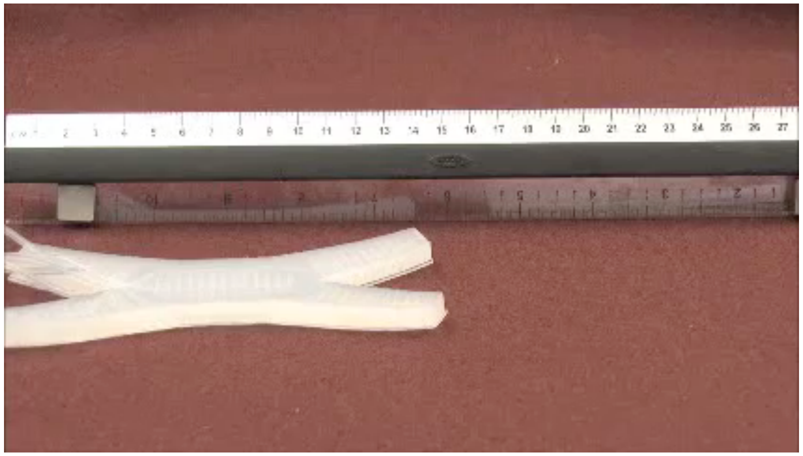
# Teaser movie: flexible robots!



R. Shepherd, Whitesides group, Harvard

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# Lecture 4: viscoelasticity and cell mechanics

S-RSI Physics Lectures:
Soft Condensed Matter Physics

Jacinta C. Conrad
University of Houston
2012

Note: I have added links addressing questions and topics from lectures at:
http://conradlab.chee.uh.edu/srsi_links.html
Email me questions/comments/suggestions!

# Soft condensed matter physics

- Lecture 1: statistical mechanics and phase transitions via colloids
  - Mechanical properties: “soft” solids and granular materials
  - Glass transitions: fluid-to-disordered-solid transition
- Lecture 2: (complex) fluid mechanics for physicists
  - Shear thickening: consequence of shear-induced structure
  - Microfluidics: low Reynolds number (laminar) flows in microscale channels
- Lecture 3: physics of bacteria motility
  - Non-time-reversible mechanisms of motility
  - Cooperative motion is glasslike
- **Lecture 4: viscoelasticity and cell mechanics**
- Lecture 5: Dr. Conrad’s work

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# Equilibrium versus non-equilibrium

Thermodynamic equilibrium: no net flow of matter, energy; no phase changes; no driving forces.

A system in thermodynamic equilibrium remains in equilibrium in isolation.

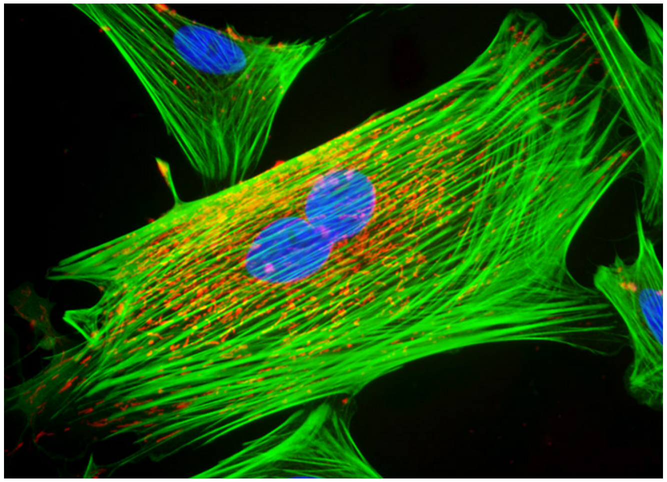
Thermodynamic non-equilibrium: one of the above conditions is violated.

Example: slow relaxation of supercooled liquids

Question: are biological systems in equilibrium?

# Big question of today's lecture

What is the role of mechanical properties (and especially viscoelasticity) in the behavior of cells (especially eukaryotic cells)?



Nikon Image Gallery; fibroblasts

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# Stress in solids and liquids

In response to an applied steady shear:

$$\gamma = \frac{\Delta}{h}$$

$$\dot{\gamma} = \frac{dv}{dy} \approx \frac{\Delta v}{h}$$

The stress felt by a liquid is proportional to the shear rate:

$$\tau = \mu\dot{\gamma}$$

The stress felt by a solid is proportional to the shear:

$$\tau = E\gamma$$

($E$ = Young's modulus; analogy: three-dimensional spring constant)

