Models for cell mechanics
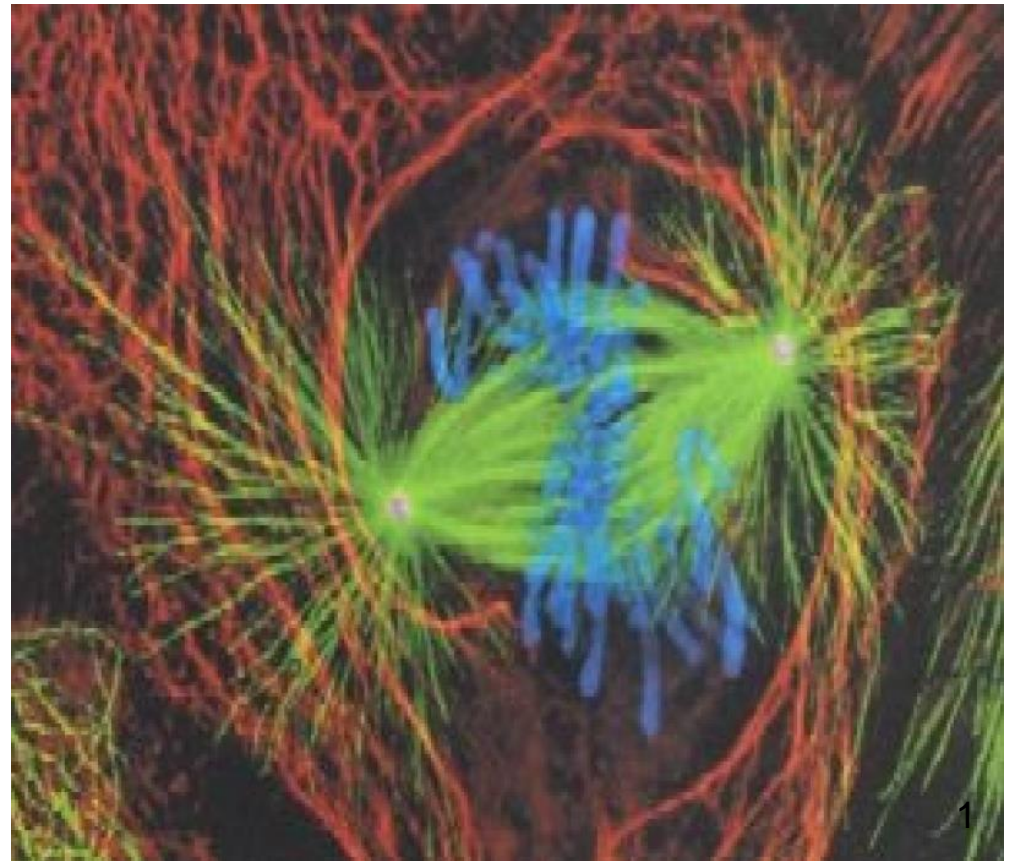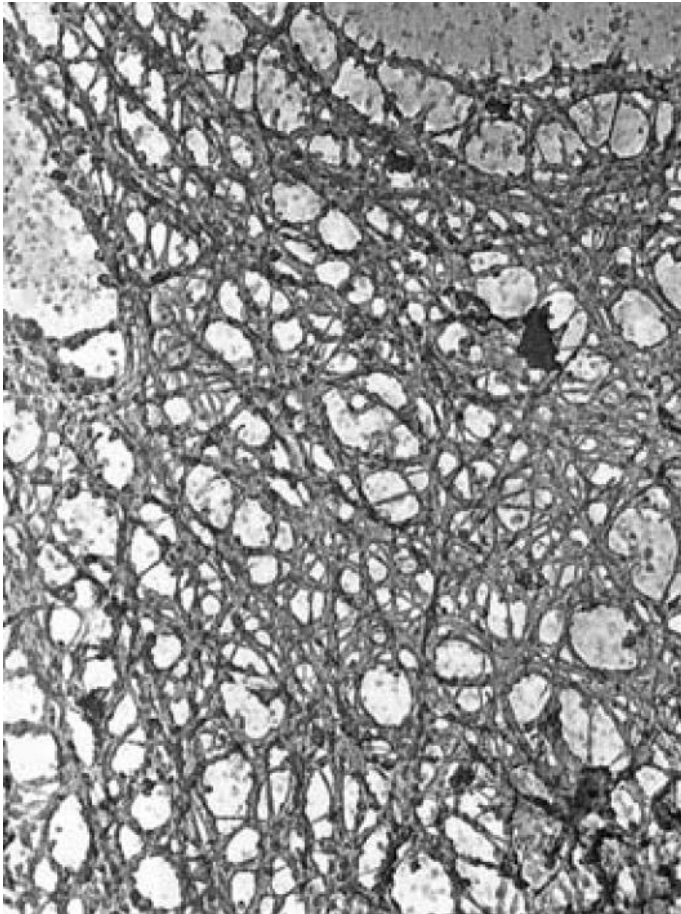
Mechanics of the cell membrane

