Reaction-diffusion equations and some applications to Biology

Mauricio Labadie

Université Pierre et Marie Curie

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présentée par

Mauricio LABADIE

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Directeur:

Henri BERESTYCKI

Directeur d'études au CAMS-EHESS et CNRS

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Résumé

La motivation de cette thèse de Doctorat est de modéliser quelques problèmes biologiques avec des systèmes et des équations de réaction-diffusion. La thèse est divisée en sept chapitres:

- Dans le Chapitre 1 on modélise des ions de calcium et des protéines dans une épine dendritique mobile (une microstructure dans les neurones). On propose deux modèles, un avec des protéines qui diffusent et un autre avec des protéines fixées au cytoplasme. On démontre que le premier problème est bien posé, que le deuxième problème est presque bien posé et qu'il y a un lien continu entre les deux modèles.

- Dans le Chapitre 2 on applique les techniques du Chapitre 1 pour un modèle d'infection virale et réponse immunitaire dans des cellules cultivées. On propose comme avant deux modèles, un avec des cellules qui diffusent et un autre avec des cellules fixées. On démontre que les deux problèmes sont bien posés et qu'il y a un lien continu entre les deux modèles. On étudie aussi le comportement asymptotique et la stabilité des solutions.

- Dans le Chapitre 3 on montre que la croissance a deux effets positives dans la formation de motifs ou patterns. Le premier est un effet *anti explosion (anti-blow-up)* car les solutions sur un domaine croissant explosent plus tard que celles sur un domain fixé, et si la croissance est suffisamment rapide alors elle peut même empêcher l'explosion. Le deuxième est un effet *stabilisant* car les valeur propres sur un domaine croissant ont des parties réelles plus petites que celles sur un domaine fixé.

- Dans le Chapitre 4 on étend la définition de front progressif à des variétés et on en étudie quelques propriétés.

- Dans le Chapitre 5 on étudie des front progressifs sur la droite réelle. On démontre qu'il y a deux fronts progressifs qui se déplacent dans des directions opposées et qu'ils se bloquent mutuellement, générant ainsi une solution stationnaire non-triviale. Cet exemple montre que pour des modèles à diffusion non-homogène les fronts progressifs ne sont pas nécessairement des invasions.

- Dans le Chapitre 6 on étudie des fronts progressifs sur la sphère. On démontre que pour des sous-domaines de la sphère avec des conditions aux limites de Dirichlet le front progressif est toujours bloqué, tandis que pour la sphère complète le front peut ou bien invahir ou bien être bloqué, tout en fonction des conditions initiales.

- Dans le Chapitre 7 on étudie un problème elliptique aux valeurs propres nonlinéaires. Sur $\mathbb{S}^1$ on démontre l'existence de multiples solutions non-triviales avec des techniques de bifurcation. Sur $\mathbb{S}^N$ on utilise les mêmes arguments pour démontrer l'existence de multiples solutions non-triviales à symétrie axiale, i.e. qui ne dépendent que de l'angle vertical.

Mot Clés : Equations de réaction-diffusion, analyse nonlinéaire, équations aux dérivées partielles paraboliques, équations aux dérivées partielles elliptiques, sur-solutions et sous-solutions, méthodes variationelles, méthodes topologiques, Biomathématiques.

Abstract

The motivation of this PhD thesis is to model some biological problems using Reaction-diffusion systems and equations. The thesis is divided in seven chapters:

- In Chapter 1 we model calcium ions and some proteins inside a moving dendritic spine (a microstructure in the neurons). We propose two models, one with diffusing proteins and another with proteins fixed in the cytoplasm. We prove that the first problem is well-posed, that the second problem is almost well-posed and that there is a continuous link between both models.

- In Chapter 2 we applied the techniques of Chapter 1 for a model of viral infection of cells and immune response in cultivated cells. We propose as well two models, one with diffusing cells and another with fixed cells. We prove that both models are well-posed and that there is a continuous link between them. We also study the asymptotic behaviour and stability of solutions for large times, and we perform numerical simulations in Matlab.

- In Chapter 3 we show that growth has two positive effects on pattern formation. First, an *anti-blow-up* effect because it allows the solution on a growing domain to blow-up later than on a fixed domain, and if growth is fast enough then it can even prevent the blow-up. Second, a *stabilising* effect because the eigenvalues on a growing domain have smaller real part than those on a fixed domain.

- In Chapter 4 we extend the definition of travelling waves to manifolds and study some of their properties.

- In Chapter 5 we study travelling waves on the real line. We prove that there are two travelling waves moving in opposite directions and that they mutually block, giving rise to a non-trivial steady-state solution. This example shows that for models with non-homogeneous diffusion the travelling waves are not necessarily invasions.

- In Chapter 6 we study travelling waves on the sphere. We prove that for sub-domains of the sphere with Dirichlet boundary conditions the travelling wave is always blocked, but for the whole sphere the wave can either invade or be blocked, depending on the initial conditions.

- In Chapter 7 we study an elliptic nonlinear eigenvalue problem on the sphere. In $\mathbb{S}^1$ we prove the existence of multiple non-trivial solutions using bifurcation techniques. In $\mathbb{S}^N$ we use the same arguments to prove the existence of multiple axis-symmetric solutions, i.e. depending only on the vertical angle.

Keywords : Reaction-diffusion equations, nonlinear analysis, parabolic partial differential equations, elliptic partial differential equations, super-solutions and sub-solutions, variational methods, topological methods, Biomathematics.

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Contents

Introduction

The motivation of this PhD thesis is to model some biological problems using Partial Differential Equations. The general framework is a set of biological entities (either ions, molecules, proteins or cells) that interact with each other and diffuse within a given domain. Therefore, building our models via reaction-diffusion systems and equations seems quite natural.

This thesis is divided in seven chapters. The first two deal with reaction-diffusion systems on Euclidean spaces and modelling:

- Chapter 1. Calcium ions in dendritic spines (microstructures in the neuron).
- Chapter 2. Viral infection of cells and immune response.

The next four chapters deal with reaction-diffusion equations on manifolds:

- Chapter 3. The stabilising effect of growth on pattern formation.
- Chapter 4. Definition and properties of generalised travelling waves on manifolds.
- Chapter 5. Generalised travelling waves on the real line.
- Chapter 6. Generalised travelling waves on the sphere.

The last chapter deals with elliptic nonlinear eigenvalues on the sphere:

- Chapter 7. Bifurcation and multiple periodic solutions on the sphere.

In all seven cases we are interested in pattern formation and the role of geometry. We prove at least local existence of solutions, but in most cases we managed to find sufficient conditions for the solutions to be globally defined.

In Chapters 1 and 2 we prove that the models are well-posed problems (global existence, uniqueness and continuous dependence on initial data) and that the solutions are non-negative. This implies that any numerical method used to approximate the solutions is robust. Moreover, in Chapter 2 we also characterised the asymptotic behaviour of the solutions, which permits to determine the stable states and the long term interaction of cells and viruses.

A recurrent finding is a link between pattern formation and geometry. In Chapter 3 we prove that growth has two effects on pattern formation. The first one is a stabilising effect:

the eigenvalues of the operator on a growing domain are smaller than the eigenvalues on the corresponding fixed domain. The second one is an anti-blow-up effect: growth enhances the possibility of having time-global solutions. We prove that for scalar equations with quadratic nonlinearities, which exhibit blow-up on the fixed domain, the blow-up time on the growing domain occurs later. Moreover, if growth is fast enough the solutions are globally defined, i.e. there is no blow-up at all.

In Chapters 5 and 6 we show that the geometry of the domain plays a crucial role in the propagation of a travelling wave. Indeed, unlike classical planar travelling waves that invade the whole Euclidean space, on the sphere the travelling waves do not necessarily invade the whole domain. More precisely, we prove existence of generalised travelling waves that are eventually blocked by non-trivial steady-state solutions, which implies that the wave cannot invade the whole sphere. Since we find the same result on the projection of the sphere to the plane, on a truncated sphere and on the whole sphere, the geometry of the sphere plays an important role in the invasive nature of the travelling front.

In Chapter 7 we deal with an elliptic nonlinear eigenvalue problem on the sphere. In the case of $\mathbb{S}^1$ we prove via topological bifurcation the existence of multiple non-trivial solutions. In the case of $\mathbb{S}^N$ we use the same arguments to prove the existence of multiple axis-symmetric solutions, i.e. solutions depending only on the vertical angle, thus independent on the horizontal angles.

Chapter 1. Calcium ions in dendritic spines

The study of synapses is a very recurrent and important topic that lies in the intersection of Medicine, Neurology, Biology and Chemistry. The current technology of microscopes has shown that the dendritic spines, the smallest structures of the neuron and the part responsible of the synapses, possess a twitching motion. The goal of our model is to propose a theoretical framework for this twitching motion and incorporate it into the dynamics of the calcium ions inside the neuron.

The motivation of Chapter 1 is the two articles of Holcman and his collaborators, [33] and [34]. In the former they use a stochastic model for each single calcium ion, whilst in the latter they pass from the microscopic description to a macroscopic reaction-diffusion model via Fokker-Planck equations and the Law of Mass Action. This reaction-diffusion models describe the twitching motion of the dendritic spine, but the assumptions on the mechanism that triggers such twitches are not very realistic. After reviewing the experimental evidence in the literature (e.g. Farah *et al* [19], Klee *et al* [36] and Shiftman *et al* [59]), we propose to modify the hypotheses on the genesis of the twitching to obtain a more accurate model from the biological point of view. With the new boundary conditions the problem is very nonlinear and strongly coupled, but we still have a well-posed problem.

We consider calcium ions interacting with some proteins that have 4 binding sites for the ions. Both calcium ions and proteins diffuse all within a moving domain Ω (a dendritic spine) full of cytoplasm. Let M be the concentration of calcium ions, U the total number of binding sites and W the total number of free sites and $\mathbf{V}$ the cytoplasmic flow field. If we suppose that the proteins are fixed in the cytoplasm (i.e. they do not diffuse) then the model is

$$\left\{\begin{array}{rcl} \partial_t M &=& \nabla \cdot [D\nabla M - \boldsymbol{V}M] - k_1 MU + k_{-1}[A-U]\,, \\ \partial_t U &=& -k_1 MU + k_{-1}[A-U]\,, \\ \mathbf{V} &=& \nabla\phi\,, \qquad \triangle\phi = 0\,. \end{array}\right. \tag{0.1}$$

with initial conditions

$$\left\{\begin{array}{rcl} M(\boldsymbol{x},0) &=& m_0(\boldsymbol{x})\,, \\ U(\boldsymbol{x},0) &=& A(\boldsymbol{x})\,, \end{array}\right. \tag{0.2}$$

and boundary conditions

$$\left\{\begin{array}{rcll} M(\sigma,t) &=& 0 & \text{on } \Gamma_a \times [0,T]\,, \\ (D\nabla M - \boldsymbol{V}M)\cdot \boldsymbol{n}(\sigma,t) &=& 0 & \text{on } \Gamma_r \times [0,T]\,, \\ \nabla\phi \cdot \boldsymbol{n}(\sigma,t) &=& a(\sigma)\lambda(t) & \text{on } \Gamma \times [0,T], \end{array}\right. \tag{0.3}$$

where $\Gamma := \partial\Omega$, $\Gamma = \Gamma_a \cup \Gamma_r$ and $\Gamma_a \cap \Gamma_r = \emptyset$. If we allow the diffusion of proteins then (0.1)-(0.3) becomes

$$\left\{\begin{array}{rcl} \partial_t M &=& \nabla \cdot [D\nabla M - \boldsymbol{V}M] - k_1 MU + k_{-1}W\,, \\ \partial_t U &=& d\triangle U - k_1 MU + k_{-1}W\,, \\ \partial_t W &=& d\triangle U + k_1 MU - k_{-1}W\,, \\ \mathbf{V} &=& \nabla\phi\,, \qquad \triangle\phi = 0\,. \end{array}\right. \tag{0.4}$$

with initial conditions

$$\left\{\begin{array}{rcl} M(\boldsymbol{x},0) &=& m_0(\boldsymbol{x})\,, \\ U(\boldsymbol{x},0) &=& A(\boldsymbol{x})\,, \\ W(\boldsymbol{x},0) &=& 0\,, \end{array}\right. \tag{0.5}$$

and boundary conditions

$$\left\{\begin{array}{rcll} M(\sigma,t) &=& 0 & \text{on } \Gamma_a \times [0,T]\,, \\ (D\nabla M - \boldsymbol{V}M)\cdot \boldsymbol{n}(\sigma,t) &=& 0 & \text{on } \Gamma_r \times [0,T]\,, \\ \nabla U \cdot \boldsymbol{n}(\sigma,t) &=& 0 & \text{on } \Gamma \times [0,T], \\ \nabla W \cdot \boldsymbol{n}(\sigma,t) &=& 0 & \text{on } \Gamma \times [0,T], \\ \nabla\phi \cdot \boldsymbol{n}(\sigma,t) &=& a(\sigma)\lambda(t) & \text{on } \Gamma \times [0,T]. \end{array}\right. \tag{0.6}$$

Note that d should be much smaller than D because the proteins we are considering are around 10^6 times bigger than the calcium ions.

The main results of the calcium ion problem is that both models admit weak, positive solutions and that there is a continuous link between both models. More precisely, we have the following three results.

Theorem 0.1 *For any $T > 0$ the reaction-diffusion system (0.1)-(0.3) has global unique weak solutions $M(\boldsymbol{x},t)$, $U(\boldsymbol{x},t)$ and $\boldsymbol{V}(\boldsymbol{x},t)$ on $\Omega \times (0,T)$ with the following properties:*

1. $M \in L^\infty(\Omega \times (0,T))$ and $0 \le M(\boldsymbol{x},t) \le \|m_0\|_\infty + k_{-1}t\|A\|_\infty$ a.e. in $\Omega \times (0,T)$.
2. $M \in L^\infty\left(0,T; H^1(\Omega)\right)$ and
$$\|M(t)\|^2 + D\int_0^t e^{C(t-s)}\|\nabla M(s)\|^2\,ds \le e^{Ct}\left[\|m_0\|^2 + k_{-1}^2 t\|A\|^2\right].$$
3. $U \in L^\infty(\Omega \times (0,T))$ and $0 \le U(\boldsymbol{x},t) \le A(\boldsymbol{x})$ a.e. in $\Omega \times (0,T)$.
4. $\boldsymbol{V} \in L^\infty\left(0,T; \left[L^2(\Omega)\right]^n\right)$ and $\|\boldsymbol{V}\|_{L^\infty(0,T;[L^2(\Omega)]^n)} \le C\|a\|_\infty\|A\|_\infty$.

Theorem 0.2 *For any $T > 0$ the reaction-diffusion system (0.4)-(0.6) is well-posed, i.e. it has global unique weak solutions $M(\boldsymbol{x},t)$, $U(\boldsymbol{x},t)$, $W(\boldsymbol{x},t)$ and $\boldsymbol{V}(\boldsymbol{x},t)$ on $\Omega \times (0,T)$ depending continuously on the initial data. Moreover, we have the following properties:*

1. $M \in L^\infty(\Omega \times (0,T))$ and $0 \le M(\boldsymbol{x},t) \le \|m_0\|_\infty + k_{-1}t\|A\|_\infty$ a.e. in $\Omega \times (0,T)$.
2. $M \in L^\infty\left(0,T; H^1(\Omega)\right)$ and
$$\|M(t)\|^2 + D\int_0^t e^{C(t-s)}\|\nabla M(s)\|^2\,ds \le e^{Ct}\left[\|m_0\|^2 + k_{-1}^2 t\|A\|^2\right].$$
3. $U, W \in L^\infty(\Omega \times (0,T))$, they are non-negative and $0 \le U(\boldsymbol{x},t) + W(\boldsymbol{x},t) \le A(\boldsymbol{x})$ a.e. in $\Omega \times (0,T)$.
4. $U, W \in L^\infty\left(0,T; H^1(\Omega)\right)$ and
$$\|U(t)\|^2 + \|W(t)\|^2 + 2d\int_0^t e^{\int_s^t c(r)dr}\left(\|\nabla U(s)\|^2 + \|\nabla W(s)\|^2\right)\,ds \le e^{\int_0^t c(s)ds}\|A\|^2,$$
where $c(t) = 2[k_{-1} + k_1\alpha(t)]$ and $\alpha(t) = \|m_0\|_\infty + k_{-1}t\|A\|_\infty$.
5. $\boldsymbol{V} \in L^\infty\left(0,T; \left[L^2(\Omega)\right]^n\right)$ and $\|\boldsymbol{V}\|_{L^\infty(0,T;[L^2(\Omega)]^n)} \le C\|a\|_\infty\|A\|_\infty$

Theorem 0.3 *If $d \to 0$ then the sequence $(M^d, U^d, W^d, \mathbf{V}^d)$ of solutions of (0.4)-(0.6) converges to the solution $(M, U, W, \mathbf{V})$ of (0.1)-(0.3) in the following senses:*

1. M^d, U^d and W^d converge weakly in $L^2\left(0,T; L^2(\Omega)\right)$ to M, U and W, respectively.
2. $\mathbf{V}^d$ converges to $\mathbf{V}$ weakly in $L^2\left(0,T; \left[L^2(\Omega)\right]^n\right)$.
3. M^d converges strongly in $L^2\left(0,T; L^2(\Omega)\right)$ to M.
4. U^d and W^d converge weakly-$\star$ in $L^\infty(\Omega \times (0,T))$ to U and W, respectively.

5. *In the limit $d = 0$ we have $U(\boldsymbol{x}, t) + W(\boldsymbol{x}, t) = A(\boldsymbol{x})$ a.s. in $\Omega \times (0, T)$.*

Finally, the solutions of both systems (0.1)-(0.3) and (0.4)-(0.6) are globally defined in time.

Theorem 0.4 *Let M, U, W and $\mathbf{V}$ be solutions of either (0.1)-(0.3) or (0.4)-(0.6). Then:*

1. $M, U, W \in L^\infty\left(0, \infty; L^1(\Omega)\right)$.

2. $\boldsymbol{V} \in L^\infty\left(0, \infty; \left[L^2(\Omega)\right]^n\right)$.

Chapter 2. Viral infection and immune response

Starting from the assumption that cells and viruses diffuse and interact with each other motivates the framework of a reaction-diffusion system for viruses, normal cells and infected cells. If we add an immune response via antibodies then we should add as well a new type of cells that become resistant to viruses when they get in contact with antibodies. Models of this kind are important because of their potential applications in Cellular Biology and molecular transport, and could shed a light towards new gene therapies.

Getto *et al* [24] constructed an Ordinary Differential Equation model for virus infection of cells and immune response. The authors completely solved the model, and in particular they found that in the limit the viruses and the non-infected cells cannot coexist. Motivated by this result, we built up a reaction-diffusion model in order to study the spatial structure and properties of the solutions. Since the boundary conditions we imposed are homogeneous Neumann (i.e. no-flux), the problem is significantly easier than the one in Chapter 1 (calcium ions), which allows a complete description of the asymptotic behaviour and stability of solutions.

We consider a model where virions (i.e. viral particles) v infect cells, but we add an immune response from the organism via interferons i. There are 3 possible types of cells: wild-type cells W that has not been in contact with virions, infected cells I that have been in contact with virions, and resistant cells R that have been in contact with interferons. All five biological particles are confined within a domain Ω with no-flux boundary conditions.

As in the calcium ion problem, we will consider two models. The first model is a reaction-diffusion (RD) system, where we allow cells to diffuse:

$$\left\{\begin{array}{rcl} \partial_t W &=& d\Delta W - iW - vW\,, \\ \partial_t I &=& d\Delta I - \mu_I I + vW\,, \\ \partial_t R &=& d\Delta R + iW\,, \\ \partial_t v &=& d_v\Delta v - \mu_v v + \alpha_v I - \alpha_4 vW\,, \\ \partial_t i &=& d_i\Delta i - \mu_i i + \alpha_i I - \alpha_3 iW\,, \end{array}\right. \tag{0.7}$$

with boundary conditions

$$\begin{cases} \nabla W \cdot \boldsymbol{n}(\sigma,t) &= 0 \quad \text{on } \Gamma\times[0,T], \\ \nabla I \cdot \boldsymbol{n}(\sigma,t) &= 0 \quad \text{on } \Gamma\times[0,T], \\ \nabla R \cdot \boldsymbol{n}(\sigma,t) &= 0 \quad \text{on } \Gamma\times[0,T], \\ \nabla v \cdot \boldsymbol{n}(\sigma,t) &= 0 \quad \text{on } \Gamma\times[0,T], \\ \nabla i \cdot \boldsymbol{n}(\sigma,t) &= 0 \quad \text{on } \Gamma\times[0,T], \end{cases} \tag{0.8}$$

and initial conditions

$$\begin{cases} W(\boldsymbol{x},0) &= W_0(\boldsymbol{x})\,, \\ I(\boldsymbol{x},0) &= I_0(\boldsymbol{x})\,, \\ R(\boldsymbol{x},0) &= R_0(\boldsymbol{x})\,, \\ v(\boldsymbol{x},0) &= v_0(\boldsymbol{x})\,. \\ i(\boldsymbol{x},0) &= i_0(\boldsymbol{x})\,. \end{cases} \tag{0.9}$$

In the second model we consider that the cells do not diffuse at all. Therefore, we set $d = 0$ and we thus obtain a hybrid model consisting of PDE equations for the interferons i and virions v and ODE equations for the three types of cells W, I, R:

$$\begin{cases} \partial_t W &= -iW - vW\,, \\ \partial_t I &= -\mu_I I + vW\,, \\ \partial_t R &= iW\,, \\ \partial_t v &= d_v\Delta v - \mu_v v + \alpha_v I - \alpha_4 vW\,, \\ \partial_t i &= d_i\Delta i - \mu_i i + \alpha_i I - \alpha_3 iW\,, \end{cases} \tag{0.10}$$

with boundary conditions

$$\begin{cases} \nabla v \cdot \boldsymbol{n}(\sigma,t) &= 0 \quad \text{on } \Gamma\times[0,T], \\ \nabla i \cdot \boldsymbol{n}(\sigma,t) &= 0 \quad \text{on } \Gamma\times[0,T]. \end{cases} \tag{0.11}$$

We prove that both the RD and the hybrid models are well-posed problems, i.e., they have unique solutions which are non-negative, uniformly bounded, and depend continuously on the initial data. We also prove that there is a “continuous link” between these two models.

Theorem 0.5 *Fix any $T > 0$. If the initial conditions (0.9) are non-negative a.e. and bounded then the RD system (0.7)-(0.8) has unique weak solutions $W(\boldsymbol{x},t)$, $I(\boldsymbol{x},t)$, $R(\boldsymbol{x},t)$, $v(\boldsymbol{x},t)$ and $i(\boldsymbol{x},t)$ on $\Omega\times[0,T]$. Moreover, these solutions are non-negative, uniformly bounded, and depend continuously on the initial data.*

Theorem 0.6 *Fix any $T > 0$. If the initial conditions (0.9) are non-negative a.e. and bounded then the hybrid system (0.10)-(0.11) has unique weak solutions $W(\boldsymbol{x},t)$, $I(\boldsymbol{x},t)$, $R(\boldsymbol{x},t)$, $v(\boldsymbol{x},t)$ and $i(\boldsymbol{x},t)$ on $\Omega\times[0,T]$. Moreover, these solutions are non-negative, bounded, and depend continuously on the initial data.*

Theorem 0.7 *If $d \to 0$ then the solutions $(W^d, I^d, R^d, v^d, i^d)$ of the RD system (0.7)-(0.8) converge to the solution (W, I, R, v, i) of the hybrid system (0.10)-(0.11), in the following sense:*

- *Strongly in $L^2\left(0, T; L^2(\Omega)\right)$.*
- *Weakly in $L^2\left(0, T; H^1(\Omega)\right)$.*
- *Weakly-$\star$ in $L^\infty(\Omega \times (0, T))$.*

So far we have (essentially) the same results we got for the calcium ion problem. However, the viral infection problem is easier because the boundary conditions are Neumann homogeneous, whilst for the calcium ions the boundary conditions were strongly coupled. This feature has allowed us to study in detail the asymptotic behaviour of solutions.

Theorem 0.8

1. *The solutions W, I, R, v, i of the RD system (0.7)-(0.8) are globally-defined and belong to $L^\infty(\Omega \times (0, \infty))$.*
2. *If W, I, R, v, i are non-negative, steady-state solutions of the RD system (0.7)-(0.8) then*

$$\begin{aligned} W(\boldsymbol{x}) &= W_0 \geq 0 \quad \text{constant}, \\ I(\boldsymbol{x}) &\equiv 0, \\ R(\boldsymbol{x}) &= R_0 \geq 0 \quad \text{constant}, \\ v(\boldsymbol{x}) &\equiv 0, \\ i(\boldsymbol{x}) &\equiv 0. \end{aligned}$$

Theorem 0.9 *If W, I, R, v, i are non-negative, steady-state solutions of the hybrid system (0.10)-(0.11) then*

$$\begin{aligned} I(\boldsymbol{x}) &\equiv 0, \\ v(\boldsymbol{x}) &\equiv 0, \\ i(\boldsymbol{x}) &\equiv 0. \end{aligned}$$

Moreover, suppose that the initial conditions belong to $L^\infty(\Omega)$. Then the solutions of the hybrid system (0.10)-(0.11) are globally-defined and have the following asymptotic properties:

1. *$I(\boldsymbol{x}, t)$ belongs to $L^1(0, \infty; L^2(\Omega))$, i.e.,*

$$\lim_{t\to\infty} \int_0^t \int_\Omega I^2(\boldsymbol{x}, s)\, d\Omega\, ds < \infty.$$

2. $v(\boldsymbol{x}, t)$ *and* $i(\boldsymbol{x}, t)$ *belong to* $L^1(0, \infty; H^1(\Omega))$, *i.e.,*

$$\lim_{t\to\infty} \int_0^t \left(\int_\Omega v^2(\boldsymbol{x}, s)\, d\Omega + \int_\Omega |\nabla v(\boldsymbol{x}, s)|^2\, d\Omega \right) ds < \infty\,,$$

$$\lim_{t\to\infty} \int_0^t \left(\int_\Omega i^2(\boldsymbol{x}, s)\, d\Omega + \int_\Omega |\nabla i(\boldsymbol{x}, s)|^2\, d\Omega \right) ds < \infty\,.$$

3. $v(\boldsymbol{x}, t)W(\boldsymbol{x}, t)$ *and* $i(\boldsymbol{x}, t)W(\boldsymbol{x}, t)$ *belong to* $L^1(0, \infty; L^1(\Omega))$, *i.e.,*

$$\lim_{t\to\infty} \int_0^t \int_\Omega v(\boldsymbol{x}, s)W(\boldsymbol{x}, s)\, d\Omega\, ds < \infty \quad \text{and} \quad \lim_{t\to\infty} \int_0^t \int_\Omega i(\boldsymbol{x}, s)W(\boldsymbol{x}, s)\, d\Omega\, ds < \infty\,.$$

4. *For any* $\boldsymbol{x} \in \Omega$,

$$\lim_{t\to\infty} I(\boldsymbol{x}, t) = 0\,, \quad \lim_{t\to\infty} v(\boldsymbol{x}, t) = 0\,, \quad \lim_{t\to\infty} i(\boldsymbol{x}, t) = 0\,.$$

5. *For any* $\boldsymbol{x} \in \Omega$, $W_0(\boldsymbol{x}) > 0$ *if and only if*

$$\lim_{t\to\infty} W(\boldsymbol{x}, t) > 0.$$

Theorem 0.10 *Consider the hybrid system (0.10)-(0.11) and suppose that* $\mu_v = 0$. *Then:*

1. *If* $v_\infty(\boldsymbol{x})$ *is a steady-state solution then* $\|\nabla v_\infty\| = 0$.

2. *Define*

$$v_\infty(\boldsymbol{x}) := \limsup_{t\to\infty} v(\boldsymbol{x}, t).$$

   If $\alpha_v \geq \alpha_4 \mu_I$ *then*

$$\int_\Omega v_\infty(\boldsymbol{x})\, d\Omega \geq \int_\Omega v_0(\boldsymbol{x})\, d\Omega.$$

   In particular, if $v_0 \not\equiv 0$ *then* $v_\infty \not\equiv 0$.

Chapter 3. The effect of growth on pattern formation

The study of pattern formation lies in the possibility of predicting the generation of certain patterns as a consequence of other factors, e.g. the strength of external stimuli and the concentration and diffusion of certain molecules. In Chapter 3 we focus our attention on the effect of growth in the existence and stability of patterns.

The study of pattern formation in reaction-diffusion systems started with the seminal paper of Turing [66], where he showed that the diffusion, a process that has a regularising effect, can drive instabilities when there are several substances interacting.

The study of the effect of growth and curvature on pattern formation is however more recent. In 1995 Kondo and Asai [38] reproduced numerically the skin patterns of a tropical fish by adding growth to the classical reaction-diffusion system. In 1999 Crampin *et al* [15] showed in 1D that the domain growth may increase the robustness of patterns. In 2004 Plaza *et al* [52] derived a reaction-diffusion model for two morphogens on 1D and 2D growing, curved domains. In 2007 Gjiorgjieva and Jacobsen [28] found that on a 2D sphere the solutions under slow growth are very similar to the solutions of the 2001 model of Chaplain *et al* [13] on a fixed sphere. They also showed numerically that the eigenmodes on the growing domain are smaller than those on the corresponding fixed domain, and that there is a continuous link between both patterns.

In Chapter 3 we prove that growth has two effects: (i) a regularising, anti-blow-up effect in the sense that growth not only delays the blow-up but it can even prevent it, and (ii) a stabilising effect in the sense that the eigenvalues of the linearisation on a growing domain have smaller real parts than those on a fixed domain.

Let $\mathcal{M}$ be an n-dimensional manifold without boundary and consider the reaction-diffusion system

$$\frac{\partial \mathbf{u}}{\partial t} = \mathcal{D}\Delta_{\mathcal{M}}\mathbf{u} + \mathbf{F}(\mathbf{u}), \quad \mathcal{D} = \begin{bmatrix} D_1 & & & \\ & D_2 & & \\ & & \ddots & \\ & & & D_M \end{bmatrix}, \; D_k > 0, \tag{0.12}$$

where $\Delta_{\mathcal{M}}$ is the Laplace-Beltrami operator. Since we are interested in the effect of growth on pattern formation, we will consider (0.12) on a growing domain $(\mathcal{M}_t)_{t\geq 0}$. In particular, for isotropic growth we will assume that there is a growth function $\rho(t)$ such that $\mathcal{M}_t := \rho(t)\mathcal{M}$.

Our first result characterises generic reaction-diffusion systems on a growing manifold.

Theorem 0.11 *Let $(\mathcal{M}_t)_{t\geq 0}$ be a growing manifold with metric $(g_{ij}(\xi,t))$. Under the hypotheses of Fick's law of diffusion and conservation of mass, any reaction-diffusion system on $\mathcal{M}_t$ has the form*

$$\partial_t \mathbf{u} = \mathcal{D}\Delta_{\mathcal{M}_t}\mathbf{u} - \partial_t[\log\sqrt{g(\xi,t)}\,]\mathbf{u} + \mathbf{F}(\mathbf{u}), \quad g := det(g_{ij}), \tag{0.13}$$

where $\Delta_{\mathcal{M}_t}$ is he Laplace-Beltrami operator on $\mathcal{M}_t$. In the case of isotropic growth we have

$$\partial_t \mathbf{u} = \frac{\mathcal{D}}{\rho^2(t)}\Delta_{\mathcal{M}}\mathbf{u} - n\frac{\dot\rho(t)}{\rho(t)}\mathbf{u} + \mathbf{F}(\mathbf{u}), \tag{0.14}$$

where the coefficients of $\Delta_{\mathcal{M}}$ do not depend on time.

We prove local existence, uniqueness and regularity of solutions of (0.14). Moreover, under extra assumptions on the nonlinearity we prove that the solutions are global.

Theorem 0.12 *There is a time $T > 0$ such that the reaction-diffusion system (0.14) with initial condition $\mathbf{u}_0 \in C\left[\mathcal{M},\mathbb{R}^M\right]$ has a unique solution*

$$\mathbf{u}(t) \in C\left([0,T], C\left[\mathcal{M},\mathbb{R}^M\right]\right).$$

Theorem 0.13 *If* $\mathbf{F} : \mathbb{R}^M \to \mathbb{R}^M$ *is* C^∞ *then*

$$\mathbf{u}(t) \in C^\infty \left[\mathcal{M} \times (0,T], \mathbb{R}^M\right] .$$

Theorem 0.14 *Let* $(\mathcal{M}_t)_{t\geq 0}$ *be an isotropic growing manifold with growth rate*

$$c(t) := n\frac{\dot{\rho}(t)}{\rho(t)} > 0 .$$

Suppose that the initial condition $\mathbf{u}_0$ *of the reaction-diffusion system (3.4) is in* $C\left[\mathcal{M}, \mathbb{R}^M\right]$ *and takes its values inside the rectangle* $\mathcal{R} = (-1,1)^M$*. Suppose further that for all* $(z,t) \in \partial\mathcal{R} \times [0,\infty)$ *we have*

$$\mathbf{F}(z) \cdot \mathbf{n}(z) < c(t) , \tag{0.15}$$

where $\mathbf{n}(z)$ *is the outer normal at* z*. Then the solution* $\mathbf{u}(t)$ *of (0.14) is global and bounded, i.e. it exists for all times* $t \geq 0$ *and takes its values inside* $\mathcal{R}$*. In particular, here is no blow-up whenever* (0.15) *holds.*

From Theorem 0.14, if the growth rate is sufficiently big to satisfy

$$c(t) > \sup\{\|\mathbf{F}(z)\| : z \in \partial\mathcal{R}\}$$

then the solution is globally bounded, which implies that there is no blow-up. Notice that since the growth rate $c(t)$ is increasing in n, which implies that the dimension of the space enhances the regularity of solutions.

We quantitatively asses this anti-blow-up effect of growth for scalar equations. For homogeneous equations we compare the corresponding ODE with and without growth. On the one hand, the ODE on a fixed domain is

$$\begin{cases} \dot{u} = u^2, \\ u(0) = u_0 > 0 , \end{cases}$$

whose solution is

$$u(t) = \left(\frac{1}{u_0} - t\right)^{-1} ,$$

which blows up when $t \to t_1 := 1/u_0$. On the other hand, the ODE on a growing domain is

$$\begin{cases} \dot{u} = -c(t)u + u^2, \\ u(0) = u_0 > 0 , \end{cases}$$

whose solution is

$$u(t) = \int_0^t \frac{ds}{\rho^n(s)} \times \left(\frac{1}{u_0} - \int_0^t \frac{ds}{\rho^n(s)}\right)^{-1} ,$$

which blows up at time t_2, where t_2 is defined as

$$\int_0^{t_2} \frac{dt}{\rho^n(t)} = \frac{1}{u_0}\,.$$

It is easy to show that (i) $t_2 > t_1 := 1/u_0$, (ii) t_1 and t_2 are decreasing functions of the initial condition u_0, (iii) t_2 is an increasing function on the spatial dimension n, and (iv) if growth is sufficiently fast, i.e. if the growth function $\rho(t)$ satisfies

$$\int_0^{\infty} \frac{dt}{\rho^n(t)} \leq \frac{1}{u_0}$$

then $t_2 = \infty$, i.e. there is no blow-up on the growing domain.

The same results hold for non-homogeneous scalar equations. Indeed, consider the scalar reaction-diffusion equation

$$\begin{aligned} \partial_t u &= \frac{1}{\rho^2(t)}\Delta_{\mathcal{M}} u - c(t)u + u^2\,,\\ u(0,\xi) &= u_0(\xi) > 0\,. \end{aligned}$$

If we define

$$\eta(t) := \iint_{\mathcal{M}} u(t,\xi)\,d\Omega\,, \quad \eta(0) = \iint_{\mathcal{M}} u_0(\xi)\,d\Omega > 0\,.$$

it can be shown that

$$\eta(t) \geq \int_0^t \frac{ds}{\rho^n(s)} \times \left(\frac{1}{\eta(0)} - \alpha \int_0^t \frac{ds}{\rho^n(s)}\right)^{-1}\,.$$

In particular, for an exponential growth $\rho(t) = e^{rt}$ such that $nr > \alpha\eta(0)$, i.e.

$$r > \frac{|\mathcal{M}|}{n} \iint_{\mathcal{M}} u_0(\xi)\,d\Omega\,,$$

we have blow-up on the fixed manifold but not on the growing manifold.

Besides the anti-blow-up effect of growth, there is a second effect that we found: under isotropic regimes, we proved that growth has a stabilizing effect on pattern formation, as the next theorem shows.

Theorem 0.15 *Let $(\mathcal{M}_t)_{0\leq t\leq T}$ be an isotropic growing manifold with growth rate $c(t)$. Define $\mathcal{S} := \mathcal{M}_T$ and notice that we will use the notation $\mathcal{S}$ for the fixed manifold and $\mathcal{M}_T$ for the final stage of the growing manifold $(\mathcal{M}_t)_{0\leq t\leq T}$. Then λ is an eigenvalue of the reaction-diffusion operator on $\mathcal{S}$,*

$$\mathcal{L}_{\mathcal{S}} := \frac{\mathcal{D}}{\rho^2(T)}\Delta_{\mathcal{S}} + d\mathbf{F}(0)$$

if and only if $\lambda - c(T)$ is an eigenvalue of the corresponding operator on $\mathcal{M}_T$,

$$\mathcal{L}_{\mathcal{M}_T} := \frac{\mathcal{D}}{\rho^2(T)}\Delta_{\mathcal{M}_T} - c(T)I + d\mathbf{F}(0)\,.$$

Theorem 3.5 says that when we compare the spectra of $\mathcal{L}_{\mathcal{S}}$ and $\mathcal{L}_{\mathcal{M}_T}$ on the same manifold $\mathcal{S} = \mathcal{M}_T$ we obtain

$$\text{spectrum}(\mathcal{L}_{\mathcal{M}_T}) = \text{spectrum}(\mathcal{L}_{\mathcal{S}}) - c(T)\,.$$

Therefore, growth shifts the eigenvalues to the left in the complex plane, which is indeed a stabilising effect since the real parts are smaller. Moreover, this shift is exactly the growth rate $c(T) > 0$, which implies that the faster growth is, the more stable the patterns are. It is important to remark that, as far as we know, Theorem 3.5 is the first analytic proof of the stabilising effect of growth on pattern formation. It is worth to mention that the proof we provide does not hold for the case of non-isotropic growth.

Chapter 4. Generalised travelling waves on manifolds

We extend the current definitions of travelling waves in Euclidean spaces to curved domains, i.e. to manifolds. This extension permits a unified framework to study the emergence and stability of patterns on manifolds, which is the main objective of Chapters 5, 6 and 7.

The study of travelling waves started in 1937 with the pioneering article of Kolmogorov [37]. Later on, in 1977 Aronson and Weinberger [3] proved the existence of multi-dimensional travelling waves, and in 1978 Fife and McLeod [20] proved that the travelling waves have an exponential decay at infinity. However, for the planar travelling waves to exist it is necessary to have an axis in the domain such that the equation is invariant under translations on that axis.

For non-planar travelling waves there are several approaches, but they could be divided in two categories: equations with coefficients that are not invariant under translations (i.e. inhomogeneous media) or domains that do not have an invariant direction (e.g. Euclidean domains with holes). For the study of such generalised travelling waves we refer the reader to Berestycki and Hamel [6], [7], [8] and Berestycki *et al* [9], .

Berestycki and Hamel [8] defined a generalised travelling wave in terms of their level sets, which are no longer hyper-plans but hyper-surfaces. We realised that the definitions and properties of generalised travelling waves were easily extended to the case of curved domains, i.e. manifolds. We adapted the existing proofs for on general Euclidean domains and found that all the conclusions of Berestycki and Hamel [8] hold for complete, unbounded, Riemannian manifolds.

It is worth to mention that of these results are straightforward, e.g. maximum principles and Harnack's inequality, because they are local in nature. However, for global results such as a priori estimates we need uniform bounds of the coefficients.

Let $\mathcal{M}$ be a complete, unbounded, Riemannian manifold and consider the reaction-diffusion equation

$$\begin{cases} \partial_t u = D\Delta_{\mathcal{M}} u + F(t,x,u)\,; & t \in \mathbb{R},\ x \in \mathcal{M}\,, \\ u(0,x) = u_0(x)\,; & x \in \mathcal{M}\,. \end{cases} \tag{0.16}$$

where $\Delta_{\mathcal{M}}$ is the Laplace-Beltrami operator. The assumptions on the nonlinearity $F(t,x,u)$ are:

- Either F is C^1 and both F and $\partial_u F$ are globally bounded, or
- Either F is bounded, continuous in (t,x) and locally Lipschitz continuous in u, uniformly in (t,x).

The goal of this project is to extend the notion of a travelling wave to manifolds. We start with several definitions. For any two subsets $A, B \subset \mathcal{M}$ denote

$$d(A,B) := \inf\{\, d(x,y) \,:\, x \in A,\, y \in B\}\,,$$

where $d(\cdot,\cdot)$ is the geodesic distance.

Definition 0.1 *A **generalised profile** is a family $(\Omega_t^{\pm}, \Gamma_t)_{t\in\mathbb{R}}$ of subsets of $\mathcal{M}$ with the following properties:*

1. *Ω_t^- and Ω_t^+ are non-empty disjoint subsets of $\mathcal{M}$, for any $t \in \mathbb{R}$.*
2. *$\Gamma_t = \partial\Omega_t^- \cap \partial\Omega_t^+$ and $\mathcal{M} = \Gamma_t \cup \Omega_t^- \cup \Omega_t^+$, for any $t \in \mathbb{R}$.*
3. *$\sup\{\, d(x,\Gamma_t) \,:\, t \in \mathbb{R},\, x \in \Omega_t^-\} = \sup\{\, d(x,\Gamma_t) \,:\, t \in \mathbb{R},\, x \in \Omega_t^+\} = +\infty$*

Suppose that there exist $p^-, p^+ \in \mathbb{R}$ such that $F(t,x,p^{\pm}) = 0$ for all $t \in \mathbb{R}$ and all $x \in \mathcal{M}$. Then $u \equiv p^{\pm}$ are solutions of (0.16).

Definition 0.2 *Let $u(t,x)$ be a time-global classical solution of (4.1) such that $u \not\equiv p^{\pm}$. Then $u(x,t)$ is a **generalized front** between p^- and p^+ if there exists a generalized front $(\Omega_t^{\pm}, \Gamma_t)_{t\in\mathbb{R}}$ such that*

$$|u(t,x) - p^{\pm}| \to 0 \text{ uniformly when } x \in \Omega_t^{\pm} \text{ and } d(x,\Gamma_t) \to +\infty.$$

Definition 0.3 *Let $u(t,x)$ be a generalized front. We say that p^+ invades p^- or that $u(t,x)$ is a **generalised invasion** of p^- by p^+ (resp. p^- invades p^+ or that $u(t,x)$ is a generalised invasion of p^+ by p^-) if*

(i) $\Omega_t^+ \subset \Omega_s^+$ *(resp.* $\Omega_s^- \subset \Omega_t^-$*) for all* $t \leq s$.

(ii) $d(\Gamma_t, \Gamma_s) \to +\infty$ *when* $|t-s| \to +\infty$.

Definition 0.4 *A generalised front $u(t,x)$ has **global mean speed** $c > 0$ if the generalised profile $(\Omega_t^{\pm}, \Gamma_t,)_{t\in\mathbb{R}}$ is such that*

$$\frac{d(\Gamma_t,\Gamma_s)}{|t-s|} \to c \quad \text{when } |t-s| \to +\infty.$$

For any $x \in \mathcal{M}$ and any $r > 0$ define

$$\begin{aligned} B(x,r) &= \{ y \in \mathcal{M} \, : \, d(x,y) \leq r \} , \\ S(x,r) &= \{ y \in \mathcal{M} \, : \, d(x,y) = r \} . \end{aligned}$$

We exhibit some properties of the level sets.

Theorem 0.16 *Let $p^- < p^+$ and suppose that $u(t,x)$ is a time-global solution of (0.16) such that*

$$p^- < u(t,x) < p^+ \quad \text{for all } (t,x) \in \mathbb{R} \times \mathcal{M}.$$

1. *Suppose $u(t,x)$ is a generalised front between p^- and p^+ (or between p^+ and p^-) with the following properties:*

   (a) There exists $\tau > 0$ such that $\sup\{ d(x, \Gamma_{t-\tau}) \, : \, t \in \mathbb{R}, \, x \in \Gamma_t \} < +\infty$, and

   (b) $\sup\{ d(y, \Gamma_t) \, : \, y \in \overline{\Omega_t^{\pm}} \cap S(x,r) \} \to +\infty$ when $r \to +\infty$, uniformly in $t \in \mathbb{R}$ and $x \in \Gamma_t$.

   Then:

   (i) $\sup\{ d(x, \Gamma_t) \, : \, u(t,x) = \lambda \} < +\infty$ for all $\lambda \in (p^-, p^+)$.

   (ii) $p^- < \inf\{ u(t,x) \, : \, d(x,\Gamma_t) \leq C \} \leq \sup\{ u(t,x) \, : \, d(x,\Gamma_t) \leq C \} < p^+$ for all $C \geq 0$.

2. *Conversely, if (i) and (ii) hold for a certain generalised profile $(\Omega_t^{\pm}, \Gamma_t,)_{t \in \mathbb{R}}$ and there exists $d_0 > 0$ such that for all $d \geq d_0$ the sets*

$$\{ (t,x) \in \mathbb{R} \times \mathcal{M} \, : \, x \in \overline{\Omega_t^{\pm}}, \, d(x,\Gamma_t) \geq d \}$$

   are connected, then $u(t,x)$ is a generalised front between p^- and p^+ (or between p^+ and p^-).

We prove that the global mean speed is unique and that generalised fronts are monotonic in time.

Theorem 0.17 *Let $p^- < p^+$ and suppose that $u(t,x)$ is a generalised front between p^- and p^+, where its associated profile $(\Omega_t^{\pm}, \Gamma_t,)_{t \in \mathbb{R}}$ satisfies (b) in Theorem 0.16. If $u(t,x)$ has a global mean speed $c > 0$ then it is independent of the generalised profile. In other words, if for any other generalised profile $(\tilde{\Omega}_t^{\pm}, \tilde{\Gamma}_t,)_{t \in \mathbb{R}}$ satisfying (b) the generalised front $u(t,x)$ has global mean speed $\tilde{c}$, then $\tilde{c} = c$.*

Theorem 0.18 Monotonicity

Let $p^- < p^+$ and suppose $F(t,x,u)$ satisfies the following conditions:

(α) *$s \mapsto F(s,x,u)$ is non-decreasing for all $(x,u) \in \mathbb{M} \times \mathbb{R}$.*

(β) *There exists $\delta > 0$ such that $q \mapsto F(t,x,q)$ is non-increasing for all $q \in \mathbb{R} \setminus (p^- + \delta, p^+ - \delta)$.*

Let $u(t,x)$ be a generalised invasion of p^- by p^+ and assume (as in Theorem 0.16) that:

(a) There exists $\tau > 0$ such that $\sup\{\, d(x, \Gamma_{t-\tau}) \,:\, t \in \mathbb{R},\, x \in \Gamma_t \,\} < +\infty$, and

(b) $\sup\{\, d(y, \Gamma_t) \,:\, y \in \overline{\Omega_t^{\pm}} \cap S(x,r) \,\} \to +\infty$ uniformly in $t \in \mathbb{R}$ and $x \in \Gamma_t$ when $r \to +\infty$.

Then:

1. *$p^- < u(t,x) < p^+$ for all $(t,x) \in \mathbb{R} \times \mathcal{M}$.*
2. *$u(t,x)$ is increasing in time, i.e. $u(t+s,x) > u(t,x)$ for all $s > 0$.*

Chapter 5. Travelling waves on the real line

As a first application of the concept of generalised travelling waves of Chapter 4, in Chapter 5 we study calcium waves on spherical eggs. We assume that the waves depend only on the horizontal angle. When we project the waves on the real line we pass from a reaction diffusion equation with constant coefficients on a curved domain to a reaction-diffusion equation with non-constant coefficients on a 1D Euclidean domain. The two striking features of the travelling waves on the real line are (i) the existence of non-trivial steady-state solutions, and (ii) the travelling wave does not invade the whole domain (as it does in the classical 1D case) but it is blocked by the non-trivial steady-state solution. Therefore, the curvature of the sphere plays a crucial role in the properties of the travelling wave.

Gilkey *et al* [25] studied calcium waves on the eggs of amphibians, which are pretty spherical. They found that the waves seem to be invariant under rotations around the vertical axis, and that the velocity of the waves is bigger on the northern hemisphere than on the southern one.

Murray [49] constructed a classical reaction-diffusion equation on the sphere in order to model these calcium waves. However, he found that the model gave the opposite result, namely that the theoretical velocity is smaller in the northern hemisphere than in the southern one. Therefore, the parabolic equation model was discarded and the research on calcium waves turned towards more complex models (e.g. mechano-chemical models based on both parabolic and hyperbolic equations).

However, we found that the conclusions of Murray seem to be wrong. Projecting the equation on the whole real line and truncating the coefficients in order to avoid the singularity of the north and south poles (which are of both mathematical and biological nature), we reproduced the conclusions of Gilkey *et al* [25], and as such we find the opposite of Murray's results [49]. Moreover, we also proved that there are two waves, one travelling from the north to the south pole and the other in the opposite sense, and that these travelling waves eventually block each other, giving rise to non-trivial solutions to the associated elliptic equation. This is an example of generalised travelling waves on the real line, whose velocity of propagation is not constant.

On the unit sphere $\mathbb{S}^2 \in \mathbb{R}^3$ we consider the reaction-diffusion equation

$$\partial_t u - \Delta_{\mathbb{S}^2} u = f(u)\,, \tag{0.17}$$

where $\Delta_{\mathbb{S}^2}$ denotes the Laplace-Beltrami operator and $s \mapsto f(s)$ is a bistable nonlinearity, i.e.

- $f(0) = 0$ and $f'(0) < 0$.
- $f(1) = 0$ and $f'(1) < 0$.
- There exists $\alpha \in (0,1)$ such that $f(\alpha) = 0$, $f'(\alpha) > 0$, $f(s) < 0$ for any $s \in (0,\alpha)$ and $f(s) > 0$ for any $s \in (\alpha, 1)$.

If we restrict our analysis to the class of solutions that are independent of the horizontal angle ϕ then (0.17) takes the form

$$\partial_t u - \partial_{\theta\theta} u - \cot\theta\, \partial_\theta u = f(u)\,, \quad (t,\theta) \in \mathbb{R} \times (0,\pi)\,. \tag{0.18}$$

Under the change of variables $x = \cot\theta$ we obtain an equation on the whole real line,

$$\partial_t u - (1+x^2)^2 \partial_{xx} u - x(1+x^2)\partial_x u = f(u)\,, \quad (t,x) \in \mathbb{R}^2\,. \tag{0.19}$$

Notice that the north and south poles ($\pm\infty$, resp.) are mathematical and biological singularities. Mathematical singularities because the parametrisation is not bijective on the poles and the coefficients explode, and biological singularities because the underlying biochemical mechanism that triggers the calcium waves is still unknown. Therefore, we will restrict our analysis to a truncated version of (0.19), i.e.

$$\partial_t u - a(x)\partial_{xx} u - b(x)\partial_x u = f(u)\,, \quad (t,x) \in \mathbb{R}^2, \tag{0.20}$$

where

$$a(x) = \begin{cases} (1+x^2)^2 & \text{if } |x| \le \rho, \\ (1+\rho^2)^2 & \text{if } |x| \ge \rho, \end{cases}$$

$$b(x) = \begin{cases} -\rho(1+\rho^2) & \text{if } x < -\rho, \\ x(1+x^2) & \text{if } |x| \le \rho, \\ \rho(1+\rho^2) & \text{if } x > \rho. \end{cases}$$

For the truncated model (0.20) we have the following four results.

Proposition 0.19 *Let (φ, c_0) be the unique solution of*

$$\varphi'' - c_0\varphi' + f(\varphi) = 0, \quad \lim_{z\to-\infty} \varphi(z) = 0, \quad \lim_{z\to+\infty} \varphi(z) = 1. \tag{0.21}$$

1. *There is a unique (up to translation) travelling wave solution*

$$\varphi_N := \varphi\left(\frac{x + c_N t}{1+\rho^2}\right), \quad c_N = (c_0 + \rho)(1+\rho^2)$$

for the equation on the north pole, i.e.

$$\partial_t u - (1+\rho^2)^2 \partial_{xx} u - \rho(1+\rho^2)\partial_x u = f(u)\,. \tag{0.22}$$

2. *There is a unique (up to translation) travelling wave solution*

$$\varphi_S := \varphi\left(\frac{x + c_S t}{1+\rho^2}\right), \quad c_S = (c_0 - \rho)(1+\rho^2)$$

for the equation on the south pole, i.e.

$$\partial_t u - (1+\rho^2)^2 \partial_{xx} u + \rho(1+\rho^2)\partial_x u = F(u)\,. \tag{0.23}$$

In particular, $c_N > c_S$.

Theorem 0.20 *Suppose that* $f(s)$ *is a bistable Lipschitz nonlinearity and let* $c_N > 0$. *Then there exists* $\beta > 0$ *such that the reaction-diffusion equation (0.20) has a unique global solution* $u(t,x)$ *satisfying*

$$0 < u(t,x) < 1 \quad \forall (t,x) \in \mathbb{R}^2$$

and

$$\left| u(t,x) - \varphi\left(\frac{x + c_N t}{1+\rho^2}\right)\right| = O(e^{\beta t}) \quad \text{when t} \to -\infty \text{, uniformly in } x \in \mathbb{R}.$$

In particular,

$$\lim_{t\to-\infty}\left| u(t,x) - \varphi\left(\frac{x + c_N t}{1+\rho^2}\right)\right| = 0 \quad \text{uniformly in } x \in \mathbb{R}.$$

Furthermore, $t \mapsto u(t,x)$ *is non-decreasing, and if the initial condition* $u_0(x)$ *is non-decreasing then* $x \mapsto u(t,x)$ *is also non-decreasing.*

Theorem 0.21 *Let* $f(s)$ *be a bistable Lipschitz nonlinearity, and suppose that* ρ *is sufficiently large such that* $c_S < 0$. *Then there exists* $\beta > 0$ *such that the reaction-diffusion equation (0.20) has a unique global solution* $v(t,x)$ *satisfying*

$$0 < v(t,x) < 1 \quad \forall (t,x) \in \mathbb{R}^2$$

and

$$\left| u(t,x) - \varphi\left(\frac{x + c_S t}{1+\rho^2}\right)\right| = O(e^{\beta t}) \quad \text{when t} \to -\infty \text{, uniformly in } x \in \mathbb{R}.$$

In particular,

$$\lim_{t\to-\infty}\left| u(t,x) - \varphi\left(\frac{x + c_S t}{1+\rho^2}\right)\right| = 0 \quad \text{uniformly in } x \in \mathbb{R}.$$

Furthermore, $t \mapsto v(t,x)$ *is non-increasing, and if the initial condition* $v_0(x)$ *is non-decreasing then* $x \mapsto v(t,x)$ *is non-decreasing.*

Theorem 0.22 *If we define*

$$u_\infty(x) := \lim_{t\to+\infty} u(t,x), \quad v_\infty(x) := \lim_{t\to+\infty} v(t,x).$$

then $u_\infty(x)$ and $v_\infty(x)$ are steady-state solutions of (0.20) *satisfying*

$$0 < u(t,x) \le u_\infty(x) \le v_\infty(x) \le v(t,x) < 1 \quad \forall (t,x) \in \mathbb{R}^2.$$

Chapter 6. Travelling waves on the sphere

Unlike Chapter 5, where we passed from a homogeneous reaction-diffusion equation on a curved domain to a non-homogeneous reaction-diffusion equation on an Euclidean domain, in Chapter 6 we work directly on the sphere and analyse the properties of generalised travelling waves. We consider here a reaction-diffusion equation with bistable nonlinearity on two domains, a truncated sphere with non-homogeneous Dirichlet boundary conditions and the whole sphere with no boundary conditions.

On the truncated sphere we prove that (i) if the nonlinearity is strong enough there are non-trivial solutions of the elliptic problem, (ii) there is a nontrivial solution of the parabolic problem that is strictly increasing in time, i.e. a generalised travelling wave, and (iii) the travelling wave is blocked by the non-trivial elliptic solution. On the whole sphere we prove that (i) there are non-trivial solutions of the elliptic problem and (ii) depending on the initial conditions, the solution $u(t,x)$ can converge or not to the stable states 0 and 1. In particular, when the solution does not converge to 0 or 1 the wave does not invade the whole sphere, it does not vanish and if it converges then its convergence is non-monotonic.

Our results on both domains are evidence of solutions that do not invade the whole domain. Whether there is invasion or not depends on the geometry of the sphere, the strength of the nonlinearity (measured in terms of λ) and the initial conditions.

Travelling waves on the truncated sphere

Let $\delta \in (0,\pi)$. We define the truncated sphere as

$$\mathcal{M} = \{x = (\theta,\varphi) \in \mathbb{S}^2 : \delta \le \theta \le \pi\,,\ 0 \le \varphi < 2\pi\}\,, \quad \partial\mathcal{M} = \{\theta = \delta\},$$

i.e. $\mathcal{M}$ is the sphere minus a symmetrical neighbourhood of the north pole of vertical angle $\delta > 0$. On $\mathcal{M}$ we will study the nonlinear elliptic equation

$$\begin{cases} -\Delta u = \lambda f(u) & \text{on } \mathcal{M}, \\ u = 1 & \text{on } \partial\mathcal{M}, \end{cases} \tag{0.24}$$

where $\lambda > 0$ and f is bistable, i.e.

- $f(0) = 0$ and $f'(0) < 0$.

- $f(1) = 0$ and $f'(1) < 0$.
- There exists $\alpha \in (0,1)$ such that $f(\alpha) = 0$, $f'(\alpha) > 0$, $f(s) < 0$ for any $s \in (0,\alpha)$ and $f(s) > 0$ for any $s \in (\alpha, 1)$.
- We extend f on $\mathbb{R} \setminus [0,1]$ in a C^1_B fashion. More precisely, we will assume that there exist $\beta_1 < 0$ and $\beta_2 > 1$ such that :
  - $f(s) \equiv 0$ for $s \in \mathbb{R} \setminus (\beta_1, \beta_2)$.
  - $f(s) > 0$ for $s \in (\beta_1, 0]$.
  - $f(s) < 0$ for $s \in (1, \beta_2]$.

Equation (0.24) is the Euler-Lagrange equation of the functional

$$J_\lambda(u) = \frac{1}{2}\int_{\mathcal{M}} |\nabla u|^2\, dx - \lambda \int_{\mathcal{M}} F(u)\, dx\,, \quad F(z) := \int_0^z f(s)\, ds\,, \tag{0.25}$$

defined on

$$\{u \in H^1(\mathcal{M})\ :\ u = 1 \text{ on } \partial\mathcal{M}\}\,.$$

It is worth to notice that $F(0) = 0$,

$$F(1) = \int_0^1 f(s)\, ds$$

and the only constant solution of (0.24) on $[0,1]$ is $u \equiv 1$.

In order to have a problem defined on $H^1_0(\mathcal{M})$ we use the following change of variables:

$$w := 1 - u\,, \quad g(s) := -f(1-s)\,.$$

Under this framework, equation (0.24) becomes

$$\begin{cases} -\Delta w = \lambda g(w) & \text{on } \mathcal{M}, \\ w = 0 & \text{on } \partial\mathcal{M}, \end{cases} \tag{0.26}$$

where g is bistable and share the same properties of f, except that its zero on $(0,1)$ is $1-\alpha$. The associated functional is

$$I_\lambda(w) = \frac{1}{2}\int_{\mathcal{M}} |\nabla w|^2\, dx - \lambda \int_{\mathcal{M}} G(w)\, dx\,, \quad G(z) := \int_0^z g(s)\, ds\,. \tag{0.27}$$

Notice that $G(0) = 0$, $G(1) = -F(1)$ and the only constant solution of (0.26) on $[0,1]$ is $u \equiv 0$.

If the non-linearity is too weak, i.e. if the parameter $\lambda > 0$ is small enough, we prove that the only solution of (0.26) is the trivial solution $w \equiv 0$.

Theorem 0.23 *There exists $\underline{\lambda} > 0$ such that for any $\lambda < \underline{\lambda}$ the only solution of* (0.26) *is $w \equiv 0$.*

Moreover, if the nonlinearity $g(s)$ does not have the good *orientation*, that is if its integral on $[0, 1]$ is non-positive, then $w \equiv 0$ is a global minimum.

Theorem 0.24 *If $G(1) \leq 0$ and $\lambda > 0$ then $w \equiv 0$ is the unique global minimum of* (0.27)*.*

If the non-linearity is strong enough, i.e. if $\lambda > 0$ is sufficiently big, we show that we have non-trivial solutions of (0.26).

Theorem 0.25 *If $G(1) > 0$ there exists $\lambda^\sharp > 0$ such that for any $\lambda > \lambda^\sharp$ we have at least one non-trivial solution of* (0.26)*.*

Theorem 0.25 is proven using variational techniques, but using topological techniques e.g. degree theory we can prove that we have at least two different, non-trivial solutions of the elliptic problem (0.26). Therefore, the non-trivial solutions of (0.26) come in pairs.

Theorem 0.26 *If $G(1) > 0$ then for any $\lambda > \lambda^\flat$ we have a pair of distinct, non-trivial solutions of* (0.26)*.*

Theorem 0.27 *Let $\lambda^\flat$ and $\lambda^\sharp$ be as in Theorems 0.25 and 0.26, respectively. Then $\lambda^\flat = \lambda^\sharp$.*

From Theorems 0.25 - 0.27 it follows that $\lambda^\flat$ is a pitchfork bifurcation point for the elliptic problem (0.26) because, if there exists one non-trivial solution then there is a second, different non-trivial solution. More precisely, choosing

$$\lambda^\flat = \inf\{\lambda > 0 \,:\, \text{(0.26) has a non-trivial solution}\}$$

then for $\lambda < \lambda^\flat$ the only solution is $w \equiv 0$ whilst for $\lambda > \lambda^\flat$ we have two distinct, non-trivial solutions.

Having proven the existence of a non-trivial solution of the elliptic problem (0.26), we can now prove that there is a time-increasing solution of

$$\begin{cases} \partial_t u = \Delta u + \lambda f(u) & \text{in } (0,\infty) \times \mathcal{M}, \\ u = 1 & \text{on } (0,\infty) \times \partial\mathcal{M}, \\ u(0,x) = 0 & \text{for all } x \in \mathcal{M}, \end{cases} \tag{0.28}$$

i.e. a generalised travelling wave, and that this wave is blocked by the non-trivial solution.

Theorem 0.28 *There is a non-trivial solution $u(t,x)$ of* (0.28) *such that $t \mapsto u(t,x)$ is strictly increasing, $0 < u(t,x) \leq u^\star(x)$ for all $t > 0$ and*

$$\lim_{t\to\infty} u(t,x) \leq u^\star(x) \quad \forall x \in \mathcal{M}\,.$$

Travelling waves on the whole sphere

Consider the elliptic nonlinear equation

$$-\Delta u = \lambda f(u) \quad \text{on } \mathbb{S}^N \subset \mathbb{R}^{N+1}. \tag{0.29}$$

where $f \in C^1(\mathbb{R})$ is the same bistable nonlinearity as in the truncated sphere model. As before, we define

$$F(z) := \int_0^z f(s)\,ds\,.$$

The first result is the same as before:

Theorem 0.29 *There exists $\underline{\lambda} > 0$ such that for any $\lambda < \underline{\lambda}$ the only solutions of* (6.18) *are constant.*

Definition 0.5 *Let u be a solution of* (6.18)*. We say that u is* **stable** *if*

$$\int_{\mathbb{S}^N} \left\{ |\nabla w|^2 - \lambda f'(u) w^2 \right\} dx \geq 0 \quad \forall w \in H^1(\mathbb{S}^N)\,. \tag{0.30}$$

Property (6.22) is equivalent to say that the first eigenvalue $\mu_1(u)$ of the operator

$$w \mapsto -\Delta w - \lambda f'(u) w$$

satisfies $\mu_1(u) \geq 0$.

Theorem 0.30 *Let u be a solution of* (0.29)*. If u is stable then it is constant.*

From Theorem 0.30, if u is a non-trivial solution of (6.18) then u is necessarily unstable and

$$\{x \in \mathbb{S}^N \,:\, f'(u(x)) > 0\,\} \neq \emptyset\,.$$

Theorem 0.30 has been proven by Casten and Holland [12] and Matano [46] in the case of an Euclidean convex domain with homogeneous Neumann boundary conditions. As far as we know, Theorem 6.8 is a new result on manifolds.

Theorem 0.31 *There exists $\lambda^\flat > 0$ such that for any $\lambda > \lambda^\flat$ we have at least one non-trivial solution $u^\star(x)$ of* (6.18) *such that $0 < u^\star < 1$.*

We have proved that on the whole sphere $\mathbb{S}^N$ there exists $\lambda_*(= \underline{\lambda})$ such that for any $\lambda \in (0, \lambda_*)$ the only solutions of (6.18) are constant, and that there exists $\lambda^*(= \lambda^\flat)$ such that for any $\lambda \in (\lambda^*, \infty)$ there is a non-trivial solutions of (6.18). We conjecture that $\lambda_* = \lambda^*$ and that this is true for any compact, connected, smooth manifold without boundary.

Conjecture 0.32 *Let $\mathcal{M}$ be a compact, connected, smooth manifold without boundary. Then $\lambda_*(\mathcal{M}) = \lambda^*(\mathcal{M})$, i.e.*

- *There is bifurcation on the elliptic nonlinear eigenvalue problem*

$$-\Delta_{\mathcal{M}} u = \lambda f(u)$$

starting at $(\lambda, u) = (\lambda_*, 0)$*,*

- *for any* $\lambda < \lambda_*$ *the only solutions are trivial (i.e. constant), and*

- *for any* $\lambda > \lambda_*$ *we have non-trivial solutions.*

In the following chapter we prove Conjecture 0.32 when $\mathcal{M} = \mathbb{S}^1$ and for a bifurcation starting at the trivial solution $u \equiv \alpha$. However, the general case of a compact, connected, smooth manifold $\mathcal{M}$ without boundary is an open problem.

We will show that, depending on the initial conditions, the solution $u(t, x)$ can converge or not to 0 or 1. In particular, when the solution does not converge to 0 or 1 we have that (i) this solution cannot invade the whole sphere, (ii) it does not vanish, and (iii) if it converges then its convergence is non-monotonic.

