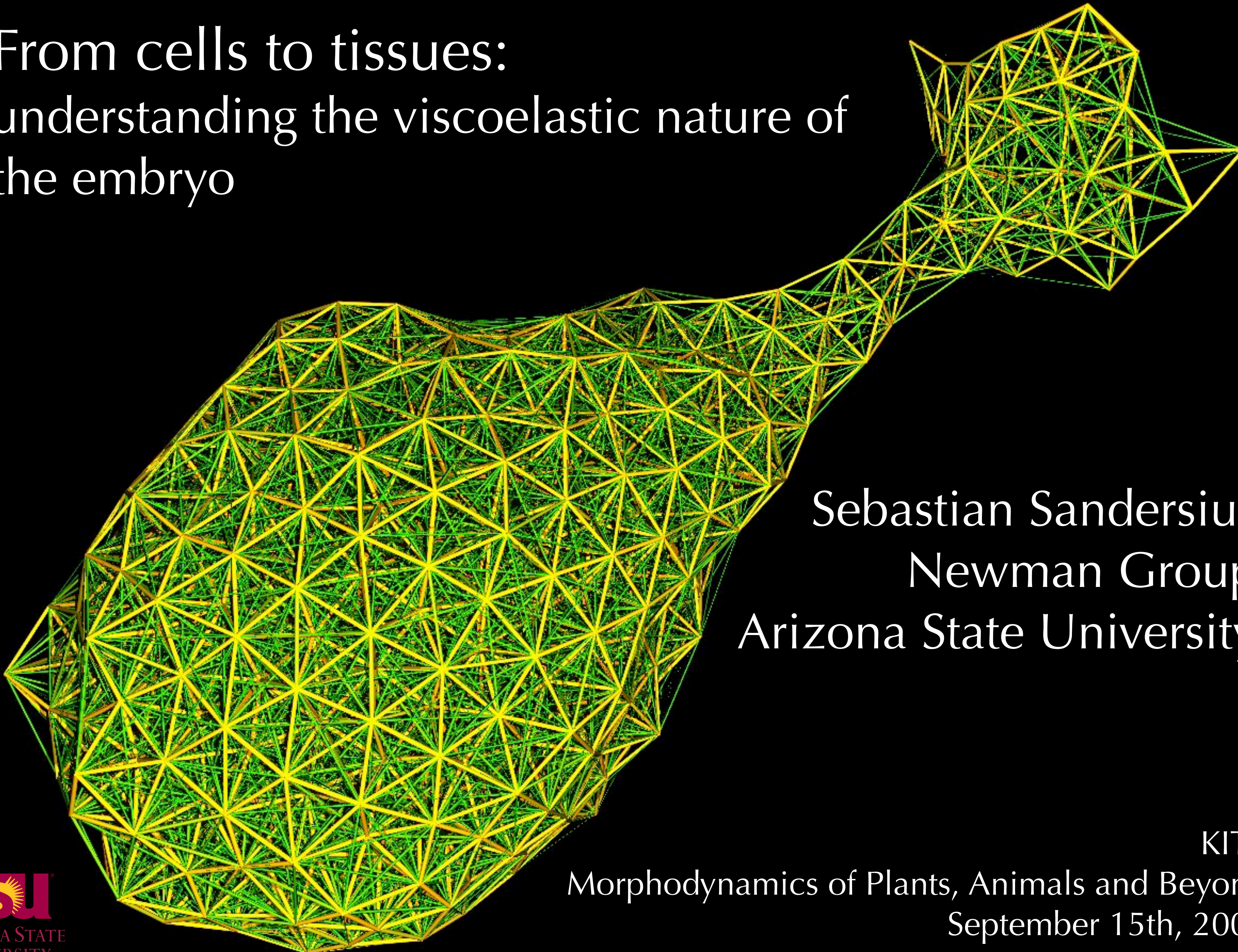
From cells to tissues:
understanding the viscoelastic nature of the embryo



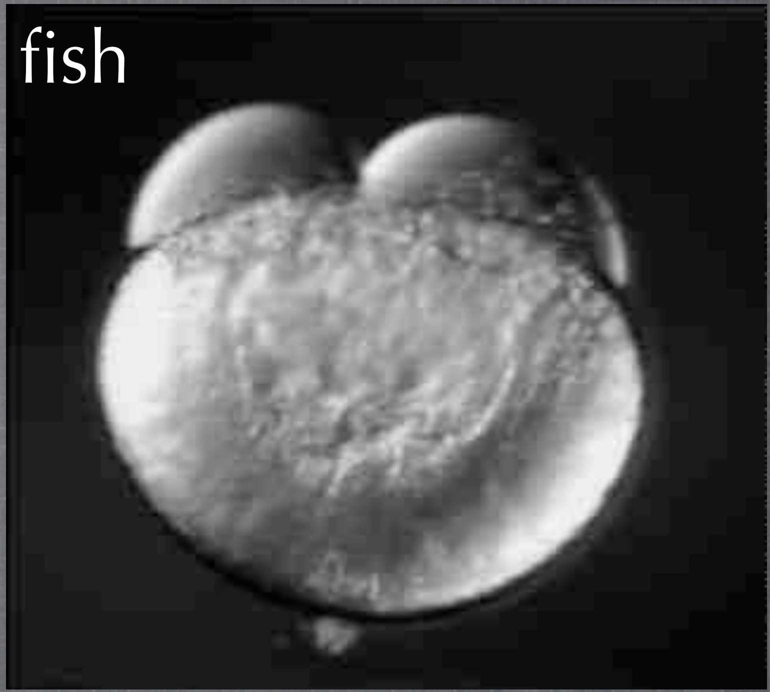
Sebastian Sandersius
Newman Group
Arizona State University

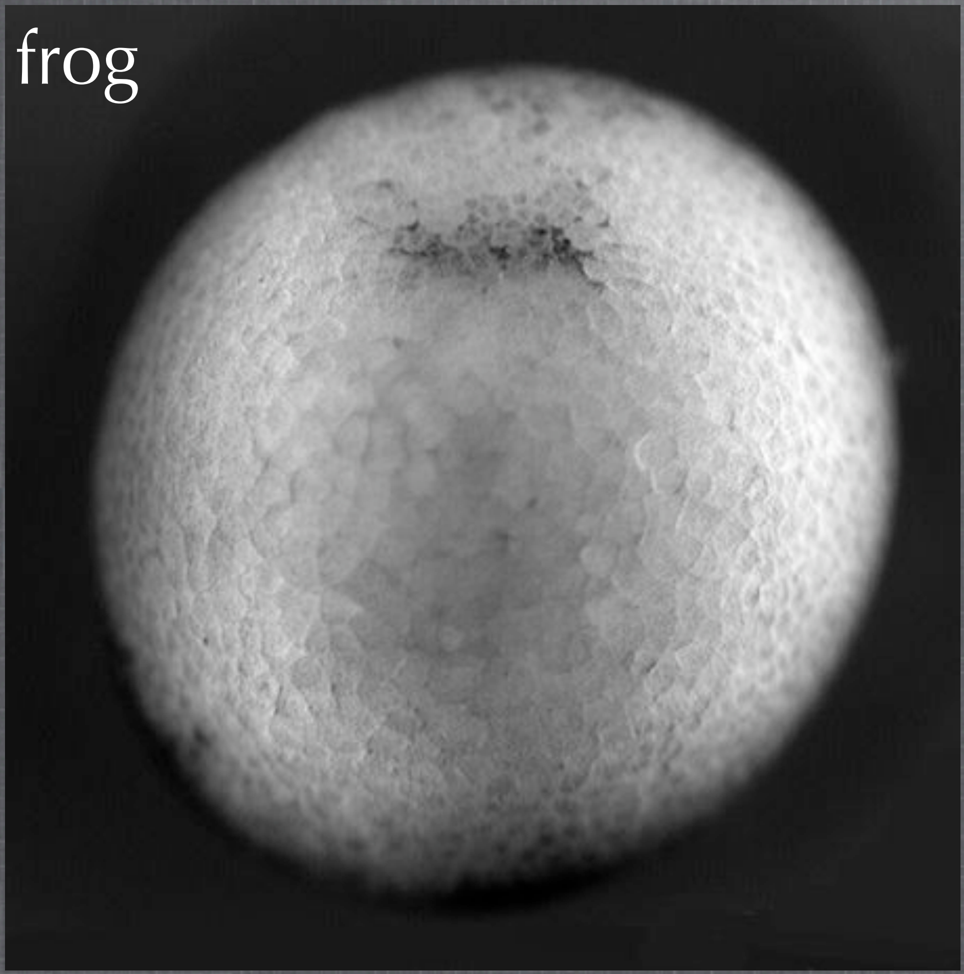
KITP
Morphodynamics of Plants, Animals and Beyond
September 15th, 2009

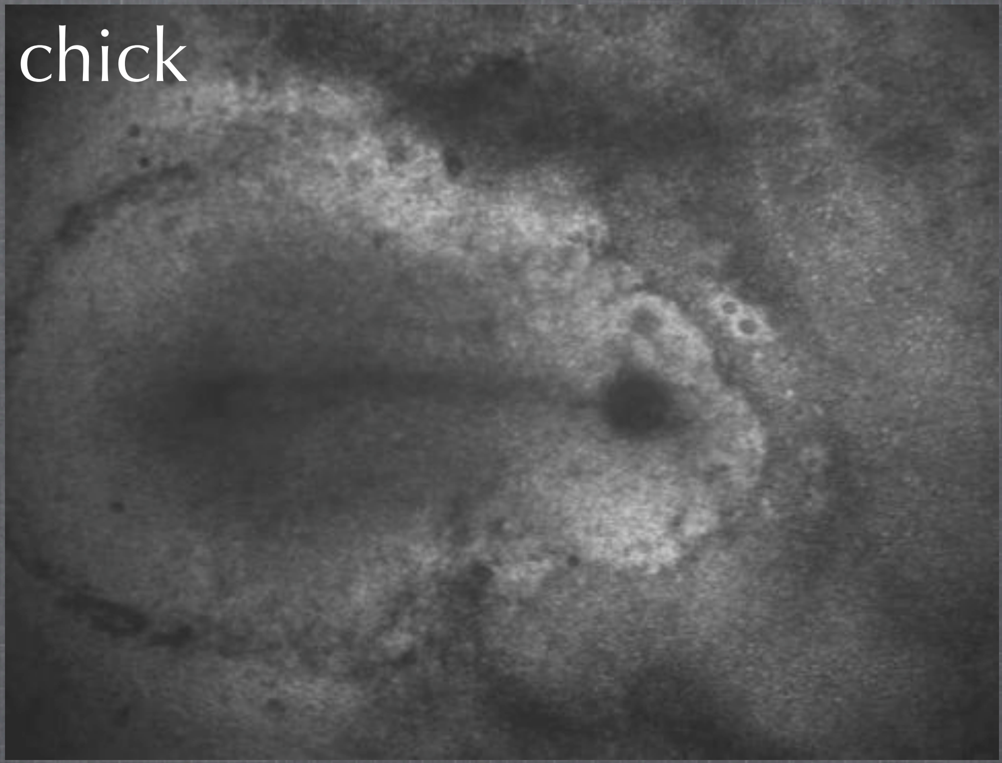
ASU
Arizona State University

Motivation

To unravel the intricacies of how large scale morphogenesis of the developing embryo is an emergent phenomenon of certain phenotypical properties of constituent cells





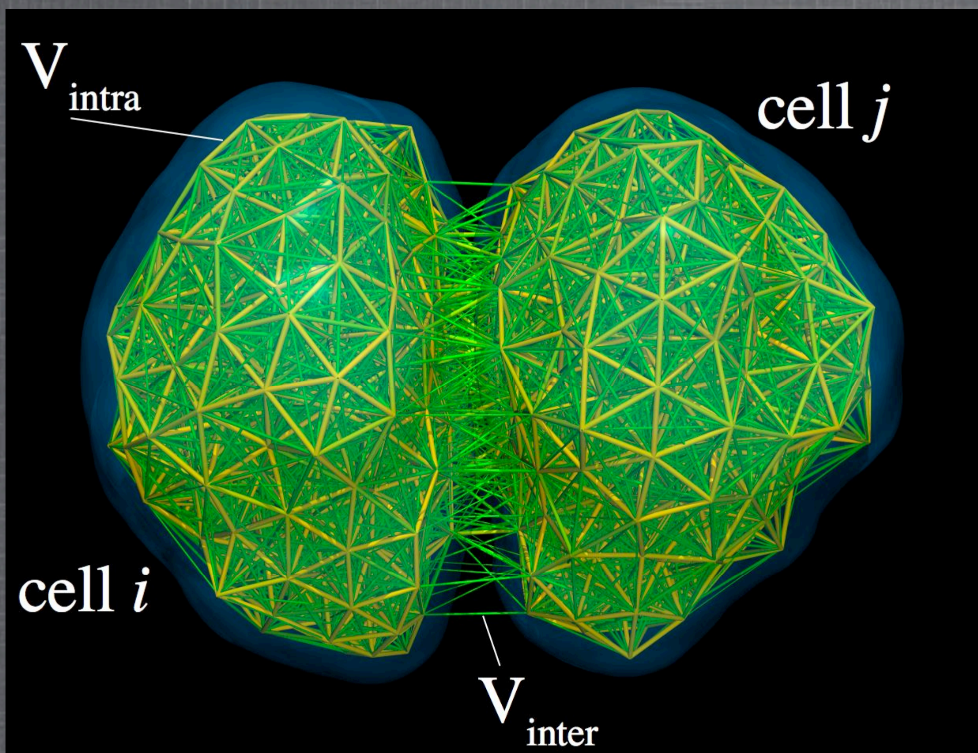


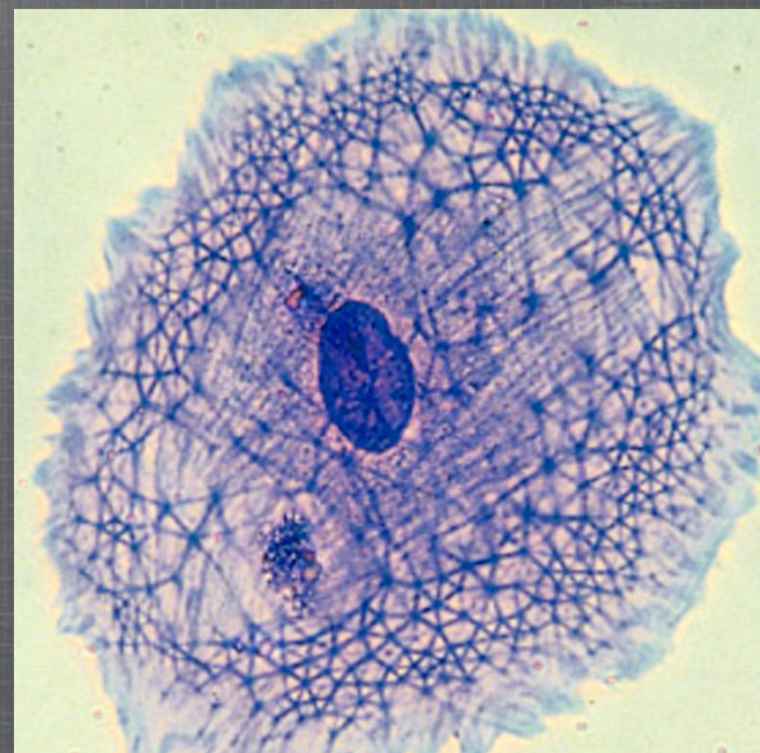
The Subcellular Element Model for multicellular systems

