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Spatial dynamics of a viral infection model with immune response and nonlinear incidence

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Abstract. Incorporating humoral immunity, cell-to-cell transmission and degenerated diffusion into a virus infection model, we investigate a viral dynamics model in heterogenous environments. The model is assumed that the uninfected and infected cells do not diffuse and the virus and B cells have diffusion. Firstly, the well-posedness of the model is discussed. And then, we calculated the reproduction number $\mathcal{R}_0$ account for virus infection, and some useful properties of $\mathcal{R}_0$ are obtained by means of the Kuratowski measure of noncompactness and the principle eigenvalue. Further, when $\mathcal{R}_0 < 1$, the infection-free steady state is proved to be globally asymptotically stable. Moreover, to discuss the antibody response reproduction number $\widetilde{\mathcal{R}}_0$ of the model and the global dynamics of virus infection, including the global stability infection steady state and the uniform persistence of infection, and to obtain the k-contraction of the model with the Kuratowski measure of noncompactness, a special case of the model is considered. At the same time, when $\mathcal{R}_0 > 1$ and $\widetilde{\mathcal{R}}_0 < 1$ ($\widetilde{\mathcal{R}}_0 > 1$), we obtained a sufficient condition on the global asymptotic stability of the antibody-free infection steady state (the uniform persistence and global asymptotic stability of infection with antibody response). Finally, the numerical examples are presented to illustrate the theoretical results and verify the conjectures.

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1. Introduction

As we all know, every infectious disease has its specific pathogen caused, which can be virus, bacteria, fungus, spirochete, protozoa and so on. Influenza, for example, is caused by a virus; tuberculosis is caused by bacteria. In fact, viruses are closely related to human diseases and about 70%-80% of infectious diseases in humans are caused by viruses. For example, the 1918 influenza pandemic was caused by an H1N1 virus with genes of avian origin, which is the most severe pandemic in recent history, and the SARS outbreak in 2003 and the ongoing pandemic of COVID-19 in the last three years are caused by coronaviruses. Of course, there are still human immunodeficiency virus (HIV) and Hepatitis B virus (HBV) which has not been eradicated are caused by the virus. Therefore, research on infectious diseases caused by viruses is essential to protect the lives and property of people all over the world, which is why more and more researchers are joining the ranks of research on infectious diseases caused by viruses and made a lot of excellent results [6,7,9,19,20,22,27,32,38,39].

The virus body is in a static state outside the cell, basically similar to inanimate substances, and it cannot replicate itself. However, once it invades susceptible host cells, the virus rely on the host cells for its own reproduction and spread, and cell division produces more viruses and then infects more cells. The pathogenic effect of the virus on the body mainly includes two aspects: (1) the virus causes the structural or functional changes of the host cells, and then causes the pathological changes and functional disorders of the tissues and organs of the body; (2) when the virus invades the host cells, it will trigger the immune response of the body and then induce the immune pathological response of the body. For

example, influenza virus has affinity to respiratory mucosa; smallpox virus has affinity to skin mucosal cells; encephalitis virus and poliovirus have affinity to nerve tissue, while HIV mainly invades human $CD4^+$ T lymphocytes, resulting in a decrease in the number of $CD4^+$ T lymphocytes, leading to immune function defects, and finally can be secondary to the infection of various pathogenic microorganisms, as well as secondary tumors, leading to death.

The human body mainly includes two immune mechanisms: cellular immunity and humoral immunity, which need to be stimulated by antigens. Cellular immunity is that after being stimulated by antigen, human T cells directly form memory T cells and effector T cells and then produce antibodies, which are specifically combined with cells to play an immune response. Humoral immunity is that after being stimulated by antigen, a kind of B cells in the body produces effective B cells and memory cells and then produces antibodies to produce immune responses to corresponding antigens [9]. The dynamics models of viral infection related to humoral and cellular immunity have attracted the attention of many researchers (see [3,4,13,14,20,25,27,31,34,37]). For example, in [4] the authors investigated the dynamical behavior of two nonlinear models for viral infection with humoral immune response, and formulated two threshold parameters for each model and obtained some sufficient conditions for the global dynamics of the models, and in [25], a generalized viral dynamics model with two nonlinear models and cellular immunity have been studied.

Recently, a variety of reaction–diffusion models have been proposed to describe the viral dynamics [7,15,19,22,27]. For instance, in [15], a reaction–diffusion viral infection model under comprehensive consideration of humoral immunity, viral infection delay and logistic growth have been studied, and their research shows that the stability of the equilibrium point can be altered by viral infection delay. Moreover, by the methods of dynamical systems and the Lyapunov function, a nonlinear viral dynamics model which integrates the influence of humoral immunity and spatial diffusion has been researched in [22]. However, most of these studies have focused on the spread of virus to cell and assumed that the diffusion ability of cells and viruses of in the body is constant, that is, their diffusion ability is independent of its location in the body. In fact, related study [19] demonstrates that the diffusion ability of different cells or viruses varies depending on the tissue or environment in which they are located. Moreover, recent data and studies suggest that there exists cell-to-cell transmission of viruses in virus dynamics. For example, in [5], the authors concluded that cell-to-cell transmission can prevent the spread of the HCV virus. Hence, in order to investigate the combined effects of heterogeneous diffusion and cell-to-cell infection on viral infection dynamics, Luo et al. [9] proposed the following viral dynamics model:

$$\begin{cases} \dfrac{\partial u_1}{\partial t} = \nabla \cdot d_1(x)\nabla u_1 + A(x) - d(x)u_1 - \beta_1(x)f(u_1,u_3) - \beta_2(x)g(u_1,u_2), \\ \dfrac{\partial u_2}{\partial t} = \nabla \cdot d_2(x)\nabla u_2 + \beta_1(x)f(u_1,u_3) + \beta_2(x)g(u_1,u_2) - \mu_2(x)u_2, \\ \dfrac{\partial u_3}{\partial t} = \nabla \cdot d_3(x)\nabla u_3 + p(x)u_2 - \mu(x)u_3 - q(x)u_3u_4, \\ \dfrac{\partial u_4}{\partial t} = \nabla \cdot d_4(x)\nabla u_4 + r(x)u_3u_4 - c(x)u_4, \end{cases} \quad t \geq 0,\ x \in \Omega \tag{1}$$

They calculated two reproduction number R_0 (the virus infection) and R_1 (the antibody response) and obtained the threshold dynamics in terms of R_0 and R_1.

However, in [2] showed that due to non-homogeneous initial distribution of the virus and the spatio-temporal patterns of virus reproduction, the virus will appear distribution heterogeneity after invasion, that is to say, the spread of the virus is heterogeneous. In fact, in the human body, most healthy cells are fixed in various tissues and organs, and only the virus invades the body and parasitize the host cells for reproduction and diffusion, thus stimulating the immune mechanism of the human body, producing effective B cells and memory cells to inhibit the virus cells. Hence, just consider the diffusion of virus and effective B cells is reasonable, which leads to the model degenerate into a hybrid system with ODEs

and PDEs. In recent years, there have been many studies on degenerated reaction–diffusion virus infection models and epidemic models (see [1,8,17,28,29,33]). Regrettably, there is no viral dynamics model incorporating humoral immunity and the transmission between cells and virus to cell in the existing degenerated diffusion virus infection dynamics models.

In this paper, we modified the model proposed by Luo et al. [9] to a degenerated diffusion viral dynamics model, which leads to the lack of compactness for solution maps of the model and makes the theoretical analysis of the model more difficult by incorporating humoral immunity and the transmission between cells and virus to cell. The details can be found in the following sections. In the following part, we describe the organization of this paper. In Sect. 2, we present the formulation of the model and give some basic preliminaries. Section 3 is devoted to defining the basic reproduction number of the model. Further, we study the extinction of disease in Sect. 4. Sections 5 and 6 investigate a special case of the model. In Sect. 7, the theoretical results and conjectures are illustrated by some numerical examples. Finally, a short discussion ends the paper.

2. Model description and preliminaries

In the spirit of the above discussion, in this section, we study the following degenerated diffusion viral dynamics model, which is divided into four compartments, namely the uninfected cells(u_1), infected cells(u_2), virus(u_3) and B cells(u_4),

$$\begin{cases} \dfrac{\partial u_1}{\partial t} = \Lambda(x) - \mu_1(x)u_1 - \sigma(x)f(u_1,u_2) - \alpha(x)g(u_1,u_3), \\ \dfrac{\partial u_2}{\partial t} = \sigma(x)f(u_1,u_2) + \alpha(x)g(u_1,u_3) - \mu_2(x)u_2, \\ \dfrac{\partial u_3}{\partial t} = \nabla\cdot d_3(x)\nabla u_3 + \xi(x)u_2 - \mu_3(x)u_3 - \gamma(x)u_3u_4, \quad t\geq 0,\ x\in\Omega, \\ \dfrac{\partial u_4}{\partial t} = \nabla\cdot d_4(x)\nabla u_4 + \theta(x)u_3u_4 - \mu_4(x)u_4, \\ u_i(0,x) = \phi_i(x), \end{cases} \tag{2}$$

with boundary conditions

$$\frac{\partial u_3}{\partial \nu} = \frac{\partial u_4}{\partial \nu} = 0,\ t\geq 0,\ x\in\partial\Omega. \tag{3}$$

Here, $\Omega\subset R^n (n\geq 1)$ is a bounded domain with the smooth boundary $\partial\Omega$, $\nabla = (\frac{\partial}{\partial x_1}, \frac{\partial}{\partial x_2}, \cdots, \frac{\partial}{\partial x_n})$ denotes the gradient operator, and $\phi_i(x)$ are the nonnegative Hölder continuous functions. The specific biological significance of each variable and parameter is summarized in Table 1. For each coefficient, we assume that $\Lambda(x)$, $\mu_i(x)$ $(i=1,2,3,4)$, $\alpha(x)$, $\sigma(x)$, $\xi(x)$, $\gamma(x)$, $\theta(x)$ and $d_i(x)$ $(i=3,4)$ are all positive, continuous and bounded functions on $\overline{\Omega}$. Moreover, the incidence functions $f(u_1,u_2)$ and $g(u_1,u_3)$ are assumed to satisfy the following assumption:

(H_1) Functions $f,g: R_+^2\to R_+$ are continuously differentiable; $f(u_1,0)\equiv 0$, $f(0,u_3)\equiv 0$, $g(u_2,0)\equiv 0$ and $g(0,u_3)\equiv 0$; $f_{u_1}(u_1,u_2)>0$, $g_{u_1}(u_1,u_3)>0$ for all $u_1>0$, $u_2>0$ and $u_3>0$, where $f_{u_1}(u_1,u_2) = \frac{\partial f_{u_1}(u_1,u_2)}{\partial u_1}$ and $g_{u_1}(u_1,u_3) = \frac{\partial g_{u_1}(u_1,u_3)}{\partial u_1}$.

Let $C(\overline{\Omega},R^n)$ denote the Banach space of continuous functions, equipped with supremum norm $\|\cdot\|$, and its positive cone is denoted by $C(\overline{\Omega},R_+^n)$. To simplify notation, we denote $\mathbb{X} = C(\overline{\Omega},R^4)$, $\mathbb{Y} = C(\overline{\Omega},R)$, $\mathbb{X}_+ = C(\overline{\Omega},R_+^4)$ and $\mathbb{Y}_+ = C(\overline{\Omega},R_+)$. Moreover, for any function $f(x)$ defined on set D, let $f^s = \sup_{x\in D} f(x)$ and $f^i = \inf_{x\in D} f(x)$.

For any $t\geq 0$, define the operators $\mathcal{O}_i(t):\mathbb{Y}\to\mathbb{Y}$ $(i=1,2)$ as follows.

$$\mathcal{O}_1(t)\phi(x) = e^{-\mu_1(x)t}\phi(x),\ \mathcal{O}_2(t)\phi(x) = e^{-\mu_2(x)t}\phi(x),\ \phi\in\mathbb{Y}.$$

TABLE 1. *Definition of variables and parameters for model (2)*

Param.	Description
$u_1(t,x)$	Density of uninfected cells at location x and time t.
$u_2(t,x)$	Density of infected cells at location x and time t.
$u_3(t,x)$	Density of virus at location x and time t.
$u_4(t,x)$	Density of B cells at location x and time t.
$\Lambda(x)$	Recruitment rate of uninfected cells at location x.
$\mu_i(x),\ i=1,2,3,4$	Death rate of the class u_i at location x.
$\alpha(x)/\sigma(x)$	Virus infection rate/ Cell-to-cell infection rate at location x.
$\xi(x)/\theta(x)$	Birth rate of virus/B cells at location x.
$\gamma(x)$	Neutralize rate of B cells at location x.
$d_3(x)/d_4(x)$	Diffusion rate of virus/B cells at location x.

Let $\mathcal{O}_i(t)$ $(i=3,4)$ be the C_0-semigroup generated by the operators $\nabla\cdot(d_i(x)\nabla)-\mu_i(x)$ under condition (3). From [19], we have

$$(\mathcal{O}_i(t)\phi)(x)=\int_\Omega G_i(t,x,y)\phi(y)\mathrm{d}y,\ i=3,4,\ \phi\in\mathbb{Y}, \tag{4}$$

where $G_i(t,x,y)$ $(i=3,4)$ are the Green function associated with $\nabla\cdot(d_i(x)\nabla)-\mu_i(x)$ under condition (3). Moreover, the compactness and strongly positiveness of $\mathcal{O}_i(t)$ $(i=3,4)$ can be obtained by Corollary 7.2.3 in [21].

Let $\mathcal{O}(t)=diag\{\mathcal{O}_1(t),\mathcal{O}_2(t),\mathcal{O}_3(t),\mathcal{O}_4(t)\}$, then $\mathcal{O}(t)$ is a strongly continuous semigroup of bounded linear operators on $\mathbb{X}$ to itself. For $\phi=(\phi_1,\phi_2,\phi_3,\phi_4)^T\in\mathbb{X}$ and $t\geq 0$, model (2) can be written as the following integral equation

$$u(t)=\mathcal{O}(t)\phi+\int_0^t\mathcal{O}(t-s)\mathcal{N}(u(\cdot,s))\mathrm{d}s,\ u(0)=\phi\in\mathbb{X}, \tag{5}$$

where $\mathcal{N}:\mathbb{X}\to\mathbb{X}$ is defined by

$$\mathcal{N}(\phi):=\begin{pmatrix}\mathcal{N}_1(\phi)\\ \mathcal{N}_2(\phi)\\ \mathcal{N}_3(\phi)\\ \mathcal{N}_4(\phi)\end{pmatrix}=\begin{pmatrix}\Lambda(\cdot)-\sigma(\cdot)f(\phi_1,\phi_2)-\alpha(\cdot)g(\phi_1,\phi_3)\\ \sigma(\cdot)f(\phi_1,\phi_2)+\alpha(\cdot)g(\phi_1,\phi_3)\\ \xi(\cdot)\phi_2-\gamma(\cdot)\phi_3\phi_4\\ \theta(\cdot)\phi_3\phi_4\end{pmatrix}.$$

From the expression of $\mathcal{N}$, we see that $\mathcal{N}$ is locally Lipschitz continuous. For any $\phi\in\mathbb{X}_+$ and $r\geq 0$, by the similar argument as in the proof of [10, Lemma 3.2], we have that $\lim_{r\to 0^+}\frac{1}{r}dist(\phi+r\mathcal{N}(\phi),\mathbb{X}_+)=0$ for any $\phi\in\mathbb{X}_+$. Therefore, by [21, Theorem 3.1 in Chapter 7] and [12, Corollary 4], we have the following result.

Lemma 1. *For any initial function $\phi\in\mathbb{X}_+$, there exists a $\tau_m=\tau_m(\phi)$ such that model (2) has a unique noncontinuable mild solution $u(t,\cdot)=u(t,\cdot;\phi)$ defined on $[0,\tau_m)$ with $u(0,\cdot;\phi)=\phi$. Moreover, $u(t,\cdot;\phi)\in\mathbb{X}_+$ is a classical solution on $[0,\tau_m)$.*

Further, by the arguments similar to [38, Theorem 1] and [9, Theorem 1], we can obtain the following result.

Theorem 1. *For any initial value function $\phi\in\mathbb{X}_+$, model (2) has a unique solution $u(t,\cdot;\phi)=(u_1(t,\cdot;\phi),u_2(t,\cdot;\phi),u_3(t,\cdot;\phi),u_4(t,\cdot;\phi))\in\mathbb{X}_+$ defined on $[0,+\infty)$, and solutions are ultimately bounded and uniformly bounded.*

Remark 1. Based on Theorem 1, we further obtain that model (2) generates a solution semiflow $\Phi(t):\mathbb{X}_+\to\mathbb{X}_+$ such that for any initial value $\phi\in\mathbb{X}_+$, $\Phi(t)\phi=u(t,\cdot,\phi)$.

3. The basic reproduction number

In this section, we first define and calculate the virus infection basic reproduction number of model (2) and then establish some properties of it. However, since the first two equations in model (2) have no diffusion term, the compactness of solution semiflows of model (2) and corresponding linearized system at the virus-free steady state can not be ensured. This will give rise to that the Krein–Rutman theorem [16, corollary 2.2] cannot directly employed. To overcome this problem, we need to introduce the following definitions on the Kuratowski measure of noncompactness of a bounded set and k-contraction of a continuous mapping.

