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GLOBAL DYNAMICS OF AN HBV MODEL WITH SPATIAL DIFFUSION AND ANTIBODY RESPONSE

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Abstract. In this paper, we investigate the dynamic of a delayed HBV model with spatial diffusion and antibody response. By analyzing the corresponding characteristic equations, the local stability of an infected steady state and an uninfected steady state is discussed. Moreover, by constructing two Lyapunov functionals, it is proved that the global dynamics for the two steady states of the model is completely determined by the basic reproductive number.

Keywords: HBV model; spatial diffusion; antibody response; stability.

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1. Introduction

Hepatitis B virus (HBV) infects 350 million persons world-wide [1]. Persistent infection with HBV may eventually suffer from a spectrum of disease, besides chronic active hepatitis, such as serum sickness-like syndrome, acute necrotizing vasculitis, membranous glomerulonephritis,

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papular acrodermatitis of childhood, cirrhosis, and hepatocellular carcinoma (see, for example, [2], [3]). Mathematical modeling combined with experimental measurements has yielded important insights into HBV pathogenesis and has enhanced progress in the understanding of HBV infection. A basic mathematical model proposed by Nowak et al. [4] and Nowak and May [5] has been widely used for studding the dynamics of infections agents such as hepatitis B virus (HBV), hepatitis C virus (HCV) and HIV, which is of the form

$$\begin{aligned} \dot{u} &= a - du - \beta uv, \\ \dot{w} &= \beta uv - \rho_1 w, \\ \dot{v} &= \rho_2 w - \rho_3 v, \end{aligned} \tag{1.1}$$

where uninfected susceptible cells u are produced at a rate a, die at a rate du and become infected by virus at a rate βuv, where β is the rate constant describing the infection process; infected cells w are produced at the same rate βuv and are lost at rate ρ_1 per cell; free virion v are produced at rate ρ_2 per infected cell and are removed at a rate $\rho_3 v$.

Note that the spatial mobility of cells and viruses has been ignored in model (1.1). However, as argued by Wu [6], in many biological systems, the species may disperse spatially as well as evolving in time. To study the spatial virus immune dynamics, Funka et al. [7] proposed a patchy model to simulate the diffusion of virus to the nearest neighboring sites that surround the site where it emerges. Wang and Wang [8] assumed that susceptible host cells and infected cells are hepatocyte and cannot move under normal conditions, but viruses move freely in liver. They introduced the random mobility for free viruses into model (1.1) and neglected the mobility of susceptible cells and infected cells. Since the size of free virus particles is much smaller than that of liver and the process of infection is usually more than 10 years or a lifetime infection for chronically infected with HBV [9], Wang and Wang assumed that the domain of free virus particles was an infinite spatial domain $(-\infty, +\infty)$. The existence of travelling waves was established via the geometric singular perturbation method.

The binding of a viral particle to a target cell initiates a cascade of events that ultimately lead to the target cell becoming productively infected, i.e. producing new virus particles. This process does not occur instantaneously. In reality, there is a time delay between initial viral

entry into a cell and subsequent viral production [10]. In view of this observation, models that include delays have been studied (see, for example, [10], [11]).

In model (1.1), the rate of infection is bilinear in the virus v and the uninfected target cells u. However, experiments reported in [12] strongly suggested that the infection rate of microparasitic infections is an increasing function of the parasite dose, and is usually sigmoidal in shape. Thus, to place the model on more sound biological grounds, it is reasonable to assume a more general saturated infection rate, $\frac{\beta u v^p}{1+\alpha v^q}$, where p, q and α are positive constants [13]. Xu and Ma [14] considered an HBV model with diffusion and saturation response of the infection rate as follows:

$$\begin{aligned}
\frac{\partial u}{\partial t} =& a - du(x,t) - \frac{\beta u(x,t)v(x,t)}{1+\alpha v(x,t)},\\
\frac{\partial w}{\partial t} =& \frac{\beta u(x,t-\tau)v(x,t-\tau)}{1+\alpha v(x,t-\tau)} - \rho_1 w(x,t),\\
\frac{\partial v}{\partial t} =& D\Delta v + \rho_2 w(x,t) - \rho_3 v(x,t),
\end{aligned}$$

where $u(x,t), w(x,t)$ and $v(x,t)$ represent the densities of uninfected cells, infected cells and free virus at location x and time t, respectively. Δ is the Laplacian operator. D is the diffusion coefficient. HBV production lags by a delay τ behind the infection of a hepatocyte. In [14], by comparison arguments, Xu and Ma investigated the global stability of the infected steady state and uninfected steady state, respectively.

During viral infections, the host immune system reacts with innate and antigen-specific immune response. Among antigen-specific responses, cytotoxic T cells (CTLs) kill infected cells, whereas antibodies neutralize free virus particles and thus inhibit infection of susceptible cells. In addition, CD4+ and CD8+ T cells can secrete cytokinesis that inhibit viral replication (e.g. IFN-γ and TNF-α) [15]. In this paper, motivated by the works mentioned above, we are concerned with the effect of the spatial diffusion of free virus of an HBV model with antibody

response. Since the size of the liver is bounded, we consider the following delayed reaction-diffusion system:

$$\begin{aligned}
\frac{\partial u}{\partial t} =& a - du(x,t) - \frac{\beta u(x,t)v(x,t)}{1+\alpha v(x,t)},\\
\frac{\partial w}{\partial t} =& \frac{\beta e^{-m\tau} u(x,t-\tau)v(x,t-\tau)}{1+\alpha v(x,t-\tau)} - \rho_1 w(x,t),\\
\frac{\partial v}{\partial t} =& D\Delta v + \rho_2 w(x,t) - \rho_3 v(x,t) - pv(x,t)z(x,t),\\
\frac{\partial z}{\partial t} =& cv(x,t) - bz(x,t)
\end{aligned} \tag{1.2}$$

