20.GEM GEM4 Summer School: Cell and Molecular Biomechanics in Medicine: Cancer
Summer 2007

A few basics of mechanics in light of cell biology

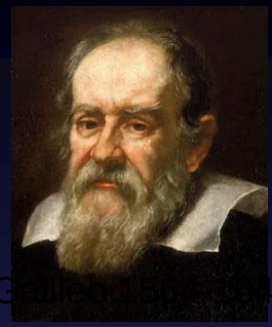
Taher Saif
Mechanical Science and Engineering

Outline

- Mechanics matters (observations)
- A few basics of mechanics
- Link between mechanics and cell behavior

Notions of mechanics

Newton 1643 - 1727

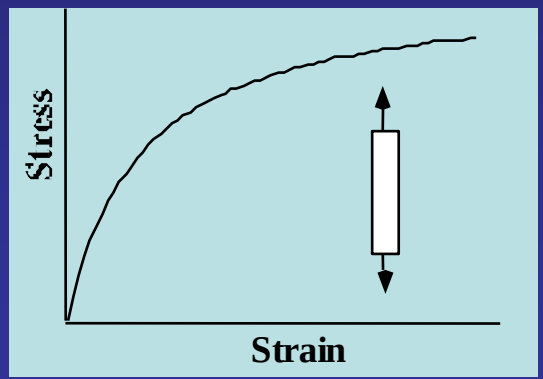


Galileo 1564 - 1642

Force

Motion

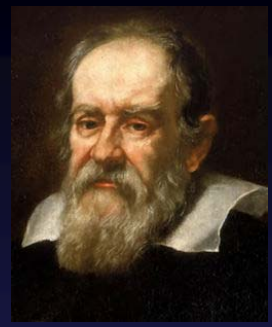
Stiffness



Energy

Deformation

Notions of mechanics



Force

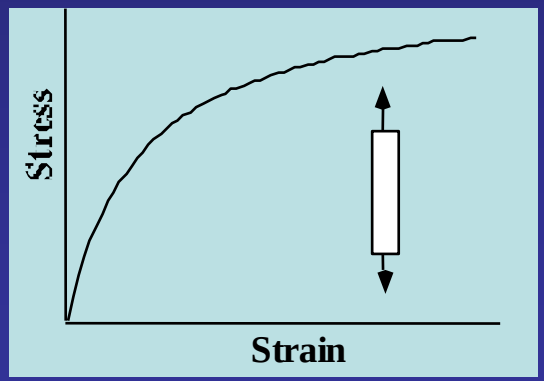
Courtesy of NASA.

Motion

Courtesy of USGS.

Courtesy of Oak Ridge National Lab.

Flow



Energy

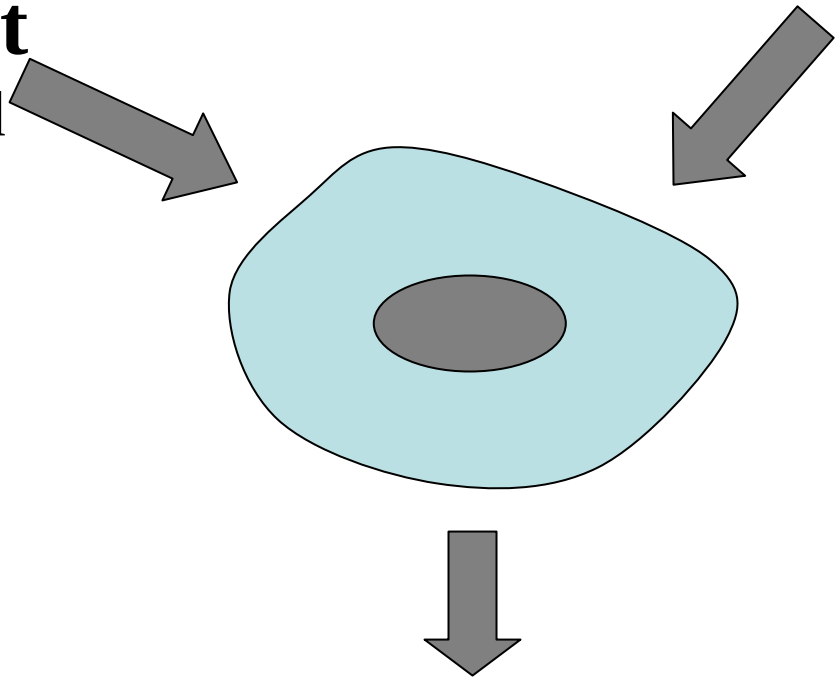
Courtesy of USGS.

Deformation

Recent discoveries on cell behavior

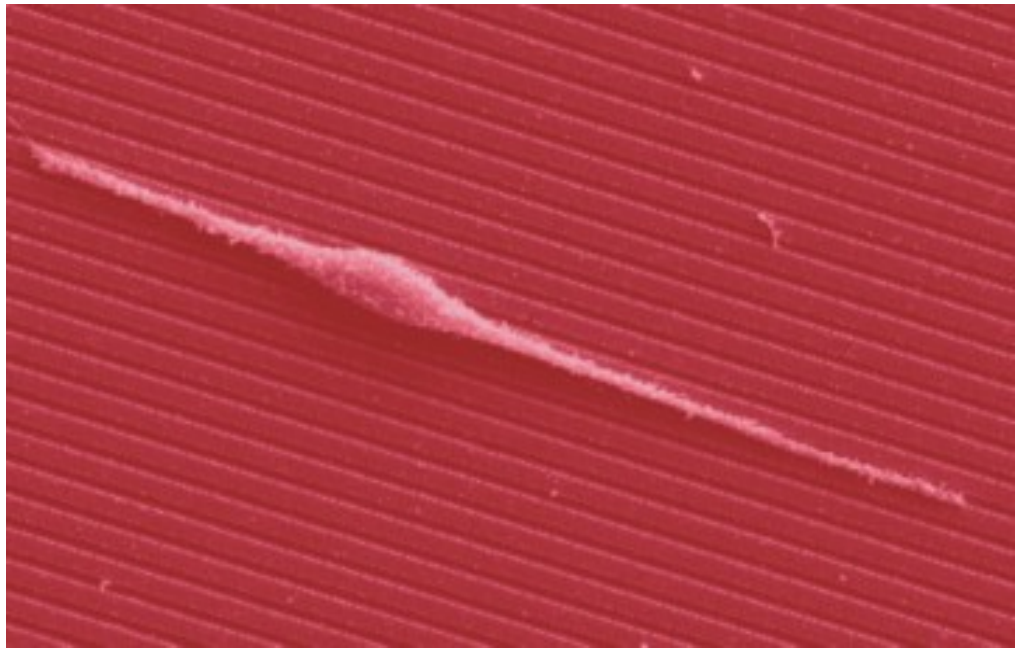
Mechanical environment
(Intracellular and extra-cellular)

Bio-chemical stimuli



Cell functionality
(Growth, Differentiation, Apoptosis, Signaling)

Sensing topography



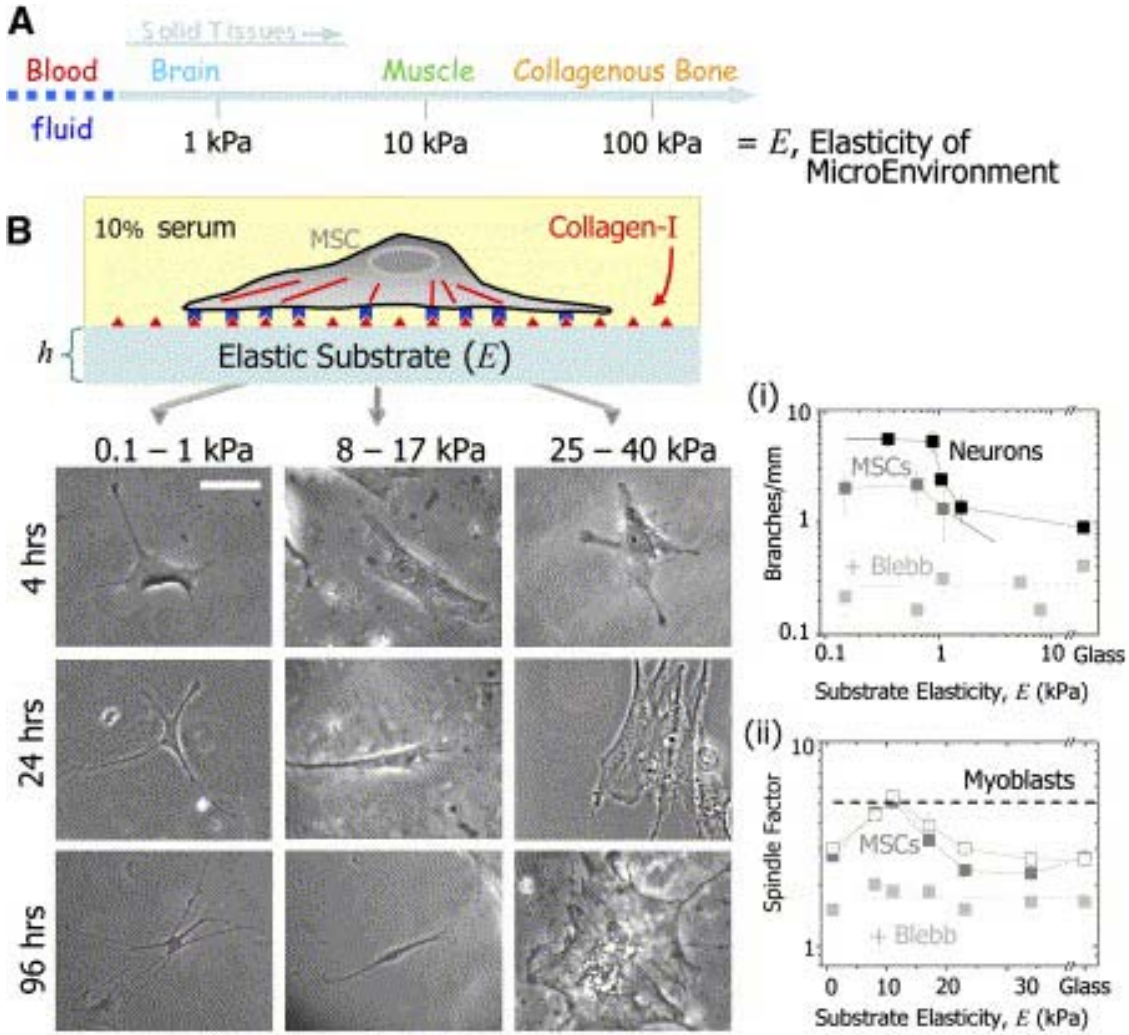
Melanocyte cell on micron structured surface
R. Kemkemer and S. Jungbauer
Max Planck Institute, Germany

Stem cell and mechanics

Image removed due to copyright restriction.

Outline of a human body; “stem cells differentiate in soft environments mimicked with polymer gels.”

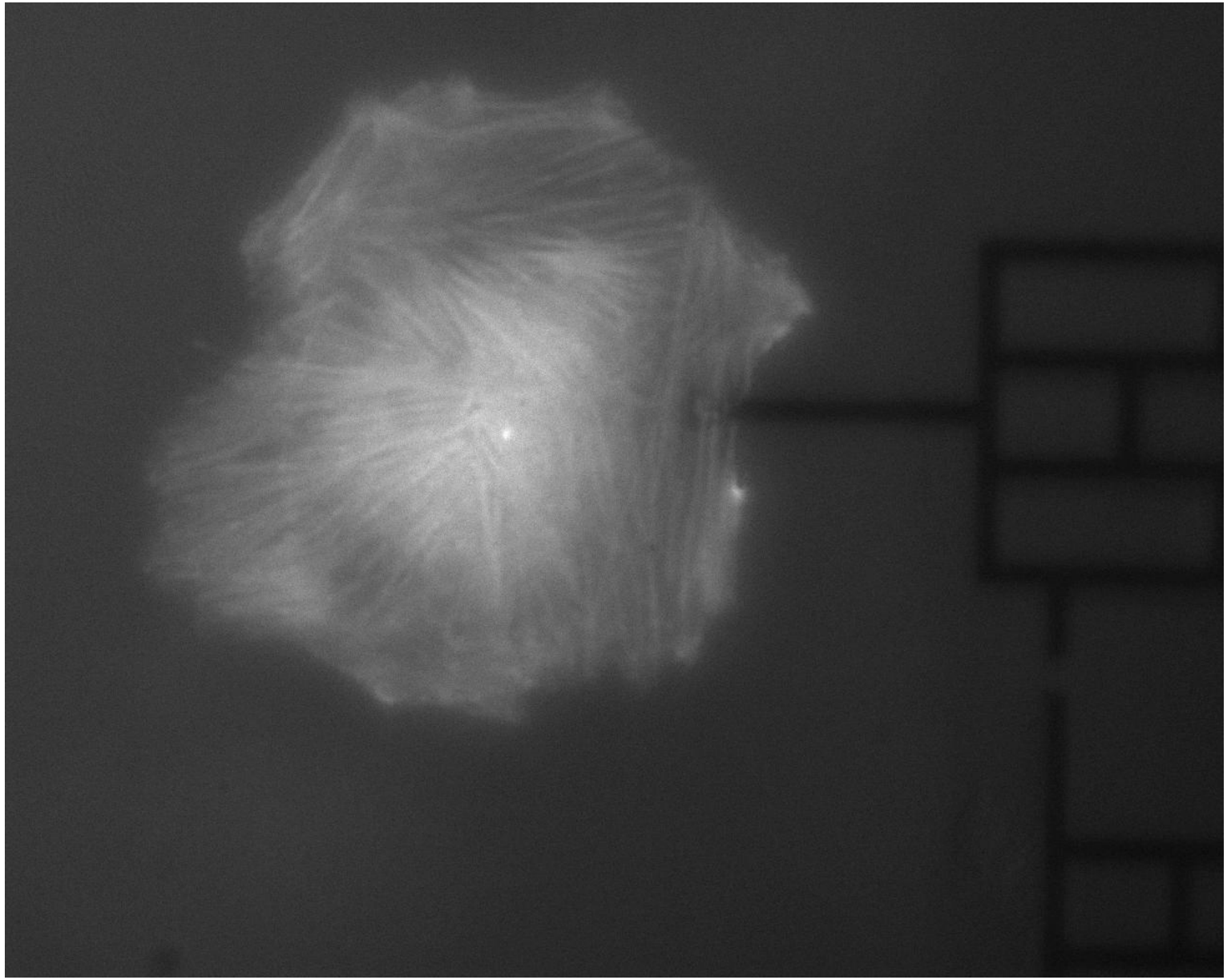
Stem Cells' differentiation is influenced by substrate stiffness



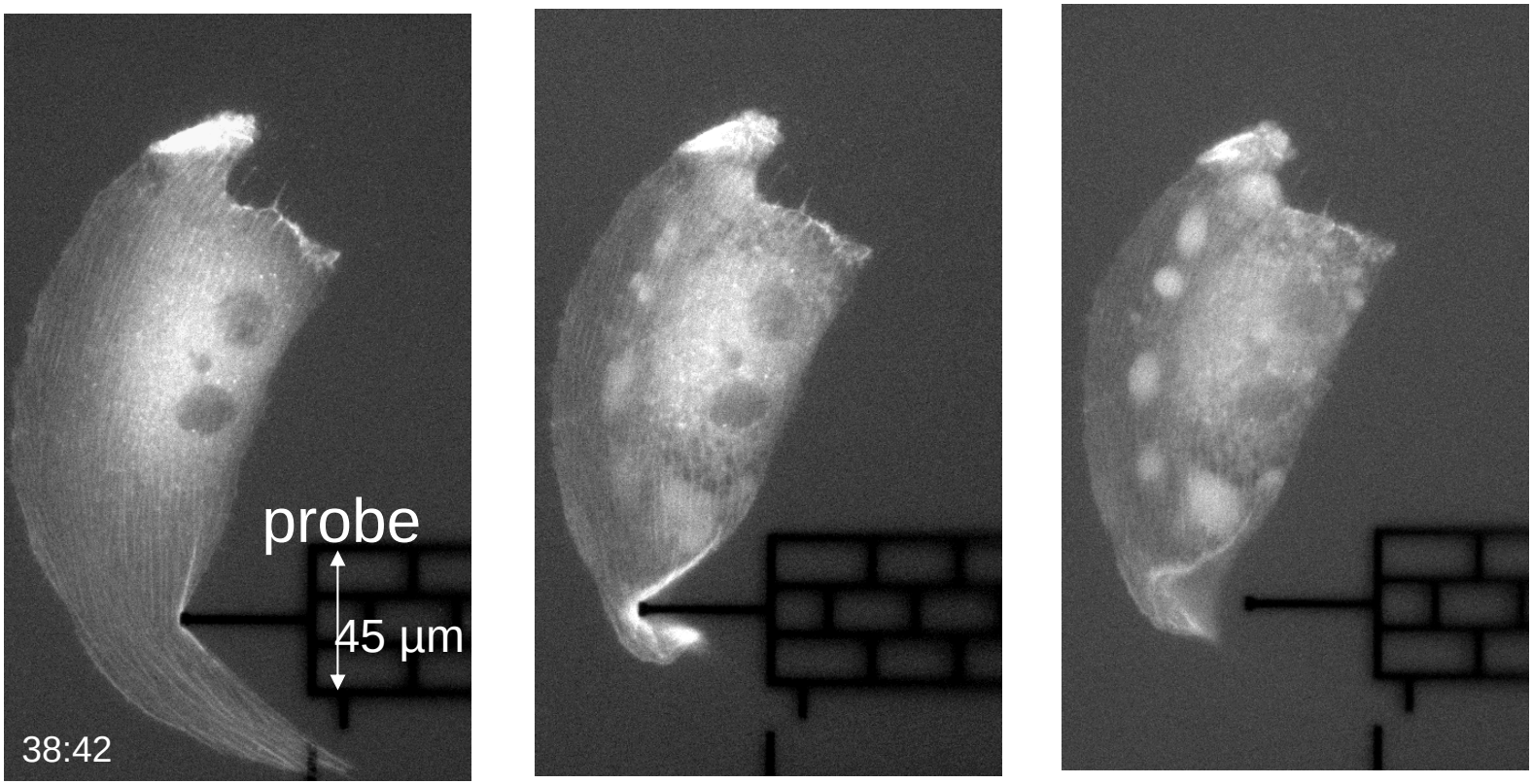
Neuron **Myoblast** **Osteoblast**

in *CELL* Aug.24, 2006
Engler, Sen, Sweeney, & Dennis Discher

Actin remodeling (cell signaling) due to mechanical probing



Yang and Saif, *Acta Biomaterialia*, Vol 3,(1), p77-87, 2007.



