bio soft-matter theory

physics department - T37

DNA dynamics and convolution theory for dynamic mechanic networks

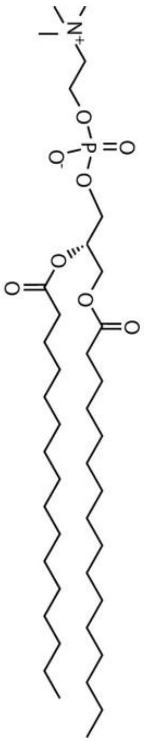
M. Hinzewski, Y. von Hansen, R. Netz,   TU München

1) **Aqueous Appetizer**:
   - a) hydration repulsion
   - b) interfacial dielectric effects
   - c) dielectric spectroscopy
   - d) hydrogen bond friction

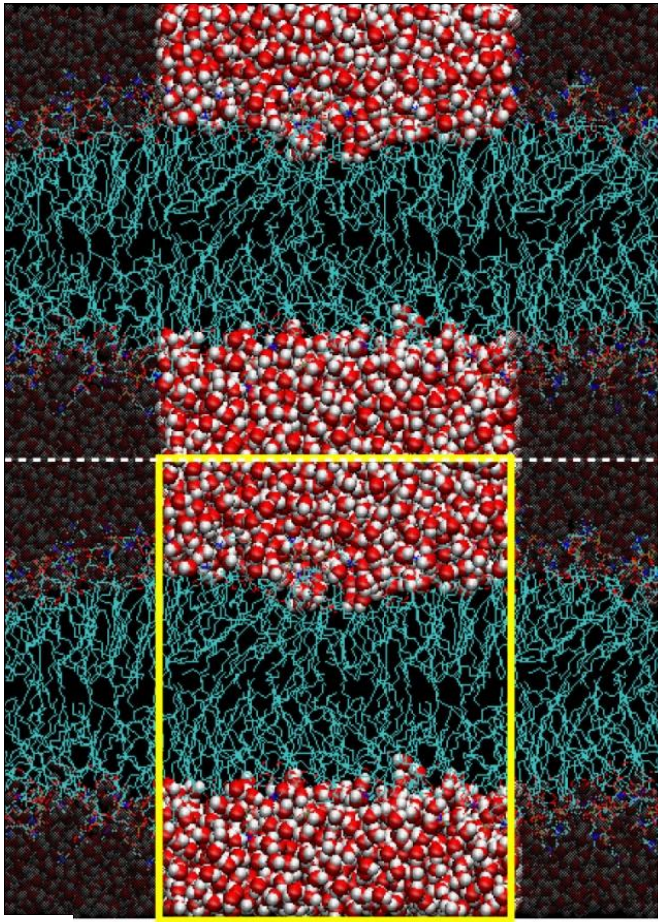
2) **Polymeric Main Course**: DNA dynamics (see KITP 2006)

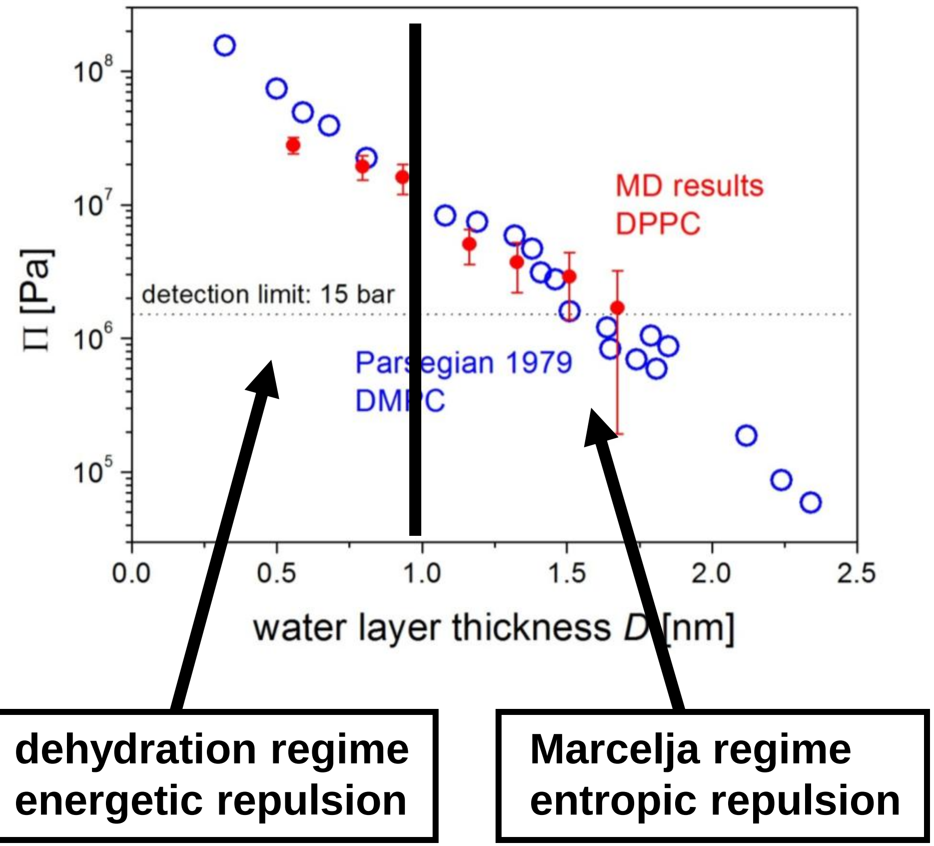
3) **Dessert:** „the measurement problem“ in single-molecule force spectroscopy (polymers as dynamic force transducers)

I) Hydration repulsion between lipid bilayers (Schneck/Netz)



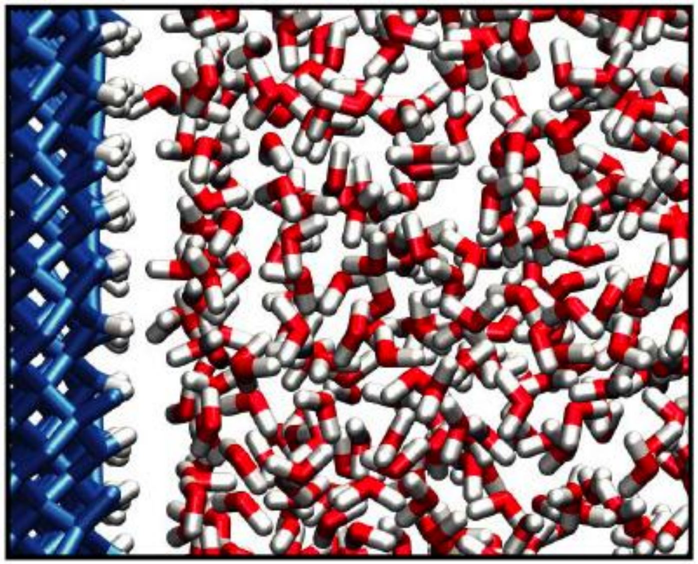
DPPC





- novel simulation method, **constant water chemical potential** via thermodynamic extrapolation
- fluid membranes (L_a-phase)
- main transition is obtained

II) Dielectric response at Planar Interface (Bonthuis, Gekle, RRN)



$$\Delta \boldsymbol{E}(\boldsymbol{r}) = \varepsilon_0^{-1} \int \varepsilon_{nl}^{-1}(\boldsymbol{r}, \boldsymbol{r}') \cdot \Delta \boldsymbol{D}(\boldsymbol{r}')\, \mathrm{d}\boldsymbol{r}'$$

$$\nabla \cdot \boldsymbol{D}(z) = 0 \quad \Longrightarrow \quad \Delta D_\perp(z) = D_\perp$$

$$\Delta \boldsymbol{E}_\perp(\boldsymbol{r}) = \varepsilon_0^{-1} \varepsilon_\perp^{-1}(\boldsymbol{r}) \cdot \Delta \boldsymbol{D}_\perp$$

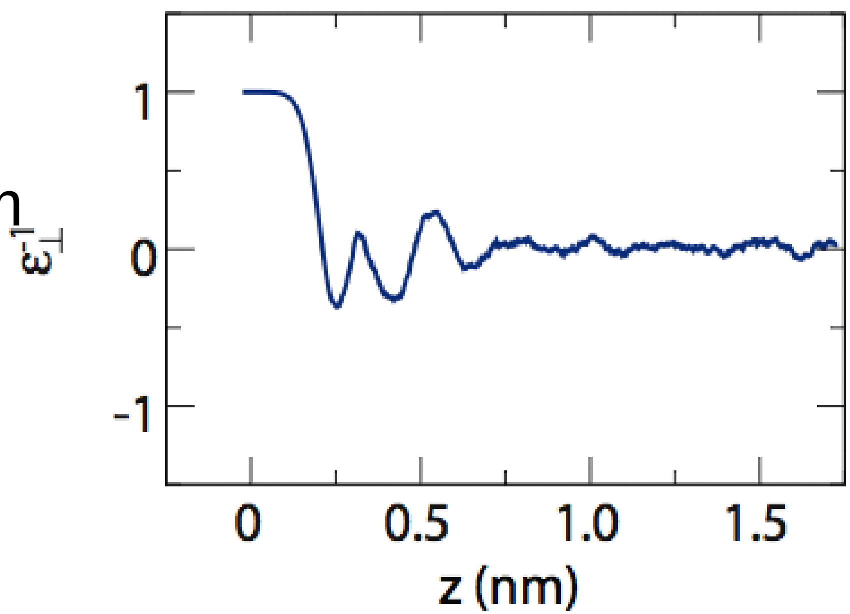
Perpendicular dielectric response

$$\varepsilon_\perp^{-1}(z) = 1 - \frac{\Delta m_\perp(z)}{D_\perp}$$

$z \longrightarrow$

Significant contribution from higher order moments

$\varepsilon_\perp^{-1} < 0$: overscreening
(bulk: Kornyshev)

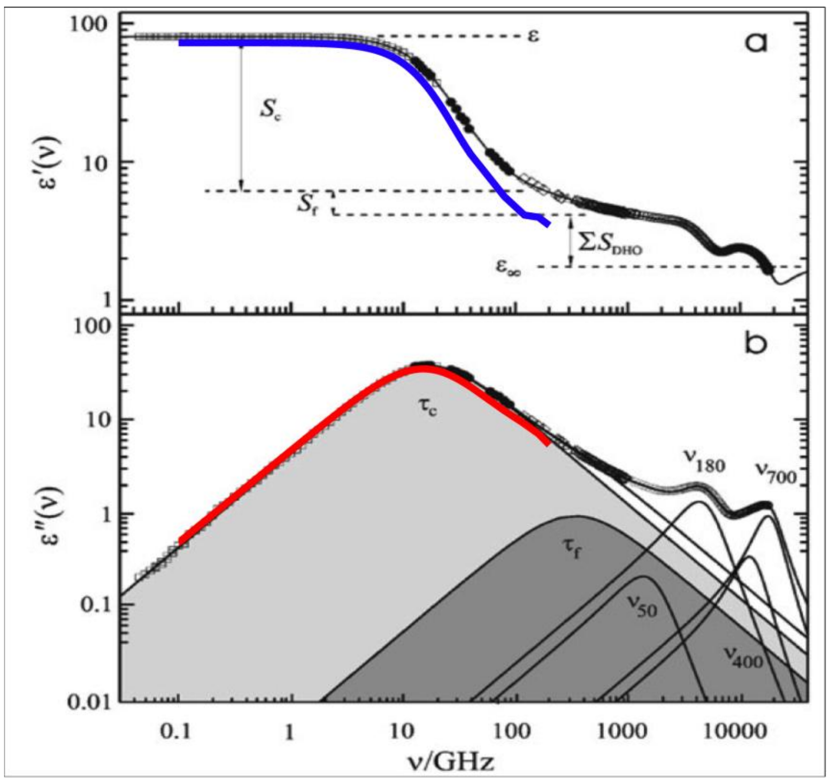


III) Dielectric spectroscopy at interfaces (Gekle/RRN)

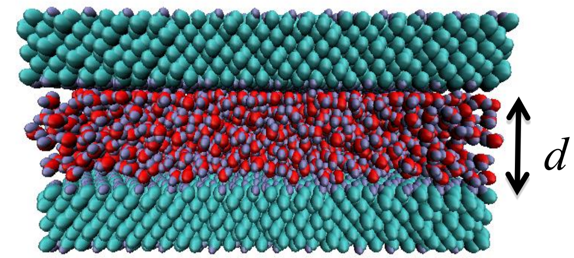
Dipole correlation function (E=0)

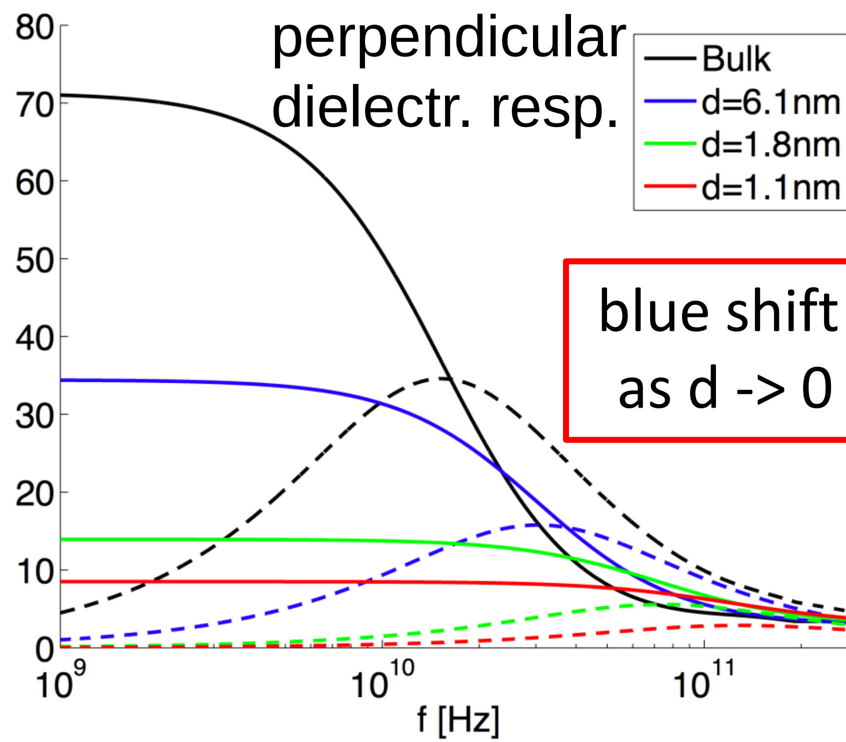
$$\Phi(t) = \frac{\langle \vec{M}(0) \cdot \vec{M}(t) \rangle}{\langle M^2 \rangle} \quad \rightarrow \quad \varepsilon(\omega) = \frac{\langle M^2 \rangle}{\varepsilon_0 V k_B T} L(-\dot{\Phi}) + 1$$

Bulk



Slab





blue shift as d -> 0

spatially resolved dielectric spectroscopy possible !

Zur Anzeige wird der QuickTime™
Dekompressor „YUV420 codec“
benötigt.

IV) H-bond friction

(Erbas, RRN)

pulling rate v=0.1 m/s

Vinci-Coulomb-Amonton law on nanoscopic scales ?

macroscopia

nanoscopia for v->0 $f_f = 5 \times 10^{-9}$ kg/s

$F_f =$ ❍F_N

❍ friction coeff.

