Modeling crawling cell movement

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1 Video from: A Video Tour of Cell Motility, http://cellix.imba.oeaw.ac.at/

- several moving cells
- Top left: mouse fibroblasts moving into an artificial wound (total video time: 3h)
- Bottom left: chick fibroblasts (total video time: 2h)
- Top right: mouse melanoma cell (total video time: 20min)
- Bottom right: trout epidermal keratocyte (total video time: 4min)
2D cell shape modeled by phase field $\rho(x, y, t)$

- $\rho = 1$: cell, $\rho = 0$: no cell
- we neglect variations in height of cell
- nucleus rolls behind the lamellipodium front

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2 Image from: F. Ziebert and I. S. Aranson, PLOS ONE, 8, e64511.
3 Video from: A Video Tour of Cell Motility, http://cellix.imba.oeaw.ac.at/
Actin cytoskeleton

- cell crawling is driven by the continuous reorganization and turnover of the actin cytoskeleton
- two functions
  - protrusion by polymerization
  - contraction by interaction with myosin
- modeled by average actin orientation field $\mathbf{p} = \left( \begin{array}{c} p_x(x, y, t) \\ p_y(x, y, t) \end{array} \right)$. 


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Adhesion sites

- adhesion sites connect the actin network to the substrate
- video: adhesion sites (red)\(^5\)
- modeled by concentration of adhesion sites \(A(x, y, t)\)
- adhesion sites do not move with the cell
- rupture of adhesion sites in the retracting region of the cell

Myosin concentration is high where actin is disassembled and could be modeled by an extra field $m(x, y, t)$ but is eliminated in our model.

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(c) Sites of actin assembly and disassembly

(d) Concentration of myosin

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Traction and substrate displacements

- cell exerts traction forces $\mathbf{T} = \begin{pmatrix} T_x(x, y, t) \\ T_y(x, y, t) \end{pmatrix}$ on substrate
- leads to substrate displacements:\n  $\mathbf{u} = \begin{pmatrix} u_x(x, y, t) \\ u_y(x, y, t) \end{pmatrix}$

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Phase field $\rho(x, y, t)$

- phase field: $\rho = 1$: cell, $\rho = 0$: no cell, $\nabla \rho \neq 0$: cell boundary

$$\partial_t \rho = D_\rho \Delta \rho - (1 - \rho)(\delta - \rho)\rho - \alpha A \mathbf{p} \cdot (\nabla \rho)$$

- $\rho(x) = 1/(1 + \exp(x/\sqrt{D_\rho 2}))$ is a steplike stationary solution for $\delta = 1/2$: Mathematica

- volume conservation by feedback
  - $\langle \rho \rangle =$ volume integral over $\rho$
  - $V_0$: initial volume
  - $\sigma|\mathbf{p}|^2$ models actin network contraction

$$\delta = \frac{1}{2} + \mu (\langle \rho \rangle - V_0) - \sigma|\mathbf{p}|^2$$

- advection of $\rho$ along the actin orientation vector $\mathbf{p}$,
  $\alpha$: propulsion strength
Actin orientation field $p(x, y, t)$

$$\partial_t p = D_p \Delta p - \tau_1^{-1} p - \tau_2^{-1} (1 - \rho^2) p - \beta f(\nabla \rho) - \gamma [\nabla \rho \cdot p] p$$

- nearest neighbour interaction by diffusion $D_p$
- degradation of actin by depolymerization inside ($\tau_1$) and outside ($\tau_2$) of the cell
- actin created by polymerization at the cell front, $f(\kappa) = \frac{\kappa}{\sqrt{1+\epsilon\kappa^2}}$ saturates for large $\kappa$
- reflection symmetry broken due to myosin motors
Myosin concentration $m(x, y, t)$

- actin disassembles where myosin concentration is higher than equilibrium value $m_0$

$$\partial_t p = D_p \Delta p - \tau_1^{-1} p - \tau_2^{-1} (1 - \rho^2) p - \beta f (\nabla \rho) - (m - m_0) p$$

- myosin
  - diffuses with coefficient $D_m$
  - relaxes to $m_0$ with rate $\tau_m$
  - moves along the actin filaments with velocity $V_m$
  - is suppressed near to front of the cell with rate $\bar{\gamma} \nabla \rho \cdot p$

$$\partial_t m = D_m \Delta m - \tau_m^{-1} (m - m_0) + V_m p \cdot \nabla m + \bar{\gamma} \nabla \rho \cdot p$$

- assume $\tau_m \ll 1$

$$m - m_0 \approx \tau_m \bar{\gamma} \nabla \rho \cdot p$$
Concentration of adhesion sites $A(x, y, t)$

$$\partial_t A = D_A \Delta A + a_0 \rho p^2 + a_{nl} \rho A^2 - sA^3 - d(|u|)A$$

