Chromatin: a multi-scale jigsaw puzzle

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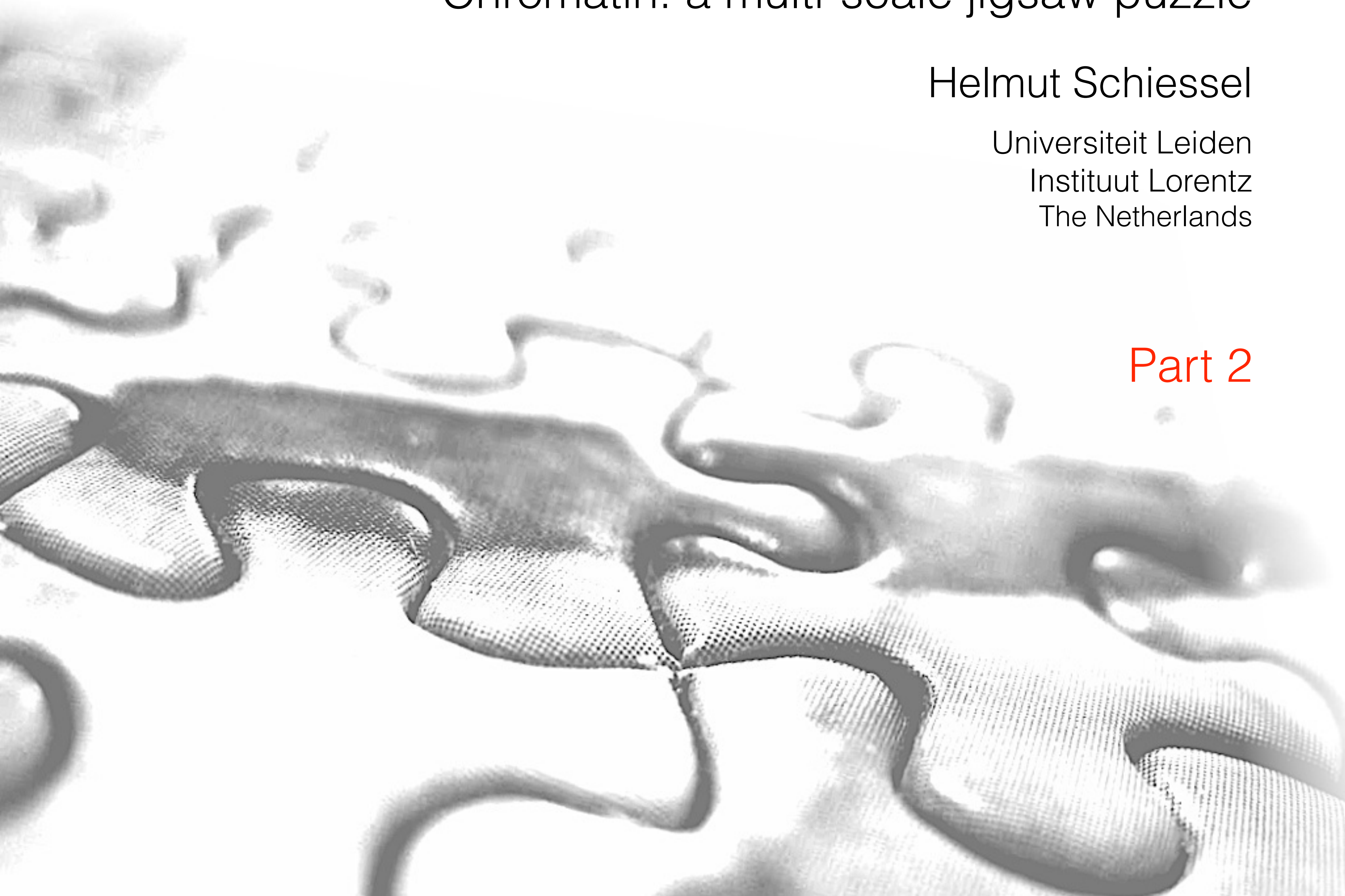
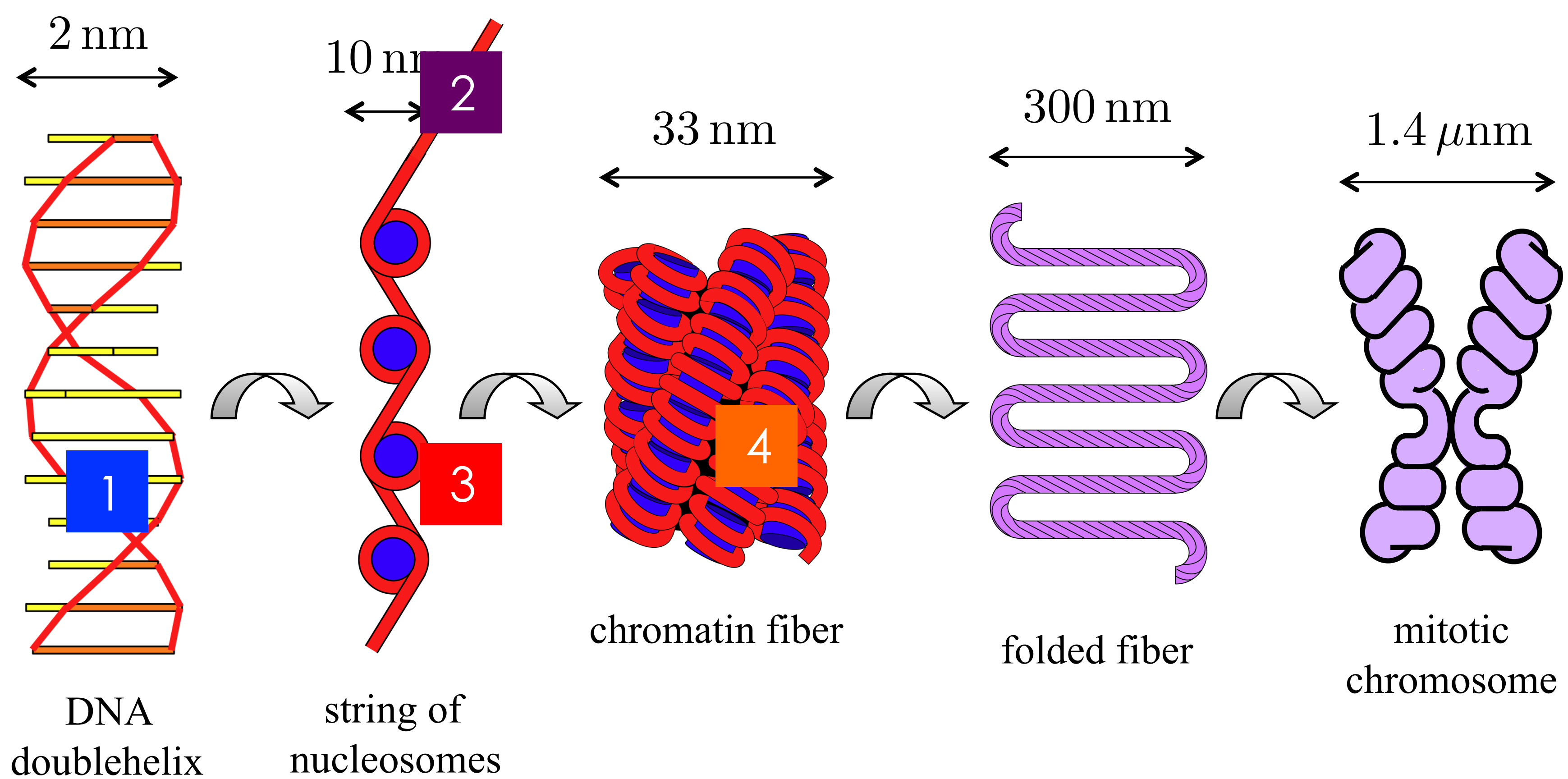
Part 2

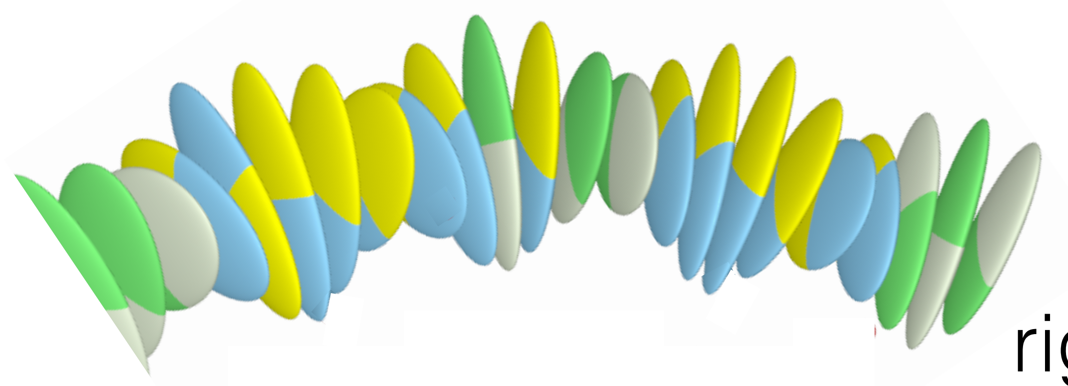


Overview

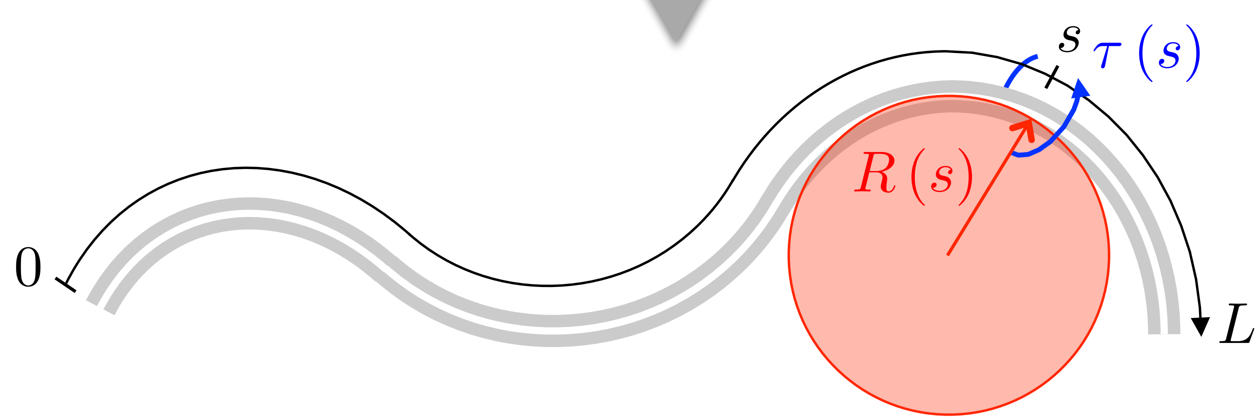


- 1 The mechanical genome
- 2 DNA as a wormlike chain
- 3 Nucleosome unspooling
- 4 Packing nucleosomes

From rigid base-pairs to a wormlike chain



rigid base-pair model



wormlike chain

The problem

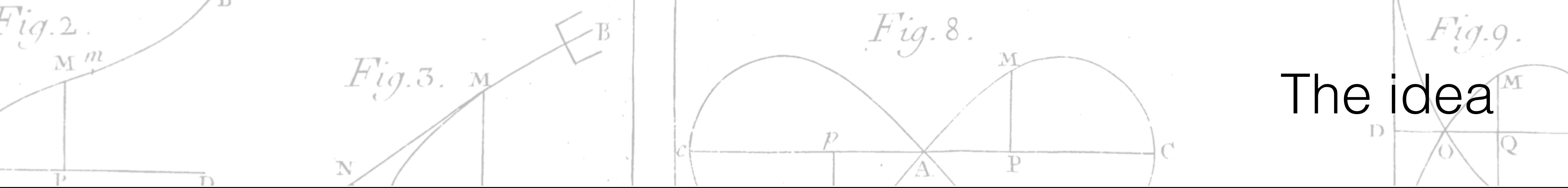
Galileo Galilei, Discorsi, 1638

DISCORSI
E
DIMOSTRAZIONI
MATEMATICHE,
intorno à due nuoue scienze
Attenenti alla
MECANICA & I MOVIMENTI LOCALI,
del Signor
GALILEO GALILEI LINCEO,
Filosofo e Matematico primario del Serenissimo
Grand Duca di Toscana.
Con vna Appendice del centro di grauità d'alcuni Solidi.

