UNIVERSIDADE DE SÃO PAULO

Reaction-diffusion in cell tissues

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Reaction-Diffusion Problems in Cell Tissues

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1. Introduction

Let $\Omega \subset \mathbb{R}^n$, $n \leq 3$ be an open, bounded and smooth domain. We regard Ω as a cell tissue and $\Gamma := \partial\Omega$ as tissue wall. Consider a reaction occurring inside the cell tissue and involving N different substances. Assuming that there is no flux of concentration through Γ; that is, the tissue wall is a barrier and taking into account the diffusion, we arrive at the following model

$$\begin{aligned} u_t &= \mathrm{Div}(\mathbf{a}_\nu \nabla u) + f(u), \quad \text{in } \Omega, \\ \frac{\partial u}{\partial \vec{n}_\nu} &= 0, \quad \text{in } \Gamma, \end{aligned} \tag{1.1}$$

where

$$\frac{\partial u}{\partial \vec{n}_\nu} = \mathbf{a}_\nu \nabla u \cdot \vec{n},$$

is the covariant normal derivative and $\vec{n}$ is the outward normal at the boundary, $u \in \mathbb{R}^N$ is the concentration vector (each coordinate represents the concentration of a substance), $\mathbf{a}_\nu$ is the diffusion coefficient.

This model states that the variation of the concentration is given by the terms arising from diffusion plus the terms arising from reaction. The fact that the cell wall is a barrier is described through the no flux condition at the boundary Γ.

To simplify the presentation let us consider the simplest nontrivial situation. Let Ω represent a single cell tissue which is divided into two compartments; the citoplasm Ω_1 and the nucleus Ω_0. Suppose that Ω_0 is a smooth open subregion of Ω with boundary Γ_0 and such that $\overline{\Omega}_0 \subset \Omega$. Assume that Γ_0 is a smooth closed surface in Ω, which encloses Ω_0. This divides Ω into two subregions; namely Ω_0 and $\Omega_1 := \Omega \backslash \overline{\Omega}_0$.

So far the model does not take into account the fact that the nucleus and the citoplasm are separated by a permeable membrane. This will be dealt with in the following way, assume that the substances diffuse quickly throughout the nucleus or citoplasm but the diffusion through the membrane Γ_0 is slow. Mathematically speaking this means that a_ν is large inside Ω_0 and Ω_1 but gets small at Γ_0. We assume that $a_\nu : \overline{\Omega} \to \mathbb{R}$ is a continuously differentiable function satisfying

$$\begin{aligned} a_\nu(x) &\geq \frac{e}{\nu}, \quad \text{for } x \in \Omega_0^{l\nu\eta(\nu)} \cup \Omega_1^{l\nu\eta(\nu)} \\ a_\nu(x) &\leq a\,\rho(\nu)\,\nu, \quad \text{for } x \in \Omega\backslash\overline{\Omega_0^{\nu l} \cup \Omega_1^{\nu l}} \\ a_\nu(x) &\geq a\,\nu, \quad \text{for } x \in \Omega. \end{aligned} \tag{1.2}$$

where $\rho : \mathbb{R}^+ \to \mathbb{R}^+$ and $\eta : \mathbb{R}^+ \to \mathbb{R}^+$ are continuous strictly decreasing functions satisfying $\rho(0) = \eta(0) = 1$ and $\Omega_i^r = \{x \in \Omega_i : \text{dist}(x, \Gamma_0) > r\}$.

With these assumptions in mind we intuitively guess that the concentrations should approach spatially constant functions in Ω_0 and Ω_1 and therefore, we should be able to approximate the problem (1.1) by a system of two coupled ordinary differential equations describing the average concentrations in the nucleus and in the citoplasm. If that is the case, it would be very interesting to determine this *limiting system* explicitly.

To establish which is the *limiting system* for the problem (1.1) we need to better understand the following eigenvalue problem

$$\begin{aligned} &\text{Div}(a_\nu \nabla\phi^\nu) = -\lambda^\nu \phi^\nu, \quad \text{in } \Omega \\ &\frac{\partial\phi^\nu}{\partial\vec{n}_\nu} = 0, \quad \text{in } \Gamma. \end{aligned} \tag{1.3}$$

Let $\lambda_1^\nu \leq \lambda_2^\nu \leq \lambda_3^\nu, \cdots$ be the sequence of eigenvalues, solutions of the problem (1.3), counting multiplicity and $\phi_1^\nu, \phi_2^\nu, \phi_3^\nu, \cdots$ be a corresponding sequence of orthonormalized eigenfunctions. Then, we expect the following result to hold (see Carvalho and Pereira [1992] for the case $n = 1$).

Lemma 1.1. *Under the assumption (1.2) we have that*

$$\begin{aligned} &\lambda_1^\nu \equiv 0, \qquad \phi_1^\nu \equiv |\Omega|^{-\frac{1}{2}} \\ &\lambda_2^\nu \to \frac{a}{2l}\frac{|\Omega|}{|\Omega_0|\,|\Omega_1|}|\Gamma_0| \\ &\phi_2^\nu \overset{s-L^2(\Omega)}{\longrightarrow} \sum_{i=0}^{1} k_i \mathcal{X}_{\Omega_i} \end{aligned}$$

as $\nu \to 0$, where $k_0 = \sqrt{\frac{|\Omega_1|}{|\Omega_0||\Omega|}}$ and $k_1 = -\sqrt{\frac{|\Omega_0|}{|\Omega_1||\Omega|}}$. Furthermore, $\lambda_3^\nu \to \infty$ as $\nu \to 0$.

Indeed, we prove that Lemma 1.1 holds in the case $n = 2$, see Section 2 for the proof.

With this result we proceed to guess which is the *limiting system*. For simplicity of notation we assume that $N = 1$, the proofs go through unchanged in the case $N > 1$. Let u be a solution of (1.1) and consider the following decomposition

$$u = u_1\phi_1^\nu + u_2\phi_2^\nu + w$$

where $u_1 = \int_\Omega u\phi_1^\nu$, $u_2 = \int_\Omega u\phi_2^\nu$ and $w = u - u_1\phi_1^\nu - u_2\phi_2^\nu$. This decomposition induces a decomposition in the equation (1.1) in the following way

$$\begin{aligned}
\dot{u}_1 &= \int_\Omega f(u_1\phi_1^\nu(x) + u_2\phi_2^\nu(x) + w(x))\phi_1^\nu dx\, dy \\
\dot{u}_2 &= -\lambda_2^\nu u_2 + \int_\Omega f(u_1\phi_1^\nu(x) + u_2\phi_2^\nu(x) + w(x))\phi_2^\nu dx\, dy \\
w_t &= \mathrm{Div}(\mathbf{a}_\nu \nabla w) + + f(u_1\phi_1^\nu + u_2\phi_2^\nu + w) - \int_\Omega f(u)\phi_1^\nu dx\, dy\ \phi_1^\nu - \int_\Omega f(u)\phi_2^\nu dx\, dy\ \phi_2^\nu \\
\frac{\partial w}{\partial \vec{n}_\nu} &= 0.
\end{aligned}$$

