Mathematical Biosciences and Engineering

http://www.aimspress.com/journal/MBE

MBE, 17(3): 2569–2591.
DOI: 10.3934/mbe.2020141
Received: 29 December 2019
Accepted: 19 February 2020
Published: 02 March 2020

Research article

Viral infection dynamics in a spatial heterogeneous environment with cell-free and cell-to-cell transmissions

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Abstract: In this paper, we investigate a diffusive viral infection model in a spatial heterogeneous environment with two types of infection mechanisms and distinct dispersal rates for the susceptible and infected target cells. After establishing well-posedness of the model system, we identify the basic reproduction number R_0 and explore the properties of R_0 when the dispersal rate for infected target cells varies from zero to infinity. Moreover, we demonstrate that the basic reproduction number is a threshold parameter: the infection and virus will be cleared out if $R_0 \leq 1$, while if $R_0 > 1$, the infection will persist and the model system admits at least one positive (chronic infection) steady state. For the special case when all model parameters are spatial homogeneous, this chronic infection steady state is unique and globally asymptotically stable.

Keywords: spatial heterogeneity; viral infection; basic reproduction number; global stability

1. Introduction

The population dynamics of in-host viral infection models has been studied intensively in the literature [1–8]. Through rigorous mathematical analysis, numerical explonation, and data fitting, the greatly enhanced understanding of viral dynamics can provide us with guidance and support for proposing feasible and effective control strategies to clear viral infections [4, 5, 9, 10]. Much of the existing mathematical modelling has been focused on the cell-free infection modes only [4, 5, 10]. In cell-free infection, only newly released free virions could infect susceptible target cells. On the other hand, most of the existing works are grounded on ordinary or functional differential equations with constant parameters, and do not consider the spatial heterogeneity, which may induce deficient understanding of the spatial spread of viral infection. So far as we know, only very few works; see for example, [11, 12], have taken into account spatial heterogeneity in viral infection modelling.

Assume that cells and virus particles live in a spatially heterogeneous but continuous environment.

Let Ω be the spatial habitat with smooth boundary $\partial\Omega$. Denote by $u_1(x,t)$, $u_2(x,t)$ and $u_3(x,t)$ the populations of susceptible target cells, infected target cells and virus particles at location x and time t, respectively. Wu et al. [12] considered a diffusive viral infection model with heterogeneous parameters and distinct dispersal rates for the susceptible and infected target cells:

$$\begin{aligned}
\frac{\partial u_1}{\partial t} &= d_1\Delta u_1 + a(x) - \beta_1(x)u_1u_3 - \mu_1(x)u_1, \quad x\in\Omega, t>0,\\
\frac{\partial u_2}{\partial t} &= d_2\Delta u_2 + \beta_1(x)u_1u_3 - \mu_2(x)u_2, \quad x\in\Omega, t>0,\\
\frac{\partial u_3}{\partial t} &= k(x)u_2 - \mu_3(x)u_3, \quad x\in\Omega, t>0,
\end{aligned} \tag{1.1}$$

with nonnegative initial conditions and the homogeneous Neumann boundary condition. Here, $d_1, d_2 > 0$ are the diffusion coefficients of susceptible target cells and infected target cells, respectively; Δ is the Laplacian operator; cell-free infection mode is modelled by the mass action mechanism with $\beta_1(x)$ being the cell-free transmission rate; $a(x)$ is the recruitment rate of susceptible target cells; $\mu_1(x), \mu_2(x)$ and $\mu_3(x)$ are the death rates of susceptible target cells, infected target cells and virus particles, respectively; $k(x)$ is the rate of virus production due to the lysis of infected cells. All these parameters are positive and continuous functions on $\bar{\Omega}$. In [12], the authors showed that model (1.1) possesses a global attractor, and identified the basic reproduction number R_0 and proved its threshold role.

Note that in [11, 12], only the cell-free infection mode was considered for the viral infection. It has been recognized that there is another major viral infection mode, namely, the cell-to-cell infection mode [13, 14], which allows viral particles to be transferred directly from an infected source cell to a susceptible target cell through the formation of virological synapses [15]. It has been revealed that more than half of viral infections are due to cell-to-cell transmission [15], and even during an antiretroviral therapy, viral particles can be transferred from infected target cells to uninfected ones through virological synapses, and the direct cell-to-cell infection affects the mechanism of HIV-1 transmission in vivo.

Motivated by the previous works, we consider the following general viral infection model incorporating spatial heterogeneity and two infection modes:

$$\begin{aligned}
\frac{\partial u_1}{\partial t} &= \nabla\cdot(d_1(x)\nabla u_1) + a(x) - f(u_1,u_2) - g(u_1,u_3) - \mu_1(x)u_1,\\
\frac{\partial u_2}{\partial t} &= \nabla\cdot(d_2(x)\nabla u_2) + f(u_1,u_2) + g(u_1,u_3) - \mu_2(x)u_2,\\
\frac{\partial u_3}{\partial t} &= k(x)u_2 - \mu_3(x)u_3,
\end{aligned} \tag{1.2}$$

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

$$u_i(x,0) = \phi_i(x) \geq 0 \ \text{ for } \ x\in\Omega, \ i = 1,2,3,$$

where $\nabla\cdot(d_i(x)\nabla u_i)$ describes the divergence of $d_i(x)\nabla u_i$ and $d_i(x)$ is the diffusion rate; $f(u_1,u_2)$ is the cell-to-cell transmission function; and $g(u_1,u_3)$ is the cell-free transmission function. Here, we consider an isolated habitat Ω, revealed by the Neumann boundary condition

$$\nabla u_i\cdot\nu = 0, \ \ i = 1,2, \ x\in\partial\Omega, \ t>0. \tag{1.3}$$

Throughout this paper, we assume that the diffusion rates $d_i(x)$ with $i = 1, 2$, the recruitment rate $a(x)$, the cell-free transmission rate $\beta_1(x)$, the cell-to-cell transmission rate $\beta_2(x)$, the virus production rate $k(x)$, and the death rates $\mu_i(x)$ with $i = 1, 2, 3$ are positive and continuous functions on $\bar{\Omega}$. We also make the following biologically motivated assumption.

($\mathbf{H}_1$) $f, g \in C^1(\mathbb{R}_+ \times \mathbb{R}_+)$ are strictly increasing with respect to both variables, and $f(v, w) = 0$ (resp. $g(v, w) = 0$) if and only if $vw = 0$. Moreover, $\partial^2 f(v, w)/\partial w^2 \leq 0$ and $\partial^2 g(v, w)/\partial w^2 \leq 0$.

In this paper, we will define the basic reproduction number R_0 with a clear biological meaning, and further prove that R_0 is a threshold parameter for the global dynamics of model (1.2). As we shall see later, the main challenge is caused by the different dispersal rates of the susceptible and infected target cells and partial degeneration of the model system.

The rest of this paper is organized as follows. In Section 2, we show that our model system admits a unique solution, which exists globally and is ultimately uniformly bounded. In Section 3, we identify the biologically meaningful basic reproduction number R_0 for the model using the standard procedure of next generation operator, and further explore the properties of R_0 when the dispersal rate for infected target cells varies from zero to infinity. Section 4 is devoted to the global dynamics of the model for the cases of $R_0 \leq 1$ and $R_0 > 1$, respectively. In Section 5, we consider a special case when all coefficients are spatial homogeneous, and give the global asymptotic stability of the unique chronic infection steady state when $R_0 > 1$.

2. Well-posedness

Denote by $X := C(\bar{\Omega}, \mathbb{R}^3)$ the Banach space of continuous functions on $\bar{\Omega}$ with the supremum norm. The nonnegative cone of X is denoted by $X^+ = C(\bar{\Omega}, \mathbb{R}^3_+)$, then (X, X^+) is a strongly ordered space [16]. For any nonnegative initial condition

$$u(x, 0) = \phi(x) := (\phi_1, \phi_2, \phi_3) \in X^+,$$

we define $T_3(t)\phi_3 = e^{-\mu_3(\cdot)t}\phi_3$. For each $i = 1, 2$, let $T_i(t)$ be the C_0 semigroups generated by the second-order linear differential operator $\nabla \cdot (d_i \nabla) - \mu_i$ with Neumann boundary condition. It then follows from [16, Corollary 7.2.3] that $T_i(t)$ is compact and strongly positive for all $t > 0$ and $i = 1, 2$. Moreover, $T(t) := (T_1(t), T_2(t), T_3(t))$ is a C_0 semigroup on X with an infinitesimal generator A_0 [17]. Then the system (1.2) can be written as an abstract differential equation

$$u'(t) = A_0 u(t) + F(u(t))$$

with nonnegative initial condition $u(0) = \phi \in X^+$, where the nonlinear operator $F = (F_1, F_2, F_3) : X^+ \to X$ is defined by

$$\begin{aligned} F_1(\varphi)(x) &= a(x) - f(\varphi_1(x), \varphi_2(x)) - g(\varphi_1(x), \varphi_3(x)), \\ F_2(\varphi)(x) &= f(\varphi_1(x), \varphi_2(x)) + g(\varphi_1(x), \varphi_3(x)), \\ F_3(\varphi)(x) &= k(x)\varphi_2(x), \end{aligned}$$

for any $\varphi = (\varphi_1, \varphi_2, \varphi_3) \in X^+$. On account of ($\mathbf{H}_1$), there exists $c > 0$ such that $f(\varphi_1(x), \varphi_2(x)) + g(\varphi_1(x), \varphi_3(x)) \leq c\varphi_1(x)$ for all $x \in \bar{\Omega}$. It is easily seen that

$$\varphi(x) + \epsilon F(\varphi)(x) \geq (\varphi_1(x)(1 - c\epsilon), \varphi_2(x), \varphi_3(x))^T \quad \text{for} \quad x \in \Omega.$$

By choosing $\epsilon > 0$ sufficiently small, we have $1 > \epsilon c$ and $\varphi + \epsilon F(\varphi) \in X^+$. Particularly,

$$\lim_{\epsilon \to 0^+} \frac{1}{\epsilon} \mathrm{dist}(\varphi + \epsilon F(\varphi), X^+) = 0.$$

Thus, by using [16, Theorem 7.3.1] or [18, Corollary 4], we establish the existence of the solution to the system (1.2). Note that the nonlinear operator F is mixed quasimontone, then all solutions are nonnegative due to the comparison principle. To summarize, we obtain the following lemma on the existence and nonnegativity of the solution to (1.2).

Lemma 2.1. *For every initial condition $\phi \in X^+$, system* (1.2) *with Neumann boundary condition* (1.3) *has a unique solution $u(x,t)$ on a maximal interval of existence $[0, t_{max})$. If $t_{max} < \infty$, then* $\limsup_{t \to t_{max}} \|u(\cdot, t)\|_X = \infty$. *Moreover, $u(x,t) \geq 0$ for all $(x,t) \in \Omega \times [0, t_{max})$.*

To prove that $t_{max} = \infty$, we need to show that the boundedness of solutions for system (1.2). Before stating this result, we need the following lemma.

