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Research Article

Analysis of a HBV Model with Diffusion and Time Delay

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This paper discussed a hepatitis B virus infection with delay, spatial diffusion, and standard incidence function. The local stability of equilibrium is obtained via characteristic equations. By using comparison arguments, it is proved that if the basic reproduction number is less than unity, the infection-free equilibrium is globally asymptotically stable. If the basic reproductive number is greater than unity, by means of an iteration technique, sufficiently conditions are obtained for the global asymptotic stability of the infected steady state. Numerical simulations are carried out to illustrate our findings.

1. Introduction

Human infection with hepatitis B virus (HBV) is a major global health problem. Between 300 and 400 million people are chronically infected worldwide. The virus is contracted through contact with blood or other fluids from the body, which could lead to develop viral persistence in the individual in the absence of strong antibody or some immune depression. Mathematical models have the potential to improve the understanding of the dynamics of this disease; one of the earliest models is referred to as the basic virus infection model, introduced by Nowak et al. [1]. They proposed a basic mathematical model for uninfected susceptible host cells (hepatocytes), u, infected host cells, w, and free virus particles, v, as follows:

$$\begin{aligned}
\dot{u}(t) &= s - \mu u(t) - \beta u(t)v(t), \\
\dot{w}(t) &= \beta u(t)v(t) - aw(t), \\
\dot{v}(t) &= kw(t) - dv(t),
\end{aligned} \tag{1.1}$$

where hepatocytes are produced at a rate s, uninfected cells die at rate μ and become and infected at rate $\beta u(t)v(t)$, infected hepatocytes are produced at rate $\beta u(t)v(t)$ and die at rate $aw(t)$. Free viruses are produced from infected cells at rate $kw(t)$ and are removed at rate $dv(t)$. It is assumed that all parameters are positive constants. Previous models assume that the infectious process is instantaneous; that is, in the very moment that the virus enters an uninfected cell, this one starts to produce virus particles; we know that this is not biologically reasonable. Thus, models with delays have been considered; in [2], the authors studied the following hepatitis B virus infection model with a time delay:

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

The authors gave results about local and global stability of feasible equilibria.

For HBV infection, susceptible host cells and infected cells are hepatocytes and cannot move under normal conditions, but viruses move freely in liver [3]; therefore, the authors introduce an HBV model with diffusion and delay. Xu and Ma [4] considered also a diffusion model with delay but instead of bilinear response of the infection rate, they considered saturation response.

In this work motivated by the work of Xu and Ma, we study the following model:

$$\begin{aligned}
\frac{\partial u}{\partial t} &= L - du(x,t) - \frac{\beta u(x,t)v(x,t)}{u(x,t)+w(x,t)},\\
\frac{\partial w}{\partial t} &= \frac{\beta e^{-m\tau}u(x,t-\tau)v(x,t-\tau)}{u(x,t-\tau)+w(x,t-\tau)} - aw(x,t),\\
\frac{\partial v}{\partial t} &= D\Delta v + kw(x,t) - pv(x,t),
\end{aligned} \tag{1.3}$$

for $t > 0$, $x \in \Omega$, with homogeneous Neumann boundary conditions

$$\frac{\partial v}{\partial \eta} = 0, \tag{1.4}$$

and initial conditions

$$\begin{aligned}
u(x,\theta) = \phi_1(x,\theta) \geq 0, \qquad w(x,\theta) = \phi_2(x,\theta) \geq 0,\\
v(x,\theta) = \phi_3(x,\theta) \geq 0, \quad \theta \in [-\tau, 0],\ x \in \overline{\Omega}.
\end{aligned} \tag{1.5}$$

In the previous problem Ω is a bounded domain in $\mathbb{R}^n$ with smooth boundary $\partial\Omega$, $\partial/\partial\eta$ denotes the outward normal derivative on $\partial\Omega$.

This paper is ordered as follows. In the next section we present a result about the existence, uniqueness, and positivity. In Section 3 we discuss the local stability of each of the feasible equilibria of system (1.3), by analyzing the corresponding characteristic equations. In Section 4, by using comparison arguments and an iterative technique, we establish sufficient conditions for the global stability of the equilibria of system (1.3). In Section 5 numerical simulations are carried out to illustrate our principal results and we compare the effect of the diffusion and the delay on the system (1.3).

2. Preliminaries

Consider problem (1.3)–(1.5) and the following definitions.

Definition 2.1. A pair of functions $\widetilde{U} = (\widetilde{u}, \widetilde{w}, \widetilde{v})$, $\widehat{U} = (\widehat{u}, \widehat{w}, \widehat{v})$ in $C([0,\infty)\times\overline{\Omega}) \cap C^{(1,2)}((0,\infty)\times\Omega)$ are called coupled upper and lower solutions to system (1.3)–(1.5) if $\widehat{u} \le \widetilde{u}$, $\widehat{w} \le \widetilde{w}$, $\widehat{v} \le \widetilde{v}$ in $\overline{\Omega}\times[-\tau,\infty)$ and the following differential inequalities hold:

$$\begin{aligned}
&\frac{\partial \widetilde{u}}{\partial t} \ge L - d\widetilde{u}(x,t) - \frac{\beta \widetilde{u}(x,t)\widehat{v}(x,t)}{\widetilde{u}(x,t) + \widehat{w}(x,t)},\\
&\frac{\partial \widetilde{w}}{\partial t} \ge \frac{\beta e^{-m\tau}\widetilde{u}(x,t-\tau)\widetilde{v}(x,t-\tau)}{\widetilde{u}(x,t-\tau) + \widetilde{w}(x,t-\tau)} - a\widetilde{w}(x,t),\\
&\frac{\partial \widetilde{v}}{\partial t} \ge D\Delta\widetilde{v} + k\widetilde{w}(x,t) - p\widetilde{v}(x,t),\\
&\frac{\partial \widehat{u}}{\partial t} \le L - d\widehat{u}(x,t) - \frac{\beta \widehat{u}(x,t)\widetilde{v}(x,t)}{\widehat{u}(x,t) + \widetilde{w}(x,t)},\\
&\frac{\partial \widehat{w}}{\partial t} \le \frac{\beta e^{-m\tau}\widehat{u}(x,t-\tau)\widehat{v}(x,t-\tau)}{\widehat{u}(x,t-\tau) + \widehat{w}(x,t-\tau)} - a\widehat{w}(x,t),\\
&\frac{\partial \widehat{v}}{\partial t} \le D\Delta\widehat{v} + k\widehat{w}(x,t) - p\widehat{v}(x,t),
\end{aligned} \tag{2.1}$$

for $(x,t)\in\Omega\times(0,\infty)$, and

$$\begin{gathered}
\frac{\partial \widehat{u}}{\partial \eta} \le 0 \le \frac{\partial \widetilde{u}}{\partial \eta}, \qquad \frac{\partial \widehat{w}}{\partial \eta} \le 0 \le \frac{\partial \widetilde{w}}{\partial \eta},\\
\frac{\partial \widehat{v}}{\partial \eta} \le 0 \le \frac{\partial \widetilde{v}}{\partial \eta} \quad (x,t)\in\partial\Omega\times(0,\infty),\\
\widehat{u}(x,t) \le \phi_1(x,t) \le \widetilde{u}(x,t), \qquad \widehat{w}(x,t) \le \phi_2(x,t) \le \widetilde{w}(x,t),\\
\widehat{v}(x,t) \le \phi_3(x,t) \le \widetilde{v}(x,t), \quad (x,t)\in\overline{\Omega}\times[-\tau,0].
\end{gathered} \tag{2.2}$$

The following lemma then follows from Theorem 3.4 developed by Redlinger [5].

Lemma 2.2. *Let $\widetilde{U}$ and $\widehat{U}$ be a pair of coupled upper and lower solutions for problem* (1.3)–(1.5) *and suppose that the initial functions ϕ_i ($i = 1,2,3$) are Hölder continuous in $[-\tau,0]\times\Omega$. Then* *problem* (1.3)–(1.5) *has exactly one regular solution* $U(x,t) = (u(x,t), w(x,t), v(x,t))$ *satisfying* $\widehat{U} \le U \le \widetilde{U}$ *in* $\overline{\Omega} \times [-\tau, \infty)$.

It is not hard to see that $0 = (0,0,0)$ and $K = (K_1, K_2, K_3)$ are a pair of coupled lower-upper solutions to problem (1.3)–(1.5), where

$$K_1 = \max\left\{\frac{L}{d}, \sup_{-\tau\le\theta\le 0} \|\phi_1(\cdot,\theta)\|_{C(\overline{\Omega},R)}\right\},$$
$$K_2 = \max\left\{\frac{k\beta e^{-m\tau}K_1}{ap}, \sup_{-\tau\le\theta\le 0} \|\phi_2(\cdot,\theta)\|_{C(\overline{\Omega},R)}\right\}, \tag{2.3}$$
$$K_3 = \max\left\{\frac{k^2\beta e^{-m\tau}K_1}{ap^2}, \sup_{-\tau\le\theta\le 0} \|\phi_3(\cdot,\theta)\|_{C(\overline{\Omega},R)}\right\}.$$

Hence, $0 \le u(x,t) \le K_1$, $0 \le w(x,t) \le K_2$, $0 \le v(x,t) \le K_3$ for $(x,t) \in \overline{\Omega} \times [-\tau, \infty)$, and also, by the maximum principle, if $\phi_i(x,0) \not\equiv 0$ $(i = 1,2,3)$, we have $u(x,t) > 0$, $w(x,t) > 0$, $v(x,t) > 0$ for all $t > 0$, $x \in \overline{\Omega}$.

