Mathematical modelling of cell adhesion in developmental biology and cancer

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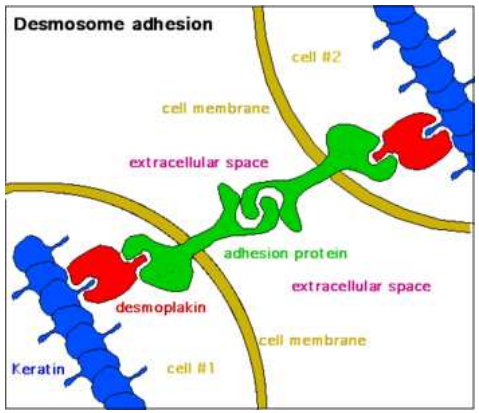
Outline

Outline

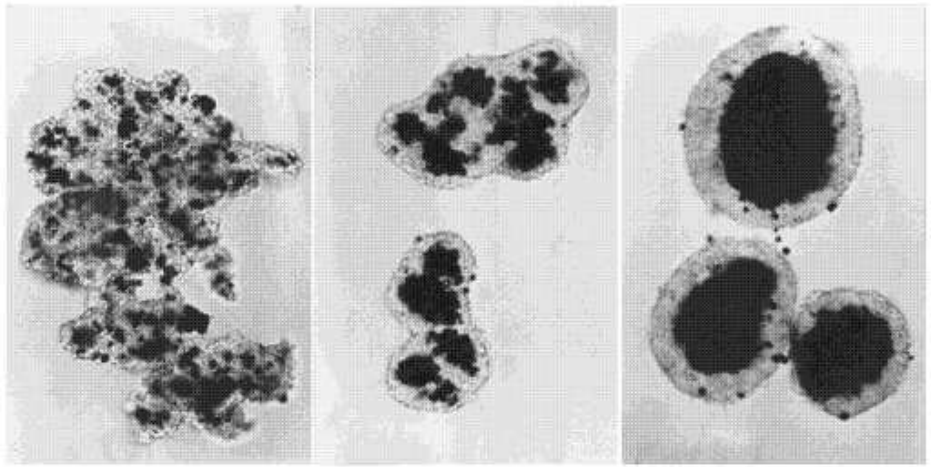
What is Cell-Cell Adhesion?

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 $J_a = \phi nF/R$
  (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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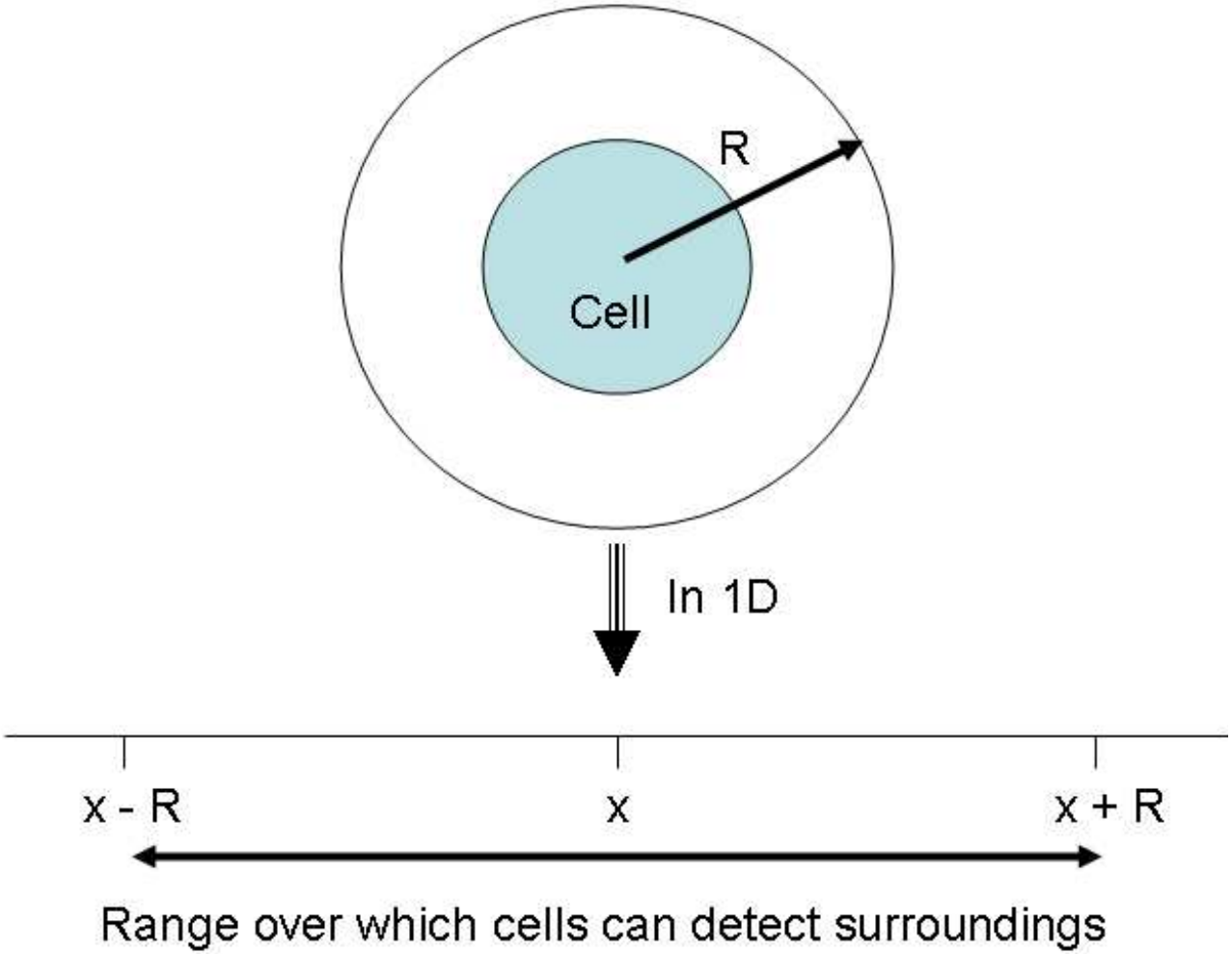
$$f(x, x_0) = \alpha \cdot g\left(n(x + x_0, t)\right) \cdot \omega(x_0)$$

