Stability Analysis and Simulation of an Anti-HBV Therapy Mathematical Model with Time-delay Immune Response

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***Abstract*—Mathematical models have been used to understand the factors that govern infectious disease progression in viral infections. Many HBV models were based on the basic virus infection model with bilinear mass action incidence of virus and the uninfected target cells introduced by Zeuzem et al. and Nowak et al. But Lequan Min et al. have set up another basic virus infection model with a standard incidence function. In this paper, base on the standard mass action incidence, an adefovir anti-HBV therapy model with time-delay immune response were set up. The globally asymptotically stable analysis of the infection-free equilibrium were given in the paper, for the endemic equilibrium, simulation shows there exist a stable switch. The simulation based on the clinical adefovir therapy data were also given.**

I. Introduction

Chronic hepatitis B caused by the hepatitis B virus(HBV) remains a major global health problem. About 2 billion people have been infected with the virus [1], with 5 million new cases each year [2]. It is estimated conservatively that there are 350 million persistent carriers of HBV worldwide, 25% of whom have chronic liver disease and cirrhosis, which could progress to hepatocellular carcinoma[3].

The study of anti-HBV infection treatment may benefit from the use of mathematical modelling. Several models have been introduced for the understanding of the HBV dynamics ([4], [5], [6], [7], [8]). Among those models, the basic virus infection model (BVIM) introduced by Zeuzem et al. [9] and Nowak et al. [4] is widely used in the studies of virus infection dynamics. The BVIM with three variables takes the form of

$$\begin{cases} \dot{x} = \lambda - dx - \beta vx \\ \dot{y} = \beta vx - ay \\ \dot{v} = ky - \mu v \end{cases} \tag{1}$$

where x, y and v are numbers of uninfected (susceptible) cells, infected cells, and free virus respectively. Uninfected cells are assumed to be produced at the constant rate λ, die at the rate of dx and become infected at the rate of βvx. Infected cells are thus produced at the rate of βvx and are assumed to die at the rate ay. Free virions are assumed to be produced from infected cells at the rate of ky and are removed at the rate of μv. This model can describe some aspects of the viral dynamics in HBV infection.

Obviously the rate of infection in model (1) is bilinear in the virus v and the uninfected target cells x, actual incidence rates are probably not strictly linear in each variable over the entire range of v and x. Clearly, model (1) has a basic infection reproductive number of $R_0 = \lambda\beta k/(ad\mu)$. Note that R_0 is proportional to λ/d (represents the number of total cells of the liver), which implies that an individual with smaller liver maybe more resistent to virus infections than an individual with a larger one. Lequan Min et al [10] pointed that this is not reasonable and gave another HBV model by using a standard mass action incidence as follows:

$$\begin{cases} \dot{x} = \lambda - dx - \dfrac{\beta vx}{x+y} \\ \dot{y} = \dfrac{\beta vx}{x+y} - ay \\ \dot{v} = ky - \mu v \end{cases} \tag{2}$$

which the variables and parameters have the same meanings as those in model (1). The basic infection reproductive number of model (2) is $R_0 = \beta k/(a\mu)$, which is independent of λ/d and seems more reasonable.

It is currently widely accepted that HBV infection is non-cytopathic. Note that the immune response after viral infection is universal and necessary to eliminate or control the disease. Antibodies, cytokines, natural killer cells, and T cells are essential components of a normal immune response to a virus. Infected hepatocytes are killed not by the virus but by HBV-specific cytotoxic T lymphocytes (CTLs)[11], [12] . It is believed that they are the main host immune factor that limits the development of virus replication in vivo and thus determines virus load([13], [14], [15]). Therefore, the population dynamics of viral infection with CTL response has been paid much attention in the last few decades.

