Cellular adhesion: Modelling and numerical simulation

Alf Gerisch
Fachbereich Mathematik, TU Darmstadt

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Joint work with K.J. Painter (Edinburgh) and M.A.J. Chaplain (Dundee)

Overview

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- Introduction to the biology of cell adhesion.
- A nonlocal partial-differential equation model.
- Method of lines approach.
- Approximation and evaluation of the nonlocal term.
- Nonperiodic boundary conditions.
- Summary and outlook.

Cell adhesion (1)

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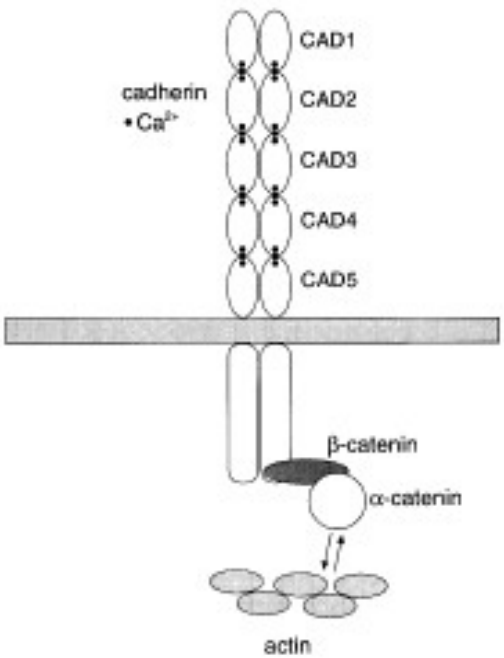

Adhesion [latin *adhaesio*] of cells in the body determined through expression and regulation of cell adhesion molecules

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

Adhesion is important for tissue integrity and cell migration!

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

Cell adhesion (2)

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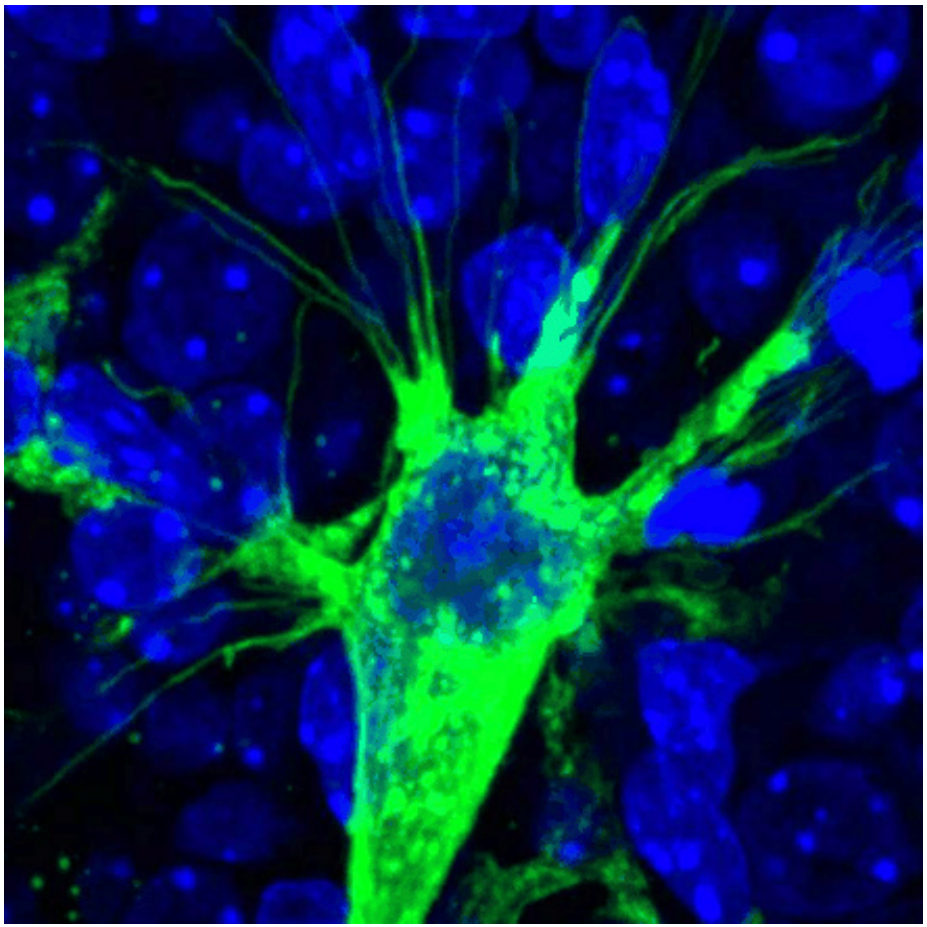

Cells *explore* their surrounding in search of suitable adhesive sites.

