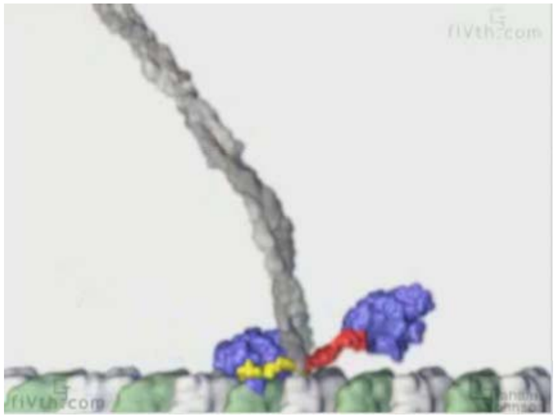
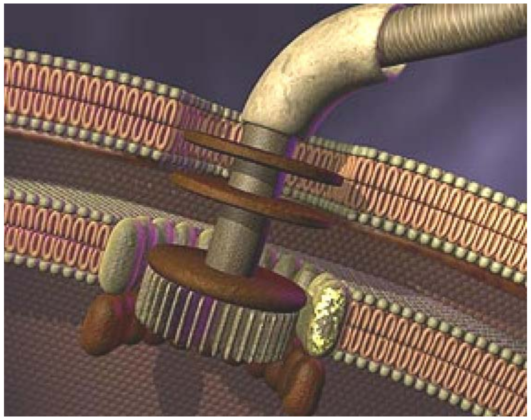
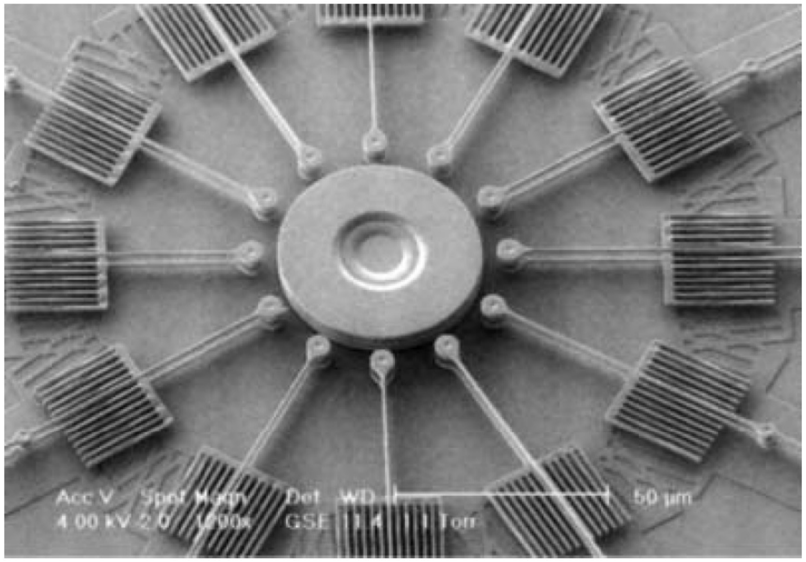
Biological Machines, Cell Mechanics and Nanotechnology







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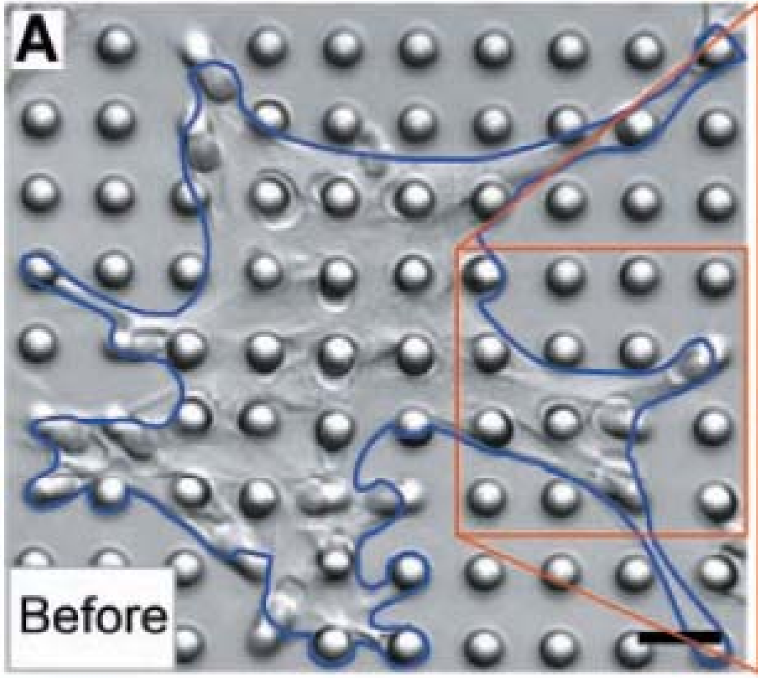
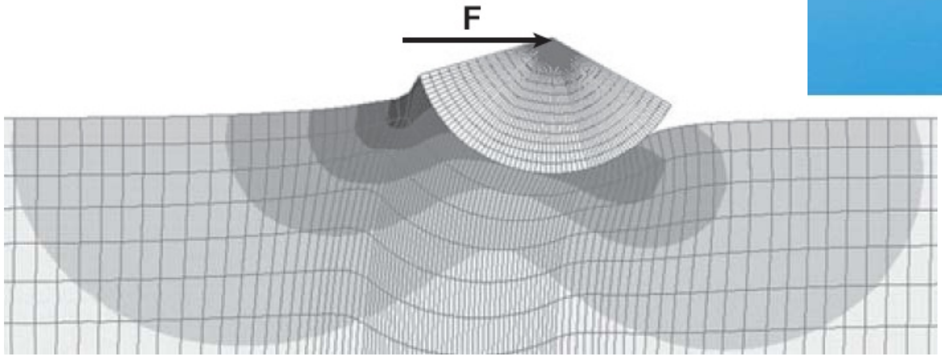
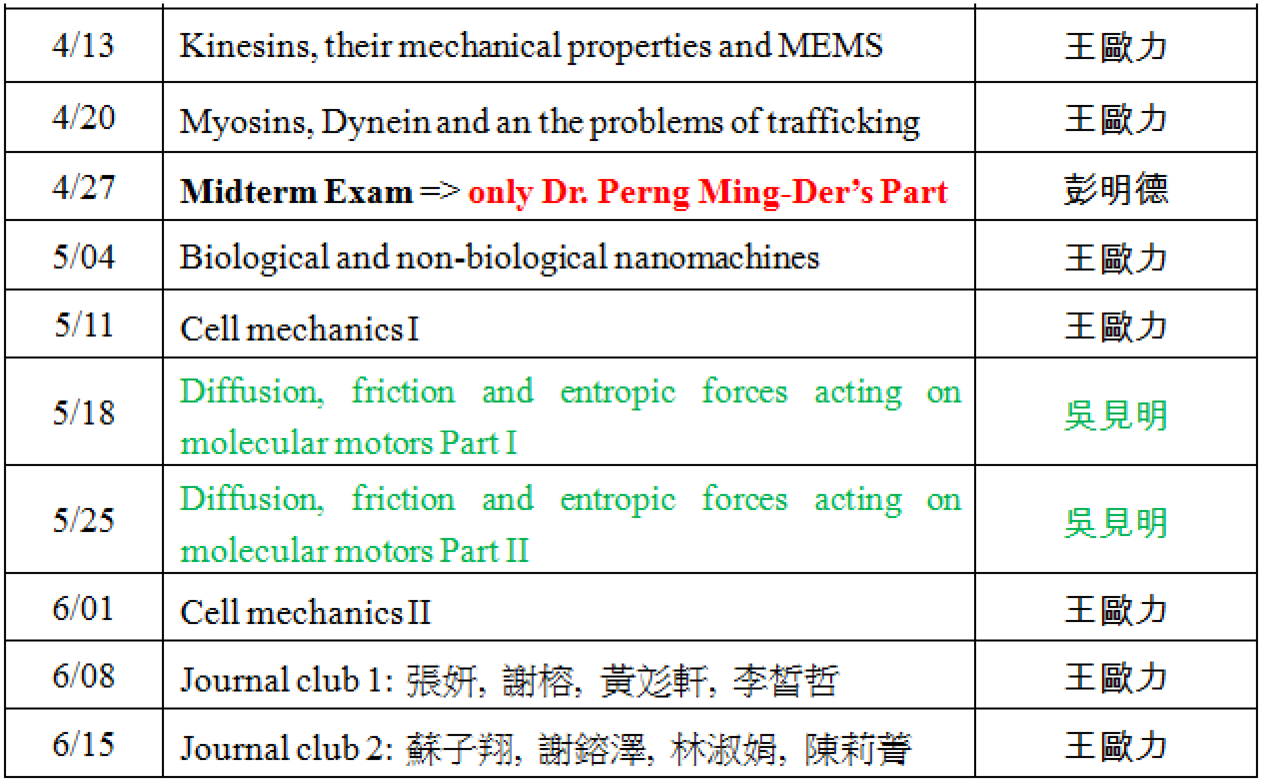




Remaining course overview



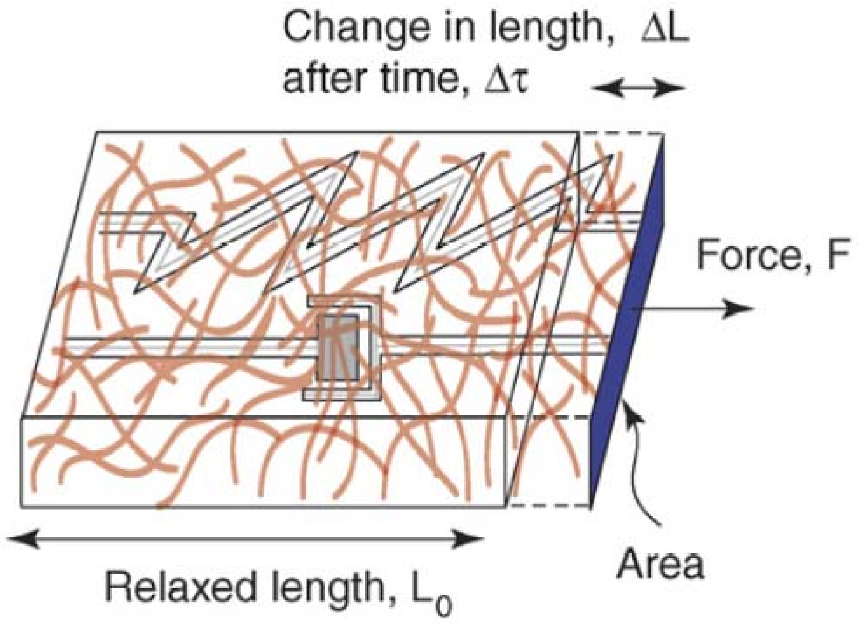
4/13	Kinesins, their mechanical properties and MEMS	王歐力
4/20	Myosins, Dynein and an the problems of trafficking	王歐力
4/27	**Midterm Exam** => **only Dr. Perng Ming-Der's Part**	彭明德
5/04	Biological and non-biological nanomachines	王歐力
5/11	Cell mechanics I	王歐力
5/18	Diffusion, friction and entropic forces acting on molecular motors Part I	吳見明
5/25	Diffusion, friction and entropic forces acting on molecular motors Part II	吳見明
6/01	Cell mechanics II	王歐力
6/08	Journal club 1: 張妍，謝榕，黃彣軒，李晢哲	王歐力
6/15	Journal club 2: 蘇子翔，謝鎔澤，林淑娟，陳莉菁	王歐力

Evaluation:
Presence 25%, Class Performance 40%, Journal Club 35%

Journal Club:
- Pick an article from a journal with IF >5 about **molecular motors** or **cell mechanics**
- Presentation time 20 min. + 10 min discussion (total 2 hours for 4 students)

The quantities of cell mechanics

Storage and loss modulus describing elastic and viscous behavior of cells



Stress: $\sigma = F / \text{Area}$

Strain: $\gamma = \Delta L / L_0$

Strain rate: $\dot{\gamma} = \Delta\gamma / \Delta\tau$ (temporal derivative of strain)

Elastic response $\boxed{\sigma = G' \gamma}$

Viscous response $\boxed{\sigma = [\, G''(\Delta\tau)\, \Delta\tau \,]\, \dot{\gamma}}$

- **Elasticity** of **biopolymer** networks allows them to <u>resist deformation</u> **like a spring**

⇒ energy of deformation is stored <u>regardless of time</u>: **storage modulus G´**

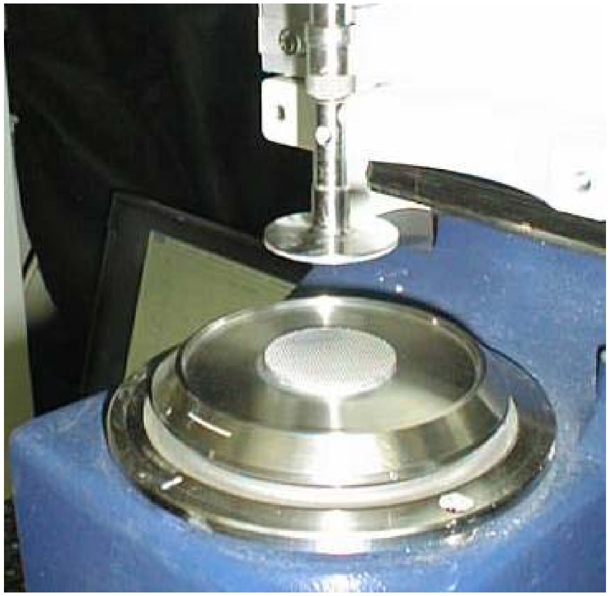
- **Viscous behavior** of **biopolymer** networks allows them to **flow as a fluid**:

⇒ <u>resistance depends</u> on the <u>rate of deformation</u> (like in a dashpot)

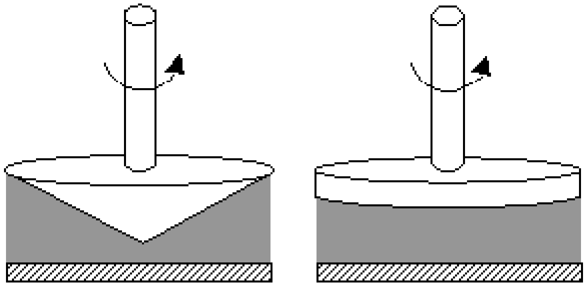
⇒ <u>energy</u> put into deformation: <u>dissipated or lost</u>: **loss modulus G´´**

Rheology: determination of viscoelastic properties of liquids

- Rheo = flow (Greek) = measuring the flow of liquids
- Most popular: cone-plate or plate-plate **rheometer** = liquid placed between 2 plates
- Upper plate rotates at defined speed and angle = **shear rate** (velocity per distance)
- Upper plate also measures the resistance (response) of the fluid to applied shear by measuring the **torque** (= twisting force) = **shear stress** (F/A)



Oscillating cone or plate



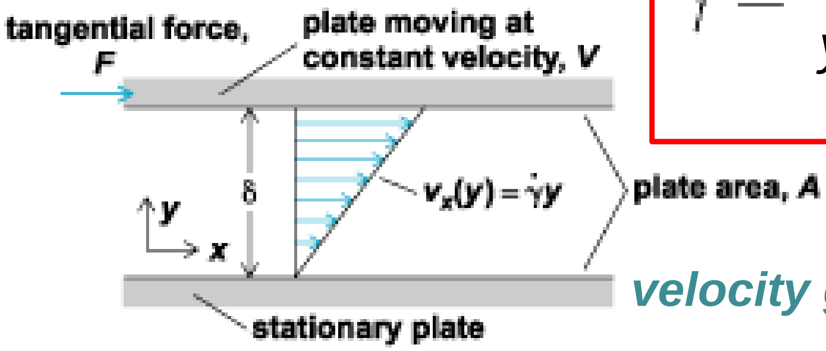
Fixed plate

Shear rate:

$$\dot{\gamma} = \frac{v}{y}$$

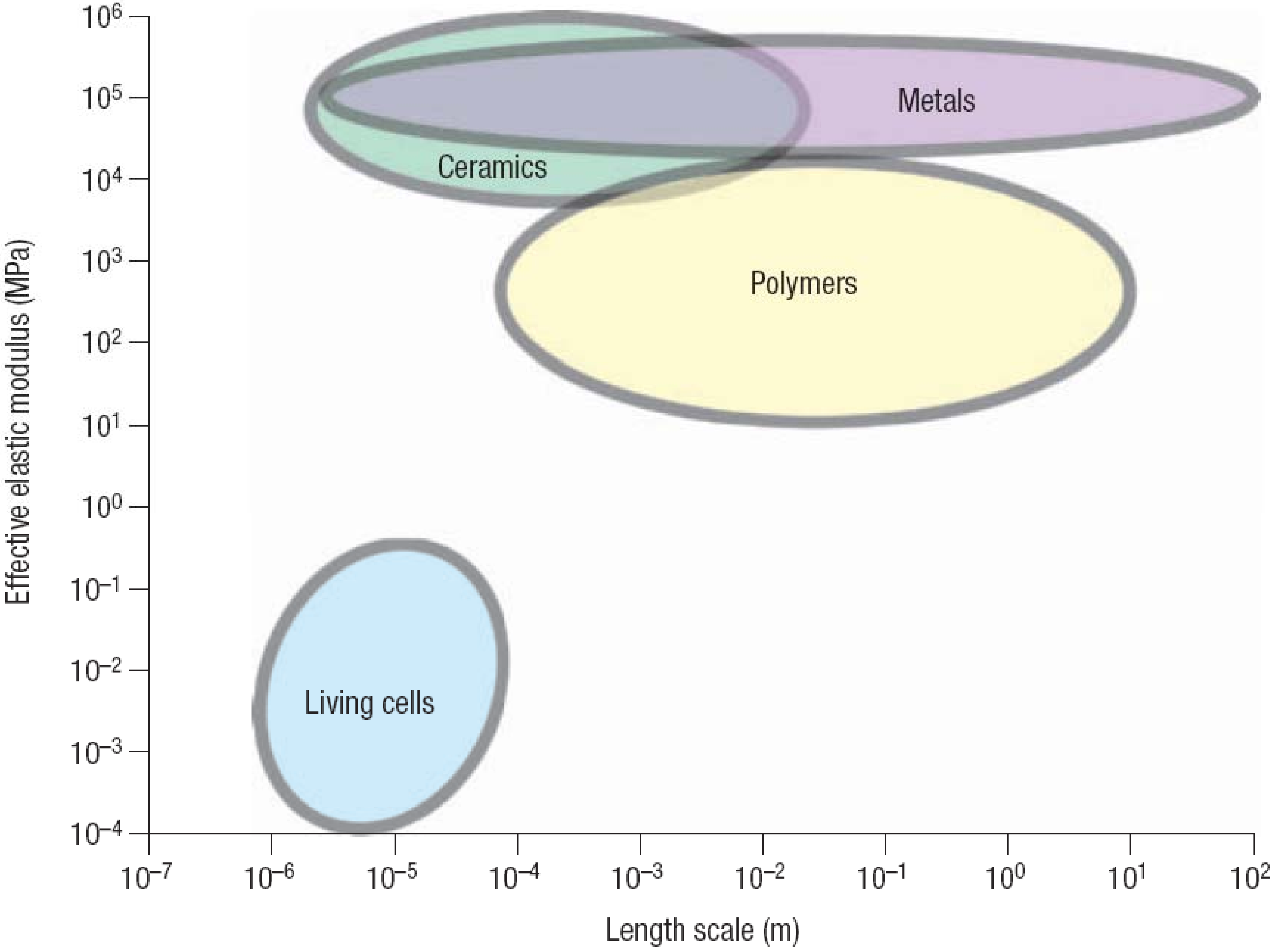
v velocity per distance

y (distances between plates)



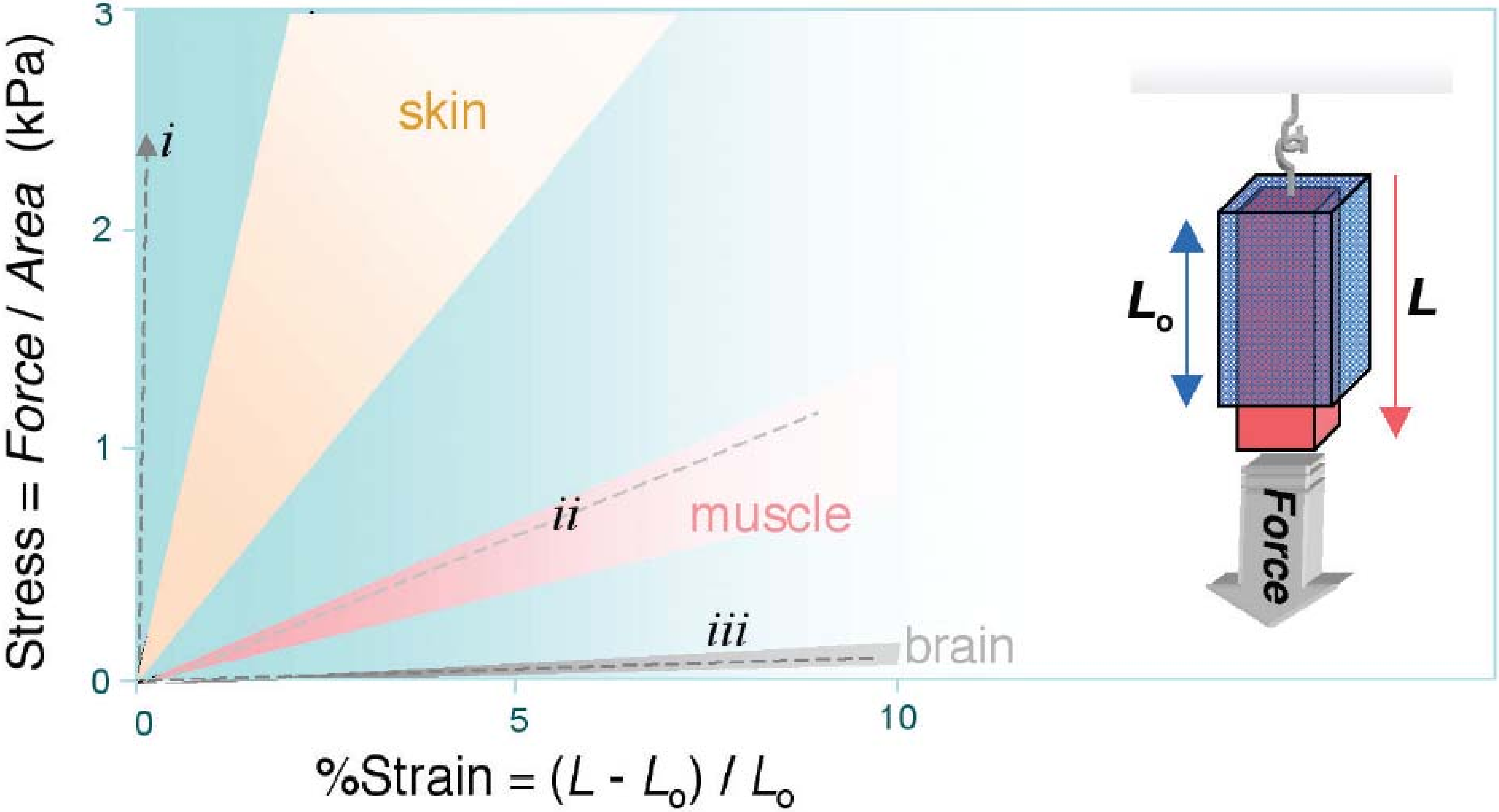
velocity gradient

Range of elastic moduli of cells compared with metals, ceramics and polymers



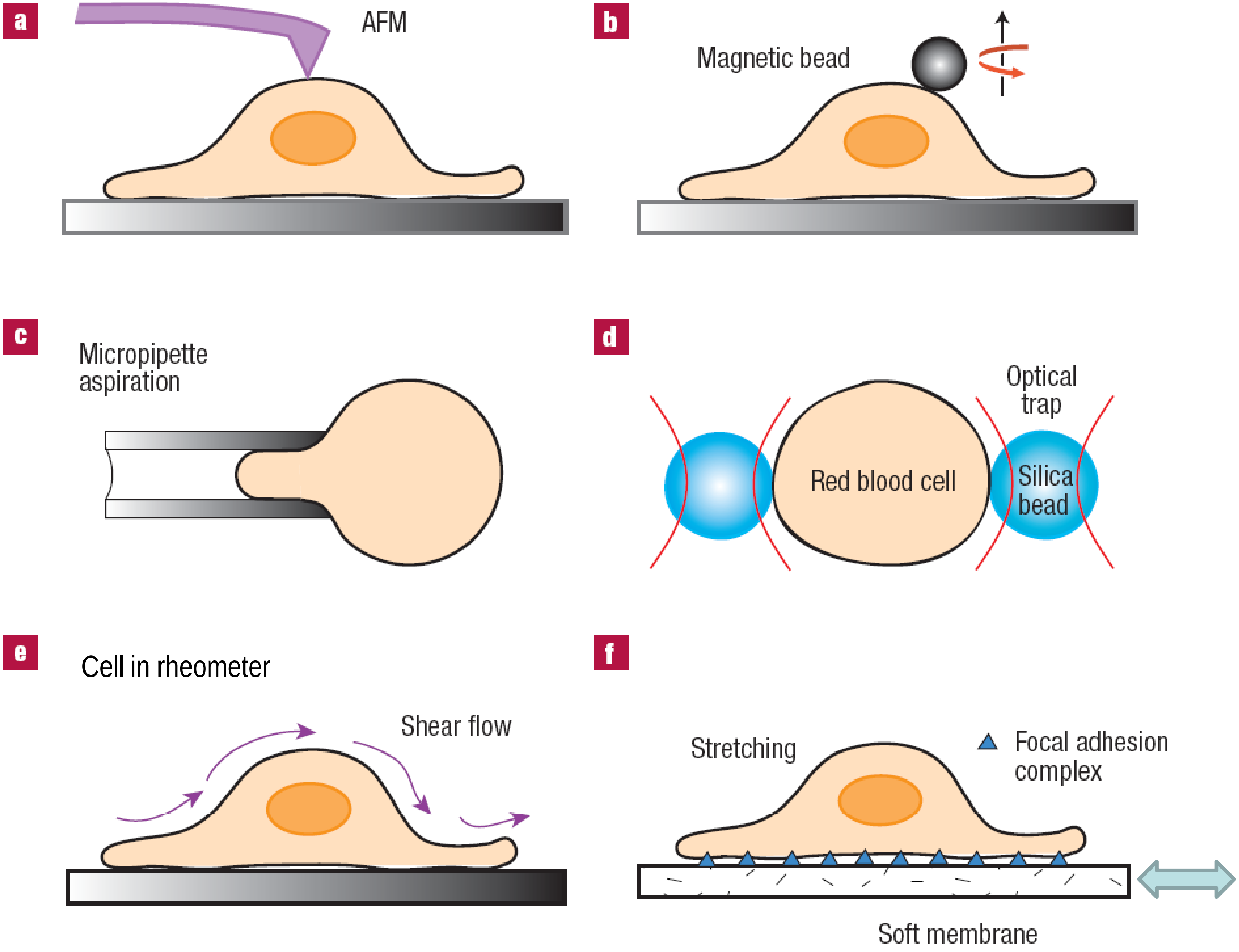
Strain/stress plot for different tissues

- To stretch (strain) **skin tissue**, a considerable amount of force (stress) is needed
- **Muscle tissues** can be deformed (strain) easily using only low forces (stress)
- **Brain tissue** does not show any elastic behavior (negligible strain/stress features)



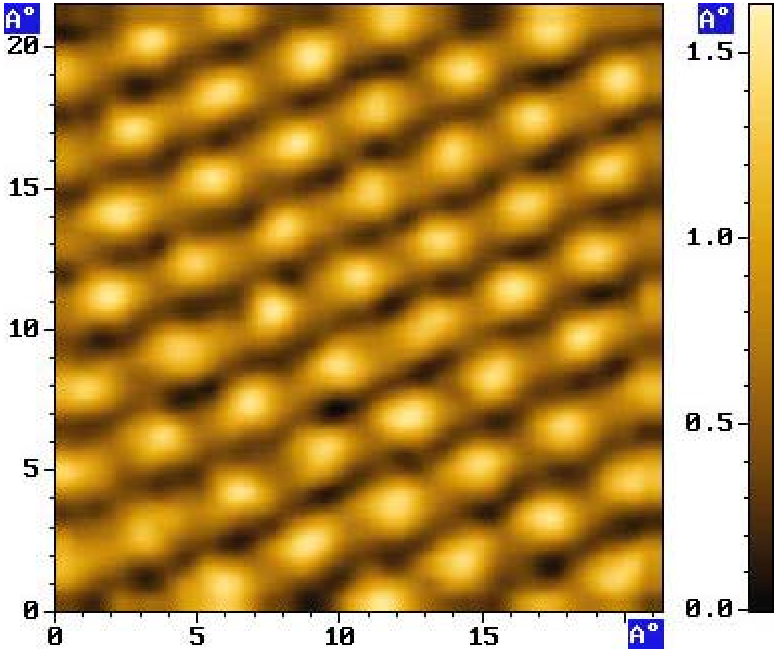
Discher et al., Science, 2005

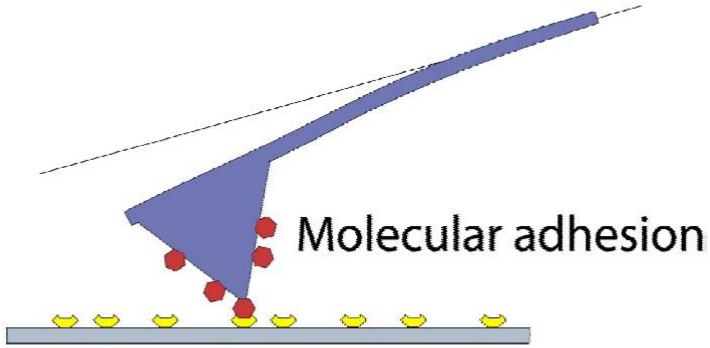
Methods to measure the mechanical properties of cells

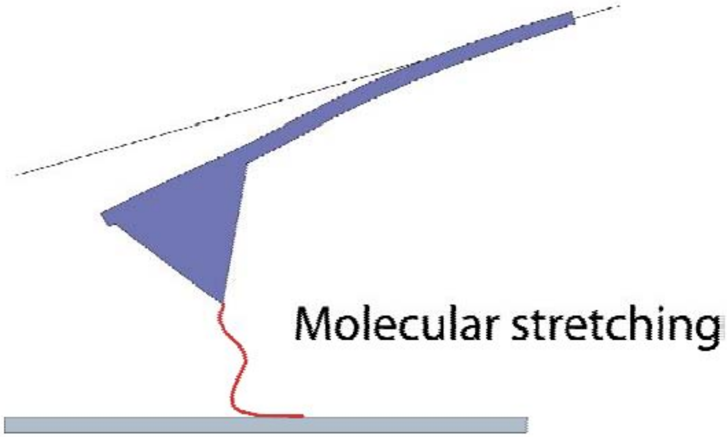


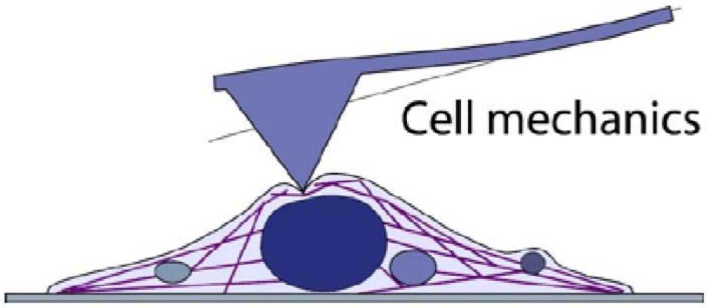
Nano-manipulation of cells and biopolymers using AFM (atomic force microscopy)

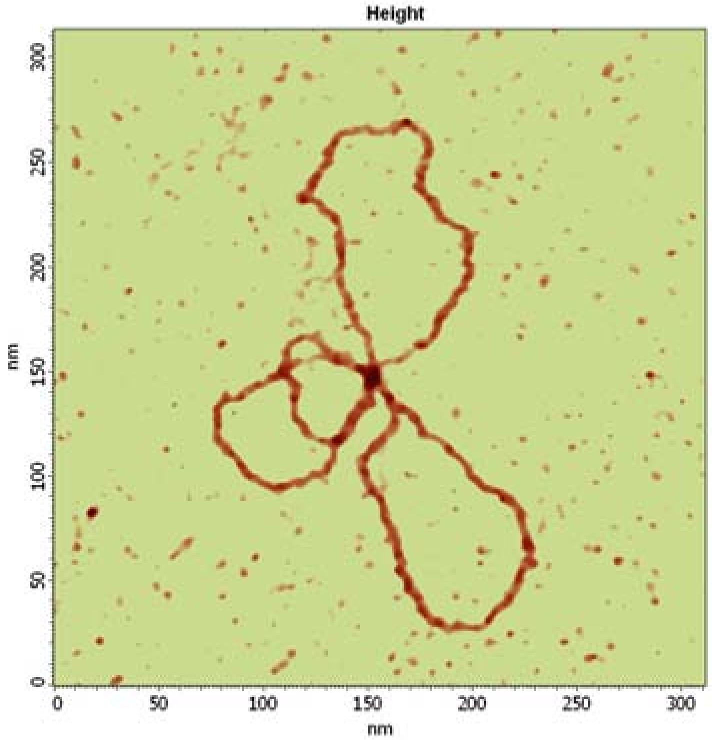
1980s scanning probe microscope (SPM) presented the first atomic-scale image of a gold-surface



