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Research Article

Asymptotic Properties of a Hepatitis B Virus Infection Model with Time Delay

Xiaohong Tian and Rui Xu

Institute of Applied Mathematics, Shijiazhuang Mechanical Engineering College, No. 97 Heping West Road, Shijiazhuang 050003, China

Correspondence should be addressed to Rui Xu, rxu88@yahoo.com.cn

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A hepatitis B virus infection model with time delay is discussed. By analyzing the corresponding characteristic equations, the local stability of each of the feasible equilibria of the model is studied. By using comparison arguments, it is proved that if the basic reproduction ratio is less than unity, the infection-free equilibrium is globally asymptotically stable. If the basic reproduction ratio is greater than unity, by means of an iteration technique, sufficient conditions are derived for the global asymptotic stability of the virus-infected equilibrium. Numerical simulations are carried out to illustrate the theoretical results.

1. Introduction

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus. It is a major global health problem and the most serious type of viral hepatitis. It can cause chronic liver disease and puts people at high risk of death from cirrhosis of the liver and liver cancer. Worldwide, estimated two billion people have been infected with the hepatitis B virus (HBV), and more than 350 million have chronic (long-term) liver infections. In the past decade, therapy for HBV has been revolutionized by the advent of drugs that directly block replication of the HBV genome. All these drugs (to date) are nucleoside or nucleotide analogues that selectively target the viral reverse transcriptase. The first successful drug, lamivudine, emerged from screening for inhibitors of the HBV reverse transcriptase and was introduced into clinical practice for the management of HBV infection.

Recently, mathematical models have been used frequently to study the transmission dynamics of HBV (see, e.g., [1–15]). In [1], Anderson and May used a simple mathematical model to illustrate the effects of carriers on the transmission of HBV. In an effort to model HBV infection dynamics and its treatment with the reverse transcriptase inhibitor

lamivudine, Nowak and Bangham [7] and Bonhoeffer et al. [2] proposed the following basic HBV infection model:

$$\begin{aligned} \dot{x}(t) &= \lambda - dx(t) - \beta x(t)v(t), \\ \dot{y}(t) &= \beta x(t)v(t) - ay(t), \\ \dot{v}(t) &= ky(t) - uv(t), \end{aligned} \tag{1.1}$$

where x, y, and v are numbers of uninfected cells, infected cells, and free-virus cells, respectively. Uninfected cells are assumed to be produced at a constant rate λ, die at rate dx, and become infected at rate βxv in which β is the mass action rate constant describing the infection process. Infected cells are killed by immune cells at rate ay and produce free virus at rate ky, here k is the so-called burst constant. Free-virus cells are cleared at rate uv. It is assumed that parameters $a, d, k, u, \lambda,$ and β are positive constants. In [4], by constructing novel Lyapunov functions, it was proven that if the basic reproduction ratio is less than unity, the infection-free equilibrium is globally asymptotically stable, and if the basic reproduction ratio is greater than unity, then the infected equilibrium is globally asymptotically stable. In [9], Thornley et al. used a hepatitis B mathematical model developed by Medley et al. [5] to develop a strategy for eliminating HBV in New Zealand. In [13], Zhao et al. proposed an age-structured model to predict the dynamics of HBV transmission and evaluate the long-term effectiveness of the vaccination programme in China. In [11], Xu and Ma investigated a hepatitis B virus model with spatial diffusion and saturation response of the infection rate. In [14], Zou et al. also proposed a mathematical model to understand the transmission dynamics and prevalence of HBV in mainland China. In [12], Yu et al. considered an HBV infection model with a nonlinear infection rate. It was shown that the model has a degenerate singular infection equilibrium, and bifurcation of cusp type with codimension two (i.e., Bogdanov-Takens bifurcation) occurs under appropriate conditions. As a result, the rich dynamical behaviors indicate that the model can display an Allee effect and fluctuation effect, which are important for making strategies for controlling the invasion of virus. In [8], Pang et al. developed a mathematical model to explore the impact of vaccination and other controlling measures of HBV infection. It was shown that the vaccination is a very effective measure to control the infection, and some useful comments were given on controlling the transmission of HBV.

Usually, the rate of infection in most HBV virus models is assumed to be bilinear in the virus v and the uninfected cells x. Under this assumption, the basic infection reproductive number is proportional to the number of total cells of the liver, which implies that an individual with a smaller liver may be more resistant to the virus infection than an individual with a larger one. Clearly, this is not true. A typical chronically infected HBV patient has a total serum daily production rate of about 2×10^{11} to 3×10^{12} virions, and an average human liver consists of billions of liver cells. These large numbers suggest that it is reasonable to assume that the infection rate is given by the standard incidence function [3]. Based on the idea above, in [6], Min et al. proposed the following basic HBV virus model:

$$\begin{aligned} \dot{x}(t) &= \lambda - dx(t) - \frac{\beta x(t)v(t)}{x(t) + y(t)}, \\ \dot{y}(t) &= \frac{\beta x(t)v(t)}{x(t) + y(t)} - ay(t), \\ \dot{v}(t) &= ky(t) - uv(t). \end{aligned} \tag{1.2}$$

For system (1.2), it was shown in [6] that if the basic infection reproductive number is less than unity, then every positive solution converges to the infection-free steady state. At the same time, it was also assumed that cells upon infection instantly begin producing virus. In [10], Wang et al. introduced an improved HBV model with standard incidence function and cytokine-mediated "cure" based on empirical evidences. By using the geometrical approach of Li and Muldowney [16] to global stability problems in $\mathbb{R}^n$, the global stability of the virus-infected equilibrium was established. However, in reality, there is a time delay between viral infection of a cell and the time the cell begins releasing virus. In [17], Nelson et al. considered a model that allows for less than perfect drug effects and includes a delay in the initiation of virus production. Compared with the outcomes of models without time delay, modelling on virus infection by suitable delay terms looks to be biologically reasonable [18–20].

Motivated by the work of Min et al. [6] and Nelson et al. [17], in this paper, we study the following hepatitis B virus infection model with a time delay:

$$\begin{aligned} \dot{x}(t) &= \lambda - dx(t) - \frac{\beta x(t) v(t)}{x(t) + y(t)}, \\ \dot{y}(t) &= \frac{\beta e^{-m\tau} x(t-\tau) v(t-\tau)}{x(t-\tau) + y(t-\tau)} - ay(t), \\ \dot{v}(t) &= ky(t) - uv(t). \end{aligned} \tag{1.3}$$

The initial conditions for system (1.3) take the form

$$\begin{aligned} x(\theta) &= \phi_1(\theta), \quad \phi_1(\theta) \geq 0, \ \phi_1(0) > 0, \\ y(\theta) &= \phi_2(\theta), \quad \phi_2(\theta) \geq 0, \ \phi_2(0) > 0, \\ v(\theta) &= \phi_3(\theta), \quad \phi_3(\theta) \geq 0, \ \theta \in [-\tau, 0], \ \phi_3(0) > 0, \end{aligned} \tag{1.4}$$

where $(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta)) \in C([-\tau, 0], \mathbb{R}^3_{+0})$, the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^3_{+0}$, here $\mathbb{R}^3_{+0} = \{(x_1, x_2, x_3) : x_i \geq 0, \ i = 1, 2, 3\}$.

