Diffusive Movement of Interacting Cell Populations

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University of Durham, 2 March 2006

In collaboration with
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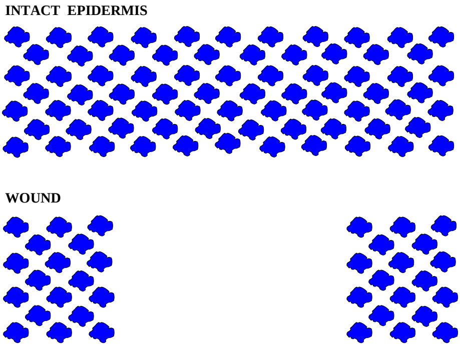
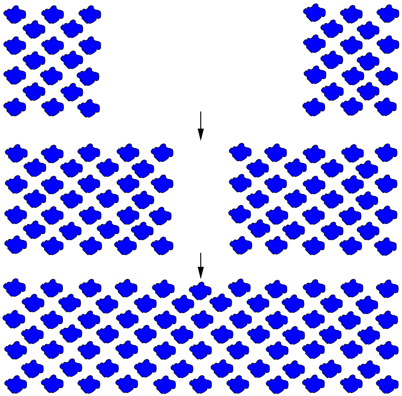
Outline

Outline

Motivating Example: Epidermal Wounds



Epidermal Wound Healing



A Simple Model for Epidermal Wound Healing

$$u(x,t) = \text{cell density}$$

$$\partial u/\partial t = \overbrace{\partial^2 u/\partial x^2}^{\text{movement}} + \underbrace{u(1-u)}_{\text{division}}$$

(after rescaling)

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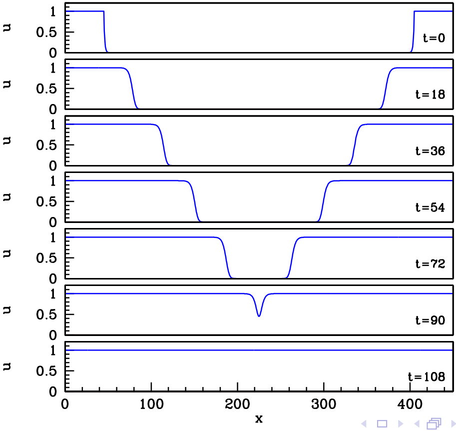
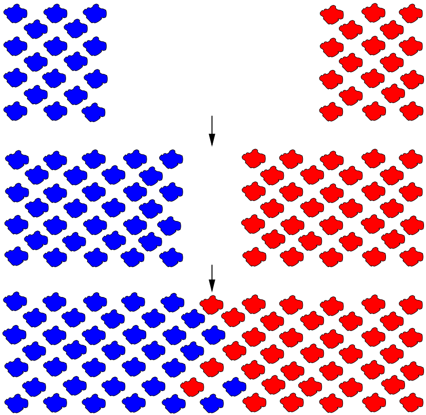


Epidermal Wound Healing With Cell Marking



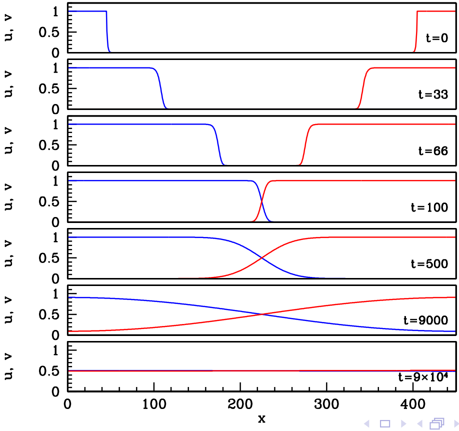
Extension of Simple Model to Cell Marking

$$u(x,t) = \text{blue cell density}$$
$$v(x,t) = \text{red cell density}$$

$$\partial u/\partial t = \partial^2 u/\partial x^2 + u(1-u-v)$$

$$\partial v/\partial t = \partial^2 v/\partial x^2 + v(1-u-v)$$

(after rescaling)



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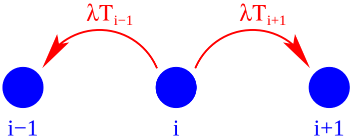
Transition Probability Approach

Cells undergo a random walk on a 1-D grid



$$\lambda T_i^{\pm} \quad = \quad \text{probability that a cell at point } i \text{ moves to the left/right (per unit time)}$$

Then $\partial u_i / \partial t = \lambda \left[T_{i-1}^{+} u_{i-1} + T_{i+1}^{-} u_{i+1} - (T_i^{+} + T_i^{-}) u_i \right]$

To obtain a PDE for given forms of $T_i^{\pm}$: define $x = ih$ and let $h \to 0$, $\lambda \to \infty$ with $\lambda h^2 \to 1$.