Yang and Saif, *Acta Biomaterialia*, Vol 3,(1), p77-87, 2007.

Actin aggregation during ischemic attack

Image removed due to copyright restrictions.

Please see figure 5(C) in Ashworth, Sharon et al. "ADF/cofilin Mediates Actin Cytoskeletal Alterations in LLC-PK Cells during ATP Depletion." *Am J Physiol Renal Physiol* 284 (2003): F852.

Porcine kidney cells

Ashworth et al. Am J. Physiol Renal Physiol 284: F852, 2003.

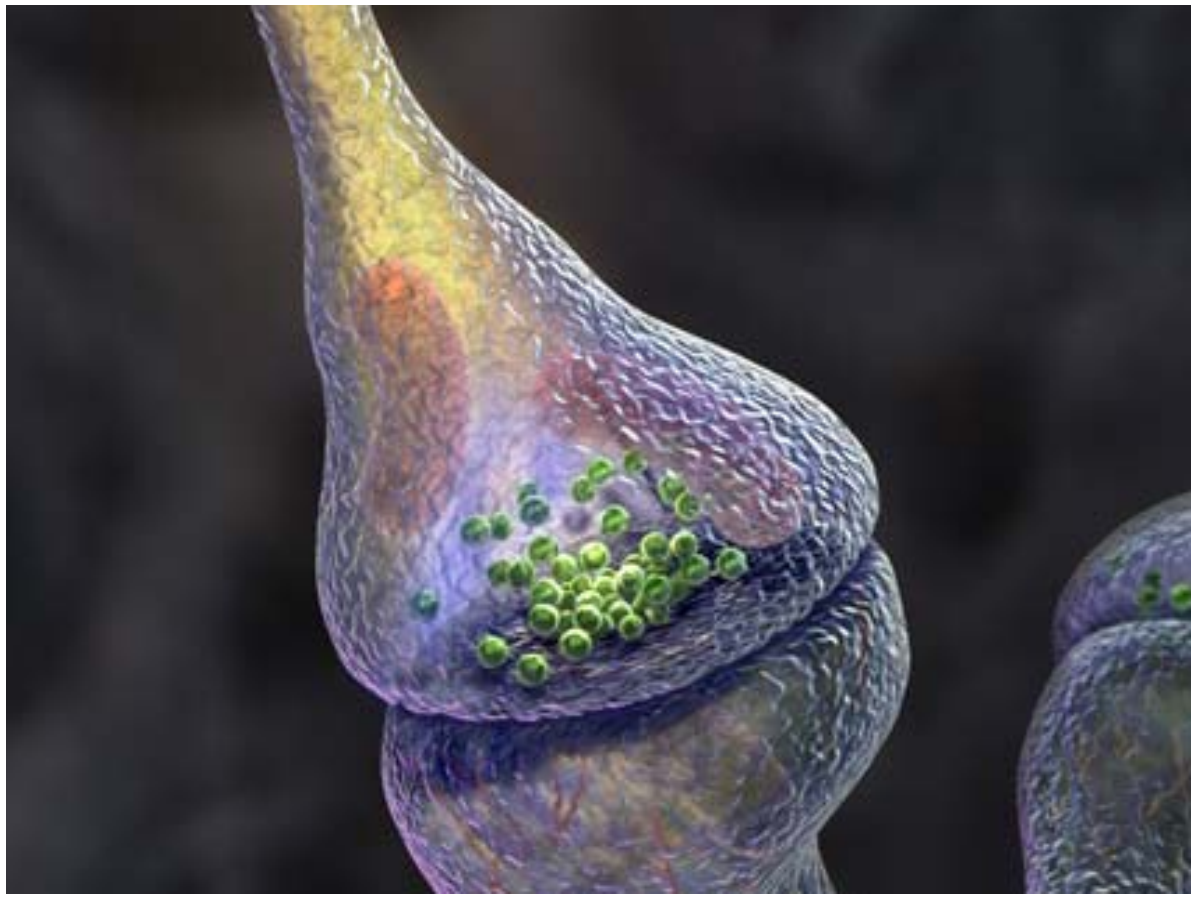
Memory and mechanics

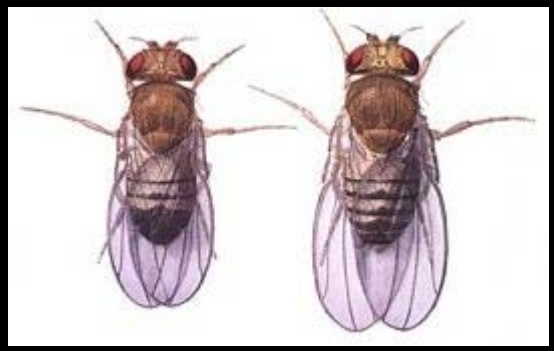
Akira Chiba and Taher Saif

Mechanical tension in axon is essential for neurotransmission and hence learning and memory

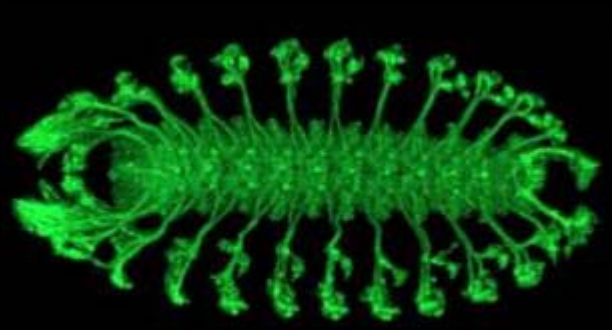
Image removed due to copyright restrictions.

2D illustration of a synapse.



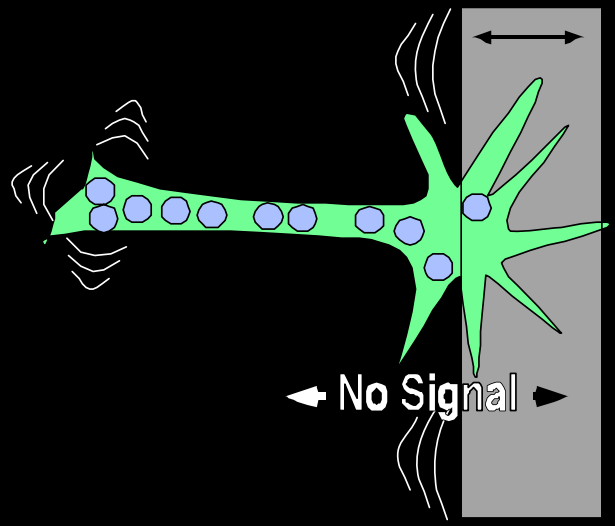


Courtesy NASA.

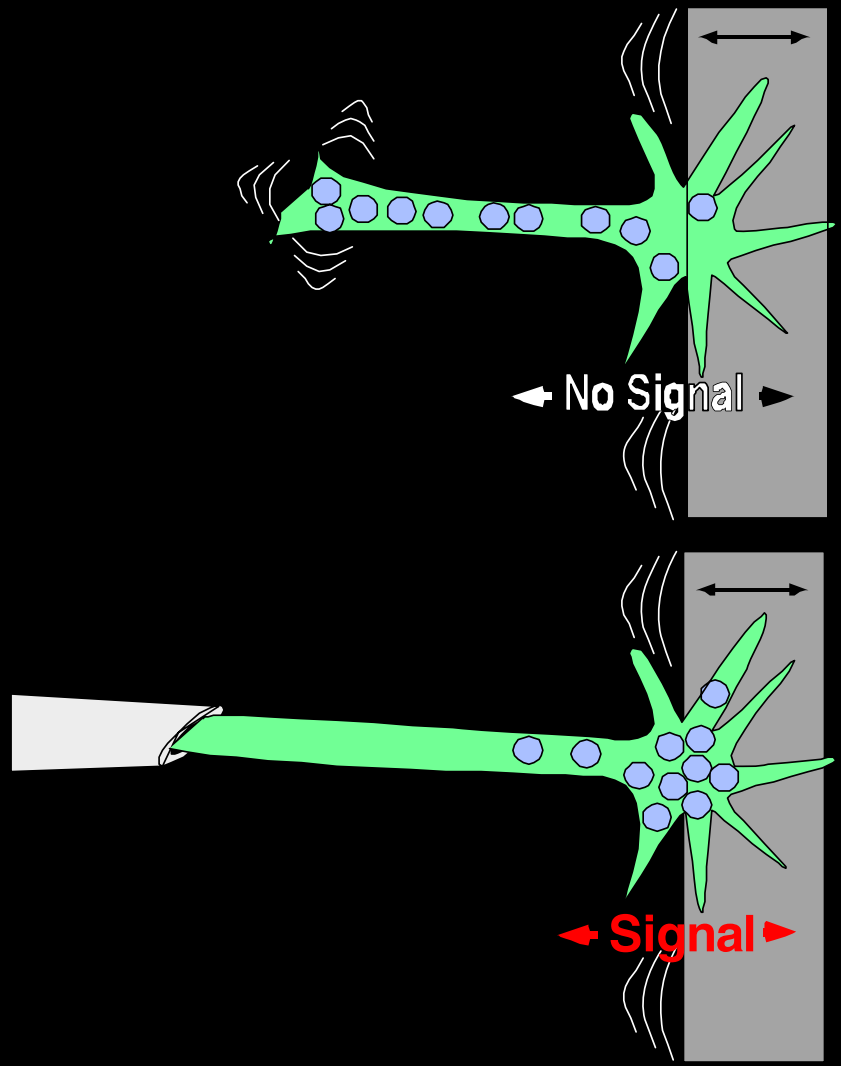


Courtesy NIH.

Drosophila embryo


No Signal

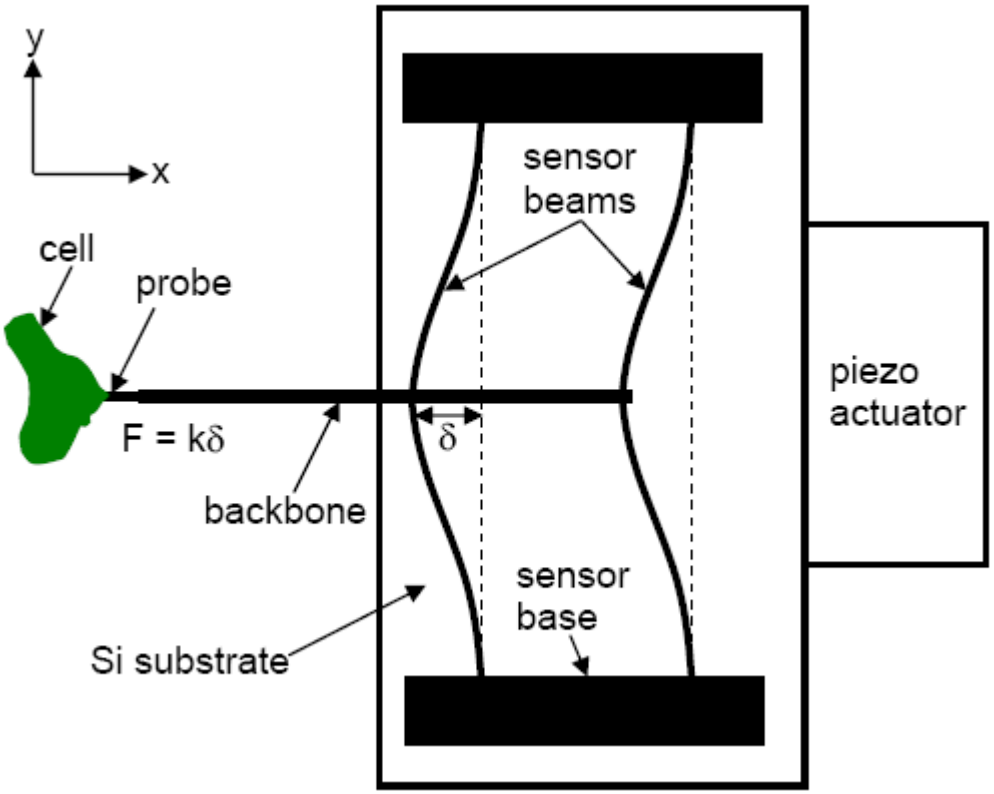
Mechanical Tension is Required for Normal Synaptic Function

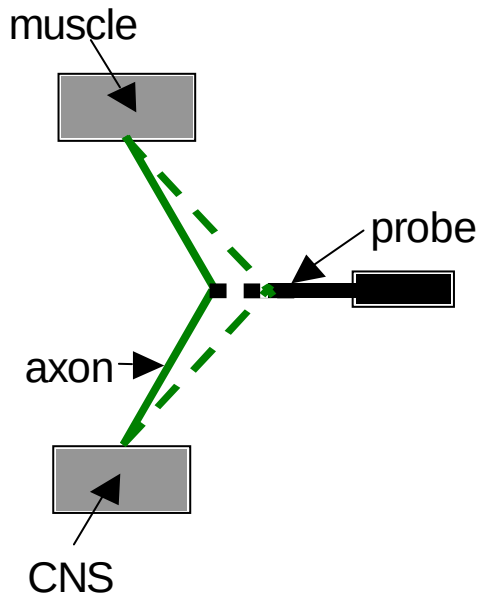


Hypothesis:

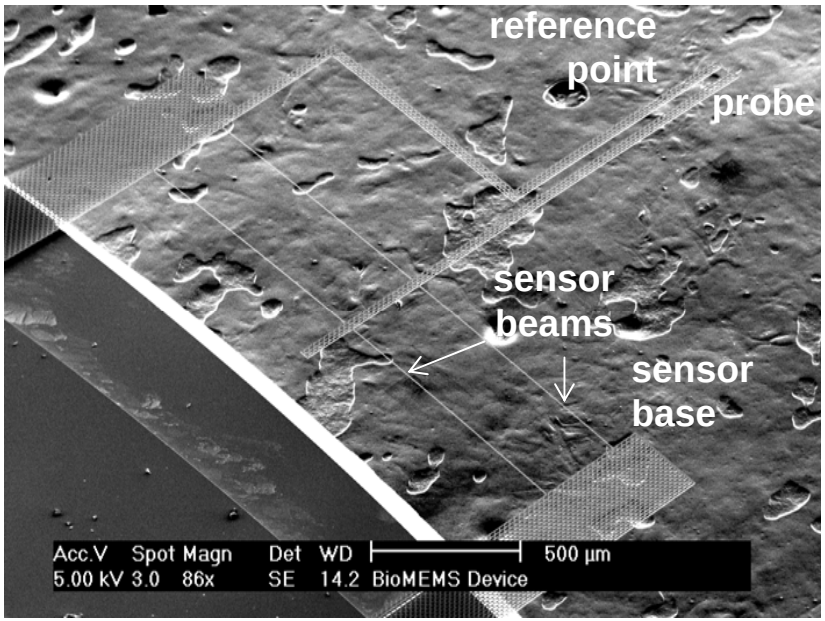
Axons must be under tension for neuro transmission.

