Dynamical behaviour of a delay differential equation of Hepatitis B Virus

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***Abstract*—In this paper, we investigate a class of virus dynamics model with intracellular delay and nonlinear infection rate of saturated functional response. The basic reproduction number R_0 for the viral infection is derived, and the global dynamics behavior are completely determined by R_0. By constructing suitable Lyapunov functional and using LaSalle invariant principle for the delay differential equations, we find when $R_0 \le 1$, the infection-free equilibrium is globally asymptotically stable, and when $R_0 > 1$, the infection equilibrium is also globally asymptotically stable .**

Keywords—intracelluar delay; Lyapunov functional; LaSalle invariant principle; Global stabiliy

I. INTRODUCTION

Hepatitis B virus (HBV) infection is a significant public health problem which may lead to chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). It is reported that some 2 billion people have been infected with the virus, with 5 million new cases every year, which means a major challenge to global public health [1-2]. Currently, about 350 million people worldwide live with chronic HBV infection [3].

Mathematical models are often used to interpret experimental and clinical results of (anti-) HIV, HBV and HCV infections [4, 5, 6, 7, 8]. A basic viral infection model [5, 7] has been widely used for investigating the dynamics behavior of infections agents such as HBV, Hepatitis C virus (HCV), which has the following forms:

$$\begin{cases} \dot{x} = \lambda - dx - \beta xv \\ \dot{y} = \beta xv - ay \\ \dot{v} = ky - \mu v \end{cases} \tag{1.1}$$

where x, y and v are numbers of uninfected(susceptible) liver cells, infected liver cells and free virus, respectively. And uninfected cells are produced at a constant rate λ, die at a density-dependent rate dx, and become infected with a rate βxv; infected cells are produced at rate βxv and die at a density-dependent rate ay; free virus particles are released from infected cells at a rate ky and die at a rate μv.

In the model (1.1), the basic infection reproductive number of model is $R_0 = \lambda\beta k / ad\mu$, which has been pointed unreasonable when used for HBV infection model [9]. Paper [9] used standard incidence $\beta vx/(x+y)$ to take the place of the bilinear mass action incidences βvx in model (1.1) and the corresponding basic infection reproductive number $R_0 = \beta k / a\mu$ is more reasonable. However, Yu Ji [10] pointed that at the beginning of the infection, the amount of virus is relatively small compared with uninfected cells, and the infection rate should be direct proportional to the viral load which can be represented as βv. Then, along with the rapid increase of viral load and the decrease of uninfected cells, the infection will reach saturated state, and the infection rate $\beta xv/(x+v)$ should be reasonable. The model given by Yu Ji [10] has following form:

$$\begin{cases} \dot{x}(t) = \lambda - dx(t) - \dfrac{\beta x(t)v(t)}{x(t)+v(t)} \\ \dot{y}(t) = \dfrac{\beta x(t)v(t)}{x(t)+v(t)} - ay(t) \\ \dot{v}(t) = ky - uv(t) \end{cases} \tag{1.2}$$

The above model has the same basic infection reproductive number of $R_0 = \beta k / a\mu$ as the model in paper [9], which shows the saturated infection rate $\beta xv/(x+v)$ can also be used for HBV infection.

On the other hand, as shown in paper [11, 12], we should take into account the latently infected cells (such cells contain the virus but are not producing it) and the actively infected cells (such cells are producing the virus). So the time delays can not be ignored in virus infection models. Based on standard incidence, Stephen A. Gourley, Yang Kuang and John D. Nagy [13] gave a delay virus infection model as following,

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$$\begin{cases} \dot{x}(t) = \lambda - dx - \dfrac{\beta v(t)x(t)}{x(t)+y(t)+e(t)} \\ \dot{e}(t) = -de(t) + \dfrac{\beta v(t)x(t)}{x(t)+y(t)+e(t)} - \dfrac{e^{-d\tau}\beta v(t-\tau)x(t-\tau)}{x(t-\tau)+y(t-\tau)+e(t-\tau)} \\ \dot{y}(t) = \dfrac{e^{-d\tau}\beta v(t-\tau)x(t-\tau)}{x(t-\tau)+y(t-\tau)+e(t-\tau)} - ay \\ \dot{v}(t) = ky(t) - \mu v(t) \end{cases} \quad (1.3)$$

where $x(t)$ represents the number of uninfected cells, $y(t)$ represents the number of infected cells, $e(t)$ represents the number of latently infected cells, and $v(t)$ represents the number of free virions. τ is the time for the latently infected cells to become productive.

