Modelling Cell Adhesion in Cancer

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Collaborators

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Outline

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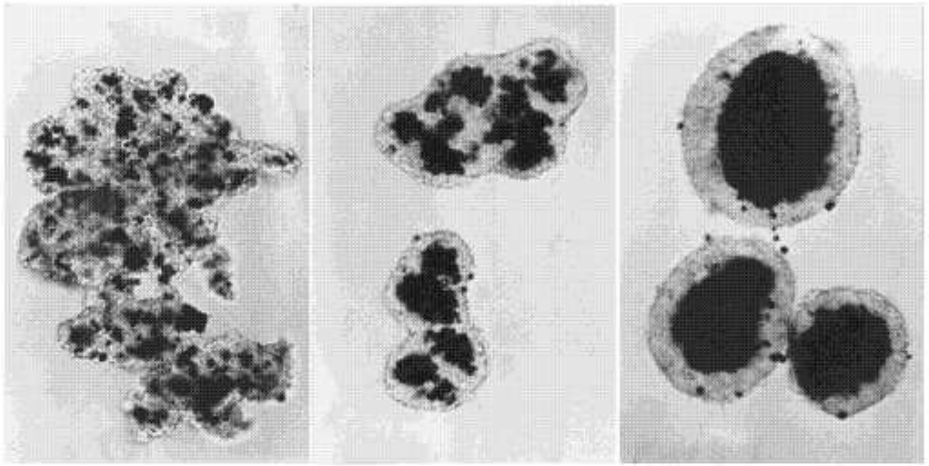
What is Cell-Cell Adhesion?

- 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

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

- We assume no cell birth/death, with movement due to random motion and adhesion

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- Diffusive flux $J_d = -D\partial n/\partial x$
- Adhesive flux $J_a = \phi nF/R$
  $F =$ 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 cells 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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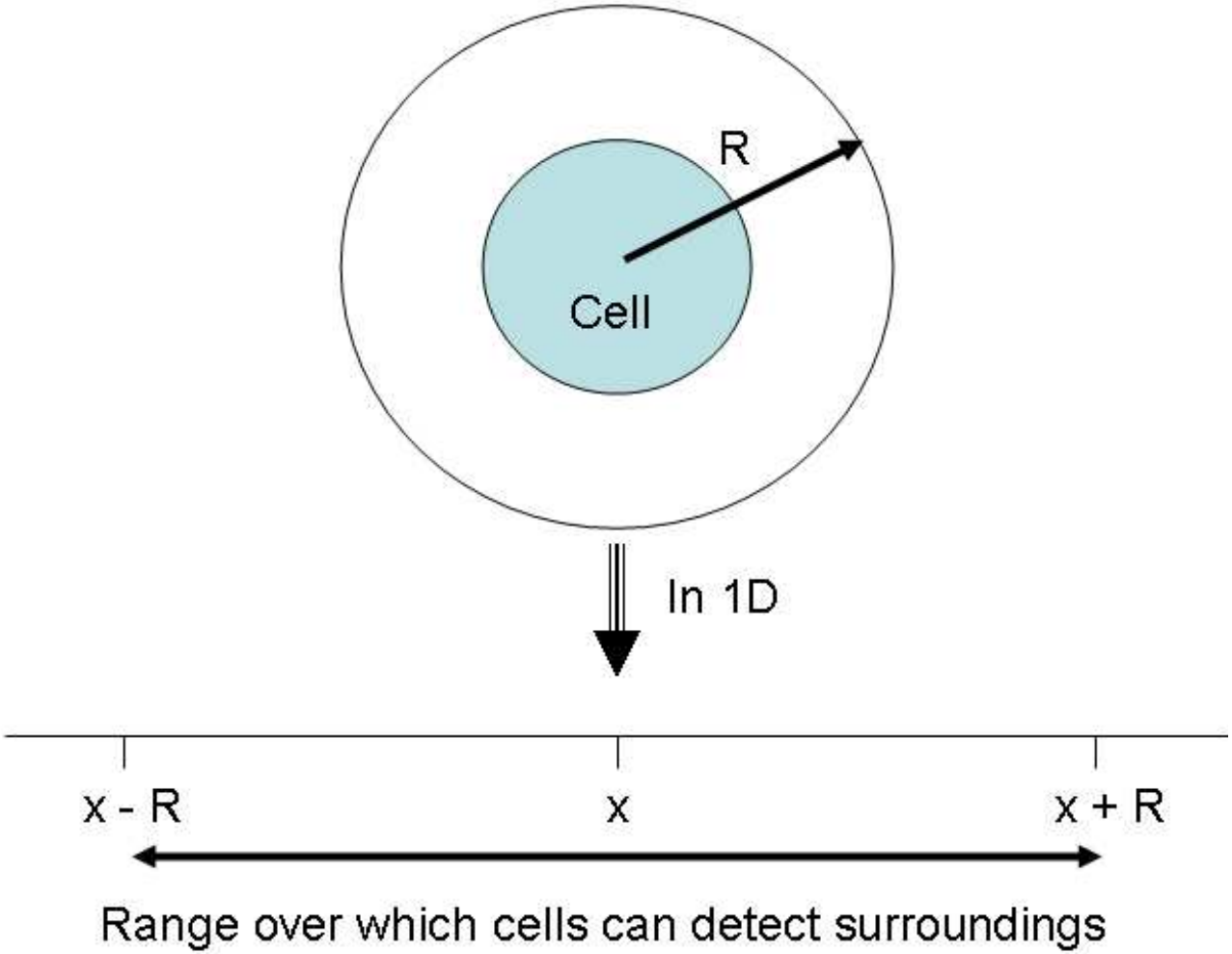
$$f(x, x_0) = \alpha \cdot g\left(n(x + x_0, t)\right) \cdot \omega(x_0)$$

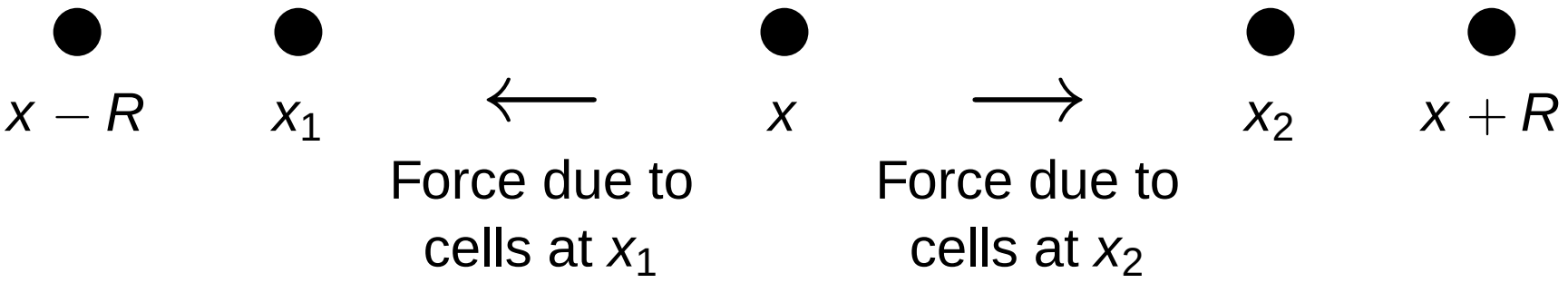
- Total force = sum of all forces acting on cells at x

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

Model Details: The Sensing Radius, R



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



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

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

Mathematical Model for One Cell Population

Nondimensionalising the model gives

$$\frac{\partial n}{\partial t} = \frac{\partial^2 n}{\partial x^2} - \frac{\partial}{\partial x}\left[nK(n)\right]$$

$$\text{where } K(n) = \alpha \int_{-1}^{+1} g(n(x + x_0, t))\omega(x_0)\, dx_0$$

