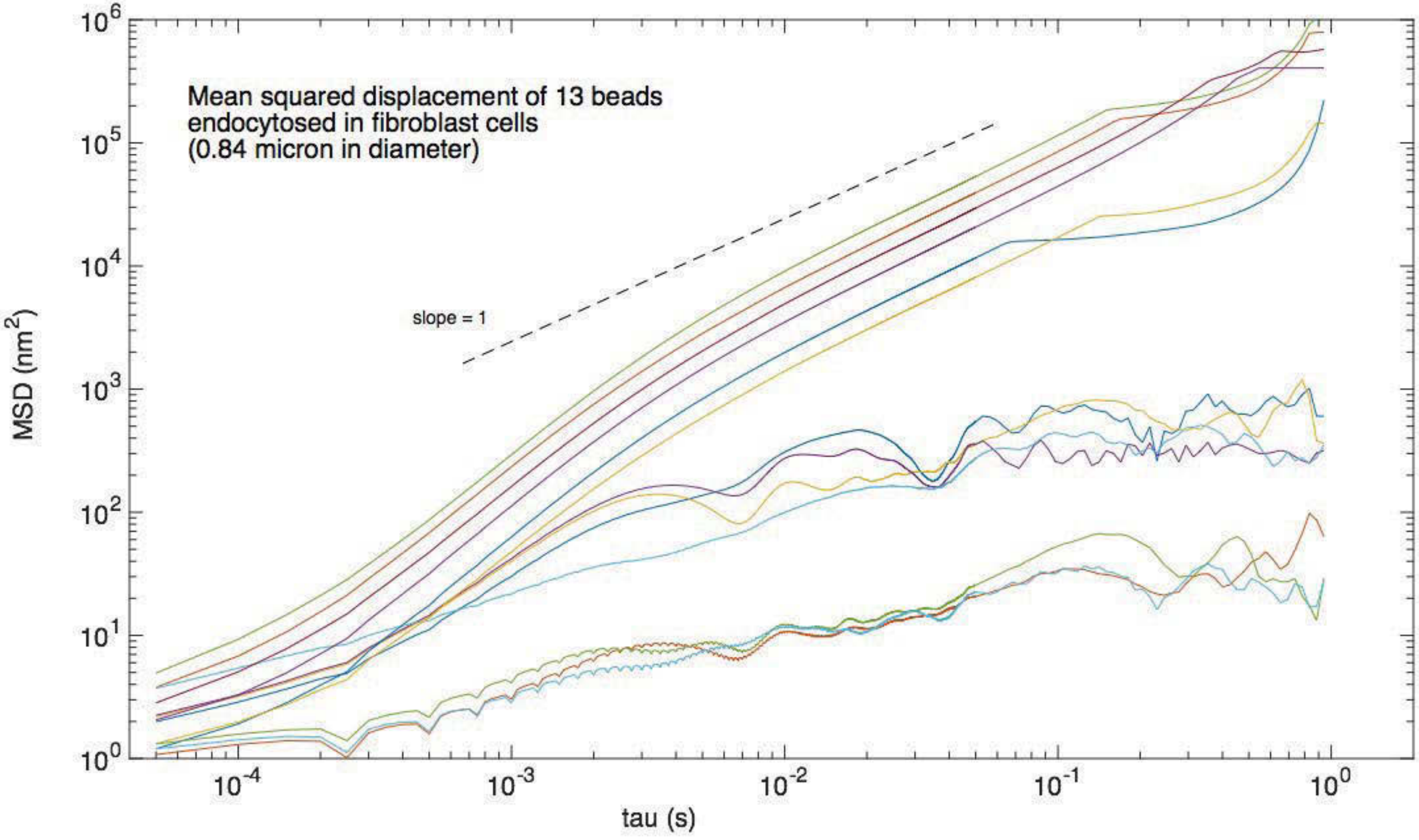
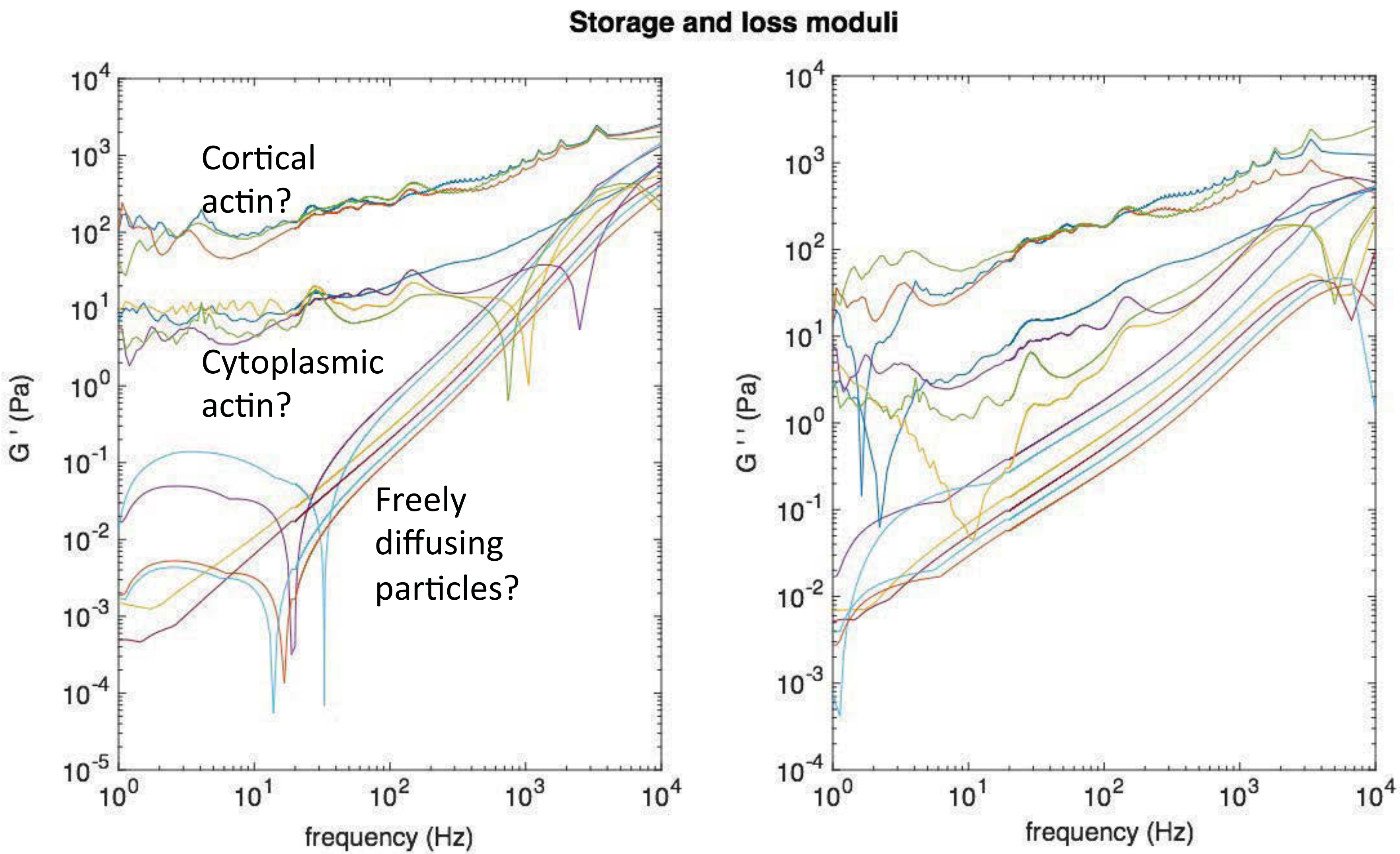
20.309 demo, 4/16/2015

