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Dynamics of a PDE viral infection model incorporating cell-to-cell transmission

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Abstract

This paper is concerned with the global dynamics of a PDE viral infection model with cell-to-cell transmission and spatial heterogeneity. The basic reproduction number $\mathfrak{R}_0$, which is a threshold value that predicts whether the infection will go to extinction or not, is defined in a variational characterization. In quite a general setting in which every parameters can be spatially heterogeneous, it is shown that if $\mathfrak{R}_0 \leq 1$, then the infection-free steady state is globally asymptotically stable, while if $\mathfrak{R}_0 > 1$, then the system is uniformly persistent and the infection steady state is globally asymptotically stable. The proof is based on the construction of the Lyapunov functions and usage of the Green's first identity. Finally, numerical simulation is performed in order to verify the validity of our theoretical results.

Keywords: HIV-1 model, Cell-to-cell transmission, Spatial heterogeneity, Global asymptotic stability, Lyapunov functions, Basic reproduction number

1. Introduction

In recent years, the in-host viral infection models incorporating spatial dispersion have been considered. In these models, it is assumed that only the free virus diffuse while the host cells do not (see e.g. [3, 7, 26] and the references cited therein). Such hybrid systems of differential equations (that is, systems of two ordinary differential equations (ODEs) for the cells and one parabolic partial differential equation (PDE) for the virus) account for the spatial dispersion of virus due to many factors: i) the interaction between the virus and the immune system is localized according to the type of tissues and also in a given tissue such as lymph nodes [3]; ii) the hepatocytes can not move under normal conditions [15, 26, 29] and viruses can move freely and their motion follows a Fickian diffusion [25]. In order to be more realistic, these models often incorporates: i) time delays, where the delays take into account the time between infection of a target cell and the emission of viral particles [26]; ii) heterogeneous parameters, where all parameters are allowed to be location dependent except the diffusion coefficient [25].

Due to the PDEs formulations, the system should be analyzed under suitable spatial domain equipped with suitable boundary condition. In Wang *et al.* [26], the densities of uninfected cells, infected cells and free viruses are assumed to be located at x at time t, which are denoted by $u_1(x,t)$, $u_2(x,t)$, $u_3(x,t)$, respectively, and the spatial domain is assumed to be one dimensional, that is, $(x,t) \in (-\infty,\infty) \times (0,\infty)$. Brauner *et al.* [3] extended the works in [26] to a two-dimensional square domain $(0,l) \times (0,l)$ with periodic boundary conditions, and provided that the recruitment rate to be space dependent. In a recent work, Wang *et al.* [25] argued that a realistic spatial domain should be bounded but is typically not a square, under suitable types of boundary conditions. They proposed a zero-flux boundary condition in a general bounded domain $\Omega \subset \mathbb{R}^n$ with smooth boundary $\partial\Omega$ (homogeneous Neumann boundary condition). The

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model studied in [25] takes the following hybrid system of two ODEs and one PDE:

$$\begin{cases} \dfrac{\partial u_1(x,t)}{\partial t} = \lambda(x) - \beta_1(x)u_1(x,t)u_3(x,t) - a(x)u_1(x,t), \\ \dfrac{\partial u_2(x,t)}{\partial t} = \beta_1(x)u_1(x,t)u_3(x,t) - b(x)u_2(x,t), \quad (x,t) \in \Omega \times (0,\infty), \\ \dfrac{\partial u_3(x,t)}{\partial t} = d\Delta u_3(x,t) + k(x)u_2(x,t) - m(x)u_3(x,t), \\ \dfrac{\partial u_3(x,t)}{\partial \nu} = 0, \quad x \in \partial\Omega, \quad t > 0, \\ u_i(x,0) = u_i^0(x) \geq 0, \quad x \in \Omega, \quad i = 1,2,3. \end{cases} \tag{1.1}$$

Here, for each $x \in \Omega$, $\lambda(x)$ denotes the number of newly produced uninfected cells, $a(x)$, $b(x)$ and $m(x)$ denote the death rates of uninfected cells, infected cells and free viruses, respectively. $\beta_1(x)$ is the transmission coefficient for virus-to-cell infection, $k(x)$ is the rate of virus production due to the lysis of infected cells, d is the diffusion coefficient and Δ is Laplacian. By analyzing the model and identifying the basic reproduction number, they only obtained the global dynamics of the model when all model parameters are constants (the spatially homogeneous case), but the global dynamics of heterogeneous parameters case was left as an open problem. Recent studies in [29], a hepatitis B virus infection with delay, diffusion and Holling type-II infection rate was investigated. They proved the global stability of infection-free steady state by comparison arguments when the basic reproductive number is less than unity, and obtained sufficient conditions for the global stability of infection steady state when the basic reproductive number is greater than unity. Chí *et al.* [5] provided a detailed analysis of similar model but with standard incidence function. By means of an iteration technique, sufficient conditions for the global stability of the infection steady state were obtained. In [15], McCluskey and Yang successfully proved the threshold dynamics of a viral infection model by constructing Lyapunov functions, which contains time delay and a general incidence function.

Recent studies reveal that the high efficiency of infection by large numbers of virions can be vital to a transfer of multiple virions to an uninfected target cell [9, 20]. The virus-induced cell-cell fusion observed from experiments is very likely the result of gp120/gp41 proteins, on the surface of infected cells, interacting with CD4 molecules on uninfected cells [14, 22]. In this case, viral particles can be transferred from infected target cells to uninfected ones through virological synapses. These findings left no doubt that direct cell-to-cell contribute to understand the mechanism(s) of HIV-1 transmission in vivo. We list some extensive literatures for studying the dynamics of cell-to-cell spread of HIV with and without delays [10, 11, 30].

Motivated by the previous works, to examine the effects of both diffusion and spatial heterogeneity, incorporating cell-to-cell transmission into system (1.1) leads to the following hybrid system of two ODEs coupled with one PDE under the homogeneous Neumann boundary condition:

$$\begin{cases} \dfrac{\partial u_1(x,t)}{\partial t} = \lambda(x) - \beta_1(x)u_1(x,t)u_3(x,t) - \beta_2(x)u_1(x,t)u_2(x,t) - a(x)u_1(x,t), \\ \dfrac{\partial u_2(x,t)}{\partial t} = \beta_1(x)u_1(x,t)u_3(x,t) + \beta_2(x)u_1(x,t)u_2(x,t) - b(x)u_2(x,t), \quad (x,t) \in \Omega \times (0,\infty), \\ \dfrac{\partial u_3(x,t)}{\partial t} = d\Delta u_3(x,t) + k(x)u_2(x,t) - m(x)u_3(x,t), \\ \dfrac{\partial u_3(x,t)}{\partial \nu} = 0, \quad x \in \partial\Omega, \quad t > 0, \\ u_i(x,0) = u_i^0(x) \geq 0, \quad x \in \Omega, \quad i = 1,2,3. \end{cases} \tag{1.2}$$

Here the meaning of each symbol is listed in Table 1.

It is well-known that the homogeneous Neumann boundary condition indicates that the system is self-contained with zero-flux across the boundary. From the viewpoint of application, it is particularly relevant to study some aspects of its global dynamics of (1.2). The organization of this paper is as follows. In Section 2, we shall establish the well-posedness of (1.2). Questions such as the existence of a unique mild solution of (1.2) and uniform boundedness of all solutions will be addressed. Furthermore, the basic reproduction number $\Re_0$, which serves as a threshold parameter that predicts whether the infection will go to extinction or persist (see, for instance, Diekmann *et al.* [6] and van den Driessche and Watmough [24]), shall be defined in a variational characterization. In Section 3, the global asymptotic stability of the infection-free steady state for $\Re_0 \leq 1$ shall be proven by using a Lyapunov function. Section 4 shall

Symbol	Meaning
$u_1(x,t)$	the density of uninfected cells at position x at time t
$u_2(x,t)$	the density of infected cells at position x at time t
$u_3(x,t)$	the density of free viruses at position x at time t
$\lambda(x)$	the number of newly produced uninfected cells at position x per unit time
$\beta_1(x)$	the transmission coefficient for virus-to-cell infection at position x
$\beta_2(x)$	the transmission coefficient for cell-to-cell infection at position x
$a(x)$	the death rate of uninfected cells at position x per capita
$b(x)$	the death rate of infected cells at position x per capita
$m(x)$	the death rate of free viruses at position x per capita
$k(x)$	the rate of virus production due to the lysis of infected cells at position x
d	the diffusion coefficient

Table 1: Meaning of each symbol in model (1.2).

be devoted to the proof of the uniform persistence of (1.2) and the existence of the infection steady state for $\Re_0 > 1$. In Section 5, the global asymptotic stability of the infection steady state for $\Re_0 > 1$ shall be proven. In Section 6, the global stability analysis shall be done again for a special case in which all parameters are independent of the space variable. In Section 7, numerical simulation shall be performed to verify the validity of our theoretical result.

2. Preliminaries

In this section, we begin with showing some basic properties of system (1.2). In what follows, we assume that $d > 0$ and all of the other parameters $\lambda(x)$, $a(x)$, $\beta_1(x)$, $\beta_2(x)$, $b(x)$, $k(x)$ and $m(x)$ of system (1.2) are continuous, strictly positive and uniformly bounded on $\bar{\Omega}$. The following notations will be used:

$$\bar{\lambda} := \sup_{x\in\bar{\Omega}} \lambda(x), \ \ \underline{c} := \min\left(\inf_{x\in\bar{\Omega}} a(x), \ \inf_{x\in\bar{\Omega}} b(x)\right), \ \ \bar{k} := \sup_{x\in\bar{\Omega}} k(x) \ \text{ and } \ \underline{m} := \inf_{x\in\bar{\Omega}} m(x).$$

Let us define the functional space for system (1.2) by $\mathbb{X} := C(\bar{\Omega},\mathbb{R}^3)$, which is endowed with the supremum norm such that

$$\|\phi\|_{\mathbb{X}} := \sup_{x\in\bar{\Omega}} \|\phi(x)\| = \sup_{x\in\bar{\Omega}} \sqrt{|\phi_1(x)|^2 + |\phi_2(x)|^2 + |\phi_3(x)|^2}, \quad \phi = (\phi_1,\phi_2,\phi_3)^T \in \mathbb{X},$$

where T denotes the transpose of the vector. Let us denote its positive cone by $\mathbb{X}^+$.

