# Microrheology's place in the rheologist's toolbox

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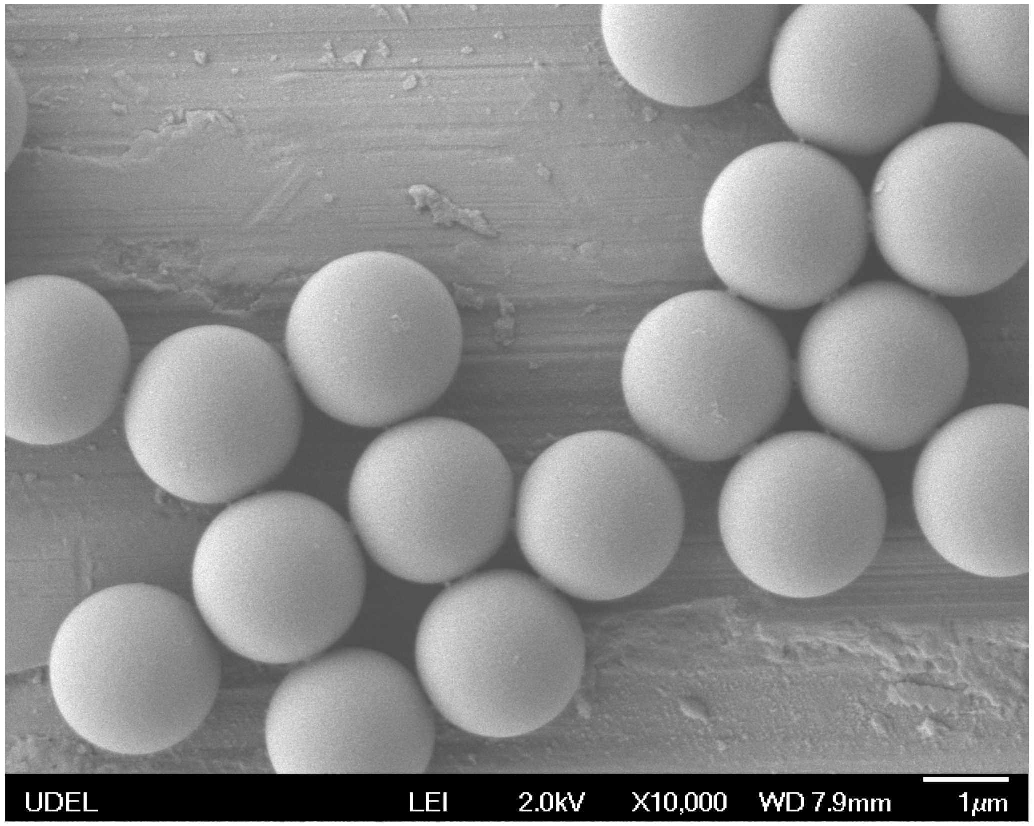
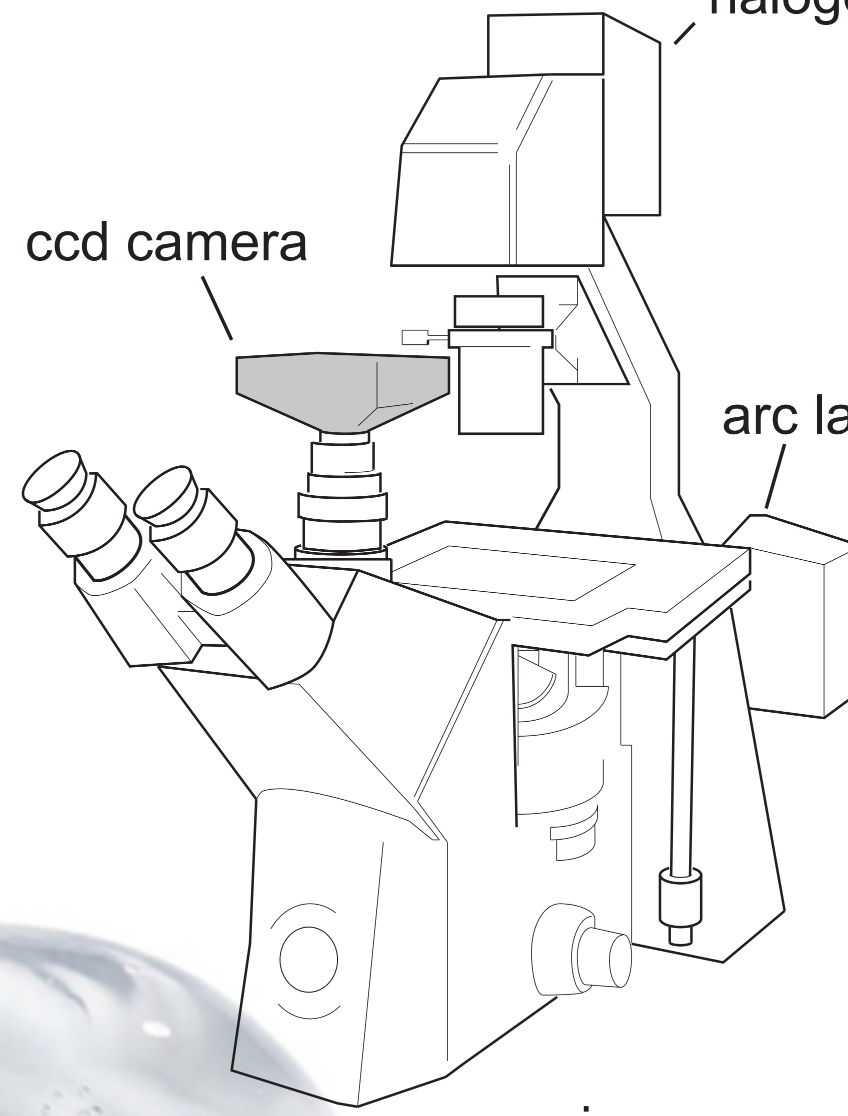
CMET
Center *for* Molecular & Engineering Thermodynamics

Society of Rheology
February 13, 2017

# monodisperse, μm colloids



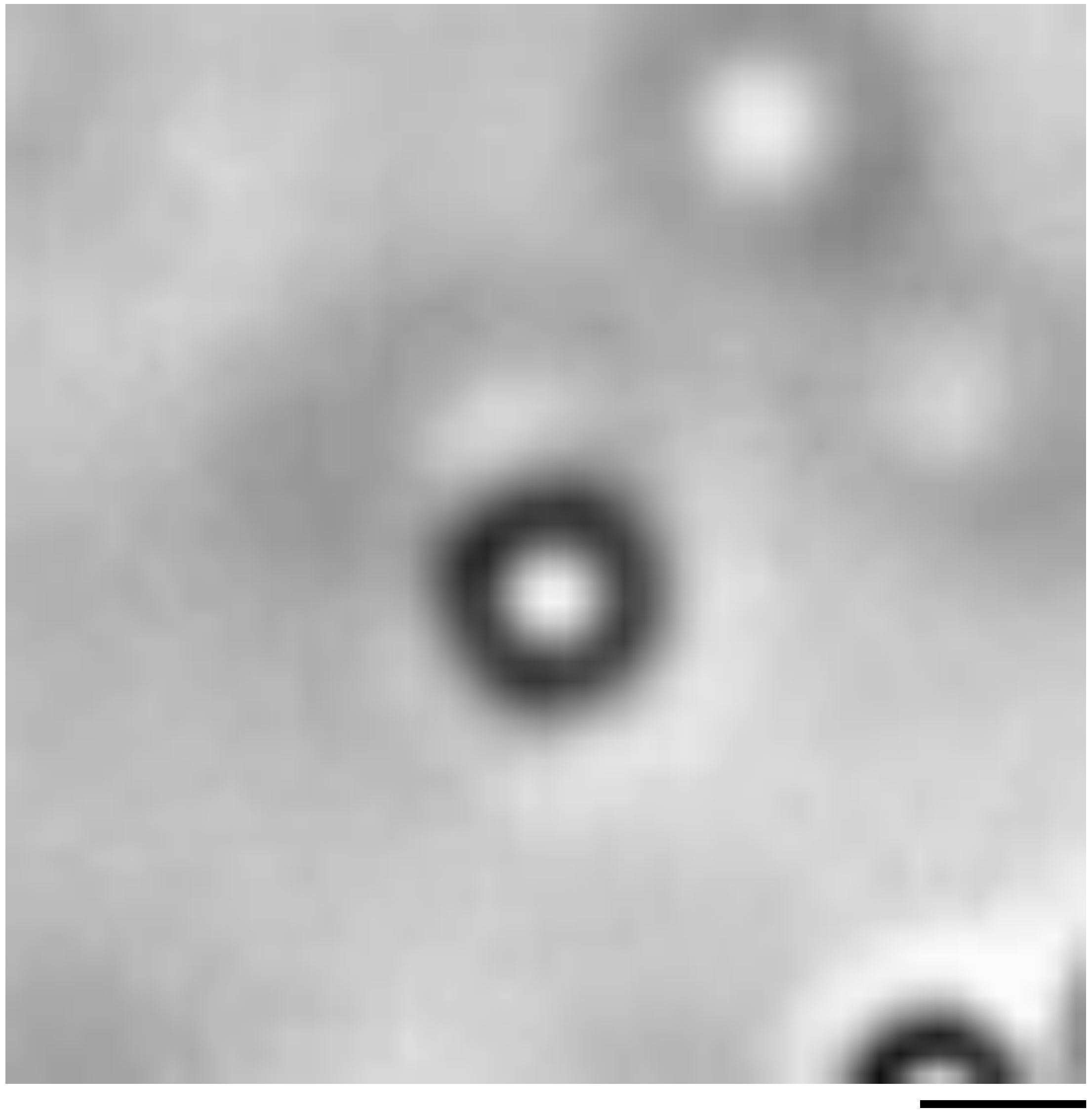

*polystyrene latex*



# Microrheology

*Measure the motion of colloidal "probe" or "tracer" particles in a material*

Mason, T. G. & Weitz, D. A., *Phys. Rev. Lett.* 74, 1250–1253 (1995).
Gittes, F., et al., *Phys. Rev. Lett.* 79, 3286–3289 (1997).
Mason, T. G., et al., *Phys. Rev. Lett.* 79, 3282–3285 (1997).

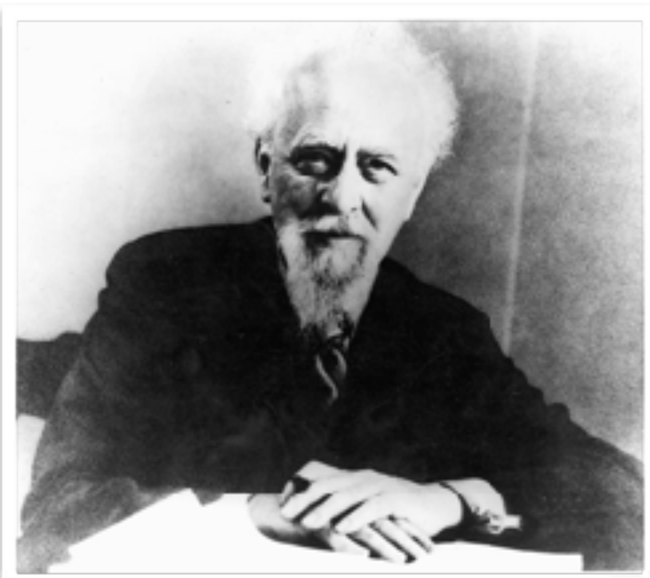


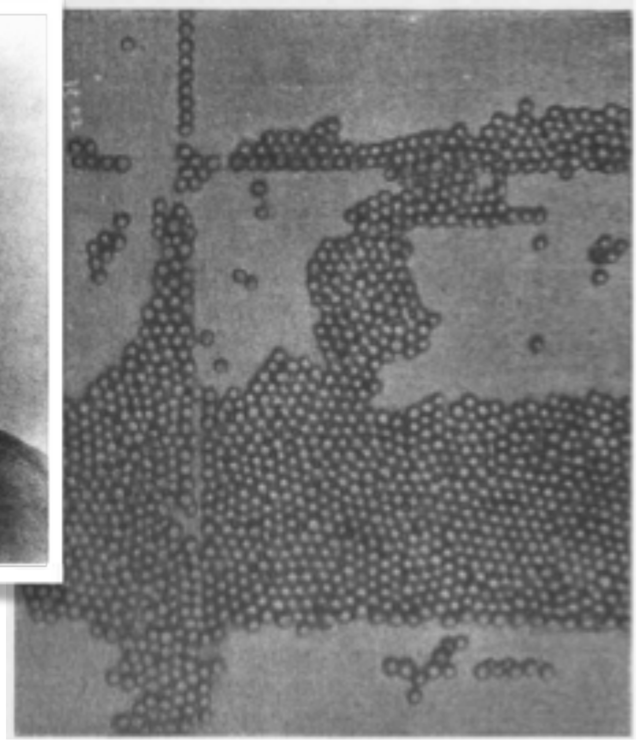
1 μm diameter polystyrene latex particle in water

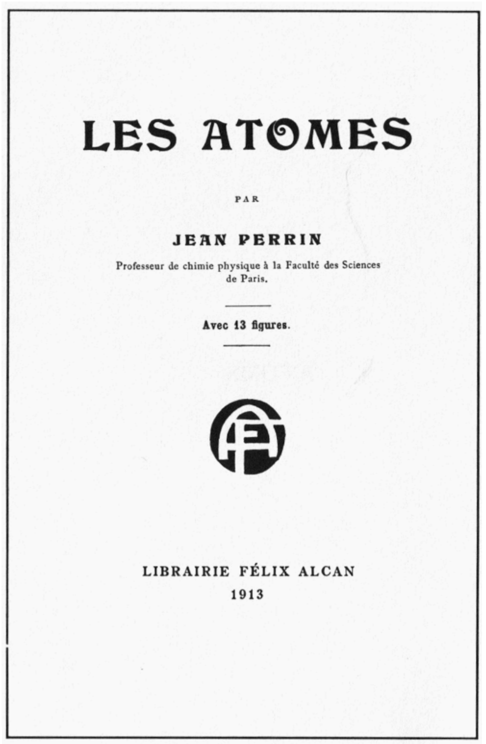
*use motion to determine rheological properties*

# Jean Perrin, 1908

*Nobel Prize, 1926*







LES ATOMES

PAR

JEAN PERRIN

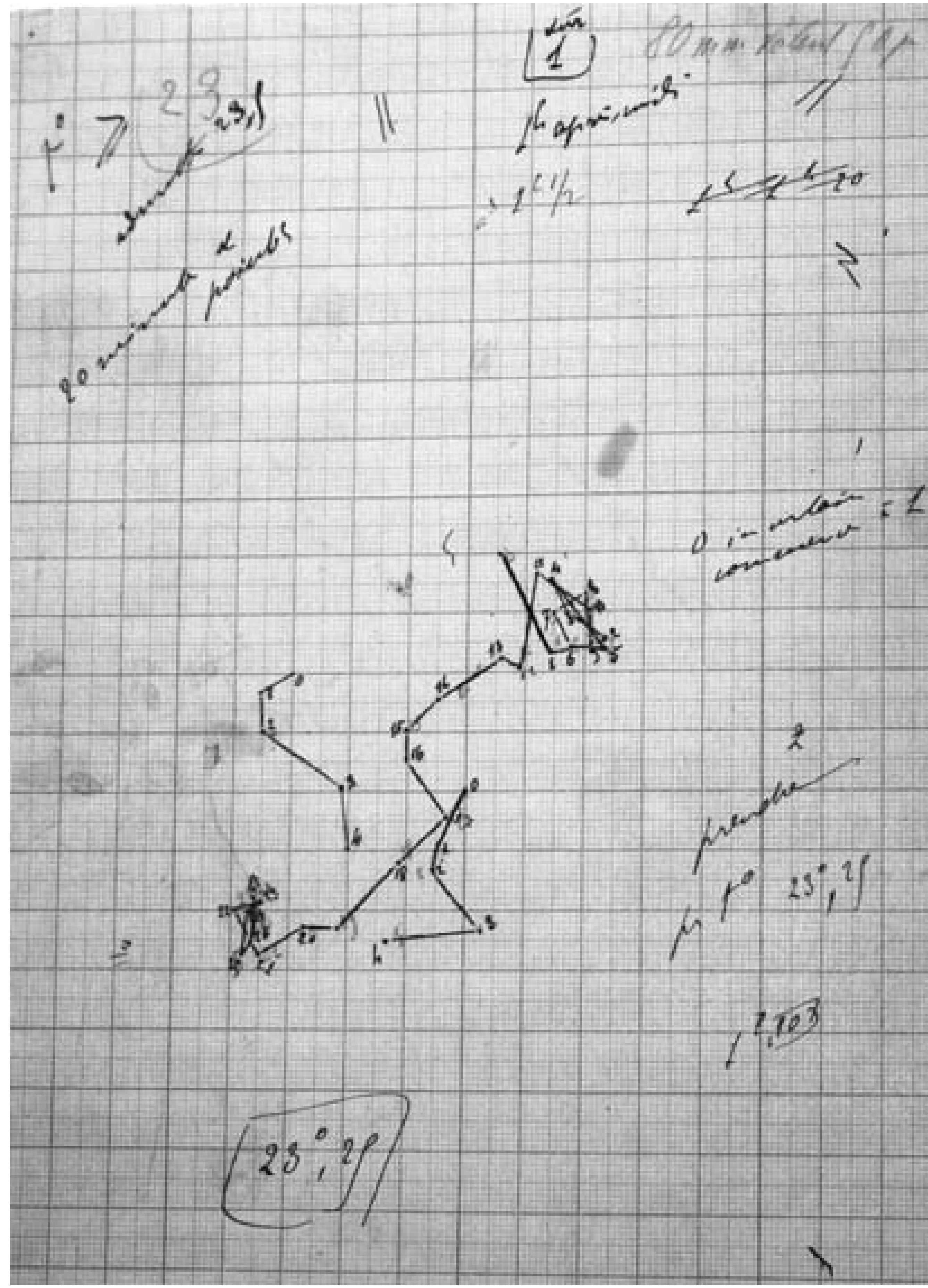
Professeur de chimie physique à la Faculté des Sciences de Paris.

Avec 13 figures.

LIBRAIRIE FÉLIX ALCAN

1913

*microscope & camera lucida*



Colloid size: > 1 µm
1 particle at a time
Position sampled every 30s / 500 positions (~ 4h)
2 students to operate

# Early microrheology

Freundlich, H. and Seifriz, W., *Z. Phys. Chem.* 104, 233 (1923).
Seifriz, W., *Brit. J. Exp. Biol.* 2, 1-11 (1924).
A. Heilbronn. Jahrb. Wiss. Bot. 61, 284–338 (1922).

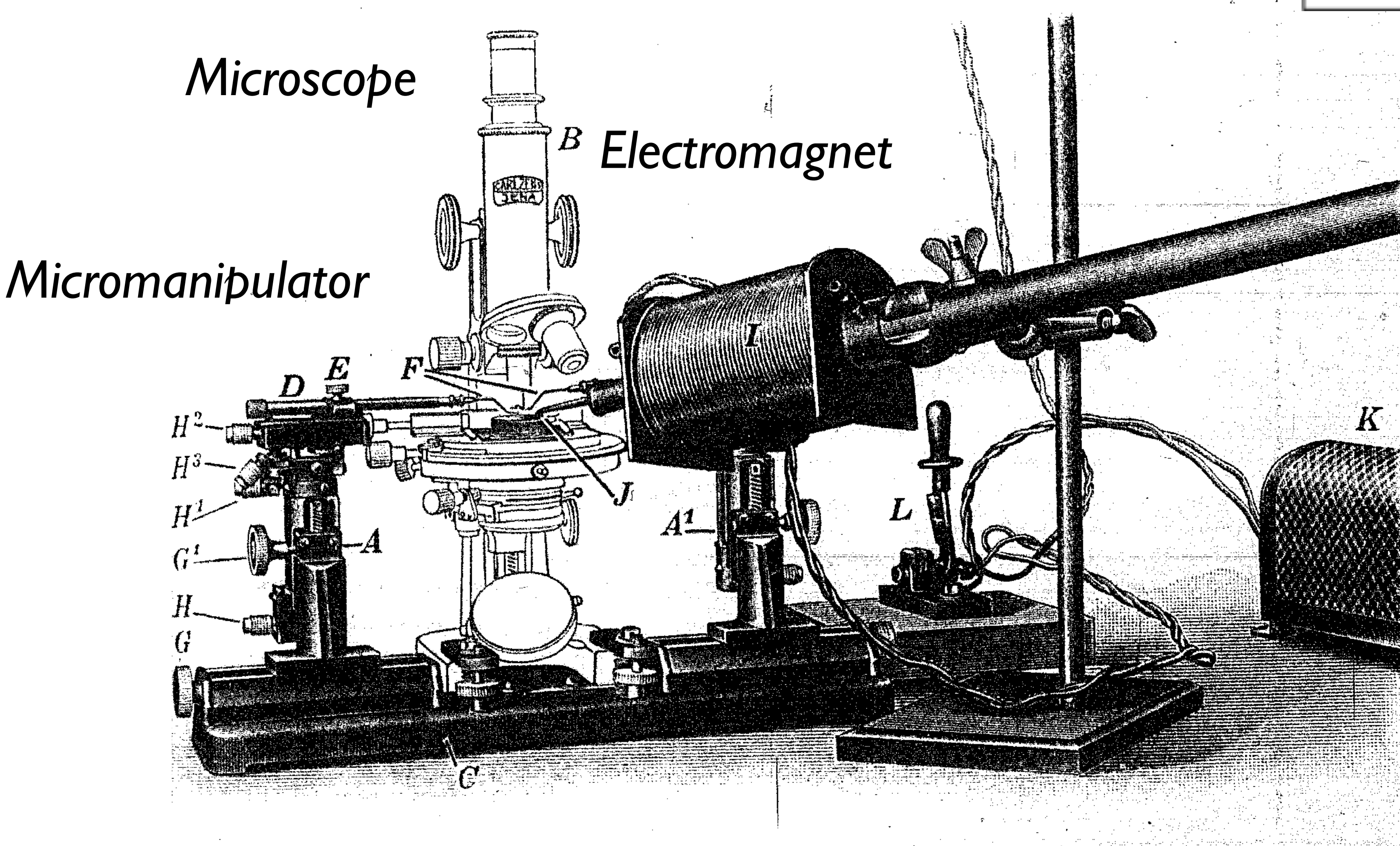
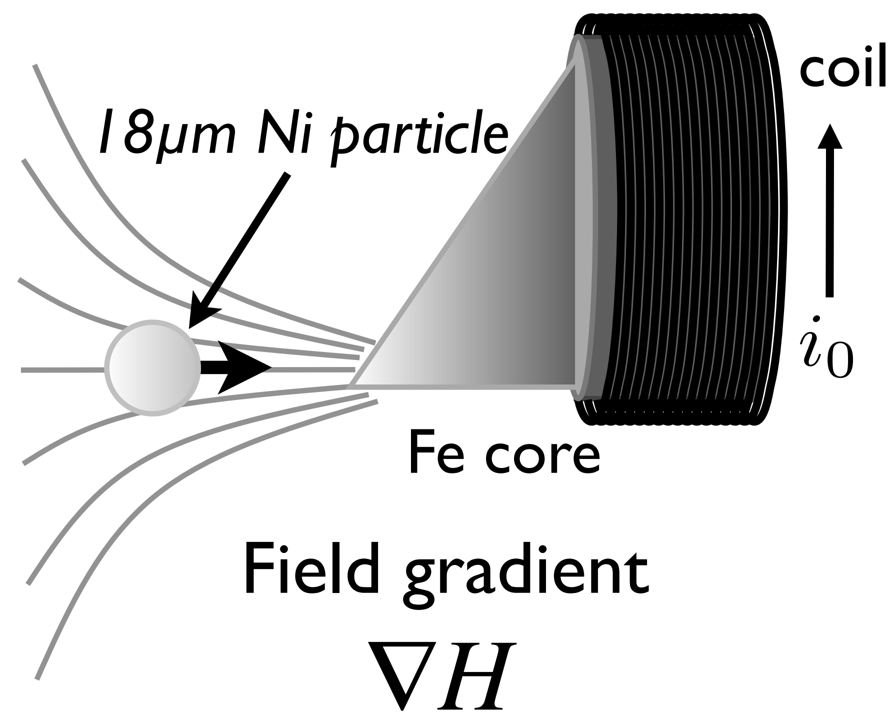
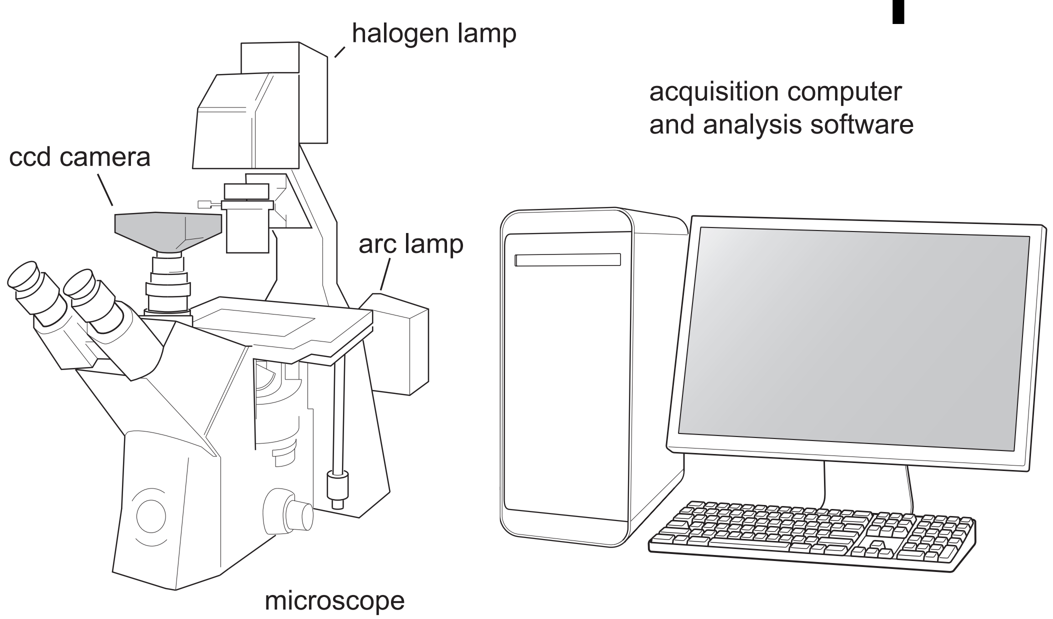



Fig. 1.

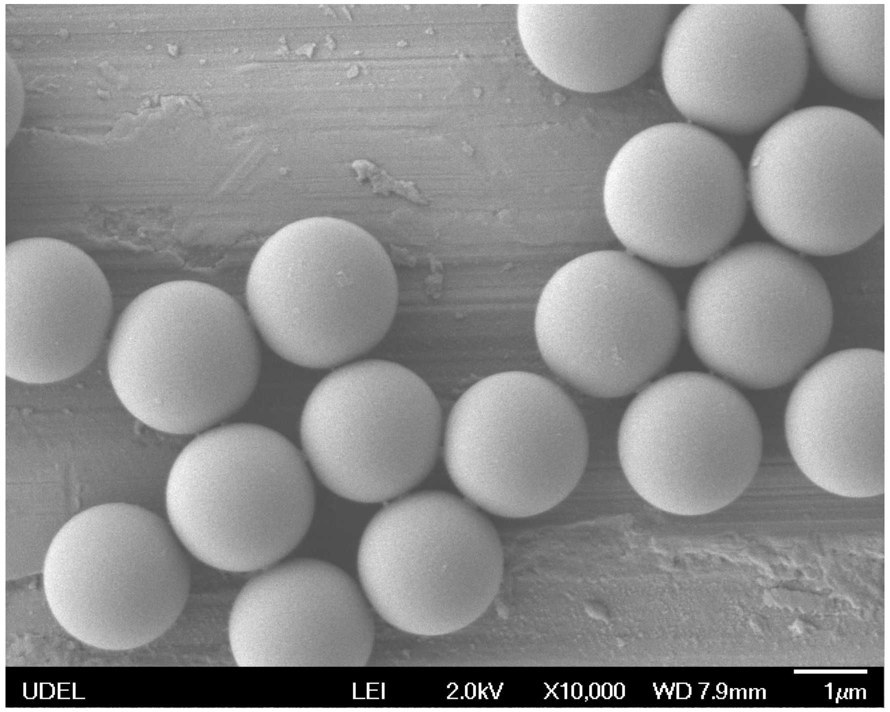



Elasticity of *Echinarachnius parma* (sand dollar) egg protoplasm, gelatin sols and gels

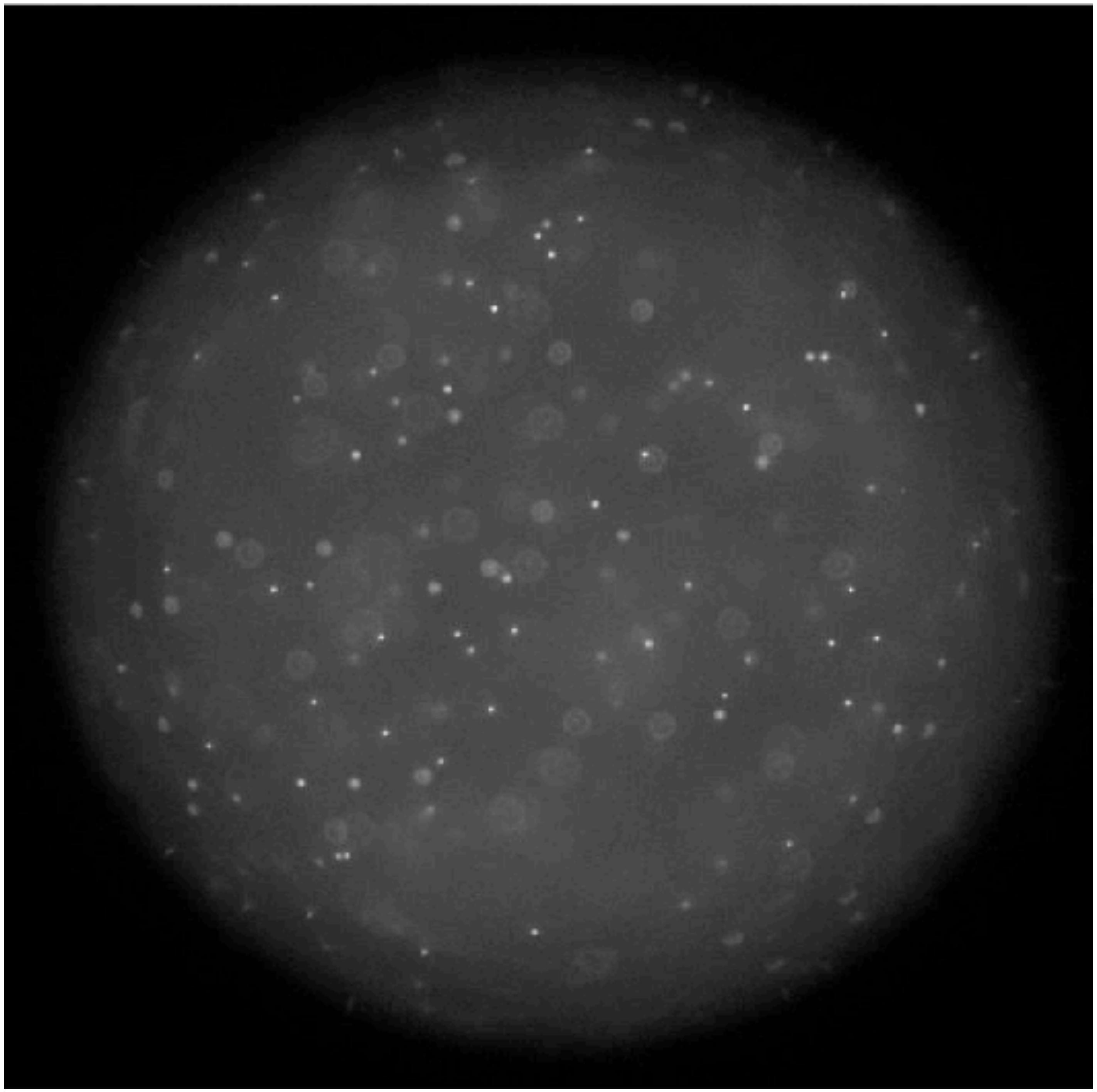
# Multiple particle tracking



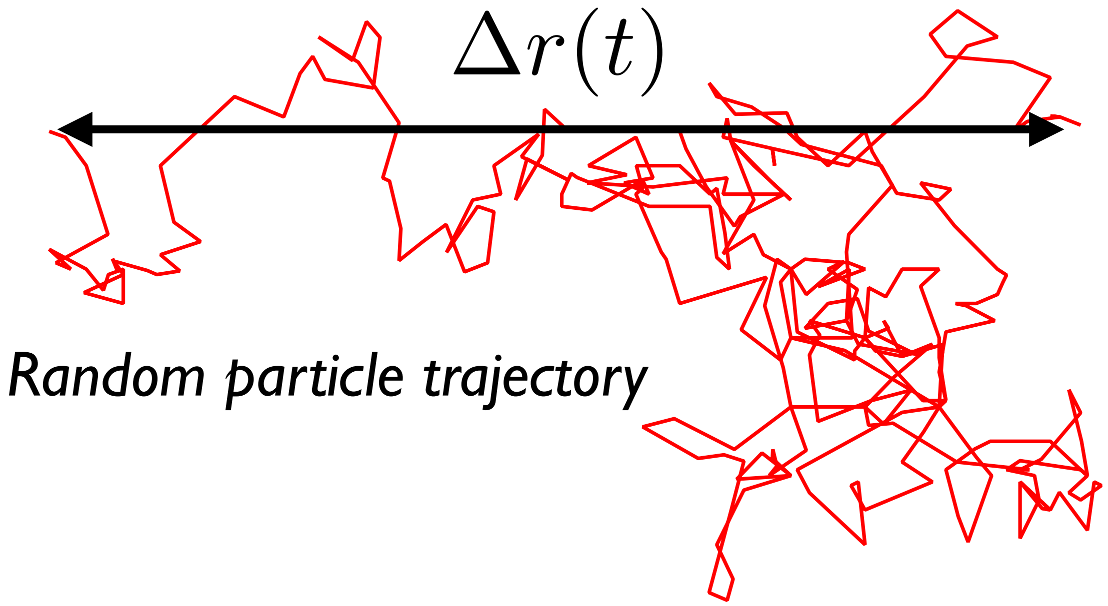

Blair, Dufresne, Weeks, Crocker, Grier
*http://site.physics.georgetown.edu/matlab/*