for $t > 0, x \in \Omega$, with initial conditions

$$\begin{aligned}
&u(x,\theta) = \phi_1(x,\theta), w(x,\theta) = \phi_2(x,\theta), v(x,\theta) = \phi_3(x,\theta),\\
&z(x,\theta) = \phi_4(x,\theta), \quad \theta \in [-\tau, 0], x \in \overline{\Omega}
\end{aligned} \tag{1.3}$$

and homogeneous Neumann boundary conditions

$$\frac{\partial v}{\partial \nu} = 0, \quad t > 0, x \in \partial\Omega, \tag{1.4}$$

where $\phi_i(x,\theta)(i = 1,2,3,4)$ are nonnegative and Hölder continuous in $\overline{\Omega} \times [-\tau, 0]$, Ω is a bounded domain in $\mathbb{R}^n$ with smooth boundary $\partial\Omega$, $\partial/\partial\nu$ denotes the outward normal derivative on $\partial\Omega$. The boundary conditions in (1.4) imply that the virus particles do not move across the boundary $\partial\Omega$. Here, $z(x,t)$ denotes the concentration of antibody responses, free virion are also neutralized via mass action kinetics by antibodies, which is described by pvz. The antibody responses are activated at a rate cv proportional to the abundances of free viruses, and die at a per capita rate b. All parameters in system (1.2) are positive constants.

The organization of this paper is as follows. In the next section, by analyzing the corresponding characteristic equations, we study the local asymptotic stability of an infected steady state and an uninfected steady state. In Section 3, we discuss the global stability of the two steady states by constructing suitable Lyapunov functionals and LaSalle's invariance principle, respectively.

2. Local stability of steady states

In this section, we investigate the local stability of an infected steady state and an uninfected steady state of problem (1.2)-(1.4), respectively.

It is easy to see that system (1.2) always has an uninfected steady state $E_1(a/d,0,0,0)$. Let

$$\mathscr{R}_0=\frac{a\beta\rho_2 e^{-m\tau}}{d\rho_1\rho_3}.$$

$\mathscr{R}_0$ is called the basic reproductive number of system (1.2), which describes the average number of newly infected cells at the beginning of the infectious process. If $\mathscr{R}_0>1$, system (1.2) admits a unique infected steady state $E^*(u^*,w^*,v^*,z^*)$, where v^* is the positive root of the following quadric equation:

$$cp\rho_1(d\alpha+\beta)v^2+\rho_1\left(bd\alpha\rho_3+cdp+b\beta\rho_3\right)v+bd\rho_1\rho_3-ab\beta e^{-m\tau}=0,$$

and

$$u^*=\frac{\rho_1(b\rho_3+cpv^*)(1+\alpha v^*)}{b\beta\rho_2 e^{-m\tau}},\quad w^*=\frac{(b\rho_3+cpv^*)v^*}{b\rho_2},\quad z^*=\frac{c}{b}v^*.$$

Let $0=\mu_1<\mu_2<\cdots$ be the eigenvalues of the operator $-\Delta$ on Ω with the homogeneous Neumann boundary conditions, and $E(\mu_i)$ be the eigenspace corresponding to μ_i in $C^1(\Omega)$. Let $\mathbb{X}=[C^1(\Omega)]^4,\{\phi_{ij};j=1,\cdots,\dim E(\mu_i)\}$ be an orthonormal basis of $E(\mu_i)$, and $\mathbb{X}_{ij}=\{c\phi_{ij}|c\in\mathbb{R}^4\}$. Then

$$\mathbb{X}=\bigoplus_{i=0}^{\infty}\mathbb{X}_i,\qquad \mathbb{X}_i=\bigoplus_{j=1}^{\dim E(\mu_i)}\mathbb{X}_{ij}.$$

Let $\mathscr{D}=\mathrm{diag}(0,0,D,0),Z=(u,w,v,z),\mathscr{L}Z=\mathscr{D}\Delta Z+\mathscr{G}(\hat{E})Z$, where

$$\mathscr{G}(\hat{E})Z=\begin{pmatrix}-\left(d+\dfrac{\beta v^0}{1+\alpha v^0}\right)u(x,t)-\dfrac{\beta u^0}{(1+\alpha v^0)^2}v(x,t)\\ -\rho_1 w(x,t)+\dfrac{e^{-m\tau}\beta v^0}{1+\alpha v^0}u(x,t-\tau)+\dfrac{e^{-m\tau}\beta u^0}{(1+\alpha v^0)^2}v(x,t-\tau)\\ \rho_2 w(x,t)-(\rho_3+pz^0)v(x,t)-pv^0z(x,t)\\ cv(x,t)-bz(x,t)\end{pmatrix}$$

and $\hat{E}(u^0,w^0,v^0,z^0)$ represents any feasible steady state of system (1.2). The linearization of system (1.2) at $\hat{E}$ is of the form $Z_t=\mathscr{L}Z$. For each $i\geqslant 1,\mathbb{X}_i$ is invariant under the operator $\mathscr{L}$,

and λ is an eigenvalue of $\mathscr{L}$ if and only if it is an eigenvalue of $-\mu_i\mathscr{D}+\mathscr{G}(\hat{E})$ for some $i \geqslant 1$, in which case, there is an eigenvector in $\mathbb{X}_i$.