- adhesion sites form only if actin is present but independent of actin direction: linear attachment $\sim \rho p^2$
- already formed adhesion complex favors formation of more adhesive contacts nearby: nonlinear attachment $\sim A^2$
- nonlinear detachment $\sim A^3$ locally saturates concentration of adhesion sites
- breakup of adhesion sites if substrate displacement $|u|$ exceeds critical displacement $U_c$: linear step-like detachment rate

$$d(|u|) = \frac{d}{2} \left(1 + \tanh \left[ b \left(u^2 - U_c^2 \right) \right]\right)$$
Substrate model: Kelvin-Voigt material

- stress tensor of 3D incompressible isotropic visco-elastic (Kelvin-Voigt) material
  
  \[
  \sigma_{ik} = \tilde{G}(u_{i,k} + u_{k,i}) + \tilde{\eta}(\dot{u}_{i,k} + \dot{u}_{k,i}) - p\delta_{ik}
  \]

- overdamped motion: \( \ddot{u}_i = 0 \), \( \sigma_{ik,k} = 0 \)

\[
\tilde{G}\nabla^2 u + \tilde{\eta}\nabla^2 \dot{u} = \nabla p, \quad \nabla \cdot u = 0
\]

- lower boundary conditions: \( u(x, y, z = 0, t) = 0 \)
- upper boundary conditions: traction force \( T, H \): height of substrate layer

\[
\sigma_{xz}(x, y, z = H, t) = T_x(x, y, t), \\
\sigma_{yz}(x, y, z = H, t) = T_y(x, y, t), \\
\sigma_{zz}(x, y, z = H, t) = 0,
\]

- periodic boundary conditions in \( x-, y- \) direction with period \( L \)
Substrate model: traction forces $\mathbf{T}(x, y, t)$

- integrate over $z$-direction
- assume height $\ll$ lateral extension: $H \ll L$, expand in $H/L$

$$
\partial_t \mathbf{u} = -\frac{1}{\eta} \left( G \mathbf{u} - \frac{1}{\xi} \left( \mathbf{T} + h \left[ 5 \Delta \mathbf{T} + 19 \nabla (\nabla \cdot \mathbf{T}) \right] \right) \right)
$$

- traction due to actin polymerization: $\mathbf{T}_{pr} = -\xi \rho \mathbf{A}_p$
- traction due to friction: $\mathbf{T}_{fr} = \rho \mathbf{A} \zeta$
- cell does not exert a net force on substrate: determine $\zeta$ by $\langle \mathbf{T}_{pr} + \mathbf{T}_{fr} \rangle = 0$

$$
\mathbf{T} = \xi \rho \mathbf{A} \frac{\langle \mathbf{A} \rho \mathbf{p} \rangle}{\langle \mathbf{A} \rho \rangle} - \xi \rho \mathbf{p}
$$

- for heterogeneous substrate, shear modulus $G$ (stiffness) depends on space

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Figure: Shape of cells in the steady moving regime. Black contour: $\rho = 0.25$. a) Actin orientation field $\mathbf{p}$. b) Traction force $\mathbf{T}$. Red (blue) corresponds to large (small) values of $|\mathbf{T}|$. c) Displacements field $\mathbf{u}$. Red (blue) corresponds to large (small) values of $|\mathbf{u}|$. 
Phase diagram
Propulsion strength $\alpha$ vs. substrate’s shear modulus $G$

Figure: Phase diagram for propulsion strength $\alpha$ vs. substrate’s shear modulus $G$. ● denotes non-moving states, ■ steady moving (gliding) states, ◆ stick-slip motion, ★ wandering bipedal and ▼, ▲ breathing and bipedal modes, respectively.

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Stick-slip motion

- top panel: $y$-component of center of mass (c.o.m.) of upper (red) and lower (green) half of cell
- $x$-component does not show oscillations
- overall c.o.m. (black line) moves in a straight line
- compare with experiment\(^a\)


**Figure:** Cell shape and substrate displacement field.
anti-phase oscillations of c.o.m. $x$- components of upper (red) and lower (green) cell half

in-phase oscillations of $y$- components

c.o.m. (black) also oscillates

compare with experiment 1

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Wandering bipedal

- instability in the propagation direction
- similar behavior found in a simple model for deformable self-propelled particles:
  - drift bifurcation leads from stationary to moving states
  - 2nd bifurcation leads from straight motion to circular motion

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9 T. Ohta, T. Ohkuma, PRL 102, 154101 (2009).

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Durotaxis (cell migration in a stiffness gradient)

Figure: A linear gradient in substrate’s stiffness $G$ in the $y$-direction from $G = 0$ (black) at the bottom to $G = 0.4$ (blue) at the top. The curves show center of mass trajectories for different initial positions. They converge to an optimal value of $G$. 