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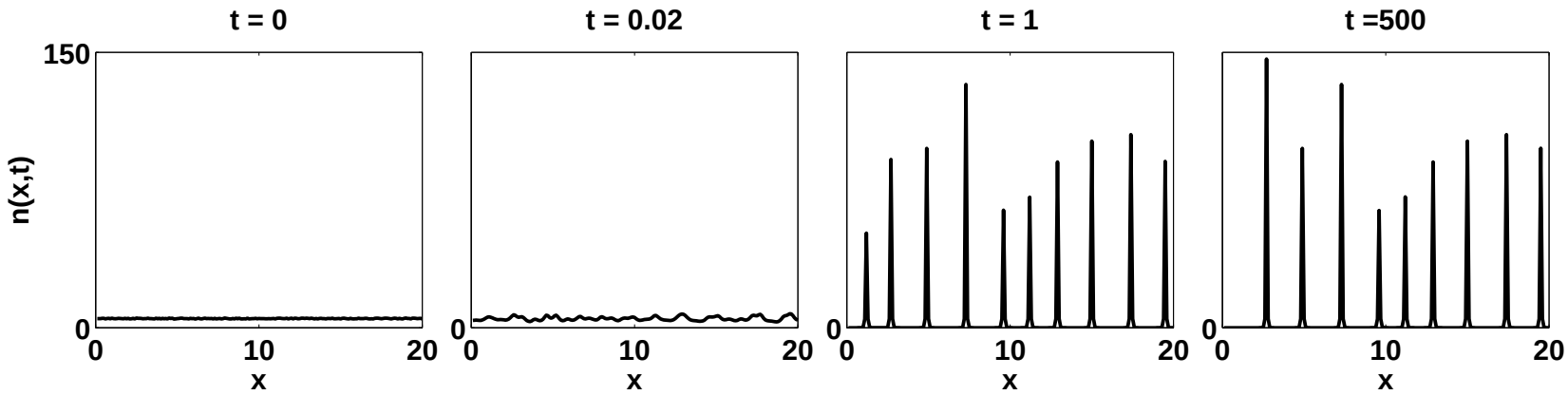
- Initially we assume $g(n) = n$
- We expect aggregation of disassociated cells
- Stability analysis and PDE approximation suggest that such aggregation does occur
- The adhesion parameter α is critical in determining model behaviour

Outline

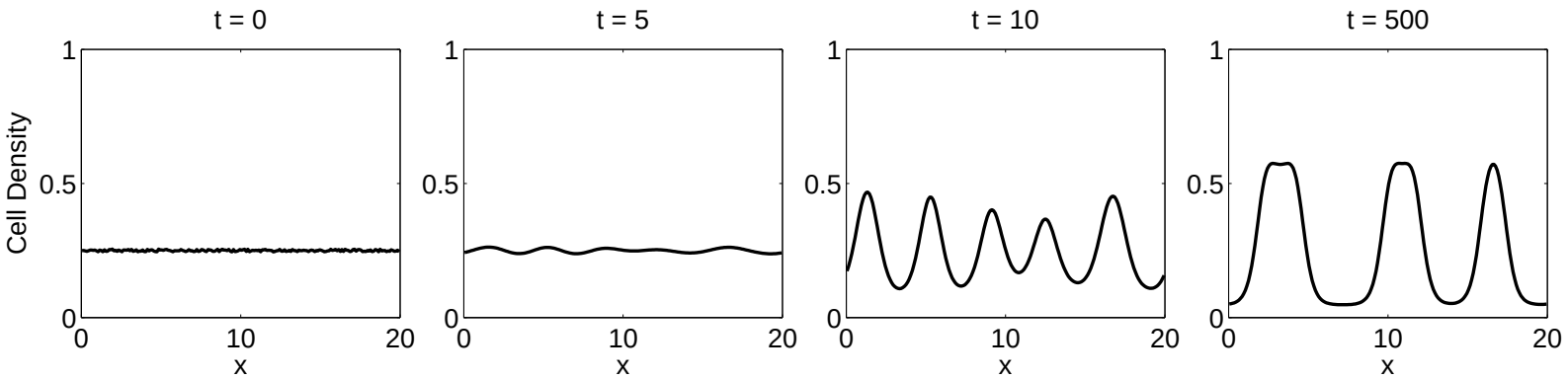
A Numerical Solution of the Basic Model



Model Improvement: Nonlinear $g(n)$

- The solutions of the basic moel 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 $g(n) = n(2n_{max} - n)$.
- We require $g(.)$ to be an increasing function, so that n_{max} corresponds to close-packed cells

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

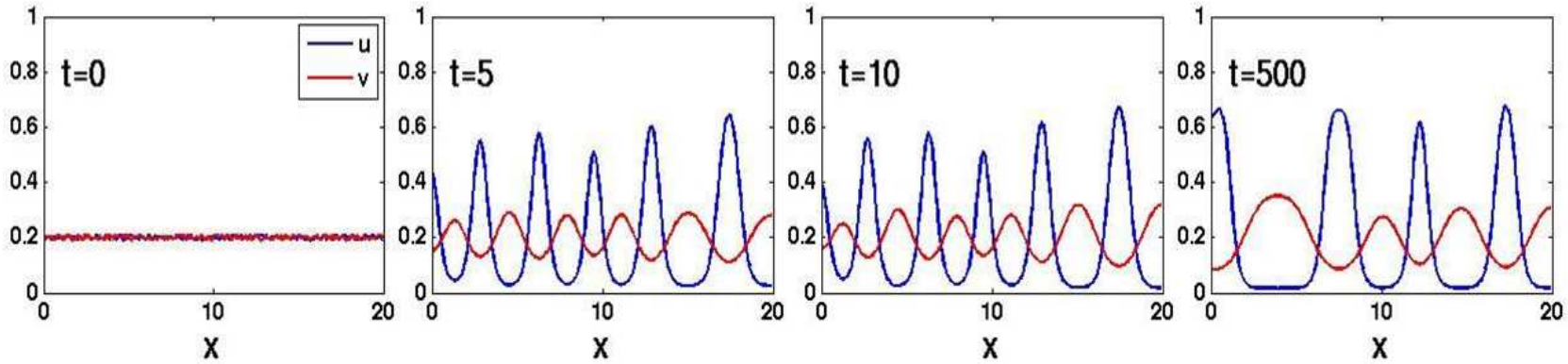
Extending the Model to Interacting Cell Populations II

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

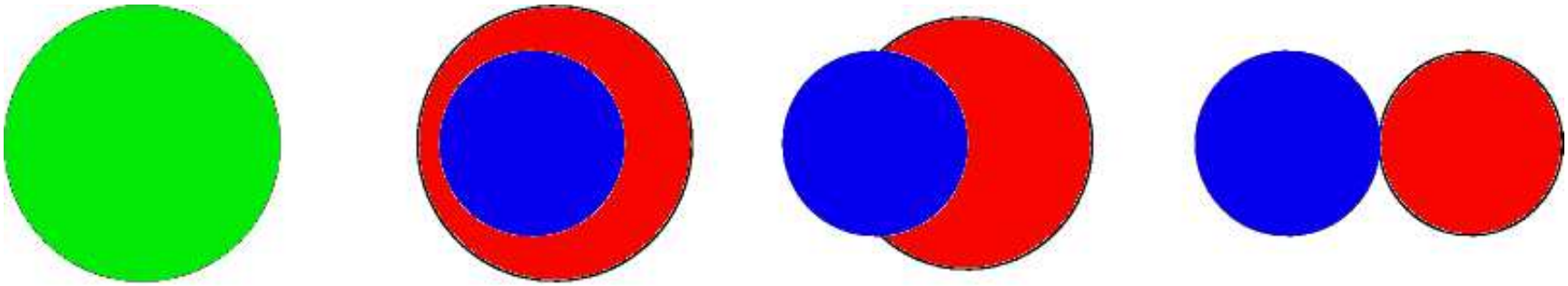
$$\begin{aligned} K_n &= S_n \int_{-1}^{+1} g_{nn}\left(n(x+x_0,t), m(x+x_0,t)\right)\omega(x_0)\,dx_0 \\ &+ C \int_{-1}^{+1} g_{nm}\left(n(x+x_0,t), m(x+x_0,t)\right)\omega(x_0)\,dx_0 \\ K_m &= S_m \int_{-1}^{+1} g_{mm}\left(n(x+x_0,t), m(x+x_0,t)\right)\omega(x_0)\,dx_0 \\ &+ C \int_{-1}^{+1} g_{mn}\left(n(x+x_0,t),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