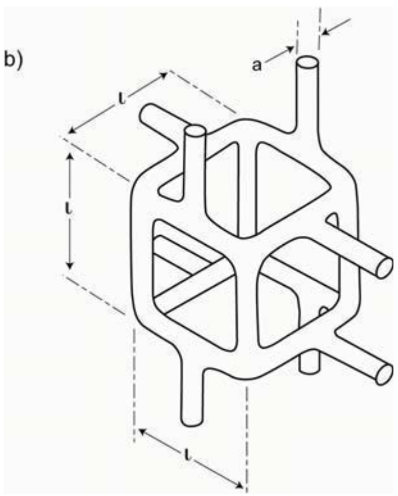


Generalized Stokes-Einstein Relation (an approximation):

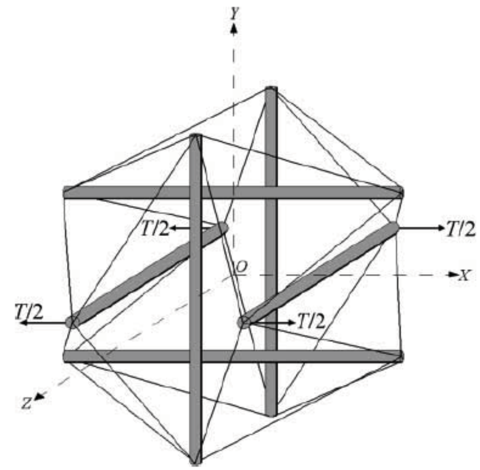
$$\left|G^*(\omega)\right| \approx \frac{2k_B T}{3\pi a\left\langle \Delta R^2(\tau)\right\rangle \Gamma\left(1+\frac{d\ln\left\langle \Delta R^2(\tau)\right\rangle}{d\ln\tau}\right)}$$



Three microstructural models for the cytoskeleton

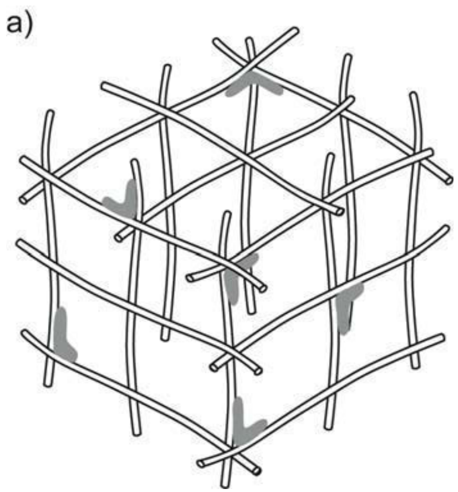


Cellular solids



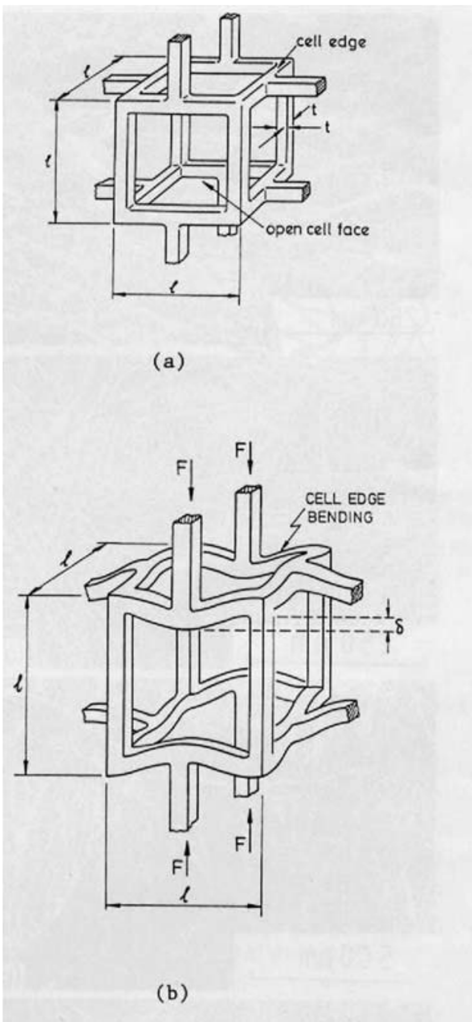
Tensegrity

Source: Stamenović, D., and Donald E. Ingber. "Models of Cytoskeletal Mechanics of Adherent Cells." *Biomechanics and Modeling in Mechanobiology* 1, no. 1 (2002): 95-108.