# Linear rheology

To measure the material properties of a material whose mechanical properties are intermediate between that of a solid, apply a <u>small oscillatory shear strain</u> and measure the stress as a function of time:

$$\gamma(t) = \frac{\Delta}{h} \sin \omega t$$

$$\gamma_0 = \frac{\Delta}{h}$$

For an oscillation with <u>small amplitude</u> $\gamma_0$ at a frequency $\omega$:

$$\tau(t) = \gamma_0 \left[ G'(\omega) \sin \omega t + G''(\omega) \cos \omega t \right]$$

$G'(\omega)$ : in-phase <u>elastic</u> modulus; energy stored (like a spring)

$G''(\omega)$ : out-of-phase <u>loss</u> modulus; energy dissipated (into heat)

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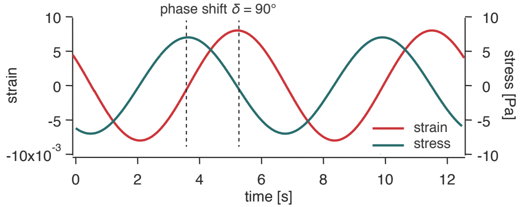
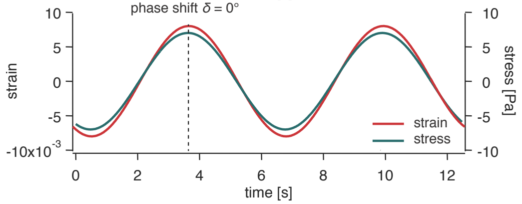
# Explicit wave forms

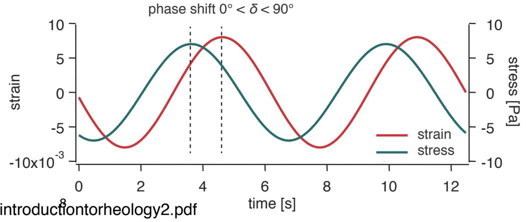
<u>Liquid</u>: perfectly out-of-phase (energy dissipation)



<u>Solid</u>: perfectly in-phase (energy storage)



<u>Viscoelastic</u>: in between (storage + dissipation)

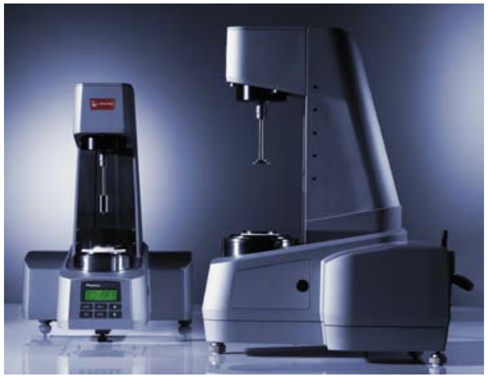


Adapted from weitzlab.seas.harvard.edu/links/tutorials/introductiontorheology2.pdf

# Typical data from a rheology experiment

Rheology is the study of the flow properties of (complex) fluids.

Rheometers with Couette (left),
cone-and-plate (right) geometries



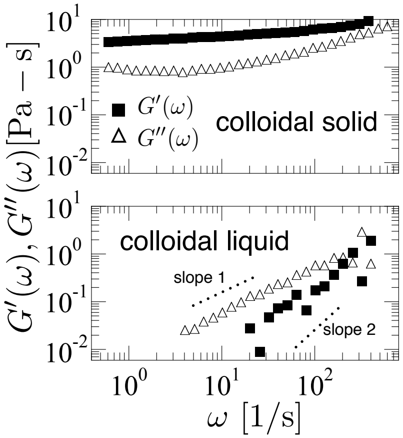


Image of rheometers from Wikipedia; Conrad *et al.*, *J. Rheol.* (2010)

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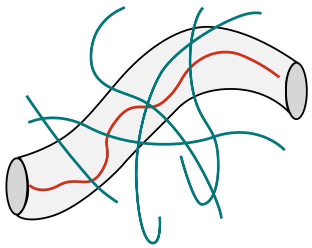
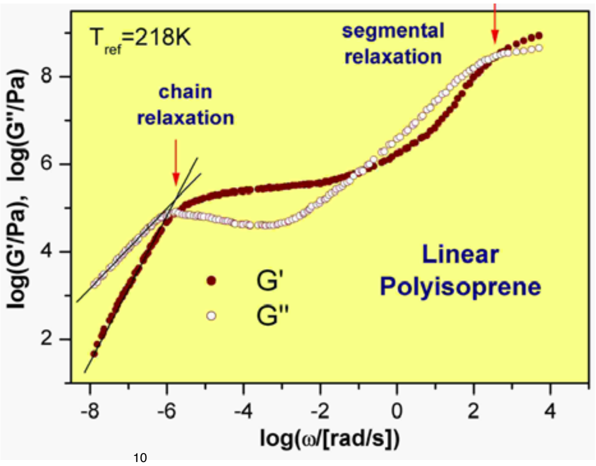
# Flexible polymer rheology

Rheological measurements on entangled polymer probe two relaxation times: the relaxation time of a single segment of the polymer (short times) and the reptation (chain relaxation) time needed to pull a polymer chain through an entangled network.