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

A Numerical Simulation of Cell Sorting in 1-D



Experimental Cell Sorting Results



A	B	C	D
Mixing	Engulfment	Partial engulfment	Complete sorting
$C > (S_n + S_m)/2$	$S_n > C > S_m$	$C < S_n$ and $C < S_m$	$C = 0$

Movie of Cell Sorting in 2-D: Case A

Click here to
play the movie

Movie of Cell Sorting in 2-D: Case B

Click here to
play the movie

Movie of Cell Sorting in 2-D: Case C

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Movie of Cell Sorting in 2-D: Case D

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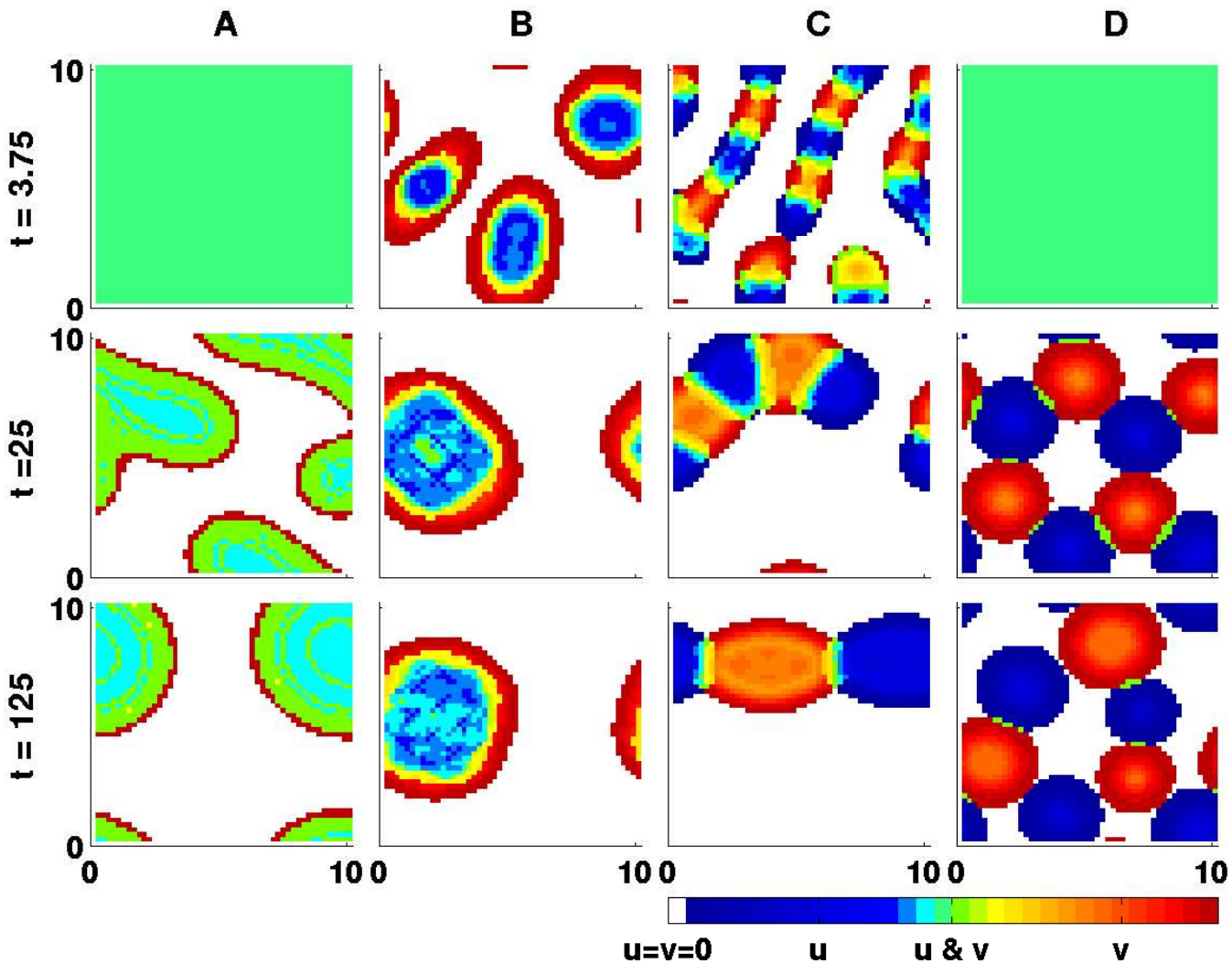
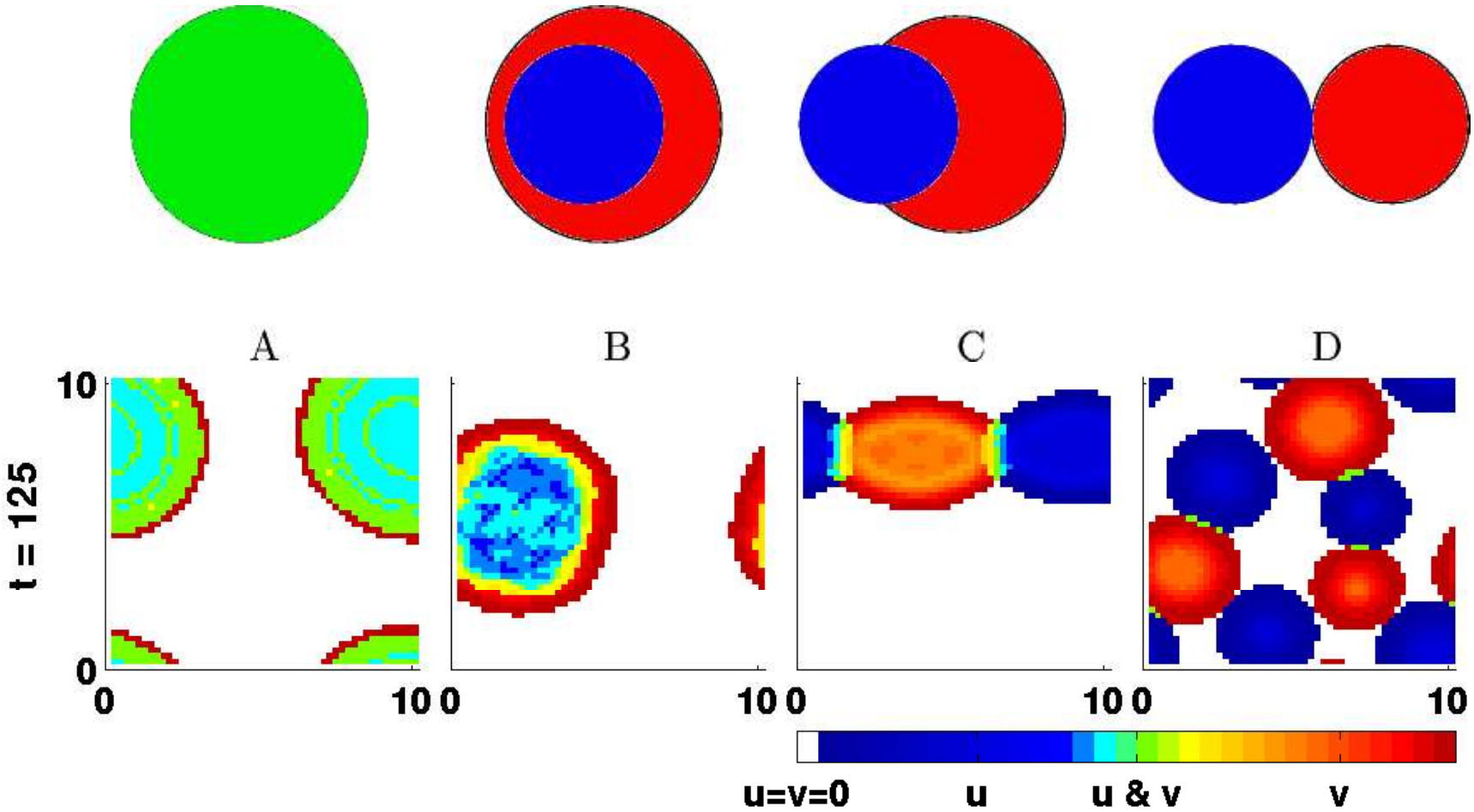
Model Solutions: Cases A–D



