Mathematical Cell Biology Graduate Summer Course
University of British Columbia, May 1-31, 2012

Leah Edelstein-Keshet

Mechanical Simulations of cell motility

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?

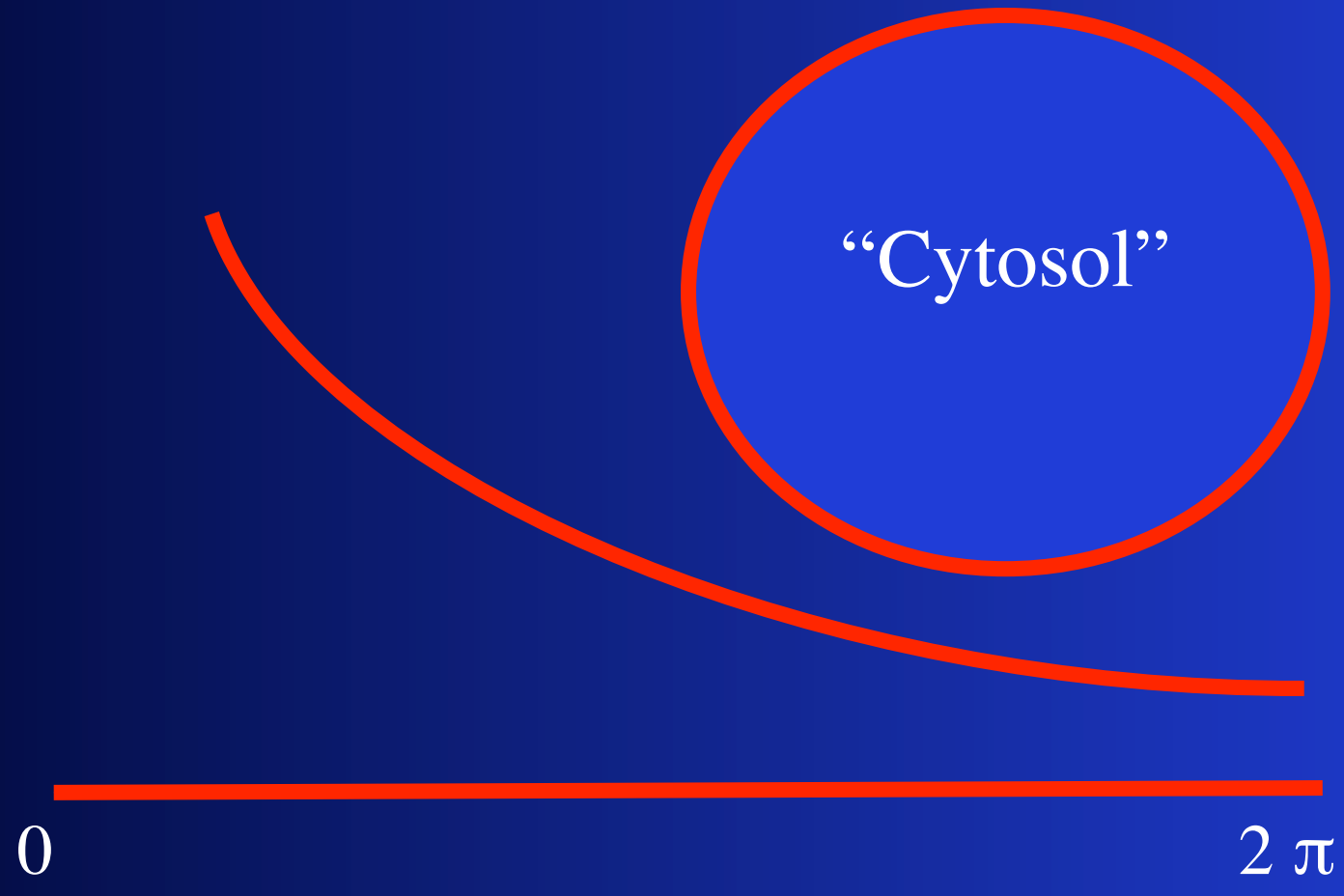
Types of models

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

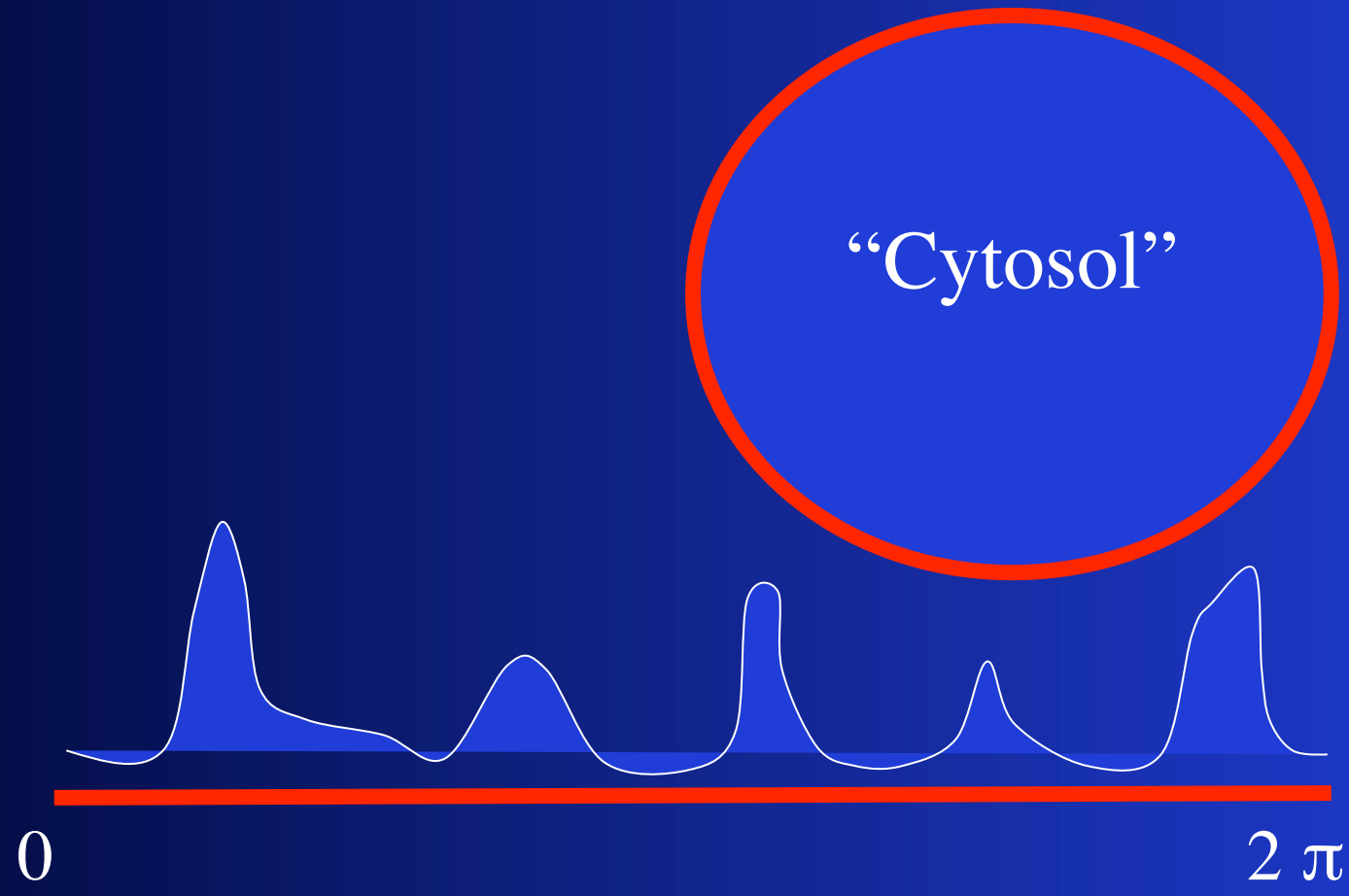
Representations

- 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



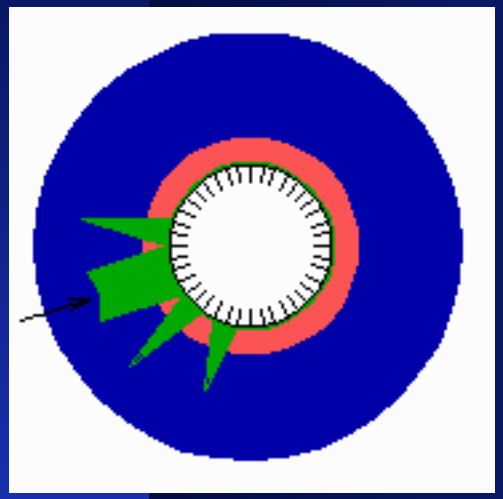
Chemistry only on the perimeter

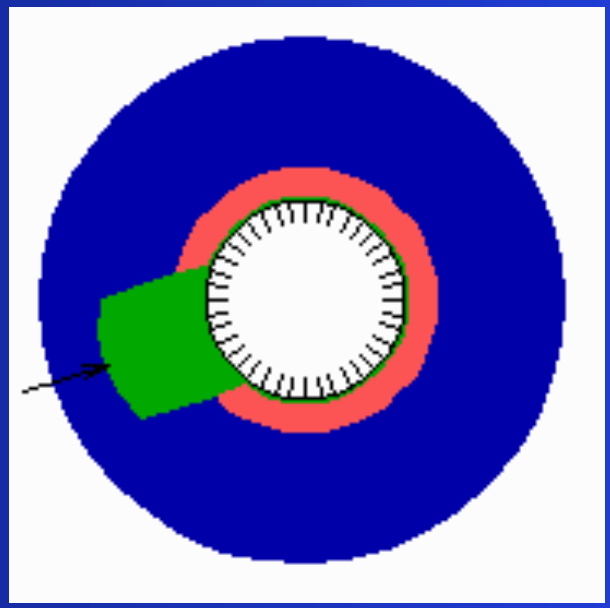


Hans Meinhardt

Local self-enhancement and long-range inhibition.

Peaks of activator on a periodic 1D domain





http://www.eb.tuebingen.mpg.de/research/emeriti/hans-meinhardt/orient.html

Journal of Cell Science 112, 2867-2874 (1999)
Printed in Great Britain © The Company of Biologists Limited 1999
JCS0389

Orientation of chemotactic cells and growth cones: models and mechanisms

Hans Meinhardt

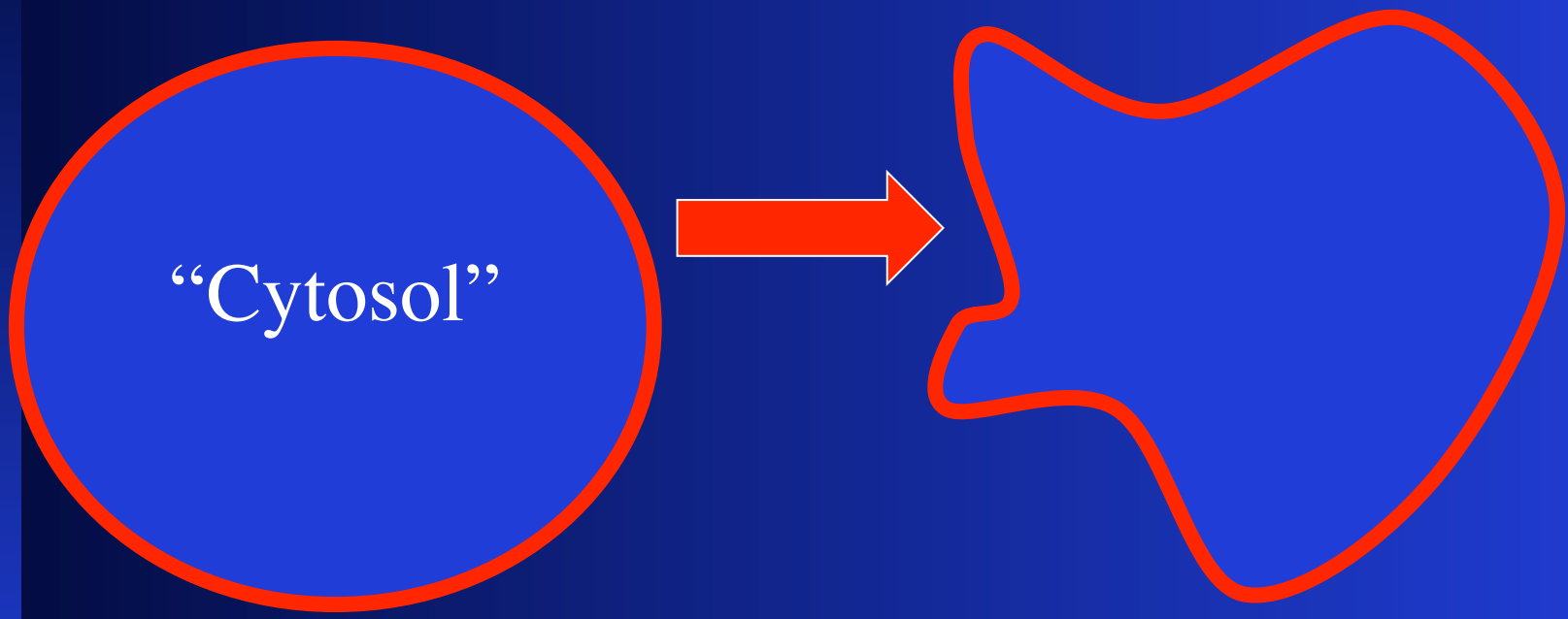
- Local activator
- Global inhibitor
- Local inhibitor

