A Reaction-Advection-Diffusion Model for Quasi-neutral Dynamics of Coinfected Strains

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Abstract

This paper studies dynamical system of coinfected strains with spatial diffusion, under a quasi similarity assumption. Such coinfection systems have been studied in several articles without spatial structure. In the present study, we add a spatial structure to comprehend the impact of spatial heterogeneity on the interaction between similar strains. The SIS model is then a reaction-diffusion system in which the coefficients are spatially heterogeneous. Two limiting cases are considered: the case of an asymptotically slow diffusion coefficient and the case of an asymptotically fast diffusion coefficient. In the case of small diffusion rates, we show that the slow system is a semilinear system of type "replicator equations," describing the spatio-temporal evolution of the strains' frequencies. This system is of the reaction-advection-diffusion type, in which the additional advection term explicitly involves the heterogeneity of the associated neutral system. In the case of fast diffusion, classical methods of aggregation of variables are used to reduce the spatialized SIS problem to a homogenized SIS system on which we can directly apply the results of the non-spatial model.

Keywords. spatial quasi-Neutral dynamics, spatial SIS multi-strain dynamics, co-infection system with diffusion, slow-fast dynamics, Tikhonov's Theorem, Central Manifold Theorem

1 Introduction

Heterogeneity is a common feature of real world infections. Heterogeneous susceptibilities may arise, for instance, through individuals having differing histories of prior exposure to infection or vaccination. Thus, it remains challenging to accurately describe diffusion process of bacteria/virus and investigate the transmission dynamics of free-living bacteria/virus in the contaminated environment on disease infection. There are many studies the mathematical framework on the predator-prey models within heterogeneous environment [26, 27]. In particular, many studies deeply solution for compartmental models in epidemiology with diffusion terms. For instants, [31, 30] studies the existence and non-existence of travelling wave solutions for a general class of diffusive KermackMcKendrick SIR models with nonlocal and delayed disease transmission. However, there is a lack of a comprehensive theoretical framework for spatial models of co-infection though it frequently appears in models with migration, evolution, and heterogeneous environment. It is known that co-infection dynamics have received considerable attention [1, 2, 21], because of their importance to biology, especially in the outbreaks of infectious diseases. For instance, [20, 32] studied different co-infection models to help diagnose and treat infectious diseases.

Even without a spatial structure, the interactions between traits and strains yield complex consequences on the population dynamics [19, 17]. However, under a quasi-neutral hypothesis, this complexity is decoded into a replicator equation. In a heterogeneous environment, the dynamics surely become a PDE system, which is more complex to studies. In this study, with diffusion terms and under appropriate conditions, the dynamical system of co-infection, now becomes a reaction-advection-diffusion system, will be coded again through a replicator equation, with or without diffusion, depending on the rate of diffusion.

In this article, we describe and study the spatial version of dynamics considered in [17], i.e. the quasi-neutral SIS model between similar strains, with diffusion and zero flux assumption on the boundaries, in two cases, including slow ($\epsilon\Delta$) and fast diffusions ($\frac{1}{\epsilon}\Delta$). The choice of terms presenting heterogeneity depends on the type of population considered. For the case of a large population in a bounded domain, which leads to a large density, diffusion is a good approach to model spatial movement because organisms are assumed to have random motions. In a mathematical sense, the term diffusion-presented by the Laplacian operator is a strongly elliptic operator. Hence, most of results of this paper may be extended for other elliptic operators.

We focus on modeling the host-to-host transmission of different strains using the SIS (susceptible-infected-susceptible) modeling approach. Despite the assumption on compactness and smoothness of domain, the main difficulty is to take into account the impact of strain traits under propagation in space. It is useful to take the viewpoint of reaction-diffusion equations, which are studied deeply in [7]. Moreover, the assumptions of

zero total flux on the boundary make our system isolated. An important point is that, in the case of slow diffusion, we assume that whole the considered domain is at high risk of infection, which means at any point in the considered domain, the transmission rate of either is larger than the sum of the clearance rate and the mortality rate. This assumption leads to the existence, the uniqueness and the stability of the endemic equilibrium. When low risk site, the set of all points in which the transmission rate is less than the clearance rate, is non empty as well, we also have a disease-free equilibrium, which is studied concretely in [3].

For each type of diffusion, we present a specific method to approximate the solutions under a quasi-neutral assumption on the parameters. In the case of slow diffusion, we first consider the reaction-diffusion model with symmetric interactions, which is the neutral system with diffusion. Similar to [17], and K_f, K_g are operators which are computed later, we find how to rewrite the original system in the form $\frac{\partial}{\partial t}f(x,t) = F(f,g,x,t,\epsilon)+K_f f$ and $\frac{\partial}{\partial t}g(x,t) = \epsilon G(f,g,x,t,\epsilon) + \epsilon K_g g$, where f describes the fast dynamics and g the slow dynamics. The Tikhonov's theorem used in [17] now is improved to a Tikhonov-like theorem applied for PDEs model with appropriate assumptions. Accordingly, at the slow time scale $\tau = \dfrac{t}{\epsilon}$, we obtain the slow dynamics on the slow manifold.

For the case of fast diffusion, the Central Manifold Theorem [8] is applied directly on the original SIS system under an appropriate rewriting, yielding to an ordinary differential (ODE) SIS system under the mean variables. In this system, we invoke the quasi-neutral assumptions on the traits to use the main result of [17]. For a clearer view, this theorem plays the main role in [8, 9].

Analogously to the non-spatial models in [17], we obtain the diffusion replicator system at the end and they are in different types due to the distinguished kinds of diffusions. The replicator system with diffusion attracts much attention and be studied in [6]. Comparing two cases of diffusion, the Tikhonov-like approximates the slow-fast form to the replicator system, in which variables are prevalences of strains. Meanwhile, the Central Manifold Theorem leads us to equations of total masses over the domain of susceptible, infected and coinfected strains. Although, both of them claim that the original system's solution can be approached based on the solution of a simpler system in any bounded time interval as $\epsilon \to 0$. Despite the distinction in variables of system in slow-manifold, error estimates in both cases are computed in L^2 and L^1 norms, respectively.

This article is organized as follows. Sections 2 and 3 are dedicated to the case when the coefficients of diffusion are ϵ. In the beginning of section 2, we present the model and state some general results including the existence of a unique solution and the introduction of new variables. Next, we analyzes the semi-neutral system and the slow-fast form to prepare for application the approximation theorems. Similarly to [17], we solve the system with slow diffusion in each elementary sub-case in which only one trait depends on the strains. For this sake, a lemma showing of to combine the elementary cases is presented, starting section 3. With these sufficient materials, the replicator system with diffusion follows with proofs and finalizes the case of small diffusion rates. The model with fast diffusion ($\frac{1}{\epsilon}\Delta$) is studied in section 4. We refer the Central Manifold Theorem in [9] and make some conventions at the beginning to apply this result. As mentioned after the application of the Central Manifold Theorem, we invoke the quasi-neutral assumptions on traits. These ingredients are combined and used to derive the replicator system, by the main result in [17], in which the variables are total masses over domain of strains. Section 5 is to compare the two cases of diffusion in some respects including the relations with basic reproduction ratio R_0 and three examples for different behaviors. Section 6 draws remarkable results and concluding. The final section Appendix A closes this article with the proofs of the theorems stated in section 2.

2 General and Semi-neutral Systems with Slow Diffusion

2.1 The general N-strain model

The dynamics studied in this article groups the pathogen types in N subsets, indexed by i, $1 \leq i \leq N$. With a set of ordinary differential equations, we then track the proportion of hosts in $1 + N + N^2$ compartments: susceptible: $S(x,t)$, hosts colonized by strain-i: $I_i(x,t)$, hosts co-colonized by strain-i then strain-j: $I_{ij(x,t)}$. Notice that we include also same strain coinfection, as argued in [17].

We formulate the general model based on the same structure as that in [17] but here allow for strains to vary in their transmission rates $\beta_i(x)$, clearance rates of single infection $\gamma_i(x)$ (or duration of carriage $1/\gamma_i(x)$), clearance rates from mixed co-colonization $\gamma_{ij}(x)$, within-host competition reflected in relative transmissibilities from mixed coinfected hosts ($p^i_{ij}(x)$ and $p^i_{ji}(x)$), as well as co-colonization vulnerabilities $k_{ij}(x)$, already studied in [17]. In a compact domain $\Omega \subset \mathbb{R}^{\mathrm{d}}$ with smooth boundary Γ, we consider the general SIS dynamics in a

coinfection system with diffusion as follows

$$\begin{cases} \dfrac{\partial S}{\partial t} &= r(1-S) + \displaystyle\sum_{i=1}^{N} \gamma_i I_i + \sum_{i,j=1}^{N} \gamma_{ij} I_{ij} - S \sum_{i=1}^{N} \beta_i J_i + \quad \epsilon \Delta S, \\ \dfrac{\partial I_i}{\partial t} &= \beta_i J_i S - (r+\gamma_i) I_i - I_i \displaystyle\sum_{j=1}^{N} k_{ij} \beta_j J_j + \qquad \epsilon \Delta I_i, \qquad 1 \le i \le N, \\ \dfrac{\partial I_{ij}}{\partial t} &= k_{ij} I_i \beta_j J_j - (r+\gamma_{ij}) I_{ij} + \qquad \epsilon \Delta I_{ij}, \qquad 1 \le i,j \le N, \end{cases} \tag{2.1}$$

where J_i is proportion of all hosts transmitting strain i, including singly- and co-colonized hosts and has the explicit formula

$$J_i = I_i + \sum_{j=1}^{N} \left(p_{ij}^i I_{ij} + p_{ji}^i I_{ji} \right).$$

We will assume no-flux boundary conditions, i.e. the Neumann boundary conditions $\partial_n S = \partial_n I_i = \partial_n I_{ij} = 0$ on the boundary Γ of Ω and the given initial values.

Note that $\beta_i J_i$ is the infection force of strain i, for all i. In (2.1), for $1 \le i,j \le N$, parameters (that all depend on space) are interpreted as follows

Table 1: **Conventions and notations of parameters**

	Parameter	**Interpretation**	Under strain similarities
1.	$\beta_i(x)$	Strain-specific transmission rates	$\beta_i(x) = \beta(x)(1+\epsilon b_i(x))$
2.	$\gamma_i(x)$	Strain-specific clearance rates of single colonization	$\gamma_i(x) = \gamma(x)(1+\epsilon \nu_i(x))$
3.	$\gamma_{ij}(x)$	Clearance rates of co-colonization with i and j	$\gamma_{ij}(x) = \gamma(x)(1+\epsilon u_{ij}(x))$
4.	$p_{ij}^s(x)$	Transmission capacity of the strain $s \in \{i,j\}$ by a host co-colonized by strain-i then strain-j, $\left(p_{ij}^i(x) + p_{ij}^j(x) = 1\right)$	$p_{ij}^s(x) = \dfrac{1}{2} + \epsilon \omega_{ij}^s(x)$
5.	$k_{ij}(x)$	Relative factor of altered susceptibility to co-colonization between colonizing strain i and co-colonizing strain j	$k_{ij}(x) = k(x) + \epsilon \alpha_{ij}(x)$
	$r(x)$	Susceptible recruitment rate (Equal to natural mortality)	

Assumption 1. We assume the regularity for the intial values and parameters as follows.

- Initial values $S(x,0)$, $I_i(x,0)$, and $I_{ij}(x,0)$ are smooth enough in $x \in \Omega$, for $1 \le i,j \le N$.
- All the parameters in (2.1), which are included in Table 1, are all smooth enough in $x \in \Omega$.

It is classical that this systems conserved the positive quadrant and then we consider only positive solutions.

For the sake of simplicity, we denote the inverse duration of a carriage episode by strain i with $m_i = r + \gamma_i$, of a co-carriage episode by strains i and j with $m_{ij} = r + \gamma_{ij}$ and the corresponding inverse duration of carriage if all strains were equivalent with $m = r + \gamma$.

In this paper, we use the notation ∇u and Δu when $u(x,\cdot) = \begin{pmatrix} u_1(x,\cdot) & u_2(x,\cdot) & \dots & u_k(x,\cdot) \end{pmatrix}$, for $k \in \mathbb{N}$, with the meaning

$$\nabla u = \begin{pmatrix} \nabla u_1 & \nabla u_2 & \dots & \nabla u_k \end{pmatrix}, \qquad \text{and} \quad \Delta u = \begin{pmatrix} \Delta u_1 & \Delta u_2 & \dots & \Delta u_k \end{pmatrix}.$$

Such a very general pattern of considered system forms $\dfrac{\partial X}{\partial t} = \tilde{F}(X,x,\epsilon) + \epsilon \Delta X$ with Neumann boundary condition, where $X = (X_1, X_2, \dots, X_n) \in \mathbb{R}^n$ and is equivalent to $\dfrac{\partial X}{\partial t} = F(X,x) + O(\epsilon) + \epsilon \Delta X$ after some algebraic transformations. The part $\dfrac{dX}{dt} = F(X,x) + \epsilon \Delta X$ is called as the *semi-neutral system*, consistently stays unaltered and be investigated in the subsection 3.1. It is important to note that this system is structurally unstable. Then, the part $O(\epsilon)$ is a slow perturbation of the neutral system. To treat such an emergence by a

Tikhonov-liked theorem, it's essential to rewrite $\dfrac{\partial X}{\partial t} = F(X,x) + O(\epsilon) + \epsilon\Delta X$ into equivalent slow-fast form

$$\begin{cases} \dfrac{dU}{dt} = & f(U,V,x) + O(\epsilon) + \epsilon\Delta U \\ \dfrac{dV}{dt} = \epsilon & (g(U,V,x) + O(\epsilon) + \Delta V) \\ \dfrac{\partial U}{\partial n} = & \dfrac{\partial V}{\partial n} = 0, \quad \text{on} \quad \partial\Omega \end{cases} \tag{2.2}$$

where $U \in \mathbb{R}^N$ is the slow variable and $V \in \mathbb{R}^N$ is the fast variable. This step is achieved thanks to the ansatz (3.2) will be yielded from the study of the semi-neutral system.
This subsection makes a change of variables then allows to rewrite the system in an equivalent structure explicitly dependent on ϵ. Then, we study the important *semi-neutral system* which is obtained for $\epsilon = 0$ **except in diffusion terms**. The study on the semi-neutral system leads to the definition of the appropriate slow and fast variables (z_i, v_i). These variables together with the ansatz (3.2) are the key for the slow-fast study of the next section.

• **Initially,** sum up all the equations of (2.1), we have that

$$\begin{cases} \dfrac{\partial}{\partial t}\left(S + \sum_{i=1}^N I_i + \sum_{i,j=1}^N I_{ij}\right) = r(1-S) - r\left(\sum_{i=1}^N I_i + \sum_{i,j=1}^N I_{ij}\right) + \epsilon\Delta\left(S + \sum_{i=1}^N I_i + \sum_{i,j=1}^N I_{ij}\right) \\ \partial_n\left(S + \sum_{i=1}^N I_i + \sum_{i,j=1}^N I_{ij}\right) = 0 \qquad \text{on} \quad \Gamma. \end{cases}$$

Denoting

$$T = \sum_{i=1}^N I_i + \sum_{i,j=1}^N I_{ij}, \tag{2.3}$$

we have the following equation

$$\frac{\partial}{\partial t}(S+T) = r[1-(S+T)] + \epsilon\Delta(S+T).$$

with the Neumann boundary condition. The assumed smoothness of $\partial\Omega$ implies that $\epsilon\Delta$ generates a C^0 semi group of contraction on $C^0\left(\bar{\Omega}\right)$, see [5].
Note that $S+T=1$ are the solution of $r[1-(S+T)] + \epsilon\Delta(S+T) = 0$ and the linearized operator becomes $\epsilon\Delta - r$ which has spectrum lies in the left-half plane (since the Laplacian has the negative spectrum and $r(x) > 0$). By the Theorem 11.20 in [29], we deduce that $S+T=1$ is asymptotically stable, which implies that $S + \sum_{i=1}^N I_i + \sum_{i,j=1}^N I_{ij} \to 1$ as $t \to \infty$ asymptotically for all x. Therefore, we can assume that $S + \sum_{i=1}^N I_i + \sum_{i,j=1}^N I_{ij} = 1$ in this article.

From this convention, we deduce that, (2.1) has unique solution for every $\epsilon > 0$. Indeed, (2.1) can be rewritten in the form of

$$\frac{\partial}{\partial t}u(x,t) = F(u(x,t), x, \epsilon) + \epsilon\Delta u(x,t), \qquad x \in \Omega \tag{2.4}$$

with $u = \begin{pmatrix} S & I_1 & \dots & I_N & I_{11} & \dots & I_{NN} \end{pmatrix}^T$. We state the following result on the unique existence of solution of (2.4). The proof is given in Appendix A.1.

Theorem 2. *Given compact domain $\Omega \in \mathbb{R}^{\mathrm{d}}$ and $u : \Omega \times [0,+\infty) \to \mathbb{R}^n$, $(x,t) \mapsto u(x,t)$. Assume that $F : \mathbb{R}^n \times \Omega \times \mathbb{R}^+$ is continuous in $x \in \Omega$ and $F : \mathbb{R}^n \times \Omega \times \mathbb{R}^+ \to \mathbb{R}^n$ is a Lipschitz map in $u \in \mathbb{R}^n$, i.e. there is a constant L such that*

$$\|Fu - Fv\| \le L\|u - v\|, \qquad \forall u, v \in \mathbb{R}^n, \quad \forall x \in \Omega.$$

Then (2.4) admits a solution in $C^2(\Omega \times \cdot, \mathbb{R}^n) \cap C^1(\cdot \times [0,\infty), \mathbb{R}^n)$, and this solution is unique.

For the sake of clarify later, we now make conventions for the norms used in this article.

Definition 3. Let $v : \Omega \times \mathbb{R}^+ \to \mathbb{R}^n$ and $v \in L^2(\Omega)$ for each $t \ge 0$, we define.

- The norm $|\cdot|_1$ for $v(x,t) \in \mathbb{R}^n$ for each $x \in \Omega$ and $t \in \mathbb{R}^+$:

$$|v(x,t)|_1 := \sum_{i=1}^{n} |v_i(x,t)| \tag{2.5}$$

with $v(x,t) = \begin{pmatrix} v_1(x,t) & v_2(x,t) & \dots & v_n(x,t) \end{pmatrix}$.

- The norm $|\cdot|_2$ for $v(x,t) \in \mathbb{R}^n$ for each $x \in \Omega$ and $t \in \mathbb{R}^+$:

$$|v(x,t)|_2 := \left(\sum_{i=1}^{n} |v_i(x,t)|^2 \right)^{1/2} \tag{2.6}$$

with $v(x,t) = \begin{pmatrix} v_1(x,t) & v_2(x,t) & \dots & v_n(x,t) \end{pmatrix}$.
However, for the sake of simplicity, we only write $|\cdot|$ instead of $|\cdot|_2$.

- The norm for $v(\cdot,t) \in L^2(\Omega)$ for each $t \in \mathbb{R}^n$:

$$\|v(\cdot,t)\|_2 := \left(\int_\Omega |v(x,t)|^2 dx \right)^{1/2}. \tag{2.7}$$

Note that in (2.4), $u(x,t) \in \mathbb{R}^{N^2+N+1}$ and in this finite-dimensional space, the norms $|\cdot|$ and $|\cdot|_1$ are equivalent, we recall our previous convention $S + \sum_{i=1}^N I_i + \sum_{i,j=1}^N I_{ij} = 1$. Then, thanks to the positivity of the solutions, $|u(\cdot,t)|_1 = S + \sum_{i=1}^N I_i + \sum_{i,j=1}^N I_{ij} = 1$ and satisfies the Theorem 2. Hence, the system (2.1) always has unique solution.