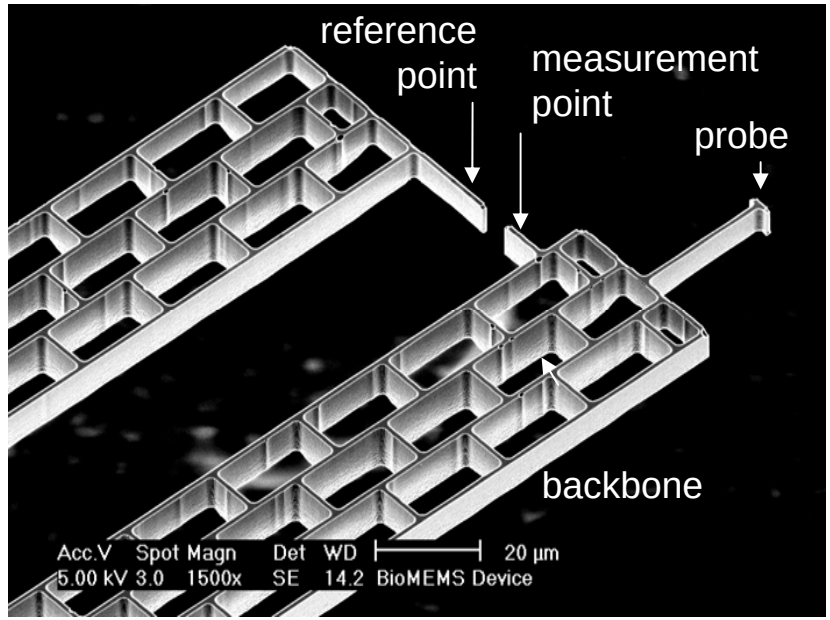
1-component micro force sensor



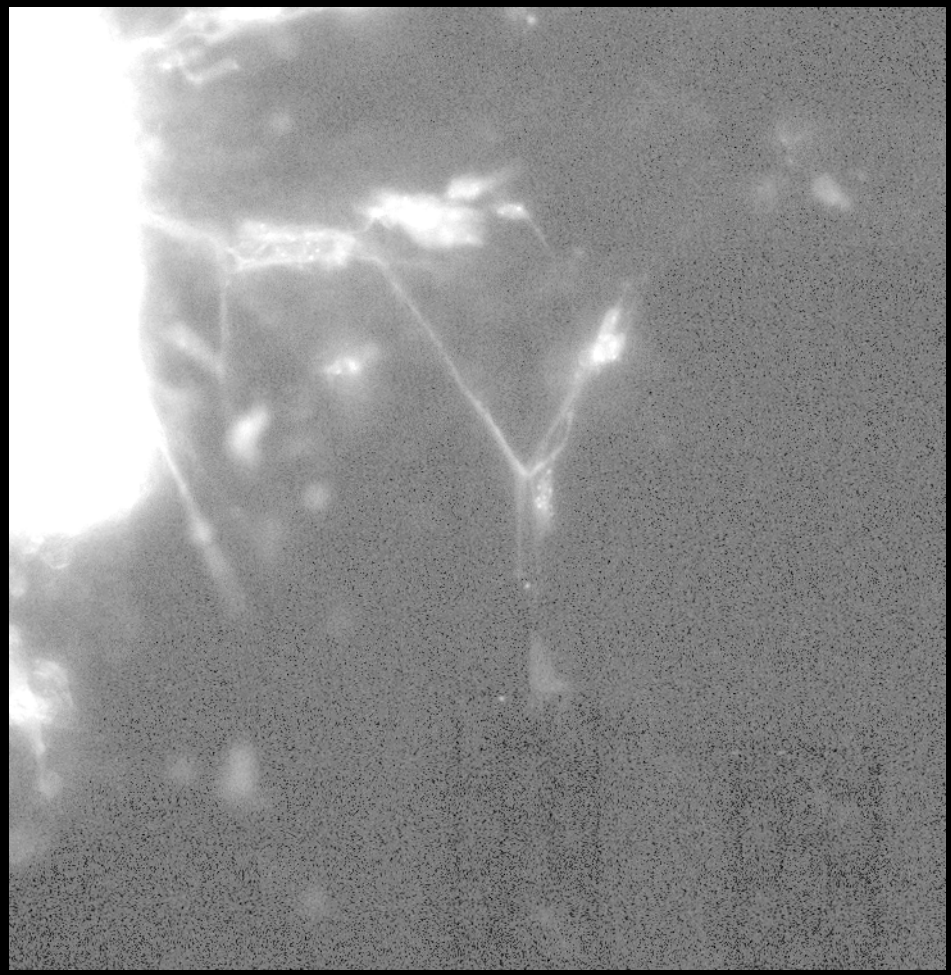


SEM of Micro force sensor



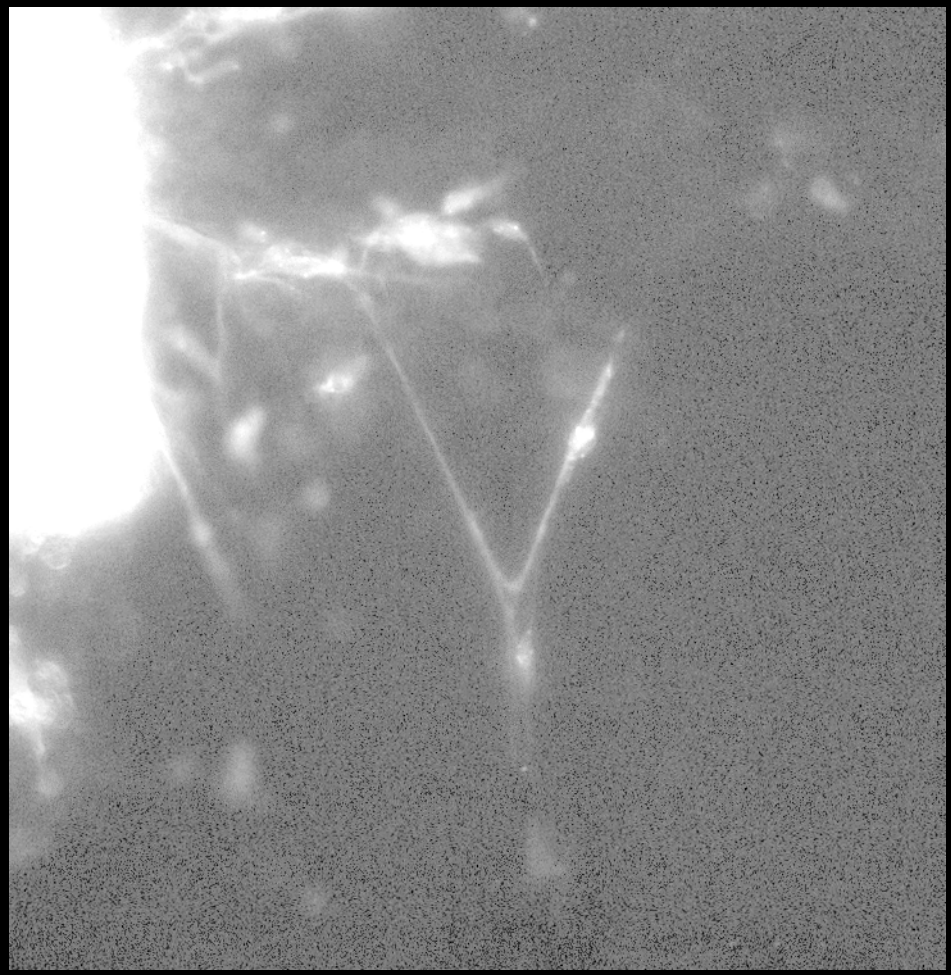


sensor beams: 2 mm x 1 µm x 10 µm,
Spring constant: k ~ 4 nN/µm, force resolution: 0.5 nN



