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Existence and uniqueness of solutions to the GRID macroscopic growth equation

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ABSTRACT

In this paper we prove the existence and uniqueness of solutions to the initial value problems associated with the GRID integro-differential equation describing macroscopic growth of an organism. We consider the general form of the macroscopic growth operator Φ and study the set of conditions on Φ that are sufficient to guarantee existence and uniqueness of solutions in $\Re^n, n = 1, 2, 3$.

1. Background

The mathematical and statistical modeling and analysis of biological growth using images collected over time are important for the understanding of normal and abnormal development. In computational anatomy [2], changes in the shape of a growing anatomical structure have been modeled by means of diffeomorphic transformations on the background coordinate space. These transformations, generated by continuum mechanics equations of motion, are usually constrained to be consistent with the material properties (elastic, visco-elastic, viscous) of the anatomy under study (e.g., the brain).

From a biological perspective, it has now been realized [1] that growth is regulated not only by material constants but also by genetic control. In an effort to accommodate the genetic control of growth, Grenander introduced the Growth as Random Iterated Diffeomorphisms (GRID) model [3,4]. The GRID model represents an modification of growth models employed in the field of computational anatomy, acknowledging that the diffeomorphic flows responsible for morphogenesis are dependent on genetic controls within an organism. As such, the GRID model is *the first genetically-based mathematical model for biological growth.*

More recently, the GRID model has been further developed by Portman [5] into a universal tool for the prediction and analysis of growth patterns at microscopic (cellular) and macroscopic (multicellular) levels. In the GRID model, the genetic control is expressed by a probability law which governs spatial–temporal patterns of cell decisions (cell division/death, enlargement) in such a way that the image of an initial organism becomes continuously transformed into the image of a grown organism. This view of a growth-related transformation is consistent with the fundamental biological principles of growth (mitosis, local arrest of growth, cell enlargement).

To generate such genetically-controlled flows that underlie shape changes of a growing organism seen in images, Grenander [3] proposed a deterministic integro-differential equation called the "thermodynamic limit" equation. We refer to it as the "GRID macroscopic growth law" since it approximates a growth pattern on a coarse time scale. In [5] it was shown that the macroscopic growth law is the continuum mechanics equation of motion with the velocity resulting from an infinite number of cell decisions at each time instant. The solution to this equation is a diffeomorphic flow which is dependent

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on local GRID variables such as the Poisson intensity of cell decisions and the relative rates of expansion/contraction. These GRID variables mathematically represent the source of the growth-related deformation in the macroscopic equation. In the case that this source is known, the GRID macroscopic growth equation predicts a typical growth pattern in the average sense. In the case that the source is unknown, the estimation/inference of the GRID parameters from image data constitutes an inverse problem. In [5], the estimation of GRID parameters was formulated as an optimal control problem: The estimated GRID variables are optimal controls of the macroscopic flow of the image of an initial organism into the image of a grown organism.

Implementation of the GRID macroscopic growth equation is a distinguishing feature of a novel algorithm for the direct image inference of biological growth properties developed in [6] and demonstrated on an example of larval development of the Drosophila wing disc [7]. It allows estimation of the intensity of elementary biological events (e.g., cell divisions) and the growth-induced transformation from micrographs of gene expression patterns elaborated during the development of an organism. It naturally leads to the field of the genetics of geometry [10], the study of links between gene expression patterns and the generation of shape in embryos due to a growth process. The GRID macroscopic growth equation is important in applications to image analysis of growth as it unveils a new drama of biological development hidden in images collected over time and expressed in terms of spatial–temporal intensity of cell divisions, biologically-meaningful deformation vector fields and displacement-magnitude scalar fields [7].

Another goal of the macroscopic growth equation is a mathematical representation of the basic law of biological shape generation induced by growth. Can we claim that this equation is a reasonable approximation to the law of a biological shape growth at a macroscopic level? To address this question we have studied its consistency with the principle of biological invariance [7]. Namely, it has been shown that the inferred GRID parameters are invariant with respect to the Euclidean group of transformations of the Darcyan coordinate system [8] of the organism. A rigorous derivation of the macroscopic growth equation using the properties of microscopic growth flows and the Law of Large Numbers [5] has revealed that the microscopic random "states" of the growth pattern (deformation fields resulting from single random cell decisions) are related to its macroscopic behaviour. The macroscopic growth pattern evolves in time as a collective effect of a large number of microscopic deformations at each time instant. This is consistent with the fact that any single elementary biological event has a small deformative effect, but a multitude of events results in visible (or macroscopic) growth of the multicellular organism.

In this paper we address the fundamental question of existence and uniqueness of solutions to the GRID macroscopic growth equation, thus validating this equation as the macroscopic law of a biological shape growth. First, we define the GRID macroscopic growth operator Φ based on the general model of the elementary deformation field and formulate the set of sufficient conditions on Φ. Second, we show existence of the unique diffeomorphic flow representing the typical (average) macroscopic growth pattern over a finite time period of growth.