We treat a single cell as a collection of elements. The equation of motion for the position vector of the single element α_i is expressed by the following Langevin equation:

$$\eta \dot{\mathbf{y}}_{\alpha_i} = \xi_{\alpha_i} - \nabla_{\alpha_i} \sum_{\beta_i \neq \alpha_i} V_{\mathrm{intra}}(|\mathbf{y}_{\alpha_i} - \mathbf{y}_{\beta_i}|) - \nabla_{\alpha_i} \sum_{j \neq i} \sum_{\beta_j} V_{\mathrm{inter}}(|\mathbf{y}_{\alpha_i} - \mathbf{y}_{\beta_j}|)$$

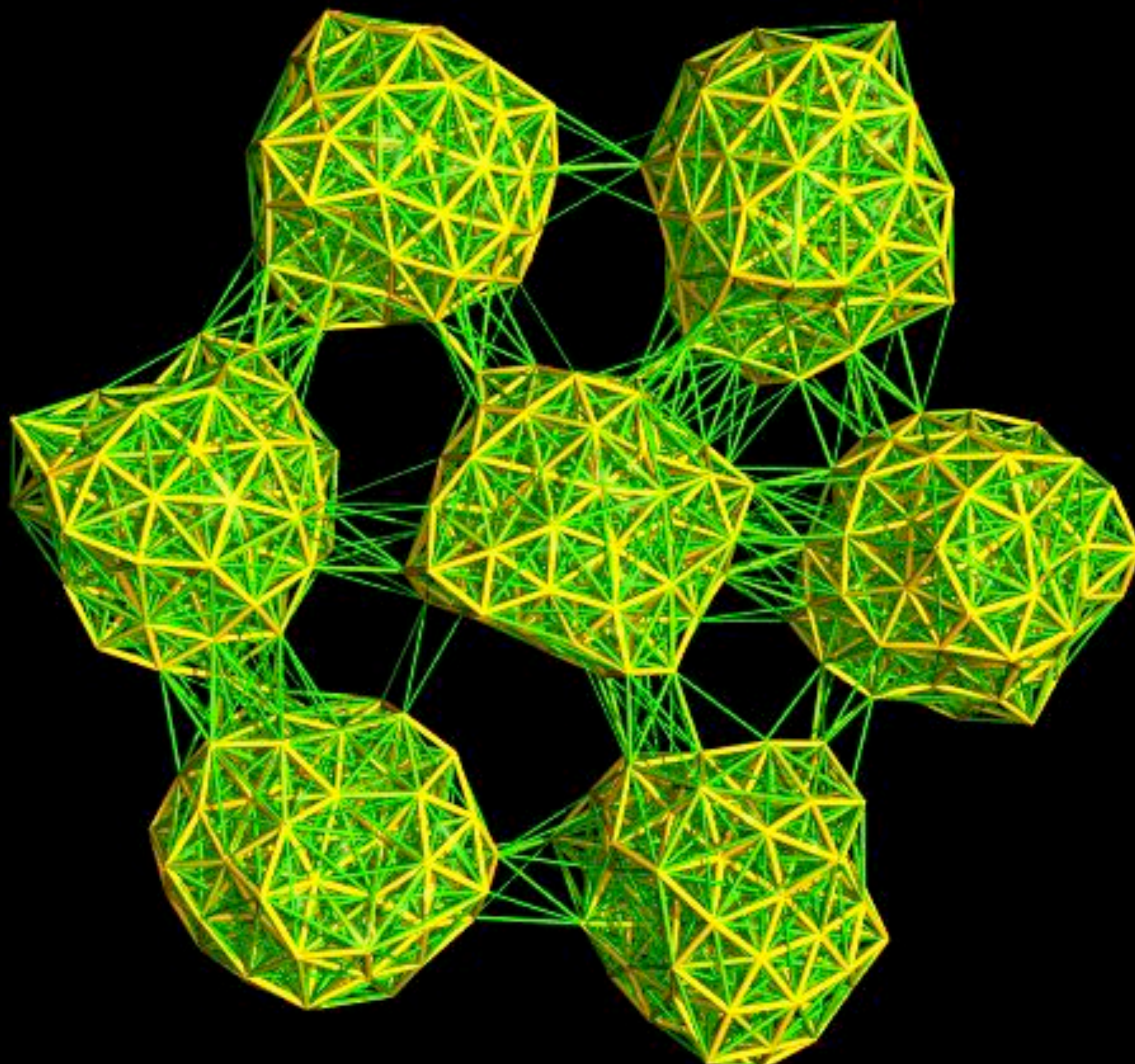
fluctuations — intra-cellular interactions — inter-cellular interactions





T. J. Newman. *Mathematical Biosciences and Engineering* (2005) **2** 611-622

Example of proliferation in a sheet of cells



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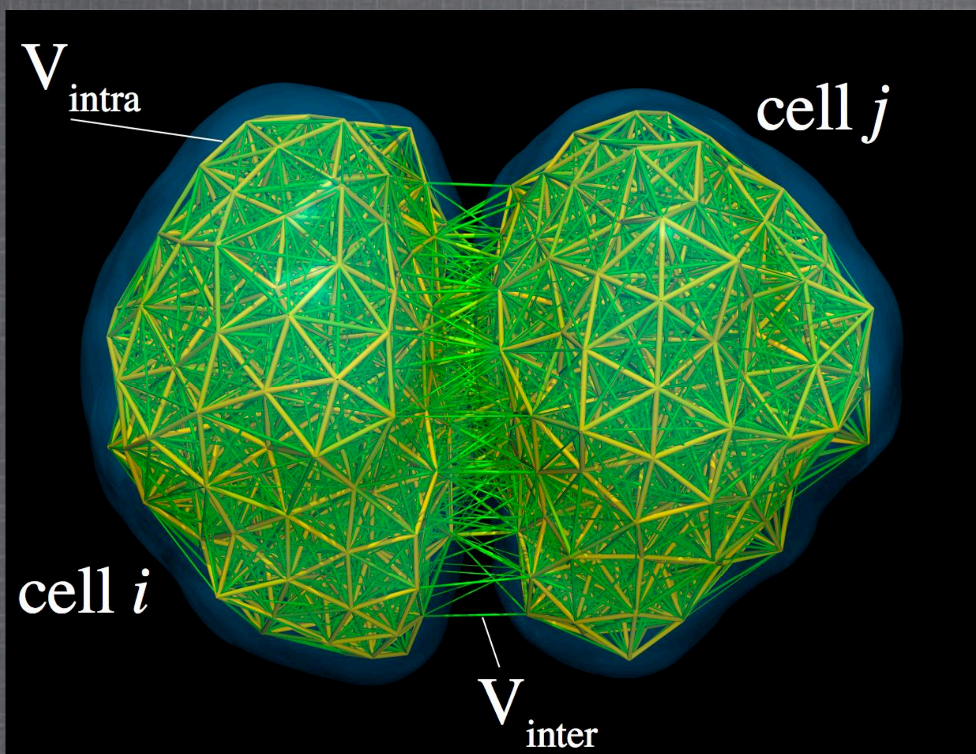
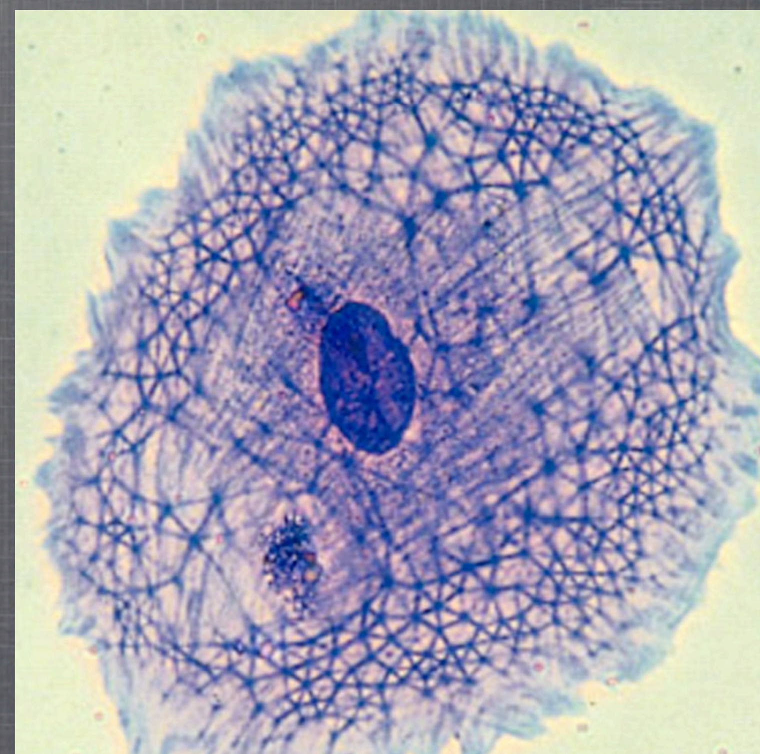
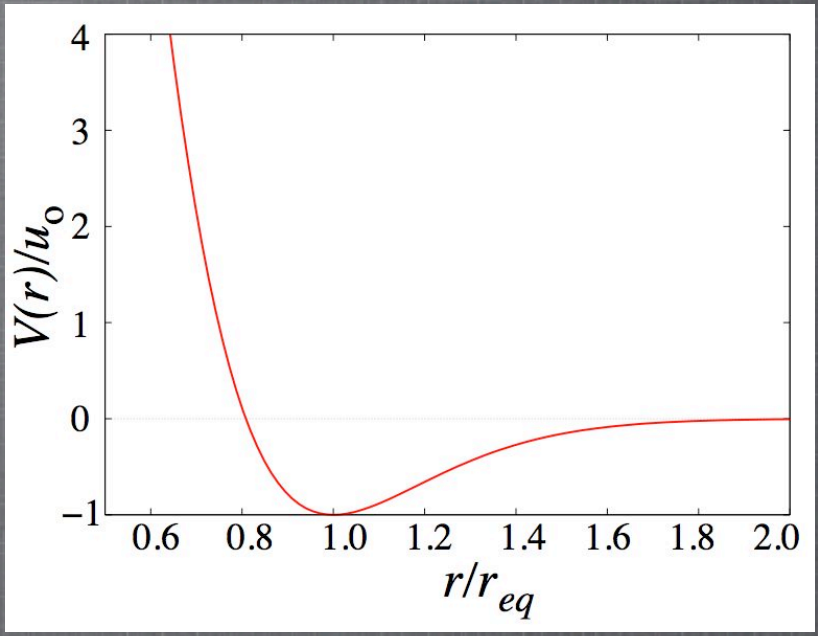




T. J. Newman. *Mathematical Biosciences and Engineering* (2005) **2** 611-622

The interaction potential between elements takes the following form

$$V(r) = u_0 e^{2\rho\left(1-\frac{r^2}{r_{eq}^2}\right)} - 2u_0 e^{\rho\left(1-\frac{r^2}{r_{eq}^2}\right)}$$

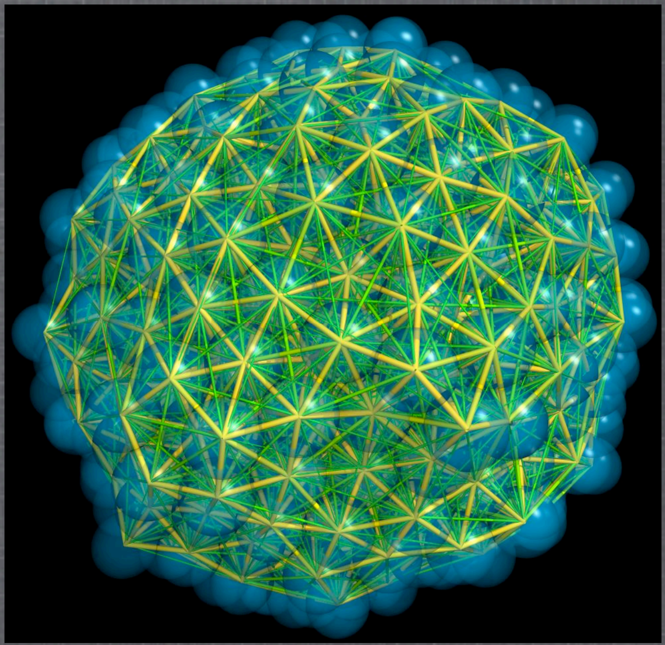


harmonic approximation of potential well

$$\kappa = \frac{8\rho^2 u_0}{r_{eq}^2}$$

Scaling a single cell

$$r_{eq}(N) = 2R_{cell}\left(\frac{p_3}{N}\right)^{\frac{1}{3}}$$



to make bulk elastic and viscous properties scale invariant with the number of elements N

