International Journal of Scientific and Innovative Mathematical Research (IJSIMR)
Volume 3, Issue 6, June 2015, PP 48-56
ISSN 2347-307X (Print) & ISSN 2347-3142 (Online)
www.arcjournals.org

Using Direct Method and Pontryagin's Maximum Principle for Solving an Optimal Control Problem of Hepatitis B Virus Dynamics

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Abstract: *We aimed in this paper to use direct approach and Pontryagin's maximum principle to solve a hepatitis B virus dynamics optimal control problem. The direct approach deals with the discretization on a regular grid of constraints of ordinary differential equations using B-spline functions equations. The numerical implementation is done using Matlab packages. By comparing, the numerical results show that there is a small difference between the optimal trajectories of determinant variables. Therefore, both numerical methods are in good agreement with experimental data*

Keywords: *Optimal control, Hepatitis B virus, Numerical simulation, Direct method, Pontryagin's maximum principle.*

1. INTRODUCTION

Hepatitis B is the world's most common liver infection that can lead to cirrhosis and liver cancer. It is caused by the hepatitis B virus (HBV), which attacks and injures the liver [1].

It is transmitted through blood, unprotected sex, shared or re-used needles, and from an infected mother to her newborn baby during delivery [2]. Most infected adults are able to get rid of the hepatitis B virus without any problems. However, most infected babies and children are unable to get rid of the virus and develop chronic infections. The hepatitis B virus can survive outside the body for at least seven days. During this time, the virus can still cause infection if it enters the body of a person who is not protected by the vaccine [3]. The virus mainly affects liver function, this is, it invades the liver cells (hepatocytes) and uses the cells' machinery to replicate within it. The hepatitis B virion binds to the hepatocyte via the domain of the viral surface antigen. The cell then engulfs the virus in a process called endocytosis. As the infection occurs, the host immune response is triggered. The body's immune system attacks the infected hepatocytes, which leads to liver injury at the same time as clearing the virus from the body. The liver damage associated with HBV infection is mainly caused by the adaptive immune response, particularly the virus-specific cytotoxic T lymphocytes (CTLs). These CTLs kill cells that contain the virus. Liver damage is also aggravated by the antigen-nonspecific inflammatory cells and activated platelets at the site of infection.

There are two possible phase of this infection [4]:

1. Acute hepatitis B infection that lasts less than six months. In this case the immune system is usually able to clear the virus from the body, and the patient should recover completely within a few months. This kind of phase is the most case for adult people who acquire hepatitis B. Chronic hepatitis B infection which lasts six months or longer. This infection manifests in the most infants infected with HBV at birth and many children infected between 1 and 6 years of age become chronically infected.

For some people, hepatitis B infection becomes chronic, means that it lasts more than six months. Having chronic hepatitis B increases the risk of developing liver failure, liver cancer or cirrhosis, a condition that causes permanent scarring of the liver [5]. For some cases, HBV results in serious liver

diseases such as chronic hepatic insufficiency, hepatocellular carcinoma, cirrhosis and can be a potential cause of the liver cancer [4]. For instance, the commonly worldwide well-known Hepatocellular carcinoma (HCC) is a cancer and more than half of HCC patients are attributable to persistent HBV infections. It is approximated that between 15 and 40% of infected patients develop cirrhosis, liver failure, or HCC which occupies the fifth place of the most frequent dangerous cancers, killing 300000-500000 each year.

Most people infected with hepatitis B as adults recover fully, even if their signs and symptoms are severe. Infants and children are more likely to develop a chronic hepatitis B infection [6].

A vaccine can prevent hepatitis B, at the early stage this disease may be cured but there is no cure for a chronic one. If you are infected, taking certain precautions can help prevent spreading HBV to others. Hepatitis B may be the only completely preventable sexually transmitted disease. A vaccine has been available that protects against the virus since 1982. Many physicians recommend routine vaccination for children and teenagers, and adults who were not vaccinated during their childhood are also good candidates for the vaccine [7]. The HBV vaccine "HB_sAg" consists of recombinant hepatitis B surface antigen. It protects individuals for at least 23 years, and is one of the safest vaccines on the market. For people who lack health insurance, or for whom the vaccine is not covered, some health departments make the vaccine available for free or at very low cost [3].

Optimal control theory has found wide-ranging applications in biological and ecological problems [8]. In biomedical problems, techniques from control theory are of great use in developing optimal therapeutic strategies. The treatment regimen is usually taken to be the control variable, with the aim of minimizing the detrimental effects of the medical condition. Optimal control theory can be used to optimize the drug doses required in the treatment of HBV infected patients [9, 10, 11].

