bio soft-matter theory

physics department - T37

Dynamics of semiflexible polymers

Y. von Hansen, M. Hinczewski, Roland Netz (TU München)
Hirofumi Wada (Yukawa Institute, Kyoto)

1) equilibrium DNA end-point dynamics

2) rotationally driven buckling of stiff polymers

3) rotationally driven flexible polymers

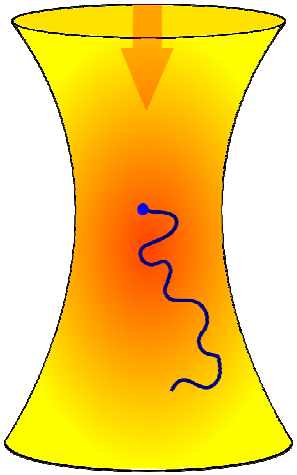
(hydrodynamic solvent-implicit simulations,
pre-averaging hydrodynamic theories
scaling arguments)

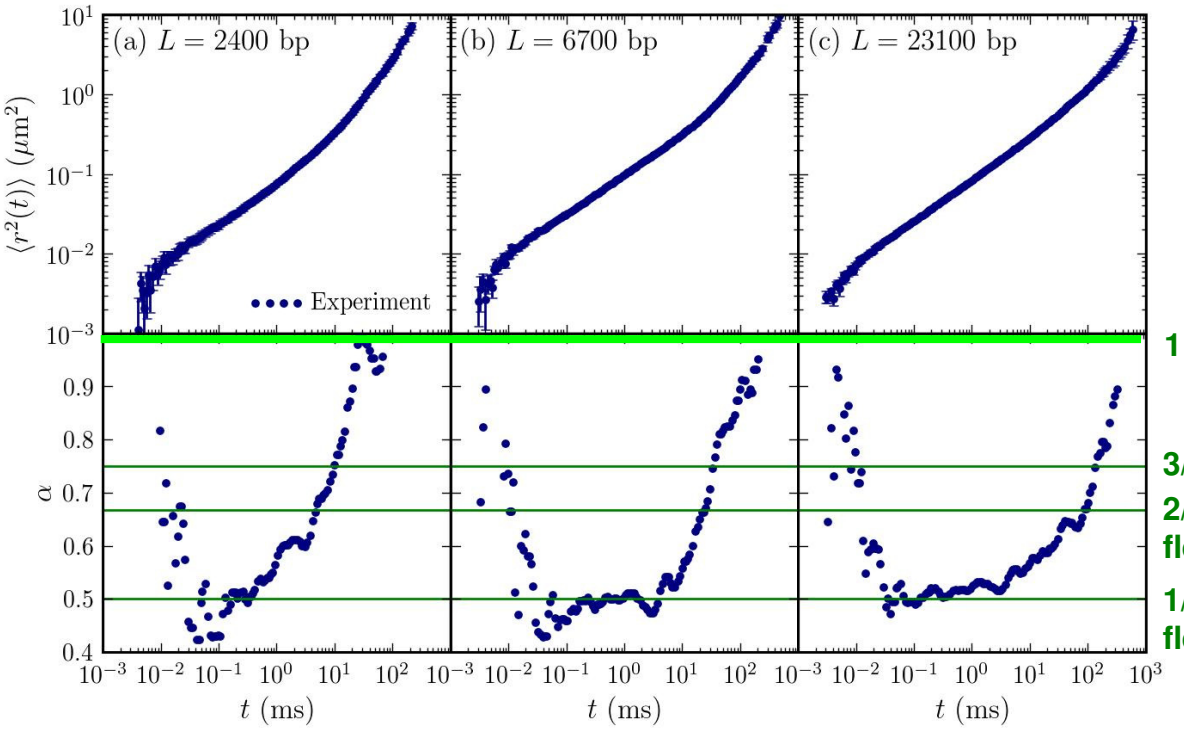
End-monomer dynamics of semiflexible polymers

O. Krichevsky et al., Phys. Rev. Lett. 92, 048303 (2004)
M. Hinczewski, X. Schlagberger, M. Rubinstein, O. Krichevsky, R.R. Netz, Macromolecules 42, 860 (2009)

Fluorescence correlation spectroscopy (FCS)

laser light





mean-squared displacement MSD

local exponent

1 center-of-mass

3/4 worm-like chain

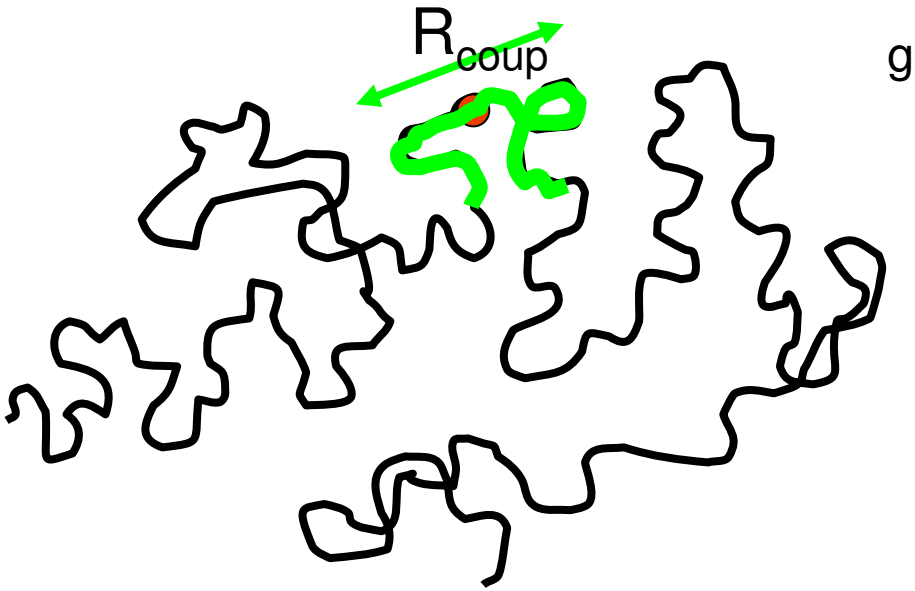
2/3 Zimm
flex. chain with hyd.

1/2 Rouse
flex. chain without hyd.

evidence of an "intermediate Rouse regime" with MSD ≈ $t^{1/2}$
===> free-draining ??

length scale 100 nm, time scale 1 ms

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 : $D \approx 1/N$

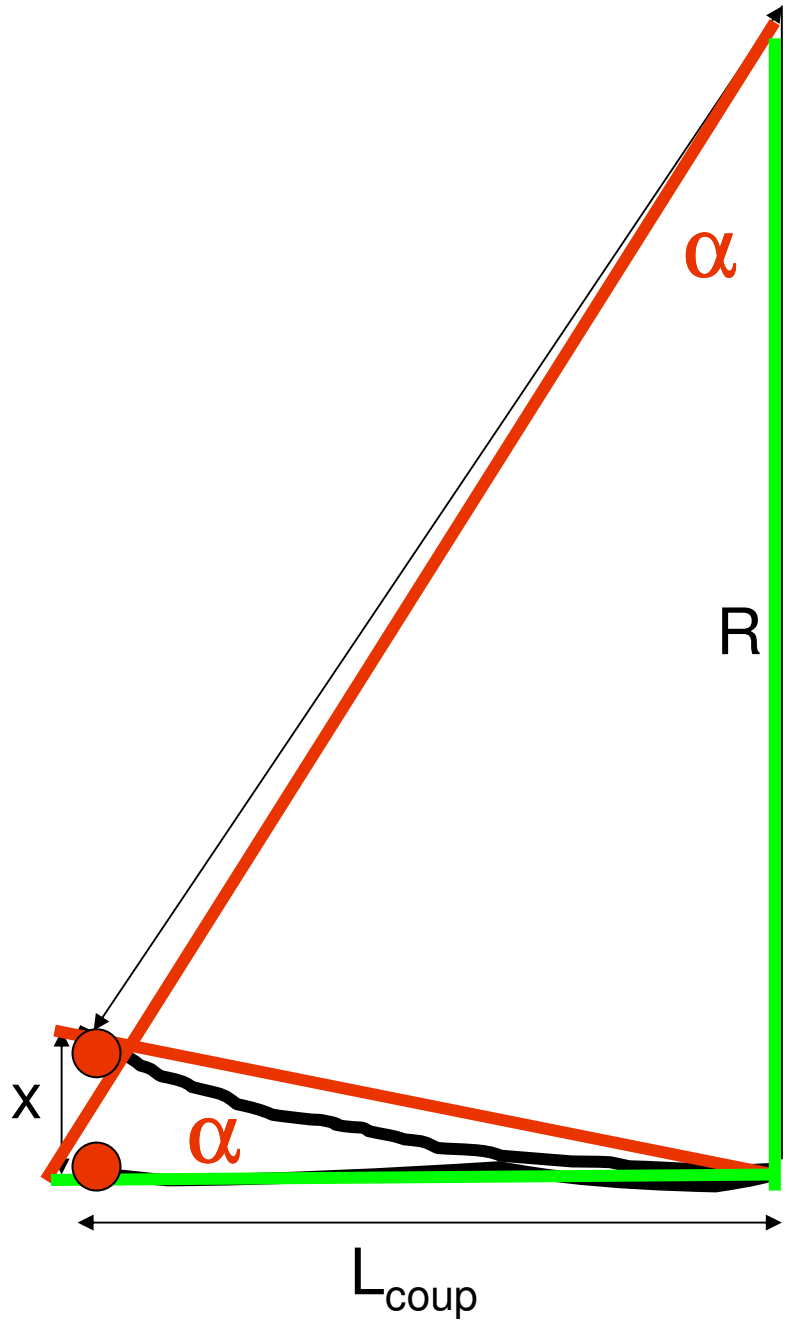
scaling assumption: diffusion radius determines coupling radius $R_{coup} \approx R_{MSD}$

Zimm: $R_{MSD}^2 \approx t^{2/3}$

Rouse: $R_{MSD}^2 \approx t^{2\nu/(1+2\nu)}$ ideal chain $\nu=1/2 \rightarrow R^2 \approx t^{1/2}$

rod $\nu=1 \rightarrow R^2 \approx t^{2/3}$ (Zimm $R^2 \approx t^{2/3} \ln^2 t$)

semiflexible chain dynamics: longitudinal motion blocked -> thermal transverse bending



equipartition theorem:

bending energy / $k_B T$ = $\frac{l_P L_{coup}}{R^2} = 1$

similarity $x/L_{coup} \approx L_{coup}/R$

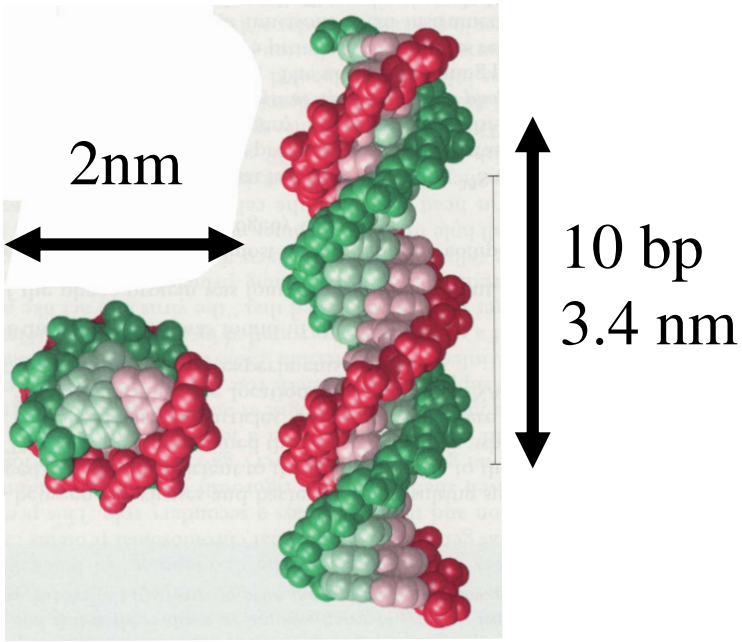
-> transverse fluctuations $x^2 \approx L_{coup}^3 / l_P$
diffusion $x^2 \approx D\,t$
diffusion constant $D \approx L_{coup}^{-1} \ln L_{coup}$

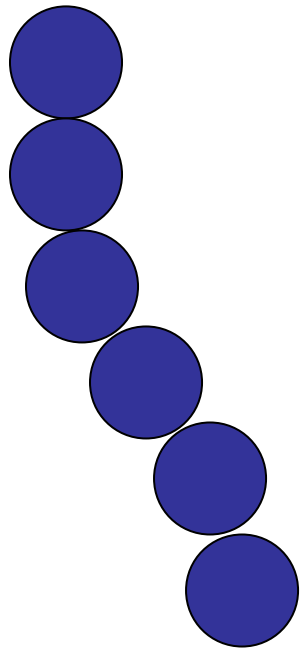
-> vertical displacement $x^2 \approx t^{3/4}\, l_P^{-1/4}\, \ln^{3/4} t$

exponents:

3/4 (rigid scale)
2/3 (flexible scale)
1 (center-of-mass scale)
1/2 Rouse ??