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

$$\frac{db}{dt} = r_b \sum_{i=1}^{n} a_i/n - r_b b$$

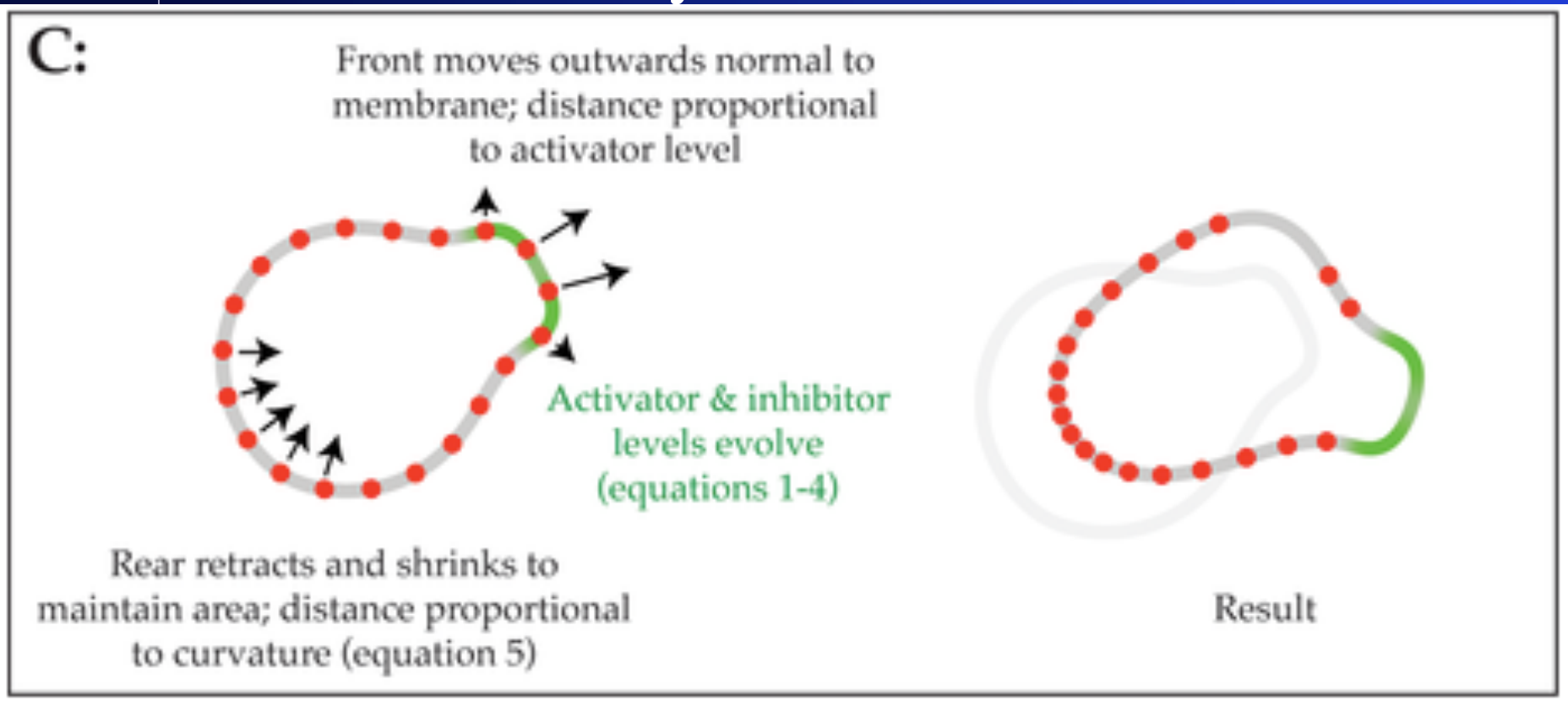
$$\frac{dc_i}{dt} = b_c a_i - r_c c_i$$

Chemistry only on the perimeter with deforming curve



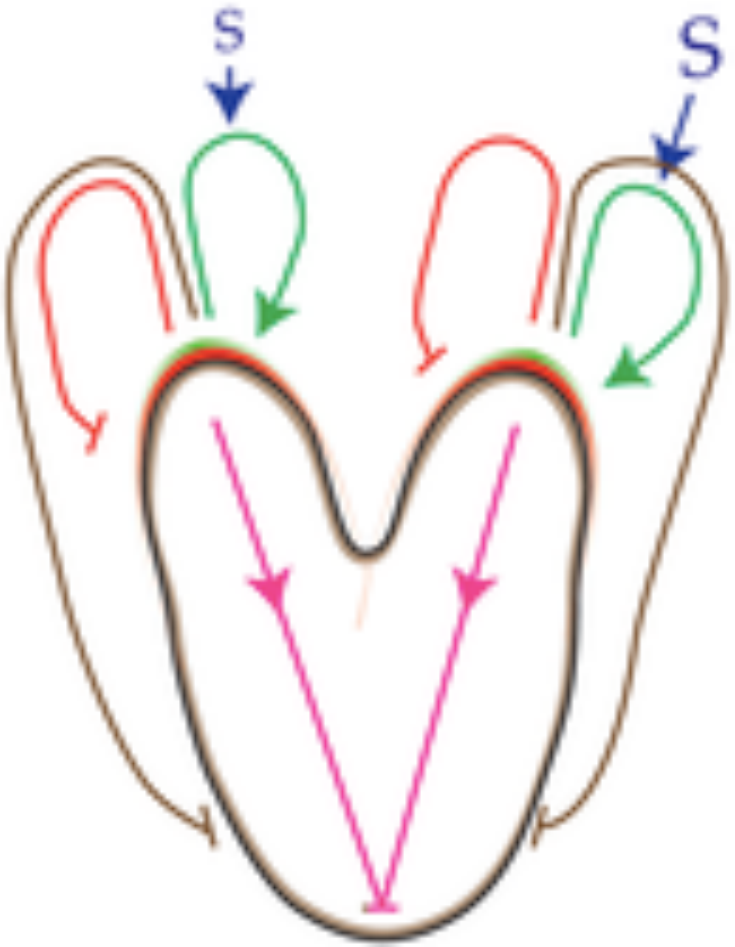
Example: Neilson et al 2011

- Model of Dictyostelium chemotaxis



Neilson MP, Veltman DM, van Haastert PJM, Webb SD, Mackenzie JA, et al. (2011) Chemotaxis: A Feedback-Based Computational Model Robustly Predicts Multiple Aspects of Real Cell Behaviour. PLoS Biol 9(5): e1000618. doi:10.1371/journal.pbio.1000618

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

$$\dot{a} + a\nabla_\Gamma \cdot \boldsymbol{u} = D_a \Delta_\Gamma a + \frac{s(a^2/b + b_a)}{(s_c + c)(1 + s_a a^2)} - r_a a,$$

$$\dot{b} + b\nabla_\Gamma \cdot \boldsymbol{u} = D_b \Delta_\Gamma b - r_b b + \frac{r_b}{|\Gamma(t)|} \oint_{\Gamma(t)} a \, \mathrm{d}\boldsymbol{x},$$

$$\dot{c} + c\nabla_\Gamma \cdot \boldsymbol{u} = D_c \Delta_\Gamma c + b_c a - r_c c.$$

Neilson MP, Veltman DM, van Haastert PJM, Webb SD, Mackenzie JA, et al. (2011) Chemotaxis: A Feedback-Based Computational Model Robustly Predicts Multiple Aspects of Real Cell Behaviour. PLoS Biol 9(5): e1000618. doi:10.1371/journal.pbio.1000618

Signal and tension

- Signal (activation and chemotaxis)
- noise

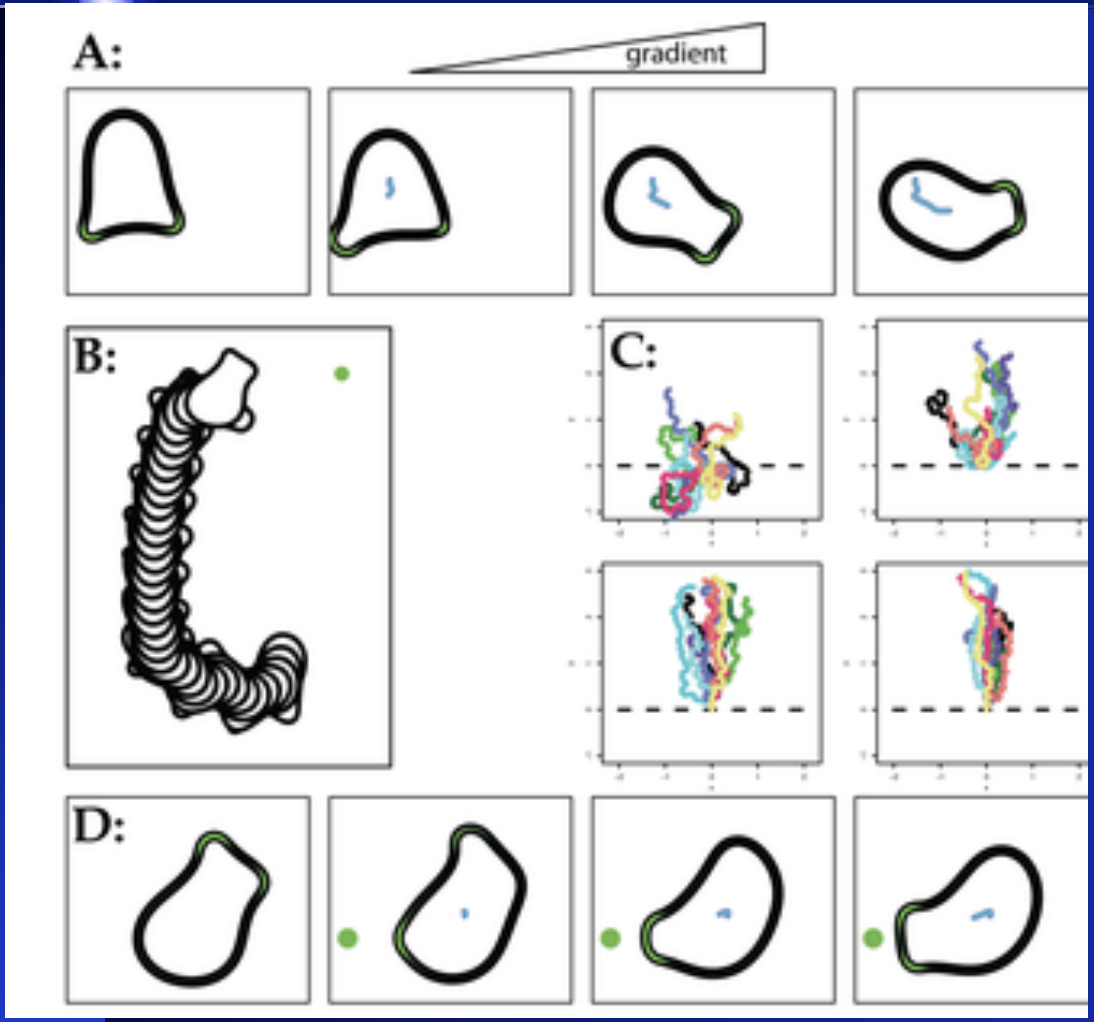
$$s(\boldsymbol{x},t) = r_a[\overbrace{(1+dr\,\mathrm{RND})}^{\text{noisy autocatalytic activation}} + \overbrace{R_o(1+dr\,\mathrm{RND})}^{\text{noisy chemotactic signal}}].$$

- Cortical tension: $\dfrac{d\lambda}{dt} = \dfrac{\lambda_0\lambda(A - A_0 + dA/dt)}{A_0(\lambda+\lambda_0)} - \beta\lambda.$
- 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.

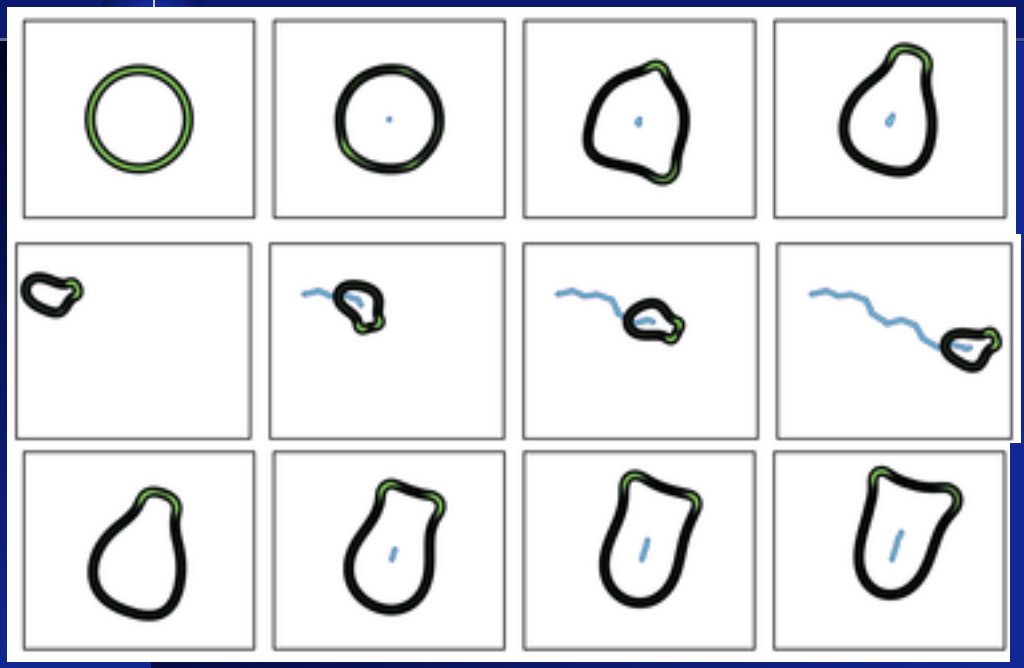
Results



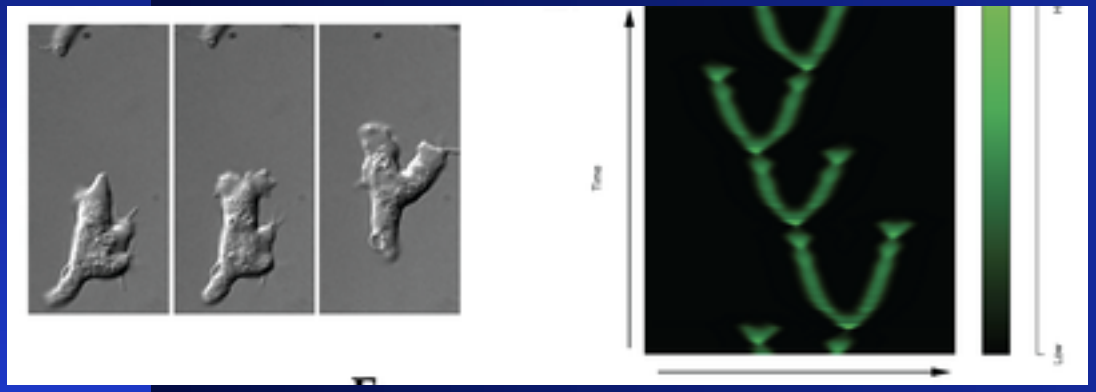
- Reorient to gradient
- Cell tracks
- Reorietation