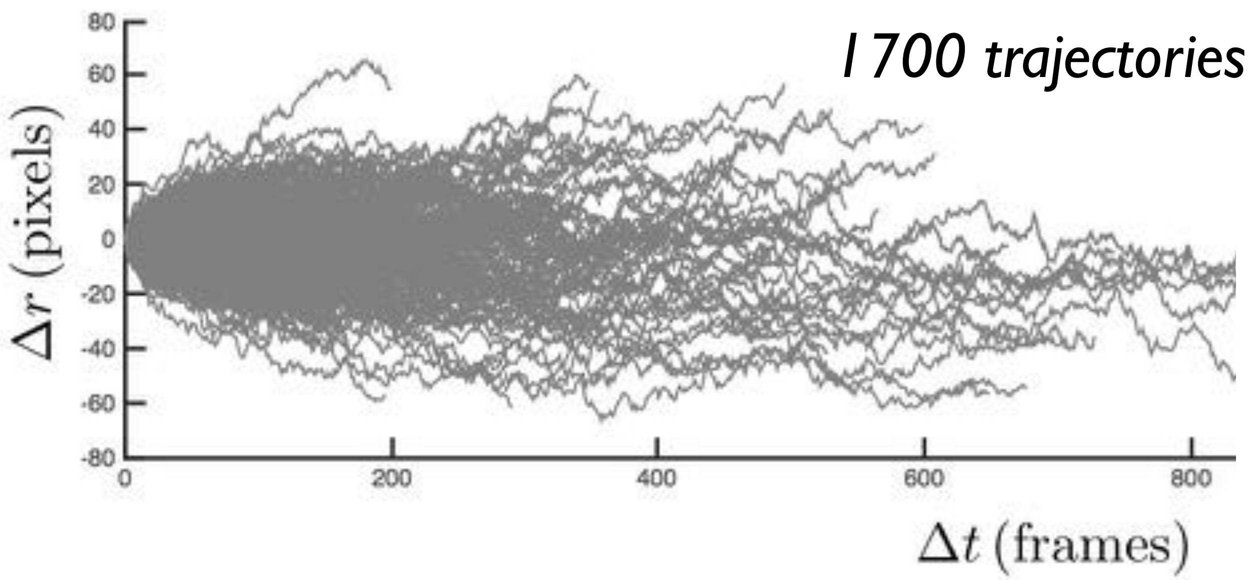


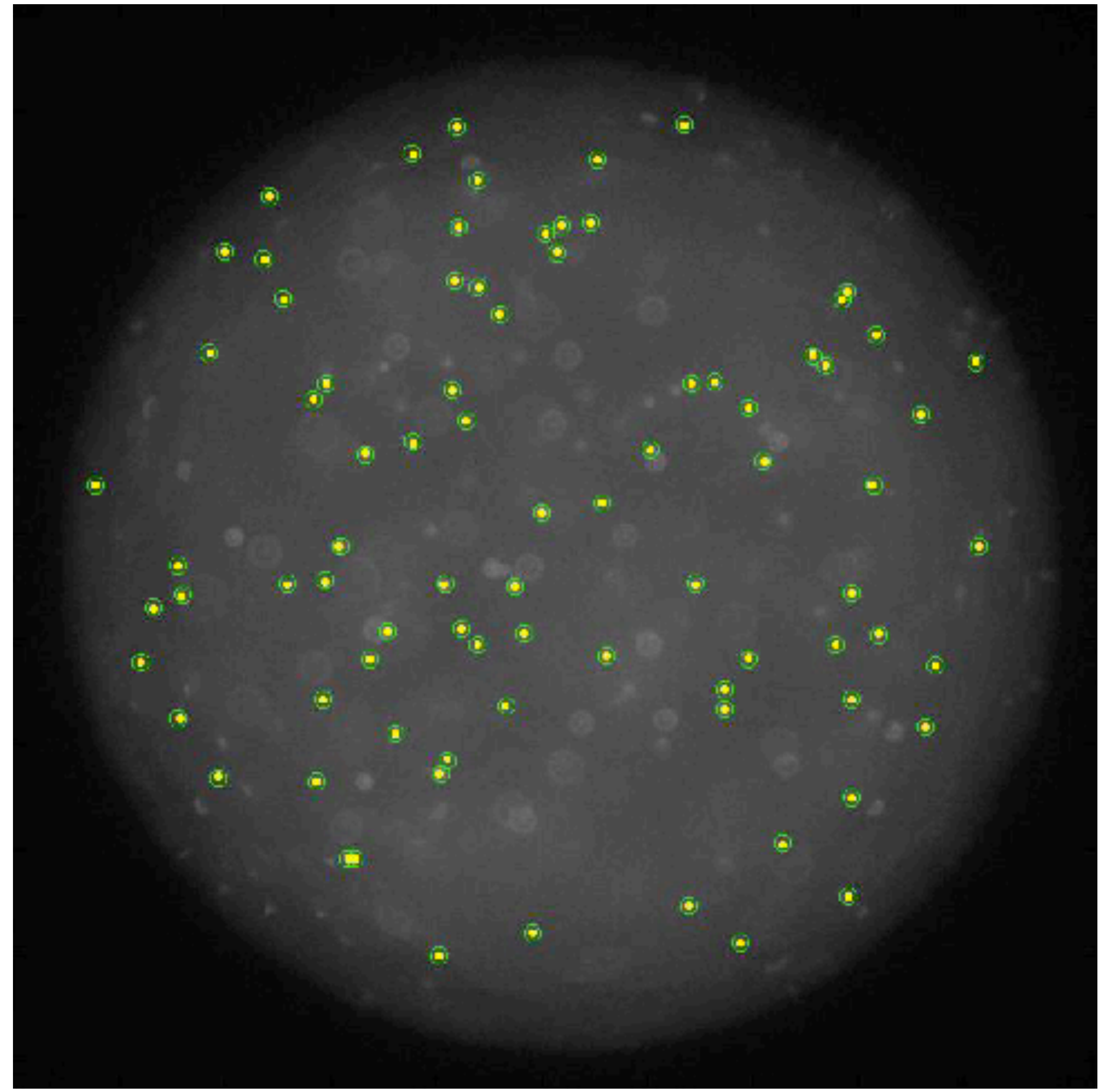

polystyrene microspheres



*1 micron fluorescent spheres in water*



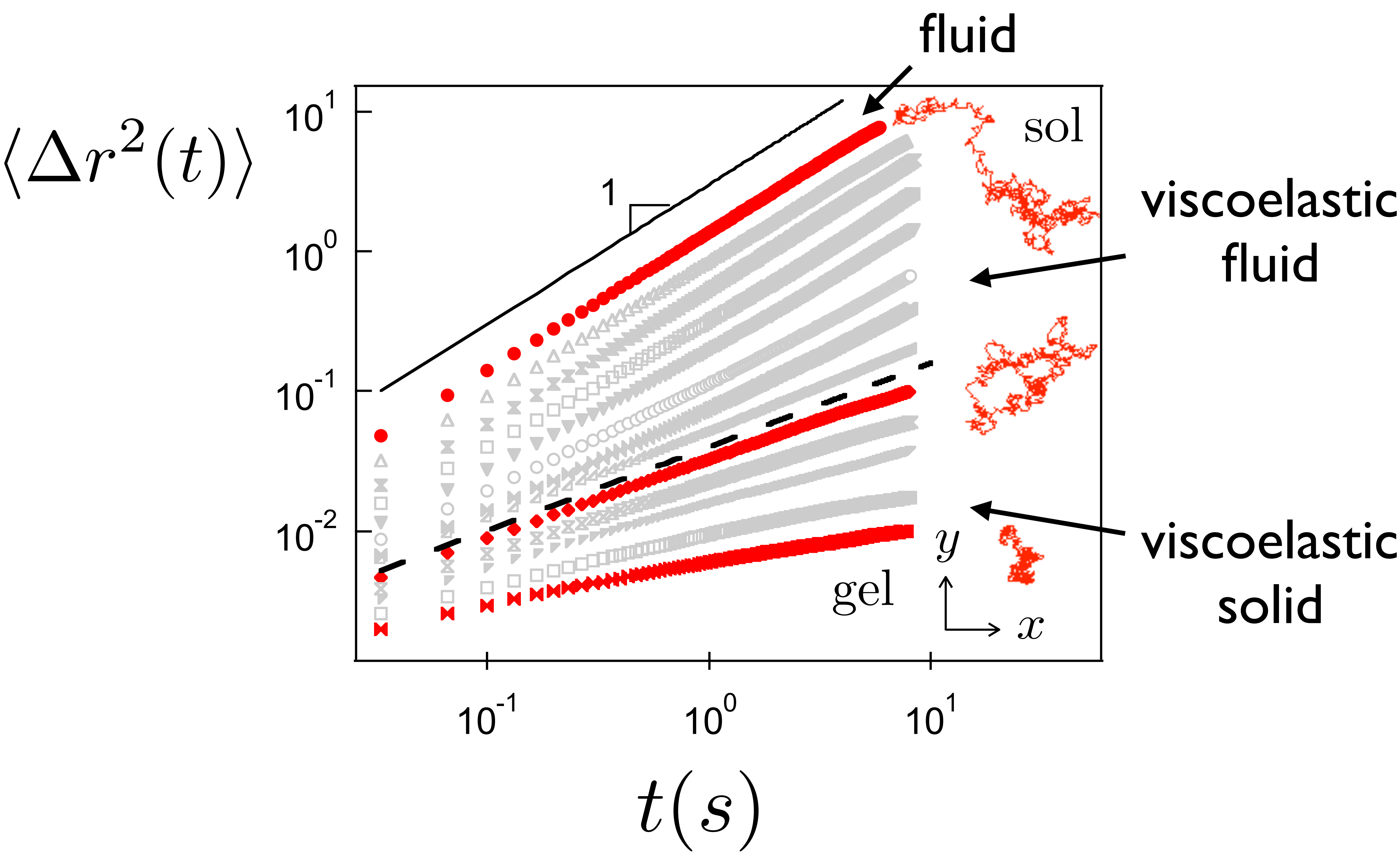



*1 micron fluorescent spheres in water*

$$\langle \Delta r^2(t) \rangle$$

# Mean-squared displacement (MSD)

# Mean-squared displacement



# Generalized Stokes-Einstein Relation (GSER)

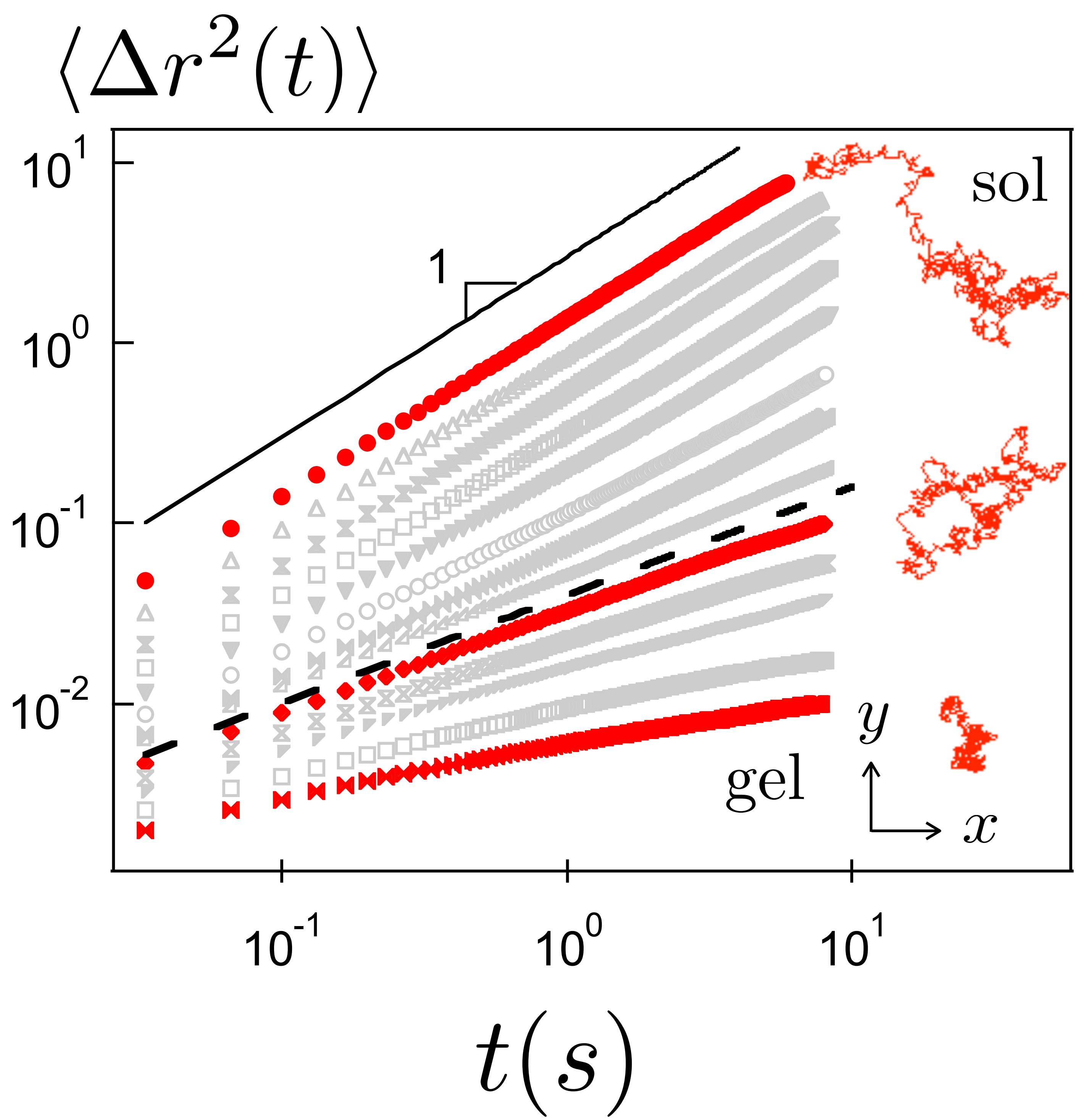
*(neglecting inertia)*

$$\hat{G}(s) = \frac{k_B T}{\pi a s \langle \Delta \hat{r}^2(s) \rangle}$$

$$G^*(\omega) = \frac{k_B T}{\pi a (i\omega) \langle \Delta \tilde{r}^2(\omega) \rangle}$$

$$\frac{1}{i\omega} = G^*(\omega) \tilde{J}(\omega)$$

$$J(t) = \frac{\pi a}{kT} \langle \Delta r^2(t) \rangle$$



# Generalized Stokes-Einstein Relation (GSER)

*(neglecting inertia)*

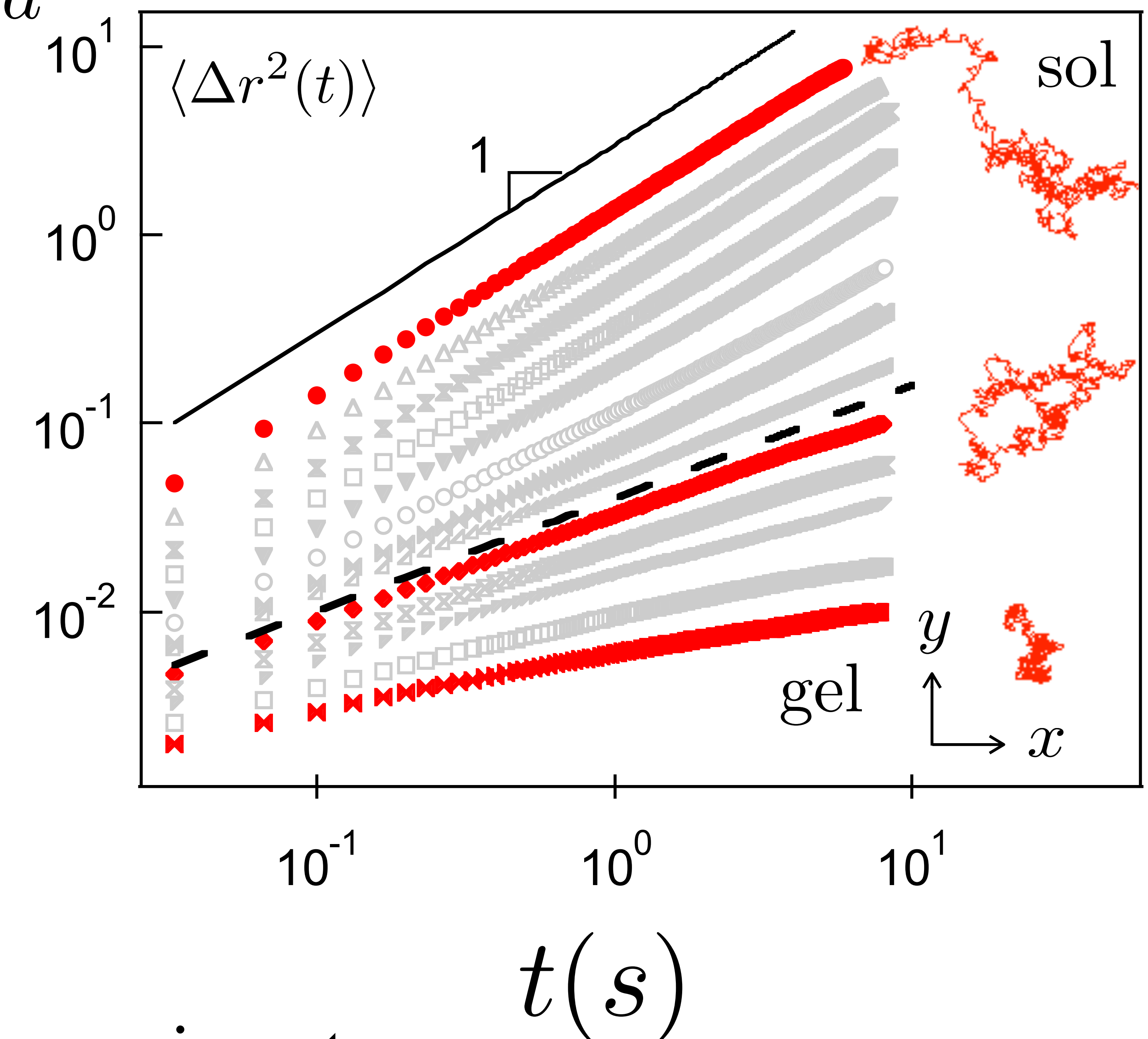
$$\hat{G}(s) = \frac{k_B T}{\pi a s \langle \Delta \hat{r}^2(s) \rangle}$$

$$\frac{kT}{\pi a} J(t)$$

$$G^*(\omega) = \frac{k_B T}{\pi a (i\omega) \langle \Delta \tilde{r}^2(\omega) \rangle}$$

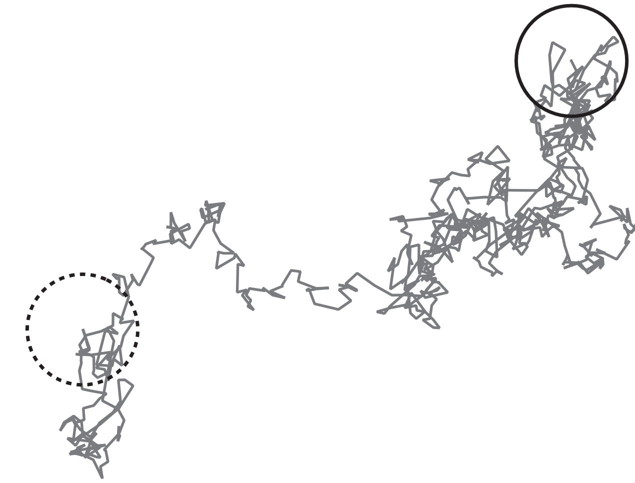
$$\frac{1}{i\omega} = G^*(\omega) \tilde{J}(\omega)$$

$$J(t) = \frac{\pi a}{kT} \langle \Delta r^2(t) \rangle$$




microrheology is a creep experiment

# Derivation of the GSER



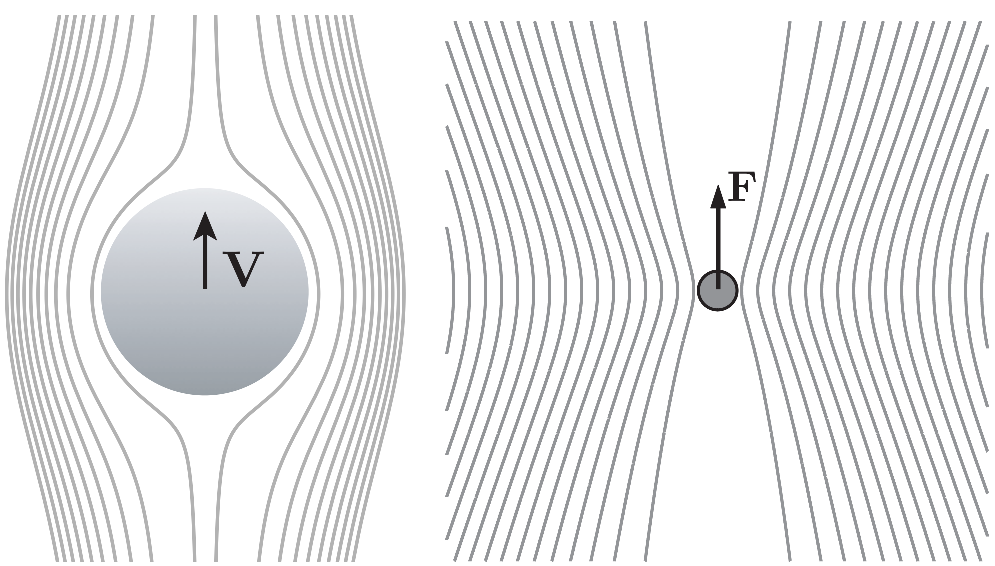
Ryogo Kubo


Generalized Langevin Equation

$$m\dot{\mathbf{V}}(t) = \mathbf{f}_B - \int_{-\infty}^{t} \zeta(t-t')\mathbf{V}(t')dt'$$

Zwanzig, R. & Bixon, M. *Phys. Rev. A* 2, 2005–2012 (1970).
Gittes, F., et al., *Phys. Rev. Lett.* 79, 3286–3289 (1997).
Mason, T. G., Gang, H. & Weitz, D. A. *J. Opt. Soc. Am.* 14, 139–149 (1997).
Indei, T., Schieber, J. D., Cordoba, A. & Pilyugina, E. *Phys. Rev. E* 85, 21504 (2012).

# Correspondence Principle




continuum limit

$$\tilde{\zeta}(\omega) = 6\pi a G^*(\omega)/i\omega$$

$$-\rho\omega^2\tilde{\mathbf{u}} = -\nabla\tilde{p} + i\omega\eta\nabla^2\tilde{\mathbf{u}}$$ – *Newtonian fluid*

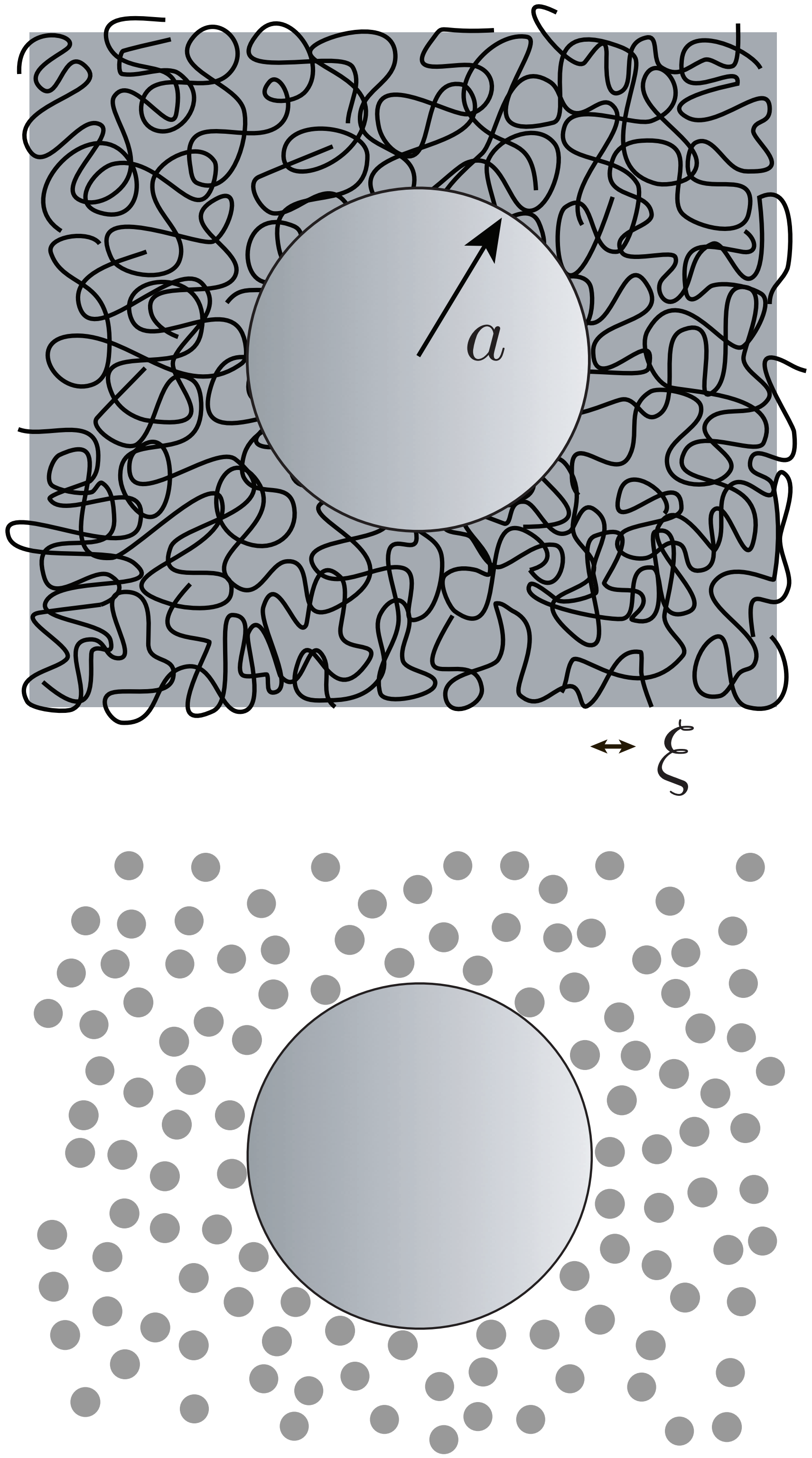
$$-\rho\omega^2\tilde{\mathbf{u}} = -\nabla\tilde{p} + G\nabla^2\tilde{\mathbf{u}}$$ – *elastic solid*

$$-\rho\omega^2\tilde{\mathbf{u}} = -\nabla\tilde{p} + G^*(\omega)\nabla^2\tilde{\mathbf{u}}$$ – *viscoelastic*

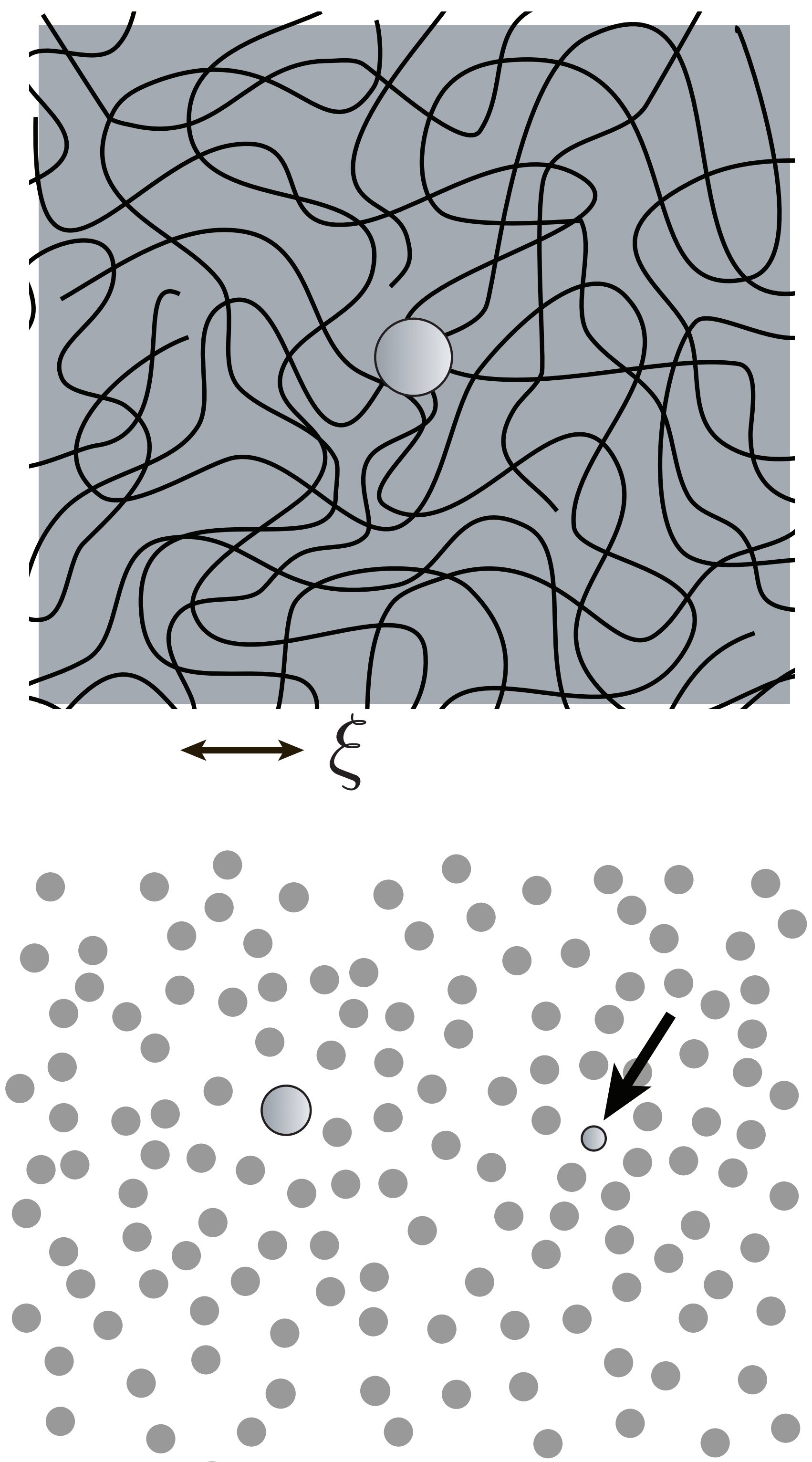
Gittes, F., et al., *Phys. Rev. Lett.* 79, 3286–3289 (1997).
Schieber, J. D., Córdoba, A. & Indei, T. J. Non-Newton. Fluid Mech. 200, 3–8 (2013).

# Limit: probes in the continuum limit

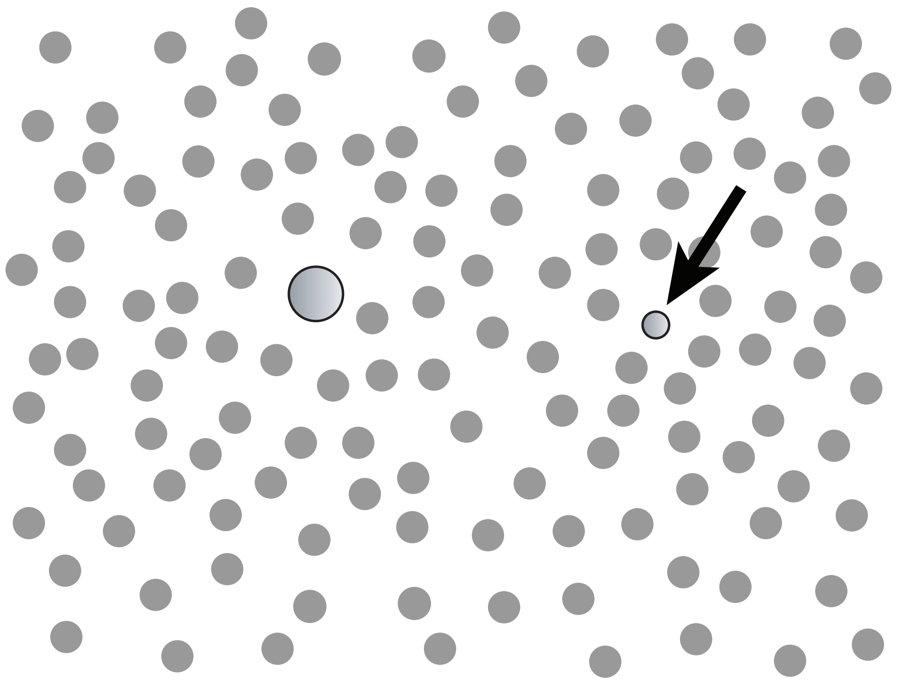
*Continuum* $a \gg \xi$




*Non-continuum* $a \leq \xi$

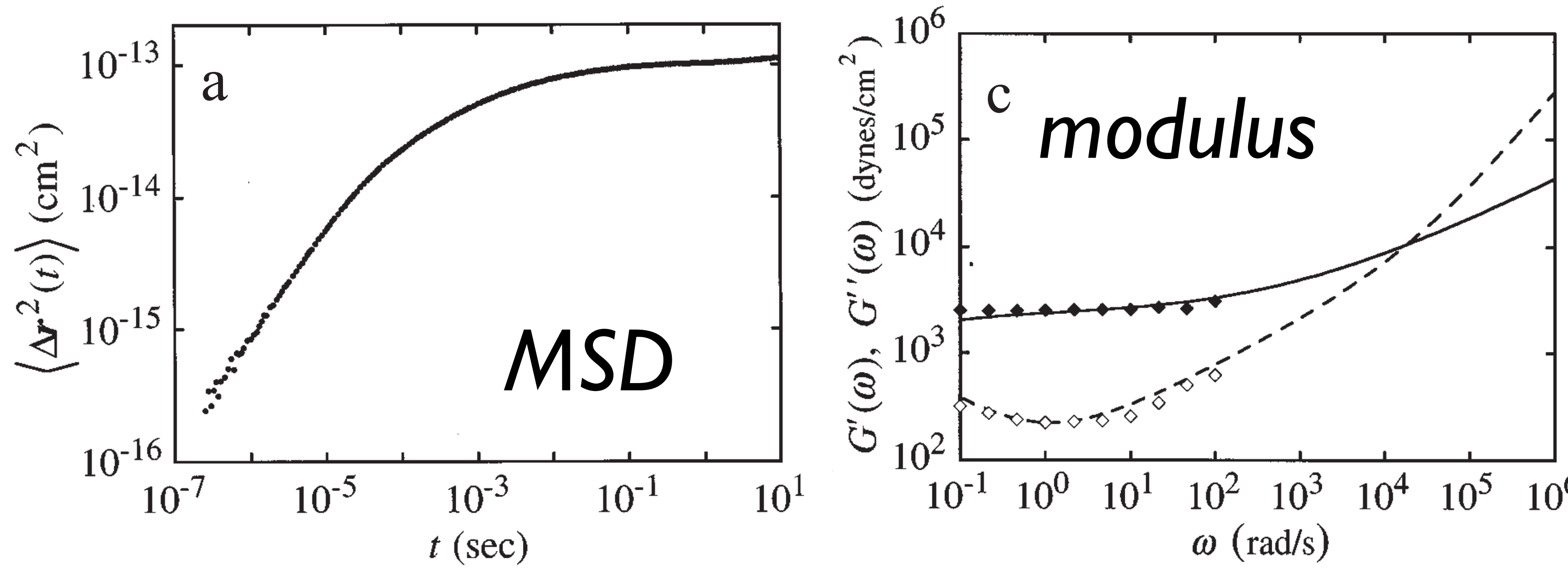


# Non-continuum limit

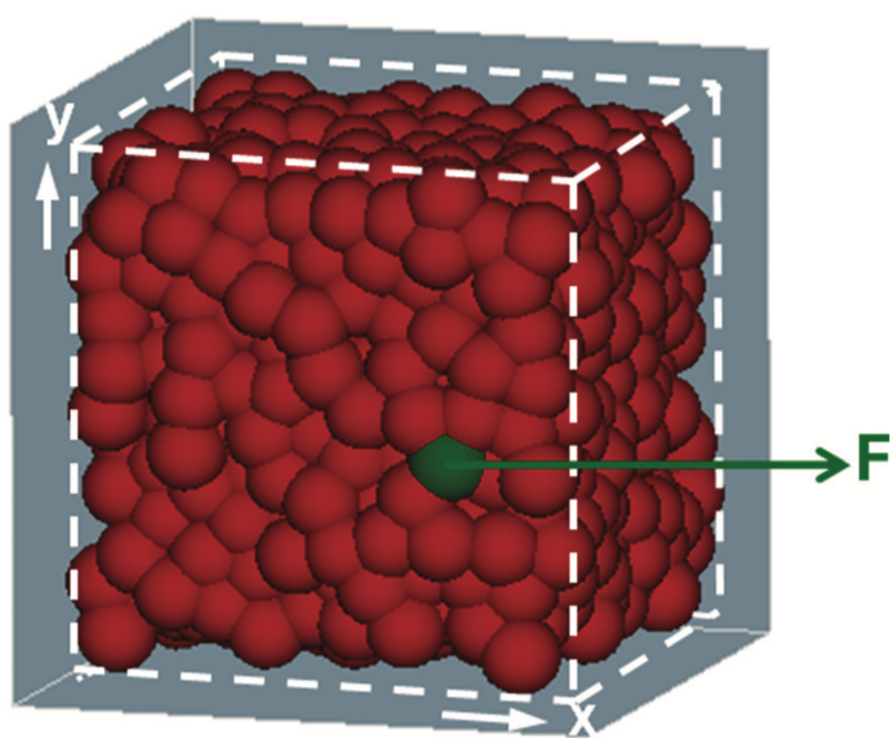


## Concentrated emulsion

Mason, T. G., Gang, H. & Weitz, D.A. *J. Opt. Soc. Am.* 14, 139–149 (1997).




Zwanzig, R. & Bixon, M. *Phys. Rev. A* 2, 2005–2012 (1970).