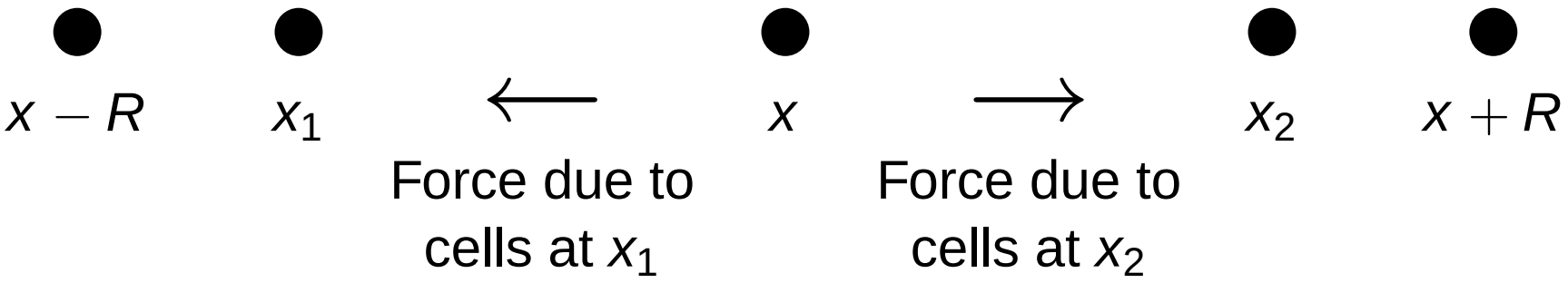
- Total force = sum of all forces acting on cells at x

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

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

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

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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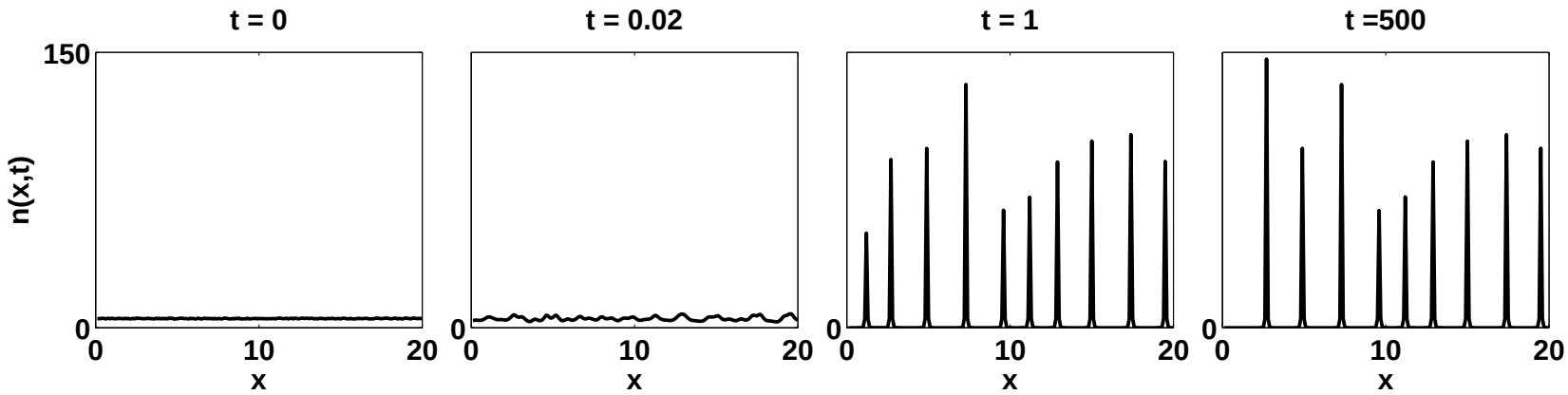
- Initially we assume $g(n) = n$
- The parameter α reflects the strength of adhesion; we expect aggregation of disassociated cells when α is large.
- Substitute $n(x,t) = n_0 + \epsilon \exp\{ikx + \lambda t\} \Rightarrow$ $\lambda(k) = -k^2 - 2n_0(-1 + \cos k)$
- This implies instability when $\alpha > 1/(n_0 \cos\theta)$ where θ is the smallest $+$ve root of $\theta = \tan\theta$.

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 $g(n) = n(n_{max} - n)$. Here n_{max} corresponds to close-packed cells.

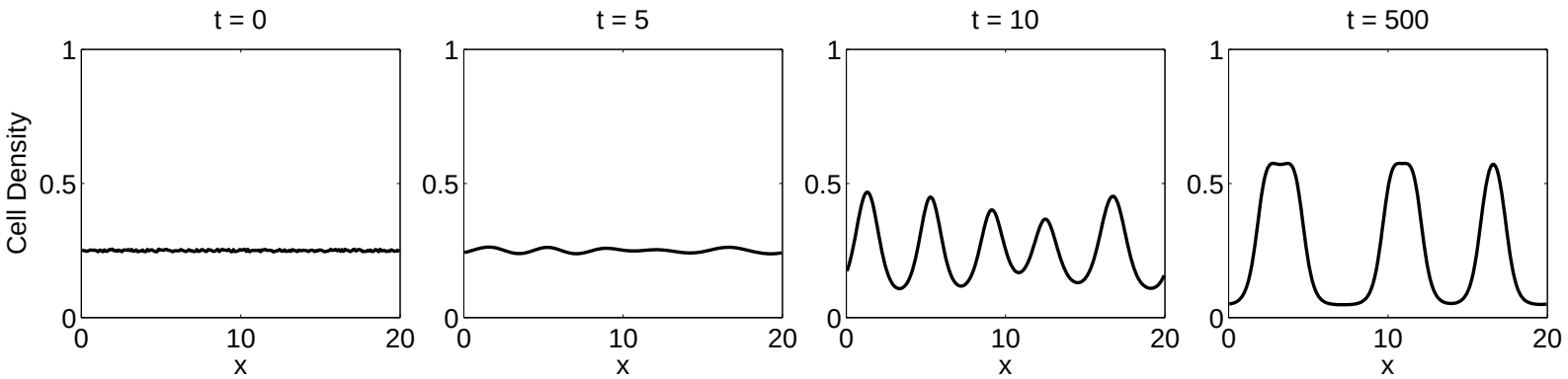
Model Improvement: Nonlinear $g(n)$: Boundedness

The improved model is:

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

- For biological realism, we require that $0 < n(x,0) < n_{max} \Rightarrow 0 < n(x,t) < n_{max}$ for all $t > 0$.
- Maximum principle arguments give:
  - $0 < n(x,0) \Rightarrow 0 < n(x,t)$ for all $t > 0$.
  - various conditions on α and ω that are sufficient for $n(x,0) < n_{max} \Rightarrow n(x,t) < n_{max}$ for all $t > 0$.
  - these sufficient conditions include $\omega(x_0) = \text{sign}(x_0)$ for any $\alpha > 0$