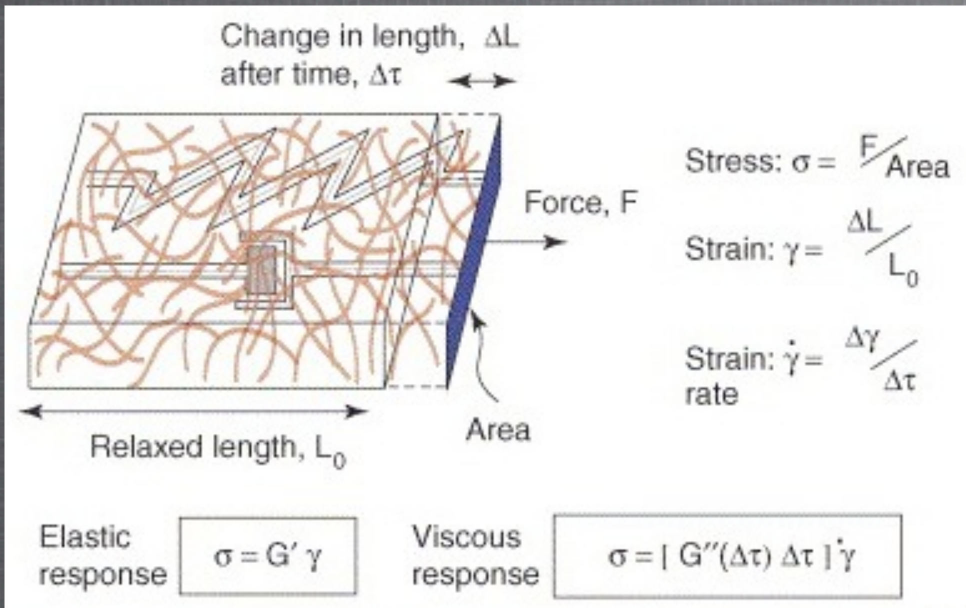
$$\kappa = \kappa_0 N^{-1/3}\left(1 - \lambda N^{-1/3}\right)$$

$$\eta = \eta_0 N^{-1}$$

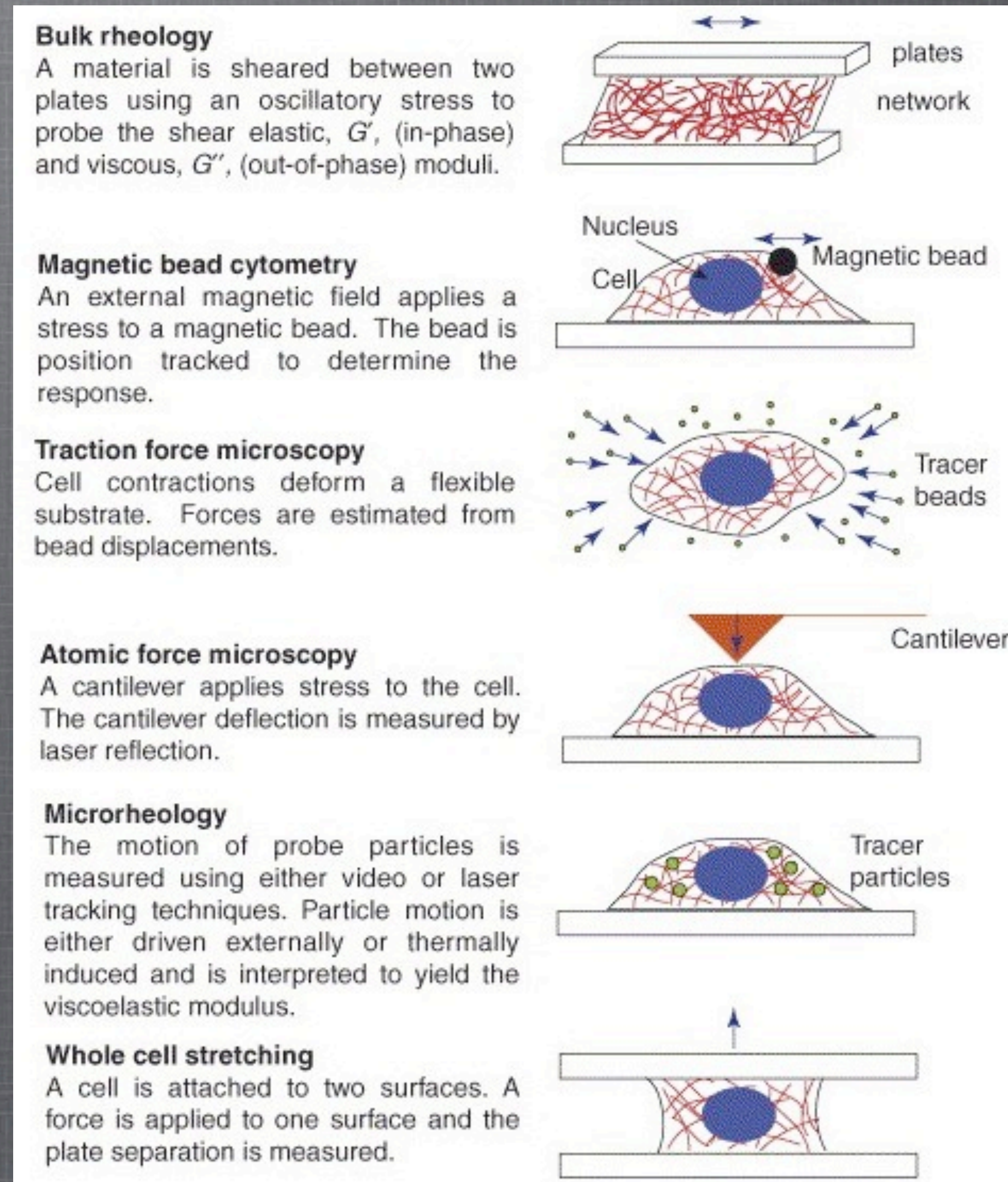
S.A. Sandersius, T.J. Newman. *Phys. Biol.* (2008) **5**, 015002

Single cell rheology

Quantities involved in mechanics measurements



Various methods to probe mechanical properties of cells



Viscoelastic (complex) Modulus

$$G^*(\omega) = G'(\omega) + iG''(\omega)$$

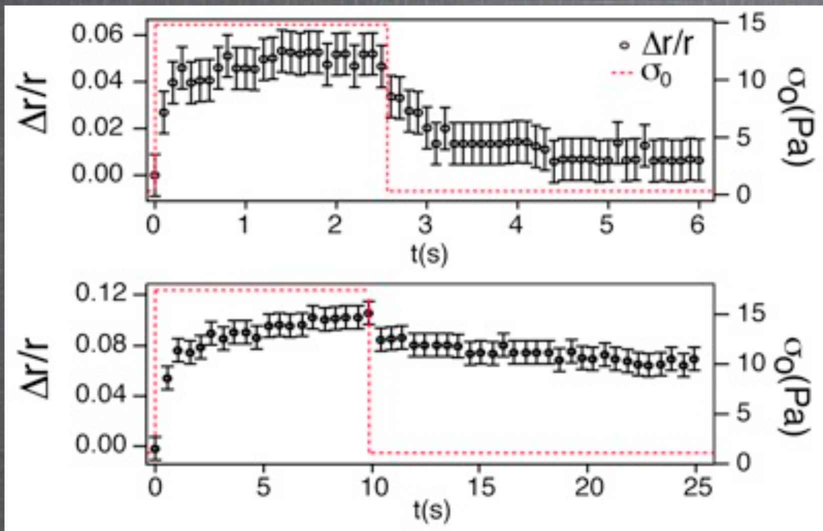
elasticity (storage modulus) — viscosity (loss modulus)

renders fluid and/or solid like properties over any time domain measured

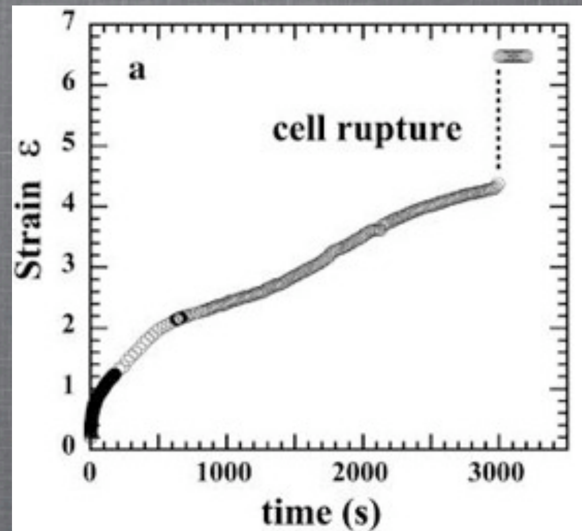
K.E. Kasza, A.C. Rowat, J. Liu, T.E. Angelini, C.P. Brangwynne, G.H. Koenderink, D.A. Weitz. *Curr Opin Cell Biol.* (2007) **19**(1) 101-7.

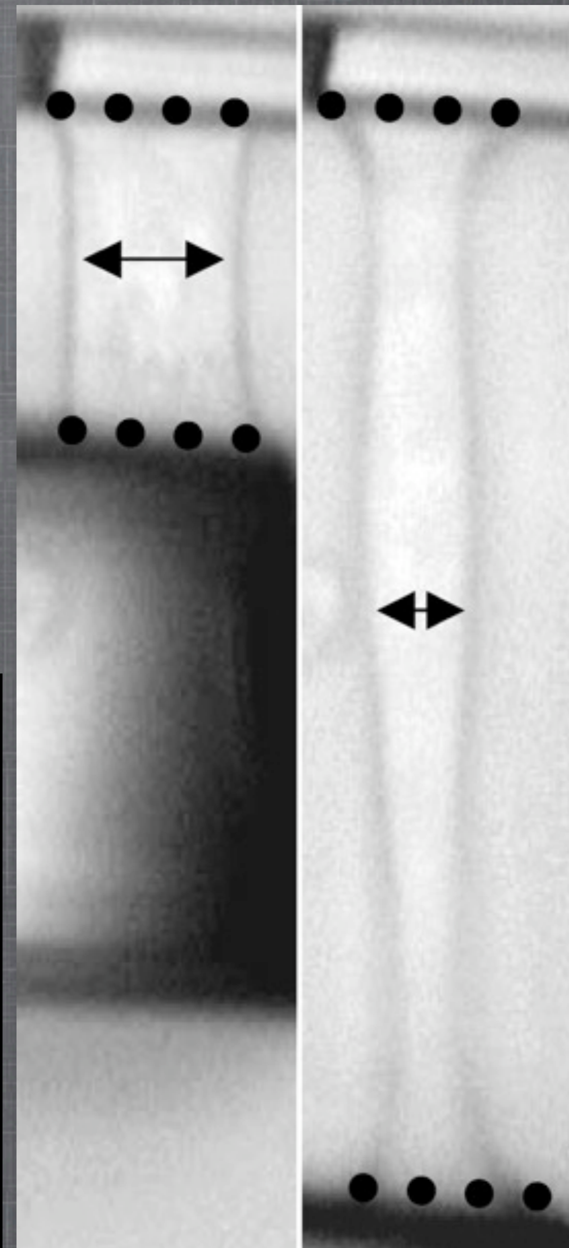
Creep response (whole cell stretching)

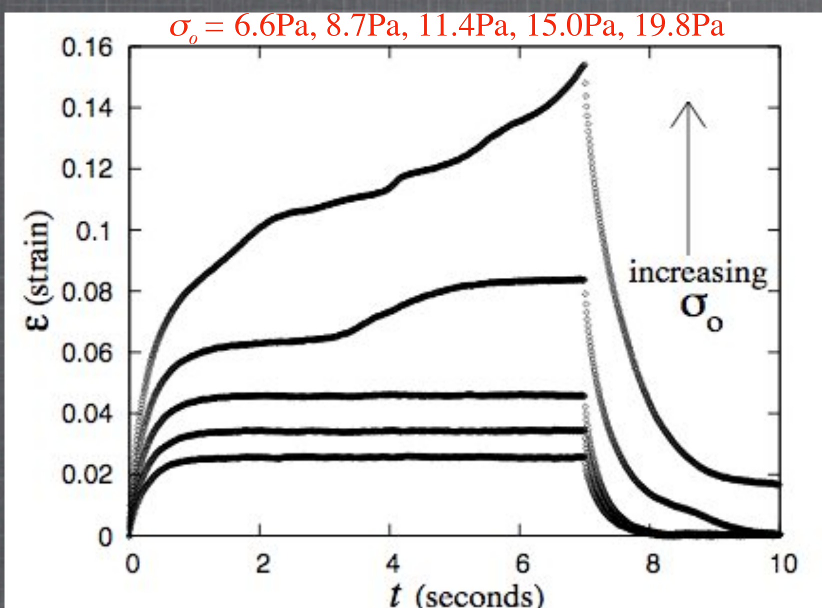
low strain (short time)