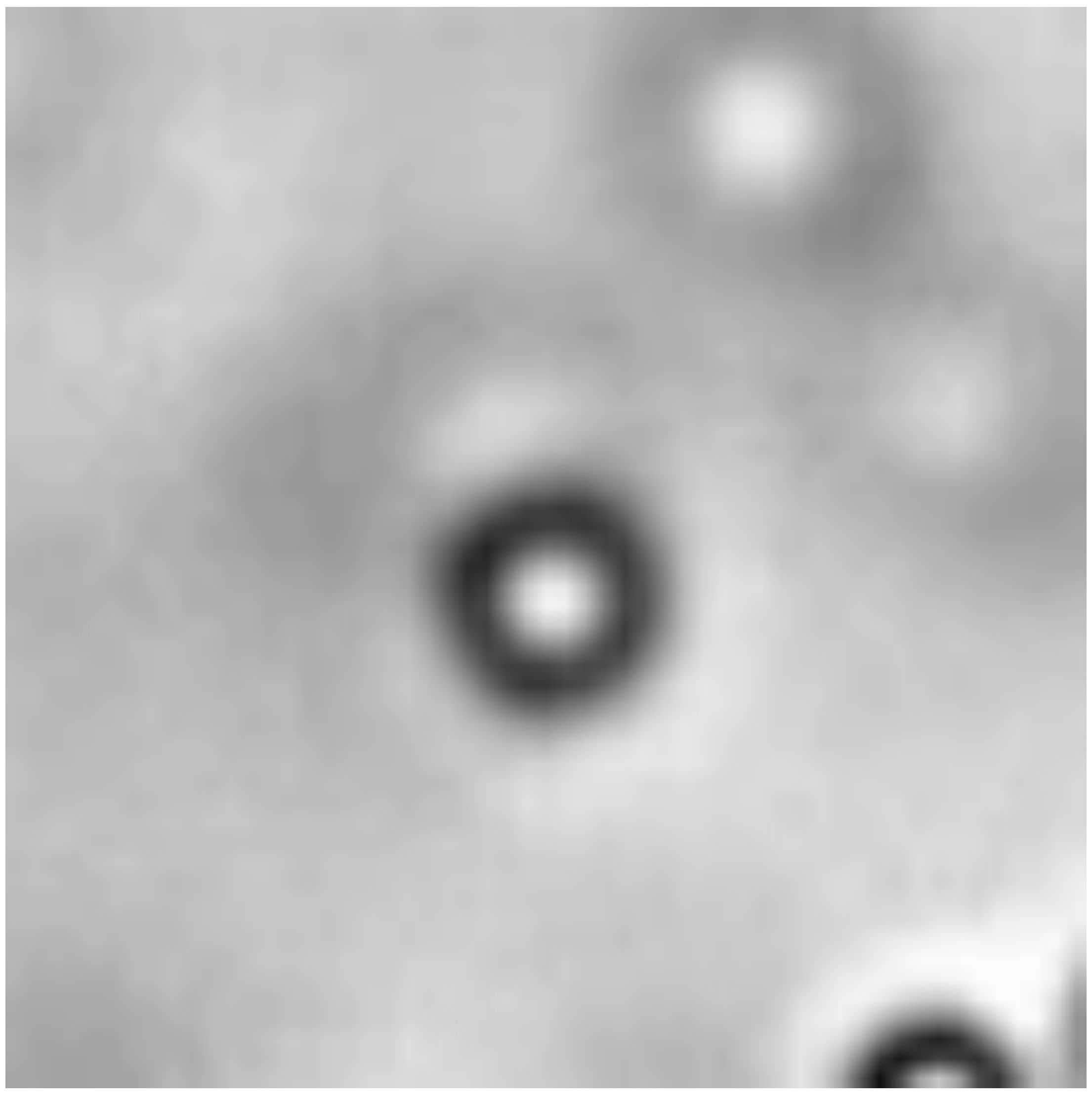

## Dense suspensions and glasses

*Fuchs, Zia, Brady, Khair, Voigtmann, Swan, Bonnecaze, Cloitre…*

Mohan, L., Cloitre, M. & Bonnecaze, R.T. *J. Rheol.* 58, 1465–1482 (2014).

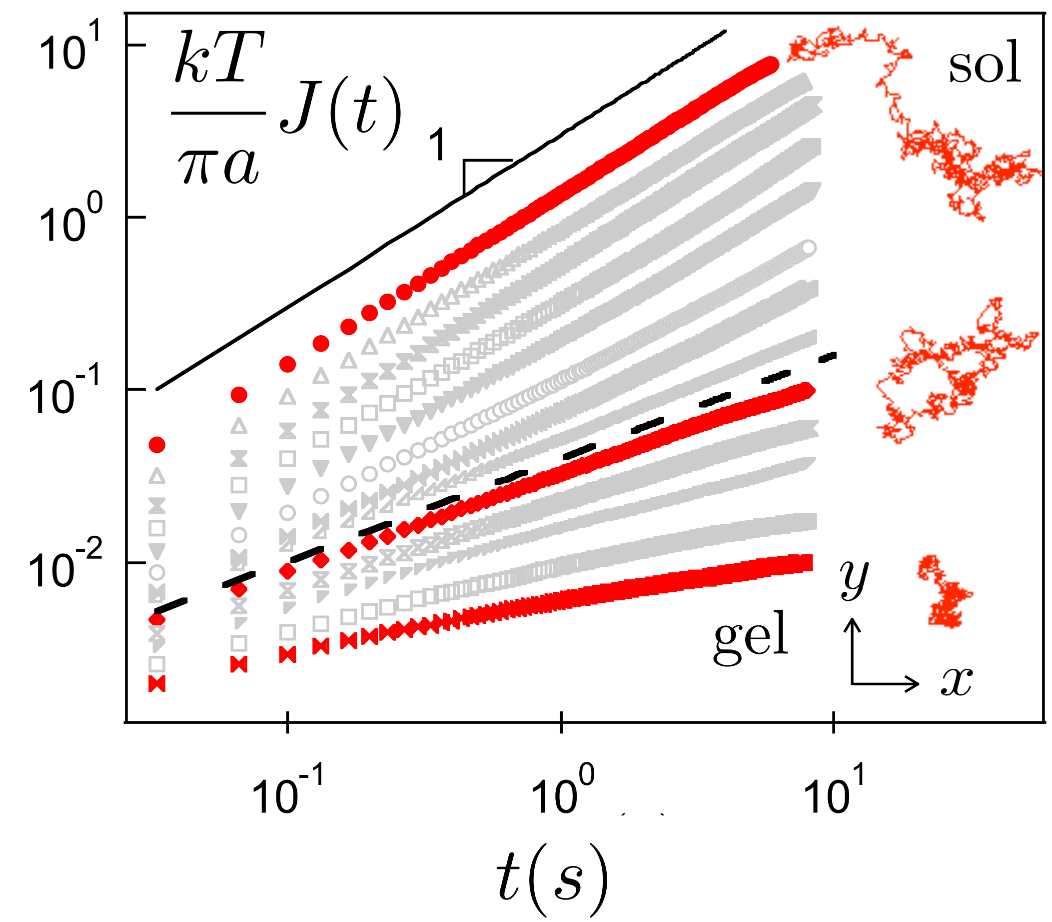
# Probe in *equilibrium* with surrounding material

Second key constraint



1 μm diameter polystyrene latex particle in water

*Linear response only!*



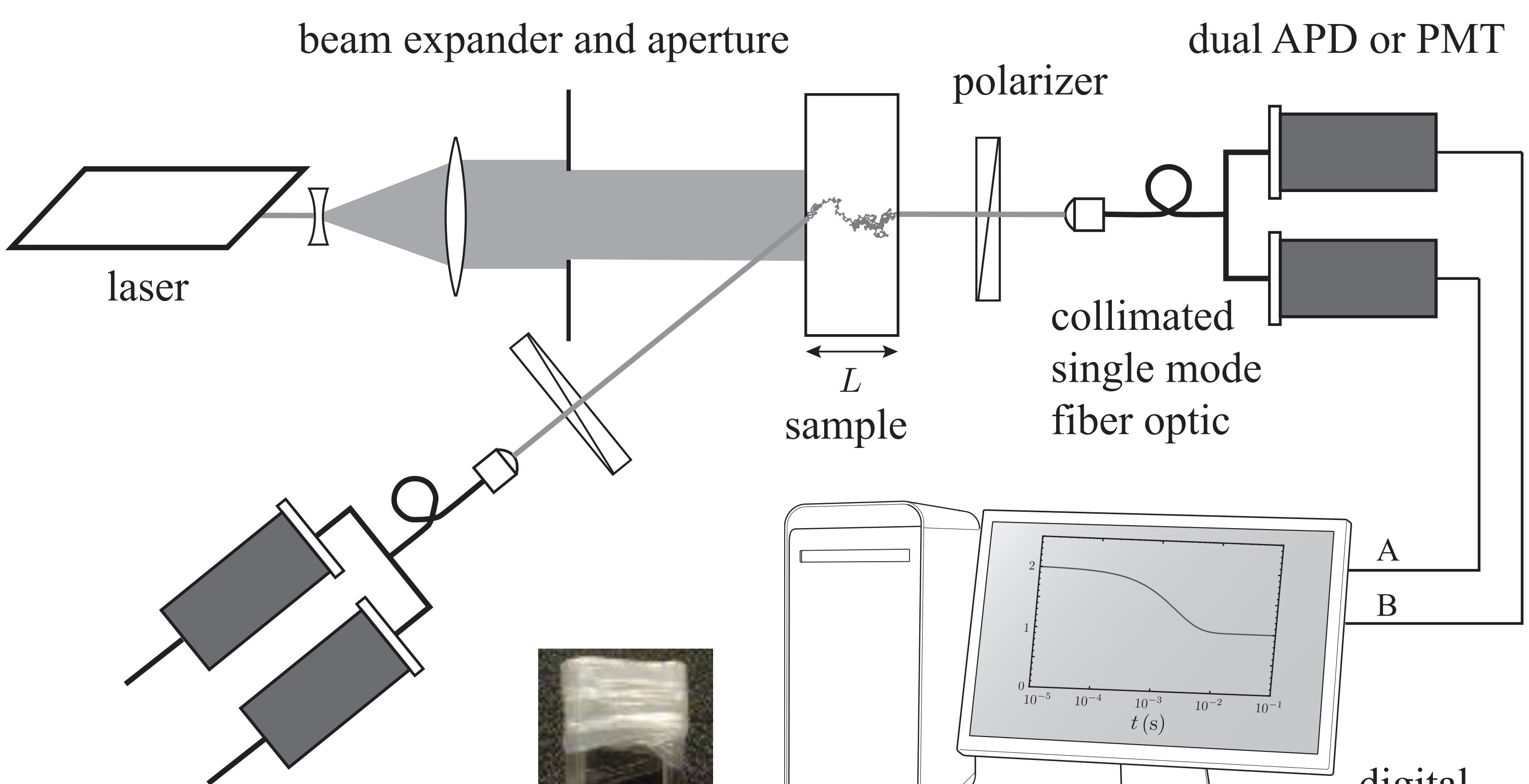

**<u>NO</u>**

*shear thinning, shear thickening, yielding, thixotropy, etc.*

# Microrheology — more tools

## DWS light scattering

P.-E. Wolf and G. Maret. *Phys. Rev. Lett.*, 55:2696–2699, 1985.
Pine, D., *et al. Phys. Rev. Lett.* 60, 1134–1137 (1988).

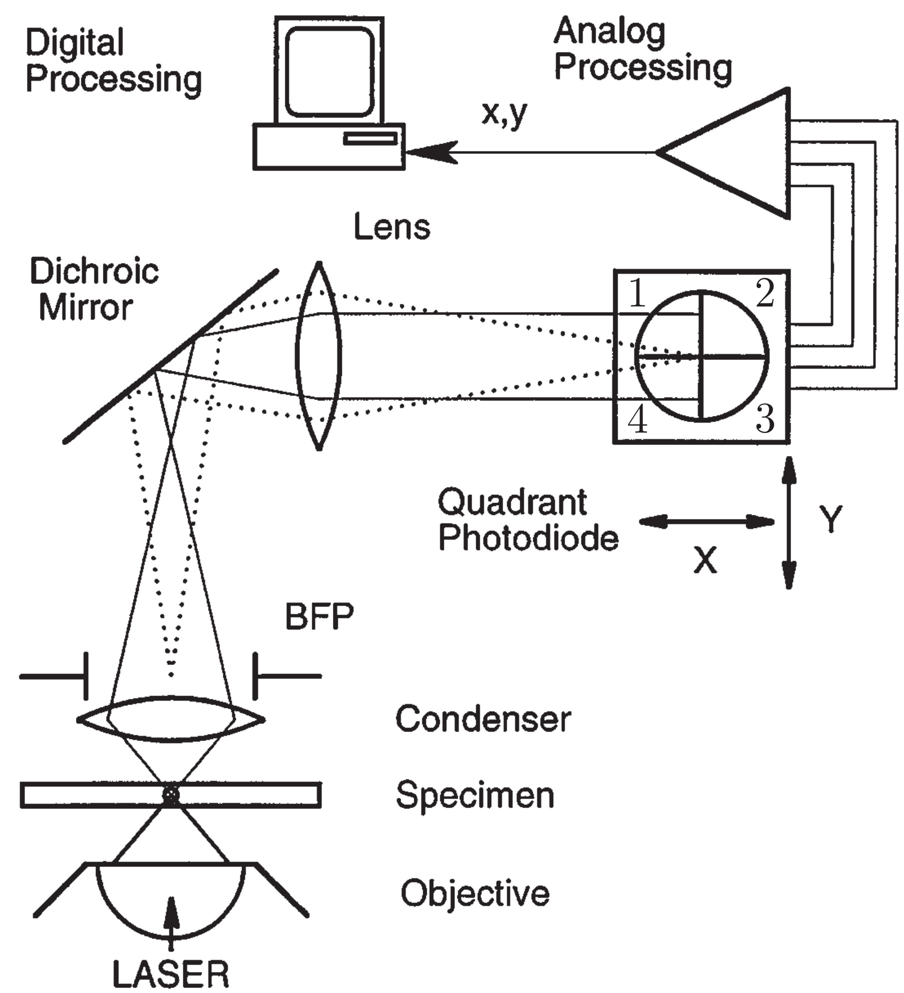


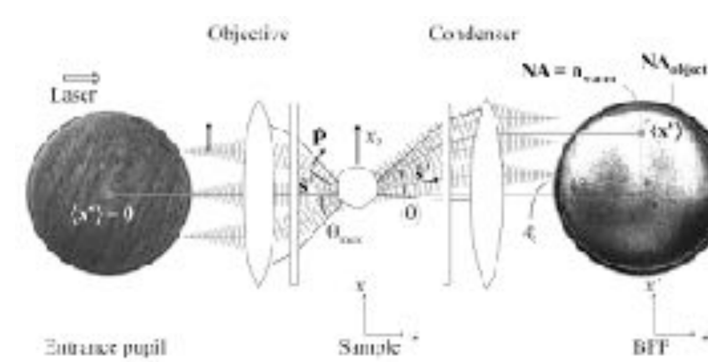

1 µm PS probe particles, 1 vol%

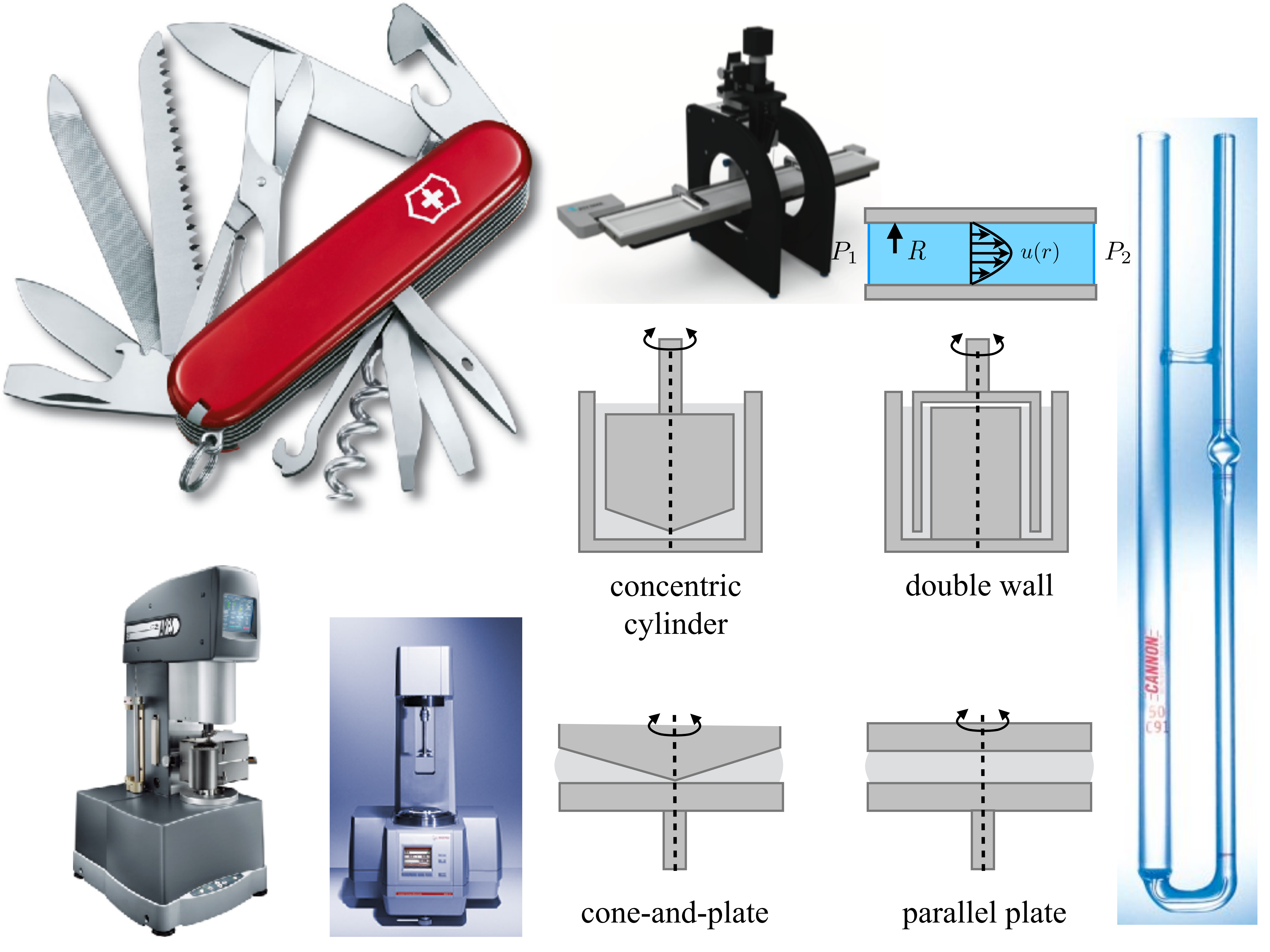
sample

## Laser tracking (LT)

Gittes, F., et al., *Phys. Rev. Lett.* 79, 3286–3289 (1997).



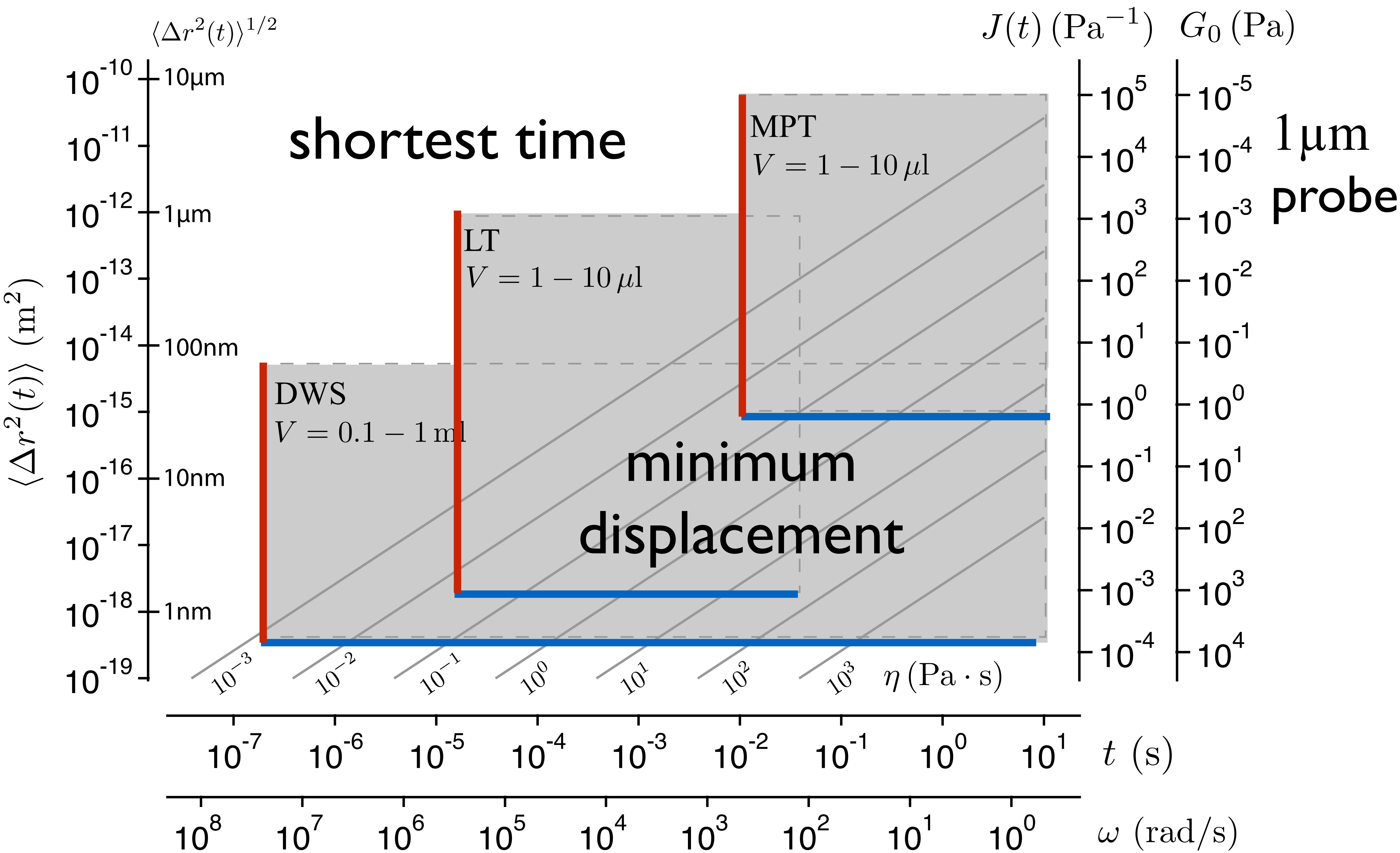





$P_1$
$R$
$u(r)$
$P_2$
concentric cylinder
double wall
cone-and-plate
parallel plate
CANNON

# Passive microrheology operating regimes

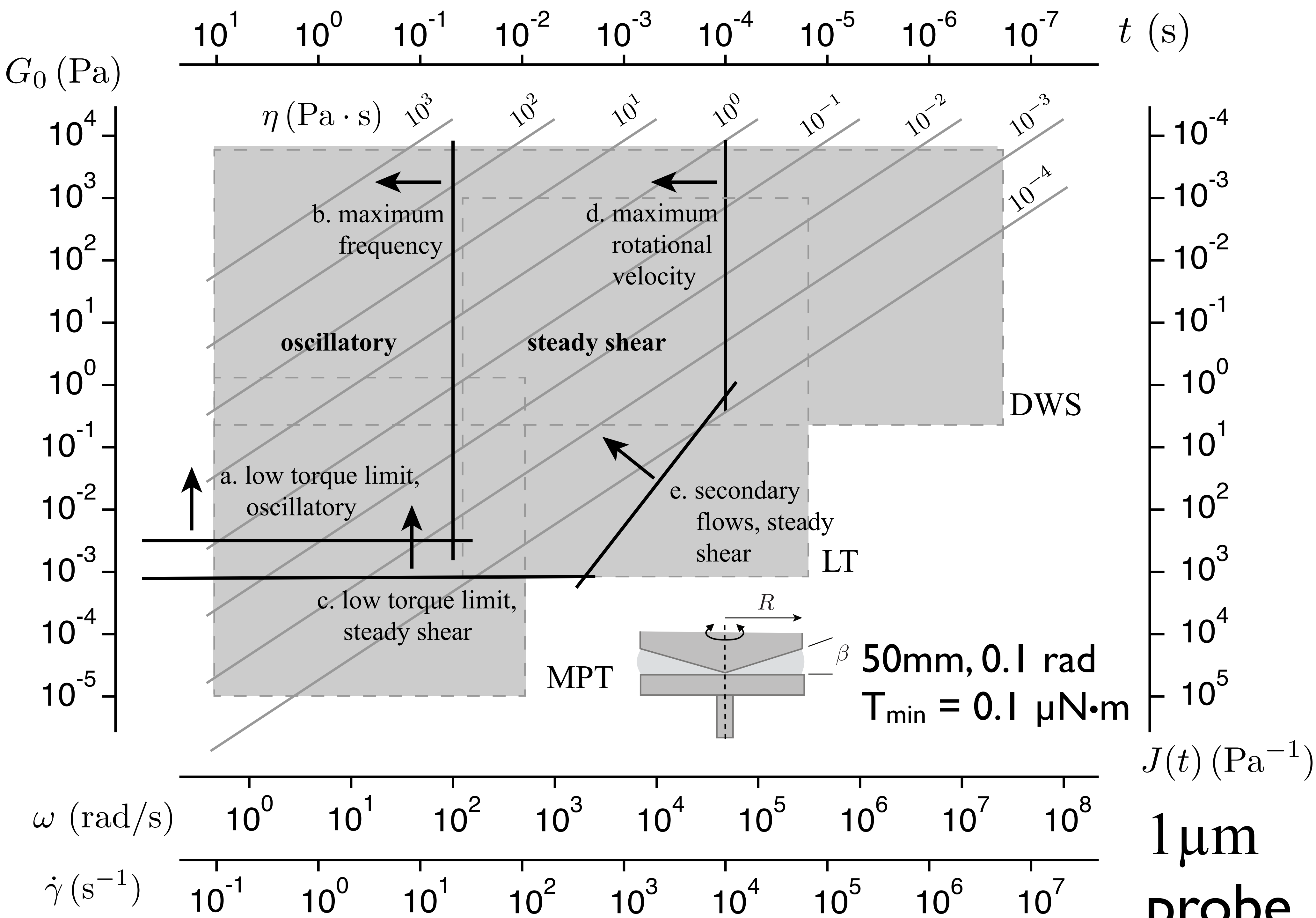
E. M. Furst and T. M. Squires, *Microrheology*, Oxford Univ. Press, 2017



# Comparison to mechanical rheometry

E. M. Furst and T. M. Squires, *Microrheology*, Oxford Univ. Press, 2017

Ewoldt, R. H., Johnston, M. T. & Caretta, L. M. in *Complex Fluids in Biological Systems* (ed. Spagnolie, S. E.) 207–243 (Springer-Verlag, 2014).

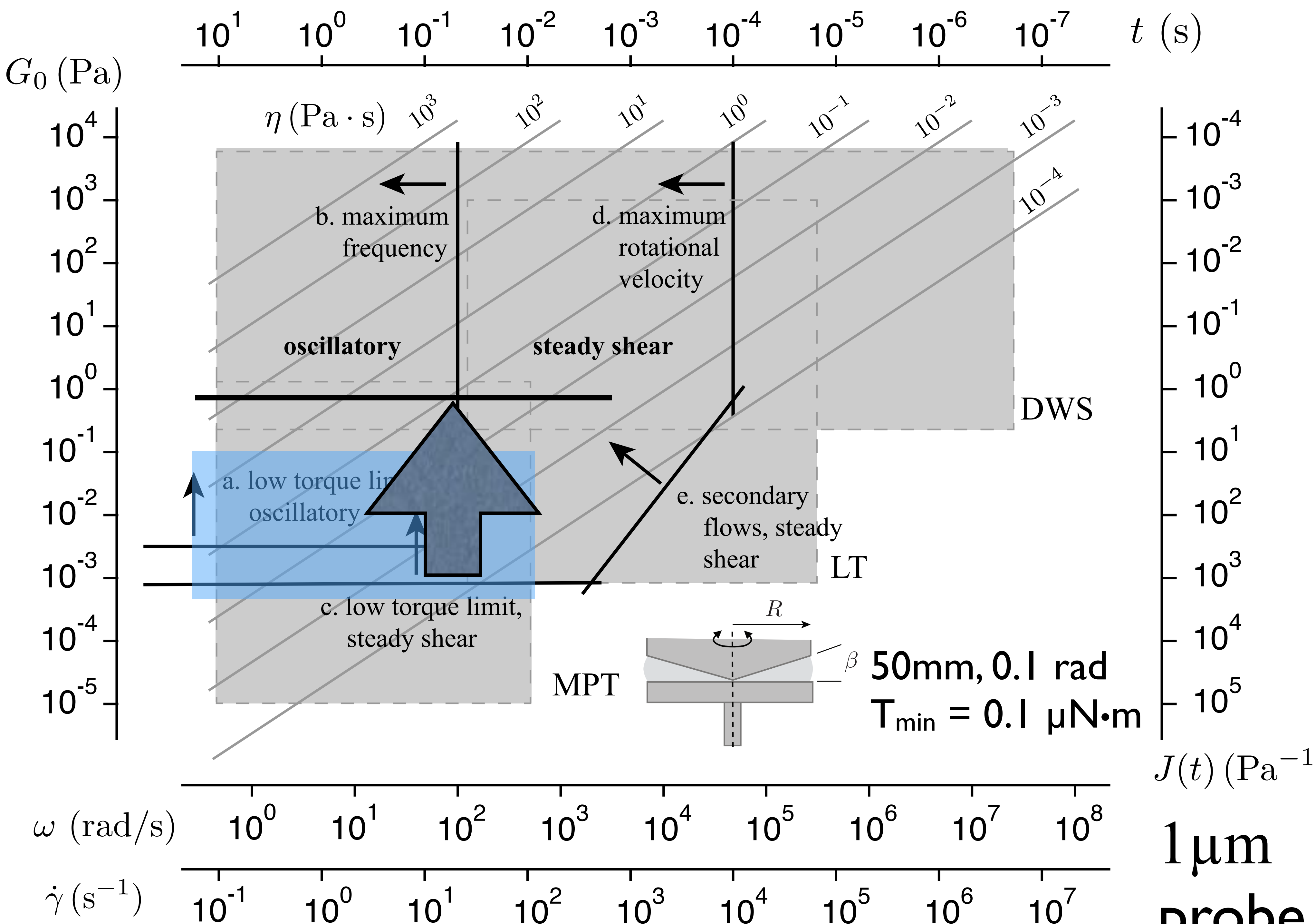



1μm probe

# Comparison to mechanical rheometry

E. M. Furst and T. M. Squires, *Microrheology*, Oxford Univ. Press, 2017

Ewoldt, R. H., Johnston, M. T. & Caretta, L. M. in *Complex Fluids in Biological Systems* (ed. Spagnolie, S. E.) 207–243 (Springer-Verlag, 2014).



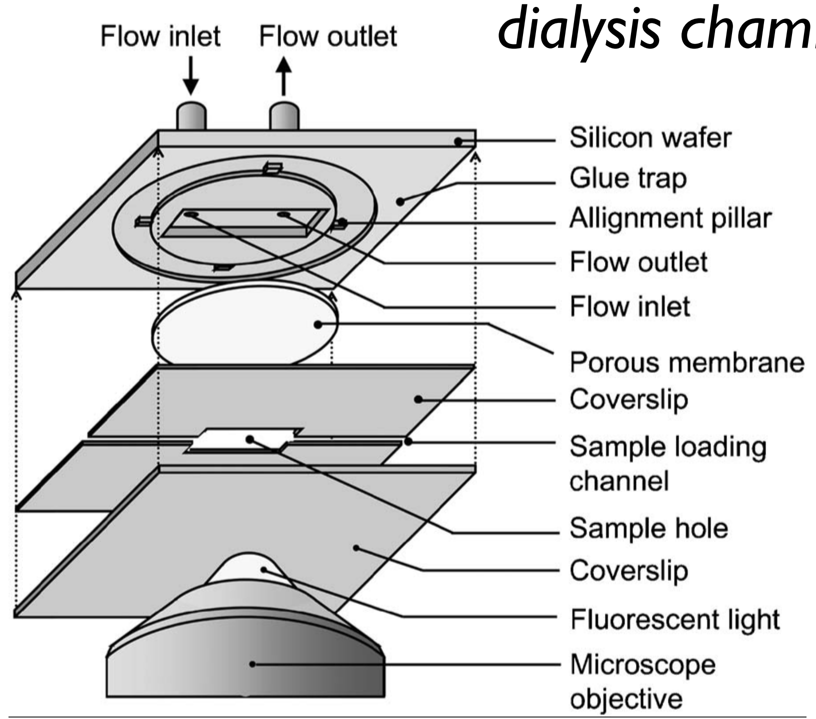
# Small sample volumes

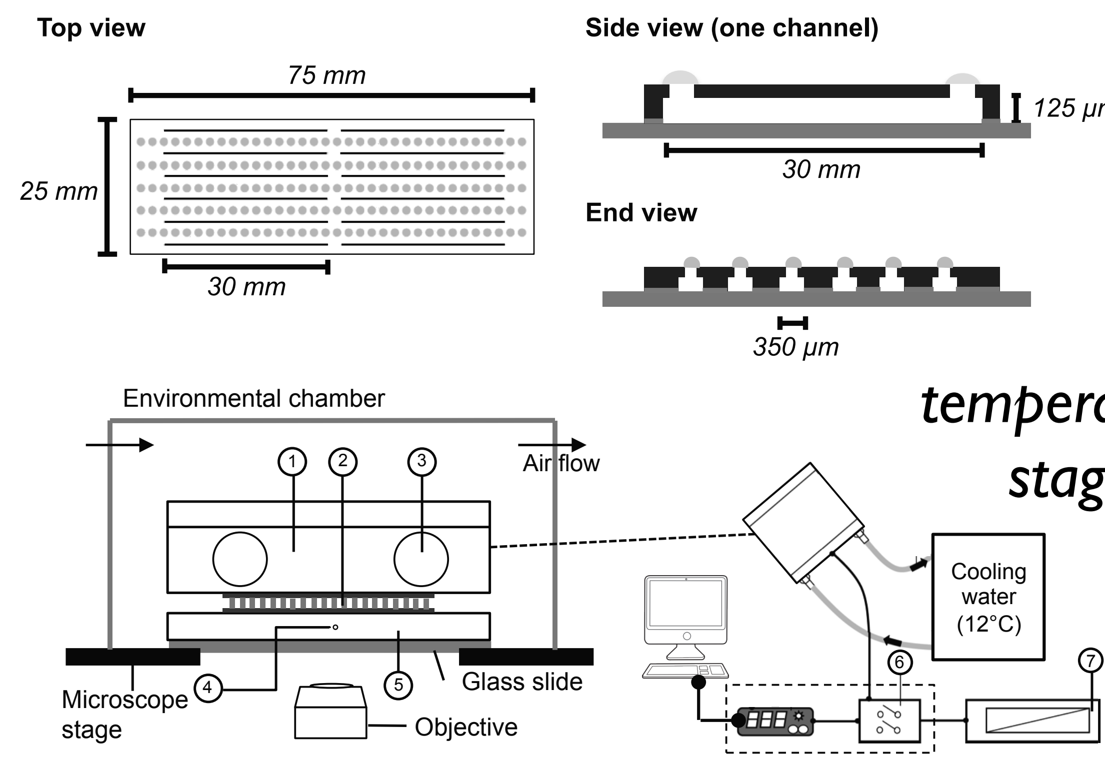
## Fast mass and heat exchange

Sato, J. & Breedveld, V., *J. Rheol.* 50, 1–19 (2006).

Josephson, L. L., Galush, W. J. & Furst, E. M. *Biomicrofluidics* 10, 43503 (2016).

