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The stabilizing effect of growth on pattern formation

Mauricio Labadie *

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Abstract

Based on abundant numerical and experimental evidence, it has been conjectured that growth should have some kind of stabilizing effect on pattern formation. In this paper we answer affirmatively this question: under an isotropic regime, the growth shifts the eigenvalues of the reaction-diffusion system towards the left in 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 the growth is fast enough we show that the solutions are always global, regardless to the form of the nonlinearity.

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 classical framework for modeling pattern formation in biological and chemical systems are reaction-diffusion systems of the type

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

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* [11] 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 to study 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). Under the light of 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* [11] 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 stabilizing 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 to quote:

“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 stabilizing effect on pattern formation. In this paper we answer affirmatively this question, showing that under an isotropic regime the growth has indeed a stabilizing effect on patterns. We also show that growth enhances the possibility of a solution to be global. 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^∞), compact, connected, oriented Riemannian manifold without boundary. We will denote its parametrization

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

and its metric $(g_{ij}(\xi))$.

Definition 2 A family of manifolds $(\mathcal{M}_t)_{t \geq 0}$ is a **growing manifold** if for any $t \geq 0$ \mathcal{M}_t is a manifold with metric $(g_{ij}(\xi, t))$ and its parametrization $X(\xi, t)$ is C^∞ in both variables ξ and t .

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

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

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

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 $\rho : [0, \infty) \rightarrow [0, \infty)$ is a **growth function** if it is a C^∞ function satisfying $\rho(0) > 0$ and $\dot{\rho}(t) \geq 0$ for all $t \in [0, 1]$.

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 $\mathcal{M}_t := \rho(t)\mathcal{M}$, meaning that if $X(\xi, t)$ is the parametrization of \mathcal{M}_t then there is a parametrization \tilde{X} of \mathcal{M} such that $X(\xi, t) = \rho(t)\tilde{X}(\xi)$.

There is an important remark we would like the reader to bear in mind. 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 the 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

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

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.

Note 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* [11]:

$$\partial_t \mathbf{u} = \mathcal{D} \Delta_{\mathcal{S}_t} \mathbf{u} - \partial_t [\log(h_1 h_2)] \mathbf{u} + \mathbf{F}(\mathbf{u}),$$

$$\partial_t \mathbf{u} = \frac{\mathcal{D}}{\rho^2(t)} \Delta_{\mathcal{S}} \mathbf{u} - 2 \frac{\dot{\rho}(t)}{\rho(t)} \mathbf{u} + \mathbf{F}(\mathbf{u}).$$

2.2 Properties of solutions: existence, uniqueness, regularity

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

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

Furthermore, under certain conditions depending on the initial condition \mathbf{u}_0 and the nonlinearity $\mathbf{F}(\mathbf{u})$, the local unique solution $\mathbf{u}(t)$ is in fact globally defined.

Theorem 4 *Let $(\mathcal{M}_t)_{t \geq 0}$ be a growing manifold. Suppose that the initial condition \mathbf{u}_0 of the reaction-diffusion system (4) is 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*

$$\mathbf{F}(z) \cdot \mathbf{n}(z) < c(t) \tag{5}$$

where $\mathbf{n}(z)$ is the outer normal at z and $c(t)$ is the **growth rate**

$$c(t) := n \frac{\dot{\rho}(t)}{\rho(t)}, \tag{6}$$

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, if

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

then there is a global bounded solution of the system (4) without any hypothesis on the nonlinearity $\mathbf{F}(\mathbf{u})$.

For example, if the growth factor is exponential, i.e. $\rho(t) = e^{rt}$, and $r > 0$ is big enough to satisfy

$$r > \frac{1}{n} \sup\{\|\mathbf{F}(z)\| : z \in \partial\mathcal{R}\}$$

then the solution is globally defined.

2.3 The stabilizing effect of growth

Under isotropic regimes, growth has a stabilizing effect on pattern formation. More precisely, we have the following theorem.