$F_f = f_f\, v\, n_{HB}$

f_f friction coeff. per H-bond

universal constant

friction force per monomer

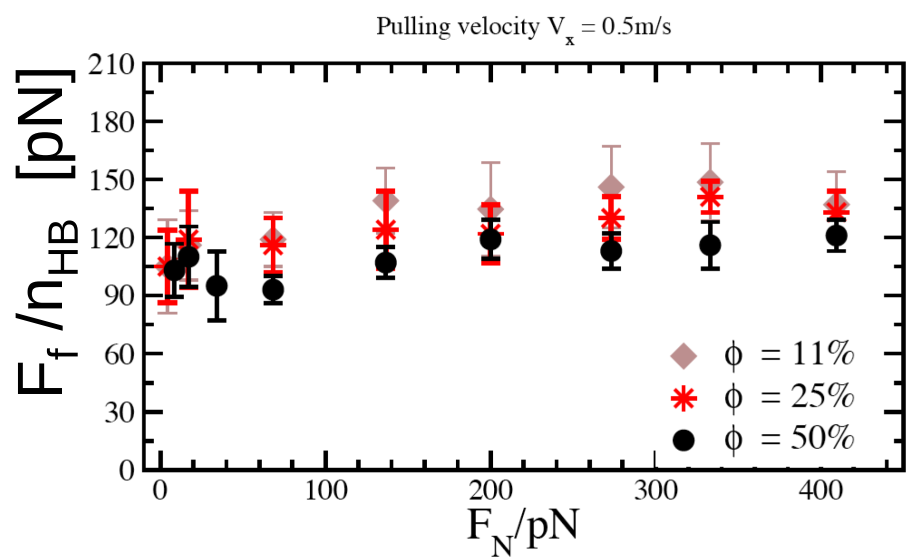
friction force per H bond

Pulling velocities on hydrophilic /
hydrophobic surfaces ***0.5 m/s***, ***10 m/s***

F_f [pN]

Zur Anzeige wird der QuickTime™
Dekompressor „“
benötigt.

normal force



Main course

how good are standard models for predicting the equilibrium DNA dynamics ?

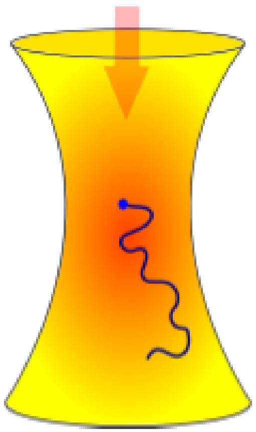
(KITP 2006, Rubinstein & RRN)

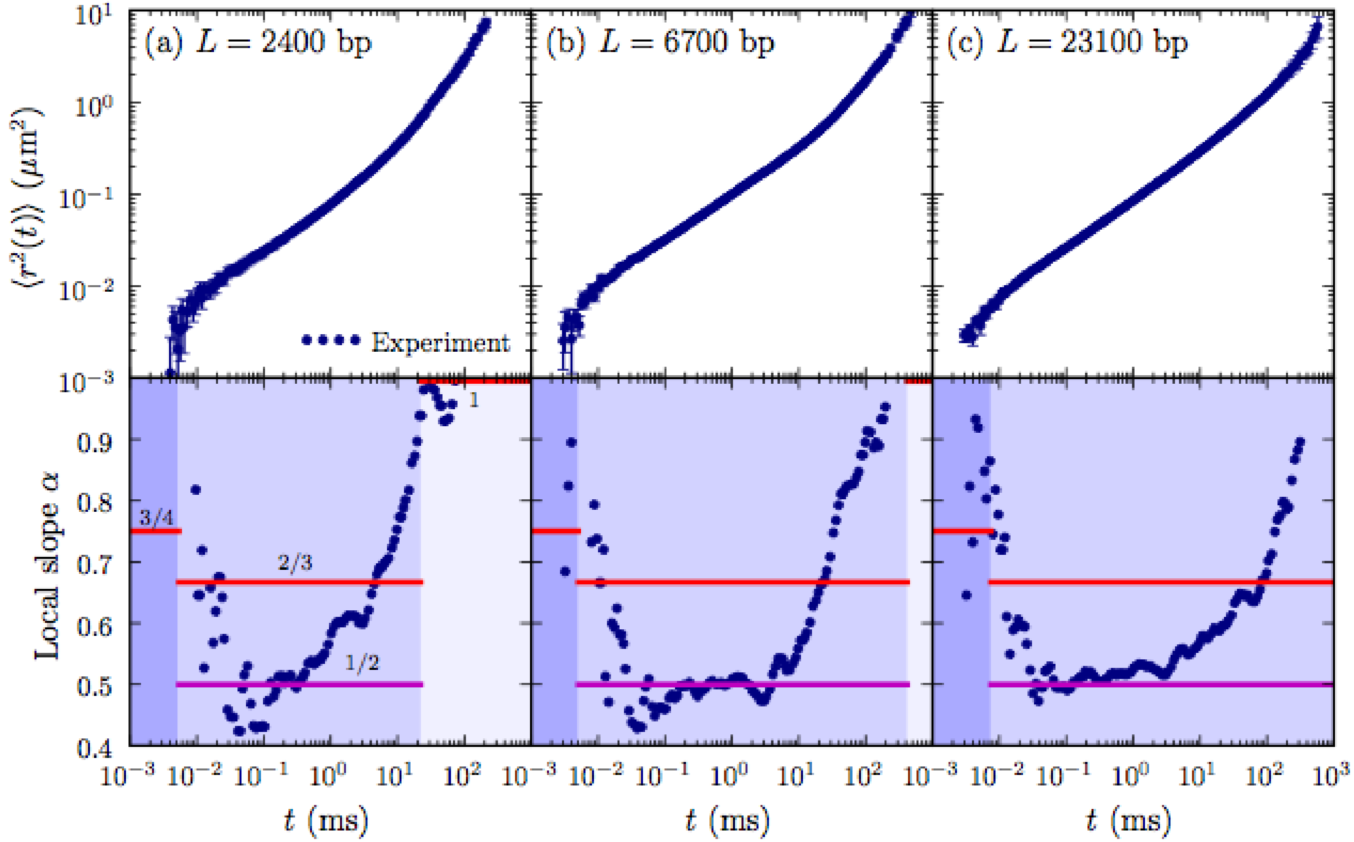
Experimental motivation

Shusterman *et. al.*, PRL 92, 048303 (2004)

M. Hinczewski, X. Schlagberger, M. Rubinstein, O. Krichevsky, R.R. Netz, Macromolecules 42, 860 (2009)

DNA
Fluorescence correlation spectroscopy



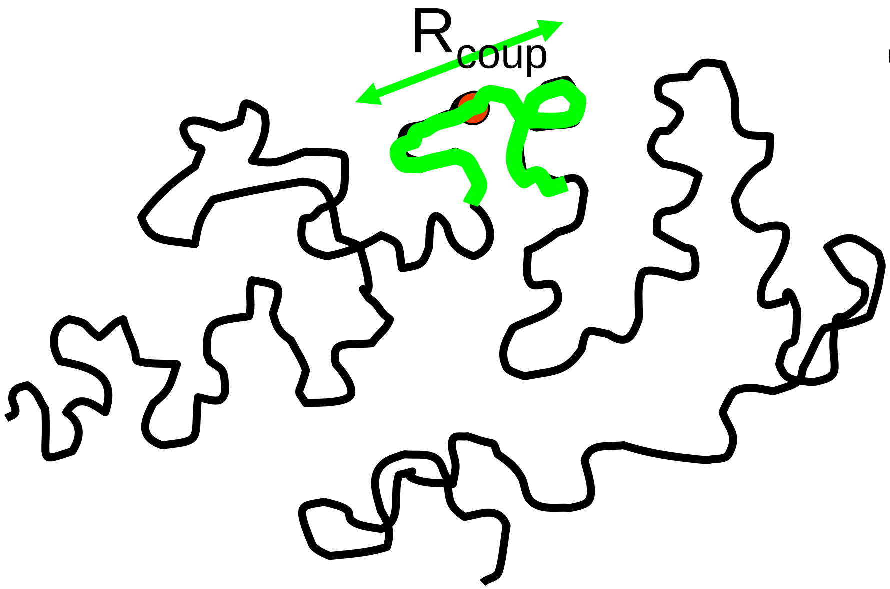


Theoretical expectations: three different power-law scaling regimes

Rouse regime with α =1/2 unclear !

fundamental problem of DNA model or theory ???

single monomer diffusion is at increasing time scales
dominated by progressively growing chain sections :



goal: monomer mean-square-displacement
as function of time

coupled chain section at time t

$R_{coup} \approx N^{\nu}$

MSD of that section $R_{MSD}^2 \approx D\ t$
Zimm: $D \approx 1/R_{coup}$
Rouse : $D \approx 1/N$

scaling assumption: diffusion radius determines coupling radius $R_{coup} \approx R_{MSD}$

Zimm: $R_{MSD}^2 \approx t^{2/3}$ sub-diffusive behavior

Rouse: $R_{MSD}^2 \approx t^{\,2\nu/(1+2\nu)}$ ideal chain $\nu=1/2$ –> $R^2 \approx t^{1/2}$
rod $\nu=1$ –> $R^2 \approx t^{2/3}$ (Zimm $R^2 \approx t^{2/3} \ln^2 t$)

End-monomer dynamics of semiflexible polymers

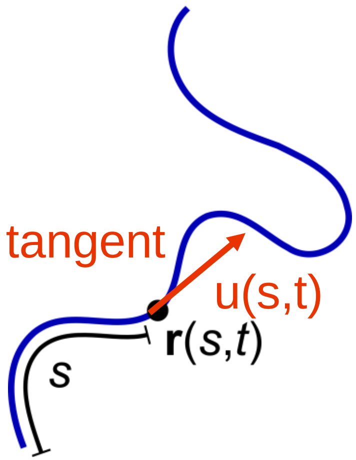
Brownian hydrodynamics simulations (Michael Hinczewski)

many independent simulations are needed !!
not applicable to long DNA chains !

polymer of 50 beads
persistence length = 20*a*
bead radius a = 1nm
-> pers length 20 nm
length 100 nm

Zur Anzeige wird der QuickTime™
Dekompressor „mpeg4“
benötigt.

Hydroynamic mean-field theory (MFT) for semiflexible chain (R. Winkler):
– ZIMM THEORY FOR SEMIFLEX. CHAINS !



$$U = \frac{\epsilon}{2} \int ds \left(\frac{\partial \mathbf{u}(s)}{\partial s} \right)^2 \qquad \text{constraint } \mathbf{u}^2(s) = 1 \text{ at each } s$$

after **saddle-point approx.** for constraint: MFT Gaussian Hamiltonian

$$U_{\mathrm{MF}} = \frac{\epsilon}{2} \int ds \left(\frac{\partial \mathbf{u}(s)}{\partial s} \right)^2 + \nu \int ds\, \mathbf{u}^2(s) + \nu_0 \left(\mathbf{u}^2(L/2) + \mathbf{u}^2(-L/2) \right)$$

where: $\mathbf{u}(s) \equiv \partial \mathbf{r}(s,t)/\partial s, \quad \epsilon = 3 l_p k_B T/2, \quad \sqrt{\nu \epsilon /2} = \nu_0 = 3 k_B T/4$

and $\left\langle u^2(s) \right\rangle = 1$

The dynamics are described by a Langevin equation:

$$\frac{\partial}{\partial t} \mathbf{r}(s,t) = -\int_{-L/2}^{L/2} ds' \overleftrightarrow{\boldsymbol{\mu}}\,(s, s'; \mathbf{r}(s,t) - \mathbf{r}(s',t)) \frac{\delta U_{\mathrm{MF}}}{\delta \mathbf{r}(s',t)} + \boldsymbol{\xi}(s,t)$$

with pre-averaged Rotne-Prager hydrodynamic interaction $\mu_{\mathrm{avg}}(s-s')$.

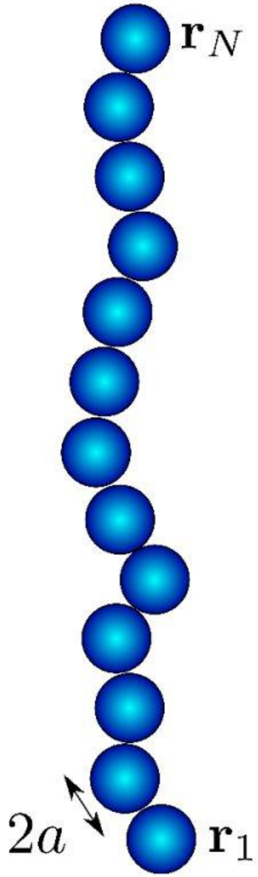
$$\frac{\partial}{\partial t} \mathbf{r}(s,t) = \int_{-L/2}^{L/2} ds'\, \mu_{\mathrm{avg}}(s-s') \left(-\frac{\delta U_{\mathrm{MF}}}{\delta \mathbf{r}(s',t)} \right) + \boldsymbol{\xi}(s,t)$$

$$\langle \xi^{(i)}(s,t) \xi^{(j)}(s',t') \rangle = 2 k_B T \delta_{ij} \delta(t-t') \mu_{\mathrm{avg}}(s-s')$$

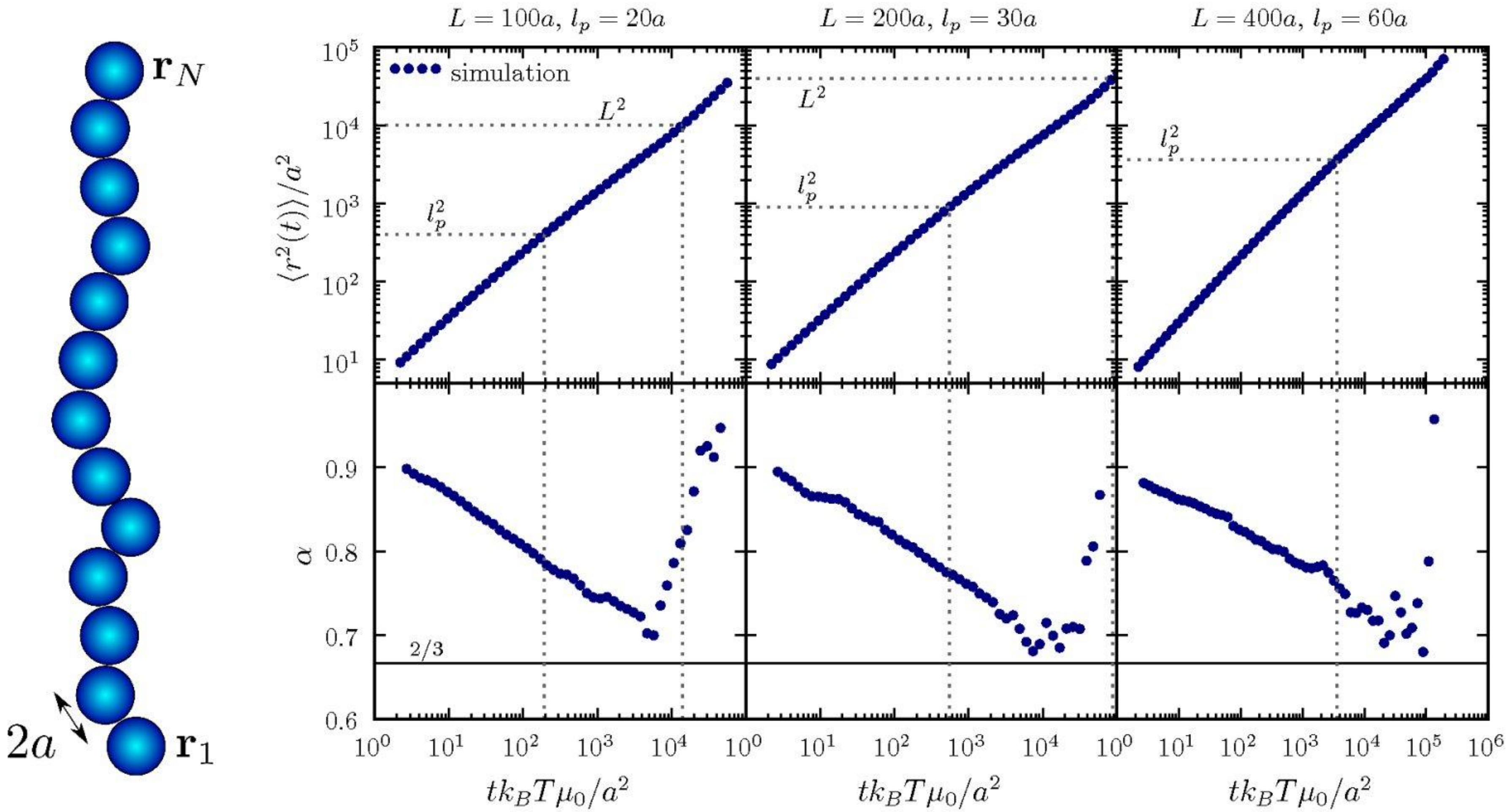
M. Hinczewski:

exact normal mode decomposition: $\mathbf{r}(s,t) = \sum_{n=0}^{\infty} \mathbf{P}_n(t) \Psi_n(s) \qquad \xi(s,t) = \sum_{n=0}^{\infty} \mathbf{Q}_n(t) \Psi_n(s)$

diagonalized Langevin equations $\frac{\partial}{\partial t} \mathbf{P}_n(t) = -\Lambda_n \mathbf{P}_n(t) + \mathbf{Q}_n(t)$



validation of the **hydrodynamic theory** by comparison
with **Brownian hydrodynamic simulations** for N=50, 100, 200