Tube model for polymer rheology





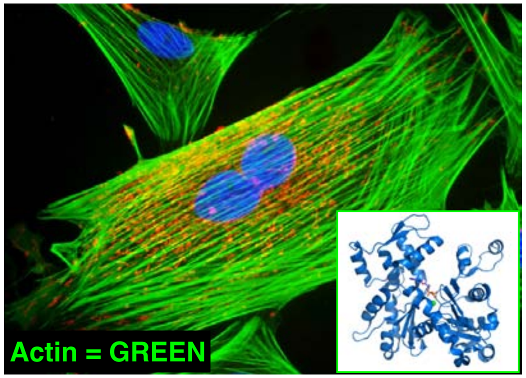
mpip-mainz.mpg.de

# Actin: a cytoskeletal protein

Actin is a biological polymer present in all eukaryotic cells (those with a nucleus).

Actin is responsible for the mechanical properties of cells as they move and spread.

It is a primary component of the extracellular matrix inside cells, and is involved in cell motility and contractile stiffness.



Nikon Image Gallery and Wikipedia

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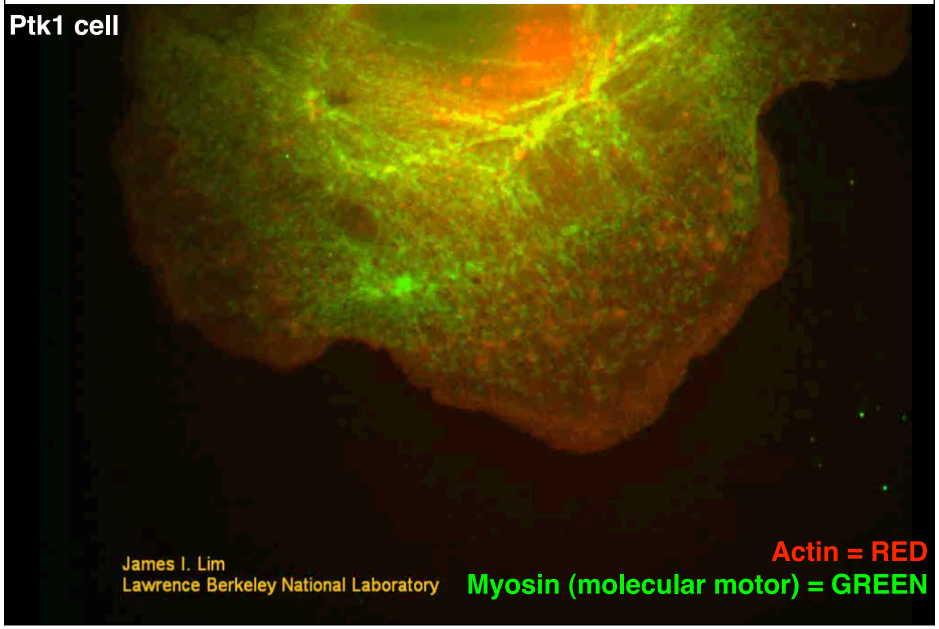
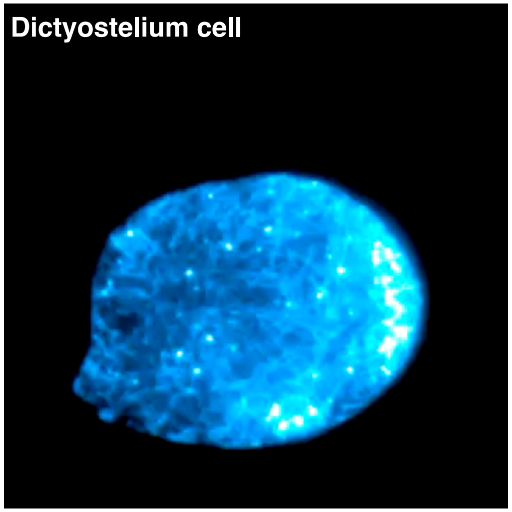
# The cytoskeletal network is dynamic



