

# Mathematical modelling of cell adhesion, and applications to cancer

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Nicola Armstrong

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# Outline

- 1 Introduction and Basic Modelling
- 2 Model Solutions and Extensions
- 3 Applying the Model to Cancer Invasion
- 4 Solutions of the Model for Cancer Invasion

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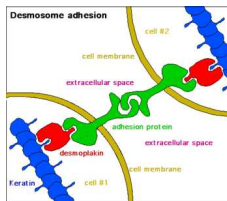
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## What is Cell-Cell Adhesion?

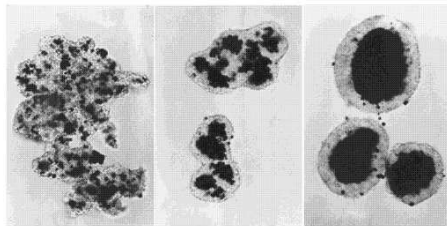
Cells bind to each other through cell adhesion molecules.

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



# Aggregation and Cell Sorting



(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

# Derivation of the Model I

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- Diffusive flux  $J_d = -D\partial n / \partial x$
- Adhesive flux  $J_a = \phi n F / R$   
(Stokes' Law: low Reynolds number)  
 $F$  = force due to breaking and forming adhesive bonds  
 $\phi$  = a constant related to viscosity  
 $R$  = the sensing radius of the cells

## 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)

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

## Derivation of the Model II

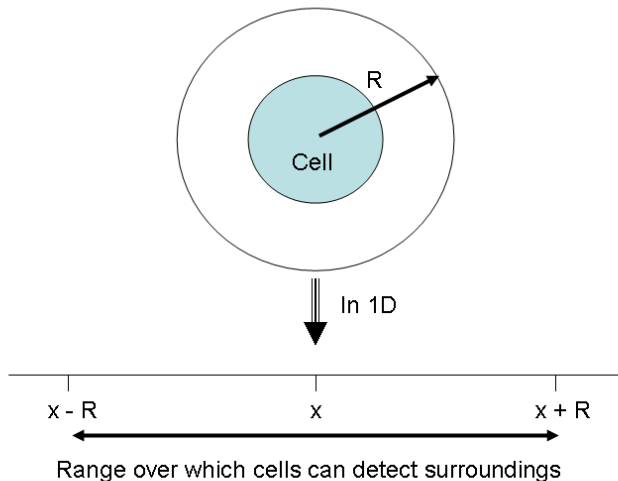
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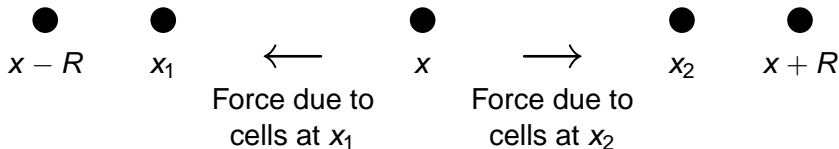
- Total force = sum of all forces acting on cells at  $x$

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

## Model Details: The Sensing Radius, $R$



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



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

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

# Mathematical Model for One Cell Population

Nondimensionalising the model gives

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

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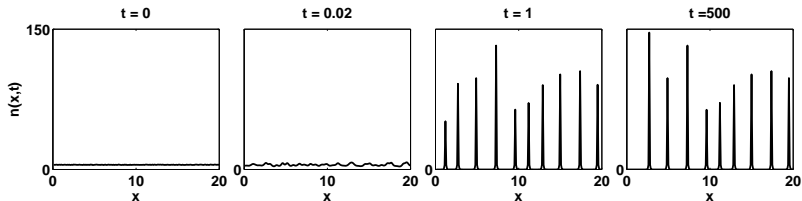
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- Initially we assume  $g(n) = n$
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- Substitute  $n(x, t) = n_0 + \epsilon \exp\{ikx + \lambda t\} \Rightarrow$   
 $\lambda(k) = -k^2 - 2n_0(-1 + \cos k)$
- This implies instability when  $\alpha > \alpha_{crit}$   
( $\alpha_{crit} = 1 / (n_0 \cos \theta)$ , with  $\theta$  the smallest +ve root of  $\theta = \tan \theta$ )

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# A Numerical Solution of the Basic Model



