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Controllability of Efficiency of Antiviral Therapy in Hepatitis B Virus Infections

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Abstract—An optimal control problem for a mathematical model of efficiency of antiviral therapy in hepatitis B virus infections is considered. The aim of the study is to control the new viral production, block the new infection cells and maintain the number of uninfected cells in the given range. The optimal controls represent the efficiency of antiviral therapy in inhibiting viral production and preventing new infections. Defining the cost functional, the optimal control problem is converted into the constrained optimization problem and the first order optimality system is derived. For the numerical simulation, we propose the steepest descent algorithm based on the adjoint variable method. A computer program in MATLAB is developed for the numerical simulations.

Keywords—Virus infection model, Optimal control, Adjoint system, Steepest descent

I. Introduction

HEPATITIS B virus (HBV) infections are of major public health importance, due to their high burden of disease. Worldwide, an estimated two billion people have been infected at some time or another, with four to five million new infections occurring each year [5]. World-wide, over 350 million people are estimated to be chronically infected with HBV and each year 600,000 people die from HBV-related liver disease or hepatocellular carcinoma. The prevalence of chronic infections is globally differentiated in high endemic areas (> 7%), intermediate endemic areas (2-7%), and low endemic areas (<2%). High prevalence areas are South-East Asia and sub-Saharan Africa, where 8 to 10% of the population are chronically infected with HBV. Western-Europe, North America, and Australia have the lowest prevalence (0.1-1%).

Chronic HBV infection is often the result of exposure early in life, leading to viral persistence in the absence of strong antibody or cellular immune responses [7]. Therapy of HBV carries can aim to either inhibit viral replication or enhance immunological responses against the virus, or both.

Mathematical models have been used to understand the factors that govern infectious disease progression in viral infections like HBV. The mathematical models of HBV including antiviral therapy have been studied by many research groups throughout the world during the last two decades [4], [7], [10]. However, all these works considered the forward problem of simulating the model for a given set of parameters /clinical data. Optimal control of efficiency of antiviral therapy in HBV model has not been discussed in the literature. In this study, we consider an optimal control problem for a mathematical model of efficiency of antiviral therapy in HBV virus infection.

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Management of chronic hepatitis B depends on the level of viral replication. Although progression to cirrhosis is more likely in severe than in mild or moderate chronic hepatitis B, all forms of chronic HBV infection can be progressive[5]. Treatment of a chronic infection is indicated if there is active viral replication (HBV DNA >105 IU/ml), combined with signs of disturbance of the liver function (elevated ALAT), or presence of liver inflammation or fibrosis [5].

The main goal of this study is to optimize the efficiency of the antiviral therapy in HBV virus infections. In other word, maintain uninfected cells in the given range, control the new viral production and block the new infection cells. The optimal controls represent the efficiency of antiviral therapy in inhibiting viral production and preventing new infections. Defining the the cost functional, we formulate the optimal control problem as a constrained minimization problem [2] and derive formally the corresponding first-order optimality system via the Lagrange functional. For the numerical computation of the optimal control variables we present a steepest descent algorithm using the adjoint variables.

The paper is organized as follows. In Section II, we present the models and define cost functional which ought to be minimized. In Section III, the first order optimality system is derived. The steepest descent algorithm is discussed in Section IV. Finally, some numerical results are presented in Section V and concluding remarks can be found in Section VI.

II. Optimal Control Problem

A. Basic Virus Infection Model

Based on studies done by [1], [4], [7], [10], we consider a simple mathematical model for basic virus infection consisting the ordinary differential equations for uninfected cells, T, infected cells, I and free virus, V:

$$\frac{dT}{dt} = \quad - \quad _T T - \quad VT \ , \tag{1a}$$

$$\frac{dI}{dt} = \quad VT - \quad _I I \ , \tag{1b}$$

$$\frac{dV}{dt} = \quad I - \quad V \ , \tag{1c}$$

where t denotes the time scale. Here we assume that the uninfected cells are produced at a rate, , die at per capita rate $_T$, and become infected cells at a rate TV, proportional to both uninfected cell concentration and the virus concentration. Infected hepatocytes are thus produced ar rate TV and are assumed to die at constant rate $_I$. Upon infection, hepatocytes produce virus at rate per infected cell, and virion are cleared ar rate per virion.

