Optimal Control of Treatment in a Basic Virus Infection Model

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Abstract

The aim of this work is the application of optimal control for the system of ordinary differential equations modeling the Hepatitis B Virus (HBV) infection. The optimal controls represent the efficiency of drug therapy in inhibiting viral production and preventing new infections. The Pontryagin’s maximum principle is used to characterize the optimal controls. The optimality system is derived and solved numerically.

Keywords: Optimal control, basic virus infection model, hepatitis B virus infection, Pontryagin’s maximum principle

1 Introduction

Infection with the hepatitis B virus (HBV) is a major health problem, which can lead to cirrhosis and primary hepatocellular carcinoma (HCC). More than 2 billion people alive today have been infected by HBV. The population of HBV carrier is about 400 million, of whom 75 are located in Asia. Accordingly, HBV causes approximately 1 million deaths each year worldwide. In China alone, nearly 15 million new infections occur annually, more than 30 million people are chronically infected, and more than 350 thousand of them die each year from cirrhosis and HCC.

Acute hepatitis B infection does not usually require treatment because most adults clear the infection spontaneously [7]. Early antiviral treatment may only be required in fewer than 1% of patients, whose infection takes a very aggressive course (“fulminant hepatitis”) or who are immunocompromised. On the
other hand, treatment of chronic infection may be necessary to reduce the risk of cirrhosis and liver cancer. Chronically infected individuals with persistently elevated serum alanine aminotransferase, a marker of liver damage, and HBV DNA levels are candidates for therapy [9]. Although none of the available drugs can clear the infection, they can stop the virus from replicating, and prevent liver damage such as cirrhosis and liver cancer. Treatments include antiviral drugs such as lamivudine, adefovir, tenofovir, telbivudine and entecavir, and immune system modulators such as interferon alpha. However, some individuals are much more likely to respond than others and this might be because of the genotype of the infecting virus or the patient’s heredity. The treatment works by reducing the viral load, (the amount of virus particles as measured in the blood), which in turn reduces viral replication in the liver.

In literature, mathematical models have been used to help understand the dynamics of viral infections, such as human immunodeficiency virus and hepatitis C infection (see [14] and [15]). Following these approaches, dynamic models were developed to analyze the changes in hepatitis B virus levels during drug therapy [13], [18], [10], [11] and [2]. Among those models, the basic virus infection model (BVIM) introduced by Nowak et al. [13] is widely used in studies of virus infection dynamic. This model typically considered uninfected ($T$) and infected ($I$) hepatocytes and free virus ($V$). The dynamics of BVIM are governed by the following equations

$$\frac{dT}{dt} = \lambda - dT - \beta VT,$$  \hspace{1cm} (1)
$$\frac{dI}{dt} = \beta VT - \delta I,$$  \hspace{1cm} (2)
$$\frac{dV}{dt} = pI - cV,$$  \hspace{1cm} (3)

where the parameters model are defined in section 2.

In this article, we introduce a control $u = (u_1, u_2)$ to the above mentioned model simulating the antiviral therapy. The control $u_2$ represents the efficiency of drug therapy in inhibiting viral production and the control $u_1(t)$ represents the efficiency of drug therapy in blocking new infection.

The paper is organized as follows. Section 2 describes a mathematical model of HBV with two control terms. The analysis of optimization problems is presented in section 3. In section 4, we present a numerical appropriate method and the simulation corresponding results. Finally, the conclusion are summarized in Section 5.
2 Mathematical Model of HBV