IN LEIDA,
Appresso gli Elsevirii. M. D. C. XXXVIII.

114 DIALOGO SECONDO

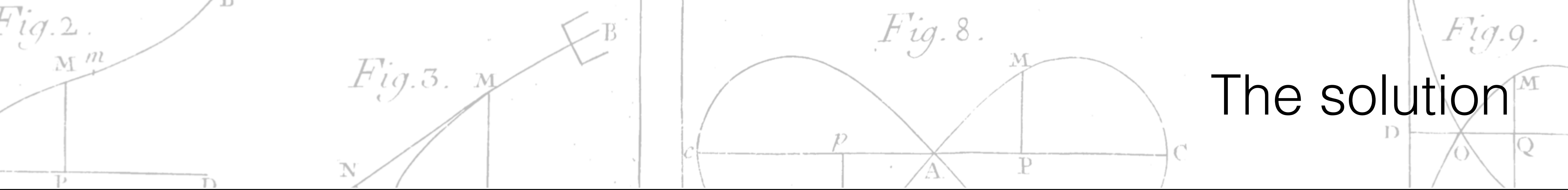
fin quì dichiarate, non sarà difficile l'intender la ragione, onde auuenga, che vn Prisma, ò Cilindro solido di vetro, acciaio, legno, ò altra materia frangibile, che sospeso per lungo sosterrà grauissimo peso, che gli sia attaccato, mà in trauerso (come poco fa diceuamo) da Prop. I. *minor peso assai potrà tal volta essere spezzato, secondo che la sua lunghezza eccederà la sua grossezza. Imperò che figuriamoci il Prisma solido* AB, CD *fitto in vn muro dalla parte* AB, *e nell'altra estremità s'intenda la forza del Peso* E. *(intendendo sempre il muro esser eretto all'Orizonte, & il Prisma, ò Cilindro fitto nel muro ad angoli retti) è manifesto che douendosi spezzare si romperà nel luogo* B, *doue il taglio del muro serue per sostegno, e la* BC *per la parte della Leua, doue si pone la forza, e la grossezza del solido* BA *e l'altra parte della Leua, nella quale è posta la resistenza, che consiste nello staccamento, che s'hà da fare della parte del solido* BD, *che è fuor del muro, da quella che è dentro; e per le cose dichiarate il momento della forza posta in* C *al momento della resistenza che stà nella*



The idea

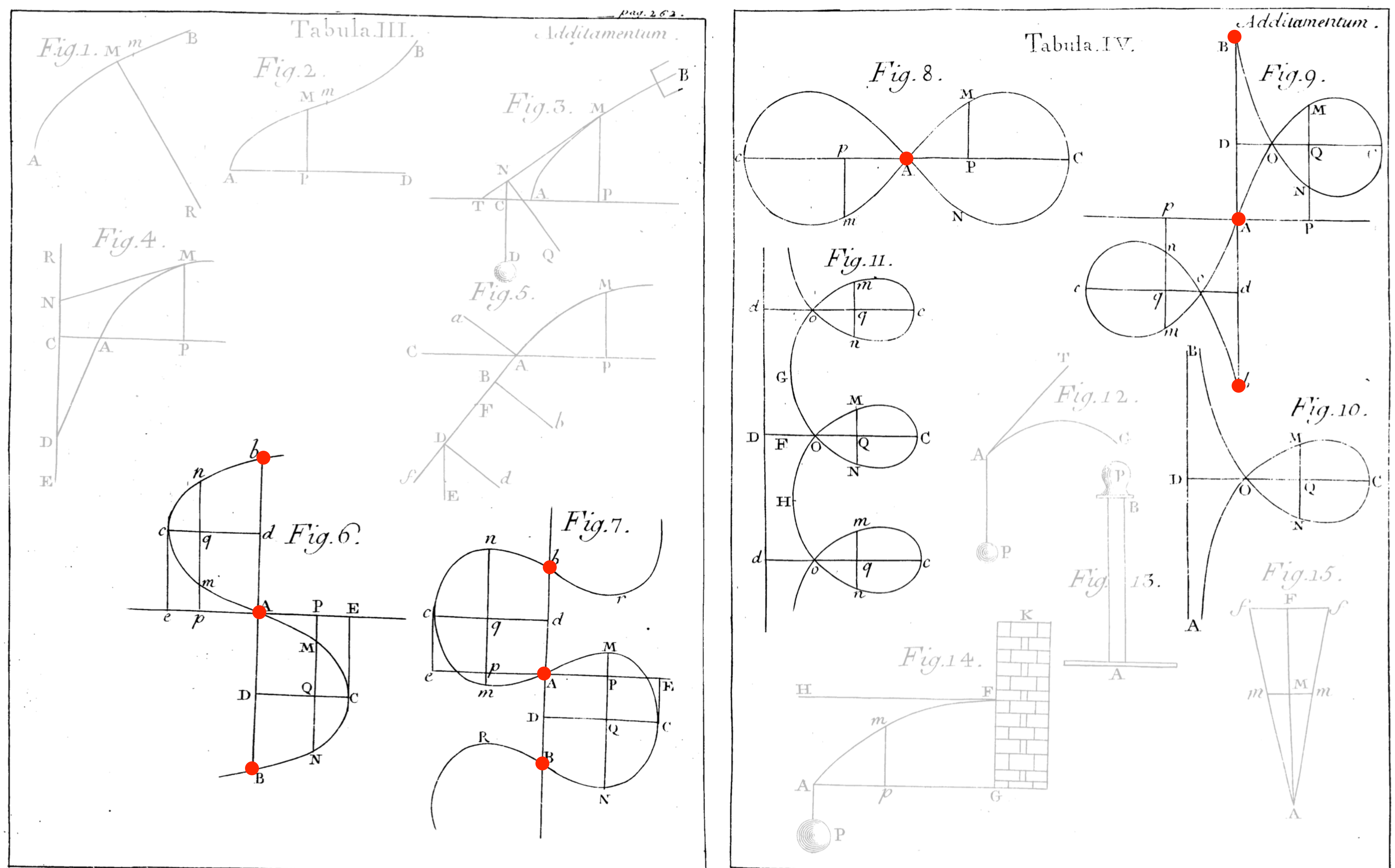
Daniel Bernoulli, letter to Euler, 1742

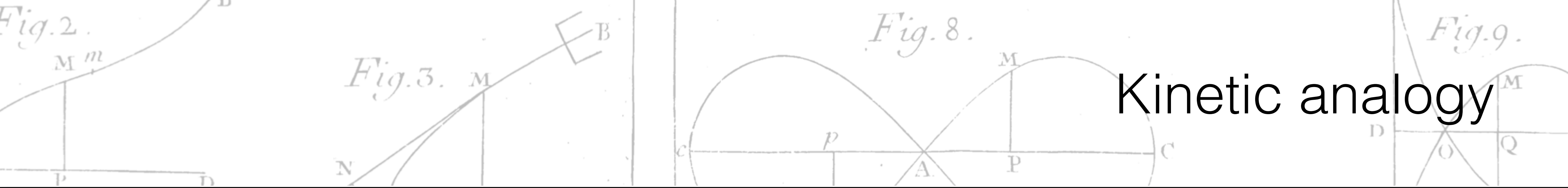
I’d like to know whether you might not solve the curvature of the elastic lamina under this condition, that on the length of the lamina on two points the position is fixed, and that the tangents at these points are given.
[…]
I’d express the potential energy of a curved elastic lamina (which is straight when in its natural position) through $\int \frac{ds}{RR}$, assuming the element ds is constant and indicating the radius of curvature by *R*. There is nobody as perfect as you for easily solving the problem....



The solution

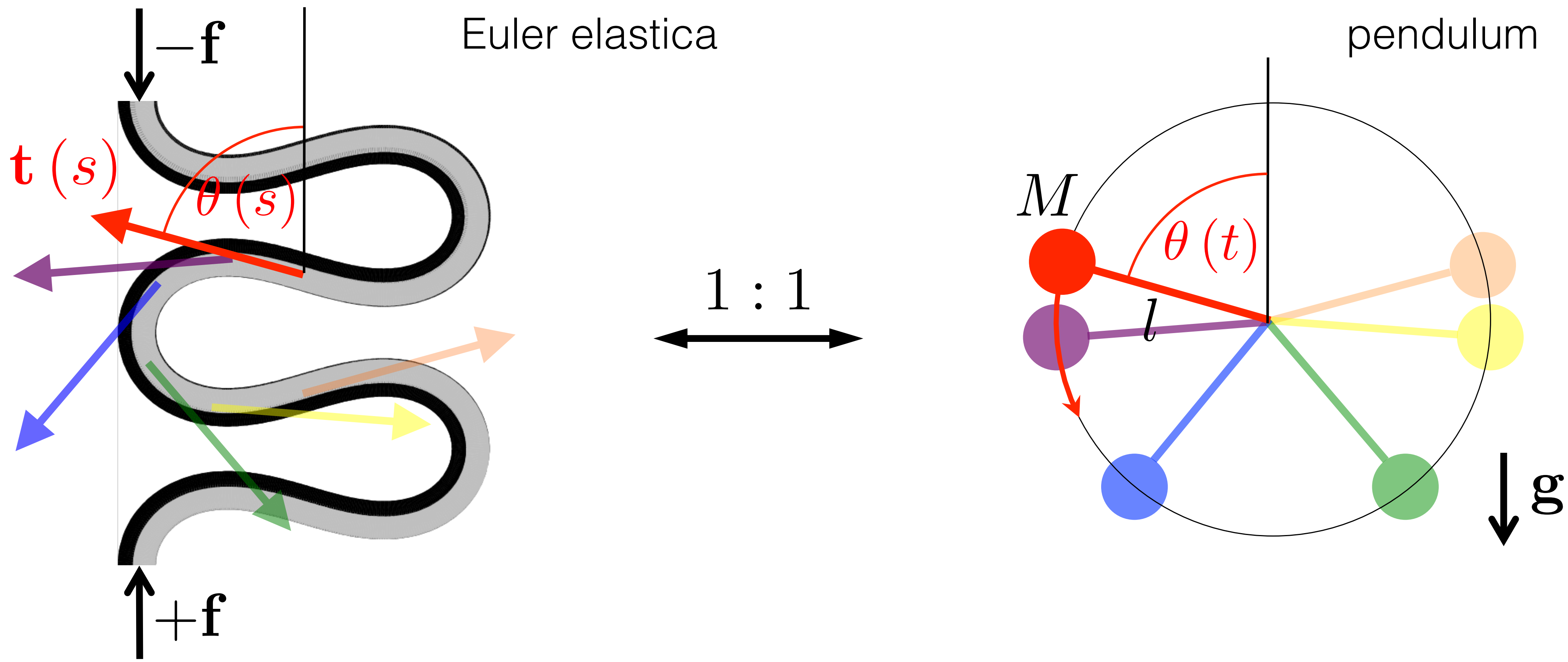
Leonard Euler, Methodus, 1744:





Kinetic analogy

Gustav Kirchhoff, 1859:



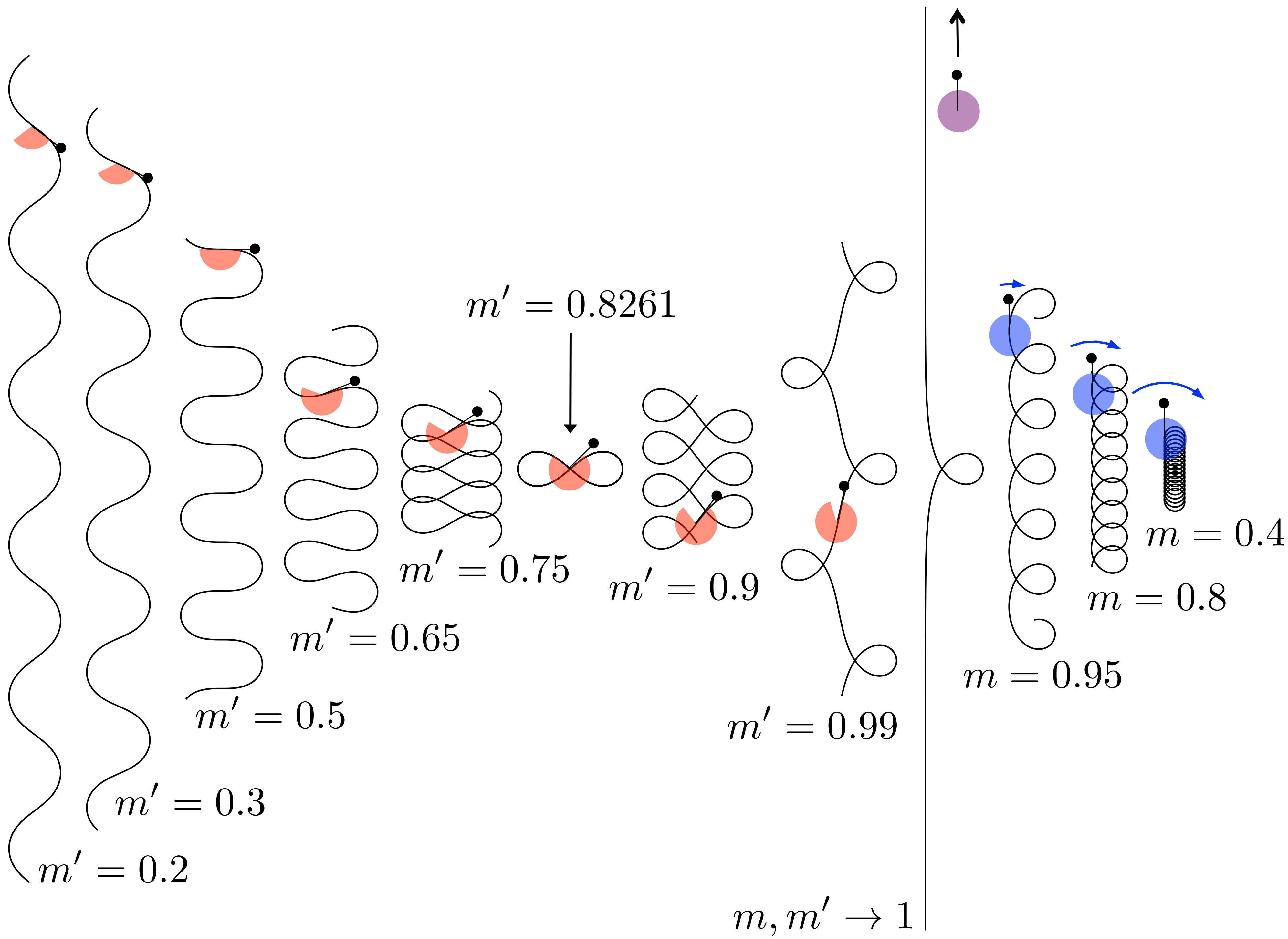
Hamiltonian (wormlike chain):

$$H = \int_0^L \left[\frac{A}{2}\dot{\theta}^2 - f\cos\theta\right] ds$$

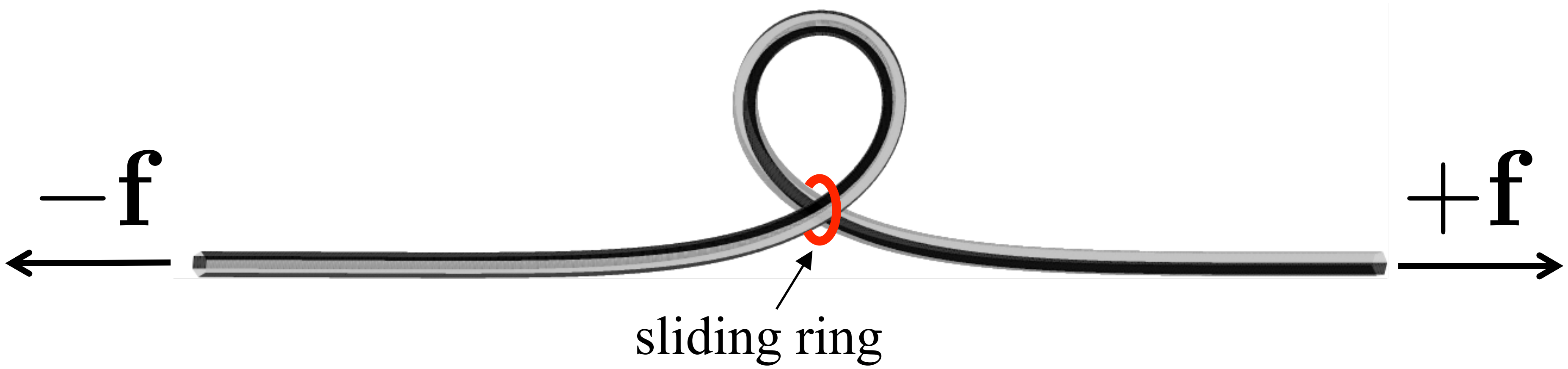
Lagrangian action:

$$S = \int_0^T \left[\frac{Ml^2}{2}\dot{\theta}^2 - Mgl\cos\theta\right] d\tau$$

Examples



DNA with a sliding loop under tension



$$H = \int_{-L/2}^{L/2} \left[\frac{A}{2}\dot{\theta}^2 - f\cos\theta \right] ds$$

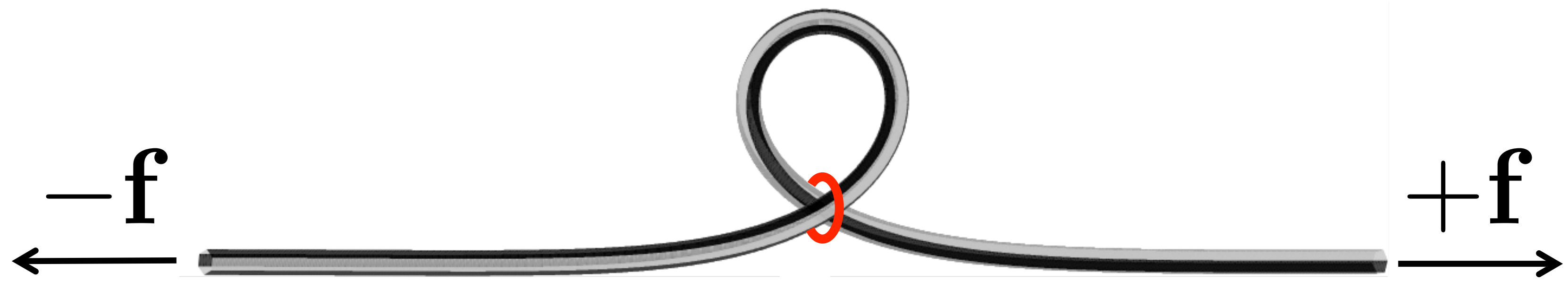
Euler-Lagrange equation: $\ddot{\theta} = \lambda^{-2}\sin\theta$