There are several methods to describe the dynamics of CTL during the HBV infection. Based on paper [11], Yongmei Su

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and Min et. al[16] discussed the following model:

$$\begin{cases} \dot{x} = \lambda - dx - \dfrac{\beta v x}{x+y} \\ \dot{y} = \dfrac{\beta v x}{x+y} - ay - pye \\ \dot{v} = ky - \mu v \\ \dot{e} = cy - be \end{cases} \tag{3}$$

which $e(t)$ is the number of CTLs, other parameters are the same as model (1) and (2).

Time delays can not be ignored in models for immune response. As shown in paper [17] and [18], antigenic stimulation generating CTLs may need a period of time τ , i.e., the CTLs response at time t may depend on the population of antigen at a previous time $t - \tau$.

Kaifa Wang[18] discussed an immune model with a time delay of the immune response by making a quasi-steady-state assumption:

$$\begin{cases} \dot{x} = \lambda - dx - \beta v y \\ \dot{y} = \beta v y - ay - pye \\ \dot{e} = cy(t-\tau) - be \end{cases} \tag{4}$$

The meaning of x, y, e are the same of those of model (3). In this paper, based on model (3) and (4), we will discuss the following HBV therapy delay immune models without making a quasi-steady-state assumption:

$$\begin{cases} \dot{x} = \lambda - dx - \dfrac{\beta v x}{x+y} \\ \dot{y} = \dfrac{\beta v x}{x+y} - ay - pye \\ \dot{v} = (k-k_2)y - \mu v \\ \dot{e} = cy(t-\tau) - be \end{cases} \tag{5}$$

which k_2 means the therapy effect of adefovir dipivoxil and $k_2 < k$, other parameters are the same as above models. In the following sections, we let $\bar{k} = k - k_2$

This paper is organized as follows. In Section 2, we give the stability analysis of infection-free equilibrium of system (5). In Section 3, system (5) is used to simulate the clinical data given by K Borroto-Esoda[19]. In section 4, the simulation of the endemic equilibrium will be given. The paper ends with a brief conclusion in Section 5.

II. Analysis of Model

We adopt the following notation to model (5): R^4 is a four-dimensional real Euclidean space with norm $|.|$. For $\tau > 0$, we denote by $C = C([-\tau, 0], R^4)$ the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into R^4 with the topology of uniform convergence, i.e., for $\phi \in C$, the norm of ϕ is defined as $\|\phi\| = \sup_{-\tau \le \theta \le 0} |\phi(\theta)|$. The nonnegative cone of C is defined by $C^+ = C([-\tau, 0], R^4_+)$. The initial conditions for system (5) is given as

$$x(\theta) = \varphi_1(\theta), y(\theta) = \varphi_2(\theta), v(\theta) = \varphi_3(\theta), e(\theta) = \varphi_4(\theta),$$

which $-\tau \le \theta \le 0$. For biological meaning, the initial function $\varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4)$ belongs to C^+. From [20] and [21], It is easily seen that the solution $(x(t), y(t), v(t), e(t))$ with above initial condition exists for all $t \ge 0$ and is unique. Furthermore, it can also be shown that

$$x(t) > 0, y(t) \ge 0, v(t) \ge, e(t) \ge 0.$$

The system (5) has two equilibrium points

$$E_0 = (\lambda/d, 0, 0, 0), E_1 = (\bar{x}, \bar{y}, \bar{v}, \bar{e})$$

which represent the disease-free equilibrium point and the endemic infection equilibrium point respectively, which

$$\bar{x} = \frac{\lambda - a\bar{y} - (pc/b)\bar{y}^2}{d}, \bar{v} = \frac{\bar{k}\bar{y}}{u}, \bar{e} = \frac{\bar{y}}{b},$$

and $\bar{y}$ is the positive of equation:

$$\begin{aligned} \frac{p^2c^2}{b^2}y^3 &+ (2\frac{pca}{b} - \frac{pc\beta\bar{k}}{bu} - \frac{pcd}{b})y^2 \\ &+ (a^2 - da - \frac{\beta\bar{k}a}{u} - \frac{pc\lambda}{b})y + \frac{\beta\bar{k}\lambda}{u} - \lambda a = 0 \end{aligned}$$

Simple analysis shows that only if $R_0 = \beta\bar{k}/a\mu > 1$, the endemic infection equilibrium could exist. The objective of this section is to study the stability of the infection-free equilibriums E_0 when $\tau > 0$.