Simplifications of cytoskeleton and membrane for the purpose of mechanical analysis
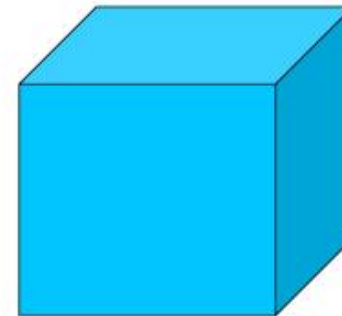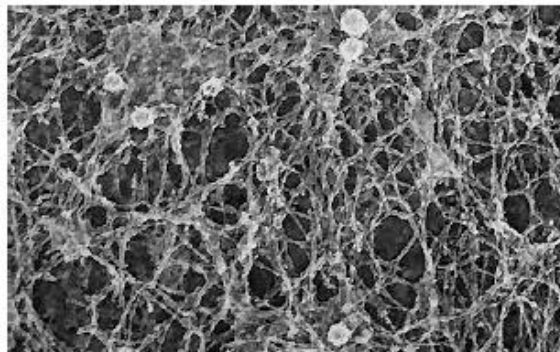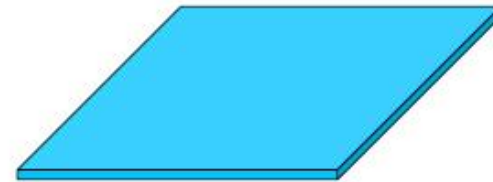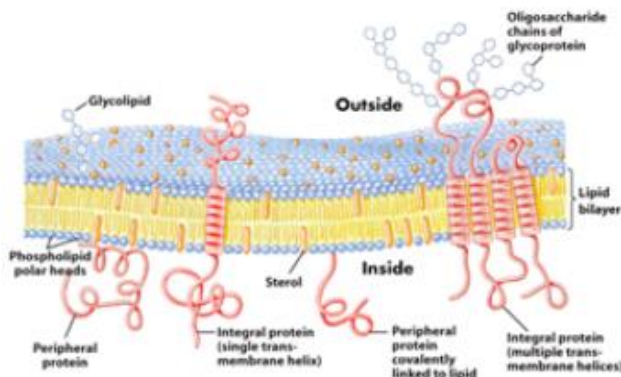
Roger Kamm, Biological Engineering, Mechanical Engineering MIT

Homogeneous, isotropic, elastic (or viscoelastic) materials

2

5

Mechanics of the cell membrane

Simple membrane deformations

Extension
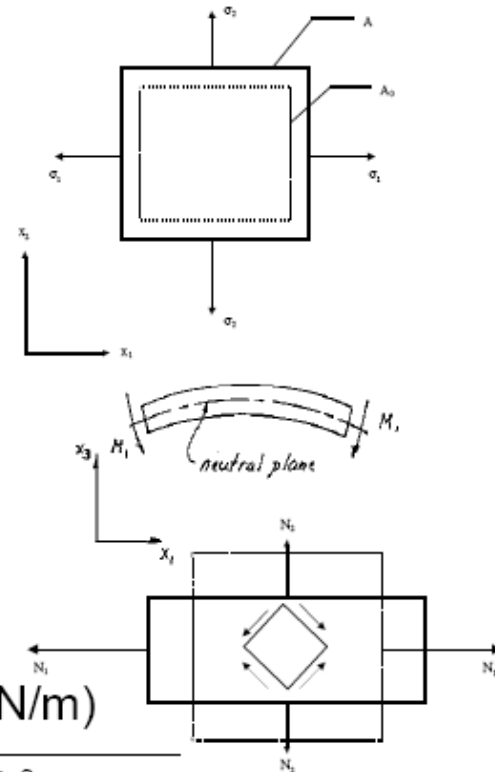
$$N = \frac{Eh}{2(1-v)}\frac{\Delta A}{A_0} \equiv K_e \frac{\Delta A}{A_0}$$

Bending

$$M_\alpha = -\frac{Et^3}{12(1-v^2)}\left(\frac{\partial^2 u_3}{\partial x_\alpha^2}\right) = -K_B\left(\frac{\partial^2 u_3}{\partial x_\alpha^2}\right)$$

Shear

$$N_{12} = \sigma_{12}h = 2G\varepsilon_{12} = K_s\varepsilon_{12}$$

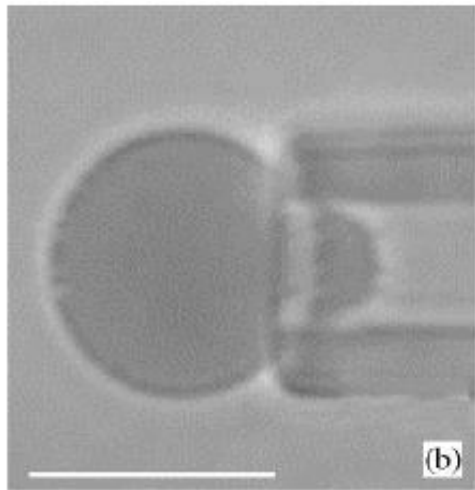|	K_e (N/m)	K_B (N·m)	K_s (N/m)
Red blood cell	0.4	$\sim 10^{-19}$	8×10^{-6}
Pure bilayer	0.1-0.2	$\sim 10^{-19}$	negligible
Neutrophil		$\sim 10^{-18}$	

Erythrocytes, red blood cells, are maybe the most fascinating cells in the human body. They deliver oxygen to the body via the blood flow through the circulatory system. Erythrocytes take up oxygen in the lungs and release it while squeezing through the body's capillaries. Adult humans have about $2.5 \cdot 10^{13}$, 25 trillion, red blood cells; those form about a quarter of the total amount of cells in the human body. Adult human red blood cells are flexible biconcave disks without a nucleus. A typical human erythrocyte has a disk diameter of 6 - 8μm, a thickness of 2μm, a volume of 90fL, and a surface of 136μm^2. It can swell to spherical shape of 150fL, without membrane distension. The membrane of red blood cells plays a key role in regulating surface deformability, flexibility, and adhesion to other cells. These functions are highly regulated by its composition. The membrane of red blood cells is composed of three layers: (i) the exterior glycocalyx, which is rich in carbohydrates; (ii) the lipid bilayer with its transmembrane proteins; and (iii) the internal membrane skeleton, a structural network of spectrin tetramers composed of roughly 33,000 hexagons giving it an appearance of a microscopic geodesic dome.