Definition 1. (see [36]) Let $\mathbb{H}$ be a metric space and $\mathbb{B} \subset \mathbb{H}$ be a bounded set, the Kuratowski measure of noncompactness of $\mathbb{B}$ is defined by

$$\kappa(\mathbb{B}) := \inf\{r : \mathbb{B} \text{ has a finite open cover of diameter } \leq r\}.$$

We set $\kappa(\mathbb{B}) = \infty$ whenever $\mathbb{B}$ is unbounded. It is easy to see that $\mathbb{B}$ is precompact if and only if $\kappa(\mathbb{B}) = 0$.

Definition 2. (see [36]) Let $g : \mathbb{R}_+ \times \mathbb{H} \to \mathbb{H}$ be a continuous mapping. If there is a continuous function $k : \mathbb{R}_+ \to \mathbb{R}_+$ satisfying $0 \leq k(t) < 1$ for all $t \in \mathbb{R}_+$ such that for any $t > 0$ and bounded set $\mathbb{B} \subset \mathbb{H}$, the set $\{g(s, \mathbb{B}) : 0 \leq s \leq t\}$ is bounded in space $\mathbb{H}$ and $\kappa(g(t, \mathbb{B})) \leq k(t)\kappa(\mathbb{B})$, where for any $t \geq 0$ the set $g(t, \mathbb{B}) = \{g(t, \phi) : \phi \in \mathbb{B}\}$, then we say that the mapping g is k-contraction with order $k(t)$.

For an operator L, we denote by $\sigma(L)$ the spectrum of L, spectral radius $r(L) = \sup\{|\lambda| : \lambda \in \sigma(L)\}$ and spectral bound $s(L) = \sup\{Re\lambda : \lambda \in \sigma(L)\}$.

Obviously, model (2) admits a unique virus-free steady state $E_0 = (u_1^*(x), 0, 0, 0)$, where $u_1^*(x) = \frac{\Lambda(x)}{\mu_1(x)}$. Linearizing model (2) at E_0, we have the linear system as follows:

$$\begin{cases} \dfrac{\partial u_1}{\partial t} = -\mu_1(x)u_1 - \sigma(x)f_{u_2}(u_1^*(x), 0)u_2 - \alpha(x)g_{u_3}(u_1^*(x), 0)u_3, \\ \dfrac{\partial u_2}{\partial t} = \sigma(x)f_{u_2}(u_1^*(x), 0)u_2 + \alpha(x)g_{u_3}(u_1^*(x), 0)u_3 - \mu_2(x)u_2, \\ \dfrac{\partial u_3}{\partial t} = \nabla \cdot d_3(x)\nabla u_3 + \xi(x)u_2 - \mu_3(x)u_3, \ x \in \Omega, \ t \geq 0, \\ \dfrac{\partial u_4}{\partial t} = \nabla \cdot d_4(x)\nabla u_4 - \mu_4(x)u_4, \\ \dfrac{\partial u_3}{\partial \nu} = \dfrac{\partial u_4}{\partial \nu} = 0, \ x \in \partial\Omega, \ t \geq 0. \end{cases}$$

Define the linear operators $\mathcal{B}$, $\mathcal{F} : \mathbb{Z} \to \mathbb{Z}$ ($\mathbb{Z} := C(\overline{\Omega}, R^2)$) as follows

$$\mathcal{B} = \begin{pmatrix} -\mu_2(\cdot) & 0 \\ \xi(\cdot) & \nabla \cdot d_3(x)\nabla - \mu_3(\cdot) \end{pmatrix}, \ \mathcal{F} = \begin{pmatrix} \sigma(\cdot)f_{u_2}(u_1^*(\cdot), 0) & \alpha(\cdot)g_{u_3}(u_1^*(\cdot), 0) \\ 0 & 0 \end{pmatrix}$$

and the linear operator $\mathcal{A} := \mathcal{B} + \mathcal{F}$.

Since u_1 and u_4 do not appear in the middle two equations, we just consider the subsystem:

$$\begin{cases} \dfrac{\partial}{\partial t}\begin{pmatrix} u_2 \\ u_3 \end{pmatrix} = \mathcal{A}\begin{pmatrix} u_2 \\ u_3 \end{pmatrix}, \ x \in \Omega, \ t \geq 0, \\ \dfrac{\partial u_3}{\partial \nu} = 0, \ x \in \partial\Omega, \ t \geq 0. \end{cases} \tag{6}$$

Denote $\bar{\Phi}(t)$ be the C^0-semigroup generated by $\mathcal{B}$. Note that $\mathcal{B}$ can be decomposed as

$$\mathcal{B} = diag(0, \nabla \cdot d_3(x)\nabla) - \mathbf{V}, \ \ \mathbf{V} = \begin{pmatrix} \mu_2(\cdot) & 0 \\ -\xi(\cdot) & \mu_3(\cdot) \end{pmatrix}.$$

Thanks to the fact that $\mathcal{B}$ and $-\mathbf{V}$ are cooperative, we know that $\bar{\Phi}(t)$ is a positive C^0-semigroup. Thus, we can define the positive operator on $\mathbb{Z}$ as follows

$$\mathscr{L}(\phi)(x) := \int_0^\infty \mathcal{F}(x)\bar{\Phi}(t)\phi(x)\mathrm{d}t = \mathcal{F}(x)\int_0^\infty \bar{\Phi}(t)\phi(x)\mathrm{d}t,\ \phi \in \mathbb{Z},$$

which is called the next generation operator. Then, the basic reproduction number $\mathcal{R}_0$ for model (2) is defined by $\mathcal{R}_0 := r(\mathscr{L})$.

In what follows, we consider a eigenvalue problem associated with system (6). Substituting $u_2(t,x) = e^{\lambda t}\psi_2(x)$ and $u_3(t,x) = e^{\lambda t}\psi_3(x)$ into system (6), we have the following eigenvalue problem,

$$\begin{cases} \lambda \begin{pmatrix} \psi_2 \\ \psi_3 \end{pmatrix} = \mathcal{A} \begin{pmatrix} \psi_2 \\ \psi_3 \end{pmatrix}, \quad x \in \Omega, \\ \dfrac{\partial \psi_3}{\partial \nu} = 0, \quad x \in \partial\Omega. \end{cases} \tag{7}$$

Denote the function $\mathcal{R}_{01}(x) = \frac{\sigma(x) f_{u_2}(u_1^*(x),0)}{\mu_2(x)}$. On the existence of principle eigenvalue with a strictly positive eigenfunction for the eigenvalue problem (7), we have the following conclusion.

Lemma 2. *Assume* $\max_{x\in\overline{\Omega}} \mathcal{R}_{01}(x) < 1$. *Then, the eigenvalue problem (7) has a principle eigenvalue, denoted by* λ_0, *with a strictly positive eigenfunction* $\psi^* = (\psi_2^*, \psi_3^*)$.

Proof. Let $Q(t) : \mathbb{Z}_+ \to \mathbb{Z}_+$ ($\mathbb{Z}_+ := C(\overline{\Omega}, R_+^2)$ be the solution semiflow of subsystem (6). We now need to prove that $Q(t)$ is k-contraction. For any initial value $\psi = (\psi_2, \psi_3) \in \mathbb{Z}_+$, we have the solution $Q(t)\psi = (u_2(t,x,\psi), u_3(t,x,\psi))$ of subsystem (6). Solve $u_2(t,x,\psi)$ directly from subsystem (6), we get

$$u_2(t,x,\psi) = e^{-(\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0))t}\psi_2 + \int_0^t \alpha(x) g_{u_3}(u_1^*(x),0) u_3(s,x,\psi) e^{-(\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0))(t-s)}\mathrm{d}s.$$

We divide $Q(t) = Q_1(t) + Q_2(t)$, where

$$Q_1(t)\psi = (S_1(t,x,\psi), u_3(t,x,\psi)),\ Q_2(t)\psi = (e^{-(\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0))t}\psi_2, 0),$$

where $S_1(t,x,\psi) = \int_0^t \alpha(x) g_{u_3}(u_1^*(x),0) u_3(s,x,\psi) e^{-(\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0))(t-s)}\mathrm{d}s$. Let $\mathbb{B} \subset \mathbb{Z}_+$ be any bounded set. Since the second equation of subsystem (6) has the diffusion term with the diffusive rate $d_3(x) \geq \inf_{x\in\overline{\Omega}} d_3(x) > 0$, we obtain that the set $\{u_3(t,x,\psi) : \psi \in \mathbb{B}\}$ is precompact in space $\mathbb{Y}$. Consequently, the set $\{S_1(t,x,\psi) : \psi \in \mathbb{B}\}$ is also precompact in $\mathbb{Y}$. Therefore, the Kuratowski measure of noncompactness $\kappa(Q_1(t)\mathbb{B}) = 0$. In addition, we have $\|Q_2(t)\| = \sup_{\psi\in\mathbb{Z}_+} \frac{\|Q_2(t)\psi\|_{\mathbb{Z}_+}}{\|\psi\|_{\mathbb{Z}_+}} \leq e^{-\delta t}$ for any $t > 0$, where $\delta = \inf_{x\in\overline{\Omega}}\{\mu_2(x) - \sigma(x)f_{u_2}(u_1^*(x),0)\}$. Obviously, we have $\delta > 0$ from $\max_{x\in\overline{\Omega}} \mathcal{R}_{01}(x) < 1$. Thus, we further obtain $\kappa(Q_2(t)\mathbb{B}) \leq \|Q_2(t)\|\kappa(\mathbb{B}) \leq e^{-\delta t}\kappa(\mathbb{B})$ for all $t \geq 0$. Therefore, we finally have $\kappa(Q(t)\mathbb{B}) \leq \kappa(Q_1(t)\mathbb{B}) + \kappa(Q_2(t)\mathbb{B}) \leq e^{-\delta t}\kappa(\mathbb{B})$ for all $t \geq 0$, which shows that $Q(t)$ is k-contraction with order $k(t) = e^{-\delta t}$. Thus, by [16, Corollary 2.2], the eigenvalue problem (7) has a principle eigenvalue λ_0 with a strictly positive eigenfunction $\psi^* = (\psi_2^*, \psi_3^*)$. This completes the proof. □

Calculating the inverse operator of $\mathcal{B}(x)$, we have

$$\mathcal{B}^{-1}(x) = \begin{pmatrix} -\mu_2^{-1}(x) & 0 \\ \mathcal{B}_{21}(x) & (\nabla \cdot d_3(x)\nabla - \mu_3(x))^{-1} \end{pmatrix},$$

where $\mathcal{B}_{21}(x) = \frac{\xi(x)}{\mu_2(x)}(\nabla \cdot d_3(x)\nabla - \mu_3(x))^{-1}$. Furthermore,

$$\mathcal{F}(x)\mathcal{B}^{-1}(x) = \begin{pmatrix} F_{11}(x) & F_{12}(x) \\ 0 & 0 \end{pmatrix},$$

where

$$F_{11}(x) = -\frac{\sigma(x) f_{u_2}(u_1^*(x), 0)}{\mu_2(x)} + \mathcal{B}_{21}(x)\alpha(x) g_{u_3}(u_1^*(x), 0),$$
$$F_{12}(x) = (\nabla \cdot d_3(x)\nabla - \mu_3(x))^{-1}\alpha(x) g_{u_3}(u_1^*(x), 0).$$

From the result in [24, Theorem 3.12], we know that the operator $\mathcal{B}(x)$ is resolvent positive. That is, $(\lambda I - \mathcal{B}(x))^{-1}\phi = \int_0^\infty e^{-\lambda t}\bar{\Phi}(t)\phi \mathrm{d}t$ for all $\lambda > s(\mathcal{B})$ and $\phi \in \mathbb{Z}$. Since $s(\mathcal{B}) < 0$, we can take $\lambda = 0$ in the above equality to deduce $-\mathcal{F}(x)\mathcal{B}^{-1}\phi = \mathcal{F}\int_0^\infty \bar{\Phi}(t)\phi \mathrm{d}t = \mathscr{L}(\phi)$. We also have the next generation operator $\mathscr{L} = -\mathcal{F}(x)\mathcal{B}^{-1}(x)$. Therefore, $\mathcal{R}_0 = r(\mathscr{L}) = r(-F_{11}(x))$.

On the other hand, $\mathcal{A} = \mathcal{B} + \mathcal{F}$ is a positive perturbation of $\mathcal{B}$ and hence is also resolvent positive. Therefore, according to Theorem 3.5 in [24], we finally have the following conclusions.

Lemma 3. *Assume* $\max_{x\in\overline{\Omega}} \mathcal{R}_{01}(x) < 1$. *Then, the following conclusions hold.*
(1) Sign$(\mathcal{R}_0 - 1)$*=Sign*$(s(\mathcal{A}))$.
(2) If $\mathcal{R}_0 < 1$, *then* $E_0(x)$ *is locally asymptotically stable.*
(3) If $\mathcal{R}_0 > 1$, *then* $E_0(x)$ *is unstable.*

Furthermore, combining Lemma 2, we can obtain the following conclusion.

Lemma 4. *Assume* $\max_{x\in\overline{\Omega}} \mathcal{R}_{01}(x) < 1$, *and* λ_0 *be the principle eigenvalue of eigenvalue problem (7). If* $\mathcal{R}_0 \geq 1$, *then* $\lambda_0 = s(\mathcal{A})$.

Proof. From the proof of Lemma 2, we further obtain that the essential growth bound $w_{ess}(Q(t))$ of $Q(t)$ satisfies $w_{ess}(Q(t)) \leq -\delta$. Hence, the essential spectrum radius of $Q(t)$ satisfies $r_e(Q(t)) \leq e^{-\delta t} < 1$ for all $t > 0$.

On the other hand, due to $\mathcal{R}_0 \geq 1$, from Lemma 3 then $s(\mathcal{A}) \geq 0$. From Lemma 3.1 in [17], we further obtain that the spectrum radius of $Q(t)$ satisfies $r(Q(t)) = e^{s(\mathcal{A})t} \geq 1$ for all $t > 0$. Therefore, $r_e(Q(t)) < r(Q(t))$ for all $t > 0$. This shows that the principle eigenvalue $\lambda_0 = s(\mathcal{A})$ from the generalized Krein–Rutman theorem [16]. This completes the proof. □

We know that $\mathcal{R}_0$ is the principle eigenvalue of the following eigenvalue problem

$$\begin{cases} -F_{11}(x)\phi = \lambda\phi, \ x \in \Omega, \\ \dfrac{\partial}{\partial\nu}\phi(x) = 0, \ x \in \partial\Omega. \end{cases}$$

Therefore, there is a strictly positive eigenfunction ϕ_* such that

$$\begin{cases} -F_{11}(x)\phi_* = \mathcal{R}_0\phi_*, \ x \in \Omega, \\ \dfrac{\partial\phi_*(x)}{\partial\nu} = 0, \ x \in \partial\Omega, \end{cases}$$

which is equivalent to

$$\begin{cases} \dfrac{\sigma(x) f_{u_2}(u_1^*(x), 0)}{\mu_2(x)}\phi_* - \dfrac{\xi(x)}{\mu_2(x)}(\nabla \cdot d_3(x)\nabla - \mu_3(x))^{-1}\alpha(x) g_{u_3}(u_1^*(x), 0)\phi_* = \mathcal{R}_0\phi_*, \ x \in \Omega, \\ \dfrac{\partial\phi_*(x)}{\partial\nu} = 0, \ x \in \partial\Omega, \end{cases} \tag{8}$$

On the other hand, we consider the following eigenvalue problem

$$\begin{cases} (\nabla \cdot d_3(x)\nabla - \mu_3(x))^{-1}\alpha(x) g_{u_3}(u_1^*(x), 0)\psi = \lambda\psi, \ x \in \Omega, \\ \dfrac{\partial\psi(x)}{\partial\nu} = 0, \ x \in \partial\Omega, \end{cases} \tag{9}$$

where λ is the eigenvalue and ψ is the corresponding eigenfunction. Obviously, it is equivalent to

$$\begin{cases} \alpha(x)g_{u_3}(u_1^*(x),0)\psi = \lambda(\nabla\cdot d_3(x)\nabla - \mu_3(x))\psi,\ x\in\Omega, \\ \dfrac{\partial\psi(x)}{\partial\nu} = 0,\ x\in\partial\Omega. \end{cases} \tag{10}$$

From Lemma 3.3 in [28], it follows that the eigenvalue problem (10) has a positive principle eigenvalue λ^* associated with the strictly positive eigenfunction $\psi_*(x)$ such that

$$\begin{cases} \alpha(x)g_{u_3}(u_1^*(x),0)\psi_* = \lambda^*(\nabla\cdot d_3(x)\nabla - \mu_3(x))\psi_*,\ x\in\Omega, \\ \dfrac{\partial\psi_*(x)}{\partial\nu} = 0,\ x\in\partial\Omega. \end{cases}$$

Hence, we further have $\int\limits_\Omega \alpha(x)g_{u_3}(u_1^*(x),0)\psi_*^2(x)\mathrm{d}x = -\lambda^*\int\limits_\Omega (d_3(x)|\nabla\psi_*(x)|^2 + \mu_3(x)\psi_*^2(x))\mathrm{d}x$. That is,

$$\lambda^* = -\frac{\int\limits_\Omega \alpha(x)g_{u_3}(u_1^*(x),0)\psi_*^2(x)\mathrm{d}x}{\int\limits_\Omega (d_3(x)|\nabla\psi_*(x)|^2 + \mu_3(x)\psi_*^2(x))\mathrm{d}x}, \tag{11}$$

and from (9), we also have

$$(\nabla\cdot d_3(x)\nabla - \mu_3(x))^{-1}\alpha(x)g_{u_3}(u_1^*(x),0)\psi_* = \lambda^*\psi_*,\ x\in\Omega. \tag{12}$$