Theorem 5 *Let $(\mathcal{M}_t)_{t \geq 0}$ be an isotropic growing manifold with growth function $\rho(t)$, and fix any $T > 0$. Then $\lambda(T)$ is an eigenvalue of the reaction-diffusion system on the fixed manifold \mathcal{M}_T , i.e.*

$$\partial_t \mathbf{u} = \frac{\mathcal{D}}{\rho^2(T)} \Delta_{\mathcal{M}} \mathbf{u} + \mathbf{F}(\mathbf{u})$$

if and only if $\lambda(T) - c(T)$ is an eigenvalue on the growing manifold $(\mathcal{M}_t)_{0 \leq t \leq T}$ at time T , i.e.

$$\partial_t \mathbf{u} = \frac{\mathcal{D}}{\rho^2(T)} \Delta_{\mathcal{M}} \mathbf{u} - c(T) \mathbf{u} + \mathbf{F}(\mathbf{u}).$$

Theorem 5 says that the growth shifts the eigenvalues to the left in the complex plane, which can be interpreted as a stabilizing effect. Indeed, let $\lambda(T)$ be the eigenvalue of the linearized system on the fixed manifold with biggest real part. If we define $\gamma(T) := \lambda(T) - c(T)$ then:

- $\lambda(T)$ is an eigenvalue of the reaction-diffusion system without growth,
- $\gamma(T)$ is an eigenvalue of the reaction-diffusion system with growth,
- $\gamma(T) \leq \lambda(T)$, and
- $\gamma(T) < \lambda(T)$ if and only if $c(T) > 0$.

Therefore, even if $\lambda(T) > 0$ we can possibly have that $\gamma(T) < 0$, which implies that the linearized system on the fixed manifold is unstable, whereas the linearized system on the growing manifold is stable.

It is important to remark that, as far as we know, Theorem 5 is the first analytic proof of the stabilizing effect of growth on pattern formation.

3 Proof of Theorem 1

We will divide the proof in three parts.

3.1 Parametrization 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^∞ 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 parameterization 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 $v = (v^1, \dots, v^n) \neq 0$.

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 parameterization 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 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.

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

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

$$\frac{d}{dt} \iint_{\Omega(t)} \phi dV = D \int_{\partial\Omega(t)} \langle \nabla\phi|_{\partial\Omega(t)}, \mathbf{n} \rangle dS. \quad (8)$$

For the sake of clarity let us recall each term in (8).

- (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 (8). 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 (8) 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

$$\iint_{\mathcal{M}} d\omega = \int_{\partial\mathcal{M}} \omega, \quad (9)$$

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 (9) becomes

$$\iint_{\Omega(t)} \operatorname{div}(F) dV = \int_{\partial\Omega(t)} \langle F|_{\partial\Omega(t)}, \mathbf{n} \rangle dS. \quad (10)$$

In the light of (10) we have that

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

Putting all two pieces together in (8) we obtain

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

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:

$$\partial_t \phi = D \operatorname{div}(\nabla \phi) - \partial_t[\log \sqrt{g}] \phi, \quad (11)$$

where the operator $\operatorname{div}(\nabla \phi)$ is the *Laplace-Beltrami operator* $\Delta_{\mathcal{M}_t}$ we introduced in Definition 3.

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 (7) takes the form

$$\frac{d}{dt} \iint_{\Omega(t)} \mathbf{u} dS = - \int_{\partial\Omega(t)} \langle J, \mathbf{n} \rangle dS + \iint_{\Omega(t)} \mathbf{F}(\mathbf{u}) dS. \quad (12)$$

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 (12) takes the form

$$\frac{d}{dt} \iint_{\Omega(t)} \mathbf{u} dS = \mathcal{D} \int_{\partial\Omega(t)} \langle \nabla \mathbf{u}|_{\partial\Omega(t)}, \mathbf{n} \rangle dS + \iint_{\Omega(t)} \mathbf{F}(\mathbf{u}) dS. \quad (13)$$

Notice that in (13) 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 (13) 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:

$$\begin{aligned} g_{ij}(\xi, t) &= \rho^2(t) \tilde{g}_{ij}(\xi), \\ g^{ij}(\xi, t) &= \frac{1}{\rho^2(t)} \tilde{g}^{ij}(\xi), \\ \sqrt{g} &= \rho^n \sqrt{\tilde{g}}, \\ \Delta_{\mathcal{M}_t} &= \frac{1}{\rho^2(t)} \Delta_{\mathcal{M}}. \end{aligned} \tag{14}$$

If we substitute the relations (14) 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

$$\partial_t \mathbf{u} = L\mathbf{u} + \mathbf{G}(t, \mathbf{u}), \quad \mathbf{u}(0) = \mathbf{u}_0, \tag{15}$$

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 $\mathbf{u} : \mathcal{M} \rightarrow \mathbb{R}^M$.
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^∞ , 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 (15) 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

$$s(t) := \int_0^t \frac{dr}{\rho^2(r)}. \quad (16)$$

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 (15). \square

Now we have all the elements to prove Theorem 2. By the Lemma 1 the problem (4) is equivalent to (15). Moreover, (15) can be expressed in the integral form

$$\mathbf{u}(t) = e^{tL} \mathbf{u}_0 + \int_0^t e^{(t-s)L} \mathbf{G}(s, \mathbf{u}(s)) ds. \quad (17)$$

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{Z} 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 $K_1 C T \leq \alpha/2$. 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 Ψ 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 (17), or equivalently a unique solution of (15).