Mechanics of the cell membrane
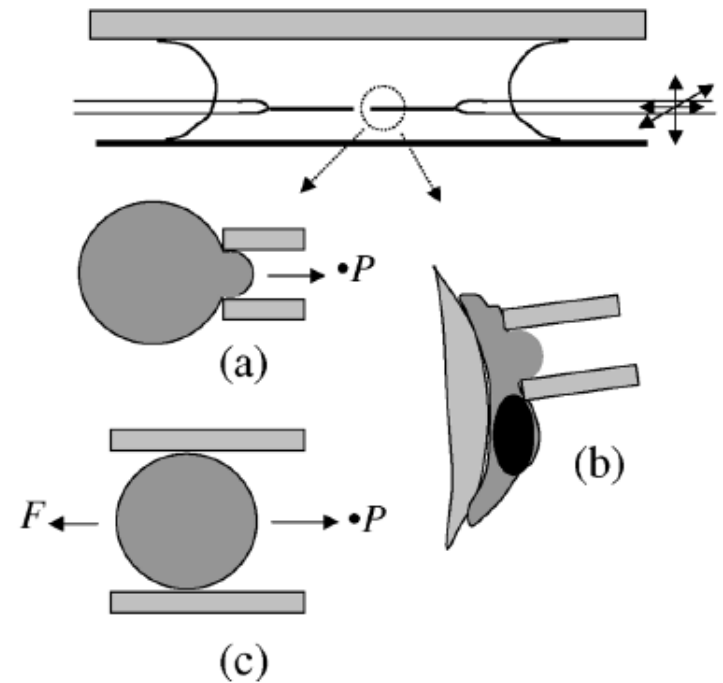

(b)

(a)

(c)

F ← ⟶ •P

(b)

Fig. 1. Two micropipettes in a chamber. A pneumatic micromanipula-tor controls the movement of a micropipette along three orthogonal axes. (a) A spherical cell being aspirated into a micropipette with a suction pressure ΔP. (b) An attached cell being aspirated into a pip-ette. (c) A closely fitting cell or bead moving freely in a pipette like a piston in a cylinder. When static, the suction pressure times the cross-sectional area of the pipette equals the attachment force F. 5

Solution :

$$\Delta P = 2T_c \left(\frac{1}{R_p} - \frac{1}{R_c} \right), \quad \left(\Delta P = \Delta P_c \text{ when } \frac{L_p}{R_p} = 1 \right)$$
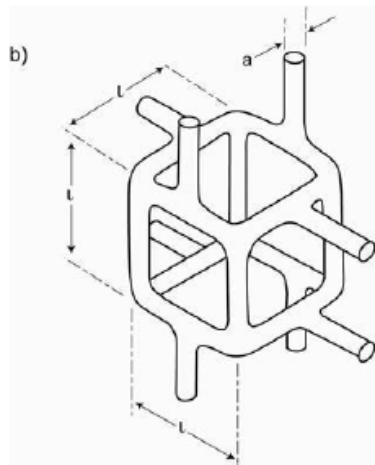
Mechanics of the cytoskeleton

Why is the cell membrane model of the previous section not sufficient to characterize cells like fibroblasts?

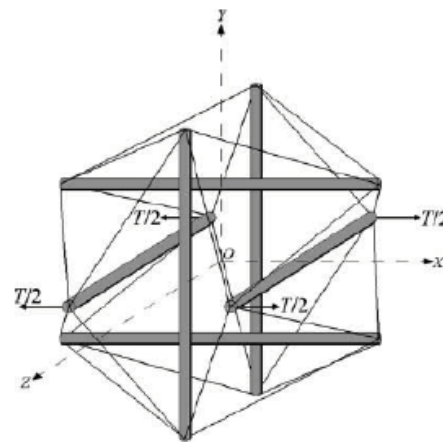What is the fundamental difference between a red blood cell and a fibroblast?

Fibroblasts not only consist of a cell membrane but also have a nucleus and cytoskeletal filaments that are, as we have seen, relevant for locomotion and force generation. How do cells move? How do cells attach to surfaces? How are forces from outside the cell transmitted to the cell nucleus where they might influence gene expression?

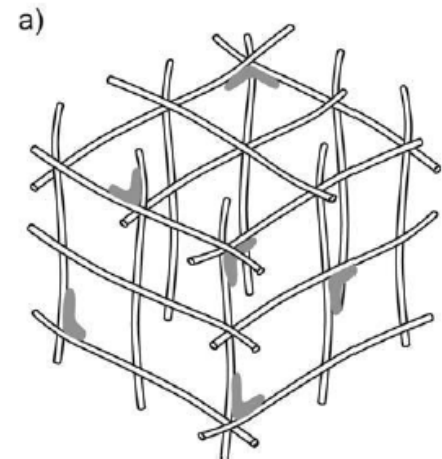# Three microstructural models for the cytoskeleton

Cellular solids

Tensegrity

Biopolymer

Cellular solids

Cellular Solids Model

(a)

(b)