From (8), we obtain

$$\frac{\sigma(x)f_{u_2}(u_1^*(x),0)}{\mu_2(x)}\phi_*\psi_* - \frac{\xi(x)}{\mu_2(x)}(\nabla\cdot d_3(x)\nabla - \mu_3(x))^{-1}\alpha(x)g_{u_3}(u_1^*(x),0)\phi_*\psi_* = \mathcal{R}_0\phi_*\psi_*,\ x\in\Omega.$$

Then, from (12) we further obtain

$$\frac{\sigma(x)f_{u_2}(u_1^*(x),0)}{\mu_2(x)}\phi_*\psi_* - \frac{\xi(x)}{\mu_2(x)}\lambda^*\psi_*\phi_* = \mathcal{R}_0\phi_*\psi_*,\ x\in\Omega.$$

Integrating on Ω, it follows that

$$\int\limits_\Omega \frac{\sigma(x)f_{u_2}(u_1^*(x),0)}{\mu_2(x)}\phi_*\psi_*\mathrm{d}x - \lambda^*\int\limits_\Omega \frac{\xi(x)}{\mu_2(x)}\psi_*\phi_*\mathrm{d}x = \mathcal{R}_0\int\limits_\Omega \phi_*\psi_*\mathrm{d}x. \tag{13}$$

We can choose that eigenfunctions ϕ_* and $\psi_*(x)$ satisfy $\int\limits_\Omega \phi_*\psi_*\mathrm{d}x = 1$. Thus, from (13) we further obtain

$$\mathcal{R}_0 = \int\limits_\Omega \frac{\sigma(x)f_{u_2}(u_1^*(x),0)}{\mu_2(x)}\phi_*\psi_*\mathrm{d}x + \int\limits_\Omega \frac{\xi(x)}{\mu_2(x)}\phi_*\psi_*\mathrm{d}x\frac{\int\limits_\Omega \alpha(x)g_{u_3}(u_1^*(x),0)\psi_*^2\mathrm{d}x}{\int\limits_\Omega (d_3(x)|\nabla\psi_*|^2 + \mu_3(x)\psi_*^2)\mathrm{d}x}.$$

Therefore, we finally obtain

$$\mathcal{R}_0 = \sup_{\phi,\psi\in H^1(\Omega),\int\limits_\Omega \phi\psi\mathrm{d}x=1}\left\{\int\limits_\Omega \frac{\sigma(x)f_{u_2}(u_1^*(x),0)}{\mu_2(x)}\phi\psi\mathrm{d}x + \int\limits_\Omega \frac{\xi(x)}{\mu_2(x)}\phi\psi\mathrm{d}x\frac{\int\limits_\Omega \alpha(x)g_{u_3}(u_1^*(x),0)\psi^2\mathrm{d}x}{\int\limits_\Omega (d_3(x)|\nabla\psi|^2 + \mu_3(x)\psi^2)\mathrm{d}x}\right\}.$$

When model (2) degenerates into the spatial homogeneous case, that is, all parameters are constants, then from the above expression of $\mathcal{R}_0$ we can directly obtain

$$\mathcal{R}_0 = \frac{\sigma f_{u_2}(u_1^*,0)}{\mu_2} + \frac{\xi\alpha g_{u_3}(u_1^*,0)}{\mu_2\mu_3},$$

where $u_1^* = \frac{\Lambda}{\mu_1}$.

On the other hand, at any fixed position $x \in \Omega$ when we do not consider the spatial diffusion, then model (2) at position x degenerates into the following form of ordinary differential equations

$$\begin{cases} \dfrac{\mathrm{d}u_1}{\mathrm{d}t} = \Lambda(x) - \mu_1(x)u_1 - \sigma(x)f(u_1,u_2) - \alpha(x)g(u_1,u_3), \\ \dfrac{\mathrm{d}u_2}{\mathrm{d}t} = \sigma(x)f(u_1,u_2) + \alpha(x)g(u_1,u_3) - \mu_2(x)u_2, \\ \dfrac{\mathrm{d}u_3}{\mathrm{d}t} = \xi(x)u_2 - \mu_3(x)u_3 - \gamma(x)u_3u_4, \\ \dfrac{\mathrm{d}u_4}{\mathrm{d}t} = \theta(x)u_3u_4 - \mu_4(x)u_4. \end{cases} \tag{14}$$

Model (14) has a unique infection-free equilibrium $E_0 = (u_1^*(x), 0, 0, 0)$. Using the next-generation matrix method, we can directly calculate the virus infection basic reproduction number of model (14) as follows

$$\mathcal{R}_0(x) = r(\mathcal{F}(x)\mathcal{V}^{-1}(x)) = \frac{\sigma(x)f_{u_2}(u_1^*(x),0)}{\mu_2(x)} + \frac{\xi(x)\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_2(x)\mu_3(x)},$$

where

$$\mathcal{F}(x) = \begin{pmatrix} \sigma(x)f_{u_2}(u_1^*(x),0) & \alpha(x)g_{u_3}(u_1^*(x),0) \\ 0 & 0 \end{pmatrix}, \quad \mathcal{V}(x) = \begin{pmatrix} \mu_2(x) & 0 \\ -\xi(x) & \mu_3(x) \end{pmatrix}.$$

Obviously, when all parameters in model (14) are constants, we have $\mathcal{R}_0(x) \equiv \frac{\sigma f_{u_2}(u_1^*,0)}{\mu_2} + \frac{\xi\alpha g_{u_3}(u_1^*,0)}{\mu_2\mu_3} = \mathcal{R}_0$. On this account, we call that $\mathcal{R}_0(x)$ is the local basic reproduction number of model (2) in spatial location $x \in \Omega$.

Denote $\mathcal{R}_{02}(x) = \frac{\xi(x)\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_2(x)\mu_3(x)}$, then $\mathcal{R}_0(x) = \mathcal{R}_{01}(x) + \mathcal{R}_{02}(x)$, where $\mathcal{R}_{01}(x)$ has been defined in the above. It is clear that $\mathcal{R}_{01}(x)$ represents the local reproduction number of cell-to-cell infection in location x and $\mathcal{R}_{02}(x)$ represents the local reproduction number of virus to cells infection in location x.

On the other hand, we consider the following eigenvalue problem

$$\begin{cases} \begin{pmatrix} 0 \\ 0 \end{pmatrix} = \begin{pmatrix} -\mu_2(x) + \sigma(x)f_{u_2}(u_1^*(x),0) & \alpha(x)g_{u_3}(u_1^*(x),0) \\ \eta\xi(x) & \nabla\cdot d_3(x)\nabla - \mu_3(x) \end{pmatrix} \begin{pmatrix} \varphi_1(x) \\ \varphi_2(x) \end{pmatrix}, \ x \in \Omega, \\ \dfrac{\partial}{\partial\nu}\varphi_2(x) = 0, \ x \in \partial\Omega, \end{cases} \tag{15}$$

where η is the eigenvalue and $\varphi = (\varphi_1(x), \varphi_2(x))^T$ is the corresponding eigenfunction. Then, we have the following conclusion.

Lemma 5. *Assume* $\max_{x\in\overline{\Omega}}\mathcal{R}_{01}(x) < 1$. *Then, the eigenvalue problem (15) has a positive principle eigenvalue* η^* *with the strictly positive eigenfunction* $\varphi^* = (\varphi_1^*, \varphi_2^*)^T \in \mathbb{Z}$.

Proof. The problem (15) is equivalent to

$$\begin{cases} -(\mu_2(x) - \sigma(x)f_{u_2}(u_1^*(x),0))\varphi_1(x) + \alpha(x)g_{u_3}(u_1^*(x),0)\varphi_2(x) = 0, \\ \eta\xi(x)\varphi_1(x) + (\nabla\cdot d_3(x)\nabla - \mu_3(x))\varphi_2(x) = 0, \\ \dfrac{\partial}{\partial\nu}\varphi_2(x) = 0, \ x \in \partial\Omega. \end{cases} x \in \Omega, \tag{16}$$

From the first equation of (16), we obtain $\varphi_1(x) = \frac{\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0)}\varphi_2(x)$. Substituting it into second equation of (16), we further obtain

$$\begin{cases} (\nabla\cdot d_3(x)\nabla - \mu_3(x))\varphi_2(x) + \eta\xi(x)\dfrac{\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_2(x) - \sigma(x)f_{u_2}(u_1^*(x),0)}\varphi_2(x) = 0, \ x \in \Omega, \\ \dfrac{\partial}{\partial\nu}\varphi_2(x) = 0, \ x \in \partial\Omega. \end{cases} \tag{17}$$

Then, from Lemma 3.3 in [28], it follows that the eigenvalue problem (17) has a positive principle eigenvalue η^* associated with the strictly positive eigenfunction $\varphi_2^*(x)$. Let $\varphi_1^*(x) = \frac{\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0)}\varphi_2^*(x)$, then it is clear that the eigenvalue problem (15) has a positive principle eigenvalue η^* with the strictly positive eigenfunction $\varphi^* = (\varphi_1^*, \varphi_2^*)^T \in \mathbb{Z}$. This completes the proof. □

Denote $\bar{\mathcal{R}}_0 = \frac{1}{\eta^*}$, then we can get some interesting conclusion as follows.

Lemma 6. *Assume* $\max_{x\in\overline{\Omega}} \mathcal{R}_{01}(x) < 1$. *Then, we have:*
(1) If $\bar{\mathcal{R}}_0 > 1$, *then* $s(\mathcal{A}) > 0$ *and* $\mathcal{R}_0 > 1$;
(2) If $\mathcal{R}_0 < 1$, *then* $s(\mathcal{A}) < 0$ *and* $\bar{\mathcal{R}}_0 < 1$.

Proof. Consider conclusion (1). Let

$$\overline{\mathcal{A}}(x) = \begin{pmatrix} -\mu_2(x) + \sigma(x)f_{u_2}(u_1^*(x),0) & \alpha(x)g_{u_3}(u_1^*(x),0) \\ \dfrac{1}{\bar{\mathcal{R}}_0}\xi(x) & \nabla\cdot d_3(x)\nabla - \mu_3(x) \end{pmatrix}.$$

If $\bar{\mathcal{R}}_0 > 1$, then from Lemma 5 we obtain $s(\overline{\mathcal{A}}(x)) > 0$. Since

$$\mathcal{A}(x) = \begin{pmatrix} -\mu_2(x) + \sigma(x)f_{u_2}(u_1^*(x),0) & \alpha(x)g_{u_3}(u_1^*(x),0) \\ \xi(x) & \nabla\cdot d_3(x)\nabla - \mu_3(x) \end{pmatrix} \geq \overline{\mathcal{A}}(x),\ x\in\overline{\Omega},$$

we can obtain $s(\mathcal{A}(x)) > s(\overline{\mathcal{A}}(x))$. Therefore, by Lemma 3 it follows that $\mathcal{R}_0 > 1$.

Consider conclusion (2). If $\mathcal{R}_0 < 1$, then from Lemma 3 we have $s(\mathcal{A}(x)) < 0$. Hence, it is clear that $\bar{\mathcal{R}}_0 < 1$. This completes the proof. □

Remark 2. From Lemma 6, we can propose the following conjecture:
Let $\max_{x\in\overline{\Omega}} \mathcal{R}_{01}(x) < 1$, then $\mathcal{R}_0 > 1\ (=1,\ <1) \Leftrightarrow \bar{\mathcal{R}}_0 > 1\ (=1,\ <1)$.

From (17), we get

$$\begin{cases} \bar{\mathcal{R}}_0(\nabla\cdot d_3(x)\nabla - \mu_3(x))\varphi_2^*(x) = -\dfrac{\xi(x)\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0)}\varphi_2^*(x),\ x\in\Omega, \\ \dfrac{\partial}{\partial\nu}\varphi_2^*(x) = 0,\ x\in\partial\Omega. \end{cases} \tag{18}$$

Hence, $\bar{\mathcal{R}}_0$ has the following expression

$$\bar{\mathcal{R}}_0 = \frac{\int\limits_{\Omega} \frac{\xi(x)\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0)}\varphi_2^{*2}(x)\mathrm{d}x}{\int\limits_{\Omega}(d_3(x)|\nabla\varphi_2^*(x)|^2 + \mu_3(x)\varphi_2^{*2}(x))\mathrm{d}x}.$$

Thus, we finally obtain

$$\bar{\mathcal{R}}_0 = \sup_{\varphi\in H^1(\Omega)} \left\{ \frac{\int\limits_{\Omega} \frac{\xi(x)\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0)}\varphi^2(x)\mathrm{d}x}{\int\limits_{\Omega}(d_3(x)|\nabla\varphi(x)|^2 + \mu_3(x)\varphi^2(x))\mathrm{d}x} \right\}.$$

From this expression of $\bar{\mathcal{R}}_0$, the following conclusion follows from a similar argument as in [33, Theorem 3.3].

Lemma 7. *Assume* $\max_{x\in\overline{\Omega}} \mathcal{R}_{01}(x) < 1$ *and* $d_3(x) = d_3 > 0$ *is a constant. Then, we have:*
(1) $\bar{\mathcal{R}}_0$ *is decreasing along with the increase of* d_3.
(2) If $d_3 \to 0$, *then* $\bar{\mathcal{R}}_0 \to \max_{x\in\overline{\Omega}}\{\frac{\xi(x)\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_3(x)(\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0))}\}$.
(3) If $d_3 \to \infty$, *then* $\bar{\mathcal{R}}_0 \to \frac{\int_{\Omega}\frac{\xi(x)\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0)}\mathrm{d}x}{\int_{\Omega}\mu_3(x)\mathrm{d}x}$.

(4) If $\int_\Omega \frac{\xi(x)\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0)}\mathrm{d}x > \int_\Omega \mu_3(x)\mathrm{d}x$, *then* $\bar{\mathcal{R}}_0 > 1$ *for all* $d_3 > 0$.

(5) If $\int_\Omega \frac{\xi(x)\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0)}\mathrm{d}x < \int_\Omega \mu_3(x)\mathrm{d}x$ *and there is a* $x \in \Omega$ *such that* $\frac{\xi(x)\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0)} > \mu_3(x)$, *then there is a* $d_3^* > 0$ *such that* $\bar{\mathcal{R}}_0 > 1$ *when* $0 < d_3 < d_3^*$, *and* $\bar{\mathcal{R}}_0 < 1$ *when* $d_3 > d_3^*$.

Particularly, when model (2) degenerates into the spatial homogeneous case, from the above expression of $\bar{\mathcal{R}}_0$ we can directly obtain

$$\bar{\mathcal{R}}_0 = \frac{\xi\alpha g_{u_3}(u_1^*,0)}{\mu_3(\mu_2-\sigma f_{u_2}(u_1^*,0))}.$$

We can directly obtain that when $\mu_2 - \sigma f_{u_2}(u_1^*,0) > 0$ then

$$\begin{aligned}\bar{\mathcal{R}}_0 > (=,<)\ 1 &\Leftrightarrow \xi\alpha g_{u_3}(u_1^*,0) > (=,<)\ \mu_2\mu_3 - \sigma f_{u_2}(u_1^*,0)\mu_3\\ &\Leftrightarrow \xi\alpha g_{u_3}(u_1^*,0) + \sigma f_{u_2}(u_1^*,0)\mu_3 > (=,<)\ \mu_2\mu_3\\ &\Leftrightarrow \mathcal{R}_0 = \frac{\xi\alpha g_{u_3}(u_1^*,0)}{\mu_2\mu_3} + \frac{\sigma f_{u_2}(u_1^*,0)}{\mu_2} > (=,<)\ 1.\end{aligned}$$

This shows that the above conjecture given in Remark 2 is right when model (2) degenerates into the spatial homogeneous case.

Lemma 8. *Assume* $\max_{x\in\overline{\Omega}}\mathcal{R}_{01}(x) < 1$. *Then,* $\bar{\mathcal{R}}_0 - 1$ *has the same sign as* η^0, *where* η^0 *is the principle eigenvalue of the following eigenvalue problem*

$$\begin{cases}(\nabla\cdot d_3(x)\nabla - \mu_3(x))\psi + \dfrac{\xi(x)\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0)}\psi = \eta\psi,\ x\in\Omega,\\ \dfrac{\partial\psi}{\partial\nu} = 0,\ x\in\partial\Omega.\end{cases} \tag{19}$$

Proof. In fact, from Lemma 3.3 in [28], it follows that problem (19) has a principle eigenvalue η^0 corresponding to a positive eigenfunction $\psi^*(x)$ such that

$$\begin{cases}(\nabla\cdot d_3(x)\nabla - \mu_3(x))\psi^* + \dfrac{\xi(x)\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0)}\psi^* = \eta^0\psi^*,\ x\in\Omega,\\ \dfrac{\partial\psi^*}{\partial\nu} = 0,\ x\in\partial\Omega.\end{cases} \tag{20}$$

Multiplying (18) by ψ^* and (20) by φ_2^*, we can obtain

$$(1-\frac{1}{\bar{\mathcal{R}}_0})\int_\Omega \frac{\xi(x)\alpha(x)g_{u_3}(u_1^*(x),0)}{\mu_2(x)-\sigma(x)f_{u_2}(u_1^*(x),0)}\psi^*\varphi_2^*\mathrm{d}x = \eta^0\int_\Omega \psi^*\varphi_2^*\mathrm{d}x.$$

This implies that $(1-\frac{1}{\bar{\mathcal{R}}_0})$ and η^0 have the same sign. Therefore, the conclusions of Lemma 8 hold. This completes the proof. □

Remark 3. In the above discussions of this section, we always assume $\max_{x\in\overline{\Omega}}\mathcal{R}_{01}(x) < 1$. This means that in model (2) the virus infection cannot be endemic only by relying on the cell-to-cell transmission. Therefore, an important open problem is to study model (2) when condition $\max_{x\in\overline{\Omega}}\mathcal{R}_{01}(x) < 1$ does not hold.

