Modeling keratinocyte wound healing dynamics

cell-cell adhesion promotes sustained collective migration

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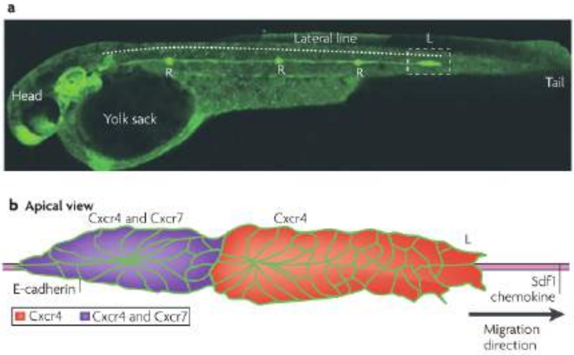
Outline

1. Introduction
2. Experiments and Model Development
3. Results
4. Conclusions and future work

Collective migration is ubiquitous in biology

Collective migration: The coordinated migration of a population of cells

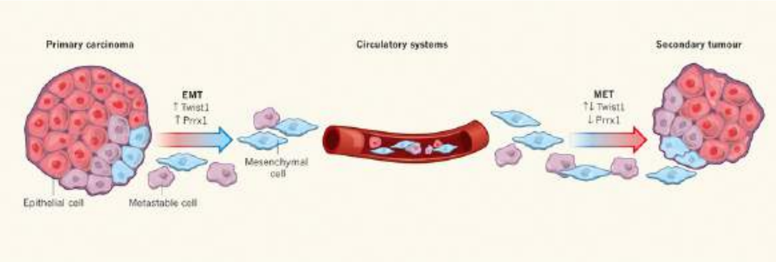


Developmental biology

(Nature Reviews. 2009. July (10))

Collective migration is ubiquitous in biology

Collective migration: The coordinated migration of a population of cells

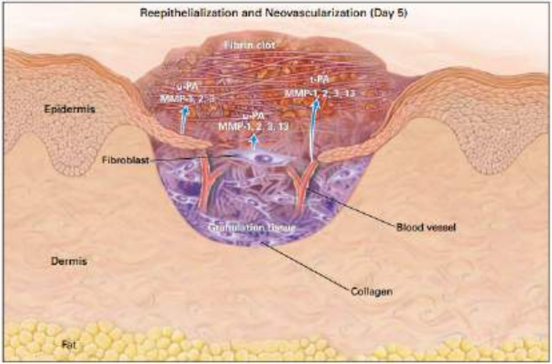


Tumorigenesis

(Nature 493, 487–488, 2013)

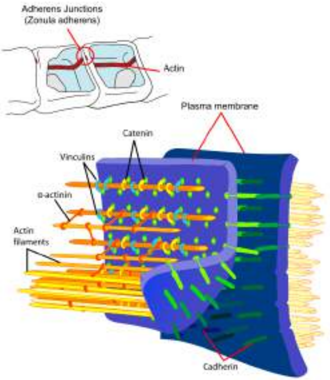
Collective migration during wound healing

Physically connected keratinocyte sheets migrate into the wound during wound healing



(NEJM 341.10, 1999: 738-746)

Cell-cell adhesion connects adjacent keratinocytes



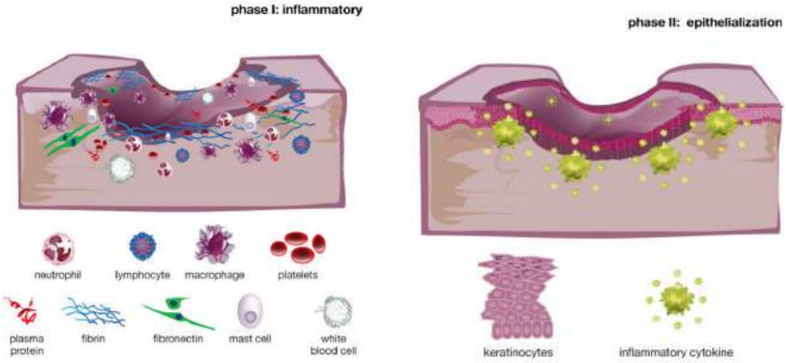
(J Biol Chem. 2006 Nov 24; 281(47):

35593–35597)

How does cell-cell adhesion affect collective migration during wound healing?

