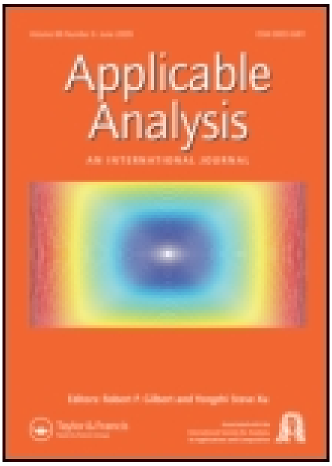

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Global dynamics of a PDE in-host viral model

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We consider an in-host virus dynamics model with spatial heterogeneity on the general bounded domain, and homogenous Neumann boundary condition. Under the assumption that only the free virus diffuse and the host cells (infected and uninfected) are not mobile, the model turns out to be hybrid in the sense that it consists of two point-wise ODEs and an PDE. We explore the virus dynamics by analyzing the model and identifying the basic reproduction number. When all model parameters are constants, the global dynamics of the model are fully determined.

Keywords: HBV; Infection; threshold; basic reproduction number; principle eigenvalue

AMS Subject Classifications: MSC(2010); 35B40; 35K57; 92D25

1. Introduction

There have been extensive investigations on population models for virus dynamics in of *in vivo*. These in-host models can be used to estimate some key factors in viral infection and replication, and to guide development of efficient anti-viral drug therapies (see, e.g. [1–4] and the references therein).

Typically, an in-host compartmental model of viral dynamics contains three compartments: the populations of uninfected susceptible host cells u_1, infected host cells u_2, and free virus particles u_3 that are produced by infected host cells. The governing equations take the form:

$$\begin{cases} \frac{du_1(t)}{dt} = \lambda - au_1 - \beta u_1 u_3, \\ \frac{du_2(t)}{dt} = \beta u_1 u_3 - bu_2, \\ \frac{du_3(t)}{dt} = ku_2 - mu_3, \end{cases} \tag{1.1}$$

where λ and a are the recruitment rate and death rate of the susceptible cells, respectively; b is the death rate of the infected cells; k and m are the recruitment rate and removed rate for

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Dedicated to Professor Wei Lin (Sun Yat-sen University) on the occasion of his 80th birthday

free viruses; $\beta u_1 u_3$ represents the lost of susceptible cells by infection (or the recruitment of infected cells). The parameters in (1.1) are all positive constants. System (1.1) has been used to study the *in vivo* dynamics of HIV-1, HBV, and other virus (see, e.g. [1–11]).

In (1.1), it is assumed that cells and viruses are well mixed, and the mobility of cells and viruses is neglected. In fact, susceptible host cells and infected cells cannot move under normal conditions while viruses move freely in the habitat. To incorporate the influences of spatial structures on virus dynamics, Wang and Wang [12] introduced the random mobility for viruses into (1.1) and proposed the following mathematical model to describe the hepatitis B virus (HBV) infection:

$$\begin{cases} \frac{\partial u_1(x,t)}{\partial t} = \lambda - a u_1(x,t) - \beta u_1(x,t) u_3(x,t), \\ \frac{\partial u_2(x,t)}{\partial t} = \beta u_1(x,t) u_3(x,t) - b u_2(x,t), \\ \frac{\partial u_3(x,t)}{\partial t} = d \Delta u_3(x,t) + k u_2(x,t) - m u_3(x,t), \end{cases} \tag{1.2}$$

in $(x,t) \in (-\infty, \infty) \times (0, \infty)$. Here, $u_1(x,t)$, $u_2(x,t)$, and $u_3(x,t)$ are the densities of uninfected cells, infected cells and free virus at location x at time t, respectively, and d is the diffusion coefficient. The parameters in (1.2) are positive constants. In (1.2), the spatial domain is taken as the one-dimensional whole space $\mathbb{R} = (-\infty, \infty)$, and accordingly, the traveling waves is investigated by appealing to the geometric singular perturbation method. Among the topics are the existence of traveling wave fronts and the minimal wave speed.[12]

More recently, Brauner et al. [13] modified (1.2) by allowing λ to be space dependent, and assumed that other parameters remain constants; in addition, for the spatial domain, they considered a square domain $(0, l) \times (0, l)$, and proposed periodic boundary conditions on this square. The dynamics of the model was explored via a principle eigenvalue.

In reality, a spatial domain where virus and cells stay and interact is bounded but is typically not a square. Even in the square domain case, there may be other types of boundary conditions. One frequently encountered scenario is zero-flux boundary condition in a bounded domain. Moreover, in addition to λ, other model parameters may also depend on the location in the domain. All these motivate us to consider a more general situation. In this paper, we consider a general bounded domain $\Omega \subset \mathbb{R}^n$ and pose zero-flux condition on the boundary of Ω (i.e. homogeneous Neumann boundary condition). We further modify the model system in Brauner et al. [13] to allow all parameters to be location dependent except the diffusion coefficient d. These considerations lead to the following problem:

$$\begin{cases} \frac{\partial u_1(x,t)}{\partial t} = \lambda(x) - a(x) u_1(x,t) - \beta(x) u_1(x,t) u_3(x,t), \\ \frac{\partial u_2(x,t)}{\partial t} = \beta(x) u_1(x,t) u_3(x,t) - b(x) u_2(x,t), \quad (x,t) \in \Omega \times (0, \infty) \\ \frac{\partial u_3(x,t)}{\partial t} = d \Delta u_3(x,t) + k(x) u_2(x,t) - m(x) u_3(x,t), \end{cases} \tag{1.3}$$

with the homogeneous Neumann boundary condition

$$\frac{\partial u_3(x,t)}{\partial \nu} = 0, \ x \in \partial\Omega, \ t > 0, \tag{1.4}$$

and initial conditions

$$u_i(x,0) = u_i^0(x) \geq 0, \quad x \in \Omega, \ i = 1, 2, 3, \tag{1.5}$$

where $\frac{\partial}{\partial \nu}$ denotes the differentiation along the outward normal ν to $\partial\Omega$. In this paper, we always assume that the location-dependent parameters are continuous and strictly positive functions on $\bar{\Omega}$.

We point out that since the first two equations in (1.3) have no diffusion terms, the semiflow associated with our model is not compact. To overcome this problem, we will prove that the semiflow associated with a linearized system around the infection-free steady state is κ-contraction, where κ is the Kuratowski measure of noncompactness (see, e.g. [14]). Then, by a generalized Krein–Rutman Theorem and some new results in [15], we can show that the principal eigenvalue of the associated eigenvalue problems exists, and hence, the stability of the infection-free steady state can be determined. Next, we can derive a condition under which, the semiflow associated with our systems is κ-contracting and thereby, conclude that the semiflow admits a connected global attractor using the results in [16] (see also [17]). Finally, we show that the basic reproduction number serves as a threshold parameter that predicts whether the infection will go to extinction or persist, by appealing to the theory of uniform persistence and the comparison theorem.

2. Analysis of the model system

In this section, we analyze the model system (1.3)–(1.5), intending to understand when the disease will go to extinct and when it will persist. We start with some basic properties for system (1.3)–(1.5).

Let $\mathbb{X} := C(\bar{\Omega}, \mathbb{R}^3)$ be the Banach space with the supremum norm $\|\cdot\|_{\mathbb{X}}$. Define $\mathbb{X}^+ := C(\bar{\Omega}, \mathbb{R}^3_+)$, then $(\mathbb{X}, \mathbb{X}^+)$ is a strongly ordered spaces. For every initial value functions $\phi = (\phi_1, \phi_2, \phi_3) \in C(\bar{\Omega}, \mathbb{R}^3)$, define

$$T_1(t)\phi_1 = e^{-a(\cdot)t}\phi_1, \quad T_2(t)\phi_2 = e^{-b(\cdot)t}\phi_2. \tag{2.1}$$

Let $T_3(t) : C(\bar{\Omega}, \mathbb{R}) \to C(\bar{\Omega}, \mathbb{R})$ be the C_0 semigroups associated with $d\Delta - m(\cdot)$ subject to the Neumann boundary condition, that is,

$$(T_3(t)\phi_3)(x) = \int_\Omega \Gamma(x, y, t)\phi_3(y)dy, \quad t \geq 0, \tag{2.2}$$

where Γ is the Green function associated with $d\Delta - m(\cdot)$ and the Neumann boundary condition. From [18, Section 7.1 and Corollary 7.2.3], it follows that $T_3(t) : C(\bar{\Omega}, \mathbb{R}) \to C(\bar{\Omega}, \mathbb{R})$ is compact and strongly positive, $\forall\, t > 0$.