Theorem 2.1: (1)If $R_0 < 1$, the disease-free equilibrium point E_0 is locally asymptotically stable for any delay $\tau \ge 0$. (2)If $R_0 > 1$, the disease-free equilibrium point E_0 is unstable for any delay $\tau \ge 0$. (3) If $R_0 = 1$, it is a critical case.

Proof: Let $\bar{E} = (\bar{x}, \bar{y}, \bar{v}, \bar{e})$ be an arbitrary equilibrium, the characteristic equation about $\bar{E}$ is given by

$$\Delta = \begin{vmatrix} J_{11} & -\dfrac{\beta\bar{v}\bar{x}}{(\bar{x}+\bar{y})^2} & \dfrac{\beta\bar{x}}{(\bar{x}+\bar{y})} & 0 \\ -\dfrac{\beta\bar{v}\bar{y}}{(\bar{x}+\bar{y})^2} & J_{22} & -\dfrac{\beta\bar{x}}{(\bar{x}+\bar{y})} & p\bar{y} \\ 0 & -\bar{k} & \lambda+\mu & 0 \\ 0 & -ce^{-\lambda\tau} & 0 & \lambda+b \end{vmatrix} = 0,$$

which

$$J_{11} = \lambda + d + \frac{\beta\bar{v}\bar{y}}{(\bar{x}+\bar{y})^2},$$

$$J_{22} = \lambda + \frac{\beta\bar{v}\bar{x}}{(\bar{x}+\bar{y})^2} + a + p\bar{e}.$$

The characteristic equation evaluated at E_0 reduces to

$$\Delta|_{E_0} = \begin{vmatrix} \lambda+d & 0 & \beta & 0 \\ 0 & \lambda+a & -\beta & 0 \\ 0 & -\bar{k} & \lambda+\mu & 0 \\ 0 & -ce^{-\lambda\tau} & 0 & \lambda+b \end{vmatrix} = 0. \tag{6}$$

Obviously, (6) has the following characteristic roots :

$$\begin{aligned} \lambda_1 &= -d,\ \lambda_2 = -b, \\ \lambda_3 &= \frac{-(a+\mu) + \sqrt{(a+\mu)^2 - 4(a\mu - \beta\bar{k})}}{2} \\ \lambda_4 &= \frac{-(a+\mu) - \sqrt{(a+\mu)^2 - 4(a\mu - \beta\bar{k})}}{2} \end{aligned}$$

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If $R_0 < 1$, the four characteristic roots are all negative, so the equilibrium point E_0 is locally asymptotically stable for any delay $\tau \geq 0$.

If $R_0 > 1$, the characteristic root λ_3 must be positive, the disease-free equilibrium point E_0 is unstable for any delay $\tau \geq 0$.

If $R_0 = 1$, characteristic roots $\lambda_1, \lambda_2, \lambda_3$ are negative, λ_4 is zero, which implies the trivial solution of the linearized system of (5) is stable for any time delay $\tau \geq 0$, this proves the conclusion (3). ■

Now we will give the globally asymptotically stability of the disease-free equilibrium point E_0 of system (5), the following lemma will be used.

Lemma 2.1: For any solution $x(t), y(t), v(t), e(t)$ of (5), we have that

$$\limsup_{t\to\infty} x(t) \leq \frac{\lambda}{d}.$$

It is clear that if $0 < x(0) < \lambda/d$, $v(0) > 0$ and $y(0) \geq 0, e(0) \geq 0$, then $0 < x(t) < \lambda/d$ for $t > 0$.

Theorem 2.2: (1) If $R_0 < 1$, the infection-free equilibrium E_0 of system (5) is globally asymptotically stable for any time delay $\tau \geq 0$. (2) If $R_0 = 1$, the infection-free equilibrium E_0 of system (5) is globally attractive for any time delay $\tau \geq 0$.

