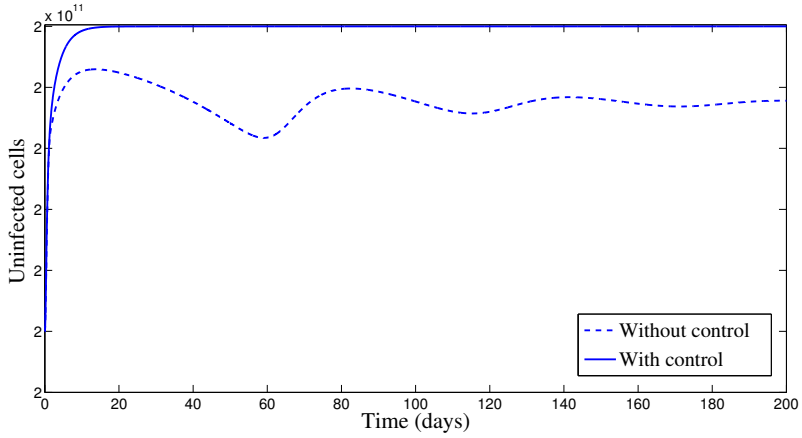

FIGURE 2. The uninfected cells as function of time.

We notice that in absence of treatment the number of infected hepatocytes increases rapidly the first four days, decreases within twenty days after and increases after 25 days. Whereas, in presence of treatment, the number of infected hepatocytes decreases asymptotically to zero. Indeed, the number of infected cells at the final time is 2.5482 in the case with control and is 2.264×10^5 in the case without control, then the efficiency of drug therapy in blocking the new infections is about 98.73%.

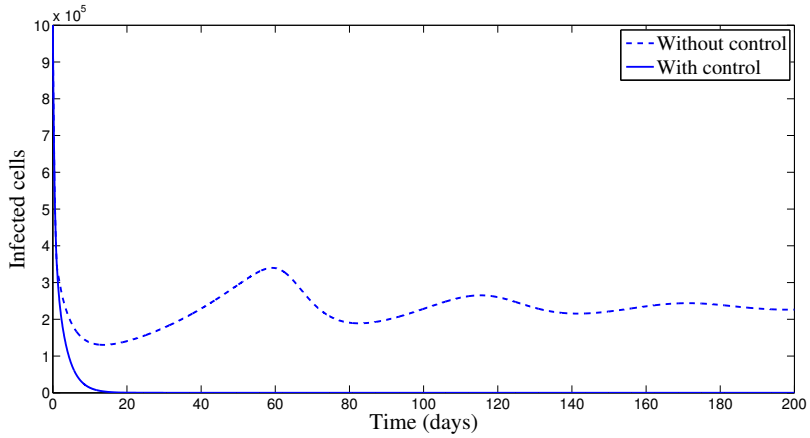

FIGURE 3. The infected cells as function of time.

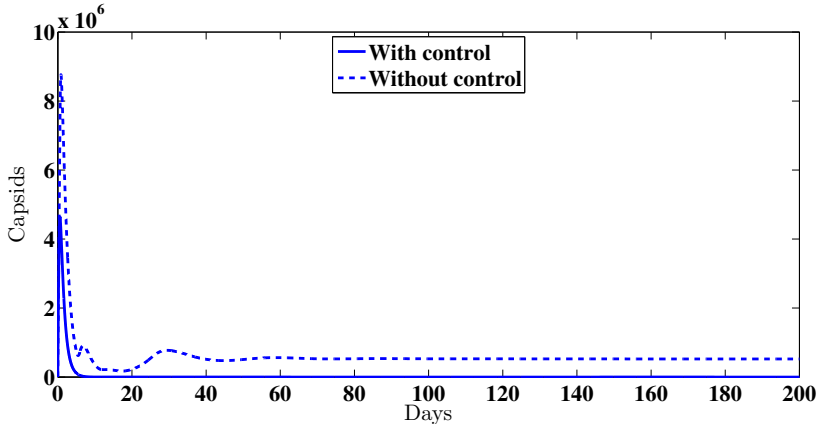

FIGURE 4. The Capsids as function of time.

In Figure 3, shows that, with control, the number of capsids vanishes after the first days of therapy. However, without control, this number remains at positive level 5.249×10^5. In Figure 4, we see that the mass of free virions decreases rapidly towards zero that after introducing therapy. Indeed, the number of free virus at the final time is 1.2112 in the case with control and is 9.768×10^6 in the case without control, then efficiency of drug therapy in inhibiting viral production is about 99,99%.

shows the Antibodies immune response as function of time (right). It can be seen that without control, the immune response is maintained at a strictly positive level. We also note that an increase of viral load corresponds, while, with control, the immune response tends toward zero when time increases.

