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Viral diffusion and cell-to-cell transmission: Mathematical analysis and simulation study

Hongying Shu [a,b], Zongwei Ma [b], Xiang-Sheng Wang [c,*], Lin Wang [d]

[a] *School of Mathematics and Information Science, Shaanxi Normal University, Xi'an 710062, China*
[b] *Department of Mathematics, Tongji University, Shanghai 200092, China*
[c] *Department of Mathematics, University of Louisiana at Lafayette, Lafayette, LA 70503, USA*
[d] *Department of Mathematics and Statistics, University of New Brunswick, Fredericton, NB E3B 5A3, Canada*

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ABSTRACT

We propose a general model to investigate the joint impact of viral diffusion and cell-to-cell transmission on viral dynamics. The mathematical challenge lies in the fact that the model system is partially degenerate and the solution map is not compact. While the simpler cases with only indirect transmission mode or weak cell-to-cell transmission mode have been extensively studied in the literature, it remains an open problem to understand the local and global dynamics of fully coupled viral infection model with partial degeneracy. In this paper, we identify the basic reproduction number as the spectral radius of the sum of two linear operators corresponding to direct and indirect transmission modes. It is well-known that viral mobility may induce infection in low-risk regions. However, as diffusion coefficient increases, we prove that the basic reproduction number actually decreases, which indicates that faster viral movements may result in a lower level of viral infection. By an innovative construction of Lyapunov functionals, we further demonstrate that the basic reproduction number is the threshold parameter which determines global picture of viral dynamics. In addition to the traditional dichonomy results of extinction and persistence as obtained in earlier works for many simpler models, we are able to prove global asymptotic stability of infection-free steady state and global attractiveness (as well as uniqueness) of chronic-infection steady state, depending on whether the basic reproduction number is smaller or greater than one. Numerical simulation supports our theoretical results and suggests an interesting phenomenon: boundary layer and internal layer may occur when the diffusion parameter tends to zero.

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RÉSUMÉ

Nous proposons un modèle général pour étudier l'impact conjoint de la diffusion virale et de la transmission de cellule à cellule sur la dynamique virale. Le défi mathématique réside dans le fait que le système modèle est partiellement dégénéré et que la carte des solutions n'est pas compacte. Alors que les cas les plus simples avec uniquement un mode de transmission indirecte ou un mode de transmission

* Corresponding author.
E-mail address: xiangsheng.wang@louisiana.edu (X.-S. Wang).

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de cellule à cellule faible ont été largement étudiés dans la littérature, il reste un problème ouvert pour comprendre la dynamique locale et globale du modèle d'infection virale entièrement couplé avec dégénérescence partielle. Dans cet article, nous identifions le nombre de reproduction de base comme le rayon spectral de la somme de deux opérateurs linéaires correspondant aux modes de transmission directe et indirecte. Il est bien connu que la mobilité virale peut induire une infection dans les régions à faible risque. Cependant, à mesure que le coefficient de diffusion augmente, nous prouvons que le nombre de reproduction de base diminue réellement, ce qui indique que des mouvements viraux plus rapides peuvent entraîner un niveau inférieur d'infection virale. Par une construction innovante des fonctionnelles de Lyapunov, nous démontrons en outre que le nombre de reproduction de base est le paramètre de seuil qui détermine l'image globale de la dynamique virale. En plus des résultats de dichonomie d'extinction et de persistance traditionnels obtenus dans des travaux antérieurs pour de nombreux modèles plus simples, nous sommes en mesure de prouver la stabilité asymptotique globale d'un état d'équilibre sans infection et l'attractivité globale (ainsi que l'unicité) d'un état d'équilibre d'infection chronique, selon si le nombre de reproduction de base est inférieur ou supérieur à un. La simulation numérique soutient nos résultats théoriques et suggère un phénomène intéressant : la couche limite et la couche interne peuvent se produire lorsque le paramètre de diffusion tend vers zéro.

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1. Introduction

Recently, there has been growing interests in the study of partially degenerate reaction-diffusion systems (see, for example, [11,30,34,35]). The reason for this is twofold: mathematical challenges and practical applications. On one hand, a partially degenerate reaction-diffusion system is a system that couples partial differential equations (PDEs) with ordinary differential equations (ODEs). Since there are no diffusion terms in those ODEs, the associated solution maps are not compact, which brings in some technical difficulties in analyzing the model dynamics as many theories of dynamical systems require compactness of the solution maps. To overcome the noncompactness issue, one may employ the Kuratowski measure of noncompactness ([3]) and a generalized Krein-Rutman Theorem [18]; see more related techniques in [15] and references therein. On the other hand, many biological processes can be modeled by partially degenerate reaction-diffusion systems. For instance, for hepatitis B virus (HBV) infection, susceptible target cells and infected cells are hepatocyte and cannot move under normal conditions, while viruses can move freely in liver. Based on this fact, a partially degenerated reaction-diffusion system was proposed in [32] to study the propagation of HBV with spatial dependence; see also [8,30]. Note that in the aforementioned works, only cell-free infection mode was considered for the viral infection. However, it has been recognized that there is another major viral infection mode, namely, the cell-to-cell infection mode [16,23], which allows viral particles to be transferred directly from an infected source cell to a susceptible target cell through the formation of virological synapses [5,12]. The impacts of both the cell-free and cell-to-cell infection modes on viral dynamics were recently discussed in [9,25].

It seems to be a challenging problem to investigate joint impact of viral diffusion and cell-to-cell transmission on viral dynamics. Even the definition of basic reproduction number is not an easy task. So far as we know, there is only one partial result in [31] where the so-called "basic reproduction number" was introduced under a crucial assumption that cell-to-cell transmission is too weak to initiate viral infection alone. If the assumption is violated, this quantity is not well-defined or even becomes negative. As we shall see later, the so-called "basic reproduction number" is incorrectly defined because the decomposition of linearized operator about infection-free steady state in [31] is not biologically relevant, though it still defines a threshold parameter under the assumption of weak cell-to-cell transmission. It has been revealed that more than half of viral infections are due to cell-to-cell transmission [13]. Thus, it is more realistic and important to consider the case when cell-to-cell infection may be strong.

In this paper, we will consider a general model without the condition of weak cell-to-cell infection. We will define a basic reproduction number R_0 which is biologically meaningful and well defined even when cell-to-cell infection is strong. When reducing to the model with weak cell-to-cell transmission assumption in [31], our basic reproduction number is still better than the one defined in [31] because we will define the next generation operator in a more biologically relevant manner. Furthermore, we will prove that R_0 is a threshold parameter for the global dynamics of our general model. To be more specific, we consider the following general viral infection model incorporating both infection modes and spatial heterogeneity:

$$\begin{aligned}
\frac{\partial u_1(x,t)}{\partial t} &= n(x,u_1(x,t)) - f(x,u_1(x,t),u_3(x,t)) - g(x,u_1(x,t),u_2(x,t)),\\
\frac{\partial u_2(x,t)}{\partial t} &= f(x,u_1(x,t),u_3(x,t)) + g(x,u_1(x,t),u_2(x,t)) - b(x)u_2(x,t),\\
\frac{\partial u_3(x,t)}{\partial t} &= d\Delta u_3(x,t) + k(x)u_2(x,t) - m(x)u_3(x,t),
\end{aligned} \tag{1.1}$$

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

$$u_i(x,0) = u_i^0(x) \geq 0, \text{ and } u_1^0(x) \not\equiv 0, \ x \in \Omega, \ i = 1,2,3,$$

and the homogeneous Neumann boundary condition

$$\frac{\partial u_3(x,t)}{\partial \nu} = 0, \ x \in \partial\Omega, \ t > 0.$$

Here, $u_1(x,t)$, $u_2(x,t)$ and $u_3(x,t)$ denote the populations of susceptible target cells, infected target cells and free virus particles at location x and time t, respectively. $d > 0$ is the diffusion coefficient and Δ is the Laplacian operator. $k(x) > 0$ is the rate of virus production due to the lysis of infected cells. $m(x) > 0$ stands for the death rate of free viruses. $\frac{\partial u_3(x,t)}{\partial \nu}$ denotes the differentiation of $u_3(x,t)$ along the outward normal direction ν to $\partial\Omega$. In comparison with the model proposed in [31], we choose very general cell reproduction function $n(x,u_1)$, cell-free transmission function $f(x,u_1,u_3)$ and cell-to-cell transmission function $g(x,u_1,u_2)$. Note that our model includes existing models such as those in [30,31] as special cases. It should be mentioned that this general model originates from the in-host viral models proposed and studied in [2,20–22].

Throughout this paper, we make the following assumptions:

($\mathbf{H}_1$) $n(x,u_1) \in C^1(\Omega \times \mathbb{R}_+)$ and $\partial_{u_1} n(x,u_1) \leq 0$ for all $x \in \Omega$ and $u_1 \geq 0$. Moreover, there exists a unique $\bar{u}_1(x) > 0$ in $C(\bar{\Omega}, \mathbb{R})$ such that $n(x,\bar{u}_1(x)) = 0$.

($\mathbf{H}_2$) $f(x,u_1,u_3), g(x,u_1,u_2) \in C^1(\Omega \times \mathbb{R}_+ \times \mathbb{R}_+)$ and all of the partial derivatives $\partial_{u_1} f(x,u_1,u_3)$, $\partial_{u_3} f(x,u_1,u_3)$, $\partial_{u_1} g(x,u_1,u_2)$ and $\partial_{u_2} g(x,u_1,u_2)$ are positive for all $x \in \Omega$, $u_1 > 0$, $u_2 > 0$ and $u_3 > 0$; $f(x,u_1,u_3) = 0$ if and only if $u_1 u_3 = 0$, and $g(x,u_1,u_2) = 0$ if and only if $u_1 u_2 = 0$; $\frac{\partial^2 f(x,u_1,u_3)}{\partial u_3^2} \leq 0$ and $\frac{\partial^2 g(x,u_1,u_2)}{\partial u_2^2} \leq 0$ for $u_i \geq 0$ $(i = 1,2,3)$.

We organize the rest of this paper as follows. In Section 2, we follow a routine process to show that the models admits a unique solution, which exists globally and is ultimately bounded. We also prove that the orbit of any bounded set is also 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 [33]. Some properties of the basic reproduction number are also analyzed in this section. Sections 4 and 5 are devoted to the global dynamics of the model for the case of $R_0 \leq 1$ and $R_0 > 1$, respectively. In Section 6, we present some numerical simulation results to support the analytical results and to further explore the asymptotic profile of steady state solutions. A brief discussion is given in the last section.

2. Preliminaries

2.1. Boundedness and global existence of solutions

Denote by $\mathbb{X}$ the Banach space $C(\bar{\Omega}, \mathbb{R}^3)$ equipped with the supremum norm. The nonnegative cone of $\mathbb{X}$ is denoted by $\mathbb{X}^+ = C(\bar{\Omega}, \mathbb{R}^3_+)$. For any nontrivial initial condition $\phi = (\phi_1, \phi_2, \phi_3) \in \mathbb{X}^+$ we define $T_1(t)\phi_1 = \phi_1$ and $T_2(t)\phi_2 = e^{-b(\cdot)t}\phi_2$. Let $T_3(t) = e^{t(d\Delta - m(\cdot))}$ be the compact and strongly positive C_0 semigroup [27, Corollary 7.2.3] generated by $d\Delta - m(\cdot)$ subject to the no flux boundary condition. It is readily seen that $T(t) = (T_1(t), T_2(t), T_3(t))$ is a C_0 semigroup with an infinitesimal generator A [19]. We rewrite (1.1) as an abstract differential equation $u'(t) = Au(t) + F(u(t))$, where

$$F(\phi)(x) := \begin{pmatrix} n(x,\phi_1(x)) - f(x,\phi_1(x),\phi_3(x)) - g(x,\phi_1(x),\phi_2(x)) \\ f(x,\phi_1(x),\phi_3(x)) + g(x,\phi_1(x),\phi_2(x)) \\ k(x)\phi_2(x) \end{pmatrix}$$

for any $\phi \in \mathbb{X}^+$. Denote $c = \min\{c_1 \geq 0 : \min_{\bar{\Omega}}[F_1(\phi)(x) + c_1\phi_1(x)] \geq 0\}$. We obtain

$$\phi(x) + hF(\phi)(x) \geq (\phi_1(x)(1 - hc),\ \phi_2(x),\ \phi_3(x))^T \quad \text{for} \quad x \in \Omega.$$

By choosing $h > 0$ sufficiently small, we have $1 > hc$ and $\phi + hF(\phi) \in \mathbb{X}^+$. Especially,

$$\lim_{h \to 0^+} \frac{1}{h} \operatorname{dist}(\phi + hF(\phi), \mathbb{X}^+) = 0.$$

The above limit is satisfied for all $\phi \in \mathbb{X}^+$. Thus, by using [17, Corollary 4] or [27, Theorem 7.3.1], we have the following lemma.