The characteristic equation of $-\mu_i\mathscr{D}+\mathscr{G}(E_1)$ takes the form

$$(\lambda+b)(\lambda+d)\left[\lambda^2+(\mu_i D+\rho_1+\rho_3)\lambda+\rho_1(\mu_i D+\rho_3)-\frac{a\beta\rho_2}{d}e^{-(\lambda+m)\tau}\right]=0. \tag{2.1}$$

Clearly, for any $i \geqslant 1$, Eq. (2.1) has two negative roots. Other roots of (2.1) are given by the following equation

$$\lambda^2+(\mu_i D+\rho_1+\rho_3)\lambda+\rho_1(\mu_i D+\rho_3)-\frac{a\beta\rho_2}{d}e^{-(\lambda+m)\tau}=0. \tag{2.2}$$

Let

$$f_1(\lambda)=\lambda^2+(\mu_i D+\rho_1+\rho_3)\lambda+\rho_1(\mu_i D+\rho_3)-\frac{a\beta\rho_2}{d}e^{-(\lambda+m)\tau}.$$

If $\mathscr{R}_0>1$, it is easy to show that for λ real and $i=1$ (in this case, $\mu_1=0$),

$$f_1(0)|_{i=1}=\rho_1\rho_3-\frac{a\beta\rho_2}{d}e^{-m\tau}<0, \quad \lim_{\lambda\to+\infty} f_1(\lambda)=+\infty.$$

Hence Eq. (2.2) has a positive real root. Therefore, there is a characristic root λ with positive real part in the spectrum of $\mathscr{L}$. Accordingly, if $\mathscr{R}_0>1$, the uninfected steady state $E_1(a/d,0,0,0)$ is unstable.

If $\mathscr{R}_0<1$, denote $p_0=\rho_1(\mu_i D+\rho_3), p_1=\mu_i D+\rho_1+\rho_3, q_0=-\frac{a\beta\rho_2}{d}e^{-m\tau}$. If $i\omega(\omega>0)$ is a solution to (2.2), separating real and imaginary parts, we derive that

$$-\omega^2+p_0=q_0\cos\omega\tau, \quad p_1\omega=-q_0\sin\omega\tau. \tag{2.3}$$

Squaring and adding the two equations of (2.3), it follows that

$$\omega^4+(p_1^2-2p_0)\omega^2+p_0^2-q_0^2=0. \tag{2.4}$$

Letting $z=\omega^2$, then Eq. (2.4) becomes

$$z^2+(p_1^2-2p_0)z+p_0^2-q_0^2=0. \tag{2.5}$$

It is easy to show that

$$p_0^2-q_0^2=\left[\rho_1(\mu_i D+\rho_3)+\frac{a\beta\rho_2}{d}e^{-m\tau}\right]\left[\rho_1\mu_i D+\frac{1}{\rho_1\rho_3}(1-R_0)\right]>0,$$

$$p_1^2-2p_0=(\mu_i D+\rho_3)^2+\rho_1^2>0.$$

Hence, if $\mathscr{R}_0 < 1$, Eq. (2.5) has no positive roots. On the other hand, it is easy to show that E_1 is locally asymptotically stable when $\tau = 0$. Therefore, if $\mathscr{R}_0 < 1$, the uninfected steady state $E_1(a/d, 0, 0, 0)$ is locally stable for all $\tau \geq 0$.

The characteristic equation of $-\mu_i \mathscr{D} + \mathscr{G}(E^*)$ is of the form

$$\lambda^4 + P_3(\tau)\lambda^3 + P_2(\tau)\lambda^2 + P_1(\tau)\lambda + P_0(\tau) + \left[Q_2(\tau)\lambda^2 + Q_1(\tau)\lambda + Q_0(\tau)\right] e^{-\lambda\tau} = 0, \tag{2.6}$$

where

$$\begin{aligned}
P_0(\tau) =& \left(d + \frac{\beta v^*}{1+\alpha v^*}\right)[b\rho_1(\mu_i D + \rho_3 + pz^*) + cp\rho_1 v^*],\\
P_1(\tau) =& \left(d + \frac{\beta v^*}{1+\alpha v^*}\right)[b\rho_1 + (\rho_1 + b)(\mu_i D + \rho_3 + pz^*) + cpv^*]\\
&+ b\rho_1(\mu_i D + \rho_3 + pz^*) + cp\rho_1 v^*,\\
P_2(\tau) =& \left(d + \frac{\beta v^*}{1+\alpha v^*}\right)(\rho_1 + b + \mu_i D + \rho_3 + pz^*)\\
&+ b\rho_1 + (\rho_1 + b)(\mu_i D + \rho_3 + pz^*) + cpv^*,\\
P_3(\tau) =& d + \frac{\beta v^*}{1+\alpha v^*} + \rho_1 + b + \mu_i D + \rho_3 + pz^*,\\
Q_0(\tau) =& \frac{bd\beta\rho_2 e^{-m\tau}u^*}{(1+\alpha v^*)^2},\\
Q_1(\tau) =& \frac{(b+d)\beta\rho_2 e^{-m\tau}u^*}{(1+\alpha v^*)^2},\\
Q_2(\tau) =& \frac{\beta\rho_2 e^{-m\tau}u^*}{(1+\alpha v^*)^2}.
\end{aligned}$$

When $\tau = 0$, Eq. (2.6) becomes

$$\lambda^4 + P_3\lambda^3 + (P_2 + Q_2)\lambda^2 + (P_1 + Q_1)\lambda + P_0 + Q_0 = 0. \tag{2.7}$$