Several researchers [4], [6], [7], [10] have modified the system (1) to include antiviral therapy. The models introduced a therapy induced block in virus production with efficacy , i.e. replaced the term I with $(1-\ )\ I$, and block in viral infection with efficacy , i.e. replaced the term VT with $(1-\ )\ VT$. Then the dynamics of system are governed by the following equations

$$\frac{dT}{dt} = \ -\ _T T - (1-\ )\ VT\ , \tag{2a}$$

$$\frac{dI}{dt} = (1-\ )\ VT - \ _I I\ , \tag{2b}$$

$$\frac{dV}{dt} = (1-\ )\ I - \ V\ . \tag{2c}$$

The system (2) is subject to the initial conditions

$$T(0) = T_0,\ I(0) = I_0,\ V(0) = V_0. \tag{2d}$$

The control (t), represents the efficiency of antiviral therapy in inhibiting viral production. If $= 1$, the inhibiting is 100% effective, whereas if $= 0$, there is no inhibition. The control (t), represents the efficiency of antiviral therapy in blocking new infection. If $= 1$, the blocking is 100% effective, whereas if $= 0$, there is no blocking.

B. Description of Parameters

The description of the model parameters and their values are listed in Table I, see [8].

C. Dimensionless Form

Introducing the dimensionless quantities

$$t^* = \frac{t}{t_f}\ ,\quad T^* = \frac{T}{T_0}\ ,\quad I^* = \frac{I}{I_0}\ ,\quad V^* = \frac{V}{V_0}$$

the system (2) can be formulated in dimensionless form. Dropping the star the system can be presented as follows

$$\frac{dT}{dt} = \frac{t_f}{T_0}\ \ -\ _T t_f T - (1-\ )\ V_0 t_f VT\ , \tag{3a}$$

$$\frac{dI}{dt} = \frac{V_0 T_0 t_f}{I_0}(1-\ )\ VT - \ _I t_f I\ , \tag{3b}$$

$$\frac{dV}{dt} = (1-\ )\ \frac{I_0 t_f}{V_0} I - \ t_f V\ . \tag{3c}$$

The system (3) is subject to the initial condition

$$T(0) = 1,\ I(0) = 1,\ V(0) = 1. \tag{3d}$$

D. Cost Functional

We want to maintain the uninfected cells in T_{ref} level, i.e. the final uninfected cells $T(1)$ close to the given T_{ref} value. On the other hand we want to minimize the cost for antiviral therapy. Hence, we consider the following cost functional

$$J = J(y,u) = \ _1(T_{ref} - y_3(1)) + \frac{2}{2}\int_0^1 u_1(t)dt + \frac{3}{2}\int_0^1 u_2(t)dt \tag{4}$$

where $y = (T, I, V) \in Y$ denotes the vector of state variables and $u = (\ ,\ ) \in U$ are the controls. The weighting coefficients $_i > 0,\ i = 1...3$ denote the benefits and costs of the antiviral treatment.

Summarizing, we consider the following constrained optimization problem

$$\text{minimize } J(y,u) \text{ with respect to } u, \text{ subject to (3).} \tag{5}$$

In the sequel, we address this problem using the calculus of adjoint variables.

III. The First-Order Optimality System

In this section we introduce the Lagrangian associated to the constrained minimization problem (5) and derive the system of first-order optimality conditions.

Let $Y = C^1([0,1];\mathbb{R}^3)$ be the state space consisting of triples of differentiable functions $y = (T, I, V)$ denoting uninfected cells, infected cells and free virus. Further, let $U = C^1([0,1];\mathbb{R}^2)$ be the control space consisting of a pair $(u_1, u_2) = (\ ,\ )$ of differentiable functions.

