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A NOTE FOR THE GLOBAL STABILITY OF A DELAY DIFFERENTIAL EQUATION OF HEPATITIS B VIRUS INFECTION

Bao-Zhu Guo

Academy of Mathematics and Systems Science
Academia Sinica, Beijing 100190, China
and
School of Computational and Applied Mathematics
University of the Witwatersrand, Wits 2050, Johannesburg, South Africa
and
School of Mathematical Sciences, Shanxi University, Taiyuan 030006, China

Li-Ming Cai

Academy of Mathematics and Systems Science
Academia Sinica, Beijing 100190, China
and
Department of Mathematics, Xinyang Normal University, Henan, 464000, China

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Abstract. The global stability for a delayed HIV-1 infection model is investigated. It is shown that the global dynamics of the system can be completely determined by the reproduction number, and the chronic infected equilibrium of the system is globally asymptotically stable whenever it exists. This improves the related results presented in *[S. A. Gourley, Y. Kuang and J.D.Nagy, Dynamics of a delay differential equation model of hepatitis B virus infection, Journal of Biological Dynamics, 2(2008), 140-153].*

1. **Introduction.** In this note, we consider a hepatitis B virus infection model with time delay that was proposed and investigated in [1]. It is a refinement of earlier basic virus model with the mass action action incidence [15]. Based on biology grounds [13], the model in [1] makes use of the more realistic standard incidence function and a time delay in virus production. Their model is as following:

$$\begin{aligned}
\dot{x}(t) &= \lambda - dx - \frac{\beta x(t)v(t)}{x(t)+y(t)+e(t)},\\
\dot{e}(t) &= -de(t) + \frac{\beta x(t)v(t)}{x(t)+y(t)+e(t)} - \frac{\beta e^{-d\tau}x(t-\tau)v(t-\tau)}{x(t-\tau)+y(t-\tau)+e(t-\tau)},\\
\dot{y}(t) &= \frac{\beta e^{-d\tau}x(t-\tau)v(t-\tau)}{x(t-\tau)+y(t-\tau)+e(t-\tau)} - ay(t),\\
\dot{v}(t) &= ky(t) - \mu v(t),
\end{aligned} \tag{1}$$

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Corresponding author: Li-Ming Cai, Department of Mathematics, Xinyang Normal University, Henan, 464000, China.

where $x(t)$ and $y(t)$ represent the number of uninfected cells and infected cells, respectively. $e(t)$ represents the number of exposed cells, that is, the cells that have acquired the virus but are not yet producing new virions. $v(t)$ denotes the number of free virions. τ is the time delay for virion production. Here, the positive constant λ is the rate at which new uninfected live cells are generated. The positive constant d is the per-capita death rate of uninfected live cells. Infected live cells are killed by immune cells at rate ay and produce free virions at rate ky, where k is what so-called 'burst' constant. Free virions are cleared by lymphatic and other mechanisms at rate μv, where μ is a constant. $\beta > 0$ is a incidence rate coefficient describing the infection process.

The initial conditions for system (1) are:

$$\begin{aligned} &x(s) = x_0(s),\ y(s) = y_0(s),\ v(s) = v_0(s),\ s \in [-\tau, 0], \\ &e_0(0) = \beta \int_{-\tau}^{0} \frac{e^{ds} v_0(s) x_0(s)}{x_0(s) + y_0(s) + e_0(s) ds}, \end{aligned} \tag{2}$$

where x_0, y_0, and v_0 are nonnegative functions.

Based on some observations of virus particles v, the system (1) is simplified in [1] as the following:

$$\begin{aligned} \dot{x}(t) &= \lambda - dx - \frac{\beta k x(t) y(t)}{\mu(x(t) + y(t))}, \\ \dot{e}(t) &= -de(t) + \frac{\beta k x(t) y(t)}{\mu(x(t) + y(t))} - \frac{\beta k e^{-d\tau} x(t-\tau) y(t-\tau)}{\mu(x(t-\tau) + y(t-\tau))}, \\ \dot{y}(t) &= \frac{\beta k e^{-d\tau} x(t-\tau) y(t-\tau)}{\mu(x(t-\tau) + y(t-\tau))} - ay(t). \end{aligned} \tag{3}$$

