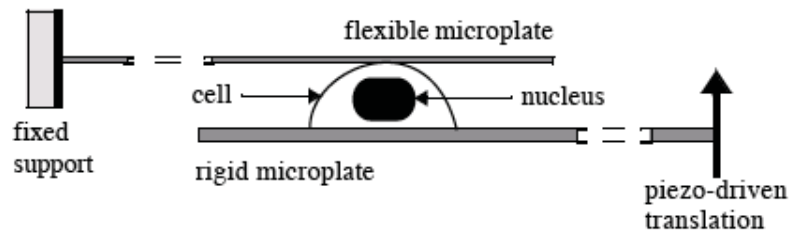
# Pathologies sin which mechanics or "*mechanobiology*" is implicated

- Asthma
- Atherosclerosis
- Cancer
- Arthritis
- Hypertension
- Bone healing
- Loss of bone mass
- Pulmonary fibrosis
- Surfactant release in lung

# Expt. #2: Cell Squashing (and AFM)

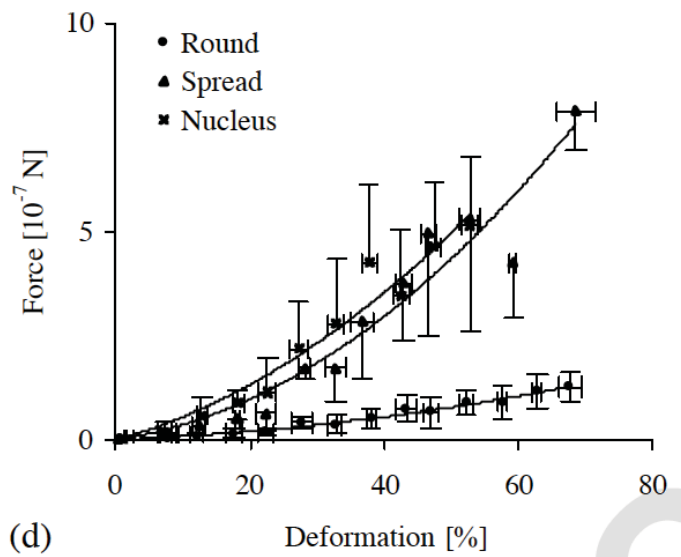


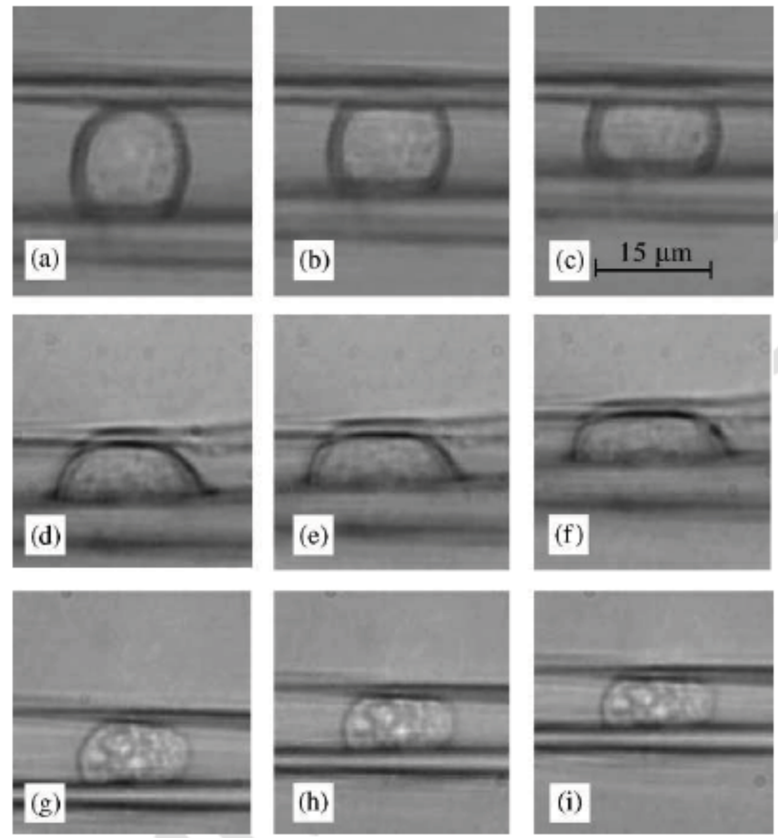

Scaling solution

$$F \sim G R^{1/2} \delta^{3/2}$$

Exact solution for a sphere

$$F = \frac{4}{3} \frac{E R^{1/2}}{1-\nu^2} \delta^{3/2}$$

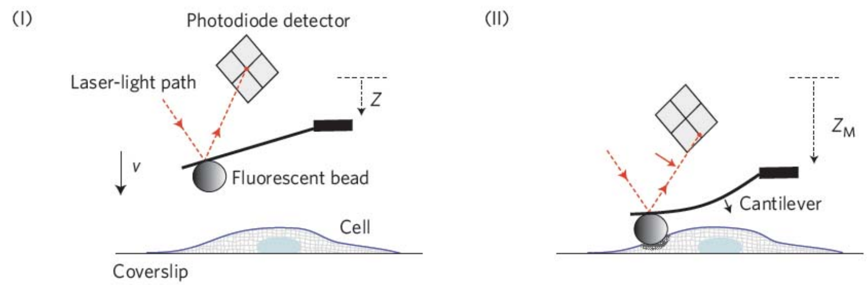


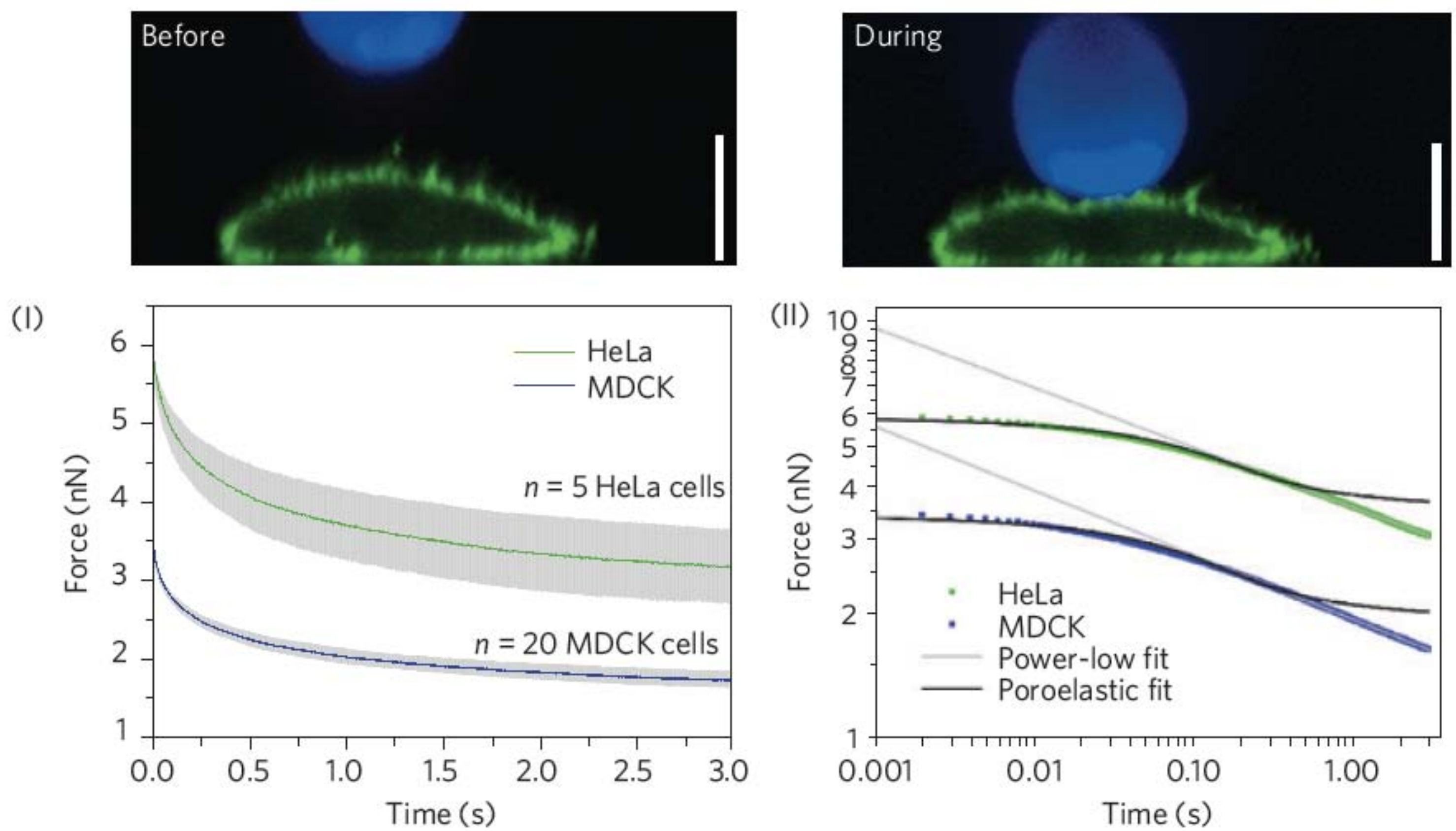




From top, a round cell, a spread cell and a nucleus. (Caille, et al., J. Biomech, 2002)


