Modelling Cell Adhesion in Development and Disease

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Collaborators

Kevin Painter

Nicola Armstrong

Stephen Gourley

Outline

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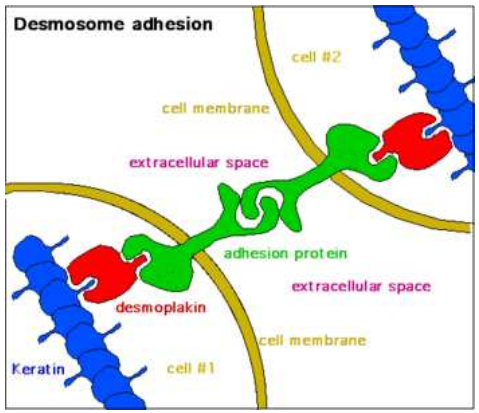
What is Cell-Cell Adhesion?

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

Derivation of the Model I

- Mass conservation $\Rightarrow \partial n/\partial t = -\partial J/\partial x +$ birth/death
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- Adhesive flux $J_a = \phi nF/R$
  (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)

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

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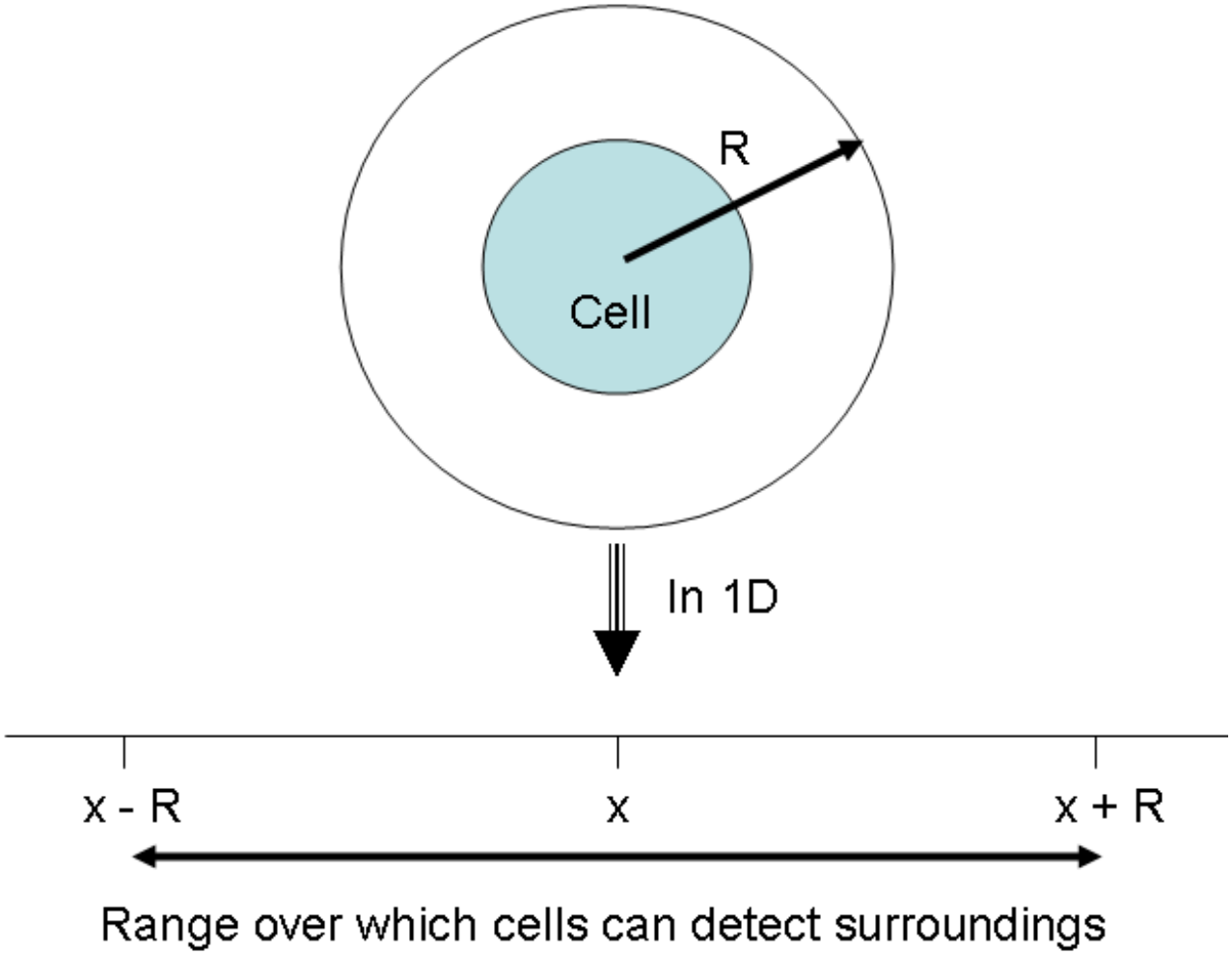
$$f(x, x_0) = \alpha \cdot g\left(n(x + x_0, t)\right) \cdot \omega(x_0)$$

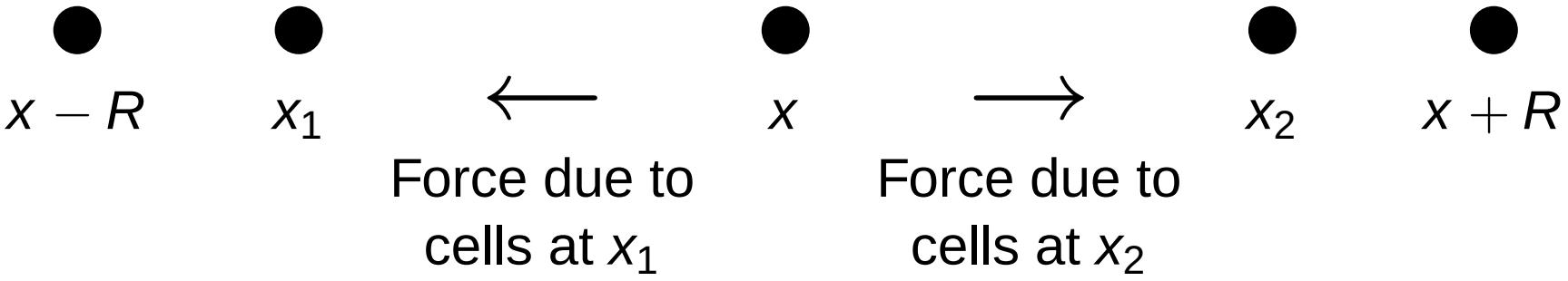
- Total force = sum of all forces acting on cells at x

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

Model Details: The Sensing Radius, R



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



$\omega(x_0)$ is an odd function. For simplicity we usually 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 $g(n)$; we take $g(n) = n(n_{max} - n)$. Here n_{max} corresponds to close-packed cells.

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

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

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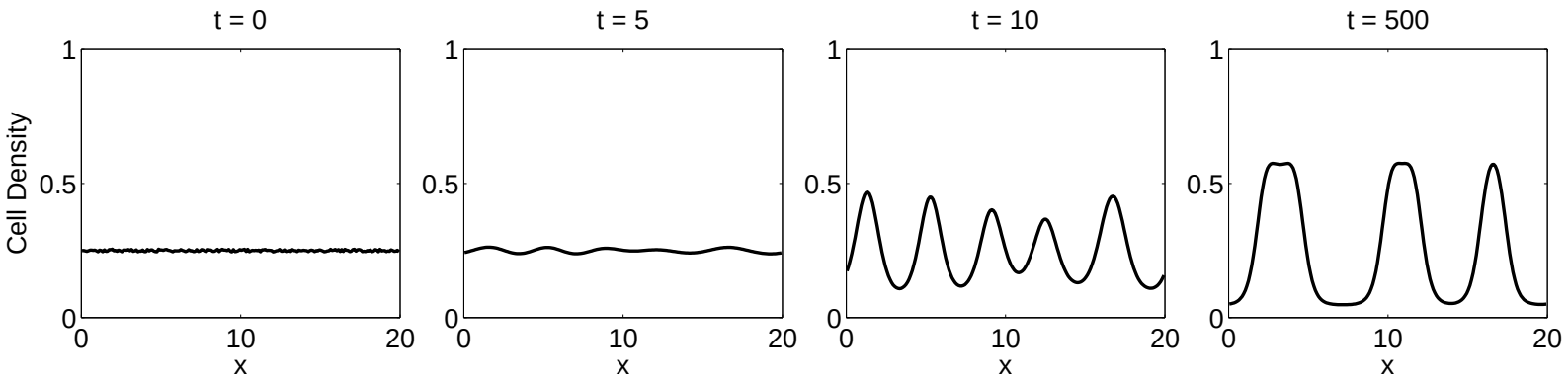
- The parameter α reflects the strength of adhesion; we expect aggregation of disassociated cells when α is large.
- Substitute $n(x,t) = n_0 + \epsilon \exp\{ikx + \lambda t\} \Rightarrow$ $\lambda(k) = -k^2 + 2\alpha n_0(1-n_0)(1-\cos k)$
- This implies instability when $\alpha > \alpha_{crit}$