3. Local Stability

System (1.3) has the equilibrium $E_1(L/d, 0, 0)$. Let $R_0 = \beta k e^{-m\tau}/ap > 1$ then system (1.3) has a unique infected steady state $E_2(u^*(\tau), w^*(\tau), v^*(\tau))$; the previous notation is because the equilibrium involves τ and we use this as the parameter for the stability analysis, where

$$u^*(\tau) = \frac{Le^{-m\tau}}{de^{-m\tau} + a(R_0 - 1)}, \qquad w^*(\tau) = \frac{Le^{-m\tau}(R_0 - 1)}{de^{-m\tau} + a(R_0 - 1)},$$
$$v^*(\tau) = \frac{Lke^{-m\tau}(R_0 - 1)}{p[de^{-m\tau} + a(R_0 - 1)]}. \tag{3.1}$$

Let $0 = \mu_1 < \mu_2 < \cdots$ be the eigenvalues of the operator $-\Delta$ on Ω with the homogeneous Neumann boundary conditions, and let $E(\mu_i)$ be the eigenspace corresponding to μ_i in $C^1(\Omega)$.

Let $\mathbb{X} = [C^1(\Omega)]^3$, let $\{\phi_{ij}; j = 1, 2, \ldots, \dim E(\mu_i)\}$ be an orthonormal basis of $E(\mu_i)$, and let $\mathbb{X}_{ij} = \{c\phi_{ij} \mid c \in \mathbb{R}^3\}$, then

$$\mathbb{X} = \bigoplus_{i=0}^{\infty} \mathbb{X}_i, \quad \mathbb{X}_i = \bigoplus_{j=1}^{\dim E(p_i)} \mathbb{X}_{ij}. \tag{3.2}$$

Let $\mathfrak{D} = \operatorname{diag}(0,0,D)$, $Z = Z(x,t) = (U(x,t), W(x,t), V(x,t))$, $\mathcal{L}Z = \mathfrak{D}\Delta Z + J_{E^*}Z + J_{\tau E^*}Z(t-\tau)$, where

$$J_{E^*} = \begin{pmatrix} -d - \dfrac{\beta\overline{w}\,\overline{v}}{(\overline{u}+\overline{w})^2} & \dfrac{\beta\overline{u}\,\overline{v}}{(\overline{u}+\overline{w})^2} & -\dfrac{\beta\overline{u}}{\overline{u}+\overline{w}} \\ 0 & -a & 0 \\ 0 & k & -p \end{pmatrix},$$
$$J_{\tau} = \begin{pmatrix} 0 & 0 & 0 \\ \dfrac{\beta e^{-m\tau}\overline{v}\,\overline{w}}{(\overline{u}+\overline{w})^2} & -\dfrac{\beta e^{-m\tau}\overline{u}\,\overline{v}}{(\overline{u}+\overline{w})^2} & \dfrac{\beta e^{-m\tau}\overline{u}}{\overline{u}+\overline{w}} \\ 0 & 0 & 0 \end{pmatrix}, \tag{3.3}$$

and $E^*(\overline{u},\overline{w},\overline{v})$ represents any feasible steady state of the system (1.3). The linearization of system (1.3) at E^* is of the form $Z_t = \mathcal{L}Z$. For each $i \geq 1$, $\mathbb{X}_i$ is invariant under the operator $\mathcal{L}$, and λ is an eigenvalue of the matrix $-\mu_i\mathfrak{D} + J_{E^*} + J_{\tau E^*}$ for some $i \geq 1$, then, there is an eigenvector in $\mathbb{X}_i$.

The characteristic equation on the equilibrium E_1 is

$$(\lambda + d)\left(\lambda^2 + a_1\lambda + a_0 + b_0(\tau)e^{-\lambda\tau}\right) = 0, \tag{3.4}$$

where

$$a_0 = a(p + \mu_I D), \qquad a_1 = a + p + \mu_i D, \qquad b_0(\tau) = -k\beta e^{-m\tau}. \tag{3.5}$$

The characteristic equation has the negative root $\lambda = -d$. All other roots of (3.4) are given by the transcendental equation

$$\lambda^2 + a_1\lambda + a_0 + b_0(\tau)e^{-\lambda\tau} = 0. \tag{3.6}$$

Let

$$f(\lambda) = \lambda^2 + a_1\lambda + a_0 + b_0(\tau)e^{-\lambda\tau}, \tag{3.7}$$

if $R_0 > 1$, note that for λ real and $i = 1$ (in this case $\mu_1 = 0$),

$$f(0) = a_0 + b_0 = ap - k\beta e^{-m\tau} < 0, \qquad \lim_{\lambda\to\infty} f(\lambda) = +\infty. \tag{3.8}$$

Hence, (3.7) has a positive root. Therefore, there is a characteristic root λ with positive real part in the spectrum of $\mathcal{L}$. Accordingly, if $R_0 > 1$, the disease-free steady state $E_1(\lambda/d, 0, 0)$ is unstable.

If $R_0 < 1$, when $\tau = 0$ the coefficients of (3.7) are a_1 and $a_0 + b_0(0)$, and under the hypothesis $R_0 < 1$ the coefficients are positive and according to the criterion of Routh-Hurwitz, the equilibrium $E_1(\lambda/d, 0, 0)$ is locally asymptotically stable.

For $\tau > 0$ if $i\omega$ $(\omega > 0)$ is a solution of (3.6), separating in real and imaginary parts, we obtain

$$-\omega^2 + a_0 = -b_0(\tau)\cos(\omega\tau),$$
$$a_1\omega = b_0(\tau)\sin(\omega\tau). \tag{3.9}$$

Squaring and adding the above equations and taking $z = \omega^2$ we obtain

$$z^2 + \left(a_1^2 - 2a_0\right)z + a_0^2 - b_0(\tau)^2 = 0, \tag{3.10}$$

where

$$a_1^2 - 2a_0 = a^2 + (p + \mu_i D)^2 > 0,$$
$$a_0^2 - b_0^2(\tau) = \left(a(p + \mu_i D) - k\beta e^{-m\tau}\right)\left(a(p + \mu_i D) + k\beta e^{-m\tau}\right) > 0, \tag{3.11}$$

the last inequality is true because $R_0 < 1$. Therefore there is no positive root $z = \omega^2$ of (3.10). In conclusion if $R_0 < 1$ the equilibrium $E_1(\lambda/d, 0, 0)$ is locally asymptotically stable.

The characteristic equation of system (1.3) at the endemic equilibrium $E_2(u^*, w^*, v^*)$ is of the form

$$\lambda^3 + a_2(\tau)\lambda^2 + a_1\lambda + a_0(\tau) + \left(b_2(\tau)\lambda^2 + b_1(\tau)\lambda + b_0(\tau)\right)e^{-\lambda\tau} = 0, \tag{3.12}$$

where

$$a_2(\tau) = a + d + p + \mu_i D + \frac{\beta v^* w^*}{(u^* + w^*)^2},$$
$$a_1 = a(p + \mu_i D) + (a + p + \mu_i D)d,$$
$$a_0(\tau) = a(p + \mu_i D)\left[d + \frac{\beta w^* v^*}{(u^* + w^*)^2}\right],$$
$$b_2(\tau) = \frac{\beta e^{-m\tau} u^* v^*}{(u^* + w^*)^*},$$
$$b_1(\tau) = (d + p + \mu_i D)\frac{\beta e^{-m\tau} u^* w^*}{(u^* + w^*)^2} - k\frac{\beta e^{-m\tau} u^*}{u^* + w^*},$$
$$b_0(\tau) = d(p + \mu_i D)\frac{\beta e^{-m\tau} u^* v^*}{(u^* + w^*)^2} - dk\frac{\beta e^{-m\tau} u^*}{u^* + w^*}, \tag{3.13}$$

when $\tau = 0$ becomes

$$\lambda^3 + (a_2(0) + b_2(0))\lambda^2 + (a_1 + b_1(0))\lambda + (a_0(0) + b_0(0)) = 0. \tag{3.14}$$

Note that $a_2(0)+b_2(0)>0$; adding $a_0(0)+b_0(0)$ and replacing $u^*(0)$ and $w^*(0)$ we obtain

$$\begin{aligned}
a_0(0)+b_0(0) &= a(p+\mu_i D)\frac{\beta w^*(0)v^*(0)}{(u^*(0)+w^*(0))^2}+d(p+\mu_i D)\frac{\beta u^*(0)v^*(0)}{(u^*(0)+w^*(0))^2}>0,\\
&(a_2(0)+b_2(0))(a_1+b_1(0))-a_0(0)+b_0(0)\\
&=\left(d(a+p+\mu_i D)+(u^*(0)+w^*(0))\frac{(p+\mu_i D)\beta v^*(0)}{(u^*(0)+w^*(0))^2}\right)\\
&\times\left(a+d+p+\mu_i D+(u^*(0)+w^*(0))\frac{\beta v^*}{(u^*(0)+w^*(0))^2}\right)\\
&+\frac{\lambda\beta v^*(0)}{(u^*(0)+w^*(0))^2}\left(a+d+(u^*(0)+w^*(0))\frac{\beta v^*(0)}{(u^*(0)+w^*(0))^2}\right)>0.
\end{aligned}\tag{3.15}$$

By the Routh-Hurwitz criteria, all roots have negative real parts if $R_0>1$.

For the case $\tau>0$ we look for solutions $\lambda=i\omega$ $(\omega>0)$ for (3.12), separating real and imaginary parts, it follows that

$$\begin{aligned}
\omega^3-a_1\omega &= \left(b_2(\tau)\omega^2-b_0(\tau)\right)\sin(\omega\tau)+b_1(\tau)\omega\cos(\omega\tau),\\
a_2(\tau)\omega^2-a_0(\tau) &= -\left(b_2(\tau)\omega^2-b_0(\tau)\right)\cos(\omega\tau)+b_1(\tau)\omega\sin(\omega\tau).
\end{aligned}\tag{3.16}$$

Squaring and adding the two equations, we derive that

$$\omega^6+C_1\omega^4+C_2\omega^2+C_3=0,\tag{3.17}$$

where

$$\begin{aligned}
C_1 &= (p+\mu_i D)^2+\left(d+\frac{\beta w^*(\tau)v^*(\tau)}{(u^*(\tau)+w^*(\tau))^2}\right)^2+\frac{au^*(\tau)}{u^*(\tau)+w^*(\tau)}\left(a+\frac{\beta e^{-m\tau}u^*(\tau)v^*(\tau)}{(u^*(\tau)+w^*(\tau))^2}\right)>0,\\
C_2 &= a^2\left(d^2+(p+\mu_i D)^2\right)\frac{w^*(\tau)(u^*(\tau)+2w^*(\tau))}{(u^*(\tau)+w^*(\tau))^2}\\
&\quad+\frac{a^2\beta w^*(\tau)v^*(\tau)}{(u^*(\tau)+w^*(\tau))^2}\left(2d+\frac{\beta w^*(\tau)v^*(\tau)}{(u^*(\tau)+w^*(\tau))^2}\right)+(p+\mu_i D)\left(d+\frac{\beta w^*(\tau)+v^*(\tau)}{(u^*(\tau)+w^*(\tau))^2}\right)>0,\\
C_3 &= \frac{a(p+\mu_i D)^2\beta v^*(\tau)(de^{-m\tau}u^*(\tau)+aw^*(\tau))}{(u^*(\tau)+w^*(\tau))^3}\left(d\left(2x^*(\tau)+w^*(\tau)+\frac{\beta w^*(\tau)v^*(\tau)}{u^*(\tau)+w^*(\tau)}\right)\right)>0,
\end{aligned}\tag{3.18}$$

implying that (3.17) has no positive roots $z=\omega^2$.