# More cytoskeletal dynamics



YouTube: TheMPIDS

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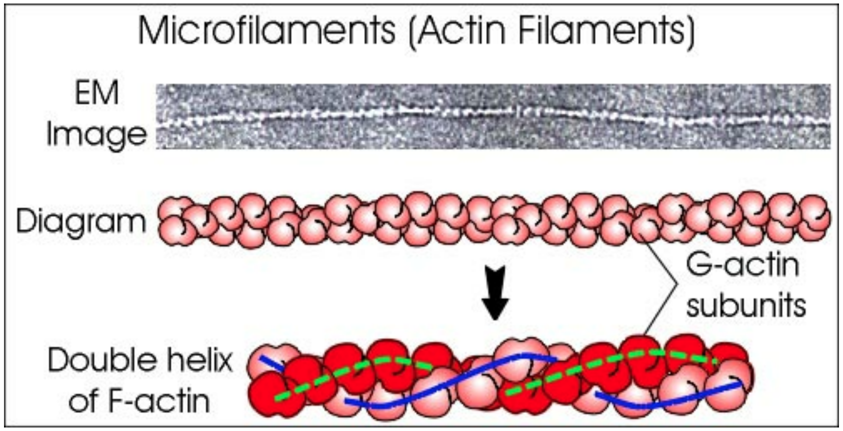
# Microfilaments are composed of actin



Dimensions of actin filaments:

Length: 20 $\mu$m

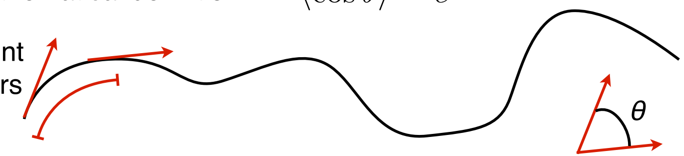
Diameter: 7 nm

erin.utoronto.edu

# Physicist's view of actin: semiflexible

The persistence length *P* of a polymer is the distance over which a segment is "locally straight".

Mathematical definition: $\langle \cos\theta \rangle = e^{-L/P}$



tangent vectors

*L* = length along the backbone

*θ* = angle between tangent vectors

Most polymers are flexible: P ≪ (total length of polymer)

Actin is semi-flexible: P ≈ (total length of polymer)

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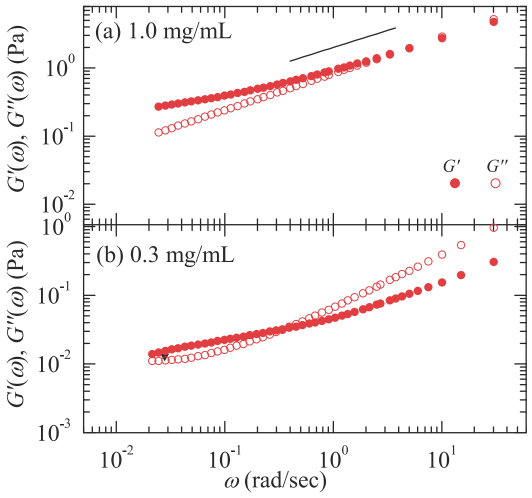
# Rheology of actin (1): linear rheology

The rheological behavior of actin depends on its concentration:

At high concentrations of actin (top): suspension of actin is largely elastic.

At lower concentrations of actin (bottom): actin exhibits a crossover to viscous dominated rheology at long times (small frequencies).

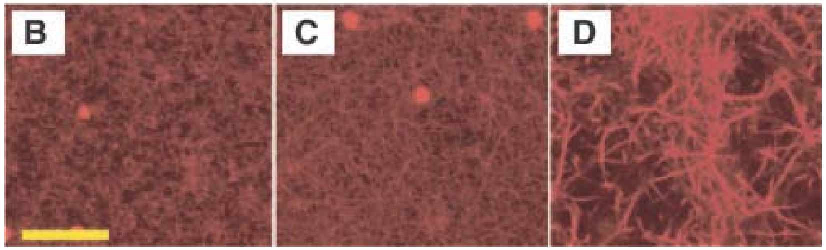


adapted from Gardel *et al*, *PRL* (2003)

# Actin bundling with cross-linkers

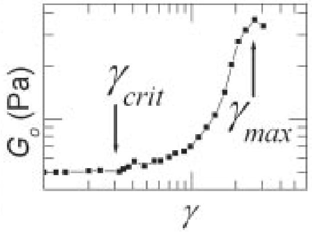
Add cross-linkers to actin to create bundles of filaments:

increasing concentration of scruin (bundling crosslinker) →



Apply a steadily increasing strain to a crosslinked actin network and measure the elastic modulus:

Bundled networks strain-stiffen: the elastic modulus increases with strain until breaking



Gardel *et al*, *Science* (2004)