2.1. Well-posedness of the problem

Let A be a linear operator on $C^2(\bar{\Omega},\mathbb{R})$ defined by

$$A\varphi(x) := d\Delta\varphi(x), \quad D(A) := \left\{\varphi \in C^2\left(\bar{\Omega},\mathbb{R}\right) : \ \frac{\partial\varphi}{\partial\nu} = 0 \text{ on } \partial\Omega\right\}.$$

It is seen from a well-known fact (see, e.g., Webb [27, Section 3]) that the operator A is the infinitesimal generator of the strongly continuous semigroup $\left\{e^{tA}\right\}_{t\geq 0}$ in $C(\bar{\Omega},\mathbb{R})$. Then, the operator $\mathscr{A} : \mathbb{X} \to \mathbb{X}$ defined by

$$\mathscr{A}\phi(x) := \begin{pmatrix} 0 \\ 0 \\ A\phi_3(x) \end{pmatrix}, \quad \phi = \begin{pmatrix} \phi_1 \\ \phi_2 \\ \phi_3 \end{pmatrix} \in D(\mathscr{A}) := C(\bar{\Omega},\mathbb{R}^2) \times D(A) \subset \mathbb{X} \tag{2.1}$$

is also the infinitesimal generator of the strongly continuous semigroup $\left\{e^{t\mathscr{A}}\right\}_{t\geq 0}$ in $\mathbb{X}$. Furthermore, we define the nonlinear operator $\mathscr{F} : \mathbb{X}^+ \to \mathbb{X}^+$ by

$$\mathscr{F}(\phi)(x) := \begin{pmatrix} \lambda(x) - \beta_1(x)\phi_1(x)\phi_3(x) - \beta_2(x)\phi_1(x)\phi_2(x) - a(x)\phi_1(x) \\ \beta_1(x)\phi_1(x)\phi_3(x) + \beta_2(x)\phi_1(x)\phi_2(x) - b(x)\phi_2(x) \\ k(x)\phi_2(x) - m(x)\phi_3(x) \end{pmatrix}, \quad \phi = \begin{pmatrix} \phi_1 \\ \phi_2 \\ \phi_3 \end{pmatrix} \in \mathbb{X}^+. \tag{2.2}$$

Then, system (1.2) can be rewritten as the following abstract Cauchy problem in $\mathbb{X}$:

$$\frac{\mathrm{d}}{\mathrm{d}t}u(t) = \mathscr{A}u(t) + \mathscr{F}(u(t)), \quad u(t) := \begin{pmatrix} u_1(t) \\ u_2(t) \\ u_3(t) \end{pmatrix}, \quad u_0 := u(0) = \begin{pmatrix} u_1^0 \\ u_2^0 \\ u_3^0 \end{pmatrix}. \tag{2.3}$$

For the existence of a local solution $u(t)$ of (2.3), we have the following proposition:

Proposition 2.1. *Let $\mathscr{A}$ and $\mathscr{F}$ be defined by* (2.1) *and* (2.2)*, respectively. For each $u_0 \in D(\mathscr{A}) \subset \mathbb{X}$, there exists a positive constant $T_0 > 0$ such that the problem* (2.3) *has the unique local solution*

$$u(t) = \mathrm{e}^{t\mathscr{A}}u_0 + \int_0^t \mathrm{e}^{(t-s)\mathscr{A}}\mathscr{F}(u(s))\mathrm{d}s, \quad t \in [0, T_0),$$

where $T_0 < +\infty$ and $\limsup_{t\to T_0-0} \|u(t)\|_{\mathbb{X}} = +\infty$ or $T_0 = +\infty$.

PROOF. It is easy to see that the operator $\mathscr{F}$ is continuously Fréchet differentiable on $\mathbb{X}$ with the derivative $\mathscr{F}'[\psi] : \mathbb{X} \to \mathbb{X}$ at $\psi = (\psi_1, \psi_2, \psi_3)^T \in \mathbb{X}$ given by

$$\mathscr{F}'[\psi]\phi(x) := \begin{pmatrix} -(\beta_1(x)\psi_3(x) + \beta_2(x)\psi_2(x) + a(x))\,\phi_1(x) - \beta_2(x)\psi_1(x)\phi_2(x) - \beta_1(x)\psi_1(x)\phi_3(x) \\ (\beta_1(x)\psi_3(x) + \beta_2(x)\psi_2(x))\,\phi_1(x) + (\beta_2(x)\psi_1(x) - b(x))\,\phi_2(x) + \beta_1(x)\psi_1(x)\phi_3(x) \\ k(x)\phi_2(x) - m(x)\phi_3(x) \end{pmatrix}.$$

Then, the claim follows from [28, Proposition 4.16]. □

In what follows, we denote the solution u of the system (1.2) with initial condition u_0 by

$$u(x,t;u_0) = (u_1(x,t;u_0),\ u_2(x,t;u_0),\ u_3(x,t;u_0))^T.$$

Next we prove the existence of the global solution u of the system (1.2). We shall use the following two lemmas.

Lemma 2.1. *[31, Theorem 2.2.1] Let $\mu(x)$ be a continuous, strictly positive and uniformly bounded function on Ω. The differential equation*

$$\frac{\partial\omega(x,t)}{\partial t} = \lambda(x) - \mu(x)\omega(x,t), \quad x \in \bar{\Omega}, \quad t > 0$$

has a unique, strictly positive and globally asymptotically stable steady state $\lambda(x)/\mu(x)$ in $C(\bar{\Omega}, \mathbb{R})$.

Lemma 2.2. *[12, Lemma 1] Let $g(x)$ and $\mu(x)$ be continuous, strictly positive and uniformly bounded functions on Ω. The differential equation*

$$\begin{cases} \dfrac{\partial\omega(x,t)}{\partial t} = d\Delta\omega(x,t) + g(x) - \mu(x)\omega(x,t), & x \in \Omega, \quad t > 0, \\ \dfrac{\partial\omega(x,t)}{\partial \nu} = 0, & x \in \partial\Omega, \quad t > 0 \end{cases}$$

has a unique, strictly positive and globally asymptotically stable steady state $\omega^*(x)$ in $C(\bar{\Omega}, \mathbb{R})$. Moreover, if $g(x) \equiv g$, $\mu(x) \equiv \mu$, then $\omega^*(x) = g/\mu$.

The positivity of the solution u can be shown as follows.

Lemma 2.3. *The solution $u(x,t;u_0)$ of the system* (1.2) *is positive on $\Omega \times [0, T_0)$ provided that the initial condition u_0 is positive.*

PROOF. Integrating the first equation in (1.2), we have

$$u_1(x,t) = u_1^0(x)\mathrm{e}^{-\int_0^t(\beta_1(x)u_3(x,s)+\beta_2(x)u_2(x,s)+a(x))\mathrm{d}s} + \lambda(x)\int_0^t \mathrm{e}^{-\int_s^t(\beta_1(x)u_3(x,\rho)+\beta_2(x)u_2(x,\rho)+a(x))\mathrm{d}\rho}\mathrm{d}s \tag{2.4}$$

and hence, u_1 is positive. Suppose that there exists a $\tilde{T}_0 \in (0,T_0)$ such that $u_2(x,t) > 0$ on $\Omega \times \left(0,\tilde{T}_0\right)$ and $u_2(x,\tilde{T}_0) = 0$ and $\partial u_2(x,\tilde{T}_0)/\partial t < 0$ for some $x \in \Omega$. In this case, from the third equation in (1.2), we have

$$\begin{cases} \dfrac{\partial u_3(x,t)}{\partial t} \geq d\Delta u_3(x,t) - m(x)u_3(x,t), \quad x \in \Omega, \ \ t \in \left(0,\tilde{T}_0\right], \\ \dfrac{\partial u_3(x,t)}{\partial \nu} = 0, \quad x \in \partial\Omega, \ \ t \in \left(0,\tilde{T}_0\right]. \end{cases} \tag{2.5}$$

Hence, it follows from the strong maximum principle (see, e.g., [21, Theorem 4, p.172]) and the Hopf boundary lemma (see, e.g., [21, Theorem 3, p.170]) that $u_3(x,t) \geq 0$ on $\Omega \times \left[0,\tilde{T}_0\right]$. Hence, from the second equation in (1.2), we have $\partial u_2(x,\tilde{T}_0)/\partial t \geq 0$, which is a contradiction. Thus, $u_2(x,t)$ is positive. For the proof of the positivity of u_3, we obtain the differential inequality (2.5) again on $\Omega \times [0,T_0]$ and hence, we can apply the strong maximum principle and the Hopf boundary lemma to conclude that the claim is true. □

To show the existence of the global solution u of the system (1.2), we set the state space

$$\mathscr{D} = \left\{ u = (u_1,u_2,u_3)^T \in \mathbb{X}^+ : \ u_1(x,\cdot) \leq \frac{\lambda(x)}{a(x)}, \ \ u_1(x,\cdot) + u_2(x,\cdot) \leq \frac{\bar{\lambda}}{\underline{c}} \ \text{ and } \ u_3(x,\cdot) \leq \frac{\bar{\lambda}}{\underline{c}}\frac{\bar{k}}{\underline{m}} \ \text{ for all } x \in \bar{\Omega} \right\} \tag{2.6}$$

and show its positive invariance. We prove the following proposition.

Proposition 2.2. *Let $\mathscr{D}$ be defined by* (2.6). *$\mathscr{D}$ is positively invariant for the system* (1.2).

PROOF. Suppose that $u_0 = \left(u_1^0,u_2^0,u_3^0\right)^T \in \mathscr{D}$. The positivity of u follows from Lemma 2.3. From (2.4), we have

$$u_1(x,t) \ \leq \ u_1^0(x)\mathrm{e}^{-a(x)t} + \lambda(x)\int_0^t \mathrm{e}^{-a(x)(t-s)}\mathrm{d}s \ = \ \left(u_1^0(x) - \frac{\lambda(x)}{a(x)}\right)\mathrm{e}^{-a(x)t} + \frac{\lambda(x)}{a(x)} \ \leq \ \frac{\lambda(x)}{a(x)}.$$

Hence, the first inequality in (2.6) holds. By adding the first two equations in (1.2) we have

$$\frac{\partial}{\partial t}\left(u_1(x,t)+u_2(x,t)\right) = \lambda(x) - a(x)u_1(x,t) - b(x)u_2(x,t) \leq \bar{\lambda} - \underline{c}\left(u_1(x,t)+u_2(x,t)\right).$$

Integration yields

$$u_1(x,t)+u_2(x,t) \ \leq \ \left(\left(u_1^0(x)+u_2^0(x)\right) - \frac{\bar{\lambda}}{\underline{c}}\right)\mathrm{e}^{-\underline{c}t} + \frac{\bar{\lambda}}{\underline{c}} \ \leq \ \frac{\bar{\lambda}}{\underline{c}}.$$

Hence, the second inequality in (2.6) holds. From the third equation in (1.2), we have

$$\begin{cases} \dfrac{\partial u_3(x,t)}{\partial t} \leq d\Delta u_3(x,t) + \bar{k}\dfrac{\bar{\lambda}}{\underline{c}} - \underline{m}u_3(x,t), \quad x \in \Omega, \ \ t > 0, \\ \dfrac{\partial u_3(x,t)}{\partial \nu} = 0, \quad x \in \partial\Omega, \ \ t > 0. \end{cases} \tag{2.7}$$

From Lemma 2.2 and the comparison principle, we see that $\limsup_{t\to+\infty} u_3(x,t) \leq \bar{\lambda}\bar{k}/(\underline{c}\cdot\underline{m})$ for all $x \in \bar{\Omega}$. In particular, if $u_3(\tilde{x},\tilde{t}) = \bar{\lambda}\bar{k}/(\underline{c}\cdot\underline{m})$ for some $\tilde{x} \in \bar{\Omega}$ and $\tilde{t} > 0$, then $\partial u_3(\tilde{x},\tilde{t})/\partial t \leq 0$ holds from the first equation in (2.7) and this implies that $u_3(x,t) \leq \bar{\lambda}\bar{k}/(\underline{c}\cdot\underline{m})$ holds for all $x \in \bar{\Omega}$ and $t > 0$ provided $u_3^0(x) \leq \bar{\lambda}\bar{k}/(\underline{c}\cdot\underline{m})$ for all $x \in \bar{\Omega}$. This completes the proof. □

From Propositions 2.1 and 2.2, we see that the system (1.2) has a unique global solution $u \in \mathscr{D}$ for any initial condition $u_0 \in \mathscr{D}$. Therefore, we can define the continuous semiflow $\{\Phi_t\}_{t\geq 0} : \mathbb{X}^+ \to \mathbb{X}^+$ for the system (1.2) by

$$\Phi_t(u_0) := u(\cdot,t;u_0), \quad t \geq 0.$$

Proposition 2.2 implies that $\Phi_t(u_0) \in \mathscr{D}$ for all $t \geq 0$ whenever $u_0 \in \mathscr{D}$.