($\alpha_{crit} = 1/\left[n_0(1-n_0)\cos^2\theta\right]$, with θ the smallest +ve root of $\theta = \tan\theta$)

A Numerical Simulation of Aggregation



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

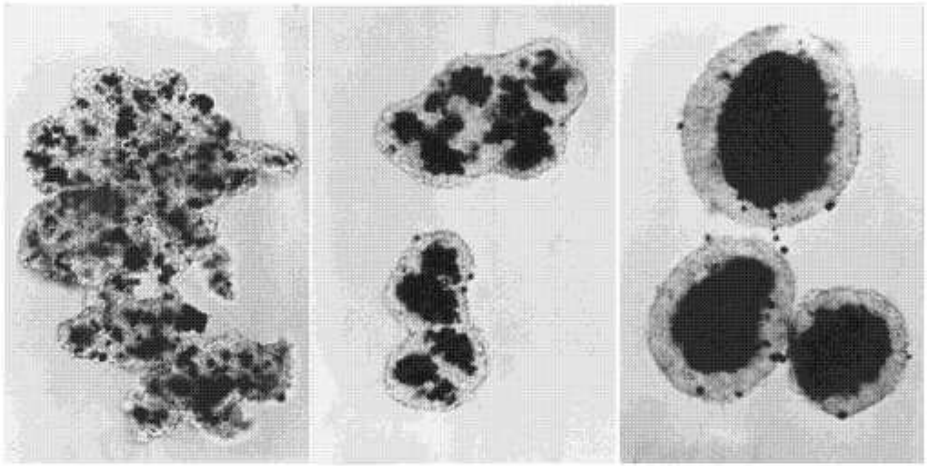
Extending the Model to Interacting Cell Populations II

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

$$\begin{aligned} K_n &= S_n \int_{-1}^{+1} g_{nn}\left(n(x+x_0,t), m(x+x_0,t)\right)\omega(x_0)\,dx_0 \\ &+ C \int_{-1}^{+1} g_{nm}\left(n(x+x_0,t), m(x+x_0,t)\right)\omega(x_0)\,dx_0 \\ K_m &= S_m \int_{-1}^{+1} g_{mm}\left(n(x+x_0,t), m(x+x_0,t)\right)\omega(x_0)\,dx_0 \\ &+ C \int_{-1}^{+1} g_{mn}\left(n(x+x_0,t), m(x+x_0,t)\right)\omega(x_0)\,dx_0 \end{aligned}$$

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

Aggregation and Sorting in an *In Vitro* Experiment

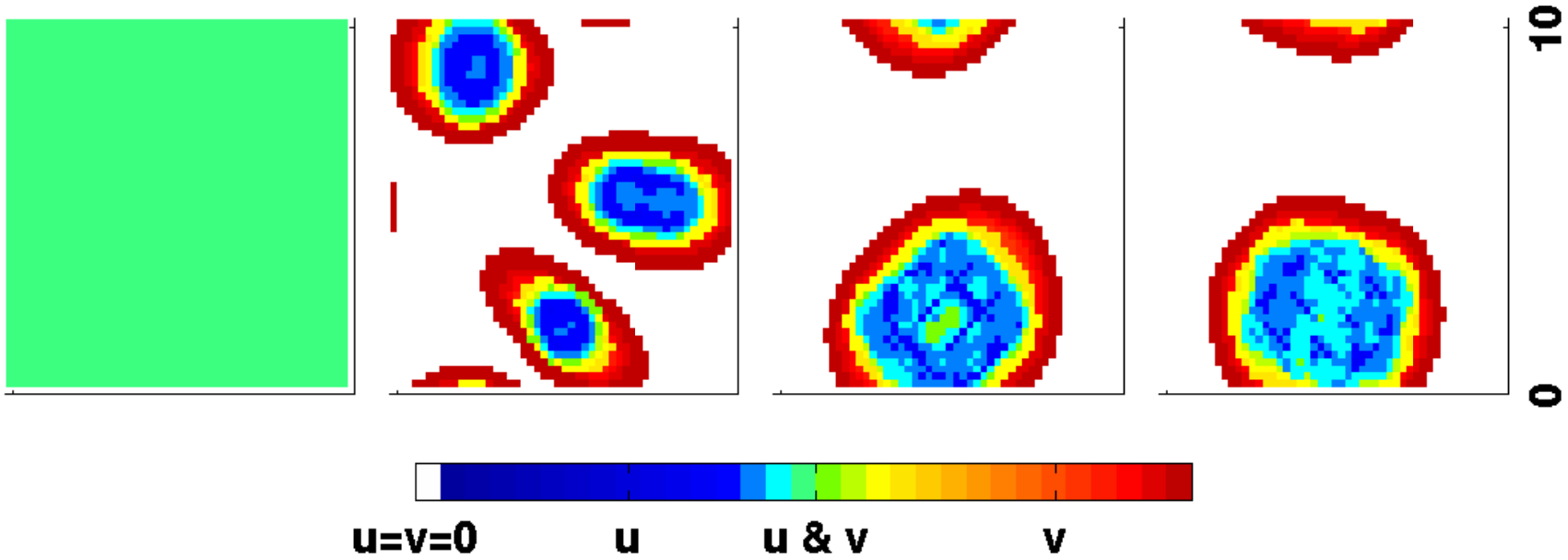


(a) (b) (c)

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

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

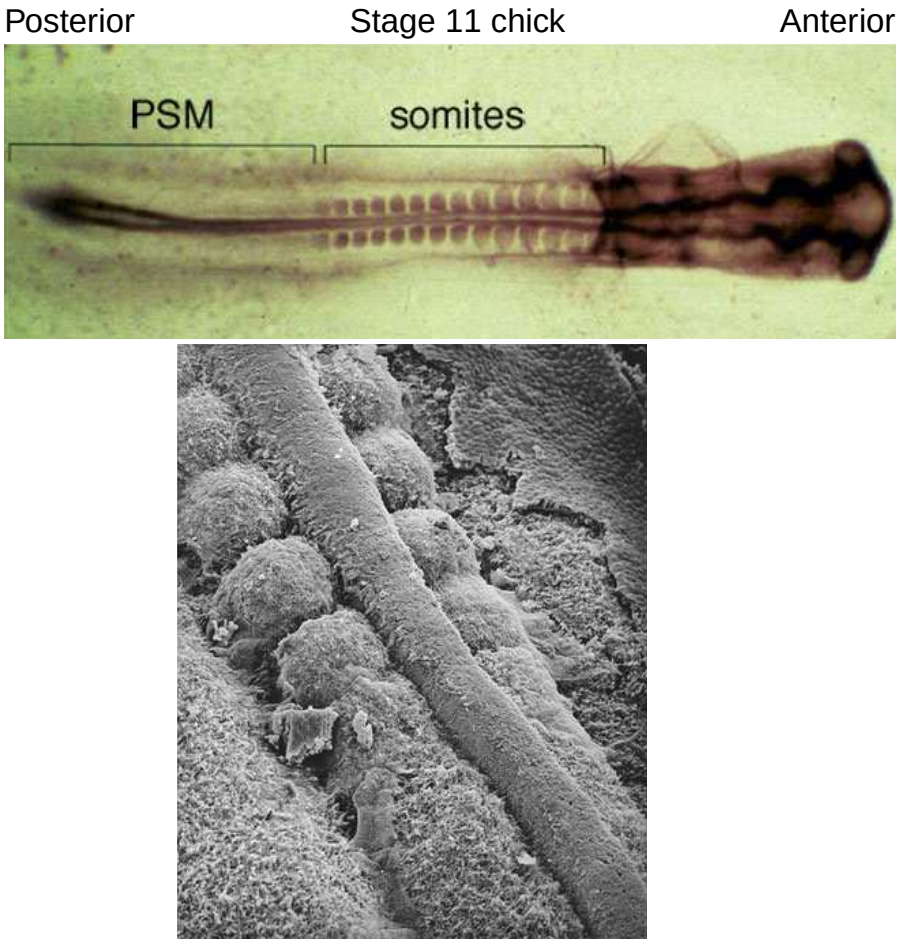
A Numerical Simulation of Aggregation and Sorting



Outline

Introduction to Somite Formation

Somites are an initial stage of segmentation along the head–tail axis of vertebrates.