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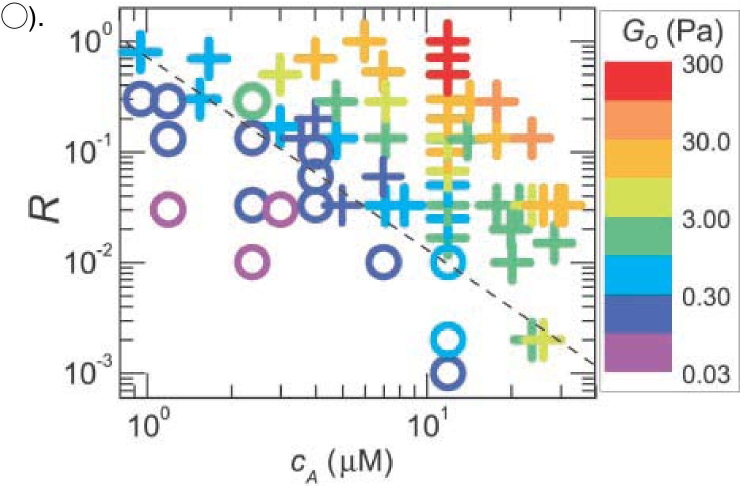
# Rheology of actin networks (2): stiffening

Networks with high concentrations of cross-linker ($R$) and filaments ($c_A$) strain-stiffen (indicated by + + symbols).

Networks with low concentrations of $R$ and $c_A$ do not strain-stiffen (○).

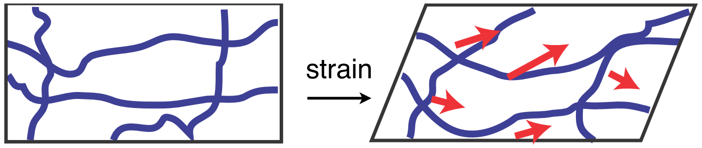


Gardel *et al*, *Science* (2004)

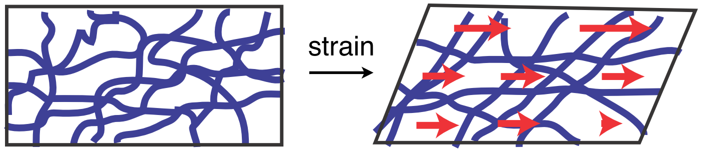
# Polymer physics of strain stiffening

Strain stiffening occurs when the network undergoes a collective deformation in which the actin filaments become aligned:

Non-affine deformation: low concentration of filaments, crosslinks: filaments bend and network does not stiffen.



Affine deformation: high concentration of filaments, crosslinks: filaments stretch and network stiffens.



Following Gardel *et al.*, *Science* (2004)

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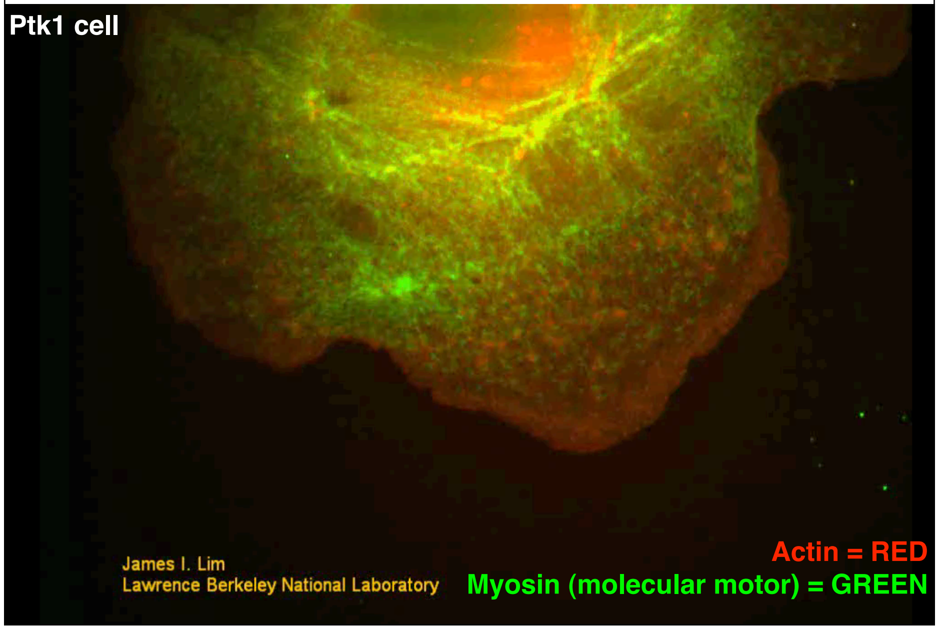
# Relationship of actin to motility?

