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A partially diffusive cholera model based on a general second-order differential operator

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ABSTRACT

We propose a new mathematical model for cholera transmission dynamics using a system of reaction-convection-diffusion equations. The model differs from previously published partial differential equations (PDEs) based cholera models in that the diffusion and convection processes are only incorporated into the bacterial dynamics, which are described by a general second-order differential operator. This feature allows us to perform a careful study on the movement and dispersal of the pathogenic bacteria in a heterogeneous aquatic environment and its impact on cholera transmission among human hosts. We rigorously analyze the well-posedness and stability of this partially diffusive system, and establish threshold results characterizing cholera transmission dynamics.

1. Introduction

Cholera, an ancient disease characterized by severe intestinal infection, remains a serious public health burden in developing countries despite a large body of theoretical and clinical studies and tremendous efforts in disease prevention, intervention and management [1,46]. Cholera is caused by the bacterium *Vibrio cholerae*. The primary source of cholera infection is the contaminated water, which constitutes the environment-to-human (or, indirect) transmission pathway. Meanwhile, the disease can be transmitted from the human-to-human (or, direct) route; for example, through body contact with infected people, or consumption of food prepared by infected individuals with dirty hands [15,22]. The persistence of cholera has been highlighted by recent outbreaks in Yemen (2016-2018), South Sudan (2014), Haiti (2010-2012), Zimbabwe (2008-2009), and many other places, which led to high morbidity and prevalence every year [45]. In particular, the Yemen cholera outbreak is regarded as the worst cholera epidemic in modern history, with more than 1.1 million cases reported by WHO as of May 2018 [47].

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In recent years, a large number of cholera transmission models have been published (see, e.g., [2,3,7,8,12,15,21,22,24–26,30,31,33,34,39]), including several ones concerned with the spatial spread of cholera. Despite the many signs of progress in these studies regarding cholera transmission and spread, the spatial dynamics of cholera are not fully understood at present. For example, it is still a nontrivial task to model and analyze cholera epidemics in a setting that incorporates spatial variations and multiple transmission pathways of cholera. It also remains a challenge to quantify the infection risk of cholera in a spatially heterogeneous environment. Meanwhile, the movement and dispersal of the pathogenic bacteria (i.e., vibrios) through water flows in fluvial systems are ubiquitous in nature and could make important contribution to the spread of cholera. To date, however, relatively few studies have been devoted to addressing these issues.

The authors of [3,25,26] developed partial differential equation (PDE) models to account for cholera spreading along a theoretical river based on an extension of Codeço's ordinary differential equation (ODE) framework [8], where only the environment-to-human transmission route was considered. In [34], a PDE cholera model based on reaction-diffusion equations was proposed that represents the spatial diffusion of the pathogen and human hosts while incorporating both the direct and indirect transmission routes. This work was extended in [33] to include a convection process for the pathogenic bacteria; e.g., the movement of the vibrios from the upstream to the downstream along a river. As a result, the dynamics of the human hosts are described by reaction-diffusion equations, whereas those of the cholera bacteria are described by a reaction-convection-diffusion equation. The well-posedness, uniform persistence and global stability of the model in [33] were rigorously analyzed in [37,38]. For all these studies, the spatial domain is restricted to be one-dimensional (1D), and the convection and diffusion rates are fixed as constants.

While it may be reasonable to consider the motion of the bacteria on a 1D domain approximating a river, the assumption of a diffusion process for the human hosts on the same 1D domain is probably not realistic. Meanwhile, the bacterial convection and diffusion rates depend on factors such as the location of the river, the speed of the water flow, and the geographical properties associated with the fluvial system, all of which would vary with space in reality. Thus, it would be more practical to consider spatially dependent convection and diffusion rates in order to reflect the spatial heterogeneity of the bacterial movement. Additionally, compared to the dispersal of the bacteria, the diffusion of the human hosts is slow and can often be disregarded [6].

The present study aims to partially overcome these challenges by formulating a PDE system in a multi-dimensional space with partial diffusion terms and with a focus on the bacterial spatial dynamics. Specifically, we describe the motion of the bacteria by a reaction-convection-diffusion equation with spatially dependent convection and diffusion rates. Meanwhile, the dynamics of the human population are represented by temporal equations, without the diffusion terms as appeared in previous models [3,26,33,34]. Thus, the spatial dynamics of human hosts are not explicitly modeled in our system (though the host variables still vary with space due to their dependence on the pathogen variable), whereas the spatial dynamics of the bacteria are fully taken into account. Our study will now be conducted in a spatial domain of an arbitrary dimension instead of being limited to 1D.

The significance of this work is twofold: (1) Biologically, we emphasize the bacterial movement and ignore the relatively small mobility of the human population. The absence of human diffusion in our model would allow us to specifically focus on the spatial dynamics of the pathogenic bacteria, so that we will be able to conduct a deep investigation into the dispersal and movement of the bacteria and their effects on cholera transmission in an otherwise homogeneously mixed and distributed human population. The incorporation of spatially-varying convection and diffusion rates would further improve our understanding of the realistic bacterial dynamics in a fluvial system. (2) Mathematically, our partially diffusive PDE system possesses unique challenges in the analysis. In particular, with zero diffusion in several equations, the system does not satisfy the uniform elliptic condition and a maximum principle is absent there. Consequently, common analytical tools for diffusive PDEs, such as the comparison principle [27,38], are not applicable to our model. Meanwhile, instead of using a standard Laplacian that is extensively studied in the literature [11,19,20,32,34,40,44], our system is based on a second-order general differential operator.

The remainder of this paper proceeds as follows. In Section 2, we describe our partially diffusive PDE model for cholera dynamics and state the main results. We provide some preliminaries in Section 3 in order to establish these results, and present the detailed proof in Section 4. We present some numerical simulation results in Section 5 to demonstrate our analytical findings. Finally, we conclude the paper with some discussion in Section 6.

2. Statement of main results

Let us consider a spatial domain denoted by $\Omega \subset \mathbb{R}^n$ for $n \in \mathbb{N}$ and assume that it is bounded with smooth boundary $\partial\Omega$. We recall that a second-order differential operator A of the form

$$A_i(x) = \sum_{k,j=1}^{n} a_{k,j}^i(x) D_k D_j + \sum_{k=1}^{n} a_k^i D_k + c(x), \tag{1}$$

where $a_{k,j}^i(x) = a_{j,k}^i(x), D_k \triangleq \frac{\partial}{\partial x_k}$ satisfies $a_{k,j}^i, a_k^i \in C^2(\overline{\Omega})$, is uniformly elliptic if there exists a constant $\mu > 0$ such that for all $\xi \in \mathbb{R}^n$ and for all $x \in \overline{\Omega}$,

$$\sum_{k,j=1}^{n} a_{k,j}^i(x)\xi_k \xi_j \geq \mu|\xi|^2. \tag{2}$$

Let us call a system partially diffusive when only some but not all equations in the system have diffusive terms. For clarification we shall not consider damping terms corresponding to $c(x)$ to be diffusive because all population models in general have damping terms due to death rates as $c(x)$.

In what follows we will focus our attention on cholera modeling. Let us denote by $S = S(x,t), I = I(x,t), R = R(x,t)$ the number of susceptible, infected, and recovered human hosts at location x and time t, respectively. Moreover, we let $B = B(x,t)$ represent the concentration of bacteria (vibrios) in the water environment. A vector (S, I, R, B) will be the solution and we denote it, along with its initial data, by

$$u \triangleq (u_1, u_2, u_3, u_4) \triangleq (S, I, R, B), \;\; (S, I, R, B)(x, 0) \triangleq \phi \triangleq (\phi_1, \phi_2, \phi_3, \phi_4)(x). \tag{3}$$

We consider a general second-order differentiation operator as a reaction-diffusion term in the equation of bacteria, with $D(x)$ and $U \in C^2(\bar{\Omega})$ as the given diffusion and convection rates, respectively. We shall assume that $D(x)$ is continuous and has a strictly positive lower bound $M > 0$ which follows from the fact that $D(\overline{\Omega})$ is compact:

$$D(x) \geq M > 0 \quad \forall\, x \in \overline{\Omega}. \tag{4}$$

Remark 2.1. We point out that this restriction (4) is necessary for our diffusion to be at least uniformly elliptic. On the other hand, allowing $D(x) = 0$ for any x should be an interesting and challenging direction of research, which is also strongly related to the direction of research on non-homogeneous and density-dependent equations in fluid mechanics from which some relevant techniques may be borrowed (see [18] and references therein).

We also note the PDE models of infectious diseases are still relatively new in comparison to the ODE models, and almost all the infectious PDE models of which we are aware simply have a Laplacian instead of a general second-order differentiation operator (1) (e.g. [11,19,32,34,40,44]). The only exception is the work by Wang and Zhao in [35] and it turns out that our condition (4) is the same as that of [35, (D2) on pg. 1655]. We point out nonetheless that while Wang and Zhao obtained local asymptotic stability of the disease-free equilibrium (DFE) in [35, Theorems 3.1 (ii) and 4.3 (i)], we obtain global asymptotic stability

Table 1
Definition of parameters in model (5).

Parameter	Definition
b	Recruitment rate of susceptible hosts
d	Natural death rate of human hosts
γ	Recovery rate of infectious hosts
σ	Rate of host immunity loss
δ	Natural death rate of bacteria
ξ	Shedding rate of bacteria by infectious hosts
β_1	Direct transmission parameter
β_2	Indirect transmission parameter
K	Half saturation rate of bacteria
K_B	Maximal carrying capacity of bacteria in the environment

of the DFE in Theorem 2.3 (1); i.e. the authors in [35, Theorems 3.1 (ii) and 4.3 (i)] work on a system linearized about the DFE while we work directly on the system (5), as we will see.

We will return to discuss the work of [35] by Wang and Zhao in Remark 2.3. We describe the other model parameters in Table 1. Let us write $\partial_t \triangleq \frac{\partial}{\partial t}$ and introduce the cholera model of our main concern as follows:

$$\partial_t S = b - \beta_1 SI - \beta_2 S\left(\frac{B}{B+K}\right) - dS + \sigma R, \tag{5a}$$

$$\partial_t I = \beta_1 SI + \beta_2 S\left(\frac{B}{B+K}\right) - I(d+\gamma), \tag{5b}$$

$$\partial_t R = \gamma I - R(d+\sigma), \tag{5c}$$

$$\partial_t B = D(x)\Delta B - (U(x)\cdot\nabla)B + \xi I + gB\left(1 - \frac{B}{K_B}\right) - \delta B. \tag{5d}$$

We impose its boundary conditions to be of Neumann type for simplicity:

$$(n\cdot\nabla)u_4(x,t) = 0, \tag{6}$$

where n is an outward unit normal vector. Robin type boundary conditions can be treated in a similar manner.

We emphasize that (5a)-(5c) have no diffusion, although they have damping terms. Thus, the system (5) does not satisfy the uniform elliptic condition. Let us denote by

$$X \triangleq C(\overline{\Omega}, \mathbb{R}^4) \triangleq \prod_{i=1}^{4} X_i, \quad X^+ \triangleq C(\overline{\Omega}, \mathbb{R}^4_+) \triangleq \prod_{i=1}^{4} X_i^+ \tag{7}$$

where $X_i \triangleq C(\overline{\Omega}, \mathbb{R})$ and $X_i^+ \triangleq \{f \in X_i : f \geq 0\}$, equipped with the usual supremum norm. Because no confusion will arise, we write $\|\cdot\|_{C(\overline{\Omega})}$ for a norm in X or X_i; in particular, we note that $\|u\|_{C(\overline{\Omega})} \triangleq \sum_{i=1}^{4}\|u_i\|_{C(\overline{\Omega})}$. The DFE for the system (5) is

$$(S, I, R, B) = (m^*, 0, 0, 0) \text{ where } m^* \triangleq \frac{b}{d}. \tag{8}$$

Let us postpone technical details to Section 3 on preliminaries and present a first result.

Theorem 2.1. (Local well-posedness) *For any $\phi \in X^+$, there exists a unique classical solution $u(x,t,\phi) \in X^+$ such that $u(x,0,\phi) = \phi(x)$ to the system (5) on $[0,T)$ for $T = T(\phi) \in (0,\infty]$. Moreover, if $T < \infty$, then $\|u\|_X \to +\infty$ as $t \to T^-$.*

We point out that the system (5) is partially diffusive and the diffusive terms are second-order general differentiation operator, not just a Laplacian. To the best of the authors' knowledge, typical literature to which readers are always referred for such a result is either [20, Theorem 1] or Lemma 3.2. There arises an issue upon applying either of such results to the system (5). Firstly, [20, Theorem 1] is applicable to a partially diffusive system but only if the diffusion is simply a Laplacian; i.e. diffusive terms are $d_i\Delta$ with $d_i \geq 0$. Secondly, Lemma 3.2 may be extended to a general second-order differentiation operator that is uniformly elliptic (see Remark 3.1); however, every equation in the system must have a strictly positive diffusive term, which are absent in (5a)-(5c). Upon a closer look at the work of [20], it turns out that [20, Theorem 1] is an application of an abstract result [20, Theorem 2, Corollary 4] and the proofs of [20, Theorem 2, Corollary 4] do not depend on the specific form of the diffusion. Therefore, we can directly apply [20, Corollary 4] in order to prove Theorem 2.1, as we will see.

