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# The stabilizing effect of growth on pattern formation

Mauricio Labadie \*

August 4, 2011

## Abstract

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.

**Keywords** Pattern formation · Reaction-diffusion · Laplace-Beltrami operator · Global existence of solutions · Stability

**Mathematical Subject Classification** 92C15 · 35K57 · 58J99 · 74G25 · 70K20

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# 1 Introduction

Since the seminal paper of Turing [14], the most frequently used framework for modeling pattern formation in biological and chemical systems are reaction-diffusion systems of the form

$$\frac{\partial \mathbf{u}}{\partial t} = \mathcal{D} \Delta \mathbf{u} + \mathbf{F}(\mathbf{u}), \quad \mathcal{D} = \begin{bmatrix} D_1 & & & \\ & D_2 & & \\ & & \ddots & \\ & & & D_M \end{bmatrix}, \quad D_k > 0, \quad (1)$$

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* [?] 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 [8] 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 (1). Based on this evidence, Meinhardt [9] 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* [2] 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 disappears. In 2004 Plaza *et al* [?] 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 Gjorgjieva and Jacobsen [6] 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* [3] 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.

## 2 Main results

### 2.1 Reaction-diffusion systems on growing manifolds

Let us define the mathematical objects we will work with throughout this paper.

**Definition 1** A *manifold*  $\mathcal{M}$  will be for us a smooth ( $C^\infty$ ), compact, connected, oriented Riemannian manifold without boundary. We will denote its parametrisation by

$$\begin{aligned} X : \hat{\Omega} \subset \mathbb{R}^n &\longrightarrow \mathcal{M} \\ \xi = (\xi_1, \dots, \xi_n) &\longmapsto X(\xi) \end{aligned}$$

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 2** The *Laplace-Beltrami operator* on a Riemannian manifold  $\mathcal{M}$  with parametrisation  $(\xi, t) = (\xi_1, \dots, \xi_n, t)$  and metric  $(g_{ij}(\xi, t))$  is (using the sum convention on repeated indices)

$$\Delta_{\mathcal{M}}\phi := \frac{1}{\sqrt{g}} \partial_{\xi_j} [\sqrt{g} g^{ij} \partial_{\xi_i} \phi], \quad (2)$$

where  $(g^{ij}) = (g_{ij})^{-1}$  and  $g = \det(g_{ij})$ .

**Definition 3** A *growing manifold* is a monparametric 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  $C^\infty$  in both variables  $\xi$  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 4** A function  $\rho : [0, \infty) \rightarrow [1, \infty)$  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 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  $\mathcal{M}_t \stackrel{\sim}{=} \rho(t)\mathcal{M}$ , meaning that if  $X(\xi, t)$  is the parametrisation of  $\mathcal{M}_t$  then there is a parametrisation  $\tilde{X}$  of  $\mathcal{M}$  such that  $X(\xi, t) = \rho(t)\tilde{X}(\xi)$ .

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 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

$$\partial_t \mathbf{u} = \mathcal{D} \Delta_{\mathcal{M}_t} \mathbf{u} - \partial_t [\log \sqrt{g(t, \xi)}] \mathbf{u} + \mathbf{F}(\mathbf{u}), \quad (3)$$

where the Laplace-Beltrami operator  $\Delta_{\mathcal{M}_t}$  is given in (2). In the case of isotropic growth we have

$$\partial_t \mathbf{u} = \frac{\mathcal{D}}{\rho^2(t)} \Delta_{\mathcal{M}} \mathbf{u} - n \frac{\dot{\rho}(t)}{\rho(t)} \mathbf{u} + \mathbf{F}(\mathbf{u}), \quad (4)$$

