Nonlocal Models for Cancer Invasion and Pattern Formation

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Nonlinear PDEs Arising in Mathematical Biology
April 19-21, 2010

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

Collaborators

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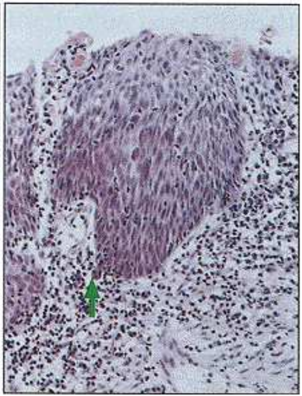
Outline

Outline

1. Modelling Adhesion in Cancer Invasion
2. Simulations of Cancer Invasion
3. The Community Effect in Differentiation

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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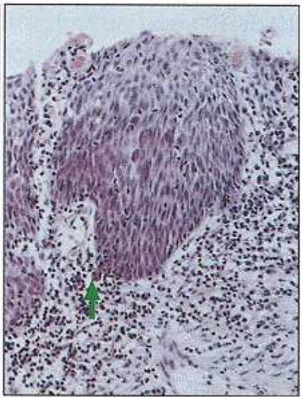

Carcinoma of the uterine cervix

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

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

$$\frac{\partial m}{\partial t} = -\underbrace{\lambda \cdot n \cdot m^2}_{\text{matrix degradation}}$$

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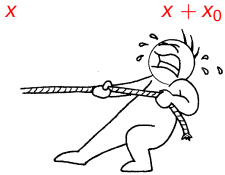
$$K_{nn} = \text{cell flux due to cell-cell adhesion}$$

$$\frac{\partial m}{\partial t} = -\underbrace{\lambda \cdot n \cdot m^2}_{\text{matrix degradation}}$$

Modelling Cell-Cell Adhesion

- Adhesive flux K_{nn} is proportional to the force due to breaking and forming adhesive bonds
(Stokes' Law: low Reynolds number)
- The force on a cell at x exerted by cells and matrix a distance x_0 away depends on:

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



$$\boxed{f(x, x_0) = g\left(n(x + x_0, t), m(x + x_0, t)\right) \cdot \omega(x_0)}$$

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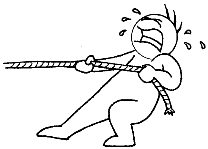
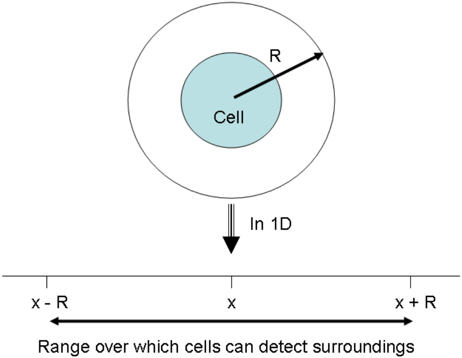


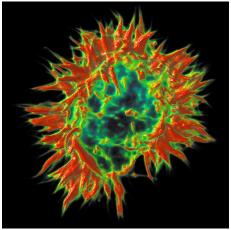
$$\boxed{f(x, x_0) = g\left(n(x + x_0, t), m(x + x_0, t)\right) \cdot \omega(x_0)}$$

- 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 $\omega(x_0)$

$x - R$ $\quad$ x_1 $\quad \longleftarrow \quad$ x $\quad \longrightarrow \quad$ x_2 $\quad$ $x + R$

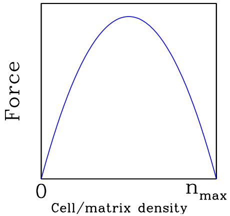
Force due to cells at x_1 $\qquad$ Force due to cells at x_2

$\omega(x_0)$ 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 $g(n, m) = n(n_{max} - n - m)$. Here n_{max} corresponds to no empty space.



