

A Computational Model of Amoeboid Cell Motility

Magdalena Stolarska

School of Mathematics
University of Minnesota
Minneapolis, MN, U.S.A.

Outline of Talk

1. Background

- Overview of chemotaxis
- Motivation for current work

2. Mechanics of cell motility

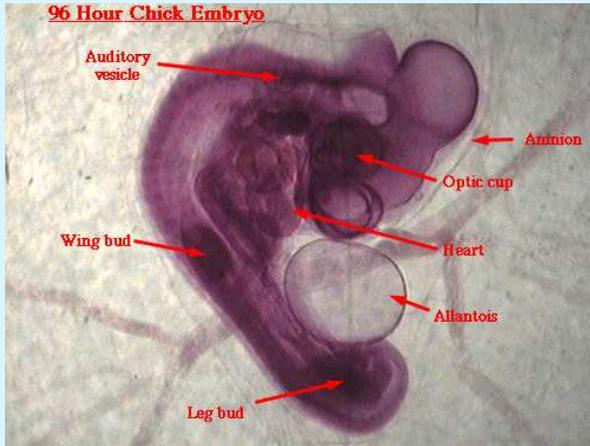
- Continuum model
- Constitutive equations and material parameters

3. Simulation

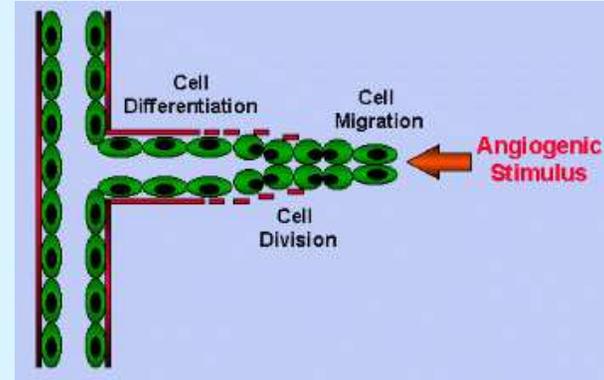
4. Conclusions

Examples of Directed Cell Motility

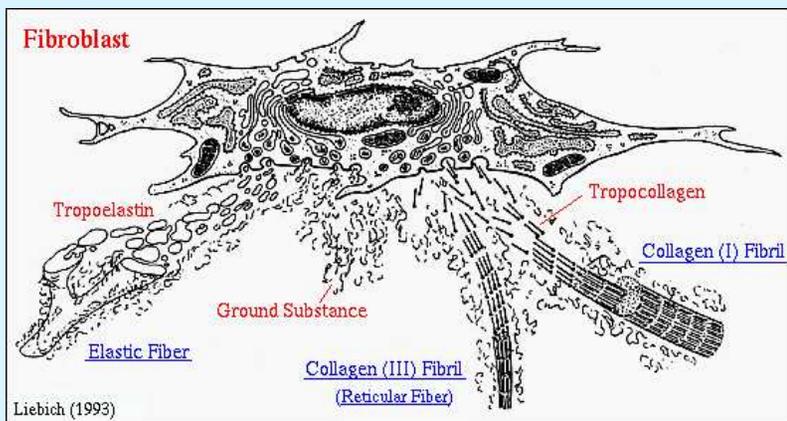
- Embryonic Development



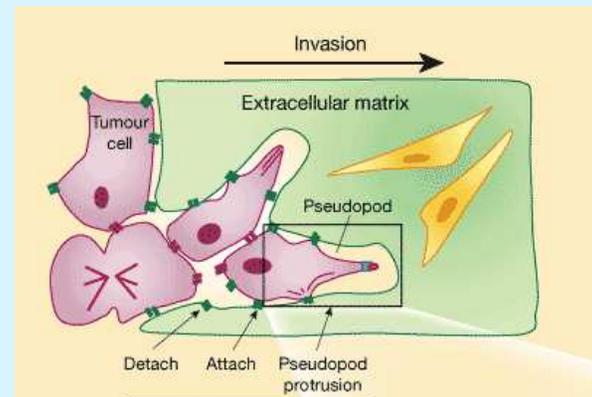
- Angiogenesis



- Wound Healing



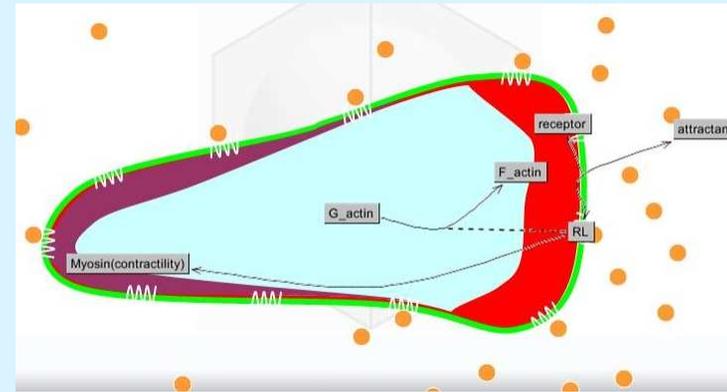
- Metastasis of Cancer



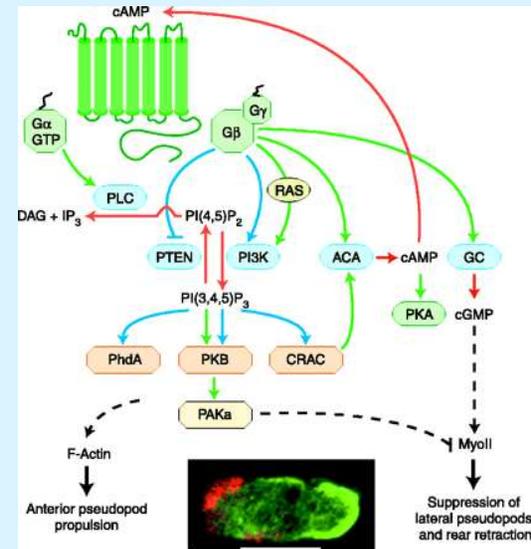
Chemotaxis and Directed Cell Movement

1. Diffusible signal binds to receptor.
2. Signal transduction.
3. Actin polymerization at leading edge.
4. Mechanics and cell translocation.