In this section, we present a mathematical model of Hepatitis B Viral (HBV). The model contains three variables, that is, uninfected target cells \( T \), infected cells \( I \) and free virions \( V \). Our HBV model is given by the following nonlinear system of differential equations

\[
\begin{align*}
\frac{dT}{dt} &= \lambda - dT - (1 - u_1(t))\beta VT, \\
\frac{dI}{dt} &= (1 - u_1(t))\beta VT - \delta I, \\
\frac{dV}{dt} &= (1 - u_2(t))pI - cV,
\end{align*}
\]

where \( T(0) = T_0, I(0) = I_0 \) and \( V(0) = V_0 \) are given and the definitions of above model parameters are listed in Tab. 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>( d )</td>
<td>Death rate of target cells</td>
</tr>
<tr>
<td>( \delta )</td>
<td>Death rate of infected cells</td>
</tr>
<tr>
<td>( c )</td>
<td>Clearance rate of free virions</td>
</tr>
<tr>
<td>( p )</td>
<td>Rate of production of virions per infected cell</td>
</tr>
<tr>
<td>( \beta )</td>
<td>Rate of infection of new target cells</td>
</tr>
<tr>
<td>( \lambda )</td>
<td>Rate of production of new target cells</td>
</tr>
</tbody>
</table>

Table 1: Parameter definitions

The control functions, \( u_1(t) \) and \( u_2(t) \), are bounded, Lebesgue integrable functions [6]. The control \( u_2(t) \), represents the efficiency of drug therapy in inhibiting viral production, such that the virion production rate under therapy is \((1 - u_2(t))p\).

If \( u_2 = 1 \), the inhibition is 100% effective, whereas if \( u_2 = 0 \), there is no inhibition.

The control \( u_1(t) \), represents the efficiency of drug therapy in blocking new infection, so that infection rate in the presence of drug is \((1 - u_1(t))\beta\).

3 The optimal control problems

The problem is to maximize the objective functional

\[
J(u_1, u_2) = \int_0^T \{ T(t) - \left[ \frac{A_1}{2} u_1^2(t) + \frac{A_2}{2} u_2^2(t) \right]\} dt
\]

where the parameters \( A_1 \geq 0 \) and \( A_2 \geq 0 \) are based on the benefits and costs of the treatment. Our target is to maximize the objective functional defined
in equation (7) 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

\[
J(u_1^*, u_2^*) = \max \{ J(u_1, u_2) : (u_1, u_2) \in U \},
\]

where \(U\) is the control set defined by

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

Pontryagin’s Maximum Principle[16] provides necessary conditions for an optimal control problem. This principle converts (4) - (6), (7) and (8) into a problem of maximizing an Hamiltonian, \(H\), pointwisely with respect to \(u_1\) and \(u_2\):

\[
H = T(t) - \left[ \frac{A_1}{2} u_1^2(t) + \frac{A_2}{2} u_2^2(t) \right] + \sum_{i=1}^{3} \lambda_i f_i,
\]

where \(f_i\) is the right hand side of the differential equation of i-th state variable. By applying Pontryagin’s Maximum Principle [16] and the existence result for the optimal control from [3], we obtain the following theorem.

**Theorem 3.1.** There exists an optimal control \(u^* = (u_1^*, u_2^*)\) and corresponding solution \(T^*, I^*\) and \(V^*\), that maximizes \(J(u_1, u_2)\) over \(U\). Furthermore, there exists adjoint functions, \(\lambda_1, \lambda_2, \lambda_3\), satisfying the equations

\[
\begin{align*}
\lambda_1' &= -1 + \lambda_1 d + (\lambda_1 - \lambda_2)(1 - u_1^*) \beta V^*, \\
\lambda_2' &= \lambda_2 \delta - \lambda_3 (1 - u_2^*) p, \\
\lambda_3' &= \lambda_3 c + (\lambda_1 - \lambda_2)(1 - u_1^*) \beta T^*,
\end{align*}
\]

with transversality conditions

\[
\lambda_i(t_f) = 0, i = 1, ..., 3.
\]