Source: Caille, Nathalie, et al. "Contribution of the Nucleus to the Mechanical Properties of Endothelial Cells." *Journal of Biomechanics* 35, no. 2 (2002): 177-87.

Population averaged force–relaxation curves showed similar trends for both HeLa and MDCK cells, with a rapid decay in the first 0.5 s followed by slower decay afterwards (Fig. 1d(I)). In Fig. 1d(II), we see that force–relaxation clearly exhibited two separate regimes: a plateau lasting ~0.1–0.2 s followed by a transition to a linear regime (Fig. 1d(II)). Hence, at short timescales, cellular force–relaxation does not follow a simple power law. Comparison with force–relaxation curves acquired on physical hydrogels[22,23], which exhibit a plateau at short timescales followed by a transition to a second plateau at longer timescales (Supplementary Fig. S3A,B), suggests that the initial plateau observed in cellular force–relaxation may correspond to poroelastic behaviour. Indeed poroelastic





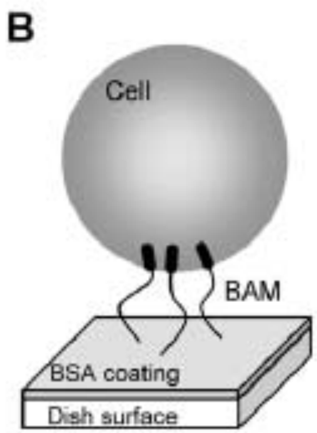
Source: Moeendarbary, Emad, et al. "The Cytoplasm of Living Cells Behaves as a Poroelastic Material." *Nature Materials* 12, no. 3 (2013): 253-61.

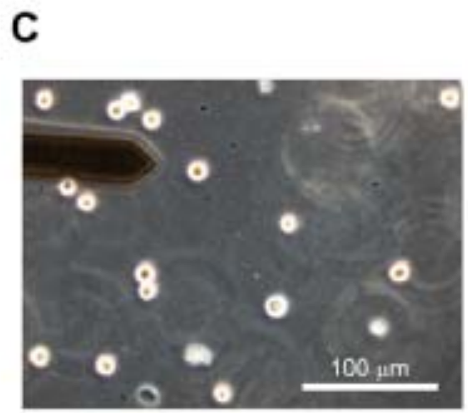
OPEN ACCESS Freely available online PLoS one

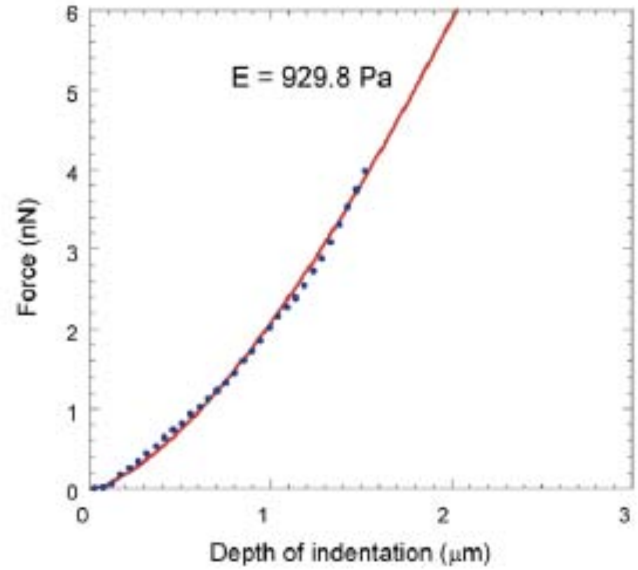
# Simple Display System of Mechanical Properties of Cells and Their Dispersion

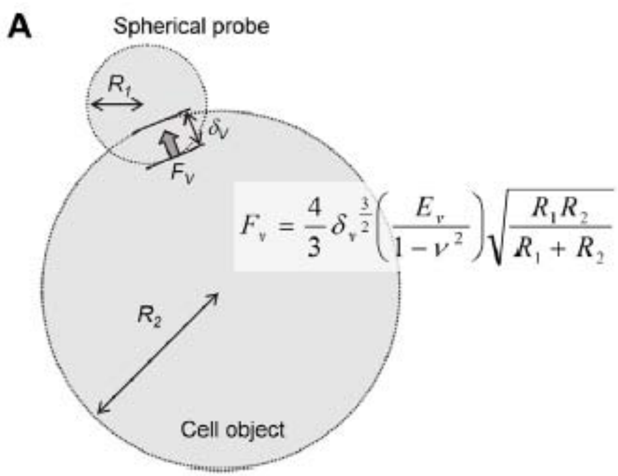
Yuji Shimizu[1], Takanori Kihara[1*], Seyed Mohammad Ali Haghparast[1], Shunsuke Yuba[2], Jun Miyake[1]

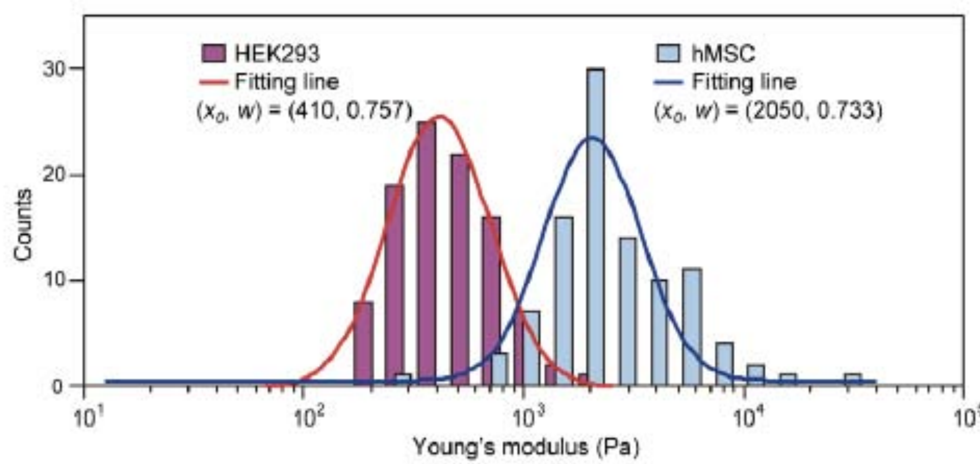
March, 2012





Source: Shimizu, Yuji, et al. "Simple Display System of Mechanical Properties of Cells and their Dispersion." *PloS ONE* 7, no. 3 (2012).

# Homogeneous??

## Cells in 3D matrix

Figures removed due to copyright restrictions.