Filopodia of endothelial cells (green).

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

Cell sorting

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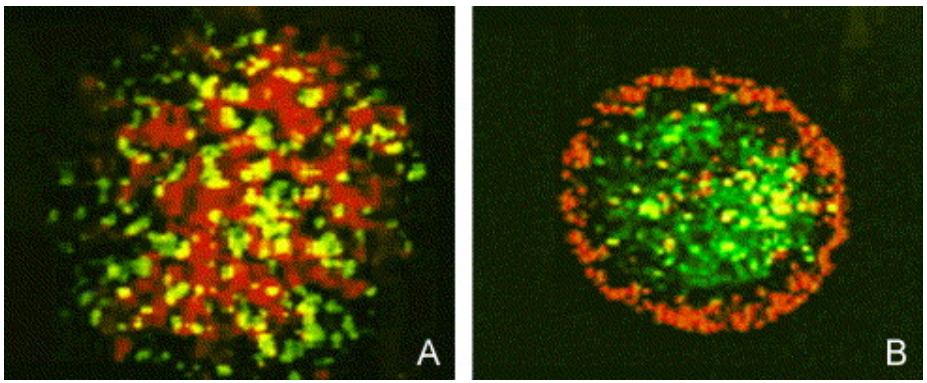


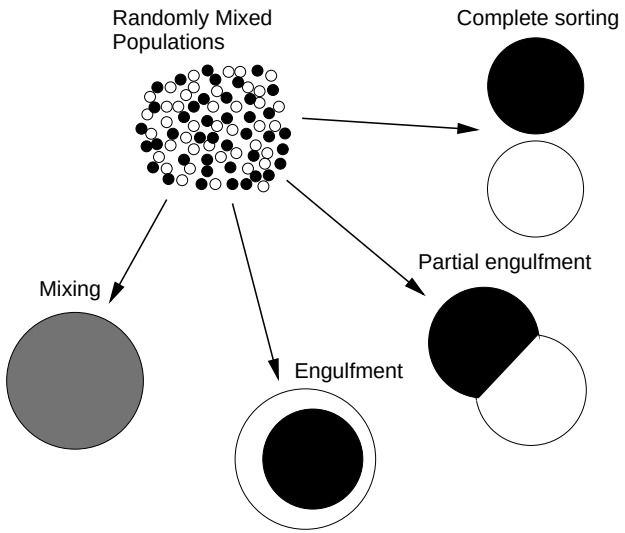
[Foty & Steinberg, Dev. Biol. (278), '05]

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.

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]

Modelling of cell adhesion

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Reasonable expectation for any model of cell adhesion at a population level

- predict aggregation of a population as “adhesiveness” of cells is increased,
- for multiple cell populations, predict the sorting properties as postulated by the Differential Adhesion Hypothesis.

Two general classes of models

- individual cell based (discrete) models
  $\rightsquigarrow$ dynamics of individual cells,
- continuous models
  $\rightsquigarrow$ dynamics of population level behaviour.

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  $\rightsquigarrow$ dynamics of individual cells,
- continuous models
  $\rightsquigarrow$ dynamics of population level behaviour. $\longleftarrow$ this is what we do.

Continuous modelling approaches

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- Cells represented through their density at the tissue level.
- Cellular scale events captured in model parametrisation.

Examples

- Cell-matrix adhesion: haptotactic migration modelled by advective-flux type 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,...) $\rightsquigarrow$ higher-order PDE models arising from expansion of nonlocal terms.
  - Integro-PDE models (Armstrong and co-workers).

The nonlocal continuous adhesion model (1)

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Cell population i with density $u_i(t,x)$ in 1D space.

Conservation of mass $\Rightarrow$

$$\frac{\partial u_i}{\partial t} = -\frac{\partial}{\partial x}\left(-D_i\frac{\partial u}{\partial x} + J_{a,i}(t,x)\right) .$$

From Stokes law for a ball (cell) of radius R in a laminar flow:

$$J_{\mathrm{a,i}}(t,x) = \frac{1}{\phi R}u_i(t,x)F_i(t,x) ,$$

- $F_i(t,x)$ ... total force acting on cells of type i at x caused by adhesion,
- ϕ ... viscosity of the medium.