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

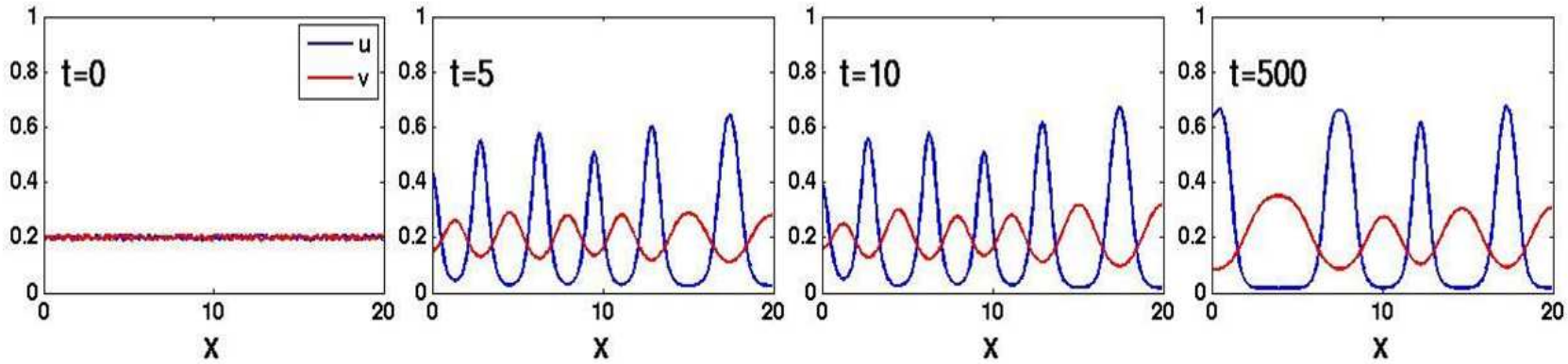
Extending the Model to Interacting Cell Populations II

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

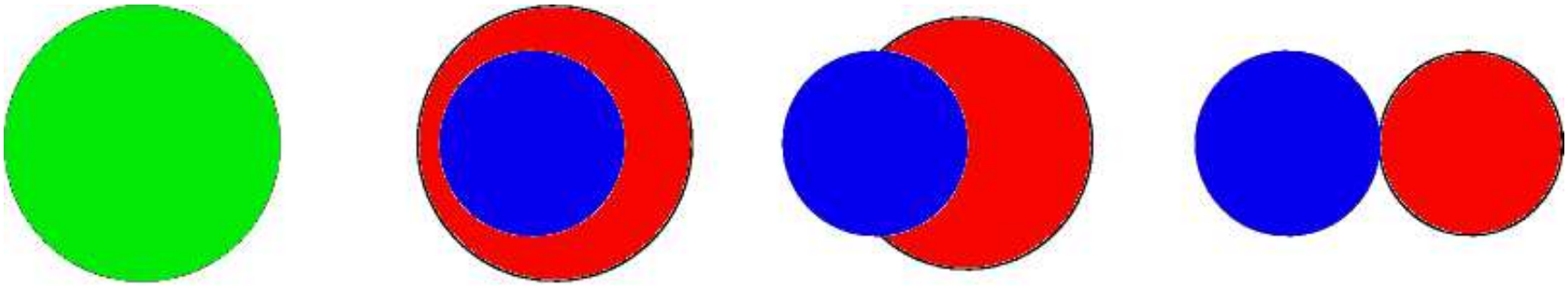
$$\begin{aligned} K_n &= S_n \int_{-1}^{+1} g_{nn}\left(n(x+x_0,t), m(x+x_0,t)\right)\omega(x_0)\,dx_0 \\ &+ C \int_{-1}^{+1} g_{nm}\left(n(x+x_0,t), m(x+x_0,t)\right)\omega(x_0)\,dx_0 \\ K_m &= S_m \int_{-1}^{+1} g_{mm}\left(n(x+x_0,t), m(x+x_0,t)\right)\omega(x_0)\,dx_0 \\ &+ C \int_{-1}^{+1} g_{mn}\left(n(x+x_0,t),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