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 (15) written in its integral form (17). 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 [13], 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^∞ 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^∞ 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*

$$\partial_t \mathbf{u} = \mathcal{D}\Delta_{\mathcal{M}}\mathbf{u} + \mathbf{F}(\mathbf{u}), \quad \mathbf{u}(\xi, t) = \mathbf{u}_0(\xi). \quad (18)$$

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

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

where $\mathbf{n}(z)$ is the outer normal at z . Then the solution $\mathbf{u}(\xi, t)$ of (18) exists for all times $t \geq 0$ and takes its values inside \mathcal{R} .

Proof: This is Proposition 4.3 in Taylor [13], 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

$$\mathbf{F}(z) \cdot \mathbf{n}(z) < c(t)\mathbf{n}(z) \cdot z, \quad (20)$$

where $\mathbf{n}(z)$ is the outer normal at z and $c(t)$ is the growth rate (6). 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 [13] we see that it also holds for nonlinearities that depend on time, provided

$$\mathbf{G}(t, z) \cdot \mathbf{n}(z) < 0 \quad \text{for all } (z, t) \in \partial\mathcal{R} \times [0, \infty), \quad (21)$$

where $\mathbf{n}(z)$ is the outer normal at z . Therefore, since condition (21) is equivalent to hypothesis (20), 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 (20) reduces to (5). Therefore, using Lemma 3 we obtain the result. \square

7 Proof of Theorem 5

Let \mathcal{M} be a fixed manifold, and choose a final time $T > 0$. From Lemma 5 in Section 8 it follows that any function $\mathbf{u} \in [\mathrm{L}^2(\mathcal{M})]^M$ can be expanded as a series in terms of the eigenfunctions of the Laplace-Beltrami operator, i.e.

$$\mathbf{u} = \sum_{j=0}^{\infty} \mathbf{u}_j \phi_j, \quad (22)$$

where $\mathbf{u}_j \in \mathbb{R}^M$ is constant.

With the change of variables

$$\mathcal{D}(T) := \frac{\mathcal{D}}{\rho^2(T)}, \quad c(T) := n \frac{\dot{\rho}(T)}{\rho(T)}$$

we can equation (4) in the more convenient form

$$\partial_t \mathbf{u} = \mathcal{D}(T) \Delta_{\mathcal{M}} \mathbf{u} - c(T) \mathbf{u} + \mathbf{F}(\mathbf{u}). \quad (23)$$

We will assume that $\mathbf{F}(0) = 0$, so that $\mathbf{u} \equiv 0$ is a solution of (23). The linearization of (23) at $\mathbf{u} \equiv 0$ is

$$\frac{\partial \mathbf{u}}{\partial t} = A(T) \mathbf{u} - c(T) \mathbf{u}, \quad A(T) := \mathcal{D}(T) \Delta_{\mathcal{M}} + d\mathbf{F}(0). \quad (24)$$

Suppose that $\mathbf{u}(\xi, t)$ is a solution of (24) and that the coefficients of its series expansion (22) depend on time, i.e. $\mathbf{u}_j = \mathbf{u}_j(t)$. Under these hypotheses we obtain an infinite ODE system

$$\frac{d\mathbf{u}_j}{dt} = B_j(T) \mathbf{u}_j - c(T) \mathbf{u}_j, \quad j \in \mathbb{N}, \quad (25)$$

where $B_j(T)$ is the projection of the linear operator $A(T)$ to the j -th mode, i.e. the $M \times M$ matrix

$$B_j(T) := -\mu_j \mathcal{D}(T) + d\mathbf{F}(0).$$

The spectra of $B_j(T)$ and $B_j(T) - c(T)I$ are simply related, as the next Lemma shows.

