Attraction and Repulsion in Biological Tissues: Challenges for Models, Analysis, and Numerics

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Overview

- Cell attraction and repulsion: some biological background.
- The nonlocal PDE model and its application.
- Analytical results.
- Derivation from a position-jump model.
- The need for efficient numerics.
  - Approximation in a periodic setting.
  - Generalizations and extensions
- Summary and outlook.

Cell contact and response

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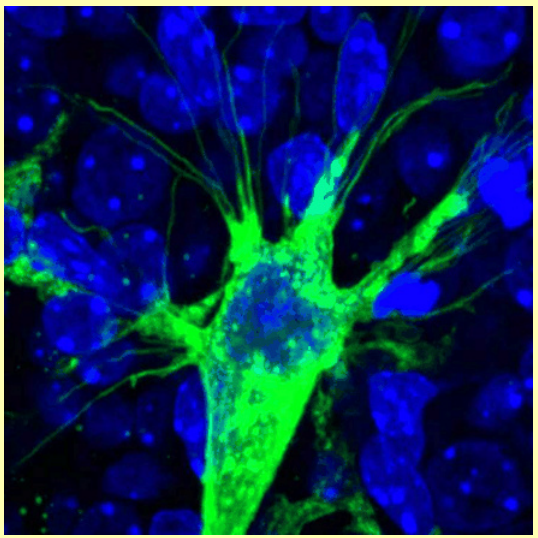
- Cells can communicate via direct contacts, e.g. membrane-membrane molecular binding.
- Contacts also occur at long distances, up to 50 cell diameters, via cell protrusions. →
- Reality is full of detail: cells are complex, morphing objects with a lot of structure and chemistry.
- Direct contact can lead to many responses, such as movement.

Cells *explore* their surrounding in search of contact sites.

Filopodia (green) of endothelial cell ↓



[Gerhardt et al., J. Cell Biol. (161), '03]

Cell contact and response

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Focus here: Direct contacts between cells

as, e.g., in cell-cell adhesion or contact inhibition.

Not considered: Indirect contacts between cells

as, e.g., mediated by diffusible chemical signalling (chemotaxis).

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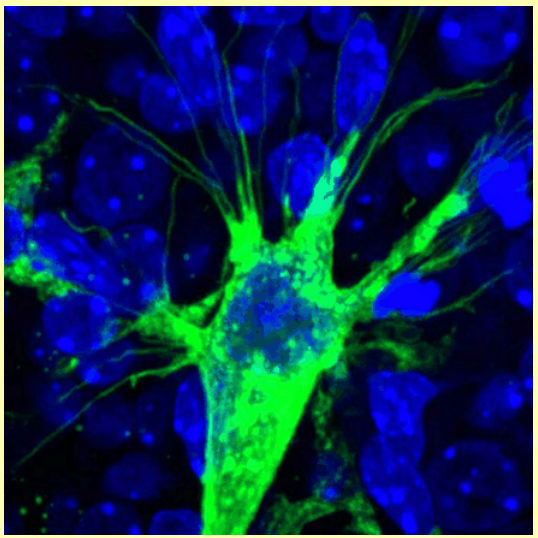

[Gerhardt et al., J. Cell Biol. (161), '03]

Cell contact and response

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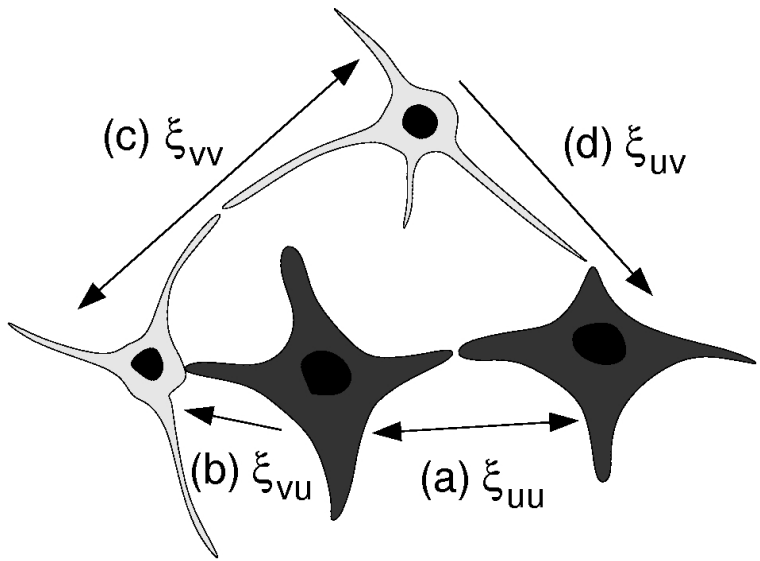
Instructing others to move is fundamental for many animal/cellular populations.

Commands

- are transmitted by contact over variable distances (short or long range),
- effect cells of the same (homotypic) or different (heterotypic) type,
- give rise to an attractive or repelling response.



These mechanisms can have a significant impact on the organisation of a tissue.

Example 1: Cell adhesion
Molecular aspects and applications

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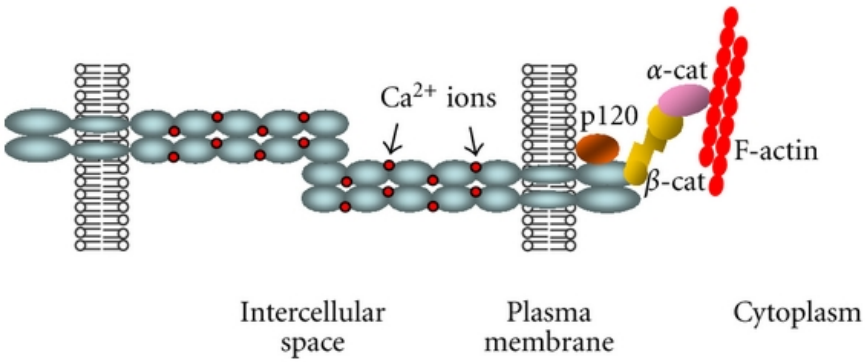

[Gama&Schmitt, Veterinary Medicine International, '12]

Adhesion [latin *adhaesio*] of cells in the body determined by expression and regulation of cell adhesion molecules

- Cadherines (cell-cell adhesion)
- Integrines (cell-matrix adhesion)
- ...a few others.

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Molecular aspects and applications

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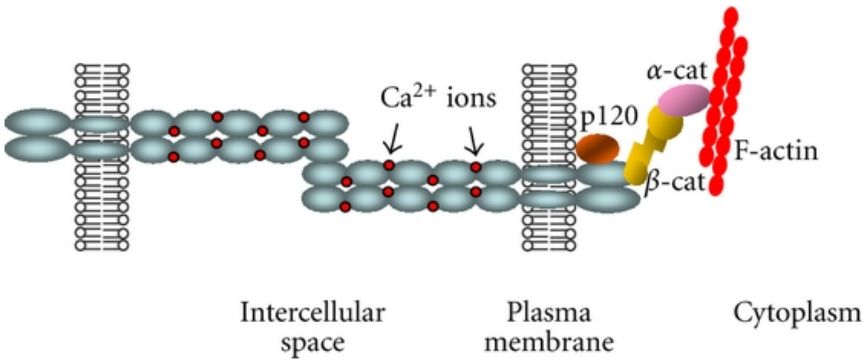

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- ...a few others.

Adhesion important for tissue integrity and cell migration!

Selected applications:

- Embryonic development: cells adhere selectively to each other and sort out to form tissue and organs.
- Cancer invasion: modified adhesive properties of cancer cells are implicated as an important factor.

Example 1: Cell adhesion
Cell sorting

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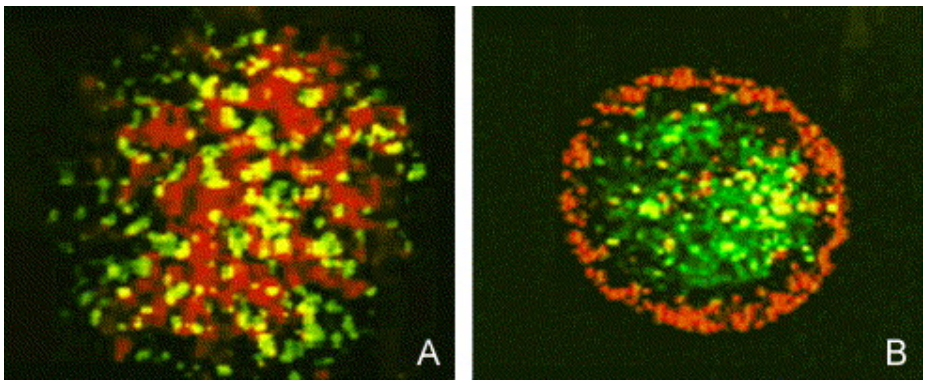

[Foty & Steinberg, Dev. Biol. (278), '05]

2 cell types, differing in number of cadherin molecules on their cell surface only.

Cell type with larger number sorts to the core of the cell pellet.

Example 1: Cell adhesion
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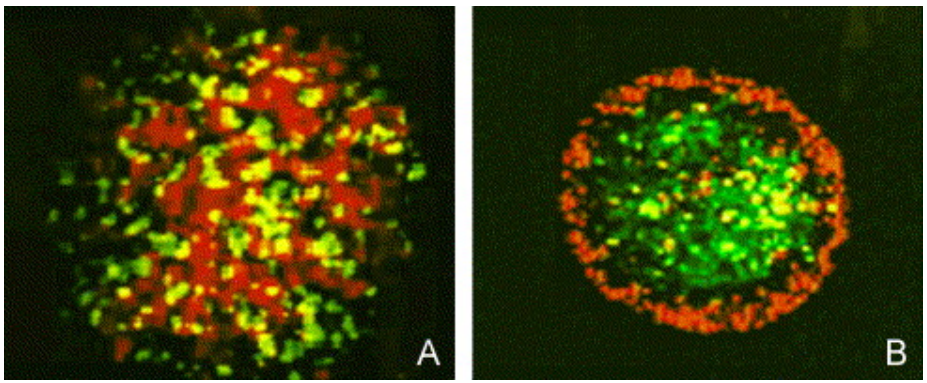

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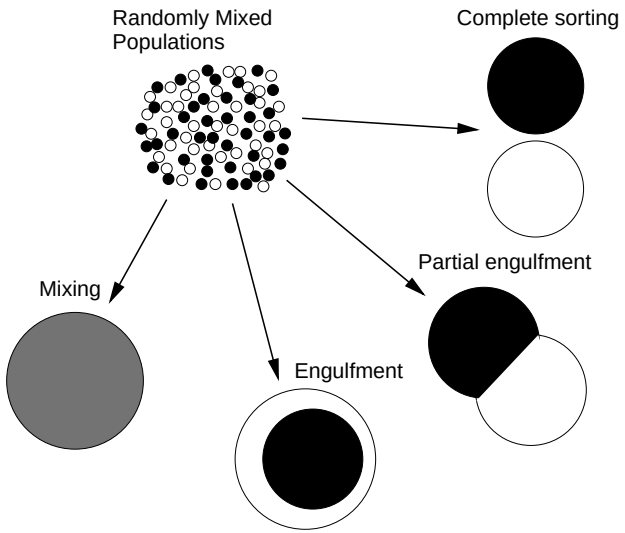
Differential Adhesion Hypothesis (Steinberg)

A mixture of two cell types sorts always to the same final configuration, independent of its initial distribution. This final configuration depends solely on the adhesive properties (self- and cross-adhesion parameters) of the cell types.