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

**Definition 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 1 says that in the case of isotropic growth the growth rate is independent of the spacial variable  $\xi$  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* [?]:

$$\begin{aligned} \partial_t \mathbf{u} &= \mathcal{D} \Delta_{\mathcal{S}_t} \mathbf{u} - \partial_t [\log(h_1 h_2)] \mathbf{u} + \mathbf{F}(\mathbf{u}), \\ \partial_t \mathbf{u} &= \frac{\mathcal{D}}{\rho^2(t)} \Delta_{\mathcal{S}} \mathbf{u} - 2 \frac{\dot{\rho}(t)}{\rho(t)} \mathbf{u} + \mathbf{F}(\mathbf{u}). \end{aligned}$$

## 2.2 Properties of solutions: existence and uniqueness

We will prove that in the case of isotropic growth, the reaction-diffusion system (4) has a time-local unique solution. Moreover, if the initial condition is continuous and the nonlinearity  $\mathbf{F}(\mathbf{u})$  is  $C^\infty$  then the local solution is  $C^\infty$  for positive times.

**Theorem 2** *There is a time  $T > 0$  such that the reaction-diffusion system (4) with initial condition  $\mathbf{u}_0 \in C[\mathcal{M}, \mathbb{R}^M]$  has a unique solution*

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

**Theorem 3** *If  $\mathbf{F} : \mathbb{R}^M \rightarrow \mathbb{R}^M$  is  $C^\infty$  then*

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

## 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 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 (4) lies in  $C[\mathcal{M}, \mathbb{R}^M]$  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*

$$\mathbf{F}(z) \cdot \mathbf{n}(z) < c(t) \quad \forall t \geq 0, \tag{5}$$

where  $\mathbf{n}(z)$  is the outer normal at  $z$ . Then the solution  $\mathbf{u}(t)$  of (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 (5) holds.

From Theorem 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 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 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  $t \rightarrow t_1 := 1/u_0$ . Now consider the equivalent problem on a growing domain, i.e. suppose  $u(t)$  is a scalar, homogeneous solution of (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 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,

$$\begin{aligned} \dot{\eta} &= \iint_{\mathcal{M}} \partial_t u(t, x) d\Omega \\ &= \iint_{\mathcal{M}} \left( \frac{1}{\rho^2(t)} \Delta_{\mathcal{M}} u - c(t)u + u^2 \right) d\Omega \\ &= \iint_{\mathcal{M}} (-c(t)u + u^2) d\Omega. \end{aligned}$$

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 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.

## 2.4 The stabilising effect of growth

Under isotropic regimes, growth has a stabilising effect on pattern formation.

**Theorem 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  $\lambda$  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 5 says that when we compare the spectra of  $\mathcal{L}_S$  and  $\mathcal{L}_{\mathcal{M}_T}$  on the same manifold  $S = \mathcal{M}_T$  we obtain

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

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 5 is the first analytic proof of the stabilising effect of growth on pattern formation.

### 3 Proof of Theorem 1

We will divide the proof in three parts.

#### 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

$$\begin{aligned} \psi_t : \hat{\Omega} \subset \mathbb{R}^n &\longrightarrow \mathcal{M}_t \\ \xi = (\xi_1, \dots, \xi_n) &\longmapsto \psi_t(\xi) = X(\xi, t) \end{aligned}$$

is  $C^\infty$  in both variables  $(\xi, t)$ . 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  $C^\infty$  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  $v = (v^1, \dots, v^n) \neq 0$ .

#### 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

$$\begin{aligned} \Omega(t) &:= \psi_t(\hat{\Omega}) = X(\hat{\Omega}, t), \\ \partial\Omega(t) &:= \psi_t(\partial\hat{\Omega}) = X(\partial\hat{\Omega}, t), \end{aligned}$$

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  $\phi$ . 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.

$$\frac{d}{dt} \iint_{\Omega(t)} \phi dV = - \int_{\partial\Omega(t)} \langle J, \mathbf{n} \rangle dS. \quad (6)$$

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

$$\frac{d}{dt} \iint_{\Omega(t)} \phi dV = D \int_{\partial\Omega(t)} \langle \nabla\phi|_{\partial\Omega(t)}, \mathbf{n} \rangle dS. \quad (7)$$