2.2. Basic reproduction number

In this section, we define the basic reproduction number $\mathfrak{R}_0$ for the system (1.2). It is easy to see that the system (1.2) always has the infection-free steady state $Q^0 = (u_1^*(x), 0, 0)^T \in \mathscr{D}$, where $u_1^*(x) = \lambda(x)/a(x)$. Let us define $\mathfrak{R}(x)$ by the local basic reproduction number for cell-to-cell infection at position $x \in \Omega$:

$$\begin{aligned}\mathfrak{R}(x) :=& \frac{\beta_2(x)u_1^*(x)}{b(x)} \\ =& (\text{the transmission coefficient } \beta_2(x) \text{ for cell-to-cell infection at position } x \in \Omega) \\ & \times (\text{the density } u_1^*(x) \text{ of uninfected cells at position } x \in \Omega \text{ in the infection-free steady state}) \\ & \times \left(\text{the average period } \frac{1}{b(x)} \text{ of infectiousness of infected cells at position } x \in \Omega\right).\end{aligned}$$

In what follows, we assume that the infection can not be endemic only by the cell-to-cell infection, that is,

$$\mathfrak{R}(x) < 1 \tag{2.8}$$

for all $x \in \Omega$. In fact, it is easy to check that if $\mathfrak{R}(x) > 1$ for some x, then the infection-free steady state Q^0 becomes unstable due to the increase of infected cells at the position x.

The system (1.2) can be linearized around the infection-free steady state Q^0 as follows.

$$\begin{cases} \dfrac{\partial u_2(x,t)}{\partial t} = \beta_1(x)u_1^*(x)u_3(x,t) + \beta_2(x)u_1^*(x)u_2(x,t) - b(x)u_2(x,t), \quad x \in \Omega, \ \ t > 0, \\ \dfrac{\partial u_3(x,t)}{\partial t} = d\Delta u_3(x,t) + k(x)u_2(x,t) - m(x)u_3(x,t), \quad x \in \Omega, \ \ t > 0, \\ \dfrac{\partial u_3(x,t)}{\partial \nu} = 0, \quad x \in \partial\Omega, \quad t > 0. \end{cases} \tag{2.9}$$

Substituting $u_2(x,t) = \mathrm{e}^{\eta t}\psi_2(x)$ and $u_3(x,t) = \mathrm{e}^{\eta t}\psi_3(x)$ into (2.9) and dividing both sides of the two equations by $\mathrm{e}^{\eta t}$, we arrive at the following eigenvalue problem.

$$\begin{cases} \eta\psi(x) = \begin{pmatrix} -b(x) + \beta_2(x)u_1^*(x) & \beta_1(x)u_1^*(x) \\ k(x) & d\Delta - m(x) \end{pmatrix} \psi(x), \quad x \in \Omega, \ \ \psi = \begin{pmatrix} \psi_2 \\ \psi_3 \end{pmatrix} \in C\left(\bar{\Omega}, \mathbb{R}^2\right), \\ \dfrac{\partial \psi_3(x)}{\partial \nu} = 0, \quad x \in \partial\Omega. \end{cases} \tag{2.10}$$

Let us define

$$\mathscr{B} = \begin{pmatrix} -b(x) + \beta_2(x)u_1^*(x) & \beta_1(x)u_1^*(x) \\ k(x) & d\Delta - m(x) \end{pmatrix} \tag{2.11}$$

and denote by $s(\mathscr{B})$ the spectral bound of $\mathscr{B}$.

On the other hand, we consider the following eigenvalue problem associated with (2.10):

$$\begin{cases} (0,0) = \Psi^T(x) \begin{pmatrix} -b(x) + \beta_2(x)u_1^*(x) & \eta\beta_1(x)u_1^*(x) \\ k(x) & d\Delta - m(x) \end{pmatrix}, \quad x \in \Omega, \ \ \Psi = \begin{pmatrix} \Psi_2 \\ \Psi_3 \end{pmatrix} \in C\left(\bar{\Omega}, \mathbb{R}^2\right), \\ \dfrac{\partial \Psi_3(x)}{\partial \nu} = 0, \quad x \in \partial\Omega. \end{cases} \tag{2.12}$$

We prove the following lemma.

Lemma 2.4. *The eigenvalue problem* (2.12) *has the principal eigenvalue* η^**, which is the only positive eigenvalue associated with a strictly positive eigenfunction* $\Psi^* = (\Psi_2^*, \Psi_3^*)^T \in C\left(\bar{\Omega}, \mathbb{R}^2\right)$.

PROOF. The problem (2.12) can be rewritten as

$$\begin{cases} 0 = -\left(b(x) - \beta_2(x)u_1^*(x)\right)\Psi_2(x) + k(x)\Psi_3(x), \quad x \in \Omega, \\ 0 = \eta\beta_1(x)u_1^*(x)\Psi_2(x) + d\Delta\Psi_3(x) - m(x)\Psi_3(x), \quad x \in \Omega, \\ \dfrac{\partial \Psi_3(x)}{\partial \nu} = 0, \quad x \in \partial\Omega. \end{cases}$$

Hence, under the assumption (2.8), we can obtain

$$\Psi_2(x) = \frac{k(x)}{b(x) - \beta_2(x)u_1^*(x)}\Psi_3(x) \tag{2.13}$$

and

$$0 = d\Delta\Psi_3(x) - m(x)\Psi_3(x) + \eta\beta_1(x)u_1^*(x)\frac{k(x)}{b(x) - \beta_2(x)u_1^*(x)}\Psi_3(x). \tag{2.14}$$

It is a well-known fact that (2.14) with the Neumann boundary condition $\partial\Psi_3/\partial\nu = 0$ on $\partial\Omega$ has the only positive principal eigenvalue $\eta^* > 0$ associated with the strictly positive eigenfunction Ψ_3^* (see, for instance, [4, Theorem 2.4]). Ψ_2^* is obtained by substituting $\Psi_3 = \Psi_3^*$ into the right-hand side of (2.13) and it is strictly positive by virtue of the assumption (2.8). This completes the proof. □

In this paper, we define the basic reproduction number $\mathfrak{R}_0$ by $1/\eta^*$. That is, the following equality holds for the strictly positive eigenfunction $\Psi^* = (\Psi_2^*, \Psi_3^*)^T \in C\left(\bar{\Omega}, \mathbb{R}^2\right)$:

$$\begin{cases} (0,0) = \Psi^{*T}(x)\begin{pmatrix} -b(x) + \beta_2(x)u_1^*(x) & \dfrac{\beta_1(x)u_1^*(x)}{\mathfrak{R}_0} \\ k(x) & d\Delta - m(x) \end{pmatrix}, \ x \in \Omega, \quad \Psi^* = \begin{pmatrix} \Psi_2^* \\ \Psi_3^* \end{pmatrix} \in C\left(\bar{\Omega}, \mathbb{R}^2\right), \\ \dfrac{\partial\Psi_3^*(x)}{\partial\nu} = 0, \quad x \in \partial\Omega. \end{cases} \tag{2.15}$$

From (2.14), we can obtain the following variational characterization of $\mathfrak{R}_0$ as in [1, Lemma 2.3] and [4, Theorem 2.4]:

$$\mathfrak{R}_0 = \sup_{\varphi \in H^1(\Omega),\ \varphi \neq 0}\left\{\frac{1}{\int_\Omega\left(d\left|\nabla\varphi\right|^2 + m(x)\varphi(x)^2\right)\mathrm{d}x}\int_\Omega \frac{\beta_1(x)u_1^*(x)k(x)}{b(x) - \beta_2(x)u_1^*(x)}\varphi(x)^2\mathrm{d}x\right\}. \tag{2.16}$$

For constant parameters, $\mathfrak{R}_0$ can be reduced to

$$\mathfrak{R}_0 = \frac{\beta_1 u_1^* k}{m\left(b - \beta_2 u_1^*\right)}, \quad u_1^* = \frac{\lambda}{a}. \tag{2.17}$$

Indeed, this $\mathfrak{R}_0$ has the same threshold property as that of $\mathfrak{R}_0^1$, which shall be defined in the spatially homogeneous case in Section 6.

In the remainder of this section, we prove the following lemma which shall be used for the proof of the uniform persistence of the system (1.2) (see the proof of Lemma 4.1 (iii)).

Lemma 2.5. *Let $\mathscr{B}$ and $\mathfrak{R}_0$ be defined by* (2.11) *and* (2.16)*, respectively. If $\mathfrak{R}_0 > 1$, then $s(\mathscr{B}) > 0$ and it is the principal eigenvalue of the problem* (2.10) *associated with a strictly positive eigenfunction.*

PROOF. Let

$$\mathscr{B}_{\mathfrak{R}_0} := \begin{pmatrix} -b(x) + \beta_2(x)u_1^*(x) & \dfrac{\beta_1(x)u_1^*(x)}{\mathfrak{R}_0} \\ k(x) & d\Delta - m(x) \end{pmatrix}.$$

Then, (2.12) and Lemma 2.4 imply that $s\left(\mathscr{B}_{\mathfrak{R}_0}\right) \geq 0$. Since $\mathscr{B} > \mathscr{B}_{\mathfrak{R}_0}$ for $\mathfrak{R}_0 > 1$ (here the inequality $>$ between the matrices implies that $\geq$ holds for each corresponding entry and these matrices are not equal), we have $s(\mathscr{B}) > s\left(\mathscr{B}_{\mathfrak{R}_0}\right) \geq 0$.

Let $\mathbb{Y} := C\left(\bar{\Omega}, \mathbb{R}^2\right)$ and $\{\Theta_t\}_{t\geq 0} : \mathbb{Y} \to \mathbb{Y}$ be the semiflow generated by the linearized system (2.9). Then, we have

$$\Theta_t(\psi) = L(t)\psi + N(t)(\psi), \quad t \geq 0, \ \ \psi = \begin{pmatrix} \psi_2 \\ \psi_3 \end{pmatrix} \in C\left(\bar{\Omega}, \mathbb{R}^2\right),$$

where

$$L(t)\psi = \begin{pmatrix} \mathrm{e}^{-\left(b(\cdot)-\beta_2(\cdot)u_1^*(\cdot)\right)t}\psi_2 \\ 0 \end{pmatrix}, \quad N(t)(\psi) = \begin{pmatrix} \int_0^t \mathrm{e}^{-\left(b(\cdot)-\beta_2(\cdot)u_1^*(\cdot)\right)(t-s)}\beta_1(\cdot)u_1^*(\cdot)u_3(\cdot,s;\psi)\,\mathrm{d}s \\ u_3(\cdot,t;\psi) \end{pmatrix}.$$

From the assumption (2.8) we see that there exists a positive constant $\underline{b} > 0$ such that

$$b(x) - \beta_2(x)u_1^*(x) \;\geq\; \underline{b} \;>\; 0 \quad \text{for all } x \in \bar{\Omega}.$$

Then, the operator norm of $L(t)$ can be estimated as

$$\|L(t)\|_{op} \;=\; \sup_{\psi\in\mathbb{Y}} \frac{\|L(t)\psi\|_{\mathbb{Y}}}{\|\psi\|_{\mathbb{Y}}} \;\leq\; \mathrm{e}^{-\underline{b}t} \sup_{\psi\in\mathbb{Y}} \frac{\|\psi\|_{\mathbb{Y}}}{\|\psi\|_{\mathbb{Y}}} \;=\; \mathrm{e}^{-\underline{b}t}.$$

On the other hand, it follows from the boundedness of $\{\Theta_t\}_{t\geq 0}$ and the compactness of the C_0-semigroup associated with the solution u_3 that the operator $N(t)$ is compact for each $t > 0$. Consequently, for any bounded subset B in $\mathbb{Y}$, we have

$$\kappa(\Theta_t B) \;=\; \kappa(L(t)B) + \kappa(N(t)(B)) \;\leq\; \|L(t)\|_{op}\,\kappa(B) + 0 \;\leq\; \mathrm{e}^{-\underline{b}t}\kappa(B),$$

where $\kappa(\cdot)$ denotes the Kuratowski measure of noncompactness defined by

$$\kappa(B) := \inf\{R \geq 0 :\; B \text{ has a finite cover of diameter less than } R\}.$$

