Nonlocal Models in Cell Biology

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This talk can be downloaded from my web site
`www.ma.hw.ac.uk/~jas`

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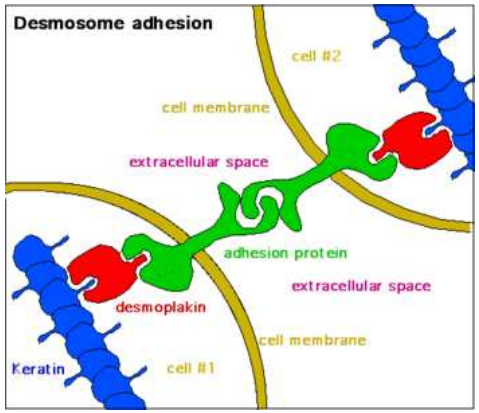
Kevin Painter Heriot-Watt University

Outline

Outline

What is Cell-Cell Adhesion?

Cells bind to each other through cell adhesion molecules.
This is important in a range of developmental and pathological contexts:



- Embryonic cells adhere selectively, enabling them to sort into tissues and organs
- Altered adhesion properties are thought to be important in tumour invasion

Mathematical Modelling of Cell Adhesion

- Representation of adhesion in individual cell-based models is relatively straightforward because they include explicit representations of the cell boundaries.
- Representation of adhesion in continuum models is much harder because they do not involve explicit representation of the cell boundaries. Importance:
  - there are many established continuum models for other aspects of development, cancer, wound healing etc
  - mathematical analysis is often possible for continuum models, but is rarely possible for discrete models

Derivation of the Model I

- Mass conservation:

Rate of change of cell density	=	Input $-$output	+	Birth/ death
$\partial n/\partial t$		$-\partial J/\partial x$		

Here $n(x,t) =$ cell density, and $J =$ cell flux

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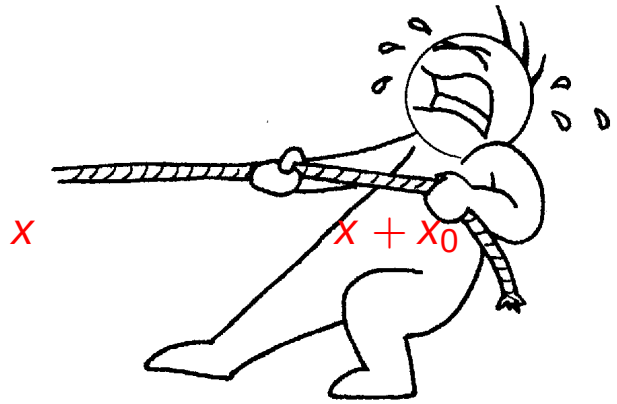
- Adhesive flux J_a is proportional to the force due to breaking and forming adhesive bonds
(Stokes' Law: low Reynolds number)

Derivation of the Model II

- The force on a cell at x exerted by cells a distance x_0 away depends on

1. cell density at $x + x_0$
2. distance $|x_0|$
3. sign of x_0 ($\Rightarrow$ direction of force)

$$f(x, x_0) = \alpha \cdot g\left(n(x + x_0, t)\right) \cdot \omega(x_0)$$



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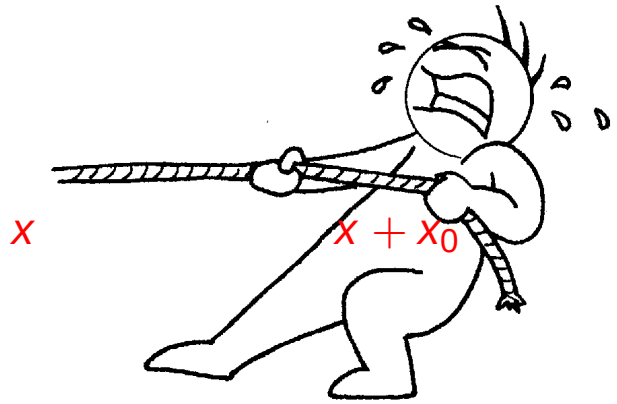
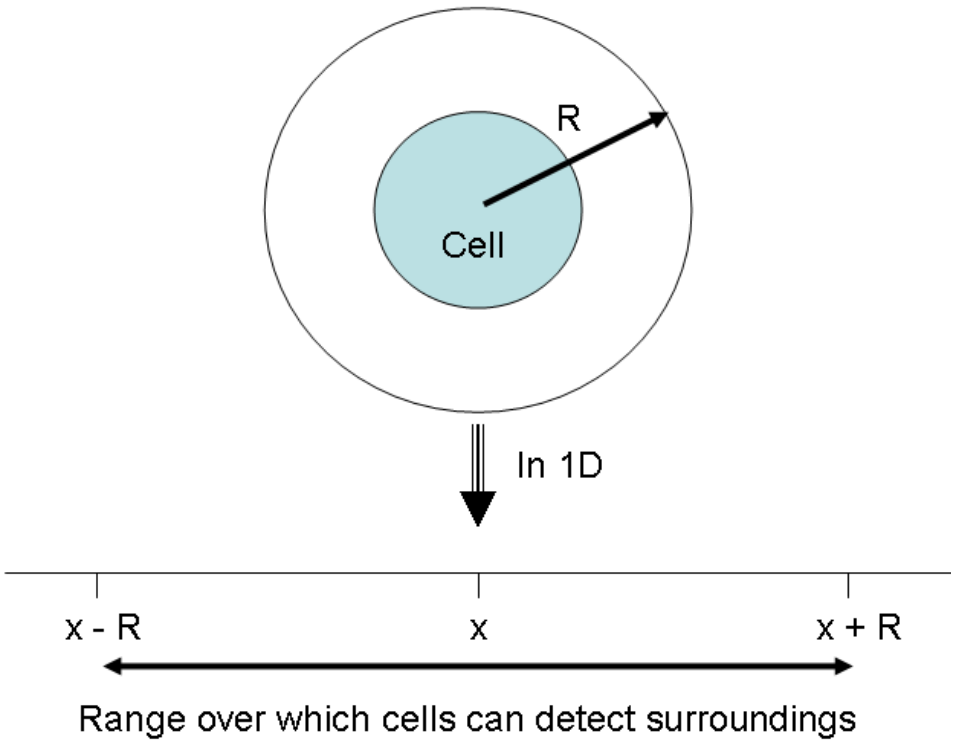


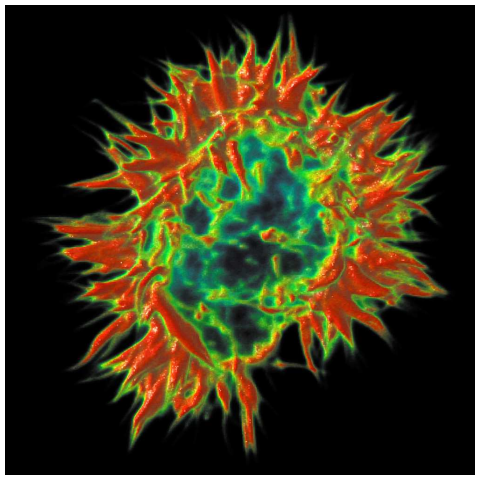
$$f(x, x_0) = \alpha \cdot g\left(n(x + x_0, t)\right) \cdot \omega(x_0)$$

- Total force = sum of all forces acting on cells at x

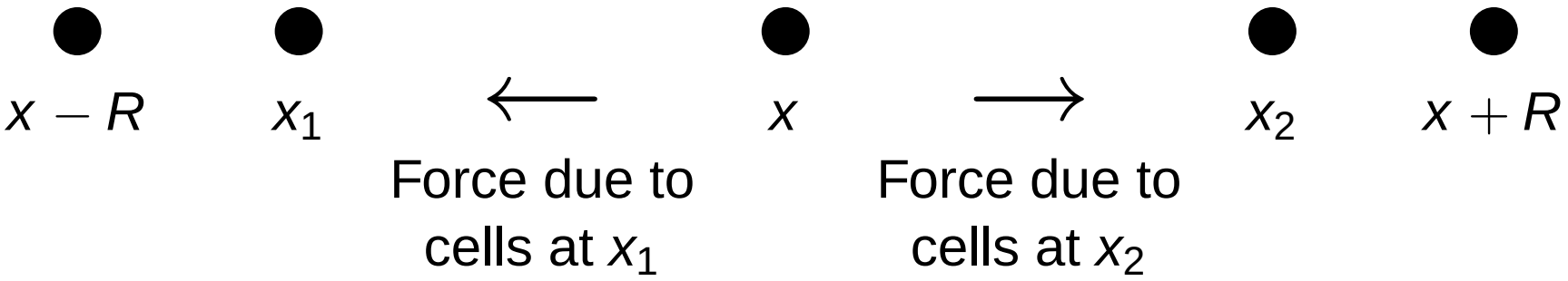
$$F(x) = \int_{-R}^{+R} f(x, x_0)\, dx_0$$

Model Details: The Sensing Radius, R





Model Details: The Function $\omega(x_0)$

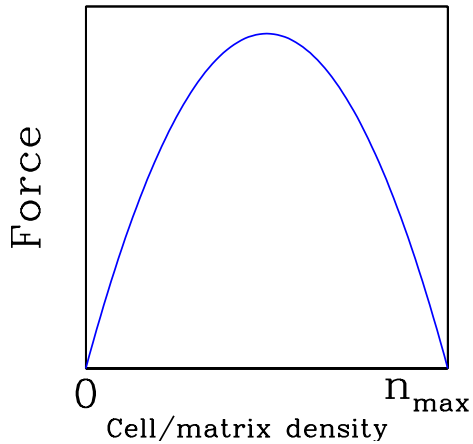


$\omega(x_0)$ is an odd function. For simplicity we take

$$\omega(x_0) = \begin{cases} -1 & \text{if} \quad -R < x_0 < 0 \\ +1 & \text{if} \quad 0 < x_0 < +R \end{cases}$$

Model Details: The Function $g(n)$

- At low cell densities, the force $f(x, x_0)$ will increase with cell density at $x + x_0$ when this is small.
- However, there will be a density limit beyond which cells will no longer aggregate.
- We account for this via a nonlinear $g(.)$; we take $g(n) = n(n_{max} - n)$. Here n_{max} corresponds to no empty space.



- We rescale to give $n_{max} = 2$.

Outline

Mathematical Model for One Cell Population

To model cell aggregation *in vitro*, we assume random (diffusive) and adhesive cell movement, with no birth/death. This gives the nondimensional model equation

$$\frac{\partial n}{\partial t} = \frac{\partial^2 n}{\partial x^2} - \alpha \frac{\partial}{\partial x}\left[n \int_{-1}^{+1} n(x + x_0, t)\,[2 - n(x + x_0, t)]\,\mathrm{sign}(x_0)\,dx_0 \right]$$

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Note that the use of nonlocal terms to represent adhesion has been suggested previously:

T. Sekimura, M. Zhu, J. Cook, P.K. Maini, J.D. Murray (1999) Pattern formation of scale cells in Lepidoptera by differential origin-dependent cell adhesion. *Bull. Math. Biol.* 61: 807.

