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

- 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.
Cell contact and response

- Cells can communicate via direct contacts, e.g., membrane-membrane molecular binding.
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- 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.

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).

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

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

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.

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

Ca\(^{2+}\) ions, P120, α-cat, β-cat, F-actin, Intercellular space, Plasma membrane, Cytoplasm
Example 1: Cell adhesion
Molecular aspects and applications

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.

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

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.

[Foty & Steinberg, Dev. Biol. (278), '05]
Example 1: Cell adhesion
Cell sorting

[Example Image]

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.

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.

[Example Diagram]
Example 1: Cell adhesion
Cancer invasion

- 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]

Invasive 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

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
Zebrasfish pigmentation pattern

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

Two general classes of models

- **individual cell based (discrete) models**
  - dynamics of individual cells,

- **continuous models**
  - 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

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,...)
  - 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 ≈140 citations to date!
The Armstrong-Painter-Sherratt model

Underlying idea

In a fluid (extracellular space) with dynamic viscosity $\eta$ ...
The Armstrong-Painter-Sherratt model
Underlying idea

In a fluid (extracellular space) with dynamic viscosity $\eta$ ...

... is a spherical object (cell) with radius $\hat{R}$ ...

The Armstrong-Painter-Sherratt model
Underlying idea

In a fluid (extracellular space) with dynamic viscosity \( \eta \)
... is a spherical object (cell) with radius \( \hat{R} \)
... being dragged along with velocity \( v \).
The Armstrong-Painter-Sherratt model
Underlying idea

In a fluid (extracellular space) with dynamic viscosity $\eta$ ...
... is a spherical object (cell) with radius $\hat{R}$ ...
... being dragged along with velocity $v$.

What is the (drag) force $F$ on the sphere?
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... is a spherical object (cell) with radius $\hat{R}$ ...  
... being dragged along with velocity $v$.

What is the (drag) force $F$ on the sphere?

Given by Stokes’s law:  
\[ F = 6\pi \eta \hat{R} v \]

or  
\[ v = \frac{1}{6\pi \eta \hat{R}} F \]
The Armstrong-Painter-Sherratt model

Underlying idea

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

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

$\rightsquigarrow$ flux of cells $u(t, x)v(t, x) = u(t, x)\frac{1}{6\pi \eta \hat{R}}F(t, x)$, where $F(t, x)$ is now the net force (due to adhesion) acting on a cell at $(t, x)$. 
The Armstrong-Painter-Sherratt model
Underlying idea

In a fluid (extracellular space) with dynamic viscosity $\eta$ ... 
... is a spherical object (cell) with radius $\hat{R}$ ... 
... being dragged along with velocity $v$.

What is the (drag) force $F$ on the sphere?

Given by Stokes’s law: \[ F = 6\pi \eta \hat{R} v \quad \text{or} \quad v = \frac{1}{6\pi \eta \hat{R}} F \]

Slight difficulty:
Stokes’s law is for a single cell, not for interacting cell populations.
... but let’s go ahead!

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

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

local force in $x + r$:

$f(t, x, r) = \text{sign}(r) \, g(u(t, x + r)) \, \Omega(|r|)$

sensing region

$x - R \quad x + R$
The net force $F$ in $(t, x)$ is the sum of “local” forces:

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Local force in $x + r$:

$$f(t, x, r) = \text{sign}(r) \, g(u(t, x + r)) \, \Omega(|r|)$$

**sign($r$)** = \frac{r}{|r|}  

force direction between the cell at $x$ and those at $x + r$.
The Armstrong-Painter-Sherratt model
Net force due to adhesion

The net force \( F \) in \((t, x)\) is the sum of “local” forces:

\[
F(t, x) := \int_{-R}^{R} f(t, x, r) \, dr
\]

\( f(t, x, r) \) is the local force in \( x + r \):

\[
f(t, x, r) = \text{sign}(r) \, g(u(t, x + r)) \, \Omega(|r|)
\]