Thus, $\{\Theta_t\}_{t\geq 0}$ is a κ-contraction on $\mathbb{Y}$ with the contraction function $\mathrm{e}^{-\underline{b}t}$. Then, we have

$$r_e(\Theta_t) \;\leq\; \mathrm{e}^{-\underline{b}t} \;<\; 1 \;\leq\; \mathrm{e}^{s(\mathscr{B})t} \;=\; r(\Theta_t),$$

where $r_e(\cdot)$ and $r(\cdot)$ denote the essential spectral radius and the spectral radius of operators, respectively. This inequality implies that the essential spectral radius is strictly less than the spectral radius and hence, from the generalized Krein-Rutman Theorem (see [17]), we see that $s(\mathscr{B})$ is the principal eigenvalue. This completes the proof. □

3. Global asymptotic stability of the infection-free steady state

In this section, for $0 < \mathfrak{R}_0 \leq 1$, we prove the global asymptotic stability of the infection-free steady state $Q^0 = (u_1^*(x), 0, 0)^T \in \mathscr{D}$. Now, (2.15) can be rewritten as follows.

$$\begin{cases} 0 = -\left(b(x) - \beta_2(x)u_1^*(x)\right)\Psi_2^*(x) + k(x)\Psi_3^*(x), & x \in \Omega, \\ 0 = \dfrac{\beta_1(x)u_1^*(x)}{\mathfrak{R}_0}\Psi_2^*(x) + d\Delta\Psi_3^*(x) - m(x)\Psi_3^*(x), & x \in \Omega, \\ \dfrac{\partial\Psi_3^*(x)}{\partial\nu} = 0, & x \in \partial\Omega. \end{cases} \tag{3.1}$$

The first and second equations in (3.1) can be rearranged as follows.

$$k(x)\Psi_3^*(x) = \left(b(x) - \beta_2(x)u_1^*(x)\right)\Psi_2^*(x) \quad \text{and} \quad \frac{\beta_1(x)u_1^*(x)}{\mathfrak{R}_0}\Psi_2^*(x) = -d\Delta\Psi_3^*(x) + m(x)\Psi_3^*(x). \tag{3.2}$$

Using this strictly positive function $\Psi^*(x) = (\Psi_2^*(x), \Psi_3^*(x))^T$, we define the following Lyapunov function:

$$\mathscr{L}_{IFE}[u_2, u_3](t) := \int_\Omega \Big(\Psi_2^*(x)u_2(x,t) + \Psi_3^*(x)u_3(x,t)\Big)\mathrm{d}x. \tag{3.3}$$

Using this function, we prove the following theorem.

Theorem 3.1. *Let $\mathscr{D}$ and $\mathfrak{R}_0$ be defined by* (2.6) *and* (2.16)*, respectively. If $0 < \mathfrak{R}_0 \leq 1$, then the infection-free steady state $Q^0 = (u_1^*(x), 0, 0)^T \in \mathscr{D}$ is globally asymptotically stable in $\mathscr{D}$.*

PROOF. The derivative of the Lyapunov function $\mathscr{L}_{IFE}[u_2,u_3]$ along the trajectory of the system (1.2) is calculated as follows.

$$\begin{aligned}
\mathscr{L}'_{IFE} &= \int_\Omega \left(\Psi_2^*(x)\frac{\partial u_2(x,t)}{\partial t} + \Psi_3^*(x)\frac{\partial u_3(x,t)}{\partial t}\right)\mathrm{d}x \\
&= \int_\Omega \left[\Psi_2^*(x)\left(\beta_1(x)u_1(x,t)u_3(x,t) + \beta_2(x)u_1(x,t)u_2(x,t) - b(x)u_2(x,t)\right) + \Psi_3^*(x)\left(d\Delta u_3(x,t) + k(x)u_2(x,t) - m(x)u_3(x,t)\right)\right]\mathrm{d}x \\
&\le \int_\Omega \left[\Psi_2^*(x)\left(\beta_1(x)u_1^*(x)u_3(x,t) + \beta_2(x)u_1^*(x)u_2(x,t) - b(x)u_2(x,t)\right) + \Psi_3^*(x)\left(d\Delta u_3(x,t) + k(x)u_2(x,t) - m(x)u_3(x,t)\right)\right]\mathrm{d}x \\
&\le \int_\Omega \left[\Psi_2^*(x)\left(\frac{\beta_1(x)u_1^*(x)}{\mathfrak{R}_0}u_3(x,t) + \beta_2(x)u_1^*(x)u_2(x,t) - b(x)u_2(x,t)\right) + \Psi_3^*(x)\left(d\Delta u_3(x,t) + k(x)u_2(x,t) - m(x)u_3(x,t)\right)\right]\mathrm{d}x.
\end{aligned}$$

From (3.2) we have

$$\mathscr{L}'_{IFE} \le d\int_\Omega \left[-u_3(x,t)\Delta\Psi_3^*(x) + \Psi_3^*(x)\Delta u_3(x,t)\right]\mathrm{d}x.$$

Then, it follows from the Green's first identity and the homogeneous Neumann boundary conditions that

$$\begin{aligned}
\mathscr{L}'_{IFE} \le & d\left[-\int_{\partial\Omega} u_3(x,t)\nabla\Psi_3^*(x)\cdot\nu\mathrm{d}S + \int_\Omega \nabla u_3(x,t)\cdot\nabla\Psi_3^*(x)\mathrm{d}x\right. \\
& \left. + \int_{\partial\Omega}\Psi_3^*(x,t)\nabla u_3(x)\cdot\nu\mathrm{d}S - \int_\Omega \nabla\Psi_3^*(x,t)\cdot\nabla u_3(x)\mathrm{d}x\right] \\
= & d\left[\langle\nabla u_3(\cdot,t),\nabla\Psi_3^*(\cdot)\rangle - \langle\nabla\Psi_3^*(\cdot),\nabla u_3(\cdot,t)\rangle\right] \;=\; 0,
\end{aligned}$$

where $\langle\cdot\rangle$ denotes the L^2-inner product. Hence, from the positivity of $\Psi^*(x)$, it is easy to see that $\mathscr{L}'_{IFE} \le 0$ and the equality holds if and only if $u_2 = u_3 \equiv 0$. Then, from the LaSalle's invariance principle, we can conclude that the infection-free steady state Q^0 is globally asymptotically stable. □

4. Uniform persistence and existence of the infection steady state

In this section, we shall prove the uniform persistence of the system (1.2) and the existence of the infection steady state when the basic reproduction number $\mathfrak{R}_0$ is greater than one. The definition of the uniform persistence is as follows.

Definition 4.1. *System (1.2) is said to be persistent (in $\mathbb{X}^+$) if any solution $u(x,t;u_0)$ with initial condition $u_0 \in \mathbb{X}^+$ is bounded away from zero, i.e., for any $u_0 \in \mathbb{X}^+$,*

$$\liminf_{t\to\infty} u_i(x,t;u_0) > 0, \quad i = 1,2,3;$$

and uniformly persistent (in $\mathbb{X}^+$) if there exists a constant $\xi > 0$ such that for any $u_0 \in \mathbb{X}^+$,

$$\liminf_{t\to\infty} u_i(x,t;u_0) > \xi, \quad i = 1,2,3.$$

Let us define

$$\mathscr{D}_0 := \left\{\phi = (\phi_1,\phi_2,\phi_3)^T \in \mathscr{D} :\ \phi_2(\cdot) \not\equiv 0 \ \text{ or } \ \phi_3(\cdot) \not\equiv 0\right\}, \tag{4.1}$$

$$\partial\mathscr{D} := \mathscr{D}\setminus\mathscr{D}_0 = \left\{\phi = (\phi_1,\phi_2,\phi_3)^T \in \mathscr{D} :\ \phi_2(\cdot) \equiv 0 \ \text{ and } \ \phi_3(\cdot) \equiv 0\right\}$$

and

$$M_\partial := \left\{\phi = (\phi_1,\phi_2,\phi_3)^T \in \partial\mathscr{D} :\ \Phi_t(\phi) \in \partial\mathscr{D} \ \text{ for all } \ t \ge 0\right\}. \tag{4.2}$$

Let us denote by $\omega(\phi)$ the omega limit set of the orbit $O^+(\phi) := \{\Phi_t(\phi) :\ t \ge 0\}$. We prove the following lemma.

Lemma 4.1. *Let $\mathfrak{R}_0$, $\mathscr{D}_0$ and M_∂ be defined by* (2.16), (4.1) *and* (4.2)*, respectively.*

(i) $\omega(u_0) = \left\{(u_1^*(x),0,0)^T\right\}$ *for any* $u_0 \in M_\partial$.

(ii) *For any* $u_0 \in \mathscr{D}_0$, $u_i(x,t;u_0) > 0$ *for all* $x \in \bar{\Omega}$ *and* $t > 0$ $(i = 1,2,3)$.

(iii) *If* $\Re_0 > 1$, *then the infection-free steady state* $Q^0 = (u_1^*(x),0,0)$ *is a uniform weak repeller for* $\mathscr{D}_0$, *that is, there exists a sufficiently small constant* $\varepsilon > 0$ *such that*

$$\limsup_{t\to+\infty} \left\| \Phi_t(u_0) - (u_1^*(\cdot),0,0)^T \right\|_{\mathbb{X}} \geq \varepsilon$$

for any $u_0 \in \mathscr{D}_0$.

PROOF. (i) For any $u_0 \in M_\partial$, the system (1.2) is reduced to

$$\frac{\partial u_1(x,t)}{\partial t} = \lambda(x) - a(x)u_1(x,t), \quad u_2(x,t) = u_3(x,t) = 0$$

and hence, $u_1(x,t) \to u_1^*(x)$ as $t \to +\infty$ for all $x \in \bar{\Omega}$. Thus, $\omega(u_0) = \left\{(u_1^*,0,0)^T\right\}$.

(ii) It obviously follows from (2.4) that $u_1(x,t) > 0$ for all $x \in \bar{\Omega}$ and $t > 0$. If $u_3^0(x) \not\equiv 0$, then it follows again from (2.5) and the strong maximum principle together with the Hopf boundary lemma that $u_3(x,t) > 0$ for all $x \in \bar{\Omega}$ and $t > 0$. Then, since we have from the second equation in (1.2) that

$$\frac{\partial u_2(x,t)}{\partial t} \geq \beta_1(x)u_1(x,t)u_3(x,t) - b(x)u_2(x,t), \tag{4.3}$$

the strict positivity of u_1 and u_3 implies that $u_2(x,t) > 0$ for all $x \in \bar{\Omega}$ and $t > 0$. On the other hand, suppose that $u_2^0(x) \not\equiv 0$. From the third equation in (1.2), u_3 can be written as

$$u_3(x,t) = T(t)\left(u_3^0(\cdot)\right)(x) + \int_0^t T(t-s)\left(k(\cdot)u_2(\cdot,s)\right)(x)\mathrm{d}s,$$

where $\{T(t)\}_{t\geq 0}$ denotes the C_0-semigroup generated by $d\Delta - m(x)$. Then, from the property of C_0-semigroup generated by Laplacian and the strict positivity of $k(x)$, we see that $u_2^0(x) \not\equiv 0$ implies that $u_3(x,t) > 0$ for all $x \in \bar{\Omega}$ and $t > 0$. Then, it follows again from the inequality (4.3) that $u_2(x,t) > 0$ for all $x \in \bar{\Omega}$ and $t > 0$.