4. Extinction of disease

In this section, we mainly focus on the stability of infection-free steady state E_0, and the details can be found in the following results.

Theorem 2. *Assume* $\max_{x\in\overline{\Omega}}\mathcal{R}_{01}(x)<1$. *When* $\mathcal{R}_0<1$, E_0 *is globally asymptotically stable.*

Proof. The local stability of E_0 directly follows from the conclusion (2) of Lemma 3. We next show the global attractivity of E_0. Let $g=(g_1,g_2,g_3,g_4)$ be defined as

$$\begin{aligned}
g_1(x,u_1,u_2,u_3,u_4)&=\Lambda(x)-\mu_1(x)u_1-\sigma(x)f(u_1,u_2)-\alpha(x)g(u_1,u_3),\\
g_2(x,u_1,u_2,u_3,u_4)&=\sigma(x)f(u_1,u_2)+\alpha(x)g(u_1,u_3-\mu_2(x)u_2,\\
g_3(x,u_1,u_2,u_3,u_4)&=\xi(x)u_2-\mu_3(x)u_3-\gamma(x)u_3u_4,\\
g_4(x,u_1,u_2,u_3,u_4)&=\theta(x)u_3u_4-\mu_4(x)u_4.
\end{aligned}\tag{21}$$

Obviously, the Jacobian matrix of $g(x,u_1,u_2,u_3,u_4)$ with respect to (u_1,u_2,u_3,u_4) is cooperative and irreducible at any point $(x,u_1,u_2,u_3,u_4)\in\Omega\times\mathbb{X}_+$. Define an operator $\mathcal{P}$ on $\mathbb{X}_+$ by

$$[\mathcal{P}(\varphi)](x)=g(x,\varphi_1(x),\varphi_2(x),\varphi_3(x),\varphi_4(x)),\ x\in\overline{\Omega},\ \varphi=(\varphi_1,\varphi_2,\varphi_3,\varphi_4)\in\mathbb{X}_+.$$

It is evident that $\mathcal{P}$ is strictly subhomogeneous on $\mathbb{X}_+$, i.e., $\mathcal{P}(s\varphi)>s\mathcal{P}(\varphi)$ for any $0<s<1$ and $\varphi\in\mathbb{X}_+$ with $\varphi\gg 0$. Furthermore, it easily follows that map $\Phi(t)$ is strongly monotone and strictly subhomogeneous using the similar arguments in the proof of [21, Theorem 7.4.1] with $\tau=0$.

From model (2), we have $\frac{\partial u_1}{\partial t}\le\Lambda(x)-\mu_1(x)u_1$. Thus, we can get $\limsup_{t\to\infty}u_1(t,x)\le u_1^*(x)$ uniformly for $x\in\overline{\Omega}$. There is no loss of generality in assuming $u_1(t,x)\le u_1^*(x)$ for all $t\ge 0$ and $x\in\overline{\Omega}$. Therefore, we have

$$\begin{cases}
\dfrac{\partial u_2}{\partial t}\le\sigma(x)f_{u_2}(u_1^*(x),0)u_2+\alpha(x)g_{u_3}(u_1^*(x),0)u_3-\mu_2(x)u_2,\\
\dfrac{\partial u_3}{\partial t}\le\nabla\cdot d_3(x)\nabla u_3+\xi(x)u_2-\mu_3(x)u_3.
\end{cases}\tag{22}$$

The corresponding comparison system is

$$\begin{cases}
\dfrac{\partial w_2}{\partial t}=\sigma(x)f_{u_2}(u_1^*(x),0)w_2+\alpha(x)g_{u_3}(u_1^*(x),0)w_3-\mu_2(x)w_2,\\
\dfrac{\partial w_3}{\partial t}=\nabla\cdot d_3(x)\nabla w_3+\xi(x)w_2-\mu_3(x)w_3.
\end{cases}\tag{23}$$

Obviously, system (23) is equivalent to subsystem (6). If $\mathcal{R}_0<1$, then $s(\mathcal{A})<0$ by Lemma 3. Denote $\omega(Q)$ as the exponential growth bound of $Q(t)$. It easily follows that $\omega(Q)=s(\mathcal{A})<0$ from [24, Theorem 3.14]. Based on the definition of $\omega(Q)$, we have $\lim_{t\to\infty}\|Q(t)\|=0$, and hence, $\lim_{t\to\infty}Q(t)\psi=0$ for all $\psi\in\mathbb{Z}_+$. Therefore, we obtain that $(w_2(t,x),w_3(t,x))\to(0,0)$ uniformly for $x\in\overline{\Omega}$ as $t\to\infty$, where $(w_2(t,x),w_3(t,x))$ is the solution of model (23) with initial value in $\mathbb{Z}_+$. Furthermore, we obtain that $(u_2(t,x),u_3(t,x))\le(w_2(t,x),w_3(t,x))$ for all $x\in\Omega$ and $t\ge 0$. Therefore, $(u_2(t,x),u_3(t,x))\to(0,0)$ uniformly for $x\in\overline{\Omega}$ as $t\to\infty$. In this case, we have the limit equations from model (2),

$$\begin{cases}
\dfrac{\partial u_1}{\partial t}=\Lambda(x)-\mu_1(x)u_1,\\
\dfrac{\partial u_4}{\partial t}=\nabla\cdot d_4(x)\nabla u_4-\mu_4(x)u_4.
\end{cases}$$

From Corollary 4.3 in [23], we further obtain that $u_4(t,x)\to 0$ and $u_1(t,x)\to u_1^*(x)$ uniformly for $x\in\overline{\Omega}$ as $t\to\infty$. To sum up, the theorem is proved. □

In particular, we can get the global stability of E_0 using Lyapunov function.

Theorem 3. *Assume that* $\max_{x\in\overline{\Omega}}\mathcal{R}_0(x)<1$, *then infection-free steady state* E_0 *of model (2) is globally asymptotically stable.*

Proof. It is clear that we only need to prove that the zero solution $(w_2, w_3) = (0, 0)$ of corresponding comparison system (23) is globally attractive. Define the Lyapunov function: $L = c_1 \int_\Omega w_2 \mathrm{d}x + c_2 \int_\Omega w_3 \mathrm{d}x$, where c_1 and c_2 are positive undetermined constants. By simple calculation, we have

$$\frac{\mathrm{d}L}{\mathrm{d}t} = \int_\Omega [c_1(\alpha(x) g_{u_3}(u_1^*(x), 0) w_3 + \sigma(x) f_{u_2}(u_1^*(x), 0) w_2 - \mu_2(x) w_2) + c_2(\xi(x) w_2 - \mu_3(x) w_3)] \mathrm{d}x.$$

Since functions $\mu_2(x)$, $\xi(x)$, $\sigma(x)$ and $u_1^*(x)$ are positive, continuous and bounded on $\overline{\Omega}$, and

$$\max_{x\in\overline{\Omega}} \mathcal{R}_0(x) < 1 \Rightarrow \max_{x\in\overline{\Omega}} \left\{ \frac{\sigma(x) f_{u_2}(u_1^*(x), 0)}{\mu_2(x)} \right\} < 1, \quad \max_{x\in\overline{\Omega}} \left\{ \frac{\xi(x)\alpha(x) g_{u_3}(u_1^*(x), 0)}{\mu_2(x)\mu_3(x)} \right\} < 1,$$

we can obtain that $c_1\mu_2(x) \geq c_2\xi(x) + c_1\sigma(x) f_{u_2}(u_1^*(x), 0)$ and $c_2\mu_3(x) \geq c_1\alpha(x) g_{u_3}(u_1^*(x), 0)$, where c_1 and c_2 are positive constants. Hence, we further obtain $\frac{\mathrm{d}L}{\mathrm{d}t} \leq \int_\Omega [c_1\alpha(x) g_{u_3}(u_1^*(x), 0) - c_2\mu_3(x)] w_3 \mathrm{d}x \leq 0$. Furthermore, it is clear that $\frac{\mathrm{d}L}{\mathrm{d}t} = 0$ implies $w_3(t, x) \equiv 0$. And then, we can get $w_2(t, x) \equiv 0$ from system (23). Thus, by the LaSalle's invariance principle (see [26, Theorem 4.2]), we finally obtain that the zero solution $(w_2, w_3) = (0, 0)$ of system (23) is globally attractive. This completes the proof. □

Remark 4. Combining Theorems 2 and 3, an interesting problem is to discuss the relationship between total basic reproduction number $\mathcal{R}_0$ and local basic reproduction number $\mathcal{R}_0(x)$. Particularly, whether we may obtain that $\max_{x\in\overline{\Omega}} \mathcal{R}_0(x) < 1 \Rightarrow \mathcal{R}_0 < 1$.

5. Virus infective dynamics without antibody response

In this section, we will be concerned with the virus infective dynamics when model (2) without antibody response. Since the first two equations in model (2) have no diffusion term, in order to obtain the existence of antibody-free steady state of model (2), we need to prove $\Phi(t) : \mathbb{X}_+ \to \mathbb{X}_+$ is k-contraction. However, it is regrettable that here we only can prove the k-contraction for the following special case of model (2)

$$\begin{cases} \dfrac{\partial u_1}{\partial t} = \Lambda(x) - \mu_1(x) u_1 - \alpha(x) u_1 h(u_3), \\ \dfrac{\partial u_2}{\partial t} = \alpha(x) u_1 h(u_3) - \mu_2(x) u_2, \\ \dfrac{\partial u_3}{\partial t} = \nabla \cdot d_3(x) \nabla u_3 + \xi(x) u_2 - \mu_3(x) u_3 - \gamma(x) u_3 u_4, \\ \dfrac{\partial u_4}{\partial t} = \nabla \cdot d_4(x) \nabla u_4 + \theta(x) u_3 u_4 - \mu_4(x) u_4. \end{cases} \tag{24}$$

That is, in model (2) we assume $\sigma(x) \equiv 0$, which means that there is no transmission between cells, and $g(u_1, u_3) = u_1 h(u_3)$. Further, for model (24) we assume $\mu_1(x) \equiv \mu_2(x)$. This shows that the infected cell individual does not have the death due to infection. In model (24), the functions $h(u_3)$ are assumed to satisfy the following assumption:

(H_2) Function $h : R_+ \to R_+$ is continuously differentiable; $h(0) \equiv 0$, $h(u_3) \leq h_{u_3}(0) u_3$.

Let $N(t, x) = u_1(t, x) + u_2(t, x)$, then $\frac{\partial N}{\partial t} = \Lambda(x) - \mu_1(x) N$. We have $\lim_{t\to\infty} N(t, x) = \frac{\Lambda(x)}{\mu_1(x)}$ for all $x \in \overline{\Omega}$. Therefore, there is no loss of generality in assuming $N(t, x) \equiv N^*(x) := \frac{\Lambda(x)}{\mu_1(x)}$. From this, model

(24) can be equivalently simplified into the following form

$$\begin{cases} \dfrac{\partial u_2}{\partial t} = \alpha(x)(N^*(x) - u_2)h(u_3) - \mu_1(x)u_2, \\ \dfrac{\partial u_3}{\partial t} = \nabla \cdot d_3(x)\nabla u_3 + \xi(x)u_2 - \mu_3(x)u_3 - \gamma(x)u_3u_4, \\ \dfrac{\partial u_4}{\partial t} = \nabla \cdot d_4(x)\nabla u_4 + \theta(x)u_3u_4 - \mu_4(x)u_4. \end{cases} \tag{25}$$

Let $\mathbb{W} := C(\overline{\Omega}, R^3)$ and $\mathbb{W}_+ := C(\overline{\Omega}, R^3_+)$. For model (25), we can first obtain a similar conclusion to Theorem 1 given in Sect. 2.

Theorem 4. *For any initial value function $\phi \in \mathbb{W}_+$, model (25) has a unique solution $u(t,\cdot,\phi) = (u_2(t,\cdot,\phi), u_3(t,\cdot,\phi), u_4(t,\cdot,\phi))$ defined on $[0,+\infty)$, and the solution is also nonnegative, ultimately bounded and uniformly bounded.*

Furthermore, we next claim the following result.

Lemma 9. *The solution semiflow $\Psi(t) := u(t,\cdot) : \mathbb{W}_+ \to \mathbb{W}_+$ of model (25) is k-contracting with the Kuratowski measure κ of noncompactness on $\mathbb{W}_+$.*

Proof. For any initial value $\phi \in \mathbb{W}_+$, throughout the proof, $u(t,\cdot,\phi) = \Psi(t)\phi = (u_2(t,\cdot,\phi), u_3(t,\cdot,\phi), u_4(t,\cdot,\phi))$ denotes the solution of model (25). From the first equations of model (25), solving $u_2(t,\cdot,\phi)$ yields

$$u_2(t,\cdot,\phi) = e^{-\int_0^t (\mu_1(\cdot)+\alpha(\cdot)h(u_3(s,\cdot,\phi)))\mathrm{d}s}\phi_2 + S_2(t,\cdot,\phi), \tag{26}$$

where $S_2(t,\cdot,\phi) = \int_0^t \alpha(\cdot)N^*(\cdot)h(u_3(s,\cdot,\phi))e^{-\int_s^t (\mu_1(\cdot)+\alpha(\cdot)h(u_3(r,\cdot,\phi)))\mathrm{d}r}\mathrm{d}s$. Based on (26), set $\Psi(t) = \Psi_1(t) + \Psi_2(t)$ for any $t \geq 0$, where

$$\Psi_1(t)\phi = (S_2(t,\cdot,\phi), u_3(t,\cdot,\phi), u_4(t,\cdot,\phi)),\ \Psi_2(t)\phi = (e^{-\int_0^t (\mu_1(\cdot)+\alpha(\cdot)h(u_3(s,\cdot,\phi)))\mathrm{d}s}\phi_2, 0, 0),\ t \geq 0.$$

For any bounded set $\mathbb{B} \subset \mathbb{W}_+$, since the last two equations of model (25) have the diffusion terms, we directly obtain that the sets $\{u_3(t,\cdot,\phi) : \phi \in \mathbb{B}, t > 0\}$ and $\{u_4(t,\cdot,\phi) : \phi \in \mathbb{B}, t > 0\}$ are precompact in $\mathbb{Y}_+$. And then, we further obtain that the set $\{S_2(t,\cdot,\phi) : \phi \in \mathbb{B}, t > 0\}$ is also precompact in $\mathbb{Y}_+$. Therefore, we have $\kappa(\Psi_1(t)\mathbb{B}) = 0$.

It is clear that $\|\Psi_2(t)\| = \sup_{\phi\in\mathbb{Z}} \frac{\|\Psi_2(t)\phi\|_{\mathbb{Z}}}{\|\phi\|_{\mathbb{Z}}} \leq e^{-\delta t}\sup_{\phi\in\mathbb{Z}} \frac{\|\phi\|_{\mathbb{Z}}}{\|\phi\|_{\mathbb{Z}}} = e^{-\delta t}$, where $\delta = \min_{x\in\overline{\Omega}}\{\mu_1(x)\}$. Therefore, we further have $\kappa(\Psi(t)\mathbb{B}) \leq \kappa(\Psi_1(t)\mathbb{B}) + \kappa(\Psi_2(t)\mathbb{B}) \leq \|\Psi_2(t)\|\kappa(\mathbb{B}) \leq e^{-\delta t}\kappa(\mathbb{B})$. This completes the proof. □

Remark 5. If $\mu_1(x) \not\equiv \mu_2(x)$, then model (24) cannot transform to model (25). Unfortunately, here we have not been able to prove the k-contraction for model (24). This will be an interesting open problem.

Remark 6. Unfortunately, if $g(u_1,u_3) \neq u_1h(u_3)$ in model (25), we cannot solve u_2 like (26) and thus cannot further prove the k-contraction for model (24). We will try to find a suitable method to overcome this problem in the future.

Based on Theorem 4 and Lemma 9, we have the following result from [11, Theorem 2.6].

Theorem 5. *The solution semiflow $\Psi(t)$ of model (25) admits a compact global attractor in $\mathbb{W}_+$.*

Next, a same argument as in Sect. 3 we can define the next generation operator for model (24) by

$$\widehat{\mathscr{L}}(\phi)(x) := \int_0^\infty \widehat{\mathcal{F}}(x)\widehat{\Phi}(t)\phi(x)\mathrm{d}t = \widehat{\mathcal{F}}(x)\int_0^\infty \widehat{\Phi}(t)\phi(x)\mathrm{d}t,\ \phi \in \mathbb{Z},$$

where

$$\widehat{\mathcal{B}}=\begin{pmatrix}-\mu_1(\cdot) & 0\\ \xi(\cdot) & \nabla\cdot d_3(x)\nabla-\mu_3(\cdot)\end{pmatrix},\ \widehat{\mathcal{F}}=\begin{pmatrix}0 & \alpha(\cdot)N^*(\cdot)h_{u_3}(0)\\ 0 & 0\end{pmatrix}.$$

and $\widehat{\Phi}(t)$ is the C^0-semigroup generated by $\widehat{\mathcal{B}}$. The basic reproduction number $\widehat{\mathcal{R}}_0$ for model (25) is defined by $\widehat{\mathcal{R}}_0:=r(\widehat{\mathscr{L}})$. In addition, a similar calculation as in Sect. 3 we also can obtain

$$\widehat{\mathcal{R}}_0=\sup_{\phi,\psi\in H^1(\Omega),\int_\Omega\phi\psi\mathrm{d}x=1}\left\{\int_\Omega\frac{\xi(x)}{\mu_1(x)}\phi\psi\mathrm{d}x\frac{\int_\Omega\alpha(x)N^*(x)h_{u_3}(0)\psi^2\mathrm{d}x}{\int_\Omega(d_3(x)|\nabla\psi|^2+\mu_3(x)\psi^2)\mathrm{d}x}\right\}.$$

Remark 7. Obviously, $\widehat{\mathcal{R}}_0$ is a special case of $\mathcal{R}_0$ defined in the above for the general case. That is, when $\sigma(x)\equiv 0$, $\mu_1(x)\equiv\mu_2(x)$ and $g(u_1,u_3)=u_1h(u_3)$, then $\mathcal{R}_0=\widehat{\mathcal{R}}_0$.