Lemma 2.2. *For any positive and continuous functions $d(x)$, $l(x)$ and $\mu(x)$ on $\bar{\Omega}$, the scalar reaction-diffusion equation*

$$\begin{aligned} &\frac{\partial w(x,t)}{\partial t} = \nabla \cdot (d(x) \nabla w(x,t)) + l(x) - \mu(x) w(x,t), \ x \in \Omega, \ t > 0, \\ &\nabla w(x,t) \cdot \nu = 0, \ x \in \partial\Omega, \ t > 0 \end{aligned} \tag{2.1}$$

admits a unique and strictly positive steady state $w^*(x)$, which is globally asymptotically stable in $C(\bar{\Omega}, \mathbb{R}_+)$. Moreover, if $d(x) \equiv d$, $l(x) \equiv l$ and $\mu(x) \equiv \mu$ for all $x \in \Omega$, then $w^*(x) \equiv l/\mu$ for all $x \in \Omega$.

Proof. In view of the standard theory of parabolic equations [19], we obtain the existence of a compact semiflow Ψ_t for (2.1) in $C(\bar{\Omega}, \mathbb{R}_+)$. Denote

$$\bar{l} = \max_{x \in \bar{\Omega}} l(x), \ \underline{l} = \min_{x \in \bar{\Omega}} l(x), \ \bar{\mu} = \max_{x \in \bar{\Omega}} \mu(x) \ \text{ and } \ \underline{\mu} = \min_{x \in \bar{\Omega}} \mu(x).$$

It then follows from the comparison theorem and maximum principle [19] that Ψ_t has a global compact attractor $K \subset (\underline{l}/\bar{\mu}, \bar{l}/\underline{\mu})$. This implies that K contains a positive steady state $w^*(x)$ due to Theorem 3.1 in [20]. By using strong maximal principle [21] and the monotonicity of $l(x) - \mu(x) w(x,t)$ w.r.t w, we can easily obtain that the positive steady state of (2.1) is unique. According to [20, Theorem 3.2], $w^*(x)$ attracts all solutions of (2.1) with nontrivial initial condition $\phi \in C(\bar{\Omega}, \mathbb{R}_+)$. This ends the proof. □

Theorem 2.3. *For every initial condition $\phi \in X^+$, system* (1.2) *has a unique global solution $u(x,t) \geq 0$ for $t \geq 0$. Moreover, there exists a constant $M > 0$ independent of ϕ such that* $\limsup_{t \to \infty} u_i(x,t) \leq M$ *for all $x \in \Omega$ and $i = 1, 2, 3$.*

Proof. To establish the solutions of (1.2) exist globally on $[0, \infty)$, it suffices to show that the boundedness of the solutions. For any initial condition $\phi \in X^+$, it follows from comparison principle and Lemma 2.2 that $u_1(x,t) \leq w(x,t)$ for all $t \in [0, t_{max})$, where $w(x,t)$ is the solution of (2.1) with $l(x) \equiv a(x)$, $\mu(x) \equiv \mu_1(x)$ and initial condition $w(x,0) = \phi_1(x)$. Note that $w(x,t) \to w^*(x)$ as $t \to \infty$, which implies that

$$\limsup_{t \to \infty} u_1(x,t) \leq w^*(x) \ \text{ uniformly for } \ x \in \bar{\Omega}. \tag{2.2}$$

Thus, there exists $K_1 > \max_{x\in\bar{\Omega}} w^*(x)$, depending on ϕ, such that $\|u_1(\cdot,t)\| \le K_1$ for all $t \ge 0$.

From the last two equations of (1.2) and the definition of $T_i(t)$ with $i = 2,3$, we have

$$u_2(\cdot,t) = T_2(t)\phi_2(\cdot) + \int_0^t T_2(t-s)\left(f(u_1(\cdot,s),u_2(\cdot,s)) + g(u_1(\cdot,s),u_3(\cdot,s))\right)ds,$$
$$u_3(\cdot,t) = T_3(t)\phi_3(\cdot) + \int_0^t T_3(t-s)ku_2(\cdot,s)ds.$$

Let $-\lambda_2 < 0$ denote the principal eigenvalue of $\nabla\cdot(d_2\nabla) - \mu_2$ with Neumann boundary condition, and $\lambda_3 = \min\{\min_{x\in\bar{\Omega}}\mu_3(x), \lambda_2/2\} > 0$. We have $\|T_2(t)\| \le e^{-\lambda_2 t}$ and $\|T_3(t)\| \le e^{-\lambda_3 t}$. By $(\mathbf{H}_1)$ and the boundedness of $u_1(x,t)$, there exists $m_1 > 0$ such that

$$f(u_1(\cdot,s),u_2(\cdot,s)) + g(u_1(\cdot,s),u_3(\cdot,s)) \le m_1\left(\|u_2(\cdot,s)\| + \|u_3(\cdot,s)\|\right)$$

for all $s \in [0, t_{max})$. It then follows that

$$\begin{aligned}\|u_2(\cdot,t)\| &\le e^{-\lambda_2 t}\|\phi_2\| + m_1\int_0^t e^{-\lambda_2(t-s)}\left(\|u_2(\cdot,s)\| + \|u_3(\cdot,s)\|\right)ds,\\ \|u_3(\cdot,t)\| &\le e^{-\lambda_3 t}\|\phi_3\| + \bar{k}\int_0^t e^{-\lambda_3(t-s)}\|u_2(\cdot,s)\|ds,\end{aligned} \tag{2.3}$$

where $\bar{k} = \max_{x\in\bar{\Omega}} k(x)$. Substituting the second inequality into the first one gives

$$\begin{aligned}\|u_2(\cdot,t)\| \le\; & e^{-\lambda_2 t}\|\phi_2\| + m_1\int_0^t e^{-\lambda_2(t-s)}\|u_2(\cdot,s)\|ds\\ &+ m_1\int_0^t e^{-\lambda_2(t-s)}\left(e^{-\lambda_3 s}\|\phi_3\| + \bar{k}\int_0^s e^{-\lambda_3(s-r)}\|u_2(\cdot,r)\|dr\right)ds\\ \le\; & \|\phi_2\| + m_1\int_0^t \|u_2(\cdot,s)\|ds + m_1\|\phi_3\|\int_0^t e^{-\lambda_3 s}ds\\ &+ m_1\bar{k}e^{-\lambda_2 t}\int_0^t e^{\lambda_3 r}\|u_2(\cdot,r)\|\int_r^t e^{(\lambda_2-\lambda_3)s}dsdr\\ \le\; & C_1 + C_2\int_0^t \|u_2(\cdot,s)\|ds,\end{aligned}$$

where $C_1 = \|\phi_2\| + m_1\|\phi_3\|/\lambda_3 > 0$ and $C_2 = m_1 + m_1\bar{k}/(\lambda_2 - \lambda_3) > 0$. Thus, Gronwall's inequality implies that

$$\|u_2(\cdot,t)\| \le C_1 e^{C_2 t} \text{ for } t \in [0, t_{max}).$$

This together with the second inequality in (2.3) yields

$$\|u_3(\cdot,t)\| \le \|\phi_3\| + \frac{\bar{k}C_1}{C_2}e^{C_2 t} \text{ for } t \in [0, t_{max}).$$

On account of Lemma 2.1, $t_{max} = \infty$ and the solution $u(x,t)$ exists for all $t \ge 0$.

Next, we will prove that the solution is ultimately bounded with the bound independent of initial conditions. It follows from (2.2) that there exist a constant $M_{11} > 0$, independent of ϕ, and $t_1 > 0$ such that $u_1(x,t) \le M_{11}$ for $t \ge t_1$. This together with ($\mathbf{H}_1$) implies that there exists $m_2 > 0$ such that

$$f(u_1(x,t), u_2(x,t)) + g(u_1(x,t), u_3(x,t)) \le m_2(u_2(x,t) + u_3(x,t)),\ x \in \Omega, t \ge t_1. \tag{2.4}$$

Denote $\bar{a} = \max_{x\in\bar{\Omega}} a(x)$, $\underline{\tilde{\mu}} = \min_{x\in\bar{\Omega}}\{\mu_i(x) : i = 1,2,3\}$ and $|\Omega|$ is the volume of Ω. By integrating (1.2) for u_1 and u_2 and adding up, we obtain

$$\frac{\partial}{\partial t}\int_\Omega (u_1 + u_2)dx \le |\Omega|\bar{a} - \underline{\tilde{\mu}}\int_\Omega (u_1 + u_2)dx.$$

It then follows from comparison principle that $\limsup_{t\to\infty} \|u_2(\cdot,t)\|_1 \le |\Omega|\bar{a}/\underline{\tilde{\mu}}$. Particularly, there exist $t_2 > t_1$ and $M_{12} > 0$, such that $\|u_2(\cdot,t)\|_1 \le M_{12}$ for $t \ge t_2$. Similarly, we can easily obtain

$$\frac{\partial}{\partial t}\int_\Omega u_3 dx \le \bar{k}M_{12} - \underline{\mu_3}\int_\Omega u_3 dx \ \text{ for } \ t \ge t_2,$$

where $\underline{\mu_3} = \min_{x\in\bar{\Omega}} \mu_3(x)$. Thus, there exist $t_3 > t_2$ and $M_{13} > 0$, such that $\|u_3(\cdot,t)\|_1 \le M_{13}$ for $t \ge t_3$. Consequently, $\limsup_{t\to\infty}(\|u_2(\cdot,t)\|_1 + \|u_3(\cdot,t)\|_1) \le M_1$, where $M_1 = M_{12} + M_{13}$ is independent of initial conditions.