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

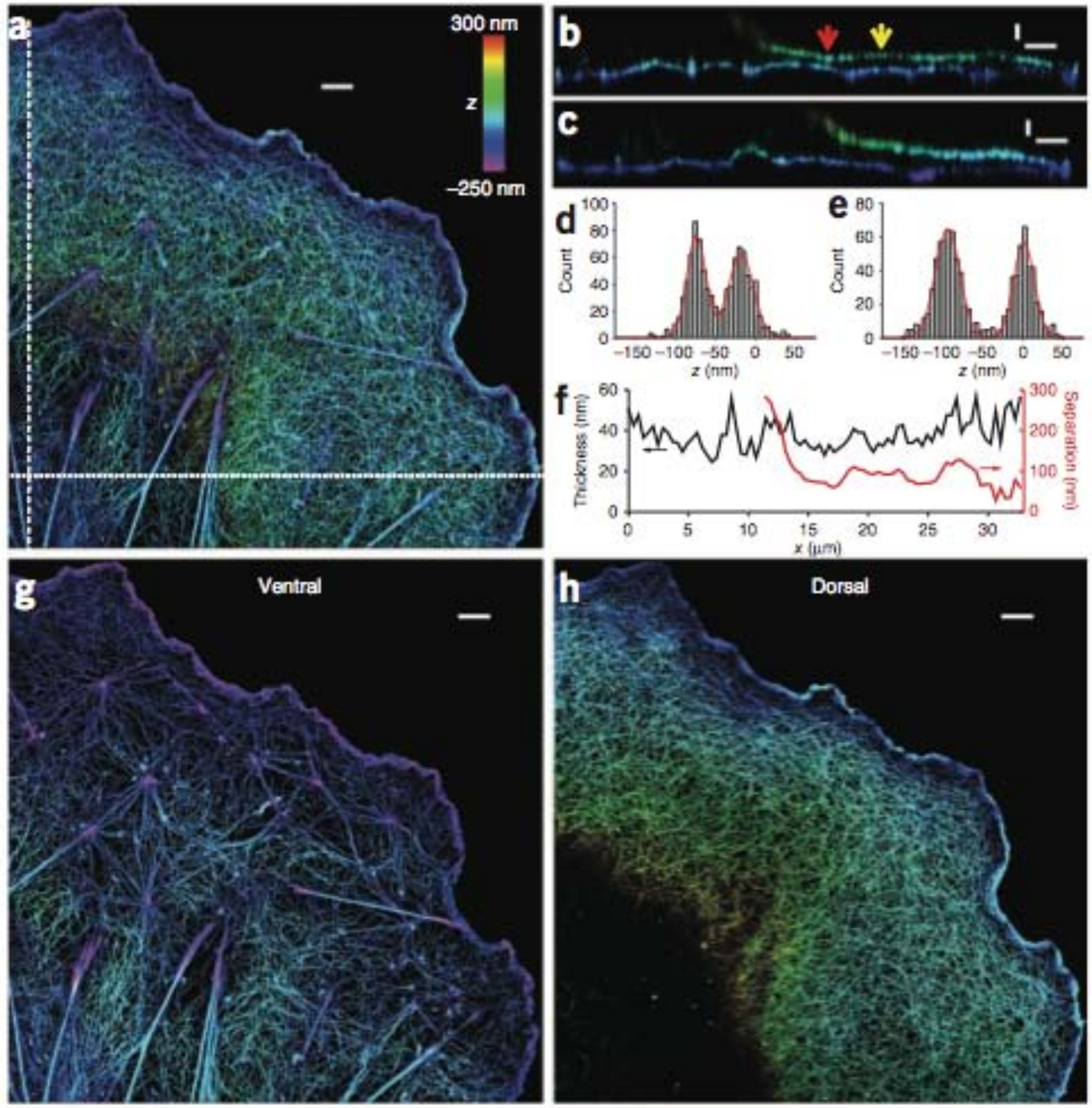
- Dense cortical actin with myosin.
- Cross-linkers more homogeneously distributed

Rajagopalan, unpublished

# Isotropic??

**Figure 3** | Sheet-like cell protrusion comprises two layers of actin networks with distinct structures. (**a**) Dual-objective STORM image of actin in a BSC-1 cell. The *z* positions are color coded (color bar). (**b**,**c**) Vertical cross sections (each 500-nm wide in *x* or *y*) of cell in **a** along dotted and dashed lines, respectively. When far from cell edge, *z* position of dorsal layer increases quickly and falls out of imaging range. (**d**,**e**) The *z* profiles for two points along vertical section (red and yellow arrows in **b**, respectively). Each histogram is fit to two Gaussians (red curves), yielding apparent thickness of ventral and dorsal layers and peak separation between the two layers. (**f**) Quantification of apparent thickness averaged over two layers and dorsal-ventral separation obtained from *x*–*z* cross-section profile in **b**. (**g**,**h**) Ventral and dorsal actin layers of cell in **a**. (**i**,**j**) Ventral and dorsal actin layers of a COS-7 cell treated with blebbistatin. (**k**,**l**) Vertical cross sections (each 500-nm wide in *x* or *y*) of cell along dotted and dashed lines, respectively. (**m**) Actin density of ventral and dorsal layers along yellow box in **i**,**j**, measured by localization density. Scale bars, 2 µm (**a**,**g**–**j**); 100 nm for *z* and 2 µm for *x* and *y* (**b**,**c**,**k**,**l**).

We observed two vertically separated actin layers in the sheet-like cell protrusion despite its small thickness (**Fig. 3a–c**). The apparent thickness of each layer was





Source: Xu, Ke, et al. "Dual-objective STORM Reveals Three-dimensional Filament Organization in the Actin Cytoskeleton." *Nature Methods* 9, no. 2 (2012): 185-8.

http://www.nature.com/nmeth/video/moy2008/index.html

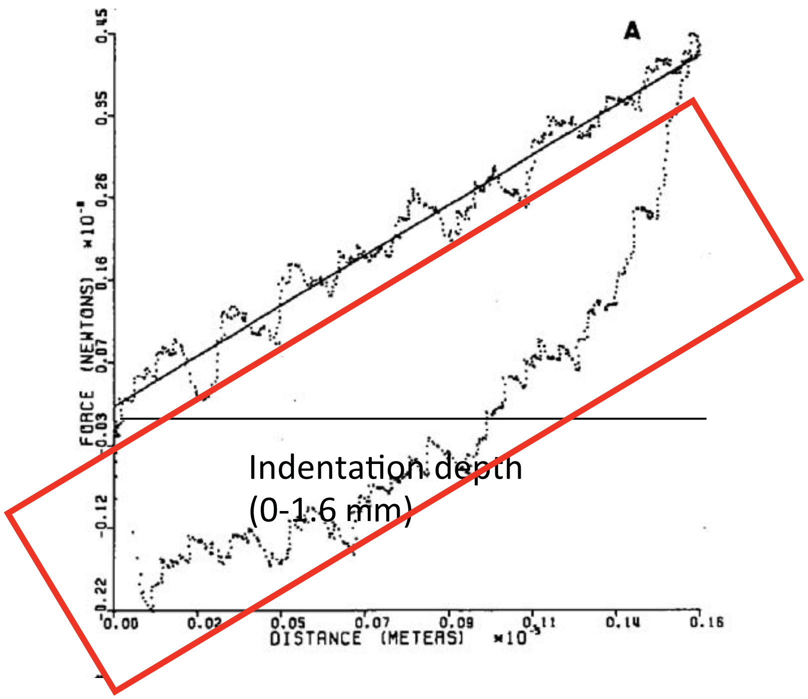
# Elastic??

Micropipette Aspiration

## Cells are viscoelastic

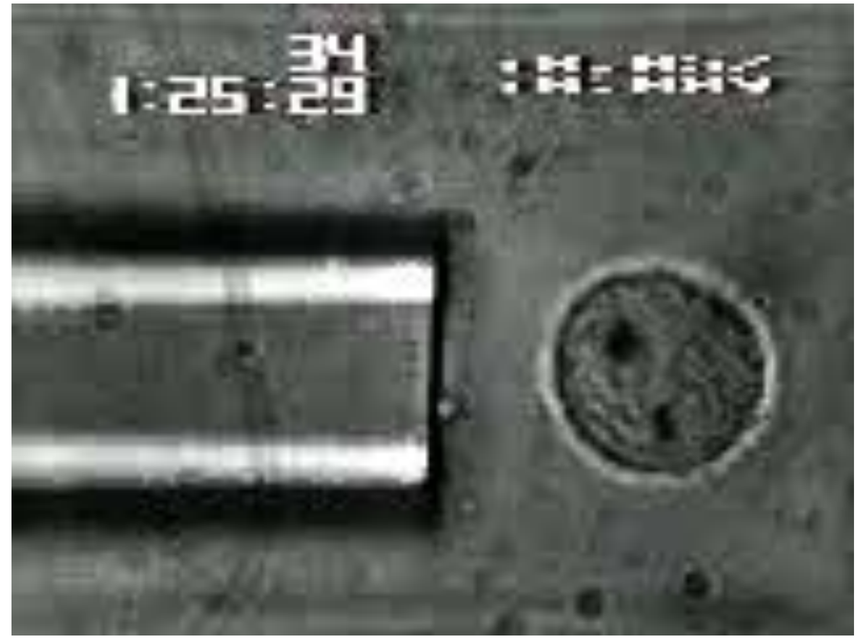
Force

(0-4.5 nN)




Indentation


Source: Zahalak, G. I., et al. "Determination of Cellular Mechanical Properties by Cell Poking, with An Application to Leukocytes." *Journal of Biomechanical Engineering* 112, no. 3 (1990): 283-94.