DNA dynamics:
length and time scales (microns and milliseconds)
require **coarse-grained simulations** techniques!





atomistic resolution
- detailed force fields
- including explicit water

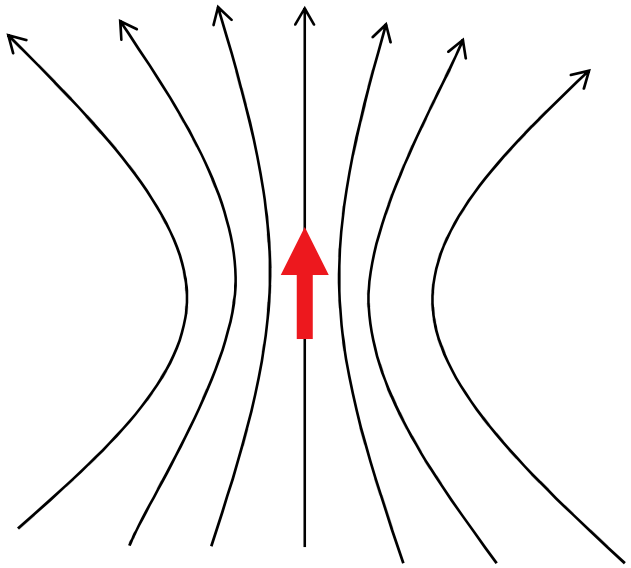
coarse-grained description
- few effective interactions
- continuous hydrodynamics

How to put in hydrodynamic effects without solvent?

Stationary Navier-Stokes equation $\eta \Delta \vec{v}(\vec{r}) - \nabla p = \rho(\vec{v} \cdot \nabla)\vec{v}$

for small Reynolds number on the micron scale $Re^{tr} = \frac{\rho}{\eta} l\, v \ll 1$

linear equation, Green's function approach valid



flow-field due to point-force at origin:

$$u^{\alpha}(r) = H^{\alpha\beta}(r)\, f^{\beta} \qquad \alpha,\beta = 1,2,3$$

$$H^{\alpha\beta}(r) = \frac{1}{8\pi\eta r}\left[\delta_{\alpha\beta} + \hat{r}^{\alpha}\hat{r}^{\beta}\right]$$

(Oseen-Tensor)

for many particles superposition principle: $u^{\alpha}(r) = \sum_i H^{\alpha\beta}(r - r_i)\, f_i^{\beta}$

Hydrodynamic Brownian simulation techniques

Velocity of i-th particle:

$$\dot{r}_i(t) = \vec{\mu}_{ij} \; f_j(t)$$

deterministic force

$$f_j(t) = -\partial U(t) / \partial r_j(t) + E$$

Mobility matrix:

$$\vec{\mu}_{ij} = D_{ij} / k_B T = \mu_0 \, \delta_{ij} + \vec{H}(r_i, r_j)$$

self mobility:

$$\mu_0 = (6\pi R \eta)^{-1}$$

hydrodyn. interact.

Random force

$$\left\langle \xi_i(t) \xi_j(t') \right\rangle = 6 \, \vec{\mu}_{ij} \; k_B T \; \delta(t - t')$$

equivalent to Smoluchowski equation for particle distribut. $W(r_j,t)$:

$$\frac{\partial W}{\partial t} = \sum_{i,j} \frac{\partial}{\partial r_i} \left[D_{ij} \frac{\partial W}{\partial r_j} - \mu_{ij} f_j W \right]$$

stat. solution:

$$W \cong e^{-U / k_B T}$$

End-monomer dynamics of semiflexible polymers

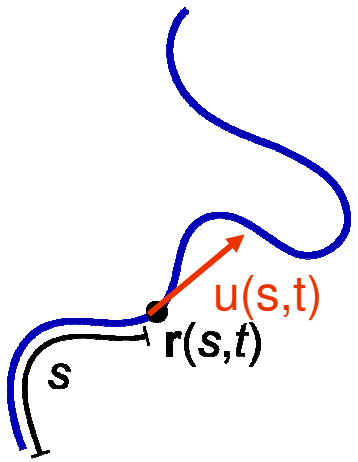
Brownian hydrodynamics simulations (Michael Hinczewski)

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

polymer of 50 beads
persistence length = 20*a*
bead radius a
-> 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):



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

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

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 $\mu_{\mathrm{avg}}(s-s')$

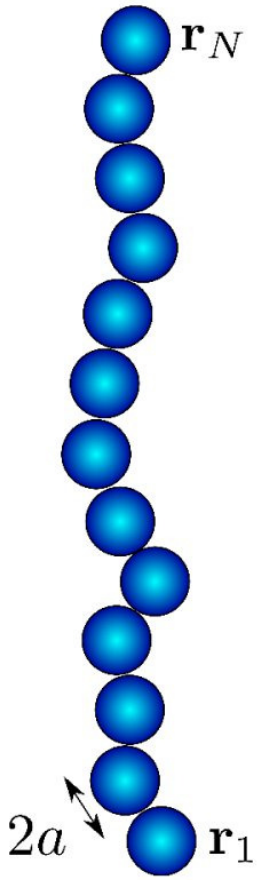
$$\frac{\partial}{\partial t}\mathbf{r}(s,t) = \int_{-L/2}^{L/2} ds'\, \mu_{\mathrm{avg}}(s-s') \left(-\frac{\delta U_{\mathrm{MF}}}{\delta \mathbf{r}(s',t)}\right) + \boldsymbol{\xi}(s,t)$$

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

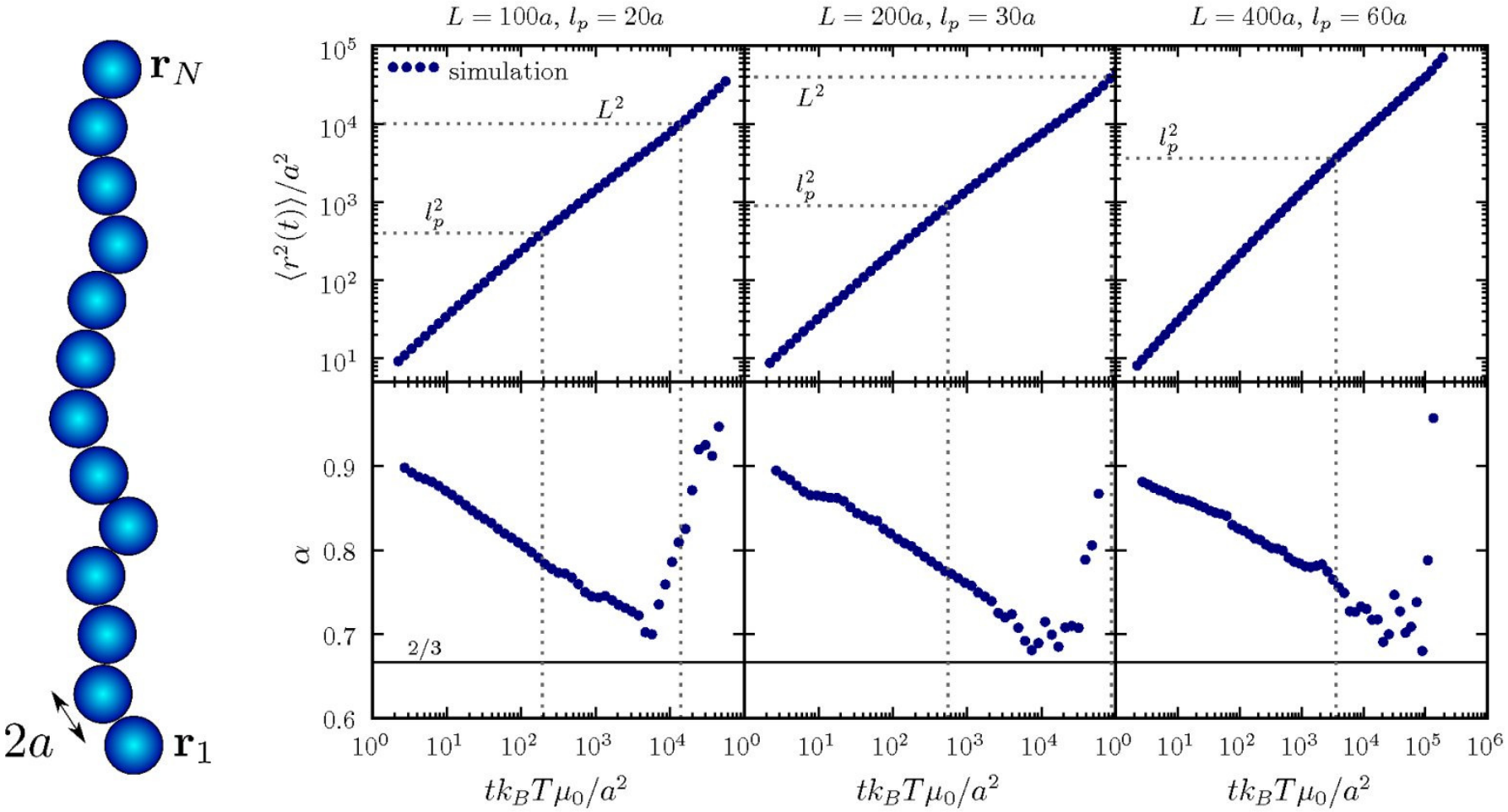
M. Hinczewski:

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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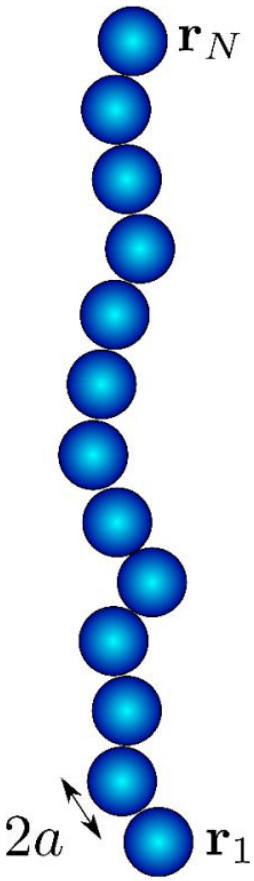
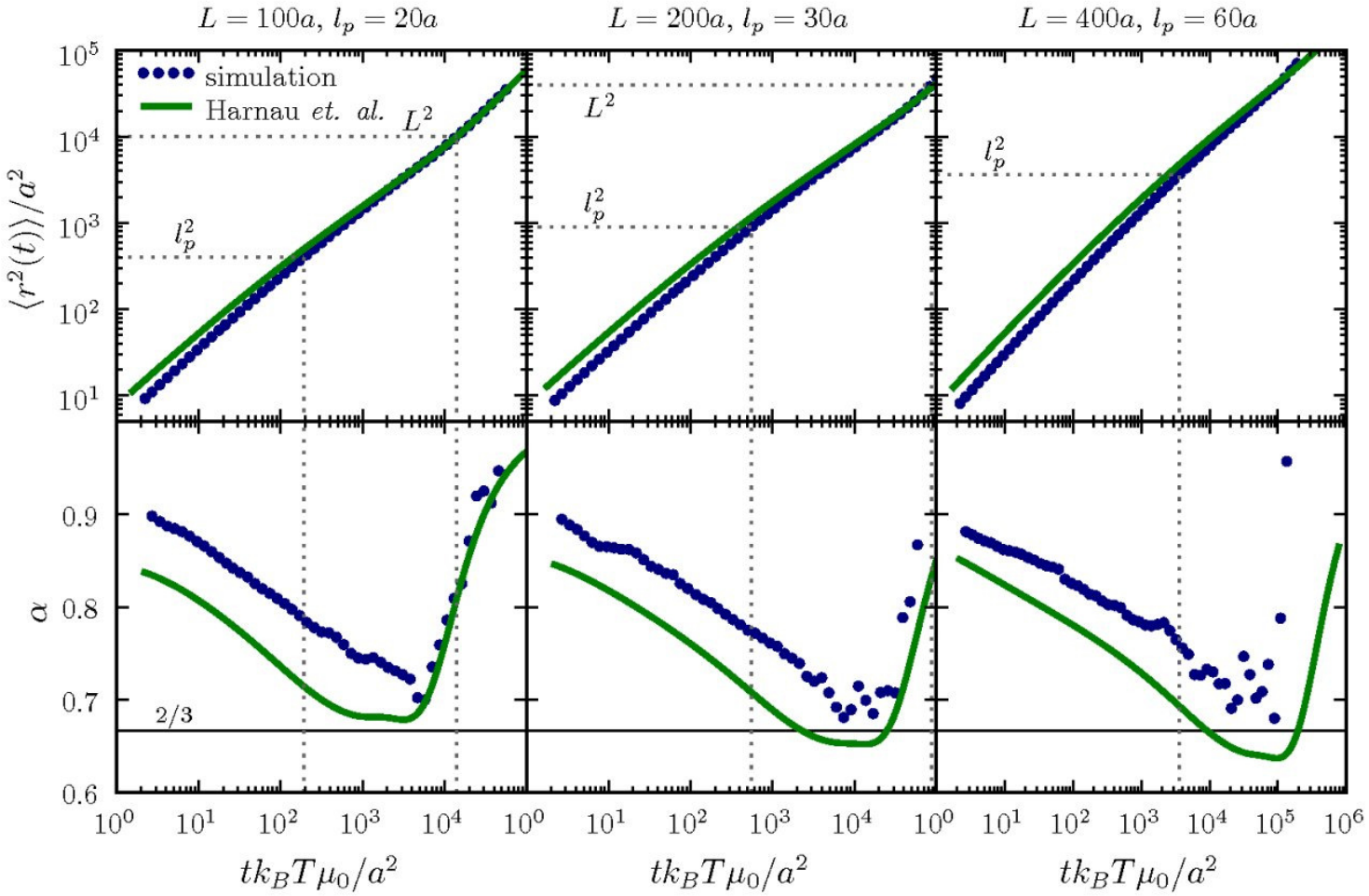
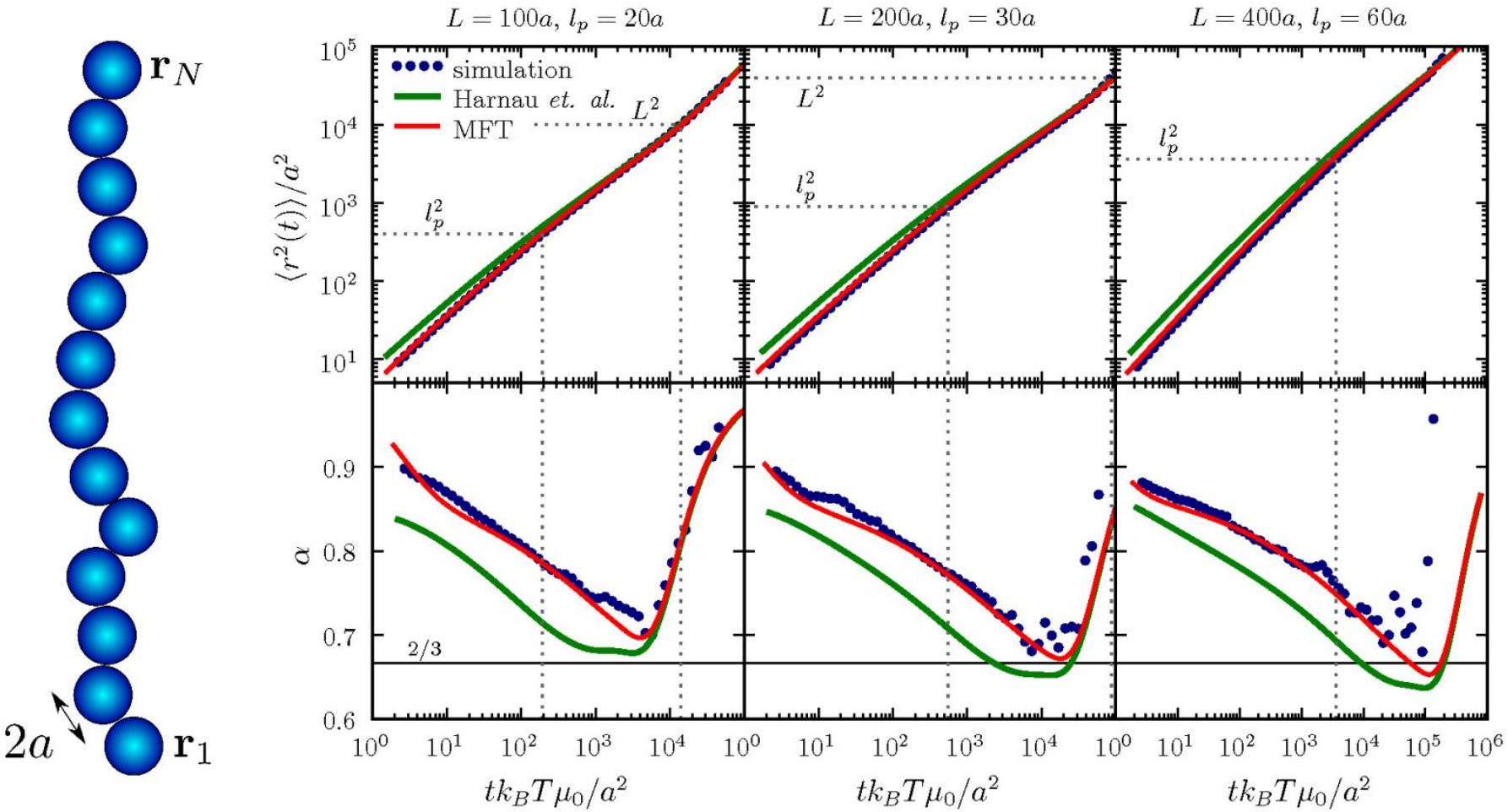




validation of the **hydrodynamic theory** by comparison
with **Brownian hydrodynamic simulations** for N=50, 100, 200

Harnau: Winkler solution with diagonal approximation
MFT: numerically exact solution
excellent agreement between the MFT and simulation data
--> confidently extend the MFT to larger chain lengths inaccessible to simulation
(pre-averaging + mean-field assumption probably ok)



validation of the **hydrodynamic theory** by comparison
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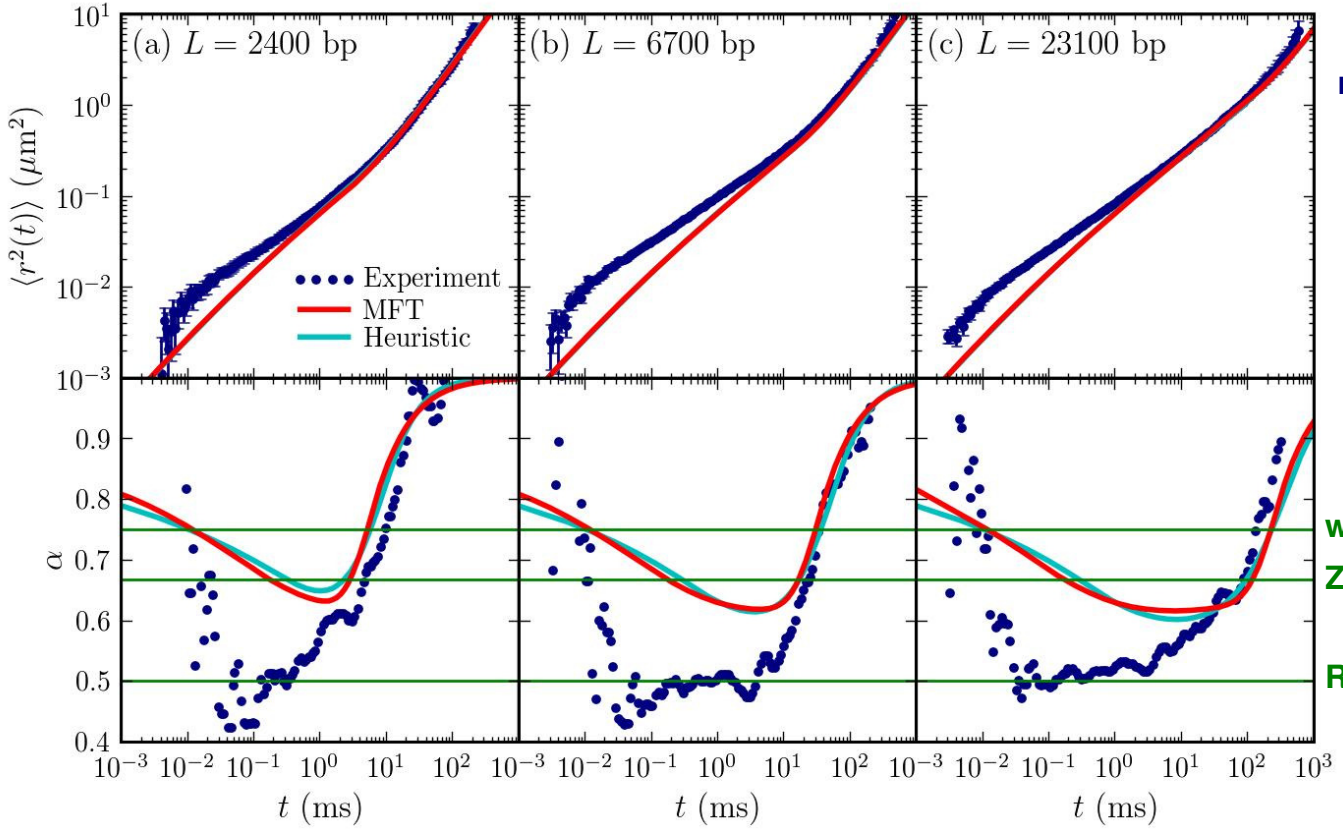
HWR: Winkler solution with diagonal approximation
MFT: numericaly exact soution
excellent agreement between the MFT and simulation data
--> confidently extend the MFT to larger chain lengths inaccessible to simulation
(pre-averaging probably ok)

END-MONOMER-DYNAMICS:

Comparison between **FCS experiment** and **hydrodynamic theory**



top row: mean-squared displacement

bottom row: local exponent

worm-like chain (3/4)

Zimm (2/3)

Rouse (1/2)

sub-Zimm scaling regime for longer chains

but still slight disagreement

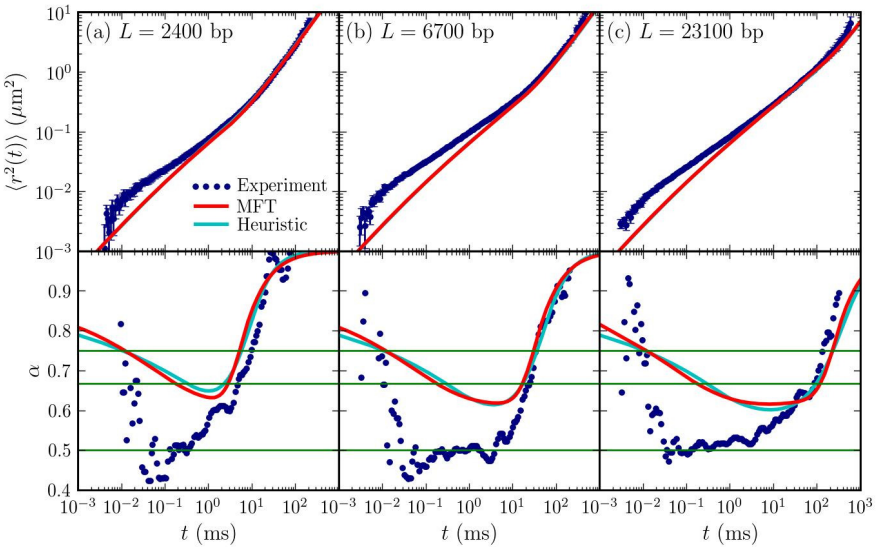
--> problem of theoretical model (neglect of charges, twist diffusion) ? --> probably no !