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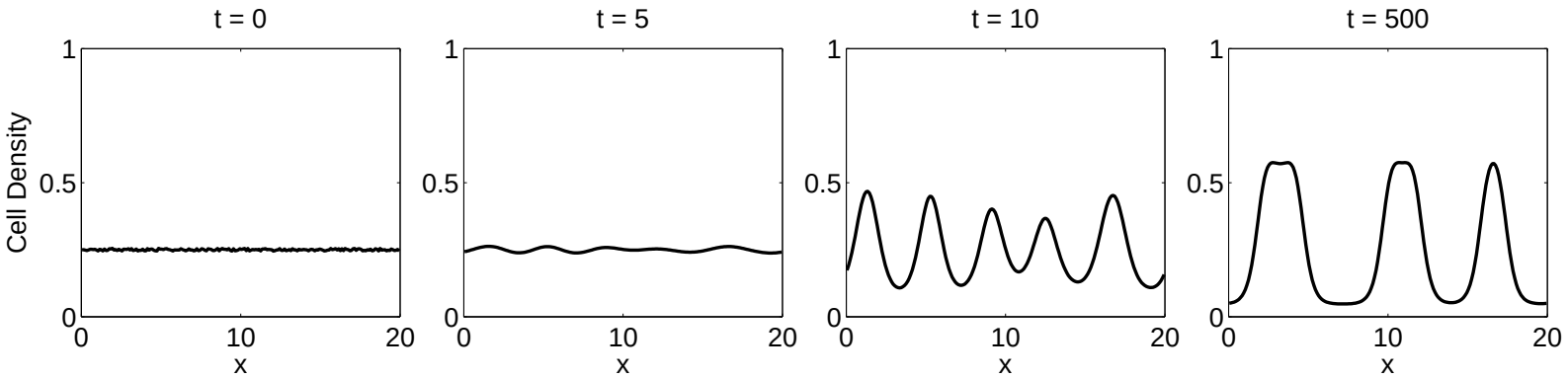
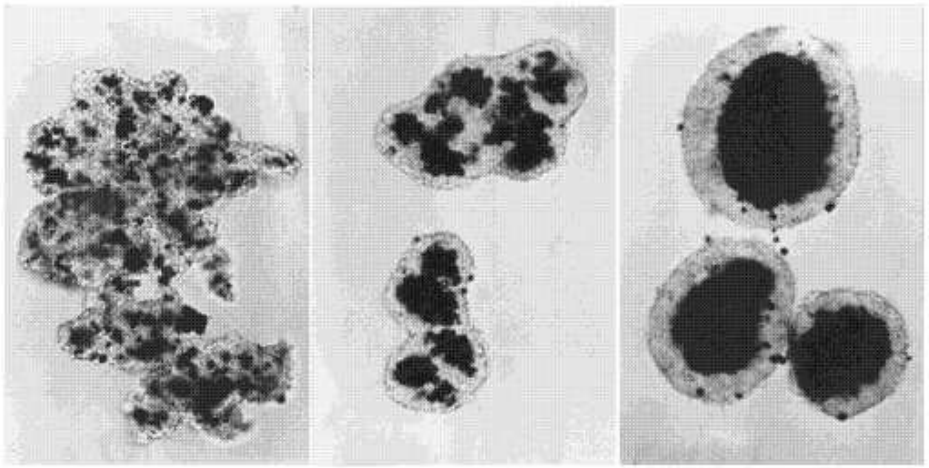
- The parameter α reflects the strength of adhesion; we expect aggregation of disassociated cells when α is large.
- Linear stability analysis implies aggregation when $\alpha > \alpha_{crit}$

A Numerical Simulation of Aggregation



Aggregation and Sorting in an *In Vitro* Experiment



(a) (b) (c)

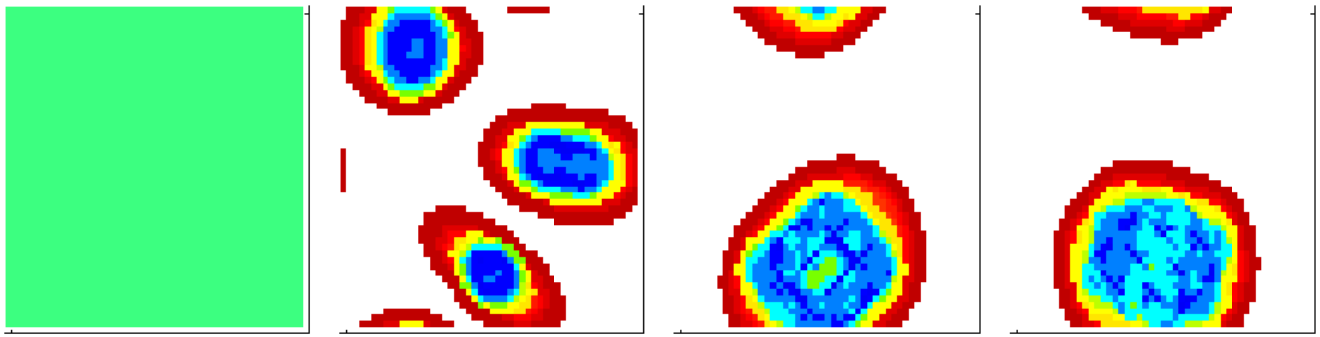
- (a) After 5 hours
- (b) After 19 hours
- (c) After 2 days

Armstrong, P.B. 1971. Wilhelm Roux' Archiv 168, 125-141

Extending the Model to Interacting Cell Populations

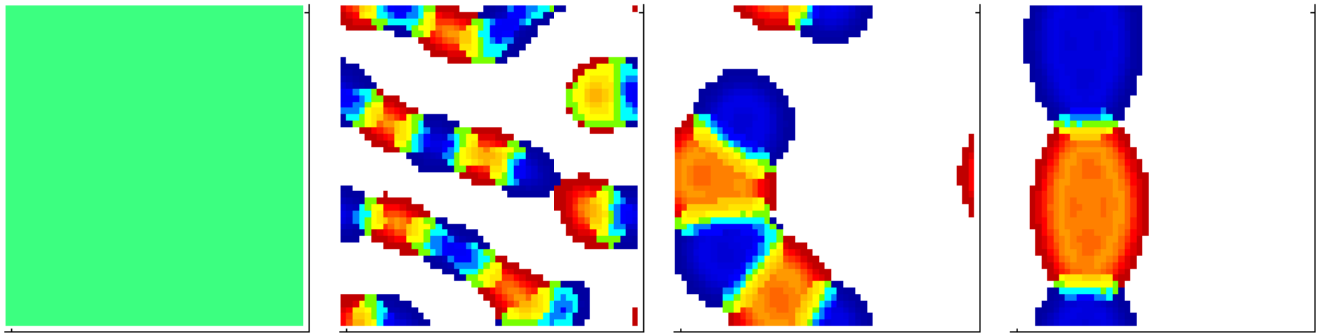
- To consider cell sorting, we extend the model to two interacting cell populations
- The extended model includes self-population adhesion and cross-population adhesion
- Extension to 2-D is valuable and straightforward

A Numerical Simulation of Aggregation and Sorting



t=0 t=3.75 t=25 t=125

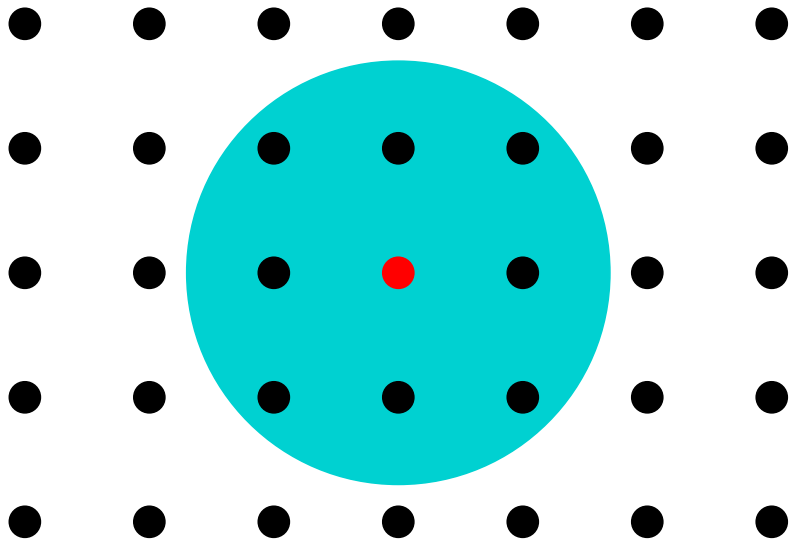
Moderate cross-adhesion



Weak cross-adhesion

Computational Issues

- Discretise equations in space and time
- At each time step, we must calculate an integral over a circular region
- Niave computation is very expensive in computer time



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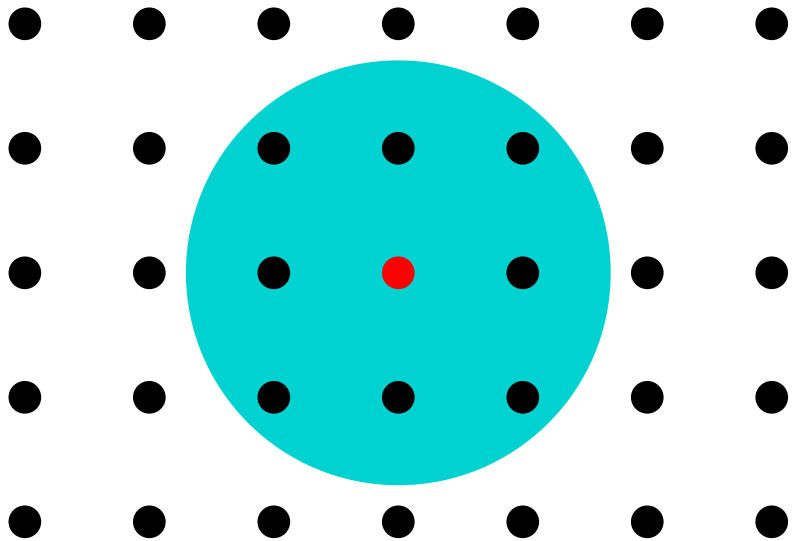

- Alf Gerisch (Darmstadt) has developed a sophisticated method based on
  1. pre-calculating weights for the projection of the spatial grid onto a radial grid within the circle
  2. using FFT to simplify the resulting system of linear equations

$\mapsto$ 20-fold speed-up (Gerisch (2010) *IMA J. Num. Anal.* 30:173)

Computational Issues

Future Challenge

Numerical methods that make 3-D simulations feasible

Other Applications of the Model Framework

Other applications of the model framework include:

- Somite formation (JAS *et al*)
- Mosaic tissues (JAS *et al*)
- Differentiation-induced patterning (JAS *et al*)
- Cancer invasion (JAS *et al*; Mark Chaplain *et al*; Glenn Webb *et al*)
- Liver cell aggregation (Edward Green *et al*)
- Bone tissue engineering (Liesbet Geris *et al*)