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

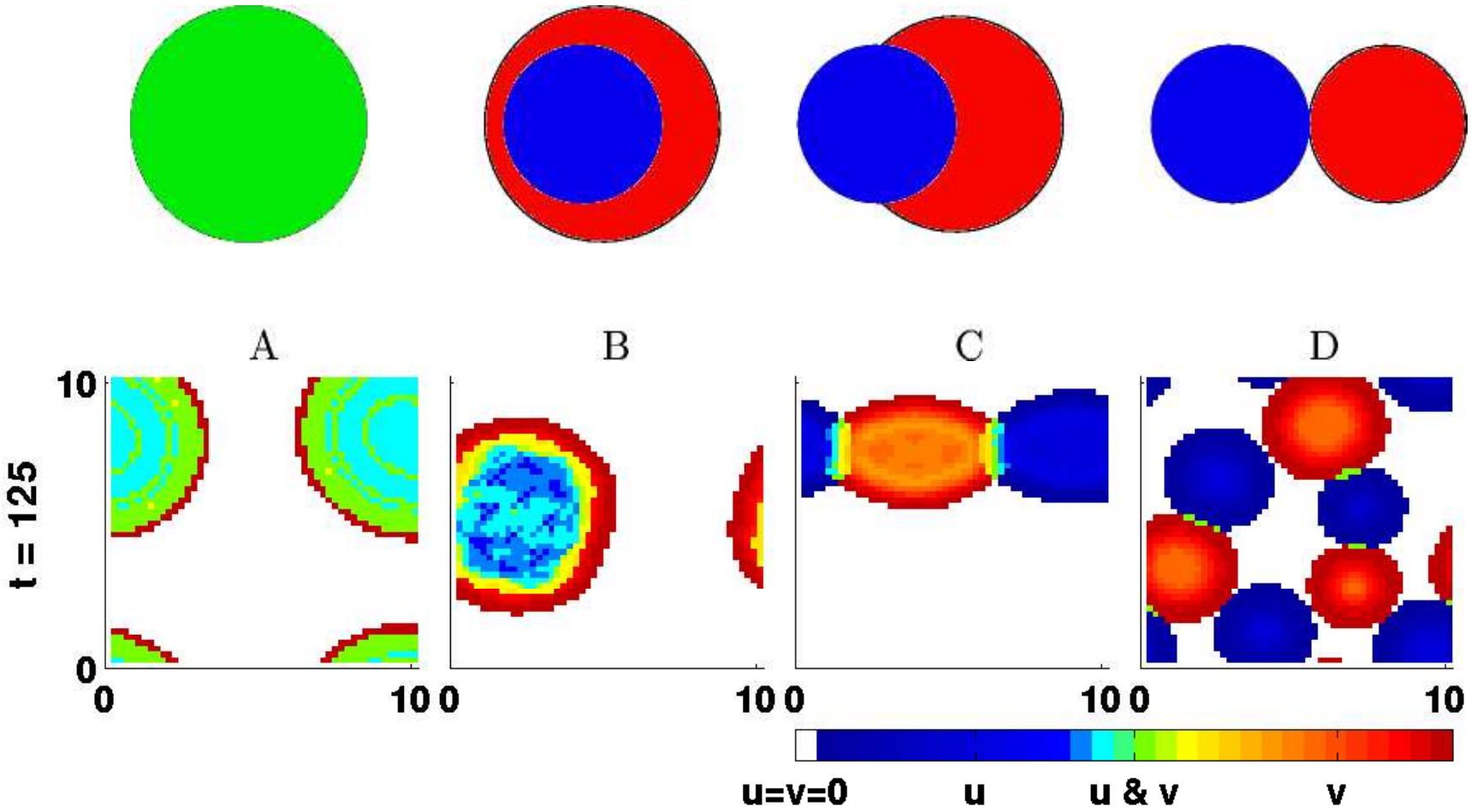


Experimental Cell Sorting Results



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 $C < S_m$	$C = 0$

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, case B

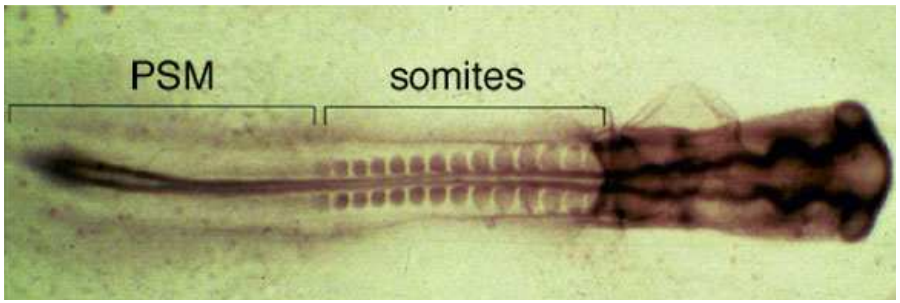
Click to play the movie, case D

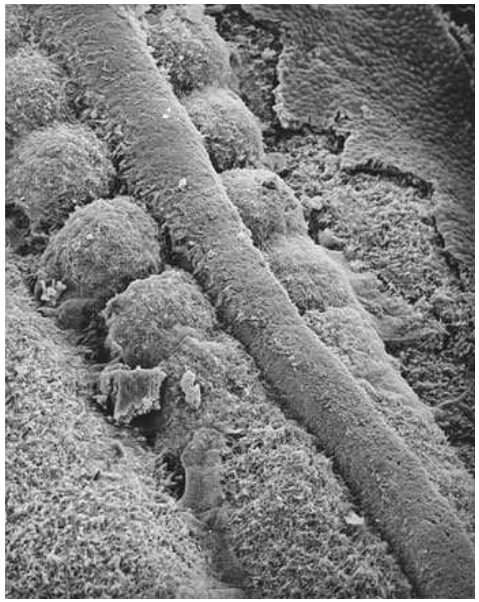
Outline

Introduction to Somite Formation

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

Posterior Stage 11 chick Anterior



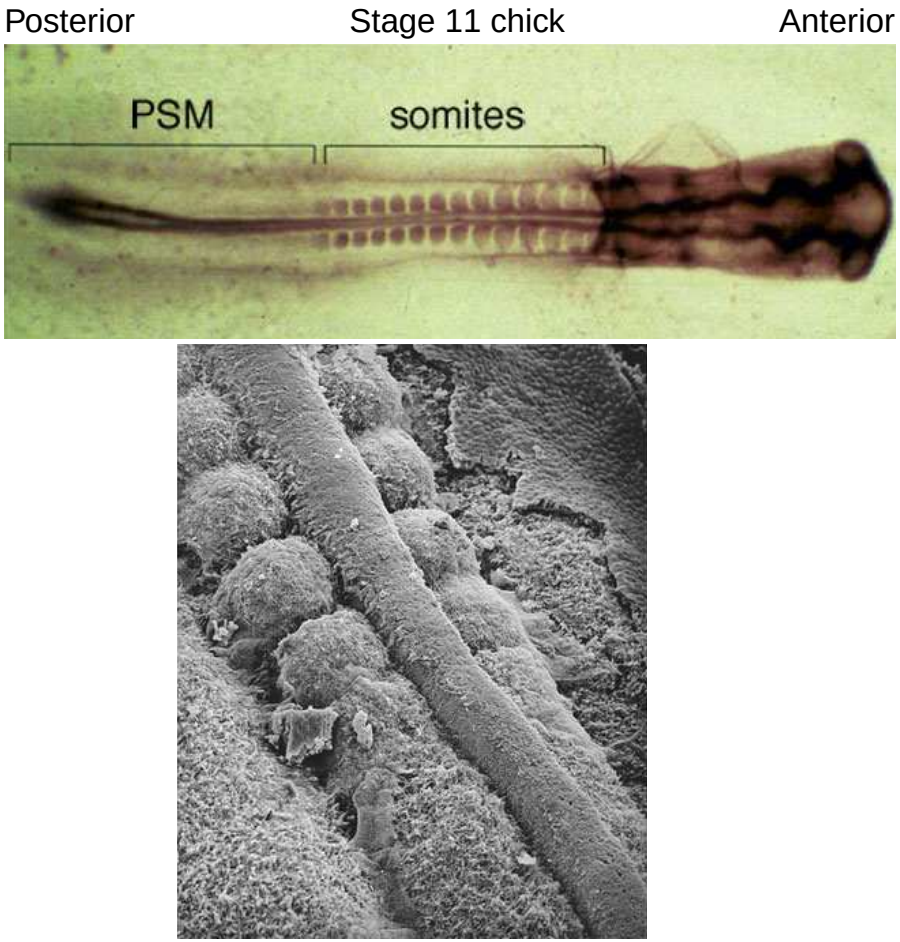


Introduction to Somite Formation

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

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

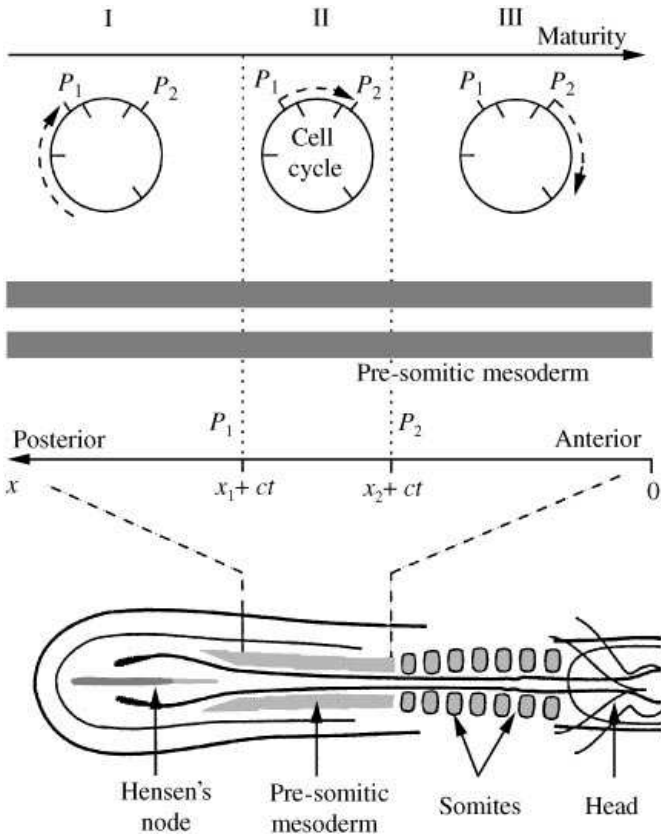
1. Pre-pattern forms in PSM
2. Cells coalesce into somites
3. Each somite differentiates into anterior and posterior halves