A direct computation shows that the basic infection reproduction number for system (3) is

$$R_0 = \frac{\beta k e^{-d\tau}}{a\mu}, \tag{4}$$

which has two equilibria: the infection free equilibrium $E_f = (x_0, 0, 0)$, and the infected equilibrium $E^* = (x^*, e^*, y^*)$, where

$$x_0 = \frac{\lambda}{d}, \quad y^* = (R_0 - 1)x^*, \quad e^* = \frac{a(e^{d\tau} - 1)}{d} x^*, \quad x^* = \frac{\lambda}{d + ae^{d\tau}(R_0 - 1)}. \tag{5}$$

The following results Theorems 1.1-1.2 come from [1].

Theorem 1.1. *If $R_0 < 1$, the infection free equilibrium E_f of system (3) is globally asymptotically stable.*

Theorem 1.2. *If $R_0 > 1$, the chronic infected equilibrium E^* of system (3) is locally asymptotically stable.*

The following result for global convergence of the infected equilibrium E^* of system (3) is a corollary of Theorem 4.3 in [1].

Theorem 1.3. *Suppose that $R_0 > 1$, and one of the following two conditions are satisfied:*

$$R_0 \geq 2 \ \text{or}\ d \geq \frac{\beta k (R_0 - 1)(2 - R_0)}{\mu R_0^2}.$$

Then the infected equilibrium E^* of system (3) is globally asymptotically stable for all non-negative initial data such that $y_0(s) \neq 0,\ s \in [-\tau, 0]$.

The object of this note is to generalize the Theorem 1.3, and show that the infected equilibrium E^* of system (3) is always globally asymptotically stable as long as it exists, The approach here is to use a Lyapunov functional, which was adopted widely in [2]–[12] to get the global dynamical properties of some epidemiological models with or without delay.

2. **Global asymptotic stability of system (3).** In this section, we shall investigate the global asymptotic stability of of system (3) by Lyapunov functional approach. It is seen that for the stability purpose, only the first and third equation of system (3) need to be considered.

Theorem 2.1. *The infected equilibrium E^* of system (3) is globally asymptotically stable for $R_0 > 1$.*

Proof. Consider the following Lyapunov functional

$$\begin{aligned} W(t) &= x(t) - x^* - \int_{x^*}^{x(t)} \frac{x^*(\theta + y^*)}{\theta(x^* + y^*)} d\theta + e^{d\tau}\left[y(t) - y^* - y^* \ln \frac{y(t)}{y^*}\right] \\ &\quad + ae^{d\tau} y^* \int_{t-\tau}^{t} g\left(\frac{\beta k x(\theta) y(\theta)}{a\mu e^{d\tau} y^*(x(\theta) + y(\theta))}\right) d\theta, \end{aligned} \tag{6}$$

where $g(x) = x - 1 - \ln x, x \in \mathbb{R}^+$. Obviously, $g : \mathbb{R}^+ \to \mathbb{R}^+$ attains its strict global minimum at $x = 1$ and $g(1) = 0$. Since

$$x(t) - x^* - \int_{x^*}^{x(t)} \frac{x^*(\theta + y^*)}{\theta(x^* + y^*)} d\theta = \frac{x^* y^*}{x^* + y^*}\left(\frac{x(t)}{x^*} - 1 - \ln \frac{x(t)}{x^*}\right) = \frac{x^* y^*}{x^* + y^*} g\left(\frac{x(t)}{x^*}\right),$$

and $g(x) \geq 0$ for $x \geq 0$, $W(t) \geq 0$ with equality holding if and only if $\frac{x(t)}{x^*} = \frac{y(t)}{y^*} = 1$ for all $t \geq 0$.