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

Modelling Adhesion in Cancer

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

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

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$\boxed{\alpha \text{ and } \beta \text{ are adhesion coefficients}}$

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Extension to 2-D is straightforward

Outline

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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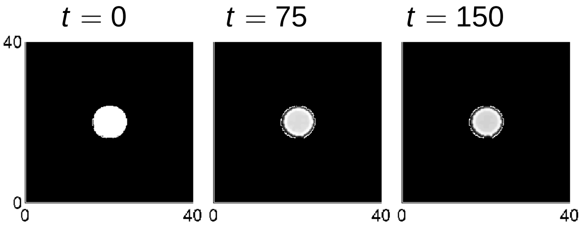

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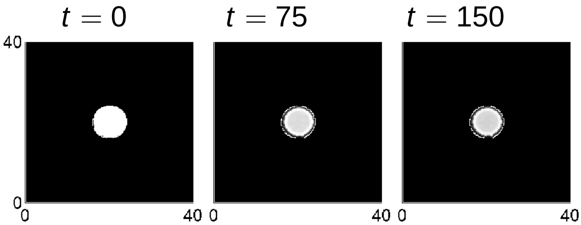
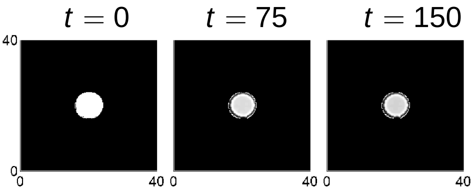


Invasion can be initiated either by decreasing cell-cell adhesion (α) or by increasing cell-matrix adhesion (β)

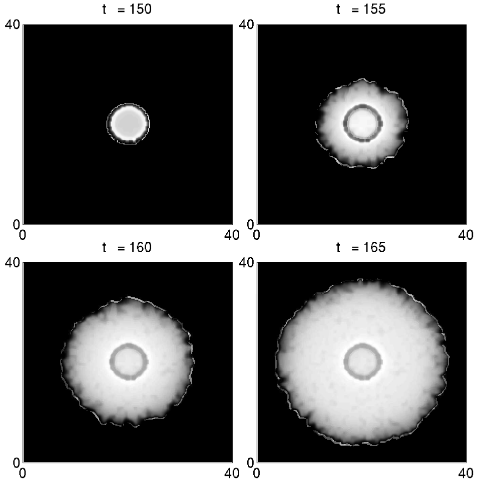
The Sequential Development of an Invasive Tumour

Stage 1:
non-invasive
tumour growth

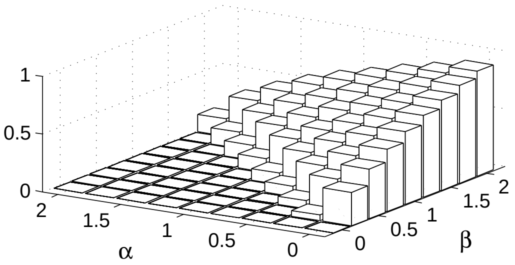


The Sequential Development of an Invasive Tumour

Stage 2:
mutation,
followed by
tumour invasion



Invasion Speed vs α and β

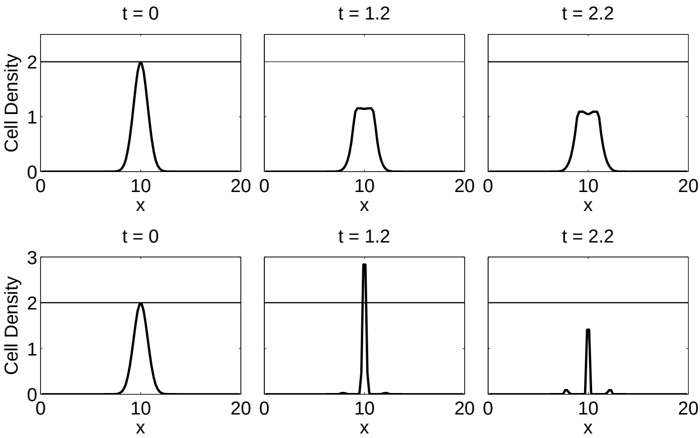


Mathematical Issue: Boundedness

- 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 $t \geq 0$?