Since the third eigenvalue λ_3^ν is blowing up to infinity , we guess that w will play no role in the asymptotic behavior and we have

$$\begin{aligned}
\dot{u}_1 &\sim \int_\Omega f(u_1\phi_1^\nu(x) + u_2\phi_2^\nu(x))\phi_1^\nu dx\, dy \\
\dot{u}_2 &\sim -\lambda_2^\nu u_2 + \int_\Omega f(u_1\phi_1^\nu(x) + u_2\phi_2^\nu(x))\phi_2^\nu dx\, dy
\end{aligned}$$

using the convergence of eigenvalues and eigenfunctions we obtain that the limiting system should be

$$\begin{aligned}
\dot{u}_1 &= \frac{|\Omega_0|}{|\Omega|^{\frac{1}{2}}} f\left(\frac{u_1}{|\Omega|^{\frac{1}{2}}} + \left(\frac{|\Omega_1|}{|\Omega_0|\,|\Omega|}\right)^{\frac{1}{2}} u_2\right) + \frac{|\Omega_1|}{|\Omega|^{\frac{1}{2}}} f\left(\frac{u_1}{|\Omega|^{\frac{1}{2}}} - \left(\frac{|\Omega_0|}{|\Omega_1|\,|\Omega|}\right)^{\frac{1}{2}} u_2\right) \\
\dot{u}_2 &= -\frac{a}{2l}\frac{|\Omega|}{|\Omega_0|\,|\Omega_1|}|\Gamma_0|\ u_2 + |\Omega_0|\ f\left(\frac{u_1}{|\Omega|^{\frac{1}{2}}} + \left(\frac{|\Omega_1|}{|\Omega_0|\,|\Omega|}\right)^{\frac{1}{2}} u_2\right)\left(\frac{|\Omega_1|}{|\Omega_0|\,|\Omega|}\right)^{\frac{1}{2}} \\
&\qquad - |\Omega_1|\ f\left(\frac{u_1}{|\Omega|^{\frac{1}{2}}} - \left(\frac{|\Omega_0|}{|\Omega_1|\,|\Omega|}\right)^{\frac{1}{2}} u_2\right)\left(\frac{|\Omega_0|}{|\Omega_1|\,|\Omega|}\right)^{\frac{1}{2}}
\end{aligned} \tag{1.4}$$

The variables u_1 and u_2 may not be the best choice of variables to study this problem. A better choice would probably be a variable that reflected the average over Ω_0 and Ω_1. To relate u_1 and u_2 with these average we consider

$$v_1 = |\Omega_0|^{-1}\int_{\Omega_0} u(x)dx, \quad \text{and} \quad v_2 = |\Omega_1|^{-1}\int_{\Omega_1} u(x)dx$$

thus,

$$\begin{aligned}
u_1 &= |\Omega|^{-\frac{1}{2}}\left(|\Omega_0|v_1 + |\Omega_1|v_2\right) \\
u_2 &= \left(\frac{|\Omega_0||\Omega_1|}{|\Omega|}\right)^{\frac{1}{2}}(v_1 - v_2)
\end{aligned}$$

and

$$\begin{aligned}
v_1 &= |\Omega|^{-\frac{1}{2}}\left(u_1 + \frac{|\Omega_1|^{\frac{1}{2}}}{|\Omega_0|^{\frac{1}{2}}}u_2\right) \\
v_2 &= |\Omega|^{-\frac{1}{2}}\left(u_1 - \frac{|\Omega_0|^{\frac{1}{2}}}{|\Omega_1|^{\frac{1}{2}}}u_2\right).
\end{aligned}$$

With this change of coordinates the system (1.4) becomes

$$\begin{aligned}\dot{v}_1 &= -\frac{a}{2l}\frac{|\Omega|}{|\Omega_0|\,|\Omega_1|}\frac{|\Gamma_0|}{|\Omega_0|}(v_1 - v_2) + f(v_1)\\ \dot{v}_2 &= \frac{a}{2l}\frac{|\Omega|}{|\Omega_1|\,|\Omega_0|}\frac{|\Gamma_0|}{|\Omega_1|}(v_1 - v_2) + f(v_2).\end{aligned} \tag{1.5}$$

Note that the concentrations in Ω_0 and in Ω_1 depend on the reaction occurring inside Ω_0 or Ω_1 respectively plus the flow through the nucleus membrane which is proportional to the difference between the concentrations in the nucleus and citoplasm. Also note that the coupling is proportional to the length of the permeable membrane. Models of this type appear in synthesis of mRNA in the nucleus and the consequent production of the inhibiting protein in the citoplasm, in this case the model should also consider a delay in the production of the inhibiting protein. The model presented here is just a simple model used to introduce the results, much more general models with several cells (or compartments) and taking into account delays can be considered. For applications of these results see Jacob and Monod [1961], Mahaffy and Pao [1984] and Mahaffy and Pao [1985].

More generally, we expect that results similar to Lemma 1.1 hold for tissues with any number of cells. That is, consider an open, bounded and smooth domain $\Omega \subset \mathbb{R}^n$, which we will regard as a cell tissue. Assume that there is a positive integer ℓ and smooth subregions Ω_i, $1 \leq i \leq \ell$, of Ω, such that

i) $\Omega_i \cap \Omega_j = \emptyset, \quad i \neq j,$
ii) $\Omega \subset \cup_{i=1}^{\ell} \overline{\Omega}_i$
iii) If $\Gamma_i = \partial\Omega_i \backslash \Gamma$ and $\Gamma_{ij} := \Gamma_i \cap \Gamma_j$. Assume that Γ_{ij} is a finite union of smooth $(n-1)$–manifolds in Ω.

The regions Ω_i are called cells and its boundary Γ_i will be referred to as cell walls or membranes. We assume that the inner walls; that is, $\Gamma_i \backslash \Gamma$ are permeable membranes whereas the outer wall, Γ, is a barrier through which no substance can pass. The no flux condition, at the boundary Γ, assumed in (1.1) reflects the fact that the outer wall is a barrier. The fact that the inner walls, Γ_{ij}, are permeable membranes is reflected through the assumption that the diffusion coefficient becomes small in a neighborhood of Γ_{ij}.

Let a, e, l, be positive constants and $\Omega_i^r := \{x \in \Omega_i : \text{dist}(x, \Gamma_i) > r\}$. Assume that the diffusion coefficient $\mathbf{a}_\nu : \overline{\Omega} \to \mathbb{R}$ is a continuous function satisfying the following conditions

$$\begin{aligned}&\mathbf{a}_\nu(x) \geq \frac{e}{\nu},\ \forall x \in \Omega_i^{l\nu\eta(\nu)}\ 1 \leq i \leq \ell\\ &\mathbf{a}_\nu(x) \leq a\,\rho(\nu)\nu,\ \forall x \in \Omega \backslash \cup_{i=1}^{\ell} \Omega_i^{l\nu}\\ &\mathbf{a}_\nu(x) \geq a\,\nu,\ \forall x \in \Omega\end{aligned} \tag{1.6}$$

where $\rho : \mathbb{R}^+ \to \mathbb{R}^+$ and $\eta : \mathbb{R}^+ \to \mathbb{R}^+$ are continuous strictly decreasing functions satisfying $\rho(0) = 1$ and $\eta(0) = 1$.

These conditions mean that for a reaction occurring inside cells of a tissue and taking into account the spatial diffusion, the diffusion is large inside the cells whereas it becomes small at the membranes. Hence, we expect that concentrations will rapidly homogenize inside the cells and any changes in the concentration will occur at the membranes.

Intuitively we guess that the equations (1.1) inside a cell will be much like an ordinary differential equation where the unknowns are the average concentrations inside the cells. Any coupling with equations describing the average concentrations of adjacent cells would be made through the membrane. Thus, the problem (1.1) would be described by a system of ℓ ordinary differential equations. Our first intent is to determine how this limiting ordinary differential equations should look like.

Consider the eigenvalue problem

$$\begin{aligned} &\mathrm{Div}(\mathbf{a}_\nu \nabla \phi) = -\lambda^\nu \phi, \quad \text{in } \Omega, \\ &\frac{\partial \phi}{\partial \vec{n}} = 0. \end{aligned} \tag{1.7}$$

and assume that $(\lambda_n^\nu, \phi_\nu^n)$ is a sequence of eigensolutions of the problem (1.7) with the eigenvalues ordered so that they are increasing and counting multiplicity.

With these assumptions in mind we expect the following result to hold.