Mathematical models can be a useful tool in controlling hepatitis B virus in order put down the infection from the population. It is in the manner the simple mathematical model has been used by Anderson and May to illustrate the effects of carriers on the transmission of HBV [12]. To develop a strategy for eliminating HBV in New Zealand [13, 14], the mathematical model has used by Medley et al [15]. An age structure model to predict the dynamics of HBV transmission and evaluate the long-term effectiveness of the vaccination programme in China has been proposed by Zhao et al. [16]. The mathematical model developed by Pang et al. [17] allowed him to explore the impact of vaccination and other controlling measures of HBV infection while Bhattacharyya and Ghosh [18], Kar and Batabyal [19], and Kar and Jana [20] proposed optimal control of infectious diseases.

Several drug therapies have been proposed for treating persons with chronic HBV including adefovir dipivoxil, alpha-interferon, lamivudine, pegylated interferon, entecavir, telbivudine, and tenofovir [9]. Hepatitis antiviral drugs prevent replication of HBVs and save the liver from cirrhosis and cancer. During the treatment, the viral load is reduced and consequently the viral replication in liver is decreased [21].

In this paper is organized as follows. Section 1 presents the model equations and optimal control problem. The section 2 is interested in the application of Pontryagin's maximum principle and the direct approach for solving an optimal control problem of Hepatitis B virus dynamics. The numerical simulation is presented in section 3. Finally, we present concluding remarks in the last section.

2. SETTING OF AN OPTIMAL CONTROL PROBLEM

Virus particles of hepatitis B known as virions consist of two or three parts: the genetic material made from either Deoxyribonucleic acid (DNA) or Ribonucleic acid (RNA), long molecules that carry genetic information; a protein coat that protects these genes; and in some cases an envelope of lipids that surrounds the protein coat when they are outside a cell. The viruses replicate through an RNA intermediate form by reverse transcription, which practice relates them to retro viruses. Although replication takes place in the liver, the virus spreads to the blood where viral proteins and antibodies against them are found in infected people. HBV clearance requires a massive adaptive immune response. If the immune system is inefficient, then the infection becomes chronic. The known therapies have limited effect in chronic disease. If the disease is in an incipient state, they have a good effect in short term, namely they reduce rapidly the viral burden. If the disease is already chronic, none of the drugs is capable to clear the infection. The Hepatitis B Virus often spreads in the blood

rapidly if there is no treatment. The liver cells must be protected to be not destroyed by the virus particles, unless they are destroyed, the Hepatitis B becomes now chronic. Our problem is to minimize the total amount of infected cells and the number of free virions and to maximize the efficiency of the action of two drugs. We solve the problem

$$\min_{u_1, u_2 \in R} J(u_1, u_2) \tag{1}$$

subject to the treatment model on the time interval $[0, T_{max}]$ which is described by the following system:

$$\begin{cases} \dfrac{dx}{dt} = \lambda - dx - \dfrac{\beta v x}{x + y} \\ \dfrac{dy}{dt} = \dfrac{\beta v x}{x + y} - a u_1 y \\ \dfrac{dv}{dt} = ky - (\mu + u_2) v \end{cases} \tag{2}$$

with initial densities

$$x(0) = x_0, y(0) = y_0, v(0) = v_0 \tag{3}$$

(all these initial values are positive) and the cost functional is:

$$J(u_1, u_2) = \int_0^{T_{max}} (Cy^2 + Dv^2 - B_1 u_1^2 - B_2 u_2^2) dt \tag{4}$$

where B_1, B_2, C and D are constant and $u = (u_1, u_2)^T$ is an admissible control vector while the table 1 summarizes the description of variables and parameters and shows their corresponding units.

Table 1:*Description of parameters and variables and their corresponding units.*

Variable/Parameter	Description	Unit
λ	Liver cell production rate	per day per ml
d	Liver cell death rate	per day per ml
β	Maximum infection rate	per day per ml
a	Death rate of infected cells	per day per ml
k	Virion production rate	per day
μ	Virion death rate	per day
x	Number of uninfected(susceptible)	per ml
y	Number of infected cells	per ml
v	Number of virions	per ml

The weight factors B_1 and B_2 represent the patient level of acceptance of the treatment, while C, D are the weights specific to the patient infected cells and the virions respectively.

