PDE Models of Controlled Growth

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Growing into the right shape







Controlling the growth of living tissues

- For higher living forms (plants, animals), growing into the right shape is essential for survival
- How can Nature control growth, sometimes in an amazingly precise way?
- Can we write PDEs describing this feedback control mechanism?

What is the **simplest** system of PDEs generating the shapes found in nature?

"With four parameters I can fit an elephant, and with five I can make him wiggle his trunk" (John von Neumann)

- One-dimensional curves, growing in \mathbb{R}^3 (tree stems, vines)
- Two-dimensional sets, growing in \mathbb{R}^2 (leaves)

numerical simulations + analytical proofs

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Stabilizing stem growth



what kind of stabilizing feedback is used here?

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Growth in the presence of obstacles



Are the growth equations still well posed, when an obstacle is present?

What additional feedback produces curling around other branches?

- New cells are born at the tip of the stem
- Length of the stem grows in time at unit rate



 $\gamma(t,s) =$ position at time t of the cell born at time s

Unit tangent vector to the stem: $\mathbf{k}(t,s) = \gamma_s(t,s)$

Stabilizing growth in the vertical direction

stem not vertical \implies local change in curvature

$$\frac{\partial}{\partial t}\gamma(t,s) = \int_0^s e^{-\beta(t-\sigma)} \left(\mathbf{k}(t,\sigma) \times \mathbf{e}_3\right) \times \left(\gamma(t,s) - \gamma(t,\sigma)\right) d\sigma$$

 $\omega(\sigma) = \mathbf{k}(t, \sigma) \times \mathbf{e}_3 =$ local angular velocity

 $e^{-\beta(t-\sigma)} = \text{stiffness factor}$



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We say that the growth equation is **stable in the vertical direction** if for any initial time $t_0 > 0$ and every $\varepsilon > 0$ there exists $\delta > 0$ such that

$$|\pi_{hor} \mathbf{k}(t_0, \mathbf{s})| \leq \delta \quad \text{for all } \mathbf{s} \in [0, t_0]$$

$$|mplies \quad |\pi_{hor} \gamma(t, \sigma)| \leq \varepsilon \quad \text{for all } t > t_0, \quad \sigma \in [0, t]$$

$$|\mathbf{k}| = \mathbf{k} + \mathbf{k} +$$

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Numerical simulations (Wen Shen, 2016),



- stability is always achieved
- increasing the stiffness reduces oscillations

 $\beta = {\rm stiffening\ constant}$

- If $\beta^4 \beta^3 4 \ge 0$, then the growth is stable in the vertical direction (non-oscillatory regime: $\beta \ge \beta_1 \approx 1.7485$)
- If $\frac{3}{5\beta} + \frac{9}{32\beta} < 1$ then the growth is still stable in the vertical direction (oscillatory regime: $\beta \ge \beta_0 \approx 0.9093$)
- What happens for $\beta > 0$ small ?

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Growth with obstacles



 $\omega(\sigma)$ = additional bending of the stem caused the obstacle, at the point $P(\sigma)$

$$\widetilde{P}(s) - P(s) = \int_0^s \omega(\sigma) \times (P(s) - P(\sigma)) d\sigma$$
 $s \in [0, t]$

Among all infinitesimal deformations that push the stem outside the obstacle,

minimize the deformation energy:
$$\mathcal{E} = \frac{1}{2} \int_0^t e^{\beta(t-\sigma)} |\omega(\sigma)|^2 d\sigma$$

An evolution problem with unilateral constraints



$$\gamma_t(t,s) = \int_0^s \left[\Psi(t,\sigma,\gamma(t,\sigma),\gamma_s(t,\sigma)) + \omega(t,s) \right] \times \left(\gamma(t,s) - \gamma(t,\sigma) \right) d\sigma$$

 $\Psi \implies$ bending as a feedback response to gravity or other external objects $\omega \implies$ bending produced by the constraint (minimizing the deformation energy)

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• In addition to the upward bending, one can assume that the stem "feels" an obstacle within a distance $\delta > 0$.

This triggers an additional bending in the direction of the obstacle.