Assume that $t > t_3$, we now estimate the upper bound of $\|u_2(\cdot,t)\|_2 + \|u_3(\cdot,t)\|_2$. By multiplying the equation for u_2 (resp. u_3) of (1.2) by u_2 (resp. u_3), and integrating on Ω, it then follows from (2.4) that

$$\begin{aligned}
&\frac{1}{2}\frac{\partial}{\partial t}\int_\Omega u_2^2 dx \le -\underline{d_2}\int_\Omega |\nabla u_2|^2 dx + m_2\int_\Omega (u_2^2 + u_2u_3)dx - \underline{\mu}\int_\Omega u_2^2 dx,\\
&\frac{1}{2}\frac{\partial}{\partial t}\int_\Omega u_3^2 dx \le \bar{k}\int_\Omega u_2u_3 dx - \underline{\mu}\int_\Omega u_3^2 dx,
\end{aligned}$$

where $\underline{d_2} = \min_{x\in\Omega} d_2(x)$. Adding the above two inequalities, together with Young's inequality

$$u_2u_3 \le \frac{\underline{\mu}}{4(m_2 + \bar{k})}u_3^2 + \frac{m_2 + \bar{k}}{\underline{\mu}}u_2^2,$$

we have

$$\frac{1}{2}\frac{\partial}{\partial t}\int_\Omega (u_2^2 + u_3^2)dx \le -\underline{d_2}\int_\Omega |\nabla u_2|^2 dx + C_{22}\int_\Omega u_2^2 dx - \underline{\mu}\int_\Omega u_2^2 dx - \frac{3}{4}\underline{\mu}\int_\Omega u_3^2 dx,$$

where $C_{22} = m_2 + \frac{(m_2+\bar{k})^2}{\underline{\mu}}$. Making use of the Gagliardo-Nirenberg interpolation inequality: there exists $c > 0$ such that $\|w\|_2^2 \le \varepsilon\|\nabla w\|_2^2 + c\varepsilon^{-n/2}\|w\|_1^2$ for any $w \in W^{1,2}(\Omega)$ and small $\varepsilon > 0$, we obtain

$$\frac{1}{2}\frac{\partial}{\partial t}\int_\Omega (u_2^2 + u_3^2)dx \le B_2M_1^2 - \delta_2\int_\Omega (u_2^2 + u_3^2)dx,$$

where $B_2 = C_2c\varepsilon^{-n/2}$, $\delta_2 = 3\underline{\mu}/4$ and $\varepsilon \in (0, \underline{d_2}/C_{22})$. Therefore,

$$\limsup_{t\to\infty}(\|u_2(\cdot,t)\|_2^2 + \|u_3(\cdot,t)\|_2^2) \le B_2M_1^2/\delta_2.$$

Especially, there exist $t_4 > t_3$ and $M_2 > 0$ such that $\|u_2(\cdot,t)\|_2^2 + \|u_3(\cdot,t)\|_2^2 \le M_2$ for $t \ge t_4$.

Denote $L_p = \limsup_{t\to\infty}(\|u_2(\cdot,t)\|_p^p + \|u_3(\cdot,t)\|_p^p)$. We multiple the equation for u_2 (resp. u_3) of (1.2) by $2^k u_2^{2^k-1}$ (resp. $2^k u_3^{2^k-1}$) and integrate on Ω, using a similar argument as in the estimation of $\|u_2(\cdot,t)\|_2^2 + \|u_3(\cdot,t)\|_2^2$ to obtain that

$$\frac{1}{2^k}\frac{\partial}{\partial t}(\|u_2(\cdot,t)\|_{2^k}^{2^k} + \|u_3(\cdot,t)\|_{2^k}^{2^k}) \le 2^{\frac{n}{2}(k-1)}B\|u_2(\cdot,t)\|_{2^{k-1}}^{2^{k+1}-2} - \delta(\|u_2(\cdot,t)\|_{2^k}^{2^k} + \|u_3(\cdot,t)\|_{2^k}^{2^k}),$$

where B and δ are constants independent of of k and ϕ. Since $L_{2^{k-1}} \le M_{2^{k-1}}$, there exist $t_{2^{k-1}} > 0$ such that $\|u_2(\cdot,t)\|_{2^{k-1}}^{2^{k-1}} + \|u_3(\cdot,t)\|_{2^{k-1}}^{2^{k-1}} \le L_{2^{k-1}} + 1$ for all $t \ge t_{2^{k-1}}$. By comparison principle, we obtain $L_{2^k} \le 2^{\frac{n}{2}(k-1)}C(L_{2^{k-1}} + 1)^2$, where C is a constant independent of k and ϕ.

Finally, according to the method of induction, we prove that $L_{2^k} \le \infty$ for all $k = 0, 1, 2, \cdots$. Define an infinite sequence $a_{k+1} = (C+1)^{2^{-k-1}} 2^{kn2^{-k-2}} a_k$ with $a_0 = L_1 + 1$ for nonnegative integer k. It is easily seen that $L_{2^k} \le a_k^{2^k}$ and $\lim_{k\to\infty} \ln a_k = \ln C(L_1 + 1) + n\ln 2/2$. Therefore, we have

$$\limsup_{k\to\infty} \sqrt[2^k]{L_{2^k}} \le \lim_{k\to\infty} a_k = C(L_1 + 1)2^{n/2}.$$

Thus we obtain $\limsup_{t\to\infty} u_i(x,t) \le M := C(M_2 + 1)2^{n/2} + M_1$ for all $x \in \Omega$ and $i = 1, 2, 3$. That is, the solution semiflow associated with (1.2) $\Theta(t)$ for $t \ge 0$ is point dissipative. This completes the proof. □

We are now in the position to address the persistence of $u_1(x,t)$.

Proposition 2.4. *Let $u(x,t)$ be the solution of* (1.2) *with initial condition $\phi \in X^+$.*

(i) $u_1(x,t) > 0$ for all $t > 0$ and $x \in \Omega$. Furthermore, there exists a positive constant m_0 independent of ϕ such that

$$\liminf_{t\to\infty} u_1(x,t) \ge m_0 \ \textit{uniformly for} \ x \in \bar{\Omega}.$$

(ii) If there exist some $x_0 \in \Omega$ and $t_0 \ge 0$ such that either $u_2(x_0,t_0) > 0$ or $u_3(x_0,t_0) > 0$, then $u_i(x,t) > 0$ for all $i = 2, 3$, $t \ge t_0$ and $x \in \Omega$.

Proof. (i) By using the strong maximum principle [21], it is easily seen the positivity of $u_1(x,t)$ for $t > 0$ and $x \in \Omega$. We then prove the persistence of $u_1(x,t)$. From Theorem 2.3, there exist $t_0 > 0$ and $M > 0$ such that $u_i(x,t) < M$ for all $t > t_0$, $i = 1, 2, 3$ and $x \in \Omega$. Then the first equation of (1.2) and ($\mathbf{H}_1$) imply that

$$\frac{\partial u_1(x,t)}{\partial t} \ge \nabla\cdot(d_1(x)\nabla u_1(x,t)) + a(x) - \mu_1(x)u_1(x,t) - c_0 u_1(x,t)$$

for all $t \ge t_0$ and some positive constant c_0. Thus, Lemma 2.2 and comparison principle yield that $u_1(x,t)$ is ultimately bounded below by a unique and strictly positive steady state $\bar{w}^*(x)$ of (2.1) with $d(x) = d_1(x)$, $l(x) \equiv a(x)$ and $\mu(x) \equiv \mu_1(x) + c_0$. Denote $m_0 = \min_{x\in\bar{\Omega}} \bar{w}^*(x)$, which is a positive constant. Then $\limsup_{t\to\infty} u_1(x,t) \ge m_0$ for all $x \in \Omega$.

(ii) Assume that either $u_2(x_0,t_0) > 0$ or $u_3(x_0,t_0) > 0$ for some $x_0 \in \Omega$ and $t_0 \ge 0$. Then from the third equation of (1.2), we have

$$u_3(x,t) = e^{-\mu_3(x)(t-t_0)}u_3(x,t_0) + \int_{t_0}^{t} e^{-\mu_3(x)(t-s)}k(x)u_2(x,s)ds > 0$$

for all $x \in \Omega$ and $t > t_0$. We then apply strong maximum principle to the second equation of (1.2) and obtain $u_2(x,t) > 0$ for all $t > t_0$ and $x \in \Omega$. □

3. Basic reproduction number

Note that Lemma 2.2 implies that (2.1) with $d(x) = d_1(x)$, $l(x) \equiv a(x)$ and $\mu(x) \equiv \mu_1(x)$ has a unique and strictly positive steady state $w^*(x)$. Thus, system (1.2) has a unique infection-free steady state $(w^*(x), 0, 0)$. For simplicity, we denote

$$\beta_d(x) = \frac{\partial f(w^*(x), 0)}{\partial u_2},\ \beta_i(x) = \frac{\partial g(w^*(x), 0)}{\partial u_3}. \tag{3.1}$$

Linearizing system (1.2) for $(u_2(x,t), u_3(x,t))$ at $(w^*(x), 0, 0)$ gives the following cooperative system for the infected cells and free virus,

$$\begin{cases} \frac{\partial u_2}{\partial t} = \nabla \cdot (d_2(x)\nabla u_2) + \beta_d(x)u_2 + \beta_i(x)u_3 - \mu_2(x)u_2,\ x \in \Omega,\ t > 0, \\ \frac{\partial u_3}{\partial t} = k(x)u_2 - \mu_3(x)u_3,\ x \in \Omega,\ t > 0, \\ \nabla u_2 \cdot \nu = 0,\ x \in \partial\Omega,\ t > 0. \end{cases} \tag{3.2}$$

The suitable functional space for the above system is $Y := C(\bar{\Omega}, \mathbb{R}^2)$. The associated linear operator of system (3.2) can be decomposed as $A = F + B$, where

$$F = \begin{pmatrix} \beta_d(\cdot) & \beta_i(\cdot) \\ 0 & 0 \end{pmatrix},\ B = \begin{pmatrix} \nabla \cdot (d_2\nabla) - \mu_2(\cdot) & 0 \\ k(\cdot) & -\mu_3(\cdot) \end{pmatrix}.$$

It then follows from [22] that the basic reproduction number R_0 is defined as the spectral radius of $-FB^{-1}$, that is, $R_0 = r(-FB^{-1})$. We can easily check that B is resolvent-positive with $s(B) < 0$, F is positive and A is also resolvent-positive. Then it follows from [22, Theorem 3.5] that $R_0 - 1$ has the same sign as $s(A)$, where $s(A) = \sup\{\mathrm{Re}\lambda,\ \lambda \in \sigma(A)\}$ is the spectral bound of A.

Let e^{Bt} be the semigroup generated by B. Then the next generation operator is $-FB^{-1} = \int_0^\infty Fe^{Bt}dt$. Wang and Zhao [23] proved local asymptotic stability of infection-free steady state when $R_0 < 1$. Here, we shall prove global asymptotic stability of infection-free steady state when $R_0 \le 1$. To derive an equivalent formula for R_0 such that the direct and indirect transmission mechanisms are clearly separated in the expression, we need to make use of the following result.