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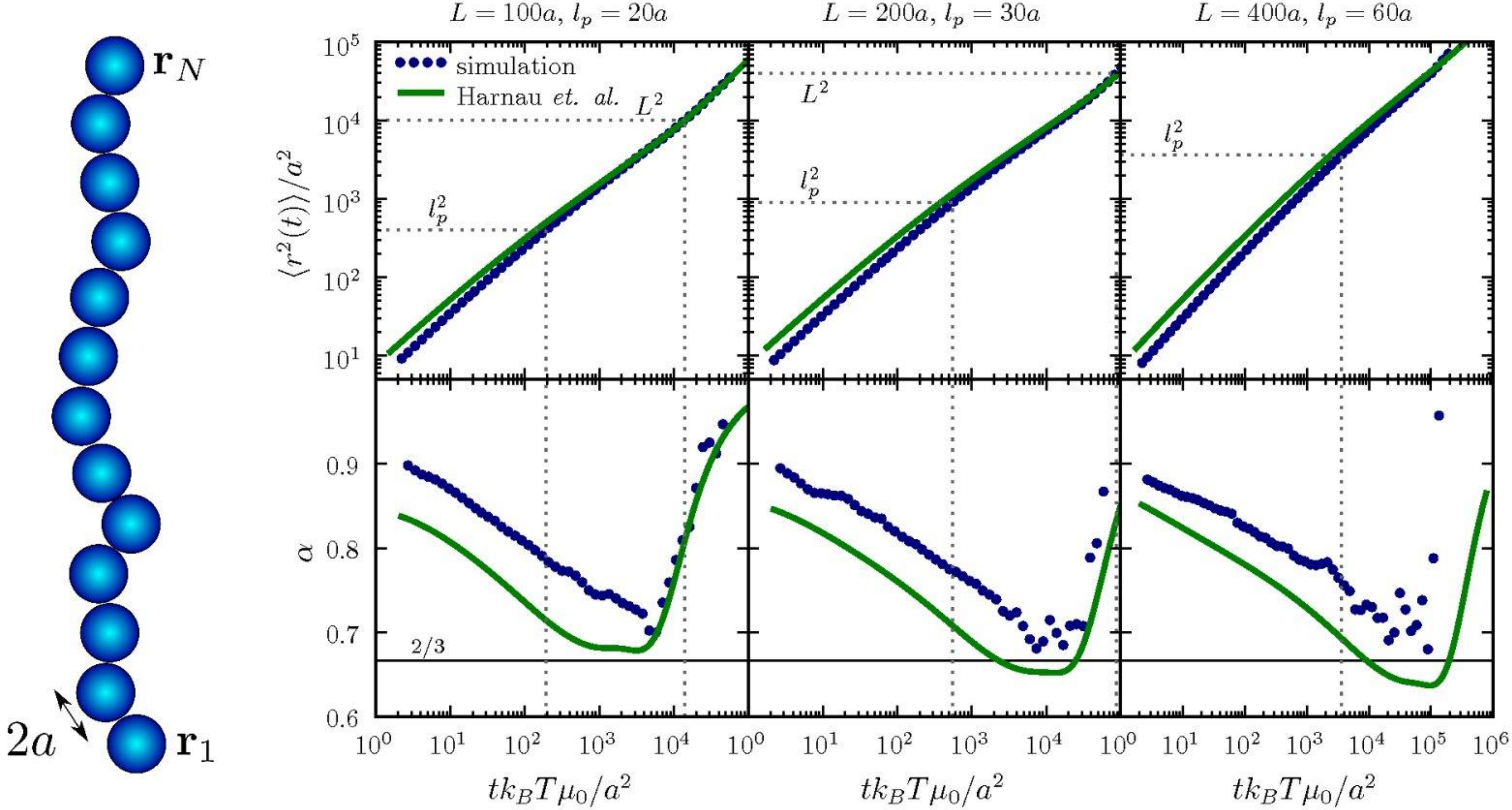
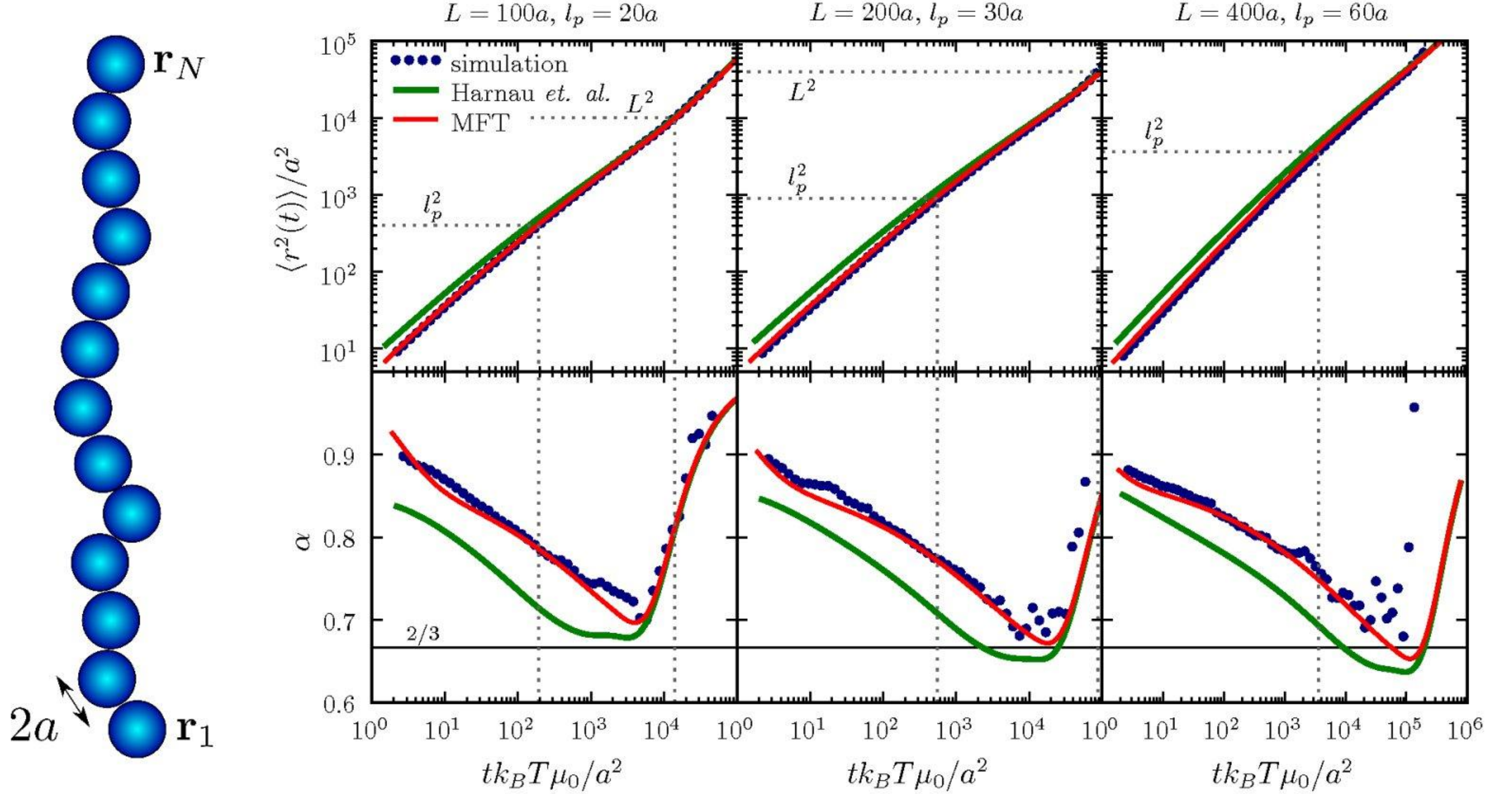


validation of the **hydrodynamic theory** by comparison with **Brownian hydrodynamic simulations** for N=50, 100, 200

Harnau-Winkler solution with diagonal approximation = **APPROX. ZIMM THEORY**



validation of the **hydrodynamic theory** by comparison
with **Brownian hydrodynamic simulations** for N=50, 100, 200

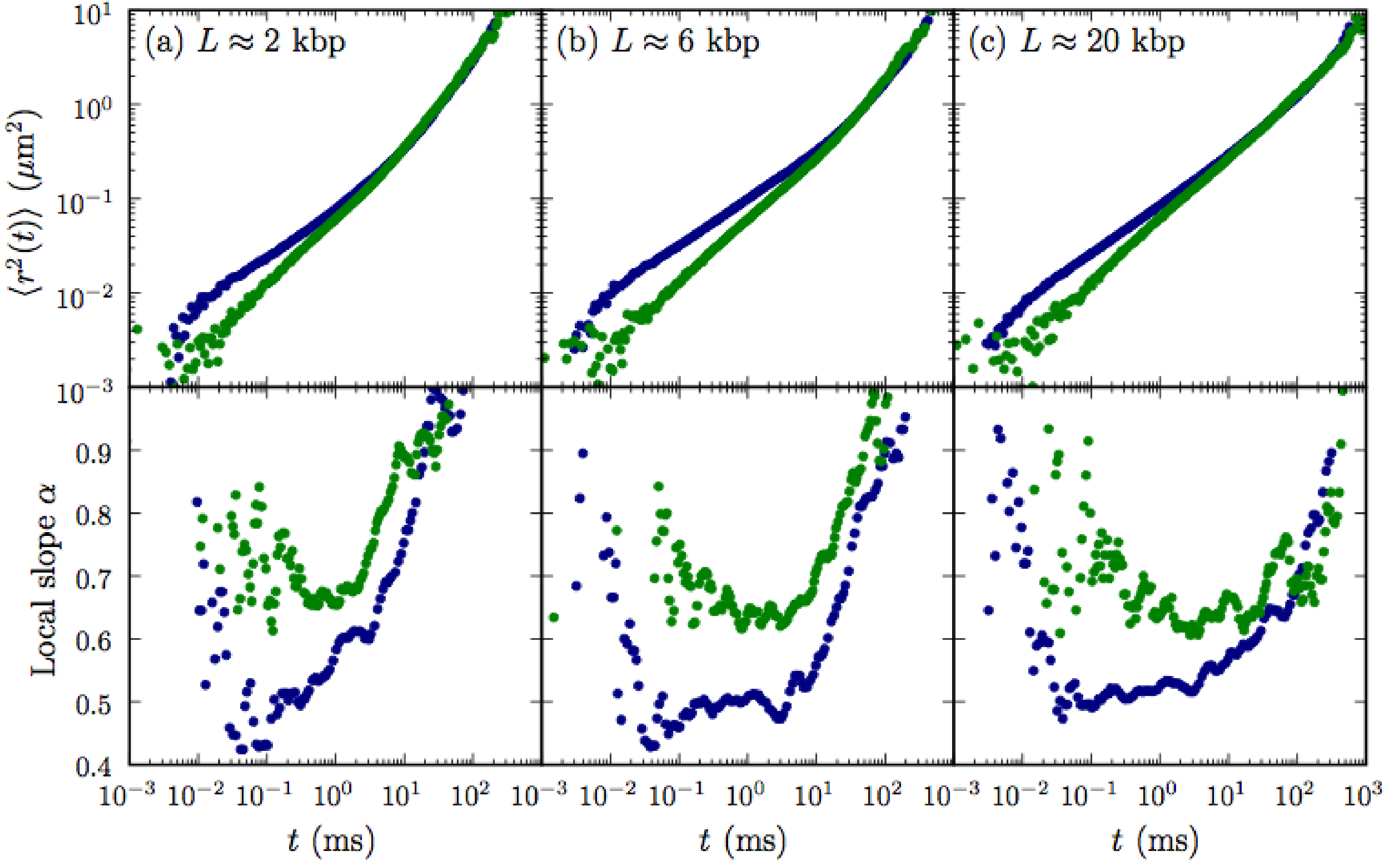
Harnau-Winkler solution with diagonal approximation = **APPROX. ZIMM THEORY**
MFT: numerically exact solution = **EXACT ZIMM THEORY**
excellent agreement between the MFT and simulation data
--> confidently extend the MFT to larger chain lengths inaccessible to simulation
(pre-averaging & MFT probably ok)

Comparison with experiments I

Blue data: Shusterman *et. al.*, PRL 92, 048303 (2004)

Green data: Petrov *et. al.*, PRL 97, 258101 (2006)

Experimental Problems ??