correlation length: $\lambda = \sqrt{A/f}$

boundary conditions: $\theta_{\text{loop}}(-\infty) = 0$

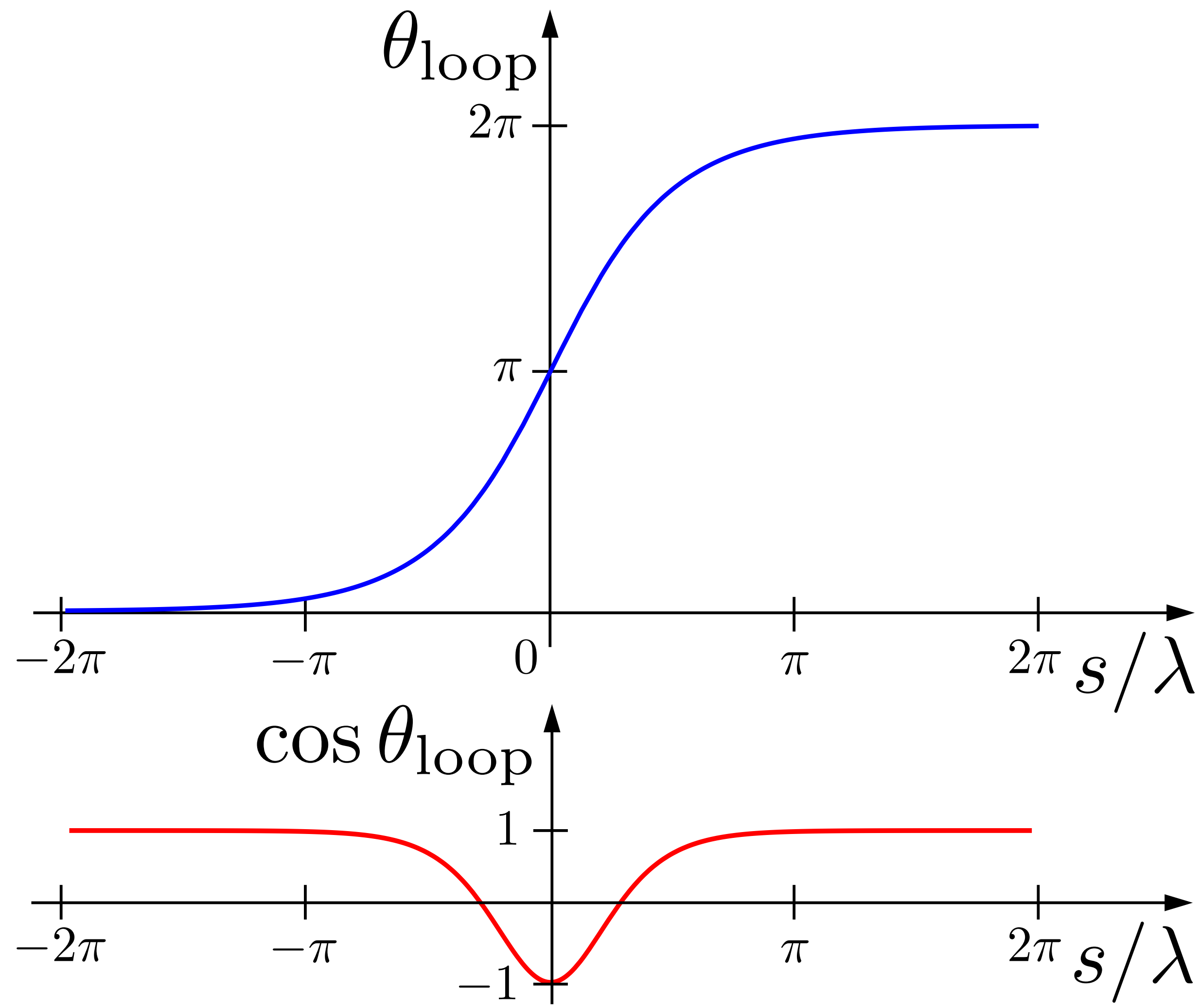
$\theta_{\text{loop}}(+\infty) = 2\pi$

DNA with a sliding loop under tension



solution:

$$\cos\theta_{\mathrm{loop}}\left(s\right) = 1 - \frac{2}{\cosh^2\left(s/\lambda\right)}$$



DNA with a sliding loop under tension

lost length:

$$\Delta L = \int_{-\infty}^{\infty} \left(1 - \cos\theta_{\text{loop}}\left(s\right)\right) ds = \int_{-\infty}^{\infty} \frac{2}{\cosh^2\left(s/\lambda\right)} ds = 4\lambda$$

extension-force relation:

$$\Delta z = L - \Delta L = L - 4\sqrt{A/f}$$

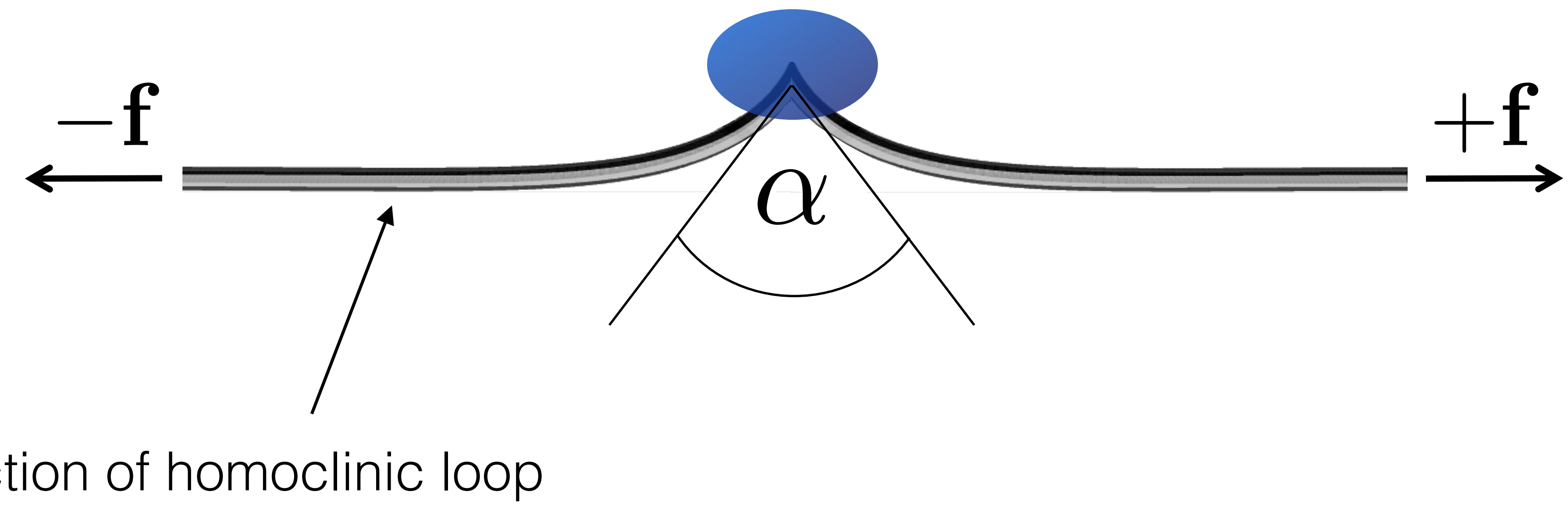
end-to-end distance

contour length

length loss due to loop

$$\Rightarrow \quad f = \frac{16A}{L^2}\frac{1}{\left(1 - \Delta z/L\right)^2}$$

DNA with a protein-induced kink



extension-force relation:

$$\Delta z = L - 4\sqrt{\frac{A}{f}}\left(1 - \cos\left(\frac{\pi - \alpha}{4}\right)\right)$$

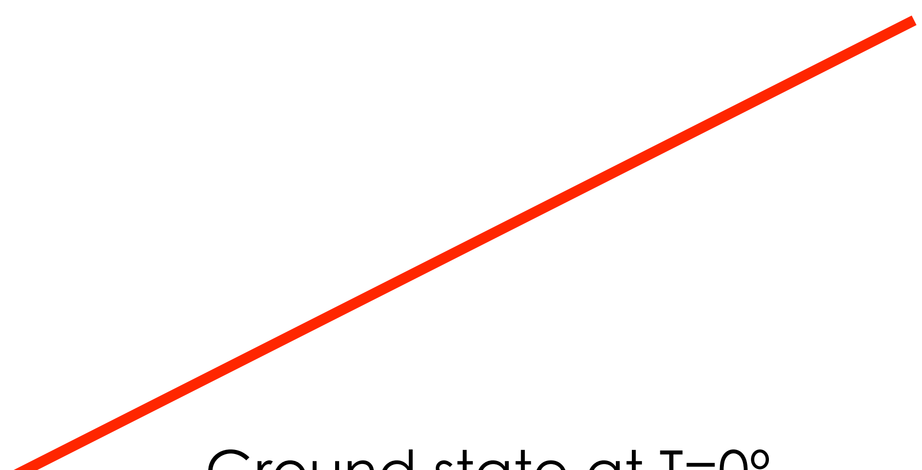
“Hot” DNA

Up to now we looked at “cold” DNA.

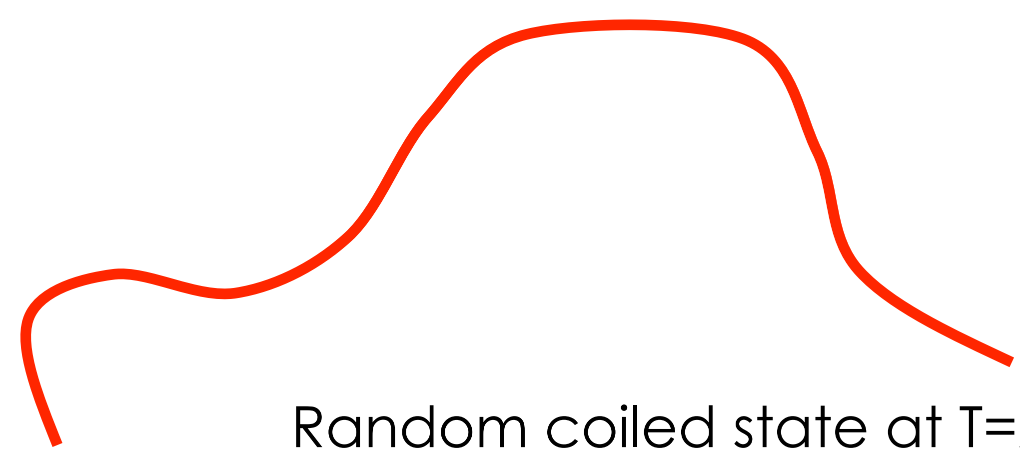
<u>But:</u> The energy scales involved in biological systems are often on the order of the thermal energy:

$$k_B T = 4.1\,\mathrm{pN\,nm}$$

In case of DNA this means that it is “coiled up” at room temperature:



Ground state at T=0°



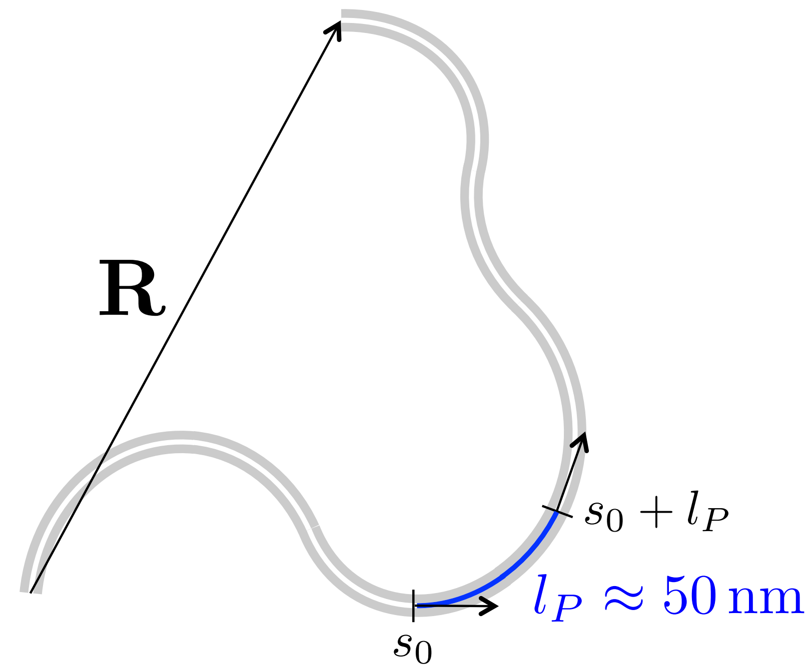
Random coiled state at T=20°

“Hot” DNA

see Omar Saleh’s lecture today

wormlike chain:

$$H = \frac{A}{2}\int \dot{\theta}^2 ds$$



tangent-tangent correlation function:

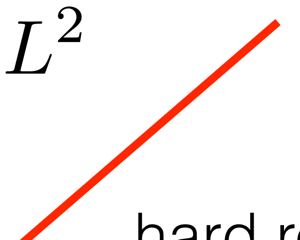
$$\langle \mathbf{t}\left(s_0\right)\mathbf{t}\left(s_0 + x\right)\rangle = e^{-x/l_P}$$

with the persistence length $l_P = A/k_BT$

limits:

$L \ll l_P$

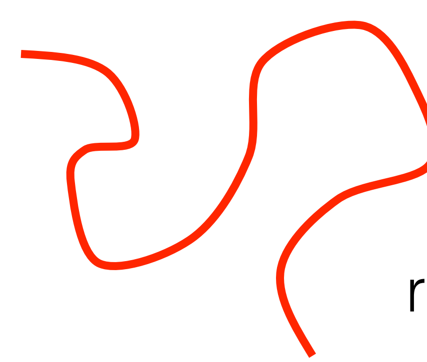
$$\langle R^2 \rangle \approx L^2$$



hard rod

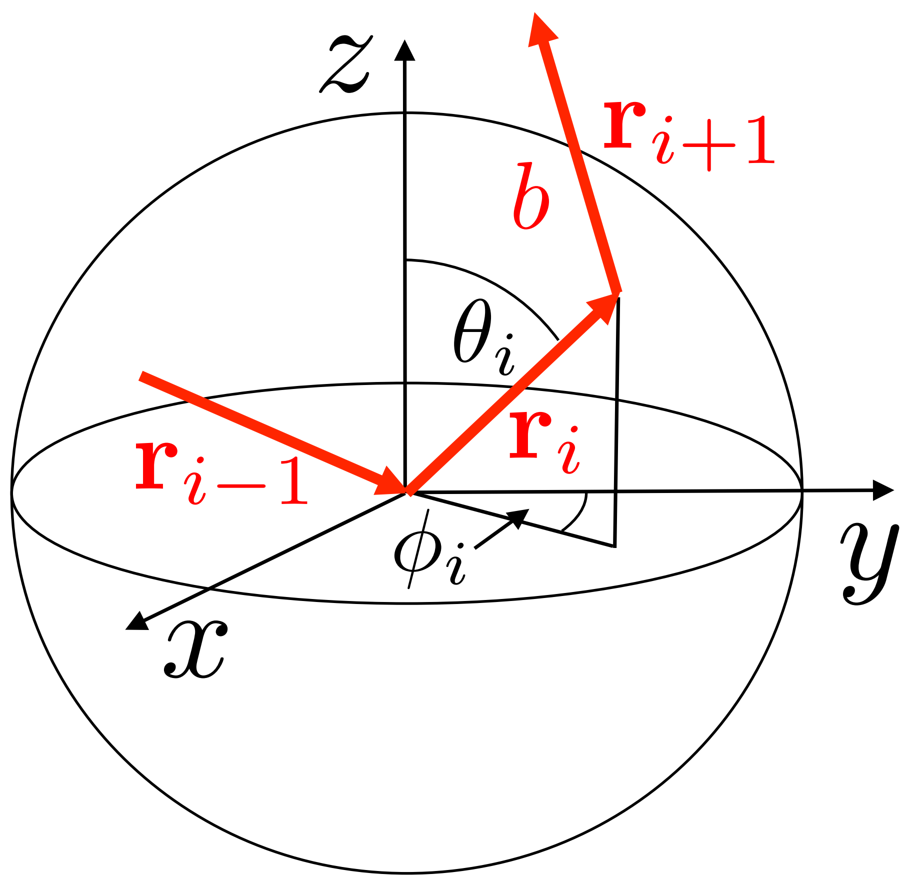
$L \gg l_P$

$$\langle R^2 \rangle \approx 2 l_P L$$



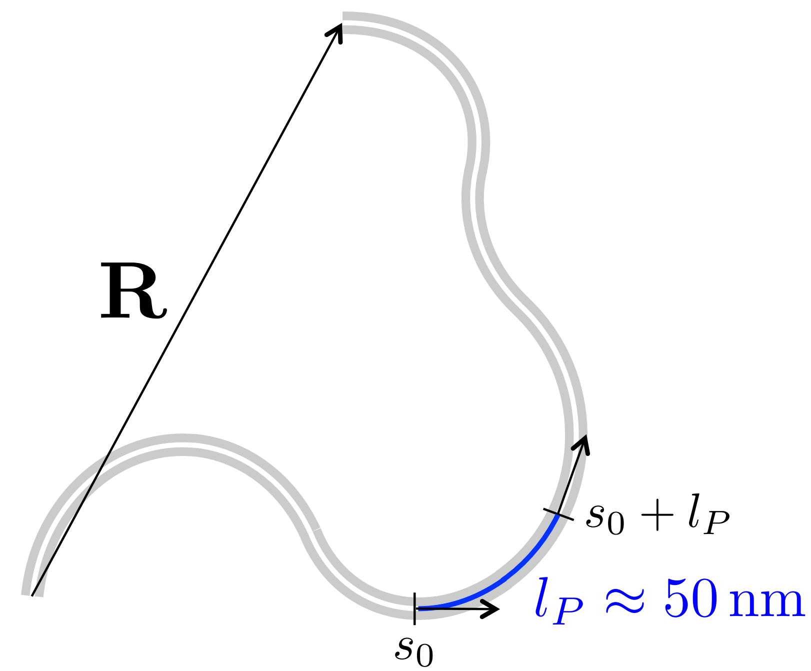
random coil

Analogy to freely jointed chain



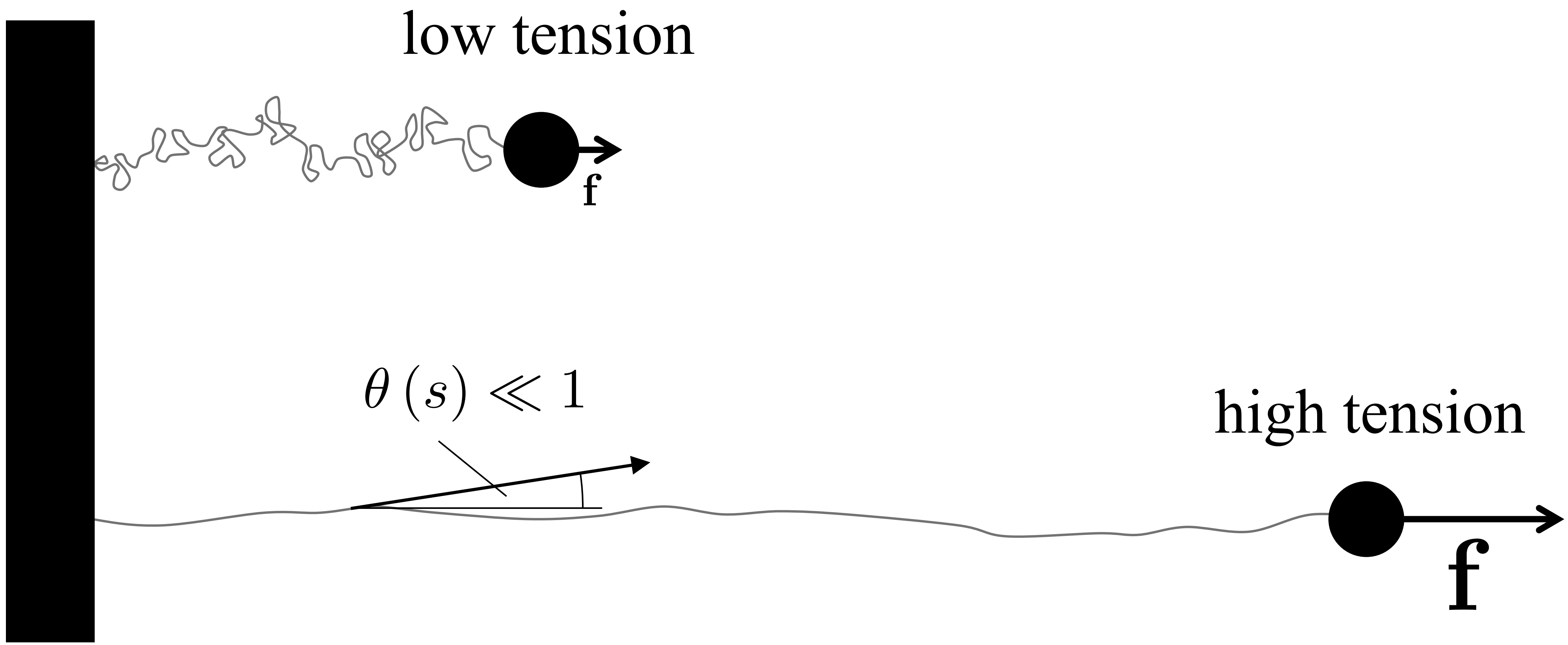
$1:1$

$b = 2l_P$



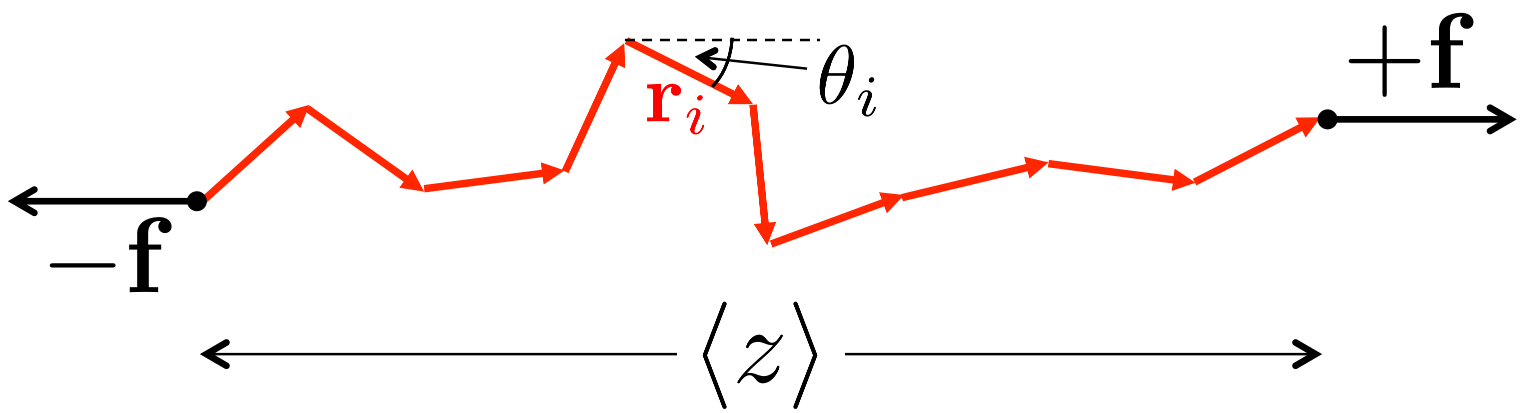
$$\langle \mathbf{R}^2 \rangle = b^2 N$$

$$\langle R^2 \rangle \approx 2 l_P L$$



Strategy: Calculate force-extension relation for freely jointed chain and then apply it to DNA with $b = 2l_P$.