Consider the following eigenvalue problem,

$$\begin{cases}\lambda\begin{pmatrix}\psi_2\\ \psi_3\end{pmatrix}=\widehat{\mathcal{A}}\begin{pmatrix}\psi_2\\ \psi_3\end{pmatrix},\ \ x\in\Omega,\\ \dfrac{\partial\psi_3}{\partial\nu}=0,\ \ x\in\partial\Omega,\end{cases}\tag{27}$$

where $\widehat{\mathcal{A}}=\widehat{\mathcal{B}}+\widehat{\mathcal{F}}$. By the similar argument of Lemmas 2 and 4, the following result is valid.

Lemma 10. *If $\widehat{\mathcal{R}}_0\geq 1$, then $s(\widehat{\mathcal{A}})$ is the principle eigenvalue of eigenvalue problem (27) with a strictly positive eigenfunction.*

Clearly, model (25) always has an infection-free steady state $E_0^*=(0,0,0)$. When $\widehat{\mathcal{R}}_0>1$, we investigate the existence of the antibody-free steady state $E_1^*=(\tilde{u}_2(x),\tilde{u}_3(x),0)$ of model (25) which satisfies the following equations:

$$\begin{cases}\alpha(x)(N^*(x)-\tilde{u}_2(x))h(\tilde{u}_3(x))-\mu_1(x)\tilde{u}_2(x)=0,\ \ x\in\Omega,\\ \nabla\cdot d_3(x)\nabla\tilde{u}_3(x)+\xi(x)\tilde{u}_2(x)-\mu_3(x)\tilde{u}_3(x)=0,\ \ x\in\Omega,\\ \dfrac{\partial\tilde{u}_3(x)}{\partial\nu}=0,\ x\in\partial\Omega,\end{cases}\tag{28}$$

On this basis, model (24) has an antibody-free steady state, denoted by $E_1=(\tilde{u}_1(x),\tilde{u}_2(x),\tilde{u}_3(x),0)$ where $\tilde{u}_1(x)=N^*(x)-\tilde{u}_2(x)$.

Theorem 6. *When $\widehat{\mathcal{R}}_0>1$, model (25) admits an antibody-free steady state $E_1^*=(\tilde{u}_2(x),\tilde{u}_3(x),0)$.*

Proof. It is easily seen that $\tilde{u}_2(x)=\frac{\alpha(x)N^*(x)h(\tilde{u}_3(x))}{\alpha(x)h(\tilde{u}_3(x))+\mu_1(x)}$ from the first equation of (28). Substituting it into the second equation of (28), we further have

$$\begin{cases}\nabla\cdot d_3(x)\nabla\tilde{u}_3(x)+\xi(x)\dfrac{\alpha(x)N^*(x)}{\alpha(x)h(\tilde{u}_3(x))+\mu_1(x)}h(\tilde{u}_3(x))-\mu_3(x)\tilde{u}_3(x)=0,\ x\in\Omega,\\ \dfrac{\partial\tilde{u}_3(x)(x)}{\partial\nu}=0,\ x\in\partial\Omega.\end{cases}$$

Obviously, we only need to prove that when $\widehat{\mathcal{R}}_0>1$,

$$\begin{cases}\nabla\cdot d_3(x)\nabla u_3(x)+\xi(x)\dfrac{\alpha(x)N^*(x)}{\alpha(x)h(u_3(x))+\mu_1(x)}h(u_3(x))-\mu_3(x)u_3(x)=0,\ x\in\Omega,\\ \dfrac{\partial u_3(x)(x)}{\partial\nu}=0,\ x\in\partial\Omega.\end{cases}\tag{29}$$

has a positive solution $\tilde{u}_3(x)$.

Firstly, from assumption (H_2), we can obtain

$$\frac{\alpha(x)N^*(x)}{\alpha(x)h(u_3(x))+\mu_1(x)}h(u_3(x)) \le \frac{\alpha(x)N^*(x)}{\alpha(x)h(u_3(x))+\mu_1(x)}h_{u_3}(0)u_3(x).$$

Further, choose an enough large constant $M > 0$ such that $h(M)$ enough large, and then, we have $\frac{\xi(x)\alpha(x)N^*(x)}{\alpha(x)h(M)+\mu_1(x)}h_{u_3}(0) - \mu_3(x) < 0$ for all $x \in \Omega$, which means that $u_3(x) = M$ is a super-solution of equation (29).

Consider the following eigenvalue problem

$$\begin{cases} \lambda\psi(x) = (\nabla\cdot d_3(x)\nabla - \mu_3(x))\psi(x) + \dfrac{\xi(x)\alpha(x)N^*(x)h_{u_3}(0)}{\mu_1(x)}\psi(x),\ x\in\Omega, \\ \dfrac{\partial}{\partial\nu}\psi(x) = 0,\ x\in\partial\Omega. \end{cases} \tag{30}$$

From Lemma 3.3 in [28], we obtain that the problem (30) has a principle eigenvalue $\lambda = \lambda^*$ associated with the strictly positive eigenfunction $\psi(x) = \psi^*(x)$. Moreover, by Lemma 4 and Lemma 5, we can obtain that when $\widehat{\mathcal{R}}_0 > 1$, then $\lambda^* > 0$. Since

$$\lambda^*\psi^*(x) = (\nabla\cdot d_3(x)\nabla - \mu_3(x))\psi^*(x) + \frac{\xi(x)\alpha(x)N^*(x)h_{u_3}(0)}{\mu_1(x)}\psi^*(x),\ x\in\Omega,$$

then for any constant $k > 0$ we also have

$$\lambda^*(k\psi^*(x)) = (\nabla\cdot d_3(x)\nabla - \mu_3(x))(k\psi^*(x)) + \frac{\xi(x)\alpha(x)N^*(x)h_{u_3}(0)}{\mu_1(x)}(k\psi^*(x)),\ x\in\Omega,$$

We have

$$\begin{aligned} &(\nabla\cdot d_3(x)\nabla - \mu_3(x))(k\psi^*(x)) + \frac{\xi(x)\alpha(x)N^*(x)}{\alpha(x)h(k\psi^*(x))+\mu_1(x)}h(k\psi^*(x)) \\ &= \lambda^*(k\psi^*(x)) + \frac{\xi(x)\alpha(x)N^*(x)}{\alpha(x)(k\psi^*(x))+\mu_1(x)}(k\psi^*(x)) - \frac{\xi(x)\alpha(x)N^*(x)}{\mu_1(x)}(k\psi^*(x)) \\ &= \left(\lambda^* - \frac{\xi(x)\alpha^2(x)N^*(x)h_{u_3}(0)h(k\psi^*(x) + \xi(x)\alpha(x)N^*(x)\mu_1(x)\left(h_{u_3}(0) - \frac{h(k\psi^*(x)}{(k\psi^*(x)}\right)}{(\alpha(x)h(k\psi^*(x))+\mu_1(x))\mu_1(x)}\right)(k\psi^*(x)). \end{aligned}$$

Obviously, we can choose an enough small constant $k = k^* > 0$ such that

$$\lambda^* - \frac{\xi(x)\alpha^2(x)N^*(x)h_{u_3}(0)h(k\psi^*(x) + \xi(x)\alpha(x)N^*(x)\mu_1(x)\left(h_{u_3}(0) - \frac{h(k\psi^*(x)}{(k\psi^*(x)}\right)}{(\alpha(x)h(k\psi^*(x))+\mu_1(x))\mu_1(x)} > 0,\ x\in\Omega.$$

Therefore, we have

$$(\nabla\cdot d_3(x)\nabla - \mu_3(x))(k^*\psi^*(x)) + \frac{\xi(x)\alpha(x)N^*(x)}{\alpha(x)h(k^*\psi^*(x))+\mu_1(x)}h(k^*\psi^*(x)) > 0,\ x\in\Omega.$$

This shows that $u_3(x) = k^*\psi^*(x)$ is a lower solution of equation (29). From Theorem 2.3.2 in [35], we can conclude that when $\widehat{\mathcal{R}}_0 > 1$, equation (29) at least has a positive solution $\tilde{u}_3(x)$. Therefore, we finally obtain that when $\widehat{\mathcal{R}}_0 > 1$ model (25) has an antibody-free steady state $E_1^* = (\tilde{u}_2(x), \tilde{u}_3(x), 0)$. This completes the proof. □

When $u_4 = 0$, then model (25) becomes to

$$\begin{cases} \dfrac{\partial u_2}{\partial t} = \alpha(x)(N^*(x) - u_2)h(u_3) - \mu_1(x)u_2, \\ \dfrac{\partial u_3}{\partial t} = \nabla\cdot d_3(x)\nabla u_3 + \xi(x)u_2 - \mu_3(x)u_3. \end{cases} \tag{31}$$

We have the following result on the global stability of steady state $\widetilde{E}_1 = (\tilde{u}_2(x), \tilde{u}_3(x))$ for model (31).

Theorem 7. *Assume* $\widehat{\mathcal{R}}_0 > 1$ *and*

$$\left(1 - \frac{\tilde{u}_2}{u_2}\right)\left(\frac{(N^*(x) - u_2)h(u_3)}{(N^*(x) - \tilde{u}_2)h(\tilde{u}_3)} - \frac{u_3}{\tilde{u}_3}\right) \leq 0, \tag{32}$$

then steady state $\widetilde{E}_1 = (\tilde{u}_2(x), \tilde{u}_3(x))$ *of model (31) is globally asymptotically stable.*

Proof. Define a Lyapunov function: $L = L_1 + L_2$, where

$$L_1 = \int_\Omega \frac{\xi(x)\tilde{u}_2\tilde{u}_3}{\alpha(x)(N^*(x) - \tilde{u}_2)h(\tilde{u}_3)}\Big(u_2 - \tilde{u}_2 - \tilde{u}_2 \ln\frac{u_2}{\tilde{u}_2}\Big)\mathrm{d}x, \quad L_2 = \int_\Omega \tilde{u}_3\Big(u_3 - \tilde{u}_3 - \tilde{u}_3 \ln\frac{u_3}{\tilde{u}_3}\Big)\mathrm{d}x$$

Further, we have

$$\begin{aligned}
\frac{\mathrm{d}L_1}{\mathrm{d}t} &= \int_\Omega \frac{\xi(x)\tilde{u}_2\tilde{u}_3}{\alpha(x)(N^*(x) - \tilde{u}_2)h(\tilde{u}_3)}\left(1 - \frac{\tilde{u}_2}{u_2}\right)\frac{\mathrm{d}u_2}{\mathrm{d}t}\mathrm{d}x \\
&= \int_\Omega \frac{\xi(x)\tilde{u}_2\tilde{u}_3}{\alpha(x)(N^*(x) - \tilde{u}_2)h(\tilde{u}_3)}\big[\alpha(x)(N^*(x) - u_2)h(u_3) - \alpha(x)(N^*(x) - \tilde{u}_2)h(\tilde{u}_3)\frac{u_2}{\tilde{u}_2} \\
&\quad - \alpha(x)(N^*(x) - u_2)h(u_3)\frac{\tilde{u}_2}{u_2} + \alpha(x)(N^*(x) - \tilde{u}_2)h(\tilde{u}_3)\big]\mathrm{d}x \\
&= \int_\Omega \xi(x)\tilde{u}_2\tilde{u}_3\left[\frac{(N^*(x) - u_2)h(u_3)}{(N^*(x) - \tilde{u}_2)h(\tilde{u}_3)} - \frac{u_2}{\tilde{u}_2} - \frac{(N^*(x) - u_2)h(u_3)\tilde{u}_2}{(N^*(x) - \tilde{u}_2)h(\tilde{u}_3)u_2} + 1\right]\mathrm{d}x
\end{aligned}$$

$$\begin{aligned}
\frac{\mathrm{d}L_2}{\mathrm{d}t} &= \int_\Omega \tilde{u}_3\left(1 - \frac{\tilde{u}_3}{u_3}\right)\frac{\mathrm{d}u_3}{\mathrm{d}t}\mathrm{d}x \\
&= \int_\Omega \tilde{u}_3\left(1 - \frac{\tilde{u}_3}{u_3}\right)\nabla\cdot d_3(x)\nabla u_3 + \int_\Omega \tilde{u}_3\left(1 - \frac{u_3}{\tilde{u}_3}\right)\nabla\cdot d_3(x)\nabla\tilde{u}_3\mathrm{d}x \\
&\quad + \int_\Omega \xi(x)\tilde{u}_2\tilde{u}_3\left(\frac{u_2}{\tilde{u}_2} - \frac{u_3}{\tilde{u}_3} - \frac{\tilde{u}_3u_2}{u_3\tilde{u}_2} + 1\right)\mathrm{d}x
\end{aligned}$$

Furthermore, we have

$$\begin{aligned}
\frac{\mathrm{d}L}{\mathrm{d}t} &= \int_\Omega \tilde{u}_3\left(1 - \frac{\tilde{u}_3}{u_3}\right)\nabla\cdot d_3(x)\nabla u_3 + \int_\Omega \tilde{u}_3\left(1 - \frac{u_3}{\tilde{u}_3}\right)\nabla\cdot d_3(x)\nabla\tilde{u}_3\mathrm{d}x \\
&\quad + \int_\Omega \xi(x)\tilde{u}_2\tilde{u}_3\left(\frac{(N^*(x) - u_2)h(u_3)}{(N^*(x) - \tilde{u}_2)h(\tilde{u}_3)} - \frac{(N^*(x) - u_2)h(u_3)\tilde{u}_2}{(N^*(x) - \tilde{u}_2)h(\tilde{u}_3)u_2} - \frac{u_3}{\tilde{u}_3} - \frac{\tilde{u}_3u_2}{u_3\tilde{u}_2} + 2\right)\mathrm{d}x \\
&= \int_\Omega \tilde{u}_3\left(1 - \frac{\tilde{u}_3}{u_3}\right)\nabla\cdot d_3(x)\nabla u_3 + \int_\Omega \tilde{u}_3\left(1 - \frac{u_3}{\tilde{u}_3}\right)\nabla\cdot d_3(x)\nabla\tilde{u}_3\mathrm{d}x \\
&\quad + \int_\Omega \xi(x)\tilde{u}_2\tilde{u}_3\left[\left(2 - \frac{\tilde{u}_3u_2}{u_3\tilde{u}_2} - \frac{u_3\tilde{u}_2}{\tilde{u}_3u_2}\right) + \left(1 - \frac{\tilde{u}_2}{u_2}\right)\left(\frac{(N^*(x) - u_2)h(u_3)}{(N^*(x) - \tilde{u}_2)h(\tilde{u}_3)} - \frac{u_3}{\tilde{u}_3}\right)\right]\mathrm{d}x \\
&\leq \int_\Omega \tilde{u}_3\left(1 - \frac{\tilde{u}_3}{u_3}\right)\nabla\cdot d_3(x)\nabla u_3 + \int_\Omega \tilde{u}_3\left(1 - \frac{u_3}{\tilde{u}_3}\right)\nabla\cdot d_3(x)\nabla\tilde{u}_3\mathrm{d}x
\end{aligned}$$

$$
\begin{aligned}
&= -\int_\Omega d_3(x)\nabla\left(\tilde{u}_3\left(1-\frac{\tilde{u}_3}{u_3}\right)\right)\nabla u_3 \mathrm{d}x - \int_\Omega d_3(x)\nabla\left(\tilde{u}_3-u_3\right)\nabla\tilde{u}_3 \mathrm{d}x\\
&= -\int_\Omega d_3(x)\sum_{j=1}^{n}\left(\frac{\partial\tilde{u}_3}{\partial x_j}-\frac{1}{u_3^2}\left(2u_3\tilde{u}_3\frac{\partial\tilde{u}_3}{\partial x_j}-\tilde{u}_3^2\frac{\partial u_3}{\partial x_j}\right)\right)\frac{\partial u_3}{\partial x_j}\mathrm{d}x - \int_\Omega d_3(x)\sum_{j=1}^{n}\left(\frac{\partial\tilde{u}_3}{\partial x_j}-\frac{\partial u_3}{\partial x_j}\right)\frac{\partial\tilde{u}_3}{\partial x_j}\mathrm{d}x\\
&= -\int_\Omega d_3(x)\sum_{j=1}^{n}\left(\left(\frac{\partial\tilde{u}_3}{\partial x_j}\right)^2-2\frac{\tilde{u}_3}{u_3}\frac{\partial u_3\partial\tilde{u}_3}{\partial x_j\partial x_j}+\left(\frac{\tilde{u}_3}{u_3}\frac{\partial u_3}{\partial x_j}\right)^2\right)\mathrm{d}x\\
&= -\int_\Omega d_3(x)\sum_{j=1}^{n}\left(\frac{\partial\tilde{u}_3}{\partial x_j}-\frac{\tilde{u}_3}{u_3}\frac{\partial u_3}{\partial x_j}\right)^2\mathrm{d}x \le 0.
\end{aligned}
$$

Furthermore, from $\frac{\mathrm{d}L}{\mathrm{d}t}=0$ we can obtain $u_2=\tilde{u}_2$ and $u_3=\tilde{u}_3$. Thus, by the LaSalle's invariance principle (see [26, Theorem 4.2]), the global attractivity of steady state $\widetilde{E}_1=(\tilde{u}_2(x),\tilde{u}_3(x))$ of model (31) is obtained. Then, by [36, Lemma 2.2.1], we obtain the global asymptotic stability of steady state $\widetilde{E}_1=(\tilde{u}_2(x),\tilde{u}_3(x))$. This completes the proof. □

From Theorems 6 and 7, we have the following result.