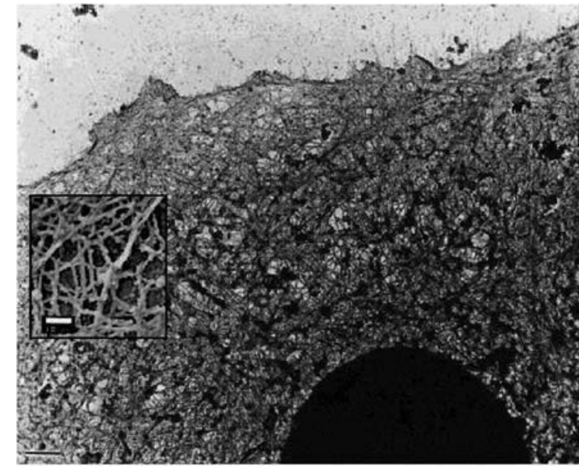


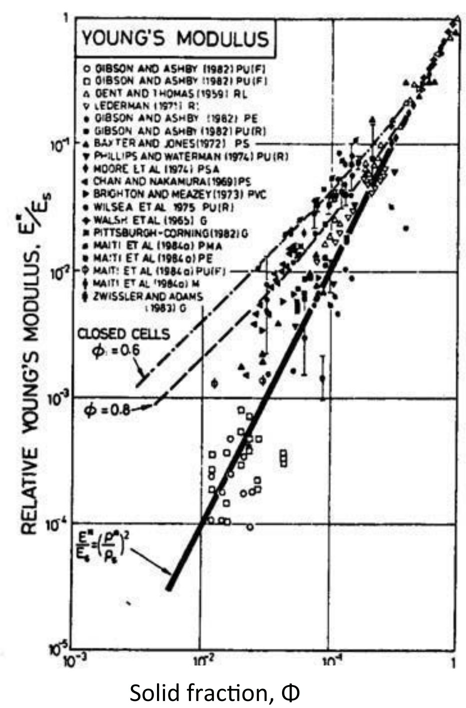
Biopolymer

Cellular Solids Model



(Gibson & Ashby, 1988, Satcher & Dewey, 1997)





$\Phi \sim (a/L)^2$ (solid fraction)

$\delta \sim FL^3/(E_f I)$ from bending analysis where $I \sim a^4$

$\sigma \sim F/L^2$

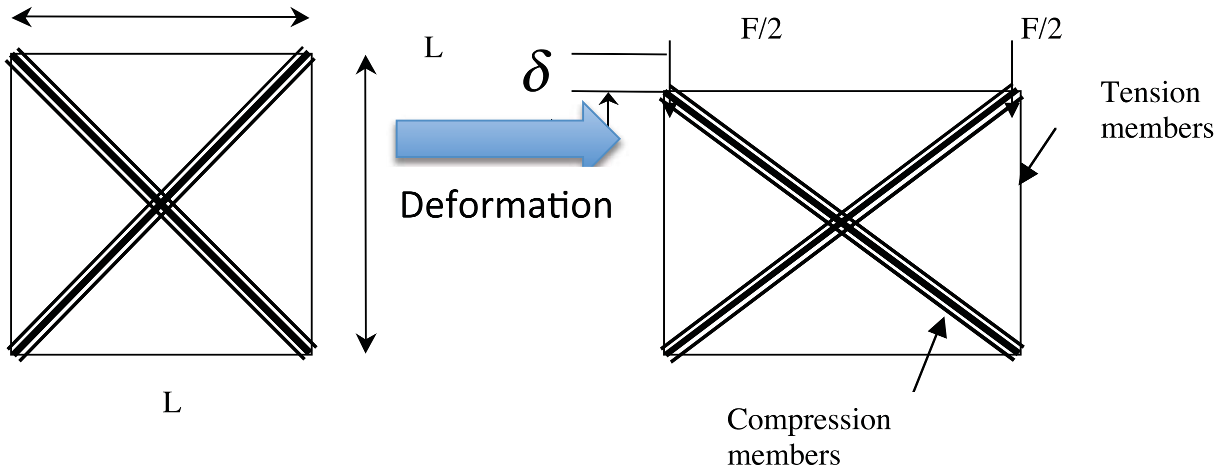
$\varepsilon \sim \delta/L$

$E_n = \sigma/\varepsilon = c_1 E_f I/L^4$ (network modulus)

$E_n/E_f = c_1\,\Phi^2$ or $G_n \sim E_f\,\Phi^2$

a = radius of filaments

Tensegrity Model



$$U \sim \int_0^{L_1} \sigma_{f1}\varepsilon_{f1}a^2\,dx + \int_0^{L_2} \sigma_{f2}\varepsilon_{f2}a^2\,dx$$

Work done = Δ (stored elastic energy)

$$F\delta \sim La^2\left(\frac{\delta}{L}\right)^2\left(2\sigma_{f0} + E_f\right)$$