*dialysis chamber*

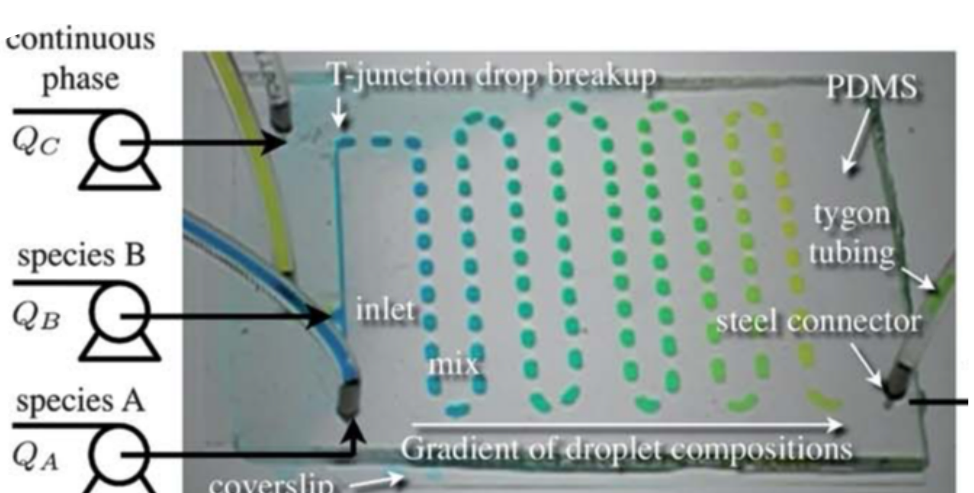



*temperature stage*

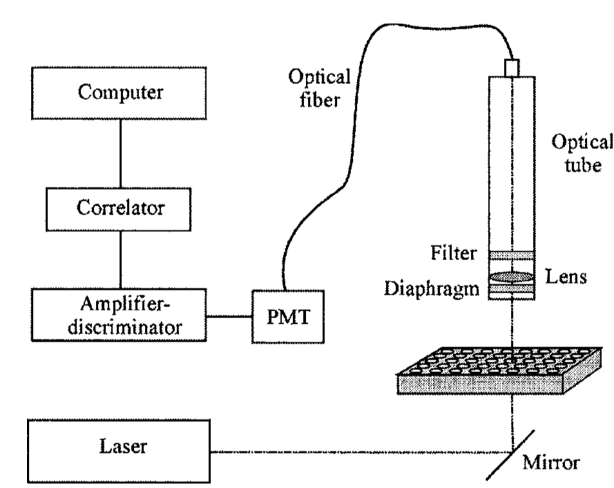
## Microfluidic sample processing

Schultz, K. M. & Furst, E. M. *Lab Chip* 11, 3802–3809 (2011).




## High-throughput

Breedveld, V. & Pine, D. J., *J. Mat. Sci.* 38, 4461–4470 (2003).

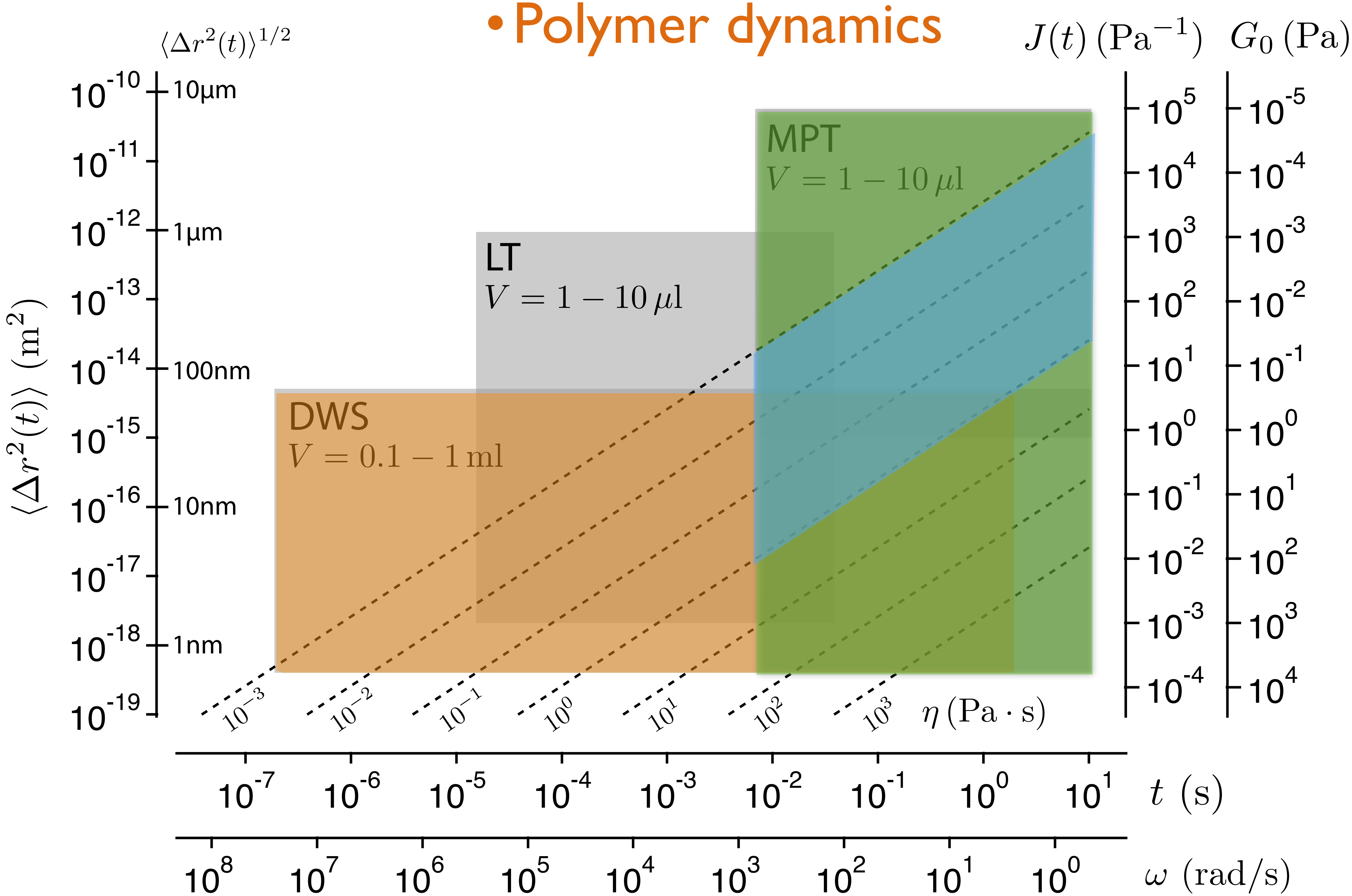


# Key advantages of microrheology

- Small sample volumes — material screening
  ~10μL *typical; as low as* ~1μL
  *Straightforward experimental methods*
  *Tracking particle motion with video microscopy*
- Fast acquisition times (as low as ~10 seconds)
  *Samples that change with time (i.e. during gelation)*
- "Incipient rheology" of gel transitions, intrinsic viscosity
  *hydrogelation, degradation*
- Extended range of frequencies
  < *1Hz to MHz*
- Local rheological properties-spatial resolution
  *Information not available to bulk rheology*
- In many cases: complementary to mechanical rheology

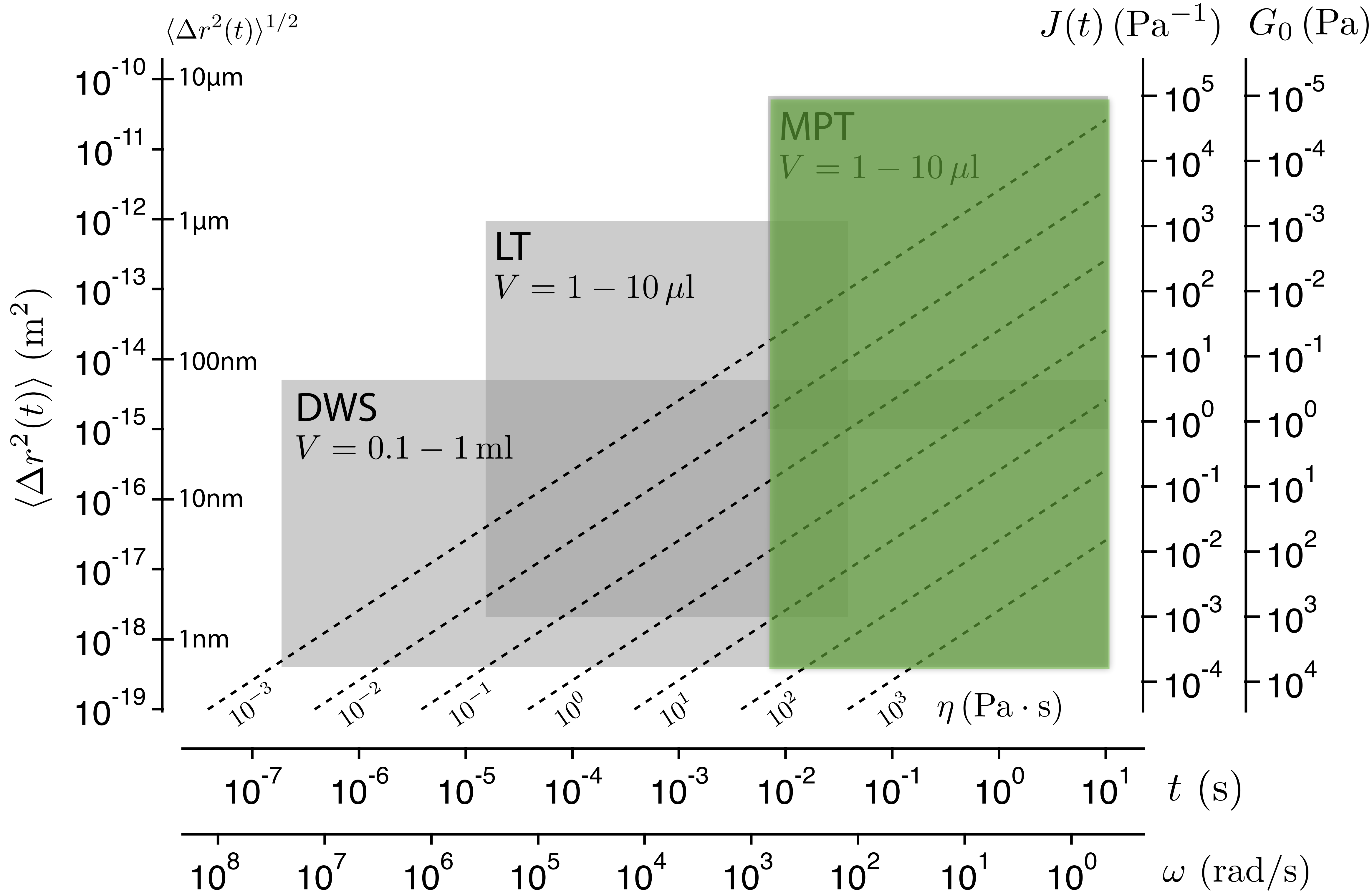
# Microrheology problem classes

- Hydrogelators
- Protein solutions
- Polymer dynamics



# Microrheology problem classes

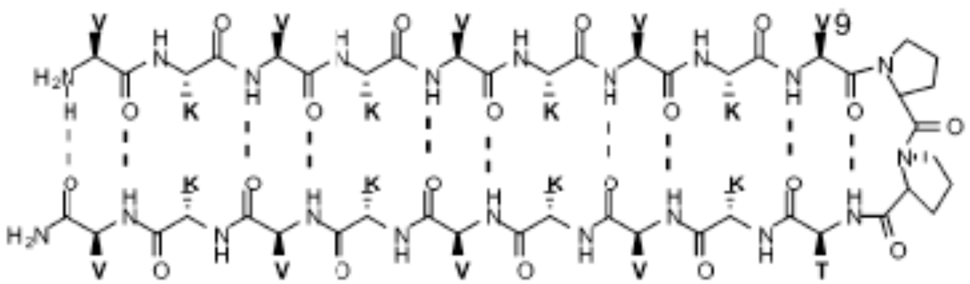
- Hydrogelators



- Microrheology of gelation & degradation
- Rheological screening of scarce materials

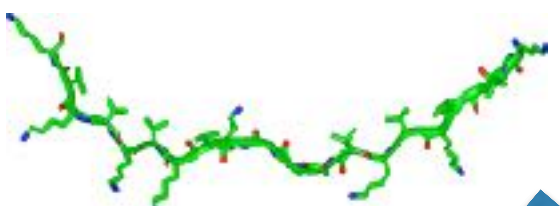
# Gelation of self-assembling peptides

Schneider, J. P. et al. *J. Am. Chem. Soc.* 124, 15030–15037 (2002).



**MAX1:** VKVKVKVKV$^{D}$PPTKVKVKVKV-$NH_2$

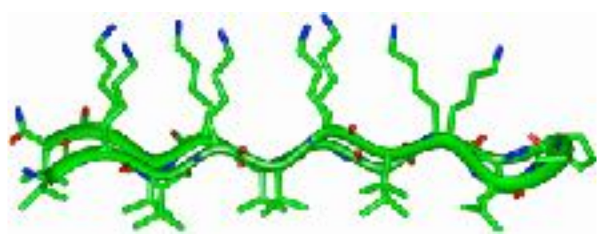
Joel P. Schneider *et al*, *JACS* 2002**,** 124, 15030.
D.J. Pochan *et al*, *JACS* 2003**,** 125, 11802.



Unfolded state

Change in pH, ionic strength, temp

(Intramolecular folding)

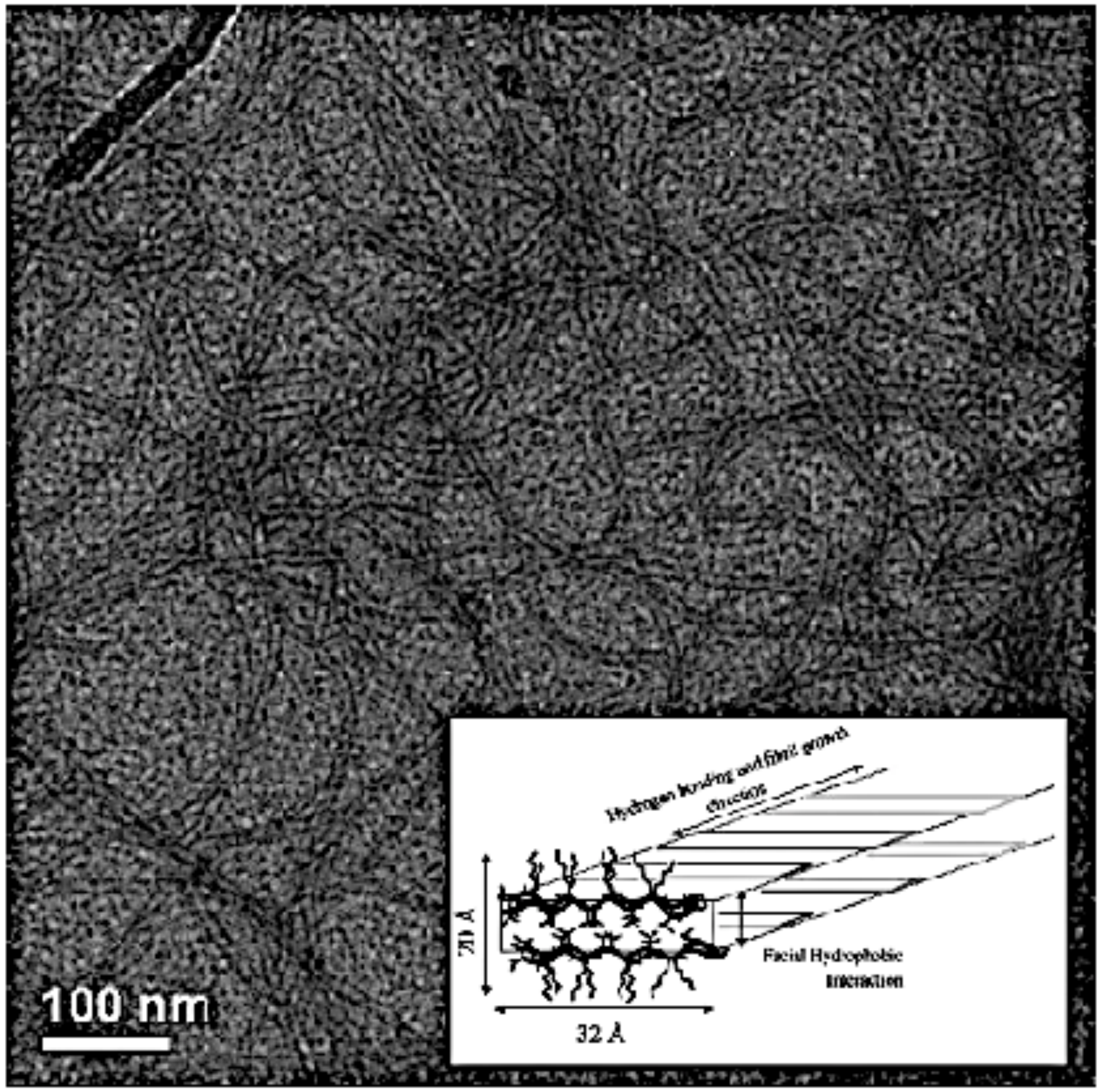


Folded state

**Reversible**
ionic strength
pH, etc.

Self-assembly
Hydrogen bonding
Hydrophobic interactions

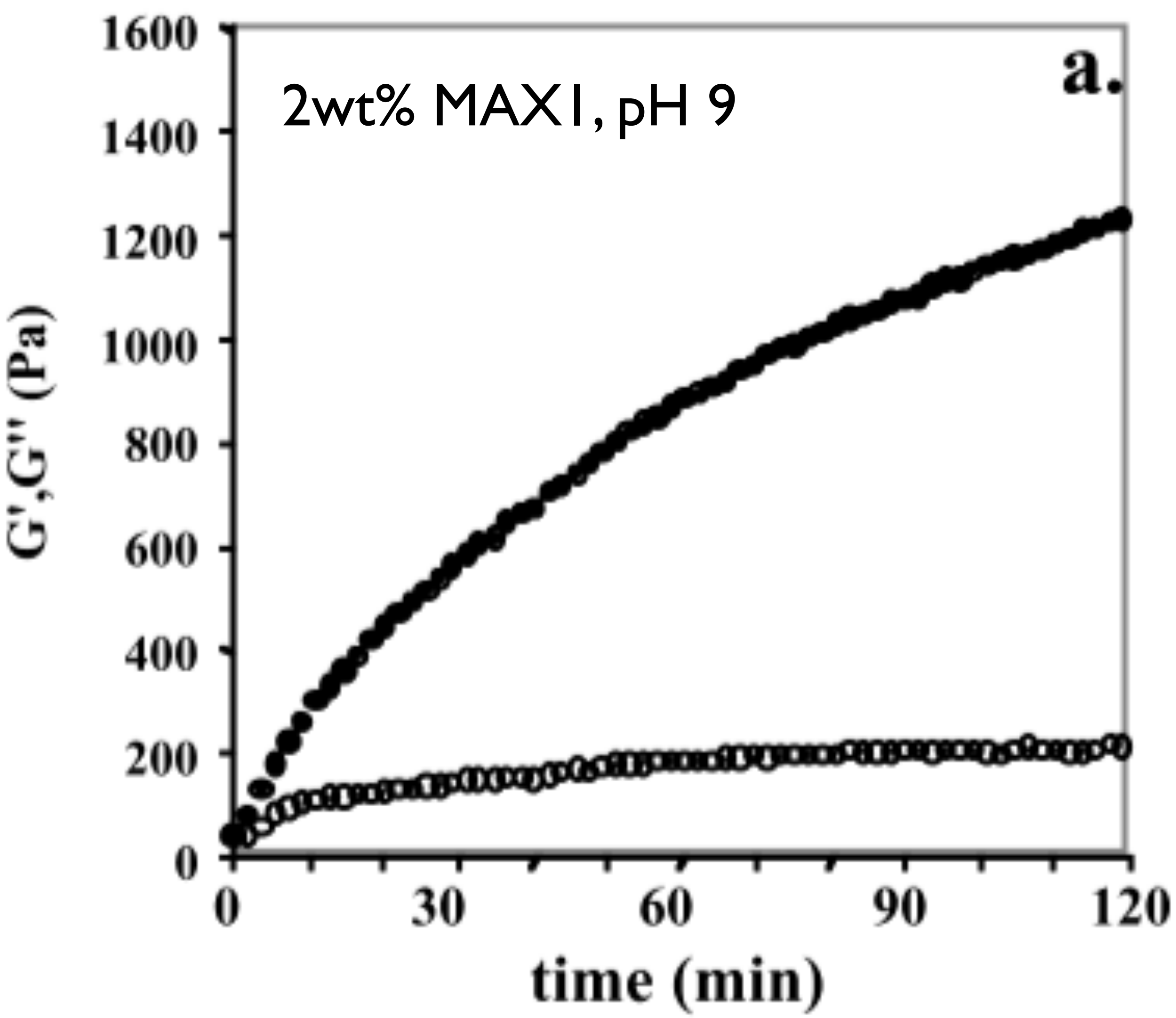
Hydrogel

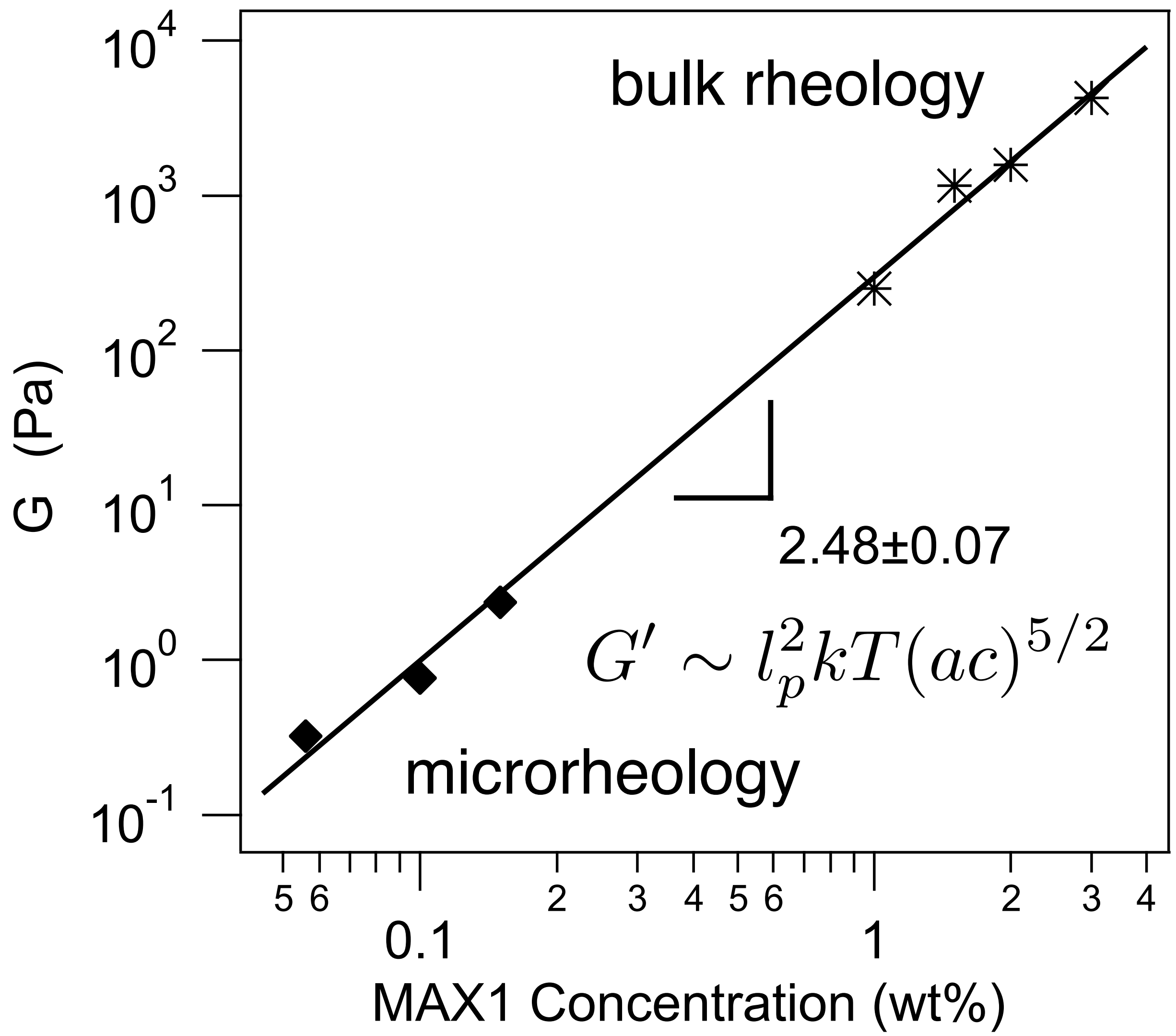



Ozbas, et al. Phys. Rev. Lett., 93:268106, 2004.

# Hydrogel rheology

Schneider, J. P. et al. *J. Am. Chem. Soc.* 124, 15030–15037 (2002).



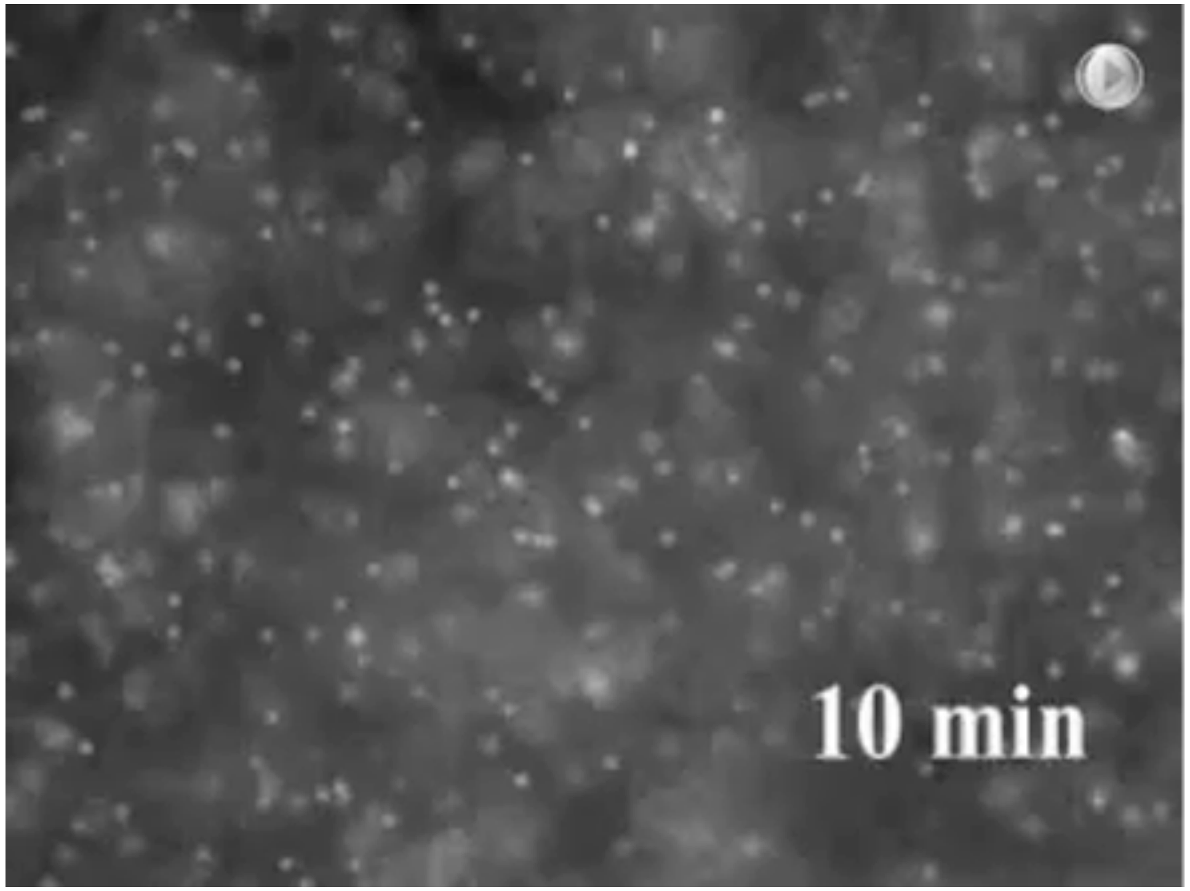

Veerman, C. et al. *Macromolecules* 39, 6608–6614 (2006).

MacKintosh, F. C., Käs, J. & Janmey, P. A. *Phys. Rev. Lett.* 75, 4425–4428 (1995).

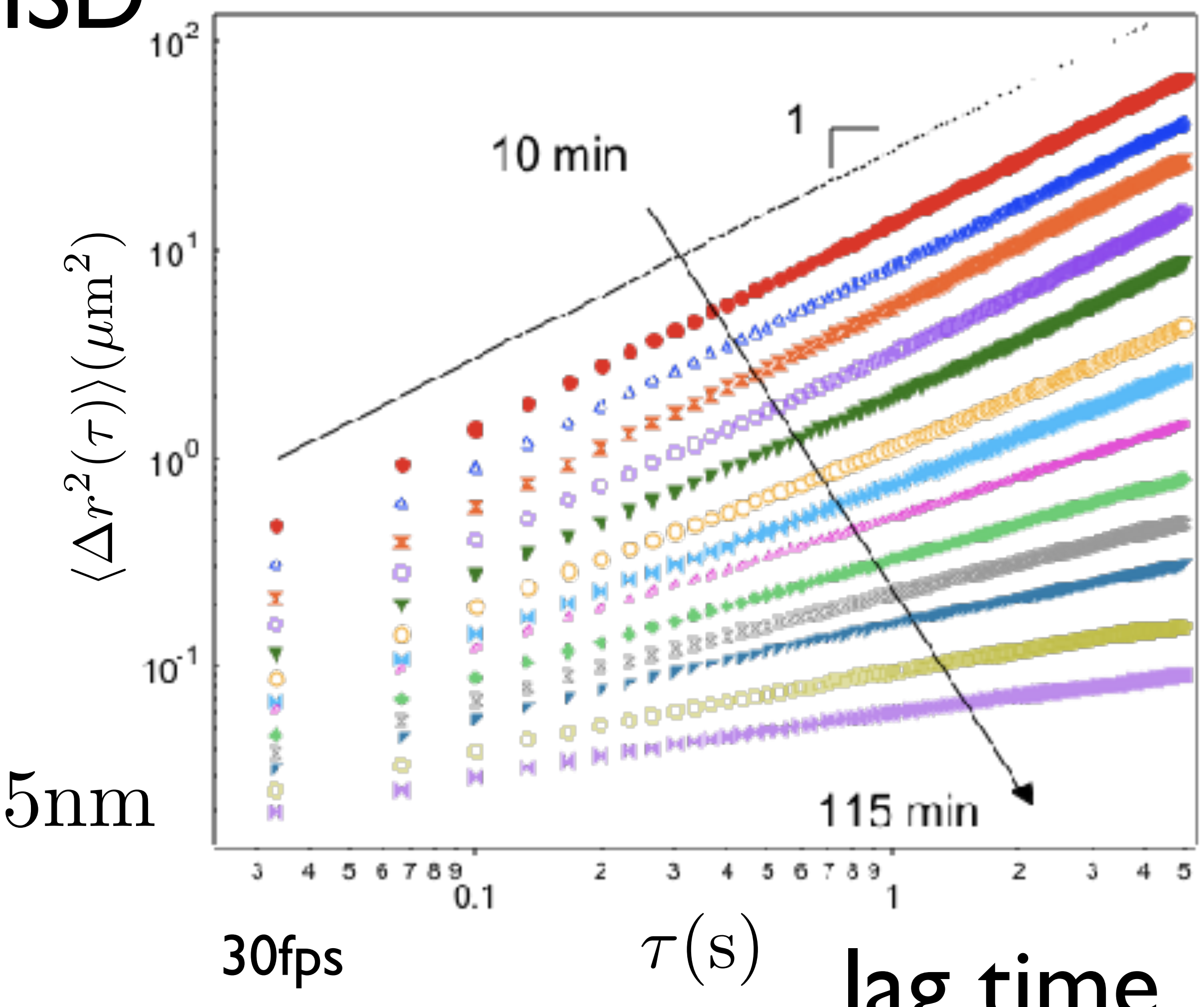
# Gelation of MAX1 hairpin peptide

Self-assembling peptide

0.15 wt% HPL17 (K15E), pH 8.5, T=25°C




MSD




45nm

30fps

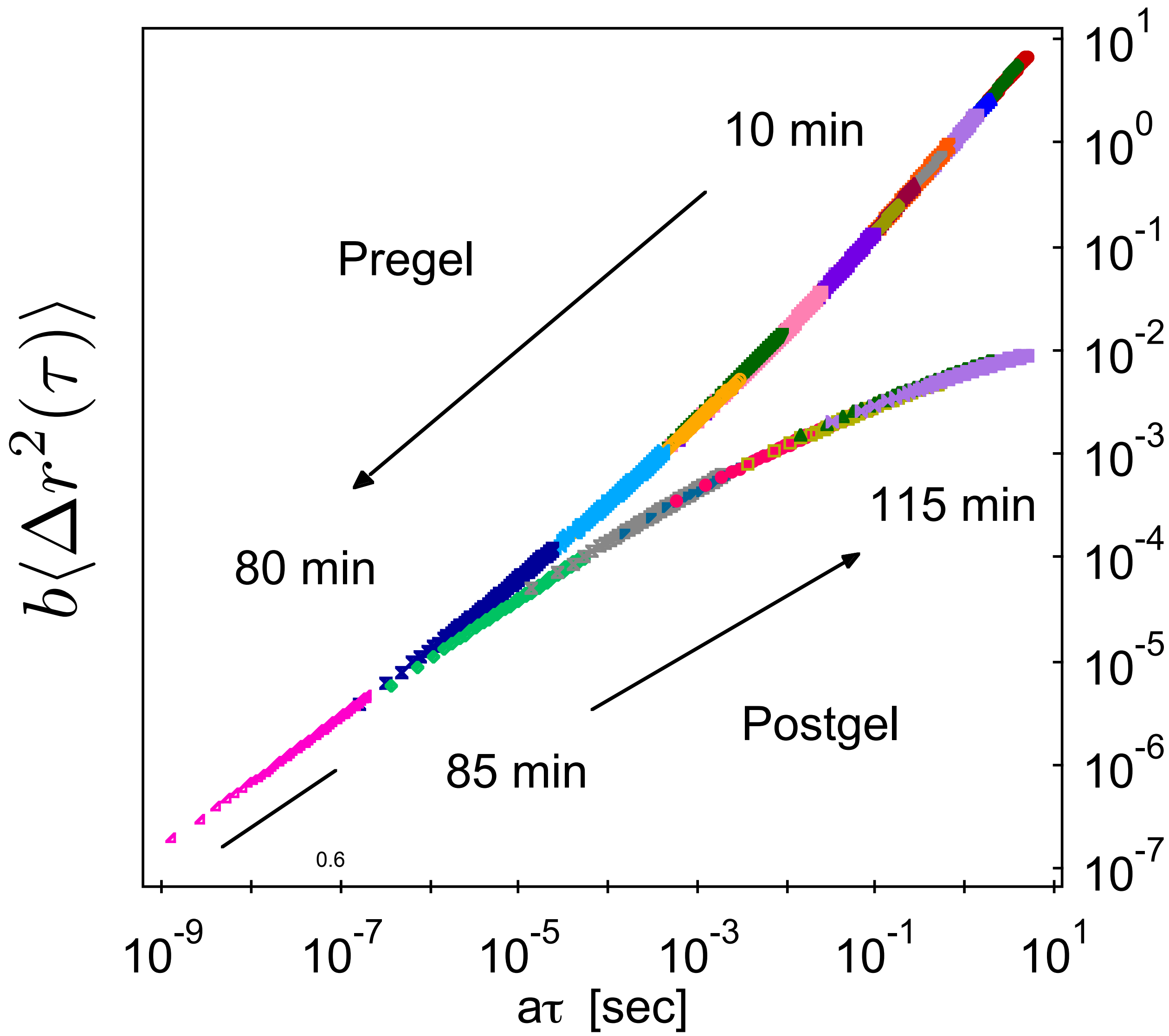
lag time

T. H. Larsen and E. M. Furst, Phys. Rev. Lett. 100, 146001 (2008).
T. H. Larsen et al. Korea-Aust. Rheol. J., 20:165–173, (2008).

