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Cytotoxic Cells and Control Strategies are Effective in Reducing the HBV Infection through a Mathematical Modelling

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Abstract A non-linear mathematical model is formulated and analysed to study the mathematical modelling of the optimal control of HBV infection in the presence of cytotoxic cells. The proposed model describes the interaction between normal cells, HBV and cytotoxic cells. The goal is to maximize the number of normal cells by evaluating the impact of optimal control strategies mainly treatment and preventions activities in terminating or restricting the spread of the disease. In this study, the existence of an optimal control pair is obtained. Also numerical simulations and sensitivity analysis are carried out to determine key parameters contributing to the spread of the disease and to illustrate analytical results. A sensitivity analysis shows that the control variable, which represents the efficiency of preventions activities, is the most sensitive parameter and the least is death rate of HBV due to treatment. Numerical studies of the model are carried out to see the effects of the key parameters on the optimal control of HBV infection in the presence of cytotoxic. The result of the study showed that application of optimal control in the presence of cytotoxic cells leads to the decrease of infection of HBV disease.

Keywords Optimal Control, Hepatitis B Virus Infection, Cytotoxic Cells

1. Introduction

Hepatitis is an inflammation of the liver, most commonly caused by a viral infection. There are five viruses that cause hepatitis, called hepatitis A, B, C, D and E. Hepatitis B virus (HBV) is the most serious type of viral hepatitis. Hepatitis B is an infection that attacks the liver and can cause both acute and chronic HBV disease. HBV is a major global health problem, and puts people at high risk of death from scarring (cirrhosis) of the liver and liver cancer. More than 240 million people have chronic (long-term) liver infections [9]. About 600000 people die every year due to the acute or chronic consequences of hepatitis B [8]. About 5% of the world's population are chronic carriers, and with an annual occurrence of more than 50 million [5]. The virus is transmitted through contact with the blood or other body fluids of an infected person, and is preventable with the currently available safe and effective vaccine.

The most common ways of infection of HBV are: through intravenous drug use, through unprotected sexual activities, from mother to baby at birth; and child-to-child transmission through household settings for example, via open wounds. Most infections occur during infancy or childhood. Since most infections in children are asymptomatic, there is little evidence of acute disease related to HBV, but the rates of chronic liver disease and liver cancer in adults are high [1].

Once infected with hepatitis B virus (HBV), there is an incubation period of four to ten weeks; the surface antigen HBsAg then becomes detectable in the blood, with anti-HBC antibodies detectable shortly after. Another surface antigen, HBeAg, is then released into the blood indicating that the virus is infecting the liver cells and the host is highly infectious [4].

Molecular techniques have provided fundamental insight into the fine detail of the interaction between HBV and immune system. However, many biologically important questions are not primarily concerned with the molecular mechanisms of immune recognition but with the population dynamics of the immune response. Mathematical models are always needed to answer the questions of the interaction between HBV and immune system.

Mathematical modelling and model analysis of the Hepatitis dynamics are important for exploring possible mechanisms and dynamical behaviours of the viral infection process, estimating key parameter values, and guiding development of efficient antiviral drug therapies.

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Cytotoxic cells, also called cytotoxic T cells or Cytotoxic T lymphocyte (CTL) are type of immune cells that can kill certain cells, including foreign cells, cancer cells, and cells infected by a virus. Cytotoxic cells are produced in small numbers in the body and could possibly be isolated from other blood cells, cultured in the laboratory by using the technique called "induced pluripotent stem-cell" to make them propagate and may be directly injected into patients for therapy.

In this paper, it is intended to determine the optimal control of hepatitis B Virus (HBV) infection in the presence of cytotoxic cells, by extending the work by [7]. It is intended to maximize the number of normal cells (cells of the main tissue of the liver).

Several studies so far have been carried out to analyse mathematically the control of HBV disease with acute and chronic stages. [7], carried out a research on optimal antiviral treatment strategies of HBV infection with logistic hepatocytes growth without considering the effect of cytotoxic cells. Therefore, this study intends to extend the work by [7], by including cytotoxic cells and determine the optimal control of the disease.

2. Model Formulation

A nonlinear mathematical model is proposed and analysed to study the optimal control of HBV infection in the presence of cytotoxic cell. In the proposed model, it is assumed that the use of prevention activities and treatment are applied as a control of the disease for a given time interval. It is assumed that, the optimal control of inhibiting viral production in the presence of cytotoxic cells will reduce the HBV infection. In modelling process, the classes considered are Normal cells, which are the main cells of the liver, HBV and cytotoxic cells.

In formulating the model, the following assumptions are taken into consideration:

i. Normal cells grow at a rate that depends on the homeostatic liver size, at a maximum per capita proliferation rate.
ii. The normal cells become infected at maximum rate
iii. Cytotoxic cell are created by normal cells at per capita rate, and rate stimulation of cytotoxic cells by HBV is
iv. Cytotoxic cells are deactivated by HBV at rate and they naturally die at rate μ2.
v. The cytotoxic cells stimulation half saturation rate is σ
vi. The HBV naturally die at rate and death rate of HBV due to treatment is
vii. HBV is distracted by cytotoxic cell at rate
viii. The control functions and are bounded Lebesgue integrable functions.
ix. The control represents the efficiency of preventions activities in blocking new infection
x. The control represents the efficiency of treatments in inhibiting viral production. All parameters in the mathematical model are strictly positive.