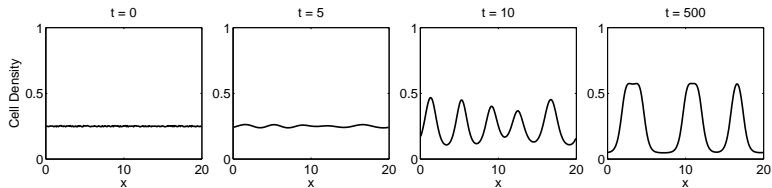
## Model Improvement: Nonlinear $g(n)$

- The solutions of the basic model suffer from steep aggregations with progressive coarsening
- In reality, there will be a density limit beyond which cells will no longer aggregate
- We can account for this via a nonlinear  $g(n)$ ; we take  $g(n) = n(n_{max} - n)$ . Here  $n_{max}$  corresponds to close-packed cells.

The improved model is:

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

# A Numerical Solution of the Improved Model



# Extending the Model to Interacting Cell Populations I

- To consider cell sorting, we extend the model to two interacting cell populations
- The extended model includes self-population adhesion and cross-population adhesion

## Extending the Model to Interacting Cell Populations II

$$\frac{\partial n}{\partial t} = \frac{\partial^2 n}{\partial x^2} - \frac{\partial}{\partial x} [nK_n(n, m)] \quad \frac{\partial m}{\partial t} = \frac{\partial^2 m}{\partial x^2} - \frac{\partial}{\partial x} [mK_m(n, m)]$$

$$K_n = S_n \int_{-1}^{+1} g_{nn}(n(x+x_0, t), m(x+x_0, t)) \omega(x_0) dx_0$$

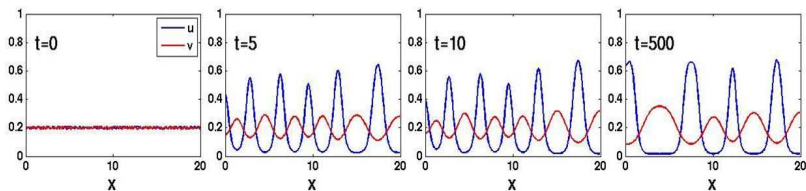
$$+ C \int_{-1}^{+1} g_{nm}(n(x+x_0, t), m(x+x_0, t)) \omega(x_0) dx_0$$

$$K_m = S_m \int_{-1}^{+1} g_{mm}(n(x+x_0, t), m(x+x_0, t)) \omega(x_0) dx_0$$

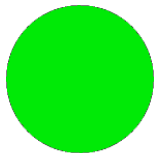
$$+ C \int_{-1}^{+1} g_{mn}(n(x+x_0, t), m(x+x_0, t)) \omega(x_0) dx_0$$