General Process

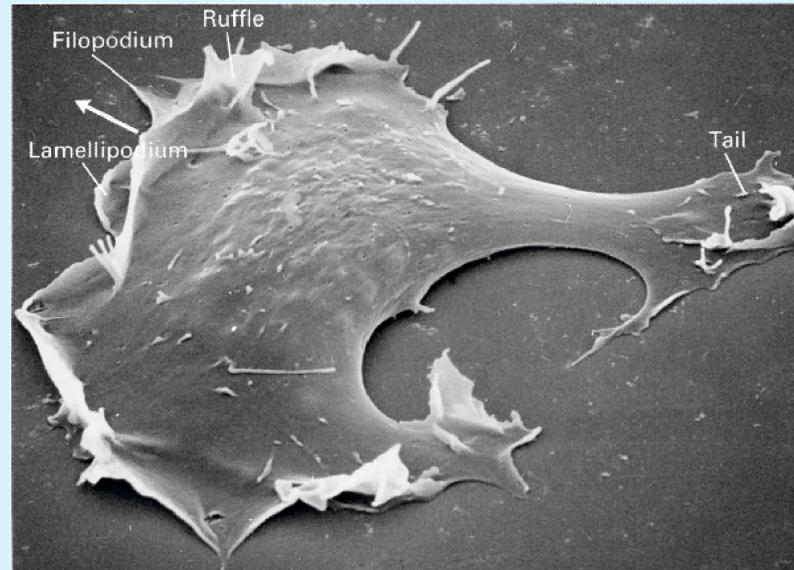
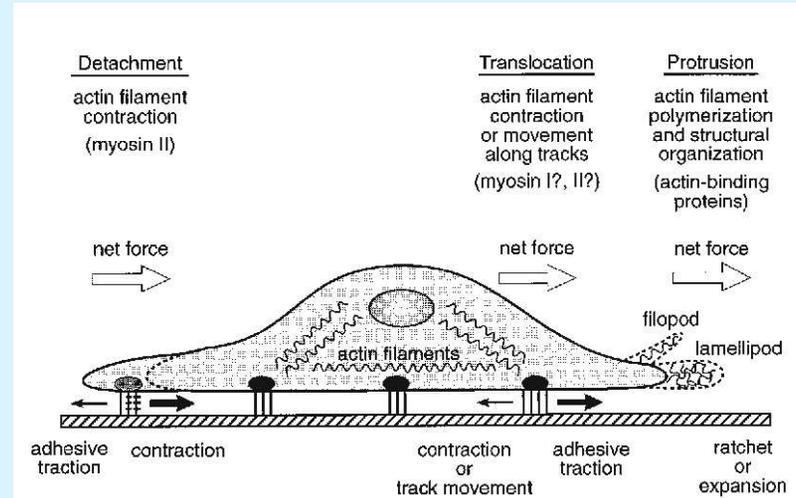


Signalling Network for *Dictyostelium discoideum*



Four Steps of Cell 'Crawling'

1. Extension of protrusions.
2. Attachment to the substrate at leading edge.
3. Translocation of the cell body.
4. Detachment at the rear.



Why Model These Processes?

- The full process of directed motility is extremely complex. To get the big picture the individual pieces need to be integrated.
- Provide hypotheses upon which laboratory experiments can be based.

“We have arrived at the stage where models are useful to suggest experiments, and the facts of the experiments in turn lead to new and improved models that suggest new experiments. By this rocking back and forth between the reality of experimental facts and the dream world of hypotheses, we can move slowly toward a satisfactory solution of the major problems of developmental biology.”

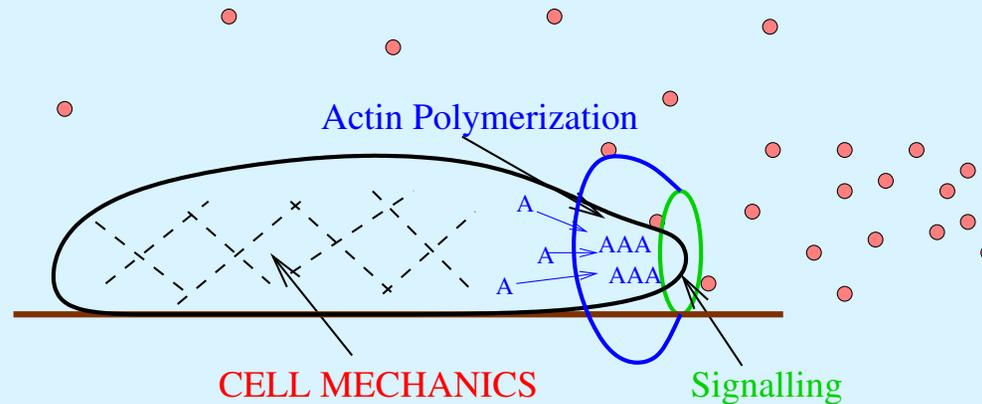
John Bonner

- Aid in the ultimate development of therapies.