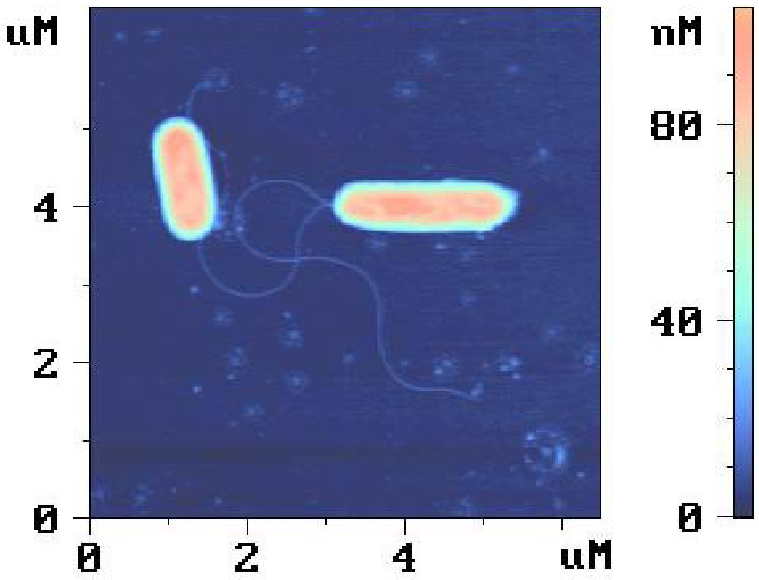




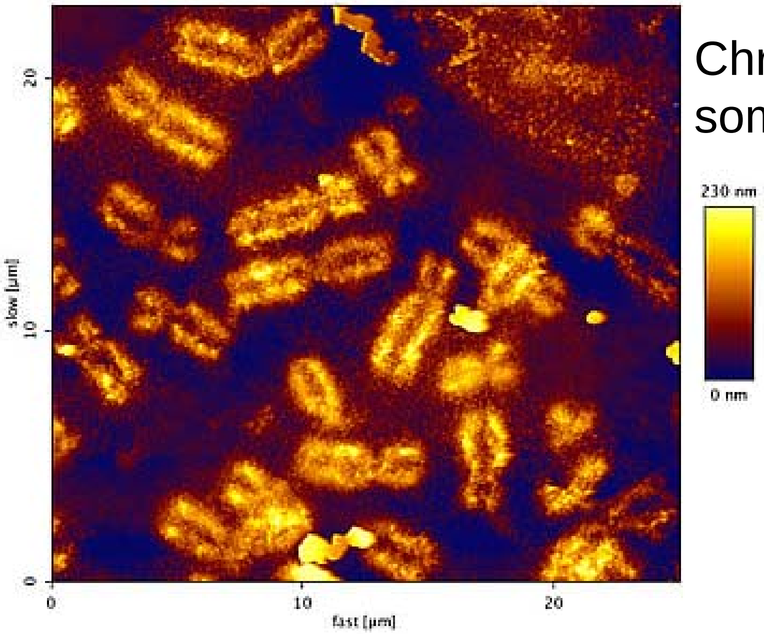




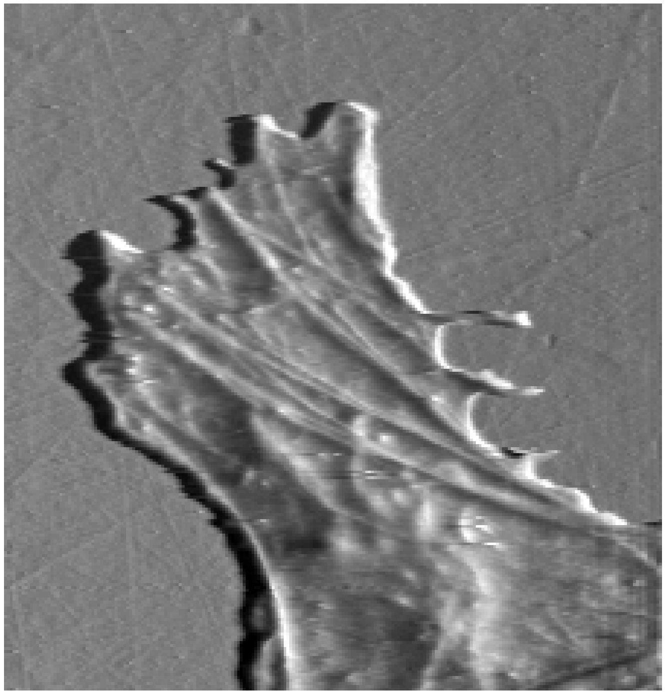
DNA



Bacteria

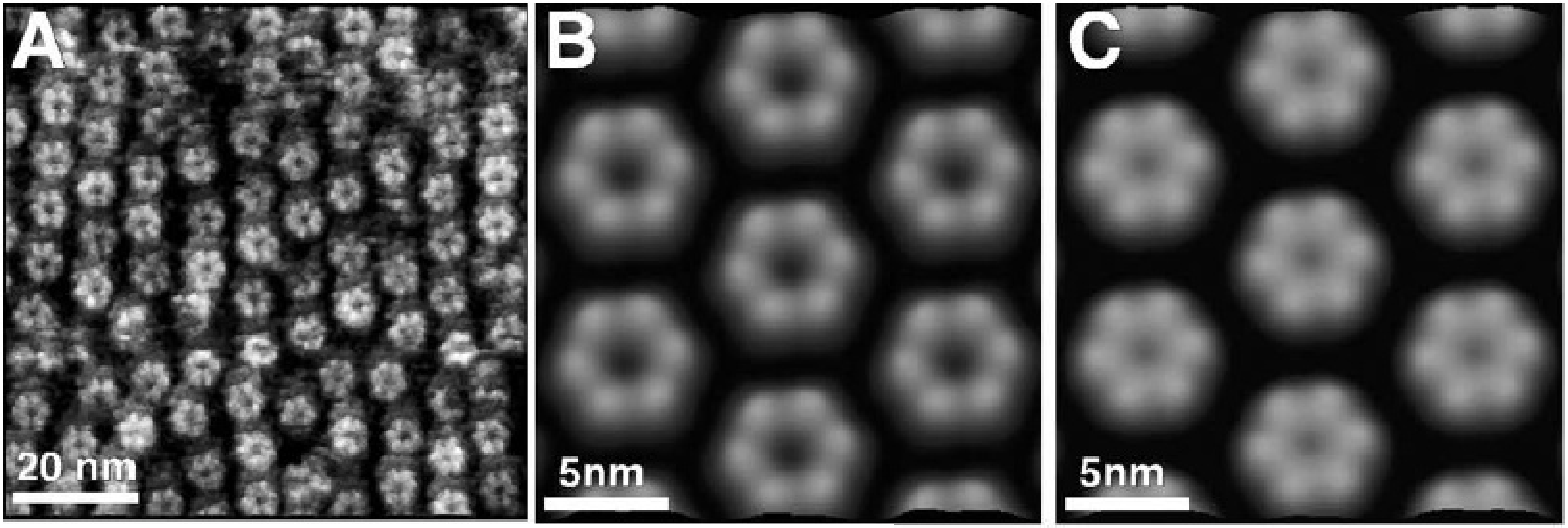


Chromo-
somes

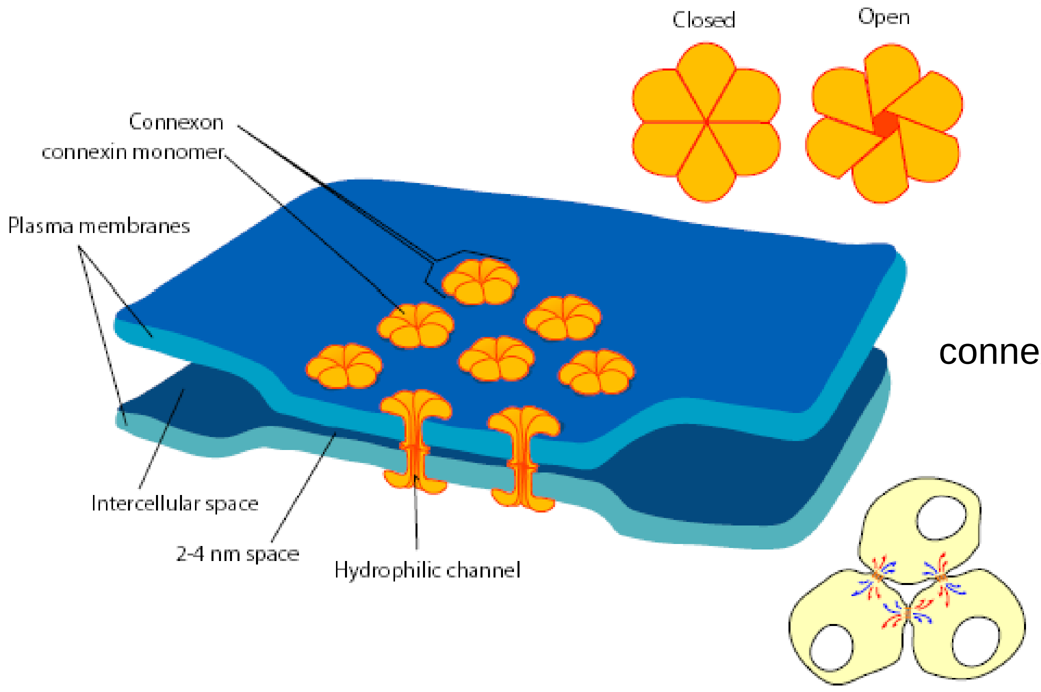


Cells
(cyto-
skeleton)

Open and closed configuration of gap junctions (connexin)

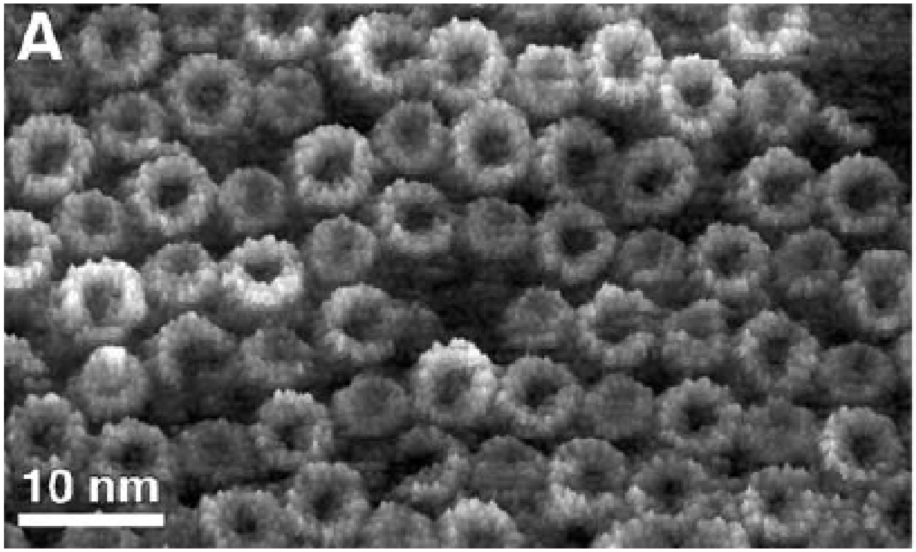


+ 0.5 mM Ca^{2+}

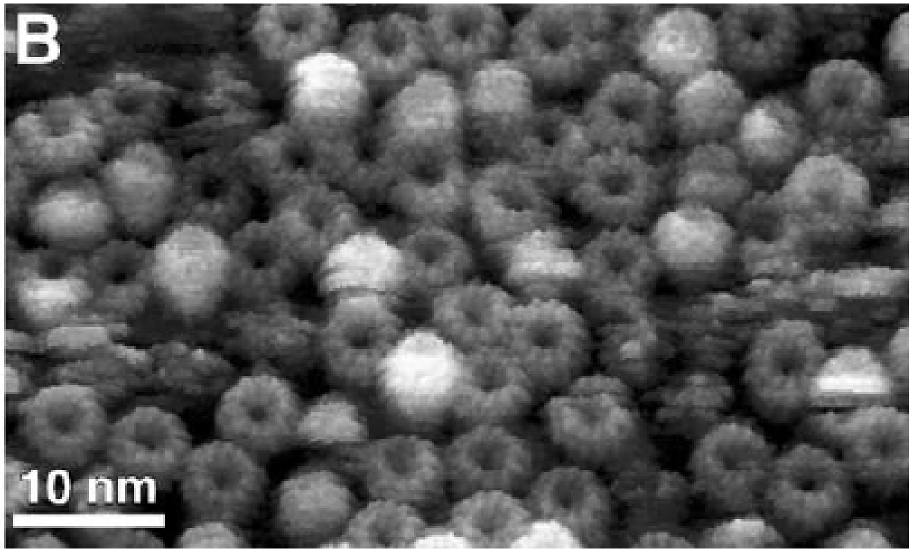


connexin is the major gap-junction protein

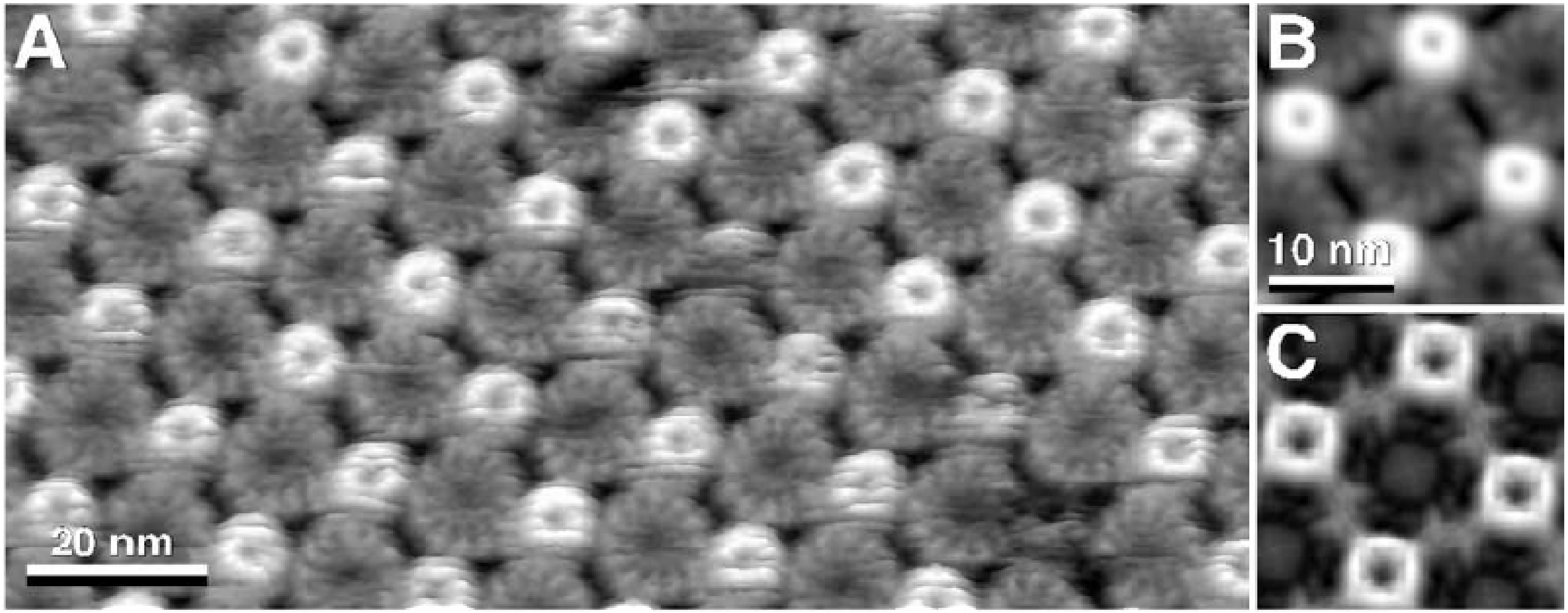
F_0F_1-ATP synthases from *I. tartaricus* with 11 subunits



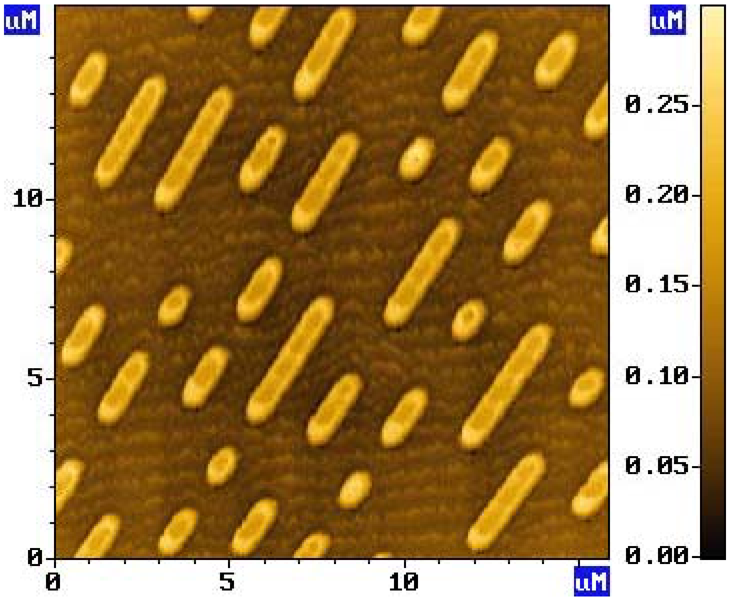
F_0F_1-ATP synthases from *spinach* with 14 subunits

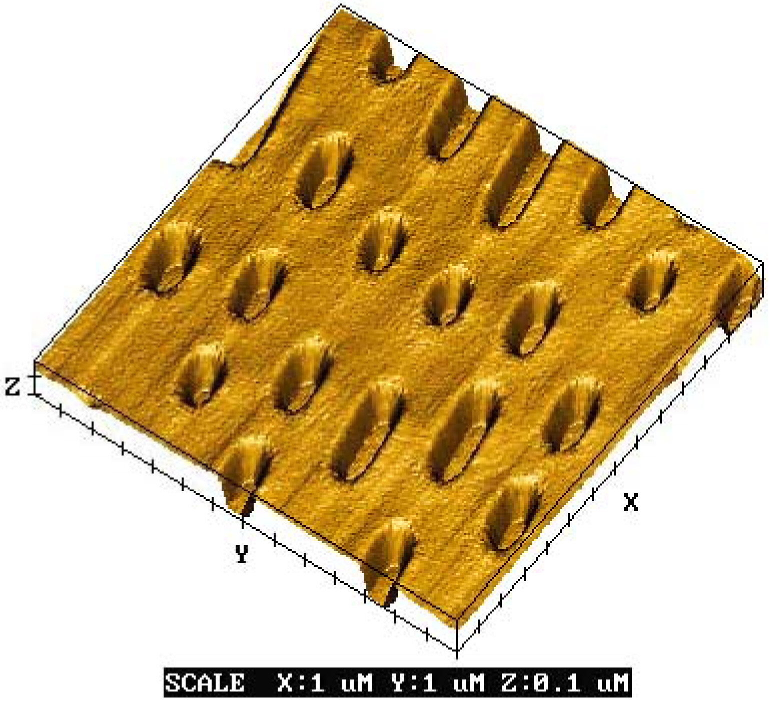


Rotary rotors from bacteriophages

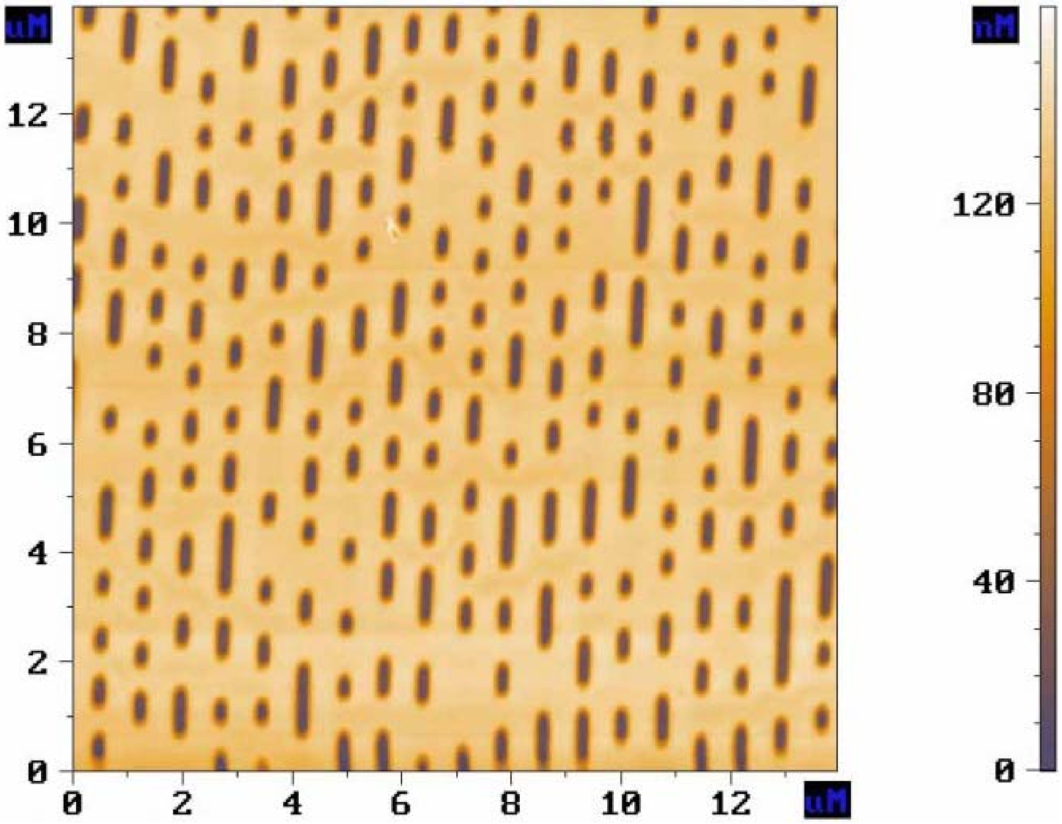


CD Disk

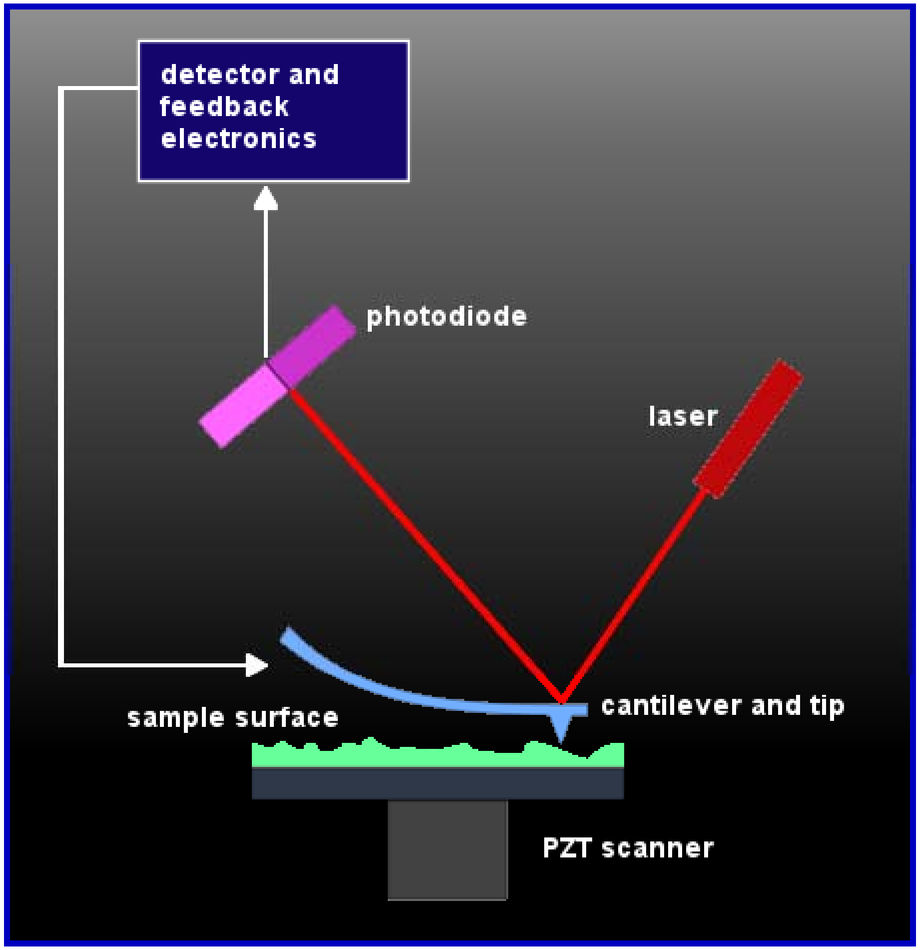




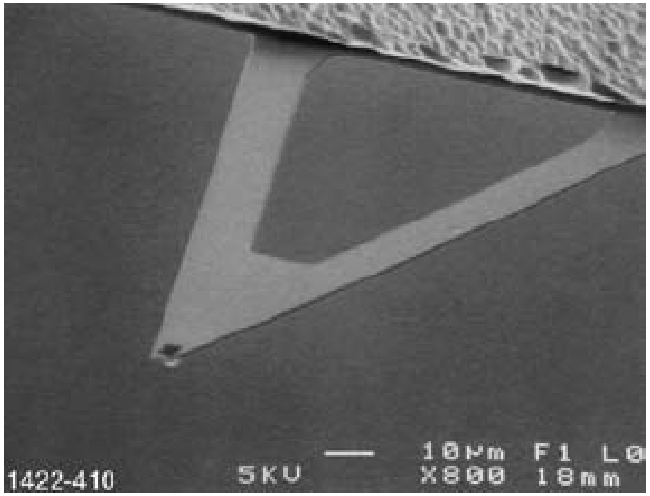
DVD Disk

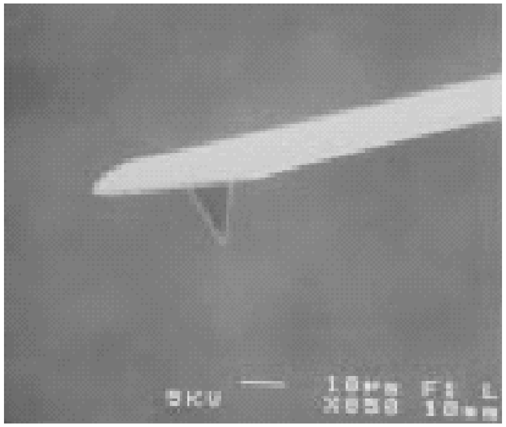


How does it work?



Spring constant (k): 0.6-0.06 N/m
Tip radius: 20-60 nm
Cantilever length: 100-200 µm





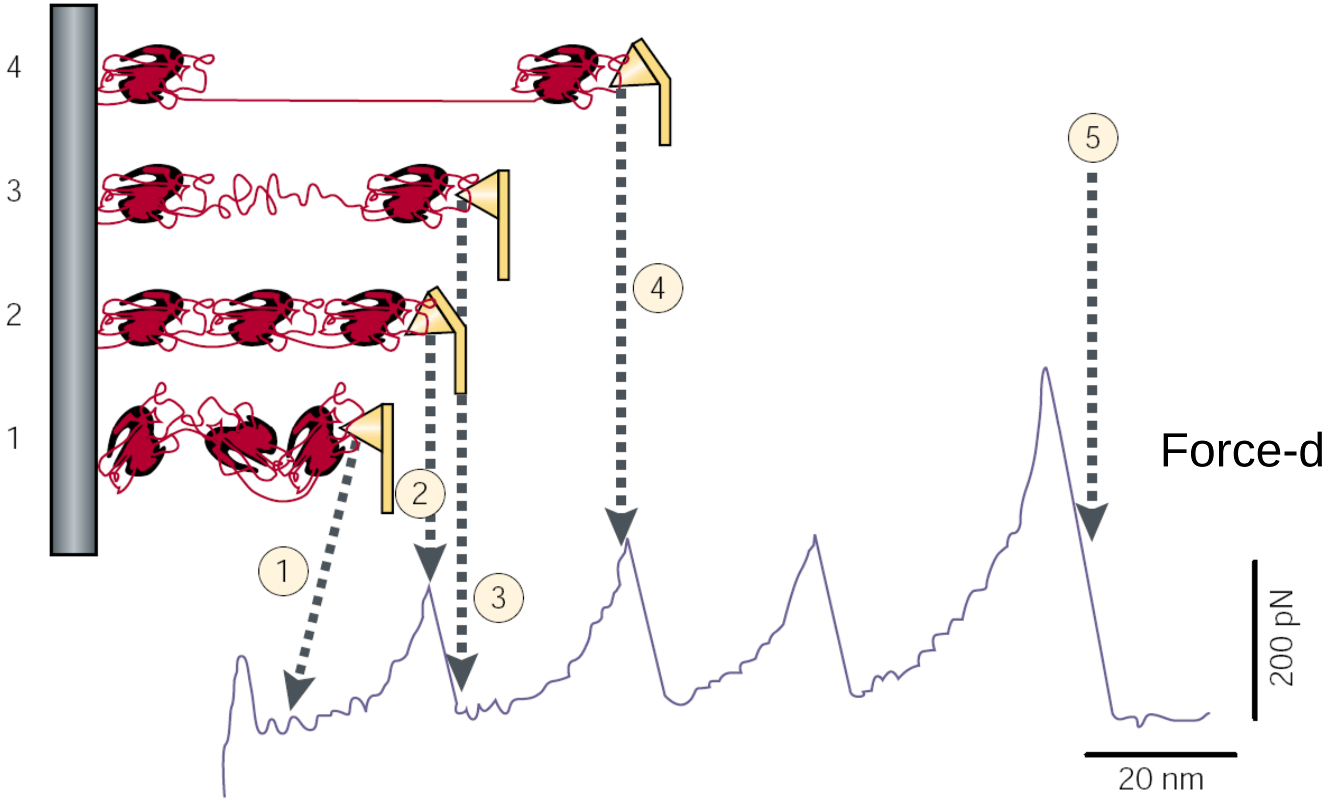
SEM of AFM tip

Animation
AFMModel.exe

Animation
pi.swf

Advanced Force Spectroscopy

- **Protein unfolding**: AFM tip grabs the end of a protein (attached to a surface) => **protein unfolds in its several domains**
- Resulting **force-distance curve** shows a series of **snap-back points** each representing the breaking of a chemical bond

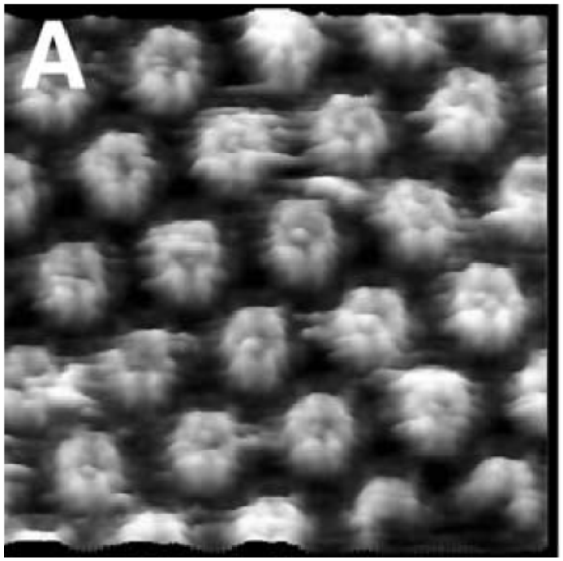


Force-distance curves

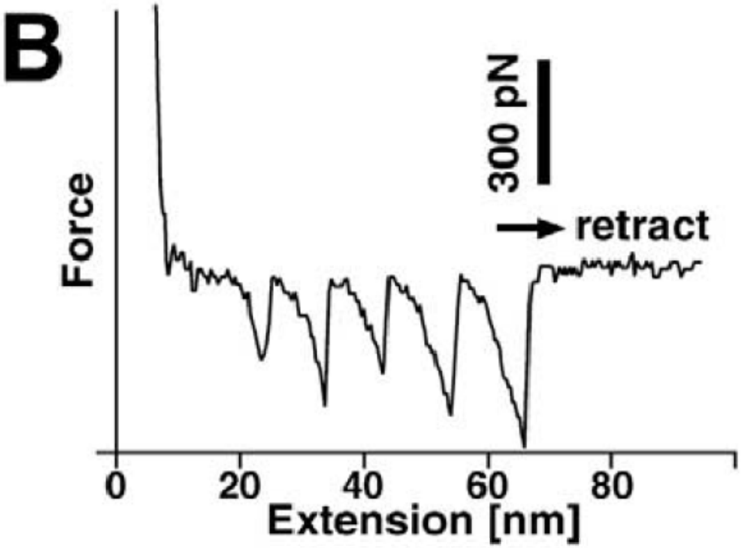
Domain unfolding of repeating immunoglobulin-like domains

Domain unfolding made visible

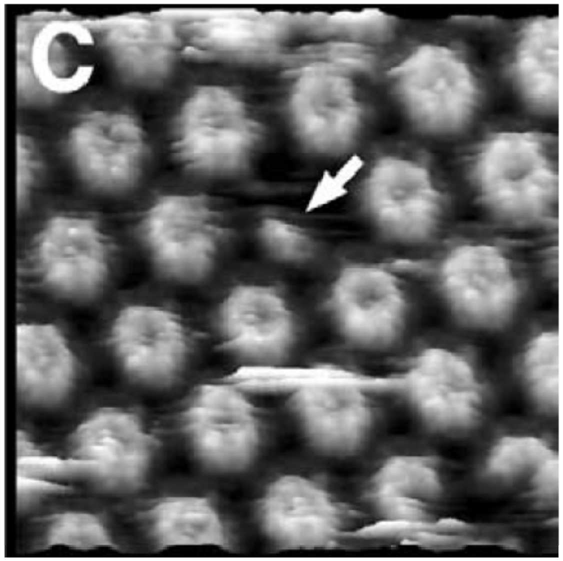
Unzipping the bacterial S-layer protein (membrane pore)



S-layer protein is a hexamer
(18 nm between hexamers)