For any $p \in (0, \pi)$ define

$$A(p) := \{x = (\varphi, \theta) \in \mathbb{S}^N \,:\, 0 \le \varphi < 2\pi,\ 0 \le \theta < p\}\,.$$

Let $u(p, t, x)$ be a solution of the problem

$$\begin{cases} \partial_t u = \Delta u + \lambda f(u) & \text{in } (0,\infty) \times \mathbb{S}^N, \\ u(p,0,x) = 0 & \text{for all } x \in \mathbb{S}^N, \end{cases} \tag{0.31}$$

where

$$u_0(p, x) = \begin{cases} 1 & \text{if } x \in A(p), \\ 0 & \text{if } x \in \mathbb{S}^N \setminus A(p). \end{cases} \tag{0.32}$$

Theorem 0.33 *1. If* $p \sim 0$ *then*

$$\lim_{t\to\infty} u(p, t, x) = 0\,.$$

2. If $p \sim \pi$ *then*

$$\lim_{t\to\infty} u(p, t, x) = 1\,.$$

3. There exists $\tilde{p} \in (0, \pi)$ *such that* $u(\tilde{p}, t, x)$ *does not converge to* 0 *or* 1*. If* $u(\tilde{p}, t, x)$ *converges to a (necessarily untable) solution then its convergence is non-monotonic.*

As a final result, we found that the case of a monostable nonlinearity f is much simpler compared to the bistable case. Indeed, not only we always have invasion but also the global solution just depends on time, i.e. it is independent of the space variables.

Let $f : [0,1] \to \mathbb{R}$ be a C^1 function such that $f(0) = f(1) = 0$, $f > 0$ on $(0,1)$ and $f'(0) > 0$. Denote $t \mapsto \xi(t)$ the unique solution of

$$\xi'(t) = f(\xi(t)),\ 0 < \xi(t) < 1 \quad \text{for all } t \in \mathbb{R} \quad \text{and } \xi(0) = \frac{1}{2}.$$

The function ξ is increasing and $\xi(-\infty) = 0$, $\xi(+\infty) = 1$. Let $\mathcal{M}$ be a connected compact smooth manifold without boundary (e.g. $\mathbb{S}^N$) and denote $\Delta_{\mathcal{M}}$ be the Laplace-Beltrami operator on $\mathcal{M}$.

Theorem 0.34 *If u is a solution of*

$$\partial_t u = \Delta_M u + f(u) \quad \text{in } \mathbb{R} \times \mathcal{M}$$

such that $0 \leq u(t,x) \leq 1$ for all $(t,x) \in \mathbb{R} \times \mathcal{M}$, then u depends only on t. More precisely, we have either $u \equiv 0$, $u \equiv 1$ or there exists $T \in \mathbb{R}$ such that $u(t,x) = \xi(t+T)$ for all $(t,x) \in \mathbb{R} \times \mathcal{M}$.

Chapter 7. Bifurcation and multiple periodic solutions on the sphere

In Chapter 6 we saw how the analysis of non-trivial steady-state solutions, in particular via topological degree, is determinant of the properties of the generalised travelling waves. In this chapter we will study in more detail the solutions of the elliptic nonlinear eigenvalue problem

$$-\Delta_{\mathbb{S}^N} u = \lambda f(u) \quad \text{on } \mathbb{S}^N. \tag{0.33}$$

We will show that the problem admits multiple non-trivial solutions, whose number is increasing in the parameter $\lambda > 0$, and each time we cross an eigenvalue μ_k there appears a new non-trivial solution. If $\lambda \in (\mu_k, \mu_{k+1})$, we prove the existence of $2k$ non-trivial solutions in $\mathbb{S}^1$ and k non-trivial solutions on $\mathbb{S}^N$, the latter depending only on the vertical angle, i.e. invariant under horizontal rotations. We also prove Conjecture 6.12 for the 1D case (i.e. $\mathbb{S}^1$), but the N-dimensional case, $N \geq 2$ it is still an open problem.

As in Chapter 6, $f(s)$ is a globally-bounded bistable nonlinearity with unstable state $\alpha \in (0,1)$. However, f is no longer C^1 because here we extend f to $\mathbb{R} \setminus [0,1]$ as zero. As before we define

$$F(z) := \int_0^z f(s)\,.$$

Case $N = 1$. Solutions on the circle

For the case $N = 1$, (0.33) reduces to the nonlinear ODE

$$\begin{cases} -u'' &= \lambda f(u), \\ u(0) &= \xi, \\ u'(0) &= 0. \end{cases} \tag{0.34}$$

Theorem 0.35 *There exist periodic solutions of* (0.34) *if and only if* $\xi \in (0,\alpha) \cup (\alpha,\beta)$, *where* $\beta := F^{-1}(0)$. *Moreover, the periodic solutions come in pairs: if* $u_1(\theta)$ *is a* T*-periodic solution then there exist another* T*-periodic solution* $u_2(\theta)$ *such that* $u_1 \neq u_2$ *and*

$$\|u_1\|_{C^0(0,T)} = \|u_2\|_{C^0(0,T)}\,.$$

Finally, there exists $\lambda_0 > 0$ *such that* (0.34) *admits* 2π*-periodic solutions if and only if* $\lambda > \lambda_0$.

We can now return to Conjecture 6.12 and prove it for $\mathbb{S}^1$ and for the trivial solution $u \equiv \alpha$.

Theorem 0.36 *Let* $\mathcal{M}$ *be a compact, connected, smooth manifold without boundary and consider the problem*

$$-\Delta_{\mathcal{M}} u = \lambda f(u) \quad \text{on } \mathcal{M}. \tag{0.35}$$

Define

$$\begin{aligned} \lambda_*(\mathcal{M}) &:= \sup\{\lambda > 0 \,:\, \text{the only solutions of (7.7) are constant}\}\,, \\ \lambda^*(\mathcal{M}) &:= \inf\{\lambda > 0 \,:\, \text{there are non-trivial solutions of (7.7)}\}\,. \end{aligned}$$

If $\mathcal{M} = \mathbb{S}^1$ *then* $\lambda_*(\mathbb{S}^1) = \lambda^*(\mathbb{S}^1)$ *and there is a bifurcation branch starting at* (λ_*, α).

We complete the bifurcation analysis with the following theorem.

Theorem 0.37 *Let* $\{\mu_k\}_{k\in\mathbb{N}}$ *be the eigenvalues of* (0.34), *i.e.*

$$\mu_k = \frac{k^2}{f'(\alpha)}\,.$$

For any $\lambda \in (\mu_k, \mu_{k+1})$ *we have at least* $2k$ *different non-trivial,* 2π*-periodic solutions of* (0.34).

Case $N \geq 2$. Axis-symmetric solutions on the sphere

We parametrise $\mathbb{S}^N$ as (θ,φ), where $\theta \in (0,\pi)$ is the vertical angle and $\varphi \in \mathbb{S}^{N-1}$ are the horizontal angles. If we search for solutions of (0.33) depending only on θ andindependent of φ, (0.33) reduces to the nonlinear ODE

$$-u'' - (N-1)\frac{\cos\theta}{\sin\theta}u' = \lambda f(u), \tag{0.36}$$

with initial conditions

$$\begin{cases} u(0) = \xi, \\ u'(0) = 0. \end{cases}$$

By studying the properties of the solutions of (0.36) we can deduce the existence of multiple axis-symmetric solutions of (0.33).

Theorem 0.38 *Let* $\{\mu_k\}_{k\in\mathbb{N}}$ *be the eigenvalues of* (0.33), *i.e.*

$$\mu_k = \frac{k(k+N-1)}{f'(\alpha)}\,.$$

For any $\lambda \in (\mu_k, \mu_{k+1})$ *there are at least* k *different non-trivial solutions of the ODE* (7.13), *i.e.* k *non-trivial solutions of the nonlinear eigenvalue problem* (7.11) *that are invariant under horizontal rotations* $\varphi \in \mathbb{S}^{N-1}$.

Part I

Reaction-diffusion systems and modelling

Chapter 1

Calcium ions in dendritic spines

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As it was pointed out by D. Holcman and Z. Schuss in *Modeling calcium dynamics in dendritic spines* (SIAM J. Appl. Math. 2005, Vol. 65, No. 3, pp. 1006-1026), the concentration of calcium ions inside the dendritic spines plays a crucial role in the synaptic plasticity, and in consequence in cognitive processes like learning and memory. The goal of this paper is to study the reaction-diffusion model of calcium dynamics in dendritic spines proposed by Holcman and Schuss. We start from the construction of the model of Holcman and Schuss and propose a modification in order to admit more realistic biological assumptions supported by experimental evidence but still mathematically solvable. We show that the dynamics of the calcium ions and the proteins interacting with them follows a system of coupled nonlinear reaction-diffusion equations, which is degenerate elliptic if the proteins are considered fixed, and strongly elliptic if they diffuse with a diffusion coefficient $d > 0$. In the first case we prove a priori estimates, global existence, global uniqueness and positivity of solutions, whereas in the second case we prove not only the same features but also that the problem is well-posed. Moreover, we show that there is a "continuous" link between the two problems in the sense that the solutions of the problem with $d > 0$ converge to the solutions of the problem with $d = 0$.

1.1 Introduction

1.1.1 Dendritic spines

Dendritic spines are tiny bud-like extensions or protrusions on the dendrites with small bulbous heads and narrow necks. They have lengths around 1 μm and volumes around 0.2 $\mu\mathrm{m}^2$. They are ubiquitous because, on the one hand, 90% of excitatory synapses occur in dendritic spines, and on the other hand there are more than 10^{13} dendritic spines inside the brain. We also find actin microfilaments, endoplasmic reticulum and polyribosomes inside the head, but other structures like mitochondria and microtubules appear to be excluded (see Nimchinsky *et al* [50]).

Synapses take place on the surface of the spine head where several specialized microstructures can be found, e.g. neuro-receptors and ion channels. Inside the head of the spine there are several molecules related to the intricate biochemical machinery that codifies the information from the pre-synaptic neuron, and eventually, emits a electric potential that flows through the post-synaptic neuron and transmits the excitatory or inhibitory information to another neuron. This means that the former post-synaptic neuron have become pre-synaptic, and the process repeats itself until the signal reaches the target neuron.

As we can see, dendritic spines are at the very basis of the information exchange inside the neural system.

1.1.2 The role of Ca^{2+} in spine twitching and synaptic plasticity

One of the main questions addressed by Holcman and his colaborators in [33] and [34] was to understand the spine twitching and the synaptic plasticity in terms of the binding reactions between the Ca^{2+} ions and some proteins inside the spine. They attributed the twitching motion of the spine to the contraction of actin-myosin AM proteins in the following way. They considered that once an AM protein has four Ca^{2+} ions bound there occurs a local contraction of the AM, and that all local contractions at a given time produces a global contraction of the spine, which has two consequences: first, it is responsible for the rapid twitching motion of the spine, and second, it produces a hydrodynamical movement of the cytoplasmic fluid in the direction of the dendrite. This motion is thus responsible of the transport of the ions, not only Ca^{2+} but also Na^{+}, into the neuron, which constitutes the electric potential we mentioned in Section 1.1.1.

Holcman *et al* [33] also mention that a protein with four Ca^{2+} ions bound contracts at a fixed rate until one Ca^{2+} ion unbinds. The contraction due to Ca^{2+} binding also appears in the works of Farah *et al* [19], Klee *et al* [36] and Shiftman *et al* [59], but in all three cases the proteins suffer a conformational change each time a Ca^{2+} ion binds, and not only when they have four Ca^{2+} ions. We will consider this experimental evidence for the new model we will propose.

The synaptic plasticity is defined as changes in the synaptic strength, i.e. in the intensity of the signal transmission between two neurons. These changes can be short-term if they occur in the range of milliseconds or minutes, or long-term if their duration is measured in hours, days, weeks or longer. The long-lasting changes in synapses are related to cognitive processes like learning and memory. These changes are divided in two: Long-Term Potentiation (LTP), if there is an increase in the synaptic strength, or Long-Term Depression (LTD), if there is a decrease in the synaptic strength. The major determinant of whether LTP or LTD appears seems to be the amount of Ca^{2+} in the post-synaptic cell: small rises in Ca^{2+} lead to depression, whereas large increases trigger potentiation (see Purves *et al* [54], Chapter 24, pp. 575-610).

As we can see, Ca^{2+} ions inside the dendritic spine play a crucial role in the twitching motion and synaptic plasticity, and therefore in cognitive processes like learning and memory.

1.1.3 The original model

The mathematical modeling of calcium dynamics related to neuroscience is a vast topic. Since we will only mention the nonlinear reaction-diffusion model proposed by Holcman and Schuss [34], we recommend [62] for discussions of the different models for calcium dynamics in neurons.

Following Holcman and Schuss [34] we will consider that the Ca^{2+} ions have a dynamics governed by the Langevin equation

$$\dot{\boldsymbol{x}}(t) = \boldsymbol{V}(\boldsymbol{x}, t) + \sqrt{2D}\dot{\boldsymbol{w}}(t)\,. \tag{1.1}$$

where $\boldsymbol{w}(t)$ is a Brownian motion that represents the thermal fluctuations of the medium, $\boldsymbol{V}(\boldsymbol{x}, t)$ is the cytoplasmic flow field and D is the diffusion coefficient

$$D = \frac{k_B T}{m\mu}$$

with k_B the Boltzmann constant, T the temperature, m the mass and μ the dynamic viscosity. The Langevin equation (1.1) has a solution $\boldsymbol{x}(t)$ if $\boldsymbol{V}(\boldsymbol{x}, t)$ is Lipschitz and satisfy the growth condition (see Øksendal [51], Theorem 5.2.1, p. 68)

$$|\boldsymbol{V}(\boldsymbol{x}, t)| \leq C\left(1 + |\boldsymbol{x}|\right)\,.$$

In order to pass from this microscopic description to a macroscopic level we will not be concerned on the dynamics of each Ca^{2+} ion $\dot{\boldsymbol{x}}(t)$ but rather on the concentration of the Ca^{2+} ions, which we will denote $M(\boldsymbol{x}, t)$. When normalized, $M(\boldsymbol{x}, t)$ can be seen as the probability density of the Ca^{2+} ions of the diffusion (1.1), and in consequence it solves solves the Fokker-Planck equation

$$\partial_t M(\boldsymbol{x}, t) = \nabla \cdot \left[D\nabla M(\boldsymbol{x}, t) - \boldsymbol{V}(\boldsymbol{x}, t)M(\boldsymbol{x}, t)\right] \tag{1.2}$$

associated to the diffusion (1.1).

Holcman and Schuss [34] also suppose, as we will do, that there are no obstacles inside the dendritic spine, like organelles and macromolecules. However, it is important to remark that this is only a simplification of the model and not a biological fact because dendritic spines do have organelles, as we mentioned in Section 1.1.1.

In the model of Holcman and Schuss [34] there is a reaction term that takes into account the binding and unbinding processes (i.e. the association and dissociation processes) between the calcium ions Ca^{2+} and some fixed proteins inside the spine like calmodulin CaM, actin-myosin AM and calcineurin. These proteins can carry up to four Ca^{2+} ions. Since we want to keep track of the number of free and bound ions at any time and position, we need to classify the proteins in terms of the number of bound ions.

Define $S^j = S^j(\boldsymbol{x}, t)$ for $j = 0, 1, 2, 3, 4$, as the number of proteins containing j bound ions (note that we are not making any distinction between CaM, AM and calcineurin). A protein

S^j can gain or lose one ion at a time with a constant reaction rate k_1 or k_{-1}, respectively. Therefore, the chemical description of S^j is

$$S^{j-1} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S^j \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} S^{j+1} \tag{1.3}$$

The Law of Mass Action states that the rate of a reaction is proportional to the product of the concentrations of the reactants. If we take into account that S^j has j occupied binding sites and $4-j$ free binding sites, and on each one the four reactions given in (1.3) we use the Law of Mass Action, it follows that the dynamics of S^j is given by

$$\frac{dS^j}{dt} = k_1 M \left[(5-j)S^{j-1} - (4-j)S^j \right] - k_{-1}\left[jS^j - (j+1)S^{j+1} \right]. \tag{1.4}$$

Now let Ω be the interior of the dendrite, which we will suppose to be a bounded open set in $\mathbb{R}^2$ or $\mathbb{R}^3$ with a piecewise smooth Lipschitz boundary. Define $\Gamma := \partial\Omega$ and consider a partition $\Gamma = \Gamma_a \cup \Gamma_r$, with Γ_a the "absorbing" part of the boundary and Γ_r the "reflecting" part. On Γ_a the ions $M(\boldsymbol{x}, t)$ leave the spine and they never return, which is expressed mathematically as a zero boundary condition. Γ_a has two components, Ca^{2+} pumps at the spine head and the bottom of the spine neck (where the ions enter the dendrite). On Γ_r the ions $M(\boldsymbol{x}, t)$ cannot leave the spine, i.e. if they hit the boundary they rebound, which is modelled as no flux boundary conditions.

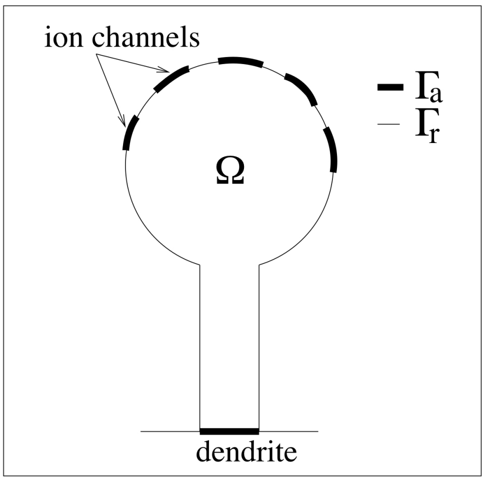

Figure 1.1: Dendritic spine. We denote Ω the interior of the spine, Γ its surface, Γ_a the absorbing boundary and Γ_r the reflecting boundary.

In the light of equations (1.2) and (1.3), the reaction-diffusion model of Holcman and Schuss

[34] is

$$\left\{\begin{array}{rcl} \partial_t M &=& \nabla\cdot[D\nabla M - \boldsymbol{V}M] - k_1 M\left[\sum_{j=0}^4 (4-j)S^j\right] + k_{-1}\left[\sum_{j=0}^4 jS^j\right] \,, \\ \partial_t S^j &=& k_1 M\big[\,(5-j)S^{j-1} - (4-j)S^j\,\big] - k_{-1}\big[\,jS^j - (j+1)S^{j+1}\,\big]\,, \\ \mathbf{V} &=& \nabla\phi\,, \qquad \Delta\phi = 0\,, \end{array}\right. \tag{1.5}$$

where, by convention $S^{-1}(\boldsymbol{x},t) = S^5(\boldsymbol{x},t) = 0$. The third equation in (1.5) implies that we suppose the cytoplasm flux $\mathbf{V}$ is incompressible and it is the gradient of a potential function ϕ.

The initial conditions for the system (1.5) are

$$M(\boldsymbol{x},0) = m_0(\boldsymbol{x}) \geq 0\,; \quad S^0(\boldsymbol{x},0) = \frac{1}{4}A(\boldsymbol{x}) \geq 0\,, \quad S^j(\boldsymbol{x},0) = 0 \quad \text{for } j = 1,2,3,4, \tag{1.6}$$

whereas the boundary conditions are

$$\left\{\begin{array}{rcll} M(\sigma,t) &=& 0 & \text{on } \Gamma_a\times[0,T]\,, \\ (D\nabla M - \boldsymbol{V}M)\cdot\boldsymbol{n}(\sigma,t) &=& 0 & \text{on } \Gamma_r\times[0,T]\,, \\ \nabla\phi\cdot\boldsymbol{n}(\sigma,t) &=& a(\sigma)\lambda(t) & \text{on } \Gamma\times[0,T], \end{array}\right. \tag{1.7}$$

where $\boldsymbol{n}(\sigma,t)$ is the outer normal of Γ, $a(\sigma)$ is given, and $\lambda(t)$ is related to the total number proteins with all four Ca^{2+} ions bound, i.e. on S^4.

1.2 The modified model and main results

1.2.1 New variables

From the system (1.5) we observe that the important variables for the description of the dynamics for $M(\boldsymbol{x},t)$ are not the proteins $S^j(\boldsymbol{x},t)$ but the quantities

$$U(\boldsymbol{x},t) = \sum_{j=0}^{4}(4-j)S^j(\boldsymbol{x},t)\,, \qquad W(\boldsymbol{x},t) = \sum_{j=0}^{4} jS^j(\boldsymbol{x},t)\,. \tag{1.8}$$

Note that $U(\boldsymbol{x},t)$ is the total number of free binding sites about $\boldsymbol{x}$ at time t, and $W(\boldsymbol{x},t)$ is the total number of occupied binding sites. This change of variables not only simplifies the notation but also reduces the system (1.5) to a new system on the variables (M,U,W). Indeed, if we develop the equations $S^j(\boldsymbol{x},t)$ in the system (1.5) it follows that

$$\begin{array}{rcl} \partial_t S^0 &=& k_1 M\big[\,0 - 4S^0\,\big] - k_{-1}\big[\,0 - 1S^1\,\big]\,, \\ \partial_t S^1 &=& k_1 M\big[\,4S^0 - 3S^1\,\big] - k_{-1}\big[1S^1 - 2S^2\,\big]\,, \\ \partial_t S^2 &=& k_1 M\big[\,3S^1 - 2S^2\,\big] - k_{-1}\big[\,2S^2 - 3S^3\,\big]\,, \\ \partial_t S^3 &=& k_1 M\big[\,2S^2 - 1S^1\,\big] - k_{-1}\big[\,3S^3 - 4S^4\,\big]\,, \\ \partial_t S^4 &=& k_1 M\big[\,1S^1 - 0\,\big] - k_{-1}\big[\,4S^4 - 0\,\big]\,. \end{array}$$

Multiplying the j-th equation by $(4-j)$ and adding them up we obtain

$$\partial_t U = -k_1 M U + k_{-1} W\,. \tag{1.9}$$

Analogously, multiplying by j and adding up we get

$$\partial_t W = k_1 M U - k_{-1} W\,. \tag{1.10}$$

In the variables U and W the equation for $M(\boldsymbol{x},t)$ takes the form

$$\partial_t M = \nabla\cdot[D\nabla M - \boldsymbol{V} M] - k_1 M U + k_{-1} W\,. \tag{1.11}$$

1.2.2 Modeling the twitching motion of the spine

In Section 1.1.2 we mentioned that each time a Ca^{2+} ion binds to a protein this latter suffers a contraction, and that the addition of all these local contractions have two effects: the twitching of the spine and changes in the cytoplasmic flow field $\boldsymbol{V}(\boldsymbol{x},t)$. In order to take into account both effects we will assume that the spine movement depends on the cytoplasmic velocity at the spine surface Γ, and that this value depends on the total number of Ca^{2+} ions that are bound to the proteins. More precisely, if we define

$$\lambda(t) := \int_\Omega W(\boldsymbol{x},t)\,d\Omega\,, \tag{1.12}$$

which is the total number of occupied binding sites at time t, then our assumption is that the spine surface Γ moves with velocity $\boldsymbol{V}\cdot\boldsymbol{n}$ proportional to $\lambda(t)$.

It is worth to mention that Holcman and Schuss [34] supposed that the contraction of a protein takes place only if it has four Ca^{2+} ions bound, which implies that

$$\lambda(t) = \int_\Omega S^4(\boldsymbol{x},t)\,d\Omega\,. \tag{1.13}$$

However, as we have already mentioned Section 1.1.2, assuming (1.12) instead of (1.13) is biologically more accurate.

Following Holcman and Schuss [34] we will also suppose that there exists a potential $\phi(\boldsymbol{x},t)$ such that $\boldsymbol{V} = \nabla\phi$, whose dynamics is given by the equation

$$\left\{\begin{array}{rcll} \Delta\phi(\boldsymbol{x},t) &=& 0 & \text{on } \Omega\times[0,T], \\ \nabla\phi\cdot\boldsymbol{n}(\sigma,t) &=& a(\sigma)\lambda(t) & \text{on } \Gamma\times[0,T]. \end{array}\right. \tag{1.14}$$

where $a(\sigma)\in L^\infty(\Gamma)$ is given, together with the orthogonality condition

$$\int_\Omega \phi(\boldsymbol{x},t)\,d\Omega = 0 \tag{1.15}$$

and the compatibility condition

$$\int_\Gamma a(\sigma,t)\,dS = 0\,. \tag{1.16}$$

For a fixed $t \geq 0$ the problem (1.14) is the Laplace equation with Neumann boundary conditions; therefore the solution ϕ exists, and is unique due to the orthogonality condition (1.15). Moreover, using integration by parts and Poincaré's inequality it can be shown that there is a constant $C > 0$ such that

$$\|\boldsymbol{V}(t)\|_{[L^2(\Omega)]^n} \leq C\|W(t)\| \qquad \text{for all } t \in [0,T], \tag{1.17}$$

where $\|\cdot\|$ denotes the norm in $L^2(\Omega)$.

1.2.3 The modified model

Observe that (1.9) and (1.10) imply that for all times

$$U(\boldsymbol{x},t) + W(\boldsymbol{x},t) = 4\sum_{j=0}^{4} S^j(\boldsymbol{x},0) = A(\boldsymbol{x})\,,$$

so we can reduce further the system (1.9)-(1.11) to

$$\left\{\begin{array}{rcl} \partial_t M &=& \nabla\cdot[D\nabla M - \boldsymbol{V}M] - k_1 MU + k_{-1}[A-U]\,, \\ \partial_t U &=& -k_1 MU + k_{-1}[A-U]\,, \\ \mathbf{V} &=& \nabla\phi\,, \qquad \Delta\phi = 0\,. \end{array}\right. \tag{1.18}$$

with initial conditions

$$\left\{\begin{array}{rcl} M(\boldsymbol{x},0) &=& m_0(\boldsymbol{x})\,, \\ U(\boldsymbol{x},0) &=& A(\boldsymbol{x})\,, \end{array}\right. \tag{1.19}$$

and boundary conditions

$$\left\{\begin{array}{rcll} M(\sigma,t) &=& 0 & \text{on } \Gamma_a \times [0,T]\,, \\ (D\nabla M - \boldsymbol{V}M)\cdot\boldsymbol{n}(\sigma,t) &=& 0 & \text{on } \Gamma_r \times [0,T]\,, \\ \nabla\phi\cdot\boldsymbol{n}(\sigma,t) &=& a(\sigma)\lambda(t) & \text{on } \Gamma \times [0,T]. \end{array}\right. \tag{1.20}$$

There is an important issue we want to remark. So far we have considered that the proteins were fixed in the cytoplasm, but this is not true in the real biological situation. In order to take into account the motion of the proteins we can suppose that they diffuse with a constant diffusion coefficient $d > 0$ and that they cannot leave the spine. Under these assumptions, the model (1.18)-(1.20) with diffusive proteins takes the form

$$\left\{\begin{array}{rcl} \partial_t M &=& \nabla\cdot[D\nabla M - \boldsymbol{V}M] - k_1 MU + k_{-1}W\,, \\ \partial_t U &=& d\Delta U - k_1 MU + k_{-1}W\,, \\ \partial_t W &=& d\Delta W + k_1 MU - k_{-1}W\,, \\ \mathbf{V} &=& \nabla\phi\,, \qquad \Delta\phi = 0\,. \end{array}\right. \tag{1.21}$$

with initial conditions

$$\left\{\begin{array}{rcl} M(\boldsymbol{x},0) &=& m_0(\boldsymbol{x})\,, \\ U(\boldsymbol{x},0) &=& A(\boldsymbol{x})\,, \\ W(\boldsymbol{x},0) &=& 0\,, \end{array}\right. \tag{1.22}$$

and boundary conditions

$$\begin{cases} M(\sigma,t) &= 0 & \text{on } \Gamma_a \times [0,T]\,, \\ (D\nabla M - \boldsymbol{V} M)\cdot \boldsymbol{n}(\sigma,t) &= 0 & \text{on } \Gamma_r \times [0,T]\,, \\ \nabla U \cdot \boldsymbol{n}(\sigma,t) &= 0 & \text{on } \Gamma \times [0,T], \\ \nabla W \cdot \boldsymbol{n}(\sigma,t) &= 0 & \text{on } \Gamma \times [0,T], \\ \nabla \phi \cdot \boldsymbol{n}(\sigma,t) &= a(\sigma)\lambda(t) & \text{on } \Gamma \times [0,T]. \end{cases} \tag{1.23}$$

Note that d should be much smaller than D because the proteins we are considering are around 10^6 times bigger than the calcium ions.

1.2.4 Main results

From now on we will always assume the following hypotheses:

$$\begin{cases} m_0(\boldsymbol{x}) \in L^\infty(\Omega)\,, \quad m_0(\boldsymbol{x}) \geq 0 \quad \text{a.e. in } \Omega, \\ A(\boldsymbol{x}) \in L^\infty(\Omega)\,, \quad A(\boldsymbol{x}) \geq 0 \quad \text{a.e. in } \Omega, \\ a(\sigma) \in L^\infty(\Gamma)\,, \quad \int_\Gamma a(\sigma) dS = 0\,. \end{cases} \tag{1.24}$$

For the model with fixed proteins (1.18)-(1.20) we prove global existence, global uniqueness, boundedness and positivity of solutions.

Theorem 1.1 *For any $T > 0$ the reaction-diffusion system (1.18)-(1.20) has global unique weak solutions $M(\boldsymbol{x},t)$, $U(\boldsymbol{x},t)$ and $\boldsymbol{V}(\boldsymbol{x},t)$ on $\Omega \times (0,T)$ with the following properties:*

1. $M \in L^\infty(\Omega \times (0,T))$ *and* $0 \leq M(\boldsymbol{x},t) \leq \|m_0\|_\infty + k_{-1}t\|A\|_\infty$ *a.e. in* $\Omega \times (0,T)$.
2. $M \in L^\infty\left(0,T;H^1(\Omega)\right)$ *and*
$$\|M(t)\|^2 + D\int_0^t e^{C(t-s)}\|\nabla M(s)\|^2\,ds \leq e^{Ct}\left[\|m_0\|^2 + k_{-1}^2 t\|A\|^2\right]\,.$$
3. $U \in L^\infty(\Omega \times (0,T))$ *and* $0 \leq U(\boldsymbol{x},t) \leq A(\boldsymbol{x})$ *a.e. in* $\Omega \times (0,T)$.
4. $\boldsymbol{V} \in L^\infty\left(0,T;\left[L^2(\Omega)\right]^n\right)$ *and* $\|\boldsymbol{V}\|_{L^\infty(0,T;[L^2(\Omega)]^n)} \leq C\|a\|_\infty\|A\|_\infty$.

For the model with diffusive proteins (1.18)-(1.20) the situation is even nicer because we have not only the same results of Theorem 1.1 but in addition the problem is well-posed.

Theorem 1.2 *For any $T > 0$ the reaction-diffusion system (1.21)-(1.23) is well-posed, i.e. it has global unique weak solutions $M(\boldsymbol{x},t)$, $U(\boldsymbol{x},t)$, $W(\boldsymbol{x},t)$ and $\boldsymbol{V}(\boldsymbol{x},t)$ on $\Omega \times (0,T)$ depending continuously on the initial data. Moreover, we have the following properties:*

1. $M \in L^\infty(\Omega \times (0,T))$ *and* $0 \leq M(\boldsymbol{x},t) \leq \|m_0\|_\infty + k_{-1}t\|A\|_\infty$ *a.e. in* $\Omega \times (0,T)$.
2. $M \in L^\infty\left(0,T;H^1(\Omega)\right)$ *and*
$$\|M(t)\|^2 + D\int_0^t e^{C(t-s)}\|\nabla M(s)\|^2\,ds \leq e^{Ct}\left[\|m_0\|^2 + k_{-1}^2 t\|A\|^2\right]\,.$$

3. *$U, W \in L^\infty(\Omega \times (0,T))$, they are non-negative and $0 \le U(\boldsymbol{x},t) + W(\boldsymbol{x},t) \le A(\boldsymbol{x})$ a.e. in $\Omega \times (0,T)$.*

4. *$U, W \in L^\infty\left(0,T; H^1(\Omega)\right)$ and*

$$\|U(t)\|^2 + \|W(t)\|^2 + 2d\int_0^t e^{\int_s^t c(r)dr}\left(\|\nabla U(s)\|^2 + \|\nabla W(s)\|^2\right) ds \le e^{\int_0^t c(s)ds}\|A\|^2,$$

where $c(t) = 2[k_{-1} + k_1\alpha(t)]$ and $\alpha(t) = \|m_0\|_\infty + k_{-1}t\|A\|_\infty$.

5. *$\boldsymbol{V} \in L^\infty\left(0,T; \left[L^2(\Omega)\right]^n\right)$ and $\|\boldsymbol{V}\|_{L^\infty(0,T;[L^2(\Omega)]^n)} \le C\|a\|_\infty\|A\|_\infty$*

There is a link between the model with fixed proteins (1.18)-(1.20) and the model with diffusive proteins (1.21)-(1.23). Indeed, we have the following "continuity" result.

Theorem 1.3 *If $d \to 0$ then the sequence $(M^d, U^d, W^d, \mathbf{V}^d)$ of solutions of (1.21)-(1.23) converges to the solution $(M, U, W, \mathbf{V})$ of (1.18)-(1.20) in the following senses:*

1. *M^d, U^d and W^d converge weakly in $L^2\left(0,T; L^2(\Omega)\right)$ to M, U and W, respectively.*

2. *$\mathbf{V}^d$ converges to $\mathbf{V}$ weakly in $L^2\left(0,T; \left[L^2(\Omega)\right]^n\right)$.*

3. *M^d converges strongly in $L^2\left(0,T; L^2(\Omega)\right)$ to M.*

4. *U^d and W^d converge weakly-$\star$ in $L^\infty(\Omega \times (0,T))$ to U and W, respectively.*

5. *In the limit $d = 0$ we have $U(\boldsymbol{x},t) + W(\boldsymbol{x},t) = A(\boldsymbol{x})$ a.s. in $\Omega \times (0,T)$.*

Finally, the solutions of both systems (1.18)-(1.20) and (1.21)-(1.23) are globally defined in time. More precisely, we have the following result.[1]

Theorem 1.4 *Let M, U, W and $\mathbf{V}$ be solutions of either (1.18)-(1.20) or (1.21)-(1.23). Then:*

1. *$M, U, W \in L^\infty\left(0,\infty; L^1(\Omega)\right)$.*

2. *$\boldsymbol{V} \in L^\infty\left(0,\infty; \left[L^2(\Omega)\right]^n\right)$.*

[1] The author would like to thank Prof. Jeff Morgan (University of Houston) for his remarks on the global definition of the solutions.

1.3 Proof of Theorem 1.1

1.3.1 A priori estimates

Lemma 1.1 *If $M(\boldsymbol{x},t)$ is a solution of (1.18)-(1.20) such that $M(\boldsymbol{x},t) \geq 0$ a.e. in $\Omega \times (0,T)$ then:*

1. $0 \leq U(\boldsymbol{x},t) \leq A(\boldsymbol{x})$ *a.e. In particular,* $U(\boldsymbol{x},t) \in L^\infty(\Omega \times (0,T))$.
2. $M(\boldsymbol{x},t) \in L^\infty(\Omega \times (0,T))$ *and* $M(\boldsymbol{x},t) \leq \alpha(t) := \|m_0\|_\infty + k_{-1}t\|A\|_\infty$ *a.e.*
3. *There exists a positive constant* $C = C(D, \|\boldsymbol{V}\cdot\boldsymbol{n}\|_\infty, \Omega)$ *such that*

$$\|M(t)\|^2 + D\int_0^t e^{C(t-s)}\|\nabla M(s)\|^2\,ds \leq e^{Ct}\left[\|m_0\|^2 + k_{-1}^2 t\|A\|^2\right] .$$

Proof:

1. Using the equations (1.18)-(1.20) we have

$$\begin{aligned} U(\boldsymbol{x},t) &= A(\boldsymbol{x})\exp\left\{-\int_0^t [k_1M(\boldsymbol{x},s)+k_{-1}]ds\right\} \\ &+ k_{-1}A(\boldsymbol{x})\int_0^t \exp\left\{-\int_s^t [k_1M(\boldsymbol{x},r)+k_{-1}]dr\right\}ds\,. \end{aligned}$$

   Therefore $U(\boldsymbol{x},t) \geq 0$ a.e., and using $M(\boldsymbol{x},t) \geq 0$ a.e. it follows that $U(\boldsymbol{x},t) \leq A(\boldsymbol{x})$ a.e.

2. Let $\alpha(t)$ be a smooth function and define $Z(\boldsymbol{x},t) := M(\boldsymbol{x},t) - \alpha(t)$. Then the equation for $Z(\boldsymbol{x},t)$ is

$$\begin{aligned} \partial_t Z - \nabla\cdot(D\nabla Z - \boldsymbol{V}Z) + k_1 ZU &= -\alpha'(t) - k_1\alpha(t)U + k_{-1}(A-U)\,, \\ Z(\boldsymbol{x},0) &= m_0(\boldsymbol{x}) - \alpha(0)\,, \\ Z(\sigma,t) &= -\alpha(t) \qquad \text{on } \Gamma_a\times[0,T]\,, \\ (D\nabla Z - \boldsymbol{V}Z)\cdot\boldsymbol{n}(\sigma,t) &= 0 \qquad \text{on } \Gamma_r\times[0,T]\,, \end{aligned}$$

   Choosing $\alpha(t) := \|m_0\|_\infty + k_{-1}t\|A\|_\infty$ it follows that

$$\begin{aligned} \partial_t Z - \nabla\cdot(D\nabla Z - \boldsymbol{V}Z) + k_1 ZU &\leq 0\,, \\ Z(\boldsymbol{x},0) &\leq 0\,, \\ Z(\sigma,t) &\leq 0 \qquad \text{on } \Gamma_a\times[0,T]\,, \\ (D\nabla Z - \boldsymbol{V}Z)\cdot\boldsymbol{n}(\sigma,t) &= 0 \qquad \text{on } \Gamma_r\times[0,T]\,. \end{aligned}$$

   Therefore, the Maximum Principle implies that $Z(\boldsymbol{x},t) \leq 0$ a.e.

3. Multiply (1.18)-(1.20) by M, integrate over Ω and use integration by parts to get

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}M^2 + D\|\nabla M\|^2 &= \frac{1}{2}\int_\Gamma \boldsymbol{V}\cdot\boldsymbol{n}M^2\,dS - k_1\int_\Omega UM^2\,d\Omega \\ &+ k_{-1}\int_\Omega [A-U]M\,d\Omega\,.\end{aligned}$$

For the first integral, notice that $\boldsymbol{V}\cdot\boldsymbol{n}\in L^\infty(\Gamma\times[0,T])$. Therefore, using trace estimates we obtain that for any $\varepsilon>0$ there exists a constant $C_1 = C_1(\varepsilon, \|\boldsymbol{V}\cdot\boldsymbol{n}\|_\infty, \Omega)$ such that

$$\frac{1}{2}\left|\int_\Gamma \boldsymbol{V}\cdot\boldsymbol{n}M^2\,dS\right| \le \varepsilon\int_\Omega |\nabla M|^2\,d\Omega + \frac{C_1}{2}\int_\Omega |M|^2\,d\Omega\,.$$

For the second and third integrals, observe that $U\ge 0$ since $M\ge 0$, and in consequence

$$k_{-1}\int_\Omega [A-U]M\,d\Omega \le \frac{k_{-1}^2}{2}\int_\Omega A^2\,d\Omega + \frac{1}{2}\int_\Omega M^2\,d\Omega\,.$$

Choosing $C := C_1 + 1$ and $\varepsilon = D/2$ we obtain

$$\frac{d}{dt}\|M\|^2 + D\|\nabla M\|^2 \le C\|M\|^2 + k_{-1}^2\|A\|^2\,.$$

Finally, multiplying by e^{-Ct} and integrating on $[0,t]$ we obtain the result. $\square$

1.3.2 The Fixed Point operator

Define

$$\mathcal{K} := \left\{M^\sharp \in L^2\left(0,T;L^2(\Omega)\right) : M(\boldsymbol{x},t)\ge 0 \quad a.e.\right\}\,.$$

Fix $M^\sharp\in\mathcal{K}$ and set

$$\partial_t U = -k_1 M^\sharp U + k_{-1}[A-U]\,,\quad U(\boldsymbol{x},0) = A(\boldsymbol{x})\,.$$

For any finite time interval $[0,T]$ this linear problem has a unique solution $U(\boldsymbol{x},t)$ given by

$$\begin{aligned}U(\boldsymbol{x},t) &= A(\boldsymbol{x})\exp\left\{-\int_0^t [k_1 M^\sharp(\boldsymbol{x},s)+k_{-1}]ds\right\} \\ &+ k_{-1}A(\boldsymbol{x})\int_0^t \exp\left\{-\int_s^t [k_1 M^\sharp(\boldsymbol{x},r)+k_{-1}]dr\right\}ds\,,\end{aligned}$$

which satisfies $0\le U(\boldsymbol{x},t)\le A(\boldsymbol{x})$ a.e. in $\Omega\times(0,T)$. With this $U(\boldsymbol{x},t)$ define

$$\lambda(t) := \int_\Omega [A(\boldsymbol{x}) - U(\boldsymbol{x},t)]\,d\Omega$$

and set the elliptic problem

$$\left\{\begin{array}{rcll}\Delta\phi(\boldsymbol{x},t) &=& 0 & \text{in } \Omega,\\ \nabla\phi\cdot\boldsymbol{n}(\sigma,t) &=& a(\sigma)\lambda(t) & \text{on } \Gamma,\end{array}\right.$$

with $a(\sigma) \in L^\infty(\Gamma)$ and $\int_\Omega \phi(\boldsymbol{x},t)\,d\Omega = \int_\Gamma a(\sigma)\,dS = 0$. This linear problem has a unique solution $\phi(\boldsymbol{x},t) \in L^\infty\left(0,T;H^1(\Omega)\right)$ satisfying

$$\|\phi\|_{H^1(\Omega)} \le C\|a\|_\infty \|A\|_\infty \,. \tag{1.25}$$

Now, define $\boldsymbol{V}(\boldsymbol{x},t) = \nabla\phi(\boldsymbol{x},t)$ and set the linear problem

$$\begin{aligned} \partial_t M = \nabla\cdot[D\nabla M - \boldsymbol{V}M] - k_1 MU + k_{-1}[A-U] &\qquad \text{in } \Omega\times(0,T), \\ M(\sigma,t) = 0 &\qquad \text{on } \Gamma_a \times [0,T], \\ (D\nabla M - \boldsymbol{V}M)\cdot \boldsymbol{n}(\sigma,t) = 0 &\qquad \text{on } \Gamma_r \times [0,T], \\ M(\boldsymbol{x},0) = m_0(\boldsymbol{x}) &\qquad \text{in } \Omega. \end{aligned}$$

For any finite time interval $[0,T]$ there exists a unique weak solution $M(\boldsymbol{x},t)$ satisfying the estimates in Lemma 1.1.

In summary, we have just constructed a chain of maps $M^\sharp \mapsto U \mapsto \boldsymbol{V} \mapsto M$, where each map is given by a solution of a differential equation. In the light of this, we can define the operator $\mathcal{R}(M^\sharp) := M$, and our task now is to show that $\mathcal{R}$ has a fixed point.

In order to apply Schauder's Fixed Point Theorem to the operator $\mathcal{R}$ we need to show that it satisfies the following conditions.

Lemma 1.2 *Fix a positive time $T>0$. Then:*

1. *$\mathcal{K}$ is a convex closed subset of $L^2\left(0,T;L^2(\Omega)\right)$.*
2. *$\mathcal{R}:\mathcal{K}\to\mathcal{K}$.*
3. *$\mathcal{R}: L^2\left(0,T;L^2(\Omega)\right) \to L^2\left(0,T;L^2(\Omega)\right)$ is continuous.*
4. *$\mathcal{R}(\mathcal{K})$ is relatively compact in $L^2\left(0,T;L^2(\Omega)\right)$.*

Proof:

1. $\mathcal{K}$ is a convex closed subset of $L^2\left(0,T;L^2(\Omega)\right)$. It is immediate.

2. $\mathcal{R}:\mathcal{K}\to\mathcal{K}$. Multiply (1.18)-(1.20) by $-M^-$, integrate over Ω and use integration by parts. After those calculations we arrive to

$$\begin{aligned} \frac{1}{2}\frac{d}{dt}\|M^-\|^2 + D\|\nabla M^-\|^2 &= \frac{1}{2}\int_\Gamma \boldsymbol{V}\cdot\boldsymbol{n}|M^-|^2\,dS - k_1\int_\Omega U|M^-|^2\,d\Omega \\ &\quad -k_{-1}\int_\Omega [A-U]M^-\,d\Omega\,. \end{aligned}$$

From Lemma 1.1 we have $0\le U\le A$ since $M^\sharp\in\mathcal{K}$. Using this fact and trace estimates we arrive to

$$\frac{1}{2}\frac{d}{dt}\|M^-\|^2 + (D-\varepsilon)\|\nabla M^-\|^2 \le C\|M^-\|^2\,,$$

where $\varepsilon > 0$ is arbitrary. Therefore $M^-(\boldsymbol{x}, t) \equiv 0$ a.e. in $\Omega \times (0, T)$, and in consequence $M \in \mathcal{K}$.

3. $\mathcal{R} : L^2\left(0, T; L^2(\Omega)\right) \to L^2\left(0, T; L^2(\Omega)\right)$ *is continuous.* Let $M_1^\sharp, M_2^\sharp \in \mathcal{K}$, and for each $i = 1, 2$ consider the chain of maps

$$M_i^\sharp \longmapsto U_i \longmapsto \boldsymbol{V}_i \longmapsto M_i \,.$$

Define $\hat{M}^\sharp := M_2^\sharp - M_1^\sharp$, $\hat{U} := U_2 - U_1$, $\hat{\varphi} := \varphi_2 - \varphi_1$, $\hat{\boldsymbol{V}} := \boldsymbol{V}_2 - \boldsymbol{V}_1$ and $\hat{M} := M_2 - M_1$. The differences $\hat{M}$ and $\hat{U}$ solve the equations

$$\begin{aligned} \partial_t \hat{M} &= \nabla \cdot [D \nabla \hat{M} - \boldsymbol{V}_1 \hat{M} - \hat{\boldsymbol{V}} M_2] - \big[k_1 M_2 + k_{-1}\big] \hat{U} + k_1 \hat{M} U_1 \,, && (1.26) \\ \partial_t \hat{U} &= -\big[k_1 M_2^\sharp + k_{-1}\big] \hat{U} + k_1 \hat{M}^\sharp U_1 \,, && (1.27) \end{aligned}$$

with homogeneous boundary and initial conditions, whereas $\hat{\boldsymbol{V}}$ solves

$$\begin{aligned} \nabla \cdot \hat{\boldsymbol{V}} &= 0 \,, && (1.28) \\ \hat{\boldsymbol{V}} \cdot \boldsymbol{n} &= -a \int_\Omega \hat{U} \, d\Omega \,. \end{aligned}$$

We can solve explicitly the equation (1.27):

$$\hat{U}(\boldsymbol{x}, t) = k_1 \int_0^t \exp\left\{ - \int_s^t \Big[k_1 M_2^\sharp(\boldsymbol{x}, r) + k_{-1} \Big] \, dr \right\} \hat{M}^\sharp(\boldsymbol{x}, s) U_1(\boldsymbol{x}, s) ds \,.$$

Since $M_2^\sharp \geq 0$ and $0 \leq U_1 \leq A$ it follows that

$$|\hat{U}(\boldsymbol{x}, t)| \leq k_1 A(\boldsymbol{x}) \int_0^t |\hat{M}^\sharp(\boldsymbol{x}, s)| ds \,.$$

Using Hölder's inequality we find that

$$|\hat{U}(\boldsymbol{x}, t)|^2 \leq k_1^2 \|A\|_\infty^2 t \int_0^t |\hat{M}^\sharp(\boldsymbol{x}, s)|^2 ds \,,$$

and integrating over Ω we obtain

$$\|\hat{U}(t)\|^2 \leq \beta(t) \|\hat{M}^\sharp\|_{L^2(0,T;L^2(\Omega))}^2 \,; \quad \beta(t) = k_1^2 \|A\|_\infty^2 t \,. \tag{1.29}$$

Multiply the equation (1.26) by $\hat{M}$, integrate over Ω and use integration by parts to obtain

$$\begin{aligned} \frac{1}{2} \frac{d}{dt} \|\hat{M}\|^2 + D \|\nabla \hat{M}\|^2 &= \frac{1}{2} \int_\Gamma \boldsymbol{V}_1 \cdot \boldsymbol{n} |\hat{M}|^2 \, dS - \int_\Omega \hat{\boldsymbol{V}} \cdot \nabla \hat{M} M_2 \, d\Omega \\ &\quad - \int_\Omega [k_1 M_2 + k_{-1}] \, \hat{U} \hat{M} \, d\Omega - k_1 \int_\Omega U_1 |\hat{M}|^2 \, d\Omega \,. \end{aligned} \tag{1.30}$$

Let us estimate the right-hand side of (1.30). For the first integral, using $\boldsymbol{V}_1 \cdot \boldsymbol{n} \in L^\infty\left((0, T) \times \Omega\right)$ and trace estimates we obtain

$$\frac{1}{2} \int_\Gamma \boldsymbol{V}_1 \cdot \boldsymbol{n} |\hat{M}|^2 \, dS \leq C_1 \int_\Omega |\hat{M}|^2 \, d\Omega + \varepsilon \int_\Omega |\nabla \hat{M}|^2 \, d\Omega \,. \tag{1.31}$$

For the second integral, using Hölder's inequality it follows that

$$\begin{aligned}\int_\Omega \hat{\boldsymbol{V}} \cdot \nabla \hat{M} M_2 \, d\Omega &\leq \|\hat{\boldsymbol{V}}(t)\|_{[L^2(\Omega)]^n} \|M_2(t)\|_{L^\infty(\Omega\times(0,T))} \|\nabla \hat{M}(t)\| \\ &\leq C_2 \|\hat{U}(t)\|^2 \alpha^2(t) + \varepsilon \|\nabla \hat{M}(t)\|^2 ,\end{aligned} \tag{1.32}$$

with $C_2 > 0$ independent of T. For the third integral we have

$$\begin{aligned}\int_\Omega [k_1 M_2 + k_{-1}] \, \hat{U} \hat{M} \, d\Omega &\leq (k_1\alpha(t) + k_{-1}) \, \|\hat{U}(t)\| \, \|\hat{M}(t)\| \\ &\leq \frac{1}{2} \left(k_1\alpha(t) + k_{-1}\right)^2 \|\hat{U}(t)\|^2 + \frac{1}{2}\|\hat{M}(t)\|^2 .\end{aligned} \tag{1.33}$$

In conclusion, from the estimates (1.31)-(1.33) it follows that

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|\hat{M}(t)\|^2 + (D - 2\varepsilon)\|\nabla \hat{M}\|^2 &\leq \left[C_1 + \frac{1}{2}\right] \|\hat{M}(t)\|^2 \\ &+ \left[C_2\alpha^2(t) + \frac{1}{2}\left(k_1\alpha(t) + k_{-1}\right)^2\right] \|\hat{U}(t)\|^2.\end{aligned}$$

Choose $\varepsilon = D/4$, integrate over $[0, t]$ and use (1.29) to obtain

$$\|\hat{M}(t)\|^2 \leq \gamma_1(t) \|\hat{M}^\sharp\|^2_{L^2(0,T;L^2(\Omega))} + C \int_0^t \|\hat{M}(s)\|^2 \, ds ,$$

where $\gamma_1(t) = 2C_2\alpha^2(t) + (k_1\alpha(t) + k_{-1})^2$ and $C = 2C_1 + 1$. Finally, using Gronwall's inequality we get

$$\|\hat{M}(t)\|^2 \leq e^{Ct}\gamma_1(t)\|\hat{M}^\sharp\|^2_{L^2(0,T;L^2(\Omega))} ,$$

and integrating on $[0, T]$ yields

$$\begin{aligned}\|\hat{M}\|^2_{L^2(0,T;L^2(\Omega))} &\leq \gamma(T)\|\hat{M}^\sharp\|^2_{L^2(0,T;L^2(\Omega))} , \\ \gamma(T) &:= Te^{CT}\gamma_1(T) ,\end{aligned} \tag{1.34}$$

which implies the continuity of the operator $\mathcal{R}$.

4. $\mathcal{R}(\mathcal{K})$ is relatively compact in $L^2\left(0, T; L^2(\Omega)\right)$. We will use Aubin's compactness theorem (see Theorem 5.1 in Lions [45], Section 5.5, pp. 57-64, and Tartar [63], Chapter 24, pp. 137-141). Suppose that the sequence $\{M_n^\sharp\}$ is uniformly bounded in $L^2\left(0, T; L^2(\Omega)\right)$. Then by the continuity of $\mathcal{R}$ the sequence $\{\mathcal{R}M_n^\sharp = M_n\}$ is also uniformly bounded in $L^2\left(0, T; L^2(\Omega)\right)$, and the estimates in Lemma 1.1 imply that $\{M_n\}$ is uniformly bounded in $L^2\left(0, T; H^1(\Omega)\right)$. Furthermore, the sequence of derivatives $\{\partial_t M_n\}$ is uniformly bounded in $L^2\left(0, T; H^{-1}(\Omega)\right)$. Indeed, we have

$$\begin{aligned}\int_0^T \int_\Omega |\boldsymbol{V}_n M_n|^2 \, d\Omega \, dt &\leq T\|M_n\|_{L^\infty(\Omega\times(0,T))}\|\boldsymbol{V}_n\|^2_{L^\infty(0,T;[L^2(\Omega)]^n)} \\ &\leq CT\alpha^2(T)\|a\|_\infty\|A\|_\infty ,\end{aligned}$$

from where it follows that for all $t \in [0, T]$ the expression

$$\partial_t M_n = \nabla \cdot [D\nabla M_n - \boldsymbol{V}_n M_n] - k_1 M_n U_n + k_{-1}[A - U_n]$$

defines a uniformly bounded sequence of distributions in $H^1(\Omega)$. Therefore, applying Aubin's theorem to the spaces $H^1(\Omega) \subset L^2(\Omega) \subset H^{-1}(\Omega)$ we obtain that the sequence $\{M_n\}$ is relatively compact in $L^2\left(0, T; L^2(\Omega)\right)$. $\square$

1.3.3 Conclusion of the proof

Lemma 1.3 *For any $T > 0$ the reaction-diffusion system (1.18)-(1.20) has global unique weak solutions $M(\boldsymbol{x}, t)$, $U(\boldsymbol{x}, t)$ and $\boldsymbol{V}(\boldsymbol{x}, t)$ in $\Omega \times (0, T)$ a.e. Furthermore, $M(\boldsymbol{x}, t) \geq 0$ a.e. in $\Omega \times (0, T)$, and the estimates of Lemma 1.1 hold.*

Proof: The four statements of Lemma 1.2 imply that we can apply Schauder's Fixed Point Theorem to the operator $\mathcal{R}$ and obtain a fixed point $M^\sharp(\boldsymbol{x}, t) = M(\boldsymbol{x}, t)$ in $\mathcal{K}$. This implies that $M(\boldsymbol{x}, t) \geq 0$ a.e. in $\Omega \times (0, T)$, and in consequence Lemma 1.1 holds.

Observing carefully the explicit expression of $\gamma(T)$ in (1.34) it follows that $\gamma(T) \to 0$ if $T \to 0$. Therefore, the operator $\mathcal{R}$ is a contraction if $T > 0$ is small enough, and in consequence we have the local uniqueness of (1.18)-(1.20) .

Now choose a time $T_0 \in (0, T)$ such that $\gamma(T_0) < 1$ and perform the very same calculations we have already made but with initial conditions $M(\boldsymbol{x}, T_0)$ and $U(\boldsymbol{x}, T_0)$ instead of $m_0(\boldsymbol{x})$ and $A(\boldsymbol{x})$, respectively. This yields a different set of bounds

$$\begin{aligned}
\alpha(T_0, t) &:= \|M(T_0)\|_\infty + k_1(t - T_0)\|U(T_0)\|_\infty\,, \\
\beta(T_0, t) &:= k_1^2\|U(T_0)\|_\infty^2(t - T_0)\,, \\
\gamma_1(T_0, t) &:= 2C_2\alpha^2(T_0, t) + (k_1\alpha(T_0, t) + k_{-1})^2\,, \\
\gamma(T_0, t) &:= (t - T_0)e^{C(t-T_0)}\gamma_1(T_0, t)\,.
\end{aligned}$$

Recall that $U(T_0) \leq A(\boldsymbol{x})$ and $\|M\|_\infty \leq \alpha(T)$ and define

$$\begin{aligned}
\widetilde{\alpha}(T) &:= \alpha(T) + k_1 t\|A\|_\infty\,, \\
\widetilde{\beta}(T) &:= \beta(T)\,, \\
\widetilde{\gamma}_1(T) &:= 2C_2\widetilde{\alpha}^2(T) + (k_1\widetilde{\alpha}(T) + k_{-1})^2\,, \\
\widetilde{\gamma}(T) &:= Te^{CT}\widetilde{\gamma}_1(T)\,.
\end{aligned}$$

These new bounds are independent of the initial conditions $M(T_0)$ and $U(T_0)$. Therefore, if T_0 was chosen such that $\widetilde{\gamma}(T_0) < 1$ we can extend the uniqueness result to the interval $[T_0, 2T_0]$, and repeating this procedure we obtain uniqueness on the whole interval $[0, T]$, i.e. global uniqueness. $\square$

From Lemmas 1.1 and 1.3 the proof of Theorem 1.1 follows immediately.

1.4 Proof of Theorem 1.2

1.4.1 A priori estimates

Lemma 1.4 *$U(\boldsymbol{x},t), W(\boldsymbol{x},t) \in L^\infty(\Omega \times (0,T))$ and*

$$0 \le U(\boldsymbol{x},t) + W(\boldsymbol{x},t) \le \|A\|_\infty \quad a.e. \tag{1.35}$$

Proof: For any $c \in \mathbb{R}$ the function $Y := U + W - c$ satisfies

$$\partial_t Y = d\Delta Y\,, \quad \frac{\partial Y}{\partial \boldsymbol{n}} = 0 \text{ on } \Gamma, \quad Y(\boldsymbol{x},0) = A(\boldsymbol{x}) - c\,.$$

Therefore, applying the Maximum Principle to the cases $c = 0$ and $c = \|A\|_\infty$ we obtain the first and second inequalities in (1.35), respectively. □

Lemma 1.5 *If $M(\boldsymbol{x},t) \ge 0$ a.e. in $\Omega \times (0,T)$ then:*

1. *$M \in L^\infty(\Omega \times (0,T))$ and $0 \le M(\boldsymbol{x},t) \le \alpha(t) := \|m_0\|_\infty + k_{-1}t\|A\|_\infty$ a.e. in $\Omega \times (0,T)$.*
2. *$M \in L^\infty\left(0,T;H^1(\Omega)\right)$ and*
$$\|M(t)\|^2 + D\int_0^t e^{C(t-s)}\|\nabla M(s)\|^2\,ds \le e^{Ct}\left[\|m_0\|^2 + k_{-1}^2 t\|A\|^2\right]\,.$$
3. *$U, W \in L^\infty(\Omega \times (0,T))$ and $0 \le U(\boldsymbol{x},t) + W(\boldsymbol{x},t) \le A(\boldsymbol{x})$ a.e. in $\Omega \times (0,T)$.*
4. *$U, W \in L^\infty\left(0,T;H^1(\Omega)\right)$ and*
$$\|U(t)\|^2 + \|W(t)\|^2 + 2d\int_0^t e^{\int_s^t c(r)dr}\left(\|\nabla U(s)\|^2 + \|\nabla W(s)\|^2\right)\,ds \le e^{\int_0^t c(s)ds}\|A\|^2\,,$$
where $c(t) = 2[k_{-1} + k_1\alpha(t)]$.
5. *$\boldsymbol{V} \in L^\infty\left(0,T;\left[L^2(\Omega)\right]^n\right)$ and $\|\boldsymbol{V}\|_{L^\infty(0,T;[L^2(\Omega)]^n)} \le C\|a\|_\infty\|A\|_\infty$.*

Proof: The only statements we need to prove are 3 and 4 because the other ones can be proved using exactly the same arguments we have already performed in Section 1.3.

Let us first prove statement 3. An integration by parts in (1.21)-(1.23) yields

$$\frac{1}{2}\frac{d}{dt}\|U^-\|^2 + d\|\nabla U^-\|^2 + k_1\int_\Omega M|U^-|^2 = -k_{-1}\int_\Omega WU^-\,d\Omega\,.$$

We affirm that $WU^- \ge 0$. Indeed, by Lemma 1.4 we have that $U + W \ge 0$, which implies that $0 \le U^-(U+W) = -|U^-|^2 + U^-W$. Therefore $U^-W \ge 0$, and in consequence $\|U^-(t)\|^2 \equiv 0$. The argument for proving $\|W^-(t)\|^2 \equiv 0$ is the same.

For statement 4, integration by parts yields

$$\begin{aligned}\frac{1}{2}\frac{d}{dt}\|U\|^2 + d\|\nabla U\|^2 + k_1\int_\Omega M|U|^2\,d\Omega &= k_{-1}\int_\Omega WU\,d\Omega\,,\\ \frac{1}{2}\frac{d}{dt}\|W\|^2 + d\|\nabla W\|^2 + k_{-1}\int_\Omega |W|^2\,d\Omega &= k_1\int_\Omega MUW\,d\Omega\,.\end{aligned}$$

Adding both equalities we get

$$\frac{1}{2}\frac{d}{dt}\left[\|U\|^2+\|W\|^2\right] + d\left[\|\nabla U\|^2+\|\nabla W\|^2\right] \le \frac{c(t)}{2}\|U\|\,\|W\|\,,$$

where $c(t)=2[k_{-1}+k_1\alpha(t)]$. Multiplying this inequality by $e^{-\int_0^t c(s)ds}$ and integrating on $[0,T]$ we obtain the result. $\square$

1.4.2 The Fixed Point operator

Define

$$\mathcal{K} := \left\{M^\sharp \in L^2\left(0,T;L^2\left(\Omega\right)\right) : 0\le M(\boldsymbol{x},t)\le \|m_0\|_\infty + k_{-1}t\|A\|_\infty \quad \text{a.e. in } \Omega\times(0,T)\right\}\,.$$

Fix $M^\sharp\in\mathcal{K}$ and set

$$\begin{aligned}\partial_t U = d\Delta U - k_1 M^\sharp U + k_{-1}W &\qquad \text{in } \Omega\times(0,T),\\ \partial_t W = d\Delta U + k_1 M^\sharp U - k_{-1}W &\qquad \text{in } \Omega\times(0,T),\\ \nabla U\cdot\mathbf{n}(\sigma,t)=0 &\qquad \text{on } \Gamma\times[0,T],\\ \nabla W\cdot\mathbf{n}(\sigma,t)=0 &\qquad \text{on } \Gamma\times[0,T].\end{aligned}$$

For any finite time interval $[0,T]$ this linear system has unique solutions $U(\boldsymbol{x},t)$ and $W(\boldsymbol{x},t)$, which are non-negative and satisfy $0\le U(\boldsymbol{x},t)+W(\boldsymbol{x},t)\le A(\boldsymbol{x})$ a.e. in $\Omega\times(0,T)$. With these $U(\boldsymbol{x},t)$ and $W(\boldsymbol{x},t)$ set

$$\left\{\begin{array}{rcll}\Delta\phi(\boldsymbol{x},t) &=& 0 & \text{in } \Omega,\\ \nabla\phi\cdot\boldsymbol{n}(\sigma,t) &=& a(\sigma)\int_\Omega W(\boldsymbol{x},t)\,d\Omega & \text{on } \Gamma,\end{array}\right.$$

with $a(\sigma)\in L^\infty(\Gamma)$ and $\int_\Omega\phi(\boldsymbol{x},t)d\Omega=\int_\Gamma a(\sigma)dS=0$. This linear problem has a unique solution $\phi(\boldsymbol{x},t)\in L^\infty\left(0,T;H^1(\Omega)\right)$ satisfying

$$\|\phi\|_{H^1(\Omega)}\le C\|a\|_\infty\|A\|_\infty\,. \tag{1.36}$$

Now, define $\boldsymbol{V}(\boldsymbol{x},t)=\nabla\phi(\boldsymbol{x},t)$ and set

$$\begin{aligned}\partial_t M = \nabla\cdot[D\nabla M - \boldsymbol{V}M] - k_1 MU + k_{-1}[A-U] &\qquad \text{in } \Omega\times(0,T),\\ M(\sigma,t)=0 &\qquad \text{on } \Gamma_a\times[0,T],\\ \nabla M\cdot\mathbf{n}(\sigma,t)=0 &\qquad \text{on } \Gamma_r\times[0,T],\\ M(\boldsymbol{x},0)=m_0(\boldsymbol{x}) &\qquad \text{in } \Omega.\end{aligned}$$

For any finite time interval $[0,T]$ there exists a unique weak solution $M(\boldsymbol{x},t)$ such that $0 \le M(\boldsymbol{x},t) \le \|m_0\|_\infty + k_{-1}t\|A\|_\infty$ a.e. in $\Omega \times (0,T)$.

We have just constructed a chain of maps $M^\sharp \mapsto (U,W) \mapsto \boldsymbol{V} \mapsto M$, and our goal is to show that the operator $\mathcal{R}(M^\sharp) := M$ has a fixed point.