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

YOUNG'S MODULUS

CLOSED CELLS
$\phi \sim 0.6$

$\phi \sim 0.8$

Solid fraction, Φ

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

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

$\tau \sim F/L^2$

$\varepsilon \sim \delta/L$

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

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

a = radius of filaments

Roger Kamm, Biological Engineering,
Mechanical Engineering MIT

Don Ingber, Scientific American

The Architecture of Life

A universal set of building rules seems to guide the design of organic structures—from simple carbon compounds to complex cells and tissues

by Donald E. Ingber

L ife is the ultimate example of complexity at work. An organism, whether it is a bacterium or a baboon, develops through an incredibly complex series of interactions involving a vast number of different components. These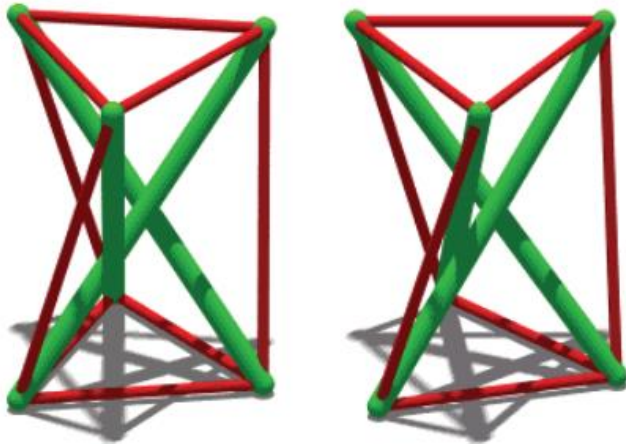 components, or subsystems, are themselves made up of smaller molecular components, which independently exhibit their own dynamic behavior, such as the ability to catalyze chemical reactions. Yet when they are combined into some larger new and us ity to move

Finally, more philosophical questions arise: Are these building principles universal? Do they apply to structures that are molded by very large scale forces as well as small-scale ones? We do not know. Snelson, however, has proposed an intriguing model of the atom based on tensegrity that takes off where the French physicist Louis de Broglie left off in 1923. Fuller himself went so far as to imagine the solar system as a structure composed of multiple nondeformable rings of planetary motion held together by continuous gravitational tension. Then, too, the fact that our expanding (tensing) universe contains huge filaments of gravitationally linked galaxies and isolated black holes that experience immense compressive forces locally can only lead us to wonder. Perhaps there is a single underlying theme to nature after all. As suggested by early 20th-century Scottish zoologist D'Arcy W. Thompson, who quoted Galileo, who, in turn, cited Plato: the Book of Nature may indeed be written in the characters of geometry. SA

One of the most elegant but maybe also most controversial models in cell mechanics can help to explain these phenomena: the tensegrity model.

Tensegrity The term tensegrity was first coined by Buckminster Fuller to describe a structure in which continuous tension in its members forms the basis for structural integrity. Fuller most famously demonstrated the concept of tensegrity in architecture through the design of geodesic domes while his student, the artist Kenneth Snelson, applied the concept of tensegrity to creating sculptures that appear to defy gravity. Snelson's tensegrity sculptures are minimal in components and achieve their stability through dynamic distribution of tension and compression forces amongst their members to create internal balance. It was upon viewing Snelson's art that Donald Ingber became inspired by the sculpture's structural efficiency and dynamic force balance to adopt tensegrity as a paradigm upon which to analyze cell structure and mechanics. It has been 30 years since the premier appearance of the cellular tensegrity model. Although the model is still largely under discussion, empirical evidence suggests that the model may explain a wide variety of phenomena ranging from tumor growth to cell motility.

we consider one of the simplest tensegrity structures consisting of six micro-tubule trusses of equivalent length L_0, arranged in three pairs of two with an original truss distance s_0, and of 24 tensile actin and intermediate filament ropes of length l_0, as illustrated in figure 4.12. We will assume that the compressive trusses are perfectly rigid while the tensile ropes act as Gaussian chains or linear entropic springs
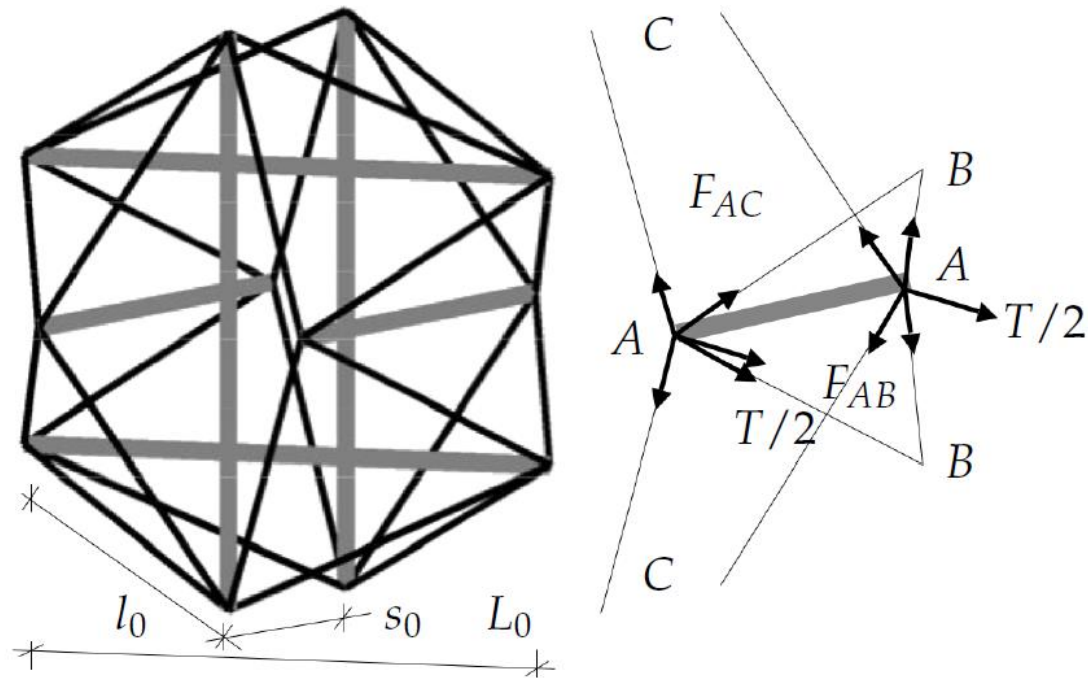
○ kinematics $\quad l_0^2 = \left[\dfrac{L_0 - s_0}{2} \right]^2 + \left[\dfrac{s_0}{2} \right]^2 + \left[\dfrac{L_0}{2} \right]^2 \rightarrow l_0 = \dfrac{1}{2} \sqrt{[L_0 - s_0]^2 + s_0^2 + L_0^2}$

