A Nonlocal Model for Cancer Invasion

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

Collaborators

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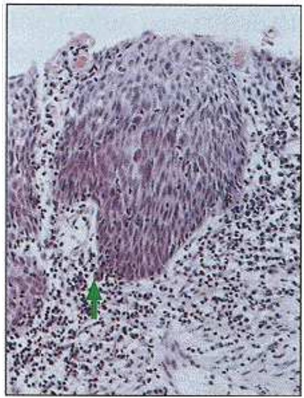
Introduction to Cancer Invasion



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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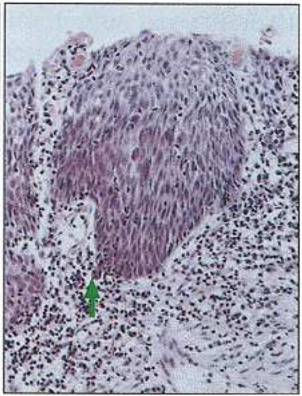

Carcinoma of the uterine cervix

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

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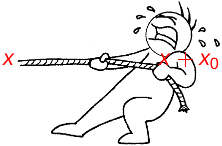
Modelling Cell-Cell Adhesion

- 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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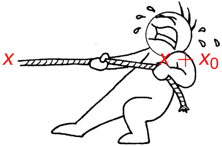

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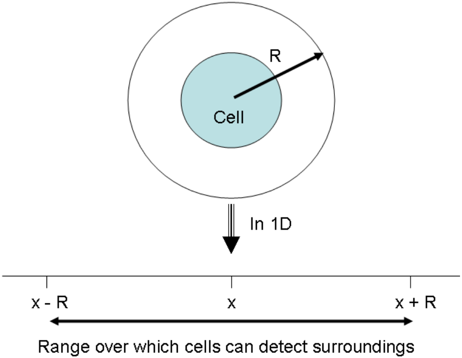
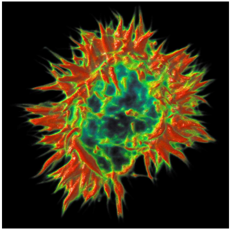
- Total force = sum of all forces acting on cells at x

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

Model Details: The Sensing Radius, R





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

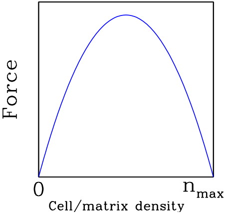
$x - R$	x_1	$\longleftarrow$ Force due to cells at x_1	x	$\longrightarrow$ Force due to cells at x_2	x_2	$x + R$

$\omega(x_0)$ 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 $n_{max} = 2$.

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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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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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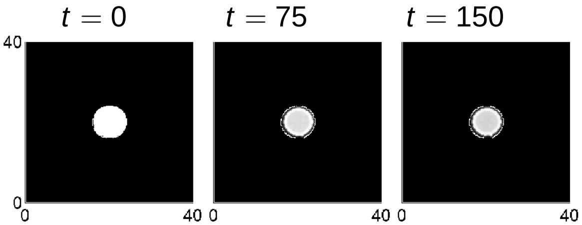

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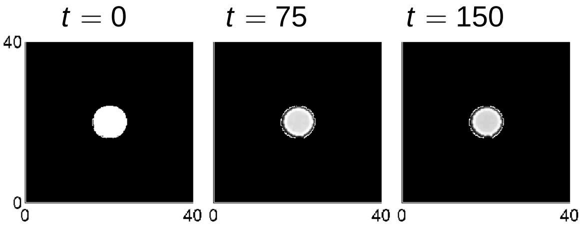
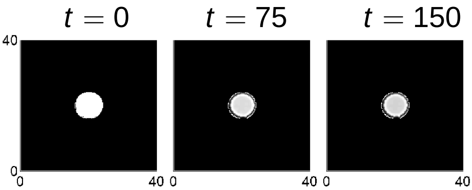


Invasion can be initiated either by decreasing cell-cell adhesion (α) or by increasing cell-matrix adhesion (β)

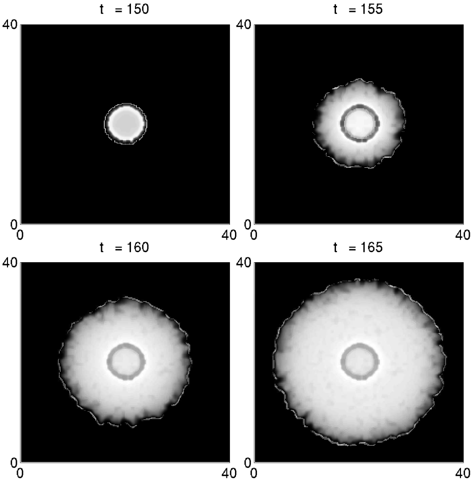
The Sequential Development of an Invasive Tumour

Stage 1:
non-invasive
tumour growth



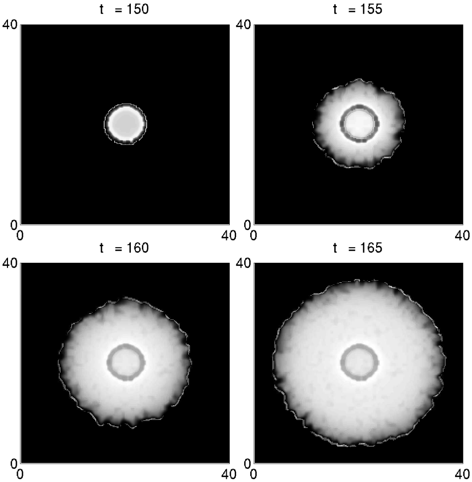
The Sequential Development of an Invasive Tumour

Stage 2:
mutation,
followed by
tumour invasion



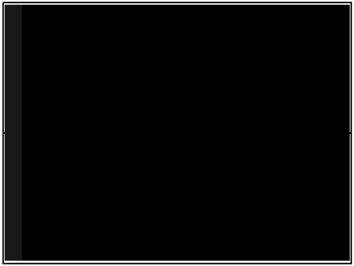
The Sequential Development of an Invasive Tumour

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.)