The nonlocal continuous adhesion model (2)

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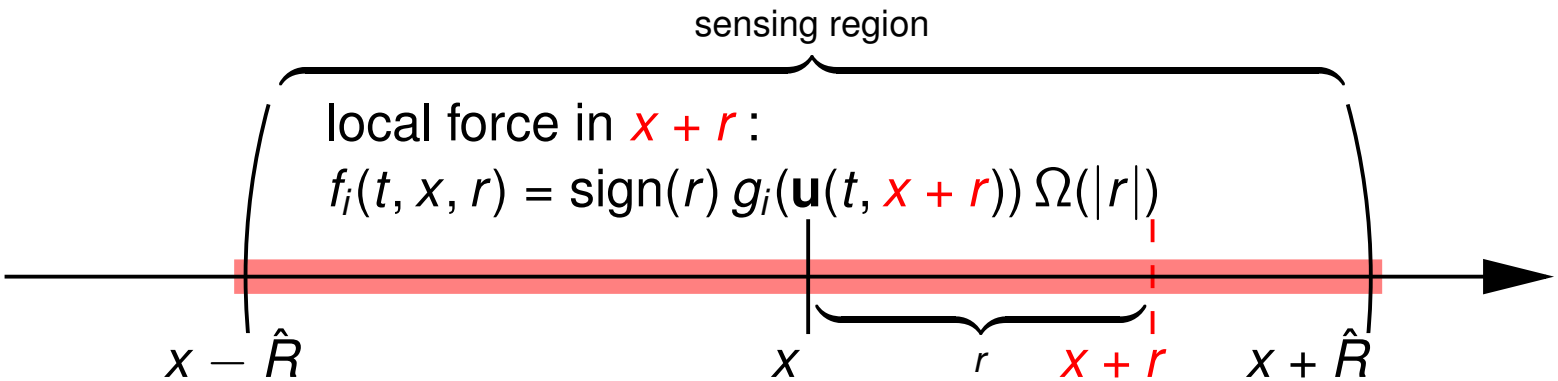
The total force F_i in x is the sum of "local" forces: $F_i(t,x) := \int_{-\hat{R}}^{\hat{R}} f_i(t,x,r)\,\mathrm{d}r$



Integro-PDE model with adhesion velocity $\mathcal{A}_i\{\mathbf{u}(t,\cdot)\}(x)$

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

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

The nonlocal continuous adhesion model (3)

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$\Omega(r) \geq 0$ for $r \geq 0$, e.g.

- constant,
- linearly decaying to zero on $[0, \hat{R}]$.

$g_A(u_A) \geq 0$ — one cell population

- linear: $g_A(u_A) = C_{AA} u_A$
  may lead to unbounded aggregation,
- logistic: $g_A(u_A) = C_{AA} u_A \max\{0, 1 - u_A\}$
  aggregate density remains bounded.

$g_i(u_A, u_B) \geq 0\,, \quad i = A, B$ — two cell populations

- logistic: $g_i(u_A, u_B) = (C_{iA} u_A + C_{iB} u_B) \max\{0, 1 - u_A - u_B\}$.

+ initial conditions and periodic boundary conditions.

The nonlocal continuous adhesion model (4)

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- Global existence and boundedness has been shown for a similar nonlocal chemotaxis model [Hillen et al., '07].
- Boundedness of solution in 1D requires additional assumptions on g and Ω [Sherratt et al. ('09)] and is open in 2D.
- One cell population: aggregation takes place for $C_{11} > 0$ sufficiently large (Turing instability).
- For $\hat{R} \to 0$: adhesion model reduces to [G., Chaplain, '08]
  standard taxis model for linear g,
  volume-filling taxis [Hillen, Painter, '01] model for logistic g.