with  $g_{nn} = g_{mn} = n(1 - n - m)$  and  $g_{mm} = g_{nm} = m(1 - n - m)$

# A Numerical Simulation of Cell Sorting in 1-D



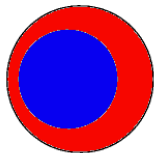
## Experimental Cell Sorting Results



A

Mixing

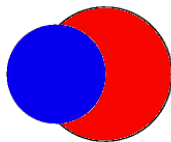
$$C > (S_n + S_m)/2$$



B

Engulfment

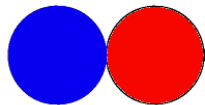
$$S_n > C > S_m$$



C

Partial  
engulfment

$$C < S_n \text{ and } C < S_m$$

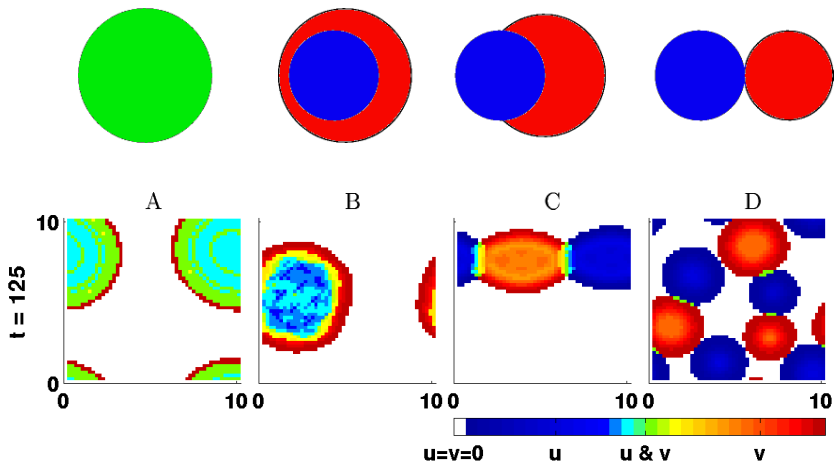


D

Complete  
sorting

$$C = 0$$

## Model Results on Cell Sorting in 2-D



## Movies of Cell Sorting in 2-D

Click to play  
the movie,  
case A

Click to play  
the movie,  
case C

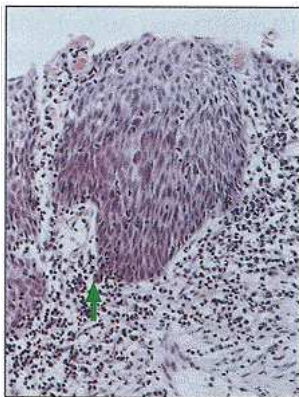
Click to play  
the movie,  
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Click to play  
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# Introduction to Cancer Invasion

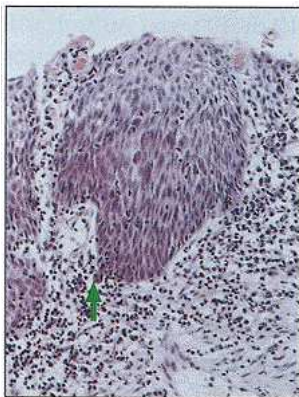


Cells in a solid tumour invade surrounding tissue due to changes in:

- migration
- protease/anti-protease production
- adhesion

Carcinoma of the uterine cervix

# Introduction to Cancer Invasion



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

Carcinoma of the uterine cervix

## Modelling Adhesion in Cancer

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

$$\frac{\partial n}{\partial t} = D \frac{\partial^2 n}{\partial x^2} - \frac{\partial}{\partial x} [n \cdot (K_{nn} + K_{nm})] + n(1 - n)$$

$$\frac{\partial m}{\partial t} = -\lambda \cdot n \cdot m^2$$

Model  
ingredients:

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

$$\frac{\partial m}{\partial t} = -\lambda \cdot n \cdot m^2$$

Model ingredients:

- random motility
- cell proliferation
- matrix degradation
- cell-cell adhesion

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

$$\frac{\partial m}{\partial t} = -\lambda \cdot n \cdot m^2$$

Model ingredients:

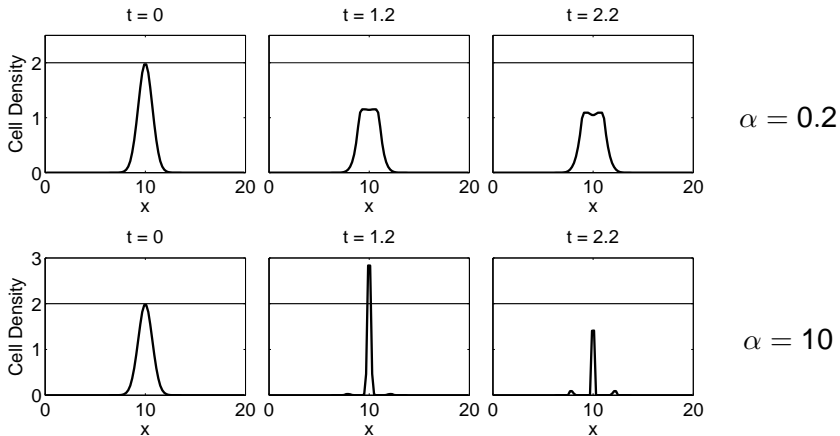
- random motility
- cell proliferation
- matrix degradation
- cell-cell adhesion
- cell-matrix adhesion

## 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 upper bound depends on parameters.

## Example of a Solution with $n > 2$



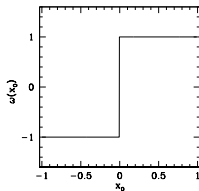
## Upper Bound for Solutions: Sufficient Conditions