Table 2.1. State variables of the HBV model

Symbols	Descriptions
x	Normal cell
y	HBV
z	Cytotoxic cell

Table 2.2. Parameters of the HBV model

Parameter	Descriptions
K	normal cell carrying capacity
r_1	growth rate of normal cell
r_2	rate stimulation of cytotoxic cells by HBV
φ	production rate of cytotoxic cell
β	contact rate (rate of infection of normal cell)
μ_1	natural death rate of HBV
μ_2	natural death rate of cytotoxic cell
u_1	control variable (due to prevention activities)
u_2	control variable (death rate of HBV due to treatment)
c_1	rate of destruction of HBV by cytotoxic cell
c_2	rate of deactivation of cytotoxic cell by HBV
σ	cytotoxic cells stimulation half saturation rate

Taking into account the above considerations, we then have the following schematic flow diagram:

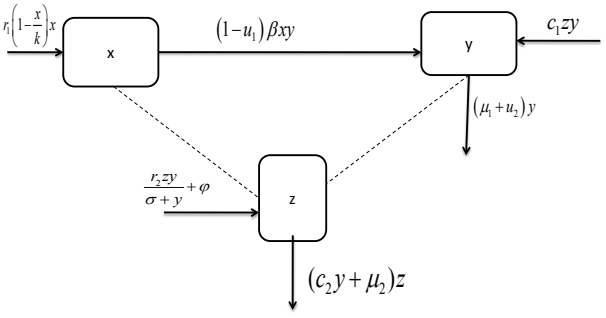


Figure 2.1. Model Flowchart

The model is thus governed by the system of non linear ordinary differential equations given in Appendix A.

3. Model Analysis

The nonlinear system (1) will be qualitatively analysed so

as to find the conditions for existence of a disease-free equilibrium points. The analysis of the model allows us to determine the impact of optimal control strategy for HBV disease in the presence of cytotoxic cells. On finding the basic reproductive number, one can determine if the disease vanishes or persists.

3.1. Positivity of the Solutions

It is necessary to prove that all solutions of system (1) with positive initial data will remain positive for all times $t > 0$. This will be established by the following Lemma.

Lemma 3.1

If $x(0),\ y(0),\ z(0),$ are nonnegative then $x(t),\ y(t),\ z(t),$ remain nonnegative for all $t \geq 0$ (Lashare *et al.,* 2012).

To prove the above Lemma the equations of the system (1) are used. From the system (1),

$$\frac{dx}{dt} = r_1 x - \frac{r_1 x}{K} + \beta xy + u_1 \beta xy$$

To determine positivity of x we consider

$$\frac{dx}{dt} \geq r_1 x.$$

which gives

$$x(t) \geq x(0)e^{r_1 t}.$$

Hence

$$x(t) > 0,\ \forall t \geq 0.$$

Similar proofs can be established for the positivity of the other solutions.

3.2. Disease-free Equilibrium Point (DFE)

The disease free equilibrium of the model (1) is obtained by setting

$$\frac{dx}{dt} = \frac{dy}{dt} = \frac{dz}{dt} = 0.$$

Let $E_0 = (x^*; y^*; z^*)$ be the equilibrium point of the system (1). Then, setting the right hand side of system (1) to zero, we get

$$y^* = 0,\ x^* = K \text{ and } z^* = \frac{\varphi}{\mu_2}$$

Therefore, the Disease-free equilibrium (DFE) denoted by E_0 of the model system (3.1) is given by,

$$E_0 = \left(K,\ 0,\ \frac{\varphi}{\mu_2} \right) \tag{2}$$

3.3. Model Reproduction Number

The reproduction number R_0 measures the average number of newly infected cells that arise from any one infected cell in the beginning of the infection. It is obtained by taking the dominant eigenvalue (spectral radius) of

$$\left[\frac{\partial F_i}{\partial x_j}(E_0) \right] \left[\frac{\partial V_i}{\partial x_j}(E_0) \right]^{-1} \tag{3}$$

where

F_i is the rate of appearance of new infection in compartment i

V_i^+ is the transfer of individuals into compartment i

V_i^- is the transfer of individuals out of compartment i by all other means.

E_0 is the DFE

$$F_i = [F_1] = [(1-u_1)\beta xy]$$

By linearization approach, the associated matrix at disease free equilibrium is obtained as

$$\mathbf{F} = [F_1] = \left[\frac{\partial F}{\partial y}(E_0) \right] \tag{4}$$

This gives

$$\mathbf{F} = [(1-u_1)\beta x]$$

At DFE $x = K$. Therefore

$$\mathbf{F} = [(1-u_1)\beta K] \tag{5}$$

The transfer of individuals out of the compartment *i* is given by

$$V_i = [V_1] = [(\mu_1 + u_2)y + c_2 z] \tag{6}$$

Using the linearization approach, the associated matrix at DFE is given by

$$\mathbf{V} = \left[\frac{\partial V_1}{\partial y}(E_0) \right] \tag{7}$$

This gives

$$\mathbf{V} = [\mu_1 + u_2] \tag{8}$$

with

$$\mathbf{V}^{-1} = \left[\frac{1}{(\mu_1 + u_2)} \right] \tag{9}$$

Thus

$$\mathbf{F}\mathbf{V}^{-1} = [(1-u_1)\beta K] \left[\frac{1}{(\mu_1 + u_2)} \right] \tag{10}$$

It follows that the effective reproduction number is given by,

$$R_0 = \frac{(1-u_1)\beta K}{(\mu_1 + u_2)} \tag{11}$$

It is observed that only the parameter, β, K and the control variables u_1 and u_2 affect the reproduction number R_0.