1.4.3 Conclusion of the proof

Let $M_1^\sharp, M_2^\sharp \in \mathcal{K}$, and for each $i = 1,2$ consider the chain of maps

$$M_i^\sharp \longmapsto U_i \longmapsto \boldsymbol{V}_i \longmapsto M_i\,.$$

Define $\hat{M}^\sharp := M_2^\sharp - M_1^\sharp$, $\hat{U} := U_2 - U_1$, $\hat{W} := W_2 - W_1$, $\hat{\varphi} := \varphi_2 - \varphi_1$, $\hat{\boldsymbol{V}} := \boldsymbol{V}_2 - \boldsymbol{V}_1$ and $\hat{M} := M_2 - M_1$. The differences $\hat{M}$, $\hat{U}$ and $\hat{W}$ solve the equations

$$\begin{aligned} \partial_t \hat{M} &= \nabla \cdot [D\nabla\hat{M} - \boldsymbol{V}_1\hat{M} - \hat{\boldsymbol{V}}M_2] - k_1\hat{U}M_2 - k_1U_1\hat{M} + k_{-1}\hat{W}\,, \\ \partial_t\hat{U} &= d\Delta\hat{U} - k_1\hat{U}M_2^\sharp - k_1U_1\hat{M}^\sharp + k_{-1}\hat{W}\,, \\ \partial_t\hat{W} &= d\Delta\hat{U}k_1\hat{U}M_2^\sharp + k_1U_1\hat{M}^\sharp - k_{-1}\hat{W}\,, \end{aligned} \tag{1.37}$$

with homogeneous initial and boundary conditions, whereas $\hat{\boldsymbol{V}} = \nabla\hat{\phi}$ solves

$$\begin{aligned} \nabla\cdot\hat{\boldsymbol{V}} &= 0\,, \\ \hat{\boldsymbol{V}}\cdot\boldsymbol{n} &= a\int_\Omega \hat{W}\,d\Omega\,. \end{aligned}$$

Lemma 1.6 *If for $i = 1,2$, $M_i^\sharp(\boldsymbol{x},t) \ge 0$ a.e. in $\Omega \times (0,T)$ then there exist positive continuous functions $C_1(t)$, $C_2(t)$ and $C_3(t)$ such that*

$$\begin{aligned} \frac{d}{dt}\|\hat{M}(t)\|^2 &\le C_1(t)\left(\|\hat{M}(t)\|^2 + \|\hat{U}(t)\|^2 + \|\hat{W}(t)\|^2\right). \\ \frac{d}{dt}\left(\|\hat{U}(t)\|^2 + \|\hat{W}(t)\|^2\right) &\le C_2(t)\left(\|\hat{U}(t)\|^2 + \|\hat{W}(t)\|^2 + \|\hat{M}^\sharp(t)\|^2\right), \\ \frac{d}{dt}\left(\|\hat{U}(t)\|^2 + \|\hat{W}(t)\|^2\right) &\le C_3(t)\left(\|\hat{U}(t)\|^2 + \|\hat{W}(t)\|^2\right). \end{aligned} \tag{1.38}$$

<u>*Proof*</u>: Multiply (1.37) by $\hat{M}$ and integrate by parts to get

$$\begin{aligned} \frac{1}{2}\frac{d}{dt}\|\hat{M}\|^2 + D\|\nabla\hat{M}\|^2 &= -k_1\int_\Omega |\hat{U}|^2\hat{\boldsymbol{V}}_1\cdot\boldsymbol{n}\,dS - \int_\Omega M_2\hat{\boldsymbol{V}}\cdot\nabla\hat{M}\,d\Omega \\ &- k_1\int_\Omega \hat{U}M_2\hat{M}\,d\Omega - k_1\int_\Omega U_1|\hat{M}|^2\,d\Omega + k_{-1}\int_\Omega \hat{W}\hat{M} \end{aligned} \tag{1.39}$$

Noticing that all the functions are in L^∞ we can deduce the first estimate in (1.38). Indeed, since $\|\hat{\boldsymbol{V}}\| \le C\|\hat{W}\|$ it follows that

$$\int_\Omega M_2\hat{\boldsymbol{V}}\cdot\nabla\hat{M}\,d\Omega \le \varepsilon\|\nabla\hat{M}\|^2 + C(t)\|\hat{W}\|^2\,,$$

and the other four integrals in (1.39) can be estimated similarly in order to get

$$\frac{d}{dt}\|\hat{M}(t)\|^2 \le C_1(t)\left(\|\hat{M}(t)\|^2 + \|\hat{U}(t)\|^2 + \|\hat{W}(t)\|^2\right).$$

Multiply (1.37) by $\hat{U}$ and integrate by parts to get

$$\frac{1}{2}\frac{d}{dt}\|\hat{U}\|^2 + d\|\nabla\hat{U}\|^2 = -k_1\int_\Omega |\hat{U}|^2 M_2^\sharp\, d\Omega - k_1\int_\Omega U_1\hat{M}^\sharp\hat{U}\, d\Omega + k_1\int_\Omega \hat{W}\hat{U}\, d\Omega\,. \tag{1.40}$$

Observe that second integral in (1.40) can be estimated in two ways, either

$$\int_\Omega U_1\hat{M}^\sharp\hat{U}\, d\Omega \le C\left(\|\hat{U}(t)\|^2 + \|\hat{M}^\sharp(t)\|^2\right)$$

or either

$$\int_\Omega U_1\hat{M}^\sharp\hat{U}\, d\Omega \le C(t)\|\hat{U}(t)\|^2\,.$$

In the first case we can deduce that

$$\frac{d}{dt}\|\hat{U}(t)\|^2 \le C(t)\left(\|\hat{U}(t)\|^2 + \|\hat{W}(t)\|^2 + \|\hat{M}^\sharp(t)\|^2\right), \tag{1.41}$$

whereas in the second case we can show that

$$\frac{d}{dt}\|\hat{M}(t)\|^2 \le C(t)\left(\|\hat{U}(t)\|^2 + \|\hat{W}(t)\|^2\right). \tag{1.42}$$

Now perform the same estimates for $\hat{W}$ and add up both the estimates for $\hat{U}$ and $\hat{W}$. It follows then that with estimates of type (1.41) we obtain the second inequality in (1.38), whereas with estimates of type (1.42) we get the third inequality in (1.38). □

Lemma 1.7 *For any $T>0$ the reaction-diffusion system (1.21)-(1.23) is a well-posed problem, i.e. it has global unique weak solutions $M(\boldsymbol{x},t)$, $U(\boldsymbol{x},t)$, $W(\boldsymbol{x},t)$ and $\boldsymbol{V}(\boldsymbol{x},t)$ which depend continuously on the initial data. Moreover, $M(\boldsymbol{x},t)$, $U(\boldsymbol{x},t)$ and $W(\boldsymbol{x},t)$ are non-negative a.e. in $\Omega\times(0,T)$ and the estimates of Lemma 1.5 hold.*

Proof: Using Gronwall's lemma in the second equation in (1.38) we have

$$\|\hat{U}(t)\|^2 + \|\hat{W}(t)\|^2 \le C_2(t)\|\hat{M}^\sharp(t)\|^2_{L^2(0,T;L^2(\Omega))}\,.$$

Plugging inequality into the first equation in (1.38) and using again Gronwall's lemma we obtain that there exists a positive continuous function $\theta(t)$ such that

$$\|\hat{M}(t)\|^2 \le \theta(t)\|\hat{M}^\sharp(t)\|^2_{L^2(0,T;L^2(\Omega))}\,.$$

Integrating on $[0,T]$ we have

$$\|\hat{M}(t)\|^2_{L^2(0,T;L^2(\Omega))} \le T\theta(T)\|\hat{M}^\sharp(t)\|^2_{L^2(0,T;L^2(\Omega))}\,,$$

which implies that the operator $\mathcal{R}$ is continuous. Therefore, applying Schauder's Fixed Point Theorem it follows that $\mathcal{R}$ has a fixed point $M(\boldsymbol{x},t)$. With this $M(\boldsymbol{x},t)$ we can construct $U(\boldsymbol{x},t)$, $W(\boldsymbol{x},t)$ and $\boldsymbol{V}(\boldsymbol{x},t)$, and the four of them are global solutions of the problem (1.21)-(1.23). Moreover, since $M(\boldsymbol{x},t)\geq 0$ a.e. in $\Omega\times(0,T)$ then the estimates of Lemma 1.5 hold.

Now suppose we have non-homogeneous initial conditions. Then adding up the first and third equations in (1.38) and using Gronwall's lemma we can show that there exists a positive continuous function $\kappa(t)$ such that

$$\|\hat{M}(t)\|^2+\|\hat{U}(t)\|^2+\|\hat{W}(t)\|^2\leq\kappa(t)\left(\|\hat{M}(0)\|^2+\|\hat{U}(0)\|^2+\|\hat{W}(0)\|^2\right).$$

Therefore, the solutions are unique and depend continuously on the initial data. □

From Lemmas 1.5 and 1.7 the proof of Theorem 1.2 follows immediately.

1.5 Proof of Theorems 1.3 and 1.4

1.5.1 Proof of Theorem 1.3

For any $0<d\leq d_0$ let $(M^d,U^d,W^d,\mathbf{V}^d)$ be the weak solutions of (1.21)-(1.23) and let $d\to 0$. First, Lemma 1.5 implies that the sequence U^d is bounded in

$$\mathcal{X}:=L^2\left(0,T;L^2\left(\Omega\right)\right)\cap L^\infty(\Omega\times(0,T)),$$

which implies that a subsequence, still denoted U^d, converges weakly-$\star$ in $\mathcal{X}$ to a limit U^0. Similarly, a subsequence W^d converges weakly-$\star$ in $\mathcal{X}$ to a limit W^0.

Second, Lemma 1.5 also affirms that the sequence $\mathbf{V}^d$ is uniformly bounded in

$$\mathcal{Y}:=L^\infty\left(0,T;\left[L^2\left(\Omega\right)\right]^n\right),$$

then there is a subsequence $\mathbf{V}^d$ converging weak-$\star$ in $\mathcal{Y}$ to a limit $\mathbf{V}^0$.

Third, from Lemma 1.5 the sequence M^d is uniformly bounded in

$$\mathcal{Z}:=L^2\left(0,T;L^2\left(\Omega\right)\right)\cap L^2\left(0,T;H^1\left(\Omega\right)\right)\cap L^\infty\left(0,T;H^1\left(\Omega\right)\right)\cap L^\infty(\Omega\times(0,T)),$$

hence a subsequence M^d converges weak-$\star$ in $\mathcal{Z}$ to a limit M^0. Moreover, using classical estimates of type

$$\int_0^T\int_\Omega|\mathbf{V}^dM^d-\mathbf{V}^0M^0|\,d\Omega dt\leq C_1\|\mathbf{V}^d-\mathbf{V}^0\|+C_2\|M^d-M^0\|$$

it follows that $\mathbf{V}^dM^d\to\mathbf{V}^0M^0$ strongly in $\left[L^1(\Omega\times(0,T))\right]^n$ and $M^dU^d\to M^0U^0$ strongly in $L^1(\Omega\times(0,T))$. This implies that the sequence ∂_tM^d is uniformly bounded in $L^2\left(0,T;H^{-1}\left(\Omega\right)\right)$, so applying Aubin's compactness theorem we have that the convergence $M^d\to M^0$ is in fact strong in $L^2\left(0,T;L^2\left(\Omega\right)\right)$.

In the light of the former convergences we obtain that a subsequence $(M^d, U^d, W^d, \mathbf{V}^d)$ of weak solutions of (1.21)-(1.23) converges weakly in $L^2\left(0,T;L^2\left(\Omega\right)\right)$ to $(M^0, U^0, W^0, \mathbf{V}^0)$, which is a weak solution of (1.18)-(1.20). However, the uniqueness of the problem (1.18)-(1.20) implies, on the one hand, that $(M^0, U^0, W^0, \mathbf{V}^0) = (M, U, W, \mathbf{V})$, and on the other hand, that the whole original sequence $(M^d, U^d, W^d, \mathbf{V}^d)$ converges weakly in $L^2\left(0,T;L^2\left(\Omega\right)\right)$. Moreover, since in the limit we have $\partial_t(U+W) = 0$ and $U, W \in L^\infty(\Omega \times (0,T))$ then $U(\boldsymbol{x},t) + W(\boldsymbol{x},t) = A(\boldsymbol{x})$ a.e. in $\Omega \times (0,T)$.

1.5.2 Proof of Theorem 1.4

From Theorems 1.1 and 1.2 we have that $U(\boldsymbol{x},t) + W(\boldsymbol{x},t) \le A(\boldsymbol{x})$ for all $t > 0$ and all $\boldsymbol{x} \in \Omega$. Therefore, $U(\boldsymbol{x},t)$ and $W(\boldsymbol{x},t)$ are globally defined in time and

$$\|U\|_{L^\infty(\Omega\times(0,\infty))} \le \|A\|_{L^\infty(\Omega)}\,, \quad \|W\|_{L^\infty(\Omega\times(0,\infty))} \le \|A\|_{L^\infty(\Omega)}\,.$$

On the model with diffusive proteins (1.21)-(1.23), if we integrate the equations for M and W and use the boundary conditions we obtain

$$\begin{aligned}\partial_t \int_\Omega \big(M(\boldsymbol{x},t) + W(\boldsymbol{x},t)\big) &= \int_\Omega \nabla\cdot[D\nabla M - \boldsymbol{V} M]\,d\Omega + \int_\Omega \Delta W\,d\Omega \\ &= D\int_{\Gamma_a} \nabla M\cdot\mathbf{n}\,dS \le 0\,.\end{aligned}$$

The last inequality holds because $M \ge 0$ in Ω and $M = 0$ on Γ_a imply $\nabla M\cdot\mathbf{n} \le 0$ on Γ_a. Therefore,

$$\int_\Omega \big(M(\boldsymbol{x},t) + W(\boldsymbol{x},t)\big)\,d\Omega \le \int_\Omega m_0(\boldsymbol{x})\,d\Omega\,,$$

and in consequence $M \in L^\infty\left(0,\infty;L^1\left(\Omega\right)\right)$. For the model with fixed proteins (1.18)-(1.20), integrating $M-U$ and repeating the previous argument it can be shown that $M \in L^\infty\left(0,\infty;L^1\left(\Omega\right)\right)$.

Notice that since the boundary condition for $\boldsymbol{V} = \nabla\phi$ depends on W, it necessarily lies in $L^\infty(\Gamma\times(0,\infty))$. Therefore, integrating we find a constant C such that

$$\int_\Omega |\nabla\phi|^2\,d\Omega = \int_\Gamma \phi a(\sigma)\lambda(t)\,dS \le C\left(\int_\Gamma |\nabla\phi|^2\,d\Omega\right)^{1/2}.$$

On the other hand, using (1.15) and trace inequalities we obtain that

$$\|\nabla\phi(t)\|_{L^2(\Omega)}\,d\Omega \le C \quad \forall t \ge 0\,.$$

In consequence, $\boldsymbol{V} = \nabla\phi$ is globally defined and $\boldsymbol{V} \in L^\infty\left(0,\infty;L^2\left(\Omega\right)\right)$.

1.6 Final remarks

1.6.1 On the cytoplasmic flux

Throughout this article we have supposed that the cytoplasmic flow field $\boldsymbol{V}$ is incompressible $(\nabla\cdot\boldsymbol{V} = 0)$ and that it comes from a potential $(\boldsymbol{V} = \nabla\phi)$. These two hypothesis are assumed in the model of Holcman and Schuss [34], but the cytoplasmic flow could have been modeled in a more realistic way without affecting the results we presented. Indeed, we could consider that $\boldsymbol{V}$ follows Stokes' equation

$$\begin{aligned} -\mu\Delta\boldsymbol{V} + \nabla p &= 0 && \text{in } \Omega, \\ \nabla\cdot\boldsymbol{V} &= 0 && \text{in } \Omega, \\ \boldsymbol{V} &= \lambda(t)\boldsymbol{f} && \text{on } \Gamma, \end{aligned} \tag{1.43}$$

with $\boldsymbol{f} \in \left[H^{1/2}(\Gamma)\cap L^\infty(\Gamma)\right]^n$. Under these assumptions the problem (1.43) has a unique solution $\boldsymbol{V} \in \left[H^1(\Omega)\right]^n$ satisfying

$$\|\boldsymbol{V}\|_{[H^1(\Omega)]^n} \leq C|\lambda(t)|\cdot\|\boldsymbol{f}\|_{\left[H^{1/2}(\Gamma)\right]^n},$$

which can be used instead of (1.17) to obtain the same results of Theorems 1.1, 1.2 and 1.3.

1.6.2 On the diffusion coefficient

If we wish to take into account the existence of obstacles inside the spine, like organelles or macromolecules, we can add them in two forms: either as "exterior domains", i.e. we take out a tiny section from the domain Ω and suppose that the boundary of the section belongs to the boundary of Ω, or either by considering that the diffusion coefficients are no longer constant. The results we presented here are still valid in both situations provided that the exterior domains have C^1 boundaries, $D, d \in C^1(\bar{\Omega}\times[0,T])$ and

$$0 < D_1 \leq D(\boldsymbol{x},t) \leq D_2\,, \quad 0 < d_1 \leq d(\boldsymbol{x},t) \leq d_2\,.$$

1.6.3 On the reactions between calcium and the proteins

As in Holcman and Schuss [34], we assumed in the model that all binding sites have the same affinity for the Ca^{2+} ions, but this is not the real case. Indeed, calcineurin has one binding site with high affinity and three with low affinity (see Klee *et al* [36]), AM-type proteins like Troponin have two low affinity sites and two high affinity sites (see Farah *et al* [19]), and CaM with two Ca^{2+} ions bound has more affinity to bind calcium than CaM with no Ca^{2+} ions bound (see Shiftman *et al* [59]). Nevertheless, such distinctions were not considered here in order to keep things as simple as possible.

1.7 Discussion

All the results we presented here are new and can be considered as the sequel of the works of Holcman *et al* [33] and [34], and in particular of [34] where Holcman and Schuss proposed the reaction-diffusion system (1.5) as a model for calcium dynamics inside a dendritic spine. Our main results are Theorem 1.1, where we proved that the system (1.5) in its modified form (1.18)-(1.20) has global unique positive solutions, Theorem 1.2, where we proved that if the proteins diffuses then the corresponding problem (1.21)-(1.23) is well-posed, and Theorem 1.3, where we showed that the solutions of (1.21)-(1.23) converge to the solutions of (1.18)-(1.20) when $d \to 0$.

We mentioned also that the experimental evidence suggests that the twitching motion of the spine should depend on the total number of occupied binding sites. We made the assumption that the spine twitching depends on the cytoplasmic velocity $\boldsymbol{V}$ at the spine surface Γ, and that this value depends on the total number of Ca^{2+} ions that are bound to the proteins. This renders a strong coupling between M, U, W and $\boldsymbol{V}$ but nevertheless we succeeded to solve this coupled system.

There are at least two tasks that we consider interesting to address in the future. First, it could be illustrative to perform numerical simulations for both reaction-diffusion models (1.21)-(1.23) and (1.21)-(1.23) in order to compare them with the simulations of the Langevin equation (1.1) that appeared in Holcman *et al* [33], [34], and also with experimental data. Second, given that the solutions are globally defined in time, we would like to study the asymptotic behaviour and stability of the solutions for large times.

Chapter 2

Viral infection and immune response

Work in collaboration with Anna Marciniak-Czochra. Already submitted.

In this work we extend the ODE model for virus infection and immune response proposed by P. Getto *et al* (*Modelling and analysis of dynamics of viral infection of cells and of interferon resistance*, J. Math. Anal. Appl., No. 344, 2008, pp. 821-850) to account for the spatial effects of the processes, such as diffusion transport of virions, biomolecules and cells. This leads to two different nonlinear PDE models, a first one where the cells and the biomolecules diffuse (which we call the reaction-diffusion model) and a second one where only the biomolecules can diffuse (the hybrid model). We show that both the reaction-diffusion and the hybrid models are well-posed problems, i.e., they have global unique solutions which are non-negative, bounded, and depend continuously on the initial data. Moreover, we prove that there exists a "continuous" link between these two models, i.e., if the diffusion coefficient of the cells tends to zero then the solution of the reaction-diffusion model converges to the solution of the hybrid model. We also prove that the solutions are uniformly bounded and integrable for all times. We characterize the asymptotic behavior of the solutions of the hybrid system and present several relations concerning the survivability of viruses and cells. Finally, we show that the solutions of the hybrid model converge to the steady state solutions, which implies that the latter are globally stable. We finish with several numerical simulations performed in Matlab.

2.1 Introduction

2.1.1 Spatial effects of viral infection and immunity response

When a virion, i.e., an individual viral particle, enters a healthy cell, it modifies the genetic structure of its host. After infection, the altered biochemical machinery of the host starts to create new virions. The virions are then released from the host cell and may infect other cells. However, the infected cell activates intrinsic host defenses, which include, among others, activation of the innate immunity system and release of biomolecules called interferons (IFN), which communicate with the other cells and induce them to deploy protective defenses. The dynamics of such complex virus-host system results from the intra- and extracellular interactions between invading virus particles and cells producing substances, which confer resistance to virus.

These key processes have been addressed by the mathematical model proposed by Getto, Kimmel and Marciniak-Czochra in [24]. The model was motivated by the experiments involving vesicular stomatitis virus (VSV) [16, 42] and respiratory syncytial virus (RSV). The work of P. Getto *et al* [24] is focused on the study of the role of heterogeneity of intracellular processes, reflected by a structure variable, in the dynamics of the system and stability of stationary states. It is shown that indeed the heterogeneity of the dynamics of cells in respect to the age of the individual cell infection may lead to the significant changes in the behavior of the model solutions, exhibiting either stabilizing or destabilizing effects.

Another interesting aspect of the dynamics of the spread of viral infection and development of resistance is related to the spatial structure of the system and the effects of spatial processes, such as random dispersal of virions and interferon particles. In a series of experiments on the vesicular stomatitis virus infection [16, 42], it was observed that the spatial structure of the system may influence the dynamics of the whole cell population. The role of spatial dimension and diffusion transport of virions and interferon molecules were experimentally studied using two type of experiments: a one-step growth experiment in which all cells were infected simultaneously, and a focal-infection experiment in which cell population was infected by a point source of virus. A spreading cicular wave of infection followed by a wave of dead cells was observed. The experiments were performed on two different cell cultures: DBT (murine delayed brain tumor) cells, which respond to IFN and can be activated to resist the replication of viruses, and BHK (baby hamster kidney) cells, which are not known to produce or respond to IFN. In case of focal infection both in DBT and BHK populations spread of infection (rings) was observed. The size of the rings was dependent on the type of the virus (N1, N2, N3, N4 -gene ectopic strains as well as M51R mutant and XK3.1). However, for all virus types, it was observed that in DBT cells the speed of the infection propagation was decreasing with time, while in case of BHK the radius of the infected area was growing linearly in time. Results of the experiments showed that the rate of infectious progeny production in one-step growth experiments was a key determinant of the rate of focal spread under the absence of IFN production. Interestingly, the correlation between one-step growth and focal growth did not apply for VSV strains XK3.1 and M51R in the cells producing IFN. Focal infection in DBT cells led only to the limited infection, the spread of which stopped after a while.

These experiments indicated suitability of focal infections for revealing aspects of virus-cell interactions, which are not reflected in one-step growth curves. Motivated by Duca *et al* experiments, we devise a model of spatio-temporal dynamics of viral infection and interferon production, which involves virions, uninfected, infected and resistant cells, as well as the interferon. We assume that interferon is produced by infected cells and spread by diffusion to neighboring uninfected cells, making them resistant. At the same time, the virus is spread, also by diffusion and the final outcome is the result of competition beween these two processes.

2.1.2 The original model

The point of departure for this work is a system of nonlinear ordinary differential equations developed by P. Getto *et al* [24] to model wild-type cells interacting with virions and the consequent interferon-based immune response. The model describes time dynamics of five different types of entities interacting in a culture: three different types of cells (wild-type, infected and resistant) and two different biomolecules (virions and interferons).

P. Getto *et al* [24] considered a culture of wild-type cells infected by virions. When a wild-type cell interacts with a virion it becomes an infected cell. Infected cells produce further virions, but they also release interferons. If an interferon reaches a wild-type cell before a virion does, then this cell becomes a resistant cell. Virions, interferons and infected cells are supposed to have an exponential death rate, whilst there is no death rate associated to wild-type and resistant cells, because they are considered to live longer than infected cells. In the other words, the model describes the time scale of *in vitro* experiments, which is short comparing to the life span of healthy cells.

Under these hypotheses the following nonlinear ODE model was proposed:

$$\left\{\begin{array}{rcll} W' &=& -iW - vW\,, & \leftarrow \text{wild-type cells} \\ I' &=& -\mu_I I + vW\,, & \leftarrow \text{infected cells} \\ R' &=& iW\,, & \leftarrow \text{resistant cells} \\ v' &=& -\mu_v v + \alpha_v I - \alpha_4 vW\,, & \leftarrow \text{virions} \\ i' &=& -\mu_i i + \alpha_i I - \alpha_3 iW\,, & \leftarrow \text{interferons} \end{array}\right. \tag{2.1}$$

where all coefficients coefficients are positive constants.

2.1.3 Biological hypotheses of the new model

In this work we will modify the ODE model (2.1) by introducing spatial random dispersion of cells, virions and IFN molecules. We consider two models: In the first model (which we call the reaction-diffusion model) we assume that all cells, virions and interferons diffuse, whilst the second model (which we call the hybrid model) is based on the hypothesis that only virions and interferons diffuse. The diffusion terms are supposed to follow Fick's Law with constant diffusion coefficients and it is modeled by adding Laplacian operators to the ODE system.

Concerning the boundary conditions, we assume that the whole system is isolated within a bounded domain $\Omega \subset \mathbb{R}^N$ ($N = 2, 3$). This implies no-flux boundary conditions, i.e., homogeneous Neumann conditions, on $\Gamma = \partial\Omega$. It is worth to remark, however, that the results presented here are also valid for other boundary conditions such as homogeneous Dirichlet and Robin (mixed).

Since the cells are far bigger than the interferon molecules and the virions, we can suppose that d is much smaller than both d_i and d_v. In order to compare the two latter diffusion coefficients, one can recall that interferons are biolomecules and virions in general have several proteins (including DNA or RNA). Under the light of this argument we assume that d_v is smaller than d_i, but both are of the same order. This leads to the following conditions,

$$0 < d \ll d_v \le d_i\,.$$

2.1.4 The reaction-diffusion (RD) model

Let $\Omega \subset \mathbb{R}^N$ $(N = 2, 3)$ be a bounded domain with Lipschitz boundary Γ, and let $T > 0$. We consider in $\Omega \times [0, T]$ a reaction-diffusion (RD) system

$$\left\{\begin{array}{rcl} \partial_t W &=& d\Delta W - iW - vW\,, \\ \partial_t I &=& d\Delta I - \mu_I I + vW\,, \\ \partial_t R &=& d\Delta R + iW\,, \\ \partial_t v &=& d_v\Delta v - \mu_v v + \alpha_v I - \alpha_4 vW\,, \\ \partial_t i &=& d_i\Delta i - \mu_i i + \alpha_i I - \alpha_3 iW\,, \end{array}\right. \tag{2.2}$$

with boundary conditions

$$\left\{\begin{array}{rcll} \nabla W\cdot \boldsymbol{n}(\sigma,t) &=& 0 & \text{on } \Gamma\times[0,T], \\ \nabla I\cdot \boldsymbol{n}(\sigma,t) &=& 0 & \text{on } \Gamma\times[0,T], \\ \nabla R\cdot \boldsymbol{n}(\sigma,t) &=& 0 & \text{on } \Gamma\times[0,T], \\ \nabla v\cdot \boldsymbol{n}(\sigma,t) &=& 0 & \text{on } \Gamma\times[0,T], \\ \nabla i\cdot \boldsymbol{n}(\sigma,t) &=& 0 & \text{on } \Gamma\times[0,T], \end{array}\right. \tag{2.3}$$

and initial conditions

$$\left\{\begin{array}{rcl} W(\boldsymbol{x},0) &=& W_0(\boldsymbol{x})\,, \\ I(\boldsymbol{x},0) &=& I_0(\boldsymbol{x})\,, \\ R(\boldsymbol{x},0) &=& R_0(\boldsymbol{x})\,, \\ v(\boldsymbol{x},0) &=& v_0(\boldsymbol{x})\,. \\ i(\boldsymbol{x},0) &=& i_0(\boldsymbol{x})\,. \end{array}\right. \tag{2.4}$$

2.1.5 The hybrid model

Since d is much smaller than both d_i and d_v it is plausible to consider that $d = 0$. Under this assumption we obtain a hybrid model consisting of PDE equations for the interferons i and virions v and ODE equations for the three types of cells W, I, R. The system takes the form

$$\left\{\begin{array}{rcl} \partial_t W &=& -iW - vW\,, \\ \partial_t I &=& -\mu_I I + vW\,, \\ \partial_t R &=& iW\,, \\ \partial_t v &=& d_v\Delta v - \mu_v v + \alpha_v I - \alpha_4 vW\,, \\ \partial_t i &=& d_i\Delta i - \mu_i i + \alpha_i I - \alpha_3 iW\,, \end{array}\right. \tag{2.5}$$

with boundary conditions

$$\left\{\begin{array}{rcll} \nabla v\cdot \boldsymbol{n}(\sigma,t) &=& 0 & \text{on } \Gamma\times[0,T], \\ \nabla i\cdot \boldsymbol{n}(\sigma,t) &=& 0 & \text{on } \Gamma\times[0,T]. \end{array}\right. \tag{2.6}$$

2.2 Main results

In this Section we formulate main results of the work. The proofs are presented in the following sections.

2.2.1 Existence and uniqueness results

Throughout this work we denote $\|\cdot\|$ the norm in $L^2(\Omega)$ and $\|\cdot\|_\infty$ the norm in $L^\infty(\Omega)$.

We will prove that both the RD and the hybrid models are well-posed problems, i.e., they have unique solutions (in the weak sense) which are non-negative, uniformly bounded, and depend continuously on the initial data.

Theorem 2.1 *Fix any $T > 0$. If the initial conditions (2.4) are non-negative a.e. and lie in $L^\infty(\Omega)$ then the RD system (2.2)-(2.3) has unique weak solutions $W(\boldsymbol{x},t)$, $I(\boldsymbol{x},t)$, $R(\boldsymbol{x},t)$, $v(\boldsymbol{x},t)$ and $i(\boldsymbol{x},t)$ on $\Omega\times[0,T]$. Moreover, these solutions are non-negative, uniformly bounded, and depend continuously on the initial data.*

Theorem 2.2 *Fix any $T > 0$. If the initial conditions (2.4) are non-negative a.e. and lie in $L^\infty(\Omega)$ then the hybrid system (2.5)-(2.6) has unique weak solutions $W(\boldsymbol{x},t)$, $I(\boldsymbol{x},t)$, $R(\boldsymbol{x},t)$, $v(\boldsymbol{x},t)$ and $i(\boldsymbol{x},t)$ on $\Omega\times[0,T]$. Moreover, these solutions are non-negative, bounded, and depend continuously on the initial data.*

We also prove that there is a "continuous link" between these two models, as the next result shows.

Theorem 2.3 *If $d \to 0$ then the solutions $(W^d, I^d, R^d, v^d, i^d)$ of the RD system (0.7)-(0.8) converge to the solution (W, I, R, v, i) of the hybrid system (0.10)-(0.11), in the following sense:*

- *Strongly in $L^2\left(0,T;L^2\left(\Omega\right)\right)$.*
- *Weakly in $L^2\left(0,T;H^1\left(\Omega\right)\right)$.*
- *Weakly-$\star$ in $L^\infty(\Omega\times(0,T))$.*

2.2.2 Asymptotic results for the RD system

Theorem 2.4

1. *The solutions W, I, R, v, i of the RD system (2.2)-(2.3) are globally-defined and belong to $L^\infty(\Omega\times(0,\infty))$.*
2. *If W, I, R, v, i are non-negative, steady-state solutions of the RD system (2.2)-(2.3) then*

$$\begin{aligned}
W(\boldsymbol{x}) &= W_0 \geq 0 \quad \text{constant},\\
I(\boldsymbol{x}) &\equiv 0,\\
R(\boldsymbol{x}) &= R_0 \geq 0 \quad \text{constant},\\
v(\boldsymbol{x}) &\equiv 0,\\
i(\boldsymbol{x}) &\equiv 0.
\end{aligned}$$

2.2.3 Asymptotic results for the hybrid system

Regularity of solutions W, I, R, v, i follows from a classical theory for evolution systems and depends on the regularity of initial conditions (see eg. [58], for reaction-diffusion systems coupled with ODEs). In the remainder of this paper we assume that the solutions are (at least) C^1.

Theorem 2.5 *If W, I, R, v, i are non-negative, steady-state solutions of the hybrid system (2.5)-(2.6) then*

$$\begin{aligned} I(\boldsymbol{x}) &\equiv 0, \\ v(\boldsymbol{x}) &\equiv 0, \\ i(\boldsymbol{x}) &\equiv 0. \end{aligned}$$

Moreover, suppose that the initial conditions belong to $L^\infty(\Omega)$. Then the solutions of the hybrid system (2.5)-(2.6) are globally-defined and have the following asymptotic properties:

1. *$I(\boldsymbol{x}, t)$ belongs to $L^1(0, \infty; L^2(\Omega))$, i.e.,*

$$\lim_{t\to\infty} \int_0^t \int_\Omega I^2(\boldsymbol{x}, s)\, d\Omega\, ds < \infty.$$

2. *$v(\boldsymbol{x}, t)$ and $i(\boldsymbol{x}, t)$ belong to $L^1(0, \infty; H^1(\Omega))$, i.e.,*

$$\lim_{t\to\infty} \int_0^t \left(\int_\Omega v^2(\boldsymbol{x}, s)\, d\Omega + \int_\Omega |\nabla v(\boldsymbol{x}, s)|^2\, d\Omega \right) ds < \infty\,,$$

$$\lim_{t\to\infty} \int_0^t \left(\int_\Omega i^2(\boldsymbol{x}, s)\, d\Omega + \int_\Omega |\nabla i(\boldsymbol{x}, s)|^2\, d\Omega \right) ds < \infty\,.$$

3. *$v(\boldsymbol{x}, t)W(\boldsymbol{x}, t)$ and $i(\boldsymbol{x}, t)W(\boldsymbol{x}, t)$ belong to $L^1(0, \infty; L^1(\Omega))$, i.e.,*

$$\lim_{t\to\infty} \int_0^t \int_\Omega v(\boldsymbol{x}, s)W(\boldsymbol{x}, s)\, d\Omega\, ds < \infty \quad \text{and} \quad \lim_{t\to\infty} \int_0^t \int_\Omega i(\boldsymbol{x}, s)W(\boldsymbol{x}, s)\, d\Omega\, ds < \infty\,.$$

4. *For any $\boldsymbol{x} \in \Omega$,*

$$\lim_{t\to\infty} I(\boldsymbol{x}, t) = 0\,, \quad \lim_{t\to\infty} v(\boldsymbol{x}, t) = 0\,, \quad \lim_{t\to\infty} i(\boldsymbol{x}, t) = 0\,.$$

5. *For any $\boldsymbol{x} \in \Omega$, $W_0(\boldsymbol{x}) > 0$ if and only if*

$$\lim_{t\to\infty} W(\boldsymbol{x}, t) > 0.$$

Theorem 2.6 *Consider the hybrid system (2.5)-(2.6) and suppose that $\mu_v = 0$. Then:*

1. *If $v_\infty(\boldsymbol{x})$ is a steady-state solution then $\|\nabla v_\infty\| = 0$.*

2. Define

$$v_\infty(\boldsymbol{x}) := \limsup_{t\to\infty} v(\boldsymbol{x}, t).$$

If $\alpha_v \geq \alpha_4\mu_I$ then

$$\int_\Omega v_\infty(\boldsymbol{x})\, d\Omega \geq \int_\Omega v_0(\boldsymbol{x})\, d\Omega.$$

In particular, if $v_0 \not\equiv 0$ then $v_\infty \not\equiv 0$.

2.3 Numerical simulations

In order to solve numerically the considered systems we used the method of lines, under which the system of nonlinear partial differential equations was converted to a large system of ordinary differential equations by discretising of Laplacian (three coordinates for the 1D Laplacian and five coordinates in the 2D case). The discretised system of ordinary differential equations was numerically solved using the CVODE package and numerical estimates of the Jacobian matrix. This program offers an implicit method for time discretization, originally developed for stiff problems of ODEs. Space discretization is a gridpoint on a unit interval. The size of the spatial grid is adjusted according to the value of the diffusion coefficient. Time discretization is performed implicitly. Homogeneous Neumann boundary conditions (zero flux) are implemented as a reflection at the boundary (see e.g. [2]). The graphical visualization of the numerical solutions in space and time is realized using Matlab.

The domain is the 2D square $[0,1]\times[0,1]$. The initial concentration in the 2D simulations are $W_0 = 1$ and $v_0 = 0.5$ on the sub-square $[0.4, 0.6]\times[0.4, 0.6]$ and zero otherwise. These initial conditions are exactly those in the numerical simulation of the ODE model in P. Getto *et al* [24]. For the simulation of the hybrid model we used a 30×30 grid in space and 50 time steps. The pictures correspond to the final stage $t = 50$. We fixed the parameters $\alpha_3 = 1$, $\alpha_4 = 4$, $\mu_I = 0.3$, $\mu_i = 0.4$ and $\alpha_i = 0.8$.

From the numerical simulations we could assess the effect of the spatial structure (i.e. the diffusion) in the virus proliferation:

- When $\mu_v > 0$ the viral diffusion plays against virions and helps the wild-type cells. In pictures 3.1-3.3 we can see that, as the diffusion coefficient grows, the concentration of wild-type cells seems to grow.

- When $\mu_v = 0$ the viral diffusion has a positive effect on the viral concentration and plays against the wild-type cells. In pictures 3.4-3.6 we can see that, as the diffusion coefficient grows, the concentration of virions grows as well.

As we can see in both cases, the spatial structure (represented by the diffusion term) has crucial effect on the final concentration of wild-type cells and virions. Indeed, if $\mu_v > 0$ the diffusion helps the cells and punishes the virions whilst if $\mu_v = 0$ it has the opposite effect.

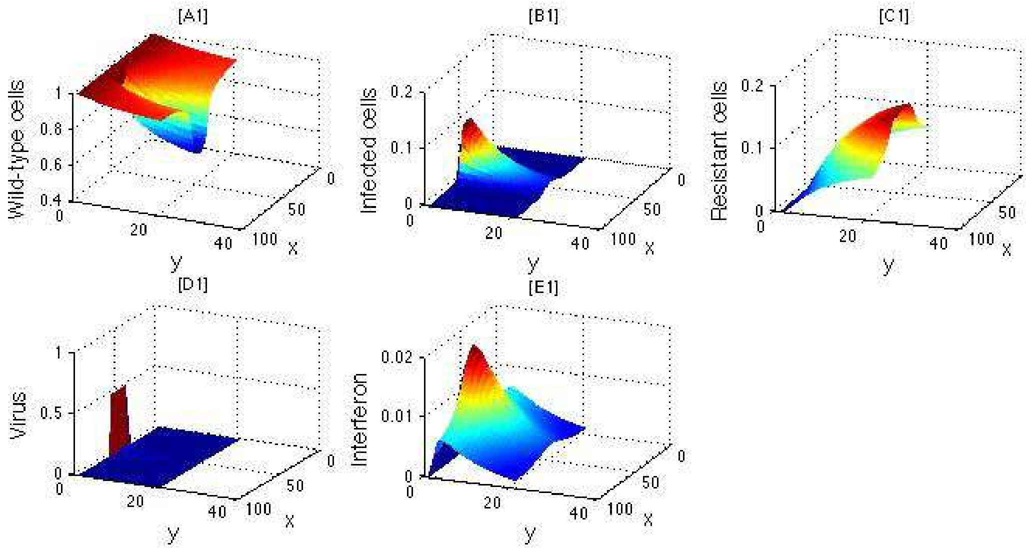

Figure 2.1: $d_v = 0.001$, $\mu_v = 0.2$ and $\alpha_v = 0.8$.

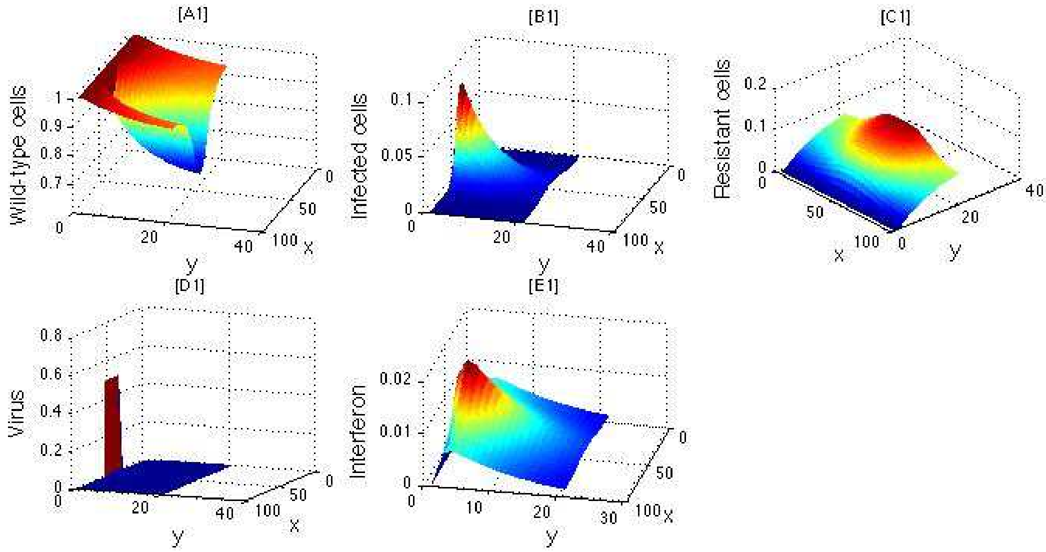

Figure 2.2: $d_v = 0.01$, $\mu_v = 0.2$ and $\alpha_v = 0.8$.

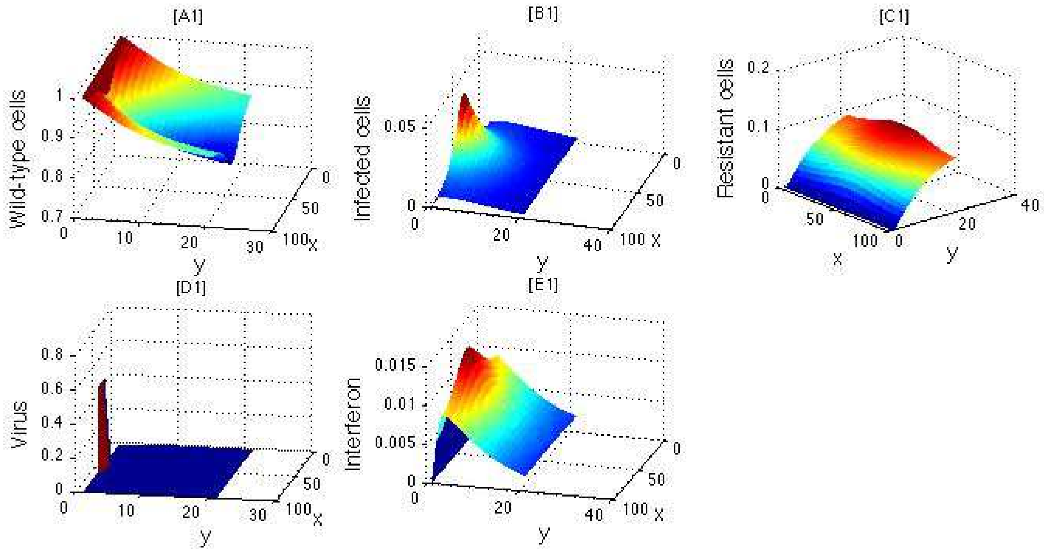

Figure 2.3: $d_v = 0.1$, $\mu_v = 0.2$ and $\alpha_v = 0.8$.

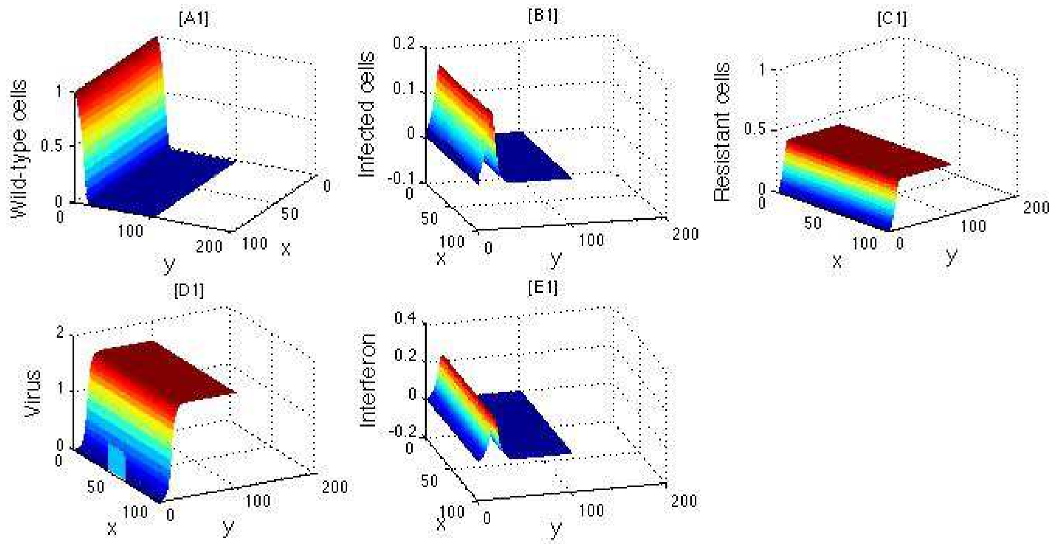

Figure 2.4: $d_v = 1$, $\mu_v = 0$ and $\alpha_v = 2$.

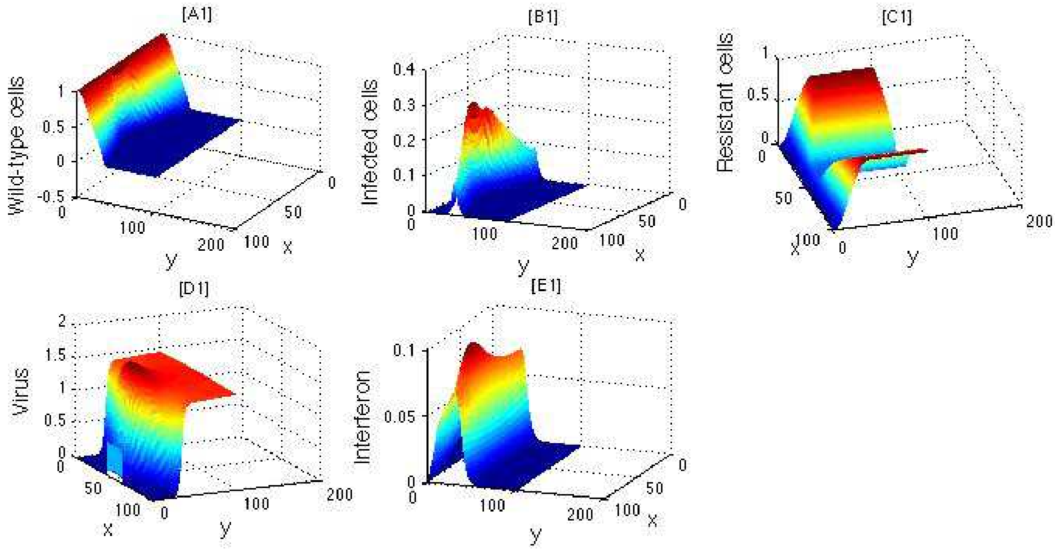

Figure 2.5: $d_v = 0.001$, $\mu_v = 0$ and $\alpha_v = 2$.

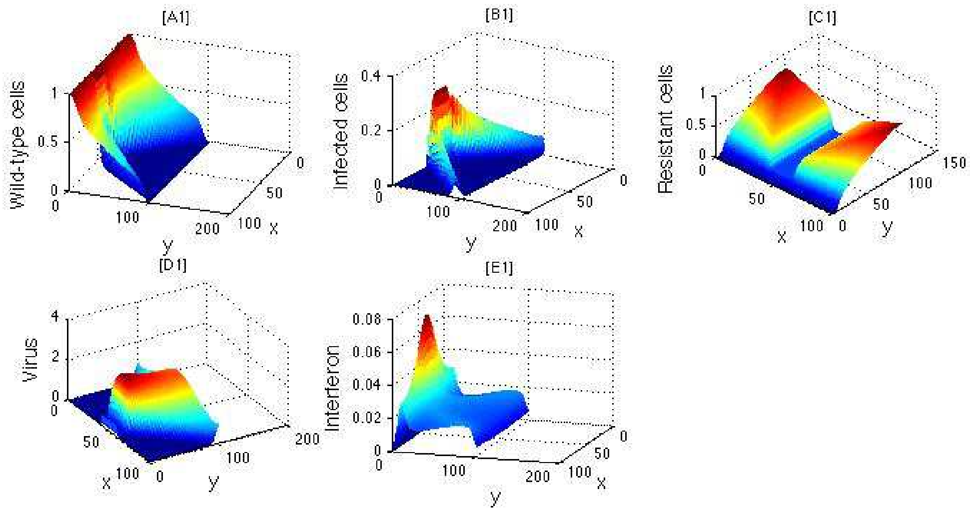

Figure 2.6: $d_v = 0.0001$, $\mu_v = 0$ and $\alpha_v = 2$.

2.4 The fixed point operator and a priori estimates

2.4.1 Construction of the fixed point operator $\mathcal{R}$

Our approach follows the ideas used by K. Hamdache and M. Labadie in [39].

Define

$$\mathcal{K} := \left\{ (v^\sharp, i^\sharp) \in L^2\left(0, T; \left[L^2(\Omega)\right]^2\right) \cap [L^\infty(\Omega \times [0,T])]^2 \,:\, v^\sharp(\boldsymbol{x}, t) \geq 0,\, i^\sharp(\boldsymbol{x}, t) \geq 0 \text{ a.e. in } \Omega \times [0,T] \right\}.$$

Fix $(v^\sharp, i^\sharp) \in \mathcal{K}$ and set

$$\begin{aligned} \partial_t W - d\Delta W + i^\sharp W + v^\sharp W &= 0 && \text{in } \Omega \times (0,T), \\ \partial_t I - d\Delta I + \mu_I I - v^\sharp W &= 0 && \text{in } \Omega \times (0,T), \\ \partial_t R - d\Delta R - i^\sharp W &= 0 && \text{in } \Omega \times (0,T), \\ \nabla W \cdot \mathbf{n}(\sigma, t) &= 0 && \text{on } \Gamma \times [0,T], \\ \nabla I \cdot \mathbf{n}(\sigma, t) &= 0 && \text{on } \Gamma \times [0,T], \\ \nabla R \cdot \mathbf{n}(\sigma, t) &= 0 && \text{on } \Gamma \times [0,T]. \end{aligned} \tag{2.7}$$

For any finite time interval $[0,T]$, the linear system (2.7) has a unique solution $(W(\boldsymbol{x},t), I(\boldsymbol{x},t), R(\boldsymbol{x},t))$, which is non-negative and bounded.

With these functions $W(\boldsymbol{x},t)$, $I(\boldsymbol{x},t)$ and $R(\boldsymbol{x},t)$ set

$$\begin{aligned} \partial_t v - d_v \Delta v + \mu_v v - \alpha_v I + \alpha_4 v W &= 0 && \text{in } \Omega \times (0,T), \\ \partial_t i - d_i \Delta i + \mu_i i - \alpha_i I + \alpha_3 i W &= 0 && \text{in } \Omega \times (0,T), \\ \nabla v \cdot \mathbf{n}(\sigma, t) &= 0 && \text{on } \Gamma \times [0,T]. \\ \nabla i \cdot \mathbf{n}(\sigma, t) &= 0 && \text{on } \Gamma \times [0,T], \end{aligned} \tag{2.8}$$

Again, for any finite time interval $[0,T]$ the linear, uncoupled system (2.8) has a unique solution $(v(\boldsymbol{x},t), i(\boldsymbol{x},t))$, which is non-negative and bounded.

Our goal is to show that the operator $\mathcal{R}[(v^\sharp, i^\sharp)] := (v, i)$, defined for the chain of maps $(v^\sharp, i^\sharp) \mapsto (W, I, R) \mapsto (i, v)$ constructed above, has a fixed point.

2.4.2 Positivity of solutions

From now on we will assume that the coefficients

$$d, d_v, d_i, \mu_I, \mu_v, \mu_i, \alpha_3, \alpha_4$$

are all positive, and that the initial conditions (2.4) are non-negative and bounded.

Lemma 2.1 *Let $(v^\sharp, i^\sharp) \mapsto (W, I, R) \mapsto (v, i)$ be solutions of (2.7)-(2.8).*

1. If $v^\sharp$ and $i^\sharp$ are non-negative and bounded then W, I and R are non-negative and bounded.

2. If W, I and R are non-negative and bounded then v and i are non-negative and bounded.

<u>*Proof*</u>:

1. The equation for W is

$$\begin{aligned} \partial_t W - d\Delta W + (i^\sharp + v^\sharp)W &= 0 && \text{in } \Omega \times (0,T), \\ \nabla W \cdot \mathbf{n}(\sigma,t) &= 0 && \text{on } \Gamma \times [0,T], \\ W(\boldsymbol{x},0) = W_0(\boldsymbol{x}) &\geq 0 && \text{in } \Omega. \end{aligned}$$

Applying Maximum Principle we obtain that $W(\boldsymbol{x},t) \geq 0$ for all $(\boldsymbol{x},t) \in \Omega \times (0,T)$.

Define $Z_1 := W - \gamma_1$, where $\gamma_1 \in \mathbb{R}$. Then Z_1 solves

$$\begin{aligned} \partial_t Z_1 - d\Delta Z_1 + (i^\sharp + v^\sharp)Z_1 &= -(i^\sharp + v^\sharp)\gamma_1 && \text{in } \Omega \times (0,T), \\ \nabla Z_1 \cdot \mathbf{n}(\sigma,t) &= 0 && \text{on } \Gamma \times [0,T], \\ Z_1(\boldsymbol{x},0) &= W_0(\boldsymbol{x}) - \gamma_1 && \text{in } \Omega. \end{aligned}$$

Choosing $\gamma_1 = \|W_0\|_\infty$ and using non-negativity of $i^\sharp$ and $v^\sharp$ we obtain

$$\begin{aligned} \partial_t Z_1 - d\Delta Z_1 + (i^\sharp + v^\sharp)Z_1 &\leq 0 && \text{in } \Omega \times (0,T), \\ \nabla Z_1 \cdot \mathbf{n}(\sigma,t) &= 0 && \text{on } \Gamma \times [0,T], \\ Z_1(\boldsymbol{x},0) &\leq 0 && \text{in } \Omega. \end{aligned}$$

Hence, Maximum Principle implies that $Z_1(\boldsymbol{x},t) \leq 0$ for all $(\boldsymbol{x},t) \in \Omega \times (0,T)$, and in consequence $W(\boldsymbol{x},t) \leq \|W_0\|_\infty$ for all $(\boldsymbol{x},t) \in \Omega \times (0,T)$.

For I, notice that $v^\sharp$ and W are non-negative. Therefore, similarly as above Maximum Principle yields that $I(\boldsymbol{x},t) \geq 0$ for all $(\boldsymbol{x},t) \in \Omega \times (0,T)$.

Now, due to the boundedness of I, the function $Z_2 := I - \gamma_2$ solves

$$\begin{aligned} \partial_t Z_2 - d\Delta I + \mu_I Z_2 &= v^\sharp W - \mu_I \gamma_2 && \text{in } \Omega \times (0,T), \\ \nabla Z_2 \cdot \mathbf{n}(\sigma,t) &= 0 && \text{on } \Gamma \times [0,T], \\ Z_2(\boldsymbol{x},0) &= I_0(\boldsymbol{x}) - \gamma_2 && \text{in } \Omega. \end{aligned}$$

Choosing

$$\gamma_2 = \max\left\{ \|I_0\|_\infty, \frac{\|v^\sharp\|_\infty \|W_0\|_\infty}{\mu_I} \right\}$$

and applying Maximum Principle, we obtain that $I(\boldsymbol{x},t) \leq \gamma_2$ for all $(\boldsymbol{x},t) \in \Omega \times (0,T)$.

Finally, Maximum Principle implies that $R(\boldsymbol{x},t) \geq 0$ for all $(\boldsymbol{x},t) \in \Omega \times (0,T)$. For the boundedness of R, define $Z_3 := R - \gamma_3(t)$. It yields

$$\begin{aligned} \partial_t Z_3 - d\Delta I = i^\sharp W - \gamma_3'(t) \qquad & \text{in } \Omega \times (0,T), \\ \nabla Z_3 \cdot \mathbf{n}(\sigma,t) = 0 \qquad & \text{on } \Gamma \times [0,T], \\ Z_3(\boldsymbol{x},0) = R_0(\boldsymbol{x}) - \gamma_3(0) \qquad & \text{in } \Omega. \end{aligned}$$

Choosing

$$\gamma_3(t) = \|R_0\|_\infty + t\|i^\sharp\|_\infty \|W_0\|_\infty$$

and applying Maximum Principle we obtain that $R(\boldsymbol{x},t) \leq \gamma_3(t)$ for all $(\boldsymbol{x},t) \in \Omega \times (0,T)$.

2. Using the same argument as before we can prove that $0 \leq v(\boldsymbol{x},t) \leq \gamma_4$ and $0 \leq i(\boldsymbol{x},t) \leq \gamma_5$ for all $(\boldsymbol{x},t) \in \Omega \times (0,T)$, where

$$\gamma_4 = \max\left\{ \|v_0\|_\infty, \frac{\alpha_v \|I_0\|_\infty}{\mu_v} \right\}, \quad \gamma_5 = \max\left\{ \|i_0\|_\infty, \frac{\alpha_i \|I_0\|_\infty}{\mu_i} \right\}. \quad \square$$

2.4.3 A priori estimates

Lemma 2.2 *Let $(v^\sharp, i^\sharp) \mapsto (W,I,R) \mapsto (v,i)$ be solutions of (2.7)-(2.8). Then the functions W,I,R,v,i belong to $L^2\left(0,T;H^1(\Omega)\right)$.*

Proof:

- Multiply (2.7) by W and integrate by parts to obtain

$$\frac{1}{2}\frac{d}{dt}\|W\|^2 + d\|\nabla W\|^2 = -\int_\Omega (i^\sharp + v^\sharp) W^2 \, d\Omega \, .$$

Since $i^\sharp$ and $v^\sharp$ are non-negative, it follows that

$$\frac{1}{2}\frac{d}{dt}\|W\|^2 + d\|\nabla W\|^2 \leq 0 \, .$$

Integrating over $[0,t]$ yields

$$\|W(t)\|^2 + 2d\int_0^t \|\nabla W(s)\|^2 \, ds \leq \|W(0)\|^2 \, .$$

- Multiply (2.7) by I and integrate by parts to obtain

$$\frac{1}{2}\frac{d}{dt}\|I\|^2 + d\|\nabla I\|^2 + \mu_I \|I\|^2 = \int_\Omega v^\sharp W I \, d\Omega \, .$$

Recall the identity

$$\int_\Omega |v^\sharp W I| \, d\Omega \leq \frac{1}{4\varepsilon}\int_\Omega |v^\sharp W|^2 \, d\Omega + \varepsilon \int_\Omega |I|^2 \, d\Omega \, .$$

Choosing $\varepsilon = \mu_I/2$ and using the uniform bounds in Lemma 2.1, it follows that there is a constant $C > 0$, depending on the L^∞ norm of the initial data, such that

$$\frac{d}{dt}\|I\|^2 + 2d\|\nabla I\|^2 + \mu_I\|I\|^2 \leq C\,.$$

Here we can keep or discard the term $\mu_I\|I\|^2$, leading to two different estimates:

– If we discard the term, the integration over $[0, T]$ yields

$$\|I(t)\|^2 + 2d\int_0^t \|\nabla I(s)\|^2\,ds \leq \|I(0)\|^2 + Ct\,,$$

which implies that $I \in L^2\big(0, T; H^1(\Omega)\big)$.

– If we keep the term, after multiplying by $e^{\mu_I t}$ and integrating over $[0, T]$,

$$\|e^{\mu_I t/2} I(t)\|^2 + 2d\int_0^t e^{\mu_I s}\|\nabla I(s)\|^2\,ds \leq \|I(0)\|^2 + C(e^{\mu_I t} - 1)\,.$$

Therefore,

$$\|I(t)\|^2 + 2d\int_0^t e^{-\mu_I(t-s)}\|\nabla I(s)\|^2\,ds \leq \|I(0)\|^2 e^{-\mu_I t} + C(1 - e^{-\mu_I t})\,.$$

This estimate will be useful for the study of the asymptotic behavior when $t \to \infty$.

- Multiply (2.7) by R and integrate by parts to obtain

$$\frac{1}{2}\frac{d}{dt}\|R\|^2 + d\|\nabla R\|^2 = \int_\Omega iWR\,d\Omega\,.$$

Therefore,

$$\frac{d}{dt}\|R\|^2 + 2d\|\nabla R\|^2 \leq C + \|R\|^2\,.$$

Multiplying by e^{-t} and integrating over $[0, t]$ leads to

$$\|R(t)\|^2 + 2d\int_0^t e^{t-s}\|\nabla R(s)\|^2\,ds \leq \|R(0)\|^2 e^t + C(e^t - 1)\,.$$

- Repeating the argument for v and i yields

$$\begin{aligned}
\|v(t)\|^2 + 2d_v\int_0^t \|\nabla v(s)\|^2\,ds &\leq \|v(0)\|^2 + Ct,\\
\|v(t)\|^2 + 2d_v\int_0^t e^{-\mu_v(t-s)}\|\nabla v(s)\|^2\,ds &\leq \|v(0)\|^2 e^{-\mu_v t} + C(1 - e^{-\mu_v t}),\\
\|i(t)\|^2 + 2d_i\int_0^t \|\nabla i(s)\|^2\,ds &\leq \|i(0)\|^2 + Ct,\\
\|i(t)\|^2 + 2d_i\int_0^t e^{-\mu_i(t-s)}\|\nabla i(s)\|^2\,ds &\leq \|i(0)\|^2 e^{-\mu_i t} + C(1 - e^{-\mu_i t}). \quad \square
\end{aligned}$$

2.4.4 Continuity of the operator $\mathcal{R}$

Let $(v_1^\sharp, i_1^\sharp) \mapsto (W_1, I_1, R_1) \mapsto (v_1, i_1)$ and $(v_2^\sharp, i_2^\sharp) \mapsto (W_2, I_2, R_2) \mapsto (v_2, i_2)$ be two solutions of the systems (2.7)-(2.8), with the same initial conditions $(v_0^\sharp = v_0, i_0^\sharp = i_0, W_0, I_0, R_0, v_0, i_0)$.

Define

$$
\begin{aligned}
\hat{v}^\sharp &= v_2^\sharp - v_1^\sharp \,, \\
\hat{i}^\sharp &= i_2^\sharp - i_1^\sharp \,, \\
\hat{W} &= W_2 - W_1 \,, \\
\hat{I} &= I_2 - I_1 \,, \\
\hat{R} &= R_2 - R_1 \,, \\
\hat{v} &= v_2 - v_1 \,, \\
\hat{i} &= i_2 - i_1 \,.
\end{aligned}
$$

Lemma 2.3 *There exists a positive continuous function $C(t)$ such that*

$$
\left[\int_0^t \left(\|\hat{v}\|^2 + \|\hat{i}\|^2 \right) ds \right] \le C(t) \left[\int_0^t \left(\|\hat{v}^\sharp\|^2 + \|\hat{i}^\sharp\|^2 \right) ds \right] . \tag{2.9}
$$

<u>*Proof*</u>: The differences $\hat{v}$, $\hat{i}$, $\hat{W}$, $\hat{I}$, $\hat{R}$ solve the system

$$
\begin{aligned}
\partial_t \hat{v} - d_v \Delta \hat{i} + \mu_v \hat{v} + \alpha_4 W_2 \hat{v} + \alpha_4 \hat{v}_1 \hat{W} - \alpha_v \hat{I} &= 0 \,, \\
\partial_t \hat{i} - d_i \Delta \hat{i} + \mu_i \hat{i} + \alpha_3 W_2 \hat{i} + \alpha_3 i_1 \hat{W} - \alpha_i \hat{I} &= 0 \,, \\
\partial_t \hat{W} - d \Delta \hat{W} + i_2^\sharp \hat{W} + W_1 \hat{i}^\sharp + v_2^\sharp \hat{W} + W_1 \hat{v}^\sharp &= 0 \,. \\
\partial_t \hat{I} - d \Delta \hat{I} + \mu_I \hat{I} + W_2 \hat{v}^\sharp + v_1^\sharp \hat{W} &= 0 \,, \\
\partial_t \hat{R} - d \Delta \hat{R} + i_2^\sharp \hat{W} + W_1 \hat{i}^\sharp &= 0 \,.
\end{aligned}
$$

with homogeneous initial and boundary conditions.