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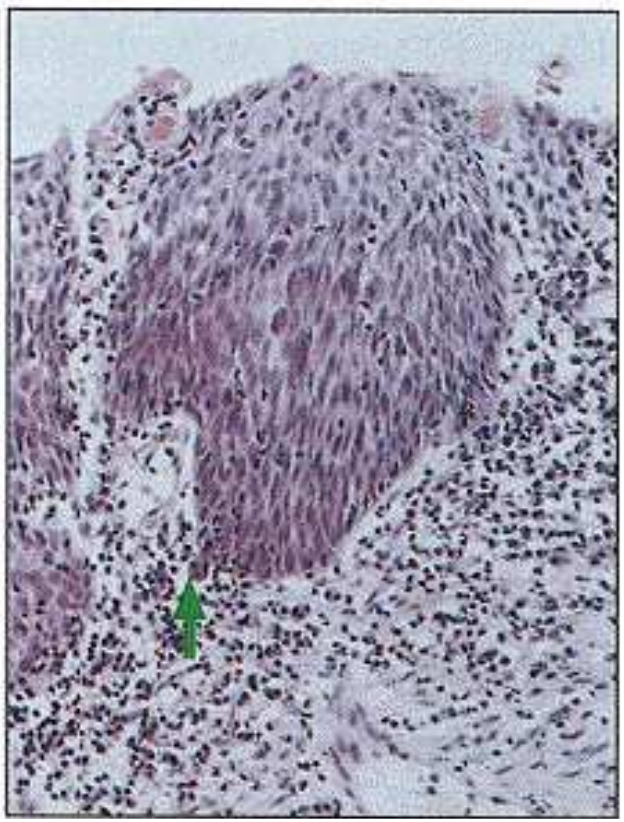
Introduction to Cancer Invasion



Carcinoma of the uterine cervix

Cells in a solid tumour invade surrounding tissue due to changes in:

- migration
- protease/anti-protease production
- adhesion

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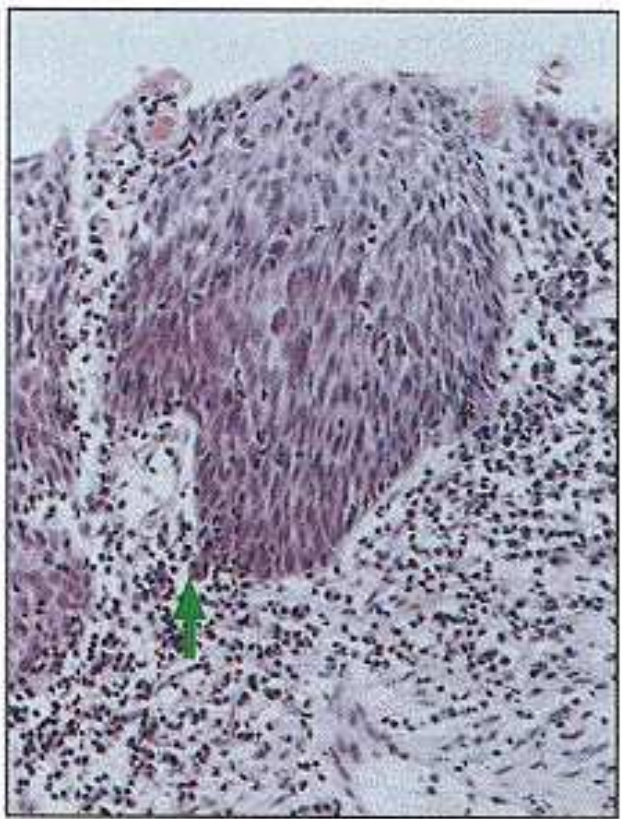

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Cells in a solid tumour invade surrounding tissue due to changes in:

- migration
- protease/anti-protease production
- adhesion: decreased cell-cell adhesion and increased cell-matrix adhesion

Modelling Adhesion in Cancer

Variables: $n(x,t)$ tumour cell density, $m(x,t)$ matrix density

$$\frac{\partial n}{\partial t} = -\overbrace{\frac{\partial}{\partial x}\left[n \cdot K_{nn}\right]}^{\text{cell-cell adhesion}} - \overbrace{\frac{\partial}{\partial x}\left[n \cdot K_{nm}\right]}^{\text{cell-matrix adhesion}} + \overbrace{n(1-n)}^{\text{cell proliferation}}$$

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$$K_{nn} = \text{cell flux due to cell-cell adhesion}$$

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$$K_{nm} = \beta \int_{-1}^{1} m(x+x_0,t) \cdot (2 - n(x+x_0,t) - m(x+x_0,t)) \cdot \omega(x_0)\, dx_0$$

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α and β are adhesion coefficients

Modelling Adhesion in Cancer

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Extension to 2-D is straightforward

Simulation of a Non-Invasive Tumour

For cell-cell adhesion (α) relatively large and cell-matrix adhesion (β) relatively small, the model predicts a non-invasive tumour

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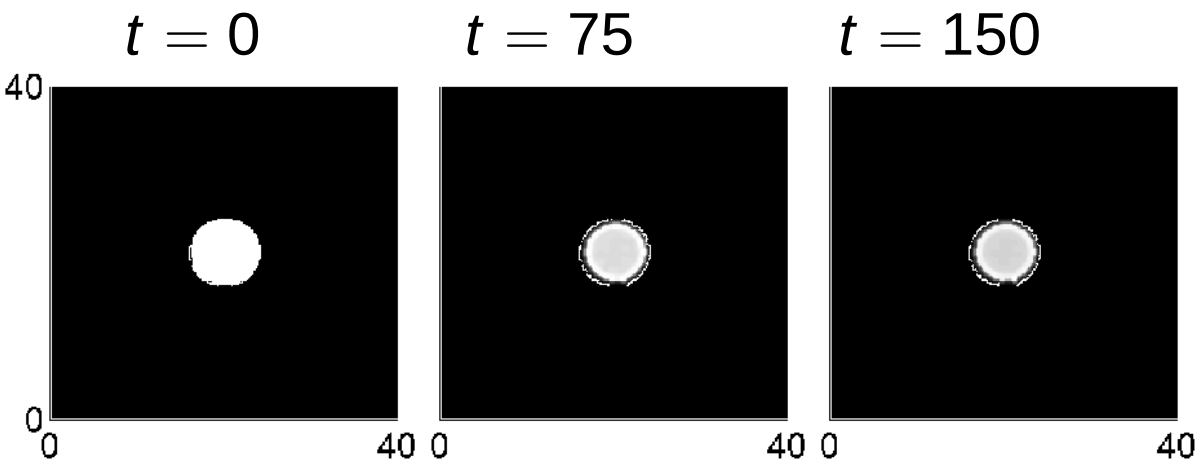

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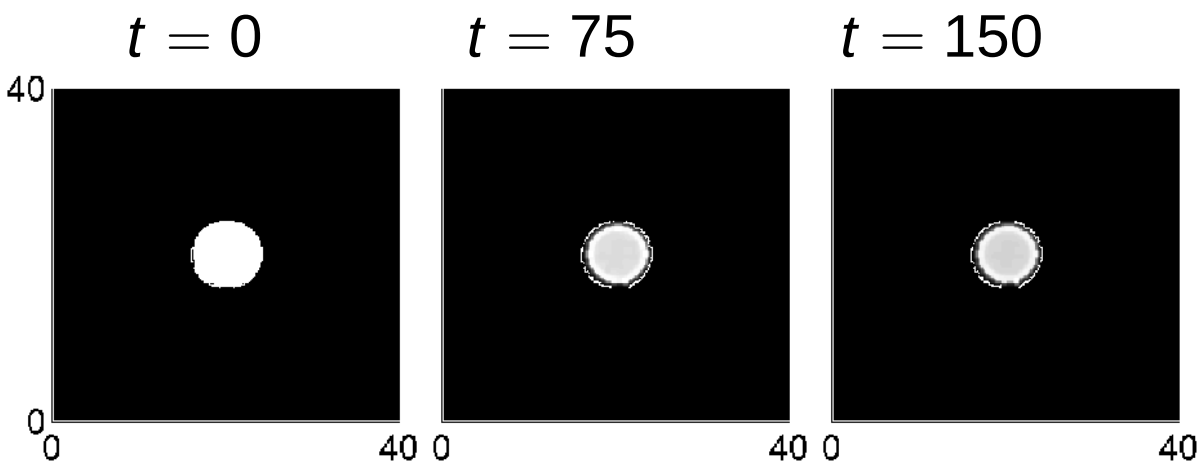
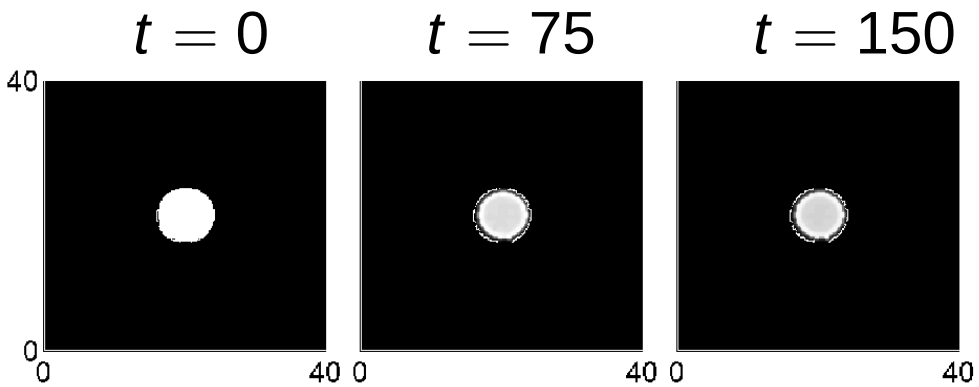


Invasion can be initiated either by decreasing cell-cell adhesion (α) or by increasing cell-matrix adhesion (β)

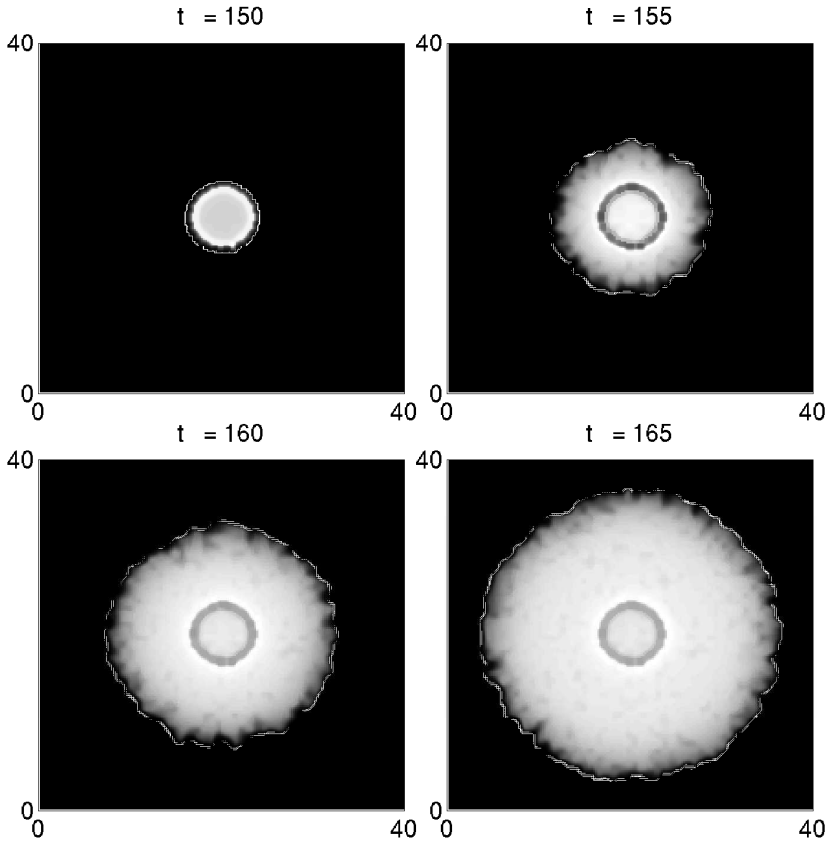
The Sequential Development of an Invasive Tumour