Suppose that  $0 \leq n(x, 0) \leq 2$  and  $0 \leq m(x, 0) \leq M$  for some  $M > 0$ , for all  $x \in \mathbb{R}$ . Then  $n(x, t) \leq 2$  for all  $t > 0$  and  $x \in \mathbb{R}$  if any of the following conditions hold:

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(i)  $\omega(x_0) = \text{sign}(x_0)$

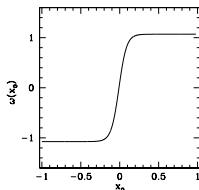


$$\begin{aligned} \frac{\partial n(x, t)}{\partial t} &= D \frac{\partial^2 n}{\partial x^2} - \frac{\partial K}{\partial x} + f(n) \\ \frac{\partial m(x, t)}{\partial t} &= -\gamma n m^2 \\ \text{with } K(x, t) &= n(x, t) \int_{-1}^{+1} [\alpha n(x + x_0, t) + \beta m(x + x_0, t)] \cdot \\ &\quad g(n(x + x_0, t) + m(x + x_0, t)) \omega(x_0) dx_0 \end{aligned}$$

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- (ii)  $\omega(x_0) = \Omega(\lambda x_0)$  with  $\Omega(\cdot)$  differentiable and  $|\Omega'(\cdot)| \in L^1(\mathbb{R})$ , and  $\lambda > 0$  sufficiently large.



$$\frac{\partial n(x, t)}{\partial t} = D \frac{\partial^2 n}{\partial x^2} - \frac{\partial K}{\partial x} + f(n)$$

$$\frac{\partial m(x, t)}{\partial t} = -\gamma n m^2$$

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$$(iii) \quad \alpha + \min\{1, M/2\}\beta < -f(2) \left[ 2 \sup\{g(\xi): 0 < \xi < 2\} \int_{-1}^1 |\omega'(x_0)| dx_0 \right]^{-1}$$

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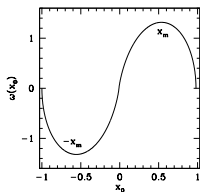
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- (iv)  $\omega(\cdot)$  differentiable with  $\omega'(x_0) > 0$  on  $|x_0| < x_m$  and  $\omega'(x_0) < 0$  on  $x_m < |x_0| < 1$  for some  $x_m \in (0, 1)$ , and
- $$\alpha + \min\{1, M/2\}\beta < -f(2) \left[ 2 \sup\{g(\xi): 0 < \xi < 2\} \int_{-x_m}^{x_m} \omega'(x_0) dx_0 \right]^{-1}$$



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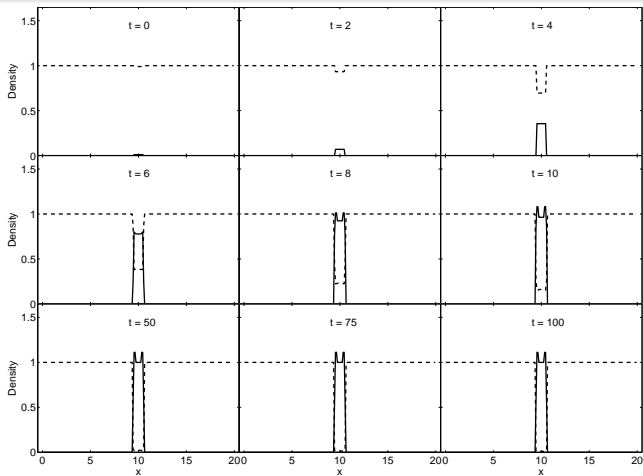
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## Model Solutions in 1-D: Non-Invasive Tumour

In all solutions, we set  $D = 0$

For  $\alpha$  relatively large and  $\beta$  relatively small, the model predicts a non-invasive tumour