Theorem 3.1. *If $R_0 < 1$ the disease-free equilibrium is locally asymptotically stable; if $R_0 > 1$ it is unstable and the endemic equilibrium exists and it is locally asymptotically stable.*

4. Global Stability

We will discuss in this section the global stability of the infected steady state and the disease-free equilibrium. The technique of proof is to use comparison arguments and to successively modify the coupled lower-upper solutions pairs.

Consider the following delay system:

$$\begin{aligned} \dot{u}_1(t) &= \frac{a_1\beta e^{-m\tau}u_2(t-\tau)}{a_1+u_1(t-\tau)} - au_1(t), \\ \dot{u}_2(t) &= ku_1(t) - pu_2(t), \end{aligned} \tag{4.1}$$

with initial conditions

$$u_i(s) = \phi_i(s) \geq 0, \quad s \in [-\tau, 0), \; \phi_i(0) > 0, \; \phi_i \in C([-\tau, 0], \mathbb{R}_+). \tag{4.2}$$

System (4.1) always have the trivial equilibrium $A^0(0,0)$. If $k\beta e^{-m\tau} > ap$, then system (4.1) has a unique positive equilibrium $A^*(u_1^*, u_2^*)$ where

$$u_1^* = \frac{a_1\left(k\beta e^{-m\tau} - ap\right)}{ap}, \qquad u_2^* = \frac{a_1 k\left(k\beta e^{-m\tau} - ap\right)}{ap^2}, \tag{4.3}$$

and according to [2], for system (4.1), one has the following.

Lemma 4.1. *If $k\beta e^{-m\tau} > ap$, then the positive equilibrium $A^*(u_1^*, u_2^*)$ is globally stable.*
If $k\beta e^{-m\tau} < ap$, then the equilibrium $A^0(0,0)$ is globally stable.

Now we stablish and prove our result about global stability.

Theorem 4.2. *Let $(u(x,t), w(x,t), v(x,t))$ be a solution to problem* (1.3)–(1.5), *let $\phi_i(x,0) \not\equiv 0$ $(i = 1,2,3)$. If $R_0 > 1$ and*

(H1) $dpe^{-m\tau} > k\beta e^{-m\tau} - ap$,

then

$$\lim_{t\to\infty} (u(x,t), w(x,t), v(x,t)) = (u^*, w^*, v^*) \quad \text{uniformly for } x \in \Omega, \tag{4.4}$$

that is, the infected steady state E^* is globally asymptotically stable.

Proof. Let $(u(x,t), w(x,t), v(x,t))$ be a solution to problem (1.3)–(1.5), let $\phi_i \not\equiv 0$ $(i = 1,2,3)$. We have $u(x,t) > 0$, $w(x,t) > 0$, and $v(x,t) > 0$ for all $x \in \overline{\Omega}$, $t > 0$. Denote

$$\begin{aligned} \overline{u} &= \limsup_{t\to\infty} \max_{x\in\overline{\Omega}} u(x,t), & \underline{u} &= \liminf_{t\to\infty} \min_{x\in\overline{\Omega}} u(x,t), \\ \overline{w} &= \limsup_{t\to\infty} \max_{x\in\overline{\Omega}} w(x,t), & \underline{w} &= \liminf_{t\to\infty} \min_{x\in\overline{\Omega}} w(x,t), \\ \overline{v} &= \limsup_{t\to\infty} \max_{x\in\overline{\Omega}} v(x,t), & \underline{v} &= \liminf_{t\to\infty} \min_{x\in\overline{\Omega}} v(x,t). \end{aligned} \tag{4.5}$$

First we look for upper solutions for the system (1.3). Let $(\overline{u}^1(x,t), \overline{w}^1(x,t), \overline{v}^1(x,t))$ be a solution for the following problem:

$$\begin{gathered} \frac{\partial \overline{u}^{(1)}}{\partial t} = L - d\overline{u}^{(1)}(x,t), \quad t > 0,\ x \in \Omega, \\ \frac{\partial \overline{w}^{(1)}}{\partial t} = \frac{\beta e^{-m\tau}\overline{u}^{(1)}(x,t-\tau)\overline{v}^{(1)}(x,t-\tau)}{\overline{u}^{(1)}(x,t-\tau) + \overline{w}^{(1)}(x,t-\tau)} - a\overline{w}^{(1)}(x,t), \quad t > 0,\ x \in \Omega, \\ \frac{\partial \overline{v}^{(1)}}{\partial t} = D\Delta\overline{v}^{(1)}(x,t) + k\overline{w}^{(1)}(x,t) - p\overline{v}^{(1)}(x,t), \quad t > 0,\ x \in \Omega, \\ \frac{\partial \overline{u}^{(1)}(x,t)}{\partial t} = \frac{\partial \overline{w}^{(1)}(x,t)}{\partial t} = \frac{\partial \overline{v}^{(1)}(x,t)}{\partial t} = 0, \quad t > 0,\ x \in \partial\Omega, \\ \overline{u}^{(1)}(x,t) = u(x,t), \qquad \overline{v}^{(1)}(x,t) = v(x,t), \\ \overline{w}^{(1)}(x,t) = w(x,t), \quad t \in [-\tau, 0],\ x \in \overline{\Omega}. \end{gathered} \tag{4.6}$$

We note that the solution of this system is an upper solution of system (1.3)–(1.5). For $t > 0$, $x \in \overline{\Omega}$ we have

$$0 \le u(x,t) \le \overline{u}^{(1)}(x,t), \qquad 0 \le w(x,t) \le \overline{w}^{(1)}(x,t), \qquad 0 \le v(x,t) \le \overline{v}^{(1)}(x,t). \tag{4.7}$$

From the first equation of (4.6)

$$\lim_{t\to\infty} \overline{u}^{(1)}(x,t) = \frac{L}{d} = M_1^u. \tag{4.8}$$

Hence, by comparison, for all $\epsilon > 0$ sufficiently small, there exists $t_1 > 0$ such that if $t > t_1$

$$\max_{x\in\overline{\Omega}} u^{(1)}(x,t) \le M_1^u + \epsilon, \tag{4.9}$$

since ϵ is arbitrary and sufficiently small we can conclude that

$$\overline{u} = \limsup_{t\to\infty} \max_{x\in\overline{\Omega}} u(x,t) \le M_1^u. \tag{4.10}$$

Now consider the problem related with the second and third equations of (4.6)

$$\begin{aligned}
\frac{\partial \omega_2^{(1)}}{\partial t} &= \frac{\beta e^{-m\tau}(M_1^u+\epsilon)\omega_3^{(1)}(x,t-\tau)}{M_1^u+\epsilon+\omega_2^{(1)}(x,t-\tau)} - a\omega_2^{(1)}(x,t), \quad t>t_1,\ x\in\Omega,\\
\frac{\partial \omega_3^{(1)}}{\partial t} &= D\Delta\omega_3^{(1)}(x,t) + k\omega_2^{(1)}(x,t) - p\omega_3^{(1)}, \quad t>t_1,\ x\in\Omega,\\
\frac{\partial \omega_2^{(1)}}{\partial \eta} &= \frac{\partial \omega_3^{(1)}}{\partial \eta} = 0, \quad t>t_1,\ x\in\partial\Omega,\\
\omega_2^{(1)}(x,t) &= w(x,t), \qquad \omega_3^{(1)}(x,t) = v(x,t), \quad t\in[-\tau,t_1],\ x\in\overline{\Omega}.
\end{aligned} \tag{4.11}$$

Consider the solution for

$$\begin{aligned}
\dot{u}_2 &= \frac{\beta e^{-m\tau}(M_1^u+\epsilon)u_3(t-\tau)}{M_1^u+\epsilon+u_2(t-\tau)} - au_2, \quad t>t_1,\\
\dot{u}_3 &= ku_2 - pu_3, \quad t>t_1,\\
u_2(t) &= \max_{x\in\overline{\Omega}} w(x,t), \quad u_3(t) = \max_{x\in\overline{\Omega}} v(x,t), \quad t\in[-\tau,t_1].
\end{aligned} \tag{4.12}$$

Note that $(u_1(t),u_2(t))$ is an upper solution for system (4.11), and using the assumption that $R_0>1$, by Lemma 4.1, it follows from (4.12) that

$$\begin{aligned}
\lim_{t\to\infty} u_2(t) &= \frac{(k\beta e^{-m\tau}-ap)(M_1^u+\epsilon)}{ap},\\
\lim_{t\to\infty} u_3(t) &= \frac{k(k\beta e^{-m\tau}-ap)(M_1^u+\epsilon)}{ap^2}.
\end{aligned} \tag{4.13}$$