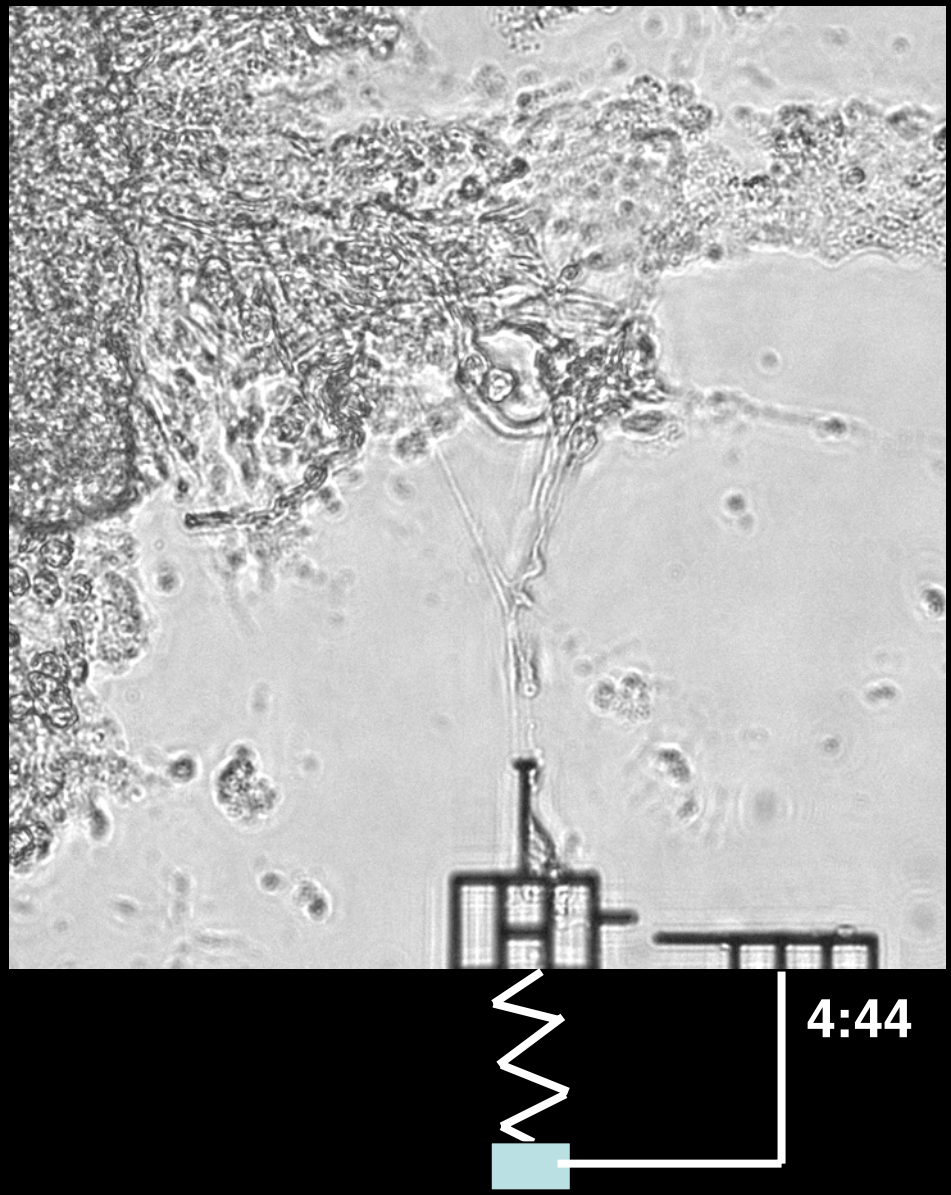
2:28

3:15

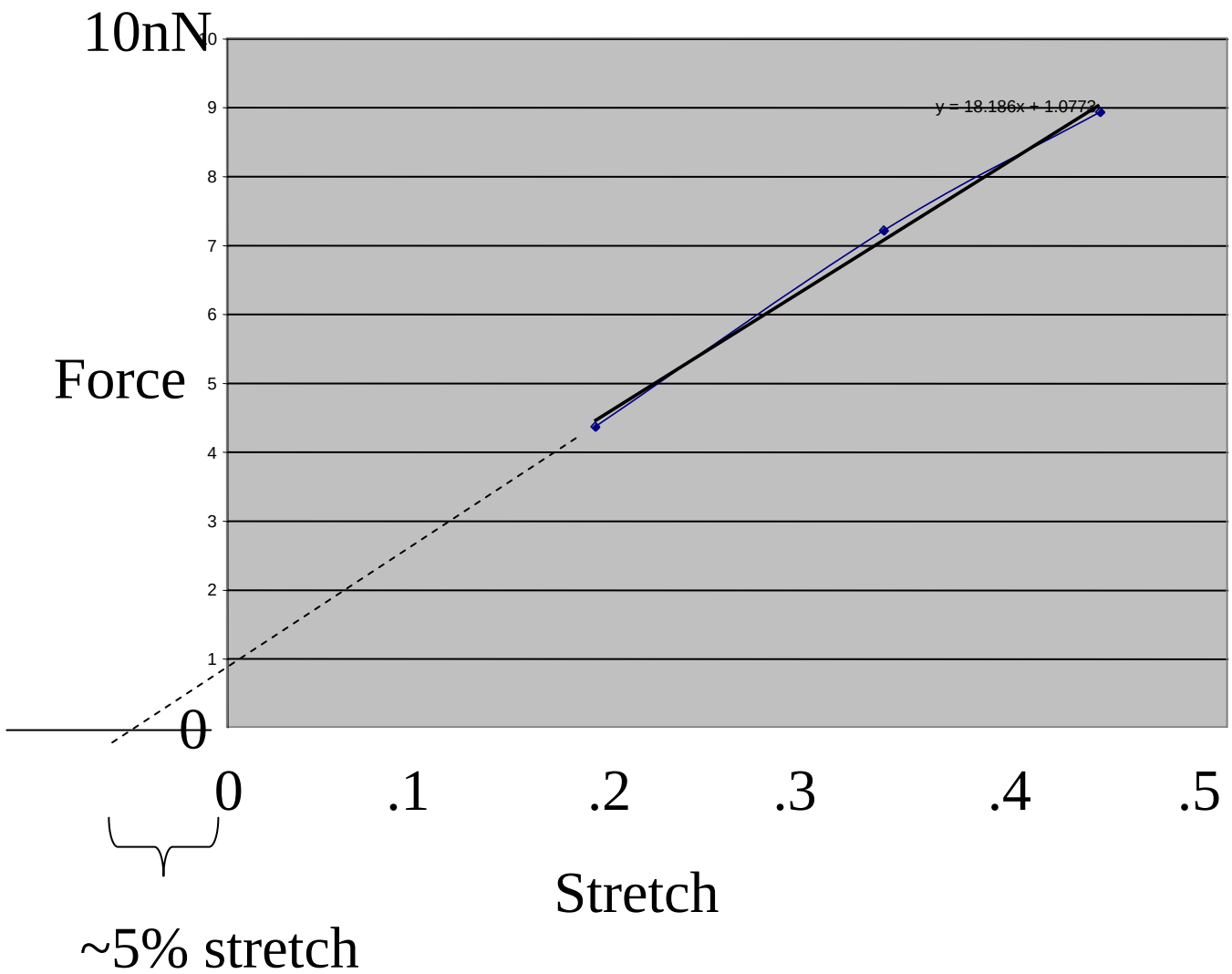


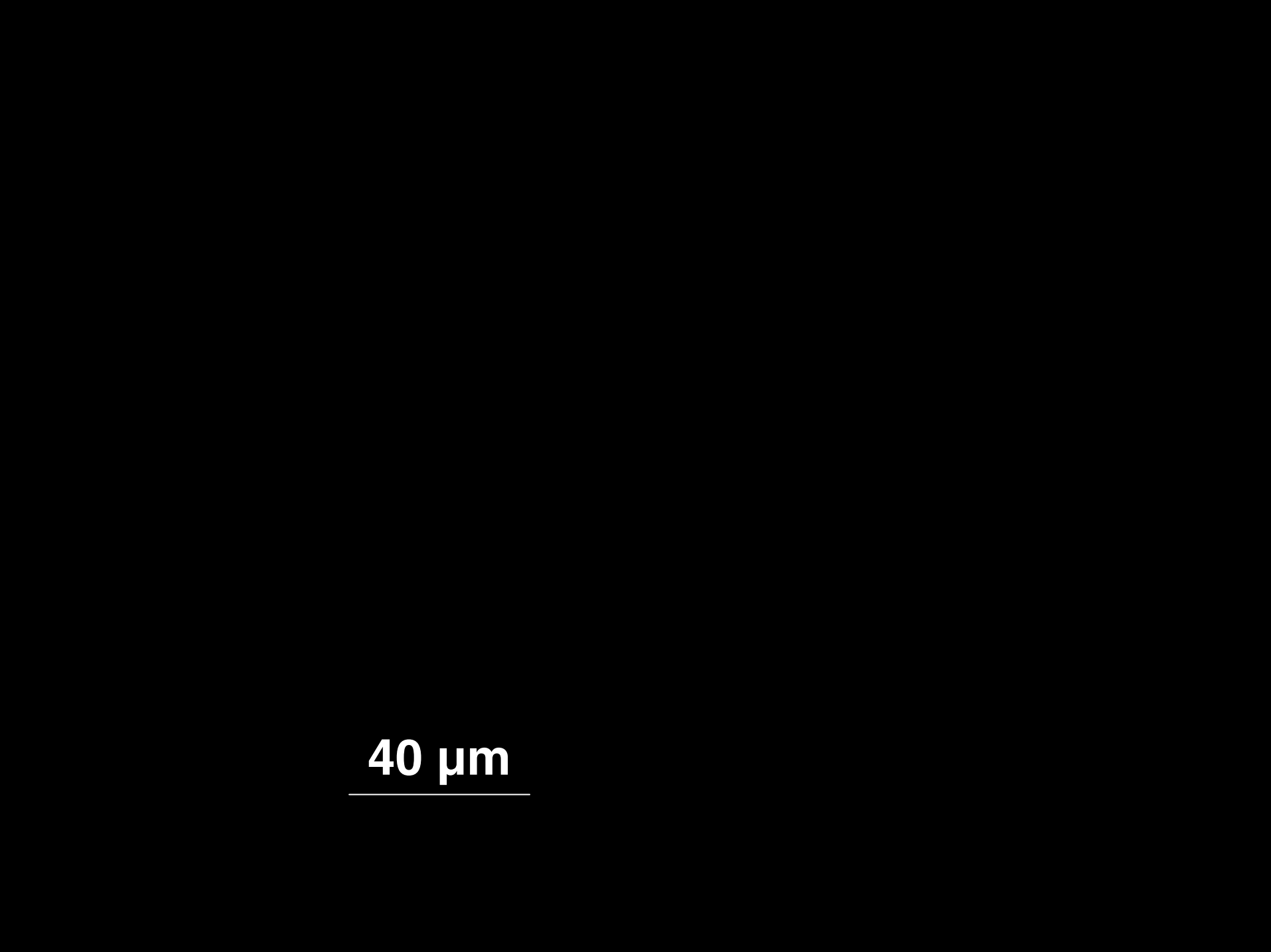
4:07

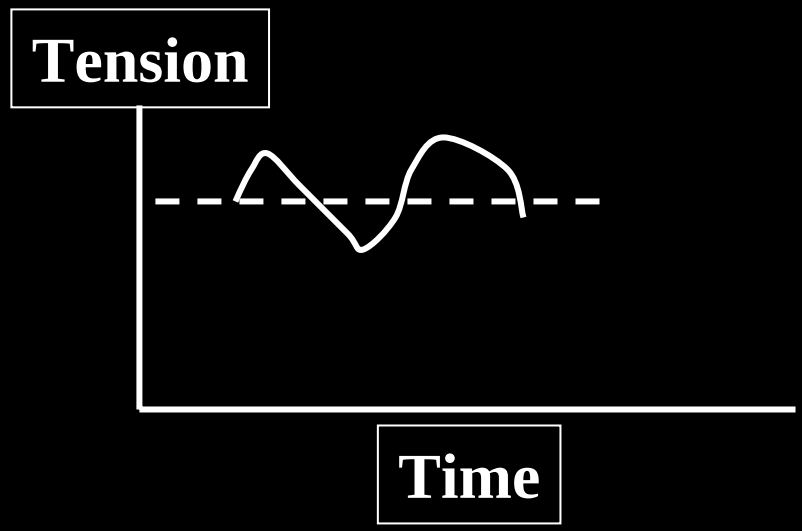
Phase Contrast



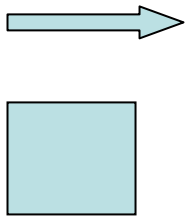
Rest tension in axon

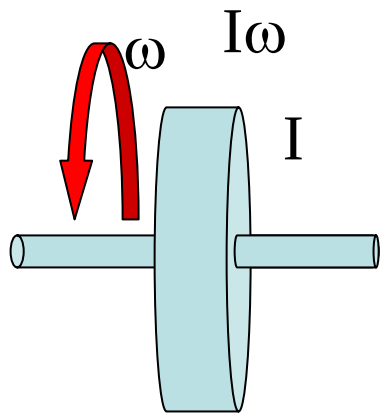



40 µm


Tension
Time

The familiar basics of mechanics:



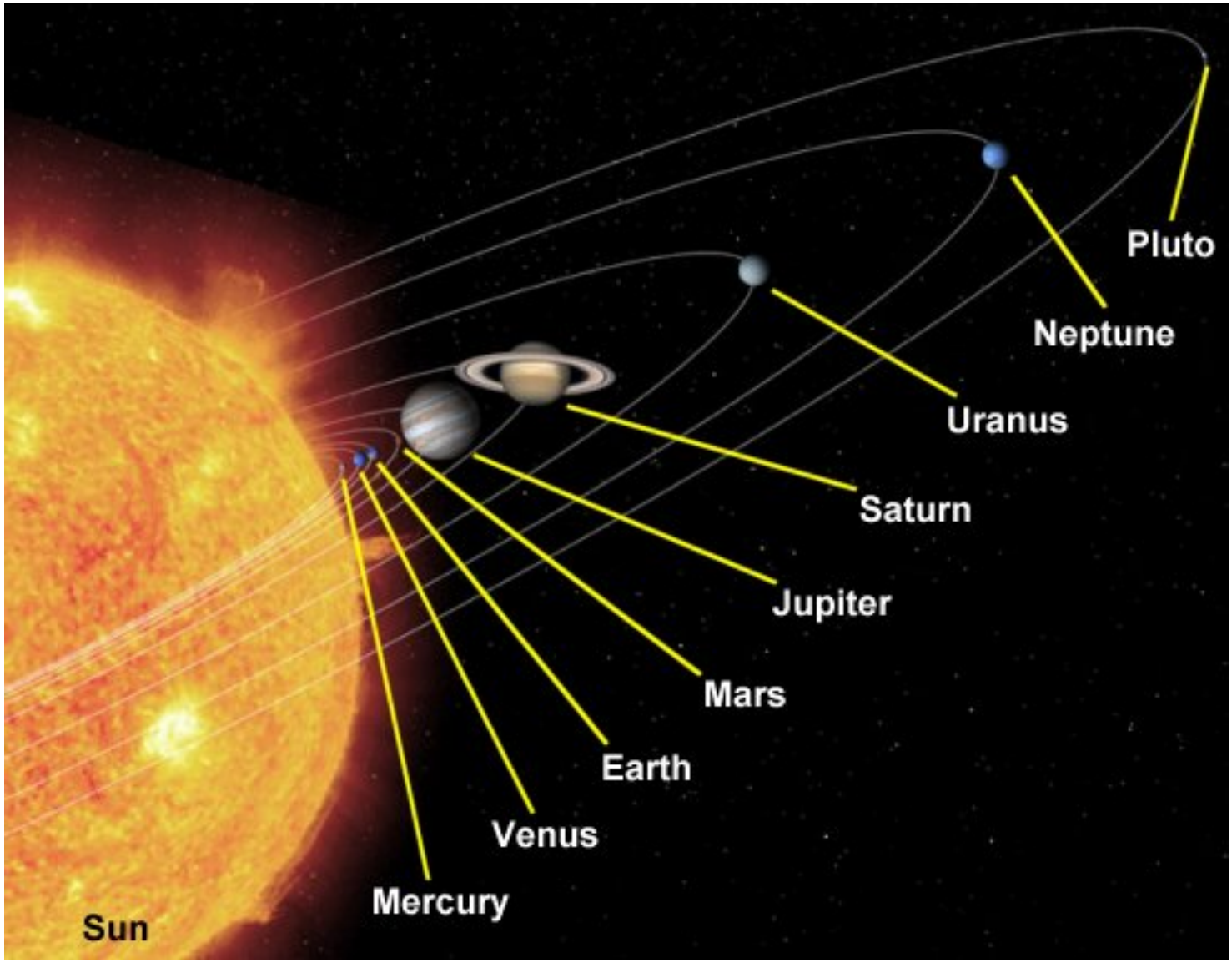


Conservation of momentum

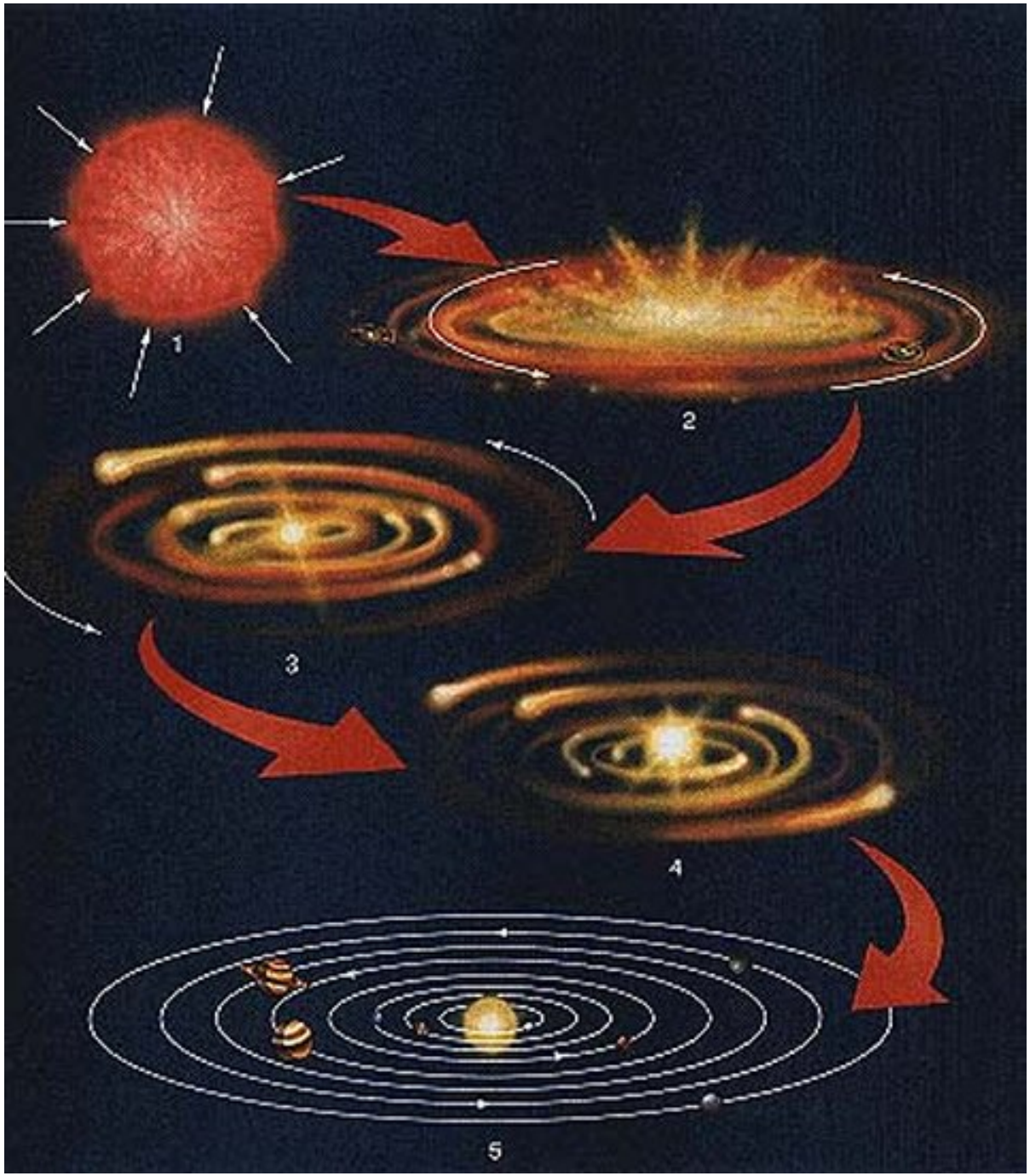
Conservation of mass

Conservation of energy

Courtesy of Aerospaceweb.org.



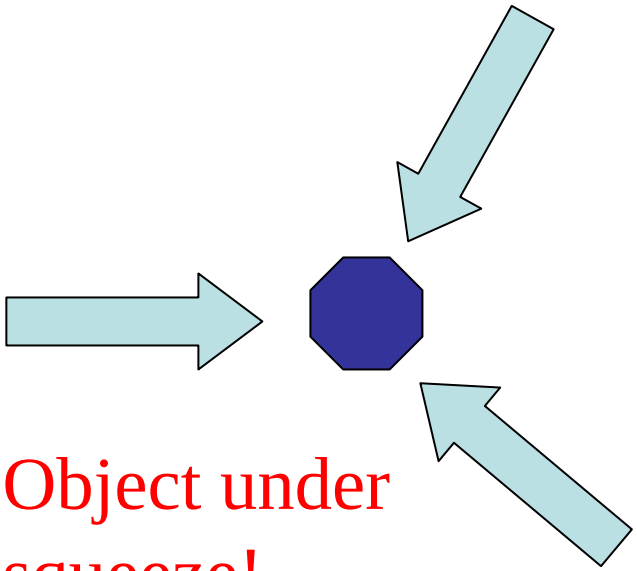
http://www.aerospaceweb.org/question/astronomy/q0247.shtml



Courtesy of Aerospaceweb.org.

Conservation of momentum

Concept of force balance

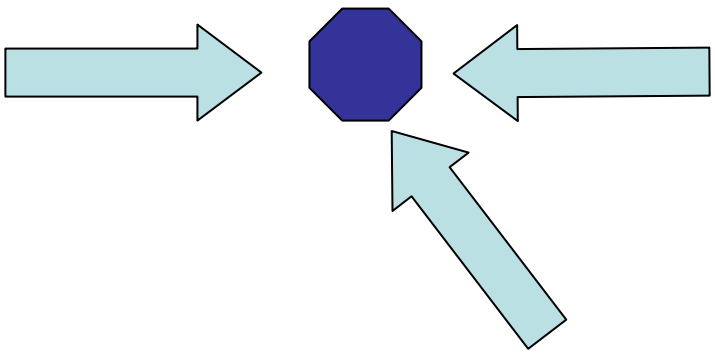


Object under squeeze!