Lemma 2.1. *For every initial condition $\phi \in \mathbb{X}^+$, system (1.1) has a unique mild solution $u(\cdot, t, \phi)$ on a maximal interval of existence $[0, T_{max})$ with $u(\cdot, 0, \phi) = \phi$ and $u(\cdot, t, \phi) \in \mathbb{X}$ for any $t \in [0, T_{max})$. If $T_{max} < \infty$, then $\limsup_{t \to T_{max}} \|u(x,t)\|_{\mathbb{X}} = \infty$.*

Let $u(x,t)$ be the solution of (1.1) with initial condition $\phi \in \mathbb{X}^+$. A standard comparison argument together with maximum principle implies $u(\cdot, t) \in \mathbb{X}^+$. Furthermore, $u_1(x,t) > 0$ for all $x \in \Omega$ and $t > 0$. Now, we want to show that $u(x,t)$ is bounded for all $t \in [0, T_{max})$, which then implies $T_{max} = \infty$. First, since $\partial_t u_1(x,t) \leq n(x, u_1(x,t))$, it follows from $(\mathbf{H}_1)$ and comparison principle that $u_1(x,t) \leq \max\{\phi_1(x), \bar{u}_1(x)\}$. Especially, there exists $K_1 > 0$ such that $u_1(x,t) \leq K_1$ for all $x \in \Omega$ and $t \in [0, T_{max})$. Adding the first two equations of (1.1) gives

$$\partial_t[u_1(x,t) + u_2(x,t)] \leq n(x,0) + b(x)K_1 - b(x)[u_1(x,t) + u_2(x,t)].$$

Let K_2 be a large positive constant such that $K_2 > K_2 + n(x,0)/b(x)$ and $K_2 > \phi_1(x) + \phi_2(x)$. It then follows from comparison principle that $u_1(x,t) + u_2(x,t) \leq K_2$ for all $x \in \Omega$ and $t \in [0, T_{max})$. Finally, we obtain from the third equation of (1.1) that $\partial_t u_3(x,t) \leq d\Delta u_3(x,t) + \bar{k}K_2 - \underline{m}u_3(x,t)$ where $\bar{k} = \max k(x) > 0$ and $\underline{m} = \min m(x) > 0$. It again follows from comparison principle that $u_3(x,t)$ is bounded by a constant K_3. Consequently, we have the following result.

Proposition 2.2. *For every initial condition in $\phi \in \mathbb{X}^+$, system (1.1) has a unique solution $u(\cdot, t) \in X^+$ on $t \in [0, \infty)$. Moreover, $u_1(x,t) > 0$ for all $(x,t) \in \Omega \times (0, \infty)$. 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. We only need to show that M is independent of ϕ. From first equation of (1.1), we have $\limsup_{t\to\infty} u_1(x,t) \le \bar{u}_1(x) \le M_1$. Especially, there exists $t_1 > 0$ such that $u_1(x,t) \le 2M_1$ for $t > t_1$. Add the first two equations of (1.1) gives

$$\partial_t[u_1(x,t)+u_2(x,t)] \le n(x,0) + 2M_1 b(x) - b(x)[u_1(x,t)+u_2(x,t)], \quad t > t_1.$$

Let $M_2 = 2M_1 + \max[n(x,0)/b(x)]$. We have $\limsup_{t\to\infty}[u_1(x,t)+u_2(x,t)] \le M_2$. Choose $t_2 > 0$ such that $u_2(x,t) \le 2M_2$ for $t > t_2$. It then follows from the third equation of (1.1) and comparison principle that $\limsup_{t\to\infty} u_3(x,t) \le 2M_2\bar{k}/\underline{m}$. This completes the proof. □

2.2. Orbits of bounded sets

Define the continuous semiflow $\{\Theta_t\}_{t\ge 0} : \mathbb{X}^+ \to \mathbb{X}^+$ for the system (1.1) by

$$\Theta_t\phi(\cdot) := u(\cdot,t,\phi), \ t \ge 0.$$

It then follows from Proposition 2.2 that each orbit $\gamma^+(\phi) = \cup_{t\ge 0}\Theta_t\phi$ is ultimately bounded with the bound independent of initial value $\phi \in \mathbb{X}^+$. However, this does not imply that the orbit $\gamma^+(U) = \cup_{\phi\in U}\gamma^+(\phi)$ is bounded for any bounded set U, a condition that should be verified in proving existence of the global attractor; see [7, Theorem 2.1]. Thus, we shall derive the following result concerning positive invariance and attractiveness of the bounded set

$$\Gamma_K = \left\{\phi \in \mathbb{X}^+ : \phi_1 \le K, \ \phi_1+\phi_2 \le K + \bar{n}/\underline{b}, \ \phi_3 \le \bar{k}(K+\bar{n}/\underline{b})/\underline{m}\right\}, \tag{2.1}$$

where K is a constant greater than the maximum of $\bar{u}_1$ on $\bar{\Omega}$, and $\bar{k}$ (resp. $\bar{n}$) is the maximum of $k(x)$ (resp. $n(x,0)$) on $\bar{\Omega}$, while $\underline{b}$ (resp. $\underline{m}$) is the minimum of $b(x)$ (resp. $m(x)$) on $\bar{\Omega}$.

Proposition 2.3. *For any $K > \|\bar{u}_1\|$, the set Γ_K defined as in (2.1) is positively invariant with respect to the semiflow Θ_t. Furthermore, for any bounded set $U \subset \mathbb{X}^+$, the orbit $\gamma^+(U)$ is bounded and there exists $t_0 \ge 0$ such that $\Theta_t\phi \in \Gamma_K$ for all $t \ge t_0$ and $\phi \in U$.*

Proof. We first use a contradiction argument to show that the set

$$\Gamma_K^1 = \left\{\phi = (\phi_1,\phi_2,\phi_3) \in \mathbb{X}^+ : \phi_1 \le K\right\}$$

is positively invariant. Let $u(x,t)$ be the solution of (1.1) with initial condition in Γ_K^1. If $u(x,t)$ leaves Γ_K^1 for the first time at $t = t_0$ and $x = x_0$, we have $u_1(x_0,t_0) = K$ and $\partial_t u_1(x_0,t_0) \ge 0$. But, the first equation of (1.1) gives $0 \le \partial_t u_1(x_0,t_0) < n(x_0,K_1) < n(x_0,\bar{u}_1(x_0)) = 0$, a contradiction. Similarly, we can add the first two equations of (1.1) and prove that the set

$$\Gamma_K^2 = \left\{\phi = (\phi_1,\phi_2,\phi_3) \in \mathbb{X}^+ : \phi_1 \le K, \ \phi_1+\phi_2 \le K + \bar{n}/\underline{b}\right\}$$

is positively invariant.

Now, for any solution $u(x,t)$ with initial condition in $\Gamma_K \subset \Gamma_K^2$, we know that $u_1(x,t) \le K$ and $u_2(x,t) \le K + \bar{n}/\underline{b}$ for all $x \in \bar{\Omega}$ and $t \ge 0$. A simple comparison method yields $u_3(x,t) \le \bar{k}(K+\bar{n}/\underline{b})/\underline{m}$ for all $x \in \bar{\Omega}$ and $t \ge 0$, thus proving the positive invariance of Γ_K.

Let U be any bounded subset in $\mathbb{X}^+$, we can find a large $K' > \|\bar{u}_1\|$ such that $U \subset \Gamma_{K'}$. The boundedness of $\gamma^+(U)$ follows immediately from the positive invariance of $\Gamma_{K'}$. For each $\phi \in U$, by Proposition 2.2, there exists t_0 such that $\Theta_t\phi \in \Gamma_K$ for all $t \ge t_0$. Here, we have to prove that the choice of t_0 is independent of ϕ,

though it should depend on K and K'. If $K' \le K$, the result is obvious by choosing $t_0 = 0$. So, we assume $K' > K$.

Since $K > \|\bar{u}_1\|$, we may choose $\varepsilon > 0$ small such that $K_1 := K - 2\varepsilon > \|\bar{u}_1\|$; for instance, $\varepsilon = (K - \|\bar{u}_1\|)/3$. For simplicity, we also denote $K_2 := K - \varepsilon + \bar{n}/\underline{b}$ and $K_3 := \bar{k}(K + \bar{n}/\underline{b})/\underline{m}$. Consider the differential equation $\partial_t v_1(x,t) = n(x, v_1(x,t))$ with initial condition $v_1(x,0) = K'$. It follows from comparison principle that $u_1(x,t) \le v_1(x,t)$ for all $x \in \bar{\Omega}$ and $t \ge 0$. On the other hand, since $n(x, v_1) \le n(x, K_1) \le \max_{x\in\bar{\Omega}} n(x, K_1) < 0$ whenever $v_1 \ge K_1$, we choose

$$t_1 = \frac{\ln(K_1/K')}{\max_{x\in\bar{\Omega}} n(x,K_1)} = \frac{\ln[(K-2\varepsilon)/K']}{\max_{x\in\bar{\Omega}} n(x,K_1)} > 0$$

such that $v_1(x,t) \le K_1$ for all $t \ge t_1$. Next, we consider the differential equation $v_2'(t) = \bar{n} + \underline{b}K_1 - \underline{b}v_2(t)$ for $t \ge t_1$ with initial condition $v_2(t_1) = K' + \bar{n}/\underline{b}$. Similarly, we obtain by comparison principle that $u_1(x,t) + u_2(x,t) \le v_2(t)$ for all $x \in \bar{\Omega}$ and $t \ge t_1$. Whenever $v_2(t) \ge K_2$, we have $v_2'(t) \le -\varepsilon\underline{b}$. By choosing

$$t_2 = \frac{\ln[K_2/(K' + \bar{n}/\underline{b})]}{-\varepsilon\underline{b}} = \frac{\ln[(K - \varepsilon + \bar{n}/\underline{b})/(K' + \bar{n}/\underline{b})]}{-\varepsilon\underline{b}} > 0,$$

we obtain $u_1(x,t) + u_2(x,t) \le v_2(t) \le K_2$ for all $x \in \bar{\Omega}$ and $t \ge t_1 + t_2$. Finally, we consider the differential equation $v_3'(t) = \bar{k}K_2 - \underline{m}v_3(t)$ for $t \ge t_1 + t_2$ with initial condition $v_3(t_1 + t_2) = \bar{k}(K' + \bar{n}/\underline{b})/\underline{m}$. Again, by comparison principle, we have $u_3(x,t) \le v_3(t)$ for all $x \in \bar{\Omega}$ and $t \ge t_1 + t_2$. Furthermore, since $v_3'(t) \le -\varepsilon\bar{k}$ whenever $v_3(t) \ge K_3$, we choose

$$t_3 = \frac{\ln[K_3\underline{m}/(\bar{k}(K' + \bar{n}/\underline{b}))]}{-\varepsilon\bar{k}} = \frac{\ln[(K + \bar{n}/\underline{b})/(K' + \bar{n}/\underline{b})]}{-\varepsilon\bar{k}} > 0$$

to obtain $u(x,t) \le v_3(t) \le K_3$ for all $x \in \bar{\Omega}$ and $t \ge t_1 + t_2 + t_3$. Let $t_0 = t_1 + t_2 + t_3$. We have $\Phi_t U \subset \Gamma_K$ for all $t \ge t_0$. This completes the proof. □

3. Basic reproduction number

Clearly, system (1.1) always has a unique infection-free steady state $(\bar{u}_1(x), 0, 0)$. For simplicity, we denote

$$\beta_d(x) = \frac{\partial g(x, \bar{u}_1(x), 0)}{\partial u_2}, \quad \beta_i(x) = \frac{\partial f(x, \bar{u}_1(x), 0)}{\partial u_3}. \tag{3.1}$$

Linearizing the system (1.1) for $(u_2(x,t), u_3(x,t))$ at $(\bar{u}_1(x), 0, 0)$ gives the following cooperative system for the infected cells and free virus,

$$\begin{aligned} \frac{\partial u_2(x,t)}{\partial t} &= \beta_i(x)u_3(x,t) + \beta_d(x)u_2(x,t) - b(x)u_2(x,t), \\ \frac{\partial u_3(x,t)}{\partial t} &= d\Delta u_3(x,t) + k(x)u_2(x,t) - m(x)u_3(x,t), \end{aligned} \tag{3.2}$$

for $x \in \Omega$ and $t > 0$. The suitable functional space for the above homogeneous linear differential system is $\mathbb{Y} := C(\bar{\Omega}, \mathbb{R}^2)$. The associated linear operator of this system can be decomposed as $A = F + B$, where

$$F = \begin{pmatrix} \beta_d(\cdot) & \beta_i(\cdot) \\ 0 & 0 \end{pmatrix}, \quad B = \begin{pmatrix} -b(\cdot) & 0 \\ k(\cdot) & d\Delta - m(\cdot) \end{pmatrix}.$$

The basic reproduction number R_0 is then defined as the spectral radius of $-FB^{-1}$, denoted by $\rho(-FB^{-1})$. In [31], a different decomposition is used: the cell-to-cell transmission rate β_d in the 11-entry of F was

misplaced in the 11-entry of B, which leads to a biologically meaningless definition of "basic reproduction number" when cell-to-cell transmission is strong. For illustration, considering the linearized homogeneous ordinary differential equations for viral transmission, the basic reproduction number should be defined as $\beta_d/b+\beta_i k/(mb)$, instead of $\beta_i k/[m(b-\beta_d)]$; note that the second quantity becomes negative when $\beta_d > b$.