Lemma 3.1. *Let* $F = \begin{pmatrix} F_{11} & F_{12} \\ 0 & 0 \end{pmatrix}$ *be a positive operator,* $B = \begin{pmatrix} \nabla \cdot (d_2\nabla) - V_{11} & 0 \\ -V_{21} & -V_{22} \end{pmatrix}$ *be a resolvent-positive operator with* $s(B) < 0$*. Then we have*

$$r(-FB^{-1}) = r\left(F_{11}(V_{11} - \nabla \cdot (d_2\nabla))^{-1} - F_{12}V_{22}^{-1}V_{21}(V_{11} - \nabla \cdot (d_2\nabla))^{-1}\right). \tag{3.3}$$

Proof. Note that B is lower triangular and $s(B) < 0$. This implies that both $V_{11} - \nabla \cdot (d_2\nabla)$ and V_{22} are invertible. Moreover, we can calculate that

$$-B^{-1} = \begin{pmatrix} (V_{11} - \nabla \cdot (d_2\nabla))^{-1} & 0 \\ -V_{22}^{-1}V_{21}(V_{11} - \nabla \cdot (d_2\nabla))^{-1} & V_{22}^{-1} \end{pmatrix}.$$

Consequently, we obtain

$$-FB^{-1} = \begin{pmatrix} F_{11}(V_{11} - \nabla\cdot(d_2\nabla))^{-1} - F_{12}V_{22}^{-1}V_{21}(V_{11} - \nabla\cdot(d_2\nabla))^{-1} & F_{12}V_{22}^{-1} \\ 0 & 0 \end{pmatrix},$$

which implies that (3.3) holds. This ends the proof. □

By using Lemma 3.1 and a standard variational method, we have an equivalent formula for the basic reproduction number

$$R_0 = r(A_d + A_i) = \sup_{\psi\in H^1(\Omega),\psi\neq 0} \frac{\int_\Omega \left(\beta_d(x) + \beta_i(x)\mu_3^{-1}(x)k(x)\right)\psi^2(x)dx}{\int_\Omega \left(d_2(x)|\nabla\psi(x)|^2 + \mu_2(x)\psi^2(x)\right)dx}, \tag{3.4}$$

where $A_d = \beta_d(\mu_2 - \nabla\cdot(d_2\nabla))^{-1}$ is the next generation operator for cell-to-cell transmission, and $A_i = \beta_i\mu_3^{-1}k(\mu_2 - \nabla\cdot(d_2\nabla))^{-1}$ is the next generation operator for cell-free transmission. In the absence of cell-free transmission, the basic reproduction number for cell-to-cell transmission is

$$R_0^d = r(A_d) = \sup_{\psi\in H^1(\Omega),\psi\neq 0} \frac{\int_\Omega \beta_d(x)\psi^2(x)dx}{\int_\Omega \left(d_2(x)|\nabla\psi(x)|^2 + \mu_2(x)\psi^2(x)\right)dx}.$$

On the other hand, if only cell-free transmission is taken into consideration, the basic reproduction number for cell-free transmission is given by

$$R_0^i = r(A_i) = \sup_{\psi\in H^1(\Omega),\psi\neq 0} \frac{\int_\Omega \beta_i(x)\mu_3^{-1}(x)k(x)\psi^2(x)dx}{\int_\Omega \left(d_2(x)|\nabla\psi(x)|^2 + \mu_2(x)\psi^2(x)\right)dx}.$$

Clearly, $R_0 \leq R_0^d + R_0^i$. We then study the dependence of R_0 on the diffusion coefficient d_2.

Theorem 3.2. *(i) R_0 is a principal eigenvalue of $A_d + A_i$ associated with a positive eigenfunction.*

(ii) Assume that d_2 is a constant on $\bar{\Omega}$, then R_0 is a monotone decreasing function of d_2, Moreover, we have

$$R_0 \to \overline{R}_0 := \max_{x\in\bar{\Omega}} \left\{ \frac{\beta_d(x)}{\mu_2(x)} + \frac{\beta_i(x)k(x)}{\mu_2(x)\mu_3(x)} \right\} \quad as \ d_2 \to 0,$$

$$R_0 \to \underline{R}_0 := \frac{\int_\Omega \left(\beta_d(x) + \beta_i(x)\mu_3^{-1}(x)k(x)\right)dx}{\int_\Omega \mu_2(x)dx} \quad as \ d_2 \to \infty.$$

Proof. (i) Since A_d and A_i are compact and positive, it then follows from Krein-Rutman theorem that R_0 is a principal eigenvalue of $A_d + A_i$ with a positive eigenfunction, denoted by $\phi^*(x)$; namely,

$$\begin{aligned} &\beta_d(\mu_2 - \nabla\cdot(d_2\nabla))^{-1}\phi^* + \beta_i(x)\frac{k(x)}{\mu_3(x)}(\mu_2 - \nabla\cdot(d_2\nabla))^{-1}\phi^* = R_0\phi^*, \quad x\in\Omega, \\ &\nabla\phi^*(x)\cdot\nu = 0, \ x\in\partial\Omega. \end{aligned}$$

Denote $\psi^* = \phi^*/(\beta_d + \beta_i\mu_3^{-1}k)$, then the above eigenvalue problem can be rewritten as

$$\begin{aligned} &\nabla\cdot(d_2(x)\nabla\psi(x)) - \mu_2(x)\psi(x) + \frac{\beta_d(x) + \beta_i(x)\mu_3^{-1}(x)k(x)}{R_0}\psi(x) = 0, \quad x\in\Omega, \\ &\nabla\psi\cdot\nu = 0, \ x\in\partial\Omega, \end{aligned} \tag{3.5}$$

(ii) Assume that d_2 is a constant on $\bar{\Omega}$. It is easily seen that R_0 is a decreasing function of d_2, and the eigenvalue problem (3.5) can be reduced as

$$\begin{aligned} & d_2\Delta\psi^* - \mu_2\psi^* + \frac{\beta_d + \beta_i\mu_3^{-1}k}{R_0}\psi^* = 0, \quad x \in \Omega, \\ & \nabla\psi^*(x)\cdot\nu = 0, \ x \in \partial\Omega. \end{aligned} \tag{3.6}$$

We first claim that $R_0 \le \overline{R}_0$, otherwise we have $-\mu_2 + (\beta_d + \beta_i\mu_3^{-1}k)/R_0 < 0$ and the principal eigenvalue of $d_2\Delta - \mu_2 + (\beta_d + \beta_i\mu_3^{-1}k)/R_0$ is negative. This contradicts to (3.6). Thus $\lim_{d_2\to 0} R_0$ exists. We next prove that $\lim_{d_2\to 0} R_0 = \overline{R}_0$. Assume to the contrary, then there exists $\epsilon_0 > 0$ such that $R_0 < \overline{R}_0 - \epsilon_0$ for all positive d_2. It follows from the continuity of coefficient functions that there exists a $x_0 \in \Omega$ and a $\delta > 0$ such that

$$\frac{\beta_d(x)}{\mu_2(x)} + \frac{\beta_i(x)k(x)}{\mu_2(x)\mu_3(x)} > \overline{R}_0 - \frac{\epsilon_0}{2} > R_0 + \frac{\epsilon_0}{2} \ \text{ for all } \ x \in B_\delta(x_0),$$

which implies that the positivity of $\beta_d(x)/\mu_2(x) + \beta_i(x)k(x)/[\mu_2(x)\mu_3(x)]$ on $B_\delta(x_0)$. Due to compactness of continuous functions on a bounded domain, there exists $\epsilon > 0$ such that

$$-\mu_2(x) + \frac{\beta_d(x) + \beta_i(x)\mu_3^{-1}(x)k(x)}{R_0} > \epsilon \ \text{ for all } \ x \in B_\delta(x_0).$$

The above inequality together with (3.6) yields $-\Delta\psi^* > \epsilon\psi^*/d_2$. Denote $\psi_+(x) = \psi^*(x)/\min_{x\in B_\delta(x_0)} \psi^*(x)$. Then we have $-\Delta\psi_+(x) > \epsilon\psi_+(x)/d_2$ and $\psi_+(x) \ge 1$ on $B_\delta(x_0)$. Let $\eta > 0$ be the principal eigenvalue of $-\Delta$ on $B_\delta(x_0)$ under Neumann boundary condition and $\psi_-(x)$ the corresponding eigenfunction, we can further normalize $\psi_-(x)$ such that $\psi_-(x) \le 1$ on $B_\delta(x_0)$. Then we have $-\Delta\psi_-(x) = \eta\psi_-(x) < \epsilon\psi_-(x)/d_2$. Thus, $\psi_+(x)$ and $\psi_-(x)$ are the super- and sub-solutions of $-\Delta\varphi = \epsilon\varphi/d_2$ with Neumann boundary condition. Thus, ϵ/d_2 is an eigenvalue of $-\Delta$ on $B_\delta(x_0)$ with Neumann boundary condition, which contradicts the facts $\epsilon/d_2 > \eta$ and η is the principal eigenvalue of $-\Delta$. Therefore, $R_0 \to \overline{R}_0$ as $d_2 \to 0$.

It is easily seen from (3.4) that $R_0 \ge \underline{R}_0$ for all $d_2 > 0$. Thus, R_0 is uniformly bounded for $d_2 > 0$ and $\lim_{d_2\to\infty} R_0$ exists. Then we divide both sides of (3.6) by d_2 to obtain

$$\Delta\psi^* + \frac{\beta_d + \beta_i\mu_3^{-1}k - R_0\mu_2}{R_0 d_2}\psi^* = 0, \quad x \in \Omega.$$

It then follows from elliptic regularity [24] that, there exists a positive constant $\bar{\psi}$ such that $\psi^* \to \bar{\psi}$ in $C(\Omega)$ as $d_2 \to \infty$. Integrating (3.6) by parts over Ω yields

$$\int_\Omega \mu_2\psi^* dx = \int_\Omega \frac{\beta_d + \beta_i\mu_3^{-1}k}{R_0}\psi^* dx.$$

Letting $d_2 \to \infty$, we obtain $R_0 \to \underline{R}_0$. This completes the proof. □

From the above theorem, we have a direct application on basic reproduction number.

Proposition 3.3. *(i) If $\beta_d(x)/\mu_2(x) + \beta_i(x)k(x)/(\mu_2(x)\mu_3(x)) \le 1$ for all $x \in \Omega$, then $R_0 < 1$ for all $d_2 > 0$ and Ω is an infection-free environment.*

(ii) *If* $\int_\Omega (\beta_d(x) + \beta_i(x)\mu_3^{-1}(x)k(x)dx \geq \int_\Omega \mu_2(x)dx,$, *then* $R_0 > 1$ *for all* $d_2 > 0$ *and* Ω *is a favorable environment for the viral infection.*

(iii) *If* $\int_\Omega (\beta_d(x) + \beta_i(x)\mu_3^{-1}(x)k(x)dx < \int_\Omega \mu_2(x)dx$ *and* $\beta_d(x)/\mu_2(x) + \beta_i(x)k(x)/(\mu_2(x)\mu_3(x)) > 1$ *for some* $x \in \Omega$, *then there exists a* $d_2^* > 0$ *such that* $R_0 \leq 1$ *if* $d_2 \geq d_2^*$ *and* $R_0 > 1$ *if* $d_2 < d_2^*$.

4. Global dynamics of the viral infection model

4.1. Existence of a global attractor

Define the continuous semiflow $\{\Theta(t)\}_{t\geq 0} : X^+ \to X^+$ for the system (1.2) by

$$\Theta(t)\phi(\cdot) := u(\cdot, t, \phi),\ t \geq 0.$$

It follows from Theorem 2.3 that the semiflow $\Theta(t)$ of system (1.2) is point dissipative and the orbit $\gamma^+(U) = \bigcup_{\phi\in U} \gamma^+(\phi)$ is bounded for any bounded set $U \subset X^+$. To apply the theory in [25], we have to show that $\Theta(t)$ is asymptotically smooth. Since $\Theta(t)$ is not compact, we introduce the weak compactness condition called κ-contraction, and Kuratowski measure of the noncompactness defined by [25]

$$\kappa(U) := \inf\{r \geq 0 : U \text{ has a finite cover of diameter less than } r\} \tag{4.1}$$

for any bounded set $U \subset X^+$. Clearly, $\kappa(U) = 0$ if and only if U is precompact. We need to show that $\Theta(t)$ is a κ-contraction, that is, there exists a continuous function $q(t) \in [0, 1) : \mathbb{R}_+ \to \mathbb{R}_+$ such that $\kappa(\Theta(t)U) \leq q(t)\kappa(U)$ for any bounded set $U \subset X^+$ and $t > 0$. To achieve this, we need the following lemma. The proof is similar to that in [12, Lemma 2.5] with some minor modifications.