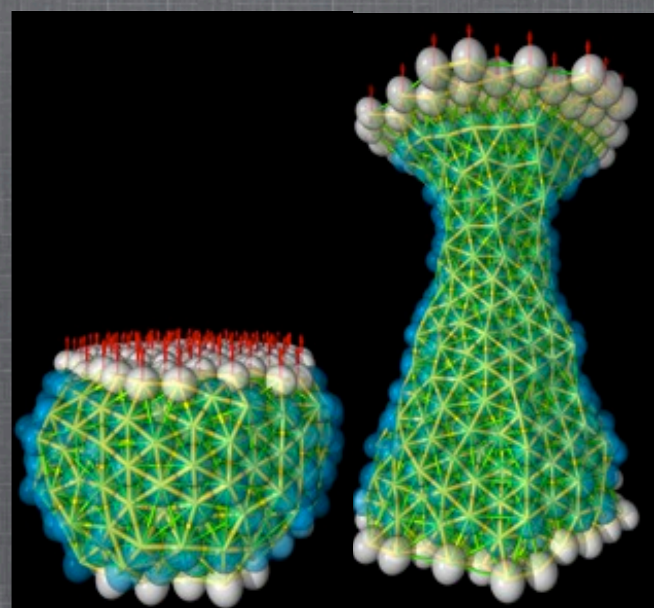


high strain (long time)







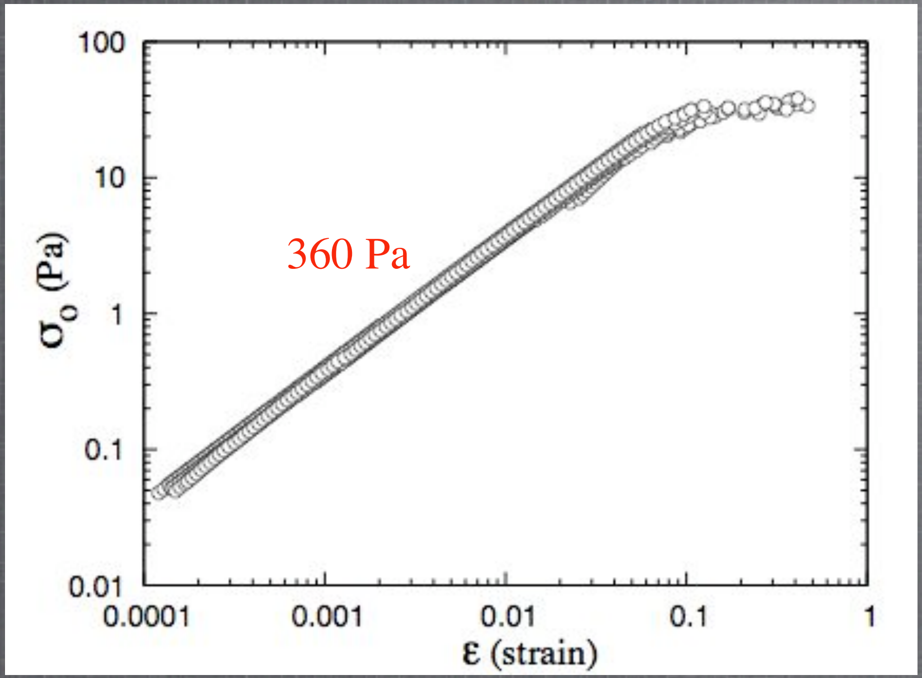


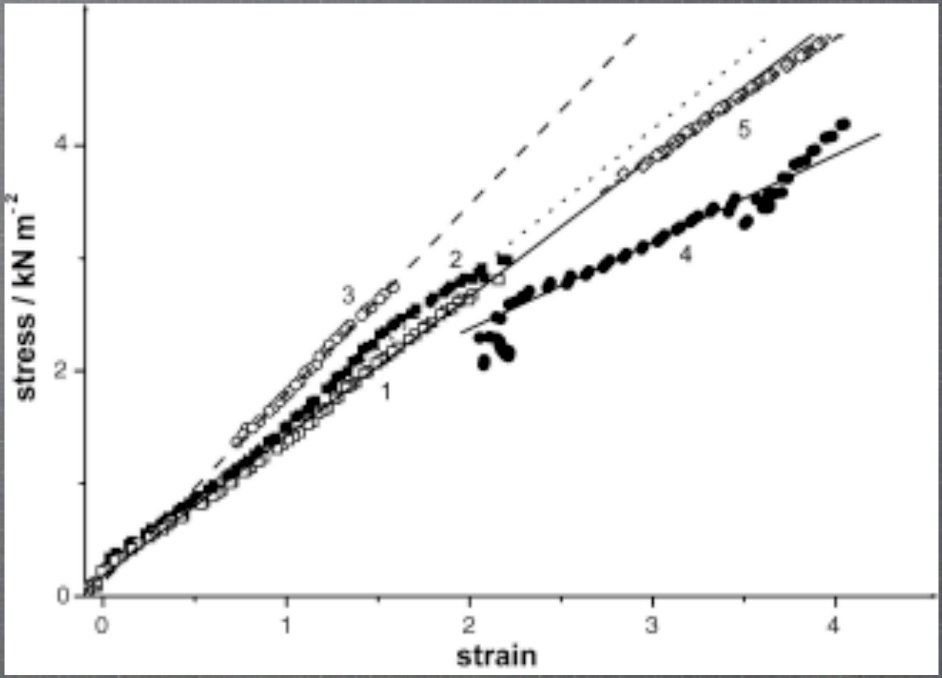
S.A. Sandersius, T.J. Newman. *Phys. Biol.* (2008) **5**, 015002

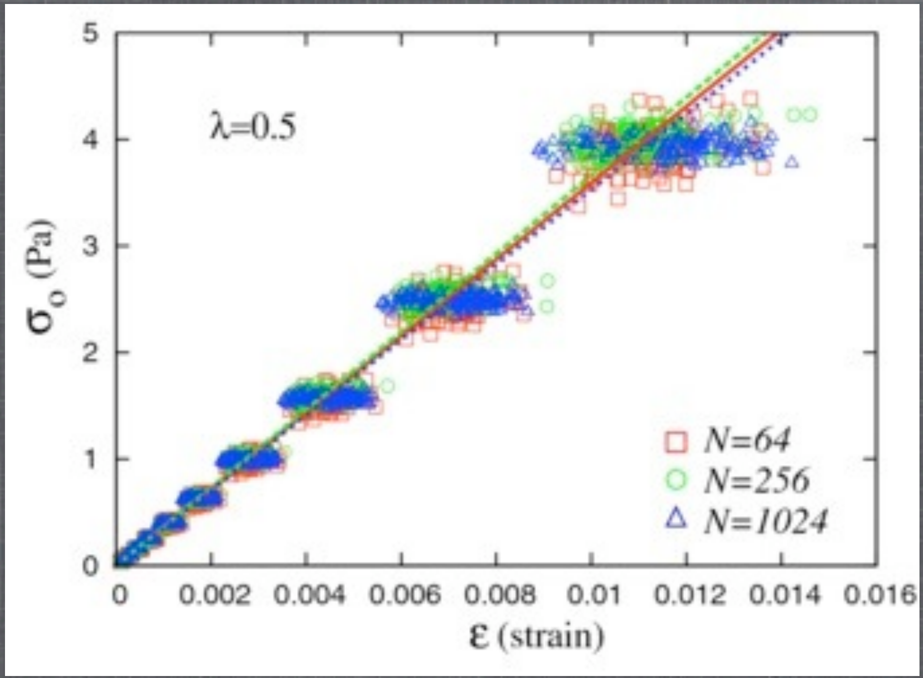
N. Desprat, A. Richert, J. Simeon, A. Asnacios. *Biophys J.* (2005) **88**(3) 2224–2233

F. Wottawah, S. Schinkinger, B. Lincoln, R. Ananthakrishnan, M. Romeyke, J. Guck and J. Kaes. *Phys. Rev. Lett.* (2005) **94** 098103

Elastic modulus (whole cell stretching)





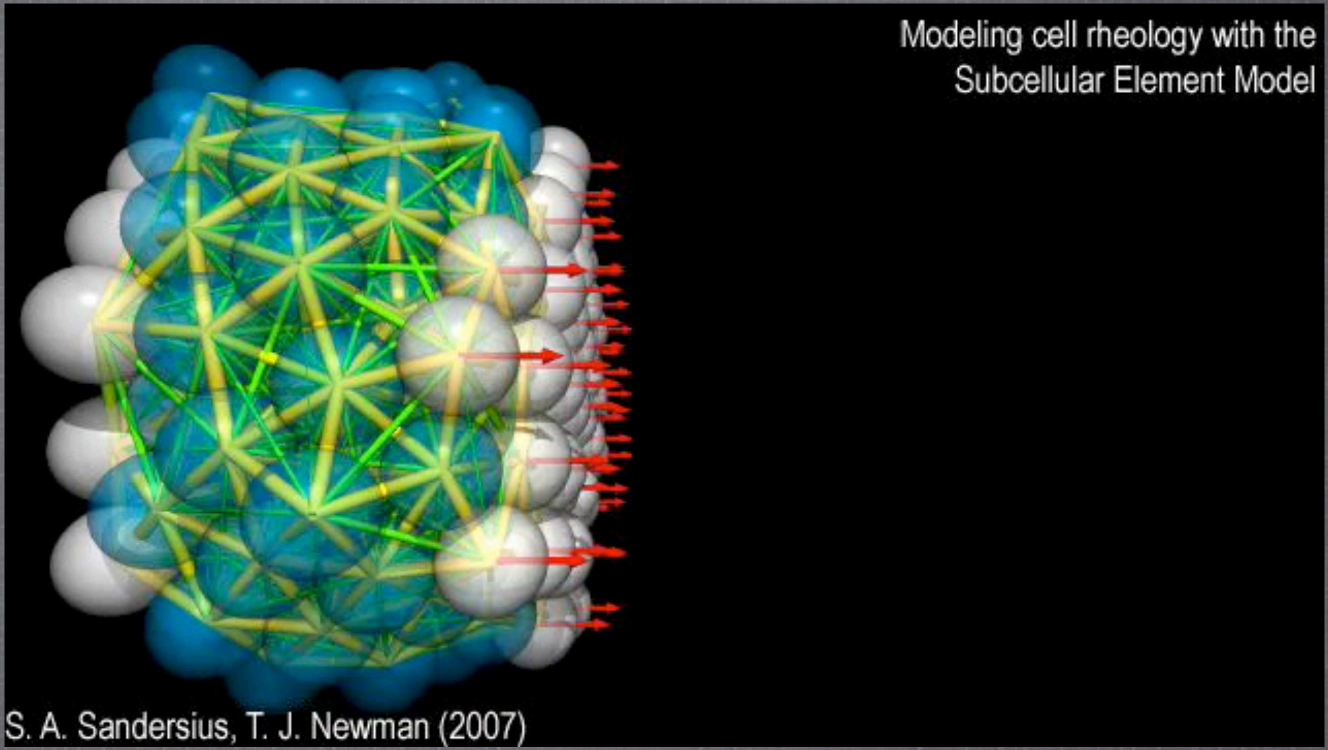


$$\kappa = \kappa_0 N^{-1/3}\left(1 - \lambda N^{-1/3}\right)$$

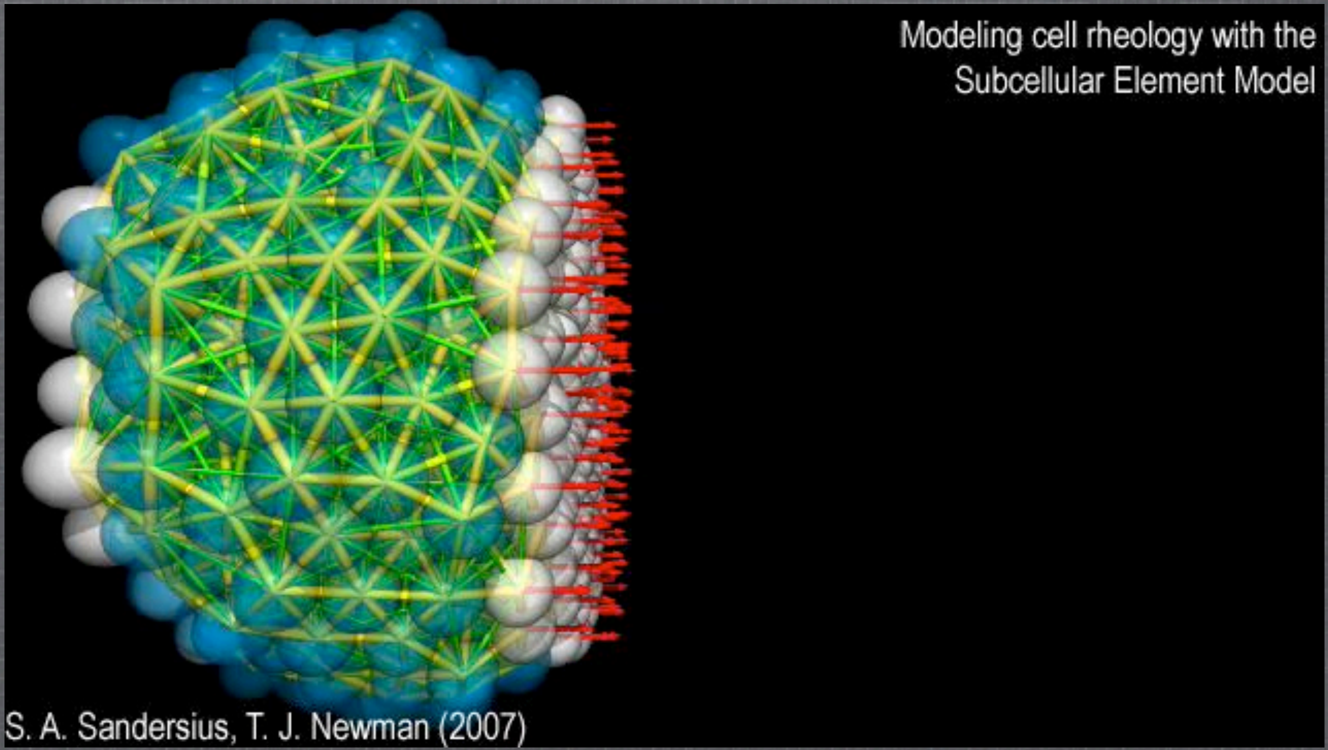
S.A. Sandersius, T.J. Newman. *Phys. Biol.* (2008) **5**, 015002