For the sake of clarity let us recall each term in (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 (7). For the left hand side, using the change of variables  $\tilde{\phi}(\xi, t) := \phi(X(\xi, t), t)$  we obtain

$$\begin{aligned} \frac{d}{dt} \iint_{\Omega(t)} \phi(X, t) dV &= \frac{d}{dt} \iint_{\hat{\Omega}} \tilde{\phi}(\xi, t) \sqrt{g} d\xi \\ &= \iint_{\hat{\Omega}} [\partial_t \tilde{\phi} \sqrt{g} + \tilde{\phi} \partial_t \sqrt{g}] d\xi \\ &= \iint_{\hat{\Omega}} \left[ \partial_t \tilde{\phi} + \tilde{\phi} \frac{\partial_t \sqrt{g}}{\sqrt{g}} \right] \sqrt{g} d\xi \\ &= \iint_{\Omega(t)} \left[ \partial_t \tilde{\phi} + \tilde{\phi} \frac{\partial_t \sqrt{g}}{\sqrt{g}} \right] dV. \end{aligned}$$

For the right hand side in (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

$$\iint_{\mathcal{M}} d\omega = \int_{\partial\mathcal{M}} \omega, \quad (8)$$

where  $\omega$  is a  $(k-1)$  differential form,  $k \leq n$ . If  $\omega$  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 (8) becomes

$$\iint_{\Omega(t)} \text{div}(F) dV = \int_{\partial\Omega(t)} \langle F|_{\partial\Omega(t)}, \mathbf{n} \rangle dS. \quad (9)$$

In the light of (9) we have that

$$\int_{\partial\Omega(t)} \langle \nabla\phi|_{\partial\Omega(t)}, \mathbf{n} \rangle dS = \iint_{\Omega(t)} \text{div}(\nabla\phi) dV.$$

Putting all two pieces together in (7) we obtain

$$\iint_{\Omega(t)} \left[ \partial_t \tilde{\phi} + \tilde{\phi} \partial_t(\log\sqrt{g}) - D \text{div}(\nabla\tilde{\phi}) \right] dV = 0.$$

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:

$$\partial_t \phi = D \text{div}(\nabla\phi) - \partial_t[\log\sqrt{g}]\phi, \quad (10)$$

where the operator  $\text{div}(\nabla\phi)$  is the *Laplace-Beltrami operator*  $\Delta_{\mathcal{M}_t}$  we introduced in Definition 2.

Now consider a morphogen vector  $\mathbf{u} = (u_1, \dots, u_M)$  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 (6) takes the form

$$\frac{d}{dt} \iint_{\Omega(t)} \mathbf{u} dS = - \int_{\partial\Omega(t)} \langle J, \mathbf{n} \rangle dS + \iint_{\Omega(t)} \mathbf{F}(\mathbf{u}) dS. \quad (11)$$

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 (11) takes the form

$$\frac{d}{dt} \iint_{\Omega(t)} \mathbf{u} dS = \mathcal{D} \int_{\partial\Omega(t)} \langle \nabla \mathbf{u} |_{\partial\Omega(t)}, \mathbf{n} \rangle dS + \iint_{\Omega(t)} \mathbf{F}(\mathbf{u}) dS. \quad (12)$$

Notice that in (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 (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 1.

### 3.3 The isotropic growth model

In the case of isotropic growth we have

$$X(\xi, t) = \rho(t) \tilde{X}(\xi),$$

which implies the following identities:

$$\begin{aligned} g_{ij}(\xi, t) &= \rho^2(t) \tilde{g}_{ij}(\xi), \\ g^{ij}(\xi, t) &= \frac{1}{\rho^2(t)} \tilde{g}^{ij}(\xi), \\ \sqrt{g} &= \rho^n \sqrt{\tilde{g}}, \\ \Delta_{\mathcal{M}_t} &= \frac{1}{\rho^2(t)} \Delta_{\mathcal{M}}. \end{aligned} \quad (13)$$

If we substitute the relations (13) in the general model given in (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 1 and concludes its proof.  $\square$