Since B is resolvent-positive with $s(B) < 0$, F is positive and A is also resolvent-positive, it follows from [29, Theorem 3.5] that $R_0 - 1$ has the same sign as $s(A)$. Let e^{Bt} be the semigroup generated by B. Wang and Zhao [33] gave a biological interpretation of the next generation operator:

$$-FB^{-1} = \int_0^\infty Fe^{Bt}dt,$$

and proved local asymptotic stability of infection-free steady state under the condition $R_0 < 1$. Here, we shall prove global asymptotic stability of infection-free steady state under the condition $R_0 \leq 1$. Also, we will derive an equivalent formula for R_0 such that the direct and indirect transmission mechanisms are clearly separated in the expression. To reach this end, we need the following result.

Lemma 3.1. *Let* $F = \begin{pmatrix} F_{11} & F_{12} \\ 0 & 0 \end{pmatrix}$ *be a positive operator and* $B = \begin{pmatrix} -V_{11} & 0 \\ -V_{21} & d\Delta - V_{22} \end{pmatrix}$ *be a resolvent-positive operator with* $s(B) < 0$. *Then we have* $\rho(-FB^{-1}) = \rho(A_d + A_i)$, *where* $A_d = F_{11}V_{11}^{-1}$ *and* $A_i = -F_{12}(V_{22} - d\Delta)^{-1}V_{21}V_{11}^{-1}$.

Proof. Let $\psi = F\varphi$ and $\varphi = -B^{-1}\phi$. It is readily seen that $V_{11}\varphi_1 = \phi_1$ and $V_{21}\varphi_1 + (V_{22} - d\Delta)\varphi_2 = \phi_2$. Solving this system gives $\varphi_1 = V_{11}^{-1}\phi_1$ and $\varphi_2 = (V_{22} - d\Delta)^{-1}[\phi_2 - V_{21}V_{11}^{-1}\phi_1]$. Consequently, $\psi_1 = F_{11}V_{11}^{-1}\phi_1 + F_{12}(V_{22} - d\Delta)^{-1}[\phi_2 - V_{21}V_{11}^{-1}\phi_1]$ and $\psi_2 = 0$. Thus, we can rewrite

$$-FB^{-1}\begin{pmatrix} \phi_1 \\ \phi_2 \end{pmatrix} = \begin{pmatrix} A_1\phi_1 + A_2\phi_2 \\ 0 \end{pmatrix},$$

where $A_1 = F_{11}V_{11}^{-1} - F_{12}(V_{22} - d\Delta)^{-1}V_{21}V_{11}^{-1}$, and $A_2 = F_{12}(V_{22} - d\Delta)^{-1}$. By iteration, we have

$$(-FB^{-1})^n\begin{pmatrix} \phi_1 \\ \phi_2 \end{pmatrix} = \begin{pmatrix} A_1^n\phi_1 + A_1^{n-1}A_2\phi_2 \\ 0 \end{pmatrix}.$$

Thus, $\|A_1^n\| \leq \|(-FB^{-1})^n\| \leq \|A_1^{n-1}\|(\|A_1\| + \|A_2\|)$. By Gelfand's formula and squeeze theorem, we obtain $\rho(-FB^{-1}) = \rho(A_1)$. The lemma is proved since $A_1 = A_d + A_i$. □

By Lemma 3.1, we have another expression of the basic reproduction number:

$$R_0 = \rho(A_d + A_i), \tag{3.3}$$

where $A_d = \beta_d/b$ is the next generation operator for direct transmission, and $A_i = \beta_i(m - d\Delta)^{-1}k/b$ is the next generation operator for indirect transmission. Remark that the integral operator $(m - d\Delta)^{-1}$ and the multiplication operator k/b do not commute. In the absence of indirect transmission, the basic reproduction number for the direct transmission is simply given as

$$R_0^d = \rho(A_d) = \max_{x\in\bar{\Omega}} \frac{\beta_d(x)}{b(x)}. \tag{3.4}$$

On the other hand, if only indirect transmission is taken into consideration, the corresponding basic reproduction number is

$$R_0^i = \rho(A_i) = \rho(\beta_i(m - d\Delta)^{-1}k/b) = \sup_{\phi\in H^1(\Omega),\phi\neq 0} \frac{\int_\Omega \beta_i(x)k(x)\phi^2(x)/b(x)dx}{\int_\Omega d|\nabla\phi(x)|^2 + m(x)\phi^2(x)dx}, \tag{3.5}$$

where the last equation is obtained by a standard variational method. It is obvious that $R_0 \leq R_0^d + R_0^i$. The equality holds if $\beta_d(x)/b(x)$ is independent of x. From the variational formula (3.5), it is also observed that R_0^i is a decreasing function of the diffusion coefficient d. However, since there is no simple variational formula for R_0, it is a nontrivial result that R_0 is also a decreasing function of d. Actually, we use the ideas in the proofs of [1, Lemma 2.2] and [14, Lemma 3.1] to find the following properties for the basic reproduction number.

Theorem 3.2. *The basic reproduction number R_0 given in (3.3) is a principal eigenvalue of A_d+A_i associated with a positive eigenfunction. If we treat d as an independent variable in $(0,\infty)$, then R_0 is a decreasing function of d. As $d\to 0$, we have*

$$R_0 \to \overline{R}_0 := \max_{x\in\bar{\Omega}} \left[\frac{\beta_d(x)}{b(x)} + \frac{\beta_i(x)k(x)}{b(x)m(x)}\right]. \tag{3.6}$$

As $d\to\infty$, we have

$$R_0 \to \underline{R}_0, \tag{3.7}$$

where $\underline{R}_0 > R_0^d$ is the unique solution of the equation

$$\int_\Omega -m(x) + \frac{k(x)\beta_i(x)/b(x)}{\underline{R}_0 - \beta_d(x)/b(x)}dx = 0. \tag{3.8}$$

Proof. Since $A_i = \beta_i(m - d\Delta)^{-1}k/b$ is compact and positive, we have

$$\rho_e(A_d + A_i) = \rho_e(A_d) = \max_{x\in\bar{\Omega}} \frac{\beta_d(x)}{b(x)} = \rho(A_d) < \rho(A_d + A_i),$$

where ρ_e and ρ are the essential spectral radius and spectral radius, respectively. The generalized Krein-Rutman Theorem [18] implies that $R_0 = \rho(A_d + A_i)$ is a principal eigenvalue of $A_d + A_i$ associated with a positive eigenfunction, denoted by $\phi(x)$. We then obtain

$$d\Delta\psi - m\psi + \frac{k\beta_i/b}{R_0 - \beta_d/b}\psi = 0, \tag{3.9}$$

where $\psi = \phi/\beta_i$. Now, we treat d as a variable, and denote φ to be the derivative of ψ with respect to d. Taking derivative on both sides of (3.9) gives

$$\Delta\psi + d\Delta\varphi - m\varphi + \frac{k\beta_i/b}{R_0 - \beta_d/b}\varphi - \frac{k\beta_i/b}{(R_0 - \beta_d/b)^2}R_0'\psi = 0, \tag{3.10}$$

where R_0' is the derivative of R_0 with respect to d. We then multiply (3.9) by φ and (3.10) by ψ, subtract the resulting equations, and integrate over Ω to obtain

$$R_0' \int_\Omega \frac{k\beta_i/b}{(R_0 - \beta_d/b)^2}\psi^2 dx = \int_\Omega \Delta\psi\cdot\psi dx = -\int_\Omega |\nabla\psi|^2 dx \leq 0.$$

Hence, $R_0' \leq 0$. Moreover, $R_0' = 0$ if and only if $\psi(x)$ is a nonzero constant function, if and only if the function $\beta_d/b + k\beta_i/(bm) \equiv R_0$ is independent of x.

It is clear that $R_0 \le \overline{R}_0$; otherwise $-m + \frac{k\beta_i/b}{R_0-\beta_d/b} < 0$ and the principal eigenvalue of $d\Delta - m + \frac{k\beta_i/b}{R_0-\beta_d/b}$ is negative, which contradicts to (3.9). So the limit of R_0 as $d \to 0$ exists. We claim that the limit is exactly $\overline{R}_0$. If not, then there exists $\varepsilon > 0$ such that $R_0 < \overline{R}_0 - 2\varepsilon$ for all $d > 0$. By continuity of coefficient functions, we may find a point $x_0 \in \Omega$ and a $\delta > 0$ such that $\beta_d(x)/b(x) + \beta_i(x)k(x)/[b(x)m(x)] > \overline{R}_0 - \varepsilon > R_0 + \varepsilon$ for all $x \in B_\delta(x_0)$. By compactness of continuous functions on a bounded domain, there exists $\varepsilon_0 > 0$ such that

$$-m(x) + \frac{k(x)\beta_i(x)/b(x)}{R_0 - \beta_d(x)/b(x)} > \varepsilon_0$$

for all $x \in B_\delta(x_0)$ and $d > 0$. Let $\mu > 0$ be principal eigenvalue of $-\Delta$ on $B_\delta(x_0)$ with Neumann boundary condition and ψ_- the corresponding eigenfunction. We may normalize ψ_- such that $\psi_-(x) \le 1$ for all $x \in B_\delta(x_0)$. On the other hand, we choose a $d \in (0, \varepsilon_0/\mu)$ and normalize the eigenfunction for (3.9) as

$$\psi_+(x) = \frac{\psi(x)}{\inf_{x\in B_\delta(x_0)} \psi(x)}.$$

Obviously, $\psi_+(x) \ge 1 \ge \psi_-(x)$ for all $x \in B_\delta(x_0)$. Moreover, we have $-\Delta\psi_+(x) > \frac{\varepsilon_0}{d}\psi_+(x)$, and $-\Delta\psi_-(x) = \mu\psi_-(x) < \frac{\varepsilon_0}{d}\psi_-(x)$. Hence, ψ_+ and ψ_- are the super- and sub-solutions of the elliptic operator $-\Delta - \varepsilon_0/d$ with Neumann boundary condition. Thus, an eigenfunction exists and $\varepsilon_0/d > \mu$ is an eigenvalue for the Laplace operator $-\Delta$ on $B_\delta(x_0)$ with Neumann boundary condition, which contradicts to the assumption that μ is the principal eigenvalue. Therefore, we have proved $R_0 \to \overline{R}_0$ as $d \to 0$.