# Model Solutions in 1-D: Non-Invasive Tumour

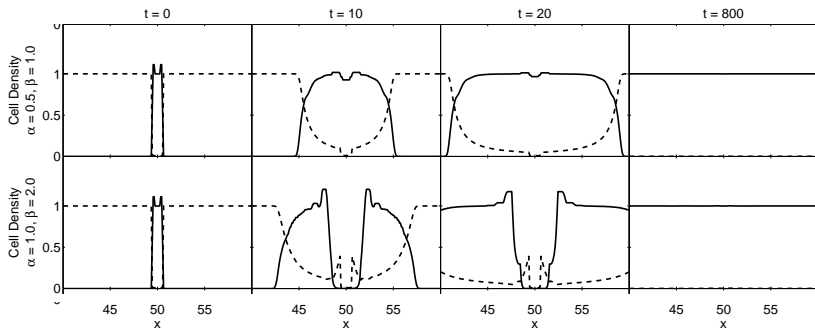


## Model Solutions in 1-D: Invasive Tumour

Starting from the non-invasive tumour ( $\alpha = \beta = 1$ ), invasion can be initiated either by decreasing cell-cell adhesion ( $\alpha$ ) or by increasing cell-matrix adhesion ( $\beta$ )

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# Tumour Morphology and Invasive Potential

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.)

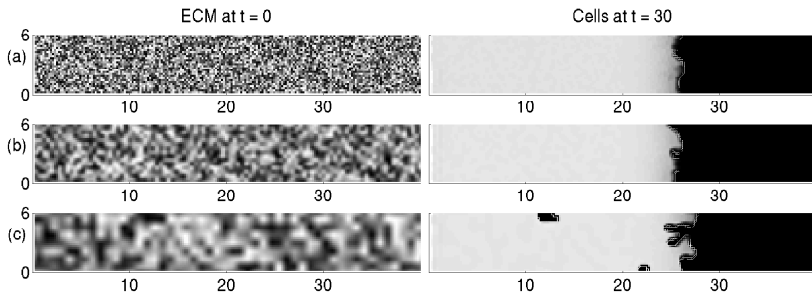
We can investigate this by solving our model in two space dimensions.

# Model Solutions in Two Dimensions

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

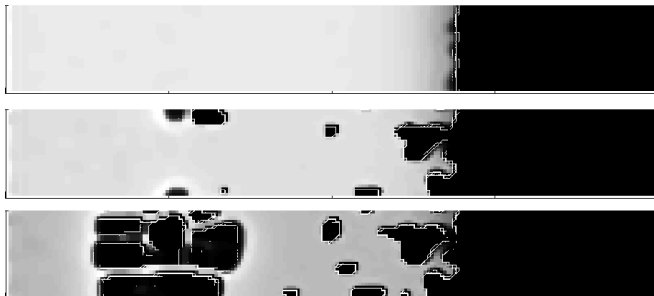
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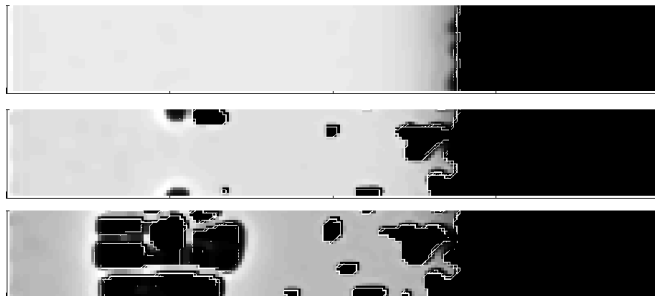
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Varying  
amplitude of  
noise in  
initial matrix  
density

## Model Solutions in Two Dimensions

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

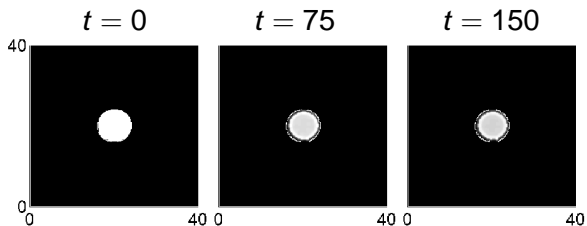


Varying  
amplitude of  
noise in  
initial matrix  
density

Basic explanation: invasion speed varies with matrix density.