## 4 Proof of Theorem 2

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

$$\partial_t \mathbf{u} = L\mathbf{u} + \mathbf{G}(t, \mathbf{u}), \quad \mathbf{u}(0) = \mathbf{u}_0, \quad (14)$$

where  $L$  is a second-order elliptic operator and the nonlinearity  $\mathbf{G}$  is  $C^\infty$  in its arguments. Let  $\mathbf{X}$  be a Banach space such that the following conditions hold:

1.  $\mathbf{X}$  is a space of functions  $\mathbf{u} : \mathcal{M} \rightarrow \mathbb{R}^M$ .
2.  $e^{tL} : \mathbf{X} \rightarrow \mathbf{X}$  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

$$\begin{aligned} \mathbf{G} : \mathbf{X} &\longrightarrow \mathbf{X} \\ \mathbf{u} &\longmapsto \mathbf{G}(t, \mathbf{u}) \end{aligned}$$

is locally Lipschitz in  $\mathbf{u}$ , uniformly in  $t$ .

**Remark 1** The space  $\mathbf{X}$  we have in mind is  $C[\mathcal{M}, \mathbb{R}^M]$ , but there are other possible choices. Indeed, if we ask the nonlinearity  $\mathbf{G}(t, \mathbf{u})$  to be  $C^\infty$ , bounded and with derivatives bounded then  $L^p[\mathcal{M}, \mathbb{R}^M]$  and  $H^k[\mathcal{M}, \mathbb{R}^M]$  are suitable spaces as well.

**Lemma 1** *The reaction-diffusion system (4) can be reduced to the system (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

$$s(t) := \int_0^t \frac{dr}{\rho^2(r)}. \quad (15)$$

Then for any function  $f(t)$  we have that

$$\partial_s f = \rho^2(t)\partial_t f.$$

Multiply the system (4) by  $\rho^2(t)$  and define  $\tilde{\mathbf{u}}(s, x) := \mathbf{u}(t(s), x)$ . Then the system (4) takes the equivalent form

$$\partial_s \tilde{\mathbf{u}} = \mathcal{D}\Delta_{\mathcal{M}}\tilde{\mathbf{u}} + \mathbf{G}(s, \tilde{\mathbf{u}}),$$

where

$$\mathbf{G}(t, \tilde{\mathbf{u}}) = -n\rho(t)\dot{\rho}(t)\tilde{\mathbf{u}} + \rho^2(t)\mathbf{F}(\tilde{\mathbf{u}}).$$

Renaming the variables  $(s, \tilde{\mathbf{u}})$  as  $(t, \mathbf{u})$  we obtain (14).  $\square$



Now we have all the elements to prove Theorem 2. By the Lemma 1 the problem (4) is equivalent to (14). Moreover, (14) can be expressed in the integral form

$$\mathbf{u}(t) = e^{tL}\mathbf{u}_0 + \int_0^t e^{(t-s)L}\mathbf{G}(s, \mathbf{u}(s)) ds. \quad (16)$$

Define the operator

$$\Psi\mathbf{u}(t) := e^{tL}\mathbf{u}_0 + \int_0^t e^{(t-s)L}\mathbf{G}(s, \mathbf{u}(s)) ds$$

on the Banach space  $C([0, T], \mathbf{X})$  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

$$\mathbf{Z} := \{\mathbf{u} \in C([0, T], \mathbf{X}) : \mathbf{u}(0) = \mathbf{u}_0, \|\mathbf{u}(t) - \mathbf{u}_0\|_{\mathbf{X}} \leq \alpha\}.$$

The final time  $T > 0$  will be chosen later in order to have that  $\Psi : \mathbf{Z} \rightarrow \mathbf{Z}$  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

$$\left\| \int_0^t e^{(t-s)L}\mathbf{G}(s, \mathbf{u}(s)) ds \right\|_{\mathbf{X}} \leq K_1 Ct.$$

Therefore, it is possible to choose  $T > 0$  such that  $K_1 CT \leq \alpha/2$ . Moreover, from the assumptions 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  $\|\Psi\mathbf{u}(t) - \mathbf{u}_0\|_{\mathbf{X}} \leq \alpha$ , which implies that  $\Psi(\mathbf{Z}) \subset \mathbf{Z}$ .