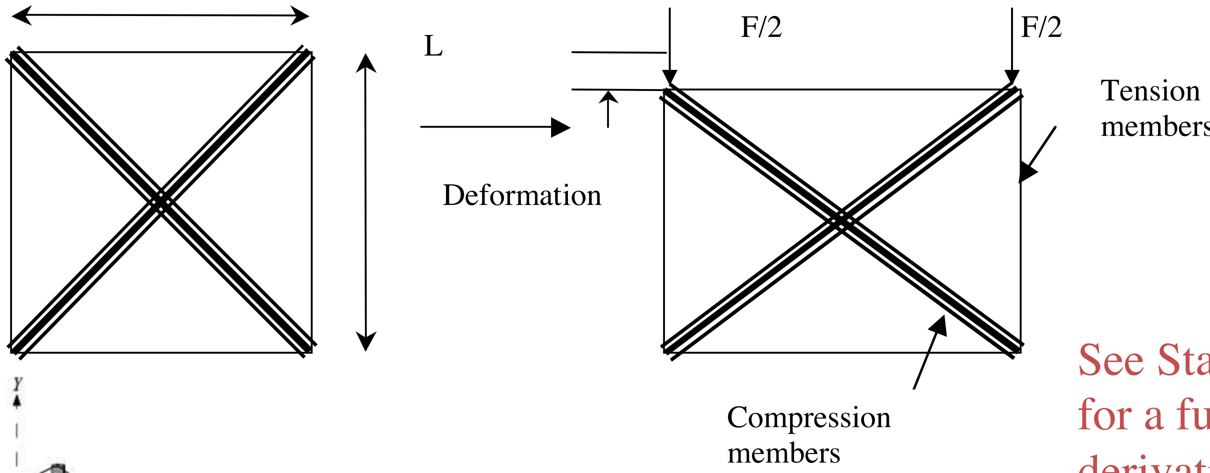
$$E_n \sim \frac{\sigma_n}{\delta/L} \propto \left(2\sigma_{f0} + E_f\right)\left(\frac{a}{L}\right)^2$$

$$\propto \left(2\sigma_{f0} + E_f\right)\Phi \propto 2\sigma_{n0} + E_f\Phi$$

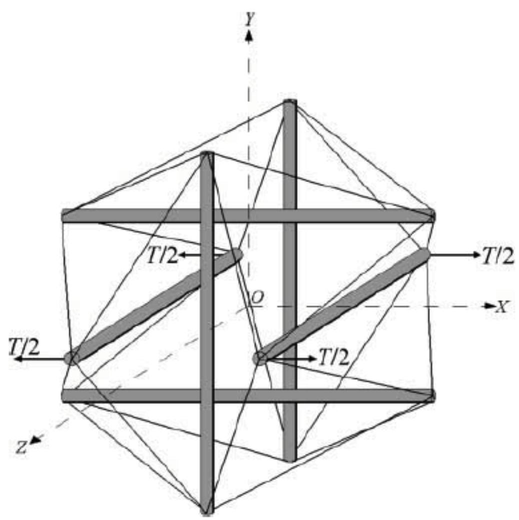
Prestress contribution

Fiber modulus dependent contribution

Tensegrity Model



See Stamenovic for a full derivation.



Source: Stamenović, D., and Donald E. Ingber. "Models of Cytoskeletal Mechanics of Adherent Cells." *Biomechanics and Modeling in Mechanobiology* 1, no. 1 (2002): 95-108.

$$E_n = \frac{\sigma_{f0}\Phi}{3}\frac{1+4\varepsilon_0}{1+12\varepsilon_0}$$

Where σ_{f0} is the prestress in the individual tensile elements and ε_0 is the initial strain in each.

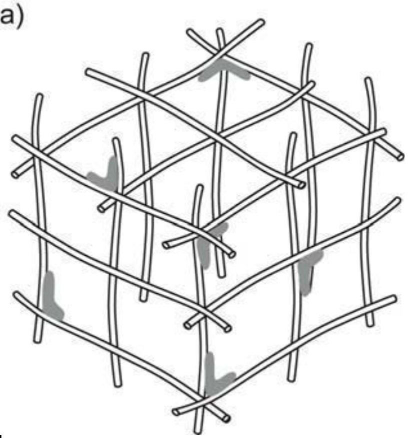
Or, in the limit of $\varepsilon_0 \rightarrow 0$,

$G_n \sim \sigma_{n0}/3$

where σ_{n0} is the pre-stress in the tensile elements per unit total cross-sectional area ($\sigma_{n0}=\pi\sigma_{f0}a^2/L^2$).

Biopolymer Models

a)



For a single segment of polymer between cross-links (Isambert and Maggs, 1997, Maggs, 1999, Storm, et al., 2005)

$$F = \frac{l_p}{l^4} K_b \delta$$

$$\varepsilon_n = \frac{\delta}{l}$$

$$\sigma_n \sim F \cdot \frac{filaments}{area} \sim \frac{F}{\xi^2}$$

Low cross-link density

$$E_n = \frac{\sigma_n}{\varepsilon_n} \sim \frac{l_p K_b}{l^3 a^2} \Phi$$

Maximum cross-link density ($l \sim \xi$)

$$E_n = \frac{\sigma_n}{\varepsilon_n} \sim \frac{l_p K_b}{a^5} \Phi^{5/2}$$

l_p = persistence length

l = distance between entanglements or cross-links

ξ = filament spacing (pore size)

ε_n = network strain

E_n = network elastic modulus

δ = change in distance between entanglements/cross-links

Φ = solid fraction

Scaling behaviors for the three models

Tensegrity

Predicts a linear dependence on prestress

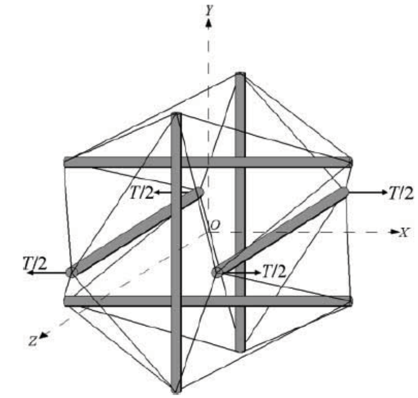
Athermal

No ability to change cross-link density

No role for cross-link mechanics

Viscoelasticity?

$$G' \sim 2\sigma_{n0} + E_f \Phi$$



Source: Stamenović, D., and Donald E. Ingber. "Models of Cytoskeletal Mechanics of Adherent Cells." *Biomechanics and Modeling in Mechanobiology* 1, no. 1 (2002): 95-108.

