Dynamics of HBV model with intermittent antiviral therapy

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Abstract—**This paper studies the dynamics of the Hepatitis B virus (HBV) model with intermittent antiviral therapy. We first propose a mathematical model of HBV and then analyze its qualitative and dynamical properties with a new treatment therapy. Combining with the clinical data and theoretical analysis, we show that the intermittent antiviral therapy regimen is one of optimal strategies to treat this kind of complex disease. There are two mainly advantages on this therapy. Firstly, it can delay the drug resistance. Secondly, it can reduce the duration of treatment time comparing with the long term continuous therapy, thereby reducing the adverse side effect. Our results clear provides a new way to treat the HBV disease.**

I. INTRODUCTION

Hepatitis B virus (HBV) infection is a major worldwide health problem. About more than 350 million people infect such a virus. HBV induces many liver diseases, such as cirrhosis, and hepatocellular carcinoma (HCC). Recently, several kinds of antiviral drugs have been approved, e.g. Lamivudine, Adefovir dipivoxil, Entecavir and so on. These treatments rely on blocking HBV replication through inhibition of the viral polymerase. Persistent HBV replication with active hepatitis leads to the disease progression and, conversely, treatments that suppress viral replication forestall disease progression. Loss of detectable hepatitis B surface antigen (HBsAg) in serum correlates with improved long-term clinical outcomes. However, as mentioned in [1], the indication for treatment should be based on HBV-DNA levels but not alanine transaminase (ALT) or HBeAg loss with seroconversion.

Recently, several methods have been used to treat HBV. The main goals are following [2]: (1) Suppress HBV-DNA levels to clinically relevant levels; (2) normalize ALT levels; (3) induce HBeAg loss with seroconversion to anti-HBe; (4) decrease serum HBsAg titer; (5) improve liver histology; and (6) not to cause serious adverse events. Also in that paper, the authors estimated the relative treatment efficacy for HBV as monotherapies or combination therapies. However, whether or not using monotherapy or combination therapy, the drug resistance can not be ignored. It can reduce the treatment efficacy. Searching more effective treatment regimens of HBV becomes an exciting area for investigators. Hence, in this paper we aim to propose an effective treatment method for HBV based on the experiment data.

The study of anti-HBV infection treatment may benefit from the use of mathematical modeling. The basic mathematical model of HBV was used by Nowak [3] and the dynamics was further studied by Pereson A.S. [4]. However, there are still many problems in the traditional models. Therefore, we propose a new model by amending the pervious one in next section, and further develop a treatment therapy to overcome the drug resistance problem.

II. MATHEMATICAL MODEL OF HBV

A. The pervious mathematical model of HBV

As mentioned in section 1, to well understand the mechanism of epidemiology of HBV in a systematic manner, it is better to resort the mathematical model. The basic model is a system of three ordinary differential equations for uninfected cells, x, productively infected cells, y, and free virus, v. The exactly form is

$$\begin{cases} \frac{dx}{dt} = \lambda - dx - \beta xv \\ \frac{dy}{dt} = \beta xv - ay \\ \frac{dv}{dt} = ky - \mu v \end{cases} \quad (1)$$

where λ is the constant production rate of uninfected susceptible cells, d is the death rate constant of those same uninfected cells, β is the infection rate constant of those cells by the free cells, a is the death rate constant of the productively infected cells, k is the viral production rate constant by the infected cells, and μ is the clearance rate constant of the free virus. It was assumed by *Nowak et al*, the inhibitor of HBV polymerase, such as Lamivudine can prevent the sythesis of new HBV-DNA from the pregenomic mRNA. It can also block the production of new virus particles from the productively infected cells. That means $k = 0$. At the same time, they also assumed that the inhibitor of HBV polymerase can prevent the generation of new productively infected cell, i.e. it means $\beta = 0$ during therapy. However, Tsiang et al [5] studied 13 Chronic hepatitis B infected patients, and they found that the above two assumptions are only valid for a short duration after the start of therapy and become inaccurate as soon as the number of infected cell, y, and drop below its equilibrium value. It means that the above system is not suitable for HBV infection.

On the another hand, the basic reproduction number of model (1) is $R_0 = \frac{\lambda \beta k}{ad\mu}$. As mentioned in Min [6], R_0 is proportional to λ/d. It also suggests that it is not a reasonable model for describing HBV virus infection since it implies that an individual with a smaller liver may be more resistent to the virus infection than an individual with a larger one. Hence, we need to improve the mathematical model in next subsection such that it can be better to reflect the natural dynamics of HBV infection.