Multiply the equation for $\hat{I}$ by $\hat{I}$ and integrate by parts to obtain

$$
\frac{1}{2} \frac{d}{dt} \|\hat{I}\|^2 + d \|\nabla \hat{I}\|^2 + \mu_I \|\hat{I}\|^2 = - \int_\Omega \hat{v}^\sharp W_2 \hat{I} \, d\Omega + \int_\Omega v_1^\sharp \hat{W} \hat{I} \, d\Omega \,.
$$

Noticing that all the functions are in L^∞, we deduce that there exists $C > 0$, depending on the initial conditions and the model coefficients, such that

$$
\frac{d}{dt} \|\hat{I}\|^2 + 2d \|\nabla \hat{I}\|^2 \le C \left(\|\hat{v}^\sharp\|^2 + \|\hat{W}\|^2 + \|\hat{I}\|^2 \right) . \tag{2.10}
$$

Using the same argument we can show that

$$
\begin{aligned}
\frac{d}{dt} \|\hat{W}\|^2 + 2d \|\nabla \hat{W}\|^2 &\le C \left(\|\hat{i}^\sharp\|^2 + \|\hat{v}^\sharp\|^2 + \|\hat{W}\|^2 \right) , \qquad (2.11) \\
\frac{d}{dt} \|\hat{R}\|^2 + 2d \|\nabla \hat{R}\|^2 &\le C \left(\|\hat{i}^\sharp\|^2 + \|\hat{W}\|^2 \right) .
\end{aligned}
$$

From (2.10)-(2.11) and $d \geq 0$, it follows that

$$\frac{d}{dt}\left(\|\hat{W}\|^2 + \|\hat{I}\|^2 + \|\hat{R}\|^2\right) \leq C\left(\|\hat{i}^\sharp\|^2 + \|\hat{v}^\sharp\|^2 + \|\hat{W}\|^2 + \|\hat{I}\|^2\right).$$

Integrating over $[0,t]$ we obtain that

$$\|\hat{W}\|^2 + \|\hat{I}\|^2 + \|\hat{R}\|^2 \leq C\left[\int_0^t \left(\|\hat{i}^\sharp\|^2 + \|\hat{v}^\sharp\|^2\right) ds\right] + C\left[\int_0^t \left(\|\hat{W}\|^2 + \|\hat{I}\|^2\right) ds\right].$$

Applying Gronwall's Lemma it follows that there exists a positive continuous function $C(t)$ such that

$$\|\hat{W}\|^2 + \|\hat{I}\|^2 + \|\hat{R}\|^2 \leq C(t)\left[\int_0^t \left(\|\hat{i}^\sharp\|^2 + \|\hat{v}^\sharp\|^2\right) ds\right]. \tag{2.12}$$

On the other hand, multiply the equation for $\hat{i}$ by $\hat{i}$ and integrate by parts to obtain

$$\frac{1}{2}\frac{d}{dt}\|\hat{i}\|^2 + d_i\|\nabla\hat{i}\|^2 + \mu_i\|\hat{i}\|^2 + \alpha_3\int_\Omega W_2\hat{i}^2\, d\Omega = -\alpha_3\int_\Omega i_1\hat{W}\hat{i}\, d\Omega + \alpha_i\int_\Omega \hat{I}\hat{i}\, d\Omega\,.$$

Proceeding as before we can show that there exists a constant $C_1 > 0$ such that

$$\frac{d}{dt}\|\hat{i}\|^2 + 2d_i\|\nabla\hat{i}\|^2 \leq C_1\left(\|\hat{i}\|^2 + \|\hat{W}\|^2 + \|\hat{I}\|^2\right).$$

Analogously, we can show that

$$\frac{d}{dt}\|\hat{v}\|^2 + 2d_v\|\nabla\hat{v}\|^2 \leq C_1\left(\|\hat{v}\|^2 + \|\hat{W}\|^2 + \|\hat{I}\|^2\right).$$

Using (2.12) we obtain that

$$\frac{d}{dt}\left(\|\hat{i}\|^2 + \|\hat{v}\|^2\right) \leq C_1\left(\|\hat{i}\|^2 + \|\hat{v}\|^2\right) + C(t)\left[\int_0^t \left(\|\hat{i}^\sharp\|^2 + \|\hat{v}^\sharp\|^2\right) ds\right].$$

Integrating over $[0,t]$ yields

$$\|\hat{i}\|^2 + \|\hat{v}\|^2 \leq C_1\left[\int_0^t \left(\|\hat{i}\|^2 + \|\hat{v}\|^2\right) ds\right] + C(t)\left[\int_0^t \left(\|\hat{i}^\sharp\|^2 + \|\hat{v}^\sharp\|^2\right) ds\right].$$

Applying Gronwall's Lemma, it follows that

$$\|\hat{i}\|^2 + \|\hat{w}\|^2 \leq C(t)\left[\int_0^t \left(\|\hat{i}^\sharp\|^2 + \|\hat{v}^\sharp\|^2\right) ds\right].$$

Integrating again over $[0,t]$ we obtain (2.9). $\Box$

2.5 Proof of the theorems

2.5.1 Proof of Theorem 2.1

Lemma 2.4 *Fix a positive time $T > 0$. Then:*

1. *$\mathcal{K}$ is a convex closed subset of $L^2\left(0, T; \left[L^2(\Omega)\right]^2\right)$.*
2. *$\mathcal{R} : \mathcal{K} \to \mathcal{K}$.*
3. *$\mathcal{R} : L^2\left(0, T; \left[L^2(\Omega)\right]^2\right) \to L^2\left(0, T; \left[L^2(\Omega)\right]^2\right)$ is continuous.*
4. *$\mathcal{R}(\mathcal{K})$ is relatively compact in $L^2\left(0, T; \left[L^2(\Omega)\right]^2\right)$.*

Proof:

1. By construction, $\mathcal{K}$ is convex and closed.

2. If $i^\sharp \geq 0$ and $v^\sharp \geq 0$ then from Lemma 2.1 it follows that $i \geq 0$ and $v \geq 0$.

3. By Lemma 2.3 the operator $\mathcal{R}$ is continuous.

4. We will use Aubin's compactness theorem (see Theorem 5.1 in Lions [45], Section 5.5, pp. 57-64, and Tartar [63], Chapter 24, pp. 137-141). Suppose that the sequence $\{(v_n^\sharp, i_n^\sharp)\}$ is uniformly bounded in $L^2\left(0, T; \left[L^2(\Omega)\right]^2\right)$. Then, by the continuity of $\mathcal{R}$, the sequence $\{\mathcal{R}[(v_n^\sharp, i_n^\sharp)] = (v_n, i_n)\}$ is also uniformly bounded in $L^2\left(0, T; \left[L^2(\Omega)\right]\right)$, and the estimates in Lemma 2.2 imply that $\{(v_n, i_n)\}$ is uniformly bounded in $L^2\left(0, T; \left[H^1(\Omega)\right]^2\right)$. Furthermore, the sequence of derivatives $\{(\partial_t v_n, \partial_t i_n)\}$ is uniformly bounded in $L^2\left(0, T; \left[H^{-1}(\Omega)\right]^2\right)$, because the expressions
$$\begin{aligned}\partial_t v_n &= \nabla \cdot (d_v \nabla v_n) - \mu_v v_n + \alpha_v I_n - \alpha_4 v_n W_n\,,\\ \partial_t i_n &= \nabla \cdot (d_i \nabla i_n) - \mu_i i_n + \alpha_i I_n - \alpha_3 i_n W_n\,,\end{aligned}$$
define two uniformly bounded sequences of distributions in $H^1(\Omega)$. Therefore, applying Aubin's theorem to the spaces $\left[H^1(\Omega)\right]^2 \subset \left[L^2(\Omega)\right]^2 \subset \left[H^{-1}(\Omega)\right]^2$, we obtain that the sequence $\{(v_n, i_n)\}$ is relatively compact in $L^2\left(0, T; \left[L^2(\Omega)\right]^2\right)$. $\square$

We can now conclude the existence of solutions of the reaction-diffusion system (2.2)-(2.3):

From Lemma 2.4 we see that the operator $\mathcal{R}$ satisfies Schauder's Fixed Point Theorem (Corollary B.3, p. 262 in Taylor [65]). Therefore, the system (2.2)-(2.3) has solutions W, I, R, v, i.

Moreover, from the fact that v and i coincide with $v^\sharp$ and $i^\sharp$, respectively, we can derive two consequences. First, from Lemma 2.1 it follows that W, I, R, v, i are non-negative and bounded. Second, from Lemma 2.2 we have that W, I, R, v, i belong to $L^2\left(0, T; \left[H^1(\Omega)\right]^2\right)$.

Lemma 2.5 *The solutions $W(\boldsymbol{x}, t)$, $I(\boldsymbol{x}, t)$, $R(\boldsymbol{x}, t)$, $v(\boldsymbol{x}, t)$ and $i(\boldsymbol{x}, t)$ of the reaction-diffusion system (2.2)-(2.3) are unique and depend continuously on the initial data (2.4).*

Proof: Notice that v and i coincide with $v^\sharp$ and $i^\sharp$, respectively. Bearing this in mind, and repeating the arguments in Lemma 2.3, we can show that there is a positive constant C such that

$$\frac{d}{dt}\left(\|\hat{W}\|^2 + \|\hat{I}\|^2 + \|\hat{R}\|^2 + \|\hat{v}\|^2 + \|\hat{i}\|^2\right) \leq C\left(\|\hat{W}\|^2 + \|\hat{I}\|^2 + \|\hat{R}\|^2 + \|\hat{v}\|^2 + \|\hat{i}\|^2\right).$$

Therefore, Gronwall's lemma implies that there exists a positive continuous function $C(t)$ such that

$$\|\hat{W}\|^2 + \|\hat{I}\|^2 + \|\hat{R}\|^2 + \|\hat{v}\|^2 + \|\hat{i}\|^2 \leq C(t)\left(\|\hat{W}_0\|^2 + \|\hat{I}_0\|^2 + \|\hat{R}_0\|^2 + \|\hat{v}_0\|^2 + \|\hat{i}_0\|^2\right). \quad \square$$

2.5.2 Proof of Theorem 2.2

So far we have only considered the reaction-diffusion system (2.2)-(2.3). However, for the hybrid system (2.5)-(2.6) the same results hold. Indeed, on one hand, in Lemmas 2.2-2.5 we have only used that $d \geq 0$. On the other hand, we can use the integral representations of W, I and R in order to deduce that they are bounded and non-negative, which proves the analogue of Lemma 2.1 in the hybrid case. $\square$

2.5.3 Proof of Theorem 2.3

For any $0 < d \leq d_0$ let $(W^d, I^d, R^d, v^d, i^d)$ be a weak solution of (2.2)-(2.3) and let $d \to 0$.

First, from Lemma 2.2 it follows that the sequence W^d is bounded in

$$L^2\left(0, T; H^1(\Omega)\right) \cap L^\infty(\Omega \times (0, T)),$$

which implies that a subsequence, still denoted W^d, converges weakly in $L^2\left(0, T; H^1(\Omega)\right)$ and weakly-$\star$ in $L^\infty(\Omega \times (0, T))$ to W^0. This result is also valid for the sequences I^d, R^d v^d and i^d.

Second, using classical estimates of type

$$\int_0^T \int_\Omega |i^d W^d - i^0 W^0| \, d\Omega dt \leq C_1 \|i^d - i^0\| + C_2 \|W^d - W^0\|$$

it can be shown that the sequence $\partial_t W^d$ is uniformly bounded in $L^2\left(0, T; H^{-1}(\Omega)\right)$. In consequence, applying Aubin's compactness theorem yields the strong convergence $i^d \to i^0$ in $L^2\left(0, T; L^2(\Omega)\right)$. This result is also valid for the sequences I^d, R^d v^d and i^0.

Finally, we obtain that a subsequence $(W^d, I^d, R^d, v^d, i^d)$ of weak solutions of (2.2)-(2.3) converges strongly in $L^2\left(0, T; L^2(\Omega)\right)$, weakly in $L^2\left(0, T; H^1(\Omega)\right)$ and weakly-$\star$ in $L^\infty(\Omega \times (0,T))$. Since the limit $(W^0, I^0, R^0, v^0, i^0)$ is by construction a weak solution of (2.5)-(2.6), the uniqueness of the hybrid system (2.5)-(2.6) implies that the limit is the same for any converging subsequence. $\square$

2.5.4 Proof of Theorem 2.4

Lemma 2.6 *The solutions W, I, R, v, i of the RD system (2.2)-(2.3) are globally-defined and belong to $L^\infty(\Omega \times (0, \infty))$.*

<u>*Proof*</u>:

1. Define $N(\boldsymbol{x}, t) := W(\boldsymbol{x}, t) + I(\boldsymbol{x}, t) + R(\boldsymbol{x}, t)$. Then N satisfies

$$\begin{cases} \partial_t N - d\Delta N \leq 0 & \text{in } \Omega \times [0, T], \\ \nabla N \cdot \boldsymbol{n} = 0 & \text{on } \Gamma \times [0, T]. \end{cases}$$

   Therefore, Maximum Principle provides

$$N(\boldsymbol{x}, t) \leq \|N_0\|_\infty \quad \forall (\boldsymbol{x}, t) \in \Omega \times [0, T].$$

   Moreover, since this bound is independent of t and T, it follows that $N(\boldsymbol{x}, t)$ is defined for all $t \in \mathbb{R}$. In consequence, the positivity of W, I, R implies that these three functions exist for all times and that they are uniformly bounded, i.e.,

$$W(\boldsymbol{x}, t),\ I(\boldsymbol{x}, t),\ R(\boldsymbol{x}, t) \leq \|N_0\|_\infty \quad \forall (\boldsymbol{x}, t) \in \Omega \times [0, \infty).$$

2. From Lemma 2.1 we obtain that $0 \leq v(\boldsymbol{x}, t) \leq \gamma_4$ and $0 \leq i(\boldsymbol{x}, t) \leq \gamma_5$ for all $(\boldsymbol{x}, t) \in \Omega \times (0, T)$, where

$$\gamma_4 = \max\left\{\|v_0\|_\infty, \frac{\alpha_v \|I_0\|_\infty}{\mu_v}\right\}, \quad \gamma_5 = \max\left\{\|i_0\|_\infty, \frac{\alpha_i \|I_0\|_\infty}{\mu_i}\right\}.$$

   Again, since the bounds are independent of t and T, the solutions v and i exist for all times. $\square$

Lemma 2.7 *If W, I, R, i, v are non-negative, steady-state solutions of the RD system (2.2)-(2.3) then*

$$\begin{aligned} W(\boldsymbol{x}) &= W_0 \geq 0 \quad \text{constant}, \\ I(\boldsymbol{x}) &\equiv 0, \\ R(\boldsymbol{x}) &= R_0 \geq 0 \quad \text{constant}, \\ v(\boldsymbol{x}) &\equiv 0, \\ i(\boldsymbol{x}) &\equiv 0. \end{aligned}$$

<u>*Proof*</u>: If W, I, R, i, v are non-negative, steady-state solutions of system (2.2)-(2.3), then

$$\left\{\begin{array}{rcl} -d\Delta W & = & -iW - vW\,, \\ -d\Delta I & = & -\mu_I I + vW\,, \\ -d\Delta R & = & iW\,, \\ -d_v\Delta v & = & -\mu_v v + \alpha_v I - \alpha_4 vW\,, \\ -d_i\Delta i & = & -\mu_i i + \alpha_i I - \alpha_3 iW\,, \end{array}\right. \tag{2.13}$$

with boundary conditions

$$\left\{\begin{array}{rcll} \nabla W\cdot \boldsymbol{n}(\sigma) & = & 0 & \text{on } \Gamma, \\ \nabla I\cdot \boldsymbol{n}(\sigma) & = & 0 & \text{on } \Gamma, \\ \nabla R\cdot \boldsymbol{n}(\sigma) & = & 0 & \text{on } \Gamma, \\ \nabla v\cdot \boldsymbol{n}(\sigma) & = & 0 & \text{on } \Gamma, \\ \nabla i\cdot \boldsymbol{n}(\sigma) & = & 0 & \text{on } \Gamma. \end{array}\right. \tag{2.14}$$

Multiplying the equation for W by W and integrating by parts we obtain

$$d\|\nabla W\|^2 + \int_\Omega (i+v)W^2\, d\Omega = 0.$$

Therefore $iW = vW = 0$ and $W(\boldsymbol{x}) = W_0$ constant. Using same argument for I yields

$$d\|\nabla I\|^2 + \mu_I\|I\|^2 = 0,$$

which implies that $I(\boldsymbol{x}) \equiv 0$. For R we obtain

$$d\|\nabla R\|^2 = 0,$$

and therefore, $R(\boldsymbol{x}) = R_0$ is constant, whilst for v, i we obtain

$$\begin{array}{rcl} d_v\|\nabla v\|^2 + \mu_v\|v\|^2 & = & 0, \\ d_i\|\nabla i\|^2 + \mu_i\|i\|^2 & = & 0, \end{array}$$

and, in consequence, $v(\boldsymbol{x}) = i(\boldsymbol{x}) \equiv 0$. $\square$.

2.5.5 Proof of Theorem 2.5

Lemma 2.8 *If W, I, R, i, v are non-negative, steady-state solutions of the hybrid system (2.5)-(2.6) then*

$$\begin{array}{rcl} I(\boldsymbol{x}) & \equiv & 0, \\ v(\boldsymbol{x}) & \equiv & 0, \\ i(\boldsymbol{x}) & \equiv & 0. \end{array}$$

Proof: The steady-state-solutions of system (2.5)-(2.6) solve

$$\left\{\begin{array}{rcl} 0 & = & -iW - vW\,, \\ 0 & = & -\mu_I I + vW\,, \\ 0 & = & iW\,, \\ -d_v\Delta v & = & -\mu_v v + \alpha_v I - \alpha_4 vW\,, \\ -d_i\Delta i & = & -\mu_i i + \alpha_i I - \alpha_3 iW\,, \end{array}\right. \tag{2.15}$$

with boundary conditions

$$\left\{\begin{array}{rclr} \nabla v\cdot \boldsymbol{n}(\sigma) & = & 0 & \text{on } \Gamma, \\ \nabla i\cdot \boldsymbol{n}(\sigma) & = & 0 & \text{on } \Gamma. \end{array}\right. \tag{2.16}$$

From the first three equations in (2.15)-(2.16) it follows immediately that

$$iW = vW = \mu_I I = 0.$$

Since $\mu_I > 0$ then necessarily $I = 0$. Moreover, v and i solve

$$\begin{array}{rcl} -d_v\Delta v & = & -\mu_v v, \\ -d_i\Delta i & = & -\mu_i i. \end{array}$$

In consequence, since $\mu_v > 0$ and $\mu_i > 0$ it follows that $v = i = 0$. It is worth to mention that in this case we have no restriction on W and R. $\Box$

Lemma 2.9 *Suppose that the initial conditions belong to $L^\infty(\Omega)$. For any $\boldsymbol{x}\in\Omega$, the solutions of the hybrid system (2.5)-(2.6) are integrable in the following sense:*

1.
$$\lim_{t\to\infty}\int_0^t I(\boldsymbol{x},s)\,ds < \infty \quad \text{and} \quad \lim_{t\to\infty}\int_0^t\int_\Omega I(\boldsymbol{x},s)\,d\Omega\,ds < \infty.$$

2.
$$\lim_{t\to\infty}\int_0^t v(\boldsymbol{x},s)W(\boldsymbol{x},s)\,ds < \infty \quad \text{and} \quad \lim_{t\to\infty}\int_0^t\int_\Omega v(\boldsymbol{x},s)W(\boldsymbol{x},s)\,d\Omega\,ds < \infty.$$

3.
$$\lim_{t\to\infty}\int_0^t i(\boldsymbol{x},s)W(\boldsymbol{x},s)\,ds < \infty \quad \text{and} \quad \lim_{t\to\infty}\int_0^t\int_\Omega i(\boldsymbol{x},s)W(\boldsymbol{x},s)\,d\Omega\,ds < \infty.$$

Proof:

1. Adding the equations of W, I, R we obtain that

$$\partial_t W + \partial_t I + \partial_t R + \mu_I I \leq 0.$$

Integrating over $[0,t]$ it follows that, for any $(\boldsymbol{x},t)\in\Omega\times[0,\infty)$ we have

$$W(\boldsymbol{x},t) + I(\boldsymbol{x},t) + R(\boldsymbol{x},t) + \mu_I\int_0^t I(\boldsymbol{x},s)ds \leq W(\boldsymbol{x},0) + I(\boldsymbol{x},0) + R(\boldsymbol{x},0). \tag{2.17}$$

Therefore, from (2.17) and using uniform boundedness of the initial conditions we can deduce that

$$\lim_{t\to\infty}\int_0^t I(\boldsymbol{x},s)\,ds<\infty \quad \text{and} \quad \lim_{t\to\infty}\int_0^t\int_\Omega I(\boldsymbol{x},s)\,d\Omega\,ds<\infty.$$

2. Integrating over $[0,t]$ the equation for I yields

$$I(\boldsymbol{x},t)-I(\boldsymbol{x},0)+\int_0^t I(\boldsymbol{x},s)\,ds=\int_0^t v(\boldsymbol{x},s)W(\boldsymbol{x},s)\,ds.$$

Therefore, using the previous result on the integrability of I we obtain that

$$\lim_{t\to\infty}\int_0^t v(\boldsymbol{x},s)W(\boldsymbol{x},s)\,ds<\infty \quad \text{and} \quad \lim_{t\to\infty}\int_0^t\int_\Omega v(\boldsymbol{x},s)W(\boldsymbol{x},s)\,d\Omega\,ds<\infty.$$

3. Integrating over $[0,t]$ the equation for W yields

$$W(\boldsymbol{x},t)-W(\boldsymbol{x},0)+\int_0^t vW(\boldsymbol{x},s)\,ds=\int_0^t i(\boldsymbol{x},s)W(\boldsymbol{x},s)\,ds.$$

Since the left-hand side has a limit so does the right-hand side, i.e.,

$$\lim_{t\to\infty}\int_0^t i(\boldsymbol{x},s)W(\boldsymbol{x},s)\,ds<\infty \quad \text{and} \quad \lim_{t\to\infty}\int_0^t\int_\Omega i(\boldsymbol{x},s)W(\boldsymbol{x},s)\,d\Omega\,ds<\infty. \quad \square$$

Lemma 2.10 *The solutions of the hybrid system satisfy the following properties:*

1. $\partial_t I$ *is uniformly bounded for* $t\in[0,\infty)$*. Moreover, for any* $\boldsymbol{x}\in\Omega$*,*

$$\lim_{t\to\infty} I(\boldsymbol{x},t)=0,\quad \lim_{t\to\infty}\int_\Omega I^2(\boldsymbol{x},t)\,d\Omega=0 \quad \text{and} \quad \lim_{t\to\infty}\int_0^t\int_\Omega I^2(\boldsymbol{x},s)\,d\Omega\,ds<\infty.$$

2.

$$\lim_{t\to\infty}\int_0^t\left(\|v(s)\|^2+\|\nabla v(s)\|^2\right)ds<\infty \quad \text{and} \quad \lim_{t\to\infty}\int_0^t\left(\|i(s)\|^2+\|\nabla i(s)\|^2\right)ds<\infty.$$

3. $\partial_t v$ *and* $\partial_t i$ *are bounded distributions in* $L^1\left(0,\infty;H^1(\Omega)\right)$*.*

Proof:

1. Since the functions I, v and W are uniformly bounded in $\Omega \times (0, \infty)$, from the equation for I it follows that $\partial_t I$ is uniformly bounded as well. Therefore, using
$$\lim_{t\to\infty} \int_0^t I(\boldsymbol{x}, s)\, ds < \infty$$
we can infer that
$$\lim_{t\to\infty} I(\boldsymbol{x}, t) = 0 \quad \text{for all } x \in \Omega.$$
Now consider a sequence
$$0 < t_0 < t_1 < \cdots < t_n \to \infty$$
and define
$$f_n(\boldsymbol{x}) := I(\boldsymbol{x}, t_n).$$
We have already proven that
$$\lim_{n\to\infty} f_n(\boldsymbol{x}) = 0 \quad \text{and} \quad 0 \le f_n(\boldsymbol{x}) \le N_0(\boldsymbol{x}),$$
where
$$N_0(\boldsymbol{x}) := W(\boldsymbol{x}, 0) + I(\boldsymbol{x}, 0) + R(\boldsymbol{x}, 0) \in L^\infty(\Omega).$$
Therefore, we can apply Lebesgue's Dominated Convergence Theorem to obtain
$$\lim_{n\to\infty} \int_\Omega f_n^2(\boldsymbol{x}) d\Omega = \int_\Omega \lim_{n\to\infty} f_n^2(\boldsymbol{x}) d\Omega = \int_\Omega 0 d\Omega = 0.$$
Since this holds for any arbitrary sequence $(t_n)_{n\in\mathbb{N}}$ then
$$\lim_{t\to\infty} \int_\Omega I^2(\boldsymbol{x}, t)\, d\Omega = 0.$$
For the last statement, if we integrate the equation for I over $\Omega \times [0, t]$ we obtain
$$\|I(t)\|^2 + 2\mu_I \int_0^t \int_\Omega I^2(\boldsymbol{x}, s)\, d\Omega\, ds = \|I(0)\|^2 + 2\|I\|_{L^\infty(\Omega\times(0,t))} \int_0^t \int_\Omega v(\boldsymbol{x}, s) W(\boldsymbol{x}, s)\, d\Omega\, ds.$$
Since the right-hand side converges as $t \to \infty$ then the left converges as well, which implies that
$$\lim_{t\to\infty} \int_0^t \int_\Omega I^2(\boldsymbol{x}, s)\, d\Omega\, ds < \infty.$$

2. Multiplying the equation for v by v and integrating by parts yields
$$\frac{1}{2}\frac{d}{dt}\|v(t)\|^2 + d_v\|\nabla v(t)\|^2 + \mu_v\|v(t)\|^2 = \alpha_v \int_\Omega I v\, d\Omega - \alpha_4 \int_\Omega v^2 W\, d\Omega.$$
Integrating over $[0, t]$ it can be shown that there is a constant $C > 0$, independent of t, such that
$$\|v(t)\|^2 + 2d_v \int_0^t \|\nabla v(s)\|^2\, ds + \mu_v \int_0^t \|v(s)\|^2\, ds \le \|v(0)\|^2 + C \int_0^t \int_\Omega I^2(\boldsymbol{x}, s)\, d\Omega\, ds.$$

But from the previous results it follows that the right-hand side converges. In consequence, the left-hand side converges, i.e.,

$$\lim_{t\to\infty}\int_0^t \left(\|v(s)\|^2 + \|\nabla v(s)\|^2\right)\, ds < \infty.$$

The proof for i is exactly the same as for v.

3. Let $\varphi(\boldsymbol{x},t)$ be a test function in $L^1\left(0,\infty;H^1(\Omega)\right)$. Calculating the dual product in $L^1\left(0,t;H^1(\Omega)\right)$ yields

$$\begin{aligned}\langle \partial_t v, \varphi\rangle &= -d_v\int_0^t\int_\Omega \nabla v\cdot\nabla\phi\, d\Omega\, dt - \mu_v\int_0^t\int_\Omega v\varphi\, d\Omega\, dt\\ &\quad +\alpha_v\int_0^t\int_\Omega I\varphi\, d\Omega\, dt - \alpha_4\int_0^t\int_\Omega vW\varphi\, d\Omega\, dt\,.\end{aligned}$$

Using the uniform boundedness and integrability of I and W it can be shown that there exist three positive constants C_1, C_2 and C_3, independent of t, such that

$$|\langle\partial_t v,\varphi\rangle| \le C_1 + C_2\|\varphi\|_{L^1(0,t;H^1(\Omega))} + C_3\|v\|_{L^1(0,t;H^1(\Omega))}\,.$$

This implies that $|\langle\partial_t v,\varphi\rangle|$ is bounded for any test function in $L^1\left(0,t;H^1(\Omega)\right)$ with norm less than one, uniformly in t. Therefore, $\partial_t v$ is a bounded distribution in $L^1\left(0,\infty;H^1(\Omega)\right)$.

The proof for i is exactly the same as for v. $\square$

Lemma 2.11 *Suppose that the initial conditions belong to $L^\infty(\Omega)$. For any $\boldsymbol{x}\in\Omega$ fixed, the solutions of the hybrid system (2.5)-(2.6) satisfy the following properties:*

1.
$$\lim_{t\to\infty} v(\boldsymbol{x},t)W(\boldsymbol{x},t) = 0 \quad\text{and}\quad \lim_{t\to\infty} i(\boldsymbol{x},t)W(\boldsymbol{x},t) = 0,$$

2.
$$\lim_{t\to\infty} v(\boldsymbol{x},t) = \lim_{t\to\infty} i(\boldsymbol{x},t) = 0.$$

3.
$$\lim_{t\to\infty}\int_0^t v(\boldsymbol{x},s)\, ds < \infty \quad\text{and}\quad \lim_{t\to\infty}\int_0^t i(\boldsymbol{x},s)\, ds < \infty\,.$$

Proof:

1. Integrating the equation for I over $[0,t]$ we obtain

$$\int_0^t v(\boldsymbol{x},s)W(\boldsymbol{x},s)dt = I(\boldsymbol{x},t) - I(\boldsymbol{x},0) + \mu_I\int_0^t I(\boldsymbol{x},s)ds\,.$$

On one hand, using the previous results it follows that the right-hand side is uniformly bounded in t. In consequence,

$$\lim_{t\to\infty}\int_0^t v(\boldsymbol{x},t)W(\boldsymbol{x},t)ds<\infty.$$

On the other hand,

$$\partial_t(vW)=v\partial_t W+W\partial_t v$$

is uniformly bounded because v, W, $\partial_t v$ and $\partial_t W$ are all uniformly bounded. In consequence,

$$\lim_{t\to\infty}v(\boldsymbol{x},t)W(\boldsymbol{x},t)=0.$$

2. Integrating over $\Omega\times[0,t]$ the equation for v and using Fubini's Theorem yields

$$\begin{aligned}\int_\Omega v(\boldsymbol{x},t)\,d\Omega-\int_\Omega v(\boldsymbol{x},0)\,d\Omega &= \int_0^t\int_\Omega \Delta v(\boldsymbol{x},t)\,d\Omega\,dt-\mu_v\int_0^t\int_\Omega v(\boldsymbol{x},t)\,d\Omega\,dt\\ &\quad+\alpha_v\int_0^t\int_\Omega I(\boldsymbol{x},s)\,d\Omega\,dt+\alpha_4\int_0^t\int_\Omega v(\boldsymbol{x},s)W(\boldsymbol{x},s)\,d\Omega\,dt.\end{aligned}$$

Now recall that v satisfies homogeneous Neumann boundary conditions. Therefore,

$$\int_0^t\int_\Omega \Delta v(\boldsymbol{x},t)\,d\Omega\,dt=\int_0^t\int_{\partial\Omega}\nabla v(\boldsymbol{x},t)\cdot\mathbf{n}\,dS\,dt=0,$$

which implies that

$$\begin{aligned}\int_\Omega v(\boldsymbol{x},t)\,d\Omega-\int_\Omega v(\boldsymbol{x},0)\,d\Omega &= -\mu_v\int_0^t\int_\Omega v(\boldsymbol{x},t)\,d\Omega\,dt+\alpha_v\int_0^t\int_\Omega I(\boldsymbol{x},s)\,d\Omega\,dt\\ &\quad+\alpha_4\int_0^t\int_\Omega v(\boldsymbol{x},s)W(\boldsymbol{x},s)\,d\Omega\,dt.\end{aligned}$$

From the previous results and the uniform boundedness of W, I and v it follows that

$$\lim_{t\to\infty}\int_0^t\int_\Omega v(\boldsymbol{x},t)\,d\Omega\,dt<\infty.$$

Since $\partial_t v$ is uniformly bounded it follows that

$$\lim_{t\to\infty}\int_\Omega v(\boldsymbol{x},t)\,d\Omega=0. \tag{2.18}$$

Now let $\varepsilon>0$ and choose $\boldsymbol{x}_0\in\Omega$. Define

$$B(\varepsilon,\boldsymbol{x}_0)=\{\boldsymbol{x}\in\Omega\,:\,|\boldsymbol{x}-\boldsymbol{x}_0|<\varepsilon\}.$$

From (2.18) there exists $T(\varepsilon)>0$ such that

$$\int_\Omega v(\boldsymbol{x},t)\,d\Omega<\varepsilon|B(\varepsilon,\boldsymbol{x}_0)|\quad\text{for all } t\geq T(\varepsilon).$$

In consequence,

$$\int_{B(\varepsilon,\boldsymbol{x}_0)} v(\boldsymbol{x},t)\,d\Omega \leq \int_\Omega v(\boldsymbol{x},t)\,d\Omega < \varepsilon|B(\varepsilon,\boldsymbol{x}_0)|,$$

which implies that

$$\frac{1}{|B(\varepsilon,\boldsymbol{x}_0)|}\int_{B(\varepsilon,\boldsymbol{x}_0)} v(\boldsymbol{x},t)\,d\Omega \leq \varepsilon.$$

Therefore, since $v(\boldsymbol{x},t)$ is continuous, we have

$$v(\boldsymbol{x}_0,t) = \lim_{|B(\varepsilon,\boldsymbol{x}_0)|\to 0} \frac{1}{|B(\varepsilon,\boldsymbol{x}_0)|}\int_{B(\varepsilon,\boldsymbol{x}_0)} v(\boldsymbol{x},t)\,d\Omega \leq \varepsilon,$$

which implies that

$$\lim_{t\to\infty} v(\boldsymbol{x}_0,t) \leq \varepsilon.$$

Since $\varepsilon > 0$ and $\boldsymbol{x}_0 \in \Omega$ are arbitrary it follows that

$$\lim_{t\to\infty} v(\boldsymbol{x},t) = 0 \quad \text{for all } \boldsymbol{x} \in \Omega.$$

The proof for $i(\boldsymbol{x},t)$ is exactly the same.

3. Define

$$C_\infty := \lim_{t\to\infty}\int_0^t \int_\Omega v(\boldsymbol{x},s)\,d\Omega\,ds.$$

From the previous results we have that C_∞ is well-defined, finite and positive. Now, for any $n \in \mathbb{N}$ define

$$A_n := \left\{\boldsymbol{x} \in \Omega \,:\, \lim_{t\to\infty}\int_0^t v(\boldsymbol{x},s)\,ds > nC_\infty\right\}.$$

On the one hand,

$$\lim_{t\to\infty}\int_0^t \int_{A_n} v(\boldsymbol{x},s)\,d\Omega\,ds > nC_\infty|A_n|\,.$$

On the other hand,

$$\lim_{t\to\infty}\int_0^t \int_{A_n} v(\boldsymbol{x},s)\,d\Omega\,ds \leq \lim_{t\to\infty}\int_0^t \int_\Omega v(\boldsymbol{x},s)\,d\Omega\,ds = C_\infty\,.$$

Therefore,

$$|A_n| < \frac{1}{n}. \tag{2.19}$$

Moreover, since

$$A_1 \supset A_2 \supset \cdots \supset A_n \supset \cdots$$

it follows that

$$A_\infty := \left\{\boldsymbol{x} \in \Omega \,:\, \lim_{t\to\infty}\int_0^t v(\boldsymbol{x},s)\,ds \quad \text{diverges}\right\} = \bigcap_{n=1}^{\infty} A_n.$$

In consequence, from (2.19) we obtain that $|A_\infty| = 0$, which implies that

$$\lim_{t\to\infty} \int_0^t v(\boldsymbol{x}, s)\, ds < \infty \quad \text{a.e. in } \Omega.$$

Finally, since $t \mapsto v(\boldsymbol{x}, t)$ is continuous we conclude that

$$\lim_{t\to\infty} \int_0^t v(\boldsymbol{x}, s)\, ds < \infty \quad \text{for all } \boldsymbol{x} \in \Omega.$$

The proof for i is the same. $\square$

Lemma 2.12 *For any $\boldsymbol{x} \in \Omega$, $W_0(\boldsymbol{x}) > 0$ if and only if*

$$\lim_{t\to\infty} W(\boldsymbol{x}, t) > 0.$$

Proof: Integrating over $[0, t]$ the equation for W we obtain

$$W(\boldsymbol{x}, t) = W_0(\boldsymbol{x}) \times \exp\left\{ -\int_0^t v(\boldsymbol{x}, s)\, ds - \int_0^t i(\boldsymbol{x}, s)\, ds \right\}.$$

In consequence, the result follows immediately from Lemma 2.11. $\square$

2.5.6 Proof of Theorem 2.6

Lemma 2.13 *If $v_\infty(\boldsymbol{x})$ is a steady-state solution of the hybrid system (2.5)-(2.6) and $\mu_v = 0$ then $\|\nabla v_\infty\| = 0$.*

Proof: Following the proof of Lemma 2.8 it follows that

$$d_v \Delta v_\infty = 0.$$

Therefore, integrating by parts yields $\|\nabla v_\infty\| = 0$. $\square$

Lemma 2.14 *If v is solution of the hybrid system (2.5)-(2.6) and $\mu_v = 0$ then*

$$\lim_{t\to\infty} \int_\Omega v(\boldsymbol{x}, t)\, d\Omega \geq \int_\Omega v_0(\boldsymbol{x})\, d\Omega + (\alpha_v - \alpha_4 \mu_I) \int_0^\infty \int_\Omega I(\boldsymbol{x}, s)\, d\Omega\, dt.$$

Proof: Integrating over $\Omega \times [0, t]$ the equation for v and using Fubini's Theorem yields

$$\int_\Omega v(\boldsymbol{x}, t)\, d\Omega - \int_\Omega v(\boldsymbol{x}, 0)\, d\Omega = \int_0^t \int_\Omega \Delta v(\boldsymbol{x}, t)\, d\Omega\, dt + \alpha_v \int_0^t \int_\Omega I(\boldsymbol{x}, s)\, d\Omega\, dt + \alpha_4 \int_0^t \int_\Omega v(\boldsymbol{x}, s) W(\boldsymbol{x}, s)\, d\Omega\, dt.$$

Now recall that v satisfies homogeneous Neumann boundary conditions. Therefore,

$$\int_0^t \int_\Omega \Delta v(\boldsymbol{x},t)\, d\Omega\, dt = \int_0^t \int_{\partial\Omega} \nabla v(\boldsymbol{x},t)\cdot \mathbf{n}\, dS\, dt = 0,$$

which implies that

$$\int_\Omega v(\boldsymbol{x},t)\, d\Omega = \int_\Omega v(\boldsymbol{x},0)\, d\Omega + \alpha_v \int_0^t \int_\Omega I(\boldsymbol{x},s)\, d\Omega\, dt + \alpha_4 \int_0^t \int_\Omega v(\boldsymbol{x},s) W(\boldsymbol{x},s)\, d\Omega\, dt.$$

On the other hand, integrating the equation for I yields

$$\int_0^t v(\boldsymbol{x},s) W(\boldsymbol{x},s)\, dt = I(\boldsymbol{x},t) - I_0(\boldsymbol{x}) + \mu_I \int_0^t I(\boldsymbol{x},s)\, dt.$$

In consequence,

$$\begin{aligned} \int_\Omega v(\boldsymbol{x},t)\, d\Omega &= \int_\Omega v_0(\boldsymbol{x})\, d\Omega + (\alpha_v - \alpha_4\mu_I) \int_0^t \int_\Omega I(\boldsymbol{x},s)\, d\Omega\, dt \\ &\quad + \alpha_4 \int_\Omega I(\boldsymbol{x},t)\, d\Omega - \alpha_4 \int_\Omega I_0(\boldsymbol{x})\, d\Omega\,. \end{aligned} \tag{2.20}$$

Now recall that $I_0(\boldsymbol{x})$ is non-negative and

$$\lim_{t\to\infty} \int_\Omega I(\boldsymbol{x},t)\, d\Omega = 0.$$

Therefore, taking the limit $t \to \infty$ and applying Lebesgue's dominated convergence theorem in (2.20) we obtain

$$\lim_{t\to\infty} \int_\Omega v(\boldsymbol{x},t)\, d\Omega \geq \int_\Omega v_0(\boldsymbol{x})\, d\Omega + (\alpha_v - \alpha_4\mu_I) \int_0^\infty \int_\Omega I(\boldsymbol{x},s)\, d\Omega\, dt. \quad \square$$

Lemma 2.15 *Define*

$$v_\infty(\boldsymbol{x}) := \limsup_{t\to\infty} v(\boldsymbol{x},t).$$

If $\alpha_v \geq \alpha_4\mu_I$ *then*

$$\int_\Omega v_\infty(\boldsymbol{x})\, d\Omega \geq \int_\Omega v_0(\boldsymbol{x})\, d\Omega.$$

In particular, if $v_0 \not\equiv 0$ *then* $v_\infty \not\equiv 0$.

<u>*Proof*</u>: If $\alpha_v \geq \alpha_4\mu_I$ then from Lemma 2.14 we have

$$\lim_{t\to\infty} \int_\Omega v(\boldsymbol{x},t)\, d\Omega \geq \int_\Omega v_0(\boldsymbol{x})\, d\Omega\,.$$

Recall that $v(\boldsymbol{x},t)$ is uniformly bounded. Therefore, applying Fatou's lemma we obtain

$$\int_\Omega v_\infty(\boldsymbol{x})\, d\Omega \geq \lim_{t\to\infty} \int_\Omega v(\boldsymbol{x},t) \geq \int_\Omega v_0(\boldsymbol{x})\, d\Omega. \quad \square$$

2.6 Discussion

We proved that both the reaction-diffusion and the hybrid models are well-posed problems, i.e., they have global unique solutions (in the weak sense), which are non-negative, bounded and depend continuously on the initial data. We also showed that, when $d \to 0$, the solution of the reaction-diffusion model coverges to the solution of the hybrid model.

We provided several asymptotic estimates for the solutions of the hybrid model. First, we proved that the solutions are uniformly bounded and integrable over $\Omega \times (0, \infty)$. Second, we showed that virions and wild-type cells cannot coexist, because the product of their concentrations tends to zero as $t \to \infty$. Third, we proved that if $\mu_v > 0$ then the virus concentration tends to zero as $t \to \infty$ and W tends to a non-zero, non-homogeneous limit. Fourth, if $\mu_v = 0$ and $\alpha_v \geq \alpha_4 \mu_I$ then the global virus concentration is bigger than the original concentration.

One striking result for the hybrid model is the global stability of the steady-state solutions. Indeed, we characterized the steady-state solutions and showed that they coincide with the limits of the corresponding time-dependent solutions. Indeed, for $\mu_v > 0$,

$$\begin{aligned} \lim_{t\to\infty} I(\boldsymbol{x}, t) &= 0 = I_\infty(\boldsymbol{x})\,, \\ \lim_{t\to\infty} v(\boldsymbol{x}, t) &= 0 = v_\infty(\boldsymbol{x})\,, \\ \lim_{t\to\infty} i(\boldsymbol{x}, t) &= 0 = i_\infty(\boldsymbol{x})\,, \end{aligned}$$

whilst $W(\boldsymbol{x}, t)$ has an explicit limit,

$$W_\infty(\boldsymbol{x}) = W_0(\boldsymbol{x}) \exp\left\{ -\int_0^\infty v(\boldsymbol{x}, s)\, ds - \int_0^\infty i(\boldsymbol{x}, s)\, ds \right\}.$$

Finally, in the numerical simulations we found that the spatial structure (i.e. the diffusion) plays a crucial role in the proliferation of virions. Indeed, d_v has a positive effect when $\mu_v = 0$ and a negative effect when $\mu_v > 0$. Therefore, the spatial structure permits the existence of richer patterns than in the original ODE system of P. Getto *et al* [24], which confirms what we have conjectured at the beginning of the project.

Part II

Reaction-diffusion equations and systems on manifolds

Chapter 3

The effect of growth on pattern formation

Based on abundant numerical and experimental evidence, it has been conjectured that growth should have some kind of stabilising effect on pattern formation. In this paper we answer affirmatively this question: under an isotropic regime, growth shifts the eigenvalues of the reaction-diffusion system towards the left on the complex plane. Since the real parts of the eigenvalues are smaller, we can interpret this fact as a gain of stability. We also prove that growth enhances the possibility of a solution to be global: a local solution (i.e. defined up to a finite time) has more chances to be global (i.e. to exist for all times) on a growing manifold than on a fixed manifold. Moreover, if growth is fast enough we show that the solutions are always global. We illustrate this *anti-blow-up* effect with two scalar examples, for which there is blow-up on fixed domains. We show that on growing domains the blow-up occurs later than in fixed domains, and that if growth is fast enough then here is no blow-up. We finish with a discussion of the results, showing that the classical linear stability analysis for bifurcations apply to this framework, and pointing out the possible applications of our results to regulatory dynamics in pattern formation, embryogenesis and tumor growth.

3.1 Introduction

Since the seminal paper of Turing [66], the most frequently used framework for modeling pattern formation in biological and chemical systems are reaction-diffusion systems of the form

$$\frac{\partial \mathbf{u}}{\partial t} = \mathcal{D}\Delta\mathbf{u} + \mathbf{F}(\mathbf{u})\,, \quad \mathcal{D} = \begin{bmatrix} D_1 & & & \\ & D_2 & & \\ & & \ddots & \\ & & & D_M \end{bmatrix}, \; D_k > 0\,, \tag{3.1}$$

where $\mathbf{u} = \mathbf{u}(x,t)$, x is the position in a domain in $\mathbb{R}^N$ and $t \geq 0$ is time. However, as Plaza *et al* [52] remark, this framework does not take into account the effects of domain growth and curvature, which are crucial for the development of an organism. Therefore, it is necessary to develop reaction-diffusion models that consider these two important features.

There have been several works aiming at studying the effect of growth on pattern formation. In 1995 Kondo and Asai [38] reproduced numerically the complex behavior of patterns on the skin of *Pomacanthus*, a tropical fish, by just adding growth to the classical reaction-diffusion system (3.1). Based on this evidence, Meinhardt [47] emphasized that this result suggests a new way to look at the process of regulatory features in embryogenesis, not only in *Pomacanthus* but also in other organisms like *Drosophila*. In 1999 Crampin *et al* [15] showed in a 1-dimensional simulation that domain growth may be a mechanism for increased robustness in pattern formation. They managed to find a critical growth rate, under which there is a sequence of mode-doubling pattern transitions, and they also showed that if the growth rate is much bigger or smaller than this critical value the mode-doubling pattern dissappears. In 2004 Plaza *et al* [52] derived a reaction-diffusion model for two morphogens on 1 and 2-dimensional growing domains. They used this model to perform numerical calculations in squares and cones with isotropic growth, and in the light of the simulations, they concluded that growth has a stabilising effect on pattern formation. More precisely, and we quote:

> "New patterns can be robustly selected due to the effect of either curvature and/or growth, which would be unstable otherwise".

In 2007 Gjiorgjieva and Jacobsen [28] studied the effect of growth on pattern formation on a 2-dimensional sphere. They showed that the solutions under slow growth are very similar to the solutions of the model of Chaplain *et al* [13] on a fixed sphere, which implies that there is a continuity link between growing and fixed patterns. But they also found something very interesting, which is worth quoting:

> "In general, the range of eigenmodes which yield Turing pattern formation for a growing sphere is larger than the range for a fixed sphere, which implies that growth increases the number of possible patterns. However, the dominant eigenmode determining the pattern is smaller for growing spheres [...] This shows that, although a larger class of patterns is allowed for growing spheres, a lower mode is typically selected".

All these four numerical examples reinforce the conjecture that growth should have some kind of stabilising effect on pattern formation. In this paper we affirmatively answer this question, showing that (*i*) under an isotropic regime growth has indeed a stabilising effect on patterns, i.e. the eigenvalues of a growing domain have real parts smaller than those on fixed domains; and (*ii*) growth enhances the possibility of a solution to be globally defined, i.e. blow-up on growing manifolds occur later than on fixed manifolds, and if growth is fast enough we can even avoid blow-up. We will finish with a discussion of the results, showing that the classical linear stability analysis for bifurcations apply to our case, and pointing out the possible applications of our findings to regulatory dynamics in pattern formation, embryogenesis and tumor growth.

3.2 Main results

3.2.1 Reaction-diffusion systems on growing manifolds

Let us define the mathematical objects we will work with throughout this paper.

Definition 3.1 *A* ***manifold*** $\mathcal{M}$ *will be for us a smooth (C^∞), compact, connected, oriented Riemannian manifold without boundary. We will denote its parametrisation by*

$$\begin{array}{rcl} X\ : \hat{\Omega} \subset \mathbb{R}^n & \longrightarrow & \mathcal{M} \\ \xi = (\xi_1, \ldots, \xi_n) & \longmapsto & X(\xi) \end{array}$$

and its metric by $(g_{ij}(\xi))$.

The following definition is standard and well-known, but it is necessary for the sake of completeness. Moreover, it will allow us to set our notation.

Definition 3.2 *The* ***Laplace-Beltrami operator*** *on a Riemannian manifold $\mathcal{M}$ with parametrisation $(\xi, t) = (\xi_1, \ldots \xi_n, t)$ and metric $(g_{ij}(\xi, t))$ is (using the sum convention on repeated indices)*

$$\Delta_{\mathcal{M}}\phi := \frac{1}{\sqrt{g}}\, \partial_{\xi_j} [\sqrt{g}\, g^{ij}\, \partial_{\xi_i}\phi]\,, \tag{3.2}$$

where $(g^{ij}) = (g_{ij})^{-1}$ and $g = det(g_{ij})$.

Definition 3.3 *A f* ***growing manifold*** *will be for us a monoparametric family of manifolds $(\mathcal{M}_t)_{t\geq 0}$ such that for any $t \geq 0$:*

- *$\mathcal{M}_t$ is a manifold with metric $(g_{ij}(\xi, t))$.*
- *The function $t \mapsto g(t, \xi) = det(g_{ij}(t, \xi))$ is strictly increasing.*
- *The parametrisation $X(\xi, t)$ is C^∞ in both variables ξ and t.*
- *The mapping $t \mapsto g(\xi, t) := det(g_{ij}(\xi, t))$ is strictly increasing.*

We will use the notation $\Delta_{\mathcal{M}_t}$ and $\Delta_{\mathcal{M}}$ to emphasize the time dependence or independence of the coefficients of the Laplace-Beltrami operator, respectively.

Definition 3.4 *A function $\rho : [0, \infty) \to [1, \infty)$ is a* ***growth function or growth factor*** *if it is a C^1 function satisfying $\rho(0) = 1$ and $\dot{\rho}(t) \geq 0$ for all $t \geq 0$.*

Definition 3.5 *A growing manifold $(\mathcal{M}_t)_{t\geq 0}$ has* ***isotropic growth*** *if there is a growth function $\rho(t)$ and a manifold $\mathcal{M}$ such that $\mathcal{M}_t := \rho(t)\mathcal{M}$, meaning that if $X(\xi, t)$ is the parametrisation of $\mathcal{M}_t$ then there is a parametrisation $\widetilde{X}$ of $\mathcal{M}$ such that $X(\xi, t) = \rho(t)\widetilde{X}(\xi)$.*

It is important to keep in mind that at time $t = T$ the growing manifold $\mathcal{M}_{0\leq t\leq T}$ coincides with the fixed manifold $\mathcal{M}_T$, but they are "dynamically" different. Indeed, in the growing manifold $\mathcal{M}_{0\leq t\leq T}$ the growth dynamics is included, whereas in the fixed manifold $\mathcal{M}_T$ growth does not play any role.

Theorem 3.1 *Let $(\mathcal{M}_t)_{t\geq 0}$ be a growing manifold with metric $(g_{ij}(\xi,t))$. Under the hypotheses of Fick's law of diffusion and conservation of mass, any reaction-diffusion system on $\mathcal{M}_t$ has the form*

$$\partial_t \mathbf{u} = \mathcal{D}\Delta_{\mathcal{M}_t}\mathbf{u} - \partial_t[\log\sqrt{g(t,\xi)}\,]\mathbf{u} + \mathbf{F}(\mathbf{u})\,, \tag{3.3}$$

where the Laplace-Beltrami operator $\Delta_{\mathcal{M}_t}$ is given in (3.2). In the case of isotropic growth we have

$$\partial_t \mathbf{u} = \frac{\mathcal{D}}{\rho^2(t)}\Delta_{\mathcal{M}}\mathbf{u} - n\frac{\dot\rho(t)}{\rho(t)}\mathbf{u} + \mathbf{F}(\mathbf{u})\,, \tag{3.4}$$

where the coefficients of $\Delta_{\mathcal{M}}$ do not depend on time.

Definition 3.6 *For a growing manifold $(\mathcal{M}_t)_{t\geq 0}$ we define its* ***growth rate*** *as*

$$c(t,\xi) := \partial_t[\log\sqrt{g(t,\xi)}\,]\,.$$

Observe that since $t \mapsto g(t,\xi)$ is strictly increasing it follows that $t \mapsto c(t,\xi)$ is strictly increasing as well. Theorem 3.1 says that in the case of isotropic growth the growth rate is independent of the spacial variable ξ and takes the form

$$c(t) = n\frac{\dot\rho(t)}{\rho(t)}\,.$$

In particular, if the growth function is exponential, i.e. $\rho(t) = ae^{rt}$ then $c(t) := nr$, hence the growth rate is constant. Note also that in the case of a 2-dimensional growing manifold $(\mathcal{S}_t)_{t\geq 0}$ with orthogonal tangent vectors we have

$$(g_{ij}) = \begin{bmatrix} h_1^2 & 0 \\ 0 & h_2^2 \end{bmatrix}$$

and thus we recover the equations in Plaza *et al* [52]:

$$\partial_t \mathbf{u} = \mathcal{D}\Delta_{\mathcal{S}_t}\mathbf{u} - \partial_t[\log(h_1 h_2)]\mathbf{u} + \mathbf{F}(\mathbf{u})\,,$$

$$\partial_t \mathbf{u} = \frac{\mathcal{D}}{\rho^2(t)}\Delta_{\mathcal{S}}\mathbf{u} - 2\frac{\dot\rho(t)}{\rho(t)}\mathbf{u} + \mathbf{F}(\mathbf{u})\,.$$

3.2.2 Properties of solutions: existence and uniqueness

We will prove that in the case of isotropic growth, the reaction-diffusion system (3.4) has a time-local unique solution. Moreover, if the initial condition is continuous and the nonlinearity $\mathbf{F}(\mathbf{u})$ is C^∞ then the local solution is C^∞ for positive times.

Theorem 3.2 *There is a time $T > 0$ such that the reaction-diffusion system (3.4) with initial condition $\mathbf{u}_0 \in C\left[\mathcal{M},\mathbb{R}^M\right]$ has a unique solution*

$$\mathbf{u}(t) \in C\left([0,T], C\left[\mathcal{M},\mathbb{R}^M\right]\right).$$

Theorem 3.3 *If $\mathbf{F}:\mathbb{R}^M \to \mathbb{R}^M$ is C^∞ then*

$$\mathbf{u}(t) \in C^\infty\left[\mathcal{M}\times(0,T],\mathbb{R}^M\right]\,.$$

3.2.3 The *anti-blow-up* effect of growth

We will show that under specific conditions, depending on the initial condition $\mathbf{u}_0$ and the nonlinearity $\mathbf{F}(\mathbf{u})$, the locally defined solution $\mathbf{u}(t)$ is in fact globally defined. Moreover, those conditions are less restrictive on growing manifolds than on fixed manifolds, which implies that growth has an enhancing effect on the regularity of solutions.

Theorem 3.4 *Let $(\mathcal{M}_t)_{t\geq 0}$ be an isotropic growing manifold with growth rate $c(t)$. Suppose that the initial condition $\mathbf{u}_0$ of the reaction-diffusion system (3.4) lies in $C\left[\mathcal{M}, \mathbb{R}^M\right]$ and takes its values inside the rectangle $\mathcal{R} = (-1,1)^M$. Suppose further that for all $(z,t) \in \partial\mathcal{R} \times [0,\infty)$ we have*

$$\mathbf{F}(z) \cdot \mathbf{n}(z) < c(t) \quad \forall t \geq 0\,, \tag{3.5}$$

where $\mathbf{n}(z)$ is the outer unit normal at z. Then the solution $\mathbf{u}(t)$ of (3.4) is global and bounded, i.e. it exists for all times $t \geq 0$ and takes its values inside $\mathcal{R}$. In particular, there is no blow-up whenever (3.5) *holds.*

From Theorem 3.4, if the growth rate is sufficiently big to satisfy

$$c(t) > \sup\{\|\mathbf{F}(z)\| : z \in \partial\mathcal{R}\}$$

then the solution is globally bounded, which implies that there is no blow-up. Notice that since the growth rate $c(t)$ is increasing in n, the dimension of the space enhances the regularity of solutions.

The next two examples show a direct consequence of Theorem 3.4 on scalar equations: if on a fixed domain we have blow-up at time t_1 then on the corresponding growing domain we have blow-up at time $t_2 > t_1$. Moreover, if growth is fast enough then a solution that blows up on a fixed domain is actually globally defined on the corresponding growing domain. This illustrates the *anti-blow-up* effect of growth on pattern formation: on growing domains the blow-up occurs later than on fixed domains, and it could even do not occur at all.

Example 3.1 *Consider the scalar ODE*

$$\begin{cases} \dot{u} = u^2, \\ u(0) = u_0 > 0\,, \end{cases}$$

whose solution is

$$u(t) = \left(\frac{1}{u_0} - t\right)^{-1},$$

which blows up when $t \to t_1 := 1/u_0$. Now consider the equivalent problem on a growing domain, i.e. suppose $u(t)$ is a scalar, homogeneous solution of (3.4)*. Then u solves the scalar ODE*

$$\begin{cases} \dot{u} = -c(t)u + u^2, \\ u(0) = u_0 > 0\,. \end{cases}$$

Under the change of variables

$$v(t) := e^{\int_0^t c(s)ds} u(t)$$

we have

$$\dot{v} = e^{-\int_0^t c(s)ds} v^2 ,$$

and since

$$c(t) = n\frac{\dot{\rho}(t)}{\rho(t)}$$

it follows that

$$e^{-\int_0^t c(s)ds} = \frac{1}{\rho^n(t)} ,$$

which implies that

$$\dot{v} = \frac{1}{\rho^n(t)} v^2 .$$

In consequence,

$$v(t) = \left(\frac{1}{u_0} - \int_0^t \frac{ds}{\rho^n(s)}\right)^{-1} ,$$

which blows up at time t_2, where t_2 is defined as

$$\int_0^{t_2} \frac{dt}{\rho^n(t)} = \frac{1}{u_0} .$$

However, since $\rho(t) > 1$ for $t > 0$ it follows that

$$\int_0^{t_1} \frac{dt}{\rho^n(t)} < t_1 := \frac{1}{u_0} .$$

Therefore (a) $t_2 > t_1 := 1/u_0$, (b) t_1 and t_2 are decreasing functions of the initial condition u_0, (c) t_2 is an increasing function on the spatial dimension n, and (d) if growth is sufficiently fast, i.e. if the growth function $\rho(t)$ satisfies

$$\int_0^{\infty} \frac{dt}{\rho^n(t)} \leq \frac{1}{u_0}$$

then $t_2 = \infty$, i.e. there is no blow-up on the growing domain.

Let us study some special cases of growth in 1D, i.e. $n = 1$.

- *If there is no growth then $\rho(t) = 1$ and $t_2 = t_1$.*
- *If growth is linear then $\rho(t) = 1 + \alpha t$, $\alpha > 0$. In consequence,*

$$t_2 = \frac{1}{\alpha}\left(e^{\alpha/u_0} - 1\right) = \frac{1}{u_0} + \frac{1}{\alpha}\sum_{n=2}^{\infty}\frac{1}{n!}\left(\frac{\alpha}{u_0}\right)^n > \frac{1}{u_0} = t_1.$$

- *Suppose that we have quadratic growth. If* $\rho(t) = 1 + \beta t^2$ *and* $u_0 > 2\sqrt{\beta}/\pi$ *then*

$$t_2 = \frac{1}{\sqrt{\beta}} \tan\left(\frac{\sqrt{\beta}}{u_0}\right) > \frac{1}{u_0} = t_1 \,.$$

However, if $u_0 \leq 2\sqrt{\beta}/\pi$ *then*

$$\int_0^\infty \frac{dt}{1+\beta t^2} = \frac{\pi}{2\sqrt{\beta}} < \frac{1}{r} \leq \frac{1}{u_0}.$$

Therefore $t_2 = \infty$*, i.e. there is no blow-up. Let us consider another quadratic growth:* $\rho(t) = (1+t)^2$*. If* $u_0 > 1$ *then*

$$t_2 = \frac{1}{u_0 - 1} > \frac{1}{u_0} = t_1 \,.$$

However, if $u_0 \leq 1$ *then* $t_2 = \infty$*, i.e. there is no blow-up.*

- *Suppose that growth is exponential, i.e.* $\rho(t) = e^{rt}$*,* $r > 0$*. If* $r < u_0$ *then*

$$t_2 = -\frac{1}{r}\log\left(1 - \frac{r}{u_0}\right) = \frac{1}{u_0} + \frac{1}{r}\sum_{n=2}^{\infty}\frac{1}{n}\left(\frac{r}{u_0}\right)^n > \frac{1}{u_0} = t_1.$$

However, if $r \geq u_0$ *then*

$$\int_0^\infty e^{-rt} dt = \frac{1}{r} \leq \frac{1}{u_0}.$$

Therefore $t_2 = \infty$*, i.e. there is no blow-up.*

Example 3.2 *Suppose* $u(t,\xi)$ *is a local solution of the scalar reaction-diffusion equation*

$$\begin{aligned} \partial_t u &= \frac{1}{\rho^2(t)}\Delta_{\mathcal{M}} u - c(t)u + u^2 \,, \\ u(0,\xi) &= u_0(\xi) > 0 \,. \end{aligned}$$

Define

$$\eta(t) := \iint_{\mathcal{M}} u(t,\xi)\, d\Omega \,, \quad \eta(0) = \iint_{\mathcal{M}} u_0(\xi)\, d\Omega > 0 \,.$$

On the one hand,

$$\eta(t) = \iint_{\mathcal{M}} u(t,\xi)\, d\Omega \leq \alpha \left(\iint_{\mathcal{M}} u^2(t,\xi)\, d\Omega\right)^{1/2} \,, \quad \alpha = |\mathcal{M}|, .$$

On the other hand,

$$\begin{aligned} \dot{\eta} &= \iint_{\mathcal{M}} \partial_t u(t,x)\, d\Omega \\ &= \iint_{\mathcal{M}} \left(\frac{1}{\rho^2(t)}\Delta_{\mathcal{M}} u - c(t)u + u^2\right) d\Omega \\ &= \iint_{\mathcal{M}} \left(-c(t)u + u^2\right) d\Omega \,. \end{aligned}$$

Therefore,

$$\dot{\eta} \geq -c(t)\eta + \alpha\eta^2 .$$

Under the change of variables

$$\zeta(t) := e^{\int_0^t c(s)ds}\eta(t)$$

we obtain

$$\dot{\zeta} \geq e^{-\int_0^t c(s)ds}\zeta^2 ,$$

which implies that

$$\zeta(t) \geq \left(\frac{1}{\eta(0)} - \alpha \int_0^t \frac{ds}{\rho^n(s)}\right)^{-1} .$$

Let t_1 be the blow-up time for the fixed manifold and t_2 the blow-up time for the growing manifold. As in Example 3.2, using $\rho(t) > 1$ for $t > 0$ we have (a) $t_2 > t_1 = (\alpha\eta(0))^{-1}$, (b) t_1 and t_2 are decreasing functions of the initial condition $\eta(0)$, (c) t_2 is an increasing function on the spatial dimension n, and (d) if growth is sufficiently fast, i.e. if the growth function $\rho(t)$ satisfies

$$\int_0^\infty \frac{dt}{\rho^n(t)} \leq \frac{1}{\alpha\eta(0)}$$

then $t_2 = \infty$, i.e. there is no blow-up on the growing manifold. In particular, for an exponential growth $\rho(t) = e^{rt}$ such that $nr > \alpha\eta(0)$, i.e.

$$r > \frac{|\mathcal{M}|}{n} \iint_{\mathcal{M}} u_0(\xi)\, d\Omega ,$$

we have blow-up on the fixed manifold but not on the growing manifold.

3.2.4 The stabilising effect of growth

Under isotropic regimes, growth has a stabilising effect on pattern formation.

Theorem 3.5 *Let $(\mathcal{M}_t)_{0\leq t\leq T}$ be an isotropic growing manifold with growth rate $c(t)$. Define $\mathcal{S} := \mathcal{M}_T$ and notice that we will use the notation $\mathcal{S}$ for the fixed manifold and $\mathcal{M}_T$ for the final stage of the growing manifold $(\mathcal{M}_t)_{0\leq t\leq T}$. Then λ is an eigenvalue of the reaction-diffusion operator on $\mathcal{S}$,*

$$\mathcal{L}_{\mathcal{S}} := \frac{\mathcal{D}}{\rho^2(T)}\Delta_{\mathcal{S}} + d\mathbf{F}(0)$$

if and only if $\lambda - c(T)$ is an eigenvalue of the corresponding operator on $\mathcal{M}_T$,

$$\mathcal{L}_{\mathcal{M}_T} := \frac{\mathcal{D}}{\rho^2(T)}\Delta_{\mathcal{M}_T} - c(T)I + d\mathbf{F}(0) .$$

Theorem 3.5 says that when we compare the spectra of $\mathcal{L}_{\mathcal{S}}$ and $\mathcal{L}_{\mathcal{M}_T}$ on the same manifold $\mathcal{S} = \mathcal{M}_T$ we obtain

$$\text{spectrum}(\mathcal{L}_{\mathcal{M}_T}) = \text{spectrum}(\mathcal{L}_{\mathcal{S}}) - c(T) .$$

Therefore, growth shifts the eigenvalues to the left in the complex plane, which is indeed as a stabilising effect since the real parts are smaller. Moreover, this shift is exactly the growth rate $c(T) > 0$, which implies that the faster growth is, the more stable the patterns are.

It is important to remark that, as far as we know, Theorem 3.5 is the first analytic proof of the stabilising effect of growth on pattern formation. Moreover, as it will be clear in the proof of Theorem 3.5, the stabilising effect is not only true for the linearisation around the trivial state $\mathbf{u} \equiv 0$, but rather for the linearisation around any steady state $\mathbf{u}_0$.

3.3 Proof of Theorem 3.1

We will divide the proof in three parts.

3.3.1 Parametrisation and Riemannian metric

Let $\mathcal{M}_t$ be a growing manifold parametrized by $X = X(\xi, t)$, and suppose that the motion

$$\begin{array}{rcl} \psi_t : \hat{\Omega} \subset \mathbb{R}^n & \longrightarrow & \mathcal{M}_t \\ \xi = (\xi_1, \ldots, \xi_n) & \longmapsto & \psi_t(\xi) = X(\xi, t) \end{array}$$

is C^∞ in both variables (ξ, t). Remark that the manifolds $\mathcal{M}_t$ are supposed to be all embedded in the same Euclidean space in order to have the motion $\psi_t(\xi)$ well defined as a function of t, and that for any fixed $t \geq 0$ the function $\psi_t(\xi)$ is a parametrisation for $\mathcal{M}_t$.

We will suppose that for all $t \geq 0$ the manifold $\mathcal{M}_t$ has a C^∞ metric $(g_{ij}(\xi, t))$ with the following properties:

(a) *Symmetric:* $g_{ij} = g_{ji}$ for all i, j.

(b) *Positive definite:* $g_{ij} v^i v^j > 0$ for all $v = (v^1, \ldots, v^n) \neq 0$.

3.3.2 The general model with growth and curvature

Let $\Omega(t)$ be a domain in $\mathcal{M}_t$ with boundary $\partial\Omega(t)$. Suppose that the parametrisation of $\Omega(t)$ is

$$\begin{array}{rcl} \Omega(t) & := & \psi_t(\hat{\Omega}) = X(\hat{\Omega}, t)\,, \\ \partial\Omega(t) & := & \psi_t(\partial\hat{\Omega}) = X(\partial\hat{\Omega}, t)\,, \end{array}$$

where $\hat{\Omega}$ is a domain in $\mathbb{R}^n$.

Suppose that $\phi = \phi(X, t)$ denotes the concentration (given in molecules per unit area) of a morphogen (i.e. a chemical substance) at a point $X \in \mathcal{M}_t$, and let J be the flux vector of the molecules ϕ. The *Fick's law of diffusion* states that the flux vector J of the molecules is proportional to the gradient of the concentration of the molecules, i.e.

$$J = -D\nabla\phi\,,$$

where D is the diffusion coefficient, which is assumed to be constant. The law of *conservation of mass* states that the rate of change on the concentration of molecules in $\Omega(t)$ is equal to the net flux of molecules on the boundary $\partial\Omega(t)$, i.e.

$$\frac{d}{dt}\iint_{\Omega(t)} \phi \, dV = -\int_{\partial\Omega(t)} \langle J, \mathbf{n}\rangle \, dS \, . \tag{3.6}$$

The minus sign comes from the fact that $\mathbf{n}$ is the unit outward normal on $\partial\Omega(t)$ and therefore $\langle J, \mathbf{n}\rangle$ is the exit flux.

Using the last two relations we obtain

$$\frac{d}{dt}\iint_{\Omega(t)} \phi \, dV = D\int_{\partial\Omega(t)} \langle \nabla\phi|_{\partial\Omega(t)}, \mathbf{n}\rangle \, dS \, . \tag{3.7}$$

For the sake of clarity let us recall each term in (3.7).

(a) dV is the volume element for the n-manifold $\Omega(t)$; in local coordinates we have $dV = \sqrt{g}\, d\xi$.

(b) dS the "area" (i.e. the $(n-1)$-volume) element for the $(n-1)$-manifold $\partial\Omega(t)$.

(c) $\nabla\phi|_{\partial\Omega(t)}$ is the restriction of the vector field $\nabla\phi$ to $\partial\Omega(t)$ and $\mathbf{n}$ is the unit outward normal.