Lemma 1.2. *Let $(\lambda_n^\nu, \phi_\nu^n)$, $n \geq 1$ be a sequence of solutions of (1.7) such that the eigenvalues λ_n^ν are ordered increasingly, counting multiplicity, and the eigenfunctions ϕ_ν^n are normalized. Then, there are $\xi_i \geq 0$, $k_i^j \in \mathbb{R}$, $1 \leq i, j \leq \ell$, such that $\xi_1 = 0$, $k_1^j = |\Omega|^{-\frac{1}{2}}$, $1 \leq j \leq \ell$ and*

$$\lim_{\nu \to 0} \lambda_i^\nu = \xi_i, \; 1 \leq i \leq \ell$$

$$\phi_\nu^i \overset{s-L^2(\Omega)}{\longrightarrow} \sum_{j=1}^{\ell} k_i^j \mathcal{X}_{\Omega_j} := \mathcal{X}_i, \; 1 \leq i \leq \ell$$

where $\sum_{j=1}^{\ell} k_i^j k_m^j |\Omega_j| = \delta_{im}$, $1 \leq i, m \leq \ell$. Furthermore, $\lambda_{\ell+1}^\nu \to \infty$ as $\nu \to 0$.

Even though we have strong numerical evidences that this result holds (see later sections), we have not been able to prove it with this degree of generality (partial results have been obtained and should appear in a future work). We have proved Lemma 1.1. Its proof is presented in Section 2. Let us obtain the *limiting system* of ordinary differential equations assuming Lemma 1.2 (it will be used for the numerical examples).

Let $v = (v_1, \cdots, v_\ell) \in \mathbb{R}^\ell$, $\Phi_\nu = (\phi_1^\nu, \cdots, \phi_\ell^\nu)$ and $\Phi_\nu \cdot v = \sum_{j=1}^{\ell} \phi_j^\nu v_j$.
If $u(t,x)$ is a solution of (1.1) in X_ν^α, it can be written as

$$u(t,x) = \Phi_\nu(x) \cdot v(t) + w(t,x) \tag{1.8}$$

where $v(t) \in \mathbb{R}^\ell$ and $w(t,\cdot) \in W_{\nu,\frac{1}{2}}^\perp$.

Using the above decomposition the equation (1.1) can be rewritten as

$$\begin{aligned} &\frac{dv}{dt} = -\mathrm{diag}(\lambda_1, \cdots, \lambda_\ell)v + \int_\Omega f(\Phi_\nu(y) \cdot v + w(t,y))\mathrm{diag}(\phi_1(y), \cdots, \phi_\ell(y))dy, \\ &w_t = \mathrm{Div}(\mathbf{a}_\nu \nabla w) + f(\Phi_\nu(x) \cdot v + w(t,x)) - \Phi_\nu(x) \cdot \int_\Omega \Phi_\nu(y) f(\Phi_\nu(y) \cdot v + w(t,y))dy, \\ &\frac{\partial w}{\partial \nu} = 0. \end{aligned}$$

From Lemma 1.2 one expects that the component w does not play much role in the asymptotic behavior of (1.1). Therefore,

$$\dot{v}_j \sim -\lambda_j^\nu v_j + \int_\Omega f\left(\sum_{i=1}^{\ell} v_i\phi_i(y)\right)\phi_j(y)dy, \quad 1 \le j \le \ell.$$

¿From the assumptions on the eigenfunctions ϕ_j^ν, one expects that

$$\dot{v}_j \sim -\lambda_j^\nu v_j + \sum_{q=1}^{\ell}\int_{\Omega_q} f\left(\sum_{i=1}^{\ell} v_i\phi_i(y)\right)\phi_j(y)dy \sim -\xi_j v_j + \sum_{q=1}^{\ell}\int_{\Omega_q} f\left(\sum_{i=1}^{\ell} k_i^q v_i\right)k_j^q dy$$
$$\sim -\xi_j v_j + \sum_{q=1}^{\ell}|\Omega_q| f\left(\sum_{i=1}^{\ell} k_i^q v_i\right)k_j^q, \quad 1 \le j \le \ell.$$

Therefore, the following *limiting* ordinary differential equation is associated with (1.1)

$$\dot{v}_j = -\xi_j v_j + f_j(v_1, \cdots, v_\ell), \quad 1 \le j \le \ell, \tag{1.9}$$

where

$$f_j(v_1, \cdots, v_\ell) = \sum_{q=1}^{\ell}|\Omega_q| f\left(\sum_{i=1}^{\ell} k_i^q v_i\right)k_j^q, \quad 1 \le j \le \ell.$$

Let us rewrite this system in a better way. Let $K = (k_1, \cdots, k_\ell)$, $k_i = (k_i^1, \cdots, k_i^\ell)^\top$, $1 \le i \le \ell$ and $\mathcal{M} = \mathrm{diag}(|\Omega_1|, \cdots, |\Omega_\ell|)$; then, from the orthogonality of the normalized eigenfunctions ϕ_i it follows that

$$\left|\int_\Omega \phi_j(x)\phi_i(x)dx - \sum_{p=1}^{\ell}\int_{\Omega_p} k_j^p k_i^p dx\right| = \left|\int_\Omega [\phi_j(x)[\phi_i(x) - \mathcal{X}_i(x)] + [\phi_j(x) - \mathcal{X}_j(x)]\mathcal{X}_i(x)]dx\right|$$
$$\le \|\phi_i - \mathcal{X}_i\|_{L^2(\Omega)} + \|\phi_j - \mathcal{X}_j\|_{L^2(\Omega)}$$

therefore,

$$\delta_{ij} = \int_\Omega \phi_j(x)\phi_i(x)dx \to \sum_{p=1}^{\ell}|\Omega_p| k_j^p k_i^p$$

and $\sum_{p=1}^{\ell}|\Omega_p| k_j^p k_i^p = \delta_{ij}$. With this information we have $K^\top \mathcal{M} K = \mathcal{M} K K^\top = I$, and

$$\sum_{j=1}^{\ell}|\Omega_j|\sum_{p=1}^{\ell} k_p^j k_p^i = 1.$$

If $w = Kv$ and $\Xi = \mathrm{diag}(\xi_1, \cdots, \xi_\ell)$, we can rewrite (1.9) as

$$\dot{w} = -K\Xi K^\top M\, w + g(w)$$

where $g(w) = (f(w_1), \cdots f(w_\ell))^\top$.

Before we can state our main result let us introduce some notation and hypotheses. We are interested in those systems for which some kind of dissipativeness is taking place and for which the existence of an asymptotic set of states (global attractor) can be assured.

Let $X = L^2(\Omega)$ and $A_\nu \subset X \to X$ be the operator defined by

$$D(A_\nu) = \{\phi \in H^2(\Omega) : \frac{\partial \phi}{\partial \vec{n}_\nu} = 0, \text{ in } \Gamma\}$$

$$A_\nu \phi = -\mathrm{Div}(\mathbf{a}_\nu \nabla \phi) + \delta\phi, \quad \phi \in D(A_\nu),$$

for some $\delta > 0$, fixed.

Then, we can define the fractional powers A_ν^α of A_ν and the associated fractional power spaces $X_\nu^\alpha = D(A_\nu^\alpha)$ endowed with the graph norm. Then, $X_\nu^{\frac{1}{2}} = H^1(\Omega)$ and $\|\phi\|_{X_\nu^{\frac{1}{2}}} = \int_\Omega \mathbf{a}_\nu |\nabla\phi|^2 dx + \delta \int_\Omega \phi^2 dx$ (see Henry [1981]).

Our first task is to guarantee the local existence of solutions for the problem (1.1). Suppose that the function $f : \mathbb{R}^N \to \mathbb{R}^N$ is a twice continuously differentiable function and that there exist constants $\bar{\xi}_i, \xi_i > 0$, $1 \le i \le N$, such that

$$s(\delta s + f(u_1, \cdots, u_{i-1}, s, u_{i+1}, \cdots, u_N)) < 0, \ \forall s \notin \Sigma_i \tag{1.10}$$

where $\Sigma_i := [\bar{\xi}_i, \xi_i]$.