(Zahalak et al., 1990)

# Expt. #3: Magnetic Twisting Cytometry

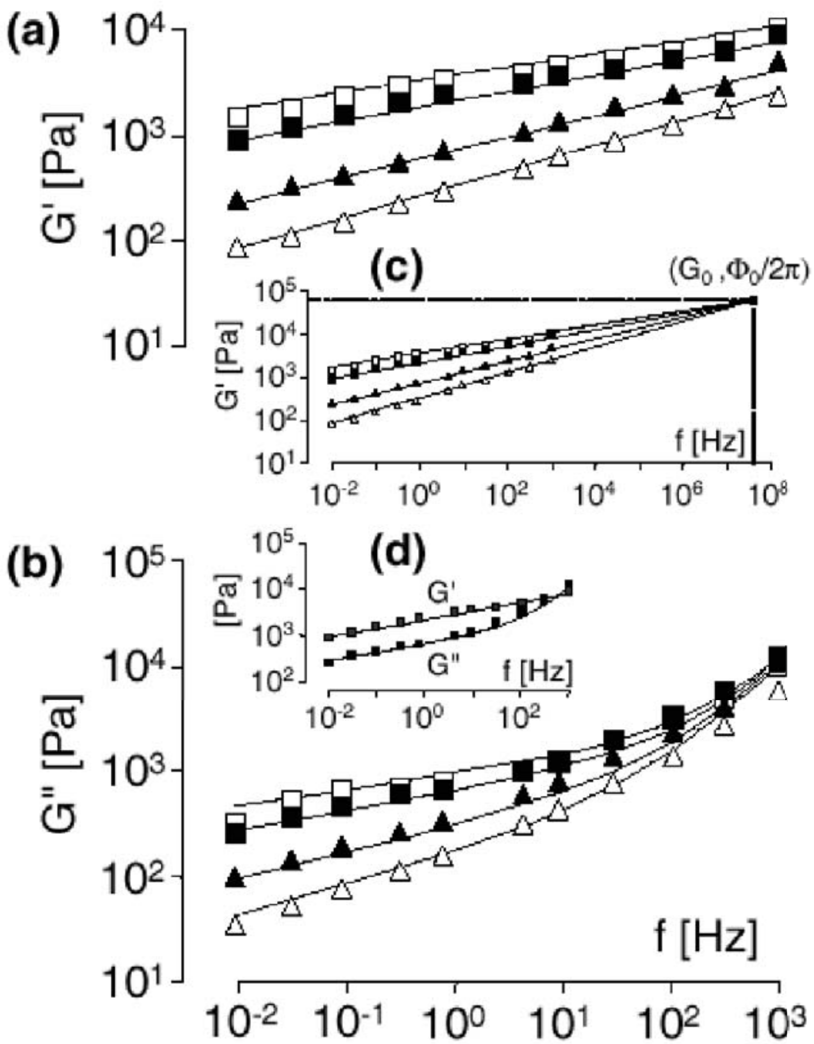
Figure 1 removed due to copyright restrictions.
Source: Fabry, Ben, et al. "Scaling The Microrheology of Living Cells." *Physical Review Letters* 87, no. 14 (2001): 148102.

VOLUME 87, NUMBER 14 PHYSICAL REVIEW LETTERS 1 OCTOBER 2001

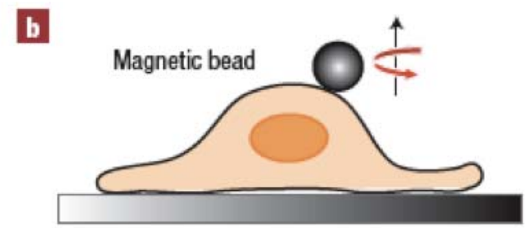
**Scaling the Microrheology of Living Cells**

Ben Fabry,[1,*] Geoffrey N. Maksym,[2] James P. Butler,[1] Michael Glogauer,[3] Daniel Navajas,[4] and Jeffrey J. Fredberg[1]

# Background: Linear Rheology of the Cytoskeleton




Fabry et al., PRL, 2001





Source: Bao, Gang, and S. Suresh. "Cell and Molecular Mechanics of Biological Materials." *Nature Materials* 2, no. 11 (2003): 715-25.

- Cells exhibit a weak power-law rheology, similar to soft glassy materials.

- This behavior is consistent over a range of experimental conditions and for all different types of cells.

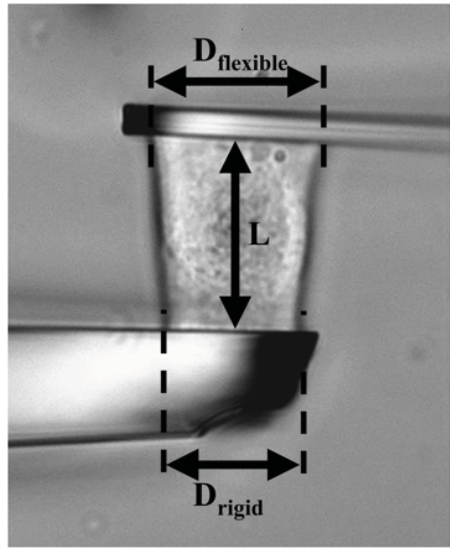
$$G^* = G' + jG'' = \alpha \frac{M(t)}{\delta(t)}$$

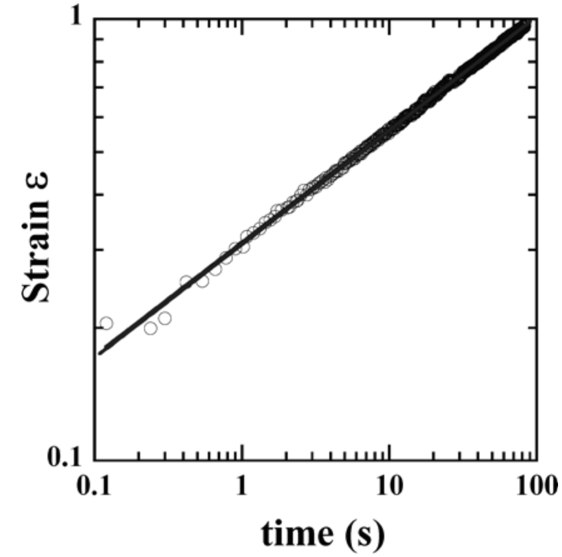
$$G = G_0 \left(\frac{\omega}{\omega_0}\right)^{x-1} \left((1 + j\bar{\eta})\Gamma(x-2)\cos\left[\frac{\pi}{2}(x-1)\right] + j\omega\mu\right.$$