Proof: Define

$$\begin{aligned} G &= \{(\varphi_1, \varphi_2, \varphi_3, \varphi_4) \in C^+ \mid \\ &\quad \lambda/d \geq \varphi_1 \geq 0, \varphi_2 \geq 0, \varphi_3 \geq 0, \varphi_4 \geq 0\}. \end{aligned}$$

Obviously, G is a positively invariant with respect to system (5).

If $R_0 < 1$, let us define a Lyapunov functional W on $\bar{G}$ as follows:

$$\begin{aligned} W(\varphi) &= \frac{\varepsilon}{2}(\varphi_1(0) - \frac{\lambda}{d})^2 + \frac{\bar{k}}{a}\varphi_2(0) + (1 - \frac{\varepsilon}{\bar{k}})\varphi_3(0) \\ &\quad + \frac{\varepsilon}{c}\varphi_4(0) + \varepsilon\int_{-\tau}^{0} \varphi_2(\xi)d\xi, \end{aligned}$$

where $\bar{k} > \varepsilon > 0$ is a positive constant to be chosen later. It is clear that $W(\varphi)$ is continuous on G. Calculating the time derivative of W along the solution of system (5), we obtain

$$\begin{aligned} \dot{W}|_{(5)} &= -\varepsilon(\frac{\lambda}{d} - \varphi_1(0))(\lambda - d\varphi_1(0) - \frac{\beta\varphi_1(0)\varphi_3(0)}{\varphi_1(0) + \varphi_2(0)}) \\ &\quad + \frac{\bar{k}}{a}(\frac{\beta\varphi_1(0)\varphi_3(0)}{\varphi_1(0) + \varphi_2(0)} - a\varphi_2(0) - p\varphi_2(0)\varphi_4(0)) \\ &\quad + \bar{k}\varphi_2(0) - u\varphi_3(0) - \varepsilon\varphi_2(0) + \frac{\varepsilon u}{\bar{k}}\varphi_3(0) \\ &\quad + \varepsilon\varphi_2(-\tau) - \frac{\varepsilon b}{c}\varphi_4(0) + \varepsilon\varphi_2(0) - \varepsilon\varphi_2(-\tau) \\ &= -\varepsilon d(\frac{\lambda}{d} - \varphi_1(0))^2 + \varepsilon(\frac{\lambda}{d} - \varphi_1(0))\frac{\beta\varphi_1(0)\varphi_3(0)}{\varphi_1(0) + \varphi_2(0)} \\ &\quad + \frac{\bar{k}\beta\varphi_1(0)\varphi_3(0)}{a(\varphi_1(0) + \varphi_2(0))} - \frac{\bar{k}p\varphi_2(0)\varphi_4(0)}{a} \\ &\quad - \frac{\varepsilon b}{c}\varphi_4(0) - \mu\varphi_3(0) + \frac{\varepsilon\mu}{\bar{k}}\varphi_3(0) \\ &\leq -d\varepsilon(\frac{\lambda}{d} - \varphi_1(0))^2 + \varepsilon(\frac{\lambda}{d} - \varphi_1(0))\beta\varphi_3(0) \\ &\quad + \frac{\bar{k}\beta\varphi_3(0)}{a} - \mu\varphi_3(0) + \frac{\varepsilon\mu}{\bar{k}}\varphi_3(0) \\ &\quad - \frac{\bar{k}p\varphi_2(0)\varphi_4(0)}{a} - \frac{\varepsilon b}{c}\varphi_4(0) \\ &= -d\varepsilon(\frac{\lambda}{d} - \varphi_1(0))^2 + (\varepsilon(\frac{\lambda}{d} - \varphi_1(0))\beta \\ &\quad + \mu(\frac{\bar{k}\beta}{a\mu} - 1) + \frac{\varepsilon u}{\bar{k}})\varphi_3(0) - \frac{\bar{k}p\varphi_2(0)\varphi_4(0)}{a} \\ &\quad - \frac{\varepsilon b}{c}\varphi_4(0) \end{aligned}$$