Note that $D_1 = P_3 > 0$,

$$\begin{aligned}
D_2 =&P_3(P_2+Q_2)-(P_1+Q_1)\\
=&cpv^*(b+u_iD+\rho_3+pz^*)+\left(\frac{\beta v^*}{1+\alpha v^*}+\rho_1+\mu_iD+\rho_3+pz^*\right)\frac{\beta\rho_2u^*}{(1+\alpha v^*)^2}\\
&+(\rho_1+b)\left[b\rho_1+(\mu_iD+\rho_3+pz^*)(\rho_1+b+\mu_iD+\rho_3+pz^*)\right]\\
&+\left(d+\frac{\beta v^*}{1+\alpha v^*}\right)^2(\rho_1+b+\mu_iD+\rho_3+pz^*)\\
&+\left(d+\frac{\beta v^*}{1+\alpha v^*}\right)(\rho_1+b+\mu_iD+\rho_3+pz^*)^2>0,
\end{aligned}$$

$$\begin{aligned}
D_3 =&(P_1+Q_1)D_2-P_3^2(P_0+Q_0)\\
=&(P_1+Q_1)(\rho_1+b)[b\rho_1+(\mu_iD+\rho_3+pz^*)(\rho_1+b+\mu_iD+\rho_3+pz^*)]\\
&+(\rho_1+b+cpv^*)(\mu_iD+\rho_3+pz^*)(\rho_1+b+\mu_iD+\rho_3+pz^*)\left(d+\frac{\beta v^*}{1+\alpha v^*}\right)^2\\
&+b[\rho_1(\rho_1+b)+cpv^*]\left(d+\frac{\beta v^*}{1+\alpha v^*}\right)^2\\
&+cpv^*(b+\mu_iD+\rho_3+pz^*)\left(d+\frac{\beta v^*}{1+\alpha v^*}\right)^3\\
&+(P_1+Q_1)\left(\frac{\beta v^*}{1+\alpha v^*}+\rho_1+\mu_iD+\rho_3+pz^*\right)\frac{\beta\rho_2u^*}{(1+\alpha v^*)^2}\\
&+cpv^*(P_1+Q_1)(b+\mu_iD+\rho_3+pz^*)>0,\\
D_4 =&(P_0+Q_0)D_3>0.
\end{aligned}$$

Then it follows from Routh-Hurwitz criterion that all roots of (2.7) have negative parts. Hence, if $\mathscr{R}_0 > 1$, the infected steady state E^* is locally stable when $\tau = 0$.

For $\tau > 0$, by calculation Eq. (2.6) becomes

$$\lambda+\mu_iD+\frac{cpv^*}{\lambda+b}+\rho_3+\frac{cpv^*}{b}=\frac{\lambda+d}{(1+\alpha v^*)(\lambda+d)+\beta v^*}\frac{\rho_1}{\lambda+\rho_1}\left(\rho_3+\frac{cpv^*}{b}\right)e^{-\lambda\tau}.$$

If $\mathrm{Re}\lambda \geq 0, \mathscr{R}_0 > 1$, it is easy to deserve that

$$\left|\frac{\lambda+d}{(1+\alpha v^*)(\lambda+d)+\beta v^*}\right|<1,\quad \left|\frac{\rho_1}{\lambda+\rho_1}\right|<1,\quad |e^{-\lambda\tau}|<1,$$

which indicate that

$$\left|\frac{\lambda+d}{(1+\alpha v^*)(\lambda+d)+\beta v^*}\frac{\rho_1}{\lambda+\rho_1}\left(\rho_3+\frac{cpv^*}{b}\right)e^{-\lambda\tau}\right|<\rho_3+\frac{cpv^*}{b}.$$

However, it is obvious that

$$\left|\lambda+\mu_i D+\frac{cpv^*}{\lambda+b}+\rho_3+\frac{cpv^*}{b}\right|>\rho_3+\frac{cpv^*}{b}.$$

This is a contradiction. Hence, the roots of (2.6) have no positive real parts. Therefore, if $\mathscr{R}_0>1$, the infected steady state E^* is locally asymptotically stable for all $\tau\geqslant 0$.

In conclusion, we have the following result.

Theorem 1. If $\mathscr{R}_0<1$, the uninfected steady state $E_1(a/d,0,0,0)$ of system (1.2) is locally asymptotically stable; if $\mathscr{R}_0>1$, E_1 is unstable and the infected steady state $E^*(u^*,w^*,v^*,z^*)$ exists and is locally asymptotically stable for all $\tau\geqslant 0$.

3. Global stability of steady states

In this section, by constructing two Lyapunov functionals and using LaSalle's invariance principle, we discuss the global stability of the uninfected steady state E_1 and the infected steady state E^* of system (1.2), respectively. The Lyapunov functionals used here are similar in nature to those used in [16, 17].

For convenience, let

$$g(x)=x-1-\ln x,\quad x\in(0,+\infty).$$

It is easy to see that $g(x)\geq 0$ for all $x\in(0,+\infty)$ and $\min_{0<x<+\infty}g(x)=g(1)=0$.

We first state and prove our result on the global stability of the uninfected steady state $E_1(a/d,0,0,0)$.

Theorem 2. If $\mathscr{R}_0\leq 1$, the uninfected steady state $E_1(a/d,0,0,0)$ of problem (1.2)-(1.4) is globally asymptotically stable.

Proof. Let $u(x,t),w(x,t),v(x,t),z(x,t)$ be any positive solution of problem (1.2)-(1.4). Denote $u_1=a/d$.

Define

$$L(x,t)=\int_\Omega\left(u_1L_1(x,t)+L_2(x,t)\right)\mathrm{d}x,$$

where

$$L_1(x,t) = g\left(\frac{u(x,t)}{u_1}\right),$$
$$L_2(x,t) = e^{m\tau}w(x,t) + \frac{\rho_1 e^{m\tau}}{\rho_2}v(x,t) + \int_{t-\tau}^{t}\frac{\beta u(x,\theta)v(x,\theta)}{1+\alpha v(x,\theta)}\mathrm{d}\theta.$$

Clearly, $L(x,t)$ is nonnegative definite in $\overline{\Omega}\times[-\tau,0]$ with respect to E_1. Next, we calculate the time derivative of $L(x,t)$ along the solution of problem (1.2)-(1.4).