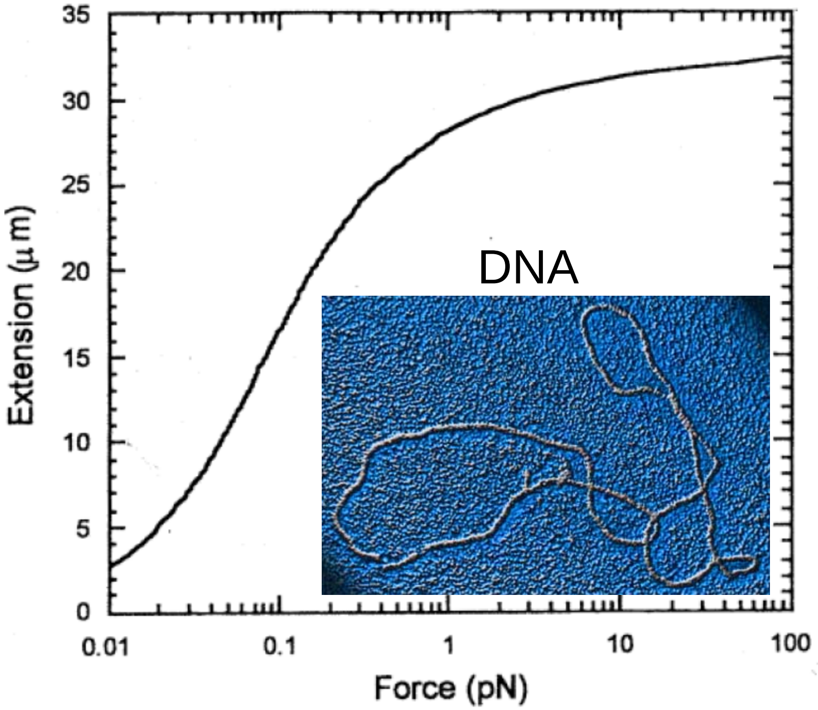


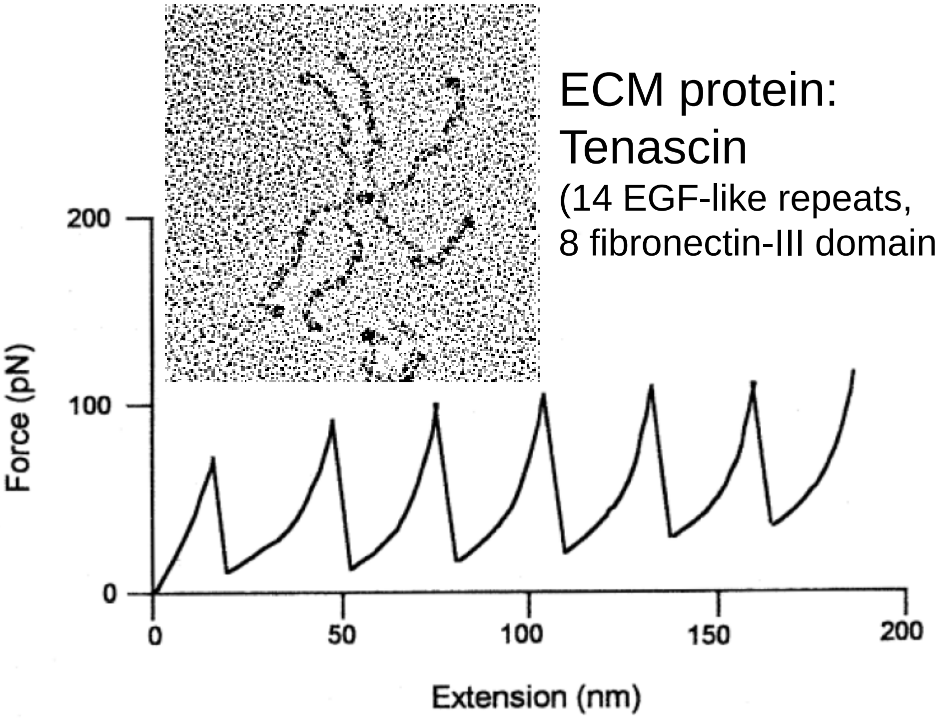
Five domains were unfolded



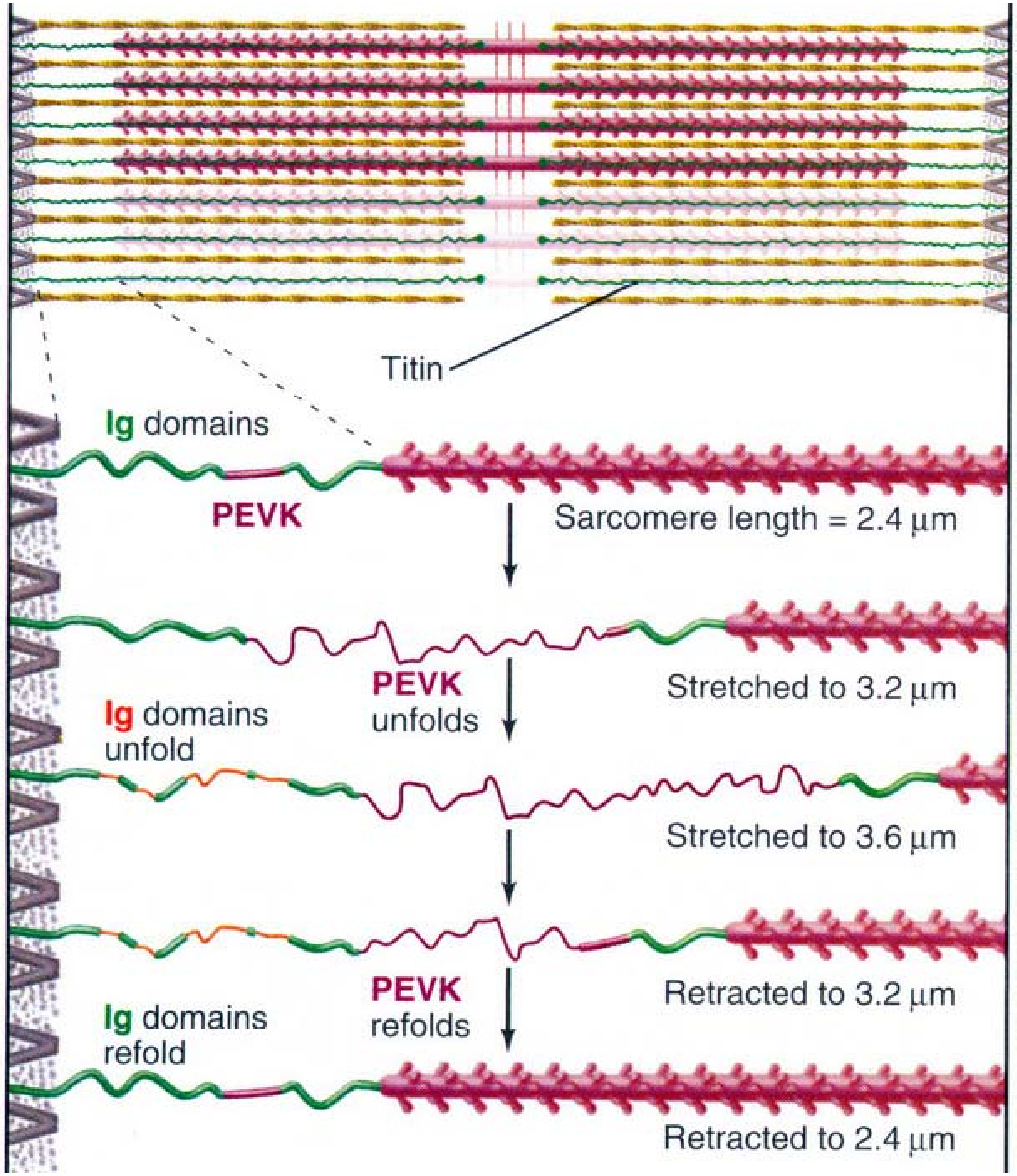
One domain is left

Force versus extension relationship for DNA and complex proteins


DNA


ECM protein:
Tenascin
(14 EGF-like repeats,
8 fibronectin-III domains)

The giant protein titin stretches the sarcomer intra-molecularly



- Titin = <u>largest protein known</u>: molecular weight of about **4 Mda**
- Giant titin <u>connects thick myosin filaments to the Z disks</u>

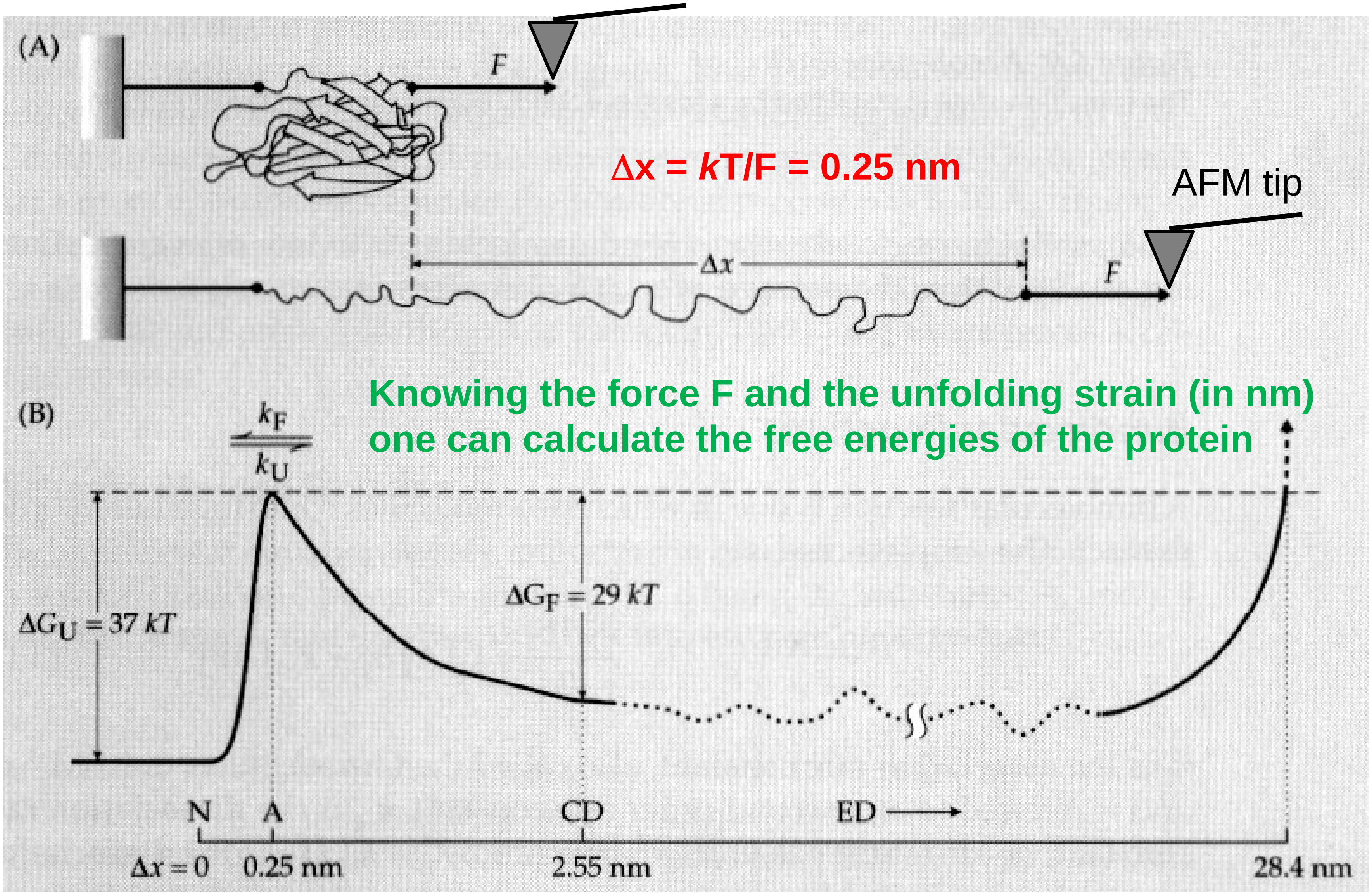
- Modest stretches extend the **PEVK domain** reversibly

- Extreme stretches unfolds **immunoglobulin** or fibronectin III **domains**

Pollard, 1st ed.

Using AFM to unfold titin

AFM was used to reversibly unfold titin: only a small strain of 0.25 nm (5% of the length of the protein) is needed to completely destabilize and unfold the protein



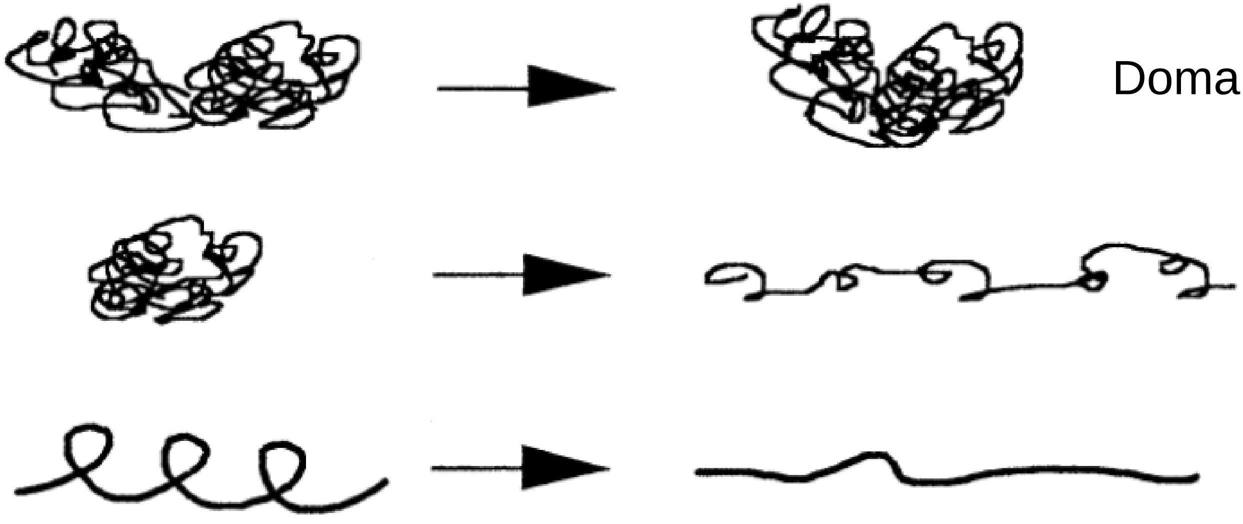
$\Delta x = kT/F = 0.25$ nm

AFM tip

Knowing the force F and the unfolding strain (in nm) one can calculate the free energies of the protein

N = native state, A = activated state, CD = compact disordered state, ED = extended state, U = Unfolding

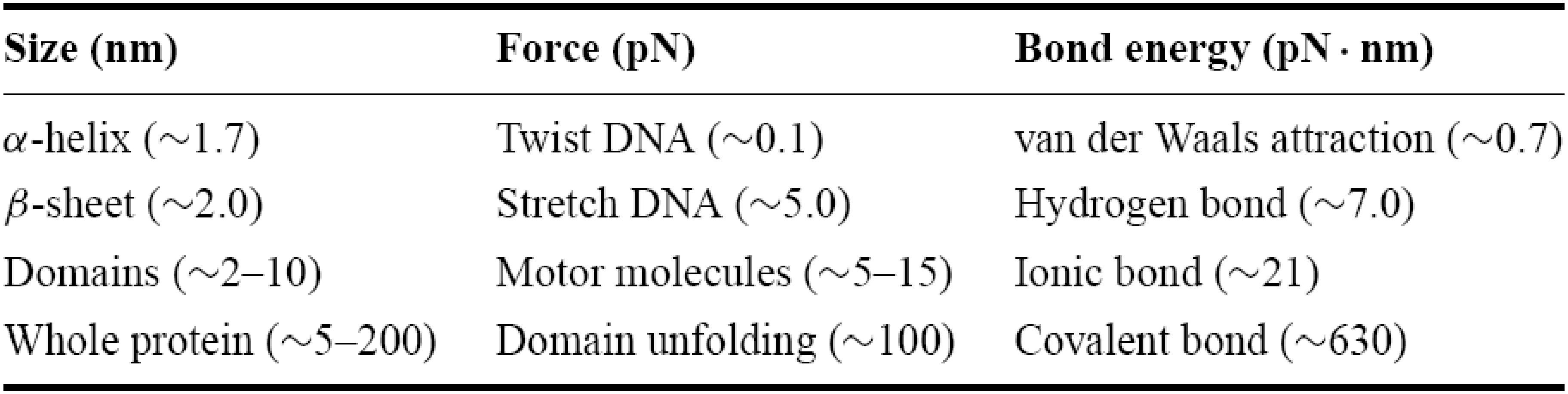
Modes of protein deformation and forces required for stretching



Domain motion

Domain
deformation & unfolding

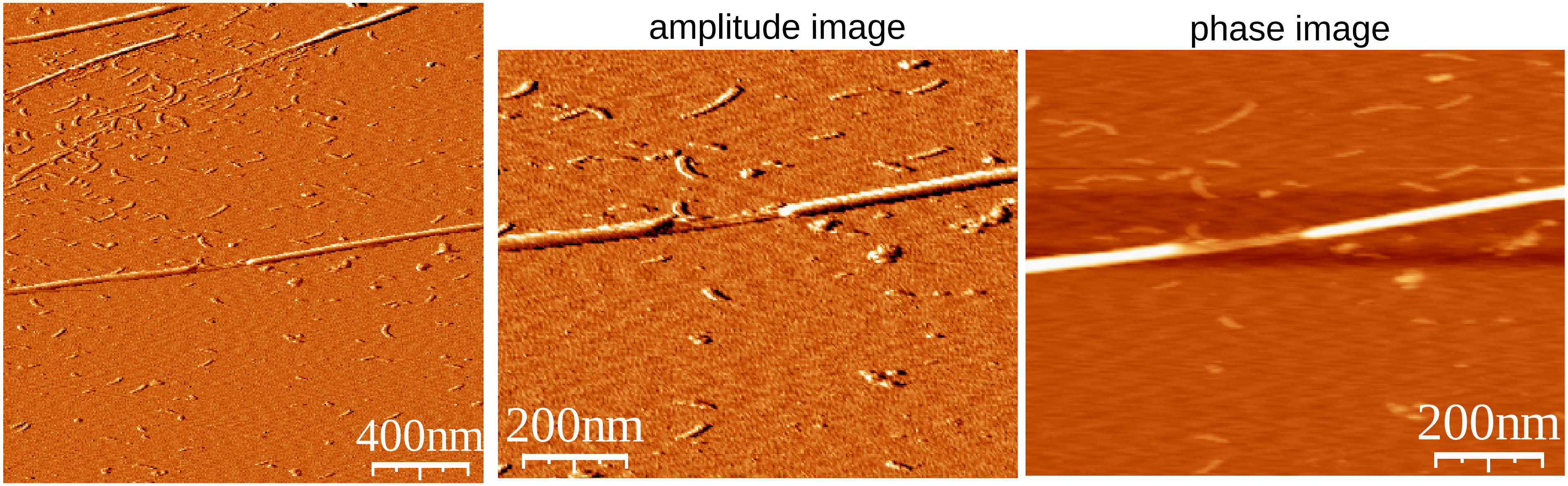
Unfolding of secondary
structures



Size (nm)	**Force (pN)**	**Bond energy (pN · nm)**
α-helix (∼1.7)	Twist DNA (∼0.1)	van der Waals attraction (∼0.7)
β-sheet (∼2.0)	Stretch DNA (∼5.0)	Hydrogen bond (∼7.0)
Domains (∼2–10)	Motor molecules (∼5–15)	Ionic bond (∼21)
Whole protein (∼5–200)	Domain unfolding (∼100)	Covalent bond (∼630)

Zhu et al., 2000, Annu Rev Biomed Eng

Nano-dissection

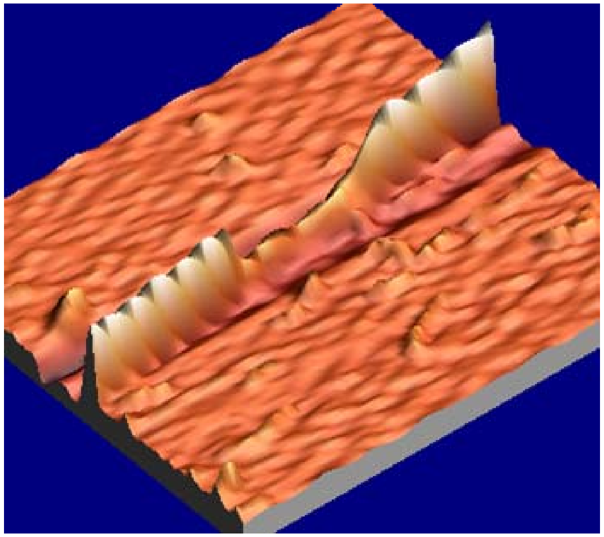


amplitude image

phase image

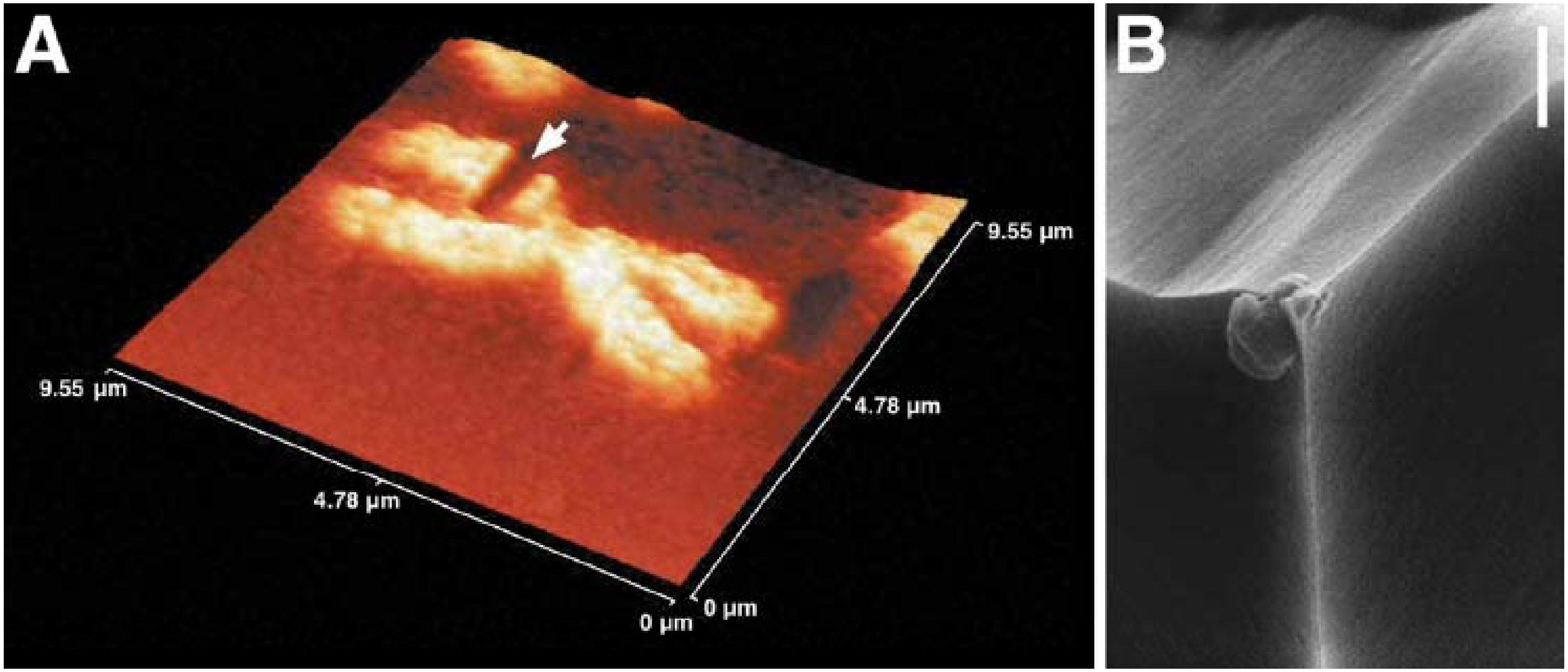
Single microtubule in buffer dissected by AFM tip

⇒ AFM to cut and shorten microtubules
to desired length for MEMS application
(e.g. MTs of defined length served as motor tracks)



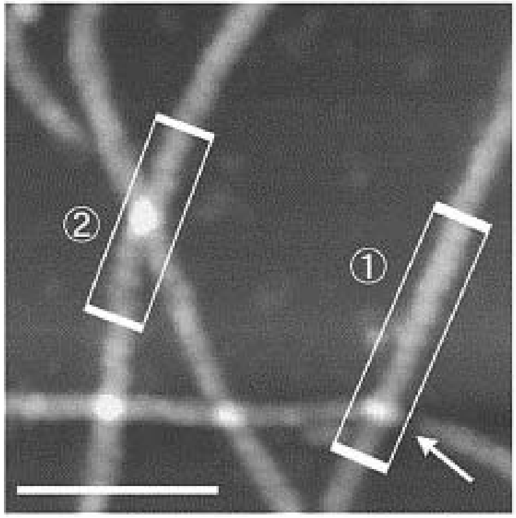
3 D image

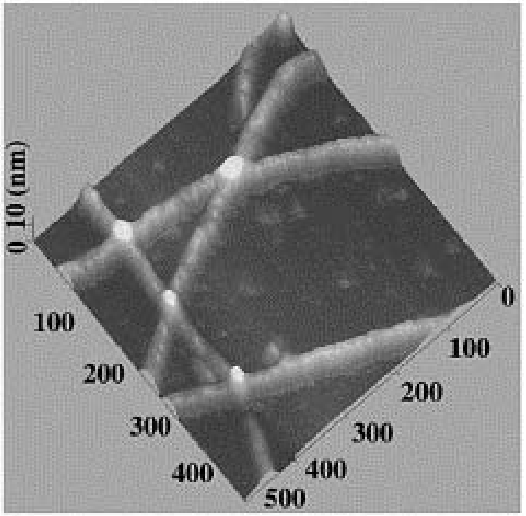
Nano-dissection



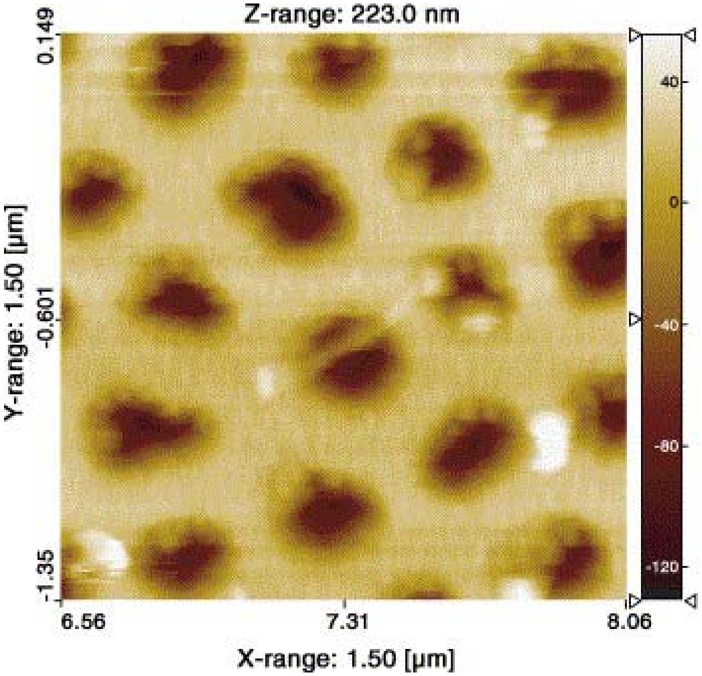
- DNA extraction from a human Chromosome
- SEM image of the tip show the piece of DNA

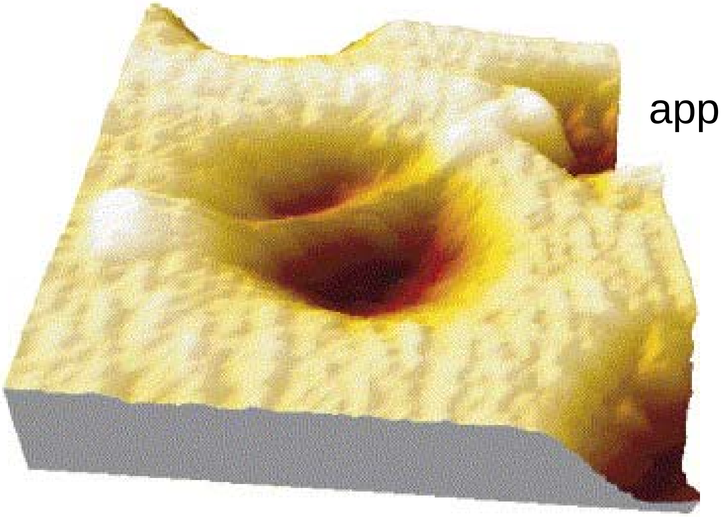
Nano-indentation





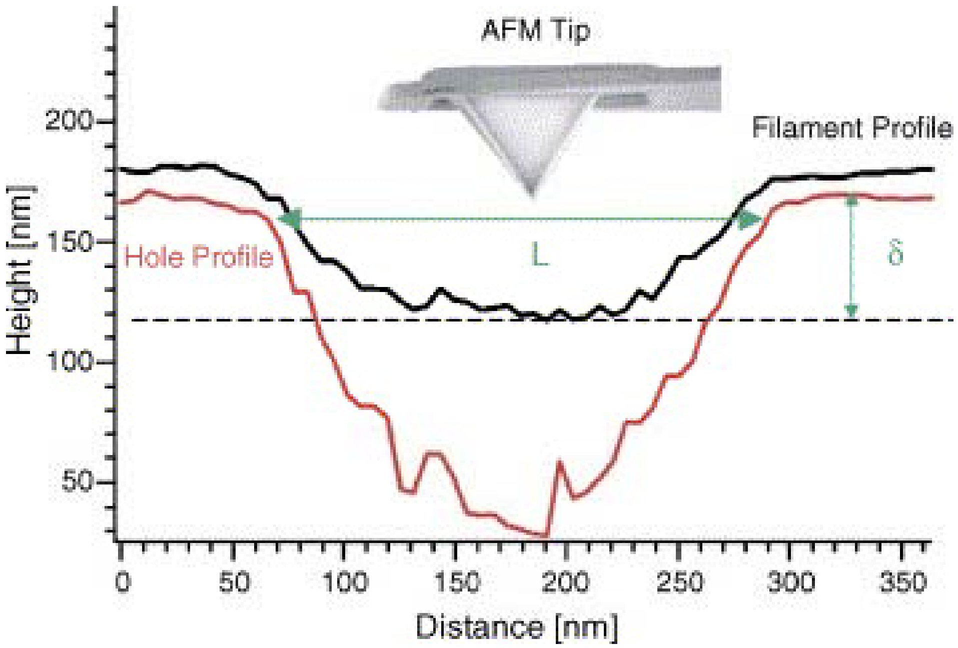
- Measuring bending properties of single vimentin IFs using an AFM
- Tip elastically **deform single filaments** hanging over a porous membrane



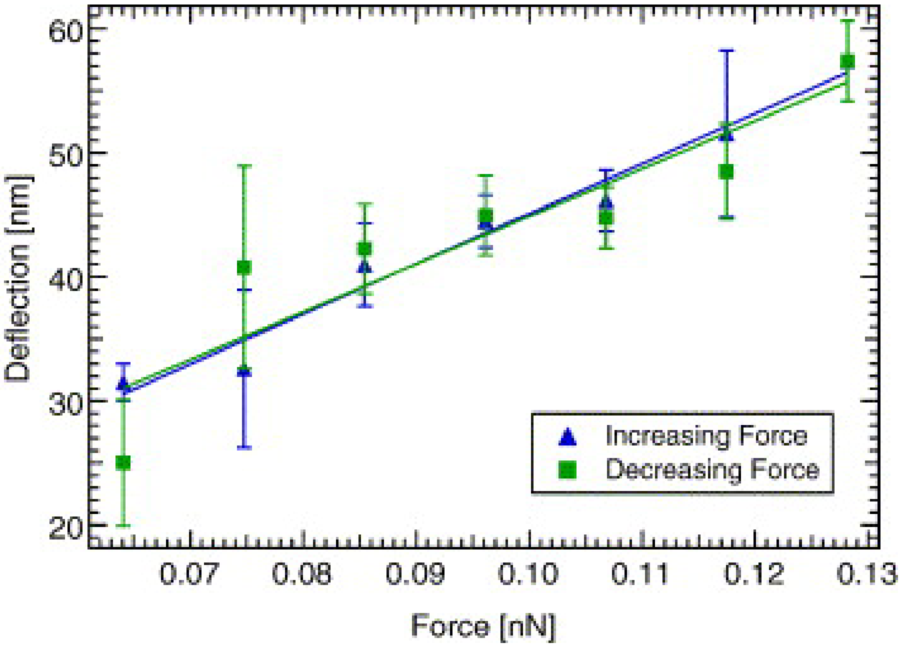


applied force 0.11 nN

Nano-indentation

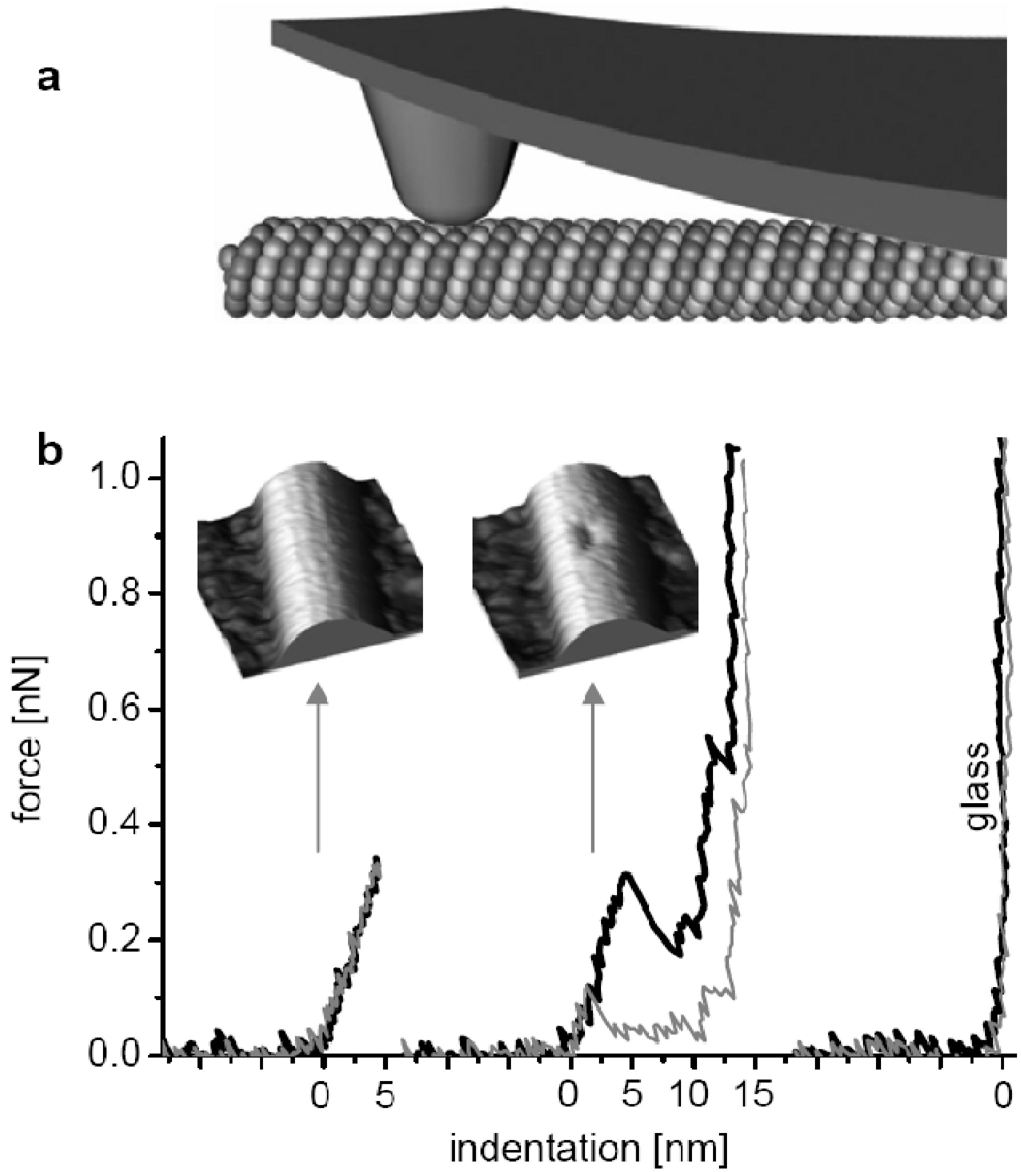


- AFM tip pushes the IF into the hole
- From the height difference between the IF's lowest point (L) and the substrate around the hole, the **deflection** can be **calculated**