Since $x(t), y(t), v(t), e(t)$ are positive, and from $x(t) \leq \frac{\lambda}{d}$, we know if $R_0 = \frac{\bar{k}\beta}{a\mu} < 1$, then there must be a positive constant $\varepsilon > 0$ such that

$$\varepsilon(\frac{\lambda}{d} - \varphi_1(0))\beta + \mu(\frac{\bar{k}\beta}{a\mu} - 1) + \frac{\varepsilon u}{\bar{k}} < 0,$$

thus $\dot{V} \leq 0$ for any $\varphi \in G$. This shows that $w(\varphi)$ is a Liapunnov functional on the subset G in C^+. Define $E = \{\varphi \in G \mid \dot{W}|_{(5)} = 0\}$, we have

$$E \subset \{\varphi \in G \mid \varphi_1(0) = \frac{\lambda}{d}, \varphi_3(0) = 0, \varphi_4(0) = 0\}.$$

Let M be the largest set in E which is invariant with respect to (5). Clearly, M is not empty since $(\lambda/d, 0, 0, 0) \in M$. For any $\varphi \in M$, let $(x(t), y(t), v(t), e(t))$ be the solution of (5) with the initial function φ. From the invariance of M, we have that$(x(t), y(t), v(t), e(t)) \in M \subset E$ for any $t \in R$. Thus $v(t) \equiv 0, e(t) \equiv 0$ for any $t \in R$. From the second equation of (5), we further have that $y(t) \to 0$ as $t \to +\infty$. We can also show that $x(t) \to 0$ as $t \to +\infty$. Hence, the invariance of M implies that $y(t) \equiv 0, x(t) = \lambda/d$ for any $t \in R$. Therefore, $M = (\lambda/d, 0, 0, 0)$. The classical Liapunov-LaSalle invariance principal [21] shows that $E_0 = (\lambda/d, 0, 0, 0)$ is globally attractive. Since E_0 is locally asymptotically stable, hence E_0 is globally asymptotically stable for any time delay $\tau \geq 0$.

If $R_0 = 1$, we define the following functional on G:

$$W(\varphi) = \frac{k}{a}\varphi_2(0) + \varphi_3(0)$$

It is clear that $W(\varphi)$ is continuous on $\bar{G}$.

$$\begin{aligned} \dot{W}|_{(5)} &= \frac{\bar{k}}{a}\frac{\beta\varphi_1(0)\varphi_3(0)}{\varphi_1(0) + \varphi_2(0)} - \bar{k}\varphi_2(0) - \frac{\bar{k}p}{a}\varphi_2(0)\varphi_3(0) \\ &\quad + \bar{k}\varphi_2(0) - \mu\varphi_3(0) \\ &\leq (\frac{\bar{k}\beta}{a} - \mu)\varphi_3(0) - \frac{\bar{k}p}{a}\varphi_2(0)\varphi_3(0) \\ &= -\frac{\bar{k}p}{a}\varphi_2(0)\varphi_3(0) \end{aligned}$$

Define $E = \{\varphi \in G \mid \dot{W}|_{(5)} = 0\}$, we have

$$E \subset \{\varphi \in G \mid \varphi_2(0) = 0 \text{ or } \varphi_3(0) = 0\}.$$