Stage 1:
non-invasive
tumour growth

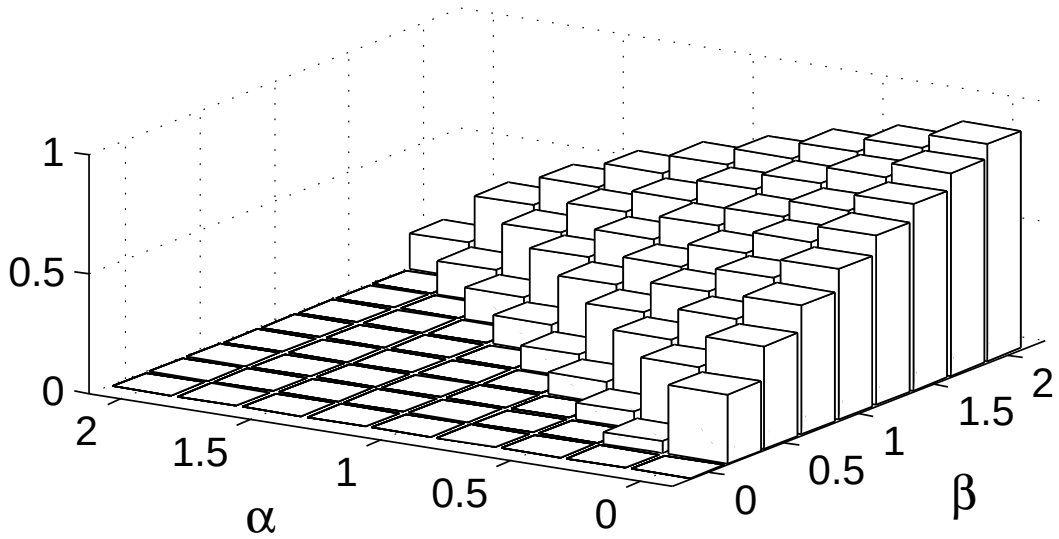


The Sequential Development of an Invasive Tumour

Stage 2:
mutation,
followed by
tumour invasion



Invasion Speed vs α and β (1-D)



Future Challenge

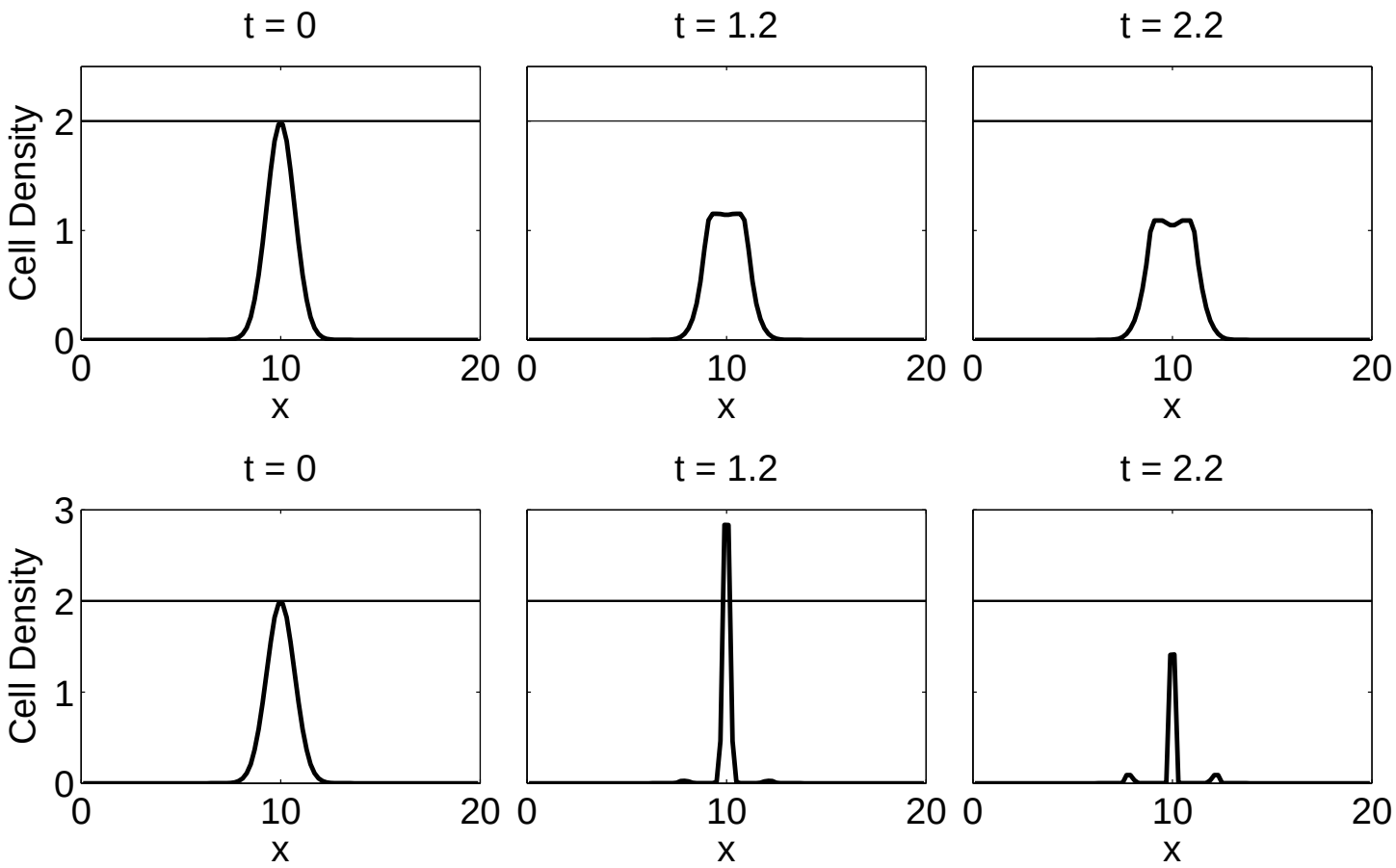
Analytical investigation of the invasion speed.

Mathematical Issue: Boundedness

- For biological realism, we require $n, m \geq 0$ for all x, t
- Recall that $n = 2$ corresponds to close cell packing
- Therefore for biological realism we also require $n \leq 2$ for all x, t

There is no standard theory from which these boundedness properties can be deduced. It is relatively straightforward to show that positivity holds in all cases, but the condition $n \leq 2$ does not always hold.

Example of a Solution with $n > 2$



$\alpha = 0.2$
$m \equiv 0$

$\alpha = 10$
$m \equiv 0$

Conditions for Boundedness

Question: What is the largest α for which $0 \leq n \leq 2$ at $t = 0 \Rightarrow$ $0 \leq n \leq 2$ for all $t \geq 0$?

Partial answer: If $0 \leq n \leq 2$ and $0 \leq m \leq M$ at $t = 0$ then $0 \leq n \leq 2$ for all $t \geq 0$ provided that

$$\alpha + \min\{1, M/2\}\beta < \text{a critical value}\,.$$

The critical value depends on $\omega(.)$; it is infinite if $\omega(\xi) = \text{sign}(\xi)$.

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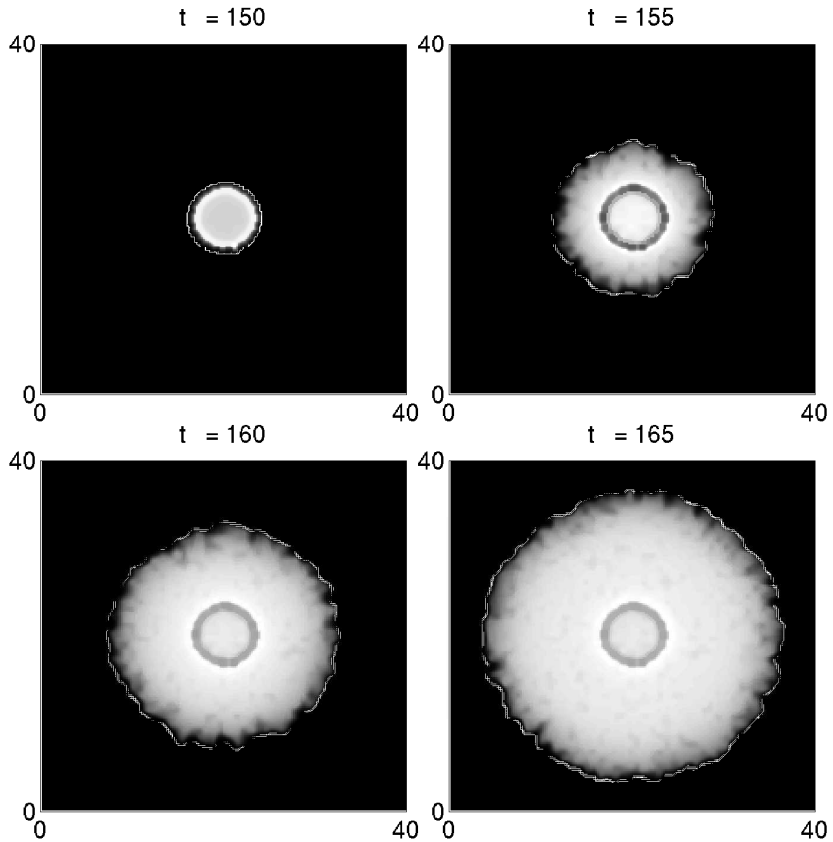
Future Challenge

Determine a full answer to this question.

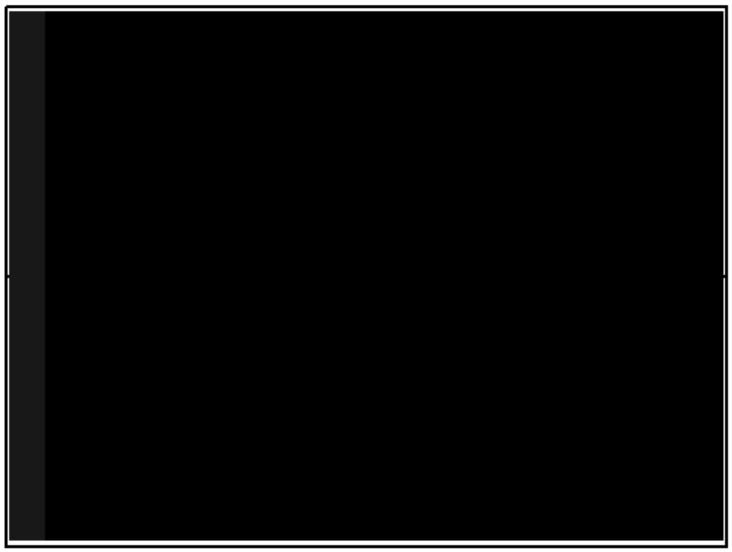
The Importance of Tumour Morphology

Tumour morphology:
Detailed studies of tumour pathology reveal a correlation between the invasive potential of tumours and their shape. (Tumour shape is often quantified via fractal dimension.)