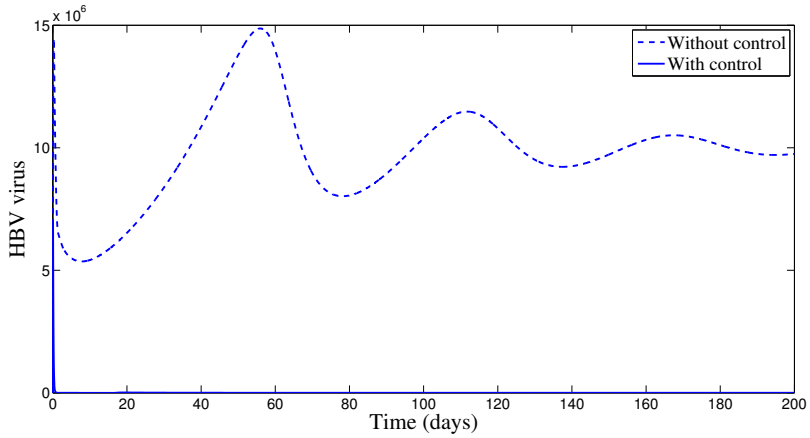

FIGURE 5. The HBV virus as function of time.

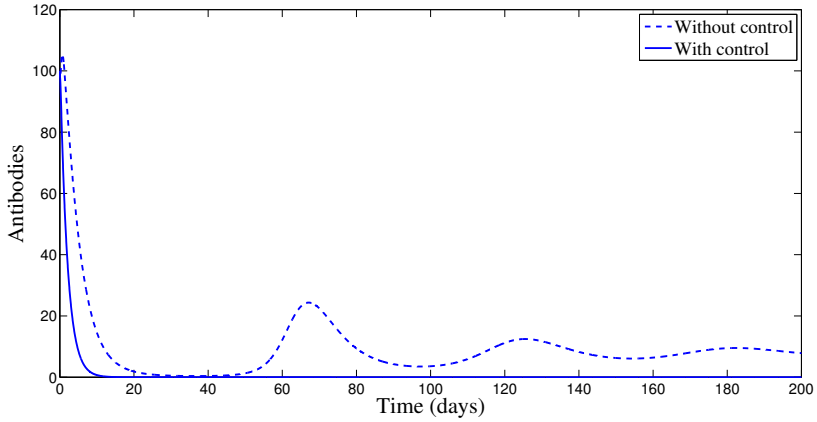

FIGURE 6. The antibody response as function of time.

Figure 5 shows the antibodies immune response as a function of time. Without the therapy, the antibody level shows relapse in count 50 days after the infection, before it persists over time. We can see clearly that the relapse of the antibody synchronised with the virus peak. On the other hand, the early therapy reduces the burden on the antibody as immune response is barely measured.

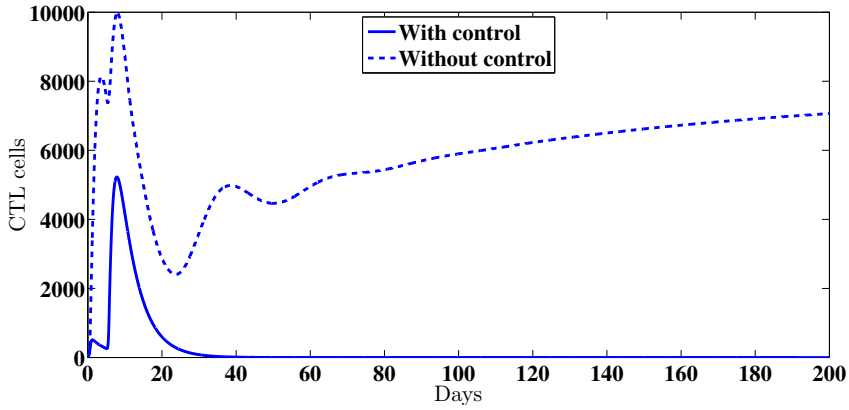

FIGURE 7. The cytotoxic T-lymphocyte (CTL) response as function of time.

The CTL cells are clearly affected by the control. This is shown in Fig 6, indeed, the curve of CTL cells converges toward zero with control, whereas, without any control, it converges toward 6.701×10^3 , which reveals the importance of adding the CTL component to HBV viral dynamics.