It is easy to show that all solutions of system (1.3) with initial condition (1.4) are defined on $[0, +\infty)$ and remain positive for all $t \geq 0$.

The organization of this paper is as follows. In the next section, we introduce some notations and state several lemmas which will be essential to our proofs. In Section 3, by analyzing the corresponding characteristic equations, the local stability of each of the feasible equilibria of system (1.3) is discussed. In Section 4, by using an iteration technique, we study the global stability of the infection-free equilibrium of system (1.3). By comparison arguments we discuss the global stability of the virus-infected equilibrium of system (1.3). Numerical simulations are carried out in Section 5 to illustrate the main theoretical results.

2. Preliminaries

In this section, based on the work developed by Xu and Ma [21], we introduce some notations and state several results which will be useful in the next section.

Let $\mathbb{R}^n_+$ be the cone of nonnegative vectors in $\mathbb{R}^n$. If $x, y \in \mathbb{R}^n$, we write $x \leq y (x < y)$ if $x_i \leq y_i (x_i < y_i)$ for $1 \leq i \leq n$. Let $\{e_1, e_2, \ldots, e_n\}$ denote the standard basis in $\mathbb{R}^n$. Suppose that $r \geq 0$, and let $C = C([-r, 0], \mathbb{R}^n)$ be the Banach space of continuous functions mapping the interval $[-r, 0]$ into $\mathbb{R}^n$ with supremum norm. If $\phi, \psi \in C$, we write $\phi \leq \psi (\phi < \psi)$ when the indicated inequality holds at each point of $[-r, 0]$. Let $C^+ = \{\phi \in C : \phi \geq 0\}$, and let $\wedge$ denote the inclusion $\mathbb{R}^n \to C([-r, 0], \mathbb{R}^n)$ by $x \to \hat{x}$, $\hat{x}(\theta) = x$, $\theta \in [-r, 0]$. Denote the space of functions of bounded variation on $[-r, 0]$ by $\mathrm{BV}[-r, 0]$. If $t_0 \in \mathbb{R}$, $A \geq 0$, and $x \in C([-t_0 - r, t_0 + A], \mathbb{R}^n)$, then for any $t \in [t_0, t_0 + A]$, we let $x_t \in C$ be defined by $x_t(\theta) = x(t + \theta)$, $-r \leq \theta \leq 0$.

We now consider

$$\dot{x}(t) = f(t, x_t). \tag{2.1}$$

We assume throughout this section that $f : \mathbb{R} \times C \to \mathbb{R}^n$ is continuous; $f(t, \phi)$ is continuously differentiable in ϕ; $f(t + T, \phi) = f(t, \phi)$ for all $(t, \phi) \in \mathbb{R} \times C^+$, and some $T > 0$. Then by [22], there exists a unique solution of (2.1) through (t_0, ϕ) for $t_0 \in \mathbb{R}, \phi \in C^+$. This solution will be denoted by $x(t, t_0, \phi)$ if we consider the solution in $\mathbb{R}^n$ or by $x_t(t_0, \phi)$ if we work in the space C. Again by [22], $x(t, t_0, \phi)(x_t(t_0, \phi))$ is continuously differentiable in ϕ. In the following, the notation $x_{t_0} = \phi$ will be used as the condition of the initial data of (2.1), by which we mean that we consider the solution $x(t)$ of (2.1) which satisfies $x(t_0 + \theta) = \phi(\theta)$, $\theta \in [-r, 0]$.

To proceed further, we need the following results. Let $r = (r_1, r_2, \ldots, r_n) \in \mathbb{R}^n_+$, $|r| = \max_i\{r_i\}$, and define

$$C_r = \prod_{i=1}^{n} C([-r_i, 0], \mathbb{R}). \tag{2.2}$$

We write $\phi = (\phi_1, \phi_2, \ldots, \phi_n)$ for a generic point of C_r. Let $C_r^+ = \{\phi \in C_r : \phi \geq 0\}$. Due to the ecological applications, we choose C_r^+ as the state space of (2.1) in the following discussions.

Fix $\phi_0 \in C_r^+$ arbitrarily. Then we set $L(t, \cdot) = D_{\phi_0} f(t, \phi_0)$, where $D_{\phi_0} f(t, \phi_0)$ denotes the Frechet derivation of f with respect to ϕ_0. It is convenient to have the standard representation of $L = (L_1, L_2, \ldots, L_n)$ as

$$L_i(t, \phi) = \sum_{j=1}^{n} \int_{-r_j}^{0} \phi_j(\theta) \mathrm{d}_\theta \eta_{ij}(\theta, t), \quad 1 \leq i \leq n, \tag{2.3}$$

in which $\eta_{ij} : \mathbb{R} \times \mathbb{R} \to \mathbb{R}$ satisfies

$$\begin{aligned} &\eta_{ij}(\theta, t) = \eta_{ij}(0, t), \quad \theta \geq 0, \\ &\eta_{ij}(\theta, t) = 0, \quad \theta \leq -r_j, \\ &\eta_{ij}(\cdot, t) \in \mathrm{BV}[-r_j, 0], \end{aligned} \tag{2.4}$$

where $\eta_{ij}(\cdot, t)$ is continuous from the left in $(-r_j, 0)$.

We make the following assumptions for (2.1).

(h0) If $\phi, \psi \in C^+, \phi \le \psi$ and $\phi_i(0) = \psi_i(0)$ for some i, then $f_i(t,\phi) \le f_i(t,\psi)$.

(h1) For all $\phi \in C_r^+$ with $\phi_i(0) = 0$, $L_i(t,\phi) \ge 0$ for $t \in \mathbb{R}$.

(h2) The matrix $A(t)$ defined by

$$A(t) = \operatorname{col}(L(t,\widehat{e}_1), L(t,\widehat{e}_2), \ldots, L(t,\widehat{e}_n)) = \left(\eta_{ij}(0,t)\right) \tag{2.5}$$

is irreducible for each $t \in \mathbb{R}$.

(h3) For each j, for which $r_j > 0$, there exists i such that for all $t \in \mathbb{R}$ and for positive constant ε sufficiently small, $\eta_{ij}(-r_j + \varepsilon, t) > 0$.

(h4) If $\phi = 0$, then $x(t,t_0,\phi) \equiv 0$ for all $t \ge t_0$.

The following result was established by Wang et al. [23].

Lemma 2.1. *Let (h1)–(h4) hold. Then hypothesis (h0) is valid and*

(i) *if ϕ and ψ are distinct elements of C_r^+ with $\phi \le \psi$ and $[t_0, t_0+\sigma)$ with $n|r| < \sigma \le \infty$ is the intersection of the maximal intervals of existence of $x(t,t_0,\phi)$ and $x(t,t_0,\psi)$, then*

$$\begin{aligned} &0 \le x(t,t_0,\phi) \le x(t,t_0,\psi) \quad \text{for } t_0 \le t < t_0+\sigma, \\ &0 \le x(t,t_0,\phi) < x(t,t_0,\psi) \quad \text{for } t_0 + n|r| \le t < t_0+\sigma; \end{aligned} \tag{2.6}$$

(ii) *if $\phi \in C_r^+, \phi \ne 0, t_0 \in \mathbb{R}$, and $x(t,t_0,\phi)$ is defined on $[t_0, t_0+\sigma)$ with $\sigma > n|r|$, then*

$$0 < x(t,t_0,\phi) \quad \text{for } t_0 + n|r| \le t < t_0+\sigma. \tag{2.7}$$

This lemma shows that if (h1)–(h4) hold, then the positivity of solutions of (2.1) follows.

