DNA supercoiling: plectonemes or curls ?

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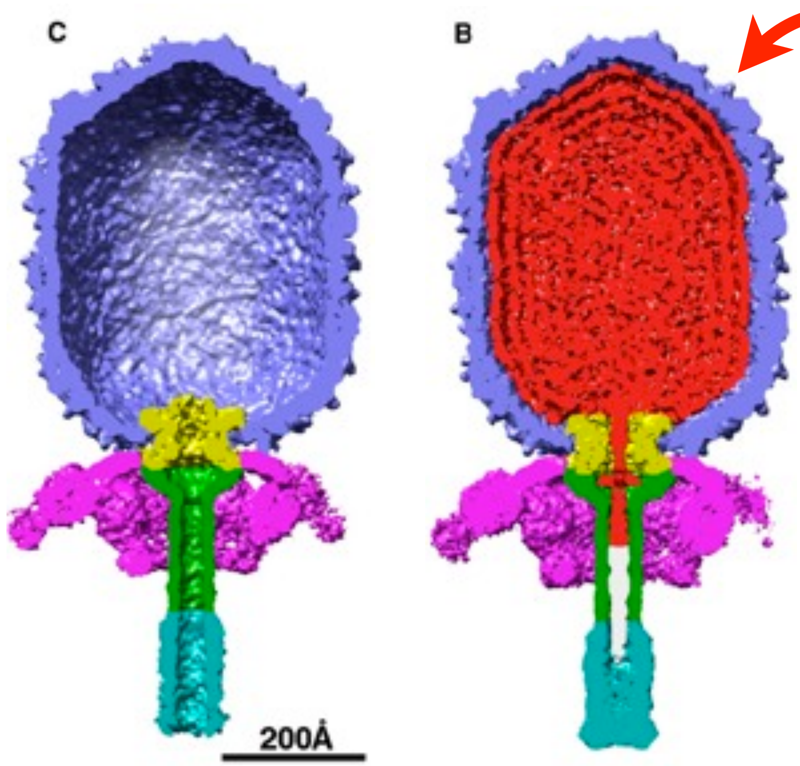
Why study DNA mechanical properties ?

mechanical properties influence biology of the cell

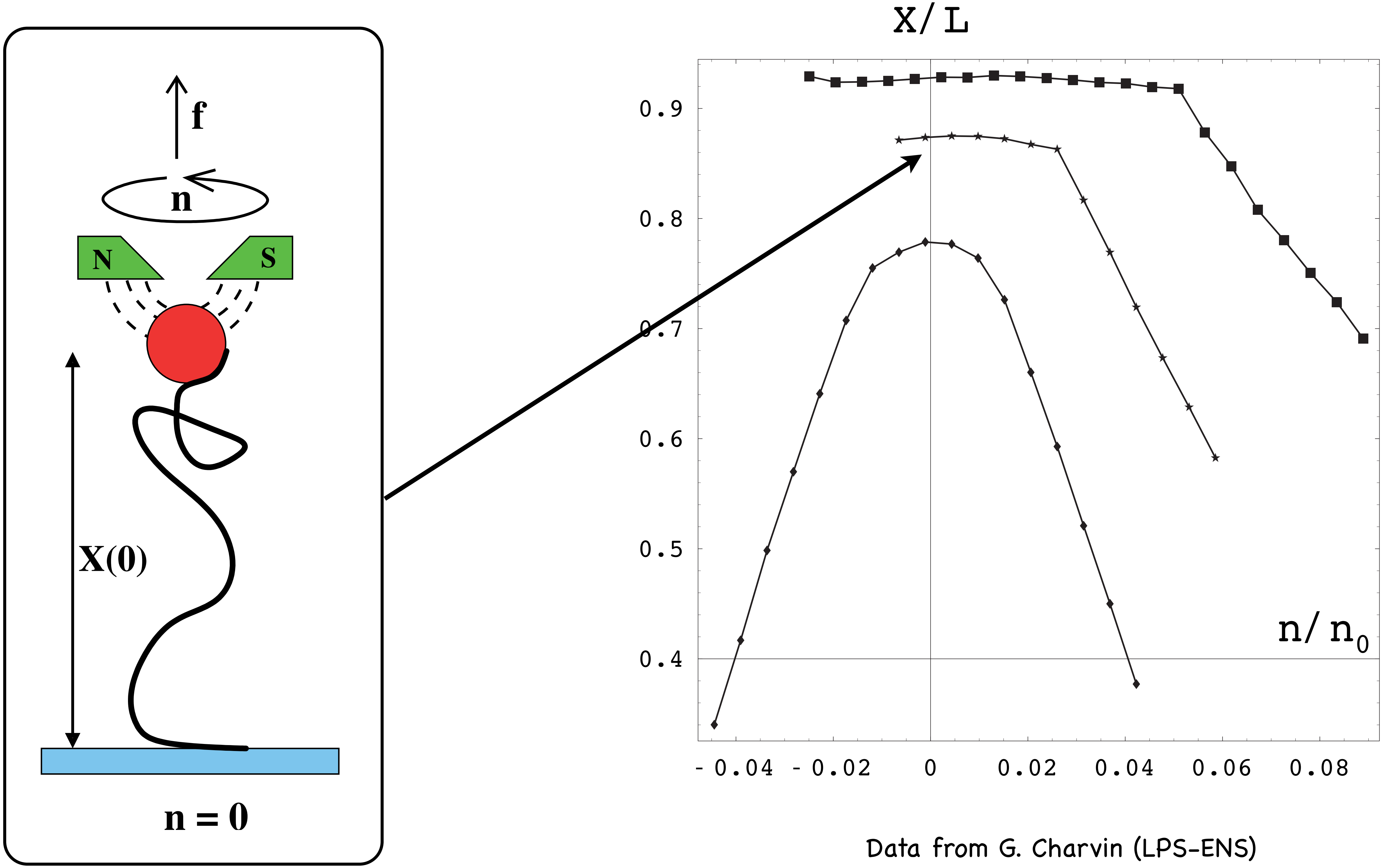
- 1 meter of DNA in a 10 micron wide nucleus
- ejection from viral capside
- transcription (RNApolymerase is torque dependent)
- protein binding is strain dependent, or induces strain on DNA
- chromatin compaction/decompaction (cell division)



20kbp dsDNA (6800nm) in 40nm wide capside

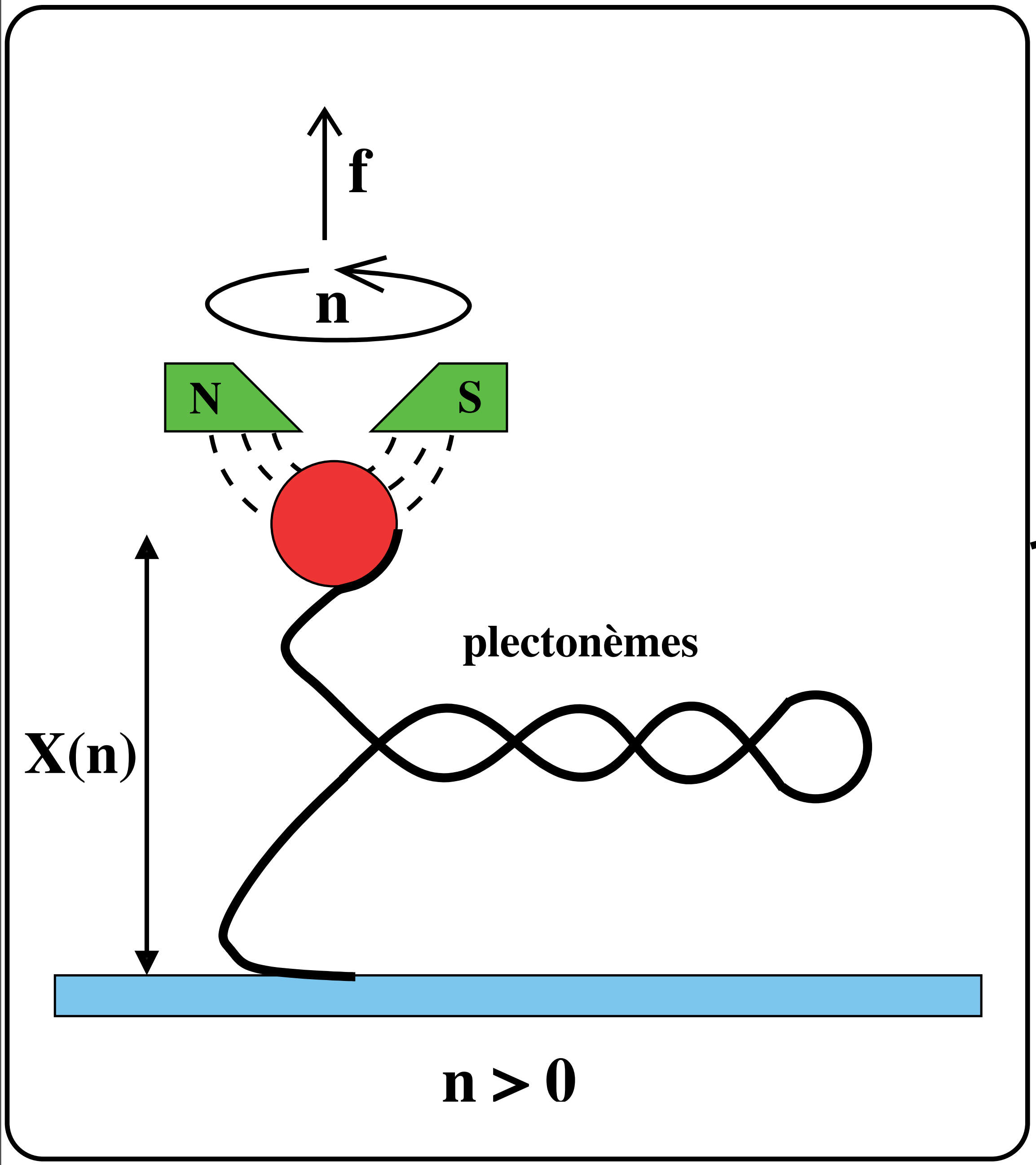
Tang et al (Structure) 2008

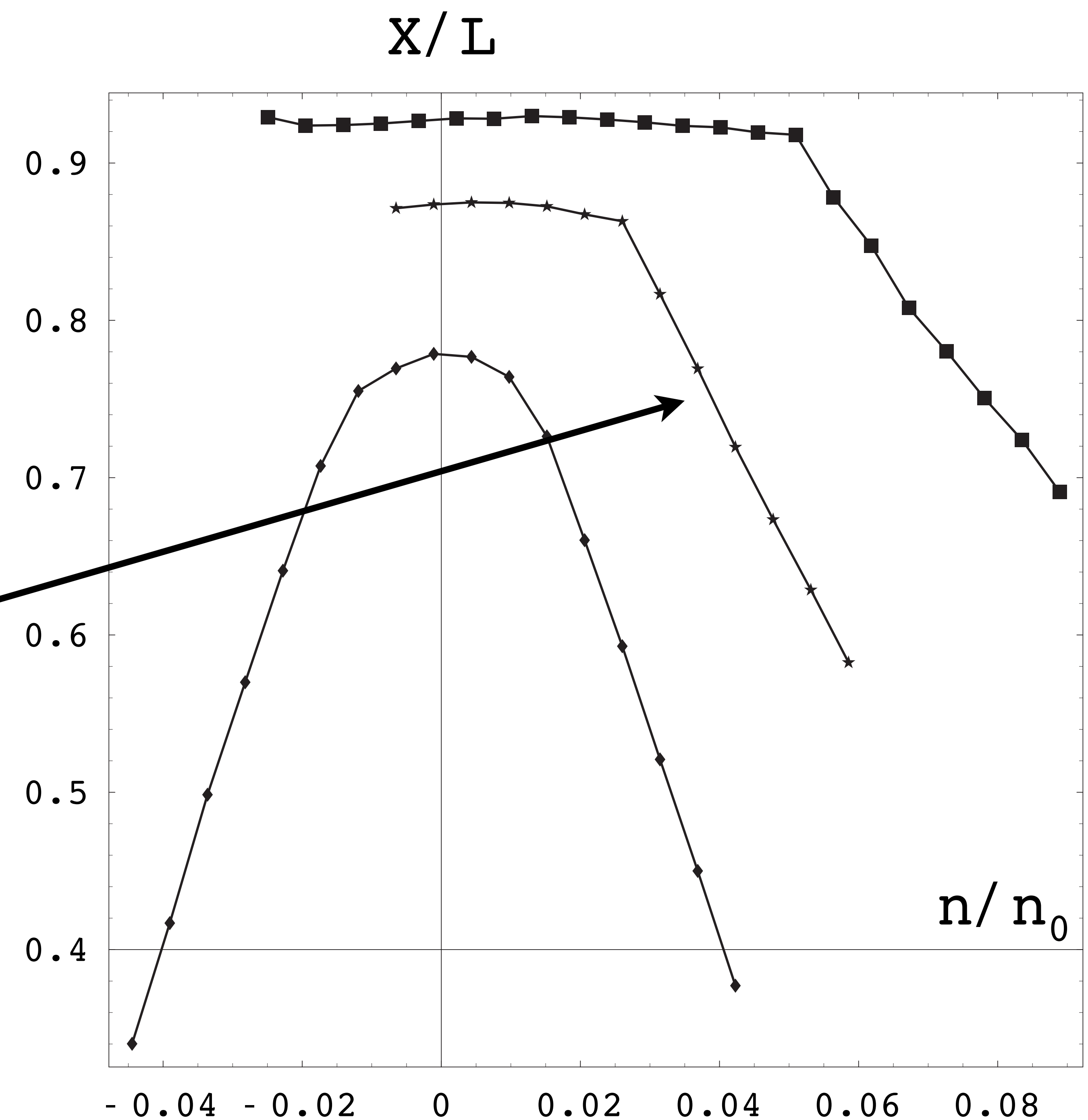
Pulling and twisting DNA



Data from G. Charvin (LPS-ENS)