2. Preliminaries

Consider an arbitrary growing organism occupying a compact region $\Omega(t)$ in $\Re^2$ at any time $t \in [0,T]$. In the GRID model, a point $X = (x_1, x_2) \in \Omega(t)$ in the organism is expressed in terms of the curvilinear "Darcyan" coordinate system [3,8], i.e.,

$$X(\xi, t) = (x_1(\xi_1, \xi_2, t), x_2(\xi_1, \xi_2, t)) \in \Omega(t), \tag{1}$$

where

$$\Xi = \{(\xi_1, \xi_2) : \ 0 < \xi_1 \leqslant 1, \ 0 < \xi_2 \leqslant 2\pi\} \tag{2}$$

defines the Darcyan coordinate space. Theoretically, the x_i and ξ_j variables are related by a diffeomorphic mapping ϕ, i.e.,

$$\phi : \ (\xi_1, \xi_2) \in \Xi \subset \Re^2 \leftrightarrow (x_1, x_2) \in \Omega(0) \subset \Re^2. \tag{3}$$

Such a map produces a natural coordinate system in the organism's domain Ω in the form of a continuum grid with radial ξ_1 and angular ξ_2 coordinate curves that conforms to the outer boundary of Ω.

The practical construction of an appropriate Darcyan coordinate system from an initial image ($t = 0$) represents an interesting as well as challenging computational problem [3,5]. An example of the Darcyan coordinate system produced inside a brain slice is shown in Fig. 1 below.

Mathematically, the Darcyan coordinate system is a Lagrangian coordinate system. The Lagrangian coordinates $\xi = (\xi_1, \xi_2)$ follow structural changes of the organism as it develops in time. Fig. 2 below illustrates discrete versions of the Darcyan space Ξ and the corresponding absolute space $X(\xi)$ of the brain slice Ω as rectangular and curvilinear grids. Observe from the Fig. 2 that points in the absolute space are given by $x_{ij} = (x_{1_{ij}}, x_{2_{ij}})$, where

$$x_{1_{ij}} = x_1(i,j), \quad 0 \leqslant i \leqslant M,$$
$$x_{2_{ij}} = x_2(i,j), \quad 0 \leqslant j \leqslant N$$

and j refers to the angle $j\frac{2\pi}{N}$.

In the GRID model, changes in the shape of an organism are produced by local expansions or contractions centered at particular *seeds* in the organism. Each local expansion/contraction represents a genetically-induced single cell decision,

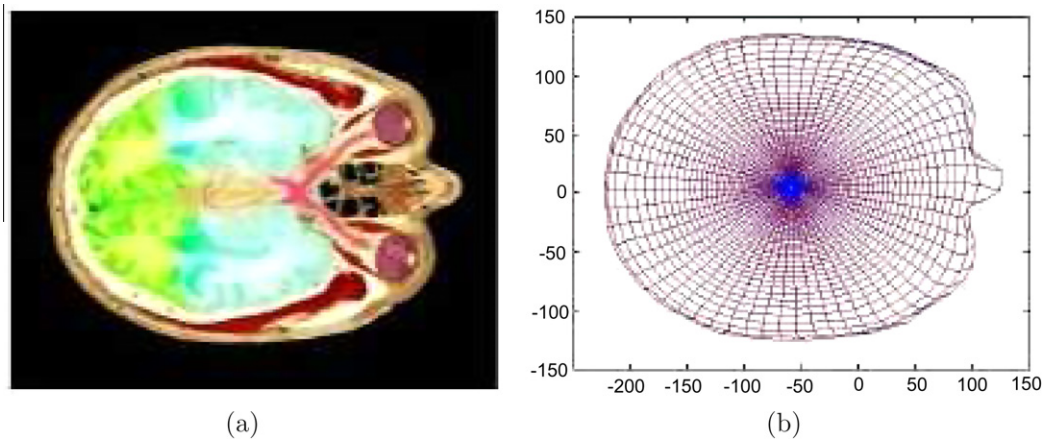

Fig. 1. (a) An MRI image of a brain slice Ω and (b) its Darcyan coordinate system $X(\xi)$.

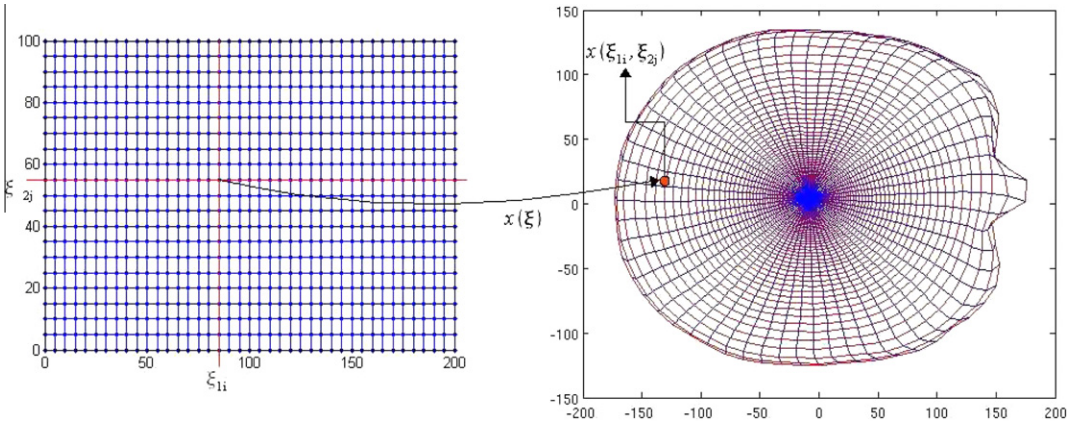

Fig. 2. Discrete Darcyan space $\Xi = \{(\xi_{1_i}, \xi_{2_j}) : i = 1, 2, \ldots, M;\ j = 1, 2, \ldots, N\}$ and the corresponding absolute coordinate space of a 2D brain slice $X(\xi) = \{x_1(\xi_{1_i}, \xi_{2_j}), x_2(\xi_{1_i}, \xi_{2_j}) : i = 1, 2, \ldots, M; j = 1, 2, \ldots, N\}$.

e.g. growth/death, at the seed. In what follows, the Darcyan coordinate of a seed will be denoted as ξ_{seed} so that its position in the organism is $x(\xi_{seed}, t) \in \Omega(t)$.