Outline

Epidermal growth factor (EGF) stimulates migration

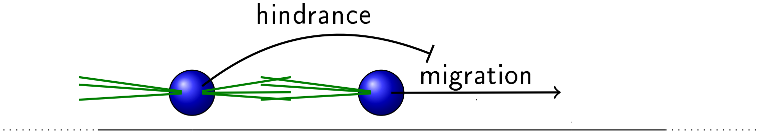


Video1

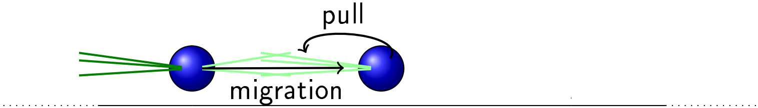
(http://atitesting.com)

Two models to investigate the role of cell-cell adhesion

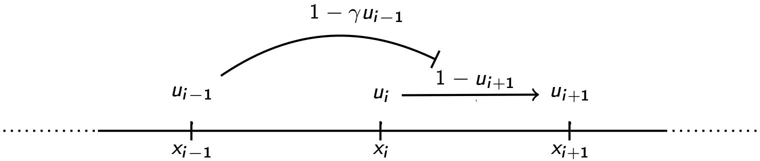
Model H: cell-cell adhesion *hinders* migration into wound (dragging force)



Model P: cell-cell adhesion *promotes* migration into wound (pulling force)



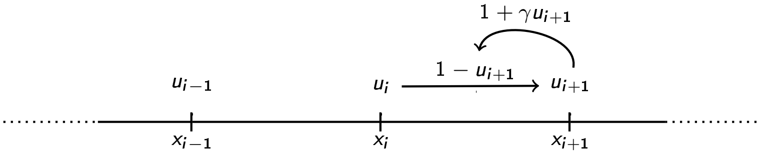
Model H: cell-cell adhesion *hinders* migration into wound



$$\begin{aligned} \tau_i^+ &= \text{Rate from } u_i \text{ to } u_{i+1} \\ &= \text{space filling} \cdot \text{cell drag} \\ &= D\frac{1 - u_{i+1}}{\Delta x} \cdot \frac{1 - \gamma u_{i-1}}{\Delta x} \end{aligned}$$

D	Rate of cell diffusion
γ	Rate of cell-cell adhesion

Model P: cell-cell adhesion *promotes* migration into wound



$$
\begin{aligned}
\tau_i^+ &= \text{Rate from } u_i \text{ to } u_{i+1} \\
&= \text{space filling} \cdot \text{cell pull} \\
&= D\frac{(1-u_{i+1})}{\Delta x} \cdot \frac{(1+\gamma u_{i+1})}{\Delta x}
\end{aligned}
$$

D	Rate of cell diffusion
γ	Rate of cell-cell adhesion

Resulting nonlinear diffusion models

The continuum limit is derived as

$$\frac{du_i}{dt} = \underbrace{\tau_{i-1}^{+} u_{i-1} + \tau_{i+1}^{-} u_{i+1}}_{\text{flux into } x_i} - \underbrace{(\tau_i^{+} + \tau_i^{-}) u_i}_{\text{flux out of } x_i}$$

which leads to

$$\begin{aligned} u_t &= ((D + 3\gamma(u - 2/3)^2 - 4/3\gamma) u_x)_x & \text{Model H} \\ u_t &= ((D + \gamma u^2) u_x)_x & \text{Model P} \end{aligned}$$

Time-dependent rates of cell-cell adhesion

Model H:

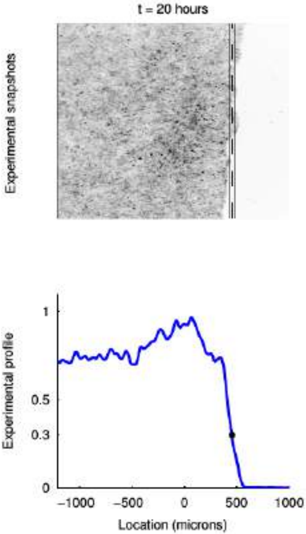
$$\begin{aligned} u_t &= ((D + 3\Gamma(t)(u - {}^2\!/_3)^2 - {}^4\!/_3\Gamma(t))u_x)_x, \\ \Gamma(t) &= \gamma_1 + \gamma_2(1 - t/t_{final}) \end{aligned}$$

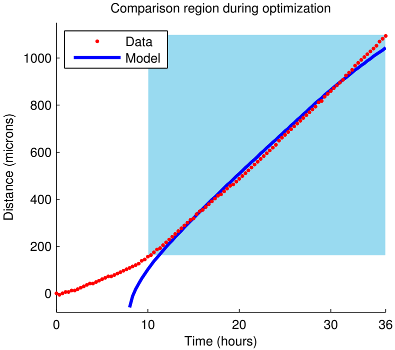
Model P:

$$\begin{aligned} u_t &= ((D + \Gamma(t)u^2)u_x)_x, \\ \Gamma(t) &= \gamma_1 + \gamma_2 t/t_{final} \end{aligned}$$