B. New hybrid model of HBV with drug resistance

As mentioned above, the basic model (1) is not reasonable for HBV due to many problems. At the same time, once the patients are infected by HBV, when the HBV-DNA level increases to certain value, they must receive antiviral therapy to suppress HBV-DNA levels to clinically relevant levels. As long as on treatment, the drugs resistance cannot be negligible. However, if we consider the drug resistance, the above model is not good enough to fit the clinical data. All these reasons suggest that the mathematical model should be modified. In fact, the authors in [6] improved the model (1) to employ a standard incidence function instead of the mass action incidence function. Here we propose the following new system

$$\begin{cases} \frac{dx}{dt} = \lambda - dx - (1-m)\frac{\beta xv}{x+y} \\ \frac{dy}{dt} = (1-m)\frac{\beta xv}{x+y} - ay \\ \frac{dv}{dt} = (1-\epsilon(t))ky - \mu v + k_1(t)v \end{cases} \quad (2)$$

where

$$m = \begin{cases} 0, & \text{off-treatment} \\ 1, & \text{on-treatment} \end{cases} \quad (3)$$

$$k_1(t) = \frac{\epsilon_0}{1 + e^{-m\epsilon_1 t + (1-m)\epsilon_2 t}}$$

$\epsilon(t)$ is drug efficacy and $k_1(t)$ is drug resistance, $0 \leq \epsilon(t) \leq 1, t \geq 0$, and $\epsilon_0, \epsilon_1, \epsilon_2$ are constants. The other parameters are the same as system (1). We should point out that the drug efficacy $\epsilon(t)$ refers to the time t. However, because $0 \leq \epsilon(t) \leq 1$, we treat it as a constant ϵ in the following analysis for simplicity. Choosing proper value $\epsilon_0, \epsilon_1, \epsilon_2$ such that the $\min_{m=1} k_1(t) \leq \min_{m=0} k_1(t)$. It means when on treatment, the drug resistance will appear and increase, when off treatment the drug resistance will decrease, but it can not be disappeared and the final level is higher than the one at the beginning of treatment. See following figure 1 for detail description. Without loss of generality, we also treat k_1 as a constant during the on treatment and off treatment which obeys the inequality above in the following analysis.

Comparing to the system (1), the above system (2) is able to describe the infection of HBV. First, here we consider the drug resistance k_1, which in system (1) it does not. Because of the previous trials, taking the Lamivudine administration for example, the incidence of resistance to Lamivudine increases with the duration of treatment. With resistance being observed in 22% of treated patients after one year, and rising to 38% after two years, 53% after three years, and 66% after four years [7]–[10]. From this point, how to reduce the drug resistance is
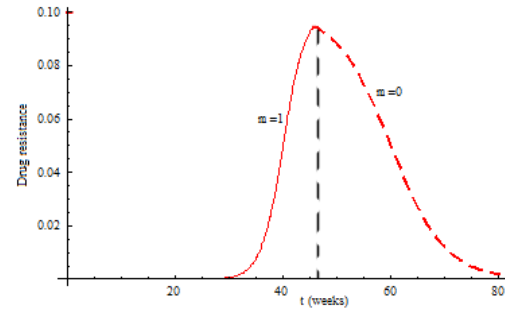

Fig. 1 The drug resistance with time scale, where $\epsilon_0 = 0.1, \epsilon_1 = 0.5, \epsilon_2 = 0.2$.

becoming an important clinical issue for HBV antiviral therapy and it is indeed necessary to modify the model. Second, we introduce an drug efficacy ϵ and also here we use a switching parameter m. For the drug efficacy ϵ, it represents the efficacy of inhibition which is consistent with the paper of Tsing et al. For the switching parameter m, so that we do not need to assume $\beta = 0$ during the therapy. Hence, we propose a new model with drug resistance, drug efficacy and the switching parameter m.

Due to the switching parameter m, the above system can be regarded as a hybrid system. Recently, hybrid system are widely used to model dynamical phenomena that characterized by interplay between continuous dynamics and discrete events. For example, the applications of hybrid system to biological and medical systems [11] and also see the papers in that issue. At the same time, it can be used in biomedical area, such as modeling the disease progression of prostate cancer under intermittent hormonal therapy, where continuous tumor dynamics is switched by interruption and reinstitution of medication. In fact, intermittent therapy regimen has already successfully used for prostate cancer [12]–[14]. It can delay or prevent the cancer relapse. It may also be very useful for other complex diseases, such as what we intend to discuss in this paper.