[G. & Painter, '10]

Example 1: Cell adhesion
Cancer invasion

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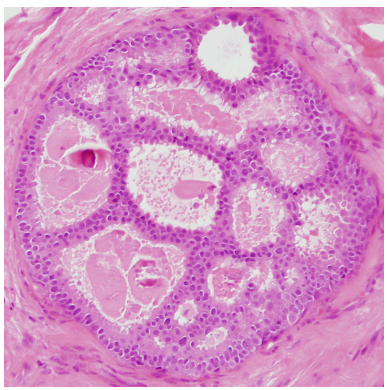
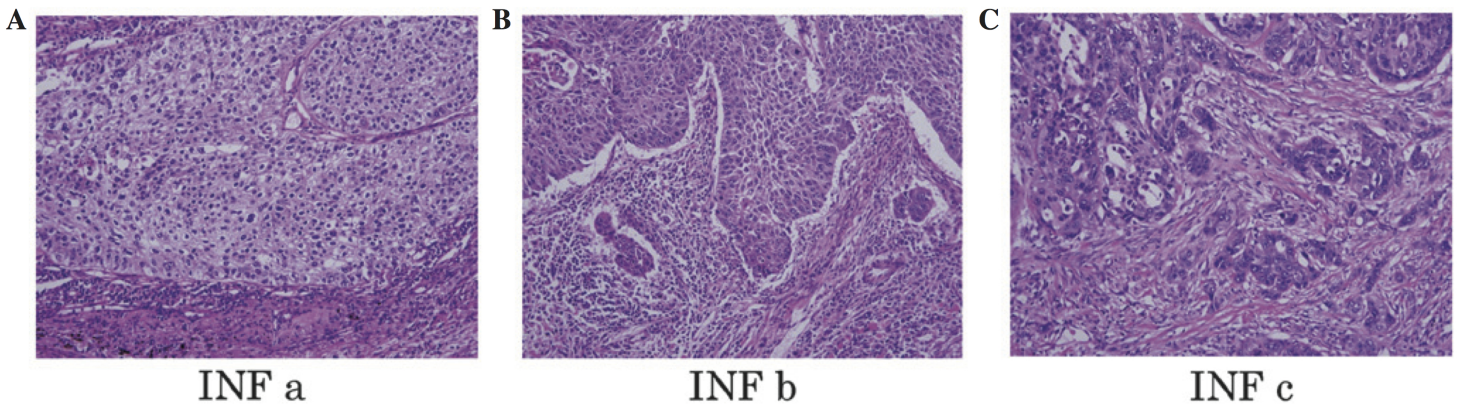
- Invasion is the process of extension of the cancer into surrounding tissue.
- It is part of the metastatic cascade, giving cancer its deadly characteristic.
- Modulation of adhesive properties of cancer cells is one of the hallmarks of cancer [Hanahan & Weinberg, '00 & '11]



ductal carcinoma in situ, intermediate grade,
[www.breastpathology.info]



lung squamous cell carcinoma, types (a) to (c) of tumour infiltrative pattern,
[Masuda et al., '12]

Example 2: Contact repulsion
Contact inhibition in neural crest cell migration

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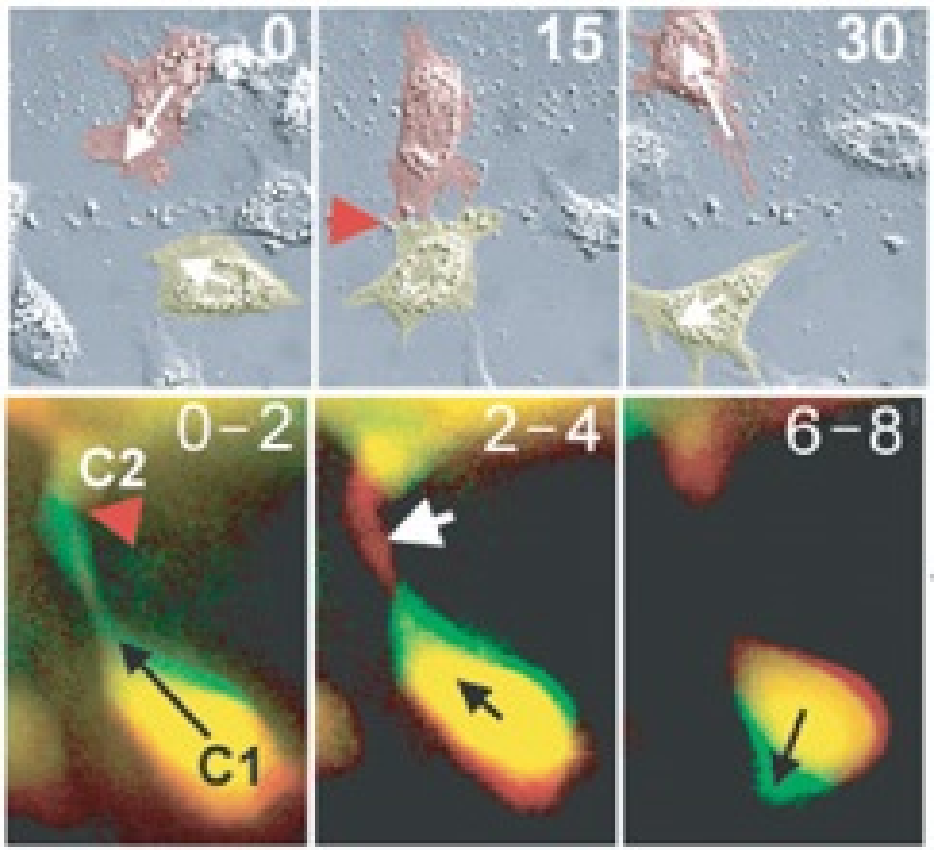
Certain cells “repel” each other on contact, a process known as “contact inhibition of locomotion” [Abercrombie & Heaysman, Exp Cell Res, 5, ’50], [Abercrombie, Nature, 281, ’79].



Contact inhibition of locomotion controls neural crest cell directional migration

[Carmona-Fontaine et al., Nature, 456, ’08]

Example 3: Mixed interaction
Zebrafish pigmentation pattern

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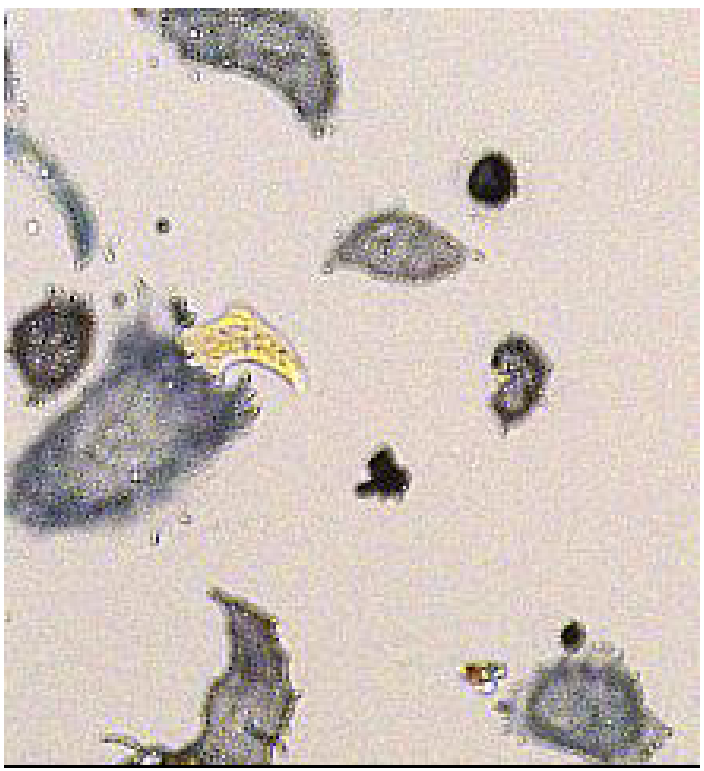
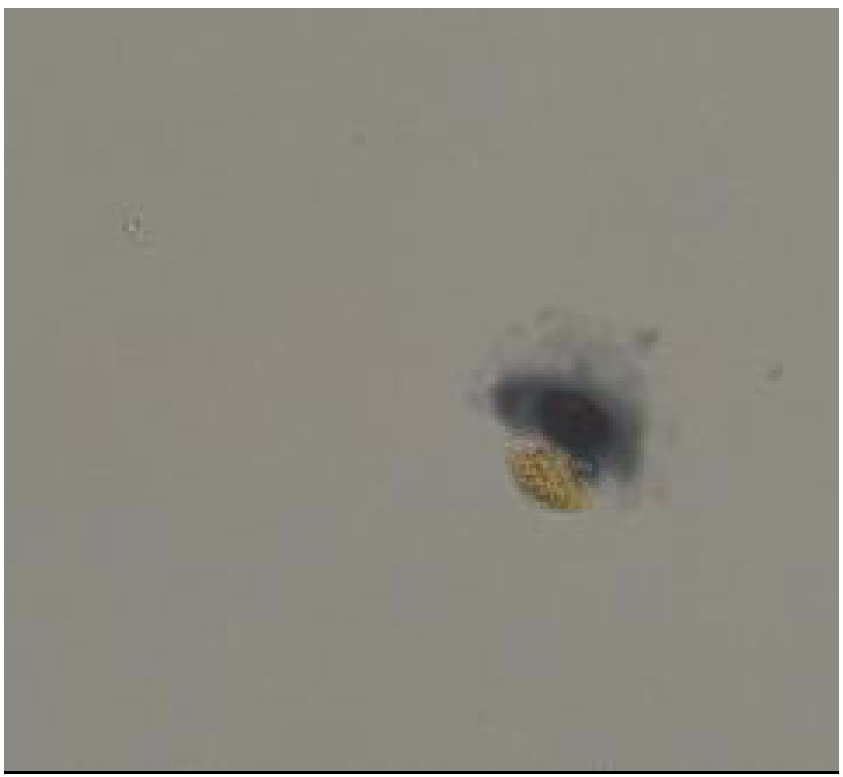
Certain heterogeneous populations: attracting and repelling interactions observed.