Stretching a freely jointed chain



$$H = -f\sum_{i=1}^{N} b\cos\theta_i = -fz$$

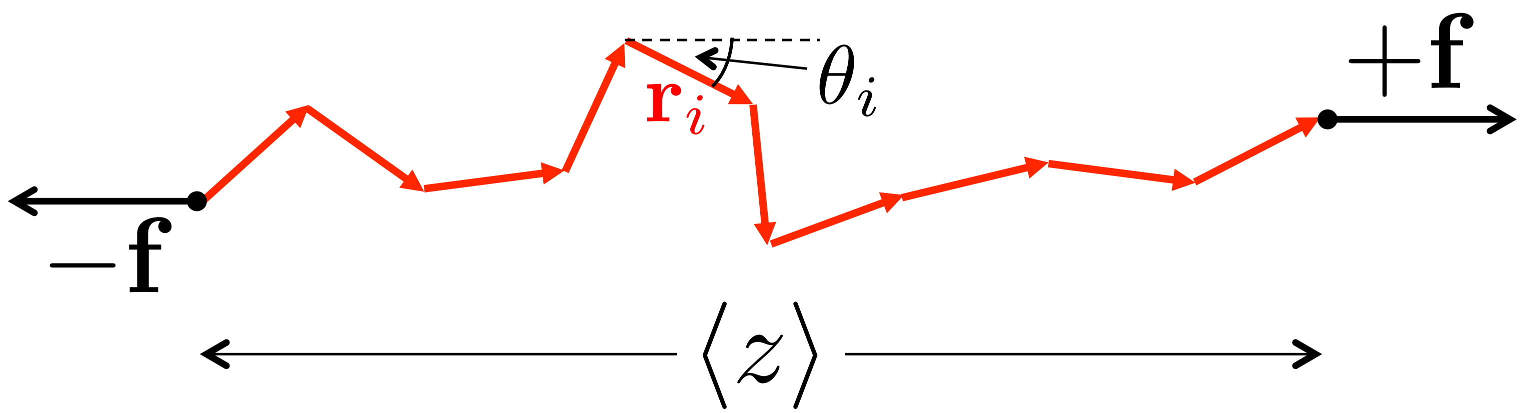
partition function:

$$Z = \int_0^{2\pi} d\phi_1 ... d\phi_N \int_0^{\pi} d\theta_1 ... d\theta_N \sin\theta_1 ... \sin\theta_N e^{-\beta H}$$

$$= (2\pi)^N \int_{-1}^{1} e^{\beta b f \sum_i \cos\theta_i} d\cos\theta_1 ... d\cos\theta_N$$

$$= (2\pi)^N \left(\int_{-1}^{1} e^{\beta b f u} du\right)^N = \left(\frac{4\pi}{\beta b f}\right)^N \sinh^N(\beta b f)$$

Stretching a freely jointed chain



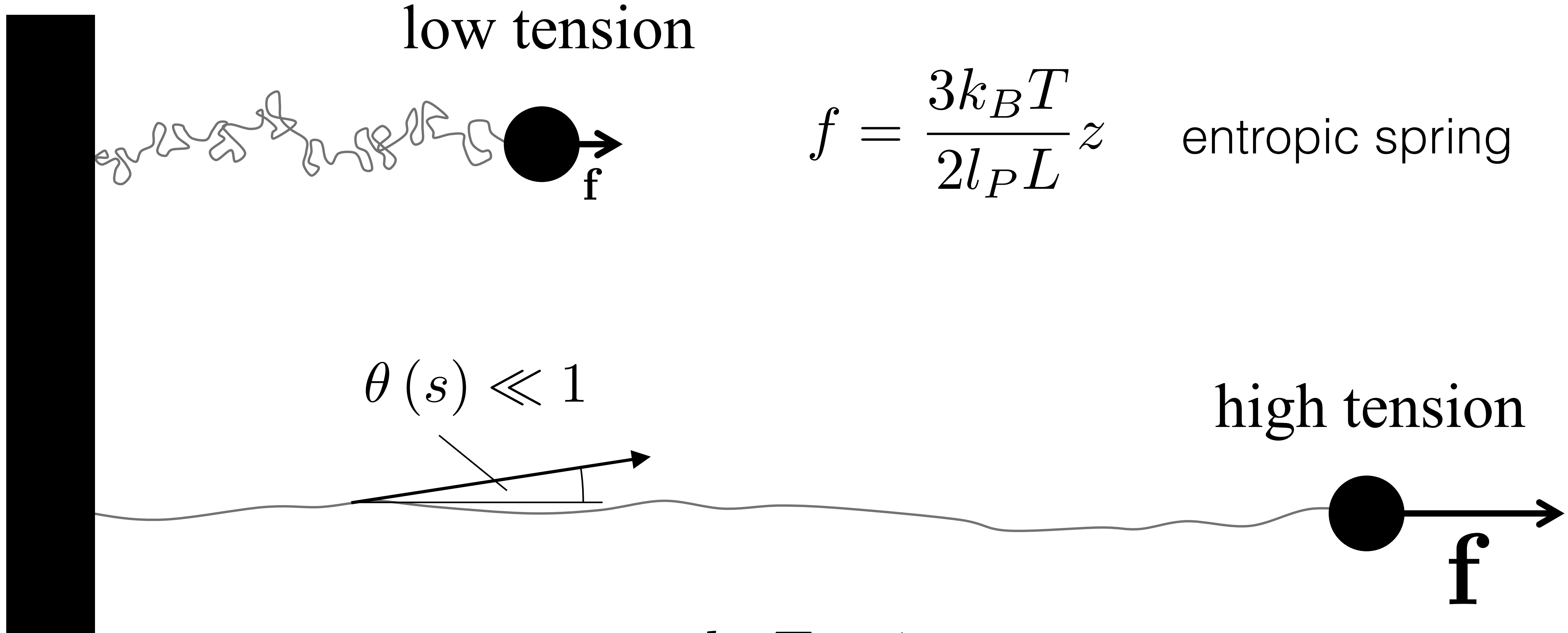
$$Z = \left(\frac{4\pi}{\beta b f}\right)^N \sinh^N(\beta b f)$$

$$\langle z \rangle = \frac{1}{\beta}\left(\frac{1}{Z}\frac{\partial Z}{\partial f}\right) = \frac{1}{\beta}\frac{\partial}{\partial f}\ln Z = \frac{N}{\beta}\frac{\partial}{\partial f}\ln\left(\frac{1}{f}\sinh(\beta b f)\right)$$

$$= bN\left(\coth(\beta b f) - \frac{1}{\beta b f}\right) = bN\mathcal{L}(\beta b f)$$

Langevin function

$$\simeq \begin{cases} \dfrac{b^2 N}{3k_B T} f & \text{for } \beta b f \ll 1 \\ bN - \dfrac{N}{\beta f} & \text{for } \beta b f \gg 1 \end{cases}$$