Define $F = (F_1, F_2, F_3) : \mathbb{X}^+ \to \mathbb{X}$ by

$$\begin{aligned} F_1(\phi)(x) &= \lambda(x) - \beta(x)\phi_1(x)\phi_3(x), \\ F_2(\phi)(x) &= \beta(x)\phi_1(x)\phi_3(x), \\ F_3(\phi)(x) &= k(x)\phi_2(x), \quad \forall\, x \in \bar{\Omega}. \end{aligned}$$

Then (1.3)–(1.5) can be rewritten as the integral equation:

$$u(t) = T(t)\phi + \int_0^t T(t-s)F(u(s))ds, \tag{2.3}$$

where

$$u(t) = \begin{pmatrix} u_1(t) \\ u_2(t) \\ u_3(t) \end{pmatrix}, \quad T(t) = \begin{pmatrix} T_1(t) & 0 & 0 \\ 0 & T_2(t) & 0 \\ 0 & 0 & T_3(t) \end{pmatrix}.$$

It is easy to show that

$$\lim_{h\to 0^+} \text{dist}(\phi + hF(\phi), \mathbb{X}^+) = 0, \quad \forall\, \phi \in \mathbb{X}^+.$$

By [19, Corollary 4], we obtain the following basic properties of the set $\mathbb{X}^+$:

LEMMA 2.1 *For every initial value functions $\phi := (\phi_1, \phi_2, \phi_3) \in \mathbb{X}^+$, system (1.3)–(1.5) has a unique mild solution $u(x, t, \phi)$ on $[0, \tau_\phi)$ with $u(\cdot, 0, \phi) = \phi$ and $u(\cdot, t, \phi) \in \mathbb{X}^+$, $\forall\, t \in [0, \tau_\phi)$, where $\tau_\phi \le \infty$.*

In order to study the infection-free steady state and its stability, we need to consider the following auxiliary point-wise scalar equation

$$\frac{\partial w(x,t)}{\partial t} = \lambda(x) - A(x)w(x,t), \quad x \in \bar{\Omega},\ t > 0, \tag{2.4}$$

and the following scalar reaction-diffusion equation

$$\begin{cases} \frac{\partial w}{\partial t} = d\Delta w + g(x) - m(x)w, & x \in \Omega,\ t > 0, \\ \frac{\partial w}{\partial \nu} = 0,\ x \in \partial\Omega,\ t > 0, \end{cases} \tag{2.5}$$

where $d > 0$; $g(x)$ and $m(x)$ are continuous and positive functions on $\bar{\Omega}$. For (2.4), by [20, Theorem 2.2.1], we have the following result.

LEMMA 2.2 *The system (2.4) admits a unique positive steady state $\frac{\lambda(x)}{A(x)}$ which is globally asymptotically stable in $C(\bar{\Omega}, \mathbb{R})$.*

For (2.5), the following result is available from [21, Lemma 1].

LEMMA 2.3 *The system (2.5) admits a unique positive steady state $w^*(x)$ which is globally asymptotically stable in $C(\bar{\Omega}, \mathbb{R})$. Moreover, if $g(x) \equiv g$, $m(x) \equiv m$, $\forall\, x \in \bar{\Omega}$, then $w^*(x) = \frac{g}{m}$.*

We are in a position to show that solutions of system (1.3)–(1.5) exist globally on $[0, \infty)$, and are ultimately bounded and uniformly bounded in $\mathbb{X}^+$.

LEMMA 2.4 *For every initial value function $\phi \in \mathbb{X}^+$, system (1.3)–(1.5) has a unique solution $u(\cdot, t, \phi)$ on $[0, \infty)$ with $u(\cdot, 0, \phi) = \phi$, and solutions of (1.3)–(1.5) are ultimately bounded and uniformly bounded in $\mathbb{X}^+$.*

Proof Let $U(x,t) := u_1(x,t) + u_2(x,t)$. Then $U(x,t)$ satisfies

$$\frac{\partial U(x,t)}{\partial t} \le \overline{\lambda} - \underline{c}U(x,t), \quad x \in \Omega,\ t > 0, \tag{2.6}$$

where

$$\overline{\lambda} = \max_{x\in\overline{\Omega}} \lambda(x) \text{ and } \underline{c} = \min\{\min_{x\in\bar{\Omega}}\{a(x)\}, \min_{x\in\bar{\Omega}}\{b(x)\}\}. \tag{2.7}$$

The comparison principle implies that $U(x,t)$ is uniformly bounded, and hence, so are $u_1(x,t)$ and $u_2(x,t)$. This, together with a comparison argument, implies that $u_3(x,t)$ in (1.3) is also uniformly bounded.

Now, we show that solutions are also ultimately bounded (point dissipative). Comparing (2.6) with (2.4), it follows from Lemma 2.2 and the comparison principle that

$$\limsup_{t\to\infty} U(x,t) \leq \frac{\overline{\lambda}}{\underline{c}}, \quad \text{uniformly for } x \in \overline{\Omega}.$$

It then follows that there exist $0 < \eta_0 \ll 1$ and $\tilde{t}_0 > 0$ such that

$$u_1(\cdot,t) + u_2(\cdot,t) := U(\cdot,t) \leq (1+\eta_0)\frac{\overline{\lambda}}{\underline{c}}, \ \forall\, t \geq \tilde{t}_0, \tag{2.8}$$

and hence,

$$u_1(\cdot,t) \leq (1+\eta_0)\frac{\overline{\lambda}}{\underline{c}}, \quad u_2(\cdot,t) \leq (1+\eta_0)\frac{\overline{\lambda}}{\underline{c}}, \ \forall\, t \geq \tilde{t}_0. \tag{2.9}$$

This implies that $u_1(\cdot,t)$ and $u_2(\cdot,t)$ are ultimately bounded.

From (2.9) and the third equation of (1.3), it follows that

$$\begin{cases} \frac{\partial u_3(x,t)}{\partial t} \leq d\Delta u_3(x,t) + (1+\eta_0)\frac{\overline{\lambda}}{\underline{c}}\overline{k} - \underline{m}u_3(x,t), \ x \in \Omega, \ t \geq \tilde{t}_0, \\ \frac{\partial u_3(x,t)}{\partial \nu} = 0, \ x \in \partial\Omega, \ t > 0, \end{cases}$$

where

$$\overline{k} = \max_{x\in\bar{\Omega}} k(x) \text{ and } \underline{m} = \min_{x\in\bar{\Omega}} m(x). \tag{2.10}$$

By Lemma 2.3, it follows that there is a $\hat{t}_0 \geq \tilde{t}_0 > 0$ such that

$$u_3(\cdot,t) \leq (1+2\eta_0)\cdot\frac{\overline{\lambda}\cdot\overline{k}}{\underline{c}\cdot\underline{m}}, \quad \forall\, t \geq \hat{t}_0. \tag{2.11}$$

It then follows that $u_3(x,t)$ is also ultimately bounded. □

From Lemma 2.4, (2.8), and (2.11), it follows that there exist $\hat{t}_0 > 0$, $\bar{K} := (1+\eta_0)\frac{\overline{\lambda}}{\underline{c}} > 0$ and $K := (1+2\eta_0)\cdot\frac{\overline{\lambda}\cdot\overline{k}}{\underline{c}\cdot\underline{m}} > 0$ such that

$$u_1(\cdot,t) + u_2(\cdot,t) \leq \bar{K}, \ u_3(\cdot,t) \leq K, \quad \forall\, t \geq \hat{t}_0.$$