• **Secondly,** for the sake of simplicity, we denote $m_i = r + \gamma_i$, $m_{ij} = r + \gamma_{ij}$ and $m = r + \gamma$. Then, we define total mass of single infected I, the total mass of double infected D and and the total mass of infected T, as in [17], which reads

$$I = \sum_{i=1}^{N} I_i, \quad D = \sum_{i=1}^{N} I_{ij}, \quad T = I + D. \tag{2.8}$$

(2.8) yields $\sum_{i=1}^N J_i = T$. For later computations, remark that $\sum_{i=1}^N \beta_i J_i = \beta T + \epsilon \sum_{i=1}^N b_i J_i$. Thanked to the new variables, the systems for (S,T), (I_i,J_i) and $(I_{ij})_{1\le i,j\le N}$ reads

$$\begin{cases}
\dfrac{\partial S}{\partial t} &= r(1-S) + \gamma T + \epsilon\gamma \left(\displaystyle\sum_{i=1}^{N} \nu_i I_i + \sum_{i,j=1}^{N} u_{ij} I_{ij} \right) - \beta S T - \epsilon \beta S \sum_{i=1}^{N} b_i J_i + \epsilon \Delta S \\
\dfrac{\partial T}{\partial t} &= \beta S T - mT + \epsilon \beta S \displaystyle\sum_{i=1}^{N} b_i J_i - \epsilon\gamma \left(\sum_{i=1}^{N} \nu_i I_i + \sum_{i,j=1}^{N} u_{ij} I_{ij} \right) + \epsilon \Delta T \\
\dfrac{\partial I_i}{\partial t} &= \beta (1+\epsilon b_i) J_i S - (m + \epsilon\gamma\nu_i) I_i - \beta I_i \displaystyle\sum_{j=1}^{N} (k + \epsilon\alpha_{ij})(1+\epsilon b_j) J_j + \epsilon \Delta I_i \\
\dfrac{\partial J_i}{\partial t} &= \beta (1+\epsilon b_i) J_i S - \beta I_i \displaystyle\sum_{j=1}^{N} (k+\epsilon\alpha_{ij})(1+\epsilon b_j) J_j - \epsilon\gamma \left[\nu_i I_i + \sum_{j=1}^{N} \left(\left(\frac{1}{2} + \epsilon\omega_{ij}^i \right) u_{ij} I_{ij} + \left(\frac{1}{2} + \epsilon\omega_{ji}^i \right) \nu_{ji} I_{ji} \right) \right] \\
&\quad - mJ_i + \beta \displaystyle\sum_{j=1}^{N} \left(\left(\frac{1}{2} + \omega_{ij}^i \right) (k+\epsilon\alpha_{ij})(1+\epsilon b_j) I_i J_j + \left(\frac{1}{2} + \epsilon\omega_{ji}^i \right) (k+\epsilon\alpha_{ji})(1+\epsilon b_i) I_j J_i \right) + \epsilon \Delta J_i \\
\dfrac{\partial I_{ij}}{\partial t} &= \beta (k+\epsilon\alpha_{ij})(1+\epsilon b_j) I_i J_j - (m + \epsilon\gamma u_{ij}) I_{ij} + \epsilon \Delta I_{ij}, \qquad 1 \le i,j \le N.
\end{cases} \tag{2.9}$$

2.2 The semi-neutral system

Take $\epsilon = 0$ in (2.9) except the diffusion rates, we obtain the *semi-neutral system*[1] for (S, T, I, I_i, J_i), which reads

$$\begin{cases} \dfrac{\partial S}{\partial t} &= m(1-S) - \beta ST &+\epsilon \Delta S \\ \dfrac{\partial T}{\partial t} &= \beta ST - mT &+\epsilon \Delta T \\ \dfrac{\partial I}{\partial t} &= \beta TS - (m + \beta kT) I &+\epsilon \Delta I, \\ \dfrac{\partial I_i}{\partial t} &= \beta J_i S - mI_i - \beta k I_i T &+\epsilon \Delta I_i, \quad 1 \le i \le N \\ \dfrac{\partial J_i}{\partial t} &= (\beta S - m) J_i - \beta k I_i T + \dfrac{\beta k}{2}(I_i T + J_i I) &+\epsilon \Delta J_i, \quad 1 \le i \le N \\ \dfrac{\partial I_{ij}}{\partial t} &= \beta k I_i J_j - mI_{ij} &+\epsilon \Delta I_{ij} \end{cases} \tag{2.10}$$

with the Neumann boundary condition and the initial condition

$$\begin{cases} \dfrac{\partial S}{\partial n} = \dfrac{\partial T}{\partial n} = \dfrac{\partial I_i}{\partial n} = \dfrac{\partial I_{ij}}{\partial n} = 0 \quad \text{on} \quad \partial\Omega \\ S(x,0) = S_0(x), \quad T(x,0) = T_0(x), \quad I(x,0) = I_{i,0}(x), \quad I_{ij}(x,0) = I_{ij,0}(x). \end{cases}$$

• **Firstly,** we consider the semi-neutral equation for (S, T), that reads

$$\begin{cases} \dfrac{\partial S}{\partial t} &= m(1-S) - \beta ST + \epsilon \Delta S \\ \dfrac{\partial T}{\partial t} &= -mT + \beta ST + \epsilon \Delta T. \\ S(x,0) &= S_0(x), \quad T(x,0) = T_0(x), \\ \dfrac{\partial S}{\partial n}|_{\partial\Omega} &= \dfrac{\partial T}{\partial n}|_{\partial\Omega} = 0. \end{cases} \tag{2.11}$$

By the Theorem 2 that (2.11) has the unique solution.

Before analyzing, similar to [3], we say that x is a low-risk site if the local disease transmission rate $\beta(x)$ is lower than the local disease recovery rate (which is the sum of clearance rate and mortality rate) $m(x)$. A high-risk site is defined in a similar manner. Let

$$H^- = \{x \in \Omega : \beta(x) < m(x)\} \quad \text{and} \quad H^+ = \{x \in \Omega : \beta(x) > m(x)\} \tag{2.12}$$

denote the set of these low- and high-risk sites, respectively. Accordingly, the term $R_0(x)$ is the local reproduction number at $x \in \Omega$. Then $R_0(x) < 1$ for low-risk sites $x \in H^-$ and $R_0(x) > 1$ for high-risk sites $x \in H^+$. It is well-known that without movement, the disease can persist at high-risk sites but not at low-risk sites. We say that, a domain Ω' is a low-risk domain if $\int_{\Omega'} \beta < \int_{\Omega'} m$ and a high-risk domain if $\int_{\Omega'} \beta > \int_{\Omega'} m$.

In this case of slow diffusion, i.e. in sections 2 and 3, we make an assume that

Assumption 4. The domain Ω is high-risk everywhere, i.e. $\beta(x) > m(x)$ for all $x \in \Omega$.

Denoting $S^*(x) = \dfrac{m(x)}{\beta(x)} = \dfrac{1}{R_0(x)}$ and $T^*(x) = 1 - S^*(x)$, then $0 \le S^*, T^* \le 1$ for all $x \in \Omega$, which is well-defined. At each $x \in \Omega$, consider the differential equations of variables $\left(\tilde{S}(\cdot,t), \tilde{T}(\cdot,t)\right)$

$$\begin{cases} \dfrac{d\tilde{S}}{dt} = m(x)\left(1 - \tilde{S}\right) - \beta(x)\tilde{S}\tilde{T} \\ \dfrac{d\tilde{T}}{dt} = -m(x)\tilde{T} + \beta(x)\tilde{S}\tilde{T} \end{cases}, \tag{2.13}$$

with initial condition $\left(\tilde{S}(0), \tilde{T}(0)\right) = (S(x,0), T(x,0))$. It is claimed that $\left(\tilde{S}(x,t), \tilde{T}(x,t)\right) \to (S^*(x), T^*(x))$ for each $x \in \Omega$ and $t \to \infty$, see [17].

[1] The name *semi-neutral system* comes from the fact that if $\epsilon = 0$, except the coefficients of diffusion terms, then the parameters do not depend on the strains as in the neutral theory.

Furthermore, noting that $\left|\tilde{S}(x,t)-S^*(x)\right|^2 \leq 2$ for all $(x,t)\in\Omega\times\mathbb{R}^+$ and Ω is compact, by Dominated Convergence Theorem, for all sequence $(t_n)_n$ satisfying $t_0<t_1<\cdots<t_n<\ldots$, $t_n\to+\infty$, we obtain that $\left\|\tilde{S}(x,t)-S^*(x)\right\|_2\to 0$ as $t\to\infty$.

Another important point is that, for any $t\in\mathbb{R}^+$, $\tilde{S}(x,t)$ is smooth enough with respect to x. Indeed, we have the differential equation for $\tilde{S}(x)-\tilde{S}(x')$ as follows

$$\frac{d}{dt}\left(\tilde{S}(x)-\tilde{S}(x')\right)=\left(\tilde{S}(x)-\tilde{S}(x')\right)\left[-(m+\beta)+\beta\left(\tilde{S}(x)+\tilde{S}(x')\right)\right].$$

Noting that $\tilde{S}(x)+\tilde{S}(x')\leq 2$ for all $t\in\mathbb{R}^+$ and $x,x'\in\Omega$, applying the Gronwall's inequality, we deduce that $\frac{|\tilde{S}(x)-\tilde{S}(x')|}{|x-x'|}$ can be controlled at each t, since $\tilde{S}(0)$ is smooth enough with respect to x.

Analogously, we observe $x\mapsto\tilde{T}(x,t)$ is smooth enough as well.

Alternatively, we have that

$$\frac{\partial}{\partial t}\left(S-\tilde{S}\right)=\left[\mathcal{F}(S)-\mathcal{F}\left(\tilde{S}\right)\right]+\epsilon\Delta S,\qquad\text{with}\quad\mathcal{F}(X)=\mathcal{F}(X,\cdot)=m(\cdot)(1-X(\cdot))-\beta(\cdot)X(\cdot)(1-X(\cdot))$$

then $\mathcal{F}(X)$ is Lipschitz continuous with coefficient $C>0$. We have the following transformations

$$\begin{aligned}&\left(S-\tilde{S}\right)\frac{\partial}{\partial t}\left(S-\tilde{S}\right)=\left(S-\tilde{S}\right)\left[\mathcal{F}(S)-\mathcal{F}\left(\tilde{S}\right)\right]+\epsilon\left(S-\tilde{S}\right)\Delta S\\ \Longrightarrow&\frac{1}{2}\frac{\partial}{\partial t}\left|S-\tilde{S}\right|^2\leq C\left|S-\tilde{S}\right|^2+\epsilon\left(S-\tilde{S}\right)\Delta\left(S-\tilde{S}\right)+\epsilon\left(S-\tilde{S}\right)\Delta\tilde{S}\\ \Longrightarrow&\frac{1}{2}\frac{\partial}{\partial t}\int_\Omega\left|S-\tilde{S}\right|^2\leq C\int_\Omega\left|S-\tilde{S}\right|^2+\epsilon\int_\Omega\left(S-\tilde{S}\right)\Delta\tilde{S}\end{aligned}$$

By the definition of $\tilde{S}$ and $\max\left|S-\tilde{S}\right|\leq 2$ then by the Gronwall's inequality we have that

$$\left\|S-\tilde{S}\right\|_2=O\left(\sqrt{\epsilon}\right),\qquad\text{since}\quad S(\cdot,0)=S^*(\cdot,0),$$

which leads to $\|S-S^*\|_2\to O\left(\sqrt{\epsilon}\right)$ as $t\to\infty$ since Ω is compact.

Recalling that $S+T=1$ then $\|T-T^*\|_2\to O\left(\sqrt{\epsilon}\right)$ when $t\to\infty$.

• **Secondly,** we consider the semi-neutral equation for $I(x,t)$ which reads

$$\begin{cases}\dfrac{\partial I}{\partial t}=\beta TS-(m+\beta kT)I+\epsilon\Delta I\\ \dfrac{\partial I}{\partial n}|_{\partial\Omega}=0\end{cases}$$

Similarly to the previous proof for the stability of $(S(x,t),T(x,t))$, we consider the equation for $\tilde{I}(\cdot,t)$ at each $x\in\Omega$

$$\frac{\partial\tilde{I}}{\partial t}=\beta T^*S^*-(m+\beta kT^*)\tilde{I},\qquad\tilde{I}(\cdot,0)=I(x,0),$$

which implies $\tilde{I}(x,t)\to I^*(x):=\dfrac{mT^*}{m+\beta kT^*}$ at each $x\in\Omega$ as $t\to\infty$, as proved in [17].

By the same arguments for $\left\|\tilde{S}(x,t)-S^*(x)\right\|_2\to 0$ as $t\to\infty$ previously, we also obtain that $\left\|\tilde{I}(x,t)-I^*(x)\right\|_2\to 0$ as $t\to\infty$.

Similarly to the proof of the smoothness of $x\mapsto\tilde{S}(x,t)$, we can prove that $x\mapsto\tilde{I}(x,t)$ is smooth enough as well, for all $t\in\mathbb{R}^+$.

Accordingly, we deduce the equation

$$\frac{\partial}{\partial t}\left(I-\tilde{I}\right)=\left[\mathcal{G}(I)-\mathcal{G}\left(\tilde{I}\right)\right]+\varphi(S,T,S^*,T^*)+\epsilon\Delta I,$$

where $\mathcal{G}(X)=\beta T^*S^*-(m+\beta kT^*)X$ and

$$\varphi(S,T,S^*,T^*)=\beta\left[(T-T^*)S^*+(S-S^*)T^*+(T-T^*)(S-S^*)\right]$$

which means $\mathcal{G}$ is Lipschitz continuous and $\|\varphi\|_2=O\left(\sqrt{\epsilon}\right)$. We make the similar process as before, then combining the Holder's inequality, we deduce that

$$\frac{1}{2}\frac{\partial}{\partial t}\int_\Omega\left|I-\tilde{I}\right|^2\leq(C+\epsilon)\int_\Omega\left|I-\tilde{I}\right|^2+\epsilon\int_\Omega\left(I-\tilde{I}\right)\Delta\tilde{I}$$

which implies $\left\|I-\tilde{I}\right\|_2 = O(\sqrt{\epsilon})$ by applying the Gronwall's inequality with noting that $I(\cdot,0) = \tilde{I}(\cdot,0)$. Thus, we have that $\|I-I^*\|_2 \to O(\sqrt{\epsilon})$ as $t\to\infty$.

For later reference, we also write

$$\boxed{S^* = \frac{m}{\beta},\quad T^* = 1-\frac{m}{\beta},\quad I^* = \frac{mT^*}{m+\beta kT^*},\quad D^* = T^*-I^* = \frac{\beta kT^{*2}}{m+\beta kT^*}.} \tag{2.14}$$

Hence, for (S,T,I) satisfying the semi-neutral system (2.10), we have that

$$\|S-S^*\|_2 \to O\left(\sqrt{\epsilon}\right),\qquad \|T-T^*\|_2 \to O\left(\sqrt{\epsilon}\right),\qquad \|I-I^*\|_2 \to O\left(\sqrt{\epsilon}\right). \tag{2.15}$$

when $t\to\infty$.

• **Thirdly,** the N^2 equations for I_{ij} in (2.10) yields that, for $1\le i\le N$,

$$\frac{\partial I_{ij}}{\partial t} = \beta k I_i J_j - mI_{ij} + \epsilon\Delta I_{ij}. \tag{2.16}$$

Whose dynamics is trivial once I_i and J_i are known. Indeed, assume that for each i, there exists $\left(\tilde{I}_i(x,t), \tilde{J}_i(x,t)\right)$ such that $\left\|I_i-\tilde{I}_i\right\|_2 = O(\sqrt{\epsilon})$ and $\left\|J_i-\tilde{J}_i\right\|_2 = O(\sqrt{\epsilon})$, then we can rewrite (2.16) into

$$\frac{\partial I_{ij}}{\partial t} = -mI_{ij} + \beta k\tilde{I}_i\tilde{J}_j + \beta k\left[\left(I_i-\tilde{I}_i\right)\tilde{J}_j + \left(J_j-\tilde{J}_j\right)\tilde{I}_i + \left(I_i-\tilde{I}_i\right)\left(J_j-\tilde{J}_j\right)\right] + \epsilon\Delta I_{ij}.$$

At each $x\in\Omega$, we consider the equation of $\tilde{I}_{ij}(\cdot,t)$

$$\frac{\partial \tilde{I}_{ij}}{\partial t} = -m\tilde{I}_{ij} + \beta k\tilde{I}_i\tilde{J}_j,\qquad \tilde{I}_{ij}(\cdot,0) = I_{ij}(x,0)$$

Once again, by the same argument for the smoothness of $x\mapsto \tilde{S}(x,t)$, we obtain that $x\mapsto \tilde{I}_{ij}(x,t)$, for all $1\le i,j\le N$.

Then we can obtain the differential equation for $\left(I_{ij}-\tilde{I}_{ij}\right)$

$$\frac{\partial}{\partial t}\left(I_{ij}-\tilde{I}_{ij}\right) = -m\left(I_{ij}-\tilde{I}_{ij}\right) + \beta k\left[\left(I_i-\tilde{I}_i\right)\tilde{J}_j + \left(J_j-\tilde{J}_j\right)\tilde{I}_i + \left(I_i-\tilde{I}_i\right)\left(J_j-\tilde{J}_j\right)\right] + \epsilon\Delta\left(I_{ij}-\tilde{I}_{ij}\right) + \epsilon\Delta\tilde{I}_{ij}.$$

Denoting

$$\phi(x,t) = \beta k\left[\left(I_i-\tilde{I}_i\right)\tilde{J}_j + \left(J_j-\tilde{J}_j\right)\tilde{I}_i + \left(I_i-\tilde{I}_i\right)\left(J_j-\tilde{J}_j\right) + \epsilon\Delta\tilde{I}_{ij}\right]$$

then $\|\phi\|_2 = O(\sqrt{\epsilon})$. By the same process as previous, we have that

$$\frac{1}{2}\frac{\partial}{\partial t}\int_\Omega \left|I_{ij}-\tilde{I}_{ij}\right|^2 = -m\int_\Omega \left|I_{ij}-\tilde{I}_{ij}\right|^2 + \int_\Omega \phi(x,t)\left(I_{ij}-\tilde{I}_{ij}\right) - \epsilon\int_\Omega \left|\nabla\left(I_{ij}-\tilde{I}_{ij}\right)\right|^2.$$

Using the Holder's inequality for the term $\int_\Omega \phi(x,t)\left(I_{ij}-\tilde{I}_{ij}\right)$ then applying the Gronwall's inequality again, note that $I_{ij}(\cdot,0) = \tilde{I}_{ij}(\cdot,0)$, we have that $\left\|I_{ij}-\tilde{I}_{ij}\right\|_2 \to O(\sqrt{\epsilon})$ as $t\to\infty$, for all $1\le i,j\le N$.

2.3 The slow-fast form and approximations theorems

Next, we consider the semi-neutral system for $\begin{pmatrix} I_i \\ J_i\end{pmatrix}$ for all $1\le i\le N$

$$\begin{cases} \dfrac{\partial I_i}{\partial t} = \beta J_i S - mI_i - \beta kI_iT & +\epsilon\Delta I_i \\ \dfrac{\partial J_i}{\partial t} = (\beta S-m)J_i - \beta kI_iT + \dfrac{\beta k}{2}(I_iT+J_iI) & +\epsilon\Delta J_i \end{cases}. \tag{2.17}$$

Denoting $D^* = T^*-I^*$, we set

$$A(x) = \begin{pmatrix} -(m+\beta kT^*) & m \\ -\dfrac{\beta kT^*}{2} & \dfrac{\beta kI^*}{2}\end{pmatrix},$$

and

$$P = \begin{pmatrix} 2T^* & I^* \\ D^* & T^* \end{pmatrix}, \qquad P^{-1} = \frac{1}{|P|} \begin{pmatrix} T^* & -I^* \\ -D^* & 2T^* \end{pmatrix}. \tag{2.18}$$

We have

$$A(x) = P(x) \begin{pmatrix} -\xi(x) & 0 \\ 0 & 0 \end{pmatrix} P^{-1}(x)$$

where $\xi = m + \beta k T^* - \frac{1}{2}\beta k I^* > 0$ and $|P(x)| = 2T^{*2} - I^* D^* > 0$.

In the equations for (I_i, J_i) in (2.17), we substitute (S, T, I) by (S^*, T^*, I^*) and note that

$$\|S - S^*\|_2 = O\left(\sqrt{\epsilon}\right), \quad \|T - T^*\|_2 = O\left(\sqrt{\epsilon}\right), \quad \|I - I^*\|_2 = O\left(\sqrt{\epsilon}\right).$$

Now, we have the semi-neutral system of equations for $(I_i, J_i)_{1 \le i \le N}$, in the sense of norm $\|\cdot\|_2$ of $L^2(\Omega)$:

$$\frac{\partial}{\partial t} \begin{pmatrix} I_i \\ J_i \end{pmatrix} = A(x) \begin{pmatrix} I_i \\ J_i \end{pmatrix} + O\left(\sqrt{\epsilon}\right) \begin{pmatrix} I_i \\ J_i \end{pmatrix} + \epsilon \begin{pmatrix} \Delta I_i \\ \Delta J_i \end{pmatrix}. \tag{2.19}$$

Applying Theorem 6, we have that

$$\left\| I_i - \tilde{I}_i \right\|_2 = O\left(\sqrt{\epsilon}\right), \qquad \left\| J_i - \tilde{J}_i \right\|_2 = O\left(\sqrt{\epsilon}\right), \tag{2.20}$$

where $(I_i, J_i)_{1 \le i \le N}$ are solutions of the semi-neutral system (2.17) and $\left(\tilde{I}_i, \tilde{J}_i\right)_{1 \le i \le N}$ are solutions of

$$\frac{\partial}{\partial t} \begin{pmatrix} I_i \\ J_i \end{pmatrix} = A(x) \begin{pmatrix} I_i \\ J_i \end{pmatrix} + \epsilon \begin{pmatrix} \Delta I_i \\ \Delta J_i \end{pmatrix} \tag{2.21}$$

Hence, it suffices to consider the system (2.21). For every $1 \le i \le N$, set

$$\begin{pmatrix} v_i \\ z_i \end{pmatrix} = P^{-1} \begin{pmatrix} I_i \\ J_i \end{pmatrix} \tag{2.22}$$

From (2.21) we infer an equation for $\begin{pmatrix} z_i \\ v_i \end{pmatrix}$ for each $1 \le i \le N$:

$$\frac{\partial}{\partial t} \begin{pmatrix} v_i \\ z_i \end{pmatrix} = \begin{pmatrix} -\xi(x) & 0 \\ 0 & 0 \end{pmatrix} \begin{pmatrix} v_i \\ z_i \end{pmatrix} + \epsilon \left[P^{-1}(x) \begin{pmatrix} \Delta & 0 \\ 0 & \Delta \end{pmatrix} P(x) \right] \begin{pmatrix} v_i \\ z_i \end{pmatrix} \tag{2.23}$$

This step of changing to (z_i, v_i) plays an important role. Since under these new variables, we can rewrite into the slow-fast form. It allows us to apply the approximation theorem introduced in the next subsection.

When $v_i = 0$ - which will be asymptotically true - then z_i is exactly $\frac{I_i}{I^*} = \frac{J_i}{T^*}$ the prevalence of strain i in the total of infected, see the proof in [19].

$$\begin{cases} \dfrac{\partial v_i}{\partial t} &= -\xi v_i + O(\epsilon) + \epsilon \Delta v_i \quad + \epsilon \dfrac{1}{|P|} \left[\left(2T^* \nabla T^* - I^* \nabla D^* \right) \nabla v_i + \left(T^* \nabla I^* - I^* \nabla T^* \right) \nabla z_i \right] \\ \dfrac{\partial z_i}{\partial t} &= O(\epsilon) + \epsilon \Delta z_i \qquad\qquad + \epsilon \dfrac{1}{|P|} \left[\left(-D^* \nabla T^* + 2T^* \nabla D^* \right) \nabla v_i + \left(-D^* \nabla I^* + 2T^* \nabla T^* \right) \nabla z_i \right] \end{cases}. \tag{2.24}$$

Next, by setting $\tau = \epsilon t$, (2.24) can be read as the slow time scale

$$\begin{cases} \epsilon \dfrac{\partial v_i}{\partial \tau} &= -\xi v_i + O(\epsilon) + \epsilon \dfrac{1}{|P|} \left[\left(2T^* \nabla T^* - I^* \nabla D^* \right) \nabla v_i + \left(T^* \nabla I^* - I^* \nabla T^* \right) \nabla z_i \right] + \epsilon \Delta v_i \\ \dfrac{\partial z_i}{\partial \tau} &= O(1) + \dfrac{1}{|P|} \left[\left(-D^* \nabla T^* + 2T^* \nabla D^* \right) \nabla v_i + \left(-D^* \nabla I^* + 2T^* \nabla T^* \right) \nabla z_i \right] + \Delta z_i. \end{cases} \tag{2.25}$$

We need to compute explicitly the perturbation $O(1)$ in (2.24). This computation is quite complex especially when involving perturbation in each parameters, so its worthwhile of dividing this progress into five sub single cases wherein only one perturbation at the time occurs.