The following definition and results are useful in proving our main result.

Definition 2.2. Let $A = (a_{ij})_{n\times n}$ be an $n \times n$ matrix, and let $P_1, \ldots, P_n$ be distinct points of the complex plane. For each nonzero element a_{ij} of A, connect P_i to P_j with a directed line $\overline{P_iP_j}$. The resulting figure in the complex plane is a directed graph for A. One says that a directed graph is strongly connected if, for each pair of nodes P_i, P_j with $i \ne j$, there is a directed path

$$\overrightarrow{P_iP_{k_1}}, \overrightarrow{P_{k_1}P_{k_2}}, \ldots, \overrightarrow{P_{k_{r-1}}P_j} \tag{2.8}$$

connecting P_i and P_j. Here, the path consists of r directed lines.

Lemma 2.3 (see [24]). *A square matrix is irreducible if and only if its directed graph is strongly connected.*

Lemma 2.4 (see [25]). *If* (2.1) *is cooperative and irreducible in D, where D is an open subset of C, and the solutions with positive initial data are bounded, then the trajectory of* (2.1) *tends to some single equilibrium.*

We now consider the following delay differential system:

$$\begin{aligned} \dot{u}_1(t) &= \frac{a_1\beta e^{-m\tau}u_2(t-\tau)}{a_1+u_1(t-\tau)} - au_1(t), \\ \dot{u}_2(t) &= ku_1(t) - uu_2(t) \end{aligned} \tag{2.9}$$

with initial conditions

$$u_i(s) = \phi_i(s) \geq 0, \quad s \in [-\tau, 0),\ \phi_i(0) > 0,\ \phi_i \in C([-\tau, 0), \mathbb{R}_+)\ (i = 1, 2). \tag{2.10}$$

System (2.9) always has a trivial equilibrium $A^0(0,0)$. If $k\beta e^{-m\tau} > au$, then system (2.9) has a unique positive equilibrium $A^*(u_1^*, u_2^*)$, where

$$u_1^* = \frac{a_1\left(k\beta e^{-m\tau} - au\right)}{au}, \qquad u_2^* = \frac{a_1 k\left(k\beta e^{-m\tau} - au\right)}{au^2}. \tag{2.11}$$

The characteristic equation of system (2.9) at the equilibrium A^0 takes the form

$$\lambda^2 + g_1\lambda + g_0 + h_0 e^{-\lambda\tau} = 0, \tag{2.12}$$

where

$$g_0 = au, \qquad g_1 = a + u, \qquad h_0 = -k\beta e^{-m\tau}. \tag{2.13}$$

Noting that

$$g_1 > 0, \qquad g_0 + h_0 = au - k\beta e^{-m\tau}, \tag{2.14}$$

if $k\beta e^{-m\tau} < au$, then the equilibrium A^0 is locally stable when $\tau = 0$; if $k\beta e^{-m\tau} > au$, then A^0 is unstable when $\tau = 0$.

It is easy to show that $g_1^2 - 2g_0 = a^2 + u^2 > 0$. If $k\beta e^{-m\tau} < au$, then $g_0^2 - h_0^2 > 0$. By Theorem 3.4.1 in the work of Kuang [26], we see that the equilibrium A^0 is locally asymptotically stable for all $\tau > 0$. If $k\beta e^{-m\tau} > au$, then A^0 is unstable for all $\tau > 0$.

The characteristic equation of system (2.9) at the positive equilibrium A^* is of the form

$$\lambda^2 + p_1\lambda + p_0 + \left(q_1\lambda + q_0\right)e^{-\lambda\tau} = 0, \tag{2.15}$$

where

$$p_0 = au, \qquad p_1 = a + u, \qquad q_0 = \frac{ua_1\beta e^{-m\tau}u_2^*}{\left(a_1 + u_1^*\right)^2} - \frac{ka_1\beta e^{-m\tau}}{a_1 + u_1^*}, \qquad q_1 = \frac{a_1\beta e^{-m\tau}u_2^*}{\left(a_1 + u_1^*\right)^2}. \tag{2.16}$$

note that

$$p_1 + q_1 > 0, \qquad p_0 + q_0 = \frac{ua_1\beta e^{-m\tau}u_2^*}{\left(a_1 + u_1^*\right)^2} > 0. \tag{2.17}$$

Hence, if $k\beta e^{-m\tau} > au$, the positive equilibrium A^* is locally stable when $\tau = 0$; if $k\beta e^{-m\tau} < au$, A^* is unstable when $\tau = 0$.

It is easy to show that

$$\begin{aligned} p_1^2 - q_1^2 - 2p_0 &= u^2 + \frac{a^2a_1\left(a_1 + 2u_1^*\right)}{\left(a_1 + u_1^*\right)^2} > 0, \\ p_0^2 - q_0^2 &= \frac{aa_1u^2\beta e^{-m\tau}u_2^*\left(2a_1 + u_1^*\right)}{\left(a_1 + u_1^*\right)^3} > 0. \end{aligned} \tag{2.18}$$

If $k\beta e^{-m\tau} > au$, then by Theorem 3.4.1 in the work of Kuang [26], we see that the positive equilibrium A^* is locally asymptotically stable for all $\tau > 0$. If $k\beta e^{-m\tau} < au$, then A^* is unstable for all $\tau > 0$.

Lemma 2.5. *For system* (2.9)*, one has the following.*

(i) *If $k\beta e^{-m\tau} > au$, then the positive equilibrium $A^*(u_1^*, u_2^*)$ is globally stable.*

(ii) *If $k\beta e^{-m\tau} < au$, then the equilibrium $A^0(0,0)$ is globally stable.*

Proof. We represent the right-hand side of (2.9) by $f(t, x_t) = (f_1(t, x_t), f_2(t, x_t))$ and set

$$L(t, \cdot) = D_\phi f(t, \phi). \tag{2.19}$$

By a direct calculation we have

$$\begin{aligned} L_1(t,h) &= -\frac{a_1\beta e^{-m\tau}\phi_2(-\tau)}{\left(a_1 + \phi_1(-\tau)\right)^2}h_1(-\tau) + \frac{a_1\beta e^{-m\tau}}{a_1 + \phi_1(-\tau)}h_2(-\tau) - ah_1(0), \\ L_2(t,h) &= kh_1(0) - uh_2(0). \end{aligned} \tag{2.20}$$

We now claim that hypotheses (h1)–(h4) hold for system (2.9). It is easily seen that (h1) and (h4) hold for system (2.9). We need only to verify that (h2) and (h3) hold.