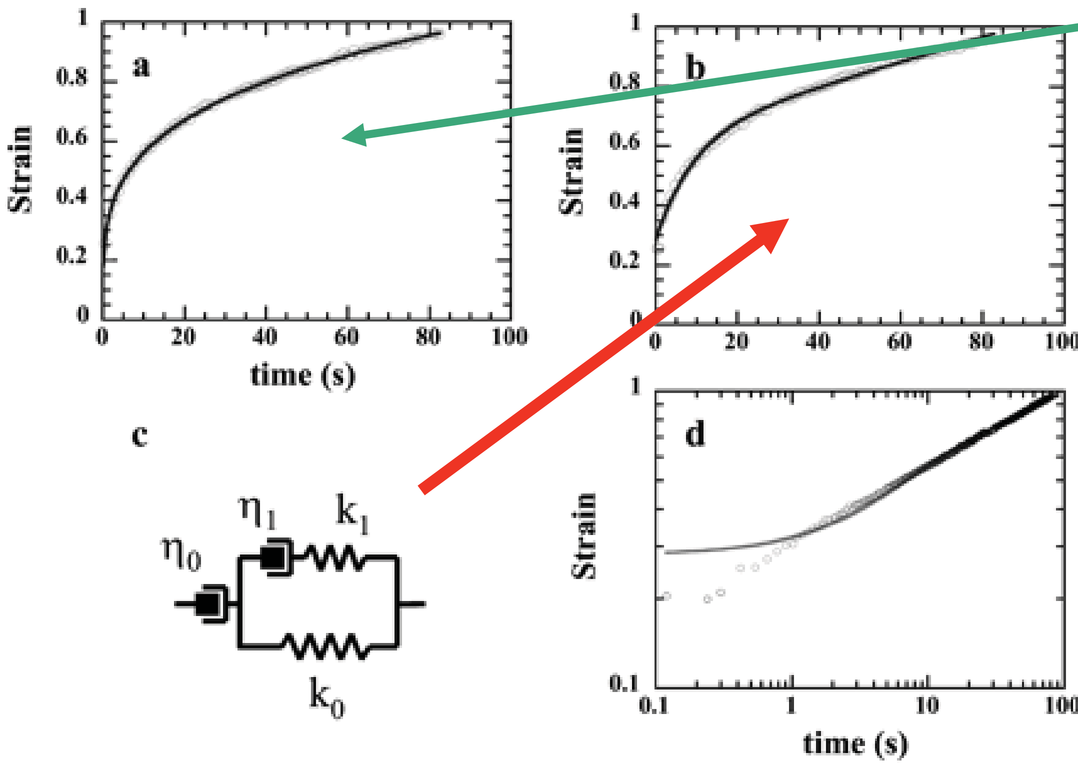
$$\bar{\eta} = \tan(x-1)\tfrac{\pi}{2}$$

# Expt. #4: Cell stretching

Desprat et al., Biophys J., 2005.




Power-law behavior observed over a wide range of strains.

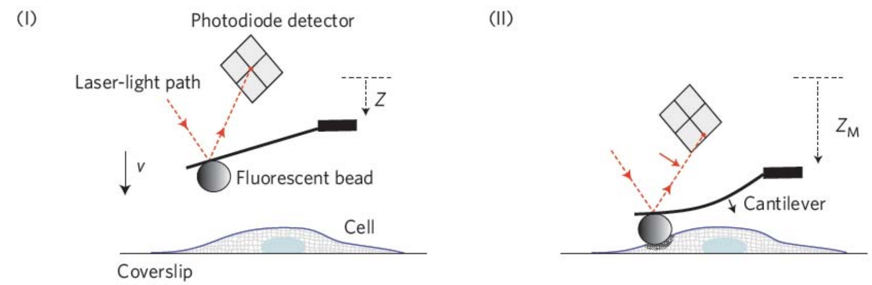
$d\varepsilon/dt = \text{const} \cdot t^{\alpha}$.

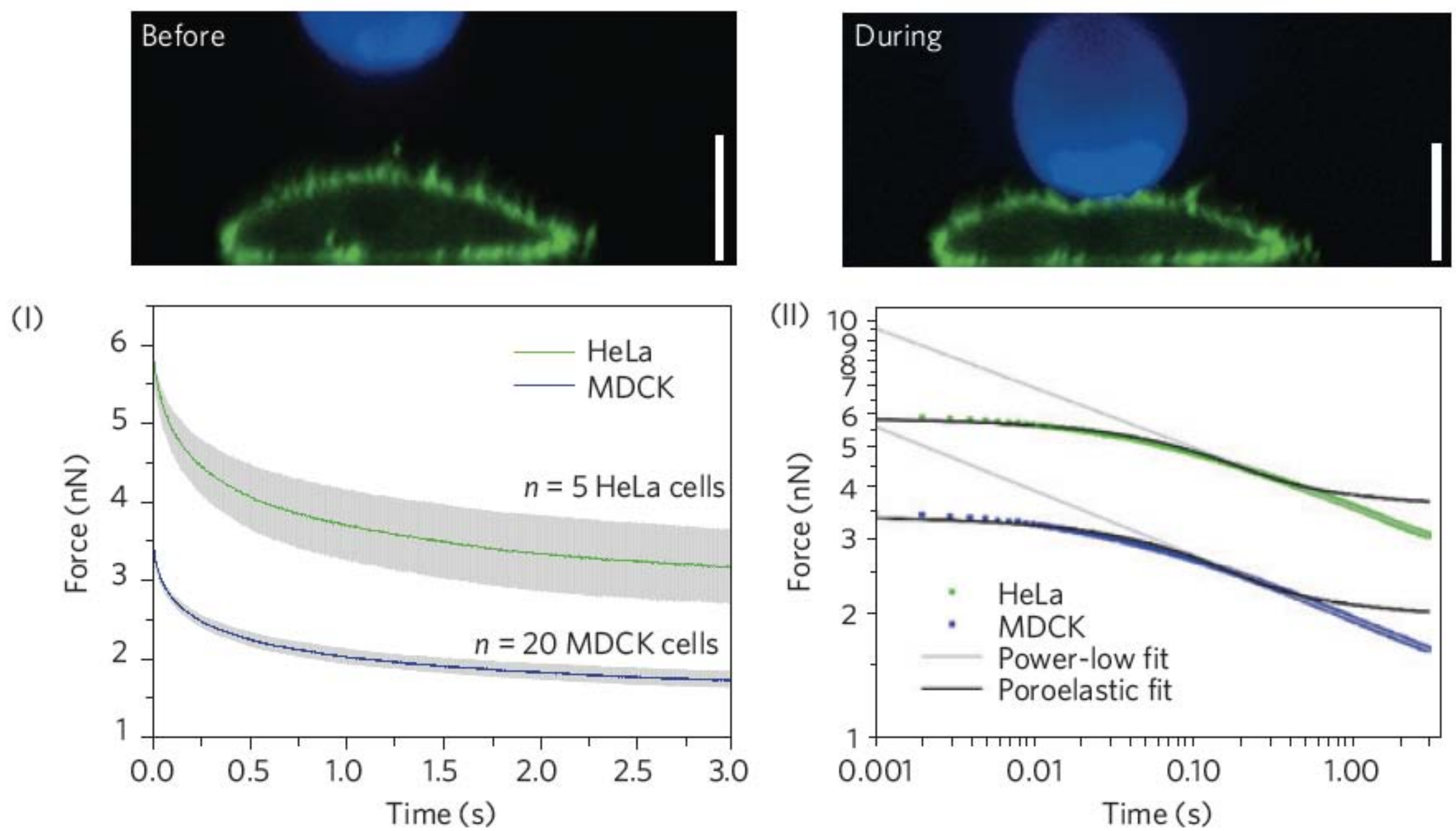
Cells can appear to exhibit simple viscoelastic behavior in a linear plot, but on log-log scales the power-law behavior becomes obvious.



Source: Desprat, Nicolas, et al. "Creep Function of a Single Living Cell." *Biophysical Journal* 88, no. 3 (2005): 2224-33.