Let

$$\mathcal{D} = \{(u_1,u_2,u_3) \in \mathbb{R}^3_+ : 0 \leq u_1 + u_2 \leq \bar{K}, \quad 0 \leq u_3 \leq K\}.$$

Define the semiflow $\Psi_t : \mathbb{X}^+ \to \mathbb{X}^+$ associated with (1.3)–(1.5) by

$$\Psi_t(\phi) = u(\cdot,t,\phi), \quad t \geq 0, \tag{2.12}$$

where $u(\cdot,t,\phi)$ is the solution of (1.3)–(1.5) with $u(\cdot,0,\phi) = \phi \in \mathbb{X}^+$. Then

$$\Psi_t(\phi) \in \mathcal{D}, \ \forall\, t \geq \hat{t}_0, \quad \phi \in \mathbb{X}^+. \tag{2.13}$$

Moreover, it is easy to see that $\bar{K}$ and K are upper solutions of systems

$$\frac{\partial U(x,t)}{\partial t} = \overline{\lambda} - \underline{c}U(x,t), \quad x \in \Omega, \ t > 0,$$

and

$$\begin{cases} \frac{\partial u_3(x,t)}{\partial t} = d\Delta u_3(x,t) + \frac{2\bar{\lambda}}{\underline{c}}\bar{k} - \underline{m}u_3(x,t), \ x \in \Omega, \ t \geq \tilde{t}_0, \\ \frac{\partial u_3(x,t)}{\partial \nu} = 0, \ x \in \partial\Omega, \ t > 0, \end{cases}$$

respectively. These facts, together with a comparison argument, imply that $\mathcal{D}$ is positively invariant for Ψ_t in the sense that $\Psi_t(\phi) \in \mathcal{D}, \ \forall\, t \geq 0, \ \phi \in \mathcal{D}$.

For convenience, we let

$$\begin{cases} f_1(x, u_1, u_3) = \lambda(x) - a(x)u_1 - \beta(x)u_1u_3, \\ f_2(x, u_1, u_2, u_3) = \beta(x)u_1u_3 - b(x)u_2, \\ g(x, u_2, u_3) = k(x)u_2 - m(x)u_3. \end{cases} \tag{2.14}$$

Then (1.3)–(1.5) can be rewritten as follows

$$\begin{cases} \frac{\partial u_1(x,t)}{\partial t} = f_1(x, u_1, u_3), \ x \in \Omega, \ t > 0, \\ \frac{\partial u_2(x,t)}{\partial t} = f_2(x, u_1, u_2, u_3), \ x \in \Omega, \ t > 0, \\ \frac{\partial u_3(x,t)}{\partial t} = d\Delta u_3(x,t) + g(x, u_2, u_3), \ x \in \Omega, \ t > 0, \\ \frac{\partial u_3(x,t)}{\partial \nu} = 0, \ x \in \partial\Omega, \ t > 0, \\ u_i(x, 0) = u_i^0(x) \geq 0, \ x \in \Omega, \ i = 1, 2, 3, \end{cases} \tag{2.15}$$

For $\mathbf{u} := (u_1, u_2)$ and $v := u_3$, we impose the following assumption: there exists a constant $r > 0$ such that

$$\mathbf{z}^T \left[\frac{\partial \mathbf{f}(x, \mathbf{u}, v)}{\partial \mathbf{u}} \right] \mathbf{z} \leq -r\mathbf{z}^T\mathbf{z}, \quad \forall\, \mathbf{z} \in \mathbb{R}^2, \ x \in \Omega, \ (\mathbf{u}, v) \in \mathcal{D}, \tag{2.16}$$

where $\mathbf{f}(x, \mathbf{u}, v) := (f_1(x, u_1, u_3), \ f_2(x, u_1, u_2, u_3))$.

Remark 2.1 Recall that $K := (1+2\eta_0)\frac{\bar{\lambda}\cdot\bar{k}}{\underline{c}\cdot\underline{m}} > 0$; $\bar{\lambda}$ and $\underline{c}$ are defined in (2.7); η_0 is defined in (2.9); $\bar{k}$ and $\underline{m}$ are defined in (2.10). Assume that

$$\frac{1}{2}\bar{\beta}K - \underline{b} < 0, \tag{2.17}$$

where $\bar{\beta} := \max_{x\in\bar{\Omega}} \beta(x)$ and $\underline{b} := \min_{x\in\bar{\Omega}} b(x)$. It is easy to see that the assumption (2.17) implies (2.16).

Since the first two equations in (1.3)–(1.5) have no diffusion terms, its solution semiflow Ψ_t is not compact. In order to overcome this difficulty, we introduce the Kuratowski measure of noncompactness (see [14]), κ, which is defined by

$$\kappa(B) := \inf\{R : B \text{ has a finite cover of diameter } < R\}, \tag{2.18}$$

for any bounded set B. We set $\kappa(B) = \infty$ whenever B is unbounded. It is easy to see that B is precompact(i.e. $\bar{B}$ is compact) if and only if $\kappa(B) = 0$. We have the following results:

LEMMA 2.5 *Let* (2.16) *hold. Then* Ψ_t *is* κ*-contracting in the sense that*

$$\lim_{t\to\infty} \kappa(\Psi_t B) = 0 \textit{ for any bounded set } B \subset \mathbb{X}^+.$$

Proof Let B be a given bounded subset in $\mathbb{X}^+$. Using a slight modification of the proof in [17, Lemma 4.1], we can show that Ψ_t is asymptotically compact on B in the sense that for any sequences $\varphi_n \in B$ and $t_n \to \infty$, there exist subsequences φ_{n_k} and $t_{n_k} \to \infty$ such that $\Psi_{t_{n_k}}(\varphi_{n_k})$ converges in $C(\overline{\Omega}, \mathbb{R}^3)$ as $k \to \infty$.

It follows from [22, Lemma 23.1 (2)] that $\omega(B)$, the omega-limit set of B, is a nonempty, compact, invariant set in $\mathbb{X}^+$, and $\omega(B)$ attracts B. In view of [16, Lemma 2.1 (b)], we see that

$$\kappa(\Psi_t(B)) \leq \kappa(\omega(B)) + \delta(\Psi_t(B), \omega(B)) = \delta(\Psi_t(B), \omega(B)) \to 0 \text{ as } t \to \infty,$$

Completing the proof. □

THEOREM 2.1 *Let* (2.16) *hold. Then* Ψ_t *admits a connected global attractor on* $\mathbb{X}^+$.

Proof By Lemma 2.4, it follows that Ψ_t is point dissipative on $\mathbb{X}^+$ and that the positive orbits of bounded subsets of $\mathbb{X}^+$ for Ψ_t are bounded. Furthermore, Ψ_t is κ-contracting on $\mathbb{X}^+$ by Lemma 2.5. By [16, Theorem 2.6], Ψ_t has a global attractor that attracts every point in $\mathbb{X}^+$. □

The following results will play an important role in establishing the persistence of (1.3)–(1.5).

LEMMA 2.6 *Suppose* $u(x, t, \phi)$ *is the solution of system* (1.3)–(1.5) *with* $u(\cdot, 0, \phi) = \phi \in \mathbb{X}^+$.

(i) *For any* $\phi \in \mathbb{X}^+$*, we always have* $u_1(x, t, \phi) > 0, \ \forall\, x \in \bar{\Omega}$*,* $t > 0$ *and*

$$\liminf_{t\to\infty} u_1(x, t, \phi) \geq h(x),$$

where $h(x)$ *is a strictly positive function on* $\bar{\Omega}$*;*

(ii) *If there exists some* $t_0 \geq 0$ *such that* $u_3(\cdot, t_0, \phi) \not\equiv 0$*, then* $u_3(x, t, \phi) > 0, \ \forall\, x \in \bar{\Omega}$*,* $t > t_0$*;*

(iii) *If there exists some* $t_0 \geq 0$ *such that* $u_i(\cdot, t_0, \phi) \not\equiv 0$*, for* $i \in \{2, 3\}$*, then* $u_2(x, t, \phi) > 0, \ \forall\, x \in \bar{\Omega}$*,* $t > t_0$.