The displacement of any point $x(\xi, t) \in \Omega(t)$ in the organism due to the expansion/contraction at $x(\xi_{seed}, t)$ is assumed to have the following form:

$$\theta^{\xi_{seed}}(x(\xi, t) - x(\xi_{seed}, t)) = k(\xi_{seed}, t)\Psi(|x(\xi, t) - x(\xi_{seed}, t)|)[x(\xi, t) - x(\xi_{seed}, t)]. \tag{4}$$

Here, $|x(\xi, t) - x(\xi_{seed}, t)|$ denotes the Euclidean distance between the two points. Note that the $\theta^{\xi_{seed}}$-map acts on vectors in the relative coordinate system with origin at the activated seed $x(\xi_{seed}, t)$. Any displacement away from $x(\xi_{seed}, t)$ occurs in the radial direction. (This simplification may be removed.) Here,

(1) $k(\xi_{seed}, t)$ is the rate of relative expansion/contraction: $k(\xi_{seed}, t) < 0$ implies contraction of the active gene area around the seed $x(\xi_{seed}, t)$ and $k(\xi_{seed}, t) > 0$ implies expansion or localized growth [5],
(2) $\Psi(|x(\xi, t) - x(\xi_{seed}, t)|)$ models the decreasing influence of the expansion/contraction as we move away from the seed of activation $x(\xi_{seed}, t)$. Along with the assumption that $\Psi(\cdot)$ maps $[0, \infty)$ onto itself diffeomorphically, we assume that
   (a) $\Psi(0) = 1$ and
   (b) $\Psi(r) \to 0$ as $r \to \infty$.

The requirement that the $\theta^{\xi_{seed}}$-map be diffeomorphic arises from the topology-reserving nature of biological growth: as the organism grows and its internal structure and shape change, it can not overlap with itself.

From the definition of the $\theta^{\xi_{seed}}$-map it is evident that $\Psi(r)$ plays a role of the distance scaling factor. As the distance $r = |x(\xi, t) - x(\xi_{seed}, t)|$ from $x(\xi_{seed}, t)$ increases, the deformation caused by an elementary cell event at $x(\xi_{seed}, t)$ decreases. In order to model the decay of deformations as we move away from seed, Grenander [3] proposed the Gaussian function, i.e.,

$$\Psi(r) = \exp\left\{-\frac{r^2}{s(x(\xi_{seed},t))^2}\right\}. \tag{5}$$

Here, the parameter $s(x(\xi_{seed},t))$ represents the *radius of influence* of the local deformation. This is an attempt to mathematically model the decay in an elastic or viscoelastic medium. Other functions are possible, e.g.,

$$\Psi(r) = \left(\frac{r}{s(x(\xi_{seed},t))}\right)\exp\left\{-\frac{r}{s(x(\xi_{seed},t))}\right\}.$$

The determination of functions $\Psi(r)$ that are consistent with continuum mechanical properties of elastic solids remains an open problem for future research. In this study, the Gaussian form in (5) has been employed. It has been shown [4] that the range of k-function, $-1 < k(\xi_{seed},t) < 2.2408$, ensures that the elementary deformation map $\theta^{\xi_{seed}}$ is one-to-one.

Examples of the effects of elementary $\theta^{\xi_{seed}}$ diffeomorphisms are illustrated in Figs. 3 and 4. In both Figures, the initial state $\Omega(0)$ of the organism was chosen to be circularly symmetric. Because of this symmetry, the initial Darcyan grid for both Figures can be represented by a 2D polar coordinate system concentric wih the organism's boundary, as shown in Fig. 3(a).

In Fig. 3(a), there is one seed of activation, $x(\xi_{seed})$, identified by the star. This seed represents an area of growth due to either cell division or cell enlargement. As such the seed map $\theta^{\xi_{seed}}$, centered at $x(\xi_{seed})$, is radially expansive about this point. In Fig. 3(b) is shown the organism $\Omega(t)$ at some time $t > 0$ along with its corresponding deformed Darcyan coordinate system. Note how the deformation of the Darcyan system reflects the localized growth as prescribed by the $\theta^{\xi_{seed}}$-map.

In Fig. 4 is shown the effect of local arrest of growth (e.g. cell death) as modelled by two seeds with local contractive seed maps $\theta^{\xi_{seed}}$, identified with stars. The combined effect of these contractions actually causes the organism's boundary to cave in.

Very briefly, the GRID macroscopic growth equation is obtained by averaging over all elementary displacement fields. (The details of the rigorous derivation are to be found in [5]). This equation approximates observed growth in instantaneous time as a result of an infinite number of cell decisions that occur randomly and independently in the growing organism's domain. By the Law of Large Numbers, the growth increment per unit time is the average value of the displacement field taken over all seed contributions,

$$\frac{\partial x(\xi,t)}{\partial t} = \lambda_t \int_{\xi_{seed}\in\Xi} \theta^{\xi_{seed}}(x(\xi,t) - x(\xi_{seed},t))p_x(x(\xi_{seed},t))d\xi_{seed}, \tag{6}$$

subject to the initial condition $x(\xi,t_0) = x_0(\xi)$. Here,

(i) Ξ is the Darcyan space of biological coordinates or seeds $\xi_{seed} = (\xi_{1seed}, \xi_{2seed})$,
(ii) $\Lambda(\xi_{seed},t) = \lambda_t \cdot p_x(x(\xi_{seed},t))$ is the Poisson intensity of seed placements in time–space $[t_0,T)\times\Re^2$ [9],
(iii) $x(\xi_{seed},t)$ are the positions of seeds in the organism, i.e., in the absolute space $\Omega(t)$. They are activated randomly and independently from one another and have a range of influence $s(x(\xi_{seed},t))$. In this study we have simply assumed that

$$s(x(\xi_{seed},t)) = \left|\frac{\partial x}{\partial \xi}\right|,$$

where the expression on the right hand side denotes the Jacobian of the transformation $x(t) = x(\xi,t)$.