Due to the blow-up criterion from Theorem 2.1, a uniform bound on the solution leads to a global result as follows:

Theorem 2.2. (Global well-posedness) *For all $\phi \in X^+$, there exists a unique solution $u(\cdot, t, \phi)$ to (5) such that $u(x, 0, \phi) = \phi(x)$ on a time interval $[0, \infty)$. Moreover, the semiflow $\Phi_t : X^+ \mapsto X^+$ of (5) defined by $\Phi_t(\phi)(\cdot) \triangleq (u_1, u_2, u_3, u_4)(\cdot, t, \phi)$ for all $x \in \overline{\Omega}, t \geq 0$, is point dissipative and the positive orbits of bounded subsets of X for Φ_t are bounded.*

Once the global well-posedness result has been established, a next result of interest concerns stability depending on the value of a basic reproduction number $\mathcal{R}_0$. Yamazaki and Wang in [37,38] considered a reaction-convection-diffusion system on a one-dimensional spatial domain:

$$\partial_t S = \overline{D}\Delta S + b - \beta_1 SI - \beta_2 S\left(\frac{B}{B+K}\right) - dS + \sigma R, \tag{9a}$$

$$\partial_t I = \overline{D}\Delta I + \beta_1 SI + \beta_2 S\left(\frac{B}{B+K}\right) - I(d+\gamma), \tag{9b}$$

$$\partial_t R = \overline{D}\Delta R + \gamma I - R(d+\sigma), \tag{9c}$$

$$\partial_t B = D\Delta B - (U\cdot\nabla)B + \xi I + gB\left(1 - \frac{B}{K_B}\right) - \delta B, \tag{9d}$$

where $\overline{D}, D, U$ are all fixed positive constants, and obtained a complete result of the global attractivity of the DFE in case $\mathcal{R}_0 < 1$, as well as the uniform persistence of the disease in case $\mathcal{R}_0 > 1$. In contrast, the system (5) lacks diffusion in (5a)-(5c) and consequently the compactness that is needed in a standard argument (e.g. [27, Theorem 7.6.1]). Therefore, similarly to the partially diffusive avian influenza model in [32] and the partially diffusive Ebola virus disease model in [40], we turn to the Kuratowski's measure of non-compactness to derive the appropriate $\mathcal{R}_0$ that is formally defined in (57) for the system (5) and obtain the following results:

Theorem 2.3. (Stability result) *Suppose that $m^* = \frac{b}{d} < \frac{d+\gamma}{\beta_1}$.*

(1) (Global attractivity) *If $\mathcal{R}_0 < 1$, then the DFE $(m^*, 0, 0, 0)$ is globally attractive for the system (5).*
(2) (Weak repeller) *If $\mathcal{R}_0 > 1$, then there exists $\epsilon_0 > 0$ such that any positive solution of the system (5) emanating from $\phi \in X^+$ satisfies*

$$\limsup_{t\to\infty} \|(S, I, R, B)(t) - (m^*, 0, 0, 0)\|_{C(\overline{\Omega})} \geq \epsilon_0. \tag{10}$$

Biologically, Theorem 2.3 establishes a threshold-type dynamics result for our cholera model (5); i.e., the disease would be eliminated if the basic reproduction number is lower than unity, whereas the disease would persist (in the weak sense) if the basic reproduction number is higher than unity.

Remark 2.2. An important tool that is typically needed to prove such a result is a comparison principle such as [27, Theorem 7.3.4]. However, [27, Theorem 7.3.4] cannot be applied to the system (5) because [27, Theorem 7.3.4] requires diffusion in every equation of the system. Upon a closer look at the proof of [27, Theorem 7.3.4], the conclusion is derived as an application of a maximum principle [27, Theorem 7.2.5]. This raises a number of suspicions whether any modification of such a proof of [27, Theorem 7.3.4] may be successfully applied to the system (5) because the non-diffusive equations such as (5a)-(5c) certainly lack a maximum principle. Nevertheless, it turns out that an abstract result [20, Proposition 3] may be applied here. The trick is that the proof of [20, Proposition 3] does not rely on any maximum principle; instead, it merely relies on local existence result [20, Theorem 2]. An analytical lesson to keep in mind from this is that a maximum principle is sufficient, and most popular if available, but not necessary in order to prove a comparison principle.

Remark 2.3. Let us point out that an ideal result in addition to the Theorem 2.3 would be the uniform persistence of the disease and the existence of an endemic equilibrium in case the initial amount of infected individuals or the bacteria is not equivalently zero and $\mathcal{R}_0 > 1$. Specifically, the following result was proven in [38] for the system (9).

Proposition 2.4. [38, Theorem 2.2] *Let a spatial domain be $[0, 1]$ and $\phi \in X^+$. Then the system (9) subjected to a Neumann boundary condition for S, I, R and a Robin boundary condition for B admits a unique global non-negative solution. Moreover, if a basic reproduction number $\mathcal{R}_0 > 1$ and $\phi_i(\cdot) \not\equiv 0$ for either $i = 2$ or 4, then there exists at least one positive steady state and additionally a constant $\eta > 0$ such that*

$$\liminf_{t\to\infty} u_i(x, t) \geq \eta, \quad \forall\, i = 1, 2, 3, 4, \tag{11}$$

uniformly for all $x \in [0, 1]$.

In the actual statement of [38, Theorem 2.2], the conclusion of $\liminf_{t\to\infty} u_i(x, t) \geq \eta$ is said to hold only for $i = 1, 2, 4$; nevertheless, it can readily be extended to $i = 3$ as well. For completeness, we include this proof in the appendix.

We believe that proving such a uniform persistence and an existence of an endemic equilibrium for the system (5) in case $\mathcal{R}_0 > 1$ will be of significant difficulty. In relevance, we mention that Wang and Zhao in [35, Theorem 4.3] also considered a partially diffusive model with a general second-order differentiation operator and obtained a local asymptotic stability of the DFE in case $\mathcal{R}_0 < 1$ and a weak repeller result in case $\mathcal{R}_0 > 1$. We emphasize that in contrast, Theorem 2.3 (1) claims not only local asymptotic stability but global attractivity of the DFE. The reason why a uniform persistence result for the system (5) seems out of reach is rather easy to explain. We are not able to obtain an analogous result to [38, Proposition 2] which is a crucial ingredient in the proof of Proposition 2.4. Specifically, [38, Proposition 2] particularly stated that if there exists $t_0 \geq 0$ such that $I(\cdot, t_0) \not\equiv 0$, then $I(x, t) > 0$ for all $t > t_0$ and all $x \in \overline{\Omega}$. A typical way to prove such a result in the case of a strictly positive diffusion is to bound (9b) from below by

$$\partial_t I = \overline{D}\Delta I + \beta_1 SI + \beta_2 S \left(\frac{B}{B + K}\right) - I(d + \gamma) \geq \overline{D}\Delta I - I(d + \gamma)$$

and apply a comparison principle and a maximum principle. However, in the case of zero diffusion as in (5b), a maximum principle is absent and only an inequality of

$$I(x,t) \geq I(x,0)e^{(d+\gamma)t}$$

can be attained, from which an assertion of $I(x,t) > 0$ for all $t > t_0$ and for all $x \in \overline{\Omega}$ certainly does not follow, given only that $I(\cdot, t_0) \not\equiv 0$ for some $t_0 \geq 0$.

We also mention that Vaidya, Wang and Zou considered a partially diffusive avian influenza model [32] and Yamazaki also considered a partially diffusive Ebola virus disease model [40]; both actually succeeded in attaining the uniform persistence results. The common trick in [32] and [40] was that in both cases, the non-diffusive equation was easy to directly solve. For example, in the case of the avian influenza PDEs model of [32], the only non-diffusive equation was

$$\partial_t V = \alpha I - c(x)V,$$

where V is the avian influenza virus, $\alpha > 0$ is the rate at which infected birds shed virus particles in their feces, $c(x)$ is the viral decay rate and I is the population of infected birds. It is obvious that this equation can be directly solved as

$$V(t) = V(0)e^{-c(x)t} + \alpha \int_0^t e^{-c(x)(t-s)} I(s)ds$$

so that positivity of I leads to the positivity of V (see [32, Lemma 3.7 (ii)] and [40, Proposition 4.7 (3)]). It is easy to see that same trick will not work for the equations (5a) and (5b) due to their complexity of multiples of non-linear terms.

3. Preliminaries

Firstly, we recall some relevant definitions. In general, for any operator T we denote the domain of T by $D(T)$.

Definition 3.1. For a closed linear operator $\Theta : D(\Theta) \mapsto X$, $\lambda \in \mathbb{C}$ is a resolvent value of Θ if $\lambda I - \Theta$ has a bounded inverse operator that is defined on all of X. The set of resolvent values of Θ is called the resolvent set of Θ and is denoted by $\rho(\Theta)$. The set $\mathbb{C} \setminus \rho(\Theta) \triangleq \sigma(\Theta)$ is called the spectrum of Θ. A closed operator Θ in X is called resolvent-positive if the resolvent set of Θ, $\rho(\Theta)$, contains a ray (η, ∞) and $(\lambda I - \Theta)^{-1}$ is a positive operator for all $\lambda > \eta$. A linear operator $\Phi : Y \mapsto X$, where Y is a linear subspace of X, is called positive if $\Phi x \in X^+$ for all $x \in Y \cap X^+$ and Φ is not the zero operator. If Ψ is a resolvent-positive operator and $\Phi : D(\Psi) \mapsto X$ is a positive linear operator, then $\Theta \triangleq \Psi + \Phi$ is called a positive perturbation of Ψ.

Definition 3.2. [27, pg. 56, 129] We recall that the spectral radius $r(\Theta)$ of a square matrix Θ is defined by $r(\Theta) \triangleq \sup\{|\lambda| : \lambda \in \sigma(\Theta)\}$ where $\sigma(\Theta)$ is the spectrum of Θ and its spectral bound is defined by $s(\Theta) \triangleq \sup\{Re\lambda : \lambda \in \sigma(\Theta)\}$. Moreover, we recall that for a C_0-semigroup $S \triangleq \{S(t); t \geq 0\}$, the exponential growth bound of S is defined by

$$w(S) \triangleq \inf\{m \in \mathbb{R} : \exists\, M \geq 1 \text{ so that } \|S(t)\| \leq Me^{mt}\ \forall t \geq 0\}.$$

An $n \times n$ matrix $M = (M_{ij})$ is irreducible if for all $I \subsetneq N = \{1, \ldots, n\}$, $I \neq \emptyset$, there exists $i \in I$ and $j \in J \triangleq N \setminus I$ such that $M_{ij} \neq 0$. Finally, $F : \overline{\Omega} \times \Lambda \mapsto \mathbb{R}^n$, where Λ is any non-empty, closed, convex subset of $\mathbb{R}^n$, is cooperative if $\frac{\partial F_i}{\partial u_j}(x,u) \geq 0$ for all $(x,u) \in \overline{\Omega} \times \Lambda$ and all $i \neq j$.

Definition 3.3. [43, pg. 2, 3, 11] Let (Y, d) be any metric space and $f : Y \mapsto Y$ a continuous map. A bounded set A is said to attract a bounded set $B \subset Y$ if $\lim_{n\to\infty} \sup_{x\in B} d(f^n(x), A) = 0$. A subset $A \subset Y$

is an attractor for f if A is non-empty, compact and invariant ($f(A) = A$), and A attracts some open neighborhood of itself. A global attractor for f is an attractor that attracts every point in Y. Moreover, f is said to be point dissipative if there exists a bounded set B_0 in Y such that B_0 attracts each point in Y.

Definition 3.4. [43, pg. 38, 40, 46] Let E be an ordered Banach space with a positive cone P such that $\text{int}(P) \neq \emptyset$. For $x, y \in E$, we write $x \geq y$ if $x - y \in P, x > y$ if $x - y \in P \setminus \{0\}$, and $x \gg y$ if $x - y \in \text{int}(P)$.

A linear operator L on E is said to be positive if $L(P) \subset P$, while strongly positive if $L(P \setminus \{0\}) \subset \text{int}(P)$. For any subset U of E, $f : U \mapsto U$ a continuous map, f is said to be monotone if $x \geq y$ implies $f(x) \geq f(y)$, strictly monotone if $x > y$ implies $f(x) > f(y)$, and strongly monotone if $x > y$ implies $f(x) \gg f(y)$.