Yang Kuang [13] didn't give full analysis of (1.3) and only prove the global asymptotically stability of the infection-free equilibrium and the infection equilibrium of the following simplified the model [14]:

$$\begin{cases} \dot{x}(t) = \lambda - dx - \dfrac{\beta k y(t)x(t)}{\mu(x(t)+y(t))} \\ \dot{e}(t) = -de(t) + \dfrac{\beta k y(t)x(t)}{\mu(x(t)+y(t))} - \dfrac{e^{-d\tau}\beta k y(t-\tau)x(t-\tau)}{\mu(x(t-\tau)+y(t-\tau))} \\ \dot{y}(t) = \dfrac{e^{-d\tau}\beta k y(t-\tau)x(t-\tau)}{\mu(x(t-\tau)+y(t-\tau))} - ay(t) \end{cases} \quad (1.4)$$

Based on above discussions, in this paper, we set up a new HBV infection delay model with saturated infection rate $\beta xv/(x+v)$:

$$\begin{cases} \dot{x}(t) = \lambda - dx(t) - \dfrac{\beta x(t)v(t)}{x(t)+v(t)} \\ \dot{y}(t) = \dfrac{\beta x(t)v(t)}{x(t)+v(t)} - \dfrac{e^{-p\tau}\beta x(t-\tau)v(t-\tau)}{x(t-\tau)+v(t-\tau)} - py(t) \\ \dot{z}(t) = \dfrac{e^{-p\tau}\beta x(t-\tau)v(t-\tau)}{x(t-\tau)+v(t-\tau)} - az(t) \\ \dot{v}(t) = kz(t) - bv(t) \end{cases} \quad (1.5)$$

where $x(t)$, $z(t)$ and $v(t)$ represent the number of uninfected cells, infected cells and free virus, respectively. $y(t)$ represents the number of the latently infected cells, In the model (1.3) and (1.4), the death rate of uninfected cells and the latently infected cells are supposed to be the same, but in our model (1.5), we needn't the suppose, which is more reasonable.

This paper is organized as follows. In the Section II, we derive the basic reproduction number R_0 and give the infection-free equilibrium and the infection equilibrium. In section III, we prove that the solution of system (1.5) is non-negative and bounded. The global stability analysis of the infection-free equilibrium and the infection equilibrium are given in Section IV. This paper ends with a brief conclusion in Section V.

II. BASIC REPRODUCTIVE NUMBER AND EQUILIBRIUM

Similar to paper [14], a direct computation shows that the basic reproductive number of model (1.5) is $R_0 = e^{-p\tau}\beta k/ab$. Obviously, it is irrelative to λ/d which is desirable. The model (1.5) has an infection-free equilibrium $E_0 = (x_0, 0, 0, 0)$, which $x_0 = \lambda/d$. If $R_0 > 1$, an infection equilibrium $E_1 = (x^*, y^*, z^*, v^*)$ exists, where

$$x^* = \frac{\lambda R_0}{dR_0 + \beta(R_0 - 1)}, \qquad y^* = \frac{\beta(1-e^{-p\tau})(R_0-1)}{pR_0}x^*,$$

$$z^* = \frac{b(R_0-1)}{k}x^*, \qquad v^* = (R_0-1)x^*.$$

III. NON-NEGATIVITY AND BOUNDEDNESS OF SOULUTIONS

Let $C = C([-\tau, 0]; R^4)$ be the Banach space of continuous functions from $[-\tau, 0]$ to R^4 equipped with the sup-norm. The initial condition of (1.5) is given as

$$x(\theta) = \phi_1(\theta), y(\theta) = \phi_2(\theta), z(\theta) = \phi_3(\theta), v(\theta) = \phi_4(\theta), \quad \theta \in [-\tau, 0],$$

where $\phi = (\phi_1, \phi_2, \phi_3, \phi_4)^T \in C$ such that $\phi_i(\theta) \geq 0 (-\tau \leq \theta \leq 0)$ for $i = 1, 2, 3, 4)$.

Proposition2.1. Let $(x(t), y(t), z(t), v(t))^T$ be any solution of system (1.5), then under the nonnegative initial conditions, all solutions $(x(t), y(t), z(t), v(t))^T$ are non-negative on $[0, +\infty)$ and bounded.