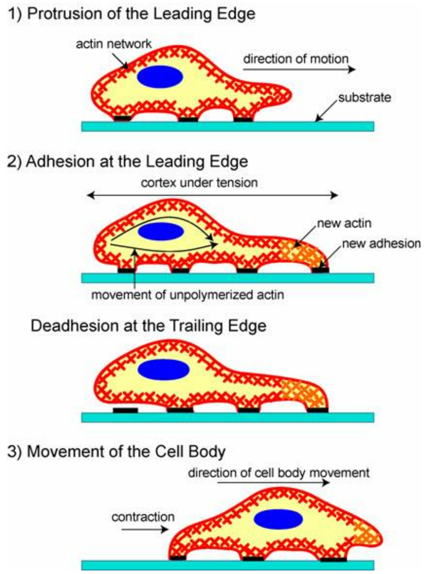


**Ptk1 cell**

James I. Lim
Lawrence Berkeley National Laboratory

**Actin = RED**
**Myosin (molecular motor) = GREEN**

# Implications for cell movement



Cells need to <u>exert force</u> to move and to attach to surfaces at the leading edge.

Cells need to <u>contract</u> at the trailing edge to follow the motion.

This requires tuning

Ananthakrishnan and Ehrlicher *et al*, *Int. J. Biol. Sci.* (2007)

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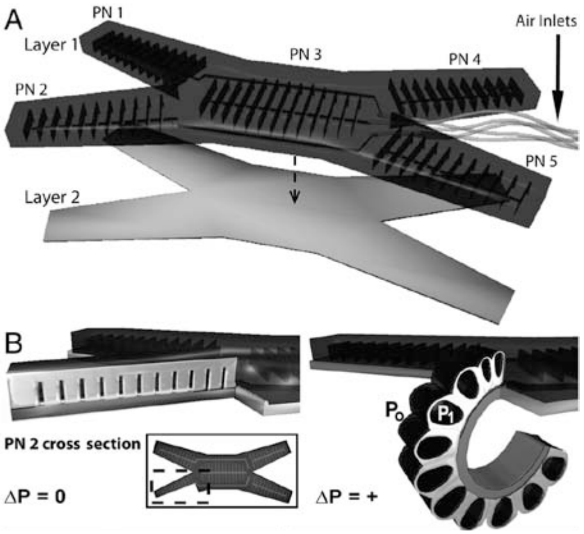
# Differential straining in robots

Ilievski *et al*, *Angew. Chem. Int. Ed.* (2011)

# Viscoelasticity and soft robots

Key for soft robots: match a <u>deformable</u> elastomeric layer to a non-deformable <u>strain-limited layer.</u>

Inflating the channels with air deforms these two layers differently, leading to motion of the robot.



Shepherd *et al.*, *PNAS* (2011)

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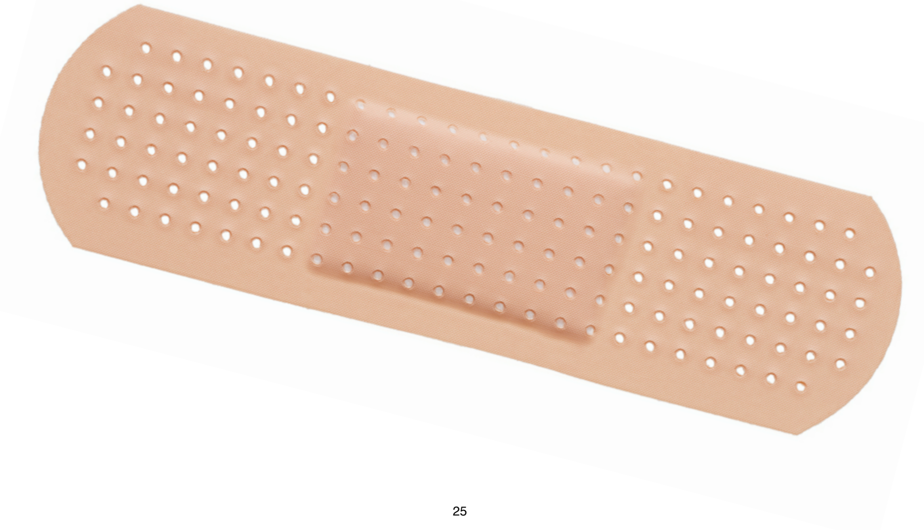
# Summary for viscoelasticity and motility

- Cell motility depends upon an <u>actin network</u> that pervades the cell.
- Actin is a <u>semiflexible polymer</u> that, when cross-linked, exhibits a dramatic increase in elastic modulus.
- The <u>strain-stiffening</u> of bundled actin allows the elastic modulus to dramatically increase with applied stress.
- This mechanism explains how cells can <u>exert force and contract</u> during motility.
  - Big open question: what are the effects of cross-linkers in non-equilibrium *in vivo* systems?
- <u>Differential strain</u> is a useful paradigm for the design of soft robot grippers and walkers.
  - Big open question: what other biological principles can inspire new artificial designs?

# Application: wound healing

Big question: How do cells collectively move to heal wounds?