Pulling and twisting DNA





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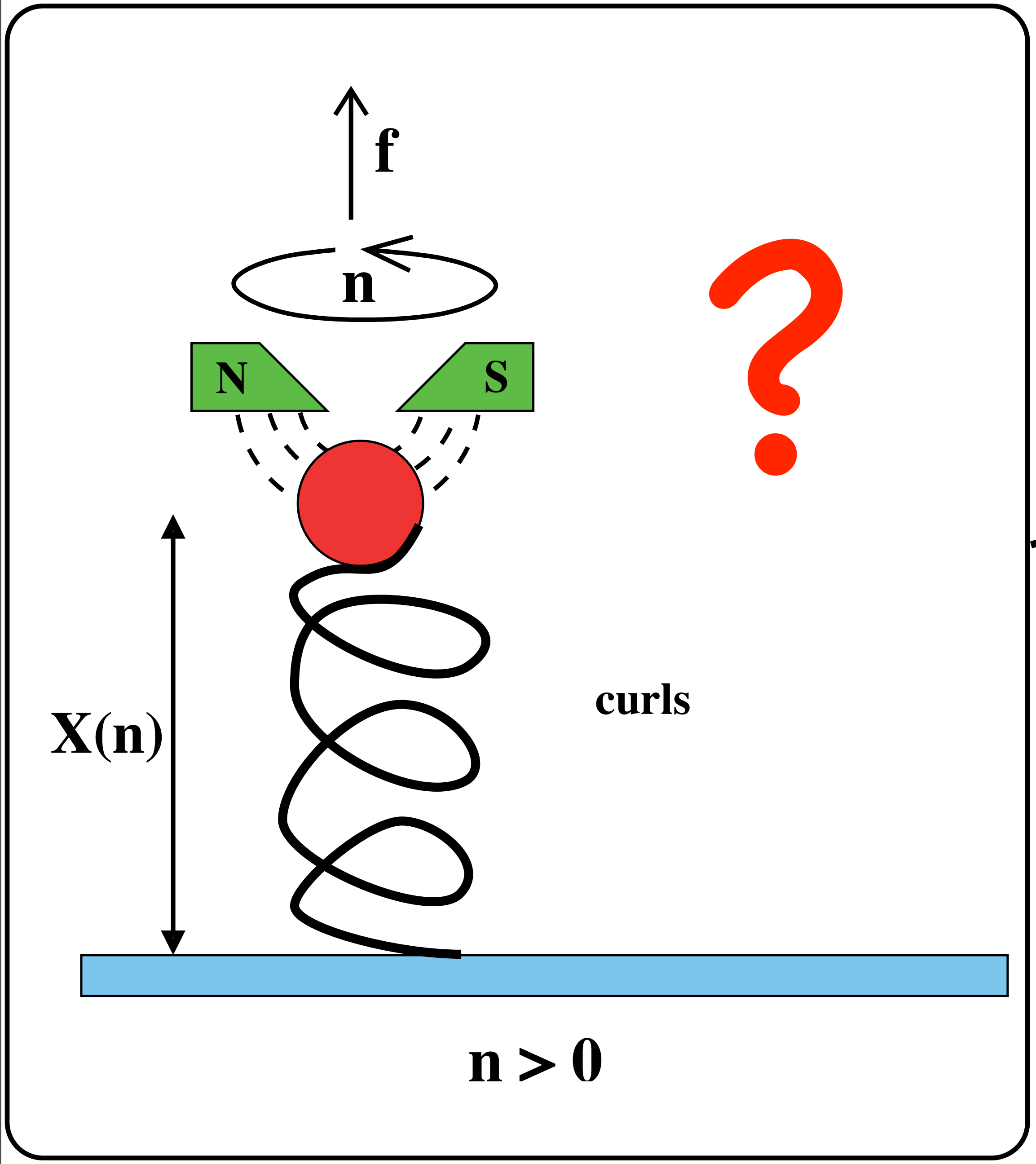
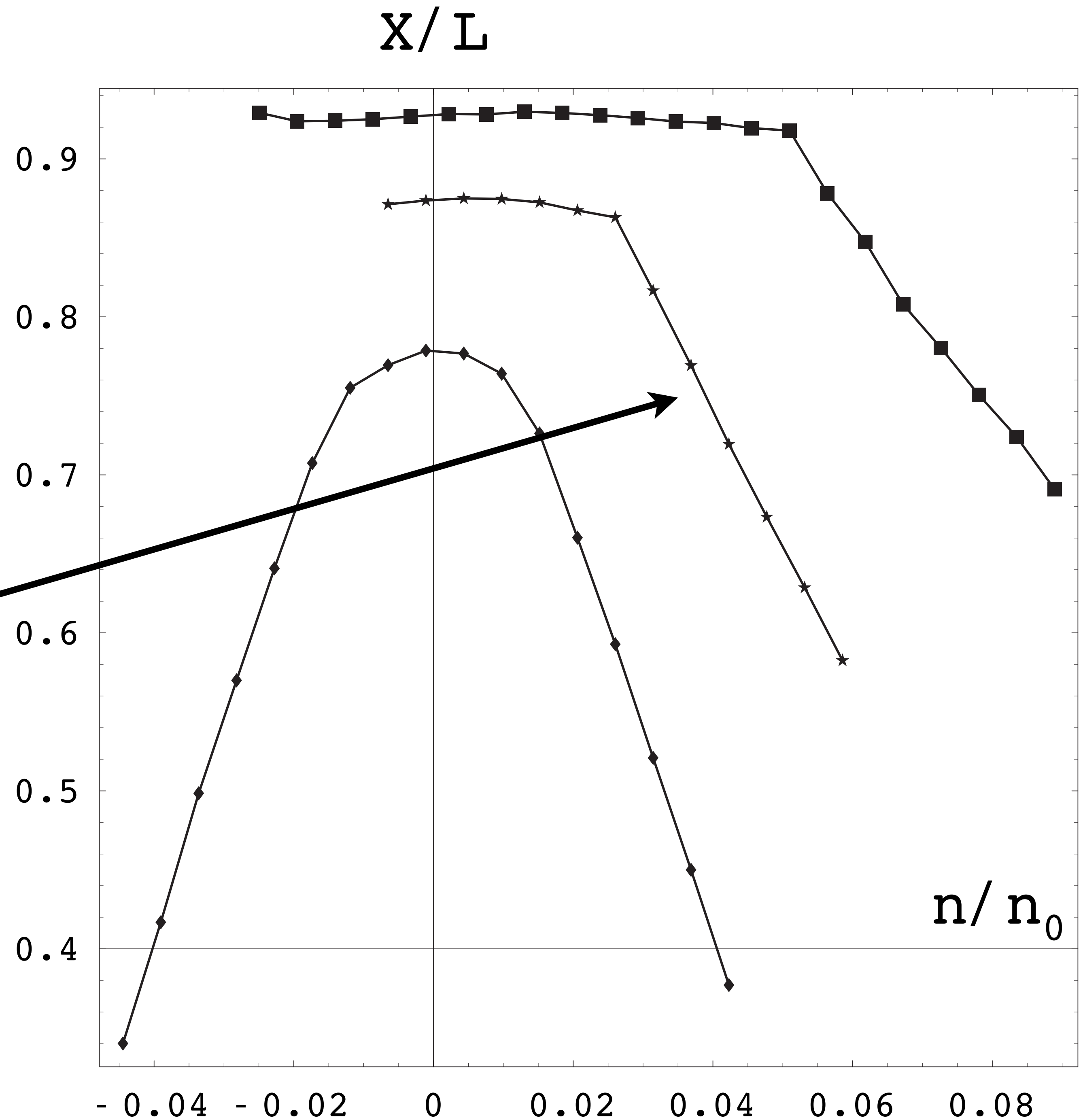
Pulling and twisting DNA

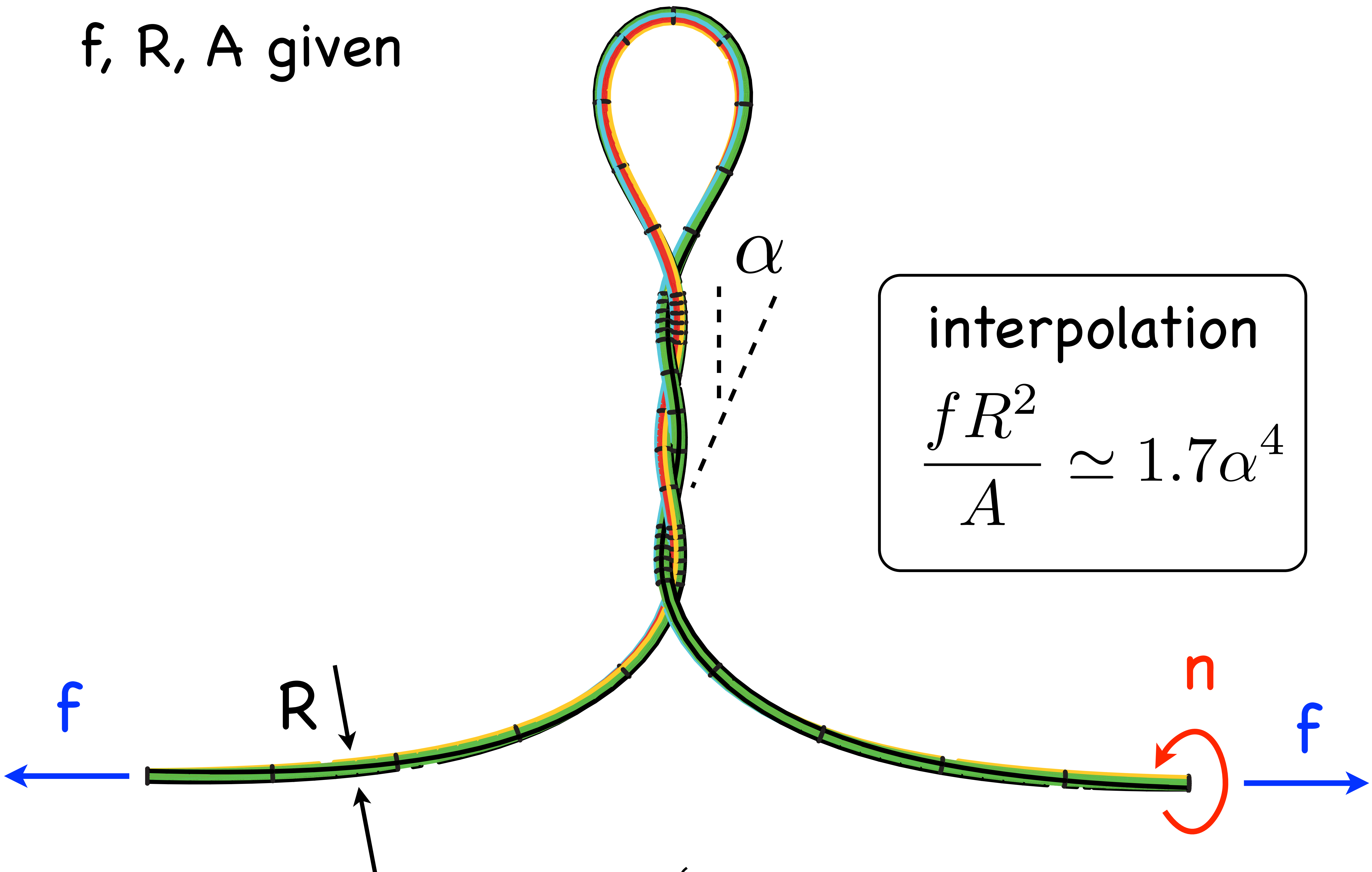




Data from G. Charvin (LPS-ENS)