The control $u_1(t)$ represent the percentage of efficiency of interferon alpha IFN-α (or its equivalent) on the immune system and $u_2(t)$ represents the treatment rate of the nucleoside/nucleotide analogues ANN at the time t. Here we stress the conjugate action against the virions, assuming that $0 \le u_1(t), u_2(t) \le 1$ for all $t \in [0, T_{max}]$. For $u_1(t) = u_2(t) = 1$, we say that the drugs act at their maximal levels (non use of therapy) and for $u_1(t) = u_2(t) = 0$, we say that the drugs have achieved their task (maximal use of therapy).

The term ay represents the rate at which the infected cells are destroyed naturally and by the

immune system $(a \geq d)$; ky is the production rate of the virions by the infected cells of the body (free virions are cleared by the lymphatic system and other mechanisms at rate v), and the term $x + y$ is the total number of liver cell.

3. NUMERICAL APPROACHES FOR SOLVING THE OPTIMAL CONTROL PROBLEM

3.1. Pontryagin's Maximum Principle

We are interested first in determination of hamiltonian and the adjoint system. Furthermore, among all admissible controls $u = u(t)$, Pontryagin's Maximum principle gives a necessary condition for it and corresponding $x = x(t)$ to be optimal. In this study we consider the treatment model given in (2) as the system to be controlled. The controls are $u_1(t)$ and $u_2(t)$, interferon alpha (or a natural equivalent that stimulates and modulates the immune system) and entecavir or lamivudine (that inhibit the viral reverse transcriptase) respectively. We consider the cost functional given by the relation (4). The Hamiltonian associated to (1)-(2) is given by

$$\begin{aligned} H(u_1, u_2, x, y, v) = {} & B_1 u_1^2 + B_2 u_2^2 - Cy^2 - Dv^2 + \lambda p_1 - dxp_1 - \frac{\beta vx}{x+y} p_1 + \\ & \frac{\beta vx}{x+y} p_2 - au_1 yp_2 + kyp_3 - (\mu + u_2) vp_3, \end{aligned} \tag{5}$$

where p_1, p_2 and p_3 are adjoint variables and the corresponding adjoint system is given by:

$$\begin{cases} \dfrac{dp_1}{dt} = dp_1 - \dfrac{\beta v y}{(x+y)^2}(p_2 - p_1) \\ \dfrac{dp_2}{dt} = 2Cy + \dfrac{\beta v x}{(x+y)^2}(p_2 - p_1) + au_1 p_2 - kp_3 \\ \dfrac{dp_3}{dt} = 2Dy - \dfrac{\beta x}{(x+y)}(p_2 - p_1) + (\mu + u_2) p_3. \end{cases} \tag{6}$$

3.2. Direct Approach

To approximate the system (), we consider

$$\mathbf{B}^N = \left\{ \psi_j^N, \ j = 1, \ldots, N \right\} \tag{7}$$

a linear B-splines basis functions on the uniform grid

$$\Omega_N = \left\{ t_k = \frac{kT_{\max}}{N}, \ k = 0, \ldots, N \right\}, \tag{8}$$

such that

$$\psi_i^N(t_k) = \delta_{ik}$$

where δ denotes Kronecker sysmbol.

Let us introduce the vector space W^N whose the basis is $\mathbf{B}^N$. We have

- $\dim W^N = N$
- $W^N \subset W^{N+1}$

Let us consider $W = C^0(0,T)$ and let us take the interpolation operator

$$\begin{aligned} \Pi^N : W &\to W^N \\ \phi &\mapsto \Pi^N \phi \end{aligned} \tag{9}$$

satisfying

$$\Pi^N \phi(t_k) = \phi(t_k), \qquad k = 1, \cdots, N. \tag{10}$$

We verify easily that

$$\left\| \Pi^N \phi - \phi \right\|_E \underset{N \to \infty}{\to} 0 \qquad \forall \phi \in E \tag{11}$$

$$\left\| \Pi^N \right\| = \sup_{\substack{\phi \neq 0 \\ \phi \in W}} \frac{\left\| \Pi^N \phi \right\|_E}{\left\| \phi \right\|_E} = 1 \tag{12}$$

Therefore, the system (2) can be approached by the following form.