Summary of Results on Cell Sorting in 2-D

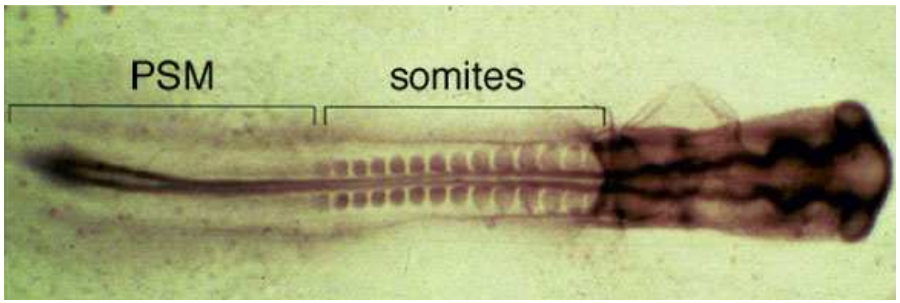


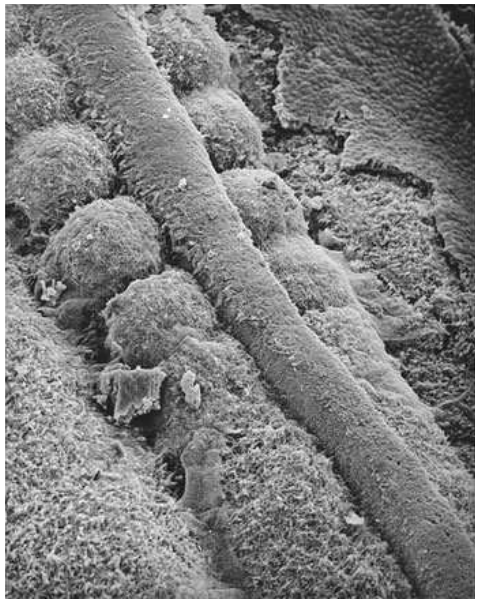
Outline

Introduction to Somite Formation

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

Posterior Stage 11 chick Anterior



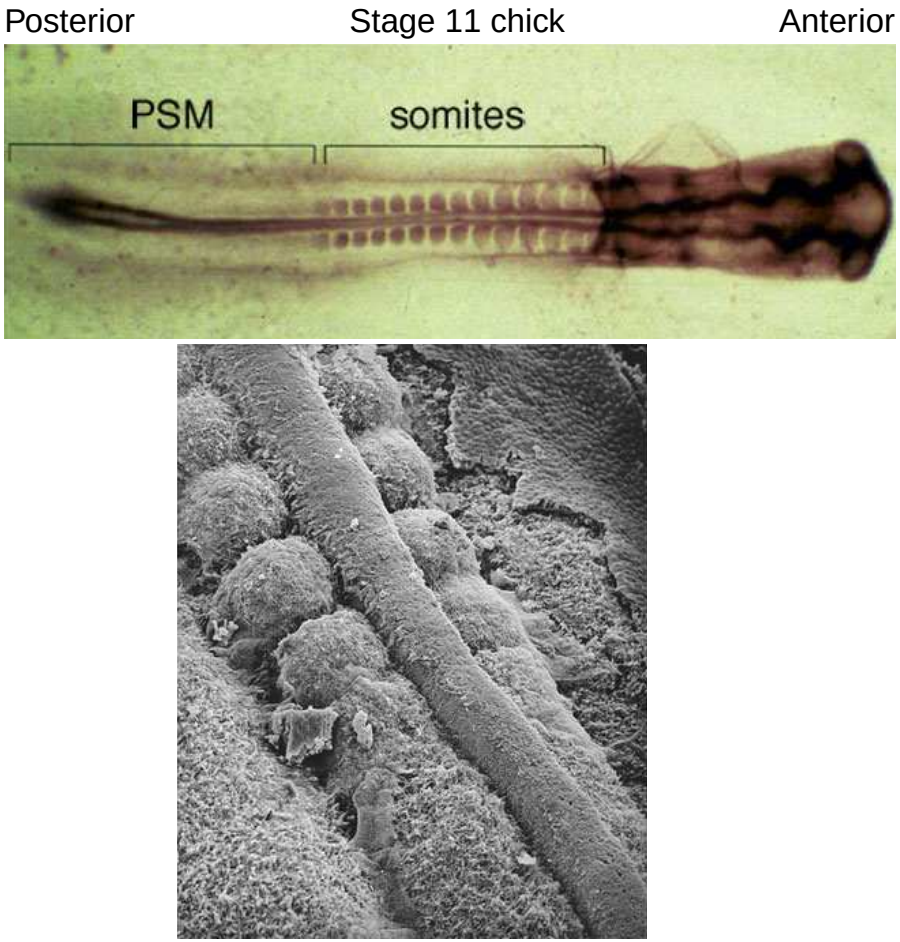


Introduction to Somite Formation

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

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

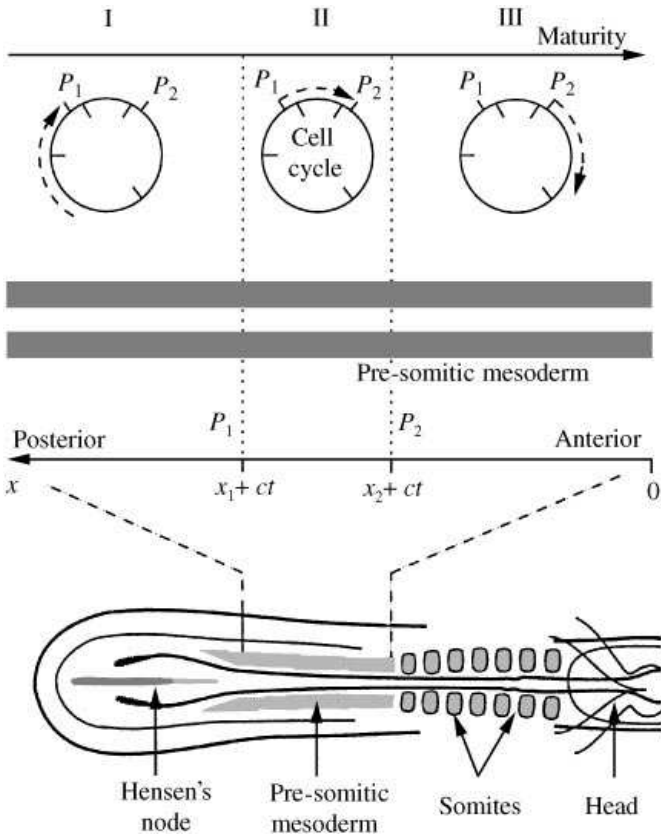
1. Pre-pattern forms in PSM
2. Cells coalesce into somites
3. Each somite differentiates into anterior and posterior halves, and later into dorsal and ventral parts



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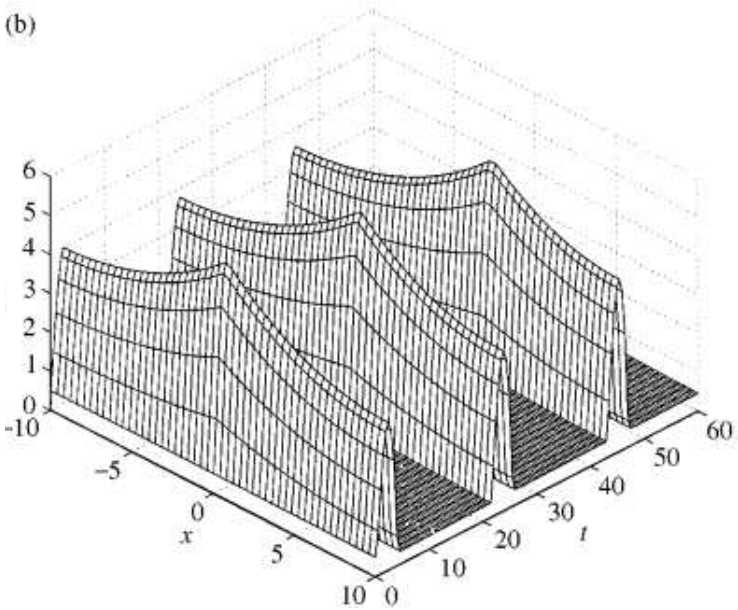
$$\frac{\partial u}{\partial t} = \frac{(u+\mu v)^2}{\gamma + \kappa u^2}\Gamma_u(x,t) - \frac{u}{\kappa}$$