Numerical simulations : twisted rod with self-contact

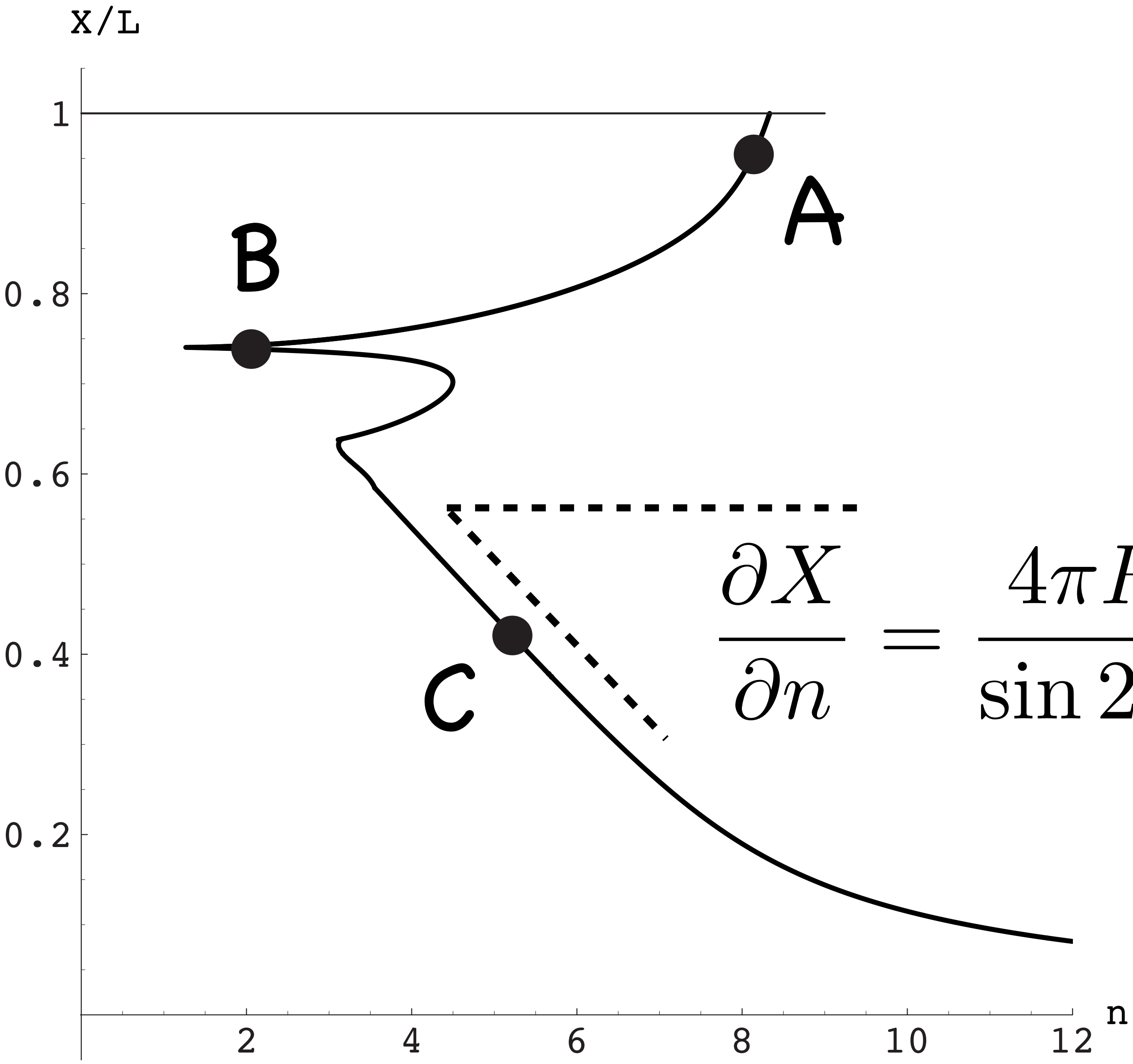
f, R, A given



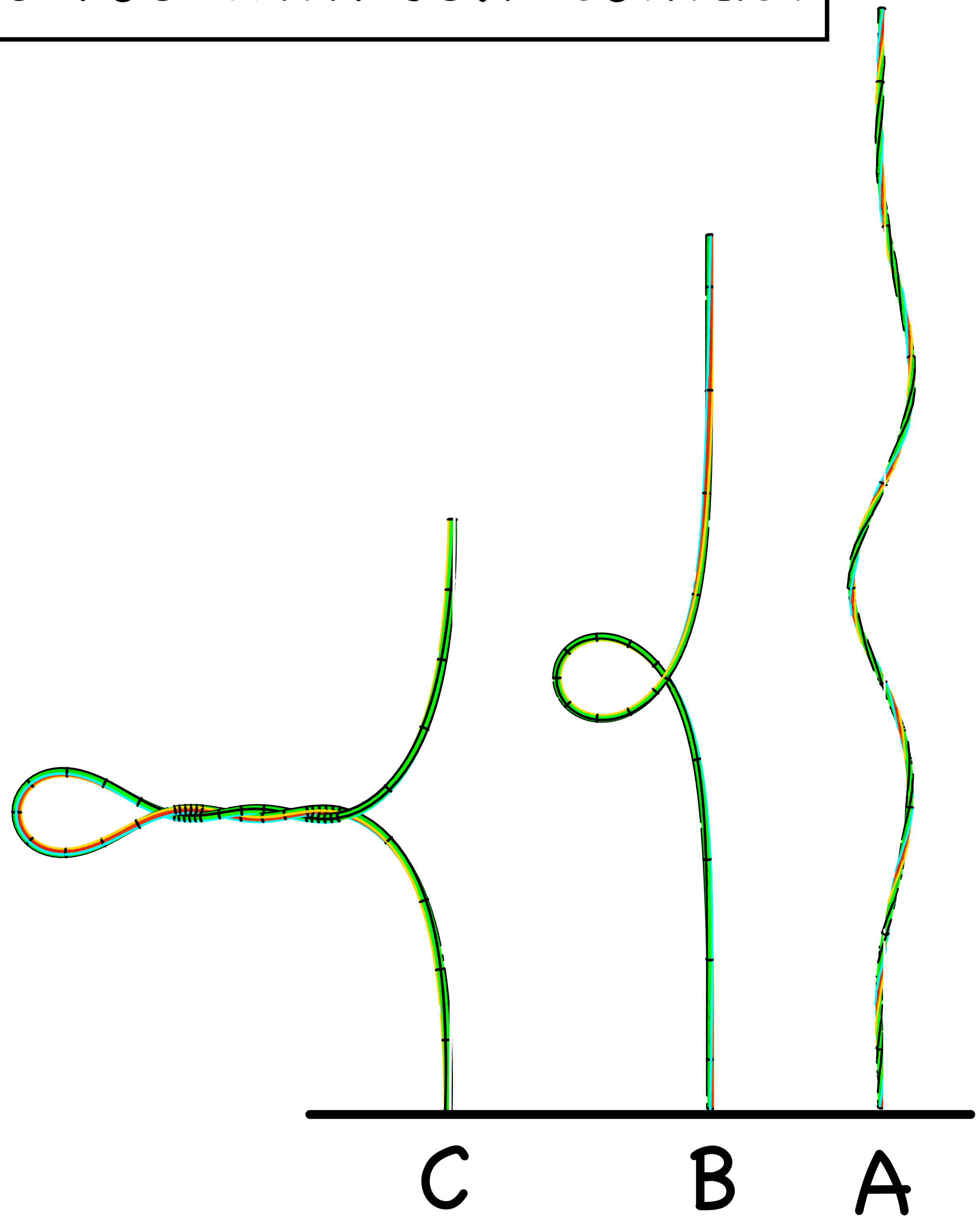
interpolation

$$\frac{fR^2}{A} \simeq 1.7\alpha^4$$

Numerical simulations : twisted rod with self-contact



$$\frac{\partial X}{\partial n} = \frac{4\pi R}{\sin 2\alpha}$$



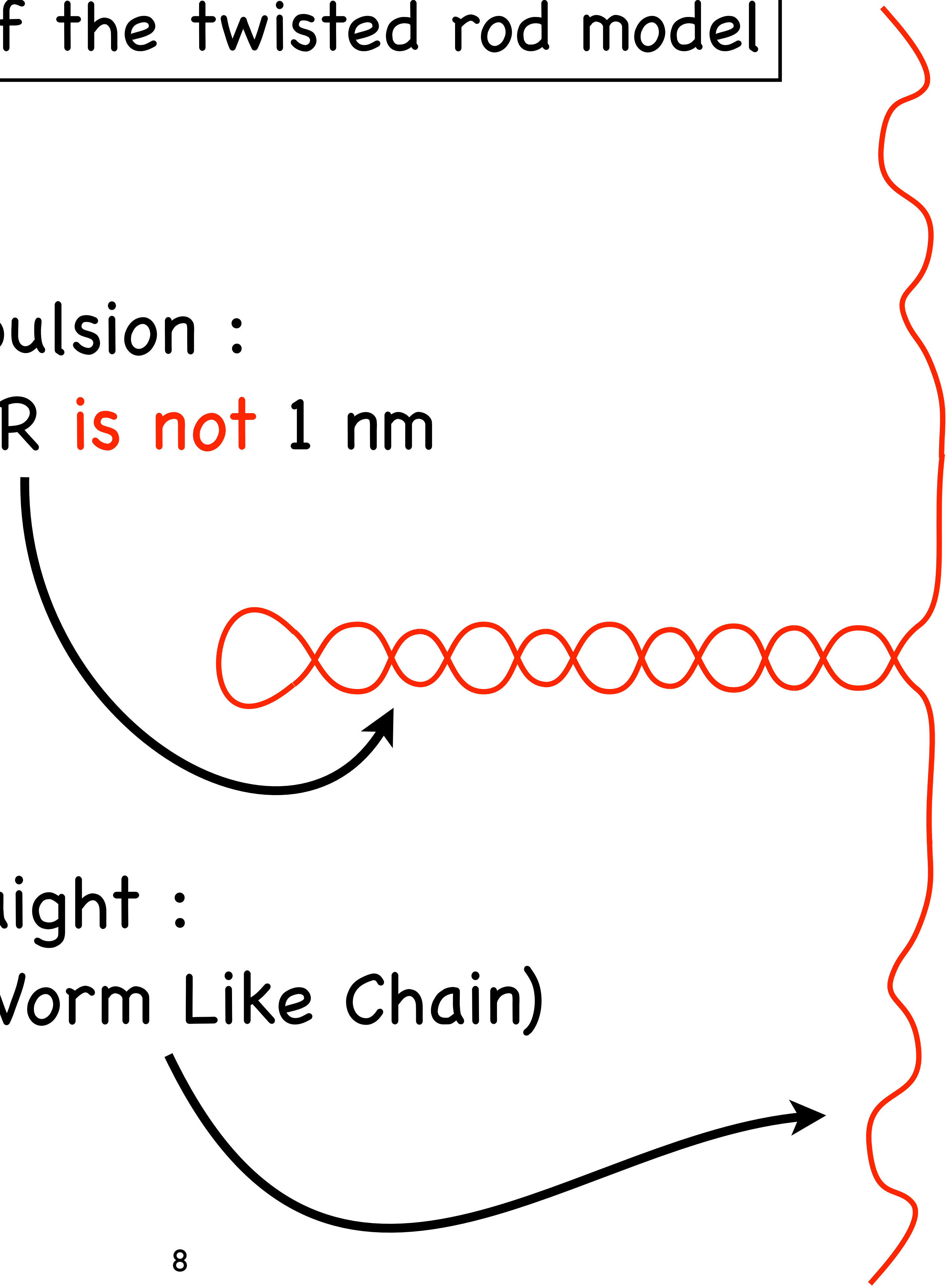
(based on Swigon+Coleman model for contact in Kirchhoff rods)

S. Neukirch, "Extracting DNA ... ", Phys. Rev. Lett. **93** (2004)

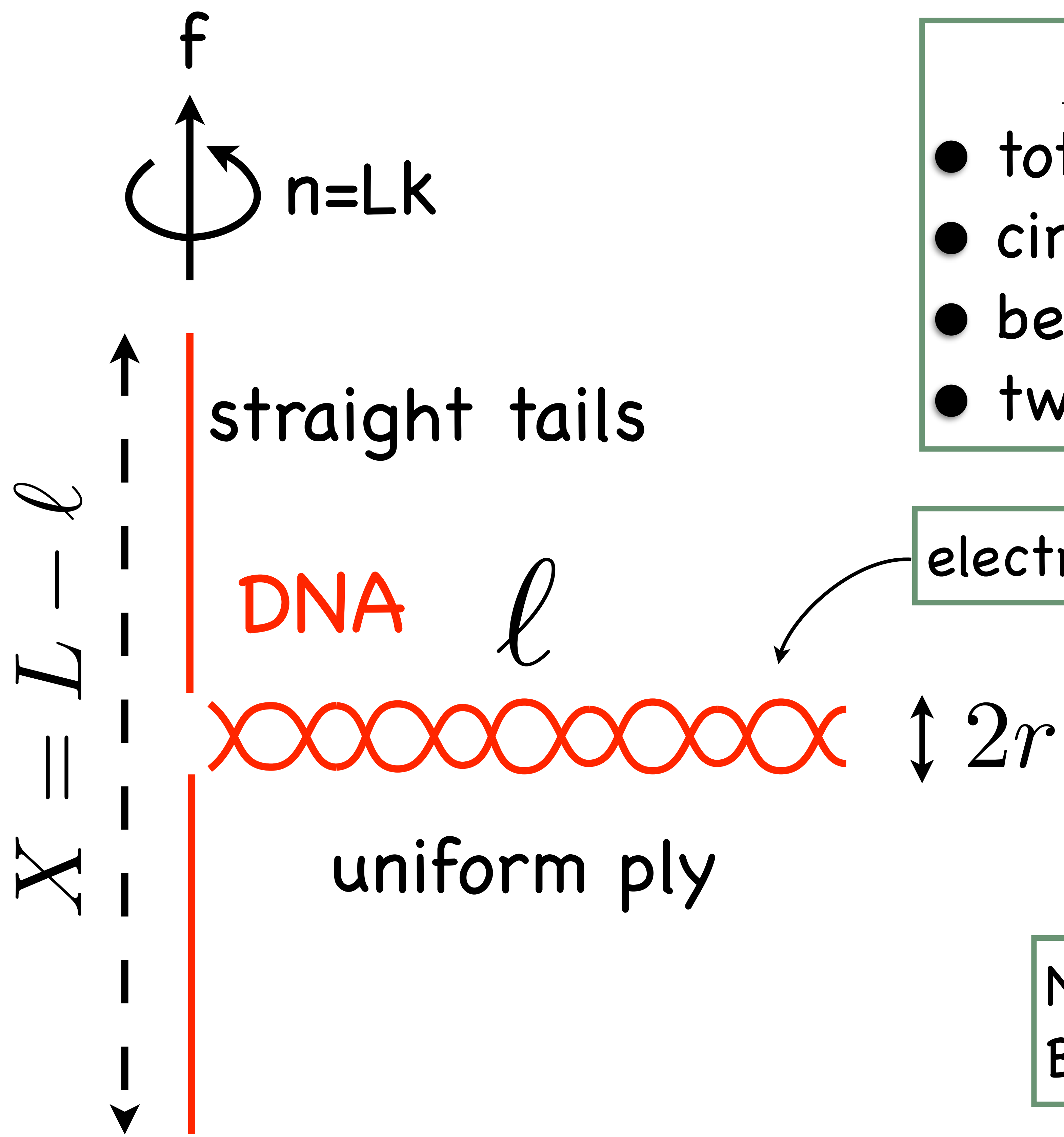
Limitations of the twisted rod model

1. Electrostatics repulsion :
supercoiling radius R is not 1 nm

2. Tails are not straight :
«disorded walk» (Worm Like Chain)



Analytical model with electrostatics repulsion



<u>Elastic rod</u> with :

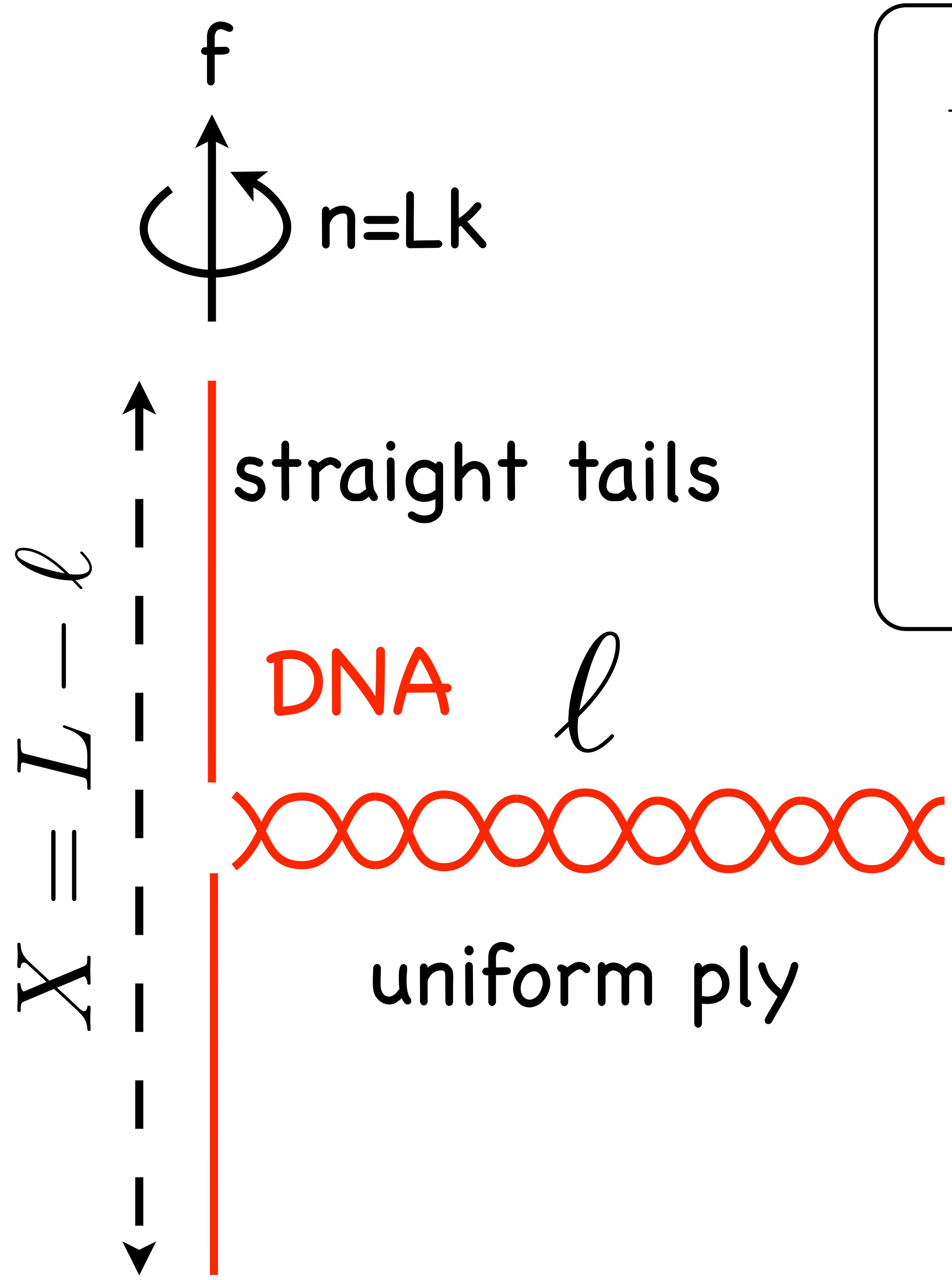
- total length L
- circular cross-section r_0
- bending rigidity A
- twist rigidity C

electrostatic repulsion: $U(r, \alpha)$

$r \neq r_0$

N. Clauvelin et al,
Biophysical Journal (2009)

Analytical model with electrostatics repulsion



$$
\begin{aligned}
V &= \frac{1}{2} A \frac{\sin^4 \alpha}{r^2} \ell && \text{bending} \\
&+ \frac{1}{2} C \tau^2 L && \text{twisting} \\
&+ U(R, \alpha) \ell && \text{electro} \\
&- f X && \text{ext. force}
\end{aligned}
$$

with constraint:

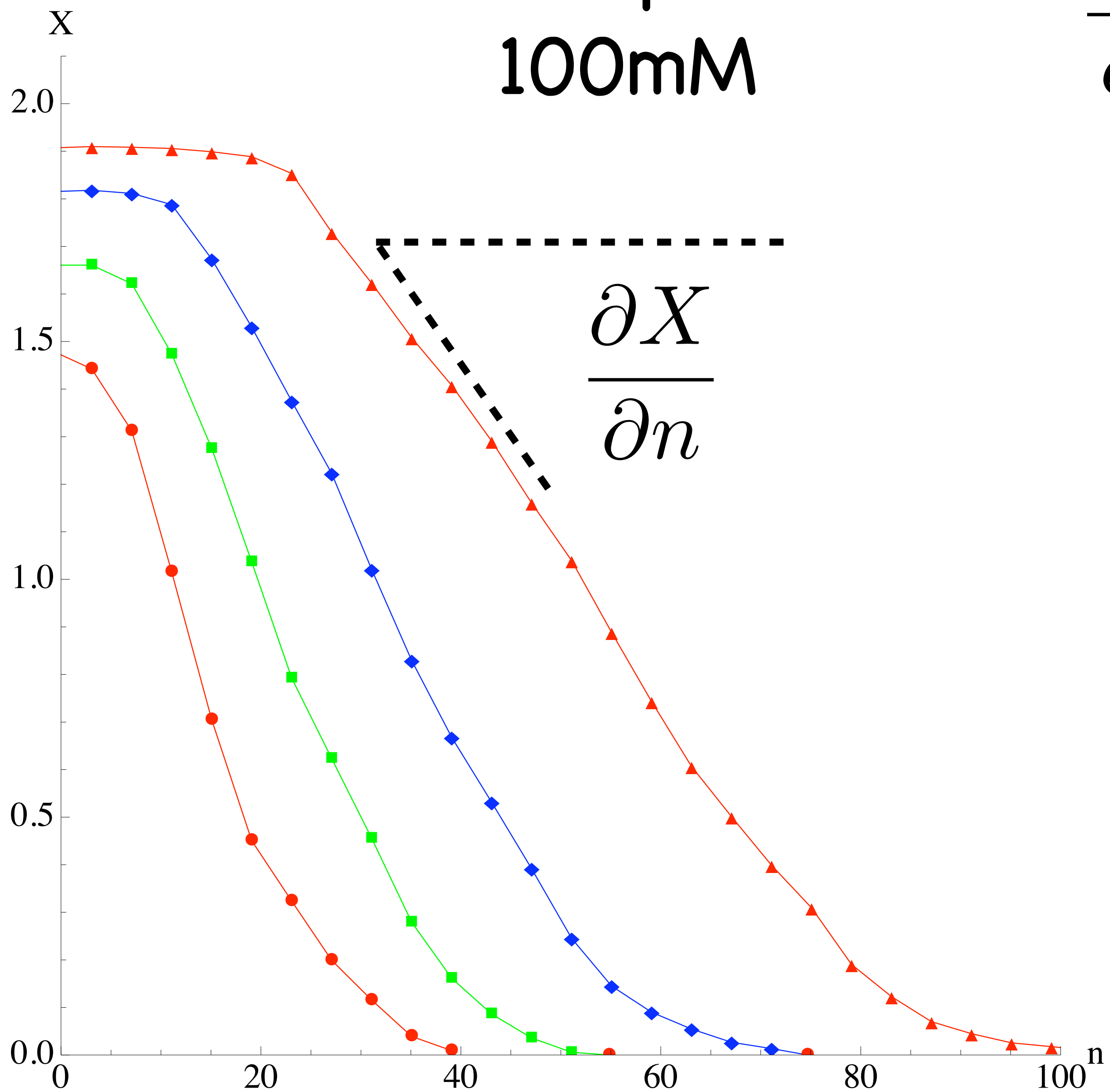
$$n = Lk = \frac{1}{2\pi} \left(\tau L + \frac{\sin 2\alpha}{2r} \ell \right)$$

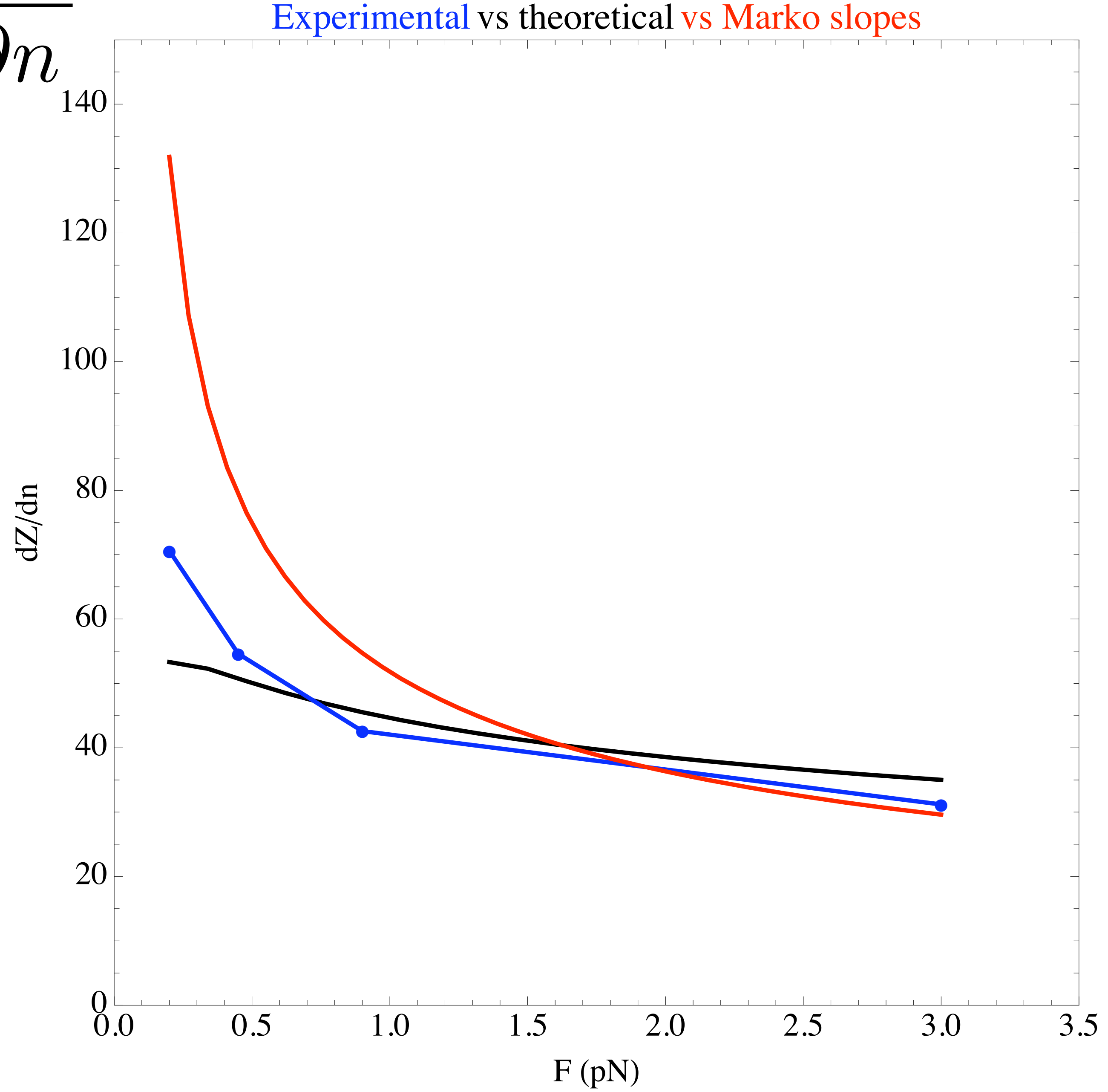
minimize V => (α, r, τ, ℓ)