Parameters	
D	Rate of cell diffusion
γ_1	Baseline rate of cell-cell adhesion
γ_2	Time-dependent rate of cell-cell adhesion

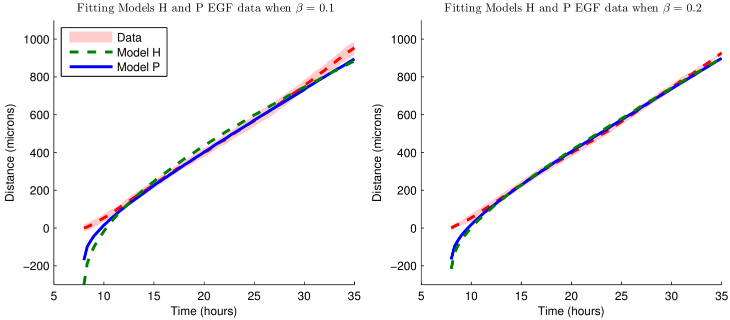
Inverse problem methodology





Outline

Both models can match leading edge data



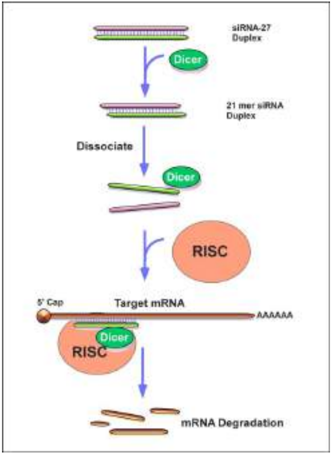
Video2

Model P is robust to leading edge definitions

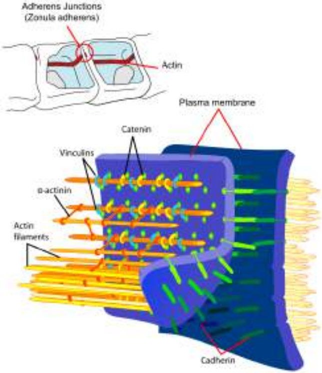
β	Model H		
	$\hat{D}$	$\hat{\gamma}_1$	$\hat{\gamma}_2$
0.1	32400 ± 1100	13100 ± 200	10300 ± 700
0.2	73100 ± 2700	20500 ± 600	32900 ± 1500
0.3	144800 ± 9800	7900 ± 700	101700 ± 1100
% change	347%	160%	882%
	Model P		
	$\hat{D}$	$\hat{\gamma}_1$	$\hat{\gamma}_2$
0.1	6 ± 13	38 ± 300	152600 ± 22500
0.2	16 ± 4	53 ± 1500	169900 ± 9400
0.3	13 ± 2	20 ± 400	198900 ± 12600
% change	146%	165%	30%

Video3

What if we decrease cell-cell adhesion expression?

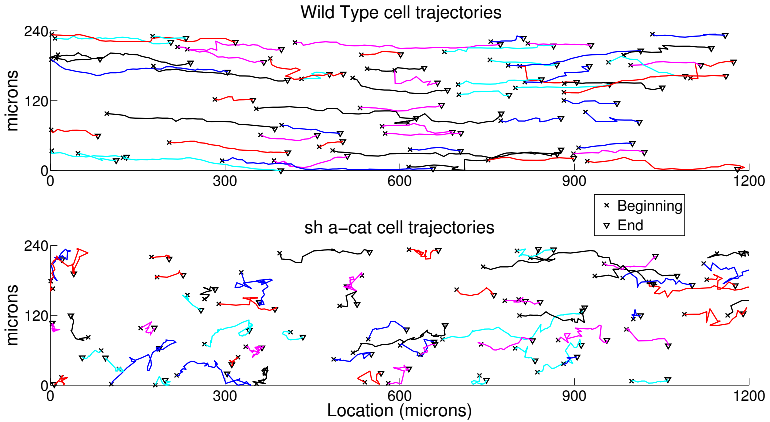


(amsbio.com)