The matrix $A(t)$ takes the form

$$\begin{pmatrix} -a - \dfrac{a_1\beta e^{-m\tau}\phi_2(-\tau)}{\left(a_1 + \phi_1(-\tau)\right)^2} & \dfrac{a_1\beta e^{-m\tau}}{a_1 + \phi_1(-\tau)} \\ k & -u \end{pmatrix}. \tag{2.21}$$

Clearly, the matrix $A(t)$ is irreducible for each $t \in \mathbb{R}$.

From the definition of $A(t)$ and η_{ij}, it is readily seen that $\eta_{12}(\theta,t) = \eta_{12}(0,t) = a_1\beta e^{-m\tau}/(a_1+\phi_1(-\tau))$, $\eta_{21}(\theta,t) = \eta_{21}(0,t) = k$ for $\theta \geq 0$, $\eta_{ij}(\theta,t) = 0$, $i \neq j$ for $\theta \leq -\tau$, and $\eta_{ij}(\cdot,t) \in \mathrm{BV}[-\tau,0]$, where η_{ij} is a positive Borel measure on $[-\tau,0]$. Therefore, $\eta_{ij}(\cdot,t) > 0$. Thus, for each j, there is $i \neq j$ such that $\eta_{ij}(-r_j+\varepsilon,t) = \eta_{ij}(-\tau+\varepsilon,t) > 0$ for all $t \in \mathbb{R}$ and for $\varepsilon > 0$ sufficiently small, $i = 1,2$. Hence, (h3) holds.

Thus, the conditions of Lemma 2.1 are satisfied. Therefore, the positivity of solutions of system (2.9) follows. It is easy to see that system (2.9) is cooperative. By Lemma 2.3, we see that any solution starting from $D = C_\tau^+$ converges to some single equilibrium. However, system (2.9) has only two equilibria: A^0 and A^*. Note that if $k\beta e^{-m\tau} > au$, then the positive equilibrium A^* is locally stable and the equilibrium A^0 is unstable. Hence, any solution starting from D converges to $A^*(u_1^*,u_2^*)$ if $k\beta e^{-m\tau} > au$. Using a similar argument one can show the global stability of the equilibrium A^0 when $k\beta e^{-m\tau} < au$. This completes the proof. □

3. Local Stability

In this section, we discuss the local stability of each of the equilibria of system (1.3) by analyzing the corresponding characteristic equations.

System (1.3) always has an infection-free equilibrium $E^0(\lambda/d,0,0)$.

Let

$$\mathcal{R}_0 = \frac{\beta k e^{-m\tau}}{au}. \tag{3.1}$$

$\mathcal{R}_0$ is called the basic reproduction ratio of system (1.3). It is easy to show that if $\mathcal{R}_0 > 1$, system (1.3) has a virus-infected equilibrium $E^*(x^*,y^*,v^*)$, where

$$x^* = \frac{\lambda e^{-m\tau}}{de^{-m\tau}+a(\mathcal{R}_0-1)}, \qquad y^* = \frac{\lambda e^{-m\tau}(\mathcal{R}_0-1)}{de^{-m\tau}+a(\mathcal{R}_0-1)}, \qquad v^* = \frac{\lambda k e^{-m\tau}(\mathcal{R}_0-1)}{u[de^{-m\tau}+a(\mathcal{R}_0-1)]}. \tag{3.2}$$

The characteristic equation of system (1.3) at the infection-free equilibrium E^0 is of the form

$$(s+d)\left(s^2+p_1s+p_0+q_0e^{-s\tau}\right) = 0, \tag{3.3}$$

where

$$p_0 = au, \qquad p_1 = a+u, \qquad q_0 = -k\beta e^{-m\tau}. \tag{3.4}$$

Obviously, (3.3) always has a negative real root $s = -d$. All other roots of (3.3) are determined by the following equation:

$$s^2+p_1s+p_0+q_0e^{-s\tau} = 0. \tag{3.5}$$

It is easy to show that $p_1 > 0, p_0+q_0 = au-k\beta e^{-m\tau}$. If $\mathcal{R}_0 < 1$, then the infection-free equilibrium E^0 of system (1.3) is locally asymptotically stable when $\tau = 0$.

If $i\omega(\omega > 0)$ is a solution of (3.5), by calculating, we have

$$\omega^4 + \left(p_1^2 - 2p_0\right)\omega^2 + p_0^2 - q_0^2 = 0. \tag{3.6}$$

Note that

$$p_1^2 - 2p_0 = a^2 + u^2 > 0, \qquad p_0^2 - q_0^2 = \left(au - k\beta e^{-m\tau}\right)\left(au + k\beta e^{-m\tau}\right). \tag{3.7}$$

If $\mathcal{R}_0 < 1$, then $p_0^2 - q_0^2 > 0$. Therefore, (3.6) has no positive roots. Accordingly, if $\mathcal{R}_0 < 1$, the infection-free equilibrium E^0 of system (1.3) is locally asymptotically stable; if $\mathcal{R}_0 > 1$, (3.6) has at least a positive real root. Accordingly, E^0 is unstable.

The characteristic equation of system (1.3) at the virus-infected equilibrium $E^*(x^*, y^*, v^*)$ takes the form

$$s^3 + g_2 s^2 + g_1 s + g_0 + \left(h_2 s^2 + h_1 s + h_0\right)e^{-s\tau} = 0, \tag{3.8}$$

where

$$\begin{gathered}
g_0 = au\left[d + \frac{\beta v^* y^*}{\left(x^* + y^*\right)^2}\right], \qquad g_1 = au + (a+u)\left[d + \frac{\beta v^* y^*}{\left(x^* + y^*\right)^2}\right], \\
g_2 = a + d + u + \frac{\beta v^* y^*}{\left(x^* + y^*\right)^2}, \\
h_0 = du\frac{\beta e^{-m\tau} v^* x^*}{\left(x^* + y^*\right)^2} - dk\frac{\beta e^{-m\tau} x^*}{x^* + y^*}, \qquad h_1 = (d+u)\frac{\beta e^{-m\tau} v^* x^*}{\left(x^* + y^*\right)^2} - k\frac{\beta e^{-m\tau} x^*}{x^* + y^*}, \\
h_2 = \frac{\beta e^{-m\tau} v^* x^*}{\left(x^* + y^*\right)^2}.
\end{gathered} \tag{3.9}$$

When $\tau = 0$, (3.8) becomes

$$s^3 + \left(g_2 + h_2\right)s^2 + \left(g_1 + h_1\right)s + g_0 + h_0 = 0. \tag{3.10}$$

Clearly, $g_2 + h_2 > 0$. By a direct calculation we have

$$g_0 + h_0 = au\frac{\beta v^* y^*}{(x^* + y^*)^2} + du\frac{\beta e^{-m\tau} v^* x^*}{(x^* + y^*)^2} > 0,$$

$$\begin{aligned}(g_2 + h_2)(g_1 + h_1) - (g_0 + h_0) = &\left[d(a+u) + (e^{-m\tau}x^* + y^*)\frac{u\beta v^*}{(x^* + y^*)^2}\right] \\ &\times \left[a + d + u + (e^{-m\tau}x^* + y^*)\frac{\beta v^*}{(x^* + y^*)^2}\right] \\ &+ \frac{\lambda\beta e^{-m\tau} v^*}{(x^* + y^*)^2}\left[a + d + (e^{-m\tau}x^* + y^*)\frac{\beta v^*}{(x^* + y^*)^2}\right] > 0.\end{aligned} \tag{3.11}$$

By the Hurwitz criteria, all roots of (3.10) have only negative real parts.