Analytical model with electrostatics repulsion : results

6kbp
100mM

$$\frac{\partial X}{\partial n}$$

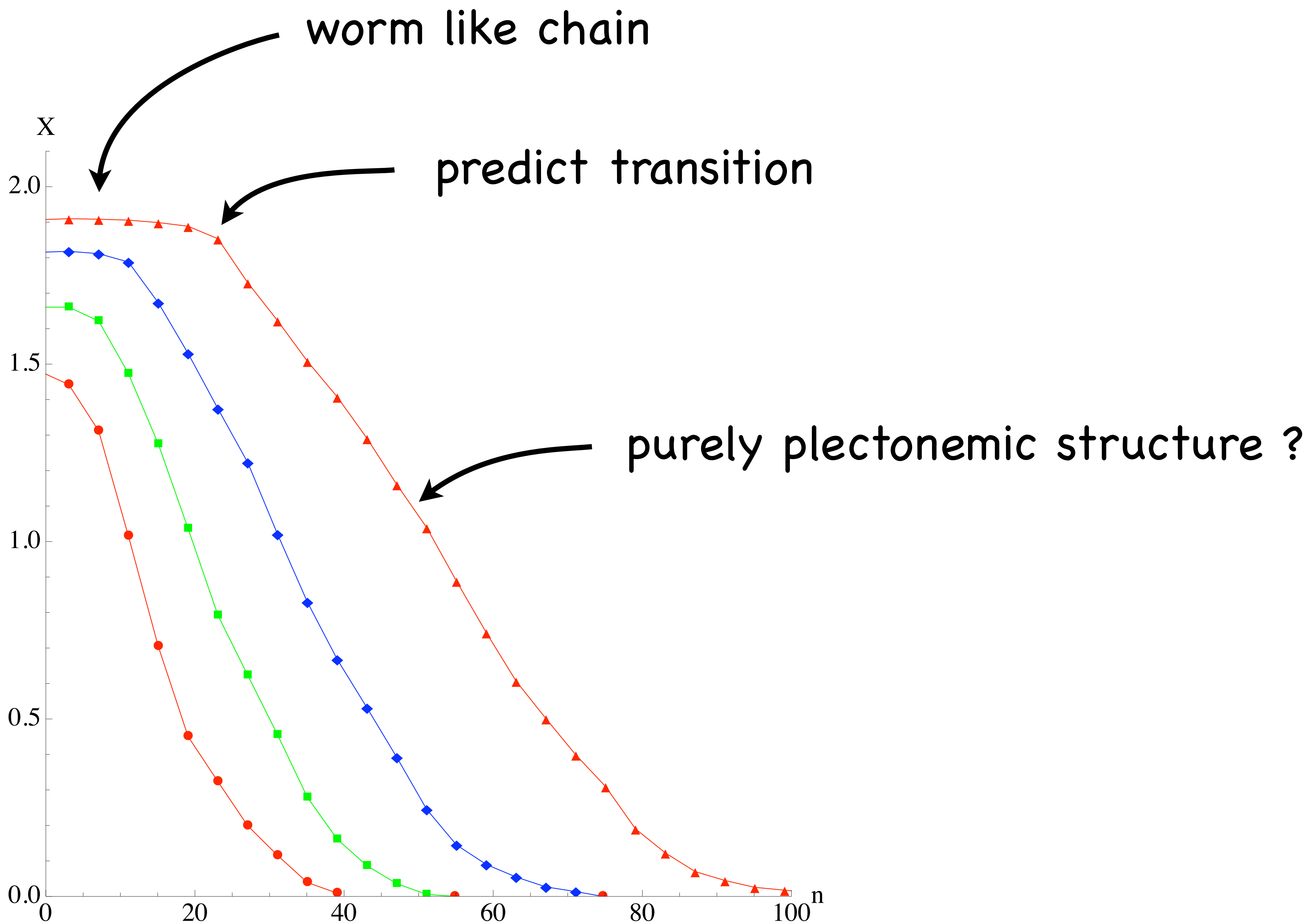




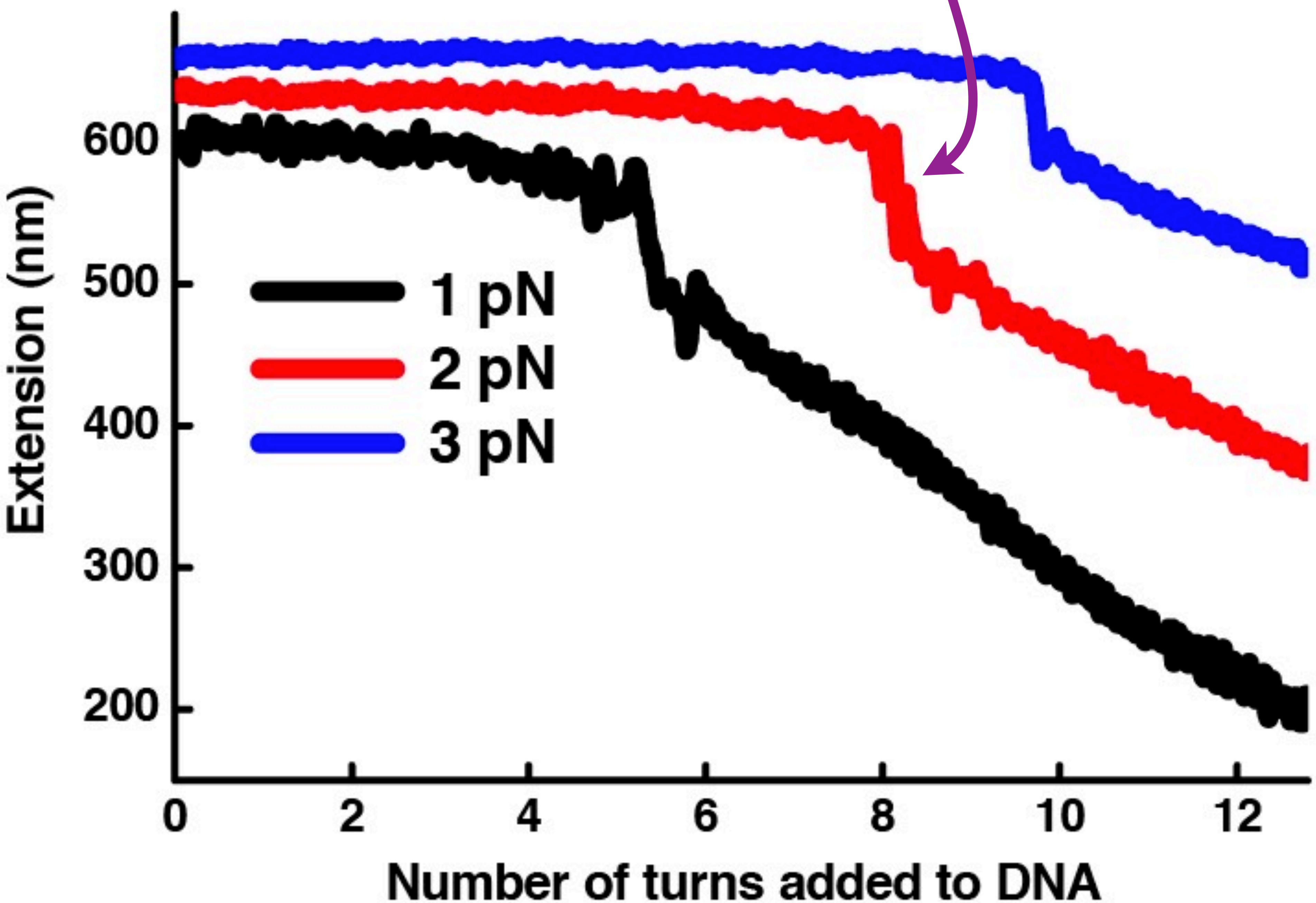
Data from G. Charvin (LPS-ENS)