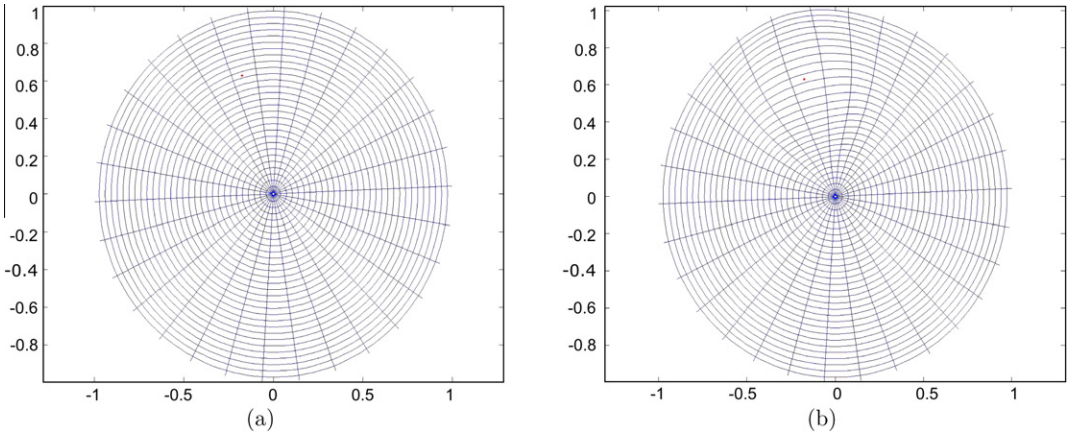

Fig. 3. (a) Darcyan coordinate system of an initially circular organism $\Omega(0)$ with a growth seed $x(\xi_{seed})$ (local expansion) denoted by a star. (b) The organism $\Omega(t)$ at some time $t > 0$ with deformed Darcyan coordinate system.

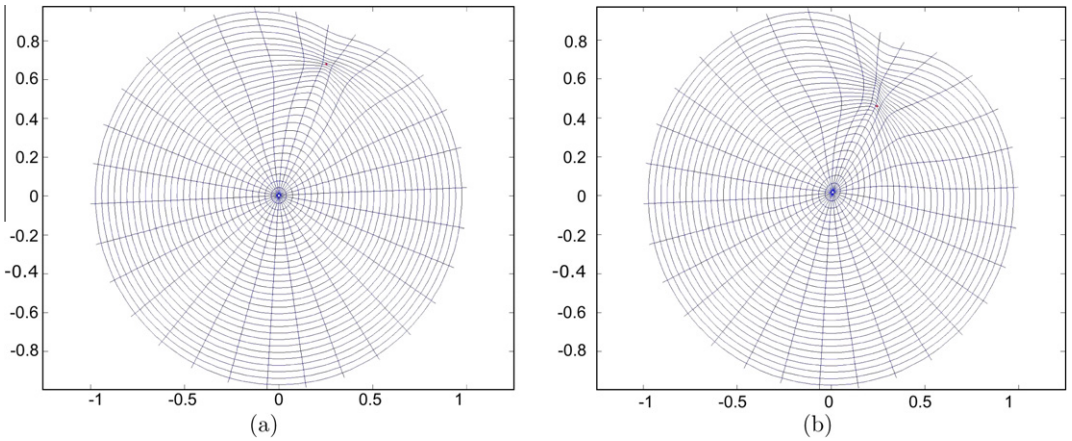

Fig. 4. Snapshots of an evolving organism undergoing local tissue decay at ages (a) $t = 1$, (b) $t = 2$. Active gene sites or seeds $x(\xi_{seed}, t)$ are indicated by stars.

3. Formulation of the initial value problem (IVP)

Consider, for simplicity, growth of a two-dimensional organism $\Omega(t)$ whose domain occupies a compact region in $\Re^2$ over a finite time interval $[0, T]$. The growing domain is represented by the interior Darcyan coordinate system $X(\xi, t)$. Initially, at time $t = 0$, the organism is comprised of the continuum of seeds $x_0(\xi_1, \xi_2)$

$$X(\xi, 0) = (x_{01}(\xi_1, \xi_2), x_{02}(\xi_1, \xi_2)) \in \Omega(0). \tag{7}$$

From the discussion in the previous section, the evolution of the organism, given the above initial condition, defines an initial value problem having the following form:

$$\frac{\partial x(\xi, t)}{\partial t} = \Phi(x(\xi, t), t), \quad x(\xi, 0) = x_0(\xi). \tag{8}$$

Here, since we are working in $\Re^2$, the nonlinear macroscopic growth operator Φ has the following vector form,

$$\Phi(x(\xi, t), t) = \begin{pmatrix} \Phi_1(x(\xi, t), t) \\ \Phi_2(x(\xi, t), t) \end{pmatrix}, \tag{9}$$

where

$$\Phi_i(x(\xi, t), t) = \lambda_t \int_{v \in \Xi} \theta^{seed}(x_i(\xi, t) - x_i(v, t)) p_x(x(v, t)) dv, \quad i = 1, 2. \tag{10}$$

The IVP formulation (8) allows the application of the classical theory of ordinary differential equations to establish existence and uniqueness of the macroscopic growth flow $x(\xi, t)$.