By calculation, we have that

$$\begin{aligned}\frac{\partial L_1(x,t)}{\partial t} &= \left(\frac{1}{u_1}-\frac{1}{u(x,t)}\right)\left(a-du(x,t)-\frac{\beta u(x,t)v(x,t)}{1+\alpha v(x,t)}\right)\\ &= -\frac{d(u(x,t)-u_1)^2}{u_1u(x,t)} - \frac{u(x,t)-u_1}{u_1u(x,t)}\frac{\beta u(x,t)v(x,t)}{1+\alpha v(x,t)},\end{aligned} \tag{3.1}$$

and

$$\frac{\partial L_2(x,t)}{\partial t} = \frac{\beta u(x,t)v(x,t)}{1+\alpha v(x,t)} - \frac{\rho_1\rho_3 e^{m\tau}}{\rho_2}v(x,t) - \frac{p\rho_1 e^{m\tau}}{\rho_2}v(x,t)z(x,t) + \frac{\rho_1 e^{m\tau}}{\rho_2}D\Delta v. \tag{3.2}$$

Consequently, (3.1) and (3.2) give that

$$\begin{aligned}\frac{\partial L(x,t)}{\partial t} &= \int_\Omega\left(-\frac{d(u(x,t)-u_1)^2}{u(x,t)} + (R_0-1)\frac{\rho_1\rho_3 e^{m\tau}}{\rho_2}\frac{v(x,t)}{1+\alpha v(x,t)} + \frac{\rho_1 e^{m\tau}}{\rho_2}D\Delta v\right)\mathrm{d}x\\ &\quad + \int_\Omega\left(\frac{\rho_1\rho_3 e^{m\tau}}{\rho_2}\frac{v(x,t)}{1+\alpha v(x,t)} - \frac{\rho_1\rho_3 e^{m\tau}}{\rho_2}v(x,t) - \frac{p\rho_1 e^{m\tau}}{\rho_2}v(x,t)z(x,t)\right)\mathrm{d}x\\ &= \int_\Omega\left(-\frac{d(u(x,t)-u_1)^2}{u(x,t)} + (R_0-1)\frac{\rho_1\rho_3 e^{m\tau}}{\rho_2}\frac{v(x,t)}{1+\alpha v(x,t)} + \frac{\rho_1 e^{m\tau}}{\rho_2}D\Delta v\right)\mathrm{d}x\\ &\quad + \int_\Omega\left(-\frac{\rho_1\rho_3 e^{m\tau}}{\rho_2}\frac{\alpha v(x,t)^2}{1+\alpha v(x,t)} - \frac{p\rho_1 e^{m\tau}}{\rho_2}v(x,t)z(x,t)\right)\mathrm{d}x.\end{aligned} \tag{3.3}$$

Since $\int_\Omega \Delta v\mathrm{d}x = 0$, Eq. (3.3) becomes

$$\begin{aligned}\frac{\partial L(x,t)}{\partial t} &= -d\int_\Omega\frac{(u(x,t)-u_1)^2}{u(x,t)}\mathrm{d}x + (R_0-1)\frac{\rho_1\rho_3 e^{m\tau}}{\rho_2}\int_\Omega\frac{v(x,t)}{1+\alpha v(x,t)}\mathrm{d}x\\ &\quad - \frac{\rho_1\rho_3 e^{m\tau}}{\rho_2}\int_\Omega\frac{\alpha v(x,t)^2}{1+\alpha v(x,t)}\mathrm{d}x - \frac{p\rho_1 e^{m\tau}}{\rho_2}\int_\Omega v(x,t)z(x,t)\mathrm{d}x.\end{aligned}$$

Hence, $\mathscr{R}_0 \le 1$ ensures $\frac{\partial L(x,t)}{\partial t} \le 0$ for all $u,w,v,z \ge 0$. Furthermore, $\frac{\partial L(x,t)}{\partial t} = 0$ if and only if $u = a/d, w = 0, v = 0, z = 0$. By LaSalle's invariant principle, if $\mathscr{R}_0 \le 1$, the positive solution to problem (1.2)-(1.4) converges to the uninfected steady state E_1. Noting that if $\mathscr{R}_0 \le 1$, $E_1(a/d,0,0,0)$ is locally asymptotically stable, we see that it is globally stable. The proof is complete.

We are now in a position to establish the global stability of the infected steady state E^* of system (1.2). Denote

$$f(u(x,t),v(x,t)) := \frac{\beta u(x,t)v(x,t)}{1+\alpha v(x,t)}.$$

Theorem 3. If $\mathscr{R}_0 > 1$, the infected steady state $E^*(u^*,w^*,v^*,z^*)$ of problem (1.2)-(1.4) is globally asymptotically stable.

Proof. Define

$$U(x,t) = \int_\Omega (U_1(x,t)+U_2(x,t)+U_3(x,t))\,\mathrm{d}x,$$

where

$$\begin{aligned}
U_1(x,t) &= e^{-m\tau}\left(u(x,t)-u^*-\int_{u^*}^{u(x,t)}\frac{f(u^*,v^*)}{f(\theta,v^*)}\mathrm{d}\theta\right),\\
U_2(x,t) &= \rho_1 w^*\int_{t-\tau}^{t} g\left(\frac{e^{-m\tau}}{\rho_1 w^*}f(u(x,\theta),v(x,\theta))\right)\mathrm{d}\theta,\\
U_3(x,t) &= w^* g\left(\frac{w}{w^*}\right)+\frac{\rho_1 v^*}{\rho_2}g\left(\frac{v}{v^*}\right)+\frac{p\rho_1 v^* z^*}{b\rho_2}g\left(\frac{z}{z^*}\right).
\end{aligned}$$

Obviously, $U(x,t)$ is nonnegative definite in $\overline{\Omega}\times[-\tau,0]$ with respect to E^*. We now show that $\frac{\partial U(x,t)}{\partial t}\le 0$ along the solution of problem (1.2)-(1.4).