Neilson MP, Veltman DM, van Haastert PJM, Webb SD, Mackenzie JA, et al. (2011) Chemotaxis: A Feedback-Based Computational Model Robustly Predicts Multiple Aspects of Real Cell Behaviour. PLoS Biol 9(5): e1000618. doi:10.1371/journal.pbio.1000618

Comparison with real cells



- Initial polarization
- Persistent migration
- Pseudopods



Real cells (Dictyostelium)

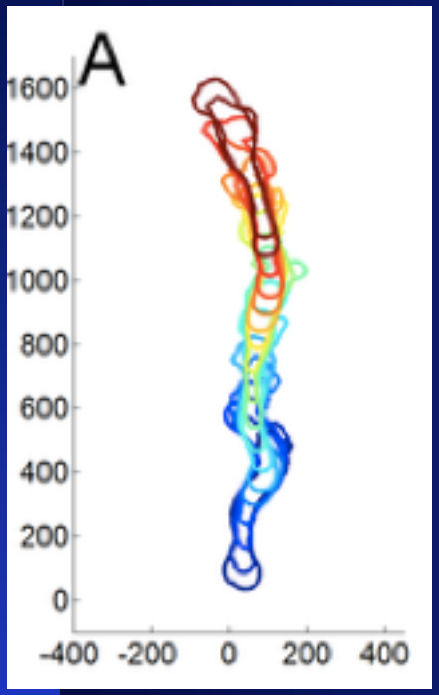
Neilson MP, Veltman DM, van Haastert PJM, Webb SD, Mackenzie JA, et al. (2011) Chemotaxis: A Feedback-Based Computational Model Robustly Predicts Multiple Aspects of Real Cell Behaviour. PLoS Biol 9(5): e1000618. doi:10.1371/journal.pbio.1000618

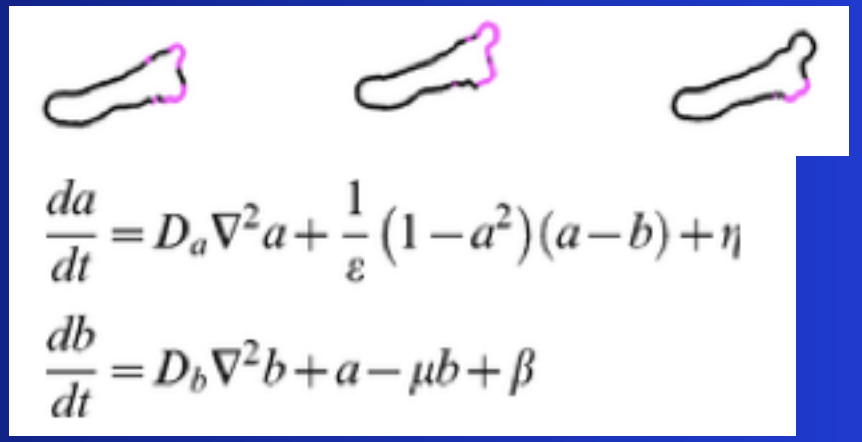
Movies

- For movies of the computations and real cells see:
- Neilson MP, Veltman DM, van Haastert PJM, Webb SD, Mackenzie JA, et al. (2011) Chemotaxis: A Feedback-Based Computational Model Robustly Predicts Multiple Aspects of Real Cell Behaviour. PLoS Biol 9(5): e1000618. doi:10.1371/journal.pbio.1000618

Similar paper from group of Levine

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





$$\frac{da}{dt} = D_a \nabla^2 a + \frac{1}{\varepsilon}(1-a^2)(a-b) + \eta$$

$$\frac{db}{dt} = D_b \nabla^2 b + a - \mu b + \beta$$

Hecht I, Skoge ML, Charest PG, Ben-Jacob E, Firtel RA, et al. (2011) Activated Membrane Patches Guide Chemotactic Cell Motility. PLoS Comput Biol 7(6): e1002044. doi:10.1371/journal.pcbi.1002044

Force normal to cell membrane

- External field $\varphi_{int} = \varphi_{ext} + \eta_{\varphi}$

- Force on membrane:

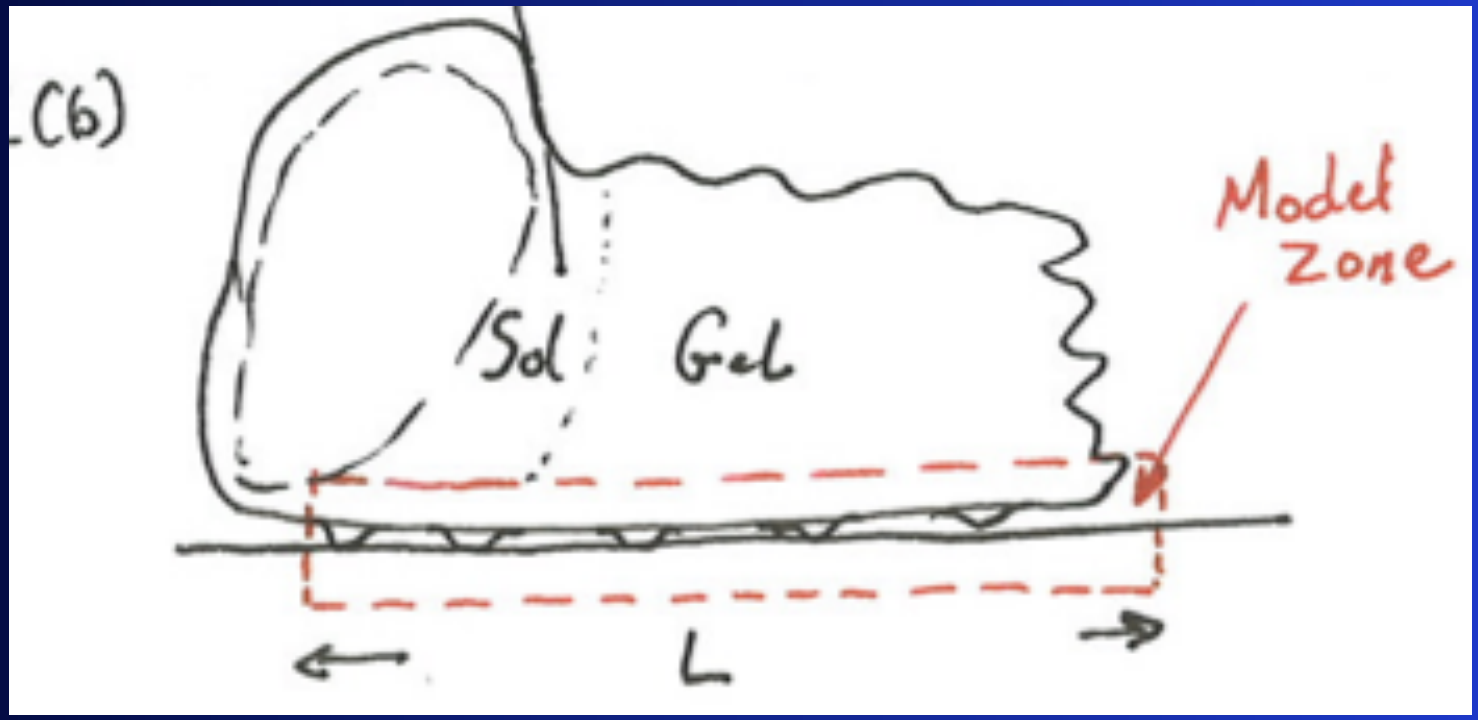
$$F_{tot} = f_p(a) - \gamma(\kappa - \kappa_0) - C_1(A - A_0) - \lambda v$$

Coupled to activator

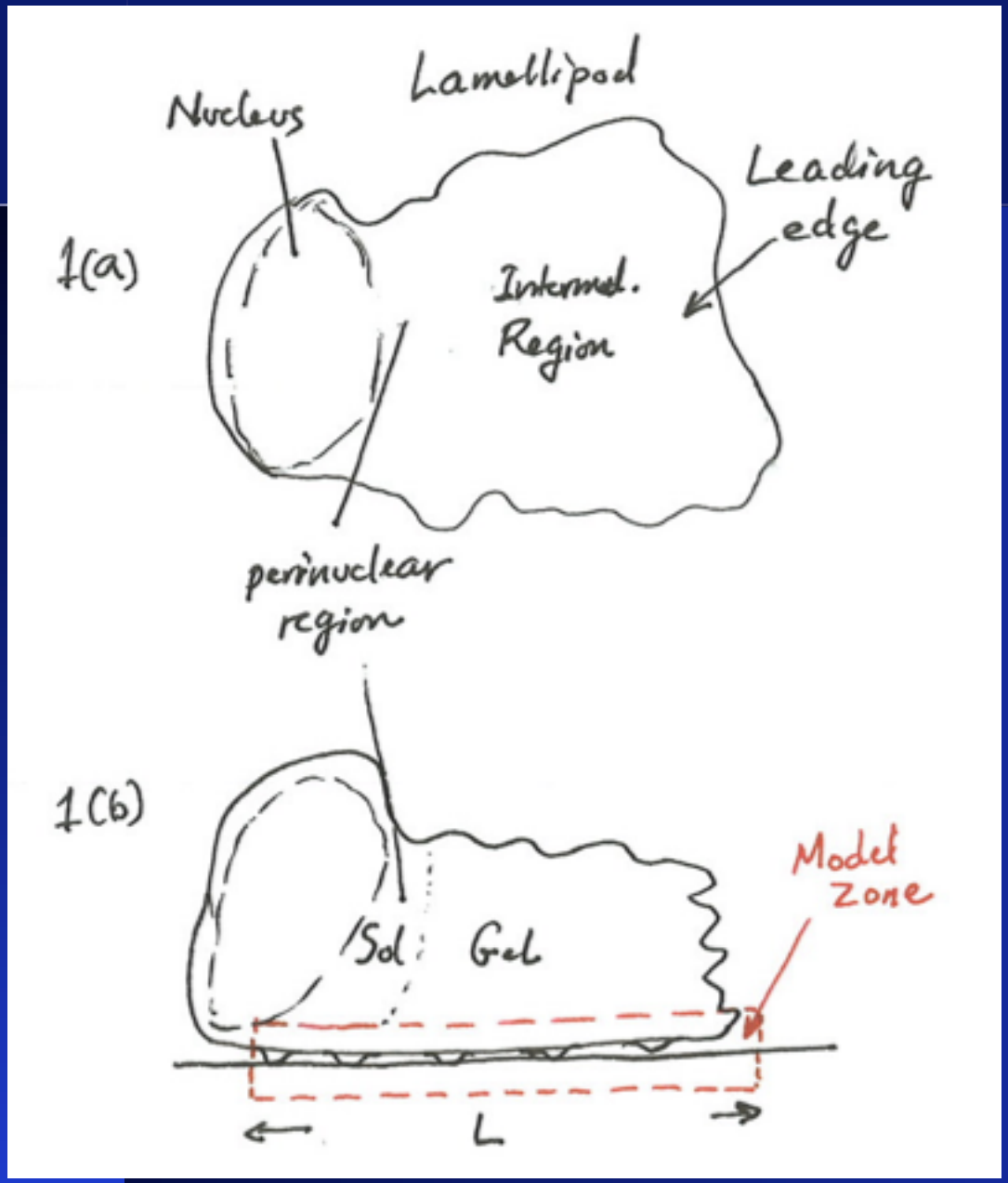
Springs and dashpots

Crawling nematode sperm

Dean Bottino, Alexander Mogilner, Tom Roberts, Murray Stewart, and George Oster (2002) **How nematode sperm crawl,** J Cell Sci 115: 367-384.