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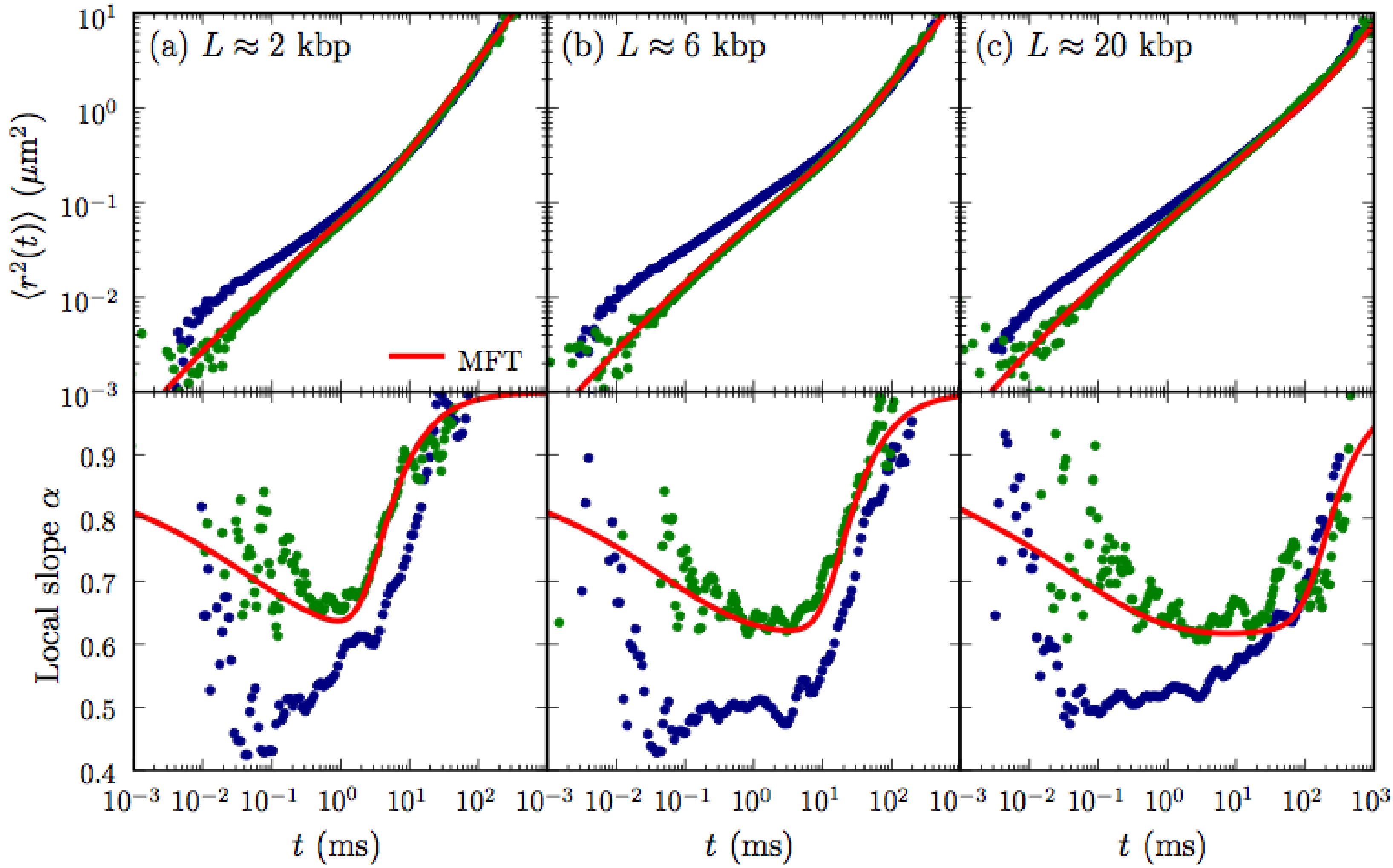


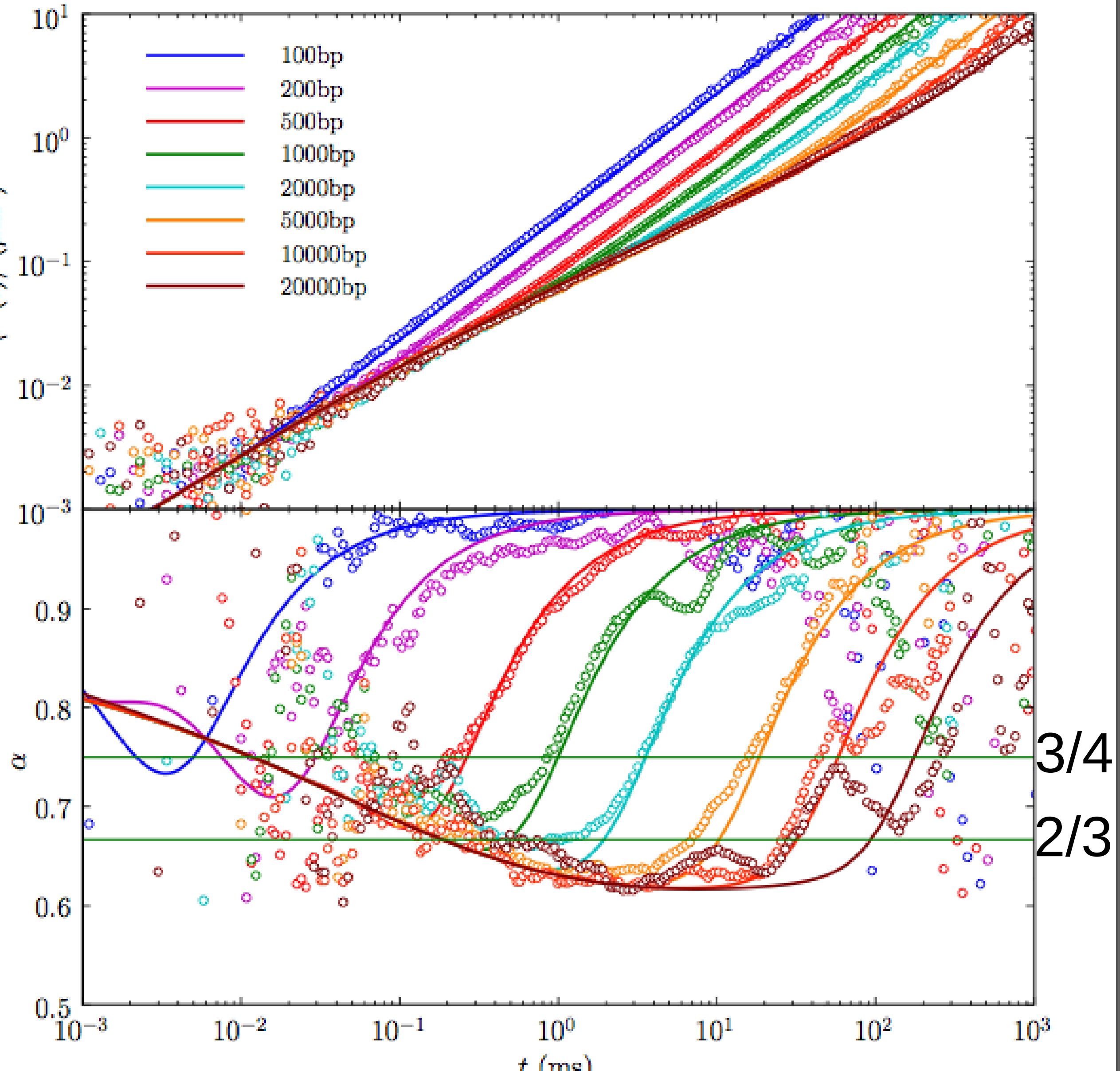
Parameters taken from the literature and experimental conditions:
$l_p = 50$ nm, $T = 293$K, viscosity of water at 293K = 1 mPa s.

Comparison with experiments II

Hinczewksi/Netz,
EPL 88, 18001 (2009)

Data: Petrov *et. al.*,
PRL 97, 258101
(2006)

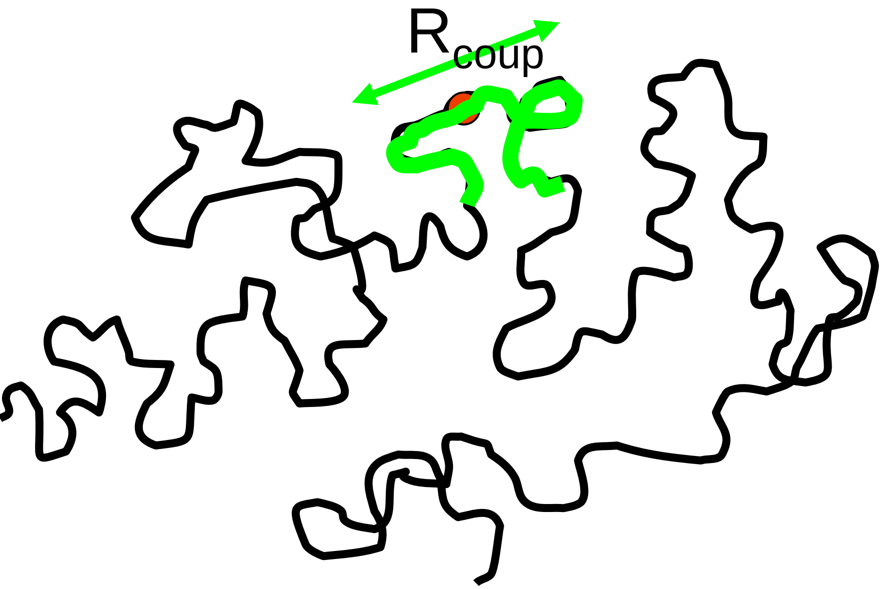
Parameters taken from the literature and experimental conditions: $l_p = 50$ nm, $T = 293$K, viscosity of water at 293K = 1 mPa s.



sub-Zimm scaling due to subtle crossover effects !

Quantitative agreement at smallest scales!

simple scaling for dynamic crossover



goal: monomer position a.s.f.o. time

coupled chain section at time t

$R_{coup} \approx N^{\nu}$

diffusion of that section $R_{MSD}^2 \approx D\, t$

general : $D \approx 1/N^c$

Zimm flex: $c = \nu = 1/2$ $\rightarrow R^2 \approx t^{2/3}$

Zimm rod: $c = 1$ $\nu = 3/2$ $\rightarrow R^2 \approx t^{3/4}$

Rouse: $c = 1$ $\nu = 1/2$ $\rightarrow R^2 \approx t^{1/2}$

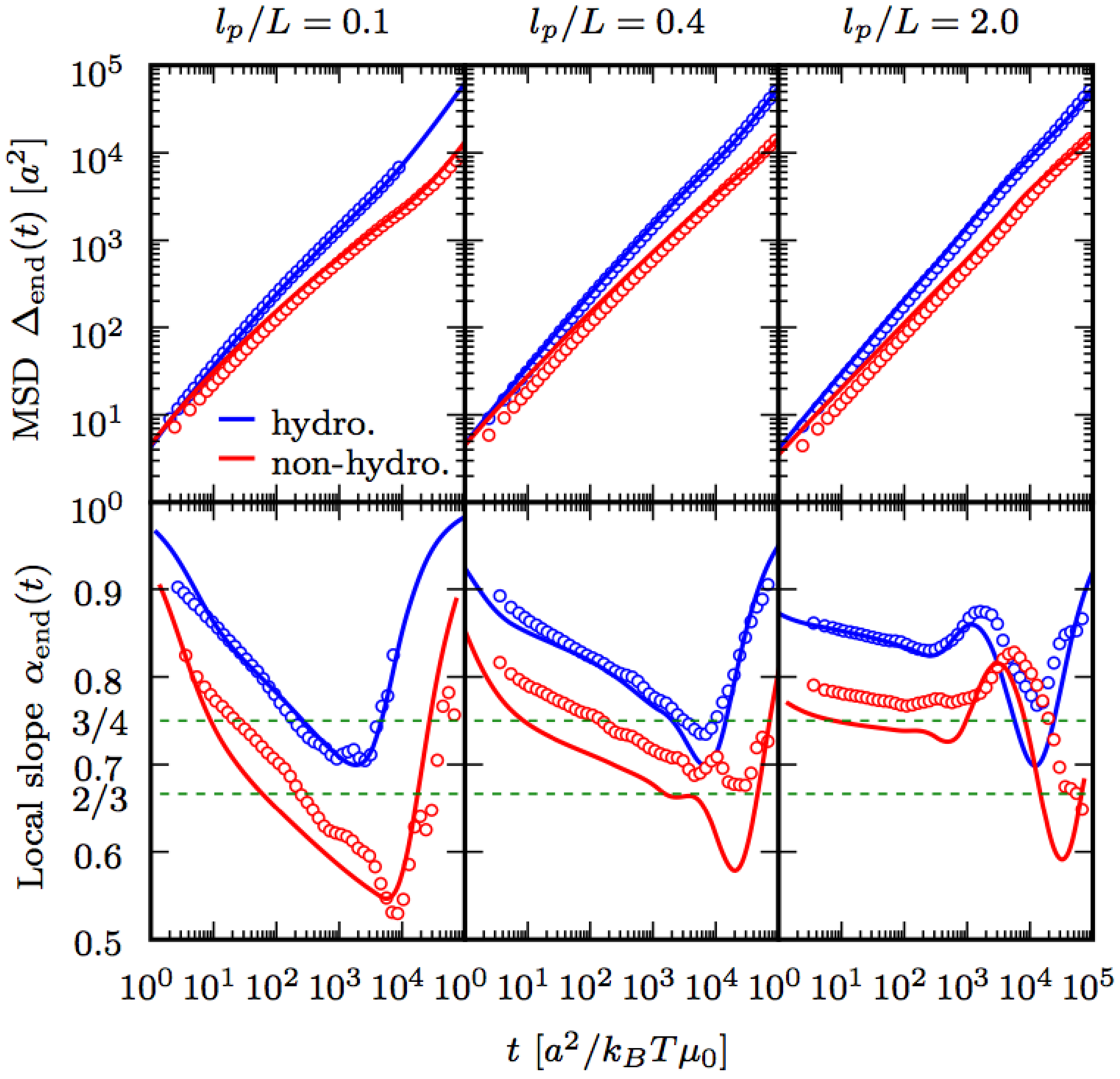
crossover from stiff rod ($c = 1$ $\nu = 3/2$)to flexible polymer ($c = \nu = 1/2$)

crossover for ν ist quite fast

crossover for c is somewhat slow

---> intermediate Rouse regime where $c = 1 > \nu = 1/2$

comparison of **simulations/theory without hydrodynamic** and **simulations/theory with hydrodynamics**



hydrodynamics relevant ! Exponent shift by + 0.1 (= logarithm)
mean-field theory better with long-range hydrodynamics !