$$f = \frac{3k_BT}{2l_PL}z$$

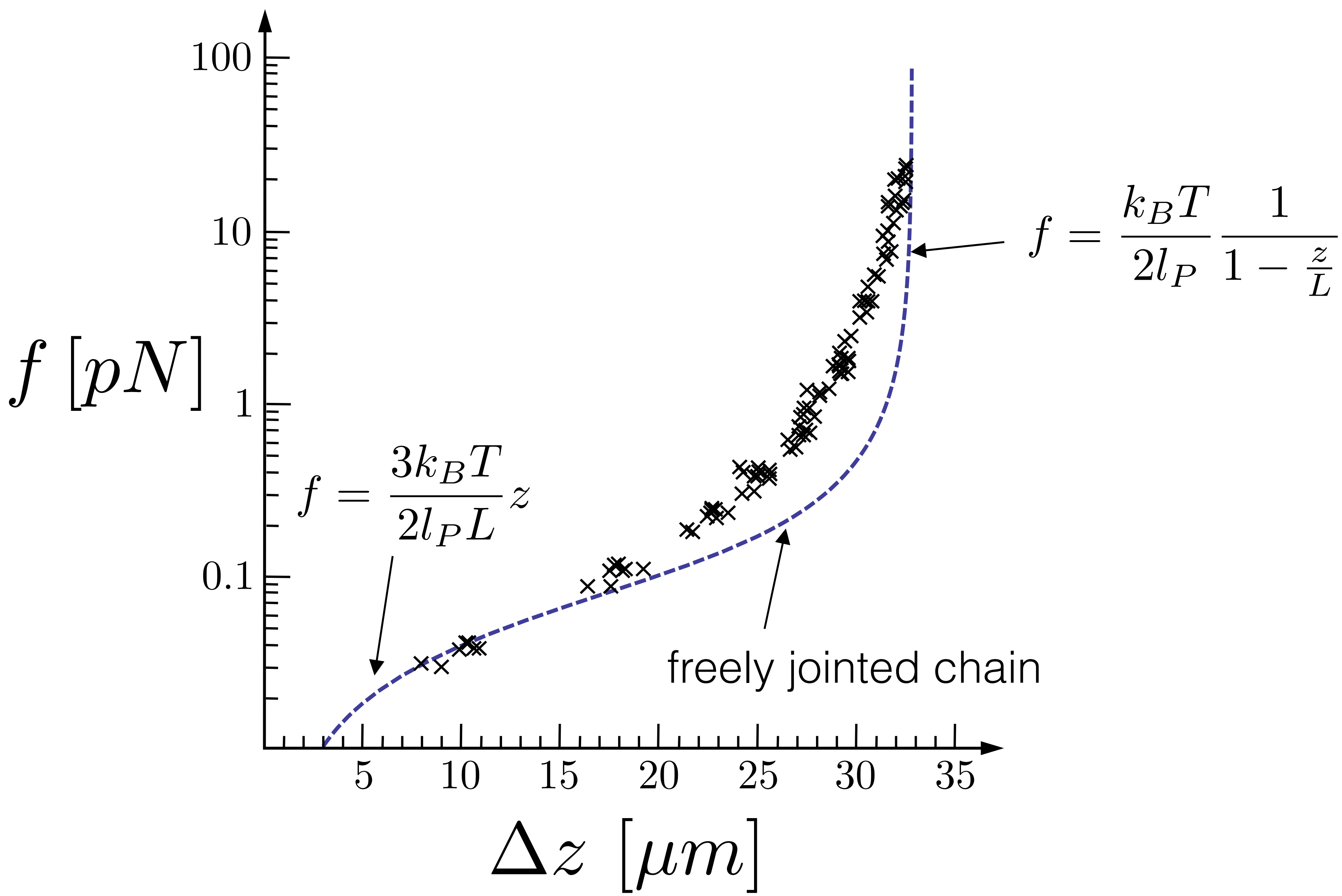
entropic spring

$$f = \frac{k_BT}{2l_P}\frac{1}{1-\frac{z}{L}}$$

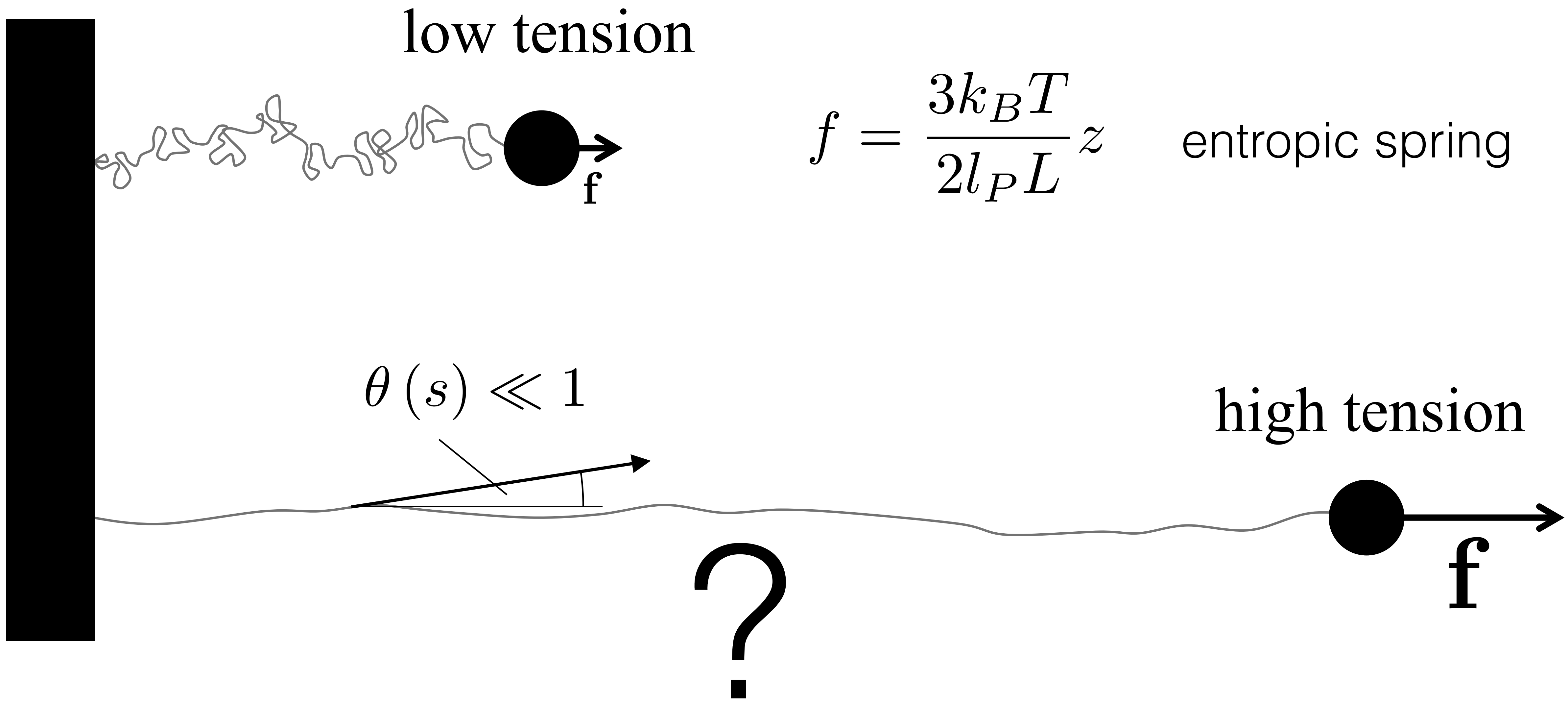
?

Comparison to experiment

force-extension relation for 97 kbp DNA:
Smith, Finzi, Bustamante, Science **258**, 1122 (1992)



Stretching DNA



$$f = \frac{3k_B T}{2l_P L} z$$

entropic spring

Stretching DNA

$$H = \int_0^L \left[\frac{A}{2}\dot{\theta}^2 + \frac{f}{2}\theta^2\right] ds - fL = \sum_n \left(\frac{2\pi^2 A}{L} n^2 + \frac{fL}{2}\right) \left|\hat{\theta}_n\right|^2 - fL$$

$$\theta \ll 1$$

$$\theta\left(s\right) = \sum_{n=-\infty}^{\infty} \hat{\theta}_n e^{-2\pi i n s/L}$$

Fourier series

equipartition theorem:

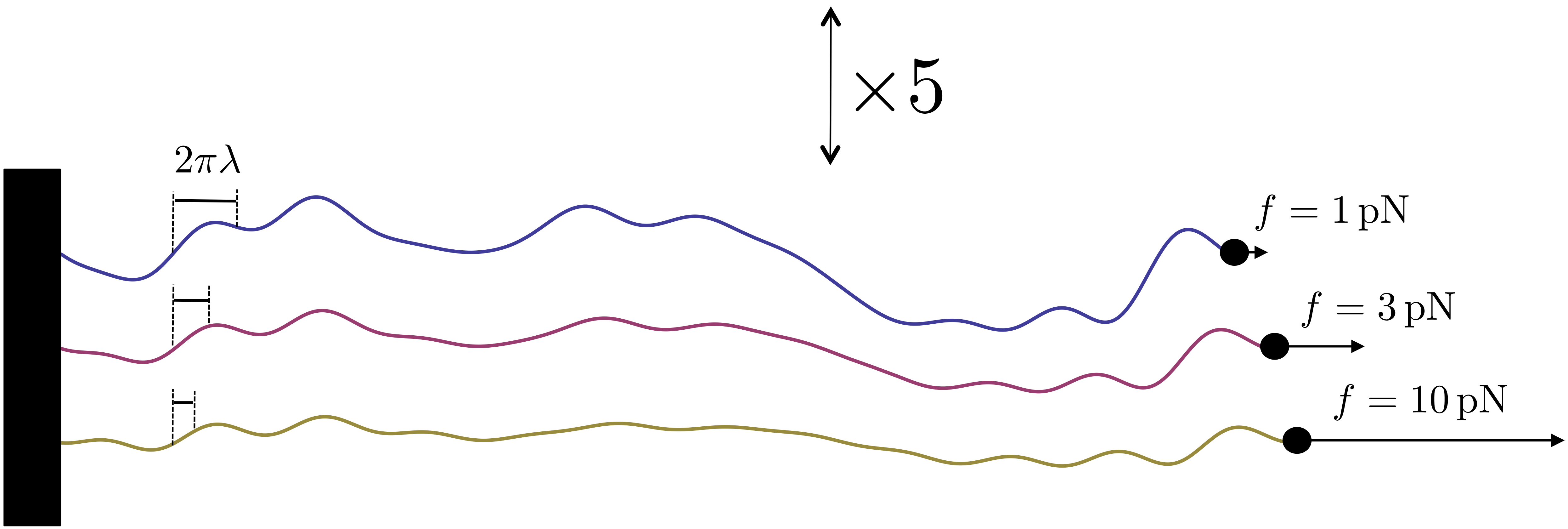
$$\left\langle \left|\hat{\theta}_n\right|^2 \right\rangle = \frac{k_B T}{\left(4A\pi^2/L\right) n^2 + fL}$$

characteristic length scale:

$$\frac{L}{n} = 2\pi\sqrt{\frac{A}{f}} = 2\pi\lambda$$

Stretching DNA

Odijk, Macromolecules **28**, 7016 (1995)



Stretching DNA

end-to-end distance (2D):

$$\langle \Delta z \rangle = \int_0^L \langle \cos\theta\,(s) \rangle \, ds \approx \int_0^L \left(1 - \frac{1}{2} \left\langle \theta^2\,(s) \right\rangle \right) ds$$

$$= L - \frac{L}{2} \sum\nolimits_n \left\langle \left| \hat{\theta}_n^2 \right| \right\rangle \approx L - \frac{L}{2} \int_{-\infty}^{\infty} \frac{k_B T}{\left(4A\pi^2/L\right) n^2 + fL} dn$$

$$= L \left(1 - \frac{k_B T}{4\sqrt{Af}} \right)$$

final result:

$$f = \frac{k_B T}{16 l_P} \frac{1}{\left(1 - \frac{\Delta z}{L}\right)^2} \quad \text{(2D)} \qquad\qquad f = \frac{k_B T}{4 l_P} \frac{1}{\left(1 - \frac{\Delta z}{L}\right)^2} \quad \text{(3D)}$$

Stretching DNA

Summary:

$$f = \frac{3k_BT}{2l_PL}\Delta z \qquad \text{for} \quad \Delta z \ll L$$

$$f = \frac{k_BT}{4l_P}\frac{1}{\left(1-\frac{\Delta z}{L}\right)^2} \qquad \text{for} \quad L-\Delta z \ll L$$