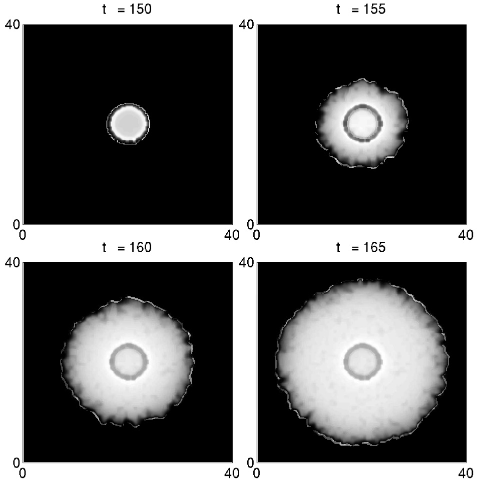
Partial answer: If $0 \leq n \leq 2$ and $0 \leq m \leq M$ at $t = 0$ then $0 \leq n \leq 2$ for all $t \geq 0$ provided that

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

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

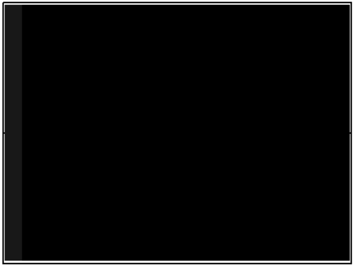
The Importance of Tumour Morphology

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.)

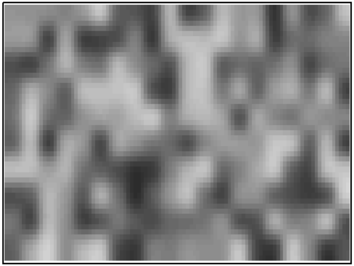


Investigation of Tumour Fingering

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



Cells



Matrix

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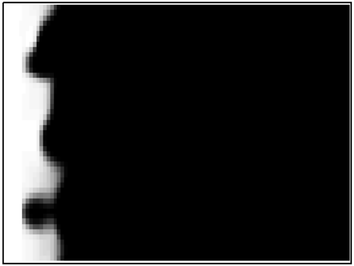
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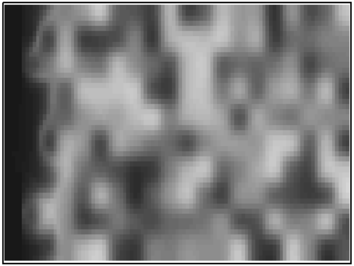
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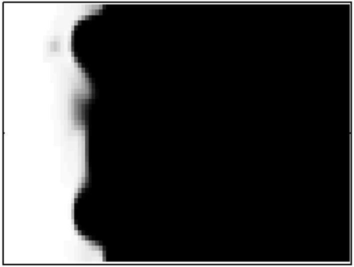

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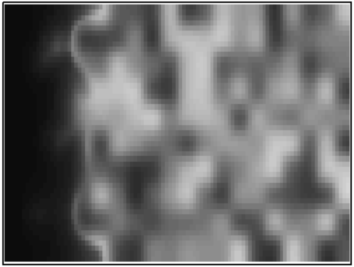

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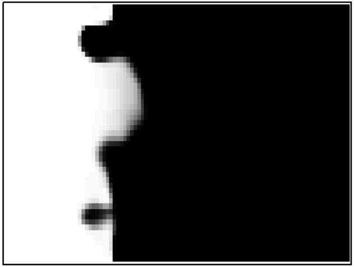

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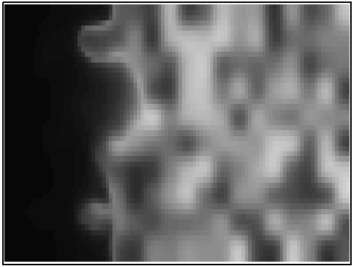

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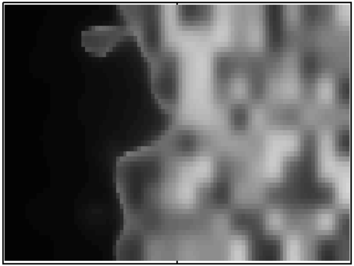