Introduction to Somite Formation

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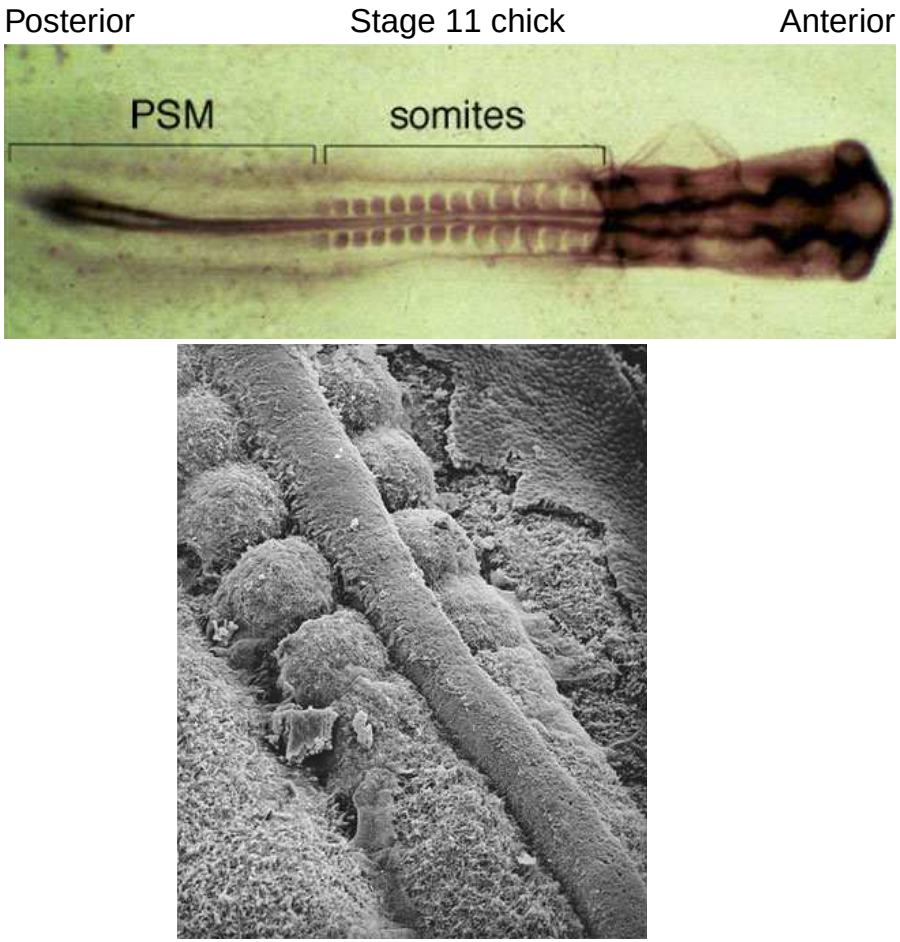
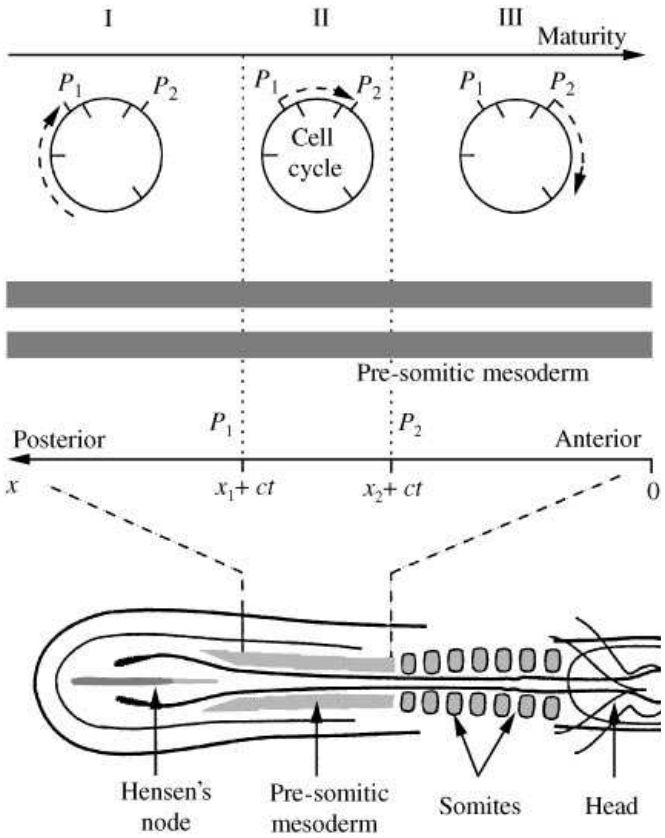
They form in a regular anterior–posterior sequence, via:

1. Pre-pattern forms in PSM
2. Cells coalesce into somites
3. Each somite differentiates into anterior and posterior halves



The Cell Cycle Model of Somite Formation

In 1998, Stern et al (Development 104S:231, 1998) proposed the conceptual "cell cycle model".
The model proposes that when cells reach a point P_2 in the cell cycle, they release a signal. In response to this signal, cells between P_2 and an earlier point P_1 in the cell cycle increase their adhesion and then coalesce into a somite.



Mathematical Formulation of the Cell Cycle Model

Collier et al (J Theor Biol 207:305, 2000) proposed a mathematical formulation of the cell cycle model.

The model variables are:

$v(x,t)$ conc of the signalling molecule

$u(x,t)$ conc of a precursor to a cell adhesion molecule

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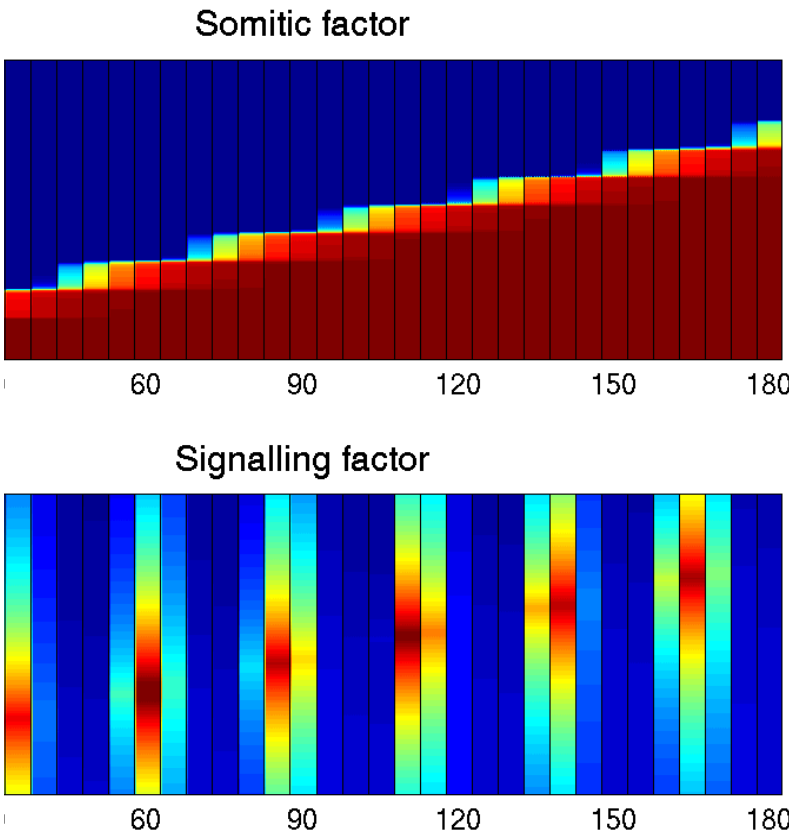
$$\frac{\partial u}{\partial t} = \frac{(u+\mu v)^2}{\kappa_1 + \kappa_2 u^2}\Gamma_u(x,t) - \frac{u}{\kappa_2}$$

$$\frac{\partial v}{\partial t} = \frac{\Gamma_v(x,t)}{\kappa_3 + u} - v + D\frac{\partial^2 v}{\partial x^2}$$

$$\Gamma_u(x,t) = H(ct - x + x_1)$$

$$\Gamma_v(x,t) = H(ct - x + x_2)$$

Typical Solution of the Collier et al Model



Adding Adhesive Cells to the Collier et al Model

We add a third equation, for the cell density $n(x,t)$

$$\frac{\partial n(x,t)}{\partial t} = \frac{\partial}{\partial x}\left[D_n \frac{\partial n(x,t)}{\partial x} + \alpha u(x,t) n(x,t) \cdot \right.$$

$$\left. \int_{-r}^{r} u(x+x_0,t)\, n(x+x_0,t)\, (n_{max} - n(x+x_0,t))\, \omega(x_0)\, dx_0 \right]$$