If $R_0 = \frac{(1-u_1)\beta K}{(\mu_1 + u_2)} < 1$, then an individual becomes HBV-free [6]. Epidemiologically, this implies that HBV can be eliminated from the society if $R_0 < 1$. That means if $R_0 < 1$, then on average, an infected normal cell produce less than one new infected normal cell over the course of infectious period and the infection cannot grow.

3.4. Sensitivity Analysis

In determining how best to reduce human mortality and morbidity due to HBV infection, the sensitivity indices of the effective reproductive number 'R_0' to the parameters in the model is calculated using approach of [2]. These indices tell us how crucial each parameter is to disease transmission and prevalence and discover parameters that have a high impact on R_0 and should be targeted by intervention strategies. The normalized forward sensitivity index of a variable to a parameter is a ratio of the relative change in the variable to the relative change in the parameter. When a variable is a differentiable function of the parameter, the sensitivity index may be alternatively defined using partial derivatives.

Definition: The forward sensitivity index of variable p that depends differentiably on index on a parameter q is defined as:

$$X_q^p = \frac{dp}{dq} \times \frac{q}{p}$$

We derive an analytical expression for sensitivity of R_0 as:

$$X_q^{R_0} = \frac{dR_0}{dq} \times \frac{q}{R_0}$$

to each parameter involved in R_0. The sensitivity calculations are performed using a set parameter estimations given in table 3.1 of the model system (1) are called out using a set of parameter values given in the Table 3.1.

For example the sensitivity indices for R_0 with respect to β, μ_2, and φ are given by;

$$X_\beta^{R_0} = \frac{dR_0}{d\beta} \times \frac{\beta}{R_0} = +1$$

$$X_{\mu_1}^{R_0} = \frac{dR_0}{d\mu_1} \times \frac{\mu_1}{R_0} = -1.9868865487$$

respectively.

Table 3.1. Parameter estimations

Parameter	Estimated value
β	0.054
μ_1	0.0033
μ_2	0.0248
K	340

The other indices, $X_{\mu_1}^{R_0}$, $X_{u_2}^{R_0}$, and $X_K^{R_0}$ are obtained following the same method and tabulated as follows:

Table 3.2. Numerical values of sensitivity indices of R_0 to parameters for the HBV model, evaluated at the baseline parameter values given in Table 3.1

Symbol	Sensitivity index
β	+1
K	+1
u_2	-1.9868865487
μ_1	-1.9868865487
u_1	-0.5

Table 3.2 above, shows that when the parameters, β and K increase while the other parameters remain constant, the value of R_0 increases implying that they increase the HBV infection as they have positive indices. When the parameter μ_1, u_1 and u_2 increase while keeping other parameters constant, the value of R_0 decreases, implying that they decrease the HBV infection as they have negative indices. But individually, the most sensitive parameter is the control rate due to prevention activities and HBV death rate.

4. Analysis of Optimal Control

In this section, the model system of equations (1) is analysed qualitatively to determine the optimal control of

HBV infection in the presence of cytotoxic cell. The aim is to maximize the objective functional

$$J(u_1(t),u_2(t)) = \int_0^{t_{end}} \left[x(t) - \left(\frac{\theta_1}{2}u_1^2 + \frac{\theta_2}{2}u_2^2 \right) \right] dt \quad (12)$$

where the parameters $\theta_1 \geq 0$ and $\theta_2 \geq 0$ are based on the benefits and cost of the treatment and prevention activities.

The aim is to maximize the objective functional in (12), by increasing the number of normal cells (cells of the main liver). That means an optimal control pair $\left(u_1^*, u_2^*\right)$, is determined such that

$$J\left(u_1^*, u_2^*\right) = \max\left\{ \frac{J\left(u_1^*, u_2^*\right)}{\left(u_1^*, u_2^*\right)} \in U \right\} \quad (13)$$

where U is the control set defined by

$$U = \{u = (u_1, u_2) : \ u_i \text{ measurable},$$
$$0 \leq u_i \leq 1, t \in \left[0, t_f\right], i = 1,2\} \quad (14)$$

4.1. Characterization of the Optimal Control

Since an optimal control exists for maximizing the functional (12) subject to equations (1), Pontryagin's maximum principle is applied to

$$H\left(x,y,z,u,\lambda_i,t\right) = L\left(x,u,t\right) + \lambda_1 \frac{dx}{dt} + \lambda_2 \frac{dy}{dt} + \lambda_3 \frac{dz}{dt} \quad (15)$$

where

$$L\left(x,u,t\right) = x - \left(\frac{\theta_1}{2}u_1^2 + \frac{\theta_2}{2}u_2^2 \right) \quad (16)$$

and $\lambda_i, = 1,2,3,$ are the adjoint functions to be determined.