Corollary 1. *If $\widehat{\mathcal{R}}_0>1$ and inequality (32) holds, then model (25) has an unique antibody-free steady state $E_1^*=(\tilde{u}_2(x),\tilde{u}_3(x),0)$.*

We linearize model (25) at antibody-free steady state E_1^* to obtain

$$
\begin{cases}
\dfrac{\partial u_2}{\partial t} = \alpha(x)(N^*(x)-\tilde{u}_2)h_{u_3}(\tilde{u}_3)u_3-(\alpha(x)h(\tilde{u}_3)+\mu_1(x))u_2,\\
\dfrac{\partial u_3}{\partial t} = \nabla\cdot d_3(x)\nabla u_3+\xi(x)u_2-\mu_3(x)u_3-\gamma(x)\tilde{u}_3u_4,\ t\ge 0,\ x\in\Omega,\\
\dfrac{\partial u_4}{\partial t} = \nabla\cdot d_4(x)\nabla u_4+\theta(x)\tilde{u}_3u_4-\mu_4(x)u_4,\\
\dfrac{\partial u_3}{\partial \nu}=\dfrac{\partial u_4}{\partial \nu}=0,\ t\ge 0,\ x\in\partial\Omega.
\end{cases}
\tag{33}
$$

Consider the isolated equation

$$
\begin{cases}
\dfrac{\partial u_4}{\partial t} = \nabla\cdot d_4(x)\nabla u_4+\theta(x)\tilde{u}_3u_4-\mu_4(x)u_4,\ t\ge 0,\ x\in\Omega,\\
\dfrac{\partial u_4}{\partial \nu}=0,\ t\ge 0,\ x\in\partial\Omega.
\end{cases}
$$

Substituting $u_4=e^{\lambda t}\phi(x)$ yields the following eigenvalue problem

$$
\begin{cases}
\lambda\phi(x)=\nabla\cdot d_4(x)\nabla\phi(x)+(\theta(x)\tilde{u}_3-\mu_4(x))\phi(x),\ \ x\in\Omega,\\
\dfrac{\partial\phi(x)}{\partial\nu}=0,\ \ x\in\partial\Omega.
\end{cases}
\tag{34}
$$

Therefore, we have the following result.

Lemma 11. *The eigenvalue problem (34) has a principle eigenvalue λ_1 with a strictly positive eigenfunction $\phi^*(x)$.*

Let $F(x)=\theta(x)\tilde{u}_3(x)$, $K(x)=\nabla\cdot d_4(x)\nabla-\mu_4(x)$. We have inverse operator $K^{-1}(x)=(\nabla\cdot d_4(x)\nabla-\mu_4(x))^{-1}$. Define the operator

$$
\mathcal{L}_1=-F(x)K^{-1}(x)=-(\nabla\cdot d_4(x)\nabla-\mu_4(x))^{-1}\theta(x)\tilde{u}_3(x).
$$

The antibody response basic reproduction number $\widetilde{\mathcal{R}}_0$ is defined by $\widetilde{\mathcal{R}}_0 = r(\mathcal{L}_1)$. Generally, $\widetilde{\mathcal{R}}_0$ is called the total antibody response reproduction number of model (25).

Furthermore, we prove the following lemma.

Lemma 12. *Assume $\widehat{\mathcal{R}}_0 > 1$ and inequality (32) holds. Then, we have*

(i) $Sign(\widetilde{\mathcal{R}}_0 - 1) = Sign(\lambda_1)$.

(ii) If $\widetilde{\mathcal{R}}_0 < 1$, then E_1^* is locally asymptotically stable.

(iii) If $\widetilde{\mathcal{R}}_0 > 1$, then E_1^* is unstable.

Proof. Consider (i). The proof is similar to Lemma 8, and hence, we omit it here.

Consider (ii). From conclusion (i), we have $\lambda_1 < 0$. Substituting $(u_2, u_3, u_4) = e^{\eta t}(\psi_2(x), \psi_3(x), \psi_4(x))$ into system (33) yields

$$\begin{cases} \eta\psi_2 = \alpha(x)(N^*(x) - \tilde{u}_2)h_{u_3}(\tilde{u}_3)\psi_3 - (\alpha(x)h(\tilde{u}_3) + \mu_1(x))\psi_2, \\ \eta\psi_3 = \nabla \cdot d_3(x)\nabla\psi_3 + \xi(x)\psi_2 - \mu_3(x)\psi_3 - \gamma(x)\tilde{u}_3\psi_4 \\ \eta\psi_4 = \nabla \cdot d_4(x)\nabla\psi_4 + \theta(x)\tilde{u}_3\psi_4 - \mu_4(x)\psi_4. \end{cases} \tag{35}$$

Let $\eta = \eta_1$ is a eigenvalue of eigenvalue problem (35). Then, from third equation of problem (35) we see that η_1 is also the eigenvalue of problem (34). Since λ_1 is the principle eigenvalue of problem (34), we have $Re(\eta_1) \leq \lambda_1 < 0$. Thereout, we obtain that all eigenvalues of problem (35) have the negative real parts. Therefore, E_1^* is locally asymptotically stable.

Consider (iii). In fact, from $\widetilde{\mathcal{R}}_0 > 1$ we have $\lambda_1 > 0$. Let $\phi^*(x)$ is the corresponding strictly positive eigenfunction of λ_1. For any solution $(u_2(t,x), u_3(t,x), u_4(t,x))$ of system (33) with initial function $(\psi_2(x), \psi_3(x), \psi_4(x))$ satisfying $\psi_4(x) > 0$ for all $x \in \overline{\Omega}$. Choose a constant $\alpha > 0$ such that $\psi_4(x) > \alpha\phi^*(x)$ for all $x \in \overline{\Omega}$, then from third equation of system (33) we have $u_4(t,x) \geq \alpha e^{\lambda_1 t}\phi^*(x)$ for all $t \geq 0$ and $x \in \overline{\Omega}$. It follows that $u_4(t,x)$ is unbounded as $t \to \infty$. This shows that the zero solution $(0,0,0)$ of system (33) is unstable. Thereout, antibody-free steady state E_1^* is unstable for model (25). This completes the proof. □

We further have that $\widetilde{\mathcal{R}}_0$ is the principle eigenvalue of the following eigenvalue problem

$$\begin{cases} -(\nabla \cdot d_4(x)\nabla - \mu_4(x))^{-1}\theta(x)\tilde{u}_3(x)\psi = \lambda\psi, \ x \in \Omega, \\ \dfrac{\partial}{\partial\nu}\psi(x) = 0, \ x \in \partial\Omega. \end{cases}$$

Therefore, there is a strictly positive eigenfunction ψ_* such that

$$-(\nabla \cdot d_4(x)\nabla - \mu_4(x))^{-1}\theta(x)\tilde{u}_3(x)\psi_* = \widetilde{\mathcal{R}}_0\psi_*, \ x \in \Omega$$

and $\frac{\partial\psi_*(x)}{\partial\nu} = 0$ for $x \in \partial\Omega$. Then, we obtain

$$\begin{cases} -\theta(x)\tilde{u}_3(x)\psi_* = \widetilde{\mathcal{R}}_0(\nabla \cdot d_4(x)\nabla - \mu_4(x))\psi_*, \ x \in \Omega, \\ \dfrac{\partial\psi_*(x)}{\partial\nu} = 0, \ x \in \partial\Omega. \end{cases}$$

Hence, we further can get

$$\widetilde{\mathcal{R}}_0 = \frac{\int\limits_\Omega \theta(x)\tilde{u}_3(x)\psi_*^2 \mathrm{d}x}{\int\limits_\Omega [d_4(x)|\nabla\psi_*|^2 + \mu_4(x)\psi_*^2]\mathrm{d}x}.$$

Thus, we finally obtain

$$\widetilde{\mathcal{R}}_0 = \sup_{\varphi \in H^1(\Omega)} \left\{ \frac{\int\limits_\Omega \theta(x)\tilde{u}_3(x)\psi^2 \mathrm{d}x}{\int\limits_\Omega [d_4(x)|\nabla\psi|^2 + \mu_4(x)\psi^2]\mathrm{d}x} \right\}.$$

We easily see that $\widetilde{\mathcal{R}}_0$ is increasing with respect to $\theta(x)$ and $\tilde{u}_3(x)$, and decreasing with respect to $\mu_4(x)$ and $d_4(x)$. Particularly, when model (25) degenerates into the spatial homogeneous model, then we further have

$$\widetilde{\mathcal{R}}_0 = \frac{\theta \tilde{u}_3}{\mu_4}.$$

We define the local antibody response basic reproduction number in location x by

$$\widetilde{\mathcal{R}}_0^*(x) = \frac{\tilde{u}_3(x)\theta(x)}{\mu_4(x)}.$$

We have the following conjecture: $\max_{x\in\overline{\Omega}} \widetilde{\mathcal{R}}_0^*(x) < 1 \Rightarrow \widetilde{\mathcal{R}}_0 < 1$, $\min_{x\in\overline{\Omega}} \widetilde{\mathcal{R}}_0^*(x) > 1 \Rightarrow \widetilde{\mathcal{R}}_0 > 1$.

Furthermore, we can obtain the similar results to Theorem 7 by using Lyapunov function method.

Theorem 8. *If $\widehat{\mathcal{R}}_0 > 1$ and inequality (32) holds, and*

$$\max_{x\in\overline{\Omega}} \left\{ \frac{\tilde{u}_3^2(x)\gamma(x)}{\mu_4(x)} \right\} \le \min_{x\in\overline{\Omega}} \left\{ \frac{\tilde{u}_3(x)\gamma(x)}{\theta(x)} \right\}, \tag{36}$$

then E_1^* is globally asymptotically stable.

Proof. Define the Lyapunov function: $V = L + c_2 \int_\Omega u_4 \mathrm{d}x$, where function L define in the proof of Theorem 6 and $c_2 > 0$ is a constant satisfying $\frac{\tilde{u}_3(x)\gamma(x)}{\theta(x)} \ge c_2 \ge \frac{\tilde{u}_3^2(x)\gamma(x)}{\mu_4(x)}$ for all $x \in \Omega$ by the condition (36). Then,

$$\begin{aligned}
\frac{\mathrm{d}V}{\mathrm{d}t} =& -\int_\Omega d_3(x)\nabla\left(\tilde{u}_3\left(1-\frac{\tilde{u}_3}{u_3}\right)\right)\nabla u_3 \mathrm{d}x - \int_\Omega d_3(x)\nabla\left(\tilde{u}_3 - u_3\right)\nabla \tilde{u}_3 \mathrm{d}x \\
&+ \int_\Omega \xi(x)\tilde{u}_2\tilde{u}_3\left[\left(2-\frac{\tilde{u}_3 u_2}{u_3\tilde{u}_2}-\frac{u_3\tilde{u}_2}{\tilde{u}_3 u_2}\right)+\left(1-\frac{\tilde{u}_2}{u_2}\right)\left(\frac{(N^*(x)-u_2)h(u_3)}{(N^*(x)-\tilde{u}_2)h(\tilde{u}_3)}-\frac{u_3}{\tilde{u}_3}\right)\right]\mathrm{d}x \\
&+ \int_\Omega \left(c_2 - \frac{\tilde{u}_3 q}{r}\right)u_3 u_4 \mathrm{d}x + \int_\Omega \left(\frac{\tilde{u}_3^2 q}{c} - c_2\right) c u_4 \mathrm{d}x \le 0.
\end{aligned}$$

Furthermore, from $\frac{\mathrm{d}V}{\mathrm{d}t} = 0$, we can obtain $u_2 = \tilde{u}_2$ and $u_3 = \tilde{u}_3$. Then, from the second equation of model (25) we further obtain $u_4 = 0$. Therefore, by the LaSalle's invariable principle (see [26, Theorem 4.2]) and Lemma 2.2.1 in [36], E_1^* is globally asymptotically stable. □

Furthermore, we can easily prove that the condition (36) implies $\max_{x\in\overline{\Omega}} \widetilde{\mathcal{R}}_0^*(x) \le 1$. Based on the discussion above, we propose a conjecture as follows.

Conjecture 1. *If $\widehat{\mathcal{R}}_0 > 1$, $\widetilde{\mathcal{R}}_0 < 1$ and inequality (32) holds, then E_1^* is global asymptotically stable.*

6. Infection with antibody response

In this section, we study the uniformly persistence of positive solutions for model (25).

Lemma 13. *If $\widehat{\mathcal{R}}_0 > 1$, then there is a constant $\delta > 0$ such that $\limsup_{t\to\infty} \|u(t,\cdot) - E_0^*\|_{\mathbb{W}_+} \ge \delta$ for any solution $u(t,\cdot)$ of model (25) satisfies initial value $\phi = (\phi_1, \phi_2, \phi_3) \in \mathbb{W}_+$ with $\phi_1 \ne 0$ and $\phi_2 \ne 0$.*

Proof. For any initial value $\phi \in \mathbb{W}_+$ with $\phi_1 \ne 0$ and $\phi_2 \ne 0$, the parabolic maximum principle (see [18]) implies $u_2(t,x) > 0$ and $u_3(t,x) > 0$ for all $t > 0$ and $x \in \overline{\Omega}$. Suppose, contrary to our claim, that $\limsup_{t\to\infty} \|u(t,\cdot) - E_0^*\|_{\mathbb{W}_+} < \delta$ for the fixed $\delta > 0$. Thus, there exists a $t_1 > 0$ such that $0 < u_2(t,x) < \delta$, $0 < u_3(t,x) < \delta$ and $0 < u_4(t,x) < \delta$ for all $x \in \Omega$ and $t \ge t_1$.

By $\widehat{\mathcal{R}}_0 > 1$ and Lemma 10, one knows that $s(\widehat{\mathcal{A}}) > 0$. Therefore, there is a sufficiently small $\delta > 0$ such that $s(\widehat{\mathcal{A}}_\delta) > 0$, where

$$\widehat{\mathcal{A}}_\delta = \begin{pmatrix} -\mu_2(\cdot) & \alpha(\cdot)(N^*(\cdot) - \delta)h_{u_3}(0) \\ \xi(\cdot) & \nabla \cdot d_3(x)\nabla - \mu_3(\cdot) \end{pmatrix}.$$

Consider the following eigenvalue problem:

$$\begin{cases} \lambda \begin{pmatrix} \psi_1 \\ \psi_2 \end{pmatrix} = \widehat{\mathcal{A}}_\delta \begin{pmatrix} \psi_1 \\ \psi_2 \end{pmatrix}, \quad x \in \Omega, \\ \dfrac{\partial \psi_2}{\partial \nu} = 0, \quad x \in \partial\Omega. \end{cases} \tag{37}$$

By the same argument as in the proofs of Lemmas 2-4, it then follows that if $s(\widehat{\mathcal{A}}_\delta) > 0$, then $s(\widehat{\mathcal{A}}_\delta)$ is the principle eigenvalue of problem (37). Let $(\phi_1^\delta(\cdot), \phi_2^\delta(\cdot))$ be the positive eigenvector corresponding to $s(\widehat{\mathcal{A}}_\delta)$ in (37). Hence, there exists a constant $c > 0$ such that $c(\phi_1^\delta(\cdot), \phi_2^\delta(\cdot)) \leq (u_2(t_1, \cdot, \phi); u_3(t_1, \cdot, \phi))$. Consequently, $(u_2(t, x), u_3(t, x))$ is the upper solution of

$$\begin{cases} \dfrac{\partial}{\partial t} \begin{pmatrix} w_2 \\ w_3 \end{pmatrix} = \widehat{\mathcal{A}}_\delta \begin{pmatrix} w_2 \\ w_3 \end{pmatrix}, \quad (x, t) \in \Omega \times (t_1, \infty), \\ \dfrac{\partial w_3}{\partial \nu} = 0, \quad (x, t) \in \partial\Omega \times (t_1, \infty), \\ (w_2(\cdot, t_1), w_3(\cdot, t_1)) = c(\phi_1^\delta(\cdot), \phi_2^\delta(\cdot)), \ x \in \overline{\Omega}. \end{cases} \tag{38}$$

Note that $(w_2(t, x), w_3(t, x)) = ce^{s(\widehat{\mathcal{A}}_\delta)(t-t_1)}(\phi_1^\delta(x), \phi_2^\delta(x))$ is the unique solution to (38). Since $s(\widehat{\mathcal{A}}_\delta) > 0$, we have $\lim_{t\to\infty} w_2(t, x) = \infty$ and $\lim_{t\to\infty} w_3(t, x) = \infty$. An application of the comparison principle obtains $(u_2(t, x), u_3(t, x)) \geq (w_2(t, x), w_3(t, x))$. Since Consequently, $u_2 \to \infty$ and $u_3 \to \infty$ as $t \to \infty$, a contradiction against with the boundedness of $(u_2(t, x), u_3(t, x))$ by Theorem 4. □