Hence, for all $\epsilon>0$ sufficiently small, by comparison there exists a $t_2>t_1$ such that if $t>t_2$

$$\max_{x\in\overline{\Omega}} \overline{w}^{(1)}(x,t) < M_1^w+\epsilon, \qquad \max_{x\in\overline{\Omega}} \overline{v}^{(1)}(x,t) < M_1^v+\epsilon, \tag{4.14}$$

where

$$M_1^w = \frac{(k\beta e^{-m\tau}-ap)M_1^u}{ap}, \qquad M_1^v = \frac{k(k\beta e^{-m\tau}-ap)M_1^u}{ap^2}. \tag{4.15}$$

Since $\epsilon>0$ is arbitrary and sufficiently small, we conclude that

$$\begin{aligned}
\overline{w} &= \limsup_{t\to\infty}\max_{x\in\overline{\Omega}} w(x,t) \le M_1^w,\\
\overline{v} &= \limsup_{t\to\infty}\max_{x\in\overline{\Omega}} v(x,t) \le M_1^v.
\end{aligned} \tag{4.16}$$

Now for lower solutions, let $(\underline{u}^{(1)}(x,t), \underline{w}^{(1)}(x,t), \underline{v}^{(1)}(x,t))$ be the solution for the following problem:

$$\begin{aligned}
&\frac{\partial \underline{u}^{(1)}}{\partial t} = L - d\underline{u}^{(1)}(x,t) - \frac{\beta \underline{u}^{(1)}(x,t)\overline{v}^{(1)}(x,t)}{\underline{u}^{(1)}(x,t) + \overline{w}^{(1)}(x,t)}, \quad t > t_2,\ x \in \Omega, \\
&\frac{\partial \underline{w}^{(1)}}{\partial t} = \frac{\beta e^{-m\tau} \underline{u}^{(1)}(x,t)\underline{v}^{(1)}(x,t)}{\underline{u}^{(1)}(x,t) + \underline{w}^{(1)}(x,t)} - a\underline{w}^{(1)}(x,t), \quad t > t_2,\ x \in \Omega, \\
&\frac{\partial \underline{v}^{(1)}}{\partial t} = D\Delta \underline{v}^{(1)}(x,t) + k\underline{w}^{(1)}(x,t) - p\underline{v}^{(1)}(x,t), \quad t > t_2,\ x \in \Omega, \\
&\frac{\partial \underline{u}^{(1)}}{\partial \eta} = \frac{\partial \underline{w}^{(1)}}{\partial \eta} = \frac{\partial \underline{v}^{(1)}}{\partial \eta} = 0, \quad t > t_2,\ x \in \partial\Omega, \\
&\underline{u}^{(1)}(x,t) = \frac{1}{2}u(x,t), \qquad \underline{w}^{(1)}(x,t) = \frac{1}{2}w(x,t), \\
&\underline{v}^{(1)}(x,t) = \frac{1}{2}v(x,t), \quad t \in [-\tau, t_2],\ x \in \overline{\Omega}.
\end{aligned} \tag{4.17}$$

Note that the solution of (4.17) is a lower solution to (1.3)–(1.5). For all $\epsilon > 0$ sufficiently small, from the first equation of (4.17) and (4.16) it follows

$$\frac{\partial \underline{u}^{(1)}}{\partial t} \geq L - d\underline{u}^{(1)}(x,t) - \beta\left(M_1^v + \epsilon\right), \quad t > t_2,\ x \in \Omega. \tag{4.18}$$

By comparing the above equation with the following problem:

$$\begin{aligned}
&\frac{\partial \omega_1^{(1)}}{\partial t} = L - d\omega_1^{(1)}(x,t) - \beta\left(M_1^v + \epsilon\right), \quad t > t_2,\ x \in \Omega, \\
&\frac{\partial \omega_1}{\omega \eta} = 0, \quad t > t_2,\ x \in \partial\Omega, \qquad \omega_1(x,t_2) = \frac{1}{2}u(x,t_2), \quad x \in \overline{\Omega},
\end{aligned} \tag{4.19}$$

we obtain

$$\lim_{t \to \infty} \omega_1(x,t) = \frac{L - \beta\left(M_1^v + \epsilon\right)}{d}, \tag{4.20}$$

so $\underline{u}^{(1)}(x,t) \geq \omega_1(x,t)$, $t > t_2$, and $x \in \Omega$. Hence, for all $\epsilon > 0$ sufficiently small, there is a $t_3 > t_2$ such that if $t > t_3$,

$$\min_{x \in \overline{\Omega}} \underline{u}^{(1)}(x,t) \geq N_1^u - \epsilon, \tag{4.21}$$

where

$$N_1^u = \frac{L - \beta M_1^v}{d}. \tag{4.22}$$

Since $\epsilon > 0$ is arbitrary sufficiently small, by comparison we conclude that

$$\underline{u} = \liminf_{t \to \infty} \min_{x \in \overline{\Omega}} u(x,t) \geq N_1^u = \frac{L - \beta M_1^v}{d}. \tag{4.23}$$

Now consider the following problem related with the second and third equations of (4.17):

$$\begin{aligned}
\frac{\partial \omega_2}{\partial t} &= \frac{\beta e^{-m\tau}(N_1^u - \epsilon)\omega_3(x,t-\tau)}{N_1^u - \epsilon + \omega_2(x,t-\tau)} - a\omega_2(x,t), \quad t > t_3,\ x \in \Omega, \\
\frac{\partial \omega_3}{\partial t} &= D\Delta\omega_3(x,t) + k\omega_2(x,t) - p\omega_3(x,t), \quad t > t_3,\ x \in \Omega, \\
\frac{\partial \omega_2}{\partial \eta} &= \frac{\partial \omega_3}{\partial \eta} = 0, \quad t > t_3,\ x \in \partial\Omega, \\
\omega_2(x,t) &= \frac{1}{2}w(x,t), \quad \omega_3(x,t) = \frac{1}{2}v(x,t), \quad t \in [-\tau, t_3],\ x \in \overline{\Omega}.
\end{aligned} \tag{4.24}$$

Now let us consider the solution for the problem

$$\begin{aligned}
\dot{u}_2(t) &= \frac{\beta e^{-m\tau}(N_1^u - \epsilon)u_3(t-\tau)}{N_1^u - \epsilon + u_2(t-\tau)} - au_2(t), \quad t > t_3, \\
\dot{u}_3(t) &= ku_2(t) - pu_3(t), \quad t > t_3, \\
u_2(t) &= \frac{1}{2}\min_{x \in \overline{\Omega}} w(x,t), \quad u_3(t) = \frac{1}{2}\min_{x \in \overline{\Omega}} v(x,t), \quad t \in [-\tau, t_3],\ t > t_3,
\end{aligned} \tag{4.25}$$

and according to Lemma 4.1

$$\begin{aligned}
\lim_{t \to \infty} u_2(t) &= \frac{(k\beta e^{-m\tau} - ap)(N_1^u - \epsilon)}{ap}, \\
\lim_{t \to \infty} u_3(t) &= \frac{k(k\beta e^{-m\tau} - ap)(N_1^u - \epsilon)}{ap^2}.
\end{aligned} \tag{4.26}$$

Hence, for all $\epsilon > 0$ sufficiently small, by comparison there exists a $t_4 > t_3$ such that if $t > t_4$

$$\min_{x \in \overline{\Omega}} \underline{w}^{(1)}(x,t) > N_1^w - \epsilon, \qquad \min_{x \in \overline{\Omega}} \underline{v}^{(1)}(x,t) > N_1^v - \epsilon, \tag{4.27}$$

where

$$N_1^w = \frac{(k\beta e^{-m\tau} - ap)N_1^u}{ap}, \qquad N_1^v = \frac{k(k\beta e^{-m\tau} - ap)N_1^u}{ap^2}. \tag{4.28}$$

Since $\epsilon > 0$ is arbitrary and sufficiently small, we conclude that

$$\begin{aligned} \underline{w} &= \liminf_{t\to\infty} \min_{x\in\overline{\Omega}} w(x,t) \geq N_1^w, \\ \underline{v} &= \liminf_{t\to\infty} \min_{x\in\overline{\Omega}} v(x,t) \geq N_1^v. \end{aligned} \tag{4.29}$$

Now we look for the closest upper and lower solutions. Let $(\overline{u}^{(2)}, \overline{w}^{(2)}, \overline{v}^{(2)})$ be a solution for the problem

$$\begin{aligned} \frac{\partial \overline{u}^{(2)}}{\partial t} &= L - d\overline{u}^{(2)}(x,t) - \frac{\beta \overline{u}^{(2)}(x,t)\underline{v}^{(1)}(x,t)}{\overline{u}^{(1)} + \overline{w}^{(1)}(x,t)}, \quad t > t_4,\ x \in \Omega, \\ \frac{\partial \overline{w}^{(2)}}{\partial t} &= \frac{\beta e^{-m\tau}\overline{u}^{(2)}(x,t-\tau)\overline{v}^{(2)}(x,t)}{\overline{u}^{(2)}(x,t-\tau) + \overline{w}^{(2)}(x,t-\tau)} - a\overline{w}^{(2)}(x,t), \quad t > t_4,\ x \in \Omega, \\ \frac{\partial \overline{v}^{(2)}}{\partial t} &= D\Delta\overline{v}(x,t) + k\overline{w}^{(2)}(x,t) - p\overline{v}^{(2)}(x,t), \quad t > t_4,\ x \in \Omega, \\ \frac{\partial \overline{u}^{(2)}}{\partial \eta} &= \frac{\partial \overline{w}^{(2)}}{\partial \eta} = \frac{\partial \overline{v}^{(2)}}{\partial \eta} = 0, \quad t > t_4,\ x \in \partial\Omega, \\ \overline{u}^{(2)}(x,t) &= u(x,t), \qquad \overline{w}^{(2)}(x,t) = w(x,t), \\ \overline{v}^{(2)}(x,t) &= v(x,t), \quad t \in [-\tau, t_4],\ x \in \overline{\Omega}. \end{aligned} \tag{4.30}$$

For all $\epsilon > 0$ sufficiently small it follows form the first equation of (4.30) and the inequalities (4.27) and (4.14) that

$$\frac{\partial \overline{u}^{(2)}}{\partial t} \leq L - d\overline{u}^{(2)}(x,t) - \frac{\beta \overline{u}^{(2)}(x,t)(N_1^v - \epsilon)}{M_1^u + \epsilon + M_1^w + \epsilon}, \quad t > t_4,\ x \in \Omega. \tag{4.31}$$