After that, we will treat the slow-fast form by a Tikhonov-like theorem, that is presented in the Theorem

5. This result is for the parameter-dependent reaction-diffusion system with Neumann boundary condition as following,

$$\begin{cases} \dfrac{\partial}{\partial t}f(x,t) = F\left(f(x,t),g(x,t),x,t\right) & + K_f f(x,t) \\ \epsilon\dfrac{\partial}{\partial t}g(x,t) = G\left(f(x,t),g(x,t),x,t\right) + \epsilon G_1(x)\cdot\nabla f\left(x,t\right) & + \epsilon K_g g(x,t) \\ \dfrac{\partial}{\partial n}f\left(x,t\right) = \dfrac{\partial}{\partial n}g\left(x,t\right) = 0, \qquad x\in\partial\Omega, \\ f\left(x,0\right) = f^0\left(x\right), \quad g\left(x,0\right) = g^0\left(x\right) \end{cases} \tag{2.26}$$

in which,

- $f:\Omega\times\mathbb{R}\to\mathbb{R}^n$ and $g:\Omega\times\mathbb{R}\to\mathbb{R}^m$,
- $G_1:\Omega\to\mathbb{R}^m$ is continuously differentiable and $\cdot$ denotes the scalar product,
- the operators K_f, K_g defined on $C^\infty\left(\Omega\times[0,t_1]\right)$ by $K_f u := a_f\left(x\right)\nabla u + \Delta u$, $K_g u := a_g\left(x\right)\nabla u + \Delta u$, in which $a_f\left(x\right)$ is an $n\times n$ diagonal matrix and $a_g\left(x\right)$ is an $m\times m$ diagonal matrix, in which entries of each matrix depends on $x\in\Omega$. We assume that $a_f\left(x\right)$ and $a_g\left(x\right)$ are differentially continuous in x.

Theorem 5. *Let $f_0(x,t):\Omega\times[t_0,t_1]\mapsto\mathbb{R}^n$, $g_0(x,t):\Omega\times[t_0,t_1]\mapsto\mathbb{R}^m$ be continuous functions satisfying equations*

$$\begin{cases} \dfrac{\partial}{\partial t}f(x,t) &= F\left(f(x,t),g(x,t),x,t\right) + K_f f(x,t) \\ 0 &= G\left(f(x,t),g(x,t),x,t\right) \\ \dfrac{\partial}{\partial n}f(x,t) &= \dfrac{\partial}{\partial n}g\left(x,t\right) = 0, \qquad x\in\partial\Omega \end{cases} \tag{2.27}$$

where $F:\mathbb{R}^n\times\mathbb{R}^m\times\mathbb{R}\mapsto\mathbb{R}^n$ and $G:\mathbb{R}^n\times\mathbb{R}^m\times\mathbb{R}\mapsto\mathbb{R}^m$ are continuous functions. We make an addition assumption that $g_0\in C^1\left(\Omega\times\mathbb{R}\right)$.

For any $(x,t)\in\Omega\times\mathbb{R}^+$ and $f\left(x,t\right)\in\mathbb{R}^n$, we denote $A\left(x,t\right)$ is the Jacobian matrix of $G\left(f\left(x,t\right),\cdot,x,t\right)$ with respect to the second variable.

Alternatively, we assume that F, G are continuously differentiable with respect to their first two arguments in a neighborhood of the trajectory $f_0(x,t)$, $g_0(x,t)$, and that $A\left(x,t\right)$ is a Hurwitz matrix, i.e. every eigenvalue of it has strictly negative real part, for all $t\in[t_0,t_1]$ and $x\in\Omega$.

Then there exists $\epsilon_0>0$ and $C>0$ such that inequalities

$$\begin{cases} \displaystyle\int_\Omega |f_0(x,t)-f(x,t)|^2dx \le C\epsilon, \qquad \forall t\in[t_0,t_1] \\ \displaystyle\int_\Omega |g_0(x,t)-g(x,t)|^2dx \le C\epsilon, \qquad \forall t\in[t_0,t_1] \end{cases} \tag{2.28}$$

for all solutions of (2.26) with $\int_\Omega |f_0(x,t_0)-f(x,t_0)|^2dx\le\epsilon$, $\int_\Omega |g_0(x,t_0)-g(x,t_0)|^2dx\le\epsilon$ and $\epsilon\in(0,\epsilon_0)$.

The conclusion of this theorem means that, for the initial values closed enough to $f_0\left(x,t_0\right)$ and $g_0\left(x,t_0\right)$ in the sense of $L^2\left(\Omega\right)$ norm, we have the approximation for the solution of (2.26). Explicitly, this can be rewritten as follows

$$\left\|f_0(x,t)-f(x,t)\right\|_2 = O\left(\sqrt{\epsilon}\right), \qquad \left\|g_0(x,t)-g(x,t)\right\|_2 = O\left(\sqrt{\epsilon}\right), \qquad \forall t\in[t_0,t_1]$$

for all solutions of (2.26) with $\left\|f_0(x,t_0)-f(x,t_0)\right\|_2 = O\left(\sqrt{\epsilon}\right)$, $\left\|g_0(x,t_0)-g(x,t_0)\right\|_2 = O\left(\sqrt{\epsilon}\right)$ and $\epsilon\in(0,\epsilon_0)$.

Next, we claim a result that allows us approximate the original system by the semi-neutral system. The following error estimate gives a more precise description of these limits.

Theorem 6. *Given $\Omega\in\mathbb{R}^n$ compact domain with smooth boundary. Let F and G be two continuously differentiable functions on $\Omega\times[0,\infty)$ and suppose that F is Lipschitz continuous. Assume there exists a bounded function u satisfies the reaction diffusion equation with Neumann boundary condition*

$$\begin{cases} \dfrac{\partial u}{\partial t} = F\left(u,x\right) + \epsilon G\left(u,x\right) + \epsilon\Delta u, \\ u\left(x,0\right) = u_0\left(x\right), \quad x\in\Omega, \\ \dfrac{\partial u}{\partial n}|_{\partial\Omega} = 0. \end{cases} \tag{2.29}$$

Then for every fixed $T>0$, $\forall t<T$, we have that $\int_\Omega |u(x,t)-v(x,t)|^2 dx = O(\epsilon)$, i.e. $\|u(x,t)-v(x,t)\|_2 = O(\sqrt{\epsilon})$, with $v(t)$ is the solution of the problem

$$\begin{cases} \dfrac{\partial v}{\partial t} = F(v) + \epsilon \Delta v, \\ v(x,0) = u_0(x), \quad x \in \Omega, \quad \forall x \in \Omega. \\ \dfrac{\partial v}{\partial n}|_{\partial\Omega} = 0. \end{cases} \tag{2.30}$$

3 Approximation theorems, derivations of original dynamics and main results for the case of slow diffusion

3.1 Lemmas and derivation of non-semi neutral dynamics

Next we develop a lemma showing allowing to linearly combine all the relevant simple cases directly into the slow equation. For this purpose, we use the following notations in system (2.1).

$$\begin{aligned} &\beta_i = \beta(1+\chi_1 \epsilon b_i); \qquad \gamma_i = \gamma(1+\chi_2 \epsilon \nu_i); \qquad \gamma_{ij} = \gamma(1+\chi_3 \epsilon u_{ij}); \\ &p_{ij}^s = \frac{1}{2} + \chi_4 \epsilon \omega_{ij}^s, \quad s \in \{i,j\}, \quad \left(\omega_{ij}^i + \omega_{ij}^j = 0\right); \qquad k_{ij} = k + \chi_5 \epsilon \alpha_{ij}, \end{aligned} \tag{3.1}$$

where $\chi_d \in \{0,1\}$ for $d = 1,2,3,4,5$.

Any combination of axes of trait variation among strains, can be captured via $\mathcal{A}$ where $\mathcal{A}$ is a subset of $\{1,2,3,4,5\}$, and for some fixed initial values given, denote $C_{\mathcal{A}}$ be the system (2.4) with $\chi_d = 1$ if $d \in \mathcal{A}$ and $\chi_d = 0$ if $d \notin \mathcal{A}$. For simplicity, we note also $C_{\{d\}}$ by C_d for $d \in \{1,2,3,4,5\}$ denote the absence/presence of perturbations in that parameter among strains.

Remark 7. If $\mathcal{A} = \emptyset$ then there is no trait perturbation and the system $C_\emptyset$ is exactly the *semi neutral* model (2.10).

In order to capture all the perturbations of order 1 in the equation of the z_i we need these additional changes of variables:

$$\boxed{S(x,t) = S^* - \epsilon X(x,t) + O\left(\epsilon^2\right); \quad T(x,t) = T^* + \epsilon X(x,t) + O(\epsilon^2); \quad I(x,t) = I^* + \epsilon Y(x,t) + O\left(\epsilon^2\right)} \tag{3.2}$$

where S^*, T^* and I^* are defined in (2.14), and for $i = 1, \cdots, N$:

$$L_i(x,t) = \frac{1}{2} \sum_{j=1}^N \left(u_{ij} I_{ij}(x,t) + u_{ji} I_{ji}(x,t)\right). \tag{3.3}$$

With these notations, $C_{\mathcal{A}}$ reads

$$\begin{cases} \dfrac{\partial X}{\partial t} &= -\beta T^* X + \chi_1 \beta S^* \sum_{i=1}^N b_i J_i - \chi_2 \gamma \sum_{i=1}^N \nu_i I_i - \chi_3 \gamma \sum_{i=1}^N L_i + \epsilon \Delta X + O(\epsilon) \\ \dfrac{\partial Y}{\partial t} &= \beta(S^* - T^* - kI^*)X - (m + \beta k T^*)Y + \chi_1 \beta (S^* - kI^*) \sum_{i=1}^N b_i J_i - \chi_2 \gamma \sum_{i=1}^N \nu_i I_i - \chi_5 \beta \sum_{i,j=1}^N \alpha_{ij} I_i J_j + \epsilon \Delta Y + O(\epsilon) \\ \dfrac{\partial L_i}{\partial t} &= -mL_i + \chi_3 \frac{1}{2} \beta \gamma k I_i \sum_{j=1}^N u_{ij} J_j + \chi_3 \frac{1}{2} \gamma \beta k J_i \sum_{j=1}^N \nu_{ji} I_j + \epsilon \Delta L_i + O(\epsilon) \end{cases} \tag{3.4}$$

together with

$$\begin{aligned} \frac{\partial}{\partial t}\begin{pmatrix} I_i \\ J_i \end{pmatrix} = &\begin{pmatrix} -(m+\beta k T^*) & m \\ -\frac{\beta k T^*}{2} & \frac{\beta k I^*}{2} \end{pmatrix}\begin{pmatrix} I_i \\ J_i \end{pmatrix} + \epsilon \begin{pmatrix} \Delta I_i \\ \Delta J_i \end{pmatrix} \\ &- \epsilon \left[\beta \begin{pmatrix} k & 1 \\ \frac{k}{2} & 1 \end{pmatrix}\begin{pmatrix} I_i \\ J_i \end{pmatrix} X + \frac{\beta k}{2}\begin{pmatrix} 0 & 0 \\ 0 & 1 \end{pmatrix}\begin{pmatrix} I_i \\ J_i \end{pmatrix} Y + \mathcal{M}_{\mathcal{A}}\begin{pmatrix} I_i \\ J_i \end{pmatrix} - \chi_3 \gamma \begin{pmatrix} 0 \\ L_i \end{pmatrix}\right] \end{aligned} \tag{3.5}$$

where $\mathcal{M}_{\mathcal{A}}$ is the matrix

$$\begin{pmatrix} -\chi_1 \beta k \sum_{i=1}^N b_i J_i - \chi_2 \gamma \nu_i - \chi_5 \beta \sum_{j=1}^N \alpha_{ij} J_j & \chi_1 \beta b_i S^* \\ \beta \sum_{j=1}^N \left(\chi_4 k \omega_{ij}^i - \chi_5 \frac{\alpha_{ij}}{2}\right) J_j - \chi_1 \frac{\beta k}{2} \sum_{i=1}^N b_i J_i - \chi_2 \gamma \nu_i & \chi_1 \beta b_i \left(S^* + \frac{kI^*}{2}\right) + \beta \sum_{j=1}^N \left(\chi_4 k \omega_{ji}^i + \chi_5 \frac{\alpha_{ji}}{2}\right) I_j \end{pmatrix} \tag{3.6}$$

In order to apply the Theorem (5), we rewrite system $C_{\mathcal{A}}$ using the changes of variables $\begin{pmatrix} v_i \\ z_i \end{pmatrix} = P^{-1} \begin{pmatrix} I_i \\ J_i \end{pmatrix}$ with P^{-1} in (2.18). Let us note

$$\mathbf{L} = (L_i)_i, \quad \mathbf{v} = (v_i)_i, \quad \mathbf{z} = (z_i)_i,$$

and $-\xi = -(m + \beta k T^*) + \dfrac{\beta k I^*}{2} < 0$. The system $C_{\mathcal{A}}$ reads now as the slow-fast form

$$\begin{cases} \dfrac{\partial X}{\partial t} &= -\beta T^* X + \chi_1 F_X^1(\mathbf{v},\mathbf{z}) + \chi_2 F_X^2(\mathbf{v},\mathbf{z}) + \chi_3 F_X^3(\mathbf{L}) + \epsilon \Delta X + O(\epsilon) \\ \dfrac{\partial Y}{\partial t} &= \beta(S^* - T^* - kI^*)X - (m + \beta k T^*)Y + \chi_1 F_Y^1(\mathbf{v},\mathbf{z}) + \chi_2 F_Y^2(\mathbf{v},\mathbf{z}) + \chi_5 F_Y^5(\mathbf{v},\mathbf{z}) + \epsilon \Delta Y + O(\epsilon) \\ \dfrac{\partial L_i}{\partial t} &= -mL_i + \chi_3 F_{L_i}(\mathbf{v},\mathbf{z}) + O(\epsilon) + \epsilon \Delta L_i \\ \dfrac{\partial v_i}{\partial t} &= -\xi v_i + O(\epsilon) + \epsilon \Delta v_i + \epsilon \dfrac{1}{|P|}\left[(2T^*\nabla T^* - I^*\nabla D^*)\nabla v_i + (T^*\nabla I^* - I^*\nabla T^*)\nabla z_i\right] \\ \dfrac{\partial z_i}{\partial t} &= \epsilon\left(F_{z_i}(X,Y,\mathbf{L},\mathbf{v},\mathbf{z}) + O(\epsilon)\right) + \epsilon \Delta z_i + \epsilon \dfrac{1}{|P|}\left[(-D^*\nabla T^* + 2T^*\nabla D^*)\nabla v_i + (-D^*\nabla I^* + 2T^*\nabla T^*)\nabla z_i\right] \end{cases} . \tag{3.7}$$

For $i = 1, \cdots, N$, the functions F_X^i, F_Y^i, F_{L_i} are obviously deduced from the right term of (3.4) and are linear in theirs variables, $X, Y, \mathbf{L}$, respectively. The function F_Y^5 is quadratic in $(\mathbf{v},\mathbf{z})$. Finally, F_{z_i} is given by the second line of the right term of (3.6) after the linear change of variables (2.22):

$$F_{z_i}(X,Y,\mathbf{L},\mathbf{v},\mathbf{z}) = \begin{pmatrix} 0 & 1 \end{pmatrix} P^{-1} \left(\beta \begin{pmatrix} -k & -1 \\ -\dfrac{k}{2} & -1 \end{pmatrix} X + \frac{\beta k}{2} \begin{pmatrix} 0 & 0 \\ 0 & 1 \end{pmatrix} Y + \mathcal{M} \right) P \begin{pmatrix} v_i \\ z_i \end{pmatrix} + \begin{pmatrix} 0 & 1 \end{pmatrix} P^{-1} \chi_3 \gamma \begin{pmatrix} 0 \\ L_i \end{pmatrix}. \tag{3.8}$$

Lemma 8. Let $\epsilon = 0$ in (3.11). Then there exist a function $\mathbf{\Phi}(\mathbf{z}) = (X^*(\mathbf{z}), Y^*(\mathbf{z}), \chi_3 \mathbf{L}^*(\mathbf{z}), 0)$ such that the solution $(X, Y, \mathbf{L}, \mathbf{v}, \mathbf{z})$ of (3.7) with any initial condition

$$(X, Y, \mathbf{L}, \mathbf{v}, \mathbf{z})(0) = (X_0, Y_0, \mathbf{L}_0, \mathbf{v}_0, \mathbf{z}_0) \in \mathbb{R} \times \mathbb{R} \times (\mathbb{R}^n)^3$$

verifies $\mathbf{z}(t) = \mathbf{z}_0$ for all $t \geq 0$ and

$$\lim_{t \to +\infty} (X, Y, \mathbf{L}, \mathbf{v})(t) = \mathbf{\Phi}(\mathbf{z}_0)$$

exponentially. Moreover, X^* and Y^* are linear function of the χ_i.

Proof. First, in (3.11), we can write the system for $X, Y, \mathbf{L}, \mathbf{v}$ when $\epsilon = 0$ in the following form

$$0 = G(\mathbf{z}, (X, Y, \mathbf{L}, \mathbf{v}))$$

with function $G(x_1, x_2) : \mathbb{R}^N \times \mathbb{R}^{2N+2} \to \mathbb{R}^{2N+2}$, $x_1 = \mathbf{z}$, $x_2 = (X, Y, \mathbf{L}, \mathbf{v})$.
The Jacobian matrix of G respected to $\begin{pmatrix} X & Y & \mathbf{L} & \mathbf{v} \end{pmatrix}$ reads as as follows

$$A(x,t) = \begin{pmatrix} -\beta T^* & 0 & * & * & \dots & * & * & & & \\ \beta(S^* - T^* - kI^*) & -(m + \beta k T^*) & 0 & \dots & 0 & * & & & & \\ 0 & 0 & -m & 0 & \dots & 0 & * & & & \\ 0 & 0 & 0 & -m & \dots & 0 & * & & & \\ \ddots & & & & & & & & & \\ 0 & 0 & 0 & 0 & \dots & -m & * & & & \\ 0 & 0 & 0 & 0 & \dots & 0 & -\xi & 0 & \dots & 0 \\ 0 & 0 & 0 & 0 & \dots & 0 & 0 & -\xi & \dots & 0 \\ \ddots & & & & & & & & & \\ 0 & 0 & 0 & 0 & \dots & 0 & 0 & 0 & \dots & -\xi \end{pmatrix}. \tag{3.9}$$

Since $A(x,t)$ is block-diagonal matrix, it is easy to find the characteristic polynomial

$$(\lambda + \beta T^*)(\lambda + m + \beta k T^*)(\lambda + m)^n (\lambda + \xi)^n$$

which implies that all the eigenvalue of A have the negative real part.