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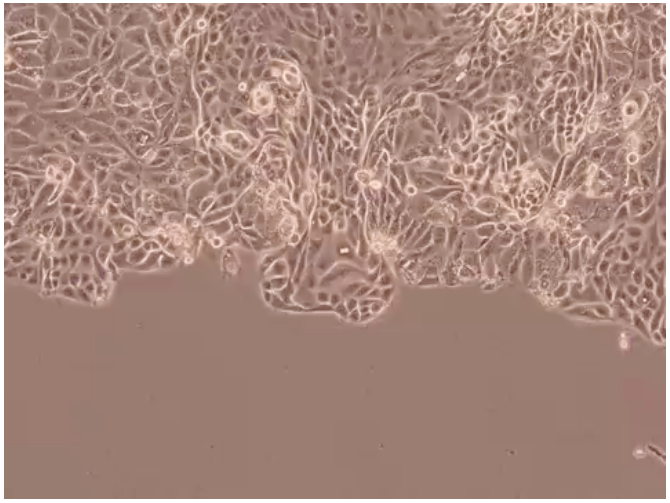
# Mass migration: confluent monolayers

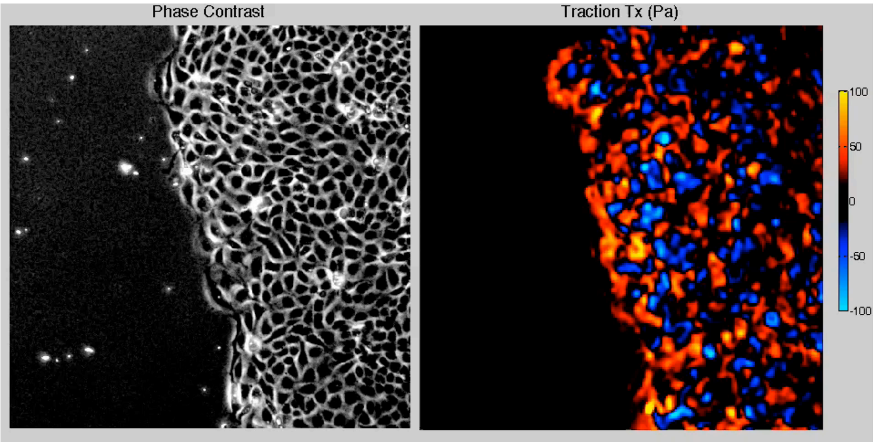
Confluent (single-layer) monolayers of epithelial cells move collectively to cover a 2-d surface.



YouTube: virtual0science

# Cells exert traction forces in migration

By measuring the displacement of tracer particles embedded in a substrate, the traction forces exerted by cells can be measured.



Trepat *et al.*, *Nat. Phys.* (2009)

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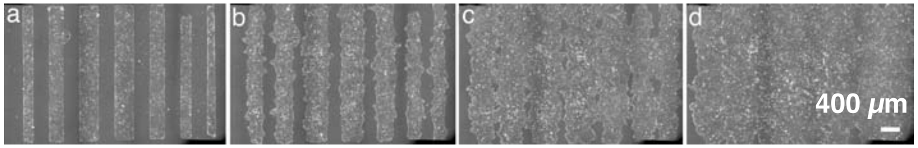
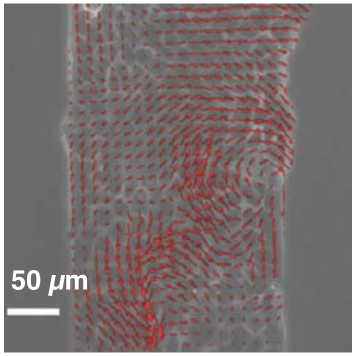
# Migration driven by free surfaces

Cells can migrate to fill gaps, driven only by a free surface:



Complex velocity profiles within migration cells again show the signs of cooperative rearrangements, with length scales of 100 $\mu$m.



Poujade *et al.*, *PNAS* (2007)

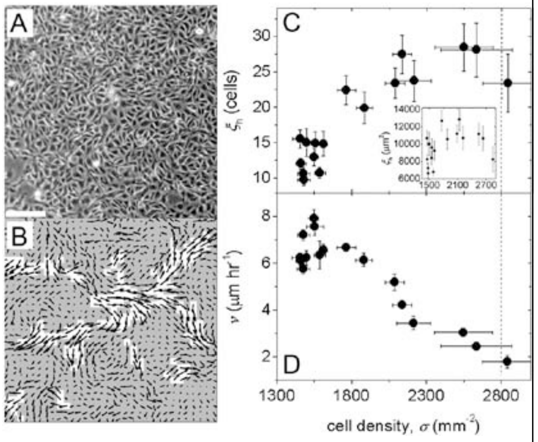
# Confluent monolayers are “glassy”

As the density of cells in the monolayer increases:

- The correlation length (or size of regions of similar velocity) increases.
- The velocity of cells decreases.