Lemma 4.1. *For any bounded set* $U \subset X^+$ *and* $t > 0$, $\{u_i(\cdot, t, \phi) : \phi \in U\}$ *and* $\{\int_0^t e^{-\mu_3(\cdot)(t-s)}k(\cdot)u_2(\cdot, s, \phi)ds : \phi \in U\}$ *with* $i = 1, 2$ *are precompact in* $C(\bar{\Omega})$.

Theorem 4.2. *The semiflow* $\Theta(t)$ *is a* κ*-contraction and asymptotically smooth. Moreover, system* (1.2) *admits a connected global attractor in* X^+.

Proof. For any initial condition $\phi = (\phi_1, \phi_2, \phi_3) \in X^+$, we have $\Theta(t)\phi = \Theta_1(t)\phi + \Theta_2(t)\phi$ for all $t \geq 0$, where

$$\Theta_1(t)\phi = \left(u_1(\cdot, t, \phi), u_2(\cdot, t, \phi), \int_0^t e^{-\mu_3(\cdot)(t-s)}k(\cdot)u_2(\cdot, s, \phi)ds\right),$$
$$\Theta_2(t)\phi = (0, 0, e^{-\mu_3(\cdot)t}\phi_3)$$

For any bounded set $U \subset X^+$, it follows from (4.1) that

$$\kappa(\Theta_2(t)U) \leq \|e^{-\mu_3(\cdot)t}\|\kappa(U) \leq e^{-\underline{\mu}_3 t}\kappa(U) \ \text{ for all } \ t \geq 0,$$

where $\underline{\mu}_3 = \min_{x\in\bar{\Omega}} \mu_3(x)$. Note that Lemma 4.1 implies that $\Theta_1(t)U$ is precompact in $C(\bar{\Omega})$ for any $t > 0$, that is, $\kappa(\Theta_1(t)U) = 0$. Hence, for any $t > 0$, we have

$$\kappa(\Theta(t)U) \leq \kappa(\Theta_1(t)U) + \kappa(\Theta_2(t)U) \leq e^{-\underline{\mu}_3 t}\kappa(U).$$

Therefore, $\Theta(t)$ is a κ-contraction. It then follows from [25, Lemma 2.3.4] that $\Theta(t)$ is asymptotically smooth. Therefore, by Theorem 2.4.6 in [25], system (1.2) admits a connected global attractor in X^+. □

4.2. Global stability of infection-free steady state

It follows from Theorem 3.1 in [23] that the infection-free steady state $(w^*(x), 0, 0)$ is locally asymptotically stable when $R_0 < 1$. To establish global asymptotic stability of infection-free steady state when $R_0 \leq 1$, we shall first develop the following approach to show local asymptotic stability of infection-free steady state not only when $R_0 < 1$, but also for the critical case $R_0 = 1$.

Denote A as the linear operator of (3.2) and e^{At} the semigroup generated by A. The exponential growth bound of e^{At} is defined as

$$\omega(e^{At}) := \lim_{t\to\infty} \frac{\ln \|e^{At}\|}{t}.$$

Lemma 4.3. *Assume that $R_0 \leq 1$, then $s(A) \leq 0$, $\omega(e^{At}) \leq 0$, and there exists a constant $M_a > 0$ such that $\|e^{At}\| \leq M_a$.*

Proof. By Theorem 3.5 in [22], $s(A) \leq 0$ if $R_0 \leq 1$. It follows from [26] that

$$\omega(e^{At}) = \max\{s(A), \omega_{ess}(e^{At})\},$$

where $\omega_{ess}(e^{At})$ is the essential growth bound of e^{At} defined by

$$\omega_{ess}(e^{At}) := \lim_{t\to\infty} \frac{\ln \sigma(e^{At})}{t}.$$

Here, $\sigma(e^{At})$ denotes the distance of e^{At} from the set of compact linear operators in $Y = C(\bar{\Omega}, \mathbb{R}^2)$. To prove that $\omega(e^{At}) \leq 0$, it is sufficient to show that $\omega_{ess}(e^{At}) \leq 0$. For any $\hat{\phi} := (\phi_2, \phi_3) \in Y$, the solution of the linear system (3.2) is $e^{At}\hat{\phi} = \Psi_2(t)\hat{\phi} + \Psi_3(t)\hat{\phi}$, where $\Psi_2(t)\hat{\phi} = (u_2(\cdot, t, \hat{\phi}), \int_0^t e^{-\mu_3(\cdot)(t-s)} k(\cdot) u_2(\cdot, s, \hat{\phi}) ds)$ and $\Psi_3(t)\hat{\phi} = (0, e^{-\mu_3(\cdot)t}\phi_3)$. Note that Lemma 4.1 implies that $\Psi_2(t)$ is a compact linear operator, that is, $\sigma(\Psi_2(t)) = 0$. Thus, we have $\sigma(e^{At}) = \sigma(\Psi_2(t) + \Psi_3(t)) = \sigma(\Psi_3(t)) \leq \|\Psi_3(t)\| \leq e^{-\underline{\mu}_3 t}$. Therefore, we compute

$$\omega_{ess}(e^{At}) \leq -\underline{\mu}_3 < 0.$$

This implies that the there exists a constant $M_a > 0$ such that $\|e^{At}\| \leq M_a$. □

Theorem 4.4. *Assume that $R_0 \leq 1$, then the infection-free steady state $(w^*(x), 0, 0)$ of (1.2) is locally asymptotically stable.*

Proof. Given any small $\delta > 0$, let $u(x, t)$ be any solution of (1.2) with initial condition satisfies $\|u_1(x, 0) - w^*(x)\| + \|u_2(x, 0)\| + \|u_3(x, 0)\| < \delta$. Denote $w_1(x, t) = u_1(x, t) - w^*(x)$ and $\underline{\mu}_1 = \min_{x\in\Omega} \mu_1(x) > 0$ which satisfies

$$\begin{aligned}\frac{\partial w_1}{\partial t} &= \nabla \cdot (d_1 \nabla w_1) - \mu_1 w_1 - f(w_1 + w^*, u_2) - g(w_1 + w^*, u_3) \\ &\leq \nabla \cdot (d_1 \nabla w_1) - \underline{\mu}_1 w_1.\end{aligned}$$

Let $-\widetilde{\lambda}_1 < 0$ be the principle eigenvalue of $\widetilde{T}_1(t)$, where $\widetilde{T}_1(t)$ is the C_0 semigroup generated by $\nabla \cdot (d_1 \nabla) - \underline{\mu}_1$ with Neumann boundary condition. It then follows from comparison principle that

$$w_1(x, t) \leq \|\widetilde{T}_1(t) w_1(x, 0)\| \leq e^{-\widetilde{\lambda}_1 t} \|u_1(x, 0) - w^*(x)\| \leq \delta e^{-\widetilde{\lambda}_1 t}$$

for all $x \in \Omega$ and $t \geq 0$. Thus, we have $u_1(x,t) \leq \widetilde{u}_1(x,t) := w^*(x) + \delta e^{-\widetilde{\lambda}_1 t}$ on $\Omega \times [0,\infty)$. By $(\mathbf{H}_1)$, we obtain

$$f(u_1,u_2) \leq f(\widetilde{u}_1,u_2) \leq \frac{\partial f(\widetilde{u}_1,0)}{\partial u_2} u_2 \;\text{ and }\; g(u_1,u_3) \leq g(\widetilde{u}_1,u_3) \leq \frac{\partial g(\widetilde{u}_1,0)}{\partial u_3} u_3.$$

We obtain from the definitions of β_d and β_i in (3.1) and the second equation of (1.2) that

$$\frac{\partial u_2}{\partial t} \leq \nabla \cdot (d_2(x)\nabla u_2) + \beta_d(x)u_2 + \beta_i(x)u_3 - \mu_2(x)u_2 + p(x,t)$$

for $x \in \Omega$ and $t > 0$, where

$$p(x,t) = \left(\frac{\partial f(\widetilde{u}_1,0)}{\partial u_2} - \beta_d\right)u_2 + \left(\frac{\partial g(\widetilde{u}_1,0)}{\partial u_3} - \beta_d\right)u_3.$$

It follows from system (1.2) and comparison principle that

$$\begin{pmatrix} u_2(\cdot,t) \\ u_3(\cdot,t) \end{pmatrix} \leq e^{At}\begin{pmatrix} u_2(\cdot,0) \\ u_3(\cdot,0) \end{pmatrix} + \int_0^t e^{A(t-s)}\begin{pmatrix} p(\cdot,s) \\ 0 \end{pmatrix} ds, \tag{4.2}$$

Recall $K_1 > \max_{x\in\bar{\Omega}} w^*(x)$ and $\|u_1(x,t)\| \leq K_1$ for all $t \geq 0$ in the proof of Theorem 2.3. Denote

$$\bar{f} = \max_{u_1\in[0,K_1]}\left|\frac{\partial^2 f(u_1,0)}{\partial u_1 \partial u_2}\right|, \;\; \bar{g} = \max_{u_1\in[0,K_1]}\left|\frac{\partial^2 g(u_1,0)}{\partial u_1 \partial u_3}\right|.$$

We then have $p(x,t) \leq \delta e^{-\widetilde{\lambda}_1 t}(\bar{f}u_2 + \bar{g}u_3)$. Set $E(t) = \max\{\max_{x\in\Omega} u_2(x,t), \max_{x\in\Omega} u_3(x,t)\}$. By Lemma 4.3 and inequality (4.2), we obtain

$$E(t) \leq \delta M_a + \delta M_a(\bar{f} + \bar{g})\int_0^t e^{-\widetilde{\lambda}_1 s}E(s)ds.$$

Then Gronwall's inequality yields

$$E(t) \leq \delta M_a e^{\int_0^t \delta M_a(\bar{f}+\bar{g})e^{-\widetilde{\lambda}_1 s}ds} \leq \delta M_a e^{\frac{\delta M_a(\bar{f}+\bar{g})}{\widetilde{\lambda}_1}} \;\text{ for all }\; t \geq 0.$$

Thus $\|u_2(\cdot,t)\| + \|u_3(\cdot,t)\| = O(\delta)$ as $\delta \to 0$. We next show that $\|u_1(\cdot,t) - w^*(x)\| = O(\delta)$ as $\delta \to 0$. Note that $(\mathbf{H}_1)$ implies that

$$\begin{aligned} f(u_1,u_2) &\leq f(K_1,u_2) \leq \frac{\partial f(K_1,0)}{\partial u_2}u_2 \leq \frac{\partial f(K_1,0)}{\partial u_2}\delta M_a e^{\frac{\delta M_a(\bar{f}+\bar{g})}{\widetilde{\lambda}_1}}, \\ g(u_1,u_3) &\leq g(K_1,u_3) \leq \frac{\partial g(K_1,0)}{\partial u_3}u_3 \leq \frac{\partial g(K_1,0)}{\partial u_3}\delta M_a e^{\frac{\delta M_a(\bar{f}+\bar{g})}{\widetilde{\lambda}_1}}. \end{aligned}$$