Let $U \subset P$ be non-empty, closed, and order convex. Then a continuous map $f : U \mapsto U$ is said to be subhomogeneous if $f(\lambda x) \geq \lambda f(x)$ for any $x \in U$ and $\lambda \in [0, 1]$, strictly subhomogeneous if $f(\lambda x) > \lambda f(x)$ for any $x \in U$ with $x \gg 0$ and $\lambda \in (0, 1)$, and strongly subhomogeneous if $f(\lambda x) \gg \lambda f(x)$ for any $x \in U$ with $x \gg 0$ and $\lambda \in (0, 1)$.

The following is a statement from [20] in a special case with zero delay for simplicity.

Lemma 3.1. *Let X be any $\mathbb{R}$ or $\mathbb{C}$ Banach space with its norm denoted by $|\cdot|$. We denote a distance between any $x \in X$ and a set $Y \subset X$ by $d(x; Y) \triangleq \inf\{|x - y| : y \in Y\}$. Suppose $T \triangleq \{T(t) : t \geq 0\}$ is a family of bounded linear operators from X into X. We consider the following conditions:*

- *(T1) $T(0)x = x, T(t)T(s)x = T(t + s)x$ for all $t, s \geq 0$.*
- *(T2) For all $x \in X$, the mapping $t \mapsto T(t)x$ is continuous for all $t \geq 0$.*
- *(T3) There exists $\hat{M} \geq 1$ and $\omega \in \mathbb{R}$ such that $\|T(t)\| \triangleq \sup_{|x| \leq 1} |T(t)x|$ satisfies $\|T(t)\| \leq \hat{M} e^{\omega t}$ for all $t \geq 0$.*

Moreover, we consider the following conditions.

- *(H1) D is a closed subset of $[0, \infty) \times X$ and $D(t) \triangleq \{x \in X : (t, x) \in D\} \neq \emptyset$ for all $t \geq 0$.*
- *(H3) For each $b > 0$, there exists $\hat{K}(b) > 0$ and a continuous non-decreasing function $\eta_b : [0, b) \mapsto [0, \infty)$, satisfying $\eta_b(0) = 0$, and that if $0 \leq t_1 < t_2 \leq b, x_1 \in D(t_1), x_2 \in D(t_2)$, then there exists a continuous function $w : [t_1, t_2] \mapsto X$ such that $w(t_1) = x_1, w(t_2) = x_2, w(t) \in D(t)$ for $t \in (t_1, t_2)$, and for all $s, t \in [t_1, t_2]$*

$$|w(t) - w(s)| \leq \eta_b(|t - s|) + \hat{K}(b)|t - s| \frac{|x_2 - x_1|}{t_2 - t_1}. \tag{12}$$

- *(H4) $F(t, x)$ is continuous from $D(F)$ into X where $D(F) = [0, \infty) \times X$.*

We consider now an abstract integral equation

$$u(t) = T(t)u_0 + \int_0^t T(t - r)F(r, u(r))dr, \quad 0 \leq t < b, \quad u(0) = u_0 \in X. \tag{13}$$

(1) *[20, Theorem 2] Suppose (T1)-(T3), (H1), (H3), (H4) hold, and for all $(t, \phi) \in D$,*

$$\lim_{h \to 0^+} \frac{1}{h} d\left(T(h)\phi + \int_t^{t+h} T(t + h - r)F(t, \phi)dr; D(t + h)\right) = 0. \tag{14}$$

Moreover, suppose that for every $R > 0$*, there exists an* $L_R > 0$ *and a continuous function* $\nu_R : [0, \infty) \mapsto [0, \infty)$ *such that* $\nu_R(0) = 0$ *and*

$$|F(t, \phi) - F(s, \psi)| \leq \nu_R(|t - s|) + L_R|\phi - \psi| \tag{15}$$

for all $(t, \phi), (s, \psi) \in D$ *such that* $|\phi|, |\psi| \leq R, 0 \leq s, t \leq R$*. Then* (13) *has a unique solution* u *on* $[0, b)$ *where* $b \in (0, \infty]$ *such that* $u(t) \in D(t)$ *for all* $t \in [0, b)$*. Moreover, if* $b < \infty$*, then* $\lim_{t\to b^-} |u(t)| = +\infty$*.*

(2) *[20, Corollary 4] Suppose (T1)-(T3), (H1), (H3), (H4) hold, and that* K *is a closed convex subset of* X *and* $D(t) \equiv K$ *for all* $t \geq 0$*. Suppose further that* (15) *holds,* $T(t) : K \mapsto K$ *for all* $t \geq 0$ *and*

$$\lim_{h\to 0^+} \frac{1}{h} d(\phi + hF(t, \phi); K) = 0 \qquad \forall\, (t, \phi) \in D. \tag{16}$$

Then (13) *has a unique solution* u *on* $[0, b)$ *where* $b \in (0, \infty]$ *such that* $u(t) \in K$ *for all* $t \in [0, b)$*. Moreover, if* $b < \infty$*, then* $\lim_{t\to b^-} |u(t)| = +\infty$*.*

(3) *[20, Proposition 3] Suppose that* X^+ *is a closed cone in* X*. We define a partial ordering* $\geq$ *on* X *by* $x \geq y$ *only if* $x - y \in X^+$*. Assume that* X *with this ordering is a vector lattice. Denote by*

$$x \vee y \triangleq \sup\{x, y\}, \quad x \wedge y \triangleq \inf\{x, y\}, \quad x_+ \triangleq x \vee 0, \quad x_- \triangleq -(x \wedge 0), \quad |x|_+ \triangleq x_+ + x_-.$$

Assume that X *is a Banach lattice and that* v^- *and* v^+ *are both continuous functions from* $[0, b)$ *into* X *such that* $v^-(t) \leq v^+(t)$ *for all* $t \in [0, b)$*. In addition to (T1)-(T3), assume that* T *is positive; i.e.* $T(t)X^+ \subset X^+$ *for all* $t \geq 0$*. Let* E *be a subset of* $[0, \infty) \times X$ *such that* $E(t) \triangleq \{x \in X : (t, x) \in E\} \neq \emptyset$ *for all* $t \geq 0$*. We assume that* F *is continuous from* E *to* X*,* $(0, u_0) \in E$*,*

$$v^-(0) \leq u_0 \leq v^+(0). \tag{17}$$

We assume that $[v^-(t), v^+(t)] \subset E(t)$ *for all* $t \in [0, b]$*. Moreover, we assume that for all* $c > 0$*, there exists* $\overline{\nu}_c : [0, c] \mapsto [0, \infty)$ *which is a continuous and increasing function such that* $\overline{\nu}_c(0) = 0$ *and*

$$|v^\pm(t) - v^\pm(s)| \leq \overline{\nu}_c(|t - s|) \quad \forall\, s, t \in [0, b] \text{ such that } |t - s| \leq c.$$

Furthermore, we assume that F^+ *and* F^- *are continuous functions from* $\mathcal{E}$ *into* X *and that* v^+ *and* v^- *satisfy for* $0 \leq t < t + h < b$

$$v^+(t + h) \geq T(h)v^+(t) + \int_t^{t+h} T(t + h - r)F^+(r, v^+(r))dr, \tag{18a}$$

$$v^-(t + h) \leq T(h)v^-(t) + \int_t^{t+h} T(t + h - r)F^-(r, v^-(r))dr. \tag{18b}$$

We assume that F *satisfies* (15) *with* D *replaced by* E*. Finally, suppose that*

- $$\lim_{h\to 0^+} \frac{1}{h} d(v^+(t) - \phi + h[F^+(t, v^+(t)) - F(t, \phi)]; X^+) = 0 \tag{19}$$

  for all $t \in [0, b), (t, \phi) \in E$ *such that* $v^-(t) \leq \phi \leq v^+(t)$*,*

-

$$\lim_{h \to 0^-} \frac{1}{h} d(\phi - v^-(t) + h[F(t,\phi) - F^-(t, v^-(t))]; X^+) = 0 \tag{20}$$

for all $t \in [0, b), (t, \phi) \in E$ *such that* $v^-(t) \leq \phi \leq v^+(t)$.

Then (13) *has a solution* u *on* $[0, \overline{b}]$ *for some* $\overline{b} \in (0, b]$ *such that* $v^-(t) \leq u(t) \leq v^+(t)$ *for all* $t \in [0, \overline{b})$.

Lemma 3.2. [27, Theorem 7.3.1, Corollary 7.3.2] *Suppose that* $F : \overline{\Omega} \times \mathbb{R}^n_+ \mapsto \mathbb{R}^n, n \in \mathbb{N}$, *has the property that*

$$F_i(x, u) \geq 0 \quad \forall\, x \in \overline{\Omega}, u \in \mathbb{R}^n_+ \text{ and } u_i = 0. \tag{21}$$

Then for all $\psi \in C(\overline{\Omega}, \mathbb{R}^n_+)$,

$$\begin{cases} \partial_t u_i(x,t) = D_i \Delta u_i(x,t) + F_i(x, u(x,t)), & t > 0, x \in \Omega, \\ \alpha_i(x) u_i(x,t) + \delta_i (n \cdot \nabla) u_i(x,t) = 0, & t > 0, x \in \partial\Omega, \\ u_i(x, 0) = \psi_i(x), & x \in \Omega, \end{cases}$$

$i \in \{1, \dots, n\}$, *has a unique non-continuable mild solution* $u(x, t, \psi) \in C(\overline{\Omega}, \mathbb{R}^n_+)$ *on* $[0, T)$ *where* $T = T(\psi) \leq \infty$ *such that if* $T < \infty$, *then* $\lim_{t \to T^-} \|u(t)\|_{C(\overline{\Omega}, \mathbb{R}^n)} = +\infty$. *Moreover,*

(1) u *is continuously differentiable in time on* $(0, T)$,
(2) *it is in fact a classical solution,*
(3) *if* $T(\psi) = +\infty$ *for all* $\psi \in C(\overline{\Omega}, \mathbb{R}^n_+)$, *then* $\Psi_t(\psi) = u(t, \psi)$ *is a semiflow on* $C(\overline{\Omega}, \mathbb{R}^n_+)$,
(4) *if* $Z \subset C(\overline{\Omega}, \mathbb{R}^n_+)$ *is closed and bounded,* $t_0 > 0$ *and* $\cup_{t \in [0, t_0]} \Psi_t(Z)$ *is bounded, then* $\Psi_{t_0}(Z)$ *has a compact closure in* $C(\overline{\Omega}, \mathbb{R}^n_+)$.

Remark 3.1. This lemma remains valid even if the Laplacian is replaced by a general second order differentiation operator (1) if it satisfies (2); in fact, all results from [27, Chapter 7] remain valid for a general second order differentiation operator (1) if (2) is satisfied (see [27, pg. 121]).