Using the triangular structure of (3.11) the idea is to compute the limits when $\epsilon \to 0$ step by step of $\mathbf{v}$,

$\mathbf{L}$, X and Y in this order. Here we make a quick formal computation by simply plugging the limits obtained at one step into the equation of the next step.
Indeed, since (3.11) is equivalent to (3.7) but in the slow motion, we take $\epsilon = 0$ in (3.7). We have directly $\mathbf{z}(t) = \mathbf{z}_0$ for all $t \geq 0$ and $v_i = e^{-\xi t} v_i(0) \to 0$ exponentially as $t \to +\infty$. Remark that taking $v_i = 0$ in the others equations leads to the simple change of variables : $I_i = I^* z_i$ and $J_i = T^* z_i$ that we can plug in (3.4)-(3.5)-(3.6) to simplify the explicit computations.
Now we have the following exponential limits

$$L_i(t) \to \chi_3 \frac{1}{m} F_{L_i}(0, \mathbf{z}_0) = \chi_3 L_i^*(\mathbf{z}_0),$$

Denoting $\mathbf{L}^* = (L_i^*)_i$ and plugging this into the equation of X we have that exponentially:

$$X(t) \to -\frac{1}{\beta T^*} \left(\chi_1 F_X^1 (0, \mathbf{z}_0) + \chi_2 F_X^2 (0, \mathbf{z}_0) + \chi_3 F_X^3 (\chi_3 \mathbf{L}^*(\mathbf{z}_0)) \right) = X^*(\mathbf{z}_0).$$

Remark that by linearity of the F_X^i and the fact that $\chi_d^2 = \chi_d$ for each d, we have the simpler formula

$$X^*(\mathbf{z}_0) = -\frac{1}{\beta T^*} \left(\chi_1 F_X^1 (0, \mathbf{z}_0) + \chi_2 F_X^2 (0, \mathbf{z}_0) + \chi_3 F_X^3 (\mathbf{L}^*(\mathbf{z}_0)) \right). \tag{3.10}$$

Finally, using the same arguments we get

$$Y(t) \to Y^*(\mathbf{z}_0) \qquad \text{exponentially}$$

wherein we have note

$$Y^*(\mathbf{z}_0) = \frac{1}{m + \beta k T^*} \left(\beta(S^* - T^* - kI^*) X^*(\mathbf{z}_0) + \chi_1 F_Y^1 (0, \mathbf{z}_0) + \chi_2 F_Y^2 (0, \mathbf{z}_0) + \chi_4 F_Y^4 (0, \mathbf{z}_0) \right).$$

□

The next step is to change the time scale. Taking $\tau = \epsilon t$ in (3.7) we obtain[2] the following system which is equivalent to (3.7) but in the slow motion τ

$$\begin{cases} \epsilon \dfrac{\partial X}{\partial \tau} &= -\beta T^* X + \chi_1 F_X^1 (\mathbf{v}, \mathbf{z}) + \chi_2 F_X^2 (\mathbf{v}, \mathbf{z}) + \chi_3 F_X^3 (\mathbf{L}) + O(\epsilon) + \epsilon \Delta X \\ \epsilon \dfrac{\partial Y}{\partial \tau} &= \beta(S^* - T^* - kI^*) X - (m + \beta k T^*) Y + \chi_1 F_Y^1 (\mathbf{v}, \mathbf{z}) + \chi_2 F_Y^2 (\mathbf{v}, \mathbf{z}) + \chi_5 F_Y^5 (\mathbf{v}, \mathbf{z}) + O(\epsilon) + \epsilon \Delta Y \\ \epsilon \dfrac{\partial L_i}{\partial \tau} &= -m L_i + \chi_3 F_{L_i} (\mathbf{v}, \mathbf{z}) + O(\epsilon) + \epsilon \Delta L_i \\ \epsilon \dfrac{\partial v_i}{\partial \tau} &= -\xi v_i + O(\epsilon) + \epsilon \dfrac{1}{|P|} \left[(2T^* \nabla T^* - I^* \nabla D^*) \nabla v_i + (T^* \nabla I^* - I^* \nabla T^*) \nabla z_i \right] + \epsilon \Delta v_i \\ \dfrac{\partial z_i}{\partial \tau} &= F_{z_i}(X, Y, \mathbf{L}, \mathbf{K}, \mathbf{v}, \mathbf{z}) + O(\epsilon) + \dfrac{1}{|P|} \left[(-D^* \nabla T^* + 2T^* \nabla D^*) \nabla v_i + (-D^* \nabla I^* + 2T^* \nabla T^*) \nabla z_i \right] + \Delta z_i \end{cases} \tag{3.11}$$

Using the notation of the Theorem 5, we see that the fast variables is $y(\tau) = (X, Y, \mathbf{L}, \mathbf{v})$ and the slow variable is $x(\tau) = \mathbf{z}(\tau)$. The first step in applying the Theorem 5 is to take $\epsilon = 0$ in (3.11) and to show that the fast variable converge exponentially to an attractor $\phi(\mathbf{z})$ which is parametrized by the slow variable.

Now, we take $\epsilon = 0$ in (3.11) and

$$(X, Y, \mathbf{L}, \mathbf{v})(\tau) = \mathbf{\Phi}(\mathbf{z}(\tau)), \tag{3.12}$$

the $2N + 2$ first equations are satisfied and the N last equations give the *slow system*

$$\frac{dz_i}{d\tau} = F_{z_i}(X^*(\mathbf{z}), Y^*(\mathbf{z}), \mathbf{L}^*(\mathbf{z}), 0, \mathbf{z}) + \frac{1}{|P|} \left(-D^* \nabla I^* + 2T^* \nabla T^* \right) \nabla z_i + \Delta z_i. \tag{3.13}$$

It's important to note that, since $\mathbf{v} = 0$ then (3.13) gives $\sum_{i=1}^N z_i = 1$. This is plausible because z_i reflects the frequency of strain i by the formula $I_i = I^* z_i$ for all i.
The Theorem 5 imply that the solutions of (3.13) together with (3.12) gives a good approximation of the original system (3.11) for a small enough but positive ϵ. Coming back to the original variables of the SIS system, we deduce the following result on error estimate, whose proof will be given in section 3.2.

[2]We use the usual notation abuse. Rigorously speaking, we have to define $\widetilde{X}(\tau) = X\left(\frac{\tau}{\epsilon}\right)$ and the same for each variables. Here we remove the $\widetilde{}$ for simplicity.

Lemma 9. Let $T > 0$ be fixed. There exists $\epsilon_0 > 0$ and $C_T > 0$ such that for any $\epsilon \in (0, \epsilon_0)$ we have for any solution of $(S, (I_i)_i, (I_{ij})_{ij})_{i,j}$ of (2.1) and $(z_i)_i$ of (3.13)

$$\int_\Omega \left| S\left(\frac{\tau}{\epsilon}\right) - S^* \right|^2 + \sum_{i=1}^N \int_\Omega \left| I_i\left(\frac{\tau}{\epsilon}\right) - I^* z_i(\tau) \right|^2 + \sum_{i,j=1}^N \int_\Omega \left| D^* z_i(\tau) z_j(\tau) - I_{ij}\left(\frac{\tau}{\epsilon}\right) \right|^2 \leq \epsilon C_T, \tag{3.14}$$

Proof. See section 3.2 □

It remains to compute explicitly the slow system (3.13). The following lemma shows that it suffices to compute independently each perturbation, that is $\mathcal{A} = \{d\}$ for $d = 1, \cdots, 5$. The case of a general $\mathcal{A}$ being just a sum of each simple case thanked to the following result.

Lemma 10. Let $\mathcal{A} \subset \{1, \cdots, 5\}$. Recall that $\chi_d = 1$ if $d \in \mathcal{A}$ and $\chi_d = 0$ if $d \notin \mathcal{A}$. The functions F_{z_i} for $i = 1, \cdots, N$ in (3.13) read

$$F_{z_i}(X^*(\mathbf{z}), Y^*(\mathbf{z}), \mathbf{L}^*(\mathbf{z}), 0, \mathbf{z}) = \sum_{d=1}^5 \chi_d z_i f_{z_i}^d(\mathbf{z}),$$

where the functions $f_{z_i}^d$ do not depend on χ_d.
In particular, if $\mathcal{A} = \{d\}$ for some $d \in \{1, 2, 3, 4, 5\}$, then

$$F_{z_i}(X^*(\mathbf{z}), Y^*(\mathbf{z}), \mathbf{L}^*(\mathbf{z}), 0, \mathbf{z}) = z_i f_{z_i}^d(\mathbf{z}).$$

Proof. Taking $v_i = 0$ in (3.8) we see that there is two constant C_X and C_Y such that

$$F_{z_i}(X^*(\mathbf{z}), Y^*(\mathbf{z}), \mathbf{L}^*(\mathbf{z}), 0, \mathbf{z}) = z_i \left(C_X X^*(\mathbf{z}), + C_Y Y^*(\mathbf{z}) + \begin{pmatrix} 0 & 1 \end{pmatrix} P \mathcal{M}_{\mathcal{A}} P^{-1} \begin{pmatrix} 0 \\ 1 \end{pmatrix} \right) + \chi_3 \gamma \begin{pmatrix} 0 & 1 \end{pmatrix} P \begin{pmatrix} 0 \\ L_i^*(\mathbf{z}) \end{pmatrix}.$$

Firstly, as it is show in the proof of the lemma 8, the expression of X^* and Y^* are both a linear combination of the χ_d.

Secondly, recalling that we have at this step $I_i = I^* z_i$, $J_i = T^* z_i$, $\mathbf{L}_i = \chi_3 \mathbf{L}^*$ and $\chi_d^2 = \chi_d$, for $d = 3$ and $d = 5$ particularly. Plugging this in (3.7), we see that the matrix $\mathcal{M}_{\mathcal{A}}$ is also a linear combination of the χ_d which yields for some functions $m_d(\mathbf{z})$ which do not depend on χ_d :

$$\begin{pmatrix} 0 & 1 \end{pmatrix} P \mathcal{M}_{\mathcal{A}} P^{-1} \begin{pmatrix} 0 \\ 1 \end{pmatrix} = \sum_{d \in \{1,2,3,4,5\}} \chi_d m_d(\mathbf{z}). \tag{3.15}$$

Thirdly, plugging $I_i = I^* z_i$ and $J_i = T^* z_i$, for all i in (3.4) we prove that

$$L_i^*(\mathbf{z}) = \frac{1}{2m} \beta k I^* T^* z_i \sum_{j=1}^N (u_{ij} + u_{ji}) z_j.$$

The result follows directly from three previous points. □

In the next section 3.2, these functions $f_{z_i}^d$ are explicitly compute for any d.

3.2 Main results and proofs

We reuse the computations in [17], in each case of $\mathcal{A} = \{d\}$, $d \in \{1, 2, 3, 4, 5\}$. We set that

$$\vec{\vartheta} = \frac{1}{|P|} \left(-D^* \nabla I^* + 2 T^* \nabla T^* \right).$$

Note that $\vec{\vartheta} = 0$ if I^* and T^* do not depend on x.

In each following case of perturbation, by the similar argument, we obtain the slow system (3.13), respectively.

- Perturbations in transmission rates, $\mathcal{A} = \{1\}$

$$\begin{cases} \dfrac{\partial z_i}{\partial \tau} = \dfrac{2\beta S^* {T^*}^2}{|P|} z_i \left(b_i - \displaystyle\sum_{j=1}^N b_j z_j \right) + \vec{\vartheta} \cdot \nabla z_i + \Delta z_i, \\ \dfrac{\partial z_i}{\partial n}|_{\partial\Omega} = 0, \end{cases} \qquad 1 \leq i \leq N.$$

- Perturbations in clearance rates γ_i, $\mathcal{A} = \{2\}$

$$\begin{cases} \dfrac{\partial z_i}{\partial \tau} = \dfrac{\gamma I^* \left(I^* + T^*\right)}{|P|} \left(\nu_i - \displaystyle\sum_{j=1}^{N} \nu_j z_j\right) z_i + \vec{\vartheta} \cdot \nabla z_i + \Delta z_i, \\ \dfrac{\partial z_i}{\partial n}|_{\partial\Omega} = 0, \qquad 1 \leq i \leq N. \end{cases}$$

- Perturbations in co-infection clearance rate γ_{ij}, $\mathcal{A} = \{3\}$

$$\begin{cases} \dfrac{\partial z_i}{\partial \tau} = \dfrac{\gamma T^* D^*}{|P|} \left[\displaystyle\sum_{j=1}^{N} \left(u_{ij} + u_{ji}\right) z_j - \sum_{j,l=1}^{N} \left(u_{jl} + u_{lj}\right) z_l z_j\right] z_i + \vec{\vartheta} \cdot \nabla z_i + \Delta z_i, \\ \dfrac{\partial z_i}{\partial n}|_{\partial\Omega} = 0, \qquad 1 \leq i \leq N. \end{cases}$$

- Perturbations in perturbations in transmission coefficients from mixed carriage p_{ij}^i, $\mathcal{A} = \{4\}$

$$\begin{cases} \dfrac{\partial z_i}{\partial \tau} = \dfrac{2mT^* D^*}{|P|} z_i \displaystyle\sum_{j=1}^{N} \left(\omega_{ij}^i - \omega_{ji}^j\right) z_j + \vec{\vartheta} \cdot \nabla z_i + \Delta z_i, \\ \dfrac{\partial z_i}{\partial n}|_{\partial\Omega} = 0, \end{cases} \qquad 1 \leq i \leq N.$$

- Perturbations co-colonization interaction k_{ij}, $\mathcal{A} = \{5\}$

$$\begin{cases} \dfrac{\partial z_i}{\partial \tau} = \dfrac{-\beta T^* I^* D^*}{|P|} z_i \left[\displaystyle\sum_{j=1}^{N} \left(\frac{T^*}{D^*}\alpha_{ji} - \frac{I^*}{D^*}\alpha_{ij}\right) z_j - \sum_{j,l=1}^{N} \alpha_{jl} z_j z_l\right] + \vec{\vartheta} \cdot \nabla z_i + \Delta z_i, \\ \dfrac{\partial z_i}{\partial n}|_{\partial\Omega} = 0, \end{cases} \qquad 1 \leq i \leq N.$$

Let $\mathcal{A} \subset \{1, 2, 3, 4, 5\}$. Using the notations in the previous section, (3.13) reads.

$$\begin{aligned} \frac{dz_i}{d\tau} =& \Theta_1 z_i \left(b_i - \sum_{j=1}^{N} b_j z_j\right) + \Theta_2 z_i \left(-\nu_i + \sum_{j=1}^{N} \nu_j z_j\right) + \Theta_3 z_i \left[-\sum_{j=1}^{N} (u_{ij} + u_{ji}) z_j + \sum_{j,l=1}^{N} (u_{jl} + u_{lj}) z_l z_j\right] \\ &+ \Theta_4 z_i \sum_{j=1}^{N} \left(\omega_{ij}^i - \omega_{ji}^j\right) z_j + \Theta_5 z_i \left[\sum_{j=1}^{N} \left(\frac{T^*}{D^*}\alpha_{ji} - \frac{I^*}{D^*}\alpha_{ij}\right) z_j - \sum_{j,l=1}^{N} \alpha_{jl} z_j z_l\right] + \quad \vec{\vartheta} \cdot \nabla z_i + \Delta z_i \end{aligned} \tag{3.16}$$

where Θ_i, $i = 1, 2, 3, 4, 5$, are given by

$$\Theta_1(x) = \chi_1 \frac{2\beta S^* {T^*}^2}{|P|}, \quad \Theta_2(x) = \chi_2 \frac{\gamma I^* \left(I^* + T^*\right)}{|P|}, \quad \Theta_3(x) = \chi_3 \frac{\gamma T^* D^*}{|P|}, \quad \Theta_4(x) = \chi_4 \frac{2mT^* D^*}{|P|}, \quad \Theta_5(x) = \chi_5 \frac{\beta T^* I^* D^*}{|P|} \tag{3.17}$$

because all the parameters β, γ, m and the values S^*, T^*, I^*, D^* depend on $x \in \Omega$.

It is useful to rewrite (3.16) using the pairwise invasion fitness between strains. Define

$$\Theta(x) = \Theta_1(x) + \Theta_2(x) + \Theta_3(x) + \Theta_4(x) + \Theta_5(x) \quad \text{and } \theta_i(x) = \frac{\Theta_i(x)}{\Theta(x)}. \tag{3.18}$$

we see that $\theta_i(x) > 0$ for each $i = 1, 2, 3, 4, 5$ and $\theta_1 + \theta_2 + \theta_3 + \theta_4 + \theta_5 = 1$ for all x. For completeness, if $\mathcal{A} = \emptyset$ then we set $\Theta = 1$. Using these notations, we obtain our main result.

Theorem 11. *Consider the system of equations*

$$\begin{cases} \dfrac{\partial z_i}{\partial \tau} = \Theta z_i \left(\left(\Lambda(x)\mathbf{z}\right)_i - \mathbf{z}^T \Lambda(x)\mathbf{z}\right) + \vec{\vartheta} \cdot \nabla z_i + \Delta z_i, \ i = 1, \cdots, N, \\ z_1 + z_2 + \cdots + z_N = 1. \end{cases} \tag{3.19}$$

where $\Lambda(x)$ *is the square matrix of size* $N \times N$ *whose coefficient* $(i;j)$ *are the pairwise fitness* $\lambda_i^j(x)$ *which satisfy*

$$\boxed{\lambda_i^j(x) = \theta_1(b_i - b_j) + \theta_2(-\nu_i + \nu_j) + \theta_3(-u_{ij} - u_{ji} + 2u_{jj}) + \theta_4\left(\omega_{ij}^i - \omega_{ji}^j\right) + \theta_5(\mu(\alpha_{ji} - \alpha_{ij}) + \alpha_{ji} - \alpha_{jj}).} \tag{3.20}$$

with $\mu = \dfrac{I^*}{D^*}$.
Then, for any initial values of (2.1)*, for each* $\tau_0 > 0$, $T > \tau_0$ *arbitrarily and independent on* ϵ*, there is* $\epsilon_0 > 0$, $C > 0$ *and a vector of positive coefficients* $\mathbf{z}_0 \in \mathbb{R}^N$ *verifying* $\sum_{i=1}^N \mathbf{z}_{0,i} = 1$*, such that* $\forall \epsilon < \epsilon_0$

$$\int_\Omega \left|S^*(x) - S\left(x, \frac{\tau}{\epsilon}\right)\right|^2 + \sum_{i=1}^N \int_\Omega \left|I^* z_i(x,\tau) - I_i\left(x, \frac{\tau}{\epsilon}\right)\right|^2 + \sum_{i,j=1}^N \int_\Omega \left|D^* z_i(x,\tau) z_j(x,\tau) - I_{ij}\left(x, \frac{\tau}{\epsilon}\right)\right|^2 \leq \epsilon C, \quad \forall \tau \in (\tau_0, T).$$

where S, $(I_1, I_2, \ldots, I_N)$, $(I_{ij})_{i,j\in\{1,\ldots,N\}}$ *is the solution of* (2.1) *and* $(z_1, z_2, \ldots, z_N)$ *is the solution of reduced system* (3.19) *together with* $\mathbf{z}(0) = \mathbf{z}_0$.

This system (3.19) is a general replicator system with diffusion, which is studied in [6]. We back to the proof of Theorem 9.

Proof. We separate this proof into three steps, in which, we respectively show the approximation for S, I_i, $i = 1, \ldots, N$ using the theorems 5, 6, then prove the approximation holds for I_{ij}, $i, j = 1, \ldots, N$.

• **Firstly,** use the Theorem 6,we have that

$$\|S(x,t) - S^*(x)\|_2 = O\left(\sqrt{\epsilon}\right). \tag{3.21}$$

On the other side, we note that the algebraic linear transformations to the new variables $(z_i, v_i)_{1\leq i\leq N}$; and $v_i \to 0$ when $\epsilon \to 0$ (by the Theorem 5), which deduces that

$$\|S(x,t) - S^*(x)\|_2 + \sum_{i=1}^N \|I_i(x,t) - I^* z_i^s(x,t)\|_2 = O\left(\sqrt{\epsilon}\right), \tag{3.22}$$

where $(z_1^s, z_2^s, \ldots, z_N^s)$ are solution of slow-fast system (3.7), noting that and changing time scale yielding the equivalent system .

• **Secondly,** by the lemma 8 and the same arguments in [17], we can verify the exponential stability condition of the Theorem 5. Hence, the solution of system (3.11) after changing time scale $\tau = \epsilon t$ tends to the solution of (3.19) as $\epsilon \to 0$ on $[\tau_0, T]$, with $\tau_0 > 0$, $T > \tau_0$. arbitrary and independent on ϵ.
Combine with the previous claim (3.22), we obtain that

$$\left\|S\left(x, \frac{\tau}{\epsilon}\right) - S^*\right\|_2 + \sum_{i=1}^N \left\|I^* z_i(x,\tau) - I_i\left(x, \frac{\tau}{\epsilon}\right)\right\|_2 = O\left(\sqrt{\epsilon}\right). \tag{3.23}$$

• **Thirdly,** we make a result for solutions $I_{ij}(x,t)$, $1 \leq i, j \leq N$. For the sake of shortness, we remark that each partial differential equation in this proof associates with Neumann boundary condition and we will not remark it in each equation. Assume $\left(I_{ij}^r\right)_{1\leq i,j\leq N}$ to be the solution of

$$\frac{\partial I_{ij}}{\partial t} = -mI_{ij} + \beta k I^* T^* z_i(x,\tau) z_j(x,\tau) + \epsilon \Delta I_{ij}, \qquad 1 \leq i, j \leq N \tag{3.24}$$

Then, for each $\tau_0 > 0$ and $T > \tau_0$, we claim that $\sum_{i,j=1}^N \left\|I_{ij}\left(x, \frac{\tau}{\epsilon}\right) - I_{ij}^r\left(x, \frac{\tau}{\epsilon}\right)\right\|_2 = O(\sqrt{\epsilon})$ for any $\tau \in [\tau_0, T]$.
Indeed, by the property of solutions of (2.16) and (3.24), we have that

$$\begin{aligned}
\frac{\partial I_{ij}}{\partial t}\left(x, \frac{\tau}{\epsilon}\right) &= -m_{ij} I_{ij}\left(x, \frac{\tau}{\epsilon}\right) + \beta_j k_{ij} I_i\left(x, \frac{\tau}{\epsilon}\right) J_j\left(x, \frac{\tau}{\epsilon}\right) + \epsilon \Delta I_{ij}\left(x, \frac{\tau}{\epsilon}\right) \\
\frac{\partial I_{ij}^r}{\partial t}\left(x, \frac{\tau}{\epsilon}\right) &= -mI_{ij}^r\left(x, \frac{\tau}{\epsilon}\right) + \beta k I^* T^* z_i(x,\tau) z_j(x,\tau) + \epsilon \Delta I_{ij}^r\left(x, \frac{\tau}{\epsilon}\right)
\end{aligned} \tag{3.25}$$

which implies

$$\begin{aligned}
\frac{\partial}{\partial t}\left(I_{ij}\left(x, \frac{\tau}{\epsilon}\right) - I_{ij}^r\left(x, \frac{\tau}{\epsilon}\right)\right) =& \epsilon \Delta\left(I_{ij}\left(x, \frac{\tau}{\epsilon}\right) - I_{ij}^r\left(x, \frac{\tau}{\epsilon}\right)\right) - m\left(I_{ij}\left(x, \frac{\tau}{\epsilon}\right) - I_{ij}^r\left(x, \frac{\tau}{\epsilon}\right)\right) \\
&+ \left(\beta_j k_{ij} I_i\left(x, \frac{\tau}{\epsilon}\right) J_j\left(x, \frac{\tau}{\epsilon}\right) - \beta k I^* T^* z_i(x,\tau) z_j(x,\tau)\right) - \epsilon \gamma u_{ij} I_{ij}\left(x, \frac{\tau}{\epsilon}\right).
\end{aligned} \tag{3.26}$$

Then for all $1 \leq i, j \leq N$, using the Theorem 6, we observe that

$$\left\| I_{ij}\left(x, \frac{\tau}{\epsilon}\right) - I_{ij}^{r}\left(x, \frac{\tau}{\epsilon}\right) \right\|_2 = O(\sqrt{\epsilon}). \tag{3.27}$$

Note that, $k\dfrac{I^*T^*}{S^*} = D^*$, it suffices to compute the solution I_{ij}^r, which satisfies $\left\| I_{ij}^r - D^* z_i(\epsilon t)\, z_j(\epsilon t) \right\|_2 = O(\sqrt{\epsilon})$ for all $1 \leq i, j \leq N$, by the Theorem 11.19 in [29] again. Combining with (3.27) implies that $\left\| I_{ij} - D^* z_i(\epsilon t)\, z_j(\epsilon t) \right\|_1 = O(\sqrt{\epsilon})$.