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

\( g(u) \) 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: \( g_1(u_1, u_2) = (C_{11}u_1 + C_{12}u_2)(1 - u_1 - u_2)^+ \).
The net force $F$ in $(t, x)$ is the sum of “local” forces: 

$$F(t, x) := \int_{-R}^{R} f(t, x, r) \, dr$$

The local force in $x + r$:

$$f(t, x, r) = \text{sign}(r) \, g(u(t, x + r)) \, \Omega(|r|)$$

**Sign direction**: 

$$\text{sign}(r) = \frac{r}{|r|}$$

**Force direction**: force direction between the cell at $x$ and those at $x + r$.

**Force magnitude**: 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: $g_1(u_1, u_2) = (C_{11}u_1 + C_{12}u_2)(1 - u_1 - u_2)^+$.

**Radial dependency**: 

$$\Omega(|r|) \geq 0$$

radial dependency: e.g. constant or decaying on $[0, R]$. 

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The Armstrong-Painter-Sherratt model

The nonlocal PDE model

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

$$\mathcal{A}_i\{u(t, \cdot)\}(x) := \frac{1}{\Phi R} \int_S \frac{r}{|r|} g_i(u(t, x + r)) \Omega(|r|) \, dr,$$

where $S$ now denotes the sensing region relative to but independent of $x$. 
The Armstrong-Painter-Sherratt model
The nonlocal PDE model

Results in nonlocal adhesion velocity \( A_i\{u(t, \cdot)\}(x) \) for cell type \( i \)

\[
A_i\{u(t, \cdot)\}(x) := \frac{1}{\Phi R} \int_S \frac{r}{|r|} g_i(u(t, x + r)) \Omega(|r|) \, dr ,
\]

where \( S \) now denotes the sensing region relative to but independent of \( x \).

Conservation of mass framework leads to nonlocal PDE model

\[
\partial_t u_i = - \nabla \cdot \left( -D_i \nabla u_i + u_i A_i\{u(t, \cdot)\} \right)
\]

where

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

The system is complemented with initial and (periodic) boundary conditions.
Two cell populations with densities $u_A(t, x)$ and $u_B(t, x)$ for $x \in (0, 10)^2$.

Model equations

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

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

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

$$g_A(u) = (C_{AA}u_A + C_{AB}u_B)(1 - u_A - u_B)^+$$

$$g_B(u) = (C_{BA}u_A + C_{BB}u_B)(1 - u_A - u_B)^+$$

with self-adhesion coefficients $C_{AA}$ and $C_{BB}$

and cross-adhesion coefficients $C_{AB} = C_{BA}$.

Equations complemented with initial and periodic boundary conditions.
Application: Cell sorting

[G. & Painter, ’10]

→→→ increasing cross-adhesion →→→

Plots show the difference $u_A - u_B$

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

Initial conditions:
← mixed
← separated

[C. & Painter, ’10]
Application: cancer invasion

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

Model with three time- and space-dependent variables:

- the cancer cell density, \( c : I_T \times D \rightarrow \mathbb{R} \),
- the extracellular matrix (ECM) density, \( v : I_T \times D \rightarrow \mathbb{R} \), and
- the matrix-degrading enzyme (MDE) concentration, \( m : I_T \times D \rightarrow \mathbb{R} \).
Model with three time- and space-dependent variables:

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

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

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

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

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]

- 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 $t$. 

![Images of cell and ECM density plots at different times](image-url)
Application: zebrafish pigmentation patterning


▶ 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:

\[ u \text{ is repelled by } v, \text{ i.e. } C_{uv} < 0, \quad v \text{ is attracted by } u, \text{ i.e. } C_{vu} > 0. \]
Application: zebrafish pigmentation patterning


(b,c) no homotypic interaction \(\rightarrow\) no pattern;

d(\(C_{uu}\) > 0 \(\rightarrow\) mixed aggregates;

e(\(C_{vv}\) > 0 \(\rightarrow\) realistic pattern;

(f) \(C_{uu}, C_{vv}\) > 0 \(\rightarrow\) no robust pattern.