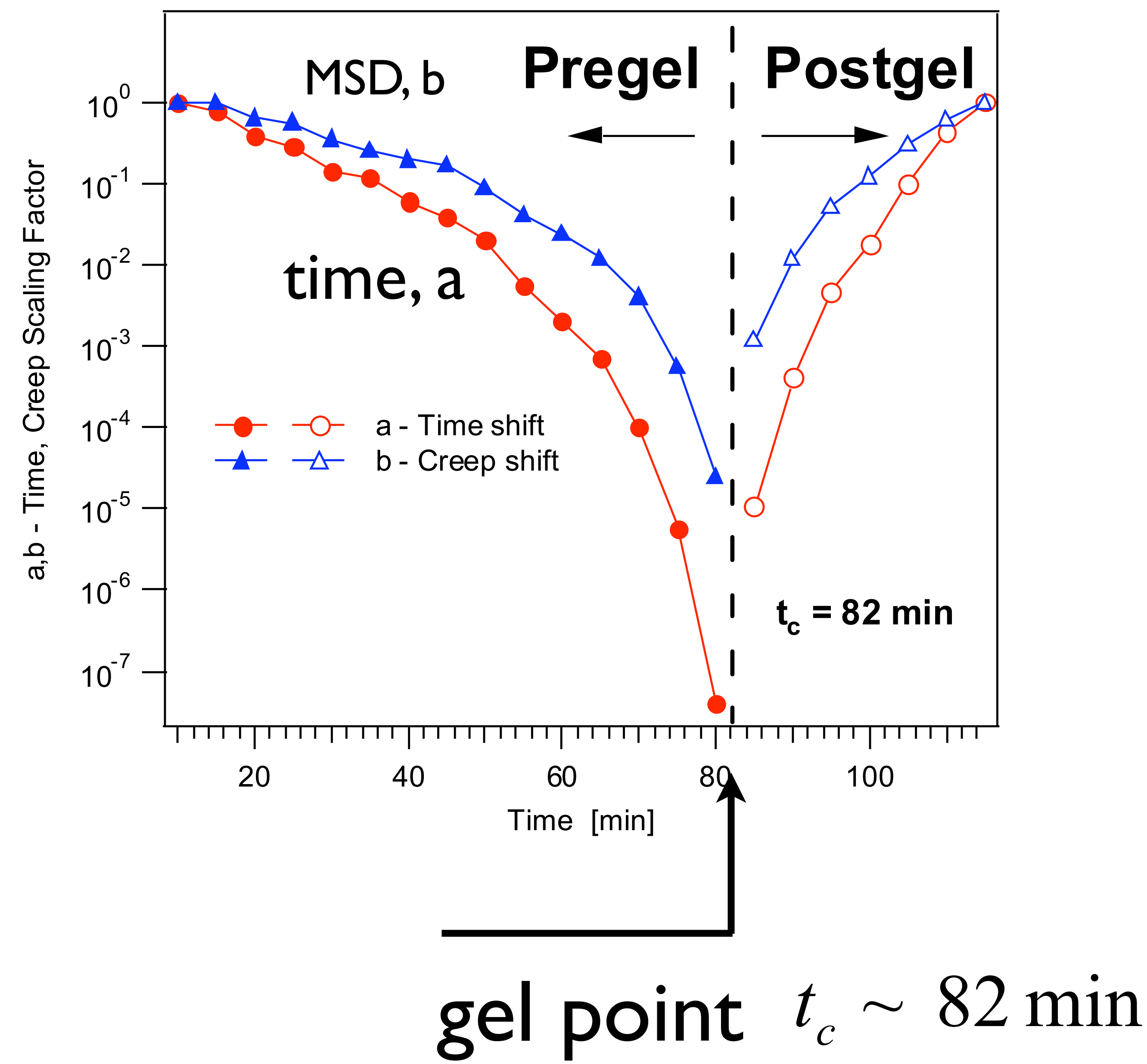
# MSD master curve shift factors

0.15 wt% HPL17, pH 8.5, T=25°C

## MSD master curves




## Shift factors




T. H. Larsen and E. M. Furst, Phys. Rev. Lett. 100, 146001 (2008).

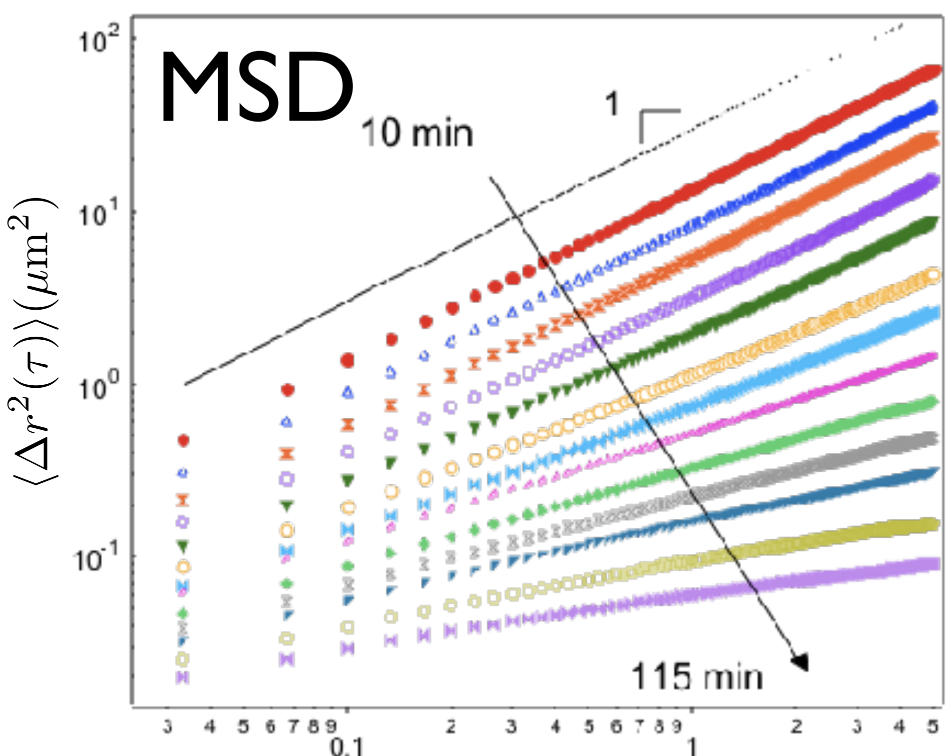
# MSD gelation time-cure superposition

T. H. Larsen and E. M. Furst, Phys. Rev. Lett. 100, 146001 (2008).
T. H. Larsen et al. Korea-Aust. Rheol. J., 20:165–173, (2008).

Master curve: $\frac{J(t/\tau_L)}{J_s^0}$

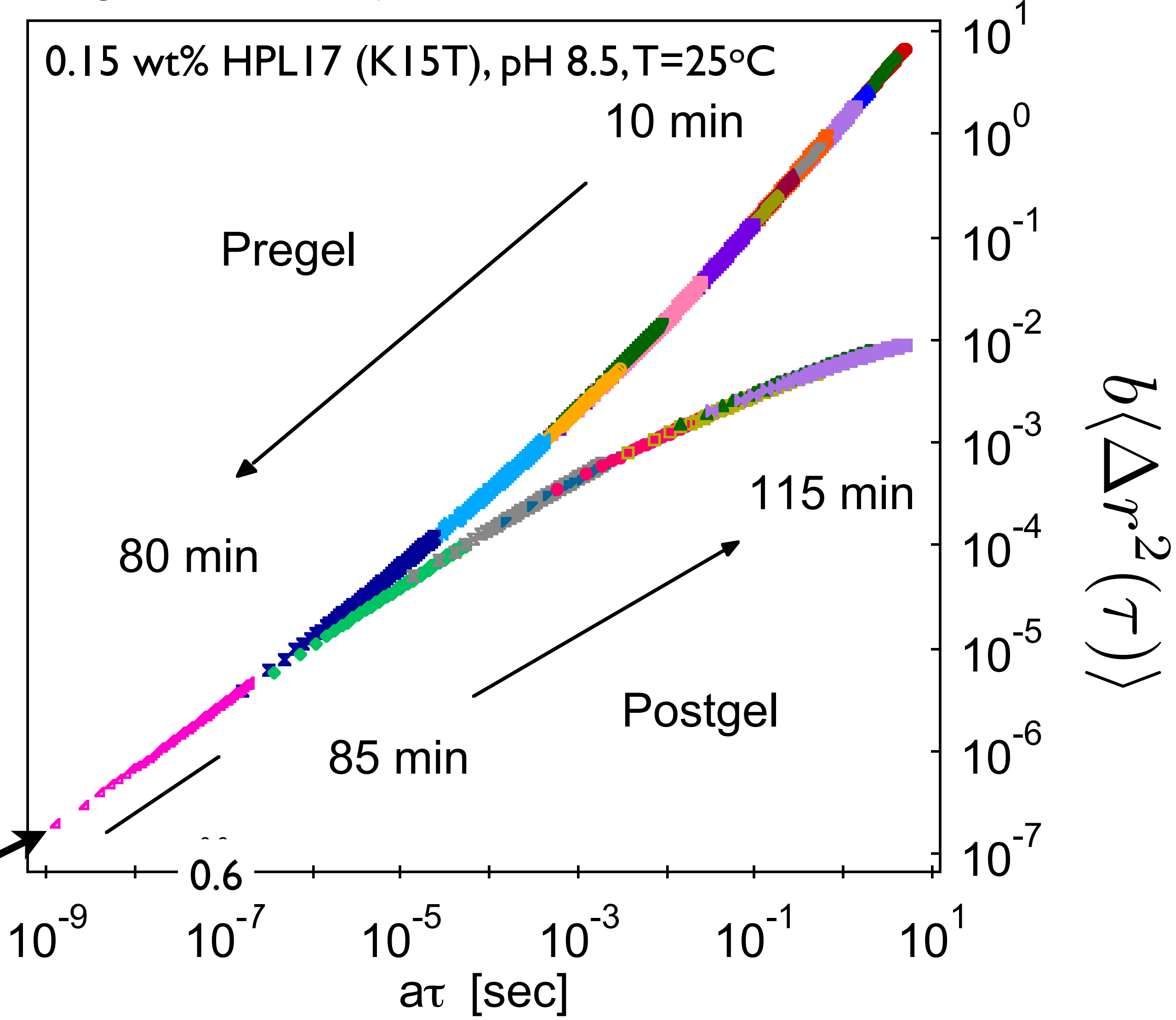
Critical extent of gelation $\varepsilon = \frac{|t - t_c|}{t_c}$

$J_s^0 = a\varepsilon^{-z}/kT \qquad \tau_L = \tau_0 \varepsilon^{-y}$




$n = 0.6$

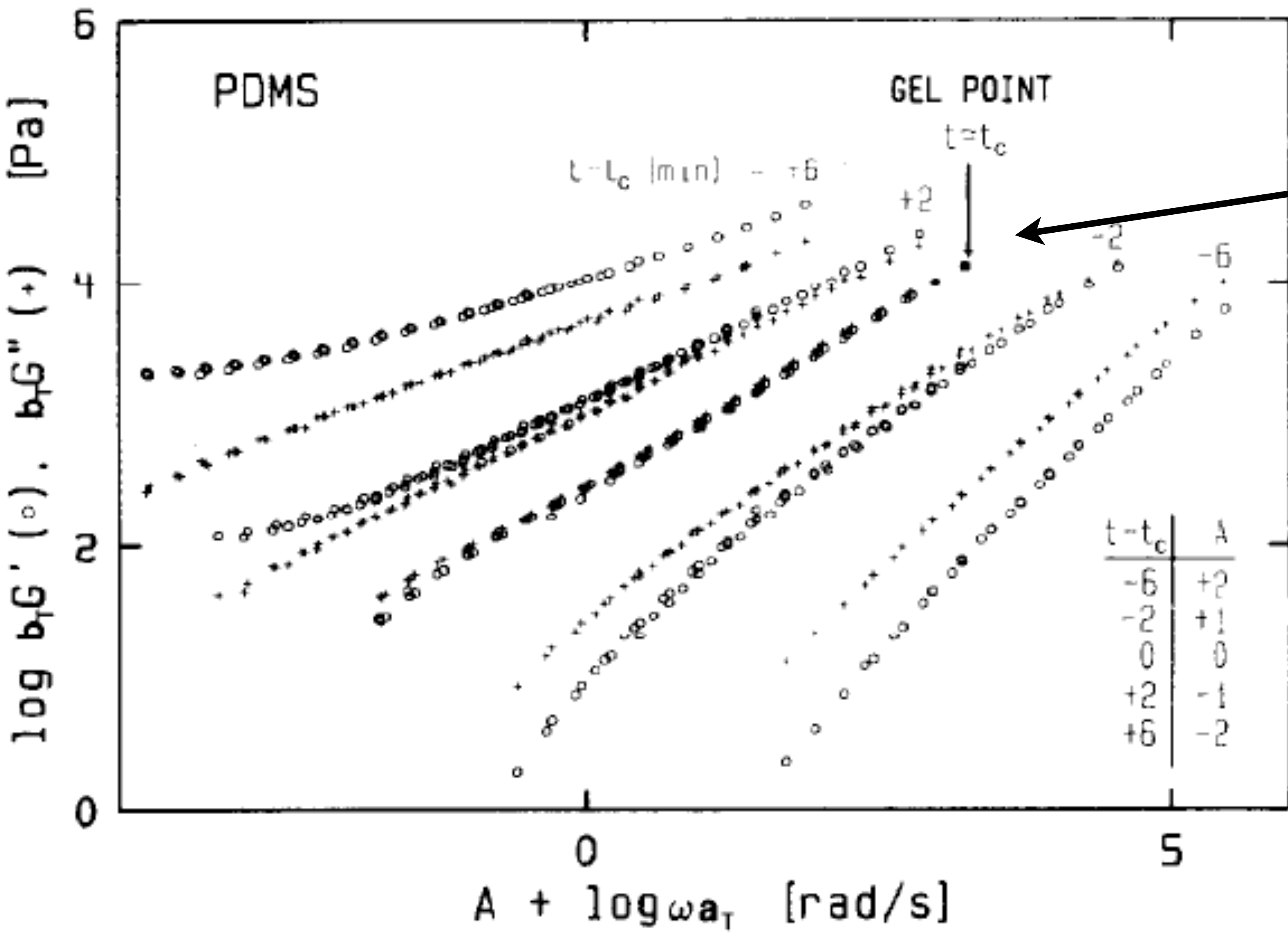
$$J_c(t) = \frac{\sin n\pi}{n\pi S} t^n$$




Winter and Chambon. J. Rheology, 30:367-382, 1986.
Winter and Chambon. J. Rheology, 31:683-697, 1987.

# Critical scaling of moduli at gel point

Winter and Chambon. J. Rheology, 30:367-382, 1986.
Winter and Chambon. J. Rheology, 31:683-697, 1987.




$$G(t) = St^{-n}$$

$$G^*(\omega) = S\Gamma(1-n)\omega^n$$

## Relaxation exponent

Self-similar structure and mechanical response

$$0.11 \le n \le 0.92$$

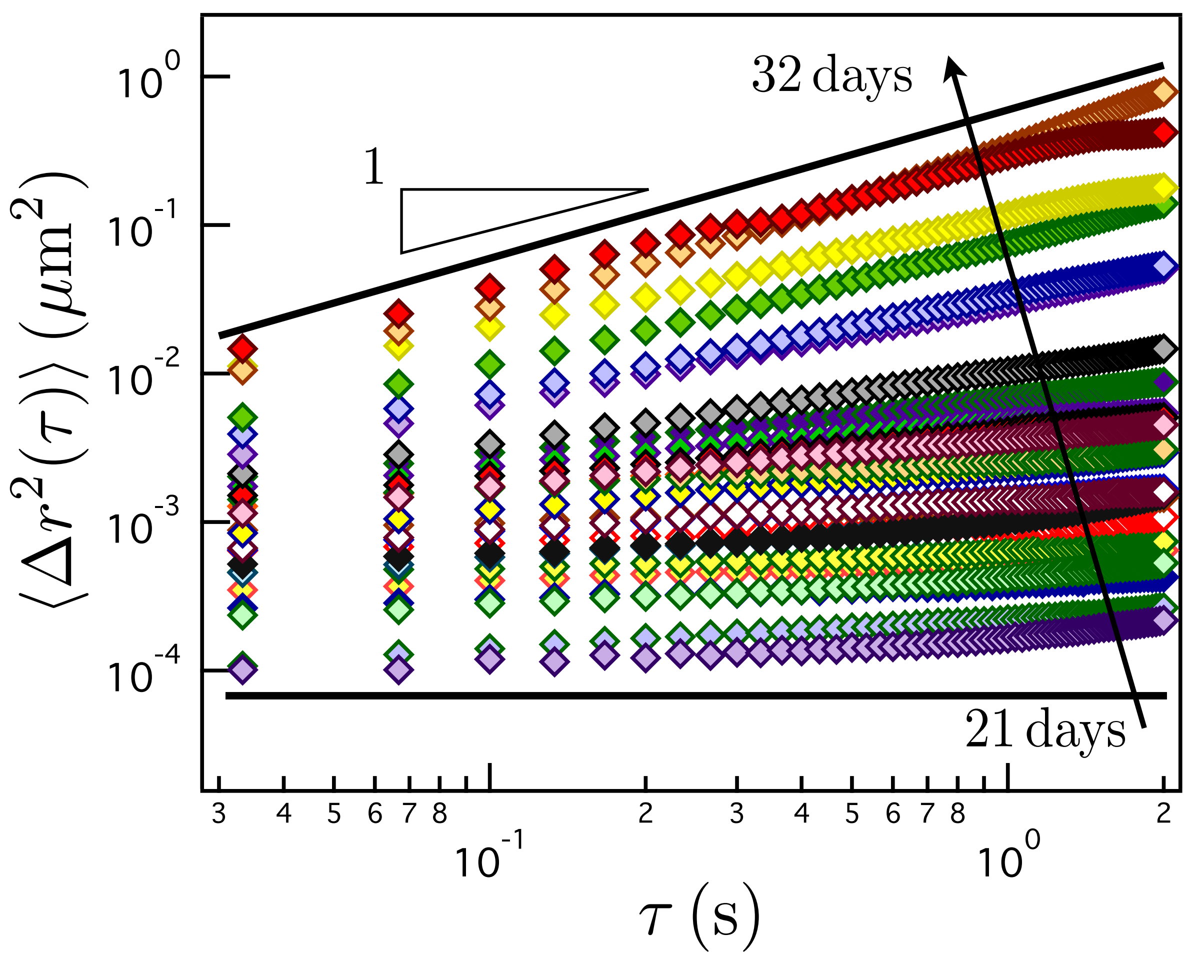
$$n = z/y$$

H. W. Richtering, et al. Macromolecules, 25:2429–2433, 1992.

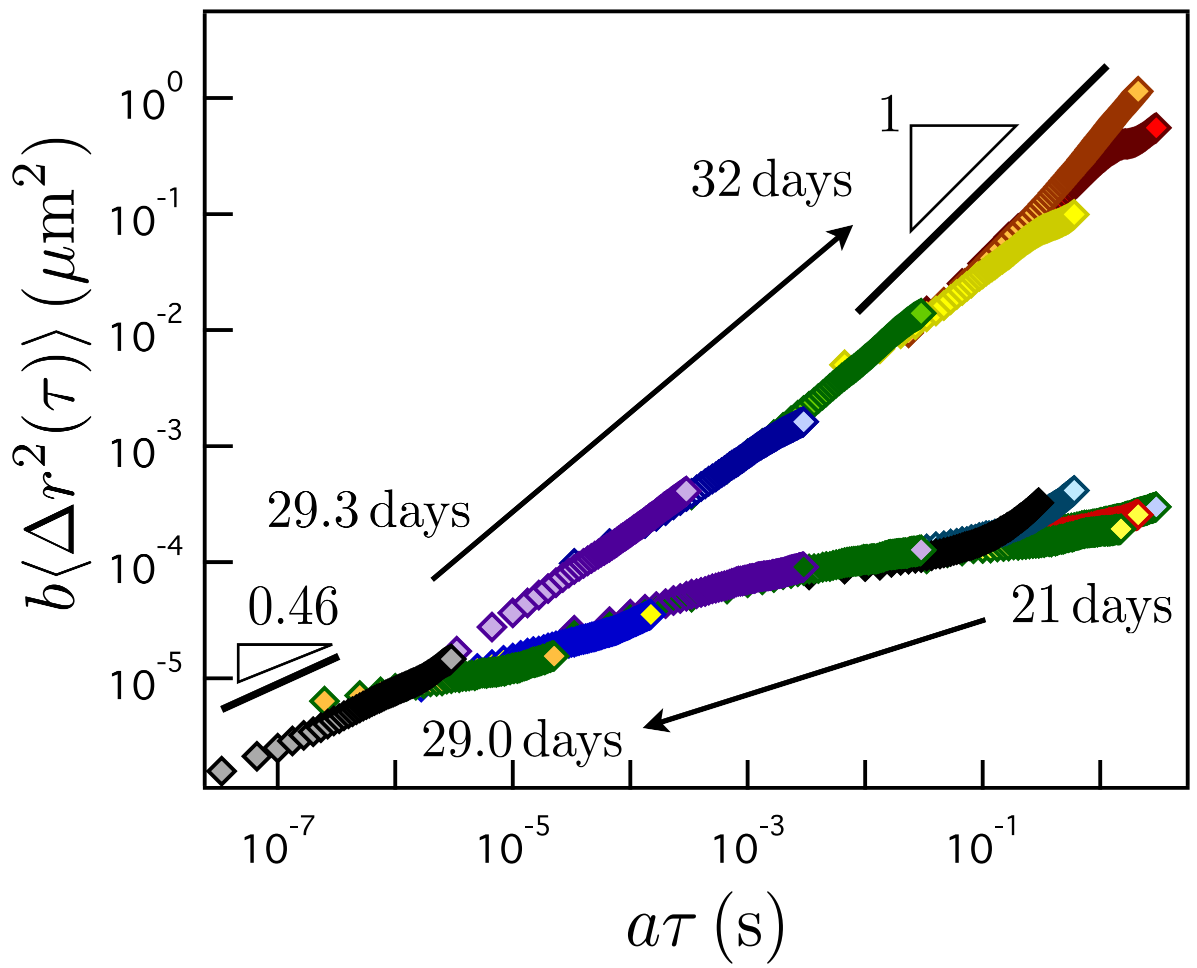
# Gel breaking: time-*degradation* superposition

K. M. Schultz, A. D. Baldwin, K. L. Kiick and E. M. Furst, *ACS Macro Lett.* 1, 706–708 (2012).

MSD

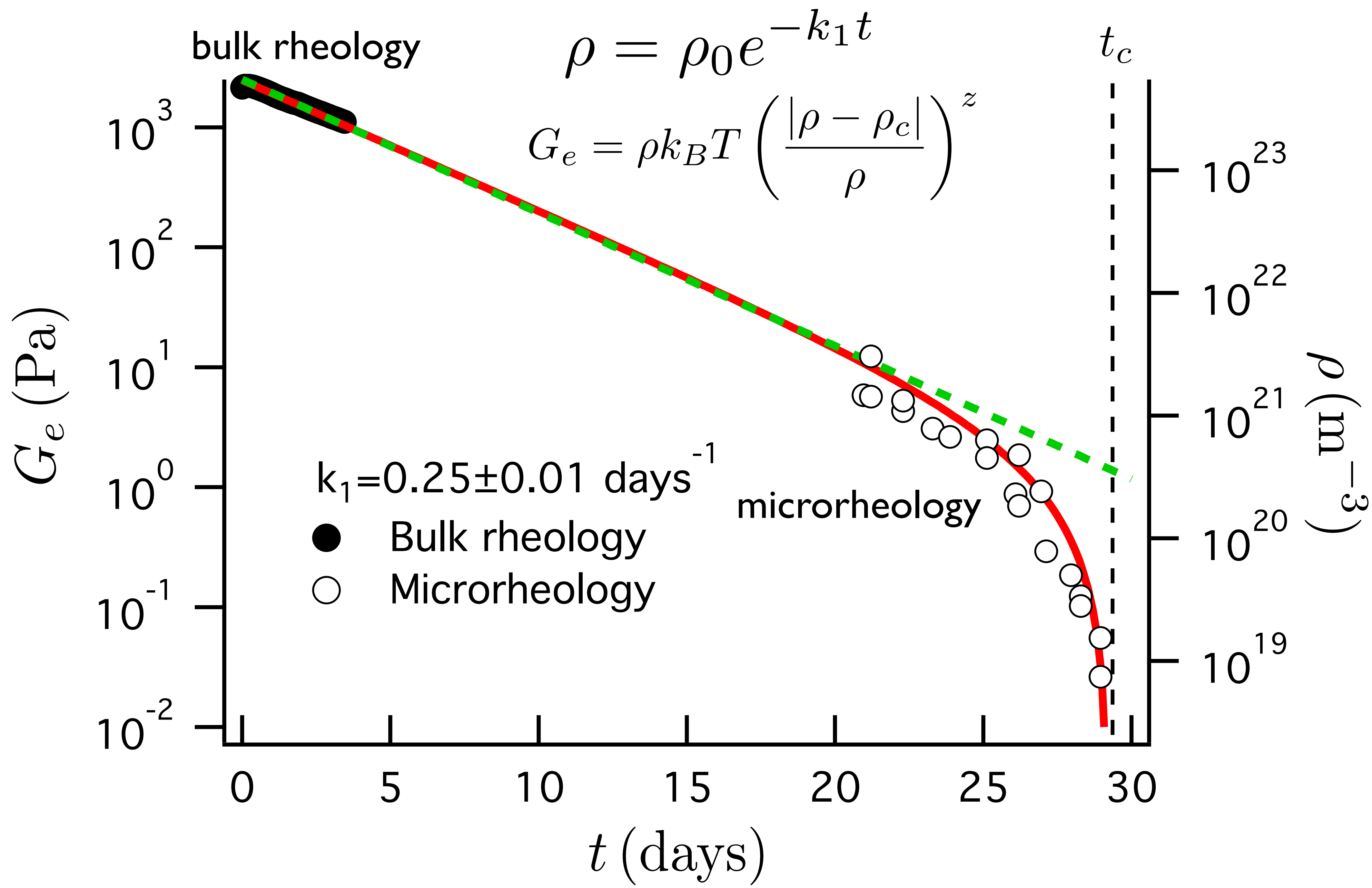



Shifted *master* curve



# *Interpolated* rheo-kinetic model of gel modulus

K. M. Schultz, A. D. Baldwin, K. L. Kiick and E. M. Furst, *ACS Macro Lett.* 1, 706–708 (2012).



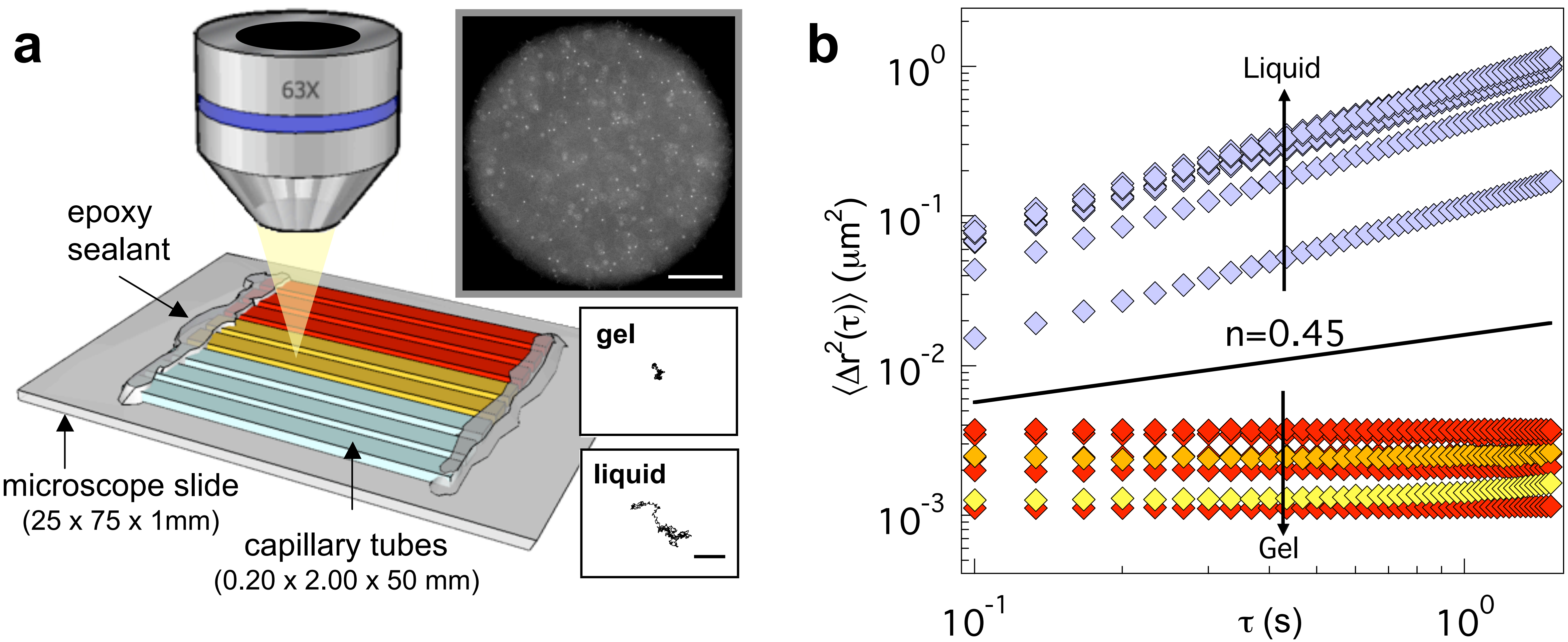

*Complementary data – modulus of hydrogel over 30 days*

# Rapid screening of gel composition space

K. M. Schultz, et al. *Soft Matter*, 5:740–742, 2009.

Cure many samples in parallel ~10-20μL

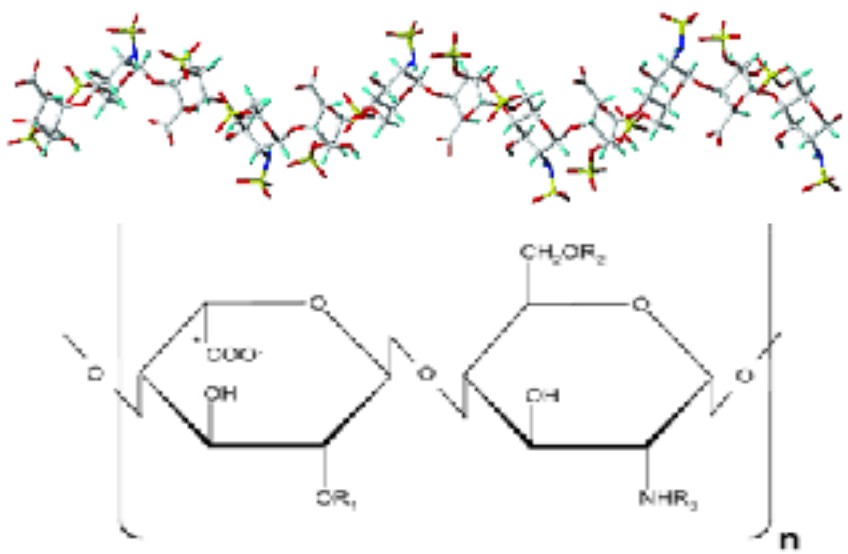
Identify gel or fluid



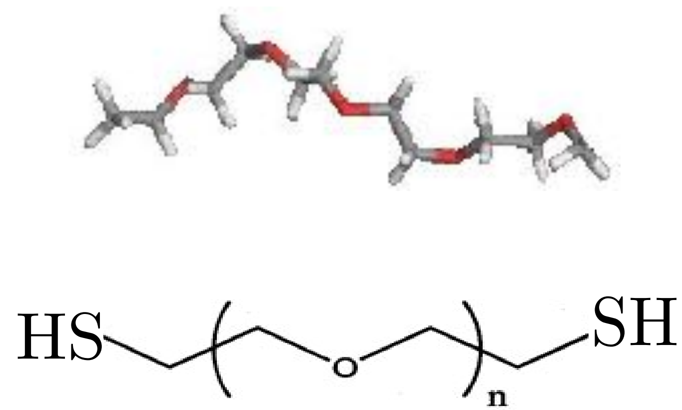
# Covalent heparin hydrogels

Yamaguchi et al., *J. Am. Chem. Soc*, 129, 3040-3041 (2007).
Yamaguchi et al., *Biomacromolecules*, 6, 1931-1940 (2006).
Yamaguchi & Kiick, *Biomacromolecules*, 6, 1921-1930 (2005).