(iii) From Lemma 2.5, $\Re_0 > 1$ implies that $s(\mathscr{B}) > 0$. Therefore, there exists a sufficiently small $\varepsilon > 0$ such that the eigenvalue problem

$$\begin{cases} \eta\psi(x) = \begin{pmatrix} -b(x) + \beta_2(x)(u_1^*(x) - \varepsilon) & \beta_1(x)(u_1^*(x) - \varepsilon) \\ k(x) & d\Delta - m(x) \end{pmatrix} \psi(x), \quad \psi(x) := \begin{pmatrix} \psi_2(x) \\ \psi_3(x) \end{pmatrix}, \ x \in \Omega, \\ \dfrac{\partial\psi_3(x)}{\partial\nu} = 0, \quad x \in \partial\Omega. \end{cases}$$

has the positive principle eigenvalue $\tilde{\eta} > 0$, which is associated with a positive eigenfunction $\tilde{\psi}(x) = (\tilde{\psi}_2(x), \tilde{\psi}_3(x))^T$ and is the spectral bound for the corresponding linearized system.

Suppose that

$$\limsup_{t\to+\infty} \left\| \Phi_t(u_0) - (u_1^*(\cdot),0,0)^T \right\|_{\mathbb{X}} < \varepsilon$$

for some $u_0 \in \mathscr{D}_0$ and show a contradiction. This implies that there exists a $t_0 > 0$ such that $u_1(x,t) > u_1^*(x) - \varepsilon$ for all $x \in \bar{\Omega}$ and $t \geq t_0$. Hence, it follows from the second and third equations in (1.2) that

$$\begin{cases} \dfrac{\partial u_2(x,t)}{\partial t} \geq \beta_1(x)(u_1^*(x) - \varepsilon)u_3(x,t) + \beta_2(x)(u_1^*(x) - \varepsilon)u_2(x,t) - b(x)u_2(x,t), \quad x \in \Omega, \ t \geq t_0, \\ \dfrac{\partial u_3(x,t)}{\partial t} = d\Delta u_3(x,t) + k(x)u_2(x,t) - m(x)u_3(x,t), \quad x \in \Omega, \ t \geq t_0, \\ \dfrac{\partial u_3(x,t)}{\partial\nu} = 0, \quad x \in \partial\Omega, \quad t \geq t_0. \end{cases}$$

Since $u_2(x,t) > 0$ and $u_3(x,t) > 0$ for all $x \in \bar{\Omega}$ and $t > 0$ (see (ii)), there exists a sufficiently small $\tilde{\varepsilon} > 0$ such that $(u_2(x,t), u_3(x,t))^T > \tilde{\varepsilon}\tilde{\psi}(x)$. Recalling that $\tilde{\varepsilon}e^{\tilde{\eta}(t-t_0)}\tilde{\psi}(x)$ is the solution of

$$\begin{cases} \dfrac{\partial u_2(x,t)}{\partial t} = \beta_1(x)\left(u_1^*(x) - \varepsilon\right)u_3(x,t) + \beta_2(x)\left(u_1^*(x) - \varepsilon\right)u_2(x,t) - b(x)u_2(x,t), \quad x \in \Omega, \ t \geq t_0, \\ \dfrac{\partial u_3(x,t)}{\partial t} = d\Delta u_3(x,t) + k(x)u_2(x,t) - m(x)u_3(x,t), \quad x \in \Omega, \ t \geq t_0, \\ \dfrac{\partial u_3(x,t)}{\partial \nu} = 0, \quad x \in \partial\Omega, \quad t \geq t_0, \end{cases}$$

we can use the comparison principle to obtain

$$(u_2(x,t), u_3(x,t))^T \geq \tilde{\varepsilon}e^{\tilde{\eta}(t-t_0)}\tilde{\psi}(x).$$

Since $\tilde{\eta} > 0$, $u(x,t)$ diverges and this is a contradiction. □

Using Lemma 4.1, the uniform persistence theory, we prove the following theorem.

Theorem 4.1. *Let $\Re_0$ be defined by* (2.16)*. If $\Re_0 > 1$, then the system* (1.2) *is uniformly persistent in $\mathscr{D}_0$ and has at least one positive infection steady state $Q^* = (\hat{u}_1(x), \hat{u}_2(x), \hat{u}_3(x))^T \in \mathscr{D}_0$.*

PROOF. From Lemma 4.1 (i)-(ii), we see that $(u_1^*(x), 0, 0)^T$ is isolated in $\mathscr{D}$ and $\mathscr{D}_0 \cap W^s\left((u_1^*(x), 0, 0)^T\right) = \emptyset$, where $W^s(\cdot)$ denotes the stable manifold. Since there is no cycle in M_∂ from $(u_1^*(x), 0, 0)^T$ to itself, we can use [23, Theorem 3] to conclude that there exists a constant $\xi > 0$ such that

$$\min_{\phi \in \omega(u_0)} \left[\min_{i=1,2,3} \inf_{x \in \bar{\Omega}} \phi_i(x) \right] > \xi$$

for all $u_0 \in \mathscr{D}_0$. This implies that $\liminf_{t \to +\infty} u_i(x,t;u_0) > \xi$ for $i = 1,2,3$ and thus, the system (1.2) is uniformly persistent.

From [13, Theorem 3.7], $\Phi_t : \mathscr{D}_0 \to \mathscr{D}_0$ admits a global attractor $\mathscr{A}_0$ that attracts every point in $\mathbb{X}^+$ Then, from [13, Theorem 4.7], Φ_t has a steady state $Q^* = (\hat{u}_1(x), \hat{u}_2(x), \hat{u}_3(x))^T \in \mathscr{D}_0$, whose positivity is guaranteed by Lemma 4.1. □

5. Global asymptotic stability of the infection steady state

In this section, we prove the global asymptotic stability of the infection steady state $Q^* = (\hat{u}_1(x), \hat{u}_2(x), \hat{u}_3(x))^T \in \mathscr{D}_0$ for $\Re_0 > 1$. We construct the following Lyapunov function:

$$\mathscr{L}_{IE}[u_1, u_2, u_3](t) := \int_\Omega \ell(x)\mathscr{W}[u_1, u_2, u_3](x,t)\mathrm{d}x, \tag{5.1}$$

where $\ell(x)$ is a strictly positive function to be defined later and

$$\mathscr{W}[u_1, u_2, u_3](x,t) := (\hat{u}_1(x), \hat{u}_2(x), \hat{u}_3(x)) \begin{pmatrix} g\left(\frac{u_1(x,t)}{\hat{u}_1(x)}\right) \\ g\left(\frac{u_2(x,t)}{\hat{u}_2(x)}\right) \\ \frac{\beta_1(x)\hat{u}_1(x)\hat{u}_3(x)}{k(x)\hat{u}_2(x)}\hat{u}_3(x)g\left(\frac{u_3(x,t)}{\hat{u}_3(x)}\right) \end{pmatrix},$$

where $g(l) := l - 1 - \ln l$, $l > 0$. The partial derivative of $\mathscr{W}[u_1, u_2, u_3]$ with respect to t satisfies

$$\frac{\partial \mathscr{W}}{\partial t} = \left[\left(1 - \frac{\hat{u}_1(x)}{u_1(x,t)}\right)\frac{\partial u_1(x,t)}{\partial t} + \left(1 - \frac{\hat{u}_2(x)}{u_2(x,t)}\right)\frac{\partial u_2(x,t)}{\partial t} + \frac{\beta_1(x)\hat{u}_1(x)\hat{u}_3(x)}{k(x)\hat{u}_2(x)}\left(1 - \frac{\hat{u}_3(x)}{u_3(x,t)}\right)\frac{\partial u_3(x,t)}{\partial t} \right].$$

Using this function, we shall prove the following theorem.

Theorem 5.1. *Let $\Re_0$ and $\mathscr{D}_0$ be defined by* (2.16) *and* (4.1)*, respectively. If $\Re_0 > 1$, then the infection steady state $Q^* = (\hat{u}_1(x), \hat{u}_2(x), \hat{u}_3(x))^T \in \mathscr{D}_0$ is globally asymptotically stable in $\mathscr{D}_0$.*

PROOF. To ease of notations, we will use the following notations in the proof,

$$\hat{u}_i = \hat{u}_i(x), \;\; u_i = u_i(x,t), \;\; i = 1,2,3.$$

The derivative of the Lyapunov function $\mathscr{L}_{IE}[u_1, u_2, u_3]$ along the trajectory of the system (1.2) is calculated as follows:

$$\begin{aligned}\mathscr{L}'_{IE} = \int_\Omega \ell(x) \Bigg[\left(1 - \frac{\hat{u}_1}{u_1}\right) \Big(\lambda(x) - \beta_1(x) u_1 u_3 - \beta_2(x) u_1 u_2 - a(x) u_1\Big) + \left(1 - \frac{\hat{u}_2}{u_2}\right) \Big(\beta_1(x) u_1 u_3 + \beta_2(x) u_1 u_2 - b(x) u_2\Big) \\ + \frac{\beta_1(x)\hat{u}_1\hat{u}_3}{k(x)\hat{u}_2} \left(1 - \frac{\hat{u}_3}{u_3}\right) \Big(d\Delta u_3 + k(x) u_2 - m(x) u_3\Big) \Bigg] \mathrm{d}x. \end{aligned} \tag{5.2}$$

Since $Q^* = (\hat{u}_1(x), \hat{u}_2(x), \hat{u}_3(x))^T$ is the steady state of the system (1.2), the following equations hold.

$$\begin{cases} \lambda(x) = \beta_1(x)\hat{u}_1\hat{u}_3 + \beta_2(x)\hat{u}_1\hat{u}_2 + a(x)\hat{u}_1, \\ b(x)\hat{u}_2 = \beta_1(x)\hat{u}_1\hat{u}_3 + \beta_2(x)\hat{u}_1\hat{u}_2, \\ m(x)\hat{u}_3 = d\Delta\hat{u}_3 + k(x)\hat{u}_2. \end{cases} \tag{5.3}$$

Then, we first rearrange (5.2) as follows.

$$\begin{aligned}\mathscr{L}'_{IE} = \int_\Omega \ell(x) \Bigg\{ \left(1 - \frac{\hat{u}_1}{u_1}\right) \Big(\lambda(x) - \beta_1(x) u_1 u_3 - \beta_2(x) u_1 u_2 - a(x) u_1\Big) \\ + \left(1 - \frac{\hat{u}_2}{u_2}\right) \Big(\beta_1(x) u_1 u_3 + \beta_2(x) u_1 u_2\Big) + \left(1 - \frac{u_2}{\hat{u}_2}\right) b(x)\hat{u}_2 \\ + \frac{\beta_1(x)\hat{u}_1\hat{u}_3}{k(x)\hat{u}_2} \left[\left(1 - \frac{\hat{u}_3}{u_3}\right) \Big(d\Delta u_3 + k(x) u_2\Big) + \left(1 - \frac{u_3}{\hat{u}_3}\right) m(x)\hat{u}_3 \right] \Bigg\} \mathrm{d}x. \end{aligned} \tag{5.4}$$

Putting (5.3) into (5.4) yields

$$\begin{aligned}\mathscr{L}'_{IE} = \int_\Omega \ell(x) \Bigg\{ a(x)\hat{u}_1 \left(2 - \frac{\hat{u}_1}{u_1} - \frac{u_1}{\hat{u}_1}\right) + \left(1 - \frac{\hat{u}_1}{u_1}\right) \Big(\beta_1(x)\hat{u}_1\hat{u}_3 + \beta_2(x)\hat{u}_1\hat{u}_2 - \beta_1(x) u_1 u_3 - \beta_2(x) u_1 u_2\Big) \\ + \left(1 - \frac{\hat{u}_2}{u_2}\right) \Big(\beta_1(x) u_1 u_3 + \beta_2(x) u_1 u_2\Big) + \left(1 - \frac{u_2}{\hat{u}_2}\right) \Big(\beta_1(x)\hat{u}_1\hat{u}_3 + \beta_2(x)\hat{u}_1\hat{u}_2\Big) \\ + \frac{\beta_1(x)\hat{u}_1\hat{u}_3}{k(x)\hat{u}_2} \left[\left(1 - \frac{\hat{u}_3}{u_3}\right) d\Delta u_3 + \left(1 - \frac{u_3}{\hat{u}_3}\right) d\Delta\hat{u}_3 \right] + \beta_1(x)\hat{u}_1\hat{u}_3 \left(\frac{u_2}{\hat{u}_2} - \frac{u_2\hat{u}_3}{\hat{u}_2 u_3} + 1 - \frac{u_3}{\hat{u}_3} \right) \Bigg\} \mathrm{d}x. \end{aligned}$$