Examples of Previous Work

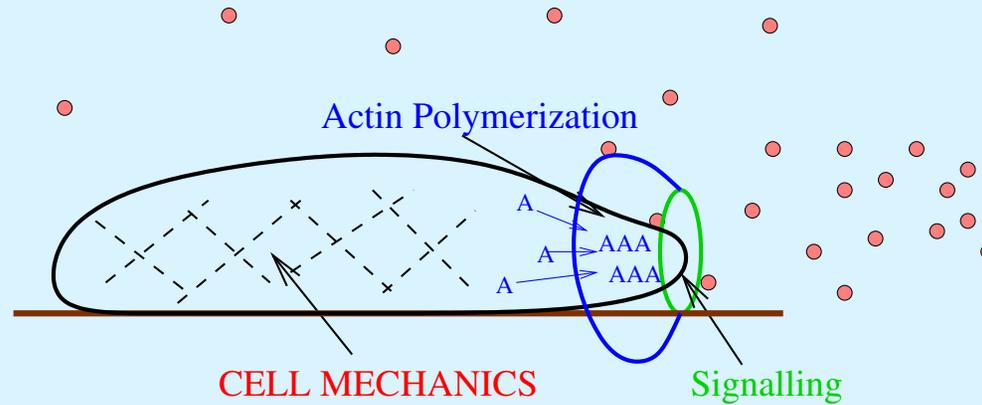
- 2D model of crawling nematode sperm. (Bottino *et al.* , 2002)
- Models of micropipette aspiration experiments and leukocyte pseudopod protrusion. (Dong & Skalak, 1992; Zhu & Skalak, 1988; Dong *et al.* , 1988; Schmid-Schonbein & Skalak, 1984)
- Models of neutrophil experiments. (Hernant *et al.* , 2003; Drury & Dembo, 1999, 2001)
- 3D viscoelastic models of magnetocytometry experiments. (Karcher *et al.* , 2003)

Compartmentalization



- Direction *sensing* and directed *motility* are naturally compartmentalized.
- **CURRENT WORK** will focus on **cell mechanics** assuming that we are given information about **signalling** and **actin polymerization**.
- By making model and code modular, adding pieces and changing material properties will be straightforward.

Compartmentalization

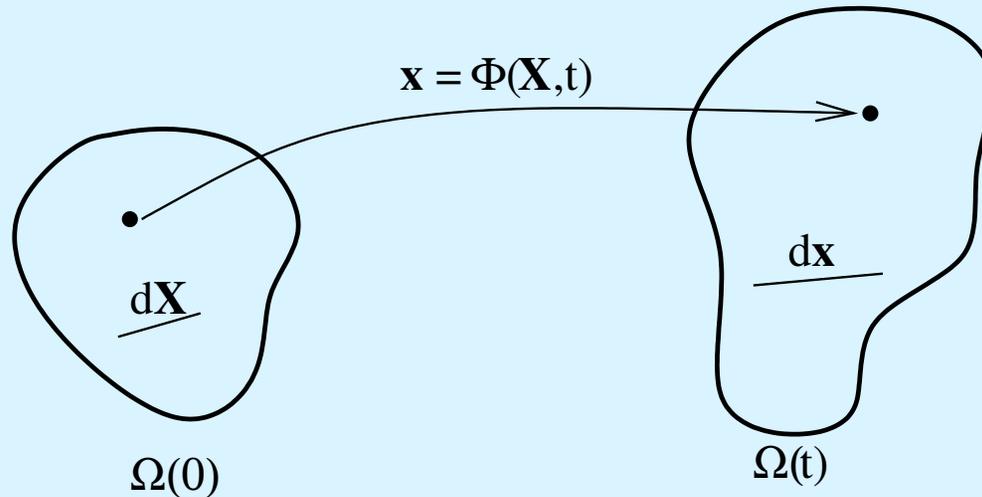


- Direction *sensing* and directed *motility* are naturally compartmentalized.
- **CURRENT WORK** will focus on **cell mechanics** assuming that we are given information about **signalling** and **actin polymerization**.
- By making model and code modular, adding pieces and changing material properties will be straightforward.

ULTIMATE GOAL: To combine mechanics and biochemistry so that we can run numerical simulations on a variety of cells in a variety of situations.

Mechanics – Deformations

Large deformations are characterized by the DEFORMATION GRADIENT: \mathbf{F}

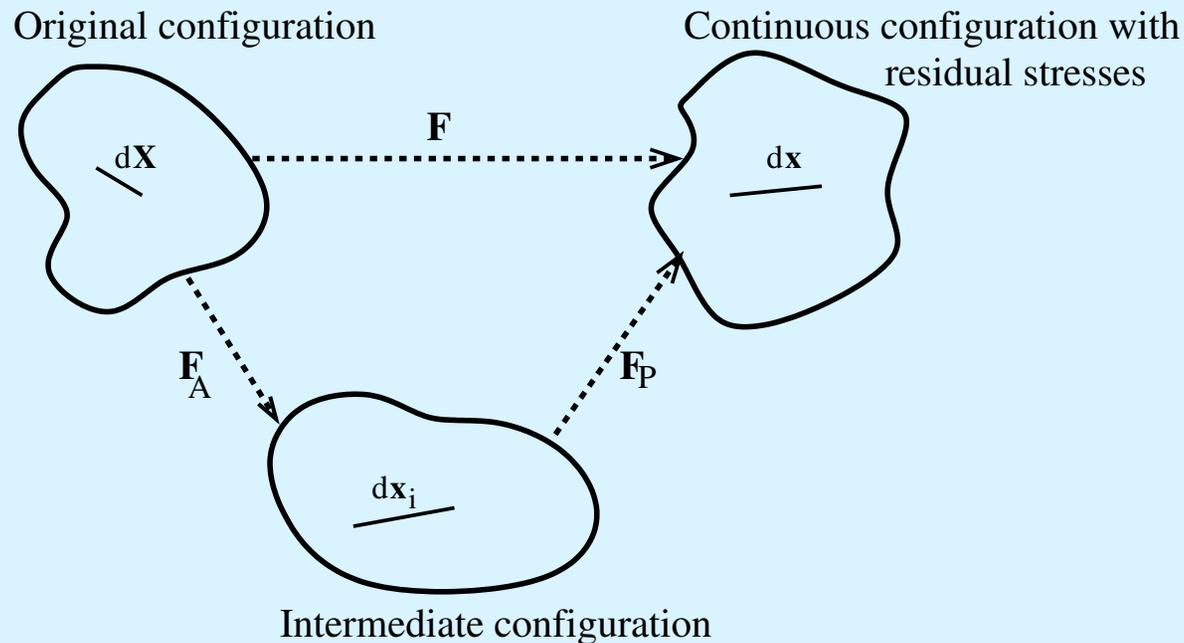


$$d\mathbf{x} = \mathbf{F} d\mathbf{X} \quad \text{where} \quad \mathbf{F} = \frac{\partial \mathbf{x}}{\partial \mathbf{X}}$$