Proof From the first equation of (1.3), it is easy to see that $u_1(x, t, \phi) > 0, \ \forall\, x \in \bar{\Omega}$, $t > 0$, for any $\phi \in \mathbb{X}^+$. From (2.11), it follows that there is a $\hat{t}_0 > 0$ such that

$$u_3(\cdot, t) \leq K, \quad \forall\, t \geq \hat{t}_0.$$

From the first equation of (1.3), it follows that

$$\frac{\partial u_1(x, t)}{\partial t} \geq \lambda(x) - (a(x) + K\beta(x))u_1(x, t), \quad x \in \bar{\Omega}, \ t \geq \hat{t}_0.$$

By Lemma 2.2 and the comparison theorem, it follows that

$$\liminf_{t\to\infty} u_1(x, t, \phi) \geq \frac{\lambda(x)}{a(x) + K\beta(x)}, \quad \forall\, x \in \bar{\Omega}.$$

Thus, Part (i) is proved.

It is easy to see that u_3 satisfies the following inequality:

$$\begin{cases} \frac{\partial u_3(x,t)}{\partial t} \geq d\Delta u_3(x,t) - m(x)u_3(x,t), \ x \in \Omega, \ t > 0, \\ \frac{\partial u_3}{\partial \nu} = 0, \ x \in \partial\Omega, \ t > 0. \end{cases}$$

By the similar arguments as in [23, Lemma 2.1] and [24, Proposition 3.1], it follows from the strong maximum principle (see, e.g. [25, p. 172, Theorem 4]) and the Hopf boundary lemma (see, e.g. [25, p. 170, Theorem 3]) that part (ii) is valid.

Assume by contradiction that the conclusion of (iii) is false, that is, there exist $x_0 \in \bar{\Omega}$ and $\hat{t} > t_0$ such that $u_2(x_0, \hat{t}, \phi) = 0$. From the second equation of (1.3), it follows that

$$0 = \frac{\partial u_2(x_0, \hat{t})}{\partial t} = \beta(x_0)u_1(x_0, \hat{t})u_3(x_0, \hat{t}) - b(x_0)u_2(x_0, \hat{t}),$$

and hence,

$$0 = \beta(x_0)u_1(x_0, \hat{t})u_3(x_0, \hat{t}),$$

which implies that $u_3(x_0, \hat{t}) = 0$. This contradicts (ii). Part (iii) is proved. □

It is easy to see that $(u_1^*(x), 0, 0)$ is the infection-free steady-state solution for the system (1.3)–(1.5), where $u_1^*(x) = \frac{\lambda(x)}{a(x)}$. Linearizing the system (1.3)–(1.5) at $(u_1^*(x), 0, 0)$ and we get the following cooperative system for the infected host cells and free virus particle:

$$\begin{cases} \frac{\partial U_2(x,t)}{\partial t} = -b(x)U_2(x,t) + \beta(x)u_1^*(x)U_3(x,t), \ x \in \Omega, \ t > 0, \\ \frac{\partial U_3(x,t)}{\partial t} = d\Delta U_3(x,t) - m(x)U_3(x,t) + k(x)U_2(x,t), \ x \in \Omega, \ t > 0, \\ \frac{\partial U_3(x,t)}{\partial \nu} = 0, \ x \in \partial\Omega, \ t > 0, \end{cases} \tag{2.19}$$

and initial conditions. We first consider the following generalized version of system (2.19):

$$\begin{cases} \frac{\partial U_2(x,t)}{\partial t} = -b(x)U_2(x,t) + \beta(x)H(x)U_3(x,t), \ x \in \Omega, \ t > 0, \\ \frac{\partial U_3(x,t)}{\partial t} = d\Delta U_3(x,t) - m(x)U_3(x,t) + k(x)U_2(x,t), \ x \in \Omega, \ t > 0, \\ \frac{\partial U_3(x,t)}{\partial \nu} = 0, \ x \in \partial\Omega, \ t > 0, \end{cases} \tag{2.20}$$

and initial conditions, where $H(x) > 0, \forall x \in \bar{\Omega}$. It is easy to see that system (2.20) is cooperative while its solution semiflows are not compact since the first equation in (2.20) has no diffusion term. Let $\mathbb{Y} = C(\bar{\Omega}, \mathbb{R}^2)$. For every initial value functions $\phi = (\phi_2, \phi_3) \in \mathbb{Y}$, the solution semiflows $\Pi_t : \mathbb{Y} \to \mathbb{Y}$ associated with the linear system (2.20) is defined by

$$\Pi_t(\phi) = (U_2(\cdot, t, \phi), U_3(\cdot, t, \phi)), \quad \forall \phi \in \mathbb{Y}, \ t \geq 0.$$

It is easy to see that Π_t is a positive C_0-semigroup on $C(\bar{\Omega}, \mathbb{R}^2)$, and its generator $\mathcal{B}^H$ can be written as

$$\mathcal{B}^H = \begin{pmatrix} -b(x) & \beta(x)H(x) \\ k(x) & d\Delta - m(x) \end{pmatrix}.$$

Further, $\mathcal{B}^H$ is a closed and resolvent positive operator (see, e.g. [26, Theorem 3.12]).

Substituting $U_i(x,t) = e^{\eta t}\psi_i(x)$, $i = 2, 3$, into (2.20) we get the following associated eigenvalue problem:

$$\begin{cases} \eta\psi_2(x) = -b(x)\psi_2(x) + \beta(x)H(x)\psi_3(x), \ x \in \Omega, \\ \eta\psi_3(x) = d\Delta\psi_3(x) - m(x)\psi_3(x) + k(x)\psi_2(x), \ x \in \Omega, \\ \frac{\partial \psi_3(x)}{\partial \nu} = 0, \quad x \in \partial\Omega. \end{cases} \tag{2.21}$$

The following lemma concerns with the existence of the principal eigenvalue of (2.21).

Lemma 2.7 *Suppose* $H(x) > 0,\ \forall\, x \in \bar{\Omega}$ *and* $s(\mathcal{B}^H)$ *is the spectral bound of* $\mathcal{B}^H$.

(i) *If* $s(\mathcal{B}^H) \geq 0$ *then* $s(\mathcal{B}^H)$ *is the principal eigenvalue of the eigenvalue problem* (2.21) *which has a strongly positive eigenfunction;*
(ii) *If* $b(x) \equiv b,\ \forall\, x \in \bar{\Omega}$, *then* $s(\mathcal{B}^H)$ *is always the principal eigenvalue of the eigenvalue problem* (2.21) *which has a strongly positive eigenfunction.*

Proof We first prove Part (i). Recall that $\underline{b} := \min_{x\in\bar{\Omega}} b(x)$ and it is easy to see that

$$b(x) \geq \underline{b}, \quad \forall\, x \in \bar{\Omega}. \tag{2.22}$$

We first show that for each $t > 0$, Π_t is an κ-contraction on $\mathbb{Y} := C(\bar{\Omega}, \mathbb{R}^2)$ in the sense that

$$\kappa(\Pi_t B) \leq e^{-\underline{b}t}\kappa(B),$$

for any bounded set B in $\mathbb{Y}$, where κ is the Kuratowski measure of noncompactness as defined in (2.18). Let $T_2(t)$ and $T_3(t)$ be the semigroup defined by (2.1) and (2.2), respectively. Define a linear operator

$$L(t)\phi = (T_2(t)\phi_2, 0), \quad \forall \phi = (\phi_2, \phi_3) \in \mathbb{Y}, \tag{2.23}$$

and a nonlinear operator

$$N(t)\phi = \left(\int_0^t e^{-b(\cdot)(t-s)}\beta(\cdot)H(\cdot)U_3(\cdot, s, \phi)ds, U_3(., t, \phi)\right),\ \forall \phi = (\phi_2, \phi_3) \in \mathbb{Y}.$$

It is easy to see that

$$\Pi_t(\phi) = L(t)\phi + N(t)\phi,\ \forall \phi \in \mathbb{Y},\ t \geq 0.$$

By (2.22) and (2.23), it follows that

$$\sup_{\phi\in\mathbb{Y}} \frac{\|L(t)\phi\|}{\|\phi\|} \leq \sup_{\phi\in\mathbb{Y}} \frac{\|e^{-b(\cdot)t}\phi_2\|}{\|\phi\|} \leq \sup_{\phi\in\mathbb{Y}} \frac{\|e^{-\underline{b}t}\phi_2\|}{\|\phi\|} \leq e^{-\underline{b}t},$$

and hence $\|L(t)\| \leq e^{-\underline{b}t}$.