Finding the time derivation of $W(t)$ along the positive solution of system (3) gives

$$\begin{aligned} \dot{W}(t)|_{(3)} &= \dot{x}\left(1 - \frac{x^*(x + y^*)}{x(x^* + y^*)}\right) + e^{d\tau}\dot{y}\left(1 - \frac{y^*}{y}\right) \\ &\quad + \frac{\beta k x y}{\mu(x + y)} - ae^{d\tau} y^* \ln \frac{\beta k x y}{\mu a e^{d\tau} y^*(x + y)} - \frac{\beta k x(t-\tau) y(t-\tau)}{\mu(x(t-\tau) + y(t-\tau))} \\ &\quad + ae^{d\tau} y^* \ln \frac{\beta k x(t-\tau) y(t-\tau)}{a\mu e^{d\tau} y^* \mu(x(t-\tau) + y(t-\tau))} \\ &= \left(\lambda - dx - \frac{\beta k x y}{\mu(x + y)}\right)\left(1 - \frac{x^*(x + y^*)}{x(x^* + y^*)}\right) \\ &\quad + e^{d\tau}\left(\frac{\beta k e^{-d\tau} x(t-\tau) y(t-\tau)}{\mu(x(t-\tau) + y(t-\tau))} - ay\right)\left(1 - \frac{y^*}{y}\right) \\ &\quad + \frac{\beta k x y}{\mu(x + y)} - ae^{d\tau} y^* \ln \frac{\beta k x y}{\mu a e^{d\tau} y^*(x + y)} - \frac{\beta k x(t-\tau) y(t-\tau)}{\mu(x(t-\tau) + y(t-\tau))} \\ &\quad + ae^{d\tau} y^* \ln \frac{\beta k x(t-\tau) y(t-\tau)}{a\mu e^{d\tau} y^* \mu(x(t-\tau) + y(t-\tau))}. \end{aligned} \tag{7}$$

Since (x^*, y^*) is a positive equilibrium of system (3), it follows that

$$\lambda = dx^* + \frac{\beta k x^* y^*}{\mu(x^* + y^*)}, \quad \frac{\beta k x^* y^*}{\mu(x^* + y^*)} = ae^{d\tau} y^*. \tag{8}$$

From (7) and (8), we have

$$
\begin{aligned}
&\dot{W}(t)|_{(3)}\\
&= d\,(x^*-x)\left(1-\frac{x^*(x+y^*)}{x(x^*+y^*)}\right)+ae^{d\tau}y^*\left(1-\frac{x^*(x+y^*)}{x(x^*+y^*)}+\frac{y(x+y^*)}{y^*(x+y)}-\frac{y}{y^*}\right)\\
&\quad-\frac{y^*}{y}\frac{\beta k\ x(t-\tau)y(t-\tau)}{\mu(x(t-\tau)+y(t-\tau))}+ae^{d\tau}y^*-ae^{d\tau}y^*\ln\frac{\beta kxy}{\mu ae^{d\tau}y^*(x+y)}\\
&\quad+ae^{d\tau}y^*\ln\frac{\beta kx(t-\tau)y(t-\tau)}{a\mu e^{d\tau}y^*\mu(x(t-\tau)+y(t-\tau))}\\
&= d\,(x^*-x)\left(1-\frac{x^*(x+y^*)}{x(x^*+y^*)}\right)+ae^{d\tau}y^*\left\{\left(1-\frac{y(x+y^*)}{y^*(x+y)}\right)\left(\frac{x+y}{x+y^*}-1\right)\right.\\
&\quad-\left[\frac{x+y}{x+y^*}-1-\ln\frac{x+y}{x+y^*}\right]-\left[\frac{x^*(x+y^*)}{x(x^*+y^*)}-1-\ln\frac{x^*(x+y^*)}{x(x^*+y^*)}\right]-\ln\frac{x+y}{x+y^*}\\
&\quad\left.-\ln\frac{x^*(x+y^*)}{x(x^*+y^*)}\right\}\\
&\quad-ae^{d\tau}y^*\left[\frac{(x^*+y^*)y(t-\tau)x(t-\tau)}{x^*y(x(t-\tau)+y(t-\tau))}-1-\ln\frac{(x^*+y^*)y(t-\tau)x(t-\tau)}{x^*y(x(t-\tau)+y(t-\tau))}\right]\\
&\quad-ae^{d\tau}y^*\left[\ln\frac{(x^*+y^*)y(t-\tau)x(t-\tau)}{x^*y(x(t-\tau)+y(t-\tau))}+\ln\frac{\beta kxy}{\mu ae^{d\tau}y^*(x+y)}\right.\\
&\quad\left.-\ln\frac{\beta kx(t-\tau)y(t-\tau)}{a\mu e^{d\tau}y^*\mu(x(t-\tau)+y(t-\tau))}\right]\\
&= d\,(x^*-x)\left[1-\frac{x^*(x+y^*)}{x(x^*+y^*)}\right]+ae^{d\tau}y^*\left(1-\frac{y(x+y^*)}{y^*(x+y)}\right)\left(\frac{x+y}{x+y^*}-1\right)\\
&\quad-ae^{d\tau}y^*g\left(\frac{x+y}{x+y^*}\right)-ae^{d\tau}y^*g\left(\frac{x^*(x+y^*)}{x(x^*+y^*)}\right)-ae^{d\tau}y^*\ln\frac{x^*(x+y)}{x(x^*+y^*)}\\
&\quad-ae^{d\tau}y^*g\left(\frac{(x^*+y^*)y(t-\tau)x(t-\tau)}{x^*y(x(t-\tau)+y(t-\tau))}\right)-ae^{d\tau}y^*\ln\frac{x(x^*+y^*)}{x^*(x+y)}.
\end{aligned}
\tag{9}
$$