Numerical simulations (Wen Shen, 2016)



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Well-posedness of the stem growth model with obstacle (A.B. - M.Palladino)

Rewrite as a differential inclusion (upper semicontinuous, with convex values)

$$rac{d}{dt}\gamma(t,\cdot) \ \in \ \Phi + {\sf \Gamma} \qquad \qquad \gamma(t,\cdot) \in {\cal H}^2([0,\,{\cal T}]\,;\,\,{\mathbb R}^3)$$

 $\Gamma=\mbox{cone}$ of admissible reactions produced by the obstacle

Solutions exist and are unique except if a (highly non-generic) breakdown configuration is reached



Continuous dependence

$$\frac{d}{dt}z(t) \in f(z) + \Gamma(z), \qquad z \notin S$$

If we could show:
$$\frac{d}{dt} \|z_1(t) - z_2(t)\|_{H^2} \leq C \|z_1(t) - z_2(t)\|_{H^2}$$
(1)
Gronwall \implies uniqueness, continuous dependence

Here (1) fails because the cones are not perpendicular to the boundary of S



Possible approach: introduce a Riemann-type metric on the Hilbert space H_{-}^{2}

Theorem (A.B. - M.Palladino, 2017)

The equations for the growing stem with obstacles have a unique solution

$$t \mapsto \gamma(t, \cdot) \in H^2([0, T]; \mathbb{R}^3)$$

defined up to the first time where a "breakdown configuration" is reached.



To model growth of a tree one needs:

- (I) A rule specifying when new branches are formed
- (II) An equation describing the growth rate of each branch
- (III) An equation describing how the orientation of each branch can change, responding to gravity and to sunlight
- (IV) A rule determining when one or more branches die out, because of lack of sunlight

The shading function

 A point P on a branch produces shade to all lower points in space Shade produced at y = (y₁, y₂, y₃) by a point located at the origin:

$$\varphi(\mathbf{y}) \doteq 2|\mathbf{y}|^{-2} \langle \mathbf{y}, \mathbf{e}_{3} \rangle_{-} = \frac{|y_{3}| - y_{3}}{y_{1}^{2} + y_{2}^{2} + y_{3}^{2}} \approx \frac{(\varepsilon + y_{3}^{2})^{1/2} - y_{3}}{\varepsilon + y_{1}^{2} + y_{2}^{2} + y_{3}^{2}}$$

 \bullet Total shade produced at point $\textbf{y} \in \mathbb{R}^3$ by all branches of a tree \mathcal{T} :

$$\Phi(\mathbf{y}) = \int_{\mathbf{x}\in\mathcal{T}} \varphi(\mathbf{y}-\mathbf{x}) \, d\ell(\mathbf{x})$$

• Sunlight received by point **y** in space: $\Psi(\mathbf{y}) = e^{-lpha \Phi(\mathbf{y})}$

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- ullet Growth speed $\ pprox$ sunlight received by the tip of the branch
- Branches bifurcate when they reach a threshold length L_b
- A group of branches dies out when

 $\frac{[\text{total amount of sunlight received}]}{[\text{total length}]} \leq \delta_0$

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Model 1. Once created, branches are rigid. The curvature of the tip is determined in response to gravity and the gradient of sunlight.

Model 2. The curvature at the tip vanishes. Branches are elastic, and modify their orientation in response to gravity and the gradient of sunlight.



Numerical simulations (Wenrui Hao, 2017) - model 1



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Figure 1

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Random branching: the probability that a branch bifurcates is proportional to the length of the branch.



Compare:

- shapes generated by a growth algorithm
- shapes of real trees
- "optimal tree shapes" defined by a variational problem

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maximize:
$$\int_{x\in\mathcal{T}} \Psi(\mathbf{x}) d\ell(\mathbf{x})$$

total amount of sunshine captured by all branches

subject to:
$$\int_{x \in \mathcal{T}} K(x) d\ell(\mathbf{x}) = C$$

a constraint on the total length (or the cost to transport nutrients from the root to all branches)

• To grow into a specific shape, different portions of the living tissue must expand at different rates. This can be achieved by a chemical gradient.