“run-and-chase” behaviour (xanthophores chase melanophores)





[Yamanaka & Kondo, PNAS, ’14]

Modelling of attraction and repulsion
Focus on cell adhesion

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Two general classes of models

- individual cell based (discrete) models
  $\rightsquigarrow$ dynamics of individual cells,
- continuous models
  $\rightsquigarrow$ dynamics of population level behaviour.
  - Cells represented through their density at the tissue level.
  - Cellular scale events captured in model parametrisation.

Modelling of attraction and repulsion
Focus on cell adhesion

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Examples of continuous modelling approaches

- Cell-matrix adhesion:
  - haptotactic migration, modelled by advective type flux term (cf. chemotaxis).
- Cell-cell adhesion: Is problematic!
  - *Some* aspects of adhesion captured by density-dependent cell motility coefficients.
  - Direct incorporation of surface tension (e.g. Byrne, Chaplain, Lowengrub, Cristini,...)
    $\rightsquigarrow$ Cahn-Hilliard type PDE models arising from expansion of nonlocal terms.
  - Nonlocal PDE model: [Armstrong, Painter & Sherratt, J Theor Biol, 243, '06].
    Had and has a substantial influence on the subject with $\approx$140 citations to date!

The Armstrong-Painter-Sherratt model
Underlying idea

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In a fluid (extracellular space) with dynamic viscosity η ...

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In a fluid (extracellular space) with dynamic viscosity η ...
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What is the (drag) force F on the sphere?

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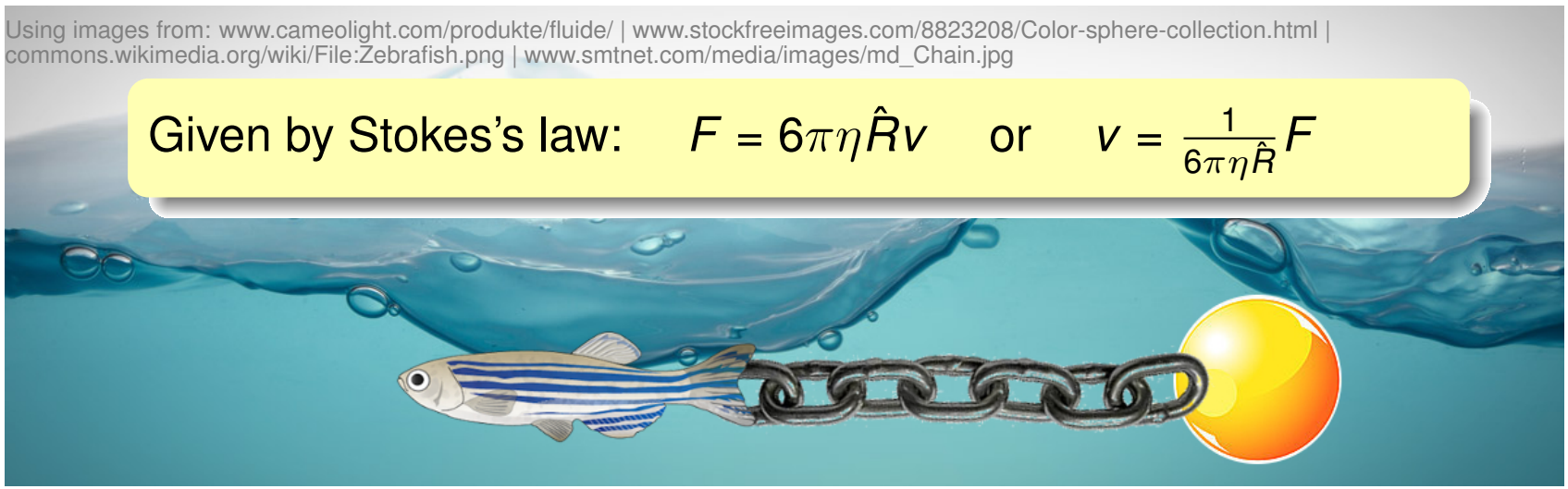

Given by Stokes's law: $F = 6\pi\eta\hat{R}v$ or $v = \frac{1}{6\pi\eta\hat{R}}F$

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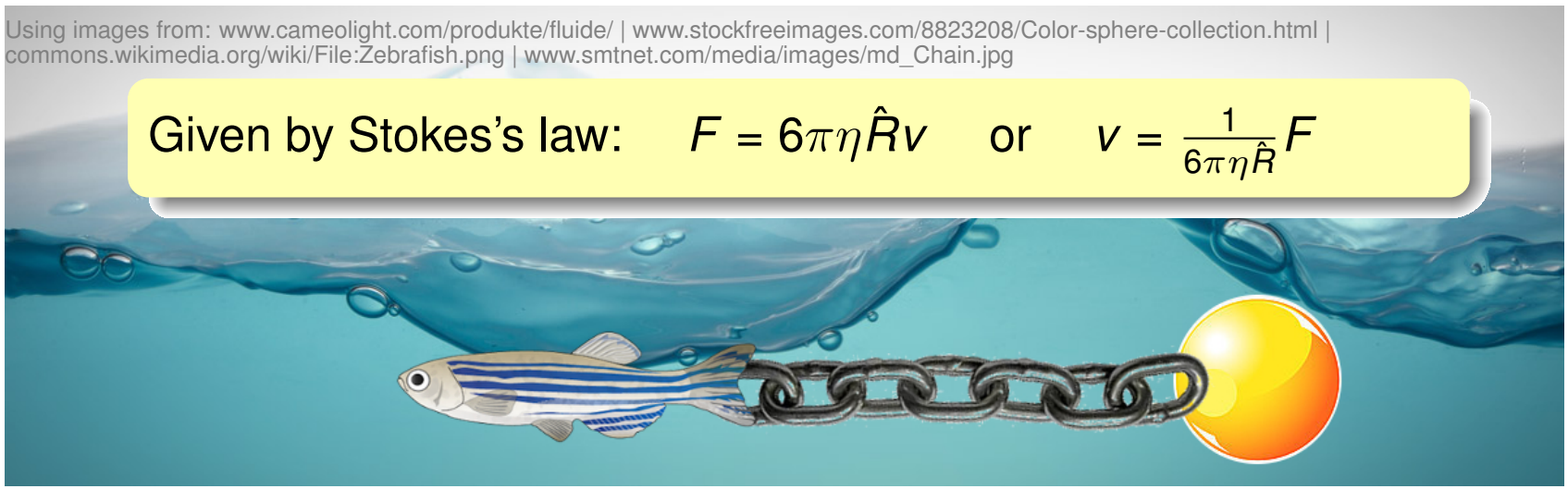

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Assume cells with density $u(t,x)$ move with velocity $v(t,x)$ due to adhesion.

$$\rightsquigarrow \text{ flux of cells } \quad u(t,x)v(t,x) = u(t,x)\frac{1}{6\pi\eta\hat{R}}F(t,x)\,,$$

where $F(t,x)$ is now the net force (due to adhesion) acting on a cell at (t,x).

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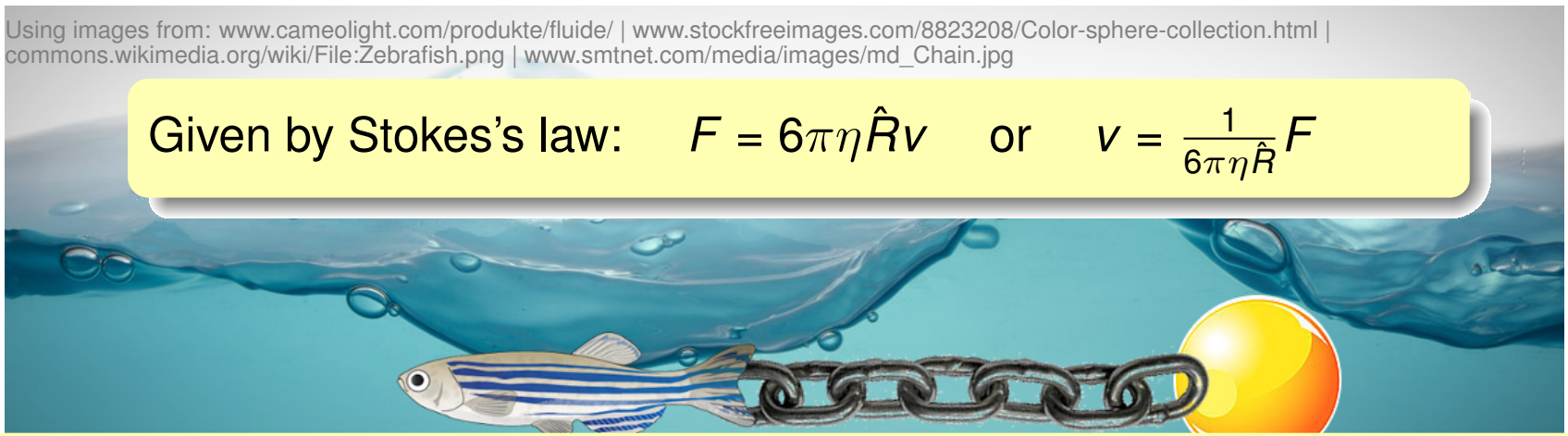

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Slight difficulty:

Stokes's law is for a single cell, not for interacting cell populations.

... but let's go ahead!

Ass

where $F(t, x)$ is now the net force (due to adhesion) acting on a cell at (t, x).