We define the operator $e = (e_T, e_I, e_V) : Y \times U \to Y^*$ via the weak formulation of the state system (3):

$$\langle e(y,u),\ \rangle_{Y,Y^*} = 0 \qquad \forall\ \in Y^*$$

where $\langle\cdot,\cdot\rangle_{Y,Y^*}$ denotes the duality pairing between Y and its dual space Y^*. Now, the minimization problem (5) reads as

$$\begin{aligned}&\text{minimize } J(y,u) \text{ with respect to } u \in U,\\ &\text{subject to } e(y,u) = 0.\end{aligned} \tag{6}$$

Introducing the Lagrangian $\mathcal{L} : Y \times U \times Y^* \to \mathbb{R}$ defined as

$$\mathcal{L}(y,u,\ ) = J(y,u) + \langle e(y,u),\ \rangle_{Y,Y^*}\ ,$$

the first–order optimality system reads as

$$\nabla_{y,u,\xi}\mathcal{L}(y,u,\ ) = 0\ .$$

Considering the variation of $\mathcal{L}$ with respect to the adjoint variable , we recover the state system

$$e(y,u) = 0$$

or in the classical form

$$\frac{dy}{dt} = f(y,u)\ ,\quad \text{with } T(0) = 1,\ I(0) = 1,\ V(0) = 1 \tag{7}$$

where

$$f(y,u) = \begin{pmatrix} \frac{t_f}{T_0}\ \ -\ _T t_f T - (1-\ )\ V_0 t_f VT \\ \frac{V_0 T_0 t_f}{I_0}(1-\ )\ VT - \ _I t_f I \\ (1-\ )\ \frac{I_0 t_f}{V_0} I - \ t_f V \end{pmatrix}.$$

Second, taking variations of $\mathcal{L}$ with respect to the state variable y we get the adjoint system

$$J_y(y,u) + e_y^*(y,u)\ \ = 0$$

TABLE I
DESCRIPTION OF PARAMETERS

Parameter	Description	Value
T_0	Initial uninfected cells	$5.5556 \cdot 10^7$
I_0	Initial infected cells	$1.1111 \cdot 10^7$
V_0	Initial free virus	$6.309 \cdot 10^9$ copies/ml
t_f	Time duration	100 days
λ	Rate of production of new target (uninfected) cells	$\frac{2}{3} \cdot 10^8 \delta_T$
δ_T	Death rate of uninfected cells	$3.7877 \cdot 10^{-3}$
δ_I	Death rate of infected cells	$3.259\delta_T$
α	Clearance rate of free virus	0.67
γ	Rate of production of virus per infected cells	$\frac{\alpha V_0 \delta_I 1.33}{0.33\lambda}$
β	Rate of infection of new uninfected cells	$\frac{\delta_I \delta_T \alpha 1.33}{\lambda \gamma}$

or in classical form

$$-\frac{d}{dt} = F(y, u, \ ),$$
$$\text{with} \quad {}_T(1) = -\ {}_1, \quad {}_I(1) = 0, \quad {}_V(1) = 0, \qquad (8)$$

where

$$F(y, u, \ ) = \left(\frac{f}{y}\right)^\top .$$

Finally, considering variations of $\mathcal{L}$ with respect to the control variable u in a direction of u we get the optimality condition

$$\langle J_u(y, u), \ u\rangle + \langle e_u(y, u)\ u, \ \rangle = 0 . \qquad (9)$$

In the optimum, this holds for all $u \in U$.

IV. Algorithm

To solve the nonlinear first–order optimality system (7), (8) and (9), we propose an iterative steepest–descent method [3].