Cell sorting experiment – two cell populations

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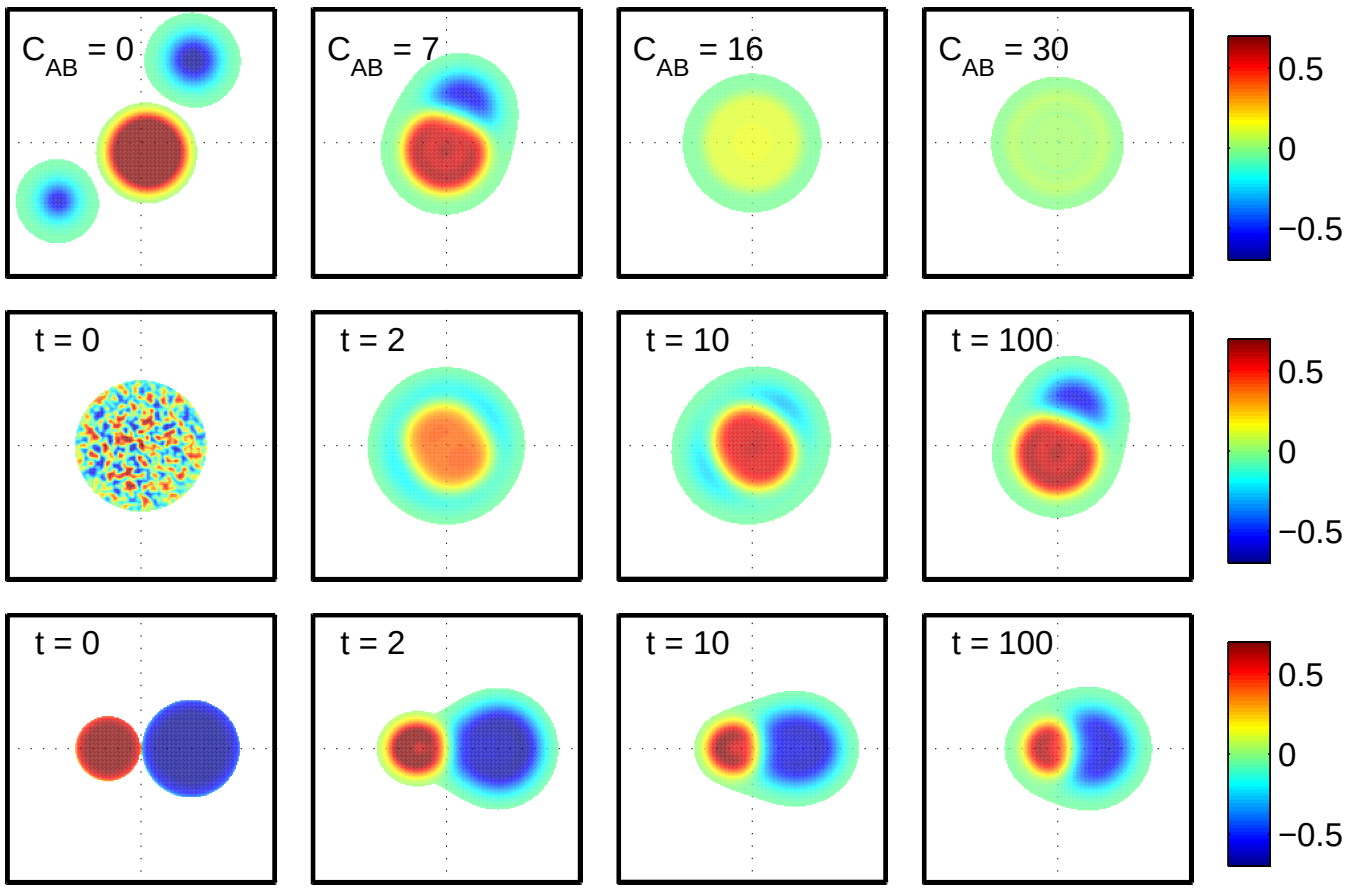
increasing cross-adhesion coefficient C_{AB} $\longrightarrow$



two cell populations
densities u_A, u_B;
shown is $u_A - u_B$

self-adhesion:
$C_{AA} = 30$
$C_{BB} = 15$

initial conditions:
$\longleftarrow$ mixed

$\longleftarrow$ separated

[G. & Painter, '10]

Numerical approach
Method of Lines

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- Uniform spatial grid (1D and 2D) with $h = 1/N$.
- 2nd order finite volume spatial discretisation

  $$\rightsquigarrow \text{ large stiff IVP for ODE system } \quad \dot{\mathbf{U}}(t) = \mathbf{f}(t, \mathbf{U}(t))$$

  for the average densities/concentrations $\mathbf{U}(t)$ in the grid cells.
- Time integration with matrix-free, linearly implicit Runge-Kutta method ROWMAP [Weiner et al., '97].
- Simulation environment in Matlab.
- Computational bottleneck is the evaluation of the nonlocal expression for the adhesion velocity within each right-hand side evaluation.

Treatment of the nonlocal term (1)
Approximation

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Adhesion velocity in 1D

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

must be evaluated on all grid cell interfaces.

1. Evaluate $g_i(\mathbf{u}(t,x))$ for averages $\mathbf{U}(t)$ to yield vector $\mathbf{G}$.
2. Compute a (pcw. constant or linear) reconstruction $\tilde{g}_i(x)$ of $g_i(\mathbf{u}(t,x))$ from $\mathbf{G}$.
3. Replace $g_i(\mathbf{u}(t,x))$ by $\tilde{g}_i(x)$ and determine weights w_l of an integration formula for the adhesion velocity (arbitrarily exact determination of the w_l possible).

$$\rightsquigarrow \qquad \mathcal{A}_i\left\{\mathbf{u}(t,\cdot)\right\}(x_j + h/2) \approx \sum_{l=-l^-}^{l^+} w_l \mathbf{G}_{j+l} =: \mathbf{a}_j$$

Collect all evaluations on the grid as

$$\mathbf{a} = M \times \mathbf{G} \quad \text{with a pre-computed matrix } M\,.$$