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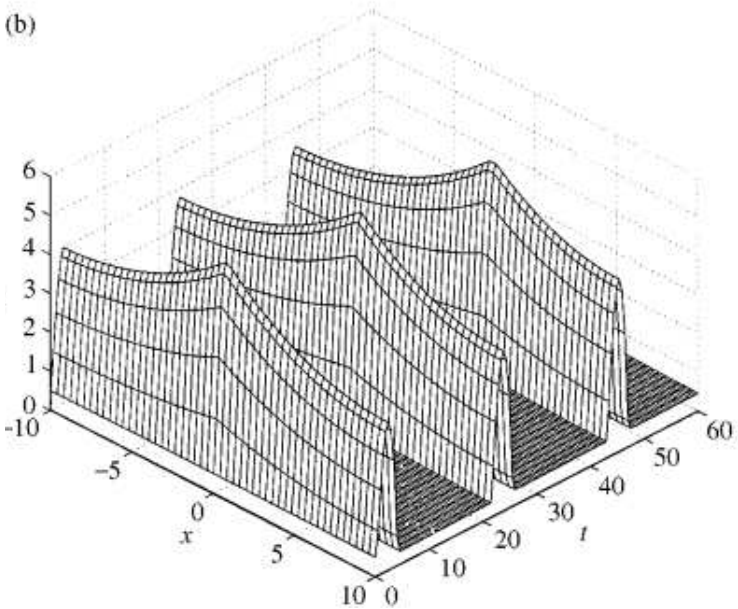
$$\frac{\partial u}{\partial t} = \frac{(u+\mu v)^2}{\kappa_1+\kappa_2 u^2}\Gamma_u(x,t) - \frac{u}{\kappa_2}$$

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

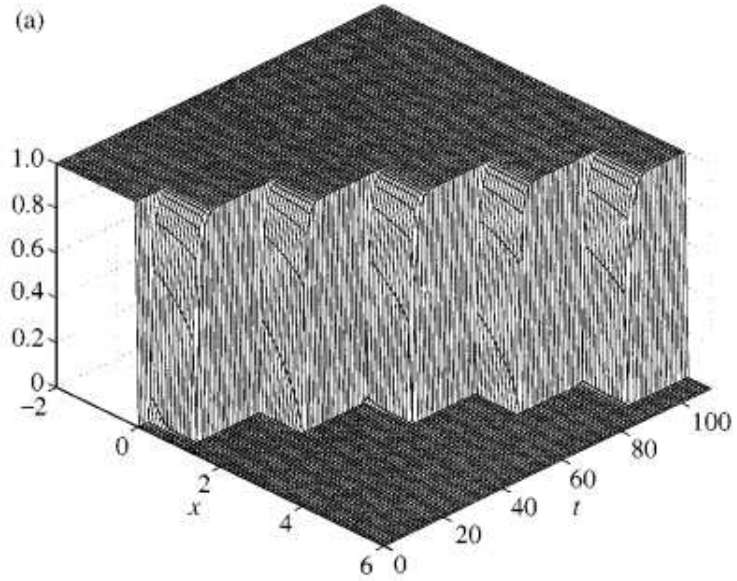
$$\Gamma_u(x,t) = H(ct-x+x_1)$$

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

Typical Solution of the Collier et al Model



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 $n(x,t)$

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

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

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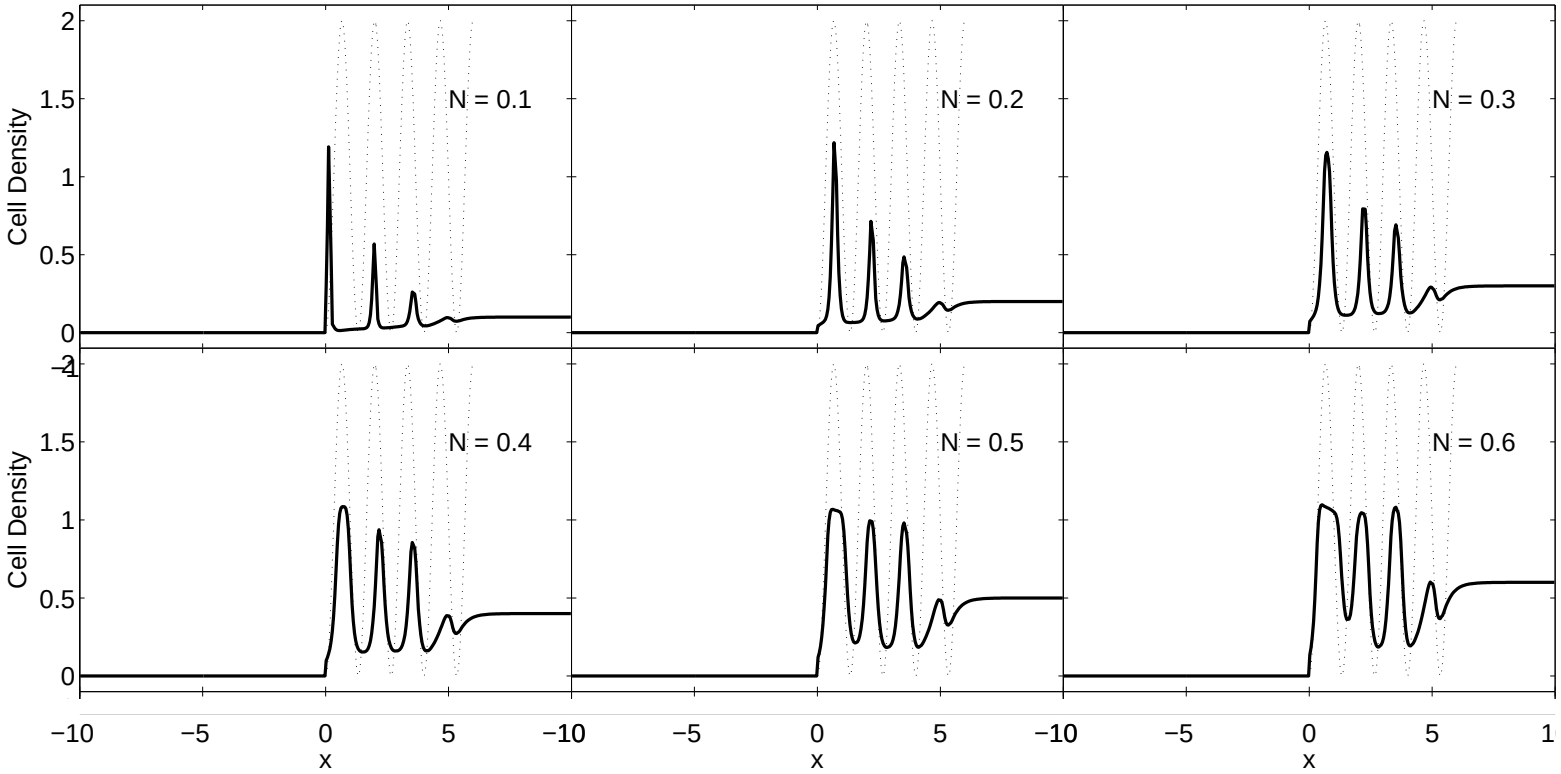
- Cell adhesion depends on the concentration of the adhesion molecule precursor, u
- The parameter α determines the strength of cell-cell adhesion
- Note that there is no feedback from the cell equation to the chemical equations

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 $n_1(x,t)$, $n_2(x,t)$.