J. Marko, "Torque and dynamics of linking number ...", Phys. Rev. E. (2007)

Statistical mechanics model



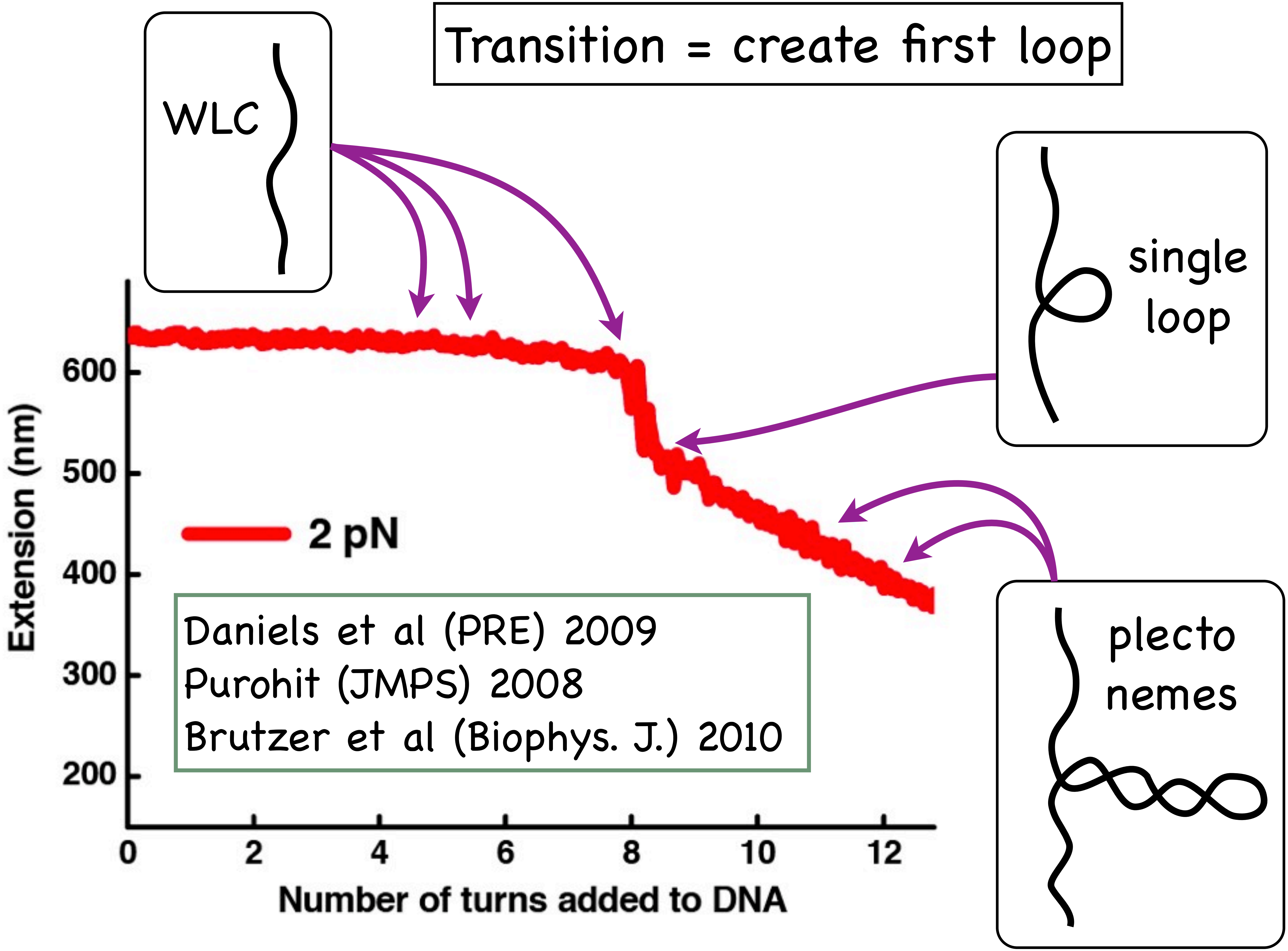
Abrupt transition



2.2 kbp
150 mM

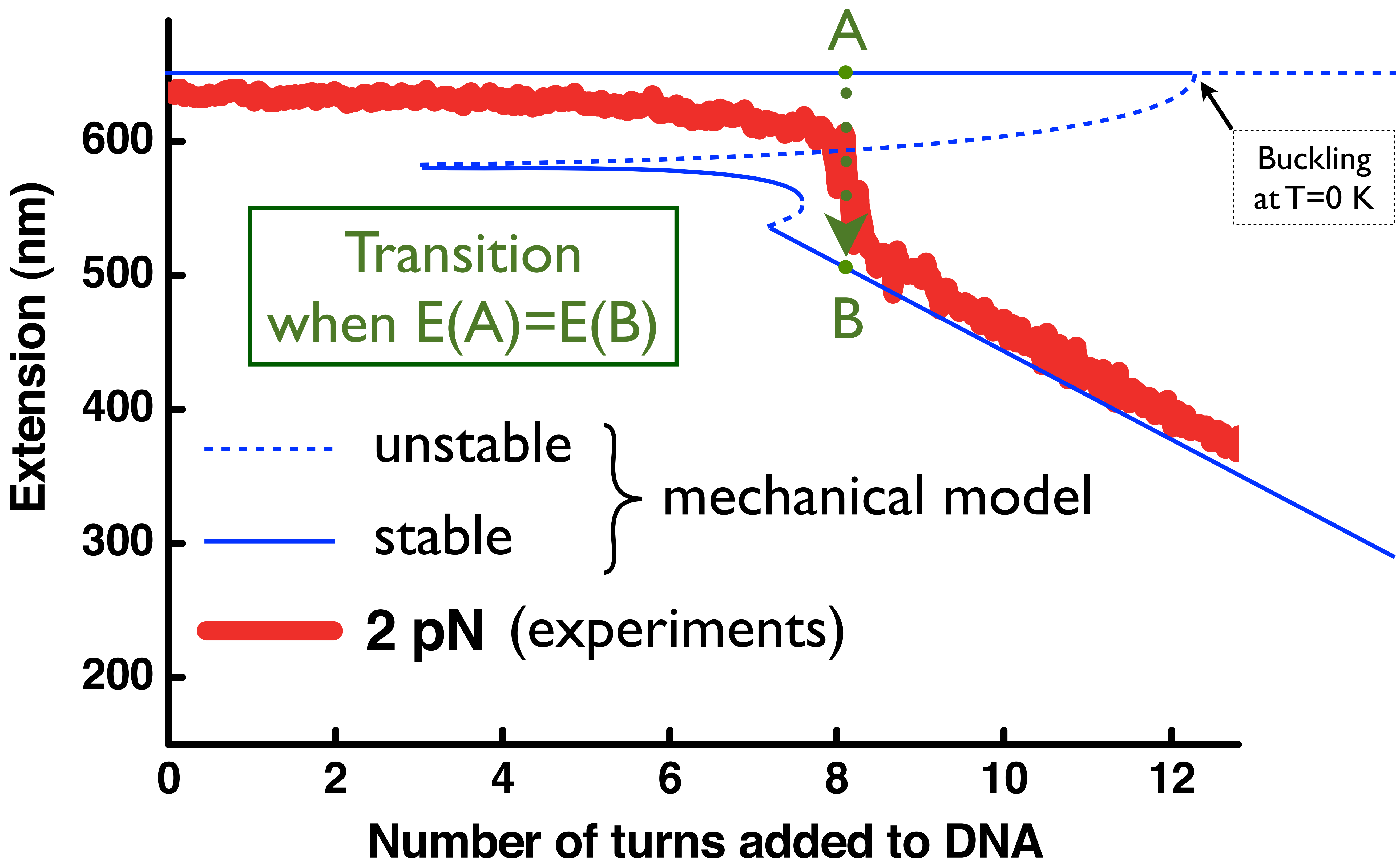
Forth et al
Phys. Rev. Let.
2008

Transition = create first loop

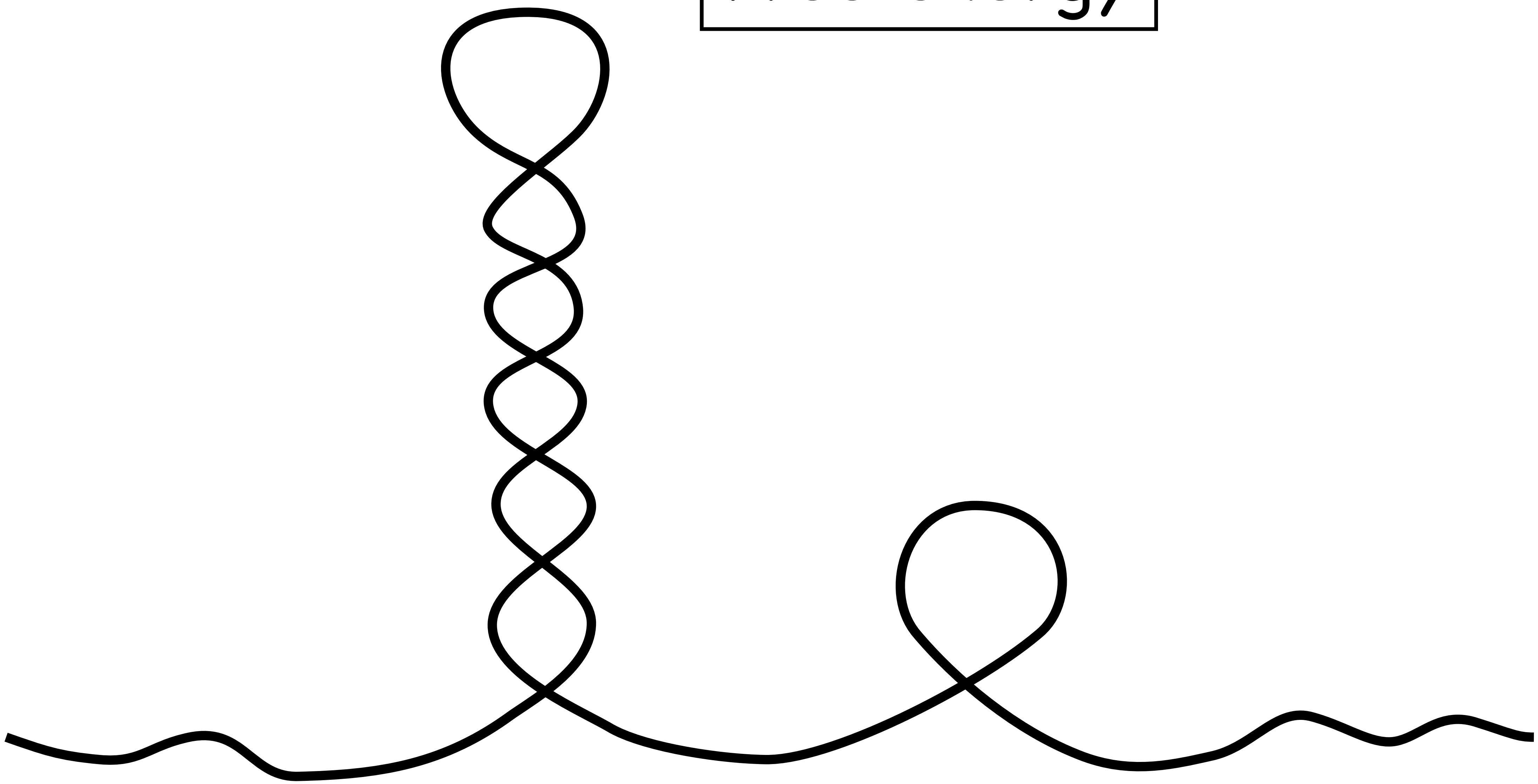


Daniels et al (PRE) 2009
Purohit (JMPS) 2008
Brutzer et al (Biophys. J.) 2010

Comparing free-energies of straight and supercoiled DNA



Free energy

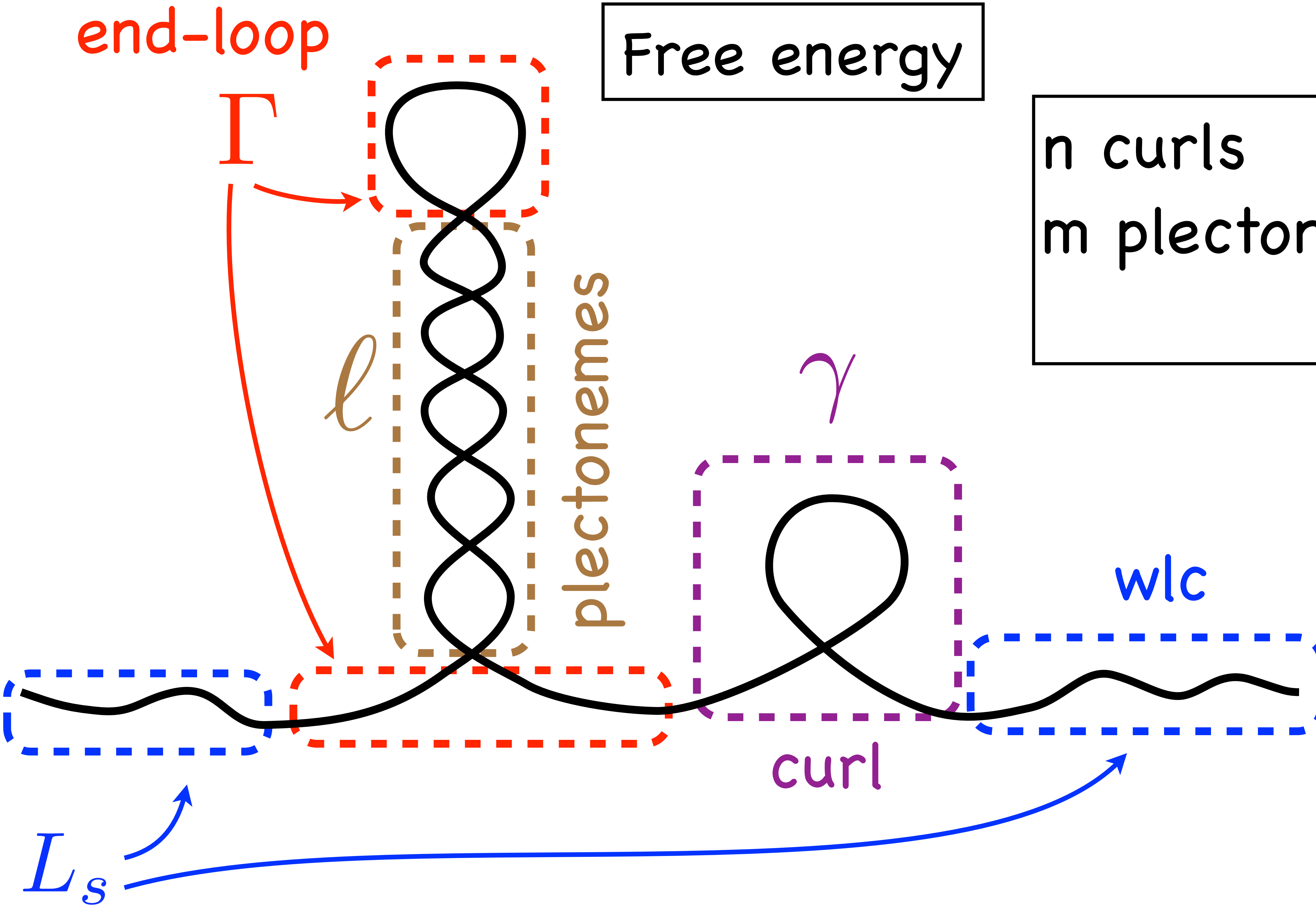


total contour length

$$L = \mathrm{nbp} \cdot 0.34\ \mathrm{nm}$$

Free energy

n curls
m plectonemic regions



$$L = \mathrm{nbp} \cdot 0.34 \ \mathrm{nm} = L_s + n\gamma + m\left(\Gamma + \ell\right)$$

Free energy

corrections to the work of the external force

entropic terms

$$L = L_s + n\gamma + m\,(\ell + \Gamma)$$

$$F = F_s + n\,F_\gamma + m\,\left(F_\Gamma + F_\ell\right) + F_f - T\,S$$

$$\begin{aligned}
F_s &= E_{twist} + E_{bend} + E_f = \frac{1}{2} C_s \tau_s^2 L_s - g(f) L_s \\
F_\gamma &= E_{twist} + E_{bend} = \frac{1}{2} C \tau_p^2 \gamma + 4\sqrt{Af} \\
F_\ell &= E_{twist} + E_{bend} + E_{electro} = \frac{1}{2} C \tau_p^2 \ell + \frac{1}{2} A \frac{\sin^4 \alpha}{r^2} \ell + U\ell \\
F_\Gamma &= E_{twist} + E_{bend} + E_{electro} = \frac{1}{2} C \tau_p^2 \Gamma + q_b \sqrt{Af} + U\Gamma \\
F_f &= 4n\sqrt{Af} + q_D m \sqrt{Af}
\end{aligned}$$

Free energy

corrections to the work of the external force

entropic terms

$$L = L_s + n\gamma + m\,(\ell + \Gamma)$$

$$F = F_s + n\,F_\gamma + m\,\left(F_\Gamma + F_\ell\right) + F_f - T\,S$$

$$U = U + \frac{1}{2}\,kT\,\left(\frac{kT}{Ar^2}\right)^{1/3}$$

confinement in a tube

$$F_\gamma = F_\gamma - \frac{1}{4}\mathrm{Log}\left(\frac{4\pi^2 A (kT)^2}{d^4 f^3}\right)$$

loop size fluctuations
(d=1nm)

$$S(L,\ell,n,m) = (n+m)\,\mathrm{Log}\left(\frac{L - m\ell}{\gamma} - n - m\right) - \mathrm{Log}\,n! - \mathrm{Log}\,m!$$

Tonks hard core gas

Free energy

$$F = F_s + n\,F_\gamma + m\,\left(F_\Gamma + F_\ell\right) + F_f - T\,S$$

study F under the two constraints:

$$L = L_s + n\gamma + m\,(\ell + \Gamma)$$

$$n = Lk = \underbrace{\frac{\tau_s}{2\pi}L_s + \frac{\tau_p}{2\pi}(m\ell + n\gamma + m\Gamma)}_{\text{Twist}} + \underbrace{\frac{\sin 2\alpha}{4\pi r}m\ell + mp + n\Lambda}_{\text{Writhe}}$$

we replace τ_s, L_s to obtain :

$$\boxed{F_{nm} = F_{nm}\,(\alpha, r, \tau_p, \ell)}$$

Computation method

$m \neq 0$ $$F_{nm} = F_{nm}\left(\alpha, r, \tau_p, \ell\right)$$

$m = 0$ $$F_{n0} = F_{n0}\left(\alpha, r, \tau_p\right)$$

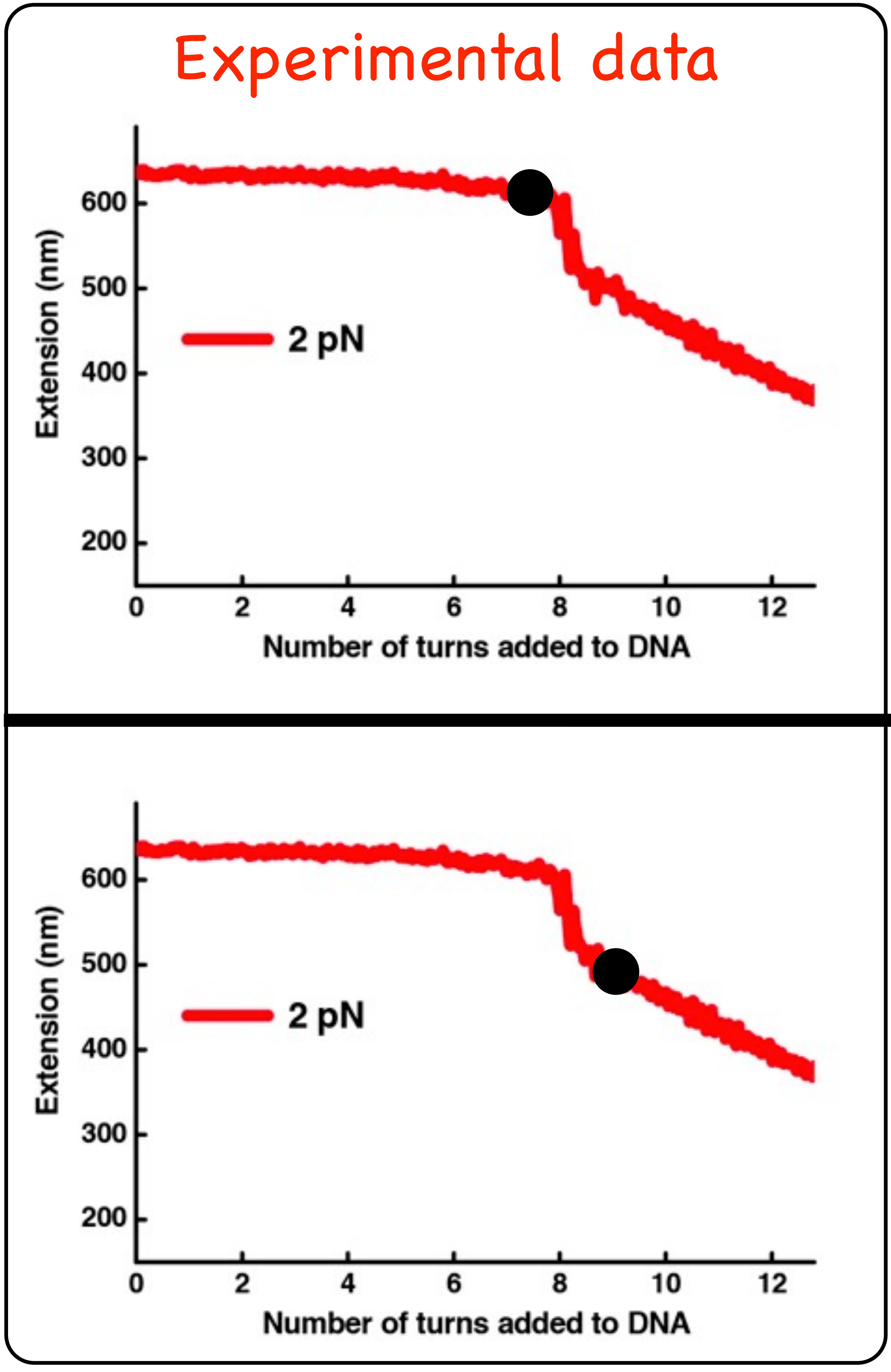
reference state $$F_{00} = -gL + \frac{1}{2}C_s\left(\frac{2\pi Lk}{L}\right)^2 L$$

$$\Delta F_{nm}(\alpha, r, \tau_p, \ell) = F_{nm} - F_{00}$$

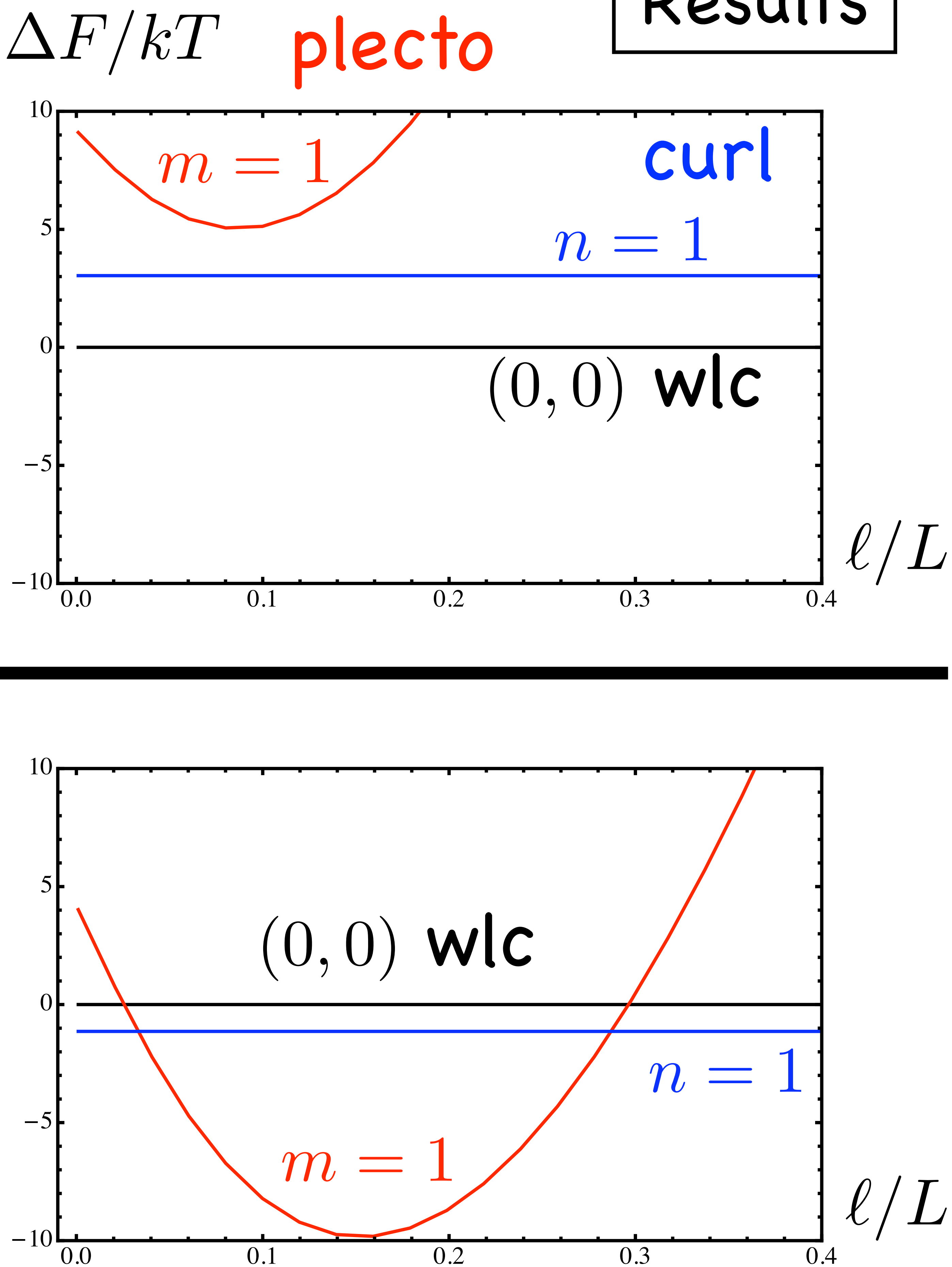
minimize with regard to α, r, τ_p (saddle point approx.)