More likely: include the impact of iridophore cells to explain patterning.
The Armstrong-Painter-Sherratt model
Analytical results

- Existence and boundedness of solution
  - [Sherratt et al., '09] boundedness in 1D requires additional assumptions on $g$ and $\Omega$.
  - [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.
The Armstrong-Painter-Sherratt model
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- One cell population: aggregation takes place for $C > 0$ sufficiently large.
The Armstrong-Painter-Sherratt model
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  - [Sherratt et al., '09] boundedness in 1D requires additional assumptions on $g$ and $\Omega$.
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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) $g$. 
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

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

\[ \partial_t u(t, x) = \lambda \int_D T(x, y) u(t, y) - T(y, x) u(t, x) \, d\mu(y) \]

where

- \((D, \mu)\) measure space representing physical space (domain or grid),
- \(\lambda\) jump rate,
- \(T(x, y)\) probability density function for jump from \(y\) to \(x\).
A position-jump model

\[ \partial_t u(t, x) = \lambda \int_D T(x, y)u(t, y) - T(y, x)u(t, x) \, d\mu(y) \]

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

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

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 \( y \).

**Lemma (Even and Odd Decomposition)**

There is a decomposition

\[ T_y(z) = S_y(z) + A_y(z) \cdot \frac{z}{|z|}, \]

where \( S_y(z) = S_y(-z) \) and \( A_y(z) = A_y(-z) \) are symmetric.
A position-jump model

\[ T_y(z) = S_y(z) + A_y(z) \cdot \frac{z}{|z|}, \]

- \( S_y(z) \) will become the motility and lead to the diffusion term.
- \( A_y(z) \) will define the cell polarization and lead to the adhesion integral term.
A position-jump model

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

Then

$$\partial_t u = \lambda h^{n-1} \left[ \frac{h^2|S^{n-1}|}{2n} \Delta (S_x u(t, x)) - \frac{h|S^{n-1}|}{n} \nabla \cdot (A_x u(t, x)) \right] + h.o.t.$$
A position-jump model
Advection-diffusion limit

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

Then the following limits exist:

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

...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

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

Then the following limits exist:

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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.
- $A_x$ is given by the net adhesive force acting on the cell that is located at $x$. 
A position-jump model
Microscopic biological assumptions

\( V_h \): 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 \( \gamma \).

\[ F_h (x + r) = \frac{r}{|r|} \gamma \left( h^n N_b(x + r) \right) \frac{f(x + r)}{\text{free space}} h\Omega(r) \left( \text{amt. of cell in } V_h. \right) \]
A position-jump model
Net adhesive force

Summing \( F_h(x + r) \) over all test volumina in the sensing region \( S \)

\[ \text{\( \mapsto \)}} \quad \text{net adhesive force } F_{\text{net}}(x) = O(h) \]

and we let \( A_x := F_{\text{net}}(x) \).
A position-jump model
Net adhesive force

Summing $F_h(x + r)$ over all test volumina in the sensing region $S$

$\leadsto$ net adhesive force $F_{net}(x) = O(h)$

and we let $A_x := F_{net}(x)$.

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

$$\alpha(x) = \int_S \gamma N_b(x + r) f(x + r) \frac{r}{|r|} \Omega(r) \, dr.$$
A position-jump model
Net adhesive force

Summing \( F_h(x + r) \) over all test volumina in the sensing region \( S \)

\[ \mapsto \text{net adhesive force } F_{\text{net}}(x) = O(h) \]

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Now, letting \( h \to 0 \) and \( \lambda \to \infty \) yields

\[ \alpha(x) = \int_S \gamma N_b(x + r) f(x + r) \frac{r}{|r|} \Omega(r) \, dr. \]

Next task: define specific \( N_b, f, \) and \( \Omega \) for particular models.
A position-jump model
The linear Armstrong-Painter-Sherratt model

1. One dimensional domain with sensing region \( S = [-R, R] \).
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 \( S \), i.e. \( \Omega(r) = \frac{1}{2R} \).

\[
\partial_t u = Du_{xx} - \left( u \int_{-R}^{R} \gamma u(t, x + r) \frac{r}{|r|} \frac{1}{2R} \, dr \right)_x
\]
A position-jump model
Adhesion with volume filling