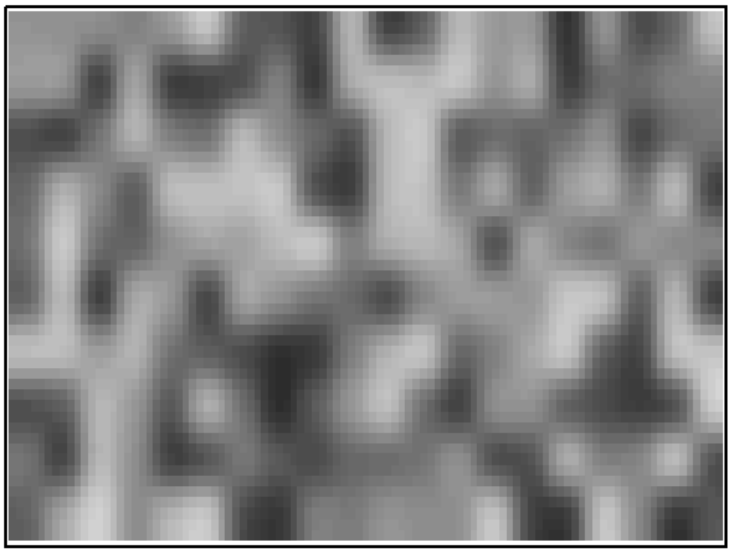


Investigation of Tumour Fingering

Model solns predict: invasion of uniform matrix $\Rightarrow$ flat boundary
invasion of non-uniform matrix $\Rightarrow$ fingering



Cells



Matrix

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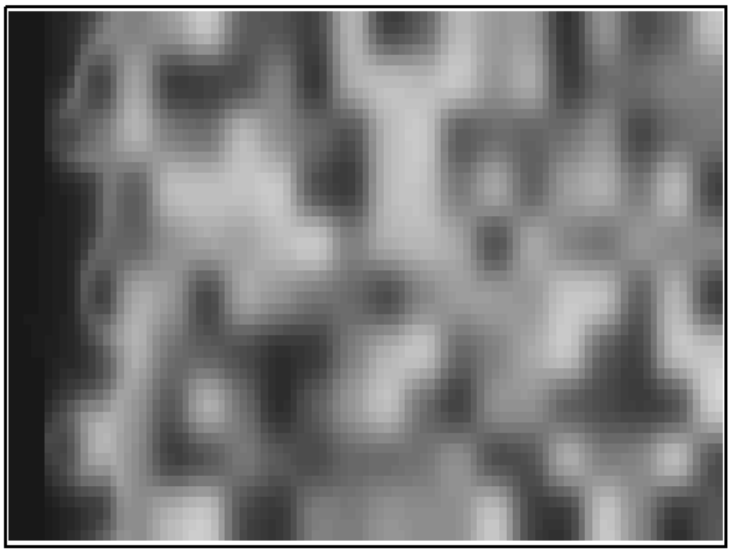

Matrix

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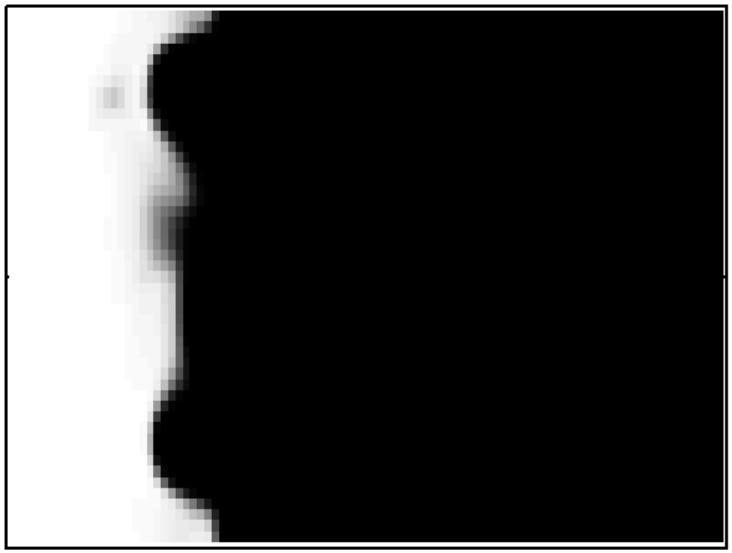
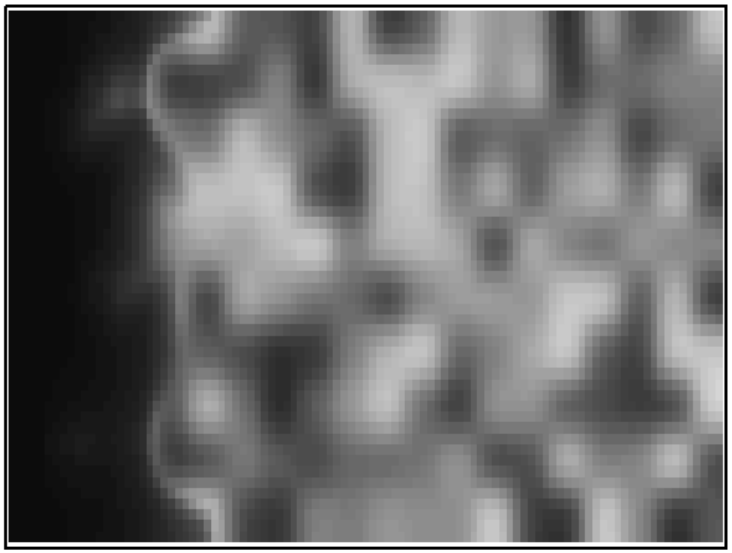
Model solns predict: invasion of uniform matrix $\Rightarrow$ flat boundary
invasion of non-uniform matrix $\Rightarrow$ fingering



Cells



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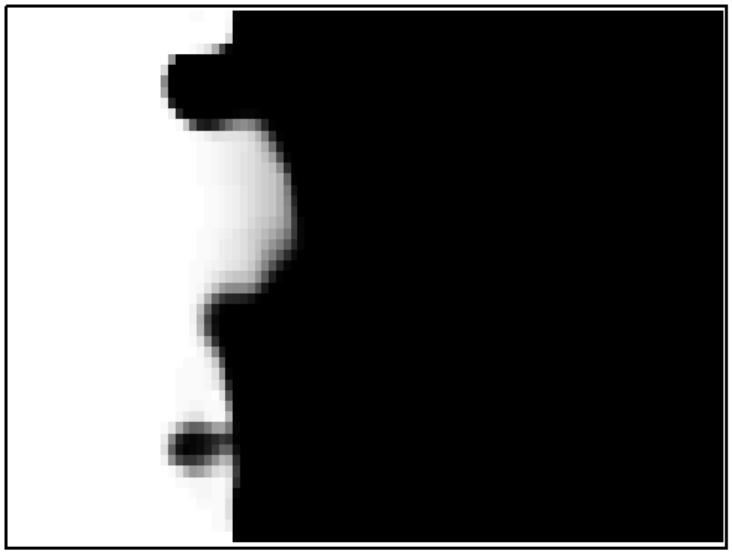

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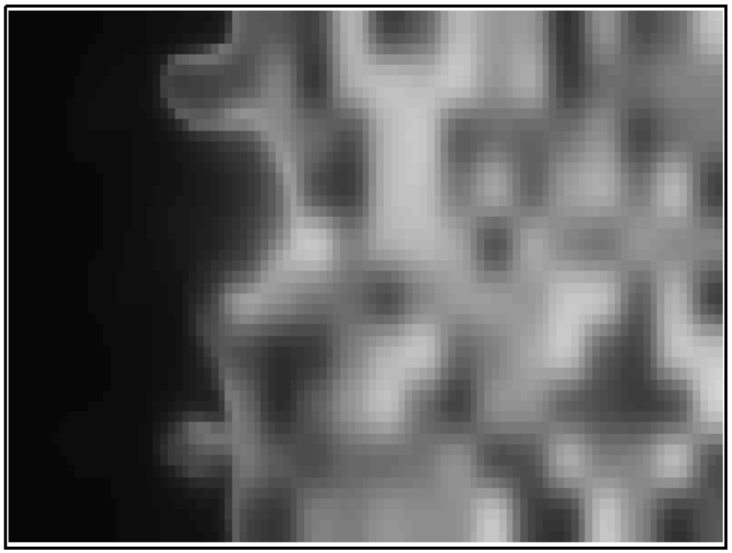

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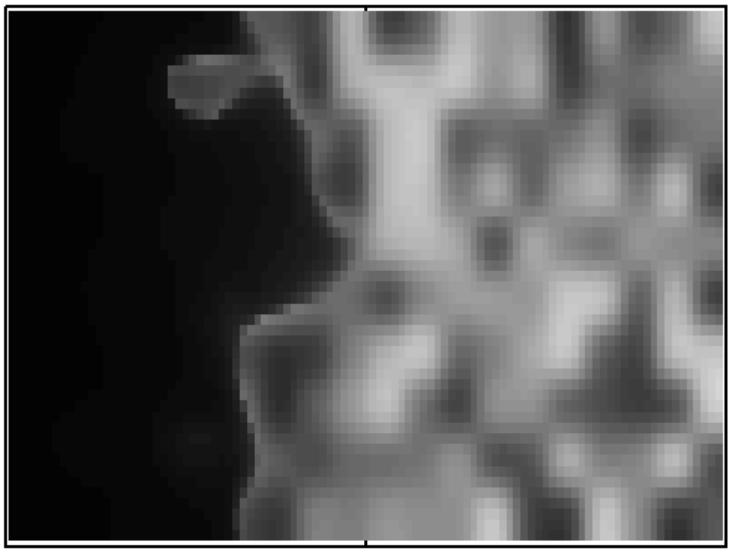

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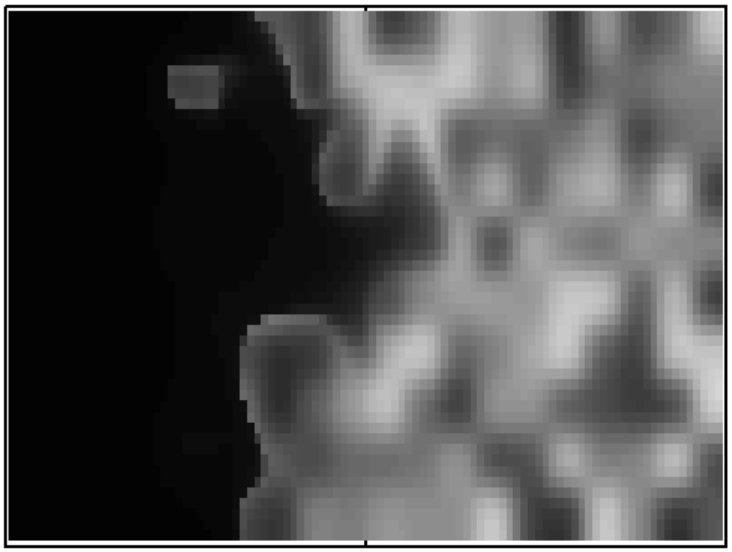