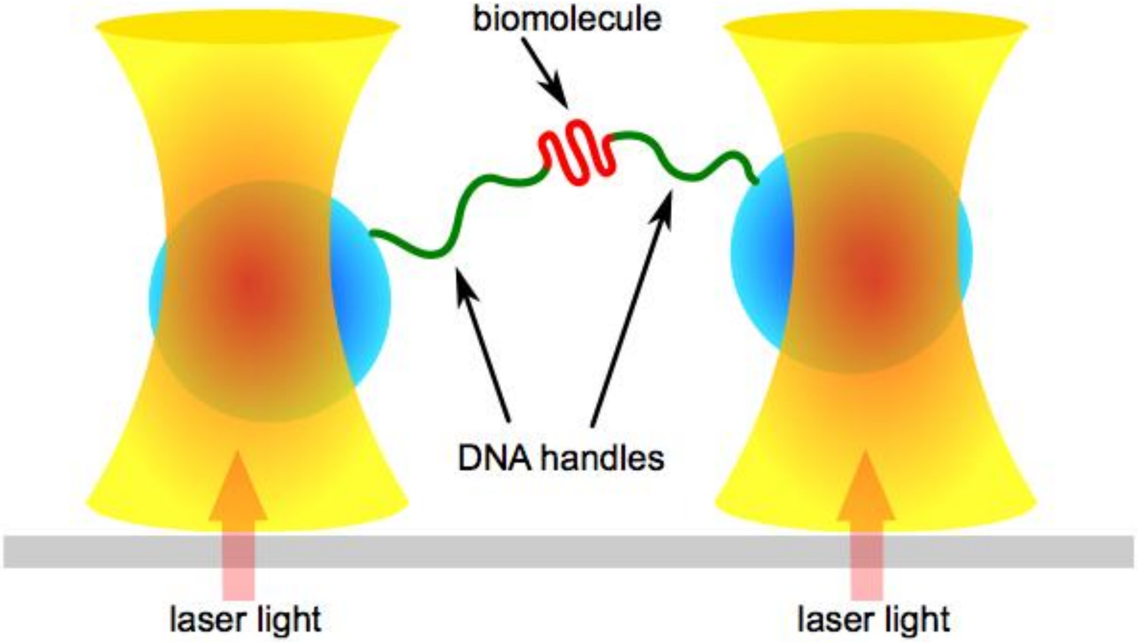
Dessert:

„the measurement problem“
in single-molecule force spectroscopy:

dynamic mechanic networks

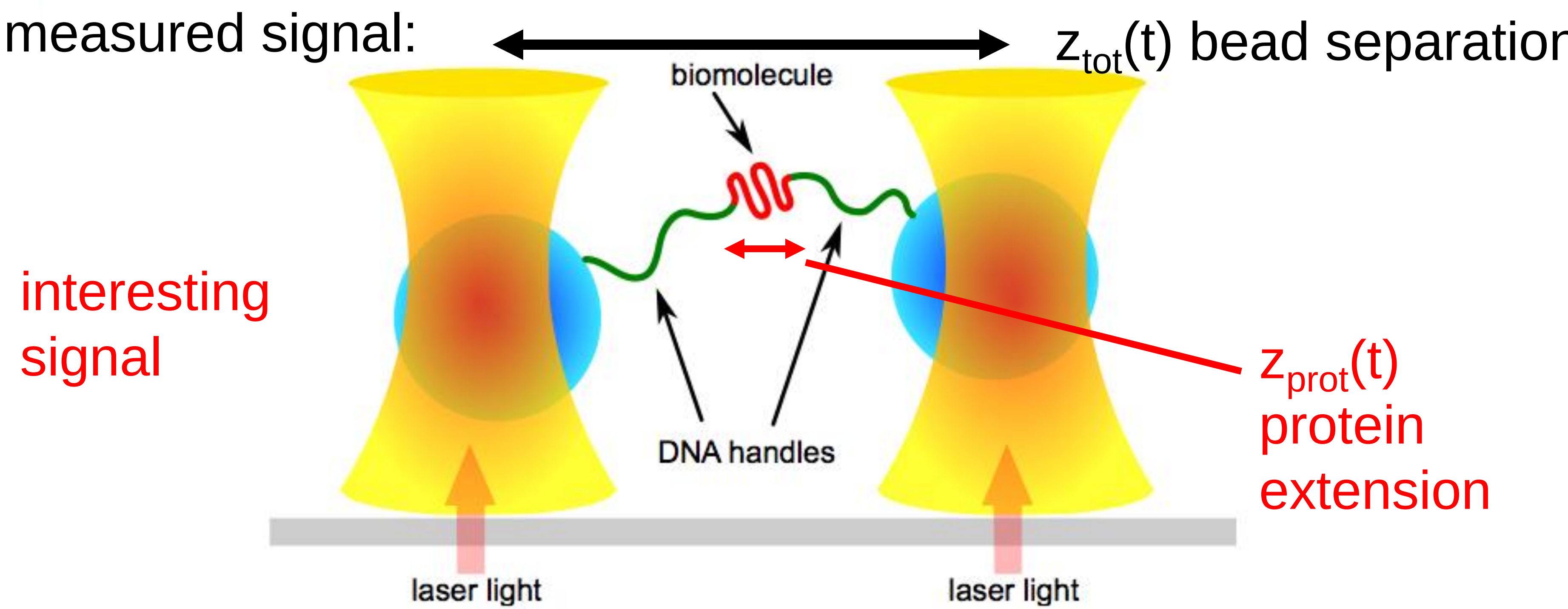
Optical Tweezers

Optical tweezer setup for studying biomolecules under tension:



- Two polystyrene / silica beads ($\sim$ 1 μm), each trapped in the focus of a laser beam.
- Double-stranded DNA handles ($\sim$ 100 nm) attached to the beads.
- The object of interest ($\sim$ 10 nm): for example a DNA/RNA hairpin, or a protein.

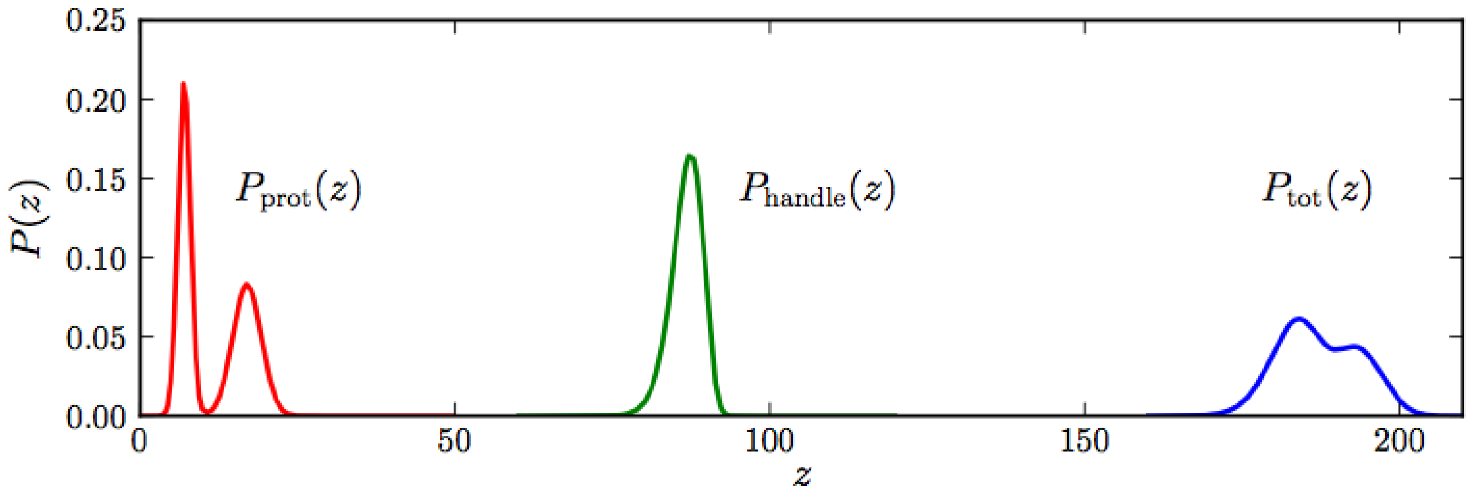
Optical Tweezers



The experimental setup is highly sensitive (force with $\ll$ 1 pN precision) and probes the intrinsic dynamics the biomolecule, though filtered through the response of the DNA handles and the beads.

Key focus: How to recover information about those intrinsic properties from the raw output data (the spatial fluctuations of the beads in the trap).

Static Deconvolution of probability distribution of extension



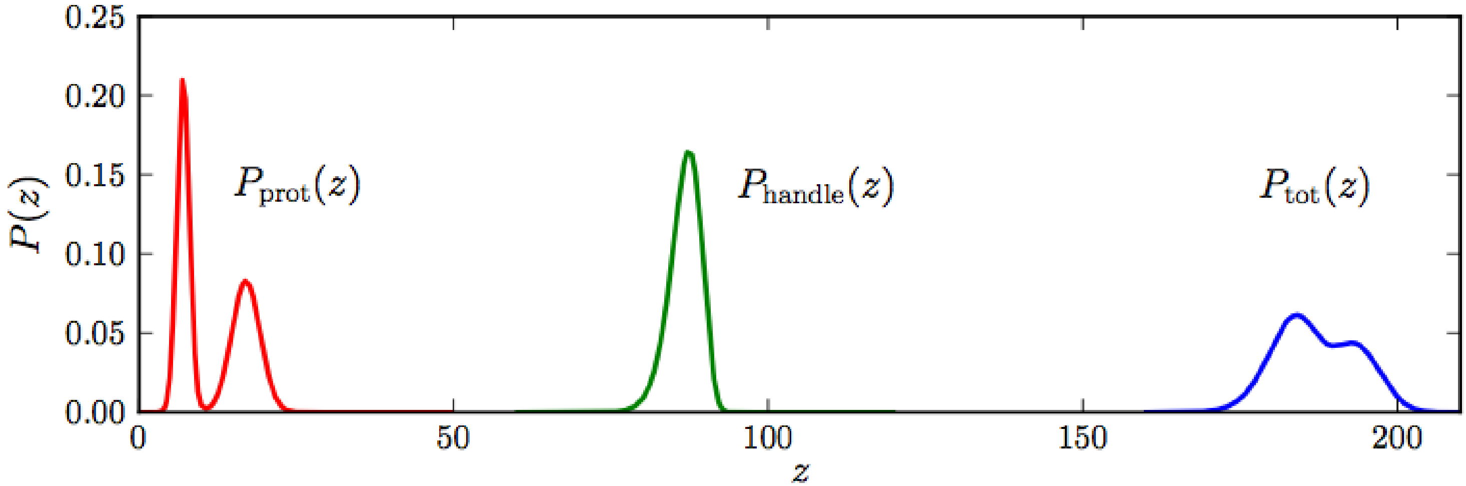
$P_{prot}(z)$ and $P_{tot}(z)$ are related through the convolution

$$P_{tot}(z) = \int dz' \int dz''\, P_{handle}(z') P_{prot}(z'') P_{handle}(z - z' - z'').$$

Knowing $P_{handle}(z)$ from experiment or using the worm-like chain theory, one can find $P_{prot}(z)$ from the experimental output $P_{tot}(z)$ using a standard deconvolution procedure. In Fourier space:

$$P_{tot}(k) = P^2_{handle}(k) P_{prot}(k).$$

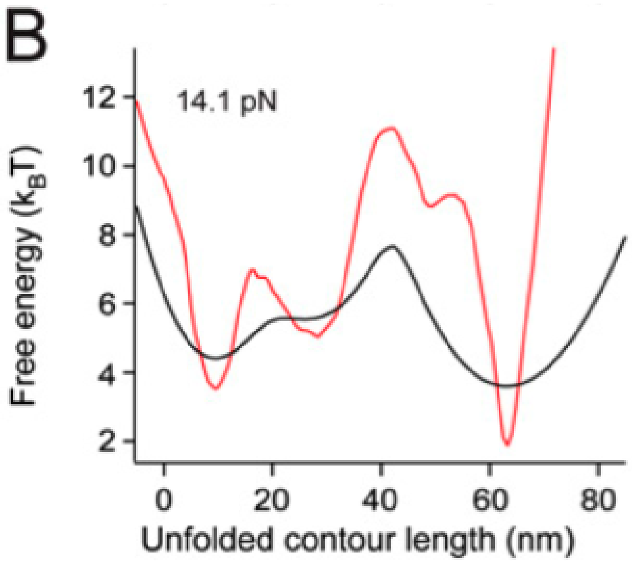
Static Deconvolution - fully understood



The protein's free energy landscape is obtained from $P_{\text{prot}}(z)$ by Boltzmann inversion:

$$F(z) = -k_B T \ln P_{\text{prot}}(z).$$

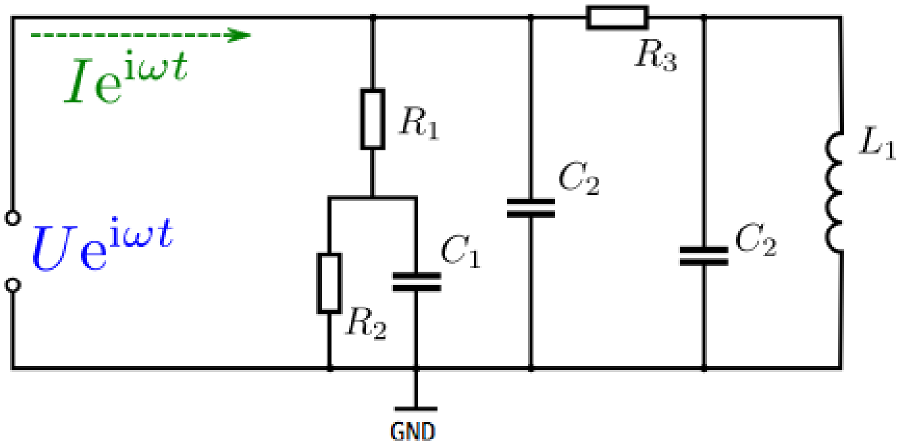
Exp. application: leucine zipper



[Gebhardt, Bornschlögl, Rief, PNAS 107 (2010)]

Dynamic (De-)Convolution of Electric Circuits

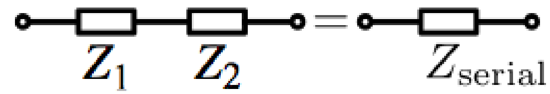
The behavior of an electric circuit



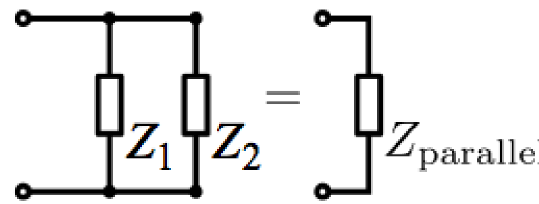
is specified by the (complex) impedance Z_{total} relating applied voltage and current

$$U = Z_{\text{total}} I.$$

Decomposing the circuit into serial



and parallel elements



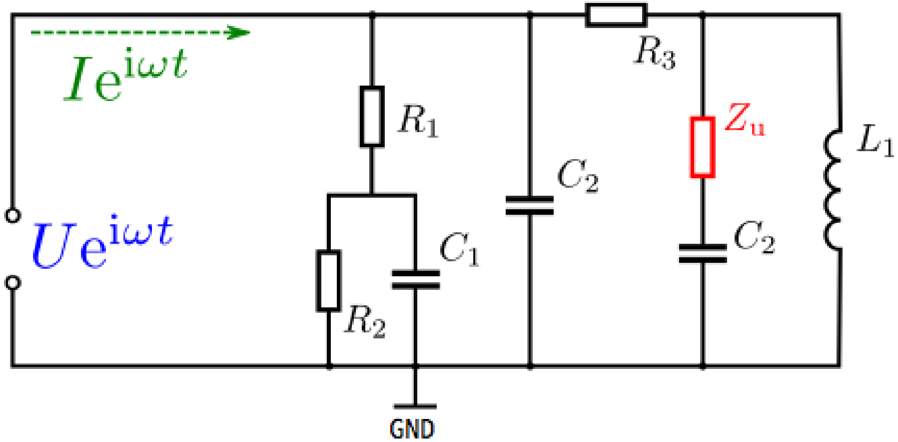
and knowledge of the basic rules

$$Z_{\text{serial}} = Z_1 + Z_2,$$
$$\frac{1}{Z_{\text{parallel}}} = \frac{1}{Z_1} + \frac{1}{Z_2},$$

allows to calculate Z_{total}.

Dynamic (De-)Convolution of Electric Circuits

The behavior of an electric circuit



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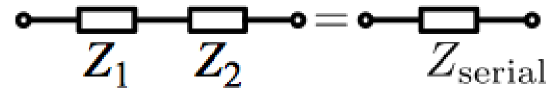

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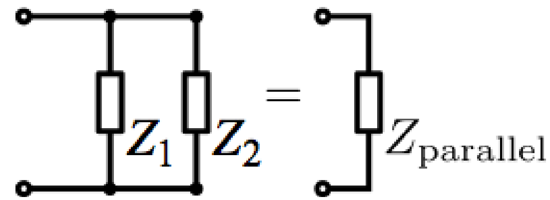


and knowledge of the basic rules

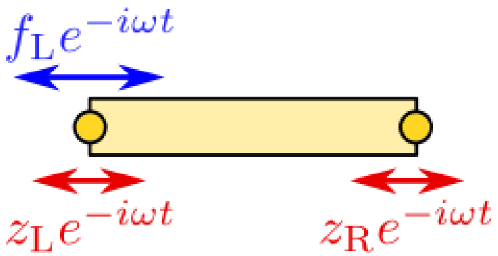
$$Z_{\text{serial}} = Z_1 + Z_2,$$
$$\frac{1}{Z_{\text{parallel}}} = \frac{1}{Z_1} + \frac{1}{Z_2},$$

allows to calculate Z_{total}.