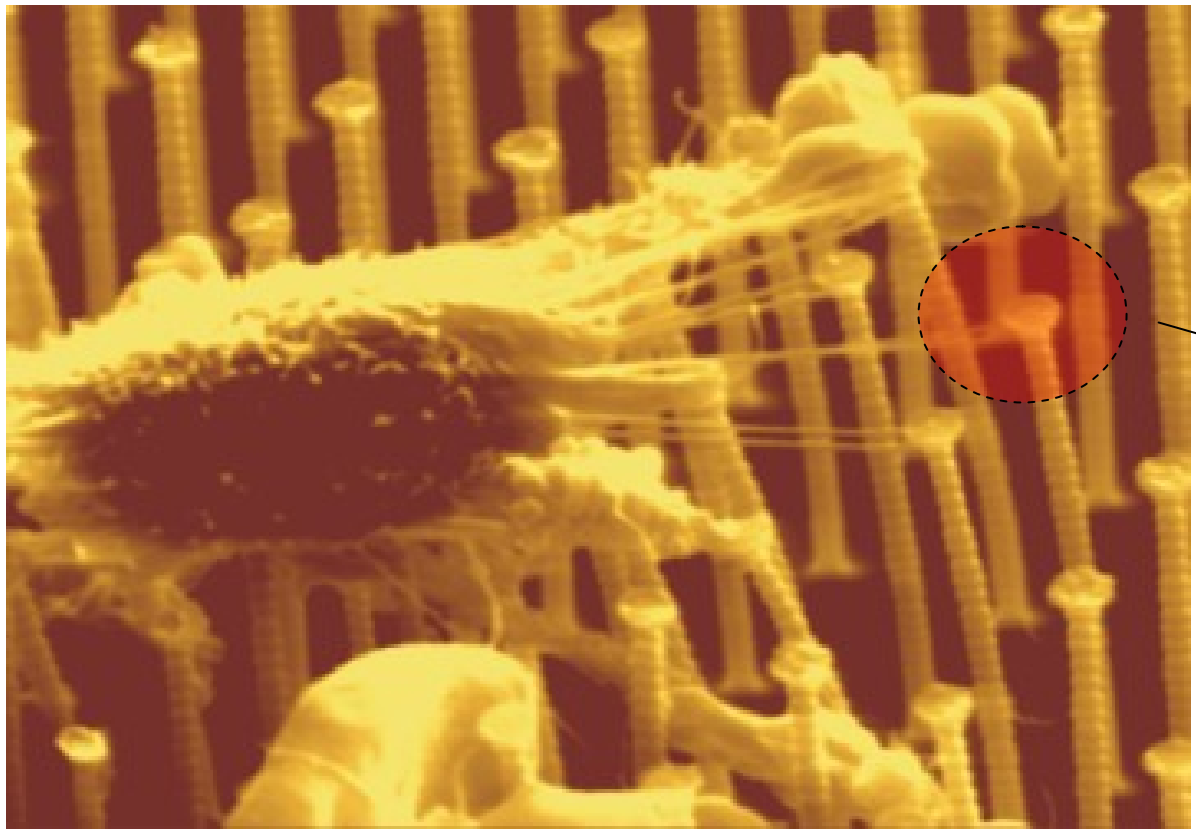
Net force on the object = 0,

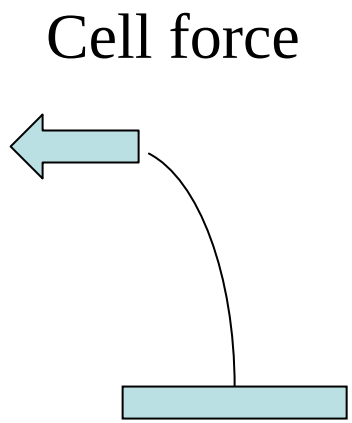
motion with constant velocity
(special case, vel = 0)

?



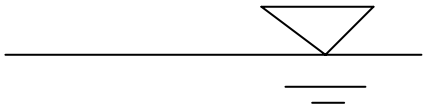
Cell force measured from pillar bending (concept of force balance)

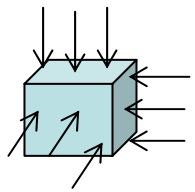




Fibroblast cell on top of pillar array
W.Roos and Spatz, Heidelberg, Germany

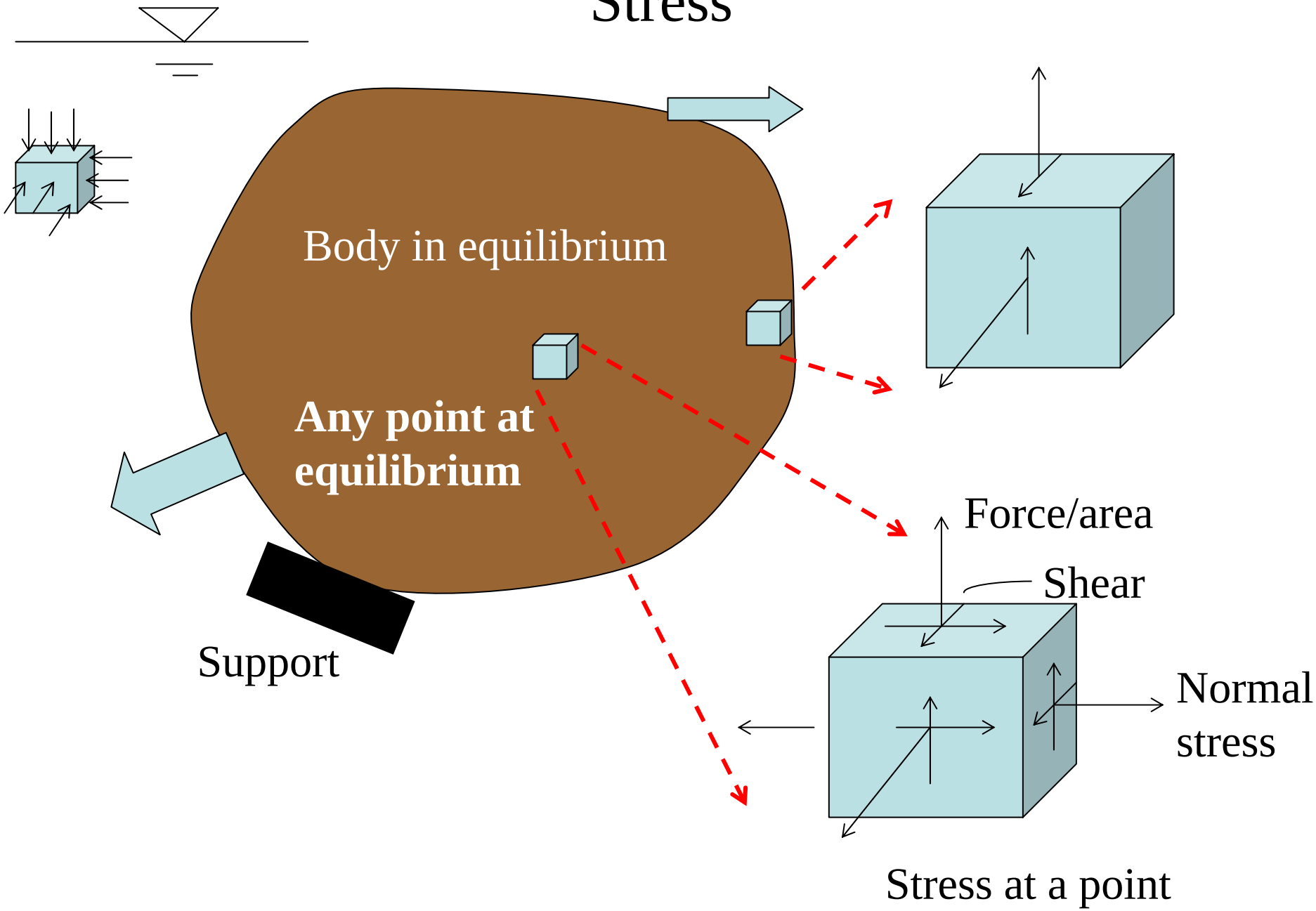
Stress



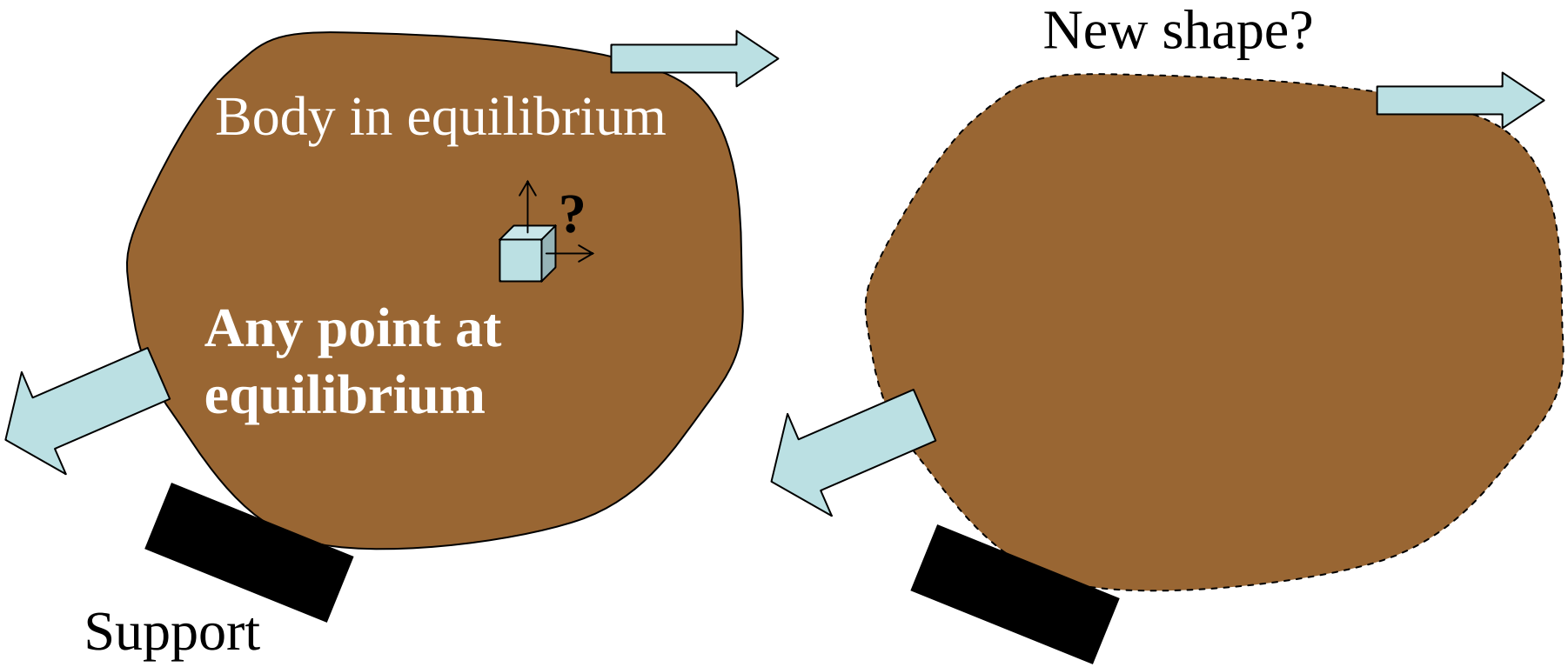


Water pressure
= force/area

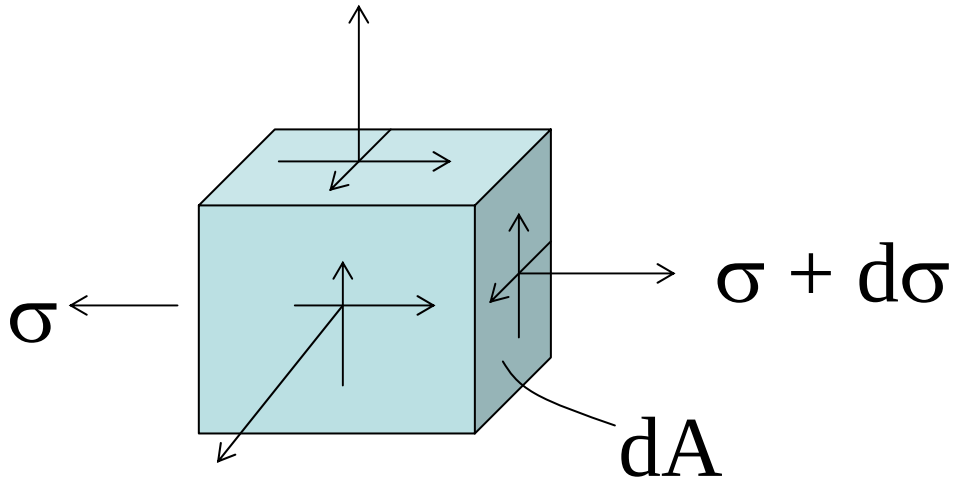
Stress


Body in equilibrium
Any point at equilibrium
Support
Force/area
Shear
Normal stress
Stress at a point

Problem statement: (a) stress distribution, (b) how do the body deform after forcing



Force balance → equation of equilibrium



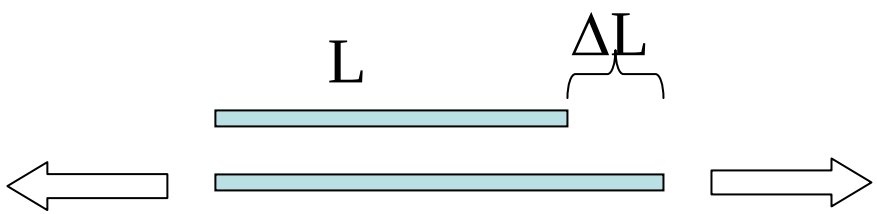
$(\sigma + d\sigma - \sigma)dA$ + force from other faces = mass x accel + body forces (e.g wt.)

Net force on the body element

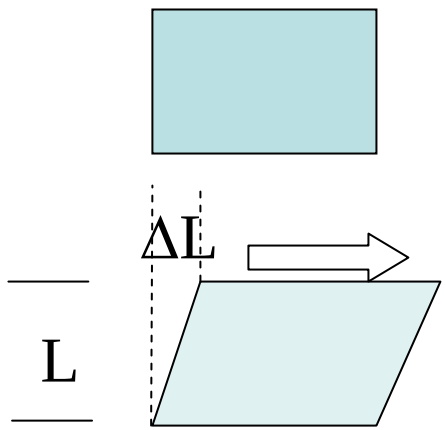
Differential equation with appropriate boundary condition

Need more info to solve a problem

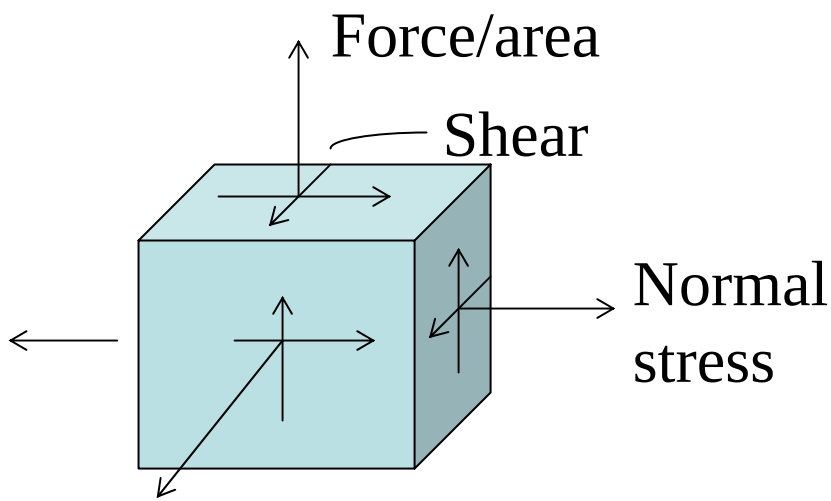
Strain



Normal strain = ΔL/L

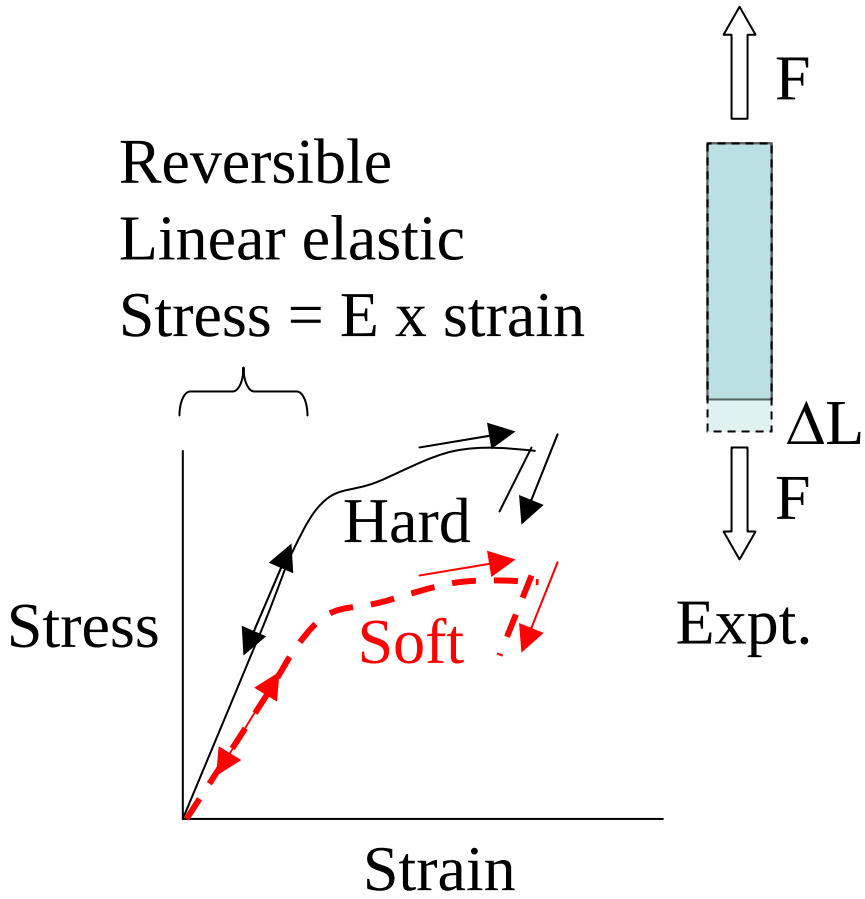


Shear strain = ΔL/L



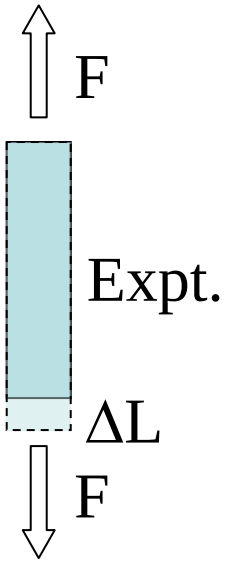
Stress - strain relation

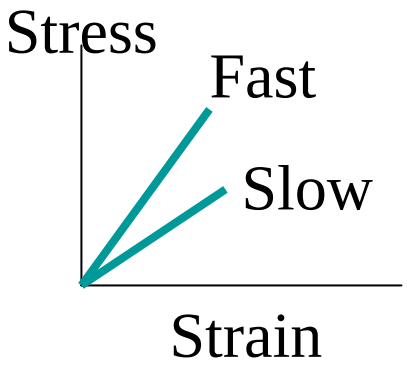
Reversible
Linear elastic
Stress = E x strain