(d) If $T_X\Omega(t)$ is the tangent plane at $X \in \Omega(t)$ then the inner product $\langle\cdot,\cdot\rangle$ is defined as

$$\langle u, v\rangle := g_{ij}(\xi, t)u^i v^j \quad \text{for any } u, v \text{ in } T_X\Omega(t).$$

Now we calculate both sides of (3.7). For the left hand side, using the change of variables $\widetilde{\phi}(\xi, t) := \phi(X(\xi, t), t)$ we obtain

$$\begin{aligned}
\frac{d}{dt}\iint_{\Omega(t)} \phi(X, t)\, dV &= \frac{d}{dt}\iint_{\hat{\Omega}} \widetilde{\phi}(\xi, t)\sqrt{g}\, d\xi \\
&= \iint_{\hat{\Omega}} [\partial_t\widetilde{\phi}\sqrt{g} + \widetilde{\phi}\partial_t\sqrt{g}]d\xi \\
&= \iint_{\hat{\Omega}} \left[\partial_t\widetilde{\phi} + \widetilde{\phi}\,\frac{\partial_t\sqrt{g}}{\sqrt{g}}\right]\sqrt{g}\, d\xi \\
&= \iint_{\Omega(t)} \left[\partial_t\widetilde{\phi} + \widetilde{\phi}\,\frac{\partial_t\sqrt{g}}{\sqrt{g}}\right] dV \, .
\end{aligned}$$

For the right hand side in (3.7) we will use Stokes' theorem, which in the general case of on a n-manifold $\mathcal{N}$ with boundary $\partial\mathcal{N}$ can be written as

$$\iint_{\mathcal{M}} d\omega = \int_{\partial\mathcal{M}} \omega \, , \tag{3.8}$$

where ω is a $(k-1)$ differential form, $k \leq n$. If ω is the $(n-1)$-form

$$\omega = \langle F|_{\partial\Omega(t)}, \mathbf{n}\rangle \, dS$$

with F a vector field on the submanifold $\Omega(t) \subset \mathcal{M}_t$ then (3.8) becomes

$$\iint_{\Omega(t)} div(F)\, dV = \int_{\partial\Omega(t)} \langle F|_{\partial\Omega(t)}, \mathbf{n}\rangle\, dS\,. \tag{3.9}$$

In the light of (3.9) we have that

$$\int_{\partial\Omega(t)} \langle \nabla\phi|_{\partial\Omega(t)}, \mathbf{n}\rangle\, dS = \iint_{\Omega(t)} div(\nabla\phi)\, dV\,.$$

Putting all two pieces together in (3.7) we obtain

$$\iint_{\Omega(t)} \left[\partial_t\widetilde{\phi} + \widetilde{\phi}\,\partial_t(log\sqrt{g}) - Ddiv(\nabla\widetilde{\phi})\right] dV = 0\,.$$

Recall that $\Omega(t)$ was an arbitrary domain in $\mathcal{M}_t$, and let us drop the tildes for a more convenient notation. Therefore we obtain the equation of the diffusive part of the model:

$$\partial_t\phi = D\, div(\nabla\phi) - \partial_t[\log\sqrt{g}]\phi\,, \tag{3.10}$$

where the operator $div(\nabla\phi)$ is the *Laplace-Beltrami operator* $\triangle_{\mathcal{M}_t}$ we introduced in Definition 3.2.

Now consider a morphogen vector $\mathbf{u} = (u_1, \ldots, u_M)$ and suppose that there is an extra term $\mathbf{F}(\mathbf{u})$ that models reaction kinetics, i.e. the chemical interactions between the morphogens. Then the mass balance equation (3.6) takes the form

$$\frac{d}{dt}\iint_{\Omega(t)} \mathbf{u}\, dS = -\int_{\partial\Omega(t)} \langle J, \mathbf{n}\rangle\, dS + \iint_{\Omega(t)} \mathbf{F}(\mathbf{u})\, dS\,. \tag{3.11}$$

Now let us assume that the flux is $J = -\mathcal{D}\nabla\mathbf{u}$, where the matrix of diffusivities $\mathcal{D}$ is diagonal, i.e.

$$\mathcal{D} = \begin{bmatrix} D_1 & & \\ & \ddots & \\ & & D_M \end{bmatrix},$$

and with constant and positive coefficients D_i. Under these assumptions the equation (3.11) takes the form

$$\frac{d}{dt}\iint_{\Omega(t)} \mathbf{u}\, dS = \mathcal{D}\int_{\partial\Omega(t)} \langle \nabla\mathbf{u}|_{\partial\Omega(t)}, \mathbf{n}\rangle\, dS + \iint_{\Omega(t)} \mathbf{F}(\mathbf{u})\, dS\,. \tag{3.12}$$

Notice that in (3.12) each morphogen diffuses independently of the other and without obstacles. Therefore we can take separately the equations for each of the components u_i of $\mathbf{u}$ in (3.12) and repeat the former calculations using $\phi = u_i$. Proceeding that way we obtain the general model for a reaction-diffusion system on the growing manifold $\mathcal{M}_t$,

$$\partial_t\mathbf{u} = \mathcal{D}\Delta_{\mathcal{M}_t}\mathbf{u} - \partial_t[\log\sqrt{g}\,]\mathbf{u} + \mathbf{F}(\mathbf{u})\,.$$

This proves part (a) of Theorem 3.1.

3.3.3 The isotropic growth model

In the case of isotropic growth we have

$$X(\xi, t) = \rho(t)\, \widetilde{X}(\xi)\,,$$

which implies the following identities:

$$\begin{aligned} g_{ij}(\xi, t) &= \rho^2(t)\, \widetilde{g_{ij}}(\xi)\,, \\ g^{ij}(\xi, t) &= \frac{1}{\rho^2(t)}\, \widetilde{g^{ij}}(\xi)\,, \\ \sqrt{g} &= \rho^n \sqrt{\widetilde{g}}\,, \\ \Delta_{\mathcal{M}_t} &= \frac{1}{\rho^2(t)}\, \Delta_{\mathcal{M}}\,. \end{aligned} \tag{3.13}$$

If we substitute the relations (3.13) in the general model given in (3.4) we obtain the model for a n-dimensional manifold with isotropic growth:

$$\partial_t \mathbf{u} = \frac{\mathcal{D}}{\rho^2(t)} \Delta_{\mathcal{M}} \mathbf{u} - n \frac{\dot{\rho}(t)}{\rho(t)} \mathbf{u} + \mathbf{F}(\mathbf{u})\,.$$

This proves part (b) of Theorem 3.1 and concludes its proof. □

3.4 Proof of Theorem 3.2

Let $\mathcal{M}$ be a manifold and consider the reaction-diffusion equation

$$\partial_t \mathbf{u} = L\mathbf{u} + \mathbf{G}(t, \mathbf{u})\,, \quad \mathbf{u}(0) = \mathbf{u}_0\,, \tag{3.14}$$

where L is a second-order elliptic operator and the nonlinearity $\mathbf{G}$ is C^∞ in its arguments. Let $\mathbf{X}$ be a Banach space such that the following conditions hold:

1. $\mathbf{X}$ is a space of functions $\mathbf{u} : \mathcal{M} \to \mathbb{R}^M$.
2. $e^{tL} : \mathbf{X} \to \mathbf{X}$ is a strongly continuous semigroup for $t \geq 0$.
3. There exists a constant $C > 0$ such that $\|e^{tL}\| \leq C$ for all $t \geq 0$.
4. The nonlinearity
$$\begin{array}{rccc} \mathbf{G} : & \mathbf{X} & \longrightarrow & \mathbf{X} \\ & \mathbf{u} & \longmapsto & \mathbf{G}(t, \mathbf{u}) \end{array}$$
is locally Lipschitz in $\mathbf{u}$, uniformly in t.

Remark 3.7 The space $\mathbf{X}$ we have in mind is $C\left[\mathcal{M}, \mathbb{R}^M\right]$, but there are other possible choices. Indeed, if we ask the nonlinearity $\mathbf{G}(t, \mathbf{u})$ to be C^∞, bounded and with derivatives bounded then $L^p\left[\mathcal{M}, \mathbb{R}^M\right]$ and $H^k\left[\mathcal{M}, \mathbb{R}^M\right]$ are suitable spaces as well.

Lemma 3.8 *The reaction-diffusion system (3.4) can be reduced to the system (3.14) with*

$$\begin{aligned} L &:= \mathcal{D}\Delta_{\mathcal{M}} , \\ \mathbf{G}(t,\mathbf{u}) &:= -n\rho(t)\dot{\rho}(t)\mathbf{u} + \rho^2(t)\mathbf{F}(\mathbf{u}) . \end{aligned}$$

Moreover, if $\mathbf{F}(z)$ *is locally Lipschitz in* $z \in \mathbb{R}^M$ *then* $\mathbf{G}(t,z)$ *is also locally Lipschitz in* $z \in \mathbb{R}^M$*, uniformly in* $t \in [0,T]$*.*

Proof: Define the change of variables

$$s(t) := \int_0^t \frac{dr}{\rho^2(r)} . \tag{3.15}$$

Then for any function $f(t)$ we have that

$$\partial_s f = \rho^2(t)\partial_t f .$$

Multiply the system (3.4) by $\rho^2(t)$ and define $\widetilde{\mathbf{u}}(s,x) := \mathbf{u}(t(s),x)$. Then the system (3.4) takes the equivalent form

$$\partial_s \widetilde{\mathbf{u}} = \mathcal{D}\Delta_{\mathcal{M}}\widetilde{\mathbf{u}} + \mathbf{G}(s,\widetilde{\mathbf{u}}) ,$$

where

$$\mathbf{G}(t,\widetilde{\mathbf{u}}) = -n\rho(t)\dot{\rho}(t)\widetilde{\mathbf{u}} + \rho^2(t)\mathbf{F}(\widetilde{\mathbf{u}}) .$$

Renaming the variables $(s,\widetilde{\mathbf{u}})$ as $(t,\mathbf{u})$ we obtain (3.14). $\square$

Now we have all the elements to prove Theorem 3.2. By the Lemma 3.8 the problem (3.4) is equivalent to (3.14). Moreover, (3.14) can be expressed in the integral form

$$\mathbf{u}(t) = e^{tL}\mathbf{u}_0 + \int_0^t e^{(t-s)L}\mathbf{G}(s,\mathbf{u}(s))\,ds . \tag{3.16}$$

Define the operator

$$\mathbf{\Psi}\mathbf{u}(t) := e^{tL}\mathbf{u}_0 + \int_0^t e^{(t-s)L}\mathbf{G}(s,\mathbf{u}(s))\,ds$$

on the Banach space $C\left([0,T],\mathbf{X}\right)$ with norm

$$\|\mathbf{u}(t)\|_{\mathbf{X}} := \sup_{s\in[0,T]} \|\mathbf{u}(s)\| ,$$

where $\|\cdot\|$ is the norm in $\mathbb{R}^M$. Now fix $\alpha > 0$ and define

$$\mathbf{Z} := \{\mathbf{u} \in C\left([0,T],\mathbf{X}\right) \,:\, \mathbf{u}(0) = \mathbf{u}_0 \,, \|\mathbf{u}(t) - \mathbf{u}_0\|_{\mathbf{X}} \le \alpha\} .$$

The final time $T > 0$ will be chosen later in order to have that $\mathbf{\Psi} : \mathbf{Z} \to \mathbf{Z}$ is a contraction.

Observe that $\mathbf{Z}$ is a closed subset of $C([0,T],\mathbf{X})$. Moreover, $\mathbf{Z}$ is bounded because if $\mathbf{u}\in\mathbf{Z}$ then for all $t\in[0,T]$ we have

$$\|\mathbf{u}(t)\|_{\mathbf{X}} \leq \|\mathbf{u}(t)-\mathbf{u}_0\|_{\mathbf{X}} + \|\mathbf{u}_0\|_{\mathbf{X}} \leq \alpha + \|\mathbf{u}_0\|_{\mathbf{X}}\,.$$

Now we affirm that there is a constant $K_1>0$ such that if $\mathbf{u}\in\mathbf{Z}$ then $\|\mathbf{G}(t,\mathbf{u}(t))\|_{\mathbf{X}}\leq K_1$ for all $t\in[0,T]$. Indeed, recall that $\mathbf{G}(t,\mathbf{u})$ is locally Lipschitz continuous uniformly in t. Hence, if K is the Lipschitz constant for $\mathbf{G}$ then for any $\mathbf{u}\in\mathbf{Z}$ we have

$$\begin{aligned}
\|\mathbf{G}(t,\mathbf{u}(t))\|_{\mathbf{X}} &\leq \|\mathbf{G}(t,\mathbf{u}(t))-\mathbf{G}(t,\mathbf{u}_0)\|_{\mathbf{X}} + \|\mathbf{G}(t,\mathbf{u}_0)\|_{\mathbf{X}}\\
&\leq K\|\mathbf{u}(t)-\mathbf{u}_0\|_{\mathbf{X}} + \|\mathbf{G}(t,\mathbf{u}_0)\|_{\mathbf{X}}\\
&\leq K\alpha + \|\mathbf{G}(t,\mathbf{u}_0)\|_{\mathbf{X}}\,.
\end{aligned}$$

The assumptions on the space $\mathbf{X}$ imply that there exists a $C>0$ such that

$$\|e^{tL}\|_{\mathcal{L}(\mathbf{X})} \leq C\,.$$

This fact and the boundedness of G imply that

$$\left\|\int_0^t e^{(t-s)L}\mathbf{G}(s,\mathbf{u}(s))\,ds\right\|_{\mathbf{X}} \leq K_1 C t\,.$$

Therefore, it is possible to choose $T>0$ such that $K_1CT\leq\alpha/2$. Moreover, from the assumpions on $\mathbf{X}$ we have that e^{tL} is a strongly continuous semigroup for $t\geq 0$, which implies that there is a $T>0$ such that $\|e^{tL}\mathbf{u}_0-\mathbf{u}_0\|_{\mathbf{X}}\leq\alpha/2$ for all $t\in[0,T]$.

In conclusion, if we choose $T>0$ is sufficiently small then $\|\mathbf{\Psi}\mathbf{u}(t)-\mathbf{u}_0\|_{\mathbf{X}}\leq\alpha$, which implies that $\mathbf{\Psi}(\mathbf{Z})\subset\mathbf{Z}$.

Let us find the conditions under which $\mathbf{\Psi}$ is a contraction. If we calculate

$$\begin{aligned}
\|\mathbf{\Psi}\mathbf{u}(t)-\mathbf{\Psi}\mathbf{v}(t)\|_{\mathbf{X}} &= \left\|\int_0^t e^{(t-s)L}\big[\mathbf{G}(s,\mathbf{u}(s))-\mathbf{G}(s,\mathbf{v}(s))\big]\,ds\right\|_{\mathbf{X}}\\
&\leq CKt\sup_{s\in[0,t]}\|\mathbf{u}(s)-\mathbf{v}(s)\|_{\mathbf{X}}\\
&\leq CKT\|\mathbf{u}(t)-\mathbf{v}(t)\|_{\mathbf{X}}
\end{aligned}$$

we can see that $\mathbf{\Psi}:\mathbf{Z}\to\mathbf{Z}$ will be a contraction if we choose $T>0$ such that $CKT<1$. In that case we obtain that there is a unique solution $\mathbf{u}(t)\in C([0,T],\mathbf{X})$ of (3.16), or equivalently a unique solution of (3.14).

This completes the proof of Theorem 3.2. $\square$

3.5 Proof of Theorem 3.3

Fix $t' \in (0, T]$ and consider a solution $\mathbf{u}(t)$ of (3.14) written in its integral form (3.16). Recall two properties of the Laplace-Beltrami operator. First, the map

$$e^{t\triangle_{\mathcal{M}}} : C(\mathcal{M}) \to C^1(\mathcal{M})$$

is continuous for all $t > 0$, and second, there exists a constant $C > 0$ such that

$$\|e^{t\triangle_{\mathcal{M}}}\|_{\mathcal{L}(C(\mathcal{M}),C^1(\mathcal{M}))} \leq Ct^{-1/2}$$

(see Taylor [65], p. 274). This implies that the operator L satisfies the same type of inequality, i.e.,

$$\|e^{tL}\|_{\mathcal{L}(C[\mathcal{M},\mathbb{R}^M],C^1[\mathcal{M},\mathbb{R}^M])} \leq Ct^{-1/2} \,,$$

with a bigger constant $C > 0$, of course, that depends on the diffusion coefficients of the matrix $\mathcal{D}$. Consequently, for any $t_1 \in (0, t']$ and $\mathbf{u}_0 \in C\left[\mathcal{M}, \mathbb{R}^M\right]$ we have that $\mathbf{u}(t_1) \in C^1\left[\mathcal{M}, \mathbb{R}^M\right]$.

Now, if we consider $\mathbf{u}(t_1)$ as a new initial condition we have that $\mathbf{u}(t_2) \in C^2\left[\mathcal{M}, \mathbb{R}^M\right]$ for any $t_2 \in (t_1, t']$. Repeating this iterative argument we can construct a sequence

$$0 < t_1 < t_2 < \cdots < t_n \to t'$$

such that $\mathbf{u}(t_n) \in C^n\left[\mathcal{M}, \mathbb{R}^M\right]$ for any $t_n \in (t_{n-1}, t']$. In the limit we get that $\mathbf{u}(t') \in C^\infty\left[\mathcal{M}, \mathbb{R}^M\right]$ for any $t' \in (0, T]$.

Concerning the time derivatives, recall that if $\mathbf{u}(\xi, t)$ is a solution of (3.4) then

$$\partial_t \mathbf{u} = \frac{\mathcal{D}}{\rho^2(t)}\Delta_{\mathcal{M}}\mathbf{u} - n\frac{\dot{\rho}(t)}{\rho(t)}\mathbf{u} + \mathbf{F}(\mathbf{u}) \,.$$

Therefore, if $\mathbf{F}(\mathbf{u})$ and $\rho(t)$ are C^∞ in their arguments then $\partial_t \mathbf{u}(\xi, t)$ is continuous in time, and in consequence $\mathbf{u}(\xi, t)$ is C^1 in time. Now, if we derivate (3.4) with respect to time we see that $\partial_t^2 \mathbf{u}(\xi, t)$ is continuous in time as well, and so $\mathbf{u}(t, x)$ is C^2 in time. Continuing this way it follows that $\mathbf{u}(t, x)$ is C^∞ in time.

In conclusion, $\mathbf{u}(\xi, t) \in C^\infty\left[(0, T] \times \mathcal{M}, \mathbb{R}^M\right]$. $\square$

3.6 Proof of Theorem 3.4

Lemma 3.9 *Let $\mathcal{M}$ be a manifold and consider the reaction-diffusion system*

$$\partial_t \mathbf{u} = \mathcal{D}\Delta_{\mathcal{M}}\mathbf{u} + \mathbf{F}(\mathbf{u}) \,, \quad \mathbf{u}(\xi, t) = \mathbf{u}_0(\xi) \,. \tag{3.17}$$

Suppose that $\mathbf{u}_0(\xi) \in C\left[\mathcal{M}, \mathbb{R}^M\right]$ and that it takes its values inside the rectangle

$$\mathcal{R} = \prod_{j=1}^{M}(a_j, b_j) \,.$$

Suppose further that for all $z \in \partial\mathcal{R}$ we have

$$\mathbf{F}(z) \cdot \mathbf{n}(z) < 0\,, \tag{3.18}$$

where $\mathbf{n}(z)$ is the outer unit normal at z. Then the solution $\mathbf{u}(\xi, t)$ of (3.17) exists for all times $t \geq 0$ and takes its values inside $\mathcal{R}$.

Proof: This is Proposition 4.3 in Taylor [65], Chapter 15 (p.295). □

Lemma 3.10 *Let $\mathcal{M}_t$ be a growing manifold. Suppose that the initial condition of the reaction-diffusion system (3.4) is in $C\left[\mathcal{M}, \mathbb{R}^M\right]$ and takes its values inside the rectangle*

$$\mathcal{R} = \prod_{j=1}^{M} (a_j, b_j)\,.$$

Suppose further that for all $(z, t) \in \partial\mathcal{R} \times [0, \infty)$ we have

$$\mathbf{F}(z) \cdot \mathbf{n}(z) < c(t)\mathbf{n}(z) \cdot z \quad \forall t \geq 0, \tag{3.19}$$

where $\mathbf{n}(z)$ is the outer unit normal at z and $c(t)$ is the growth rate. Then the solution $\mathbf{u}(t)$ of (3.4) is global and bounded, i.e. it exists for all times $t \geq 0$ and takes its values inside $\mathcal{R}$.

Proof: From Lemma 3.8 the reaction-diffusion system (3.4) can be transformed into

$$\partial_t \mathbf{u} = \mathcal{D}\Delta_{\mathcal{M}}\mathbf{u} + \mathbf{G}(t, \mathbf{u})\,,$$

where $\mathbf{G}(t, \mathbf{u}) := -n\rho(t)\dot{\rho}(t)\mathbf{u} + \rho^2(t)\mathbf{F}(\mathbf{u})$. Taking a careful look at the proof of Lemma 3.9 in Taylor [65] we see that it also holds for nonlinearities that depend on time, provided

$$\mathbf{G}(t, z) \cdot \mathbf{n}(z) < 0 \quad \text{for all } (z, t) \in \partial\mathcal{R} \times [0, \infty), \tag{3.20}$$

where $\mathbf{n}(z)$ is the outer unit normal at z. Therefore, since condition (3.20) is equivalent to hypothesis (3.19), we can apply Lemma 3.9 to obtain that the solution $\mathbf{u}(t)$ of (3.4) exists for all times $t \geq 0$ and takes its values inside $\mathcal{R}$. □

Now we can conclude the proof of Theorem 3.4. If $\mathcal{R} = (-1, 1)^M$ then $\mathbf{n}(z) \cdot z = 1$ for all $z \in \partial\mathcal{R}$, which implies that (3.19) reduces to (3.5). Therefore, using Lemma 3.10 we obtain the result. □

3.7 Proof of Theorem 3.5

Let $(\mathcal{M}_t)_{0 \leq t \leq T}$ be an isotropic growing manifold and define the fixed manifold $\mathcal{S} := \mathcal{M}_T$. The linearisation of the operator on the fixed manifold $\mathcal{S}$ is

$$\mathcal{L}_{\mathcal{S}} := \frac{\mathcal{D}}{\rho^2(T)}\Delta_{\mathcal{S}} + d\mathbf{F}(0)$$

whilst the linearisation on the growing manifold $(\mathcal{M}_t)_{0\leq t\leq T})$ at time $t = T$ is

$$\mathcal{L}_{\mathcal{M}_T} := \frac{\mathcal{D}}{\rho^2(T)}\Delta_{\mathcal{M}_T} - c(T)I + d\mathbf{F}(0)\,, \quad c(T) := n\frac{\dot\rho(T)}{\rho(T)}\,.$$

Since $\mathcal{L}_{\mathcal{S}}$ and $\mathcal{L}_{\mathcal{M}_T}$ are second-order elliptic linear operators, their spectra consists of pure eigenvalues, i.e. the continuum spectrum for any of both spectra is empty. Let $\lambda \in \mathbb{C}$ be an eigenvalue on $\mathcal{L}_{\mathcal{S}}$. Then there exists a non-trivial function $\phi : \mathcal{S} \to \mathbb{C}$ solution of

$$\mathcal{L}_{\mathcal{S}}\phi = \lambda\phi.$$

Therefore, since

$$\mathcal{L}_{\mathcal{M}_T} = \mathcal{L}_{\mathcal{S}} - c(T)I$$

it follows that $\phi : \mathcal{M}_T \to \mathbb{C}$ is a non-trivial solution of

$$\mathcal{L}_{\mathcal{M}_T}\phi = (\lambda - c(T))\phi\,,$$

which implies that $\lambda - c(T)$ is an eigenvalue of $\mathcal{L}_{\mathcal{M}_T}$. $\square$

3.8 Discussion

Reaction-diffusion systems on growing manifolds

We have shown here that the same results presented by Plaza *et al* [52] hold in the case of any n-dimensional manifold (in the sense of Definition 3.1). Moreover, the techniques we used to prove Theorem 3.1 are independent of the choice of an orthogonal parametrisation. This implies that one can choose the coordinate system that is better for explicit calculations, regardless if it is orthogonal or not.

Linear stability analysis

The following lemma summarizes the properties of the Laplace-Beltrami operator $\Delta_{\mathcal{M}}$.

Lemma 3.11 *Let $\mathcal{M}$ be a manifold and consider the operator $-\Delta_{\mathcal{M}}$. Then:*

1. *All eigenvalues of $-\Delta_{\mathcal{M}}$ are real and nonnegative.*
2. *Zero is an eigenvalue with multiplicity one.*
3. *All eigenspaces are finite dimensional.*
4. *There exists infinitely eigenvalues*

   $$0 = \lambda_1 < \lambda_2 \leq \cdots \leq \lambda_k \to \infty\,,$$

   and they accumulate only at infinity (i.e. theres is no finite accumulation point.
5. *The eigenvectors of $-\Delta_{\mathcal{M}}$ constitute an orthonormal basis of $L^2(\mathcal{M})$.*

6. *All eigenvectors are smooth.*

Proof: See Rosenberg [57], Theorems 1.29 (p.32) and 1.31 (p.35). □

Lemma 3.11 states that the Laplace-Beltrami operator $\Delta_{\mathcal{M}}$ possesses the very same spectral properties than the Laplacian operator in euclidean, regular and bounded domains with Neumann boundary conditions. Therefore, all the linear stability analysis performed by Murray [49] can be applied to the case of a manifold, *mutatis mutandis*. Furthermore, the statement of Gjorgjieva and Jacobsen [28] we quoted in the Introduction holds for any 2-dimensional manifold: growth increases the number of possible patterns but (generically) chooses lower eigenmodes. Indeed, let us assume the following conditions:

- The manifold $\mathcal{M}$ is 2-dimensional.
- We have only two morphogens, whose diffusion coefficients are different (say 1 and $d > 1$).
- The nonlinearity $\mathbf{F}(\mathbf{u})$ depends on a real parameter γ in the form

$$\mathbf{F}(\gamma, \mathbf{u}) = \gamma \begin{bmatrix} f(u, v) \\ g(u, v) \end{bmatrix}$$

- The growth factor is exponential: $\rho(t) = e^{rt}$.

Under these conditions the system becomes

$$\begin{aligned} u_t &= e^{-rt}\Delta_{\mathcal{M}} u - 2ru + \gamma f(u, v)\,, \\ v_t &= e^{-rt} d\Delta_{\mathcal{M}} v - 2rv + \gamma g(u, v)\,, \end{aligned}$$

which is exactly the system (5)-(6) in Gjorgjieva and Jacobsen [28]. Moreover, if we substitute the spherical harmonics they use by the corresponding eigenvectors for $\Delta_{\mathcal{M}}$ we can perform the same analysis they have already done, thus obtaining the same results for a general 2-dimensional manifold. An open question we would like to address in the future is whether the linear stability analysis of Gjorgjieva and Jacobsen [28] is also valid for n-dimensional manifolds with more general growth functions.

Qualitative properties of solutions

Whenever a pattern formation problem is addressed there are several “natural” questions related to the system (3.4). In this work we answered affirmatively the questions of existence, uniqueness and regularity, and we showed that growth shifts the eigenvalues of the system (3.4) towards the left in the complex plane (Theorem 3.5). We have also noticed that the linear stability results of Gjorgjieva and Jacobsen [28] can be extrapolated to general surfaces. However, the bifurcation analysis is far from being complete, and symmetry breaking and asymptotic behavior for large times are open questions. We aim to study these properties in future works.

The *anti-blow-up* effect of growth on pattern formation

Growth has an *anti-blow-up* effect because it enhances the possibility of global existence of solutions. Indeed, condition (3.5) in Theorem 3.4 is less restrictive than condition (3.18) in Lemma 3.9 because even if (3.18) does not hold (3.5) can be fulfilled. In that case, a solution of the system (3.17) on the fixed manifold $\mathcal{M}$ is perhaps only a time-local solution, but as a solution of the system (3.4) on the growing manifold $(\mathcal{M}_t)_{t\geq 0}$ it could be globally defined in time. In order to quantitatively assess this anti-blow-up effect we provided two examples on the scalar case, where there is blow-up for the corresponding equation. We found that on a growing manifold the blow-up occurs at a later time than on the fixed manifold, and if growth is fast enough then the blow-up does not occur at all.

The stabilising effect of growth on pattern formation

As it was shown in Theorem 3.5, growth shifts the spectrum towards the left in the complex plane by the explicit factor $c(T) > 0$. This implies that the real parts of the eigenvalues are smaller on the growing manifold $(\mathcal{M}_t)_{0\leq t\leq T}$ at time $t = T$ than on the corresponding fixed manifold $\mathcal{S} = \mathcal{M}_T$, which is a gain of stability. It is worth to mention that our proof does not work for non-isotropic growing manifolds because we considered the growth rate to be independent of the space variable ξ. It would be interesting to see if the stabilising effect of growth holds for not only for non-isotropic growing manifolds property but also for more general growth regimes, e.g. then the growth factor is not exogenous but it is also one of the unknowns of the problem. From Theorem 3.5 we can also infer that growth is a regulatory mechanism for stability, in the sense that it enhances stability and selects the most stable patterns for expression. This fact is very important because it suggests that growth is an important factor in self-regulation features occurring in embryogenesis (see Meinhardt [47]) and tumor growth (see Chaplain *et al* [13]). Whether these applications are possible is a crucial problem, which we would like to study in detail in the future.

Exponential growth factor

A very special type of growth factor is $\rho(t) = ae^{rt}$ because $c(t)$ is constant if and only if the growth factor $\rho(t)$ is of exponential type. This observation implies that the simplest case of growth to be added on a model is exponential, and therefore it is important to work on the exponential case before approaching a more general growth factor in order to gain some insight. In that spirit we have shown that if $r > 0$ is big enough then the solutions of the system (3.4) are globally defined (i.e. there is no blow-up). But there are more features of the exponential growth. For example, Gjiorgjieva [27] showed that the system (3.4) on a 2-dimensional sphere with two morphogens and exponential isotropic growth has a constant equilibrium solution if and only if $\rho(t)$ is exponential (see Lemma 5.1, p.50), and we can show that her result holds for any manifold and for any number of morphogens. Indeed, (3.4) has a constant equilibrium $\mathbf{u}_0 = (u_1^0, \dots, u_M^0)$ if and only if

$$n\frac{\dot{\rho}(t)}{\rho(t)}\mathbf{u}_0 = \mathbf{F}(\mathbf{u}_0)\,.$$

Therefore, if $\mathbf{u}_0 \not\equiv 0$ then for any $u_i^0 \neq 0$ we have

$$\frac{\dot{\rho}(t)}{\rho(t)} = \frac{F_i(\mathbf{u}_0)}{n u_i^0}\,, \tag{3.21}$$

which implies that $\dot{\rho}(t)/\rho(t)$ is constant, and in consequence $\rho(t)$ is exponential. Therefore, if we have a constant equilibrium then the growth function is exponential and its growth rate is completely determined by the nonlinearity. In other words, whenever we find a constant equilibrium the growth factor is necessarily exponential, i.e. $\rho(t) = ae^{rt}$, and we can calculate the growth exponent $r > 0$ using (3.21).

Chapter 4

Generalised travelling waves on manifolds

In the article of H. Berestycki and F. Hamel, *Generalised transition waves and their properties*, there is a generalization of the classical definition of a transition wave in Euclidean spaces (e.g. a travelling wave or an invasive front) to the case where the level sets of the wave are no longer planes but surfaces. We will prove that the same results and properties on general transition waves that appear in the cited article hold in the case of a non-compact complete Riemannian manifold, namely: (1) the wave is associated to a generalised front, which moves "close" to the level sets of the wave; (2) there is a mean propagation speed of the wave, which is independent of the choice of the associated front; (3) in the case of an invasion the wave is an increasing function of time.

4.1 Definition of general travelling waves on manifolds

4.1.1 Complete Riemannian manifolds

Let $\mathcal{M}$ be a n-dimensional, C^∞ Riemannian manifold, and let $g_{ij}(\xi)$ be its metric in the local coordinates $\xi \in \mathbb{R}^n$. We will suppose that $\mathcal{M}$ is closed, connected, without boundary, unbounded (i.e. non-compact) and complete. Recall that a manifold $\mathcal{M}$ is complete if any of the following statements hold (see Bishop and Crittenden [11], Theorem 5, p. 154):

1. $\mathcal{M}$ is complete as a metric space, i.e. any Cauchy sequence in $\mathcal{M}$ has a limit in $\mathcal{M}$.

2. All bounded closed subsets of $\mathcal{M}$ are compact.

3. All geodesics are infinitely extendible.

These conditions are equivalent, and they imply the next result:

(∗) Any $x, y \in \mathcal{M}$ can be joined by a geodesic whose arc length equals the geodesic distance $d(x, y)$.

The geodesic distance is defined as:

$$d(x,y) := \inf\{\,|\gamma| : \gamma \in G\,\}\,,$$

where G is the set of all continuous and piecewise C^∞ curves from x to y, and $|\gamma|$ is the arc length of a curve γ. Moreover, the geodesic distance is a continuous functions, and the topology it generates is equivalent to the topology of $\mathcal{M}$ as a manifold (see Bishop and Crittenden [11], pp. 124-125).

4.1.2 Reaction-diffusion equations on manifolds

From now on, we will work on a manifold $\mathcal{M}$ with the properties stated in Section 4.1.1.

Consider the scalar reaction-diffusion equation

$$\begin{cases} \partial_t u = D\Delta_{\mathcal{M}} u + F(t,x,u)\,; & t \in \mathbb{R},\ x \in \mathcal{M}\,, \\ u(0,x) = u_0(x)\,; & x \in \mathcal{M}\,. \end{cases} \tag{4.1}$$

$\Delta_{\mathcal{M}}$ is the Laplace-Beltrami operator, which in local coordinates takes the form (note that we use the sum convention)

$$\Delta_{\mathcal{M}} u = \frac{1}{\sqrt{g}}\,\partial_j[\,\sqrt{g}\,g^{ij}\,\partial_i u\,]\,, \tag{4.2}$$

where $\partial_i := \partial_{\xi_i}$, $(g^{ij}) = (g_{ij})^{-1}$ and $g = det(g_{ij})$. Another way of expressing the Laplace-Beltrami operator is

$$\begin{aligned} \Delta_{\mathcal{M}} u &= g^{ij}\partial_{ij}u + \frac{1}{\sqrt{g}}\partial_j[\,g^{ij}\sqrt{g}\,]\partial_i u \\ &= g^{ij}\partial_{ij}u - g^{ij}\Gamma^k_{ij}\partial_k u\,, \end{aligned}$$

where $\partial_{ij} = \partial^2_{\xi_i\xi_j}$ and

$$\Gamma^k_{ij} = \frac{1}{2}g^{kl}[\partial_j g^{il} + \partial_i g^{jl} - \partial_l g^{ij}]$$

are the Schwartz-Christoffel symbols.

The assumptions on the nonlinearity $F(t,x,u)$ are:

- Either F is C^1 and both F and $\partial_u F$ are globally bounded, or
- Either F is bounded, continuous in (t,x) and locally Lipschitz continuous in u, uniformly in (t,x).

We can also suppose that F does not depend on the variables (t,x), i.e. $F = F(u)$.

4.1.3 Fronts, waves and invasions

For any two subsets $A, B \subset \mathcal{M}$ denote

$$d(A,B) := \inf\{\, d(x,y) \,:\, x \in A,\, y \in B\}\,.$$

Definition 4.1 Generalised profile
A generalised profile is a family $(\Omega_t^\pm, \Gamma_t)_{t\in\mathbb{R}}$ of subsets of $\mathcal{M}$ with the following properties:

1. *Ω_t^- and Ω_t^+ are non-empty disjoint subsets of $\mathcal{M}$, for any $t \in \mathbb{R}$.*
2. *$\Gamma_t = \partial\Omega_t^- \cap \partial\Omega_t^+$ and $\mathcal{M} = \Gamma_t \cup \Omega_t^- \cup \Omega_t^+$, for any $t \in \mathbb{R}$.*
3. *$\sup\{\, d(x,\Gamma_t) \,:\, t \in \mathbb{R},\, x \in \Omega_t^-\} = \sup\{\, d(x,\Gamma_t) \,:\, t \in \mathbb{R},\, x \in \Omega_t^+\} = +\infty$*

Suppose that there exist $p^-, p^+ \in \mathbb{R}$ such that $F(t,x,p^\pm) = 0$ for all $t \in \mathbb{R}$ and all $x \in \mathcal{M}$. Then $u \equiv p^\pm$ are solutions of (4.1).

Definition 4.2 Generalised front
Let $u(t,x)$ be a time-global classical solution of (4.1) such that $u \not\equiv p^\pm$. Then $u(x,t)$ is a generalised front between p^- and p^+ if there exists a generalised profile $(\Omega_t^\pm, \Gamma_t)_{t\in\mathbb{R}}$ such that

$$|u(t,x) - p^\pm| \to 0 \text{ uniformly when } x \in \Omega_t^\pm \text{ and } d(x,\Gamma_t) \to +\infty.$$

Observe that the generalised profile $(\Omega_t^\pm, \Gamma_t,)_{t\in\mathbb{R}}$ is not uniquely determined. However, it is important to bear in mind that any generalised front $u(t,x)$ is by definition associated to a certain generalised profile.

Definition 4.3 Generalised invasion
Let $u(t,x)$ be a generalised front. We say that p^+ invades p^- or that $u(t,x)$ is a generalised invasion of p^- by p^+ (resp. p^- invades p^+ or that $u(t,x)$ is a generalised invasion of p^+ by p^-) if

(i) $\Omega_t^+ \subset \Omega_s^+$ (resp. $\Omega_s^- \subset \Omega_t^-$) for all $t \le s$.

(ii) $d(\Gamma_t, \Gamma_s) \to +\infty$ when $|t-s| \to +\infty$.

Remark that if p^+ invades p^- (resp. p^- invades p^+) then $u(t,x) \to p^\pm$ when $t \to \pm\infty$ (resp. when $t \to \mp\infty$), locally uniformly in $\mathcal{M}$ with respect to the geodesic distance $d(\cdot,\cdot)$.

Example 4.1 *Let us consider the reaction diffusion equation (4.1) in $\mathcal{M} = \mathbb{R}^n$ with $D = 1$. In this case the Laplace-Beltrami operator $\Delta_{\mathcal{M}}$ is the classical Laplacian $\Delta = \partial_{ii}$, and (4.1) takes the form*

$$\begin{cases} \partial_t u = \Delta u + F(u)\,; & t \in \mathbb{R},\ x \in \mathbb{R}^n\,, \\ u(0,x) = u_0(x)\,; & x \in \mathbb{R}^n\,. \end{cases} \qquad . \tag{4.3}$$

If we are looking for generalised travelling waves of the form $u(t,x) = \phi(x \cdot e - ct)$, with $e \in \mathbb{R}^n$ is a unit vector and $c > 0$, the natural choice for the generalised front is

$$\Gamma_t = \{x \in \mathbb{R}^n \,:\, x \cdot e - ct = 0\}\,, \quad \Omega_t^\pm = \{x \in \mathbb{R}^n \,:\, \pm(x \cdot e - ct) > 0\}\,.$$

In this framework, (4.1) becomes

$$c\phi' + \phi'' + F(\phi) = 0\,.$$

Example 4.2 *Consider the parametrization*

$$\begin{array}{rcl} S^1 \times \mathbb{R} & \longrightarrow & \mathcal{M} \subset \mathbb{R}^3 \\ (\xi, z) & \longmapsto & (x, y, z) = (r\cos\xi\,, \sin\xi, z) \end{array}$$

where $\xi \in [0, 2\pi)$ and $r > 0$ is fixed. The Laplace-Beltrami operator is

$$\Delta_{\mathcal{M}} = \frac{1}{r^2}\partial_{\xi\xi} + \partial_{zz}\,.$$

If we want to study travelling waves in the axial direction z, it is a natural guess to consider $u(t, x) = \phi(z - ct)$. In this case (4.1) takes the same form as in Example 4.1, i.e.

$$c\phi' + \phi'' + F(\phi) = 0\,,$$

and the corresponding front is

$$\Gamma_t = \{(x, y, z) \in \mathcal{M}\, :\, z - ct = 0\}\,, \quad \Omega_t^{\pm} = \{(x, y, z) \in \mathcal{M}\, :\, \pm(z - ct) > 0\}\,.$$

From now on, for the sake of simplicity, we will call a *profile* any generalised profile, a *front* any generalised front, and a *invasion* any generalised invasion.

Definition 4.4 Global mean speed

A front $u(t, x)$ has global mean speed $c > 0$ if the profile $(\Omega_t^{\pm}, \Gamma_t,)_{t\in\mathbb{R}}$ is such that

$$\frac{d(\Gamma_t, \Gamma_s)}{|t - s|} \to c \quad \text{when } |t - s| \to +\infty.$$

In Example 4.1 we have

$$\Gamma_t = \{x \in \mathbb{R}^n\, :\, x \cdot e - ct = 0\}\,,$$

which implies that

$$d(\Gamma_t, \Gamma_s) = c|t - s|\,.$$

In consequence, the velocity of propagation of the profile $(\Omega_t^{\pm}, \Gamma_t,)_{t\in\mathbb{R}}$ coincides with its global mean speed.

Remark 4.5 *All these definitions hold also in the case of a reaction-diffusion equation or system on a growing manifold $\mathcal{M}_t$ (see Labadie [39] and Plaza* et al *[52] for the definition and properties of reaction-diffusion equations on growing manifolds).*

4.2 Properties of fronts on manifolds

For any $x \in \mathcal{M}$ and any $r > 0$ define

$$\begin{aligned} B(x,r) &= \{\, y \in \mathcal{M} \,:\, d(x,y) \leq r \,\}, \\ S(x,r) &= \{\, y \in \mathcal{M} \,:\, d(x,y) = r \,\}. \end{aligned}$$

Theorem 4.1 Level sets
Let $p^- < p^+$ and suppose that $u(t,x)$ is a time-global solution of (4.1) such that

$$p^- < u(t,x) < p^+ \quad \text{for all } (t,x) \in \mathbb{R} \times \mathcal{M}.$$

1. *Suppose $u(t,x)$ is front between p^- and p^+ (or between p^+ and p^-) with the following properties:*

   (a) There exists $\tau > 0$ such that $\sup\{\, d(x, \Gamma_{t-\tau}) \,:\, t \in \mathbb{R},\, x \in \Gamma_t \,\} < +\infty$, and

   (b) $\sup\{\, d(y,\Gamma_t) \,:\, y \in \overline{\Omega_t^{\pm}} \cap S(x,r) \,\} \to +\infty$ when $r \to +\infty$, uniformly in $t \in \mathbb{R}$ and $x \in \Gamma_t$.

   Then:

   (i) $\sup\{\, d(x,\Gamma_t) \,:\, u(t,x) = \lambda \,\} < +\infty$ for all $\lambda \in (p^-, p^+)$.

   (ii) $p^- < \inf\{\, u(t,x) \,:\, d(x,\Gamma_t) \leq C \,\} \leq \sup\{\, u(t,x) \,:\, d(x,\Gamma_t) \leq C \,\} < p^+$ for all $C \geq 0$.

2. *Conversely, if (i) and (ii) hold for a certain profile $(\Omega_t^{\pm}, \Gamma_t,)_{t\in\mathbb{R}}$ and there exists $d_0 > 0$ such that for all $d \geq d_0$ the sets*

   $$\{\, (t,x) \in \mathbb{R} \times \mathcal{M} \,:\, x \in \overline{\Omega_t^{\pm}},\, d(x,\Gamma_t) \geq d \,\}$$

   are connected, then $u(t,x)$ is a front between p^- and p^+ (or between p^+ and p^-).

Theorem 4.2 Uniqueness of the global mean speed
Let $p^- < p^+$ and suppose that $u(t,x)$ is a front between p^- and p^+, where its associated profile $(\Omega_t^{\pm}, \Gamma_t,)_{t\in\mathbb{R}}$ satisfies (b) in Theorem 4.1. If $u(t,x)$ has a global mean speed $c > 0$ then the speed is independent of the profile. In other words, if for any other profile $(\tilde{\Omega}_t^{\pm}, \tilde{\Gamma}_t,)_{t\in\mathbb{R}}$ satisfying (b) the front $u(t,x)$ has global mean speed $\tilde{c}$, then $\tilde{c} = c$.

Theorem 4.3 Monotonicity
Let $p^- < p^+$ and suppose $F(t,x,u)$ satisfies the following conditions:

(α) *$s \mapsto F(s,x,u)$ is non-decreasing for all $(x,u) \in \mathbb{M} \times \mathbb{R}$.*

(β) *There exists $\delta > 0$ such that $q \mapsto F(t,x,q)$ is non-increasing for all $q \in \mathbb{R} \setminus (p^- + \delta, p^+ - \delta)$.*

Let $u(t,x)$ be an invasion of p^- by p^+ and assume (as in Theorem 4.1) that:

(a) There exists $\tau > 0$ such that $\sup\{\, d(x,\Gamma_{t-\tau}) \,:\, t \in \mathbb{R},\, x \in \Gamma_t \,\} < +\infty$, and

(b) $\sup\{\, d(y,\Gamma_t) \,:\, y \in \overline{\Omega_t^\pm} \cap S(x,r) \,\} \to +\infty$ uniformly in $t \in \mathbb{R}$ and $x \in \Gamma_t$ when $r \to +\infty$.

Then:

1. *$p^- < u(t,x) < p^+$ for all $(t,x) \in \mathbb{R} \times \mathcal{M}$.*
2. *$u(t,x)$ is increasing in time, i.e. $u(t+s,x) > u(t,x)$ for all $s > 0$.*

4.3 Proofs

4.3.1 Proof of Theorem 4.1

Proposition 4.4 $\sup\{\, d(x,\Gamma_t) \,:\, u(t,x) = \lambda \,\} < +\infty$ *for all $\lambda \in (p^-,p^+)$.*

Proof: Suppose it is not true. Then there is a $\lambda \in (p^-,p^+)$ and a sequence $(t_n,x_n)_{n\in\mathbb{N}}$ in $\mathbb{R}\times\mathcal{M}$ such that $u(t_n,x_n) = \lambda$ and $d(x_n,\Gamma_{t_n}) \to +\infty$ when $n \to +\infty$.

Up to extraction of a subsequence, either $x_n \in \overline{\Omega_{t_n}^-}$ for all n, or either $x_n \in \overline{\Omega_{t_n}^+}$ for all n. Since $u(t,x)$ is a generalised wave then in the first case $u(t_n,x_n) \to p^-$, whilst in the second case $u(t_n,x_n) \to p^+$, hence in any case we reach a contradiction. □

Proposition 4.5 $p^- < \inf\{\, u(t,x) \,:\, d(x,\Gamma_t) \le C \,\} \le \sup\{\, u(t,x) \,:\, d(x,\Gamma_t) \le C \,\} < p^+$ *for all $C \ge 0$.*

Proof: Suppose it is not true. Then there exist $C > 0$ and a sequence $(t_n,x_n)_{n\in\mathbb{N}}$ in $\mathbb{R}\times\mathcal{M}$ such that $d(x_n,\Gamma_{t_n}) \le C$ and $u(t_n,x_n) \to p^-$ or p^+ when $n \to +\infty$. Since both cases can be treated with similarly let us only prove the case

$$u(t_n,x_n) \to p^- \quad \text{when} \quad n \to +\infty\,. \tag{4.4}$$

Since $d(x_n,\Gamma_{t_n}) \le C$ for all n, Property (a) implies that there exist $\tau > 0$ and a sequence $(\tilde{x}_n)_{n\in\mathbb{N}}$ such that $\tilde{x}_n \in \Gamma_{t_n-\tau}$ for all n and

$$\sup\{\, d(x_n,\tilde{x}_n) \,:\, n \in \mathbb{N} \,\} < +\infty\,.$$

From the definition of a front it follows that there exists $d > 0$ such that

$$d(y,\Gamma_t) \ge d \quad \text{implies that} \quad u(t,y) \ge \frac{p^- + p^+}{2} \quad \text{for all } (t,y) \in \mathbb{R}\times\overline{\Omega_t^+}.$$

From Property (b) there exists $r > 0$ such that, for each n, there exists $y_n \in \overline{\Omega_{t_n-\tau}^+}$ satisfying

$$d(\tilde{x}_n,y_n) = r \quad \text{and} \quad d(y_n,\Gamma_{t_n-\tau}) \ge d\,.$$

Therefore

$$u(t_n-\tau,y_n) \ge \frac{p^- + p^+}{2} \quad \text{for all } n. \tag{4.5}$$

On the other hand, the function $v(t,x) := u - p^-$ is non-negative. Moreover, recalling $F(t,x,p^-) = 0$ it follows that v satisfies the nonlinear equation

$$\partial_t v = D\Delta_{\mathcal{M}} v + F(t,x,u) \quad \text{in } \mathbb{R} \times \mathcal{M}.$$

This implies that v satisfies the linear equation

$$\partial_t v = D\Delta_{\mathcal{M}} v + b(t,x)v \quad \text{in } \mathbb{R} \times \mathcal{M},$$

where

$$b(t,x) = \begin{cases} \frac{F(t,x,u(t,x)) - F(t,x,p^-)}{u(t,x)-p^-} = \frac{F(t,x,u(t,x))}{u(t,x)-p^-}, & \text{if } u(t,x) \neq p^-, \\ \Theta, & \text{if } u(t,x) = p^-, \end{cases}$$

- $\Theta = \partial_u F(t,x,p^-)$ if F is C^1 in u, uniformly in (t,x), and both F and $\partial_u F$ are globally bounded, or
- $\Theta = K$, if $F(t,x,\cdot)$ is Lipschitz continuous and bounded in u, uniformly in (t,x).

In both cases $b(t,x)$ is at least bounded and measurable. Therefore we can apply Harnack's inequality to $v(t,x)$ and obtain that there exists $C_1 > 0$ such that

$$u(t_n - \tau, y_n) - p^- = v(t_n - \tau, y_n) \leq C_1 v(t_n, x_n) = C_1 [u(t_n, x_n) - p^-] .$$

It is important to remark that C_1 depends on τ but is independent of n. In consequence, we can take the limit $n \to +\infty$ and use (4.4)-(4.5) to obtain

$$\frac{p^+ - p^-}{2} \leq 0 ,$$

which is a contradiction. $\square$

We suppose here that Propositions 4.4 and 4.5 hold, and that there exists $d_0 > 0$ such that for all $d \geq d_0$ the sets

$$\{ (t,x) \in \mathbb{R} \times \mathcal{M} \, : \, x \in \overline{\Omega_t^\pm}, \, d(x, \Gamma_t) \geq d \}$$

are connected.

Define

$$\begin{aligned} m^- &:= \liminf \{ u(t,x) \, : \, x \in \overline{\Omega_t^-}, \, d(x,\Gamma_t) \to +\infty \} , \\ M^- &:= \limsup \{ u(t,x) \, : \, x \in \overline{\Omega_t^-}, \, d(x,\Gamma_t) \to +\infty \} . \end{aligned}$$

We affirm that $m^- = M^-$. Indeed, if $m^- < M^-$ then $\lambda := (m^- + M^-)/2 \in (m^-, M^-)$. Moreover, by hypothesis $p^- \leq m^- \leq M^- \leq p^+$, which implies that $\lambda \in (p^-, p^+)$. Therefore, using Property (i) it follows that there exists $C > 0$ such that

$$d(x, \Gamma_t) < C \;\text{ for all }\; (t,x) \in \mathbb{R} \times \mathcal{M} \;\text{ with }\; u(t,x) = \lambda.$$

On the other hand, by definition of lim inf and lim sup there exists two points $(t_1, x_1), (t_2, x_2) \in \mathbb{R} \times \overline{\Omega_t^-}$ such that

$$u(t_1, x_1) < \lambda < u(t_2, x_2) \text{ and } d(x_i, \Gamma_{t_i}) \geq \max\{C, d_0\} \text{ for } i = 1, 2.$$

Now recall that by hypothesis the set

$$\{ (t, x) \in \mathbb{R} \times \mathcal{M} : x \in \overline{\Omega_t^-},\, d(x, \Gamma_t) \geq \max\{C, d_0\} \}$$

is connected. Therefore, since $u(t, x)$ is continuous there exist

$$(t, x) \in \mathbb{R} \times \overline{\Omega_t^-} \text{ such that } d(x, \Gamma_t) \geq \max\{C, d_0\} \text{ and } u(t, x) = \lambda,$$

which contradicts the definition of C_0.

Therefore $m^- = M^-$, and in consequence $u(t, x)$ has a limit, i.e.

$$u(t, x) \to m^- \text{ uniformly in } x \in \overline{\Omega_t^-} \text{ when } d(x, \Gamma_t) \to +\infty\,.$$

Similarly, switching all $-$ signs by $+$ we obtain that

$$u(t, x) \to m^+ \text{ uniformly in } x \in \overline{\Omega_t^+} \text{ when } d(x, \Gamma_t) \to +\infty\,.$$

We now affirm that $p^- = \min\{m^-, m^+\}$ and $p^+ = \max\{m^-, m^+\}$. Indeed, if $p^- < \min\{m^-, m^+\}$ then there exist $\varepsilon > 0$ and $C > 0$ such that

$$u(t, x) \geq p^- + \varepsilon > p^- \text{ for all } (t, x) \text{ with } d(x, \Gamma_t) \geq C.$$

But by Property (ii) we also have that

$$\inf\{ u(t, x) : d(x, \Gamma_t) \leq C \} > p^-\,.$$

In consequence,

$$\inf\{ u(t, x) : (t, x) \in \mathbb{R} \times \mathcal{M} \} > p^-\,,$$

which contradicts the fact that the range of $u(t, x)$ is the whole interval (p^-, p^+).

In conclusion, $p^- = \min\{m^-, m^+\}$, and analogously we can show that $p^+ = \max\{m^-, m^+\}$.

Finally, note that if $m^- = p^-$ and $m^+ = p^+$ then $u(t, x)$ is a front between p^- and p^+, whilst if $m^- = p^+$ and $m^+ = p^-$ then $u(t, x)$ is a front between p^+ and p^-.

This concludes the proof of Theorem 4.1.

4.3.2 Proof of Theorem 4.2

Let $p^- < p^+$ and suppose that the front $u(t,x)$ has global mean speed $c > 0$ with respect to the profile $(\Omega_t^\pm, \Gamma_t)_{t\in\mathbb{R}}$. Let $(\tilde{\Omega}_t^\pm, \tilde{\Gamma}_t)_{t\in\mathbb{R}}$ be another profile for $u(t,x)$ satisfying (b) in Theorem 4.1. We have to prove that $u(t,x)$ has also a global mean speed with respect to the new profile $(\tilde{\Omega}_t^\pm, \tilde{\Gamma}_t)_{t\in\mathbb{R}}$, and that it is precisely c.

Proposition 4.6 *There exists $C > 0$ such that*

$$d(x, \tilde{\Gamma}_t) \leq C \text{ for all } t \in \mathbb{R} \text{ and all } x \in \Gamma_t \ . \tag{4.6}$$

<u>*Proof*</u>: If (4.6) does not hold then there is a sequence $(t_n, x_n)_{n\in\mathbb{N}}$ such that

$$x_n \in \Gamma_{t_n} \text{ and } d(x_n, \tilde{\Gamma}_{t_n}) \to +\infty \text{ when } n \to +\infty \ . \tag{4.7}$$

Up to extraction of a subsequence, either $x_n \in \tilde{\Omega}_{t_n}^-$ for all n, or either $x_n \in \tilde{\Omega}_{t_n}^+$ for all n. Since both cases can be proven similarly, we will suppose that $x_n \in \tilde{\Omega}_{t_n}^-$ for all n.

Since $u(t,x)$ is a front then there exists $A > 0$ such that

$$|u(t,x) - p^+| \leq \frac{p^+ - p^-}{2} \text{ for all } (t,x) \in \mathbb{R} \times \overline{\Omega_t^+} \text{ with } d(x, \Gamma_t) \geq A. \tag{4.8}$$

Property (b) implies that for each n there exists $r > 0$ and $y_n \in \overline{\Omega_{t_n}^+}$ such such that

$$d(x_n, y_n) = r \text{ and } d(y_n, \Gamma_{t_n}) \geq A \ . \tag{4.9}$$

Note that the uniformity of the limit in (b) implies that $r > 0$ is independent of n. Therefore, using (4.7) and (4.9) it follows that

$$d(y_n, \tilde{\Gamma}_{t_n}) \to +\infty \text{ when } n \to +\infty \ .$$

Moreover, if n is sufficiently big then $y_n \in \tilde{\Omega}_{t_n}^-$ because, should $y_n \in \overline{\tilde{\Omega}_{t_n}^+}$, then using $\tilde{\Gamma}_{t_n} = \partial\tilde{\Omega}_{t_n}^- \cap \partial\tilde{\Omega}_{t_n}^+$ we would obtain

$$d(x_n, \tilde{\Gamma}_{t_n}) \leq d(x_n, \overline{\tilde{\Omega}_{t_n}^+}) \leq d(x_n, y_n) = r \, ,$$

which contradicts (4.7).

In the light of this we have that $u(t_n, y_n) \to p^-$ when $n \to +\infty$. But we also have that $y_n \in \overline{\Omega_{t_n}^+}$, so using (4.8)-(4.9) we obtain

$$|u(t_n, y_n) - p^+| \leq \frac{p^+ - p^-}{2} \quad \text{for all } n.$$

In consequence, making $n \to +\infty$ it follows that

$$|p^- - p^+| \leq \frac{p^+ - p^-}{2} \, ,$$

which is a contradiction. In conclusion, (4.6) holds. □

Now let $\varepsilon > 0$. Then for any two times $t, s \in \mathbb{R}$:

- There exist $x \in \Gamma_t$ and $y \in \Gamma_s$ such that $d(x,y) \le d(\Gamma_t, \Gamma_s) + \varepsilon$.
- There exist $\tilde{x} \in \tilde{\Gamma}_t$ and $\tilde{y} \in \tilde{\Gamma}_s$ such that $d(\tilde{x},\tilde{y}) \le d(\tilde{\Gamma}_t, \tilde{\Gamma}_s) + \varepsilon$.
- $d(x,\tilde{x}) \le d(x,\tilde{\Gamma}_t) + \varepsilon$ and $d(y,\tilde{y}) \le d(y,\tilde{\Gamma}_s) + \varepsilon$.

Therefore, by virtue of (4.6) we have

$$\begin{aligned} d(\tilde{x},\tilde{y}) &\le d(\tilde{x},x) + d(x,y) + d(y,\tilde{y}) \\ &\le (C+\varepsilon) + (d(\Gamma_t,\Gamma_s)+\varepsilon) + (C+\varepsilon) \\ &\le d(\Gamma_t,\Gamma_s) + 2C + 3\varepsilon\,. \end{aligned}$$

and in consequence

$$d(\tilde{\Gamma}_t,\tilde{\Gamma}_s) \le d(\Gamma_t,\Gamma_s) + 2C + 3\varepsilon\,.$$

Since $\varepsilon > 0$ was arbitrary then

$$d(\tilde{\Gamma}_t,\tilde{\Gamma}_s) \le d(\Gamma_t,\Gamma_s) + 2C \quad \text{for all } \; t,s \in \mathbb{R},$$

which implies that

$$\limsup_{|t-s|\to+\infty} \frac{d(\tilde{\Gamma}_t,\tilde{\Gamma}_s)}{|t-s|} \le \limsup_{|t-s|\to+\infty} \frac{d(\Gamma_t,\Gamma_s)}{|t-s|} = c\,. \tag{4.10}$$

Now observe that interchanging the roles of the sets $\Omega_t^{\pm}$ and $\tilde{\Omega}_t^{\pm}$ it can be shown that there exists $\tilde{C} > 0$ such that

$$d(\tilde{x},\Gamma_t) \le \tilde{C} \quad \text{for all } \; t \in \mathbb{R} \; \text{ and all } \; \tilde{x} \in \tilde{\Gamma}_t\;,$$

i.e. the "tilde" version of (4.6). In the light of this, it can be shown as well that

$$d(\Gamma_t,\Gamma_s) \le d(\tilde{\Gamma}_t,\tilde{\Gamma}_s) + 2\tilde{C} \quad \text{for all } \; t,s \in \mathbb{R},$$

and in consequence

$$c = \liminf_{|t-s|\to+\infty} \frac{d(\Gamma_t,\Gamma_s)}{|t-s|} \le \liminf_{|t-s|\to+\infty} \frac{d(\tilde{\Gamma}_t,\tilde{\Gamma}_s)}{|t-s|}\,. \tag{4.11}$$

From (4.10) and (4.11) we deduce that the limit

$$\lim_{|t-s|\to+\infty} \frac{d(\tilde{\Gamma}_t,\tilde{\Gamma}_s)}{|t-s|}$$

exists and is equal to c.

This concludes the proof of Theorem 4.2.

4.3.3 Proof of Theorem 4.3

Proposition 4.7 *$p^- < u(t,x) < p^+$ for all $(t,x) \in \mathbb{R} \times \mathcal{M}$.*

Proof: Define

$$m := \inf\{\, u(t,x) - p^- \;:\; (t,x) \in \mathbb{R} \times \mathcal{M}\,\}$$

and suppose $m < -\delta < 0$. Let $(t_n, x_n)_{n\in\mathbb{N}}$ be a sequence in $\mathbb{R} \times \mathcal{M}$ such that

$$u(t_n, x_n) - p^- \to m \quad \text{when } n \to \infty\,.$$

Since $u(t,x)$ is a front and

$$u(t_n, x_n) \to m + p^- < p^- < p^+$$

we have that the sequence $d(x_n, \Gamma_{t_n})$ is bounded (otherwise $u(t_n, x_n)$ would converge to either p^- or p^+ by definition). From Property (a) it follows that, for any $n \in \mathbb{N}$, there exists a point $\tilde{x}_n \in \Gamma_{t_n - \tau}$ such that the sequence $d(x_n, \tilde{x}_n)_{n\in\mathbb{N}}$ is bounded. Since $u(t,x)$ is a front there exists $d > 0$ such that $u(t,x) \geq p^-$ whenever $d(x, \Gamma_t) \geq d$.

From Property (b) there is a sequence $(y_n)_{n\in\mathbb{N}}$ such that, for any $n \in \mathbb{N}$:

- $y_n \in \overline{\Omega^+_{t_n-\tau}}$,
- $d(y_n, \tilde{x}_n) = r$,
- $d(y_n, \Gamma_{t_n-\tau}) \geq d$.

Using this properties we have that

$$u(t_n - \tau, y_n) \geq p^- \quad \text{for all } \; n \in \mathbb{N}. \tag{4.12}$$

Define

$$w(t,x) := u(t,x) - p^- + m \geq 0\,.$$

If $n \in \mathbb{N}$ is big enough then it follows from condition (β) that w satisfies

$$\partial_t w \geq D\Delta_{\mathcal{M}} w + F(t,x,u) \geq D\Delta_{\mathcal{M}} w + F(t,x,w) \quad \text{for all } t \geq t_n.$$

Therefore, using the same argument of Proposition 4.5 we can show that there exists a function $b \in L^\infty(\mathbb{R} \times \mathcal{M})$ such that w satisfies the linear equation

$$\partial_t w \geq D\Delta_{\mathcal{M}} w + b(t,x) w \quad \text{in } \mathbb{R} \times \mathcal{M}.$$

As before, we apply Harnack's inequality to $w(t,x)$ and obtain that there exists $C_1 > 0$, independent of n, such that

$$w(t_n - \tau, y_n) - p^- = u(t_n - \tau, y_n) - p^- - m \leq C_1 v(t_n, x_n) = C_1[u(t_n, x_n) - p^- - m]\,.$$

Making $n \to +\infty$ and using (4.4)-(4.5) it follows that the left-hand side converges to

$$p^+ - p^- - m > 0\,,$$

whilst the right-hand side converges by definition to zero. In consequence, we have obtained a contradiction.

We have thus shown that $m \geq 0$, which implies that $p^- < u(t,x)$ for all $(t,x) \in \mathbb{R} \times \mathcal{M}$. The inequality $u(t,x) < p^+$ can be proven with the same arguments. $\square$

Remark 4.6 *Decreasing $\delta > 0$ if necessary we can assume that $2\delta < p^+ - p^-$. Moreover, from Definition 4.2 there exists $A > 0$ such that for all $(t,x) \in \mathbb{R} \times \mathcal{M}$:*

- *If $x \in \overline{\Omega_t^-}$ and $d(x, \Gamma_t) \geq A$ then $u(t,x) \leq p^- + \delta$.*
- *If $x \in \overline{\Omega_t^+}$ and $d(x, \Gamma_t) \geq A$ then $u(t,x) \geq p^+ - \delta/2$.*

Since p^+ invades p^- there exists $s_0 > 0$ such that

$$\Omega_{t+s}^+ \subset \Omega_t^+ \text{ and } d(\Gamma_{t+s}, \Gamma_t) \geq 2A \text{ for all } t \in \mathbb{R} \text{ and all } s \geq s_0. \tag{4.13}$$

Let $t \in \mathbb{R}$, $s \geq s_0$ and $x \in \overline{\Omega}$ be fixed. On the one hand, if $x \in \overline{\Omega_t^+}$ then (4.13) implies that $x \in \overline{\Omega_{t+s}^+}$ and $d(, \Gamma_{t+s}) \geq 2A$ because any continuous path from x to $\overline{\Gamma_{t+s}}$ meets $\overline{\Gamma_t}$. On the other hand, if $x \in \overline{\Omega_t^-}$ and $d(, \Gamma_t) \leq 2A$ then using (4.13) it follows that $d(, \Gamma_{t+s}) \geq A$ and $x \in \overline{\Omega_{t+s}^+}$. In both cases we obtain that

$$u^s(t,x) := u(t+s, x) \geq p^+ - \delta/2 \geq p^+ - \delta\,.$$

Proposition 4.8 *Define*

$$\omega_A^- := \{\, (t,x) \in \mathbb{R} \times \mathcal{M} \,:\, x \in \overline{\Omega_t^-} \text{ and } d(x, \Gamma_t) \geq A \,\}\,.$$

Then for all $s \geq s_0$ we have

$$u^s(t,x) \geq u(t,x) \text{ for all } (t,x) \in \omega_A^-.$$

<u>*Proof*</u>: Fix $s \geq s_0$ and define

$$\varepsilon^* := \inf\{\, \varepsilon > 0 \,:\, u^s \geq u - \varepsilon \quad \text{in } \omega_A^- \,\} \tag{4.14}$$

Since $u(t,x)$ is bounded it follows that $\varepsilon^* \geq 0$ is well defined.

We claim that $\varepsilon^* = 0$. Indeed, let us suppose that $\varepsilon^* > 0$. Then there exists a sequence

$$0 < \varepsilon_1 < \varepsilon_2 < \cdots < \varepsilon_n$$

such that $\varepsilon_n < \varepsilon^*$ for all $n \in \mathbb{N}$ and $\varepsilon_n \to \varepsilon^*$. Moreover, using (4.14) we have, for each $n \in \mathbb{N}$, a point $(t_n, x_n) \in \omega_A^-$ such that

$$u(t_n + s, x_n) < u(t_n, x_n) - \varepsilon_n\,.$$

Observe that the sequence $d(x_n, \Gamma_{t_n})$ is bounded. If it is not, we can find a subsequence such that $d(x_n, \Gamma_{t_n}) \to +\infty$, which implies that

$$u(t_n, x_n) - p^- \to 0\,. \tag{4.15}$$

But on the other hand we have

$$u(t_n, x_n) - p^- > u(t_n + s, x_n) + \varepsilon_n - p^- \geq \varepsilon_n\,,$$

and in consequence

$$u(t_n, x_n) - p^- \to \varepsilon^* > 0$$

which contradicts (4.15).