Lemma 14. *If $\widehat{\mathcal{R}}_0 > 1$, $\widetilde{\mathcal{R}}_0 > 1$ and inequality (32) holds, then there is a constant $\delta_1 > 0$ such that $\limsup_{t\to\infty} \|u(t, \cdot) - E_1^*\|_{\mathbb{W}_+} \geq \delta_1$ for any solution $u(t, \cdot)$ of model (25) satisfies initial value $\phi = (\phi_1, \phi_2, \phi_3) \in \mathbb{W}_+$ with $\phi_1 \neq 0$ and $\phi_3 \neq 0$.*

Proof. From $\widetilde{\mathcal{R}}_0 > 1$, we can obtain that $r^i(\tilde{u}_3^i - \delta_1) - \mu_4^s > 0$, where δ_1 is an enough small constant. Suppose the conclusion doesn't hold, then for an enough large t_2, we have $\tilde{u}_3^i - \delta_1 < u_3(t, \cdot) < \tilde{u}_3^s + \delta_1$, and $u_4(t, \cdot) < \delta_1$ for all $t \geq t_2$. Therefore, from model (25) one has

$$\frac{\partial u_4}{\partial t} \geq \nabla \cdot d_4(x)\nabla u_4 + [r^i(\tilde{u}_3^i - \delta_1) - \mu_4^s]u_4.$$

Then, use the similar arguments in [9, Lemma 5]; we can finally get $\lim_{t\to\infty} u_4(t, x) = \infty$, which contradicts the result of Theorem 1. This completes the proof. □

Define

$$X_0 = \{\phi \in \mathbb{W}_+ : \phi_1 \neq 0, \phi_2 \neq 0, \phi_3 \neq 0\}$$

and

$$\partial X_0 := \mathbb{W}_+ \setminus X_0 = \{\phi \in \mathbb{W}_+ : \phi_1 = 0 \text{ or } \phi_2 = 0 \text{ or } \phi_3 = 0\}.$$

Furthermore, set

$$M_\partial := \{\phi \in \mathbb{W}_+ : \Psi(t)\phi \in \partial X_0 \text{ for all } t \geq 0\}.$$

Lemma 15. *Let $\omega(\phi)$ be the omega limit set of solution $\Psi(t)\phi$ and set $M_1 = \{E_0^*, E_1^*\}$. Then, $\cup_{\phi\in M_\partial}\omega(\phi) = M_1$.*

Proof. This clearly forces $M_1 \subset \cup_{\phi\in M_\partial}\omega(\phi)$, because $\Psi(t)E_0^* = E_0^*$ and $\Psi(t)E_1^* = E_1^*$ for all $t \geq 0$. Therefore, the proof is completed by showing that $\cup_{\phi\in M_\partial}\omega(\phi) \subset M_1$. In fact, the details of the proof $\cup_{\phi\in M_\partial}\omega(\phi) \subset M_1$ can use the similar arguments in [9, Lemma 6]; here we omit it. □

Theorem 9. *Assume $\widehat{\mathcal{R}}_0 > 1$, $\widetilde{\mathcal{R}}_0 > 1$ and inequality (32) holds, then there exists a constant $\varepsilon > 0$ such that for any solution $U(t,x,\phi) = (u_2(t,x), u_3(t,x), u_4(t,x))$ of model (25) with $\phi_1 \neq 0$, $\phi_2 \neq 0$ and $\phi_3 \neq 0$ one has*

$$\liminf_{t\to\infty} U_i(t,x) \geq \varepsilon,\ U_i(t,x) = (u_2(t,x), u_3(t,x), u_4(t,x))$$

uniformly for $x \in \Omega$.

Proof. Define a continuous function $p : \mathbb{W}_+ \to [0,+\infty)$ by

$$p(\phi) = \min\{\min_{x\in\overline{\Omega}} \phi_1(x), \min_{x\in\overline{\Omega}} \phi_2(x), \min_{x\in\overline{\Omega}} \phi_3(x)\},\quad \phi \in \mathbb{W}_+.$$

Hence, it is easy to get p is a generalized distance function for semiflow $\Psi(t) : \mathbb{W}_+ \to \mathbb{W}_+$(see Theorem 3 in [36]). By Lemmas 13 and 14 and similar arguments in [9, Theorem 5], we can prove that there is no subset of M_1 forms a cycle in ∂X_0. Further, combining Theorem 5 and [36, Theorem 3], we can finally complete the proof. □

As a consequence of Theorem 9, we have the following conclusion.

Corollary 2. *Assume $\widehat{\mathcal{R}}_0 > 1$, $\widetilde{\mathcal{R}}_0 > 1$ and inequality (32) holds. Then, model (25) has at least one an antibody response infection steady state $E_2^* = (\hat{u}_2(x), \hat{u}_3(x), \hat{u}_4(x))$.*

Remark 8. It is regrettable that in the following we only can obtain the global asymptotic stability of steady state $E_2^* = (\hat{u}_2(x), \hat{u}_3(x), \hat{u}_4(x))$ in the spatial homogeneous case. For the spatial heterogeneous case, it will still be an interesting open problem.

When model (25) degenerates into the spatial homogeneous case, that is, all parameters are constants, except for the diffusion coefficients. By the next-generation matrix method, we obtain, respectively, the virus infection and antibody response basic reproduction numbers

$$\widehat{\mathcal{R}}_0 = \frac{\xi\alpha N^* h_{u_3}(0)}{\mu_1\mu_3},\quad \widetilde{\mathcal{R}}_0 = \frac{\xi\alpha\theta N^* h(\frac{\mu_4}{\theta})}{\mu_3\mu_4[\alpha h(\frac{\mu_4}{\theta}) + \mu_1]},$$

where $N^* = \frac{\Lambda}{\mu_1}$. We have the following conclusion.

Theorem 10. *Assume that $\widehat{\mathcal{R}}_0 > 1$, $\widetilde{\mathcal{R}}_0 > 1$ and*

$$\left(1 - \frac{\hat{u}_2}{u_2}\right)\left(\frac{(N^* - u_2)h(u_3)}{(N^* - \hat{u}_2)h(\hat{u}_3)} - \frac{u_3}{\hat{u}_3}\right) \leq 0.$$

Then, model (25) has a unique antibody response infection equilibrium $E_2^* = (\hat{u}_2, \hat{u}_3, \hat{u}_4)$ which is globally asymptotically stable.

Proof. Directly calculating implies that model (25) has the antibody response infection equilibrium $E_2^* = (\hat{u}_2, \hat{u}_3, \hat{u}_4)$ when $\widetilde{\mathcal{R}}_0 > 1$ as follows

$$\hat{u}_2 = \frac{\alpha N^* h(\frac{\mu_4}{\theta})}{\alpha h(\frac{\mu_4}{\theta}) + \mu_1},\ \hat{u}_3 = \frac{\mu_4}{\theta},\ \hat{u}_4 = \frac{\xi\alpha\theta N^* h(\frac{\mu_4}{\theta}) - \mu_3\mu_4[\alpha h(\frac{\mu_4}{\theta}) + \mu_1]}{\gamma\mu_4[\alpha h(\frac{\mu_4}{\theta}) + \mu_1]}.$$

Define a Lyapunov function: $J = J_1 + J_2 + J_3$, where

$$J_1 = \frac{\xi\hat{u}_2}{\alpha(N^* - \hat{u}_2)h(\hat{u}_3)}\int_\Omega (u_2 - \hat{u}_2 - \hat{u}_2 \ln\frac{u_2}{\hat{u}_2})\mathrm{d}x,\quad J_2 = \int_\Omega (u_3 - \hat{u}_3 - \hat{u}_3 \ln\frac{u_3}{\hat{u}_3})\mathrm{d}x$$

$$J_3 = \frac{\gamma}{\theta}\int_\Omega (u_4 - \hat{u}_4 - \hat{u}_4 \ln\frac{u_4}{\hat{u}_4})\mathrm{d}x$$

Therefore, we have

$$\frac{\mathrm{d}J_1}{\mathrm{d}t} =\xi\hat{u}_2\int_\Omega\left[\frac{(N^*-u_2)h(u_3)}{(N^*-\hat{u}_2)h(\hat{u}_3)}-\frac{u_2}{\hat{u}_2}-\frac{(N^*-u_2)h(u_3)\hat{u}_2}{(N^*-\hat{u}_2)h(\hat{u}_3)u_2}+1\right]\mathrm{d}x$$

and

$$\begin{aligned}\frac{\mathrm{d}J_2}{\mathrm{d}t} =&\int_\Omega\left(1-\frac{\hat{u}_3}{u_3}\right)\frac{\mathrm{d}u_3}{\mathrm{d}t}\mathrm{d}x\\ =&\int_\Omega(1-\frac{\hat{u}_3}{u_3})\nabla\cdot d_3(x)\nabla u_3\mathrm{d}x+\int_\Omega\left(\xi u_2-\xi\hat{u}_2\frac{u_3}{\hat{u}_3}-\frac{\hat{u}_3}{u_3}\xi u_2+\xi\hat{u}_2\right)\mathrm{d}x\\ &+\int_\Omega\left(\gamma\hat{u}_4u_3-\gamma u_3u_4+\gamma u_4\hat{u}_3-\gamma\hat{u}_4\hat{u}_3\right)\mathrm{d}x\\ =&-\int_\Omega\frac{\hat{u}_3}{u_3^2}d_3(x)\|\nabla u_3\|^2\mathrm{d}x+\xi\hat{u}_2\int_\Omega\left(\frac{u_2}{\hat{u}_2}-\frac{u_3}{\hat{u}_3}-\frac{\hat{u}_3u_2}{u_3\hat{u}_2}+1\right)\mathrm{d}x\\ &+\gamma\hat{u}_4\hat{u}_3\int_\Omega\left(\frac{u_3}{\hat{u}_3}+\frac{u_4}{\hat{u}_4}-\frac{u_3u_4}{\hat{u}_4\hat{u}_3}-1\right)\mathrm{d}x.\end{aligned}$$

Similarly, we have

$$\begin{aligned}\frac{\mathrm{d}J_3}{\mathrm{d}t} =&\frac{\gamma}{\theta}\int_\Omega\left(1-\frac{\hat{u}_4}{u_4}\right)\frac{\mathrm{d}u_4}{\mathrm{d}t}\mathrm{d}x\\ =&\int_\Omega\left(1-\frac{\hat{u}_4}{u_4}\right)\nabla\cdot d_4(x)\nabla u_4\mathrm{d}x+\gamma\hat{u}_4\hat{u}_3\int_\Omega\left(\frac{u_3u_4}{\hat{u}_4\hat{u}_3}-\frac{u_4}{\hat{u}_4}-\frac{u_3}{\hat{u}_3}+1\right)\mathrm{d}x\\ =&-\int_\Omega\frac{\hat{u}_4}{u_4^2}d_4(x)\|\nabla u_4\|^2\mathrm{d}x+\gamma\hat{u}_4\hat{u}_3\int_\Omega\left(\frac{u_3u_4}{\hat{u}_4\hat{u}_3}-\frac{u_4}{\hat{u}_4}-\frac{u_3}{\hat{u}_3}+1\right)\mathrm{d}x.\end{aligned}$$

Furthermore, we have

$$\begin{aligned}\frac{\mathrm{d}J}{\mathrm{d}t} =&-\int_\Omega\frac{\hat{u}_3}{u_3^2}d_3(x)\|\nabla u_3\|^2\mathrm{d}x-\int_\Omega\frac{\hat{u}_4}{u_4^2}d_4(x)\|\nabla u_4\|^2\mathrm{d}x\\ &+\xi\hat{u}_2\int_\Omega\left(\frac{(N^*-u_2)h(u_3)}{(N^*-\hat{u}_2)h(\hat{u}_3)}-\frac{(N^*-u_2)h(u_3)\hat{u}_2}{(N^*-\hat{u}_2)h(\hat{u}_3)u_2}-\frac{u_3}{\hat{u}_3}-\frac{\hat{u}_3u_2}{u_3\hat{u}_2}+2\right)\mathrm{d}x\\ \le&\xi\hat{u}_2\int_\Omega\left[\left(2-\frac{\hat{u}_3u_2}{u_3\hat{u}_2}-\frac{u_3\hat{u}_2}{\hat{u}_3u_2}\right)+\left(1-\frac{\hat{u}_2}{u_2}\right)\left(\frac{(N^*-u_2)h(u_3)}{(N^*-\hat{u}_2)h(\hat{u}_3)}-\frac{u_3}{\hat{u}_3}\right)\right]\mathrm{d}x\le 0.\end{aligned}\tag{39}$$

Furthermore, from $\frac{\mathrm{d}J}{\mathrm{d}t}=0$ we can obtain $u_2=\hat{u}_2$ and $u_3=\hat{u}_3$. Then, from the second equation of model (25) we further obtain $u_4=\hat{u}_4$. Thus, by the LaSalle's invariance principle (see [26, Theorem 4.2]), the global asymptotic stability of equilibrium $E_2^*=(\hat{u}_2,\hat{u}_3,\hat{u}_4)$ of model (25) is obtained. □

7. Numerical examples

In this section, we mainly give three examples to illustrate our theoretical analysis results. For convenience, we assume $f(u_1,u_2)=u_1u_2$, $g(u_1,u_3)=u_1u_3$, $h(u_3)=u_3$.

TABLE 2. Values of all parameters in model (2) for Example 1

Parameter	Value	Parameter	Value	Parameter	Value
$\Lambda(x)$	$100 + 0.005\sin(2\pi x)$	$\mu_1(x)$	$0.1 + 0.005\sin(2\pi x)$	$\alpha(x)$	$0.003 + 0.00005\sin(2\pi x)$
$\sigma(x)$	$0.004 + 0.00005\sin(2\pi x)$	$\mu_2(x)$	$6 + 0.05\sin(2\pi x)$	$\xi(x)$	$0.09 + 0.005\sin(2\pi x)$
$\mu_3(x)$	$6 + 0.05\sin(2\pi x)$	$\theta(x)$	$1.2 + 0.005\sin(2\pi x)$	$\gamma(x)$	$0.8 + 0.0005\sin(2\pi x)$
$\mu_4(x)$	$2 + 0.005\sin(2\pi x)$	$d_3(x)$	$0.09 + 0.005\sin(2\pi x)$	$d_4(x)$	$0.02 + 0.002\sin(2\pi x)$
$u_1(0,x)$	$8924e^{-10(x-5)^2}$	$u_2(0,x)$	$2e^{-10(x-5)^2}$	$u_3(0,x)$	$8e^{-10(x-5)^2}$
$u_4(0,x)$	$2e^{-10(x-5)^2}$				

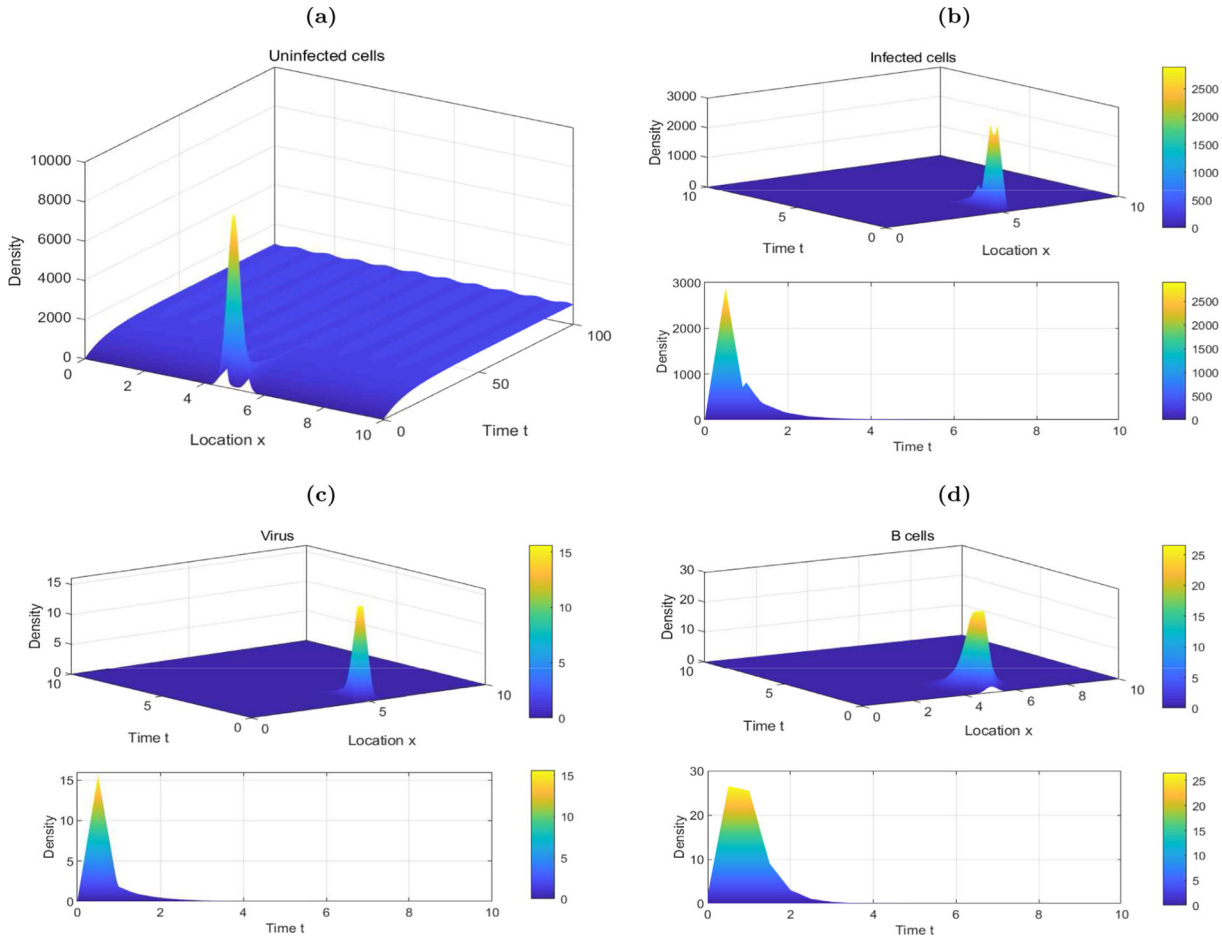

FIG. 1. Global asymptotically stability of the infection-free steady state E_0 of model (2)

Example 1. To illustrate Theorem 3, we choose the parameter values of model (2) shown in Table 2.