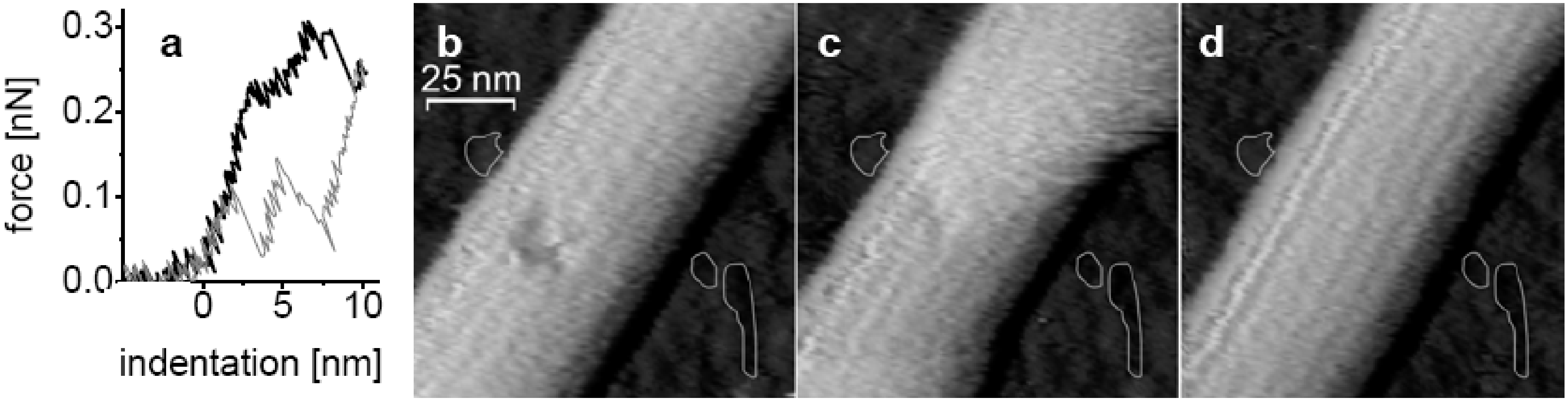
- **Deflection** of one IF as a function of the applied **force**
- E_{Bending} = 300 MPa determined from the slope of the linear fit
- Graph shows that the **filament is elastic** (i.e. it returns to its original position after the force is decreased)

Nano-indentation

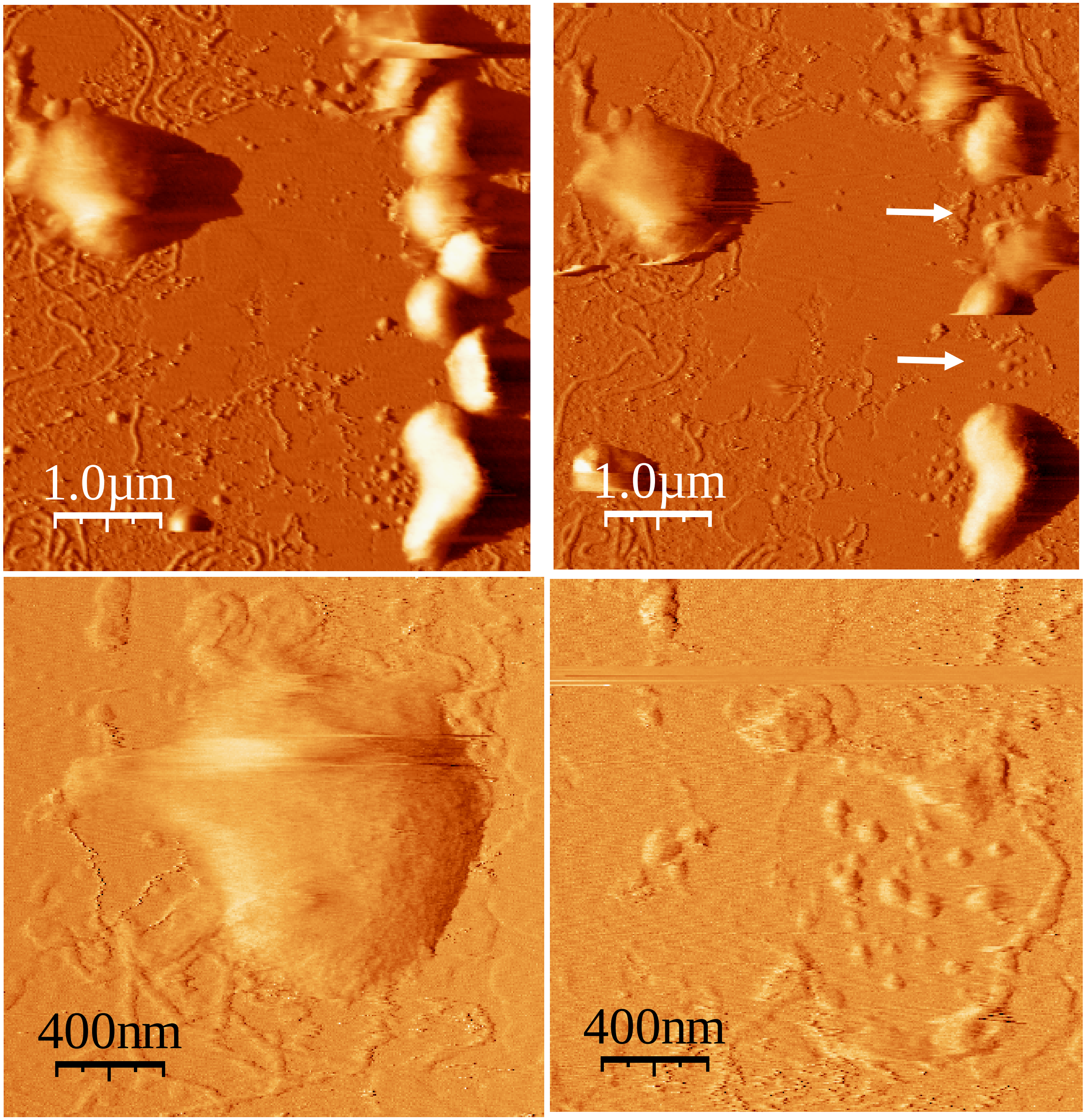


- Measuring **mechanical properties of single microtubules** by lateral indentation with the AFM
- Indentations up to ~ 3.6 nm resulted in an **linear elastic response**, and indentations were reversible
- Higher forces caused substantial damage to the microtubules, which either led to depolymerization or, occasionally, to slowly reannealing holes in the microtubule wall

Nano-manipulation (nano-indentation)



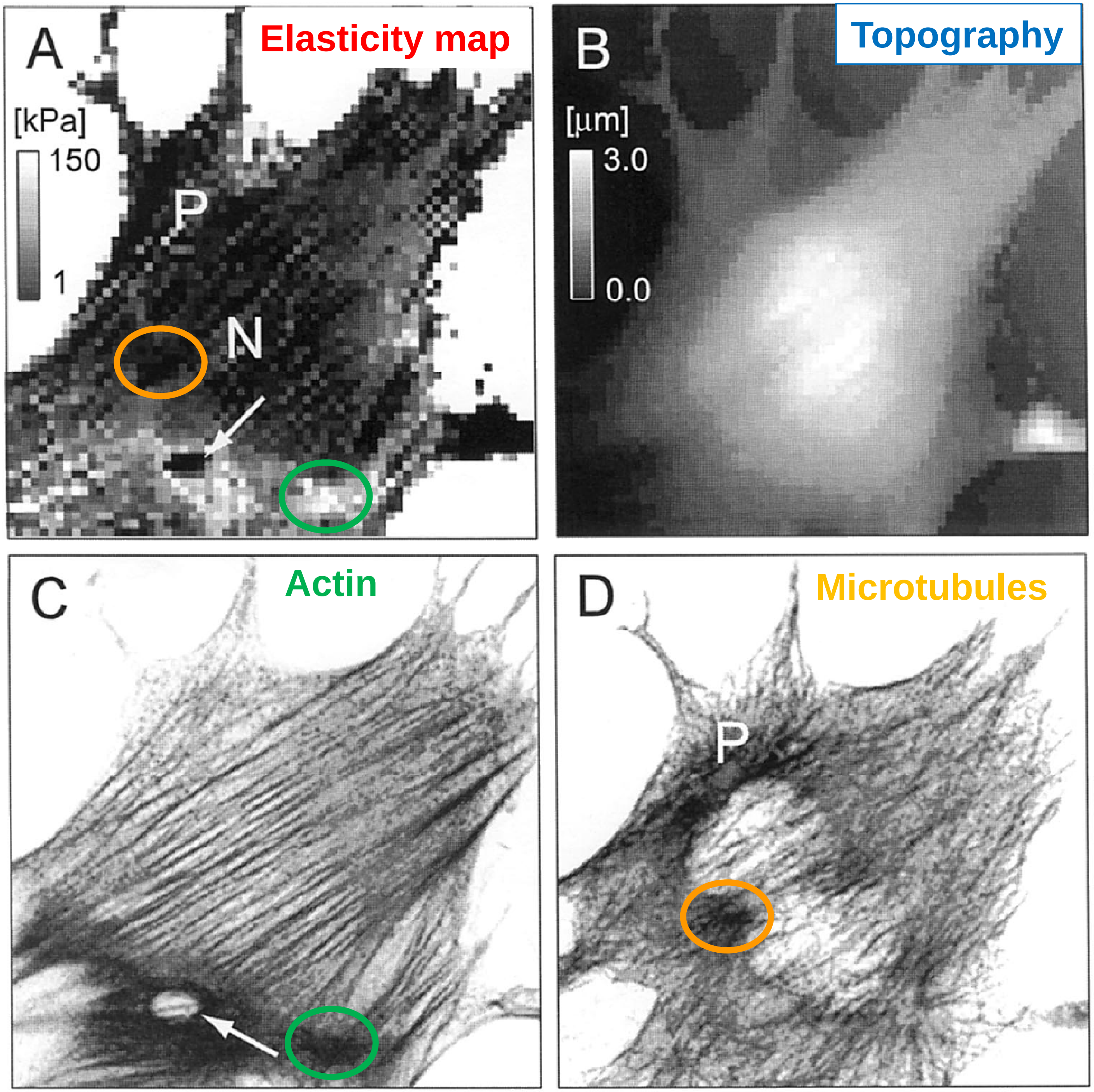
“Self-healing” of microtubules: Higher forces by the tip can cause microtubule damage; however, these holes can undergo a <u>slow reannealing process</u>



“Destructive nano-identation”

by Oliver...

Possible to analyze single cristae compartments on their specific proteincontent?



Elasticity Map:

White = Stiff

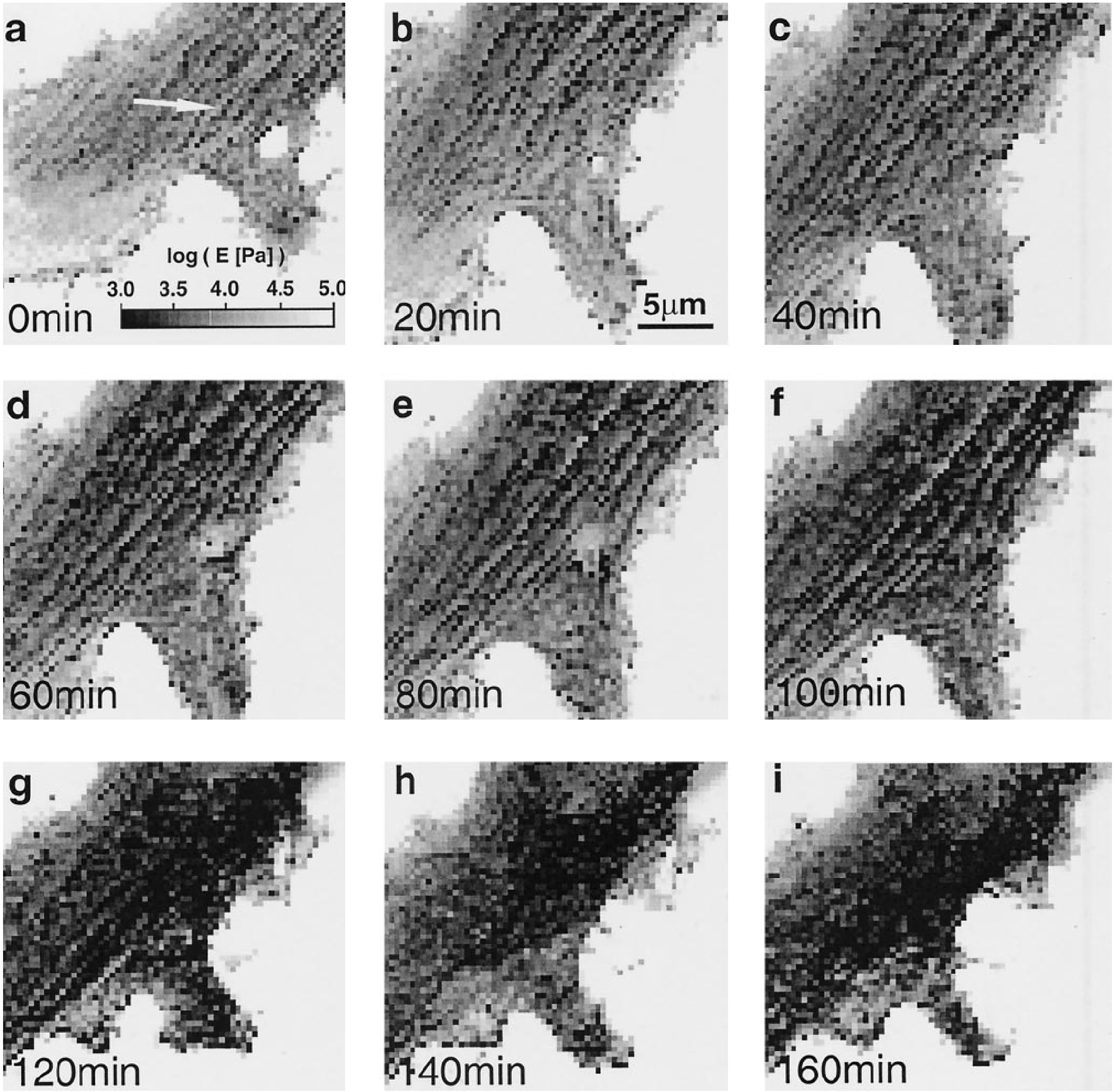
Black = Soft

Nucleus surprisingly soft (arrow A and C)

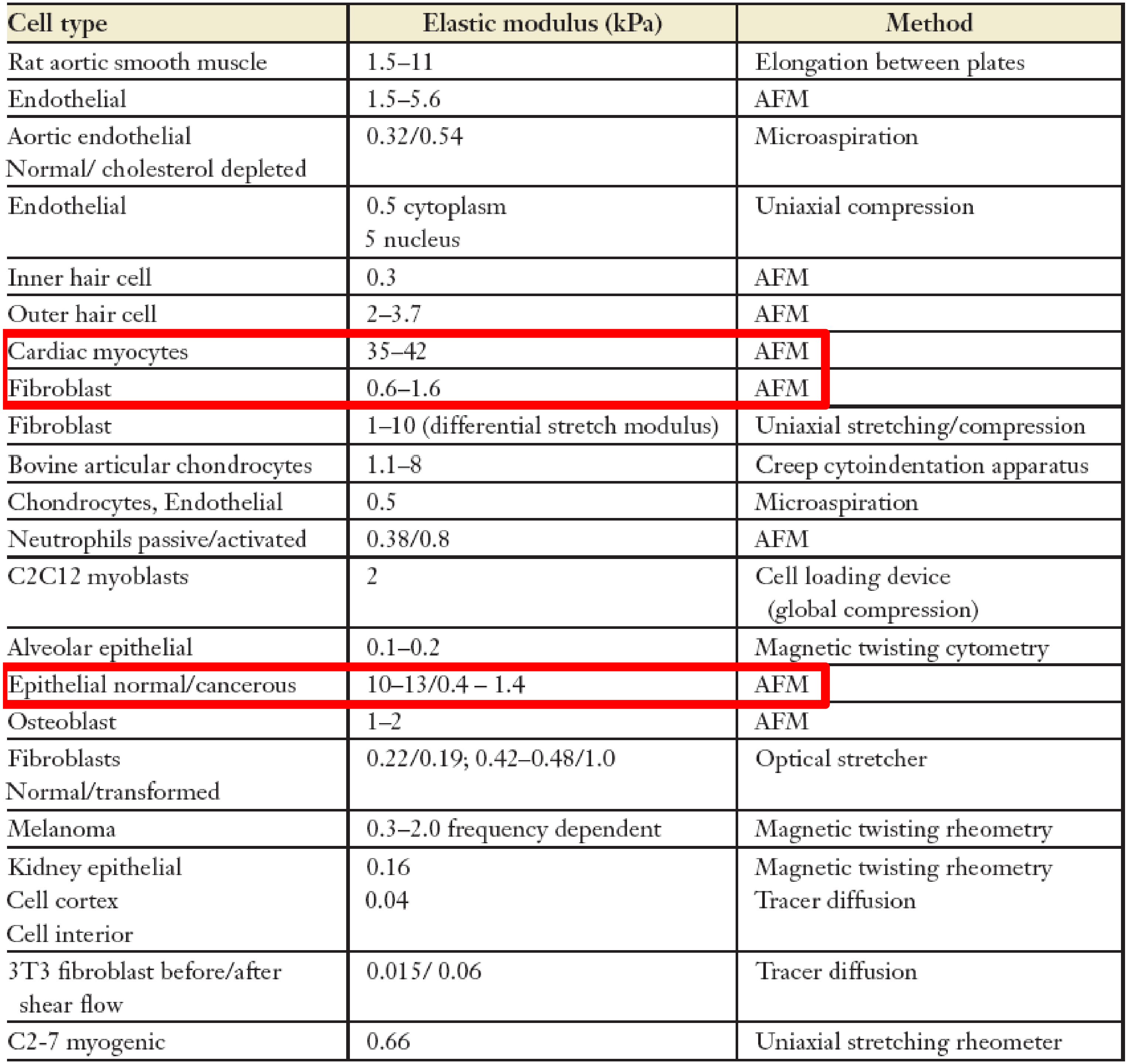
Occurrences of dense F-actin surprisingly **stiff** (A, C)

Occurrences of dense microtubules surprisingly **soft** (A, D)

Living fibroblast



The drug “cyto-chalasin” cuts actin filaments => the cell becomes softer



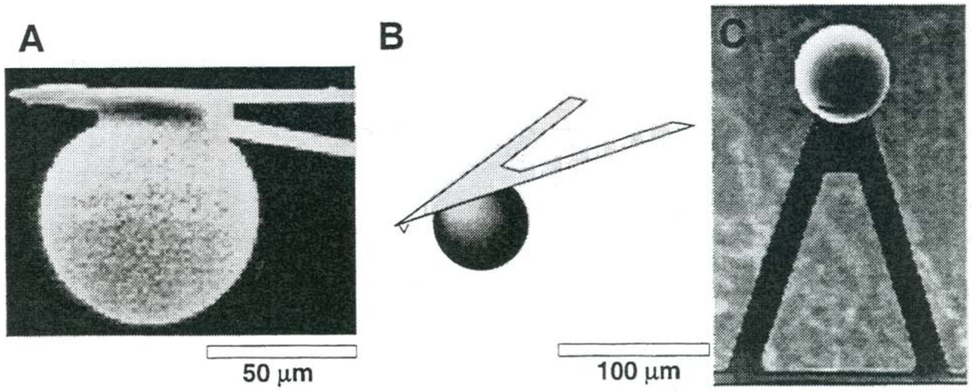
Cell type	Elastic modulus (kPa)	Method
Rat aortic smooth muscle	1.5–11	Elongation between plates
Endothelial	1.5–5.6	AFM
Aortic endothelial Normal/ cholesterol depleted	0.32/0.54	Microaspiration
Endothelial	0.5 cytoplasm 5 nucleus	Uniaxial compression
Inner hair cell	0.3	AFM
Outer hair cell	2–3.7	AFM
Cardiac myocytes	35–42	AFM
Fibroblast	0.6–1.6	AFM
Fibroblast	1–10 (differential stretch modulus)	Uniaxial stretching/compression
Bovine articular chondrocytes	1.1–8	Creep cytoindentation apparatus
Chondrocytes, Endothelial	0.5	Microaspiration
Neutrophils passive/activated	0.38/0.8	AFM
C2C12 myoblasts	2	Cell loading device (global compression)
Alveolar epithelial	0.1–0.2	Magnetic twisting cytometry
Epithelial normal/cancerous	10–13/0.4 – 1.4	AFM
Osteoblast	1–2	AFM
Fibroblasts Normal/transformed	0.22/0.19; 0.42–0.48/1.0	Optical stretcher
Melanoma	0.3–2.0 frequency dependent	Magnetic twisting rheometry
Kidney epithelial Cell cortex Cell interior	0.16 0.04	Magnetic twisting rheometry Tracer diffusion
3T3 fibroblast before/after shear flow	0.015/ 0.06	Tracer diffusion
C2-7 myogenic	0.66	Uniaxial stretching rheometer

Heart cells have more actin and stress fibers

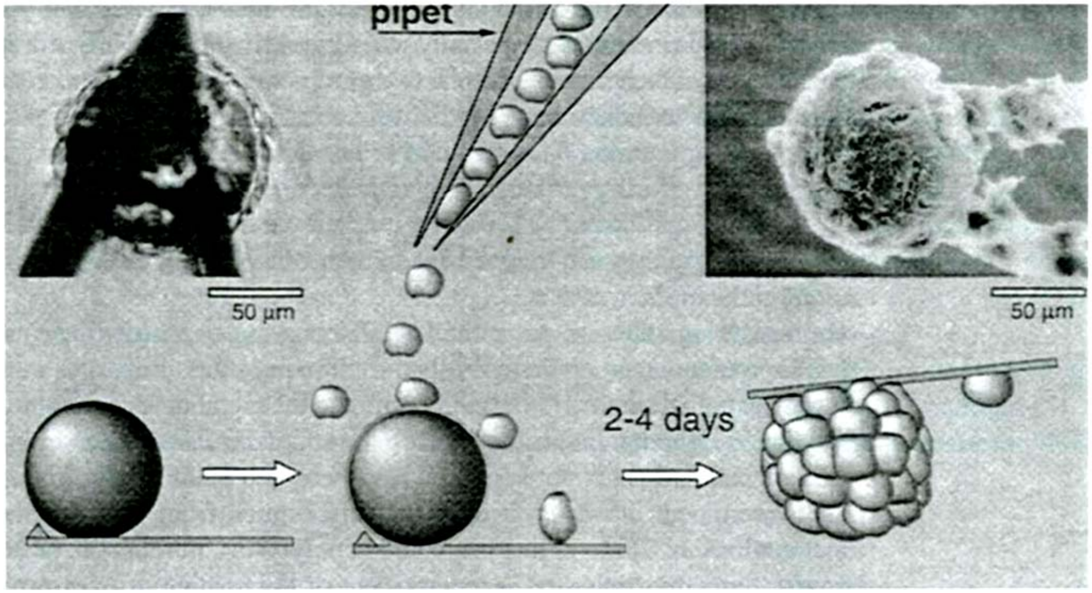
Cancer cells are less elastic

Janmey et al., 2007, Annu Rev Biomed Eng

Cell adhesion measured by force spectroscopy

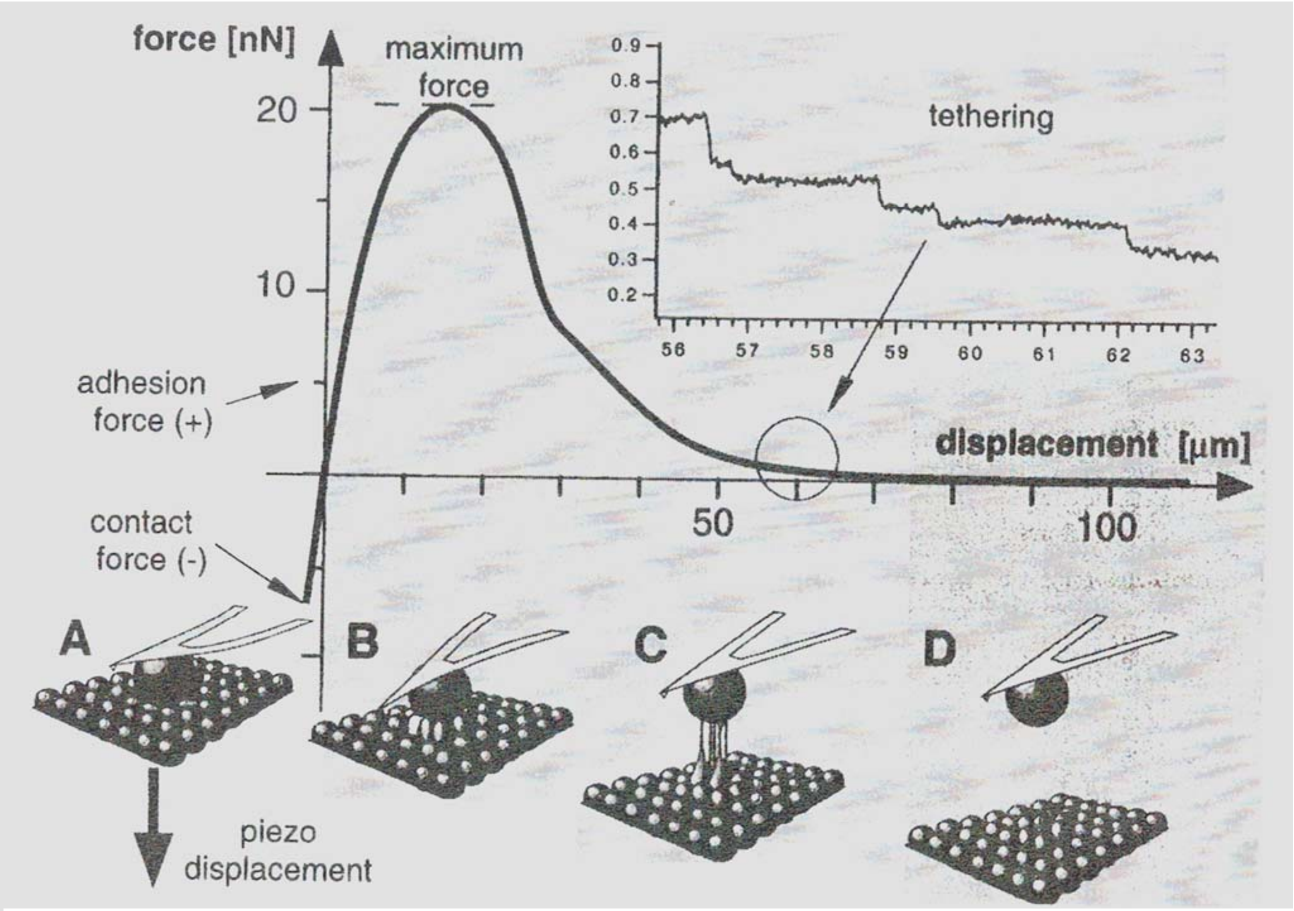


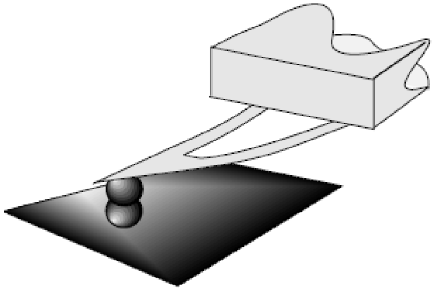
attaching glass or plastic spheres (60 µm)
to a cantilever



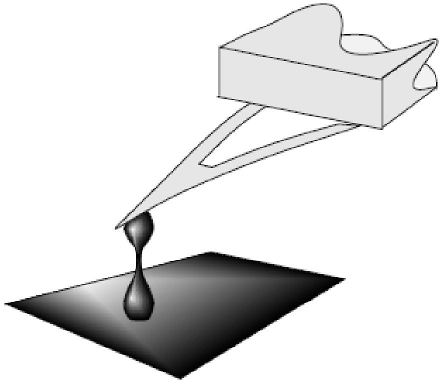
growing cells on the speres

Cell adhesion measured by force spectroscopy

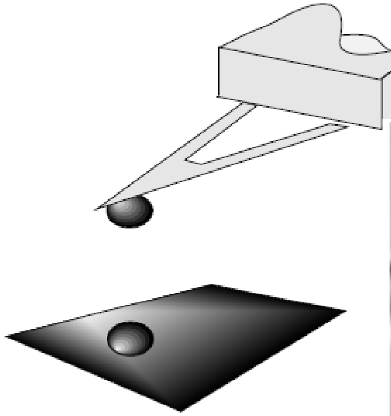




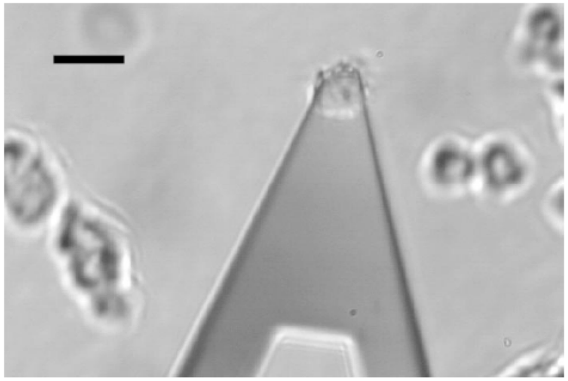
Contact formation



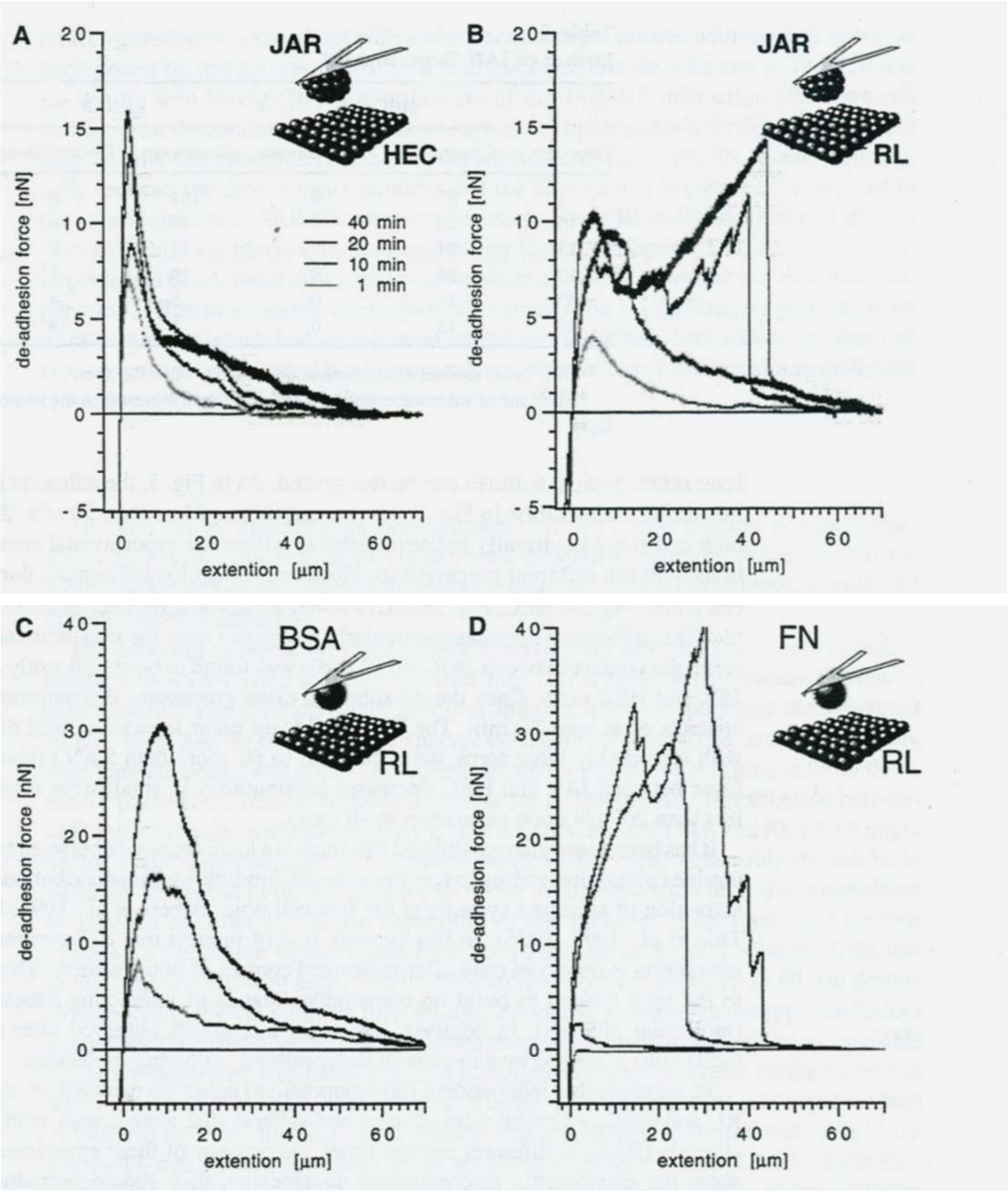
Adhesion



Bond rupture



Cell adhesion measured by force spectroscopy



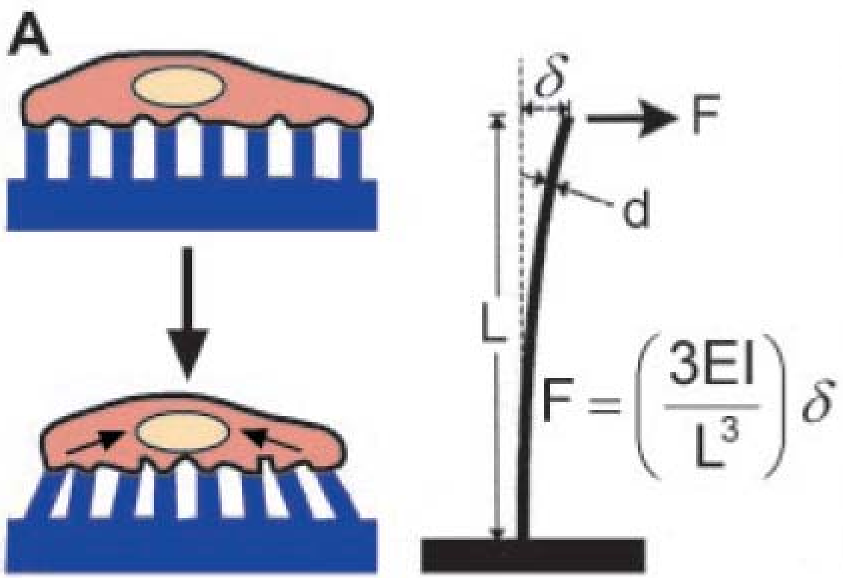
Adhesion between three types of epithelial cells are measured: JAR, RL and HEC cells.

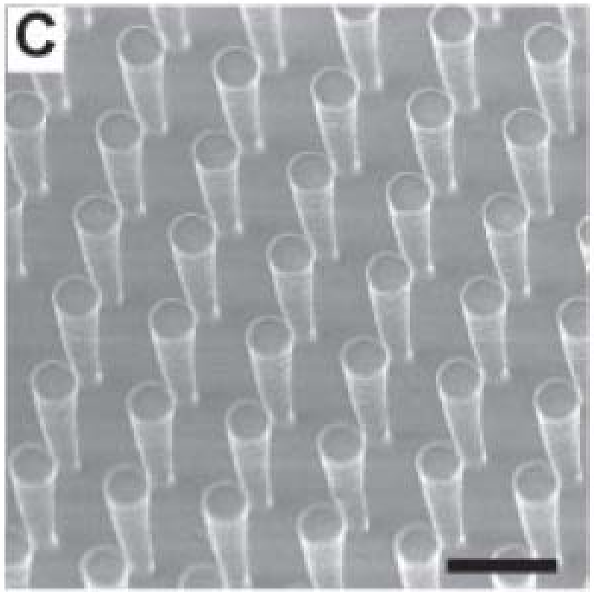
It is well known that JAR and HEC do not form cell-cell contacts, but JAR and RL.