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$$W^{\mathrm{mac}} \doteq W^{\mathrm{mic}} \qquad \text{or} \qquad \frac{\partial W^{\mathrm{mac}}}{\partial s_x} \doteq \frac{\partial W^{\mathrm{mic}}}{\partial s_x}$$

$$W^{\mathrm{mac}} = \frac{1}{2}\,\varepsilon\, E\, \varepsilon \qquad \text{thus} \qquad \frac{\partial W^{\mathrm{mac}}}{\partial s_x} = \frac{\partial W^{\mathrm{mac}}}{\partial \varepsilon}\,\frac{\partial \varepsilon}{\partial s_x} = E\,\varepsilon\,\frac{\partial \varepsilon}{\partial s_x}$$

$$\varepsilon = \frac{s_x - s_0}{s_0} \qquad \text{such that} \qquad \frac{\partial \varepsilon}{\partial s_x} = \frac{1}{s_0}$$

$$W^{\mathrm{mic}} = \frac{1}{V_0} \int_{s_0}^{s_x} T\,\mathrm{d}x \qquad \text{thus} \qquad \frac{\partial W^{\mathrm{mic}}}{\partial s_x} = \frac{T}{V_0}$$

$$\frac{\partial W^{\mathrm{mac}}}{\partial s_x} \doteq \frac{\partial W^{\mathrm{mic}}}{\partial s_x} \qquad \text{thus} \qquad E = \frac{s_0\, T}{\varepsilon\, V_0}$$

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$$E = \frac{s_0 \, T}{\varepsilon \, V_0}$$

We can further simplify this expression by plugging in the discrete values for the original cell volume $V_0 = 5\,L_0/16$, the distance of the parallel trusses $s_0 = l_0\,/\,2$, and the original rope length $l_0 = \sqrt{3/8}\,L_0$. We then obtain an expression for Young's modulus of the cell under uniaxial tension which we can further simplify for the case of small strains,

$$E = \frac{2\sqrt{3}}{5\sqrt{2}l_0} \frac{T}{s_x - s_0} \qquad \text{small strain} \qquad E_0 = 5.85 \, \frac{F_0}{l_0^2} \frac{1 + 4\varepsilon_0}{1 + 12\varepsilon_0}$$

where $\varepsilon_0 = l_0/l_r - 1$ is prestrain in the ropes under resting conditions and $F_0 = k\,[l_0 - l_r]$ is the corresponding prestress of the ropes. We see that Young's modulus scales linearly with the prestress in the ropes F_0, and is inversely proportional to the initial rope length l_0^2.

$$P \approx \frac{1}{3} \nu^{\text{actin}} \sigma^{\text{actin}}$$

Herein, ν^{actin} represents the volume fraction of actin filaments,

$$\nu^{\text{actin}} = \frac{V^{\text{actin}}}{V_0} = \frac{24 A^{\text{actin}} l_0}{[5\sqrt{2}]/[3\sqrt{3}] l_0^3} = \frac{24 A^{\text{actin}}}{1.3608 l_0^2}$$
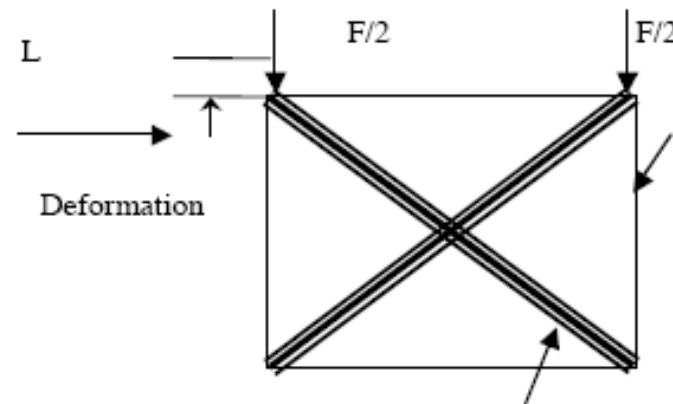
and σ^{actin} is the stress acting on one actin filament with a typical cross section A^{actin}.

$$\sigma^{\text{actin}} = \frac{F_0}{A^{\text{actin}}}$$

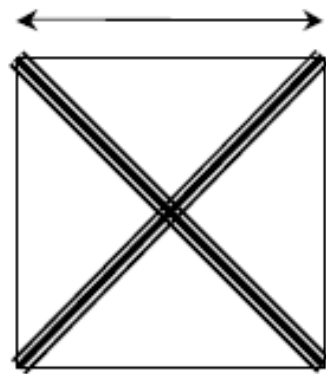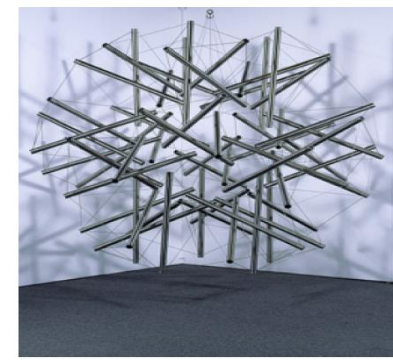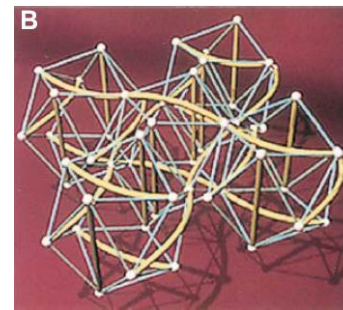The prestress can thus be approximated by

$$P \approx \frac{1}{3} \nu^{\text{actin}} \sigma^{\text{actin}} = \frac{1}{3} \frac{24 A^{\text{actin}}}{1.3608 l_0^2} \frac{F_0}{A^{\text{actin}}} \qquad \longrightarrow \qquad \underline{\underline{P \approx 5.85 \frac{F_0}{l_0^2} = E}}$$