By numerical calculation, we obtain $\mathcal{R}_0 = 0.7065 < 1$ and $\max_{x\in\overline{\Omega}} \mathcal{R}_0(x) = 0.6751 < 1$. The numerical simulations are given in Fig. 1. From Fig. 1, it is easy to see that the density of uninfected cells $u_1(t,x)$ converges to positive state (Fig. 1a), and the density of infected cells $u_2(t,x)$, virus $u_3(t,x)$ and B cells $u_4(t,x)$ converges to zero (Fig. 1b–d) as time evolves, which implies the infection-free steady state E_0 is globally asymptotically stable.

Example 2. In order to verify Conjecture 1, we choose the parameter values of model (24) shown in Table 3.

By numerical calculation, we obtain $\widehat{\mathcal{R}}_0 \approx 1.2034 > 1$ and $\widetilde{\mathcal{R}}_0 \approx 0.415 < 1$. The numerical simulations are given in Fig. 2. Obviously, the plots in Fig. 2 show that the density of uninfected cells $u_1(t,x)$, infected cells $u_2(t,x)$ and virus $u_3(t,x)$ converges to positive state (Fig. 2a–c), and the density of B cells $u_4(t,x)$ converges to zero (Fig. 2d) as time evolves, which implies the antibody-free steady state $(\tilde{u}_1(x), \tilde{u}_2(x), \tilde{u}_3(x), 0)$ is globally asymptotically stable.

Example 3. In order to verify Theorem 10, we choose the parameter values of model (24) shown in Table 4.

TABLE 3. Values of all parameters in model (24) for Example 2

Parameter	Value	Parameter	Value	Parameter	Value
$\Lambda(x)$	$100 + 0.005\sin(2\pi x)$	$\mu_1(x)$	$0.1 + 0.005\sin(2\pi x)$	$\alpha(x)$	$0.0012 + 0.00005\sin(2\pi x)$
$\xi(x)$	$2.9 + 0.005\sin(2\pi x)$	$\mu_3(x)$	$3 + 0.05\sin(2\pi x)$	$\theta(x)$	$0.006 + 0.0005\sin(2\pi x)$
$\gamma(x)$	$0.08 + 0.0005\sin(2\pi x)$	$\mu_4(x)$	$6 + 0.005\sin(2\pi x)$	$d_3(x)$	$0.09 + 0.005\sin(2\pi x)$
$d_4(x)$	$0.02 + 0.002\sin(2\pi x)$	$u_1(0,x)$	$892e^{-10(x-5)^2}$	$u_2(0,x)$	$2e^{-10(x-5)^2}$
$u_3(0,x)$	$8e^{-10(x-5)^2}$	$u_4(0,x)$	$20e^{-10(x-5)^2}$		

TABLE 4. Values of all parameters in model (24) for Example 3

Parameter	Value	Parameter	Value	Parameter	Value
$\Lambda(x)$	$100 + 0.005\sin(2\pi x)$	$\mu_1(x)$	$0.1 + 0.005\sin(2\pi x)$	$\alpha(x)$	$0.003 + 0.00005\sin(2\pi x)$
$\xi(x)$	$2.9 + 0.005\sin(2\pi x)$	$\mu_3(x)$	$3 + 0.05\sin(2\pi x)$	$\theta(x)$	$0.2 + 0.0005\sin(2\pi x)$
$\gamma(x)$	$0.08 + 0.0005\sin(2\pi x)$	$\mu_4(x)$	$6 + 0.005\sin(2\pi x)$	$d_3(x)$	$0.09 + 0.005\sin(2\pi x)$
$d_4(x)$	$0.02 + 0.002\sin(2\pi x)$	$u_1(0,x)$	$1812e^{-10(x-5)^2}$	$u_2(0,x)$	$2e^{-10(x-5)^2}$
$u_3(0,x)$	$8e^{-10(x-5)^2}$	$u_4(0,x)$	$2e^{-10(x-5)^2}$		

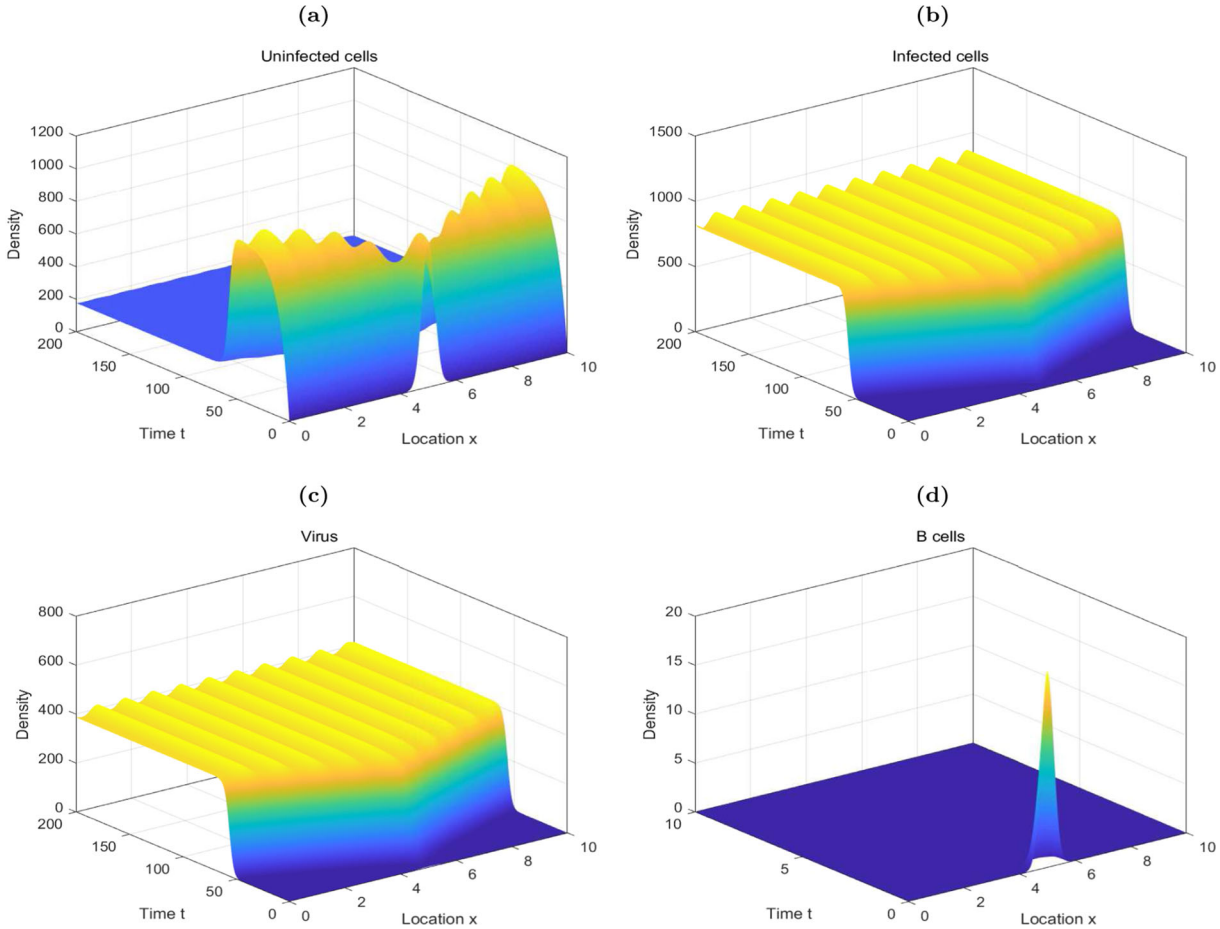

FIG. 2. Global asymptotically stability of the antibody-free steady state $(\tilde{u}_1(x),\tilde{u}_2(x),\tilde{u}_3(x),0)$

By numerical calculation, we obtain $\widehat{\mathcal{R}}_0 \approx 3.2656 > 1$ and $\widetilde{\mathcal{R}}_0 \approx 3.213 > 1$. The numerical simulations are given in Fig. 2. As we can see, Fig. 3 shows that the density of uninfected cells $u_1(t,x)$, infected cells $u_2(t,x)$, virus $u_3(t,x)$ and B cells $u_4(t,x)$ converges to positive state as time evolves, which implies the antibody response infection steady state $(\hat{u}_1(x),\hat{u}_2(x),\hat{u}_3(x),\hat{u}_4(x))$ is globally asymptotically stable.

8. Conclusions

In this paper, since the virus invade the body and parasitize the host cells for reproduction and diffusion, thus producing effective B cells and memory cells to inhibit the virus cells, we investigate a degenerated diffusion virus infection model which incorporates virus and B cells diffusion. Firstly, we establish the global existence, uniform boundedness and ultimate boundedness of the solutions in Sect. 2. In Sect. 3, for model (2), we define the virus infection reproduction number as the spectral radius of the next-generation operator, and then by the method given in [30], we calculate the variational formula of $\mathcal{R}_0$. Since the first equation of system (6) has no diffusion term, the solution semiflow of system (6), $Q(t)$, is not compact. Therefore, we introduce a condition, $\max_{x\in\overline{\Omega}} \mathcal{R}_{01}(x) < 1$, to ensure the κ-contraction condition of $Q(t)$, where $\mathcal{R}_{01}(x)$ represent the local reproduction number of cells to cells infection in location x. Based

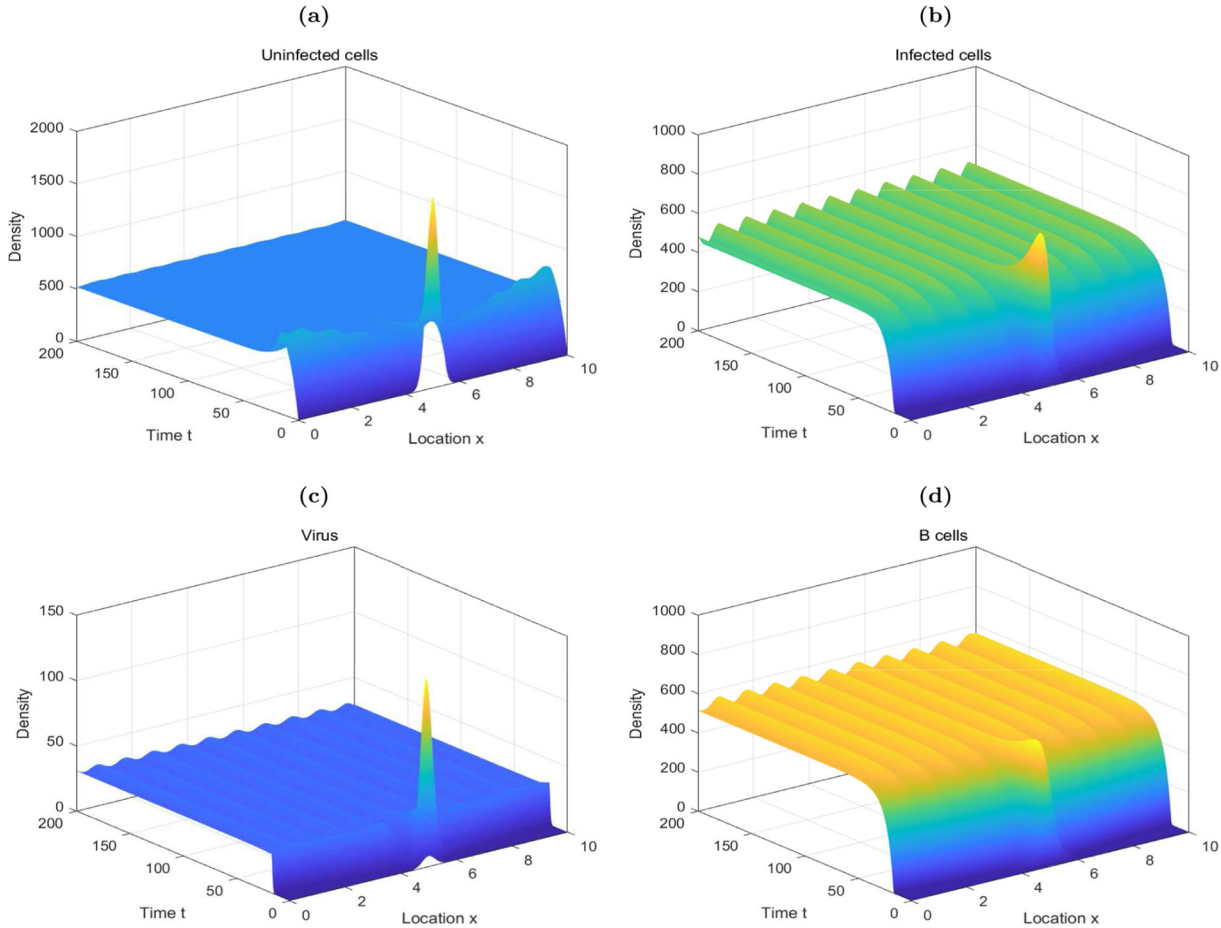

FIG. 3. Global asymptotically stability of the antibody-free steady state $(\hat{u}_1(x), \hat{u}_2(x), \hat{u}_3(x), \hat{u}_4(x))$

on this, we obtain some results about $\mathcal{R}_0$ (see Lemmas 4–9) under the condition $\max_{x\in\overline{\Omega}} \mathcal{R}_{01}(x) < 1$. Further, we obtain the global stability of E_0 when $\mathcal{R}_0 < 1$, which implies that the virus will be die out when $\mathcal{R}_0 < 1$ (see Sect. 4).

Since some equations of model (2) have no diffusion terms, the solution semiflow $\Phi(t)$ of model (2) is not compact. In order to discuss the existence of $E_1 = (\tilde{u}_1(x), \tilde{u}_2(x), \tilde{u}_3(x), 0)$ of model (2), we need to prove that the solution semiflow $\Phi(t) : \mathbb{X}_+ \to \mathbb{X}_+$ of model (2) is k-contraction. However, it is regrettable that we only prove the k-contraction for a special case of model (2), that is, there is not cell-to-cell transmission ($\sigma(x) \equiv 0$) and the infected cell does not have the death due to infection ($\mu_1(x) = \mu_2(x)$). For this special model (25), we calculate reproduction number $\widehat{\mathcal{R}}_0$ and the antibody response reproduction number $\widetilde{\mathcal{R}}_0$, and study the virus infective dynamics when the antibody does not produce responses and the antibody produce response in terms of $\widehat{\mathcal{R}}_0$ and $\widetilde{\mathcal{R}}_0$. Theorem 6 shows that model (25) has an antibody-free steady state E_1^* under $\widehat{\mathcal{R}}_0 > 1$. Moreover, if $\widehat{\mathcal{R}}_0 > 1$ and $\widetilde{\mathcal{R}}_0 < 1$, then E_1^* is locally asymptotically stable. Theorem 8 indicates that E_1^* is globally asymptotically stable under $\widehat{\mathcal{R}}_0 > 1$ and a additional condition. Furthermore, a conjecture is given, that is, if $\widehat{\mathcal{R}}_0 > 1$ and $\widetilde{\mathcal{R}}_0 < 1$ then E_1^* is globally asymptotically stable. For the virus infection with antibody response, we prove the uniform persistence of virus, infected cells and B cells by Lemmas 13-15 and Theorem 9 and then obtain the existence of antibody-present

infection steady state E_2^* under $\widehat{\mathcal{R}}_0 > 1$ and $\widetilde{\mathcal{R}}_0 > 1$. Unfortunately, we only can obtain the global asymptotic stability of $E_2^* = (\hat{u}_2(x), \hat{u}_3(x), \hat{u}_4(x))$ in the spatial homogeneous case. Biologically, the virus and infected cells will not be killed and will still exist in human's body through the antibody response when $\widehat{\mathcal{R}}_0 > 1$ and $\widetilde{\mathcal{R}}_0 > 1$. Finally, we give three numerical examples to illustrate the theoretical results.

However, there are still some interesting open problems. For example, in Remark 3 we have pointed out an important open problem, that is, to study model (2) when condition $\max_{x\in\overline{\Omega}} \mathcal{R}_{01}(x) < 1$ does not hold. This means in model (2) that the cell-to-cell transmission will also be important in the virus infection. Moreover, if there is cell-to-cell transmission (i.e., $\sigma(x) \not\equiv 0$) and the infected cells do have the death due to infection (i.e., $\mu_2(x) \geq \mu_1(x)$) for model (2), in this paper, we have not proved that the solution semiflow $\Phi(t)$ of model (2) is $\kappa-$contraction, and we will try to find appropriate methods to solve it in the future. Based on the $\kappa-$contraction of the solution semiflow $\Phi(t)$, we can further study the dynamics of the solutions in the cases of infections with antibody-free response and occurrence of antibody response. Therefore, we will try our best to study these open problems in our future works. Of course, in contrast with the model proposed in Luo et al. [9], the incidence rate function in model (2) is simple. Therefore, in the future, we will also consider incorporate the nonlinear incidence rate function, such as saturation incidence, Beddington–DeAngelis incidence and so on.

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