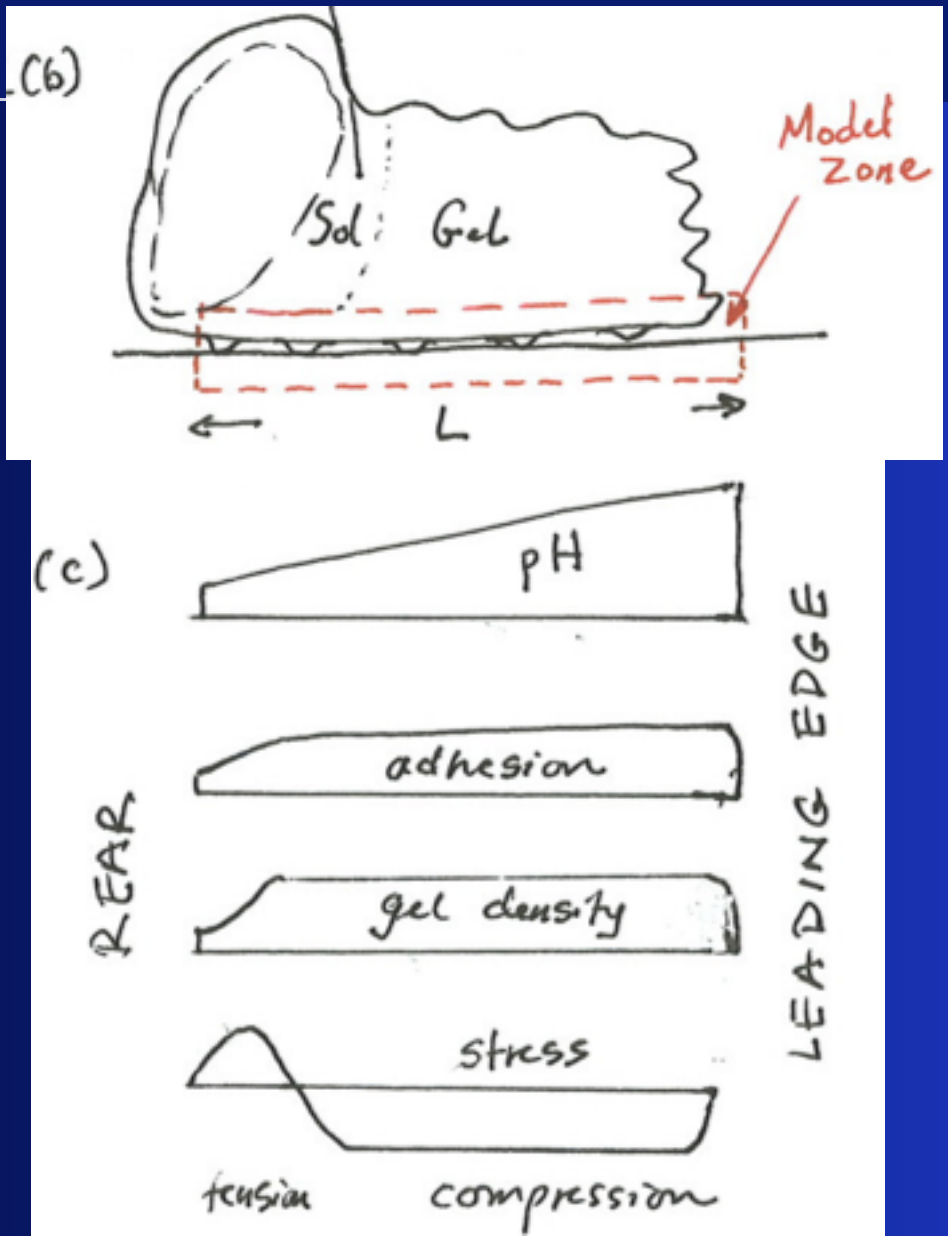


The cell



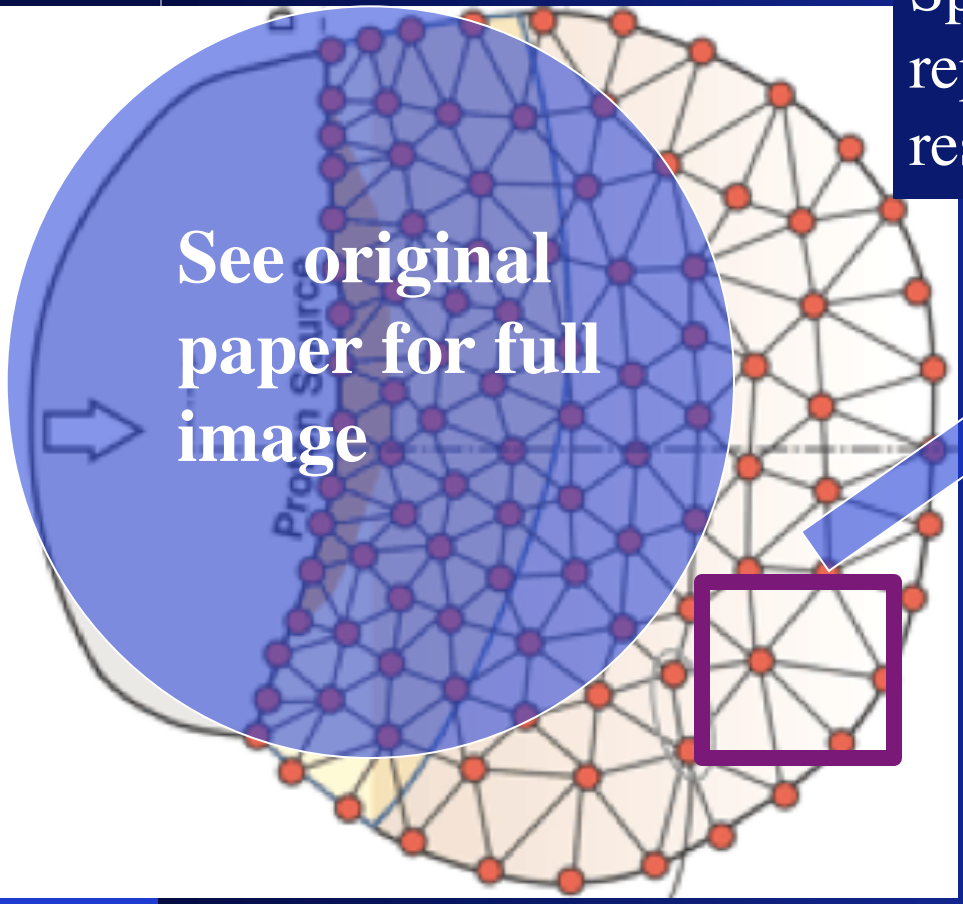
Lamellipod contains Major Sperm Protein (MSP) polymer and fluid cytosol

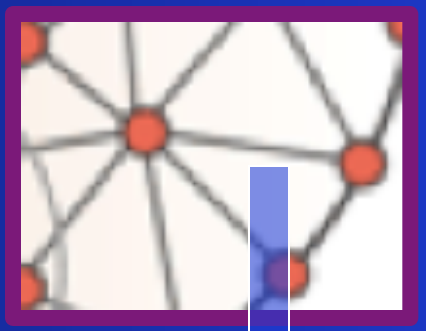
Variation of properties across the cell

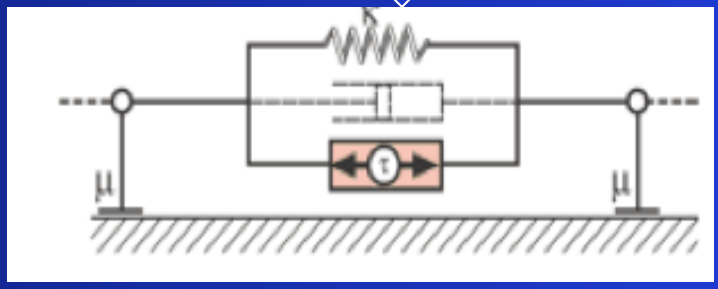


2D simulations

Springs and dashpots to represent elastic material with resistance







Dean Bottino, et al (2002) J Cell Sci 115: 367-384.

Simulation frames

See original paper for images, removed here for copyright reasons

Bottino,et al (2002) J Cell Sci 115: 367-384.

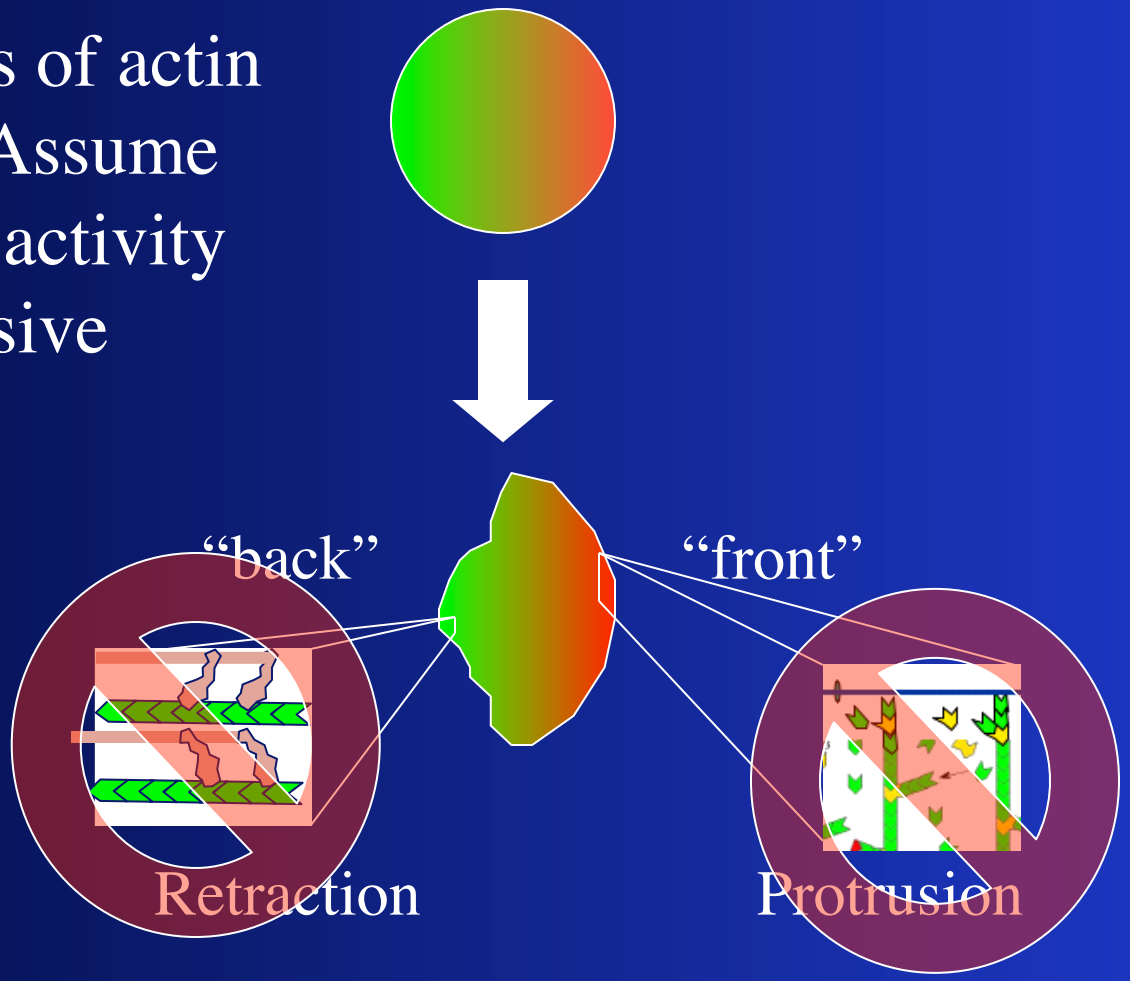
Movies

- http://jcs.biologists.org/content/115/2/367/suppl/DC1

Mechanical boundary simulations: the immersed boundary method

Protrusion and motility

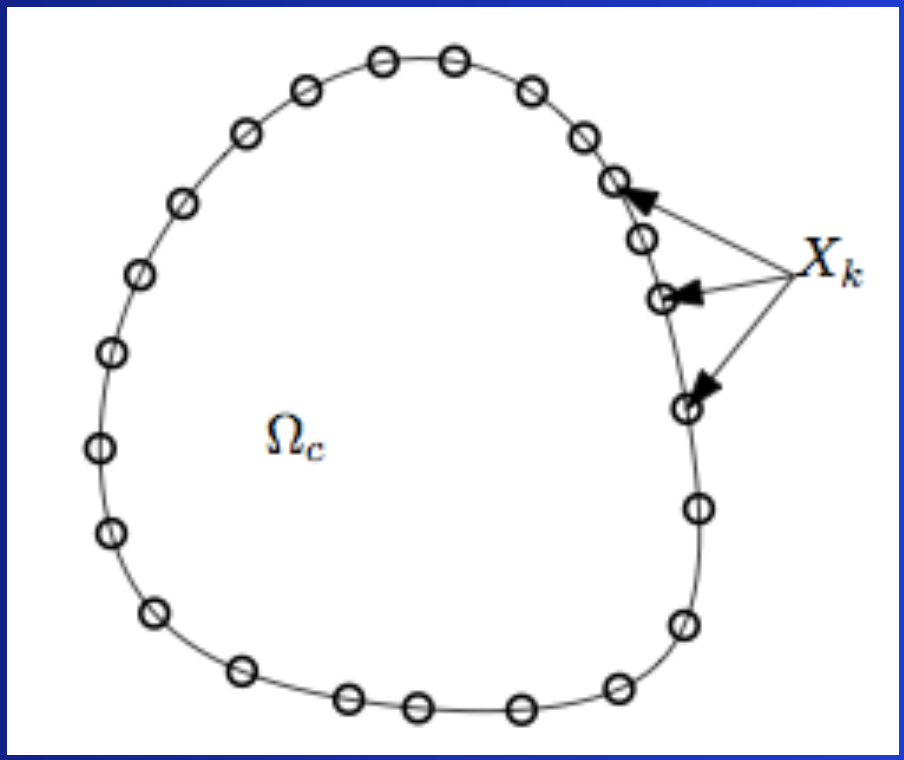
Many models leave out explicit details of actin and myosin.. Assume some signal's activity creates protrusive force.



Basic ideas

B Venderlei, J. Feng, UBC

2D cell domain enclosed by an elastic perimeter. Nodes connected by springs.



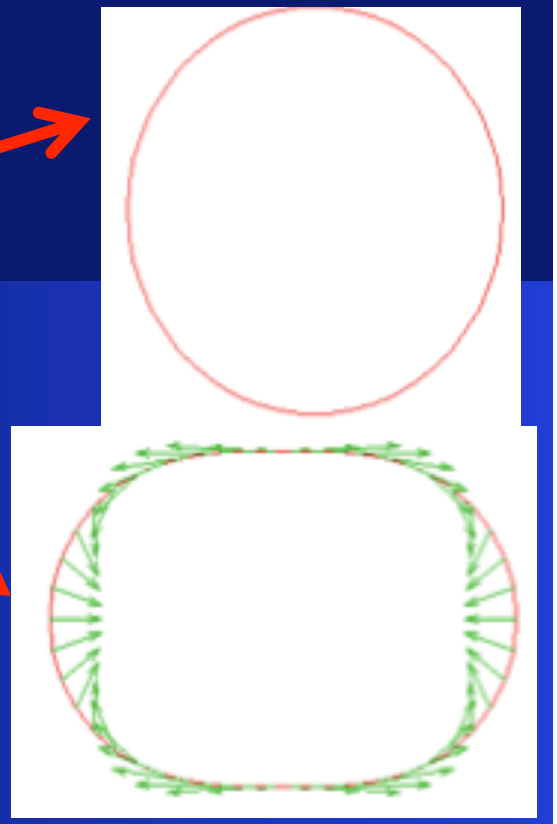
Vanderlei B, Feng J, LEK (2011) SIAM MMS

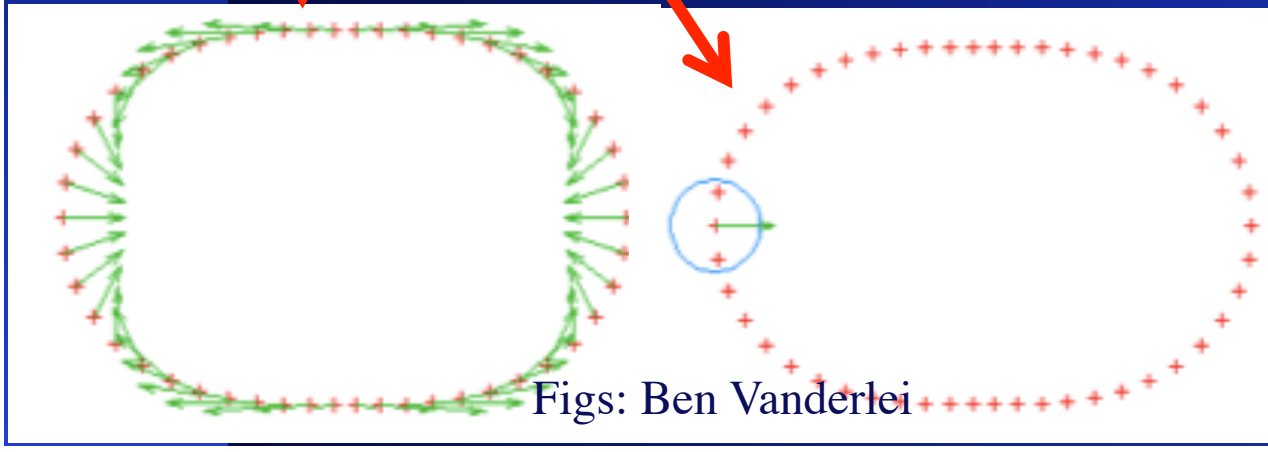
Immersed boundary: "Fluid-based computation"

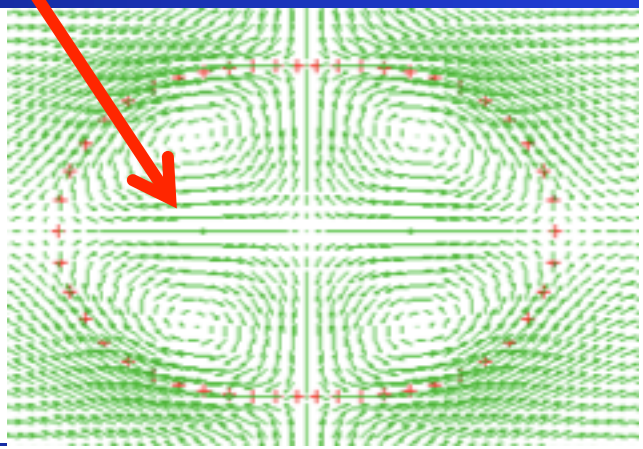
Cell boundary imparts forces on the computational "fluid", and the "fluid" convects the cell boundary.