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

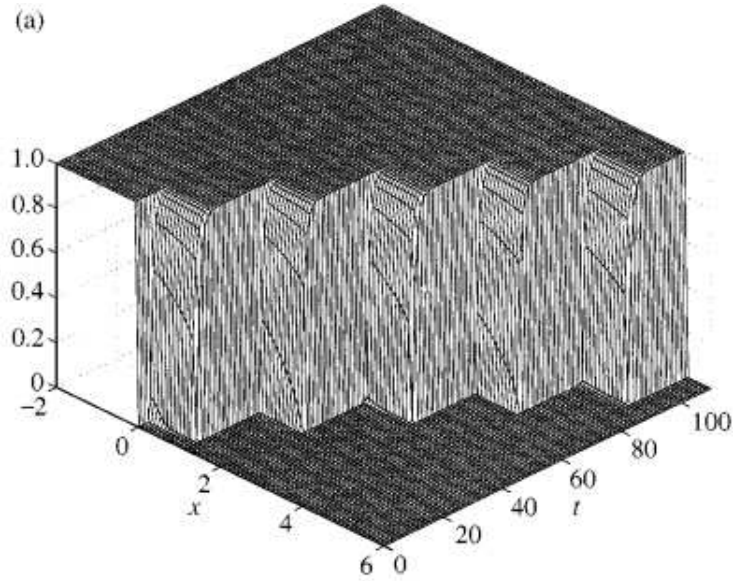
$$\Gamma_u(x,t) = H(ct - x + x_1)$$

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

Typical Solution of the Collier et al Model



Signalling molecule $v(x,t)$



Precursor to adhesion molecule $u(x,t)$

Outline

Adding Adhesive Cells to the Collier et al Model

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

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

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- Cell adhesion depends on the concentration of the adhesion molecule precursor, u
- The parameter α determines the strength of cell-cell adhesion
- Note that there is no feedback from the cell equation to the chemical equations

Parameter Constraints for the Extended Model

The extended model predicts somite formation provided that:

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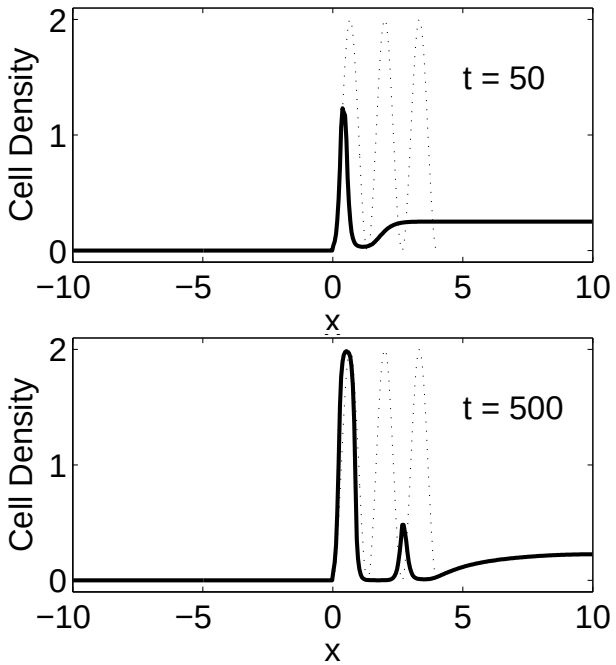

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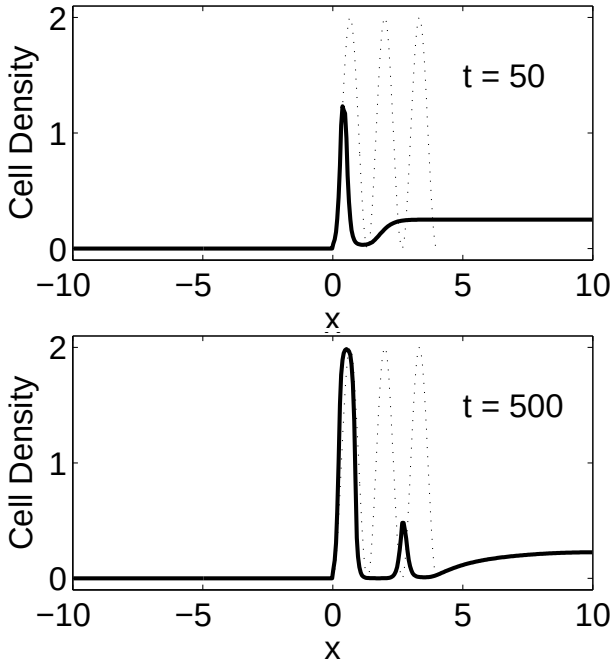

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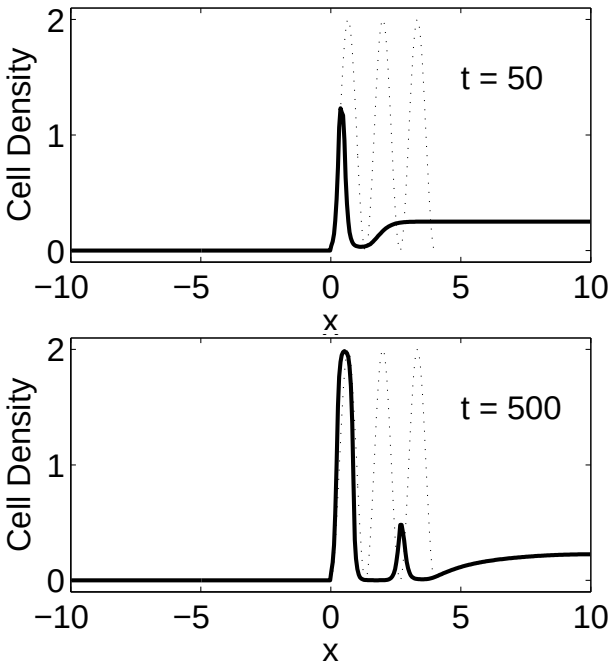
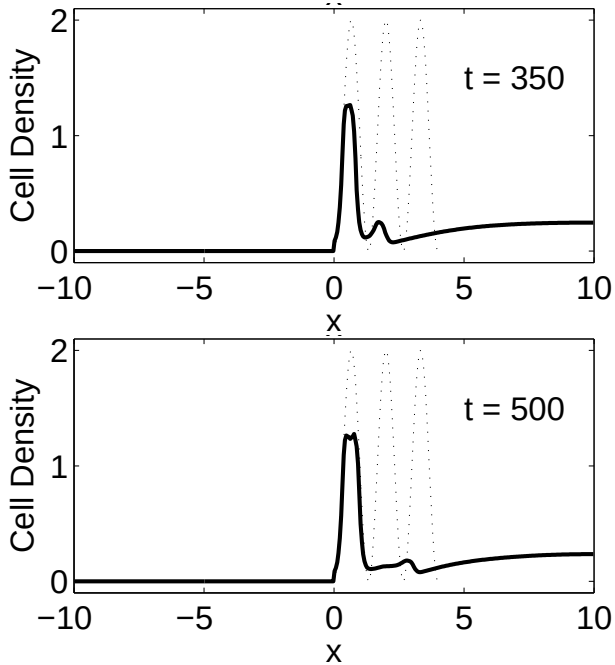