Using the arithmetic-geometric mean, we have the following inequality.

$$\begin{aligned}\mathscr{L}'_{IE} &\le \int_\Omega \ell(x) \Bigg\{ \beta_1(x)\hat{u}_1\hat{u}_3 \left(3 - \frac{\hat{u}_1}{u_1} - \frac{u_1 u_3 \hat{u}_2}{\hat{u}_1\hat{u}_3 u_2} - \frac{u_2\hat{u}_3}{\hat{u}_2 u_3}\right) \\ &\qquad + \beta_2(x)\hat{u}_1\hat{u}_2 \left(2 - \frac{\hat{u}_1}{u_1} - \frac{u_1}{\hat{u}_1}\right) + \frac{\beta_1(x)\hat{u}_1\hat{u}_3}{k(x)\hat{u}_2} \left[\left(1 - \frac{\hat{u}_3}{u_3}\right) d\Delta u_3 + \left(1 - \frac{u_3}{\hat{u}_3}\right) d\Delta\hat{u}_3 \right] \Bigg\} \mathrm{d}x \\ &\le \int_\Omega \ell(x) \frac{\beta_1(x)\hat{u}_1\hat{u}_3}{k(x)\hat{u}_2} \left[\left(1 - \frac{\hat{u}_3}{u_3}\right) d\Delta u_3 + \left(1 - \frac{u_3}{\hat{u}_3}\right) d\Delta\hat{u}_3 \right] \mathrm{d}x. \end{aligned} \tag{5.5}$$

Now we define

$$\ell(x) = \frac{k(x)\hat{u}_2}{\beta_1(x)\hat{u}_1}.$$

Then, using the Green's first identity and the homogeneous Neumann boundary condition, we have

$$\begin{aligned}
\mathscr{L}'_{IE} &\leq d\int_\Omega \hat{u}_3\left[\left(1-\frac{\hat{u}_3}{u_3}\right)\Delta u_3+\left(1-\frac{u_3}{\hat{u}_3}\right)\Delta\hat{u}_3\right]\mathrm{d}x\\
&= d\left[\int_{\partial\Omega}\hat{u}_3\left(1-\frac{\hat{u}_3}{u_3}\right)\nabla u_3\cdot\nu\,\mathrm{d}S-\int_\Omega\nabla\left(\hat{u}_3\left(1-\frac{\hat{u}_3}{u_3}\right)\right)\cdot\nabla u_3\mathrm{d}x\right.\\
&\quad\left.+\int_{\partial\Omega}\hat{u}_3\left(1-\frac{u_3}{\hat{u}_3}\right)\nabla\hat{u}_3\cdot\nu\,\mathrm{d}S-\int_\Omega\nabla\left(\hat{u}_3\left(1-\frac{u_3}{\hat{u}_3}\right)\right)\cdot\nabla\hat{u}_3\mathrm{d}x\right]\\
&= -d\left[\int_\Omega\sum_{j=1}^n\left(\frac{\partial\hat{u}_3}{\partial x_j}-\frac{1}{u_3^2}\left(2u_3\hat{u}_3\frac{\partial\hat{u}_3}{\partial x_j}-\hat{u}_3^2\frac{\partial u_3}{\partial x_j}\right)\right)\frac{\partial u_3}{\partial x_j}\mathrm{d}x+\int_\Omega\sum_{j=1}^n\left(\frac{\partial\hat{u}_3}{\partial x_j}-\frac{\partial u_3}{\partial x_j}\right)\frac{\partial\hat{u}_3}{\partial x_j}\mathrm{d}x\right]\\
&= -d\int_\Omega\sum_{j=1}^n\left(\frac{\hat{u}_3^2}{u_3^2}\left(\frac{\partial u_3}{\partial x_j}\right)^2-2\frac{\hat{u}_3}{u_3}\frac{\partial u_3}{\partial x_j}\frac{\partial\hat{u}_3}{\partial x_j}+\left(\frac{\partial\hat{u}_3}{\partial x_j}\right)^2\right)\mathrm{d}x\;=\;-d\int_\Omega\sum_{j=1}^n\left(\frac{\hat{u}_3}{u_3}\frac{\partial u_3}{\partial x_j}-\frac{\partial\hat{u}_3}{\partial x_j}\right)^2\mathrm{d}x\;\leq\;0.
\end{aligned}$$

It is easy to see from (5.5) that the equality holds if and only if $(u_1(x,t),u_2(x,t),u_3(x,t))^T=(\hat{u}_1(x),\hat{u}_2(x),\hat{u}_3(x))^T$. Thus, the LaSalle's invariance principle implies the global asymptotic stability of the infection steady state $Q^*=(\hat{u}_1(x),\hat{u}_2(x),\hat{u}_3(x))^T$. □

6. The spatially homogeneous case

In this section, we are concerned with a case study, where all coefficients in (1.2) are independent of the variable x. The model to be studied takes the following form:

$$\begin{cases}
\dfrac{\partial u_1(x,t)}{\partial t}=\lambda-au_1(x,t)-\beta_1u_1(x,t)u_3(x,t)-\beta_2u_1(x,t)u_2(x,t),\\
\dfrac{\partial u_2(x,t)}{\partial t}=\beta_1u_1(x,t)u_3(x,t)+\beta_2u_1(x,t)u_2(x,t)-bu_2(x,t),\\
\dfrac{\partial u_3(x,t)}{\partial t}=d\Delta u_3(x,t)+ku_2(x,t)-mu_3(x,t),\\
\dfrac{\partial u_3(x,t)}{\partial\nu}=0,\ x\in\partial\Omega,\ t>0,\\
u_i(x,0)=u_i^0(x)\geq 0,\ x\in\Omega,\ i=1,2,3.
\end{cases}\tag{6.1}$$

Clearly, system (6.1) has an infection-free steady-state solution $Q^0_{(6.1)}=(\tilde{u}_1,0,0)^T$, where $\tilde{u}_1=\lambda/a$. The constant positive steady-state solution is uniquely given by

$$Q^*_{(6.1)}:=(\bar{u}_1,\bar{u}_2,\bar{u}_3)^T=\left(\frac{bm}{\beta_1k+\beta_2m},\frac{am(\Re_0^1-1)}{\beta_1k+\beta_2m},\frac{ak(\Re_0^1-1)}{\beta_1k+\beta_2m}\right)^T,$$

where

$$\Re_0^1=\frac{\beta_1\lambda k}{abm}+\frac{\beta_2\lambda}{ab}.\tag{6.2}$$

The existence of $Q^*_{(6.1)}$ is guaranteed if and only if $\Re_0^1>1$. In fact, $\Re_0^1>1$ is equivalent to

$$\frac{\beta_1\lambda k}{am}+\frac{\beta_2\lambda}{a}>b\;\Leftrightarrow\;\frac{\beta_1\tilde{u}_1k}{m}>b-\beta_2\tilde{u}_1\;\Leftrightarrow\;\frac{\beta_1\tilde{u}_1k}{m(b-\beta_2\tilde{u}_1)}>1$$

for $b-\beta_2\tilde{u}_1>0$. The last expression is $\Re_0>1$ as mentioned in (2.17) and hence, $\Re_0^1$ and $\Re_0$ may have the same threshold property. In the following, we are concerned with the global asymptotic stability of the steady states of (6.1) by using the technique of Lyapunov functions.

Theorem 6.1. *Let $\mathscr{D}$, $\mathscr{D}_0$ and $\Re_0^1$ be defined by* (2.6)*,* (4.1) *and* (6.2)*, respectively. Then the following statements hold:*

(i) If $\mathfrak{R}_0^1 < 1$, then the infection-free steady state $Q^0_{(6.1)} = (\tilde{u}_1, 0, 0)^T \in \mathscr{D}$ is globally asymptotically stable in $\mathscr{D}$;

(ii) If $\mathfrak{R}_0^1 > 1$, then the infection steady state $Q^*_{(6.1)} = (\bar{u}_1, \bar{u}_2, \bar{u}_3)^T \in \mathscr{D}_0$ is globally asymptotically stable in $\mathscr{D}_0$.

PROOF. Proof of (i). For an arbitrary positive solution $(u_1(x,t), u_2(x,t), u_3(x,t))^T$ of (6.1), we define

$$\mathscr{L}_{DFE}[u_1,u_2,u_3](t) := \int_\Omega \mathscr{U}_2[u_1,u_2,u_3](x,t)\mathrm{d}x,$$

where

$$\mathscr{U}_2[u_1,u_2,u_3](x,t) := (\tilde{u}_1, u_2(x,t), u_3(x,t)) \begin{pmatrix} g\left(\frac{u_1(x,t)}{\tilde{u}_1}\right) \\ 1 \\ \frac{\lambda\beta_1}{am} \end{pmatrix}.$$

Recalling that $\tilde{u} = \lambda/a$, we obtain the following inequality by direct computation:

$$\begin{aligned}
\frac{\partial \mathscr{U}_2}{\partial t} &= \frac{\partial \mathscr{U}_2}{\partial u_1}\frac{\partial u_1}{\partial t} + \frac{\partial \mathscr{U}_2}{\partial u_2}\frac{\partial u_2}{\partial t} + \frac{\partial \mathscr{U}_2}{\partial u_3}\frac{\partial u_3}{\partial t} \\
&= \left(1 - \frac{\tilde{u}_1}{u_1}\right)(a\tilde{u}_1 - au_1 - \beta_1 u_1 u_3 - \beta_2 u_1 u_2) + (\beta_1 u_1 u_3 + \beta_2 u_1 u_2 - bu_2) + \frac{\lambda\beta_1}{am}(ku_2 - mu_3) \\
&= a\tilde{u}_1\left(2 - \frac{\tilde{u}_1}{u_1} - \frac{u_1}{\tilde{u}_1}\right) + \beta_1\tilde{u}_1 u_3 + \beta_2\tilde{u}_1 u_2 - bu_2 + \frac{\lambda\beta_1 k}{am}u_2 - \frac{\lambda\beta_1}{a}u_3 \\
&= a\tilde{u}_1\left(2 - \frac{\tilde{u}_1}{u_1} - \frac{u_1}{\tilde{u}_1}\right) + bu_2\left(\frac{\beta_1\lambda k}{abm} + \frac{\beta_2\lambda}{ab} - 1\right) \\
&= a\tilde{u}\left(2 - \frac{u_1}{\tilde{u}_1} - \frac{\tilde{u}_1}{u_1}\right) + bu_2(\mathfrak{R}_0^1 - 1) \le 0.
\end{aligned}$$

Hence, $\mathscr{L}_{DFE}$ is the Lyapunov function for the system (6.1). It is easy to see that $\left\{(u_1,u_2,u_3)^T \in \mathbb{X}^+ : \mathscr{L}'_{DFE} = 0\right\} = \left\{Q^0_{(6.1)} = (\tilde{u}_1,0,0)^T\right\}$. Therefore, LaSalle's invariance principle (see, e.g., [8, Theorem 1.1]) implies that the system (6.1) admits a connected global attractor on $\mathbb{X}^+$ and

$$\lim_{t\to\infty}(u_1(\cdot,t), u_2(\cdot,t), u_3(\cdot,t))^T = (\tilde{u}_1, 0, 0)^T,$$

that is, $Q^0_{(6.1)} = (\tilde{u}_1,0,0)^T$ is globally asymptotically stable for (6.1).