Since $d(x_n, \Gamma_{t_n})$ is bounded, from assumption (a) there exists a sequence of points $\tilde{x}_n \in \mathcal{M}$ such that $\tilde{x}_n \in \Gamma_{t_n-\tau}$ and

$$\sup\{\, d(x_n, \tilde{x}_n) \,:\, n \in \mathbb{N}\,\} < +\infty\,.$$

By hypothesis p^+ invades p^-, which implies that $\Omega^-_{t_n-t} \supset \Omega^-_{t_n}$ for all $t \geq 0$. In consequence, using that $x_n \in \overline{\Omega^-_{t_n}}$ and $d(x_n, \Gamma_{t_n}) \geq A$ it follows that $x_n \in \overline{\Omega^-_{t_n-\tau}}$ and $d(x_n, \Gamma_{t_n-\tau}) \geq A$ for all $n \in \mathbb{N}$. Therefore, we can find a sequence $y_n \in \overline{\Omega^-_{t_n-\tau}}$ such that

$$A = d(y_n, \Gamma_{t_n-\tau}) = d(x_n, \Gamma_{t_n-\tau}) - d(x_n, y_n)\,.$$

Hence

$$\begin{aligned} d(x_n, y_n) &= d(x_n, \Gamma_{t_n-\tau}) - A \\ &\leq d(x_n, \tilde{x}_n) - A < +\infty\,. \end{aligned}$$

Since the sequence $d(x_n, y_n)$ is bounded we can construct a sequence of continuous paths in $\mathcal{M}$

$$P_n := \gamma_n([0,1])\,, \quad \gamma_n : [0,1] \to \overline{\Omega^-_{t_n-\tau}}$$

such that $\gamma_n(0) = x_n$ and $\gamma_n(1) = y_n$ for all $n \in \mathbb{N}$. Moreover, the completeness of the manifold $\mathcal{M}$ alows us to choose the paths P_n such as their length is precisely $d(x_n, y_n)$ and

$$d(\gamma_n(\sigma), \Gamma_{t_n-\tau}) \geq A \quad \text{for all } \sigma \in [0,1].$$

In consequence, using Remark 4.6 we can infer that

$$u(t_n - t, \gamma_n(\sigma)) \leq p^- + \delta \quad \text{for all } \sigma \in [0,1],\ n \in \mathbb{N} \text{ and } t \geq 0.$$

In the light of this we obtain that

$$u(t_n - \tau, x_n) - \varepsilon^* < u(t_n - \tau, x_n) \leq p^- + \delta\,.$$

Moreover, from standard parabolic estimates we have that $u(t,x)$ is uniformly continuous, which implies that there exists a small ρ independent of $n \in \mathbb{N}$ such that

$$u(t,x) - \varepsilon^* < p^- + \delta$$

for all $(t,x) \in \mathbb{R} \times \mathcal{M}$ satisfying

$$t \in (t_n - \tau - \rho, t_n - \tau + \rho) \quad \text{and} \quad d(x, x_n) < \rho\,.$$

Let us focus in the region where $u - \varepsilon^* \leq p^- + \delta$. On the one hand, since $F(t,x,\cdot)$ is non-increasing in this region it follows that

$$\begin{aligned} \partial_t (u - \varepsilon^*) &= D\Delta(u - \varepsilon^*) + F(t,x,u) \\ &\leq D\Delta(u - \varepsilon^*) + F(t,x,u - \varepsilon^*)\,. \end{aligned}$$

On the other hand, due to the fact that $F(\cdot, x, q)$ is non-decreasing for all $(x,q) \in \mathcal{M} \times \mathbb{R}$ we have that

$$\begin{aligned} \partial_t u^s &= D\Delta u^s + F(t+s, x, u^s) \\ &\geq D\Delta u^s + F(t,x,u^s)\,. \end{aligned}$$

Therefore, we can use the arguments in Proposition 4.5 to obtain that there exists $b(t,x) \in L^\infty(\mathbb{R} \times \mathcal{M})$ such that the function

$$v := u^s - (u - \varepsilon^*) \geq 0$$

satisfies the linear inequality

$$\partial_t v \geq D\Delta_{\mathcal{M}} v + b(t,x) v\,.$$

In consequence, applying Harnack's inequality we obtain that there exists a constant $C_1 > 0$ such that

$$v(t_n - \tau, y_n) \leq C_1 v(t_n, y_n)\,.$$

On the one hand, if we recall that $y_n \in \overline{\Omega^-_{t_n - \tau}}$ and $d(y_n, \Gamma_{t_n - \tau})$ we obtain that

$$\begin{aligned} v(t_n - \tau, y_n) &= u^s(t_n - \tau, y_n) - u(t_n - \tau, y_n) + \varepsilon^* \\ &\geq (p^+ - \delta) - (p^- + \delta) + \varepsilon^* \\ &> \varepsilon^* > 0. \end{aligned}$$

But on the other hand we have that

$$\begin{aligned} v(t_n, y_n) &= u(t_n + s, y_n) - u(t_n, y_n) + \varepsilon^* \\ &< -\varepsilon_n + \varepsilon^* \to 0\,. \end{aligned}$$

Since this contradicts Harnack's inequality, we conclude that $\varepsilon^* = 0$, and the proof of the proposition is complete. □

Proposition 4.9 *$u^s \geq u$ in $\mathbb{R} \times \mathcal{M}$ for all $s \geq s_0$.*

<u>*Proof*</u>: Fix $s \geq s_0$. From Proposition 4.8 we have that $u^s(t,x) \geq u(t,x)$ for all $(t,x) \in \omega_A^-$, but the inequality is also valid when $(t,x) \in \mathbb{R} \times \mathcal{M} \setminus \omega_A^-$. Indeed, this can be proven using the same argument of Proposition 4.8, taking into that $F(t,x,\dot{)}$ is non-increasing in $[p^+ - \delta, +\infty)$ and that $u^s(t,x) \geq u(t,x)$ when $(t,x) \notin \omega_A^-$. $\square$

Proposition 4.10 *Define*

$$s^* := \inf\{s > 0 \,:\, u^\sigma \geq u \quad \text{for all } \sigma \geq s\}\,.$$

Then $s^* = 0$.

<u>*Proof*</u>: By definition $0 \leq s^* \leq s_0$. Let us assume that $s^* > 0$ in order to reach a contradiction. Since $u^{s^*} \geq u$ in $\mathbb{R} \times \mathcal{M}$ we have two possibilities:

- **Case 1.** $\inf\{\, u^{s^*}(t,x) - u(t,x) \,:\, d(x,\Gamma_t) \leq A\} > 0.$

- **Case 2.** $\inf\{\, u^{s^*}(t,x) - u(t,x) \,:\, d(x,\Gamma_t) \leq A\} = 0.$

We will show that none of these two cases can hold.

Proof of Case 1.

Using standard parabolic estimates it follows that $\partial_t u$ is globally bounded, which implies that there exists η_0 such that

$$u^{s^*-\eta}(t,x) \geq u(t,x) \text{ for all } \eta \in [0,\eta_0] \text{ and all } (t,x) \text{ satisfying } d(x,\Gamma_t) \leq A. \tag{4.16}$$

We claim that

$$u^{s^*-\eta} \geq u \quad \text{for all } \eta \in [0,\eta_0] \text{ and all } x \in \omega_A^-. \tag{4.17}$$

Indeed, let $x \in \overline{\Omega_t^-}$. If $d(x,\Gamma_t) = A$ then (4.16) implies that $u^{s^*-\eta}(t,x) \geq u(t,x)$, whilst if $d(x,\Gamma_t) > A$ then by Remark 4.6 it follows that $u(t,x) \geq p^- + \delta$. This implies that we can repeat the same arguments presented in Proposition 4.8 to prove that the claim holds.

On the other hand, by Remark 4.6 we also obtain that

$$u^{s^*}(t,x) \geq u(t,x) \geq p^- - \delta/2 \quad \text{if } x \in \overline{\Omega_t^+} \text{ and } d(x,\Gamma_t) \geq A.$$

In consequence, using standard parabolic estimates and decreasing η_0 if necessary, we have that

$$u^{s^*-\eta}(t,x) \geq p^- - \delta \quad \text{for all } \eta \in [0,\eta_0] \text{ and all } x \in \overline{\Omega_t^+} \text{ such that } d(x,\Gamma_t) \geq A. \tag{4.18}$$

In consequence, form (4.17), (4.16) and (4.18) it follows that

$$u^{s^*-\eta}(t,x) \geq u(t,x) \quad \text{for all } (t,x) \in \mathbb{R} \times \mathcal{M}.$$

Since this contradicts the minimality of s^*, Case 1 cannot hold.

Proof of Case 2.

By definition of the infimum, there exists a sequence $(t_n, x_n) \in \mathbb{R} \times \mathcal{M}$ such that

$$d(x_n, \Gamma_{t_n}) \le A \text{ and } u^{s^*}(t_n, x_n) - u(t_n, x_n) \to 0 \text{ when } n \to +\infty.$$

Let us again remark that u^{s^*} is a supersolution of (4.1) and $u^{s^*} \ge u$. Therefore, applying Harnack inequality to the difference there exists $C_1 > 0$ such that

$$0 \le u^{s^*}(t_n - s^*, x_n) - u(t_n - s^*, x_n) \le C_1[u^{s^*}(t_n, x_n) - u(t_n, x_n)]\,.$$

Therefore, using $u^{s^*}(t_n - s^*, x_n) = u(t_n, s_n)$ it follows that

$$u(t_n, x_n) - u(t_n - s^*, x_n) \to 0 \text{ when } n \to +\infty.$$

Moreover, by induction we can show that

$$u(t_n, x_n) - u(t_n - ks^*, x_n) \to 0 \text{ when } n \to +\infty, \text{ for all } k \in \mathbb{N}.$$

Now fix $\varepsilon > 0$. By Definition 4.2 and Proposition 4.7 there exists $B_\varepsilon > 0$ such that

$$p^- < u(t, x) \le p^- + \varepsilon \quad \text{for all } x \in \overline{\Omega_t^-} \text{ satisfying } d(x, \Gamma_t) \ge B_\varepsilon.$$

Since p^+ invades p^- then for all $s \le t$ it follows that $\Omega_s^- \supset \Omega_t^+$, and also that $d(\Gamma_s, \Gamma_t) \to +\infty$ when $|t - s| \to +\infty$. These two properties and the boundedness of the sequence $d(x_n, \Gamma_{t_n})$ imply that there exists $m \in \mathbb{N}$ such that

$$x_n \in \overline{\Omega_{t_n - ms^*}^-} \text{ and } d(x_n, \Gamma_{t_n - ms^*}) \ge B_\varepsilon \text{ for all } n \in \mathbb{N}.$$

Therefore, for all $n \in \mathbb{N}$ we obtain that

$$p^- < u(t_n - ms^*, x_n) \le p^- + \varepsilon\,.$$

In consequence,

$$u(t_n, x_n) - p^- \to 0 \text{ when } n \to +\infty. \tag{4.19}$$

From Definition 4.2 and Remark 4.6 there exist two positive real numbers B and $2\delta < p^+ - p^-$ such that

$$p^+ - \delta/2 \le u(t, x) < p^+ \quad \text{for all } x \in \overline{\Omega_t^+} \text{ satisfying } d(x, \Gamma_t) \ge B.$$

Using Hypothesis (a) and the boundedness of the sequence $d(x_n, \Gamma_{t_n})$ we can construct a sequence $\tilde{x}_n$ such that

$$\tilde{x}_n \in \Gamma_{t_n - \tau} \text{ for all } n \in \mathbb{N} \text{ and } \sup\{d(x_n, \tilde{x}_n) : n \in \mathbb{N}\} < +\infty.$$

Moreover, by Hypothesis (b) there exist $r > 0$ and a sequence y_n such that

$$y_n \in \overline{\Omega_{t_n - \tau}^+},\ d(y_n, \tilde{x}_n) = r \text{ and } d(y_n, \Gamma_{t_n - \tau} \ge B \text{ for all } n \in \mathbb{N}.$$

In consequence, we have that

$$p^+ - \delta/2 \le u(t_n - \tau, y_n)\ < p^+ \quad \text{for all } n \in \mathbb{N}.$$

Let us recall some important facts:

- $u(t,x)$ and p^- are both solutions of (4.1).
- $F(t,x,q)$ is locally Lipschitz and continuous in q, uniformly in (t,x).
- The sequence $d(x_n,y_n)$ is bounded.

Using these facts and Harnack inequality on the function

$$v := u - p^- > 0$$

we obtain that there is a $C_1 > 0$ such that

$$v(t_n - \tau, y_n) \leq C_1 v(t_n, x_n)\,.$$

On the one hand we know that $v(t_n,y_n) \to 0$ because of (4.19), but on the other hand we have that

$$\begin{aligned} v(t_n - \tau, y_n) &= u(t_n - \tau, y_n) - p^- \\ &\geq p^+ - \delta/2 - p^- \\ &> \delta/2 > 0\,. \end{aligned}$$

Thus we have reached a contradiction, which implies that Case 2 cannot hold. $\square$

Proposition 4.11 *If $s > 0$ then $u^s(t,x) > u(t,x)$ for all $(t,x) \in \mathbb{R} \times \mathcal{M}$.*

Proof: Choose any $s > 0$ and assume there is a point $(t_0,x_0) \in \mathbb{R} \times \mathcal{M}$ such that $u^s(t_0,x_0) = u(t_0,x_0)$. Since u^s is a supersolution of (4.1) and $u^s \geq u$, using the maximum principle we obtain that $u^s(t,x) = u(t,x)$ for all $(t,x) \in (-\infty, t_0] \times \mathcal{M}$.

Consider an arbitrary point $(t,x) \in (-\infty, t_0] \times \mathcal{M}$. Then for any $k \in \mathbb{N}$ we have that

$$0 \leq u(t,x) - p^- = u(t - ks, x) - p^-\,.$$

If we recall that $u(t,x)$ is a invasion of p^- by p^+ and take the limit $k \to +\infty$ it follows that $u(t,x) \equiv p^-$, which contradicts Proposition 4.7. $\square$

This concludes the proof of Theorem 4.3.

Chapter 5

Travelling waves on the real line

In the present work we consider a classical reaction-diffusion model on the sphere with truncated (hence bounded) coefficients. We show that this problem admits a global solution, which belongs to the family of generalised travelling waves defined by H. Berestycki and F. Hamel (*Generalized travel ling waves for reaction-diffusion equations*), and whose propagating speed is greater on the northern half of the sphere than on the southern half. This result is important because it seems to contradict the findings of J.D. Murray (see his book *Mathematical Biology*), and thus reopens the discussion on the modeling of fertilization waves on eggs. We also prove that there is a second generalised travelling wave, moving in the opposite direction of the first one. Both waves eventually block each other, giving rise to non-trivial steady-state solutions.

5.1 Introduction

5.1.1 Calcium waves and fertilized eggs

The study of embryos after fertilization is a primary topic in Developmental Biology. The experiments performed in this area help us understand the processes involved in the development of the embryo, and in particular cellular proliferation and differentiation. Two of those experiments concern the eggs of the fruit fly *Drosophila* and the fresh-water fish *Medaka*.

In the present work we will discuss the biological and chemical mechanisms that are triggered after fertilization of a *Medaka* egg (see Murray [49] and the references therein for a full description of the phenomenon). Gilkey and his collaborators ([25] and [56]) observed that, just after fertilization, there appears a calcium wave on the surface of the egg, moving from the fertilization point (which we will call north pole N) to the diametrically opposite point (south pole S). Moreover, the wave front is independent of rotations around the axis NS (see Figure 5.1).

According to Gilkey *et al* [25], the wave front takes an average of 2 minutes to cross the egg from N to S. Therefore, given that the egg has 1100 μm of diameter, the wave moves at an average propagation speed of 12.5 μm/s.

One of the most striking discoveries in Gilkey *et al* [25] is that the velocity of the wave front decreases as it crosses the egg. They noticed that it takes about 30-60% longer to cross

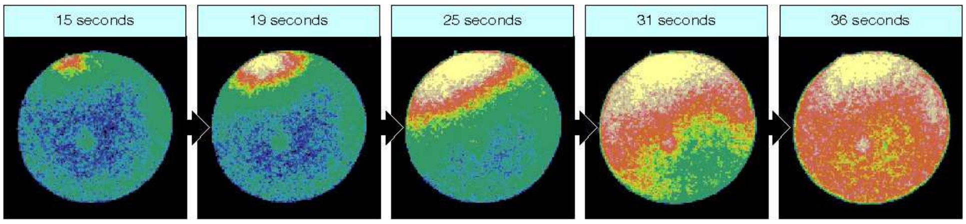

Figure 5.1: Activation fronts in real experiments. Source: L.R. Wolpert (2002) *Principles of Development.*

the vegetal half (the southern half of the egg) than the animal one (the northern half). They measured the velocity on the animal and vegetal halves, and they found that in average it is 14.6 μm/s and 10.2 μm/s, respectively.

5.1.2 The reaction-diffusion model on the sphere

The goal of this work is to prove that a classical reaction-diffusion model on the sphere admits a travelling wave, whose propagating speed is greater on the northern half than on the southern half. This result is important because in some sense it contradicts the findings of Murray [49], and thus reopens the discussion on the modeling of fertilization waves on eggs.

In order to obtain a travelling wave, it is standard to consider reaction-diffusion models of the form

$$\partial_t u - D\Delta_M u = f(u)\,, \tag{5.1}$$

where M is the unit sphere in $\mathbb{R}^3$ and Δ_M is the Laplacian operator on M. The nonlinearity $f(u)$ that describes the calcium kinetics must be of calcium-stimulate-calcium-release type (see Gilkey *et al* [25]): (a) f is globally bounded and Lipschitz; (b) it has only three steady states (i.e. equilibria) $u_1 < u_2 < u_3$; (c) u_1 and u_3 are stable whilst u_2 is unstable. These features imply that the nonlinearity $f(u)$ has to be of bistable type. Up to normalization, suppose that $u_1 = 0$ and $u_3 = 1$. More precisely, we will assume that (1) $f \in C^1([0,1])$; (2) $f(0) = f(1) = 0$; (3) $f'(0) < 0$, $f'(1) < 0$; (4) there exists $\alpha \in (0,1)$ such that $f(s) < 0$ for $s \in (0,\alpha)$ and $f(s) > 0$ for $s \in (\alpha, 1)$; (5) f is extended by zero outside the interval $[0,1]$. An example of a nonlinearity f satisfying these properties is

$$f(u) = Au(u-\alpha)(1-u)\,, \quad A > 0.$$

In spherical coordinates, a point $p = (x, y, z)$ can be written as (r, θ, φ), where r is the distance between p and the origin O, $\theta \in (0,\pi)$ is the vertical angle between the segment Op and the z axis, and $\phi \in (0, 2\pi)$ is the horizontal angle between the x axis and the projection of Op to the xy plane. The Laplacian in spherical coordinates is

$$\Delta u = \frac{1}{r^2}\partial_{rr}(ru) + \frac{1}{r^2\sin\theta}\partial_\theta(\sin\theta\,\partial_\theta u) + \frac{1}{r^2\sin^2\theta}\partial_{\phi\phi}u\,.$$

Let $r > 0$ and consider the sphere

$$M = \{(x, y, z) \in \mathbb{R}^3 : x^2 + y^2 + z^2 = r\}\,.$$

If r is constant then the Laplace-Beltrami operator is

$$\Delta_M u = \frac{1}{r^2 \sin\theta}\partial_\theta(\sin\theta\,\partial_\theta u) + \frac{1}{r^2\sin^2\theta}\partial_{\phi\phi}u\,.$$

Recall that, in the experiments with amphibian eggs, the calcium waves are almost independent of the horizontal angle ϕ. In that case the Laplace-Beltrami operator reduces to

$$\Delta_M u = \frac{D}{r^2}[\partial_{\theta\theta}u + \text{cot}\theta\,\partial_\theta u]\,.$$

From now on, we will only consider solutions that are independent of ϕ. In that framework, (5.1) reduces to

$$\partial_t u - \frac{D}{r^2}[\partial_{\theta\theta}u + \text{cot}\theta\,\partial_\theta u] = f(u)\,,\quad (t,\theta) \in \mathbb{R}\times(0,\pi)\,. \tag{5.2}$$

Assuming after re-scaling that $D = 1$ and $r = 1$, it follows that (5.2) simply becomes

$$\partial_t u - \partial_{\theta\theta}u - \text{cot}\theta\,\partial_\theta u = f(u)\,,\quad (t,\theta) \in \mathbb{R}\times(0,\pi)\,. \tag{5.3}$$

5.1.3 Murray's approach

Murray's goal was to find a travelling wave solution of (5.3), i.e. a function $\varphi(z)$ such that

$$u(t,\theta) = \varphi(\theta - ct)\,;\quad \varphi(-\infty) = 1\,,\quad \varphi(+\infty) = 0.$$

Suppose that such a solution exists. Then it satisfies the equation

$$\varphi'' + [c + \cot\theta]\varphi' + f(\varphi) + 0\,. \tag{5.4}$$

Now consider in (5.4) that θ is fixed. From the classical results of Fife and Mcleod [20] on travelling waves, it follows that there exists a travelling wave $\varphi(z)$ moving with velocity

$$c = c_0 - \cot\theta$$

where c_0 is the unique velocity of the travelling wave

$$U'' + c_0U' + f(U) + 0,\quad U(-\infty) = 1,\quad U(+\infty) = 0,\quad U' < 0 \text{ in } \mathbb{R},$$

which moves from the left to the right in the real line.

Observe that on the northern hemisphere $\{0 < \theta < \pi/2\}$ we have $\cot\theta > 0$, whilst on the southern hemisphere $\{\pi/2 < \theta < \pi\}$ we have $\cot\theta < 0$. Therefore, the asymptotic velocity on the northern hemisphere is smaller that the velocity on the southern hemisphere. This remark led Murray to search for a different model (based on a mechanochemical approach) in order to describe calcium waves on eggs, and the reaction-diffusion model was thus abandoned.

Actually, the previous argument shows that the *ansatz* $u(t,\theta) = \varphi(\theta - ct)$ is not possible. Indeed, there cannot exist a travelling wave moving in the θ direction with constant speed. However, we will see that other solutions do exist, and that they belong to the class of generalised travelling waves introduced by H. Berestycki and F. Hamel [8].

5.1.4 Modified equation

In order to overcome the difficulty mentioned in the previous paragraph, we will consider the change of variables, i.e.

$$x = \cot\theta, \qquad x \in \mathbb{R}.$$

One can readily compute

$$\begin{aligned}
\frac{\partial x}{\partial \theta} &= -(1+x^2), \\
\frac{\partial}{\partial \theta} &= -(1+x^2)\frac{\partial}{\partial x}, && (5.5) \\
\frac{\partial^2}{\partial \theta^2} &= (1+x^2)^2\frac{\partial^2}{\partial x^2} + 2x(1+x^2)\frac{\partial}{\partial x}. && (5.6)
\end{aligned}$$

Using the former identities one can show that equation (5.2) becomes

$$\partial_t u - (1+x^2)^2\partial_{xx}u - x(1+x^2)\partial_x u = f(u)\,, \quad (t,x) \in \mathbb{R}^2\,. \tag{5.7}$$

Notice that $\theta = 0$ corresponds to $x = +\infty$, whilst $\theta = \pi$ corresponds to $x = -\infty$. As we have seen in the previous section, we cannot expect to have classical travelling wave solutions. Therefore, the solutions we will be looking for are generalised travelling waves, moving from N to S.

In the biological experiment, the calcium wave is triggered by the fertilisation of the egg. Before fertilisation there is no wave, and after fertilisation the wave is already in motion. Moreover, the underlying biochemical mechanism that ignites the travelling wave is still unknown. Therefore, the fertilisation can be considered as a "biological singularity", in the same spirit as the lighting of a match is a "physical singularity" (commonly modelled as a Dirac delta).

In the light of the former argument, we will consider a version of equation (5.7) where the coefficients are bounded when $x \to \pm\infty$. More precisely, we will consider the reaction-diffusion problem

$$\partial_t u - a(x)\partial_{xx}u - b(x)\partial_x u = f(u)\,, \quad (t,x) \in \mathbb{R}^2, \tag{5.8}$$

where

$$a(x) = \begin{cases} (1+x^2)^2 & \text{if } |x| \le \rho, \\ (1+\rho^2)^2 & \text{if } |x| \ge \rho, \end{cases}$$

$$b(x) = \begin{cases} -\rho(1+\rho^2) & \text{if } x < -\rho, \\ x(1+x^2) & \text{if } |x| \le \rho, \\ \rho(1+\rho^2) & \text{if } x > \rho. \end{cases}$$

5.1.5 On intuition and the real dynamics of the travelling waves

From (5.5) we can see that the drift term in the θ variable is

$$\cot\theta\frac{\partial}{\partial\theta} = -x(1+x^2)\frac{\partial}{\partial x}$$

whilst the drift term in the x variable is

$$x(1+x^2)\frac{\partial}{\partial x}\,.$$

Therefore, the drift term in the x variable is the negative of the drift in the θ variable, which implies that the waves move in opposite directions because the sign of their corresponding velocities is different (see Fife and Mcleod [20]). In consequence, when considering θ as fixed we are not seeing the whole picture because, as it can be seen in (5.6), there is a first-order term that is "hidden" in the second-order derivative. Moreover, the fact that θ and x move in opposite directions implies that any intuition we have for the travelling wave should be considered for waves moving backwards, i.e. from right to left instead of the classical left to right sense.

Recalling the argument of the previous section, the asymptotic velocity near $x = +\infty$ is bigger that the velocity near $x = -\infty$. But on the x variable we have $N = +\infty$ and $S = -\infty$ because the travelling wave moves from right to left. Therefore, the velocity on the north pole is bigger than the velocity on the south pole, i.e. $c_N > c_S$. However, without the change of variables one would be considering that the travelling wave moves from left to right, which leads to the opposite conclusion.

5.2 Main results

Let us start studying the behavior of the solutions when $|x| > \rho$, which corresponds to neighborhoods of the north and south poles.

Proposition 5.1 Asymptotic velocities of the travelling waves
Let (φ, c_0) be the unique solution of

$$\varphi'' - c_0\varphi' + f(\varphi) = 0, \qquad \lim_{z\to-\infty}\varphi(z) = 0, \qquad \lim_{z\to+\infty}\varphi(z) = 1. \tag{5.9}$$

1. *There is a unique (up to translation) travelling wave solution*

$$\varphi_N := \varphi\left(\frac{x + c_N t}{1+\rho^2}\right), \quad c_N = (c_0+\rho)(1+\rho^2)$$

for the equation on the north pole, i.e.

$$\partial_t u - (1+\rho^2)^2\partial_{xx}u - \rho(1+\rho^2)\partial_x u = f(u)\,. \tag{5.10}$$

2. *There is a unique (up to translation) travelling wave solution*

$$\varphi_S := \varphi\left(\frac{x + c_S t}{1+\rho^2}\right), \quad c_S = (c_0-\rho)(1+\rho^2)$$

for the equation on the south pole, i.e.

$$\partial_t u - (1+\rho^2)^2\partial_{xx}u + \rho(1+\rho^2)\partial_x u = f(u)\,. \tag{5.11}$$

In particular, $c_N > c_S$.

Proof: From the standard theory, equation (5.9) has a unique (up to translations) solution $(\varphi(z), c_0)$. Now, if we define

$$u(t,x) = \varphi\left(\frac{x + c_N t}{1+\rho^2}\right)$$

and choose $c_N = (c_0 + \rho)(1+\rho^2)$ then it is easy to see that $u(t,x)$ satisfies (5.10), i.e. the equation on the north pole. Analogously,

$$\varphi\left(\frac{x + c_S t}{1+\rho^2}\right), \quad c_S = (c_0 - \rho)(1+\rho^2)$$

is the unique (up to translations) solution of (5.11), i.e. the equation on the south pole. □

From Proposition 5.1 we have that $c_N > c_S$, which is consistent with the experimental results in Gilkey *et al* [25] and in a certain sense contradicts the conclusions of Murray [49]. From now on we will consider the truncated equation (5.8).

Theorem 5.1 Global solution for N

Suppose that $f(s)$ *is a bistable Lipschitz nonlinearity and let* $c_N > 0$. *Then there exists* $\beta > 0$ *such that the reaction-diffusion equation (5.8) has a unique global solution* $u(t,x)$ *satisfying*

$$0 < u(t,x) < 1 \quad \forall (t,x) \in \mathbb{R}^2$$

and

$$\left| u(t,x) - \varphi\left(\frac{x + c_N t}{1+\rho^2}\right)\right| = O(e^{\beta t}) \quad \text{when t} \to -\infty, \text{ uniformly in } x \in \mathbb{R}.$$

In particular,

$$\lim_{t\to-\infty} \left| u(t,x) - \varphi\left(\frac{x + c_N t}{1+\rho^2}\right)\right| = 0 \quad \text{uniformly in } x \in \mathbb{R}.$$

Furthermore, $t \mapsto u(t,x)$ *is non-decreasing, and if the initial condition* $u_0(x)$ *is non-decreasing then* $x \mapsto u(t,x)$ *is also non-decreasing.*

If ρ is sufficiently large such that $\rho > c_0$, the travelling wave φ_S moves from left to right, i.e. from the the south pole S to the north pole N. Therefore, it travels in the opposite direction of the wave φ_N. We will now construct a generalised travelling wave $v(t,x)$ related to the classical travelling wave φ_S, in the same way we did for the wave $u(t,x)$ related to φ_N.

Theorem 5.2 Global solution for S

Let $f(s)$ *be a bistable Lipschitz nonlinearity, and suppose that* ρ *is sufficiently large such that* $c_S < 0$. *Then there exists* $\beta > 0$ *such that the reaction-diffusion equation (5.8) has a unique global solution* $v(t,x)$ *satisfying*

$$0 < v(t,x) < 1 \quad \forall (t,x) \in \mathbb{R}^2$$

and

$$\left|u(t,x) - \varphi\left(\frac{x + c_S t}{1+\rho^2}\right)\right| = O(e^{\beta t}) \quad \text{when t} \to -\infty \text{, uniformly in } x \in \mathbb{R}.$$

In particular,

$$\lim_{t\to-\infty}\left|u(t,x) - \varphi\left(\frac{x + c_S t}{1+\rho^2}\right)\right| = 0 \quad \text{uniformly in } x \in \mathbb{R}.$$

Furthermore, $t \mapsto v(t,x)$ is non-increasing, and if the initial condition $v_0(x)$ is non-decreasing then $x \mapsto v(t,x)$ is non-decreasing.

So far we have constructed two globally-defined generalised travelling waves: $u(t,x)$ moving from right to left and $v(t,x)$ moving in the opposite direction. We will show that $u(t,x)$ and $v(t,x)$ are ordered and they mutually block each other, giving rise to two steady-state (not necessarily distinct) solutions of (5.8).

Theorem 5.3 Steady-state solutions

If we define

$$u_\infty(x) := \lim_{t\to+\infty} u(t,x), \quad v_\infty(x) := \lim_{t\to+\infty} v(t,x).$$

then $u_\infty(x)$ and $v_\infty(x)$ are steady-state solutions of (5.8) *satisfying*

$$0 < u(t,x) \leq u_\infty(x) \leq v_\infty(x) \leq v(t,x) < 1 \quad \forall (t,x) \in \mathbb{R}^2.$$

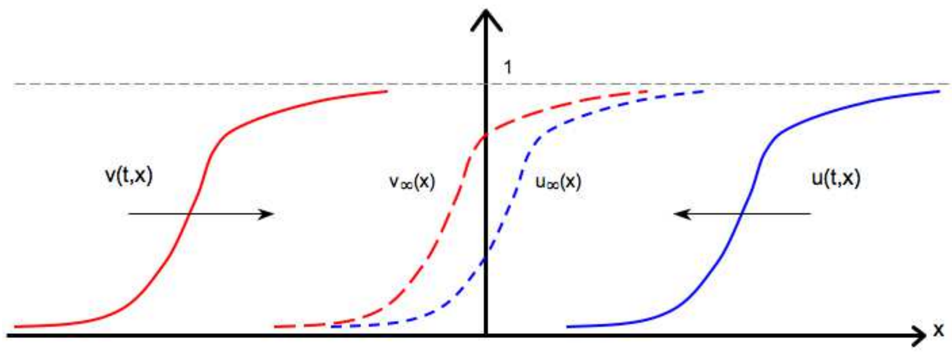

Figure 5.2: generalised travelling waves and their steady-state limits. The arrows indicate the dynamics of the solutions as $t \to \infty$.

5.3 Proofs

5.3.1 Supersolutions and subsolutions

Lemma 5.1 Exponential decay

Let $\varphi(z)$ be the solution of (5.9) *and consider the functions*

$$\varphi(z), \quad \varphi'(z), \quad \varphi''(z), \quad f(\varphi(z)). \tag{5.12}$$

1. *If $z < 0$ then all functions in* (5.12) *are asymptotically equivalent to $e^{\lambda z}$, where*

$$\lambda = \frac{c_0 + \sqrt{c_0^2 - 4f'(0)}}{2} > 0.$$

2. *If $z > 0$ then all functions in* (5.12) *are asymptotically equivalent to $e^{-\mu z}$, where*

$$\mu = \frac{c_0 + \sqrt{c_0^2 - 4f'(1)}}{2} > 0.$$

Proof: Let us start recalling the following properties of the travelling front $\varphi(z)$ (see Fife *et al* [20] and Guo *et al* [29]):

$$z < 0 \quad \Rightarrow \quad \begin{cases} \alpha_0 e^{\lambda z} \leq \varphi(z) \leq \beta_0 e^{\lambda z}, \\ \gamma_0 e^{\lambda z} \leq \varphi'(z) \leq \delta_0 e^{\lambda z}, \end{cases} \tag{5.13}$$

$$z > 0 \quad \Rightarrow \quad \begin{cases} \alpha_1 e^{-\mu z} \leq 1 - \varphi(z) \leq \beta_1 e^{-\mu z}, \\ \gamma_1 e^{-\mu z} \leq \varphi'(z) \leq \delta_1 e^{-\mu z}, \end{cases}$$

where $\alpha_j, \beta_j, \gamma_j, \delta_j$ are positive constants. In the light of (5.13), if $z < 0$ then $\varphi_N(z)$ and $\varphi'(z)$ are asymptotically equivalent to $e^{\lambda z}$. Moreover, since F is Lipschitz then also $f(\varphi(z))$ shares the same property. Finally, from (5.9) we can deduce that $\varphi''(z)$ has the same behavior. Analogously, if $z > 0$ then all functions are asymptotically equivalent to $e^{-\mu z}$. □

Lemma 5.2 Supersolution and subsolution for N

Suppose that f is Lipschitz, i.e. there exists $K > 0$ such that

$$|f(s_2) - f(s_1)| \leq K|s_2 - s_1| \quad \forall s_1, s_2 \in \mathbb{R}.$$

Assume that ρ is sufficiently large such that

$$K < L := \lambda(c_0 + \rho).$$

If we define

$$w^{\pm}(t,x) := \varphi\left(\frac{x + c_N t}{1 + \rho^2}\right) \pm e^{\beta t}$$

then for any $\beta \in (K, L)$ there exists a time $T < 0$ such that w^+ is a supersolution (resp. w^- is a subsolution) of (5.8) *for all $(t,x) \in (-\infty, T] \times \mathbb{R}$.*

Proof: Define

$$\mathcal{L}u := \partial_t u - a(x)\partial_{xx}u - b(x)\partial_x u - f(u).$$

Since φ_N is solution of (5.10) then a straightforward calculation yields

$$\mathcal{L}w^{\pm} = \pm\beta e^{\beta t} + [\,\rho(1+\rho^2) - b(x)\,]\,\varphi' + [\,(1+\rho^2)^2 - a(x)\,]\,\varphi'' + f(\varphi) - f(w^{\pm}).$$

We will study now the sign of $\mathcal{L}w^{\pm}$ in all possible cases.

1. Case $x \geq \rho$.

   In this case we have

   $$\mathcal{L}w^{\pm} = \pm\beta e^{\beta t} + f(\varphi) - f(w^{\pm}).$$

   From the Lipschitz condition of F we have

   $$|f(\varphi) - f(w^{\pm})| \leq K e^{\beta t}\,,$$

   which implies that

   $$\begin{aligned} f(\varphi) - f(w^{+}) &\geq -K e^{\beta t}, \\ f(\varphi) - f(w^{-}) &\leq K e^{\beta t}. \end{aligned}$$

   In consequence

   $$\begin{aligned} \mathcal{L}w^{+} &\geq (\beta - K)e^{\beta t}, \\ \mathcal{L}w^{-} &\leq (K - \beta)e^{\beta t}. \end{aligned}$$

   Therefore, choosing $\beta > K$ it follows that $\mathcal{L}w^{+} > 0$ and $\mathcal{L}w^{-} < 0$ for all $t \in \mathbb{R}$ and all $x \geq \rho$.

2. Case $x \leq \rho$.

   Define

   $$z := \frac{x + c_N t}{1+\rho^2}.$$

   Since

   $$\lim_{t\to-\infty} z = -\infty$$

   there exists $T < 0$ such that $z < 0$ for all $(t,x) \in (-\infty, T] \times (-\infty, \rho]$.

   (a) Suppose that $x \leq -\rho$. Then

   $$\mathcal{L}w^{\pm} = \pm\beta e^{\beta t} + 2\rho(1+\rho^2)\varphi' + f(\varphi) - f(w^{\pm}).$$

From the Lipschitz condition on f it follows that

$$\begin{aligned}\mathcal{L}w^+ &> (\beta - K)e^{\beta t} + 2\rho(1+\rho^2)\varphi', \\ \mathcal{L}w^- &< (K - \beta)e^{\beta t} + 2\rho(1+\rho^2)\varphi'.\end{aligned}$$

From Lemma 5.1 we have

$$\varphi'(z) = O(e^{\lambda z}) = O(e^{Lt}) \quad \forall x \le \rho.$$

Therefore,

$$\begin{aligned}\mathcal{L}w^+ &> (\beta - K)e^{\beta t} + O(e^{Lt}), \\ \mathcal{L}w^- &< (K - \beta)e^{\beta t} + O(e^{Lt}).\end{aligned}$$

In consequence, if $\beta \in (K, L)$ and $T < 0$ is small enough then $\mathcal{L}w^+ > 0$ and $\mathcal{L}w^- < 0$ for all $(t, x) \in (-\infty, T] \times (-\infty, -\rho]$.

(b) Suppose that $-\rho \le x \le \rho$. Then

$$\begin{aligned}\mathcal{L}w^+ &> \beta e^{\beta t} + [\,\rho(1+\rho^2) - b(x)\,]\,\varphi' + [\,(1+\rho^2)^2 - a(x)\,]\,\varphi'', \\ \mathcal{L}w^- &< -\beta e^{\beta t} + [\,\rho(1+\rho^2) - b(x)\,]\,\varphi' + [\,(1+\rho^2)^2 - a(x)\,]\,\varphi''.\end{aligned}$$

From Lemma 5.1 we also have

$$\varphi''(z) = O(e^{\lambda z}) = O(e^{Lt}) \quad \forall x \le \rho.$$

Therefore,

$$\begin{aligned}\mathcal{L}w^+ &> \beta e^{\beta t} + O(e^{Lt}), \\ \mathcal{L}w^- &< -\beta e^{\beta t} + O(e^{Lt}).\end{aligned}$$

In consequence, if $\beta \in (K, L)$ and $T < 0$ is small enough then $\mathcal{L}w^+ > 0$ and $\mathcal{L}w^- < 0$ for all $t \le T$ and $x \in [-\rho, \rho]$. $\square$

5.3.2 Global solution for N

We will start constructing a sequence of local solutions (u_n). Afterwards, passing to the limit $n \to +\infty$ we will obtain a global solution.

Lemma 5.3 Local solution
For any $n \in \mathbb{N}$ such that $n > -T$ the equation

$$\partial_t u - a(x)\partial_{xx} u - b(x)\partial_x u = f(u)\,, \quad (t, x) \in [-n, T] \times \mathbb{R} \tag{5.14}$$

with initial condition

$$u(-n, x) = \max\{w^-(\sigma, x) : \sigma \le -n\} \quad \forall x \in \mathbb{R} \tag{5.15}$$

has a solution $u_n(t, x)$ satisfying

$$w^-(t, x) \le u_n(t, x) < 1 \quad \forall (t, x) \in [-n, T] \times \mathbb{R}.$$

Proof: From Lemma 5.2, w^+ and w^- are super and subsolution of (5.14)-(5.15) satisfying

$$u_n(-n,x) \geq w^-(\sigma,x) \quad \forall \sigma \leq -n.$$

Therefore, from the standard theory (e.g. Evans [18], Theorem 1, p.508) and the strong maximum principle we obtain that the problem (5.14)-(5.15) has a solution $u_n(t,x)$ such that

$$w^-(t,x) \leq u_n(t,x) \leq 1 \quad \forall (t,x) \in [-n,T] \times \mathbb{R}. \quad \square$$

Lemma 5.4 Monotonicity of the local solutions

1. *$t \mapsto u_n(t,x)$ is non-decreasing.*
2. *The sequence $(u_n)_{n>-T}$ is non-decreasing.*

Proof:

1. From the definition of $u_n(-n,x)$ it follows that

$$u_n(-n,x) \geq w^-(\sigma,x) \quad \forall \sigma \leq -n.$$

From the maximum principle it follows that

$$u_n(-n+t,x) \geq w^-(\sigma+t,x) \quad \forall \sigma \leq -n, \quad \forall t \in [0,T+n], \quad \forall x \in \mathbb{R}. \tag{5.16}$$

In consequence,

$$\begin{aligned} u_n(-n+t,x) &\geq \max\{w^-(\sigma+t,x) : \sigma \leq -n\} \\ &= \max\{w^-(\sigma,x) : \sigma \leq -n+t\} \\ &\geq \max\{w^-(\sigma,x) : \sigma \leq -n\} \\ &= u_n(-n,x)\,. \end{aligned}$$

In consequence, the maximum principle implies that $t \mapsto u_n(t,x)$ is non-decreasing.

2. Using (5.16) and $t = 1$ we obtain

$$\begin{aligned} u_n(-n+1,x) &\geq \max\{w^-(\sigma,x) : \sigma \leq -n+1\} \\ &= u_{n-1}(-n+1,x). \end{aligned}$$

Once again, the maximum principle yields

$$u_n(t,x) \geq u_{n-1}(t,x) \quad \forall t \in [-n+1,T], \quad \forall x \in \mathbb{R},$$

which implies that the sequence $(u_n)_{n>-T}$ is non-decreasing. $\square$

Lemma 5.5 Definition of the global solution
Define

$$u(t,x) := \lim_{n\to\infty} u_n(t,x). \tag{5.17}$$

Then $u(t,x)$ is a global, non-trivial solution of (5.8).

Proof: From Lemma 5.4 the sequence $(u_n)_{n>-T}$ is non-decreasing, and it is bounded from above because

$$u_n(t,x) < 1 \quad \forall n > -T.$$

Therefore, the limit (5.17) is well defined. Moreover, since the sequence $(u_n)_{n>-T}$ and the coefficients in (5.8) are bounded, it follows that $u(t,x)$ is a solution of (5.8) defined for $(t,x) \in (-\infty,T] \times \mathbb{R}$.

We claim that $u(t,x)$ is non-trivial. Indeed, recall that $w^+(t,x)$ is supersolution and that $t \mapsto w^+(t,x)$ is increasing. Therefore,

$$w^-(\sigma,x) \le w^+(\sigma,x) \le w^+(-n,x) \quad \forall \sigma \le -n, \quad \forall x \in \mathbb{R},$$

which implies that

$$\begin{array}{rcl} u_n(-n,x) & = & \max\{w^-(\sigma,x) : \sigma \le -n\} \\ & \le & w^+(-n,x). \end{array}$$

In consequence, the maximum principle implies that

$$w^-(t,x) \le u_n(t,x) \le w^+(t,x) \quad \forall t \in [-n,T], \quad \forall x \in \mathbb{R}.$$

Taking the limit $n \to +\infty$ yields

$$w^-(t,x) \le u(t,x) \le w^+(t,x) \quad \forall t \in (-\infty,T], \quad \forall x \in \mathbb{R},$$

and hence $u(t,x)$ is a non-trivial solution of (5.8).

Now notice that the coefficients of (5.8) are bounded. Therefore, we can use standard parabolic estimates (e.g. Ladyženskaja *et al* [41]) to show that $u(t,x)$ is in fact a globally defined solution of (5.8). □

Theorem 5.2 Global solution for N
Suppose that $f(s)$ is a bistable Lipschitz nonlinearity with Lipschitz constant K, and suppose ρ is large enough such that

$$K < L := \lambda(c_0 + \rho).$$

For any $\beta \in (K,L)$ the reaction-diffusion equation (5.8) has a unique global solution $u(t,x)$ such that

$$0 < u(t,x) < 1 \quad \forall (t,x) \in \mathbb{R}^2$$

and

$$\left|u(t,x) - \varphi\left(\frac{x + c_N t}{1+\rho^2}\right)\right| = O(e^{\beta t}) \quad \text{when } t \to -\infty, \text{ uniformly in } x \in \mathbb{R}. \tag{5.18}$$

In particular,

$$\lim_{t\to-\infty} \left|u(t,x) - \varphi\left(\frac{x + c_N t}{1+\rho^2}\right)\right| = 0 \quad \text{uniformly in } x \in \mathbb{R}, \tag{5.19}$$

Furthermore, $t \mapsto u(t,x)$ is non-decreasing, and if the initial condition $u_0(x)$ is non-decreasing then $x \mapsto u(t,x)$ is also non-decreasing.

Proof:

1. From Lemma 5.5 we have a global nontrivial solution $u(t,x)$ of (5.8). Moreover, since $v \equiv 0$ and $v \equiv 1$ are solutions of (5.8) then the maximum principle implies that $0 < u(t,x) < 1$.

2. By construction we have

$$\lim_{t\to-\infty} \left|w^{\pm}(t,x) - \varphi\left(\frac{x + c_N t}{1+\rho^2}\right)\right| = 0 \quad \text{uniformly in } x \in \mathbb{R}.$$

   Therefore, since $w^-(t,x) < u(t,x) < w^+(t,x)$ we deduce (5.19).

3. Let $\sigma > 0$. From Lemma 5.4 we have that $t \mapsto u_n(t,x)$ is non-decreasing, i.e.

$$u_n(t+\sigma,x) \geq u_n(t,x) \quad \forall t \in [-n, T-\sigma], \quad \forall x \in \mathbb{R}.$$

   Therefore, taking the limit $n \to +\infty$ we obtain

$$u(t+\sigma,x) \geq u(t,x) \quad \forall t \in (-\infty, T-\sigma], \quad \forall x \in \mathbb{R}.$$

   Finally, since both mappings $t \mapsto u_n(t,x)$ and $t \mapsto u_n(t,x)$ are globally defined, the maximum principle yields

$$u(t+\sigma,x) \geq u(t,x) \quad \forall (t,x) \in \mathbb{R}^2.$$

4. Define $v(t,x) := \partial_x u(t,x)$. Then $v(t,x)$ solves the equation

$$\partial_t v - a(x)\partial_{xx} v - [a'(x) + b(x)]\partial_x v + b'(x)v - f'(u)v = 0\,.$$

   Recalling that $u_0(x)$ is increasing it follows that $v_0(x) \geq 0$ for all $x \in \mathbb{R}$. In consequence, the Maximum Principle yields

$$\partial_x u(t,x) = v(t,x) \geq 0 \quad \forall (t,x) \in \mathbb{R}^2.$$

5. Using the same arguments as in Berestycki *et al* [9], Section 3, we can prove that condition (5.18) ensures uniqueness of the solution. $\square$

5.3.3 Global solution for S

Theorem 5.3 Global solution for S

Suppose that $f(s)$ is a bistable Lipschitz nonlinearity with Lipschitz constant K, and suppose ρ is large enough such that

$$K < M := \lambda(\rho - c_0).$$

For any $\beta \in (K, M)$ the reaction-diffusion equation (5.8) has a unique global solution $v(t,x)$ such that

$$0 < v(t,x) < 1 \quad \forall (t,x) \in \mathbb{R}^2$$

and

$$\left| v(t,x) - \varphi\left(\frac{x + c_S t}{1+\rho^2}\right) \right| = O(e^{\beta t}) \quad \text{when } t \to -\infty, \text{ uniformly in } x \in \mathbb{R}. \tag{5.20}$$

In particular,

$$\lim_{t \to -\infty} \left| v(t,x) - \varphi\left(\frac{x + c_N t}{1+\rho^2}\right) \right| = 0 \quad \text{uniformly in } x \in \mathbb{R}, \tag{5.21}$$

Furthermore, $t \mapsto v(t,x)$ is non-increasing, and if the initial condition $u_0(x)$ is non-decreasing then $x \mapsto v(t,x)$ is also non-decreasing.

<u>*Proof*</u>: The same arguments in the proof of Theorem 5.2 hold here as well. Indeed:

1. If we define

   $$p^{\pm}(t,x) := \varphi\left(\frac{x + c_S t}{1+\rho^2}\right) \pm e^{\beta t}$$

   and we take a careful look at the proof of Theorem 5.2 we can see that it holds for $p^{\pm}(t,x)$, provided $\beta \in (K, M)$. Therefore, p^+ is a supersolution (resp. p^- is a subsolution) of (5.8) for all $(t,x) \in (-\infty, T] \times \mathbb{R}$.

2. Define

   $$v_n(t,x) := \min\{p^+(\sigma, x) \,:\, \sigma \le n\}.$$

   Following the proofs of Lemmas 5.3 and 5.4, it can be shown that

   - There exists a non-trivial solution $v_n(t,x)$ of (5.8) for all $(t,x) \in [-n, T] \times \mathbb{R}$.
   - The mapping $t \mapsto v_n(t,x)$ is non-increasing.
   - The sequence $(v_n)_{n > -T}$ is non-increasing.

3. In the light of the former properties, it can be shown that (see Lemma 5.5)

   $$v(t,x) := \lim_{n \to +\infty} v_n(t,x)$$

   is a global, nontrivial solution of (5.8). Moreover, the mapping $t \mapsto v(t,x)$ is non-increasing, and if the initial condition $v_0(x)$ is non-decreasing then $x \mapsto v(t,x)$ is non-decreasing (see Theorem 5.2).

4. From the definition of $p^{\pm}$ it follows that $v(t,x)$ satisfies (5.20) and (5.21), and applying the results of Berestycki *et al* [9], Section 3, it can be proven that it is unique. □

5.3.4 Steady-state solutions and blocking of the waves

Theorem 5.4 Steady-state solutions
If we define

$$u_\infty(x) := \lim_{t\to+\infty} u(t,x), \quad v_\infty(x) := \lim_{t\to+\infty} v(t,x).$$

then $u_\infty(x)$ and $v_\infty(x)$ are steady-state solutions of (5.8) *satisfying*

$$0 < u(t,x) \le u_\infty(x) \le v_\infty(x) \le v(t,x) < 1 \quad \forall (t,x) \in \mathbb{R}^2. \tag{5.22}$$

Proof:

1. Recall that $t \mapsto u(t,x)$ is non-decreasing and bounded from above by 1. Therefore, the limit
$$u_\infty(x) := \lim_{t\to+\infty} u(t,x)$$
is well-defined and satisfies
$$0 < u(t,x) \le u_\infty(x) \le 1 \quad \forall (t,x) \in \mathbb{R}^2. \tag{5.23}$$
Similarly, since $t \mapsto v(t,x)$ is non-increasing and bounded from below by 0 it follows that
$$v_\infty(x) := \lim_{t\to+\infty} v(t,x)$$
is well-defined and satisfies
$$0 \le v_\infty(x) \le v(t,x) < 1 \quad \forall (t,x) \in \mathbb{R}^2. \tag{5.24}$$
Now notice that the coefficients of (5.8) are uniformly bounded. Therefore, we can use standard parabolic estimates to show that both $u_\infty(x)$ and $v_\infty(x)$ are steady-state solutions of (5.8).

2. Let $\mathcal{C}$ be an arbitrary compact subset of $\mathbb{R}$. Then
$$\lim_{t\to-\infty} p^+(t,x) = \varphi(+\infty) = 1 \quad \text{and} \quad \lim_{t\to-\infty} w^-(t,x) = \varphi(-\infty) = 0 \quad \text{uniformly in } \mathcal{C}.$$
Therefore, there exists $T < 0$ such that
$$p^+(t,x) > \frac{1}{2} > w^-(t,x) \quad \forall (t,x) \in (-\infty, T] \times \mathcal{C}.$$
In consequence, if $n > -T$ and $x \in \mathcal{C}$ then
$$\begin{aligned} v_n(-n,x) &= \min\{p^+(\sigma,x) \,:\, \sigma \le -n\} \\ &\ge \max\{w^-(\sigma,x) \,:\, \sigma \le -n\} \\ &= u_n(-n,x). \end{aligned}$$

Using the maximum principle we obtain

$$v_n(t,x) \geq u_n(t,x) \quad \forall (t,x) \in [-n,T] \times \mathcal{C},$$

and taking the limit $n \to +\infty$ it follows that

$$v(t,x) \geq u(t,x) \quad \forall (t,x) \in (-\infty,T] \times \mathcal{C}.$$

Now recall that u and v are both global solutions of (5.8). Hence, from the maximum principle we can infer that

$$v(t,x) \geq u(t,x) \quad \forall (t,x) \in \mathbb{R} \times \mathcal{C}.$$

Therefore, taking the limit $t \to +\infty$ and using (5.23) and (5.24) we obtain

$$0 < u(t,x) \leq u_\infty(x) \leq v_\infty(x) \leq v(t,x) < 1 \quad \forall (t,x) \in \mathbb{R} \times \mathcal{C}.$$

Finally, $\mathcal{C}$ being arbitrary it follows that (5.22) holds. □

5.4 Discussion

We have proven the existence of two generalised travelling waves, which move in opposite directions and mutually block. This is an important mathematical result *per se* because it illustrates the pertinence of a general definition of a travelling wave beyond the classical framework $u(t,x) = \varphi(x - ct)$, even in the case of regular and bounded coefficients.

From the biological point of view, we managed to show that the reaction-diffusion model is good enough to produce calcium waves, which travel from the north pole to the south pole, whose velocities decrease as they advance, and that eventually stop before reaching the south pole. This is good news because we recovered the qualitative properties of the experiments form the original reaction-difusion equation without adding new equations (as it is done in the mechano-chemical models).

It is important to remark that the boundedness of the coefficients was of crucial in the proofs we used, which were based on sub- and super-solutions and in the asymptotic behaviour of the waves as $|t| \to \infty$. In that regard, the original problem with unbounded coefficients was not completely solved. We plan to study the behaviour of the generalised travelling waves as $\rho \to \infty$ in further projects.

Chapter 6

Travelling waves on the sphere

Work in collaboration with Henri Berestycki and François Hamel. To be submitted.

In the previous chapter we projected the equation from the sphere to the real line, but now we will work directly on the sphere. We consider the classical reaction-diffusion equation with bistable nonlinearity on two domains, a truncated sphere with non-homogeneous Dirichlet boundary conditions and the whole sphere with no boundary conditions.

On the truncated sphere we prove that (1) if the nonlinearity is strong enough there are non-trivial solutions of the elliptic problem, (2) there is a nontrivial solution of the parabolic problem that is strictly increasing in time, i.e. a generalised travelling wave, and (3) the travelling wave is blocked by the non-trivial elliptic solution. On the whole sphere we prove that (1) there are non-trivial solutions of the elliptic problem and (2) depending on the initial conditions, the solution $u(t, x)$ can converge or not to the stable states 0 and 1. In particular, when the solution does not converge to 0 or 1 we have that (1) this solution cannot invade the whole sphere, (2) it does not vanish, and (3) if it converges then its convergence is non-monotonic.

Our results on both domains (the truncated and the whole sphere) evidence that having solution that does not invade the whole domain depends on the geometry of the sphere, the strength of the nonlinearity (measured in terms of λ) and the initial conditions.

6.1 Elliptic equation on the truncated sphere

Let us consider the sphere $\mathbb{S}^2 \subset \mathbb{R}^3$ with spherical co-ordinates

$$0 \leq \theta \leq \pi\,, \quad 0 \leq \varphi < 2\pi\,.$$

We will denote $\mathcal{M}$ a truncated sphere (see Figure 6.1):

$$\mathcal{M} = \{x = (\theta, \varphi)\,:\, \delta < \theta \leq \pi\;\; 0 \leq \phi < 2\pi\}\,, \quad \partial\mathcal{M} = \{\theta = \delta\}.$$

On $\mathcal{M}$ we will study the nonlinear elliptic equation

$$\begin{cases} -\Delta u = \lambda f(u) & \text{on } \mathcal{M}, \\ u = 1 & \text{on } \partial\mathcal{M}, \end{cases} \tag{6.1}$$

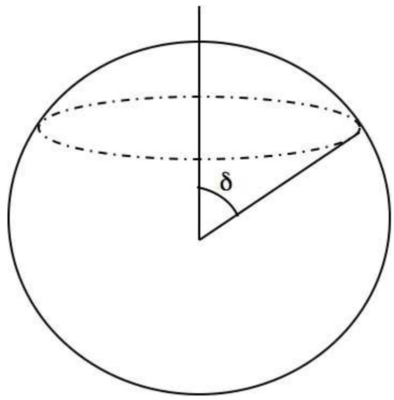

Figure 6.1: Truncated sphere.

where $\lambda > 0$ and f is bistable (see Figure 6.2):

- $f(0) = 0$ and $f'(0) < 0$.
- $f(1) = 0$ and $f'(1) < 0$.
- There exists $\alpha \in (0,1)$ such that $f(\alpha) = 0$, $f'(\alpha) > 0$, $f(s) < 0$ for any $s \in (0,\alpha)$ and $f(s) > 0$ for any $s \in (\alpha, 1)$.
- We extend f on $\mathbb{R} \setminus [0,1]$ in a C^1_B fashion. More precisely, we will assume that there exist $\beta_1 < 0$ and $\beta_2 > 1$ such that :
  - $f(s) \equiv 0$ for $s \in \mathbb{R} \setminus (\beta_1, \beta_2)$.
  - $f(s) > 0$ for $s \in (\beta_1, 0]$.
  - $f(s) < 0$ for $s \in (1, \beta_2]$.

Equation (6.1) is the Euler-Lagrange equation of the functional

$$J_\lambda(u) = \frac{1}{2}\int_{\mathcal{M}} |\nabla u|^2\, dx - \lambda \int_{\mathcal{M}} F(u)\, dx\,, \quad F(z) := \int_0^z f(s)\, ds\,, \tag{6.2}$$

defined on

$$\{u \in H^1(\mathcal{M}) \,:\, u = 1 \text{ on } \partial\mathcal{M}\}\,.$$

It is worth to notice that $F(0) = 0$,

$$F(1) = \int_0^1 f(s)\, ds$$

and the only constant solution of (6.1) is $u \equiv 1$. In order to have a problem defined on $H^1_0(\mathcal{M})$ we use the following change of variables:

$$w := 1 - u\,, \quad g(s) := -f(1-s)\,.$$

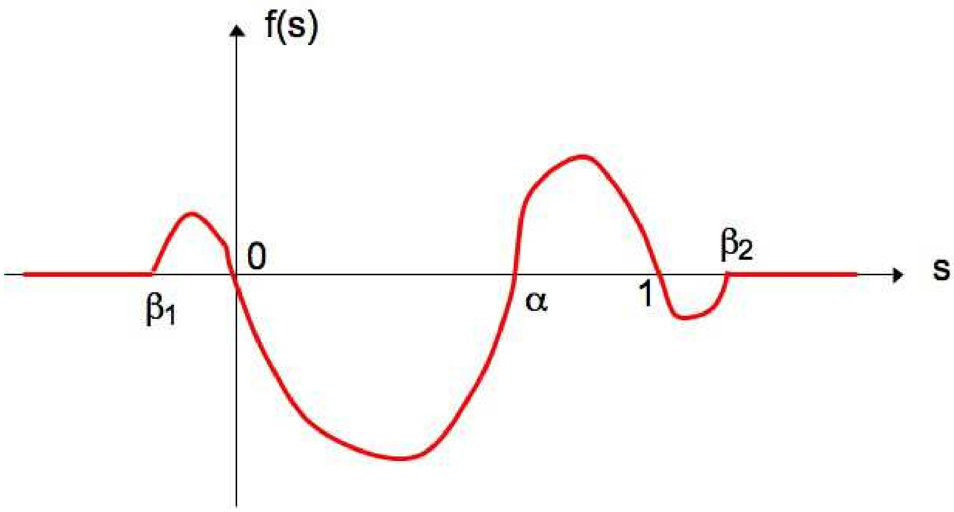

Figure 6.2: Bistable nonllinearity $f(s)$.

Under this framework, equation (6.1) becomes

$$\begin{cases} -\Delta w = \lambda g(w) & \text{on } \mathcal{M}, \\ w = 0 & \text{on } \partial\mathcal{M}, \end{cases} \tag{6.3}$$

where g is bistable and shares the same properties of f, except that its zero on $(0,1)$ is $1-\alpha$. The associated functional is

$$I_\lambda(w) = \frac{1}{2}\int_{\mathcal{M}} |\nabla w|^2\,dx - \lambda\int_{\mathcal{M}} G(w)\,dx\,, \quad G(z) := \int_0^z g(s)\,ds\,. \tag{6.4}$$

Notice that $G(0)=0$, $G(1)=-F(1)$ and the only constant solution of (6.3) is $w\equiv 0$.

6.1.1 Trivial solutions

Theorem 6.1 *There exists $\underline{\lambda}>0$ such that for any $\lambda<\underline{\lambda}$ the only solution of* (6.3) *is $w\equiv 0$.*

Proof: Let w be a solution of (6.3). On the one hand, from (6.3) we have

$$\int_{\mathcal{M}} |\nabla w|^2\,dx = \lambda\int_{\mathcal{M}} g(w)w\,dx\,.$$

Therefore, since g is Lipschitz, it follows that

$$\int_{\mathcal{M}} |\nabla w|^2\,dx \le \lambda K\int_{\mathcal{M}} w^2\,dx\,, \tag{6.5}$$

where $K>0$ is the Lipschitz constant of g. On the other hand, if μ_1 is the first eigenvalue of the Dirichlet problem

$$\begin{cases} -\Delta\phi = \mu_1\phi & \text{on } \mathcal{M}, \\ \phi = 0 & \text{on } \partial\mathcal{M}, \\ \phi > 0 & \text{on } \mathcal{M}\setminus\partial\mathcal{M}, \end{cases}$$

then we have Rayleigh's formula (see Evans, Theorem 2, p. 336)

$$0 < \mu_1 = \min\left\{ \frac{\int_{\mathcal{M}} |\nabla w|^2\, dx}{\int_{\mathcal{M}} w^2\, dx} \;:\; w \in H_0^1(\mathcal{M})\,,\ v \not\equiv 0 \right\}.$$

Therefore,

$$\mu_1 \int_{\mathcal{M}} w^2\, dx \le \int_{\mathcal{M}} |\nabla w|^2\, dx\,. \tag{6.6}$$

Combining (6.5) and (6.6) we get

$$\mu_1 \int_{\mathcal{M}} w^2\, dx \le \lambda K \int_{\mathcal{M}} w^2\, dx\,.$$

In consequence, if $\lambda < \underline{\lambda} := \mu_1/K$ then necessarily $w \equiv 0$. $\square$

Observe that $\underline{\lambda}$ does not depend on the solution w of (6.3). Moreover, the argument in the proof of Theorem 6.1 relies on having a positive first eigenvalue for the Laplace-Beltrami operator on $\mathcal{M}$. Therefore, we cannot extend this result (at least with the current proof) for either Neumann conditions or the whole sphere $\mathbb{S}^2$.

Theorem 6.2 *If $G(1) \le 0$ and $\lambda > 0$ then $w \equiv 0$ is the unique global minimum of* (6.4).

Proof: If $G(1) \le 0$ and $\lambda > 0$ then $-\lambda G(z)$ has a minimum at $z = 0$. In consequence, $w \equiv 0$ is the unique minimum of (6.4). $\square$

6.1.2 Non-trivial solution: variational approach

Theorem 6.3 *If $G(1) > 0$ there exists $\lambda^\sharp > 0$ such that for any $\lambda > \lambda^\sharp$ we have at least one non-trivial solution of* (6.3).