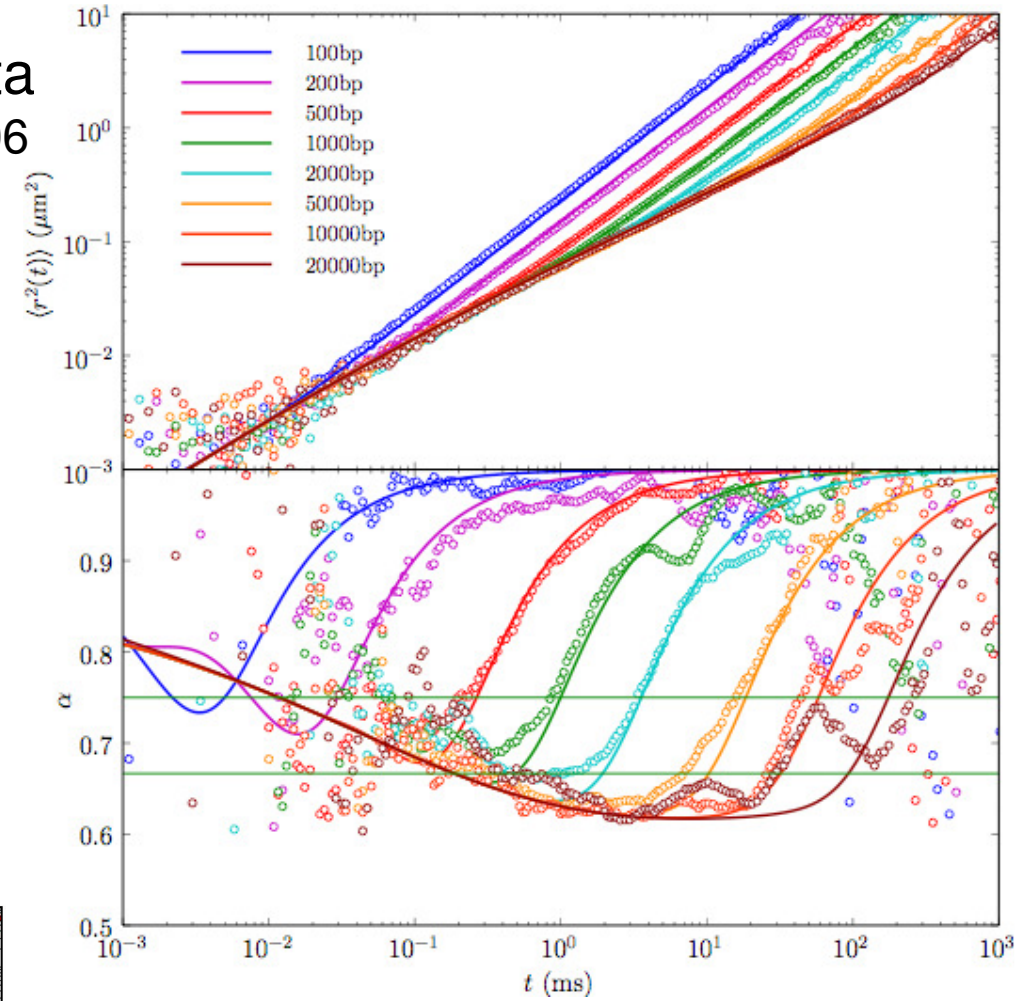
--> problem of sample preparation / FCS experimental technique?

reanalysis of Petrov/Schwille data

Petrov, Winkler, Schwille et al, PRL 2006

no hidden fitting parameter in mean-field theory:
rise per bp 0.34nm
hydrodyn. radius 1nm
persist. length l_P = 50nm

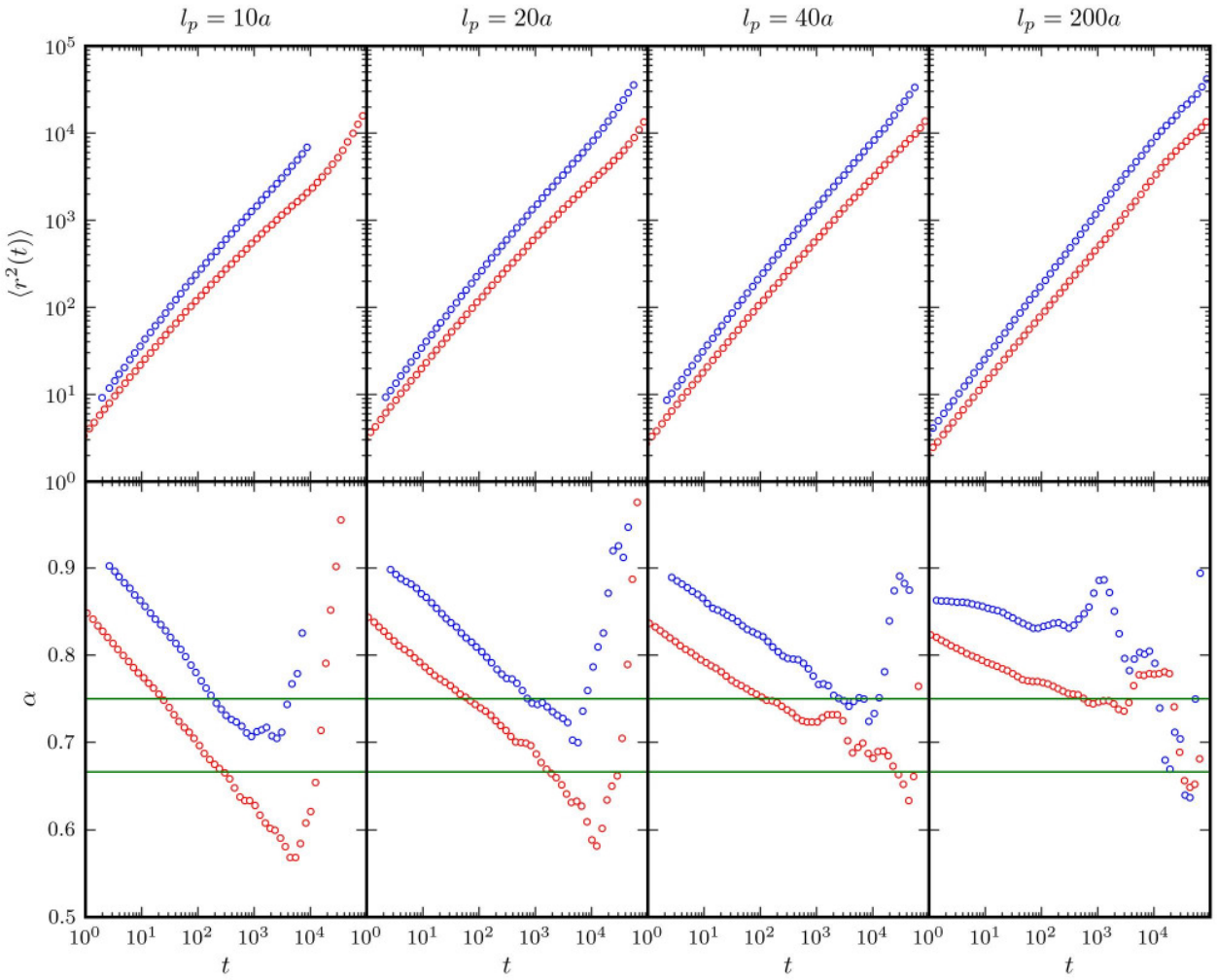




Oleg Krichevsky's data

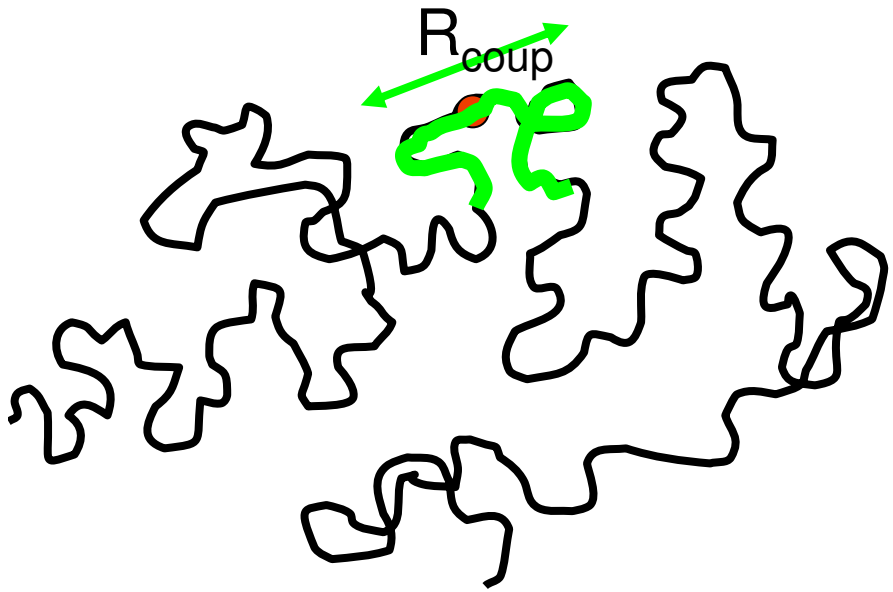
further directions:
DNA-peptide binding rates
dynamic DNA force transduction

comparison of **Langevin simulations without hydrodynamic** and **Langevin simulations with hydrodynamics**



for exponents hydrodynamics always relevant !
shift by + 0.1 (= logarithmic effects)

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 $c = 1 > \nu = 1/2$

DNA dynamics far from equilibrium:

1) DNA sedimentation
   Schlagberger / Netz, PRL 2007

2) DNA in strong shear fields
   Sendor / Netz, EPL 2009

3) DNA under constant twist injection
   Hirofumi Wada / Netz

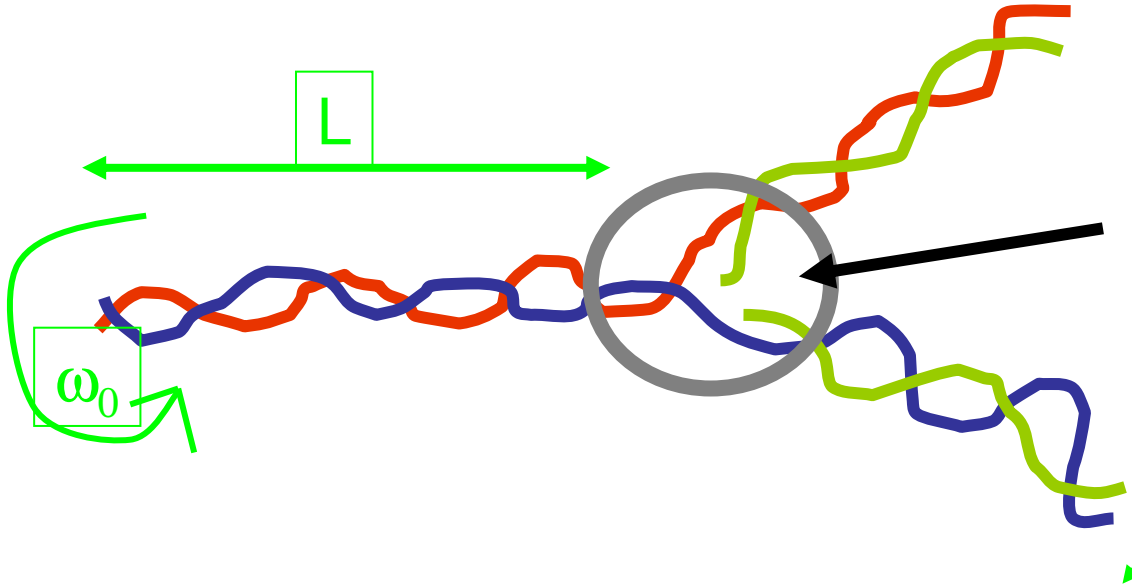
ON THE UNWINDING OF DNA

By C. Levinthal and H. R. Crane

Department of Physics, University of Michigan

Communicated by D. M. Dennison, May 10, 1956

There have been a number of discussions of the problem of the mechanism of the unwinding of the two strands of the double helix structure of DNA during replication. In particular, these efforts have been directed toward finding ways in which the two strands can become separated without requiring rotation of the whole molecule through a large number of turns. Rotation has been considered to



replication fork,
-> rotation of mother strand

axial-spinning torque due to rotational friction: $M = a^2 L \eta \omega_0$

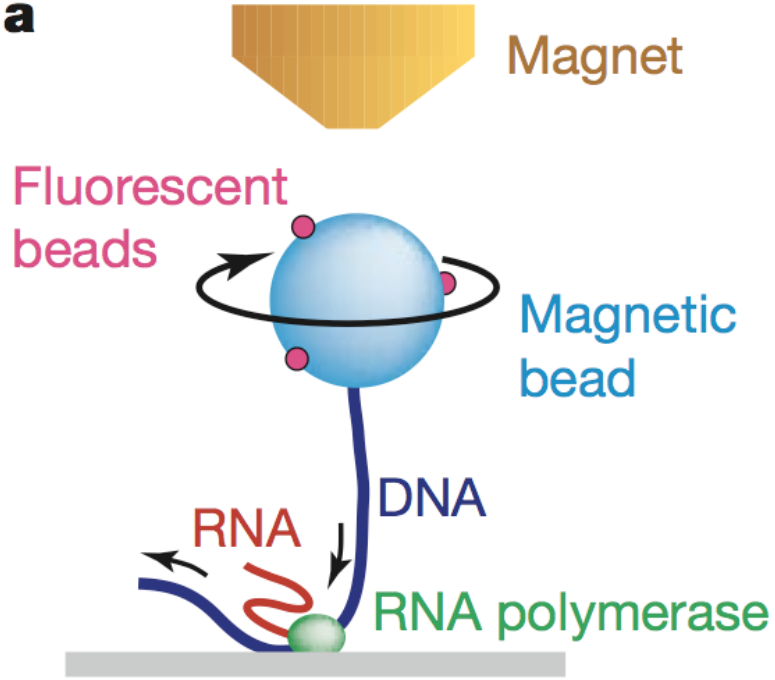
for $L=10\mu m$, $\omega_0=10^4$ -> $M=k_BT$ (Heslot et al., PRL 2002)
biologically $\omega_0=10-100$, power consumption $P = M \omega_0$ of order k_BT / s

Yoshie Harada*†‡, Osamu Ohara§, Akira Takatsuki*, Hiroyasu Itoh†‖, Nobuo Shimamoto¶ & Kazuhiko Kinosita Jr*†

NATURE | VOL 409 | 4 JANUARY 2001 |

an actin filament only poorly[3]. For DNA-based motors such as RNA polymerase, transcription-induced supercoiling of DNA[4] supports the general picture of tracking along the DNA helix[5]. Here we report direct and real-time optical microscopy measurements of rotation rate that are consistent with high-fidelity tracking. Single RNA polymerase molecules attached to a glass surface rotated DNA for >100 revolutions around the right-handed screw axis of the double helix with a rotary torque of >5 pN nm. This real-time observation of rotation

a



Proc. Natl. Acad. Sci. USA
Vol. 84, pp. 7024–7027, October 1987
Biochemistry

Supercoiling of the DNA template during transcription

(DNA topology/topoisomerases/transcriptional swivel/translocation along DNA/gene regulation)

LEROY F. LIU*† AND JAMES C. WANG†‡

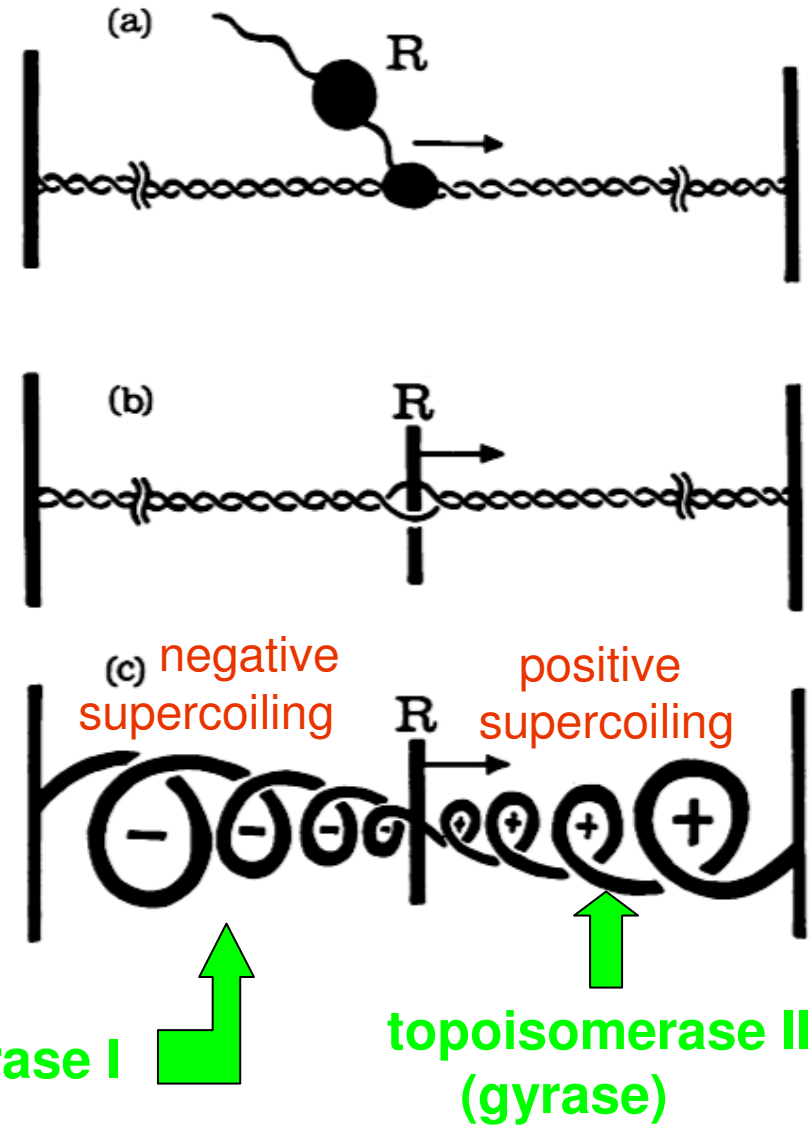
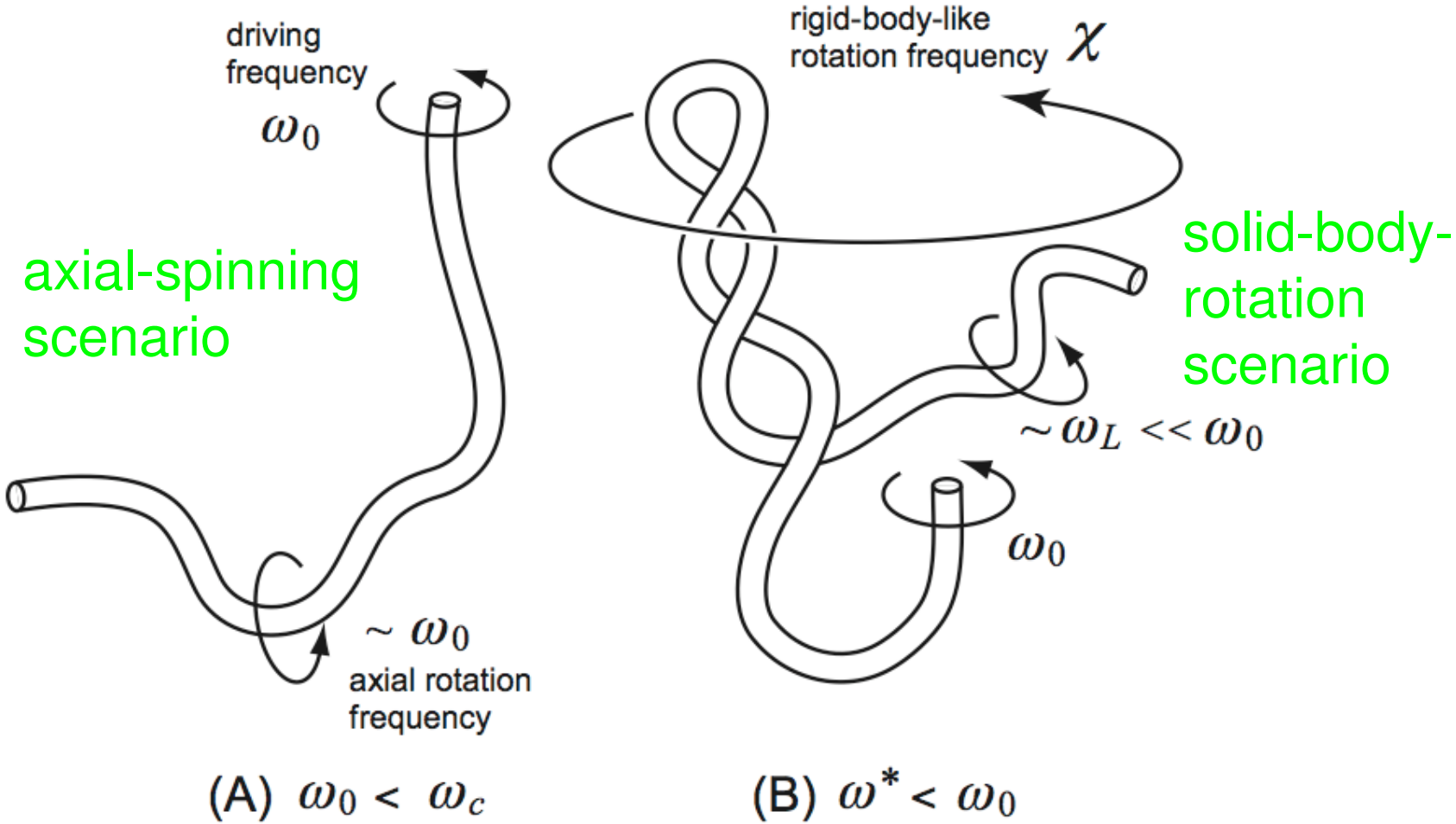


FIG. 1. A graphical illustration of the mechanics of transcription. (*a*) A transcription ensemble R including the polymerase, the nascent RNA, and proteins bound to the RNA is moving in the direction of the arrow along a DNA segment; the ends of the DNA segment are anchored on a large structure represented by the solid bars. (*b*) The transcription ensemble can be viewed as a divider separating the helical DNA into two parts. (*c*) If R is moving from left to right without turning around the DNA, the DNA in front of the polymerase becomes overwound, or positively supercoiled; the DNA behind the polymerase becomes underwound, or negatively supercoiled.