Treatment of the nonlocal term (2)
Efficient evaluation

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$$\mathbf{a} = M \times \mathbf{G}$$

In 1D with periodic BCs:

$\rightsquigarrow$ circulant matrix M

Exploit structure!

$$\begin{pmatrix} 1 & 2 & 3 & 0 & 0 & 6 & 7 \\ 7 & 1 & 2 & 3 & 0 & 0 & 6 \\ 6 & 7 & 1 & 2 & 3 & 0 & 0 \\ 0 & 6 & 7 & 1 & 2 & 3 & 0 \\ 0 & 0 & 6 & 7 & 1 & 2 & 3 \\ 3 & 0 & 0 & 6 & 7 & 1 & 2 \\ 2 & 3 & 0 & 0 & 6 & 7 & 1 \end{pmatrix}$$

Theorem

Every circulant matrix M, defined by its first column $\mathbf{m}$, is diagonalised by the discrete Fourier transform matrix F, *i.e.*

$$M = F^{\mathrm{H}} \Lambda F \quad \text{with} \quad \Lambda = \mathrm{diag}(F \times \mathbf{m})\,.$$

$$\mathbf{a} = M \times \mathbf{G} = F^{\mathrm{H}} \mathrm{diag}(F \times \mathbf{m}) F \times \mathbf{G} = \mathtt{iFFT}(\mathtt{FFT}(\mathbf{m}) .* \mathtt{FFT}(\mathbf{G}))\,.$$

Treatment of the nonlocal term (3)
Numerical test

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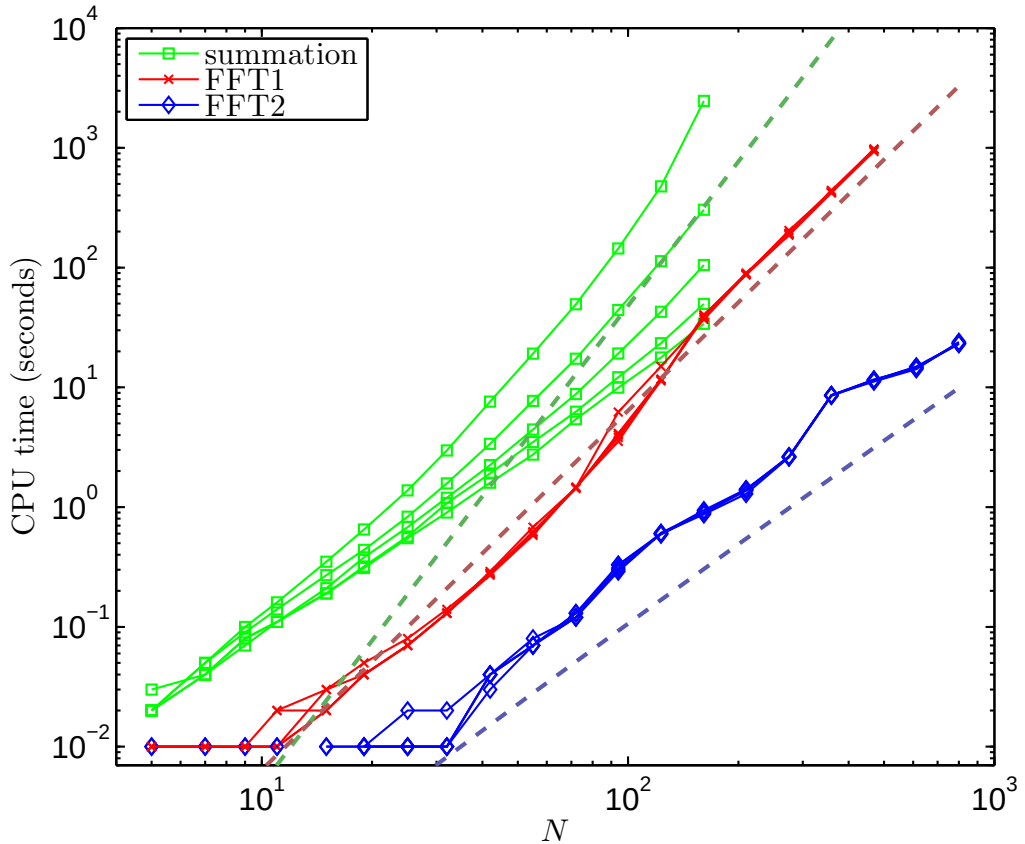
Similar approach but in 2D leads to matrix-vector product $\mathbf{a} = M \times \mathbf{G}$.

Due to periodicity:
M is block-circulant
with circulant blocks.

$\rightsquigarrow$ efficient evaluation
Use 2D version of FFT.