Moreover, the optimal control is given by

\[
u_1^* = \min(1, \max(0, \frac{1}{A_1} (\lambda_1 - \lambda_2) \beta V^* T^*))
\]

and

\[
u_2^* = \min(1, \max(0, \frac{-1}{A_2} \lambda_3 p I^*))
\]
Proof.
Due to the convexity of integrand of $J$ with respect to $u$, a priori boundedness of the state solutions, and the Lipschitz property of the state system with respect to the state variables. The existence of an optimal control has been given by [3] (see Corollary 4.1). The adjoint equations and transversality conditions can be obtained by using Pontryagin’s Maximum Principle such that

$$
\lambda_1' = -\frac{\partial H}{\partial T}, \quad \lambda_1(t_f) = 0,
$$

$$
\lambda_2' = -\frac{\partial H}{\partial I}, \quad \lambda_2(t_f) = 0,
$$

$$
\lambda_3' = -\frac{\partial H}{\partial V}, \quad \lambda_3(t_f) = 0.
$$

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

$$
\frac{\partial H}{\partial u_1} = 0, \quad \frac{\partial H}{\partial u_2} = 0
$$

That is

$$
\frac{\partial H}{\partial u_1} = -A_1 u_1 + (\lambda_1 - \lambda_2) \beta V T = 0,
$$

and

$$
\frac{\partial H}{\partial u_2} = -A_2 u_2 - \lambda_3 p I = 0
$$

By the bounds in $U$ of the controls, it is easy to obtain $u_1^*$ and $u_2^*$ in the form of (10) and (11), respectively. ■

4 Numerical simulations

The numerical algorithm presented below is a semi-implicit finite difference method.

We discretize the interval $[t_0, t_f]$ at the points $t_i = t_0 + ih$ ($i = 0, 1, ..., n$), where $h$ is the time step such that $t_n = t_f$, [4]. Next, we define the state and adjoint variables $T(t)$, $I(t)$, $V(t)$, $\lambda_1(t)$, $\lambda_2(t)$, $\lambda_3(t)$ and the controls $u_1(t)$, $u_2(t)$ in terms of nodal points $T_i$, $I_i$, $V_i$, $\lambda_1^i$, $\lambda_2^i$, $\lambda_3^i$, $u_1^i$ and $u_2^i$. Now a combination of forward and backward difference approximation is used as follows:

The Method, developed by [5] and presented in [6] and [8], is then read as

$$
\frac{T_{i+1} - T_i}{h} = \lambda - d T_{i+1} - (1 - u_1^i(t)) \beta V_i T_{i+1},
$$

$$
\frac{I_{i+1} - I_i}{h} = (1 - u_1^i(t)) \beta V_i T_{i+1} - \delta I_{i+1},
$$

$$
\frac{V_{i+1} - V_i}{h} = (1 - u_2^i(t)) p I_{i+1} - c V_{i+1}.
$$
By using a similar technique, we approximate the time derivative of the adjoint variables by their first-order backward-difference and we use the appropriated scheme as follows

\[
\frac{\lambda_i^{n-i} - \lambda_i^{n-i-1}}{h} = -1 + \lambda_i^{n-i-1}d + (\lambda_i^{n-i-1} - \lambda_i^{n-i})(1 - u_i^i)\beta V_{i+1},
\]

\[
\frac{\lambda_2^{n-i} - \lambda_2^{n-i-1}}{h} = \lambda_2^{n-i-1}\delta - \lambda_3^{n-i}(1 - u_2^i)p,
\]

\[
\frac{\lambda_3^{n-i} - \lambda_3^{n-i-1}}{h} = \lambda_3^{n-i-1}c + (\lambda_1^{n-i-1} - \lambda_2^{n-i-1})(1 - u_1^i)\beta T_{i+1}.
\]

The algorithm describing the approximation method for obtaining the optimal control is the following

**Algorithm**

**step 1 :**

\[T(0) = T_0, \quad I(0) = I_0, \quad V(0) = V_0, \quad \lambda_i(t_f) = 0 \quad (i=1, ..., 3), \quad u_1(0) = 0 = u_2(0).\]