Basic idea

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

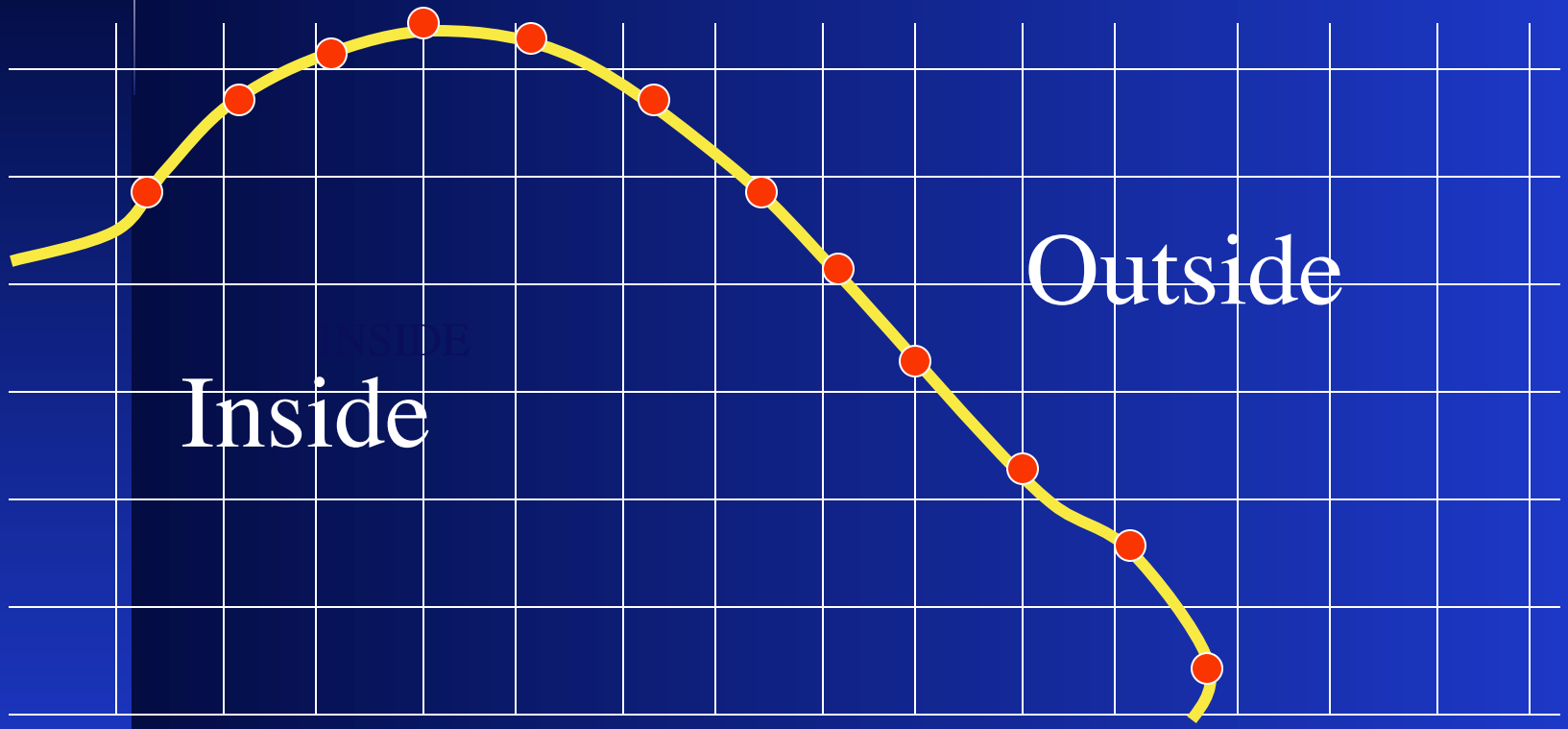




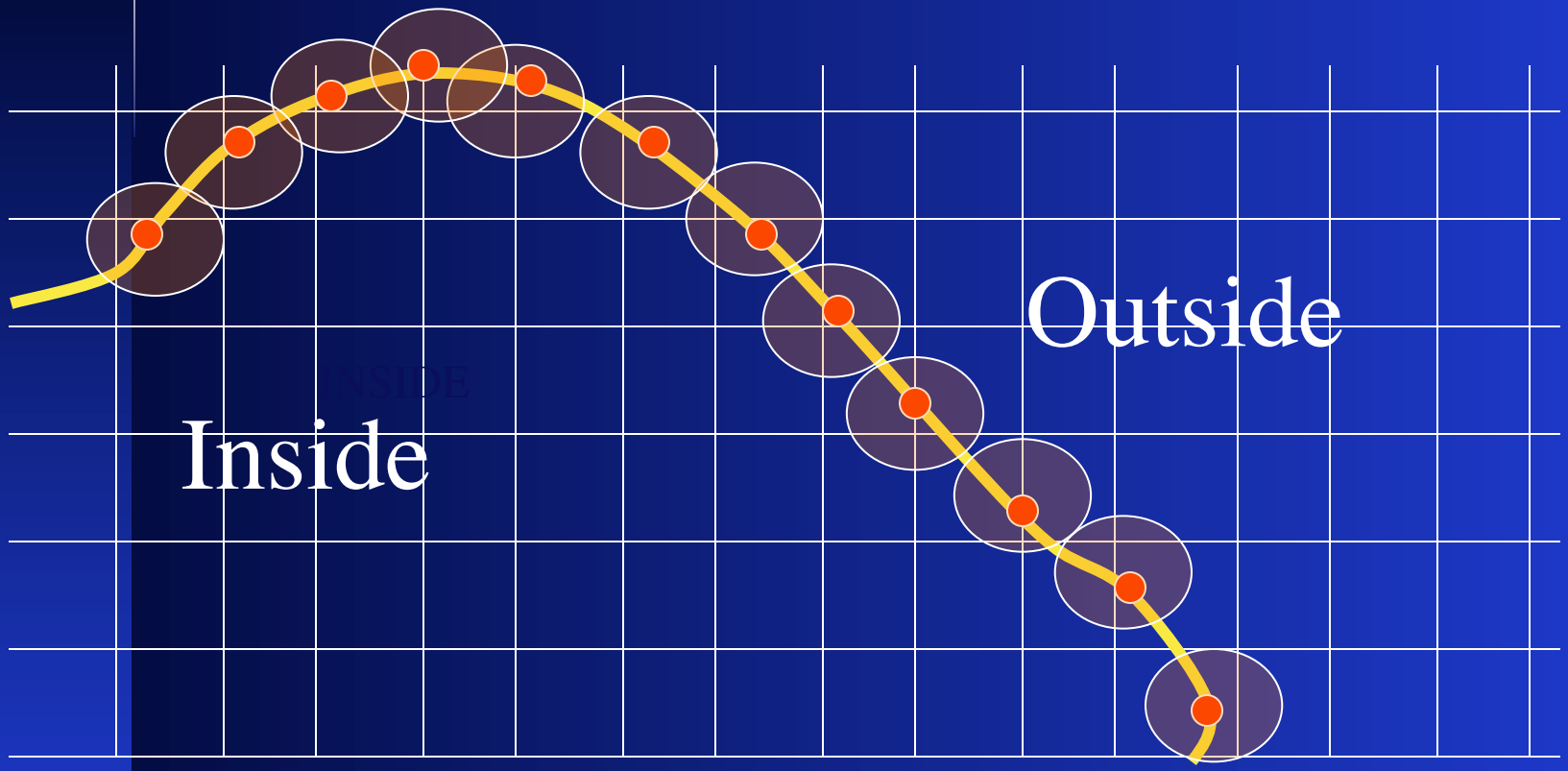


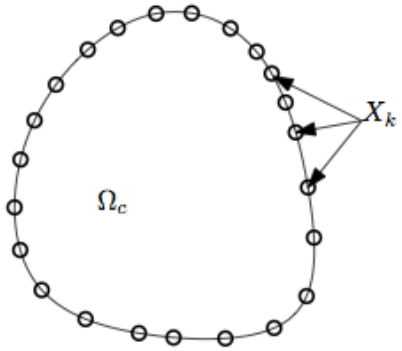
Figs: Ben Vanderlei

Immersed boundary method: delta-function "forces" at boundary



“Regularized” (spread) delta functions





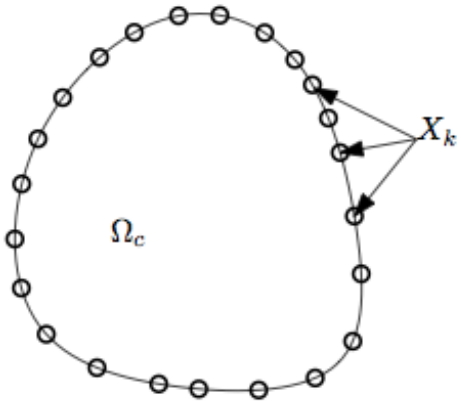
Fluid equations

- 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

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

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

Elastic force *protrusive force*

The motion of nodes

- The boundary nodes move with the local fluid velocity:

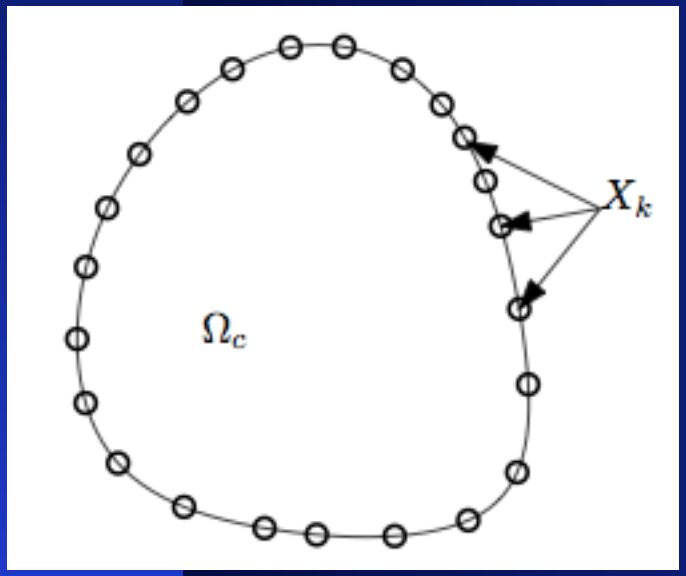
$$\frac{\partial \mathbf{X}}{\partial t} = \mathbf{u}(\mathbf{X}(s,t),t)$$

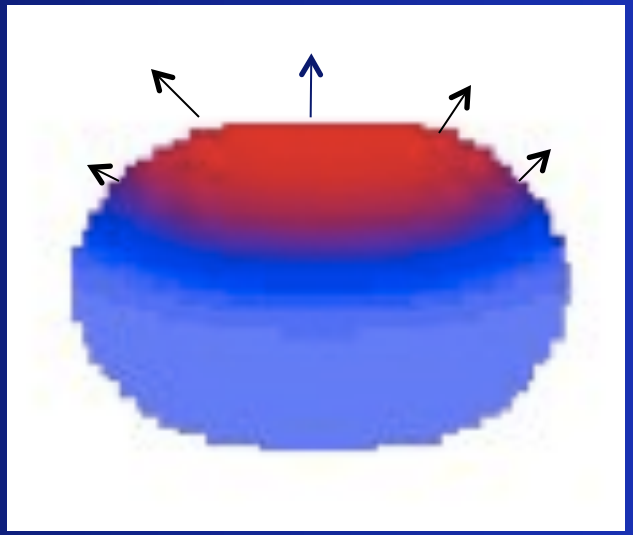
Internal signaling causes force

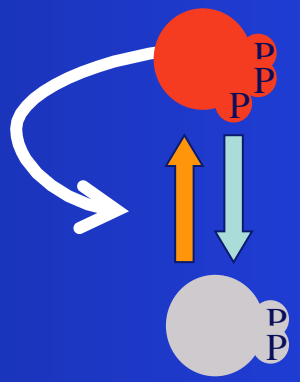
B Vanderlei

J Feng

Signaling affects protrusive force







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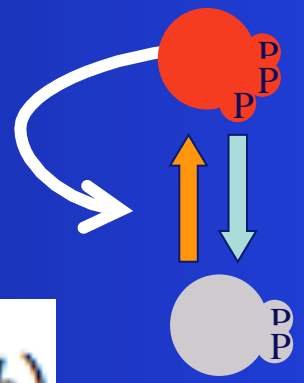
GTPase Signaling:

- Active and inactive GPAses:



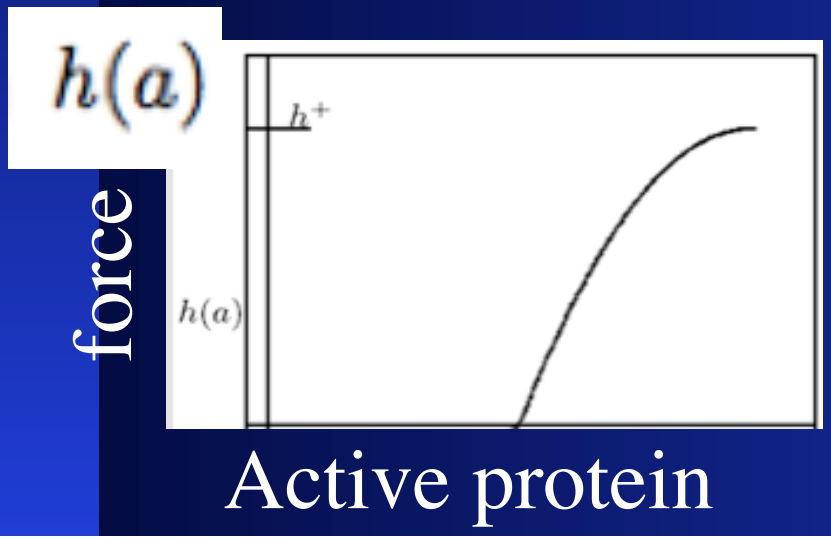
$$
\begin{aligned}
a_t + \mathbf{u} \cdot \nabla a &= D_a \Delta a + g(a,b) \\
b_t + \mathbf{u} \cdot \nabla b &= D_b \Delta b - g(a,b),
\end{aligned}
$$

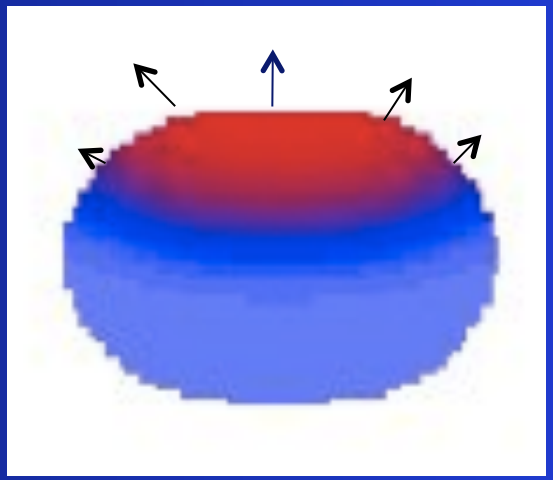
$$
g(a,b) = \left(k_0 + \frac{\gamma a^2}{K^2 + a^2} \right) b - \delta a.
$$

Protrusion force

Force on perimeter depends on level of signal

$$F_{net} = h(a)\mathbf{n}(s,t).$$





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

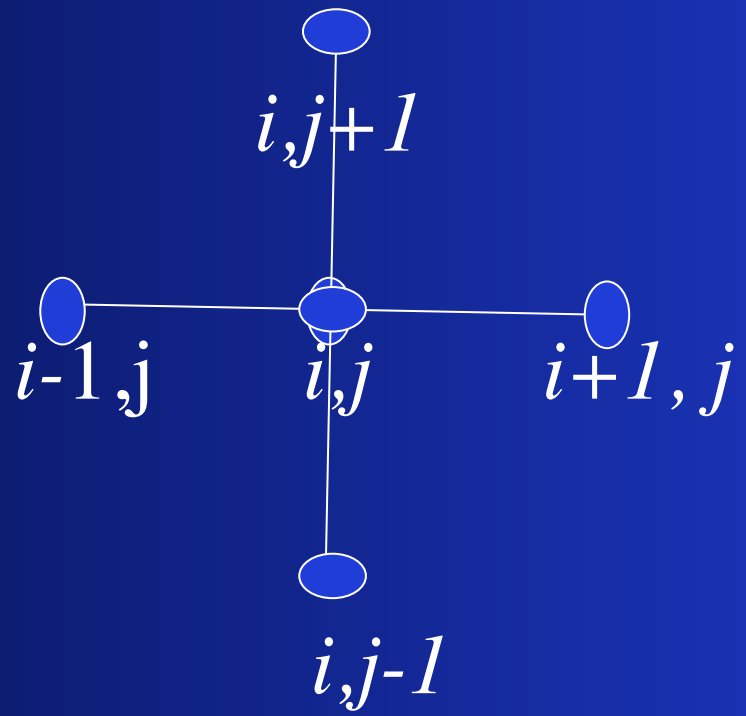
- Centered (finite) difference:

$$\frac{\partial^2 c}{\partial x^2} \approx \frac{c_{i+1,j} - 2c_{i,j} + c_{i-1,j}}{(\delta x)^2}.$$

i-1 *i* *i+1*

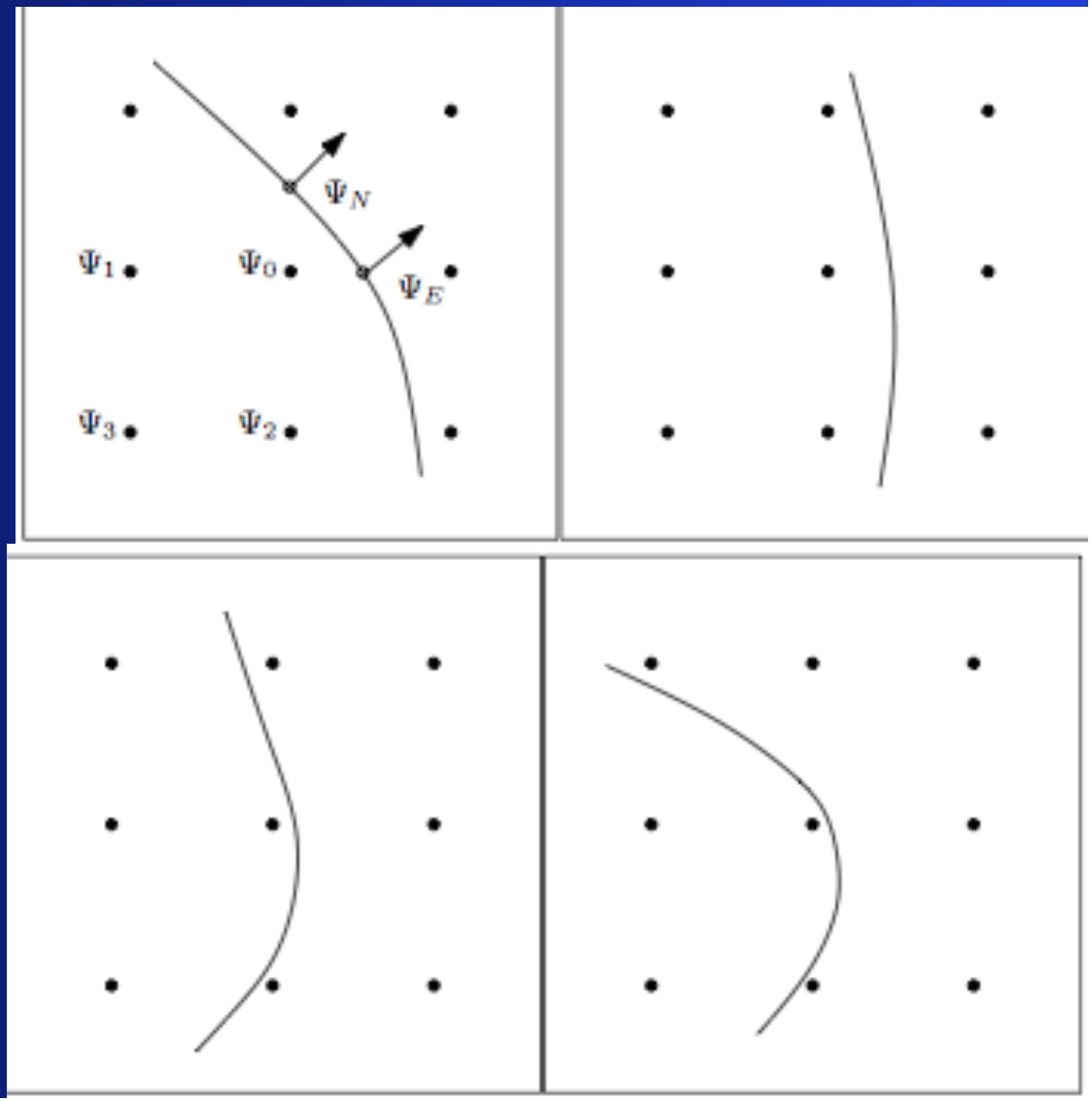
Approximating diffusion in 2D

- Centered (finite) difference in 2 directions:

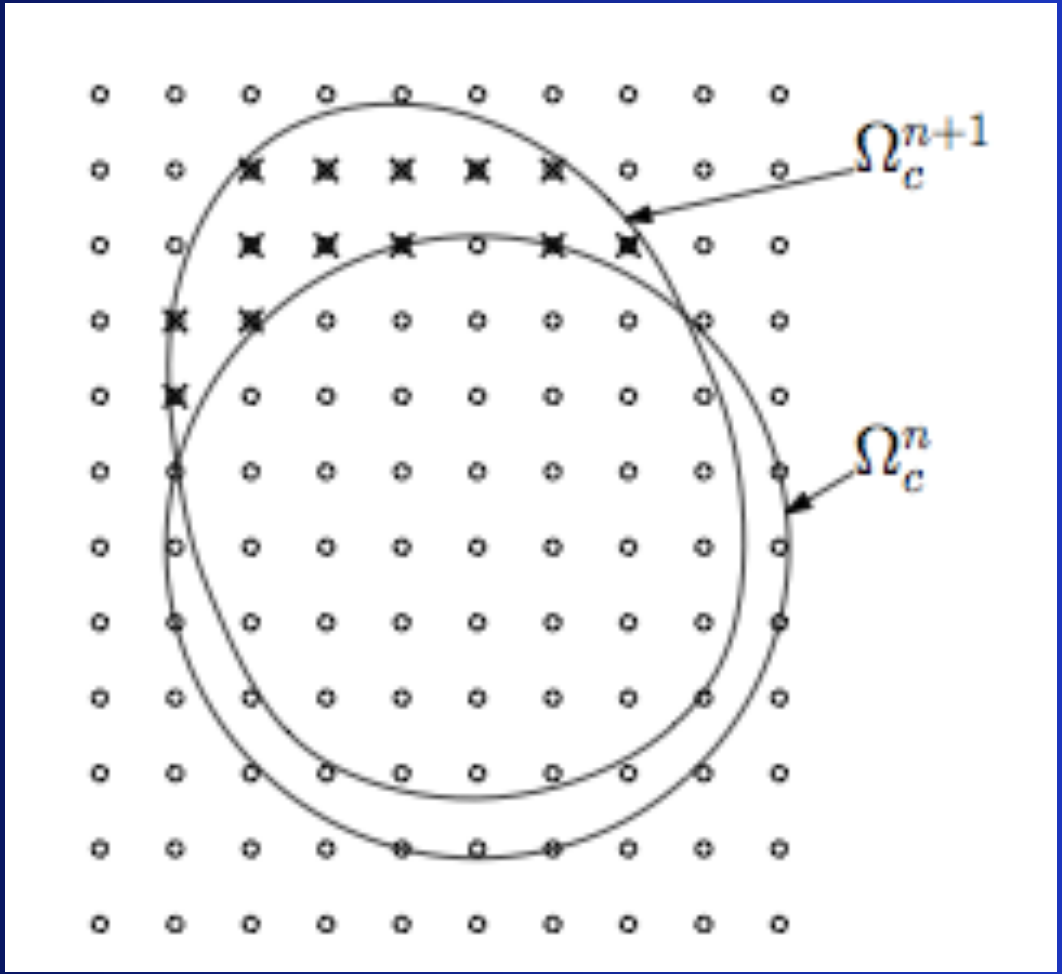


Challenges: The diffusion

- Acceptable:
- Not acceptable

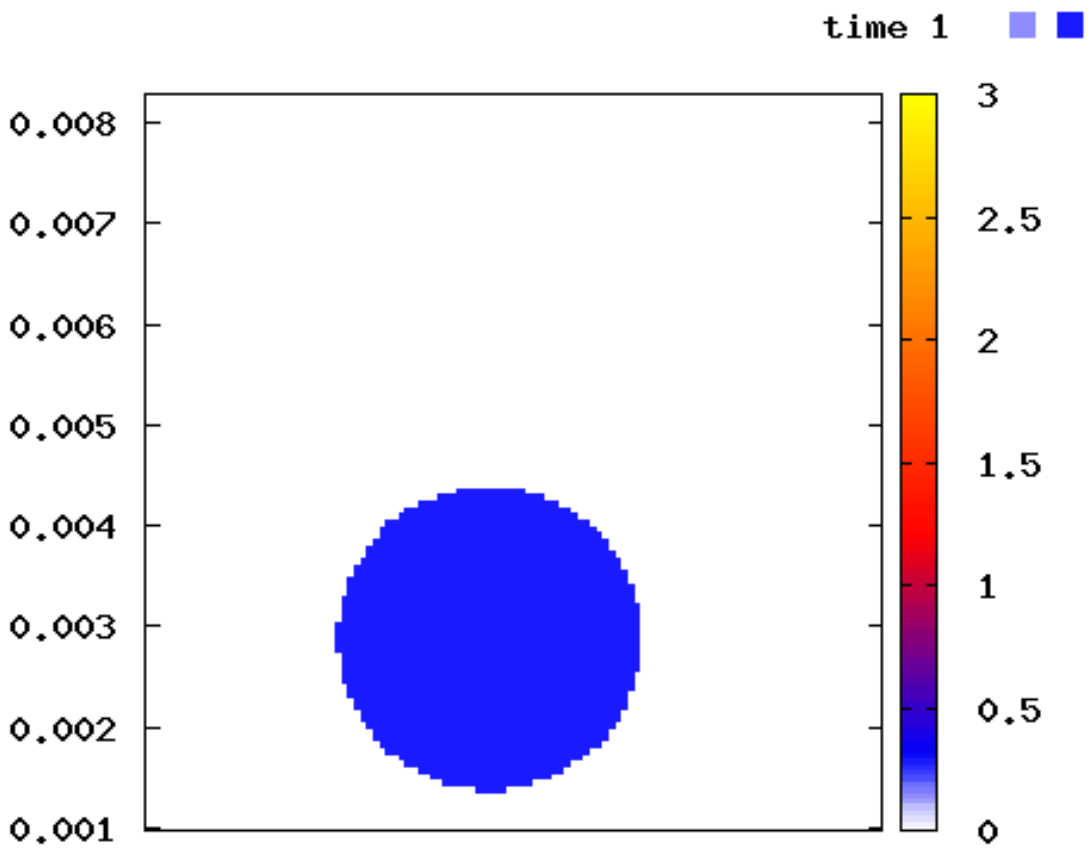


The advection: issues with conservation of mass



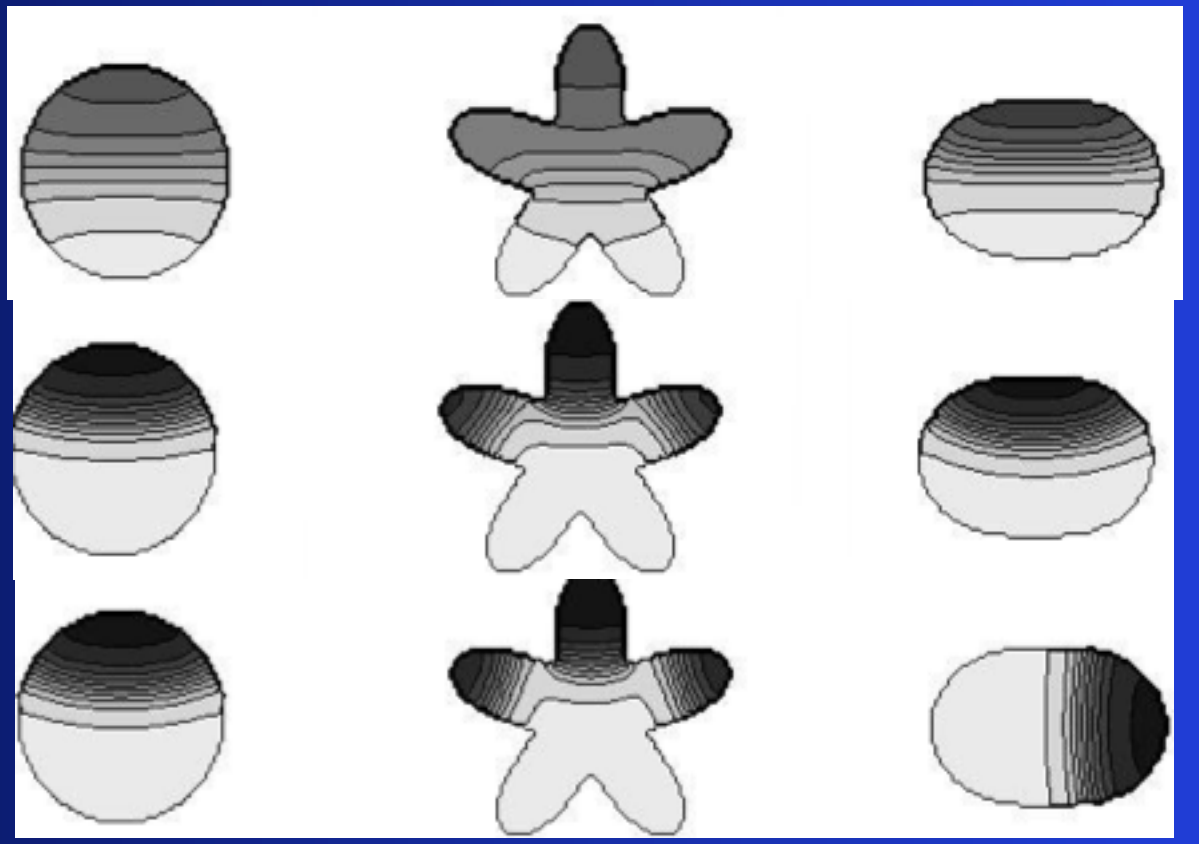
Some results

Cell motion:



The shape influences the chemistry

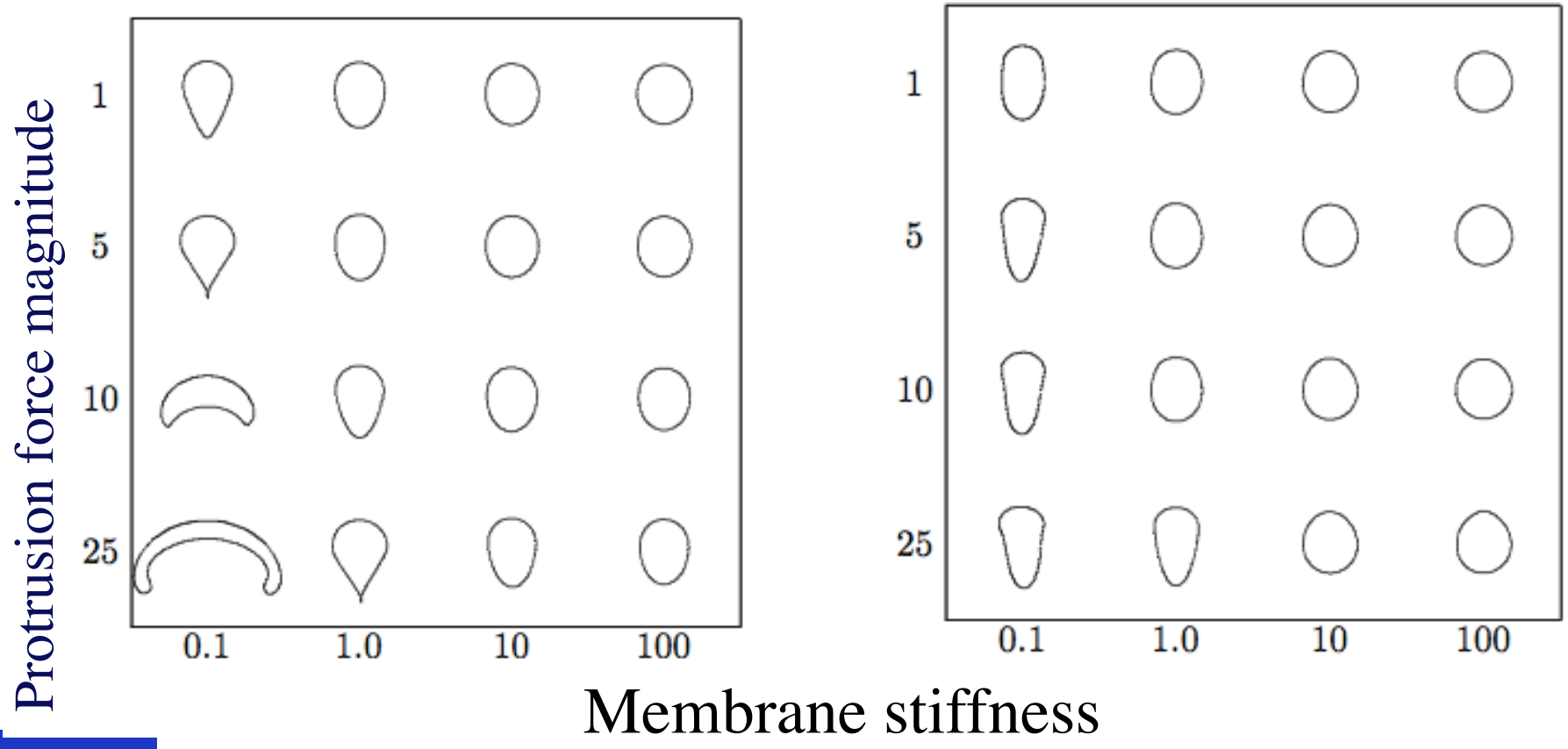
- t = 0
- Later
- Later



Cell shape

Mechanics alone

Mechanics and biochem



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?

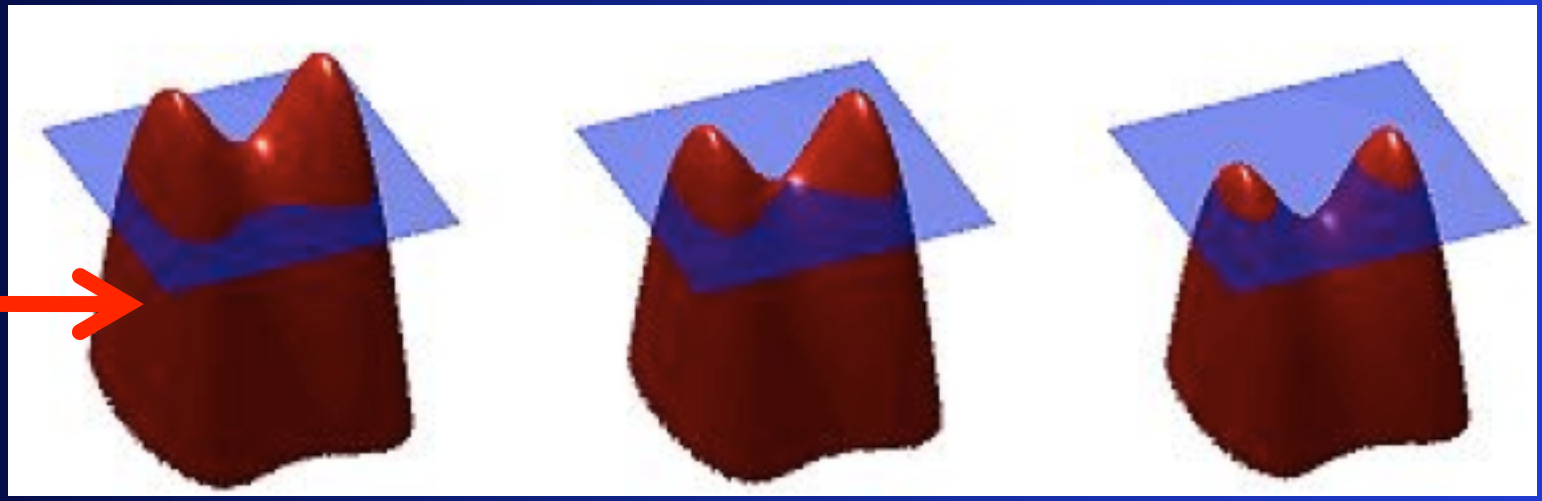
http://en.wikipedia.org/wiki/File:Level_set_method.jpg

Level set methods

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

Define some function ψ(r) such that boundary is a “level set” of that function

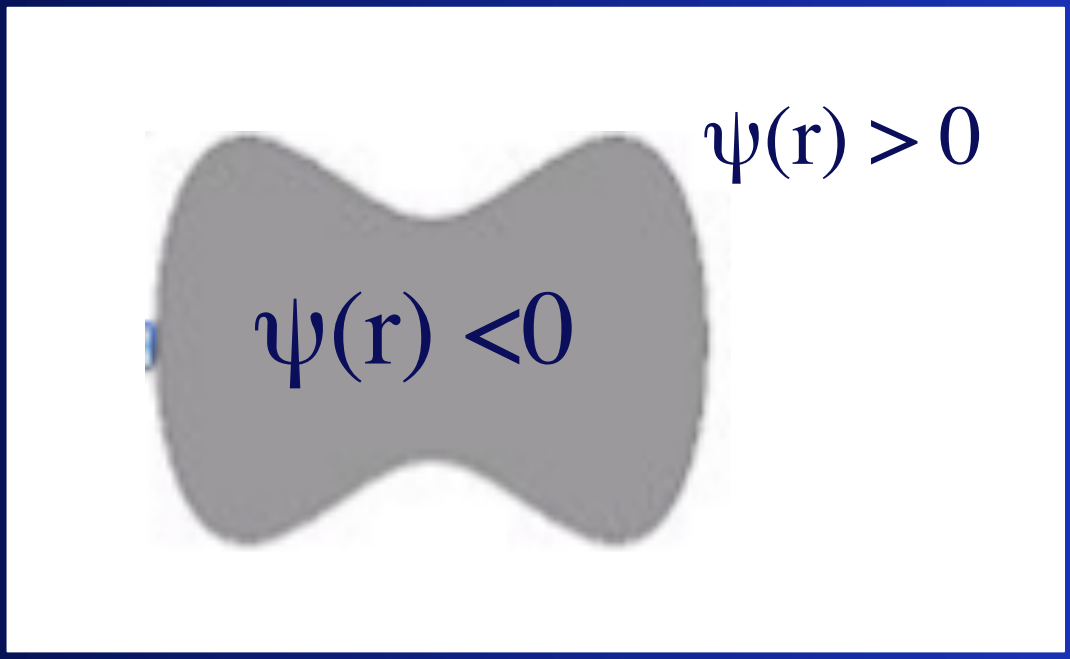
ψ(r)