Under these conditions, it has been proved in Carvalho [1993] that the problem (1.1) has a global attractor $\mathcal{A}_\nu$ in X_ν^α, $1 > \alpha > \max\{\frac{n}{4}, \frac{1}{2}\}$. It has also been proved in Carvalho [1993] that

$$u(x) \in \Sigma := \Pi_{i=1}^N \Sigma_i, \ \forall x \in \Omega, \ \forall u \in \mathcal{A}_\nu, \ \forall \nu > 0.$$

This result enables us to cut the nonlinearity f in such a way that: *i*) the new nonlinearity is globally bounded with first and second derivatives globally bounded; *ii*) the new system has a global attractor which coincides with $\mathcal{A}_\nu$ (this is accomplished by cutting the nonlinearity in a way that preserves condition (1.10) and that does not change f in a neighborhood of Σ). Therefore, without loss of generality, we assume that f is globally bounded with first and second derivative globally bounded throughout this paper.

If the nonlinearity f satisfy (1.10), it is not hard to see that this system of ordinary differential equations (1.9) has a global attractor $\mathcal{A}_0 \subset \mathbb{R}^{2\ell}$. For example, we could use the Liapunov function

$$V(w) = \frac{1}{2}\langle K\Xi K^\perp w, w\rangle - \sum_{i=1}^{\ell} |\Omega_i|^{-1} \int_0^{w_i} f(s)ds$$

to prove the existence of such global attractor.

Consider the following decomposition of X_ν^α,

$$X_\nu^\alpha = W \oplus W_{\nu,\frac{1}{2}}^\perp$$

where

$$W = \mathrm{span}[\phi_1, \cdots, \phi_\ell], \quad W_{\nu,\frac{1}{2}}^\perp = \{\phi \in X_\nu^\alpha : \langle \phi, \Phi_\nu \cdot v\rangle = 0, \ v \in \mathbb{R}^\ell\},$$

$$\langle \phi, \psi \rangle = \int_\Omega \phi(x)\psi(x)dx.$$

Let

$$P_j : \mathbb{R}^\ell \oplus W^\perp_{\nu,\frac{1}{2}} \to \mathbb{R}, \quad 1 \le j \le \ell$$

$$P_j(v,\psi) = \int_\Omega f\left(\sum_{i=1}^{\ell} v_i\phi_i(y) + \psi(y)\right)\phi_j(y)dy - f_j(v), \quad 1 \le j \le \ell$$

Lemma 1.3. *Assume that f is smooth. Then, for $\|(v,w)\|_{X^\alpha_\nu} \le r$ there exist $L_{P_j}(r,\nu)$, $M_{P_j}(r,\nu)$ such that*

$$\|P_j(v,w)\|_{\mathbb{R}} \le L_{P_j}\|w\|_{X^\alpha_\nu} + M_{P_j}(r,\nu)$$

and

$$\|\nabla_v P_j(v,w)\|_{\mathbb{R}^\ell} \le L_{P_j}\|w\|_{X^\alpha_\nu} + M_{P_j}(r,\nu)$$

where $L_{P_j}(r,\nu)$, $M_{P_j}(r,\nu) \to 0$ as $\nu \to \infty$.

Theorem 1.4. *There exists an exponentially attracting invariant manifold S_ν given by the graph of $\sigma_\nu : \mathbb{R}^\ell \to X^\alpha_\nu$ such that the attractor $\mathcal{A}_\nu$ is contained in S_ν. The flow in S_ν is given by $(v(t),w(t)) = (v(t),\sigma_\nu(v(t)))$, where $v(t)$ is the solution of*

$$\dot{v} = -diag(\lambda_1,\cdots,\lambda_\ell)v + \begin{pmatrix} f_1(v) \\ \vdots \\ f_\ell(v)\end{pmatrix} + P_\nu(v,\sigma_\nu(v)), \tag{1.11}$$

where $P_\nu(v,w) = (P_1(v,w),\cdots,P_\ell(v,w))^\top$. If f is smooth and the flow defined by (1.9) is structurally stable, for ν small enough, the flow defined by (1.11) is structurally stable and they are topologically equivalent; in addition, the family of attractors $\{\mathcal{A}_\nu,\ \nu \ge 0\}$ is continuous at zero.

The proof of this result follows from the invariant manifold theory (see, Henry [1981] or Carvalho [1992]) and from Lemma 1.3.

2. Proof of the Results

Proof of Lemma 1.1. The statements about $(\lambda_1^\nu,\phi_\nu^1)$ are trivial. Let us show that the second eigenvalue λ_2^ν remains bounded as $\nu \to 0$; that is, that there exist a constant $m > 0$ such that

$$\lambda_2^\nu \le m, \quad \forall \nu > 0.$$

To that end we find a family of functions $\{\zeta^\nu,\ \nu > 0\}$ in $H^1(\Omega)$ and a constant $m > 0$, such that $\zeta^\nu \perp 1$, $\|\zeta^\nu\|_{L^2(\Omega)} = 1$ and

$$\int_\Omega \mathbf{a}_\nu(x,y)\left[\left(\frac{\partial\zeta^\nu}{\partial x}\right)^2 + \left(\frac{\partial\zeta^\nu}{\partial y}\right)^2\right]dx\,dy \le m. \tag{2.1}$$

To construct the family ζ_ν we introduce some notation. First assume that

$$\vec{\gamma} = (\gamma_1,\gamma_2) : (0,|\Gamma_0|) \to \Omega$$

is a parametrization of the curve Γ_0 by arc length. Let

$$R_\nu = \{(x,y) \in \Omega : (x,y) = \vec{\gamma}(s) + t\vec{n}(s),\ s \in (0,|\Gamma_0|),\ t \in (-\nu l, \nu l)\},$$

where $\vec{n}(s) = (n_1(s), n_2(s)) = (-\gamma_2(s), \gamma_1(s))$ is the normal vector to the curve Γ_0 at s.

We define ζ_ν in the following way

$$\zeta_\nu = \tilde{k}_0, \quad (x,y) \in \Omega_0 \backslash R_\nu$$

$$\zeta_\nu = \tilde{k}_1, \quad (x,y) \in \Omega_1 \backslash R_\nu$$

if $(x,y) \in R_\nu$ we can write

$$(x,y) = \vec{\gamma}(s) + t\vec{n}(s),$$

and we define

$$\zeta_\nu(x,y) = \tilde{k}_0 + \frac{\tilde{k}_1 - \tilde{k}_0}{2\nu l}(t + \nu l).$$

Finally we choose $\tilde{k}_i$ such that $\|\zeta_\nu\|_{L^2(\Omega)} = 1$ and $\zeta_\nu \perp 1$ and this implies that $\tilde{k}_i = k_i + o(1)$, $i = 0, 1$.

Let us now verify the condition (2.1). To that end we need to consider the change of coordinates

$$T : (0, |\Gamma_0|) \times (-\nu l, \nu l) \to R_\nu$$
$$(s,t) \longrightarrow (x,y) = \vec{\gamma}(s) + t\vec{n}(s).$$

Its Jacobian Matrix is given by

$$J(T) = \begin{bmatrix} \gamma_1'(s) + t n_1'(s) & \gamma_2'(s) + t n_2'(s) \\ n_1(s) & n_2(s) \end{bmatrix}$$

and $\det J(T) = 1$. Here we use that $\vec{n}(s) = (-\gamma_2(s), \gamma_1(s))$, that $|\vec{\gamma}'(s)| = 1$ and that $\vec{\gamma}''(s) = k(s)\vec{n}(s)$, where $k(s)$ is the curvature at $\vec{\gamma}(s)$.