As for the mathematical model proposed above, our aim is to use the idea of intermittent therapy method to show that it is one of the optimal strategies to treat HBV. In order to better understand the mechanism of intermittent therapy regimen for HBV, we study the dynamical properties of our model. Hence, in the next section, we study the dynamical properties of the proposed model with intermittent therapy regimen.

III. ANALYSIS AND INTERMITTENT THERAPY REGIMEN OF THE HBV MODEL

So far, the most common way for treating HBV is long term using drugs. From the previous literatures the long term continuous therapy caused the drug resistance severely. Maybe by using the intermittent therapy is an optimal regimen. As is known, for antiviral therapy of HBV, an important index is HBV-DNA level (log copies/ml). In 2005, Lau K.K. et al [15] investigated a total 814 patients with HBeAg-positive chronic B receiving drug therapy, peginterferon alfa-2a plus placebo,

peginterferon alfa-2a plus Lamivudine and Lamivudine, respectively, with 48 weeks and followed up for an additional 24 weeks. They showed that peginterferon alfa-2a alone or in combination with Lamivudine is superior to Lamivudine alone. Because after withdrawing drug therapy, the HBV-DNA relapse to the higher value than peinterferon alfa-2a alone or in combination with Lamivudine. Besides these fact, we think the intermittent therapy regimen is an optimal method for HBV. There are two mainly advantages: firstly, it can delay the resistance of the drugs. Secondly, it can reduce the duration of treatment time, because long term using drugs, such as Lamivudine, can cause adverse side effect [16].

In order to show the intermittent therapy regimen is one of the optimal methods for treatment of HBV, we need to analyze the dynamical properties of system (2). Combining with the clinical data set, we intend to show our idea is realistic. Now we give some quantitative analysis of system (2). By the method of the next generation matrix proposed by Van den Driessche [17], it is clearly that the basic infection reproduce number is

$$R_0 = \frac{(1-m)(1-\epsilon)\beta k}{(\mu + k_1)a}$$

Before drug therapy, that means $m = \epsilon = k_1 = 0$, the basic reproduce number becomes $R_0 = \frac{\beta k}{a\mu}$. If $R_0 = \frac{\beta k}{a\mu} < 1$, there is just one equilibrium $E^\star = \left(\frac{\lambda}{d}, 0, 0\right)$. If $R_0 = \frac{\beta k}{a\mu} > 1$, there is another equilibrium

$$
\begin{aligned}
E^* &= \left(\frac{\lambda}{d + a(R_0 - 1)}, \frac{\lambda(R_0 - 1)}{d + a(R_0 - 1)}, \right.\\
&\quad \left. \frac{\lambda(1-\epsilon)(R_0 - 1)}{\mu[d + a(R_0 - 1)]} \right) \quad (4)
\end{aligned}
$$

It can be proved that it is locally asymptotically stable when $R_0 > 1$. We give the following theorem as a by-product. The proof is mainly based on the sign of the eigenvalue of system (2), which is omitted for the simplicity. The detail proof can also be found in Min [6].

Theorem 1: If $R_0 < 1$, then the equilibrium $E^\star$ is locally asymptotically stable and E^* does not exist. If $R_0 > 1$, then the equilibrium of system (4) is locally asymptotically stable and $E^\star$ is unstable.

According to the system (2), at the beginning, the HBV-DNA level is high, from the reference [15], before treatment it was 10.1 log copies/ml. Then starting to treatment period, that means $m = 1$, supposing the drug efficacy $\epsilon = 1$ (the best drug effect), from the last two equations of system (2) we get

$$y(t) = y_0 e^{-at} \quad \text{and} \quad v(t) = v_0 e^{(-\mu + k_1)t}$$

where y_0 and v_0 are the infected cells and free virus at the beginning of therapy. That means under drug treatment, the infected cells and free virus cells decrease exponential, plotting the figure of viral load (HBV-DNA level) in Fig.2. However, it is just an ideal case. In practice, the drug efficacy cannot be 100%, and drug resistance really exists. If there is no drug resistance and drug efficacy is 100%, the virus can be eliminated completely after 8 weeks treatment based on the figure.
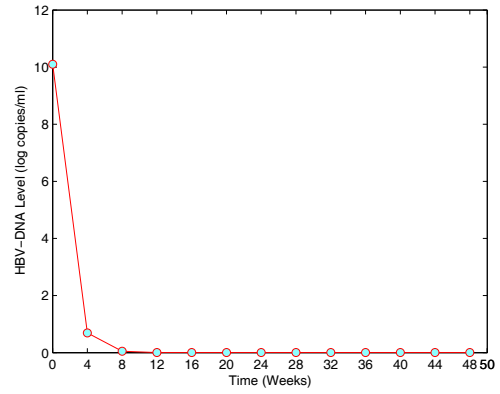