Note that

$$a = du^* + f(u^*,v^*),\quad e^{-m\tau}f(u^*,v^*) = \rho_1 w^*,\quad \rho_2 w^* = \rho_3 v^* + p v^* z^*,\quad cv^* = bz^*.$$

Calculating the time derivative of $U_1(x,t), U_2(x,t)$ and $U_3(x,t)$ along the positive solution of system (1.2), it follows that

$$\begin{aligned}
\frac{\partial U_1(x,t)}{\partial t} =& e^{-m\tau}\left(1-\frac{f(u^*,v^*)}{f(u(x,t),v^*)}\right)(a-du(x,t)-f(u(x,t),v(x,t)))\\
=& -\frac{de^{-m\tau}(u(x,t)-u^*)^2}{u(x,t)}+e^{-m\tau}f(u^*,v^*)\left(1-\frac{f(u^*,v^*)}{f(u(x,t),v^*)}\right)\\
& -e^{-m\tau}f(u(x,t),v(x,t))+e^{-m\tau}f(u^*,v^*)\frac{f(u(x,t),v(x,t))}{f(u(x,t),v^*)}\\
=& -\frac{de^{-m\tau}(u(x,t)-u^*)^2}{u(x,t)}+\rho_1 w^*\left(1-\frac{f(u^*,v^*)}{f(u(x,t),v^*)}\right)\\
& +\rho_1 w^*\frac{f(u(x,t),v(x,t))}{f(u(x,t),v^*)}-e^{-m\tau}f(u(x,t),v(x,t)),
\end{aligned}\tag{3.4}$$

$$\begin{aligned}\frac{\partial U_2(x,t)}{\partial t} =& e^{-m\tau}(f(u(x,t),v(x,t)) - f(u(x,t-\tau),v(x,t-\tau))) \\ &+ \rho_1 w^* \ln\frac{f(u(x,t-\tau),v(x,t-\tau))}{f(u(x,t),v(x,t))},\end{aligned} \tag{3.5}$$

and

$$\begin{aligned}\frac{\partial U_3(x,t)}{\partial t} =& \frac{\partial w(x,t)}{\partial t}\left(1-\frac{w^*}{w(x,t)}\right) + \frac{\rho_1}{\rho_2}\frac{\partial v(x,t)}{\partial t}\left(1-\frac{v^*}{v(x,t)}\right) \\ &+ \frac{p\rho_1 v^*}{b\rho_2}\frac{\partial z(x,t)}{\partial t}\left(1-\frac{z^*}{z(x,t)}\right) \\ =& e^{-m\tau} f(u(x,t-\tau),v(x,t-\tau)) - w^* e^{-m\tau}\frac{f(u(x,t-\tau),v(x,t-\tau))}{w(x,t)} \\ &+ \rho_1 w^* + \frac{\rho_1}{\rho_2}\left(1-\frac{v^*}{v(x,t)}\right) D\Delta v - \rho_1 v^*\frac{w(x,t)}{v(x,t)} - \frac{\rho_1\rho_3}{\rho_2}v(x,t) + \frac{\rho_1\rho_3 v^*}{\rho_2} \\ &- \frac{p\rho_1}{\rho_2}v(x,t)z(x,t) + \frac{cp\rho_1 v^*}{b\rho_2}v(x,t) - \frac{cp\rho_1 v^* z^*}{b\rho_2}\frac{v(x,t)}{z(x,t)} + \frac{p\rho_1 v^* z^*}{\rho_2} \\ =& e^{-m\tau} f(u(x,t-\tau),v(x,t-\tau)) - \rho_1 w^*\frac{w^*}{w(x,t)}\frac{f(u(x,t-\tau),v(x,t-\tau))}{f(u^*,v^*)} \\ &+ \rho_1 w^* + \frac{\rho_1}{\rho_2}\left(1-\frac{v^*}{v(x,t)}\right) D\Delta v - \rho_1 v^*\frac{w(x,t)}{v(x,t)} + \rho_1 w^* \\ &- \frac{p\rho_1}{\rho_2}\frac{v(x,t)}{z(x,t)}(z(x,t)-z^*)^2 - \rho_1 w^*\frac{v(x,t)}{v^*}.\end{aligned} \tag{3.6}$$

Consequently, we obtain from (3.4)-(3.6) that

$$\begin{aligned}\frac{\partial U(x,t)}{\partial t} =& -de^{-m\tau}\int_\Omega \frac{(u(x,t)-u^*)^2}{u(x,t)}\mathrm{d}x - \frac{p\rho_1}{\rho_2}\int_\Omega \frac{v(x,t)}{z(x,t)}(z(x,t)-z^*)^2\mathrm{d}x \\ &+ \frac{D\rho_1}{\rho_2}\int_\Omega\left(1-\frac{v^*}{v(x,t)}\right)\Delta v\mathrm{d}x + \rho_1 w^*\int_\Omega \ln\frac{f(u(x,t-\tau),v(x,t-\tau))}{f(u(x,t),v(x,t))}\mathrm{d}x \\ &+ \rho_1 w^*\int_\Omega\left(3-\frac{f(u^*,v^*)}{f(u(x,t),v^*)} - \frac{w^*}{w(x,t)}\frac{f(u(x,t-\tau),v(x,t-\tau))}{f(u^*,v^*)}\right)\mathrm{d}x \\ &+ \rho_1 w^*\int_\Omega\left(-\frac{w(x,t)}{w^*}\frac{v^*}{v(x,t)} - \frac{v(x,t)}{v^*} + \frac{f(u(x,t),v(x,t))}{f(u(x,t),v^*)}\right)\mathrm{d}x.\end{aligned} \tag{3.7}$$