Here we mention that Eq. (8) may be viewed as an evolution equation involving a continuous distribution of "seeds" that are interacting with each other according to "forces" that eventually decay as we move away from their sources. As time t increases, the positions of these seeds changes, representing the morphological change of the organism.

As mentioned above, $\Xi = [0, 1] \times [0, 2\pi]$ is the Darcyan space of biological coordinates. At each time $t > 0, X(\xi, t)$ is a continuous and one-to-one mapping of Ξ-space, including the boundaries, to the physical space of the organism's domain $\Omega(t)$. We do not constrain $X(\xi, t)$ to be diffeomorphic since in applications a complex geometry of three-dimensional differentiable manifolds (a human brain, for instance) is represented by connected parametric coordinate systems. This means that parametric coordinate curves are not necessarily smooth at the points of junction of neighbouring coordinate systems.

Let Y be a space of two-dimensional vector-functions continuous with respect to ξ coordinates and to time coordinate t. That is,

$$Y = C^0(\Xi \times [0, T]). \tag{11}$$

With the following norm on Y,

$$\|x\|_Y = \sup_{0 \leqslant t \leqslant T} \left\{ \max_{i \in \{1,2\}} \left\{ \sup_{\xi \in \Xi} |x_i| \right\} \right\}, \tag{12}$$

Y is a Banach space. Then the diameter of Y is given by

$$\mathrm{diam}(Y) = \sup_{x, y \in Y} \{\|x - y\|_Y\}. \tag{13}$$

The domain of the Φ-operator is

$$\mathrm{Dom}(\Phi) = Y \times [0,T]. \tag{14}$$

4. Existence and uniqueness of solutions to the initial value problem

Theorem 1. *Let Y be the Banach space Y (11) with the norm (12). Consider the IVP (8) for the two-dimensional GRID macroscopic growth equation, where $\Phi(\cdot,\cdot)$ is the nonlinear operator defined in (9) and (10). Further assume the following:*

(1) *λ_t is a continuous function of time t,*
(2) *$\Psi : [0,\infty) \to [0,\infty)$ is diffeomorphic, having the form $\Psi = \psi(r)$ where r is the Euclidean distance between the seeds in the organism $\Omega(t)$ (defined earlier) and*

$$\psi(0) = 1, \tag{15}$$
$$\psi(r) \to 0 \text{ as } r \to \infty. \tag{16}$$

(3) *$p_x(x) \in C^1(Y)$, where $x = x(\xi,t) \in \Omega(t)$, the domain of the organism at time t,*
(4) *$k(\xi,t) \in C^1(\Xi) \times C^0([0,T])$ with the range $m_1 \leqslant k(\xi,t) \leqslant m_2$ that ensures diffeomorphic property of the elementary transformation $\theta^{\xi_{seed}}$ in (4).*

Then for a $T > 0$ sufficiently small there exists a unique solution to the IVP (8).

Proof. Since $\theta^{\xi_{seed}}(x(\xi,t) - x(v,t))$ and $p_x(x(v,t))$ are integrable on $\Xi \times [0,T]$, $\Phi(x(\xi,t),t)$ is well-defined. Integrating the differential Eq. (8) with respect to t we obtain the following integral equation:

$$x(\xi,t) = x_0(\xi) + \int_0^t \Phi(x(\xi,s),s)\,ds \quad \text{for } 0 \leqslant t \leqslant T. \tag{17}$$

Therefore, if $x(\xi,t)$ is a solution to the IVP (8), then it is also a solution to the integral Eq. (17) on the Banach space Y. In other words, $x(\xi,t)$ is the fixed point of the following Picard integral operator $M : Y \to Y$,

$$M(x(\xi,t),t) = x_0(\xi) + \int_0^t \Phi(x(\xi,s),s)\,ds. \tag{18}$$

As in the classical case, the existence and uniqueness of solutions to (17) will be established via the contractive property of the mapping M. To ensure that M is a strict contraction on $Y \times [0,T]$ it suffices to show that Φ given by (10) is a Lipschitz continuous operator on the Banach space Y. We carry out the proof in the following three steps:

(1) Compute the Gateaux derivative $D\Phi$ of the operator Φ,
(2) Show that $D\Phi$ is linear and bounded,
(3) Show Lipschitz-continuity of Φ-operator in x.