To investigate the limit of R_0 as $d \to \infty$, we first note that $R_0 \ge R_0^d = \max_{x\in\Omega} \frac{\beta_d(x)}{b(x)}$ and thus such a limit $\underline{R}_0$ exists. We can find a sequence $d_n \to \infty$ and the corresponding eigenfunctions of (3.9) formulate a monotone sequence that tends to a nonzero constant function. Such a sequence can be constructed recursively using super- and sub-solutions technique, where a large constant function is regarded as the super-solution for (3.9) with any $d_n > 0$, and the eigenfunction corresponding to d_n is used as a sub-solution to find an eigenfunction of (3.9) with $d = d_{n+1}$. The limit function is a constant function because it is harmonic and satisfies Neumann boundary condition. For this sequence, we integrate (3.9) over Ω and take the limit $d_n \to \infty$ to obtain (3.8), which has a unique root in (R_0^d, ∞) because, the integral on the right-hand side is a decreasing function of $\underline{R}_0$, and it is positive near the left end point R_0^d and negative if $\underline{R}_0$ is sufficiently large. This completes the proof. □

A direct application of the above theorem is the following classification of viral infection environment.

Proposition 3.3.

(i) If $\beta_d(x) \ge b(x)$ for some $x \in \Omega$, then $R_0 > 1$. The disease will persist if the cell-to-cell transmission is strong at some point.

(ii) If $\beta_d(x)/b(x) + \beta_i(x)k(x)/[b(x)m(x)] \le 1$ for all $x \in \Omega$, then $R_0 \le 1$ and the environment is infection-free.

(iii) If $\beta_d(x) < b(x)$ for all $x \in \Omega$, and $\beta_d(x)/b(x) + \beta_i(x)k(x)/[b(x)m(x)] > 1$ for some $x \in \Omega$, we consider the following cases:

- *If $\int_\Omega \frac{\beta_i(x)k(x)}{b(x)-\beta_d(x)}dx > \int_\Omega m(x)dx$, then $R_0 > 1$ and the environment is favorable for the viral infection.*
- *If $\int_\Omega \frac{\beta_i(x)k(x)}{b(x)-\beta_d(x)}dx \le \int_\Omega m(x)dx$, then there exists a $d^* > 0$ such that $R_0 \le 1$ if $d \ge d^*$ and $R_0 > 1$ if $d < d^*$.*

We make some further biological interpretations of our mathematical results on basic reproduction number.

Remark 3.4.

(i) Recall that $R_0 = R_0^d + R_0^i$ if $\beta_d(x)/b(x)$ is a constant but $R_0 \le R_0^d + R_0^i$ in a general case. This means that spatial heterogeneity may reduce the joint impact of cell-free and cell-to-cell transmissions.
(ii) Since R_0 is a decreasing function of d, the spatial diffusion of virus will reduce the effect of viral infection.
(iii) When $d = 0$, there is no interaction between different locations, and the diffusion model reduces to a patch model (with infinitely many patches). As $d \to 0$, the basic reproduction number tends to $\overline{R}_0$, which is exactly the basic reproduction number for the patch model. So, the formula (3.6) gives a link between diffusion model and patch model.

4. Global stability of infection-free steady state

Note that [33, Theorem 3.1] only gives local asymptotic stability of infection-free steady state when $R_0 < 1$. To establish global asymptotic stability of infection-free steady state when $R_0 \le 1$, we shall construct a suitable Lyapunov functional and make use of LaSalle invariance principle. First, we will develop the following uniform approach to prove local asymptotic stability of infection-free steady state not only when $R_0 < 1$, but also for the critical case $R_0 = 1$.

Lemma 4.1. *Let A be the linear operator of the system (3.2) and e^{At} the semigroup generated by A. If $R_0 \le 1$, then $s(A) \le 0$ and $\lim_{t\to\infty} \frac{\ln \|e^{At}\|}{t} \le 0$. Actually, there exists $M > 0$ such that $\|e^{At}\| \le M$.*

Proof. By [29, Theorem 3.5], $R_0 - 1$ and $s(A)$ have the same sign. Thus, $s(A) \le 0$ if $R_0 \le 1$. On account of [4, Section 4.2], it suffices to show that $\lim_{t\to\infty} \frac{\ln \|\widehat{e^{At}}\|}{t} \le 0$, where $\|\widehat{e^{At}}\|$ denotes the distance of e^{At} from the set of compact linear operators in $\mathbb{Y}$; see [4, page 248]. Let $(u_2(x,t), u_3(x,t))$ be any solution of (3.2); namely,

$$\begin{pmatrix} u_2(\cdot,t) \\ u_3(\cdot,t) \end{pmatrix} = e^{At} \begin{pmatrix} u_2(\cdot,0) \\ u_3(\cdot,0) \end{pmatrix} = \begin{pmatrix} e^{(\beta_d - b)t} u_2(\cdot,0) + \int_0^t e^{(\beta_d - b)(t-s)} \beta_i u_3(\cdot,s) ds \\ e^{(d\Delta - m)t} u_3(\cdot,0) + \int_0^t e^{(d\Delta - m)(t-s)} k u_2(\cdot,s) ds \end{pmatrix},$$

where $e^{(d\Delta - m)t}$ is the compact semigroup generated by the operator $d\Delta - m$ with Neumann boundary condition. Clearly, the second component of e^{At} is compact for each $t > 0$; namely, the operator that maps $(u_2(\cdot,0), u_3(\cdot,0))^T$ to $u_3(\cdot,t)$ is compact. Since the limit of compact operators is also compact, we conclude that the operator that maps $(u_2(\cdot,0), u_3(\cdot,0))^T$ to $\int_0^t e^{(\beta_d - b)(t-s)} \beta_i u_3(\cdot,s) ds$ is also compact for all $t > 0$. It then follows that $\|\widehat{e^{At}}\| \le \|e^{(\beta_d - b)t}\|$. Since $R_0^d \le R_0 \le 1$, we have $\beta_d(x) \le b(x)$ for all $x \in \Omega$, which implies $\|e^{(\beta_d - b)t}\| \le 1$. Consequently, we obtain $\ln \|\widehat{e^{At}}\| \le 0$ for all $t > 0$, and $\lim_{t\to\infty} \frac{\ln \|\widehat{e^{At}}\|}{t} \le 0$. This together with $s(A) \le 0$ implies that the semigroup e^{At} is stable; i.e., $\|e^{At}\| \le M$ for some $M > 0$. □

Theorem 4.2. *If $R_0 \le 1$, then the infection-free steady state $(\bar{u}_1(x), 0, 0)^T$ for (1.1) is locally asymptotically stable.*

Proof. Given any small $\delta > 0$, we let $u(x,t)$ be any solution of (1.1) with initial profile such that $|u_1(x,0) - \bar{u}_1(x)| + |u_2(x,0)| + |u_3(x,0)| < \delta$. Define $v_1(x,t) = u_1(x,t)/\bar{u}_1(x) - 1$ which satisfies the equation

$$\frac{\partial v_1}{\partial t} = -\alpha v_1 - \frac{f(x,u_1,u_3) + g(x,u_1,u_2)}{\bar{u}_1},$$

where $\alpha(x,t) = -\frac{n(x,u_1(x,t))-n(x,\bar{u}_1(x))}{u_1(x,t)-\bar{u}_1(x)} > 0$ by $(\mathbf{H}_1)$. Since $v_1(x,0) \le \delta$, we observe from positiveness of f and g that $v_1(x,t) \le \delta$ for all $x \in \Omega$ and $t \ge 0$. Let $\underline{\alpha} > 0$ be the minimum of $-\frac{\partial n(x,u_1)}{\partial u_1}$ for $x \in \bar{\Omega}$ and $0 \le u_1 \le K_1(1+\delta)$. Recall that $K_1 > \max_{x\in\Omega} \bar{u}_1(x)$ and $n(x,u_1)$ is decreasing in u_1. We then obtain $v_1(x,t) \le \delta e^{-\underline{\alpha}t}$ for all $x \in \Omega$ and $t \ge 0$. That is, $u_1(x,t) \le \hat{u}_1(x,t) := (1+\delta e^{-\underline{\alpha}t})\bar{u}_1(x)$. It then follows from $(\mathbf{H}_2)$ that

$$f(x,u_1,u_3) \le f(x,\hat{u}_1,u_3) \le \frac{\partial f(x,\hat{u}_1,0)}{\partial u_3}u_3, \quad g(x,u_1,u_3) \le g(x,\hat{u}_1,u_2) \le \frac{\partial g(x,\hat{u}_1,0)}{\partial u_2}u_2.$$

We obtain from the definition of β_d and β_i in (3.1) and the second equation of (1.1) that

$$\frac{\partial u_2}{\partial t} \le \beta_i u_3 + (\beta_d - b)u_2 + (\frac{\partial f(x,\hat{u}_1,0)}{\partial u_3} - \frac{\partial f(x,\bar{u}_1,0)}{\partial u_3})u_3 + (\frac{\partial g(x,\hat{u}_1,0)}{\partial u_2} - \frac{\partial g(x,\bar{u}_1,0)}{\partial u_2})u_2.$$

By comparison principle, we have

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

where e^{At} is the solution semigroup of the linear system (3.2) with A being the infinitesimal generator, and $h = (\frac{\partial f(x,\hat{u}_1,0)}{\partial u_3} - \frac{\partial f(x,\bar{u}_1,0)}{\partial u_3})u_3 + (\frac{\partial g(x,\hat{u}_1,0)}{\partial u_2} - \frac{\partial g(x,\bar{u}_1,0)}{\partial u_2})u_2$. Denote

$$\bar{f} = \max_{\substack{x\in\bar{\Omega} \\ 0\le u_1\le K_1}} |\frac{\partial^2 f(x,u_1,0)}{\partial u_1 \partial u_3}|, \quad \bar{g} = \max_{\substack{x\in\bar{\Omega} \\ 0\le u_1\le K_1}} |\frac{\partial^2 g(x,u_1,0)}{\partial u_1 \partial u_2}|.$$

We then have $|h(x,s)| \le \delta K_1 e^{-\underline{\alpha}s}(\bar{f}u_3(x,s) + \bar{g}u_2(x,s))$. Let

$$E(t) = \max\{\max_{x\in\Omega} u_2(x,t), \max_{x\in\Omega} u_3(x,t)\}.$$

It follows from $\|e^{At}\| \le M$ that

$$E(t) \le \delta M + \delta M K_1(\bar{f}+\bar{g}) \int_0^t e^{-\underline{\alpha}s}E(s)ds.$$

By Gronwall's inequality, we obtain

$$E(t) \le \delta M e^{\int_0^t \delta M K_1(\bar{f}+\bar{g})e^{-\underline{\alpha}s}ds} \le \delta M e^{\delta M K_1(\bar{f}+\bar{g})/\underline{\alpha}}$$

for all $t \ge 0$. It then follows from $(\mathbf{H}_2)$ that

$$f(x,u_1,u_3) \le f(x,K_1(1+\delta),u_3) \le \hat{f}u_3 \le \delta M \hat{f} e^{\delta M K_1(\bar{f}+\bar{g})/\underline{\alpha}},$$

and

$$g(x,u_1,u_2) \le g(x,K_1(1+\delta),u_2) \le \hat{g}u_2 \le \delta M \hat{g} e^{\delta M K_1(\bar{f}+\bar{g})/\underline{\alpha}},$$

where

$$\hat{f} = \max_{x\in\bar{\Omega}} \frac{\partial f(x, K_1(1+\delta), 0)}{\partial u_3}, \quad \hat{g} = \max_{x\in\bar{\Omega}} \frac{\partial g(x, K_1(1+\delta), 0)}{\partial u_2}.$$

Substituting the above inequalities into the first equation of (1.1) yields

$$\frac{\partial u_1(x,t)}{\partial t} \geq n(x, u_1(x,t)) - \delta M(\hat{f}+\hat{g}) e^{\delta M K_1(\bar{f}+\bar{g})/\underline{\alpha}}.$$

By comparison principle, we have $u_1(x,t) \geq \bar{u}_1^\delta(x)$ where $\bar{u}_1^\delta(x)$ is the solution of

$$n(x, \bar{u}_1^\delta(x)) = \delta M(\hat{f}+\hat{g}) e^{\delta M K_1(\bar{f}+\bar{g})/\underline{\alpha}}.$$

Since the right-hand side of the above equality is of order $O(\delta)$, such solution exists for sufficiently small δ and $\max_{x\in\Omega} |\bar{u}_1^\delta(x) - \bar{u}_1(x)| = O(\delta)$ as $\delta \to 0$. Recall that $u_1(x,t)$ is bounded above by $\hat{u}_1(x,t) \leq (1+\delta)\bar{u}_1(x)$. We conclude that $\|u_1(\cdot,t) - \bar{u}_1(\cdot)\| + \|u_2(\cdot,t)\| + \|u_2(\cdot,t)\| = O(\delta)$ as $\delta \to 0$, thus proving local stability of infection-free steady state under the condition $R_0 \leq 1$. □

We now construct a Lyapunov functional and use LaSalle invariance principle to establish global asymptotic stability of infection-free steady state. By comparison principle, $\limsup_{t\to\infty} u_1(x,t) \leq \bar{u}_1(x)$. However, it is not necessary that $u_1(x,t) \leq \bar{u}_1(x)$ for sufficiently large t. Special care is needed to be taken in the construction of Lyapunov functional.