plot as function of ℓ

Results



Experimental data
Extension (nm)
600
500
400
300
200
2 pN
0
2
4
6
8
10
12
Number of turns added to DNA
Extension (nm)
600
500
400
300
200
2 pN
0
2
4
6
8
10
12
Number of turns added to DNA



$\Delta F/kT$
plecto
curl
$m=1$
$n=1$
$(0,0)$ wlc
10
5
0
−5
−10
0.0
0.1
0.2
0.3
0.4
ℓ/L
(0,0) wlc
$n=1$
$m=1$
10
5
0
−5
−10
0.0
0.1
0.2
0.3
0.4
ℓ/L

Computing mean values

At fixed Lk

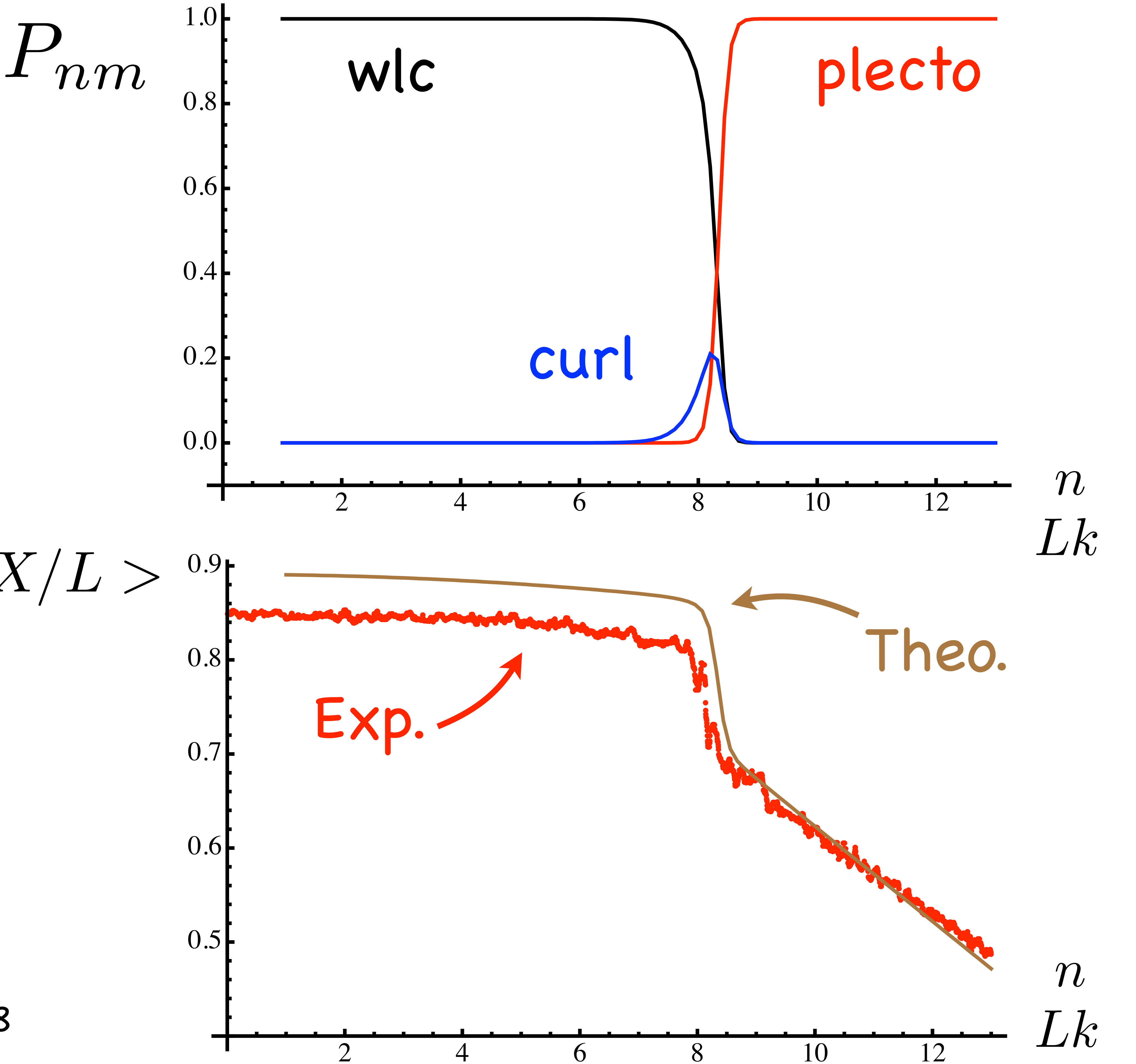
$$Z = \sum_n \sum_m \int_\ell e^{-F_{nm}(\ell)}\,\mathrm{d}\ell$$

Probability of seeing a configuration with
n curls and
m plectonemic parts: $P_{nm}(n = Lk) = \dfrac{\int e^{-F_{nm}(\ell)} d\ell}{\sum_{n,m} \int e^{-F_{nm}(\ell)} d\ell}$

Mean extension of the system (considering all possible configurations:

$$< X > (n = Lk) = \frac{\sum_{n,m} \int X_{nm}(\ell) e^{-F_{nm}(\ell)} d\ell}{\sum_{n,m} \int e^{-F_{nm}(\ell)} d\ell}$$

Results



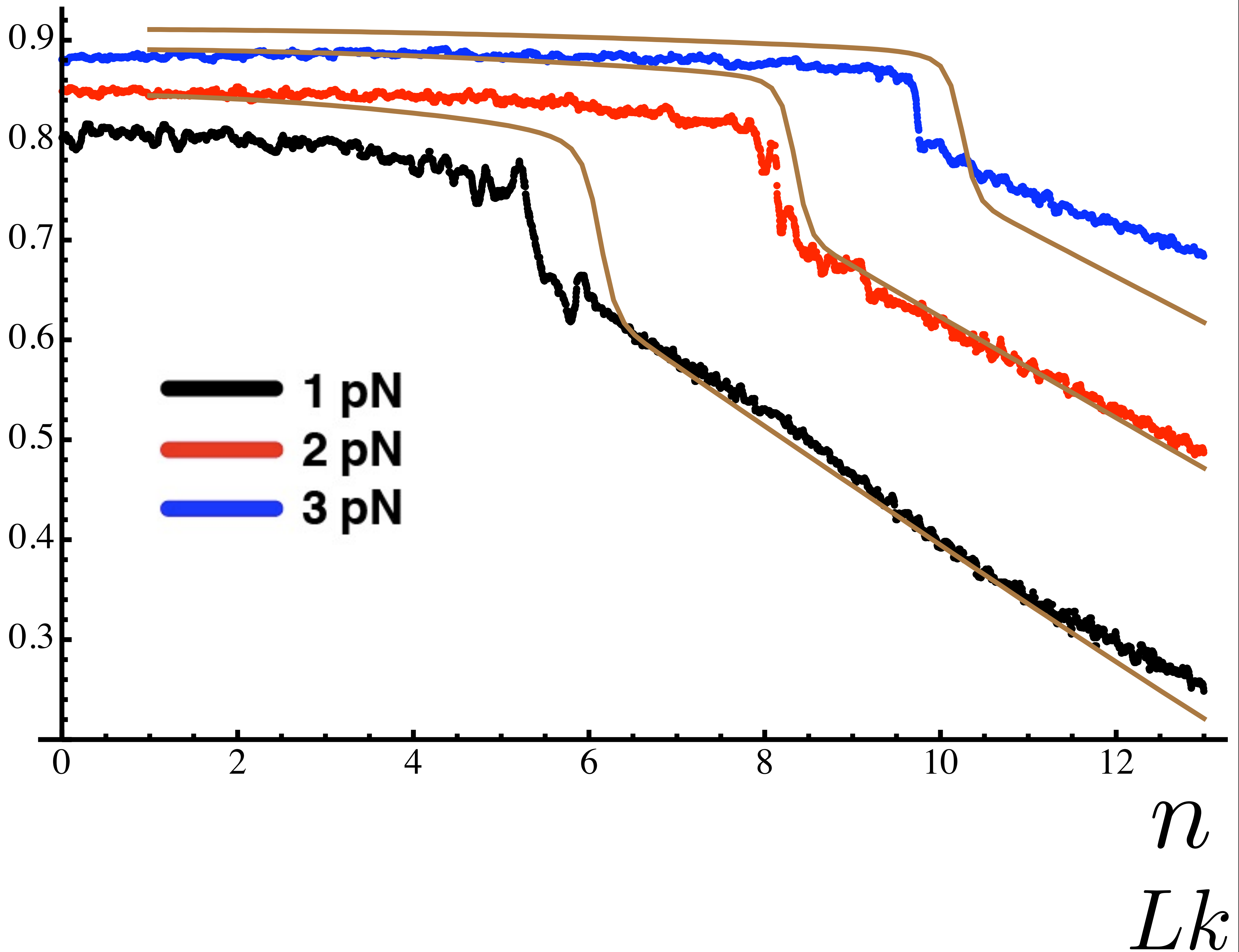
2.2 kbp

150 mM

2 pN

data : Forth et al
(Phys. Rev. Let.) 2008

Results



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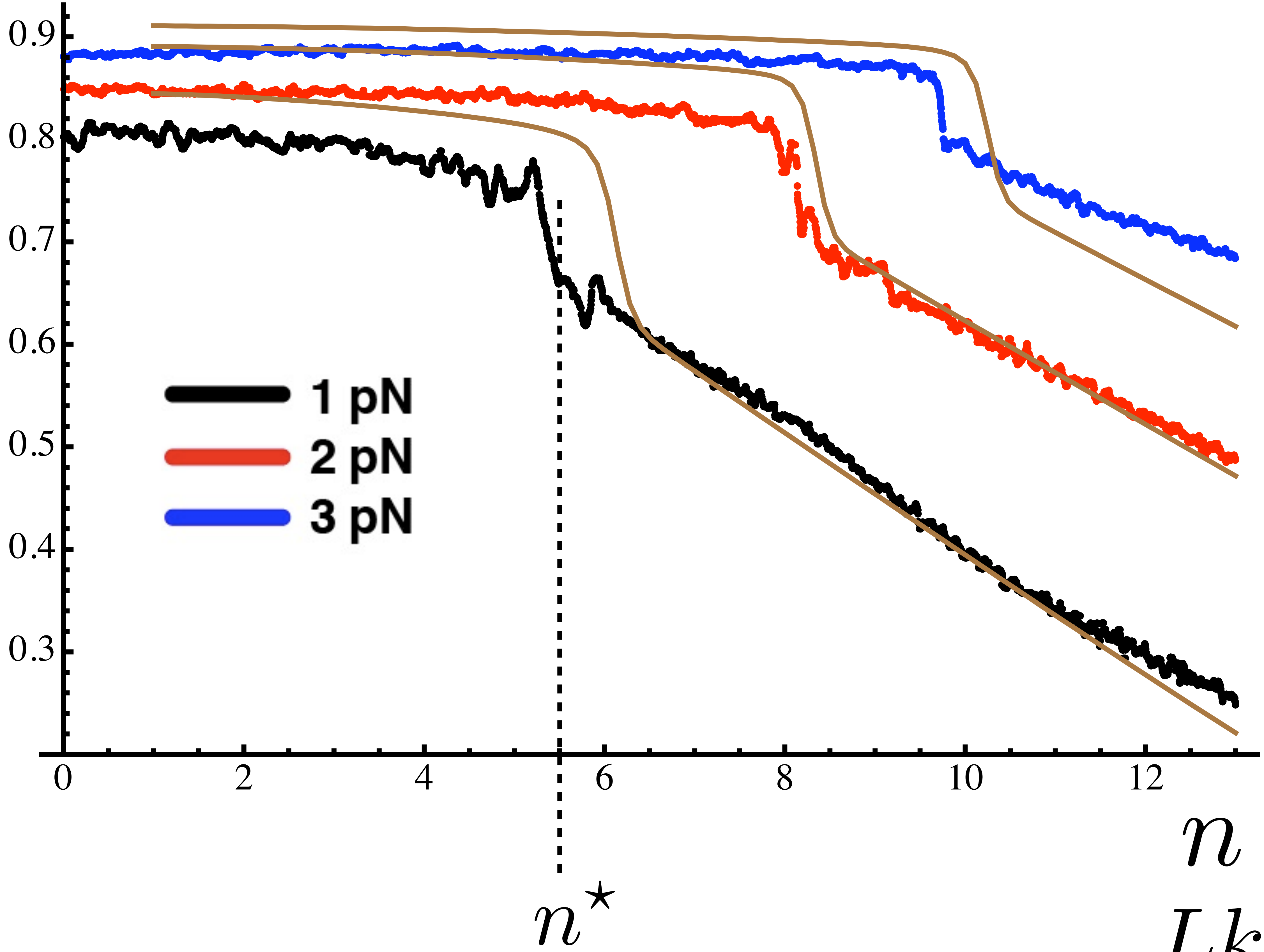
Results