Mechanics – Deformations

- We are postulating a multiplicative decomposition of the deformation gradient into its active and passive parts:

$$\mathbf{F} = \mathbf{F}_A \mathbf{F}_P$$



- \mathbf{F}_A depends on actin polymer concentration and orientation.
- \mathbf{F}_P defines the passive deformation due to residual effects from the active response and to external forces.

Mechanics – Deformations

- As an initial simplification we assume that the active deformation gradient is isotropic.

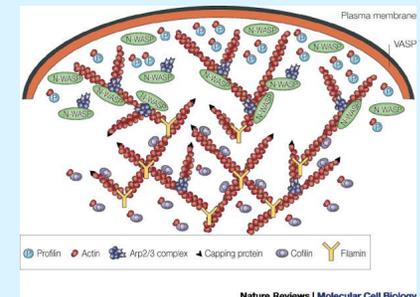
$$\mathbf{F}_A = \begin{pmatrix} \mathcal{J}^{\frac{1}{3}} & 0 & 0 \\ 0 & \mathcal{J}^{\frac{1}{3}} & 0 \\ 0 & 0 & \mathcal{J}^{\frac{1}{3}} \end{pmatrix}$$

- The above is equivalent to

$$\mathbf{F} = \mathcal{J}^{\frac{1}{3}} \mathbf{F}_P \quad \text{where} \quad \det(\mathbf{F}) = \mathcal{J}.$$

We assume that the passive response is incompressible.

- Can generalize to make \mathbf{F}_A an anisotropic tensor.



Mechanics – Governing Equations

Given an actin polymerization term, $S(\mathbf{x}, \mathbf{c}_a, t)$, where \mathbf{c}_a is the concentration and orientation of an actin polymer:

- Mass balance

$$\begin{aligned}\nabla \cdot \mathbf{v}(\mathbf{x}, t) - S(\mathbf{x}, \mathbf{c}_a, t) &= 0 \\ \int_{\Omega} S(\mathbf{x}, \mathbf{c}_a, t) d\mathbf{x} &= 0 \\ \frac{\partial \mathcal{J}}{\partial t} = \nabla \cdot \mathbf{v}(\mathbf{x}, t) \mathcal{J} &= S(\mathbf{x}, \mathbf{c}_a, t) \mathcal{J}\end{aligned}$$

- Momentum balance (assume accelerations to be negligible)

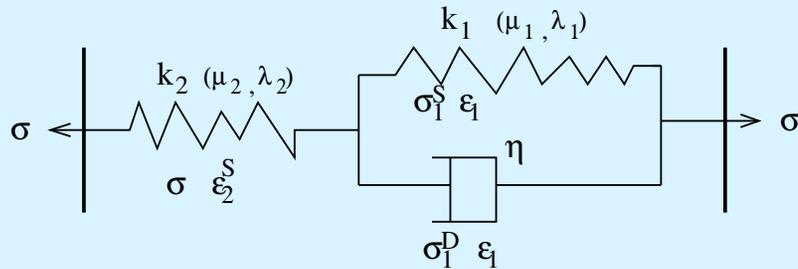
$$\nabla \cdot (\boldsymbol{\sigma} - p\mathbf{I}) + \rho \mathbf{f}_b = \rho \mathbf{v} S(\mathbf{x}, \mathbf{c}_a, t)$$

- Constitutive equation

$$\begin{aligned}\mathbb{C}_1 \boldsymbol{\sigma} + \mathbb{C}_2 \boldsymbol{\sigma}^\circ - \mathbb{C}_3 \boldsymbol{\epsilon} - \mathbb{C}_4 \boldsymbol{\epsilon}^\diamond &= 0 \\ \text{(strain)} \quad \boldsymbol{\epsilon} &= \frac{1}{2} \left(\mathbf{I} - \mathcal{J}^{\frac{2}{3}} \mathbf{F}^{-\top} \mathbf{F}^{-1} \right) \\ \text{(strain-rate)} \quad \boldsymbol{\epsilon}^\diamond &= \frac{1}{2} \left(\nabla \mathbf{v}^\top + \nabla \mathbf{v} \right) - \frac{1}{3} \left(S \mathcal{J}^{\frac{2}{3}} \mathbf{F}^{-\top} \mathbf{F}^{-1} \right)\end{aligned}$$

Mechanics – Constitutive Equation

Cells have been shown to exhibit viscoelastic behavior.



$$\text{In 1D:} \quad \left(1 + \frac{k_1}{k_2}\right)\sigma + \frac{\mu_1}{k_2}\dot{\sigma} = k_1\epsilon + \eta\dot{\epsilon}$$

$$\text{In 3D:} \quad \mathbb{C}_1\boldsymbol{\sigma} + \mathbb{C}_2\boldsymbol{\sigma}^\circ - \mathbb{C}_3\boldsymbol{\epsilon} - \mathbb{C}_4\boldsymbol{\epsilon}^\diamond = 0,$$

where \mathbb{C}_m is 4th order tensor

To determine 3D material parameters from 1D data:

- Assume elasticity (springs) to be isotropic and viscous effects (dashpots) to be identical in all directions:

$$\sigma_{ij}^S = 2\mu\epsilon_{ij}^S + \lambda \sum_k \epsilon_{kk}^S \delta_{ij} \quad \sigma_{ij}^D = \eta \frac{\partial \epsilon_{ij}^D}{\partial t}$$

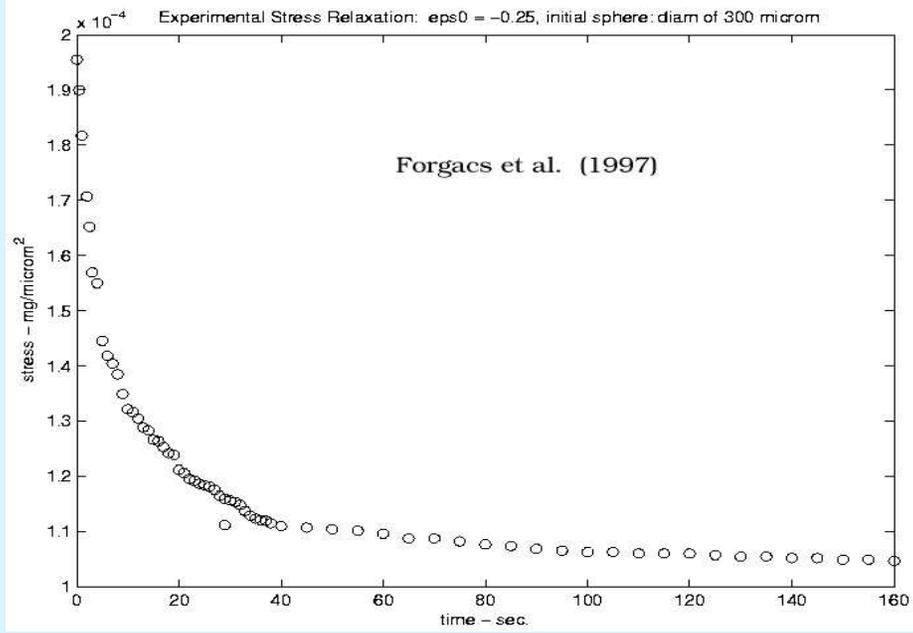
- Combining to represent spring-dashpot system results in

$$L_{ijkl}^\sigma \sigma_{kl} = L_{ijkl}^\epsilon \epsilon_{kl}$$

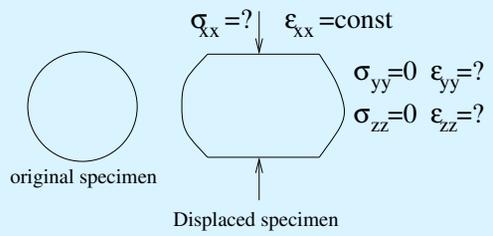
Mechanics – Constitutive Equation

- σ and ϵ are symmetric due to conservation of angular momentum.
- Equations for shear stresses are not considered.
- Three equations for bulk stresses

$$\sigma_{ii}^{\circ} = f_i(\sigma_{xx}, \sigma_{yy}, \sigma_{zz}, \epsilon_{xx}, \epsilon_{yy}, \epsilon_{zz}, \epsilon_{xx}^{\diamond}, \epsilon_{yy}^{\diamond}, \epsilon_{zz}^{\diamond}, \mu^{(1)}, \lambda^{(1)}, \mu^{(2)}, \lambda^{(2)}, \eta)$$



- In experiment: σ_{xx} and $\epsilon_{yy} = \epsilon_{zz}$ are unknown while ϵ_{xx} is the experimental strain and $\sigma_{yy} = \sigma_{zz} = 0$.



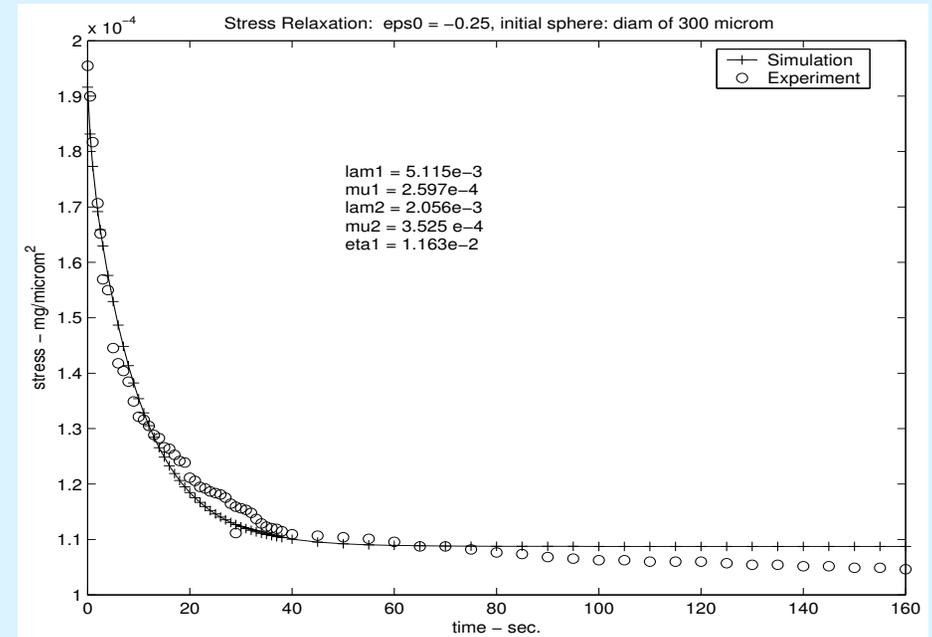
- ◆ $\sigma_{xx}^{\circ} = f_x(\sigma_{xx}, 0, 0, \epsilon_{exp}, \epsilon_{yy}, \epsilon_{yy}, 0, \epsilon_{yy}^{\diamond}, \epsilon_{yy}^{\diamond}, \mu^{(1)}, \lambda^{(1)}, \mu^{(2)}, \lambda^{(2)}, \eta)$
- ◆ $0 = f_y(\sigma_{xx}, 0, 0, \epsilon_{exp}, \epsilon_{yy}, \epsilon_{yy}, 0, \epsilon_{yy}^{\diamond}, \epsilon_{yy}^{\diamond}, \mu^{(1)}, \lambda^{(1)}, \mu^{(2)}, \lambda^{(2)}, \eta)$

- Determine parameters using method of steepest decent.