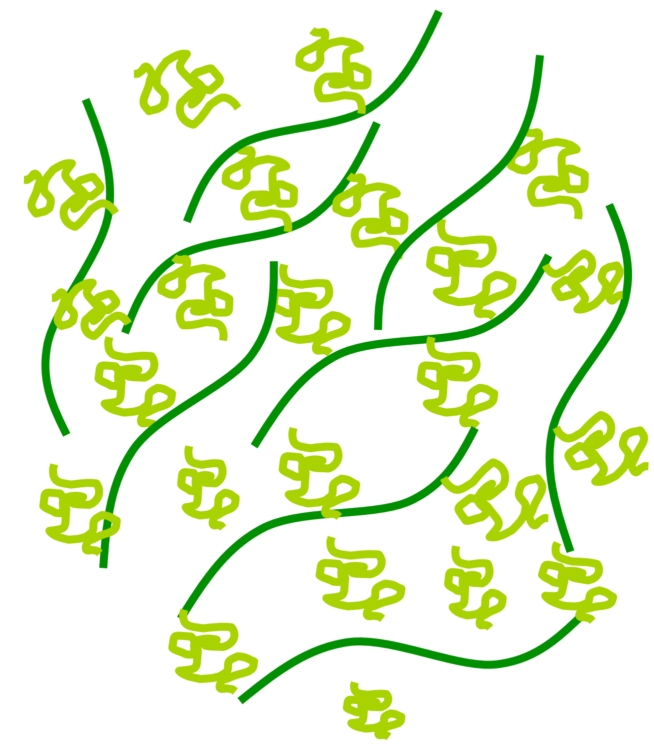
Maleimide functionalized high molecular weight heparin (HMWH)




Poly(ethylene glycol)-$(SH)_2$ (PEG)

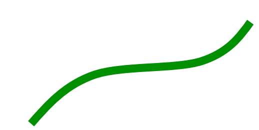



Covalent hydrogel network

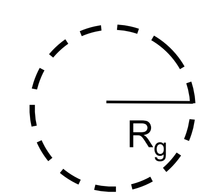


## Composition space

1. MHWM functionality
2. Fraction HMWH
3. PEG molecular weight
4. Total concentration

High molecular weight heparin 

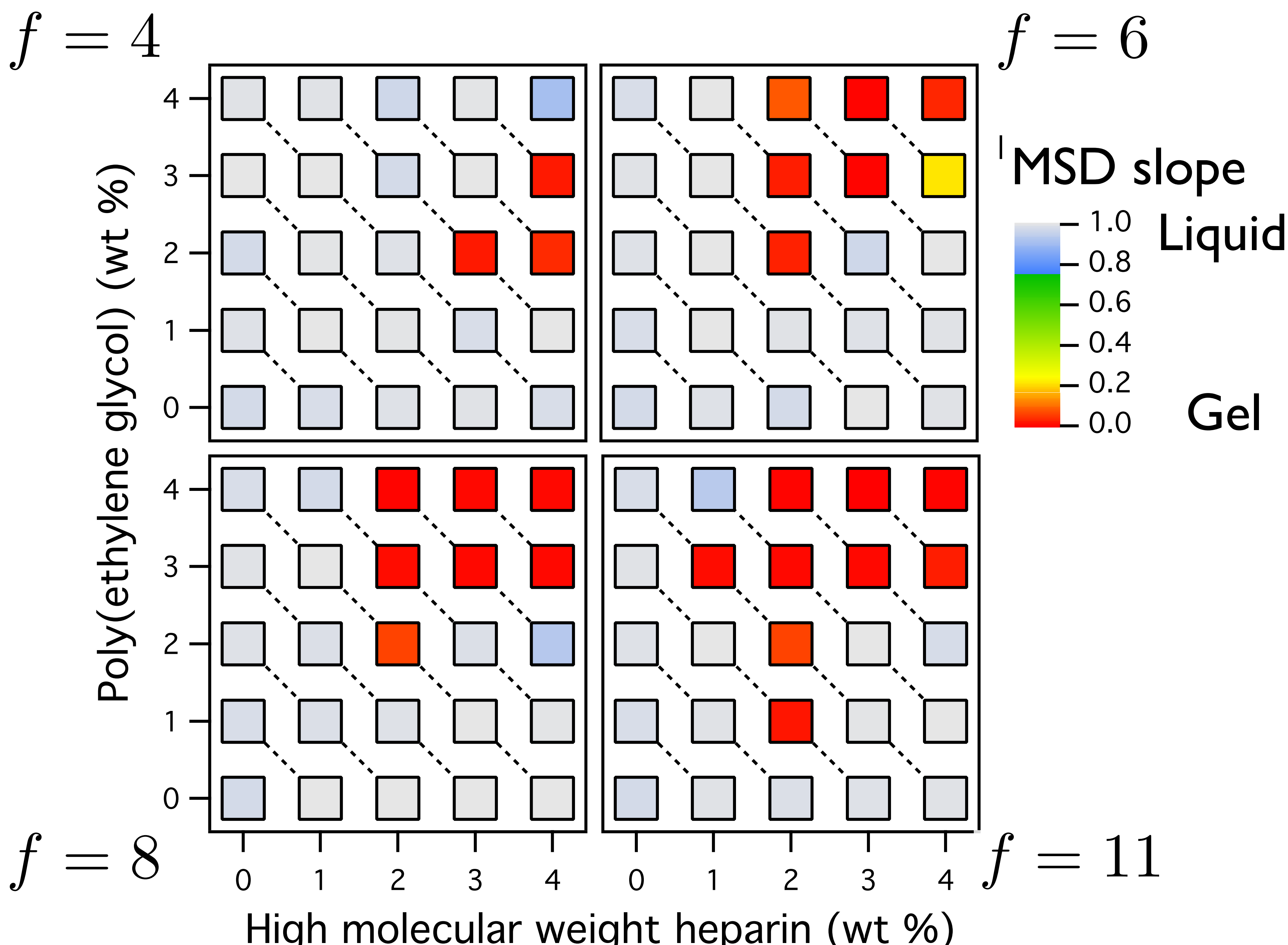
Poly(ethylene glycol) 

Radius of gyration 

# Gelation state diagram

K. M. Schultz, et al. *Soft Matter*, 5:740–742, 2009.

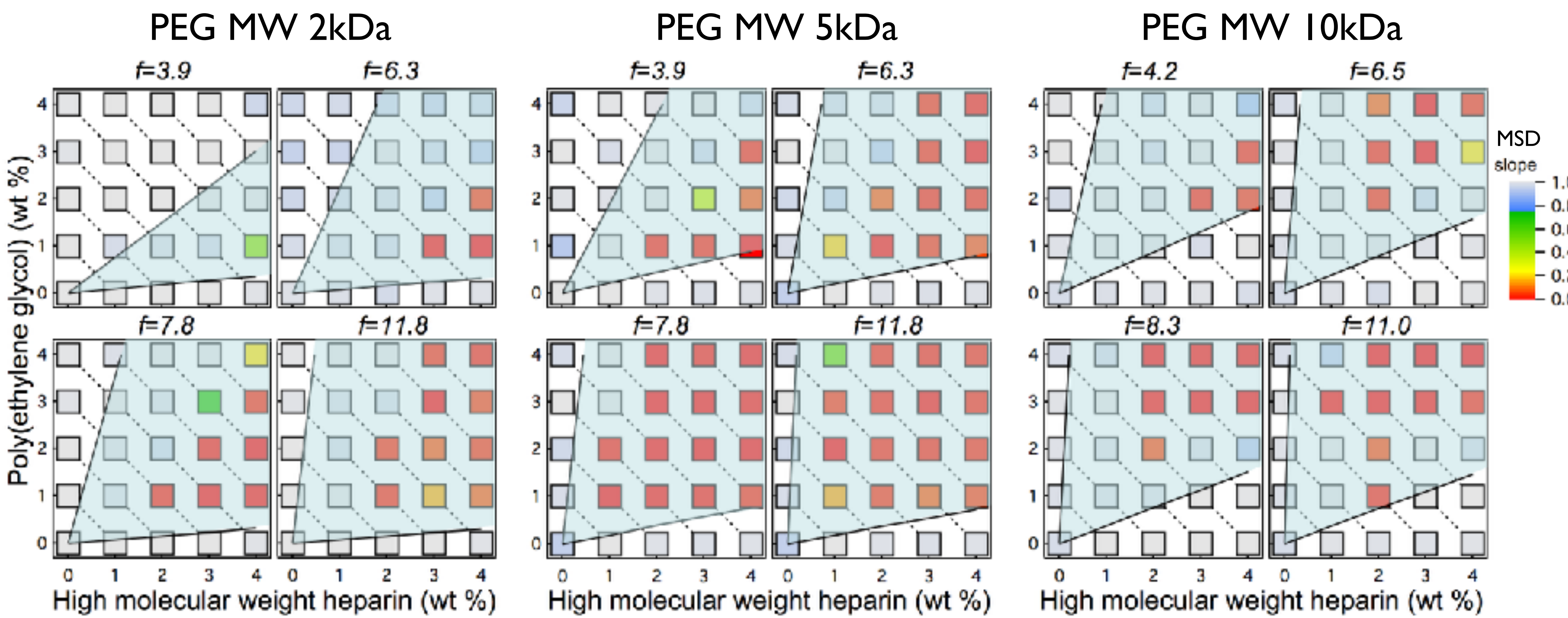
73 Samples measured in approximately 1 day



# "Hydrogel materialome"

## *219 rheological measurements*

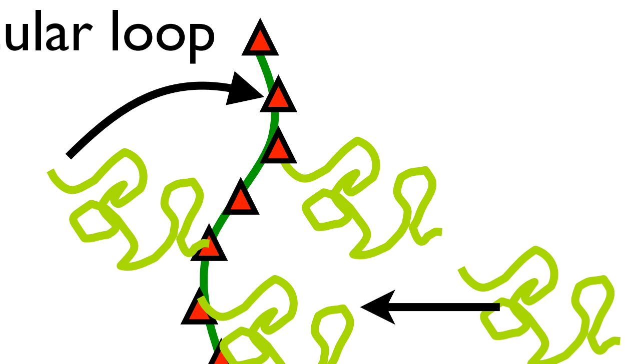
K. M. Schultz et al., Macromolecules, 42:5310–5316, 2009.




$$f = 11$$

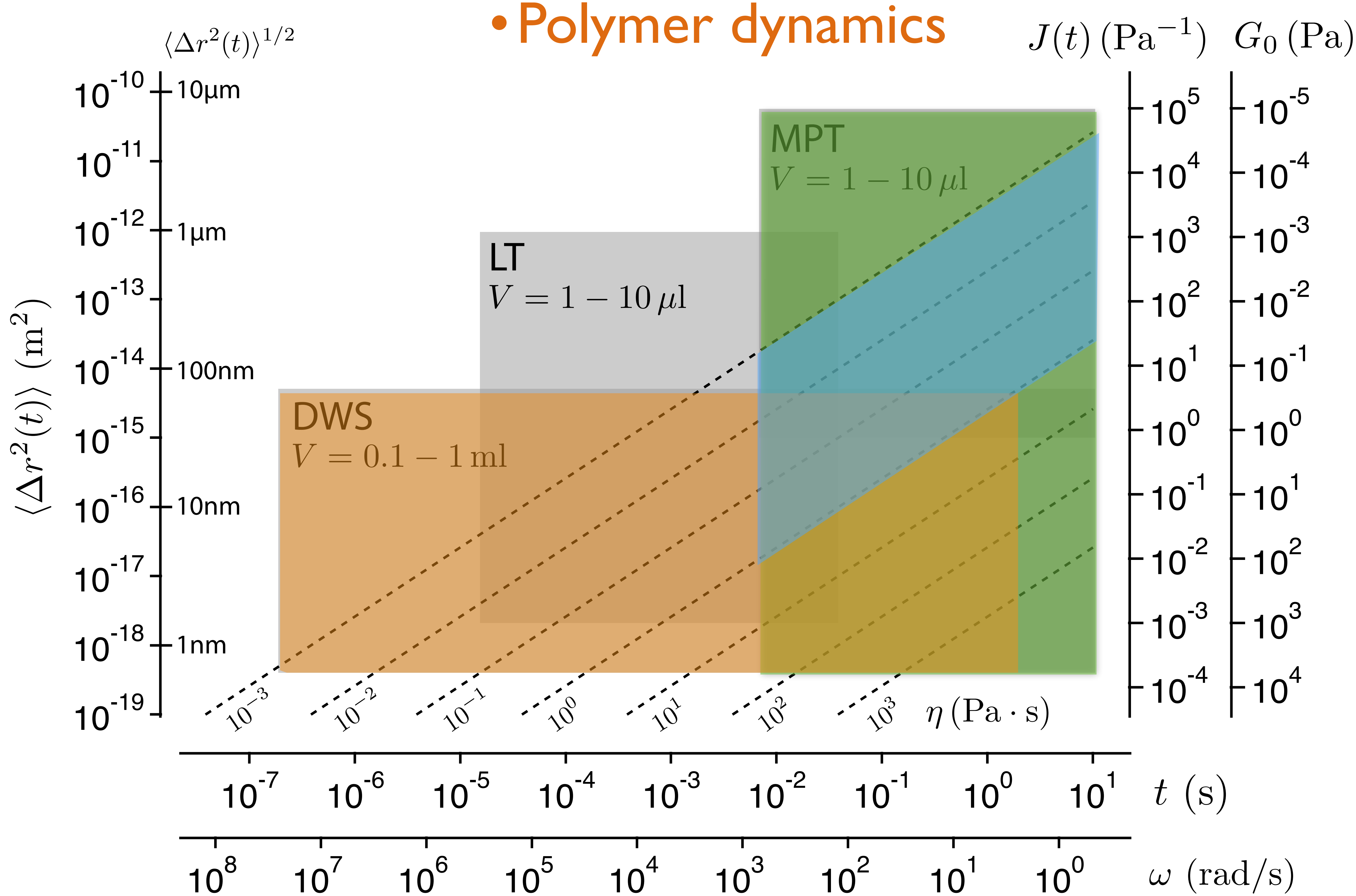
Average maleimide group spacing $\bar{d} = 2.4\text{nm}$

10kDa PEG end-to-end length $\langle R \rangle = 7.5\text{nm}$



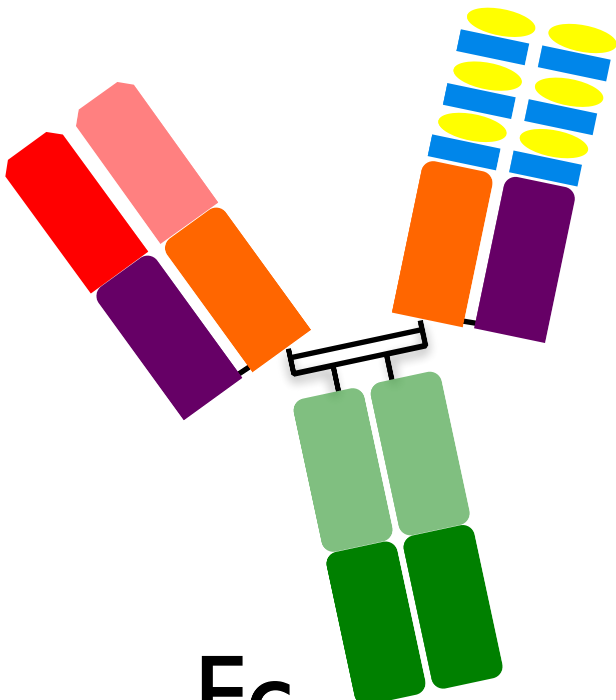
# Microrheology problem classes

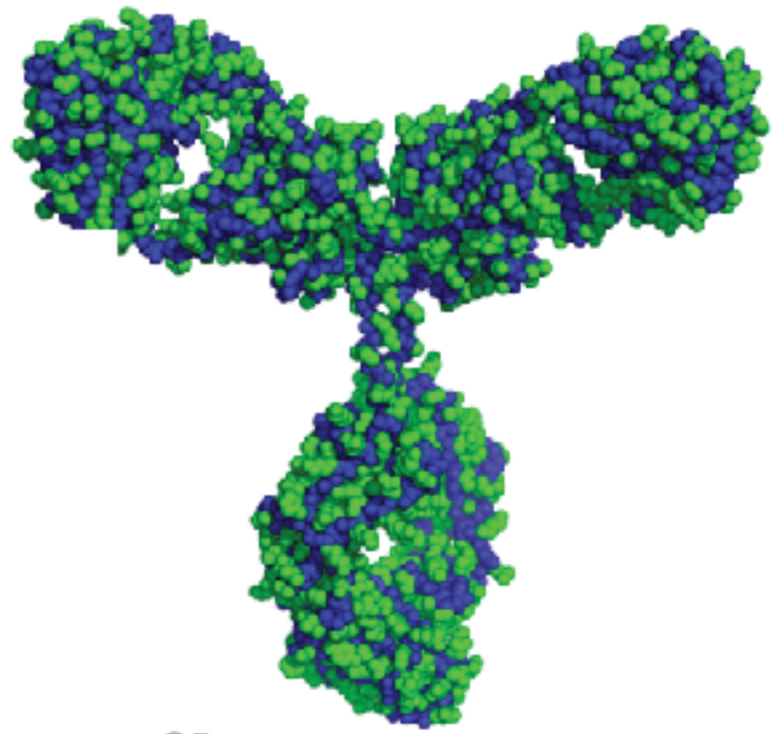
- Hydrogelators
- Protein solutions
- Polymer dynamics

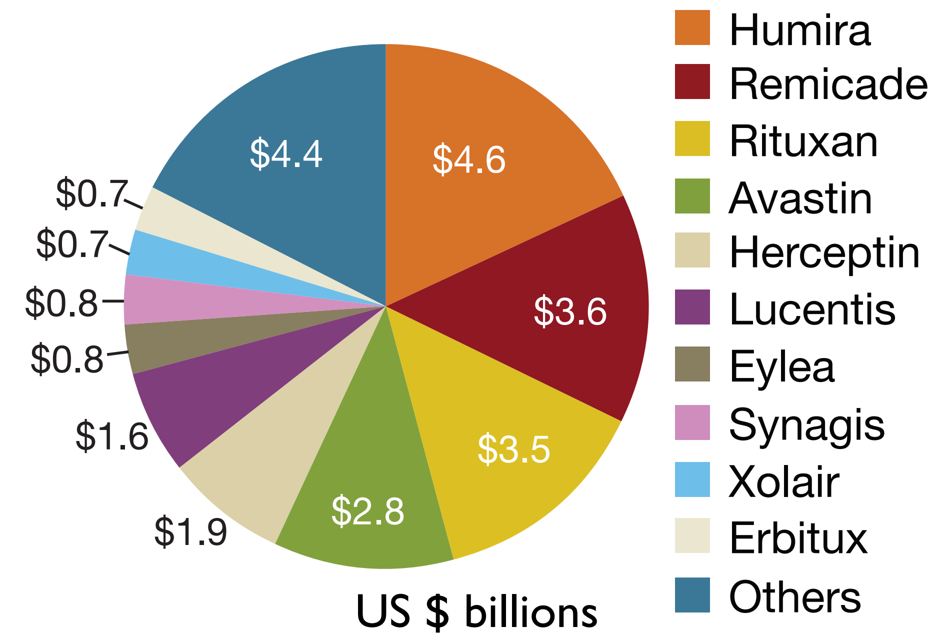


# Monoclonal antibodies (mAbs)

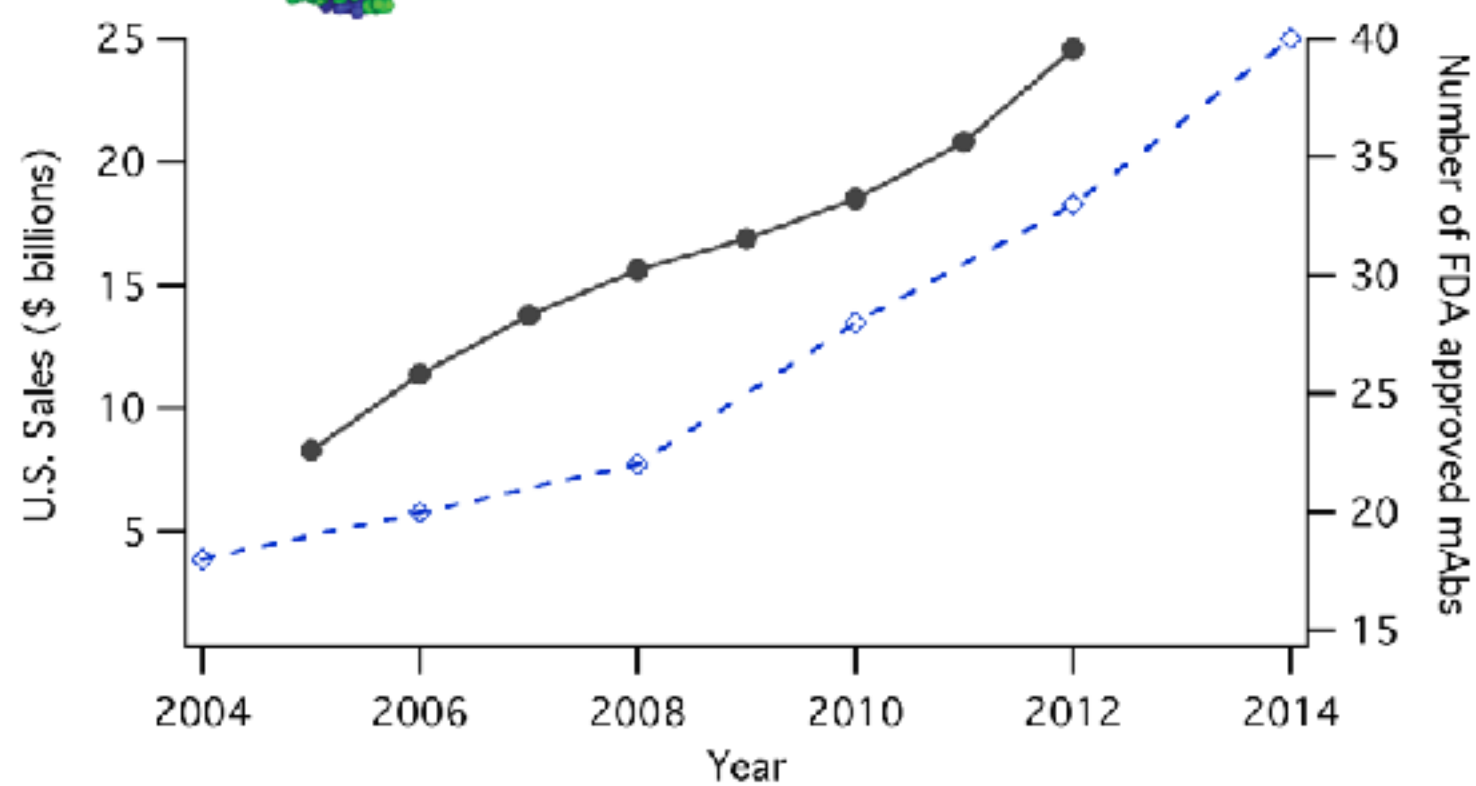
Aggarwal, *Nature Biotech.* **32**, 2014



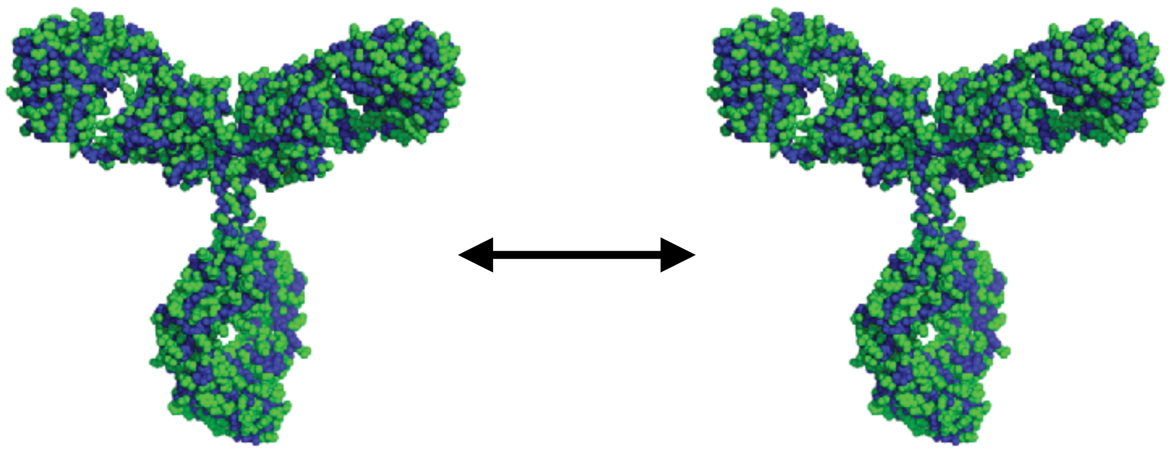



Follicular lymphoma
Hodgkin's lymphoma/ALCL
Relapsed/refractory lymphocytic leukemia
Ulcerative colitis
Rheumatoid arthritis
Lupus
Age-related macular degeneration



# Protein rheology

*Molecular interactions*



*Processing*

*Delivery*

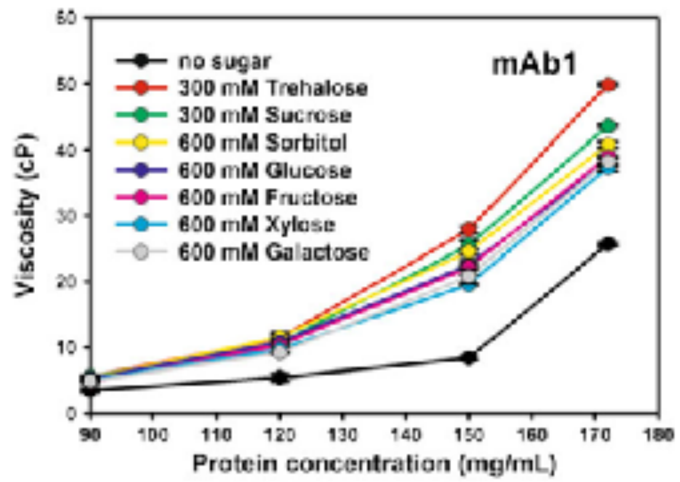
*Protein stability, viscosity at high concentration*

# mAb biologics upstream development bottleneck

*Development bottleneck*
Only small amounts of protein available, but a large composition space

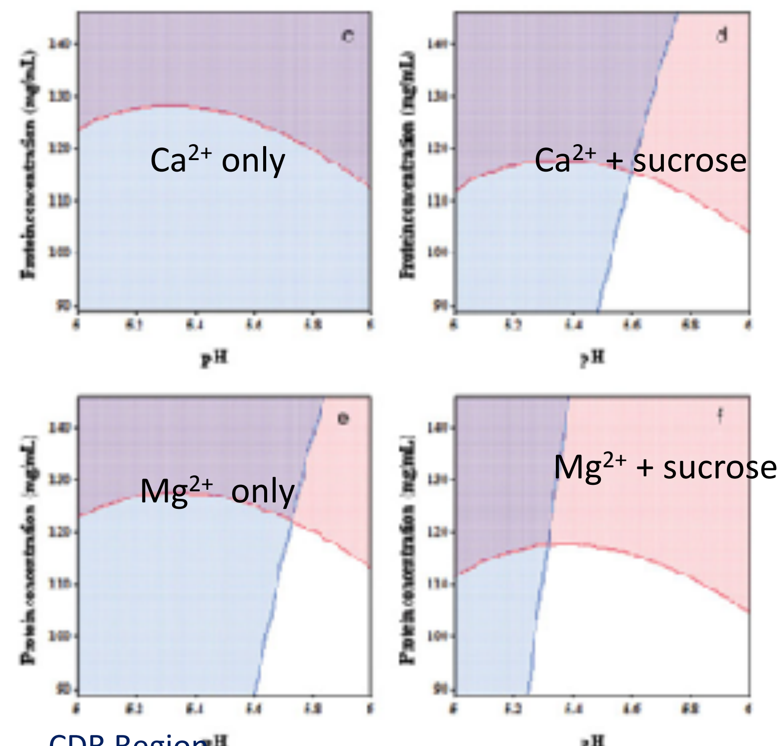
## *Type and amount of excipients*

He et al., Pharm. Res. 28(7), 1552-1560, 2011




## *Effect of ions, sugars, pH*

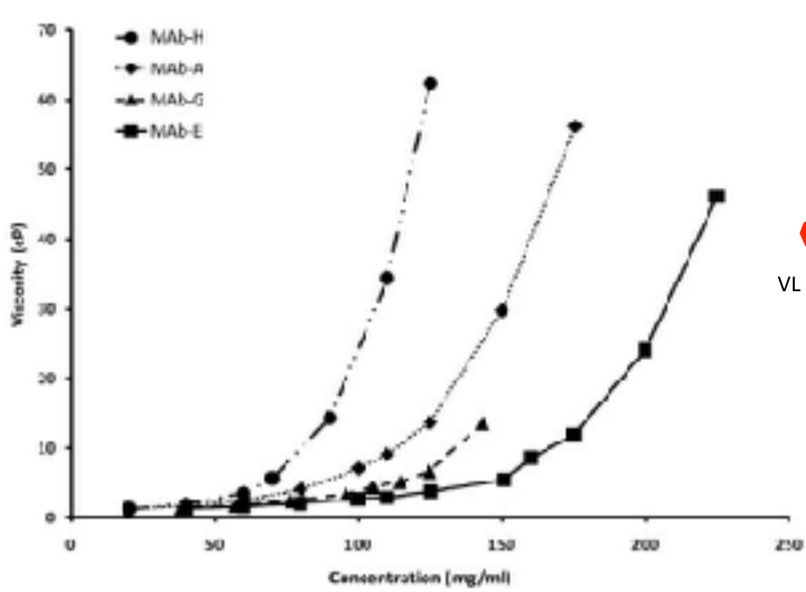
He et al., J. Pharm. Sci. 100(4), 1330-1340, 2010

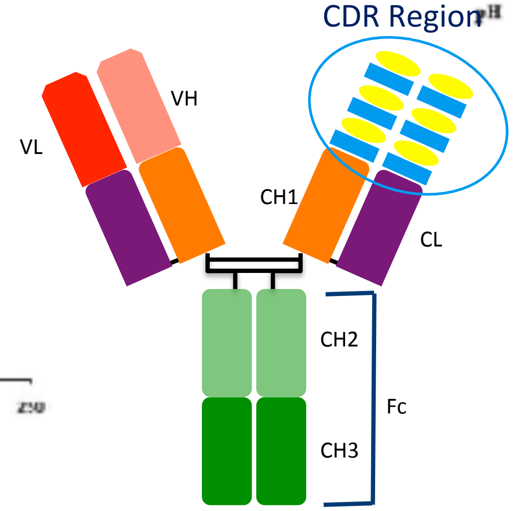


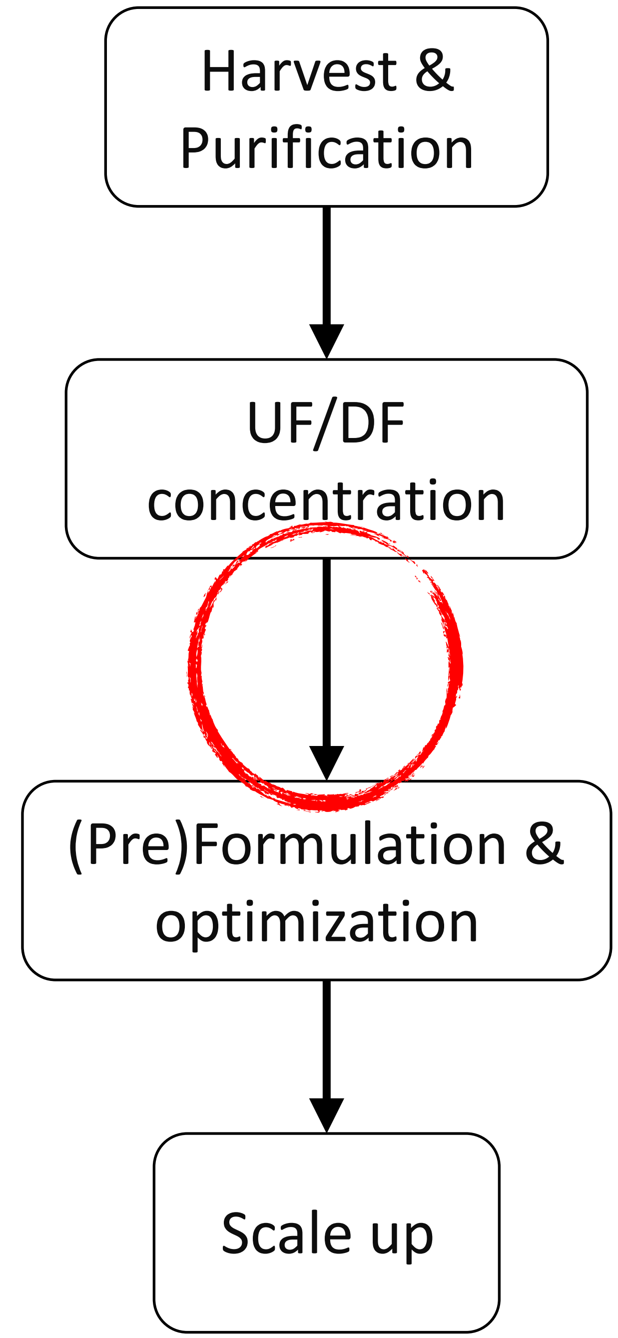

*81 experiments to screen 4 variables (conc., pH, ions, excipients)*

## *Protein sequence / engineering*

Yadav et al., J. Pharm. Sci. 99(12), 4812-4829, 2010

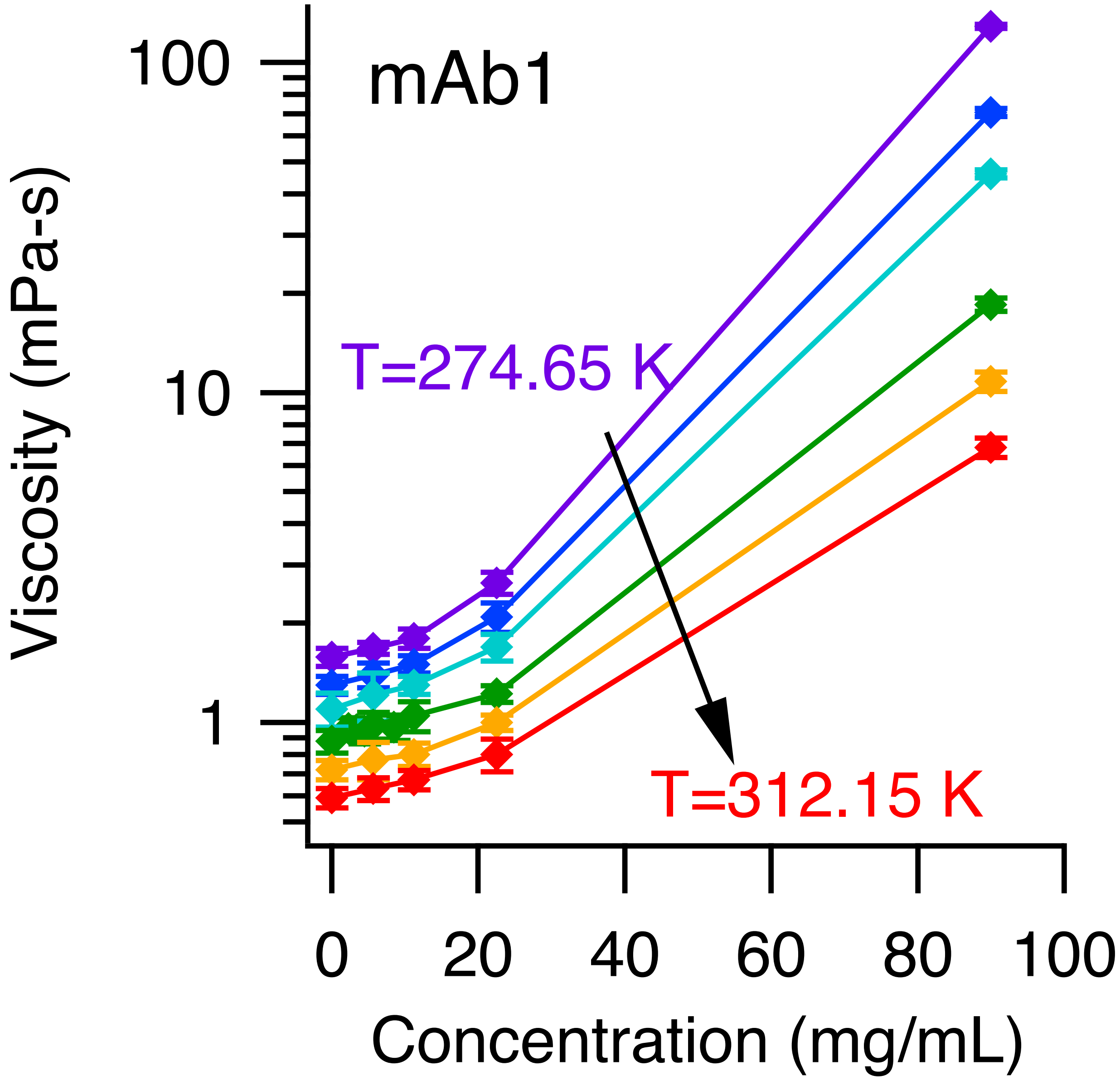


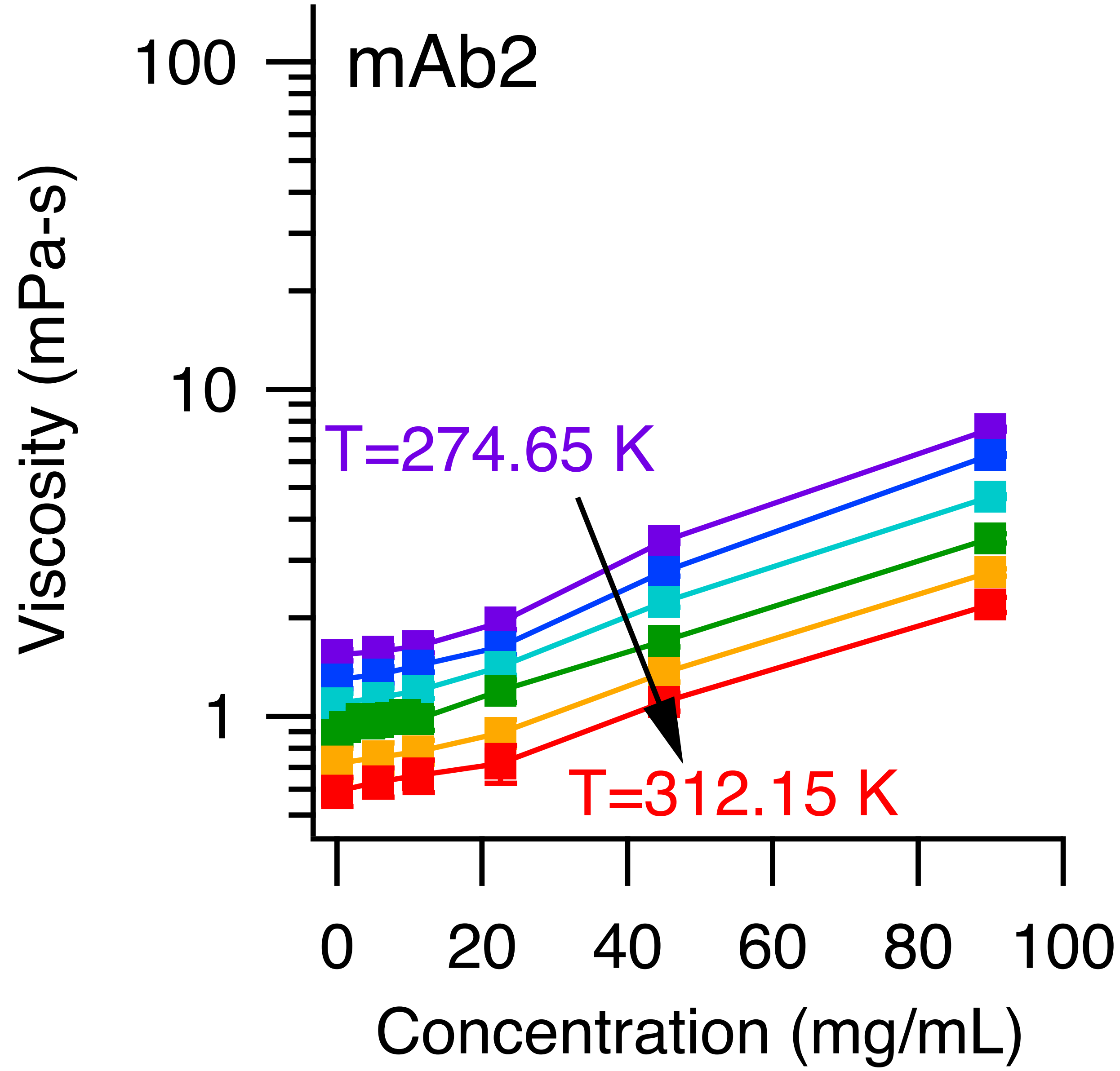



# mAb microviscosity – concentration & temperature

*Josephson, L. L., Galush, W. J. & Furst, E. M. Biomicrofluidics 10, 43503 (2016).*