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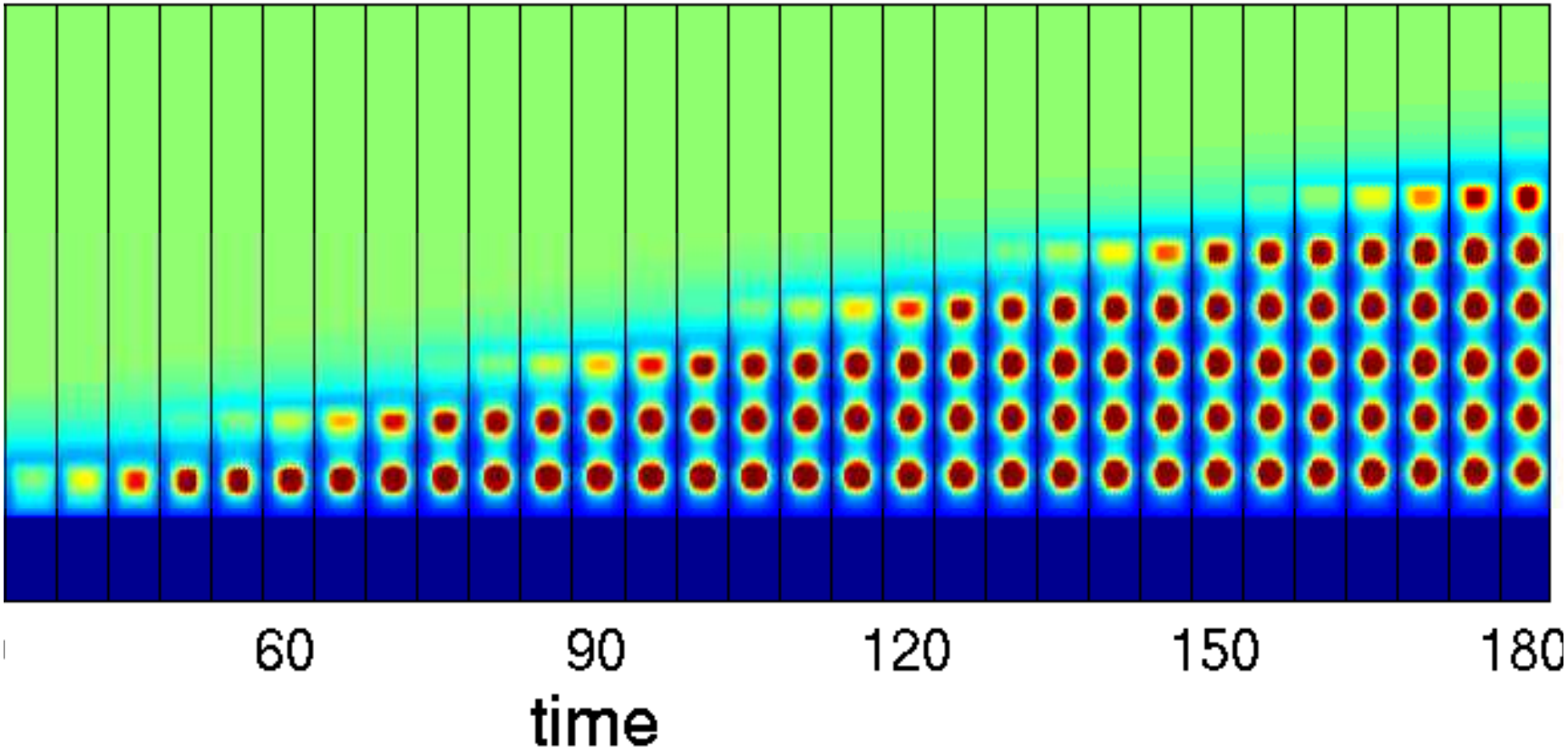
- The parameter α determines the strength of cell-cell adhesion
- Note that there is no feedback from the cell equation to the chemical equations

Simulation of Somite Formation



Further Model Extension:Two Cell Populations

We investigate differentiation of somites into anterior and posterior halves by considering two cell populations $n_1(x,t)$, $n_2(x,t)$.

$$\frac{\partial n_1(x,t)}{\partial t} = D\frac{\partial^2 n_1(x,t)}{\partial x^2} + \frac{\partial}{\partial x}\left[u(x,t)n_1(x,t)\right.$$
$$\left.(\alpha_1 K_1(u,n_1,n_2) + \beta K_2(u,n_1,n_2))\right]$$

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Provided that cross-adhesion is weak ($0 < \beta < \alpha_1, \alpha_2$), the model does predict anterior/posterior differentiation.

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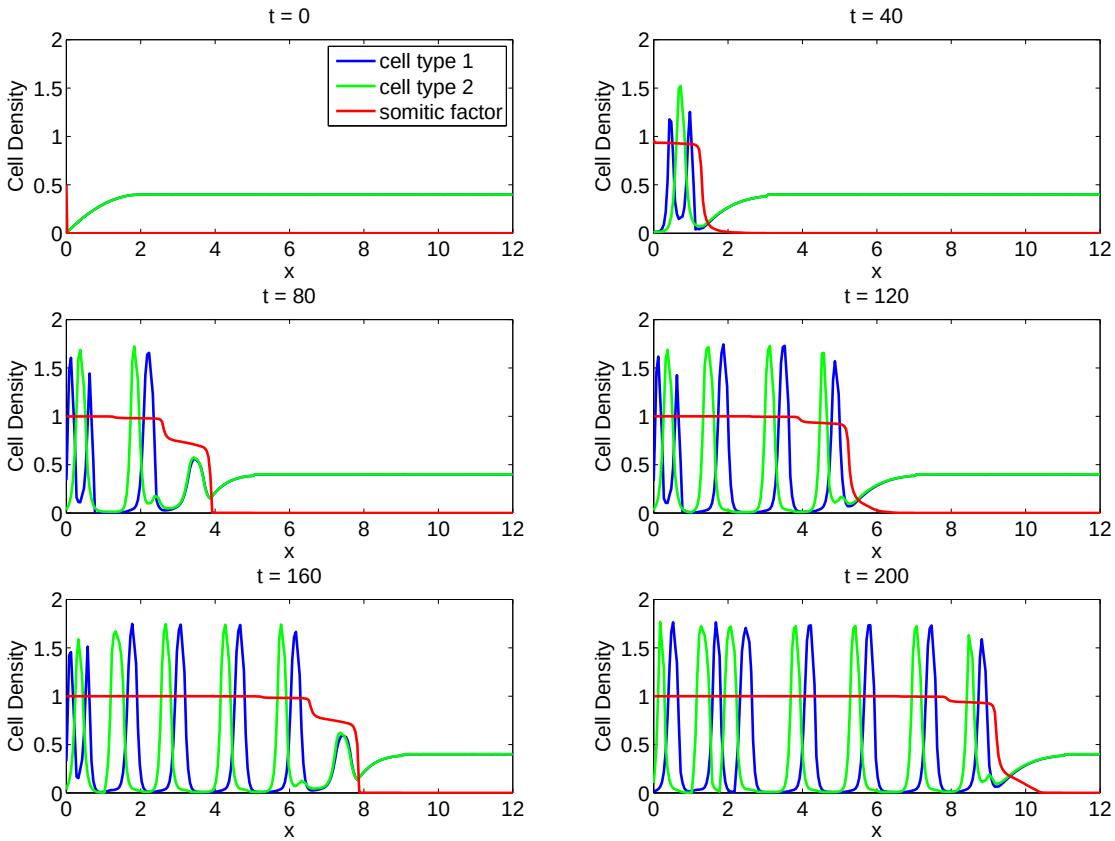


Overview of Somite Application

Conceptual cell cycle model (Stern et al)