What does that mean? According to the tensegrity model, the prestress P in a cell scales linearly with Young's modulus E. That is somewhat unexpected. Does it make sense? Let's look at cell experiments to validate this finding: measurements on human airway smooth muscle cells by Wang et al. [2001] who measured the relation between prestress P and shear modulus G, which, for the case of incompressibility, can be correlated to Young's modulus through $E = 3\,G$. The diagram in figure 4.13 demonstrates
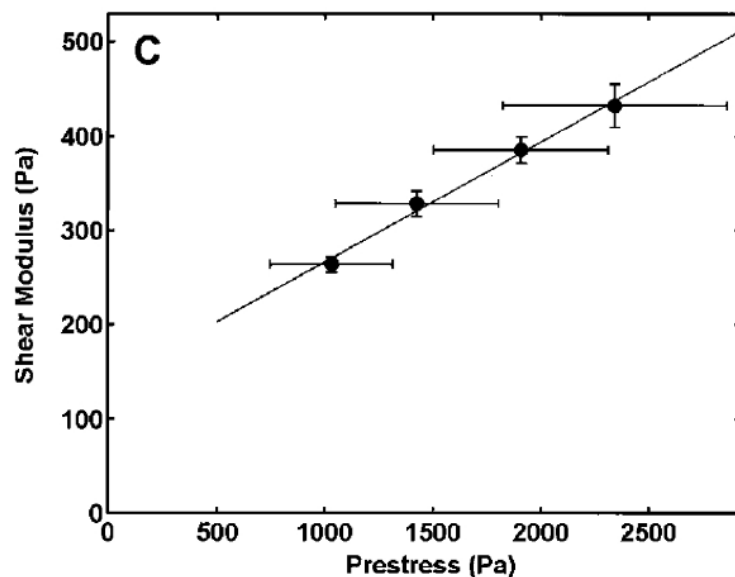
that the prestress P varies linearly with Young's modulus E. The E over P slope, however, is ≈ 0.4 rather than 1 as predicted by the tensegrity model. The large scatter in E values for different measuring techniques raises the question: What is the effective Young's modulus E of a cell? The cell is alive, and it is difficult to probe a cell without changing its Young's modulus.
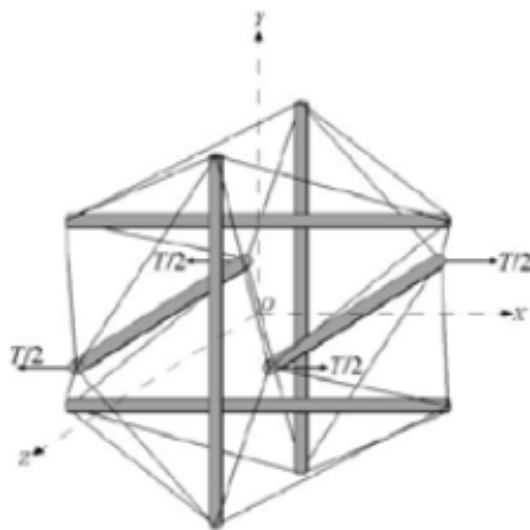
Tensegrity Model

$$E = \frac{\sigma_c \Phi}{3} \frac{1+4\varepsilon}{1+12\varepsilon}$$
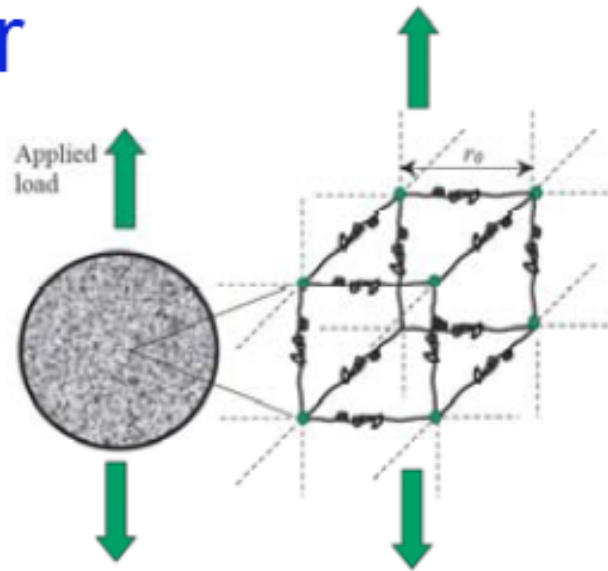
where σ_c is the prestress in the individual tensile elements and ε is the initial strain in each.

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

$$G_n \sim P/3$$

where P is the pre-stress in the tensile elements per unit total cross-sectional area ($P = \sigma_c \pi a^2/L^2$).

See Stamenovic for a full derivation.