Cellular Solids

Filament bending stiffness dominates

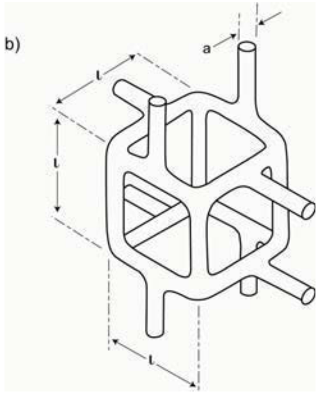
Maximal cross-link density

Athermal

No role for cross-link mechanics

Viscoelasticity?

$$G' \sim E_f \Phi^2$$



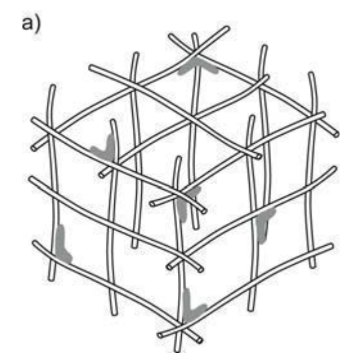
Biopolymer

Thermal (WLC at high extensions)

Viscoelastic. Captures ¾ power law at high frequency

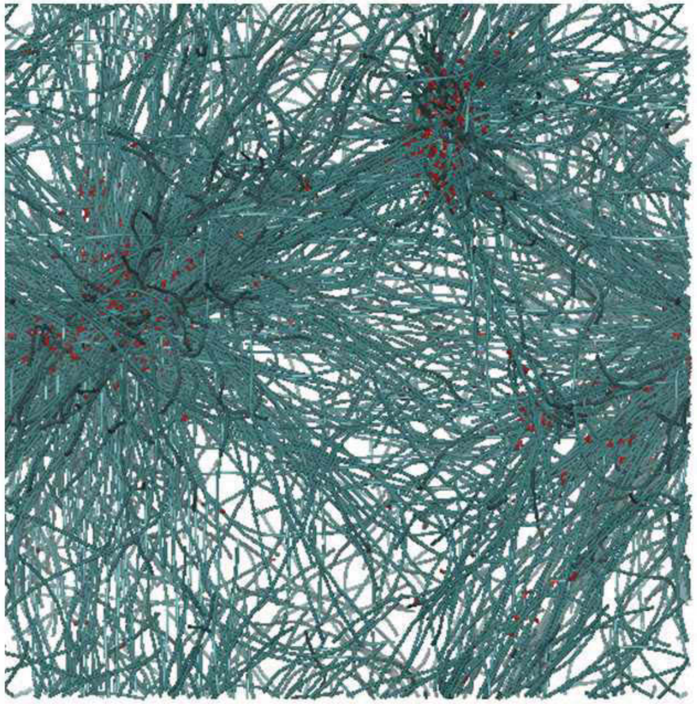
Cross-link density and mechanics?

$$G' \sim K_b^2 \Phi^1 \rightarrow K_b^2 \Phi^{5/2}$$



Computational Models of the Cytoskeleton

- Individual monomers and cross-linking proteins self assemble into a 3D network
- Motors can be added to simulate the effects of myosin II
- Networks are thermally active, fully 3D and exhibit many of the characteristics of cells and actin gels
- Mechanical properties such as G', G" and generated internal stress can be readily computed.