Our next step is to determine the gradient in this new set of coordinates as a function of the gradient in the old coordinates. We have that, if $\tilde{\zeta}_\nu(s,t) = \zeta_\nu(\vec{\gamma}(s) + t\vec{n}(s))$,

$$\frac{\partial \tilde{\zeta}_\nu}{\partial s} = \frac{\partial \zeta_\nu}{\partial x}\frac{\partial x}{\partial s} + \frac{\partial \zeta_\nu}{\partial y}\frac{\partial y}{\partial s} = 0$$
$$\frac{\partial \tilde{\zeta}_\nu}{\partial t} = \frac{\partial \zeta_\nu}{\partial x}\frac{\partial x}{\partial t} + \frac{\partial \zeta_\nu}{\partial y}\frac{\partial y}{\partial t} = \frac{\tilde{k}_1 - \tilde{k}_0}{2\nu l}.$$

It follows that

$$\left(\frac{\partial \tilde{\zeta}_\nu}{\partial s}\right)^2 + \left(\frac{\partial \tilde{\zeta}_\nu}{\partial t}\right)^2 = (1 + r\gamma_1'(s)^2)\left(\frac{\partial \zeta_\nu}{\partial x}\right)^2 + (1 + r\gamma_2'(s)^2)\left(\frac{\partial \zeta_\nu}{\partial y}\right)^2 + 2r\gamma_1'(s)\gamma_2'(s)\frac{\partial \zeta_\nu}{\partial x}\frac{\partial \zeta_\nu}{\partial y}$$

where $r = r(t,s) = -2tk(s) + t^2 k(s)^2$.

If $k_{\max} = \max_{s\in(0,|\Gamma_0|)} |k(s)|$ and $b(\nu) = \frac{9}{4}\nu\,(2+\nu\,l\,k_{\max})k_{\max}$, we have that

$$(1-b(\nu))\left[\left(\frac{\partial\zeta_\nu}{\partial x}\right)^2+\left(\frac{\partial\zeta_\nu}{\partial y}\right)^2\right] \le \left(\frac{\partial\tilde{\zeta}_\nu}{\partial s}\right)^2+\left(\frac{\partial\tilde{\zeta}_\nu}{\partial t}\right)^2 \le (1+b(\nu))\left[\left(\frac{\partial\zeta_\nu}{\partial x}\right)^2+\left(\frac{\partial\zeta_\nu}{\partial y}\right)^2\right].$$

It follows from the estimates above that

$$\begin{aligned}
\lambda_2^\nu &\le \int_\Omega \mathbf{a}_\nu(x,y)\left[\left(\frac{\partial\zeta_\nu}{\partial x}\right)^2+\left(\frac{\partial\zeta_\nu}{\partial y}\right)^2\right] dx\,dy \\
&\le \int_{R_\nu} \mathbf{a}_\nu(x,y)\left[\left(\frac{\partial\zeta_\nu}{\partial x}\right)^2+\left(\frac{\partial\zeta_\nu}{\partial y}\right)^2\right] dx\,dy + o(1) \\
&\le \frac{a\,\nu}{1-b(\nu)}\int_{-\nu l}^{\nu l}\int_0^{|\Gamma_0|}\left[\left(\frac{\partial\tilde{\zeta}_\nu}{\partial s}\right)^2+\left(\frac{\partial\tilde{\zeta}_\nu}{\partial t}\right)^2\right] ds\,dt \\
&\le \frac{a}{2l}(k_1-k_0)^2|\Gamma_0| + o(1) \\
&\le \frac{a}{2l}\frac{|\Omega|}{|\Omega_0||\Omega_1|}|\Gamma_0| + o(1)
\end{aligned}$$

Thus we obtain that

$$\limsup_{\nu\to 0}\lambda_2^\nu \le \frac{a}{2l}\frac{|\Omega|}{|\Omega_0||\Omega_1|}|\Gamma_0|.$$

To prove that there are only two eigenvalues that stay bounded as ν tends to zero we must first to understand a little better the behavior of the eigenfunctions associated to those eigenvalues that stay bounded. Let (λ^ν,ϕ_ν) be a solution of (1.7) such that $\phi_\nu \perp 1$, $\|\phi_\nu\|_{L^2(\Omega)} = 1$ and $\limsup_{\nu\to 0}\lambda^\nu = m < \infty$; then,

$$\|\phi_\nu - \mathcal{X}\|_{L^2(\Omega)} \to 0$$

as $\nu \to 0$, where $\mathcal{X} = \sum_{i=1}^2 k_i \mathcal{X}_{\Omega_i}$. In fact, given $r > 0$ there exists $\nu_0 > 0$ such that

$$\|\phi_\nu\|_{H^1(\Omega_i^r)} \le 1 + \frac{m}{e}\nu_0.$$

This implies that there exists a sequence $\nu_j \to 0$ and constants k_0, k_1 such that

$$\|\phi_{\nu_j} - k_i\|_{L^2(\Omega_i^r)} \to 0$$

as $\nu_j \to 0$.

It is easy to see that k_i do not depend on the sequence $\nu_j \to 0$ and on r.

Claim. *For all $(\lambda_n^\nu,\phi_\nu^n)$ solutions of (1.7) such that $\limsup_{\nu\to 0}\lambda_n^\nu < \infty$, we have*

$$\|\phi_\nu^n\|_{L^2(R_\nu^r)} \to 0, \quad \text{as } \nu \to 0.$$

where $R_\nu^\eta = \Omega \backslash \cup_{i=0}^{1} \Omega_i^{l\nu\eta(\nu)}$. This condition is obviously satisfied if there exists a constant $K > 0$ such that $\|\phi_\nu^n\|_\infty < K$.

It follows from the Claim that

$$|\Omega_1| k_0^2 + |\Omega_2| k_1^2 = 1, \quad |\Omega_1| k_0 + |\Omega_2| k_1 = 0.$$

It follows from the orthogonality of eigenfunctions that $\lambda_3^\nu \to \infty$ as $\nu \to 0$.

Let us now prove that

$$\liminf_{\nu \to 0} \lambda_2^\nu \geq \frac{a}{2l} \frac{|\Omega|}{|\Omega_0||\Omega_1|} |\Gamma_0|.$$

Let ϕ denote the second eigenfunction, thus we have

$$\begin{aligned}
\lambda_2^\nu = \int_\Omega \mathbf{a}_\nu(x,y) \left[\left(\frac{\partial \phi}{\partial x}\right)^2 + \left(\frac{\partial \phi}{\partial y}\right)^2 \right] dx\, dy &\geq \int_{R_\nu^\eta} \mathbf{a}_\nu(x,y) \left[\left(\frac{\partial \phi}{\partial x}\right)^2 + \left(\frac{\partial \phi}{\partial y}\right)^2 \right] dx\, dy \\
&\geq a\,\nu \int_{R_\nu^\eta} \left[\left(\frac{\partial \phi}{\partial x}\right)^2 + \left(\frac{\partial \phi}{\partial y}\right)^2 \right] dx\, dy \\
&\geq \frac{a}{1-b(\nu)} \nu \int_{-\nu l \eta}^{\nu l \eta} \int_0^{|\Gamma_0|} \left[\left(\frac{\partial \phi}{\partial s}\right)^2 + \left(\frac{\partial \phi}{\partial t}\right)^2 \right] dt\, ds \\
&\geq \frac{a}{1-b(\nu)} \nu \int_{-\nu l \eta}^{\nu l \eta} \int_0^{|\Gamma_0|} \left(\frac{\partial \phi}{\partial t}\right)^2 dt\, ds \\
&\geq \frac{a}{1-b(\nu)} \frac{1}{2l} \int_0^{|\Gamma_0|} |\phi(\vec{\gamma}(s) - \nu l \eta \vec{n}(s)) - \phi(\vec{\gamma}(s) + \nu l \eta \vec{n}(s))|^2 ds \\
&\geq \frac{a}{1-b(\nu)} \frac{1}{2l} \left[\left(\int_0^{|\Gamma_0|} |\phi(\vec{\gamma} - \nu l \eta \vec{n})|^2 ds \right)^{\frac{1}{2}} - \left(\int_0^{|\Gamma_0|} |\phi(\vec{\gamma} + \nu l \eta \vec{n})|^2 ds \right)^{\frac{1}{2}} \right]^2.
\end{aligned}$$

Since

$$\frac{1}{|\Gamma_0|} \int_0^{|\Gamma_0|} [\phi(\vec{\gamma}(s) - \nu l \eta \vec{n}(s))]^2 ds \longrightarrow {k_0}^2$$

and

$$\frac{1}{|\Gamma_0|} \int_0^{|\Gamma_0|} [\phi(\vec{\gamma}(s) + \nu l \eta \vec{n}(s))]^2 ds \longrightarrow {k_1}^2$$

we have that

$$\limsup_{\nu \to 0} \lambda_2^\nu \geq \frac{a}{2l} (k_0 - k_1)^2 |\Gamma_0| = \frac{a}{2l} \frac{|\Omega|}{|\Omega_1||\Omega_2|} |\Gamma_0|$$

and the lemma follows. It only remains to prove the Claim.