2. The imposed speed c is neither too low nor too high.
c too low $\Rightarrow$ coarsening



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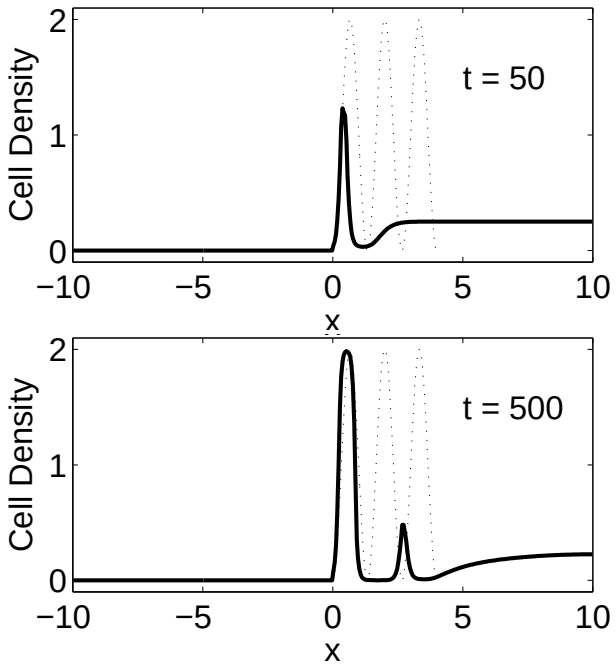

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c too high $\Rightarrow$ somites do not have time to form

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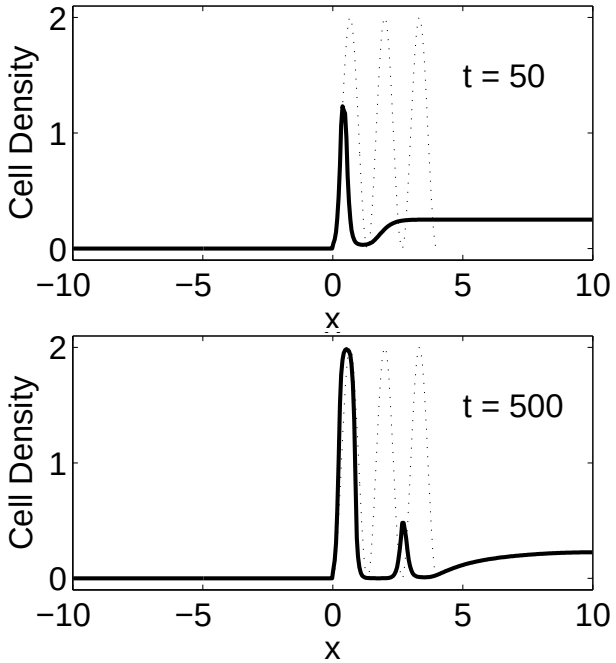

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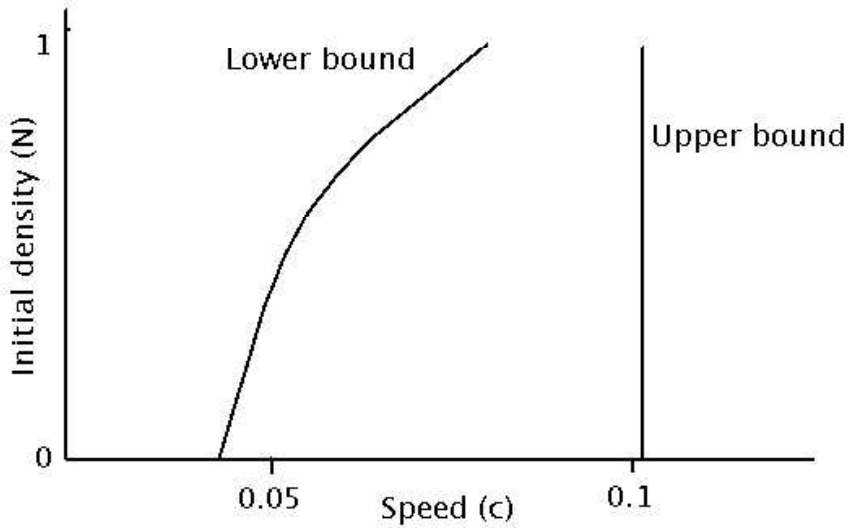
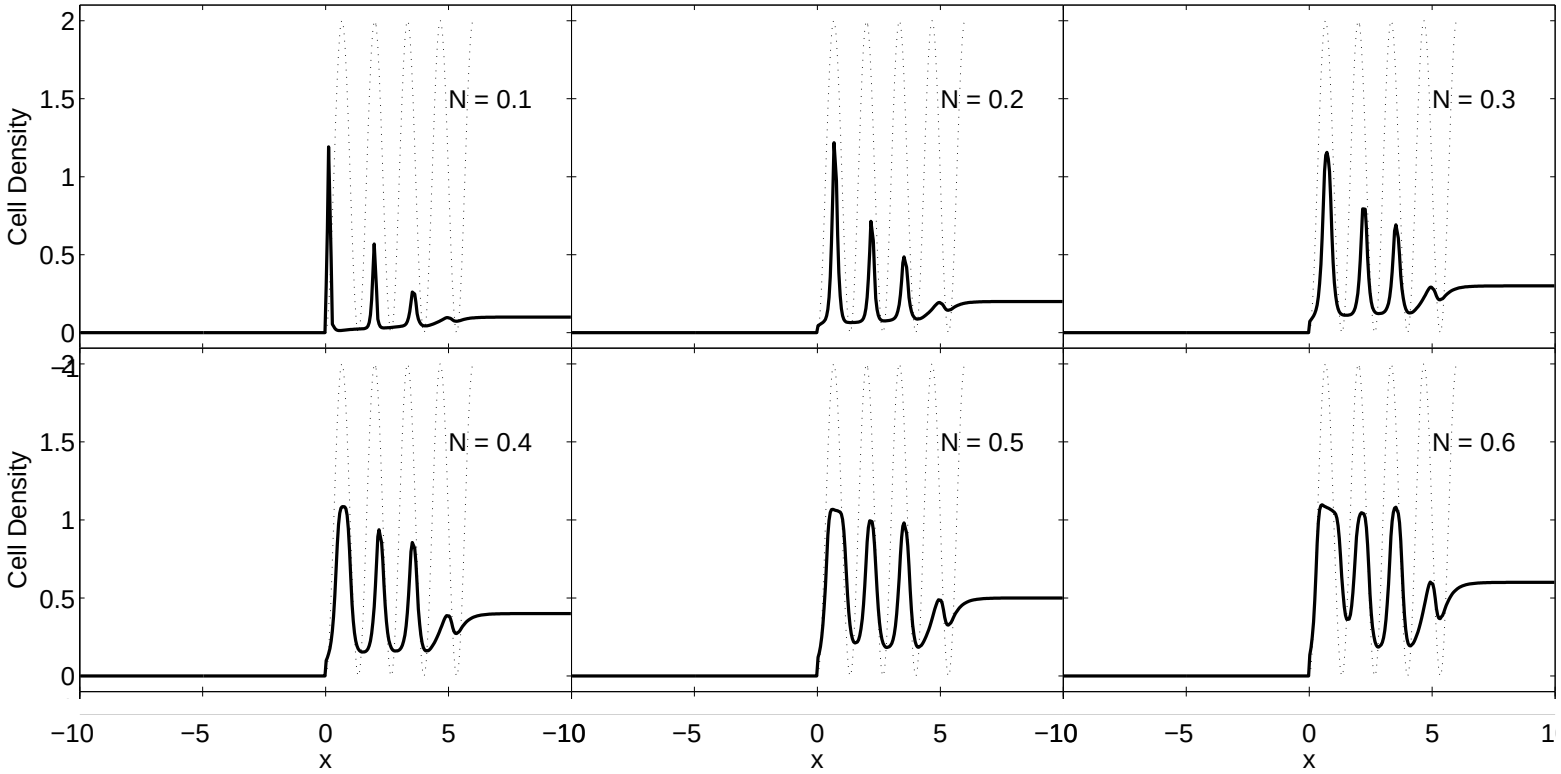