Kim, et al., PLoS Comp Biol, 2009

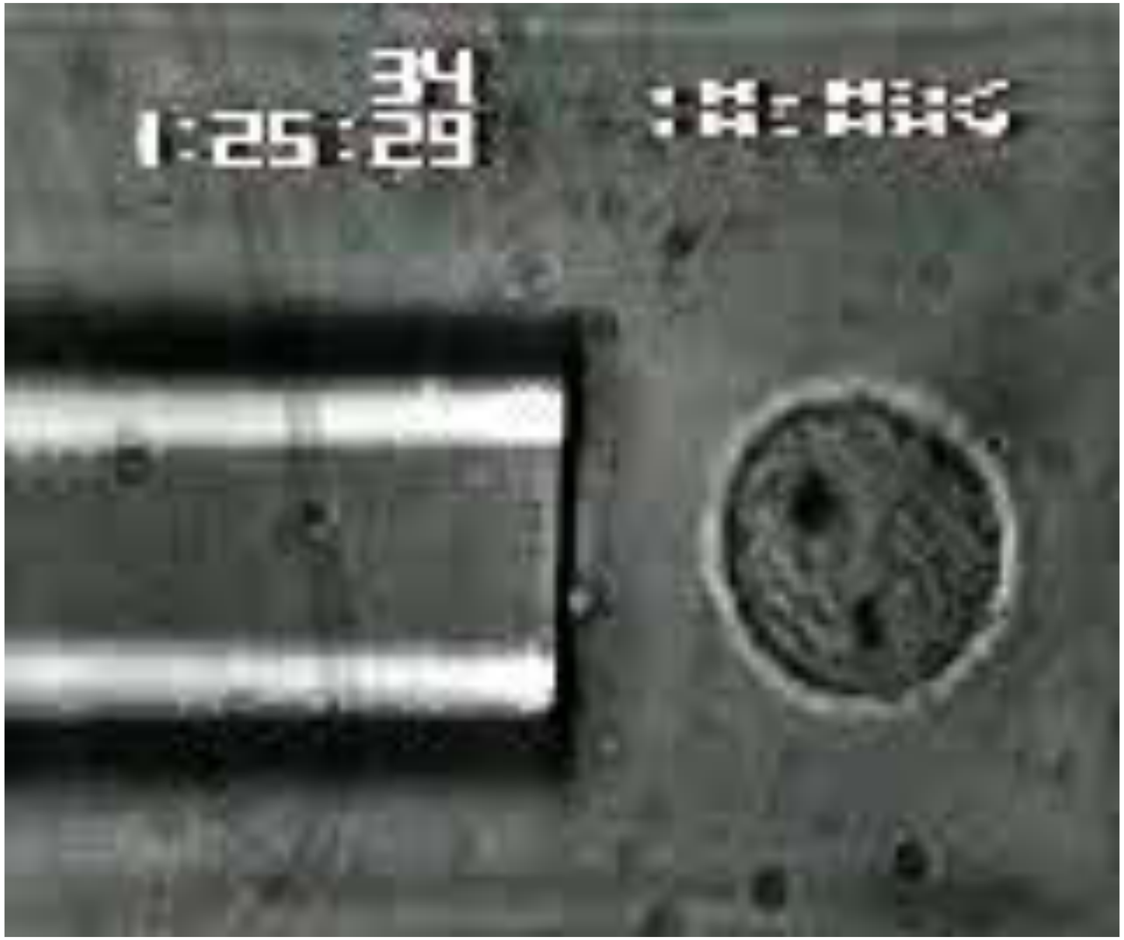
Take home messages

- Cells exhibit a weak power-law rheology
- With increasing strain: linear, strain-stiffening, strain softening
- Fluidization (role of cross-links?)
- Simulations show that tensed networks are consistent with much of the observed static behavior
- Cytoskeletal networks behave athermally, and cross-link rupture appears to be more important than unfolding in network fluidization and remodeling
- Motor activity is a significant determinant of network morphology
- Motors induce prestress and thereby actively control cytoskeletal stiffness

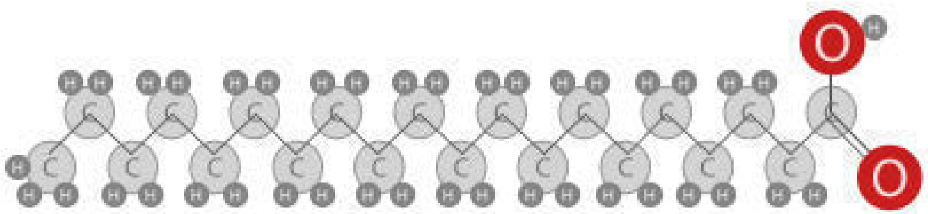
Membrane mechanics:

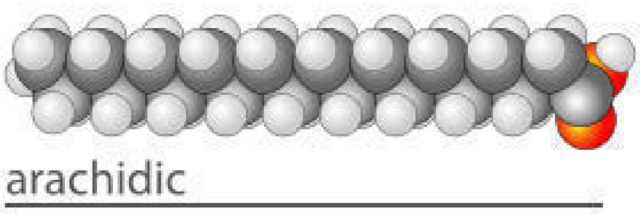
Micropipette Aspiration

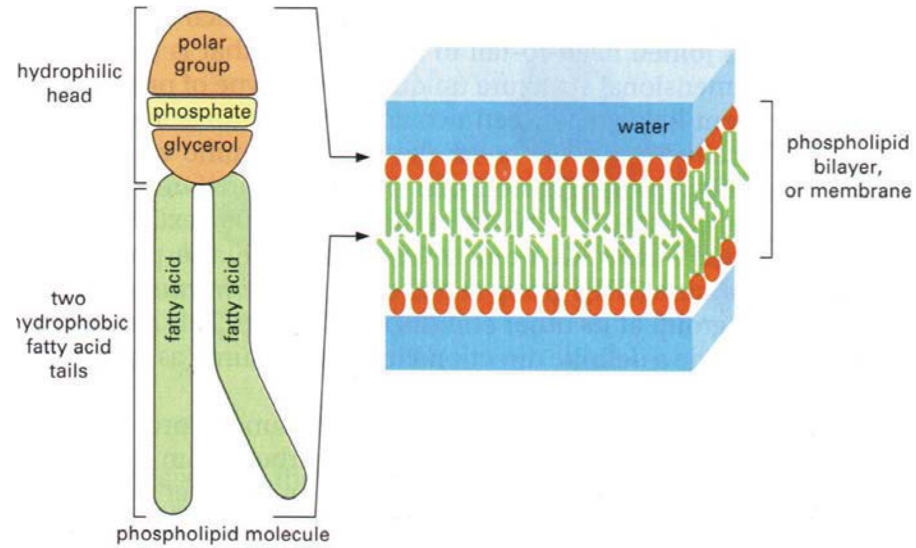
Measurements suggest a model consisting of a viscous core and a membrane of constant surface tension.



A fatty acid molecule (left)
and aggregation of phospholipids
to form a cell membrane (below)







<u>Attractive</u>: hydrophobic tails.

<u>Repulsive</u>: hydrophilic heads, ionic groups, steric effects.

B. Alberts et al. (2004)

Figure 11-4 removed due to copyright restrictions.
Source: Nelson, David L., et al. *Lehninger Principles of Biochemistry*. Macmillan, 2008.