Proof. If $x(t)$ were to lose its non-negativity on some local existence interval $[0, T]$ for some constant $T > 0$, there would be a time at $t_1 > 0$ such that $x(t_1) = 0$. By the first equation of (1.5) we have $x'(t_1) = \lambda > 0$. That means $x(t) < 0$ for $t \in (t_1 - \varepsilon, t_1)$, where ε is an arbitrarily small positive constant. This leads to a contradiction. It follows that $x(t)$ is always positive. Further, from the third and forth equation in (1.5), we have

$$z(t) = z(0)e^{-pt} + \int_0^t \frac{e^{-p\tau}\beta x(\theta-\tau)v(\theta-\tau)}{x(\theta-\tau)+v(\theta-\tau)} e^{-p(t-\theta)} d\theta$$

$$v(t) = v(0)e^{-bt} + \int_0^t kz(\theta)e^{-b(t-\theta)} d\theta$$

Then, it is easy to see that $z(t)$ and $v(t)$ are non-negative on $[0, T]$.

From the second equation of system (1.5), we know that

$$e(t) = \beta \int_{t-\tau}^{t} \frac{e^{-p(t-\theta)}v(\theta)x(\theta)}{v(\theta)+x(\theta)} d\theta$$

Therefore, we get that $e(t)$ is non-negative.

Adding the first three equations of (1.5), we get

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$$(x(t)+y(t)+z(t))' = \lambda - dx(t) - py(t) - az(t)$$
$$\le \lambda - \tilde{\mu}(x(t)+y(t)+z(t))$$

where $\tilde{\mu} = \min\{d, p, a\}$, thus we can have

$$\limsup_{t\to\infty}(x(t)+(y)+z(t)) \le \frac{\lambda}{\tilde{\mu}}.$$

So by the fourth equation of (1.5), we have

$$v'(t) = kz(t) - bv(t) \le k\frac{\lambda}{\tilde{\mu}} - bv(t).$$

which imply $\limsup_{t\to\infty} v(t) \le \frac{k\lambda}{b\tilde{\mu}}$, so $x(t), y(t), z(t), v(t)$ are ultimately bounded.

IV. GLOBAL ASYMPTOTIC STABILITY

In this section, we shall investigate the global asymptotic stability of system (1.5) by Lyapunov functional approach. It is seen that for the stability purpose, only the first, third and forth equation of system (1.5) need to be considered.

Theorem 4.1. If $R_0 \le 1$, the infection-free equilibrium point E_0 is global asymptotically stable.

Proof. Consider the following Lyapunov functional

$$L_0(t) = x(t) - \int_{x_0}^{x(t)} \frac{x_0}{x_0+v(t)}\frac{\eta+v(t)}{\eta}d\eta + e^{p\tau}z(t) + e^{p\tau}\frac{a}{k}v(t)$$
$$+\int_{t-\tau}^{t}\frac{\beta x(\theta)v(\theta)}{x(\theta)+v(\theta)}d\theta$$

By calculating the time derivative of $L_0 = (x, y, z, v)$ along the positive solutions of model (1.5), we obtain

$$\dot{L}_0(t) = \dot{x}(t) - \frac{x_0}{x_0+v}\frac{x+v}{x}\dot{x}(t) + e^{p\tau}\dot{z}(t) + e^{p\tau}\frac{a}{k}\dot{v}(t) + \frac{\beta x(t)v(t)}{x(t)+v(t)}$$
$$-\frac{\beta x(t-\tau)v(t-\tau)}{x(t-\tau)+v(t-\tau)}$$

$$= [1 - \frac{x_0}{x_0+v(t)}\frac{x(t)+v(t)}{x(t)}][\lambda - dx(t) - \frac{\beta x(t)v(t)}{x(t)+v(t)}]$$
$$+e^{p\tau}[\frac{e^{-p\tau}\beta x(t-\tau)v(t-\tau)}{x(t-\tau)+v(t-\tau)} - az(t)] + e^{p\tau}\frac{a}{k}[kz(t) - bv(t)]$$
$$+\frac{\beta x(t)v(t)}{x(t)+v(t)} + \frac{\beta x(t-\tau)v(t-\tau)}{x(t-\tau)+v(t-\tau)}$$

$$= \lambda - dx(t) - \frac{x_0}{x_0+v(t)}\frac{x(t)+v(t)}{x(t)}[\lambda - dx(t) - \frac{\beta x(t)v(t)}{x(t)+v(t)}]$$
$$-e^{p\tau}\frac{abv(t)}{k}$$

Note that $\lambda = dx_0$, $R_0 = \frac{e^{-p\tau}k\beta}{ab}$, we can have

$$\dot{L}_0(t) = -\frac{dv(t)(x_0-x(t))^2}{x(t)(x_0+v(t))} + \frac{\beta x_0 v(t)}{x_0+v(t)} - \frac{e^{p\tau}abv(t)}{k}$$

$$\le -\frac{dv(t)(x_0-x(t))^2}{x(t)(x_0+v(t))} + \beta v(t) - \frac{e^{p\tau}abv(t)}{k}$$

$$= -\frac{dv(t)(x_0-x(t))^2}{x(t)(x_0+v(t))} + \frac{e^{p\tau}ab}{k}(\frac{e^{-p\tau}k\beta}{ab} - 1)v(t)$$

$$= -\frac{dv(t)(x_0-x(t))^2}{x(t)(x_0+v(t))} + \frac{e^{p\tau}ab}{k}(R_0 - 1)v(t)$$