From the boundedness of Π_t and the compactness of $T_3(t)$ for $t > 0$, it follows that $N(t) : \mathbb{Y} \to \mathbb{Y}$ is compact for each $t > 0$. For any bounded set B in $\mathbb{Y}$, there holds $\kappa(N(t)B) = 0$ since $N(t)B$ is precompact, and consequently,

$$\kappa(\Pi_t B) \leq \kappa(L(t)B) + \kappa(N(t)B) \leq \|L(t)\|\kappa(B) \leq e^{-\underline{b}t}\kappa(B),\ \forall\, t > 0.$$

Thus, Π_t is a κ-contraction on $\mathbb{Y}$ with a contracting function $e^{-\underline{b}t}$. This implies that the essential spectral radius $r_e(\Pi_t)$ of Π_t satisfies

$$r_e(\Pi_t) \leq e^{-\underline{b}t} < 1, \quad \forall\, t > 0.$$

On the other hand, the spectral radius $r(\Pi_t)$ of Π_t satisfies

$$r(\Pi_t) = e^{s(\mathcal{B}^H)t} \geq 1, \quad \forall\, t > 0.$$

This implies that $r_e(\Pi_t) < r(\Pi_t),\ \forall\, t > 0$. Since Π_t is a strongly positive and bounded operator on $\mathbb{Y}$, it follows from a generalized Krein–Rutman Theorem (see, e.g. [27]) that the conclusion of Part (i) is true.

Next, we are in a position to prove Part (ii). In order to make use of the results in [15, Theorem 2.3 (i)], we define an one-parameter family of linear operators on $C(\bar{\Omega}, \mathbb{R})$:

$$\mathcal{L}_\eta = d\Delta - m(x) + \frac{k(x)\beta(x)H(x)}{\eta + b}, \quad \forall\, \eta > -b.$$

Let $A := \min_{x\in\bar{\Omega}}[k(x)\beta(x)H(x)] > 0$. It is easy to see that the eigenvalue problem

$$\begin{cases} \eta\phi(x) = d\Delta\phi(x) - m(x)\phi(x), & x \in \Omega, \\ \frac{\partial\phi(x)}{\partial\nu} = 0,\ x \in \partial\Omega, \end{cases}$$

has a principal eigenvalue, denoted by η^0, with an associated eigenvector $\phi^0 \gg 0$. Let

$$\eta^* = \frac{1}{2}\left[(\eta^0 - b) + \sqrt{(\eta^0 - b)^2 + 4(A + \eta^0 b)}\right].$$

Then, $\eta^* = \frac{1}{2}\left[(\eta^0 - b) + \sqrt{(\eta^0 + b)^2 + 4A}\right] > -b$. It is easy to see that

$$\mathcal{L}_{\eta^*}\phi^0 = d\Delta\phi^0 - m(x)\phi^0 + \frac{k(x)\beta(x)H(x)}{\eta^* + b}\phi^0 \geq (\eta^0 + \frac{A}{\eta^* + b})\phi^0 = \eta^*\phi^0.$$

By [15, Theorem 2.3 (i)], we complete the proof of (ii). □

Notice that the second and the third equations are decoupled from the first one in (2.19) and they form a subsystem which is closely related to the basic reproduction number. In the following, we shall adopt the same ideas as in [15,28–30] to identify the basic reproduction number for system (1.3)–(1.5). To this end, we first need to separate the transfer part from the infection part in the $u_2 - u_3$ subsystem of (2.19) as below.

Let $S(t) : C(\bar{\Omega}, \mathbb{R}^2) \to C(\bar{\Omega}, \mathbb{R}^2)$ be the C_0-semigroup generated by the following system

$$\begin{cases} \frac{\partial U_2(x,t)}{\partial t} = -b(x)U_2(x,t),\ x \in \Omega,\ t > 0, \\ \frac{\partial U_3(x,t)}{\partial t} = d\Delta U_3(x,t) - m(x)U_3(x,t) + k(x)U_2(x,t),\ x \in \Omega,\ t > 0, \\ \frac{\partial U_3(x,t)}{\partial \nu} = 0,\ x \in \partial\Omega,\ t > 0, \\ U_2(x,0) = \varphi_2(x),\ U_3(x,0) = \varphi_3(x),\ x \in \Omega. \end{cases} \tag{2.24}$$

In order to define the basic reproduction number for the system (1.3)–(1.5), we assume that the population is near the Disease-free equilibrium $(u_1^*(x), 0, 0)$. Then, we introduce the distribution of initial infection described by $\varphi := (\varphi_2, \varphi_3) \in C(\bar{\Omega}, \mathbb{R}^2)$. Hence, $S(t)\varphi$ represents the distribution of those infective members as time evolves. Thus, the distribution of new infection at time t is

$$\begin{pmatrix} 0 & \beta(\cdot)u_1^*(\cdot) \\ 0 & 0 \end{pmatrix}(S(t)\varphi)(\cdot).$$

Consequently, the distribution of total new infections is

$$\mathbf{L}(\varphi)(\cdot) := \int_0^\infty \begin{pmatrix} 0 & \beta(\cdot)u_1^*(\cdot) \\ 0 & 0 \end{pmatrix}(S(t)\varphi)(\cdot)dt.$$

Then **L** is a continuous and positive operator which maps the initial infection distribution φ to the distribution of the total infective members produced during the infection period. Following the idea of next generation operators (see, e.g. [15,26,30–32]), the basic reproductive number for system (1.3)–(1.5) is given by the spectral radius of **L**, that is,

$$\mathbf{R}_0 := r(\mathbf{L}). \tag{2.25}$$

By the general results in [26] and [15, Theorem 2.5 and Remark 2.3], we have the following observation.

LEMMA 2.8 *$\mathbf{R}_0 - 1$ and $s(\mathcal{B}^{u_1^*})$ have the same sign.*

Now we are ready to prove the main result of this section, which indicates that $\mathbf{R}_0$ is a threshold index for disease persistence.

THEOREM 2.2 *Assume that (2.16) is true. Suppose $u(x, t, \phi)$ is the solution of system (1.3)–(1.5) with $u(\cdot, 0, \phi) = \phi \in \mathbb{X}^+$. Then the following statements hold.*

(i) *If $\mathbf{R}_0 < 1$ and $b(x) \equiv b,\ \forall\, x \in \bar{\Omega}$, then the disease-free equilibrium $(u_1^*(x), 0, 0)$ is globally attractive in $\mathbb{X}^+$, where $u_1^*(x) := \frac{\lambda(x)}{a(x)}$;*
(ii) *If $\mathbf{R}_0 > 1$, then system (1.3)–(1.5) admits at least one positive steady state $\hat{u}(x)$ and there exists a $\sigma > 0$ such that for any $\phi \in \mathbb{X}^+$ with $\phi_i(\cdot) \not\equiv 0$ for $i = 2, 3$, we have*

$$\liminf_{t\to\infty} u_i(x, t) \geq \sigma, \quad \forall\, i = 1, 2, 3,$$

uniformly for all $x \in \bar{\Omega}$.

Proof We first assume that $\mathbf{R}_0 < 1$, that is, $s(\mathcal{B}^{u_1^*}) < 0$ by Lemma 2.8. It follows from Lemma 2.7(ii) that $s(\mathcal{B}^{u_1^*})$ is the principal eigenvalue of the eigenvalue problem (2.21) with $H \equiv u_1^*$. By Lemma 2.7(ii) and the continuity, there is a $\rho_0 > 0$ such that $s(\mathcal{B}^{u_1^*+\rho_0})$ is still the principal eigenvalue of the eigenvalue problem (2.21) with $H \equiv u_1^* + \rho_0$ and $s(\mathcal{B}^{u_1^*+\rho_0}) < 0$.