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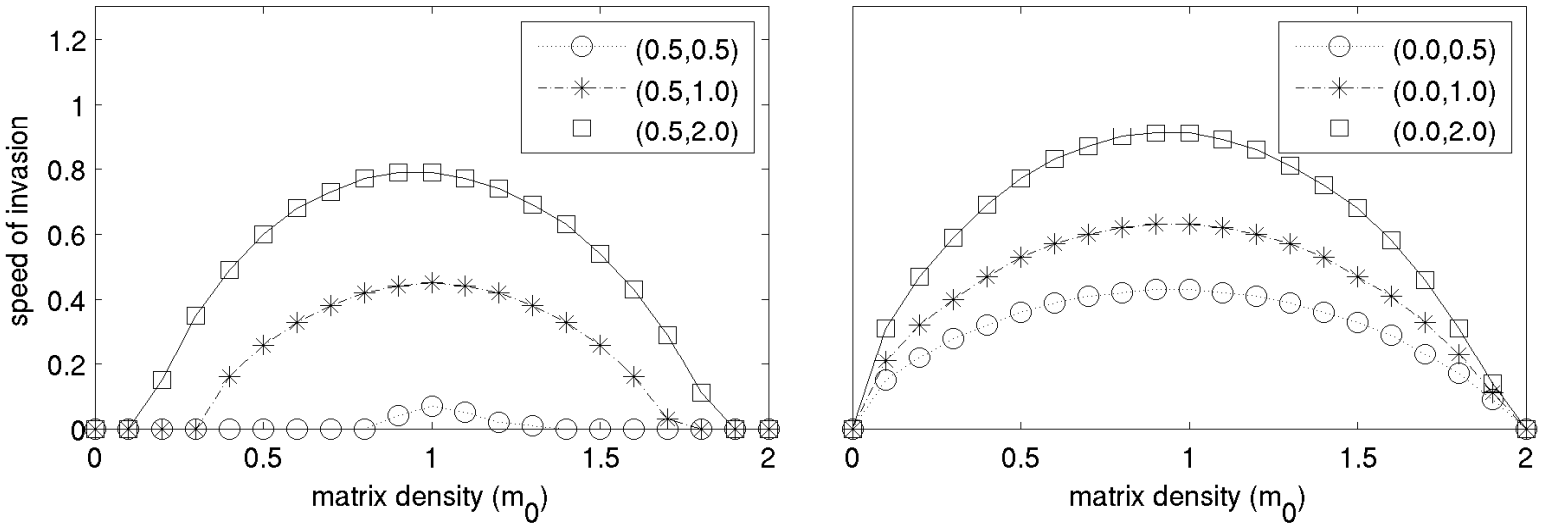
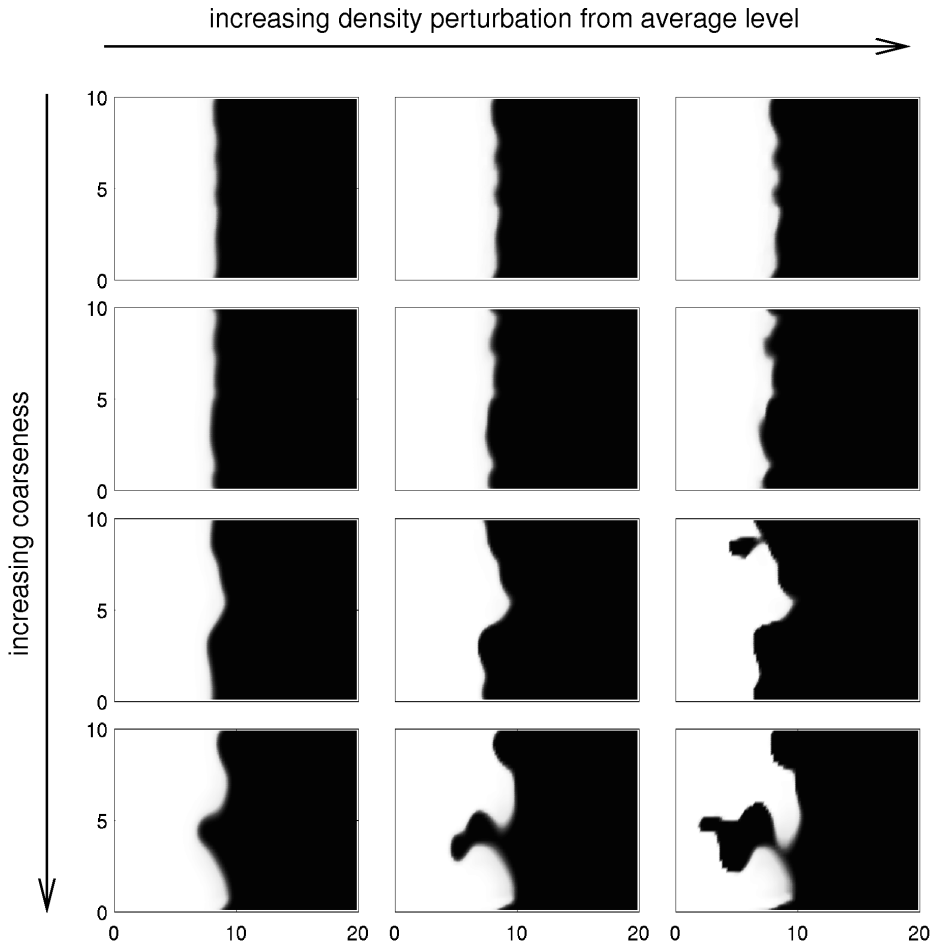


Basic explanation: invasion speed varies with matrix density.

Varying the Initial (Random) Matrix Density



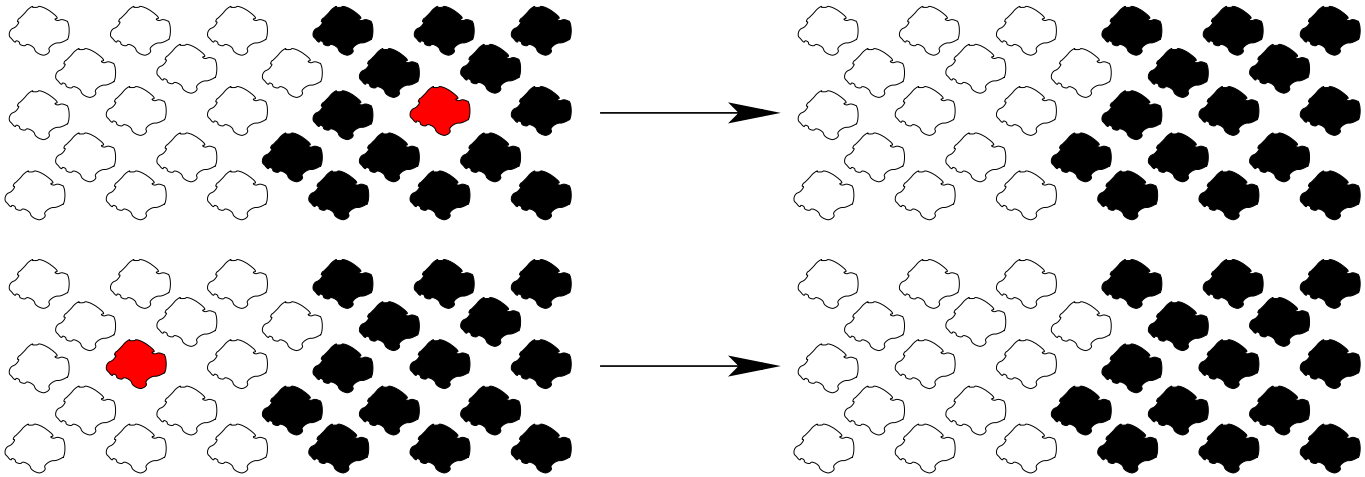
Conclusions and Challenges

- Our model results are consistent with traditional thinking on cancer invasion.
- The model makes quantitative predictions on how invasion speed depends on adhesion strengths and matrix density, which are experimentally testable.
- The model makes detailed predictions on how tumour fingering depends on matrix heterogeneity; these are also experimentally testable.
- The model raises many analytical and computational challenges for the future.

Outline

Introduction to the Community Effect

- Our modelling framework can also be used to study other phenomena that depend on nonlocal cell interactions
- Specific example: community effect in differentiation (Gurdon, Nature 336: 772, 1988)



Introduction to the Community Effect

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Key question 1: What are the biochemical mechanisms causing community effects? (Monk, Bull. Math. Biol. 59: 409, 1997)

Key question 2: Can a community effect cause spatial patterning? (Moreira & Deutsch, Dev. Dyn. 232: 33, 2005)

A Model for Community-Based Differentiation

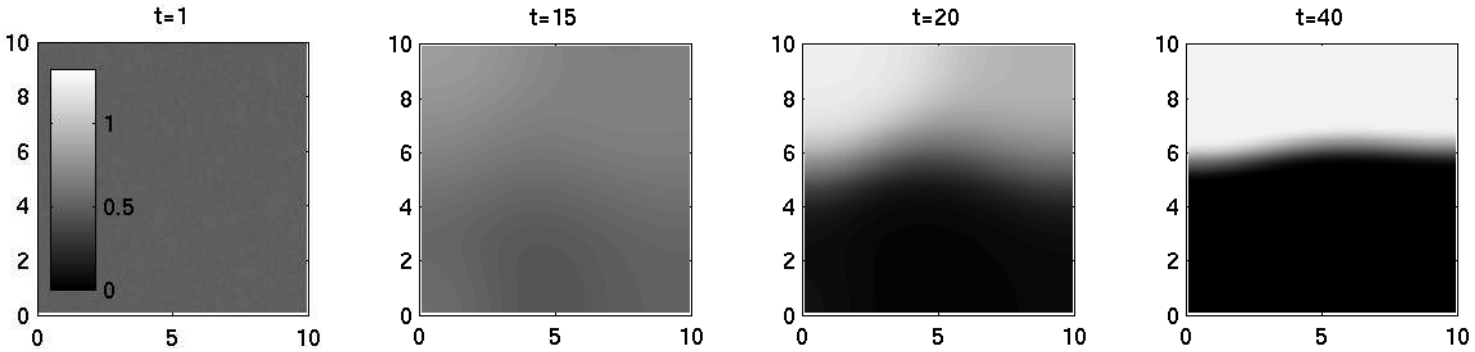
$$\begin{aligned} \partial b/\partial t &= f(I_b) - d_b\, b \\ \partial w/\partial t &= f(I_w) - d_w\, w \end{aligned} \qquad \boxed{f(I_b) + f(I_w) = 1}$$

where

$$I_b = \frac{1}{A} \iint_{\odot} \frac{b(\underline{x} + \underline{r})}{b(\underline{x} + \underline{r}) + w(\underline{x} + \underline{r})} dA$$

$$I_w = \frac{1}{A} \iint_{\odot} \frac{w(\underline{x} + \underline{r})}{b(\underline{x} + \underline{r}) + w(\underline{x} + \underline{r})} dA = 1 - I_b$$

Example of Pattern Formation ($d_b = d_w = 0.75$)



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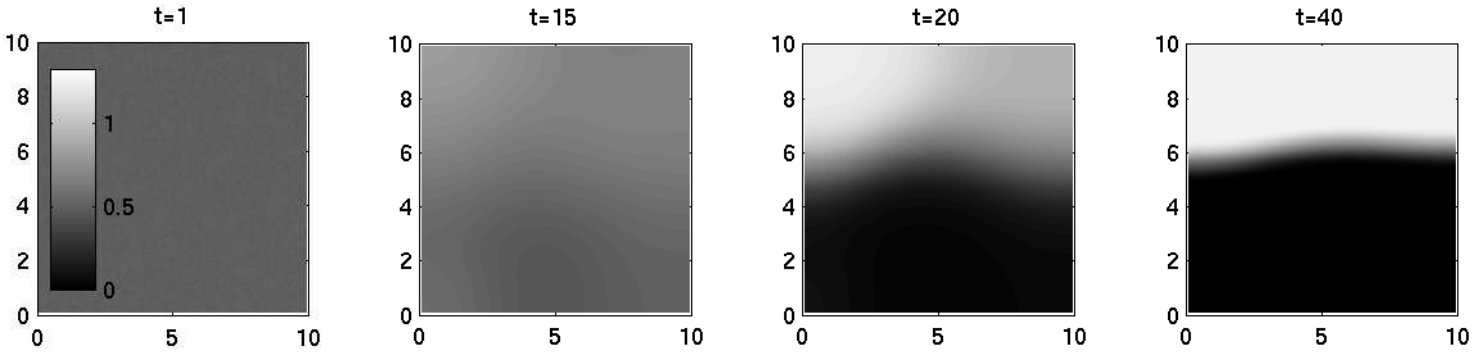

Prototype system: zebrafish pigmentation

Conclusion

Nonlocal equations enable continuum models to be applied to a wide range of problems in cell biology.