The system of PDEs should include:

- (1) One or more diffusion equations, describing the density of growth-inducing nutrients/morphogens inside the living tissue
- (2) A dynamic equation, describing how particles on the tissue move, as a result of bulk growth



A linear diffusion-adsorption equation

 $\Omega(t) =$ region occupied by living tissue at time t

w(t,x) density of (morphogen-producing) signaling cells, at time t, at point $x \in \Omega(t)$

$$\left\{ egin{array}{ll} u_{ au} &=& w+\Delta u-u & \qquad x\in\Omega(t) \ &
abla u\cdot {f n} &=& 0 & \qquad x\in\partial\Omega(t) \end{array}
ight.$$

u = density of growth-inducing chemical. Determined by

production + diffusion + adsorption

Diffusion of chemicals within the living tissue is much faster than the growth of the tissue itself

By separation of time scales, it is appropriate to consider the steady state

$\mathbf{v}(t,x) =$ velocity determined by bulk growth

Uniquely determined (up to a rigid motion) by the variational problem

$$\begin{cases} \text{minimize:} & E(\mathbf{v}) \doteq \frac{1}{2} \int_{\Omega(t)} |\operatorname{sym} \nabla \mathbf{v}|^2 \, dx \\ \text{subject to:} & \operatorname{div} \mathbf{v} = u \end{cases}$$

 $E(\mathbf{v}) =$ elastic energy of the infinitesimal deformation

sym
$$A \doteq \frac{A + A^T}{2}$$
, skew $A \doteq \frac{A - A^T}{2}$

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The growth equations

Finally, we assume that morphogen-producing cells are passively transported within the tissue, so that

$$w_t + \operatorname{div}(w\mathbf{v}) = 0$$
 $x \in \Omega(t)$

This has to be supplemented by assigning an initial domain and an initial distribution of morphogen-producing cells:



• Density of morphogen

$$u = \operatorname{argmin} \int_{\Omega} \left(\frac{|\nabla u|^2}{2} + \frac{u^2}{2} - wu \right) dx \qquad \Longleftrightarrow \qquad \begin{cases} u - \Delta u = w & x \in \Omega \\ \nabla u \cdot \mathbf{n} = 0 & x \in \partial \Omega \end{cases}$$

• Velocity field determined by bulk growth

$$\mathbf{v} = \operatorname{argmin} \int_{\Omega} |\operatorname{sym} \nabla \mathbf{v}|^2 \, dx \qquad \Longleftrightarrow \qquad \begin{cases} -\Delta \mathbf{v} + 2\nabla p = \nabla u & x \in \Omega \\ \operatorname{div} \mathbf{v} = u & x \in \Omega \\ (\operatorname{sym} \nabla \mathbf{v} - p\mathbf{I})\mathbf{n} = 0 & x \in \partial\Omega \end{cases}$$

• Density of morphogen-producing cells

$$w_t + \operatorname{div}(\mathbf{v} w) = 0$$

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Construction of solutions

Theorem (A.B., Marta Lewicka, 2016)

- Initial domain: $\Omega(0) = \Omega_0$, with boundary $\partial \Omega_0 \in C^{2,\alpha}$
- Initial density of signaling cells: w₀ ∈ C^α(Ω₀).

A classical solution exists, locally in time, with

$$\left\{ egin{array}{ll} \partial\Omega(t) &\in \mathcal{C}^{2,lpha} \ w(t,\cdot) &\in \mathcal{C}^{lpha}(\Omega(t)) \end{array}
ight. \left\{ egin{array}{ll} u(t,\cdot) &\in \mathcal{C}^{2,lpha}(\Omega(t)) \ \mathbf{v}(t,\cdot) &\in \mathcal{C}^{2,lpha}(\Omega(t)) \end{array}
ight.$$

The solution is unique, up to rigid motions.

Proof: based on Schauder type regularity estimates, in *Agmon-Douglis-Nirenberg (1964)*

• Construction breaks down as the inner or outer curvature radius \rightarrow 0.



 For Hele-Shaw problems, or models of tumor growth, at each time t the velocity v(t, ·) minimizes

$$\int_{\Omega(t)} |\mathbf{v}(t, x)|^2 \, dx$$
$$\implies \qquad \text{solution is unique}$$

• In the present case, the velocity $\mathbf{v}(t,\cdot)$ minimizes

$$\int_{\Omega(t)} |\operatorname{sym} \nabla \mathbf{v}(t, x)|^2 \, dx$$

 \implies

solution is unique up to a rigid motion

- **Controllability.** How can the shape of the growing tissue be controlled by the signaling cells?
- Anisotropic diffusion and stress-strain response



• Stratified domains: the growing domain $\mathcal{M} = \mathcal{M}_1 \cup \cdots \cup \mathcal{M}_n$ is the union of manifolds of different dimensions



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Growth of curved surfaces in \mathbb{R}^3





- \bullet diffusion of morphogen takes place on a 2D Riemann manifold immersed in \mathbb{R}^3
- elastic deformation energy must be carefully defined

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Happy Anniversary Piermarco !

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