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Let M be the largest set in E which is invariant with respect to (5). Clearly, M is not empty since $(\lambda/d, 0, 0, 0) \in M$. For any $\varphi \in M$, let $(x(t), y(t), v(t), e(t))$ be the solution of (5) with the initial function φ. From the invariance of M, we have that$(x(t), y(t)v(t), e(t)) \in M \subset E$ for any $t \in R$. If $\varphi_2(0) = 0$, thus $y(t) \equiv 0$ for any $t \in R$. From the third equation of (5), we further have that $v(t) \to 0$ as $t \to +\infty$. Hence, the invariance of M implies that $v(t) \equiv 0$ for any $t \in R$. Similarly we can show $e(t) \equiv 0$ for any $t \in R$. From the first equation of (5), we can know $x(t) = \lambda/d$ for any $t \in R$. Therefore, $M = (\lambda/d, 0, 0, 0)$. If $\varphi_3(0) = 0$, thus $v(t) \equiv 0$ for any $t \in R$. From the second equation of (5), we further have that $y(t) \to 0$ as $t \to +\infty$. Hence, the invariance of M implies that $y(t) \equiv 0$ for any $t \in R$. Similarly we can show $e(t) \equiv 0$ for any $t \in R$. From the first equation of (5), we can know $x(t) = \lambda/d$ for any $t \in R$. Therefore, we can also have $M = (\lambda/d, 0, 0, 0)$. Liapunov-LaSalle invariance principal [21] shows that $E_0 = (\lambda/d, 0, 0, 0)$ is globally attractive for any time delay $\tau \geq 0$. ■

III. Application of Adefovir anti-viral therapy model to clinical data

In this section, we will use the model (5) to simulate the clinical data given by K Borroto-Esoda[19]. K Borroto et al. investigated incidence of adeforvir (AD) resistance over 5 years of therapy in HBeAg-negative patients. The HBV DNA load of a sample patient were given. The patient received 96 months' treatment of AD and a 6 months' off treatment followed by continuous treatment. The following are detailed steps involved in the estimation of model parameters.

1) A human liver contains about 2×10^{11} hepatocytes[4]. A patient has about total 3000ml plasma. Usually, tested virus qualities are in copies/ml. Consequently, we can assume that
$$\lambda/d \approx 2 \times 10^{11}/3000.$$

2) In order to make the solution of the model (5) fit well with respect to the above clinic data, we need to assume that the half-life of a hepatocytes is about 100 days which is shorter than half a year suggested in Ref. [22]. In other words, this is an unknown. And we also assume the half-life of a infected hepatocytes is the same as a uninfected hepatocytes , hence
$$d = a = -\ln(0.5)/100 = 6.9 \times 10^{-3}.$$

3) We assume that $u = 0.68$, that is equivalent to assume that the half life of a virus is about one day [4].

Based on the clinic data and numerical simulation, during the first 24 months' treatment, we can select the other parameters as follows:

$$[\beta, p, k, k_2, c, b, \tau\} = \{0.0708, 1.5 \times 10^{-9}, 2.9, 2.834, 0.25, 0.2251, 10.6].$$

We choose the initial condition as follows:

$$[x(0), y(0), v(0), e(0)] = [5.5556 \times 10^7, 1.1111 \times 10^7, 1.2589 \times 10^7, 5].$$

During the off treatment, since k_2 stands for the therapy effect, we choose $k_2 = 0$, $p = 1.5\times10^{-6}$, $\tau = 2.3$ with other parameters unchanged. During the continuous treatment, we still us the same parameters as the first phase. The simulation result is shown in fig.1

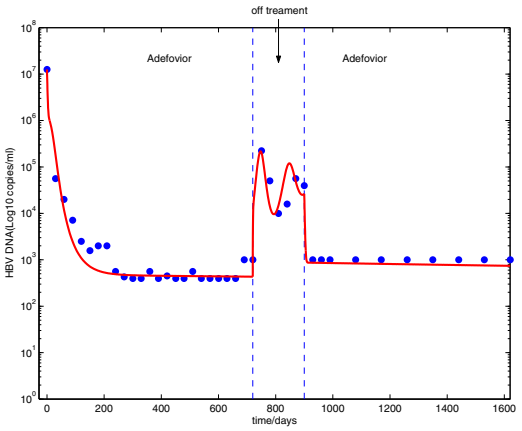

Fig. 1. The dynamic simulation (solid lines)of the treatment model (5), the clinical data are marked by dots.