As a control, BSA and the extracellular matrix protein fibronectin (which connects cells to different kinds of matrices)

- JAR = placenta cancer cell line
- RL = human B lymphoma cells
- HEK = human embryonic kidney cell line

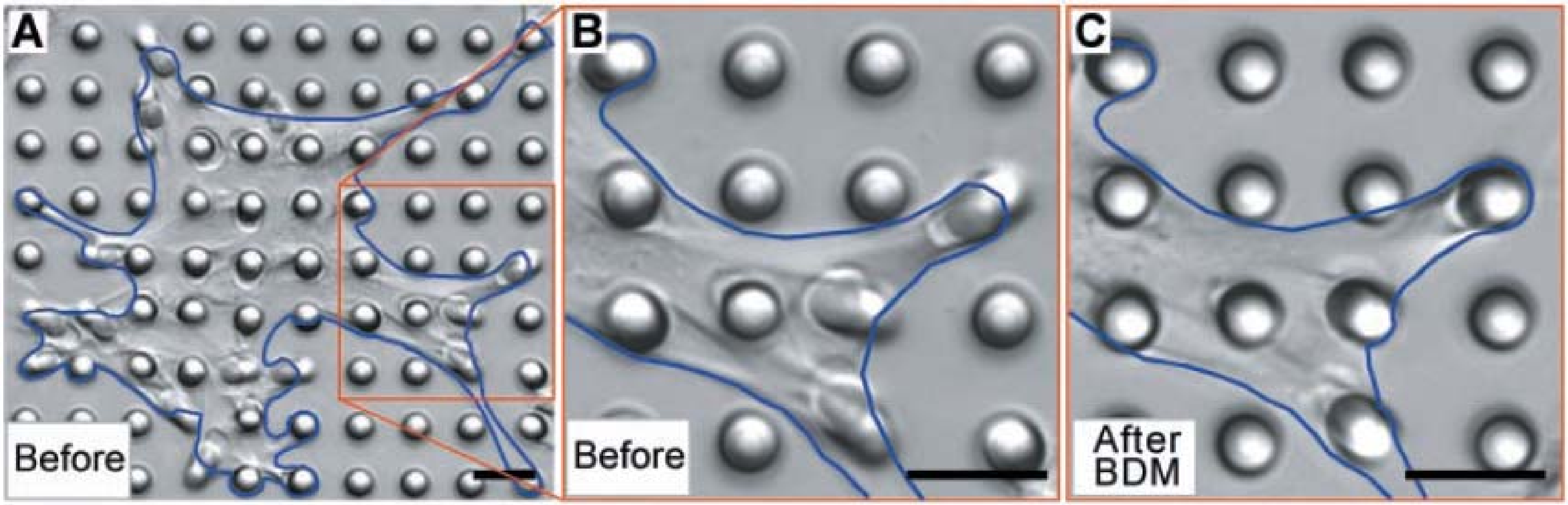
Microelectromechanical (MEMS) devices for measuring cytomechanics





Cells on microneedles

Exerted force determined by needle bending (need to know spring constant)

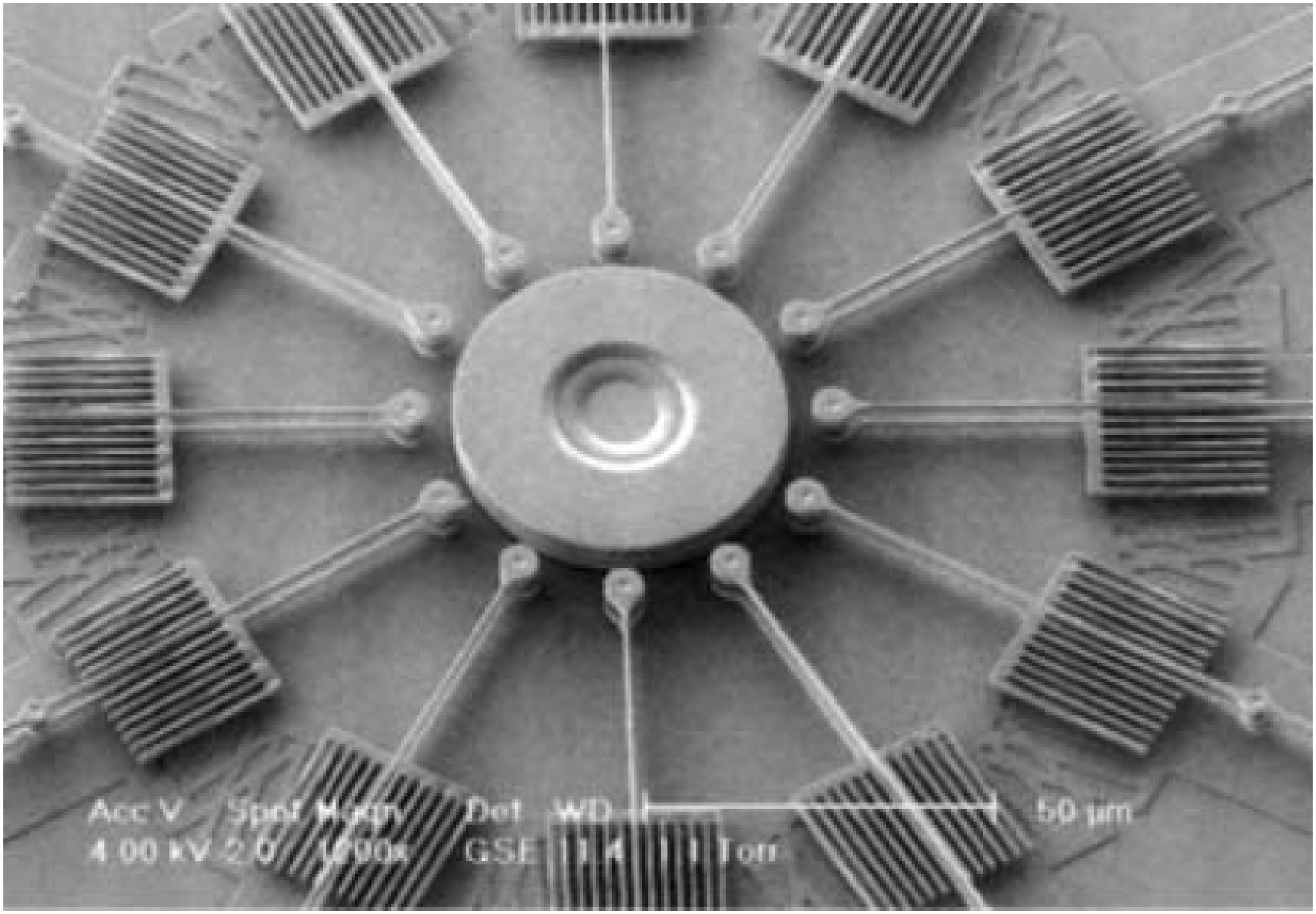


BDM inhibits actin-myosin interactions

Tan et al., PNAS, 2003

Microelectromechanical (MEMS) devices for measuring cytomechanics

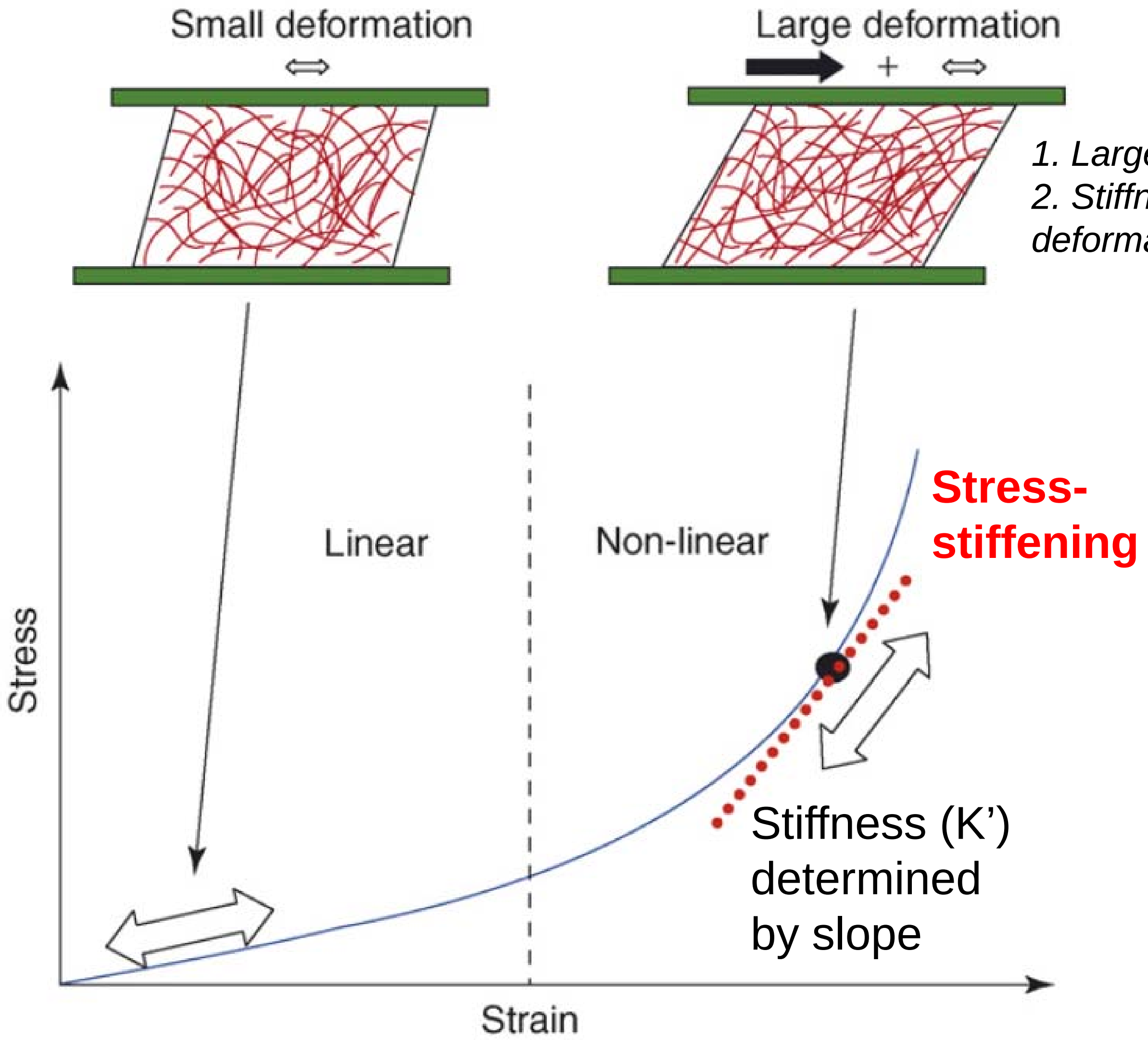
- MEMS device with multiple **active and passive cantilevers** to measure forces generated by a cell at different locations
- **Localized shear forces** can be applied using the **electrostatic actuators**



Bao and Suresh
Nat Mater., 2003

Newtonian and non-newtonian behavior of viscoelastic materials

- Under <u>small deformations</u>, <u>stress</u> is <u>proportional to strain</u>: material is in **linear regime**
- Under <u>large deformations</u>, <u>stress</u> <u>increase more rapidly</u>: material is in **non-linear regime**

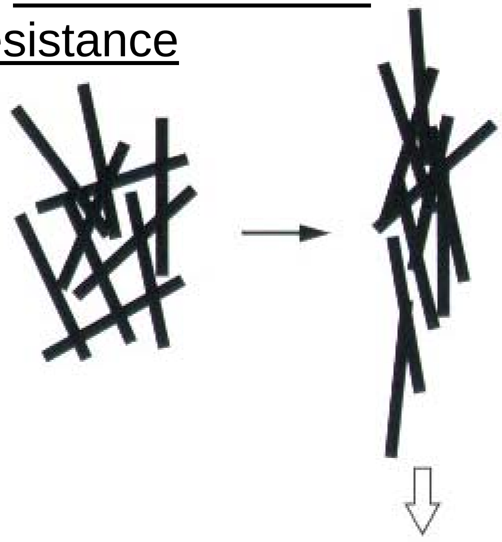


1. Large and steady deformation applied
2. Stiffness determined by applying small deformations

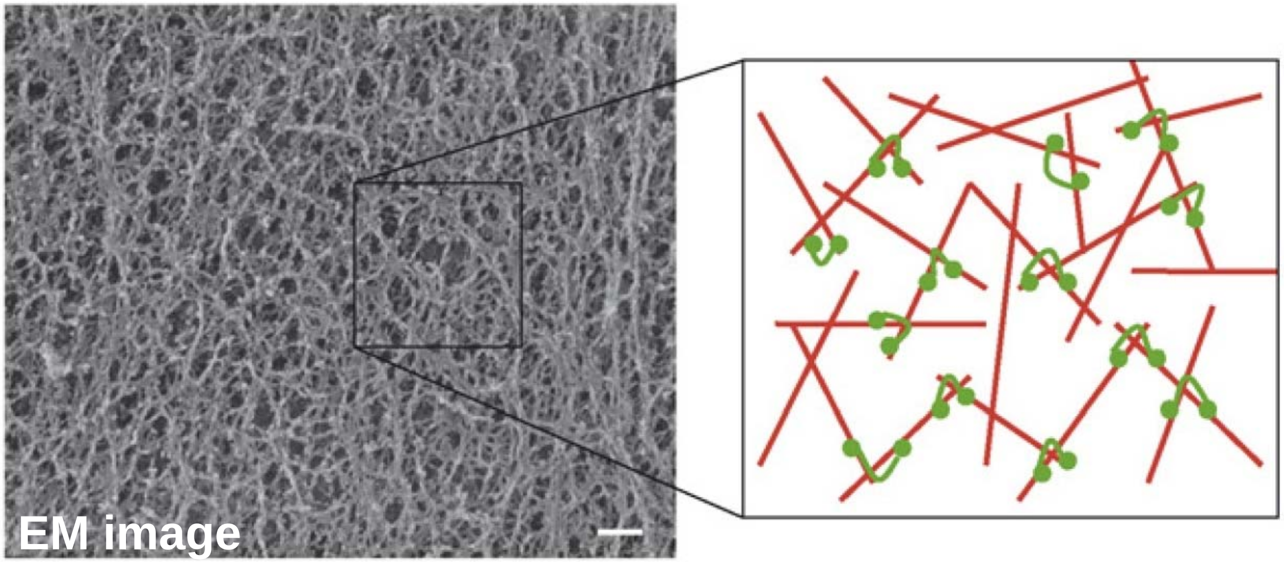
Stress-stiffening

Stiffness (K') determined by slope

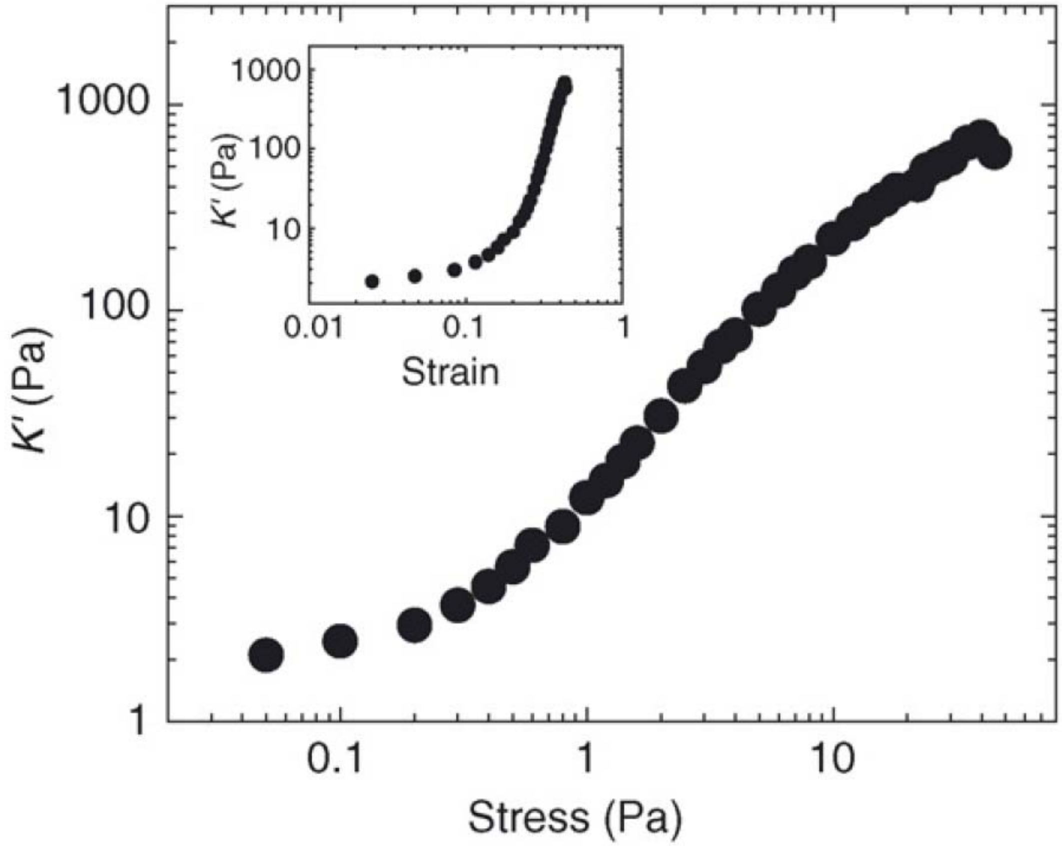
Application of tension leads to <u>alignment of filaments</u>, leading to <u>increased elastic resistance</u>



Strain-Stiffening of cross-linked actin-networks



F-actin cross-linked with filamin

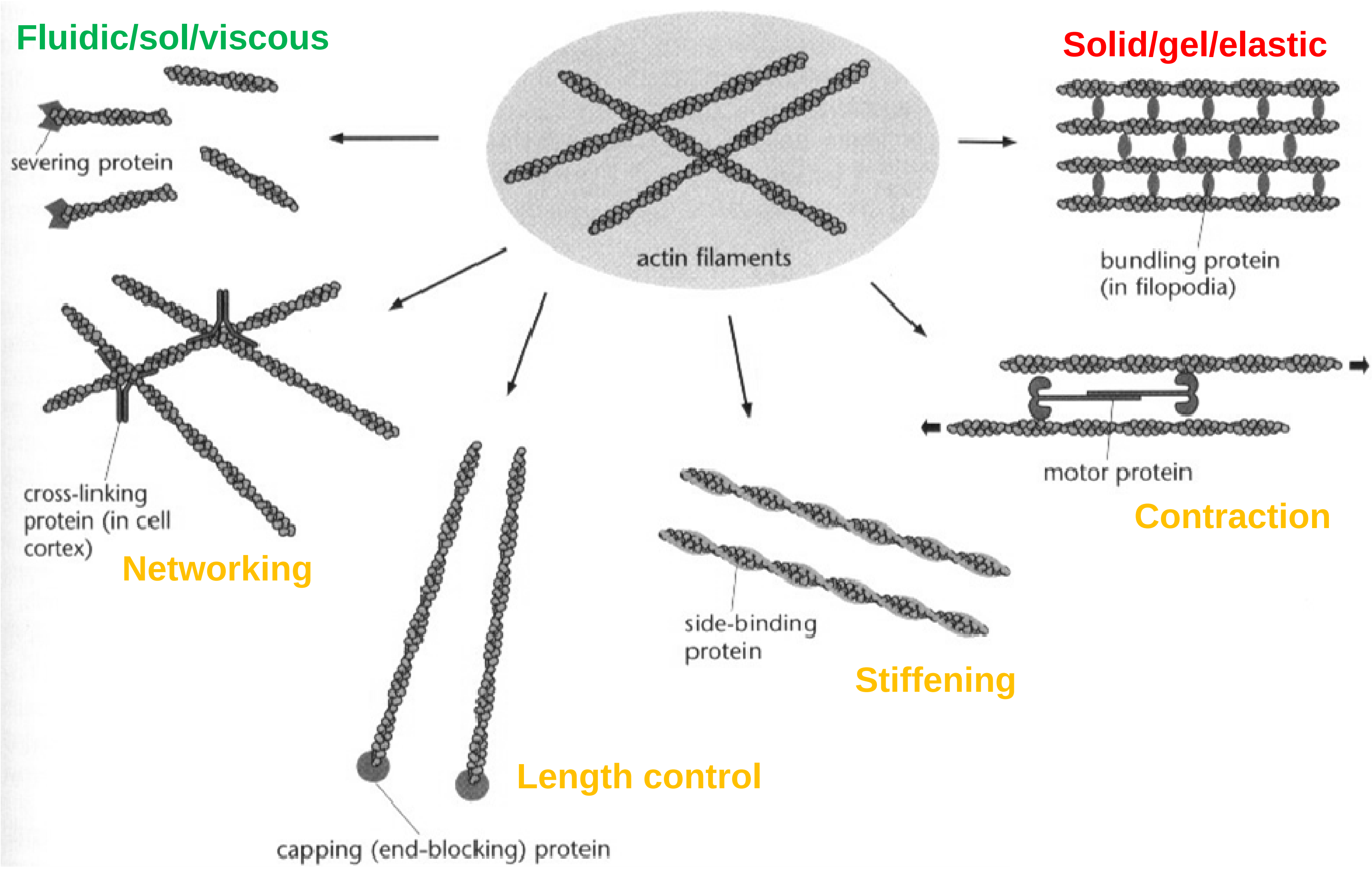


Experiment: Rheology of actin

Dramatic **stiffening per strain** (inset) of cross-linked f-actin

If stress keeps increasing, the whole **network brakes**

Modes of actin cross-linking



Fluidic/sol/viscous

Solid/gel/elastic

Contraction

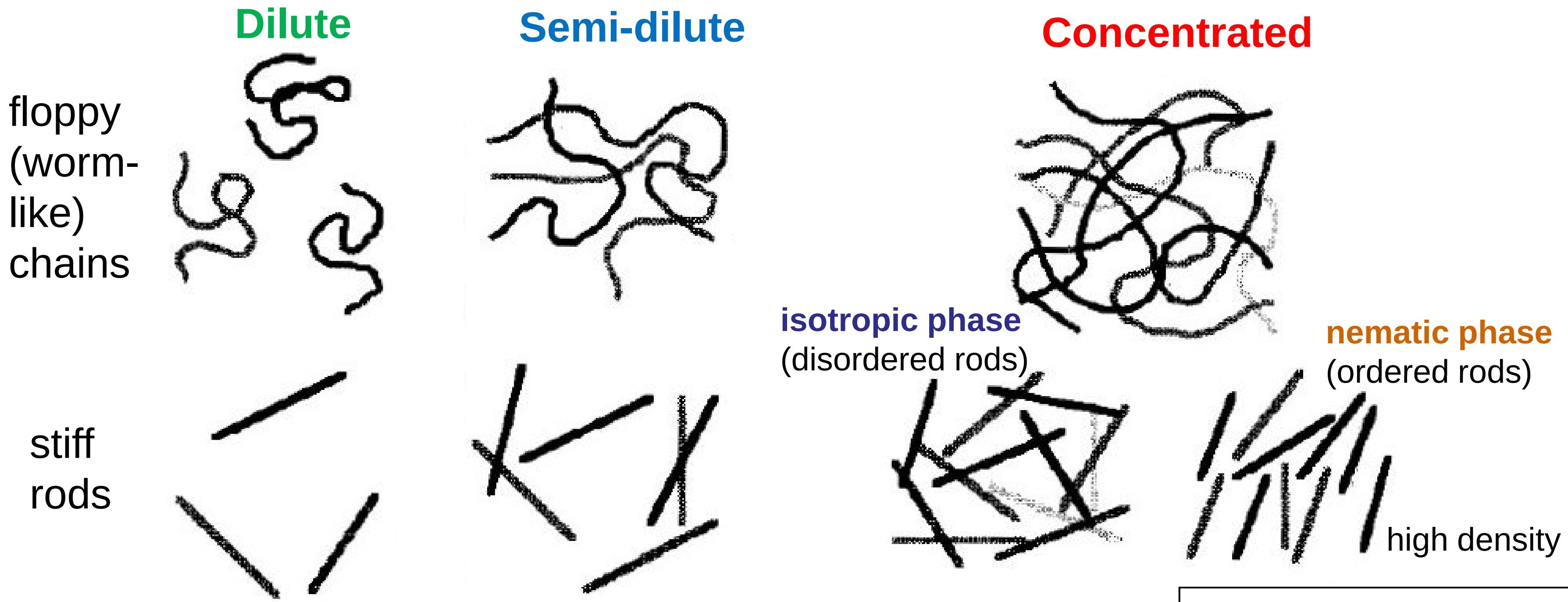
Networking

Stiffening

Length control

Liquid phase changes during polymer concentration

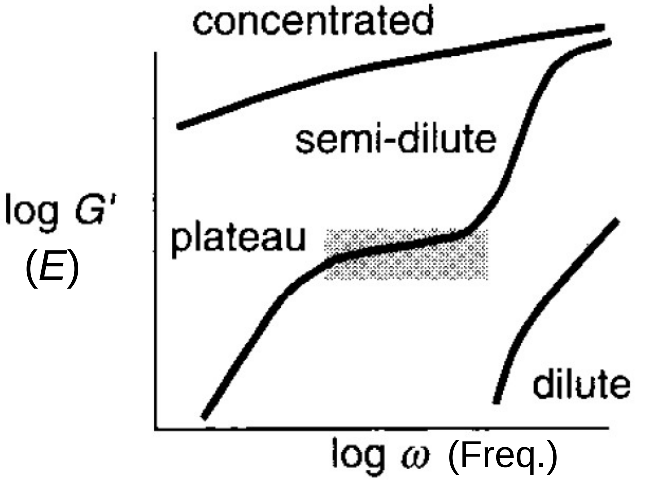
Polymer solutions can be classified based on their concentrations



Polymer density affects viscoelastic properties:

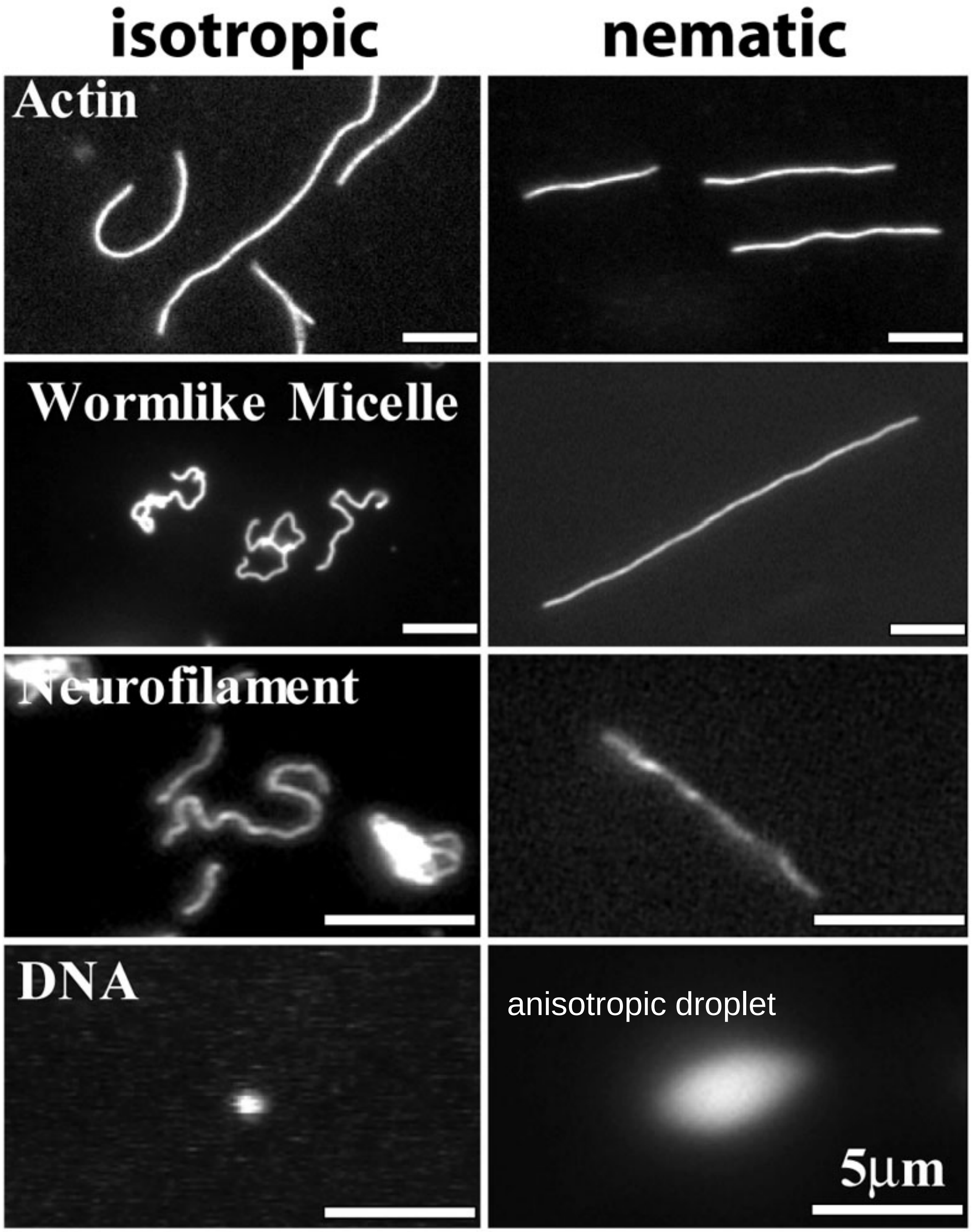
- **Dilute regime**, stiff filaments can rotate largely without colliding: viscosity is close to that of the solvent (buffer)
- **Highly concentrated solutions** do not allow filament to rotate; isotropic phase: *higher* viscosity, nematic phase: *lower* viscosity
- In-between is the **semi-dilute regime** which is characteristic for many biopolymer solutions

Freq. dependence of E



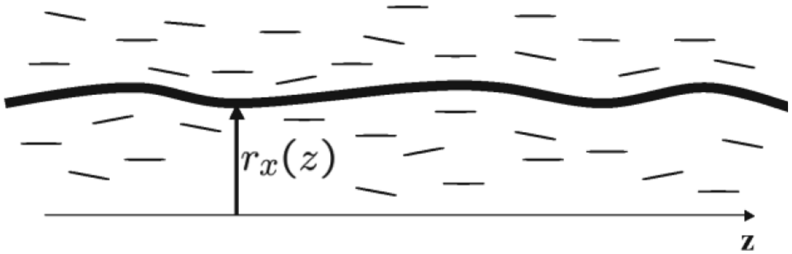
David Boal, Mechanics of the Cell, 1st Ed.

Elastic fluctuations of biopolymers in nematic phase



Changes of appearance of cytoskeletal elements, DNA and micelles after embedding in a nematic phase (composed of **rodlike fd virus**)

All worm-like chains undergo a transition from a coild-form to a rod-like form



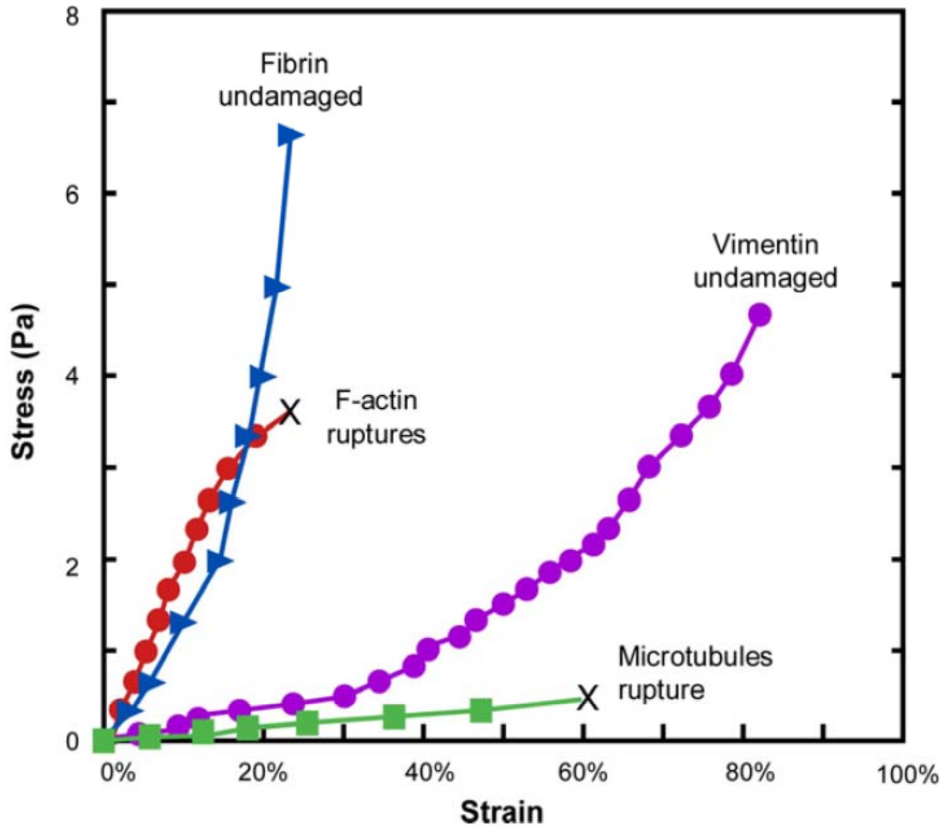
Measuring fluctuations reveals mechanical properties of polymer (**flexual rigidity**)

Fluorescently labeled specimens observed with an fluorescence microscope

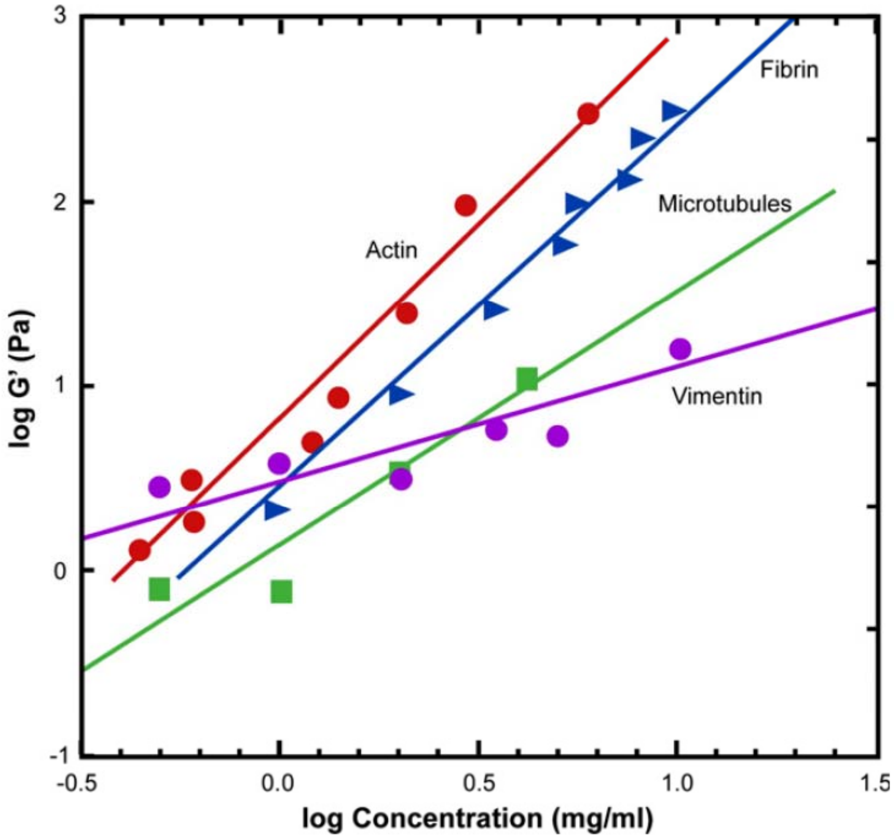
Dogic et al., 2004, Phys. Rev. Lett.