Proof of (ii). Suppose $u(x,t,\phi)$ is the solution of system (6.1) with $u(\cdot,t,\phi) = \phi \in \mathbb{R}^+$. We define

$$\mathscr{L}_{EE}[u_1,u_2,u_3](t) := \int_\Omega \mathscr{U}_1[u_1,u_2,u_3](x,t)\mathrm{d}x,$$

where

$$\mathscr{U}_1[u_1,u_2,u_3](x,t) := (\bar{u}_1,\bar{u}_2,\bar{u}_3) \begin{pmatrix} g\left(\frac{u_1(x,t)}{\bar{u}_1}\right) \\ g\left(\frac{u_2(x,t)}{\bar{u}_2}\right) \\ \frac{\beta_1\bar{u}_1\bar{u}_3}{k\bar{u}_2} g\left(\frac{u_3(x,t)}{\bar{u}_3}\right) \end{pmatrix}.$$

The partial derivative of $\mathscr{U}_1[u_1,u_2,u_3]$ with respect to t satisfies

$$\frac{\partial \mathscr{U}_1}{\partial t} = \left[\left(1 - \frac{\bar{u}_1}{u_1(x,t)}\right)\frac{\partial u_1(x,t)}{\partial t} + \left(1 - \frac{\bar{u}_2}{u_2(x,t)}\right)\frac{\partial u_2(x,t)}{\partial t} + \frac{\beta_1\bar{u}_1\bar{u}_3}{k\bar{u}_2}\left(1 - \frac{\bar{u}_3}{u_3(x,t)}\right)\frac{\partial u_3(x,t)}{\partial t}\right].$$

Note that the steady state of the system (6.1) satisfy the following equations:

$$\begin{cases} \lambda = \beta_1\bar{u}_1\bar{u}_3 + \beta_2\bar{u}_1\bar{u}_2 + a\bar{u}_1, \\ b\bar{u}_2 = \beta_1\bar{u}_1\bar{u}_3 + \beta_2\bar{u}_1\bar{u}_2, \\ m\bar{u}_3 = k\bar{u}_2. \end{cases} \tag{6.3}$$

Directly computing the derivative of $\mathscr{L}_{EE}$ gives

$$\begin{aligned} \mathscr{L}'_{EE} = \int_\Omega \Bigg\{ & \left(1-\frac{\bar{u}_1}{u_1}\right)\left(\lambda - \beta_1 u_1 u_3 - \beta_2 u_1 u_2 - a u_1\right) + \left(1-\frac{\bar{u}_2}{u_2}\right)\left(\beta_1 u_1 u_3 + \beta_2 u_1 u_2\right) + \left(1-\frac{u_2}{\bar{u}_2}\right) b\bar{u}_2 \\ & + \frac{\beta_1\bar{u}_1\bar{u}_3}{k\bar{u}_2}\left[\left(1-\frac{\bar{u}_3}{u_3}\right)\left(d\Delta u_3 + k u_2\right) + \left(1-\frac{u_3}{\bar{u}_3}\right) m\bar{u}_3\right]\Bigg\}\mathrm{d}x. \end{aligned} \tag{6.4}$$

Putting (6.3) into (6.4) yields

$$\begin{aligned} \mathscr{L}'_{EE} = \int_\Omega \Bigg\{ & a\hat{u}_1\left(2 - \frac{\bar{u}_1}{u_1} - \frac{u_1}{\bar{u}_1}\right) + \left(1-\frac{\bar{u}_1}{u_1}\right)\left(\beta_1\bar{u}_1\bar{u}_3 + \beta_2\bar{u}_1\bar{u}_2 - \beta_1 u_1 u_3 - \beta_2 u_1 u_2\right) \\ & + \left(1-\frac{\bar{u}_2}{u_2}\right)\left(\beta_1 u_1 u_3 + \beta_2 u_1 u_2\right) + \left(1-\frac{u_2}{\bar{u}_2}\right)\left(\beta_1\bar{u}_1\bar{u}_3 + \beta_2\bar{u}_1\bar{u}_2\right) \\ & + \frac{\beta_1\bar{u}_1\bar{u}_3}{k\bar{u}_2}\left(1-\frac{\bar{u}_3}{u_3}\right) d\Delta u_3 + \beta_1\bar{u}_1\bar{u}_3\left(\frac{u_2}{\bar{u}_2} - \frac{u_2\bar{u}_3}{\bar{u}_2 u_3} + 1 - \frac{u_3}{\bar{u}_3}\right)\Bigg\}\mathrm{d}x. \end{aligned}$$

Using the arithmetic-geometric mean, we have the following inequality.

$$\begin{aligned} \mathscr{L}'_{EE} &\le \int_\Omega \left\{\beta_1\bar{u}_1\bar{u}_3\left(3 - \frac{\bar{u}_1}{u_1} - \frac{u_1 u_3\bar{u}_2}{\bar{u}_1\bar{u}_3 u_2} - \frac{u_2\bar{u}_3}{\bar{u}_2 u_3}\right) + \beta_2\bar{u}_1\bar{u}_2\left(2 - \frac{\bar{u}_1}{u_1} - \frac{u_1}{\bar{u}_1}\right) + \frac{\beta_1\bar{u}_1\bar{u}_3}{k\bar{u}_2}\left(1-\frac{\bar{u}_3}{u_3}\right) d\Delta u_3\right\}\mathrm{d}x \\ &\le \int_\Omega \frac{\beta_1\bar{u}_1\bar{u}_3}{k\bar{u}_2}\left(1-\frac{\bar{u}_3}{u_3}\right) d\Delta u_3 \mathrm{d}x \;=\; d\frac{\beta_1\bar{u}_1\left(\bar{u}_3\right)^2}{k\bar{u}_2}\int_\Omega\left(\frac{1}{\bar{u}_3} - \frac{1}{u_3}\right)\Delta u_3 \mathrm{d}x. \end{aligned}$$

Hence, using the Green's first identity, we have

$$\mathscr{L}'_{EE} \le -d\frac{\beta_1\bar{u}_1\left(\bar{u}_3\right)^2}{k\bar{u}_2}\int_\Omega \frac{|\nabla u_3|^2}{u_3^2}\mathrm{d}x \le 0.$$

Therefore, $\mathscr{L}_{EE}$ is a Lyapunov function for the system (6.1). Similar to the proof of (i), it can be easily verified that $\{(u_1,u_2,u_3)^T \in \mathbb{X}^+ : \mathscr{L}'_{EE} = 0\} = \{Q^*_{(6.1)} = (\bar{u}_1,\bar{u}_2,\bar{u}_3)^T\}$ and we can use LaSalle's invariance principle to show that the system (6.1) admits a connected global attractor on $\mathbb{X}^+$ and

$$\lim_{t\to\infty}\left(u_1(\cdot,t),u_2(\cdot,t),u_3(\cdot,t)\right)^T = \left(\bar{u}_1,\bar{u}_2,\bar{u}_3\right)^T.$$

That is, $Q^*_{(6.1)} = (\bar{u}_1,\bar{u}_2,\bar{u}_3)^T$ is globally asymptotically stable for (6.1). This completes the proof. □

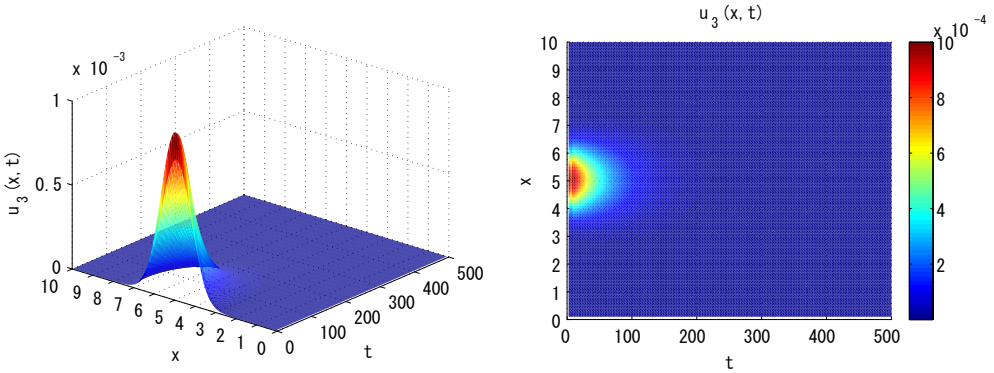
7. Numerical simulation

In this section, we perform numerical simulation in order to verify the validity of our theoretical result.

7.1. For artificial parameters

First, we consider the spatially homogeneous case (6.1) in Section 6. Let $d = 0.01$ and fix

$$\begin{aligned} &\lambda = 0.35, \quad a = 1, \quad b = 1, \quad \beta_2 = 2, \quad k = 2, \quad m = 1, \\ &u_1^0(x) = 0.99, \quad u_2^0(x) = 0, \quad u_3^0(x) = \mathrm{e}^{-(x-5)^2}\times 10^{-3}, \quad x \in \Omega = [0,10] \subset \mathbb{R} \end{aligned} \tag{7.1}$$



(a) $\Re_0^1 \approx 0.9761 < 1$ $(\beta_1 = 0.47)$

(b) $\Re_0^1 \approx 0.9761 < 1$ $(\beta_1 = 0.47)$

(c) $\Re_0^1 \approx 1.0292 > 1$ $(\beta_1 = 0.55)$

(d) $\Re_0^1 \approx 1.0292 > 1$ $(\beta_1 = 0.55)$

Figure 1: Time variation of the density of free virus $u_3(x,t)$ in model (6.1) with parameters (7.1) and $d = 0.01$.

Parameter	Value (unit)	Reference
L	10	Assumed
$\lambda(x)$	$0.5\times 10^6/L$ (cells/day ml)	Nakaoka *et al.* [16]
$\beta_1(x)$	$\bar{\beta}\times 10^{-8}$	Varied
$\beta_2(x)$	1.0×10^{-10}	Assumed
$a(x)$	0.01 (ml/cells day)	Boer and Perelson [2]
$b(x)$	0.7 (ml/cells day)	Perelson *et al.* [19]
$m(x)$	30 (ml/viruses day)	Perelson *et al.* [18]
$k(x)$	1.0×10^3 (ml viruses/cells)	Nakaoka *et al.* [16]
d	1.0×10^{-5}	Assumed

Table 2: Parameters for numerical simulation in Section 7.2.

and vary β_1. In this case, $b-\beta_2 u_1^* = 0.3360 > 0$ and hence, the assumption (2.8) holds. For $\beta_1 = 0.47$, we have $\mathfrak{R}_0^1 = 0.9761 < 1$ and hence, it follows from Theorem 6.1 (i) that the infection-free steady state Q^0 is globally asymptotically stable. In fact, in Figure 1 (a) and (b), the density of free virus $u_3(x,t)$ converges to zero. On the other hand, for $\beta_1 = 0.55$, we have $\mathfrak{R}_0^1 = 1.0292 > 1$ and hence, it follows from Theorem 6.1 (ii) that the infection steady state Q^* is globally asymptotically stable. In fact, in Figure 1 (c) and (d), the density of free virus $u_3(x,t)$ converges to a spatially homogeneous positive distribution.