Fig. 2 The ideal case of HBV on-treatment with drug efficacy is 100% ($\epsilon = 1$)

In fact, according to data [15], HBV-DNA level just decreases to a clinically relevant levels. Further using drugs there is no obviously decreasing of the HBV-DNA level. Hence, we suppose to stop treatment. After 24 weeks, the HBV-DNA level will increase to the level of almost 10.1 log copies/ml. Then it should start the therapy again. We want to predict that this strategy is useful for HBV antiviral therapy. Although antiviral therapy of HBV has significantly evolved over the last decade with the development of new antiviral agents, it is still not possible to eradicate the virus. Choosing optimal treatment regimens is much important for HBV. Hence, choosing the intermittent therapy may be one of the optimal methods.

Just as mentioned in [5], there exists biphasic clearance kinetics, the productively infected cells and the free virus cells. In that paper, the authors assumed that Lamivudine can prevent the generation of new productively infected cells. It means that $\beta = 0$. However, in our model we do not need this assumption. Because of the drug resistance, we assume that the drug efficacy is not 100%, that means $0 \leq \epsilon < 1$. Now we consider the on treatment case, in which the system becomes

$$
\begin{cases}
\frac{dx}{dt} = \lambda - dx \\
\frac{dy}{dt} = -ay \\
\frac{dv}{dt} = (1-\epsilon)ky - \mu v + k_1 v
\end{cases} \quad (5)
$$

From the second equation of system (5), we get $y(t) = y_0 e^{-at}$. Then from the third equation of system (5), we get

$$\frac{dv}{dt} = (1-\epsilon)ky_0 e^{-at} - \mu v + k_1 v \quad (6)$$

Solving equation (6), we get

$$v(t) = \frac{(1-\epsilon)ky_0}{\mu - a + k_1} e^{-at} + C e^{(k_1 - \mu)t} \quad (7)$$

where C is a constant which need to be determined later. If we choose proper value C, for simplicity, we suppose that before treatment the free virus is at steady-state. It means the production and clearance rates are equal, $ky_0 = \mu v_0, k_1 = 0$. Hence, we can get $C = v_0 - \frac{(1-\epsilon)\mu v_0}{\mu - a}$ substituting it into

equation (7), we get the viral load

$$v(t) = \frac{(1-\epsilon)\mu v_0}{\mu - a}(e^{-at} - e^{-\mu t}) + v_0 e^{-\mu t} \qquad (8)$$

We simulate the viral load $v(t)$ with the clinical data [15] in Figure 3. From the figure, one can see that it fits the data well. In [5], the authors also gave the simulation with the assumption of $\beta = 0$. However, by considering the hybrid system (2), we do not need this assumption in this paper.
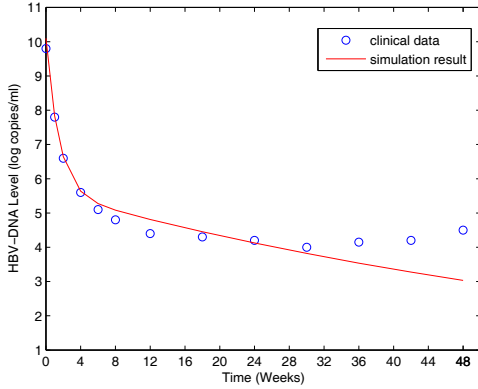

Fig. 3 The simulation of clinical data (blue circle) and the solution (8) (red solid line)

Just based on [4], [18], the following are involved in the estimation of model parameters.