Potential future applications include:

- Specific cancers
- Wound healing
- Other developmental processes

References

N.J. Armstrong, K.J. Painter, J.A. Sherratt: A continuum approach to modelling cell adhesion. *J. Theor. Biol.* **243**, 98-113 (2006).

N.J. Armstrong, K.J. Painter, J.A. Sherratt: Adding adhesion to the cell cycle model for somite formation. *Bull. Math. Biol.* **71**, 1-24 (2009).

J.A. Sherratt, S.A. Gourley, N.J. Armstrong, K.J. Painter: Boundedness of solutions of a nonlocal reaction-diffusion model for adhesion in cell aggregation and cancer invasion. *Eur. J. Appl. Math.* **20**, 123-144 (2009).

K.J. Painter, N.J. Armstrong, J.A. Sherratt: The impact of adhesion on cellular invasion processes in cancer and development. *J. Theor. Biol.* **264**, 1057-1067 (2010).

J.M. Bloomfield, J.A. Sherratt, K.J. Painter, G. Landini: Cellular automata and integrodifferential equation models for cell renewal in mosaic tissues. *J. R. Soc. Interface* **7**, 1525-1535 (2010).

J.M. Bloomfield, K.J. Painter, J.A. Sherratt: How does cellular contact affect differentiation mediated pattern formation? *Bull. Math. Biol.* **73**, 1529-1558 (2011).

List of Frames

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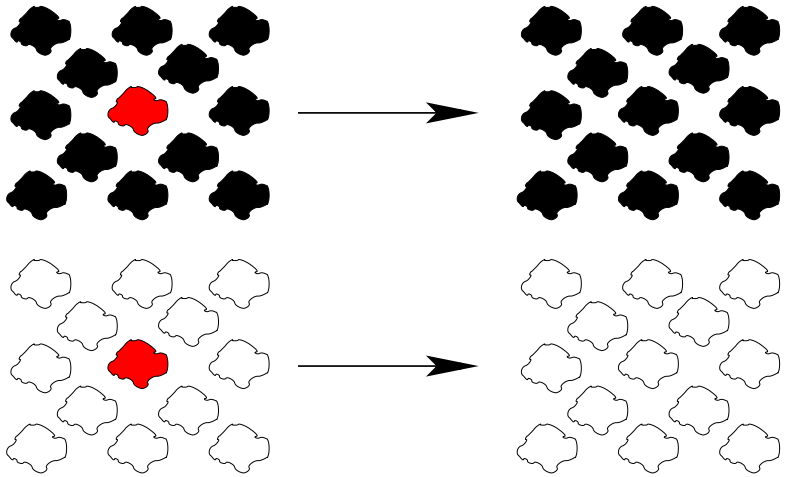

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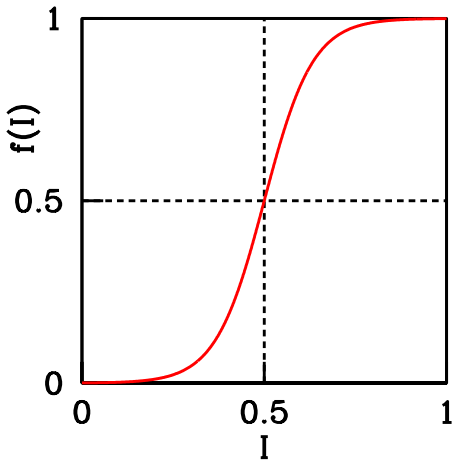

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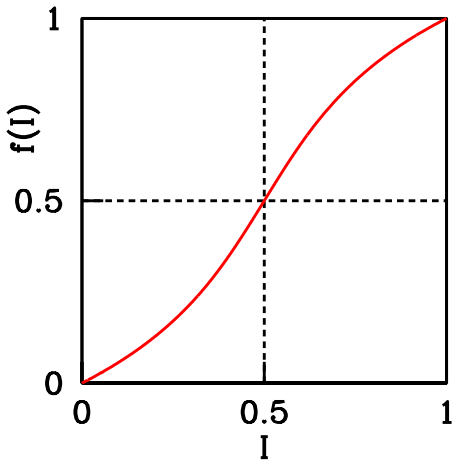

Weak community effect

$$I_a = \frac{1}{A}\iint_{\odot} \frac{a(\underline{x}+\underline{r})}{a(\underline{x}+\underline{r}) + b(\underline{x}+\underline{r})}\, dA$$

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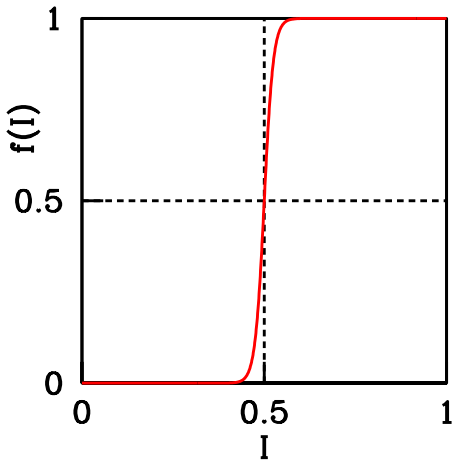

Strong community effect

$$I_a = \frac{1}{A}\iint_{\odot} \frac{a(\underline{x}+\underline{r})}{a(\underline{x}+\underline{r}) + b(\underline{x}+\underline{r})}\, dA$$

$$I_b = \frac{1}{A}\iint_{\odot} \frac{b(\underline{x}+\underline{r})}{a(\underline{x}+\underline{r}) + b(\underline{x}+\underline{r})}\, dA = 1 - I_a$$

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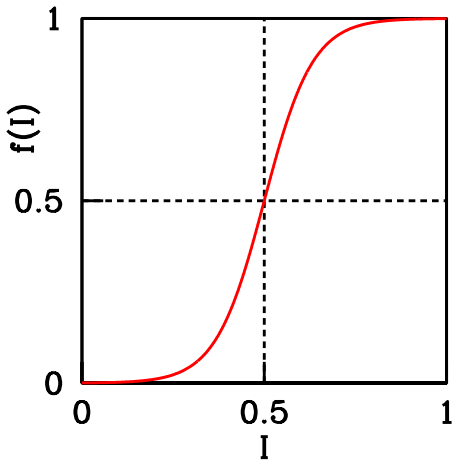

$$f(1-I) = 1 - f(I)$$

$$I_a = \frac{1}{A}\iint_{\odot} \frac{a(\underline{x}+\underline{r})}{a(\underline{x}+\underline{r}) + b(\underline{x}+\underline{r})}\, dA$$

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$$\begin{aligned} \partial a/\partial t &= f(I_a) - d_a\, a \\ \partial b/\partial t &= f(I_b) - d_b\, b \end{aligned}$$

d_a, d_b are dimensionless and reflect the ratio of the death rate to the differentiation rate

$$I_a = \frac{1}{A}\iint_{\odot} \frac{a(\underline{x}+\underline{r})}{a(\underline{x}+\underline{r}) + b(\underline{x}+\underline{r})} dA$$

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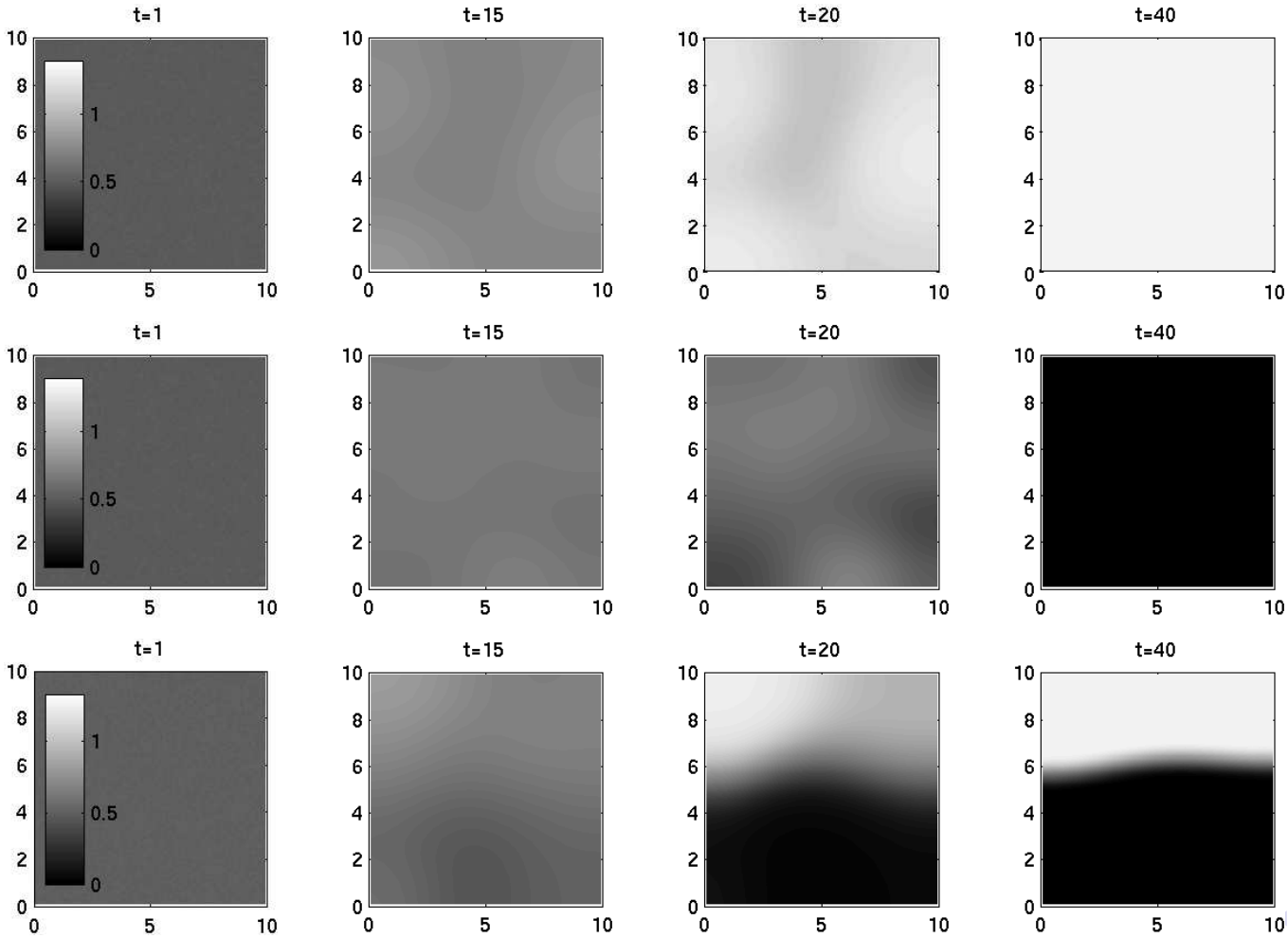
Homogeneous Steady States of the Community Model