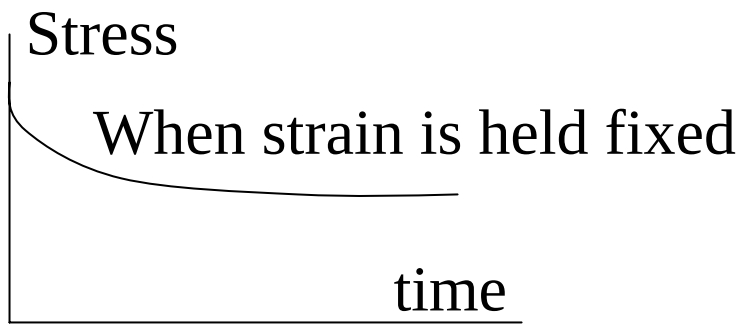


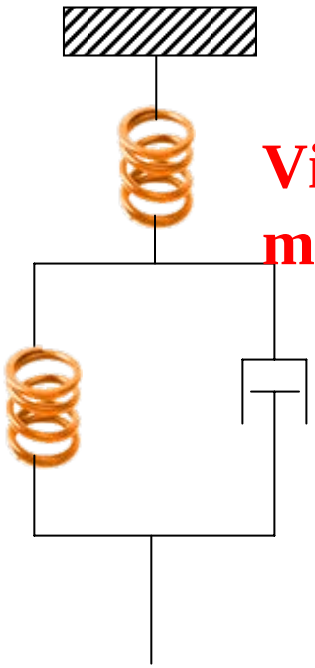
Independent of dimension

Time dependence

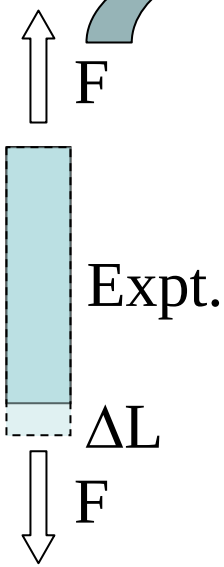




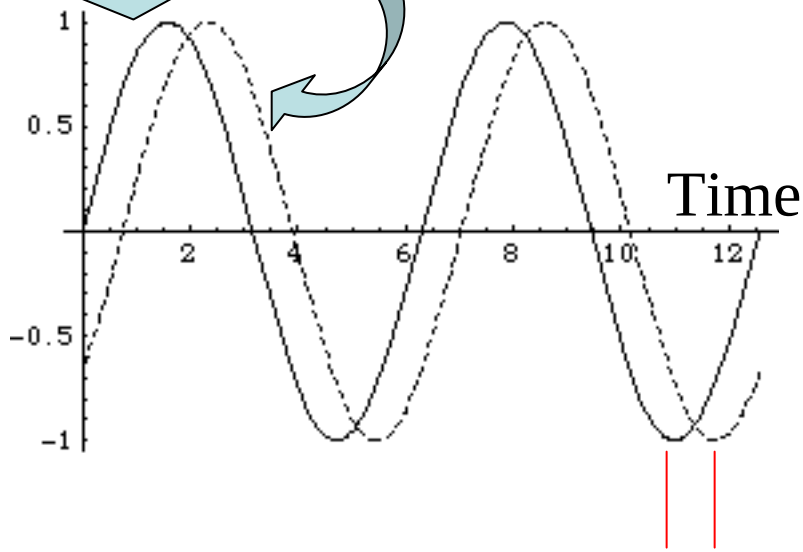




Viscoelastic model

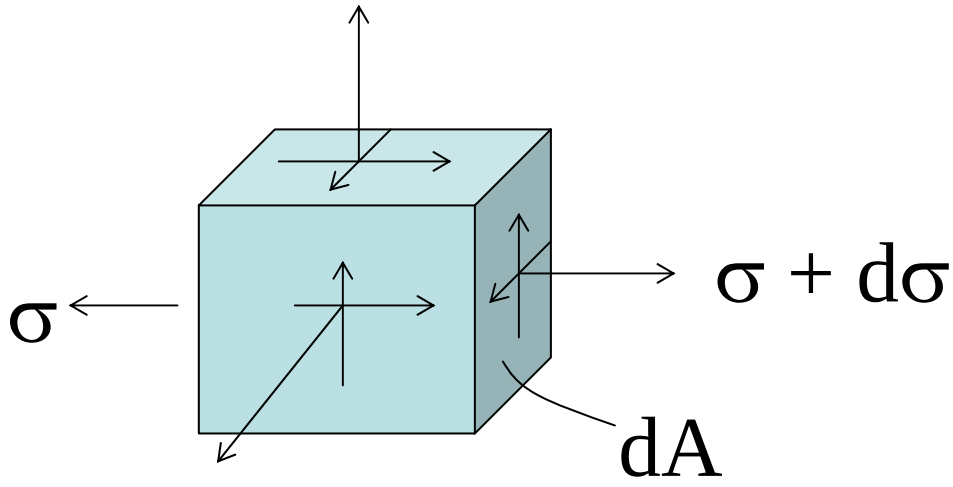


Deformation response



Phase lag

Force balance → equation of equilibrium



$(\sigma + d\sigma - \sigma)dA$ + force from other faces = mass x accel + body forces (e.g wt.)

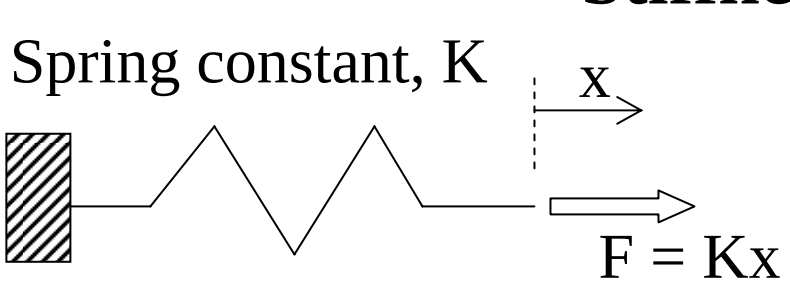
Net force on the body element

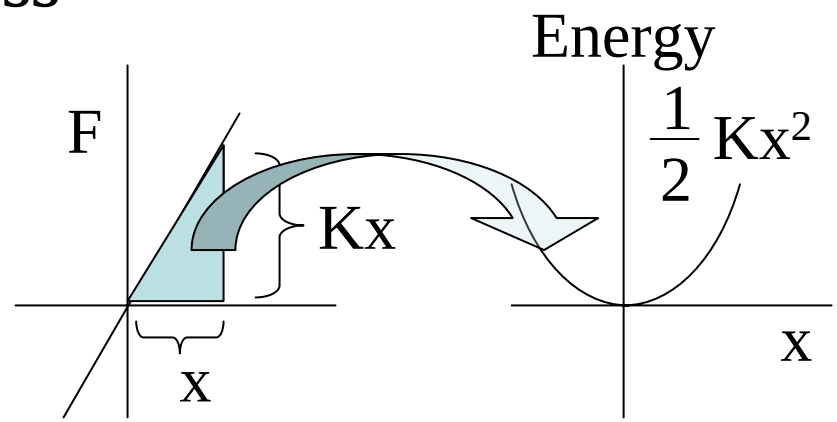
Differential equation with appropriate boundary condition

Energy minima → ↓ ← **Material properties (Constitutive relations)**

Often solved numerically (for example Finite Element Method)

Stiffness

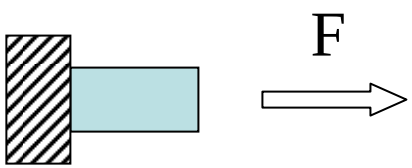




Stiffness, K = F/ΔL

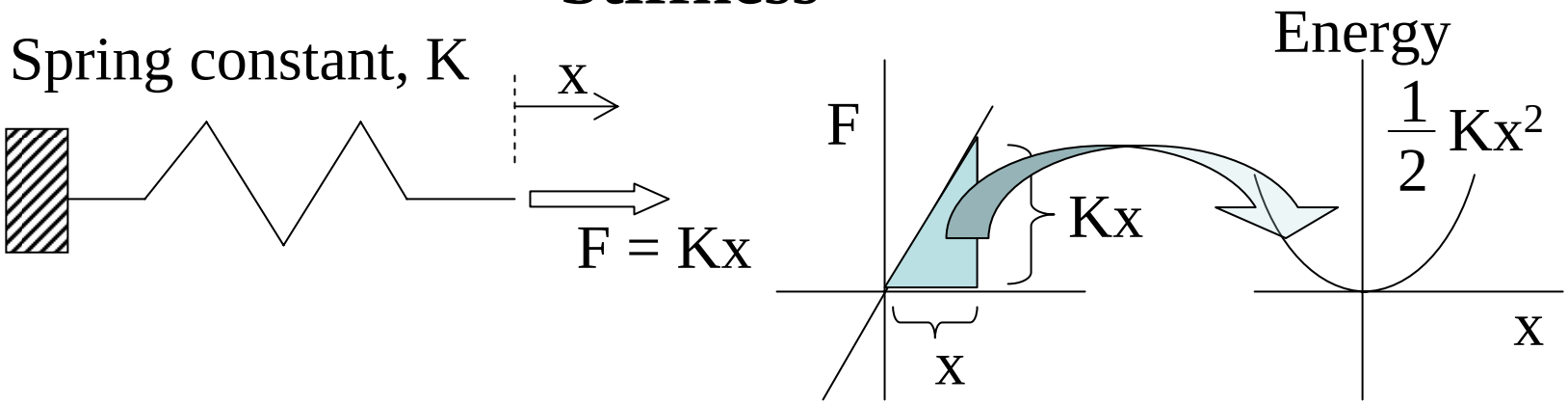
(Spring constant)

Depends on: material, dimension, boundary conditions



Which one is stiffer?

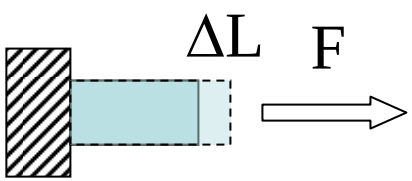
Stiffness



Stiffness, $K = F/\Delta L$

(Spring constant)

Depends on: material, dimension, boundary conditions

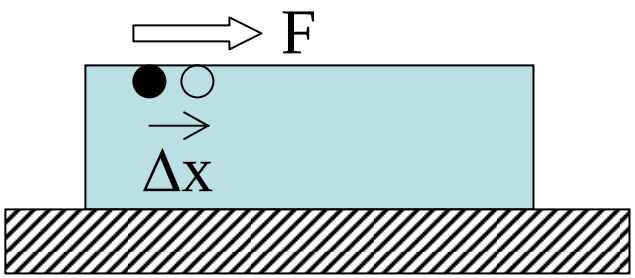


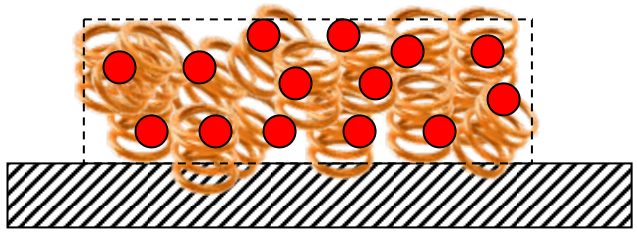
$K = F/\Delta L$ (small ΔL)

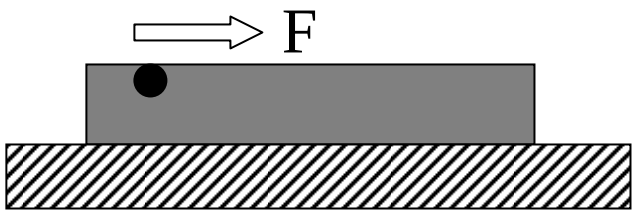
Stiff

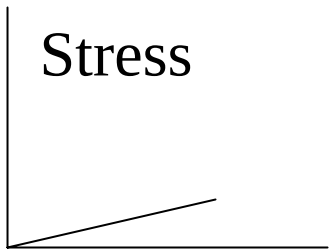
$K = F/\Delta L$ (large ΔL)

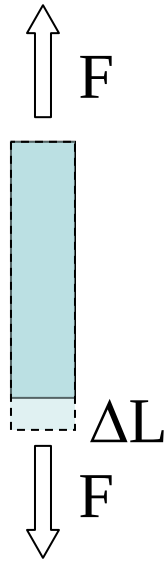
Soft



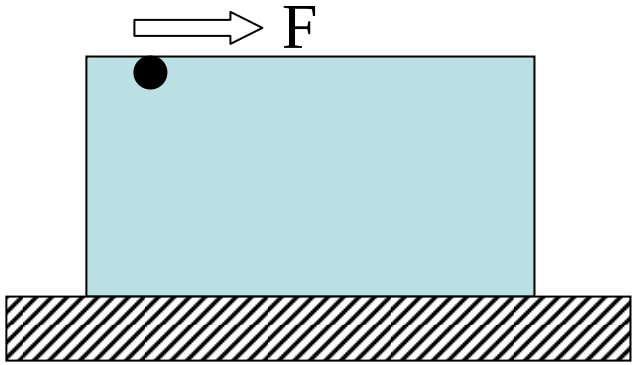


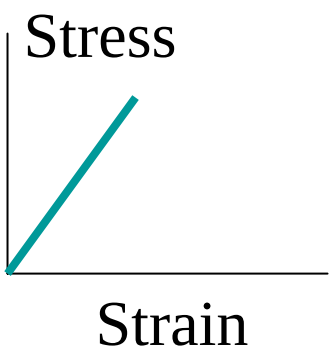






Expt.





Which one is stiffer?