Theorem 4.3. *If $R_0 \leq 1$, then the infection-free steady state $(\bar{u}_1(x), 0, 0)^T$ for (1.1) is globally asymptotically stable.*

Proof. We first define a subset $D = \{\phi \in \mathbb{X}^+ : \phi(x) \leq \bar{u}_1(x)\}$ and prove that for any initial profile $\phi \in \mathbb{X}^+$, the omega limit set of ϕ is contained in D. Given any $x \in \Omega$, it follows from the first equation of (1.1) and a simple contradiction argument that if $u_1(x,t_0) \leq \bar{u}_1(x)$ for some $t_0 \geq 0$, then $u_1(x,t) \leq \bar{u}_1(x)$ for all $t \geq t_0$. Now, we divide the domain Ω into two sub-domains $\Omega_\pm$, where

$$\Omega_+ := \{x \in \Omega : u_1(x,t) > \bar{u}_1(x) \text{ for all } t \geq 0\},$$
$$\Omega_- := \{x \in \Omega : u_1(x,t) \leq \bar{u}_1(x) \text{ for some } t \geq 0\}.$$

It is obvious that Ω_- is closed in Ω, and there exists $t_0 \geq 0$ that $u_1(x,t) \leq \bar{u}_1(x)$ for all $x \in \Omega_-$. Without loss of generality, we may assume $t_0 = 0$.

For any $x \in \Omega_+$, it follows from $(\mathbf{H}_1)$ that $n(x, u_1(x,t)) < 0$ for all $t \geq 0$. Thus, the first equation of (1.1) implies that $u_1(x,t)$ is a decreasing function in t. Since $u_1(x,t) \geq \bar{u}_1(x)$, the limit of $u_1(x,t)$ as $t \to \infty$ exists, and $u_1(x,\infty) \geq \bar{u}_1(x)$. If the strict inequality holds, then we obtain from $(\mathbf{H}_1)$ and the first equation of (1.1) that

$$0 = \lim_{t\to\infty} \frac{\partial u_1(x,t)}{\partial t} \leq \lim_{t\to\infty} n(x, u_1(x,t)) \leq n(x, u_1(x,\infty)) < 0,$$

a contradiction. Hence, we have $u_1(x,t) \to \bar{u}_1(x)$ as $t \to \infty$. This implies that the omega limit set of ϕ is contained in D.

Next, we consider the solution map restricted on the invariant domain D and show that the infection-free steady state $(\bar{u}_1(x), 0, 0)^T$ attracts all initial profiles in D. To achieve this, we define a Lyapunov functional

$$V(\phi_1, \phi_2, \phi_3) = \frac{1}{2} \int_\Omega \frac{k(x)}{\beta_i(x)} \phi_2^2(x) + \phi_3^2(x) dx.$$

Taking the derivative along the solution, we obtain

$$\frac{d}{dt}V(u_1,u_2,u_3)=\int_\Omega \frac{k}{\beta_i}u_2[f(x,u_1,u_3)+g(x,u_1,u_2)-bu_2]+u_3(d\Delta u_3+ku_2-mu_3)dx.$$

Since $u_1(x,t)\le \bar{u}_1(x)$, it is readily seen from $(\mathbf{H}_2)$ that $f(x,u_1,u_3)\le f(x,\bar{u}_1,u_3)\le \beta_i u_3$ and $g(x,u_1,u_2)\le g(x,\bar{u}_1,u_2)\le \beta_d u_2$; see the definitions of β_d and β_i in (3.1). A simple calculation gives

$$\begin{aligned}\frac{d}{dt}V(u_1,u_2,u_3)&\le \int_\Omega -(k/\beta_i)(b-\beta_d)u_2^2+2ku_2u_3+u_3(d\Delta u_3-mu_3)dx\\&\le \int_\Omega \frac{k\beta_i}{b-\beta_d}u_3^2-mu_3^2-d|\nabla u_3|^2dx,\end{aligned}$$

where we have made use of the fact that $b>\beta_d$ (since $R_0^d<\underline{R}_0\le R_0\le 1$) and

$$-\frac{k(b-\beta_d)}{\beta_i}u_2^2+2ku_2u_3=-\frac{k(b-\beta_d)}{\beta_i}(u_2-\frac{\beta_i u_3}{b-\beta_d})^2+\frac{k\beta_i u_3^2}{b-\beta_d}\le \frac{k\beta_i u_3^2}{b-\beta_d}.$$

We claim

$$\int_\Omega \frac{k\beta_i}{b-\beta_d}\phi^2\le \int_\Omega m\phi^2+d|\nabla\phi|^2dx \tag{4.1}$$

for any $\phi\in H^1(\Omega)$. Once this is proved, it then follows that the derivative of Lyapunov functional $V'\le 0$. Let $\mathcal{K}$ be an invariant set on which $V'=0$. We observe that $\mathcal{K}$ is a singleton $\{(\bar{u}_1(x),0,0)\}$. This is because for any $(\phi_1,\phi_2,\phi_3)\in\mathcal{K}$, $V'=0$ implies that all inequalities in deriving $V'\le 0$ should be equal, and thus $(\phi_1(x),\phi_2(x),\phi_3(x))=(\bar{u}_1(x),0,0)$. Note that the infection-free steady state is the unique point in the largest invariant set on which $V'=0$. By LaSalle invariance principle, this steady state is globally attractive in D.

We now prove the claim (4.1). For this purpose, we shall make another decomposition of the linear operator A associated with the linear system (3.2): $A=F_1+B_1$, where

$$F_1=\begin{pmatrix}0&\beta_i(\cdot)\\0&0\end{pmatrix},\quad B_1=\begin{pmatrix}-[b(\cdot)-\beta_d(\cdot)]&0\\k(\cdot)&d\Delta-m(\cdot)\end{pmatrix}. \tag{4.2}$$

Since $b>\beta_d$ (by $R_0^d<R_0\le 1$), the operator B_1 is still resolvent-positive with $s(B_1)<0$. An application of [29, Theorem 3.5] together with $R_0\le 1$ yields $s(A)\le 0$ and $\rho(-F_1B_1^{-1})\le 1$. By [33, Theorem 3.3 (i)] or a simple direct calculation, we have

$$\rho(-F_1B_1^{-1})=\rho(\beta_i(m-d\Delta)^{-1}k(b-\beta_d)^{-1})=\sup_{\phi\in H^1(\Omega),\phi\neq 0}\frac{\int_\Omega \frac{\beta_i(x)k(x)\phi^2(x)}{b(x)-\beta_d(x)}dx}{\int_\Omega d|\nabla\phi(x)|^2+m(x)\phi^2(x)dx}.$$

The claim (4.1) follows immediately from the above variational representation.

Finally, we apply [36, Lemma 1.2.1] to find that the omega limit set of any initial profile $\phi\in\mathbb{X}^+$ is internally chain transitive. Since this omega limit set is contained in D and the infection-free steady state attracts D, it follows from [36, Theorem 1.2.1] that the infection-free steady state is globally attractive in $\mathbb{X}^+$. On account of local stability result in Theorem 4.2, this steady state is globally asymptotically stable in $\mathbb{X}^+$. The proof is completed. □

5. Global dynamic of system (1.1) when $R_0 > 1$

5.1. Persistence of infection

It follows from Proposition 2.2 and Proposition 2.3 that the semiflow Θ_t of system (1.1) is point dissipative and the orbit of any bounded set is also bounded. To apply [7, Theorem 2.1], we have to show that Θ_t is asymptotically smooth. But Θ_t is not compact because the first two equations in (1.1) have no diffusion terms. Here we shall introduce the Kuratowski measure of the noncompactness defined by [6]

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

We set $\kappa(U) = \infty$ whenever U is unbounded. Clearly, $\kappa(U) = 0$ if and only if U is precompact. Let

$$G(u_1, u_2, u_3) = \begin{pmatrix} n(x, u_1) - f(x, u_1, u_3) - g(x, u_1, u_2) \\ f(x, u_1, u_3) + g(x, u_1, u_2) - b(x)u_2 \end{pmatrix}$$

be the vector field corresponding to the first two equations of (1.1). The Jacobian of G with respect to (u_1, u_2) is calculated as

$$G_{12} := \frac{\partial G(u_1, u_2, u_3)}{\partial(u_1, u_2)} = \begin{pmatrix} \partial(n - f - g)/\partial u_1 & -\partial g/\partial u_2 \\ \partial(f + g)/\partial u_1 & \partial g/\partial u_2 - b \end{pmatrix}.$$

We obtain a similar lemma as in [11, Lemma 4.1] and [30, Lemma 2.5].

Lemma 5.1. *Θ_t is asymptotically smooth and κ-contracting if there exists a $r > 0$ such that*

$$v^T G_{12} v \leq -r v^T v, \text{ for all } v \in \mathbb{R}^2, \ x \in \bar{\Omega}, \ u \in \Gamma_K. \tag{5.1}$$

Proof. Actually, one can use a similar proof in [11, Lemma 4.1] to show that Θ_t is asymptotically compact on any closed bounded set U for which $TU \subset U$. It then follows from [24, Lemma 23.1 (2)] that the omega limit set $\omega(U)$ is nonempty, compact and invariant, and attracts U. This proves asymptotic smoothness of Θ_t. On account of [15, Lemma 2.1 (b)], we have

$$\kappa(\Theta_t U) \leq \kappa(\omega(U)) + \delta(\Theta_t U, \omega(U)) = \delta(\Theta_t U, \omega(U)),$$

where $\delta(\Theta_t U, \omega(U))$ is the distance from $\Theta_t U$ to $\omega(U)$, which tends to zero as $t \to \infty$. Therefore, we prove that Θ_t is κ-contracting. □

The following result is a simple application of [7, Theorem 2.1].

Theorem 5.2. *Assume (5.1) holds. (1.1) admits a connected global attractor in $\mathbb{X}^+$.*

Remark 5.3. A sufficient condition for (5.1) is that

$$(\mathbf{H}_3) \ \ \frac{\partial g(x,u_1,u_2)}{\partial u_2} < \frac{\partial g(x,u_1,u_2)}{\partial u_1} + \frac{\partial f(x,u_1,u_3)}{\partial u_1} < \underline{b} \text{ for all } u \in \Gamma_K.$$

Denote $\mathcal{Q}_t : \mathbb{Y} \to \mathbb{Y}$ to be the solution semiflow associated with the linear system (3.2); that is,

$$\mathcal{Q}_t \phi = (u_2(\cdot, t, \phi), u_3(\cdot, t, \phi)) \ \text{ for } \ \phi \in \mathbb{Y} := C(\bar{\Omega}, \mathbb{R}^2), \ t \geq 0.$$

It is clear that $\mathcal{Q}_t$ is a positive C_0-semigroup on $\mathbb{Y}$, and its infinitesimal generator $A = F + B$ is closed and resolvent positive.

Lemma 5.4. *If $R_0 > 1$ and $(\boldsymbol{H}_3)$ holds, then $s(A) > 0$ is the principal eigenvalue of the eigenvalue problem*

$$\begin{aligned}
&\beta_i(x)\phi_3 + \beta_d(x)\phi_2 - b(x)\phi_2 = \lambda\phi_2, \quad && x \in \Omega,\\
&d\Delta\phi_3 + k(x)\phi_2 - m(x)\phi_3 = \lambda\phi_3, && x \in \Omega,\\
&\tfrac{\partial\phi_3}{\partial\nu} = 0, && x \in \partial\Omega,
\end{aligned}$$

and there is a strongly positive eigenfunction associated with $s(A)$.