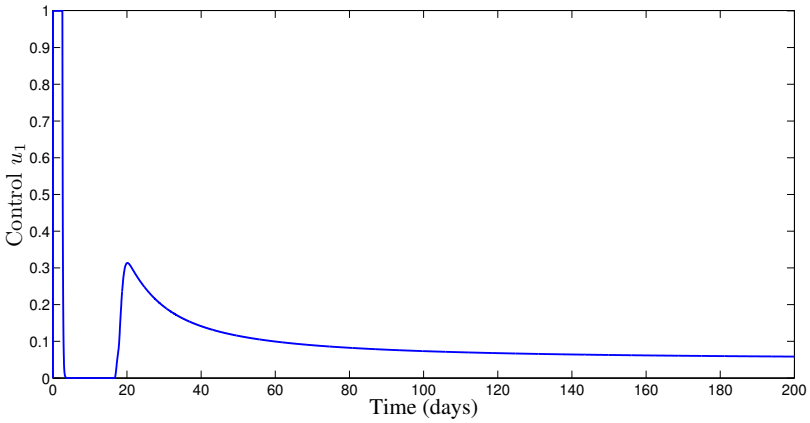

FIGURE 8. The optimal control u1 versus time.

Figure 7 and Figure 8 The curves present the drug administration schedule during the time of treatment. The two controls start from zero and oscillate between zero and one. When the first immune boosting drug is administered in full scale the second is zero and the new infection is totally blocked.

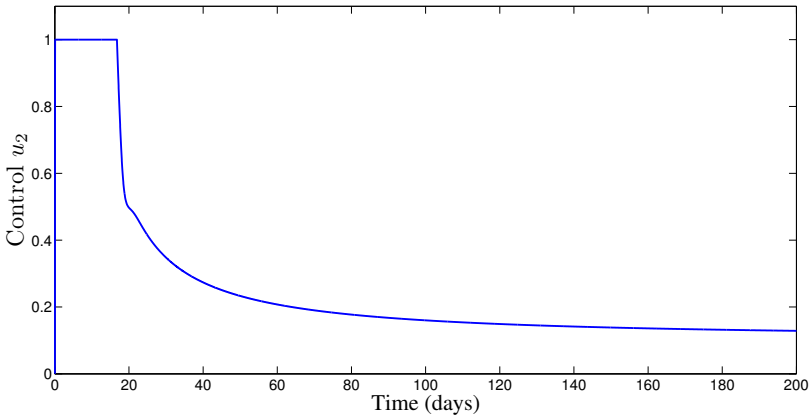

FIGURE 9. The optimal control u2 versus time.

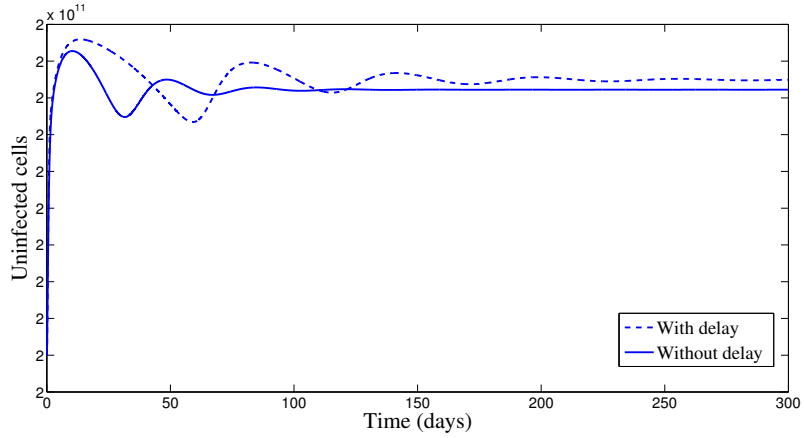

FIGURE 10. The uninfected cells versus time.

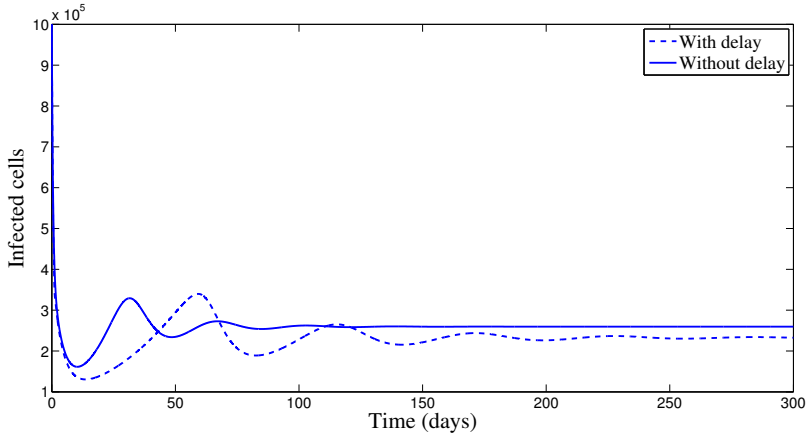

FIGURE 11. The infected cells versus time.