Find $(T^N, I^N, V^N) \in (W^N)^3$ solution of the system

$$\begin{cases} \dfrac{dx^N}{dt} = \lambda - dx^N - \dfrac{\beta v x^N}{x^N + y^N} \\ \dfrac{dy^N}{dt} = \dfrac{\beta v x^N}{x^N + y^N} - a u_1 y^N \\ \dfrac{dv^N}{dt} = k y^N - (\mu + u_2) v^N \end{cases} \tag{13}$$

$$T^N(0) = T^{N,0}, \quad I^N(0) = I^{N,0}, \quad V^N(0) = V^{N,0} \tag{14}$$

such that

$$\left| x^0 - c^{N,0} \right| \underset{N \to \infty}{\to} 0 \tag{15}$$

$$\left| y^0 - y^{N,0} \right| \underset{N \to \infty}{\to} 0. \tag{16}$$

$$\left| v^0 - v^{N,0} \right| \underset{N \to \infty}{\to} 0. \tag{17}$$

The discretization of the optimal problem (1) with (4) is done as follows.

$$\min_{\lambda \in Q} J^N(\lambda) = \int_0^{T_{\max}} \left(\left(C\left(y^N(t)\right)^2 + D\left(v^N(t)\right)^2 - \sum_{j=1}^{2} q_j . \left(\lambda_j(t)\right)^2 \right) dt \right) \tag{18}$$

where

$$\lambda = (u_1, u_2)^T \text{ and } q = (-B_1, -B_2)^T$$

with λ_j and q_i respectively the j^{th} component of the vectors λ and q respectively.

We are looking for $\lambda^M = (\lambda_1^M, \lambda_2^M) \in Q^M$ a approximated solution of (18) in the set $Q^M = (W^M)^2$ such that

$$\lambda_j^M = \sum_{k=0}^{M} \lambda_{j,k}^M \psi_k(t), \quad j = 1, 2. \tag{19}$$

Therefore the cost function (18) becomes

$$J^N(\lambda^M \quad \approx \quad \sum_{k=1}^{M} \left(\left(C\left(y^N(t)\right)^2 + D\left(v^N(t)\right)^2 - \sum_{j=1}^{2} q_j . \left(\lambda_j(t)\right)^2 \right) h, \qquad \text{wi} \quad \text{th } h = \frac{T_{\max}}{M}, \tag{20}$$

where (20) is determined using rectangular method such that the discretization is done on a regular grid Ω_M .

Finally the discrete formulation of optimal problem (1) with (4) subject to (2) is written as follows.

$$\min_{\lambda^M \in \mathbb{R}^{(M+1)} \times \mathbb{R}^{(M+1)}} J^N(\underline{\lambda}^M) \approx h\left((Y^T R Y) + \left(\underline{\lambda}^M\right)^T B \underline{\lambda}^M \right) \tag{21}$$

where $\underline{\lambda}^M$ is a matrix $(M+1)\times 2$ such that the components $\lambda^M_{j,k}$ are components of the function λ^N_j in the set $\mathbf{B}^N$ and Y represents the matrix with $(i,k)^{th}$ component, $\left(x^N(t_k), y^N(t_k), v(t_k)\right)^T$ denotes the components of solution of the system (13) associated to $\lambda = \lambda^N$, R and B are matrix defined by

$$R = \begin{pmatrix} C & 0 \\ 0 & D \end{pmatrix}, \qquad B = \begin{pmatrix} -B_1 & 0 \\ 0 & -B_2 \end{pmatrix}$$

Furthermore, the optimal control problem (1) with (4) subject to (2) is a minimisation problem with constraint. The discrete formulation of such problem can be written as follows.

Find $\lambda^{*,M} \in \mathbb{R}^{(M+1)} \times \mathbb{R}^{(M+1)}$ solution of

$$\min_{\lambda^M \in \mathbb{R}^{(M+1)} \times \mathbb{R}^{(M+1)}} J^N(\underline{\lambda}^M) \approx h\left((Y^T R Y) + \left(\underline{\lambda}^M\right)^T B \underline{\lambda}^M \right), \tag{22}$$

subject to

$$\begin{cases} \dfrac{dx^N}{dt} = \lambda - dx^N - \dfrac{\beta v x^N}{x^N + y^N} \\ \dfrac{dy^N}{dt} = \dfrac{\beta v x^N}{x^N + y^N} - a u_1 y^N \\ \dfrac{dv^N}{dt} = k y^N - (\mu + u_2) v^N \end{cases} \tag{23}$$

where $\underline{\lambda}^M$ is a matrix $(M+1)\times 2$ such that the components $\lambda^M_{j,k}$ are those function λ^N_j in $\mathbf{B}^N$ and Y is the matrix such that the $(i,k)^{th}$ component is $y^N_i(t_k)$ with $y^N = (x^N, y^N, v^N)^T$ the solution of (23) associated to $\lambda = \lambda^N$.