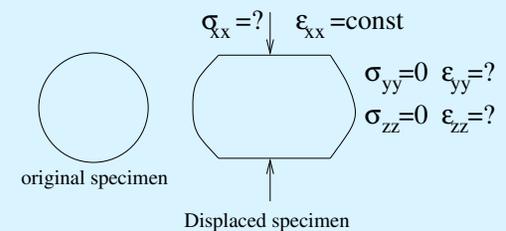
Mechanics – Constitutive Equation

- σ and ϵ are symmetric due to conservation of angular momentum.
- Equations for shear stresses are not considered.
- Three equations for bulk stresses

$$\sigma_{ii}^{\circ} = f_i(\sigma_{xx}, \sigma_{yy}, \sigma_{zz}, \epsilon_{xx}, \epsilon_{yy}, \epsilon_{zz}, \epsilon_{xx}^{\diamond}, \epsilon_{yy}^{\diamond}, \epsilon_{zz}^{\diamond}, \mu^{(1)}, \lambda^{(1)}, \mu^{(2)}, \lambda^{(2)}, \eta)$$



- In experiment: σ_{xx} and $\epsilon_{yy} = \epsilon_{zz}$ are unknown while ϵ_{xx} is the experimental strain and $\sigma_{yy} = \sigma_{zz} = 0$.



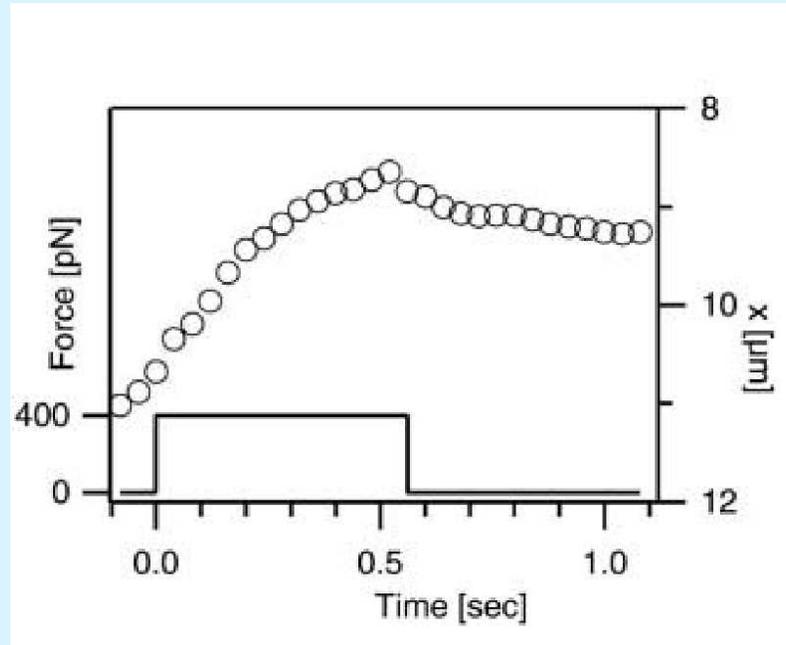
$$\diamond \quad \sigma_{xx}^{\circ} = f_x(\sigma_{xx}, 0, 0, \epsilon_{\text{exp}}, \epsilon_{yy}, \epsilon_{yy}, 0, \epsilon_{yy}^{\diamond}, \epsilon_{yy}^{\diamond}, \mu^{(1)}, \lambda^{(1)}, \mu^{(2)}, \lambda^{(2)}, \eta)$$

$$\diamond \quad 0 = f_y(\sigma_{xx}, 0, 0, \epsilon_{\text{exp}}, \epsilon_{yy}, \epsilon_{yy}, 0, \epsilon_{yy}^{\diamond}, \epsilon_{yy}^{\diamond}, \mu^{(1)}, \lambda^{(1)}, \mu^{(2)}, \lambda^{(2)}, \eta)$$

- Determine parameters using method of steepest decent.

Mechanics – Constitutive Equation

Another example of cell viscoelasticity ...

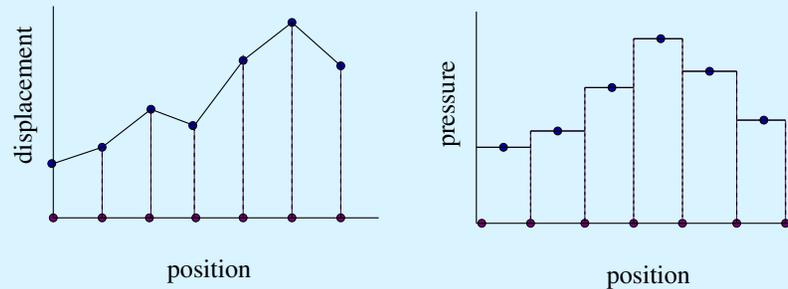


From Feneberg & Westphal. *Eur. Biophys. J.*, 2001.

- Laurent *et al.* . *Trans. ASME*, 2002.
- Fabry *et al.* . *Phys. Rev. E*, 2003.