Theorem 3.4

Given optimal controls u_1^*, u_2^* and solutions x^*, y^* and z^* of the corresponding state system (1), there exists adjoint parameters λ_1, λ_2 and λ_3 satisfying

$$H\left(x,y,z,u,\lambda_i,t\right) = L\left(x,u,t\right) + \lambda_1 \frac{dx}{dt} + \lambda_2 \frac{dy}{dt} + \lambda_3 \frac{dz}{dt} \quad (17)$$

Substituting equations 1 and (16) in (17), we get

$$H\left(x,y,z,u,\lambda_i,t\right) = x - \left(\frac{\theta_1}{2}u_1^2 + \frac{\theta_2}{2}u_2^2 \right)$$
$$+\lambda_1 (r_1 \left(1 - \frac{x}{k}\right)x - \left(1-u_1\right)\beta xy)$$
$$+\lambda_2 \left(\left(1-u_1\right)\beta xy - c_1 zy - \left(\mu_1 + u_2\right)y \right)$$
$$+\lambda_3 \left(\varphi + \frac{\sigma r_2 y}{\sigma + y} - c_2 zy - \mu_2 z \right) \quad (18)$$

where, λ_1, λ_2 and λ_3 are the adjoint variables.

This can be determined by solving the system by using Pontryagin's Maximum Principle, of which;

$$\frac{d\lambda_1}{dt} = \left(1-u_1\right)\beta y\left(\lambda_1 - \lambda_2\right) - \lambda_1 (r_1 - \frac{2x}{k}) - 1,$$
$$\frac{d\lambda_2}{dt} = \left(1-u_1\right)\beta x\left(\lambda_1 - \lambda_2\right)$$
$$+\lambda_2 \left(c_1 z + \mu_1 + u_2\right) - \lambda_3 \left(\frac{r_2 zy}{(\sigma + y)^2} - c_2 z \right),$$
$$\frac{d\lambda_3}{dt} = \lambda_2 c_1 y - \lambda_3 \left(\frac{r_2 y}{\sigma + y} - c_2 y - \mu_2 \right).$$

with transversality conditions;

$$\lambda_i\left(t_{end}\right) = 0, i = 1,2,3. \quad (19)$$

The optimal control is given by:

$$u_1^* = \min\left(\max\left(\frac{\beta x^* y^* \left(\lambda_1 - \lambda_2\right)}{\theta_1}, 0 \right), 1 \right), \quad (20)$$

$$u_2^* = \min\left(\max\left(\frac{-\lambda_2 y^*}{\theta_2}, 0 \right), 1 \right) \quad (21)$$

Proof

The Hamiltonian (18) is used in order to determine the adjoint equations as well as the transversality conditions.

Let $x = x^*$, $y = y^*$ and $z = z^*$. Differentiating the Hamiltonian with respect to x, y, and z, one obtains

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial x} = \left(1-u_1\right)\beta y\left(\lambda_1 - \lambda_2\right) - \lambda_1 (r_1 - \frac{2x}{K}) - 1,$$
$$\frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial y} = \left(1-u_1\right)\beta x\left(\lambda_1 - \lambda_2\right)$$
$$+\lambda_2 \left(c_1 z + \left(\mu_1 + u_2\right)\right) - \lambda_3 \left(\frac{\sigma r_2 y}{(\sigma + y)^2} - c_2 z \right),$$
$$\frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial z} = \lambda_2 c_1 y - \lambda_3 \left(\frac{r_2 y}{\sigma + y} - c_2 y - \mu_2 \right). \quad (22)$$

By applying optimality condition, it is found that;

$$\frac{\partial H}{\partial u_1} = \beta x^* y^* \left(\lambda_1 - \lambda_2\right) - \theta_1 u_1 = 0 \quad \text{at} \quad u_1 = u_1^* \quad (23)$$

This gives

$$\beta x^* y^* (\lambda_1 - \lambda_2) - \theta_1 u_1^* = 0$$

$$u_1^* = \frac{\beta x^* y^* (\lambda_1 - \lambda_2)}{\theta_1} \quad (24)$$

$$\frac{\partial H}{\partial u_2} = -\theta_2 u_2 - \lambda_2 y^* = 0 \quad \text{At} \quad u_2 = u_2^* \quad (25)$$

Thus

$$-\theta_2 u_2^* - \lambda_2 y^* = 0$$

$$u_2^* = \frac{-\lambda_2 y^*}{\theta_2} \quad (26)$$

4.2. The Optimality System

The optimality system consists of the state system coupled with the adjoint system with the initial conditions, transversally conditions, and characterization of the optimal control [7].