Proof of the Claim. Let (s,t) and (s,τ), be points in $R_{\nu\eta(\nu)}$. Therefore, for any normalized eigenfunction ϕ associated to one eigenvalue λ which stays bounded as $\nu \to 0$, we have

$$|\phi(s,t) - \phi(s,\tau)|^2 \leq |\int_\tau^t \phi_t(s,\theta) d\theta|^2 \leq \left| (t-\tau) \int_\tau^t \phi_t(s,\theta)^2 d\theta \right| \leq 2\nu l \int_{-\nu\eta l}^{\nu\eta l} \phi_t(s,\theta)^2 d\theta$$

and

$$\int_0^{|\Gamma_0|}\int_{-\nu\eta l}^{\nu\eta l}|\phi(s,t)-\phi(s,\tau)|^2 ds\,dt \le 4\,\nu^2\,\eta^2\,l^2\int_{-\nu\eta l}^{\nu\eta l}\int_0^{|\Gamma_0|}\phi_t(s,\theta)^2 ds\,d\theta$$

thus

$$\left(\int_0^{|\Gamma_0|}\int_{-\nu\eta l}^{\nu\eta l}|\phi(s,t)|^2 ds\,dt\right)^{\frac12}-\left(\int_0^{|\Gamma_0|}\int_{-\nu\eta l}^{\nu\eta l}|\phi(s,\tau)|^2 ds\,dt\right)^{\frac12}$$

$$=\left(\int_0^{|\Gamma_0|}\int_{-\nu\eta l}^{\nu\eta l}|\phi(s,t)|^2 ds\,dt\right)^{\frac12}-(2\nu\,\eta\,l)^{\frac12}\left(\int_0^{|\Gamma_0|}|\phi(s,\tau)|^2 ds\right)^{\frac12}.$$

$$\le 2\nu\,\eta\,l\left(\int_{-\nu\eta l}^{\nu\eta l}\int_0^{|\Gamma_0|}\phi_t(s,\theta)^2 ds\,d\theta\right)^{\frac12}$$

$$\le 2\,l\,\eta\left(\frac{m}{a}\right)^{\frac12}\nu^{\frac12}$$

Similarly, we obtain that for some $t_0 > 0$

$$\int_0^{|\Gamma_0|}\int_{-t_0}^{-\nu l\eta}|\phi(s,t)-\phi(s,\tau)|^2 ds\,dt \le t_0^2\int_{-t_0}^{-\nu\eta l}\int_0^{|\Gamma_0|}\phi_t(s,\theta)^2 ds\,d\theta$$

and

$$\left(\int_0^{|\Gamma_0|}\int_{-t_0}^{-\nu l\eta}|\phi(s,\tau)|^2 ds\,dt\right)^{\frac12}-\left(\int_0^{|\Gamma_0|}\int_{-t_0}^{-\nu l\eta}|\phi(s,t)|^2 ds\,dt\right)^{\frac12}$$

$$=t_0^{\frac12}\left(\int_0^{|\Gamma_0|}|\phi(s,\tau)|^2 ds\right)^{\frac12}-\left(\int_0^{|\Gamma_0|}\int_{-t_0}^{-\nu l\eta}|\phi(s,t)|^2 ds\,dt\right)^{\frac12}.$$

$$\le t_0\left(\int_{-t_0}^{-\nu\eta l}\int_0^{|\Gamma_0|}\phi_t(s,\theta)^2 ds\,d\theta\right)^{\frac12}$$

$$\le t_0\left(\frac{m}{e}\right)^{\frac12}\nu^{\frac12}$$

and it follows that

$$t_0^{\frac12}\left(\int_0^{|\Gamma_0|}|\phi(s,\tau)|^2 ds\right)^{\frac12}-\left(\int_0^{|\Gamma_0|}\int_{-t_0}^{-\nu l\eta}|\phi(s,t)|^2 ds\,dt\right)^{\frac12}\le 1+t_0\left(\frac{m}{e}\right)^{\frac12}\nu^{\frac12}$$

and

$$\left(\int_0^{|\Gamma_0|}\int_{-\nu\eta l}^{\nu\eta l}|\phi(s,t)|^2 ds\,dt\right)^{\frac12}\to 0$$

as $\nu \to 0$.

Proof of Lemma 1.3. For $\|(v,w)\|_{X^\alpha_\nu} \le r$

$$
\begin{aligned}
-P_j(v,w) &= \sum_{i=1}^{\ell} |\Omega_i| f\left(\sum_{k=1}^{\ell} v_k k_k^i\right) k_j^i - \int_\Omega f\left(\sum_{k=1}^{\ell} v_k(t)\phi_k(y) + w(t,y)\right)\phi_j(y)dy \\
&= \sum_{i=1}^{\ell}\int_{\Omega_i}\left[f\left(\sum_{k=1}^{\ell} v_k k_k^i\right)k_j^i - f\left(\sum_{k=1}^{\ell} v_k(t)\phi_k(y) + w(t,y)\right)\phi_j(y)\right]dy \\
&= \sum_{i=1}^{\ell}\int_{\Omega_i}\left[f\left(\sum_{k=1}^{\ell} v_k k_k^i\right)k_j^i - f\left(\sum_{k=1}^{\ell} v_k \phi_k(y)\right)k_j^i\right]dy \\
&+ \sum_{i=1}^{\ell}\int_{\Omega_i}\left[f\left(\sum_{k=1}^{\ell} v_k \phi_k(y)\right)k_j^i - f\left(\sum_{k=1}^{\ell} v_k \phi_k(y)\right)\phi_j(y)\right]dy \\
&+ \sum_{i=1}^{\ell}\int_{\Omega_i}\left[f\left(\sum_{k=1}^{\ell} v_k \phi_k(y)\right)\phi_j(y) - f\left(\sum_{k=1}^{\ell} v_k(t)\phi_k(y) + w(t,y)\right)\phi_j(y)\right]dy.
\end{aligned}
$$

Let $M = \left\{\sup_{\{s\in\mathbb{R}\}} |f'(s)|\right\}$. Then,

$$
\begin{aligned}
|P_j(v,w)| &\le M\sum_{i=1}^{\ell}\int_{\Omega_i}\left|\sum_{k=1}^{\ell} v_k k_k^i - \sum_{k=1}^{\ell} v_k\phi_k(y)\right| |k_j^i| dy \\
&+ C(r)\int_\Omega |\mathcal{X}_j(y) - \phi_j(y)|^2 dy + \sum_{i=1}^{\ell}\int_{\Omega_i} M|w(y)|\,|\phi_j(y)|dy \\
&\le M\|w(y)\|_{L^2(\Omega)} + M_{P_j}(r,\nu)
\end{aligned}
$$

From Lemma 1.2, it follows that

$$
|P_j(v,w)| \le M\frac{1}{\lambda_{\ell+1}(\nu)^\alpha}\|w(y)\|_{X^\alpha_\nu} + M_{P_j}(r,\nu)
$$

and the first part of the lemma is proved. The second part of the lemma follows similarly.