In turn, if the circuit's structure is known, the unknown impedance Z_u can be determined by measuring $Z_{\text{total}} = U/I$.

Force Response of Single Mechanical Elements

A small oscillatory force f_L on the left end-point of a mechnical component



results in (average) oscillations of magnitude z_L and z_R of the two ends.

Within the regime of linear response force and position amplitudes are related by the complex self response function $J_{\mathrm{self,L}}(\omega)$ of the left end and the cross response function $J_{\mathrm{cross}}(\omega)$:

$$z_L = J_{\mathrm{self,L}}(\omega)\ f_L$$

$$z_R = J_{\mathrm{cross}}(\omega)\ f_L$$

Force Response of Single Mechanical Elements

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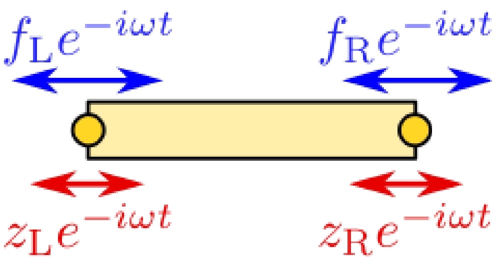

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$$z_L = J_{\text{self,L}}(\omega)\, f_L + J_{\text{cross}}(\omega)\, f_R,$$
$$z_R = J_{\text{cross}}(\omega)\, f_L + J_{\text{self,R}}(\omega)\, f_R.$$

Real and imaginary parts of the response functions

$$J(\omega) = J'(\omega) + \mathrm{i}\, J''(\omega),$$

are not independent. They are connected via Kramers-Kronig relations.

The fluctuation-dissipation theorem relates equilibrium fluctuations and the response w.r.t. external forces

$$S(\omega) = \frac{2k_B T}{\omega} J''(\omega).$$

Recording the power-spectrum $S(\omega)$ in equilibrium is thus sufficient!

Constructing Basic Mechanical Networks

[Hinczewski, von Hansen, Netz, PNAS Dec. 2010

„RULES“

Serial Connection

Left end of X and right end of Y coincide and feel the same force.

Rules for response functions in series:

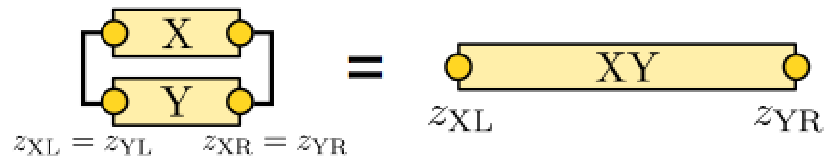
$$J^{XY}_{\text{self},X} = J^{X}_{\text{self},L} - \frac{\left(J^{X}_{\text{cross}}\right)^2}{J^{X}_{\text{self},R} + J^{Y}_{\text{self},L}},$$

$$J^{XY}_{\text{self},Y} = J^{Y}_{\text{self},R} - \frac{\left(J^{Y}_{\text{cross}}\right)^2}{J^{X}_{\text{self},R} + J^{Y}_{\text{self},L}},$$

$$J^{XY}_{\text{cross}} = \frac{J^{X}_{\text{cross}} J^{Y}_{\text{cross}}}{J^{X}_{\text{self},R} + J^{Y}_{\text{self},L}}.$$

Parallel Connection

Both ends of X and Y coincide, the force is split between X and Y.

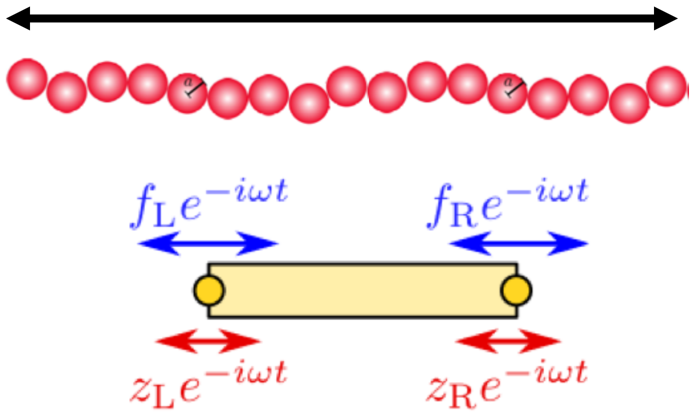


Rules for response functions in parallel:

$$\overleftrightarrow{J}^{\alpha} \equiv \begin{pmatrix} J^{\alpha}_{\text{self},L} & J^{\alpha}_{\text{cross}} \\ J^{\alpha}_{\text{cross}} & J^{\alpha}_{\text{self},R} \end{pmatrix}, \quad \alpha \in \{X, Y, XY\}$$

$$\left(\overleftrightarrow{J}^{XY}\right)^{-1} = \left(\overleftrightarrow{J}^{X}\right)^{-1} + \left(\overleftrightarrow{J}^{Y}\right)^{-1}$$

DNA response functions from experiments AND theory/simulations

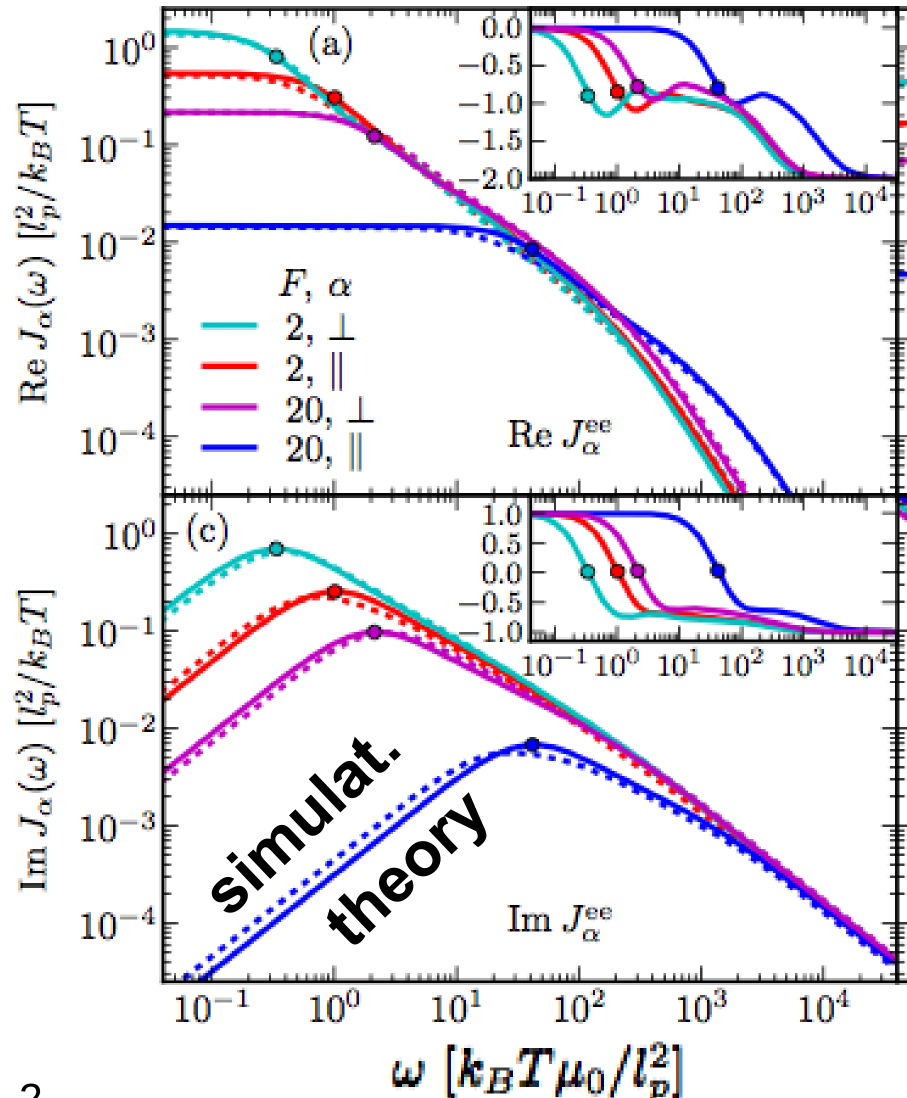


$$z_{\mathrm{L}} = J_{\mathrm{self,L}}(\omega)\, f_{\mathrm{L}} + J_{\mathrm{cross}}(\omega)\, f_{\mathrm{R}},$$

$$z_{\mathrm{R}} = J_{\mathrm{cross}}(\omega)\, f_{\mathrm{L}} + J_{\mathrm{self,R}}(\omega)\, f_{\mathrm{R}}.$$

$$J_{\mathrm{ee}} = J_{\mathrm{self,L}} + J_{\mathrm{self,R}} - 2J_{\mathrm{cross}}.$$

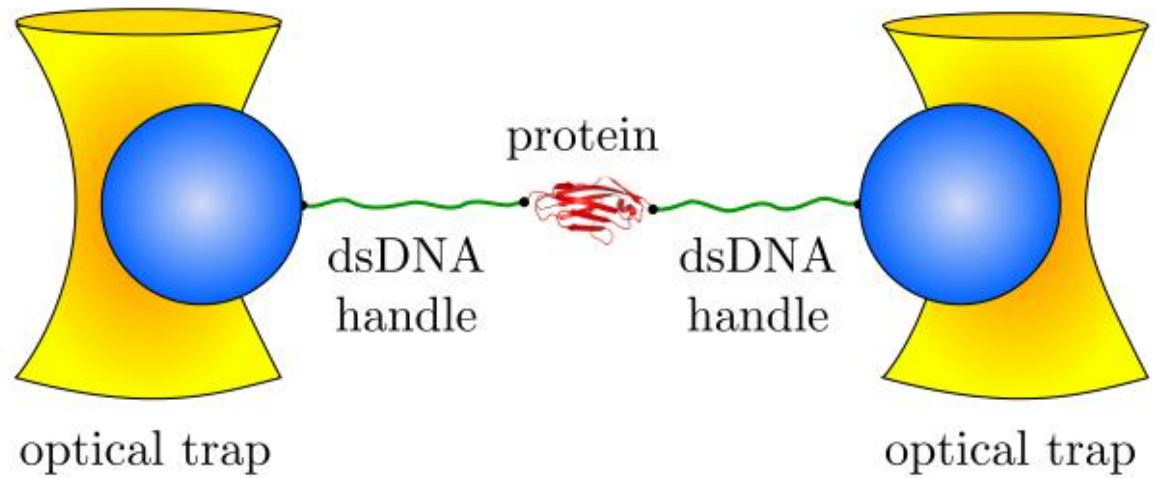
$$J_{ee} = \sum_m \frac{\mu_m}{\mu_m k_m - i\omega_m} = \sum_m \frac{\mu_m^2 k_m + i\omega_m \mu_m}{\mu_m^2 k_m^2 + \omega_m^2}$$



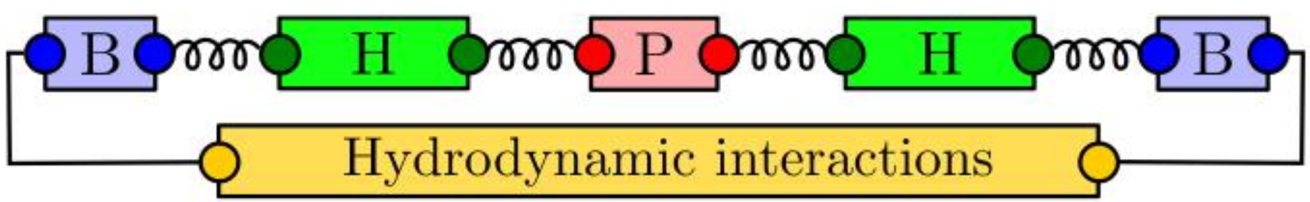
as $\omega \to 0$: $J'_{ee}=k^{-1}$, $J''_{ee}=\omega\mu k^{-2}$

Application To Optical Tweezers I

Optical tweezers dual trap setup:



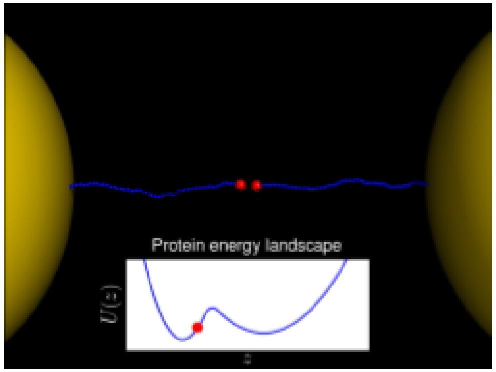
Equivalent mechanical network:



The beads in the traps, the DNA-handles, the protein as well as hydrodynamic interactions contribute to the total response of the system!

Application To Optical Tweezers II

Validation through BD simulation data:

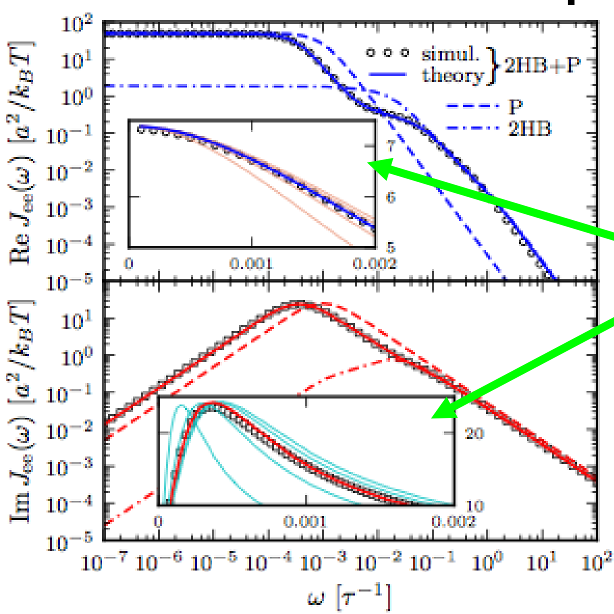


mobility/internal friction of protein extracable !!

application to exp. data: work in progress ….