From the first equation of (1.3), it follows that

$$\frac{\partial u_1(x, t)}{\partial t} \leq \lambda(x) - a(x)u_1(x, t), \tag{2.26}$$

From Lemma 2.2, (2.26) and the comparison principle, it follows that there is a $t_0 := t_0(\phi)$ such that

$$u_1(x, t, \phi) \leq u_1^*(x) + \rho_0, \quad \forall\, t \geq t_0,\ x \in \bar{\Omega}.$$

Thus,

$$\begin{cases} \frac{\partial u_2(x,t)}{\partial t} \leq \beta(x)(u_1^*(x) + \rho_0)u_3(x, t) - b(x)u_2(x, t),\ x \in \Omega,\ t \geq t_0. \\ \frac{\partial u_3(x,t)}{\partial t} = d\Delta u_3(x, t) + k(x)u_2(x, t) - m(x)u_3(x, t),\ x \in \Omega,\ t \geq t_0. \\ \frac{\partial u_3}{\partial \nu} = 0,\ x \in \partial\Omega,\ t \geq t_0. \end{cases} \tag{2.27}$$

By Lemma 2.7(ii), there is a strongly positive eigenfunction $\hat{\psi} := (\hat{\psi}_2, \hat{\psi}_3)$ corresponding to $s(\mathcal{B}^{u_1^*+\rho_0})$. Since for any given $\phi \in \mathbb{X}^+$, there exists some $\alpha > 0$ such that $(u_2(x, t_0, \phi), u_3(x, t_0, \phi)) \le \alpha\hat{\psi}(x),\ \forall\, x \in \bar{\Omega}$. Note that the following linear system

$$\begin{cases} \frac{\partial u_2(x,t)}{\partial t} = \beta(x)(u_1^*(x) + \rho_0)u_3(x, t) - b(x)u_2(x, t),\ x \in \Omega,\ t \ge t_0. \\ \frac{\partial u_3(x,t)}{\partial t} = d\Delta u_3(x, t) + k(x)u_2(x, t) - m(x)u_3(x, t),\ x \in \Omega,\ t \ge t_0. \\ \frac{\partial u_3}{\partial \nu} = 0,\ x \in \partial\Omega,\ t \ge t_0, \end{cases} \tag{2.28}$$

admits a solution $\alpha e^{s(\mathcal{B}^{u_1^*+\rho_0})(t-t_0)}\hat{\psi}(x),\ \forall\, t \ge t_0$. The comparison principle implies that

$$(u_2(x, t, \phi), u_3(x, t, \phi)) \le \alpha e^{s(\mathcal{B}^{u_1^*+\rho_0})(t-t_0)}\hat{\psi}(x),\ \forall\, t \ge t_0,$$

and it then follows that $\lim_{t\to\infty}(u_2(x, t, \phi), u_3(x, t, \phi)) = 0$ uniformly for $x \in \bar{\Omega}$. Then, the equation for u_1 is asymptotic to

$$\frac{\partial u_1(x, t)}{\partial t} = \lambda(x) - a(x)u_1(x, t), \tag{2.29}$$

and then we get $\lim_{t\to\infty} u_1(x, t, \phi) = u_1^*(x)$ uniformly for $x \in \bar{\Omega}$ by Lemma 2.2 and the theory for asymptotically autonomous semiflows (see, e.g. [33, Corollary 4.3]). Thus Part (i) is proved.

We consider the case where $\mathbf{R}_0 > 1$, that is, $s(\mathcal{B}^{u_1^*}) > 0$ by Lemma 2.8.

Let

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

and

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

By Lemma 2.6, it follows that for any $\phi \in \mathbb{W}_0$, we have $u_i(x, t, \phi) > 0,\ \forall\, x \in \bar{\Omega},\ t > 0,\ i = 2, 3$. In other words, $\Psi_t\mathbb{W}_0 \subseteq \mathbb{W}_0,\ \forall\, t \ge 0$. Let

$$M_\partial := \{\phi \in \partial\mathbb{W}_0 : \Psi_t\phi \in \partial\mathbb{W}_0, \quad \forall\, t \ge 0\},$$

and $\omega(\phi)$ be the omega limit set of the orbit $O^+(\phi) := \{\Psi_t\phi : t \ge 0\}$.

Claim: $\omega(\psi) = \{(u_1^*, 0, 0)\},\ \forall\, \psi \in M_\partial$.

Since $\psi \in M_\partial$, we have $\Psi_t\psi \in M_\partial,\ \forall\, t \ge 0$. Thus, $u_2(\cdot, t, \psi) \equiv 0$ or $u_3(\cdot, t, \psi) \equiv 0,\ \forall\, t \ge 0$. In case where $u_3(\cdot, t, \psi) \equiv 0,\ \forall\, t \ge 0$. Then, u_1 satisfies the Equation (2.29), $\forall\, t \ge 0$; and hence, we get $\lim_{t\to\infty} u_1(x, t, \psi) = u_1^*(x)$ uniformly for $x \in \bar{\Omega}$. Further, it is easy to see that $\lim_{t\to\infty} u_2(x, t, \psi) = 0$ uniformly for $x \in \bar{\Omega}$ from the equation of u_2 in (1.3). In case where $u_3(\cdot, \tilde{t}_0, \psi) \not\equiv 0$, for some $\tilde{t}_0 \ge 0$. Then Lemma 2.6 implies that $u_3(x, t, \psi) > 0,\ \forall\, x \in \bar{\Omega}, \forall\, t > \tilde{t}_0$. Hence, $u_2(\cdot, t, \psi) \equiv 0,\ \forall\, t > \tilde{t}_0$. In view of the u_3 equation in (1.3), it is easy to see that $\lim_{t\to\infty} u_3(x, t, \psi) = 0$ uniformly for $x \in \bar{\Omega}$. Again, the equation for u_1 is asymptotic to the Equation (2.29) and the theory for asymptotically autonomous semiflows (see, e.g. [33, Corollary 4.3]) implies that $\lim_{t\to\infty} u_1(x, t, \psi) = u_1^*(x)$ uniformly for $x \in \bar{\Omega}$. Hence, $\omega(\psi) = \{(u_1^*, 0, 0)\},\ \forall\, \psi \in M_\partial$.

By the similar arguments to those in Lemma 2.7 (i) and [34, Lemma 4.5], we can show that there is a small $\delta_0 > 0$ such that $s(\mathcal{B}^{u_1^*-\delta_0})$ is the principal eigenvalue of the eigenvalue problem (2.21) with $H \equiv u_1^* - \delta_0$ and $s(\mathcal{B}^{u_1^*-\delta_0}) > 0$. Let $\tilde{\psi} := (\tilde{\psi}_2, \tilde{\psi}_3)$ be the strongly positive eigenfunction corresponding to $s(\mathcal{B}^{u_1^*-\delta_0})$.

Claim: $(u_1^*, 0, 0)$ is a uniform weak repeller for $\mathbb{W}_0$ in the sense that

$$\limsup_{t\to\infty} \|\Psi_t\phi - (u_1^*, 0, 0)\| \geq \delta_0, \quad \forall\, \phi \in \mathbb{W}_0.$$

Suppose, by contradiction, there exists $\phi_0 \in \mathbb{W}_0$ such that

$$\limsup_{t\to\infty} \|\Psi_t\phi_0 - (u_1^*, 0, 0)\| < \delta_0.$$

Then, there exists $t_1 > 0$ such that $u_1(x, t, \phi_0) > u_1^*(x) - \delta_0, \forall\, t \geq t_1, x \in \bar{\Omega}$. Thus, $u(x, t, \phi_0)$ satisfies

$$\begin{cases} \frac{\partial u_2(x,t)}{\partial t} \geq \beta(x)(u_1^*(x) - \delta_0)u_3(x, t) - b(x)u_2(x, t),\ x \in \Omega,\ t \geq t_1, \\ \frac{\partial u_3(x,t)}{\partial t} = d\Delta u_3(x, t) + k(x)u_2(x, t) - m(x)u_3(x, t),\ x \in \Omega,\ t \geq t_1, \\ \frac{\partial u_3}{\partial \nu} = 0,\ x \in \partial\Omega,\ t \geq t_1. \end{cases} \tag{2.30}$$