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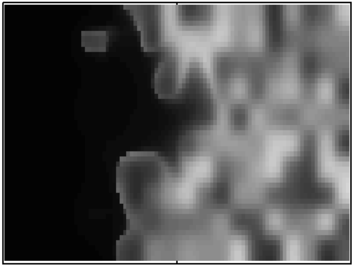

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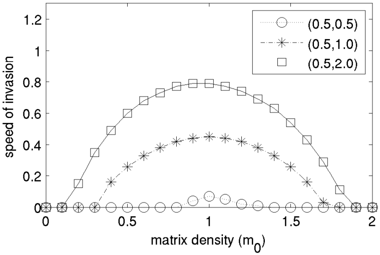
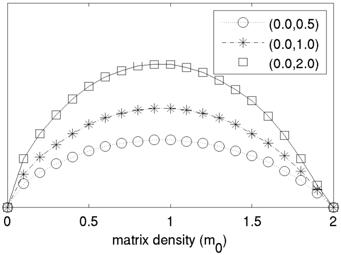
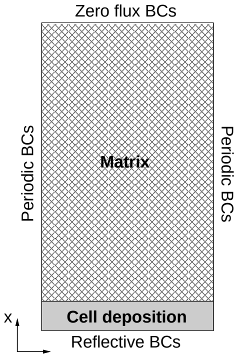


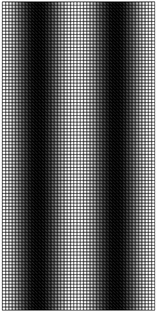


Basic explanation: invasion speed varies with matrix density.

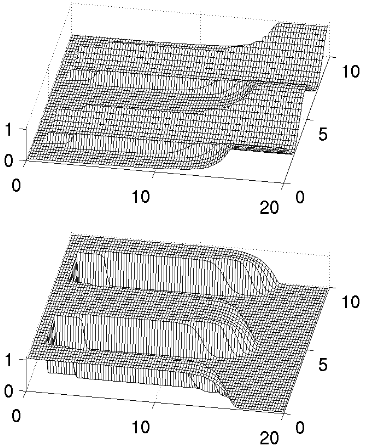
Fingering due to a Pattern in the Initial Matrix Density



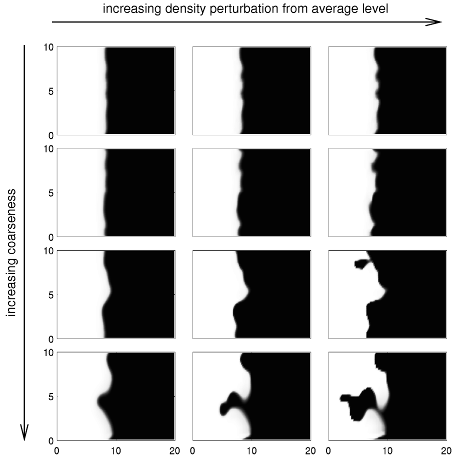
(a)



(c)



Varying the Initial (Random) Matrix Density



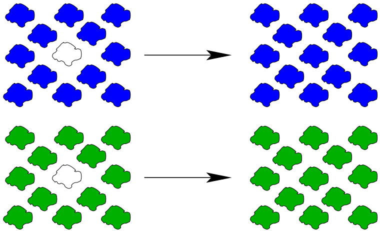
Conclusions and Challenges

- 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 computational challenges, in particular concerning extension to 3-D.

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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- Specific example: community effect in differentiation (Gurdon, Nature 336: 772, 1988)

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)

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)
- Prototype system: zebrafish pigmentation

A Model for Community-Based Differentiation

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

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

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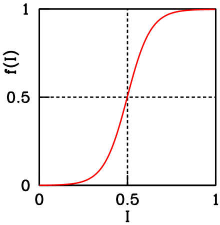

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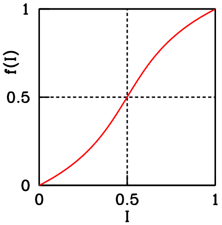

Weak community effect

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

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

A Model for Community-Based Differentiation

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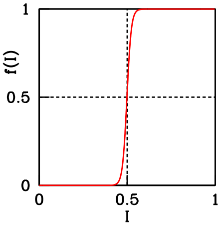