If $i\omega(\omega > 0)$ is a solution of (3.8), separating real and imaginary parts, it follows that

$$\begin{aligned}\omega^3 - g_1\omega &= \left(h_2\omega^2 - h_0\right)\sin\omega\tau + h_1\omega\cos\omega\tau, \\ g_2\omega^2 - g_0 &= -\left(h_2\omega^2 - h_0\right)\cos\omega\tau + h_1\omega\sin\omega\tau.\end{aligned} \tag{3.12}$$

Squaring and adding the two equations of (3.12), we derive that

$$\omega^6 + C_1\omega^4 + C_2\omega^2 + C_3 = 0, \tag{3.13}$$

where

$$\begin{aligned}C_1 &= u^2 + \left(d + \frac{\beta v^* y^*}{(x^* + y^*)^2}\right)^2 + \frac{ax^*}{x^* + y^*}\left(a + \frac{\beta e^{-m\tau} x^* v^*}{(x^* + y^*)^2}\right) > 0, \\ C_2 &= a^2\left(d^2 + u^2\right)\frac{y^*(x^* + 2y^*)}{(x^* + y^*)^2} + \frac{a^2\beta v^* y^*}{(x^* + y^*)^2}\left(2d + \frac{\beta v^* y^*}{(x^* + y^*)^2}\right) + u^2\left(d + \frac{\beta v^* y^*}{(x^* + y^*)^2}\right)^2 > 0, \\ C_3 &= \frac{au^2\beta v^*(de^{-m\tau}x^* + ay^*)}{(x^* + y^*)^3}\left(d(2x^* + y^*) + \frac{\beta v^* y^*}{x^* + y^*}\right) > 0.\end{aligned} \tag{3.14}$$

Hence, (3.13) has no positive roots. Accordingly, by the general theory of characteristic equations of delay differential equations in the work of Kuang [26] (Theorem 4.1), if $\mathcal{R}_0 > 1$, the virus-infected equilibrium E^* of system (1.3) exists and is locally asymptotically stable.

Based on the discussions above, we have the following result.

Theorem 3.1. *For system* (1.3)*, one has the following.*

(i) *If* $\mathcal{R}_0 < 1$*, the infection-free equilibrium* $E^0(\lambda/d, 0, 0)$ *is locally asymptotically stable. If* $\mathcal{R}_0 > 1$*, then* $E^0(\lambda/d, 0, 0)$ *is unstable.*

(ii) *If* $\mathcal{R}_0 > 1$*, the virus-infected equilibrium* $E^*(x^*, y^*, v^*)$ *is locally asymptotically stable.*

4. Global Stability

In this section, we discuss the global stability of the infection-free equilibrium and the virus-infected equilibrium of system (1.3), respectively. The technique of proofs is to use a comparison argument and an iteration scheme (see, e.g., [27]).

Theorem 4.1. *Let* $\mathcal{R}_0 > 1$*. If*

(H1) $adu^2 > k\beta(k\beta e^{-m\tau} - au)$,

then the virus-infected equilibrium $E^*(x^*, y^*, v^*)$ *of system* (1.3) *is globally asymptotically stable.*

Proof. Let $(x(t), y(t), v(t))$ be any positive solution of system (1.3) with initial condition (1.4). Let

$$\begin{aligned} U_1 &= \limsup_{t\to+\infty} x(t), & V_1 &= \liminf_{t\to+\infty} x(t), \\ U_2 &= \limsup_{t\to+\infty} y(t), & V_2 &= \liminf_{t\to+\infty} y(t), \\ U_3 &= \limsup_{t\to+\infty} v(t), & V_3 &= \liminf_{t\to+\infty} v(t). \end{aligned} \tag{4.1}$$

Now we claim that $U_1 = V_1 = x^*, U_2 = V_2 = y^*,$ and $U_3 = V_3 = v^*$.

It follows from the first equation of system (1.3) that

$$\dot{x}(t) \le \lambda - dx(t). \tag{4.2}$$

By comparison we derive that

$$U_1 = \limsup_{t\to+\infty} x(t) \le \frac{\lambda}{d} := M_1^x. \tag{4.3}$$

Hence, for $\varepsilon > 0$ sufficiently small there exists a $T_1 > 0$ such that if $t > T_1$, $x(t) \le M_1^x + \varepsilon$. We therefore derive from the second and the third equations of system (1.3) that, for $t > T_1 + \tau$,

$$\begin{aligned} \dot{y}(t) &\le \frac{\beta e^{-m\tau}\left(M_1^x + \varepsilon\right)v(t-\tau)}{M_1^x + \varepsilon + y(t-\tau)} - ay(t), \\ \dot{v}(t) &= ky(t) - uv(t). \end{aligned} \tag{4.4}$$

Consider the following auxiliary equations:

$$\begin{aligned} \dot{u}_1(t) &= \frac{\beta e^{-m\tau}\left(M_1^x+\varepsilon\right)u_2(t-\tau)}{M_1^x+\varepsilon+u_1(t-\tau)} - au_1(t), \\ \dot{u}_2(t) &= ku_1(t) - uu_2(t). \end{aligned} \tag{4.5}$$

Since $\mathcal{R}_0 > 1$, by Lemma 2.5 it follows from (4.5) that

$$\begin{aligned} \lim_{t\to+\infty} u_1(t) &= \frac{\left(k\beta e^{-m\tau}-au\right)\left(M_1^x+\varepsilon\right)}{au}, \\ \lim_{t\to+\infty} u_2(t) &= \frac{k\left(k\beta e^{-m\tau}-au\right)\left(M_1^x+\varepsilon\right)}{au^2}. \end{aligned} \tag{4.6}$$

By comparison, we obtain that

$$\begin{aligned} U_2 = \limsup_{t\to+\infty} y(t) &\le \frac{\left(k\beta e^{-m\tau}-au\right)\left(M_1^x+\varepsilon\right)}{au}, \\ U_3 = \limsup_{t\to+\infty} v(t) &\le \frac{k\left(k\beta e^{-m\tau}-au\right)\left(M_1^x+\varepsilon\right)}{au^2}. \end{aligned} \tag{4.7}$$

Since these inequalities are true for arbitrary $\varepsilon > 0$, it follows that $U_2 \le M_1^y$, $U_3 \le M_1^v$, where

$$M_1^y = \frac{\left(k\beta e^{-m\tau}-au\right)M_1^x}{au}, \qquad M_1^v = \frac{k\left(k\beta e^{-m\tau}-au\right)M_1^x}{au^2}. \tag{4.8}$$

Hence, for $\varepsilon > 0$ sufficiently small, there is a $T_2 \ge T_1 + \tau$ such that if $t > T_2$, $y(t) \le M_1^y + \varepsilon$, $v(t) \le M_1^v + \varepsilon$.