Since $u_i(x, t, \phi_0) > 0,\ \forall\ x \in \bar{\Omega},\ t > 0,\ i = 2, 3$, there exists $\epsilon_0 > 0$ such that $(u_2(x, t_1, \phi_0), u_3(x, t_1, \phi_0)) \geq \epsilon_0\tilde{\psi}$. Note that $\epsilon_0 e^{s(\mathcal{B}^{u_1^*-\delta_0})(t-t_1)}\tilde{\psi}$ is a solution of the following linear system:

$$\begin{cases} \frac{\partial u_2(x,t)}{\partial t} = \beta(x)(u_1^*(x) - \delta_0)u_3(x, t) - b(x)u_2(x, t),\ x \in \Omega,\ t \geq t_1, \\ \frac{\partial u_3(x,t)}{\partial t} = d\Delta u_3(x, t) + k(x)u_2(x, t) - m(x)u_3(x, t),\ x \in \Omega,\ t \geq t_1, \\ \frac{\partial u_3}{\partial \nu} = 0,\ x \in \partial\Omega,\ t \geq t_1. \end{cases} \tag{2.31}$$

The comparison principle implies that

$$(u_2(x, t, \phi_0), u_3(x, t, \phi_0)) \geq \epsilon_0 e^{s(\mathcal{B}^{u_1^*-\delta_0})(t-t_1)}\tilde{\psi},\ \forall\, t > t_1,\ x \in \bar{\Omega}.$$

Since $s(\mathcal{B}^{u_1^*-\delta_0}) > 0$, it follows that $u(x, t, \phi_0)$ is unbounded. This contradiction proves the claim.

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

$$p(\phi) := \min\{\min_{x\in\bar{\Omega}} \phi_2(x),\ \min_{x\in\bar{\Omega}} \phi_3(x)\}, \quad \forall\, \phi \in \mathbb{X}^+.$$

By Lemma 2.6, it follows that $p^{-1}(0, \infty) \subseteq \mathbb{W}_0$ and p has the property that if $p(\phi) > 0$ or $\phi \in \mathbb{W}_0$ with $p(\phi) = 0$, then $p(\Psi_t\phi) > 0,\ \forall\, t > 0$. That is, p is a generalized distance function for the semiflow $\Psi_t : \mathbb{X}^+ \to \mathbb{X}^+$ (see, e.g. [35]). From the above claims, it follows that any forward orbit of Ψ_t in M_∂ converges to $(u_1^*, 0, 0)$ which is isolated in $\mathbb{X}^+$ and $W^s(u_1^*, 0, 0) \cap \mathbb{W}_0 = \emptyset$, where $W^s(u_1^*, 0, 0)$ is the stable set of $(u_1^*, 0, 0)$ (see [35]). It is obvious that there is no cycle in M_∂ from $\{(u_1^*, 0, 0)\}$ to $\{(u_1^*, 0, 0)\}$. By [35, Theorem 3], it follows that there exists an $\tilde{\sigma} > 0$ such that

$$\min_{\psi\in\omega(\phi)} p(\psi) > \tilde{\sigma}, \quad \forall\, \phi \in \mathbb{W}_0.$$

Hence, $\liminf_{t\to\infty} u_i(\cdot, t, \phi) \geq \tilde{\sigma},\ \forall\, \phi \in \mathbb{W}_0,\ i = 2, 3$. From Lemma 2.6, there exists an $0 < \sigma \leq \tilde{\sigma}$ such that

$$\liminf_{t\to\infty} u_i(\cdot, t, \phi) \geq \sigma, \quad \forall\, \phi \in \mathbb{W}_0,\ i = 1, 2, 3.$$

Hence, the uniform persistence stated in the conclusion (ii) are valid. By [16, Theorem 3.7 and Remark 3.10], it follows that $\Psi_t : \mathbb{W}_0 \to \mathbb{W}_0$ has a global attractor A_0. It then follows from [16, Theorem 4.7] that Ψ_t has an equilibrium $\tilde{u}(\cdot) \in \mathbb{W}_0$. Further, Lemma 2.6 implies that $\tilde{u}(\cdot)$ is a positive steady state of (1.3)–(1.5). The proof is complete. □

Remark 2.2 If $\mathbf{R}_0 < 1$ and $b(x)$ is not a constant function, then we are unable to show that the disease-free equilibrium $(u_1^*(x), 0, 0)$ is globally attractive in $\mathbb{X}^+$. This is because we can NOT prove $s(\mathcal{B}^{u_1^*})$ is the principal eigenvalue of the eigenvalue problem (2.21) with $H \equiv u_1^*$ (see Lemma 2.7(ii)) in this situation.

3. Global attractivity – spatially homogeneous case

In this section, we shall consider a special case where all the coefficients in (1.3) are independent of the variable x, that is,

$$\begin{cases} \frac{\partial u_1(x,t)}{\partial t} = \lambda - au_1(x,t) - \beta u_1(x,t)u_3(x,t), \\ \frac{\partial u_2(x,t)}{\partial t} = \beta u_1(x,t)u_3(x,t) - bu_2(x,t), \\ \frac{\partial u_3(x,t)}{\partial t} = d\Delta u_3(x,t) + ku_2(x,t) - mu_3(x,t), \end{cases} \tag{3.1}$$

in $(x, t) \in \Omega \times (0, \infty)$ with the homogeneous Neumann boundary condition (1.4) and initial conditions (1.5). In such a special case, the global dynamics can be completely obtained, as is shown below.

Following,[12] the basic reproduction number for ODE model corresponding to the system (3.1), is given by $\frac{k\beta\lambda}{abm}$, which describes the average number of newly infected cells generated from one infected cell at the beginning of the infectious process. In the following, we are going to find the basic reproduction number for the system (3.1):

Lemma 3.1 *The basic reproduction number for the system (3.1), is also given by $\mathcal{R}_0 = \frac{k\beta\lambda}{abm}$.*

Proof By the similar arguments to those in [15, Lemma 4.2, Theorem 3.2], we first consider the following eigenvalue problem:

$$\begin{cases} -d\Delta\phi(x) + m\phi(x) = \mu \frac{k\beta u_1^*}{b}\phi(x), \ x \in \Omega, \\ \frac{\partial\phi(x)}{\partial\nu} = 0, \ x \in \partial\Omega, \end{cases} \tag{3.2}$$

where $u_1^* \equiv \frac{\lambda}{a}$. Note that $(\eta^0, \phi^0(x)) = (0, 1)$ is the pair of principal eigenvalue–eigenfunction of

$$\begin{cases} \eta\phi(x) = d\Delta\phi(x), \ x \in \Omega, \\ \frac{\partial\phi(x)}{\partial\nu} = 0, \ x \in \partial\Omega. \end{cases}$$

Let μ_1 be the principal eigenvalue of (3.2), it then follows that $m - \mu_1\frac{k\beta u_1^*}{b} = 0$, that is, $\mu_1 = \frac{bm}{k\beta u_1^*} = \frac{abm}{k\beta\lambda} > 0$. Hence, (3.2) admits a unique positive eigenvalue μ_1 with a positive eigenfunction $\phi^0(x)$. By [15, Theorem 3.2], it follows that $\mathcal{R}_0 = \frac{1}{\mu_1} = \frac{k\beta\lambda}{abm}$. The proof is complete. □

Clearly, system (3.1) has an infection-free steady-state solution $Q_0 := (\frac{\lambda}{a}, 0, 0)$. It is not hard to see that $\hat{Q} := (\hat{u}_1, \hat{u}_2, \hat{u}_3) \equiv \left(\frac{\lambda}{a}\frac{1}{\mathcal{R}_0}, \frac{am}{\beta k}(\mathcal{R}_0 - 1), \frac{a}{\beta}(\mathcal{R}_0 - 1)\right)$ is the unique constant positive steady-state solution of (3.1), provided that $\mathcal{R}_0 > 1$. In the following, we shall adopt a technique of Lyapunov functional to prove $\mathcal{R}_0$ is the threshold index for the global attractivity of the positive steady state $\hat{Q} := (\hat{u}_1, \hat{u}_2, \hat{u}_3)$.