The third step completes the proof. □

Step 1. Fixing the time $t \geqslant 0$, we calculate the Gateaux derivative of $\Phi(x(\xi,t),t) = \Phi(x_1,x_2)$ in the direction $[\eta_1,\eta_2]^T$ as follows:

$$D\Phi\begin{bmatrix}\eta_1\\ \eta_2\end{bmatrix} = \frac{\partial}{\partial\varepsilon}\begin{bmatrix}\Phi_1(x_1+\varepsilon\eta_1,x_2)+\Phi_1(x_1,x_2+\varepsilon\eta_2)\\ \Phi_2(x_1+\varepsilon\eta_1,x_2)+\Phi_2(x_1,x_2+\varepsilon\eta_2)\end{bmatrix}_{\varepsilon=0}. \tag{19}$$

Recalling that

$$\Phi_i(x_1,x_2) = \lambda_t \int_{v\in\Xi} k(v,t)(x_i(\xi,t) - x_i(v,t))\psi(|x(\xi,t) - x(v,t)|^2)p_x(x(v,t))\,dv, \quad i = 1,2, \tag{20}$$

we find that

$$\begin{aligned}\frac{\partial}{\partial\varepsilon}\Phi_1(x_1+\varepsilon\eta_1,x_2)|_{\varepsilon=0} = {}& \lambda_t \int_{v\in\Xi} k(v,t)[\eta_1(\xi,t) - \eta_1(v,t)]\psi(|x(\xi,t) - x(v,t)|^2)p_x(x(v,t))dv + 2\lambda_t \int_{v\in\Xi} k(v,t)[x_1(\xi,t)\\ & - x_1(v,t)]\psi'(|x(\xi,t) - x(v,t)|^2)\cdot(x_1(\xi,t) - x_1(v,t))(\eta_1(\xi,t) - \eta_1(v,t))p_x(x(v,t))dv\\ & + \lambda_t \int_{v\in\Xi} k(v,t)[x_1(\xi,t) - x_1(v,t)]\psi(|x(\xi,t) - x(v,t)|^2\cdot p_{x x_1}(x(v,t))\eta_1(v,t)dv.\end{aligned} \tag{21}$$

Analogously, we find that

$$\begin{aligned}\frac{\partial}{\partial\varepsilon}\Phi_1(x_1, x_2+\varepsilon\eta_2)|_{\varepsilon=0} &= 2\lambda_t\int_{v\in\Xi} k(v,t)[x_1(\xi,t)-x_1(v,t)]\psi'(|x(\xi,t)-x(v,t)|^2)\cdot(x_2(\xi,t)-x_2(v,t))(\eta_2(\xi,t)\\ &\quad-\eta_2(v,t))p_x(x(v,t))dv+\lambda_t\int_{v\in\Xi} k(v,t)[x_1(\xi,t)-x_1(v,t)]\psi(|x(\xi,t)-x(v,t)|^2\\ &\quad\cdot p_{xx_2}(x(v,t))\eta_2(v,t)dv.\end{aligned}\tag{22}$$

Here, $p_{xx_1}(x(v,t))$ and $p_{xx_2}(x(v,t))$ are partial derivatives of the probability density $p_x(x_1(v,t),x_2(v,t))$ with respect to absolute space coordinates x_1 and x_2, respectively, of the domain $\Omega(t)$ of the organism.

As a result,

$$\begin{aligned}D\Phi_1\begin{bmatrix}\eta_1\\ \eta_2\end{bmatrix} &= \frac{\partial}{\partial\varepsilon}(\Phi_1(x_1+\varepsilon\eta_1,x_2)+\Phi_1(x_1,x_2+\varepsilon\eta_2))|_{\varepsilon=0}\\ &= \lambda_t\int_{v\in\Xi} k(v,t)[\eta_1(\xi,t)-\eta_1(v,t)]\psi\left(|x(\xi,t)-x(v,t)|^2\right)p_x(x(v,t))dv+2\lambda_t\int_{v\in\Xi} k(v,t)[x_1(\xi,t)\\ &\quad-x_1(v,t)]\psi'\left(|x(\xi,t)-x(v,t)|^2\right)\cdot\langle x(\xi,t)-x(v,t),\eta(\xi,t)-\eta(v,t)\rangle p_x(x(v,t))dv\\ &\quad+\lambda_t\int_{v\in\Xi} k(v,t)[x_1(\xi,t)-x_1(v,t)]\psi\left(|x(\xi,t)-x(v,t)|^2\right)\cdot\langle\nabla p_x(x(v,t)),\eta(v,t)\rangle dv,\end{aligned}\tag{23}$$

where $\langle\cdot,\cdot\rangle$ denotes the scalar product in $\Re^2$. In a similar manner,

$$\begin{aligned}D\Phi_2\begin{bmatrix}\eta_1\\ \eta_2\end{bmatrix} &= \frac{\partial}{\partial\varepsilon}(\Phi_2(x_1+\varepsilon\eta_1,x_2)+\Phi_2(x_1,x_2+\varepsilon\eta_2))|_{\varepsilon=0}\\ &= \lambda_t\int_{v\in\Xi} k(v,t)[\eta_2(\xi,t)-\eta_2(v,t)]\psi\left(|x(\xi,t)-x(v,t)|^2\right)p_x(x(v,t))dv+2\lambda_t\int_{v\in\Xi} k(v,t)[x_2(\xi,t)\\ &\quad-x_2(v,t)]\psi'\left(|x(\xi,t)-x(v,t)|^2\right)\cdot\langle x(\xi,t)-x(v,t),\eta(\xi,t)-\eta(v,t)\rangle p_x(x(v,t))dv\\ &\quad+\lambda_t\int_{v\in\Xi} k(v,t)[x_2(\xi,t)-x_2(v,t)]\psi\left(|x(\xi,t)-x(v,t)|^2\right)\cdot\langle\nabla p_x(x(v,t)),\eta(v,t)\rangle dv.\end{aligned}\tag{24}$$