Reduction of operations ($h = \frac{1}{N}$)
$\sim N^4 \longrightarrow \sim N^2 \log(N)$.

Speed-up: $10 - 100$ for matrix-vector product.



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

Nonperiodic boundary conditions (1)

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

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

Periodic Lead to $\mathbf{a} = M \times \mathbf{G}$ with circulant $M \in \mathbb{R}^{N_1,N_1}$.

Zero-flux *No* adhesive interaction outside of $\Omega \rightsquigarrow$ extend g_i by zero outside of $\Omega \rightsquigarrow$ rectangular Toeplitz matrix $M \in \mathbb{R}^{N_1+1,N_1}$.

Symmetry *There is* adhesive interaction outside of $\Omega \rightsquigarrow$ extend g_i by symmetry outside of $\Omega \rightsquigarrow$ rectangular Toeplitz matrix $M \in \mathbb{R}^{N_1+1,N_{\text{left}}+N_1+N_{\text{right}}}$.

Dirichlet What does this mean for adhesive interaction outside of Ω? Requires specific experimentalist/modeller input!

Nonperiodic boundary conditions (2)
Toeplitz to circulant conversion

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Theorem

Let $\mathbf{G} \in \mathbb{R}^n$ and $M \in \mathbb{R}^{m,n}$ be a banded Toeplitz matrix with upper and lower bandwidth l^+ and l^-, respectively, and entry w_j on its jth diagonal, $j = -l^-, \ldots, l^+$. Then

$$M\mathbf{G} = \left[C\tilde{\mathbf{G}}\right]_{1,\ldots,m}$$

for the circulant matrix $C \in \mathbb{R}^{\ell,\ell}$ with $\ell := \max\{n + l^-, m + l^+\}$ and its first column $\mathbf{c}$ is given by

$$\mathbf{c} := (w_0\, w_{-1} \ldots w_{-l^-} \quad \underbrace{0 \ldots 0}_{\ell - l^+ - l^- - 1 \text{ zeros}} \quad w_{l^+} w_{l^+ - 1} \ldots w_1)^{\mathsf{T}},$$

together with $\tilde{\mathbf{G}} := (\mathbf{G}\ \mathbf{0})^{\mathsf{T}} \in \mathbb{R}^{\ell}$.

Nonperiodic boundary conditions (3)
Steady states

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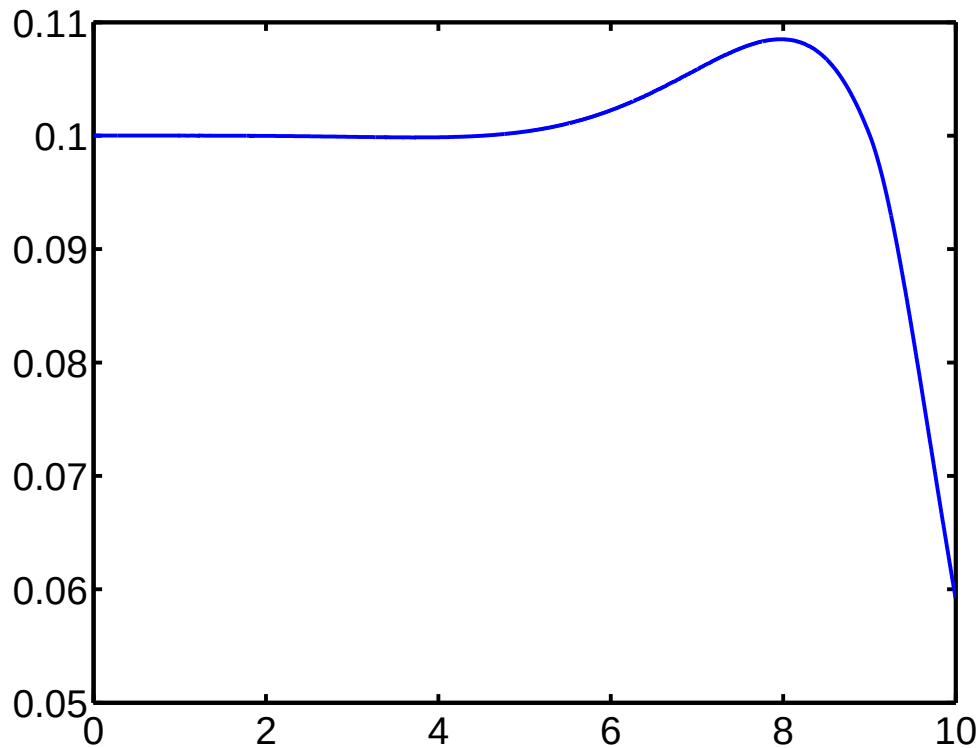
Periodic, symmetry BCs:
Homogeneous steady state.