Such that:

$$\frac{dx^*}{dt} = r_1\left(1 - \frac{x^*}{k}\right)x^* - \left(1 - u_1^*\right)\beta x^* y^*,$$

$$\frac{dy^*}{dt} = \left(1 - u_1^*\right)\beta x^* y^* - c_1 z^* y^* - \left(\mu_1 + u_2^*\right)y^*,$$

$$\frac{dz^*}{dt} = \varphi + \frac{r_2 z^* y^*}{\sigma + y} - c_2 z^* y^* - \mu_2 z^*,$$

$$\frac{d\lambda_1}{dt} = \frac{\lambda_1 r_1}{k} + \left(1 - u_1^*\right)\beta y^*(\lambda_1 - \lambda_2) - 1,$$

$$\frac{d\lambda_2}{dt} = \left(1 - u_1^*\right)\beta x^*(\lambda_1 - \lambda_2) + \lambda_2\left(c_1 z^* + \mu_1 + u_2^*\right) - \lambda_3\left(\frac{\sigma r_2 z^*}{(\sigma - y^*)^2} - c_2 z^*\right),$$

$$\frac{d\lambda_3}{dt} = \lambda_2 c_1 y^* - \lambda_3\left(\frac{r_2 y^*}{\sigma + y^*} - c_2 y^* - \mu_2\right),$$

with $\lambda_1(t_{end}) = 0, \lambda_2(t_{end}) = 0, \lambda_3(t_{end}) = 0$

$x(0) = x_0, y(0) = y_0, v(0) = v_0.$

5. Numerical Simulation

In order to illustrate the analytical results of the study, numerical simulations of the model system (1) are carried out using the set of estimated parameter values below others from the literature. The control variable u_1 represents the control variable meant to reduce the HBV infection due to prevention activities and the control variable u_2 represents control variable meant to eliminate HBV through treatment.

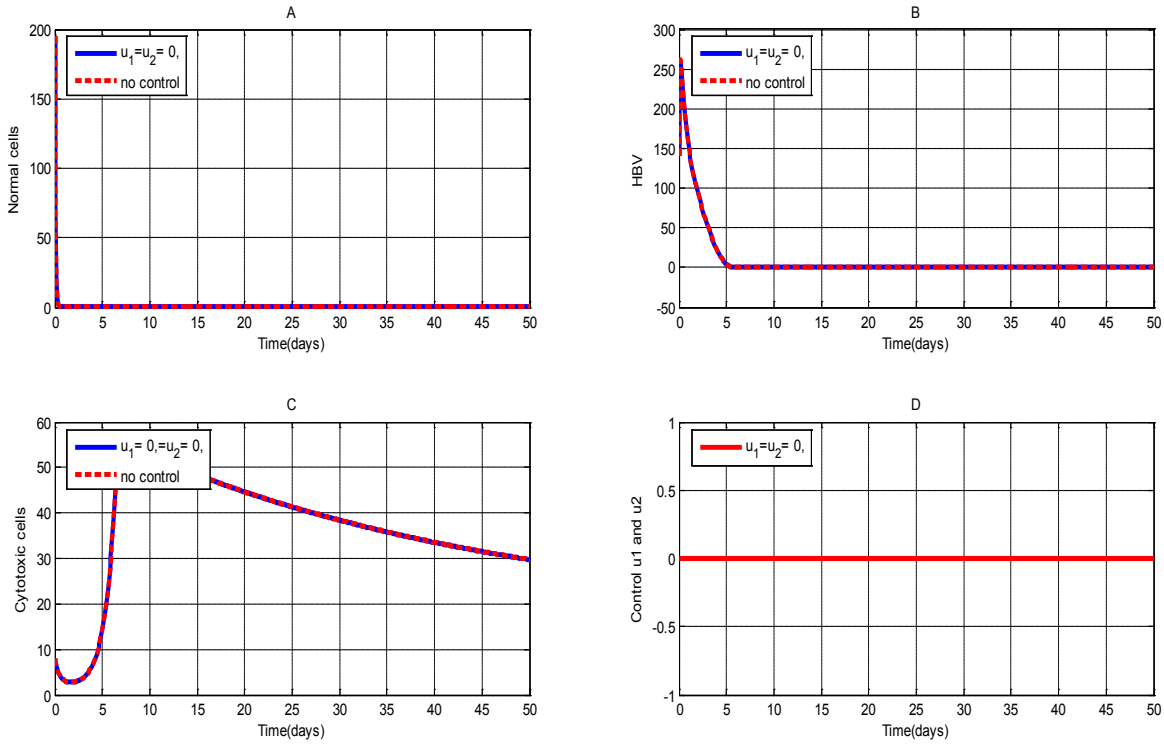
Computer simulations are done to verify the effectiveness of the model by comparing the disease progression before and after introducing the two optimal control variables u_1 and u_2. The model system is simulated using MATLAB program, and the following initial conditions have been considered: $x(0) = 195$, $y(0) = 140$, and $z(0) = 8$.