Step 2. The results of Step 1 may be compactly expressed as follows:

$$\begin{aligned}D\Phi_i\begin{bmatrix}\eta_1\\ \eta_2\end{bmatrix} &= \lambda_t\int_{v\in\Xi} k(v,t)[\eta_i(\xi,t)-\eta_i(v,t)]\cdot\psi\left(|x(\xi,t)-x(v,t)|^2\right)p_x(x(v,t))dv\\ &\quad+2\lambda_t\int_{v\in\Xi} k(v,t)[x_i(\xi,t)-x_i(v,t)]\psi'\left(|x(\xi,t)-x(v,t)|^2\right)\cdot\langle x(\xi,t)-x(v,t),\eta(\xi,t)\\ &\quad-\eta(v,t)\rangle p_x(x(v,t))dv+\lambda_t\int_{v\in\Xi} k(v,t)[x_i(\xi,t)-x_i(v,t)]\psi\left(|x(\xi,t)-x(v,t)|^2\right)\cdot\langle\nabla p_x(x(v,t)),\eta(v,t)\rangle dv.\end{aligned}\tag{25}$$

We see that the Gateaux derivative $D\Phi_i$ is a linear operator for $i=1,2$ on Y. We now show that $D\Phi$ is bounded using the vector norm

$$\|D\Phi\eta\| = \max\{\|D\Phi_1\eta\|,\|D\Phi_2\eta\|\}.\tag{26}$$

For $i=1,2$, we consider the absolute value of each of the three integral terms on the right-hand side of (25):

$$\begin{aligned}|\text{Term 1}| &= \left|\lambda_t\int_{v\in\Xi} k(v,t)[\eta_i(\xi,t)-\eta_i(v,t)]\psi\left(|x(\xi,t)-x(v,t)|^2\right)p_x(x(v,t))dv\right|\\ &\leqslant|\lambda_t|\int_{v\in\Xi}|k(v,t)|\cdot|\eta_i(\xi,t)-\eta_i(v,t)|\left|\psi\left(|x(\xi,t)-x(v,t)|^2\right)\right|\cdot|p_x(x(v,t))|dv\end{aligned}\tag{27}$$

From the assumptions of (1) continuity of λ on $[0,T]$,

$$|\lambda_t|\leqslant\max_{0\leqslant t\leqslant T}|\lambda_t| = M_1.\tag{28}$$

From diffeomorphic property of θ^{seed} and Ψ on their respective finite domains Ξ and $\Omega(t)$,

$$|k(v,t)|\leqslant m_2\tag{29}$$

and

$$\left|\psi\left(|x(\xi,t)-x(v,t)|^2\right)\right| = |\psi(r^2)|\leqslant\sup_{0\leqslant r\leqslant\mathrm{diam}(Y)}|\psi(r^2)| = M_2.\tag{30}$$

And from the assumption that $p_x\in C^1(Y)$,

$$|p_x(x)|\leqslant\sup_{x\in Y}|p_x(x)| = M_3.\tag{31}$$

Finally,

$$|\eta_i(\xi,t)-\eta_i(v,t)| \leqslant |\eta_i(\xi,t)| + |\eta_i(v,t)| \leqslant \sup_{\xi\in\Xi}|\eta_i(\xi,t)| + \sup_{v\in\Xi}|\eta_i(v,t)| \leqslant 2\|\eta\|_Y. \tag{32}$$

Combining individual factor estimates (28)–(32) together, we have that

$$|\text{Term } 1| \leqslant C_1\|\eta\|_Y, \tag{33}$$

where

$$C_1 = 2M_1M_2M_3m_2\ A(\Xi). \tag{34}$$

Here $A(\Xi)$ denotes the area/Lebesgue measure of the Darcyan space Ξ.

We now examine the second term on the right-hand side of (25),

$$\begin{aligned}|\text{Term } 2| \leqslant 2|\lambda_t| \int_{v\in\Xi} |k(v,t)||x_i(\xi,t)-x_i(v,t)|\left|\psi'\left(|x(\xi,t)-x(v,t)|^2\right)\right| \cdot |\langle x(\xi,t)-x(v,t), \eta(\xi,t)\\ -\eta(v,t)\rangle||p_x(x(v,t))|dv.\end{aligned} \tag{35}$$

In order to bound the scalar product term, we use (32) and the fact that

$$|x_i(\xi,t)-x_i(v,t)| \leqslant \text{diam}(Y) \tag{36}$$

to obtain

$$|\langle x(\xi,t)-x(v,t), \eta(\xi,t)-\eta(v,t)\rangle| \leqslant \text{diam}(Y)|\eta(\xi,t)-\eta(v,t)]| \leqslant 2\text{diam}(Y)\|\eta\|_Y. \tag{37}$$

From the assumption that ψ is C^1 on Y, it follows that

$$\left|\psi'\left(|x(\xi,t)-x(v,t)|^2\right)\right| = |\psi'(r^2)| \leqslant \sup_{0\leqslant r\leqslant \text{diam}(Y)} |\psi'(r^2)| = M_4. \tag{38}$$

From these and previous bounds, we conclude that

$$|\text{Term } 2| \leqslant C_2\|\eta\|_Y, \tag{39}$$

where

$$C_2 = M_1M_4m_2A(\Xi)\ \text{diam}(Y). \tag{40}$$

Finally, we examine the third term on the right-hand side of (25),

$$|\text{Term } 3| \leqslant |\lambda_t| \int_{v\in\Xi} |k(v,t)||x_i(\xi,t)-x_i(v,t)|\left|\psi\left(|x(\xi,t)-x(v,t)|^2\right)\right||\langle\nabla p_x(x(v,t)), \eta(v,t)\rangle|dv. \tag{41}$$

From the assumption of C^1-smoothness of the density function p_x,

$$|\langle\nabla p_x(x(v,t)), \eta(v,t)\rangle| \leqslant \|\nabla p_x\|\|\eta\|_Y = M_5\|\eta\|_Y. \tag{42}$$

As a result,

$$|\text{Term } 3| \leqslant C_3\|\eta\|_Y, \tag{43}$$

where

$$C_3 = M_1M_2M_5m_2A(\Xi)\ \text{diam}(Y)A(\Xi). \tag{44}$$

We now combine all estimates obtained above to obtain

$$|D\Phi_i\eta| \leqslant C_1\|\eta\|_Y + C_2\|\eta\|_Y + C_3\|\eta\|_Y = C_\Phi\|\eta\|_Y \quad \text{for } i=1,2. \tag{45}$$

It therefore follows that $D\Phi$ is a linear bounded operator.