↓

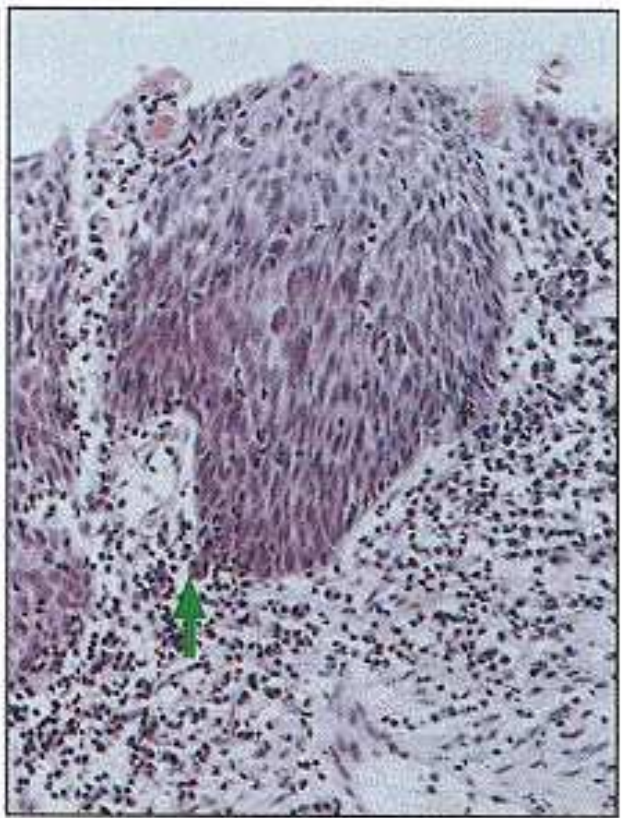
Mathematical cell cycle model (Collier et al)

↓

Our extended mathematical model $\longrightarrow$ Predictions on the values of α, c and N

Outline

Introduction to Cancer Invasion



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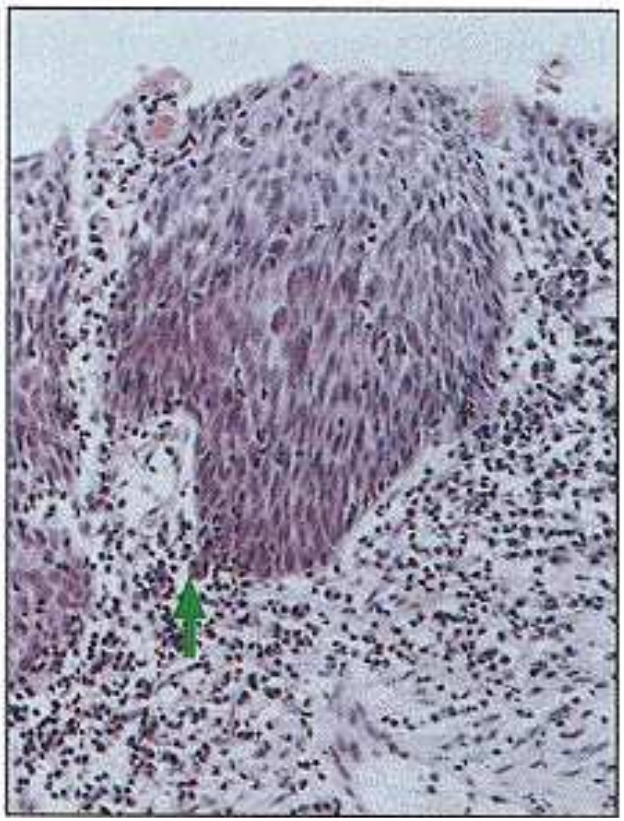

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- adhesion: decreased cell-cell adhesion and increased cell-matrix adhesion

Modelling Adhesion in Cancer

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

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

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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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Model Solutions in 1-D: Non-Invasive Tumour

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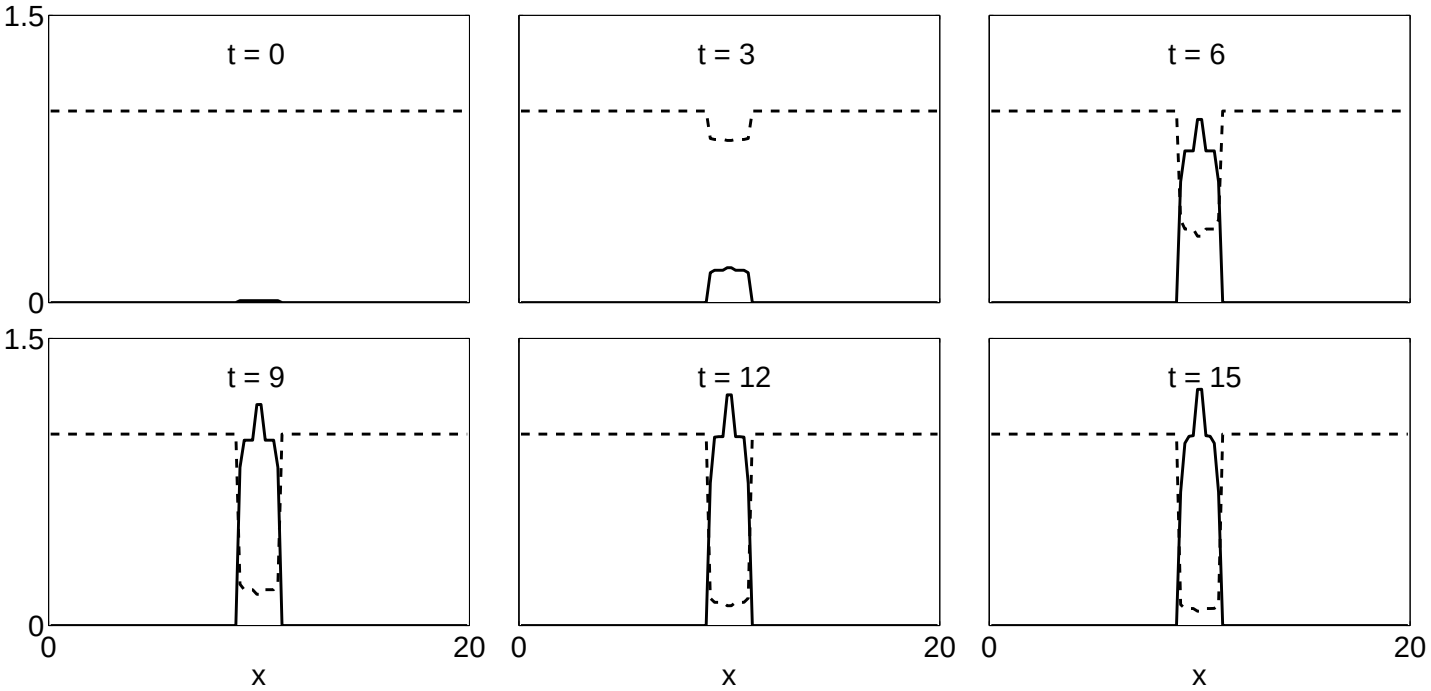

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Starting from the non-invasive tumour ($\alpha = \beta = 1$), invasion can be initiated either by decreasing cell-cell adhesion (α) or by increasing cell-matrix adhesion (β)

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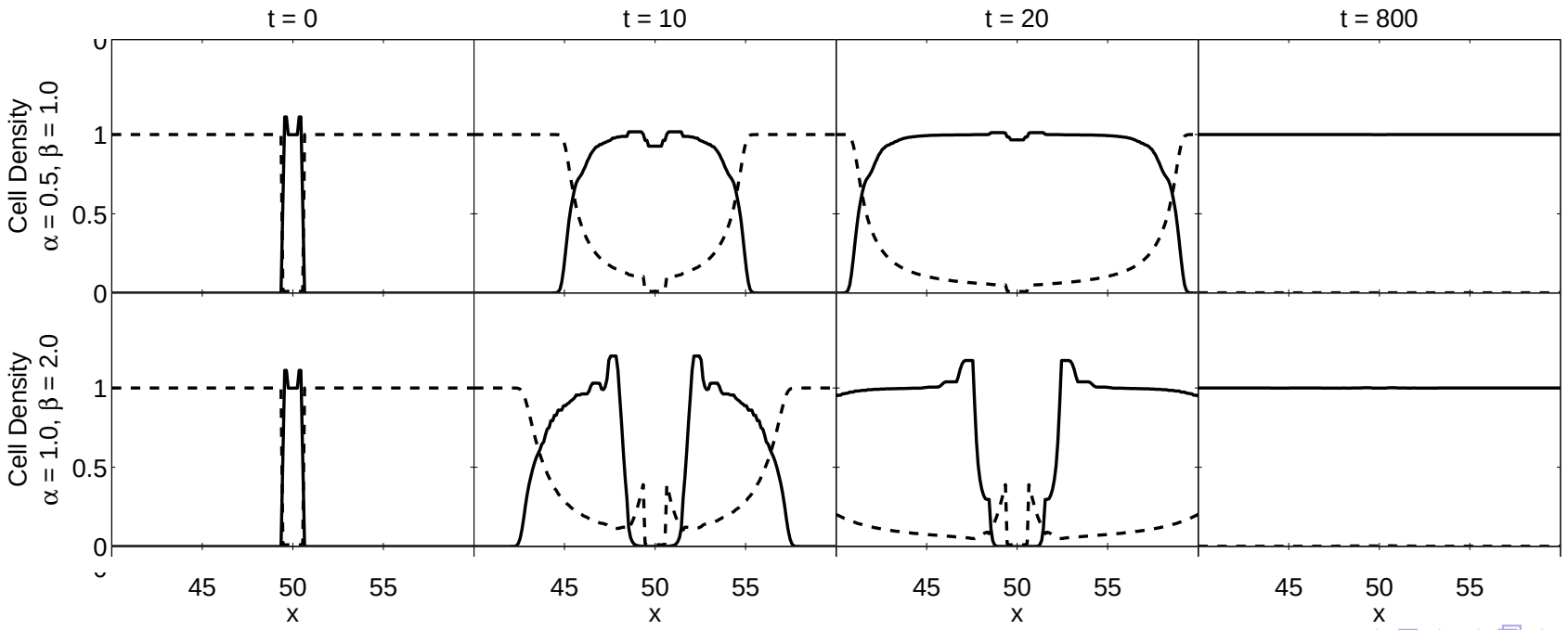

Tumour Morphology and Invasive Potential

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.