1) *Set $k = 0$ and choose initial control $u^{(0)} \in U$.*
2) *Given the control $u^{(k)}$. Solve the state system* (7) *to obtain $y^{(k+1)}$.*
3) *Solve the adjoint system* (8) *to obtain* $^{(k+1)}$.
4) *Compute the gradient $g^{(k+1)}$ of the cost functional.*
5) *Given update the control $u^{(k+1)} = u^{(k)} - g^{(k+1)}$.*
6) *Compute the cost functional $J^{(k+1)} = J(y^{(k+1)}, u^{(k+1)})$.*
7) *If $\left|g^{(k+1)}\right| \geq$ Tol, goto 2.*

Here, Tol is some prescribed relative tolerance for the termination of the optimization procedure. In each iteration step, we need to solve two initial value problems, i.e. the state system (7) and the adjoint system (8) in the step 2 and 3 of the algorithm.

Crucial for the convergence of the algorithm is the choice of the step size (in step 5 of the algorithm) in the direction of the gradient. Clearly, the best choice would be the result of a line search

$$^* = \text{argmin}_{\vartheta > 0} J(u_k - \ g_k).$$

However this is numerically quite expensive although it is a one dimensional minimization problem. Instead of the exact line search method, the heuristic method is used and it gives [3]

$$= \min\left(1, \|g\|_\infty^{-1}\right).$$

A. Solving Procedure for Adjoint System

We reformulate the adjoint system by substituting $\tilde{t} = 1 - t$.

$$-\frac{d}{dt} = F(y, u, \ ), \text{ with } {}_T(1) = -\ {}_1, \ {}_I(1) = 0, \ {}_V(1) = 0.$$

Let $\tilde{t} = 1 - t$ then $\frac{d}{d\tilde{t}} = -\frac{d}{dt}$.

$$\frac{d}{dt} = F(y, u, \ ) \text{ with } {}_T(0) = \ {}_1, \ {}_I(0) = 0, \ {}_V(0) = 0.$$

Now we can consider adjoint system as an initial value problem.

B. Numerics

Both state and adjoint system of ODE were solved using the `MATLAB` routine `ode23tb`. This routine uses an implicit method with backward differentiation to solve stiff differential equations. It is an implementation of `TR-BDF2` [9], an implicit two stage Runge-Kutta formula where the first stage is a trapezoidal rule step and the second stage is a backward differentiation formula of order two.

V. Results and Discussion

In Figure 1 shows the uninfected, infected and free virus profiles before and after antiviral treatment of control. Before introducing the antiviral treatment the profile of uninfected cells decreases from $5.555 \cdot 10^7$ to $3.85 \cdot 10^7$. 100 days after the therapy treatment, the uninfected cells can be maintained in $5.36 \cdot 10^7$ level with 97% efficiency. From Figure 1, in an absence of antiviral treatment one can see the infected cells increase rapidly from $1.111 \cdot 10^7$ to $1.753 \cdot 10^7$. With presence of antiviral treatment after 100 days it decreases to $6.827 \cdot 10^6$ and it indicates 67% efficiency to block the new infections. It can be seen that without control the viral load increases from $6.31 \cdot 10^9$ to $2.17 \cdot 10^{10}$. Whereas, 100 days after treatment it reduces to $4.887 \cdot 10^9$. The total cases in blocking viral production at the end of the control program (100 days after introducing the antiviral therapy) is $1.6813 \cdot 10^{10}$. It indicates 78% efficiency to blocking new viral production.