A. Micoulet, J.P. Spatz and A. Ott. *Chem. Phys. Chem. (2005)* **6** 663–70

$N = 256$
$\sigma_o = 28$ Pa
applied for
10 seconds



$N = 1024$
$\sigma_o = 21$ Pa
applied for
10 seconds



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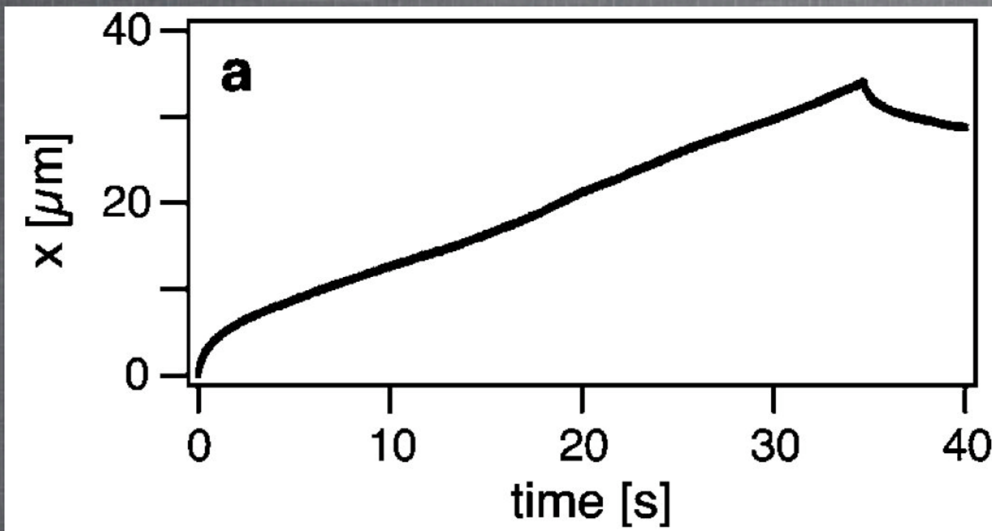
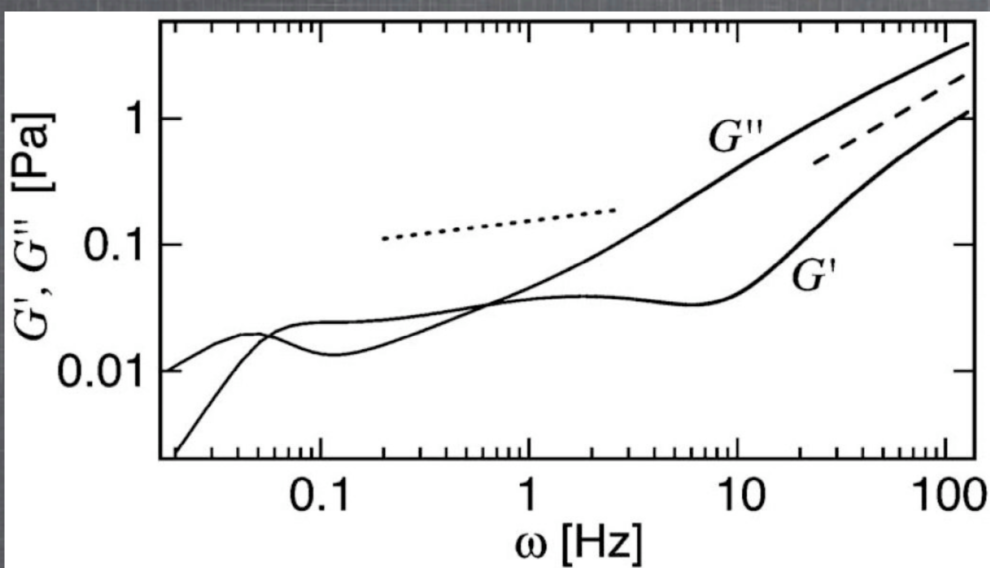
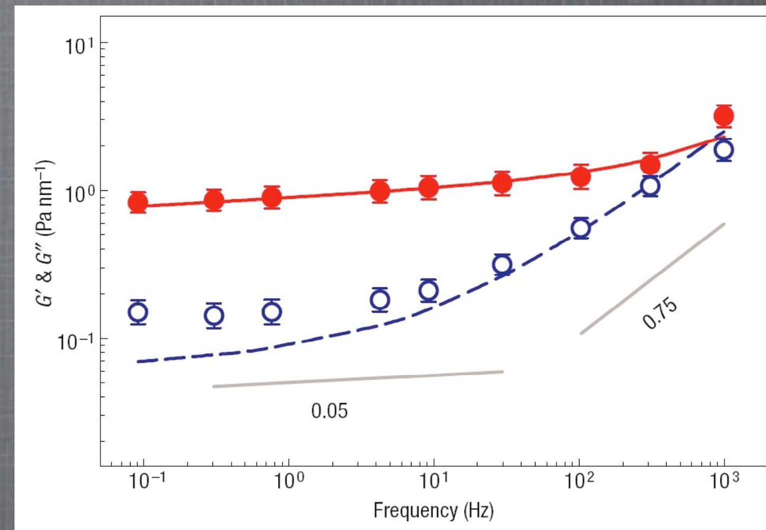
a microscopic look

Entangled F-actin solutions (bead cytometry)
no associated proteins

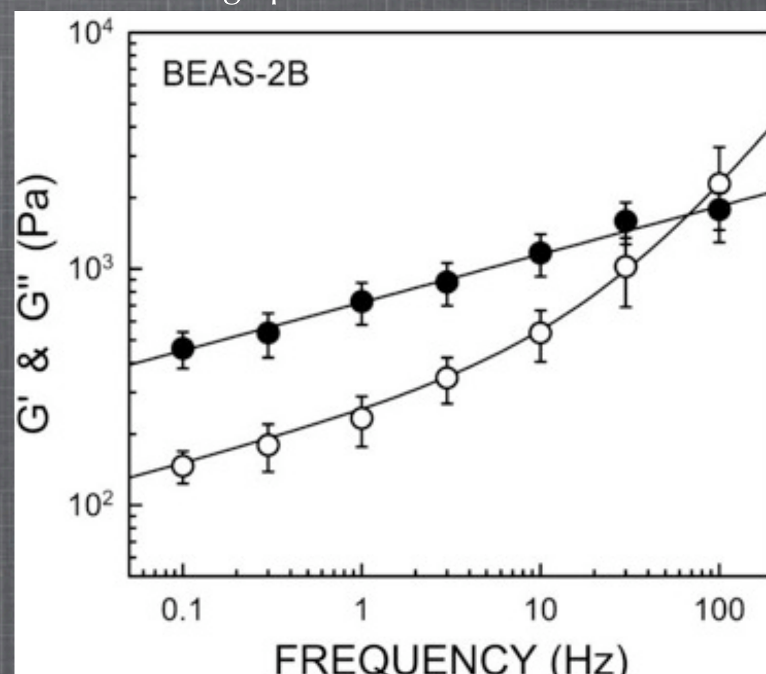




Bovine smooth muscle (bead cytometry)



Human lung epithelium (AFM)

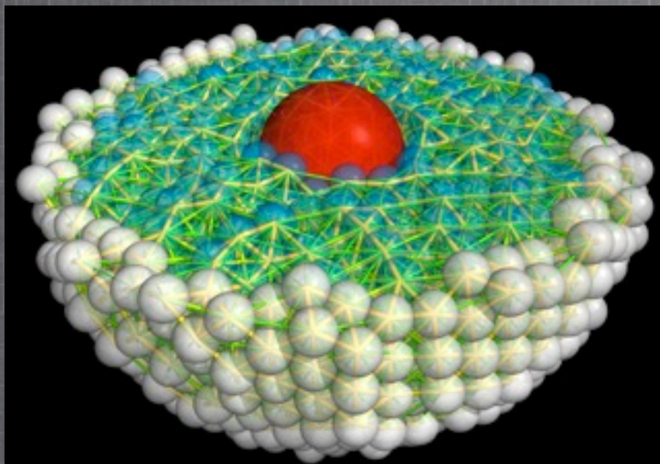


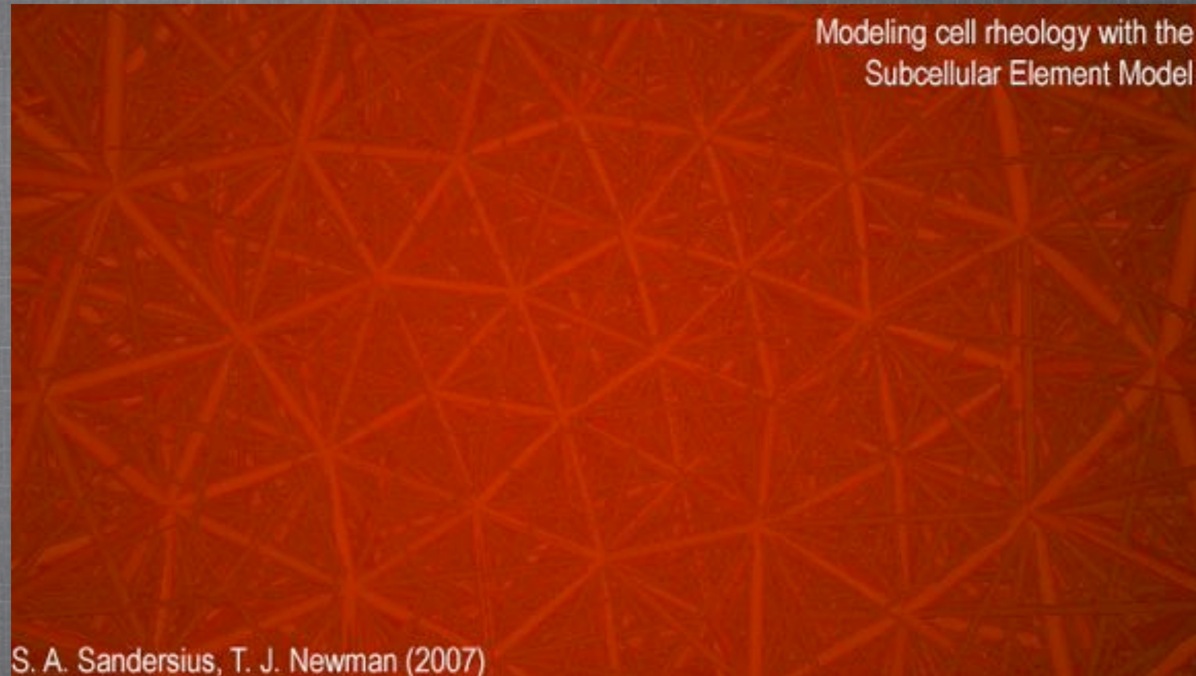
J. Uhde, N. Ter-Oganessian, D.A. Pink, E. Sackmann, A. Boulbitch. *Phys. Rev. E* (2005) **72** 061916

L. Deng, X. Trepat, J.P. Butler, E. Millet, K.G. Morgan, D.A. Weitz, J.J. Fredberg. *Nat Mater.* (2006) **5**(8):597-8

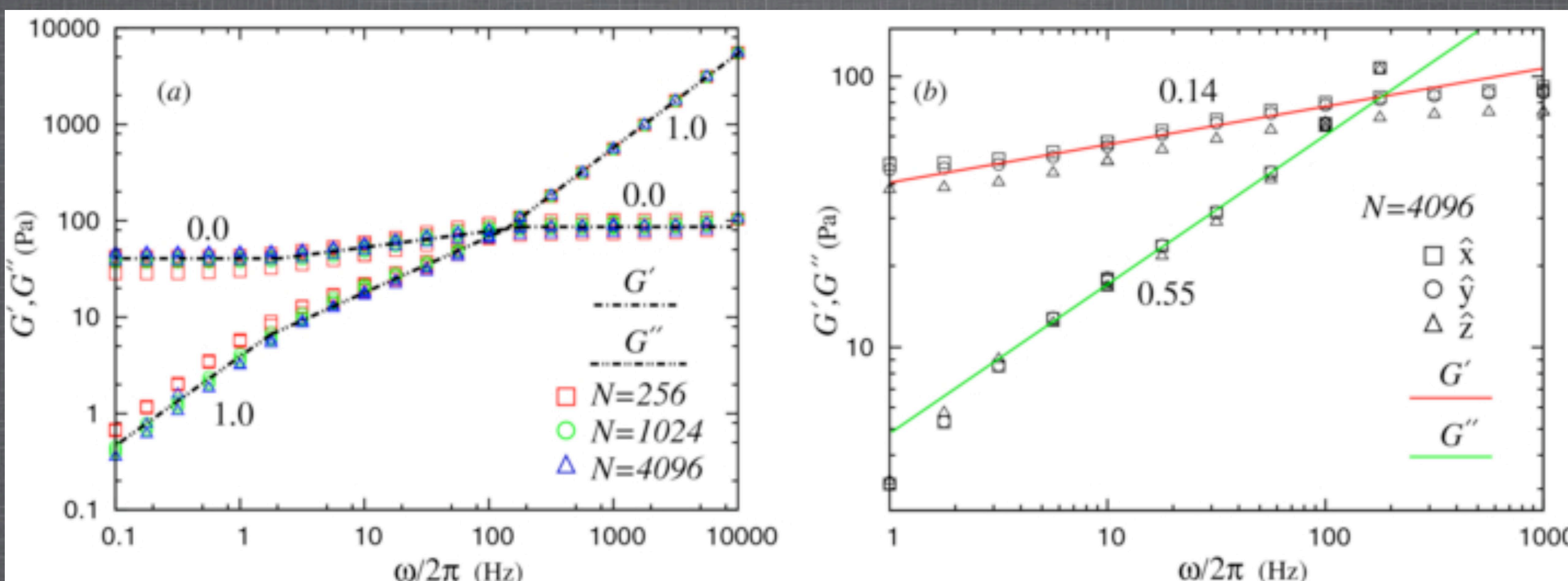
J. Alcaraz, L. Buscemi, M. Grabulosa, X. Trepat, B. Fabry, R. Farre, D. Navajas. *Biophys J.* (2003) **84**(3): 2071–2079