Population averaged force–relaxation curves showed similar trends for both HeLa and MDCK cells, with a rapid decay in the first 0.5 s followed by slower decay afterwards (Fig. 1d(I)). In Fig. 1d(II), we see that force–relaxation clearly exhibited two separate regimes: a plateau lasting ~0.1–0.2 s followed by a transition to a linear regime (Fig. 1d(II)). Hence, at short timescales, cellular force–relaxation does not follow a simple power law. Comparison with force–relaxation curves acquired on physical hydrogels[22,23], which exhibit a plateau at short timescales followed by a transition to a second plateau at longer timescales (Supplementary Fig. S3A,B), suggests that the initial plateau observed in cellular force–relaxation may correspond to poroelastic behaviour. Indeed poroelastic





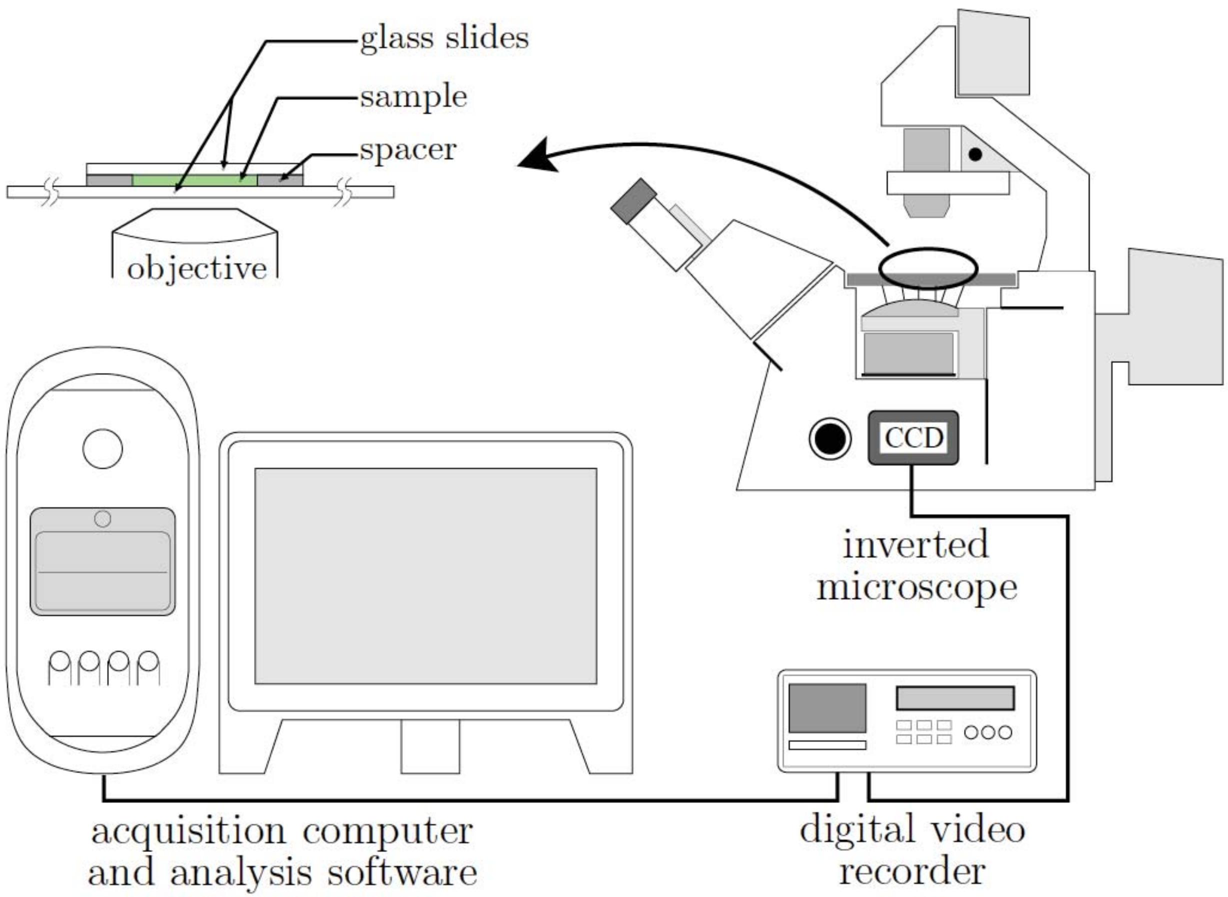
Source: Moeendarbary, Emad, et al. "The Cytoplasm of Living Cells Behaves as a Poroelastic Material." *Nature Materials* 12, no. 3 (2013): 253-61.

# Expt. #5: Particle Tracking Microrheology (PTM)

(T. Savin)

- Standard video microscopy tracking setup

IDL programs

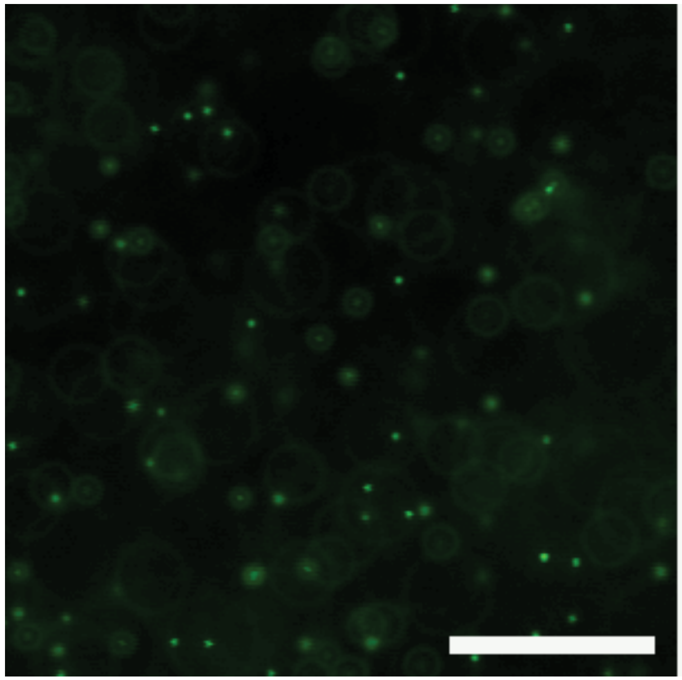



Courtesy of MIT.
Source: Savin, Thierry. "Multiple Particle Tracking to Assess the Microstructure of Biological Fluids." PhD Dissertation, Massachusetts Institute of Technology, 2006.

# Video Microscopy Particle Tracking

- Tracking algorithms

Example:
1 μm diameter spheres in water, $T$=25°C



30 μm



Crocker and Grier, 1996

http://www.physics.emory.edu/~weeks/idl/

# Particle tracking microrheology

- Thermal fluctuations of particles reflect the mechanics of their local environment
- Evaluate the mean-squared displacement of the particles :

$$\left\langle \Delta x^2(t) \right\rangle = \left\langle \left| x(t) - x(0) \right|^2 \right\rangle$$

- Two limits

<u>Viscous</u>

$$\left\langle \Delta x^2(t) \right\rangle = \frac{k_B T}{\pi a \mu} t$$

<u>Elastic</u>

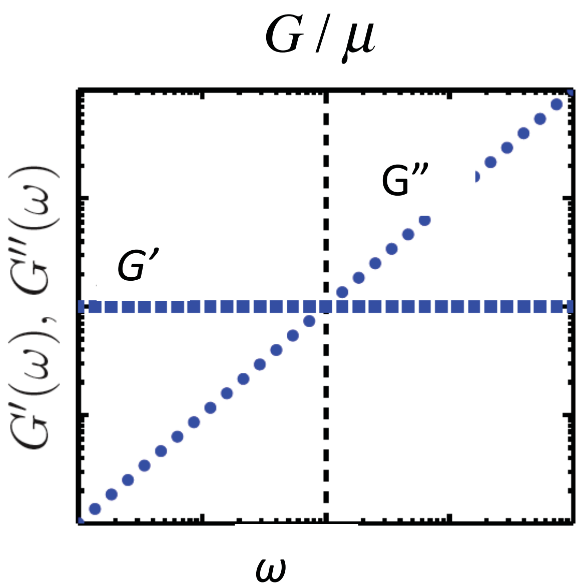
$$\left\langle \Delta x^2(t) \right\rangle = \frac{k_B T}{\pi a G}$$

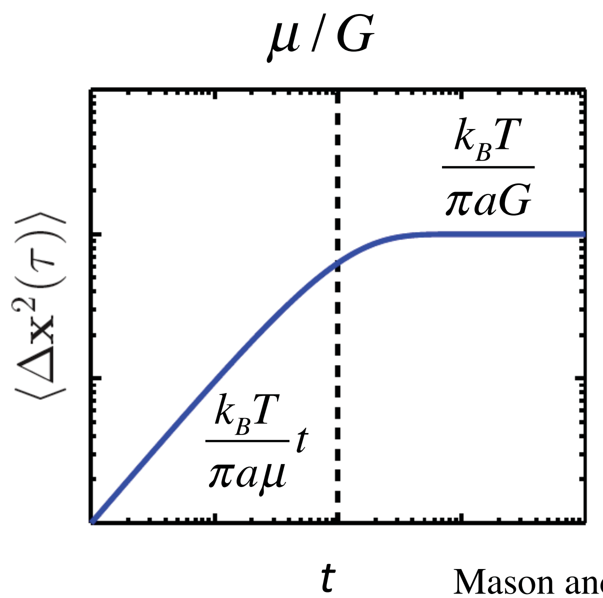
# Particle tracking microrheology

- Generalized Stokes-Einstein Relation (GSER)

$$\hat{G}(\omega)=\frac{k_B T}{\pi a j\omega F_t^u\left[\left\langle \Delta x^2(t)\right\rangle\right]}=G'(\omega)+jG''(\omega)$$