4. NUMERICAL SIMULATION

The parameters may be taken in order to implement the results of an optimal control problem. The calculation can be done using several plateforms, the Matlab packages have been chosen. The table 2 summarizes the values used in numerical simulation.

Table 2: *Value of parameters used in numerical simulation [22].*

Parameter	λ	d	β	a	k	μ	α	γ	B_1	B_2	C	D	T_{max}
Value	3×10^{2}	1.81×10^{-2}	8×10^{-6}	0.07	120	0.67	1	2	1	2	1	2	100

The initial densities for the treatment model are x_0, y_0 and v_0 and their corresponding values are 500, 300, and 400 respectively and the used initial values for the adjoint system (6) are $p_1(0) = 10^2$, $p_2(0) = 0.19047$, and $p_3(0) = 5\times10^{-3}$.

The trajectories of optimal controls are plotted in figure 1 and the trajectories of determinants variables are shown in the figure 2.

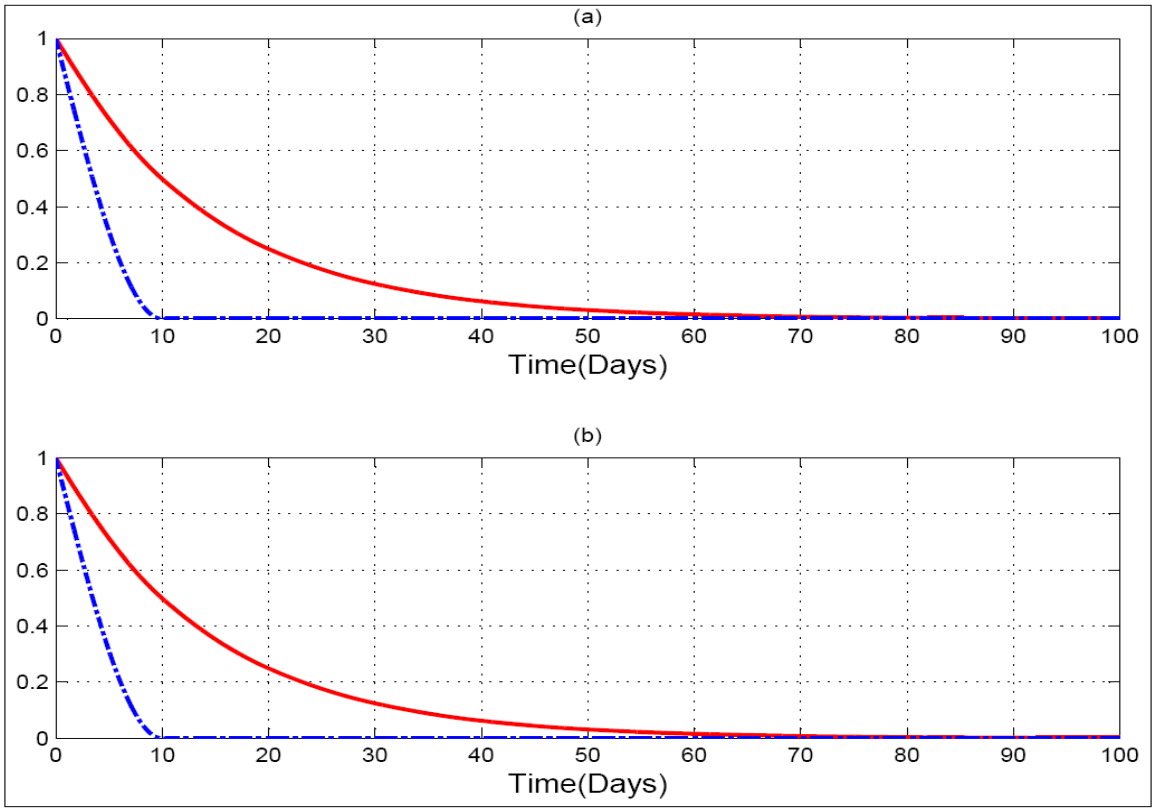

Figure 1: *Variation of controls u1(a) and u2(b) where the solid lines related to the indirect method while the dashdot lines related to the direct method.*