For $\varepsilon > 0$ sufficiently small, we derive from the first equation of system (1.3) that, for $t > T_2$,

$$\dot{x}(t) \ge \lambda - dx(t) - \beta\left(M_1^v+\varepsilon\right). \tag{4.9}$$

A comparison argument shows that

$$V_1 = \liminf_{t\to+\infty} x(t) \ge \frac{\lambda-\beta\left(M_1^v+\varepsilon\right)}{d}. \tag{4.10}$$

Since this is true for arbitrary $\varepsilon > 0$ sufficiently small, we conclude that $V_1 \ge N_1^x$, where

$$N_1^x = \frac{\lambda-\beta M_1^v}{d}. \tag{4.11}$$

Hence, for $\varepsilon > 0$ sufficiently small, there is a $T_3 \ge T_2$ such that if $t > T_3$, $x(t) \ge N_1^x - \varepsilon$.

For $\varepsilon > 0$ sufficiently small, we derive from the second and the third equations of system (1.3) that, for $t > T_3 + \tau$,

$$\begin{aligned} \dot{y}(t) &\geq \frac{\beta e^{-m\tau}\left(N_1^x - \varepsilon\right)v(t-\tau)}{N_1^x - \varepsilon + y(t-\tau)} - ay(t), \\ \dot{v}(t) &= ky(t) - uv(t). \end{aligned} \tag{4.12}$$

Consider the following auxiliary equations:

$$\begin{aligned} \dot{u}_1(t) &= \frac{\beta e^{-m\tau}\left(N_1^x - \varepsilon\right)u_2(t-\tau)}{N_1^x - \varepsilon + u_1(t-\tau)} - au_1(t), \\ \dot{u}_2(t) &= ku_1(t) - uu_2(t). \end{aligned} \tag{4.13}$$

Since (H1) holds, by Lemma 2.5, it follows from (4.13) that

$$\begin{aligned} \lim_{t\to+\infty} u_1(t) &= \frac{\left(k\beta e^{-m\tau} - au\right)\left(N_1^x - \varepsilon\right)}{au}, \\ \lim_{t\to+\infty} u_2(t) &= \frac{k\left(k\beta e^{-m\tau} - au\right)\left(N_1^x - \varepsilon\right)}{au^2}. \end{aligned} \tag{4.14}$$

By comparison we derive that

$$\begin{aligned} V_2 = \liminf_{t\to+\infty} y(t) &\geq \frac{\left(k\beta e^{-m\tau} - au\right)\left(N_1^x - \varepsilon\right)}{au}, \\ V_3 = \liminf_{t\to+\infty} v(t) &\geq \frac{k\left(k\beta e^{-m\tau} - au\right)\left(N_1^x - \varepsilon\right)}{au^2}. \end{aligned} \tag{4.15}$$

Since these two inequalities hold for arbitrary $\varepsilon > 0$ sufficiently small, we conclude that $V_2 \geq N_1^y, V_3 \geq N_1^v$, where

$$\begin{aligned} N_1^y &= \frac{\left(k\beta e^{-m\tau} - au\right)N_1^x}{au}, \\ N_1^v &= \frac{k\left(k\beta e^{-m\tau} - au\right)N_1^x}{au^2}. \end{aligned} \tag{4.16}$$

Therefore, for $\varepsilon > 0$ sufficiently small, there is a $T_4 \geq T_3 + \tau$ such that if $t > T_4$, $y(t) \geq N_1^y - \varepsilon, v(t) \geq N_1^v - \varepsilon$.

For $\varepsilon > 0$ sufficiently small, it follows from the first equation of system (1.3) that, for $t > T_4$,

$$\dot{x}(t) \leq \lambda - dx(t) - \frac{\beta\left(N_1^v - \varepsilon\right)x(t)}{M_1^x + \varepsilon + M_1^y + \varepsilon}. \tag{4.17}$$

A comparison argument yields

$$U_1 = \limsup_{t\to+\infty} x(t) \le \frac{\lambda\left(M_1^x + \varepsilon + M_1^y + \varepsilon\right)}{d\left(M_1^x + \varepsilon + M_1^y + \varepsilon\right) + \beta\left(N_1^v - \varepsilon\right)}. \tag{4.18}$$

Since this is true for arbitrary $\varepsilon > 0$, it follows that $U_1 \le M_2^x$, where

$$M_2^x = \frac{\lambda\left(M_1^x + M_1^y\right)}{d\left(M_1^x + M_1^y\right) + \beta N_1^v}. \tag{4.19}$$

Hence, for $\varepsilon > 0$ sufficiently small there is a $T_5 \ge T_4$ such that if $t > T_5$, $x(t) \le M_2^x + \varepsilon$. It therefore follows from the second and the third equations of system (1.3) that, for $t > T_5 + \tau$,

$$\begin{aligned} \dot{y}(t) &\le \frac{\beta e^{-m\tau}\left(M_2^x + \varepsilon\right)v(t-\tau)}{M_2^x + \varepsilon + y(t-\tau)} - ay(t), \\ \dot{v}(t) &= ky(t) - uv(t). \end{aligned} \tag{4.20}$$

By Lemma 2.5 and a comparison argument we derive from (4.20) that

$$\begin{aligned} U_2 = \limsup_{t\to+\infty} y(t) &\le \frac{\left(k\beta e^{-m\tau} - au\right)\left(M_2^x + \varepsilon\right)}{au}, \\ U_3 = \limsup_{t\to+\infty} v(t) &\le \frac{k\left(k\beta e^{-m\tau} - au\right)\left(M_2^x + \varepsilon\right)}{au^2}. \end{aligned} \tag{4.21}$$

Since these inequalities are true for arbitrary $\varepsilon > 0$, it follows that $U_2 \le M_2^y$, $U_3 \le M_2^v$, where

$$\begin{aligned} M_2^y &= \frac{\left(k\beta e^{-m\tau} - au\right)M_2^x}{au}, \\ M_1^v &= \frac{k\left(k\beta e^{-m\tau} - au\right)M_2^x}{au^2}. \end{aligned} \tag{4.22}$$

Hence, for $\varepsilon > 0$ sufficiently small, there exists a $T_6 \ge T_5 + \tau$ such that if $t > T_6$, $y(t) \le M_2^y + \varepsilon, v(t) \le M_2^v + \varepsilon$.

Again, for $\varepsilon > 0$ sufficiently small, we derive from the first equation of system (1.3) that, for $t > T_6$,

$$\dot{x}(t) \ge \lambda - dx(t) - \frac{\beta x(t)\left(M_2^v + \varepsilon\right)}{N_1^x - \varepsilon + N_1^y - \varepsilon}. \tag{4.23}$$

A comparison argument shows that

$$V_1 = \liminf_{t\to+\infty} x(t) \geq \frac{\lambda\left(N_1^x - \varepsilon + N_1^y - \varepsilon\right)}{d\left(N_1^x - \varepsilon + N_1^y - \varepsilon\right) + \beta\left(M_2^v + \varepsilon\right)}. \tag{4.24}$$

Since this is true for arbitrary $\varepsilon > 0$, we derive that $V_1 \geq N_2^x$, where

$$N_2^x = \frac{\lambda\left(N_1^x + N_1^y\right)}{d\left(N_1^x + N_1^y\right) + \beta M_2^v}. \tag{4.25}$$

Hence, for $\varepsilon > 0$ sufficiently small, there is a $T_7 \geq T_6$ such that if $t > T_7$, $x(t) \geq N_2^x - \varepsilon$.