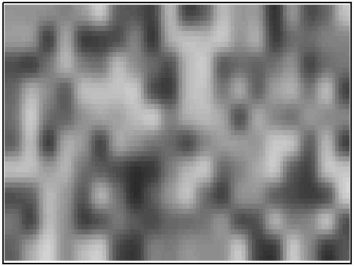


Explanation of Tumour Fingering

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



Cells



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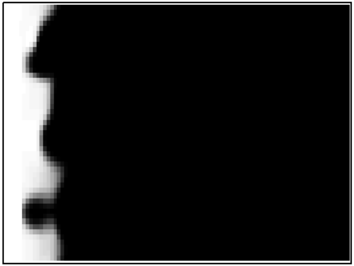

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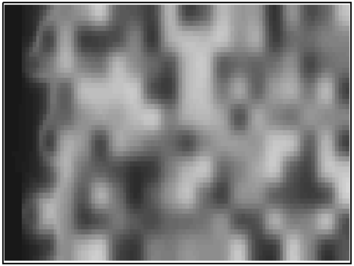

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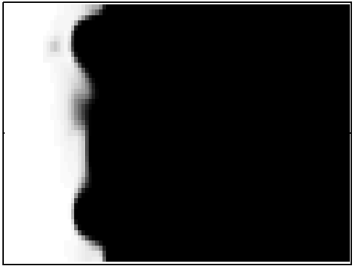

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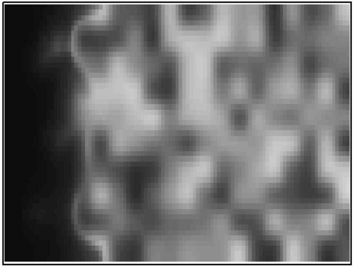

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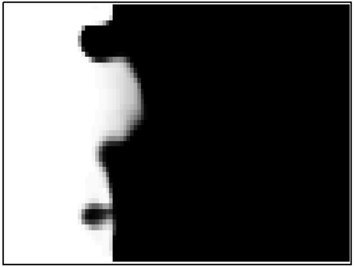

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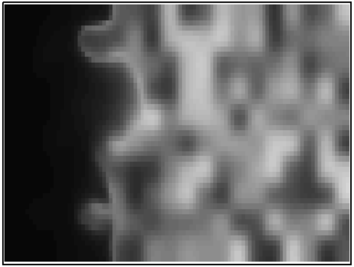

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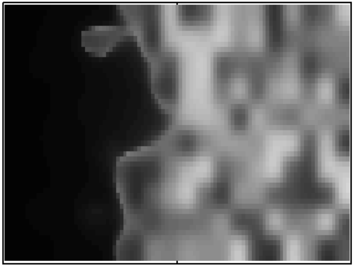

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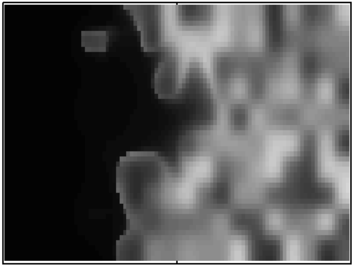

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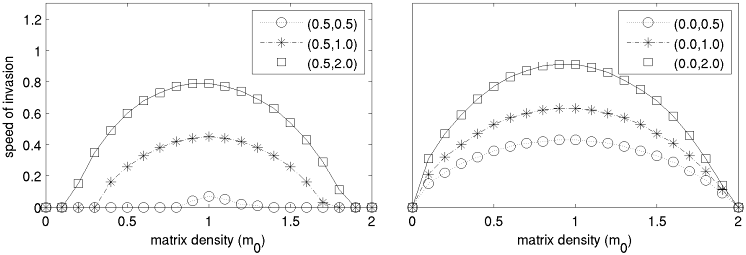

Basic explanation: invasion speed varies with matrix density.

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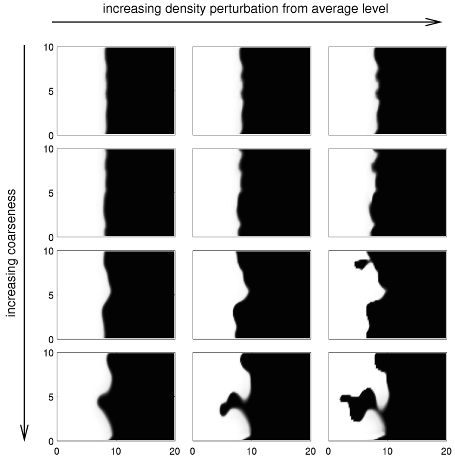

Conclusions and Challenges

- 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.

References

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

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.* in press.

List of Frames