Active Stresses and Self-organization in Cytoskeletal Networks

- Cytoskeleton: rich mechanics, dynamics and activity
- Mechanics:
  - nonlinear elasticity, stiffening, anomalous stresses
- Active stresses and non-equilibrium fluctuations
- Disordered self-organization of acto-myosin
- Stability of networks by stress
- Inspiration for materials

- Collaborators:
  networks *in vitro* and *in vivo*
  Janmey, Schmidt, Weitz, Yao, Brangwynne, Silva, Koenderink, Mizuno, Gardel, Murrel

  theory of networks
  Broedersz, Sheinman, Levine, Mao, Lubensky
The cytoskeleton, a semiflexible composite

The Cell

intermediate filament  F-actin  microtubule

Vale lab, UCSF
The cytoskeleton, a semiflexible composite

The Cell

- Intermediate filament
- F-actin
- Microtubule

Extracellular matrix

- Blood clot
- Fibrin

Challenges:
- Origins of elasticity
- Nonlinear response
- Role of connectivity
- Motor/contractile activity
Storm, et al. *Nature* (2005);
also:
Gardel et al., *Science* (2004);
Gardel et al., *PRL* (2004);
Lin et al., *PRL* (2010); &
Yao et al., *Biophys J* (2010).
Nonlinear Elasticity: strain stiffening

\[ \frac{d\sigma}{d\gamma} \] (Pa)

\[ 10^3 \]
\[ 10^2 \]
\[ 10^1 \]
\[ 10^0 \]
\[ 10^{-1} \]
\[ 10^{-2} \]
\[ 10^{-3} \]

\[ \sigma \] (Pa)

3/2

\[ \text{neurofilaments} \]

\[ \tau \sim 1/|x_0 - x|^2 \]
\[ \sigma \sim (\gamma_0 - \gamma)^{-2} \]

Flexible limit:
Marko & Siggia 1994

Stiff limit:
FCM, Kas, Janmey 1995

see also Fixman & Kovac 1972

Non-equilibrium stiffening of active gels

- Design of artificial model system with cell-like activity
- Control of mechanics by motor activity

Mizuno, Tardin, Schmidt, FCM, Science, (2007);
FCM & Levine, PRL (2008);
Koenderink et al., PNAS (2009).
Motion in Cells

What governs motion in cell?
- Directed/active processes
- Random/thermal fluctuations
- Non-directed active motion?

w/ Brangwynne et al.,
*PNAS* **104**: 16128 (2007);
*PRL* **100**: 118104 (2008);
*J Cell Biol*, **183**: 583 (2008);
Thermal Motion, Equilibrium Fluctuations

\[ \langle \delta x^2(t) \rangle = 2D t \text{ (one dimension only)} \]

\[ = \frac{2kT}{6\pi\eta a} t \]

\[ D = \mu \times kT \]

\[ \mu = 1/(6\pi\eta a) \quad \text{Stokes - (Sutherland) - Einstein} \]

→ Fluctuation-Dissipation Theorem
Effect of molecular motors: Active gels


Along with these contractile fluctuations, there is a nearly 100-fold ATP-dependent stiffening of the network, which is consistent with tensions ~ few pN.

\[ C(\omega) = \int \langle x(t)x(0) \rangle e^{i\omega t} dt \neq \frac{2kT}{\omega} \alpha''(\omega) \]

\[ x_\omega = \alpha(\omega) f_\omega \]
Effect of molecular motors: Active gels

with A Levine, PRL 2008; JPC 2009

Unbinding & release

\[ f(t) \]

force fluctuations

passive

active

time
Effect of molecular motors: Active gels

with A Levine, PRL 2008; JPC 2009

\[
\mathbb{G} \quad \begin{cases} \text{elastic} \\ \text{active} \end{cases}
\]

\[
G(t) \quad f(t) \quad \frac{\langle |f_\omega|^2 \rangle}{\omega^2} \sim 1/\omega^2
\]
Cell activity probed by injected beads

Open symbols: 10 μM Blebbistatin treated (inhibit Myosin II motors).
Lines: Sodium Azide + 2-deoxy-D-glucose treated (deplete ATP).

with Guo and Weitz
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with A Levine, PRL 2008

with Guo and Weitz
Athermal Fluctuations of MTs

\[ \theta(s) = \sum_q a_q \sin(qs) \]

\[ \langle |a_q(t) - a_q(0)|^2 \rangle \sim t \]

Myosin coalescence, aggregation

Martin, Kaschube & Wieschaus, Nature 2009
Contractile fluctuations and aggregation

Green = myosin
Red = actin

Soares e Silva, Sturhmann, Depken, FCM, Koenderink, PNAS, 2011.

see also Koehler, Schaller, Bausch, Nature Materials, 2011.
Contractile fluctuations and aggregation

Green = myosin
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Soares e Silva, Sturhmann, Depken, FCM, Koenderink, PNAS, 2011.

see also Koehler, Schaller, Bausch, Nature Materials, 2011.
Buckling of actin leads to coalescence of aggregates

Buckling of actin leads to accumulation of actin and coalescence of aggregates

Soares e Silva, Sturhmann, Depken, FCM, Koenderink, PNAS, 2011.
Connectivity and isostaticity

$z_c = 2d$

J. C. Maxwell, Philos. Mag. 27, 27 (1864)
M. Wyart et al., PRL. 101, 215501 (2008)
Connectivity and isostaticity

J. C. Maxwell, Philos. Mag. 27, 27 (1864)
M. Wyart et al., PRL. 101, 215501 (2008)

isostatic coordination

$z_c = 2d$

collagen (in vitro)  actin-cortex  vimemtin (in vitro)  red blood cell (actin-spectrin)

$z < z_c$  $z < z_c$  $z < z_c$  $z > z_c$

J. C. Maxwell, Philos. Mag. 27, 27 (1864)
M. Wyart et al., PRL. 101, 215501 (2008)
Critical behavior and shear-induced non-affine fluctuations

2D triangular lattice

3D FCC lattice

\[ G \]

\[ P_b \]

\[ \kappa \]

bend rigidity

\[ B = 0 \]

\[ B > 0 \]

CP Broedersz, X Mao, T Lubensky and FCM, Nature Phys (2011)
Phase diagram under load

S Alexander (1998)
Stress-induced stability of floppy networks
See also Cai et al., J Cell Sci (2010).

with Broedersz and Sheinman
Phase diagram under load

Stiffness

Strain

connectivity

rigid

floppy

\( z_c \)

http://www.youtube.com/watch?v=ANSQePygfYU

See also Cai et al., J Cell Sci (2010).

Phase diagram under load

Stress-induced stability of floppy networks

connectivity $\zeta$

rigid

floppy

theory

fluctuations

Stiffness

Strain

$Z_C$
Phase diagram under load

$\zeta$ vs. stress/strain

Connectivity $\zeta$:
- Rigid
- Floppy


with Broedersz and Sheinman

$z_c$
Phase diagram under load

connectivity $\zeta$

rigid

floppy

stress/strain

$z_c$


with Broedersz and Sheinman

Y27632 washout
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