3. Dirichlet Boundary Conditions

In this section we consider the eigenvalue problem

$$
\begin{aligned}
&\mathrm{Div}(\mathbf{a}_\nu \nabla u) = -\lambda u, \text{ in } \Omega, \\
&u = 0, \text{ in } \Gamma.
\end{aligned} \tag{3.1}
$$

with $\mathbf{a}_\nu$ satisfying (1.2). In this case we expect that the first eigenvalue converges and that the second eigenvalue blows up to $+\infty$. As before, independently of the boundary condition we expect that any eigenfunction associated to an eigenvalue that stays bounded must converge to a step function of the form $\mathcal{X} = k_0\mathcal{X}_{\Omega_0} + k_1\mathcal{X}_{\Omega_1}$. Since the eigenfunction must satisfy the boundary condition we must have that $k_1 = 0$. This justifies the fact that only one eigenvalue may stay bounded since an eigenfunction associated to another eigenvalue must be orthogonal to the first and both must converge to $\mathcal{X}$. In fact the following result holds

Lemma 3.1. *Let λ_n^ν be the sequence of eigenvalues of the problem (3.1) and ϕ_n^ν be an orthonormalized sequence of associated eigenfunctions. Under the assumption (1.2) we have that*

$$\lambda_1^\nu \to \frac{a}{2l}|\Omega_0|\,|\Gamma_0|$$
$$\phi_1^\nu \overset{s-L^2(\Omega)}{\longrightarrow} |\Omega_0|^{-\frac{1}{2}}\mathcal{X}_{\Omega_i}$$

as $\nu \to 0$. Furthermore, $\lambda_2^\nu \to \infty$ as $\nu \to 0$.

The proof of this results follows similarly to the proof of Lemma 1.1 and we omit it.

More generally we expect that the following result holds

Lemma 3.2. *Assume that $\mathbf{a}_\nu$ satisfy (1.6) and let $(\lambda_n^\nu, \phi_\nu^n)$, $n \geq 1$ be a sequence of solutions of (3.1) such that the eigenvalues λ_n^ν are ordered increasingly, counting multiplicity, and the eigenfunctions ϕ_ν^n are normalized. Let $p < \ell$ be the number cells which do not touch Γ; then, there are $\xi_i \geq 0$, $k_i^j \in \mathbb{R}$, $1 \leq i,j \leq p$, such that*

$$\lim_{\nu\to 0} \lambda_i^\nu = \xi_i,\ 1 \leq i \leq p$$
$$\phi_\nu^i \overset{s-L^2(\Omega)}{\longrightarrow} \sum_{j=1}^{p} k_i^j \mathcal{X}_{\Omega_j} := \mathcal{X}_i,\ 1 \leq i \leq p$$

where $\sum_{j=1}^{p} k_i^j k_m^j |\Omega_j| = \delta_{im}$, $1 \leq i,m \leq p$. Furthermore, $\lambda_{p+1}^\nu \to \infty$ as $\nu \to 0$.

If this last result holds then a result similar to Theorem 1.3 holds with identical proof. Numerical evidences that Lemma 3.1 holds are shown in the next section.

4. Numerical Experiments

In this section we present a series of numerical experiments which were implemented, using the package PLTMG (Bank [1990]).

4.1 Neumann Boundary Condition

The first three examples support the claims of lemma 1.2 for different configurations and levels of geommetric complexities. The fourth example is an instance of the claims of lemma 1.1

1. First Experiment

Let $\Omega = (0,4) \times (0,2)$ and assume that this tissue is divided into three cells as follows:

$$\Omega_1 = \{(x,y) \in \mathbb{R}^2 : x > 0, y > 0, y > x-1 \text{ and } y < 2\},$$
$$\Omega_2 = \{(x,y) \in \mathbb{R}^2 : y > 0, y < x-1 \text{ and } y < 3-x\}$$

and

$$\Omega_3 = \{(x,y) \in \mathbb{R}^2 : y > 0, x < 4, y < 2, y < x-1 \text{ and } y > x-3\}.$$

Let $\Gamma_{ij} = \partial\Omega_i \cap \partial\Omega_j$, $1 \leq i,j \leq 3$ and $\Omega_i^r = \{(x,y) \in \Omega_i : \text{dist}((x,y),\Gamma_{ij}) > r,\ 1 \leq j \leq 3\}$. Assume that $\mathbf{a}_\nu$ is defined by

$$\mathbf{a}_\nu(x,y) = \frac{1}{\nu},\ \forall (x,y) \in \Omega_i^{\nu(1+\nu^s)}$$
$$\mathbf{a}_\nu(x,y) = \nu,\ \forall (x,y) \in \Omega \setminus \cup_{i=1}^{3} \overline{\Omega_i^\nu}$$
linear and continuous elsewhere

For this we obtain, numerically, that $\lambda_1 \equiv 0$ and

$$\text{for } \nu = 0.2 \text{ and } \epsilon = 0.05, \text{ we have } \lambda_2 = 0.639,\ \lambda_3 = 2.08 \text{ and } \lambda_4 = 6.83,$$
$$\text{for } \nu = 0.1 \text{ and } \epsilon = 0.05, \text{ we have } \lambda_2 = 0.769,\ \lambda_3 = 2.23 \text{ and } \lambda_4 = 14.1,$$
$$\text{for } \nu = 0.05 \text{ and } \epsilon = 0.05, \text{ we have } \lambda_2 = 0.822,\ \lambda_3 = 2.28 \text{ and } \lambda_4 = 28.8.$$

and this suggests that the first three eigenvalues converge whereas the fourth blows up to $+\infty$.

2. Second Experiment

Let $\Omega = (0,2) \times (0,2)$ and assume that this tissue is divided into three cells as follows:

$$\Omega_1 = \{(x,y) \in \mathbb{R}^2 : x > 0, y > 0 \text{ and } x < 1\},$$

$$\Omega_2 = \{(x,y) \in \mathbb{R}^2 : 2 > x > 1 \text{ and } 2 > y > 1\}$$

and

$$\Omega_3 = \{(x,y) \in \mathbb{R}^2 : 1 < x < 2 \text{ and } 0 < y < 1\}.$$

Let $\Gamma_{ij} = \partial\Omega_i \cap \partial\Omega_j$, $1 \le i,j \le 3$ and $\Omega_i^r = \{(x,y) \in \Omega_i : \text{dist}((x,y),\Gamma_{ij}) > r,\ 1 \le j \le 3\}$. Assume that $\mathbf{a}_\nu$ is defined by

$$\mathbf{a}_\nu(x,y) = \frac{1}{\nu},\ \forall (x,y) \in \Omega_i^{\nu(1+\nu^\epsilon)}$$
$$\mathbf{a}_\nu(x,y) = \nu,\ \forall (x,y) \in \Omega \setminus \cup_{i=1}^3 \overline{\Omega_i^\nu}$$
$$\text{linear and continuous elsewhere}$$

For this we obtain, numerically, that $\lambda_1 \equiv 0$ and

$$\text{for } \nu = 0.14 \text{ and } \epsilon = 0.1, \text{ we have } \lambda_2 = 1.02,\ \lambda_3 = 1.49 \text{ and } \lambda_4 = 13.1,$$
$$\text{for } \nu = 0.07 \text{ and } \epsilon = 0.1, \text{ we have } \lambda_2 = 1.01,\ \lambda_3 = 1.50 \text{ and } \lambda_4 = 39.7,$$
$$\text{for } \nu = 0.035 \text{ and } \epsilon = 0.1, \text{ we have } \lambda_2 = 1.01,\ \lambda_3 = 1.51 \text{ and } \lambda_4 = 77.0.$$

and this suggests that the first three eigenvalues converge whereas the fourth blows up to $+\infty$.