THEOREM 3.1 *Let* $\mathcal{R}_0 = \frac{k\beta\lambda}{abm}$. *Then the following statements hold*

(i) *If* $\mathcal{R}_0 > 1$, *then* $\hat{Q} := (\hat{u}_1, \hat{u}_2, \hat{u}_3)$ *exists and is globally asymptotically stable in the interior of* $\mathbb{X}^+$;
(ii) *If* $\mathcal{R}_0 < 1$, *then* $Q_0 := (\frac{\lambda}{a}, 0, 0)$ *is globally asymptotically stable in* $\mathbb{X}^+$.

Proof We first prove Part (i). Motivated by [36, Theorm 1.1], we define

$$\begin{aligned}
V(u_1, u_2, u_3) &= \hat{u}_1(\frac{u_1}{\hat{u}_1} - \ln \frac{u_1}{\hat{u}_1}) + \hat{u}_2(\frac{u_2}{\hat{u}_2} - \ln \frac{u_2}{\hat{u}_2}) + \frac{b}{k}\hat{u}_3(\frac{u_3}{\hat{u}_3} - \ln \frac{u_3}{\hat{u}_3}),\\
W(t) &= \int_\Omega V(u_1(x,t), u_2(x,t), u_3(x,t))dx,
\end{aligned}$$

where $(u_1(x,t), u_2(x,t), u_3(x,t))$ is an arbitrary positive solution of (3.1). Denote the reaction terms of (3.1) as follows:

$$\begin{aligned}
f_1(u_1, u_2, u_3) = \lambda - au_1 - \beta u_1 u_3,\ \ f_2(u_1, u_2, u_3)\\
= \beta u_1 u_3 - bu_2,\ \ f_3(u_1, u_2, u_3) = ku_2 - mu_3.
\end{aligned} \tag{3.3}$$

By direct computations and similar arguments to those in the proof of [36, Theorem 1.1], we get

$$\begin{aligned}
&V_{u_1}(u_1, u_2, u_3) f_1(u_1, u_2, u_3) + V_{u_2}(u_1, u_2, u_3) f_2(u_1, u_2, u_3)\\
&\quad + V_{u_3}(u_1, u_2, u_3) f_3(u_1, u_2, u_3)\\
&= a\hat{u}_1(2 - \frac{u_1}{\hat{u}_1} - \frac{\hat{u}_1}{u_1}) + b\hat{u}_2(3 - \frac{\hat{u}_1}{u_1} - \frac{u_1}{\hat{u}_1}\cdot\frac{u_3}{\hat{u}_3}\cdot\frac{\hat{u}_2}{u_2} - \frac{u_2}{\hat{u}_2}\cdot\frac{\hat{u}_3}{u_3}).
\end{aligned}$$

Since the arithmetical mean is greater than or equal to the geometrical mean, the functions

$$2 - \frac{u_1}{\hat{u}_1} - \frac{\hat{u}_1}{u_1} \text{ and } 3 - \frac{\hat{u}_1}{u_1} - \frac{u_1}{\hat{u}_1}\cdot\frac{u_3}{\hat{u}_3}\cdot\frac{\hat{u}_2}{u_2} - \frac{u_2}{\hat{u}_2}\cdot\frac{\hat{u}_3}{u_3}$$

are nonnegative for all $u_i > 0,\ i = 1, 2, 3$. Hence,

$$\begin{aligned}
&V_{u_1}(u_1, u_2, u_3) f_1(u_1, u_2, u_3) + V_{u_2}(u_1, u_2, u_3) f_2(u_1, u_2, u_3)\\
&\quad + V_{u_3}(u_1, u_2, u_3) f_3(u_1, u_2, u_3) \le 0,
\end{aligned}$$

for all $u_i > 0,\ i = 1, 2, 3$.

It then follows that

$$\begin{aligned}
\dot{W}(t) &= \int_\Omega \left[V_{u_1}(u_1,u_2,u_3)\frac{\partial u_1}{\partial t} + V_{u_2}(u_1,u_2,u_3)\frac{\partial u_2}{\partial t} + V_{u_3}(u_1,u_2,u_3)\frac{\partial u_3}{\partial t} \right] dx \\
&= \frac{b}{k}\hat{u}_3 \int_\Omega \left(\frac{1}{\hat{u}_3} - \frac{1}{u_3} \right)(d\Delta u_3)dx + \int_\Omega \big[V_{u_1}(u_1,u_2,u_3) f_1(u_1,u_2,u_3) \\
&\quad + V_{u_2}(u_1,u_2,u_3) f_2(u_1,u_2,u_3) + V_{u_3}(u_1,u_2,u_3) f_3(u_1,u_2,u_3) \big] dx \\
&= -d\frac{b}{k}\hat{u}_3 \int_\Omega \frac{1}{u_3^2}|\nabla u_3|^2 dx + \int_\Omega \big[V_{u_1}(u_1,u_2,u_3) f_1(u_1,u_2,u_3) \\
&\quad + V_{u_2}(u_1,u_2,u_3) f_2(u_1,u_2,u_3) + V_{u_3}(u_1,u_2,u_3) f_3(u_1,u_2,u_3) \big] dx \\
&\le 0.
\end{aligned}$$

Therefore, W is a Lyapunov functional for the system (3.1), namely, for any $t > 0$, $\dot{W}(t) \le 0$ along trajectories. Let $\mathbf{C} := \{(u_1,u_2,u_3) \in \mathbb{X}^+ : \dot{W}(t) = 0\}$. Note that

$$\dot{W}(t) = 0 \Leftrightarrow (u_1,u_2,u_3) = (\hat{u}_1,\hat{u}_2,\hat{u}_3).$$

By the similar arguments as in Theorem 2.1, we can show that the solution maps of (3.1) admit a connected global attractor on $\mathbb{X}^+$ and

$$\lim_{t\to\infty}(u_1(\cdot,t),u_2(\cdot,t),u_3(\cdot,t)) \to \mathbf{C}$$

by LaSalle Invariant Principle (see, e.g. [37, Theorem 4.3.4]). Thus, $(\hat{u}_1,\hat{u}_2,\hat{u}_3)$ is globally asymptotically stable for (3.1).

We next point out that the result in Part (ii) is a special case of that in Theorem 2.2 (i). For the completeness, we define the following functional ([36, Theorm 1.1]):

$$\begin{aligned}
U(u_1,u_2,u_3) &= \tilde{u}_1\left(\frac{u_1}{\tilde{u}_1} - \ln\frac{u_1}{\tilde{u}_1}\right) + u_2 + \frac{b}{k}u_3, \\
\mathcal{W}(t) &= \int_\Omega U(u_1(x,t),u_2(x,t),u_3(x,t))dx,
\end{aligned}$$

where $(u_1(x,t),u_2(x,t),u_3(x,t))$ is an arbitrary positive solution of (3.1) and $\tilde{u}_1 = \frac{\lambda}{a}$.

By direct computations and the same arguments as in the proof of [36, Theorm 1.1], we get

$$\begin{aligned}
&U_{u_1}(u_1,u_2,u_3) f_1(u_1,u_2,u_3) + U_{u_2}(u_1,u_2,u_3) f_2(u_1,u_2,u_3) \\
&\quad + U_{u_3}(u_1,u_2,u_3) f_3(u_1,u_2,u_3) \\
&= \lambda\left(2 - \frac{u_1}{\tilde{u}_1} - \frac{\tilde{u}_1}{u_1}\right) + \frac{bm}{k}(\mathcal{R}_0 - 1)u_3 \le 0, \ \forall\, u_i > 0, \ i = 1,2,3,
\end{aligned}$$

where f_i is defined in (3.3), for all $i = 1,2,3$. By the similar arguments as in Part(i), we can also prove that $\mathcal{W}$ is a Lyapunov functional for the system (3.1), namely, for any $t > 0$, $\dot{\mathcal{W}}(t) \le 0$ along trajectories. The proof is completed. □

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