Obviously, $-\frac{dv(t)(x_0-x(t))^2}{x(t)(x_0+v(t))} \le 0$, and if $R_0 < 1$, so we have that for all $x, y, z, v > 0$, $\dot{L}_0(x, y, z, v) \le 0$. Therefore, the infection-free equilibrium E_0 is stable. $\dot{L}_0(x, y, z, v) = 0$ if and only if $x = x_0$, $v = 0$. Let M be the largest invariant set in $\{(x, y, z, v) \in R_+^4 : \dot{L}_0(x, y, z, v) = 0\}$, then from the second and forth equation of (1.5), we obtain $y = z = 0$, so $M = \{E_0\}$. Then we get the global asymptotical stability of by the LaSalle invariance principle. When $R_0 = 1$ we have $\dot{W}_0(x, y, z, v) = 0$ if and only if $x = x_0$ Let M be the largest invariant set in $\{(x, y, z, v) \in R_+^4 : \dot{L}_0(x, y, z, v) = 0\}$ from the first equation of (1.5), we obtain $v = 0$. Then from the second and third equation of (1.5), we also obtain $y = z = 0$, then it is easy to know the largest invariant set of is E_0, so by LaSelle invariance principle, we can know $R_0 = 1$ can also ensure the globally asymptotical stability of E_0.

Theorem 4.2. If $R_0 > 1$, the infection equilibrium E_1 of system (1.5) is globally asymptotically stable for any time delay $\tau \ge 0$.

Proof. Define a Lyapunov functional

$$L_1(t) = x(t) - x^* - \int_{x^*}^{x(t)}\frac{x^*}{\theta}\frac{\theta+v^*}{x^*+v^*}d\theta + e^{p\tau}[z(t) - z^* - z^*\ln\frac{z(t)}{z^*}]$$
$$+e^{p\tau}\frac{a}{k}[v(t) - v^* - v^*\ln\frac{v(t)}{v^*}]$$
$$+e^{p\tau}az^*\int_{t-\tau}^{t} g(\frac{\beta x(\theta)v(\theta)}{e^{p\tau}az^*(x(\theta)+v(\theta))})d\theta$$

where $g(x) = x - 1 - \ln x, x > 0$.

By calculating the time derivative of $L_0 = (x, y, z, v)$ along the positive solutions of model (1.5), we derive

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$$\dot{L}_1(t)=\dot{x}(t)-\frac{x^*}{x(t)}\frac{x(t)+v^*}{x^*+v^*}\dot{x}(t)+e^{p\tau}[\dot{z}(t)-\frac{z^*}{z(t)}\dot{z}(t)]$$
$$+e^{p\tau}\frac{a}{k}[\dot{v}(t)-\frac{v^*}{v}\dot{v}(t)]+\frac{\beta x(t)v(t)}{x(t)+v(t)}-\frac{\beta x(t-\tau)v(t-\tau)}{x(t-\tau)+v(t-\tau)}$$
$$+e^{p\tau}az^*\ln\frac{x(t-\tau)v(t-\tau)}{x(t-\tau)+v(t-\tau)}\frac{x(t)+v(t)}{x(t)v(t)}$$
$$=\lambda-dx(t)-\frac{\beta x(t)v(t)}{x(t)+v(t)}-\frac{x^*}{x(t)}\frac{x(t)+v^*}{x^*+v^*}[\lambda-dx(t)-$$
$$-\frac{\beta x(t)v(t)}{x(t)+v(t)}]+e^{p\tau}[\frac{e^{-p\tau}\beta x(t-\tau)v(t-\tau)}{x(t-\tau)+v(t-\tau)}-az(t)]-e^{p\tau}\frac{z^*}{z}$$
$$[\frac{e^{-p\tau}\beta x(t-\tau)v(t-\tau)}{x(t-\tau)+v(t-\tau)}-az(t)]+e^{p\tau}\frac{a}{k}[kz(t)-bv(t)]$$
$$-e^{p\tau}\frac{a}{k}\frac{v^*}{v(t)}[kz(t)-bv(t)]+\frac{\beta x(t)v(t)}{x(t)+v(t)}-\frac{\beta x(t-\tau)v(t-\tau)}{x(t-\tau)+v(t-\tau)}$$
$$+e^{p\tau}az^*\ln\frac{x(t-\tau)v(t-\tau)}{x(t-\tau)+v(t-\tau)}\frac{x(t)+v(t)}{x(t)v(t)}$$