We collect some useful properties concerning Kuratowski measure of non-compactness:

Lemma 3.3. [43, pg. 3] *Let* Y *be any metric space and denote the Kuratowski measure of non-compactness for any bounded set* B *of* Y *by*

$$\kappa(B) \triangleq \inf\{r : B \text{ has a finite cover of diameter } r\}.$$

Firstly, $\kappa(B) = 0$ *if and only if* $\overline{B}$ *is compact. Moreover, a continuous mapping* $f : Y \mapsto Y$ *is* κ*-condensing* (κ*-contraction of order* $0 \leq k < 1$) *if* f *takes bounded sets to bounded sets and* $\kappa(f(B)) < \kappa(B)$ ($\kappa(f(B)) \leq k\kappa(B)$) *for any non-empty closed bounded set* $B \subset Y$ *such that* $\kappa(B) > 0$. *Moreover,* f *is asymptotically smooth if for any non-empty closed bounded set* $B \subset Y$ *for which* $f(B) \subset B$, *there exists a compact set* $J \subset B$ *such that* J *attracts* B. *It is well known that a compact map is an* κ*-contraction of order* 0, *and a* κ*-contraction of order* k *is* κ*-condensing. Finally, by [14, Lemma 2.3.5], any* κ*-condensing maps are asymptotically smooth.*

4. Proof

4.1. Proof of Theorem 2.1

In order to apply [20, Corollary 4] to the proof of Theorem 2.1, let us first set up various notations. Following [27, pg. 121] we let A_4^0 be a differentiation operator

$$A_4^0 u_4 \triangleq D(x)\Delta u_4 - (U(x)\cdot\nabla)u_4 \tag{22}$$

with its domain

$$D(A_4^0) \triangleq \{\psi \in C^2(\Omega)\cap C^1(\overline{\Omega}) : A_4^0\psi \in C(\overline{\Omega}), (n\cdot\nabla)u_4(x,t)|_{\partial\Omega} = 0\}. \tag{23}$$

Then we define A_4 to be the closure of A_4^0 so that A_4 on X_4 generates an analytic compact semigroup of bounded linear operator $T_4(t) : X_4 \mapsto X_4, t \geq 0$, such that $v_4(x,t) = (T_4(t)\phi_4)(x)$ satisfies

$$\partial_t v_4(t) = A_4 v_4(t), \quad v_4(0) = \phi_4 \in D(A_4) \tag{24}$$

where

$$D(A_4) \triangleq \{\psi \in X_4 : \lim_{t\to 0^+} \frac{(T_4(t)-I)\psi}{t} \text{ exists } \} \tag{25}$$

(see [27, pg. 121] and [36, Theorem 2.2 in Chapter 1]). By [27, Corollary 7.2.3] we know that T_4 is positive; i.e. $T_4(t)X_4^+ \subset X_4^+$ (recall Remark 3.1). On the other hand, we let

$$(T_1(t)\phi_1)(x) \triangleq e^{-dt}\phi_1(x),\ (T_2(t)\phi_2)(x) \triangleq e^{-(d+\gamma)t}\phi_2(x),\ (T_3(t)\phi_3)(x) \triangleq e^{-(d+\sigma)t}\phi_3(x). \tag{26}$$

Moreover, for all $v = (v_1, v_2, v_3, v_4) \in X^+$, we define

$$F_1(v) \triangleq b - \beta_1 v_1 v_2 - \beta_2 v_1\left(\frac{v_4}{v_4+K}\right) + \sigma v_3, \quad F_2(v) \triangleq \beta_1 v_1 v_2 + \beta_2 v_1\left(\frac{v_4}{v_4+K}\right), \tag{27a}$$

$$F_3(v) \triangleq \gamma v_2, \qquad F_4(v) \triangleq \xi v_2 + g v_4\left(1-\frac{v_4}{K_B}\right) - \delta v_4. \tag{27b}$$

We denote by

$$u(t) \triangleq \begin{pmatrix} u_1\\ u_2\\ u_3\\ u_4\end{pmatrix}(t) \text{ and } T(t) \triangleq \begin{pmatrix} T_1 & 0 & 0 & 0\\ 0 & T_2 & 0 & 0\\ 0 & 0 & T_3 & 0\\ 0 & 0 & 0 & T_4\end{pmatrix}(t),$$

so that T is clearly a linear C_0-semigroup on X^+. Now we can rewrite (5) as

$$u(t) = T(t)\phi + \int_0^t T(t-s)F(u(s))ds. \tag{28}$$

We apply Lemma 3.1 (2) now; it essentially suffices to just check the limit (16). We follow the argument in the proof of [27, Corollary 7.3.2]. If $\phi_i(x) > 0$, then $\phi_i(x) + hF_i(\phi(x)) > 0$ for all $h > 0$ sufficiently small. On the other hand, if $\phi_i(x) = 0$, then $F_i(\phi(x)) \geq 0$ for all $i = 1, 2, 3, 4$ by (27). Therefore, $d(\phi + hF(x,\phi); X^+) = 0$ for all $h > 0$ sufficiently small. This implies (16) and the proof of Theorem 2.1 is complete.

4.2. Proof of Theorem 2.2

In order to prove Theorem 2.2 we need the following proposition; the original version by Lou and Zhao in [19, Lemma 1] was only in the case of a full Laplacian as a diffusion while the generalized version in [38, Proposition 1] was only in the one-dimensional domain $[0, 1]$.

Proposition 4.1. *Consider a spatial domain $\Omega \subset \mathbb{R}^n$ for $n \in \mathbb{N}$ that is bounded with smooth boundary $\partial\Omega$ and the following equation:*

$$\partial_t w(x,t) = \overline{D}(x)\Delta w(x,t) - (\overline{U}(x)\cdot\nabla)w(x,t) + g(x) - \lambda w(x,t), \tag{29a}$$

$$(n\cdot\nabla)w(x,t)|_{\partial\Omega} = 0 \text{ for } t > 0, \text{ and } w(x,0) = \psi(x) \text{ for } x \in \overline{\Omega}, \tag{29b}$$

where $\bar{U} \in C^2(\bar{\Omega})$, $\overline{D}(x)$ is continuous and $\overline{D}(x) \geq M > 0$ for all $x \in \overline{\Omega}$, $g(x) > 0$ is a continuous function, and n is an outward unit normal vector. Then for all $\psi \in C(\overline{\Omega}, \mathbb{R}_+)$ there exists a unique positives steady state w^* which is globally attractive in $C(\overline{\Omega}, \mathbb{R})$. Moreover, if $g(x) \equiv g$, then $w^* \equiv \frac{g}{\lambda}$.

Proof. For completeness, we leave this proof in the Appendix. □

Now firstly we realize that denoting by $N \triangleq S + I + R$, we have due to (5a) - (5c)

$$N(t) = N(0)e^{-dt} + m^*[1 - e^{-dt}] \qquad \text{for all } x \in \overline{\Omega} \tag{30}$$

from which we immediately conclude that

$$\lim_{t\to\infty} N(t) = m^* \text{ and } N(t) \leq N(0) + m^* \ \forall\, t > 0, \forall\, x \in \overline{\Omega}. \tag{31}$$

By the non-negativity of the local solution due to Theorem 2.1, we can deduce that

$$\max\{\|S(t)\|_{C(\overline{\Omega})}, \|I(t)\|_{C(\overline{\Omega})}, \|R(t)\|_{C(\overline{\Omega})}\} \leq \|N(0)\|_{C(\overline{\Omega})} + m^* \qquad \forall\, t > 0. \tag{32}$$

This leads to

$$\partial_t B \leq D(x)\Delta B - (U(x)\cdot\nabla)B + \xi(\|N(0)\|_{C(\overline{\Omega})} + m^*) + \frac{K_B g}{4} - \delta B \tag{33}$$

by (5d) and Young's inequality. By comparison principle [27, Theorem 7.3.4] and an application of Proposition 4.1, we see that for all $\phi \in C(\overline{\Omega}, \mathbb{R}_+)$ there exists $\bar{t} = \bar{t}(\phi) > 0$ such that

$$B(x,t) \leq \frac{2[\xi(\|N(0)\|_{C(\overline{\Omega})} + m^*) + \frac{K_B g}{4}]}{\delta} \quad \forall\, x \in \overline{\Omega} \text{ and all } t \geq \bar{t}. \tag{34}$$

This implies that solution (S, I, R, B) to (5) exists globally in time due to the blow-up criterion from Theorem 2.1. Therefore, (5) defines a solution semiflow $\Phi_t : X^+ \mapsto X^+$ by $\Phi_t(\phi) = u(x, t, \phi)$. From (32) and (34) it follows that for all $x \in \overline{\Omega}$ and all $t > 0$,

$$B(x,t) \leq \max\{\sup_{t\in[0,\bar{t}]} \|B(t)\|_{C(\overline{\Omega})}, \frac{2}{\delta}[\xi(\|N(0)\|_{C(\overline{\Omega})} + m^*) + \frac{K_B g}{4}]\} \triangleq \overline{B}. \tag{35}$$

We conclude that Φ_t is point dissipative; it can be also shown very similarly that the positive orbits of bounded subset of X for Φ_t are bounded. For details, we refer to the proof of [41, Proposition 3.2].

4.3. Proof of Theorem 2.3

We linearize the system (5) about the DFE $(m^*, 0, 0, 0)$ as

$$\partial_t S = - dS - \beta_1 m^* I + \sigma R - \beta_2 m^* \frac{B}{K}, \tag{36a}$$

$$\partial_t I = - (d+\gamma)I + \beta_1 m^* I + \beta_2 m^* \frac{B}{K}, \tag{36b}$$

$$\partial_t R = - (d+\sigma)R + \gamma I, \tag{36c}$$

$$\partial_t B = D(x)\Delta B - (U(x)\cdot\nabla)B + \xi I + (g-\delta)B. \tag{36d}$$

We can formally write the right side of (36) as

$$\tilde{\Theta}(S, I, R, B) \triangleq \begin{pmatrix} -dS - \beta_1 m^* I + \sigma R - \beta_2 m^* \frac{B}{K} \\ -(d+\gamma)I + \beta_1 m^* I + \beta_2 m^* \frac{B}{K} \\ -(d+\sigma)R + \gamma I \\ D(x)\Delta B - (U(x)\cdot\nabla)B + \xi I + (g-\delta)B \end{pmatrix}. \tag{37}$$

Now we first consider the infection-related variables I, B (see [32, pg. 2833]):

$$\partial_t u_2 = -(d+\gamma)u_2 + \beta_1 m^* u_2 + \beta_2 m^* \frac{u_4}{K}, \tag{38a}$$

$$\partial_t u_4 = D(x)\Delta u_4 - (U(x)\cdot\nabla)u_4 + \xi u_2 + (g-\delta)u_4, \tag{38b}$$

$$(n\cdot\nabla)u_4|_{\partial\Omega} = 0 \quad \forall\, t > 0. \tag{38c}$$

As we will see, it will be convenient to consider the following more generalized system of PDEs:

$$\partial_t u_2 = -(d+\gamma)u_2 + \beta_1 H_1(x) u_2 + \beta_2 H_2(x) u_4, \tag{39a}$$

$$\partial_t u_4 = D(x)\Delta u_4 - (U(x)\cdot\nabla)u_4 + \xi u_2 + g u_4 H_3(x) - \delta u_4, \tag{39b}$$

$$(n\cdot\nabla)u_4|_{\partial\Omega} = 0 \quad \forall\, t > 0, \tag{39c}$$

where $H_i(x), i \in \{1, 2, 3\}$, will have conditions to be given subsequently. We notice that the case $H_1(x) = m^*, H_2(x) = \frac{m^*}{K}, H_3(x) = 1$ recovers the original system (38). We substitute $u_i(x,t) = e^{\lambda t}\psi_i(x), i \in \{2, 4\}$, and divide by $e^{\lambda t}$ to obtain

$$\lambda\psi_2 = -(d+\gamma)\psi_2 + \beta_1 H_1(x)\psi_2 + \beta_2 H_2(x)\psi_4, \tag{40a}$$

$$\lambda\psi_4 = D(x)\Delta\psi_4 - (U(x)\cdot\nabla)\psi_4 + \xi\psi_2 + (gH_3(x) - \delta)\psi_4, \tag{40b}$$

of which we may write the right side as

$$\begin{pmatrix} G_2 \\ G_4 \end{pmatrix}(\psi_2, \psi_4) \triangleq \begin{pmatrix} -(d+\gamma)\psi_2 + \beta_1 H_1(x)\psi_2 + \beta_2 H_2(x)\psi_4 \\ D(x)\Delta\psi_4 - (U(x)\cdot\nabla)\psi_4 + \xi\psi_2 + (gH_3(x) - \delta)\psi_4 \end{pmatrix}. \tag{41}$$

Thus, we can compute

$$\frac{\partial G_2}{\partial \psi_4} = \beta_2 H_2(x) \geq 0, \quad \frac{\partial G_4}{\partial \psi_2} = \xi \geq 0, \tag{42}$$

if $H_2(x) \geq 0$ so that this system is cooperative but not compact due to the lack of diffusion and consequently [27, Theorem 7.6.1] is not applicable. Nevertheless, we can turn to the notion of Kuratowski's measure of non-compactness to obtain the following result; it is inspired by the proof of [16, Lemma 3.2].