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Biopolymer Models

Applied load

r_0

Bending stiffness

$l_p = \kappa \ / \ k_B T$

$F = \kappa^2/(k_B T \ l^4) \ \delta$

$F = \kappa l_p / l^4 \ \delta$

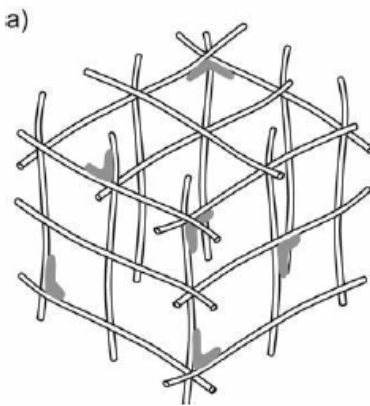l_p = persistence length

l = distance between entanglements

ξ = filament spacing

ε_n = network strain

E_n = network elastic modulus

Φ = solid fraction

Biopolymer Models

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

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

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

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

l_p = persistence length

l = distance between entanglements or cross-links
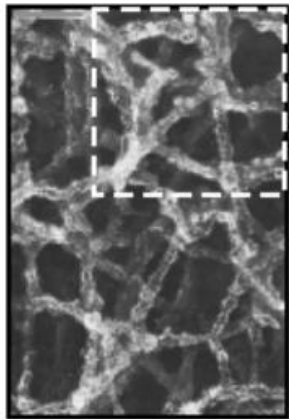
ξ = filament spacing

ε_n = network strain

E_n = network elastic modulus

δ = change in distance between entanglements/cross-links

Φ = solid fraction

Low cross-link density
$$E_n = \frac{\sigma_n}{\varepsilon_n} \sim \frac{l_p K_b}{l^3 a^2} \Phi$$

$1/\xi^2$ chains per unit area

Maximum cross-link density ($l \sim \xi$)
$$E_n = \frac{\sigma_n}{\varepsilon_n} \sim \frac{l_p K_b}{a^5} \Phi^{5/2}$$

For a densely cross-linked gel, ξ is also the typical distance between cross-links, and therefore entanglement points; $L_e \simeq \xi$.
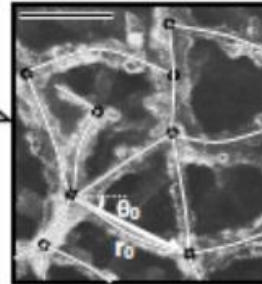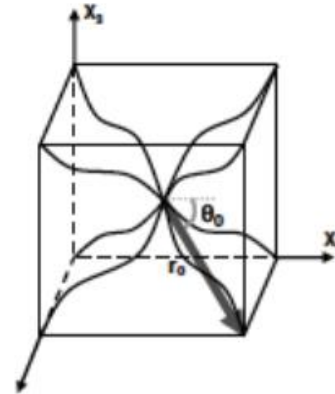
(a) Random actin network   (b) Irregular chain network   (c) Volume averaged network

Photograph of Mary Boyce removed due to copyright restrictions.

Unit cell   Mary Boyce, MIT

The initial shear modulus is given by

$$G_0 = \frac{n k_B T r_0}{3 l_p} \left(\frac{1}{4(1 - r_0/L_c)^2} \right) \left(\frac{L_c/l_p - 6(1 - r_0/L_c)}{L_c/l_p - 2(1 - r_0/L_c)} \right)$$

n = filament density
l_p = persistence length
r_0 = rest junction-to-junction distance
L_c = contour length

n = # filaments/vol = $\Phi/(a^2 L_c)$

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Scaling behaviors for the three models

Tensegrity

Predicts a linear dependence on prestress (alone!)

Athermal

No ability to change cross-link density

No role for cross-link mechanics

Viscoelasticity?

Not valid in the limit of zero prestress

$$G' \sim \sigma_n$$

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.
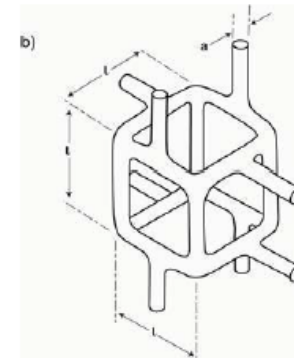
Cellular Solids

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
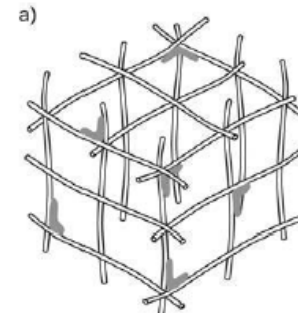
Cross-link density and mechanics?

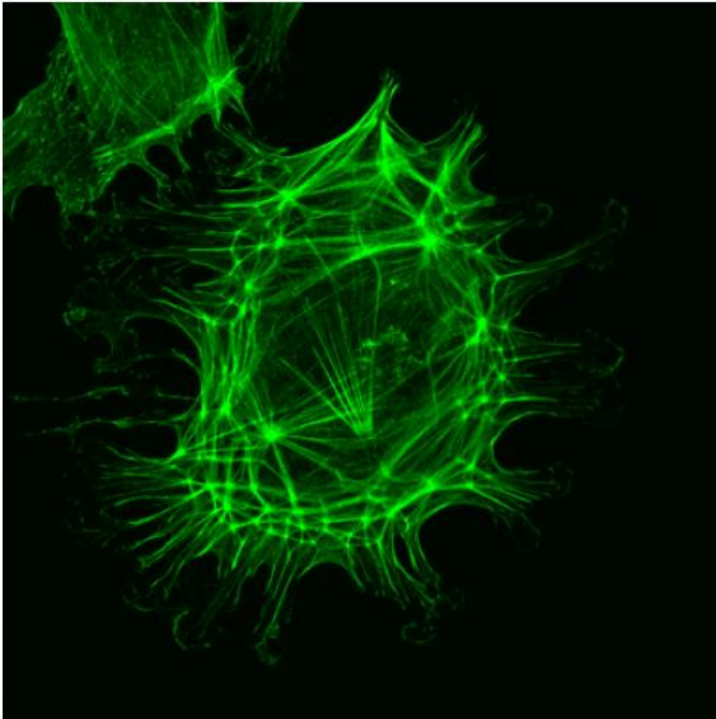$$G' \sim K_b^2 \Phi^1 \rightarrow K_b^2 \Phi^{5/2}$$