We cannot tell just by inspection (needs analysis)

What we know:

- Each material point is in equilibrium
- Material stress-strain behavior
- How it is held together (Boundary conditions)

Each point of the body should move just that much such that the overall energy is minimum

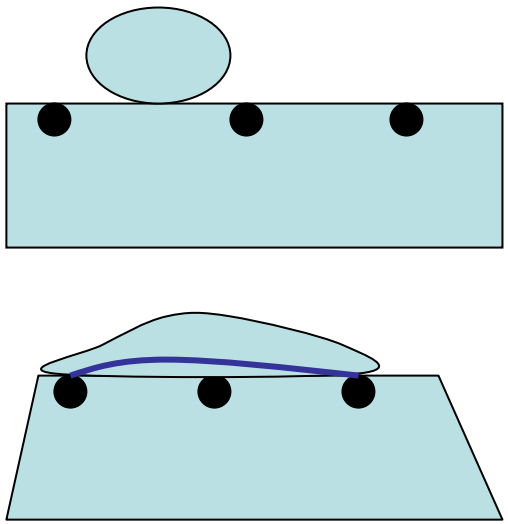
What we want to know:

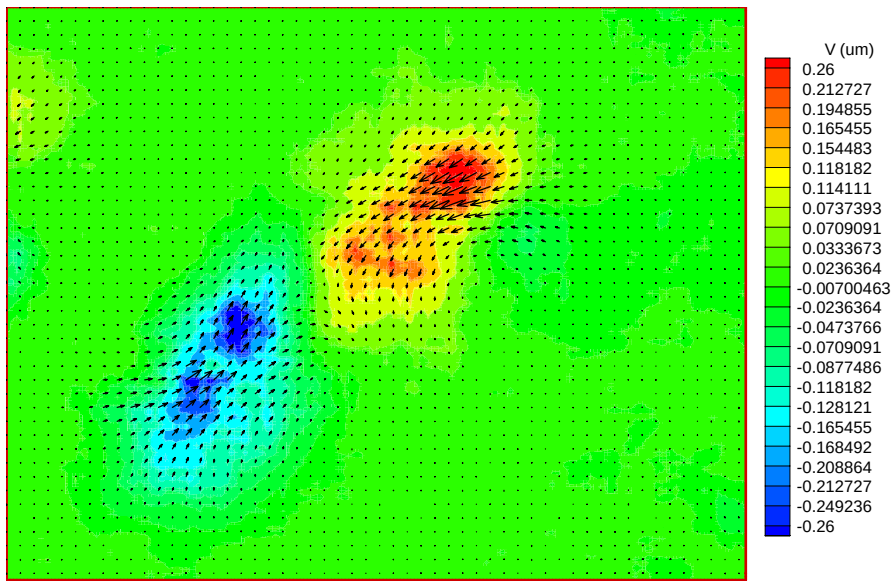
- Where will they move (by energy minimization)

Finite element analysis

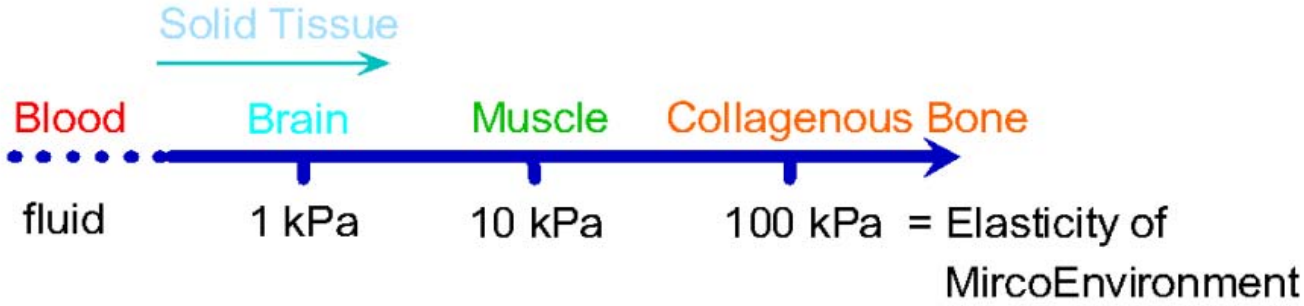
Cells apply force on the substrate

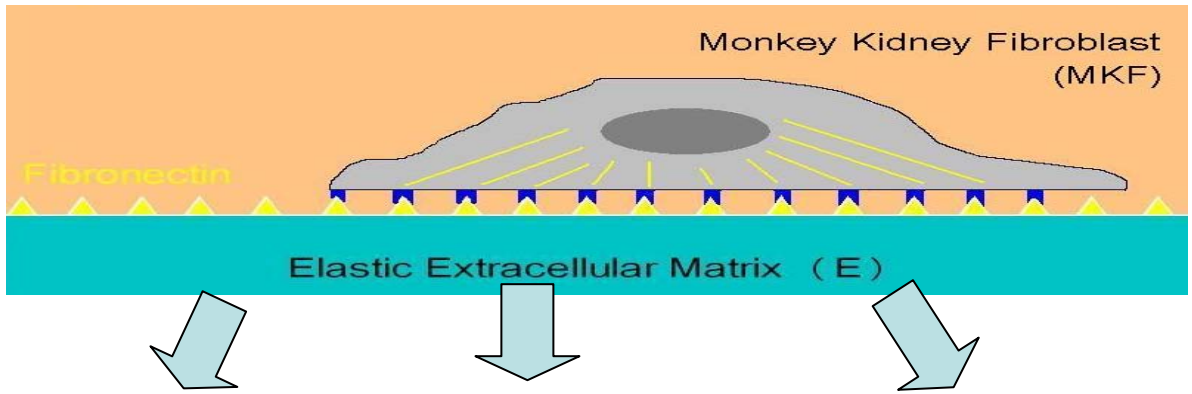
Images removed due to copyright restrictions.





Cells' sensitivity to substrate stiffness

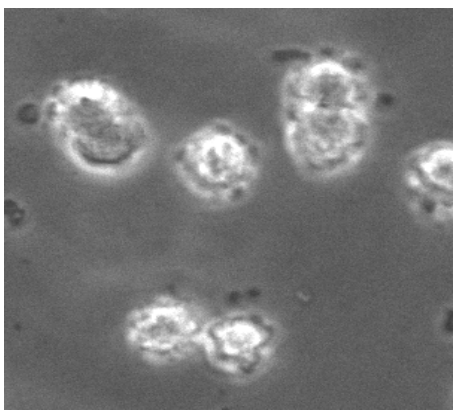


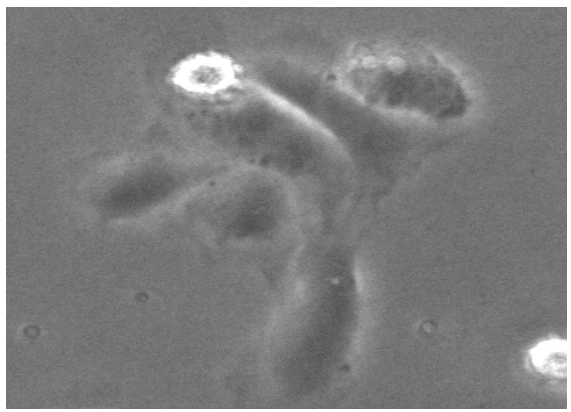


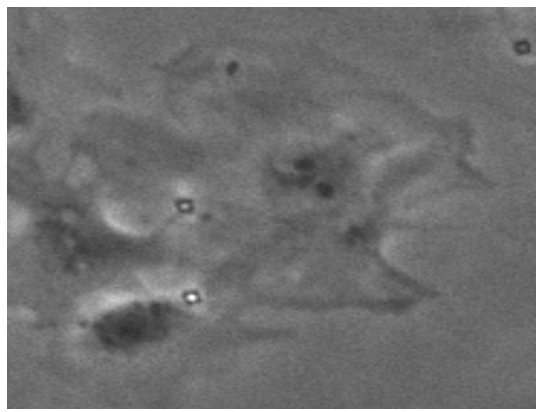
0.1 kPa – 1 kPa **1 kPa – 8 kPa** **> 8 kPa**

Fibroblasts

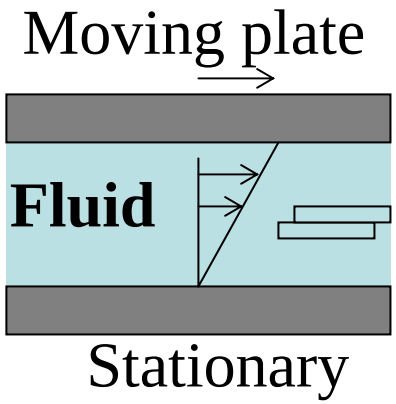
8 hrs

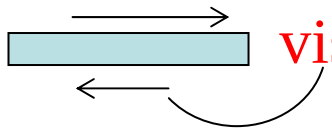






Flowing fluids

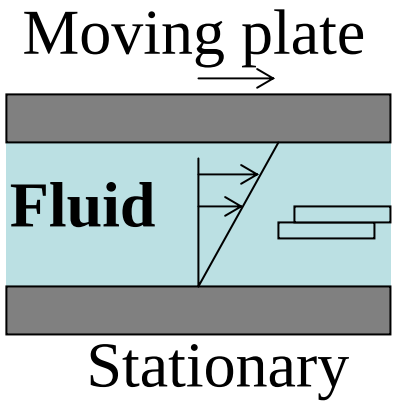


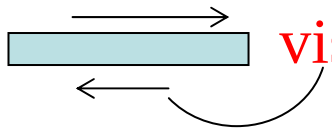


Shear stress due to viscosity

Shear stress ~ vel gradient x viscosity

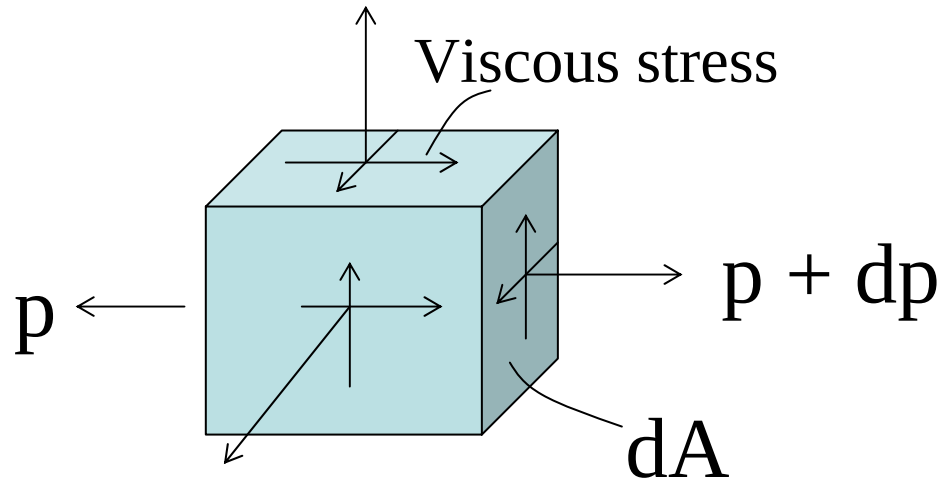
Flowing fluids





Shear stress due to viscosity

Shear stress ~ vel gradient x viscosity



Viscous force + pressure force + body force = mass x accl.

Shear stress on endothelial cells in blood vessels

endothelial

Section of an artery

Image removed due to copyright restrictions. Please see:
http://en.wikipedia.org/wiki/Image:Anatomy_artery.png

Images removed due to copyright restrictions.

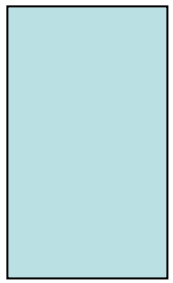
Please see figures 3 A and E (respectively) in Sho, E. et al. "Blood Flow Decrease Induces Apoptosis of Endothelial Cells in Previously Dilated Arteries Resulting From Chronic High Blood Flow." *Arteriosclerosis, Thrombosis, and Vascular Biology* 21 (2001): 1139.

Increased blood flow rate
➡ higher density of endothelial cells

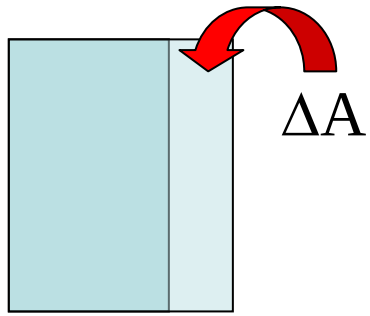
Reduced blood flow rate
➡ Endothelial cell apoptosis

E. Sho et al, *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2001;21:1139

Surface energy

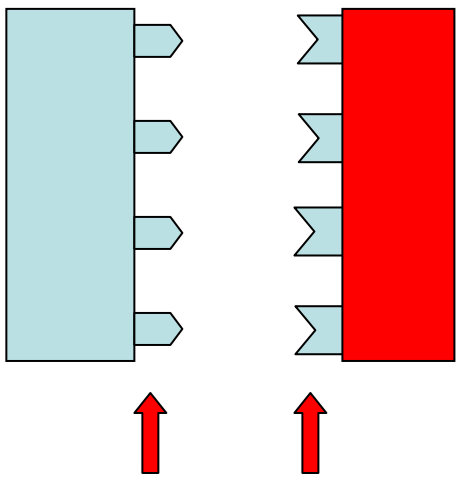


Surface of a medium
(e.g., water/vapor interface)

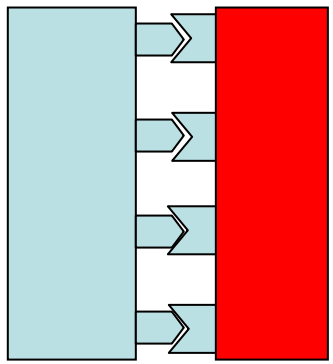


Energy cost to increase area = $\gamma\Delta A$

Surface energy

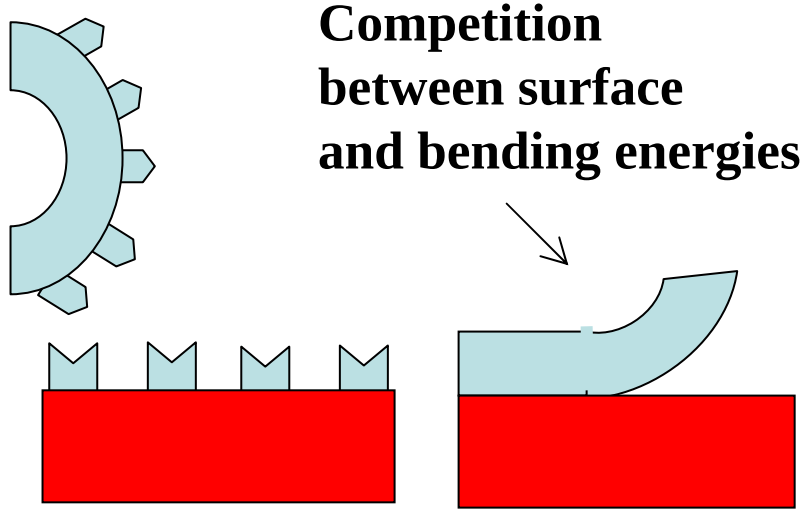


Higher total surface energy

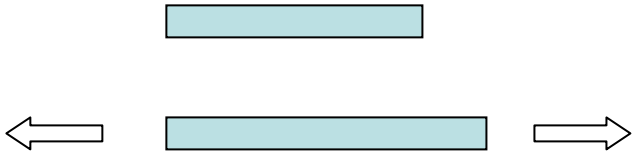


Lower total interfacial energy

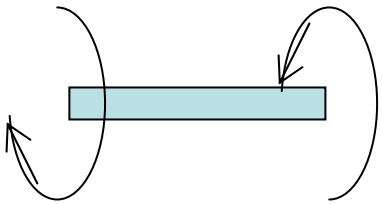
Competition between surface and bending energies



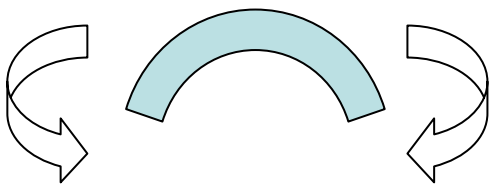
Deformation



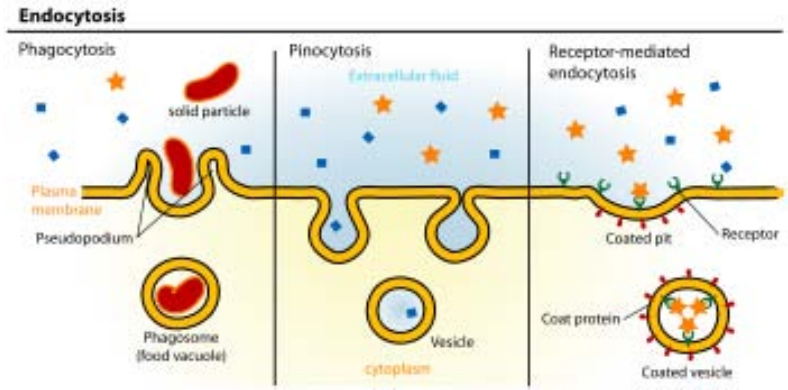
Stretching



Twisting

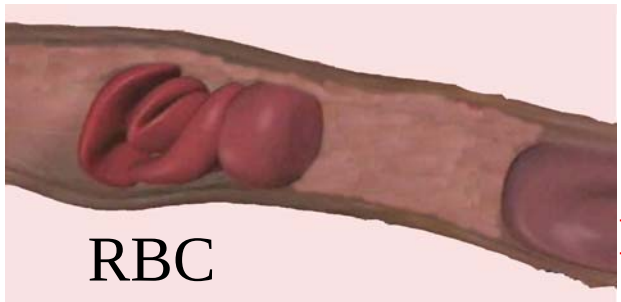


Bending

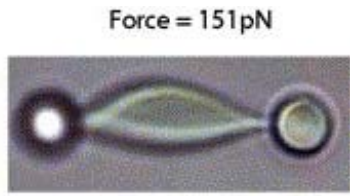


http://en.wikipedia.org/wiki/Endocytosis

Endocytosis size might be limited by membrane bending energy



Courtesy of UC San Diego Jacobs School of Engineering. Used with permission.