Proposition 4.2. *Let $H_j(x)$ for $j \in \{1,2,3\}$ be continuous. Suppose that $\max_{x\in\overline{\Omega}} H_1(x) \triangleq \overline{H}_1 < \frac{d+\gamma}{\beta_1}$ and $H_2(x) \geq 0$. Then the eigenvalue problem (40) has a principal eigenvalue denoted by $\lambda(H_1, H_2, H_3)$ and a corresponding eigenfunction $\psi^* = (\psi_2^*, \psi_4^*) \gg 0$.*

Proof. We define $Y \triangleq C(\overline{\Omega}, \mathbb{R}^2)$ so that for all $\phi = (\phi_2, \phi_4) \in Y$, we may repeat the similar proof of Theorems 2.1, 2.2 to deduce the existence of a solution map $\Pi_t : Y \mapsto Y$ of (39). Now we focus on (39a) which can be solved as

$$u_2(t) = e^{-[(d+\gamma)-\beta_1 H_1(x)]t}\phi_2 + \beta_2 H_2(x)\int_0^t u_4(s)e^{-[(d+\gamma)-\beta_1 H_1(x)](t-s)}ds. \tag{43}$$

We define

$$L(t)\phi \triangleq (e^{-[(d+\gamma)-\beta_1 H_1(x)]t}\phi_2, 0), \tag{44a}$$

$$Q(t)\phi \triangleq (\beta_2 H_2(x)\int_0^t u_4(s)e^{-[(d+\gamma)-\beta_1 H_1(x)](t-s)}ds, u_4(t)), \tag{44b}$$

for all $\phi = (\phi_2, \phi_4) \in Y$. Then $\Pi_t(\phi) = L(t)\phi + Q(t)\phi$. Thus, for all bounded set $E \subset Y$, by [9, Proposition 7.2 (b)], we have

$$\kappa(\Pi_t E) \leq \kappa(L(t)E) + \kappa(Q(t)E). \tag{45}$$

Since $Q(t) : Y \mapsto Y$ is compact for all $t > 0$, [9, Proposition 7.2 (a)] implies that $\kappa(Q(t)E) = 0$ for all $t \geq 0$. On the other hand,

$$\sup_{\phi\in Y, \phi\not\equiv 0} \frac{\|L(t)\phi\|_Y}{\|\phi\|_Y} \leq e^{-[(d+\gamma)-\beta_1\overline{H}_1]t} \sup_{\phi\in Y,\phi\not\equiv 0} \frac{\|\phi_2\|_{X_2}}{\|\phi\|_Y} \leq e^{-[(d+\gamma)-\beta_1\overline{H}_1]t} \tag{46}$$

and therefore

$$\|L(t)\|_{ope} \leq e^{-[(d+\gamma)-\beta_1\overline{H}_1]t}. \tag{47}$$

Thus,

$$\kappa(\Pi_t E) \leq e^{-[(d+\gamma)-\beta_1\overline{H}_1]t}\kappa(E) \tag{48}$$

by (45) and (47). Because $\overline{H}_1 < \frac{d+\gamma}{\beta_1}$ by hypothesis, we have $e^{-[(d+\gamma)-\beta_1\overline{H}_1]t} < 1$ so that

$$\kappa(\Pi_t E) \leq e^{-[(d+\gamma)-\beta_1\overline{H}_1]t}\kappa(E) < \kappa(E) \tag{49}$$

for all bounded sets E in Y such that $\kappa(E) > 0$. This implies by Lemma 3.3 that Π_t is κ-contraction of order $e^{-[(d+\gamma)-\beta_1\overline{H}_1]t} \in [0, 1)$ and hence κ-condensing for all $t > 0$. We already showed that the eigenvalue problem is cooperative in (42). Thus, by the generalized Krein-Rutman theorem (e.g. [23, Theorem 2.2], [17, Lemma 2.2], [42] also see [9, Theorems 19.2 and 19.3]), the eigenvalue problem has a principal eigenvalue denoted by $\lambda(H_1, H_2, H_3)$ with eigenvector $\psi^* = (\psi_2^*, \psi_4^*) \gg 0$ (see [32, Lemma 3.4], [16, Lemma 3.3], [40, Lemma 3.3]). This completes the proof of Proposition 4.2. □

We saw in (38) that the equations of the infection-related variables of the linearized system are

$$\begin{aligned}
&\partial_t u_2 = -(d+\gamma)u_2 + \beta_1 m^* u_2 + \beta_2 m^* \frac{u_4}{K},\\
&\partial_t u_4 = D(x)\Delta u_4 - (U(x)\cdot\nabla)u_4 + \xi u_2 + (g-\delta)u_4,\\
&(n\cdot\nabla)u_4|_{\partial\Omega} = 0 \quad \forall\, t>0.
\end{aligned}$$

We split the right side of (38) as

$$\begin{aligned}
&\begin{pmatrix} -(d+\gamma)u_2 + \beta_1 m^* u_2 + \beta_2 m^* \frac{u_4}{K} \\ D(x)\Delta u_4 - (U(x)\cdot\nabla)u_4 + \xi u_2 + (g-\delta)u_4 \end{pmatrix}\\
&= \left(\begin{pmatrix} -(d+\gamma) & 0 \\ 0 & D(x)\Delta - (U(x)\cdot\nabla) - \delta \end{pmatrix} + \begin{pmatrix} \beta_1 m^* & \beta_2 \frac{m^*}{K} \\ \xi & g \end{pmatrix} \right) \begin{pmatrix} u_2 \\ u_4 \end{pmatrix}. \qquad (50)
\end{aligned}$$

We assume that the population is near the DFE $(m^*, 0, 0, 0)$. Repeating the proof of Theorems 2.1, 2.2, we can prove the existence of the solution semiflow $\Theta(t)$ to

$$\partial_t u_2 = -(d+\gamma)u_2 \text{ and } \partial_t u_4 = D(x)\Delta u_4 - (U(x)\cdot\nabla)u_4 - \delta u_4. \qquad (51)$$

We can solve this as

$$u_4(x,t,\phi) = e^{-t[-D(x)\Delta + (U(x)\cdot\nabla)]} e^{-\delta t}\phi_4(x) = e^{-\delta t} T_4(t)\phi_4(x) \qquad (52)$$

by definition of T_4 in (24). We also defined $(T_2(t)\phi_2)(x) = e^{-(d+\gamma)t}\phi_2(x)$ in (26) so that $u_2(x,t,\phi) = T_2(t)\phi_2(x)$. Thus, for $\phi = (\phi_2, \phi_4)$,

$$\Theta(t)\phi = (u_2, u_4)(t) = (T_2(t)\phi_2, e^{-\delta t} T_4(t)\phi_4) \qquad (53)$$

by (51) and (52). Because $T_4(t)$ is positive by [27, Corollary 7.2.3], it follows that $T_4(t)\phi_4 \in C(\overline{\Omega}, \mathbb{R}_+)$ for all $\phi_4 \in C(\overline{\Omega}, \mathbb{R}_+)$ so that $e^{-\delta t} T_4(t)\phi_4 \in C(\overline{\Omega}, \mathbb{R}_+)$. Similarly, $e^{-(d+\gamma)t}\phi_2 \in C(\overline{\Omega}, \mathbb{R}_+)$ for all $\phi_2 \in C(\overline{\Omega}, \mathbb{R}_+)$. Therefore, $\Theta(t)$ is a positive C_0-semigroup on $Y = C(\overline{\Omega}, \mathbb{R}^2)$ and $\Theta(t)\phi$ represents the spatial distribution of u_2, u_4 at time $t > 0$. We let C be a positive linear operator on Y defined by

$$C(\phi)(x) \triangleq \begin{pmatrix} \beta_1 m^* & \beta_2 \frac{m^*}{K} \\ \xi & g \end{pmatrix} \begin{pmatrix} \phi_2 \\ \phi_4 \end{pmatrix}(x) = (C_2(\phi), \xi\phi_2 + g\phi_4)^T(x) \qquad (54)$$

for al $\phi = (\phi_2, \phi_4) \in Y$ for all $x \in \overline{\Omega}$; i.e.

$$C_2(\phi) = \beta_1 m^* \phi_2 + \beta_2 \frac{m^*}{K}\phi_4. \qquad (55)$$

Thus, at time $t > 0$ and location x, there will be $C_2(\Theta(t)\phi)(x)$ individuals added per unit time into u_2 compartment. Hence, the spatial distribution of total new infected individuals caused by the initial distribution $\phi = (\phi_2, \phi_4)$ may be computed as

$$\int_0^\infty C_2(\Theta(t)\phi)dt = \beta_1 m^* \int_0^\infty T_2(t)\phi_2 dt + \beta_2 \frac{m^*}{K} \int_0^\infty e^{-\delta t} T_4(t)\phi_4 dt \qquad (56)$$

due to (53). We now define the next generation operator L and the basic reproduction number $\mathcal{R}_0$ as

$$L(\phi) \triangleq C \int_0^\infty \Theta(t)\phi dt \text{ and } \mathcal{R}_0 \triangleq r(L) \tag{57}$$

where $r(L)$ is the spectral radius of L (see Definition 3.2).

Proposition 4.3. *Suppose $m^* < \frac{d+\gamma}{\beta_1}$. Then $\mathcal{R}_0 - 1$ and the principal eigenvalue $\lambda(m^*, \frac{m^*}{K}, 1)$ corresponding to (40) with $H_1 \equiv m^*, H_2 \equiv \frac{m^*}{K}, H_3 \equiv 1$ have same signs.*

Proof. We let $\zeta : D(\zeta) \mapsto Y$, where $Y = C(\overline{\Omega}, \mathbb{R}^2)$, be the generator of $\Theta(t)$ from (53) and also denote $Y^+ \triangleq C(\overline{\Omega}, \mathbb{R}_+^2)$. We already verified after (53) that Θ is a positive semigroup. Thus, by [29, Theorem 3.12] we see that ζ is resolvent-positive (see Definition 3.1) and

$$(\lambda I - \zeta)^{-1}\phi = \int_0^\infty e^{-\lambda t}\Theta(t)\phi dt \quad \forall\, \lambda > s(\zeta),\ \forall\, \phi \in Y, \tag{58}$$

where $s(\zeta)$ is the spectral bound of ζ (see Definition 3.2). Now by (53) and (26),

$$\Theta(t)\phi = (e^{-(d+\gamma)t}\phi_2, e^{-\delta t}T_4(t)\phi_4);$$

thus, we may find $\epsilon_0 > 0$ sufficiently small so that

$$\lim_{t\to\infty} e^{\epsilon_0 t}\Theta(t)\phi = 0 \quad \forall\, \phi \in Y. \tag{59}$$

By [29, Theorem 3.13] this implies $s(\zeta) < 0$. Hence, we may take $\lambda = 0 > s(\zeta)$ in (58) to deduce

$$-C\zeta^{-1}\phi = C(\int_0^\infty \Theta(t)\phi dt) = L(\phi) \quad \forall\, \phi \in Y. \tag{60}$$

Thus, $L = -C\zeta^{-1}$. We now let $A \triangleq \zeta + C$. Then firstly we realize that C defined by (54) is clearly a positive linear operator, while we already showed that ζ is a resolvent-positive operator. Thus, A is a positive perturbation of ζ by Definition 3.1. Furthermore, ζ being the generator of $\Theta(t)$ where

$$\Theta(t)\phi = (T_2(t)\phi_2, e^{-\delta t}T_4(t)\phi_4) = (e^{-(d+\gamma)t}\phi_2, e^{-\delta t}T_4(t)\phi_4)$$

by (53) and (26) and

$$C(\phi) = \begin{pmatrix} \beta_1 m^* & \beta_2 \frac{m^*}{K} \\ \xi & g \end{pmatrix} \begin{pmatrix} \phi_2 \\ \phi_4 \end{pmatrix}$$

by (54), we see that A generates a positive C_0-semigroup. By [29, Theorem 3.12] again, this implies that A is resolvent-positive. The facts that ζ is a resolvent-positive operator such that $s(\zeta) < 0$, and $A = \zeta + C$ is a positive perturbation of ζ while being resolvent-positive itself, impy that $s(A)$ has the same sign as $r(-C\zeta^{-1}) - 1$ due to [29, Theorem 3.5]. As $L = -C\zeta^{-1}$ by (60) and $\mathcal{R}_0 = r(L)$ by (57), we see that

$$\mathcal{R}_0 - 1 = r(L) - 1 = r(-C\zeta^{-1}) - 1$$

has a same sign as $s(A) = s(\zeta + C)$. Because we split the right side of (38) as

$$\left(\begin{pmatrix} -(d+\gamma) & 0 \\ 0 & D(x)\Delta - (U(x)\cdot\nabla) - \delta \end{pmatrix} + \begin{pmatrix} \beta_1 m^* & \beta_2 m^* \frac{1}{K} \\ \xi & g \end{pmatrix}\right)\begin{pmatrix} u_2 \\ u_4 \end{pmatrix}$$

in (50), set $\Theta(t)$ as the solution semiflow of (51), ζ as the generator of $\Theta(t)$, and C in (54), this implies that $\mathcal{R}_0 - 1$ has a same sign as $\lambda(m^*, \frac{m^*}{K}, 1)$. □

We remark that an immediate corollary of Proposition 4.3 is the following local asymptotic stability of the DFE:

Corollary 4.4. *Suppose $m^* < \frac{d+\gamma}{\beta_1}$. If $\mathcal{R}_0 < 1$, then the DFE $(m^*, 0, 0, 0)$, is locally asymptotically stable.*

Proof. This can be proven similarly to that of [37, Theorem 2.3 (1)]; it serves as an analogous statement to [35, Theorem 4.3]. We skip its proof while only mentioning that it follows from [10, Theorem 2.1], because we will prove a stronger result in Theorem 2.3 (1), specifically the global stability of the DFE. □