Force response: Simulation vs Theory

2HB: 2 handle/beads without protein, 2HB+P: with protein

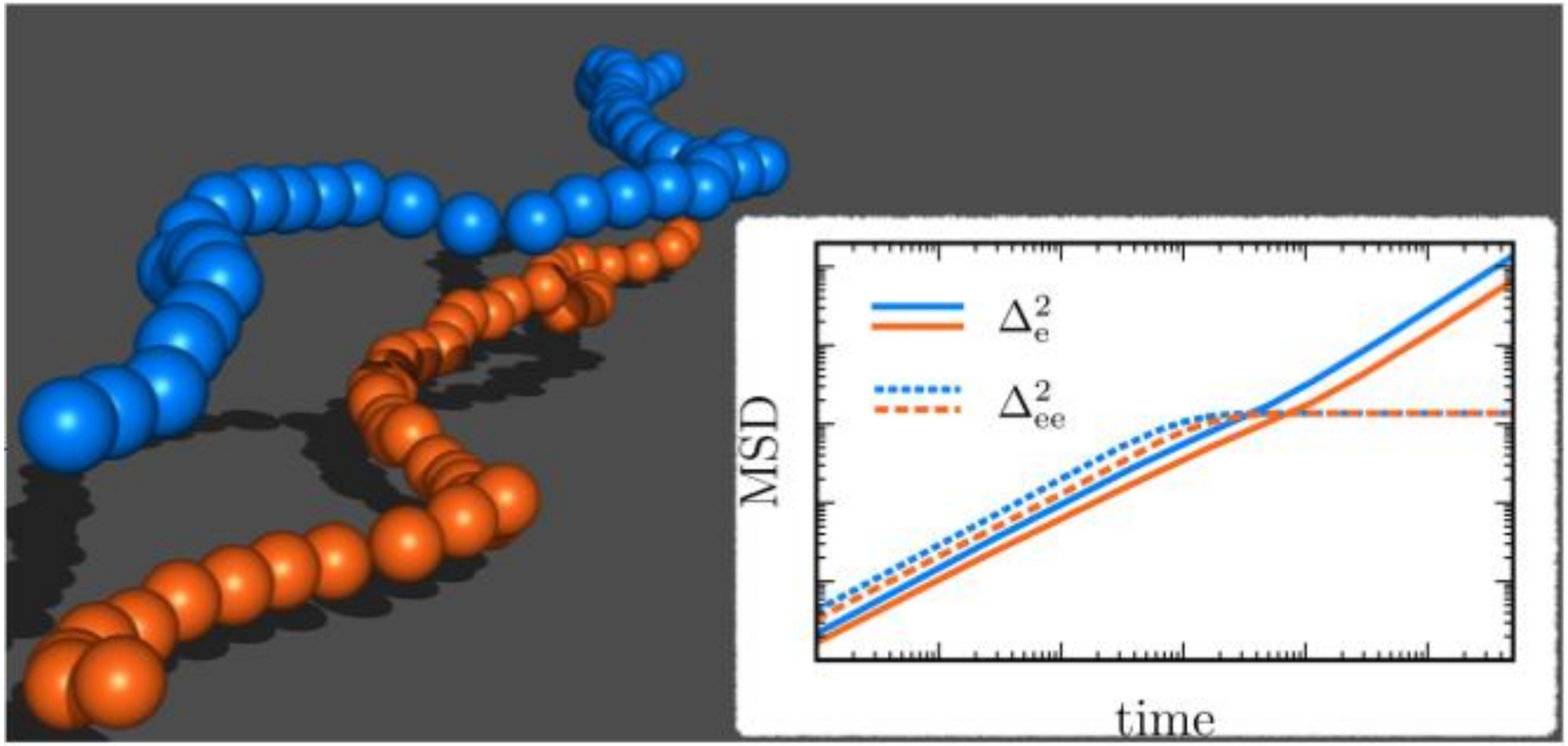


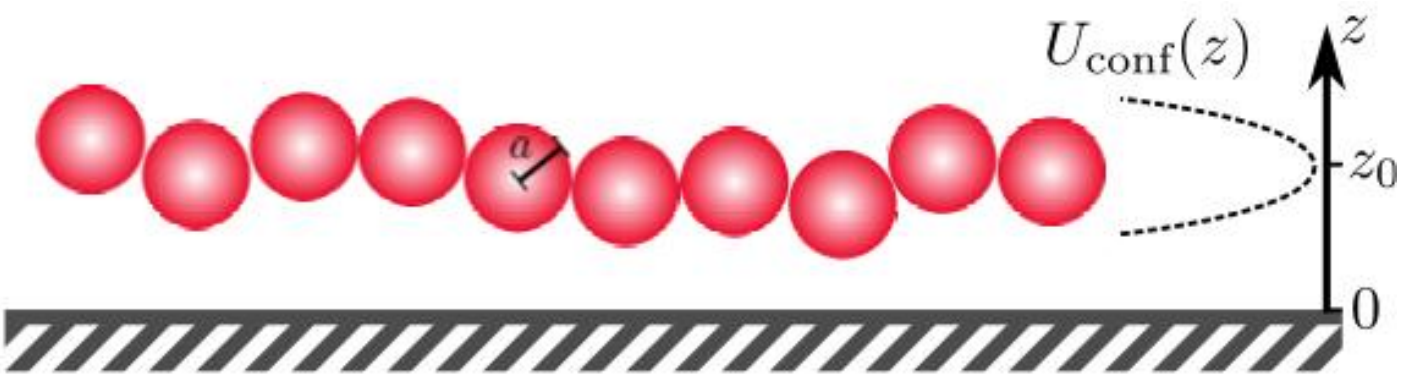
real part of total response funct. (storage contribution)

total convoluted signal with different protein viscosities

imaginary part (loss contribution)

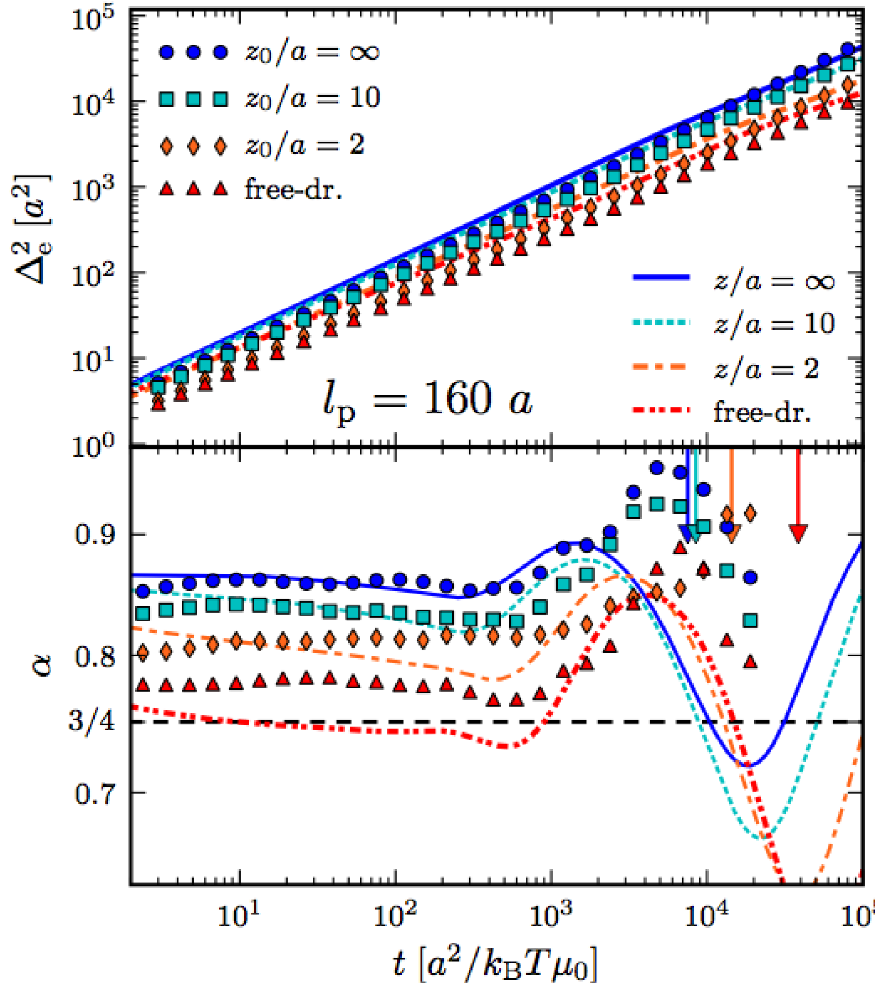
effects of nearby surface: hydrodyn. screening, crowding ....





end-point MSD at varying distance z/a from a no-slip surface

L=100a



effect of wall only strong at small distances of z/a = 2 !
even at distance z/a strong deviations from Rouse !

Tracer Studies on F-Actin Fluctuations

Loïc Le Goff,[1,*] Oskar Hallatschek,[2] Erwin Frey,[2,3] and François Amblard[1]

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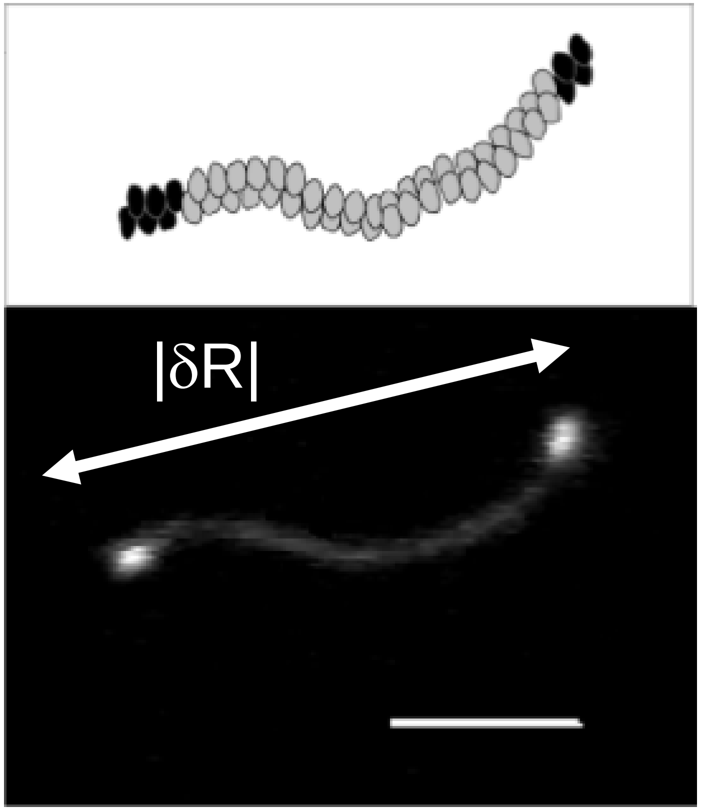
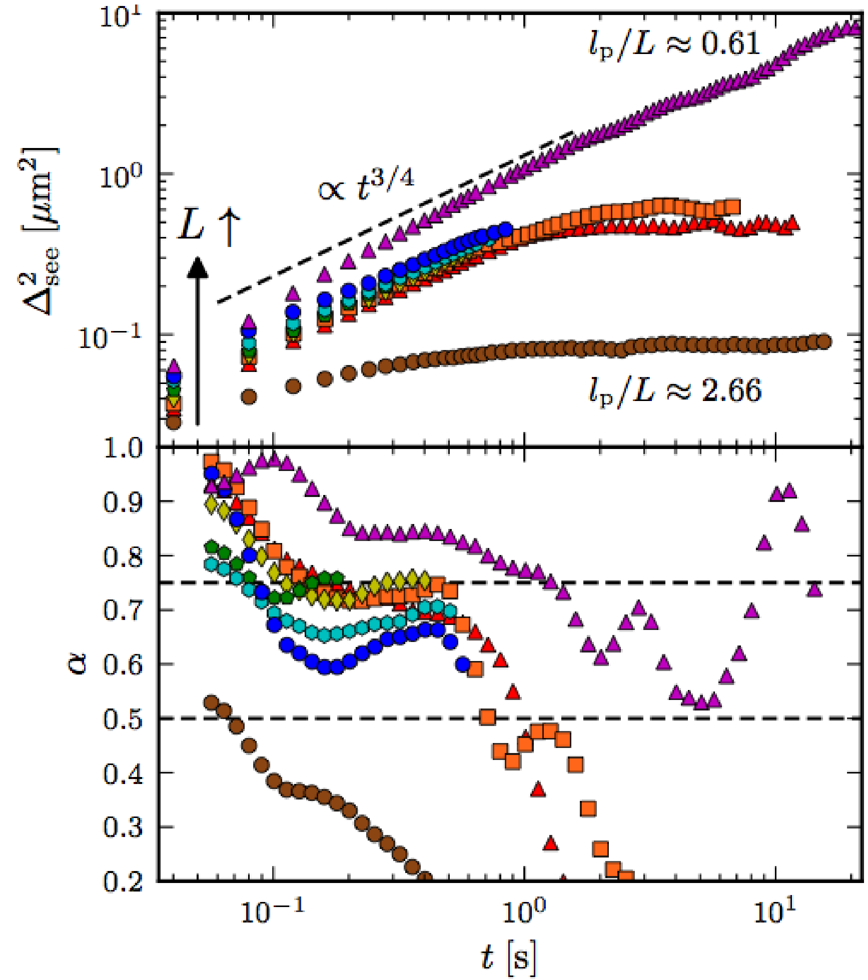
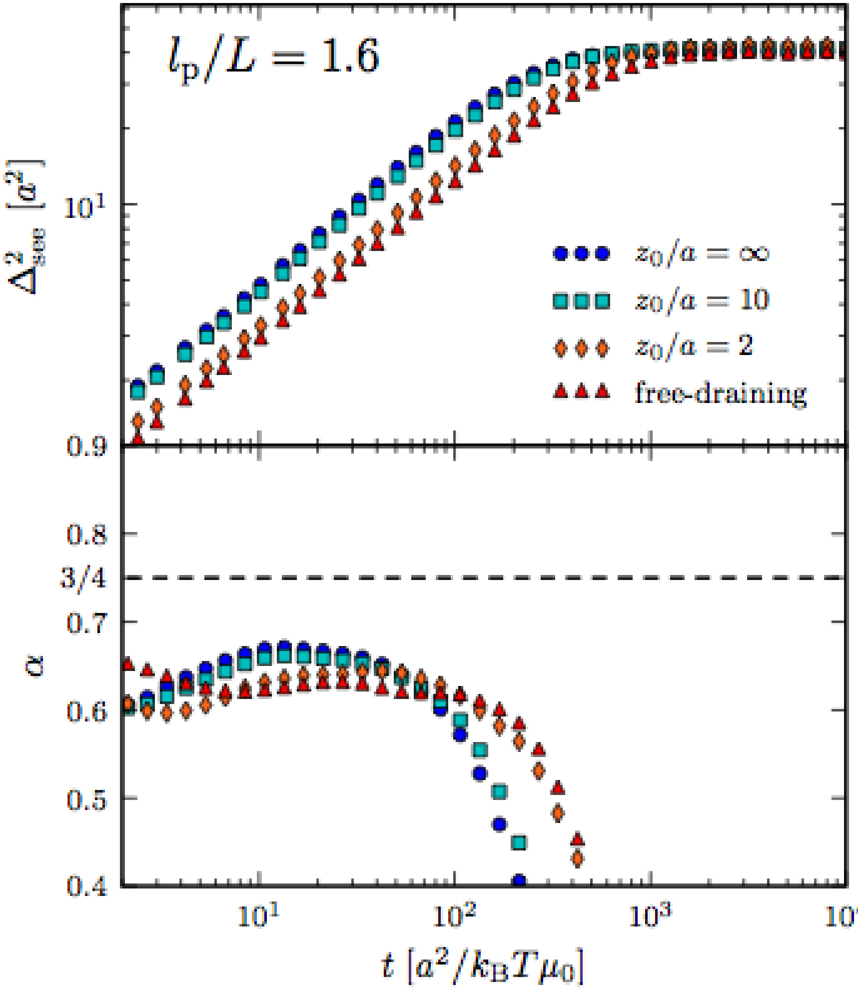




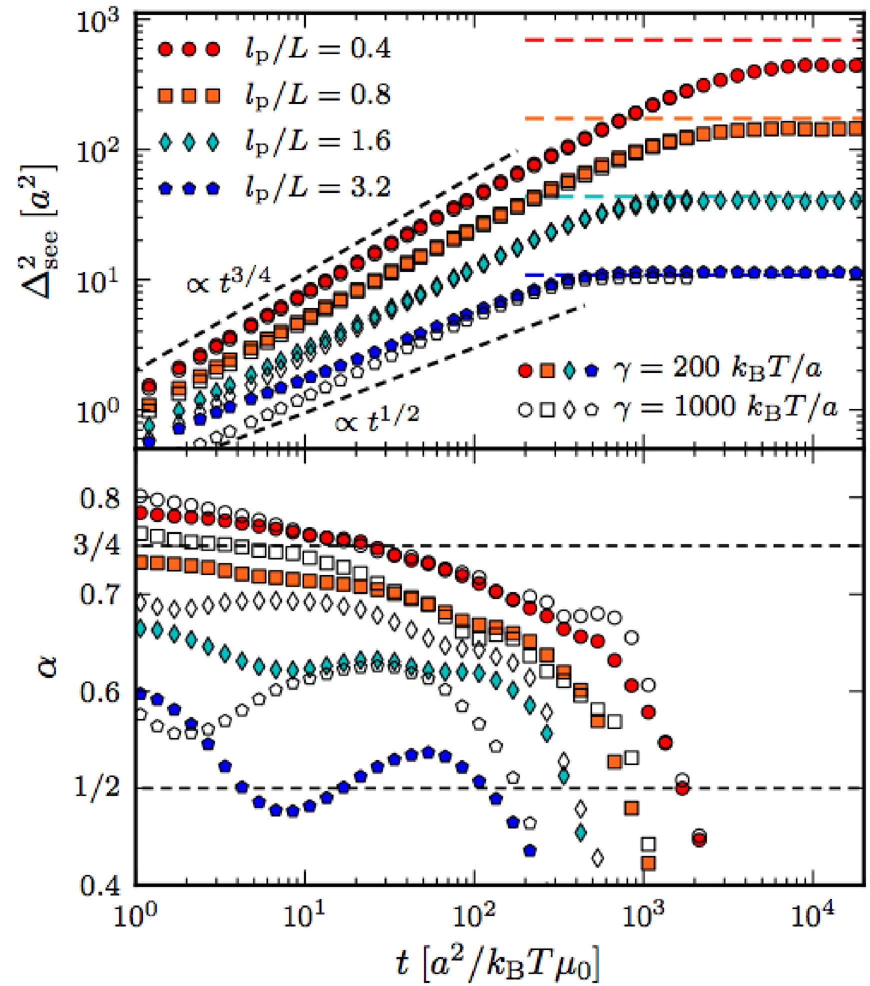
analysis based on
scalar end-to-end distance
(difficult in MFT !)

our re-analysis of exp. data:
systematic depend. on l_P/L in data

no hydrodynamic effects on scalar e.-to-e. distance



but dependence on stretching modulus !