The Armstrong-Painter-Sherratt model
Net force due to adhesion

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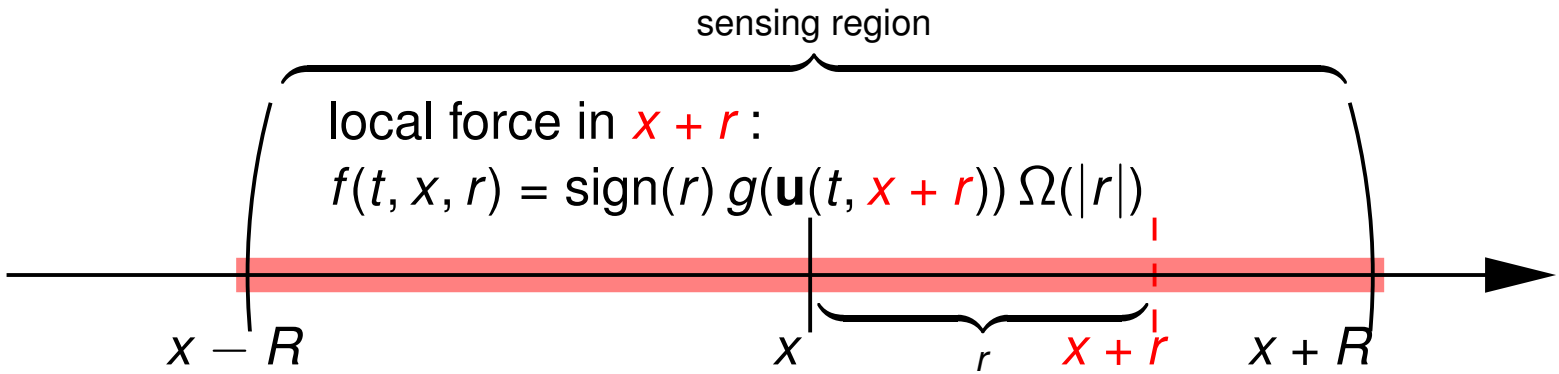
The net force F in (t, x) is the sum of "local" forces: $F(t,x) := \int_{-R}^{R} f(t,x,r)\,\mathrm{d}r$



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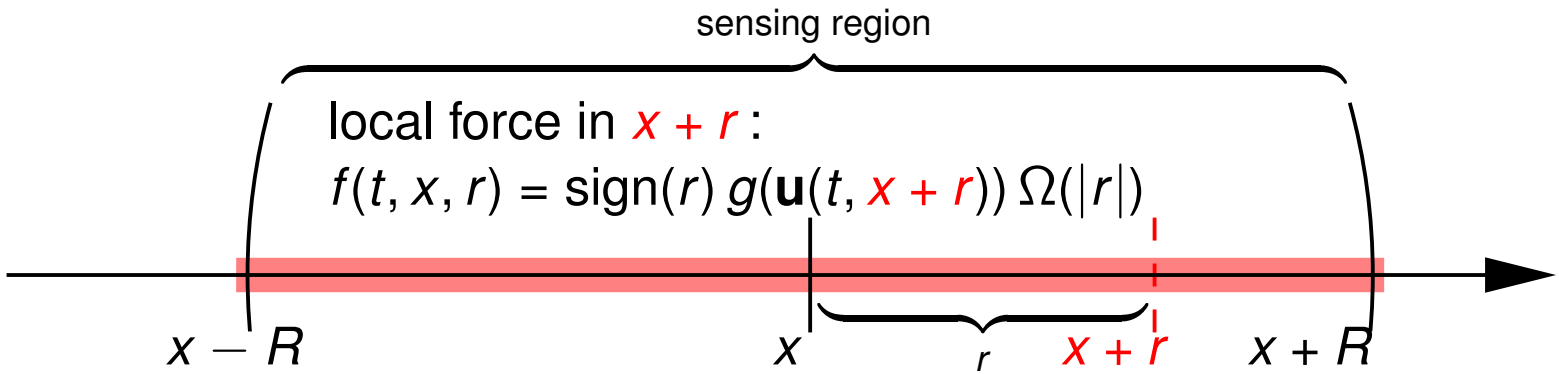

$\mathrm{sign}(r) = \frac{r}{|r|}$ force direction between the cell at x and those at $x + r$.

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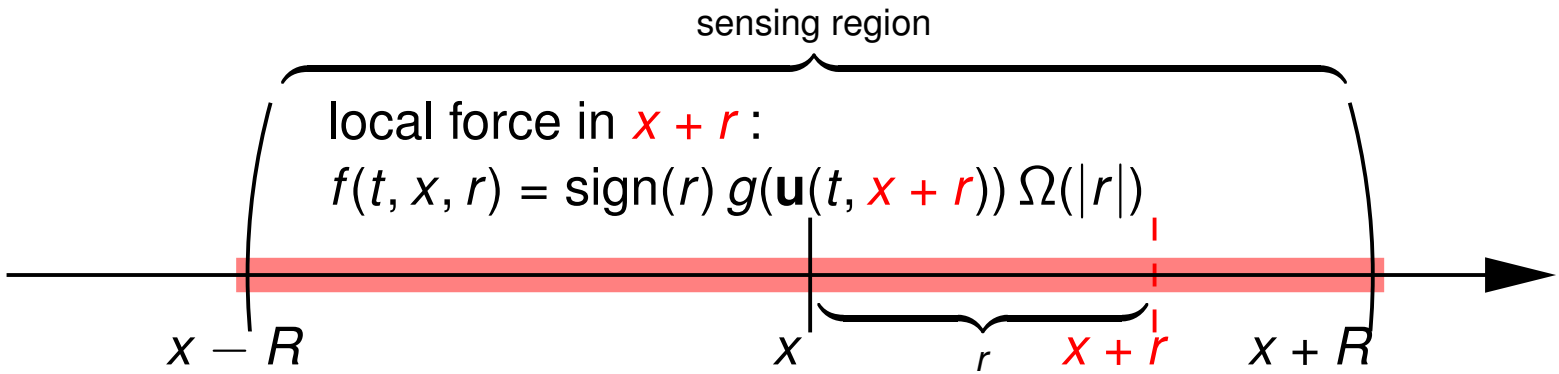

$\mathrm{sign}(r) = \frac{r}{|r|}$ force direction between the cell at x and those at $x + r$.

$g(\mathbf{u})$ force magnitude between the cell at x and those at $x + r$:

One cell type: $g(u) = Cu$ or $g(u) = Cu(1-u)^+$;
Two cell types: $g_1(u_1, u_2) = (C_{11}u_1 + C_{12}u_2)(1 - u_1 - u_2)^+$.

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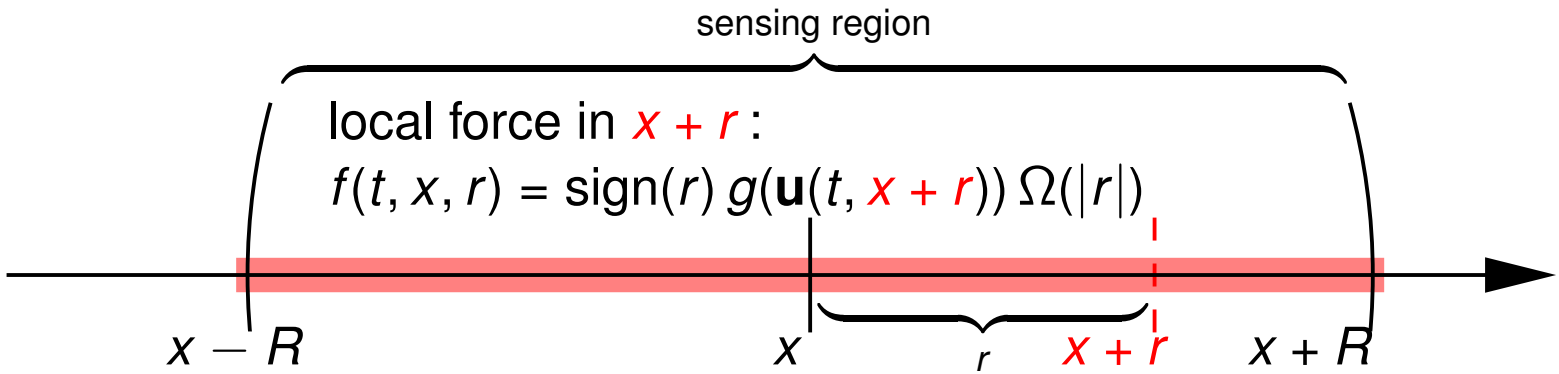

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$\Omega(|r|) \geq 0$ radial dependency: e.g. constant or decaying on $[0, R]$.

The Armstrong-Painter-Sherratt model
The nonlocal PDE model

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Results in nonlocal adhesion velocity $\mathcal{A}_i\{\mathbf{u}(t,\cdot)\}(x)$ for cell type i

$$\mathcal{A}_i\{\mathbf{u}(t,\cdot)\}(x) := \frac{1}{\Phi R}\int_{\mathcal{S}} \frac{r}{|r|}\, g_i(\mathbf{u}(t,x+r))\,\Omega(|r|)\,\mathrm{d}r\,,$$

where $\mathcal{S}$ now denotes the sensing region relative to but independent of x.

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Conservation of mass framework leads to nonlocal PDE model

$$\partial_t u_i = -\nabla\cdot\left(-D_i\nabla u_i + u_i\mathcal{A}_i\{\mathbf{u}(t,\cdot)\}\right)$$

where

- $-D_i\nabla u_i$ is a Fickian diffusive flux and
- $+u_i\mathcal{A}_i\{\mathbf{u}(t,\cdot)\}$ is the flux due to adhesion.

The system is complemented with initial and (periodic) boundary conditions.

Application: Cell sorting

[G. & Painter, '10]

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- Two cell populations with densities $u_A(t,x)$ and $u_B(t,x)$ for $x \in (0,10)^2$.
- Model equations

$$\partial_t u_A = -\nabla \cdot \left(-D\nabla u_A + u_A \mathcal{A}_A\{\mathbf{u}(t,\cdot)\}\right)$$
$$\partial_t u_B = -\nabla \cdot \left(-D\nabla u_B + u_B \mathcal{A}_B\{\mathbf{u}(t,\cdot)\}\right)$$

where $\mathcal{S}$ is the unit circle, $D = R = \Phi = 1$, $\Omega \equiv 1$, and

$$g_A(\mathbf{u}) = (C_{AA}u_A + C_{AB}u_B)(1 - u_A - u_B)^+$$
$$g_B(\mathbf{u}) = (C_{BA}u_A + C_{BB}u_B)(1 - u_A - u_B)^+$$

with self-adhesion coefficents C_{AA} and C_{BB}
and cross-adhesion coefficents $C_{AB} = C_{BA}$.

- Equations complemented with initial and periodic boundary conditions.