Proof. It follows from [29, Theorem 3.5] that $R_0 - 1$ has the same sign as $s(A)$, which implies that $s(A) > 0$ if $R_0 > 1$. Define linear operators $L(t)$ and $N(t)$ on $\mathbb{Y}$ as

$$\begin{aligned}
L(t)\phi &= (e^{-(b(\cdot)-\beta_d(\cdot))t}\phi_2, 0),\\
N(t)\phi &= \left(\int_0^t e^{-(b(\cdot)-\beta_d(\cdot))(t-s)}\beta_i(\cdot)u_3(\cdot,s,\phi)ds,\ u_3(\cdot,t,\phi)\right)
\end{aligned}$$

for any $\phi = (\phi_1, \phi_2) \in \mathbb{Y}$. It follows from $(\mathbf{H}_3)$ that $b(x) > \beta_d(x)$ for all $x \in \bar{\Omega}$; namely, $q := \min_{x\in\bar{\Omega}}\{b(x) - \beta_d(x)\} > 0$. In view of the definition of $L(t)$, we have

$$\|L(t)\| = \sup_{\phi\in\mathbb{Y}} \frac{\|L(t)\phi\|}{\|\phi\|} \le \sup_{\phi\in\mathbb{Y}} \frac{\|e^{-(b(\cdot)-\beta_d(\cdot))t}\phi_2\|}{\|\phi\|} \le \sup_{\phi\in\mathbb{Y}} \frac{\|e^{-qt}\phi_2\|}{\|\phi\|} \le e^{-qt}.$$

Let $T_3(t) = e^{t(d\Delta - m)}$ be the semigroup associated with $d\Delta - m(\cdot)$ subject to Neumann boundary condition. Then $T_3(t)$ is compact for any $t > 0$, which together with the boundedness of $\mathcal{Q}_t$, implies that $N(t)$ is compact for any $t > 0$. Let U be any bounded set in $\mathbb{Y}$. We have $\kappa(N(t)U) = 0$ for any $t > 0$ since $N(t)U$ is precompact. Consequently,

$$\kappa(\mathcal{Q}_t U) \le \kappa(L(t)U) + \kappa(N(t)U) \le \|L(t)\|\kappa(U) \le e^{-qt}\kappa(U) \quad \text{for any} \quad t > 0.$$

Thus, we obtain

$$\rho_e(\mathcal{Q}_t) \le e^{-qt} < 1 \le e^{s(A)t} = \rho(\mathcal{Q}_t), \quad \text{for all} \quad t > 0,$$

where $\rho_e(\mathcal{Q}_t)$ and $\rho(\mathcal{Q}_t)$ are the essential spectral radius and spectral radius of $\mathcal{Q}_t$, respectively. Meanwhile, $\mathcal{Q}_t$ is a strongly positive and bounded operator on $\mathbb{Y}$. It follows from the generalized Krein-Rutman Theorem [18] that $s(A)$ is the principal eigenvalue associated with a strictly positive eigenfunction. □

To establish the existence of the chronic-infection steady state, we first apply the permanence theorem in [28, Theorem 3] to obtain the following persistence result.

Theorem 5.5. *If $R_0 > 1$ and $(\boldsymbol{H}_3)$ holds, then system (1.1) is uniformly persistent in $\mathbb{X}^+$ in the sense that there exists an $\epsilon > 0$ such that for any $\phi \in \mathbb{X}^+$ with $\phi_j \not\equiv 0$ for all $j = 2, 3$, we have*

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

Moreover, system (1.1) admits at least one chronic-infection steady state $(u_1^*(x), u_2^*(x), u_3^*(x))$.

Proof. We need to validate all conditions in [7, Theorem 4.2]. Denote

$$\mathbb{X}_0 := \{\phi = (\phi_1, \phi_2, \phi_3) \in \mathbb{X}^+ : \ \phi_2(\cdot) \not\equiv 0 \text{ and } \phi_3(\cdot) \not\equiv 0\}$$

and

$$\partial\mathbb{X}_0 := \mathbb{X}^+\backslash\mathbb{X}_0 = \{\phi = (\phi_1, \phi_2, \phi_3) \in \mathbb{X}^+ : \ \phi_2(\cdot) \equiv 0 \text{ or } \phi_3(\cdot) \equiv 0\}.$$

It is obvious that $\mathbb{X}_0 \cap \partial\mathbb{X}_0 = \emptyset$, $\mathbb{X}^+ = \mathbb{X}_0 \cup \partial\mathbb{X}_0$, $\mathbb{X}_0$ is open and dense in $\mathbb{X}^+$, and $\Theta_t\partial\mathbb{X}_0 \subseteq \partial\mathbb{X}_0$. We shall also prove that $\Theta_t\mathbb{X}_0 \subseteq \mathbb{X}_0$, that is, $\mathbb{X}_0$ is positively invariant with respect to Θ_t. In fact, let $\phi = (\phi_1, \phi_2, \phi_3) \in \mathbb{X}_0$ such that $\phi_2 \not\equiv 0$ and $\phi_3 \not\equiv 0$. It follow from non-negativeness of the solution $(u_1(x,t), u_2(x,t), u_3(x,t))$ and the third equation of (1.1) that $\partial u_3(x,t)/\partial t \geq d\Delta u_3(x,t) - m(x)u_3(x,t)$. Thus, $u_3(x,t)$ is an upper solution of

$$\begin{aligned}
&\tfrac{\partial w(x,t)}{\partial t} = d\Delta w(x,t) - m(x)w(x,t), && x \in \Omega, t > 0,\\
&\tfrac{\partial w(x,t)}{\partial \nu} = 0, && x \in \partial\Omega, \ t > 0,\\
&w(x,0) = \phi_3 \not\equiv 0, && x \in \Omega.
\end{aligned}$$

By maximum principle and comparison principle, we have $u_3(x,t) \geq w(x,t) > 0$ for all $x \in \bar{\Omega}$ and $t > 0$. Moreover, from second equation of (1.1), we have

$$u_2(x,t) = e^{-b(x)t}\phi_2 + \int_0^t e^{-b(x)(t-s)}\left(f(x, u_1(x,s), u_3(x,s)) + g(x, u_1(x,s), u_2(x,s))\right) ds, \tag{5.2}$$

which, together with the positiveness of $u_1(x,t)$ (in Proposition 2.2) and $u_3(x,t)$, implies that $u_3(x,t) > 0$ for all $x \in \bar{\Omega}$ and $t > 0$. Therefore, $\Theta_t\mathbb{X}_0 \subseteq \mathbb{X}_0$.

Now, we let $\omega(\phi)$ be the omega limit set of the orbit $\gamma^+(\phi) := \bigcup_{t\geq 0}\{\Theta_t\phi\}$, and denote

$$M_\partial := \{\phi \in \partial\mathbb{X}_0 : \Theta_t\phi \in \partial\mathbb{X}_0, \quad \text{for all} \ \ t \geq 0\}.$$

We need to prove $\omega(\phi) = \{(\bar{u}_1(x), 0, 0)\}$ for all $\phi \in M_\partial$. This is true if we can show that $M_\partial \subseteq \{(\phi_1, 0, 0) : \phi_1 \in C(\bar{\Omega}, \mathbb{R}_+)\}$. If, to the contrary, there exists $\psi = (\psi_1, \psi_2, \psi_3) \in M_\partial$ but $\psi \notin \{(\phi_1, 0, 0) : \phi_1 \in C(\bar{\Omega}, \mathbb{R}_+)\}$. There are two cases to be considered: (i) $\psi_2 \equiv 0$ and $\psi_3 \not\equiv 0$; (ii) $\psi_2 \not\equiv 0$ and $\psi_3 \equiv 0$. For case (i), it follows from the proof of $\Theta_t\mathbb{X}_0 \subseteq \mathbb{X}_0$ that $u_i(x,t) > 0$ for all $x \in \bar{\Omega}$ and $t > 0$ with $i = 1, 2$. Thus, we have $\Theta_t\psi \in \mathbb{X}_0$ for all $t > 0$, which contradicts the definition of M_∂. For case (ii), it follows from (5.2) that $u_2(\cdot, t) \not\equiv 0$ for all $t > 0$. In view of $\phi \in C(\bar{\Omega}, \mathbb{R}_+)$ and Proposition 2.2, we obtain that $u_1(x,t) > 0$ for all $x \in \bar{\Omega}$ and $t > 0$. From the third equation of (1.1), we have

$$u_3(\cdot, t) = T_3(t)\psi_3 + \int_0^t T_3(t-s)k(\cdot)u_2(\cdot, s)ds,$$

where $T_3(t)$ is the semigroup associated with $d\Delta - m(\cdot)$ subject to Neumann boundary condition. Thus, $u_3(x,t) > 0$ for all $x \in \bar{\Omega}$ and $t > 0$. It then follows from (5.2) that $u_2(x,t) > 0$ for all $x \in \bar{\Omega}$ and $t > 0$. Again, we obtain $\Theta_t\psi \in \mathbb{X}_0$ for $t > 0$, a contradiction to the fact that $\psi \in M_\partial$. Therefore, $\omega(\phi) = \{(\bar{u}_1(x), 0, 0)\}$ for all $\phi \in M_\partial$.

Define a continuous function $\varrho : \mathbb{X}^+ \to [0, \infty)$ by

$$\varrho(\phi) = \min\{\phi_i(x) : x \in \bar{\Omega}, i = 2, 3\} \ \ \text{for} \ \ \phi \in \mathbb{X}^+.$$

Note that $\varrho(\Theta_t\phi) > 0$ for all $\phi \in \varrho^{-1}(0, \infty) \cup (\mathbb{X}_0 \cap \varrho^{-1}(0))$. Thus, $\varrho(x)$ is a generalized distance function for the semiflow Θ_t; see [28]. Denote $W^s((\bar{u}_1(x), 0, 0))$ as the stable manifold of $(\bar{u}_1(x), 0, 0)$. We shall verify that $W^s((\bar{u}_1(x), 0, 0)) \cap \varrho^{-1}(0, \infty) = \emptyset$. It suffices to show that there exists a $\delta > 0$ such that

$$\limsup_{t\to\infty}\|\Theta_t\phi-(\bar{u}_1(x),0,0)\|\geq\delta \quad \text{for any} \quad \phi\in\varrho^{-1}(0,\infty).$$

If not, then for any $\delta>0$, there exists $\tilde{\phi}=(\tilde{\phi}_1,\tilde{\phi}_2,\tilde{\phi}_3)\in\varrho^{-1}(0,\infty)$ such that

$$\limsup_{t\to\infty}\|\Theta_t\tilde{\phi}-(\bar{u}_1(x),0,0)\|<\delta.$$

Here, $\tilde{\phi}_1\geq 0$, $\tilde{\phi}_2>0$ and $\tilde{\phi}_3>0$ for all $x\in\Omega$, and $\Theta_t\tilde{\phi}=(u_1(\cdot,t,\tilde{\phi}),u_2(\cdot,t,\tilde{\phi}),u_3(\cdot,t,\tilde{\phi}))$. Hence, there exists a $\tilde{t}>0$ such that $u_1(\cdot,t,\tilde{\phi})>\bar{u}_1(x)-\delta$ and $u_i(\cdot,t,\tilde{\phi})<\delta$ $(i=2,3)$ for all $t\geq\tilde{t}$. Moreover, for $t\geq\tilde{t}$, $(u_2(x,t,\tilde{\phi}),u_3(x,t,\tilde{\phi}))$ is an upper solution of the following system

$$\begin{aligned}
&\tfrac{\partial w_2(x,t)}{\partial t}=\eta_i(x)w_3(x,t)+\eta_d(x)w_2(x,t)-b(x)w_2(x,t), && x\in\Omega,\ t>\tilde{t},\\
&\tfrac{\partial w_3(x,t)}{\partial t}=d\Delta w_3(x,t)+k(x)w_2(x,t)-m(x)w_3(x,t), && x\in\Omega,\ t>\tilde{t},\\
&\tfrac{\partial w_3(x,t)}{\partial \nu}=0, && x\in\partial\Omega,\ t>\tilde{t},\\
&w_2(x,0)\leq u_2(x,\tilde{t},\tilde{\phi}),\ w_3(x,0)\leq u_3(x,\tilde{t},\tilde{\phi}), && x\in\Omega,
\end{aligned}\tag{5.3}$$

where $\eta_i=\partial f(x,\bar{u}_1(x)-\delta,\delta)/\partial u_3$ and $\eta_d=\partial g(x,\bar{u}_1(x)-\delta,\delta)/\partial u_2$. Denote $\lambda_0(\delta)$ as the principle eigenvalue of the eigenvalue problem

$$\begin{aligned}
&d\Delta\psi-m(x)\psi+\tfrac{k(x)\eta_i(x)}{b(x)-\eta_d(x)}\psi=\lambda\psi, && x\in\Omega,\\
&\tfrac{\partial\psi}{\partial\nu}=0, && x\in\partial\Omega.
\end{aligned}$$