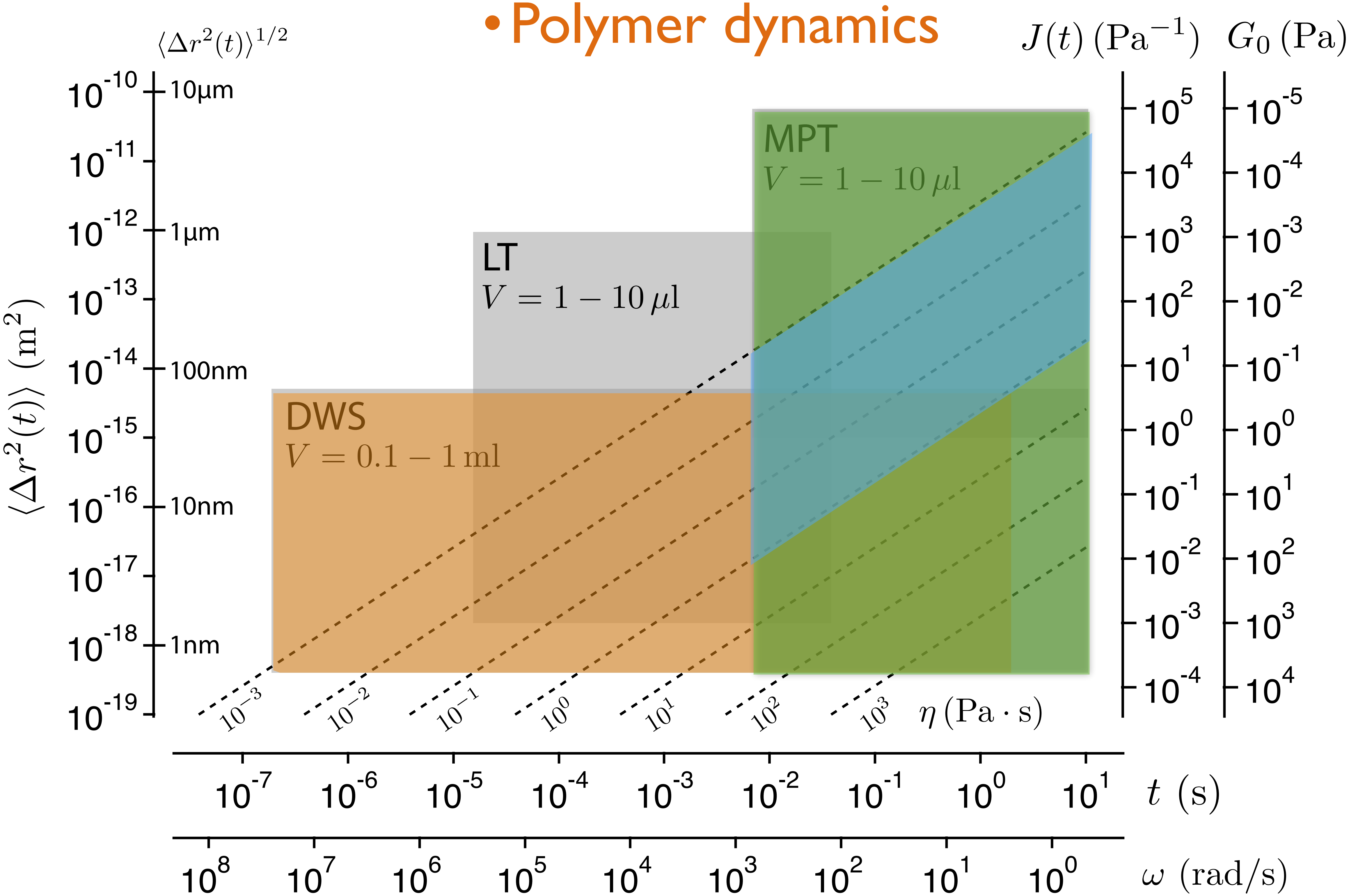




2 mAbs x 6 temperatures x 6 concentrations
= *72 measurements in ~5 hours*

Total 1.5 mg sample per mAb

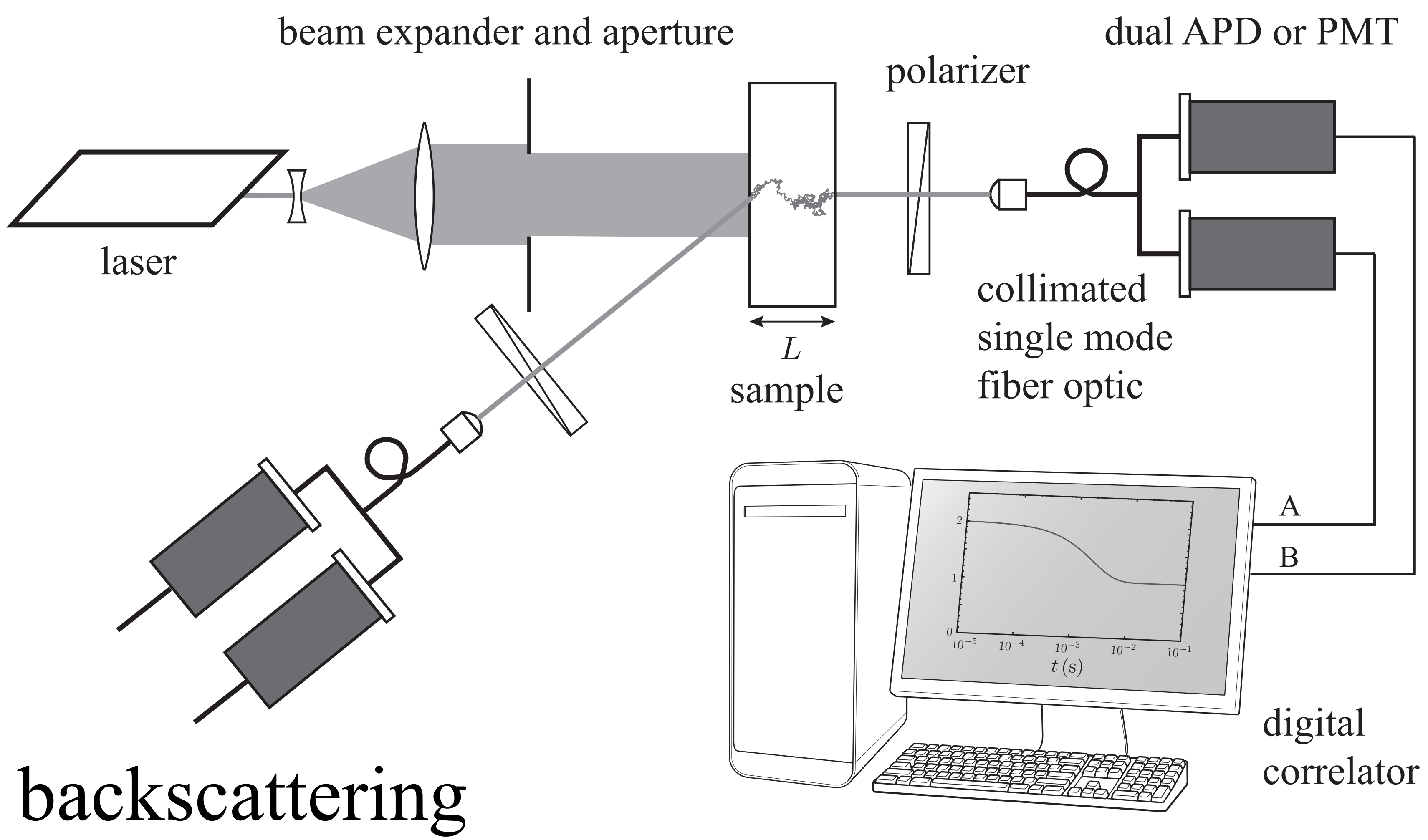
# Microrheology problem classes

- Hydrogelators
- Protein solutions
- Polymer dynamics



# Diffusing wave spectroscopy

P.-E. Wolf and G. Maret. *Phys. Rev. Lett.*, 55:2696–2699, 1985.
Pine, D., Weitz, D., Chaikin, P. & Herbolzheimer, E. *Phys. Rev. Lett.* 60, 1134–1137 (1988).

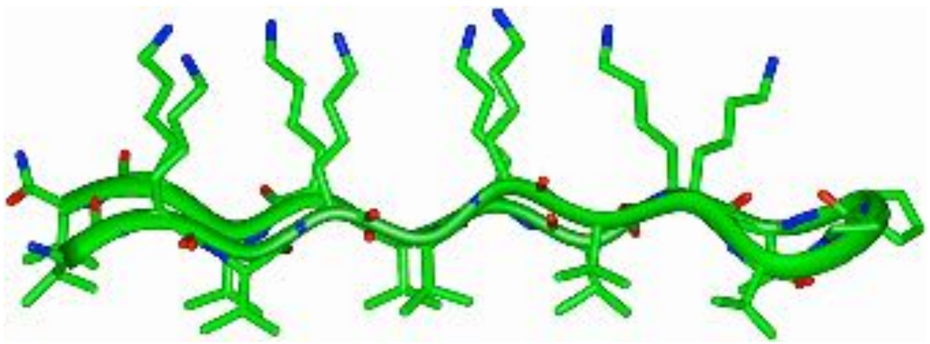



sample

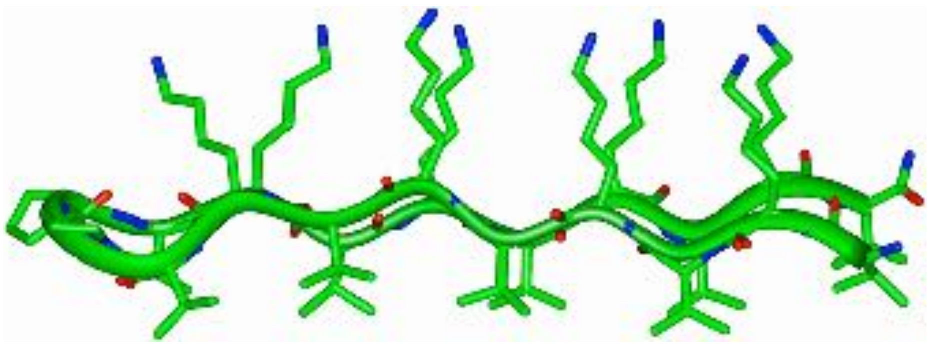
1 μm PS probe particles, 1 vol%

# Peptide enantiomers

Peter Beltramo with Joel Schneider, Katelyn Nagy (NIH)

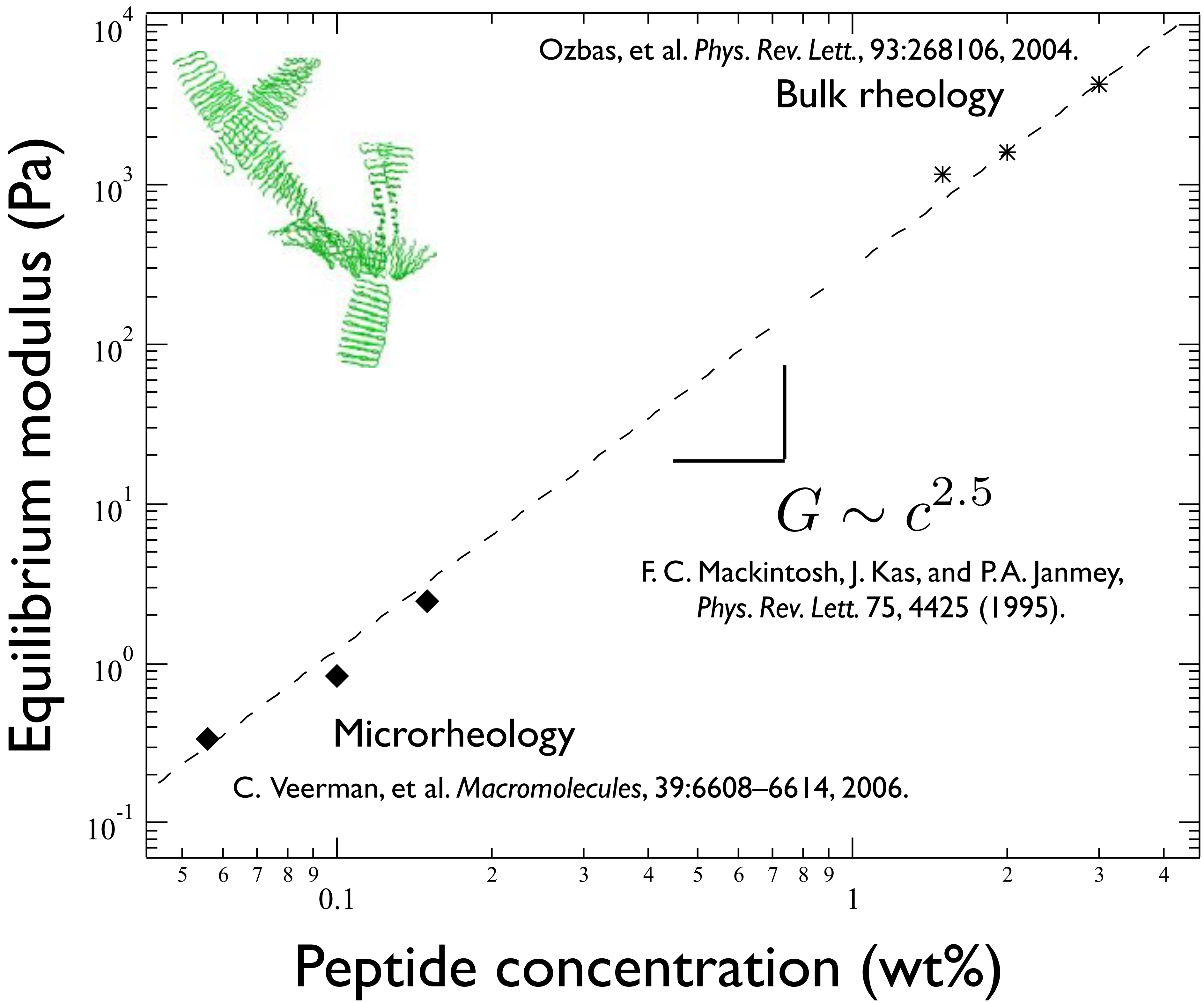


MAX1
*levo*

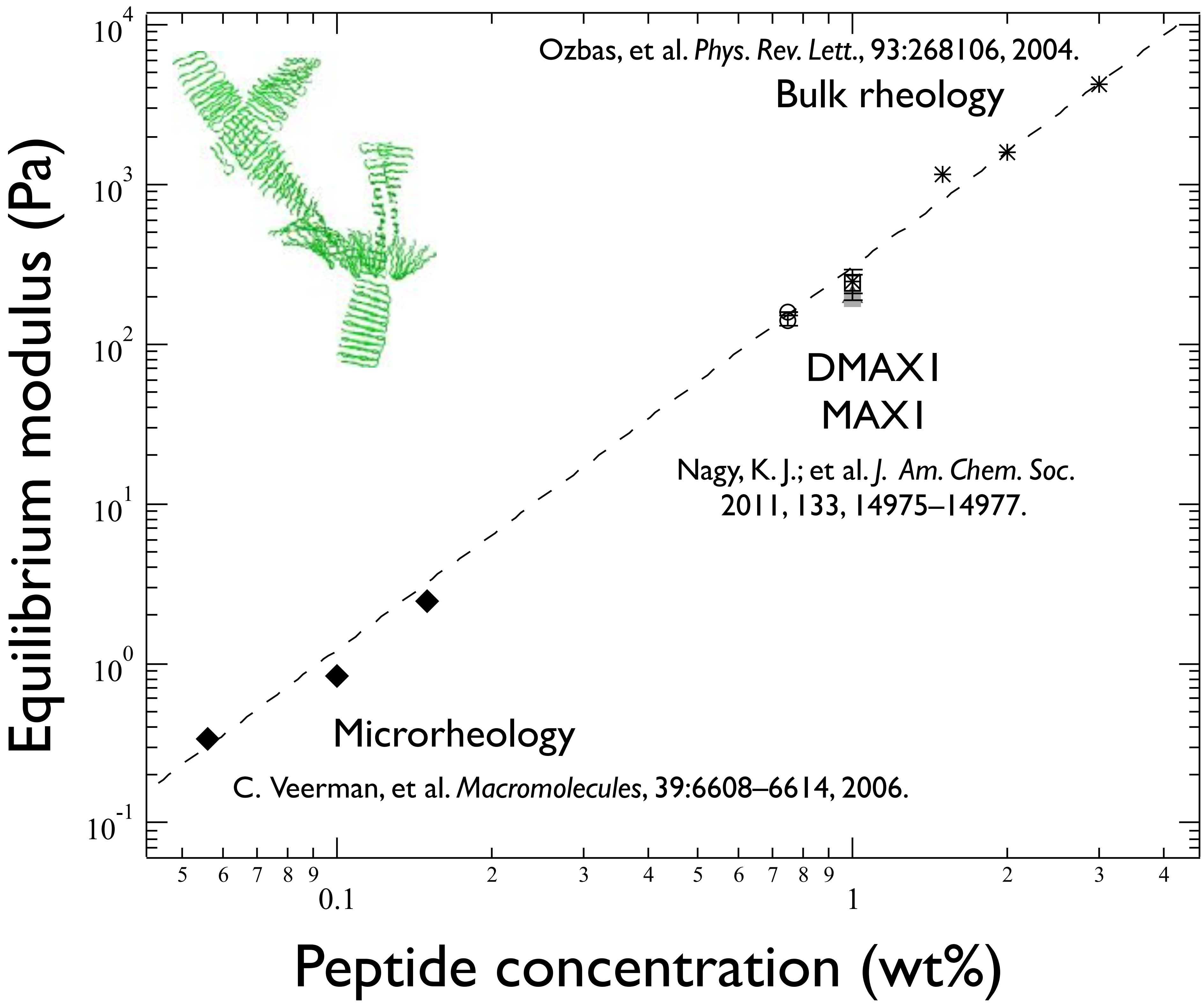


DMAX1
*dextro*

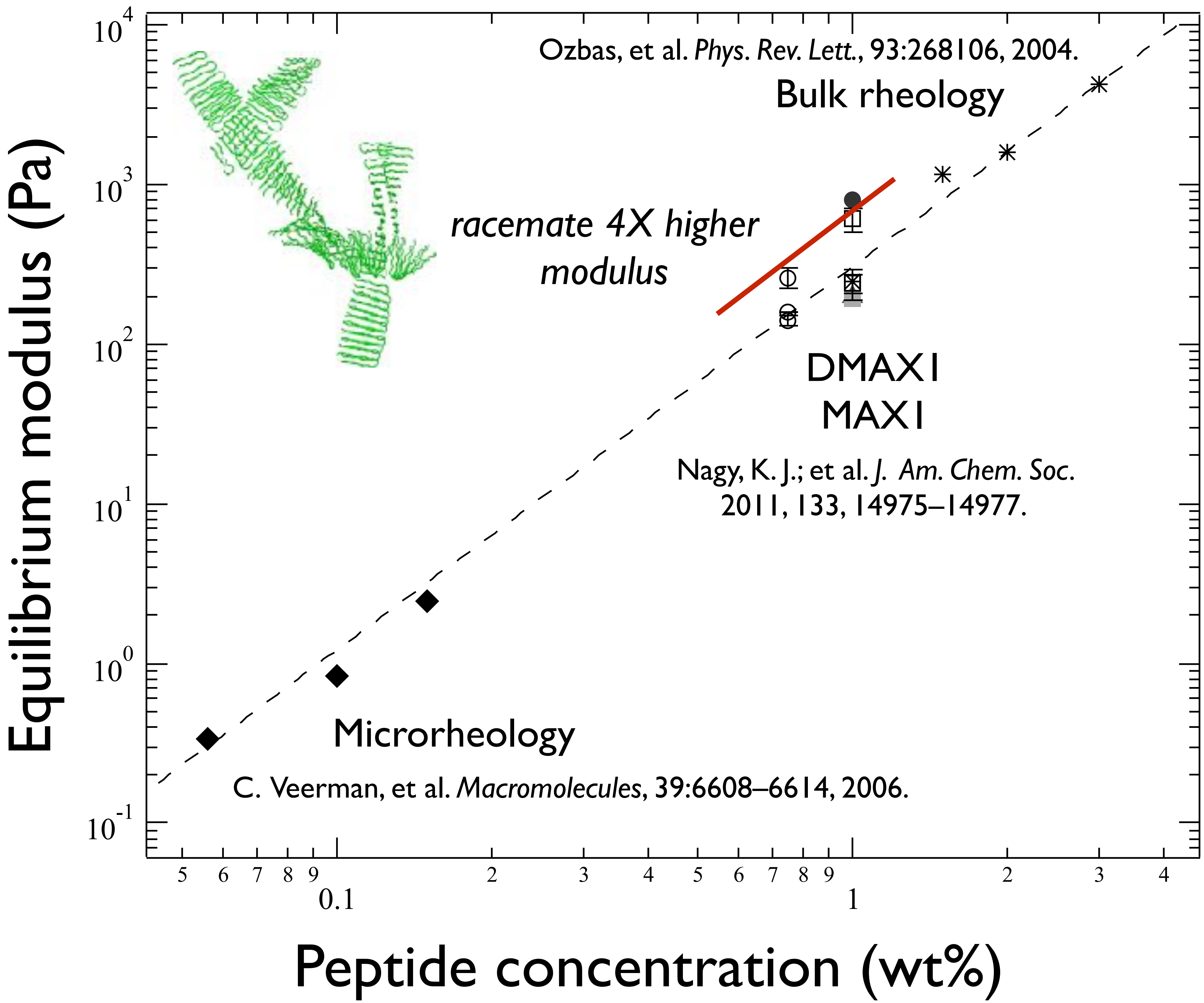
# Enantiomer hydrogels



# Enantiomer hydrogels

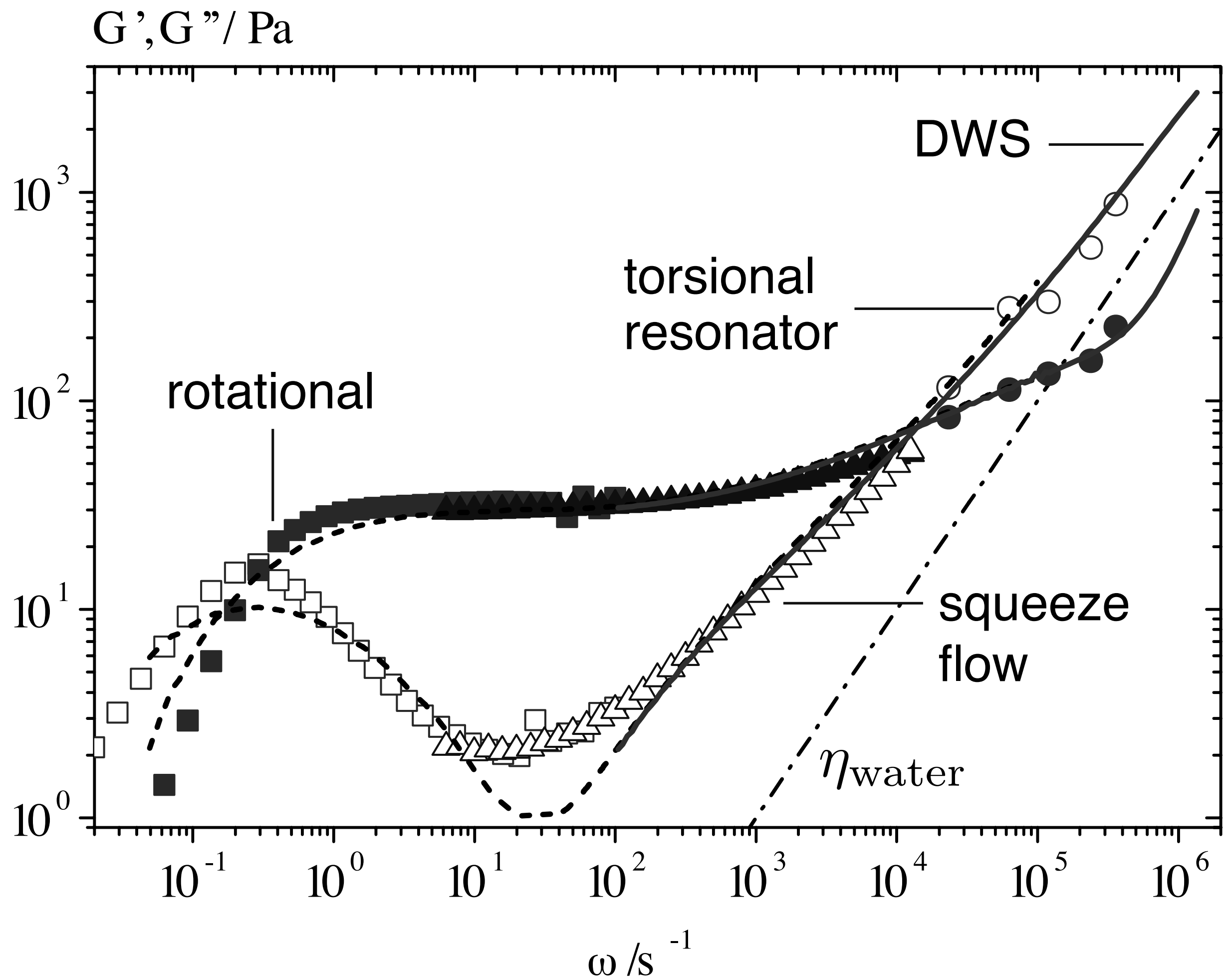


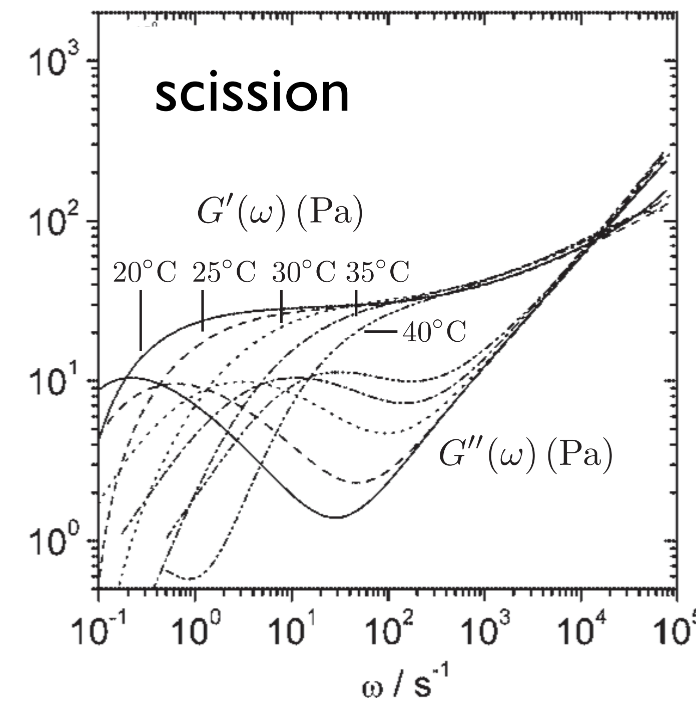
# Enantiomer hydrogels



# Worm-like micellar solutions

Oelschlaeger, C., Schopferer, M., Scheffold, F. & Willenbacher, N. *Langmuir* 25, 716–723 (2009).
Willenbacher, N. et al. *Phys. Rev. Lett.* 99, 68302 (2007).

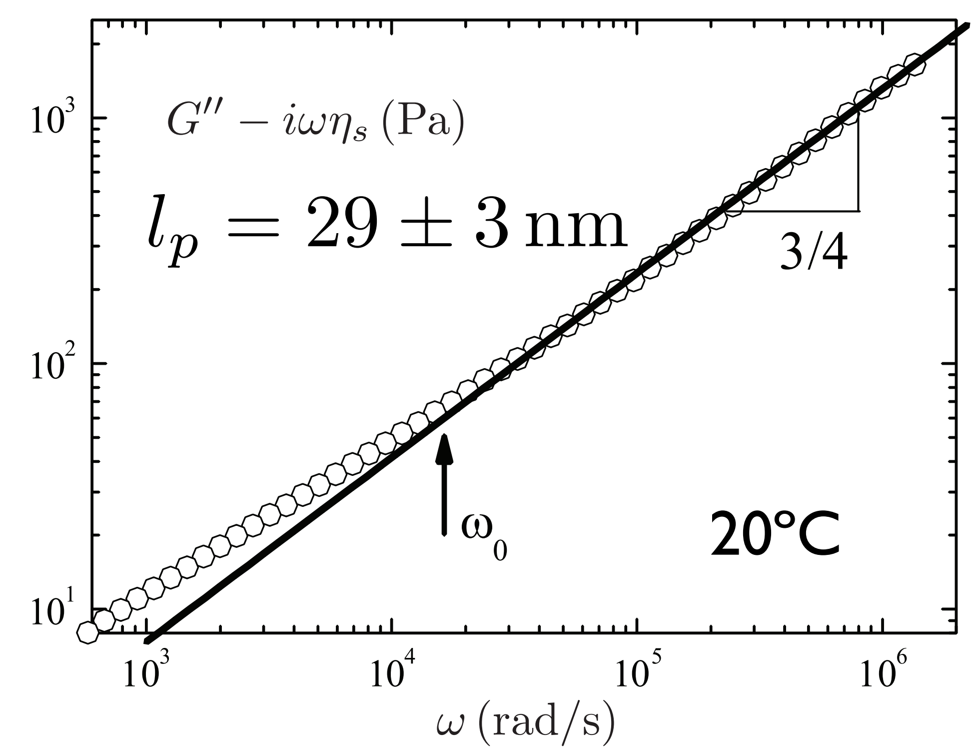



## Filament mechanics

$$G^*(\omega) \approx \frac{1}{15}\rho\kappa l_p(-2i\zeta_\perp/\kappa)^{3/4}\omega^{3/4} + i\omega\eta$$

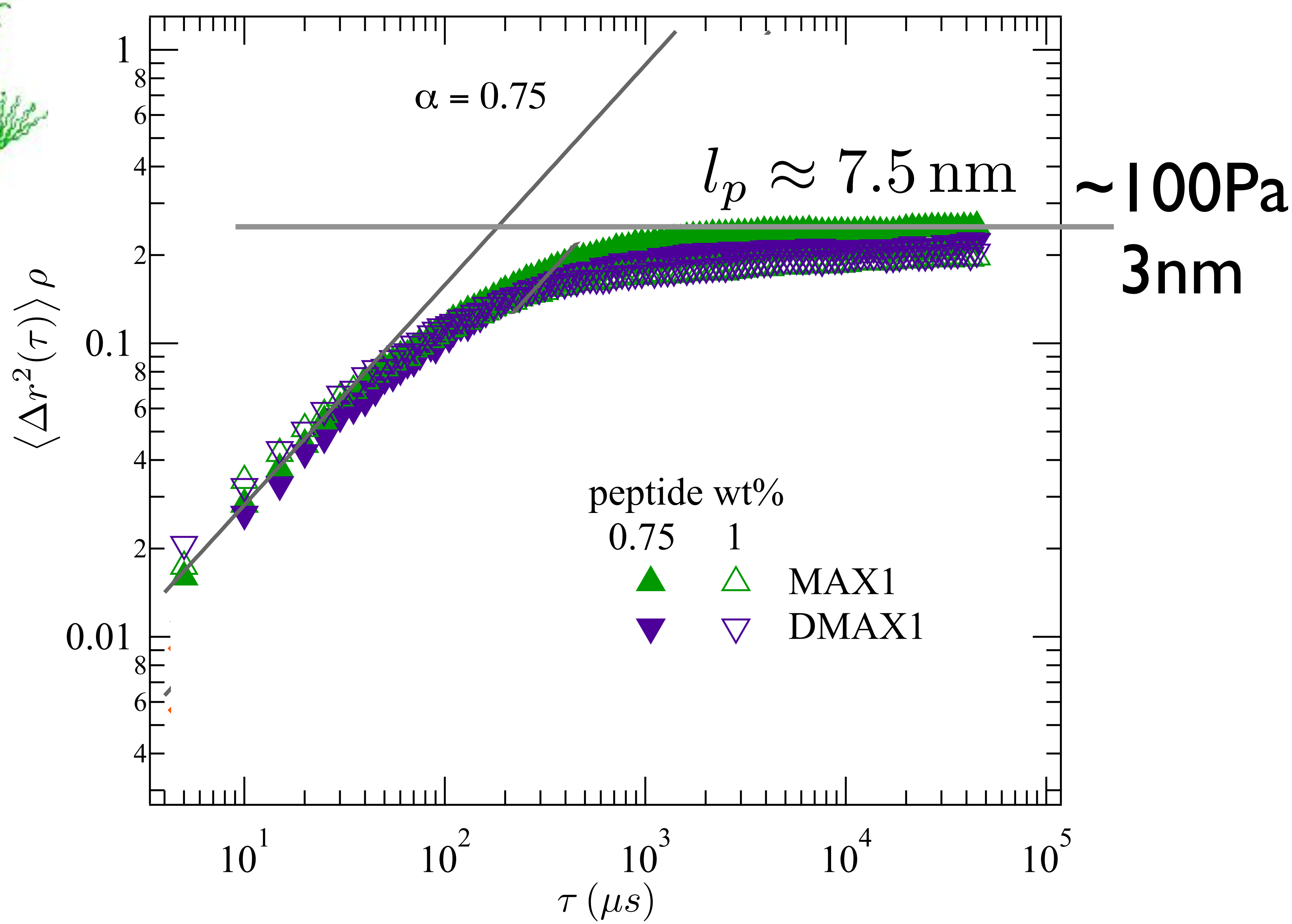
Morse, D. C. *Phys. Rev. E* 58, R1237–R1240 (1998).
Gittes, F. & MacKintosh, F. C. *Phys. Rev. E* 58, R1241-1244 (1998).