Note that

$$\lambda=dx^*+\frac{\beta x^*v^*}{x^*+v^*},\ \frac{\beta x^*v^*}{x^*+v^*}=az^*e^{p\tau},\ \frac{b}{k}=\frac{z^*}{v^*}.$$

$$\dot{L}_1=\frac{-dv^*(x(t)-x^*)^2}{x(t)(x^*+v^*)}-e^{p\tau}az^*[\frac{x^*}{x(t)}\frac{x(t)+v^*}{x^*+v^*}-1-\ln\frac{x^*}{x(t)}\frac{x(t)+v^*}{x^*+v^*}]$$
$$-e^{p\tau}az^*\ln\frac{x^*}{x(t)}\frac{x(t)+v^*}{x^*+v^*}-e^{p\tau}az^*[\frac{z^*}{z(t)}\frac{x(t-\tau)v(t-\tau)}{x^*v^*}\frac{x^*+v^*}{x(t-\tau)+v(t-\tau)}$$
$$-1-\ln\frac{z^*}{z(t)}\frac{x(t-\tau)v(t-\tau)}{x^*v^*}\frac{x^*+v^*}{x(t-\tau)+v(t-\tau)}]-e^{p\tau}az^*\ln\frac{z^*}{z}$$
$$\frac{x(t-\tau)v(t-\tau)}{x^*v^*}\frac{x^*+v^*}{x(t-\tau)+v(t-\tau)}-e^{p\tau}az^*[\frac{x(t)+v(t)}{x(t)+v^*}-1-\ln\frac{x(t)+v(t)}{x(t)+v^*}]$$
$$-e^{p\tau}az^*\ln\frac{x(t)+v(t)}{x(t)+v^*}-e^{p\tau}az^*[\frac{z(t)v^*}{z^*v(t)}-1-\ln\frac{z(t)v^*}{z^*v(t)}]-e^{p\tau}az^*\ln\frac{z(t)v^*}{z^*v(t)}$$
$$+e^{p\tau}az^*[-1-\frac{v(t)}{v^*}+\frac{v(t)}{v^*}\frac{x(t)+v^*}{x(t)+v(t)}+\frac{x(t)+v(t)}{x(t)+v^*}]$$
$$+e^{p\tau}az^*\ln\frac{x(t-\tau)v(t-\tau)}{x(t-\tau)+v(t-\tau)}\frac{x(t)+v(t)}{x(t)v(t)}$$
$$=\frac{-dv^*(x(t)-x^*)^2}{x(t)(x^*+v^*)}-e^{p\tau}az^*g(\frac{x^*}{x(t)}\frac{x(t)+v^*}{x^*+v^*})$$
$$-e^{p\tau}az^*g(\frac{z^*}{z(t)}\frac{x(t-\tau)v(t-\tau)}{x^*v^*}\frac{x^*+v^*}{x(t-\tau)+v(t-\tau)})$$
$$-e^{p\tau}az^*g(\frac{z(t)}{z^*}\frac{v^*}{v(t)})-e^{p\tau}az^*g(\frac{x(t)+v(t)}{x(t)+v^*})$$
$$-\frac{e^{p\tau}az^*x(t)(v(t)-v^*)^2}{v^*(x(t)+v(t))(x(t)+v^*)}$$

Since for all $x>0, g(x)\le 0$ and $\frac{-dv^*(x(t)-x^*)^2}{x(t)(x^*+v^*)}\le 0$, so we know that $\dot{L}_1(t)\le 0$. From above, we obtain $\dot{L}_1(t)=0$ if and only if $x=x^*, z=z^*, v=v^*$. Let M be the largest compact invariant set in $\Gamma=\{(x(t),y(t),z(t),v(t)\ \big|\dot{L}_1(t)=0\}$, then from the second equation, we obtain $y=y^*$. So M is just the singleton E_1. By the LaSalle invariance principle, we conclude that the infected equilibrium E_1 of system (1.5) is globally asymptotically stable.

V. SUMMARY AND DISCUSSIONS

In this paper, we consider a new model with intracellular delay and nonlinear infection rate of saturated functional response. By constructing suitable Lyapunov functions and using LaSalle invariance principle, we have proven that the infection-free equilibrium is global asymptotic stable when $R_0\le 1$. And if $R_0>1$, there exists an infection equilibrium and we also get its global asymptotic stability by constructing Lyapunov functional .

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