Proof: Since $g(s)$ is Lipschitz continuous of constant K then

$$s \mapsto h(s) := Ks + g(s)$$

is monotone non-decreasing on $[0,1]$. We extend the function h as $h \equiv 0$ on $\mathbb{R} \setminus [0,1]$. Define the operator

$$\mathcal{L}_\lambda w := -\Delta w + \lambda K w$$

It is easy to see that w is solution of (6.3) if and only if it is a solution of

$$\begin{cases} \mathcal{L}_\lambda w = \lambda h(w) & \text{on } \mathcal{M}, \\ \quad w = 0 & \text{on } \partial\mathcal{M}. \end{cases} \tag{6.7}$$

Define $w_0 \equiv 1$ and let w_1 be a solution of

$$\begin{cases} \mathcal{L}_\lambda w_1 = \lambda h(w_0) & \text{on } \mathcal{M}, \\ \quad w_1 = 0 & \text{on } \partial\mathcal{M}. \end{cases} \tag{6.8}$$

Using the maximum principle we obtain $0 \leq w_1 \leq w_0$, and the strong maximum principle gives $w_1 < 1$ on $\mathcal{M}$. Recursively, given $0 \leq w_n \leq 1$ define w_{n+1} as the solution of

$$\begin{cases} \mathcal{L}_\lambda w_{n+1} = \lambda h(w_n) & \text{on } \mathcal{M}, \\ w_{n+1} = 0 & \text{on } \partial\mathcal{M}. \end{cases} \tag{6.9}$$

Since h is non-decreasing, it follows from the maximum principle that the sequence $\{w_n\}_{n\in\mathbb{N}}$ is non-increasing and bounded from below, hence it converges (both pointwise and in $H_0^1(\mathcal{M})$) to a solution $0 \leq w(\lambda) \leq 1$ of (6.7). Furthermore, w_λ is the maximal solutions of (6.7). Indeed, if ϕ is also a solution then the maximum principle implies $0 \leq \phi \leq 1 = w_0$. Applying the maximum principle again we obtain by recurrence that $0 \leq \phi \leq w_n$ for all $n \in \mathbb{N}$. Therefore, in the limit we obtain $0 \leq \phi \leq w(\lambda)$. Define

$$I_1(w) := \frac{1}{2}\int_{\mathcal{M}} |\nabla w|^2 \, dx \,, \quad I_2(\lambda, w) := -\lambda \int_{\mathcal{M}} G(w) \, dx \,,$$

that is $I_\lambda(w) = I_1(w) + I_2(\lambda, w)$. Since G is Lipschitz continuous then there exists a constant $C > 0$ such that

$$|I_2(\lambda, w)| \leq \lambda C I_1(w)^{1/2} \quad \forall w \in H_0^1(\mathcal{M}) \,.$$

In consequence,

$$I_\lambda(w) \geq I_1(x) - \lambda C I_1(w)^{1/2} \,,$$

which implies that there exists a constant $C > 0$ such that if $\|w\|_{H_0^1(\mathcal{M})} \geq R(\lambda) := C\lambda$ then $I_\lambda \geq 1$. Define

$$Z_\lambda := \left\{ w \in H_0^1(\mathcal{M}) \,:\, \|w\|_{H_0^1(\mathcal{M})} \leq R(\lambda) \right\} \,,$$

which is a bounded, convex, closed subset of $H_0^1(\mathcal{M})$. It can be shown that the functional $I_\lambda(w)$ is coercive and weakly lower semi-continuous. In consequence, I_λ has a minimum $\tilde{w}(\lambda) \in Z_\lambda$. Moreover, since $I_\lambda(0) = 0$ and $I_\lambda(w) \geq 1$ on ∂Z_λ, it follows that $\tilde{w}(\lambda) \in \mathrm{Int}(Z_\lambda)$. Therefore, $\tilde{w}(\lambda)$ is a weak solution of (6.3). Since $G(1) > 0$, we can find $\phi_0 \in H_0^1(\mathcal{M})$ such that

$$\int_{\mathcal{M}} G(\phi_0) \, dx > 0.$$

Therefore, if $\lambda > 0$ is sufficiently large then $\phi_0 \in Z_\lambda$ and $I_\lambda(\phi_0) < 0$, which implies that $\tilde{w} \not\equiv 0$. Observe that $\lambda \mapsto R(\lambda)$ is non-decreasing and for any $\phi \in H_0^1(\mathcal{M})$ the mapping $\lambda \mapsto I_\lambda(\phi)$ is decreasing. Therefore, if $\phi \in Z_\lambda$ and $I_\lambda(\phi) < 0$ then $\phi \in Z_\mu$ and $I_\mu(\phi) < 0$ for all $\mu > \lambda$. In conclusion, if we define

$$\lambda^\sharp := \inf \left\{ \lambda > 0 \,:\, \min_{H_0^1(\mathcal{M})} I_\lambda < 0 \right\}$$

then for any $\lambda > \lambda^\sharp$ we have a solution $\tilde{w}(\lambda)$ of (6.3) such that $\tilde{w}((\lambda) \not\equiv 0$. Therefore, the maximal solution $w(\lambda)$ that we constructed before is non-trivial. $\square$

6.1.3 Pair of non-trivial solutions: topological approach

Theorem 6.4 *If $G(1) > 0$ then there exists $\lambda^\flat > 0$ such that for any $\lambda > \lambda^\flat$ we have a pair of distinct, non-trivial solutions of* (6.3).

The proof of Theorem 6.4 will be done in several steps. Define

$$\begin{aligned} \Gamma^+ &:= \{s \in \mathbb{R} \,:\, g(s) > 0\} = (0, 1-\alpha)\,, \\ \Gamma^- &:= \{s \in \mathbb{R} \,:\, g(s) < 0\} = (1-\alpha, 1)\,, \end{aligned}$$

and let $\mathcal{T}$ be the set of functions $\theta \in C^1_B(\mathbb{R})$ such that $\theta \geq 1/2$ on $\mathbb{R}$, $\theta < 1$ on Γ^+, $\theta > 1$ on Γ^- and $\theta = 1$ on $\mathbb{R} \setminus (0,1)$. For any $\theta \in \mathcal{T}$ define

$$I_\lambda(\theta, w) = \frac{1}{2}\int_{\mathcal{M}} |\nabla w|^2\, dx - \lambda \int_{\mathcal{M}} G_\theta(w)\, dx\,, \quad G_\theta(z) := \int_0^z \theta(s) g(s)\, ds\,. \tag{6.10}$$

Using Lebesgue's dominated convergence theorem, if $\theta \in \mathcal{T}$ is such that $\|1-\theta\|_{L^\infty(\mathcal{M})}$ is small enough then $G_\theta(1) > 0$. Therefore, we can apply Theorem 6.3 to the functional $I_\lambda(\theta, \cdot)$ to ensure that there exists $\lambda^\flat = \lambda^\flat(\theta) > 0$ such that for any $\lambda > \lambda^\flat$ there exists a maximal, non-trivial solution $y(\lambda)$ of

$$\begin{cases} -\Delta y = \lambda \theta(y) g(y) & \text{on } \mathcal{M}, \\ \quad y = 0 & \text{on } \partial\mathcal{M}. \end{cases} \tag{6.11}$$

Since $\theta(z)g(z) \leq g(z)$ for all $z \in \mathbb{R}$ and the inequality is strict on $\Gamma^+ \cup \Gamma^-$, it follows that $y(\lambda)$ is a strict sub-solution of (6.3) for any $\lambda > \lambda^\flat$. As in the proof of Theorem 6.3, we canconstruct an increasing sequence $\{z_n\}_{n\in\mathbb{N}}$ that converges to a solution of (6.3). We start with $z_0 = y(\lambda)$ and recursively define

$$\begin{cases} \mathcal{L}_\lambda z_{n+1} = \lambda h(z_n) & \text{on } \mathcal{M}, \\ \quad z_{n+1} = 0 & \text{on } \partial\mathcal{M}. \end{cases} \tag{6.12}$$

In the limit we obtain a solution of (6.3), that we will denote $z(\lambda)$. Recall that $w_1(\lambda)$ (as defined in the proof of Theorem 6.3) is the solution of (6.8), which implies that it is a strict super-solution of (6.3). In consequence, applying the strong maximum principle and Hopf's lemma we obtain

$$\begin{aligned} 0 < y(\lambda) < z(\lambda) < w_1(\lambda) < 1 \qquad & \text{on } \mathcal{M}, \\ 0 > \partial_\nu y(\lambda) > \partial_\nu z(\lambda) > \partial_\nu w_1(\lambda) \qquad & \text{on } \partial\mathcal{M}. \end{aligned}$$

Using Schauder estimates, it can be shown that for every $\lambda \geq 0$ there exists a constant $q(\lambda) > 0$ such that for any $U \in L^\infty(\mathcal{M})$ with $\|U\|_{L^\infty(\mathcal{M})} \leq K+1$, the solution V of the problem

$$\begin{cases} \mathcal{L}_\lambda V = \lambda U & \text{on } \mathcal{M}, \\ \quad V = 0 & \text{on } \partial\mathcal{M}, \end{cases} \tag{6.13}$$

satisfies $\|U\|_{C^{1,\beta}(\overline{\mathcal{M}})} \leq q(\lambda)$ for any $\beta \in (0,1)$. We consider the space

$$\mathrm{E} = \{u \in C^1(\mathcal{M}) \,:\, u = 0 \text{ on } \partial\mathcal{M}\}$$

and define the operator $T : \mathbb{R} \times \mathrm{E} \to \mathrm{E}$ as the unique solution $v = T(\lambda, u)$ of the linear equation

$$\begin{cases} \mathcal{L}_\lambda v = \lambda h(u) & \text{on } \mathcal{M}, \\ \quad v = 0 & \text{on } \partial\mathcal{M}. \end{cases} \tag{6.14}$$

For any $\lambda > \lambda^\flat$ define $\mathcal{A}_\lambda$ as the set of all functions $\phi \in \mathrm{E}$ such that

$$y(\lambda) < \phi < w_1(\lambda) \quad \text{on } \mathcal{M},$$

$$\partial_\nu y(\lambda) > \partial_\nu \phi > \partial_\nu w_1(\lambda) \quad \text{on } \partial\mathcal{M}, \text{ and}$$

$$\|\phi\|_{C^{1,\beta}(\overline{\mathcal{M}})} < q(\lambda)\,.$$

It is easy to see that $\mathcal{A}_\lambda$ is an open, bounded, convex subset of E. Choose any $\phi \in \mathcal{A}_\lambda$. Since $y(\lambda)$ (resp. $w_1(\lambda)$) is a strict, nontrivial sub-solution (resp. super-solution) of (6.3), the strong maximum principle and the monotonicity of $s \mapsto h(s)$ yield

$$y(\lambda) < T(\lambda, y(\lambda) \le T(\lambda, \phi) \le T(\lambda, w_1(\lambda)) < w_1(\lambda) \quad \text{on } \mathcal{M},$$

$$\partial_\nu y(\lambda) > \partial_\nu T(\lambda, y(\lambda) \ge \partial_\nu T(\lambda, \phi) \ge \partial_\nu T(\lambda, w_1(\lambda)) > \partial_\nu w_1(\lambda) \quad \text{on } \partial\mathcal{M}$$

and $\|h(\phi)\|_{L^\infty(\mathcal{M})} \le K+1$. Therefore $\|T(\lambda,\phi)\|_{C^1(\overline{\mathcal{M}})} < q(\lambda)$, which implies that $T(\lambda, \overline{\mathcal{A}}_\lambda) \subset \mathcal{A}_\lambda$. Moreover, from Schauder estimates it follows that $T(\lambda, \overline{\mathcal{A}}_\lambda)$ is compact in E.

Define $\Phi(\lambda, u) := u - T(\lambda, u)$. Since $T(\lambda, \cdot)$ has no fixed point on $\partial\mathcal{A}_\lambda$ then $\Phi(\lambda, u) \neq 0$ on $\partial\mathcal{A}_\lambda$ for all $\lambda > \lambda^\flat$. Therefore, its Leray-Schauder degree

$$\deg\left(\Phi(\lambda, \cdot),\, \mathcal{A}_\lambda,\, 0\right)$$

is well defined. Choose $a \in \mathcal{A}_\lambda$ and for $t \in [0,1]$ define

$$\Psi_t(\lambda, u) := t\,[u - T(\lambda, u)] + (1-t)\,[u - a]\ .$$

We claim that $\Psi_t(\lambda, u) \neq 0$ on $\partial\mathcal{A}_\lambda$. Indeed, $\Psi_1(\lambda, u) = \Phi(\lambda, u)$, which does not vanish on $\partial\mathcal{A}_\lambda$. On the other hand, $\Psi_0(\lambda, u) = u - a$, which it has no zeroes on $\partial\mathcal{A}_\lambda$. Finally, if $t \in (0,1)$ then from the convexity of $\mathcal{A}_\lambda$ it follows that

$$t\,T(\lambda, u) + (1-t)a \in \mathcal{A}_\lambda\,.$$

Therefore, $\Psi_t(\lambda, u) \neq 0$ on $\partial\mathcal{A}_\lambda$. In consequence, the degree

$$\deg\left(\Psi_t(\lambda, \cdot),\, \mathcal{A}_\lambda,\, 0\right)$$

is well defined and constant for $t \in [0,1]$. But since

$$\deg\left(\Psi_0(\lambda, \cdot),\, \mathcal{A}_\lambda,\, 0\right) = 1$$

it follows that

$$\deg\left(\Phi(\lambda, \cdot),\, \mathcal{A}_\lambda,\, 0\right) = 1\,.$$

In conclusion, $\Phi(\lambda,\cdot)$ has a zero in $\mathcal{A}_\lambda$, which is equivalent to a non-trivial solution $z^\flat(\lambda)$ of (6.3).

Now we will find a second, non-trivial solution of (6.3). Since $g \in C^1_B(\mathbb{R})$ then $G \in C^2_B(\mathbb{R})$, which implies that for any $z \in \mathbb{R}$ we have

$$G(z) = G(0) + G'(0)\,z + \frac{G''(0)}{2}\,z^2 + o(z^2) = \frac{g'(0)}{2}\,z^2 + o(z^2)\,.$$

Moreover, from the regularity of G it follows that the functional

$$\mathcal{G} : H^1_0(\mathcal{M}) \to \mathbb{R}\,, \quad \mathcal{G}(w) = \int_{\mathcal{M}} G(w)\,dx$$

is a C^2-functional. In consequence, for any $\phi \in H^1_0(\mathcal{M})$ we have that

$$\mathcal{G}(\phi) = \frac{g'(0)}{2} \int_{\mathcal{M}} |\phi|^2\,dx + o\left(\|\phi\|^2_{H^1_0(\mathcal{M})}\right)\,.$$

Therefore, $I_\lambda : H^1_0(\mathcal{M}) \to \mathbb{R}$ is a C^2-functional, which implies that for any $\phi \in H^1_0(\mathcal{M})$ small we have

$$I_\lambda(\phi) = \frac{1}{2}\int_{\mathcal{M}} |\nabla\phi|^2\,dx - \frac{\lambda g'(0)}{2}\int_{\mathcal{M}} |\phi|^2\,dx + o\left(\|\phi\|^2_{H^1_0(\mathcal{M})}\right)\,.$$

Since $g'(0) < 0$ then $I_\lambda(\cdot)$ is equivalent to the norm in $H^1(\mathcal{M})$ for ϕ small. In consequence, if $\rho > 0$ is sufficiently small and $\phi \in H^1_0(\mathcal{M})$ is a solution of (6.3) such that $\|\phi\|_{H^1_0(\mathcal{M})} \leq \rho$ then necessarily we have $\phi \equiv 0$.

Fix $\lambda > \lambda^\flat$ and define

$$\begin{aligned}
\mathrm{P}^+ &:= \{\phi \in \mathrm{E} \,:\, \phi > 0 \text{ in } \mathcal{M} \quad\text{and}\quad \partial_\nu\phi < 0 \text{ on } \partial\mathcal{M}\}\,,\\
\mathcal{B}(\lambda) &:= \left\{(\mu,\phi) \in [0,\lambda] \times \mathrm{P}^+ \,:\, \rho < \|\phi\|_{\mathrm{C}^1(\overline{\mathcal{M}})} < \mathrm{q}(\mu)\right\}\,,\\
\mathcal{B}_\mu(\lambda) &:= \{\phi \in \mathrm{E} \,:\, (\mu,\phi) \in \mathcal{B}(\lambda)\}\,.
\end{aligned}$$

Let $\partial\mathcal{B}(\lambda)$ the topological boundary of $\mathcal{B}(\lambda)$ in the space $[0,\lambda]\times\mathrm{E}$. Since $\Phi(\cdot,\cdot)$ does not vanish on $\partial\mathcal{B}(\lambda)$ and the degree is constant under homotopy, it follows that

$$\deg\left(\Phi(\mu,\cdot),\,\mathcal{B}_\mu(\lambda),\,0\right)$$

is well-defined and constant for any $\mu \in [0,\lambda]$. However, if μ is small enough then Theorem 6.1 implies that the only zero of $\Phi(\mu,u)$ is $u \equiv 0$, which lies outside of $\overline{\mathcal{B}}_\mu(\lambda)$. Therefore,

$$\deg\left(\Phi(\mu,\cdot),\,\mathcal{B}_\mu(\lambda),\,0\right) = 0 \quad \forall\mu \in [0,\lambda]\,,$$

and in particular

$$\deg\left(\Phi(\lambda,\cdot),\,\mathcal{B}_\lambda(\lambda),\,0\right) = 0\,.$$

Using the additive and excision properties of the degree it follows that

$$\deg\left(\Phi(\lambda,\cdot),\,\mathcal{B}_\lambda(\lambda)\setminus\mathcal{A}_\lambda,\,0\right) = -\deg\left(\Phi(\lambda,\cdot),\,\mathcal{A}_\lambda,\,0\right) = -1\,.$$

Therefore, there exists a nontrivial solution $z^\sharp(\lambda)$ of (6.3) such that $z^\sharp(\lambda) \not\equiv z^\flat(\lambda)$. $\square$

Lemma 6.1 *Let $\theta \in \mathcal{T}$ and denote $I_\lambda(w)$ and $I_\lambda(\theta, w)$ the functionals associated to the nonlinear elliptic equations* (6.3) *and* (6.11) *(resp.). Define*

$$A^\flat(\theta) := \left\{ \lambda > 0 \,:\, \min_{H_0^1(\mathcal{M})} I_\lambda(\theta, \cdot) < 0 \right\}, \quad \lambda^\flat(\theta) := \inf A^\flat(\theta)\,,$$

$$A^\sharp := \left\{ \lambda > 0 \,:\, \min_{H_0^1(\mathcal{M})} I_\lambda(\cdot) < 0 \right\}, \quad \lambda^\sharp := \inf A^\sharp\,.$$

Then

1. $\lambda^\flat(\theta) \le \lambda^\sharp$.
2. *Given $\varepsilon > 0$ there exists $\theta(\varepsilon) \in \mathcal{T}$ such that $\lambda^\sharp \le \lambda^\flat(\theta(\varepsilon)) + \varepsilon$.*

Proof:

1. Let $\lambda \in A^\flat(\theta)$ and let $y \in H_0^1(\mathcal{M})$ be the global minimum of $I_\lambda(\theta, \cdot)$. Then $I_\lambda(\theta, y) < 0$ and y is a non-trivial solution of (6.3) such that $0 \le y \le 1$. Moreover,
$$\begin{aligned} I_\lambda(\theta, y) - I_\lambda(y) &= \lambda \int_{\mathcal{M}} [G(y) - G_\theta(y)]\, dx \\ &= \lambda \int_{\mathcal{M}} \int_0^y [1 - \theta(s)] g(s)\, ds\, dx \ge 0\,. \end{aligned} \tag{6.15}$$
Therefore $I_\lambda(y) \le I_\lambda(\theta, y) < 0$, which implies that $\lambda \in A^\sharp$.

2. Let $\lambda \in A^\flat(\theta)$, denote $u \in H_0^1(\mathcal{M})$ the global minimum of $I_\lambda(\cdot)$ and consider a sequence $\{\theta_n\}_{n\in\mathbb{N}} \subset \mathcal{T}$ such that
$$\|1 - \theta_n\|_{L^\infty(\mathcal{M})} \le \frac{1}{n}\,.$$
For any $n \in \mathbb{N}$ and $x \in \mathcal{M}$ define
$$G_n(x) := \int_0^{u(x)} [1 - \theta_n(s)] g(s)\, ds\,.$$
Then $G_n \ge 0$, $G_n \in C^0(\overline{\mathcal{M}})$ and there exists a constant $C > 0$ such that
$$\|G_n\|_{L^\infty(\mathcal{M})} \le \frac{C}{n}\,.$$
Therefore, using Lebesgue's dominated convergence theorem if follows that
$$\lim_{n\to\infty} \int_{\mathcal{M}} G_n(x)\, dx = 0\,. \tag{6.16}$$
Since $I_\lambda(u) < 0$ then if $\varepsilon > 0$ is small enough we have $I_\lambda(u) + \varepsilon < 0$. In consequence, choosing n large enough we obtain that
$$I_\lambda(\theta_n, u) < I_\lambda(u) + \varepsilon < 0\,,$$
which implies that $\lambda \in A^\flat(\theta_n)$. $\square$

Theorem 6.5 *Let $\lambda^\flat$ and $\lambda^\sharp$ be as in Theorems 6.3 and 6.4, respectively. Then $\lambda^\flat = \lambda^\sharp$.*

Proof: Notice that in the definition of $\lambda^\flat$ given in the proof of Theorem 6.4, the function $\theta \in C^1_B(\mathbb{R})$ can be chosen arbitrarily as long as $\theta \in \mathcal{T}$ is close enough to $\theta \equiv 1$ in the $L^\infty(\mathbb{R})$ norm. Therefore, if we choose a sequence $\{\theta_n\}_{n\in\mathbb{N}} \subset \mathcal{T}$ such that

$$\lim_{n\to\infty} \|1-\theta_n\|_{L^\infty(\mathcal{M})} = 0$$

then using Lemma 6.1 we obtain the result. □

From Theorems 6.3 - 6.5 it follows that $\lambda^\flat$ is a pitchfork bifurcation point for the elliptic problem (6.3) because, if there exists one non-trivial solution then there is a second, different non-trivial solution. More precisely, choosing

$$\lambda^\flat = \inf\{\lambda > 0 \,:\, (6.3) \text{ has a non-trivial solution}\}$$

then for $\lambda < \lambda^\flat$ the only solution is $w \equiv 0$ whilst for $\lambda > \lambda^\flat$ we have two distinct, non-trivial solutions.

6.2 Reaction-diffusion equations on the truncated sphere

Let $\lambda > \lambda^\flat (= \lambda^\sharp)$ and let $z^\flat(x)$ a non-trivial solution of the elliptic problem (6.3). Then $u^\star(x) := 1 - z^\flat(x)$ is a non-trivial solution of (6.1). The next theorem shows that the problem

$$\begin{cases} \partial_t u = \Delta u + \lambda f(u) & \text{in } (0,\infty)\times\mathcal{M}, \\ u = 1 & \text{on } (0,\infty)\times\partial\mathcal{M}, \\ u(0,x) = 0 & \text{for all } x \in \mathcal{M}, \end{cases} \tag{6.17}$$

admits a generalised travelling wave solution $u(t,x)$, strictly increasing in time, which is blocked by the non-trivial solution $u^\star(x)$.

Theorem 6.6 *There is a non-trivial solution $u(t,x)$ of (6.17) such that $t \mapsto u(t,x)$ is strictly increasing, $0 < u(t,x) \le u^\star(x)$ for all $t > 0$ and*

$$\lim_{t\to\infty} u(t,x) \le u^\star(x) \quad \forall x \in \mathcal{M}\,.$$

Proof: Observe that $u \equiv 0$ and $u^\star$ are strict sub-solution and super-solution of (6.17), respectively. Therefore, the strong maximum principle implies that there exists a solution $u(t,x)$ of (6.17) such that $0 < u(t,x) < u^\star(x)$ for all $t > 0$. Moreover, $t \mapsto u(t,x)$ is increasing. Indeed, if we differentiate (6.17) we obtain that $\partial_t u(t,x)$ solves a linear equation with non-negative initial and boundary conditions . Therefore, from the strong maximum principle it follows that $\partial_t u(t,x) > 0$ for all $(t,x) \in (0,\infty)\times\mathcal{M}$. □

6.3 Elliptic equation on the N-sphere

Consider the elliptic nonlinear equation

$$-\Delta u = \lambda f(u) \quad \text{on } \mathbb{S}^N \subset \mathbb{R}^{N+1}. \tag{6.18}$$

where $f \in C^1_B(\mathbb{R})$ is a bistable nonlinearity with the same properties as in Section 6.1.

6.3.1 Trivial solutions

Lemma 6.2 *There exists $\lambda_0 > 0$ such that for any $\lambda < \lambda_0$ the only constant solutions of* (6.18) *are* 0*,* α *and* 1*.*

Proof: Suppose that the conclusion is false. Then there exist a decreasing sequence $\lambda_n \to 0$ and a sequence of non-constant solutions $0 < u_n < 1$ such that the pair (λ_n, u_n) is a solution of (6.18). From (6.18) it follows that

$$\lim_{n\to\infty} \int_{\mathbb{S}^N} |\nabla u_n|^2 \, dx = 0 \, .$$

Therefore, up to a sub-sequence we can suppose that u_n converges in $H^1(\mathbb{S}^N)$ to a constant $\rho \in [0, 1]$. Moreover, using standard elliptic estimates and regularity results, it follows that $u_n \to \rho$ in $C^1(\mathbb{S}^N)$. In consequence, since f is Lipschitz we obtain

$$\lim_{n\to\infty} f(u_n) = f(\rho).$$

But integrating (6.18) on $\mathbb{S}^N$ we obtain

$$\int_{\mathbb{S}^N} f(u_n) = 0 \quad \forall n \in \mathbb{N} \, . \tag{6.19}$$

In consequence, $f(\rho) = 0$, which implies that $\rho \in \{0, \alpha, 1\}$. However, if $\rho \neq \alpha$ then for n sufficiently large we would have either $0 < u_n(x) < \alpha$ or $\alpha < u_n(x) < 1$, which would contradict (6.19). Therefore $\rho = \alpha$.

If we write $u_n = k_n + v_n$ where

$$k_n := \int_{\mathbb{S}^N} u_n \, dx \quad \text{and} \quad \int_{\mathbb{S}^N} v_n \, dx = 0 \, ,$$

then $k_n \to \alpha$ and $v_n \to 0$ in $C^1(\mathbb{S}^N)$. From (6.18) we deduce that v_n is solution of

$$-\Delta v_n = \lambda_n f(k_n) + \lambda_n [\, f(k_n + v_n - f(k_n) \,] \, . \tag{6.20}$$

Using standard elliptic estimates and Poincaré-Wirtinger inequality it can be shown that

$$\|v_n\|_{L^\infty(\mathbb{S}^N)} \leq \lambda_n |f(k_n)| + \lambda_n K \|v_n\|_{L^\infty(\mathbb{S}^N)} \, ,$$

which implies that

$$\|v_n\|_{L^\infty(\mathbb{S}^N)} \leq \frac{\lambda_n}{1-K\lambda_n}|f(k_n)|\,.$$

Since u_n is not constant then $\|v_n\|_{L^\infty(\mathbb{S}^N)} > 0$ and $f(k_n) \neq 0$ for all $n \in \mathbb{N}$. In consequence,

$$\lim_{n\to\infty} \frac{\|v_n\|_{L^\infty(\mathbb{S}^N)}}{f(k_n)} = 0\,.$$

Define

$$w_n := \frac{v_n}{\lambda_n f(k_n)}\,.$$

Then w_n is solution of

$$-\Delta w_n = 1 + A_n(x)\,, \quad A_n(x) := \frac{f(k_n+v_n)-f(k_n)}{f(k_n)}\,. \tag{6.21}$$

On the one hand, since

$$\lim_{n\to\infty} |A_n(x)| \leq \lim_{n\to\infty} \frac{K\|v_n\|_{L^\infty(\mathbb{S}^N)}}{|f(k_n)|} = 0\,,$$

we have that

$$\lim_{n\to\infty} \int_{\mathbb{S}^N} A_n\,dx = 0\,.$$

But on the other hand, integrating (6.21) we obtain

$$|\mathbb{S}^N| + \int_{\mathbb{S}^N} A_n\,dx = 0 \quad \forall n \in \mathbb{N}\,,$$

which is a contradiction. $\square$

The proof of Lemma 6.2, albeit non-constructive, holds for any arbitrary manifold without boundary.

Lemma 6.3 *Let φ be any spherical angle in the parametrisation of $\mathbb{S}^N$. Then ∂_φ and the Laplace-Beltrami operator commute.*

Proof: For $N=1$ the Riemannian metric is $g_{ij} = [1]$, which implies that the Laplace-Beltrami is constant, and as such it commutes with the angular derivative.

For $N=2$, we choose the spherical coordinates (φ,θ) such that $\varphi \in (0,2\pi)$ is the horizontal angle and $\theta \in (0,\pi)$ is the vertical angle. Then the Riemanian metric is

$$g_{ij} = \begin{pmatrix} \sin^2\theta & 0 \\ 0 & 1 \end{pmatrix}\,.$$

Therefore, the coefficients of the Laplace-Beltrami operator do not depend on the horizontal angle φ, which implies that the partial derivative ∂_φ commutes with the Laplace-Beltrami operator.

For $N \geq 3$, we use the parametrisation

$$\begin{aligned}
x_1 &= \cos\varphi_1\,,\\
x_2 &= \sin\varphi_2\,\cos\varphi_2\,,\\
x_3 &= \sin\varphi_2\,\sin\varphi_2\,\cos\varphi_3\,,\\
&\vdots\\
x_N &= \sin\varphi_2\,\sin\varphi_2\cdots\sin\varphi_{N-1}\,\cos\varphi_N\,,\\
x_{N+1} &= \sin\varphi_2\,\sin\varphi_2\cdots\sin\varphi_{N-1}\,\sin\varphi_N\,,
\end{aligned}$$

where $(\varphi_1,\ldots,\varphi_n) \in (0,\pi)^{N-1}\times(0,2\pi)$. Then the Riemannian metric is

$$g_{ij} = \begin{pmatrix} 1 & 0 & 0 & \cdots & 0\\ 0 & \sin^2\varphi_1 & 0 & \cdots & 0\\ 0 & 0 & \sin^2\varphi_1\,\sin^2\varphi_2 & \cdots & 0\\ & & & \ddots & \\ 0 & 0 & 0 & \cdots & \sin^2\varphi_1\,\sin^2\varphi_2\cdots\sin^2\varphi_{N-1}\end{pmatrix},$$

which implies that the coefficients of the Laplace-Beltrami operator are independent of the angle φ_N. Therefore, choosing $\varphi = \varphi_N$ we obtain that ∂_φ and the Laplace-Beltrami operator commute. $\square$

Theorem 6.7 *There exists $\underline{\lambda} > 0$ such that for any $\lambda < \underline{\lambda}$ the only solutions of* (6.18) *are constant.*

<u>*Proof*</u>: Let u be a solution of (6.18) and let φ be any spherical angle. Differentiating (6.18) and using Lemma 6.3 we find that $\partial_\varphi u$ satisfies the equation

$$-\Delta\partial_\varphi u = \lambda f'(u)\partial_\varphi u\,.$$

Integrating by parts we find

$$\int_{\mathbb{S}^2} |\nabla\left(\partial_\varphi u\right)|^2\,dx = \lambda\int_{\mathbb{S}^2} f'(u)|\partial_\varphi u|^2\,dx\,.$$

Moreover, since

$$\int_{\mathbb{S}^N} \partial_\varphi u\,dx = 0$$

it follows that

$$\mu_2\int_{\mathbb{S}^N} |\partial_\varphi u|^2\,dx \leq \lambda K\int_{\mathbb{S}^N} |\partial_\varphi u|^2\,dx\,.$$

where μ_2 is the first non-zero eigenvalue of the Laplace-Beltrami operator satisfying the minimax relation

$$\mu_2 = \inf\left\{\frac{\int_{\mathbb{S}^N}|\nabla u|^2\,dx}{\int_{\mathbb{S}^N} u^2\,dx}\;:\;u\in H^1(\mathbb{S}^N),\;\int_{\mathbb{S}^N} u\,dx = 0\right\}.$$

Therefore, if $\lambda < \underline{\lambda} := \mu_2/K$ then $\partial_\varphi u \equiv 0$. But since φ was an arbitrary spherical angle then u is constant. $\square$

The proof of Theorem 6.7 is constructive and gives an explicit interval $[0, \underline{\lambda})$ for which there only solutions of (6.18) are constant. However, it only holds for the N-sphere because it relies strongly on the invariance under rotations.

6.3.2 Stability of solutions

Definition 6.4 *Let u be a solution of* (6.18). *We say that u is* **stable** *if*

$$\int_{\mathbb{S}^N} \left\{ |\nabla w|^2 - \lambda f'(u) w^2 \right\} \, dx \geq 0 \quad \forall w \in H^1(\mathbb{S}^N)\,. \tag{6.22}$$

Property (6.22) is equivalent to say that the first eigenvalue $\mu_1(u)$ of the operator

$$w \mapsto -\Delta w - \lambda f'(u) w$$

satisfies $\mu_1(u) \geq 0$.

Theorem 6.8 *Let u be a solution of* (6.18). *If u is stable then it is constant and $u \in \mathbb{R} \setminus (0, 1)$.*

Proof: Let u be a stable solution of 6.18 and φ any spherical angle. Using Lemma 6.3 it follows that

$$-\Delta \partial_\varphi u - \lambda f'(u) \partial_\varphi u = 0\,,$$

and in consequence

$$\int_{\mathbb{S}^N} \left\{ |\nabla \left(\partial_\varphi u\right)|^2 - \lambda f'(u) |\partial_\varphi u|^2 \right\} \, dx = 0\,.$$

Therefore $\partial_\varphi u$ is an eigenfunction associated to the first eigenvalue, which implies that $\partial_\varphi u \geq 0$. However, since

$$\int_{\mathbb{S}^N} \partial_\varphi u \, dx = 0$$

we necessarily have $\partial_\varphi u \equiv 0$. Finally, since φ was arbitrary then u is constant. Moreover, if u is stable then

$$\{ x \in \mathbb{S}^N \, : \, f'(u(x)) > 0 \; \} = \emptyset\,.$$

In particular, if $u \equiv c$ is a constant solution on $(0, 1)$ then $c = \alpha$ and $u \equiv \alpha$ is unstable. $\square$

Theorem 6.8 has been proven by Casten and Holland [12] and Matano [46] in the case of an Euclidean convex domain with homogeneous Neumann boundary conditions. As far as we know, Theorem 6.8 is a new result on manifolds.

6.3.3 Non-trivial solutions

Theorem 6.9 *There exists $\lambda^\flat > 0$ such that for any $\lambda > \lambda^\flat$ we have at least one non-trivial solution $u^\star(x)$ of* (6.18) *such that* $0 < u^\star < 1$.

<u>*Proof*</u>: If u is solution of (6.18) then $w := 1 - u$ is solution of

$$-\Delta u = \lambda g(u)\,, \tag{6.23}$$

where $g(s) := -f(1-s)$ and

$$G(z) := \int_0^z g(s)\,ds\,.$$

Since $G(1) = -F(1)$, without loss of generality we can suppose that $F(1) \geq 0$. Define

$$\Gamma := \left\{\gamma \in C\left([0,1]; H_0^1(\mathbb{S}^N)\right) \,:\, \gamma(0) = 0,\ \gamma(1) = 1\right\}\,,$$

$$c(\lambda) := \inf_{\gamma\in\Gamma} \max_{0\leq t\leq 1} I_\lambda(\gamma(t))\,.$$

Suppose that $F \in C_B^2(\mathbb{R})$. Therefore, for any $z \in \mathbb{R}$ small we have

$$F(z) = F(0) + F'(0)z + \frac{F''(0)}{2}z^2 + o\left(z^2\right) = \frac{f'(0)}{2}\,z^2 + o\left(z^2\right)\,.$$

This implies that $I_\lambda : H^1(\mathbb{S}^N) \to \mathbb{R}$ is a C^2 functional. Therefore, for any $\phi \in H^1(\mathbb{S}^N)$ small we have

$$I_\lambda(\phi) = \frac{1}{2}\int_{\mathbb{S}^N} |\nabla\phi|^2\,dx - \frac{\lambda g'(0)}{2}\int_{\mathbb{S}^N} |\phi|^2\,dx + o\left(\|\phi\|^2_{H^1(\mathbb{S}^N)}\right)\,.$$

Therefore, using that $g'(0) < 0$ it follows that $I_\lambda(\cdot)$ is equivalent to the norm in $H^1(\mathbb{S}^N)$ near zero, i.e. there exist $a > 0$ and $\eta > 0$ such that $I_\lambda(w) \geq a$ whenever $\|w\|_{H^1(\mathbb{S}^N)} \leq \eta$. On the other hand, $I_\lambda(1) = -\lambda F(1)|\mathbb{S}^2| \leq 0$, and it is easy to show (see e.g. Evans [18], p. 482) that $I_\lambda(\cdot)$ satisfies the Palais-Smale condition. Therefore, applying the Mountain Pass Theorem we obtain a critical point $u^\star \in H^1(\mathbb{S}^N)$ of $I_\lambda(\cdot)$ such that $I_\lambda(u^\star) = c(\lambda) \geq a$, i.e. a solution of (6.18) different from $u \equiv 0$ and $u \equiv 1$.

In order to show that $u_0 \not\equiv \alpha$, observe that $I_\lambda(\alpha) = -\lambda F(\alpha) > 0$, hence $I_\lambda(\alpha)$ grows linearly in λ. On the other hand, as it will be shown in Lemma 6.5, $c(\lambda)$ grows as $\sqrt{\lambda}$. In consequence, there exists $\lambda^\flat > 0$ such that for any $\lambda > \lambda^\flat$ we have $I_\lambda(u_0) = c(\lambda) < I_\lambda(\alpha)$.

To finish we have to prove that $0 < u^\star < 1$. By regularity we have that $u^\star \in C(\mathbb{S}^N)$, hence it attains its minimum at x_0. In consequence $\Delta u^\star(x_0) \geq 0$, which implies that $f(u^\star(x_0)) \leq 0$, and it follows that $u(x_0) \leq \beta_1$ or $u(x_0) \geq 0$. Suppose $u(x_0) \leq \beta_1$. Then $v(x) := u(x) - \beta_1$ is a non-negative solution of the linear equation

$$-\Delta v = \lambda b(x) v\,, \quad b(x) = \begin{cases} f'(\beta_1) & \text{if } u(x) = \beta_1, \\ \frac{f(u(x)) - f(\beta_1)}{u(x)-\beta_1} & \text{if } u(x) \neq \beta_1. \end{cases}$$

From Harnack's Inequality, for any open neighbourhood $\mathcal{U}$ there exists $C = C(\mathcal{U}) > 0$ such that

$$0 \leq \sup_{\mathcal{U}} v \leq C \inf_{\mathcal{U}} v \,,$$

and $\mathbb{S}^N$ being compact then

$$0 \leq \sup_{\mathbb{S}^N} v \leq C \inf_{\mathbb{S}^N} v \,.$$

In consequence, since $v(x_0) = 0$ it follows than $v \equiv 0$, which contradicts the fact that $u^\star$ is non-trivial. Therefore $u^\star(x) \geq u^\star(x_0) > \beta_1$ for all $x \in \mathbb{S}^N$. Repeating the previous argument several times it can be shown that $0 < u^\star < 1$. $\square$

Notice that we have used the notation $\lambda^\flat$ in both the truncated sphere $\mathcal{M}$ and the N-sphere $\mathbb{S}^N$. We did so in order to stress that in both cases $\lambda^\flat$ is the potential first bifurcation point. However, it is a slight abuse of notation: we invite the reader to bear in mind that $\lambda^\flat = \lambda^\flat(\mathcal{M})$ and $\lambda^\flat = \lambda^\flat(\mathbb{S}^N)$ are not necessarily equal.

Lemma 6.5 *There is a constant $\kappa > 0$ such that $c(\lambda) \leq \kappa\sqrt{\lambda}$.*

Proof: It suffices to show that there is a path $\gamma(t)$ from $u \equiv 0$ to $u \equiv 1$ such that $I_\lambda(\gamma(t)) \leq \kappa\sqrt{\lambda}$ for all $t \in [0, 1]$.

For $N = 2$ let $\mu \in (0, \pi)$ and for any $x = (\phi, \theta) \in \mathbb{S}^2$ define

$$v_1(x) := \begin{cases} 1 - \theta/\mu & \text{if } \theta \in [0, \mu], \\ 0 & \text{if } \theta \in (\mu, \pi], \end{cases}$$

$$v_2(x) := \begin{cases} 1 & \text{if } \theta \in [0, \pi - \mu], \\ \pi/\mu - \theta/\mu & \text{if } \theta \in (\pi - \mu, \pi]. \end{cases}$$

We readily compute

$$\int_{\mathbb{S}^2} |\nabla v_i|^2 \, dx = 2\pi \int_0^\pi |\partial_\theta v_i|^2 \sin\theta \, d\theta \leq 2\pi \frac{1}{\mu^2} \mu = \frac{2\pi}{\mu} \,, \tag{6.24}$$

$$\int_{\mathbb{S}^2} |G(v_i)| \, dx = 2\pi \int_0^\pi |G(v_i)| \sin\theta \, d\theta \leq 2\pi K \int_0^\pi v_i \, d\theta = \pi K \mu \,.$$

Now define the path

$$\gamma(t) := \begin{cases} 3t v_1(x) & \text{if } t \in [0, 1/3], \\ 3(2/3 - t) v_1(x) + 3(t - 1/3) v_2(x) & \text{if } t \in (1/3, 2/3], \\ 3(1 - t) v_2(x) + 3(t - 2/3) \cdot 1 & \text{if } t \in (2/3, 1]. \end{cases}$$

Then $\gamma(t)$ is a piecewise linear path passing by $0 \mapsto v_1 \mapsto v_2 \mapsto 1$ (see Figure 6.3)

Using (6.24) it is easy to see that

$$I_\lambda(\gamma(t)) \leq \frac{2\pi}{\mu} + \lambda \pi K \mu \,.$$

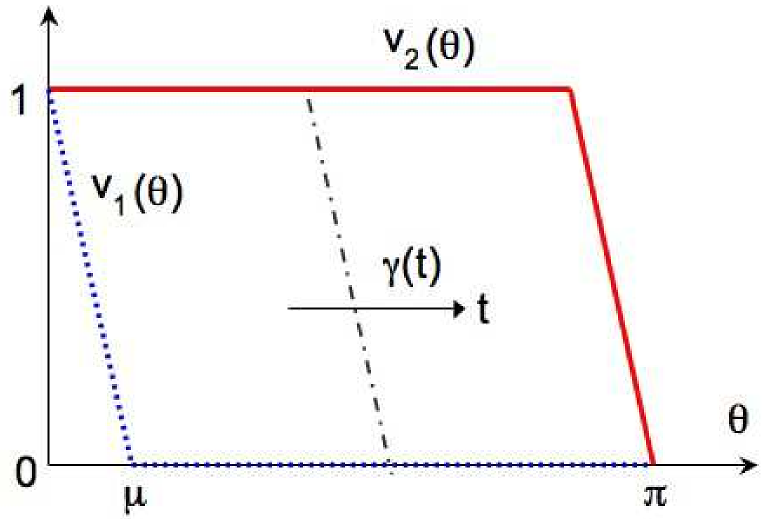

Figure 6.3: The path $\gamma(t)$. It passes through $v_1 = \gamma(1/3)$ (dotted blue line) and $v_2 = \gamma(2/3)$ (solid red line).

Therefore, if we choose $\mu = \sqrt{1/\lambda}$ and define $\kappa := \max\{2\pi, K\pi\}$ we obtain

$$I_\lambda(\gamma(t)) \le \kappa\sqrt{\lambda} \quad \forall t \in [0,1]\,.$$

For N arbitrary, we repeat the previous argument with v_1 and v_2 depending only on an arbitrary spherical angle $\varphi \in (0,\pi)$. Proceeding that way we can find a constant $C > 0$ depending only on $|\mathbb{S}^{N-1}|$ such that

$$I_\lambda(\gamma(t)) \le \frac{C}{\mu} + \lambda C K \mu\,,$$

Therefore, if we choose $\mu = \sqrt{1/\lambda}$ and define $\kappa := \max\{C, CK\}$ we obtain the result. $\square$

Observe that the proof of Lemma 6.5 implies $\lambda^\flat > 1/\pi^2$.

6.4 Reaction-diffusion equation on the N-sphere

6.4.1 Bistable nonlinearity

Let $\lambda > \lambda^\flat$ and let $u^\star(x)$ a non-trivial solution of the elliptic problem (6.18) such that $0 < u^\star(x) < 1$. We will consider the parabolic problem

$$\begin{cases} \partial_t u = \Delta u + \lambda f(u) & \text{in } (0,\infty)\times\mathbb{S}^N, \\ u(0,x) = u_0(x) \in [0,1] & \text{for all } x \in \mathbb{S}^N. \end{cases} \tag{6.25}$$

If $u_0(x)$ is not constant then (6.25) has a non-trivial solution $0 < u(t,x) < 1$ for all $t > 0$ because $u \equiv 0$ and $u \equiv 1$ are strict sub and super-solutions, respectively.

Lemma 6.6 *Let $u(t,x)$ be a solution of* (6.25). *Then*

1.
$$\lim_{t\to\infty} u(t,x) = 0$$

if and only if there exists $t_0 = t_0(\lambda) > 0$ such that $u(t_0,x) < \alpha$ for all $x \in \mathbb{S}^N$.

2.
$$\lim_{t\to\infty} u(t,x) = 1$$

if and only if there exists $t_1 = t_1(\lambda) > 0$ such that $u(t_1,x) > \alpha$ for all $x \in \mathbb{S}^N$.

Proof:

1. Suppose that $u(t,x)$ be a solution of (6.25). If

$$\lim_{t\to\infty} u(t,x) = 0$$

then for any $x \in \mathbb{S}^N$ there exists $t(\lambda,x) > 0$ such that $u(t(\lambda,x),x) < \alpha$. Therefore, from the compactness of $\mathbb{S}^N$ it follows that there exists $t_0 = t_0(\lambda) > 0$ such that $u(t_0,x) < \alpha$ for all $x \in \mathbb{S}^N$.

If $u(t_0,x) < \alpha$ for all $x \in \mathbb{S}^N$ then there exists $\delta \in (0,\alpha)$ such that $u(t_0,x) \le \delta < \alpha$for all $x \in \mathbb{S}^N$. Let $v(t)$ be the solution of the ODE

$$\begin{cases} \dot{v} = \lambda f(v) & \text{in } (0,\infty), \\ v(0) = \delta \,. \end{cases}$$

Since $v(t)$ is a solution of (6.25) with initial condition $v(0) = \delta$ and $u(t_0,x) \le v(0)$ for all $x \in \mathbb{S}^N$, the maximum principle implies that $u(t_0+t,x) \le v(t)$ for all $(t,x) \in [0,\infty) \times \mathbb{S}^N$. But since f is bistable then

$$\lim_{t\to\infty} v(t) = 0\,.$$

In consequence,

$$\lim_{t\to\infty} u(t,x) = 0\,.$$

2. The previous argument can be applied to $w = 1 - u$. □

For any $p \in (0,\pi)$ define

$$A(p) := \{x = (\varphi,\theta) \in \mathbb{S}^N \,:\, 0 \le \varphi < 2\pi,\ 0 \le \theta < p\}\,.$$

We will study the parabolic problem (6.25) with initial condition

$$u_0(p,x) = \begin{cases} 1 & \text{if } x \in A(p), \\ 0 & \text{if } x \in \mathbb{S}^N \setminus A(p). \end{cases} \tag{6.26}$$

Lemma 6.7 *For any $p \in (0,\pi)$ let $u(p,t,x)$ be a solution of* (6.25) *with initial condition* (6.26)*. Define*

$$\begin{array}{rcl} L_0 & := & \{p \in (0,\pi) \,:\, \exists t_0 = t_0(p,\lambda) \text{ s.t. } u(p,t_0,x) < \alpha \ \forall x \in \mathbb{S}^N\}\,, \\ L_\pi & := & \{p \in (0,\pi) \,:\, \exists t_1 = t_1(p,\lambda) \text{ s.t. } u(p,t_1,x) > \alpha \ \forall x \in \mathbb{S}^N\}\,. \end{array}$$

Then:

1. *If p is small (resp. $\pi - p$ small) then $p \in L_0$ (resp. $p \in L_\pi$).*
2. *L_0 and L_π are non-empty, open, connected and disjoint.*

Proof:

1. Let $v(p,t,x)$ a solution of the heat equation

$$\left\{ \begin{array}{rcl} \partial_t v - \Delta v & = & 0, \\ v_0(x) & = & u_0(p,x). \end{array} \right.$$

Then $e^{\lambda K t} v(p,t,x)$ is a super-solution of (6.25), and thus the maximum principle implies that

$$u(p,t,x) \le e^{\lambda K t} v(p,t,x).$$

If $\mathcal{K}(x,y,t)$ is the kernel of the heat equation on $\mathbb{S}^N$ then

$$\begin{array}{rcl} u(1,x) & \le & e^{\lambda K} v(1,x) \\ & = & e^{\lambda K} \displaystyle\int_{\mathbb{S}^N} \mathcal{K}(x,y,1) u_0(p,y)\, dy \\ & = & e^{\lambda K} \displaystyle\int_{A(p)} \mathcal{K}(x,y,1)\, dy\,. \end{array}$$

By the properties of heat kernels, there is a constant $C > 0$ such that $\mathcal{K}(x,y,1) \le C$ for all $x, y \in \mathcal{M}$, which implies that

$$u(p,1,x) \le e^{\lambda K} C |A(p)|.$$

If $|A(p)| < \varepsilon$ then $u(p,1,x) \le e^{\lambda K} C\varepsilon$. Choosing $\varepsilon > 0$ small enough we can ensure that

$$u(p,1,x) < \alpha \quad \forall x \in \mathbb{S}^N\,.$$

In consequence, if p is small then $p \in L_0$. Using $w := 1 - p$ and the previous argument it can be shown that if $\pi - p$ is small then $p \in L_\pi$.

2. L_0 and L_π are disjoint from Lemma 6.6. Let us prove that L_0 is open and connected; the argument for L_π will be the same with $w = 1 - u$. The connectedness is an immediate consequence of the monotonicity of the initial condition on p and the maximum principle.

We prove now the openness of L_0. Let $u(p,t,x)$ and $u(q,t,x)$ be two solutions of (6.25) and suppose that $p \in L_0$. Since any solution $u(t,x)$ of (6.25) satisfies

$$u(t,x) = e^{t\Delta}u_0(x) + \lambda \int_0^t e^{(t-s)\Delta} f(u(s))\, ds$$

and f is Lipschitz, using Gronwall's inequality it can be shown that there exists a positive, continuous function $C(\lambda,t)$ for $t>0$ such that $h(t,x) \le C(\lambda,t)h(0,x)$, where

$$h(t,x) := |u(q,t,x) - u(p,t,x)|\,.$$

Therefore, if $|p-q|$ is sufficiently small and $u(p,t_0,x) < \alpha$ then $u(q,t_0,x) < \alpha$, and in consequence $q \in L_0$. $\square$

Theorem 6.10 *There exists $\tilde{p} \in (0,\pi)$ such that $u(\tilde{p},t,x)$ does not converge to* 0 *or* 1*. If $u(\tilde{p},t,x)$ converges to a (necessarily unstable) solution then its convergence is non-monotonic.*

Proof: From Lemma 6.7 it follows that there exists at least one $\tilde{p} \in (0,\pi)$ such that for any $t>0$ the function $x \mapsto u(\tilde{p},t,x) - \alpha$ changes sign. In consequence, Lemma 6.6 implies that $u(\tilde{p},t,x)$ cannot converge to 0 or 1 as $t \to \infty$.

Let $\hat{u}(x)$ be an unstable solution of (6.18). Denote $\varphi_1 > 0$ be the first eigenfunction and μ_1 its corresponding eigenvalue of the linear operator

$$\mathcal{L}\phi = \mu\phi\,, \quad \mathcal{L}\phi := -\Delta\phi - \lambda f'(\hat{u})\phi\,.$$

From the instability of $u^\star$ it follows that $\mu_1 < 0$. We claim that there exists $\varepsilon > 0$ such that $v(x) := \hat{u}(x) - \varepsilon\phi_1$ is a strict super-solution of (6.18). Indeed,

$$\begin{aligned}
-\Delta v - \lambda f(v) &= -\Delta\hat{u} - \Delta\varepsilon\phi_1 - \lambda f(\hat{u} - \varepsilon\phi_1)\\
&= -\Delta\varepsilon\phi_1 - \Delta u^\star - \lambda\big[f(u^\star) - f'(u^\star)\varepsilon\phi_1 + o\left(|\varepsilon\phi_1|^2\right)\big]\\
&= \mu_1\varepsilon\phi_1 + \lambda o\left(|\varepsilon\phi_1|^2\right)\,,
\end{aligned}$$

which is negative for ε sufficiently small. In consequence, if $u(\tilde{p},t,x) < u^\star(x)$ and $t \mapsto u(\tilde{p},t,x)$ is increasing then for ε small enough we have

$$\lim_{t\to\infty} u(\tilde{p},t,x) \le v(x) < u^\star(x)\,.$$

If the convergence is from above then it can be shown analogously that $w(x) := u^\star(x) + \varepsilon\phi_1$ is a strict super-solution. $\square$

6.4.2 Monostable nonlinearity

We will show that the dynamics in the monostable case is much simpler compared to the bistable case because the generalised travelling wave solutions invade the whole domain regardless of the initial condition and depend only on time.

Let $f : [0,1] \to \mathbb{R}$ be a C^1 function such that $f(0) = f(1) = 0$, $f > 0$ on $(0,1)$ and $f'(0) > 0$. Denote $t \mapsto \xi(t)$ the unique solution of

$$\xi'(t) = f(\xi(t)),\ 0 < \xi(t) < 1 \quad \text{for all } t \in \mathbb{R} \quad \text{and } \xi(0) = \frac{1}{2}.$$

The function ξ is increasing and $\xi(-\infty) = 0$, $\xi(+\infty) = 1$.

Let $\mathcal{M}$ be a connected compact smooth manifold without boundary (e.g. $\mathbb{S}^N$) and denote $\Delta_{\mathcal{M}}$ be the Laplace-Beltrami operator on $\mathcal{M}$.

Theorem 6.11 *If u is a solution of*

$$\partial_t u = \Delta_M u + f(u) \quad \textit{in } \mathbb{R} \times \mathcal{M}$$

such that $0 \le u(t,x) \le 1$ for all $(t,x) \in \mathbb{R} \times \mathcal{M}$, then u depends only on t. More precisely, we have either $u \equiv 0$, $u \equiv 1$ or there exists $T \in \mathbb{R}$ such that $u(t,x) = \xi(t+T)$ for all $(t,x) \in \mathbb{R}\times\mathcal{M}$.

Proof: From the strong parabolic maximum principle, either $u = 0$ in $\mathbb{R} \times \mathcal{M}$, or $u = 1$ in $\mathbb{R} \times \mathcal{M}$, or $0 < u < 1$ in $\mathbb{R} \times \mathcal{M}$. From now on, we consider the case $0 < u < 1$ in $\mathbb{R} \times \mathcal{M}$. Our goal is to prove that there exists $T \in \mathbb{R}$ such that $u(t,\cdot) = \xi(t+T)$ for all $t \in \mathbb{R}$. Define

$$m(t) := \min_{\mathcal{M}} u(t,\cdot) \ \text{ and } \ M(t) := \max_{\mathcal{M}} u(t,\cdot), \quad t \in \mathbb{R}.$$

One has

$$0 < m(t) \le M(t) < 1 \ \text{ for all } t \in \mathbb{R}. \tag{6.27}$$

We first claim that $M(t) \to 0$ as $t \to -\infty$. Assume not. Then there exist $\varepsilon \in (0,1)$ and a sequence $(t_n)_{n\in\mathbb{N}} \to -\infty$ such that $M(t_n) \ge \varepsilon$ for all $n \in \mathbb{N}$. Since $\mathcal{M}$ is compact, connected and without boundary, the Harnack inequality yields the existence of a constant $C \in (0,1)$ such that

$$m(t+1) \ge C\, M(t) \ \text{ for all } t \in \mathbb{R}. \tag{6.28}$$

In particular, $m(t_n+1) \ge C\varepsilon$ for all $n \in \mathbb{N}$. Observe that $C\varepsilon \in (0,1)$ and let τ be the unique real number such that $\xi(\tau) = C\varepsilon$. Therefore, $m(t_n+1) \ge \xi(\tau)$ for all $n \in \mathbb{N}$. The parabolic maximum principle implies that $m(t) \ge \xi(t - t_n - 1 + \tau)$ for all $n \in \mathbb{N}$ and for all $t \ge t_n + 1$. Passing to the limit as $n \to +\infty$ for every fixed $t \in \mathbb{R}$ yields $m(t) \ge 1$, which contradicts (6.27). In consequence $M(t) \to 0^+$ as $t \to -\infty$ and $m(t) \to 0^+$ as $t \to -\infty$.

Define

$$L := \sup\left\{ \frac{f(v)}{v} \ : \ v \in (0,1] \right\} > 0\,.$$

For any fixed $s \in \mathbb{R}$ we have $u(s,\cdot) \le M(s)$ in $\mathcal{M}$ and

$$\partial_t u \le \Delta_M u + Lu\,.$$

Therefore, from the parabolic maximum principle it follows that $M(t) \le M(s)\, e^{L(t-s)}$ for all $t \ge s$, and in particular $M(t) \le M(t-1)\, e^{L}$ for all $t \in \mathbb{R}$. From (6.28) one infers that

$$M(t) \le C^{-1} e^{L}\, m(t) \quad \text{for all } t \in \mathbb{R},$$

which implies that the function $t \mapsto M(t)/m(t)$ is bounded from above by $C^{-1}e^{L}$ and from below by 1 in $\mathbb{R}$. Define $t \mapsto \delta_m(t)$ and $t \mapsto \delta_M(t)$ as

$$m(t) = \xi(t + \delta_m(t)) \text{ and } M(t) = \xi(t + \delta_M(t)) \text{ for all } t \in \mathbb{R}.$$

Since $\xi : \mathbb{R} \to (0,1)$ is increasing and onto, δ_m and δ_M are well defined. Furthermore, $\delta_m(t) \le \delta_M(t)$ for all $t \in \mathbb{R}$, and

$$\lim_{t \to -\infty} (t + \delta_m(t)) = \lim_{t \to -\infty} (t + \delta_M(t)) = -\infty$$

because $m(t) \to 0^+$ and $M(t) \to 0^+$ when $t \to -\infty$. Since there exists a constant $K > 0$ such that

$$\xi(t) \sim K\, e^{f'(0)t} \quad \text{as } t \to -\infty, \tag{6.29}$$

there holds

$$\frac{M(t)}{m(t)} \sim e^{f'(0)(\delta_M(t) - \delta_m(t))} \quad \text{as } t \to -\infty.$$

The boundedness of $M(t)/m(t)$ and the positivity of $f'(0)$ imply that

$$\limsup_{t \to -\infty} \big(\delta_M(t) - \delta_m(t)\big) < +\infty. \tag{6.30}$$

We now claim that

$$\liminf_{t \to -\infty} \delta_M(t) > -\infty. \tag{6.31}$$

Assume not. Then there exists a sequence $(t_n)_{n \in \mathbb{N}} \to -\infty$ such that $\delta_M(t_n) \to -\infty$ as $n \to +\infty$. Let τ be any fixed real number. Let $n_0 \in \mathbb{N}$ be such that $\delta_M(t_n) \le \tau$ for all $n \ge n_0$. For all $n \ge n_0$, there holds

$$u(t_n, \cdot) \le M(t_n) = \xi(t_n + \delta_M(t_n)) \le \xi(t_n + \tau),$$

whence from the maximum principle it follows that $u(t,\cdot) \le \xi(t+\tau)$ and $M(t) \le \xi(t+\tau)$ for all $t \ge t_n$. Taking the limit $n \to +\infty$ implies that $M(t) \le \xi(t+\tau)$ for all $t \in \mathbb{R}$. Since τ is arbitrary in $\mathbb{R}$, one gets by taking the limit $\tau \to -\infty$ that $M(t) \le 0$ for all $t \in \mathbb{R}$, which is a contradiction. Thus (6.31). Similarly, one can prove that

$$\limsup_{t \to -\infty} \delta_m(t) < +\infty. \tag{6.32}$$

Together with (6.30)-(6.32) and $\delta_m \le \delta_M$ it follows that

$$\limsup_{t \to -\infty} \big(|\delta_m(t)| + |\delta_M(t)|\big) < +\infty. \tag{6.33}$$

Define

$$T := \limsup_{t \to -\infty} \delta_M(t).$$

Our goal is to prove that $u(t,x) = \xi(t+T)$ for all $(t,x) \in \mathbb{R} \times \mathcal{M}$. Let $(t_n)_{n\in\mathbb{N}}$ be a sequence such that $t_n \to -\infty$ and $\delta_M(t_n) \to T$ as $n \to +\infty$. For all $n \in \mathbb{N}$ and $(t,x) \in \mathbb{R} \times \mathcal{M}$, set

$$u_n(t,x) = \frac{u(t+t_n,x)}{\xi(t+t_n+T)}.$$

Then there holds

$$\frac{\xi(t+t_n+\delta_m(t+t_n))}{\xi(t+t_n+T)} \le \frac{m(t+t_n)}{\xi(t+t_n+T)} \le u_n(t,x) \le \frac{M(t+t_n)}{\xi(t+t_n+T)} = \frac{\xi(t+t_n+\delta_M(t+t_n))}{\xi(t+t_n+T)}$$

for all $n \in \mathbb{N}$ and $(t,x) \in \mathbb{R} \times \mathcal{M}$. From (6.29) and (6.33) it follows that the functions u_n are locally bounded from below and above by two positive constants, that is, for all $R > 0$, there is a constant $C_R > 1$ such that $C_R^{-1} \le u_n(t,x) \le C_R$ for all $n \in \mathbb{N}$ and $(t,x) \in [-R,R] \times \mathcal{M}$. On the other hand, the functions u_n are solutions of

$$\partial_t u_n = \Delta_M u_n + \Big(\frac{f\big(u_n(t,x)\xi(t+t_n+T)\big)}{u_n(t,x)\xi(t+t_n+T)} - \frac{f\big(\xi(t+t_n+T)\big)}{\xi(t+t_n+T)}\Big)u_n(t,x) \quad \text{in } \mathbb{R} \times \mathcal{M},$$

with $\xi(t+t_n+T) \to 0$ as $n \to +\infty$ locally uniformly in $t \in \mathbb{R}$. From standard parabolic estimates, the functions u_n converge then locally uniformly in $\mathbb{R} \times \mathcal{M}$, up to extraction of a subsequence, to a classical positive solution u_∞ of

$$\partial_t u_\infty = \Delta_M u_\infty \quad \text{in } \mathbb{R} \times \mathcal{M}.$$

Furthermore, for all $t \in \mathbb{R}$, there holds

$$\max_M u_n(t,\cdot) \le \frac{M(t+t_n)}{\xi(t+t_n+T)} = \frac{\xi(t+t_n+\delta_M(t+t_n))}{\xi(t+t_n+T)}.$$

Hence (6.29) and the definition of T imply that $\limsup_{n\to+\infty} \max_M u_n(t,\cdot) \le 1$ for all $t \in \mathbb{R}$. Thus $\max_M u(t,\cdot) \le 1$ for all $t \in \mathbb{R}$. On the other hand, there exists a sequence $(x_n)_{n\in\mathbb{N}}$ of points of $\mathcal{M}$ such that

$$u_n(0,x_n) = \frac{M(t_n)}{\xi(t_n+T)} = \frac{\xi(t_n+\delta_M(t_n))}{\xi(t_n+T)} \to 1 \quad \text{as } n \to +\infty.$$

Therefore, there exists a point $x_\infty \in \mathcal{M}$ such that $u_\infty(0,x_\infty) = 1$. The strong maximum principle yields $u_\infty = 1$ in $(-\infty,0] \times \mathcal{M}$ and $u_\infty = 1$ in $\mathbb{R} \times \mathcal{M}$. It follows in particular that $\min_M u_n(0,\cdot) \to 1$ as $n \to +\infty$. But

$$\min_M u_n(0,\cdot) = \frac{m(t_n)}{\xi(t_n+T)} = \frac{\xi(t_n+\delta_m(t_n))}{\xi(t_n+T)} \sim e^{f'(0)(\delta_m(t_n)-T)} \quad \text{as } n \to +\infty.$$

Since $f'(0) > 0$, one infers that $\delta_m(t_n) \to T$ as $n \to +\infty$.

In order to conclude, let ε be any positive real number, and let $n_0 \in \mathbb{N}$ be such that

$$T - \varepsilon \le \delta_m(t_n) \le \delta_M(t_n) \le T + \varepsilon \quad \text{for all } n \ge n_0.$$

Since ξ is increasing, there holds

$$\xi(t_n + T - \varepsilon) \leq \xi(t_n + \delta_m(t_n)) \leq u(t_n, \cdot) \leq \xi(t_n + \delta_M(t_n)) \leq \xi(t_n + T + \varepsilon) \quad \text{for all } n \geq n_0,$$

whence from the maximum principle we have $\xi(t + T - \varepsilon) \leq u(t, \cdot) \leq \xi(t + T + \varepsilon)$ for all $n \geq n_0$ and $t \geq t_n$. By letting $n \to +\infty$ and then $\varepsilon \to 0^+$, one concludes that $u(t, \cdot) = \xi(t + T)$ for all $t \in \mathbb{R}$. $\square$

6.5 Discussion

We analysed a classical elliptic equation with bistable nonlinearity and a 1D parameter λ on two domains, a truncated sphere and the whole sphere. In both cases we found that when $\lambda > 0$ is small the solutions have to be constant whilst when $\lambda > 0$ is sufficiently big there are non-trivial solutions. In order to find the non-trivial solutions we used variational and topological arguments, and in the case of the truncated sphere we showed that there are at least two distinct non-trivial solutions.

On the truncated sphere we proved the existence of a generalised travelling wave, i.e. a non-trivial solution $u(t, x)$ of the corresponding parabolic equation that is increasing in time, and we showed that $u(t, x)$ is blocked by the non-trivial elliptic solution $u^\star(x)$.

On the whole sphere the existence of a generalised wave depends on the initial condition $u_0(x)$ given in (6.26): (a) if $p \sim 0$ then the solution converges to 0, (b) if $p \sim \pi$ then it converges to 1, and (c) there exists $\tilde{p} \in (0, \pi)$ such that the solution does not converge to 0 or 1. In particular, when the solution does not converge to 0 or 1 we have that *(i)* this solution cannot invade the whole sphere, *(ii)* it does not vanish, and *(iii)* if it converges then its convergence is non-monotonic.

Our results on both domains (the truncated and the whole sphere) evidence that having solution that does not invade the whole domain depends on the geometry of the sphere, the strength of the nonlinearity (measured in terms of λ) and the initial conditions. On the contrary, when the nonlinearity f is monostable we always have invasion, even for more general domains. This illustrates the importance of the bistable nonlinearity and its interplay with the geometry of the domain in the diversity of patterns that we can have.

We have proved that on the whole sphere $\mathbb{S}^N$ there exists $\lambda_*(= \underline{\lambda})$ such that for any $\lambda \in (0, \lambda_*)$ the only solutions of (6.18) are constant, and that there exists $\lambda^*(= \lambda^\flat)$ such that for any $\lambda \in (\lambda^*, \infty)$ there is a non-trivial solutions of (6.18). We conjecture that $\lambda_* = \lambda^*$ and that this is true for any compact, connected, smooth manifold without boundary, i.e.

Conjecture 6.12 *Let $\mathcal{M}$ be a compact, connected, smooth manifold without boundary. Then $\lambda_*(\mathcal{M}) = \lambda^*(\mathcal{M})$, i.e.*

- *There is bifurcation on the elliptic nonlinear eigenvalue problem*

$$-\Delta_{\mathcal{M}} u = \lambda f(u)$$

starting at $(\lambda, u) = (\lambda_*, 0)$*,*

- *for any* $\lambda < \lambda_*$ *the only solutions are trivial (i.e. constant), and*
- *for any* $\lambda > \lambda_*$ *we have non-trivial solutions.*

In the following chapter we prove Conjecture 6.12 when $\mathcal{M} = \mathbb{S}^1$ and for a bifurcation starting at the trivial solution $u \equiv \alpha$.

It is worth to mention that G. Flores and R. Plaza [21] found the same result, namely that the travelling wave does not invade the whole sphere, using the mechanochemical model of Lane *et al* [40]. This model consists on two equations, a nonlinear parabolic equation for the calcium concentration, coupled with a nonlinear hyperbolic equation for the elastic deformation of the egg surface. Since in both the reaction-diffusion and the mechanochemical models the waves are blocked, this suggests that the blockage of the wave could be considered as the effect of the geometry of the sphere and the bistable nonlinearity. It would be interesting to study other curved domains in the future in order to assess the exact role of geometry in pattern formation.

Part III

Elliptic equations and nonlinear eigenvalues on the sphere

Chapter 7

Bifurcation and multiple periodic solutions on the sphere

Work in collaboration with Henri Berestycki and François Hamel. To be submitted.