Proof of Theorem 2.3 (1). We are now ready to prove the first part of Theorem 2.3. By hypothesis $\mathcal{R}_0 < 1$ so that $\mathcal{R}_0 - 1 < 0$. Then $\lambda(m^*, \frac{m^*}{K}, 1)$ the principal eigenvalue of the eigenvalue problem (40) with $H_1 \equiv m^*, H_2 \equiv \frac{m^*}{K}, H_3 \equiv 1$,

$$\begin{aligned} \lambda\psi_2 &= -(d+\gamma)\psi_2 + \beta_1 m^* \psi_2 + \beta_2 \frac{m^*}{K}\psi_4, \\ \lambda\psi_4 &= D(x)\Delta\psi_4 - (U(x)\cdot\nabla)\psi_4 + \xi\psi_2 + (g-\delta)\psi_4, \end{aligned}$$

has the corresponding eigenvector $\psi^* = (\psi_2^*, \psi_4^*) \gg 0$ due to Proposition 4.2, and it satisfies $\lambda(m^*, \frac{m^*}{K}, 1) < 0$ due to Proposition 4.3. Hence, we may fix $\epsilon_0 > 0$ sufficiently small so that $\lambda(m^* + \epsilon_0, \frac{1}{K}(m^* + \epsilon_0), 1) < 0$. By hypothesis we know that $m^* < \frac{d+\gamma}{\beta_1}$ so that we may choose $\epsilon_0 > 0$ smaller if necessary to satisfy $m^* + \epsilon_0 < \frac{d+\gamma}{\beta_1}$. From (31) we know that $\lim_{t\to\infty} N(t) = m^*$. By non-negativity of S, I, R for all $t \geq 0$, for this fixed $\epsilon_0 > 0$ and $\phi \in X$, we know that there exists $t_0 = t_0(\phi)$ such that for all $t \geq t_0$ and all $x \in \overline{\Omega}$,

$$S(x,t) \leq m^* + \epsilon_0, \; R(x,t) \leq m^* + \epsilon_0. \tag{61}$$

Therefore, for all $t \geq t_0$ and all $x \in \overline{\Omega}$,

$$\partial_t I \leq \beta_1(m^* + \epsilon_0)I + \beta_2(m^* + \epsilon_0)(\frac{B}{K}) - I(d+\gamma), \tag{62}$$

$$\partial_t B \leq D(x)\Delta B - (U(x)\cdot\nabla)B + \xi I + (g-\delta)B, \tag{63}$$

due to (5b) and (5d). We consider a system

$$\partial_t v_2 = \beta_1(m^* + \epsilon_0)v_2 + \frac{\beta_2}{K}v_4(m^* + \epsilon_0) - v_2(d+\gamma), \tag{64a}$$

$$\partial_t v_4 = D(x)\Delta v_4 - (U(x)\cdot\nabla)v_4 + \xi v_2 + (g-\delta)v_4. \tag{64b}$$

We substitute $(e^{\lambda t}\psi_2(x), e^{\lambda t}\psi_4(x))$ for $(v_2, v_4)(x,t)$ in (64) and divide by $e^{\lambda t}$ to deduce its eigenvalue problem of

$$\lambda\psi_2 = \beta_1(m^* + \epsilon_0)\psi_2 + \frac{\beta_2}{K}\psi_4(m^* + \epsilon_0) - \psi_2(d+\gamma), \tag{65a}$$

$$\lambda\psi_4 = D(x)\Delta\psi_4 - (U(x)\cdot\nabla)\psi_4 + \xi\psi_2 + (g-\delta)\psi_4. \tag{65b}$$

By Proposition 4.2 with $H_1 \equiv m^* + \epsilon_0, H_2 \equiv (m^* + \epsilon_0)\frac{1}{K}, H_3 \equiv 1$ because $m^* + \epsilon_0 < \frac{d+\gamma}{\beta_1}$, this eigenvalue problem has a real eigenvalue $\lambda(m^* + \epsilon_0, (m^* + \epsilon_0)\frac{1}{K}, 1)$ with a corresponding eigenvector $\hat{\psi} = (\hat{\psi}_2, \hat{\psi}_4) \gg 0$ and therefore a solution of

$$e^{\lambda(m^*+\epsilon_0,(m^*+\epsilon_0)\frac{1}{K},1)(t-t_0)}\hat{\psi}(x), \quad \forall\, t \geq t_0. \tag{66}$$

We can find $\eta > 1$ sufficiently large so that

$$(I, B)(x, t_0) \leq \eta\hat{\psi}(x) \quad \forall\, x \in \overline{\Omega} \tag{67}$$

because $\hat{\psi} \gg 0$. Now the next step is the comparison principle with which we claim

$$(I, B)(x, t_0) \leq \eta e^{\lambda(m^*+\epsilon_0,(m^*+\epsilon_0)\frac{1}{K},1)(t-t_0)}\hat{\psi}(x). \tag{68}$$

The typical strategy here is to rely on [27, Theorem 7.3.4] or its variant; however, although [27, Theorem 7.3.4] may be applied to a uniformly elliptic second-order differentiation operator (see Remark 3.1), it is only for a system that is fully diffusive (see [27, pg. 120]). A typical proof of a comparison principle relies on a maximum principle; yet, there is no maximum principle for a non-diffusive equation in general and hence in particular (64a). Therefore, it is actually not trivial at all how to apply a comparison principle to a coupled system of a partially diffusive system.

In fact, we can appeal to [20, Proposition 3] here. The trick in the proof of [20, Proposition 3] is to not rely on a maximum principle but in fact the local existence theorem in X^+ [20, Theorem 2] and generalize X^+ to $[v^-(t), v^+(t)]$ where the v^- and v^+ are the lower and upper solutions, respectively.

Let us continue to denote $Y = C(\overline{\Omega}, \mathbb{R}^2)$ and $Y^+ = C(\overline{\Omega}, \mathbb{R}^2_+)$ and verify the main hypothesis [20, Equation (2.9)] of [20, Proposition 3]. In order to do so, it suffice to show for all $t \in [0, b), \phi \in Y^+$ such that $v^-(t) \leq \phi \leq v^+(t)$ that

$$\begin{aligned}\lim_{h\to 0^+} \inf_{y\in Y^+} \frac{1}{h} &\|v_2(t) - \phi_2 + h[F_2^+((v_2, v_4)(t)) - F_2(\phi)] - y_2\|_{C(\overline{\Omega})} \\ &+ \|v_4(t) - \phi_4 + h[F_4^+((v_2, v_4)(t)) - F_4(\phi)] - y_4\|_{C(\overline{\Omega})} = 0.\end{aligned} \tag{69}$$

In fact, (69) can be proven very similarly to the proof of Theorem 2.1. Therefore, by [20, Proposition 3] we deduce (68), where the right side vanishes to zero as $t \to \infty$ because $\lambda(m^* + \epsilon_0, (m^* + \epsilon_0)\frac{1}{K}, 1) < 0$. Consequently, we can fix $t_1 \geq t_0$ sufficiently large so that $\|I(t)\|_{C(\overline{\Omega})} \leq 1$ and compute from (5c) that

$$R(t) \leq e^{-(d+\sigma)t}[R(t_1) + \gamma \int_{t_1}^{t} I(s)e^{(d+\sigma)s}ds] \leq e^{-(d+\sigma)t}(m^* + \epsilon_0) + \frac{\gamma e^{-(d+\sigma)t_1}}{d+\sigma} \to 0 \tag{70}$$

due to (61) as $t_1 \to \infty$ so that $t \to \infty$. Finally, because we know $\lim_{t\to\infty} N(t) = m^*$ for all $x \in \overline{\Omega}$ from (31), we deduce that $\lim_{t\to\infty} S(t) = m^*$ for all $x \in \overline{\Omega}$ since we already showed that $(I, R)(t) \to (0, 0)$ as $t \to \infty$ for all $x \in \overline{\Omega}$. This completes the proof of Theorem 2.3 (1). □

Proof of Theorem 2.3 (2). We are now ready to prove the second part of Theorem 2.3. By hypothesis, $m^* < \frac{d+\gamma}{\beta_1}$ and $\mathcal{R}_0 > 1$ so that $\mathcal{R}_0 - 1 > 0$. Thus, $\lambda(m^*, \frac{m^*}{K}, 1)$ the principal eigenvalue of the eigenvalue problem (40) with $H_1 \equiv m^*, H_2 \equiv \frac{m^*}{K}, H_3 \equiv 1$,

$$\begin{aligned}\lambda\psi_2 &= -(d+\gamma)\psi_2 + \beta_1 m^*\psi_2 + \beta_2\frac{m^*}{K}\psi_4, \\ \lambda\psi_4 &= D(x)\Delta\psi_4 - (U(x)\cdot\nabla)\psi_4 + \xi\psi_2 + (g-\delta)\psi_4,\end{aligned}$$

which has the corresponding eigenvector $\psi^* = (\psi_2^*, \psi_4^*) \gg 0$ due to Proposition 4.2 also satisfies $\lambda(m^*, \frac{m^*}{K}, 1) > 0$ due to Proposition 4.3. To reach a contradiction, suppose that there exists $\psi_0 \in X^+$ such that for all $\delta_0 > 0$, and hence taking it smaller if necessary, for all $\delta_0 \in (0, m^*)$, it holds that

$$\limsup_{t\to\infty} \|\Phi_t(\psi_0) - (m^*, 0, 0, 0)\|_{C(\overline{\Omega})} < \delta_0, \tag{71}$$

where we recall that Φ_t is the semiflow from Theorem 2.2. Thus, there exists $t_1 > 0$ sufficiently large such that

$$S(x,t) - m^* < \delta_0,\ m^* - \delta_0 < S(x,t), \tag{72a}$$

$$I(x,t) < \delta_0,\ R(x,t) < \delta_0,\ B(x,t) < \delta_0, \tag{72b}$$

for all $t \geq t_1$ and all $x \in \overline{\Omega}$. We see from (5b) and (5d) that

$$\partial_t I \geq \beta_1(m^* - \delta_0)I + \beta_2(m^* - \delta_0)(\frac{1}{\delta_0 + K})B - I(d+\gamma), \tag{73}$$

$$\partial_t B \geq D(x)\Delta B - (U(x)\cdot\nabla)B + \xi I + gB\left(1 - \frac{\delta_0}{K_B}\right) - \delta B \tag{74}$$

for all $x \in \overline{\Omega}$ and all $t \geq t_1$. Now $m^* < \frac{d+\gamma}{\beta_1}$ by hypothesis so that $m^* - \delta_0 < \frac{d+\gamma}{\beta_1}$; hence, by Proposition 4.2 with $H_1 \equiv m^* - \delta_0, H_2 \equiv (\frac{m^*-\delta_0}{\delta_0+K}), H_3 \equiv 1 - \frac{\delta_0}{K_B}$, an eigenvalue problem of

$$\partial_t v_2 = \beta_1(m^* - \delta_0)v_2 + \beta_2(\frac{m^* - \delta_0}{\delta_0 + K})v_4 - v_2(d+\gamma), \tag{75a}$$

$$\partial_t v_4 = D(x)\Delta v_4 - (U(x)\cdot\nabla)v_4 + \xi v_2 + gv_4\left(1 - \frac{\delta_0}{K_B}\right) - \delta v_4, \tag{75b}$$

specifically

$$\lambda\psi_2 = \beta_1(m^* - \delta_0)\psi_2 + \beta_2\frac{m^* - \delta_0}{\delta_0 + K}\psi_4 - \psi_2(d+\gamma), \tag{76a}$$

$$\lambda\psi_4 = D(x)\Delta\psi_4 - (U(x)\cdot\nabla)\psi_4 + \xi\psi_2 + g\psi_4(1 - \frac{\delta_0}{K_B}) - \delta\psi_4, \tag{76b}$$

has a principal eigenvalue $\lambda(m^* - \delta_0, \frac{m^*-\delta_0}{\delta_0+K}, 1 - \frac{\delta_0}{K_B})$ with a corresponding eigenvector $\hat{\psi} = (\hat{\psi}_2, \hat{\psi}_4) \gg 0$ for all $x \in \overline{\Omega}$. We emphasize that we also just used the fact that $H_2 \equiv \frac{m^*-\delta_0}{\delta_0+K} > 0$ where the strict positivity is due to our choice of $\delta_0 \in (0, m^*)$. As $\lambda(m^*, \frac{m^*}{K}, 1) > 0$, for $\delta_0 > 0$ sufficiently small we obtain

$$\lambda(m^* - \delta_0, \frac{m^* - \delta_0}{\delta_0 + K}, 1 - \frac{\delta_0}{K_b}) > 0. \tag{77}$$

By the hypothesis that the solution is positive, for $\eta > 0$ sufficiently small we can obtain

$$(I(x, t_1, \psi_0), B(x, t_1, \psi_0)) \geq \eta\hat{\psi}(x) \quad \forall\, x \in \overline{\Omega}. \tag{78}$$