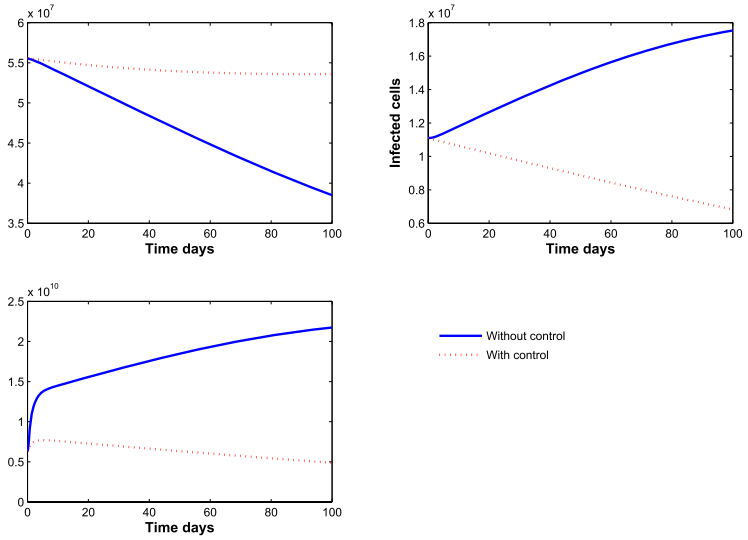

Fig. 1. Uninfected cells (up-left), Infected cells (up-right), Free Virus (down-left). solid: without antiviral treatment, dotted: with control.

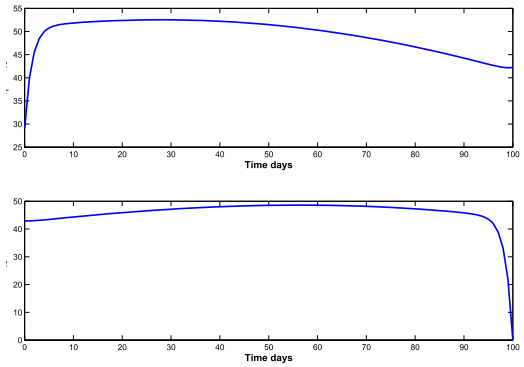

Fig. 2. The controls η and ε.

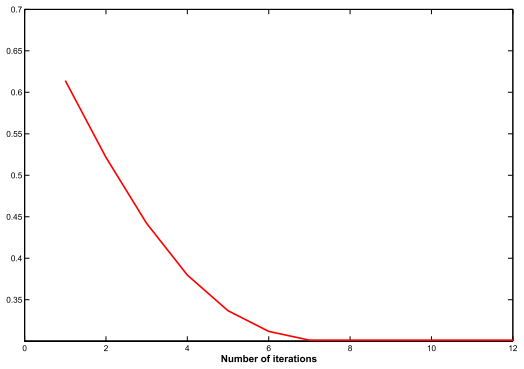

Fig. 3. Cost functional.

Figure 2 shows the profile of two control parameters and . The efficiency of drug therapy in blocking new infection, i.e. the control shows 50% of efficiency during first 40 days and after that it decreases to 40%. The efficiency of antiviral therapy in inhibiting viral production shows more-or-less 40% efficiency during the control program. From Figure 2, it can be easily seen that the efficiency of antiviral treatment process more-or-less close to 50% through out the therapy period.

Figure 3 visualizes the corresponding cost functional. One can see that after 7^{th} iteration, it almost equal to zero.

VI. Conclusions

We studied an optimal control problem for a HBV viral infection model to identify the best antiviral treatment strategy in order to block new infection and prevent the viral production. Defining the cost functional we converted this problem into the constrained optimization problem and derived the first order optimality system. For the numerical solution we proposed steepest descent algorithm based on adjoint variable method.

It can be seen that maintaining 50% of drug efficiency helps to keep the uninfected cells in $5.36 \cdot 10^7$ level. It counts that maintaining the uninfected cells, blocking the new infections, preventing the new viral production in 97%, 67% and 78% efficiency levels respectively.

Most icteric patients with an acute HBV infection resolve their infection and do not require treatment, since the rate of recovery is not likely to be improved. Treatment of chronic HBV infections with lamivudine leads to a rapid and sustained decline of plasma virus levels, but clinical benefit with reduced risk of cirrhosis and development of liver cancer will greatly depend on the decline of infected cells. It can be seen that eradication of the virus infection depends on whether the efficacy of the drug is sufficiently high to reduce the basic reproductivity ratio of the virus [10]. Therefore, the quantitative understanding of HBV dynamics derived here would make

it possible to devise optimal treatment strategies for individual patient.

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