Strain damage and strain resistance of cytoskeletal elements

Under **high stress** (e.g. leading edge)
actin networks are able to fluidize
that facilitates cell locomotion



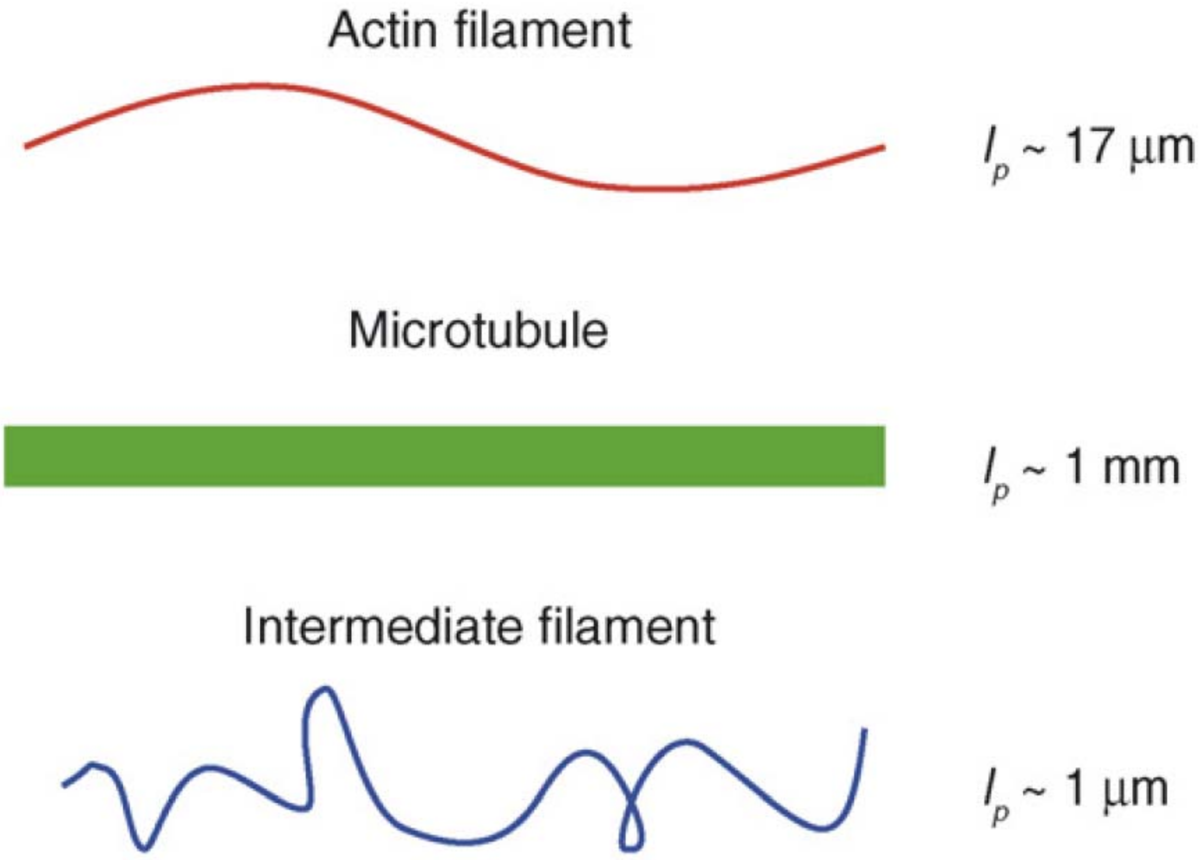
Actin stores more energy than **MTs**



- **MTs** show negligible elastic behavior (few contribution to cell viscoelasticity)
- But MTs act to stabilize the cytoskeleton (very resistant to compression)
- Strain hardening feature of **IFs** help to **support the weaker actin networks**

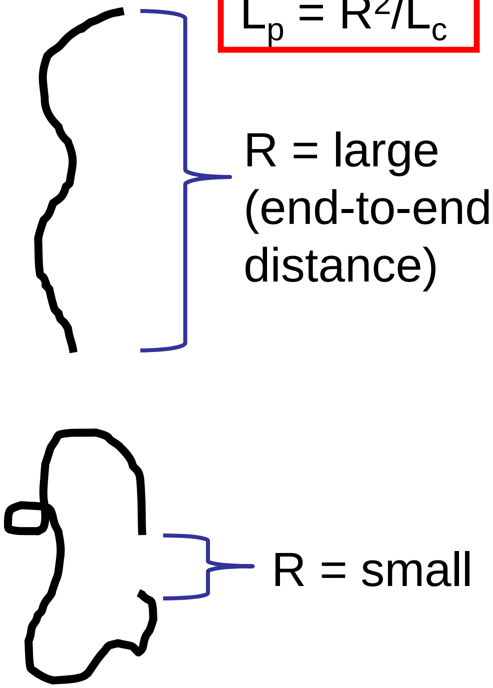
Stiffness/Floppiness of worm-like chains determined by persistence length

- Stiffness or floppiness of semi-flexible polymers can vary to a large extent
- **MT** are very **stiff** and have a large persistence length (1 mm)
- **IFs** are very **floppy** with a low persistence length (1 µm)
- Other examples: DNA = 50 nm / Spaghetti = 10 cm



Approximation of persistence length L_p

$$\boxed{L_p = R^2/L_c}$$



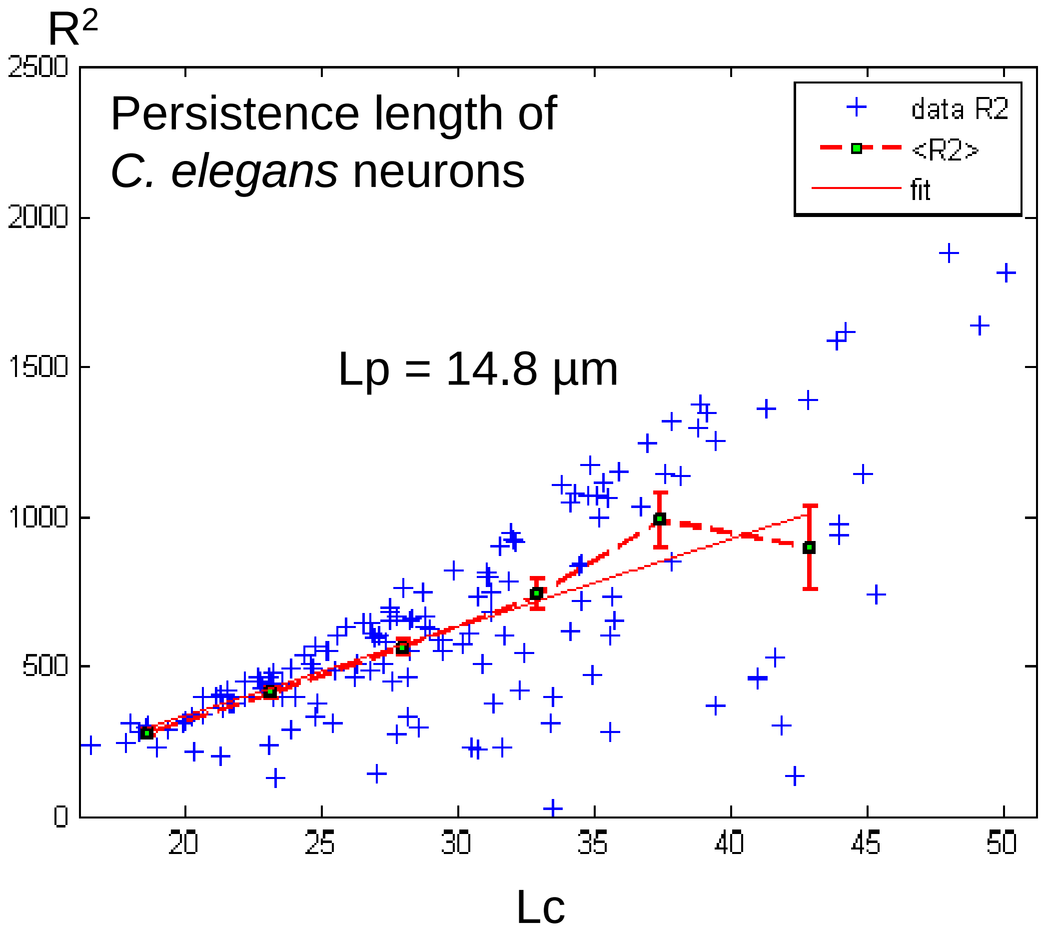
R = large (end-to-end distance)

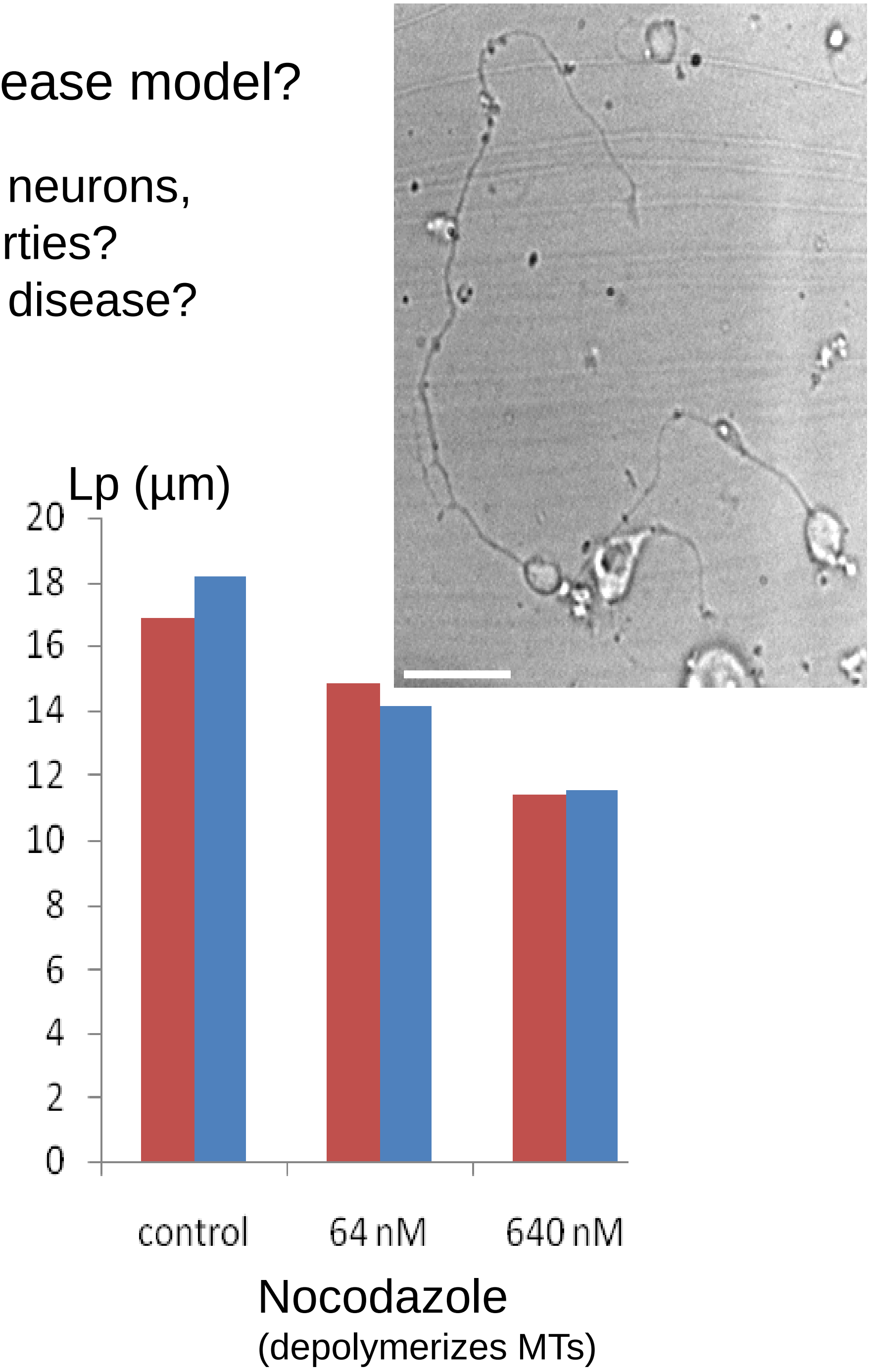
R = small

L_c = contour lenght

Flexual rigidity of neurons as a neuron-disease model?

If nocodazole affects mechanical properties of neurons,
do tau or NF accumulations affect these properties?
If yes, can we relate them to the degree of the disease?



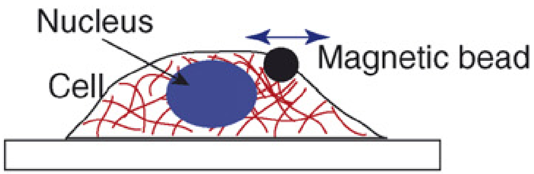


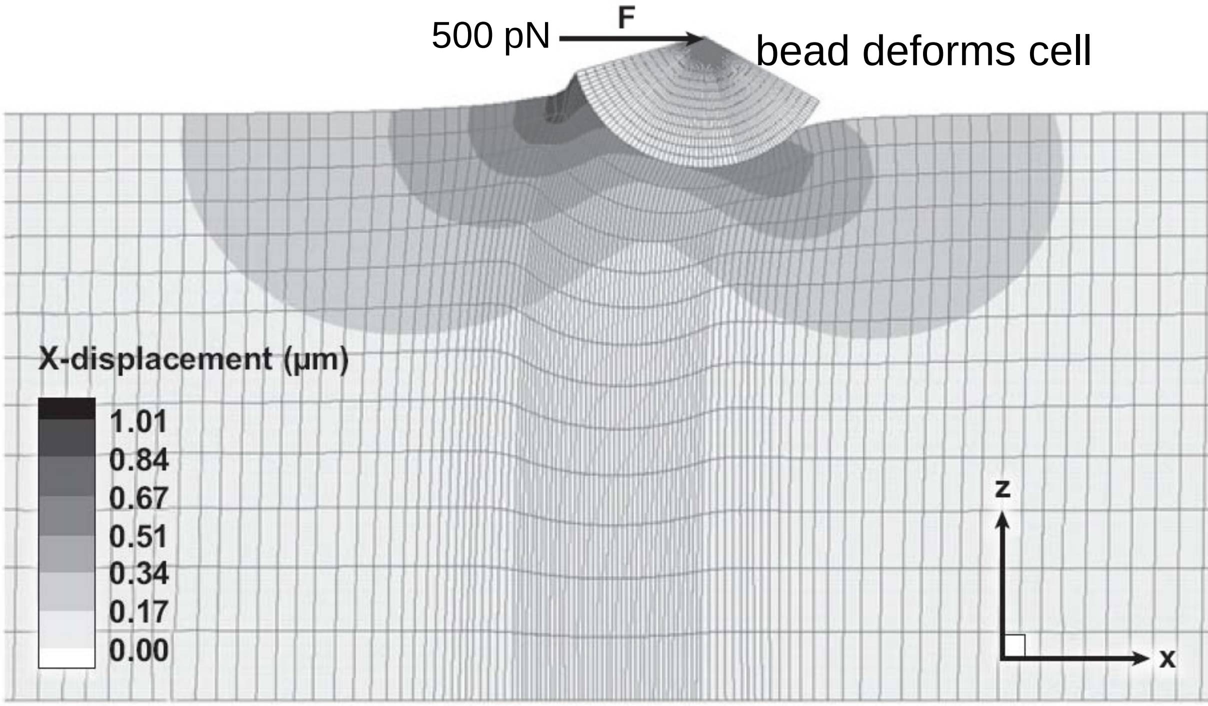
Cytoskeletal proteins involved in neurodegenerative diseases (and available *C. elegans* mutants)

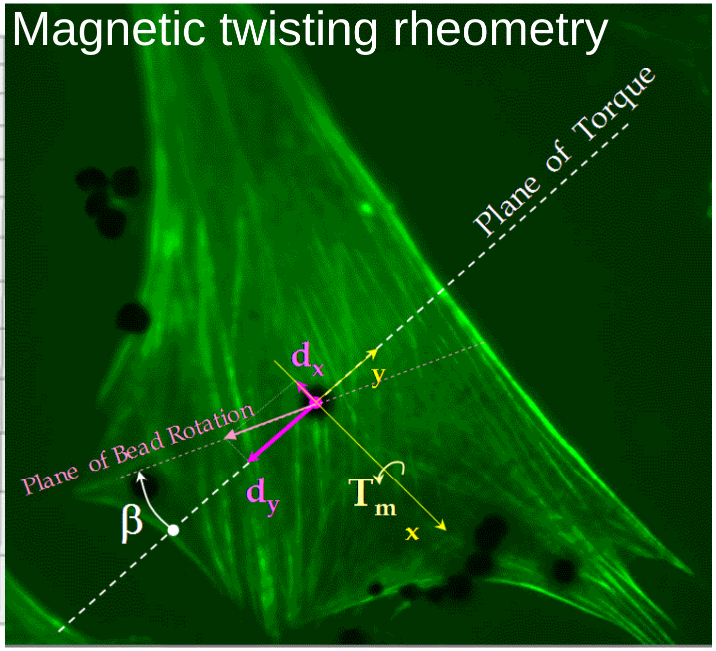
Strains	**Mutation**	**Mammalian protein**	**Involved in disease**
VC275 tag-63(*ok471*)I	1603 bp del	Heavy neurofilament protein	NF accumulations in ALS, Parkinson, Alzheimer
RB809 ptl-1(*ok621*)III	1 bp ins, 1933 bp del	Tau	neurofibrillary tangles; taopathies, Alzheimer, FTDP17
VC117 vab-10(*gk45*)I; CB698 vab-10(*e698*)I	275 bp del; 1 bp sub	dystonin/BPAG1/plakin /plectin	NF perturbations, skin blistering
FX776 sod-1(*tm776*)II	612 bp del	superoxide dismutase SOD-1	NF accumulations; ALS
DH235 zyg-8(*b235*)III	n/a	doublecortin	lissencephaly LIS1
VC346 atx-3(*gk193*)V	366 bp del	ataxin	PolyQ diseases, Machado-Joseph
CB3323 che-13(*e1805*)I; MT3575 che-13(*n1520*)I		HIP-1 interactor (Hippi)	Huntington
AN87 sel-12(*ty11*)X; GS1894 sel-12(ar*131*)X		presenilin	Alzheimer
RB1102 ZK370.3(*ok1081*)III	1444 bp del	Sla2/Hip1	Huntington
VC1024 pdr-1(*gk448*)III	355 bp del	parkin	Parkinson

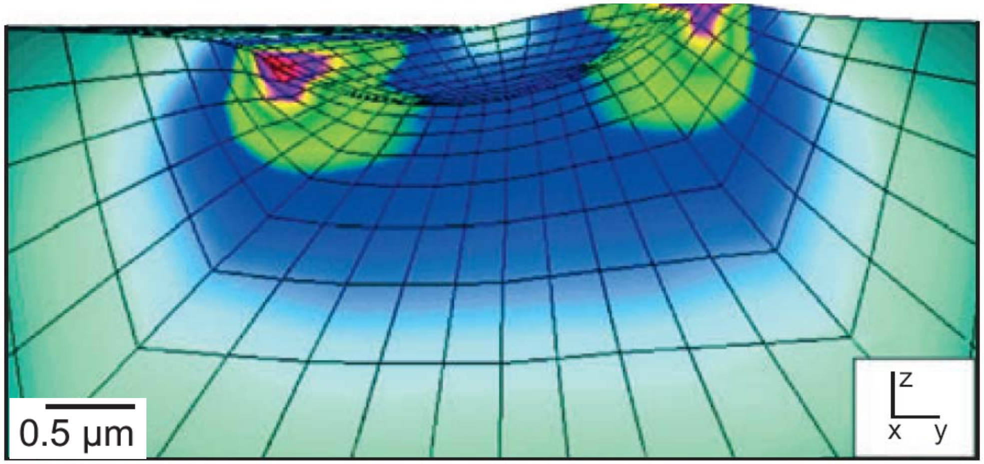
Theoretical predictions of the stress field in a model cell

Finite element modeling: provides maps of how forces applied to a cell are transmitted through its interior





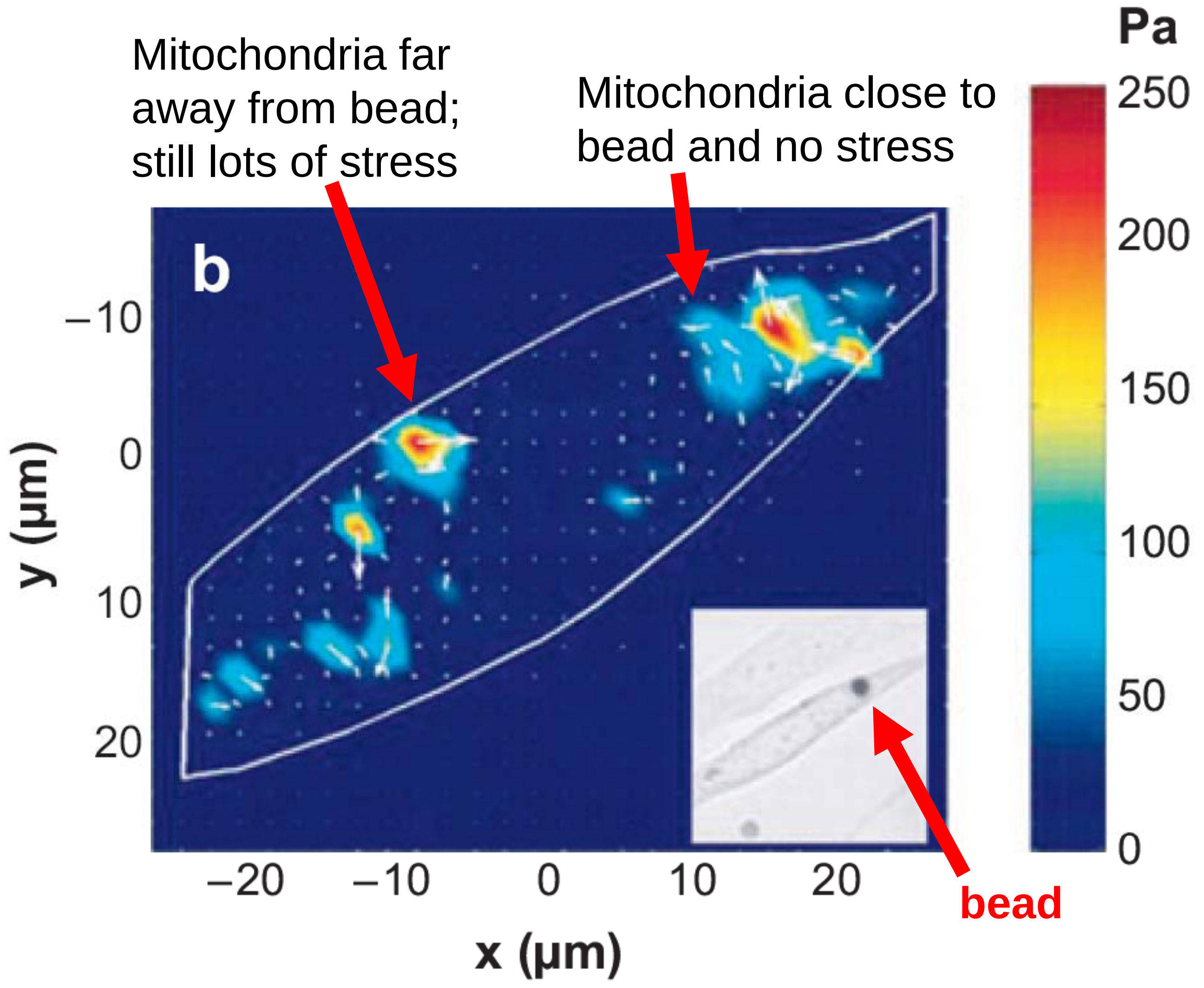




- Forces are transmitted uniformly **(affine deformation)** but only a few microns away from the point of force application
- Conclusion: largest cytoskeletal deformation and organelle displacement should be near the edges of the bead
- Confirm by magnetic bead rheometry?

Experimental measurements of intracellular strains caused by extracellular forces

Mitochondria move in unexpected directions from what would be expected based on infinite element modeling

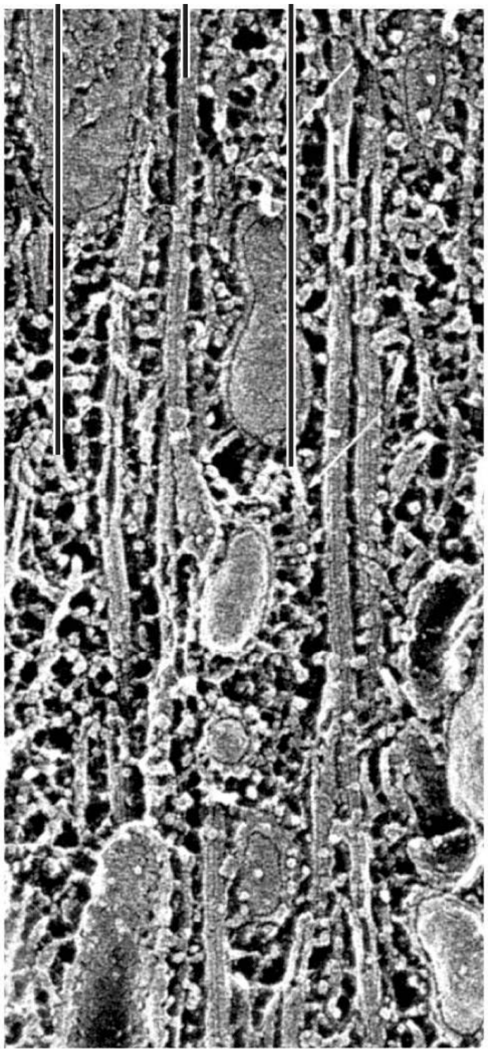


Mitochondria far away from bead; still lots of stress

Mitochondria close to bead and no stress

bead

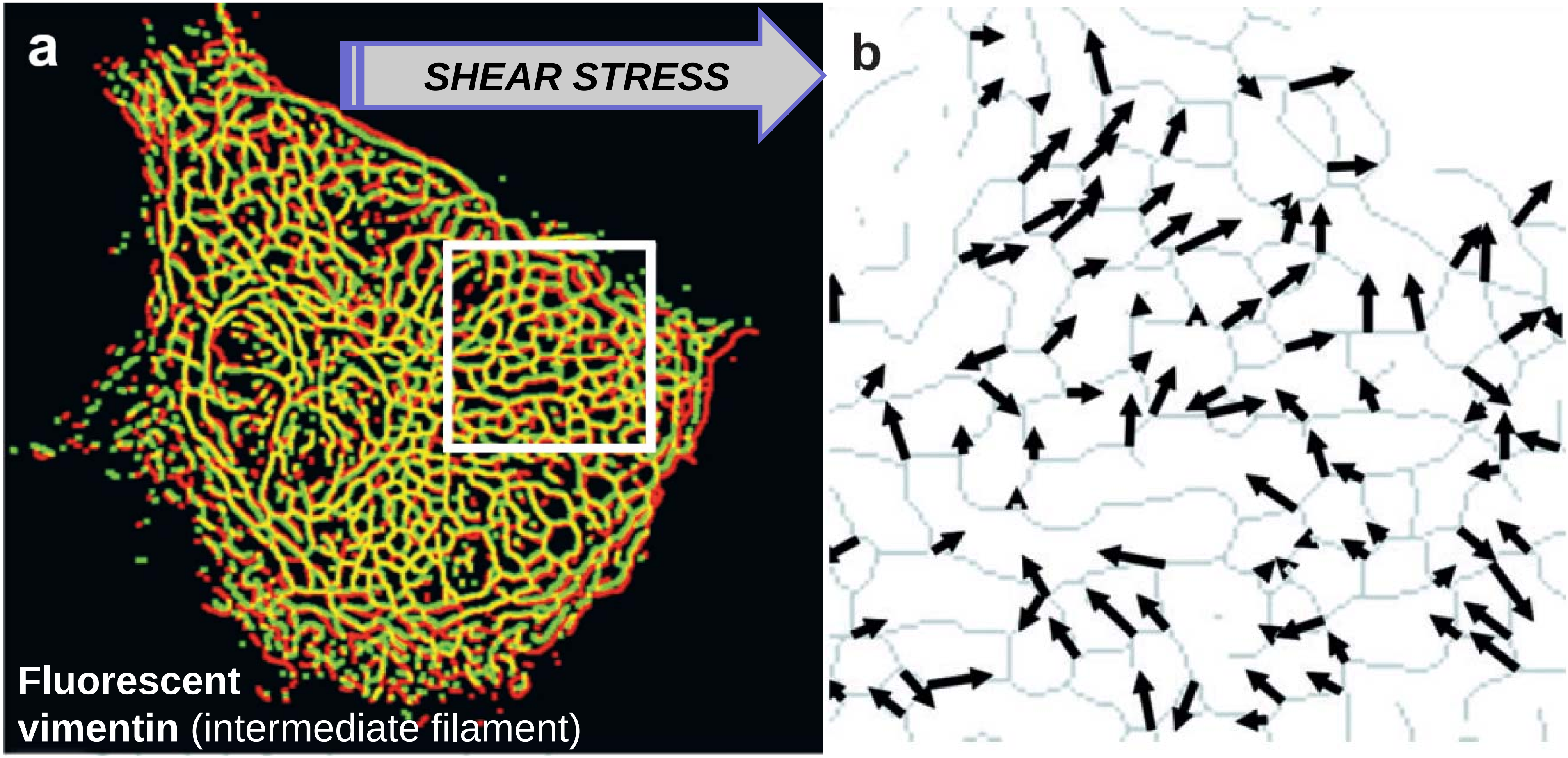
Mitochondria are closely connected to the cytoskeleton and can be used as a strain/stress marker after cell deformation



Experimental measurements of intracellular strains caused by extracellular forces

Non-affine deformation: because interior of the cell is **anisotropic**, cell deformation does not respond to shear stress as predicted for a homogenous viscoelastic material

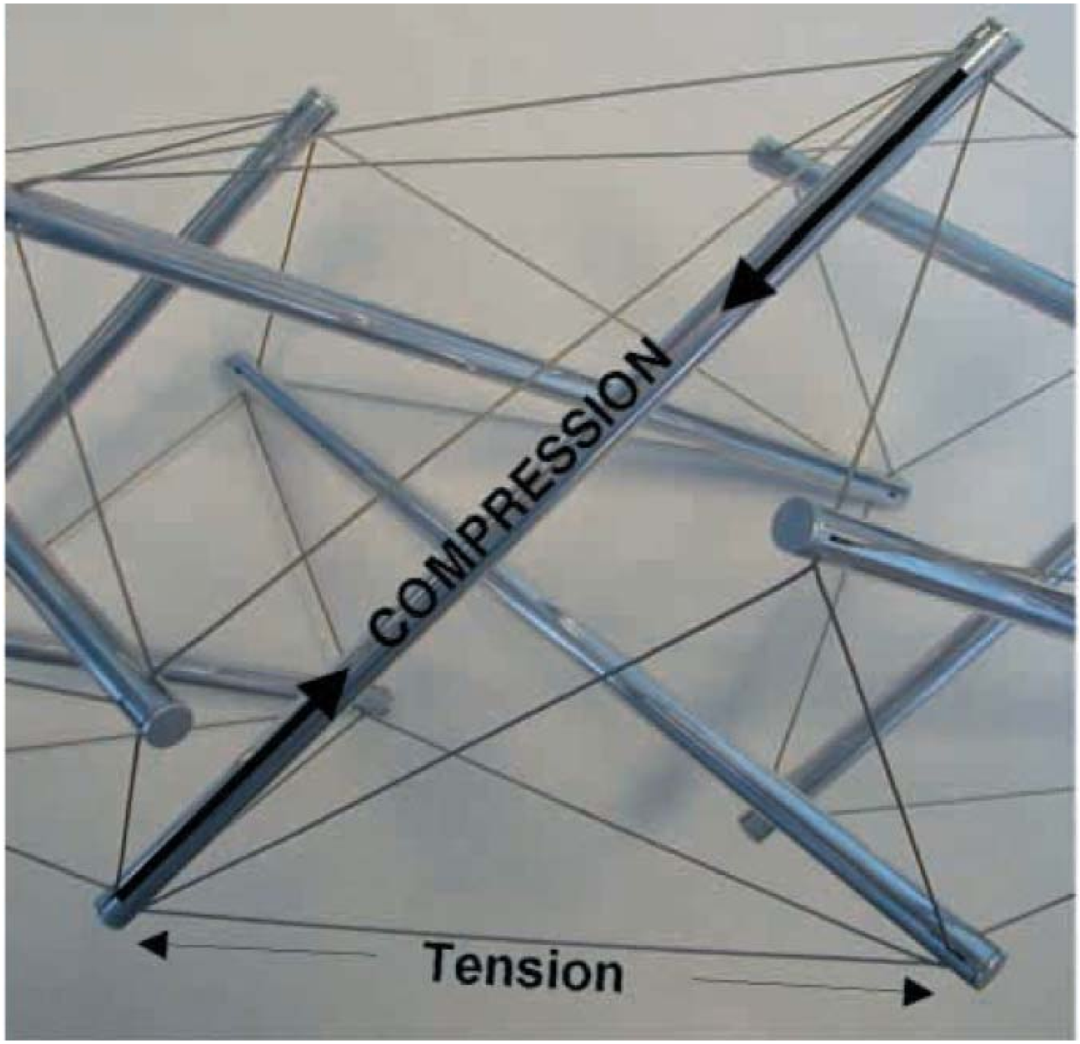
Microscopic displacements of vimentin do not follow the direction of applied shear stress



RED = BEFORE stress, GREEN = AFTER stress, YELLOW = Zero displacement

Tensegrity model might explain non-affine behavior of cells

- Stress carried by cytoskeletal elements depend on their **intrinsic elastic properties** and on how they are connected (**cross-linked**) to each other
- Experimental results on non-uniform behavior of the cytoskeleton (after applied stress) is consistent with the tensegrity model