Table 4.1. Parameter values

Parameter	Estimated value
β	0.054
μ_1	0.0033
μ_2	0.0248
r_1	0.069
r_2	0.85
σ	0.00062
φ	0.403
K	340
θ_1	4
θ_2	10

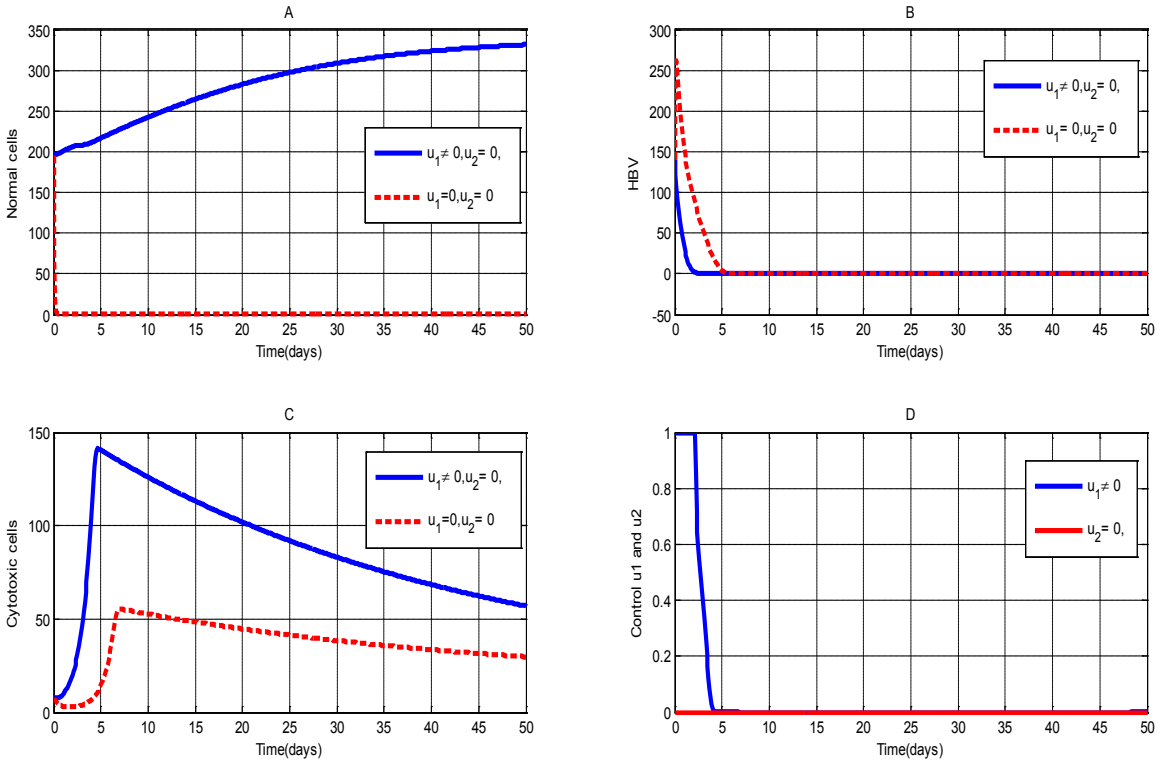
Figures 4.1 show the variation of normal cells, HBV and cytotoxic cells without control.

In the absence of optimal control, the normal cells decrease with time as shown in Figure 4.1(A). The decrease in normal cells with time may be due to the higher contact rate because there is no control while the disease is there. The number of HBV in Figure 4.1(B) increases rapidly for certain amount of time leading to the decrease in cytotoxic cells in Figure 4.1(C). This is due to deactivation process of cytotoxic cells by HBV. Then, HBV starts to decrease with time due to the increase in cytotoxic cells. This is because of the stimulation of cytotoxic cells by HBV. The increase in cytotoxic cells leads to the increase in rate of destruction of HBV by cytotoxic cells, hence, decrease of HBV. However the increase in cytotoxic cells does not persist due to the fact that some of them die naturally and others are deactivated by HBV. Also as it is observed that in Figure 4.1(A) the normal cells almost vanishes within a short time leading to the decrease in cytotoxic cells and HBV. Figure 4.1(D) represents the control variables $u_1 = 0$ and $u_2 = 0$.



Figures 4.1. Variation in normal cells, HBV and cytotoxic cells without control

Figures 4.2 show Variation in normal cells, HBV and cytotoxic cells in presence of one control.



Figures 4.2. Variation in normal cells, HBV and cytotoxic cells in presence of one control

Figure 4.2(A) shows variation of normal cells when there is only one control variable which controls the contact rate. The blue line presents the variation of normal cells in the presence of one optimal control while the red line presents the variation of normal cells without optimal control. Comparing the two cases it is observed that normal cells increase with time in the presence of prevention activities which control the contact rate. The presence of prevention activities reduces HBV as seen in figure 4.2(B)). In figure 4.2 (c), the cytotoxic cells show some similar behaviour with and without control but the increase is more higher in the presence of prevention activities because the HBV have been instantly reduced when control condition is in place and some undergoes natural death hence reduces the deactivation of cytotoxic cells. Figure 4.2(D) represents control variable $u_1 \neq 0$ while control variable $u_2 = 0$.