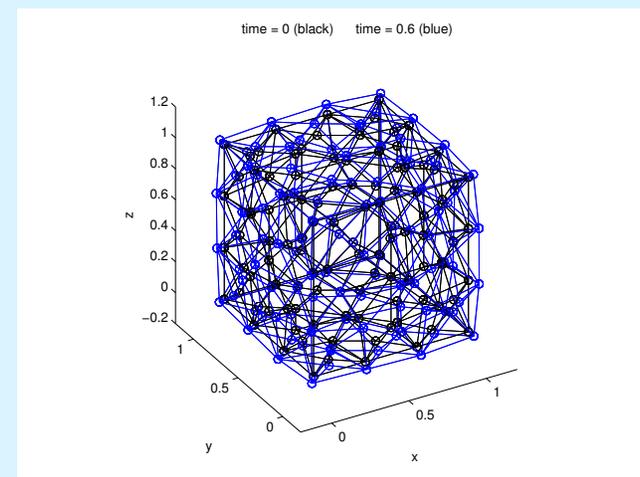
Simulation

- Galerkin Finite Element Method with piecewise linear displacement and stress approximations and piecewise constant pressure approximation.



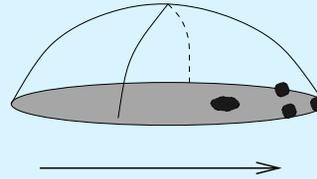
- Mesh moves with the deformation.
- Backward Euler time discretization
- Solved nonlinear system using NITSOL (Pernice & Walker, *SIAM J. Sci. Comp.*, 1998).

- Currently in testing stage.



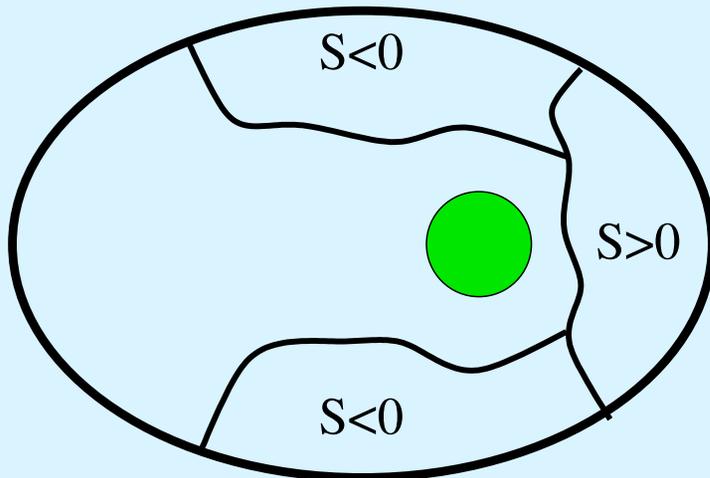
Simulation

PROTRUSION, ATTACHMENT, RETRACTION ...

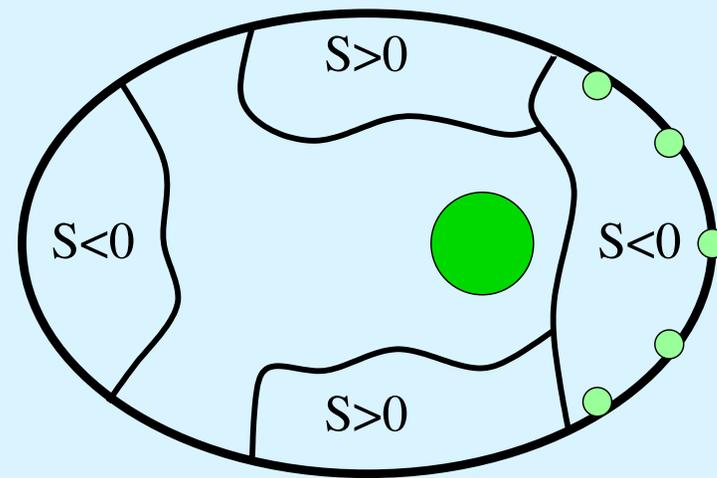


- Phenomenological model to capture general cell crawling behavior.
- No remeshing yet – about 5% deformation
- Boundary Conditions: (1) All displacements fixed at focal adhesions, (2) u_z fixed at $z = 0$, (3) Zero tractions on hemispherical surface.