It then follows from the above inequalities and the first equation of (1.2) that

$$\frac{\partial u_1}{\partial t} \geq \nabla \cdot (d_1(x)\nabla u_1) + a(x) - q\delta - \mu_1(x)u_1, \tag{4.3}$$

where $q = (\partial f(K_1, 0)/\partial u_2 + \partial g(K_1, 0)/\partial u_3)\, M_a e^{\delta M_a(\bar{f}+\bar{g})/\widetilde{\lambda}_1}$ is positive and finite. By Lemma 2.1, for any small $\delta > 0$, the following reaction-diffusion equation

$$\begin{aligned}&\frac{\partial w}{\partial t} = \nabla \cdot (d_1(x)\nabla w) + a(x) - q\delta - \mu_1(x)w,\ x \in \Omega,\ t > 0,\\ &\nabla w(x,t)\cdot \nu = 0,\ x \in \partial\Omega,\ t > 0\end{aligned}$$

admits a unique and strictly positive steady state $w^{\delta}(x)$, which is globally asymptotically stable in $C(\bar{\Omega}, \mathbb{R}_+)$. Moreover, $\|w^*(x) - w^{\delta}(x)\| = O(\delta)$ as $\delta \to 0$. Thus, it follows from (4.3) and comparison principle that

$$u_1(x,t) \geq w^{\delta}(x) \geq w^*(x) + O(\delta)\ \text{ as }\ \delta \to 0.$$

Recall that $u_1(x,t) \leq w^*(x) + \delta e^{-\widetilde{\lambda}_1 t}$ on $\Omega\times[0,\infty)$. Therefore, $\|u_1(\cdot,t) - w^*(\cdot)\| + \|u_2(\cdot,t)\| + \|u_2(\cdot,t)\| = O(\delta)$ as $\delta \to 0$, thus proving local stability of $(w^*(x), 0, 0)$ if $R_0 \leq 1$. □

We are now in the position to establish global attractivity of infection-free steady state by constructing a suitable Lyapunov functional and LaSalle invariance principle.

Theorem 4.5. *If $R_0 \leq 1$, then the infection-free steady state $(w^*(x), 0, 0)$ of (1.2) is globally asymptotically stable.*

Proof. We establish the global asymptotic stability of $(w^*(x), 0, 0)$ by proving the following two claims. Define a region $D = \{\phi \in X^+ : \phi(x) \leq w^*(x)\}$.

Claim 1. For any initial data $\phi \in X^+$, the omega limit set of ϕ is contained in D.

Clearly, for any $x \in \Omega$, if $u_1(x,t_0) \leq w^*(x)$ for some $t_0 \geq 0$, then $u_1(x,t) \leq w^*(x)$ for all $t \geq t_0$. Then we divide the domain Ω into two sub-domains $\Omega_1 := \{x \in \Omega : u_1(x,t) > w^*(x)$ for all $t \geq 0\}$ and $\Omega_2 := \{x \in \Omega : u_1(x,t) \leq w^*(x)$ for some $t \geq 0\}$. Here, Ω_2 is closed in Ω, and there exists $t_0 \geq 0$ that $u_1(x,t) \leq w^*(x)$ for all $x \in \Omega_2$. Without loss of generality, we assume $t_0 = 0$.

For any $x \in \Omega_1$, Lemma 2.1 and the first equation of (1.2) imply that $\partial u_1(x,t)/\partial t \leq 0$, that is, $u_1(x,t)$ is a decreasing function in t. It then follows from $u_1(x,t) \geq w^*(x)$ for $x \in \Omega_1$ that $\lim_{t\to\infty} u_1(x,t)$ exists, and $\lim_{t\to\infty} u_1(x,t) \geq w^*(x)$. Moreover, if $\lim_{t\to\infty} u_1(x,t) > w^*(x)$, then we obtain from the first equation of (1.2) that $0 = \lim_{t\to\infty} \partial u_1(x,t)/\partial t < 0$. This is a contradiction. Therefore, $\lim_{t\to\infty} u_1(x,t) = w^*(x)$, which implies that the omega limit set of ϕ is contained in D.

Claim 2. The infection-free steady state $(w^*(x), 0, 0)$ attracts all initial profiles in D.

We consider the solution semiflow restricted on the invariant set D and construct a Lyapunov functional $V_1 : D \to \mathbb{R}$ given by

$$V_1(u_1, u_2, u_3) = \int_D \left(u_2^2(x,t) + \frac{\beta_i(x)}{k(x)} u_3^2(x,t) \right) dx.$$

Taking the derivative of V_1 along the solution, we obtain

$$\frac{dV_1}{dt} = \int_D \left(u_2 \left[\nabla \cdot (d_2 \nabla u_2) + f(u_1, u_2) + g(u_1, u_3) - \mu_2 u_2\right] + \frac{\beta_i}{k} u_3 (k u_2 - \mu_3 u_3) \right) dx.$$

Note that $u_1(x,t) \le w^*(x)$ in D, it is readily seen from ($\mathbf{H}_1$) that $f(u_1,u_2) \le f(w^*(x),u_2) \le \beta_d u_2$ and $g(u_1,u_3) \le g(w^*(x),u_3) \le \beta_i u_3$. These inequalities and Neumann boundary condition yield that

$$\begin{aligned}\frac{dV_1}{dt} &\le \int_D \left(-d_2|\nabla u_2|^2 - (\mu_2-\beta_d)u_2^2 + 2\beta_i u_2 u_3 - \frac{\beta_i\mu_3}{k}u_3^2\right)dx\\ &\le \int_D \left(-d_2|\nabla u_2|^2 - (\mu_2-\beta_d)u_2^2 + \frac{\beta_i k}{\mu_3}u_2^2 - \beta_i(\sqrt{\frac{\mu_3}{k}}u_3 - \sqrt{\frac{k}{\mu_3}}u_2)^2\right)dx\\ &\le \int_D \left(-d_2|\nabla u_2|^2 - (\mu_2-\beta_d)u_2^2 + \frac{\beta_i k}{\mu_3}u_2^2\right)dx.\end{aligned}$$

We next prove

$$\int_\Omega \frac{\beta_i k}{\mu_3}\psi^2 dx \le \int_\Omega \left(d_2|\nabla\psi|^2 + (\mu_2-\beta_d)\psi^2\right)dx. \tag{4.4}$$

holds for any $\psi \in H^1(\Omega)$ if $R_0 \le 1$. We make another decomposition of the linear operator $A = F_1 + B_1$ associated with the linear system (3.2), where

$$F_1 = \begin{pmatrix} 0 & \beta_i(\cdot)\\ 0 & 0\end{pmatrix},\quad B_1 = \begin{pmatrix} \nabla\cdot(d_2\nabla) - (\mu_2(\cdot)-\beta_d(\cdot)) & 0\\ k(\cdot) & -\mu_3(\cdot)\end{pmatrix}. \tag{4.5}$$

Note that Theorem 3.2 implies that $\mu_2 > \beta_d$ when $R_0 \le 1$. Thus the operator B_1 is resolvent-positive with $s(B_1) < 0$. Then it follows from [22, Theorem 3.5] and $R_0 \le 1$ that $s(A) \le 0$ and

$$\begin{aligned} r(-F_1B_1^{-1}) &= r\left(\frac{\beta_i k}{\mu_3}(\mu_2-\beta_d-\nabla\cdot(d_2\nabla))^{-1}\right)\\ &= \sup_{\psi\in H^1(\Omega),\psi\ne 0} \frac{\int_\Omega \beta_i(x)\mu_3^{-1}(x)k(x)\psi^2(x)dx}{\int_\Omega \left(d_2(x)|\nabla\psi(x)|^2 + (\mu_2(x)-\beta_d(x))\psi^2(x)\right)dx} \le 1.\end{aligned}$$

Hence, we obtain (4.4) for any $\psi \in H^1(\Omega)$ if $R_0 \le 1$. This implies that $dV_1/dt \le 0$ if $R_0 \le 1$. Moreover, $\mathcal{K} = \{(\bar{w}^*(x),0,0)\}$, where $\mathcal{K}$ is an invariant set on which $dV_1/dt = 0$. Note that $(\bar{w}^*(x),0,0)$ is the unique point in the largest invariant set on which $dV_1/dt = 0$. By the LaSalle invariance principal, $(\bar{w}^*(x),0,0)$ is globally attractive in D.

Finally, it follows from Lemma 1.2.1 in [27] that the omega limit set of any initial data $\phi \in X^+$ is internally chain transitive. The above two claims and [27, Theorem 1.2.1] yield $(w^*(x),0,0)$ is globally attractive in X^+. This, together with the local stability result in Theorem 4.4, implies the global asymptotic stability of $(w^*(x),0,0)$ in X^+ when $R_0 \le 1$. This ends the proof. □

4.3. Persistence of infection when $R_0 > 1$

By using the same idea in [12, Lemma 3.7], we show that $s(A)$ is actually the principal eigenvalue of A when $R_0 \ge 1$.

Lemma 4.6. *If $R_0 \ge 1$, then $s(A)$ is the principal eigenvalue of A with a strongly positive eigenfunction.*

Proof. The eigenvalue problem of A is given by

$$\begin{aligned}&\lambda\varphi_2(x) = \nabla\cdot(d_2(x)\nabla\varphi_2(x)) + \beta_d(x)\varphi_2(x) + \beta_i(x)\varphi_3(x) - \mu_2(x)\varphi_2(x),\ x\in\Omega,\\ &\lambda\varphi_3(x) = k(x)\varphi_2(x) - \mu_3(x)\varphi_3(x),\ x\in\Omega,\\ &\nabla\varphi_2(x)\cdot\nu = 0,\ x\in\partial\Omega.\end{aligned} \tag{4.6}$$

Then we define a one-parameter family of linear operators with Neumann boundary condition on $C(\bar{\Omega})$:

$$L_\lambda = \nabla \cdot (d_2 \nabla) + \beta_d + \frac{\beta_i k}{\lambda + \mu_3} - \mu_2.$$

Let $T_\lambda(t)$ be the semigroup generated by L_λ. Since $\beta_d + \frac{\beta_i k}{\lambda+\mu_3} - \mu_2$ is cooperative and irreducible for all $x \in \Omega$, it then follows from Theorem 7.5.1 in [16] that $T_\lambda(t)$ is a compact and strongly positive operator for all $t > 0$. By Krein-Rutman theorem, $s(L_\lambda)$ is a principal eigenvalue of L_λ with positive eigenfunction $\varphi_2^*(x)$. Clearly, $s(L_\lambda)$ is decreasing and continuously with respect to λ, and $s(L_\lambda)$ is finite when λ is large.