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 \( S \).

\[
\partial_t u = D \Delta u - \nabla \cdot \left( u \int_S \gamma u(t, x + r)(1 - u(t, x + r))^+ \frac{r}{|r|} \Omega(r) \, dr \right)
\]

Objective from spatial constraint:
Areas of high cell density in \( x + S \) contribute less to the adhesive force in \( x \).
A position-jump model
Non-local background population

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

$$N_b(x) \sim \int_S u(t, x + r) \eta(r) \, dr.$$ 

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

$$\partial_t u = D \Delta u - \nabla \cdot \left( u \int_S \gamma \int_S u(t, x + y + r) \eta(y) \, dy \frac{r}{|r|} \Omega(r) \, dr \right)$$
Numerical technique
The need for efficient numerics

\[ \partial_t u_i(t, x) = -\nabla \cdot \left( u_i(t, x) A_i\{\mathbf{u}(t, \cdot)\}(x) \right) + \ldots \]

▶ Spatial discretisation (FV, FD, FE) [we use 2nd order finite volumes]:
\[ A_i\{\mathbf{u}(t, \cdot)\}(x) \text{ must be evaluated for given approximations of } \mathbf{u}(t, \cdot) \text{ in many points } x, \text{ related to the spatial grid, of spatial domain } \mathcal{D}. \]

▶ 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

\[ A\{u(t, \cdot)\}(x) := \frac{1}{\Phi R} \int_S \frac{r}{|r|} g(u(t, x + r)) \Omega(|r|) \, dr , \]

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

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

The replacement of \( g(u(t, \cdot)) \) 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

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

$$v(x^*) := \frac{1}{\Phi R} \int_S \frac{r}{|r|} \tilde{g}(x^* + r) \Omega(|r|) \, dr = \sum_{i \in \mathcal{N}} g_i \frac{1}{\Phi R} \int_S \frac{r}{|r|} \chi_i(x^* + r) \Omega(|r|) \, dr \quad := w_i^* \text{(integration weight)}.$$
Nonlocal term after approximation for $x^* \in \mathcal{D}$

$$v(x^*) := \frac{1}{\Phi R} \int_{S} \frac{r}{|r|} \tilde{g}(x^* + r) \Omega(|r|) \, dr = \sum_{i \in \mathcal{N}} g_i \frac{1}{\Phi R} \int_{S} \frac{r}{|r|} \chi_i(x^* + r) \Omega(|r|) \, dr .$$

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 $x^*_m$. 

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Numerical technique
Nonlocal term approximation — periodic setting

\[ v(x^*_m) = \sum_{i \in \mathcal{N}} g_{i+m} w_i^* . \]

Do we need all \( w_i^* \)? — If \( \{x^* + S\} \cap \mathcal{D}_i = \emptyset \) 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

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

Do we need all \( w_i^* \)? — If \( \{x^* + S\} \cap D_i = \emptyset \) 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 \( w_i^* = 0 \).

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

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

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; ...
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

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

- Thus

$$V = WG = F \text{diag}(Fw) F^* G = \text{FFT}(\text{FFT}(w)) \ast \text{iFFT}(G) ,$$

where FFT denotes the Fast Fourier Transform algorithm and iFFT its inverse; $\ast$ is element-wise multiplication.

- This cuts the operation count down from $O(N_1^2)$ to $O(N_1 \log(N_1))$ operations.

**General $d$:** replace FFT by its $d$-dimensional counterpart FFT$d$.
Numerical technique
Nonlocal term approximation — extensions

- From periodic to non-periodic boundary conditions:
  - Need to specify values of $g(u)$ 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

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

\( \leadsto \) 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**

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

Tests for increasing sensing region $S$.

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

Matrix-vector product: speed-up: $10 - 100$
Numerical technique
Nonlocal term approximation — Efficiency

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

Tests for increasing sensing region \( S \).

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

Full cell sorting simulation:
speed-up: \( \approx 20 \) (2 h to 6 min).
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

- 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

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Many thanks to collaborators:
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Thank you very much for your attention!