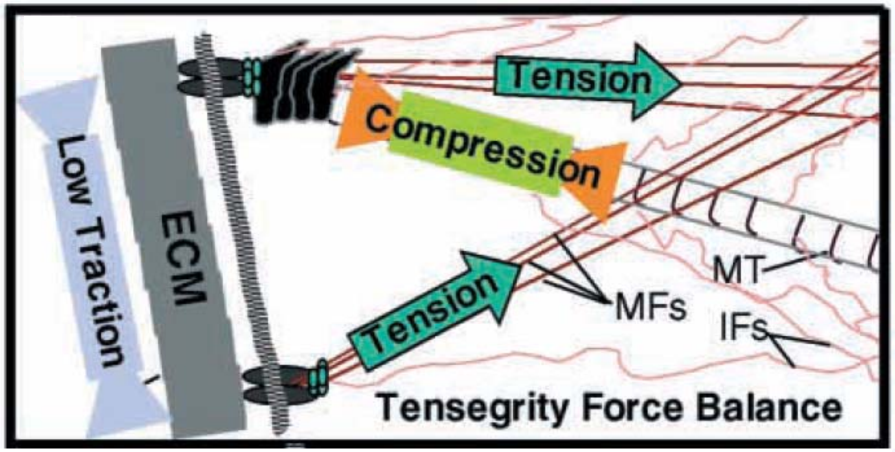


- Tensegrity model **focus on the geometry of the network** elements and the interplay of tension and compression
- "**Tensegrity systems** keep their structure by **continuous tension** rather than by continuous compression (e.g., stone arc)"
R. Buckminster Fuller, 1961
- Tensegrity = Tensional integrity

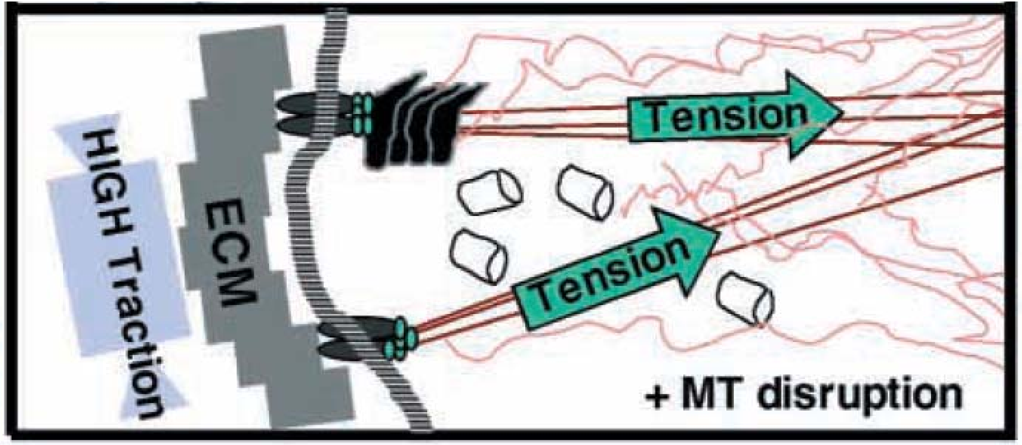
Cellular tensegrity model (by Donald E. Ingber)

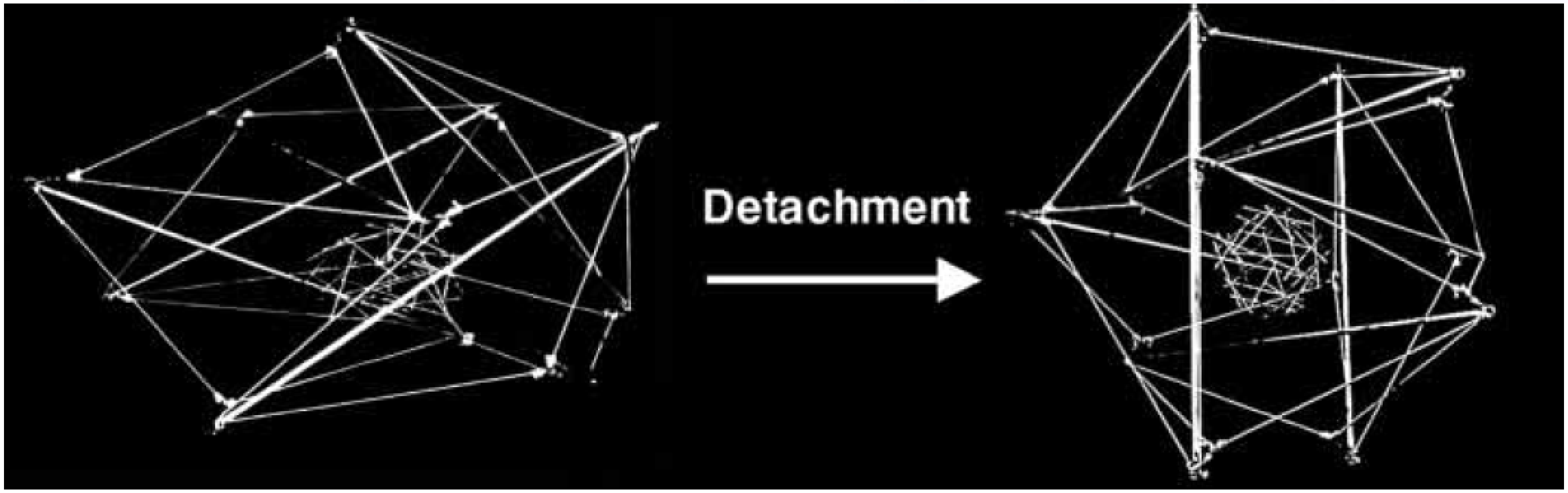
- Cellular tensegrity model proposes that the **cell is a pre-stressed structure** based on **tensional forces** provided by **f-actin** and **intermediate filaments** while **microtubules** act to balance these forces (**compression resistant**)
- Our body: the **tone** (prestress) in our **muscle** is also balanced by the stiff bones

- MTs resist the pull of tensile stress-fibers
- Cytoskeleton connects to the ECM via integrins



If microtubules are depolymerized, tension generated by stress-fibers is released
=> cell pulls on substrate

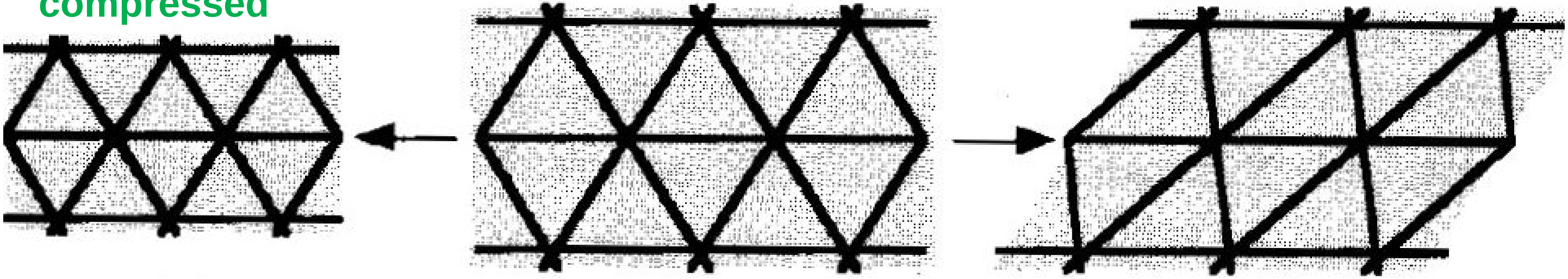




Tensegrity model
of experimentally
observed
cell detachment
(after MT disrupt)

Difference between shear stress and compression

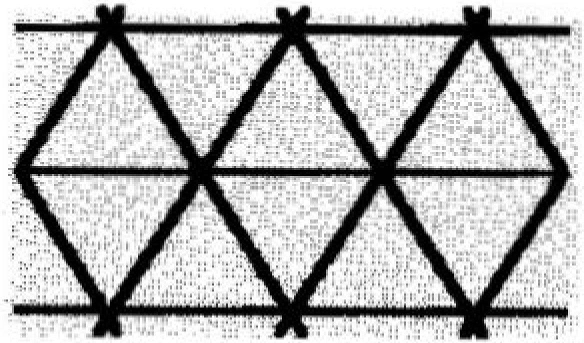
compressed **undeformed** **sheared**



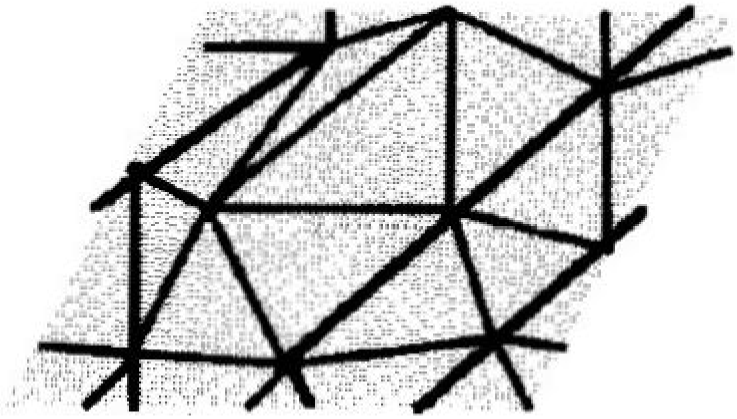
network area changed but <u>no changes in internal angles</u>

<u>internal network angles changes</u> but **area unchanged**

Effect of **thermal fluctuations**



Zero-temperature network



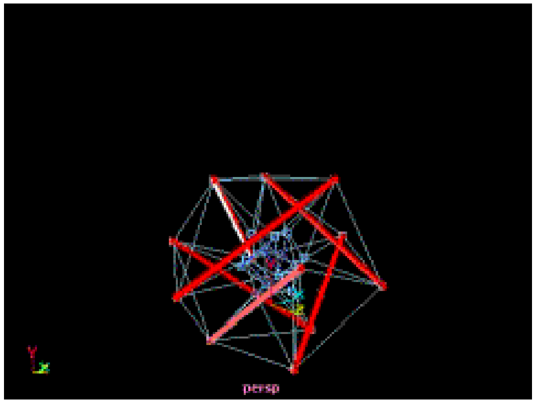
Network becomes more erratic similar after applying a two-dimensional stress

David Boal, Mechanics of the Cell, 1st Ed.

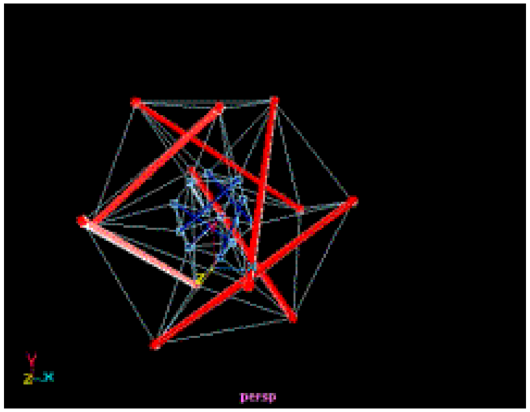
Computer model of cellular tensegrity

Computer model shows how hierarchical tensegrity structures, such as a cell with a nucleus, behave when pulled, sheared and stretched

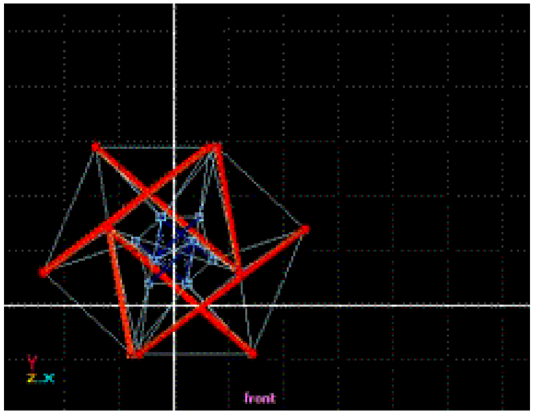
Pull



Shear

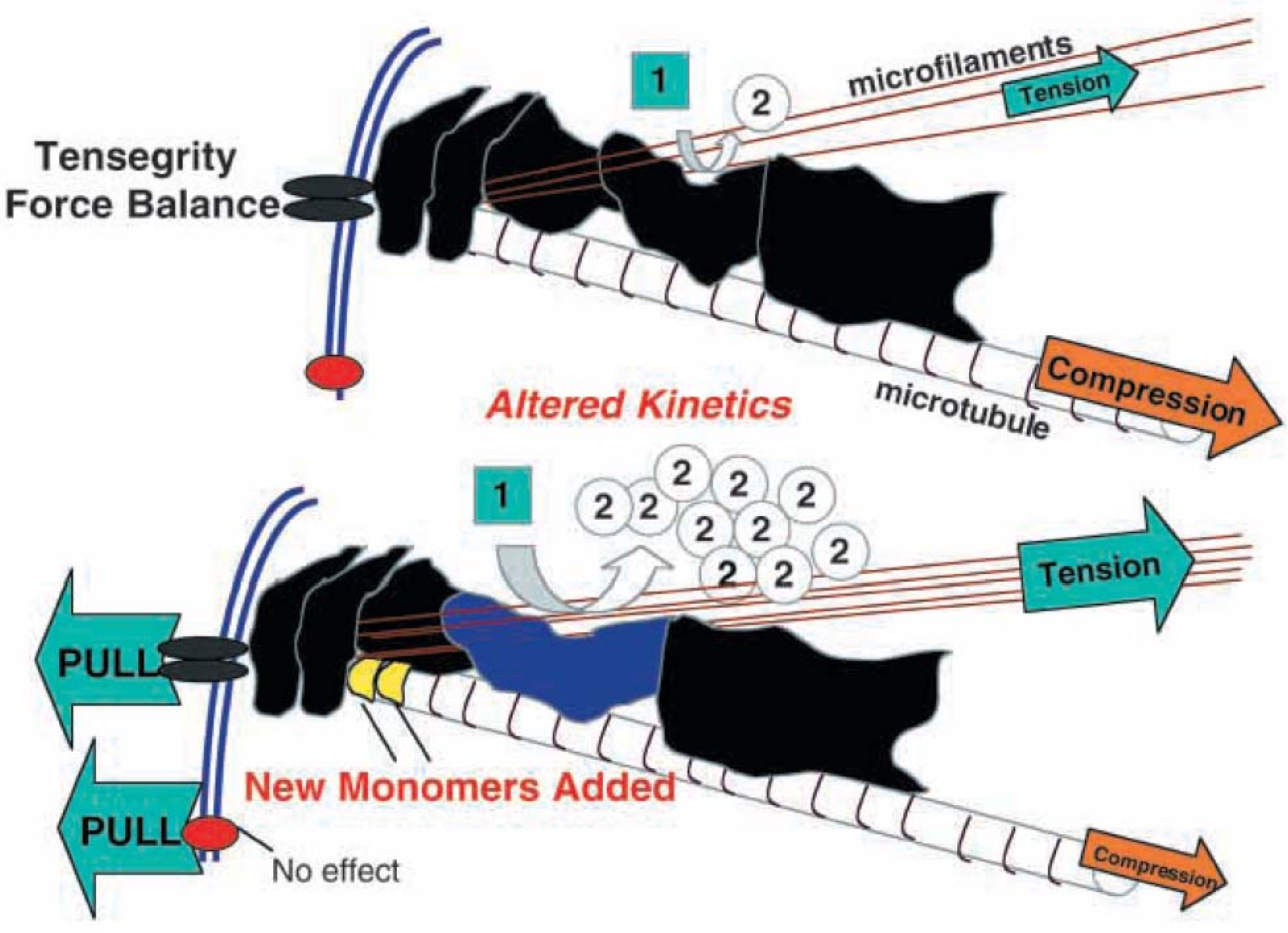


Stretch



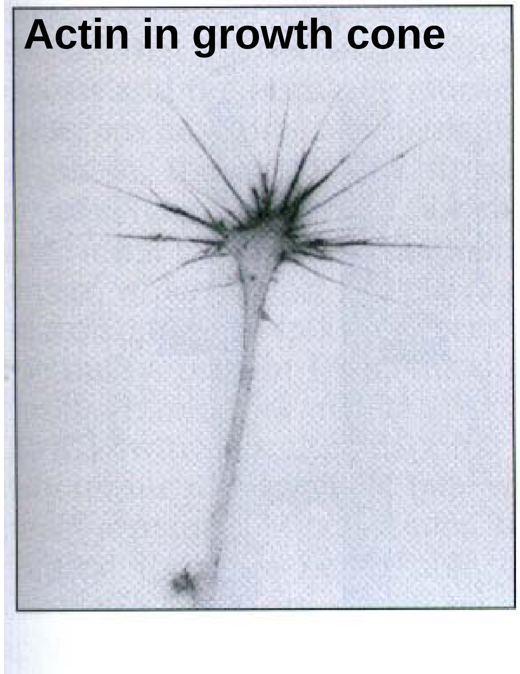
Contribution of cellular tensegrity to mechanochemical transduction

- Mechanical stress (pulling on cells) might enable MT polymerization at the plasma membrane leading to **decompression of MTs** and <u>increasing tension on stress-fibers</u>
- An **enzyme** closely associated to stress-fibers might <u>change its conformation and thus its kinetics</u> (“**mechanochemical transduction**”)

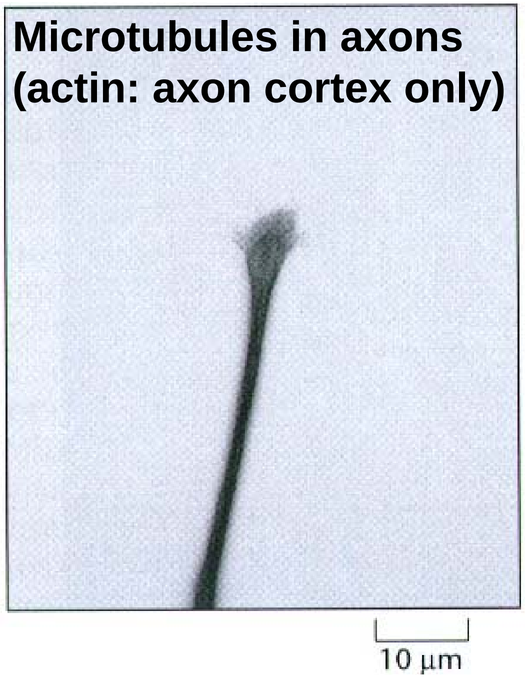


Ingber, J Cell Sci, 2003

Axonal tensegrity: Mechanical properties of neurons

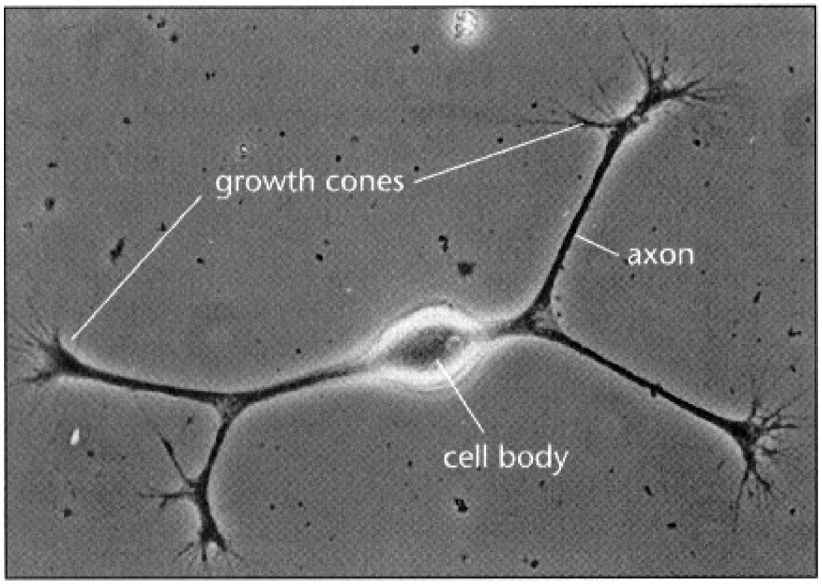


Actin in growth cone

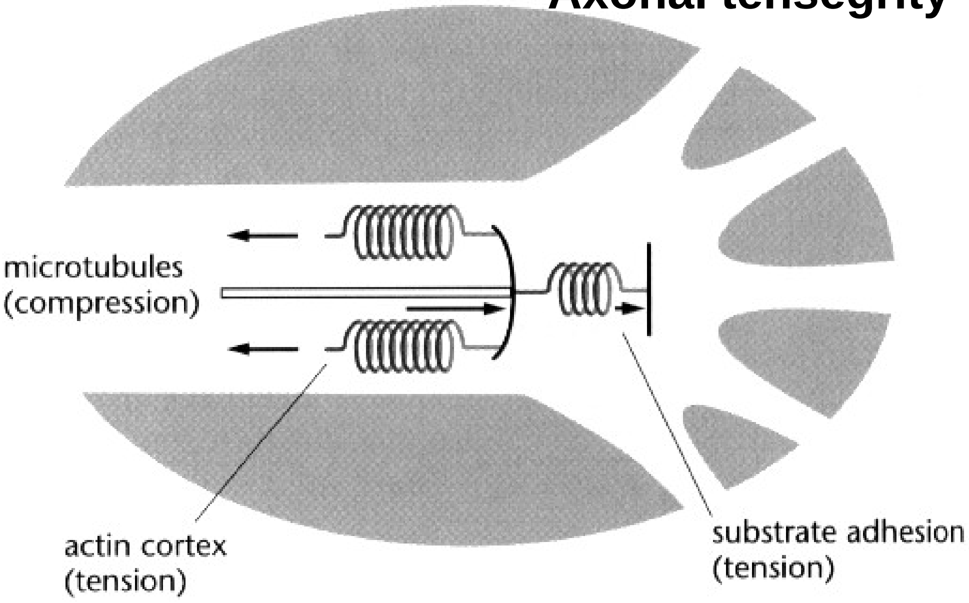


Microtubules in axons (actin: axon cortex only)

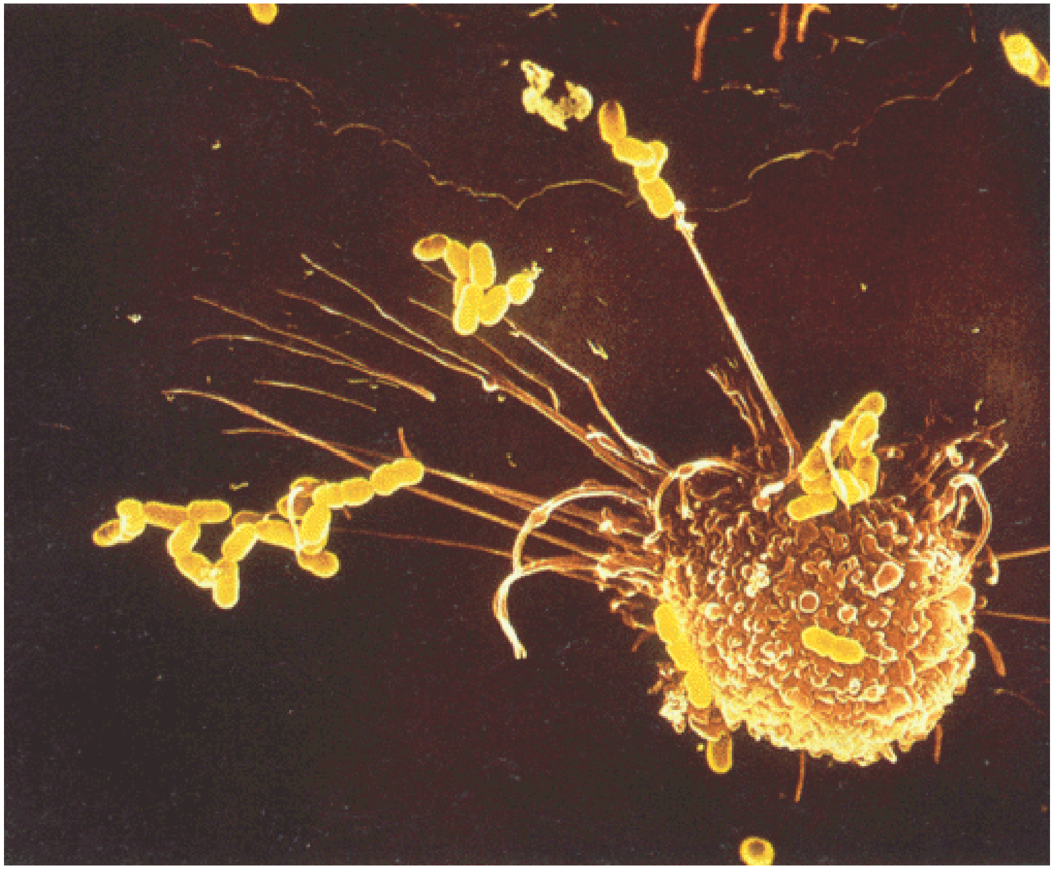
Abrupt axon retraction observed after nocodazole treatment (MT depolymerization):
=> **Mechanical balance** of an axon is provided by creating a **tension** of **actin** along the cortex (as well as substrate adhesion) and antagonistic **compression** forces provided by **microtubules**



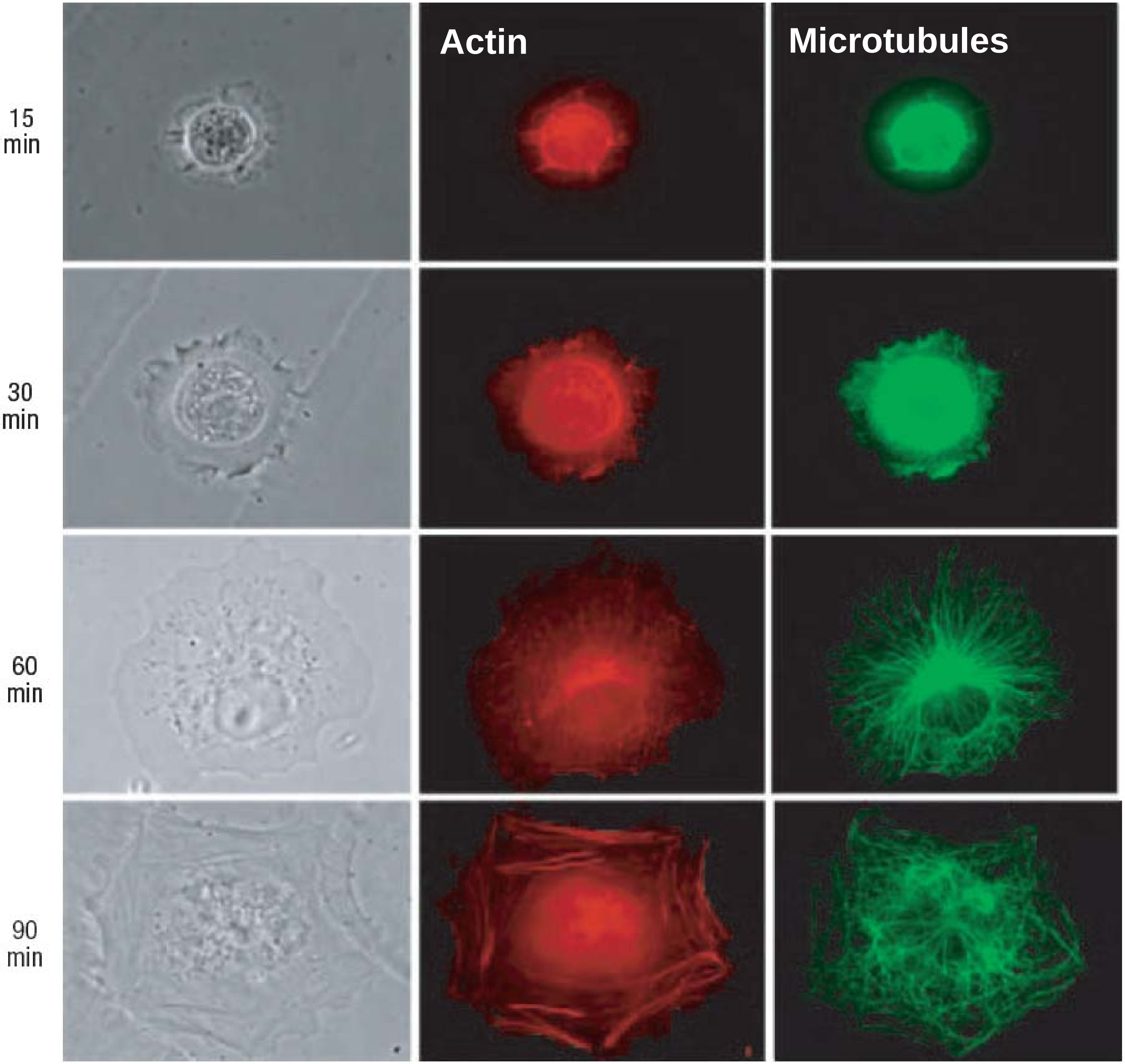
Axonal tensegrity



Importance of cytoskeleton and cytomechanics in environmental cell responses



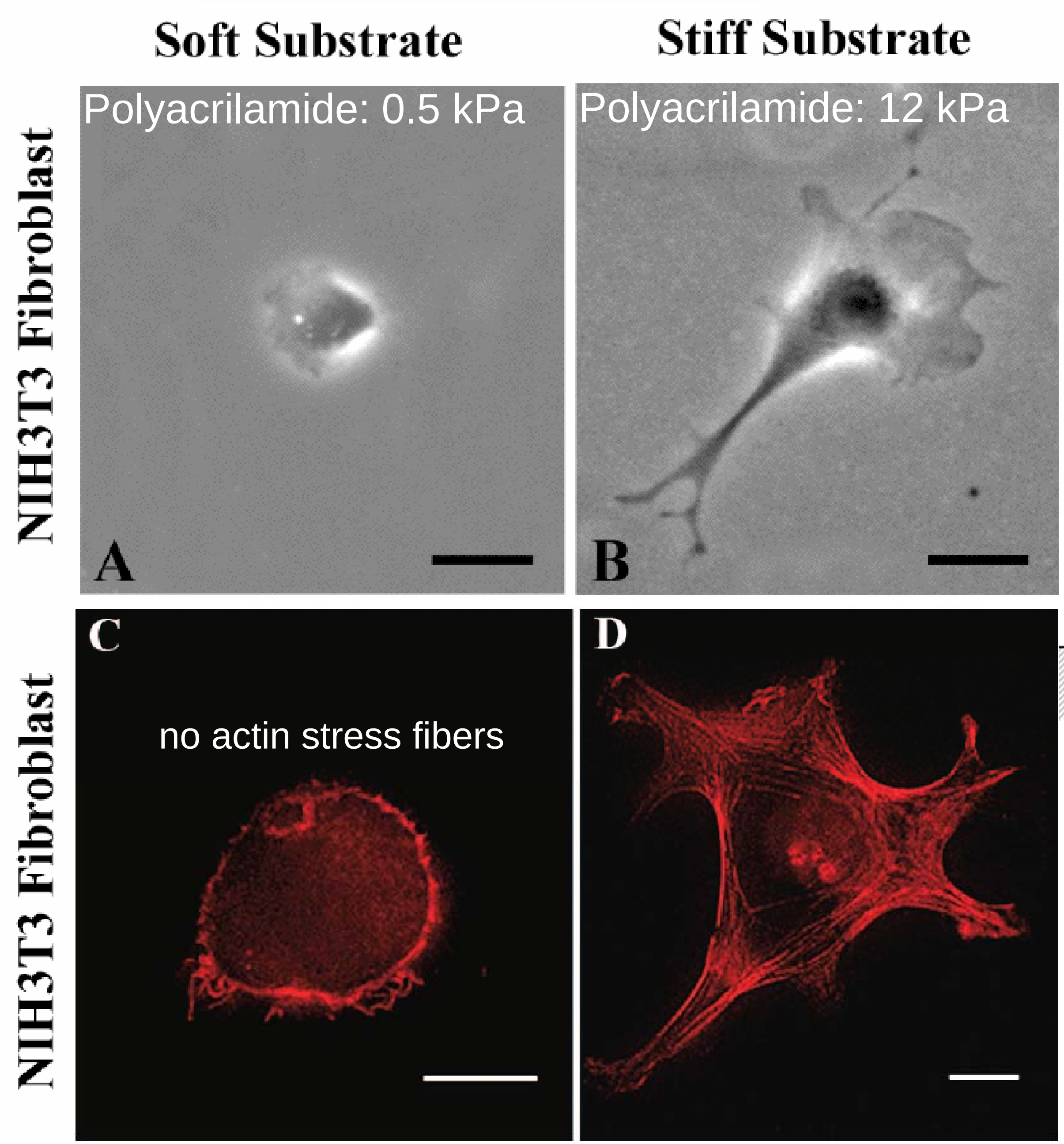
Filopodia (made of thick microtubule bundles) of white blood cells catching bacteria for lysosomal digestion



Cytoskeletal response to cell spreading

Stress fiber development upon spreading of a fibroblast on glass

Cellular response to substrate stiffness



Soft Substrate

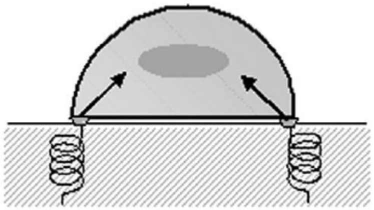
Stiff Substrate

Polyacrilamide: 0.5 kPa

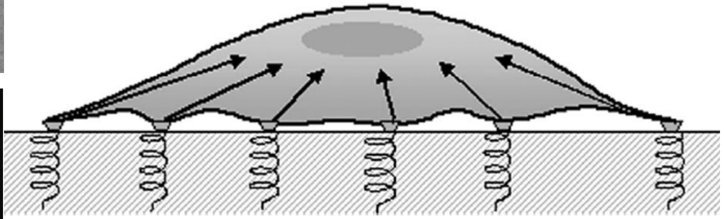
Polyacrilamide: 12 kPa

no actin stress fibers

Model



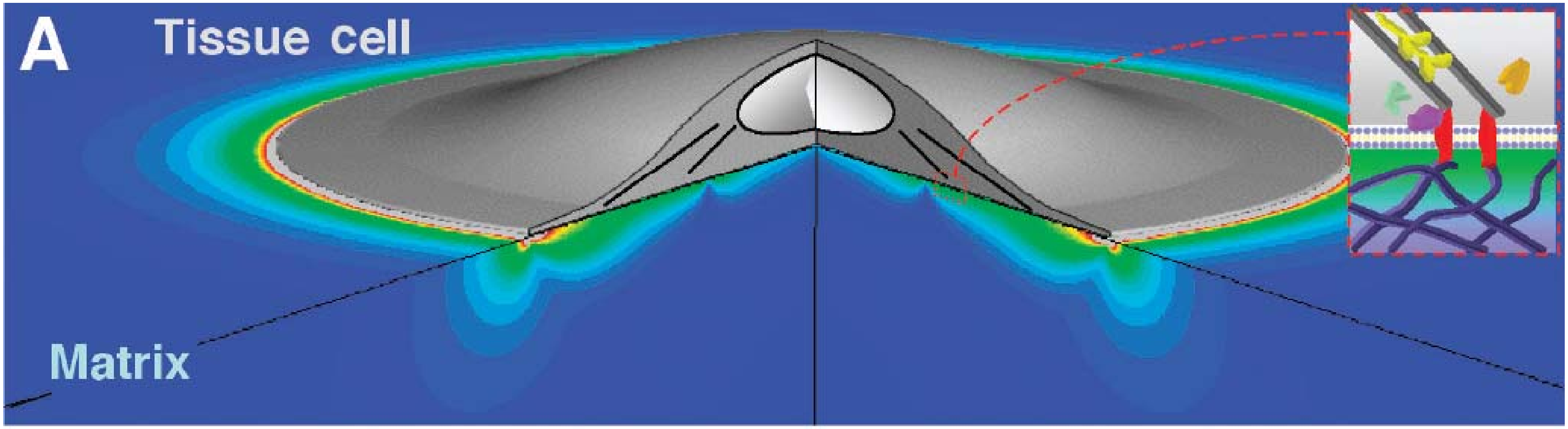
<u>Soft substrate</u> with **small spring constant** (k):
Cell can easily pull on the gel
(no need for stress fibers)



<u>Stiff substrate</u> with **larger spring constant** (k):
Cell need greater force to displace the polyacrilamide gel
(cell need power of stress fibers)

Prestress visualized in a computer model

- A rounded cell on a soft substrate exhibits a **uniform and constant prestress** from the edge (cell border) to the nucleus (cell center)
- Prestress is generated by **actin-myosin contraction** and transmitted to the substrate
- This computed strain distribution is consistent with the tensegrity model

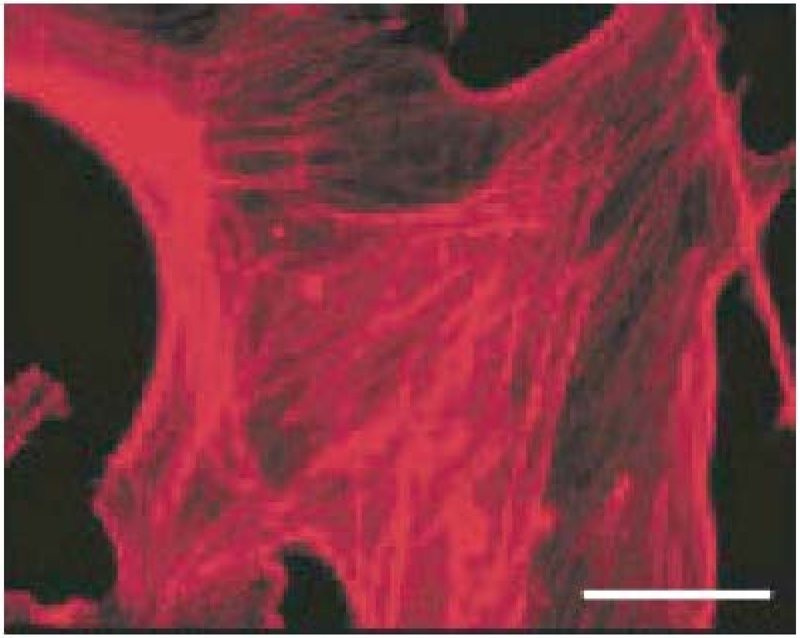


Discher et al., Science, 2005

Rearrangement of stress fibers after cyclic cell stretching

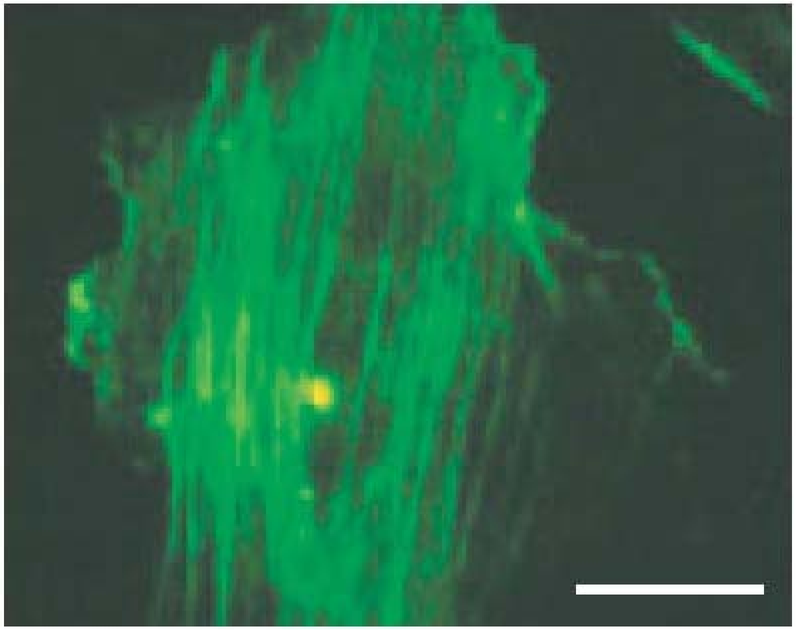
How do cells handle mechanical forces generated in organs as the heart or the blood pressure in vessels?