Microrheology: computational results





$$G'(\omega) = \frac{f_0}{g\,|x_0(\omega)|} cos\left[\phi(\omega)\right] \qquad G''(\omega) = \frac{f_0}{g\,|x_0(\omega)|} sin\left[\phi(\omega)\right]$$



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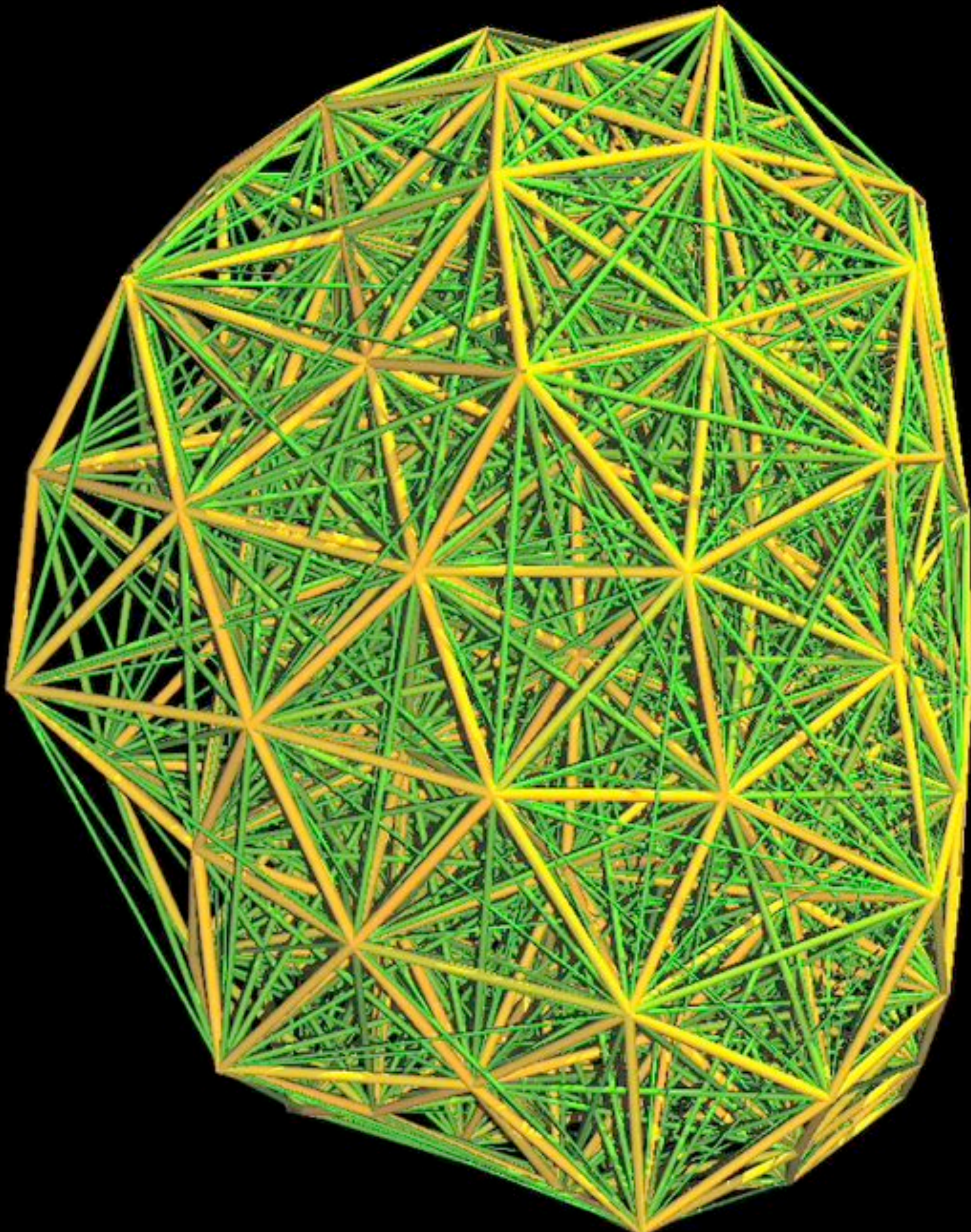
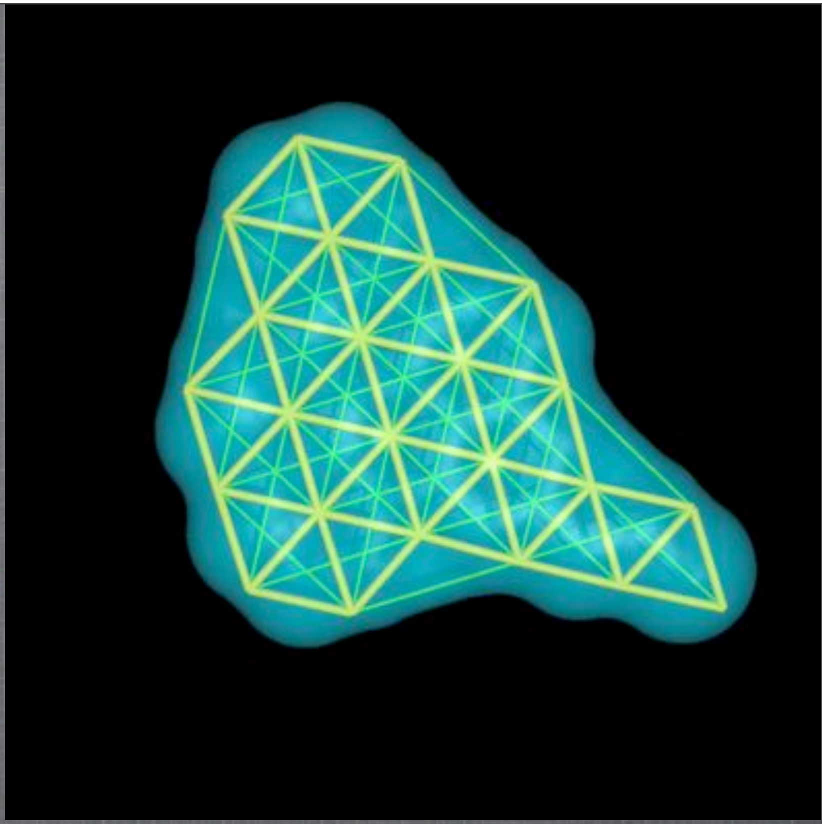
Cell stretching with polymerization/depolymerization



Cell Migration

Migration is a cyclical process on which a cell extends protrusions at its front and retracts its trailing end. It is spurred into action by migration-promoting or chemotactic agents that induce an initial polarization.



Dictyostelium cells in slug phase (CJ Weijer lab)

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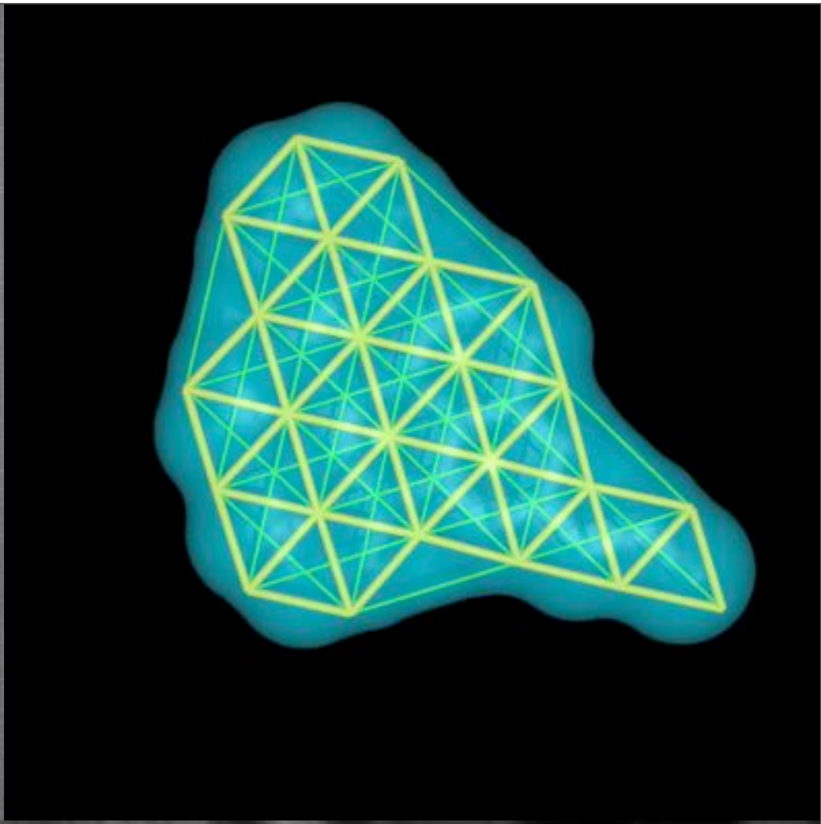

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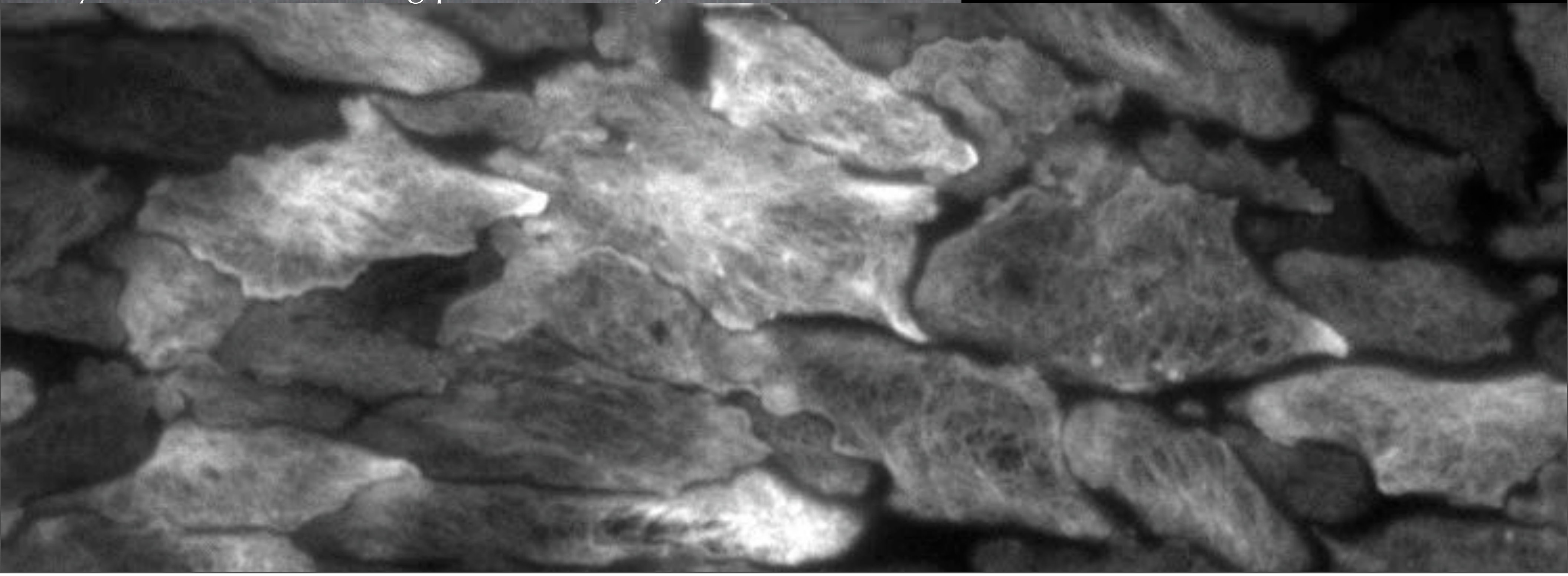


Migration in multicellular system

cells polarized via mechanotaxis, white cells forced to the right

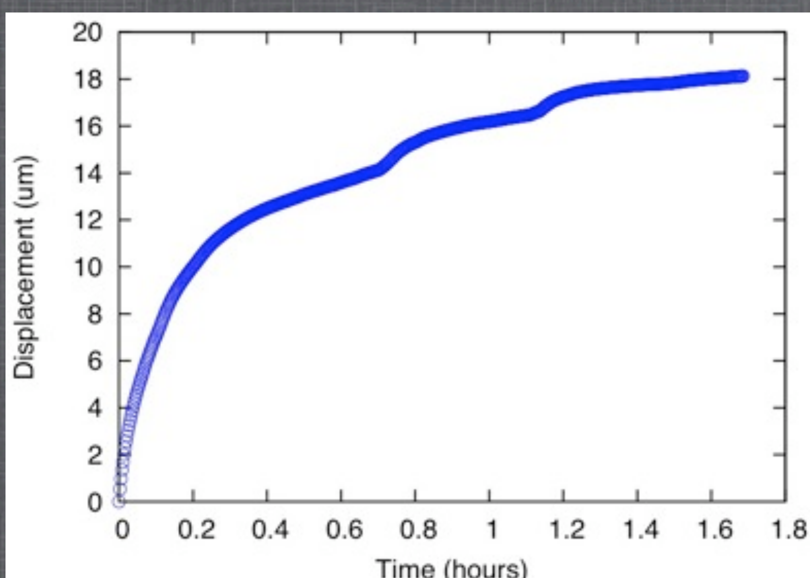
Migration in multicellular system

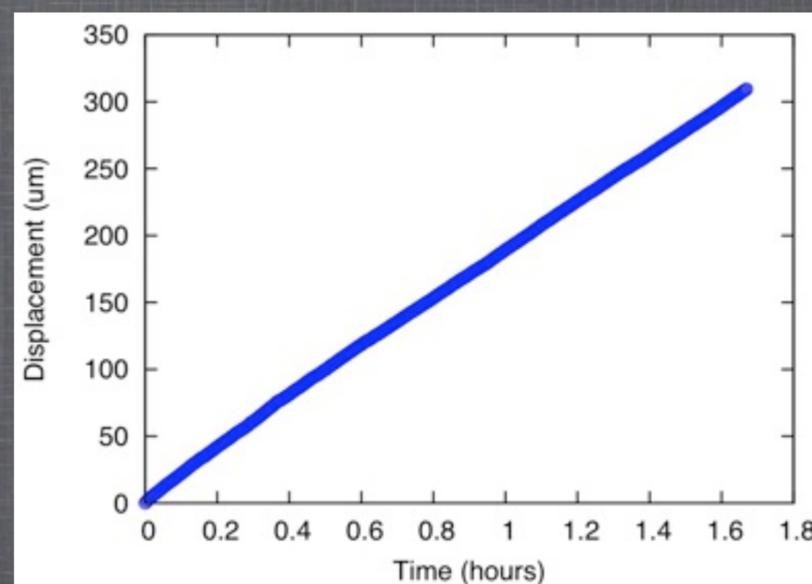
cells polarized via mechanotaxis, white cells forced to the right