In this chapter we prove that the nonlinear eigenvalue problem

$$-\Delta_{\mathbb{S}^N} u = \lambda f(u) \quad \text{on } \mathbb{S}^N$$

admits multiple non-trivial solutions, whose number is increasing in the parameter $\lambda > 0$, and each time we cross an eigenvalue μ_k there appears a new non-trivial solution. If $\lambda \in (\mu_k, \mu_{k+1})$, we prove the existence of $2k$ non-trivial solutions in $\mathbb{S}^1$ and k non-trivial solutions on $\mathbb{S}^N$, the latter depending only on the vertical angle, i.e. invariant under horizontal rotations.

The bifurcation analysis proves Conjecture 6.12 of Chapter 6 for $\mathcal{M} = \mathbb{S}^1$. However, Conjecture 6.12 is an open problem for manifolds other than $\mathbb{S}^1$, in particular for $\mathbb{S}^N$, $N \geq 2$.

7.1 Bifurcation on $\mathbb{S}^1$

We will study the nonlinear ODE

$$\begin{cases} -u'' &= \lambda f(u), \\ u(0) &= \xi, \\ u'(0) &= 0, \end{cases} \tag{7.1}$$

where $\lambda > 0$ is a parameter, $f(s)$ is a Lipschitz, globally bounded bistable nonlinearity, and

$$F(z) := \int_0^z f(s)\,.$$

We extend f to $\mathbb{R} \setminus [0,1]$ as zero (see Figure 7.1).

7.1.1 Properties of solutions

We begin proving global existence and uniqueness of solutions of (7.1).

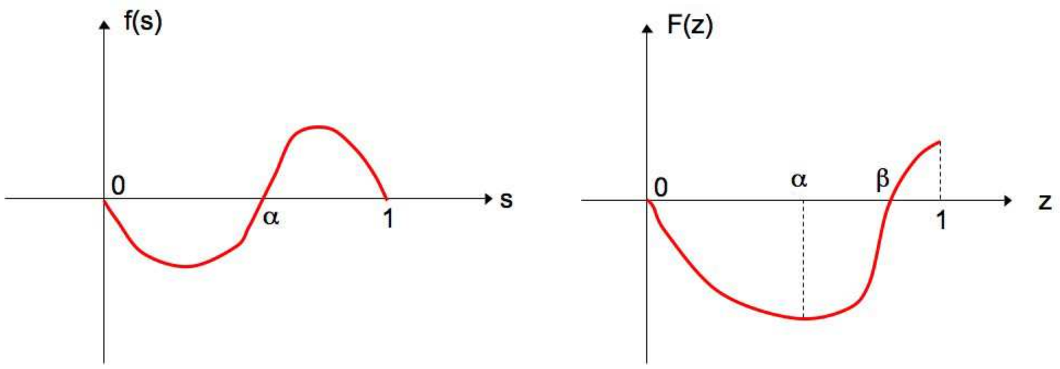

Figure 7.1: Bistable nonlinearity $f(s)$ and its integral $F(z)$. We define $f \equiv 0$ on $\mathbb{R} \setminus [0,1]$.

Theorem 7.1 *For any* $\xi \in [0,1]$ *there exists a unique global solution* $u(\theta)$ *of* (7.1)*. In particular, if there exists* $\theta^* \geq 0$ *such that* $u(\theta^*) = \alpha$ *and* $u'(\theta^*) = 0$ *then* $u \equiv \alpha$*.*

Proof: If we multiply (7.1) by u' and integrate over $[0,\theta]$ we obtain

$$\frac{(u'(\theta))^2}{2} = \lambda\big[F(\xi) - F(u(\theta))\big]\,. \tag{7.2}$$

Therefore, using that f and F are continuous and globally bounded it follows that u' and u'' are globally bounded. In consequence, the existence and uniqueness of ODEs implies that we have a unique, globally-defined solution $u(\theta)$.

Now suppose that there exists $\theta^* \geq 0$ such that $u(\theta^*) = \alpha$ and $u'(\theta^*) = 0$. Notice that $F(\alpha)$ is the unique global minimum of $F(z)$. Therefore, multiplying (7.1) by u' and integrating from θ^* to θ we obtain

$$\frac{(u'(\theta))^2}{2} = \lambda\big[F(\alpha) - F(u(\theta))\big] \leq 0 \quad \forall \theta \geq 0\,.$$

In consequence $u' \equiv 0$, which implies that $u \equiv \alpha$. $\square$

We will study in detail the properties and dynamics of the solutions of (7.1).

1. If $\xi \in (\alpha, 1)$ then $u''(0) < 0$.

   Proof: From (7.1) we have $u''(0) = -\lambda f(\xi) < 0$.

2. Let $\xi \in (\alpha, 1)$. There exists $\theta_1 > 0$ such that $u(\theta) > \alpha$ for all $\theta \in [0, \theta_1)$, $u(\theta_1) = \alpha$ and $u'(\theta_1) > 0$. Moreover, u is strictly decreasing on $[0, \theta_1]$ (see Figure 7.2).

   Proof: Since $u'(0) = 0$ and $u''(0) < 0$ there exists $\theta_0 > 0$ such that $u'(\theta_0) < 0$. Denote by $l(\theta)$ the tangent of u at θ_0. Since l is not parallel to the horizontal line $u = \alpha$ then

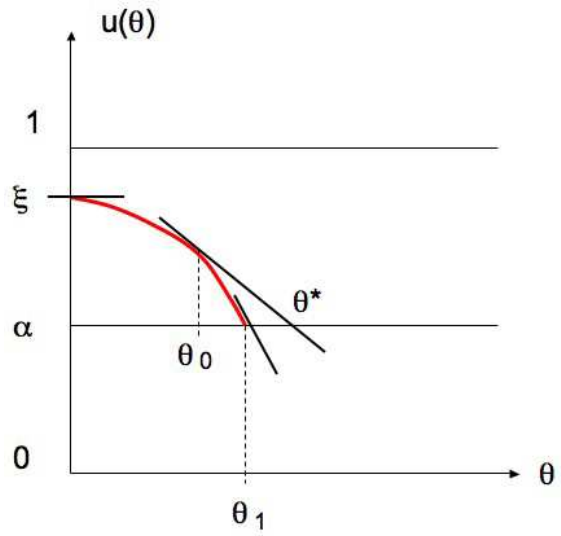

Figure 7.2: The solution $u(\theta)$ intersects the line $u = \alpha$ the first time in θ_1 with $u'(\theta_1) < 0$.

they intersect at $\theta^* < \infty$. But since u is concave, i.e. $u'' < 0$ if $u \in (\alpha, 1)$, it follows that $u(\theta) \leq l(\theta)$. In consequence, there exists $\theta_1 < \theta^*$ such that $u(\theta_1) = 0$. On the other hand, since $u''(\theta) < 0$ for all $\theta \in [0, \theta_1)$ it follows that u is strictly decreasing and $u'(\theta_1) < u'(\theta_0) < 0$.

3. For any $\xi \in (\alpha, \beta)$ define $\bar{\xi}$ as the unique point on $(0, \alpha)$ such that $F(\bar{\xi}) = F(\xi)$ (see Figure 7.3). Then there exists $\theta_2 > \theta_1$ such that $u(\theta_2) = \bar{\xi}$, $u'(\theta_2) = 0$ and $u''(\theta_2) < 0$. In particular, $u(\theta_2) = \bar{\xi}$ is not only a strict local minimum of u but also its global minimum (see Figure 7.4).

   <u>*Proof*</u>: Suppose that $u(\theta) > \bar{\xi}$ for all $\theta \in [0, \infty)$. Since $u'(\theta_1) < 0$, from (7.2) and the continuity of u' it follows that $u'(\theta) < 0$ for all $\theta > \theta_1$. This implies that u is strictly decreasing and bounded from below, hence there exists $L \in [\bar{\xi}, \alpha) \subset (0, \alpha)$ such that

$$\lim_{\theta \to \infty} u(\theta) = L\,.$$

   Applying Rolle's Theorem twice we obtain that

$$\lim_{\theta \to \infty} u'(\theta) = \lim_{\theta \to \infty} u''(\theta) = 0\,.$$

   Therefore, using (7.1) and the continuity of f yields $f(L) = 0$, which contradicts the fact that $L \in (0, \alpha)$. In consequence, there exists $\theta_2 > \theta_1$ such that $u(\theta_2) = \bar{\xi}$, and from (7.2) we also have $u'(\theta_2) = 0$. Moreover, $u''(\theta_2) = -\lambda f(\bar{\xi}) > 0$, which implies that u has a strict local minimum at θ_2, which coincides with the global minimum of u by using (7.2).

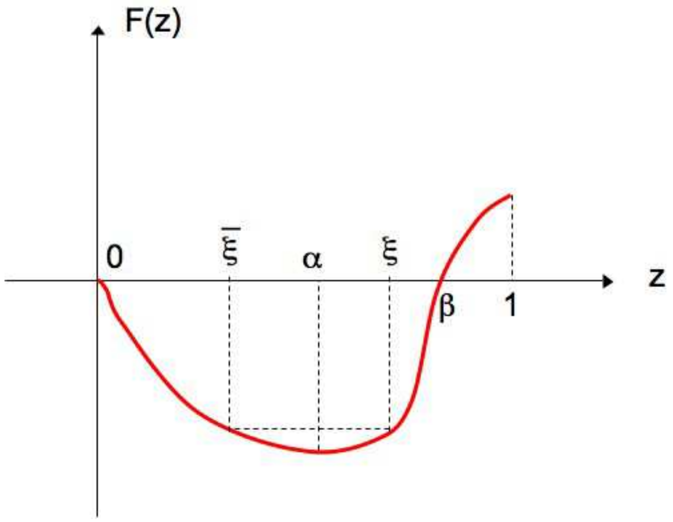

Figure 7.3: Definition of $\bar{\xi}$.

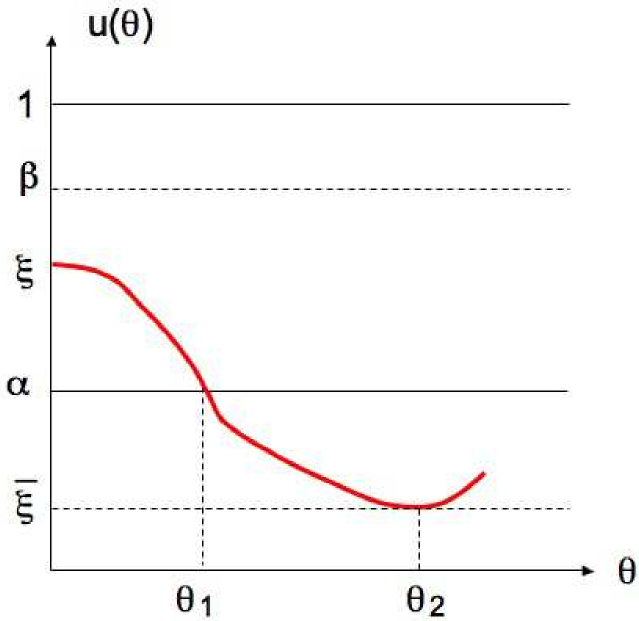

Figure 7.4: There exists $\theta_2 > \theta_1$ such that $u(\theta_2) = \bar{\xi}$ is not only a strict local minimum of u but also its global minimum.

4. If $\xi \in (\alpha, \beta)$ there exists $\theta_3 > \theta_2$ such that $u(\theta_3) = 0$, $u'(\theta_3) > 0$ and $u''(\theta_3) = 0$ (see Figure 7.5).

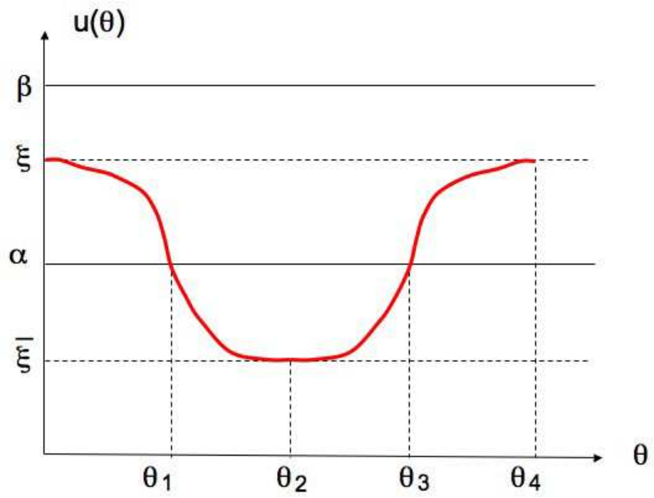

Figure 7.5: The solution u and its four important points θ_i, $i = 1, 2, 3, 4$.

<u>*Proof*</u>: Same proof as for θ_1.

5. If $\xi \in (\alpha, \beta)$ there exists $\theta_4 > \theta_3$ such that $u(\theta_4) = \xi$, $u'(\theta_4) = 0$ and $u''(\theta_4) > 0$. In particular, $u(\theta_4) = \xi$ is a strict local maximum and the global maximum of u (see Figure 7.5).

<u>*Proof*</u>: Same proof as for θ_2.

6. If $\xi \in (\alpha, \beta)$ then $u(\theta)$ is T-periodic, where $T := \theta_4$.

<u>*Proof*</u>: Define $v(\theta) := u(\theta + \theta_4)$. Then v is solution of (7.1) with $v(0) = u(\theta_4) = \xi$ and and $v'(0) = u'(\theta_4) = 0$. Therefore, from the uniqueness of the solutions of (7.1) (Theorem 7.1) it follows that $v(\theta) = u(\theta)$ for all $\theta \geq 0$, i.e. $u(\theta) = u(\theta + \theta_4)$ for all $\theta \geq 0$. But the previous analysis shows that θ_4 is the first $\theta > 0$ for which $u(\theta) = \xi$. In consequence, u is periodic of period $T := \theta_4$.

7. The periodic solution u is symmetric with respect to the half period $T/2$, i.e. $u(\xi, \theta) = u(\xi, T - \theta)$ for all $\theta \in [0, T/2]$. In particular, $u(\xi, T/2) = u(\bar{\xi}, 0) = \bar{\xi}$.

<u>*Proof*</u>: Both $u(\xi,\theta)$ and $u(\xi,T-\theta)$ are solutions of (7.1) with the same initial conditions $u(\xi)=0$ and $u'(0)=0$. Therefore, the local uniqueness of the solutions yields the result.

8. Let $u(\xi,\theta)$ the T-periodic solution of (7.1) with $u(\xi,0)=\xi$. If $\bar{\xi}\in(0,\alpha)$ then $\xi\in(0,\beta)$ and $u(\bar{\xi},\theta)=u(\xi,\theta+T/2)$.

   <u>*Proof*</u>: Both $u(\bar{\xi},\theta)$ and $u(\xi,\theta+T/2)$ are solutions of (7.1) with the same initial conditions $u(0)=\bar{\xi}$ and $u'(0)=0$.

9. If $\xi\in[\beta,1)$ then $u'(\theta)<0$ for all $\theta>0$, i.e. u is strictly decreasing. In particular, u cannot be periodic.

   <u>*Proof*</u>: Recall that for any $\xi\in[\beta,1)\subset(\alpha,1)$ there exists $\theta_1>0$ such that $u(\theta_1)=\alpha$ and $u'(\theta_1)<0$ (see Figure 7.2). If there exists $\theta^*>\theta_1$ such that $u'(\theta^*)=0$ and $u(\theta^*)<\alpha$ then $u(\theta^*)\le\alpha$ and $F(\xi)\ge 0>F(u(\theta^*))$, which contradicts (7.2).

10. Let $\xi\in(\alpha,\beta)$ and suppose $u(\xi,t)$ is a T-periodic solution of (7.1). Then T satisfies the inequality

$$T\ge\frac{h(\xi)}{\sqrt{\lambda}}\,,\qquad h(\xi):=\frac{2|\xi-\bar{\xi}|}{\sqrt{2[F(\xi)-F(\alpha)]}}\,. \tag{7.3}$$

   In particular,

$$\lim_{\xi\to\alpha}h(\xi)=\frac{4}{\sqrt{\lambda f'(\alpha)}}\,. \tag{7.4}$$

   <u>*Proof*</u>: On the one hand, from (7.2) we have

$$|u'|_\infty=\sqrt{2\lambda[F(\xi)-F(\alpha)]}\,.$$

   On the other hand, from the mean-value theorem there exists $\theta^*\in(0,T/2)$ such that

$$|u'(\theta^*)|=\frac{2|\xi-\bar{\xi}|}{T}\,.$$

   Therefore, since $\xi>\alpha>\bar{\xi}$ and $F(\xi)=F(\bar{\xi})$ we have

$$\begin{aligned}T &\ge \frac{2|\xi-\bar{\xi}|}{|u'|_\infty}\\ &= \frac{2|\xi-\bar{\xi}|}{\sqrt{2\lambda[F(\xi)-F(\alpha)]}}\\ &= \frac{2|\xi-\alpha|}{\sqrt{2\lambda\left[F(\xi)-F(\alpha)\right]}}+\frac{2|\bar{\xi}-\alpha|}{\sqrt{2\lambda\left[F(\bar{\xi})-F(\alpha)\right]}}\,.\end{aligned}$$

If $|\xi - \alpha|$ is small then $|\bar{\xi} - \alpha|$ is small as well and

$$F(\zeta) - F(\alpha) \sim \frac{f'(\alpha)}{2}(\zeta - \alpha)^2 , \quad \zeta \in \{\xi, \bar{\xi}\} ,$$

which implies that

$$\frac{2|\xi - \bar{\xi}|}{\sqrt{2\lambda[F(\xi) - F(\alpha)]}} \sim \frac{4}{\sqrt{\lambda f'(\alpha)}} .$$

Theorem 7.2 *There exist periodic solutions of* (7.1) *if and only if* $\xi \in (0, \alpha) \cup (\alpha, \beta)$. *Moreover, the periodic solutions come in pairs:* $u(\xi, \theta)$ *is a* T*-periodic solution if and only if* $u(\bar{\xi}, \theta) = u(\xi, T/2 + \theta)$ *is a* T*-periodic solution and*

$$\|u(\xi, \cdot)\|_{C^0(0,T)} = \|u(\bar{\xi}, \cdot)\|_{C^0(0,T)} = \xi .$$

Finally, there exists $\lambda_0 > 0$ *such that* (7.1) *admits* 2π*-periodic solutions if and only if* $\lambda > \lambda_0$.

<u>*Proof*</u>: We have already proven that there exist periodic solutions of (7.1) if and only if $\xi \in (0, \alpha) \cup (\alpha, \beta)$. Moreover, the previous analysis also showed that $\|u(\xi, \cdot)\|_{C^0(0,T)} = \xi$ and $u(\bar{\xi}, \theta) = u(\xi, T + \theta)$. In consequence, the periodic solutions come in pairs and

$$\|u(\xi, \cdot)\|_{C^0(0,T)} = \|u(\bar{\xi}, \cdot)\|_{C^0(0,T)} = \xi .$$

Let us fix $\lambda = 1$ and consider the problem

$$\left\{ \begin{array}{rcl} -u'' & = & f(u), \\ u(0) & = & \xi, \\ u'(0) & = & 0. \end{array} \right. \tag{7.5}$$

Define

$$\mathcal{T} := \{T > 0 \, : \, \text{there exists } \xi \in (\alpha, \beta) \text{ such that } u(\xi, \theta) \text{ is a } T\text{-periodic solution of (7.1)}\} .$$

From (7.3)-(7.4) it can be shown that

$$T_0 := \inf \mathcal{T} \geq \inf\{\, h(\xi) \, : \, \xi \in (\alpha, \beta)\,\} > 0 .$$

Now, let $\xi \sim \alpha$ and define (as before) θ_1 and θ_2 as the first positive times such that $u(\xi, \theta_1) = \alpha$ and $u(\xi, \theta_2) = \bar{\xi}$, respectively. On the one hand, since $f(\alpha) = 0$ we have

$$\begin{array}{rcl} \dfrac{(u'(\xi, \theta_1))^2}{2} & = & \dfrac{(u'(\xi, \theta_1))^2}{2} + \dfrac{(u'(\xi, \theta_2))^2}{2} \\ & = & F(\bar{\xi}) - F(\alpha) \\ & = & \dfrac{f'(\alpha)}{2}(\bar{\xi} - \alpha)^2 , \end{array}$$

which implies that

$$\lim_{\bar{\xi}\to\alpha}\left|\frac{u'(\xi,\theta_1)}{\bar{\xi}-\alpha}\right| = \sqrt{f'(\alpha)} > 0\,.$$

On the other hand, since f is Lipschitz continuous on $\mathbb{R}$ then it is Hölder continuous on the bounded interval $[\bar{\xi},\alpha]$ of any exponent $\gamma \in (0,1)$. In consequence,

$$\begin{aligned}
|u'(\xi,\theta_1)| &= |u'(\xi,\theta_1) - u'(\xi,\theta_2)| \\
&= |u''(\theta^*)|\cdot|\theta_1-\theta_2| \qquad \theta^*\in(\theta_1,\theta_2) \\
&= |f(u(\xi,\theta^*))|\cdot|\theta_1-\theta_2| \qquad u(\xi,\theta^*)\in(\bar{\xi},\alpha) \\
&\le K_\gamma|u(\xi,\theta^*)-\alpha|^\gamma\cdot|\theta_1-\theta_2| \\
&\le K_\gamma|\bar{\xi}-\alpha|^\gamma\cdot|\theta_1-\theta_2|\,,
\end{aligned}$$

where $K_\gamma > 0$ is the Hölder constant. Therefore,

$$\liminf_{\bar{\xi}\to\alpha}|\theta_1-\theta_2|\cdot|\bar{\xi}-\alpha|^{1-\gamma} \ge \frac{1}{\sqrt{f'(\alpha)}} > 0\,,$$

which implies that

$$\liminf_{\bar{\xi}\to\alpha}|\theta_1-\theta_2| = \infty\,.$$

In conclusion $\sup\mathcal{T} = \infty$. Moreover, from the continuous dependence of $u(\xi,\theta)$ on ξ it can be shown that $\mathcal{T}$ is connected, i.e. $\mathcal{T} = (T_0,\infty)$ or $\mathcal{T} = [T_0,\infty)$. In consequence, there is a T-periodic solution of (7.5) if and only if $T > T_0$. Therefore, for any $\lambda > 0$ if follows that there exists a T-periodic solution of (7.1) if and only if

$$T > \frac{T_0}{\sqrt{\lambda}}\,.$$

In particular, there exist 2π-periodic solutions of (7.1) if and only if

$$\lambda > \lambda_0 := \left(\frac{T_0}{2\pi}\right)^2. \quad \square$$

Notice that the proof of Theorem (7.2) also implies that, for any integer $k \ge 1$, we have $2\pi/k$-periodic solutions of (7.1) if and only if

$$\lambda > \lambda_0(k)\,, \qquad \lambda_0(k) := \left(\frac{kT_0}{2\pi}\right)^2. \tag{7.6}$$

Moreover, Theorem (7.2) states that if there is a solution $u(\xi,\theta)$ of (7.1) in $\mathbb{R}$ and $\xi \in (0,\alpha)\cup(\alpha,\beta)$ then necessarily $u(\xi,\theta)$ is periodic.

7.1.2 Proof of Conjecture 6.12 for $\mathbb{S}^1$

We return to Conjecture 6.12 and prove it for $\mathbb{S}^1$ and for a bifurcation starting at the trivial solution $u \equiv \alpha$.

Theorem 7.3 *Let $\mathcal{M}$ be a compact, connected, smooth manifold without boundary and consider the problem*

$$-\Delta_{\mathcal{M}} u = \lambda f(u) \quad \text{on } \mathcal{M}. \tag{7.7}$$

Define

$$\begin{aligned} \lambda_*(\mathcal{M}) &:= \sup\{\lambda > 0 : \text{the only solutions of (7.7) are constant}\}, \\ \lambda^*(\mathcal{M}) &:= \inf\{\lambda > 0 : \text{there are non-trivial solutions of (7.7)}\}. \end{aligned}$$

If $\mathcal{M} = \mathbb{S}^1$ then $\lambda_*(\mathbb{S}^1) = \lambda^*(\mathbb{S}^1)$ and there is a bifurcation branch starting at (λ_*, α).

Proof: Let $\mathcal{M} = \mathbb{S}^1$. From Theorem 7.2, there exists $\lambda_0 > 0$ such that (7.7) admits non-trivial, 2π-periodic solutions if and only if $\lambda > \lambda_0$. In consequence, $\lambda_*(\mathbb{S}^1) = \lambda^*(\mathbb{S}^1) = \lambda_0$. □

7.1.3 Bifurcation analysis

Lemma 7.1 *On the space of 2π-periodic solutions, the eigenvalues and eigenvectors of* (7.1) *around the unstable state α of the bilinear nonlinearity f are $\{(\mu_k, \phi_k)\}_{k\geq 1}$, where*

$$\mu_k := \frac{k^2}{f'(\alpha)}, \qquad \phi_k := (\xi - \alpha)\cos(k\theta).$$

Proof: Let $u(\xi, \theta)$ be a 2π-periodic solution of (7.1) and define $v := u - \alpha$. It follows that the linearisation of (7.1) around $u \equiv \alpha$ is

$$\begin{cases} -v'' &= \lambda f'(\alpha) v, \\ v(0) &= \xi - \alpha, \\ v'(0) &= 0. \end{cases} \tag{7.8}$$

The general solution of (7.8) is

$$v(\theta) = a\cos(\omega\theta) + b\sin(\omega\theta), \qquad \omega = \sqrt{\lambda f'(\alpha)}.$$

Using the initial conditions we obtain that $a = \xi - \alpha$ and $b = 0$. Moreover, if v is 2π-periodic then $\omega = k$, where k is a positive integer. □

Let us show there exists a bifurcation branch and exhibit some of its properties.

1. **Global Rabinowitz Alternative**. Let $(\mathbf{B}, \|\cdot\|)$ be a Banach space. Let $F : \mathbb{R} \times \mathbf{B} \to \mathbf{B}$ be a map of the form
$$F(\lambda, x) = x - \lambda K x - g(\lambda, x),$$
with K compact and $g(\lambda, x) = o(\|x\|)$. Assume λ_0 is a characteristic value of K of odd algebraic multiplicity. Then there is a continuum $\mathcal{C}$ of non-trivial zeroes of F, starting at $(\lambda_0, 0)$, which

(a) either goes to infinity in $\mathbb{R} \times \mathbf{B}$

(b) or returns to a different bifurcation point $(\lambda_1, 0)$.

Proof: This is a very well-known result in topological bifurcation. For a proof see e.g. the original paper of Rabinowitz [55].

2. Each time λ crosses μ_k we have a bifurcation branch $\mathcal{C}_k$ starting at (μ_k, α).

Proof: Notice that $\mathrm{E}_k := \ker(-\phi'' - \mu_k \phi)$ has dimension 1 and $\lambda \mapsto \lambda - \mu_k$ changes sign when λ crosses μ_k. Moreover, the operator $K := (\Delta_{\mathbb{S}^1})^{-1}$ is compact because it is the Green function of the Laplace-Beltrami operator. Therefore, we can apply the Global Rabinowitz Alternative, which implies that there is a bifurcation branch $\mathcal{C}_k$ that starts at (μ_k, α).

3. Define $\lambda_0(k)$ as in (7.6). Then $\mathcal{C}_k$ in unbounded, confined in the box

$$B_k := \left\{(\lambda, u) \in \mathbb{R} \times C^0(\mathbb{S}^1) \, : \, \lambda > \lambda_0(k)\,, \quad \alpha < \|u\|_{C^0(\mathbb{S}^1)} < \beta \right\}\,.$$

and does not come back to another bifurcation point. Moreover, if $u \in \mathcal{C}_k$ then $u - \alpha$ has exactly $k + 1$ zeroes on $(0, 2\pi)$ (see Figure 7.6).

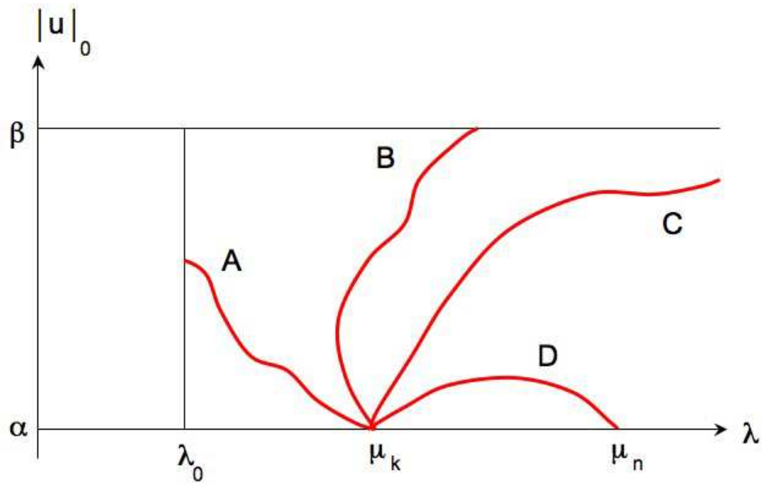

Figure 7.6: Global Rabinowitz Alternative. Scenarios A, B and D are discarded, hence C holds.

Proof: We will consider all possibilities for $\mathcal{C}_k$ (see Figure 7.6). (i) According to (7.6), we have $2\pi/k$-periodic solutions if and only if $\lambda > \lambda_0(k)$, which implies that A cannot hold. (ii) If there exists $w \in \mathcal{C}_k$ and $\hat{\theta} \in [0, 2\pi]$ such that $u(\hat{\theta}) = \beta$ then from Theorem 7.2 u would be non-periodic. Therefore, B cannot hold. (iii) If $\mathcal{C}$ returns to a bifurcation point then by continuity we have that along the path $\mathcal{C}_k$ there is a function $w \in \mathcal{C}_k$ and a point $\theta^* \in [0, 2\pi]$ such that $w(\theta^*) = \alpha$ and $w'(\theta^*) = 0$ (see Figure 7.7). But from Theorem 7.1 it follows that $w \equiv \alpha$. In consequence D cannot hold.

We thus conclude that the only possibility is C, i.e. $\mathcal{C}_k$ is unbounded and $\mathcal{C}_k \in B_k$. Moreover, if $u \in \mathcal{C}_k$ then $u - \alpha$ has exactly $k+1$ zeroes on $(0, 2\pi)$, the same as $\cos(k\theta)$.

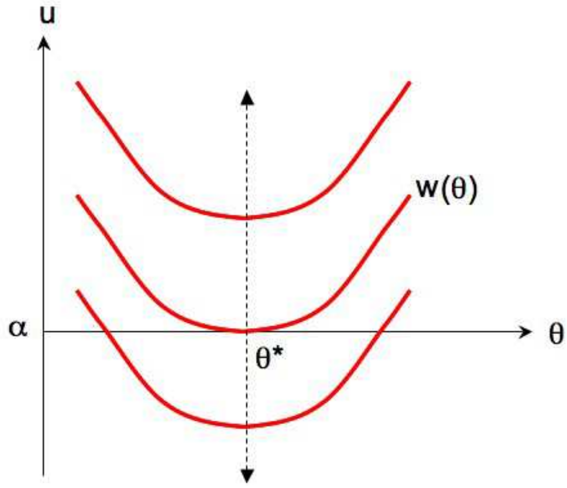

Figure 7.7: If the functions on $\mathcal{C}_k$ lose or gain a zero (they move upwards or downwards, respectively) then there is a double zero of $u - \alpha$, i.e. there exists $w \in \mathcal{C}_k$ such that $w(\theta^*) = \alpha$ and $w'(\theta^*) = 0$.

4. There are two distinct bifurcation branches, $\mathcal{C}_k$ and $\mathcal{S}_k$, starting at (μ_k, α).

Proof: As we saw in Theorem 7.2, the solutions of (7.1) come in pairs, $u(\xi, \theta)$ and $u(\bar{\xi}, \theta)$. We will call $\mathcal{C}_k$ the branch for $\xi \in (\alpha, \beta)$ and $\mathcal{S}_k$ the branch for $\xi \in (0, \alpha)$.

Theorem 7.4 *For any $\lambda \in (\mu_k, \mu_{k+1})$ we have at least $2k$ different non-trivial, 2π-periodic solutions of* (7.1).

Proof: According to the previous analysis, each time λ crosses μ_k there are two distinct bifurcation branches $\mathcal{C}_k$ and $\mathcal{S}_k$. Moreover, all solutions the branches $\mathcal{C}_k$ and $\mathcal{S}_k$ have exactly $k+1$ zeroes, which imply that the branches do not intersect (see Figure 7.8). Therefore, by induction it can be shown that for $\lambda \in (\mu_k, \mu_{k+1})$ we have at least $2k$ different non-trivial, 2π-periodic solutions of (7.1), one for each $\mathcal{C}_n$ and another for each $\mathcal{S}_n$, $1 \leq n \leq k$. $\square$

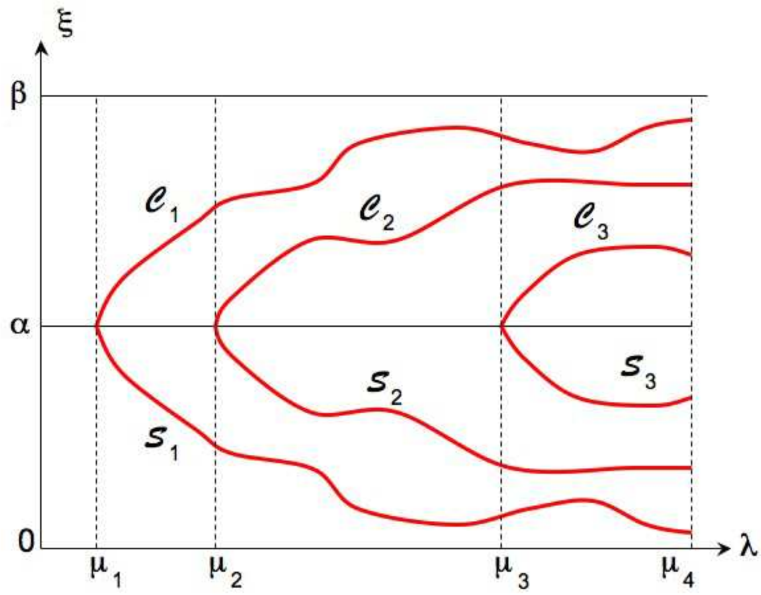

Figure 7.8: Bifurcation diagram in terms of the initial condition $u(0) = \xi$. For any $k \in \mathbb{N}$ the branches $\mathcal{C}_k$ are above α whilst the branches $\mathcal{S}_k$ are below α. For any $\lambda \in (\mu_k, \mu_{k+1})$ we have at least $2k$ different solutions.

7.2 Bifurcation on $\mathbb{S}^N$

7.2.1 Eigenvalues and eigenvectors

Lemma 7.2 *The Laplace-Beltrami operator satisfies the following properties on $L^2(\mathbb{S}^N)$:*

1. *$L^2(\mathbb{S}^N)$ is the direct sum of the orthogonal eigenspaces E_k, $k \geq 0$, where E_k is the space of harmonic polynomials of degree k, related to the eigenvalue $k(k+N-1)$, and*

$$\dim \mathrm{E}_k = \begin{pmatrix} N+k-1 \\ N-2 \end{pmatrix} + \begin{pmatrix} N+k-2 \\ N-2 \end{pmatrix} .$$

2. *Under the parametrisation $(\theta, \varphi) \in \mathbb{S}^N$, where $\theta \in (0, \pi)$ is the vertical angle and $\varphi \in \mathbb{S}^{N-1}$, the Laplace-Beltrami operator is*

$$\Delta_{\mathbb{S}^N} Y = \partial_{\theta\theta} Y + (N-1)\frac{\cos\theta}{\sin\theta}\partial_\theta Y + \frac{1}{\sin^2\theta}\Delta_{\mathbb{S}^{N-1}} Y . \tag{7.9}$$

3. *The subspace of E_k of harmonic polynomials that are independent of $\varphi \in \mathbb{S}^{N-1}$ is one-dimensional. Its generator Y_k^0 is for $N = 2$ the Lagrange (spherical) polynomial of degree 2 whilst for $N \geq 3$ is the Gegenbauer (ultraspherical) polynomial of degree k and order $(N-1)/2$.*

4. *Since Y_0^k is independent of φ then $Y_0^k(\theta)$ solves*

$$\partial_{\theta\theta}Y + (N-1)\frac{\cos\theta}{\sin\theta}\partial_\theta Y + k(k+N-1)Y_0^k = 0\,. \tag{7.10}$$

5. *The explicit solution of (7.10) is $Y_0^k(\theta) = P_{k,N}(\cos\theta)$, where*

$$P_{k,N}(t) = \frac{(-1)^k}{2^k}\frac{\Gamma\left(\frac{N}{2}\right)}{\Gamma\left(k+\frac{N}{2}\right)}\frac{1}{(1-t^2)^{\frac{N-2}{2}}}\frac{d^k}{dt^k}\left[(1-t^2)^{k+\frac{N-2}{2}}\right]\,.$$

6. *$P_{k,N}(t)$ has exactly k distinct roots on $(-1,1)$ and between two consecutive roots of $P_{k,N}(t)$ there is exactly one root of $P_{k-1,N}(t)$. In consequence, Y_0^k changes sign exactly $k+1$ times and Y_0^{k-1} and Y_0^k do not have a common zero.*

Proof: These are well-known facts. For the proofs see e.g. Gallier [23], Gurarie [30] and Morimoto [48]. □

7.2.2 Groups, actions and equivariance

Let $\mathbf{E}$ and $\mathbf{F}$ be two Banach spaces and suppose there exists a Lie group Γ that acts linearly on both spaces. We denote γ (resp. $\tilde\gamma$ the linear action of Γ on $\mathbf{E}$ (resp. $\mathbf{F}$). A nonlinear operator $T:\mathbf{E}\to\mathbf{F}$ is called Γ-equivariant if it commutes with the action of Γ, i.e. if

$$T(\gamma x) = \tilde\gamma T(x) \qquad \forall(\lambda,x)\in\mathbb{R}\times\mathbf{E}\,, \qquad \forall\gamma\in\Gamma\,.$$

For scalar functions $u:\mathbb{S}^N\to\mathbb{R}$ the action is defined as

$$\gamma * u(x) := u(\gamma^{-1}x)\,.$$

For any $x\in\mathbf{E}$ we define the isotropy group of x as

$$\Gamma_x := \{\gamma\in\Gamma\,:\,\gamma x = x\}\,.$$

From the continuity of the action of Γ on $\mathbf{E}$ it follows that Γ_x is a closed subgroup of Γ.

Let H be a closed subgroup of γ. We define the space of fixed points of H as

$$\mathbf{E}^{\mathrm{H}} := \{x\in\mathbf{E}\,:\,\gamma x = x \quad \forall\gamma\in\mathrm{H}\}\,.$$

It is easy to check that $\mathbf{E}^{\mathrm{H}}$ is closed and that if $T:\mathbf{E}\to\mathbf{F}$ is Γ-equivariant then $T(\mathbf{E}^{\mathrm{H}})\subset\mathbf{F}^{\mathrm{H}}$. This last feature is very important because if we are looking for solutions that are symmetric with respect to H, i.e. solutions whose isotropy group is H, then we can restrict our analysis to $T^{\mathrm{H}}:\mathbf{E}^{\mathrm{H}}\to\mathbf{F}^{\mathrm{H}}$.

7.2.3 Symmetries and reduction to an ODE

Our goal is to prove the existence of multiple non-trivial solutions of

$$-\Delta_{\mathbb{S}^N} u = \lambda f(u)\,, \tag{7.11}$$

where f is the same bistable nonlinearity as in the $\mathbb{S}^1$ case, extended as zero on $\mathbb{R} \setminus [0,1]$ (see Figure 7.1). We will collect the necessary ingredients to prove the existence of solutions of (7.11) that depend only on the vertical angle θ, thus independent of the equatorial variables $\varphi \in \mathbb{S}^{N-1}$.

1. Define the nonlinear differential operator

$$T : \mathbb{R} \times C^2(\mathbb{S}^N) \subset \mathbb{R} \times C^0(\mathbb{S}^N) \to C^0(\mathbb{S}^N)$$

as

$$T(\lambda, u) := \Delta_{\mathbb{S}^N} u + \lambda f(u)\,.$$

Then T is $\mathbf{SO}(N+1)$-equivariant, i.e. it commutes with the rotations on $\mathbb{R}^{N+1}$.

Proof: It is well-known (and easy to prove) that the Laplacian operator on $\mathbb{R}^{N+1}$ is $\mathbf{SO}(N+1)$-equivariant. Therefore, since $\mathbb{S}^N$ is $\mathbf{SO}(N+1)$-invariant and

$$\Delta_{\mathbb{R}^{N+1}}|_{\mathbb{S}^N} = \Delta_{\mathbb{S}^N}$$

it follows that the Laplace-Beltrami operator $\Delta_{\mathbb{S}^N}$ is $\mathbf{SO}(N+1)$-equivariant i.e. it commutes with the rotations on $\mathbb{R}^{N+1}$. Moreover, since f is autonomous, i.e. it does not depend explicitly on $(\theta, \varphi) \in \mathbb{S}^N$, we have that $u \mapsto f(u)$ is $\mathbf{SO}(N+1)$-equivariant. Therefore T is $\mathbf{SO}(N+1)$-equivariant. □

2. The eigenspaces E_k are also irreducible subspaces on the action of $\mathbf{SO}(N+1)$. In consequence, the action of $\mathbf{SO}(N+1)$ on the diagonal decomposition

$$L^2(\mathbb{S}^N) = \bigoplus_{k=1}^{\infty} \mathrm{E}_k$$

is also diagonal.

Proof: See e.g. Gurarie [30]. □

3. Let $\mathrm{H} \subset \mathbf{SO}(N+1)$ be the isotropy subgroup of the north pole $e_{N+1} = (0, \ldots, 0, 1) \in \mathbb{S}^N$. Then

$$\mathrm{H} = \{\text{rotations in the horizontal variables } \varphi \in \mathbb{S}^{N-1}\} = \mathbf{SO}(N)$$

and

$$\left[L^2(\mathbb{S}^N)\right]^{\mathrm{H}} = \bigoplus_{k=1}^{\infty} \mathrm{F}_k\,, \qquad \mathrm{F}_k = (\mathrm{E}_k)^{\mathrm{H}} = \mathrm{span}(Y_0^k)\,, \qquad \dim F_k = 1\,. \tag{7.12}$$

Proof: The rotations that leave the north pole invariant are those on the equatorial variables $\varphi \in \mathbb{S}^{N-1}$, which implies that $\mathrm{H} \cong \mathbf{SO}(N)$. moreover, since we have already proved that the action of $\mathbf{SO}(N+1)$ is diagonal and that the only subspace of E_k that is invariant with respect to rotations on φ is the 1D sub-space generated by Y_0^k, we obtain (7.12). □

4. The operator
$$T(\lambda, u) = \Delta_{\mathbb{S}^N} u + \lambda f(u)$$
restricted to $\left[C^2(\mathbb{S}^N)\right]^{\mathrm{H}}$, i.e. to functions $u = u(\theta)$, takes the form
$$T^{\mathrm{H}}(\lambda, u) = u'' + (N-1)\frac{\cos\theta}{\sin\theta}u' + \lambda f(u)\,.$$

Proof: Direct application of (7.9). □

7.2.4 Existence and uniqueness of axis-symmetric solutions

We will study the nonlinear ODE

$$-u'' - (N-1)\frac{\cos\theta}{\sin\theta}u' = \lambda f(u), \tag{7.13}$$

with initial conditions

$$\begin{cases} u(0) = \xi, \\ u'(0) = 0, \end{cases}$$

and we define $\bar{\xi}$ as before (see Figure 7.4).

Theorem 7.5 *For any $\xi \in (\alpha, 1)$ there exists a unique solution $u(\xi, \theta)$ of (7.13) defined at least on $[0, \pi/2]$ and satisfying $\bar{\xi} \le u \le \xi$ on that interval. Moreover, $0 \le u \le 1$ on its whole interval of existence. Finally, if there exists $\theta^* \ge 0$ such that $u(\xi, \theta^*) = \alpha$ and $u'(\xi, \theta^*) = 0$ then $u \equiv \alpha$.*

Proof: Choose $\theta > 0$ in the interval of existence of the solution $u(\xi, \cdot)$. Multiplying (7.13) by u' and integrating over $[0, \theta]$ yields

$$\frac{(u'(\theta))^2}{2} + (N-1)\int_0^{\theta} \frac{\cos\eta}{\sin\eta}(u'(\eta))^2\, d\eta = \lambda[F(\xi) - F(u(\theta))]\,. \tag{7.14}$$

From (7.14) it follows that u' is uniformly bounded on $[0,\pi/2]$, and from (7.13) we obtain that u'' is uniformly bounded as well on $[0,\pi/2]$. Therefore, u is bounded on $[0,\pi/2]$.

Since $u'(\xi,0)=0$ and $u''(\xi,0)<0$, for small $\theta>0$ we have $\bar{\xi}<u(\xi,\theta)<\xi$. Suppose there exists $\theta_1\in(0,\pi/2)$ such that $u(\xi,\theta_1)=\bar{\xi}$. From (7.14) it follows that $u'(\theta_1)=0$, hence using (7.13) we get $u''(\xi,\theta_1)>0$. This implies that $\bar{\xi}$ is strict local minimum of u. Similarly, if there exists $\theta_2\in(0,\pi/2)$ such that $u(\theta_2)=\xi$ then ξ is a strict local maximum of u. Therefore, we conclude that $\bar{\xi}\le u\le\xi$ on $[0,\pi/2]$.

Suppose now that there exists θ_0 such that $u(\xi,\theta_0)>1$. By continuity, if $\varepsilon>0$ is sufficiently small then $u(\xi,\theta)>1$ for any $\theta\in[\theta_0-\varepsilon,\theta_0+\varepsilon]$. But recall that $f\equiv 0$ on $\mathbb{R}\setminus[0,1]$. Therefore $f(u(\theta))\equiv 0$ on $[\theta_0-\varepsilon,\theta_0+\varepsilon]$, which implies that $u\in\ker\Delta_{\mathbb{S}^N}$, and as such u is necessarily constant. Since this contradicts the hypothesis of an initial condition $\xi\in(0,1)$, we thus have $u\le 1$. The same argument applies for $u<0$.

Now suppose there exists θ^* such that $u(\xi,\theta^*)=\alpha$ and $u'(\xi,\theta^*)=0$. Since $F(\alpha)$ is the unique global minimum of F, if we integrate from θ^* to θ we obtain

$$\frac{(u'(\xi,\theta))^2}{2}+(N-1)\int_{\theta^*}^{\theta}\frac{\cos\eta}{\sin\eta}(u'(\xi,\eta))^2\,d\eta=\lambda[F(\alpha)-F(u(\theta))]\le 0\,.$$

Therefore, choosing $\theta\sim\theta^*$ and the adequate side (either $\theta<\theta^*$ or $\theta>\theta^*$) for having a non-negative integral we can show that $u'\equiv 0$ on a non-empty open set. In consequence, the local existence and uniqueness of solutions of (7.13) yields $u\equiv\alpha$. $\square$

7.2.5 Bifurcation analysis of axis-symmetric solutions

The linearisation of (7.13) at $u=\alpha$ is, using the notation $u=\alpha+v$,

$$-v''-(N-1)\frac{\cos\theta}{\sin\theta}v'=\lambda f'(\alpha)v\,. \tag{7.15}$$

If we restrict ourselves to the space of functions that are invariant under horizontal rotations $\varphi\in\mathbb{S}^{N-1}$, i.e. to the space of fixed points of the isotropy group $\mathrm{H}=\mathbf{SO}(N)$, we have the following bifurcation theorem.

Theorem 7.6 *Each time λ crosses an eigenvalue of* (7.15)*, i.e.*

$$\mu_k:=\frac{k(k+N-1)}{f'(\alpha)}\,,\qquad k\ge 0\,,$$

there is a bifurcation branch $\mathcal{C}_k$ starting at (μ_k,α). Moreover, any $u\in\mathcal{C}_k$ crosses exactly $k+1$ times the value α. Finally, $\mathcal{C}_k$ is unbounded and is contained in the cylinder

$$Z_0:=\left\{(\lambda,u)\in\mathbb{R}\times\left[C^0(\mathbb{S}^N)\right]^{\mathrm{H}}\,:\,\lambda>0\,,\quad 0<\|u\|_{C^0(\mathbb{S}^1)}<1\right\}\,.$$

Proof: Consider the linear operator

$$L^{\mathrm{H}} : \mathbb{R} \times \left[C^2(\mathbb{S}^N)\right]^{\mathrm{H}} \subset \mathbb{R} \times \left[C^0(\mathbb{S}^N)\right]^{\mathrm{H}} \to \left[C^0(\mathbb{S}^N)\right]^{\mathrm{H}} ,$$

$$L^{\mathrm{H}} v := v'' + (N-1)\frac{\cos\theta}{\sin\theta} v' + \lambda f'(\alpha) v .$$

The projection of L^{H} to the eigenspace F_k yields the scalar linear equation $l_n(\lambda) v_n$, where

$$l_n(\lambda) := \lambda f'(\alpha) - n(n+N-1) , \quad n \in \mathbb{N} .$$

Since $l_n(\lambda)$ changes sign when λ crosses μ_k if and only if $n = k$, the Global Rabinowitz Alternative yields the existence of a bifurcation branch $\mathcal{C}_k$ starting at (μ_k, α), which is either unbounded or returns to another bifurcation point.

Observe that the starting point of the branch is the corresponding eigenfunction in F_k, i.e. the Gegenbauer polynomial $P_{k,N}(\cos\theta)$. Since $P_{k,N}(t)$ has exactly $k+1$ roots it follows that $P_{k,N}(\cos\theta)$ crosses α exactly $k+1$ times. By continuity, all functions in $\mathcal{C}_k$ close to (μ_k, α) have exactly $k+1$ crossings of α. If $\mathcal{C}_k$ returns to a different bifurcation point (μ_n, α) with $n \neq k$, then the same argument implies that near (μ_n, α) the functions in $\mathcal{C}_n$ have exactly $n+1$ zeroes. By continuity, there must be a function $u_0 \in \mathcal{C}_k \cap (\mathbb{R} \times \{\alpha\})^c$ and a point θ_0 such that $u_0(\theta_0) = \alpha$ and $u_0'(\theta_0) = 0$. But from Theorem (7.5) that implies $u_0 \equiv \alpha$, which contradicts the definition of u_0.

Therefore $\mathcal{C}_k$ cannot return to a bifurcation point. In consequence, the Global Rabinowitz Alternative implies that $\mathcal{C}_k$ is unbounded. Moreover, the previous argument also shows that all functions in $\mathcal{C}_k$ have exactly $k+1$ crossings of α, because if there were a gain or a loss of a zero along $\mathcal{C}_k$ then the branch would return to $\mathbb{R} \times \{\alpha\}$, i.e. to another bifurcation point, which we have proved to be impossible.

We claim that the solutions of (7.13) at ∂Z_0 are constant. Indeed, if $\lambda = 0$ then the solutions are in the kernel of the Laplace-Beltrami operator, and as such are constant. If $\|u\|_{C^0(\mathbb{S}^N)^{\mathrm{H}}} = 1$ then by continuity there exists θ_0 such that $u_0(\theta_0) = 1$ and $u_0'(\theta_0) = 0$. However, since $u \equiv 1$ is a solution of (7.13) then Theorem 7.5 implies that $u_0 \equiv 1$. In consequence, if $u \in \mathcal{C}_k \cap \partial Z_0$ then u_0 is constant, and as such u_0 either never crosses α or $u_0 \equiv \alpha$. Since both possibilities contradict that $\mathcal{C}_k$ is continuous and cannot return to another bifurcation point, respectively, we obtain that $\mathcal{C}_k \cap \partial Z_0 = \emptyset$, hence $\mathcal{C}_k$ cannot leave the cylinder Z_0. $\square$

Theorem 7.7 *For any $\lambda \in (\mu_k, \mu_{k+1})$ there are at least k different non-trivial solutions of* (7.13)*, i.e. k solutions of* (7.11) *that are invariant under horizontal rotations $\varphi \in \mathbb{S}^{N-1}$.*

Proof: From Theorem 7.6, each time we cross an eigenvalue μ_k there is an unbounded bifurcation branch $\mathcal{C}_k$ starting at (μ_k, α) (see Figure 7.9). Since $\mathcal{C}_k \subset Z_0$, it follows that for any $\lambda > \mu_k$ the branch $\mathcal{C}_k$ intersects at least once the transversal section of the Z_0 of level λ. Therefore, by induction, for any $\lambda \in (\mu_k, \mu_{k+1})$ we have k solutions of (7.13), one for each bifurcation branch $\mathcal{C}_n$, $1 \leq n \leq k$. $\square$

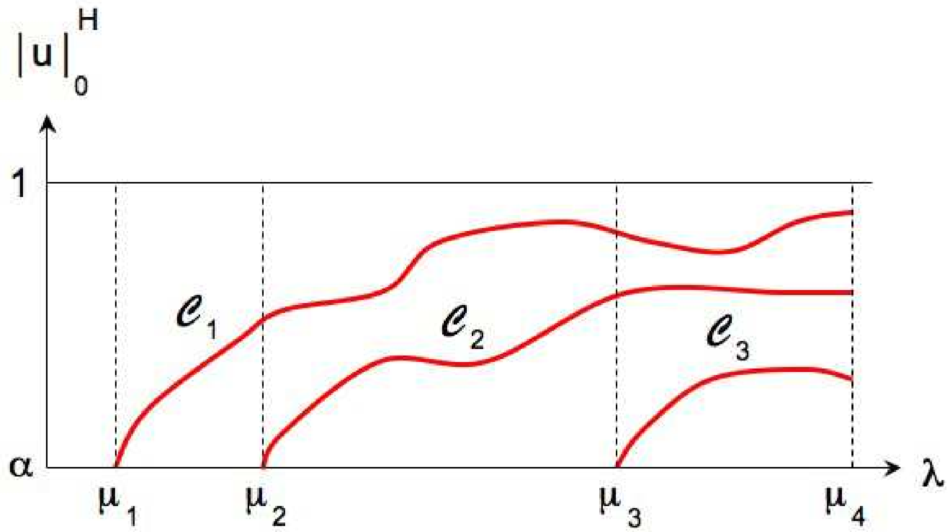

Figure 7.9: Bifurcation diagram. For any $\lambda \in (\mu_k, \mu_{k+1})$ we have at least k different solutions with symmetry H, hence k orbits of solutions under the action of $\mathbf{SO}(N+1)$.

7.3 Discussion

We have proved the existence of multiple non-trivial solutions for the semilinear elliptic problem (7.11) on $\mathbb{S}^N$. More precisely, if $\lambda \in (\mu_k, \mu_{k+1})$ then for $N = 1$ there are at least $2k$ non-trivial solutions whilst for $N \geq 2$ there are at least k non-trivial solutions.

The analysis on $N = 1$ is complete, but for $N \geq 2$ we have only proved the existence of axis-symmetric solutions. Therefore, an open problem is to prove the existence of multiple solutions that are not axis-symmetric. However, this is not straightforward because our analysis relies on the Global Rabinowitz Alternative, and as such we need to have eigenspaces of odd dimension and bifurcation branches $\mathcal{C}_k$ that are bounded on the u-direction (i.e. the function space)and unbounded on the λ-direction (i.e. the parameter space).

We proved Conjecture 6.12 for $\mathcal{M} = \mathbb{S}^1$ and for a bifurcation starting at the trivial solution $u \equiv \alpha$. However, the general case of a N-dimensional manifold, $N \geq 2$ it is still an open problem. We plan to address the case $\mathcal{M} = \mathbb{S}^N$ in future works.

The parity of the dimension of the eigenspaces depends on N, which suggests that the argument we presented cannot be extended for all N. However, since the eigenspaces for $N = 2$ have odd dimension, the Global Rabinowitz alternative gives the existence of a bifurcation branch $\mathcal{C}_k$ starting at (μ_k, α) for all $k \in \mathbb{N}$. We could try to prove that $\mathcal{C}_k$ is bounded on the u- direction and unbounded on the λ-direction, but the arguments we used are based on a double zero argument(if $u(\theta) = \alpha$ and $u'(\theta) = 0$ then $u \equiv \alpha$), which cannot be applied to non-axis-symmetric functions because the variables are no longer 1D.

The equivalent to zeroes in more dimensions are nodal sets, i.e. the number of connected parts of $u^{-1}(\mathbb{R} \setminus \{0\})$. But unlike zeroes on $\mathcal{C}_k$, the number of nodal sets are not a topological invariant and their study is still still a current research topic (for more details see e.g. Eremenko *et al* [17] and Leydold [43]). In consequence, there is still some work to do before we can affirm that that $\mathcal{C}_k$ in unbounded on λ. We plan to address this problem in future research.

Part IV

Perspectives

Chapter 8

Conclusions

The aim of this thesis was to study several biological problems via reaction-diffusion systems in order to assess the effect of some parameters on pattern formation. The parameters we chose were the coupling of nonlinear terms, the effect of diffusion on a previously studied ODE system, the effect of growth on a domain on the stability of the patterns, the effect of the domain geometry on patterns and the intensity of the nonlinear term.

8.1 Reaction-difusion systems and modelling

8.1.1 Calcium dynamics in neurons

In the calcium project we constructed a model with a strong nonlinear coupling, which was necessary in order to have a realistic model that takes into account the twitching of the dendritic spine. Despite the complexity of the realistic model, we managed to prove that the reaction-diffusion system admits non-negative, globally-defined solutions. We studied separately two sub-models, one with fixed proteins and at the other with diffusive proteins, and we proved that there is a continuous link between both models: as the diffusion parameter of the proteins goes to zero, the solutions of the model with diffusive proteins converge to the solutions of the model with fixed proteins.

There are some open problems that we would like to address in future works. We would like to implement some numerical simulations in order to get a better understanding of the solutions at large times. With the insight of the simulations, we could try to assess the decay rate of the calcium concentration, which according the approximations of Holcman and Schuss [34] it has two different exponential decay rates, one faster at the beginning of the process and one slower at the end. The numerical evidence could also shed light on the existence and stability of non-trivial steady-state solutions.

8.1.2 Virus infection and immune response

One of the main goals of the virus project was to assess the effect of viral diffusion on both the cells and the viral particles. We found that this effect depends on the virions' (viral particles) decay rate μ_v. If $\mu_v > 0$ then the diffusion plays against the virions and favours the wild-type cells, whilst if $\mu = 0$ we have the opposite pattern,i.e. the diffusion favours the proliferation of viruses and plays against the wild-type cells. One interpretation is that the strength of the viral infection comes in numbers, i.e. for a cell to become infected several particles are needed; in terms of concentration, this suggests that there is a minimal concentration threshold that has to be present in order to transform a wild-type cell into an infected cell.

As virions diffuse their concentration diminishes. Therefore, if there is a decay rate then the diffusion makes it harder for the virions to reach the furthest cells in enough numbers to infect them, which leads to thir eventual extinction. On the other hand, in the absence of a decay rate the virions will eventually invade the whole domain. Indeed, the current amount of virions does not decrease because they cannot die, but in fact it increases because there are new virions that are produced by the newly infected cells.

We plan in the future to apply our results to real biological situations using real data. One ambitious goal we have is to study a real virus (say AIDS) and measure the effect of diffusion in *in vitro* experiments. In the light of our results we conjecture that, if it were possible to indirectly modify the decay rate and/or the diffusion rate of the virions then we could drastically impact the final state of contagion.

8.2 Reaction-diffusion equations and systems on manifolds

8.2.1 The effect of growth on pattern formation

We showed that growth has two effects on pattern formation.

The first is a *regularising effect* in the sense that growth gives more chances for solutions to be global in time. In particular, growth delays nay possible blow-up and can even prevent it. This was to be intuitively expected because, as the domain grows, the solution has more room to move around before blowing up, and if growth is faster than the solution then there is no room for the latter to reach the "boundaries" and "explode".

The second is a *stabilising effect* in the sense that the eigenvalues have smaller real parts on (isotropic) growing domains than on fixed domains. The striking fact is that this stabilising effect is clearly quantifiable: it is a parallel shift to the left on the complex plane, which depends on the growth rate, and is constant in the case of exponential growth.

There are several open problems that we would like to address in the future. First, it would be interesting to check the regularising and stabilising effects of isotropic growth via numerical simulations. Second, we would like to extend the analysis to non-isotropic growth because for several biological applications such as tumour growth and embryo development it is more realistic to assume a non-homogeneous growth function. Third, for several other applications such as wound healing and tissue interaction, adding a priori an exogenous growth function is not very realistic. We plan to study other models where growth is endogenous and unknown, i.e. it is another unknown of the problem.

8.2.2 Generalised travelling waves on manifolds

H. Berestycki and F. Hamel [8] generalised the usual definition of travelling waves, in a very general setting. These new notions, which cover all usual situations, were motivated by several of their works on domains with obstacles (holes), in which the distance is no longer a straight line but a geodesic distance can still be defined. The level sets of the travelling waves in this new framework are no longer hyper-planes moving at a constant velocity but hyper-surfaces parametrised by time.

Since the new definition does not depend on the geometry of the Euclidean space but only on the definition of a geodesic distance, we could extend the notion of a travelling wave to manifolds. We needed to reformulate the classical results for parabolic equation to the framework of manifolds. Some of these results were straightforward, e.g. maximum principles and Harnack's inequality, because they are local in nature. However, for global results such as a priori estimates we needed to have uniform bounds of the coefficients.

Under this framework we managed to recover the results of H. Berestycki and F. Hamel [8] in a very direct fashion. This permits to extend the analysis of travelling waves as solutions of reaction-diffusion equations on curved domains (manifolds).

8.2.3 Travelling waves on the real line

Motivated by the previous project, where we defined travelling waves on manifolds, we wanted to tackle the problem of calcium waves on the 2-sphere, which is a well-known problem in Mathematical Biology. Our first model consisted on considering solutions that depends only on the vertical angle. As we projected the equation on the real line, the singularity of the poles rendered the coefficients unbounded.

In order to overcome this technical difficulty, we considered a new model, where the coefficients were truncated at a certain level $\pm\rho$. It turned out that there were three different patterns: (i) On (ρ, ∞) there is a wave moving from right to left, with an asymptotic velocity c_N. (ii) On $(-\infty, -\rho)$ there is a wave moving from left to right with asymptotic velocity $c_S < c_N$. (iii) On $[-\rho, \rho]$ there are two generalised travelling waves, one moving from left to right and the other from right to left, and they eventually block each other. These waves are *generalised* because even if they are monotone in time they are not of the form $\varphi(x \pm ct)$. Moreover, their asymptotic velocity does not exist because the waves are blocked and hence their velocities tend to zero.

This project provides an example of a generalised, non-classical travelling wave without asymptotic velocity. Furthermore, the analysis indirectly implies the existence of non-trivial solutions of the corresponding elliptic equation.

Since the model was truncated, a natural open problem is to study the behaviour of solutions as the truncating parameter $\rho \to \infty$. We are not sure about whether in the limit the travelling wave remains blocked or it becomes an invasion: on the one hand, it seems that the blocking was originated by the truncation because it allowed the existence of pseudo-classical travelling waves near $\pm\infty$. But on the other hand, given the geometry of the sphere, as the wave invades the south pole ($x = -\infty$) there is less space for the diffusion, which could lead to a slow-down of the wave and eventually a total stop. We plan to study future works which possibility holds.

8.2.4 Travelling waves on the sphere

We constructed two models on the sphere one on a truncated 2-sphere with Dirichlet boundary conditions and another on the N-sphere.

On both domains we proved that for $\lambda \in (0, \underline{\lambda})$ the only solutions are constant whilst for $(\lambda^\flat, \infty)$ we have a non-trivial solution $u^\star$ of the corresponding elliptic problem. In the case of the truncated sphere, we proved that there is a generalised travelling wave, which is increasing in time, and that this wave is blocked by $u^\star$. In the case of the whole sphere the result is more subtle: depending on the initial conditions, the travelling wave can either converge to zero, to 1 or do not converge to any of those two stable states.

Our results show that the fact that we do not necessarily have invasion on the sphere, i.e. the generalised travelling wave does not converge towards $u \equiv 1$. Given that this finding is common in our three models on the sphere, it seems safe to assume that the fact of not having an invasion is an intrinsic property of the geometry of the sphere. It is important to stress that the results on the truncated sphere are also valid on the N-truncated sphere because we never used arguments concerning $\mathbb{S}^2$ or $\mathbb{R}^3$.

On the contrary, when the nonlinearity f is monostable instead of bistable we always have invasion, even for more general domains. This illustrates the importance of the bistable nonlinearity and its interplay with the geometry of the domain in the diversity of patterns that we can have. However, the complete analysis of the reaction-diffusion problem on the sphere with monostable nonlinearity is still an open problem that we plan to address in future works.

8.3 Elliptic equations and nonlinear eigenvalues on the sphere

8.3.1 Bifurcation and multiple periodic solutions on the sphere

We have proved the existence of multiple non-trivial solutions for the semilinear elliptic problem (7.11) on $\mathbb{S}^N$. More precisely, if $\lambda \in (\mu_k, \mu_{k+1})$ there are at least $2k$ non-trivial solutions whilst for $N \geq 2$ there are at least k non-trivial solutions.

For $N = 1$ the analysis is complete. We proved that the solutions of (7.1) on $\mathbb{R}$ are periodic and that given $\lambda > \lambda_0$ we have 2π-periodic solutions. Moreover, for each $\lambda \in (\mu_k, \mu_{k+1})$ there are at least $2k$ non-trivial solutions of (7.1).

We also proved Conjecture 6.12 for $\mathcal{M} = \mathbb{S}^1$ and for a bifurcation starting at the trivial solution $u \equiv \alpha$. However, the general case of a manifold of dimension $N \geq 2$ is an open problem.

For $N \geq 2$ we proved that for each $\lambda \in (\mu_k, \mu_{k+1})$ there are at least k non-trivial solutions of (7.11) that are axis-symmetric, i.e. they depend only on the vertical angle θ. Unfortunately, the arguments we presented cannot extended directly to a non-axis-symmetric framework. On the one hand, the equivalent of zeroes to higher dimensions, i.e. the concepts of nodal sets and nodal domains, are not a topological invariant and they are not completely studied. On the other hand, the argument we used to characterise the boundedness of the bifurcation branches on the u-direction relies on the fact that the variable θ is one-dimensional.

Therefore, an open problem is to prove the existence of multiple solutions on $\mathbb{S}^N$ that are not axis-symmetric. For $N = 2$ the eigenspaces have odd dimension, hence from the Global Rabinowitz Alternative it follows that each time we cross an eigenvalue μ_k there is a bifurcation branch $\mathcal{C}_k$ starting from (μ_k, α). We conjecture that for $\mathbb{S}^2$ the bifurcation branches have the same qualitative features as in the axis-symmetric case, i.e. they are bounded on the u-direction and unbounded on the λ-direction. However, this is an open problem as well.

Another open problem is the bifurcation analysis for a monostable nonlinearity. In this case the bifurcation will start at $(\mu_k, 0)$ because $f'(0) > 0$. We plan to address this topic in future works.

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