Lemma 4 *$\lambda(T)$ is an eigenvalue of the matrix $B_j(T)$ if and only if $\lambda(T) - c(T)$ is an eigenvalue of the matrix $B_j(T) - c(T)I$.*

Proof: Let $P(T)$ be the matrix that renders $B_j(T)$ in its Jordan canonical form $\Lambda_j(T)$, i.e. $\Lambda_j(T) = P(T)^{-1} B_j(T) P(T)$. Then

$$\begin{aligned} P(T)^{-1} [B_j(T) - c(T)I] P(T) &= P(T)^{-1} B_j(T) P(T) - P(T)^{-1} [c(T)I] P(T) \\ &= \Lambda_j(T) - c(T)I. \end{aligned}$$

Sinceny block of $\Lambda_j(T)$ has the form

$$\begin{bmatrix} \lambda(T) & & & & \\ 1 & \lambda(T) & & & \\ & & \ddots & & \\ & & & \ddots & \\ & & & & 1 & \lambda(T) \end{bmatrix}$$

Then the corresponding block of $\Lambda_j(T) - c(T)I$ has the form

$$\begin{bmatrix} \lambda(T) - c(T) & & & & \\ 1 & \lambda(T) - c(T) & & & \\ & & \ddots & & \\ & & & \ddots & \\ & & & & 1 & \lambda(T) - c(T) \end{bmatrix},$$

and the Lemma follows. \square

Now we can conclude the proof of Theorem 5. Since the eigenfunctions $(\phi_j)_{j \in \mathbb{N}}$ of the Laplace-Beltrami operator form a basis of $L^2(\mathcal{M})$, it follows that $\lambda(T)$ is an eigenvalue of the operator $A(T)$ if and only if $\lambda(T)$ is an eigenvalue of the matrix $B_j(T)$ for some $j \in \mathbb{N}$. Moreover, this argument also applies to $A(T) - c(T)I$ and $B_j(T) - c(T)I$, which implies that we can use Lemma 4 to get that $\lambda(T)$ is an eigenvalue of the operator $A(T)$ if and only if $\lambda(T) - c(T)$ is an eigenvalue of the operator $A(T) - c(T)I$. \square

8 Discussion

Reaction-diffusion systems on growing manifolds

We have shown here that the same results presented by Plaza *et al* [11] 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 parameterization. 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 5 *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 5 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:

1. The manifold \mathcal{M} is 2-dimensional.
2. We have only two morphogens, whose diffusion coefficients are different (say 1 and $d > 1$).
3. The nonlinearity $\mathbf{F}(\mathbf{u})$ depends on a real parameter γ in the form

$$\mathbf{F}(\gamma, \mathbf{u}) = \gamma \begin{bmatrix} f(u, v) \\ g(u, v) \end{bmatrix}$$

4. 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 the 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 globalizing effect of growth on pattern formation

The growth has a “globalizing effect” because it enhances the possibility of global existence of solutions. Indeed, condition (5) in Theorem 4 is less restrictive than condition (19) in Lemma 2 because even if (19) does not hold (5) can be fulfilled. In that case, a solution of the system (18) on the fixed manifold \mathcal{M} is perhaps only a local solution (i.e. it can only exist up to a finite time $T > 0$), but as a solution of the system (4) on the growing manifold $(\mathcal{M}_t)_{t \geq 0}$ it exists globally (i.e. for all times $t \geq 0$).

Moreover, if $c(t)$ is large enough then we have global existence of solutions of the system (4) without any hypothesis on the nonlinearity $\mathbf{F}(\mathbf{u})$. This is particularly true for exponential growth factors $\rho(t) = e^{rt}$ with $r > 0$ big enough.

The stabilizing effect of growth on pattern formation

As it was shown in Theorem 5, the 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 $(\mathcal{M}_t)_{0 \leq t \leq T}$ than on the fixed manifold \mathcal{M}_T , which can be interpreted as a gain of stability. Of course, this was only showed for isotropic and exogenous growth conditions, and it would be interesting to see if this property holds for more general growth regimes.

From Theorem 5 we can also infer that growth is a regulatory mechanism for stability, in the sense that it 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 pattern formation, 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

$$\rho(t) = e^{rt}$$

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 regardless of the nonlinearity $\mathbf{F}(\mathbf{u})$, 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

$$\frac{\dot{\rho}(t)}{\rho(t)} = \frac{F_i(\mathbf{u}_0)}{n u_i^0}, \quad (26)$$

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 rate is completely determined by the nonlinearity. In other words, whenever we find a constant equilibrium the growth factor is necessarily exponential, i.e. $\rho(t) = Ae^{rt}$ ($A > 0$ constant), and we can calculate the growth exponent $r > 0$ using (26).

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