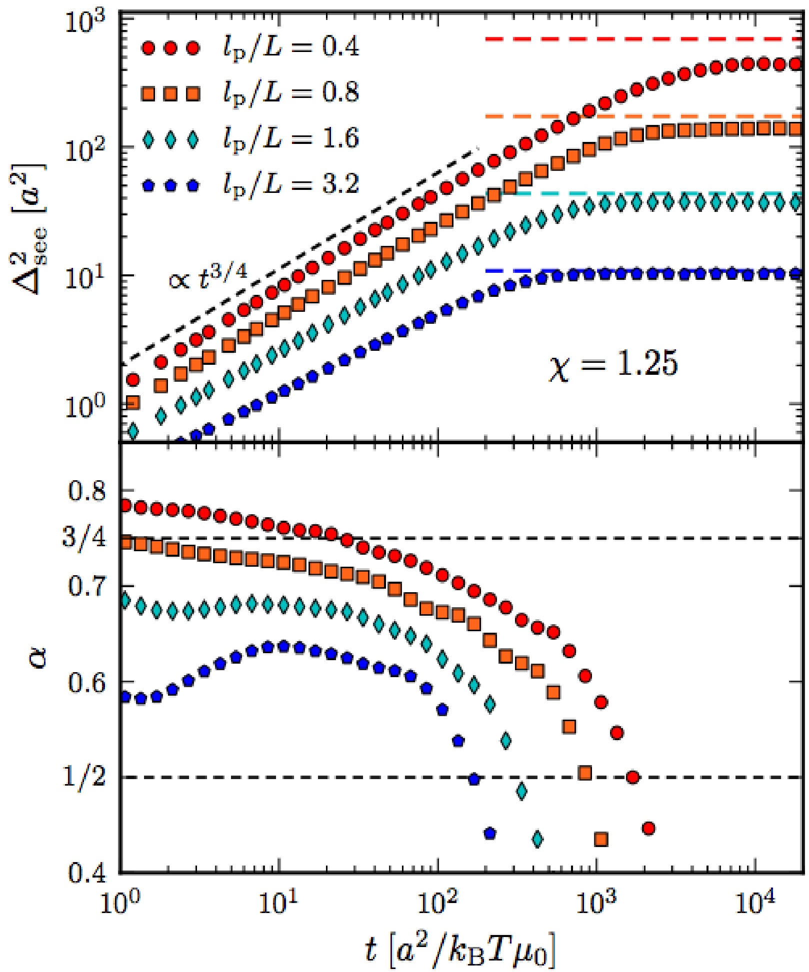


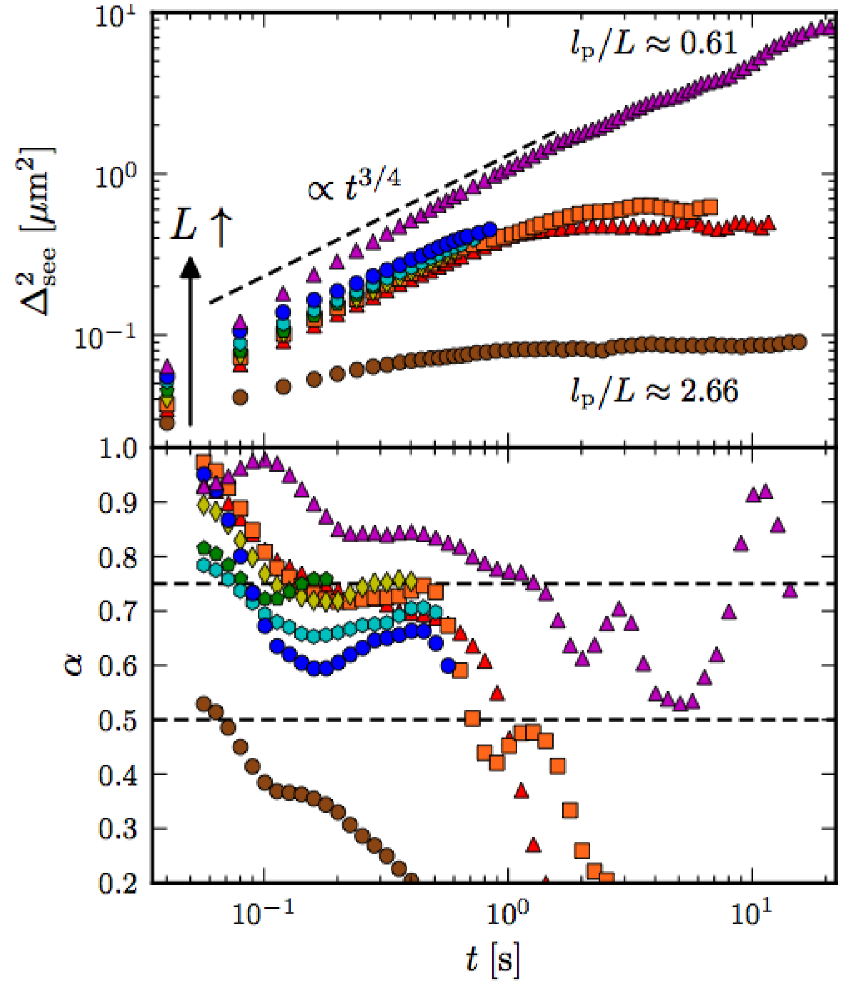
stretching modulus **bending modulus**

$$U_{\mathrm{WLC}} = \frac{\gamma}{4a}\sum_{i=1}^{M-1}(r_{i+1,i} - 2a)^2 + \frac{\kappa}{2a}\sum_{i=2}^{M-1}(1 - \cos\theta_i)$$

free-drain. BD simulation for constant elasticity ratio $\chi \equiv \frac{\gamma a^2}{4\kappa}$

L = 100 a





universal l_P/L dependence
for isotropic elastic material ?
(= weak L dependence ?)

comparison with exp. data
for actin L = 6 - 25 μm

self mobilities at no-slip surface on Rotne-Prager level

$$\mu_{\parallel}^{\mathrm{RPB}}(z) = \mu_0 \left(1 - \frac{9a}{16z} + \frac{1}{8}\left(\frac{a}{z}\right)^3\right) + \mathcal{O}(a^4),$$

$$\mu_{\perp}^{\mathrm{RPB}}(z) = \mu_0 \left(1 - \frac{9a}{8z} + \frac{1}{2}\left(\frac{a}{z}\right)^3\right) + \mathcal{O}(a^4).$$

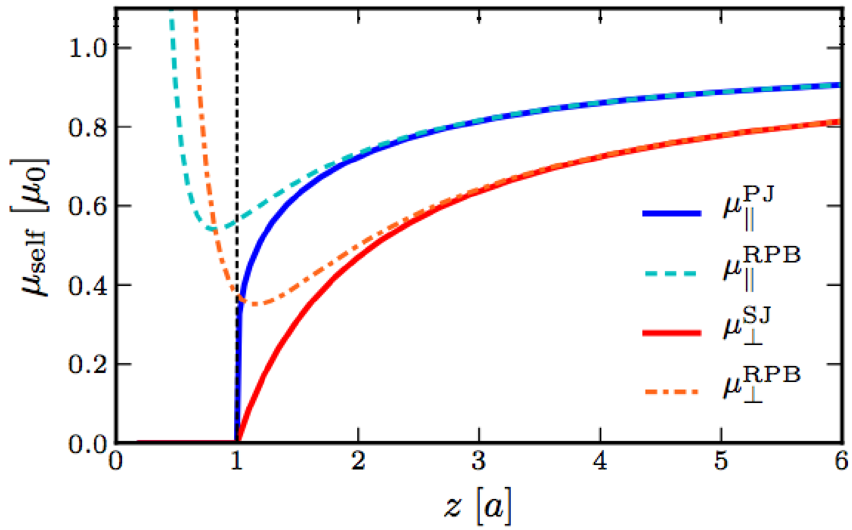
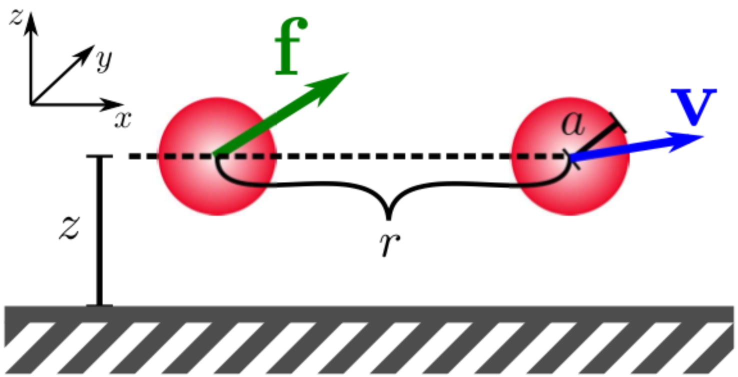
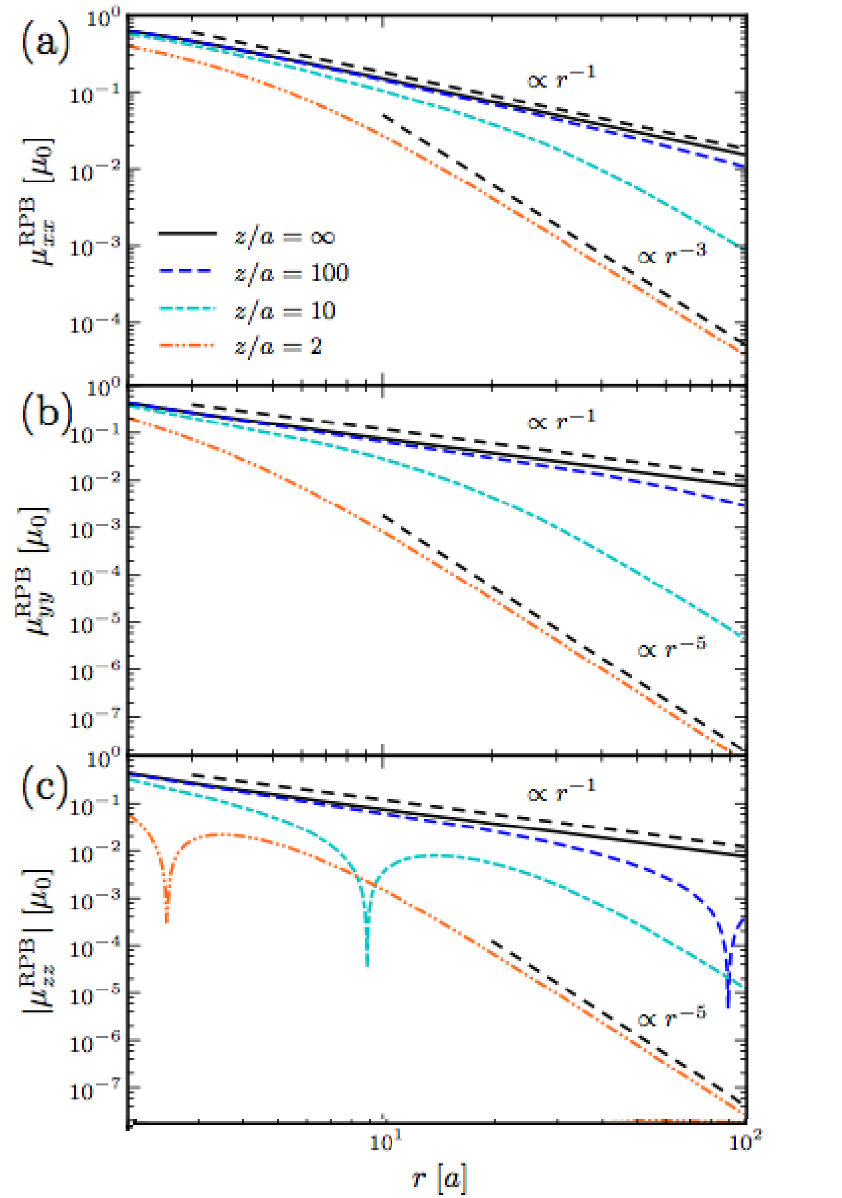


FIG. 1. Parallel ($\parallel$) and perpendicular ($\perp$) self-mobilities of a sphere of radius a located at a vertical distance z from a no-slip wall ($z = 0$). The approximations of Eqs. 8 and 9 (*dashed lines*) are compared to the result for the parallel mobility of Eq. 10 (*solid blue line*), and to the exact expression for the perpendicular mobility of Eq. 11 (*solid red line*). Self-mobilities are given in units of the bare self-mobility $\mu_0 = 1/(6\pi\eta a)$ in a fluid of viscosity η; the region $z < a$ is inaccessible due to excluded-volume effects.

hydrodynamic screening at a surface





Entropic Repulsion between Fluctuating Surfaces

$$V_{Fl}(\ell) \approx c_{Fl} T^2 / \kappa \ell^2$$

$$V_{Fl}(\ell) \approx (b_0 T / a_{\|}^2) e^{-\ell / l_\sigma} (l_\sigma / \ell)^{1/4}$$

$$l_\sigma \equiv \sqrt{T / 2\pi\overline{\sigma}}.$$

$\sigma \simeq 10^{-9}$ to $10^{-6} J/m^2$,

tension of rupture, which is $\simeq 10^{-3} J/m^2$.

crossover length $\quad l^* = \hat{z}^* \sqrt{T/\sigma} \simeq 2 - 2000 nm$

crossover pressure $\quad P^* \simeq (\hat{p}^* / c_{max}^2) \sqrt{\sigma^3 T / \kappa^2} \simeq 10^{-7} - 10^2 J/m^3$,

Netz, Lipowsky, EPL 29, 345 (1995)