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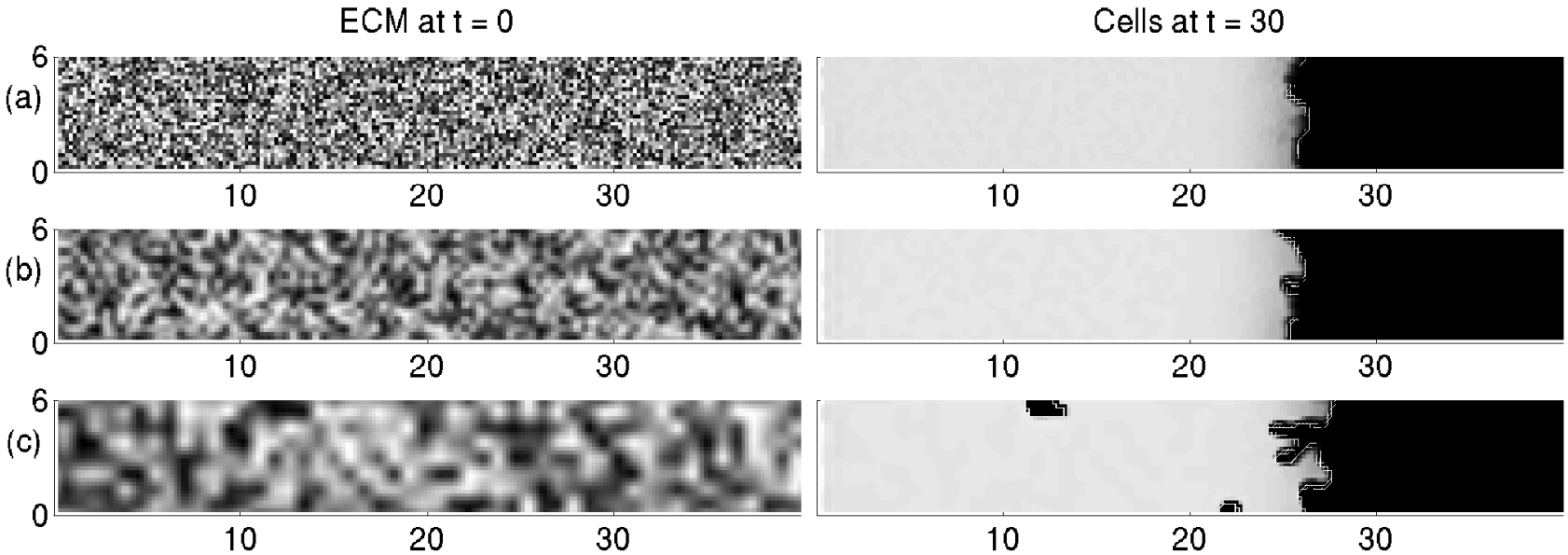

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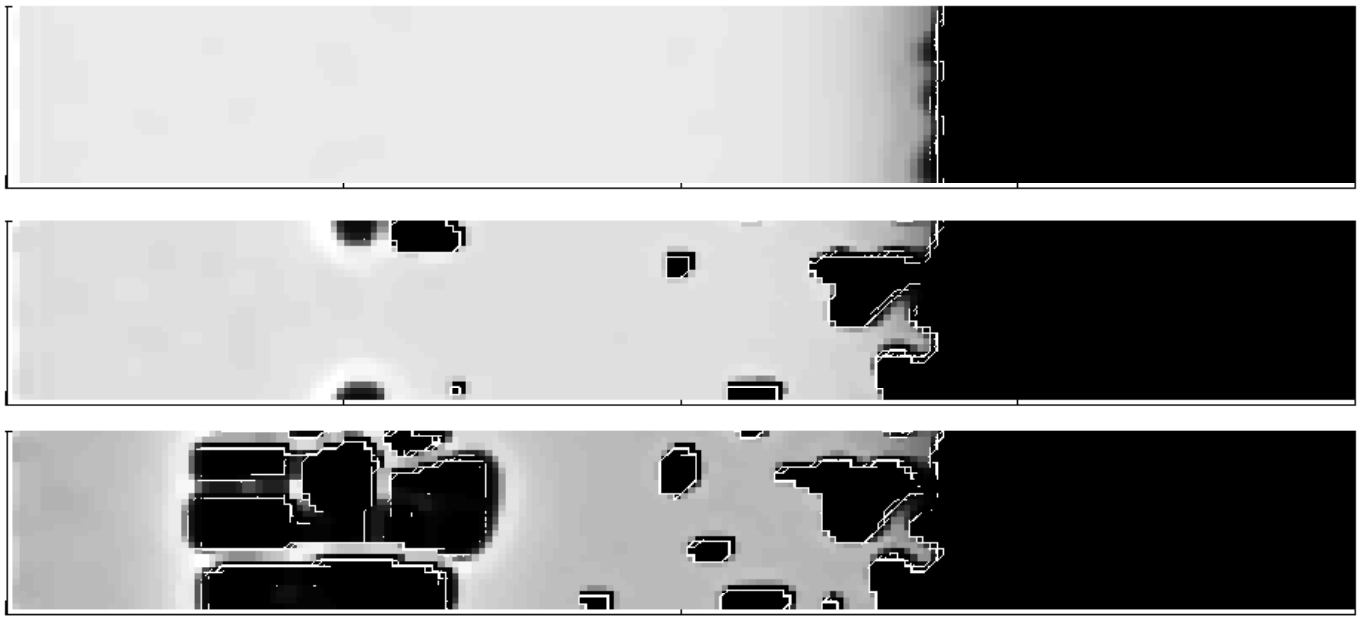