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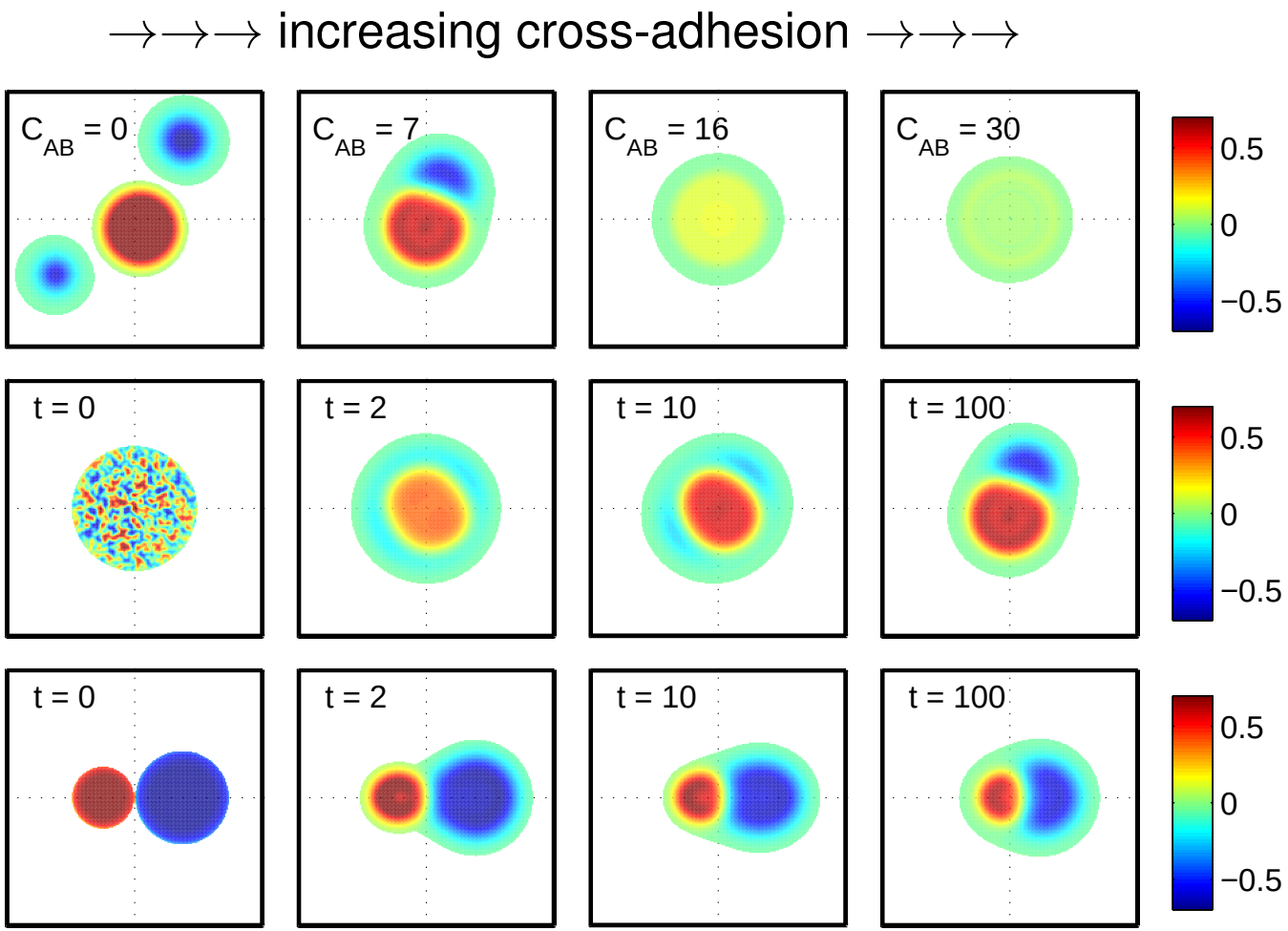

Plots show the difference $u_A - u_B$

Parameter:
$C_{AA} = 30$
$C_{BB} = 15$

Initial conditions:
← mixed

← separated

[G. & Painter, ’10]

Application: cancer invasion

[Domschke et al., J Theor Biol, 361, '14], also [G. & Chaplain, J Theor Biol, 250, '08]

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Model with three time- and space-dependent variables:

- the cancer cell density, $c : \mathcal{I}_T \times \mathcal{D} \to \mathbb{R}$,
- the extracellular matrix (ECM) density, $v : \mathcal{I}_T \times \mathcal{D} \to \mathbb{R}$, and
- the matrix-degrading enzyme (MDE) concentration, $m : \mathcal{I}_T \times \mathcal{D} \to \mathbb{R}$.

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$$
\begin{aligned}
\frac{\partial c}{\partial t} &= -\nabla \cdot \left[-D_1 \nabla c + c\mathcal{A}\{t, \mathbf{u}(t,\cdot)\} \right] + \mu_{1,1} c(1-u-v)) \,, \\
\frac{\partial v}{\partial t} &= -\gamma m v + \mu_2 (1-u-v))^+ \,, \\
\frac{\partial m}{\partial t} &= -\nabla \cdot [-D_3 \nabla m] + \alpha_1 c - \lambda m \,,
\end{aligned}
$$

where $\mathbf{u} := (c, v)$ and function g of the nonlocal term $\mathcal{A}$ specified by:

$$
g(t, \mathbf{u}) = [S_{cc}(t)c + S_{cv}(t)v] \cdot (1-u-v)^+ \,.
$$

Complemented with initial and zero-flux boundary conditions.

Application: cancer invasion

[Domschke et al., J Theor Biol, 361, '14], also [G. & Chaplain, J Theor Biol, 250, '08]

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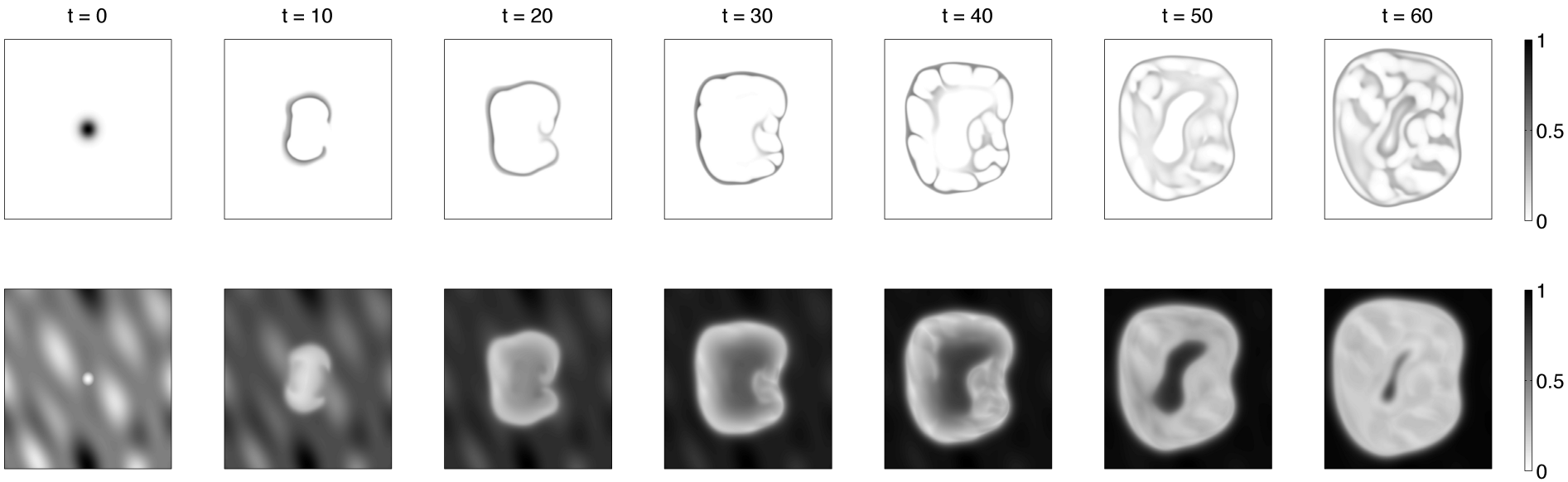
- Heterogeneous initial ECM density; ECM remodelling at rate $\mu_2 = 0.05$.
- Cell-matrix adhesion coefficient increases from 0.25 to 0.5 at $t = 10$
- Cell-cell adhesion coefficient decreases from 0.5 to 0.25 at $t = 40$.
- Plots of cell density (top row) and ECM density (bottom row) at various times t.



Application: zebrafish pigmentation patterning

[Painter et al., Bull Math Biol, 77, '15]

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- Stripe/interstripe pattern with thin separating strip without pigment cells:
  - black melanophores (u) and some light reflecting iridophores;
  - yellowish xanthophores (v) and light reflecting iridophores.
- Turing-type, morphogen-based models in the '90, but...
  ...no chemical morphogenes were found!
- Here: minimal set of pattern-generating interactions, cf. [Yamanaka & Kondo, PNAS, '14].
- "Run and Chase" proposed to explain pigmentation in zebrafish and related species:

u is repelled by v, i.e. $C_{uv} < 0$, v is attracted by u, i.e. $C_{vu} > 0$.

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[Painter et al., Bull Math Biol, 77, '15]