Somite Formation in the Extended Model



Further Model Extension:Two Cell Populations

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

$$\begin{aligned}
\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. \\
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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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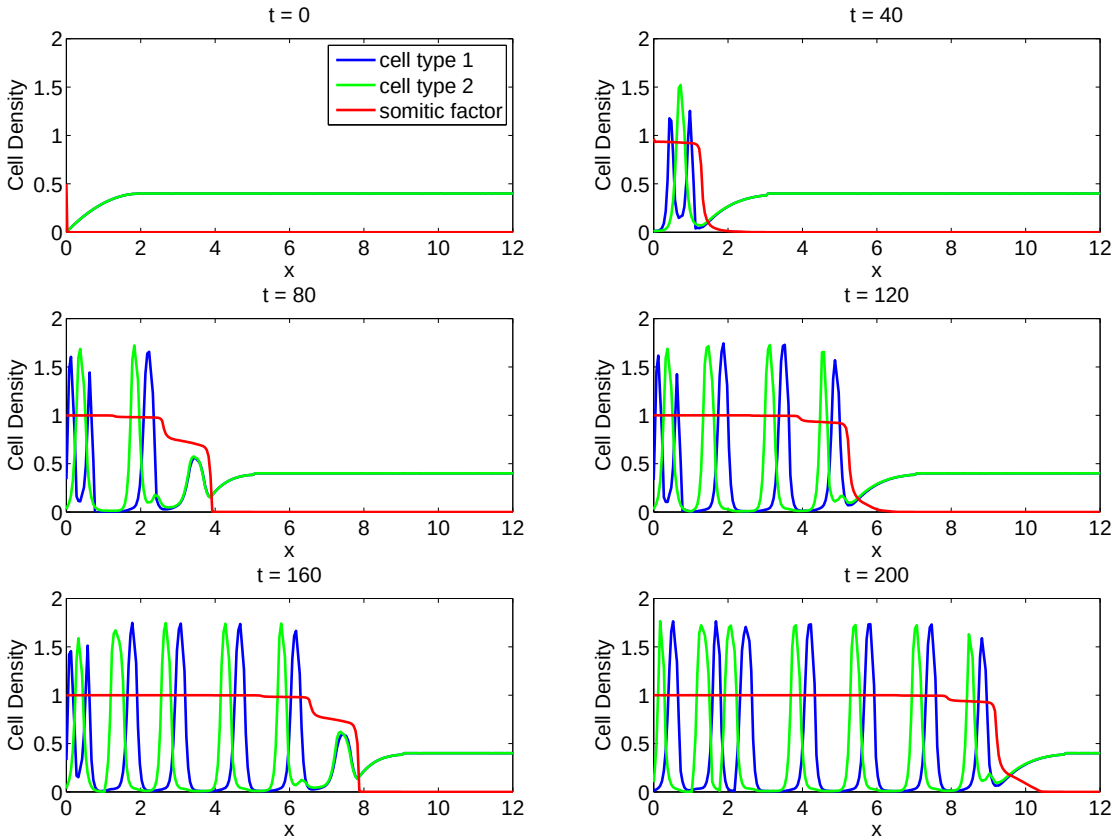

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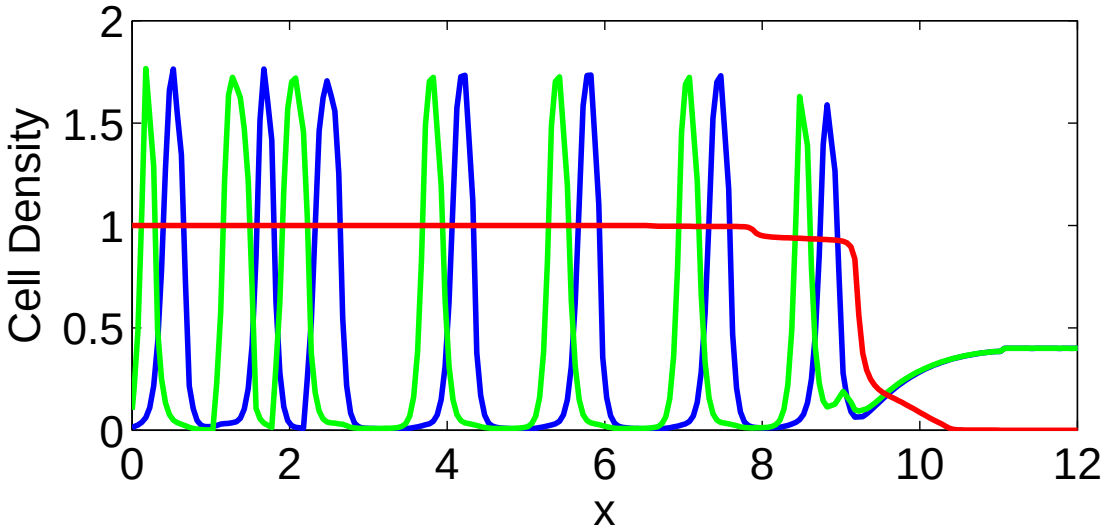


Conclusions of Somite Application

Conceptual cell cycle model (Stern et al)

↓

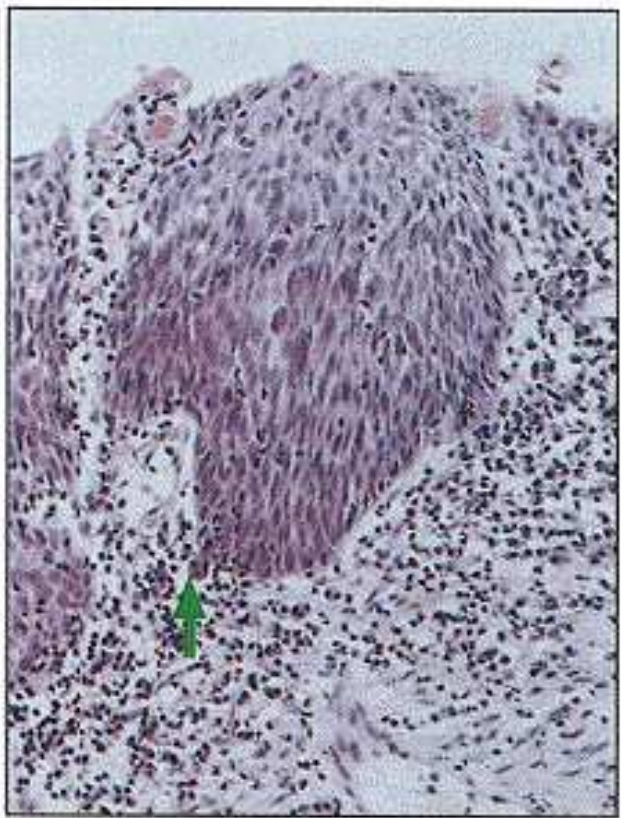
Mathematical cell cycle model (Collier et al) → Predictions on the diffusion and decay rates of the signalling molecule, and on the outcome of new heat shock expts

↓

Our extended mathematical model → Predictions on the values of α, c and N

Outline

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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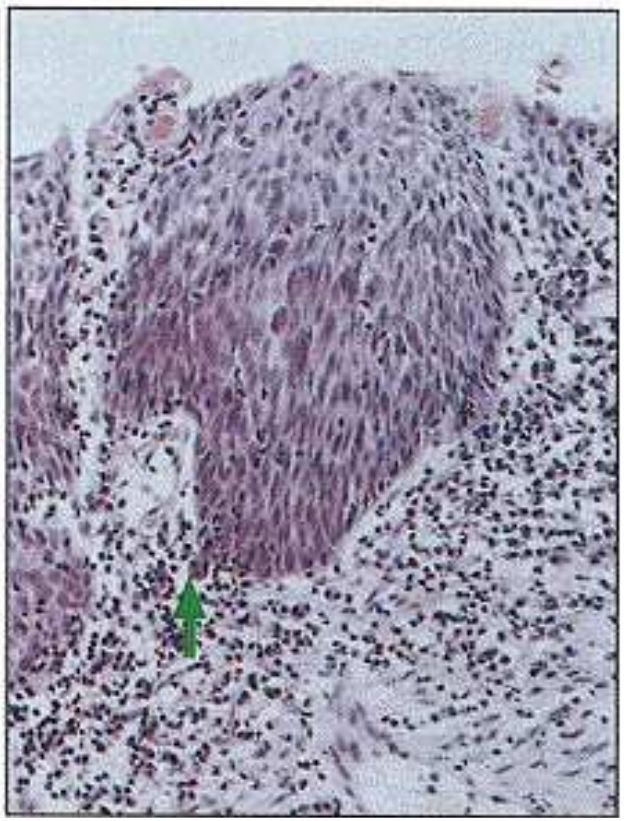