1200 cells, 20 elements per cell, 40nN of force

without migration

with migration





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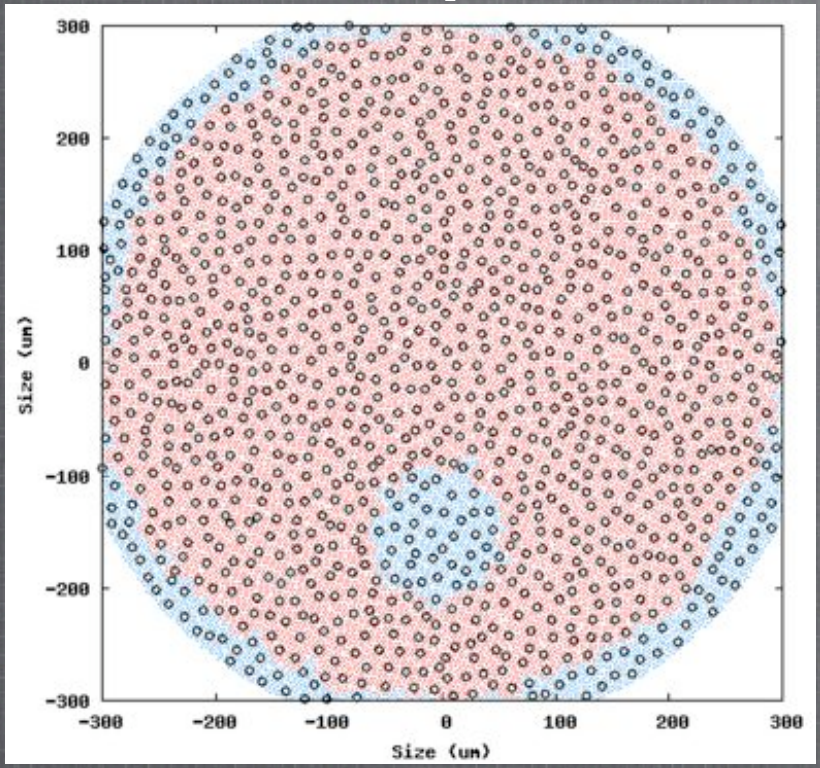
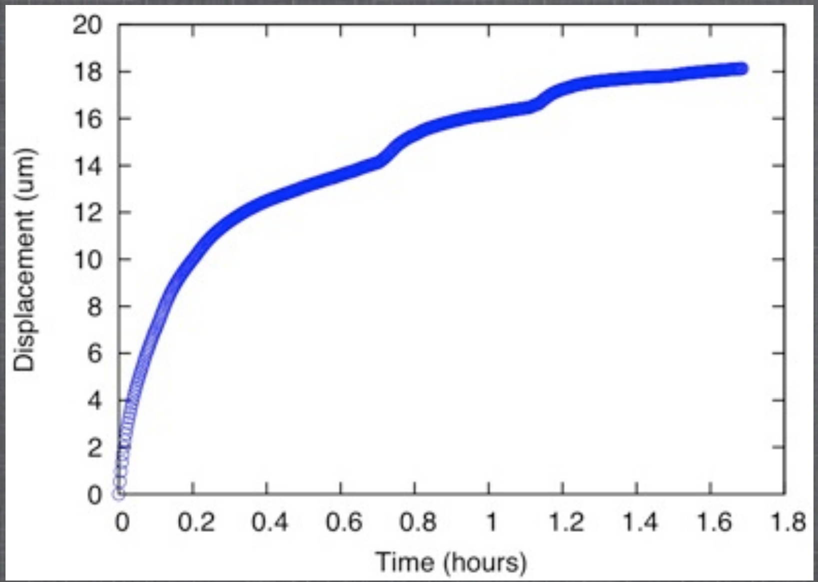
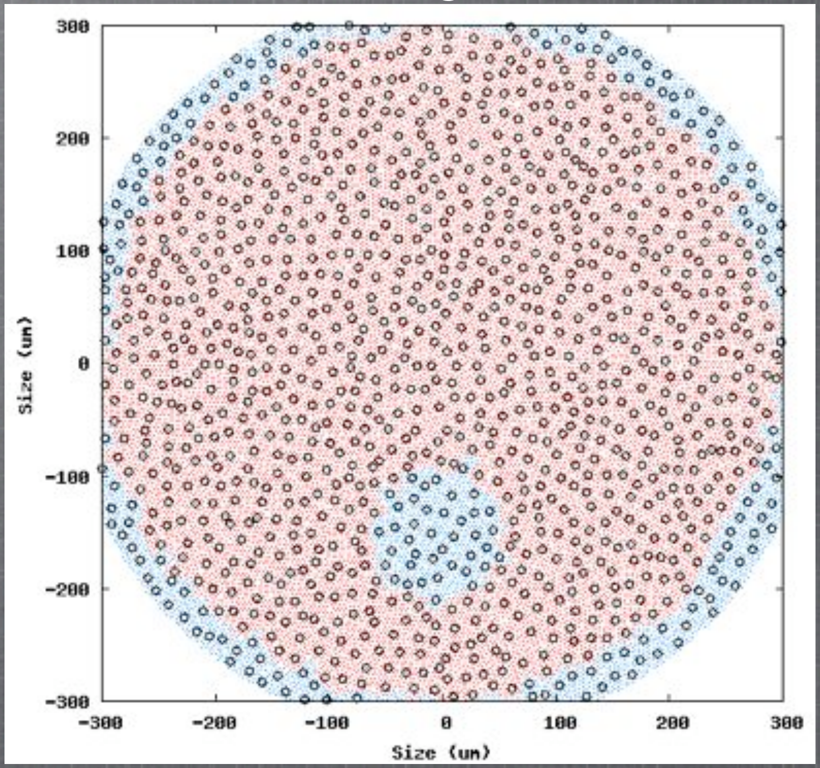
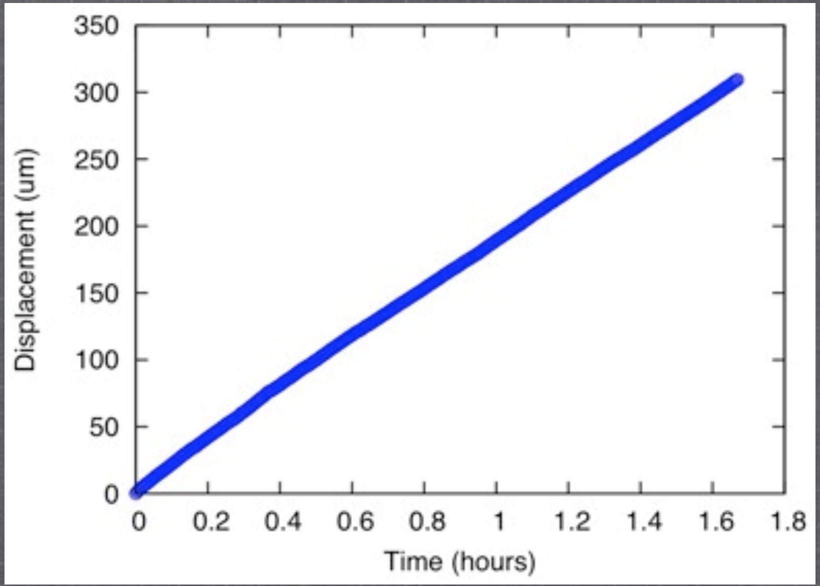