According to Lemma 2.3(d) in [28], we obtain that $R_0 - 1$ and $s(A)$ have the same sign as λ_0, where λ_0 is the principal eigenvalue of L_0. This yields that $s(L_0) = \lambda_0 \geq 0$. Thus, there exists a unique $\lambda^* \geq 0$ such that $s(L_{\lambda^*}) = \lambda^*$. Note that the problem (4.6) can be written as $L_\lambda \varphi_2(x) = \lambda \varphi_2(x)$. Therefore, if $R_0 \geq 1$, then $s(L_{\lambda^*}) = \lambda^* > 0$ is a principal eigenvalue of A with a strongly positive eigenfunction $(\varphi_2^*(x), \varphi_3^*(x))$, where $\varphi_3^*(x) = \frac{k(x)}{s(L_\lambda)+\mu_3(x)} \varphi_2^*(x)$. Finally, we can further obtain $\lambda^* = s(A)$ by using Theorem 2.3 in [23]. □

To establish the existence of the chronic infection steady state when $R_0 > 1$, we now apply the permanence theorem in [29, Theorem 3] and use an argument similar to that in the proof of [11, Theorem 2.2] to obtain the following persistence result.

Theorem 4.7. *If $R_0 > 1$, then system (1.2) is uniformly persistent in X^+, that is, there exists a $\eta > 0$ such that for any $\phi \in X_0$, we have*

$$\liminf_{t \to \infty} u_i(x, t, \phi) \geq \eta, \ (i = 1, 2, 3) \ \textit{uniformly for all} \ \ x \in \bar{\Omega}.$$

Moreover, system (1.2) admits at least one chronic infection steady state $(u_1^*(x), u_2^*(x), u_3^*(x))$.

Proof. Denote $X_0 := \{(\phi_1, \phi_2, \phi_3) \in X^+ : \ \phi_2(\cdot) \not\equiv 0 \text{ and } \phi_3(\cdot) \not\equiv 0\}$ and

$$\partial X_0 := X^+ \backslash X_0 = \{(\phi_1, \phi_2, \phi_3) \in X^+ : \ \phi_2(\cdot) \equiv 0 \text{ or } \phi_3(\cdot) \equiv 0\}.$$

Obviously, $X_0 \cap \partial X_0 = \emptyset$, $X_0 \cup \partial X_0 = X^+$, X_0 is open and dense in X^+, and $\Theta(t)\partial X_0 \subseteq \partial X_0$. Note that Proposition 2.4(ii) implies that $\Theta(t) X_0 \subseteq X_0$ for all $t \geq 0$. Denote M_∂ as the largest positively invariant set in ∂X_0. It follows from Proposition 2.4(ii) that

$$M_\partial = \{(\phi_1, \phi_2, \phi_3) \in X^+ : \ \phi_2 \equiv 0 \text{ and } \phi_3 \equiv 0\}.$$

For any initial data $\phi \in M_\partial$, we can easily obtain that $u_i(x, t, \phi) \equiv 0$ for all $i = 2, 3$, $x \in \Omega$ and $t \geq 0$. Then in view of Lemma 2.1, the limiting system when $u_i \equiv 0$ for $i = 2, 3$ has a unique globally asymptotically stable steady state $u_1(x, t) = w^*(x)$. We then obtain from [30, Theorem 4.1] that $(w^*(x), 0, 0)$ is globally attractive in M_∂. We now define a generalized distance function $\rho : X^+ \to [0, \infty)$ by

$$\rho(\phi) = \min_{x \in \bar{\Omega}} \{\phi_2(x), \phi_3(x)\} \ \text{ for any } \ \phi \in X^+.$$

From strong maximum principle, we have $\rho(\Theta(t)\phi) > 0$ for all $\phi \in X_0$. Since $\rho^{-1}(0, \infty) \subset X_0$, the condition (P) in [29, Section 3] is satisfied.

Denote $W^s((w^*(x),0,0))$ as the stable manifold of $(w^*(x),0,0)$. We next verify that $W^s((w^*(x),0,0)) \cap \rho^{-1}(0,\infty) = \emptyset$. It suffices to show that there exists a $\eta_0 > 0$ such that

$$\limsup_{t\to\infty} \|\Theta_t\phi - (w^*(x),0,0)\| \ge \eta_0 \text{ for any } \phi \in \rho^{-1}(0,\infty).$$

Suppose, to the contrary, for any $\eta_0 > 0$ there exists $\tilde{\phi} \in \rho^{-1}(0,\infty)$ such that

$$\limsup_{t\to\infty} \|\Theta_t\tilde{\phi} - (w^*(x),0,0)\| < \eta_0. \tag{4.7}$$

In view of Lemma 4.6, $\lambda_0 = s(A) > 0$ is the principal eigenvalue of $A = F + B$ with a strongly positive eigenfunction if $R_0 > 1$. For any sufficiently small $\varepsilon > 0$, we consider a small perturbation of F:

$$F_\varepsilon = \begin{pmatrix} \beta_d - \varepsilon & \beta_i - \varepsilon \\ 0 & 0 \end{pmatrix}.$$

Similar as in the proof of Lemma 4.6, one can show that the eigenvalue problem

$$\begin{aligned} &\lambda\varphi_2 = \nabla\cdot(d_2\nabla\varphi_2) + (\beta_d - \varepsilon)\varphi_2 + (\beta_i - \varepsilon)\varphi_3 - \mu_2\varphi_2,\ x \in \Omega, \\ &\lambda\varphi_3 = k\varphi_2 - \mu_3\varphi_3,\ x \in \Omega, \\ &\nabla\varphi_2\cdot\nu = 0,\ x \in \partial\Omega. \end{aligned}$$

has a principle eigenvalue λ_ε with strongly positive eigenfunction $(\varphi_2^\varepsilon, \varphi_3^\varepsilon)$. By continuity of the operator, we have $\lambda_\varepsilon \to \lambda_0 > 0$ as $\varepsilon \to 0^+$. We then choose a small $\varepsilon > 0$ such that $\lambda_\varepsilon > 0$. It follows from (4.7) and $(\mathbf{H}_1)$ that there exists a $\tilde{t} > 0$ such that

$$f(u_1,u_2) \ge (\beta_d - \varepsilon)u_2 \text{ and } g(u_1,u_3) \ge (\beta_i - \varepsilon)u_3 \text{ for all } t \ge \tilde{t}.$$

Thus, for all $t \ge \tilde{t}$, $(u_2(x,t,\tilde{\phi}), u_3(x,t,\tilde{\phi}))$ satisfies

$$\begin{cases} \frac{\partial u_2}{\partial t} \ge \nabla\cdot(d_2(x)\nabla u_2) + (\beta_d - \varepsilon)u_2 + (\beta_i - \varepsilon)u_3 - \mu_2 u_2, & x \in \Omega,\ t > \tilde{t}, \\ \frac{\partial u_3}{\partial t} = k(x)u_2 - \mu_3(x)u_3, & x \in \Omega,\ t > \tilde{t}, \\ \nabla u_2\cdot\nu = 0, & x \in \partial\Omega,\ t > \tilde{t}. \end{cases} \tag{4.8}$$

Since $u_i(x,t,\tilde{\phi}) > 0$ for all $x \in \bar{\Omega}$, $t > 0$ and $i = 2,3$, there exists $\delta > 0$ such that $u_2(x,\tilde{t},\tilde{\phi}) \ge \delta\varphi_2^\varepsilon$ and $u_3(x,\tilde{t},\tilde{\phi}) \ge \delta\varphi_3^\varepsilon$. It then follows from (4.8) and comparison principle that

$$(u_2(x,t,\tilde{\phi}), u_3(x,t,\tilde{\phi})) \ge (\delta e^{\lambda_\varepsilon(t-\tilde{t})}\varphi_2^\varepsilon,\ \delta e^{\lambda_\varepsilon(t-\tilde{t})}\varphi_3^\varepsilon) \text{ for } x \in \bar{\Omega},\ t \ge \tilde{t}.$$

Therefore, $u_i(x,t,\tilde{\phi}) \to \infty$ as $t \to \infty$ for $i = 2,3$, which contradicts to Theorem 2.3. Thus, we prove $W^s((w^*(x),0,0)) \cap \rho^{-1}(0,\infty) = \emptyset$. Then by applying [29, Theorem 3], there exists $\eta_0 > 0$ such that $\liminf_{t\to\infty} \rho(\Theta(t)\phi) \ge \eta_0$ for any $\phi \in X^+$. This, together with Proposition 2.4 implies that $\liminf_{t\to\infty} u_i(x,t) \ge \eta$ for all $i = 1,2,3$ and $x \in \bar{\Omega}$, where $\eta = \min\{\eta_0, m_0\}$.

Furthermore, in view of [31, Theorem 4.7] and Theorem 4.2, system (1.2) admits at least one positive steady state. This ends the proof. □

5. Spatially homogeneous case

In this section, we consider the special case where all the coefficients in (1.2) are independent of the variable x, that is, $d_1(x) = d_1,\ a(x) = a,\ \mu_j(x) = \mu_j\ (j = 1, 2, 3),\ d_2(x) = d_2,\ k(x) = k$ for all $x \in \bar{\Omega}$. We further assume that

(**C**) $f(u_1, u_2) = h(u_1)f_1(u_2)$ and $g(u_1, u_3) = h(u_1)g_1(u_3)$, where $h, f_1, g_1 \in C^1(\mathbb{R}_+ \times \mathbb{R}_+)$ are increasing functions, and $h(v) = 0$ (resp. $f_1(v) = 0, g_1(v) = 0$) if and only if $v = 0$. Moreover, $d^2 f_1(v)/dv^2 \leq 0$ and $d^2 g_1(v)/dv^2 \leq 0$.

System (1.2) becomes homogeneous, that is,

$$\begin{aligned} \frac{\partial u_1}{\partial t} &= d_1 \Delta u_1 + a - h(u_1)f_1(u_2) - h(u_1)g_1(u_3) - \mu_1 u_1, \\ \frac{\partial u_2}{\partial t} &= d_2 \Delta u_2 + h(u_1)f_1(u_2) + h(u_1)g_1(u_3) - \mu_2 u_2, \\ \frac{\partial u_3}{\partial t} &= k u_2 - \mu_3 u_3, \end{aligned} \tag{5.1}$$

for $x \in \Omega, t > 0$ with the homogeneous Neumann boundary condition and nonnegative initial conditions. It then follows that $w^*(x) = a/\mu_1$. By applying Krein-Rutman theorem, $A_d + A_i$ is a compact and positive operator with a positive eigenfunction 1 corresponding to a positive principle eigenvalue

$$R_0 = \frac{\beta_d}{\mu_2} + \frac{\beta_i k}{\mu_2 \mu_3},$$

where $\beta_d = h(a/\mu_1) f_1'(0)$ and $\beta_i = h(a/\mu_1) g_1'(0)$ are constants. This implies that the basic reproduction numbers for system (5.1) and the corresponding diffusive-free ($d_1 = d_2 = 0$) system are same. Denote (u_1^*, u_2^*, u_3^*) as the positive constant steady state, which satisfy the following equilibrium equations

$$a - \mu_1 u_1^* = h(u_1^*)\left(f_1(u_2^*) + g_1(u_3^*)\right) = \mu_2 u_2^* = \frac{\mu_2 \mu_3}{k} u_3^*. \tag{5.2}$$

Since the existence of constant steady state for system (5.1) same as for the corresponding ODE system. This, together with Theorem 3.1 in [8], yields the following lemma.