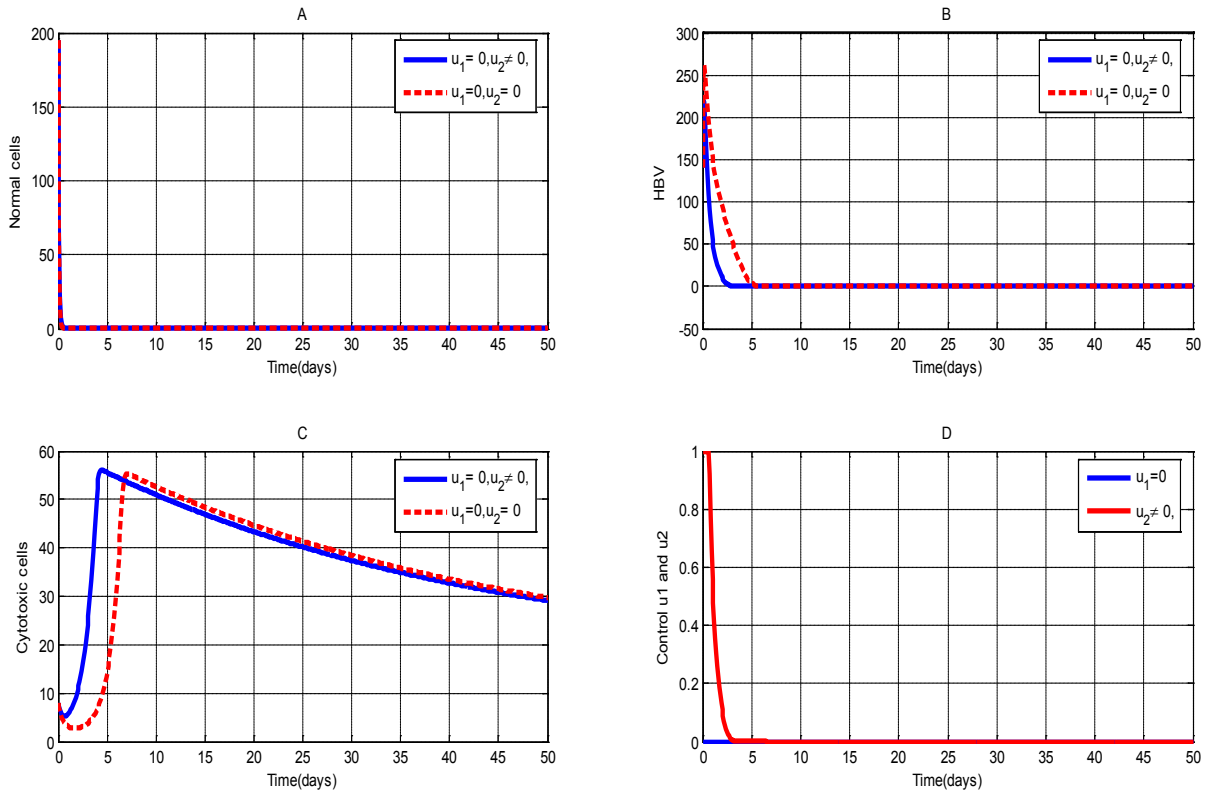
Figures 4.3 show the variation of normal cells, HBV and cytotoxic cells in the presence of only one control variable u_2.

When the control condition u_2 is in place, the normal cells first decrease with time, then start to build up as seen in Figure 4.3(A). This is because of the control of HBV through treatment, but it shows that the response to treatment takes much time compared to prevention activities as seen in Figure 4.2(A). Figure 4.2(B) shows that HBV have been instantly reduced when control condition is in place, and also due to the reason that some undergo natural death. Cytotoxic cells show some similar behaviour with and without control but the increase and decrease starts in earlier when there is control compared to when there is no control condition. Figure 4.3(D) represents control variable $u_1 = 0$ while control variable $u_2 \neq 0$.

Figures 4.4 show the variation of normal cells, HBV and cytotoxic cell in the presence of two control variables.

Figure 4.4(A) shows variation of normal cells when there are two control variables which control the contact rate. The control variable u_1 represents the control variable meant to reduce the HBV infection due to prevention activities and the control variable u_2 represents control variable meant to eliminate HBV through treatment.

The blue line represents the variation of normal cells in the presence both optimal control variables while the red line represents the variation of normal cells without optimal control. Comparing the two cases, it shows that normal cells increase with time in the presence of control conditions u_1 and u_2. The presence of control variables reduces HBV (see Figure 4.4(B)). In Figure 4.2(c), the cytotoxic cells show some similar behaviour with and without control but the increase is higher in the presence of control variables because the HBV have been instantly reduced when control condition is in place and some undergo natural death, hence, reduce the deactivation of cytotoxic cells. Figure 4.4(D) represents control variable $u_1 \neq 0$ and the control variable $u_2 \neq 0$.