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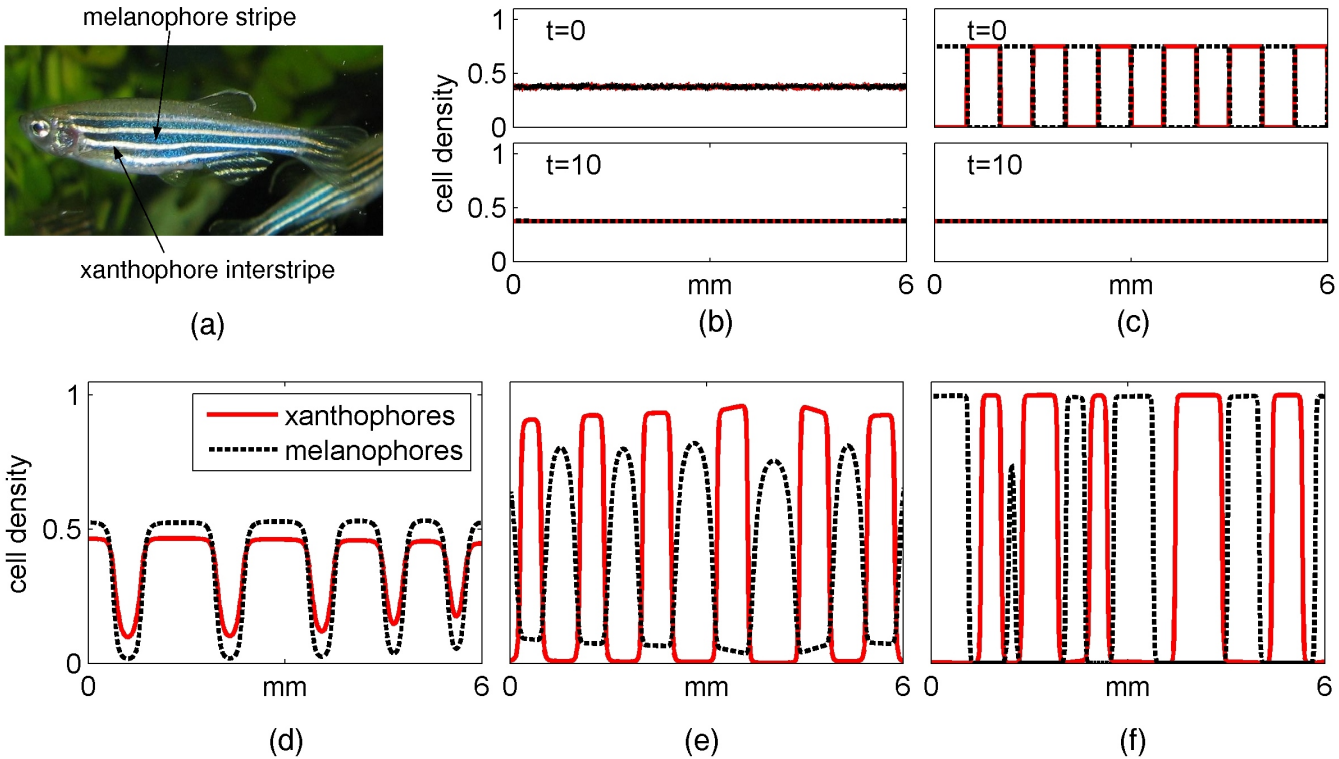

(b,c) no homotypic interaction $\rightsquigarrow$ no pattern; (d) $C_{uu} > 0 \rightsquigarrow$ mixed aggregates;

(e) $C_{vv} > 0 \rightsquigarrow$ realistic pattern; (f) $C_{uu}, C_{vv} > 0 \rightsquigarrow$ no robust pattern.

More likely: include the impact of iridophore cells to explain patterning.

The Armstrong-Painter-Sherratt model
Analytical results

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- Existence and boundedness of solution
  - [Sherratt et al., '09] boundedness in 1D requires additional assumptions on g and Ω.
  - [Chaplain et al., '11] local and global existence for nonlocal cancer-ECM adhesion model.
  - [Hillen et al., '17] local and global existence and boundedness for Armstrong-Painter-Sherratt and cancer invasion model.

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- One cell population: aggregation takes place for $C > 0$ sufficiently large.
- For sensing radius $R \to 0$: nonlocal model reduces to [G., Chaplain, '08]
  - standard taxis model for linear g,
  - volume-filling taxis [Hillen, Painter, '01] model for logistic (volume filling) g.

Derivation of the nonlocal PDE model from a position-jump model

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In [Gerisch & Painter, '10] we state:

A highly desirable objective is to develop continuous models for cellular adhesion as the appropriate limit from an underlying individual model for cell movement [...].

We propose to fill this gap via a position-jump model (spatial stochastic random walk).

[Buttenschön et al, J Math Biol, 76, '18]

Goals:

- a better understanding of underlying modelling assumptions and
- a framework to modify the continuous model as needed.

A position-jump model

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Master equation for a position jump process [Othmer, Dunbar, Alt, '88]:

$$\partial_t u(t,x) = \lambda \int_{\mathcal{D}} T(x,y)u(t,y) - T(y,x)u(t,x)\, d\mu(y)$$

where

- $(\mathcal{D}, \mu)$ measure space representing physical space (domain or grid),
- λ jump rate,
- $T(x,y)$ probability density function for jump from y to x.

A position-jump model

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$$\partial_t u(t,x) = \lambda \int_{\mathcal{D}} T(x,y)u(t,y) - T(y,x)u(t,x)\, d\mu(y)$$

Define:

- Heading $z := x - y$, such that $T_y(z) := T(y+z,y) = T(x,y)$,
- symmetric set D^y, the set of possible headings from y.

A position-jump model

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$$\partial_t u(t,x) = \lambda \int_{\mathcal{D}} T(x,y)u(t,y) - T(y,x)u(t,x)\, d\mu(y)$$

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Lemma (Even and Odd Decomposition)

There is a decomposition

$$T_y(z) = S_y(z) + \mathbf{A}_y(z) \cdot \frac{z}{|z|},$$

where $S_y(z) = S_y(-z)$ and $\mathbf{A}_y(z) = \mathbf{A}_y(-z)$ are symmetric.

A position-jump model

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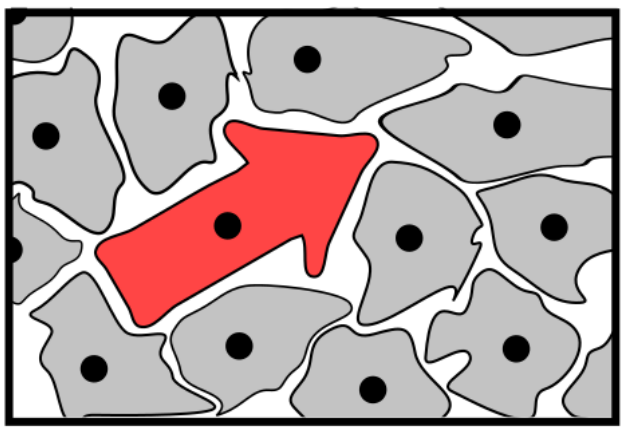
$$T_y(z) = S_y(z) + \mathbf{A}_y(z) \cdot \frac{z}{|z|},$$

- $S_y(z)$ will become the motility and lead to the diffusion term.
- $\mathbf{A}_y(z)$ will define the cell polarization and lead to the adhesion integral term.



A position-jump model

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- Consider myopic random walk, that is $S_y(z) = S_y$ and $\mathbf{A}_y(z) = \mathbf{A}_y$.
- Substitute $T_y(z)$ into the master equation and rearrange.
- Consider small jumps of length h in any direction in $\mathbb{S}^{n-1}$.
- Use Taylor expansion in h.

Then

$$\partial_t u = \lambda h^{n-1} \left[\frac{h^2 |\mathbb{S}^{n-1}|}{2n} \Delta \left(S_x u(t,x) \right) - \frac{h |\mathbb{S}^{n-1}|}{n} \nabla \cdot \left(\mathbf{A}_x u(t,x) \right) \right] + h.o.t.$$

A position-jump model
Advection-diffusion limit

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Assume $\mathbf{A}_x = O(h)$ and consider the parabolic scaling, i.e. $1/\lambda \sim h^{n+1}$.

Then the following limits exist:

$$\lim_{h\to 0,\lambda\to\infty} \frac{\lambda h^n |\mathbb{S}^{n-1}|}{n} \mathbf{A}_x = \alpha(x) \quad \text{and} \quad \lim_{h\to 0,\lambda\to\infty} \frac{\lambda h^{n+1} |\mathbb{S}^{n-1}|}{n} S_x = D(x)$$

...leading to the following limit equation

$$\partial_t u(t,x) + \nabla \cdot (\alpha(x) u(t,x)) = \Delta (D(x) u(t,x))$$

Note: spatial diffusion parameter appears inside Laplacian (expected for transition rates based on local information, cf. [Stevens & Othmer, '97]).

A position-jump model
Advection-diffusion limit

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$$\partial_t u(t,x) + \nabla \cdot (\alpha(x) u(t,x)) = \Delta (D(x) u(t,x))$$

Note: spatial diffusion parameter appears inside Laplacian (expected for transition rates based on local information, cf. [Stevens & Othmer, '97]).

We assume

- S_x is constant, i.e. D is constant.
- $\mathbf{A}_x$ is given by the net adhesive force acting on the cell that is located at x.

A position-jump model
Microscopic biological assumptions

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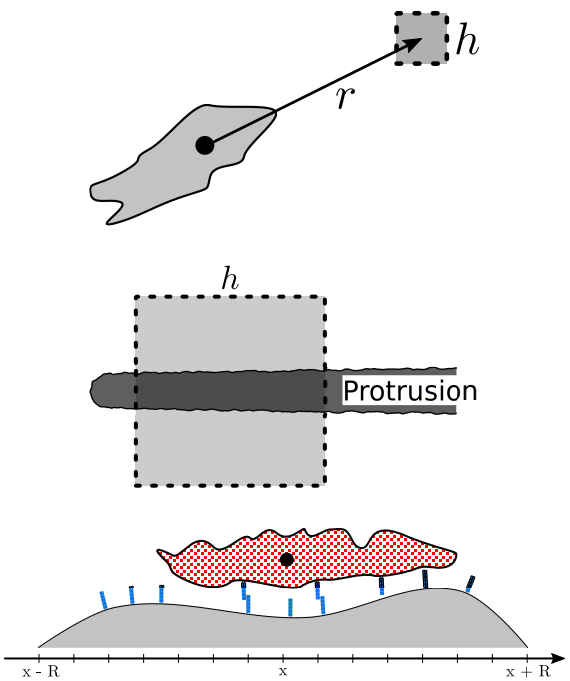

V_h: small test volume inside sensing region of cell at x.

- The distance from V_h to the cell body is r.
- Direction of generated force is $r/|r|$.
- The free space in V_h is $f(x+r)$.
- The part of the cell protrusion that is inside V_h is independent of x and called $\Omega(r)$.
- The density of adhesion bonds formed with background population in V_h is called $N_b(x+r)$.
- The adhesive strength per bond is γ.

$\rightsquigarrow$ adhesive force generated in V_h

$$\mathbf{F_h}(x+r) = \frac{r}{|r|}\,\gamma\,\underbrace{h^n N_b(x+r)}_{\text{\#of adhesion bonds}}\,\underbrace{f(x+r)}_{\text{free space}}\,\underbrace{h\Omega(r)}_{\text{amt. of cell in } V_h}$$

A position-jump model
Net adhesive force

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Summing $\mathbf{F_h}(x + r)$ over all test volumina in the sensing region $\mathcal{S}$

$$\rightsquigarrow \quad \text{net adhesive force } \mathbf{F}_{\text{net}}(x) = O(h)$$

and we let $\mathbf{A}_x := \mathbf{F}_{\text{net}}(x)$.