Combine the results in three above steps, we get the conclusion of the lemma 9. □

4 Models with fast diffusion

4.1 The general model and the Central Manifold Theorem

Keeping the same notations of the previous sections, we now study the following system, where the rates of diffusion are large.

$$\begin{cases} \dfrac{\partial S}{\partial t} &= r(x)(1-S) + \displaystyle\sum_{i=1}^{N} \gamma_i(x) I_i + \sum_{i,j=1}^{N} \gamma_{ij}(x) I_{ij} - S \sum_{i=1}^{N} \beta_i J_i \quad + \dfrac{d}{\epsilon}\Delta S \qquad\qquad , \\ \dfrac{\partial I_i}{\partial t} &= \beta_i J_i S - \left(r(x) + \gamma_i(x)\right) I_i - I_i \displaystyle\sum_{j=1}^{N} k_{ij}\beta_j J_j \qquad + \dfrac{d}{\epsilon}\Delta I_i, \qquad 1 \leq i \leq N, \\ \dfrac{\partial I_{ij}}{\partial t} &= k_{ij}(x)\beta_j I_i J_j - \left(r(x) + \gamma_{ij}(x)\right) I_{ij} \qquad + \dfrac{d}{\epsilon}\Delta I_{ij}, \qquad 1 \leq i, j \leq N, \end{cases} \tag{4.1}$$

with the Neumann boundary conditions $\dfrac{\partial S}{\partial n} = \dfrac{\partial I_i}{\partial n} = \dfrac{\partial I_{ij}}{\partial n} = 0$ for all $1 \leq i, j \leq N$ on the boundary of Ω and given initial conditions.
Accordingly, this system (4.1) can be shortly written as

$$\begin{cases} \dfrac{\partial}{\partial t}\mathbf{W}(x,t) = \mathcal{F}\left(x, \mathbf{W}(x,t)\right) + \dfrac{1}{\epsilon} K \mathbf{W}(x,t), \\ \dfrac{\partial}{\partial n}\mathbf{W}(x,t) = 0, \qquad x \in \partial\Omega \end{cases} \tag{4.2}$$

where

$$\mathbf{W}(x,t) = (S, I_1, \ldots, I_N, I_{11}, \ldots, I_{NN})$$

and K is the operator $\begin{pmatrix} d\Delta\cdot & \ldots & 0 \\ \vdots & \ddots & \vdots \\ 0 & \ldots & d\Delta \end{pmatrix}$.

We set the notation $A = d\Delta$. When seen as an operator on $L^2(\Omega)$, the operator A^2 with the formula of A, accompanied with homogeneous Neumann boundary conditions, is defined as follows, see [9].

$$\begin{aligned} &D\left(A^2\right) = \left\{ U \in H^1(\Omega) : \exists V \in L^2(\Omega), \forall \phi \in H^1(\Omega), \int \nabla U(x)\, \nabla \phi(x)\, dx = -d \int V(x)\, \phi(x)\, dx \right\}, \\ &A^2 U := V, \quad U \in D\left(A^2\right). \end{aligned} \tag{4.3}$$

In order to obtain uniform estimates, we prefer to focus on the operator $A^\infty := A$ acting on $C^0(\bar{\Omega})$ with sup norm. Hence, we define

$$\begin{aligned} &D\left(A^\infty\right) := \left\{ U \in D\left(A^2\right) \cap C\left(\bar{\Omega}\right), A^2 U \in C\left(\bar{\Omega}\right) \right\}, \\ &A^\infty U = A^2 U, \quad U \in D\left(A^\infty\right). \end{aligned} \tag{4.4}$$

Then we have that

$$E_0 := \ker\left(A^\infty\right) = \operatorname{span}(1) = \mathbb{R} \text{ and } \operatorname{Im}\left(A^\infty\right) \subset \left\{ U \in C^0(\bar{\Omega}), \int_\Omega U = 0 \right\} = F_0. \tag{4.5}$$

One gets $C^0\left(\bar{\Omega}\right) = \ker A^\infty \oplus \operatorname{Im} A^\infty$. Now we define the Banach space $\left(C^0\left(\bar{\Omega}\right)\right)^{N^2+N+1}$ together with the norm

$$\left\| (U_1, \ldots, U_{N^2+N+1}) \right\|_\infty = \|U_1\|_\infty + \cdots + \|U_{N^2+N+1}\|_\infty \tag{4.6}$$

and the operator $(A^\infty)^{N^2+N+1}$ acting on each coordinate of $\left(C^0\left(\bar{\Omega}\right)\right)^{N^2+N+1}$. The kernel and the range of this operator are respectively

$$E := \ker\left((A^\infty)^{N^2+N+1}\right) = \mathbb{R}^{N^2+N+1} \qquad \text{and} \qquad F := (F_0)^{N^2+N+1}. \tag{4.7}$$

Hence we have $\left(C^0\left(\bar{\Omega}\right)\right)^{N^2+N+1} = E \oplus F$. The projection of $\left(C^0\left(\bar{\Omega}\right)\right)^{N^2+N+1}$ on E and F, denoted by Π_E and Π_F respectively, given explicit by

$$\Pi_E\left(V_1, \ldots, V_{N^2+N+1}\right) = \frac{1}{|\Omega|}\left(\int_\Omega V_1, \ldots, \int_\Omega V_{N^2+N+1}\right); \qquad \Pi_F = \mathrm{Id} - \Pi_E. \tag{4.8}$$

For all $u \in \left(C^0\left(\bar{\Omega}\right)\right)^{N^2+N+1}$ we rewrite it into $u = \mathbf{X} + \mathbf{Y}$ with $\mathbf{X} \in E$ and $\mathbf{Y} \in F$. We change the system (4.1) on an equivalent slow-fast form by projecting (4.1) on E and F respectively. The slow variable $\mathbf{X} := \Pi_E(\mathbf{W}) \in E$ is the vector

$$\mathbf{X} = \left(\frac{1}{|\Omega|}\int_\Omega S, \frac{1}{|\Omega|}\int_\Omega I_1, \ldots, \frac{1}{|\Omega|}\int_\Omega I_N, \frac{1}{|\Omega|}\int_\Omega I_{11}, \ldots, \frac{1}{|\Omega|}\int_\Omega I_{NN}\right) \in \mathbb{R}^{N^2+N+1}$$

and the fast variable is $\mathbf{Y} := \Pi_F \mathbf{W} = \mathbf{W} - \mathbf{X} \in F$. Projecting the system (4.1) on E and F yields to the equivalent system

$$(S_\epsilon): \begin{cases} \dfrac{d}{dt}\mathbf{X}(t) = f(\mathbf{X}, \mathbf{Y}) \\ \dfrac{d}{dt}\mathbf{Y}(t) = g(\mathbf{X}, \mathbf{Y}) + \dfrac{1}{\epsilon}K\mathbf{Y} \\ \dfrac{\partial}{\partial n}\mathbf{X} = 0 \\ \dfrac{\partial}{\partial n}\mathbf{Y} = 0 \\ \mathbf{X}(0) = \Pi_E(\mathbf{W}(0)) \\ \mathbf{Y}(0) = \Pi_F(\mathbf{W}(0)) \end{cases} \tag{4.9}$$

For the end of this section, we state the Central Manifold Theorem 12 and the Theorem of convergence towards the central manifold. These theorems may be proved in [8, 9]. Let us begin by a version of the central manifold Theorem for an elliptic operator K. This Theorem claims the existence of an invariant manifold for the slow-fast system which allows to defined several reduced systems.

Theorem 12. ***(Central Manifold Theorem)*** *Let E and F be two Banach spaces. Defines $f(X,Y) \in C^1(E \times F; E)$ and $g(X,Y) \in C^1(E \times F; F)$. Assume that f and g are uniformly bounded as well than there first derivatives. Let K be an operator with domain $D(K) \subset F$. Assume that K generates an analytical semi-group $\exp(tK)$ of linearly operators on F and that there exists $\mu > 0$ such that*

$$\forall t \geq 0; \qquad \forall \epsilon \in (0,1], \qquad \left\|\exp\left(\frac{t}{\epsilon}K\right)Y\right\|_F \leq C\|Y\|_F \exp\left(-\mu\frac{t}{\epsilon}\right). \tag{4.10}$$

For all initial condition $(x_0, y_0) \in E \times F$ and for all $\epsilon \in (0,1]$, one defines $X^\epsilon(t, x_0, y_0) \equiv X^\epsilon(t)$ and $Y^\epsilon(t, x_0, y_0) \equiv Y^\epsilon(t)$ the solution, for $t \geq 0$, of the differential system

$$(S_\epsilon): \qquad \begin{cases} \dfrac{d}{dt}X^\epsilon(t) = f(X^\epsilon(t), Y^\epsilon, \epsilon), \\ \dfrac{d}{dt}Y^\epsilon(t) = g(X^\epsilon(t), Y^\epsilon, \epsilon) + \dfrac{1}{\epsilon}KY^\epsilon(t), \\ X^\epsilon(0) = x_0, Y^\epsilon(0) = y_0. \end{cases} \tag{4.11}$$

Then there exists $\epsilon_0 > 0$ such that, for all $\epsilon \in (0, \epsilon_0)$, the system (S_ϵ) admits a central manifold C_ϵ in the following sense.

1. *There exists a function $h(X,\epsilon) \in C^1(E \times [0,\epsilon_0]; F)$ such that, for all $\epsilon \in (0,\epsilon_0]$, $C_\epsilon = \{(X, h(X,\epsilon)); X \in E\}$ is invariant under the semi flow generated by S_ϵ for $t \geq 0$. Moreover, we have that $\|h(\cdot,\epsilon)\|_{L^\infty(E,F)} = O(\epsilon)$ as $\epsilon \to 0$.*

2. *The function $h(x,\epsilon)$ satisfies the partial differential equation*

$$D_x h(x,\epsilon) f(x, h(x,\epsilon), \epsilon) = \frac{K}{\epsilon}h(x,\epsilon) + g(x, h(x,\epsilon), \epsilon), \tag{4.12}$$

where $D_x h$ stands for $\dfrac{Dh}{Dx}$. On top of that, any bounded function $\tilde{h}$ such that $\left\|\tilde{h}\right\|_{L^\infty}, \left\|D_x\tilde{h}\right\|_{L^\infty} \leq 1$, and such that we have

$$D_x\tilde{h}(x,\epsilon) f\left(x,\tilde{h}(x,\epsilon),\epsilon\right) = \frac{K}{\epsilon}\tilde{h}(x,\epsilon) + g\left(x,\tilde{h}(x,\epsilon),\epsilon\right) + O(\epsilon) \tag{4.13}$$

in L^∞, also necessarily satisfies

$$\left\|h-\tilde{h}\right\|_{L^\infty} = O(\epsilon). \tag{4.14}$$

This Theorem provides the existence of a manifold C_ϵ which is invariant for the system (4.11) and parametrized by the slow variable $X^\epsilon \in E$ In our application, E is finite dimensional so that the system on C^ϵ is a finite dimensional system. After showing that the solutions are close to the central manifold, up to an exponentially small error term, we can reduce the study to a system on the invariant manifold C^ϵ. This finite dimensional system approach the original problem in a sense that is specified below.
More precisely, let us define the following reduced system. We do not precise the initial data at this step.

$$\left(S_\epsilon^{[\infty]}\right): \quad \frac{d}{dt}X^{\epsilon,[\infty]}(t) = f\left(X^{\epsilon,[\infty]}(t), h\left(X^{e,[\infty]}(t),\epsilon\right),\epsilon\right), \quad Y^{\epsilon,[\infty]}(t) = h\left(X^{\epsilon,[\infty]}(t),\epsilon\right). \tag{4.15}$$

When the original data belongs to this manifold, that is if $Y^\epsilon(0) = h(X^\epsilon(0),0)$, (4.15) describes the exact dynamics of (4.11). In general, if $Y^\epsilon(0) \neq h(X^\epsilon(0),\epsilon)$ and the solutions do not belong to C_ϵ. However, the initial data can be slightly modified so that the solution of (4.11) are exponentially close to the solution of (4.15).

Note that, $h(X,\epsilon)$ admits an asymptotic expansion of the form $h(X,\epsilon) = \sum_{k=1}^{r-1}\epsilon^k h_k(X) + O(\epsilon^r)$, which is explicitly calculable provided the functions f and f have C^r smoothness. The approximate $h(X,\epsilon) \approx \sum_{k=1}^{r}\epsilon^k h_k(X)$ leads to the writing of reduced systems of order r (see [8]). This paper focus only on the case $r=1$. By this assumption, we obtain the following reduced system

$$\left(S_\epsilon^{[0]}\right): \quad \frac{d}{dt}X^{\epsilon,[0]}(t) = f\left(X^{\epsilon,[0]}(t),0,\epsilon\right), \quad Y^{\epsilon,[0]}(t) = h\left(X^{\epsilon,[0]}(t),\epsilon\right). \tag{4.16}$$

An important fact in the sequel is that the dynamic of $S_\epsilon^{[\infty]}$ is completely determined by its first equation: the following O.D.E system

$$(S_\epsilon^c): \quad \frac{d}{dt}X^{\epsilon,[\infty]}(t) = f\left(X^{\epsilon,[\infty]}(t), h\left(X^{\epsilon,[\infty]}(t),\epsilon\right)\right)$$

and S_ϵ^c can be seen as a regular perturbation of the first equation of $S_\epsilon^{[0]}$, that is

$$(S_0^c), \quad \frac{d}{dt}X^{[0]}(t) = f\left(X^{[0]}(t),0\right).$$

4.2 Application of the Central Manifold Theorem and main results

In order to apply the Central Manifold Theorem and related results, we need that the operator K define a C^0 semi-group of contraction on F. Note that, the assumed smoothness of $\partial\Omega$ implies that the operator A^∞ generates a C^0 semi group of contraction on $\left(C\left(\bar{\Omega}\right)\right)^{N^2+N+1}$, see [5]. Denoting $\exp\left(tA_2^\infty\right)$ this semi-group, we deduce that

$$\forall t \geq 0, \qquad \left\|\exp\left(tT^\infty\right)v\right\|_\infty \leq \|v\|_\infty. \tag{4.17}$$

Lemma 13. The restriction of $\tilde{A}$ of A^∞ to the subspace $F_0 = \left\{u \in C^0\left(\bar{\Omega}\right) : \int_\Omega u = 0\right\}$ is the generator of a C^0 semi-group of strict contraction $\exp\left(t\tilde{A}\right)$ on F_0 verifying for some $\mu > 0$

$$\forall v \in F_0, \qquad \left\|\exp\left(t\tilde{A}\right)v\right\|_\infty \leq e^{-\mu t}\|v\|_\infty. \tag{4.18}$$

Proof. F_0 is closed in $C^0\left(\bar{\Omega}\right)$ and is clearly invariant under $\exp\left(tA^\infty\right)$ by its definition. It follows (from [25] p. 123) that $\tilde{A}$ is the generator of a C^0 semi-group of contraction on F_0.

On the other side, it is well known that the the Laplacian operator on $C^0\left(\bar{\Omega}\right)$ has the discrete spectrum $\sigma(A)$ which totally lies in the negative half line. Since $\sigma\left(\tilde{A}\right) \subset \sigma\left(A^\infty\right)$ and $0 \notin \sigma\left(\tilde{A}\right)$, one has that $\sigma\left(\tilde{A}_2\right) \subset (-\infty,-\lambda_1]$ (for some $\lambda_1 > 0$). Apply the Theorem 4.3 (p.118) in [25], we have the conclusion of the lemma. □

We have the following result.

Proposition 14. K is the generator of a C^0 semi group $\exp(tK)$ on F verifying

$$\|\exp(tK)v\|_F \leq e^{-\mu t}\|v\|_F. \tag{4.19}$$

Now, we need to show that the function $f = \Pi_E \mathcal{F}$ and $g = \Pi_F \mathcal{F}$ are smooth enough. By the same arguments of Lemma 4.3 in [9] and note that $\mathcal{F}$ is the vector-valued function whose each component is a multi-variable polynomial. This result can be stated as follows.

Lemma 15. The function f and g have C^1 smoothness when acting on $E \times F$.

By the Central Manifold Theorem, there exists a manifold $\mathcal{M}^\epsilon = \{(x, h(x,\epsilon)), x \in E\} \in E \times F$ which is invariant for (S^ϵ). It verifies moreover $h(x^\epsilon, \epsilon) = O(\epsilon)$ and $\mathcal{M}^\epsilon$ attracts any trajectory exponentially fast in time.

Recalling E_0 defined in (4.5) and denoting $\Pi_{E_0}(U) = \frac{1}{|\Omega|}\int_\Omega U$, for all $U \in C^0(\bar{\Omega})$.
Setting that $\bar{S} = \Pi_{E_0}(S)$, $\bar{I}_i = \Pi_{E_0}(I_i)$ and $\bar{I}_{ij} = \Pi_{E_0}(I_{ij})$, for all $1 \leq i, j \leq N$.
Since $h(x^\epsilon, \epsilon) = O(\epsilon)$ as $\epsilon \to 0$, one obtains the approximation of the slow manifold to be $\dfrac{\partial \mathbf{X}}{\partial t} = f(\mathbf{X}, 0)$ as follows

$$\begin{cases} \dfrac{d}{dt}\bar{S} &= \Pi_{E_0}(r)\left(1-\bar{S}\right) + \Pi_{E_0}(\gamma_i)\bar{I}_i + \Pi_{E_0}(\gamma_{ij})\bar{I}_{ij} - \bar{S}\displaystyle\sum_{i=1}^N \Pi_{E_0}(\beta_i J_i) \\ \dfrac{d}{dt}\bar{I}_i &= \Pi_{E_0}(\beta_i J_i)\bar{S} - \left(\Pi_{E_0}(r) + \Pi_{E_0}(\gamma_i)\right)\bar{I}_i - \bar{I}_i \displaystyle\sum_{j=1}^N \left(\Pi_{E_0}(\beta_j k_{ij})\bar{I}_i + \sum_{j=1}^N \left(\Pi_{E_0}\left(\beta_j p_{ij}^i k_{ij}\right)\bar{I}_{ij} + \Pi_{E_0}\left(\beta_j p_{ji}^i k_{ij}\right)\bar{I}_{ji}\right)\right) \\ \dfrac{d}{dt}\bar{I}_{ij} &= \bar{I}_i\left(\Pi_{E_0}(\beta_j k_{ij})\bar{I}_j + \displaystyle\sum_{l=1}^N \left(\Pi_{E_0}\left(\beta_j p_{jl}^j k_{ij}\right)\bar{I}_{jl} + \Pi_{E_0}\left(\beta_j p_{lj}^j k_{ij}\right)\bar{I}_{lj}\right)\right) - \left(\Pi_{E_0}(r) + \Pi_{E_0}(\gamma_{ij})\right)\bar{I}_{ij} \end{cases} \tag{4.20}$$

Now, we make a *quasi neutral* assumption as in Table 1 and wish to transform (4.20) to apply result in [17]. It suffices to write the parameters $\Pi_{E_0}(\beta_j k_{ij})$, $\Pi_{E_0}\left(\beta_j p_{ij}^i k_{ij}\right)$, etc, in (4.20) as the forms in [17].

Indeed, we first denote

$$\begin{aligned} &\bar{r} = \Pi_{E_0}(r), \quad \bar{\beta} = \Pi_{E_0}(\beta), \quad \bar{\gamma} = \Pi_{E_0}(\gamma), \\ &\bar{b}_i = \frac{\Pi_{E_0}(\beta b_i)}{\Pi_{E_0}(\beta)}, \quad \bar{\nu}_i = \frac{\Pi_{E_0}(\gamma \nu_i)}{\Pi_{E_0}(\gamma)}, \quad \bar{u}_{ij} = \frac{\Pi_{E_0}(\gamma u_{ij})}{\Pi_{E_0}(\gamma)}, \quad 1 \leq i, j \leq N \end{aligned} \tag{4.21}$$

then $\Pi_{E_0}(\beta_i) = \bar{\beta}\left(1 + \epsilon \bar{b}_i\right) := \bar{\beta}_i$, $\Pi_{E_0}(\gamma_i) = \bar{\gamma}(1 + \epsilon\bar{\nu}_i) := \bar{\gamma}_i$ and $\Pi_{E_0}(\gamma_{ij}) = \bar{\gamma}(1 + \epsilon \bar{u}_{ij}) := \bar{\gamma}_{ij}$. Next, we set that

$$\bar{p}_{ij}^s = \frac{1}{2} + \epsilon \bar{\omega}_{ij}^s, \qquad \text{with} \quad \bar{\omega}_{ij}^s = \frac{\Pi_{E_0}\left(\beta_i \omega_{ij}^s\right)}{\Pi_{E_0}(\beta_i)};$$

and

$$\bar{k}_{ij} = \bar{k} + \epsilon \bar{\alpha}_{ij}, \qquad \text{with} \quad \bar{k} = \frac{\Pi_{E_0}(\beta k)}{\Pi_{E_0}(\beta)} \quad \text{and} \quad \bar{\alpha}_{ij} = \frac{1}{\epsilon}\left[\frac{\Pi_{E_0}(\beta_j k_{ij})}{\Pi_{E_0}(\beta_j)} - \bar{k}\right]. \tag{4.22}$$

It is necessary to note that $\bar{p}_{ij}^s \neq \Pi_{E_0}\left(p_{ij}^s\right)$ and $\bar{k}_{ij} \neq \Pi_{E_0}(k_{ij})$ to not make mistakes.