Zero-flux BCs:
Homogeneous steady states are not possible by construction!

Example $\longrightarrow$

Boundary conditions:
- Left: symmetry
- Right: zero-flux

Initial condition: $u(0, x) = 0.1$



Complex geometries (1)

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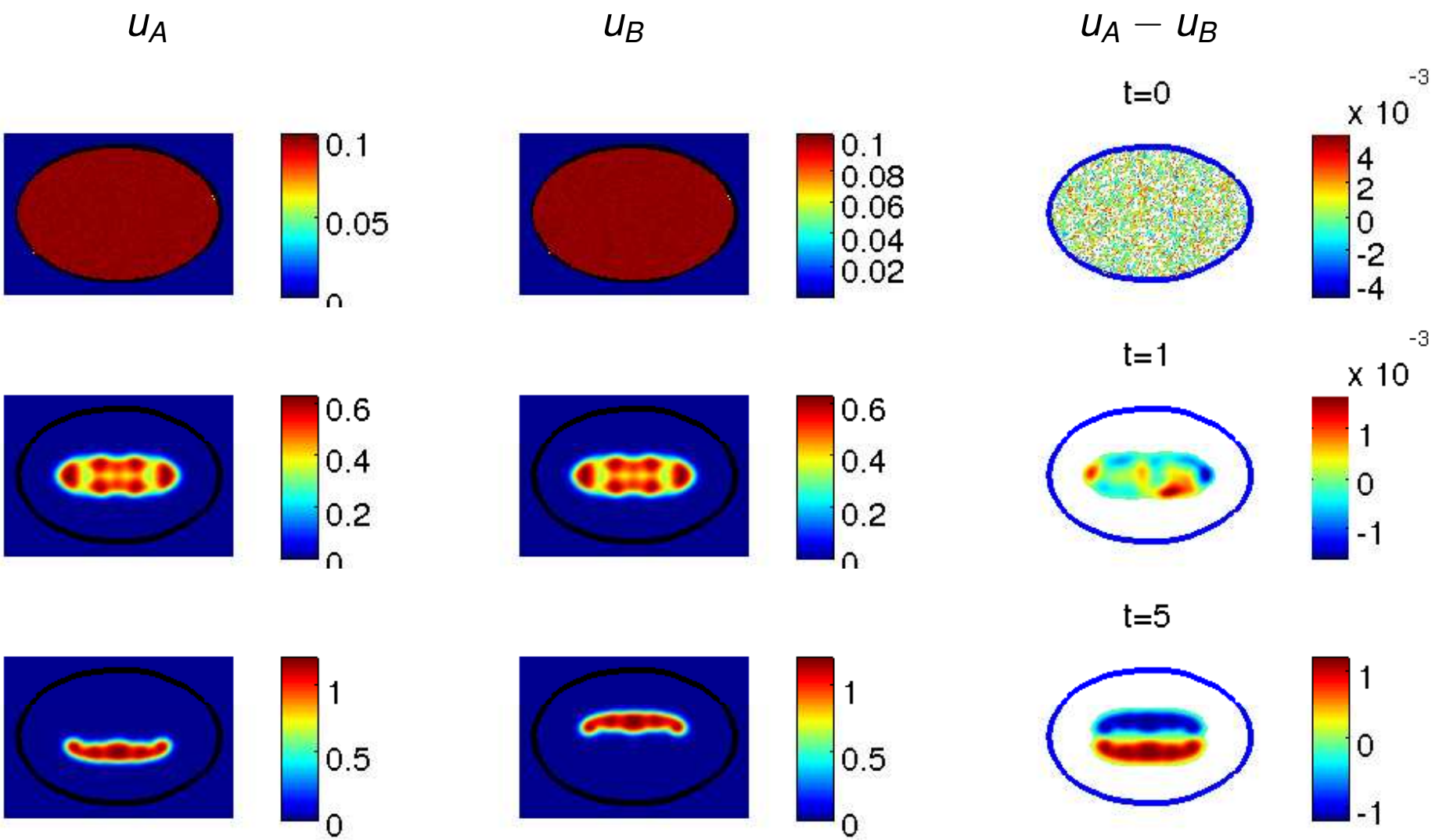

Complex geometries (2)