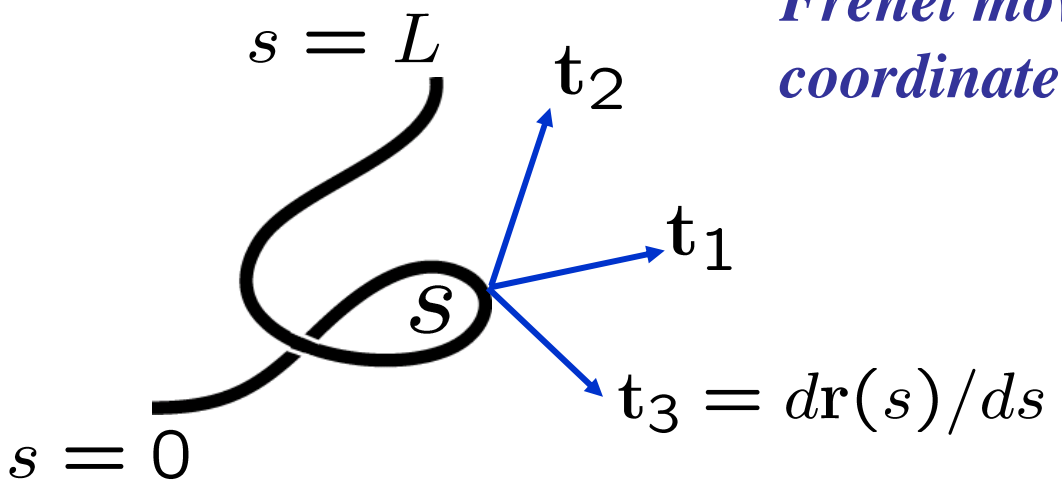
question:
what is degree of twisting ?
--> how big is rotational friction?

ABSTRACT Transcription of a right-handed double-helical DNA requires a relative rotation of the RNA polymerase and its nascent RNA around the DNA. We describe conditions under which the resistance to the rotational motion of the transcription ensemble around the DNA can be large. In such cases, the advancing polymerase generates positive supercoils in the DNA template ahead of it and negative supercoils behind it. Mutual annihilation of the positively and negatively supercoiled regions may be prevented by anchoring points on the DNA to a large structure, or, in the case of an unanchored plasmid, by the presence of two oppositely oriented transcription units. In prokaryotes, DNA topoisomerase I preferentially removes negative supercoils and DNA gyrase (topoisomerase II) removes positive ones. Our model thus provides an explanation for the experimentally observed high degree of negative or positive supercoiling of intracellular pBR322 DNA when DNA topoisomerase I or gyrase is respectively inhibited. We

- what is the rotation mode ?? *(irrelevant for biology …)*
- what is the rotational friction ?? *(is replication possible, does transcribed DNA rotate ?)*
- what is the twist density ?? *(topo-isomerase activity ?)*
- are supercoils (plectonemes) formed ??



General mathematical theory of an elastic filament



Frenet moving coordinate

strongly non-local … not suitable for efficient dynamic simulation models

generalized Frenet equation

$$\frac{d\mathbf{t}_j}{ds} = \Omega \times \mathbf{t}_j$$

strain rate vector field

$$\Omega = \Omega_1 \mathbf{t}_1 + \Omega_2 \mathbf{t}_2 + \Omega_3 \mathbf{t}_3$$

elastic energy of a deformed filament (linear elastic theory)

$$E[\Omega] = \frac{A}{2}\int_0^L ds(\Omega_1 - \Omega_1^0)^2 + \frac{A}{2}\int_0^L ds(\Omega_2 - \Omega_2^0)^2 + \frac{C}{2}\int_0^L ds(\Omega_3 - \Omega_3^0)^2$$

A: bending modulus, C: twisting modulus

local parameterization in a discrete model

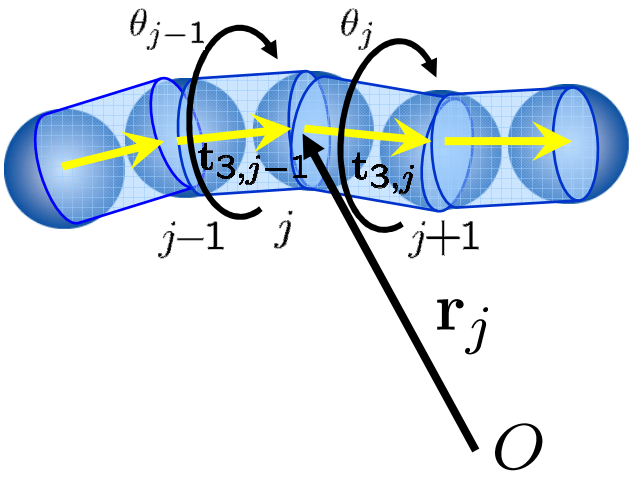
Alternative expression of the Frenet equation

$$\Omega_1 = -\mathbf{t}_2 \cdot d\mathbf{t}_3/ds$$
$$\Omega_2 = \mathbf{t}_1 \cdot d\mathbf{t}_3/ds$$
$$\Omega_3 = \mathbf{t}_2 \cdot d\mathbf{t}_1/ds$$

$$\Omega = \Omega(\mathbf{r}, \theta)$$

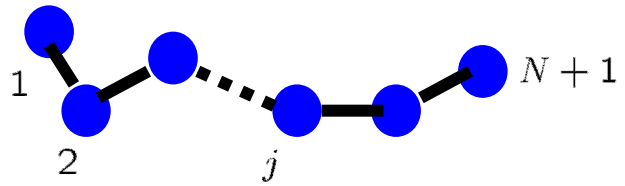
Elastic energy is described in terms of only beads positions and angles

$$E[\Omega] \Rightarrow E[\mathbf{r}, \theta]$$



Stokesian dynamics simulation

A filament is modeled as a chain of
N+1 connected spheres



Elastic translational force

$$\mathbf{F}_i = -\left.\frac{\delta E}{\delta \mathbf{r}_i}\right|_{\delta\phi=0}$$

Torque about the tangent

$$T_i = -\left.\frac{\delta E}{\delta \phi_i}\right|_{\delta\mathbf{r}=0}$$

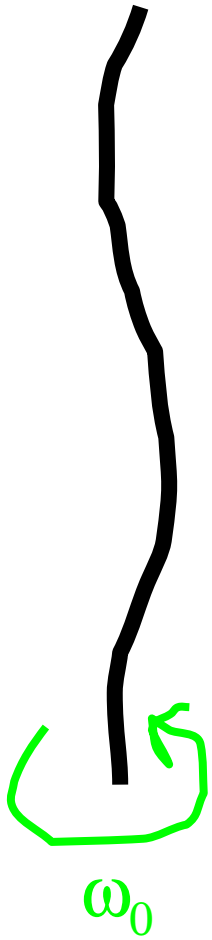
Chirico & Langowski
Biopolymers **34**, 415 (1994).

Equations of motion

$$\partial_t \mathbf{r}_i = \sum_{j=1}^{N} \mu_{ij} \cdot \mathbf{F}_j \quad \text{and} \quad \partial_t \phi_i = \mu_{r0} T_i$$

μ_{ij} : Stokeslet on Rotne-Prager level ,
no rotational hydrodynamic coupling

stiff case $L<L_p$: buckling frequency



Dynamic buckling condition (linear stability)

injected torque — bending torque

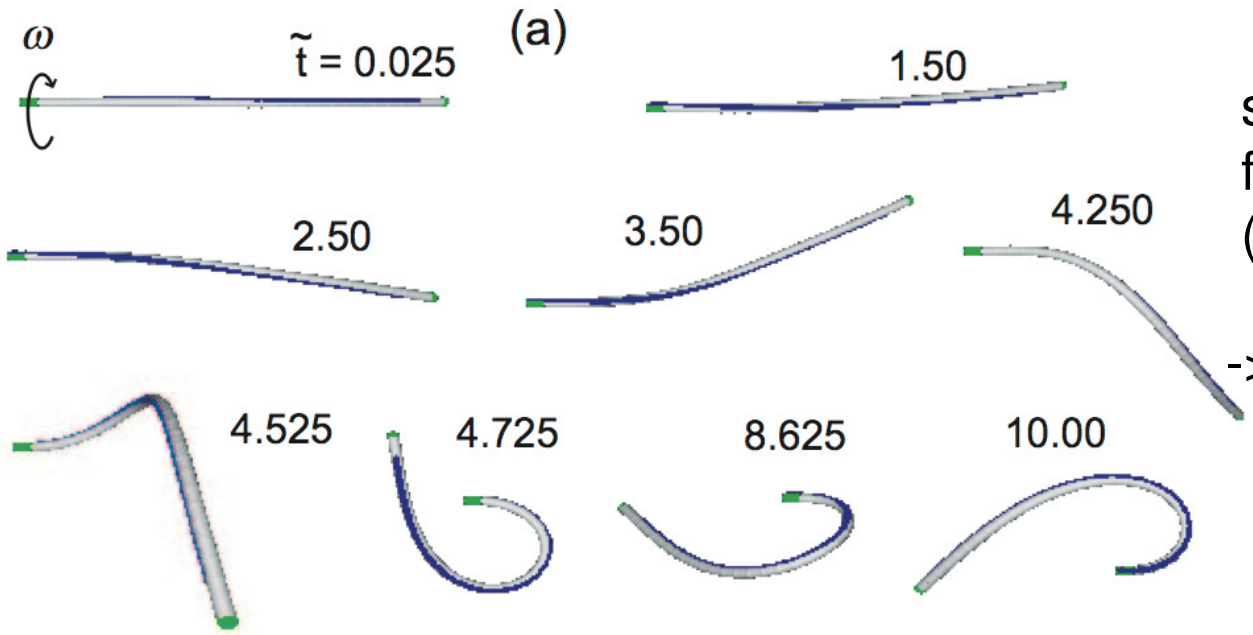
$$N_c \sim \zeta_r \omega_c L \sim A/L$$