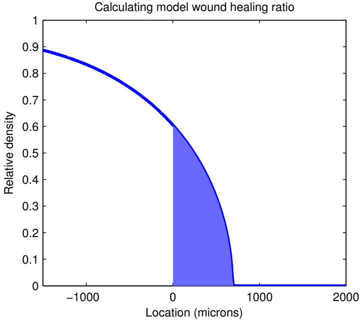


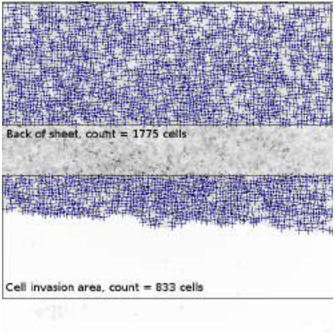
Video4

Knockdown populations exhibit weakened migration



Defining wound healing ratios (WHRs)

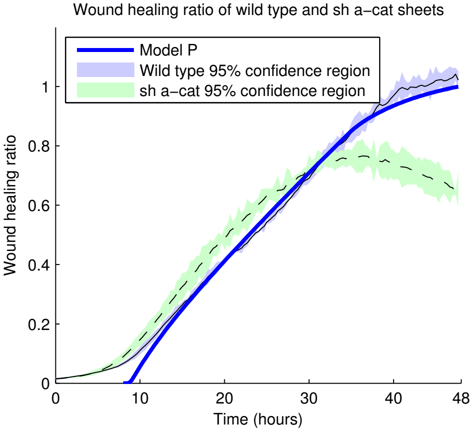




$$\text{WHR} = \int_0^{1200} u(t,x)dx$$

$$\text{WHR} = \frac{\#\ \text{cells in cell invasion area}}{\text{confluent cell count}}$$

Knockdown experiments do not properly heal



Outline

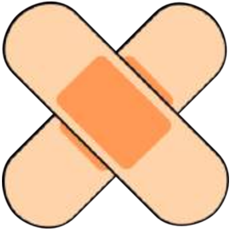
Conclusions

- Model P provides robust and accurate matches to data
- Cell populations with decreased physical connections show
  - slightly faster migration at front of sheet
  - decreased population-wide migration

During wound healing, keratinocytes primarily use cell-cell adhesion to pull other cells forward to promote collective migration

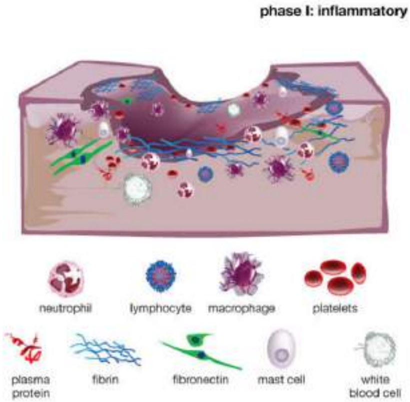
EGF as potential therapy for chronic wounds

- Chronic wounds do not properly heal
  - Foot ulcers are common in diabetic patients
- Clinical EGF trials have been ineffective
  - Can we take advantage of cell-cell adhesions?



Future work: more complex models of wound healing

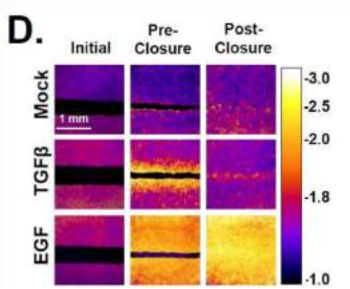
- Inclusion of cell-substrate adhesion (active transport)
- Interaction of different cell types, growth factors



(http://atitesting.com)

Future work: biochemically-structured population models

EGF treatment activates the mitogen-activated protein kinase signaling cascade



(Liu Lab, unpublished)

$$u_t + (g(m)u)_m = D(m)u_{xx} + \lambda(m)u(1-u)$$

where $u = u(t, x, m)$

- Traveling waves
- Nonautonomous dynamical systems

Publications

1. **J. Nardini**, D.A.C., X. L., D.M.B. Modeling keratinocyte wound healing dynamics: cell-cell adhesion promotes sustained collective migration. *J. Theor. Biol.*, 7 July 2016, 103-117.
2. K.A., R. B., K. F., **J. Nardini**, H.T.B., W.C.T. Correlation of parameter estimators for models admitting multiple parameterizations. *I.J.P.A.M.*, 105(3) 497, 2015.
3. T. H., K. L., **J. Nardini**, L.P., K.F, H.T.B., B.B., J.J., J.D. A mathematical model of RNA3 recruitment in the replication cycle of brome mosaic virus. *I.J.P.A.M.*, 92(1) 27, 2014.
4. H.T.B., A.C., T.H., **J. Nardini**, L.P., W.C.T. Quantifying CFSE label decay in flow cytometry data. *Appl. Math. Lett.*, 26(5) 571, 2013.

Thank you!

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- Members of the Bortz lab

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Questions?