D. L. Nelson and M. M. Cox (2005)

Image of lipid bilayer removed due to copyright restrictions.

H. Lodish et al. (2004)

Lipid bi-layer characteristics

Figure 11-1 removed due to copyright restrictions.
Source: Nelson, David L., et al. *Lehninger Principles of Biochemistry*. Macmillan, 2008.

Thickness ~ 5 nm

Normal (resting) tension ~ 0.01 mN/m

Maximum areal strain ~4%

Rupture tension ~10 mN/m

(Surface tension of water ~ 70 mN/m)

(1 mN/m = 1 dyn/cm)

D. L. Nelson and M. M. Cox (2005)

Red blood cells (erythrocytes)

Uniform, disc-shaped normal erythrocyte →

Red Blood Cells

Molecular Biology of the Cell, Bruce Alberts, Dennis Bray, Julian Lewis, Martin Raff, Keith Roberts, James D. Watson © 1994

White blood cells (leukocytes)

Images removed due to copyright restrictions.

Scanning electron micrographs showing a) an intact "passive" neutrophils with many membraneous folds and microvilli and b) a neutrophil that has been treated with 4 M-5M Triton-X to dissolve away the membrane and leave the underlying cytoskeleton in the exposed cortical region.

http://mems.egr.duke.edu/Faculty/rhochmuth.html

Homogeneous??
Cells in 3D matrix

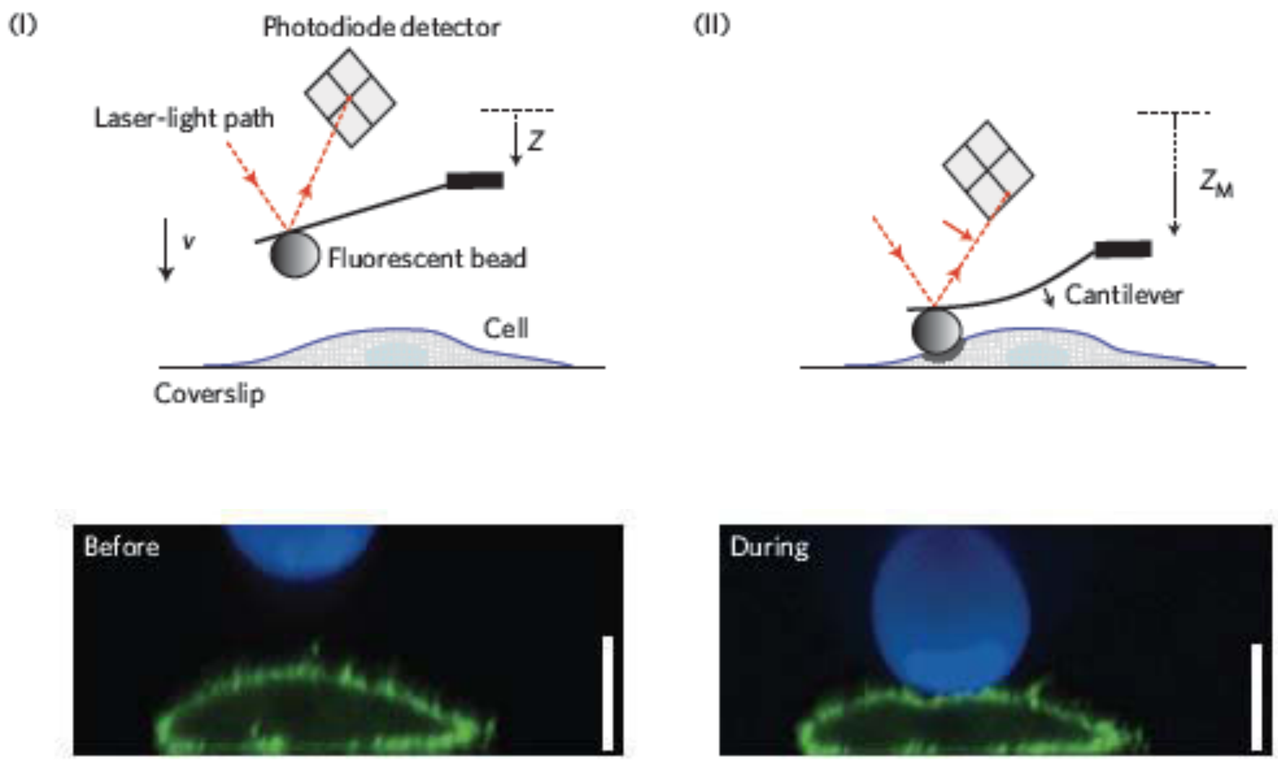
Images removed due to copyright restrictions.

MDA-MB-231 breast cancer cells migrating inside a collagen gel.

- Dense cortical actin with myosin.
- Cross-linkers more homogeneously distributed