Then, we have that,

$$\Pi_{E_0}\left(\beta_i p_{ij}^s\right) = \bar{\beta}_i \bar{p}_{ij}^s, \qquad \Pi_{E_0}(\beta_j k_{ij}) = \bar{\beta}_j \bar{k}_{ij}, \quad \forall 1 \leq i, j \leq N. \tag{4.23}$$

We will show that $\bar{\alpha}_{ij} = O(1)$, indeed,

$$\begin{aligned} \bar{\alpha}_{ij} &= \frac{1}{\epsilon}\left[\frac{\int_\Omega (\beta + \epsilon b_j)(k + \epsilon \alpha_{ij})}{\int_\Omega \beta + \epsilon \int_\Omega b_j} - \frac{\int_\Omega \beta k}{\int_\Omega \beta}\right] \\ &= \frac{1}{\epsilon}\left[\left(\frac{\int_\Omega \beta k}{\int_\Omega \beta + \epsilon \int_\Omega b_j} - \frac{\int_\Omega \beta k}{\int_\Omega \beta}\right) + \epsilon \frac{\int_\Omega (k b_j + \beta \alpha_{ij})}{\int_\Omega \beta + \epsilon \int_\Omega b_j} + \epsilon^2 \frac{\int_\Omega b_j \alpha_{ij}}{\int_\Omega \beta + \epsilon \int_\Omega b_j}\right] \\ &= \frac{\int_\Omega \beta k}{\int_\Omega \beta} \cdot \frac{-\frac{\int_\Omega b_j}{\int_\Omega \beta}}{1 + \epsilon \frac{\int_\Omega b_j}{\int_\Omega \beta}} + \frac{\int_\Omega (k b_j + \beta \alpha_{ij})}{\int_\Omega \beta + \epsilon \int_\Omega b_j} + \epsilon \frac{\int_\Omega b_j \alpha_{ij}}{\int_\Omega \beta + \epsilon \int_\Omega b_j}. \end{aligned}$$

Combining this with direct calculations, we have that

$$\left\|\Pi_{E_0}\left(\beta_j k_{ij} p^s_{mn}\right) - \bar{\beta}_j \bar{k}_{ij} \bar{p}^s_{mn}\right\| = O\left(\epsilon\right), \quad s \in \{m,n\}, \qquad \forall 1 \le i,j,m,n \le N.$$

Indeed, for $s \in \{m,n\}$, for all $1 \le i,j,m,n \le N$, denote that $\epsilon\psi^{s,ij}_{mn}$ to be $\Pi_{E_0}\left(\beta_j k_{ij} p^s_{mn}\right) - \bar{\beta}_j \bar{k}_{ij} \bar{p}^s_{mn}$ then

$$\begin{aligned}
\epsilon\psi^{s,ij}_{mn} = &\epsilon\left[\frac{1}{2}\left(\Pi_{E_0}\left(kb_j\right) - \bar{k}\bar{b_j}\right) + \left(\Pi_{E_0}\left(\beta k \omega^s_{mn}\right) - \bar{\beta}\bar{k}\bar{\omega}^s_{mn}\right)\right] \\
&+\epsilon^2\left[\frac{1}{2}\left(\Pi_{E_0}\left(\alpha_{ij} b_j\right) - \bar{\alpha}_{ij}\bar{b}_j\right) + \frac{1}{2}\left(\Pi_{E_0}\left(\beta\alpha_{ij}\omega^s_{mn}\right) - \bar{\beta}\bar{\alpha}_{ij}\bar{\omega}^s_{mn}\right) + \left(\Pi_{E_0}\left(kb_j\omega^s_{mn}\right) - \bar{k}\bar{b}_j\bar{\omega}^s_{mn}\right)\right] \\
&+\epsilon^3\left[\Pi_{E_0}\left(\alpha_{ij}b_j\omega^s_{mn}\right) - \bar{\alpha}_{ij}\bar{b}_j\bar{\omega}^s_{mn}\right].
\end{aligned}$$

For the sake of applying the result in [17], we make an assumption that

Assumption 16. p^s_{ij} does not depend on x for all $1 \le i,j \le N$ and $s \in \{i,j\}$.

Hence, $\Pi_{E_0}\left(\beta_j k_{ij} p^s_{mn}\right) = \bar{\beta}_j \bar{k}_{ij} \bar{p}^s_{mn}$ and the system (4.20) becomes

$$\begin{cases}
\dfrac{d\bar{S}}{dt} &= \bar{r}\left(1-\bar{S}\right) + \displaystyle\sum_{i=1}^N \bar{\gamma}_i \bar{I}_i + \sum_{i,j=1}^N \bar{\gamma}_{ij}\bar{I}_{ij} - \bar{S}\sum_{i=1}^N \bar{\beta}_i \bar{J}_i \\
\dfrac{d\bar{I}_i}{dt} &= \bar{\beta}_i \bar{J}_i \bar{S} - \left(\bar{r}+\bar{\gamma}_i\right)\bar{I}_i - \bar{I}_i \displaystyle\sum_{j=1}^N \bar{k}_{ij}\bar{\beta}_j\bar{J}_j, \qquad 1 \le i \le N, \\
\dfrac{d\bar{I}_{ij}}{dt} &= \bar{k}_{ij}\bar{\beta}_j\bar{I}_i\bar{J}_j - \left(\bar{r}+\bar{\gamma}_{ij}\right)\bar{I}_{ij}, \qquad 1 \le i,j \le N,
\end{cases} \tag{4.24}$$

where

$$\bar{\beta}_i = \bar{\beta}\left(1+\epsilon\bar{b}_i\right), \quad \bar{\gamma}_i = \bar{\gamma}\left(1+\epsilon\bar{\nu}_i\right), \quad \bar{\gamma}_{ij} = \bar{\gamma}\left(1+\bar{u}_{ij}\right), \quad \bar{p}^s_{ij} = \frac{1}{2} + \epsilon\bar{\omega}^s_{ij}, \quad \bar{k}_{ij} = \bar{k} + \epsilon\bar{\alpha}_{ij}$$

and

$$\bar{J}_i = \bar{I}_i + \sum_{j=1}^N \left(\bar{p}^i_{ij}\bar{I}_{ij} + \bar{p}^i_{ji}\bar{I}_{ji}\right), \qquad \forall 1 \le i \le N$$

Before applying the result in [17], we make the following assumption on the basic reproduction ratio.

Assumption 17. Assume that $\int_\Omega \beta\left(x\right)dx > \int_\Omega m\left(x\right)dx$, which means $\dfrac{\int_\Omega \beta\left(x\right)dx}{\int_\Omega m\left(x\right)dx} > 1$.

Applying the result in [17] for (4.24), we have the following theorem. Initially, we define that

$$\boxed{S^* = \frac{\bar{m}}{\bar{\beta}}, \qquad T^* = 1 - S^*, \qquad I^* = \frac{\bar{m}T^*}{\bar{m} + \bar{\beta}\bar{k}T^*}, \qquad D^* = T^* - I^*} \tag{4.25}$$

and

$$\Theta = \Theta_1 + \Theta_2 + \Theta_3 + \Theta_4 + \Theta_5 \quad \text{ and } \theta_i = \frac{\Theta_i}{\Theta} \tag{4.26}$$

where

$$\Theta_1 = \chi_1 \frac{2\bar{\beta}S^*T^{*2}}{|P|}, \quad \Theta_2 = \chi_2 \frac{\bar{\gamma}I^*\left(I^*+T^*\right)}{|P|}, \quad \Theta_3 = \chi_3 \frac{\bar{\gamma}T^*D^*}{|P|}, \quad \Theta_4 = \chi_4 \frac{2\bar{m}T^*D^*}{|P|}, \quad \Theta_5 = \chi_5 \frac{\bar{\beta}T^*I^*D^*}{|P|}. \tag{4.27}$$

We see that $\theta_i > 0$ for each $i = 1,2,3,4,5$ and $\theta_1+\theta_2+\theta_3+\theta_4+\theta_5 = 1$. Using these notations, we obtain our main result.

Theorem 18. *Consider the system of equations*

$$\boxed{\begin{cases}
\dfrac{dz_i}{d\tau} = \Theta z_i\left(\left(\bar{\Lambda}\mathbf{z}\right)_i - \mathbf{z}^T\bar{\Lambda}\mathbf{z}\right), \ i = 1,\cdots,N, \\
z_1 + z_2 + \cdots + z_N = 1.
\end{cases}} \tag{4.28}$$

where $\bar{\Lambda}$ is the square matrix of size $N \times N$ whose coefficient $(i;j)$ are the pairwise fitness $\bar{\lambda}_i^j$ which satisfy

$$\boxed{\bar{\lambda}_i^j = \theta_1\left(\bar{b}_i - \bar{b}_j\right) + \theta_2\left(-\bar{\nu}_i + \bar{\nu}_j\right) + \theta_3\left(-\bar{u}_{ij} - \bar{u}_{ji} + 2\bar{u}_{jj}\right) + \theta_4\left(\bar{\omega}_{ij}^i - \bar{\omega}_{ji}^j\right) + \theta_5\left(\mu\left(\bar{\alpha}_{ji} - \bar{\alpha}_{ij}\right) + \bar{\alpha}_{ji} - \bar{\alpha}_{jj}\right).} \tag{4.29}$$

with $\mu = \dfrac{I^*}{D^*}$.
Then, for any initial values of (4.1)*, for each* $\tau_0 > 0$, $T > \tau_0$ *arbitrarily and independent on* ϵ, *there is* $\epsilon_0 > 0$, $C > 0$ *and a vector of positive coefficients* $\mathbf{z}_0 \in \mathbb{R}^N$ *verifying* $\sum_{i=1}^N \mathbf{z}_{0,i} = 1$, *such that* $\forall \epsilon < \epsilon_0$

$$\left|\bar{S}\left(\frac{\tau}{\epsilon}\right) - S^*\right| + \sum_{i=1}^N \left|I^* z_i(\tau) - \bar{I}_i\left(\frac{\tau}{\epsilon}\right)\right| + \sum_{i,j=1}^N \left|D^* z_i(\tau) z_j(\tau) - \bar{I}_{ij}\left(\frac{\tau}{\epsilon}\right)\right| \leq \epsilon C, \quad \forall \tau \in (\tau_0, T). \tag{4.30}$$

where $\bar{S}$, $(\bar{I}_1, \bar{I}_2, \ldots, \bar{I}_N)$, $\left(\bar{I}_{ij}\right)_{i,j\in\{1,\ldots,N\}}$ *are the mean values over* Ω *of the solution for* (4.1) *and* $(z_1, z_2, \ldots, z_N)$ *is the solution of reduced system* (4.28) *together with* $\mathbf{z}(0) = \mathbf{z}_0$.

5 Comparison between two cases of slow and fast diffusions

Initially, we recall the two replicator system used to approximate in both cases

Case 1. Slow diffusion $\epsilon\Delta$:

$$\begin{cases} \dfrac{\partial z_i}{\partial \tau} = \Theta z_i\left(\left(\Lambda(x)\,\mathbf{z}\right)_i - \mathbf{z}^T \Lambda(x)\,\mathbf{z}\right) + \vec{\vartheta}\cdot\nabla z_i + \Delta z_i,\ i = 1, \cdots, N, \\ z_1 + z_2 + \cdots + z_N = 1. \end{cases} \tag{5.1}$$

where $\vec{\vartheta}(x) = \dfrac{1}{|P|}\left(-D^*\nabla I^* + 2T^*\nabla T^*\right)$ and $\Lambda(x)$ is the square matrix of size $N \times N$ whose coefficient $(i;j)$ are the pairwise fitness λ_i^j which satisfy

$$\lambda_i^j(x) = \theta_1(b_i - b_j) + \theta_2(-\nu_i + \nu_j) + \theta_3(-u_{ij} - u_{ji} + 2u_{jj}) + \theta_4\left(\omega_{ij}^i - \omega_{ji}^j\right) + \theta_5\left(\mu\left(\alpha_{ji} - \alpha_{ij}\right) + \alpha_{ji} - \alpha_{jj}\right). \tag{5.2}$$

Case 2. Fast diffusion $\dfrac{1}{\epsilon}\Delta$:

$$\begin{cases} \dfrac{dz_i}{d\tau} = \Theta z_i\left(\left(\bar{\Lambda}\mathbf{z}\right)_i - \mathbf{z}^T\bar{\Lambda}\mathbf{z}\right),\ i = 1, \cdots, N, \\ z_1 + z_2 + \cdots + z_N = 1. \end{cases} \tag{5.3}$$

where $\bar{\Lambda}$ is the square matrix of size $N \times N$ whose coefficient $(i;j)$ are the pairwise fitness $\bar{\lambda}_i^j$ which satisfy

$$\bar{\lambda}_i^j = \theta_1\left(\bar{b}_i - \bar{b}_j\right) + \theta_2\left(-\bar{\nu}_i + \bar{\nu}_j\right) + \theta_3\left(-\bar{u}_{ij} - \bar{u}_{ji} + 2\bar{u}_{jj}\right) + \theta_4\left(\bar{\omega}_{ij}^i - \bar{\omega}_{ji}^j\right) + \theta_5\left(\mu\left(\bar{\alpha}_{ji} - \bar{\alpha}_{ij}\right) + \bar{\alpha}_{ji} - \bar{\alpha}_{jj}\right). \tag{5.4}$$

We first note that, in Case 1, the replicator system is partial differential equations, in which, its variables are prevalences of strains depending in space $x \in \Omega$ and time (in slow time scale) $\tau \in \mathbb{R}^+$. Moreover, it is not actually the same type of replicator equations with diffusion studied in [6] since there is a term of gradient in each equation, which is interesting. The parameters in the replicator system of this case, including the pairwise invasion fitness matrix $\left(\lambda_i^j\right)_{1\leq i,j\leq N}$ and $\vec{\vartheta} = \frac{1}{|P|}\left(-D^*\nabla I^* + 2T^*\nabla T^*\right)$, are taken from the parameters of the neutral equations then depends on space. In Case 2, meanwhile, the replicator system is ordinary differential equations, in which, its variables are total masses over the domain of strain frequencies. Thus, the system's parameters- the pairwise invasion fitness matrix, can be taken directly from original model's ones, but their mean values over domain Ω.

One point need to note is the basic reproductive ratio R_0. In Case 1, we assume in Assumption 4 that all domain Ω is high-risk site, i.e. $\beta(x) > m(x)$ for all $x \in \Omega$. Hence, the equilibrium of susceptible $S^* = \dfrac{m(x)}{\beta(x)}$ is well-defined and proved to be stable as in section 2. In this case, we denote spatial basic reproductive ratio $R_0(x) = \dfrac{\beta(x)}{m(x)}$, which exceeds 1, leading to the equilibrium of endemic mentioned in the Introduction.

However, in Case 2, we make a slighter assumption that Ω is a high-risk domain, i.e. $\int_\Omega \beta(x) > \int_\Omega m(x)$. Hence, there can exist non empty low risk site, i.e. the set H^- in (2.12) is non empty. Next, we make some analyzing on the basic reproductive ratio for the quasi-neutral SIS system with fast diffusion (i.e. Case 2). First, we assume that

Assumption 19. 1. $\int_\Omega T(x,0)\,dx > 0$, i.e. at the beginning, the total mass of infected and coinfected individuals is positive.

2. H^+ and H^- are nonempty, with H^+, H^- are in (2.12).

Thank the singular perturbation in transmission rates $\beta_i = \beta(1+\epsilon b_i)$ and clearance rates $\gamma_i = \gamma(1+\epsilon\nu_i)$, $\gamma_{ij} = \gamma(1+u_{ij})$, we now define a basic reproductive ratio R_0 for (4.1), recalling $m = \gamma + r$.

Theorem 20. *Similarly in [3], for each $\epsilon > 0$, let*

$$R_0 = \sup_{\substack{\phi\in H^1(\Omega),\\ \phi\neq 0}} \left\{ \frac{\int_\Omega \beta\phi^2}{\int_\Omega \left(\frac{1}{\epsilon}|\nabla\phi|^2 + m\phi^2\right)} \right\}. \tag{5.5}$$

Then, we have that

$$R_0 \to \frac{\int_\Omega \beta}{\int_\Omega m} \qquad as \quad \epsilon \to 0.$$

Note that, our variational characterization of the basic reproduction number R_0 is in keeping with the next generation approach for heterogeneous populations [10] which occupy a continuous spatial habitat. It is interesting that $\frac{\int_\Omega \beta}{\int_\Omega m}$ is the basic reproductive ratio R_0 of (4.24).

Proof. Firstly, we recall the semi-neutral system for (S,T) in Case 2

$$\begin{cases} \dfrac{\partial S}{\partial t} = mT - \beta TS + \dfrac{1}{\epsilon}\Delta S \\ \dfrac{\partial T}{\partial t} = -mT + \beta ST + \dfrac{1}{\epsilon}\Delta T \end{cases}. \tag{5.6}$$

with the same initial value condition of (4.1) and Neumann boundary condition.

By similar proof for Theorem 6, we have that the solution (S,T) of (4.1) can be approximated by the solution (S,T) of (5.6) with error $O(\epsilon)$.

Apply the Theorem 2 in [3], we have that $R_0 \to \dfrac{\int_\Omega \beta}{\int_\Omega m}$ as $\epsilon \to 0$. □

Next, we come to three following examples, to see more detailed comparison between two cases.

Example 21. Firstly, we consider the simplest example of an N-strain system and compact domain Ω, when all the parameters in Table 1 do not depend on x. In addition in this example, we consider the perturbations are only in the transmission rates β_i, i.e. ν_i, u_{ij}, ω_{ij}^s and α_{ij} are all zeros, for all i,j and $s \in \{i,j\}$. Without loss of generality, we assume that $b_1 > b_2 \geq b_3 \geq \cdots \geq b_N$.
In the Case 2, when diffusion is fast $\frac{1}{\epsilon}\Delta$, apply the result in [17], the strain with biggest transmission rate, in this case is strain 1, becomes the unique survivor.
Meanwhile, in the Case 2, when diffusion rates are singular $\epsilon\Delta$, we have the replicator equation system as follows

$$\begin{cases} \dfrac{\partial z_i}{\partial \tau} = \Theta_1 z_i \displaystyle\sum_{j=1}^{N} (b_i - b_j) z_j + \Delta z_i, \quad i = 1,\ldots,N \\ z_1 + z_2 + \cdots + z_N = 1 \end{cases} \tag{5.7}$$

with $\Theta_1 = \dfrac{2\beta S^* T^{*2}}{|P|}$ which can be regarded as $\dfrac{\partial \mathbf{z}}{\partial \tau} = f(\mathbf{z}) + \Delta\mathbf{z}$. We can compute the linearized operator $df|_{\bar{\mathbf{z}}} + \Delta$ with stable state $\bar{\mathbf{z}} = (1,0,\ldots,0)$ as follows

$$df|_{\bar{\mathbf{z}}} + \Delta = \begin{pmatrix} \Delta & \Theta_1(b_1-b_2) & \Theta_1(b_1-b_3) & \ldots & \Theta_1(b_1-b_N) \\ 0 & \Delta & 0 & \ldots & 0 \\ 0 & 0 & \Delta & \ldots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \ldots & \Delta \end{pmatrix}$$

which has the negative spectrum, since $b_1 - b_j > 0$ for all $j \neq 1$ and the Laplacian has negative spectrum. Apply Theorem 11.20 in [29], the state $(1, 0, \dots, 0)$ is linearly stable, implying the unique survival of strain 1.

In this example, the survival outcomes in two strain are the same.

When perturbations are only in single-infection clearance rates γ_{ij} or transmission capacity of the strain s by a co-colonized host by strain-i then strain-j p^s_{ij}, we can have the similar results by applying the same arguments.

Roughly speaking, it can happen that, in both cases: slow diffusion and fast diffusion, the unique survivors are the same.

To close this section, we consider two other examples, in which, the longtime behaviors of strains distinguish in two cases of diffusions.

Example 22. We consider in two cases the systems of two strains $N = 2$ and $\Omega = [0, 1]$ when the neutral values of parameters as follows

$$\beta = 3, \qquad k = 0.1, \qquad m = \frac{3(\psi - 0.36) + 3\sqrt{\psi(\psi - 0.8)}}{2(1.62 + \psi)}, \quad \text{with} \quad \psi(x) = \frac{1}{-\frac{1}{3}x + \frac{1}{2}}, \forall x \in [0, 1]. \tag{5.8}$$

It can be verified directly that $m < \beta$ for all x, which satisfies our assumption 4.