Let us find the conditions under which  $\Psi$  is a contraction. If we calculate

$$\begin{aligned} \|\Psi\mathbf{u}(t) - \Psi\mathbf{v}(t)\|_{\mathbf{X}} &= \left\| \int_0^t e^{(t-s)L} [\mathbf{G}(s, \mathbf{u}(s)) - \mathbf{G}(s, \mathbf{v}(s))] ds \right\|_{\mathbf{X}} \\ &\leq CKt \sup_{s \in [0, t]} \|\mathbf{u}(s) - \mathbf{v}(s)\|_{\mathbf{X}} \\ &\leq CKT \|\mathbf{u}(t) - \mathbf{v}(t)\|_{\mathbf{X}} \end{aligned}$$

we can see that  $\Psi : \mathbf{Z} \rightarrow \mathbf{Z}$  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 (16), or equivalently a unique solution of (14).

This completes the proof of Theorem 2.  $\square$

## 5 Proof of Theorem 3

Fix  $t' \in (0, T]$  and consider a solution  $\mathbf{u}(t)$  of (14) written in its integral form (16). Recall two properties of the Laplace-Beltrami operator. First, the map

$$e^{t\Delta_{\mathcal{M}}} : C(\mathcal{M}) \rightarrow C^1(\mathcal{M})$$

is continuous for all  $t > 0$ , and second, there exists a constant  $C > 0$  such that

$$\|e^{t\Delta_{\mathcal{M}}}\|_{\mathcal{L}(C(\mathcal{M}), C^1(\mathcal{M}))} \leq Ct^{-1/2}$$

(see Taylor [?], 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  $\mathbf{u}_0 \in C[\mathcal{M}, \mathbb{R}^M]$  we have that  $\mathbf{u}(t_1) \in C^1[\mathcal{M}, \mathbb{R}^M]$ .

Now, if we consider  $\mathbf{u}(t_1)$  as a new initial condition we have that  $\mathbf{u}(t_2) \in C^2[\mathcal{M}, \mathbb{R}^M]$  for any  $t_2 \in (t_1, t']$ . Repeating this iterative argument we can construct a sequence

$$0 < t_1 < t_2 < \dots < t_n \rightarrow t'$$

such that  $\mathbf{u}(t_n) \in C^n[\mathcal{M}, \mathbb{R}^M]$  for any  $t_n \in (t_{n-1}, t']$ . In the limit we get that  $\mathbf{u}(t') \in C^\infty[\mathcal{M}, \mathbb{R}^M]$  for any  $t' \in (0, T]$ .

Concerning the time derivatives, recall that if  $\mathbf{u}(\xi, t)$  is a solution of (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  $C^\infty$  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 (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  $C^\infty$  in time.

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

## 6 Proof of Theorem 4

**Lemma 2** *Let  $\mathcal{M}$  be a manifold and consider the reaction-diffusion system*

$$\partial_t \mathbf{u} = \mathcal{D} \Delta_{\mathcal{M}} \mathbf{u} + \mathbf{F}(\mathbf{u}), \quad \mathbf{u}(\xi, t) = \mathbf{u}_0(\xi). \quad (17)$$

*Suppose that  $\mathbf{u}_0(\xi) \in C[\mathcal{M}, \mathbb{R}^M]$  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*

$$\mathbf{F}(z) \cdot \mathbf{n}(z) < 0, \quad (18)$$

*where  $\mathbf{n}(z)$  is the outer normal at  $z$ . Then the solution  $\mathbf{u}(\xi, t)$  of (17) exists for all times  $t \geq 0$  and takes its values inside  $\mathcal{R}$ .*