**step 2 :**

for i=1, ..., n-1, do :

\[T_{i+1} = \frac{T_i + h\lambda}{1 + h[d + (1 - u_1^i)\beta V_i]},\]

\[I_{i+1} = \frac{I_i + h(1 - u_1^i)\beta V_i T_{i+1}}{1 + h\delta},\]

\[V_{i+1} = \frac{V_i + h(1 - u_1^i)p I_{i+1}}{1 + hc},\]

\[\lambda_1^{n-i-1} = \frac{\lambda_1^{n-i} + h[1 + (1 - u_1^i)\beta V_{i+1}]}{1 + h[d + (1 - u_1^i)\beta V_{i+1}]},\]

\[\lambda_2^{n-i-1} = \frac{\lambda_2^{n-i} + h\lambda_3^{n-i}(1 - u_2^i)p}{1 + h\delta},\]

\[\lambda_3^{n-i-1} = \frac{\lambda_3^{n-i} + h(\lambda_2^{n-i-1} - \lambda_1^{n-i-1})(1 - u_1^i)\beta T_{i+1}}{1 + hc},\]

\[R_{1i+1}^{i+1} = \frac{1}{A_1}(\lambda_1^{n-i-1} - \lambda_2^{n-i-1})\beta V_{i+1} T_{i+1},\]

\[R_{2i+1}^{i+1} = -\frac{1}{A_2}\lambda_3^{n-i-1}p I_{i+1},\]

\[u_1^{i+1} = \min(1, \max(R_{1i+1}^{i+1}, 0)),\]

\[u_2^{i+1} = \min(1, \max(R_{2i+1}^{i+1}, 0)),\]

end for
Control of HBV

step 3:
for i=1, ..., n-1, write
\[ T^*(t_i) = T_i, \quad I^*(t_i) = I_i, \quad V^*(t_i) = V_i, \quad u^*_1(t_i) = u^*_1, \quad u^*_2(t_i) = u^*_2. \]
end for

The following parameters and initial values are used for the simulation which we have taken from [12]:
\[ T_0 = 5.5556 \times 10^7 \text{ cells}, \quad I_0 = 1.1111 \times 10^7 \text{ cells}, \quad V_0 = 6.3096 \times 10^9 \text{ copies/ml}, \quad c = 0.67, \quad h = 1, \quad d = 3.7877 \times 10^{-3}, \quad \delta = 3.259d, \quad \lambda = \frac{2}{3} \times 10^8d, \quad R_0 = 1.33, \quad p = \frac{cV_0\delta R_0}{\lambda(R_0-1)} \quad \text{and} \quad \beta = \frac{d\delta c R_0}{\lambda p}. \]
The period of the therapy considered is 100 days.

The graphs from simulating the model, given below, help to compare the uninfected cells (T), the infected cells (I) and the viral load (V) before and after the treatments with controls. In figure 1, shows that before treatment, the uninfected cells decreases rapidly. Whereas, after the treatments the uninfected cells increases after 52 days. In figure 2, we remark that in absence of treatment the infected cells (I) (solid curve) with HBV increase. Whereas, in presence of treatment, the infected cells I (dashed curve) decreases after 10 days. In figure 3, shows that after introducing therapy, the viral load decreases after 10 days, in addition the number of free virus at the final time \( t_f = 100 \text{ (days) is} 1.938 \times 10^9 \text{ in the case with control and} 13.916 \times 10^9 \text{ without control, and the total cases in blocking viral production at the end of the control program is} 13.916 \times 10^9 - 1.938 \times 10^9 \text{ (= 11.978} \times 10^9 \text{), then the efficiency of drug therapy in inhibiting viral production is} 86\%. \text{ Finally, the figure 4 represent the optimal controls } u^*_1 \text{ and } u^*_2 \text{ in blocking new infection and inhibiting viral production.}

\[ \begin{align*}
T(t) & & \text{T without control} \\
T & & \text{T with control}
\end{align*} \]

Figure 1: Function T with and without control
Figure 2: Function $I$ with and without control

Figure 3: Function $V$ with and without control

Figure 4: The controls $u_1$ and $u_2$
5 Conclusion

In this work, we discuss an efficient numerical method based on optimal control to identify the best treatment strategy of hepatitis B viral (HBV) in order to block new infection and prevent viral production by using drug therapy with minimum side effects. Our numerical results show that viral load decreases after 10 days of treatment and the population of uninfected cells increases after 52 days of therapy.

References


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