From (3.17), we recall that $\mu = \dfrac{1}{k(R_0 - 1)}$ and

$$\frac{\Theta_1}{\Theta_5 \mu} = 2k^2 (\mu + 1)^2 (R_0 - 1). \tag{5.9}$$

Substituting (5.8) into (5.9), by direct calculation, we can verify that

$$\frac{\Theta_5 \mu}{\Theta_1} = -\frac{1}{3}x + \frac{1}{2}. \tag{5.10}$$

In this case, we consider perturbations in transmission rates β_i and co-colonization interaction k_{ij}, which are given as follows

$$\begin{aligned} &b_1(x) = \frac{x}{3}, \qquad b_2(x) = \frac{1 - x}{3}, \\ &\alpha_{12} = x, \qquad \alpha_{21} = 1 - x, \qquad \alpha_{11} = \alpha_{12}, \quad \alpha_{22} = \alpha_{21}, \end{aligned} \tag{5.11}$$

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

In the case of fast diffusion $\frac{1}{\epsilon}\Delta$, using (5.3) and (5.4), we only need to compute the pairwise-invasion fitness for the slow-system to determine the unique survivor. From (5.11), we have that $\int_0^1 b_1 dx = \int_0^1 b_2 dx$, leading to $\bar{b}_1 = \bar{b}_2$ and $\bar{\beta}_1 = \bar{\beta}_2$. From the definition of $\bar{\alpha_{ij}}$ in (4.22), we deduce that $\bar{\lambda}^2_1 + \bar{\lambda}^1_2 < 0$, indeed, we recall the formula (5.4) in this case

$$\begin{cases} \bar{\lambda}^2_1 = \theta_5 \left(\mu \left(\bar{\alpha}_{21} - \bar{\alpha}_{12}\right) + \bar{\alpha}_{21} - \bar{\alpha}_{22}\right) \\ \bar{\lambda}^1_2 = \theta_5 \left(\mu \left(\bar{\alpha}_{12} - \bar{\alpha}_{21}\right) + \bar{\alpha}_{12} - \bar{\alpha}_{11}\right) \end{cases}. \tag{5.12}$$

Then we have that

$$\begin{aligned} \frac{1}{\theta_5}\left(\bar{\lambda}^2_1 + \bar{\lambda}^1_2\right) &= \left(\bar{\alpha}_{12} - \bar{\alpha}_{11}\right) + \left(\bar{\alpha}_{21} - \bar{\alpha}_{22}\right) = \frac{1}{\epsilon \int_0^1 \beta_1 dx} \int_0^1 (k_{21} - k_{12})(\beta_1 - \beta_2)\, dx \\ &= \frac{\beta}{\epsilon \int_0^1 \beta_1 dx} \int_0^1 (\epsilon\alpha_{21} - \epsilon\alpha_{12})(\epsilon b_1 - \epsilon b_2)\, dx = -\frac{2\epsilon}{3\int_0^1 (1 + \epsilon b_1)} \int_0^1 \left(x - \frac{1}{2}\right)^2 dx \\ &= -\frac{\beta\epsilon}{18\int_0^1 (1 + \epsilon b_1)} < 0. \end{aligned}$$

Moreover, we observe that

$$\bar{\alpha}_{12} - \bar{\alpha}_{21} = \frac{1}{\epsilon}\left[\frac{\int_0^1 \beta_2 k_{12} dx}{\int_0^1 \beta_2 dx} - \frac{\int_0^1 \beta_1 k_{21} dx}{\int_0^1 \beta_1 dx}\right] = \frac{1}{\epsilon \int_0^1 \beta_1 dx}\left[\int_0^1 (3 + \epsilon(1 - x))(0.1 + \epsilon x)\, dx - \int_0^1 (3 + \epsilon x)(0.1 + \epsilon(1 - x))\, dx\right]$$

which implies $\bar{\alpha}_{12} = \bar{\alpha}_{21}$. From (5.12), we have that

$$\bar{\lambda}^1_2 - \bar{\lambda}^2_1 = \bar{\alpha}_{22} - \bar{\alpha}_{11} = \frac{\epsilon}{\int_0^1 (1 + \epsilon b_1)\, dx} \int_0^1 (b_2\alpha_{21} - b_1\alpha_{12})\, dx = 0.$$

Then $\bar{\lambda}_1^2 = \bar{\lambda}_2^1$. Combining with $\bar{\lambda}_1^2 + \bar{\lambda}_2^1 < 0$ then $\bar{\lambda}_1^2 = \bar{\lambda}_2^1 < 0$, which leads to the bistability.

When the diffusion is slow $\epsilon\Delta$, we compute the pairwise invasion fitnesses of both strains at each $x \in [0,1]$. From (5.2), we have the explicit formulas for pairwise invasion fitness in this case as follows

$$\begin{cases} \lambda_1^2(x) = \theta_1 (b_1 - b_2) + \theta_5 \mu (\alpha_{21} - \alpha_{12}) \\ \lambda_2^1(x) = \theta_1 (b_2 - b_1) + \theta_5 \mu (\alpha_{12} - \alpha_{21}) \end{cases} \tag{5.13}$$

It is easy to see that $\lambda_1^2(x) + \lambda_2^1(x) = 0$ for all $x \in [0,1]$. We claim that $\lambda_1^2 > 0$ for all $x \in [0,1]$. Indeed, we will show that

$$b_1 - b_2 \geq \frac{\Theta_5 \mu}{\Theta_1} (\alpha_{12} - \alpha_{21}). \tag{5.14}$$

Because $3(b_1 - b_2) = \alpha_{12} - \alpha_{21} = 2x - 1$ and $\frac{\Theta_5 \mu}{\Theta_1} = -\frac{1}{3}x + \frac{1}{2}$, we have that

$$(b_1 - b_2) - \frac{\Theta_5 \mu}{\Theta_1} (\alpha_{12} - \alpha_{21}) = \frac{1}{3} (2x-1)^2 \geq 0,$$

implies the inequality (5.14). According to the formulas for pairwise invasion fitnesses (5.13), this means that, at every point $x \in \Omega$, strain 1 excludes strain 2 in the case of asymptotically small diffusion.

Roughly speaking, it can happen that, when the diffusion rates are singular, a strain is the unique survivor at each point of domain; meanwhile, in the case of large rates of diffusion, the longtime behavior is bistability.

The following example is similar to the Example 22. In which, strain 1 is the unique survivor at each point of domain in the case of slow diffusion, but strain 2 excludes strain 1 when the diffusion is asymptotically fast.

Example 23. We consider in two cases the systems of two strains $N = 2$ and $\Omega = [0,1]$ when the neutral values of parameters as follows

$$\beta = 2, \qquad k = 0.2, \qquad m = \frac{\psi - 0.64 + \sqrt{\psi(\psi - 1.6)}}{1.28 + \psi}, \quad \text{with} \quad \psi(x) = \frac{1}{-\frac{1}{3}x + \frac{1}{2}}, \forall x \in [0,1]. \tag{5.15}$$

It can be verified directly that $m < \beta$ for all x, which satisfies our assumption 4.

Analogously to the previous Example 22, by direct calculation, we can verify that

$$\frac{\Theta_5 \mu}{\Theta_1} = -\frac{1}{3}x + \frac{1}{2}. \tag{5.16}$$

In this case, we consider perturbations in transmission rates β_i and co-colonization interaction k_{ij}, which are given as follows

$$\begin{aligned} &b_1(x) = \frac{x}{2}, \qquad b_2(x) = \frac{1-x}{2}, \\ &\alpha_{12} = x(x+1), \qquad \alpha_{21} = (1-x)(x+1), \qquad \alpha_{11} = \alpha_{12}, \quad \alpha_{22} = \alpha_{21}, \end{aligned} \tag{5.17}$$

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

When the diffusion rates are singular $\epsilon\Delta$, we compute the pairwise invasion fitnesses of both strains at each $x \in [0,1]$. From (5.2), we have the explicit formula for pairwise invasion fitnesses in this case as follows

$$\begin{cases} \lambda_1^2(x) = \theta_1 (b_1 - b_2) + \theta_5 \mu (\alpha_{21} - \alpha_{12}) \\ \lambda_2^1(x) = \theta_1 (b_2 - b_1) + \theta_5 \mu (\alpha_{12} - \alpha_{21}) \end{cases} \tag{5.18}$$

It is easy to see that $\lambda_1^2(x) + \lambda_2^1(x) = 0$ for all $x \in [0,1]$. We claim that $\lambda_1^2 > 0$ for all $x \in [0,1]$. Indeed, we will show that

$$b_1 - b_2 \geq \frac{\Theta_5 \mu}{\Theta_1} (\alpha_{12} - \alpha_{21}). \tag{5.19}$$

Because $2(b_1 - b_2) = 2x - 1$, $\alpha_{12} - \alpha_{21} = (2x-1)(x+1)$ and $\frac{\Theta_5 \mu}{\Theta_1} = -\frac{1}{3}x + \frac{1}{2}$, we have that

$$(b_1 - b_2) - \frac{\Theta_5 \mu}{\Theta_1} (\alpha_{12} - \alpha_{21}) = \frac{1}{6} x (2x-1)^2 \geq 0,$$

implies the inequality (5.19). According to the formulas for pairwise invasion fitnesses (5.18), this means that, at every point $x \in \Omega$, strain 1 excludes strain 2 in the case of asymptotically slow diffusion.

Meanwhile, in the case of fast diffusion $\frac{1}{\epsilon}\Delta$, using (5.3) and (5.4), we only need to compute the pairwise-invasion fitness for the slow-system to determine the unique survivor. From (5.17), we have that $\int_0^1 b_1 dx = \int_0^1 b_2 dx$, leading to $\bar{b}_1 = \bar{b}_2$ and $\bar{\beta}_1 = \bar{\beta}_2$.

From the definition of $\bar{\alpha_{ij}}$ in (4.22), we deduce that $\bar{\lambda}_1^2 + \bar{\lambda}_2^1 \to 0$ as $\epsilon \to 0$, indeed, we recall the formula (5.4) in this case

$$\begin{cases} \bar{\lambda}_1^2 = \theta_5 \left(\mu \left(\bar{\alpha}_{21} - \bar{\alpha}_{12}\right) + \bar{\alpha}_{21} - \bar{\alpha}_{22}\right) \\ \bar{\lambda}_2^1 = \theta_5 \left(\mu \left(\bar{\alpha}_{12} - \bar{\alpha}_{21}\right) + \bar{\alpha}_{12} - \bar{\alpha}_{11}\right) \end{cases}. \tag{5.20}$$

Then we have that

$$\begin{aligned} \frac{1}{\theta_5}\left(\bar{\lambda}_1^2 + \bar{\lambda}_2^1\right) &= \left(\bar{\alpha}_{12} - \bar{\alpha}_{11}\right) + \left(\bar{\alpha}_{21} - \bar{\alpha}_{22}\right) = \frac{1}{\epsilon \int_0^1 \beta_1 dx} \int_0^1 \left(k_{21} - k_{12}\right)\left(\beta_1 - \beta_2\right) dx \\ &= \frac{\beta}{\epsilon \int_0^1 \beta_1 dx} \int_0^1 \left(\epsilon\alpha_{21} - \epsilon\alpha_{12}\right)\left(\epsilon b_1 - \epsilon b_2\right) dx = -\frac{2\epsilon}{\int_0^1 \left(1 + \epsilon b_1\right)} \int_0^1 \left(x - \frac{1}{2}\right)^2 (x+1)\, dx \\ &= -\frac{\beta\epsilon}{4\int_0^1 \left(1 + \epsilon b_1\right)} \to 0 \quad \text{when} \quad \epsilon \to 0. \end{aligned}$$

Moreover, we observe that

$$\begin{aligned} \bar{\alpha}_{12} - \bar{\alpha}_{21} &= \frac{1}{\epsilon}\left[\frac{\int_0^1 \beta_2 k_{12} dx}{\int_0^1 \beta_2 dx} - \frac{\int_0^1 \beta_1 k_{21} dx}{\int_0^1 \beta_1 dx}\right] \\ &= \frac{1}{\int_0^1 \beta_1 dx}\left[\int_0^1 \left(2 + \epsilon\left(1 - x\right)\right)\left(0.2 + \epsilon x\left(x + 1\right)\right) dx - \int_0^1 \left(2 + \epsilon x\right)\left(0.2 + \epsilon\left(1 - x\right)\left(x + 1\right)\right) dx\right] \\ &= \frac{1}{\int_0^1 \beta_1 dx} \int_0^1 \left(2x - 1\right)\left(2x + 1.8\right) dx = \frac{1}{3\int_0^1 \beta_1 dx} > 0. \end{aligned}$$

From (5.20), we have that

$$\bar{\lambda}_2^1 - \bar{\lambda}_1^2 = \left(2\mu + 1\right)\left(\bar{\alpha}_{12} - \bar{\alpha}_{21}\right) + \left(\bar{\alpha}_{22} - \bar{\alpha}_{11}\right) = \frac{1}{\int_0^1 \left(1 + \epsilon b_1\right) dx}\left[\left(\frac{2\mu + 1}{6}\right) - \frac{1}{6} - \frac{\epsilon}{12}\right] = \frac{1}{\int_0^1 \left(1 + \epsilon b_1\right) dx}\left(\frac{\mu}{3} - \frac{\epsilon}{12}\right) > 0$$

for ϵ small enough. Then $\bar{\lambda}_1^2 < 0 < \bar{\lambda}_2^1$ for ϵ small enough, since $\bar{\lambda}_2^1 - \bar{\lambda}_1^2 = O(1)$. Therefore, when the diffusion is fast, strain 2 excludes strain 1 in long time.

Roughly speaking, it can happen that, when the diffusion rates are singular, a strain, denoted by strain 1, is the unique survivor at each point of domain; meanwhile, in the case of large rates of diffusion, the other strain, denoted strain 2, will exclude strain 1 over the domain.

6 Conclusion

Epidemiology for homogeneous environment receives many intention so far [4] because invasion of disease is now an international public health problem. In reality, populations tend not to be homogeneous and there are nonlocal interactions. Hence, people investigate more theory on the geographical spread of infectious diseases. The mechanisms of invasion of disease to new territories may take many different forms and there are several ways to model such problems [12, 16, 18, 23], in which, the equilibrium behavior has been studied. This mathematical study provides a fundamental advance in understanding analytically quasi-neutral dynamics between multiple strains in a co-infection diffusion system. Until now, explicit and general derivations of coinfection dynamics among N strains are very rare in the literature, especially models with diffusion. Nevertheless, many models have been proposed to investigate effect of diffusion of disease infection [24, 14, 13, 28].

Motivated by the dynamics without diffusion in [17], we formulate an SIS-type reaction diffusion equations among similar strains, in both cases of slow and fast diffusions. Naturally in this present model, infectious strains compete for susceptible and singlycolonized hosts, which are the only resources that can favor their growth and propagation. The different traits provide each strain with variable fitness advantages or disadvantages in exploiting such dynamic resources in the system, and interact together to shape multi-strain selection. We aim to simplify the dynamics when small perturbations arise in the clearance rates, transmission rates, within-host competitiveness coefficients, as well as co-colonization susceptibility interaction factors between strains. However, with spatial structure, it requires us to add some appropriate assumptions, especially, the assumption of high-risk site Ω with slow diffusion and the assumption of

When diffusion rates are singular ($\epsilon\Delta$), we base on the framework in [17] and adapt for our current system, including proving a Tikhonov-like Theorem. The details of this framework are not mentioned again here. We derive the corresponding slow-fast form for the global dynamics, with the system of strain frequencies completely explicit, and provide the formal approximation for solutions of all epidemiological variables by quantifying error estimates. We reduce the complexity of $N^2 + N + 1$ equations of the original SIS compartmental model to the N-equations of replicator dynamics with diffusion, which reduces substantially time for computation. Meanwhile, for the case of fast diffusion ($\frac{1}{\epsilon}\Delta$), we apply the Central Manifold Theorem to obtain an SIS system for total masses of susceptible, infected and coinfected individuals, which allows us to use the main result in [17]. Accordingly, the reduced system in this case is the replicator equation, which is studied widely [15]. A similar point in both approaches is that, the error in approximation is estimated for total masses of susceptible, infected and coinfected strains.

When the diffusion is fast, we can use the result about survival outcome of strains in [17] to study the longtime behavior of total mass of each strain. However, there is not much study on the replicator equations with diffusion and gradient, so there is no general theory for the long time phenomena of individuals in the case of slow diffusion. Though, it is exciting to envision how this approach could be extended to other epidemiological models of multi- strain dynamics with diffusion or even more with general spatial structure. Like the non-spatial model, an essential requirement is that their embedded neutral system admits a central manifold which is globally stable. The challenge would then be to identify the equations governing slow motion on this manifold in each specific model. It is essential to note that we use strong assumption of high-risk site Ω in Case 1 and high-risk domain Ω in Case 2, which lead to the endemic equilibrium. In general, without these assumption, people are interested in the theory of disease-free equilibrium and endemic equilibrium, [3, 33].

In Case 1, when diffusion rates are singular, without the assumption of high risk site Ω, i.e. $H^- \neq \emptyset$, there are points x's at which $S^* = 1$, that may not allow the smoothness of S^* in x. Then, our approach may not work because $\|S - S^*\|_2 \to O(\sqrt{\epsilon})$ may not hold anymore.

One more thing, until now we have not considered a spatial component of intermediate diffusion ($d\Delta$, $d > 0$) to the multi-strain dynamics. A further perspective is considering the application of the Central Manifold Theorem to this model.

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A Appendix: Proof for theorems

A.1 Proof for theorem 2

In this proof, we will show that equation, recalling Ω compact,

$$\begin{cases} \dfrac{\partial u}{\partial t} = F\left(u\left(x,t\right),x\right) + d\Delta u, \\ \dfrac{\partial u}{\partial n} = 0 \quad \text{on} \quad \partial\Omega, \qquad u\left(x,0\right) = u_0\left(x\right) \end{cases} \tag{A.1}$$

has unique solution $u : \Omega \times [0,\infty) \to \mathbb{R}^n$, satisfying $u \in C^2\left(\Omega \times \cdot, \mathbb{R}^n\right) \cap C^1\left(\cdot \times [0,\infty), \mathbb{R}^n\right)$ when $F : \mathbb{R}^n \times \Omega \to \mathbb{R}^n$ is a Lipschitz map with respect to the first variable, i.e. there exists a constant L such that

$$\left\|F\tilde{u} - F\tilde{v}\right\| \leq L\left\|\tilde{u} - \tilde{v}\right\|, \qquad \forall \tilde{u}, \tilde{v} \in \mathbb{R}^n, \quad \forall x \in \Omega. \tag{A.2}$$

First, we denote that $Q_{\mathcal{T}} = \Omega \times [0,\infty)$ and $\bar{Q}_{\mathcal{T}} = \Omega \times [0,\infty)$ and $u\left(x,t\right) \in \mathbb{R}^n$ for $(x,t) \in \bar{Q}_{\mathcal{T}}$. When seen the Laplacian as an operator on $L^2\left(\Omega\right)$, the operator A^2 with homogeneous Neumann boundary conditions is defined as

$$\begin{aligned} &D\left(A^2\right) = \left\{U \in H^1\left(\Omega\right) : \exists V \in L^2\left(\Omega\right), \forall \phi \in H^1\left(\Omega\right), \int \nabla U\left(x\right)\nabla\phi\left(x\right)dx = -d\int V\left(x\right)\phi\left(x\right)dx\right\}, \\ &A^2U := V, \quad U \in D\left(A^2\right). \end{aligned} \tag{A.3}$$

In order to obtain uniform estimates, we prefer to focus on the operator $A^\infty := A$ acting on $C^2(\Omega)$. Denoting by operator A to be the Laplacian Δ acting on $\left(C^2\left(\Omega \times \cdot\right)\right)^n$. Hence, we define

$$\begin{aligned} &D\left(A^\infty\right) := \left\{U \in D\left(A^2\right) \cap C\left(\bar{\Omega}\right), A^2U \in C\left(\bar{\Omega}\right)\right\}, \\ &A^\infty U = A^2U, \quad U \in D\left(A^\infty\right). \end{aligned} \tag{A.4}$$

Firstly, by Duhamel's formula and [25], (A.1) implies that

$$u\left(x,t\right) = e^{At}u_0 + \int_0^t e^{A(t-s)}F\left(u\left(x,s\right),x\right)ds, \qquad \forall\left(x,t\right) \in Q_{\mathcal{T}} \tag{A.5}$$

where $\exp\left(At\right)$ is the semi-group generated by the operator Δ with the Neumann boundary condition. We consider the operator T defined by

$$Tu\left(x,t\right) := e^{At}u_0 + \int_0^t e^{A(t-s)}F\left(u\left(x,s\right),x\right)ds, \qquad \forall\left(x,t\right) \in Q_{\mathcal{T}}.$$

Given $k > 0$, to be fixed later, set

$$X = \left\{u \in C^1\left(\Omega \times [0,+\infty), \mathbb{R}^n\right); \sup_{\substack{t\geq 0 \\ x\in\Omega}} e^{-kt}\left\|u\left(x,t\right)\right\| \leq +\infty\right\}$$

We can check that X is a Banach space for the norm

$$\left\|u\right\|_X = \sup_{\substack{t\geq 0 \\ x\in\Omega}} e^{-kt}\left\|u\left(x,t\right)\right\|.$$

For every $u \in X$, the Tu also belongs to X. To prove this, using the argument in the beginning of subsection 4.2,we first recall that A is the generator of a C^0 semi-group $\exp\left(tA\right)$ on $C^2\left(\Omega \times \cdot\right)$ verifying $\left\|\exp\left(tA\right)v\right\| \leq \exp\left(-\mu t\right)\left\|v\right\|$, for $\mu \geq 0$.

Then we observe that

$$\begin{aligned} e^{-kt}\left\|Tu\right\| &\leq \left\|e^{(A-kI)t}u_0\right\| + e^{-kt}\int_0^t \left\|e^{A(t-s)}F\left(u\left(x,s\right),x\right)\right\|ds \\ &\leq \left\|e^{(A-kI)t}u_0\right\| + e^{-kt}\int_0^t e^{-\mu(t-s)}\left\|F\left(u\left(x,s\right),x\right)\right\|ds \\ &\leq \left\|e^{(A-kI)t}u_0\right\| + e^{-kt}\int_0^t \left(L\left\|u\left(x,s\right) - u_0\right\| + \left\|Fu_0\right\|\right)ds \end{aligned}$$

according to (A.2). Hence, we deduce that

$$e^{-kt}\|Tu\| \leq \left\|e^{(A-kI)t}u_0\right\| + e^{-kt}t\left(L\|u_0\| + \|Fu_0\|\right) + e^{-kt}L\int_0^t \|u(x,s)\|\,ds.$$

Alternatively, we have that

$$e^{-kt}L\int_0^t \|u(x,s)\|\,ds = e^{-kt}L\int_0^t e^{-ks}\|u(x,s)\|\cdot e^{ks}ds \leq e^{-kt}L\|u\|_X\int_0^t e^{ks}ds$$

which implies

$$e^{-kt}\|Tu\| \leq \left\|e^{(A-kI)t}u_0\right\| + e^{-kt}t\left(L\|u_0\| + \|Fu_0\|\right) + \frac{1}{k}L\|u\|_X\left(1-e^{-kt}\right),$$

leading to $Tu \in X$ whenever $u \in X$.

Moreover, for all $u, v \in X$, we have that

$$\begin{aligned}\|Tu - Tv\|_X &\leq e^{-kt}\int_0^t \left\|e^{A(t-s)}\left[F(u(x,s),x) - F(v(x,s),x)\right]\right\| ds\\ &\leq e^{-kt}\int_0^t e^{-\mu(t-s)}\|F(u(x,s),x) - F(v(x,s),x)\|\,ds\\ &\leq Le^{-(k+\mu)t}\int_0^t e^{(\mu+k)s}\cdot e^{-ks}\|u(x,s)-v(x,s)\|\,ds \leq \frac{L}{\mu+k}\left(1-e^{-(\mu+k)t}\right)\|u-v\|_X.\end{aligned}$$

Fixing $k > 0$ such that $k + \mu > L$ then applying the Banach fixed point theorem, we obtain that (A.1) has at least one solution.