Recall that $\int_\Omega \Delta v/v \mathrm{d}x = \int_\Omega \|\nabla v\|^2/v^2 \mathrm{d}x$, and the equality

$$\begin{aligned}\ln\frac{f(u(x,t-\tau),v(x,t-\tau))}{f(u(x,t),v(x,t))} =& \ln\frac{f(u^*,v^*)}{f(u(x,t),v^*)} + \ln\frac{w(x,t)}{w^*}\frac{v^*}{v(x,t)}\\ &+\ln\frac{w^*}{w(x,t)}\frac{f(u(x,t-\tau),v(x,t-\tau))}{f(u^*,v^*)}\\ &+\ln\frac{v(x,t)}{v^*}\frac{f(u(x,t),v^*)}{f(u(x,t),v(x,t))}.\end{aligned}$$

Eq. (3.7) becomes

$$\begin{aligned}\frac{\partial U(x,t)}{\partial t} =& -de^{-m\tau}\int_\Omega \frac{(u(x,t)-u^*)^2}{u(x,t)}\mathrm{d}x - \frac{p\rho_1}{\rho_2}\int_\Omega \frac{v(x,t)}{z(x,t)}(z(x,t)-z^*)^2\mathrm{d}x\\ &-\frac{D\rho_1 v^*}{\rho_2}\int_\Omega \frac{\|\nabla v\|^2}{v^2}\mathrm{d}x - \frac{\alpha\rho_1 w^*}{v^*(1+\alpha v^*)}\int_\Omega \frac{(v(x,t)-v^*)^2}{1+\alpha v(x,t)}\mathrm{d}x\\ &-\rho_1 w^*\int_\Omega\left[g\left(\frac{f(u^*,v^*)}{f(u(x,t),v^*)}\right)+g\left(\frac{w^*}{w(x,t)}\frac{f(u(x,t-\tau),v(x,t-\tau))}{f(u^*,v^*)}\right)\right]\mathrm{d}x\\ &-\rho_1 w^*\int_\Omega\left[g\left(\frac{w(x,t)}{w^*}\frac{v^*}{v(x,t)}\right)+g\left(\frac{v(x,t)}{v^*}\frac{f(u(x,t),v^*)}{f(u(x,t),v(x,t))}\right)\right]\mathrm{d}x.\end{aligned}$$

Hence, if $\mathscr{R}_0 > 1$, $\frac{\partial U(x,t)}{\partial t} \le 0$ for all $u,w,v,z \ge 0$. While $\frac{\partial U(x,t)}{\partial t} = 0$ if and only if $u = u^*, w = w^*, v = v^*$ and $z = z^*$. Noting that if $\mathscr{R}_0 > 1$, the infected steady state E^* is locally stable, we see it is globally asymptotically stable following from LaSalle's invariance principle. The proof is complete.

4. Numerical simulation

In this section, we implement numerical simulations to illustrate the main results obtained in Section 2. For convenience, we truncate the spatial domain $\mathbb{R}$ by $[0,5]$ and use the following function as the initial condition:

$$(u(x,t),w(x,t),v(x,t),z(x,t)) = (100,0.05,0.01,0.001), 0 \leqslant x < 5, -\tau \leqslant t \leqslant 0. \tag{4.1}$$

Example 1. In system (1.2), we let $a = 10^7, b = 0.1, c = 500, d = 0.1, m = 0.1, p = 5\times 10^{-8}, D = 0.0001, \alpha = 0.01, \beta = 5\times 10^{-12}, \rho_1 = 0.1, \rho_2 = 500, \rho_3 = 5, \tau = 7.8$. It is easy to show that the reproductive number $\mathscr{R}_0 = 0.2292 < 1$. By Theorem 1, we see that the uninfected steady state $E_1(10^8,0,0,0)$ of problem (1.2)-(1.4) is globally asymptotically stable. Numerical simulation illustrate this observation (see Fig. 1).

Example 2. In system (1.2), we let $a = 10^7, b = 0.1, c = 500, d = 0.1, m = 0.1, p = 5 \times 10^{-8}, D = 0.0001, \alpha = 0.01, \beta = 5 \times 10^{10}, \rho_1 = 0.1, \rho_2 = 500, \rho_3 = 5, \tau = 7.8$. Note that $\mathscr{R}_0 = 22.9203 > 1$. System (1.2) has an uninfected steady state $E_1(10^8, 0, 0, 0)$ and an infected steady state $E^*(1.0035 \times 10^8, 21.9004, 1991.7, 9.96 \times 10^6)$. Using Theorem 1, we see that the infected steady state E^* of problem (1.2)-(1.4) is globally asymptotically stable. Numerical simulation illustrate this observation (see Fig. 2).