Case 1: $T_i^{\pm} = D$, a constant

$$du_i/dt = \lambda\left[u_{i-1} + u_{i+1} - 2u_i\right]$$

$$\Rightarrow u_t = Du_{xx}$$

Case 2: $T_i^{\pm} = f(w_i) + g(w_{i\pm1})$

(Notation: $w = u + v$)

$$
\begin{aligned}
du_i/dt &= \lambda\left[\{f(w_{i-1}) + g(w_i)\}\, u_{i-1} + \{f(w_{i+1}) + g(w_i)\}\, u_{i+1}\right. \\
&\quad \left. - \{2f(w_i) + g(w_{i+1}) + g(w_{i-1})\}\, u_i\right]
\end{aligned}
$$

$$
\begin{aligned}
\Rightarrow u_t &= \left[\{f(w) + g(w)\}\, u_x + \{f(w) - g(w)\}_x\, u\right]_x \\
&= \left[A(w)u_x + \frac{u}{w} B(w)w_x\right]_x
\end{aligned}
$$

Intuitive Interpretation of the Improved Model

$$
\begin{aligned}
u_t &= \left[A(w)u_x + \frac{u}{w}B(w)w_x\right]_x \\
v_t &= \left[A(w)v_x + \frac{v}{w}B(w)w_x\right]_x \\
\Rightarrow w_t &= \left[\{A(w)+B(w)\}\, w_x\right]_x
\end{aligned}
$$

Nonlinear diffusion for total cell population

Intuitive Interpretation of the Improved Model

$$\begin{aligned} u_t &= \left[A(w)u_x + \frac{u}{w}B(w)w_x\right]_x \\ v_t &= \left[A(w)v_x + \frac{v}{w}B(w)w_x\right]_x \\ \Rightarrow w_t &= \left[\{A(w)+B(w)\}\, w_x\right]_x \end{aligned}$$

Nonlinear diffusion for total cell population

$A(w)w_x$ represents movement of cells down gradients of their own density

$B(w)w_x$ represents movement of cells down gradients of total cell density

Extreme Cases of the Improved Model

$A = 1, B = 0$: cells move entirely down gradients of their own density

$$u_t = u_{xx} \qquad v_t = v_{xx}$$

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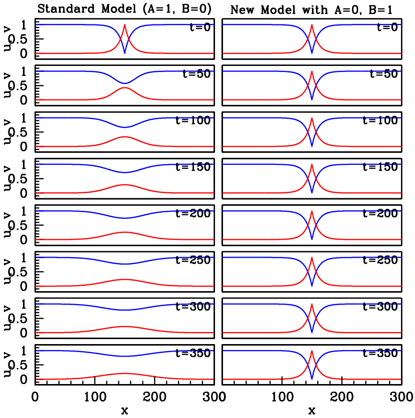
$A = 0, B = 1$: cells move entirely down gradients of total cell density

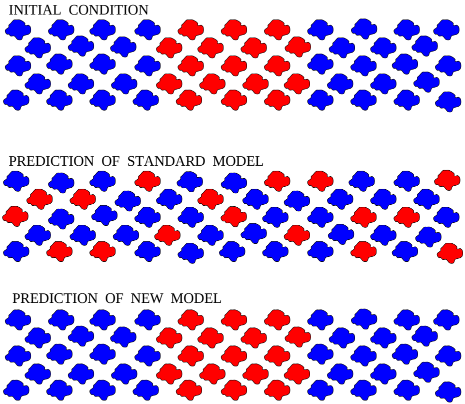
$$u_t = \left[\frac{u}{w} w_x\right]_x \qquad v_t = \left[\frac{v}{w} w_x\right]_x$$

Outline

Isolated Cell Population (Extreme Cases)



Schematic Illustration of Model Solutions



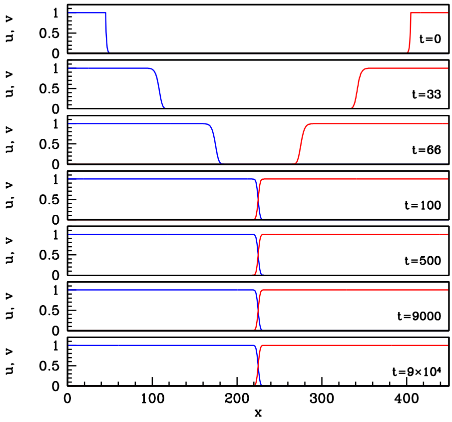
Wound Healing: A More Realistic Model

Assume that the probability of a cell moving to the left/right is a decreasing function of the cell density at the potential destination