Figures 4.3. Variation in normal cells, HBV and cytotoxic cells in the presence of only one control variable u_2

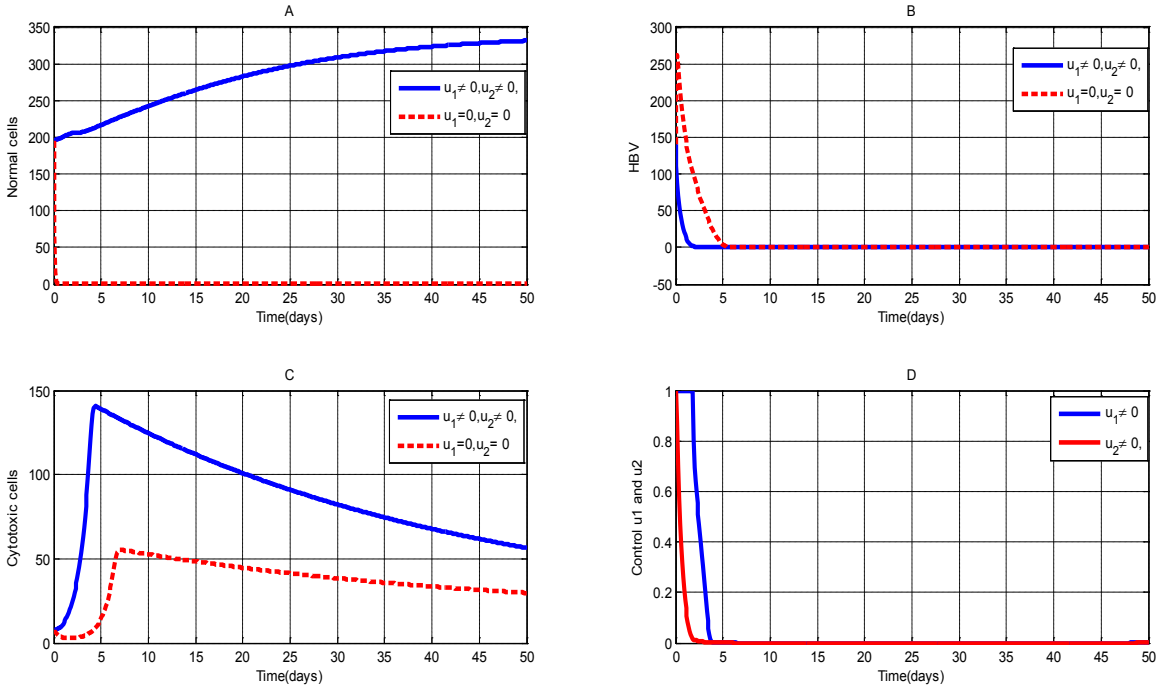


Figure 4.4. Variation in normal cells, HBV and cytotoxic cell in the presence of two control variables

6. Discussion

In this paper, the qualitative and numerical results were presented. A non-linear mathematical model has been formulated and analysed to study the optimal control of HBV infectiology in the presence of cytotoxic cells. The main objective of this work was to develop and analyse an optimal control of mathematical model of HBV infectiology in the presence of cytotoxic cells by extending the model developed by Laarabi *et al*., 2013.

On analysing the model, it is found that system (1) for Normal cells, HBV and cytotoxic cells interaction model is positive and bounded.

Also numerical simulations and sensitivity analysis were carried out to determine key-parameters contributing to the spread of the disease and to illustrate analytical results obtained in the study.

The sensitivity analysis shows that the control which represents the efficiency of preventions is the most sensitive parameter and the least is death rate of HBV due to treatment.

Numerical study of the model is carried out to see the effects of the key parameters on the optimal control of HBV infectiology in the presence of cytotoxic cells. Some of the main findings of this work include:

(i) In the absence of optimal control, the normal cells decrease with time as shown in Figure 4.1(A). The decrease in normal cells with time may be due to the higher contact rate because there is no control while the disease is there

(ii) The normal cells increase with time in the presence of prevention activities that control the contact rate. The presence of prevention activities reduces HBV, (see Figure 4.2(B)).

(iii) It shows that the response to treatment takes much time compared to prevention activities see figure 4.3(A) and figure 4.2(A). Figure 4.2(B) shows that HBV have been reduced when control condition is in place, and also due to the reason that some undergo natural death.

(iv) The normal cells increase with time in the presence of control conditions and. The presence of control variables reduces HBV (see Figure 4.4(B), hence maximizing the normal cells.

Generally, the model analysis shows that the presence of cytotoxic cells, the control conditions, prevention activities and treatment have the effect of reducing the HBV infection. It is observed that when the control conditions are in place the normal cells are significantly increased compared to the case where there are no control conditions.

7. Conclusions

The model of HBV infection in the presence of cytotoxic cells includes two control variables: the control u_1 which represents the efficiency of preventions activities in blocking new infection, and the control u_2 which represents the efficiency of treatments in inhibiting viral production. The objective was to maximize the normal cells (main cells of the liver). The optimal control theory is used to prove the existence and characterization of optimal control pair. The results show that preventions activities alone or treatment alone may succeed in elimination of

infection from an individual, from figure. The study further showed that a combination of both controls has much impact than individual controls. The conclusion is that, the presence of cytotoxic cells and the proposed control strategies are effective in reducing the HBV infection and maximizing the normal cells.

Appendix A: Model Equations

$$\frac{dx}{dt} = r_1\left(1-\frac{x}{k}\right)x-(1-u_1)\beta xy,$$

$$\frac{dy}{dt} = (1-u_1)\beta xy - c_1 zy - (\mu_1+u_2)y, \qquad (1)$$

$$\frac{dz}{dt} = \varphi + \frac{r_2 zy}{\sigma+y} - c_2 zy - \mu_2 z,$$

$$x(0)=x_0\geq 0, y(0)=y_0\geq 0, z(0)=z_0\geq 0.$$

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