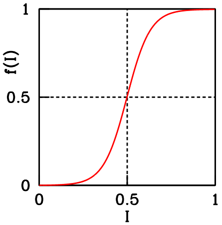
Strong community effect

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

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

A Model for Community-Based Differentiation

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



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

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

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

A Model for Community-Based Differentiation

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

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

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

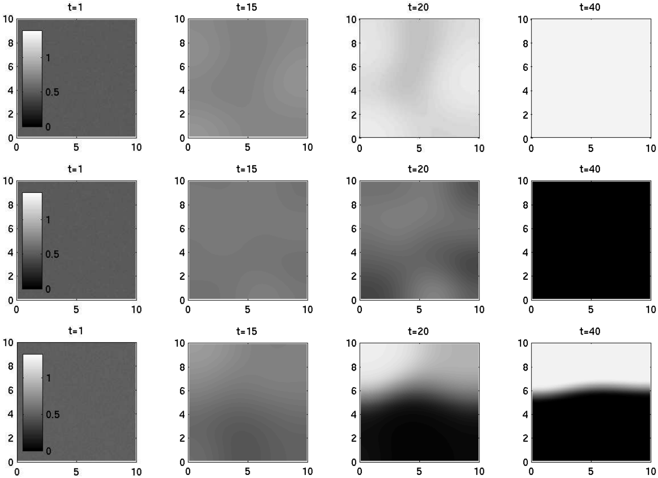
Homogeneous Steady States of the Community Model

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

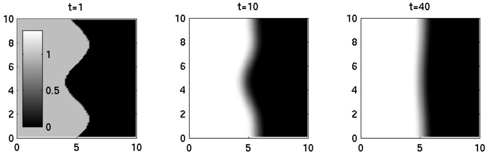
Question: are there (stable) patterns in which the solution alternates between the two cell types?

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

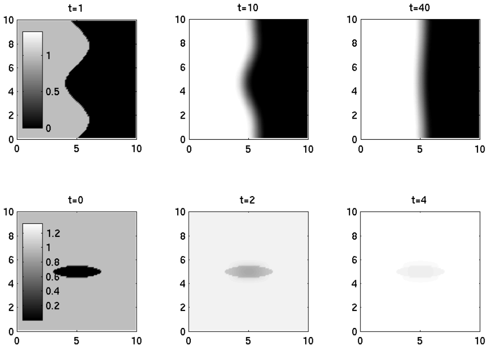
Typical Model Solutions ($d_a = d_b = 0.75$)



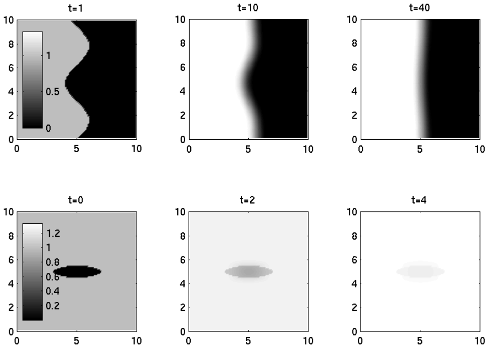
The Shape of the Interface



The Shape of the Interface

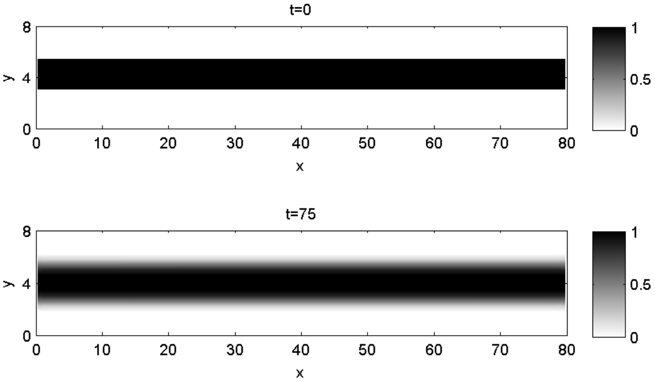


The Shape of the Interface



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*
- A future computational challenge is to simulate the model on larger spatial scales, e.g. corresponding to a whole zebrafish

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