A position-jump model
Net adhesive force

TECHNISCHE UNIVERSITÄT DARMSTADT

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Now, letting $h \to 0$ and $\lambda \to \infty$ yields

$$\alpha(x) = \int_{\mathcal{S}} \underbrace{\gamma \; N_b(x + r) \; f(x + r)}_{=g(\mathbf{u}(t,x+r))} \; \frac{r}{|r|} \Omega(r) \, \mathrm{d}r.$$

A position-jump model
Net adhesive force

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Next task: define specific N_b, f, and Ω for particular models.

A position-jump model
The linear Armstrong-Painter-Sherratt model

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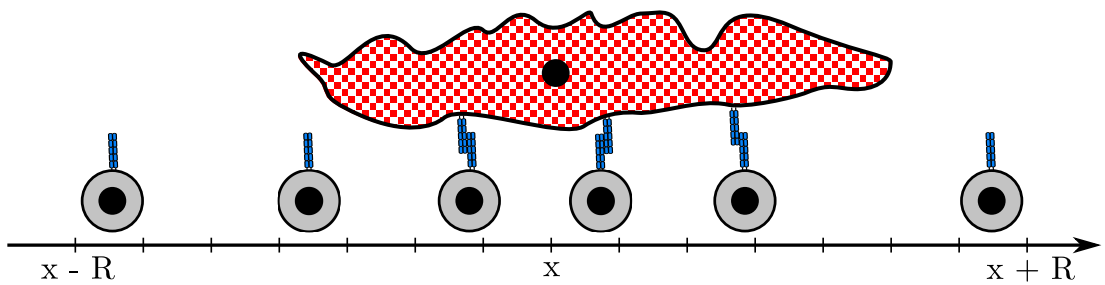
1. One dimensional domain with sensing region $\mathcal{S} = [-R, R]$.
2. Assume law of mass action kinetics for the adhesion bonds, i.e.

$$N_b(x) \sim u(x)$$

3. Assume there is always free space, i.e. $f \equiv 1$.
4. Let $\Omega(r)$ be the uniform distribution on $\mathcal{S}$, i.e. $\Omega(r) = \frac{1}{2R}$.

$$\partial_t u = D u_{xx} - \left(u \int_{-R}^{R} \gamma u(t, x + r) \frac{r}{|r|} \frac{1}{2R} \, \mathrm{d}r \right)_x$$



A position-jump model
Adhesion with volume filling

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1. Assume law of mass action kinetics for the adhesion bonds, i.e.

$$N_b(x) \sim u(x)$$

2. Assume space is limited $f(u(t,x)) = (1 - u(t,x))^+$.
3. Let $\Omega(r)$ be the uniform distribution on $\mathcal{S}$.

$$\partial_t u = D\Delta u - \nabla \cdot \left(u \int_{\mathcal{S}} \gamma u(t, x+r)(1 - u(t, x+r))^+ \frac{r}{|r|} \Omega(r)\, \mathrm{d}r \right)$$

Objective from spatial constraint:

Areas of high cell density in $x + \mathcal{S}$ contribute less to the adhesive force in x.

A position-jump model
Non-local background population

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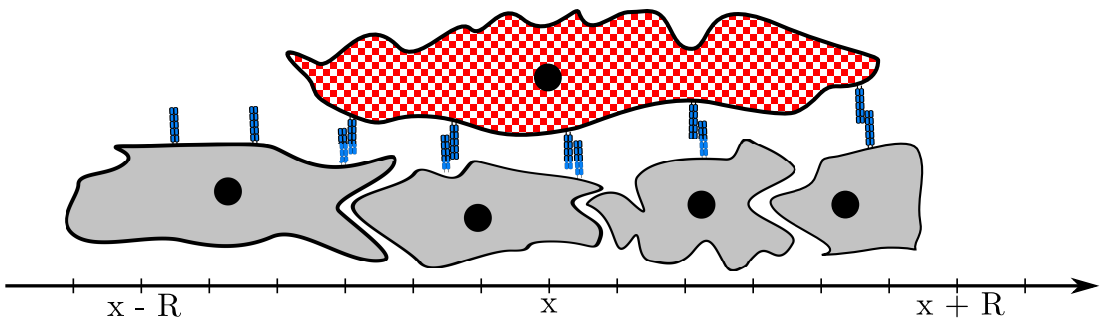
1. Assume cells in the background have spatial distribution of adhesion bonds $\eta(r)$ around their cell center:

$$N_b(x) \sim \int_{\mathcal{S}} u(t, x + r)\eta(r)\,\mathrm{d}r\,.$$

2. Assume there is always free space, i.e. $f \equiv 1$.

$$\partial_t u = D\Delta u - \nabla \cdot \left(u \int_{\mathcal{S}} \gamma \int_{\mathcal{S}} u(t, x + y + r)\eta(y)\,\mathrm{d}y \frac{r}{|r|}\Omega(r)\,\mathrm{d}r \right)$$



Numerical technique
The need for efficient numerics

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$$\partial_t u_i(t,x) = -\nabla \cdot \left(u_i(t,x) \mathcal{A}_i\{\mathbf{u}(t,\cdot)\}(x) \right) + \ldots$$

- Spatial discretisation (FV, FD, FE) [we use 2nd order finite volumes]:

  $\mathcal{A}_i\{\mathbf{u}(t,\cdot)\}(x)$ *must be evaluated for given approximations of* $\mathbf{u}(t,\cdot)$ *in many points* x*, related to the spatial grid, of spatial domain* $\mathcal{D}$*.*

- Time integration [we use linearly implicit Runge-Kutta method ROWMAP]:

  The spatial discretisation must be evaluated repeatedly over time for changing $\mathbf{u}(t,\cdot)$*.*

The evaluation of the nonlocal term quickly becomes the computational bottleneck of any numerical scheme.

Numerical technique
Nonlocal term approximation — periodic setting

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$$\mathcal{A}\{\mathbf{u}(t,\cdot)\}(x) := \frac{1}{\Phi R}\int_{\mathcal{S}} \frac{r}{|r|}\, g(\mathbf{u}(t,x+r))\,\Omega(|r|)\,\mathrm{d}r\,,$$

- Uniform $N_1 \times N_2 \times \cdots \times N_d$ grid on spatial domain $\mathcal{D}$.
- Grid cells $\mathcal{D}_i$ of size $h_1 \times h_2 \times \cdots \times h_d$ indexed with $i \in \mathcal{N}$ (multi-index set).
- Assume $\mathbf{u}$ is given as centre value or volume average $\mathbf{u}_i$ for each $\mathcal{D}_i$.
- Define $g_i := g(\mathbf{u}_i)$ for all $i \in \mathcal{N}$ and extend periodically beyond $\mathcal{N}$.
- Approximate $g(\mathbf{u}(t,x))$ by piecewise constant reconstruction from

$$g(\mathbf{u}(t,x)) \approx \tilde{g}(x) := \sum_{i\in\mathcal{N}} g_i \chi_i(x)$$

The replacement of $g(\mathbf{u}(t,\cdot))$ by $\tilde{g}$ is the only approximation in the scheme.
From now on everything will be essentially exact.

Numerical technique
Nonlocal term approximation — periodic setting

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Nonlocal term after approximation for $x^* \in \mathcal{D}$

$$v(x^*) := \frac{1}{\Phi R} \int_{\mathcal{S}} \frac{r}{|r|} \tilde{g}(x^* + r)\, \Omega(|r|)\, \mathrm{d}r = \sum_{i \in \mathcal{N}} g_i \underbrace{\frac{1}{\Phi R} \int_{\mathcal{S}} \frac{r}{|r|} \chi_i(x^* + r)\, \Omega(|r|)\, \mathrm{d}r}_{:= w_i^* \text{ (integration weight)}} .$$

Numerical technique
Nonlocal term approximation — periodic setting

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All points $x_m^* := x^* + (m_j h_j)_{j=1}^d$ with $m \in \mathbb{Z}^d$ share the same integration weights!

$$v(x_m^*) = \sum_{i \in \mathcal{N}} g_{i+m} w_i^* .$$

Integration weights w_i^*

- depend only on known quantities,
- can be precomputed with your favourite method to arbitrary accuracy, and
- can be applied to evaluate the nonlocal term for arbitrary $\tilde{g}$ and all x_m^*.

Numerical technique
Nonlocal term approximation — periodic setting

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$$v(x_m^*) = \sum_{i \in \mathcal{N}} g_{i+m} w_i^* \ .$$

Do we need all w_i^*? — If $\{x^* + \mathcal{S}\} \cap \mathcal{D}_i = \emptyset$ then $w_i^* = 0$.

Let $\tilde{\mathcal{N}} \subset \mathbb{Z}^d$ be an interval such that for all $i \in \mathcal{N} \setminus \{i^* + \tilde{\mathcal{N}}\}$ holds $w_i^* = 0$.

Numerical technique
Nonlocal term approximation — periodic setting

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Let $\tilde{\mathcal{N}} \subset \mathbb{Z}^d$ be an interval such that for all $i \in \mathcal{N} \setminus \{i^* + \tilde{\mathcal{N}}\}$ holds $w_i^* = 0$.

- Apply integration rule by executing the sum. Can become expensive!
- Combined evaluation at same location within each grid cell $\mathcal{D}_n$, $\forall n \in \mathcal{N}$:

$$v_n := v(x_{n-i^*}^*) = \sum_{i \in \tilde{\mathcal{N}}} g_{i+n} w_i \ , \quad w_i := w_{i+i^*}^* \ .$$

This provides a linear map from $G := (g_n)_{n \in \mathcal{N}}$ to $V := (v_n)_{n \in \mathcal{N}}$.

Structure of corresponding matrix W:

$d = 1$: (banded) circulant matrix W of weights;

$d = 2$: (banded) block-circulant matrix with (banded) circulant blocks; ...

Numerical technique
Nonlocal term approximation — periodic setting

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Evaluation of the matrix-vector product $V = WG$ (case $d = 1$).

- Circulant matrix W defined by its first column, denoted w.
- Any circulant W is diagonalized by the Fourier transform matrix F and

$$WF = F\,\mathrm{diag}(Fw)\,.$$

- Thus

$$V = WG = F\,\mathrm{diag}(Fw)F^*G = \texttt{FFT}(\texttt{FFT}(w).*\texttt{iFFT}(G))\,,$$

  where `FFT` denotes the Fast Fourier Transform algorithm and `iFFT` its inverse; $.*$ is element-wise multiplication.
- This cuts the operaton count down from $\mathcal{O}(N_1^2)$ to $\mathcal{O}(N_1 \log(N_1))$ operations.

General d: replace `FFT` by its d-dimensional counterpart `FFT`d.