$(a, b) = (1/d_a, 0)$	stable to homogeneous perturbations
$(a, b) = (a_s, b_s)$	unstable
$(a, b) = (0, 1/d_b)$	stable to homogeneous perturbations

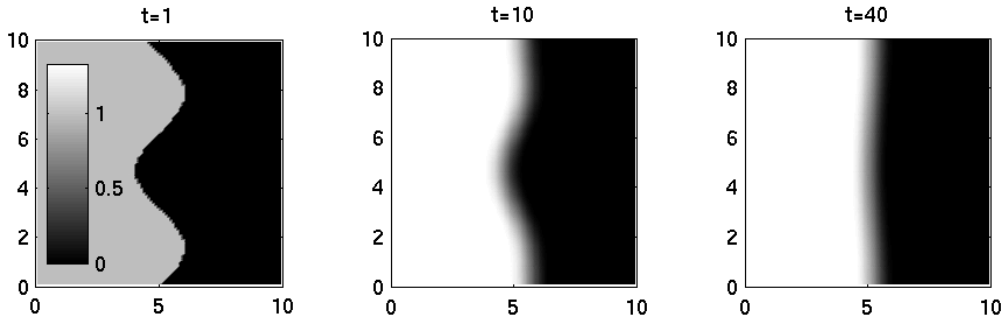
Question: are there (stable) patterns in which the solution alternates between the two cell types?

$a = 1/d_a$	$a = 0$	$a = 1/d_a$	$a = 0$	$a = 1/d_a$	$a = 0$
$b = 0$	$b = 1/d_b$	$b = 0$	$b = 1/d_b$	$b = 0$	$b = 1/d_b$

Typical Model Solutions ($d_a = d_b = 0.75$)



The Shape of the Interface



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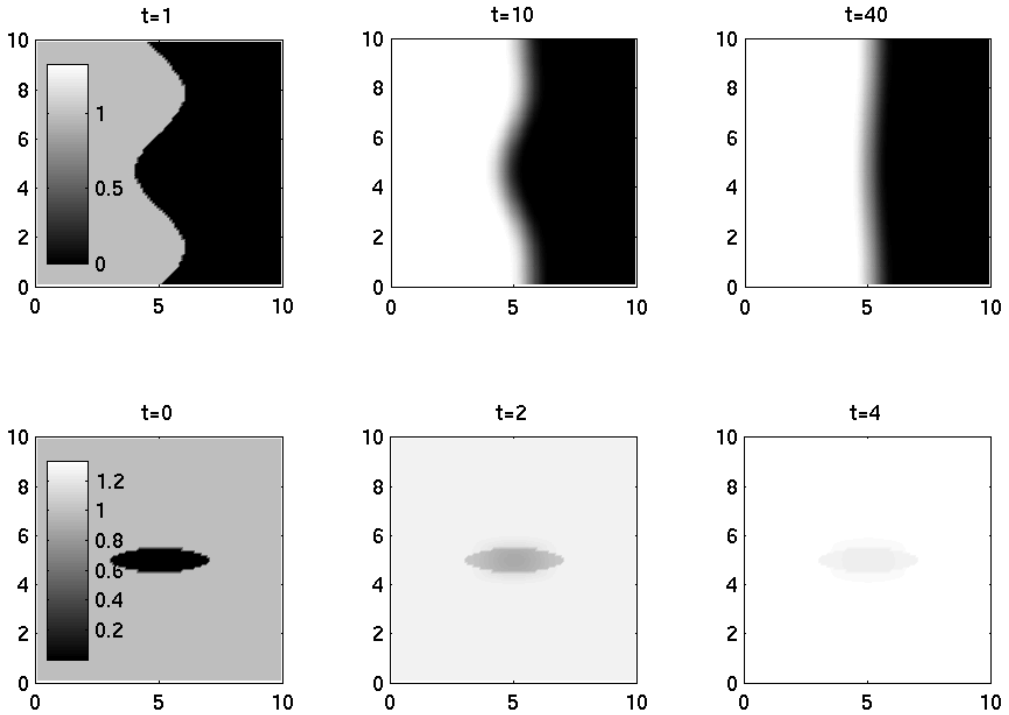

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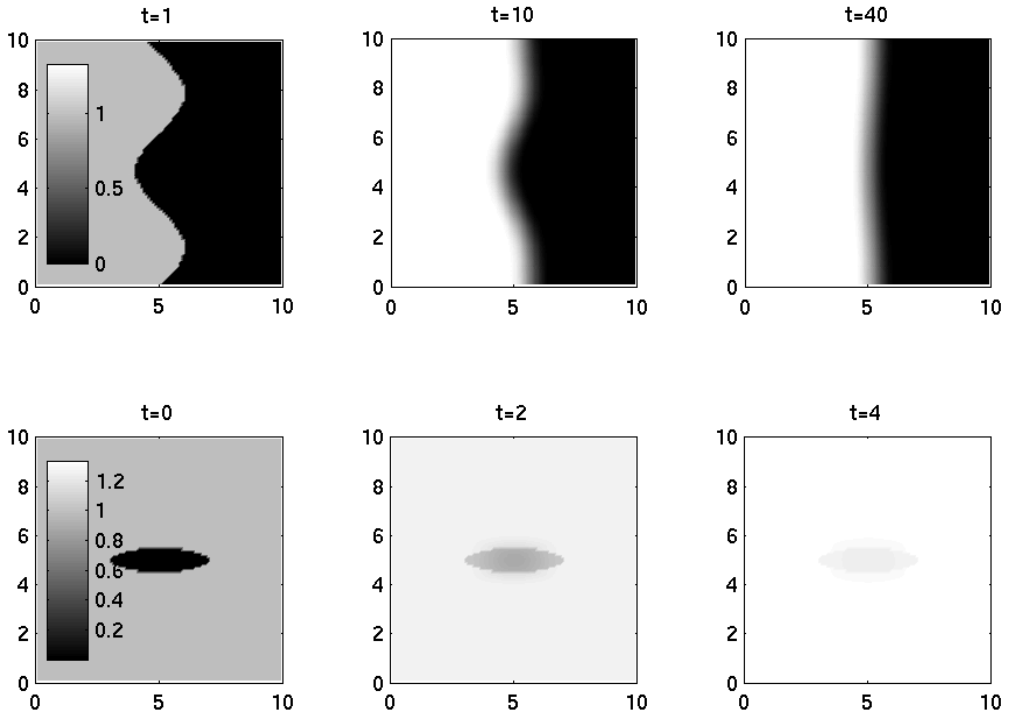
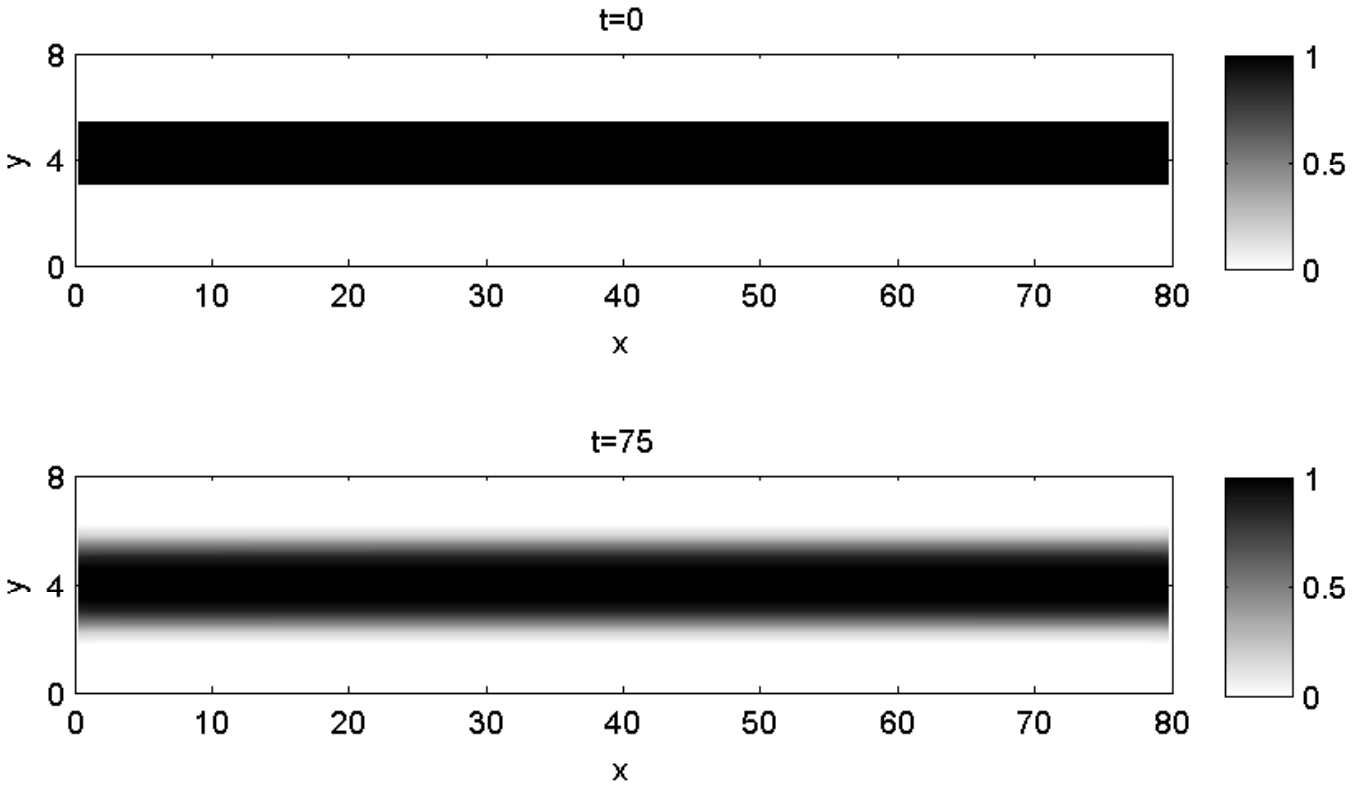


Community effect $\Rightarrow$ stripes not spots

Stripe Maintainance



Conclusions

- Question: Can a community effect cause spatial patterns?
  Answer: Yes, but it requires suitable initial conditions: a mechanism for pattern maintainance
- Patterning also requires $d_a \approx d_b$, i.e. approximately equal death rates of the two cell types
- The interfaces between pattern regions are always flat: *stripes not spots*

Future Challenge

Simulate the model on larger spatial scales, e.g. corresponding to a whole zebrafish

Outstanding Applications

Future Challenge: New Applications

- Specific cancers
- Wound healing
- Other developmental processes