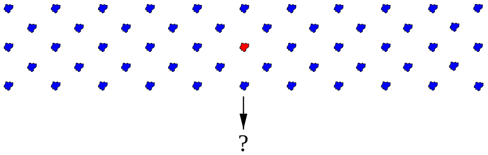
$$T_i^{\pm} = 1 - w_{i\pm 1} \Rightarrow A(w) = 1 - w, \; B(w) = w$$

$$\begin{aligned} \Rightarrow u_t &= [u(1-u-v)]_{xx} + u(1-u-v) \\ v_t &= [v(1-u-v)]_{xx} + v(1-u-v) \end{aligned}$$

Wound Healing: Solutions of the More Realistic Model



Second Biological Example: Early Tumour Growth

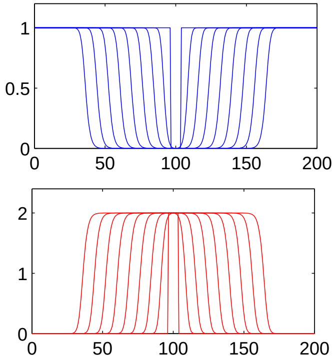


Assumptions:

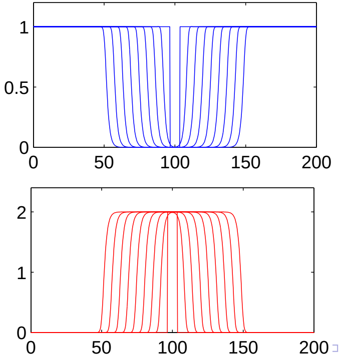
- Both cell populations show unbiased movement
- Both cell populations divide, with growth limited by overall cell density
- Mutant cells have a higher growth rate and carrying capacity than normal cells

Tumour Growth Solutions

$$
\begin{aligned}
u_t &= u_{xx} + u(1-u-v) \\
v_t &= v_{xx} + v(2-u-v)
\end{aligned}
$$



$$
\begin{aligned}
u_t &= u_{xx} - \frac{1}{3}\left[u(u+v)\right]_{xx} + u(1-u-v) \\
v_t &= v_{xx} - \frac{1}{3}\left[v(u+v)\right]_{xx} + v(2-u-v)
\end{aligned}
$$



Outline

The Mathematical Problem

What are the speeds of the travelling waves for tumour growth in the two extreme cases?

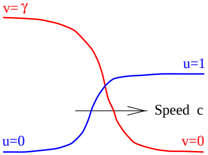
Case 1: ($A = 1$, $B = 0$; $\gamma > 1$)

$$\begin{aligned} u_t &= u_{xx} + u(1 - u - v) \\ v_t &= v_{xx} + v(\gamma - u - v) \end{aligned}$$

Case 2: ($A = 0$, $B = 1$; $\gamma > 1$)

$$\begin{aligned} u_t &= \left[\frac{u}{u+v} (u_x + v_x) \right]_x + u(1 - u - v) \\ v_t &= \left[\frac{v}{u+v} (u_x + v_x) \right]_x + v(\gamma - u - v) \end{aligned}$$

Wave Speed: Standard Model



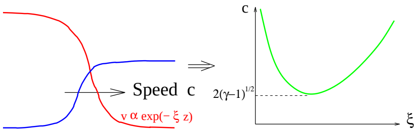
Travelling wave solns $u(x,t)=U(z)$, $v(x,t)=V(z)$, $z=x-ct$

$$\begin{aligned}\Rightarrow U''+cU'+U(1-U-V) &= 0\\ V''+cV'+V(\gamma-U-V) &= 0\end{aligned}$$

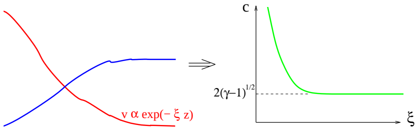
Linearise ahead of wave: V equation decouples.
Look for solutions $V=V_0\exp(-\xi z)$:

$$\xi^2-c\xi+(\gamma-1)=0 \quad \Rightarrow c=\xi+(\gamma-1)/\xi$$

Wave Speed: Standard Model (contd)

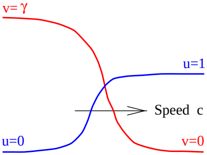


By analogy with scalar reaction−diffusion equations:



In applications, we are interested in localised initial data.
I.e. ξ is large, so wave speed = $2(\gamma-1)^{1/2}$