rotational torque

$$\omega_c \sim A/\zeta_r L^2 \sim k_B T \ell_p/\zeta_r L^2$$

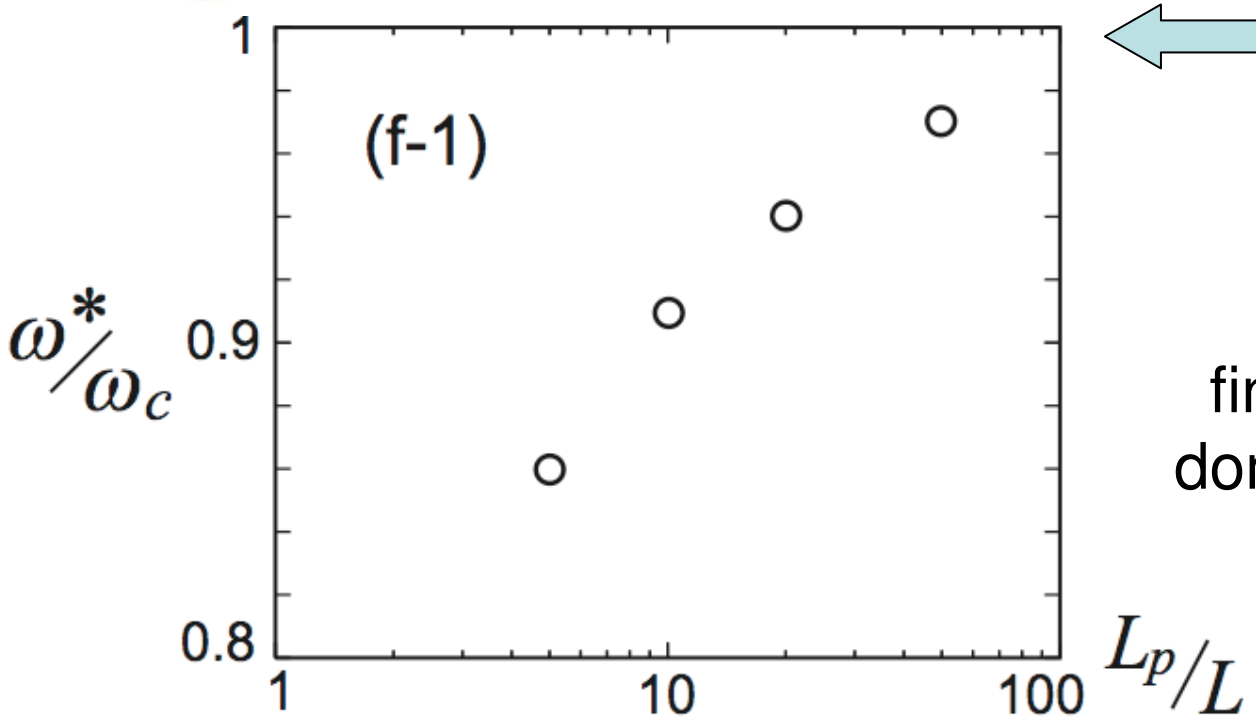
exact linear stability analysis (Powers, Goldstein 2000) :

$$\omega_c \cong 8.9A/(\zeta_r L^2)$$



simulation snapshots
for $\omega = 1.2\ \omega_C$, $L_P/L=10^3$
(Wada, RRN, EPL 2006)

-> strongly discontinuous
dynamic shape transition
from twirling to whirling



asymptotic
theoretical
result

finite-T effects
dominant as $L_P/L < 1$

Experimental realization
(Powers et al, 2008)

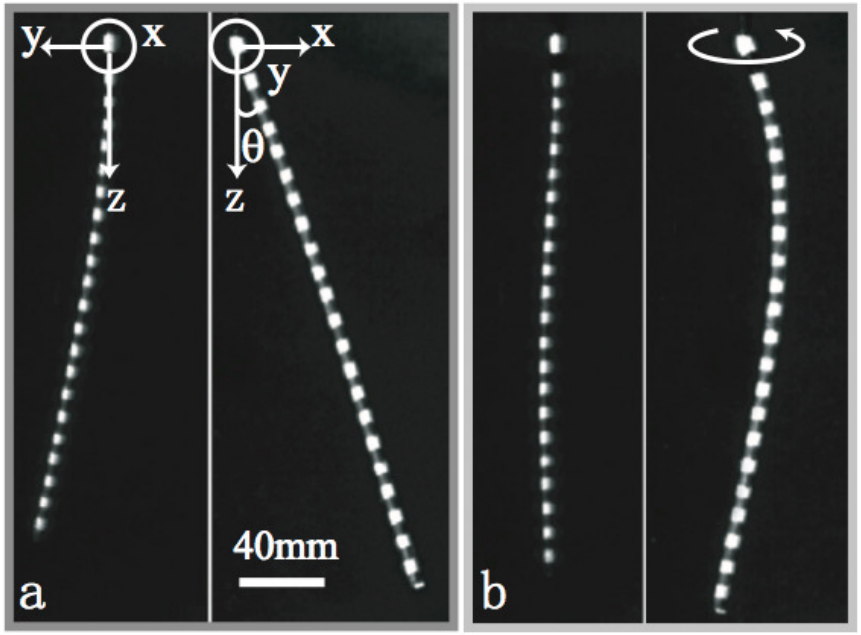
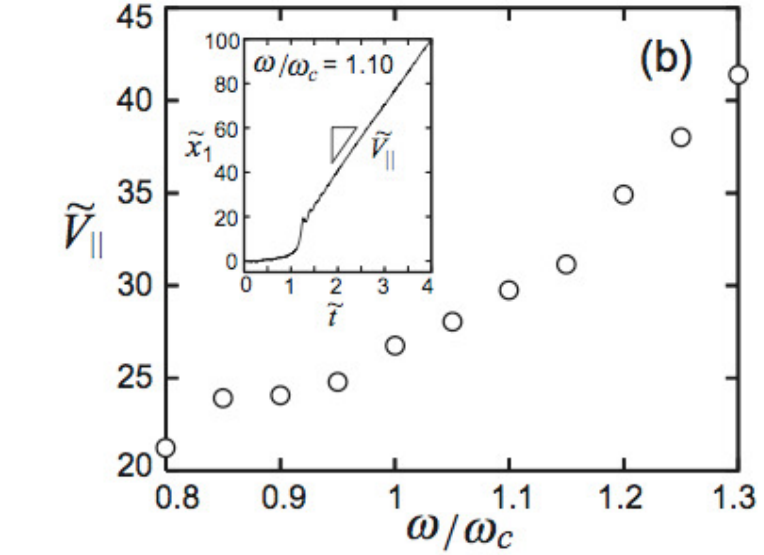
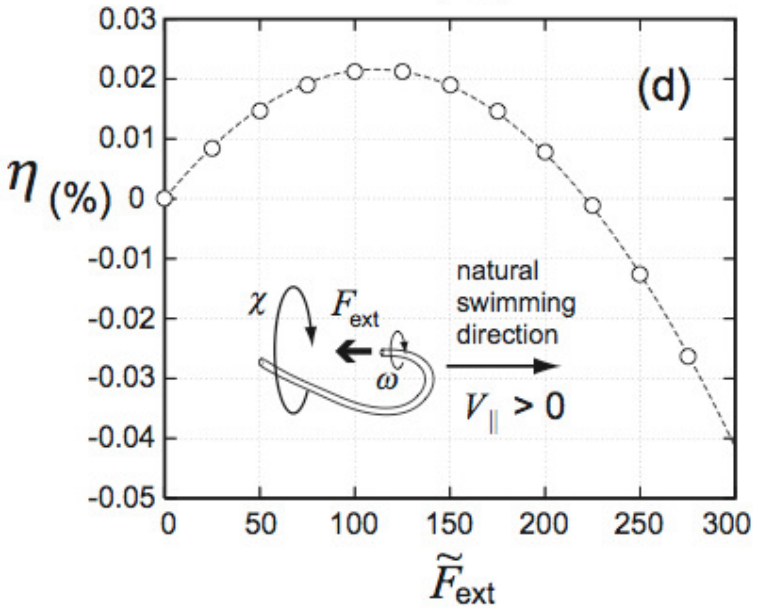


FIG. 1: Orthogonal images of steady-state shapes of rotatin
rod with torque just below (a) and just above (b) the critic
torque. The motor (not shown) is at the top, with rotatio
axis along z. Gravity points down. In (a) and (b), the le

propulsion possible …





but highly inefficient

Now flexible limit, slow rotation $L/L_P = 10 \quad \omega/\omega_c = 0.2$

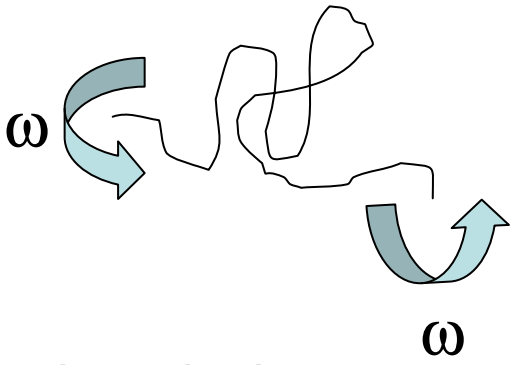
Zur Anzeige wird der QuickTime™ Dekompressor „YUV420 codec“ benötigt.

fast rotation

$$L/L_P = 10 \quad \omega/\omega_c = 40$$

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

three dissipation channels

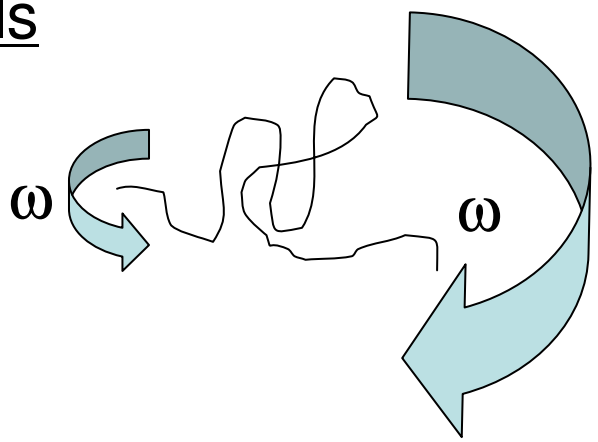


1) axial spinning

$P_{AS} = \eta\, La^2\, \omega^2$

steady state :

$$\frac{d}{dt} Lk = \frac{d}{dt}(Tw + Wr) = 0$$



2) solid-body rotation

$P_{SB} = \eta\, R^3\, \omega^2$

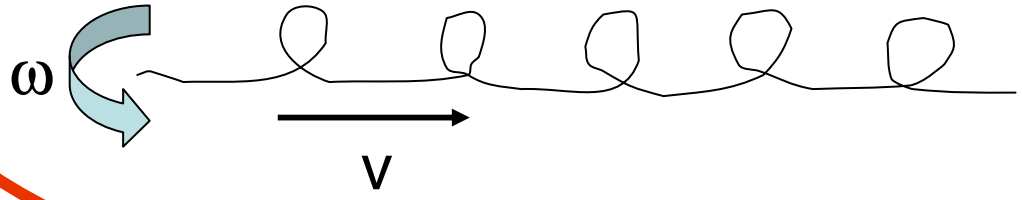
--> influx/outflux of twist Tw and writhe Wr must cancel

minimal dissipation for

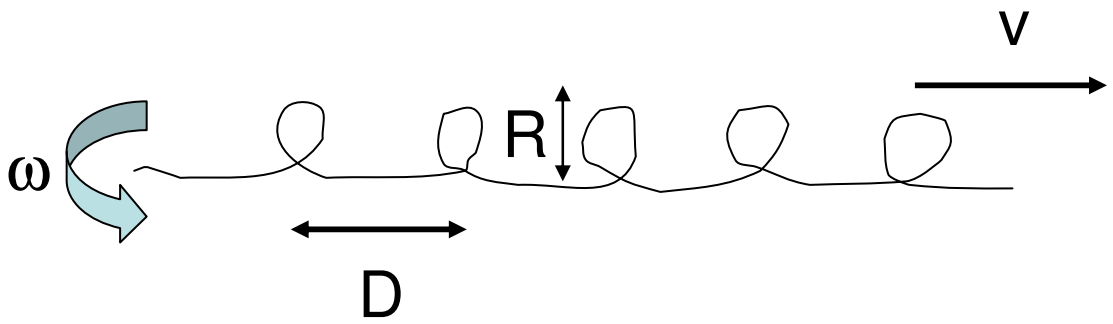
$\omega > \omega^*$

3) plectoneme diffusion

$P_{PD} = \eta^{1/3}\, L^{1/3}\, \omega^{4/3}\, l_P^{4/3}$



The plectoneme diffusion mechanism



elastic energy to produce one plectoneme (in units of k_BT) : l_P/R
one plectoneme per full turn -> power dissipation $P_1 = \omega\, l_P/R$

excess length $2\pi R$ is needed at forced end at frequency ω
-> whole chain is moving at velocity $R\,\omega$ –> friction force $R\omega\,\eta\,L$
power dissipation $P_2 = R^2\,\omega^2\,\eta\,L$

power consumption due to plectomene motion is irrelevant
-> minimize P_1+P_2 with respect to R