It follows from [29, Theorem 3.5] that $R_0>1$ implies $\lambda_0(0)=s(A)>0$. Since $\lambda_0(\delta)$ is a continuous in δ, we can choose $\delta>0$ sufficient small such that $\lambda_0(\delta)>0$. Similar as in the proof of Lemma 5.4, one can show that the eigenvalue problem

$$\begin{aligned}
&\eta_i(x)\phi_3+\eta_d(x)\phi_2-b(x)\phi_2=\lambda\phi_2, && x\in\Omega,\\
&d\Delta\phi_3+k(x)\phi_2-m(x)\phi_3=\lambda\phi_3, && x\in\Omega,\\
&\tfrac{\partial\phi_3}{\partial\nu}=0, && x\in\partial\Omega,
\end{aligned}$$

has a principle eigenvalue $\tilde{\lambda}_0(\delta)$ with a strongly positive eigenfunction $(\phi_2^\delta,\phi_3^\delta)$. Choose a sufficiently small $\varepsilon>0$ and $w_i(x,0)$ such that $w_i(x,0)=\varepsilon\phi_i^\delta\leq u_i(\cdot,\tilde{t},\tilde{\phi})$ for $i=2,3$. Then the linear system (5.3) has a unique solution

$$(w_2(x,t),w_3(x,t))=(\varepsilon e^{\tilde{\lambda}_0(\delta)(t-\tilde{t})}\phi_2^\delta,\ \varepsilon e^{\tilde{\lambda}_0(\delta)(t-\tilde{t})}\phi_3^\delta) \quad \text{for} \quad t\geq\tilde{t}.$$

By comparison principle, we have

$$(u_2(x,t,\tilde{\phi}),u_3(x,t,\tilde{\phi}))\geq(\varepsilon e^{\tilde{\lambda}_0(\delta)(t-\tilde{t})}\phi_2^\delta,\ \varepsilon e^{\tilde{\lambda}_0(\delta)(t-\tilde{t})}\phi_3^\delta) \quad \text{for} \quad x\in\bar{\Omega},\ t\geq\tilde{t}.$$

Therefore, $u_i(x,t,\tilde{\phi})\to\infty$ as $t\to\infty$ for $i=2,3$, which contradicts to Proposition 2.2. Thus, we prove $W^s((\bar{u}_1(x),0,0))\cap\varrho^{-1}(0,\infty)=\emptyset$. Clearly, there is no cycle in M_∂ from $(\bar{u}_1(x),0,0)$ to $(\bar{u}_1(x),0,0)$.

Summarizing the above results, we obtain from Theorem 5.2 and abstract persistence theory in [28] that Θ_t is uniformly persistent; namely, there exists a $\epsilon>0$ such that $\liminf_{t\to\infty}\varrho(\Theta_t\phi)\geq\epsilon$ for any $\phi\in\mathbb{X}_0$. This, together with the definition of ϱ, implies that

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

Next, we shall prove $\liminf_{t\to\infty} u_1(\cdot,t,\phi) > 0$ by contradiction. If $\liminf_{t\to\infty} u_1(\cdot,t,\phi) = 0$, then there exists a sequence $t_n \to \infty$ such that $u_1(\cdot,t_n,\phi) \to 0$ and $\partial u_1(\cdot,t_n,\phi)/\partial t = 0$, which contradicts to the first equation of (1.1). Thus, by choosing $\epsilon > 0$ sufficiently small, we have $\liminf_{t\to\infty} u_1(\cdot,t,\phi) \geq \epsilon$ uniformly for all $x \in \bar{\Omega}$.

By Theorem 5.2 and $W^s((\bar{u}_1(x),0,0)) \cap \varrho^{-1}(0,\infty) = \emptyset$, the semiflow $\Theta_t\ |_{\mathbb{X}_0}\colon \mathbb{X}_0 \to \mathbb{X}_0$ has a connected global attractor. This together with Theorem 4.7 in [15] implies that Θ_t has a steady state $(u_1^*(x), u_2^*(x), u_3^*(x))$ in $\mathbb{X}_0$. Moreover, Proposition 2.2 and the first part of this proof imply that $(u_1^*(x), u_2^*(x), u_3^*(x))$ is a chronic-infection steady state. This ends the proof. □

5.2. Global attractivity of the chronic-infection steady state

We now establish global attractivity of the chronic-infection steady state $(u_1^*(x), u_2^*(x), u_3^*(x))$ by combining the method of Lyapunov functionals and LaSalle invariance principle. To this end, we shall make use of the following additional assumption.

($\mathbf{H}_4$) $f(x,u_1,u_3)/g(x,u_1,u_2)$ is independent on u_1, namely, there exists a function $h_0(x,u_1)$ such that $f(x,u_1,u_3) = h_0(x,u_1)f_1(x,u_3)$, $g(x,u_1,u_2) = h_0(x,u_1)g_1(x,u_2)$.

The biological interpretation of this condition is that the transmission via two infection modes have the same response function on uninfected target cells.

Theorem 5.6. *Assume that* ($\boldsymbol{H}_1$)-($\boldsymbol{H}_4$) *hold. If* $R_0 > 1$, *then the chronic-infection steady state* $(u_1^*(x), u_2^*(x), u_3^*(x))$ *of* (1.1) *is globally attractive in* $\mathbb{X}_0$. *Moreover,* u^* *is the unique chronic-infection steady state for* (1.1).

Proof. It follows from Theorem 5.5 that the chronic-infection steady state exists if $R_0 > 1$. Proposition 2.2 implies that $\mathbb{X}_0 \cap \Gamma$ is positively invariant and absorbing in $\mathbb{X}_0$. Thus, it suffices to show that the chronic-infection steady state is globally attractive in $\mathbb{X}_0 \cap \Gamma$. Denote $p(\theta) = \theta - 1 - \ln\theta$. It is readily seen that $p(\theta) \geq 0$ for $\theta > 0$, and $p(\theta) = 0$ if and only if $\theta = 1$. Motivated by [25,26], we construct a Lyapunov functional $W : \mathbb{X}_0 \cap \Gamma \to \mathbb{R}$ as follows.

$$W(u_1(x,t), u_2(x,t), u_3(x,t)) = \int_\Omega \mu(x) E(u_1(x,t), u_2(x,t), u_3(x,t))\, dx,$$

where $\mu(x) = k(x)u_2^*(x)u_3^*(x)/f(x,u_1^*(x),u_3^*(x))$ is strictly positive in Ω, and

$$E(u_1,u_2,u_3) = u_1(x,t) - \int_{u_1^*(x)}^{u_1(x,t)} \frac{f(x,u_1^*(x),u_3^*(x))}{f(x,\theta,u_3^*(x))}\, d\theta + u_2^*(x)\ p\Big(\frac{u_2(x,t)}{u_2^*(x)}\Big) + \frac{f(x,u_1^*(x),u_3^*(x))u_3^*(x)}{k(x)u_2^*(x)}\ p\Big(\frac{u_3(x,t)}{u_3^*(x)}\Big).$$

Since the solutions are bounded (see Proposition 2.2) and the system (1.1) is uniform persistent (see Theorem 5.5), the above functionals W and E are well-defined. Notice that the steady state solution $(u_1^*(x), u_2^*(x), u_3^*(x))$ of (1.1) satisfies

$$n(x,u_1^*(x)) = b(x)u_2^*(x) = f(x,u_1^*(x),u_3^*(x)) + g(x,u_1^*(x),u_2^*(x)),$$
$$d\Delta u_3^*(x) = m(x)u_3^*(x) - k(x)u_2^*(x), \text{ and } \frac{\partial u_3^*(x)}{\partial \nu}|_{\partial\Omega} = 0.$$

From a tedious calculation, the time derivative of W along a positive solution of system (1.1) is

$$\begin{aligned}\frac{dW}{dt} &= \int_\Omega \mu(x)\left((n(u_1)-n(u_1^*))\left(1-\frac{f(x,u_1^*,u_3^*)}{f(x,u_1,u_3^*)}\right)+f(x,u_1^*,u_3^*)\Phi_1+g(x,u_1^*,u_2^*)\Phi_2\right)dx\\ &\quad-\int_\Omega \mu(x)f(x,u_1^*,u_3^*)\left(p(\frac{f(x,u_1^*,u_3^*)}{f(x,u_1,u_3^*)})+p(\frac{u_3f(x,u_1,u_3^*)}{u_3^*f(x,u_1,u_3)})+p(\frac{u_2^*f(x,u_1,u_3)}{u_2f(x,u_1^*,u_3^*)})+p(\frac{u_2u_3^*}{u_2^*u_3})\right)dx\\ &\quad-\int_\Omega \mu(x)g(x,u_1^*,u_2^*)\left(p(\frac{f(x,u_1^*,u_3^*)}{f(x,u_1,u_3^*)})+p(\frac{u_2^*g(x,u_1,u_2)}{u_2g(x,u_1^*,u_2^*))})+p(\frac{u_2f(x,u_1,u_3^*)g(x,u_1^*,u_2^*)}{u_2^*f(x,u_1^*,u_3^*)g(x,u_1,u_2)})\right)dx\\ &\quad+d\int_\Omega\left(u_3^*(1-\frac{u_3^*}{u_3})\Delta u_3+(u_3^*-u_3)\Delta u_3^*\right)dx,\end{aligned}$$

where

$$\begin{aligned}\Phi_1&=\frac{u_3}{u_3^*}\left(\frac{f(x,u_1,u_3)}{f(x,u_1,u_3^*)}-1\right)\left(\frac{u_3^*}{u_3}-\frac{f(x,u_1,u_3^*)}{f(x,u_1,u_3)}\right),\\ \Phi_2&=\left(\frac{u_2}{u_2^*}-\frac{f(x,u_1^*,u_3^*)g(x,u_1,u_2)}{f(x,u_1,u_3^*)g(x,u_1^*,u_2^*)}\right)\left(\frac{f(x,u_1,u_3^*)g(x,u_1^*,u_2^*)}{f(x,u_1^*,u_3^*)g(x,u_1,u_2)}-1\right).\end{aligned}$$

Making use of $(\mathbf{H}_4)$, we can simply Φ_2 as

$$\Phi_2=\left(\frac{u_2}{u_2^*}-\frac{g_1(x,u_2)}{g_1(x,u_2^*)}\right)\left(\frac{g_1(x,u_2^*)}{g_1(x,u_2)}-1\right).$$

In view of $(\mathbf{H}_2)$, $g_1(x,u_2)$ is strictly increasing and concave down with respect to u_2. Hence, $\Phi_2\le 0$ in $\mathbb{X}_0\cap\Gamma$. Similarly, it follows from the monotonicity and concavity of $f(x,u_1,u_3)$ with respect to u_3 that $\Phi_1\le 0$ in $\mathbb{X}_0\cap\Gamma$. Moreover, by $(\mathbf{H}_1)$-$(\mathbf{H}_2)$, $n(x,u_1)$ and $f(x,u_1,u_3)$ are decreasing with respect to u_1. Therefore,

$$(n(x,u_1)-n(x,u_1^*))\left(1-\frac{f(x,u_1^*,u_3^*)}{f(x,u_1,u_3^*)}\right)\le 0\quad\text{for all}\quad(x,u_1)\in\Omega\times(0,K_1].$$

By using the Green's first identity and Neumann boundary condition, we obtain

$$\begin{aligned}\int_\Omega\left(u_3^*(1-\frac{u_3^*}{u_3})\Delta u_3+(u_3^*-u_3)\Delta u_3^*\right)dx&=\int_\Omega\left(-\nabla(u_3^*-\frac{u_3^{*2}}{u_3})\nabla u_3-\nabla(u_3^*-u_3)\nabla u_3^*\right)dx\\ &=-\int_\Omega\sum_{j=1}^n\left(\frac{u_3^*}{u_3}\frac{\partial u_3}{\partial x_j}-\frac{\partial u_3^*}{\partial x_j}\right)^2dx\le 0.\end{aligned}$$