Wave Speed: New Model



Travelling wave solns $u(x,t) = U(z)$, $v(x,t) = V(z)$, $z = x - ct$

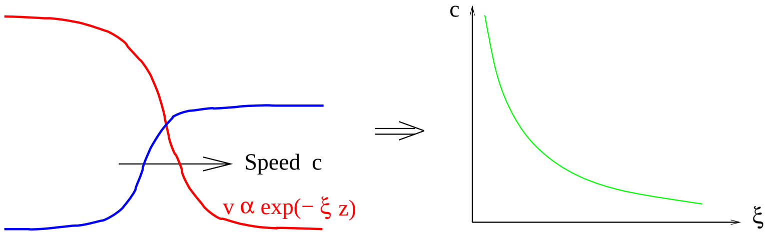
$$\Rightarrow \left[\frac{U}{U+V}(U' + V')\right]' + cU' + U(1 - U - V) = 0$$

$$\left[\frac{V}{U+V}(U' + V')\right]' + cV' + V(\gamma - U - V) = 0$$

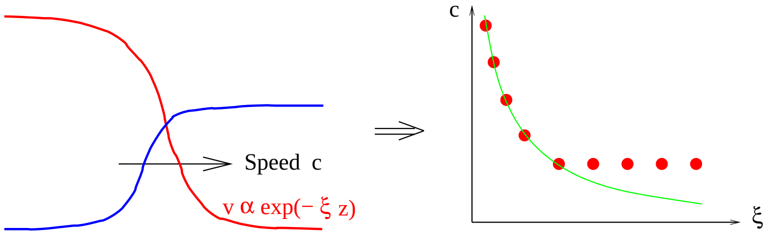
Linearise ahead of wave: V equation decouples.

$$V = V_0 \exp(-\xi z) \Rightarrow -c\xi + \gamma - 1 = 0 \Rightarrow c = (\gamma - 1)/\xi$$

Wave Speed: New Model (contd)



Wave Speed: New Model (contd)



Numerical simulations show a minimum speed.

By analogy with scalar reaction−diffusion equations: ?

Outline

Changing Variables in the Travelling Wave Equations

$$\begin{aligned}\left[\frac{U}{U+V}(U'+V')\right]' + c\,U' + U(1-U-V) &= 0\\ \left[\frac{V}{U+V}(U'+V')\right]' + c\,V' + V(\gamma-U-V) &= 0\end{aligned}$$

This is a third order system. Reformulating in terms of

$$N = U+V-1 \quad Y = V/(U+V) \quad \Omega = -N'/(1+N) = (U'+V')/(U+V)$$

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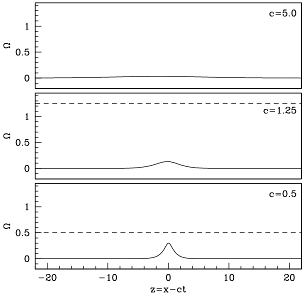
$$\begin{aligned}\Rightarrow dN/dz &= -\Omega(1+N)\\ dY/dz &= -(\gamma-1)Y(1-Y)/(c-\Omega)\\ d\Omega/dz &= \Omega(\Omega-c)+(\gamma-1)Y-N\end{aligned}$$

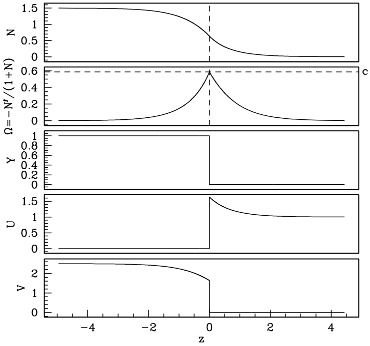
Explaining the Minimum Speed (I)

We have $dY/dz = -(\gamma - 1)Y(1 - Y)/(c - \Omega)$
This equation has a singularity if $\Omega_{max} > c$



Explaining the Minimum Speed (II)

This suggests that c_{min} is determined by the equation $c = \Omega_{max}(c)$



Calculating the Minimum Speed (I)

Take the Y-transition to be at $z = 0$.
Then to find the minimum speed, we must solve $c = \Omega(z = 0; c)$ where

$$\begin{aligned} dN/dz &= -\Omega(1+N) \\ d\Omega/dz &= \Omega(\Omega - c) + (\gamma - 1)Y - N \\ \text{with} \quad Y &= 1 \text{ for } z < 0 \\ \text{and} \quad Y &= 0 \text{ for } z > 0\,. \end{aligned}$$

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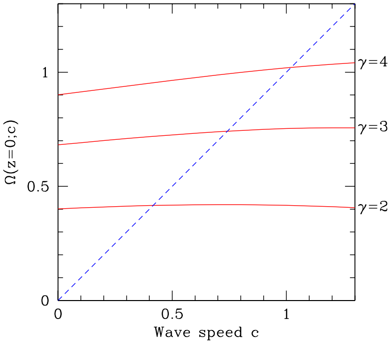
Numerical solution: shooting from $z = 0$ is very laborious.
Easiest to take N as the independent variable.