Next we consider the spatially heterogeneous case. As in the argument in [1, Theorem 2 (a)], we can obtain the following approximation of the basic reproduction number $\mathfrak{R}_0$:

$$\mathfrak{R}_0 \approx \begin{cases} \max\left\{\dfrac{\beta_1(x)u_1^*(x)k(x)}{m(x)\left(b(x)-\beta_2(x)u_1^*(x)\right)}\right\}, & \text{for sufficiently small } d, \\ \dfrac{1}{\int_\Omega m(x)\mathrm{d}x}\displaystyle\int_\Omega \frac{\beta_1(x)u_1^*(x)k(x)}{b(x)-\beta_2(x)u_1^*(x)}\mathrm{d}x, & \text{for sufficiently large } d. \end{cases} \tag{7.2}$$

In what follows, we fix the parameters as in (7.1) and vary d and $\beta_1(x)$ with the following form:

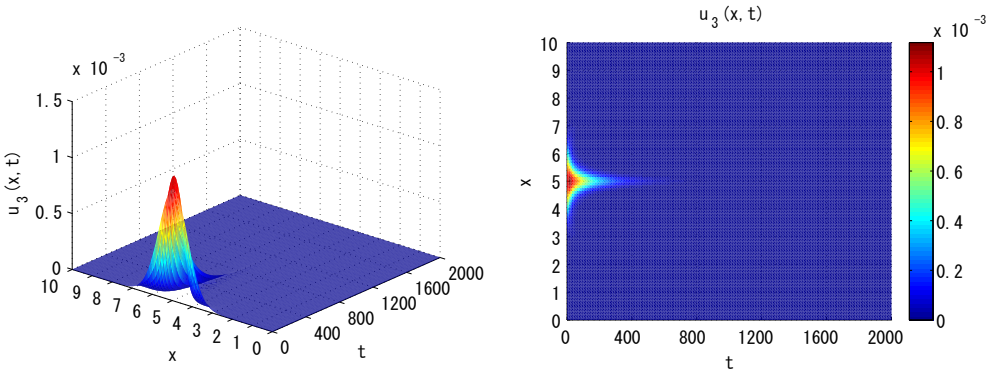
$$\beta_1(x) = \tilde{\beta}\left(1+0.1\sin\frac{9\pi x}{10}\right),$$

where $\tilde{\beta}$ is a positive parameter. Let $d = 1.0\times 10^{-5}$. In this case, the approximate value of $\mathfrak{R}_0$ can be calculated as the first expression in (7.2). For $\tilde{\beta} = 0.45$, we have $\mathfrak{R}_0 \approx 0.9782 < 1$. Hence, it follows from Theorem 3.1 that the infection-free steady state Q^0 is globally asymptotically stable. In fact, in Figure 2 (a) and (b), the density of free virus $u_3(x,t)$ converges to zero. On the other hand, for $\tilde{\beta} = 0.5$, we have $\mathfrak{R}_0 \approx 1.0869 > 1$. Hence, it follows from Theorem 5.1 that the infection steady state Q^* is globally asymptotically stable. In fact, in Figure 2 (c) and (d), the density of free virus $u_3(x,t)$ converges to a positive distribution.

Let $d = 1.0\times 10^5$. In this case, the approximate value of $\mathfrak{R}_0$ can be calculated as the second expression in (7.2). For $\tilde{\beta} = 0.48$, we have $\mathfrak{R}_0 \approx 0.9553 < 1$. Hence, from Theorem 3.1, we see that the infection-free steady state Q^0 is globally asymptotically stable. In fact, in Figure 3 (a) and (b), the density of free virus $u_3(x,t)$ converges to zero. On the other hand, for $\tilde{\beta} = 0.53$, we have $\mathfrak{R}_0 \approx 1.0548 > 1$. Hence, it follows from Theorem 5.1 that the infection steady state Q^* is globally asymptotically stable. In fact, in Figure 3 (c) and (d), the density of free virus $u_3(x,t)$ converges to a positive distribution.

7.2. For biologically justified parameters

For the HIV infection models, some parameter values have been estimated in previous studies (see, for instance, [2, 16, 18, 19]). Using biologically justified parameter values as in Table 2, we observe the stability change with different transmission coefficient $\beta_1(x) = \bar{\beta}\times 10^{-8}$. For $\bar{\beta} = 0.40$, we have $\mathfrak{R}_0 \approx 0.9531 < 1$. From Theorem 3.1, we see that the infection-free steady state Q^0 is globally asymptotically stable. In fact, we obtain Figure 4 (a) and (b) which exhibit the density of free virus $u_3(x,t)$ converging to zero. On the other hand, for $\bar{\beta} = 0.45$, we have



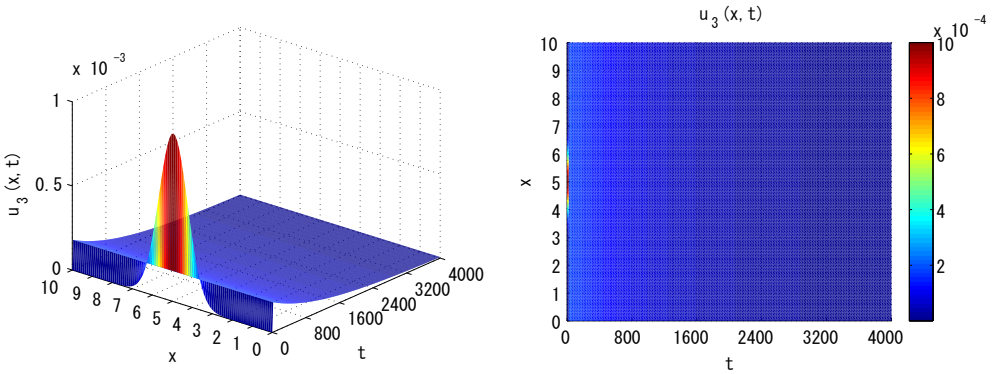
(a) $\Re_0 \approx 0.9782 < 1$ $\left(\tilde{\beta} = 4.5\right)$

(b) $\Re_0 \approx 0.9782 < 1$ $\left(\tilde{\beta} = 4.5\right)$

(c) $\Re_0 \approx 1.0869 > 1$ $\left(\tilde{\beta} = 5.0\right)$

(d) $\Re_0 \approx 1.0869 > 1$ $\left(\tilde{\beta} = 5.0\right)$

Figure 2: Time variation of the density of free virus $u_3(x,t)$ in model (1.2) with parameters (7.1) and $d = 1.0 \times 10^{-5}$.



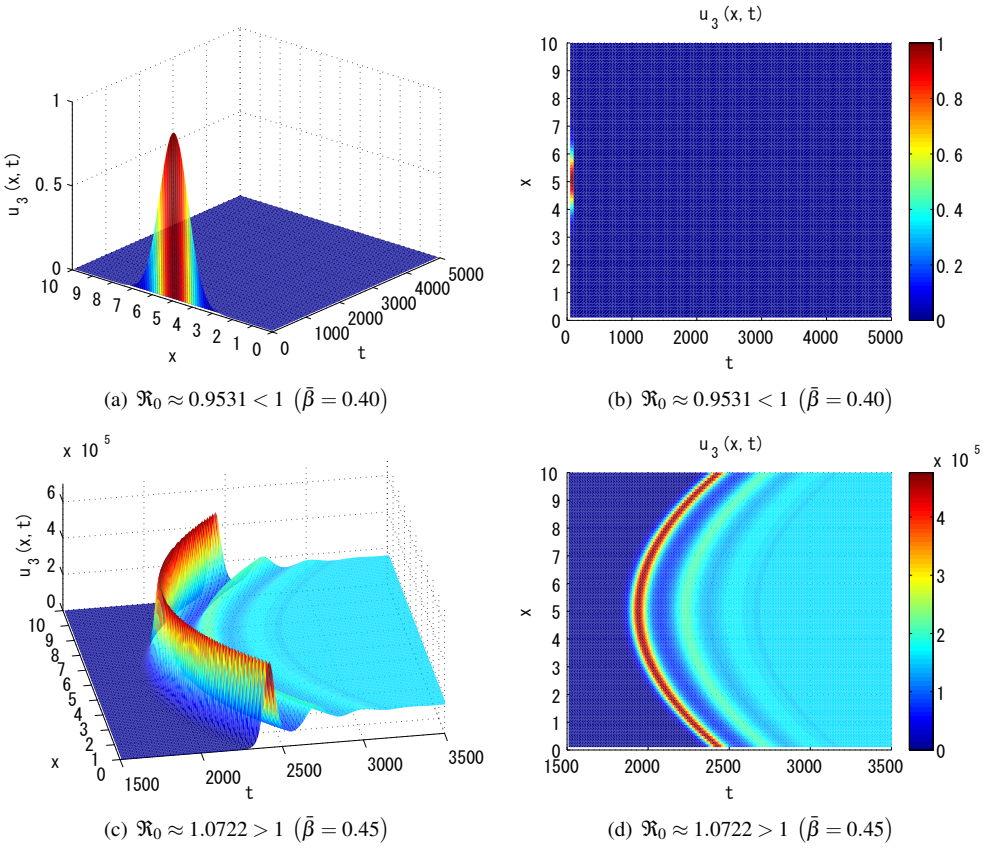
(a) $\Re_0 \approx 0.9553 < 1$ $\left(\tilde{\beta} = 0.48\right)$

(b) $\Re_0 \approx 0.9553 < 1$ $\left(\tilde{\beta} = 0.48\right)$

(c) $\Re_0 \approx 1.0548 > 1$ $\left(\tilde{\beta} = 0.53\right)$

(d) $\Re_0 \approx 1.0548 > 1$ $\left(\tilde{\beta} = 0.53\right)$

Figure 3: Time variation of the density of free virus $u_3(x,t)$ in model (1.2) with parameters (7.1) and $d = 1.0 \times 10^5$.



(a) $\Re_0 \approx 0.9531 < 1$ $\left(\bar{\beta} = 0.40\right)$

(b) $\Re_0 \approx 0.9531 < 1$ $\left(\bar{\beta} = 0.40\right)$

(c) $\Re_0 \approx 1.0722 > 1$ $\left(\bar{\beta} = 0.45\right)$

(d) $\Re_0 \approx 1.0722 > 1$ $\left(\bar{\beta} = 0.45\right)$

Figure 4: Time variation of the density of free virus $u_3(x,t)$ in model (1.2) with parameters (7.1) and $d = 10^{-5}$.

$\mathfrak{R}_0 \approx 1.0722 > 1$. Hence, from Theorem 5.1, we see that the endemic steady state Q^* is globally asymptotically stable. In fact, in Figure 4 (c) and (d), the density of free virus $u_3(x,t)$ converges to a positive distribution.

8. Discussion

In this paper, we have investigated the in-host viral infection model (1.2) incorporating the cell-to-cell infection and spatial heterogeneity. We have obtained the basic reproduction number $\mathfrak{R}_0$ in a variational characterization (see (2.16)). For $\mathfrak{R}_0 \leq 1$, the Lyapunov function $\mathscr{L}_{IFE}$ was constructed as in (3.3) and $\mathscr{L}'_{IFE} \leq 0$ was shown by using the Green's first identity. Thus, using the LaSalle's invariance principle, we have obtained that the infection-free steady state $Q^0 = (u_1^*(x), 0, 0)^T \in \mathscr{D}$ is globally asymptotically stable (see Theorem 3.1). On the other hand, for $\mathfrak{R}_0 > 1$, it was shown that the spectral bound $s(\mathscr{B})$ corresponding to the linearized system (2.9) is positive and hence, from Lemma 2.5, it is the principal eigenvalue associated with a strictly positive eigenfunction. Using this fact, the uniform persistence of the system (1.2) was shown and it results in the existence of the infection steady state $Q^* = (\hat{u}_1(x), \hat{u}_2(x), \hat{u}_3(x))^T \in \mathscr{D}_0$ (see Theorem 5.1). Then, constructing the Lyapunov function $\mathscr{L}_{IE}$ as in (5.1) and using the Green's first identity and the LaSalle's invariance principle again, we have proved the global asymptotic stability of the infection steady state Q^*. For the case of constant parameters, it was shown that the basic reproduction number $\mathfrak{R}_0$ has a similar threshold property as that of $\mathfrak{R}_0^1 = \beta_1 \lambda k / (abm) + \beta_2 \lambda / (ab)$ (see Section 6). The numerical simulation was performed to verify the validity of these theoretical results (see Section 7).

Our construction method of Lyapunov functions may be applicable to other epidemic models including a single PDE with a diffusion term. However, if they include two or more PDEs with diffusion terms, our method may not be applicable. The global asymptotic stability of the infection equilibrium has been an open problem even for some spatially heterogeneous ODE epidemic models with patch structure, in which every patches are strongly connected.

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