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

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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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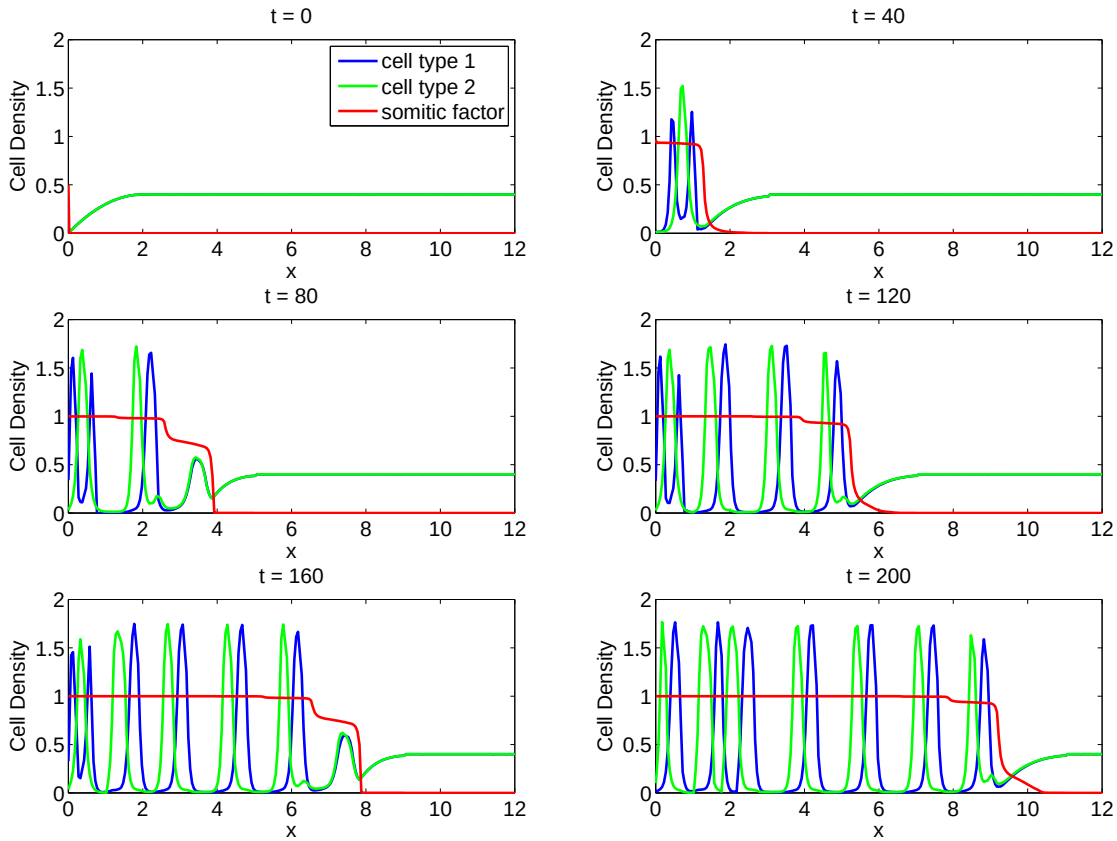

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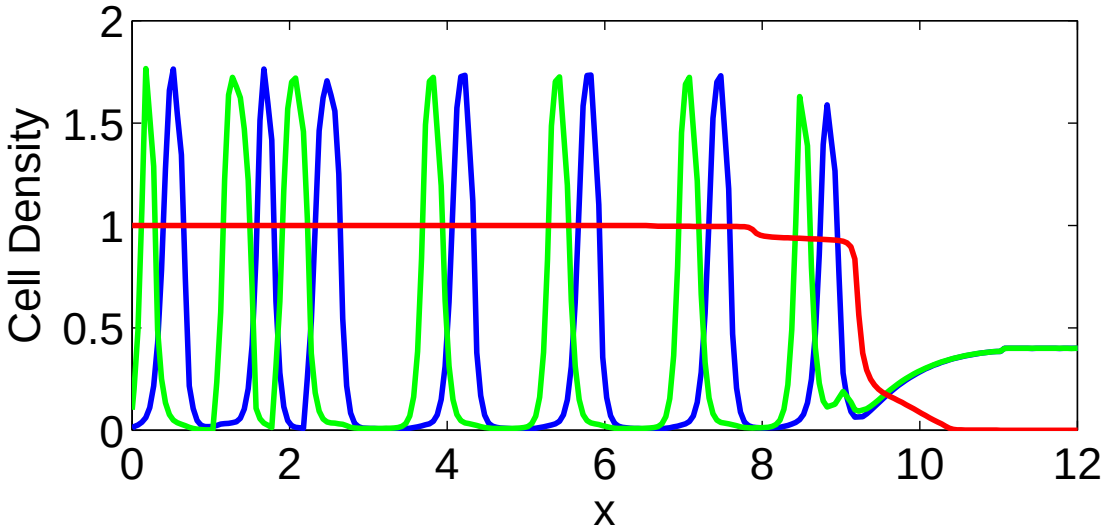

Conclusions of Somite Application

Conceptual cell cycle model (Stern et al)

