Mechanical Simulations of cell motility

www.math.ubc.ca/~keshet/MCB2012/
What are the overarching questions?

- How is the shape and motility of the cell regulated?
- How do cells polarize, change shape, and initiate motility?
- How do they maintain their directionality?
- How can they respond to new signals?
- What governs cell morphology, and why does it differ over different cell types?
Types of models

- Fluid-based
- Mechanical (springs, dashpots, elastic sheets)
- Chemical (reactions in deforming domain)
- Level Set methods
- Other (agent-based, filament based, etc)
Representations

- Deforming closed curve with chemistry only on that curve (RD in 1D with periodic BCs)
- Deforming 2D domain with interior biochemistry
- Mechanical (elastic) perimeter
- “Level set” methods
Chemistry only on the perimeter

“Cytosol”

0 2π
Chemistry only on the perimeter

"Cytosol"
Local self-enhancement and long-range inhibition.

Peaks of activator on a periodic 1D domain

http://www.eb.tuebingen.mpg.de/research/emergti/hans-meinhardt/orient.html
• Local activator

\[
\frac{da_i}{dt} = \frac{s_i(a_i^2/b + b_a)}{(s_c + c_i)(1 + s_a a_i^2)} - r_da_i
\]

• Global inhibitor

\[
\frac{db}{dt} = r_b \sum_{i=1}^{n} a_i/n - r_bb
\]

• Local inhibitor

\[
\frac{dc_i}{dt} = b_ca_i - r_cc_i
\]
Chemistry only on the perimeter with deforming curve

“Cytosol”
Example: Neilson et al 2011

- Model of Dictyostelium chemotaxis

What’s put in:

S (attractant signal)
A (pseudopod activator)
B (global inhibitor)
C (local inhibitor)
G (geometric change)
Typical equations:

Activator, Local and Global inhibitors

\[
\begin{align*}
\dot{a} + a \nabla \Gamma \cdot \mathbf{u} &= D_a \Delta_{\Gamma} a + \frac{s(a^2/b + b_a)}{(s_c + c)(1 + s_a a^2)} - r_a a, \\
\dot{b} + b \nabla \Gamma \cdot \mathbf{u} &= D_b \Delta_{\Gamma} b - r_b b + \frac{r_b}{|\Gamma(t)|} \int_{\Gamma(t)} a \, d\mathbf{x}, \\
\dot{c} + c \nabla \Gamma \cdot \mathbf{u} &= D_c \Delta_{\Gamma} c + b_c a - r_c c.
\end{align*}
\]

Signal and tension

- Signal (activation and chemotaxis)
- Noise

\[
s(\mathbf{x}, t) = r_a \left[ (1 + d_r \text{RND}) + R_0 (1 + d_r \text{RND}) \right].
\]

- Cortical tension:
- Retraction rate proportional to local tension (curvature); cell tends to constant area.
Motion:

- Perimeter nodes moved perpendicular to boundary
- Velocity proportional to the local activator
- Retractions governed by the local mean curvature of boundary
- Cell area approx constant with time.
- Use of “level set toolbox” for perimeter integrity.
Results

• Reorient to gradient
• Cell tracks
• Reorientation

Comparison with real cells

- Initial polarization
- Persistent migration
- Pseudopods

Real cells (Dictyostelium)

For movies of the computations and real cells see:

Similar paper from group of Levine

- Simulated cell in shallow gradient
  - Tip splitting in Real cell (top) and simulated cell (bottom)

Force normal to cell membrane

- External field

- Force on membrane:

\[ F_{tot} = f_p(a) - \gamma (\kappa - \kappa_0) - C_1 (A - A_0) - \lambda v \]

Coupled to activator
Springs and dashpots
Crawling nematode sperm

The cell

Lamellipod contains Major Sperm Protein (MSP) polymer and fluid cytosol.
Variation of properties across the cell
2D simulations

Springs and dashpots to represent elastic material with resistance.

See original paper for full image.

Simulation frames

See original paper for images, removed here for copyright reasons

Movies

- http://jcs.biologists.org/content/115/2/367/suppl/DC1
Mechanical boundary simulations: the immersed boundary method
Many models leave out explicit details of actin and myosin. Assume some signal’s activity creates protrusive force.

Retraction

Protrusion

“back”

“front”
Basic ideas

2D cell domain enclosed by an elastic perimeter. Nodes connected by springs.
Immersed boundary:
“Fluid-based computation”

Cell boundary imparts forces on the computational “fluid”, and the “fluid” convects the cell boundary.
Basic idea

- Cell at equilibrium and strained configurations
- Discretize boundary
- Spread the force
- Compute fluid velocity

Figs: Ben Vanderlei
Immersed boundary method: delta-function “forces” at boundary

Inside

Outside

INSIDE

Outside

Inside
“Regularized” (spread) delta functions
Fluid equations

- Navier-Stokes equation (neglects inertial term)
  
  \[ 0 = -\nabla p + \mu \Delta \mathbf{u} + \mathbf{f}(x, t), \]

- Incompressible fluid:
  
  \[ 0 = \nabla \cdot \mathbf{u}, \]
The forces

$$f(x, t) = \int_{\Gamma} F(s, t) \delta(x - X(s, t)) ds,$$

$$F(s, t) = F_{el} + F_{net},$$

Elastic force  protrusive force
The motion of nodes

- The boundary nodes move with the local fluid velocity:

\[ \frac{\partial X}{\partial t} = u(X(s, t), t) \]
Internal signaling causes force

Signaling affects protrusive force

Vanderlei B, Feng J, LEK (2011) SIAM MMS
GTPase Signaling:

- Active and inactive GPAses:

\[
\begin{align*}
  a_t + u \cdot \nabla a &= D_a \Delta a + g(a, b) \\
  b_t + u \cdot \nabla b &= D_b \Delta b - g(a, b),
\end{align*}
\]

\[
g(a, b) = \left( k_0 \frac{\gamma a^2}{K^2 + a^2} \right) b - \delta a.
\]
Protrusion force

Force on perimeter depends on level of signal

\[ F_{net} = h(a)n(s, t). \]
The steps:

1. Compute the force distribution along the cell boundary.
2. Compute the flow field at the boundary marker points.
3. Advect the membrane using the computed velocity.
4. Advect the solution of $a$ and $b$ according to the current fluid velocity.
5. Evolve the solution of $a$ and $b$ according to the reaction-diffusion system.
Some issues and challenges
Challenges to simulations with interior biochemistry

- Edge nodes of boundary become irregularly placed relative to cartesian grid, and time iteration causes effective loss of mass ("leaky boundary")
- If nodes or grid is refined, need interpolation consistent with mass conservation
Approximating diffusion in 1D

- Centered (finite) difference:

\[
\frac{\partial^2 c}{\partial x^2} \approx \frac{c_{i+1,j} - 2c_{i,j} + c_{i-1,j}}{(\delta x)^2}.
\]
Approximating diffusion in 2D

- Centered (finite) difference in 2 directions:

\[
\begin{align*}
(i,j-1) & \quad \quad (i,j) \\
(i,j) & \quad \quad (i+1,j) \\
(i,j+1) & \quad \quad (i-1,j)
\end{align*}
\]
Challenges: The diffusion

- Acceptable:
- Not acceptable
The advection: issues with conservation of mass
Some results
Cell motion:
The shape influences the chemistry

- $t = 0$
- Later
- Later
Cell shape

Mechanics alone

Mechanics and biochem

Protrusion force magnitude

Membrane stiffness
Level Set methods:
A way to represent the free boundary
Level Set Methods

- **Motivation:** How can we represent the evolution of the boundary of such a region?

Level set methods

This is a method that is used to displace the edge of a "cell" in many current simulations.

Define some function $\psi(r)$ such that boundary is a "level set" of that function.
Level set methods

\[ \psi = \text{distance away from the boundary curve.} \]

\[ \psi(r) = 0 \text{ represents the boundary} \]

\[ \psi(r) > 0 \]

\[ \psi(r) < 0 \]
Level Set Methods

Evolving the boundary

The normal vector to any level curve of $\psi$ is given by the gradient:

$$\hat{N} = \frac{\nabla \psi}{|\nabla \psi|}.$$

The motion of boundary assumed to be along normal vectors; velocity $V$ depends on biochemistry and local conditions:

$$\frac{\partial \psi}{\partial t} = -V \cdot \nabla \psi.$$
Typical output

“Level curves of the distance function”

- Figure kindly provided by C Wolgemuth
- Based on Wolgemuth & Zajac J Comp Sci 2009
Two-phase fluids

\( \phi \) = fraction of cytoskeleton,
(1-\( \phi \)) = fraction cytosol

Net cytoplasmic flux, \( J = \)
(net volume is conserved)

\( V_S, V_f = \) veloc of solid and fluid phases

Balance equation:
Conservation of momentum (force balance)

- On fluid fraction:

\[-(1-\phi) \nabla p = \xi_0 (\dot{V}_f - \dot{V}_s)\]

- Similar eqn for solid fraction
Movies

Kindly provided by C Wolgemuth
Actin Polymerization-based models
Protrusion-adhesion at the leading edge
Elastic 2-D sheet ("actin network")
actin-myosin contraction at rear
reaction-diffusion-transport of G-actin
free boundary problem, finite element method
Results:

Figure kindly supplied by Boris Rubinstein
Movies

http://www.math.ucdavis.edu/~mogilner/CellMov.html
3D Cell simulations

Marc Herant* and Micah Dembo
Form and Function in Cell Motility: From Fibroblasts to Keratocytes
Biophysical Journal Volume 98 April 2010 1408–1417

• 2-phase fluid, 3D computation
Mass and momentum conservation

- Volume fractions:
  \[ \theta_n + \theta_s = 1. \]

- Cytoskeleton mass balance:
  \[ \frac{\partial \theta_n}{\partial t} = -\nabla \cdot (\theta_n \mathbf{v}_n) + J. \]

- Fluid momentum balance (neglect inertia):
  \[ -\theta_s \nabla P + \mathcal{H} \theta_s \theta_n (\mathbf{v}_n - \mathbf{v}_s) = 0. \]
Actin polymerization driven by signaling protein

- Signal to actin made at “activated” portion of front edge

\[
\frac{\partial m}{\partial t} = -\frac{m}{\tau_m} + D_m \nabla^2 m,
\]

- \( M \) contributes to actin network source \( J \).
Further

- Assumptions about internal and external stresses (due to forces of network on membrane, etc)
Main conclusions

- Keratocyte vs fibroblast shapes:

- Main difference: % of front edge that polymerizes actin (25% vs 50%)

- Tear-shaped cells (like fibroblasts) tend to lose their tails
Future prospects

- Best to pay attention to the biology
- Look for biologists willing and interested in collaborations
- Use mathematics/physics/computational tools as appropriate
- Read some current papers every week to keep up with what’s new and exciting
Final words:

• Understanding the behaviour and mechanics of cell motion and shape change is still itself an evolving science, with lots of opportunities for math, physics, and computational contributions!

• The field is still wide open for young scientists with quantitative minds..