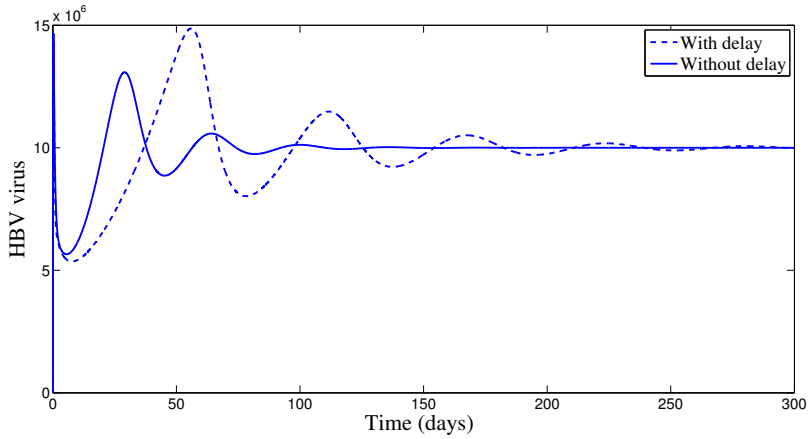

FIGURE 12. the HBV virus versus time.

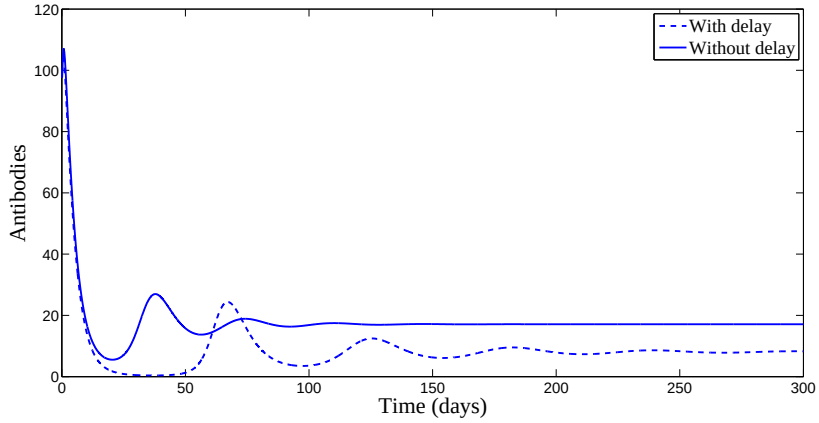

FIGURE 13. The antibody response versus time.

Finally, Figure 9, Figure 10, Figure 11 and Figure 12, present the uninfected cells, the infected cells, the free viruses and antibodies as function of time in the case without control. The solid curves represent the case of without delay and the dashed curves the case of with delay. The curves corresponding to the first case are shifted to the left compared to the second case until they match each other after nearly cent days of treatment.We note that similar behavior is observed for the free viruses and antibodies which means that the time delay has a significant effect for the period of treatment, and we proved that the solutions of our model converge as time converges to infinity, implying that these solutions are not periodic. Hence, the delay can

not cause periodic oscillations. Hence the intracellular delay plays a crucial role in order to prevent the virus.

5. Conclusion

In this paper, we have proposed an optimal control of a delayed HBV infection model with intracellular HBV DNA-containing capsids with logistic hepatocyte growth and adaptive immune response. The considered model includes six differential equations describing the interaction between the uninfected cells, infected cells, , capsids, free viruses, CTL and antibody immune responses. The aim of this paper is twofold. Firstly, we gave a delay mathematical model with two controls that describe HBV infection of hepatocytes cells during therapy. Hence, we presented an optimal therapy in order to minimize the cost of treatment, reduce the viral load, and improve immune response. Secondly, we presented an efficient numerical method based on optimal control to identify the best treatment strategy of HBV infection in order to block new infection and prevent viral production by using drug therapy with minimum side effects.
Our numerical results show that the optimal treatment strategies reduce viral load and increase the uninfected hepatocytes count after five days of therapy.
We believe that the analysis presented in this paper, combined with pharmacokinetics studies, could play an important role in developing improved HBV treatment regimen.

Conflict of Interests

The authors declare that there is no conflict of interests.

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