Using the trivial inequalities following

$$
\begin{aligned}
1-\frac{x^*(x+y^*)}{x(x^*+y^*)}&\geq 0 \quad \text{for} \quad x\geq x^*,\\
1-\frac{x^*(x+y^*)}{x(x^*+y^*)}&< 0 \quad \text{for} \quad x< x^*.
\end{aligned}
$$

Thus, we have

$$
d\,(x^*-x)\left(1-\frac{x^*(x+y^*)}{x(x^*+y^*}\right)\leq 0 \text{ for } x=x^*. \tag{10}
$$

Similarly, since

$$
\begin{aligned}
1-\frac{y(x+y^*)}{y^*(x+y)}<0,\ \frac{x+y}{x+y^*}-1>0 \text{ for } y>y^*,\\
1-\frac{y(x+y^*)}{y^*(x+y)}>0,\ \frac{x+y}{x+y^*}-1<0 \text{ for } y<y^*,
\end{aligned}
$$

we have

$$
\left(1-\frac{y(x+y^*)}{y^*(x+y)}\right)\left(\frac{x+y}{x+y^*}-1\right)\leq 0 \text{ for } y=y^*. \tag{11}
$$

By (9)-(11) and the fact $g(x) \geq 0$ for $x \geq 0$, we finally get

$$\begin{aligned}\dot{W}|_{(3)} = d\,(x^* - x)\left(1 - \frac{x^*(x+y^*)}{x(x^*+y^*)}\right) + ae^{d\tau}y^*\left(1 - \frac{y(x+y^*)}{y^*(x+y)}\right)\left(\frac{x+y}{x+y^*} - 1\right) \\ - ae^{d\tau}y^* g\left(\frac{x+y}{x+y^*}\right) - ae^{d\tau}y^* g\left(\frac{x^*(x+y^*)}{x(x^*+y^*)}\right) \\ - ae^{d\tau}y^* g\left(\frac{(x^*+y^*)y(t-\tau)x(t-\tau)}{x^* y(x(t-\tau)+y(t-\tau))}\right) \leq 0.\end{aligned} \tag{12}$$

From (12), we have

$$\dot{W}|_{(3)} = 0$$

if and only if $x = x^*, y = y^*$. So, the largest compact invariant set in $\Gamma = \{(x(t), e(t), y(t)) | \dot{W}(t) = 0\}$ is just the singleton E^*. By Theorem 1.2 and the LaSalle invariance principle, we conclude that the infected equilibrium E^* of system (3) is globally asymptotically stable.

The proof is completed. □

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E-mail address: limingcai@amss.ac.cn
E-mail address: Bao-Zhu.Guo@wits.ac.za