Now we apply [20, Proposition 3] again. We recall that $Y = C(\overline{\Omega}, \mathbb{R}^2)$ and $Y^+ = C(\overline{\Omega}, \mathbb{R}^2_+)$, and verify the main hypothesis [20, Equation (2.10)] of [20, Proposition 3]; in order to do so, it suffices to show for $(v_2, v_4)(t) \leq \phi$ that

$$\frac{1}{h}\inf_{y\in Y^+}\|\phi_2 - v_2(t) + h[F_2(\phi) - F_2^-((v_2,v_4)(t))] - y_2\|_{C(\overline{\Omega})}$$
$$+ \|\phi_4 - v_4(t) + h[F_4(\phi) - F_4^-((v_2,v_4)(t))] - y_4\|_{C(\overline{\Omega})} = 0. \quad (79)$$

Similarly to (69), (78) can be proven very similarly to our proof of Theorem 2.1. Therefore, we deduce that

$$(I,B)(x,t,\psi_0) \geq \eta e^{\lambda(m^*-\delta_0,(\frac{m^*-\delta_0}{\delta_0+K}),1-\frac{\delta_0}{K_B})(t-t_1)}\hat{\psi}(x), \quad (80)$$

where

$$\lim_{t\to\infty} e^{\lambda(m^*-\delta_0,(\frac{m^*-\delta_0}{\delta_0+K}),1-\frac{\delta_0}{K_B})(t-t_1)} = \infty$$

due to (77). As $\hat{\psi} \gg 0$, this implies $\|I(t,\psi_0)\|_{C(\overline{\Omega})}, \|B(t,\psi_0)\|_{C(\overline{\Omega})}$ grows unbounded. This contradicts our assumption (71) and (72) that

$$\limsup_{t\to\infty}\|\Phi_t(\psi) - (m^*,0,0,0)\|_{C(\overline{\Omega})} = \limsup_{t\to\infty}\|S(t,\psi_0) - m^*\|_{C(\overline{\Omega})}$$
$$+ \|I(t,\psi_0)\|_{C(\overline{\Omega})} + \|R(t,\psi_0)\|_{C(\overline{\Omega})} + \|B(t,\psi_0)\|_{C(\overline{\Omega})} < \delta_0.$$

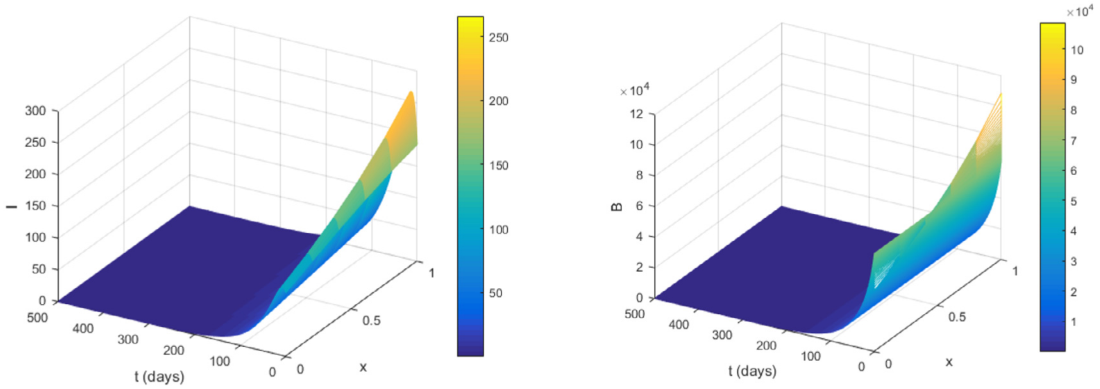
This concludes the proof of Theorem 2.3 (2). □

5. Numerical results

In order to verify our analytical results, we have conducted numerical simulation to our PDE model (5). The system (5) can be computed by a standard finite difference method, such as the leapfrog (i.e., centered difference in time and space), or simply the forward difference in time and centered difference in space. When such explicit finite difference schemes are employed, we have to be careful for the choice of the time step size, which needs to be relatively small, to ensure the numerical stability.

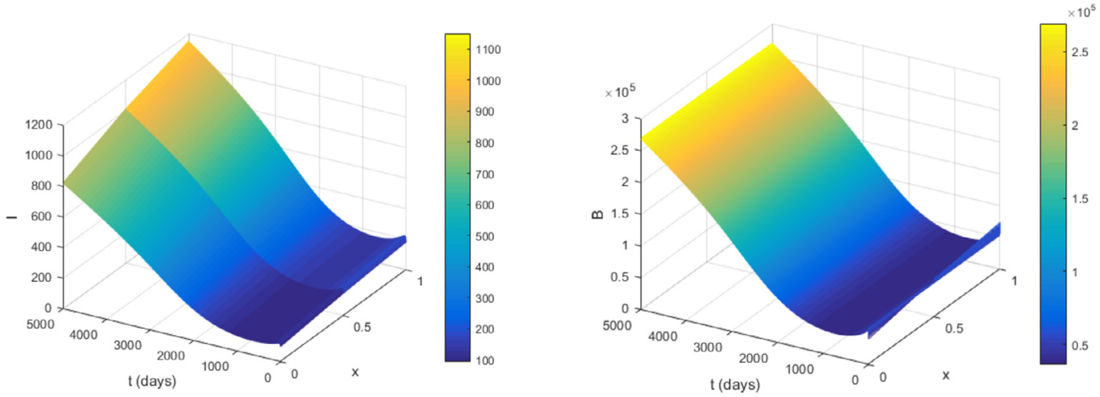
Meanwhile, we have also numerically calculated the basic reproduction number associated with our PDE model. The equation (57) characterizes the basic reproduction number $\mathcal{R}_0$. The formula, however, is expressed in terms of an operator and not directly applicable to the numerical evaluation of $\mathcal{R}_0$. To overcome this difficulty, we transfer the evaluation of the spectral radius of the operator L to the calculation of the spectral radius of a corresponding matrix, in the approximate means. That is, we numerically reduce the operator eigenvalue problem to a matrix eigenvalue problem that can be easily computed. A numerical algorithm for the computation of $\mathcal{R}_0$ has been developed and the detail is provided in the Appendix, Section A.3.

Using this algorithm, we are able to evaluate $\mathcal{R}_0$ and demonstrate the threshold results predicted by our mathematical analysis. For illustration, we have chosen a one-dimensional spatial domain, [0, 1]. Figs. 1 and 2 show two typical scenarios, $\mathcal{R}_0 < 1$ and $\mathcal{R}_0 > 1$ respectively, of the simulation results for the model (5). We clearly observe that when $\mathcal{R}_0 = 0.96$ (Fig. 1), the number of infected hosts and the concentration of the pathogenic bacteria, though started with a non-uniform distribution over the space, both approach 0 quickly and uniformly, indicating the elimination of the disease. In contrast, when $\mathcal{R}_0 = 1.29$ (Fig. 2), the infected population and bacterial concentration both remain positive throughout the time and space, indicating the persistence of the disease. Furthermore, by running the numerical simulation sufficiently long, we find that the solution actually converges to an endemic state, as illustrated in Fig. 3 for I and B at $x = 0.5$. In Theorem 2.3, we proved the weak persistence result when $\mathcal{R}_0 > 1$. The numerical findings in Figs. 2 and 3 as well as other similar results (based on different diffusion and convection rates and different initial conditions), not shown here, provide evidences for a stronger persistence result that there exists an



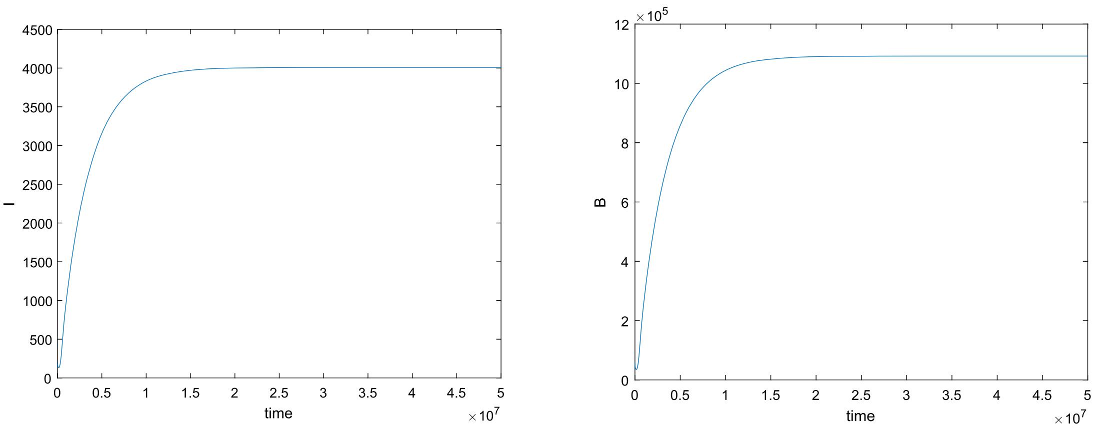
(a) (b)

Fig. 1. A typical scenario of the spatiotemporal dynamics of the model (5) when $\mathcal{R}_0 < 1$. Here $D(x) = 10+10\sin(\pi x)$, $U(x) = 5+5x$, and $\mathcal{R}_0 = 0.96$. (a) The number of infected hosts quickly approaches 0; (b) The concentration of pathogenic bacteria quickly approaches 0. (For interpretation of the colors in the figure(s), the reader is referred to the web version of this article.)



(a) (b)

Fig. 2. A typical scenario of the spatiotemporal dynamics of the model (5) when $\mathcal{R}_0 > 1$. Here $D(x) = 10+10\sin(\pi x)$, $U(x) = 5+5x$, and $\mathcal{R}_0 = 1.29$. (a) The number of infected hosts remains positive; (b) The concentration of pathogenic bacteria remains positive.



(a) (b)

Fig. 3. Long-term behavior of the solution to the model (5) when $\mathcal{R}_0 > 1$, under the same setting as in Fig. 2. (a) The infected number at $x = 0.5$ converges to a positive endemic state over time; (b) The bacterial concentration at $x = 0.5$ converges to a positive endemic state over time.

endemic equilibrium that is asymptotically stable when $\mathcal{R}_0 > 1$. This is very interesting because, as we elaborated in Remark 2.3, proving the uniform persistence and the existence of an endemic equilibrium in case $\mathcal{R}_0 > 1$ rigorously seems to be very difficult for partially diffusive systems of PDEs such as (5) due to the absence of a maximum principle.

6. Conclusion

We have presented a new cholera modeling framework based on a partially diffusive PDE system that describes the temporal variation of the human hosts and the dispersal and movement of the pathogenic bacteria along a river with spatial heterogeneity. We have conducted a careful mathematical analysis on the well-posedness and stability of our model. Additionally we have conducted some numerical simulation to verify the analytical results.

It is a nontrivial task to quantify the risk of cholera infection in a spatially heterogeneous environment. In this study, we have focused our attention on the characterization of the environmental bacterial dynamics, especially their spatial movement in a heterogeneous fluvial system, which plays an important role in shaping a cholera epidemic. The spatial variation of the human population dynamics can still be reflected (at least partially) in our model, through the interaction between human hosts and environmental bacteria. Our investigation has put a special emphasis on the interplay of the biological, environmental and physical factors that all contribute to the complexity of cholera transmission and spread. Our model differs from previously published cholera PDE models (such as those in [3,26,33,34]) in the following aspects: (1) the system is partially diffusive in the sense that the diffusion term only appears in the bacterial equation; (2) the convection and diffusion rates for the bacteria are spatially dependent; (3) the spatial domain can have an arbitrary dimension (instead of being limited to 1D).

Due to the partial diffusion (so that the uniform elliptic condition and the maximum principle are not satisfied) and the complex non-linear terms involved in our model, mathematical treatment of our PDE system is challenging. We have utilized several (standard and non-standard) mathematical tools, particularly the positive operator theory and Kuratowski's measure of non-compactness, to analyze this system. We have established the local and global well-posedness for our system, and rigorously derived the basic reproduction number $\mathcal{R}_0$ for this model. We have also established the global asymptotic stability of the DFE when $\mathcal{R}_0 < 1$ and the persistence of the solution flow in the weak sense when $\mathcal{R}_0 > 1$. In addition, our numerical results are consistent with the analytical predictions, and provide evidences for the uniform persistence of the solution and the asymptotic stability of the endemic state when $\mathcal{R}_0 > 1$.