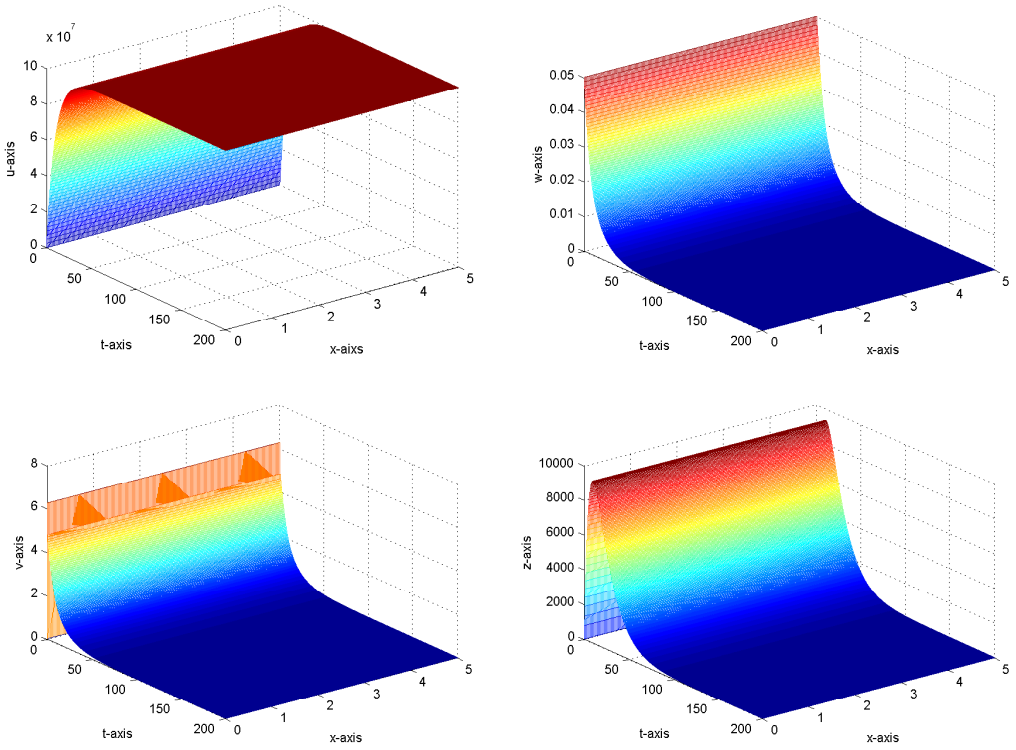

Fig.1. The solution of system (1.2) starting from initial condition (4.1) with parameters: $a = 10^7, b = 0.1, c = 500, d = 0.1, m = 0.1, p = 5 \times 10^{-8}, D = 0.0001, \alpha = 0.01, \beta = 5 \times 10^{-12}, \rho_1 = 0.1, \rho_2 = 500, \rho_3 = 5, \tau = 7.8$.

Conflict of Interests

The authors declare that there is no conflict of interests.

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Mechanical Engineering College (No. YJJXM 13008, No. JCYJ14011), the Science Foundation of Basic Courses Department of OEC (Jcky 1302).

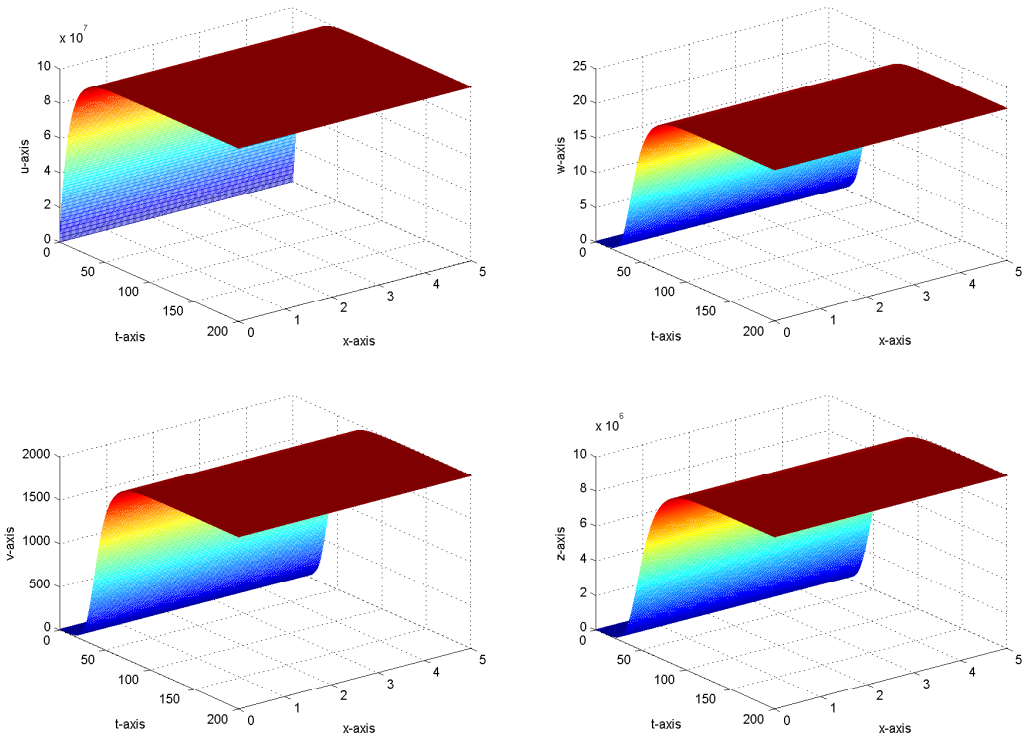

Fig.2. The solution of system (1.2) starting from initial condition (4.1) with parameters: $a = 10^7, b = 0.1, c = 500, d = 0.1, m = 0.1, p = 5 \times 10^{-8}, D = 0.0001, \alpha = 0.01, \beta = 5 \times 10^{-10}, \rho_1 = 0.1, \rho_2 = 500, \rho_3 = 5, \tau = 7.8$.

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