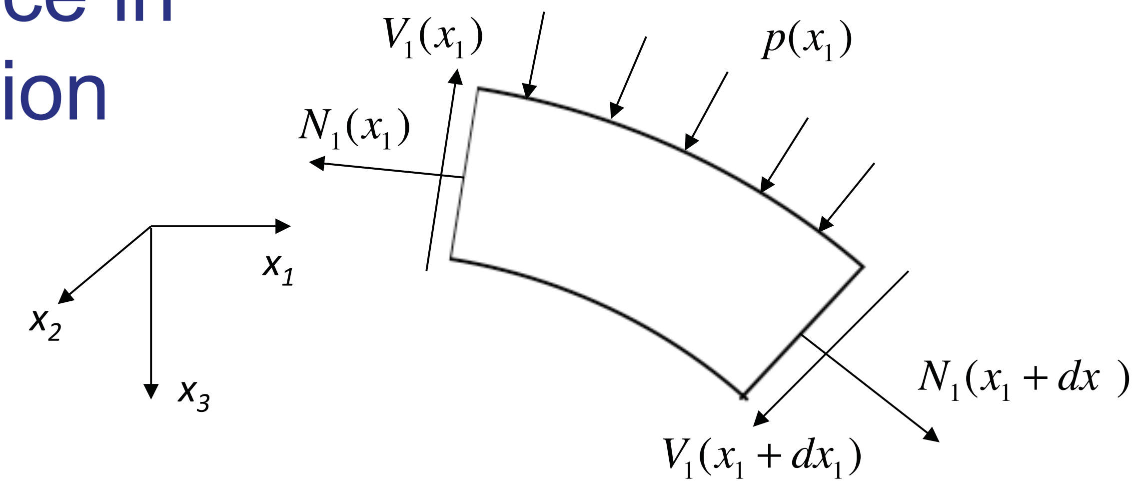
Rajagopalan, unpublished

Indentation by a microsphere
Importance of the cortex



Courtesy of Macmillan Publishers Limited. Used with permission.
Source: Moeendarbary, Emad, et al. "The Cytoplasm of Living Cells Behaves as a Poroelastic Material." *Nature Materials* 12, no. 3 (2013): 253-61.

Force balance in the x_3 direction



$$V = \int_0^h \sigma_{13} dx_3$$

$$p dx_1 - V_1(x_1) - N_1(x_1)\theta(x_1) + V_1(x_1 + dx_1) + N_1(x_1 + dx_1)\theta(x_1 + dx_1) = 0$$

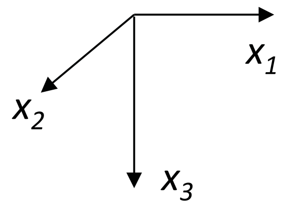
Use Taylor expansions for V_1 and $N_1\theta_1$

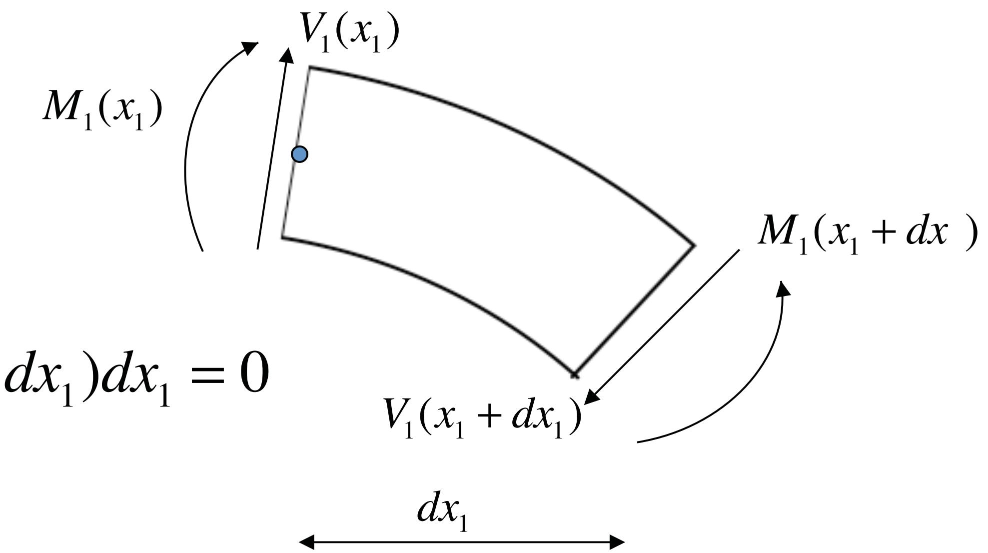
$$V_1(x_1 + dx_1) = V_1(x_1) + \frac{\partial V_1}{\partial x_1} dx$$

Combine and divide by dx_1:

$$p(x_1) + \frac{\partial V_1}{\partial x_1} + \frac{\partial}{\partial x_1}\left(N_1\theta_1\right) = p(x_1) + \frac{\partial V_1}{\partial x_1} + \frac{\partial}{\partial x_1}\left[N_1\left(\frac{\partial u_3}{\partial x_1}\right)\right] = 0$$

Moment (torque) balance about the x_2 axis





$$-M_1(x_1) + (M_1 + \frac{\partial M_1}{\partial x_1} dx_1) - V_1(x_1 + dx_1)dx_1 = 0$$

$$\frac{\partial M_1}{\partial x_1} = V_1(x_1)$$

$$M_1(x_1) = -K_b^{'} \frac{\partial^2 u_3}{\partial x_1^2}$$

$$p - K_b^{'} \frac{\partial^4 u_3}{\partial x_1^4} + \frac{\partial}{\partial x_1}\left(N_1 \frac{\partial u_3}{\partial x_1} \right) = 0$$

in 1D

Full governing equations for linear deformations, and the reduced forms for bending or tension dominance

Bending stiffness — Membrane tension

$$K_b^{'}\left(\frac{\partial^4 u_3}{\partial x_1^4}\right) - N\left(\frac{\partial^2 u_3}{\partial x_1^2}\right) - p = 0$$

$$\frac{Bending}{Tension} \propto \frac{K_b^{'}\bar{u}/\lambda^4}{N\bar{u}/\lambda^2} \propto \frac{K_b}{N\lambda^2} >> 1$$

$$\frac{K_b^{'}}{N\lambda^2} << 1$$

$$K_b^{'}\left(\frac{\partial^4 u_3}{\partial x_1^4}\right) = p$$

$$p = -N\left(\frac{\partial^2 u_3}{\partial x_1^2}\right) \cong N\left(\frac{1}{R}\right)$$

u = displacement — p = pressure difference — N = membrane tension

R = radius of curvature — x = spatial coordinate — λ = characteristic length