The simulation data of our model are qualitatively agreement with the clinical ones, especially the HBV DNA rebound shaking data during the off-treatment.

The results show that our time-delay immune model may possibly capture the dynamics of HBV infection and anti-HBV infection treatment.

During above simulation, $R_0 = (k-k_2)\beta/(a*u) = 0.99591 < 1$. We still use the same parameters as above to simulate ten years' therapy, the simulation result is shown in fig.2. The simulation results implies that even without mutation, the patient may need life-long times' therapy.

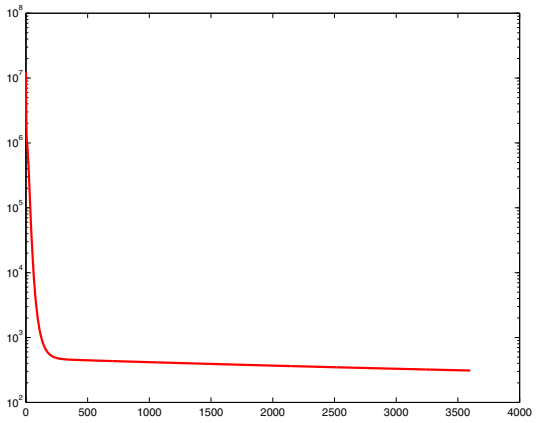

Fig. 2. The dynamic simulation of the treatment model (5) to ten years.

IV. Simulation of the endemic equilibrium E_1

In this section, we will choose some parameters to simulate the dynamical behavior of the endemic equilibrium E_1, and the chosen parameters must satisfy $R_0 = (k-k_2)\beta/(a*u) > 1$.

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First, we chose the same parameters used in fig.2 except for β and k_2, we chose $\beta = 0.0354$ and $k_2 = 1.885$, thus $R_0 = 7.65793 > 1$. The simulation result is shown in fig.3 .

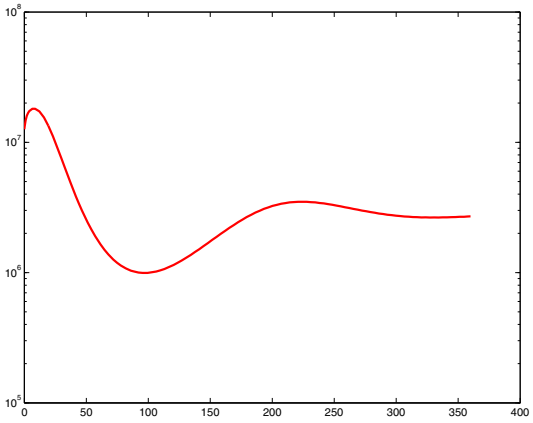

Fig. 3. The simulation of dynamical behaviors of the endemic equilibrium E_1, $R_0 = 7.65793 > 1$.

In clinical test, we often find some patients' HBV DNA couldn't reduce consistently and often rebound and keep shaking in some range under therapy. The simulation in fig.3 shows that if the therapy effect parameter k_2 couldn't make the $R_0 < 1$, the patient couldn't be cured, and the level of HBV DNA would keep near the endemic equilibrium E_1.

On the other hand, in order to find the complex behavior of model (5), we chose the parameters as follows:

$$[\lambda/d, \beta, a, p, \bar{k}, \mu, c, b] = [200, 0.1, 1.2, 0.3, 0.05, 0.45, 0.4, 0.2, 0.3]$$

which $R_0 = \bar{k}\beta/a\mu = 4.5 > 1$. We choose the initial condition$[x(0), y(0), v(0), e(0)] = [1000, 10, 10, 10]$. The simulation of uninfected cells, HBV DNA load and CTL load are showed in figure 4,5,6 under different delay τ. The (x, v, e) phase-space plot is also showed in each figure.