For $\varepsilon > 0$ sufficiently small, it follows from the second and the third equations of system (1.3) that, for $t > T_7 + \tau$,

$$\begin{aligned} \dot{y}(t) &\geq \frac{\beta e^{-m\tau}\left(N_2^x - \varepsilon\right)v(t-\tau)}{N_2^x - \varepsilon + y(t-\tau)} - ay(t), \\ \dot{v}(t) &= ky(t) - uv(t). \end{aligned} \tag{4.26}$$

Since (H1) holds, by Lemma 2.5 and a comparison argument, it follows from (4.26) that

$$\begin{aligned} V_2 &= \liminf_{t\to+\infty} y(t) \geq \frac{\left(k\beta e^{-m\tau} - au\right)\left(N_2^x - \varepsilon\right)}{au}, \\ V_3 &= \liminf_{t\to+\infty} v(t) \geq \frac{k\left(k\beta e^{-m\tau} - au\right)\left(N_2^x - \varepsilon\right)}{au^2}. \end{aligned} \tag{4.27}$$

Since these two inequalities hold for arbitrary $\varepsilon > 0$ sufficiently small, we conclude that $V_2 \geq N_2^y, V_3 \geq N_2^v$, where

$$\begin{aligned} N_2^y &= \frac{\left(k\beta e^{-m\tau} - au\right)N_2^x}{au}, \\ N_2^v &= \frac{k\left(k\beta e^{-m\tau} - au\right)N_2^x}{au^2}. \end{aligned} \tag{4.28}$$

Therefore, for $\varepsilon > 0$ sufficiently small, there exists a $T_8 \geq T_7 + \tau$ such that if $t > T_8$, $y(t) \geq N_2^y - \varepsilon, v(t) \geq N_2^v - \varepsilon$.

Continuing this process, we derive six sequences M_n^x, M_n^y, M_n^v, N_n^x, N_n^y, and N_n^v ($n = 1, 2, \ldots$) such that, for $n \geq 2$,

$$\begin{aligned}
M_n^x &= \frac{\lambda\left(M_{n-1}^x + M_{n-1}^y\right)}{d\left(M_{n-1}^x + M_{n-1}^y\right) + \beta N_{n-1}^v}, \\
M_n^y &= \frac{\left(k\beta e^{-m\tau} - au\right) M_n^x}{au}, \\
M_n^v &= \frac{k\left(k\beta e^{-m\tau} - au\right) M_n^x}{au^2}, \\
N_n^x &= \frac{\lambda\left(N_{n-1}^x + N_{n-1}^y\right)}{d\left(N_{n-1}^x + N_{n-1}^y\right) + \beta M_n^v}, \\
N_n^y &= \frac{\left(k\beta e^{-m\tau} - au\right) N_n^x}{au}, \\
N_n^v &= \frac{k\left(k\beta e^{-m\tau} - au\right) N_n^x}{au^2}.
\end{aligned} \tag{4.29}$$

It is readily seen that

$$N_n^x \leq V_1 \leq U_1 \leq M_n^x, \quad N_n^y \leq V_2 \leq U_2 \leq M_n^y, \quad N_n^v \leq V_3 \leq U_3 \leq M_n^v. \tag{4.30}$$

It is easy to show that the sequences M_n^x, M_n^y, and M_n^v are nonincreasing and the sequences N_n^x, N_n^y, and N_n^v are nondecreasing. Hence, the limit of each sequence in M_n^x, M_n^y, M_n^v, N_n^x, N_n^y, and N_n^v exists. Denote

$$\begin{aligned}
\overline{x} &= \lim_{n \to +\infty} M_n^x, \qquad \underline{x} = \lim_{n \to +\infty} N_n^x, \\
\overline{y} &= \lim_{n \to +\infty} M_n^y, \qquad \underline{y} = \lim_{n \to +\infty} N_n^y, \\
\overline{v} &= \lim_{n \to +\infty} M_n^v, \qquad \underline{v} = \lim_{n \to +\infty} N_n^v.
\end{aligned} \tag{4.31}$$

We therefore obtain from (4.29) and (4.31) that

$$\frac{dk\beta e^{-m\tau}}{au}\overline{x} + \frac{k\beta\left(k\beta e^{-m\tau} - au\right)}{au^2}\underline{x} = 0, \tag{4.32}$$

$$\frac{dk\beta e^{-m\tau}}{au}\underline{x} + \frac{k\beta\left(k\beta e^{-m\tau} - au\right)}{au^2}\overline{x} = 0. \tag{4.33}$$

By having (4.32) minus (4.33),

$$(\overline{x} - \underline{x})\left[\frac{dk\beta e^{-m\tau}}{au} - \frac{k\beta(k\beta e^{-m\tau} - au)}{au^2}\right] = 0. \tag{4.34}$$

Noting that (H1) holds and $\mathcal{R}_0 > 1$, it follows that

$$\frac{dk\beta e^{-m\tau}}{au} > \frac{k\beta(k\beta e^{-m\tau} - au)}{au^2}, \tag{4.35}$$

which, together with (4.34), yields $\overline{x} = \underline{x}$. We therefore derive from (4.31) that $\overline{y} = \underline{y}, \overline{v} = \underline{v}$. Noting that if (H1) holds, by Theorem 3.1, the virus-infected equilibrium E^* is locally stable, we conclude that E^* is globally stable. The proof is complete. □

Theorem 4.2. *If $\mathcal{R}_0 < 1$ holds, the infection-free equilibrium $E^0(\lambda/d, 0, 0)$ of system (1.3) is globally asymptotically stable.*

Proof. Let $(x(t), y(t), v(t))$ be any positive solution of system (1.3) with initial condition (1.4). It follows from the first equation of system (1.3) that

$$\dot{x}(t) \leq \lambda - dx(t). \tag{4.36}$$

A standard comparison argument shows that

$$\limsup_{t \to +\infty} x(t) \leq \frac{\lambda}{d}. \tag{4.37}$$

Hence, for $\varepsilon > 0$ sufficiently small, there is a $T_1 > 0$ such that if $t > T_1$, $x(t) \leq \lambda/d + \varepsilon$. We derive from the second and the third equations of system (1.3) that for $t > T_1 + \tau$,

$$\begin{aligned} \dot{y}(t) &\leq \frac{\beta e^{-m\tau}(\lambda/d + \varepsilon)v(t-\tau)}{\lambda/d + \varepsilon + y(t-\tau)} - ay(t), \\ \dot{v}(t) &= ky(t) - uv(t). \end{aligned} \tag{4.38}$$

Consider the following auxiliary equation:

$$\begin{aligned} \dot{u}_1(t) &= \frac{\beta e^{-m\tau}(\lambda/d + \varepsilon)u_2(t-\tau)}{\lambda/d + \varepsilon + u_1(t-\tau)} - au_1(t), \\ \dot{u}_2(t) &= ku_1(t) - uu_2(t). \end{aligned} \tag{4.39}$$

If $\mathcal{R}_0 < 1$, then by Lemma 2.5 it follows from (4.37) and (4.39) that

$$\lim_{t \to +\infty} u_1(t) = 0, \qquad \lim_{t \to +\infty} u_2(t) = 0. \tag{4.40}$$

Table 1: Rapid deline in plasma virus: mean HBV DNA levels (log copies/ml) in response to the therapy, and the virus level returning rapidly after the treatment was stopped.