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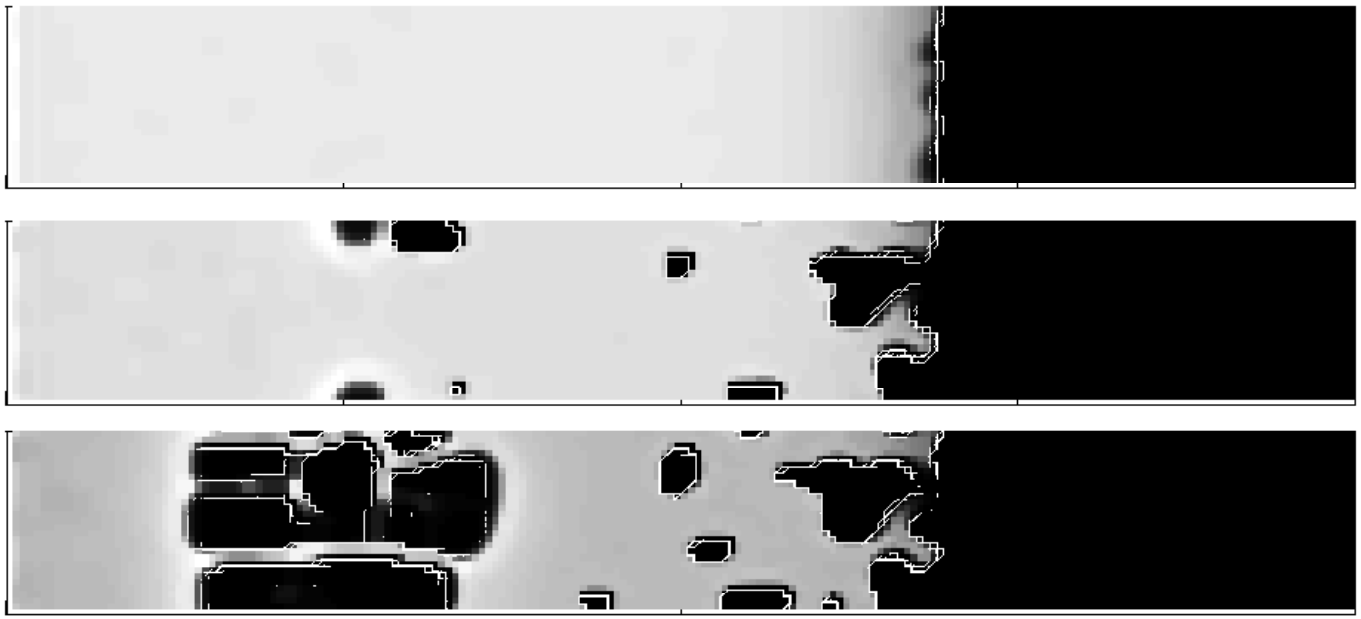
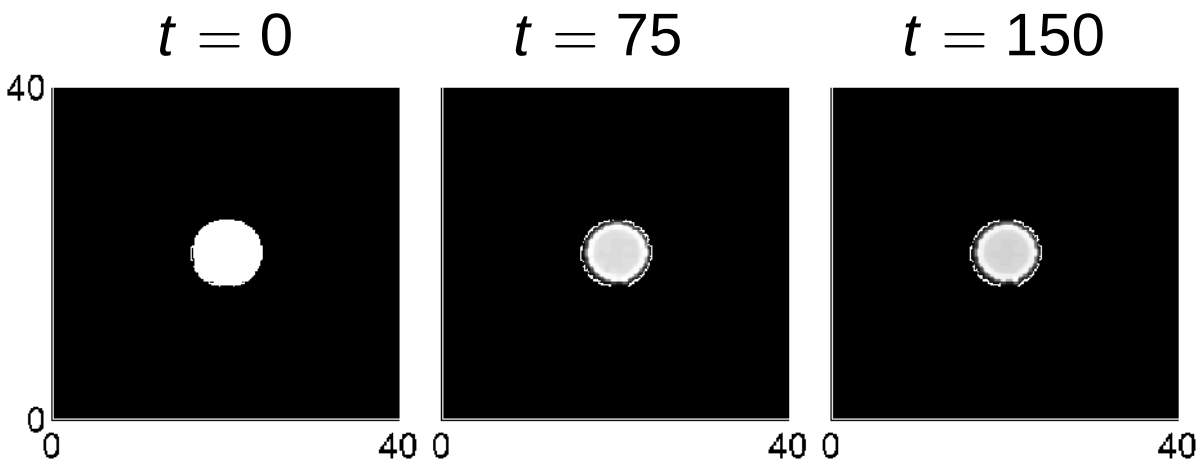


Varying amplitude of noise in initial matrix density

Basic explanation: invasion speed varies with matrix density.

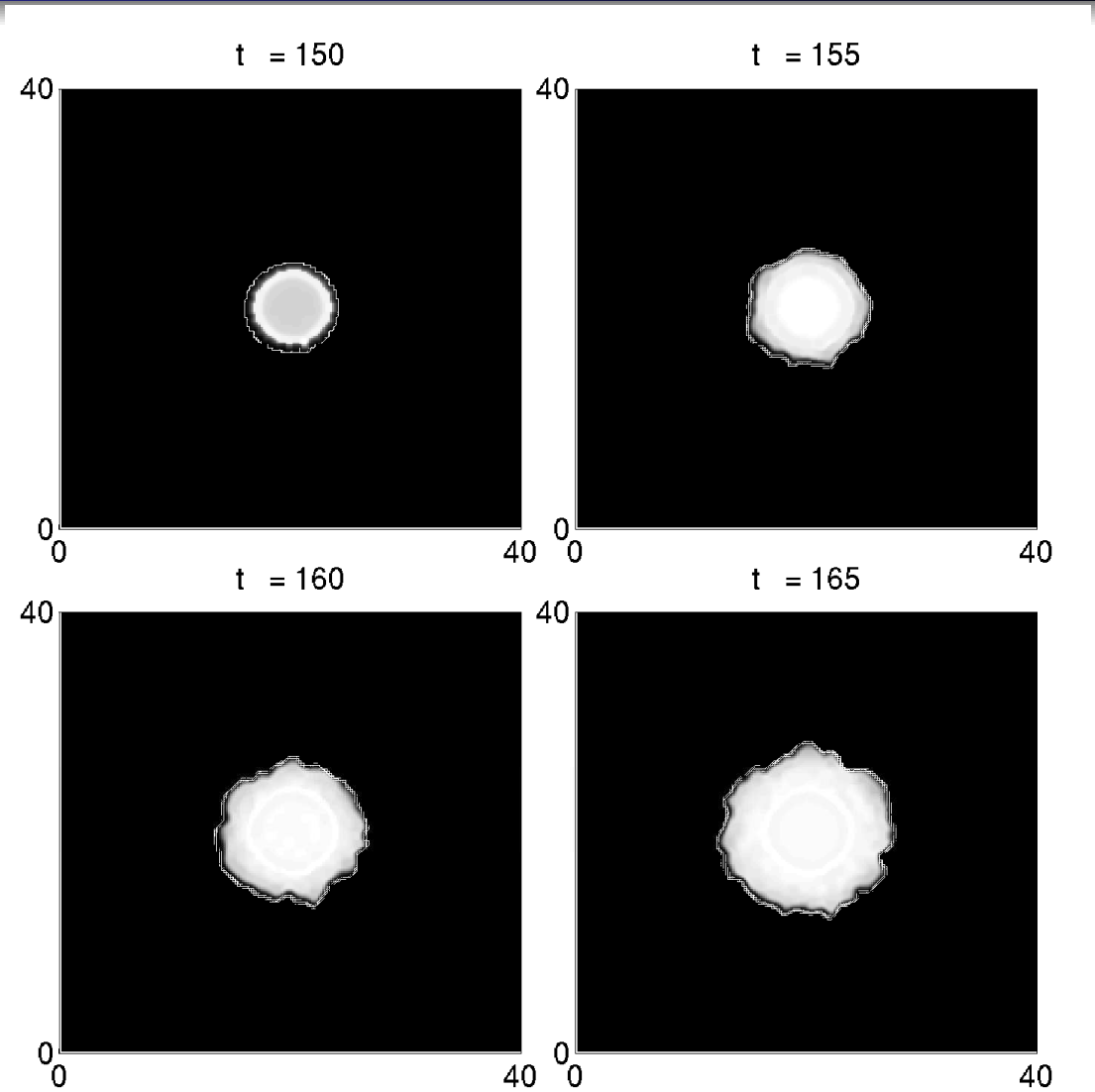
The Sequential Development of an Invasive Tumour