Numerical technique
Nonlocal term approximation — extensions

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- From periodic to non-periodic boundary conditions:
  - Need to specify values of $g(\mathbf{u})$ outside of $\mathcal{D}$ for definition of the integral.
  - Banded circulant matrices replaced by banded Toeplitz matrices.
  - Toeplitz-to-circulant embedding saves efficient FFT-based algorithm.
- From uniform to non-uniform grids:
  - The integration weights independent of evaluation position property breaks down and so the combined evaluation via FFT.
  - Combined evaluation via fixed uniform intermediate grid works (it's not perfect).

Numerical technique
Nonlocal term approximation — Accuracy

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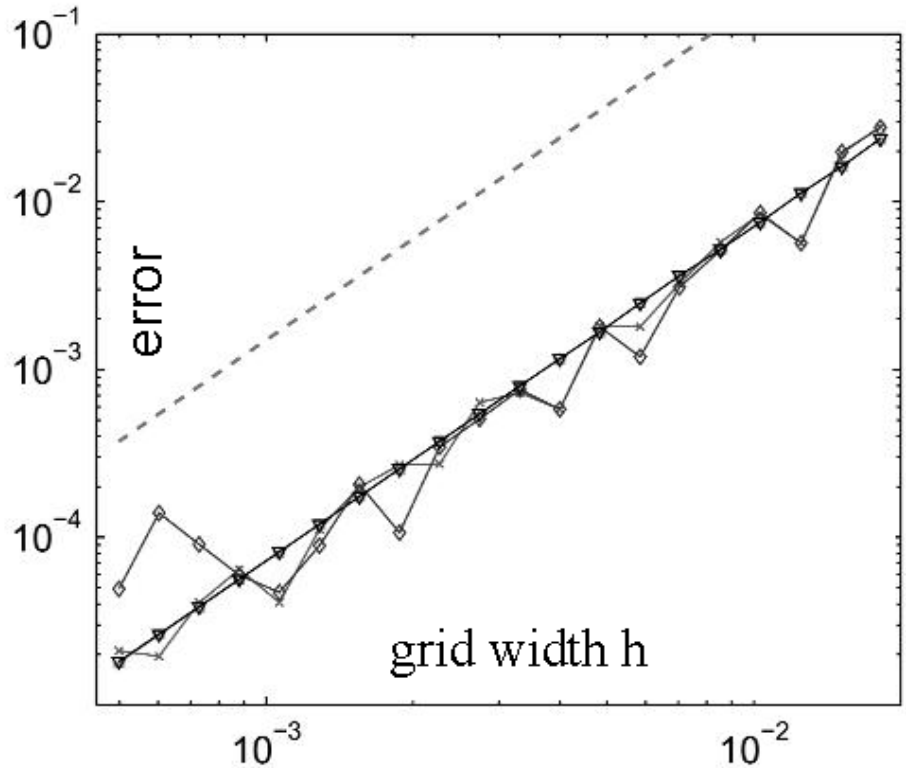
- $\mathcal{D} \subset \mathbb{R}$
- $\tilde{g}(x) = \sin(8\pi x)$
- $\mathcal{S} = B(0, 0.1)$
- $\Omega \equiv 1$

$\rightsquigarrow$ nonlocal term in analytical form

error for decreasing grid width $\rightarrow$



Nonlocal term evaluation converges with order two for grid width to zero.

Numerical technique
Nonlocal term approximation — Efficiency

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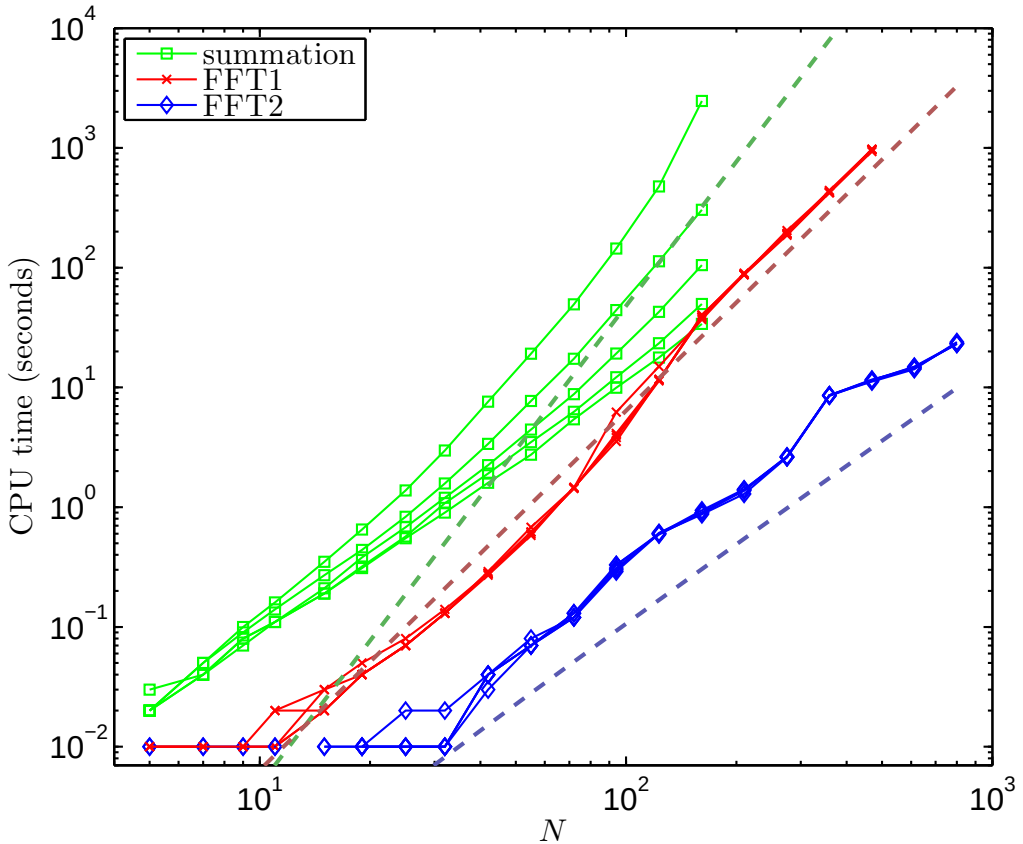
d = 2-dimensional square domain $\mathcal{D}$ with $N \times N$ grid, periodic BCs.

Tests for increasing sensing region $\mathcal{S}$.

FFT2 vs. summation:
reduction of operations ($h = \frac{1}{N}$)
$\sim N^4 \rightarrow \sim N^2 \log(N)$.

Matrix-vector product:
speed-up: $10 - 100$



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Matrix-vector product:
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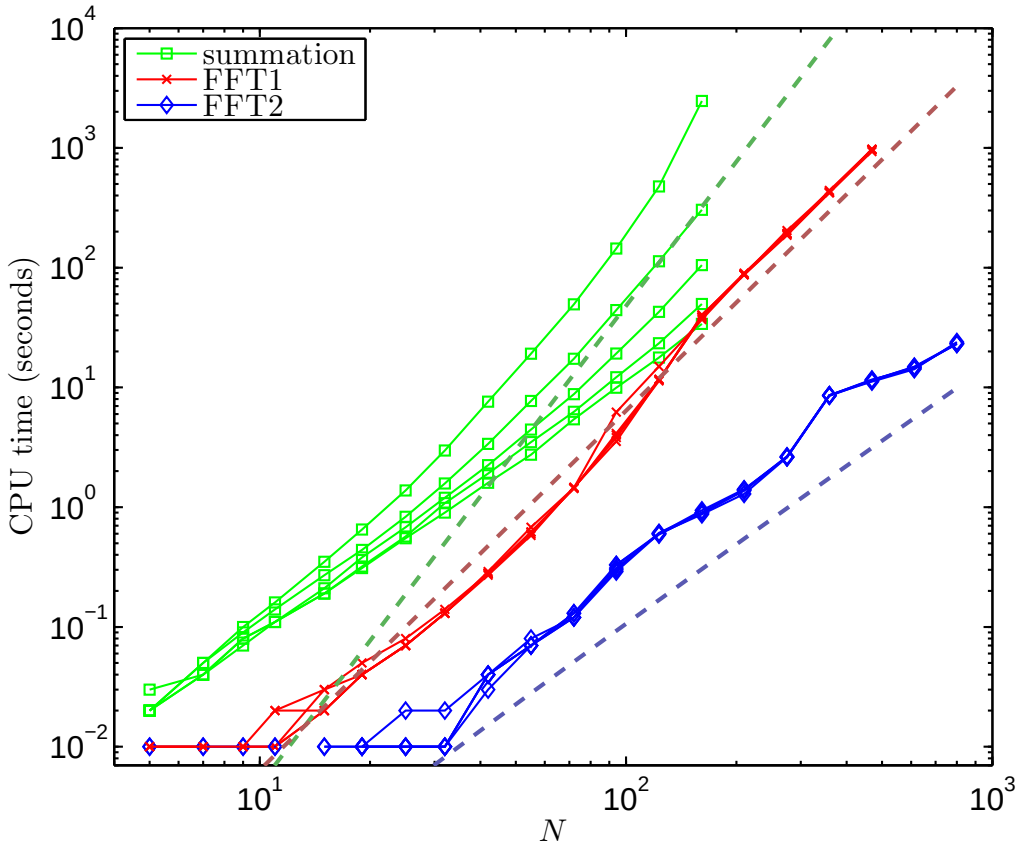
Full cell sorting simulation:
speed-up: ≈ 20 (2 h to 6 min).



Summary

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- Cell attraction and repulsion are important basic mechanisms in biology.
- A flexible nonlocal continuous model is available and successfully applied in models in developmental and cancer biology.
- These models can be efficiently simulated by making use of the FFT; spatially highly resolved long time simulations are feasible.
- The requirements of periodic boundary conditions and uniform spatial grids can be relaxed while maintaining favourable algorithmic properties.
- The nonlocal continuous model can be derived from a stochastic random walk. This allows for better insight into the parametrisation of the continuous model.

Ongoing work and outlook

TECHNISCHE UNIVERSITÄT DARMSTADT

- Cross-diffusion, instead of Fickian diffusion, in models with multiple cell types can significantly sharpen interfaces.
- Modelling neural crest cell invasion requires nonlocal term on growing domains. Efficient numerics?
- More tests and experience for non-uniform grids.

Ongoing work and outlook

TECHNISCHE UNIVERSITÄT DARMSTADT

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Many thanks to collaborators:
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A. Buttenschön (UBC), D. Trucu (Dundee), P. Domschke (Darmstadt), ...

Ongoing work and outlook

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Thank you very much for your attention!