The above estimates together with the positive definiteness of $p(\theta)$ yield

$$\frac{dW}{dt}\le 0\quad\text{for all}\quad(u_1(x,t),u_2(x,t),u_3(x,t))\in\mathbb{X}_0\cap\Gamma.$$

Denote $\mathcal{M}$ as the largest compact invariant subset of $\{(u_1,u_2,u_3)\in\mathbb{X}_0\cap\Gamma : W'(t)=0\}$. By the LaSalle invariance principle [10], the omega limit sets of solutions are contained in $\mathcal{M}$. It can be verified that $dW/dt=0$ implies

$$u_1(x,t)=u_1^*,\ \frac{u_2^*f(x,u_1,u_3)}{u_2f(x,u_1^*,u_3^*)}=\frac{u_2^*g(x,u_1,u_2)}{u_2g(x,u_1^*,u_2^*)}=1,\ \text{and}\ \frac{u_2u_3^*}{u_2^*u_3}=1.$$

Substituting the above relations into the second equation of (1.1) gives

$$\frac{\partial u_2(x,t)}{\partial t} = (f(x,u_1^*(x),u_3^*(x)) + g(x,u_1^*(x),u_2^*(x)))\frac{u_2(x,t)}{u_2^*(x)} - b(x)u_2(x,t) = 0.$$

Note that $u_1(x,t) = u_1^*(x)$. Adding the first two equations of (1.1) gives $u_2(x,t) = n(x,u_1^*(x))/b(x) = u_2^*(x)$, which together with $u_2u_3^* = u_2^*u_3$ implies that $u_3(x,t) = u_3^*(x)$. Therefore, we obatin $\mathcal{M} = \{(u_1^*(x),u_2^*(x),u_3^*(x))\}$. Thus we prove the global attractivity of the chronic-infection steady state $(u_1^*(x),u_2^*(x),u_3^*(x))$ in $\mathbb{X}_0$. The uniqueness of chronic-infection steady state follows immediately form the global attractivity of u^*. □

6. Numerical simulation

In this section, we use numerical simulation to illustrate our analytical results on the properties of basic reproduction number and global dynamics of model system. Following the work in [20], we choose the cell reproduction function as $n(x,u_1(x,t)) = s-\mu u_1(x,t)+ru_1(x,t)[1-u_1(x,t)/T_m]$, where $s = 10$ day^{-1}mm^{-3} is the supply rate from precursors, $\mu = 0.02$ day^{-1} is the death rate, $r = 0.03$ day^{-1} is the growth rate, and $T_m = 1500$ mm^{-3} is the maximum cell population level. The cell-free and cell-to-cell transmissions are bilinear functions: $f(x,u_1,u_3) = \beta_1u_1u_3$ and $g(x,u_1,u_2) = \beta_2u_1u_2$, where the per capita infection rates $\beta_1 = 2.4e{-}5$ mm^{3}day^{-1} and $\beta_2 = 1.2e{-}4$ mm^{3}day^{-1}, respectively. For simplicity, we assume the domain is a one-dimensional interval [0 mm, 1 mm] and spatial heterogeneity occurs in the following three functions:

$$b(x) = 0.24(1+x),\ k(x) = 24(1-x/2),\ m(x) = 2.4(1+x)$$

with the same unit day^{-1}. As seen in Fig. 1, the basic reproduction number R_0 is a decreasing function of the diffusion coefficient d. Its maximum $\bar{R}_0$ is achieved at $d = 0$, while $R_0 \to \underline{R}_0$ as $d \to \infty$. There is a critical value $d^* = 0.12$ mm^{2}day^{-1} near which the values of $R_0 - 1$ switch signs. Numerical computation confirms that the infection-free steady state is globally asymptotically stable when $d > d^*$. On the other hand, if $d < d^*$, all solution converges to the chronic-infection steady state.

We choose a positive diffusion coefficient $d = 0.01$ mm^{2}day^{-1}, and compare the steady state solution with that for the diffusion-free system. When $d = 0$, we should drop the Neumann boundary condition because it may be inconsistent with the reduced ordinary differential system. For this reduced system, we can define local basic reproduction numbers:

$$R_0^l(x) := \frac{\beta_d(x)}{b(x)} + \frac{\beta_i(x)k(x)}{b(x)m(x)},$$

where β_d and β_i are the direct and indirect transmission rates as defined in (3.1). It is natural (see for example [1]) to divide the whole domain into high-risk region

$$\Omega_h := \{x \in \Omega : R_0^l(x) > 1\}$$

and low-rick region

$$\Omega_l := \{x \in \Omega : R_0^l(x) < 1\}.$$

For the diffusion-free system, the infection persists only in the high-risk region, while for the positive diffusion system, the virus may pervade into the low-risk region; see Fig. 2. In the simulations of two systems, we have chosen the initial profile as a small perturbation of infection-free steady state: $u_1(x,0) = \bar{u}_1(x)$, $u_2(x,0) = 0$, and $u_3(x,0) = 1$.

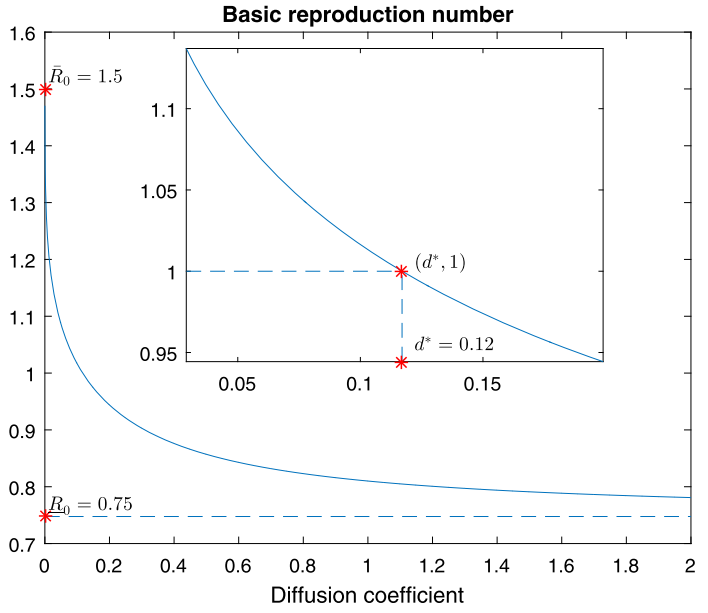

Fig. 1. The basic reproduction number R_0 as a function of the diffusion coefficient d.

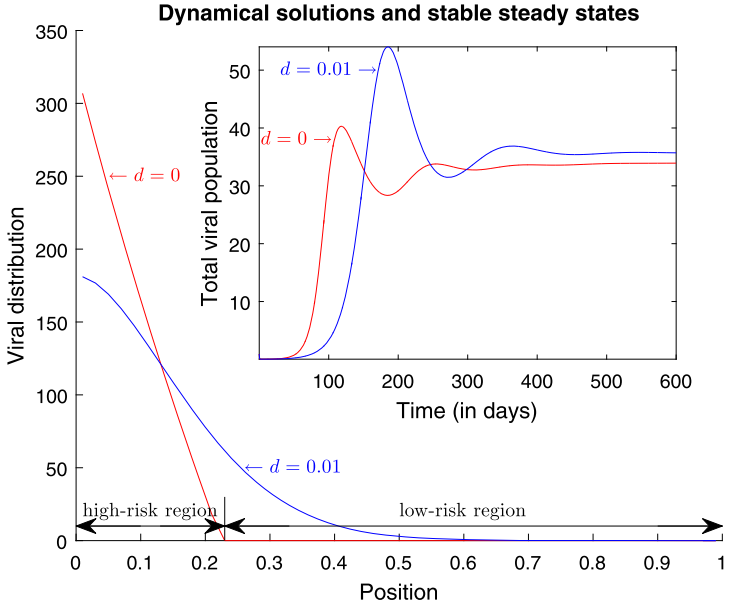

Fig. 2. The dynamic solutions and stable steady states for diffusion-free and positive diffusion systems, respectively. The initial conditions are chosen as a small portion of virus introduced to the infection-free steady state.

To further understand the asymptotic profile of steady state solution as $d \to 0^+$, we choose a small diffusion coefficient $d = 0.0001$ mm^{2}day^{-1}. It is observed that the steady state solution is very close to that for diffusion-free system everywhere except near the boundary or near the interface between high-risk and low-risk regions; see Fig. 3. In the figure, we also plot the gradients of steady state solutions (i.e., $\partial_x u_3(x, T)$ with T sufficiently large) for small diffusion and diffusion-free systems. It is noted that boundary layer occurs near the high-risk boundary (i.e., $x = 0$) but not near the low-risk boundary (i.e., $x = 1$). This is because the steady state solution for the diffusion-free system is inconsistent with the Neumann boundary condition near the high-risk boundary. A similar reason explains the existence of internal boundary layer

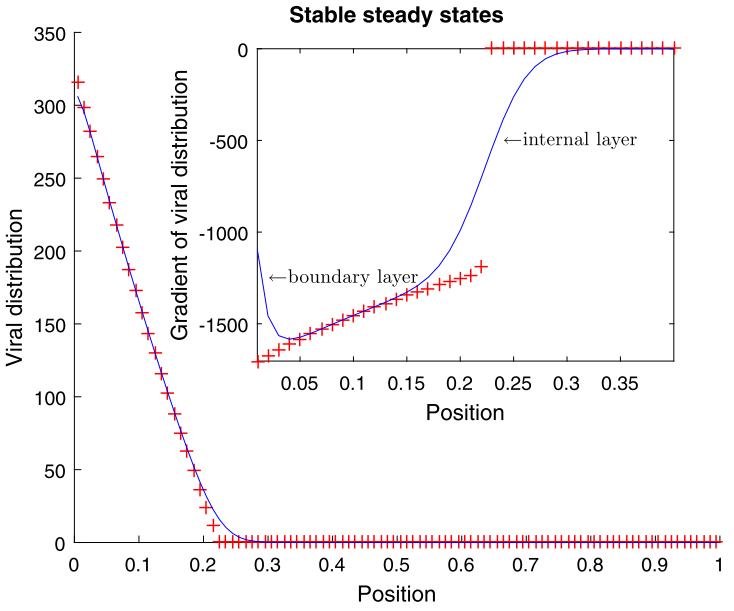

Fig. 3. The stable steady states and their gradients of viral distributions for diffusion-free system (crosses) and low diffusion system (lines), respectively. The initial conditions are chosen as a small portion of virus introduced to the infection-free steady state.

near the interface of high-risk and low-risk regions. Both boundary and internal layers have the thickness of order $O(\sqrt{d})$ as $d \to 0$.

7. Summary and discussion

In this paper, we have studied a general in-host model with spatial heterogeneity and general cell-free and cell-to-cell modes. We defined and studied the basic reproduction number R_0, which serves as a threshold parameter determining the global dynamics of the model system. When $R_0 < 1$, we first obtained local asymptotic stability of the infection-free steady state, and then by Lyapunov functional method and LaSalle invariance principle, we proved that the infection-free steady state is indeed globally asymptotically stable.

Since only the free virus diffuses, the model is a partially degenerate reaction-diffusion system, which poses a non-compactness problem. To overcome this, we made use of the Kuratowski measure of non-compactness, and showed that the semiflow associated with our systems is asymptotically smooth (i.e., κ-contracting) under certain conditions. If $R_0 > 1$, we also obtained the persistence of infection which guarantees the existence of a chronic-infection steady state. Finally, we established global attractiveness of the chronic-infection steady state by constructing a suitable Lyapunov functional and using LaSalle invariance principle. This idea may also be used to study global dynamics of other hybrid epidemic models with partial degeneracy.

Numerical simulation supports our theoretical results that viral diffusion has an opposite effect on the basic reproduction number, and in some scenarios, the virus may be cleared out due to large diffusion but persist by reducing random spatial movement and staying only in high-risk region. A mathematical challenge arises from the simulation results for small diffusion coefficients. It is observed that boundary layer may occur due to the mismatch of steady state solution of the diffusion-free system with the Neumann boundary condition. Moreover, the non-smoothnees of such steady state solution across the interface between high-risk and low-risk regions may induce internal layer. It is believed that singular perturbation analysis is necessary to study the asymptotic profile of steady state solution when the diffusion coefficient decreases to zero.

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