**Proof:** This is Proposition 4.3 in Taylor [?], Chapter 15 (p.295).  $\square$

**Lemma 3** *Let  $\mathcal{M}_t$  be a growing manifold. Suppose that the initial condition of the reaction-diffusion system (4) is in  $C[\mathcal{M}, \mathbb{R}^M]$  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

$$\mathbf{F}(z) \cdot \mathbf{n}(z) < c(t)\mathbf{n}(z) \cdot z \quad \forall t \geq 0, \quad (19)$$

where  $\mathbf{n}(z)$  is the outer normal at  $z$  and  $c(t)$  is the growth rate. Then the solution  $\mathbf{u}(t)$  of (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 1 the reaction-diffusion system (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 2 in Taylor [?] we see that it also holds for nonlinearities that depend on time, provided

$$\mathbf{G}(t, z) \cdot \mathbf{n}(z) < 0 \quad \text{for all } (z, t) \in \partial\mathcal{R} \times [0, \infty), \quad (20)$$

where  $\mathbf{n}(z)$  is the outer normal at  $z$ . Therefore, since condition (20) is equivalent to hypothesis (19), we can apply Lemma 2 to obtain that the solution  $\mathbf{u}(t)$  of (4) exists for all times  $t \geq 0$  and takes its values inside  $\mathcal{R}$ .  $\square$

Now we can conclude the proof of Theorem 4. If  $\mathcal{R} = (-1, 1)^M$  then  $\mathbf{n}(z) \cdot z = 1$  for all  $z \in \partial\mathcal{R}$ , which implies that (19) reduces to (5). Therefore, using Lemma 3 we obtain the result.  $\square$

## 7 Proof of Theorem 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 on pure eigenvalues, i.e. there is no continuum spectrum for any of both. Let  $\lambda \in \mathbb{C}$  be an eigenvalue on  $\mathcal{L}_{\mathcal{S}}$ . Then there exists a non-trivial function  $\phi : \mathcal{S} \rightarrow \mathbb{C}$  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  $\phi : \mathcal{M}_T \rightarrow \mathbb{C}$  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  $\mathcal{L}_{\mathcal{M}_T}$ .  $\square$

## 8 Discussion

### Reaction-diffusion systems on growing manifolds

We have shown here that the same results presented by Plaza *et al* [?] hold in the case of any  $n$ -dimensional manifold (in the sense of Definition 1). Moreover, the techniques we used to prove Theorem 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 4** *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*

$$0 = \lambda_1 < \lambda_2 \leq \dots \leq \lambda_k \rightarrow \infty,$$

*and they accumulate only at infinity (i.e. there 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 [12], Theorems 1.29 (p.32) and 1.31 (p.35).  $\square$

Lemma 4 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 [10] can be applied to the case of a manifold, *mutatis mutandis*. Furthermore, the statement of Gjorgjieva and Jacobsen [6] 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  $\gamma$  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 [6]. 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 [6] 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 (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 (4) towards the left in the complex plane (Theorem 5). We have also noticed that the linear stability results of Gjorgjieva and Jacobsen [6] 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 (5) in Theorem 4 is less restrictive than condition (18) in Lemma 2 because even if (18) does not hold (5) can be fulfilled. In that case, a solution of the system (17) on the fixed manifold  $\mathcal{M}$  is perhaps only a time-local solution, but as a solution of the system (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 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  $\xi$ . 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 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 [9]) and tumor growth (see Chaplain *et al* [3]). 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 (4) are globally defined (i.e. there is no blow-up). But there are more features of the exponential growth. For example, Gjorgjieva [5] showed that the system (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, (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  $\mathbf{u}_0 \neq 0$  then for any  $u_i^0 \neq 0$  we have

$$\frac{\dot{\rho}(t)}{\rho(t)} = \frac{F_i(\mathbf{u}_0)}{n u_i^0}, \quad (21)$$

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.  $\rho(t) = a e^{rt}$ , and we can calculate the growth exponent  $r > 0$  using (21).

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