Week	0	1	2	4	6	8	12	18
Patient Nos.	272	272	272	267	267	267	267	267
Virus load	9.8	7.8	6.6	5.6	5.1	4.8	4.4	4.3
Week	24	30	36	42	48	52	60	72
Patient Nos.	263	263	259	260	249	248	228	241
Virus load	4.2	4.0	4.15	4.2	4.5	7.0	8.0	8.20

By comparison, we obtain that

$$\lim_{t\to+\infty} y(t) = 0, \qquad \lim_{t\to+\infty} v(t) = 0. \tag{4.41}$$

Therefore, for $\varepsilon > 0$ sufficiently small, there is a $T_2 > T_1 + \tau$ such that if $t > T_2$, $y(\mathrm{t}) < \varepsilon, v(t) < \varepsilon$.

It follows from the first equation of system (1.3) that for $t > T_2$,

$$\dot{x}(t) \geq \lambda - dx(t) - \beta\varepsilon. \tag{4.42}$$

By comparison, we derive that

$$\liminf_{t\to+\infty} x(t) \geq \frac{\lambda - \beta\varepsilon}{d}. \tag{4.43}$$

Letting $\varepsilon \to 0$, it follows that

$$\liminf_{t\to+\infty} x(t) \geq \frac{\lambda}{d}. \tag{4.44}$$

This together with (4.37) yields

$$\lim_{t\to+\infty} x(t) = \frac{\lambda}{d}. \tag{4.45}$$

This completes the proof. □

5. Numerical Example

In this section, we give one example to illustrate the main result in Section 4.

In [28], one group of HBeAg-Positive chronic hepatitis B patients received 100 mg of lamivudine once daily. The study comprised 48 weeks of treatment and a 24-week treatment-free followup. While the onset of therapy and viral levels decline rapidly, the virus returns as soon as the drug is withdrawn (see Table 1).

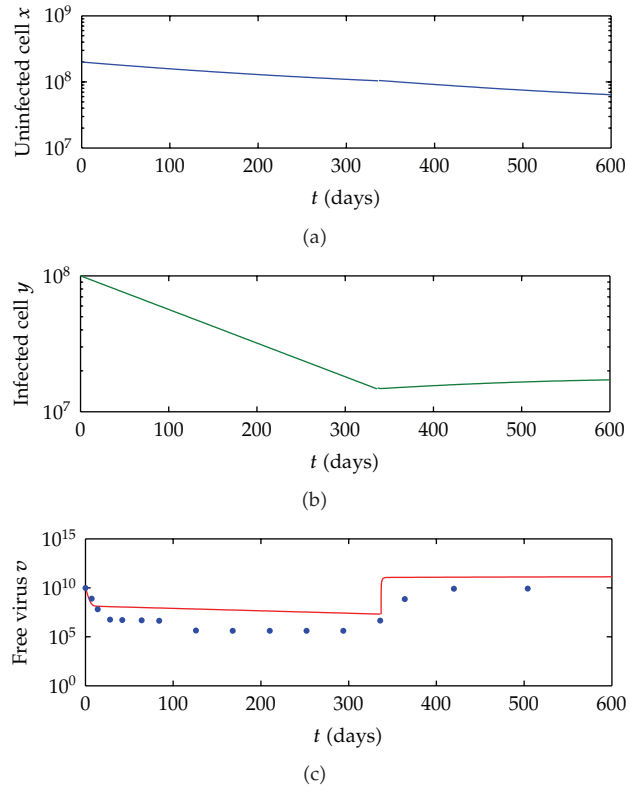

Figure 1: The numerical solution of system (5.1). (a) Uninfected cells x; (b) infected cells y; (c) virus declines in response to drug treatment and virus resurges as soon as the drug is withdrawn in which the clinical data are marked by dots.

In the following, we will use the set of clinical data to formulate a hepatitis B virus infection therapy model. Assume that, during the lamivudine drug treatment, the dynamic model of the patient with the mean load HBV DNA is of the form

$$\begin{aligned}
\dot{x}(t) &= \lambda - dx(t) - (1-n_1)\frac{\beta x(t)v(t)}{x(t)+y(t)},\\
\dot{y}(t) &= (1-n_1)\frac{\beta e^{-m\tau}x(t-\tau)v(t-\tau)}{x(t-\tau)+y(t-\tau)} - ay(t),\\
\dot{v}(t) &= (1-n_2)ky(t) - uv(t).
\end{aligned} \tag{5.1}$$

Clearly, if $n_1 = n_2 = 0$, then system (5.1) becomes system (1.3), which means that the patients are assumed to return to the stable state before the drug therapy.

Example 5.1. In system (5.1), based on the work of [6] and clinical data, we let $\lambda = 2\times10^{11}, d = 3.7877\times10^{-3}, a = 3.38d, u = 0.67, \beta = 1.4557\times10^{-6}, k = 5.1885\times10^{3}, \tau = 2, m = 0.2, n_1 = 0$, and $n_2 = 0.99982$.

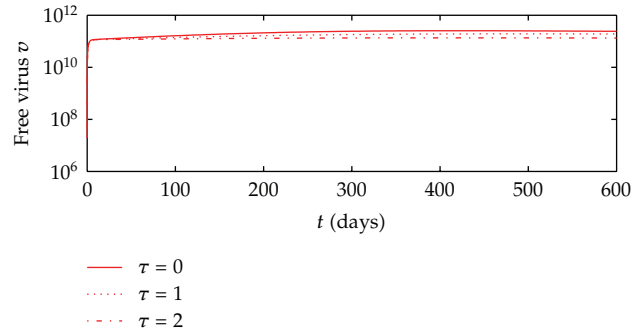

Figure 2: The numerical solution for viral decay of system (1.3) when $\tau = 0, 1$ and 2 days.

Before the therapy, that is, $n_1 = n_2 = 0$, by a direct calculation, we have the basic reproduction ratio $\mathcal{R}_0 \approx 1.33$, and system (1.3) has a virus-infected equilibrium E^*. Clearly, (H1) holds. By Theorem 4.1, we see that the virus-infected equilibrium E^* of system (1.3) is globally asymptotically stable. Numerical simulation illustrates the previous result (see Figure 1).

Biologically, as can be seen from Figure 1(c), based on system (5.1), during the 48 weeks of treatment, the viral levels decline rapidly. As soon as the drug is withdrawn, by Theorem 4.1, virus level returns rapidly and tends to the virus-infected equilibrium. Figure 1(c) indicates that the simulation of model (5.1) agrees well with the clinical data reported. Furthermore, compared with the work of Min et al. [6], it is easy to show that the simulation results are similar. However, for system (1.3), numerical simulation shows that the slopes of the curves generated with different delays differ, and notice the slopes of the decay with and without a delay are parallel. When the time delay increases, it is easy to see that the viral load reduces; numerical simulation illustrates that the change in the slope is affected by the delay (see Figure 2).

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