# Hydrogel of semiflexible filaments

$$J(\tau) = \frac{15}{\rho l_p^2 kT \Gamma\left(\frac{7}{4}\right)} \left(\frac{kT l_p \tau}{2\zeta}\right)^{3/4}$$

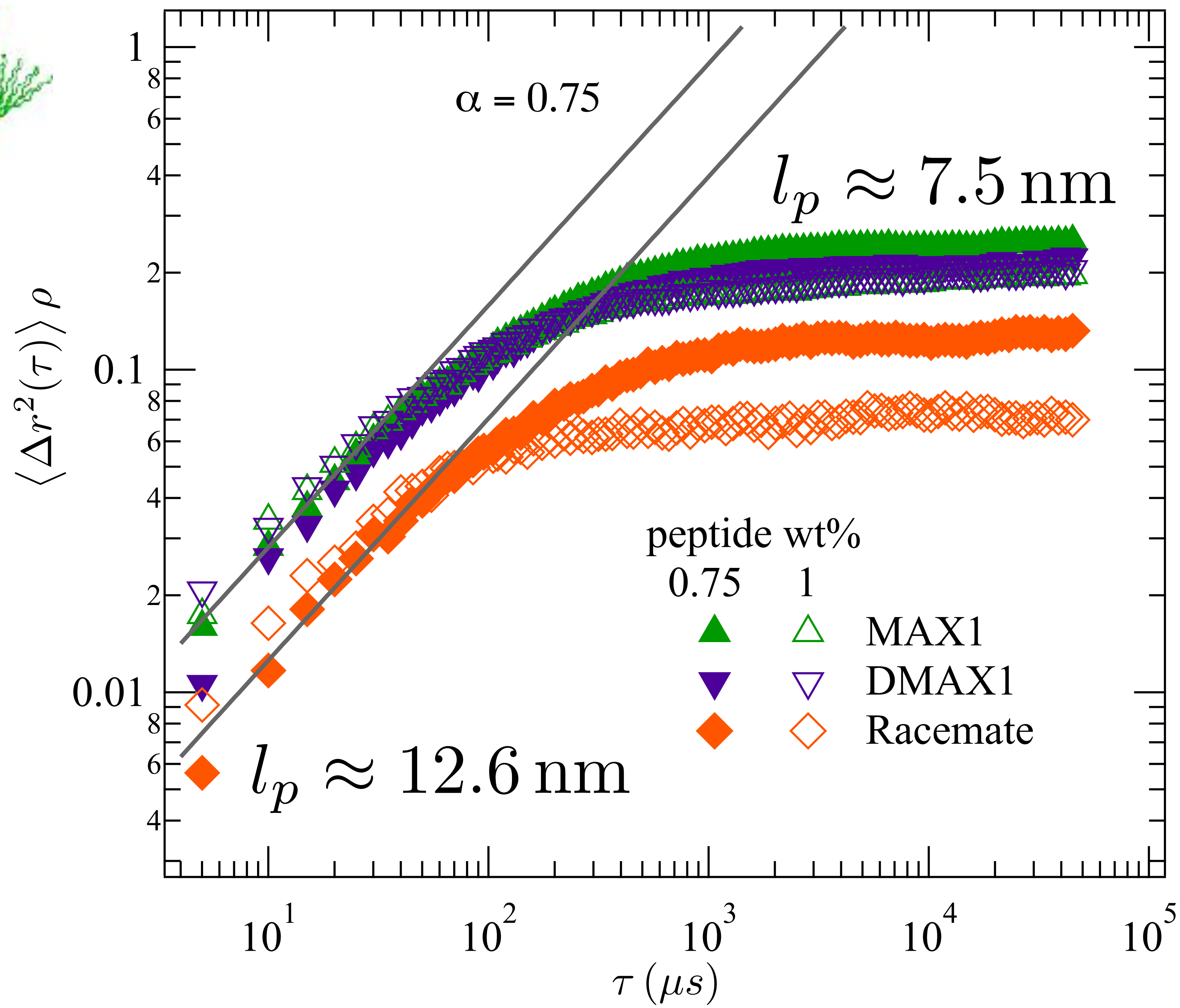

Morse, D. C. *Macromolelcules* 1998, 31, 7044–7076.
Gittes, F.; MacKintosh, F. C. *Phys. Rev. E* 1998, 58, R1241–1244.

# Racemate filaments are ~2x stiffer

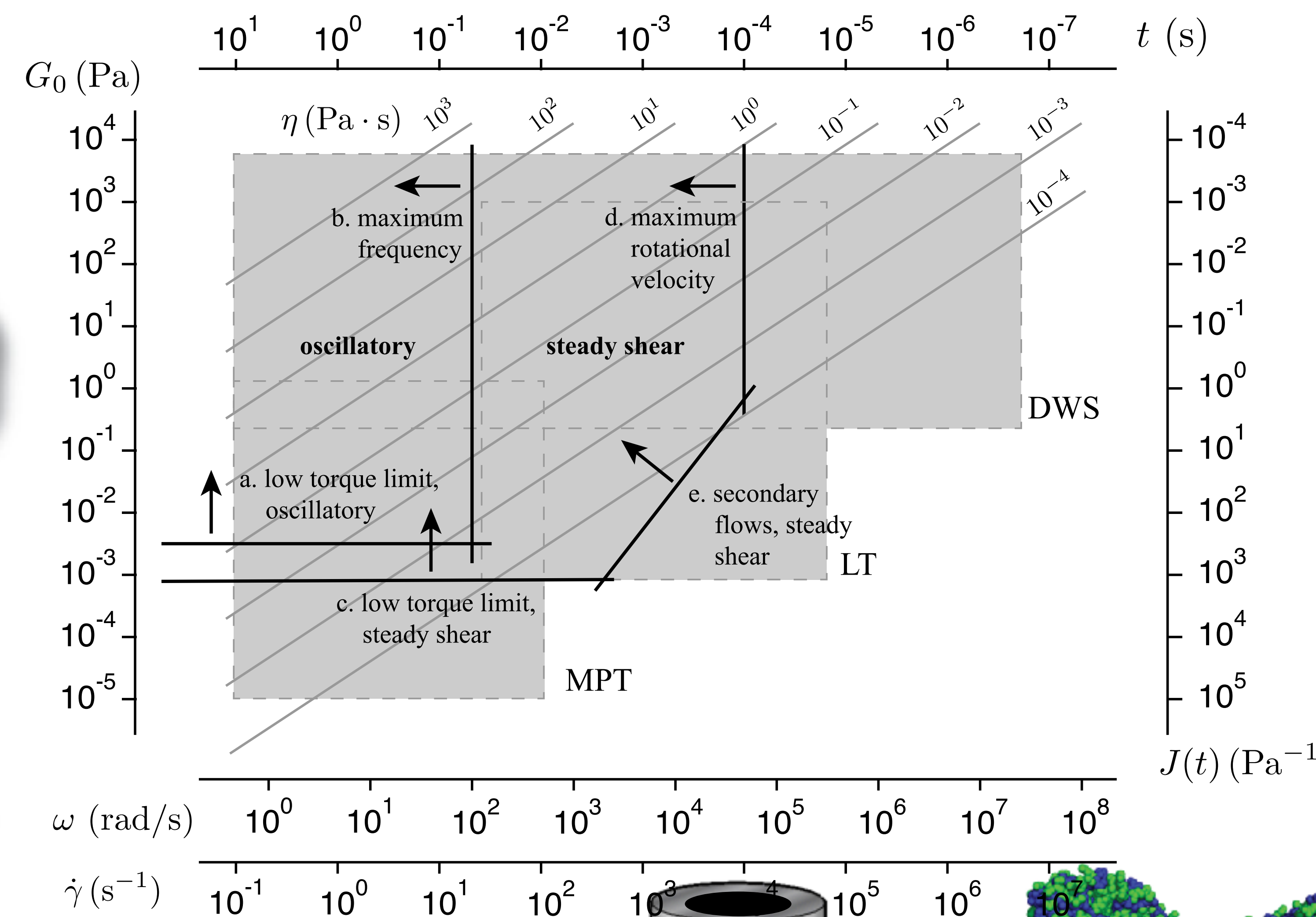
$$J(\tau) = \frac{15}{\rho l_p^2 kT\Gamma\left(\frac{7}{4}\right)}\left(\frac{kTl_p\tau}{2\zeta}\right)^{3/4}$$

Morse, D. C. *Macromolelcules* 1998, 31, 7044–7076.
Gittes, F.; MacKintosh, F. C. *Phys. Rev. E* 1998, 58, R1241–1244.

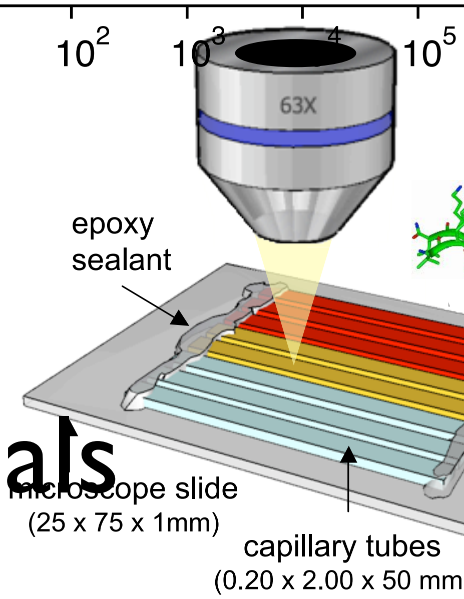


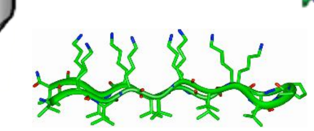

$$G' \sim l_p^2 kT(ac)^{5/2}$$

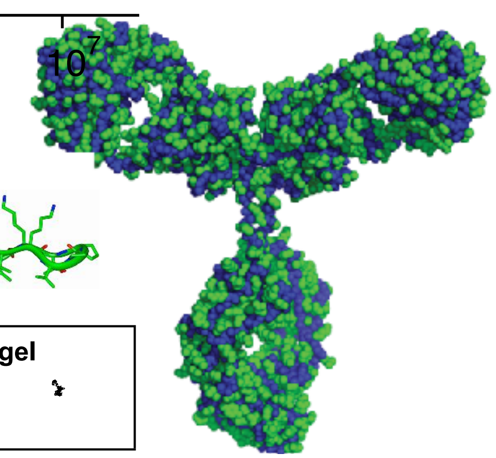
# Probe microrheology

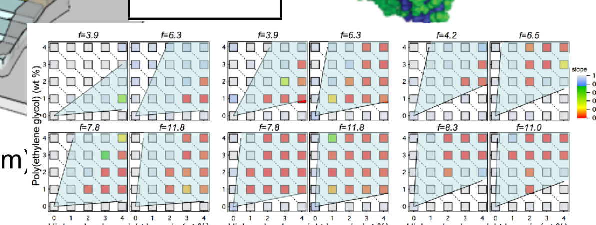



- Small volume rheology
- Rapid screening of scarce materials
- Extended operating regime







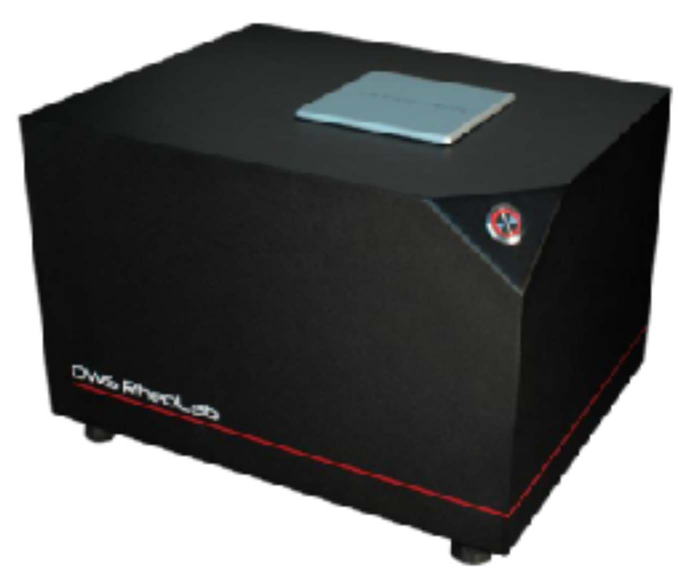
# Sophisticated, robust, and economical instruments

Macosko, C.W. *Joe Starita: Father of modern rheometry.* Rheol. Bulletin 79, 11 (2010).

"Unfortunately, except for the Rheogoniometer, such equipment is not yet commercially available, although it is expected that some enterprising company will manufacture this kind of apparatus shortly."

– Van Wazer, et al. (1963). *Viscosity and Flow Measurement: A Laboratory Handbook of Rheology*. Interscience, New York.

## DLS and DWS microrheology




# Non-linear microrheology

## Generalized Stokes Equation

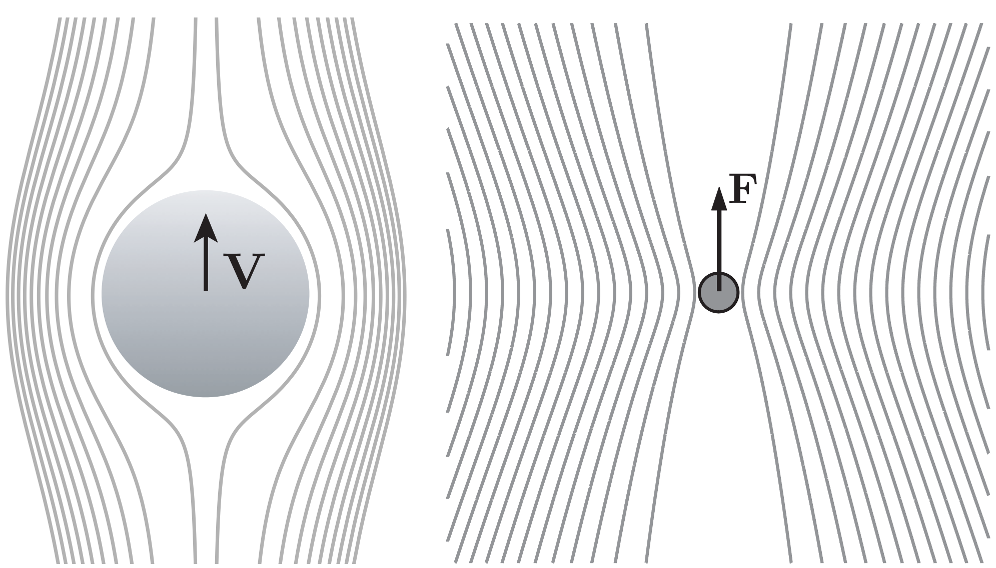
$$\eta(V) = \frac{F}{6\pi a V}$$

## Correspondence Principle

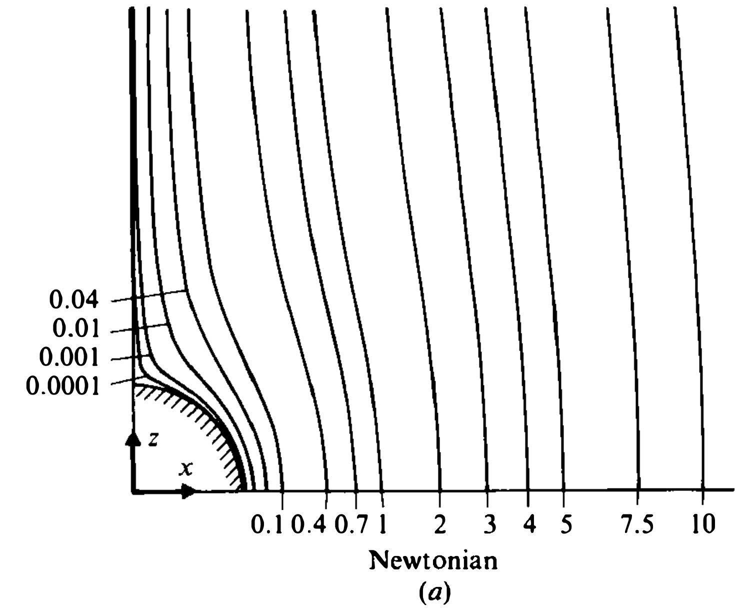
$$-\rho\omega^2\tilde{\mathbf{u}} = -\nabla\tilde{p} + i\omega\eta\nabla^2\tilde{\mathbf{u}}$$ – *Newtonian fluid*

$$-\rho\omega^2\tilde{\mathbf{u}} = -\nabla\tilde{p} + G\nabla^2\tilde{\mathbf{u}}$$ – *elastic solid*

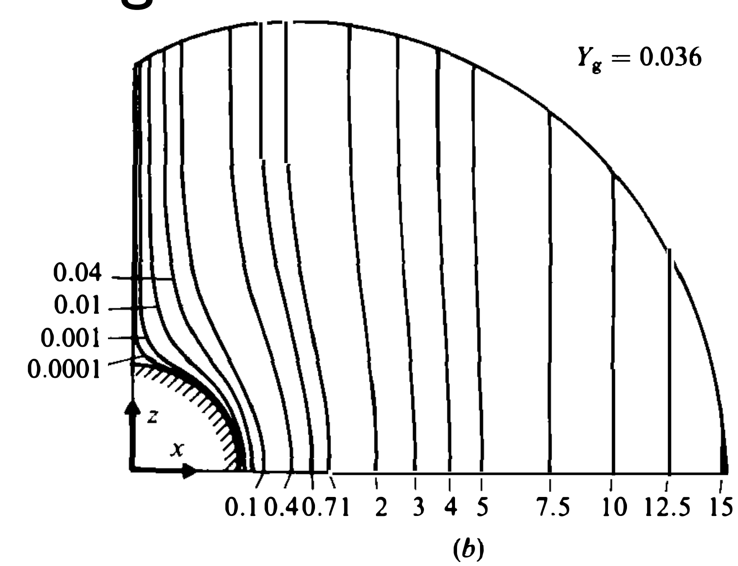
$$-\rho\omega^2\tilde{\mathbf{u}} = -\nabla\tilde{p} + G^*(\omega)\nabla^2\tilde{\mathbf{u}}$$ – *viscoelastic*




## Newtonian




## Bingham fluid

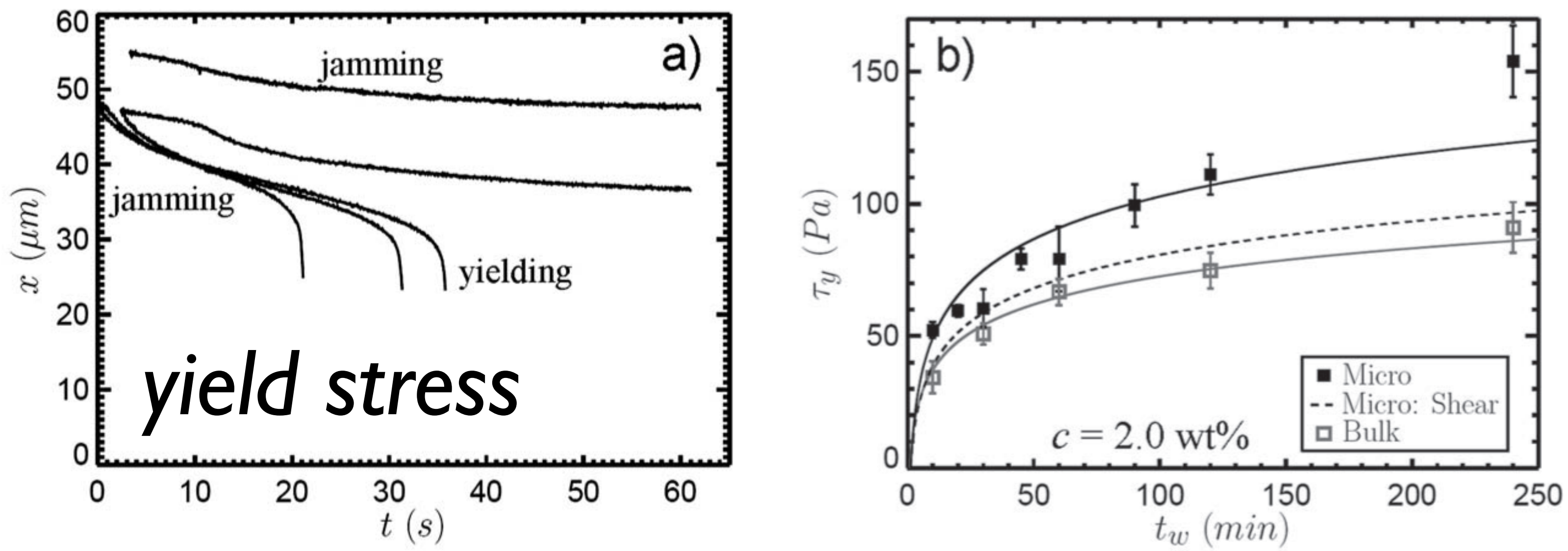



Beris, A. N., *et al.*, *J. Fluid Mech.* 158, 219–244 (1985).

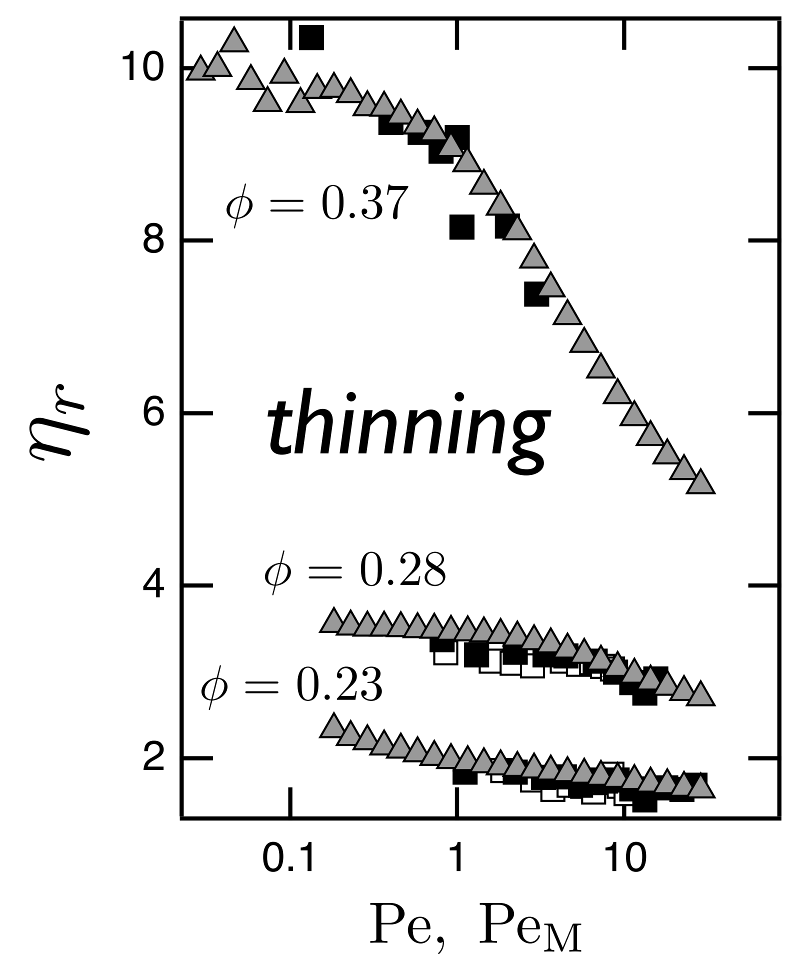
# Active, non-linear microrheology

## Laponite

Rich, J. P., *et al.*, *Soft Matter* 7, 9933 (2011).



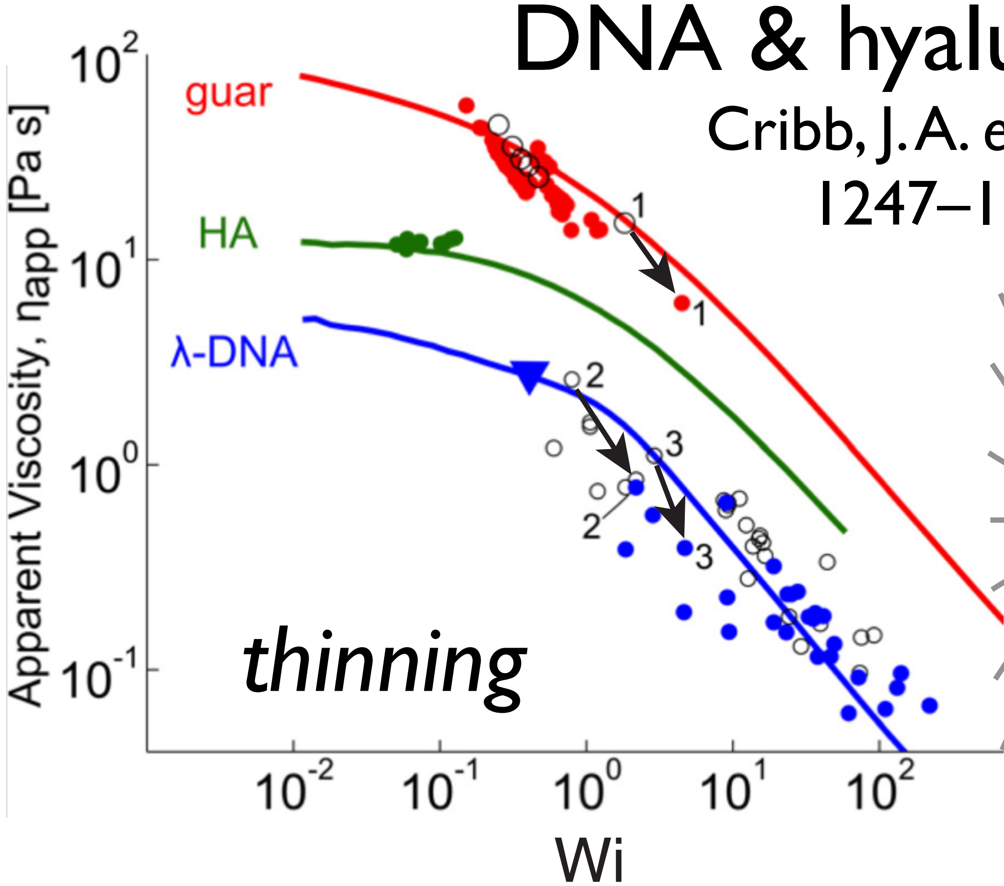

## Colloidal suspension

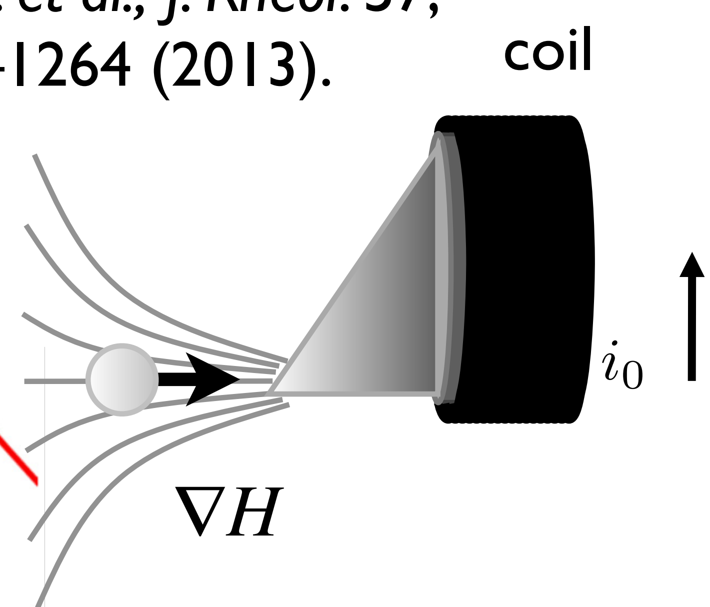



Meyer, A., *et al.*, *J. Rheol.* 50, 77–92 (2006).

## DNA & hyaluronic acid

Cribb, J. A. *et al.*, *J. Rheol.* 57, 1247–1264 (2013).

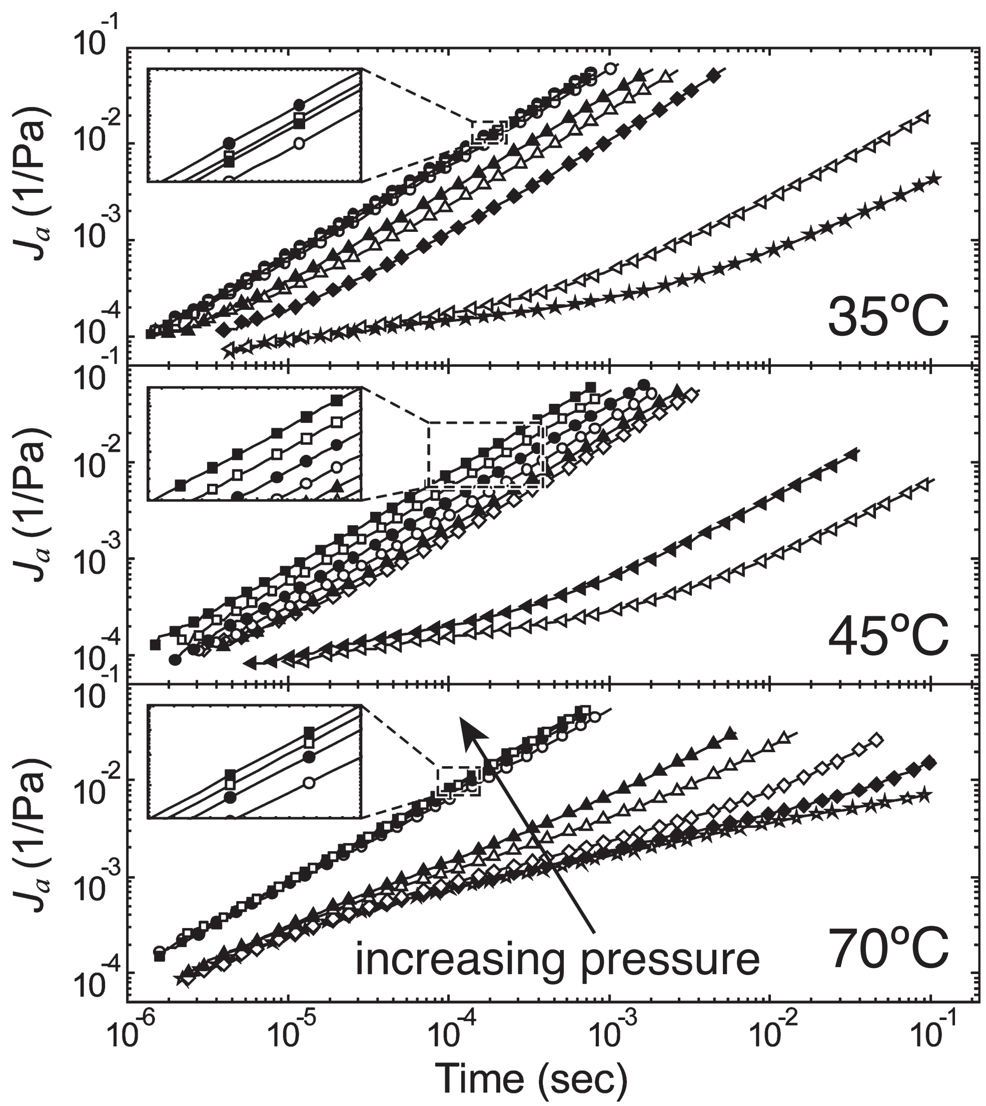


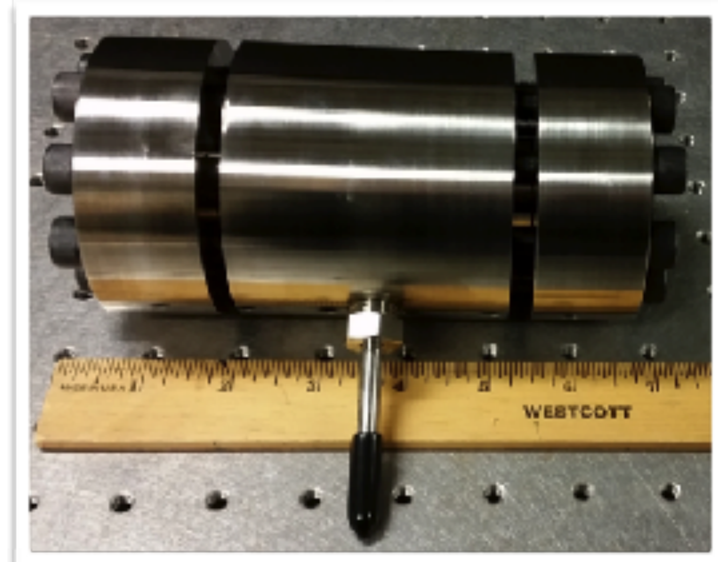
# Extreme sample environments

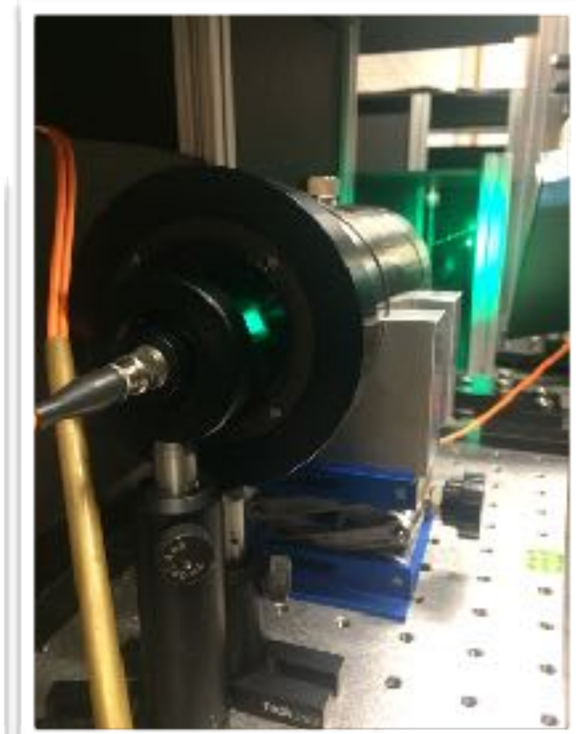
*Rheology at 30,000 psi*

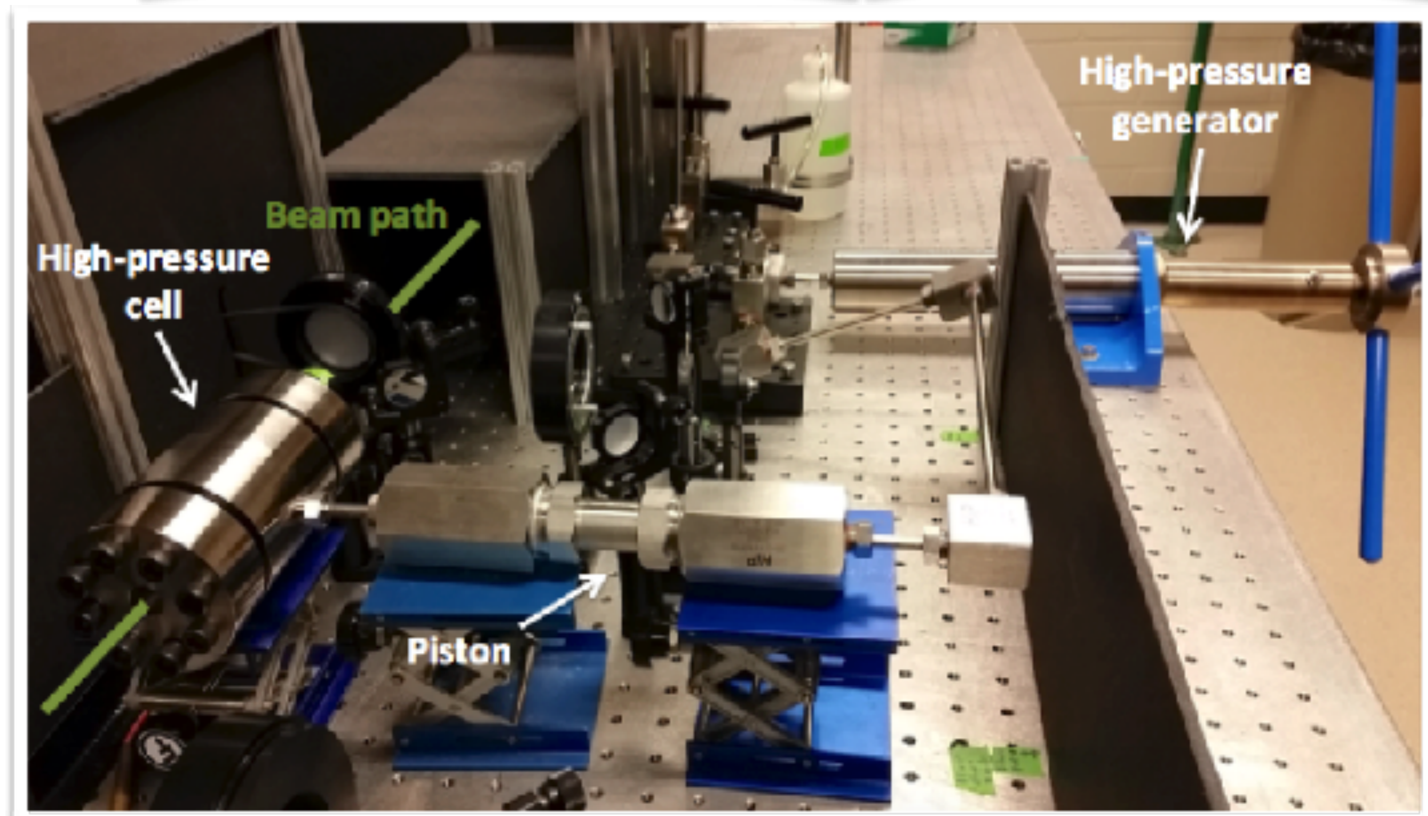
PEO-PPO-PEO triblock copolymer solutions to 207MPa




Kloxin, C. J. & van Zanten, J. H. *Macromolelcules* 43, 2084–2087 (2010).






See Kimberly Dennis, poster # P08

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