3. Third Experiment

Let $\Omega = (0,1) \times (0,4)$ and assume that this tissue is divided into three cells as follows:

$$\Omega_1 = \{(x,y) \in \mathbb{R}^2 : x > 0,\ y > 0,\ y > x - 1 \text{ and } y < 1\},$$

$$\Omega_2 = \{(x,y) \in \mathbb{R}^2 : y > 0,\ y < x - 1, \text{ and } y < 3 - x\}$$

and

$$\Omega_3 = \{(x,y) \in \mathbb{R}^2 : 1 > y > 0,\ y > 3 - x \text{ and } x < 4\}.$$

Let $\Gamma_{ij} = \partial\Omega_i \cap \partial\Omega_j$, $1 \le i,j \le 3$ and $\Omega_i^r = \{(x,y) \in \Omega_i : \text{dist}((x,y),\Gamma_{ij}) > r,\ 1 \le j \le 3\}$. Assume that $\mathbf{a}_\nu$ is defined by

$$\mathbf{a}_\nu(x,y) = \frac{1}{\nu},\ \forall (x,y) \in \Omega_i^{\nu(1+\nu^\epsilon)}$$
$$\mathbf{a}_\nu(x,y) = \nu,\ \forall (x,y) \in \Omega \setminus \cup_{i=1}^3 \overline{\Omega_i^\nu}$$
$$\text{linear and continuous elsewhere}$$

For this we obtain, numerically, that $\lambda_1 \equiv 0$ and

$$\text{for } \nu = 0.14 \text{ and } \epsilon = 0.05, \text{ we have } \lambda_2 = 0.558, \ \lambda_3 = 2.45 \text{ and } \lambda_4 = 27.3,$$
$$\text{for } \nu = 0.07 \text{ and } \epsilon = 0.05, \text{ we have } \lambda_2 = 0.618, \ \lambda_3 = 2.59 \text{ and } \lambda_4 = 66.6,$$
$$\text{for } \nu = 0.035 \text{ and } \epsilon = 0.05, \text{ we have } \lambda_2 = 0.643, \ \lambda_3 = 2.64 \text{ and } \lambda_4 = 146.0.$$

and this suggests that the first three eigenvalues converge whereas the fourth blows up to $+\infty$.

4. Fourth experiment

Let $\Omega = \{(x,y) \in \mathbb{R}^2 : (x^2+y^2)^{\frac{1}{2}} < 2\}$ and assume that this tissue is divided into two cells as follows:

$$\Omega_0 = \{(x,y) \in \mathbb{R}^2 : (x^2+y^2)^{\frac{1}{2}} < 1\},$$

and

$$\Omega_2 = \{(x,y) \in \mathbb{R}^2 : 1 < (x^2+y^2)^{\frac{1}{2}} < 2\}.$$

Let $\Gamma_0 = \{(x,y) \in \mathbb{R}^2 : (x^2+y^2)^{\frac{1}{2}} = 1\}$ and $\Omega_i^r = \{(x,y) \in \Omega_i : \text{dist}((x,y),\Gamma_0) > r\}$, $i = 0,1$. Assume that $\mathbf{a}_\nu$ is defined by

$$\mathbf{a}_\nu(x,y) = \frac{1}{\nu}, \ \forall (x,y) \in \Omega_i^{\nu(1+\nu^\epsilon)}$$
$$\mathbf{a}_\nu(x,y) = \nu, \ \forall (x,y) \in \Omega \setminus \cup_{i=0}^1 \overline{\Omega_i^\nu},$$

also, assume that $\mathbf{a}_\nu$ can be obtained by rotation of a piecewise linear function defined in [-2,2].

For this we obtain, numerically,

$$\text{for } \nu = 0.1 \text{ and } \epsilon = 0.1, \text{ we have } \lambda_2 = 1.42, \text{ and } \lambda_3 = 28.7,$$
$$\text{for } \nu = 0.06 \text{ and } \epsilon = 0.1, \text{ we have } \lambda_2 = 1.38, \text{ and } \lambda_3 = 51.3.$$

and this suggests that the first two eigenvalues converge whereas the third blows up to $+\infty$.

4.1 Dirichlet Boundary Condition

For the Dirichlet case in the experiments 1 through 3 there is no eigenvalue which stays bounded since all the cells touch the cell wall. For the fourth experiment we obtain one eigenvalue which stay bounded whereas the second blows up. In fact we obtain

Let Ω, Ω_0, Ω_1, Γ_0 and $\mathbf{a}_\nu$ be as in the fourth experiment. For this we obtain, numerically,

$$\text{for } \nu = 0.1 \text{ and } \epsilon = 0.1, \text{ we have } \lambda_1 = 1.02, \text{ and } \lambda_2 = 24.3,$$
$$\text{for } \nu = 0.06 \text{ and } \epsilon = 0.1, \text{ we have } \lambda_1 = 1.01, \text{ and } \lambda_2 = 50.0.$$

and this suggests that the first eigenvalue converge whereas the second blows up to $+\infty$.

A few pictures of the eigenfunctions are attached so that the reader can cross check the remaining conclusions of lemma 1.2 and 3.1. Many other experiments have been carried out and they all show evidences that Lemma 1.2 holds. We remark that these numerical experiments played a fundamental role in the understanding the eigenvalue problem and consequently in the proof of lemmas 1.1 and 3.1. We strongly believe that the few technical difficulties that we have found to prove Lemma 1.2 should be solved soon.

5. The Software

The numerical results presented in the last section were obtained with the software package PLTMG. This package solves the following boundary value problem:

$$-\mathrm{Div}(a(x,y,u,\nabla u,\lambda)) + f(x,y,u,\nabla u,\lambda), \quad \text{in } \Omega \tag{5.1}$$

with boundary conditions given by

$$u = g_1(x,y,\lambda) \quad \text{on } \Gamma' \tag{5.2}$$

$$(a_1\frac{\partial u}{\partial x}, a_1\frac{\partial u}{\partial y})\cdot\vec{n} = g_2(x,y,\lambda) \quad \text{on } \partial\Omega\backslash\Gamma' = \Gamma'' \tag{5.3}$$

where Ω is a connected region in $\mathbb{R}^2$, $\partial\Omega = \Gamma' \cup \Gamma''$, $\vec{n}$ is the unit normal, a_1, a_2, f, g_1 and g_2 are scalar functions and λ is a parameter. The user can also specify a constraint on the solution of the form:

$$\rho(u,\lambda) = \int_\Omega p_1(x,y,u,\nabla u,\lambda)dxdy + \int_{\partial\Omega} p_2(x,y,u,\nabla u,\lambda)ds \tag{5.4}$$

with p_1 and p_2 scalar functions.

PLTMG implements a finite element method based on triangular elements and C^0 piecewise linear functions. The resulting nonlinear system of equations arising from the discretization of (5.1) and from the normalizing equations (5.4) is solved by a damped Newton iteration combined with the hierarchical basis multigrid iteration.

As for the errors in the numerical solution produced by PLTMG it implements a posteriori error estimates in the $L^2(\Omega)$ and $H^1(\Omega)$ norms. The rationale behind a posteriori error estimates is that one can control the errors in the numerical solution by adapting the grid to the underlying behaviour of the true solution. This would be of no use were it not possible to show that by controlling the a posteriori errors one in fact controls the error in the solution. A priori error estimates are also available and they are much easier to derive, however they are not of so much use regarding error control.

Let u be the solution of problem (5.1),(5.2),(5.3) and u_h be the numerical solution computed by PLTMG. Here h denotes the mesh parameter, that is, if $T_i, i = 1,\cdots,nT$ is a triangle in the triangulation of Ω, then

$$h = Max_{i=1,\cdots,nT} h_i$$

where h_i is the diameter of T_i.

We then have the a priori error estimates (see, Strang and Fix [1973])

$$\|u - u_h\|_{L^2(\Omega)} \le C_1 h^2 \|u\|_{H^2(\Omega)}$$

$$\|u - u_h\|_{H^1(\Omega)} \le C_2 h \|u\|_{H^2(\Omega)}$$

The results above prove that the finite element approximation converges to the exact solution when the mesh parameter shrinks to zero, but does not provide for error estimates to be used for error control because it depends on the exact solution u. A posteriori error estimates, on the other hand, provide for error control as well as the convergence of the numerical method. For the case of a linear selfadjoint and positive definite problem Bank and Weiser [1985] prove the following a posteriori error estimates:

$$C|||u - u_h||| \leq |||e||| \leq (1 - C_e)|||u - u_h|||$$

C and C_e are constants, $|||.|||$ is the energy norm and e is the a posteriori error estimate. Bank and Weiser [1985] give all the details for the calculation of e.

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