Step 3. It now remains to show that Φ is Lipschitz continuous in x on Y. We use the following lemma:

Lemma 1. *Let K be a convex subset of a Banach space W. If $\Phi : K \to K$ satisfies $\|D\Phi(x)\| \leqslant \alpha\ \forall x \in K$ then Φ is Lipschitz continuous, i.e.,*

$$\|\Phi(x)-\Phi(y)\| \leqslant \alpha\|x-y\| \quad \forall\ x,y\in K. \tag{46}$$

Proof. We start with

$$\Phi(x)-\Phi(y) = \Phi(y+z)-\Phi(y), \quad z = x-y \in K. \tag{47}$$

From the Fundamental Theorem of Calculus for Gateaux derivatives, for any $z \in K$,

$$\Phi(y+z) - \Phi(y) = \int_0^1 \frac{\partial}{\partial s}\Phi(y+sz)\,ds. \tag{48}$$

From the convexity of K, it follows that $y + sz \in K$ for all $s \in [0,1]$. Taking norms of both sides of (48),

$$\|\Phi(y+z) - \Phi(y)\| = \left\| \int_0^1 \frac{\partial}{\partial s}\Phi(y+sz)\,ds \right\| = \left\| \int_0^1 D\Phi(y+sz)\; z\,ds \right\| \leqslant \int_0^1 \|D\Phi(y+sz)\|\;\|z\|\,ds \leqslant \alpha\;\|z\|. \tag{49}$$

Substituting $z = x - y$ in (49) we obtain the desired result

$$\|\Phi(x) - \Phi(y)\| \leqslant \alpha\|x - y\|, \tag{50}$$

thus completing the proof of the Lemma.

Note that the conditions of Lemma 1 are satisfied for the GRID macroscopic growth operator Φ defined on the convex space Y for a fixed time $t \geqslant 0$. Since the Gateaux derivative $D\Phi$ is a linear bounded operator, the operator Φ is Lipschitz continuous in $x \in Y$ for any time $t \in [0,T]$.

The proof of this Theorem concludes rather trivially in the usual way, with recourse to the well-known existence and uniqueness theorem for initial value problems on Banach spaces. Recalling the definition of the Picard integral operator in (18), it follows that, for $x, y \in Y$,

$$\|Mx - My\|_Y \leqslant \int_0^t \|\Phi(x(\xi,s),s) - \Phi(y(\xi,s),s)\|_Y\,ds \leqslant C_\Phi T\|x - y\|_Y. \tag{51}$$

For $T < C_\Phi^{-1}$, M is a contraction mapping on the Banach space Y, implying the existence of a unique fixed point $x \in Y$ which, from (18), is the solution to the IVP in (8). □

Remark: The above existence and uniqueness result also holds for scaling functions $k(\xi,t)$ that are piecewise differentiable with respect to ξ. Such k-functions are useful in modelling non-smooth interregional variations of the mechanical properties of a multicellular organism.

Theorem 1 automatically implies the following result:

Corollary 2. *Let $[0,T]$ be the time interval over which there exists a unique solution $x(\xi,t)$ to the IVP (8). Then for all $t \in [0,T]$, individual trajectories of the macroscopic growth flow $x(\xi,t)$ do not intersect. This, in turn, implies that the mapping $x : \xi \to x(\xi,t)$ is one-to-one for all $t \in [0,T]$.*

Proof. The result follows easily along the same lines as for the classical result of nonintersecting trajectories for IVPs of systems of ODEs, as we now briefly show. From the above proof, for each $\xi \in \Xi$, the solution $x(\xi,t)$ will trace out a unique trajectory emanating from $x_0(\xi)$ as t increases from 0 to T. Suppose that for a pair of distinct seeds, i.e., $(\xi^1,\xi^2) \in \Xi : \xi^1 \neq \xi^2$, the trajectories $x(\xi^1,t)$ and $x(\xi^2,t)$, intersect at some time $t^* \in (0,T)$, i.e.,

$$x(\xi^1,t^*) = x(\xi^2,t^*) =: x^*. \tag{52}$$

Since, however, the assumptions of the above Theorem are satisfied over the space Y, it is guaranteed that the following IVP,

$$\frac{\partial x(\xi,t)}{\partial t} = \Phi(x(\xi,t),t), \quad x(\xi,t^*) = x^*, \tag{53}$$

has a unique solution over the time interval $(t^* - \delta, t^* + \delta) \subset [0,T]$ for some $\delta > 0$. Therefore (52) cannot occur. This contradiction completes the proof of the Corollary. □

5. Final remarks

The above result provides the theoretical basis of the evolution pictured in Figs. 3 and 4. It may also be extended to the three-dimensional (3D) case in a straightforward way. In this case, the Darcyan coordinate space Ξ is three-dimensional, requiring the use of a spherical polar coordinate system.

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