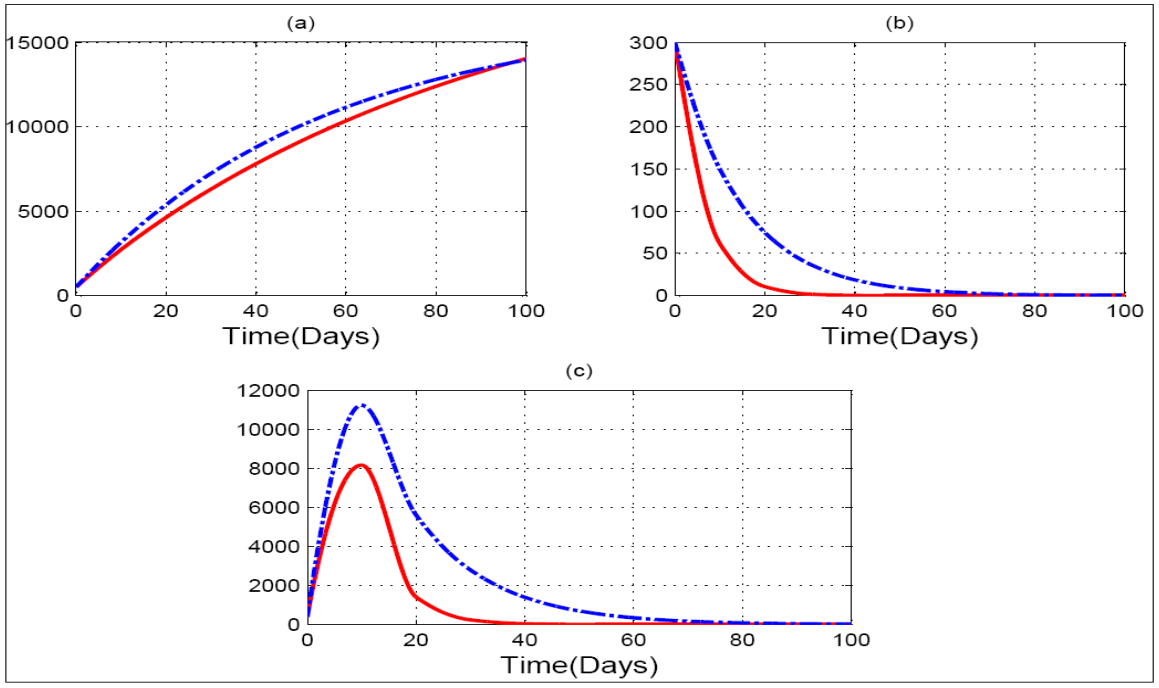

Figure 2: *Variation of uninfected cells x (a), infected cells y(b) , and free virions v(c). The solid lines are related to the indirect method while the dashdot lines are related to the direct method.*

In the figure 1 the two drugs u_1 and u_2 act on their maximal level at the beginning and they end by taking the minimal value. This means that they have made the viruses disappeared. The figure 2(b) illustrates the infected cells for a period of 100 days. In the figure, we see that before the treatment, the number of infected cells was very high, but after its response, these cells diminish and at the end they are all disappeared. As we know, the lymphocytes fight against the virus. Their action is shown in the figure 2(c) where the number of free virions increases rapidly before the treatment. But, with action of the drugs, the viruses are completely disappeared. The results for the problem are presented

in figure 1 ; the value for two controls (u_1 and u_2) was initially one, this to say that there is action of drugs on the viruses, in other words, the process of treatment was very strong. At this stage, the number of free virions increases rapidly and by consequence the liver cells are being infected at the highest level. During the treatment period, the number of free virions is decreasing step by step, as well as the number of infected cells. When the drugs (u_1 and u_2) act on its minimal level (at this stage the controls reach their minimum value equal to zero), the drugs fight against the antibodies and the number of free viruses decreases rapidly until when it reaches the value zero (no free virions in the body). This makes all liver cells to be free; and consequently, no infected liver cells. We say that: as the controls act with maximum level, both the free virions and infected cells are all disappeared as shown in figure 2. Since the response of drugs allows the virions and infected cells to be in decreasing process, the uninfected cells are increasing progressively as shown in the figure 2(a).

5. CONCLUDING REMARKS

In this work, we have been dealing with an optimal control problem related to Hepatitis B virus dynamics. To handle that problem, two numerical approaches have been compared to determine the optimal trajectories of uninfected cells, infected cells and free virions as response to hepatitis B virus optimal problem subject two drugs. The findings show that those two used methods are satisfactory and provide the closer results. Consequently, the approach that involves direct approach and Pontryagin's maximum principle can be seen to play an important role for the resolution of the optimal control problem. In particular, it gives the optimal trajectories in the same way it ensures healthy

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