$$P_{PD} = \eta^{1/3}\, L^{1/3}\, \omega^{4/3}\, l_P^{4/3}$$

$$\text{rot. friction } \Gamma = P/\omega^2 = \eta^{1/3}\, L^{1/3}\, \omega^{-2/3}\, l_P^{4/3}$$

critical frequency from comparing P_{PD} and P_{AS} -> $\omega^* = l_P/(a^2L^2\,\eta)$

rotational friction (related to replication/transcription efficiency)

$$\frac{\Gamma_r}{\zeta_r L} \sim \begin{cases} 1 \\ \left(\frac{L^2}{a^2}\right)^{1/3} \left(\frac{\omega_0}{\omega_c}\right)^{-2/3} \end{cases}$$

axial spinning regime $\Gamma_r \propto L$

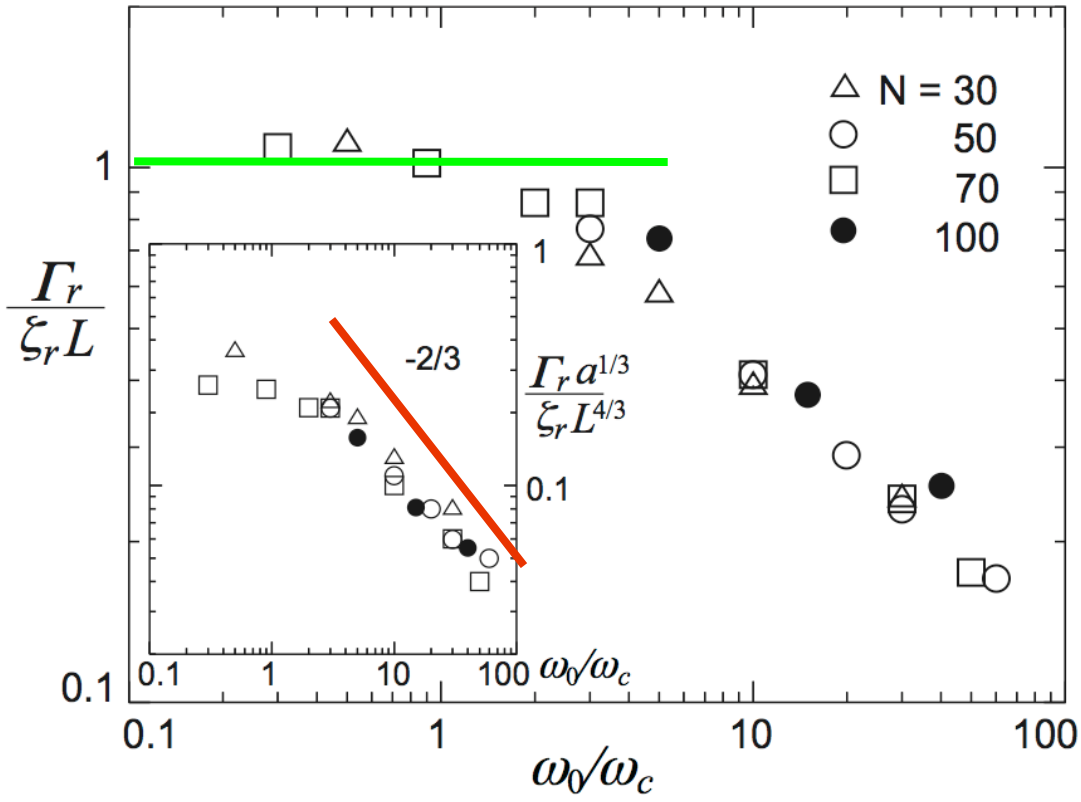
plectoneme diff. regime

$$\Gamma_r \propto L^{1/3} \omega_0^{-2/3}$$

in plectoneme diff. regime
torque $N_0 = \omega_0 \Gamma_r$ and
power $P = \omega_0 N_0$
goes as $L^{1/3}$

no problem of rotating very long DNA in replication or transcription !

critical torques reached easily by anchoring DNA !



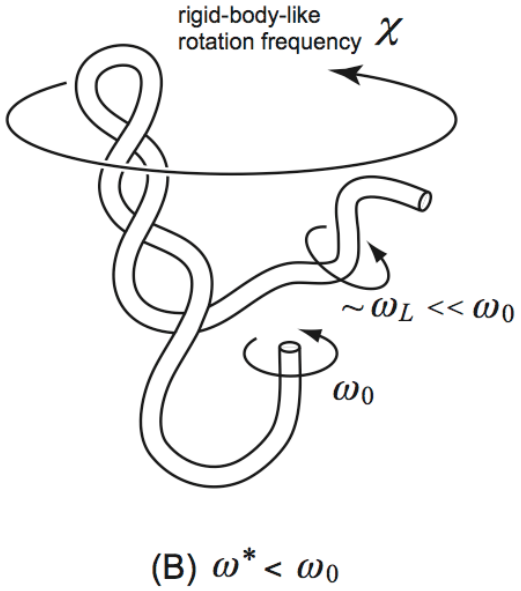
rotation at free end (biologically irrelevant)

$$\frac{\omega_L}{\omega_c} \sim \begin{cases} \dfrac{\omega_0}{\omega_c} & (\omega_0 < \omega^*) \\ \left(\dfrac{LL_p}{a^2}\right)^{1/3} \left(\dfrac{\omega_0}{\omega_c}\right)^{1/3} & (\omega_0 > \omega^*) \end{cases}$$

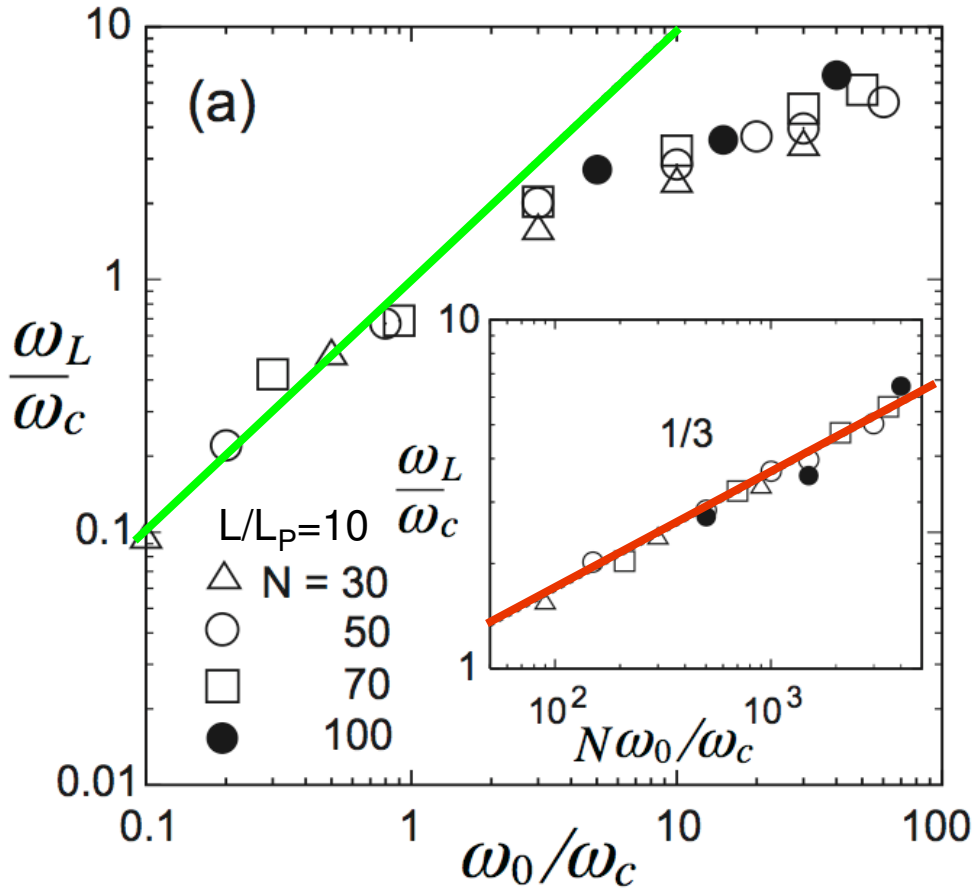
axial spinning regime

$$\omega_L \propto \omega_0^{1/3} / L$$

plectoneme diffusion regime



(B) $\omega^* < \omega_0$



total twist (related to attack probability of topo-isomerase)

$$|Tw| \sim \begin{cases} 0.71 \dfrac{A}{C} \dfrac{\omega_0}{\omega_c} \\ \dfrac{A}{C} \left(\dfrac{L L_p}{a^2} \right)^{1/3} \left(\dfrac{\omega_0}{\omega_c} \right)^{1/3} \end{cases}$$

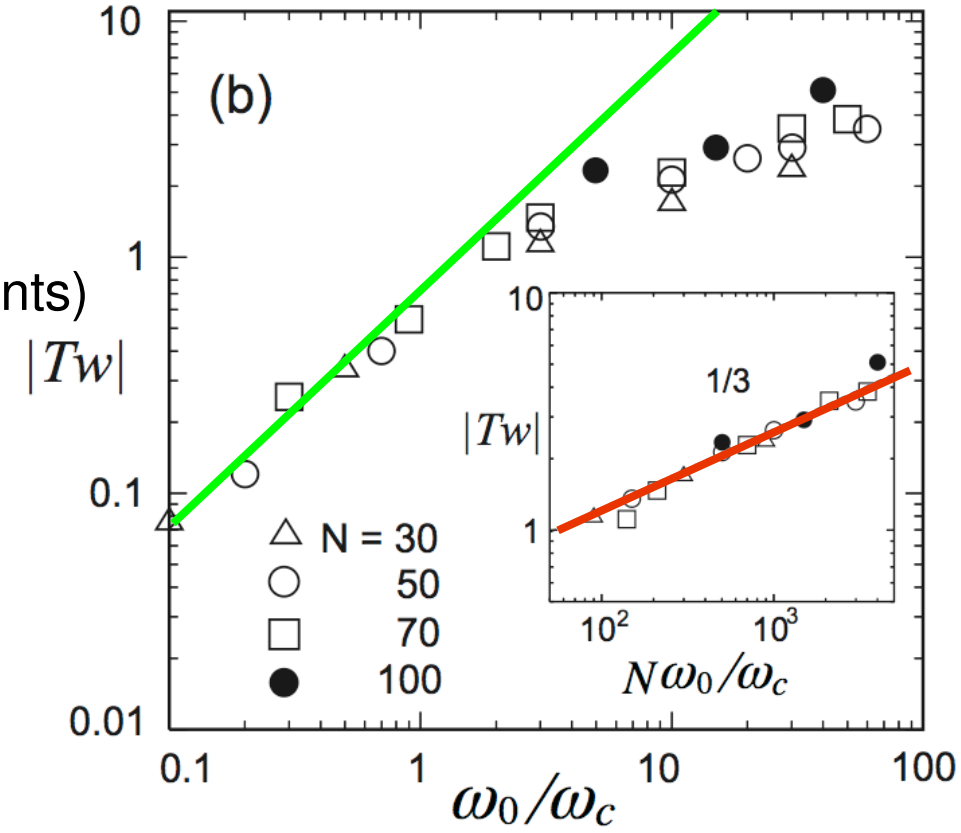
axial spinning regime

$$Tw/L \propto \omega_0 L$$

solid-body rotation regime

$$Tw/L \propto \omega_0^{1/3} L^{1/3}$$

twist density localized close
to twist-injection in
plectoneme-diffusion regime
-> twist-sensitive topo-isomerase
will locally attack (as in experiments)



main result: plectonemes are formed in steady state
while rotation friction (power) is reduced !

in plectoneme-diffusion regime:

- DNA twist is confined to a small region where plectonemes are created

- plectonemes are formed continuously (interactions with histones ?)

- power dissipation quite small !