Let $\omega_1^{(2)}(x,t)$ be the solution for the following problem:

$$\begin{aligned} \frac{\partial \omega_1^{(2)}}{\partial t} &= L - d\omega_1^{(2)}(x,t) - \frac{\beta \omega_1^{(2)}(x,t)(N_1^v - \epsilon)}{M_1^u + \epsilon + M_1^w + \epsilon}, \quad t > t_4,\ x \in \Omega, \\ \frac{\partial \omega_1^{(2)}}{\partial \eta} &= 0, \quad t > t_4,\ x \in \partial\Omega, \\ \omega_1^{(2)}(x,t_4) &= u(x,t_4), \quad x \in \overline{\Omega}, \end{aligned} \tag{4.32}$$

it follows that

$$\lim_{t\to\infty}\omega_1^{(2)}(x,t)=\frac{L\left(M_1^u+M_1^w+2\epsilon\right)}{d\left(M_1^u+M_1^w+2\epsilon\right)+\beta\left(N_1^v-\epsilon\right)}. \tag{4.33}$$

By comparison we have that $\overline{u}^{(2)}\leq\omega_1^{(2)}$, $t>t_4$, and $x\in\overline{\Omega}$. Hence, for all $\epsilon>0$ sufficiently small, by comparison, there is a $t_5>t_4$ such that if $t>t_5$

$$\max_{x\in\overline{\Omega}}\overline{u}^{(2)}(x,t)=M_2^u+\epsilon, \tag{4.34}$$

where

$$M_2^u=\frac{L\left(M_1^u+M_1^w\right)}{d\left(M_1^u+M_1^w\right)+\beta\left(N_1^v\right)}. \tag{4.35}$$

Since (4.34) is valid for $\epsilon>0$ arbitrary and sufficiently small, by comparison we conclude that

$$\overline{u}=\limsup_{t\to\infty}\max_{x\in\overline{\Omega}}u(x,t)\leq M_2^u. \tag{4.36}$$

Now consider the following problem related with the second and third equations of (4.30):

$$\begin{gathered}
\frac{\partial\omega_2^{(2)}}{\partial t}=\frac{\beta e^{-m\tau}\left(M_2^u+\epsilon\right)\omega_3^{(2)}(x,t)}{M_2^u+\omega_2^{(2)}(x,t-\tau)}-a\omega_2^{(2)}(x,t),\quad t>t_5,\ x\in\Omega,\\
\frac{\partial\omega_3^{(2)}}{\partial t}=D\Delta\omega_3^{(2)}(x,t)+k\omega_2^{(2)}(x,t)-p\omega_3^{(2)}(x,t),\quad t>t_5,\ x\in\Omega,\\
\frac{\partial\omega_2^{(2)}}{\partial\eta}=\frac{\partial\omega_3^{(2)}}{\partial\eta}=0,\quad t>t_5,\ x\in\partial\Omega,\\
\omega_2^{(2)}(x,t)=w(x,t),\quad\omega_3^{(2)}(x,t)=v(x,t),\quad t\in[-\tau,t_5],\ x\in\overline{\Omega}.
\end{gathered} \tag{4.37}$$

Let $(u_2(t),u_3(t))$ be the positive solution to the following problem:

$$\begin{aligned}
\dot{u}_2(t)&=\frac{\beta e^{-m\tau}\left(M_2^u+\epsilon\right)u_3(t-\tau)}{M_2^u+\epsilon+u_2(t-\tau)}-au_2(t),\quad t>t_5,\\
\dot{u}_3(t)&=ku_2(t)-pu_3(t),\quad t>t_5,\\
u_2(t)&=\max_{x\in\overline{\Omega}}w(x,t),\quad u_3(t)=\max_{x\in\overline{\Omega}}v(x,t),\quad t\in[-\tau,t_5].
\end{aligned} \tag{4.38}$$

Then by Lemma 4.1 and the previous system we have

$$\lim u_2(t) = \frac{\left(k\beta e^{-m\tau} - ap\right)\left(M_2^u + \epsilon\right)}{ap},$$
$$\lim u_3(t) = \frac{k\left(k\beta e^{-m\tau}\right)\left(M_2^u + \epsilon\right)}{ap^2}. \tag{4.39}$$

Hence for all $\epsilon > 0$ sufficiently small, by comparison there is a $t_6 > t_5$ such that if $t > t_6$

$$\max_{x\in\overline{\Omega}} \overline{w}(x,t) < M_2^w + \epsilon, \qquad \max_{x\in\overline{\Omega}} \overline{v}(x,t) < M_2^v + \epsilon, \tag{4.40}$$

where

$$M_2^w = \frac{\left(k\beta e^{-m\tau} - ap\right)M_2^u}{ap},$$
$$M_2^v = \frac{k\left(k\beta e^{-m\tau}\right)M_2^u}{ap^2}. \tag{4.41}$$

Since $\epsilon > 0$ is arbitrary and sufficiently small, we conclude that

$$\overline{w} = \limsup_{t\to\infty} \max_{x\in\overline{\Omega}} w(x,t) \le M_2^w, \qquad \overline{v} = \limsup_{t\to\infty} \max_{x\in\overline{\Omega}} v(x,t) \le M_2^v. \tag{4.42}$$

Let $(\underline{u}^{(2)}, \underline{w}^{(2)}, \underline{v}^{(2)})$ be a solution for the following problem:

$$\frac{\partial \underline{u}^{(2)}}{\partial t} = L - d\underline{u}^{(2)}(x,t) - \frac{\beta \underline{u}^{(2)}(x,t)\overline{v}^{(1)}(x,t)}{\underline{u}^{(1)}(x,t) + \underline{w}^{(1)}(x,t)}, \quad t > t_6,\ x \in \Omega,$$
$$\frac{\partial \underline{w}^{(2)}}{\partial t} = \frac{\beta e^{-m\tau}\underline{u}^{(2)}(x,t-\tau)\underline{v}^{(2)}(x,t-\tau)}{\underline{u}^{(2)}(x,t-\tau) + \underline{w}^{(2)}(x,t-\tau)} - a\underline{w}^{(2)}(x,t) \quad t > t_6,\ x \in \Omega,$$
$$\frac{\partial \underline{v}^{(2)}}{\partial t} = D\Delta \underline{v}^{(2)}(x,t) + k\underline{w}^{(2)} - p\underline{v}^{(2)}(x,t) \quad t > t_6,\ x \in \Omega,$$
$$\underline{u}^{(2)}(x,t) = \frac{1}{2}u(x,t), \qquad \underline{w}^{(2)}(x,t) = \frac{1}{2}w(x,t),$$
$$\underline{w}^{(2)}(x,t) = \frac{1}{2}v(x,t), \quad t \in [-\tau, t_6],\ x \in \overline{\Omega}. \tag{4.43}$$

Then $(\underline{u}^{(2)}, \underline{w}^{(2)}, \underline{v}^{(2)})$ and $(\overline{u}^{(2)}, \overline{w}^{(2)}, \overline{v}^{(2)})$ are a pair of coupled lower and upper solutions to system (1.3)–(1.5). Hence we have that for $t \ge t_6$, $x \in \overline{\Omega}$

$$\underline{u}^{(2)}(x,t) \le u(x,t) \le \overline{u}^{(2)}(x,t), \qquad \underline{w}^{(2)}(x,t) \le w(x,t) \le \overline{w}^{(2)}(x,t),$$
$$\underline{v}^{(2)}(x,t) \le v(x,t) \le \overline{v}^{(2)}(x,t). \tag{4.44}$$

For all $\epsilon > 0$ sufficiently small, it follow from the first equation of (4.43), and the inequalities

$$\frac{\partial \underline{u}^{(2)}}{\partial t} \geq L - d\underline{u}^{(2)}(x,t) - \frac{\beta \underline{u}^{(2)}(x,t)\left(M_1^v + \epsilon\right)}{N_1^u - \epsilon + N_1^w - \epsilon}. \tag{4.45}$$

By comparison we have that $\underline{u}^{(2)}(x,t) \geq v_1^{(2)}(x,t)$, $t > t_6$, and $x \in \overline{\Omega}$ where $v_1^{(2)}$ is the solution to problem

$$\begin{gathered}\frac{\partial v_1^{(2)}}{\partial t} = L - dv_1^{(2)}(x,t) - \frac{\beta v_1^{(2)}(x,t)\left(M_1^v + \epsilon\right)}{N_1^u - \epsilon + N_1^w - \epsilon}, \\ \frac{\partial v_1^{(2)}}{\partial \eta} = 0, \quad t > t_6,\ x \in \partial\Omega,\end{gathered} \tag{4.46}$$

which has satisfies

$$\lim_{t\to\infty} v_1^{(2)}(x,t) = \frac{L\left(N_1^u - \epsilon + N_1^w - \epsilon\right)}{d\left(N_1^u - \epsilon + N_1^w - \epsilon\right) + \beta\left(M_1^v + \epsilon\right)}. \tag{4.47}$$

Hence for all $\epsilon > 0$ sufficiently small, by comparison, there is a $t_7 > t_6$ such that if $t > t_7$

$$\min \underline{u}^{(2)}(x,t) \geq N_2^u - \epsilon, \tag{4.48}$$

with

$$N_2^u = \frac{L\left(N_1^u + N_1^w\right)}{d\left(N_1^u + N_1^w\right) + \beta M_1^v}. \tag{4.49}$$

Since this holds true for arbitrary $\epsilon > 0$ sufficiently small, by comparison we conclude that

$$\underline{u} = \liminf_{t\to\infty} \min_{x\in\overline{\Omega}} u(x,t) \geq N_2^u. \tag{4.50}$$