These features are shared by the liquid-to-glass transition!

Current thrust in biophysics: use non-equilibrium phase transitions to explain biological processes.



Angelini *et al.*, *PNAS* (2011)

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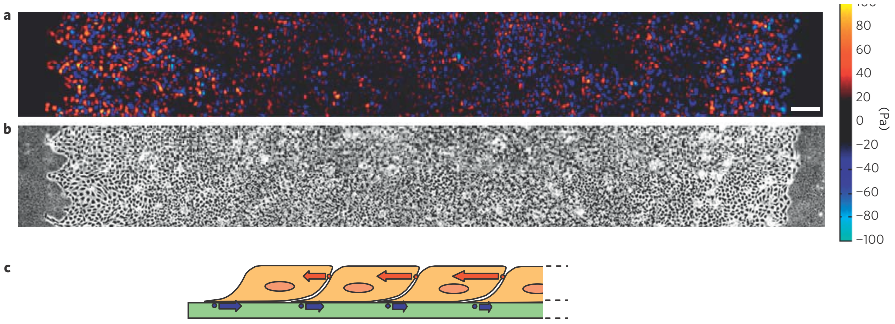
# Cooperativity: transmission of forces

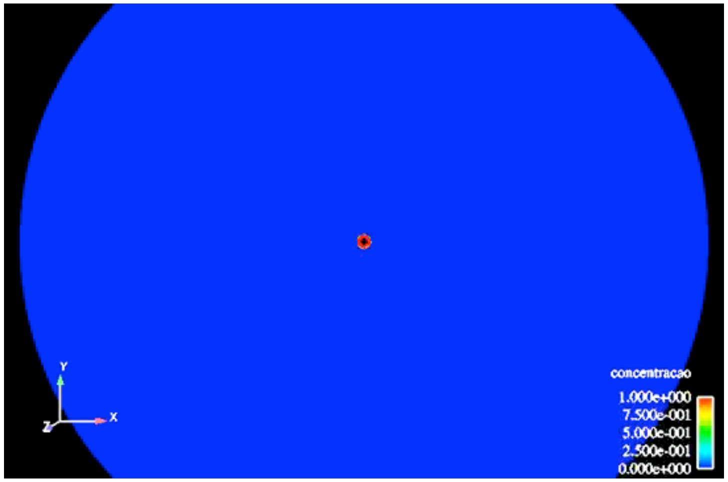


Cells move on a substrate using a tug-of-war: some of the traction force with which cells pull on the substrate gets transmitted to the backwards-neighbor.

Trepat *et al.*, *Nat. Phys.* (2009)

# Interlude: viscous fingering

Injecting a less-viscous fluid into a more-viscous fluid leads to the formation of “fingers” driven by <u>surface tension</u> at the interface.



YouTube: NACADlabs

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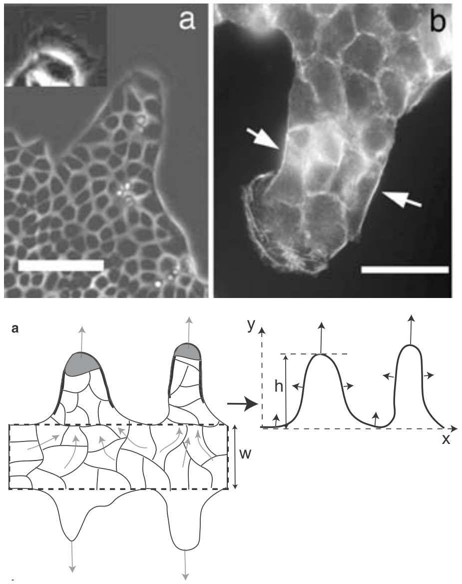
# Forces in edge growth



The formation of “fingers” of cells is reminiscent of the formation of “fingers” of viscous fluids.

For cells, the physical model is a deformation of an <u>elastic membrane</u> including <u>bending</u> and <u>surface tension</u>.

Poujade *et al.*, *PNAS* (2007); Mark *et al.*, *Biophys. J.* (2010)

# Summary and open questions

- To heal wounds, epithelial cells on substrates move collectively in confluent layers.
- Adjacent cells transmit force to move collectively.
- Confluent cells show features of glassy behavior: collective motion and increasing size of cooperatively moving regions.
- The rippled edge of a confluent layer reflects the importance of bending elasticity and surface tension.
- Open questions:
  - 2-d versus 3-d?
  - Role of intercellular signaling?