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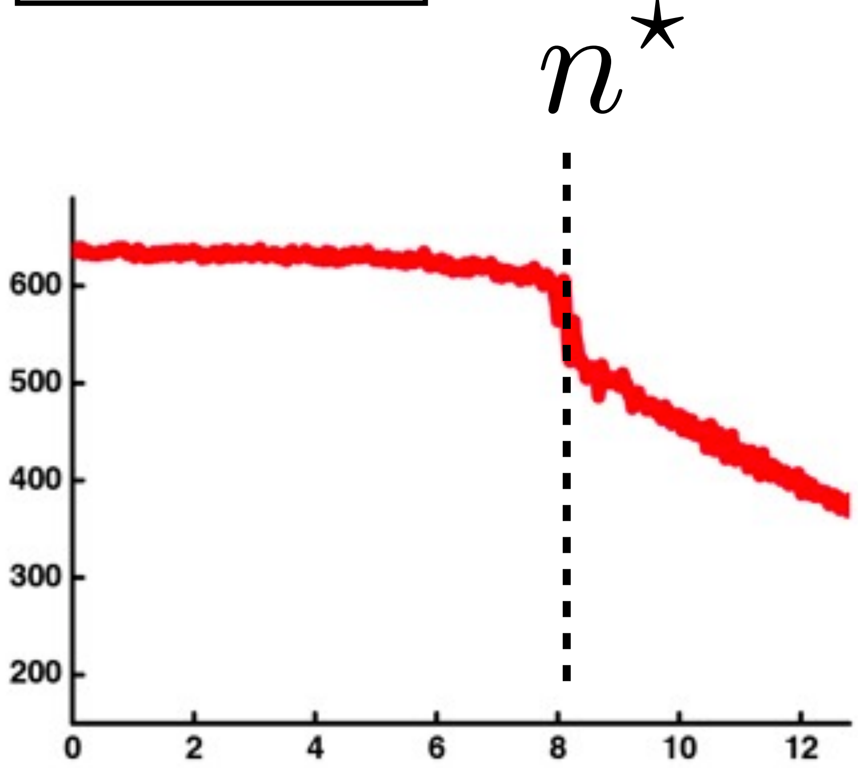
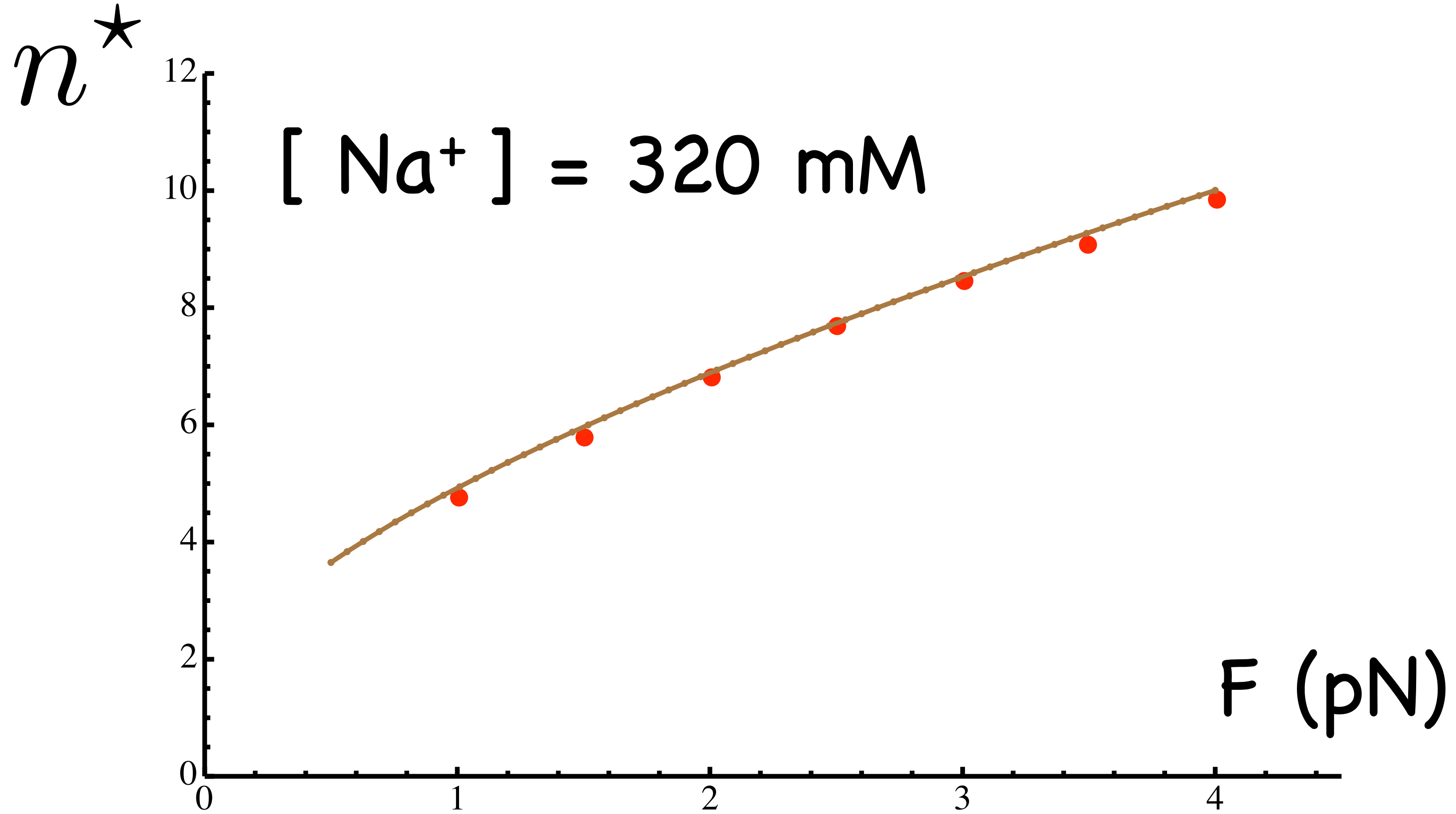
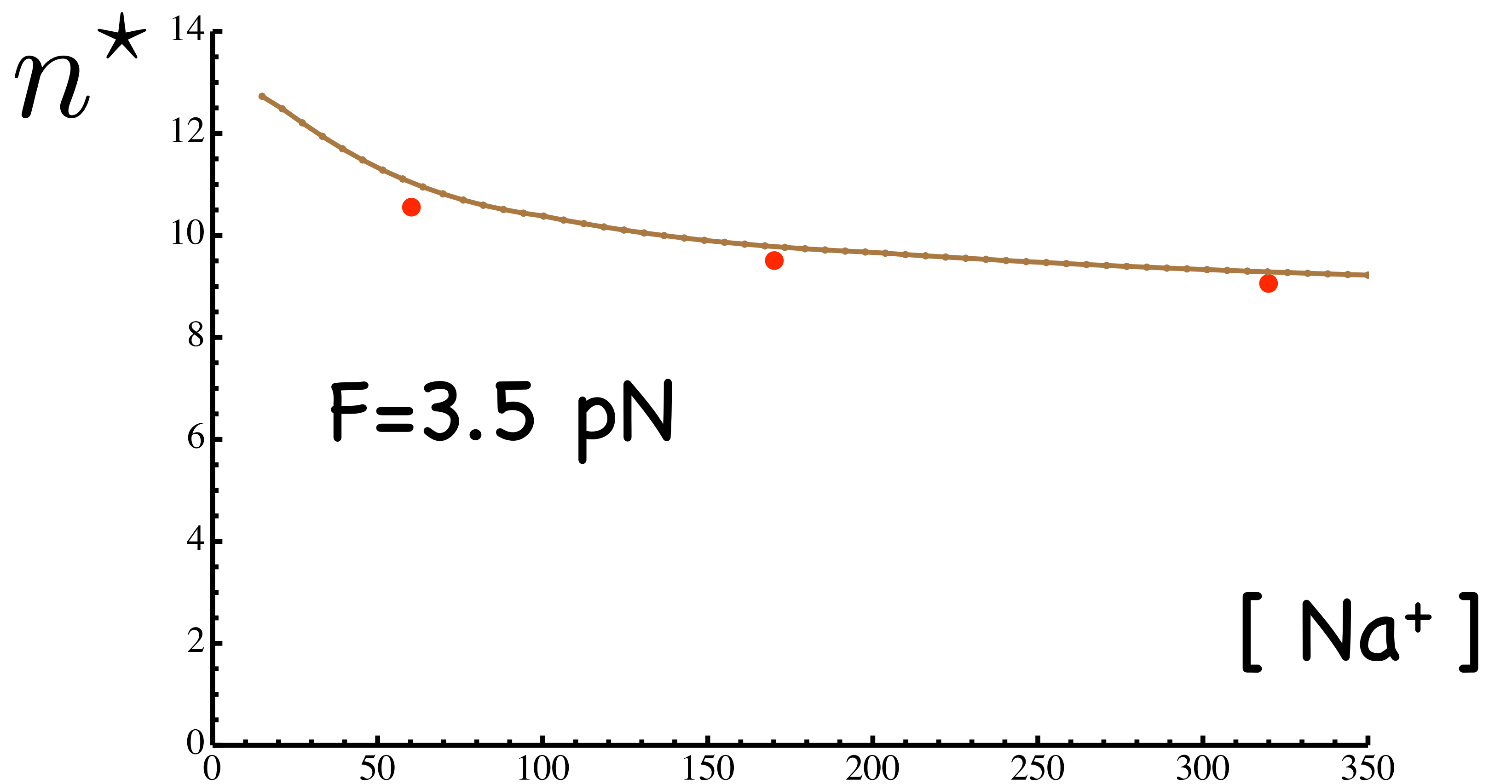
Results





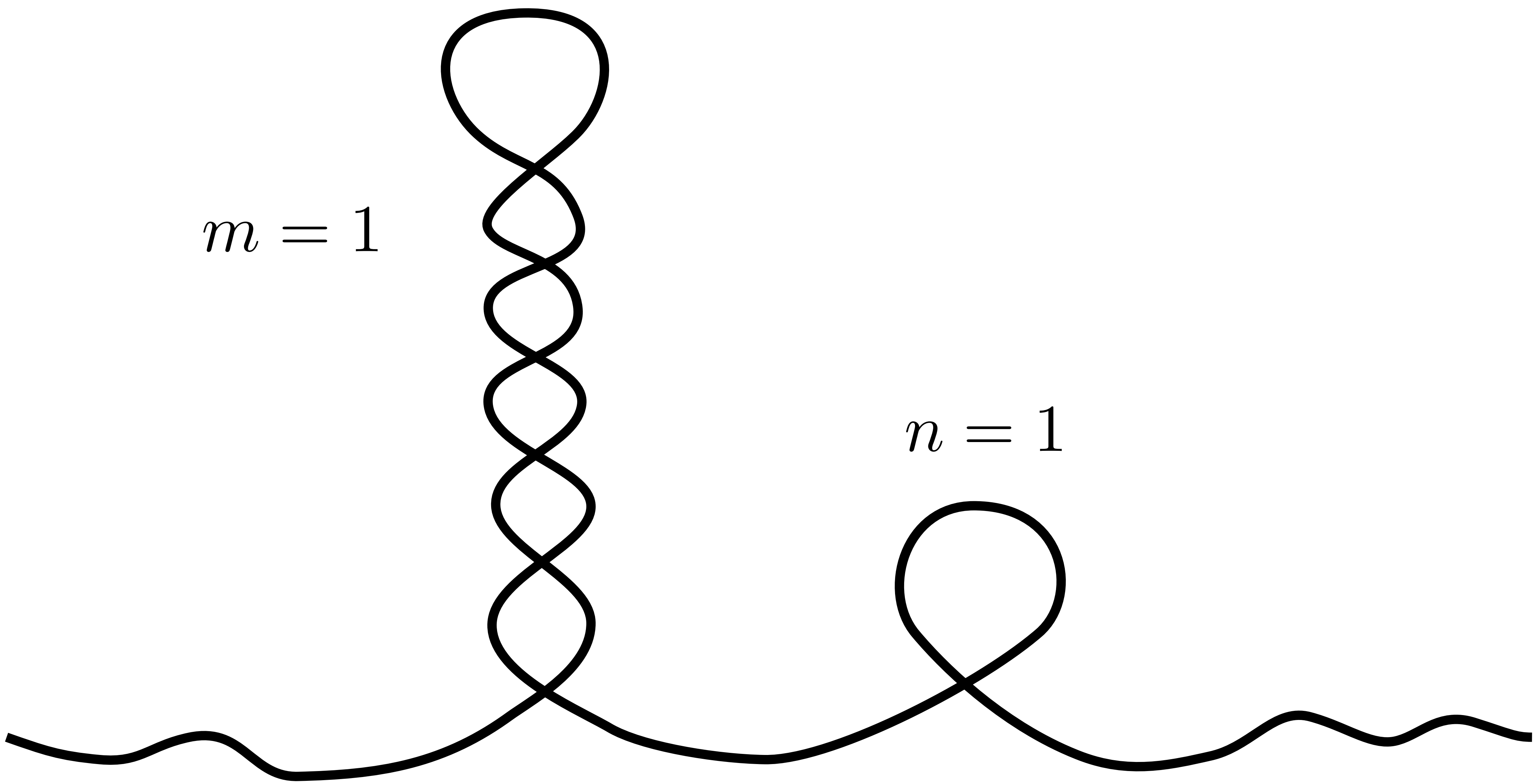


1900 bp

data : Brutzer et al (Biophys. J.) 2010

Mean number of curls
Mean number of plectonemes

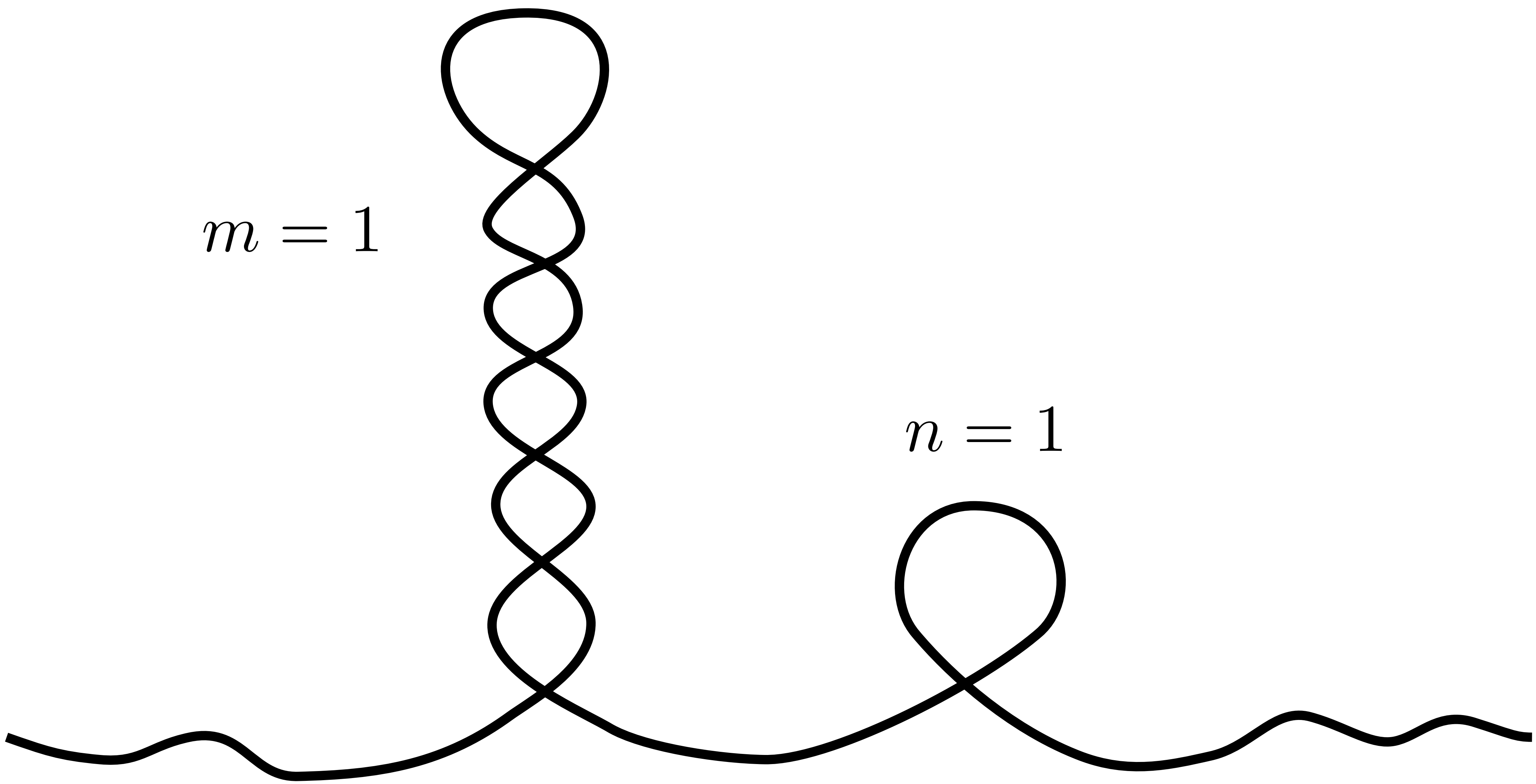
curls $$< n >= \frac{\sum_{n,m} \int n \, e^{-F_{nm}(\ell)} d\ell}{Z}$$