Now consider the following problem:

$$\begin{gathered}\frac{\partial v_2^{(2)}}{\partial t} = \frac{\beta e^{-m\tau}\left(N_2^u - \epsilon\right)v_3^{(2)}(x,t-\tau)}{N_2^u - \epsilon + v_2^{(2)}(x,t-\tau)} - av_2^{(2)}(x,t), \quad t > t_7,\ x \in \Omega, \\ \frac{\partial v_3^{(2)}}{\partial t} = D\Delta v_3^{(2)}(x,t) + kv_2^{(2)} - pv_3^{(2)}(x,t), \quad t > t_7,\ x \in \Omega, \\ \frac{\partial v_2^{(2)}}{\partial \eta} = \frac{\partial v_3^{(2)}}{\partial \eta} = 0, \quad t > t_7,\ x \in \Omega, \\ v_2^{(2)}(x,t) = \frac{1}{2}w(x,t), \quad v_3^{(2)}(x,t) = \frac{1}{2}v(x,t), \quad t \in [-\tau, t_7],\ x \in \overline{\Omega}.\end{gathered} \tag{4.51}$$

Let $(u_2(t), u_3(t))$ be the positive solution for the following problem:

$$\begin{aligned}
\dot{v}_2(t) &= \frac{\beta e^{-m\tau}(N_2^u - \epsilon)u_2(t-\tau)}{N_2^u - \epsilon + u_2(t-\tau)} - au_2(t), \quad t > t_7, \\
\dot{v}_3(t) &= kv_2(t) - pv_3(t), \quad t > t_7, \\
v_2(t) &= \frac{1}{2}\min_{x\in\overline{\Omega}}, \quad v_3(t) = \frac{1}{2}\min_{x\in\overline{\Omega}} v(x,t), \quad t \in [-\tau, t_7].
\end{aligned} \tag{4.52}$$

By Lemma 4.1 it follows

$$\lim_{t\to\infty} v_2(t) = \frac{(N_2^u - \epsilon)(k\beta e^{-m\tau} - ap)}{ap}, \qquad \lim_{t\to\infty} v_3(t) = \frac{k(N_2^u - \epsilon)(k\beta e^{-m\tau} - ap)}{ap^2}, \tag{4.53}$$

hence, for all $\epsilon > 0$ sufficiently small, by comparison there exists a $t_8 > t_7$ such that if $t > t_8$,

$$\min_{x\in\overline{\Omega}} \underline{w}^{(2)}(x,t) > N_2^w - \epsilon, \qquad \min_{x\in\overline{\Omega}} \underline{v}^{(2)}(x,t) > N_2^v - \epsilon, \tag{4.54}$$

where

$$N_2^w = \frac{N_2^u(k\beta e^{-m\tau} - ap)}{ap}, \qquad N_2^v = \frac{kN_2^u(k\beta e^{-m\tau} - ap)}{ap^2}. \tag{4.55}$$

Since $\epsilon > 0$ is arbitrary and sufficiently small, we conclude that

$$\underline{w} = \liminf_{t\to\infty} \min_{x\in\overline{\Omega}} w(x,t) \geq N_2^w, \qquad \underline{v} = \liminf_{t\to\infty} \min_{x\in\overline{\Omega}} v(x,t) \geq N_2^v, \tag{4.56}$$

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

$$\begin{aligned}
M_n^u &= \frac{L(M_{n-1}^u + M_{n-1}^w)}{d(M_{n-1}^u + M_{n-1}^w) + \beta N_{n-1}^v}, \\
M_n^w &= \frac{(k\beta e^{-m\tau} - ap)M_n^u}{ap}, \\
M_n^v &= \frac{k(k\beta e^{-m\tau} - ap)M_n^u}{ap^2}, \\
N_n^u &= \frac{L(N_{n-1}^u + N_{n-1}^w)}{d(N_{n-1}^u + N_{n-1}^w) + \beta M_n^v},
\end{aligned}$$

$$N_n^w = \frac{\left(k\beta e^{-m\tau} - ap\right) N_n^u}{ap},$$
$$N_n^v = \frac{k\left(k\beta e^{-m\tau} - ap\right) N_n^u}{ap^2}. \tag{4.57}$$

It is readily seen that

$$N_n^u \le \underline{u} \le \overline{u} \le M_n^u, \qquad N_n^w \le \underline{w} \le \overline{w} \le M_n^w, \qquad N_n^v \le \underline{v} \le \overline{v} \le M_n^v. \tag{4.58}$$

The sequences M_n^u, M_n^w, and M_n^v are nonincreasing and the sequences N_n^u, N_n^w, and N_n^v are nondecreasing. □

To prove the monotonicity of N_n^u and M_n^u, we follow the ideas of Uh Zapata et al. [6]; consider $R_0 = \beta k e^{-m\tau}/ap$ and the following expressions for N^u, N^w, N^v, M^u, M^w, and M^v

$$M_n^u = \frac{L\left(M_{n-1}^u + M_{n-1}^w\right)}{d\left(M_{n-1}^u + M_{n-1}^w\right) + \beta N_{n-1}}, \qquad M_n^w = (R_0 - 1) M_n^u, \qquad M_n^v = \frac{k}{p}(R_0 - 1) M_n^u,$$
$$N_n^u = \frac{L\left(N_{n-1}^u + N_{n-1}^w\right)}{d\left(N_{n-1}^u + N_{n-1}^w\right) + \beta M_n^v}, \qquad N_n^w = (R_0 - 1) N_n^u, \qquad N_n^v = \frac{k}{p}(R_0 - 1) N_n^u. \tag{4.59}$$

We prove the result by induction so we first show that $M_2^u - M_1^u \le 0$,

$$M_2^u - M_1^u = \frac{L e^{-m\tau} M_1^u}{d e M_1^u + a(R_0 - 1) N_1^u} - \frac{L}{d} \le \frac{L}{d} - \frac{L}{d} = 0 \tag{4.60}$$

and $N_2^u - N_1^u > 0$,

$$\begin{aligned}
N_2^u - N_1^u &= \frac{L R_0 N_1}{d R_0 N_1^u + (\beta h/p)(R_0 - 1) M_2^u} - N_1 = N_1^u \left(\frac{L R_0 - d R_0 N_1^u - (\beta h/p)(R_0 - 1) M_2^u}{d R_0 N_1^u + (\beta h/p)(R_0 - 1) M_2^u} \right) \\
&= \frac{N_1^u}{d R_0 N_1^u + (\beta h/p)(R_0 - 1) M_2^u} \left(L R_0 - L R_0 + \beta R_0 M_1^v - \frac{h\beta}{p}(R_0 - 1) M_2^u \right) \\
&= \frac{N_1^u}{d R_0 N_1^u + (\beta h/p)(R_0 - 1) M_2^u} \left(\frac{\beta h}{p} R_0 (R_0 - 1) M_1^u - \frac{h\beta}{p}(R_0 - 1) M_2^u \right) \\
&= \frac{\beta h (R_0 - 1) N_1^u}{p\left(d R_0 N_1^u + (\beta h/p)(R_0 - 1) M_2^u\right)} \left(R_0 M_1^u - M_2^u\right) \\
&> \frac{\beta h (R_0 - 1) N_1^u}{p\left(d R_0 N_1^u + (\beta h/p)(R_0 - 1) M_2^u\right)} \left(R_0 M_1^u - M_2^u\right) > 0.
\end{aligned} \tag{4.61}$$

For the next step consider the function $f(x) = ax/(bx + c)$, with a, b, and c positive, which is monotone increasing. The induction hypothesis is $M_n^u \le M_{n-1}^u$ and $N_n^u \ge N_{n-1}^u$,

$$M_{n+1}^u = \frac{LR_0 M_n^u}{dR_0 M_n^u + \beta N_n^u} = \frac{LR_0 M_n^u}{dR_0 M_n^u + (\beta h/p)(R_0 - 1) N_n^u}. \tag{4.62}$$

The last function is increasing and by the induction hypothesis we have

$$M_{n+1}^u \le \frac{LR_0 M_{n-1}^u}{dR_0 M_{n-1}^u + (\beta h/p)(R_0 - 1) N_n^u} \le \frac{LR_0 M_{n-1}^u}{dR_0 M_{n-1}^u + (\beta h/p)(R_0 - 1) N_n^u} = M_n^u, \tag{4.63}$$

therefore the sequence M_n^u is nonincreasing. For the sequence N_n^u we use similar ideas and the behaviour of the sequence M_n^u just proved. One has

$$N_{n+1}^u = \frac{LR_0 N_n^u}{LR_0 N_n^u + \beta M_{n+1}^v} = \frac{LR_0 N_n^u}{LR_0 N_n^u + (\beta h/p)(R_0 - 1) M_{n+1}^u}. \tag{4.64}$$

The last function is increasing and by the induction hypothesis we have

$$N_{n+1}^u \ge \frac{LR_0 N_{n-1}}{LR_0 N_{n-1} + (\beta h/p)(R_0 - 1) M_{n+1}^u} \ge \frac{LR_0 N_{n-1}}{LR_0 N_{n-1} + (\beta h/p)(R_0 - 1) M_n^u} = N_n^u, \tag{4.65}$$

therefore the sequence N_n^u is nondecreasing. The behaviour for the sequences N_n^w, N_n^v, M_n^w, and M_n^v follows from the nonincreasing sequence M_n^u and the nondecreasing sequence N_n^u.

Hence, the limit of each sequence in N_n^u, N_n^w, N_n^v, M_n^u, M_n^w, and M_n^v exists. Denote

$$\begin{aligned} \overline{x} &= \lim_{n\to\infty} M_n^u, & \underline{x} &= \lim_{n\to\infty} N_n^u, \\ \overline{y} &= \lim_{n\to\infty} M_n^w, & \underline{y} &= \lim_{n\to\infty} N_n^w, \\ \overline{z} &= \lim_{n\to\infty} M_n^v, & \underline{z} &= \lim_{n\to\infty} N_n^v. \end{aligned} \tag{4.66}$$

We therefore obtain from (4.57) and (4.66) that

$$(\overline{x} - \underline{x})\left[\frac{dk\beta e^{-m\tau}}{ap} - \frac{k\beta(k\beta e^{-m\tau}) - ap}{ap^2}\right] = 0. \tag{4.67}$$

Noting that (H1) holds and $R_0 > 1$, it follows that

$$\frac{dk\beta e^{-m\tau}}{ap} > \frac{k\beta\left(k\beta e^{-m\tau} - ap\right)}{ap^2}, \tag{4.68}$$

which together with the previous equation yields $\overline{x} = \underline{x}$. We therefore derive from (4.57) y (4.66) that $\overline{y} = \underline{y}$, $\overline{z} = \underline{z}$. Noting that if $R_0 > 1$, by Theorem 3.1, the virus-infected equilibrium E_2 is locally asymptotically stable, and if in addition (H1) holds, we conclude that E_2 is globally asymptotically stable.