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Figure: Examples for the behavior of cells colliding with a step in the substrate stiffness (blue: $G = 0.4$, black: $G = 0.05$). The center of mass trajectories are shown in white. Top row: $\alpha = 4 = 2\beta$, bottom row: $\alpha = 4, \beta = 1.5$. Other parameters: $U_c^2 = 0.25$. 
Cell-cell interaction with multiple phase fields

- phase fields \( \rho_i \) for \( N \) cells

\[
\partial_t \rho_i + \alpha A p \cdot \nabla \rho_i = D_\rho \Delta \rho_i - \frac{\partial}{\partial \rho_i} V(\rho_i) - \frac{\partial}{\partial \rho_i} W(\rho_1, \ldots, \rho_N), \quad i = 1, \ldots, N.
\]

- \( V \) : self-interaction

\[
\frac{\partial}{\partial \rho_i} V(\rho_i) = \rho_i (\rho_i - \delta_i)(\rho_i - 1)
\]

- \( W \) : volume (steric) interaction avoids interpenetration of cells

\[
W(\rho_1, \ldots, \rho_N) = \sum_{j,k} W_2(\rho_j, \rho_k)
\]

- two cell pair potential

\[
W_2(\rho_1, \rho_2) = \frac{\lambda}{2} \rho_1^m \rho_2^n
\]

  - large and positive if the two cells overlap
  - zero for no overlap
  - \( W_2 \) does not depend on \( m, n \) in the sharp interface limit \( D_\rho \to 0 \)
  - for \( D_\rho > 0 \) perturbations could lead to \( \rho_i < 0 \) \( \Rightarrow \) choose even exponents \( m = n = 2 \) to avoid attraction

- all other fields are shared between cells. Video. Experiment.\(^{10}\)

\(^{10}\)http://cellix.imba.oeaw.ac.at/

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Figure: The angle of incidence of two cells colliding in a symmetric fashion is larger than their exit angles. White: phase field contours with \( \rho = 0.5 \). Colored: trajectories of colliding cell for different angles of incidence. See video.
Unidirectional collective motion

Figure: Initially, cells move uncorrelated. The alignment mechanism leads to an unidirectional collective motion towards the top left corner. Time is increasing from left to right. Video. Experiment from Phys. Rev. E 74, 061908 (2006).
Coexistence of moving and stationary cells

Figure: Initially moving cells gather in stationary clusters. See video.

Figure: Initially, some cells are moving while some are stationary. Cell-cell collisions set the stationary cells into motion. See video.
Collective rotational motion

Figure: Clockwise rotational motion in a confined medium. Adhesion is larger inside. Video. Experiment (Phys. Rev. E 74, 061908 (2006)).

order parameter $\phi$

$$\phi(t) = \frac{1}{N} \sum_{i=1}^{N} \hat{e}_\theta(t) \cdot \hat{v}_i(t)$$

normalized velocity vector $\hat{v}_i(t) = \frac{v_i(t)}{|v_i(t)|}$ for each cell $i$ is projected onto the unit vector $\hat{e}_\theta$ tangential to a circle.

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Adhesion between cells

- keratocytes are responsible for wound healing ⇒ can build cell monolayers
- cell boundaries located at $\nabla \rho_i$
- adhesion = interaction between cell boundaries: $\nabla \rho_i \cdot \sum_{j \neq i} \nabla \rho_j$

$$\frac{\partial}{\partial t} \rho_i + \alpha A p \cdot \nabla \rho_i + \kappa \nabla \rho_i \cdot \sum_{j \neq i} \nabla \rho_j = D_p \Delta \rho_i - \frac{\partial}{\partial \rho_i} V(\rho_i) - \frac{\partial}{\partial \rho_i} W(\rho_1, ..., \rho_N)$$

- multiple cells with cell-cell adhesion
- increasing adhesion strength $\kappa$ should yield a transition to tissue (= cells sticking firmly together) but gives numerical instabilities instead
- other possibilities:\(^{11}\)

\(^{11}\)Study on multicellular systems using a phase field model, M. Nonomura, PloS one 7, e33501 (2012).
Summary

- phenomenological model for crawling cells based on a reaction-diffusion system
- cells exhibit different modes of movement accompanied by shape changes similar to experiments
  - stick-slip motion
  - bipedal motion
- migration of cells is sensitive to mechanical properties of substrate
- collective motion of multiple cells modeled with interacting phase fields
Outlook

- introduce different adhesion terms to model tissue
- fit model parameters to specific cell types
- avoid breakup of cells
- derive model equations in a more fundamental way as e.g. in (12)

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Modeling crawling cell movement on soft engineered substrates. 

F. Ziebert, S. Swaminathan, and I. S. Aranson.  

F. Ziebert, and I. S. Aranson.  
PLOS ONE, **8**, e64511.


For Further Reading III

Toward a thermodynamically consistent picture of the phase-field model of vesicles: Curvature energy.

Thermodynamically consistent picture of the phase-field model of vesicles: Elimination of the surface tension.

Towards a thermodynamically consistent picture of the phase-field model of vesicles: Local membrane incompressibility.

Phase-field approach to three-dimensional vesicle dynamics.