Calculating the Minimum Speed(II)

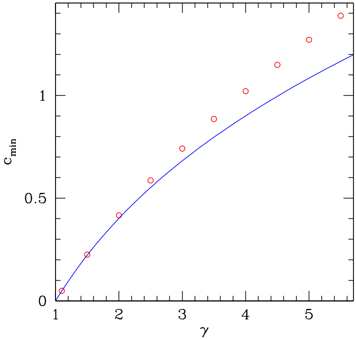
Equation to solve:

$c_{min} = \Omega(z = 0; c_{min})$

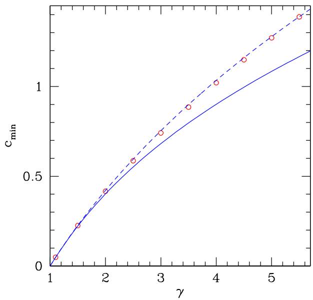


Analytical approx:

$c_{min} \approx \Omega(z = 0; c = 0)$



Calculating the Minimum Speed (III)



The approximation is significantly improved by taking

$$
\begin{aligned}
N(z;c) &= N_0(z) + c\,N_1(z) + \color{red}{O(c^2)} \quad \color{red}{\textit{neglect}} \\
\Omega(z;c) &= \Omega_0(z) + c\,\Omega_1(z) + \color{red}{O(c^2)} \quad \color{red}{\textit{neglect}}
\end{aligned}
$$

Calculating the Minimum Speed (IV)

$$c_{min} \approx \frac{\xi\sqrt{1+2\xi/3}}{\left\{1+\xi-\xi\sqrt{1+2\xi/3}\cdot[\mathcal{R}(\xi)\Upsilon+\mathcal{S}(\xi)-\Upsilon/(1+\xi)]\right\}}$$

where

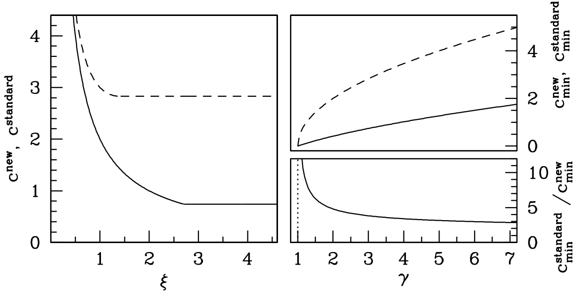
$$\Upsilon = \left[\gamma^{-1/2}\mathcal{S}\left(\frac{\xi-\gamma+1}{\gamma}\right)+\mathcal{S}(\xi)\right] \Big/ \left[\gamma^{-1}\mathcal{R}\left(\frac{\xi-\gamma+1}{\gamma}\right)-\mathcal{R}(\xi)\right]$$

$$\mathcal{R}(\xi) = (1+\xi)/(\xi(1+\tfrac{2}{3}\xi))$$

$$\mathcal{S}(\xi) = \frac{3}{5\xi^2}\left[(\xi-1)(1+\tfrac{2}{3}\xi)^{1/2}+(1+\tfrac{2}{3}\xi)^{-1}\right]$$

$$\xi = \sqrt{(\gamma^2+\gamma+1)/3}-1$$

Comparison of the Wave Speeds in the Two Models



$$\text{Recall: } c^{standard}_{min} = 2\sqrt{\gamma - 1}$$

$$\text{Approx soln} \Rightarrow c^{new}_{min} \sim \tfrac{1}{2}(\gamma - 1) \quad \text{as} \quad \gamma \to 1^{+}$$

$$\text{and} \quad c^{new}_{min} \sim 0.825\sqrt{\gamma} \quad \text{as} \quad \gamma \to \infty$$

Outline

Conclusion

The standard model over-estimates the expansion rate of the mutant cell population by a factor that is at least 2.4, and is much higher when the mutation is slight.

Experimental Testing of the New Model

- Test model predictions experimentally.
- (*Better*). Relate the functions $A(.)$ and $B(.)$ to cell properties that can be measured experimentally. This can be done using either transition probabilities or a velocity jump approach.

Open Mathematical Questions

- Can results on wave front existence and speed be proved for the new model?
- What is the appropriate form of the new model when the mutation affects cell movement?
- What is the behaviour of reaction-diffusion systems with the new motility term but different kinetics?