In our future research, we may consider more general representation of the bacterial convection and diffusion rates, which could be depending on both the space and time. We may also explore ways to realistically model human movement and explicitly incorporate the spatial heterogeneity into the human population. One possibility is to consider the dynamics of the human hosts and the pathogen on two different (but adjacent) spatial domains, such as a 1D domain (e.g., a river) for the bacteria, and a 2D domain (e.g., a field) for the human hosts, and investigate their interactions. Such a modeling approach has been used to study invasions of biological species [4,5], and we hope to pursue the effort along this line for cholera modeling.

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Appendix A

A.1. Proof of Proposition 4.1

By hypothesis, $\Omega \subset \mathbb{R}^n$ is bounded so that $\overline{\Omega}$ is closed and bounded. Thus, $\overline{\Omega}$ is compact by Heine-Borel theorem, implying that $g(\overline{\Omega})$ is also compact by the continuity of g; thus,

$$0 < \underline{g} \triangleq \min_{x\in\overline{\Omega}} g(x) \le g(x) \le \max_{x\in\overline{\Omega}} g(x) \triangleq \overline{g} \quad \forall\, x \in \overline{\Omega}.$$

We define $F(x,w) \triangleq g(x) - \lambda w(x,t)$. For (29) we can apply Lemma 3.2 because $\overline{D}(x)\Delta - (\overline{U}(x)\cdot\nabla)$ is uniformly elliptic due to the hypothesis that $\overline{D}(x) \ge M > 0$ for all $x \in \overline{\Omega}$ (see Remark 3.1). Thus, via [27, Corollary 7.3.2] we can deduce the existence of a unique solution $w(x,t,\psi) \in C(\overline{\Omega},\mathbb{R}_+)$ for all $\psi \in C(\overline{\Omega},\mathbb{R}_+)$ on some interval $[0,\sigma)$ where $\sigma = \sigma(\psi)$ and $\lim_{t\to\sigma^-}\|w(t,\psi)\|_{C(\overline{\Omega})} = \infty$ if $\sigma < \infty$. We fix $\psi \in C(\overline{\Omega},\mathbb{R}_+)$, take a function $v \equiv N$ such that

$$N > \max\{\max_{x\in\overline{\Omega}} \psi(x), \frac{\overline{g}}{\lambda}\}.$$

Then it follows from [27, Theorem 7.3.4] (Remark 3.1) that $w(x,t) \le v(x,t) \equiv N$ for all $x \in \overline{\Omega}$. By the blow up criterion from local well-posedness result, we deduce that $w(x,t)$ exists globally in time. Thus, there exists P_t the solution semiflow such that $P_t(\psi) = w(t,\psi)$ for all $\psi \in C(\overline{\Omega},\mathbb{R}_+)$. For all $x \in \overline{\Omega}$ and for all $t > 0$,

$$\underline{g} - \lambda w(x,t) \le F(x,w) \le \overline{g} - \lambda w(x,t),$$

and F is trivially cooperative; thus, by [27, Theorem 7.3.4] again we see that the omega limit set $\omega(\psi)$ for $\psi \in C(\overline{\Omega},\mathbb{R}_+)$ satisfies

$$\omega(\psi) \subset \{\phi : \frac{\underline{g}}{\lambda} \le \phi \le \frac{\overline{g}}{\lambda}\}. \tag{81}$$

By comparison theorem [27, Corollary 7.3.5, Theorem 7.4.1] again, it follows that $P_t(\psi_1) \gg P_t(\psi_2)$ for all $t > 0$ if $\psi_1 > \psi_2$; this implies that P_t is strongly monotone (e.g. [43, pg. 38, 40, 46]). Moreover, F is strictly subhomogeneous in the sense that $F(x,\beta w) > \beta F(x,w)$ for all $\beta \in (0,1)$ as $g(x) > 0$. Next, following the proof of [13, Theorem 2.2], it follows that P_t is strictly subhomogeneous (see the proof of [38, Proposition 1] for details). Because we already showed that P_t is strongly monotone and P_t also admits a non-empty compact invariant set in $intC(\overline{\Omega},\mathbb{R}_+)$, by [43, Theorem 2.3.2], we deduce that P_t has a fixed point $w^*(x) \gg 0$ such that $\omega(\psi) = w^* \in C(\overline{\Omega},\mathbb{R}_+)$ for all $\psi \in C(\overline{\Omega},\mathbb{R}_+)$. Finally, if $g(x) \equiv g$ for all $x \in \overline{\Omega}$, it follows from (81) that $w^* \equiv \frac{g}{\lambda}$.

A.2. Proof of Proposition 2.4

Firstly, say $\phi_2 > 0$. Then by [38, Proposition 2], we know $I(x,t) > 0$ for all $t > 0$ and all $x \in [0,1]$. Now if for any $t_0 > 0, u_3(\cdot,t_0,\phi) \equiv 0$, then from (9c) we deduce $\partial_t R|_{t=t_0} = \gamma I|_{t=t_0} > 0$ and $R(\cdot,t_0) \equiv 0$. This contradicts that $R \ge 0$ for all $t \ge 0$ from [38, Theorem 2.1]. Thus, for all $t_0 > 0, u_3(\cdot,t_0,\phi) \not\equiv 0$. But then by [37, Proposition 2] we deduce that $R(x,t) > 0$ for all $t > 0$ and all $x \in [0,1]$.

Secondly, say $\phi_4 > 0$. Then by [38, Proposition 2] we deduce that $B(x,t) > 0$ for all $t > 0$ and all $x \in [0,1]$. It is explained in the proof of [38, Proposition 5] that this implies $I(x,t) > 0$ for all $t > 0$ and all $x \in [0,1]$. By the same argument in the case $\phi_2 > 0$ that we already explained, this leads to $R(t,x) > 0$ for all $t > 0, x \in [0,1]$.

This implies that upon showing that

$$p(\psi) \triangleq \min\{\min_{x\in[0,1]} \psi_2(x), \min_{x\in[0,1]} \psi_4(x)\}$$

is a generalized distance function (see [28, pg. 6172]) in the process of proving [38, Theorem 2], an identical proof would have gone through with

$$p(\psi) \triangleq \min\{\min_{x\in[0,1]} \psi_2(x), \min_{x\in[0,1]} \psi_3(x), \min_{x\in[0,1]} \psi_4(x)\};$$

this concludes the proof of Proposition 2.4.

A.3. Numerical calculation of $\mathcal{R}_0$

Denote $-\zeta^{-1}(\phi) = \begin{bmatrix} h_2(\phi_2) \\ h_4(\phi_4) \end{bmatrix}$ where the operator ζ is defined in equation (58). Then $\begin{bmatrix} -(d+\gamma) & 0 \\ 0 & D(x)\Delta - U(x)\cdot\nabla - \delta \end{bmatrix} \cdot \begin{bmatrix} -h_2(\phi_2) \\ -h_4(\phi_4) \end{bmatrix} = \begin{bmatrix} \phi_2 \\ \phi_4 \end{bmatrix}$ implies

$$h_2(\phi_2) = \frac{\phi_2}{d+\gamma} \tag{82}$$

and

$$(D(x)\Delta - U(x)\cdot\nabla - \delta)(h_4(\phi_4)) = -\phi_4\,. \tag{83}$$

For simplicity, let us consider a 1D domain: $x \in [0, 1]$, and denote $y(x) = (h_4\phi_4)(x)$. Then we have

$$D(x)\frac{d^2y(x)}{dx^2} - U(x)\frac{dy(x)}{dx} - \delta y(x) = -\phi_4(x). \tag{84}$$

Fix a sufficiently large integer $N > 0$ and let $x_n = n/N$, $D_n = D(x_n)$, $U_n = U(x_n)$, and $y_n = y(x_n)$ for $n = 0, 1, ..., N$. Using a standard second-order centered difference method to approximate equation (84), we obtain

$$D_n\frac{y_{n+1} - 2y_n + y_{n-1}}{1/N^2} - U_n\frac{y_{n+1} - y_{n-1}}{2/N} - \delta y_n \approx -\phi_4(x_n), \tag{85}$$

or, equivalently,

$$-N\left(D_nN - \frac{U_n}{2}\right)y_{n+1} + (2D_nN^2 + \delta)y_n - N\left(D_nN + \frac{U_n}{2}\right)y_{n-1} \approx \phi_4(x_n), \tag{86}$$

for $n = 0, 1, ..., N$. Note that the Neumann boundary conditions at $x = 0, 1$ yield $y_{-1} \approx y_1$ and $y_{N+1} \approx y_{N-1}$ up to second order accuracy. Rewrite these $N + 1$ approximate equations in matrix form

$$AY \approx \Phi_4, \tag{87}$$

where

$$A = \begin{bmatrix} d_0 & s_0 & & & \\ v_1 & d_1 & \overline{v_1} & & \\ & \ddots & \ddots & \ddots & \\ & & v_{N-1} & d_{N-1} & \overline{v_{N-1}} \\ & & & s_N & d_N \end{bmatrix}, \quad Y = \begin{bmatrix} y_0 \\ y_1 \\ \vdots \\ y_{N-1} \\ y_N \end{bmatrix}, \quad \text{and} \quad \Phi_4 = \begin{bmatrix} \phi_4(x_0) \\ \phi_4(x_1) \\ \vdots \\ \phi_4(x_{N-1}) \\ \phi_4(x_N) \end{bmatrix},$$

with $d_n = 2D_nN^2 + \delta$, $v_n = -N\left(D_nN + \frac{U_n}{2}\right)$, $\overline{v_n} = -N\left(D_nN - \frac{U_n}{2}\right)$, and $s_n = v_n + \overline{v_n}$ for all $0 \le n \le N$. Note that $v_n < 0$ and $\overline{v_n} < 0$ for sufficiently large N, since $D(x) \ge M > 0$. By the Gershgorin circle theorem, any eigenvalue λ_A of matrix A satisfies $|\lambda_A - d_p| \le |v_p| + |\overline{v_p}| = 2D_pN^2$ for some $p \in \{0, 1, ..., N\}$, which implies $\mathrm{Re}(\lambda_A) \ge \delta$. Therefore, A is invertible, and we obtain $Y \approx A^{-1}\Phi_4$.

We know that $L(\phi) = -C\zeta^{-1}(\phi) = \begin{bmatrix} \beta_1 m^* & \beta_2 \frac{m^*}{K} \\ \xi & g \end{bmatrix} \cdot \begin{bmatrix} h_2(\phi_2) \\ h_4(\phi_4) \end{bmatrix} = \begin{bmatrix} \frac{\beta_1 m^*}{d+\gamma}\phi_2 + \beta_2 \frac{m^*}{K} y(x) \\ \frac{\xi}{d+\gamma}\phi_2 + g y(x) \end{bmatrix}$. For any eigenvalue λ of the operator L, we have

$$L(\phi) = \lambda\phi\,. \tag{88}$$

Consequently, we obtain

$$\begin{bmatrix} \frac{\beta_1 m^*}{d+\gamma}\phi_2(x) + \beta_2 \frac{m^*}{K} y(x) \\ \frac{\xi}{d+\gamma}\phi_2(x) + g y(x) \end{bmatrix} = \lambda \begin{bmatrix} \phi_2(x) \\ \phi_4(x) \end{bmatrix}, \tag{89}$$

which yields

$$\begin{bmatrix} \frac{\beta_1 m^*}{d+\gamma}\Phi_2 + \beta_2 \frac{m^*}{K} Y \\ \frac{\xi}{d+\gamma}\Phi_2 + gY \end{bmatrix} = \lambda \begin{bmatrix} \Phi_2 \\ \Phi_4 \end{bmatrix}, \tag{90}$$

where $\Phi_2 = [\phi_2(x_0), \phi_2(x_1), ..., \phi_2(x_N)]^T$. It then follows from equation (87) that

$$\begin{bmatrix} \frac{\beta_1 m^*}{d+\gamma} I_{N+1} & \beta_2 \frac{m^*}{K} A^{-1} \\ \frac{\xi}{d+\gamma} I_{N+1} & gA^{-1} \end{bmatrix} \cdot \begin{bmatrix} \Phi_2 \\ \Phi_4 \end{bmatrix} \approx \lambda \begin{bmatrix} \Phi_2 \\ \Phi_4 \end{bmatrix}. \tag{91}$$

Thus, the operator eigenvalue problem (88) can be approximated by the matrix eigenvalue problem (91). Let us denote

$$L_N = \begin{bmatrix} \frac{\beta_1 m^*}{d+\gamma} I_{N+1} & \beta_2 \frac{m^*}{K} A^{-1} \\ \frac{\xi}{d+\gamma} I_{N+1} & gA^{-1} \end{bmatrix}. \tag{92}$$

Then the spectral radius of the matrix L_N; i.e., $\rho(L_N)$, approximates the spectral radios of the operator L; i.e., $\rho(L)$. Hence, for sufficiently large N, we have

$$\mathcal{R}_0 = \rho(L) \approx \rho(L_N). \tag{93}$$

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