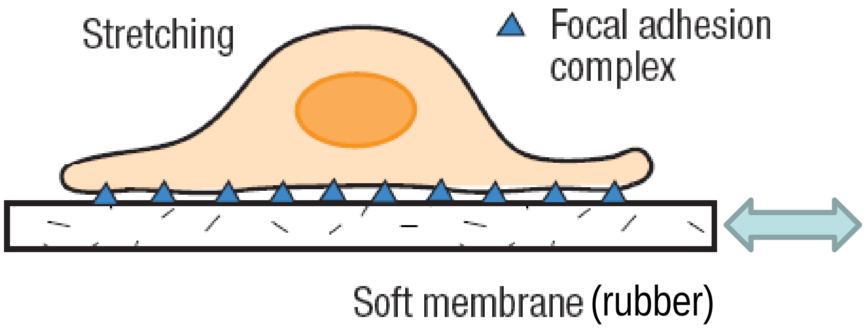
Unstretched human aortic endothelial cell: random distributed stress fibers



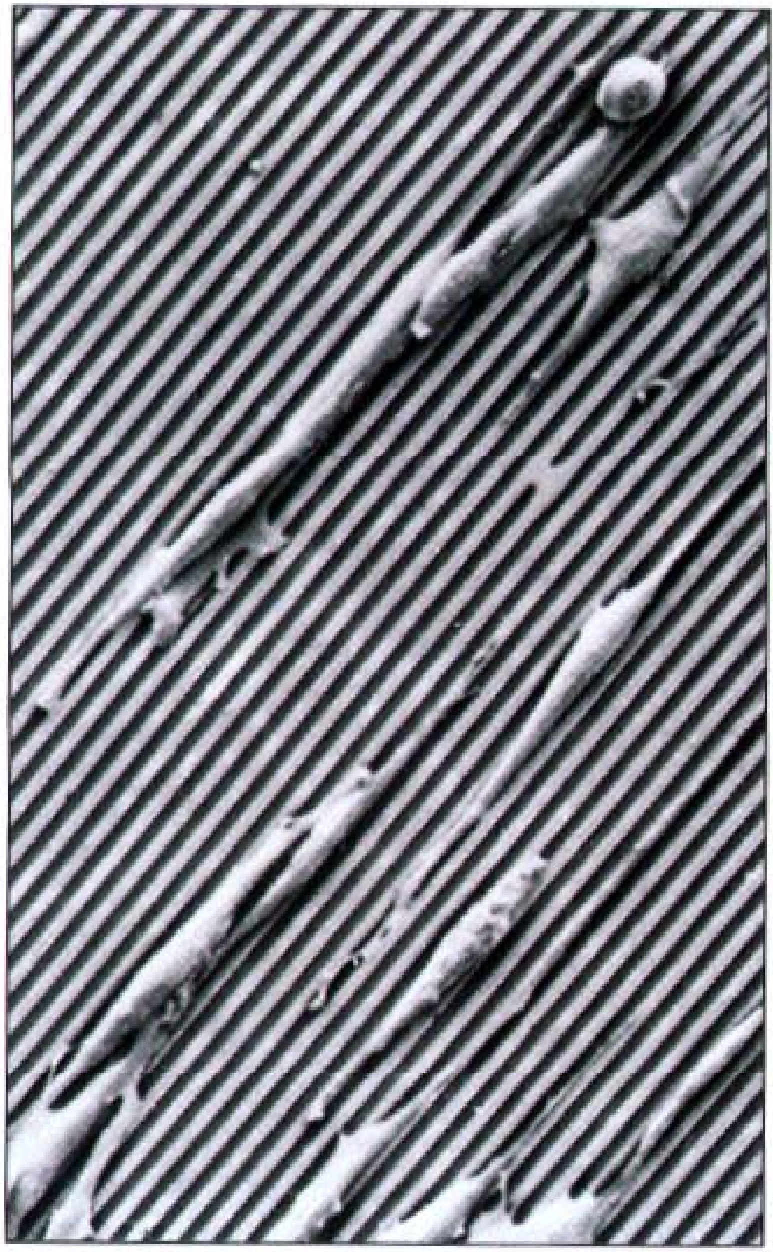
Very dynamic features of stress fibers are critical for **force sensing** and **force transduction**

After 3 hours of stretching: stress fibers are oriented into direction of stretching



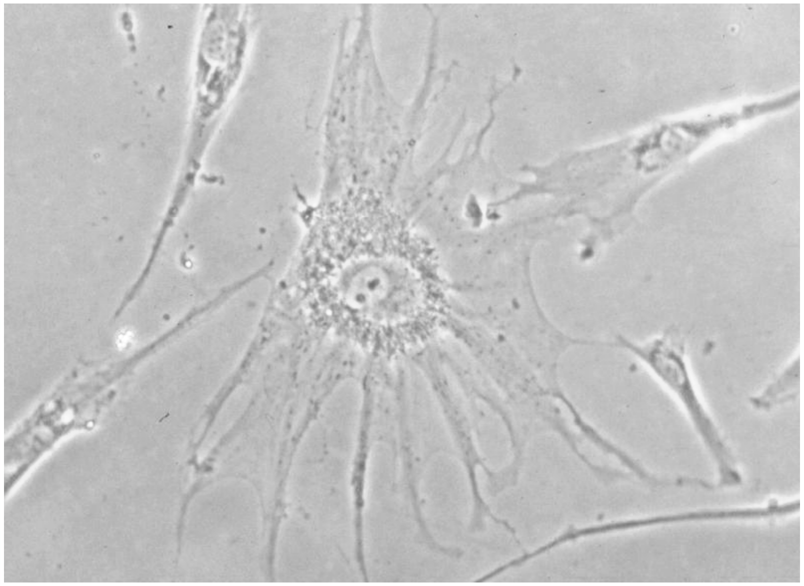


Cellular response to substrate composition



Cultured fibroblast align on a furrowed surface in the direction of the grooves

Preference of the substrate coating is obvious since growing does not occur across the furrows

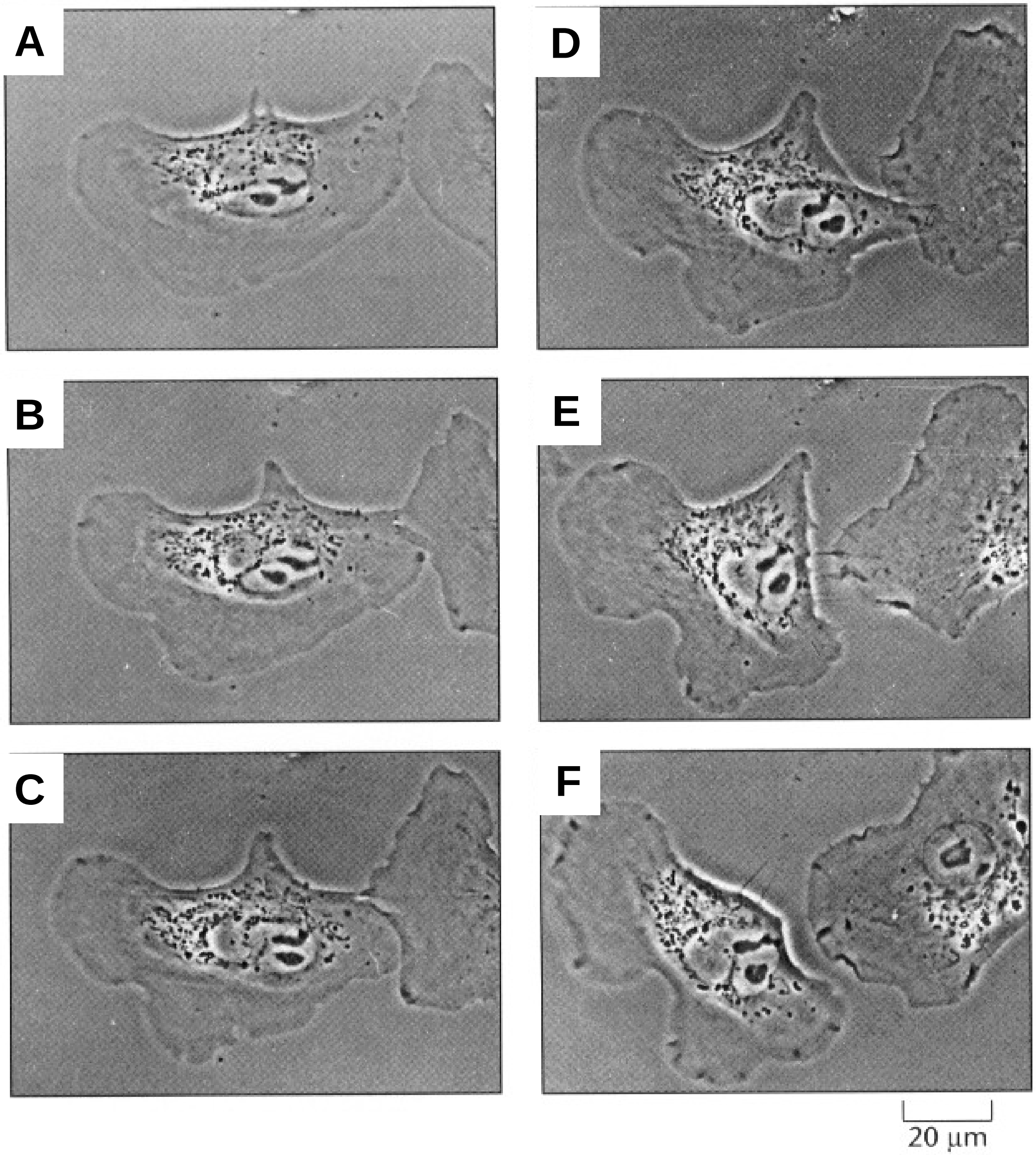


Normal fibroblast cells

Groove dimensions:
2 µm deep
3 µm wide
3 µm spaced apart

Bray, Cell Movements, 2nd Ed.

Cellular response to “cell traffic”: contact inhibition

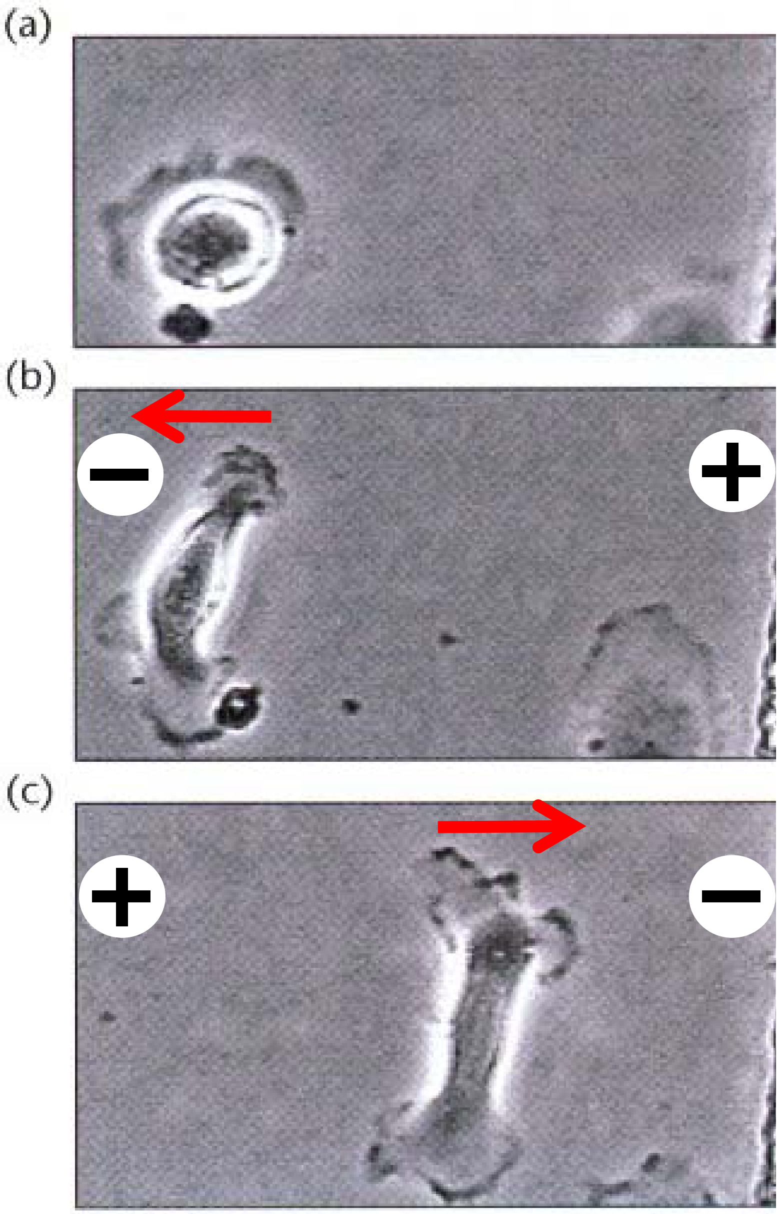


When one <u>cell collides with another</u> a phenomenon named **contact inhibition** occurs:

- At the region of contact (cell’s ruffles) a **stationary (quiet) zone** is formed in which cells seemed to form **contact by filopodia**
- <u>Ruffling now occurs in the opposite direction</u>
- Cells are moving away from each other

Bray, Cell Movements, 2nd Ed.

Cellular response to an electric field



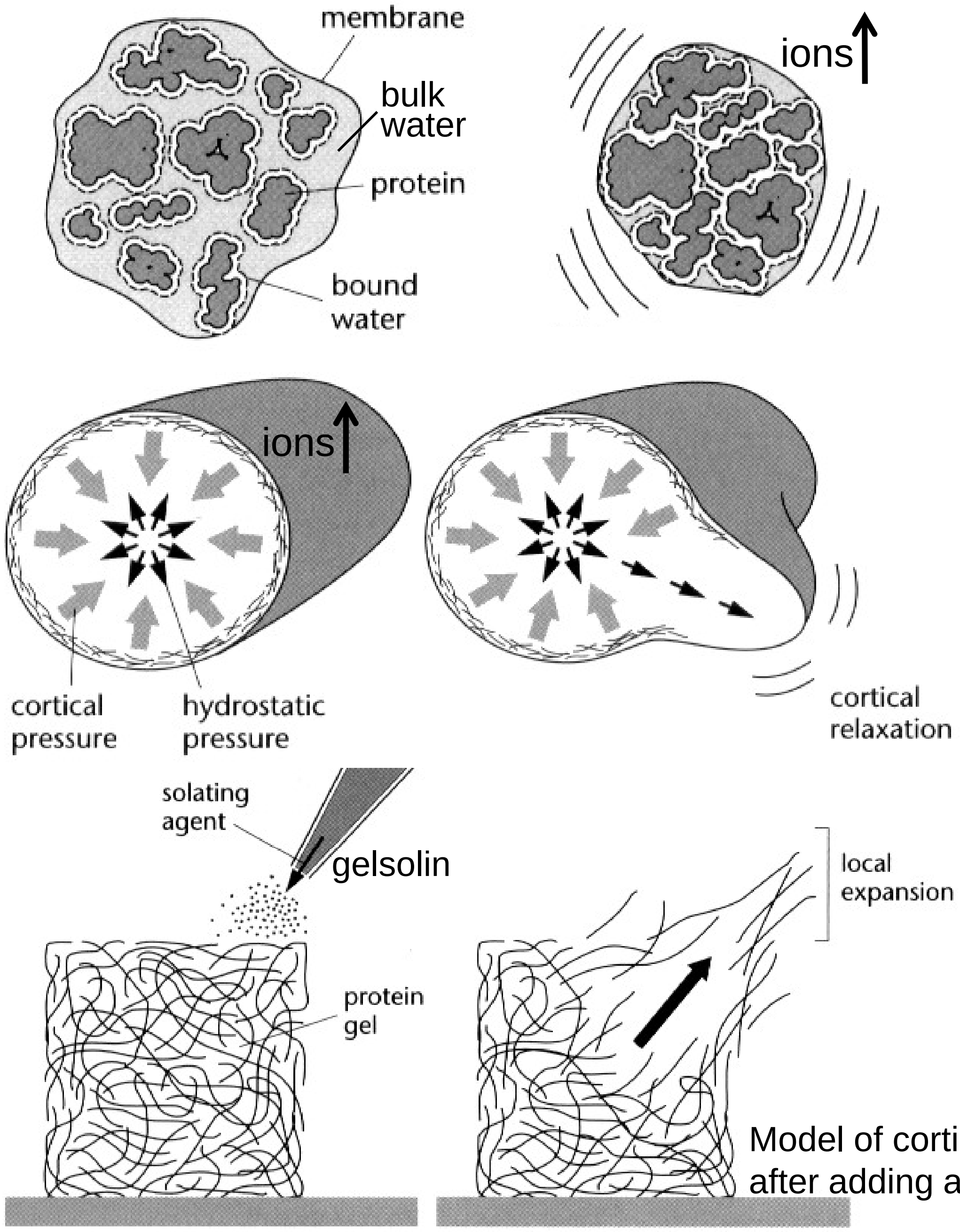
Before the field, the epithelial **cell rounded**

After 1 hour exposure to an electric field of 150 mV/mm **cell becomes elongated** (90° to the field) and starts to move to the minus-pole

Switching the polarity of the field results in a movement to the preferred minus-pole (the cathode)

Bray, Cell Movements, 2nd Ed.

Internal cellular hydrostatic pressure as a cytomechanical factor

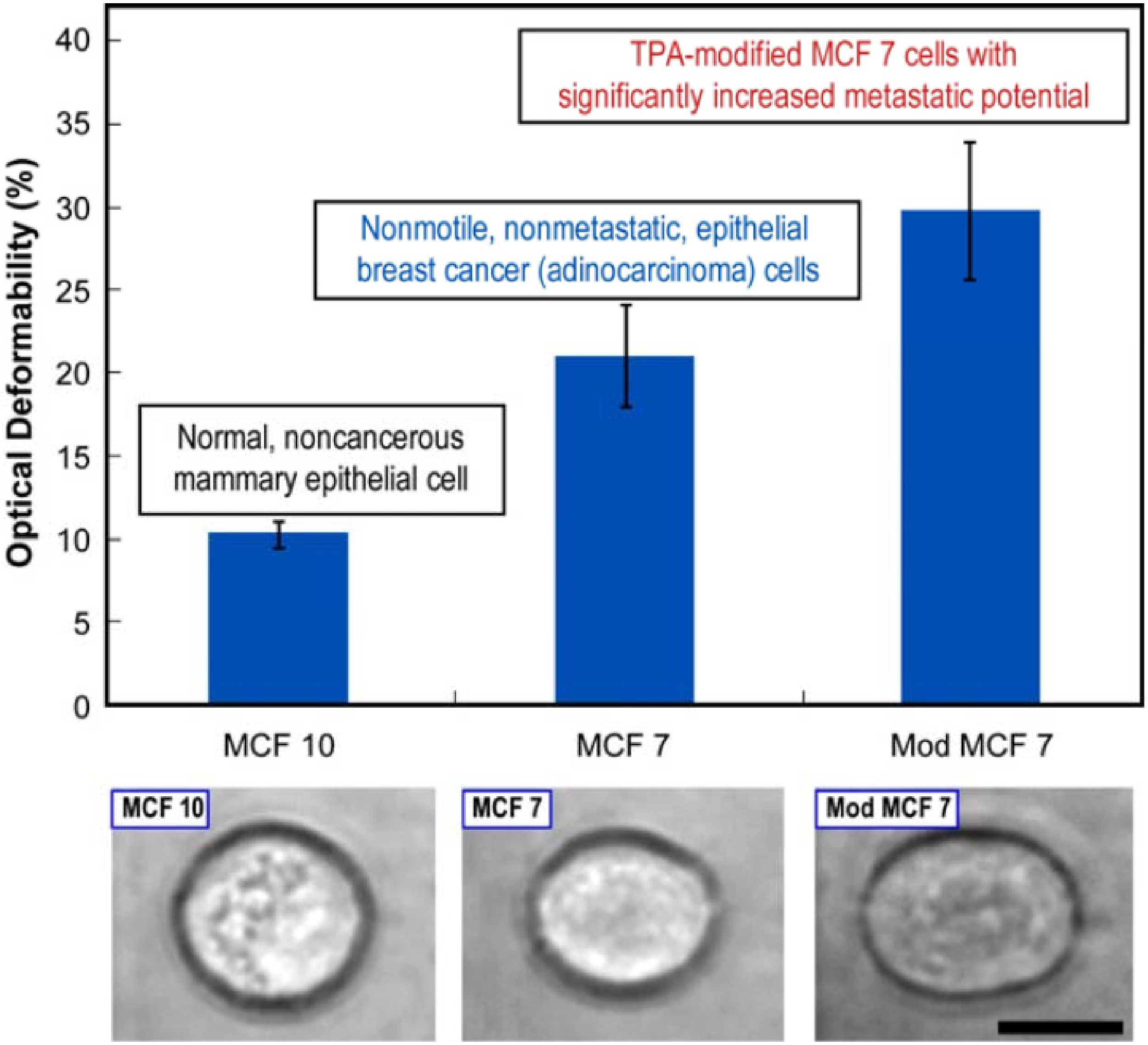


- Cell contains **bulk water** (free water) and **bound water** (bound by proteins)
- Under hyperosmotic conditions, only the bulk water will be lost
- On the other hand, the **high ionic content in the cell** might lead to a **constant flow of water inside** the cell
- To avoid this, the cell develop and maintains a constant hydrostatic pressure to stop water flowing inside
- Some plant cells and bacteria can develop internal pressures up to 10^6Pa
- Relaxation of cortical tension might result in redirecting of internal pressure that may drive cell membrane extension
- Water ingress might also **swell the cytoskeleton** leading to **increased osmotic forces**
- How much does hydrostatic pressure contribute to cell mechanics?

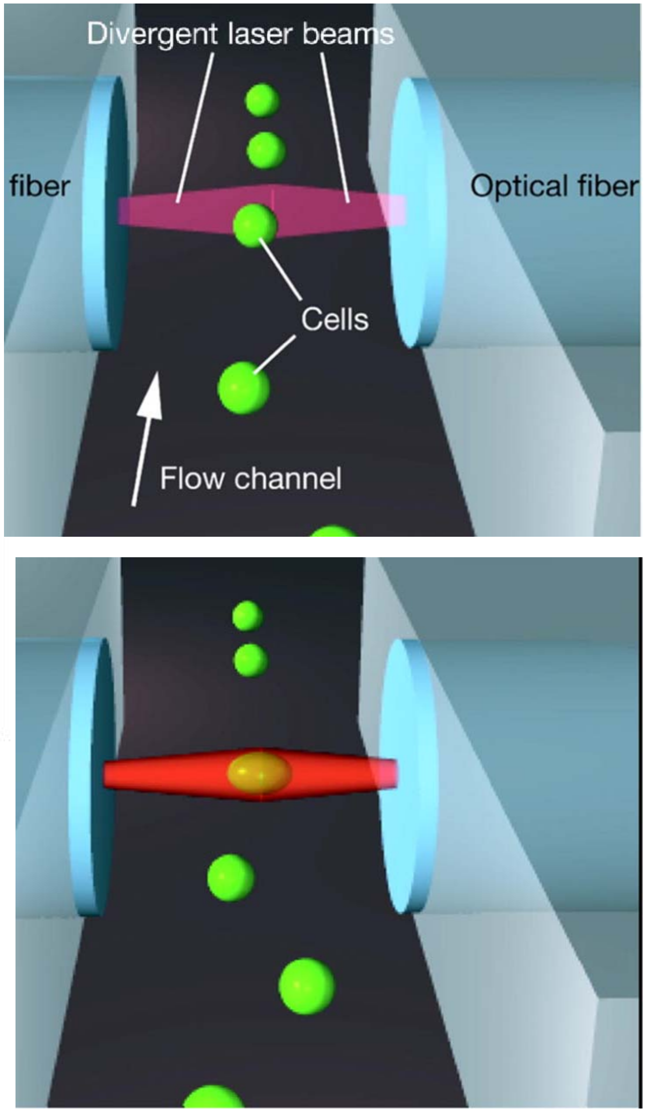
Model of cortical relaxation (based on osmotic forces)
after adding an actin depolymerizing factor (gelsolin)

Biomechanics and biophysics of cancer cells

Deformability of breast cancer cell is **increased** (based on f-actin reduction) that also increases metastatic potential



Microfluidic optical stretcher: trapping and stretching cells with two laser beams



Guck et al., Biophys. J, 2005

TPA is a type of phorbol ester to treat leukemia or lymphoma cancer

Invasion of Panc-1 epithelial tumor cells in the human pancreas by the bioactive lipid SPC

The substance SPC decreases the IF network which in turn increases metastatic potential

Structure

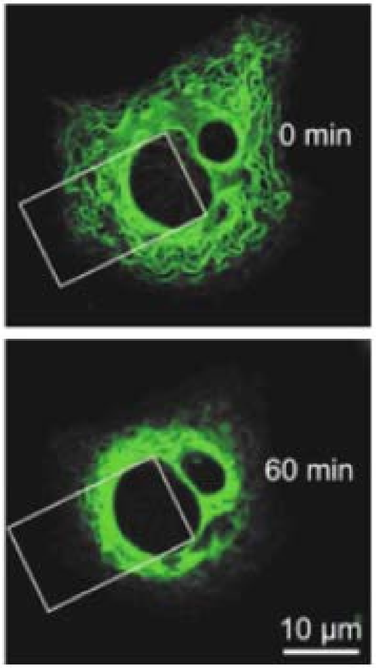
Dramatic reorganization of the intermediate filament (keratin) network in the perinuclear region

Property

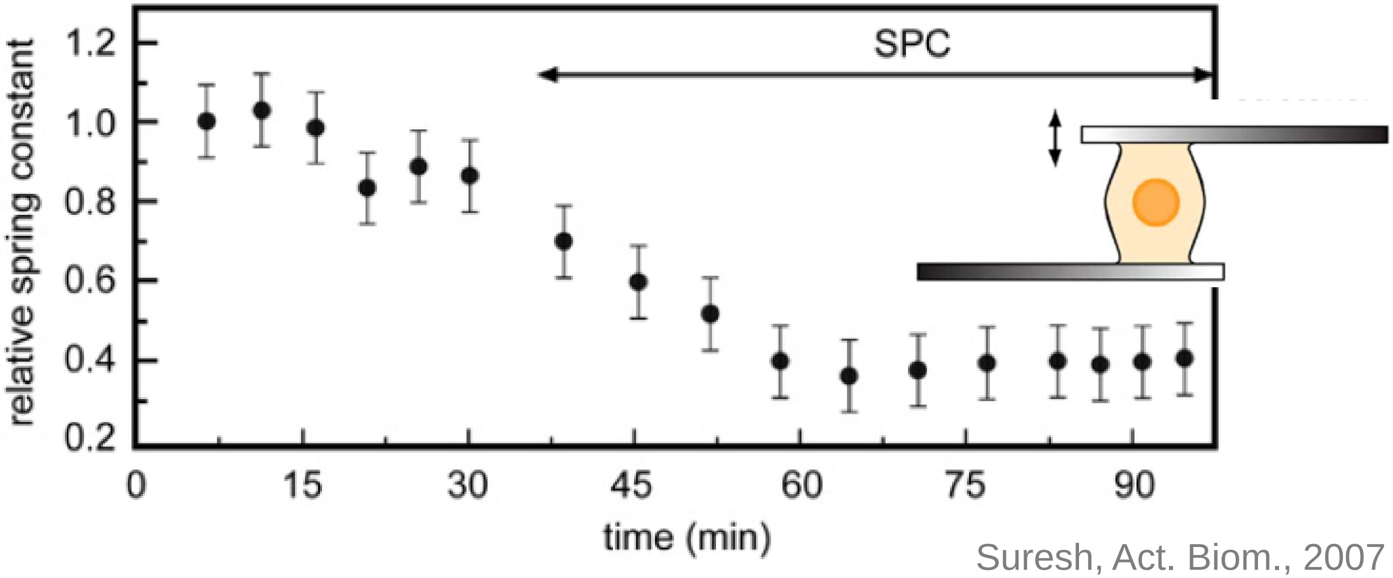
More than three-fold reduction in Panc-1 cell elastic modulus and increase in hysteretic energy dissipation during cell deformation

Disease

Greater motility of tumor cells through size-limiting pores and metastatic invasion?



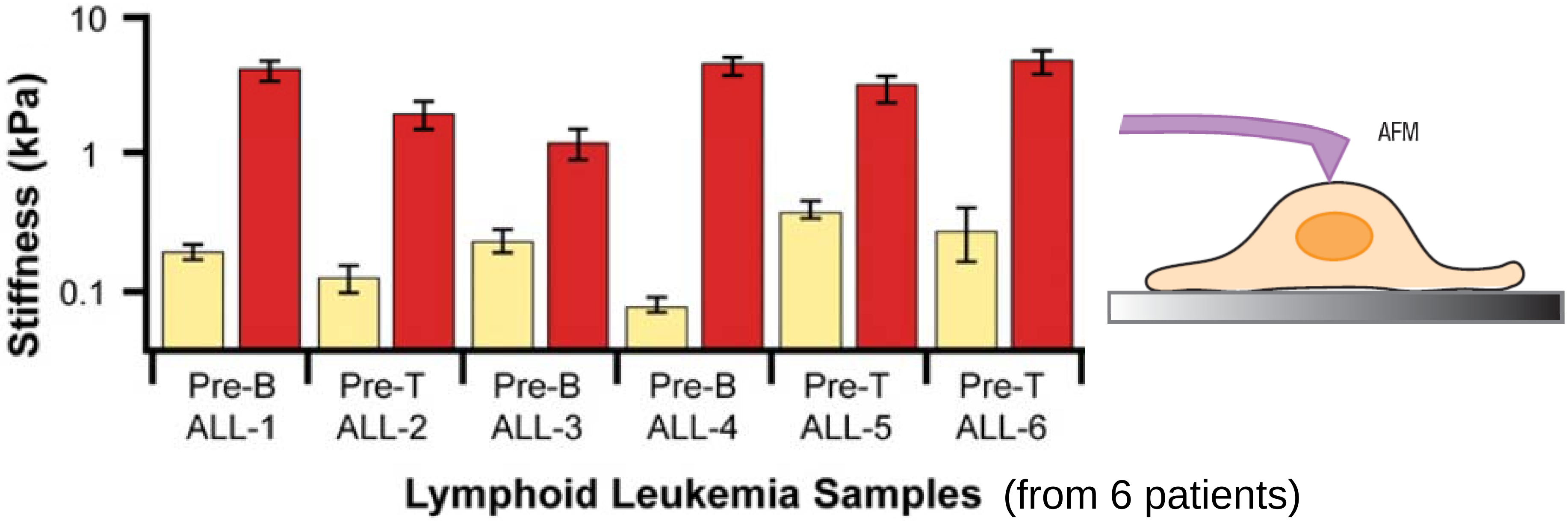
(High SPC levels found in blood in patients with pancreatic tumors)



Suresh, Act. Biom., 2007

Effects of chemotherapy on elastic properties of cancer cells

- Chemotherapy to treat leukemia leads to cell stiffening that might explain observed vascular compilations (atherosclerosis etc.)
- Parallel treatment with cytochalasin D to weaken the actin-network helped to make the dead cells softer for better dead-cell recycling (not shown)



Yellow bars: blood cells **before** chemotherapy

Red bars: dead cells **after** chemotherapy (drug: daunorubicin)