with migration





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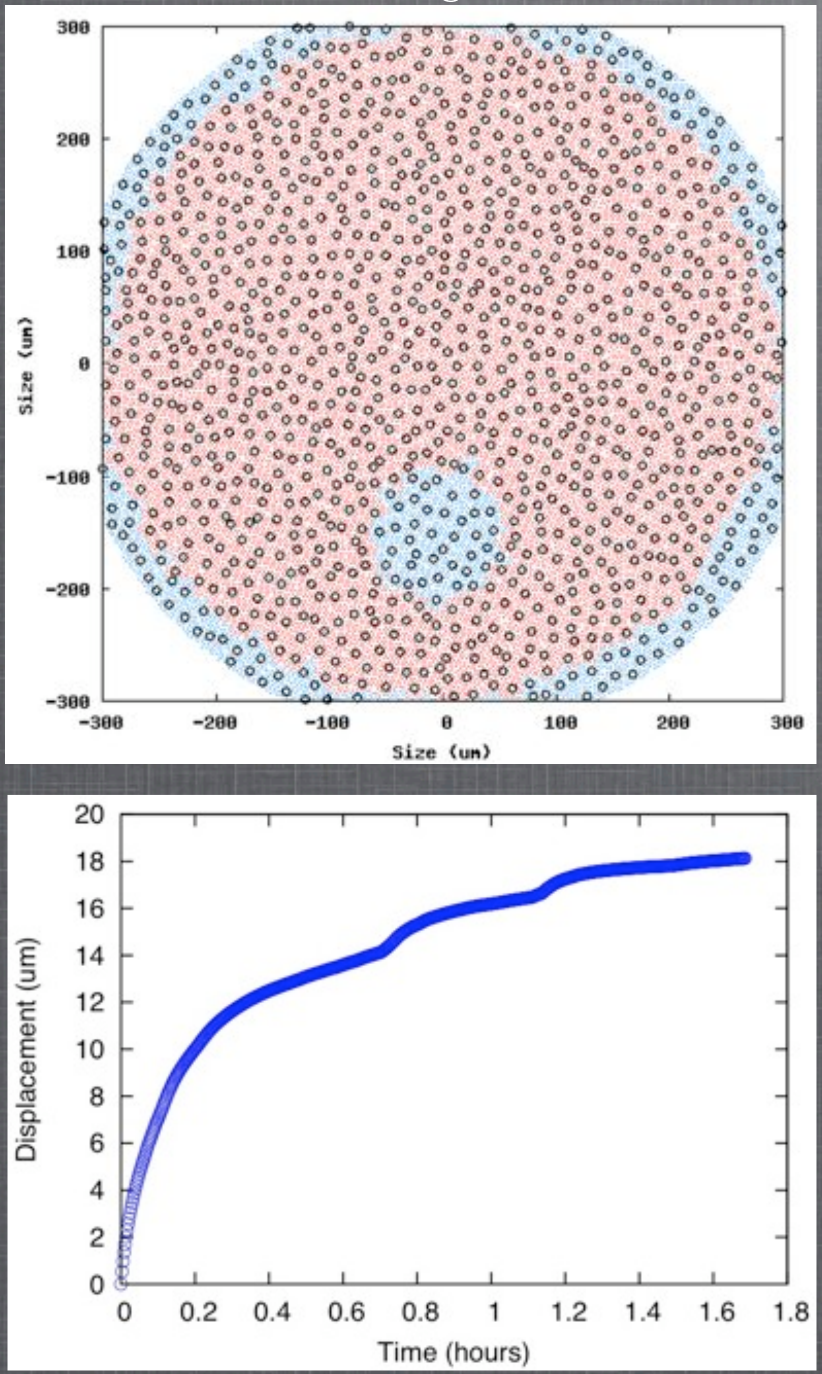
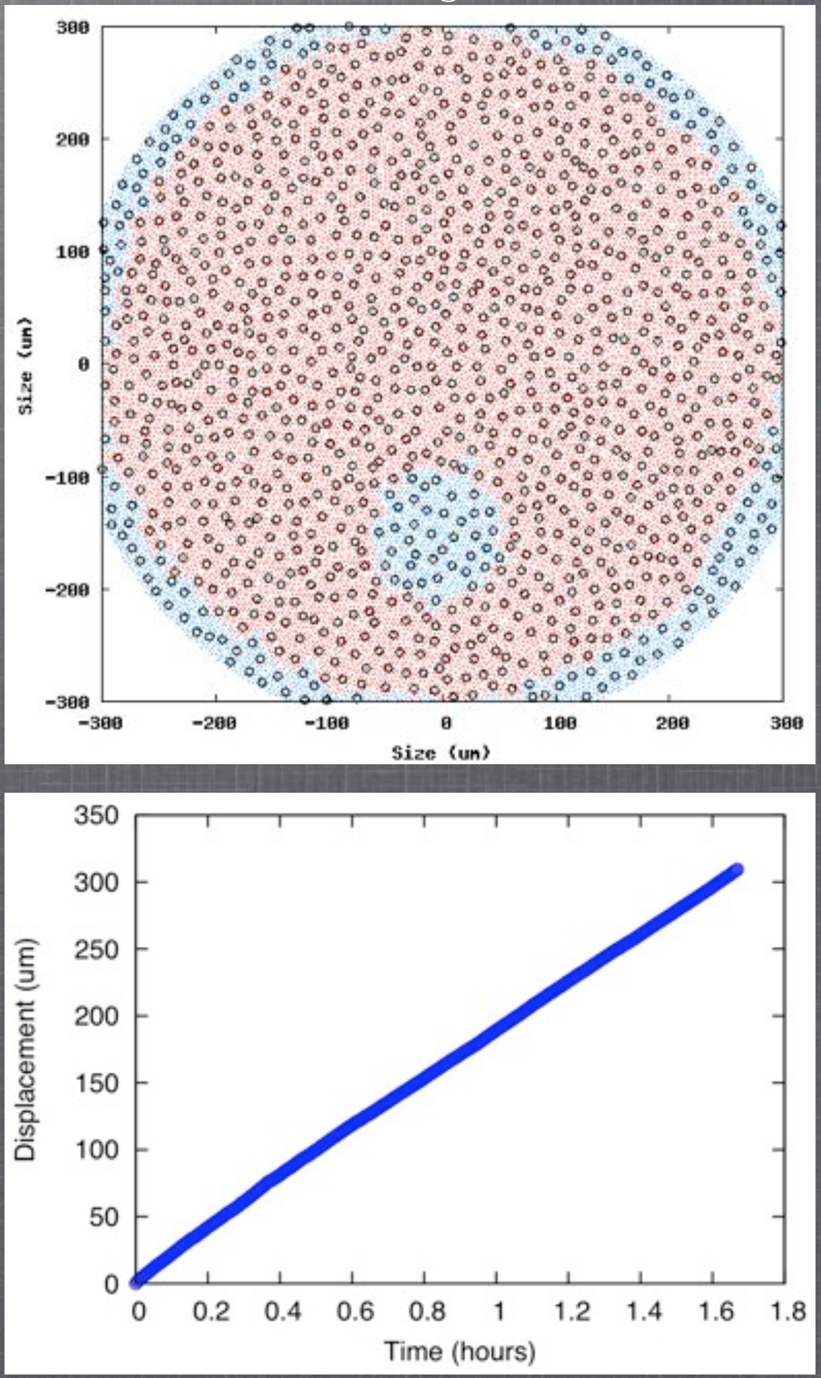
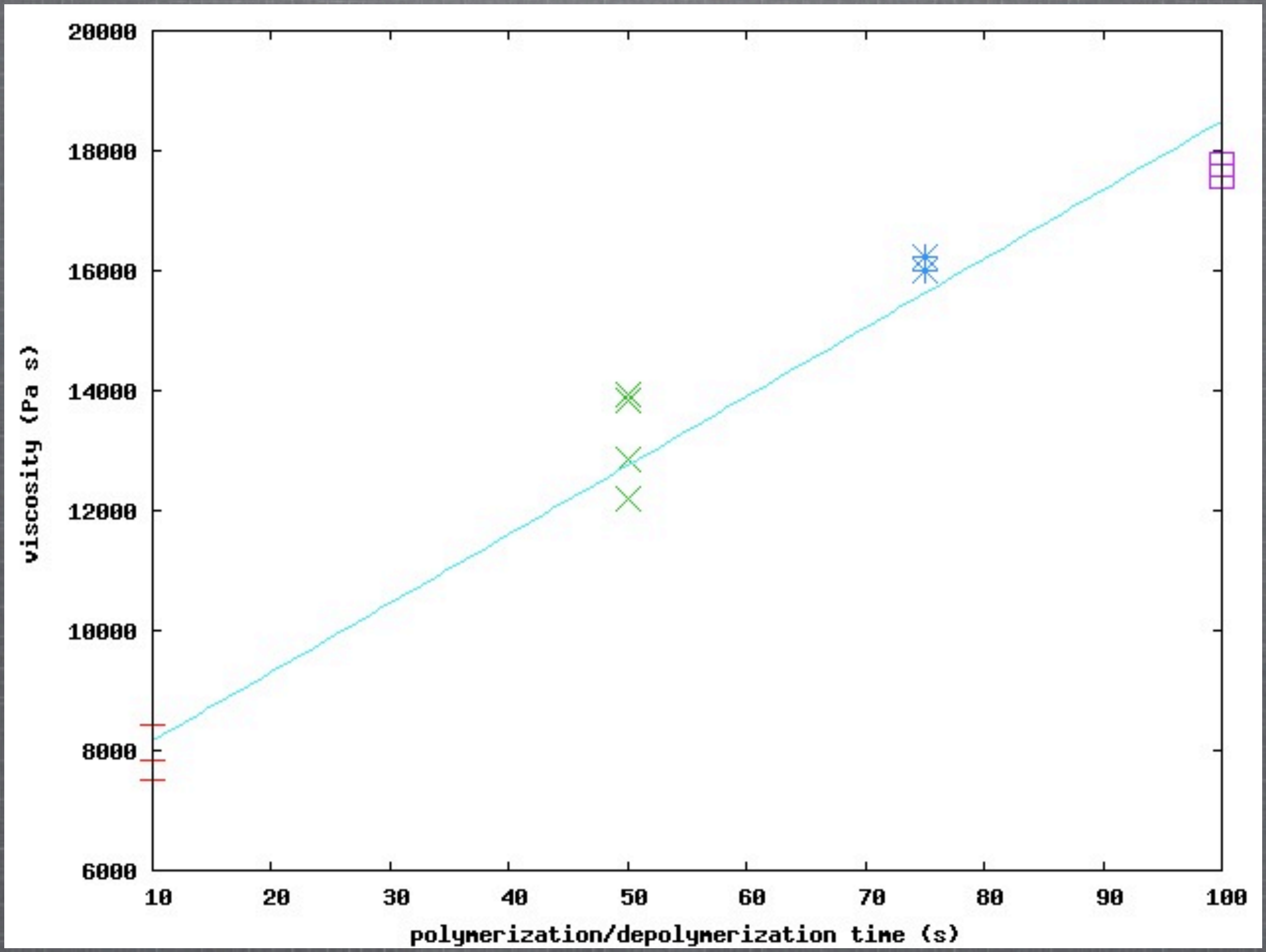


with migration



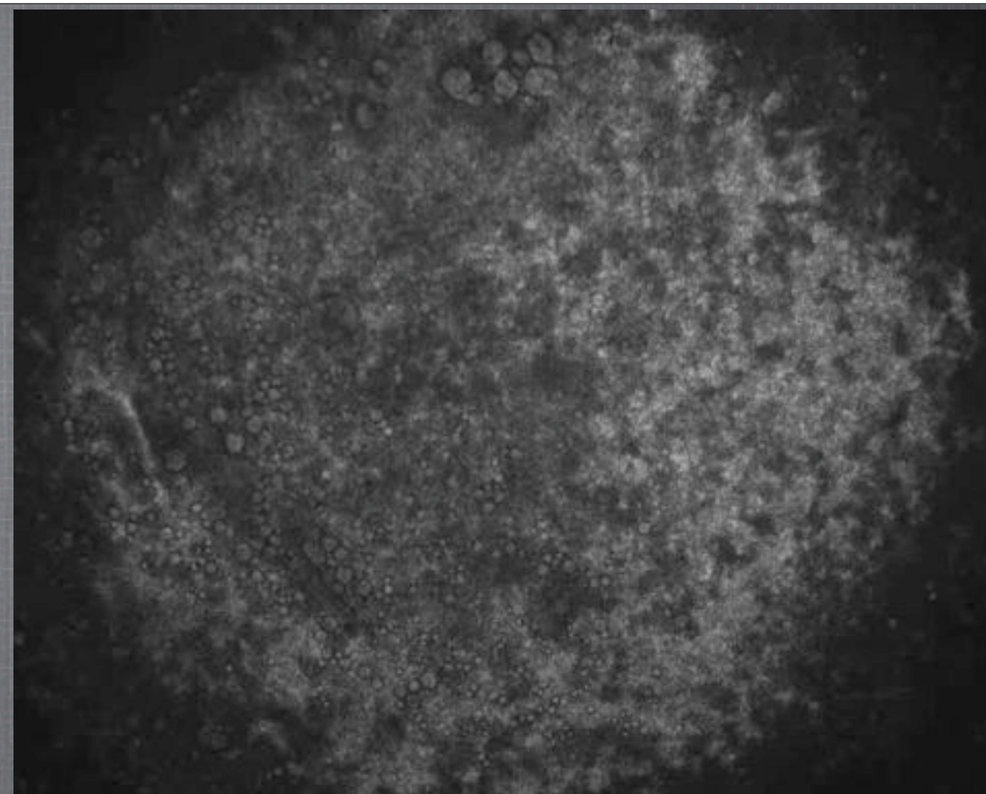
Tissue Viscosity is inversely proportional to cell mobility



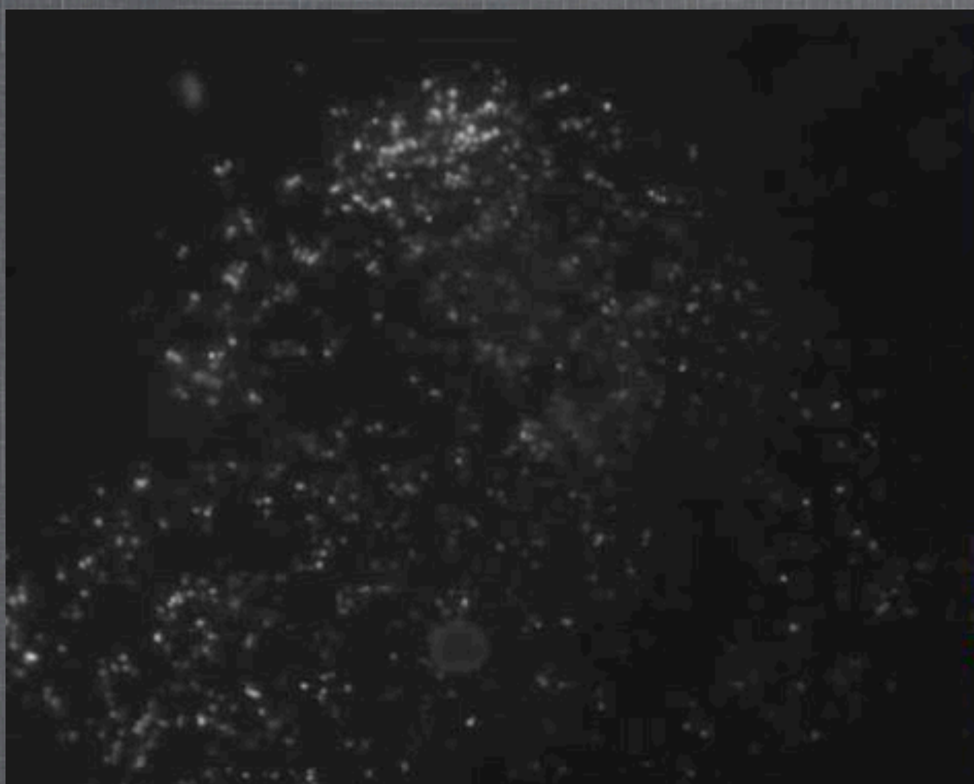
Polymerization/Depolymerization time is the time for which an element in the back of the cell "depolymerizes" while an element "polymerizes" at the front of the cell. The shorter this time is, the faster the cell migrates.

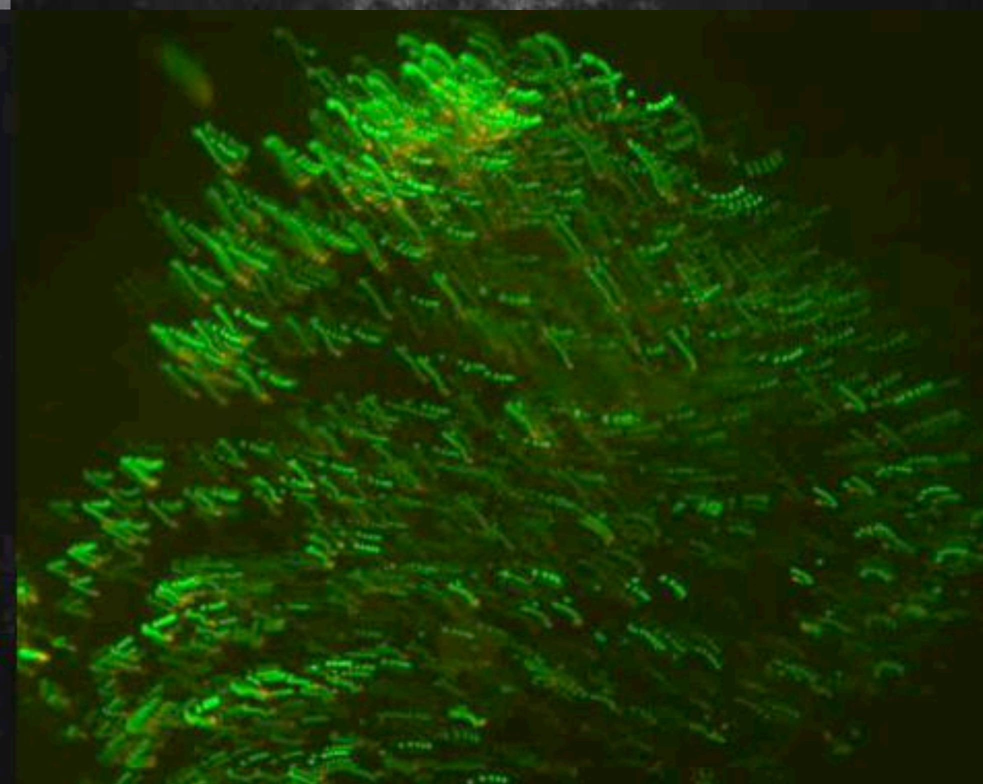
Current Application

Modeling organizing mechanisms driving primitive streak formation in the early chick embryo.



Manli Chuai, CJ Weijer lab





Conclusions

Cells and tissues are viscoelastic: solid-like and fluid-like depending on the time scale you observe them.

The cell is an active material in which remodeling of the cytoskeleton and active migration result in the "fluidization" of tissues over long timescales (hours).

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