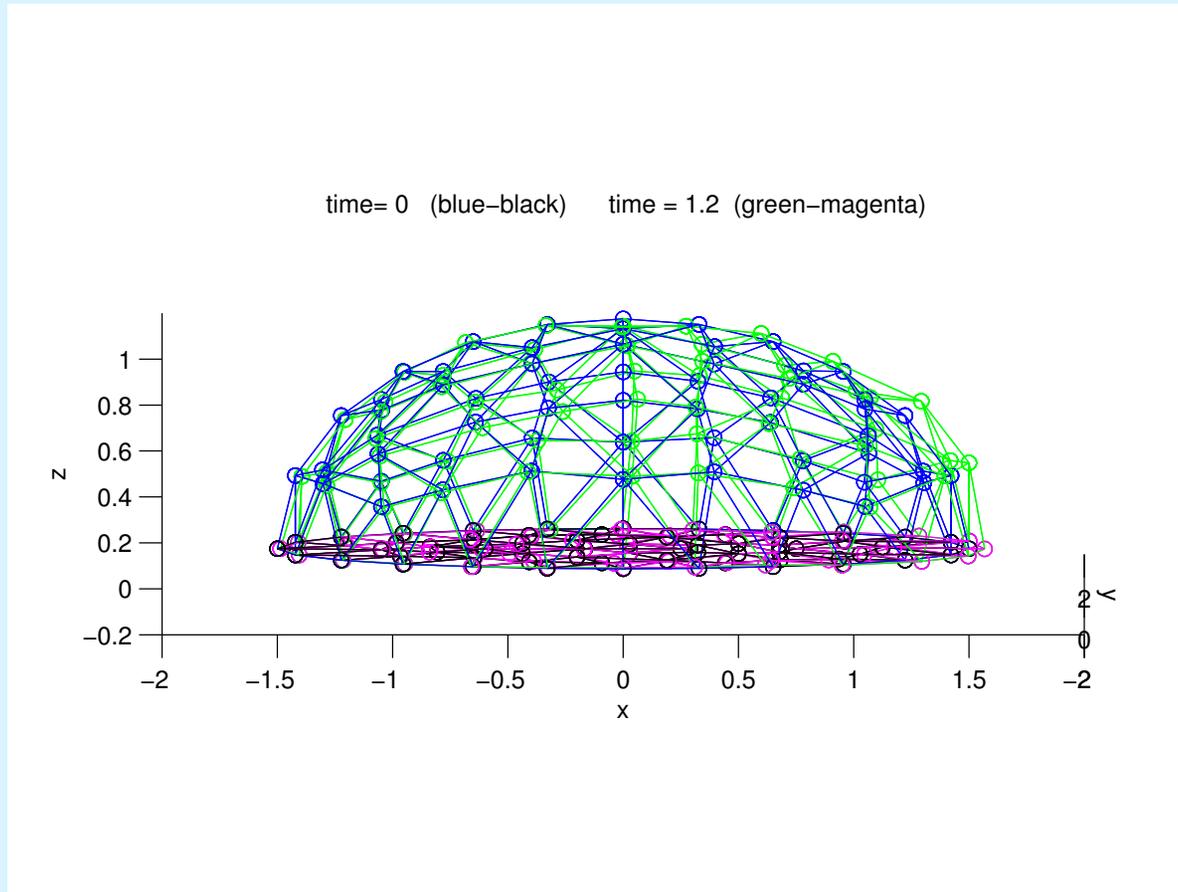
Time < 1



$1 \leq \text{Time} \leq 1.25$

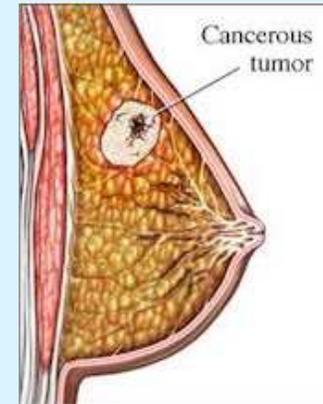
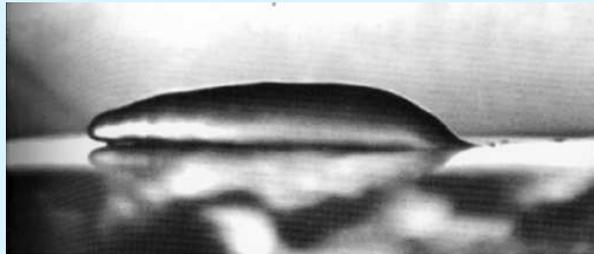


Simulation



Conclusions

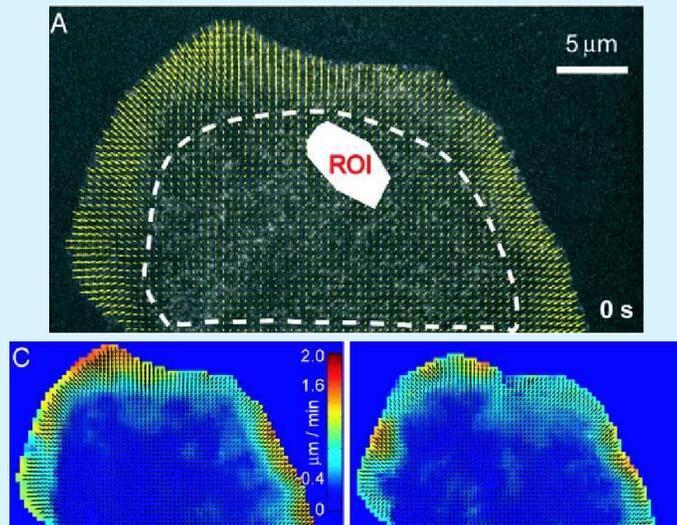
- By changing constitutive equation and/or material parameters, model can be applied to a variety of cell types *as well as multicellular tissues*.



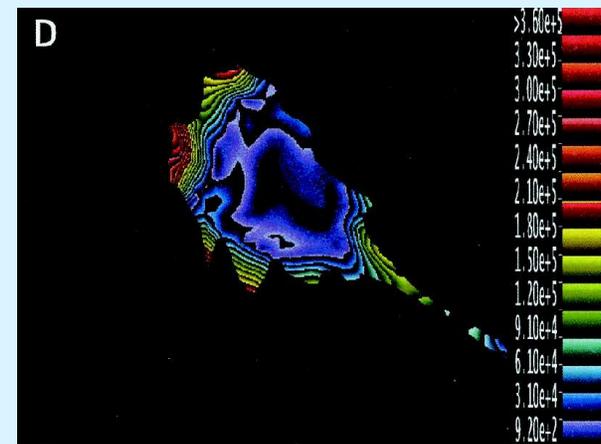
- Model captures large deformation, viscoelastic behavior.
- By mathematical modeling and simulation we will be able to perform numerical experiments that 1) verify existing lab experiments and 2) cannot be easily done in a lab.
- The model and simulations will shed light on the synthesis of a the complex process involved in directed cell motility.

Issues for the Future ...

- Remeshing.
- Calculate material parameters appropriate for cell type.
- Combine with signal transduction model.
 - ◆ Expressing the stress and deformation due to actin polymerization in a continuum framework.
 - ◆ Modeling the dynamics of focal adhesions.
- Verify the model and simulations by comparison to experimental results.



(from Vallotton *et al.* , PNAS, 2004)



(from Munevar *et al.* , *Biophys. J.*, 2001)

Acknowledgments

- Collaborator: Hans G. Othmer
- National Science Foundation DMS – 0317372
- Minnesota Supercomputing Institute