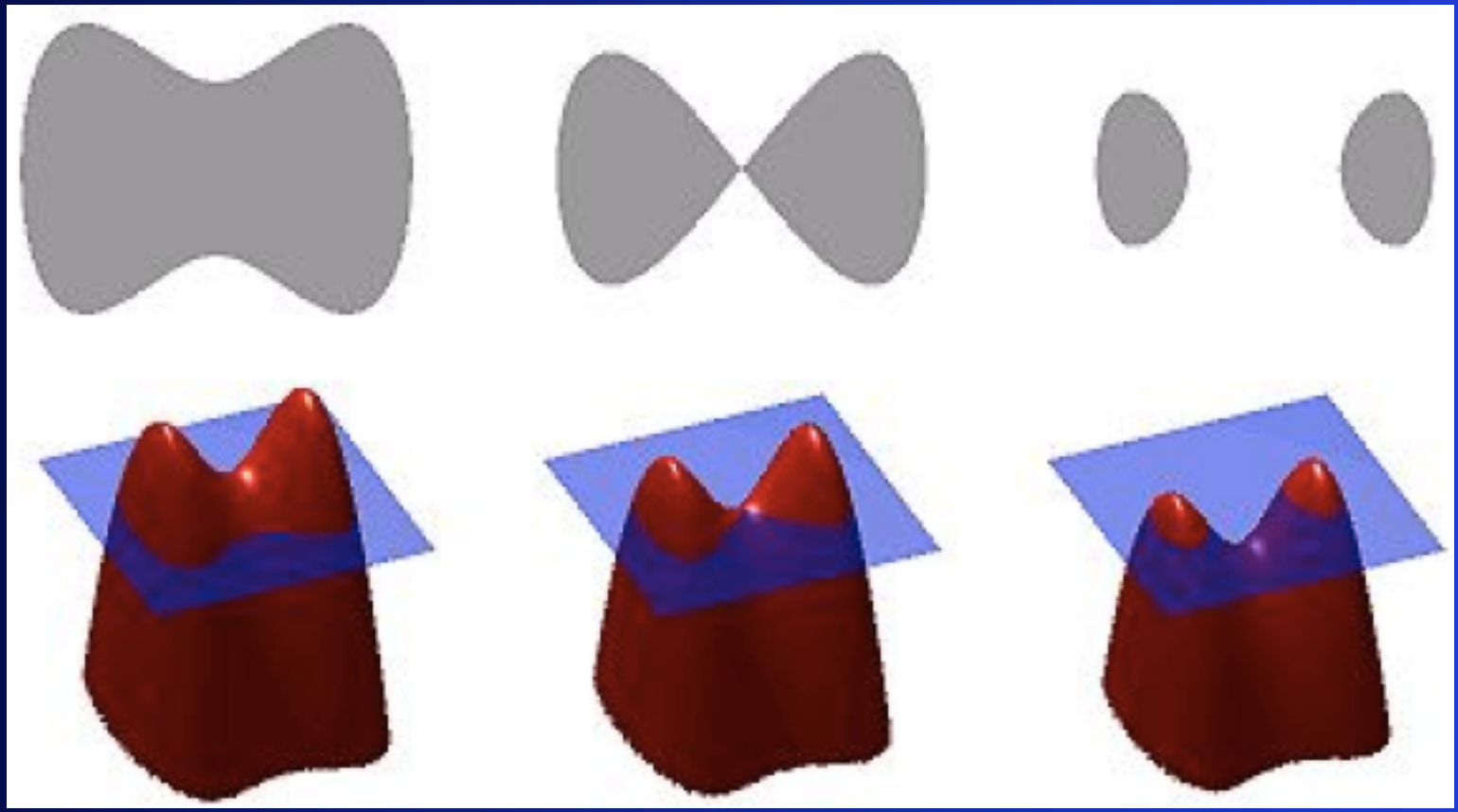
Level set methods

ψ = distance away from the boundary curve.

$\psi(r) = 0$ represents the boundary



Level Set Methods



http://en.wikipedia.org/wiki/File:Level_set_method.jpg

Evolving the boundary

The normal vector to any level curve of ψ is given by the gradient:

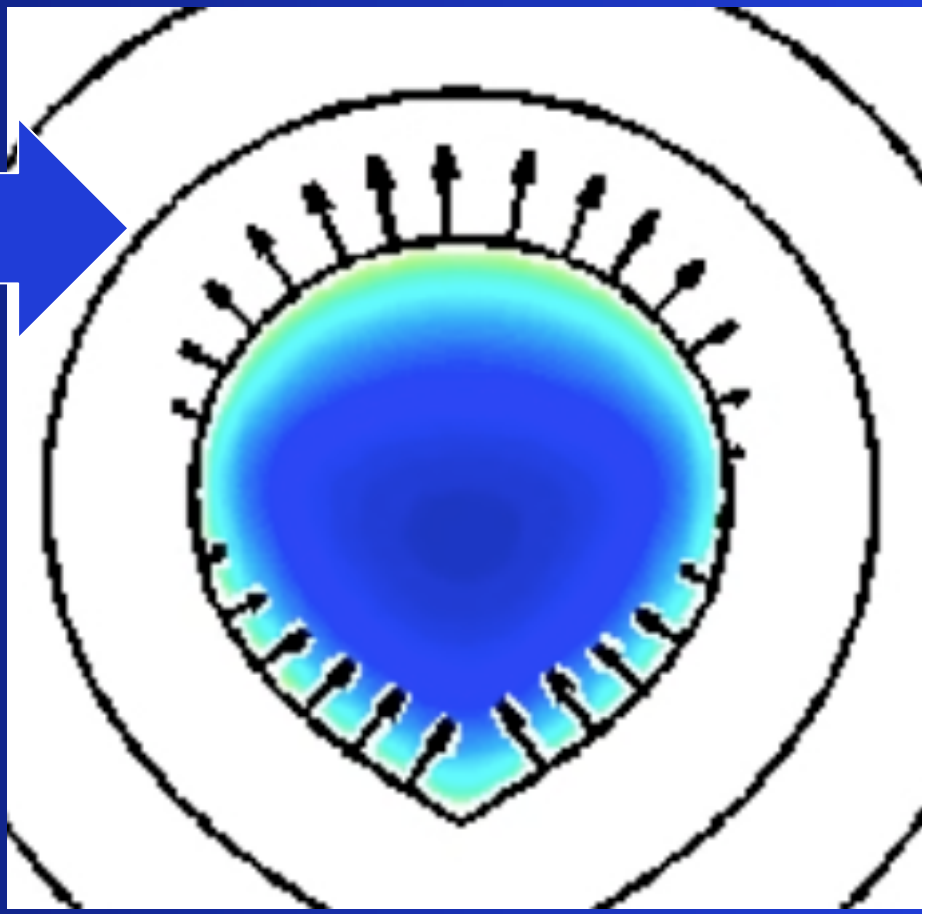
$$\hat{\mathbf{N}} = \frac{\nabla\psi}{|\nabla\psi|} .$$

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

$$\frac{\partial\psi}{\partial t} = -\mathbf{V}\cdot\nabla\psi$$

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

Model by Zajac et al (2008)

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

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

$$\mathbf{J} = \overbrace{\phi \mathbf{V}_s}^{\text{Solid Flux}} + \overbrace{(1-\phi)\mathbf{V}_f}^{\text{Fluid Flux}},$$

$$\nabla \cdot \mathbf{J} = 0,$$

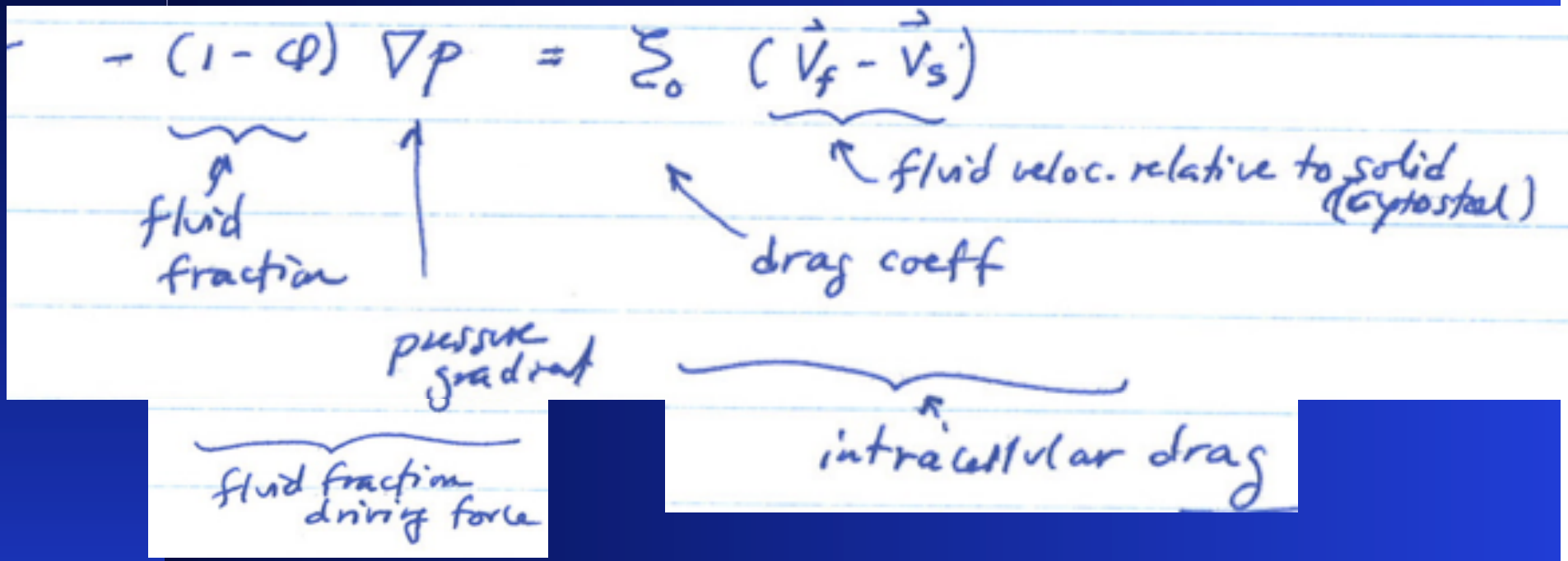
V_s, V_f = veloc of solid and fluid phases

Balance equation:

$$\frac{\partial \phi}{\partial t} = -\overbrace{\nabla \cdot (\phi \mathbf{V}_s)}^{\text{Cytoskeletal Drift}} - \underbrace{k_s \phi}_{\text{Cytoskeletal Disassembly}}$$

Conservation of momentum (force balance)

- On fluid fraction:



- Similar eqn for solid fraction

Movies

Kindly provided by C Wolgemuth

Actin Polymerization-based models

MULTISCALE MODEL. SIMUL.
Vol. 3, No. 2, pp. 413–439

MULTISCALE TWO-DIMENSIONAL MODELING OF A MOTILE SIMPLE-SHAPED CELL*

B. RUBINSTEIN†, K. JACOBSON‡, AND A. MOGILNER†

- 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:

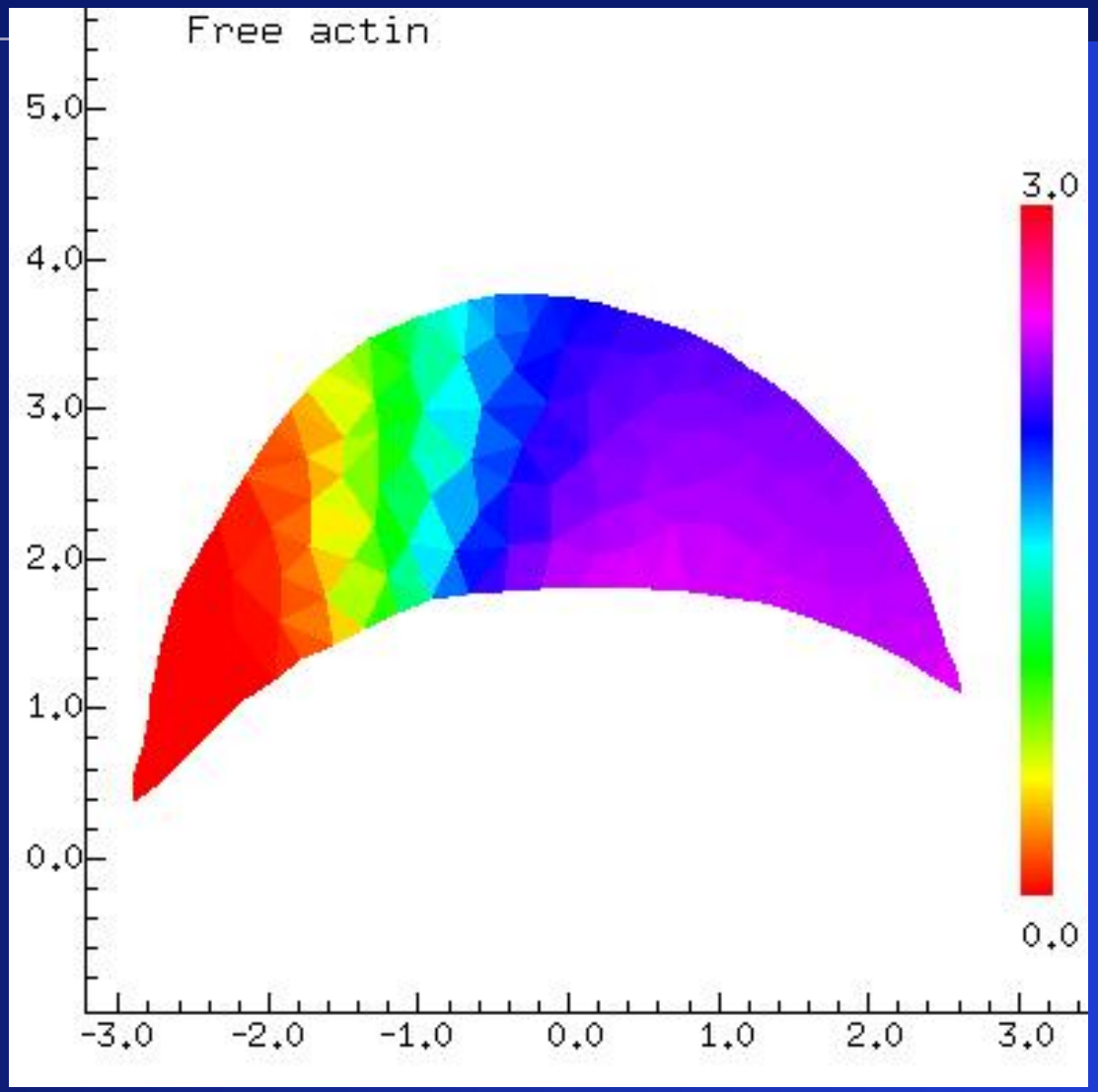


Figure kindly supplied by Boris Rubinstein

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:

$$\theta_{\mathrm{n}} + \theta_{\mathrm{s}} = 1.$$

- Cytoskeleton mass balance:
-

$$\frac{\partial \theta_{\mathrm{n}}}{\partial t} = -\nabla \cdot (\theta_{\mathrm{n}} \mathbf{v}_{\mathrm{n}}) + J.$$

- Fluid momentum balance (neglect inertia):

$$-\theta_{\mathrm{s}} \nabla P + \mathcal{H} \theta_{\mathrm{s}} \theta_{\mathrm{n}} (\mathbf{v}_{\mathrm{n}} - \mathbf{v}_{\mathrm{s}}) = 0.$$

Actin polymerization driven by signaling protein

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

$$\frac{\partial m}{\partial t} = -\frac{m}{\tau_{\mathrm{m}}} + D_{\mathrm{m}}\nabla^2 m,$$

- 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

Movies

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..