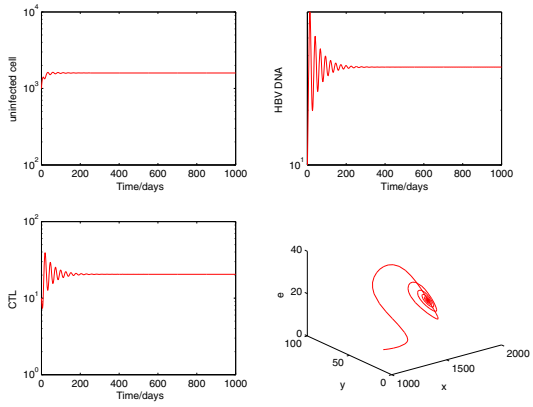

Fig. 4. The simulation of uninfected cells, HBV DNA load and CTL load of model (5) with $\tau = 5.2$.

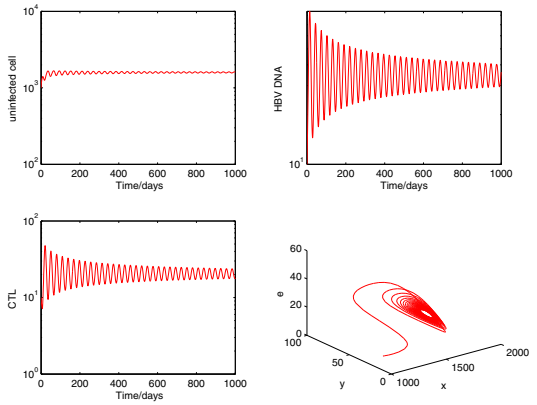

Fig. 5. The simulation of uninfected cells, HBV DNA load and CTL load of model (5) with $\tau = 6.2$.

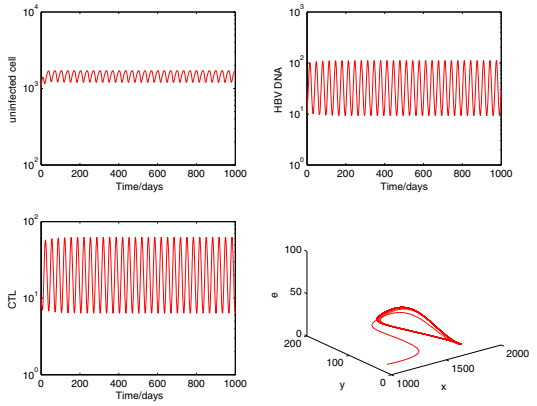

Fig. 6. The simulation of uninfected cells, HBV DNA load and CTL load of model (5) with $\tau = 7.2$.

From the simulation we can see there appears a stability switch $\tau*$ with the increasing of delay τ. when $\tau < \tau*$, the endemic equilibrium E_1 is stable, when $\tau > \tau*$, the E_1 is unstable.

V. Conclusions

In this paper, based on standard mass action incidence, we have discussed a HBV infection therapy model with delayed immune response. A detailed analysis of the local and global asymptotic stability about the viral free equilibrium E_0 are carried out , When $R_0 < 1$, (hence the endemic equilibrium E_1 is not feasible), E_0 is locally asymptotically stable for any $\tau \geq 0$, When $R_0 = 1$(the endemic equilibrium E_1 is also not feasible), the linearized system of model (5) at E_0 is stable for any $\tau \geq 0$. By LyapunovCLaSalle type theorem, we have also proved that the the viral free equilibrium E_0 is global asymptotically stable for any time delay $\tau \geq 0$ if $R_0 < 1$. Simulation shows that the virus could be cleared if therapy effect parameter k_2 could make the $R_0 = \bar{k}\beta/(au) < 1$, but if the treatment was stopped, that is $k_2 = 0$, which make $R_0 > 1$, the level of HBV DNA would rebound quickly and may keep shaking.

On the other hand, if $R_0 > 1$, our model (5) would have endemic equilibrium E_1. For given parameters, simulation shows that there may exist a stable switch $\tau*$, when $\tau < \tau*$, the endemic equilibrium E_1 is stable, but if $\tau > \tau*$, the endemic equilibrium E_1 would be unstable.

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