- Example - Voigt fluid: $\hat{G}(\omega)=G+j\mu\omega$



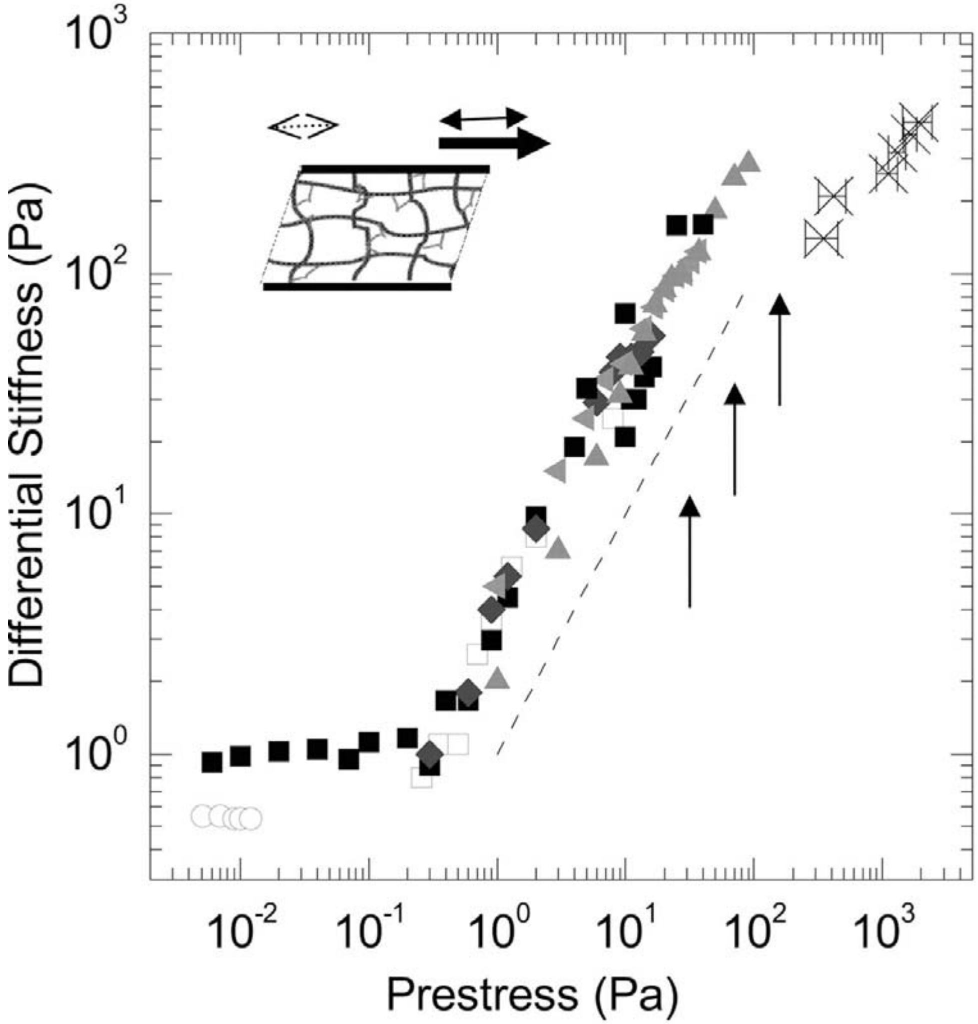

Mason and Weitz, 1995

# Tumor cell escaping from the circulation

Figure removed due to copyright restrictions.
Source: Chen, Michelle B., et al. "Mechanisms of Tumor Cell Extravasation in an in Vitro Microvascular Network Platform." *Integrative Biology* 5, no. 10 (2013): 1262-71.

Michelle Chen, Integr Biol, 2013

# Nonlinear modulus at higher levels of prestress





Source: Gardel, M. L., et al. "Prestressed F-actin Networks Cross-linked by Hinged Filamins Replicate Mechanical Properties of Cells." *Proceedings of the National Academy of Sciences* 103, no. 6 (2006): 1762-7.

A prestress is applied to the network and the deformation is measured in response to an additional oscillatory stress

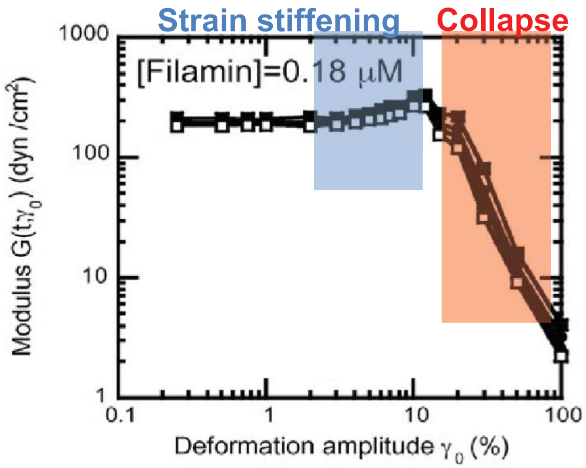
The response is **approximately linear** with prestress above a threshold value

Incremental modulus is **independent of actin or cross-link concentration**

Gardel M. L. et.al. PNAS 2006

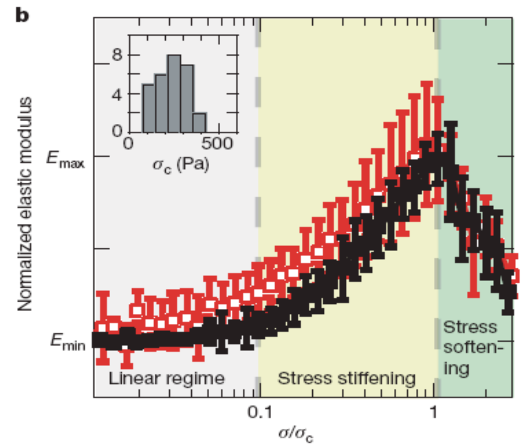
# Pre-stress increases moduli of reconstituted F-actin networks, up to a critical point

Reconstituted actin gels




(Tseng et. al. 2004)


Source: Tseng, Yiider, et al. "The Bimodal Role of Filamin in Controlling the Architecture and Mechanics of F-actin Networks." *Journal of Biological Chemistry* 279, no. 3 (2004): 1819-26.




Reconstituted cellular cytoskeletons

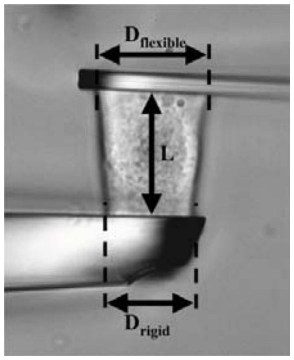
(Chaudhuri et al. 2007)

Courtesy of Macmillan Publishers Limited. Used with permission.
Source: Chaudhuri, Ovijit, et al. "Reversible Stress Softening of Actin Networks." *Nature* 445, no. 7125 (2007): 295-8.