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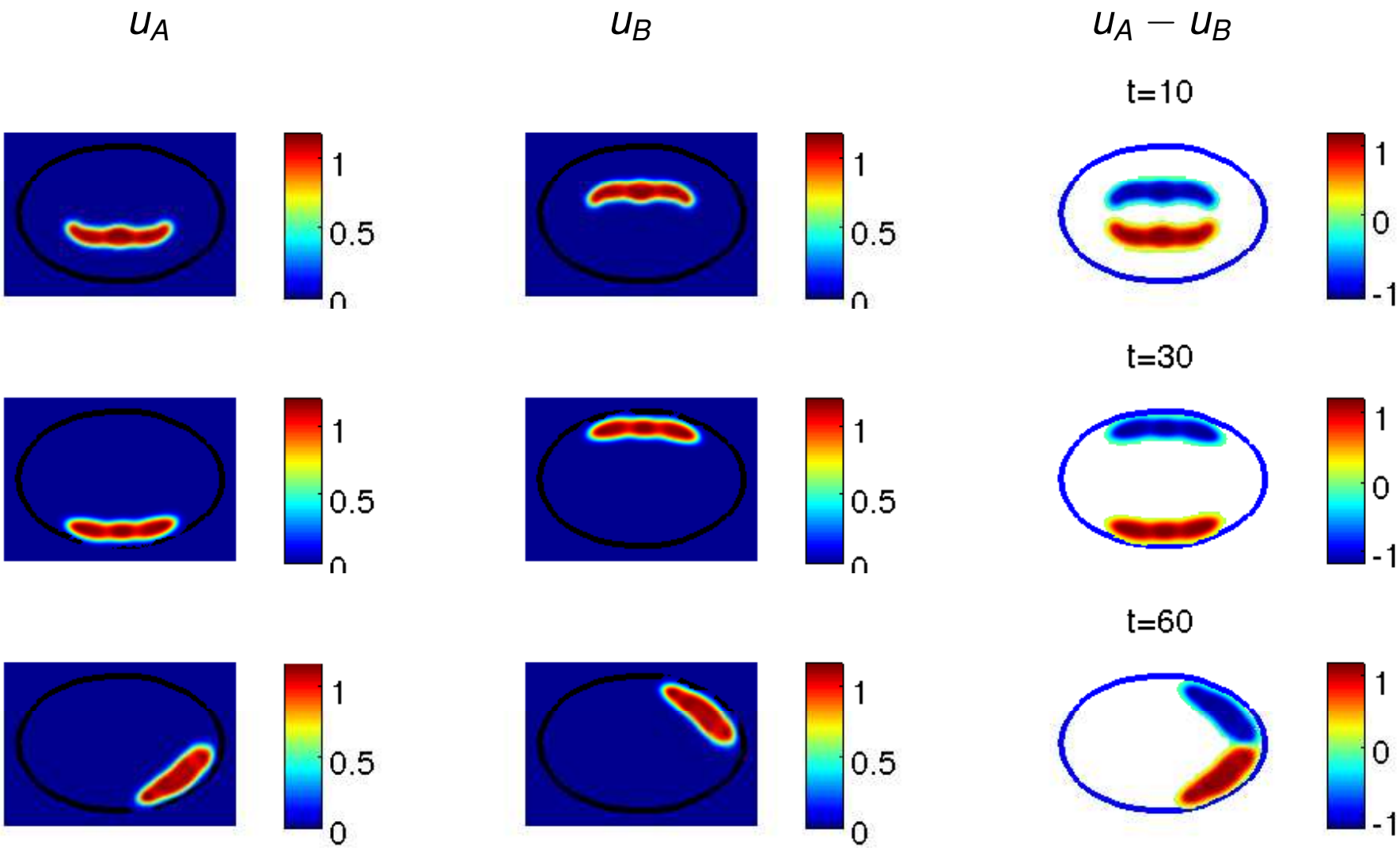

Summary...

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- Cell adhesion is important as a basic mechanism in biology but also in biomedical applications.
- We studied a flexible continuous model of cell adhesion; capable to correctly reproduce many aspects of cellular adhesion.
- This model can be efficiently simulated [G., '10]. The technique allows for spatially highly resolved long time simulations with reasonable CPU time requirements.
- The requirements of periodic boundary conditions and rectangular domains can be relaxed without destroying favourable algorithmic properties.
- The modelling approach can be utilised in more complex applications; we have demonstrated that for tumour invasion [G. & Chaplain, '08; G. & Painter '10].

... and Outlook

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- What are the implications of nonperiodic boundary conditions for biology and mathematics?
- Improve the pre-processing for nonlocal term evaluation.
- Extend the analytical results regarding the model equations, in particular refined boundedness results.
- Derive (or at least justify) parameter functions like $g_i(\mathbf{u})$ from microscopic models of cell adhesion.
- Cell adhesion does not only cause forces resulting in cell migration but also impacts, through the signalling initiated by binding events, on other aspects of cell behaviour including cell division and apoptosis (programmed cell death).

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Merci beaucoup pour votre attention!