Deformable healthy RBC

Hard malaria infected RBC

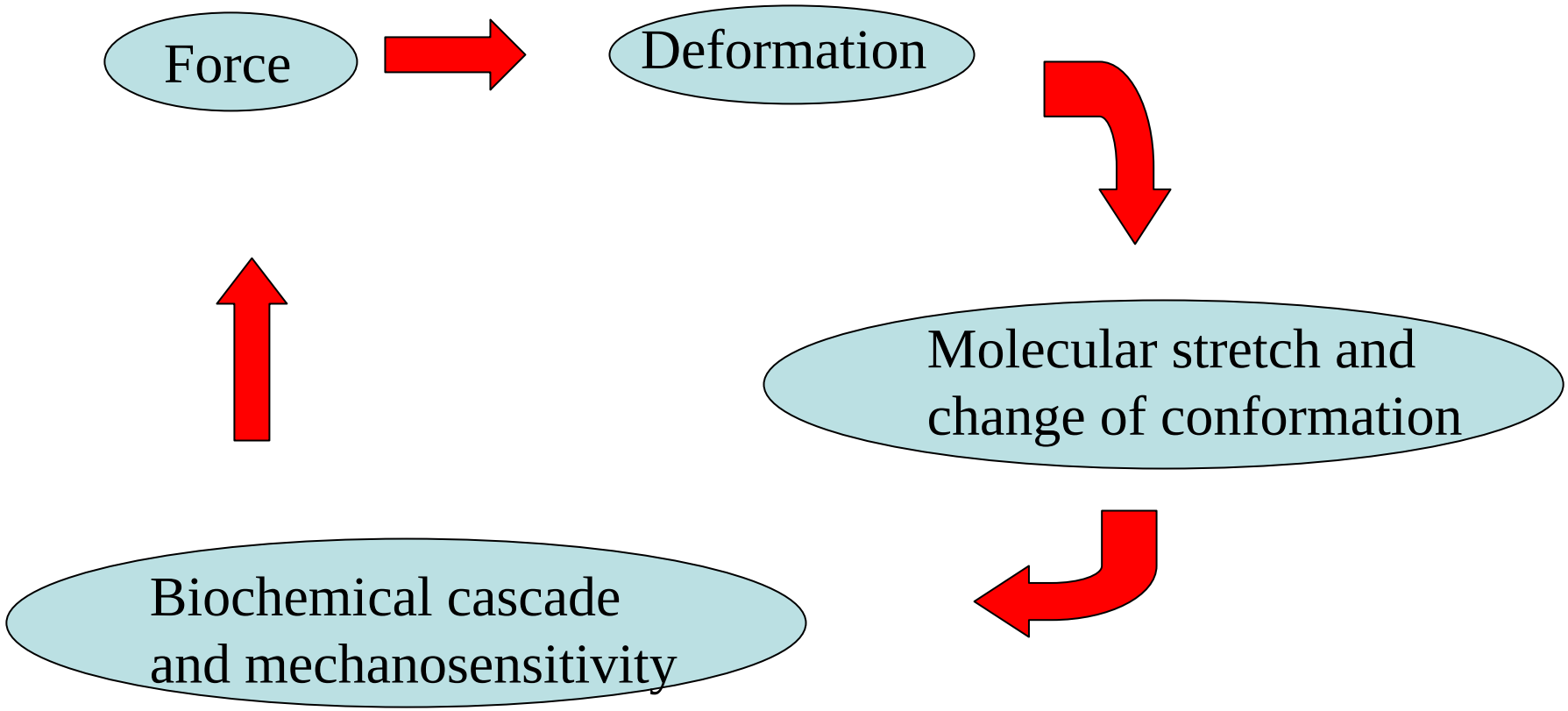
Courtesy Elsevier, Inc., http://www.sciencedirect.com. Used with permission.

Low bending stiffness of RBCs allow them them to go through smaller capillaries

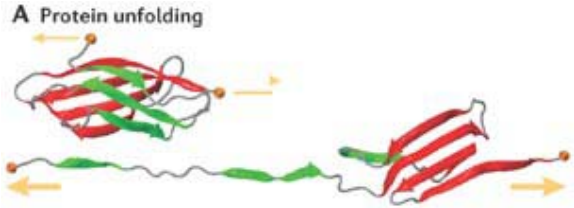
http://www.jacobsschool.ucsd.edu/news/news_releases/release.sfe?id=484

Suresh et al. *Acta Biomaterialia*, 1(1), 200

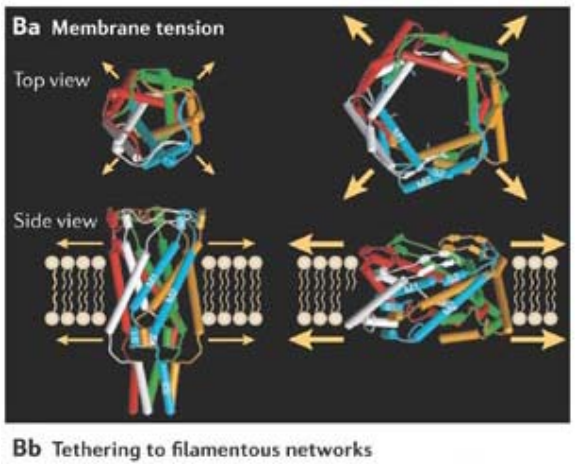
Mechanics link to cell functionality



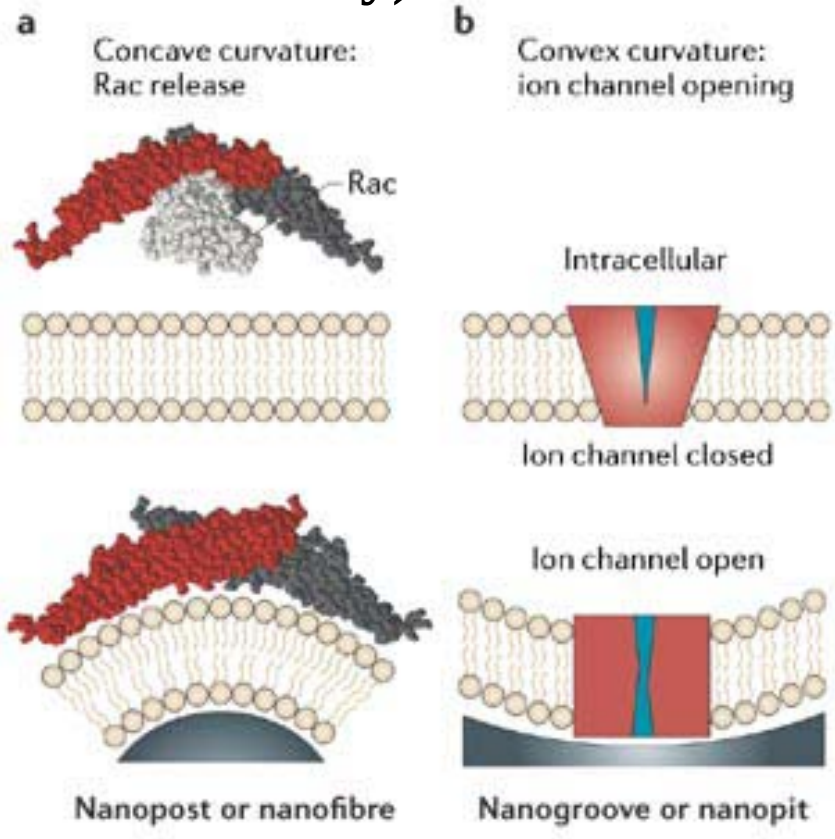
Deformation ➡ change of conformation (change of functionality)



Unveiling cryptic sites by mechanical tension
(e.g., fibronectin unfolding by cytoskeletal contraction)



Opening of ion channel by membrane tension



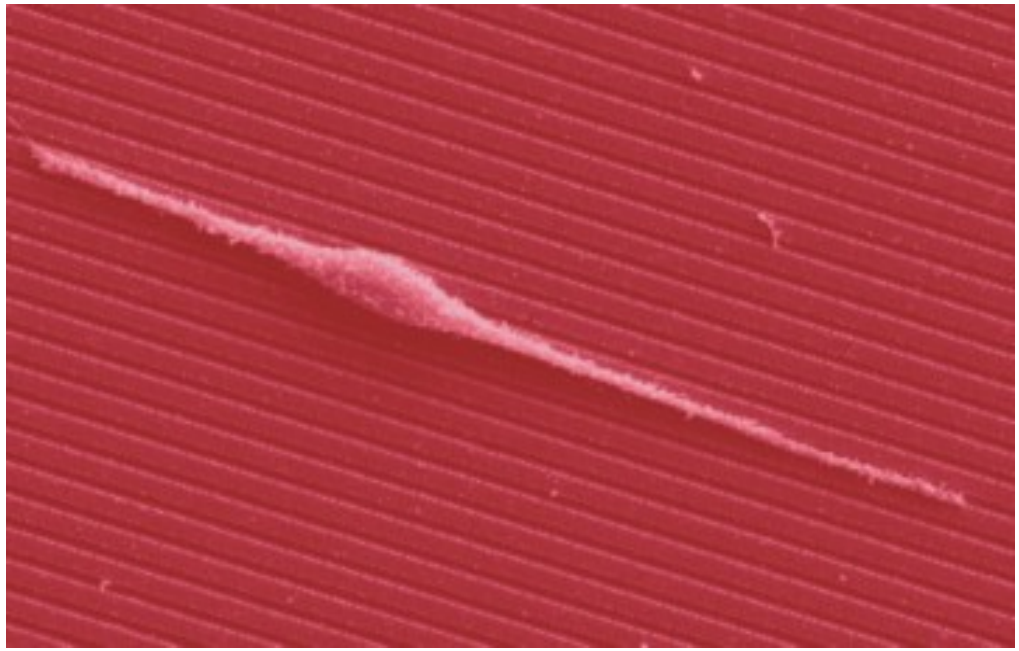
BAR domain attaches to convex membrane
➡ Rac release
➡ Integrin activation
➡ increased traction force

Convex curvature opens mechanosensitive Ion channels (K^+)

Courtesy of Michael Sheetz.

Viola and Sheetz. Nature Reviews Molecular Cell Biology 7, 265-275, 2006

Sensing topography



Melanocyte cell on micron structured surface
R. Kemkemer and S. Jungbauer
Max Planck Institute, Germany

Focal adhesion complex - a gateway to the cellular forces

Image removed due to copyright restrictions.

Please see Horwitz, A. F. “Integrins and Health.” *Scientific American* 276 (1997): 68-75.

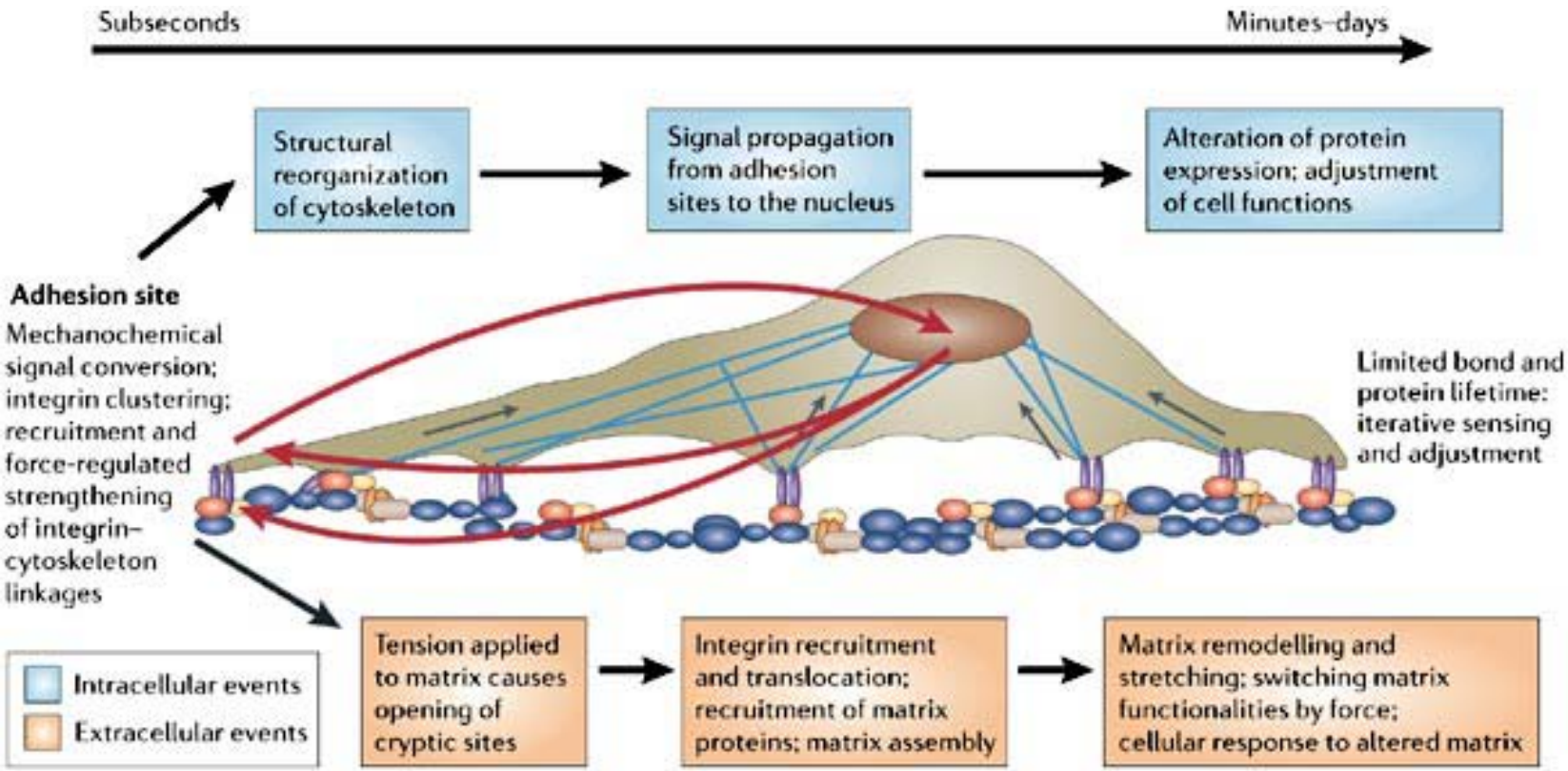
FAC

Horwitz, *Scientific American*,
276, 68-75, 1997.

Actin

Actin: a predominant contractile component

- **Conserved during eucaryotic evolution**
- **Its amino acid sequence is 90% identical in different species**

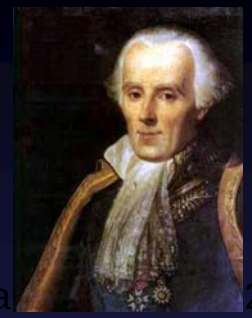


Courtesy of Michael Sheetz.

Viola and Sheetz. Nature Reviews Molecular Cell Biology 7, 265-275, 2006

Notions of mechanics

Newton 1643 - 1727



Ga 2

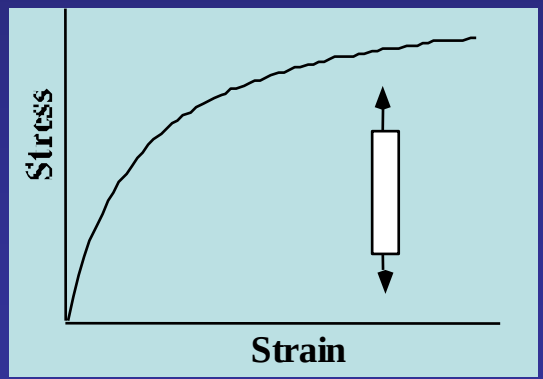
Force

Surface energy

Flow

Conservation principles

Stiffness



Deformation

Energy

Viscoelasticity