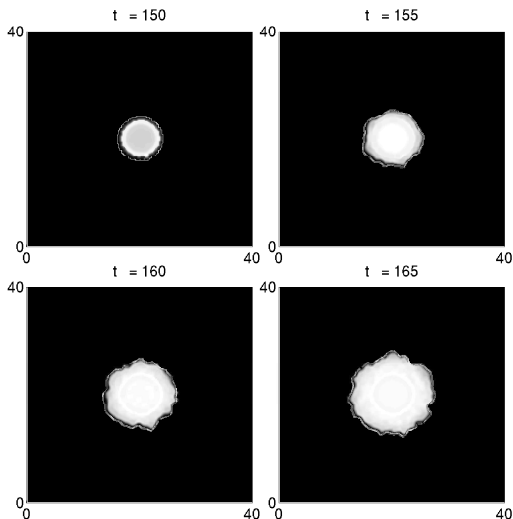
# The Sequential Development of an Invasive Tumour

Stage 1:  
non-invasive  
tumour growth



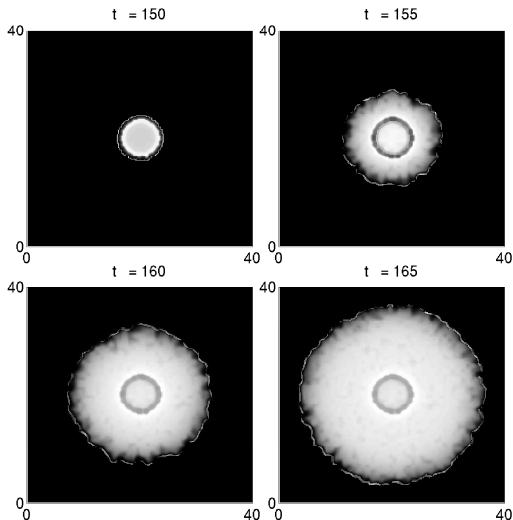
# The Sequential Development of an Invasive Tumour

Stage 2:  
mutation,  
followed by  
tumour invasion  
(small increase  
in cell-matrix  
adhesion)



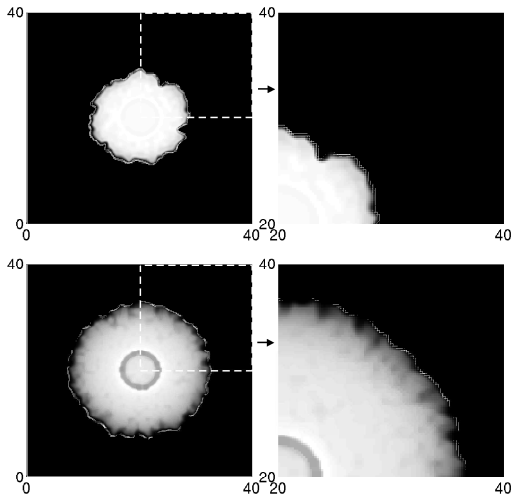
# The Sequential Development of an Invasive Tumour

Stage 2:  
mutation,  
followed by  
tumour invasion  
(large increase  
in cell-matrix  
adhesion)



# The Sequential Development of an Invasive Tumour

Stage 2:  
mutation,  
followed by  
tumour invasion



## Conclusions and Future Work

### Conclusions:

- Our model framework successfully reproduces experimental results on cell aggregation and sorting, and is consistent with traditional thinking on cancer invasion
- The model predicts that tumour fingering depends on noise in the extracellular matrix around the tumour

### Future Work on Cancer Application:

- Addition of normal tissue cells and multiple matrix types
- Addition of other aspects of the invasive phenotype

# List of Frames

- 1 Introduction and Basic Modelling
- What is Cell-Cell Adhesion?
  - Aggregation and Cell Sorting
  - Derivation of the Model
  - Model Details
  - Mathematical Model for One Cell Population

- 2 Model Solutions and Extensions
- A Numerical Solution of the Basic Model
  - Model Improvement: Nonlinear  $g(n)$
  - Extending the Model to Interacting Cell Populations
  - Experimental Cell Sorting Results
  - Model Results on Cell Sorting in 2-D

- 3 Applying the Model to Cancer Invasion
- Introduction to Cancer Invasion
  - Modelling Adhesion in Cancer
  - Mathematical Issue: Boundedness
  - Upper Bound for Solutions: Sufficient Conditions

- 4 Solutions of the Model for Cancer Invasion
- Model Solutions in One Dimension
  - Tumour Morphology and Invasive Potential
  - Model Solutions in Two Dimensions
  - The Sequential Development of an Invasive Tumour
  - Conclusions and Future Work