For the uniqueness, assume there exists functions u and v, which satisfy for (A.5). For any given $\mathcal{T} > 0$, we have that

$$\begin{aligned}\|u(x,t) - v(x,t)\| &\leq \left\|e^{At}(u_0 - v_0)\right\| + \int_0^t \left\|e^{A(t-s)}\left[F(u(x,s),x) - F(v(x,s),x)\right]\right\| ds\\ &\leq ML\int_0^t \|u(x,s) - v(x,s)\|\,ds, \qquad \forall 0 \leq t \leq \mathcal{T}\end{aligned}$$

By the Gronwall's inequality and the same initial value of u and v, we have that $u(,t) = v(x,t)$, for all $x \in \Omega$ and $0 \leq t \leq \mathcal{T}$. This holds for all $\mathcal{T} \geq 0$, which yields the uniqueness of solution.

Therefore, the equation (2.4) has the unique solution.

A.2 Proof for theorem 5

The idea of our proof bases on the technique mentioned in [22].

Proof. Firstly, we make a convention for the norm using in this proof. For each $t \in \mathbb{R}^+$, for every $f_1, f_2 \in L^2(\Omega \times \mathbb{R}, \mathbb{R}^n)$ we denote

$$\langle f_1, f_2\rangle = \int_\Omega f_1(x,t)\cdot f_2(x,t)\,dx,$$

where the $f_1 \cdot f_2$ representing for the usual scalar product $\sum_{i=1}^n f_1^i f_2^i$ in $\mathbb{R}^n$. This scalar product $\langle\cdot,\cdot\rangle$ induces the norm

$$\|f(\cdot,t)\|_2 = \left(\int_\Omega f(x,t)\cdot f(x,t)\,dx\right)^{1/2}$$

For the sake of convenience in this proof, we only write $\|\cdot\|$ instead of $\|\cdot\|_2$.

We do the same convention for $\langle g_1, g_2\rangle$ and $\|g(\cdot,t)\|$ for all $g_1, g_2, g \in C^1(\Omega \times \mathbb{R}, \mathbb{R}^m)$.

Because in the finite dimensional space, all norms are equivalent, we then denote $|\cdot|$ to be the usual 2-Euclidean norm. Moreover, we recall the notation $A \prec 0$ for a symmetric matrix A if A is definitely negative, and $A \succ 0$ for definitely positive symmetric matrix.

First, let us show that the interval $[t_0, t_1]$ can be subdivided into subinterval $\Delta_k = [\tau_{k-1}, \tau_k]$, where $k \in \{1, 2, \ldots, N\}$ and $t_0 = \tau_0 < \tau_1 < \cdots < \tau_N = t_1$ in such a way that for every k, there exists a symmetric matrix $P_k = P_k^T \succ 0$ for which

$$P_k A(x,t) + A^T(x,t)P_k \prec -I. \tag{A.6}$$

Indeed, since $A(x,t)$ is a Hurwitz matrix for every $t \in [t_0, t_1]$, according to [11], there exists $P(x,t) = P^T(x,t) \succ 0$ such that

$$P(x,t)A(x,t) + A^T(x,t)P(x,t) \prec -I.$$

Since A depends continuously on t, there exists an open interval $\Delta(t)$ such that $t \in \Delta(t)$ and

$$P(x,t)A(x,\tau) + A^T(x,\tau)P(x,t) \prec -I, \quad \forall \tau \in \Delta(t).$$

Now the open intervals $\Delta(t)$ with $t \in [t_0, t_1]$ cover the whole closed bounded interval $[t_0, t_1]$ and taking a finite number of τ_k, $k = 1, \ldots, N$ such that $[t_0, t_1]$ is completely covered by $\Delta(\tau_k)$ yields the desired partition subdivision.

We can note that a strictly negative upper bound is not required on the real parts eigenvalues uniformly in space, because the spatial domain is supposed to be compact.
Note that, from (A.6), for all $y \in \mathbb{R}^m$ we have that

$$y^T \left(P_k A + A^T P_k\right) y \prec -y^T y. \tag{A.7}$$

Second, because F, G are continuously differential in x and t, then for every $\mu > 0$ there exists $C, r > 0$ such that

$$\left\|F\left(f_0(x,t) + \bar{\delta}_f(x,t), g_0(x,t) + \bar{\delta}_g(x,t), x, t\right) - F\left(f_0, g_0, x, t\right)\right\| \leq C\left(\left\|\bar{\delta}_f(x,t)\right\| + \left\|\bar{\delta}_g(x,t)\right\|\right) \tag{A.8}$$

for all $t \in \mathbb{R}$, $\bar{\delta}_f(x,t) \in \mathbb{R}^n$, $\bar{\delta}_g(x,t) \in \mathbb{R}^m$ satisfying

$$\forall t \in [t_0, t_1], \forall x \in \Omega, \qquad |\bar{\delta}_f(x,t)| \leq r, \qquad |\bar{\delta}_g(x,t)| \leq r.$$

For the sake of simplicity, we write $\bar{\delta}_f$ and $\bar{\delta}_g$ instead of $\bar{\delta}_f(x,t)$ and $\bar{\delta}_g(x,t)$. We now have the Taylor expansion as follows, noting that $G(f_0(x,t), g_0(x,t), x, t) = 0$,

$$G\left(f_0(x,t) + \bar{\delta}_f, g_0(x,t) + \bar{\delta_g}, x, t\right) = A(x,t)\,\bar{\delta_g} + B(x,t)\bar{\delta}_f + o\left(|\bar{\delta_g}|\right) + o\left(|\bar{\delta_g}|\right), \tag{A.9}$$

with $B(x,t)$ is the Jacobian matrix of $G(\cdot,\cdot,t)$ with respect to the first variable.

For each $k = 1, \ldots, N$, and $u \in \mathbb{R}^m$, set $|u|_k = \left(u^T P_k u\right)^{1/2}$, then $|\cdot|_k$ is a norm in $\mathbb{R}^m$. Indeed, because $P_k \succ 0$ then $|\cdot|_k$ is well-defined, it suffices to check the condition $|u+v|_k \leq |u|_k + |v|_k$, which is equivalent to

$$\left(u^T P_k v\right)^2 \leq \left(u^T P_k u\right)\left(v^T P_k v\right).$$

It now becomes

$$\left(\left(L^T u\right)^T \left(L^T v\right)\right)^2 \leq \left(\left(L^T u\right)^T \left(L^T u\right)\right)\left(\left(L^T v\right)^T \left(L^T v\right)\right), \tag{A.10}$$

thanks to the Cholesky's factorization, which states that, if $P_k \succ 0$, there exist a square matrix such that $P_k = L_k^T L_k$. Note that, (A.10) holds because of the inequality Cauchy-Schwarz. Hence, $|\cdot|_k$ is a norm in $\mathbb{R}^m$ and it is equivalent to an arbitrary norm in $\mathbb{R}^m$.

Then, for $\delta_f(x,t) = f(x,t) - f_0(x,t)$, $\delta_g(x,t) = g(x,t) - g_0(x,t)$, we have that

$$\begin{cases} \dfrac{d}{dt}\|\delta_f\|^2 & \leq C_1\left(\|\delta_f\| + \|\delta_g\|\right)\|\delta_f\|, \\ \epsilon\dfrac{d}{dt}\|\delta_g\|_k^2 & \leq -q\|\delta_g\|_k^2\,dt + C_1\left(\|\delta_f\|^2 + \epsilon\right)dt \end{cases} \tag{A.11}$$

as long as δ_f, δ_g are sufficiently small, where C_1, q are positive constants which do not depend on k.
Initially, for the sake of simplicity, in the following arguments, we write f, g instead of $f(x,t)$ and $g(x,t)$, respectively. Then, we have the equation for $\delta_f(x,t)$ as follows

$$\frac{\partial}{\partial t}\delta_f = F\left(f_0 + \delta_f, g_0 + \delta_g, x, t\right) - F\left(f_0, g_0, x, t\right) + K\delta_f \quad .$$

By the convention of $\|\cdot\|$, we have that

$$\begin{aligned} \frac{d}{dt}\|\delta_f\|^2 &= \frac{d}{dt}\langle\delta_f, \delta_f\rangle = 2\langle\frac{\partial}{\partial t}\delta_f, \delta_f\rangle \\ &= \langle F\left(f_0 + \delta_f, g_0 + \delta_g, x, t\right) - F\left(f_0, g_0, x, t\right) + K\delta_f, \delta_f\rangle \\ &= \langle F\left(f_0 + \delta_f, g_0 + \delta_g, x, t\right) - F\left(f_0, g_0, x, t\right), \delta_f\rangle + \langle K\delta_f, \delta_f\rangle \\ &\leq \|F\left(f_0 + \delta_f, g_0 + \delta_g, x, t\right) - F\left(f_0, g_0, x, t\right)\|\,\|\delta_f\| + \langle K\delta_f, \delta_f\rangle \\ &\leq C\left(\|\delta_f\| + \|\delta_g\|\right)\|\delta_f\| + \langle K\delta_f, \delta_f\rangle. \end{aligned}$$

On the other hand, recalling that $K_f = a_f(x)\nabla + \Delta$ implies

$$\langle K_f\delta_f, \delta_f\rangle = \langle \Delta\delta_f, \delta_f\rangle + \langle a_f(x)\nabla\delta_f, \delta_f\rangle = -\int_\Omega |\nabla\delta_f|^2 dx + \int_\Omega a_f(x)\nabla\delta_f\cdot\delta_f dx$$

which leads to, when we apply the Young inequality for the term $\int_\Omega a(x)\nabla\delta_f\cdot\delta_f dx$,

$$\langle K_f\delta_f, \delta_f\rangle \le -\int_\Omega |\nabla\delta_f|^2 dx + \max_{x\in\Omega}(|a_f(x)|)\left[\frac{1}{\max\limits_{x\in\Omega}(|a_f(x)|)}\int_\Omega |\nabla\delta_f|^2 dx + C\left(\max_{x\in\Omega}(|a_f(x)|)\right)\int_\Omega |\delta_f|^2 dx\right],$$

where $|a_f(x)|$ is the matrix in which entries are absolute values of corresponding coordinates of $a_f(x)$.

Accordingly, we have the estimation for $\frac{d}{dt}\|\delta_f\|^2$ as follows

$$\frac{d}{dt}\|\delta_f\|^2 \le C_1(\|\delta_f\| + \|\delta_g\|)\|\delta_f\| \tag{A.12}$$

Next, we come to control the growth of $\|\delta_g\|_k$. We first observe that

$$\epsilon\frac{\partial}{\partial t}\delta_g = G(f_0(x,t)+\delta_f, g_0(x,t)+\delta_g, x, t) + \epsilon K_g\delta_g + \epsilon\left[K_g g_0(x,t) + \frac{\partial}{\partial t}g_0(x,t) + G_1(x)\cdot\nabla f_0\right] + \epsilon G_1(x)\cdot\nabla\delta_f.$$

We denote $\epsilon\left[K_g g_0(x,t) + \frac{\partial}{\partial t}g_0(x,t) + G_1(x)\cdot\nabla f_0\right]$ as $O(\epsilon)$, then

$$\epsilon\frac{\partial}{\partial t}\delta_g = G(f_0(x,t)+\delta_f, g_0(x,t)+\delta_g, x, t) + \epsilon K_g\delta_g + O(\epsilon) + \epsilon G_1(x)\cdot\nabla\delta_f. \tag{A.13}$$

Using the Taylor expansion for G in (A.9) and the equation (A.13), we obtain the following computations

$$\begin{aligned}
\epsilon\frac{d}{dt}\|\delta_g\|_k^2 &= \epsilon\frac{d}{dt}\langle\delta_g, P_k\delta_g\rangle = \epsilon\langle\frac{\partial}{\partial t}\delta_g, P_k\delta_g\rangle + \epsilon\langle\delta_g, P_k\frac{\partial}{\partial t}\delta_g\rangle\\
&= (\langle A\delta_g, P_k\delta_g\rangle + \langle\delta_g, P_k A\delta_g\rangle) + 2B(x,t)\langle\delta_f,\delta_g\rangle + \langle o(|\delta_g|) + o(|\delta_g|) + O(\epsilon), P_k\delta_g + \delta_g\rangle\\
&+ 2\epsilon\langle G_1(x)\cdot\nabla\delta_f, P_k\delta_g + \delta_g\rangle + \epsilon\langle K_g\delta_g, P_k\delta_g + \delta_g\rangle\\
&= \langle\delta_g, \left(A^T P_k + P_k A\right)\delta_g\rangle + 2B(x,t)\langle\delta_f,\delta_g\rangle + \langle o(|\delta_f|) + o(|\delta_g|) + O(\epsilon), P_k\delta_g + \delta_g\rangle\\
&+ 2\epsilon\langle G_1(x)\cdot\nabla\delta_f, P_k\delta_g + \delta_g\rangle + \epsilon\langle K_g\delta_g, P_k\delta_g + \delta_g\rangle\\
&\le -\|\delta_g\|^2 + 2C_1\|\delta_f\|\|\delta_g\| + \langle o(|\delta_f|) + o(|\delta_g|) + O(\epsilon), P\delta_g + \delta_g\rangle + 2\epsilon\langle G_1(x)\cdot\nabla, P_k\delta_g + \delta_g\rangle + \epsilon\langle K_g\delta_g, P\delta_g + \delta_g\rangle.
\end{aligned} \tag{A.14}$$

Using the Young inequality, we have the estimation for $\langle o(|\delta_f|) + o(|\delta_g|) + O(\epsilon), P\delta_g + \delta_g\rangle$ as follows

$$\langle o(|\delta_f|) + o(|\delta_g|) + O(\epsilon), P\delta_g + \delta_g\rangle \le O(\epsilon) + \tilde{C}\|\delta_g\|^2, \qquad \text{with} \quad \tilde{C} \ll 1. \tag{A.15}$$

Alternatively, applying the Young inequality, we have that

$$\langle G_1(x)\cdot\nabla\delta_f, P_k\delta_g + \delta_g\rangle \le C(G_1)\|\nabla\delta_f\|^2 + \|\delta_g\|^2 \le C(G_1) + \|\delta_g\|^2 \tag{A.16}$$

since $\nabla\delta_f$ is bounded in Ω.

For the term $\langle K_g\delta_g, P\delta_g + \delta_g\rangle$, we get that

$$\begin{aligned}
\langle K_g\delta_g, P\delta_g + \delta_g\rangle &= \langle\Delta\delta_g, P\delta_g\rangle + \langle\Delta\delta_g,\delta_g\rangle + \langle a_g(x)\nabla\delta_g, P\delta_g\rangle + \langle a_g(x)\nabla\delta_g,\delta_g\rangle\\
&= \int_\Omega \Delta\delta_g\cdot P\delta_g dx + \int_\Omega \Delta\delta_g\cdot\delta_g dx + \int_\Omega a_g(x)\nabla\delta_g\cdot P\delta_g dx + \int_\Omega a_g(x)\nabla\delta_g\cdot\delta_g dx\\
&= -\int_\Omega \nabla\delta_g\cdot\nabla(P\delta_g)dx - \int_\Omega |\nabla\delta_g|^2 dx + \int_\Omega a_g(x)\nabla\delta_g\cdot P\delta_g dx + \int_\Omega a_g(x)\nabla\delta_g\cdot\delta_g dx\\
&= -\int_\Omega \nabla\delta_g P\nabla\delta_g dx - \int_\Omega \nabla\delta_g\cdot(\nabla P)\delta_g dx - \int_\Omega |\nabla\delta_g|^2 dx + \int_\Omega a_g(x)\nabla\delta_g\cdot P\delta_g dx + \int_\Omega a_g(x)\nabla\delta_g\cdot\delta_g dx.
\end{aligned}$$

Note that $P\succ 0$ then $\int_\Omega \nabla\delta_g P\nabla\delta_g dx \ge \lambda\|\nabla\delta_g\|^2$. Applying the Young inequality once more for the terms

$$\int_\Omega \nabla\delta_g\cdot(\nabla P)\delta_g dx, \qquad \int_\Omega a_g(x)\nabla\delta_g\cdot P\delta_g dx, \qquad \int_\Omega a_g(x)\nabla\delta_g\cdot\delta_g dx,$$

we have that

$$\langle K_g\delta_g, P\delta_g+\delta_g\rangle \leq -(1+\lambda)\left\|\nabla\delta_g\right\|^2+(1+\lambda)\left\|\nabla\delta_g\right\|^2+C(1+\lambda)\left\|\delta_g\right\|^2$$

which implies

$$\langle K_g\delta_g, P\delta_g+\delta_g\rangle \leq C(1+\lambda)\left\|\delta_g\right\|^2, \tag{A.17}$$

with $C(1+\lambda)$ denoting a constant depending on $1+\lambda$.

Combining these equations (A.14), (A.15), (A.16), and (A.17), and noting that two norms $\|\cdot\|_k$ and $\|\cdot\|_k$ are equivalent, we observe that

$$\epsilon\frac{\partial}{\partial t}\left\|\delta_g\right\|_k^2 \leq (2\epsilon+\epsilon C(1+\lambda)-1)\left\|\delta_g\right\|_k^2+C_1\left\|\delta_f\right\|\left\|\delta_g\right\|+C_1\epsilon$$

which implies when ϵ small enough

$$\epsilon\frac{\partial}{\partial t}\left\|\delta_g\right\|_k^2 \leq -q\left\|\delta_g\right\|_k^2+C_1\left\|\delta_f\right\|\left\|\delta_g\right\|+C_1\epsilon \tag{A.18}$$

Thus, combine (A.12) and (A.18) and we obtain that

$$\frac{d}{dt}\left(\left\|\delta_f\right\|^2+\epsilon\frac{C_1}{q}\left\|\delta_g\right\|^2\right) \leq C_1\left\|\delta_f\right\|^2-\left\|\delta_g\right\|_k^2+C_1\epsilon. \tag{A.19}$$

for some constant C_1 independent of k.

By the Gronwall's inequality for $\left(\left\|\delta_f\right\|^2+\frac{\epsilon C_1}{q}\left\|\delta_g\right\|_k^2\right)dx$, for each $k\geq 1$, we can regard τ_{k-1} as the initial value, and then deduce that

$$\left\|\delta_f(\tau_{k-1}+\tau)\right\|^2 \leq e^{C_3\tau}\left(\left\|\delta_f(x,\tau_{k-1})\right\|^2+\epsilon\frac{C_1}{q}\left\|\delta_g(x,\tau_{k-1})\right\|_k^2\right)dx+C_1\epsilon$$

for $\tau\in[0,\tau_k-\tau_{k-1}]$. With the aid of this bound for the growth of $|\delta_f|$, the second inequality of (A.11) implies a bound for $\left\|\delta_g\right\|_k$ as following

$$\left\|\delta_g(\tau_{k-1}+\tau)\right\|_k^2 dx \leq e^{-q\tau/\epsilon}\left\|\delta_g(\tau_{k-1})\right\|_k^2+C_4\left(\left\|\delta_f(x,\tau_{k-1})\right\|^2 dx+\epsilon\frac{C_1}{q}\left\|\delta_g(x,\tau_{k-1})\right\|_k^2\right)+C_4\epsilon.$$

We already have that $\delta_f(x,t_0)=\delta_f(x,\tau_0)\leq\epsilon$ and $\delta_g(x,t_0)=\delta_g(x,\tau_0)\leq\epsilon_0$ for ϵ_0 small enough. Then, by the compactness of Ω, for $\tau\in[0,\tau_1-\tau_0]$, $\left\|\delta_f(\tau)\right\|^2\leq O(\epsilon)$, for all $x\in\Omega$. Make a process similarly and successively for $k=1,2,\ldots$, we have that $\left\|\delta_f\right\|^2\leq O(\epsilon)$ for all $x\in\Omega$. Analogously, we can also prove that $\left\|\delta_g\right\|^2\leq O(\epsilon)$.

Therefore, $\int_\Omega|f(x,t)-f_0(x,t)|^2dx\leq C\epsilon$ and $\int_\Omega|g(x,t)-g_0(x,t)|^2dx\leq C\epsilon$, and we have the conclusion of the theorem. □

A.3 Proof for theorem 6

Proof. Note that $\left\|F(u_1,x)-F(u_2,x)\right\|\leq C\left\|u_1-u_2\right\|, \forall u_1,u_2\in D(F)$ and $|G(u,x)v|$ is bounded, $\forall u,v$ bounded due to the continuous differentiability of G in a bounded domain. Consider

$$\begin{aligned}\frac{1}{2}\frac{\partial}{\partial t}|u-v|^2=(u-v)\frac{\partial}{\partial t}(u-v)&=(u-v)\left[F(u,x)-F(v,x)\right]+\epsilon(u-v)G(u,x)+\epsilon(u-v)\Delta(u-v)\\&\leq C|u-v|^2+O(\epsilon)+\epsilon(u-v)\Delta(u-v).\end{aligned} \tag{A.20}$$

Taking the integral of (A.20) over Ω and using the Neumann boundary condition implies that

$$\frac{1}{2}\frac{\partial}{\partial t}\int_\Omega|u-v|^2dx\leq C\int_\Omega|u-v|^2dx+O(\epsilon)-\epsilon\int_\Omega\left\|\nabla(u-v)\right\|^2dx,$$

which leads to

$$\frac{\partial}{\partial t}\int_\Omega|u-v|^2dx\leq C\int_\Omega|u-v|^2dx+O(\epsilon).$$

Apply the Gronwall's in equality, we have that

$$\int_\Omega|u-v|^2dx\leq O(\epsilon)+O(\epsilon)e^{Ct},$$

which implies $\int_\Omega|u-v|^2dx=O(\epsilon)$ for all $t<T$ with given $T>0$, by the compactness of Ω. □