Lemma 5.1. *If $R_0 > 1$, then system (5.1) has a unique positive constant steady state (u_1^*, u_2^*, u_3^*).*

We next establish that R_0 is a threshold role for the global dynamics of system (5.1), and further give the global stability of the positive constant steady state.

Theorem 5.2. *(i) If $R_0 \leq 1$, then the infection-free steady state $(a/\mu_1, 0, 0)$ for system (5.1) is globally asymptotically stable in X^+.*

(ii) If $R_0 > 1$, then system (5.1) admits a unique chronic infection steady state (u_1^*, u_2^*, u_3^*), which is also homogeneous and globally asymptotically stable in X_0.

Proof. Theorem 4.5 implies that (i) holds. We next prove the local asymptotic stability of the positive constant steady state (u_1^*, u_2^*, u_3^*) when $R_0 > 1$. Linearizing system (5.1) at (u_1^*, u_2^*, u_3^*), we obtain

$$\frac{dU(t)}{dt} = d\Delta U(t) + L(U(t)),$$

where $U(t) = (u_1(x,t), u_2(x,t), u_3(x,t))^T$, $b = h'(u_1^*)(f_1(u_2^*) + g_1(u_3^*)) > 0$,

$$d\Delta = \begin{pmatrix} d_1\Delta & 0 & 0 \\ 0 & d_2\Delta & 0 \\ 0 & 0 & 0 \end{pmatrix}, \; L(\phi) = \begin{pmatrix} -b-\mu_1 & -h(u_1^*)f_1'(u_2^*) & -h(u_1^*)g_1'(u_3^*) \\ b & h(u_1^*)f_1'(u_2^*) - \mu_2 & h(u_1^*)g_1'(u_3^*) \\ 0 & k & -\mu_3 \end{pmatrix},$$

and $\mathrm{dom}(d\Delta) = \{(u_1, u_2)^T : u_i \in W^{2,2}(\Omega), \frac{\partial u_i}{\partial \nu} = 0 \text{ for } i = 1, 2.\}$. Then the characteristic equation for the above linear system is

$$\lambda y - d\Delta y - L(y) = 0 \;\text{ for } y \in \mathrm{dom}(d\Delta),\; y \neq 0.$$

It is well known that the eigenvalue problem

$$\begin{aligned} -\Delta\psi &= \zeta\psi, \qquad x \in \Omega, \\ \frac{\partial \psi}{\partial \nu} &= 0, \qquad x \in \partial\Omega, \end{aligned}$$

has eigenvalues $0 = \zeta_0 < \zeta_1 \leq \zeta_2 \leq \cdots \leq \zeta_n \leq \zeta_{n+1} \leq \cdots$, with the corresponding eigenfunctions $\hat{\psi}_n(x)$. Substituting $y = \sum_{n=0}^{\infty} y_n \hat{\psi}_n(x)$ into the characteristic equation gives

$$(\lambda + b + \mu_1 + d_1\zeta_n)(\lambda + \mu_2 + d_2\zeta_n)(\lambda + \mu_3) = (\lambda + \mu_1 + d_1\zeta_n)\Phi_1(\lambda)$$

for $n = 0, 1, 2, \cdots$, where $\Phi_1(\lambda) = (\lambda+\mu_3)h(u_1^*)f_1'(u_2^*) + kh(u_1^*)g_1'(u_3^*)$. The above characteristic equation is equivalent to

$$(\lambda + b + \mu_1 + d_1\zeta_n)(\frac{\lambda}{\mu_2} + 1 + \frac{d_2\zeta_n}{\mu_2})(\lambda + \mu_3) = (\lambda + \mu_1 + d_1\zeta_n)\Phi_2(\lambda) \tag{5.3}$$

where

$$\Phi_2(\lambda) = \left(\frac{1}{1 + kg_1'(u_3^*)/(\mu_3 f_1'(u_2^*))}\lambda + \mu_3\right)\left(\frac{h(u_1^*)f_1'(u_2^*)}{\mu_2} + \frac{kh(u_1^*)g_1'(u_3^*)}{\mu_2\mu_3}\right).$$

We claim that all eigenvalues of (5.3) have negative real parts. Otherwise, suppose that $\lambda = \sigma + \omega i$ is an eigenvalue satisfying $\sigma \geq 0$. Then for any nonnegative integer n, we have

$$|\lambda + b + \mu_1 + d_1\zeta_n| > |\lambda + \mu_1 + d_1\zeta_n|, \; |\frac{\lambda}{\mu_2} + 1 + \frac{d_2\zeta_n}{\mu_2}| \geq 1.$$

It follows from (**C**) and (5.2) that

$$\frac{h(u_1^*)f_1'(u_2^*)}{\mu_2} + \frac{kh(u_1^*)g_1'(u_3^*)}{\mu_2\mu_3} \leq \frac{h(u_1^*)f_1(u_2^*)}{\mu_2 u_2^*} + \frac{kh(u_1^*)g_1(u_3^*)}{\mu_2\mu_3 u_3^*} = 1,$$

which implies that $|\Phi_2(\lambda)| \leq |\lambda + \mu_3|$. Therefore, we obtain

$$|(\lambda + b + \mu_1 + d_1\zeta_n)(\frac{\lambda}{\mu_2} + 1 + \frac{d_2\zeta_n}{\mu_2})(\lambda + \mu_3)| > |(\lambda + \mu_1 + d_1\zeta_n)\Phi_2(\lambda)|$$

for all integer $n \geq 0$. This is a contradiction. Hence we proved the claim, and (u_1^*, u_2^*, u_3^*) is locally asymptotically stable when $R_0 > 1$.

Denote $q(z) = z - 1 - \ln z$. Clearly, $q(z) \geq 0$ for $z > 0$, and $q(z) = 0$ if and only if $z = 1$. We next prove global attractiveness of (u_1^*, u_2^*, u_3^*) in X_0 by constructing a Lyapunov functional $V_2 : X_0 \to \mathbb{R}$ as follows.

$$V_2(u_1, u_2, u_3) = \int_\Omega W(u_1, u_2, u_3)dx,$$

where

$$W(u_1, u_2, u_3) = u_1 - \int_{u_1^*}^{u_1} \frac{h(u_1^*)}{h(s)} ds + u_2^* \, q\left(\frac{u_2}{u_2^*}\right) + \frac{h(u_1^*)g_1(u_3^*)u_3^*}{k u_2^*} q\left(\frac{u_3}{u_3^*}\right).$$

It follows from Theorems 2.3 and 4.7 that the solutions of system (5.1) are bounded and uniform persistent, which implies that V_2 and W are well-defined. Making use of the equilibrium equations (5.2), the time derivative of W along a positive solution of system (5.1) after a tedious calculation, is given by

$$\begin{aligned}
\frac{dW}{dt} =& d_1(1 - \frac{h(u_1^*)}{h(u_1)})\Delta u_1 + d_2(1 - \frac{u_2^*}{u_2})\Delta u_2 - \mu_1(u_1 - u_1^*)\left(1 - \frac{h(u_1^*)}{h(u_1)}\right) \\
& - h(u_1^*)g_1(u_3^*)\left[q\left(\frac{h(u_1^*)}{h(u_1)}\right) + q\left(\frac{u_2 u_3^*}{u_2^* u_3}\right) - q\left(\frac{u_3 g_1(u_3^*)}{u_3^* g_1(u_3)}\right) - q\left(\frac{u_2^* h(u_1) g_1(u_3)}{u_2 h(u_1^*) g_1(u_3^*)}\right)\right] \\
& - h(u_1^*)f_1(u_2^*)\left[q\left(\frac{h(u_1^*)}{h(u_1)}\right) + q\left(\frac{u_2 f_1(u_2^*)}{u_2^* f_1(u_2)}\right) + q\left(\frac{u_2^* h(u_1) f_1(u_2)}{u_2 h(u_1^*) f_1(u_2^*)}\right)\right] \\
& + h(u_1^*)g_1(u_3^*)\frac{u_3}{u_3^*}\left(\frac{g_1(u_3)}{g_1(u_3^*)} - 1\right)\left(\frac{u_3^*}{u_3} - \frac{g_1(u_3^*)}{g_1(u_3)}\right) \\
& + h(u_1^*)f_1(u_2^*)\left(\frac{u_2}{u_2^*} - \frac{f_1(u_2)}{f_1(u_2^*)}\right)\left(\frac{f_1(u_2^*)}{f_1(u_2)} - 1\right).
\end{aligned}$$

Note from the Green's identity and Neumann boundary condition that

$$\int_\Omega d_1\left(1 - \frac{h(u_1^*)}{h(u_1)}\right)\Delta u_1 dx = -d_1 \int_\Omega \frac{h(u_1^*)h'(u_1)}{h^2(u_1)} |\nabla u_1|^2 dx \leq 0,$$
$$\int_\Omega d_1\left(1 - \frac{u_2^*}{u_2}\right)\Delta u_2 dx = -d_2 \int_\Omega \frac{u_2^*}{u_2^2} |\nabla u_2|^2 dx \leq 0.$$

Since h, f_1 and g_1 are increasing functions, f_1 and g_1 are concave down, then we have $(u_1 - u_1^*)(1 - h(u_1^*)/h(u_1)) \geq 0$ and

$$\left(\frac{g_1(u_3)}{g_1(u_3^*)} - 1\right)\left(\frac{u_3^*}{u_3} - \frac{g_1(u_3^*)}{g_1(u_3)}\right) \leq 0, \quad \left(\frac{u_2}{u_2^*} - \frac{f_1(u_2)}{f_1(u_2^*)}\right)\left(\frac{f_1(u_2^*)}{f_1(u_2)} - 1\right) \leq 0.$$

Thus, $dV_2/dt = \int_\Omega (dW/dt)dx \leq 0$. The largest invariant subset of $dV_2/dt = 0$ is the singleton (u_1^*, u_2^*, u_3^*). By LaSalle-Lyapunov invariance principle, the positive constant steady state (u_1^*, u_2^*, u_3^*) is globally attractive in X_0. The uniqueness of chronic infection steady state follows immediately from the global attractivity. This, together with the local asymptotic stability, yields that the global asymptotic stability of the positive constant steady state (u_1^*, u_2^*, u_3^*) in X_0 if $R_0 > 1$. □

Acknowledgments

H. Shu was partially supported by the National Natural Science Foundation of China (No.11971285, No.11601392), and the Fundamental Research Funds for the Central Universities.

Conflict of interest

The authors declare there is no conflicts of interest.

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