Now we prove the global stability for the disease-free equilibrium

Theorem 4.3. *If $R_0 < 1$ the disease-free equilibrium $E_1(L/d, 0, 0)$ of* (1.3) *is globally asymptotically stable.*

Proof. Let $(u(x,t), w(x,t), v(x,t))$ be a solution to problem with $\phi_i(x,0) \neq 0$, $(i = 1,2,3)$. We have $u(x,t) > 0$, $w(x,t) > 0$, and $v(x,t) > 0$ for all $x \in \overline{\Omega}$. Let $(u^{(1)}(x,t), w^{(1)}(x,t), v^{(1)}(x,t))$ be a solution to the following problem:

$$\begin{aligned}
\frac{\partial u^{(1)}}{\partial t} &= L - du^{(1)}(x,t), \\
\frac{\partial w^{(1)}}{\partial t} &= \frac{\beta e^{-m\tau} u^{(1)}(x,t-\tau) v^{(1)}(x,t-\tau)}{u^{(1)}(x,t-\tau) + w^{(1)}(x,t-\tau)} - aw^{(1)}(x,t), \\
\frac{\partial v^{(1)}}{\partial t} &= D\Delta v^{(1)}(x,t) + kw^{(1)}(x,t) - pv^{(1)}(x,t).
\end{aligned} \tag{4.69}$$

Therefore for $t > 0$, $x \in \overline{\Omega}$ we have

$$0 \le u(x,t) \le u^{(1)}(x,t), \qquad 0 \le w(x,t) \le w^{(1)}(x,t), \qquad 0 \le v(x,t) \le v^{(1)}(x,t). \tag{4.70}$$

We derive from the first equation that

$$\lim_{t\to\infty} u^{(1)}(x,t) = \frac{L}{d}, \tag{4.71}$$

so we can conclude

$$\limsup_{t\to\infty} \max u(x,t) \le \frac{L}{d}. \tag{4.72}$$

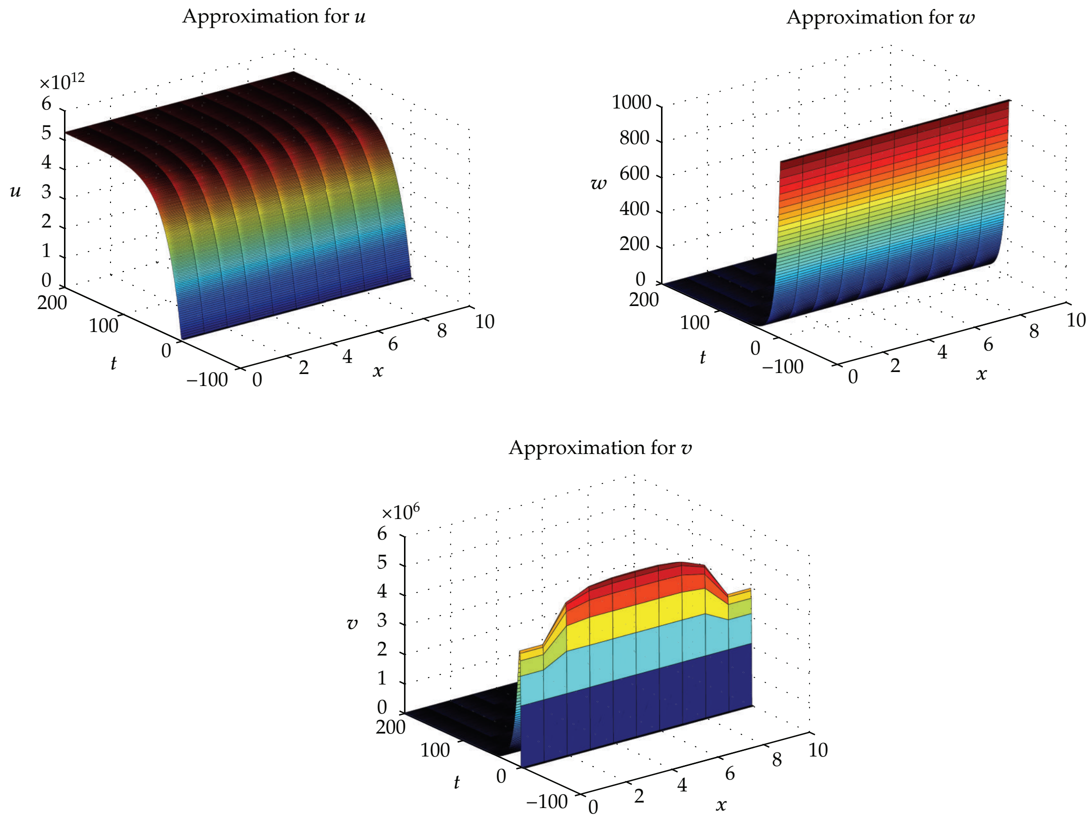


Figure 1: Simulations with parameters $L = 2^{11}$, $d = 3.78^{-2}$, $a = 3.38d$, $p = 0.67$, $\beta = 1.45^{-6}$, $k = 5.18^3$, $m = 0.2$, and $D = 0.5$. $R_0 = 0.039426$.

Hence, for $\epsilon > 0$ sufficiently small, there exists a t_1 such that $u^{(1)}(x,t) \le L/d + \epsilon$ for all $x \in \overline{\Omega}$ and $t \ge t_1$. Hence, $(w(x,t), v(x,t))$ is a lower solution to the following problem:

$$\begin{gathered}
\frac{\partial \omega_2^{(1)}}{\partial t} = \frac{\beta e^{(-m\tau)} (L/d + \epsilon) v^{(1)}(x, t-\tau)}{L/d + \epsilon + \omega_2^{(1)}(x, t-\tau)} - a\omega_2^{(1)}(x,t), \\
\frac{\partial \omega_3^{(1)}}{\partial t} = D\Delta\omega_3^{(1)} + k\omega_2^{(1)}(x,t) - p\omega_3^{(1)}(x,t), \\
\frac{\partial \omega_2^{(1)}}{\partial \eta} = \frac{\partial \omega_3^{(1)}}{\partial \eta} = 0, \quad t > t_1;\ x \in \partial\widehat{\Omega}, \\
\omega_2^{(1)}(x,t) = w(x,t), \quad \omega_3^{(1)}(x,t) = v(x,t), \quad t \in [-\tau, t_1],\ x \in \overline{\Omega}.
\end{gathered} \tag{4.73}$$

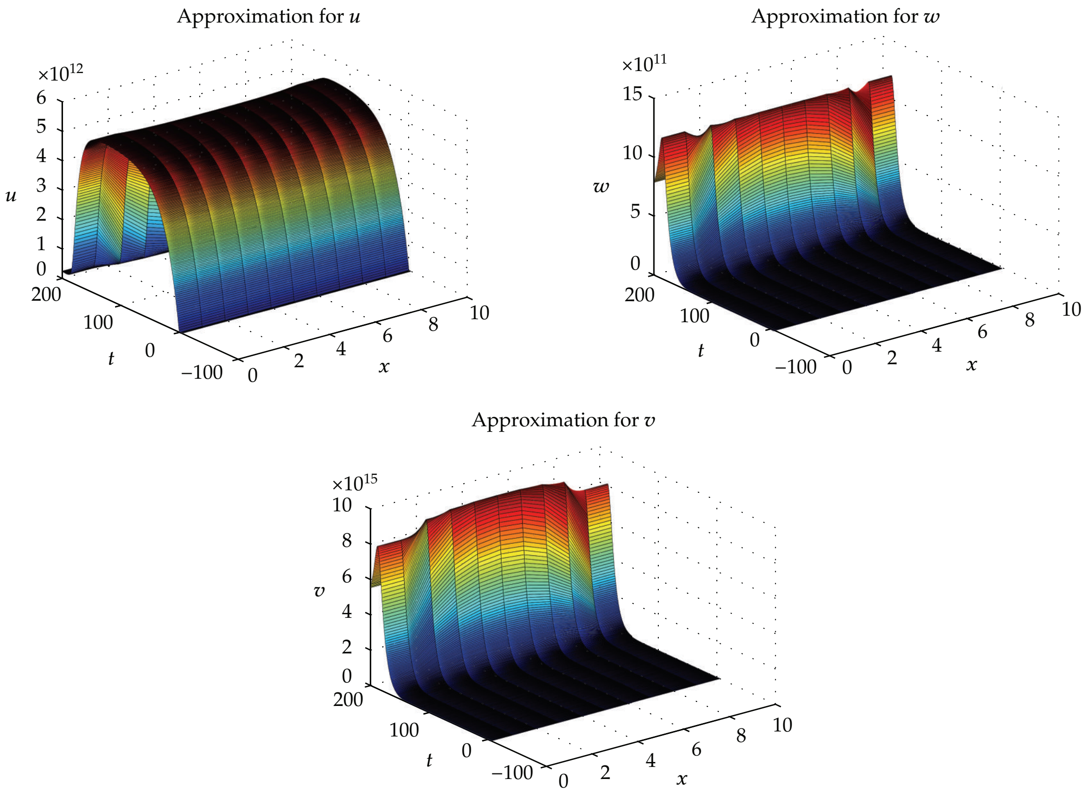


Figure 2: Simulations with parameters $L = 2^{11}$, $d = 3.78^{-2}$, $a = 3.38d$, $p = 0.67$, $\beta = 1.45^{-4}$, $k = 5.18 \times 10^3$, $m = 0.2$, and $D = 0.1$. $R_0 = 3.9426$.