Carcinoma of the uterine cervix

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

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

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

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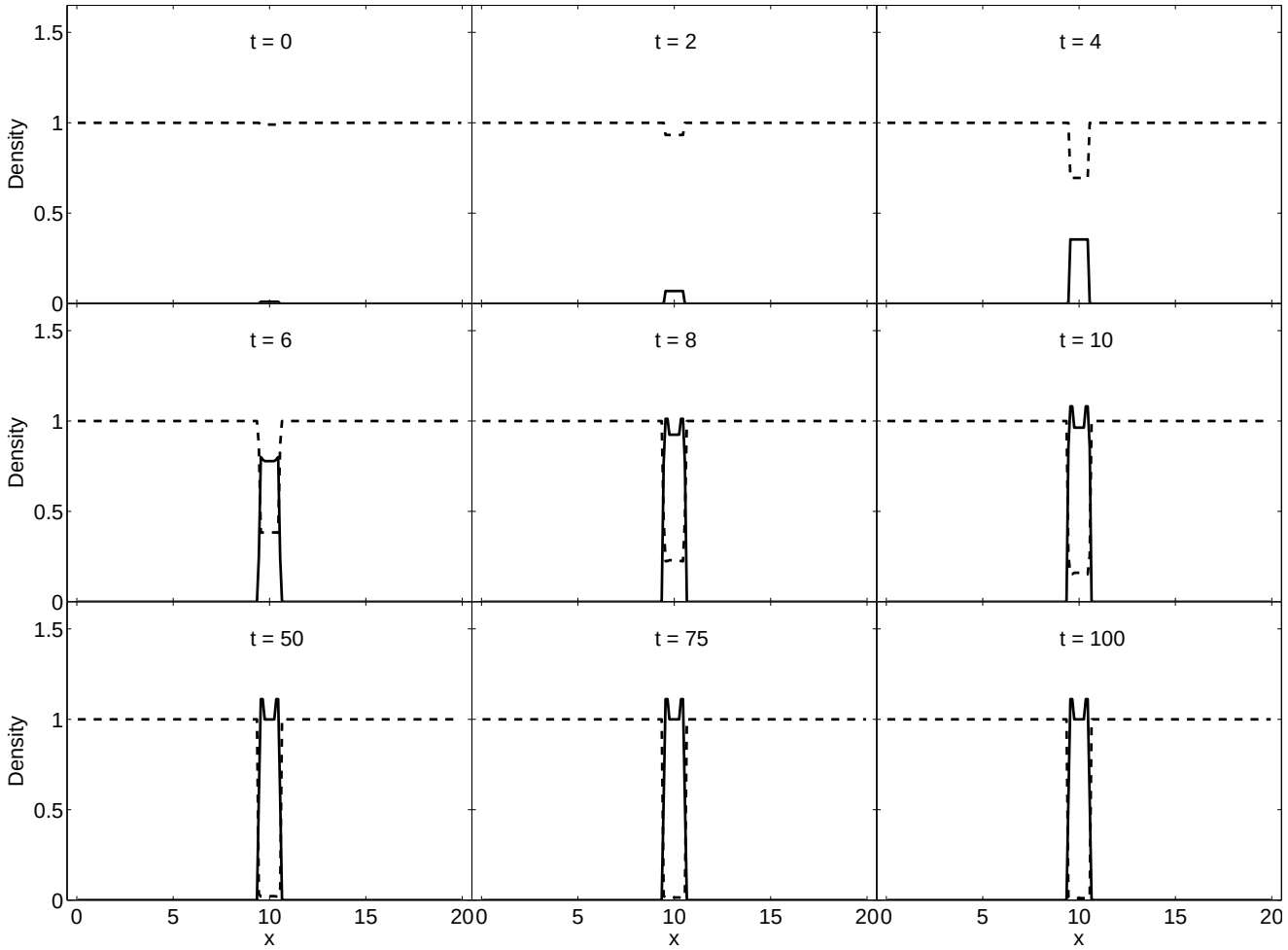
Model ingredients:

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

Model Solution: Non-Invasive Tumour

For α relatively large and β relatively small, the model predicts a non-invasive tumour

Model Solution: Non-Invasive Tumour



Model Solution: Invasive Tumour

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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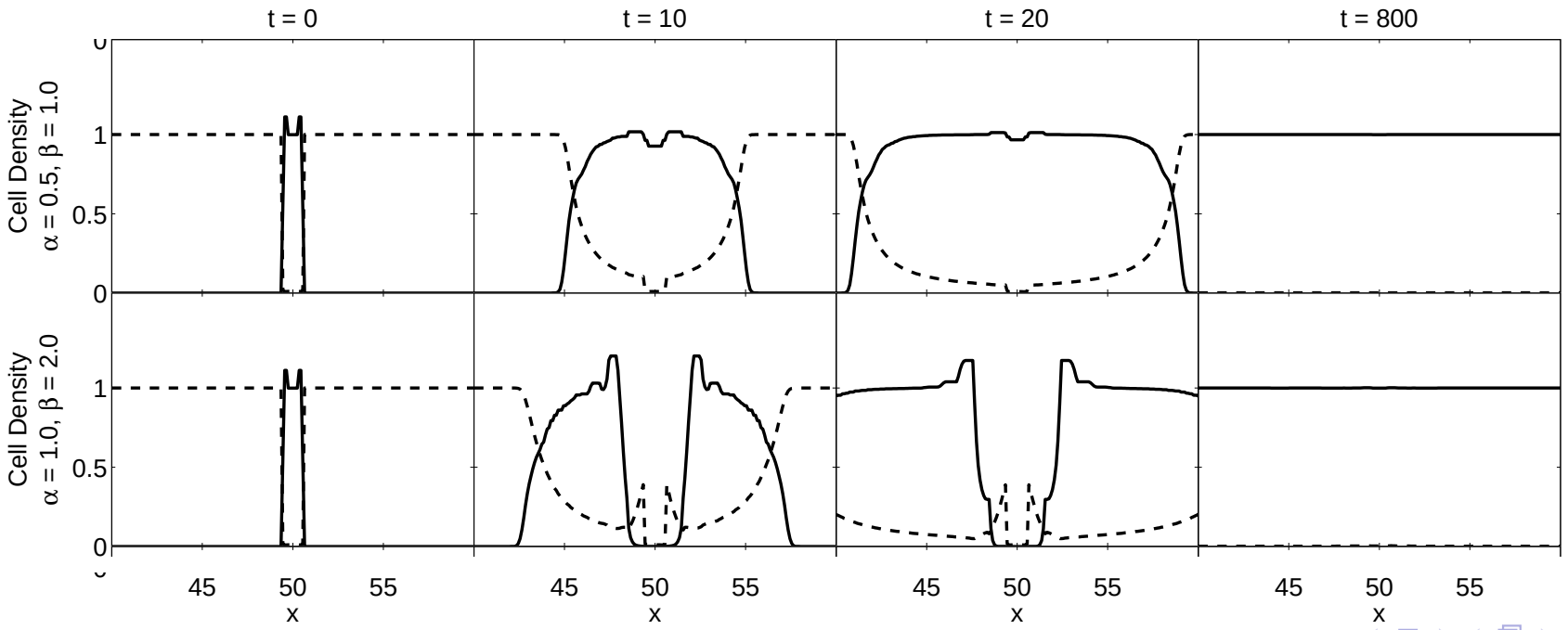

Future Work on Cancer Application

- Numerical solutions in two space dimensions
- Addition of normal tissue cells and multiple matrix types
- Addition of other aspects of the invasive phenotype

List of Frames