Stage 1:
non-invasive
tumour growth



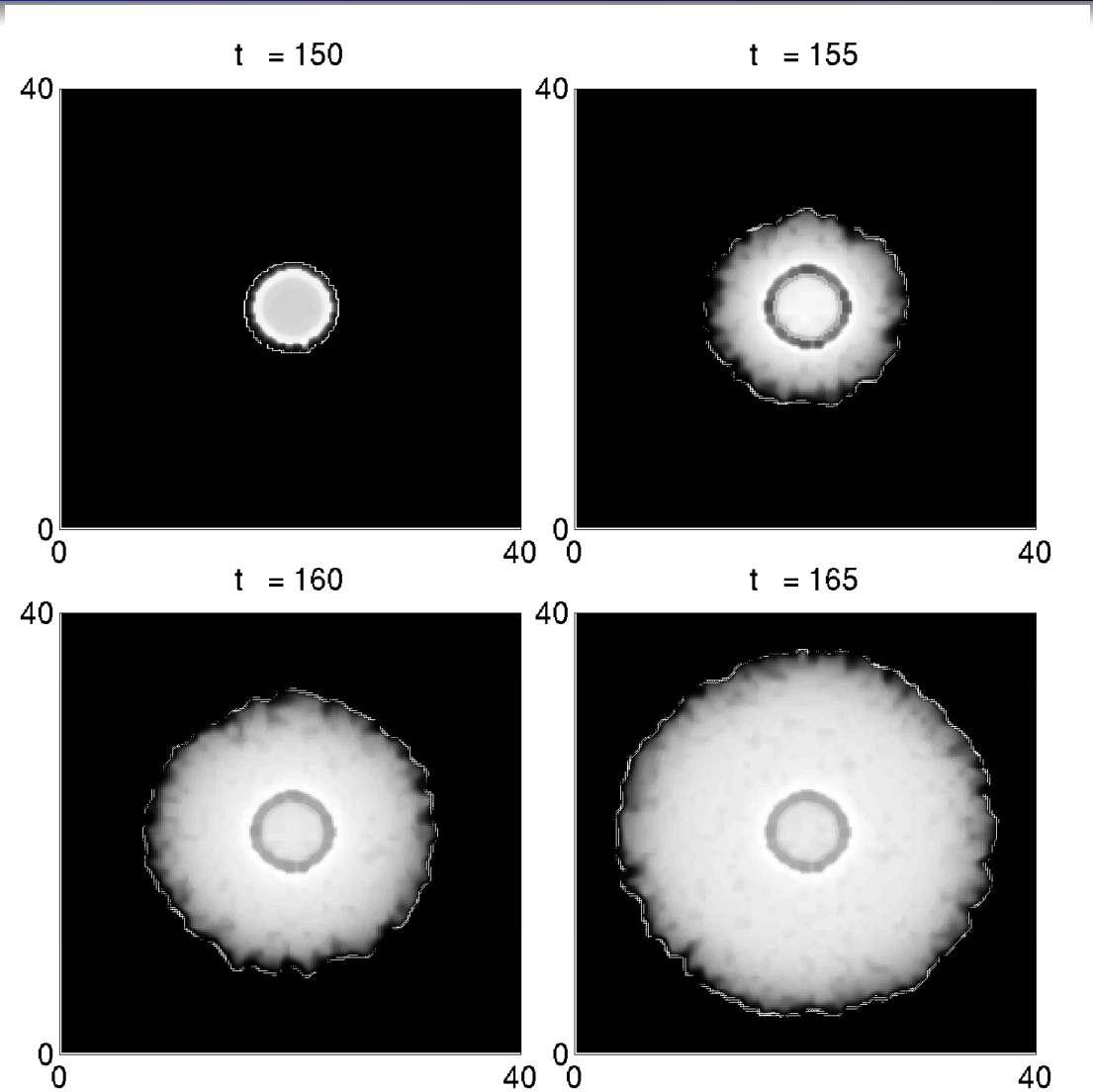
The Sequential Development of an Invasive Tumour

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)



Conclusions and Future Work

Conclusions:

- Our model framework successfully reproduces experimental results on cell aggregation and sorting, predicts somite formation when added to the chemical cell cycle model, and is consistent with traditional thinking on cancer invasion
- The model predicts parameter constraints for the validity of the cell cycle model for somite formation
- The model predicts that tumour fingering depends on noise in the extracellular matrix around the tumour

Conclusions and Future Work

Future Work on Somites Application:

- Addition of feedback from the cells to the chemical
- Addition of cell adhesion to other models of somite pre-patterning (e.g. clock/wavefront model)

Future Work on Cancer Application:

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

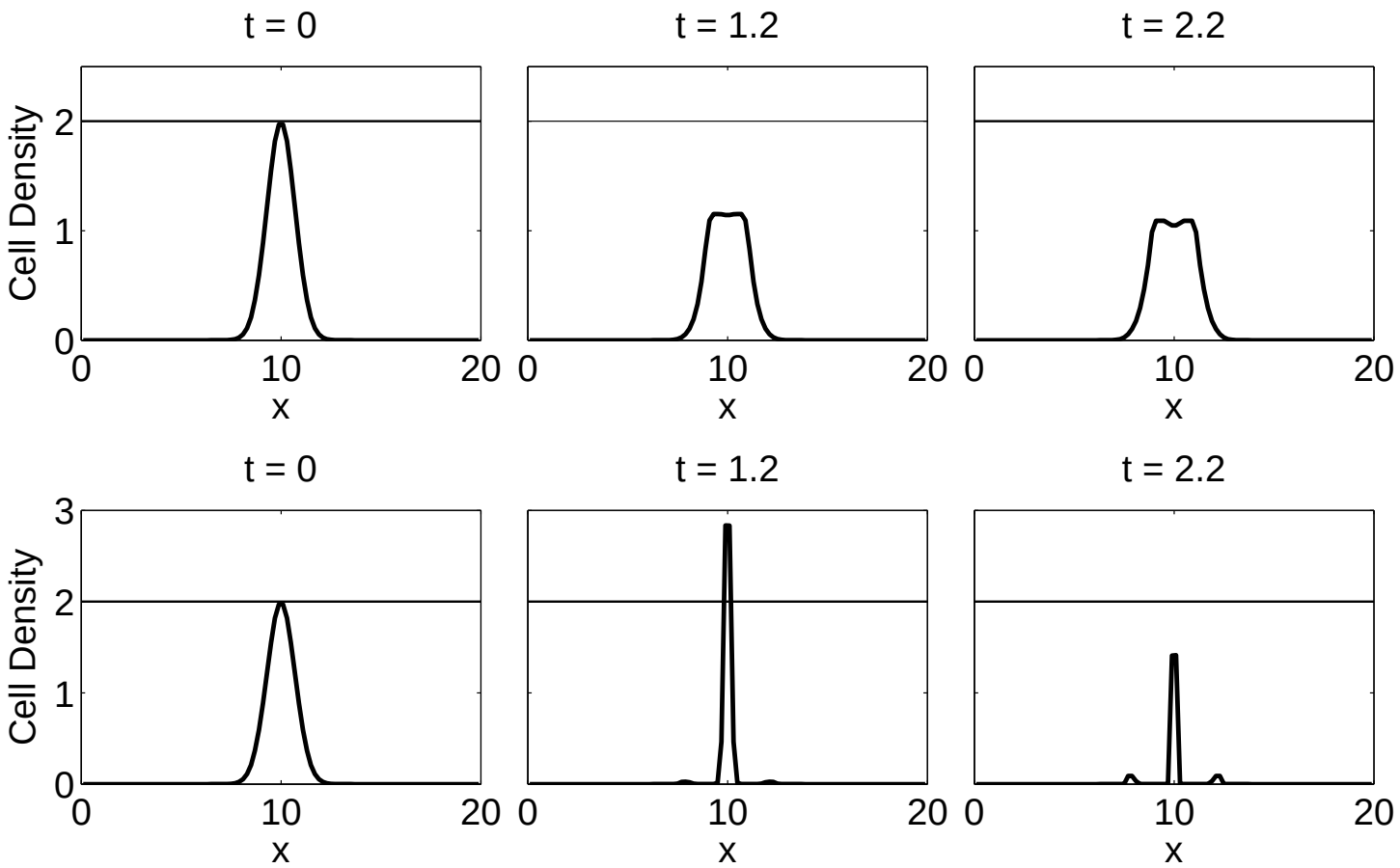
List of Frames

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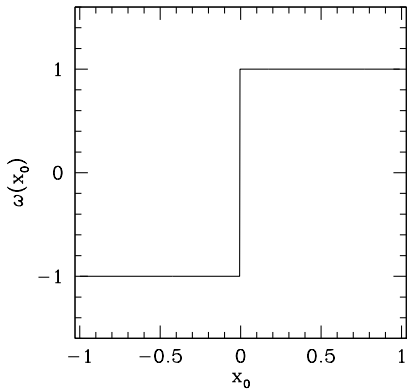
(i) $\omega(x_0) = \text{sign}(x_0)$



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

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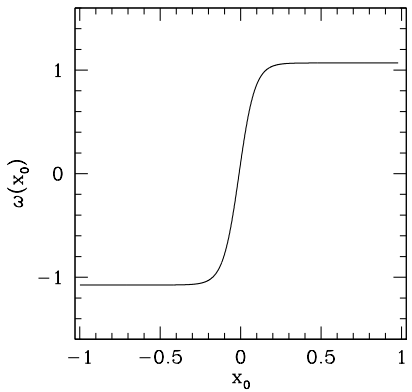
(ii) $\omega(x_0) = \Omega(\lambda x_0)$ with $\Omega(.)$ differentiable and $|\Omega'(.)| \in L^1(\mathbb{R})$, and $\lambda > 0$ sufficiently large.



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

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

$$\text{with } K(x,t) = n(x,t)\int_{-1}^{+1} [\alpha n(x+x_0,t) + \beta m(x+x_0,t)] \cdot g(n(x+x_0,t) + m(x+x_0,t))\,\omega(x_0)\,dx_0$$

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

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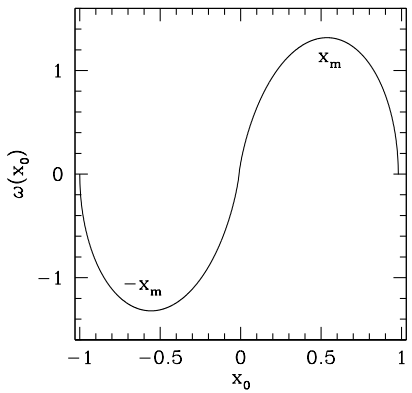

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