Mean number of curls
Mean number of plectonemes

plectonemes

$$< m >= \frac{\sum_{n,m} \int m \, e^{-F_{nm}(\ell)} d\ell}{Z}$$



2.2kbp

150mM

0.25 pN blue

0.5 pN green

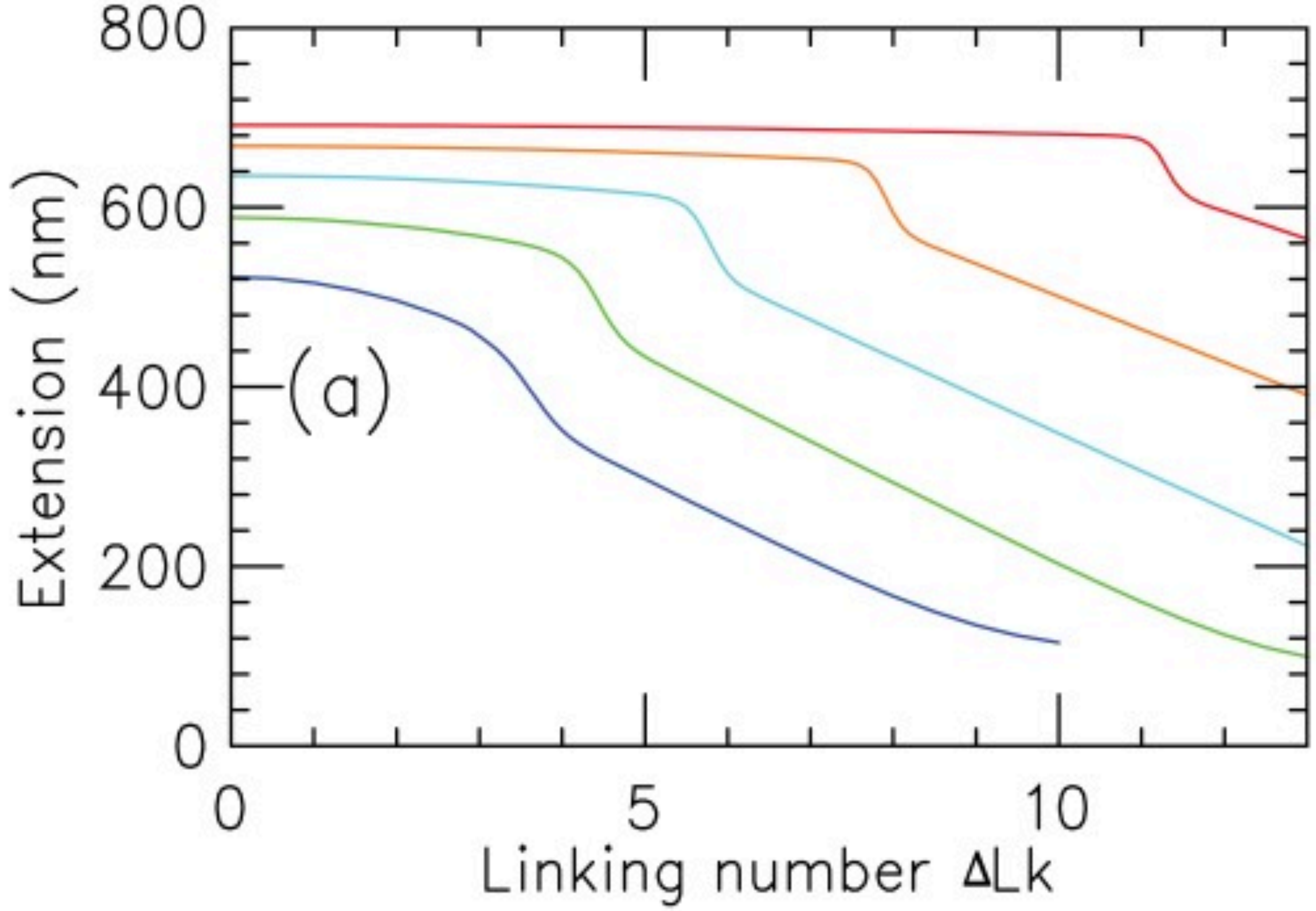
1 pN cyan

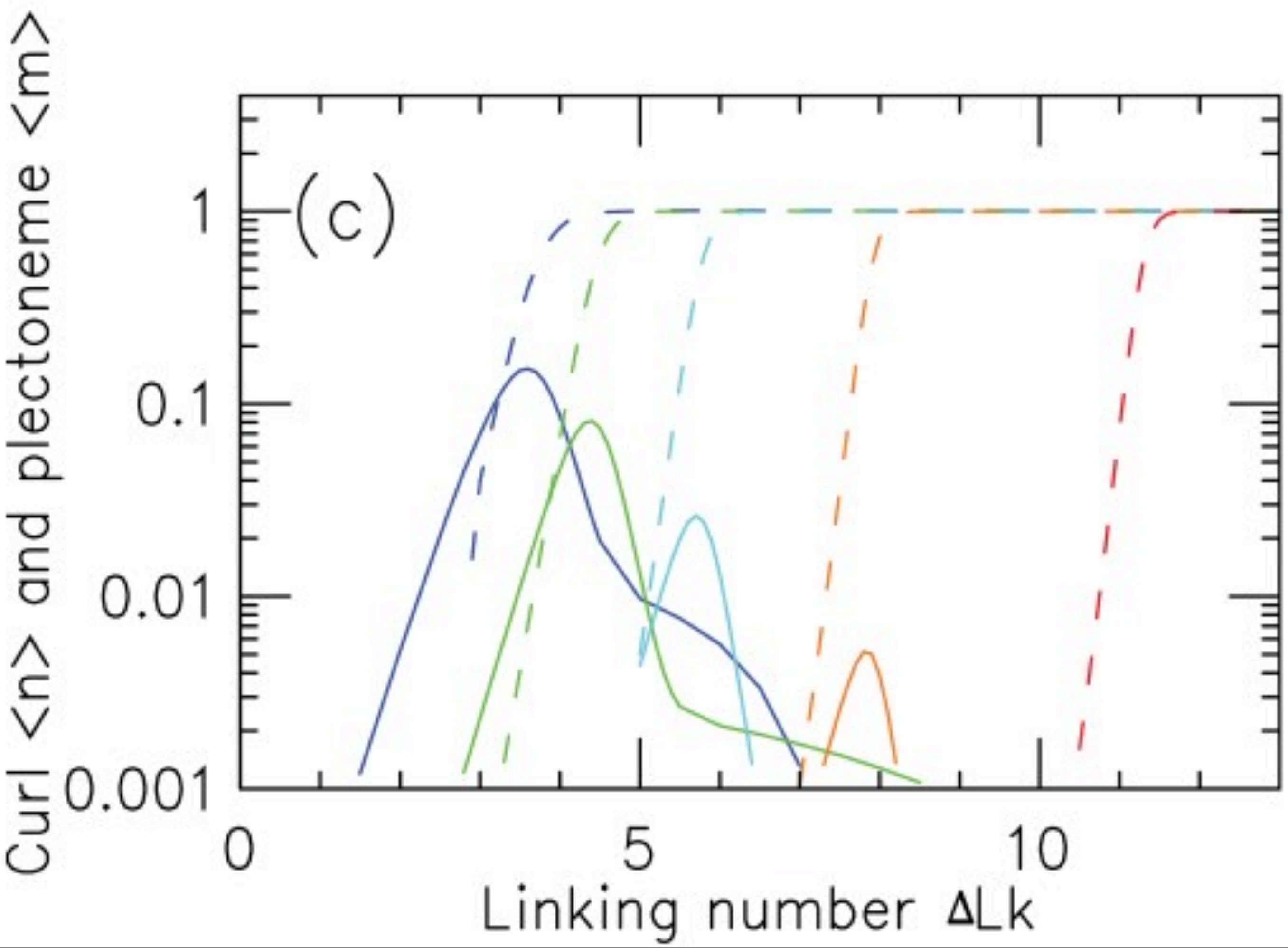
2 pN orange

4 pN red

<m> dashed

<n> plain





10kbp

150mM

0.25 pN blue

0.5 pN green

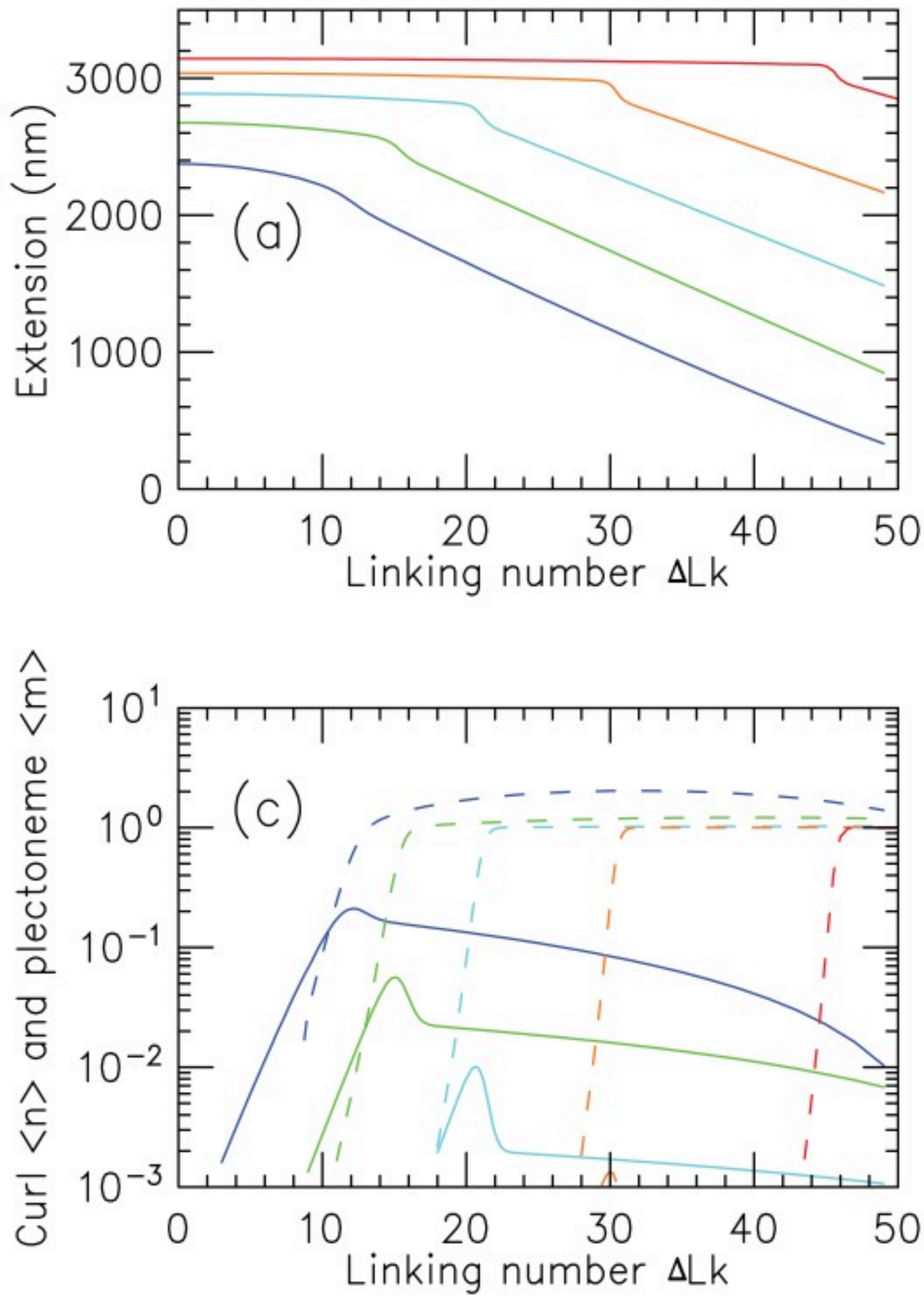
1 pN cyan

2 pN orange

4 pN red

<m> dashed

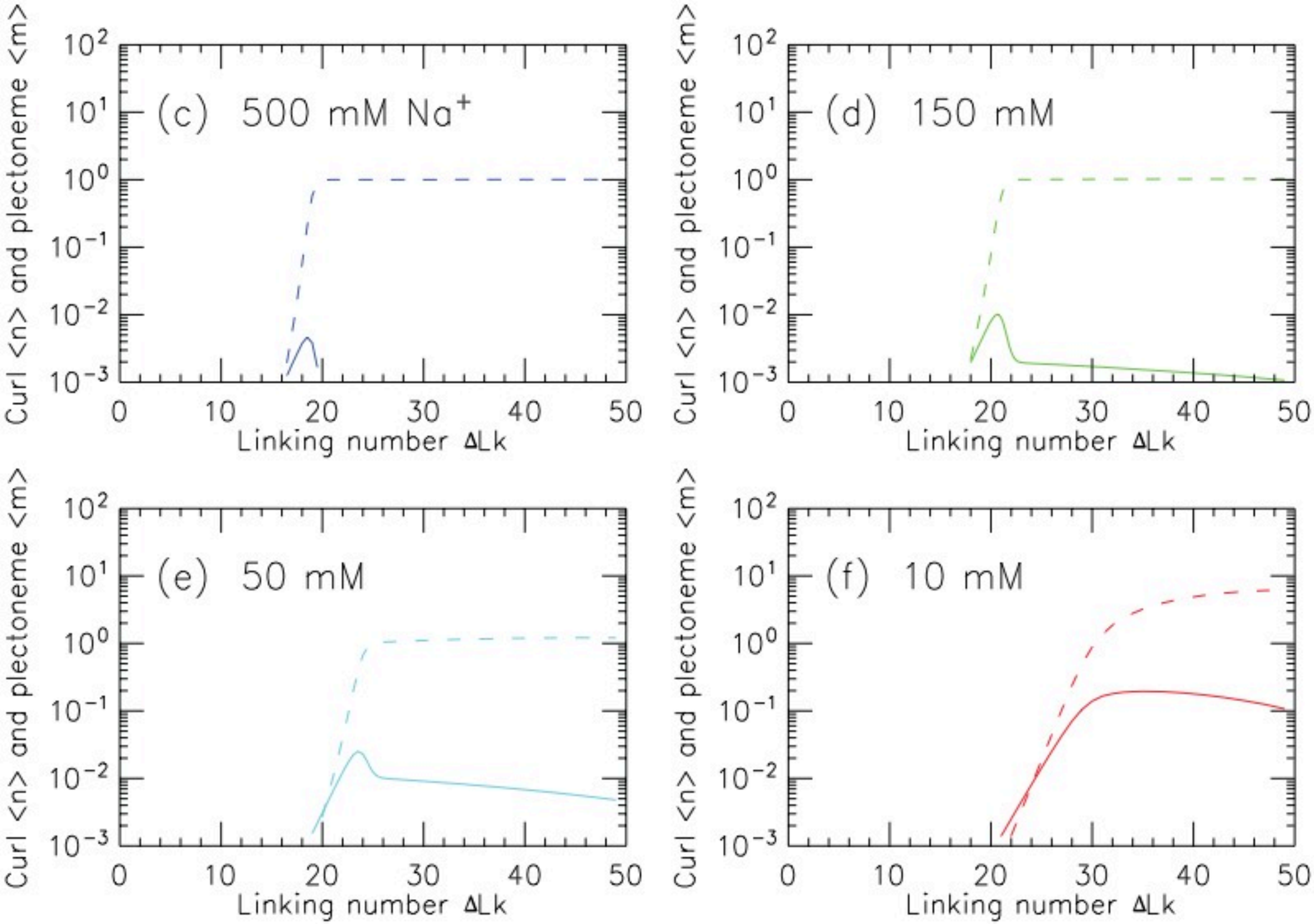
<n> plain



10kbp

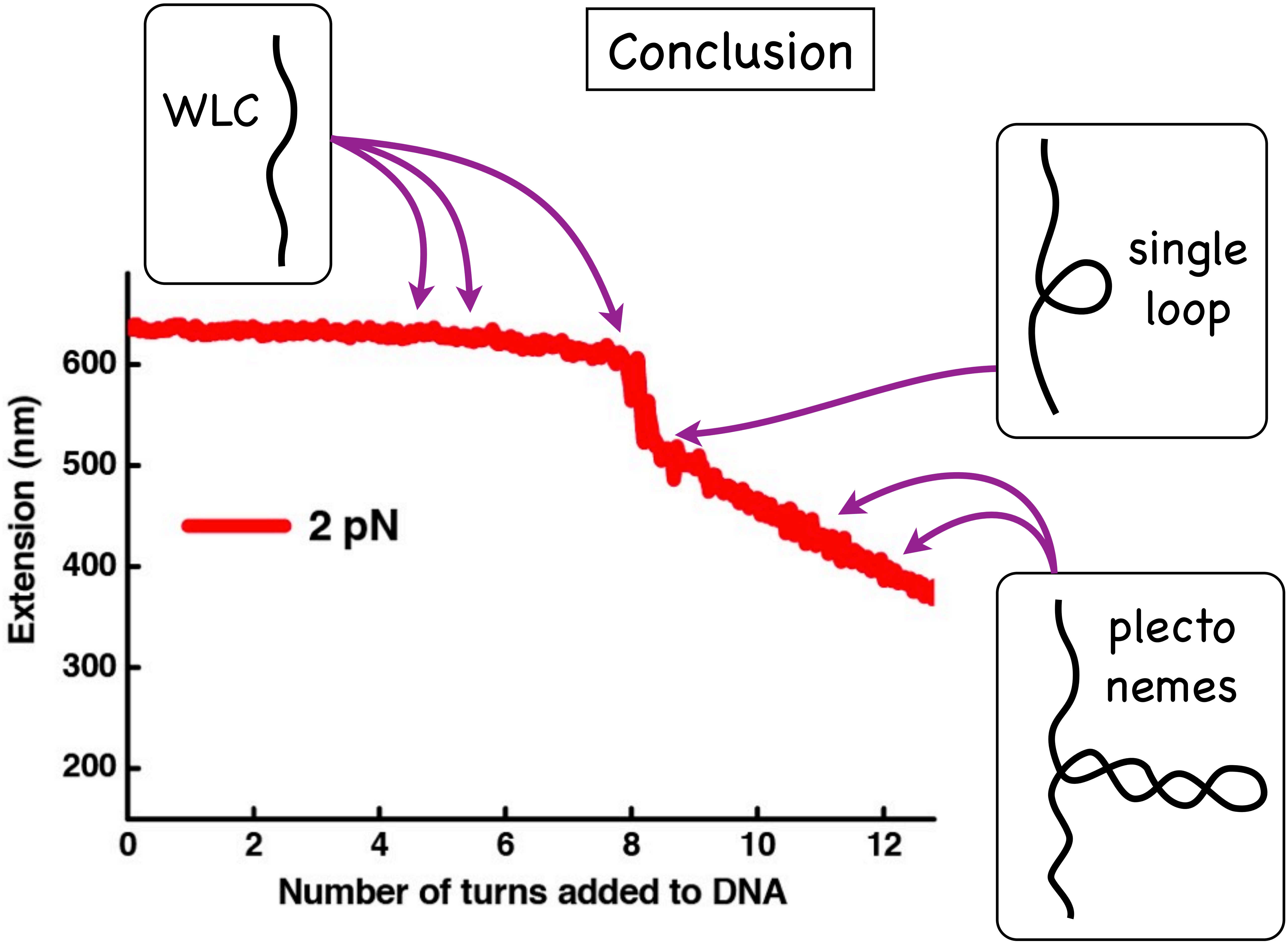
1 pN

Salt dependence



=> lots of plectonemes and curls at low salt

Conclusion


WLC
single loop
plecto nemes
Extension (nm)
600
500
400
300
200
2 pN
0
2
4
6
8
10
12
Number of turns added to DNA

Thank you

Work was done with:

N. Clauvelin (Rutgers)

B. Audoly (Paris)

J. Marko (Northwestern)