(a) A human liver contains about 2×10^{11} hepatocytes [18]. A patient has about total 3000 ml plasma. Usually, tested virus qualities are in $copies/ml$. Consequently, we can assume that

$$\lambda/d \approx 2 \times 10^{11}/3000.$$

(b) Since the half-life of a hepatocyte is about half a year [4], we can assume that

$$d = -\ln(0.5)/183 \approx 0.00379.$$

(c) We select that $\mu = 0.67$, which is equivalent to assuming that the half life of a virus is about one day. The other parameters are selected as following

$$\{\epsilon, a, v_0, \beta, k, k_1\} = \{0.4552, 3.38d, 10.1, 1.33a\mu/k,$$
$$\mu v_0(d + 0.33a)/(0.33\lambda), 0.0001\}$$

As for the following system (9), the other parameters are the same as above except $\epsilon = 0$. Because this is the off-treatment case, the drug efficiency is zero. The above figure shows the viral load will decrease exponentially under the drug treatment. At the beginning of 4 weeks, the viral load decreases promptly. From 4 weeks to 8 weeks, the viral load also decreases, but it is not so as promptly as the first 4 weeks. This is also observed in Fig. 2. This is the first phase which reflects the clearance of the free virus v_0. As mentioned above, if the drug efficient is 100%, the virus will be eliminated completely. However, from 8 weeks to 48 weeks due to the drug resistance, the variation of the viral load is almost 0 log copies/ml. This is the second phase which mirrors the decay rate of productively

infected cells. It seems that our model fits the clinical data well. Also from the above figure, there is little effect to use drugs between 8 weeks and 48 weeks. Therefore, we suggest that after 48 weeks, the therapy can be stopped. In other words, the HBV model becomes

$$\begin{cases} \frac{dx}{dt} = \lambda - dx - \frac{\beta xv}{x+y} \\ \frac{dy}{dt} = \frac{\beta xv}{x+y} - ay \\ \frac{dv}{dt} = (1-\epsilon)ky - \mu v + k_1 v \end{cases} \qquad (9)$$

It is just the model that modified by Min [6] except the drug resistance term. System (9) is a system of nonlinear differential equations. It is hard to obtain its analytical solution. We just simulate the viral load as follows (Fig. 4)
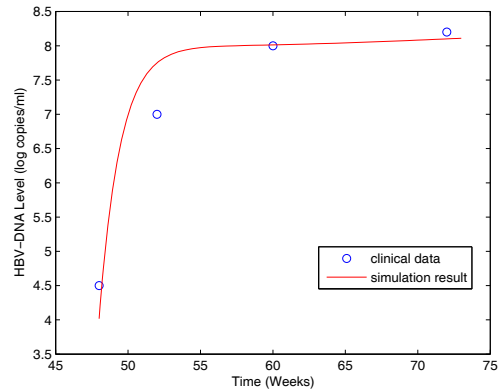

Fig. 4 The simulation of clinical data (blue circle) and the virus load v of system (9) (solid line), where $x_0 = 3.1515, y_0 = 6.3096, v_0 = 1.04$ (log copies/ml).

From the figure 4, we can see that after 24 weeks the viral load almost increases to the level of before therapy (10.1 log copies/ml). But it is nearly half a year. From the figure 1 in section II, we can see that the drug resistance decreases from 0.10 to nearly 0.0001 after half a year. It suggests that for a patient with HBV, this will delay the drug resistance during these free-treatment period. It also suggests that comparing with the continuous long-term treatment, it will reduce the duration of the treatment. On the other hand, also from the figure 1, if extending the duration of treatment, the drug resistance will increase. As a result, side effect will appear. From this view point, we can say by using intermittent antiviral therapy, it will reduce the side effect such as cirrhosis, hepatocellular carcinoma (HCC) or other adverse effect.

In a word, from the dynamical analysis and simulation, we can see that our model is effective and fits the clinical data well. And from the simulation and clinical data it also implies that intermittent therapy can be used for HBV. For the intermittent regimen of HBV model, it should be further analyzed. For example, the diagram of the intermittent antiviral therapy, the dose of the drug, the outcome of the therapy regimen, the bifurcation analysis of the regimen, and so on. However, due to the limitation of the space, we must stop here. Further discussion will be made elsewhere.

IV. Conclusion and discussion

In this paper, we proposed a mathematical model of HBV with intermittent antiviral therapy. Giving the quantitative and dynamical properties analysis, we showed that intermittent therapy regimen is one of the optimal ways to treat patient with HBV. It can delay the drug resistance and reduce the duration of treatment, thereby reducing the side effect.

However, HBV is really a complex disease. The mechanism of the viral dynamics is still not so clear. In the past decade, several kinds of drugs have been approved and regimens have been proposed. Whether to use one drug or combination drugs is still controversial. There is no fixed method to therapy HBV. Quantitative understanding of HBV dynamics will make it possible to devise optimal treatment strategies for individual patients. More detail assay data are needed for modeling in a more accurate manner.

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