Consider $(u_2(t), u_3(t))$ as the solution for

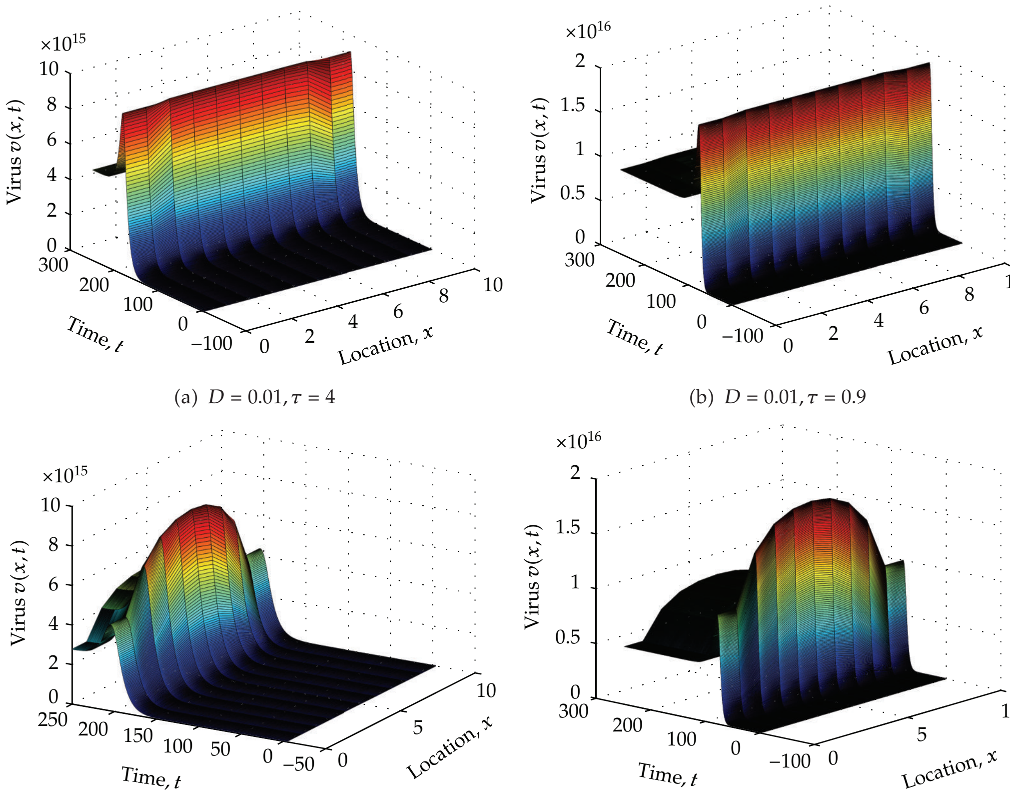
$$\dot{u}_2 = \frac{\beta e^{-m\tau}(L+\epsilon)u_3(t-\tau)}{L/d+\epsilon+u_2(t-\tau)} - a u_2(t),$$
$$\dot{u}_3 = k u_2(t) - p u_3(t), \tag{4.74}$$
$$u_2(t) = \max_{x\in\overline{\Omega}} w(x,t), \quad u_3(t) = \max_{x\in\overline{\Omega}} v(x,t), \quad t \in [-\tau, t_1].$$

Then with $R_0 < 1$ according to Lemma 4.1 we have that

$$\lim_{t\to\infty} u_2(t) = 0, \qquad \lim_{t\to\infty} u_3(t) = 0. \tag{4.75}$$

By comparison, it follows that

$$\lim_{t\to\infty} w(t) = 0, \qquad \lim_{t\to\infty} v(t) = 0 \tag{4.76}$$



(a) $D = 0.01, \tau = 4$

(b) $D = 0.01, \tau = 0.9$

(c) $D = 1, \tau = 4$

(d) $D = 1, \tau = 0.9$

Figure 3: In this case the parameters are $L = 2^{11}$, $d = 3.78^{-2}$, $a = 3.38d$, $p = 0.67$, $\beta = 1.45^{-4}$, $k = 5.18^3$ and $m = 0.2$.

uniformly for $x \in \overline{\Omega}$. Hence, for $\epsilon > 0$ sufficiently small, by comparison there is a $t_2 \geq t_1$ such that if $t \geq t_2$, $w(x,t) < \epsilon$, $v(x,t) < \epsilon$ for all $x \in \overline{\Omega}$ and $t \geq t_2$.

As in the proof of Theorem 4.2 $u(x,t)$ is an upper solution for the following problem:

$$\partial \omega_1^{(1)} = L - d\omega_1^{(1)} - \beta\omega_1^{(1)}\epsilon,$$
$$\frac{\partial \omega_1^{(1)}}{\partial \eta} = 0, \quad t \geq t_2,\ x \in \overline{\Omega}, \qquad \omega_1^{(1)}(x,t_2) = \frac{1}{2}u(x,t_2), \quad x \in \overline{\Omega}, \tag{4.77}$$

from the above equation we have that

$$\lim_{t\to\infty} \omega_1^{(1)}(x,t) = \frac{L}{d+\beta\epsilon} \tag{4.78}$$

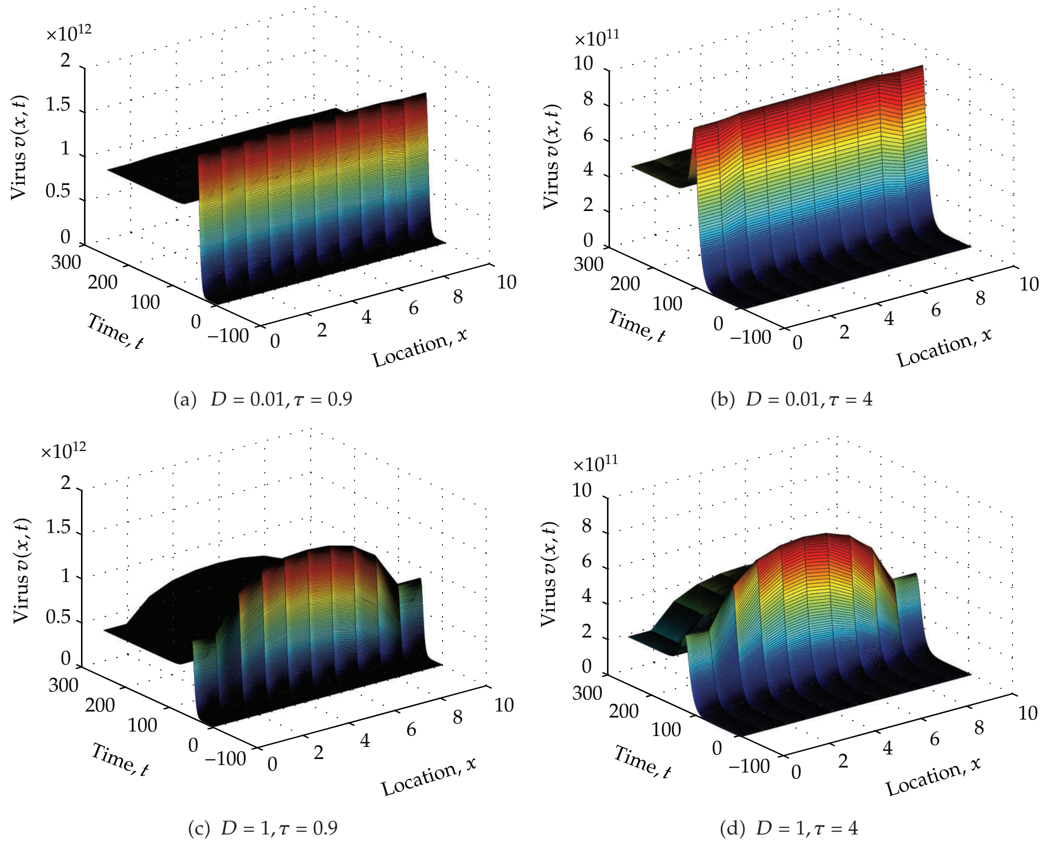


Figure 4: In this case the parameter are $L = 2^7$, $d = 3.78^{-2}$, $a = 3.38d$, $p = 0.67$, $\beta = 1.45^{-4}$, $k = 5.18^3$ and $m = 0.2$.

uniformly for $x \in \overline{\Omega}$. Since this holds for arbitrary $\epsilon > 0$ sufficiently small, by comparison we conclude that

$$\liminf_{t\to\infty} \min u(x,t) \geq \frac{L}{d}, \tag{4.79}$$

which together with (4.72) gives

$$\lim_{t\to\infty} u(x,t) = \frac{L}{d} \tag{4.80}$$

uniformly for $x \in \overline{\Omega}$. We already have by Theorem 3.1 that the disease-free equilibrium E_1 is locally asymptotically stable. And now we have proved that it is also globally asymptotically stable. □

5. Numerical Simulations

In this section we illustrate some numerical solutions for systems (1.3). In the numerical simulation display in Figure 1 we illustrate the stability for the disease-free equilibrium according to Theorem 3.1. In this case the basic reproductive number is $R_0 = 0.039426$. In the graphics we see how the level of uninfected cells increases from the initial condition and the number of infected cells and virus in the body goes to zero.

In Figure 2 consider the case $R_0 > 1$ in this case we consider a bigger rate of infection for the cells in the graphics we see how the number of infected cells and viruses increases when the time passes, and when the number of susceptible cells decreases the number of virus also decreases to the value v^*.

Now in Figure 3 we just show the level of virus in different for different values of the diffusion constant D and the delay τ. We see that a bigger delay increases the time needed for the virus to reach the value v^*, meanwhile a mayor value for the constant D just affects the levels of the virus according to the space and does not affect significantly the time needed for the virus to reach v^*. In Figure 4 we consider a lower value for λ, which is the uninfected cell production rate. In this case we see how the time to reach the value v^* of the endemic equilibrium is lower and again the diffusion rate has no significant effect on the time; its effect is on the level of virus in the system. The delay is what really affect the time to reach the value v^*.

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