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Cell motility

Phases of Cell Migration

- Polarization
- Protrusion and adhesion
- Contraction
- Rear release
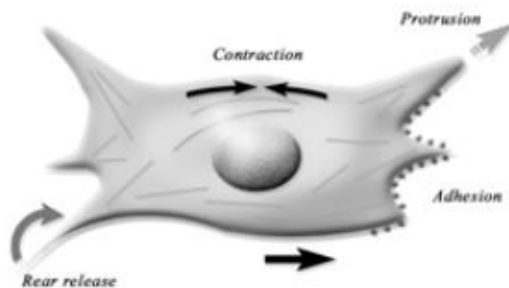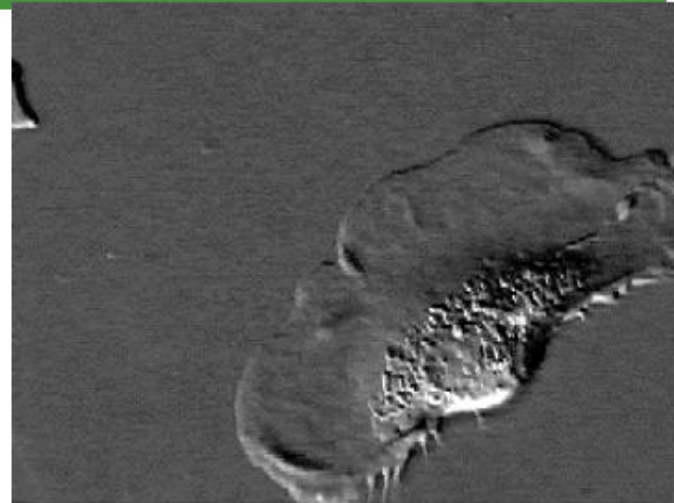
Cell motility with actin networks

It polymerizes in the presence of ATP to give the microfilaments.It is a reversible process.

Thus, there is a dynamic equilibrium in the density and organization of actin networks.

The mechanisms of polymerization and depolymerization generate cell movements

Cell motility with actin networks

Cell Motility: Actin Ruffles and Blebs in Motile Cells
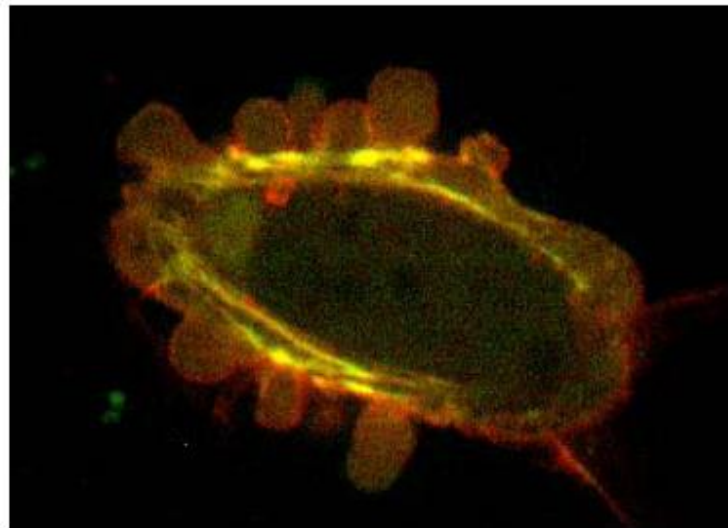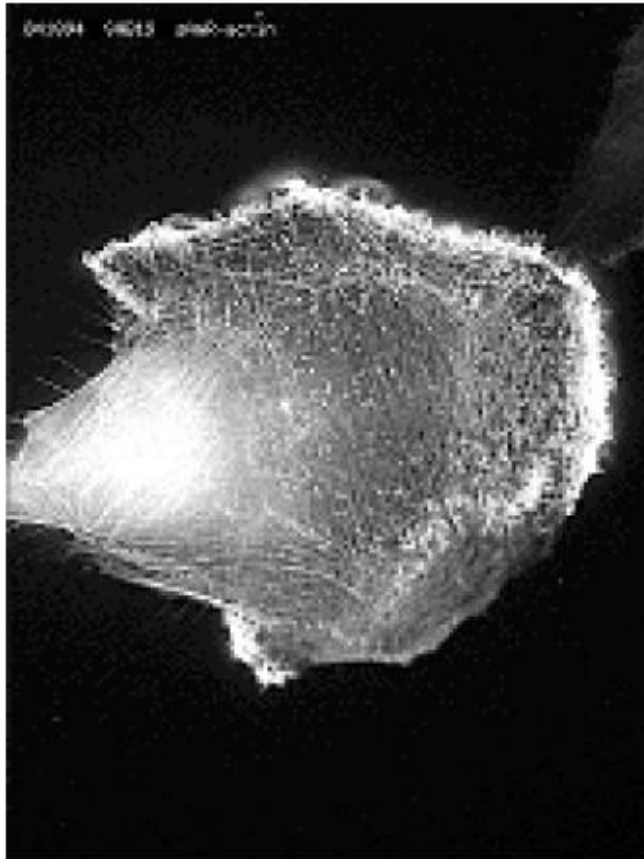
Charras, et al., Nature, 2005.

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- biomechanics.stanford.edu/Mechanics_of_the_cell_08