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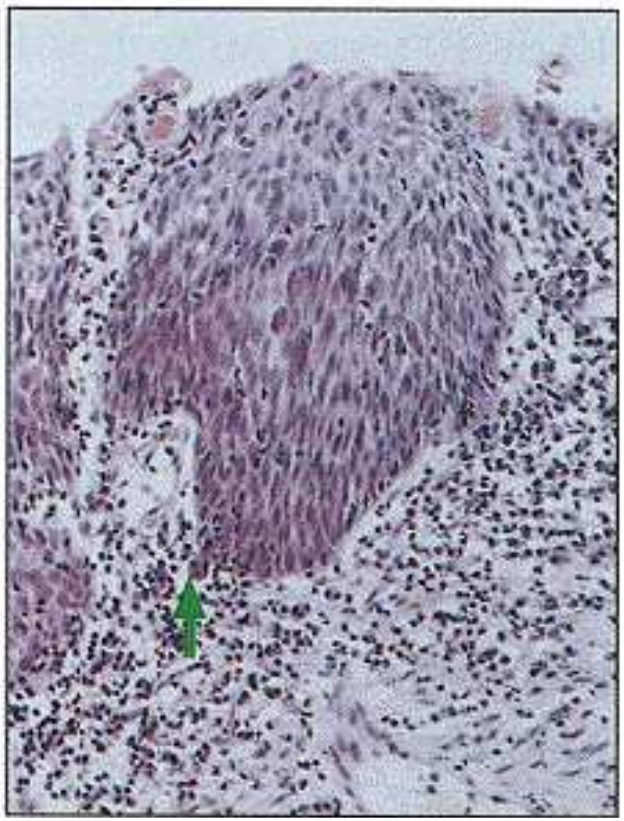
Mathematical cell cycle model (Collier et al)

↓

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

Outline

Introduction to Cancer Invasion

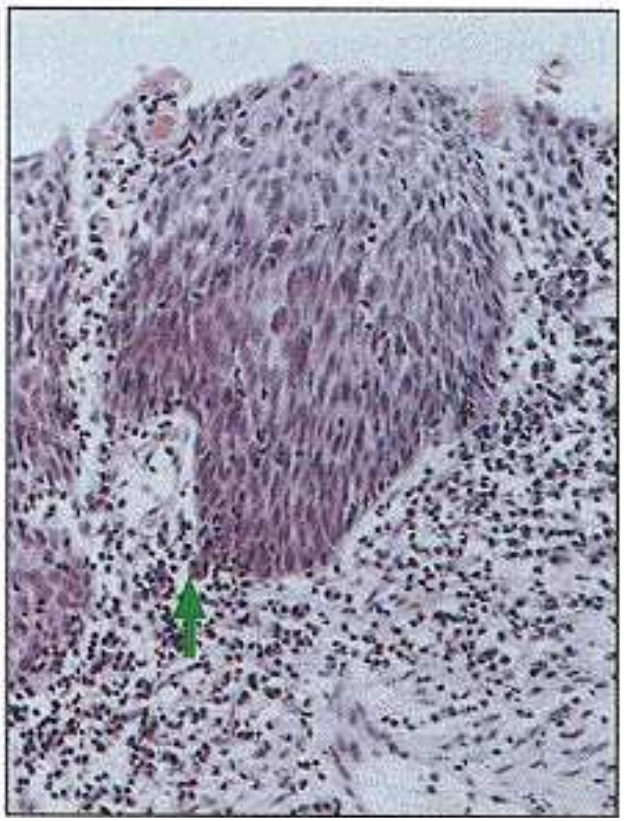


Carcinoma of the uterine cervix

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

- migration
- protease/anti-protease production
- adhesion

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: 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

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

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

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

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

Model ingredients:

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Model ingredients:

- random motility

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

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

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

Model ingredients:

- random motility
- cell–cell adhesion

Modelling Adhesion in Cancer

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

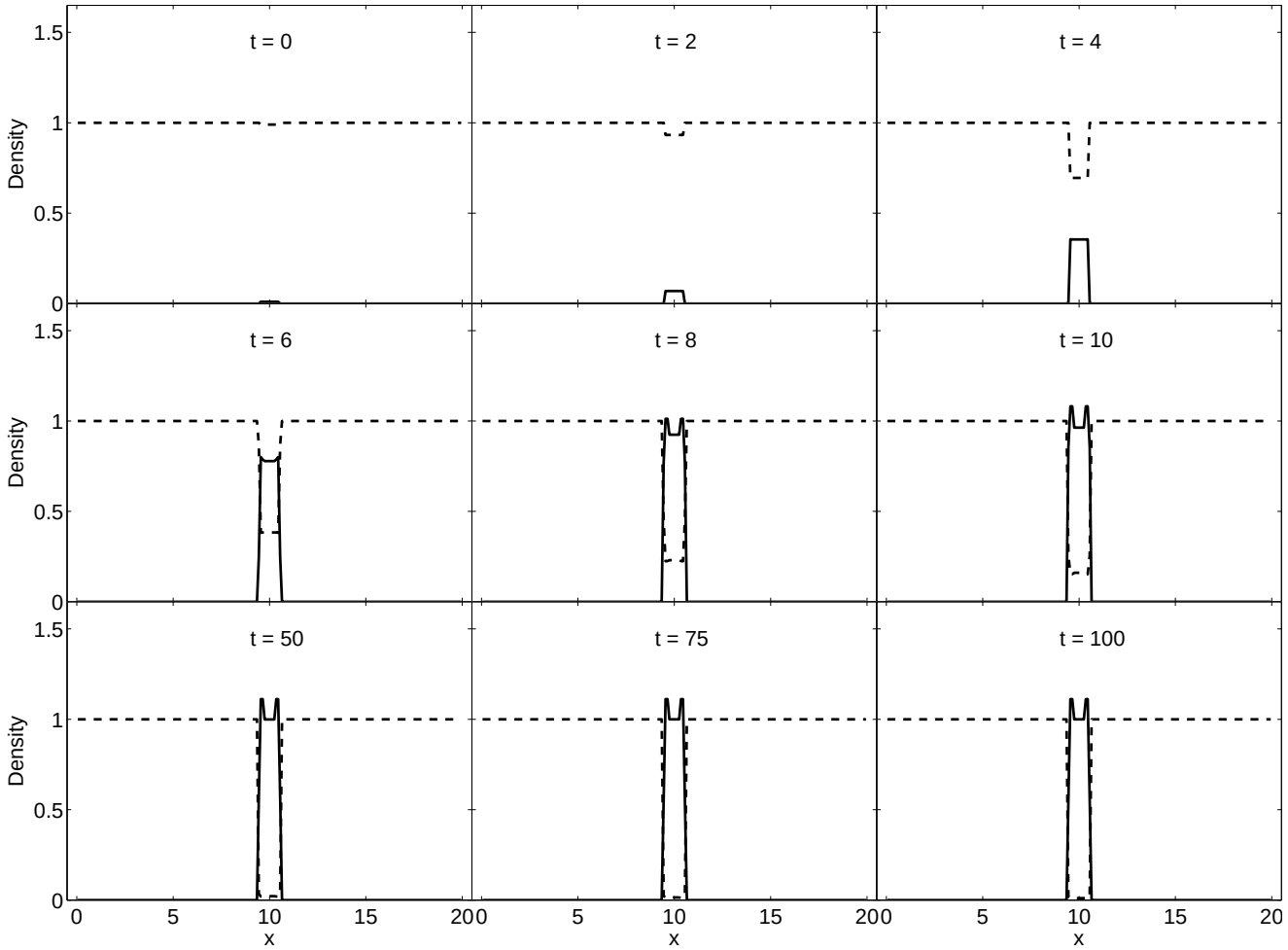
Model ingredients:

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

Model Solutions in 1-D: Non-Invasive Tumour

For α relatively large and β 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 (α) or by increasing cell-matrix adhesion (β)

Model Solutions in 1-D: Invasive Tumour

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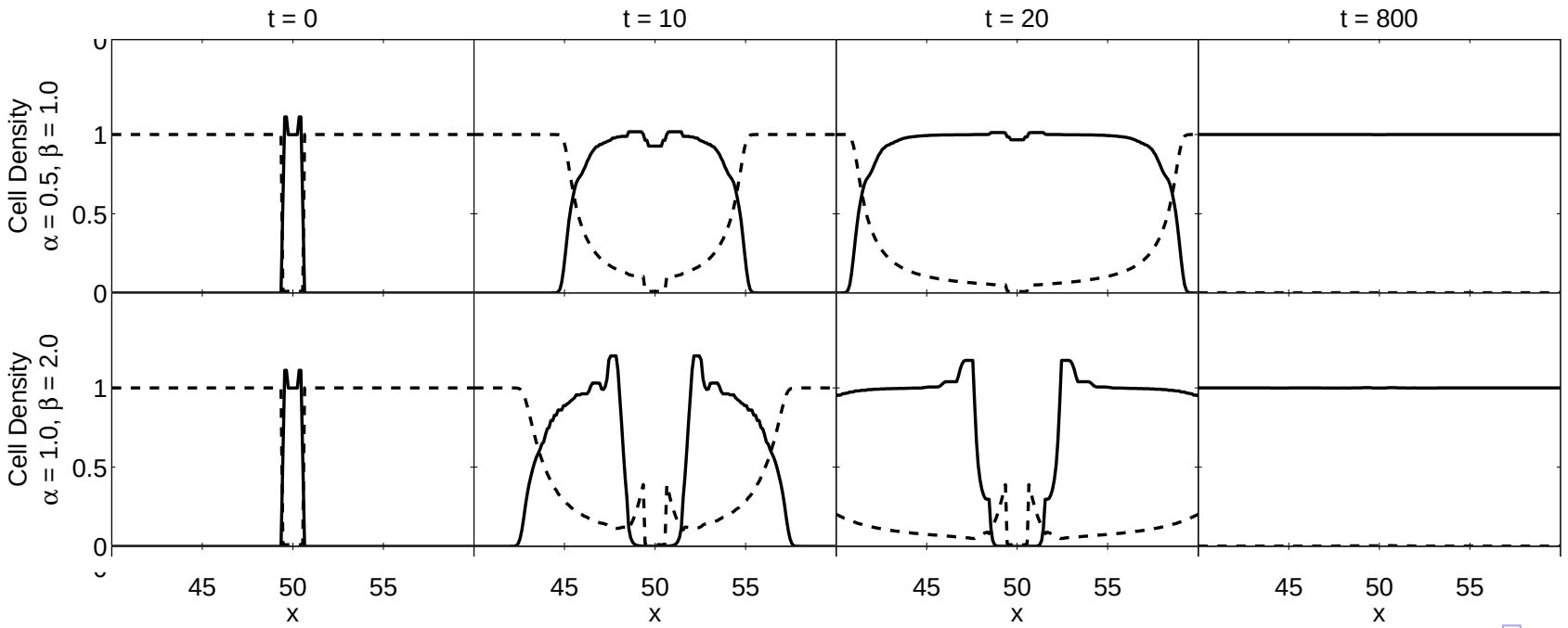
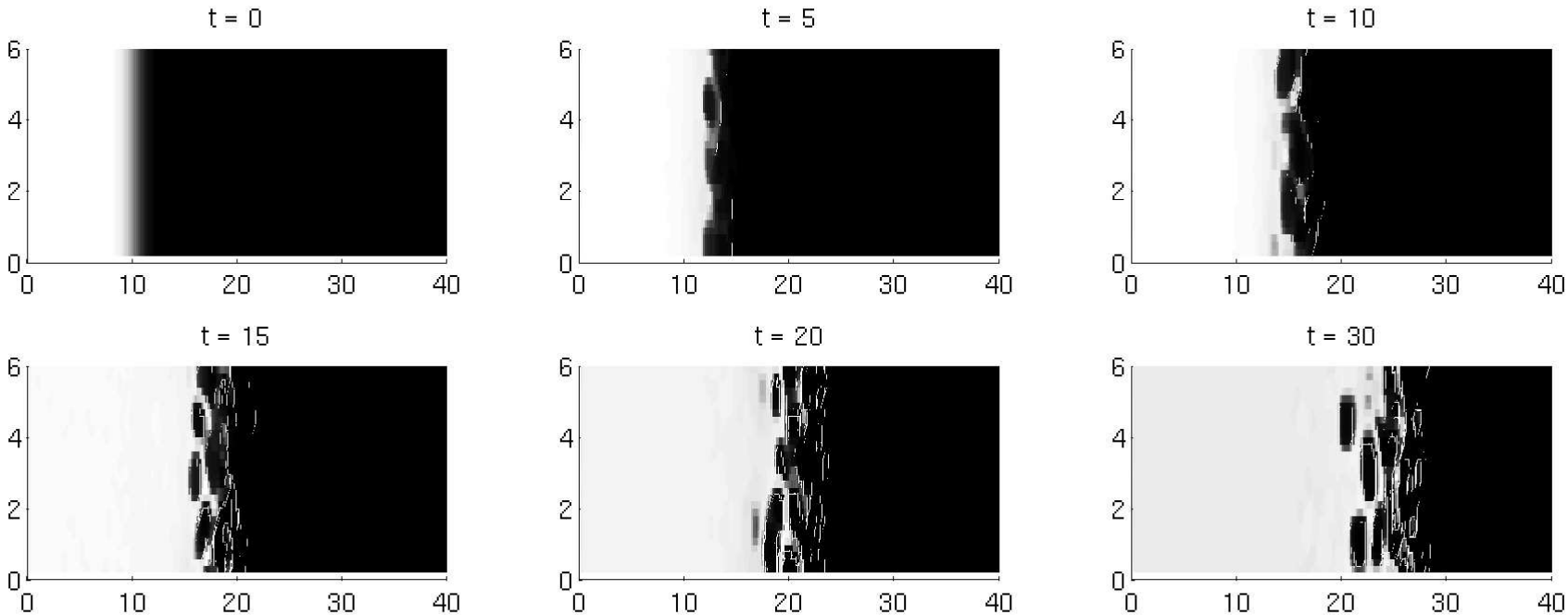


Model Solutions in 2-D: Fingering



Future Work on Cancer Application

- Further numerical work in two space dimensions
- Addition of normal tissue cells and multiple matrix types
- Addition of other aspects of the invasive phenotype

List of Frames