Strain-stiffening of F-actin/ABP at low strains

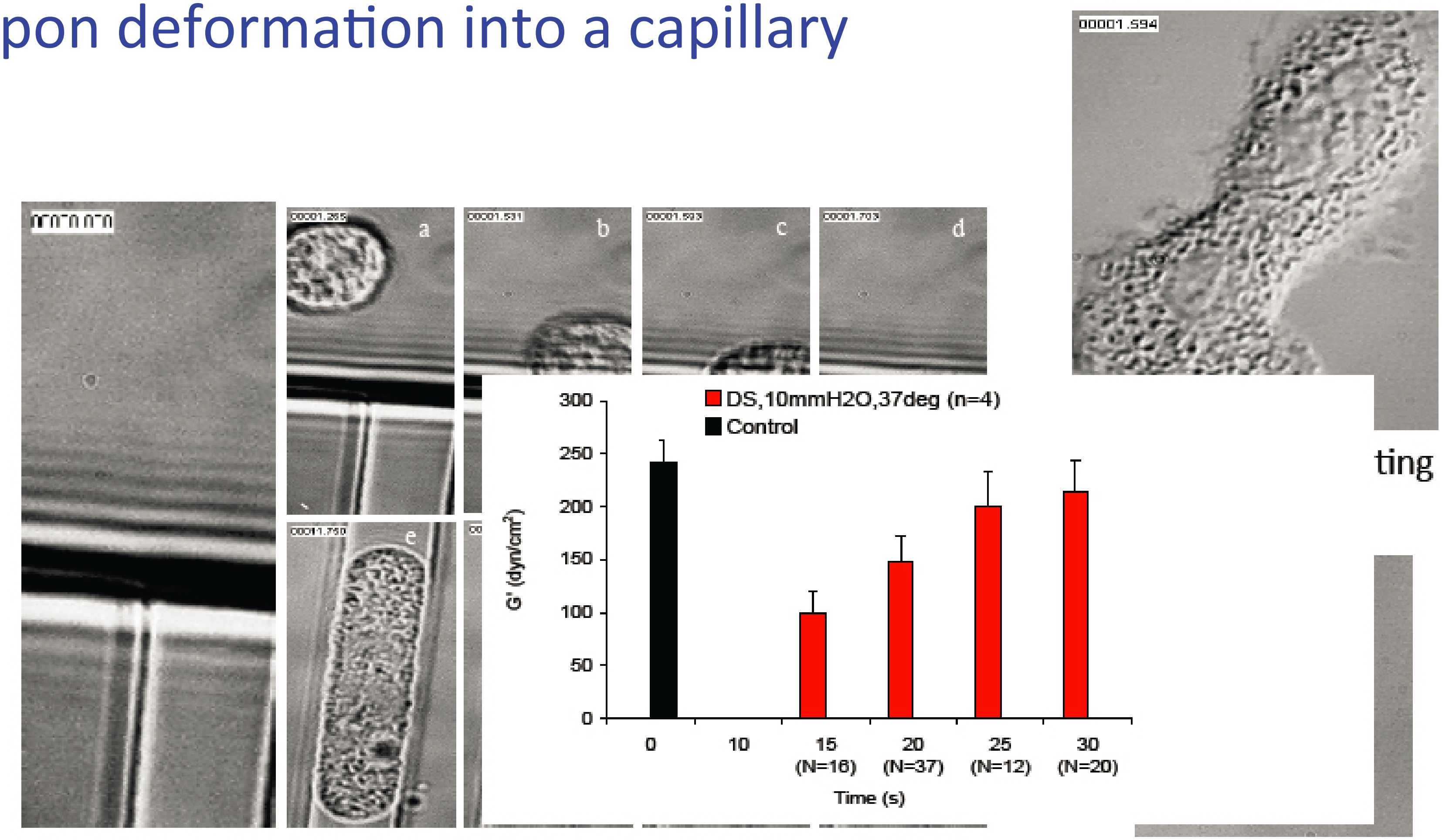
Nonlinear stress response and matrix collapse at large strain

Reversible stress stiffening and softening




Courtesy of Elsevier, Inc., http://www.sciencedirect.com. Used with permission.
Source: Desprat, Nicolas, et al. "Creep Function of a Single Living Cell." *Biophysical Journal* 88, no. 3 (2005): 2224-33.

# Neutrophil elastic moduli fall abruptly upon deformation into a capillary




As a function of time after entering channel, until protrusion

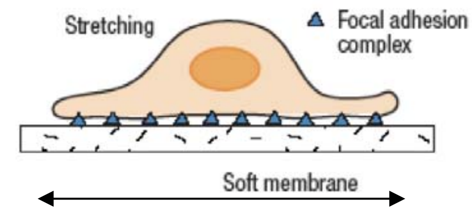
In non-adherent, neutrophils



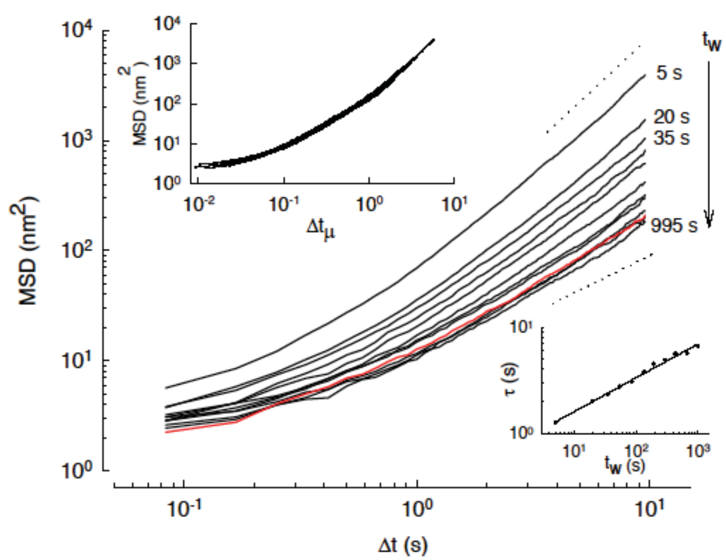
Source: Yap, Belinda, and Roger D. Kamm. "Mechanical Deformation of Neutrophils into Narrow Channels Induces Pseudopod Projection and Changes in Biomechanical Properties." *Journal of Applied Physiology* 98, no. 5 (2005): 1930-39.

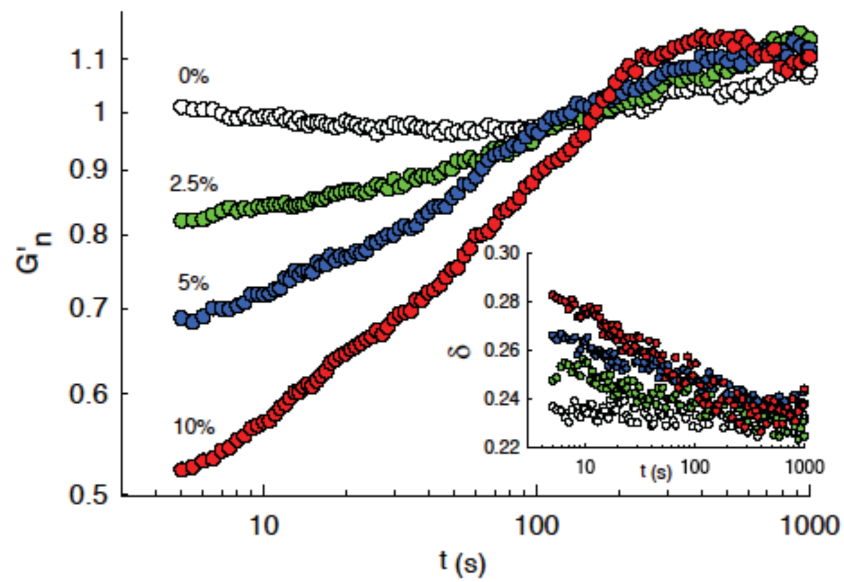
(Yap & Kamm, J Appl Physiol, 2005)

# Cells that have been suddenly stretched immediately exhibit a lower G' but recover in ~ 200s




Courtesy of Nature Publishing Group. Used with permission.
Source: Bao, Gang, and S. Suresh. "Cell and Molecular Mechanics of Biological Materials." *Nature Materials* 2, no. 11 (2003): 715-25.




Courtesy of Macmillan Publishers Limited. Used with permission.
Source: Trepat, Xavier, et al. "Universal Physical Responses to Stretch in the Living Cell." *Nature* 447, no. 7144 (2007): 592-5.

**Universal physical responses to stretch in the living cell**

10 November 2006


Xavier Trepat[1], Linhong Deng[1,2], Steven S. An[1,3], Daniel Navajas[4], Daniel J. Tschumperlin[1], William T. Gerthoffer[5], James P. Butler[1], and Jeffrey J. Fredberg[1]


Cytoskeletal fluidization is a common attribute of cells