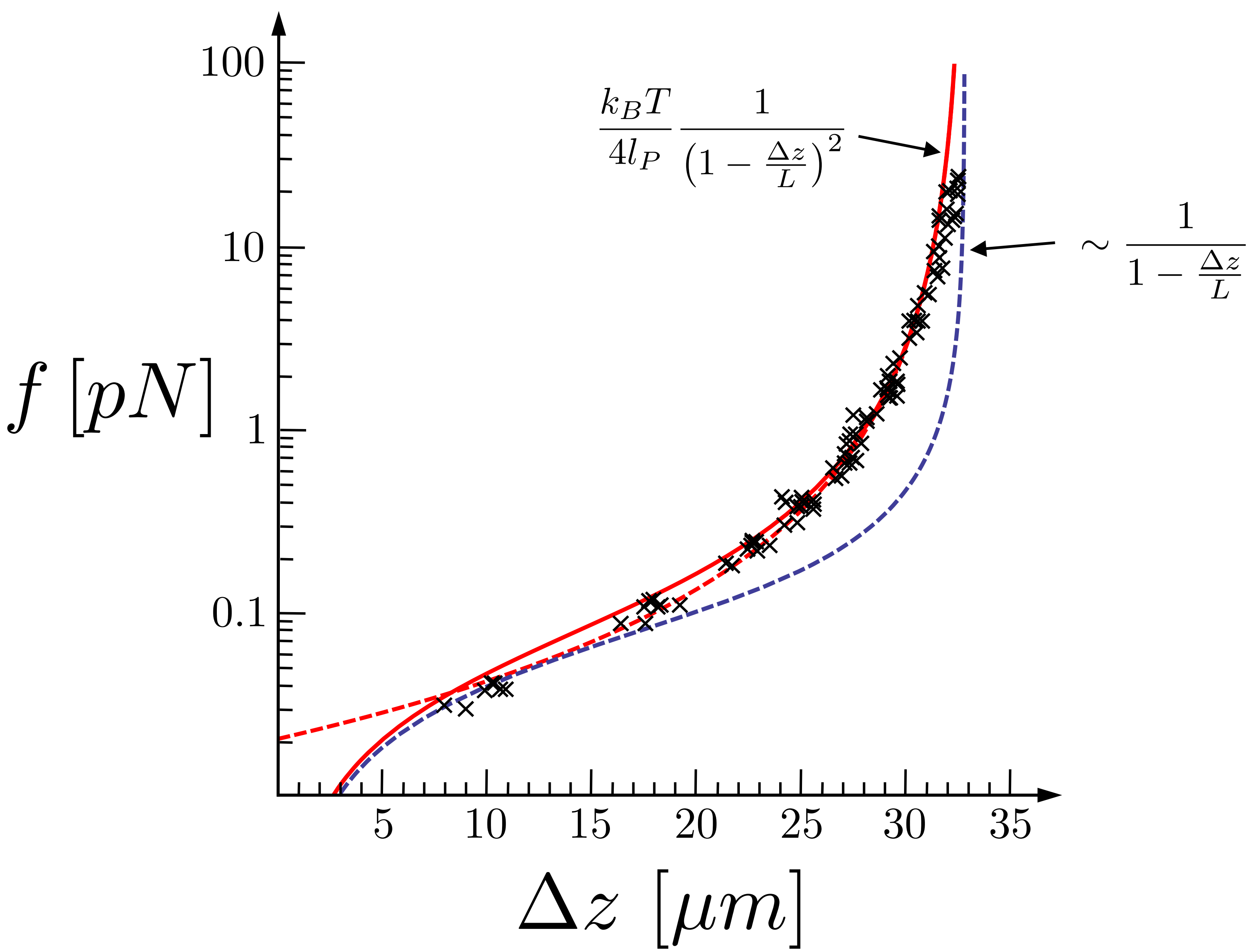
Interpolation formula:

Bustamante, Marko, Siggia, Smith, Science, **265**, 1599 (1994)

$$f = \frac{k_BT}{l_P}\left(\frac{1}{4}\frac{1}{\left(1-\frac{\Delta z}{L}\right)^2} - \frac{1}{4} + \frac{\Delta z}{L}\right)$$

Stretching DNA

force-extension relation for 97 kbp DNA:
Smith, Finzi, Bustamante, Science **258**, 1122 (1992)



freely jointed chain

$$f = \frac{k_B T}{4 l_P} \frac{1}{(1-\frac{\Delta z}{L})^2}$$

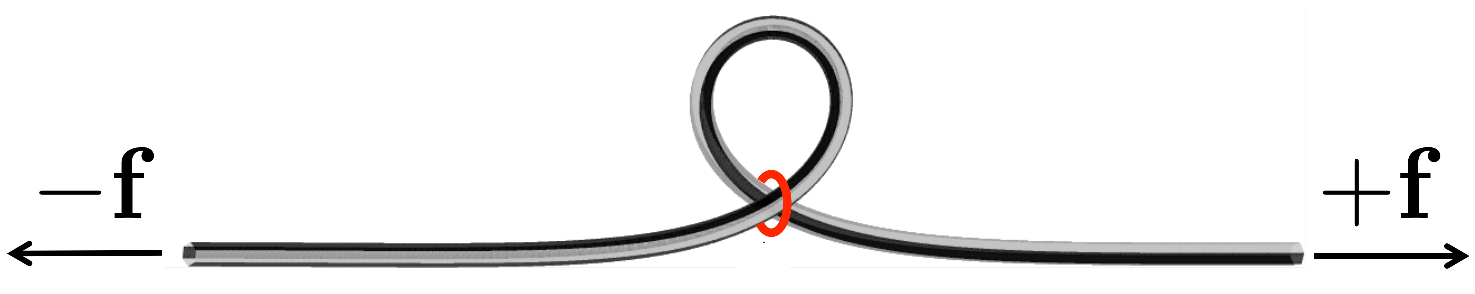
$$f = \frac{k_B T}{l_P}\left(\frac{1}{4}\frac{1}{(1-\frac{\Delta z}{L})^2} - \frac{1}{4} + \frac{\Delta z}{L}\right)$$

$$L = 32.8\,\mu\text{m}$$

$$l_P = 50\,\text{nm}$$

Comparison

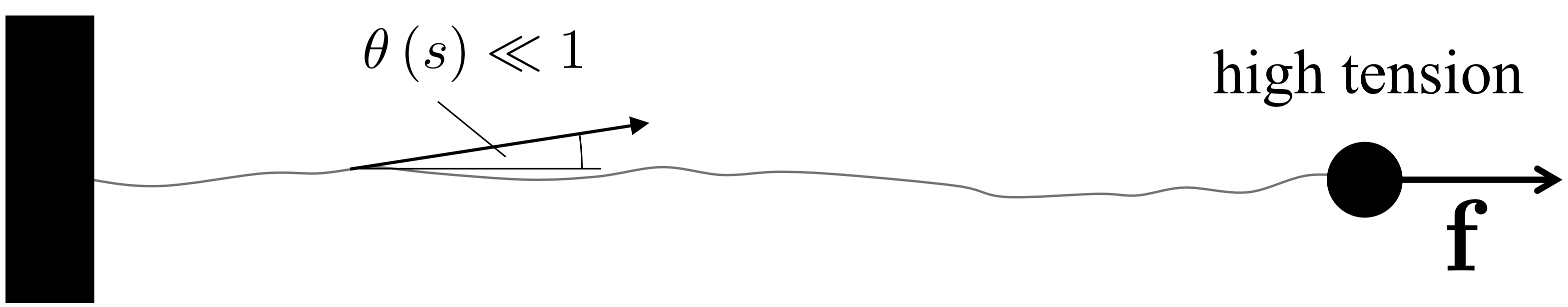
loop under tension at zero temperature:



$$f = \frac{16A}{L^2}\frac{1}{(1-\Delta z/L)^2}$$

same functional form

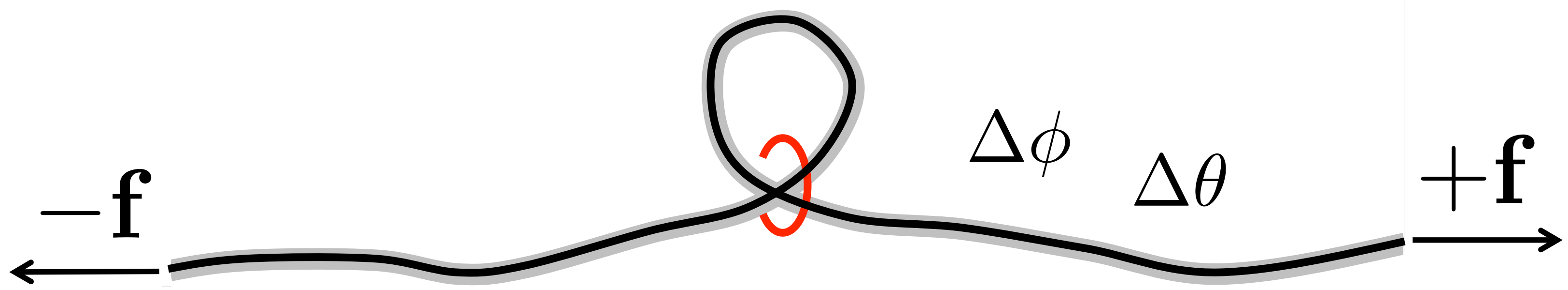
high tension limit at finite temperature:



$$f = \frac{k_B T}{4 l_P}\frac{1}{(1-\Delta z/L)^2}$$

Sliding loop with fluctuations

Kulic, Mohrbach, Lobaskin, Thaokar, HS, Phys. Rev. E **72** (2005) 041905



long calculation gives:

$$\langle \Delta z \rangle = L - \frac{k_B T}{2\sqrt{Af}} L - 4\sqrt{\frac{A}{f}} + \cancel{\frac{9 k_B T}{4 f}}$$

length loss due to

fluctuations around straight configuration

loop

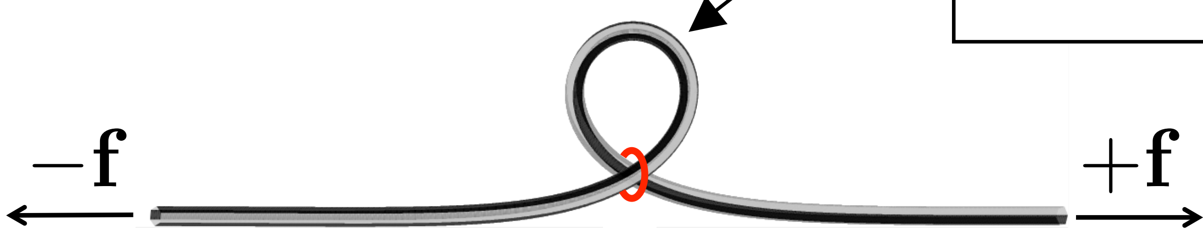
fluctuation correction
due to loop

Looped/kinked DNA appears softer

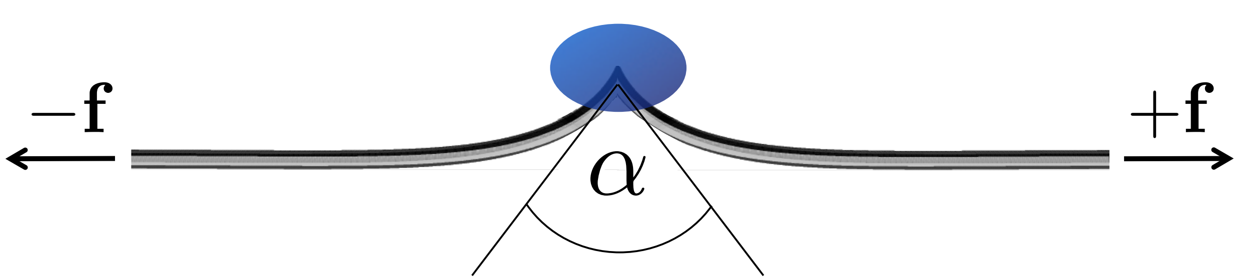
$$f = \frac{k_B T}{4 l_P^{\mathrm{app}}} \frac{1}{\left(1 - \langle \Delta z \rangle / L\right)^2}$$

Example:

$l_P^{\mathrm{app}} \approx 0.74 l_P$ for $L/l_P = 50$



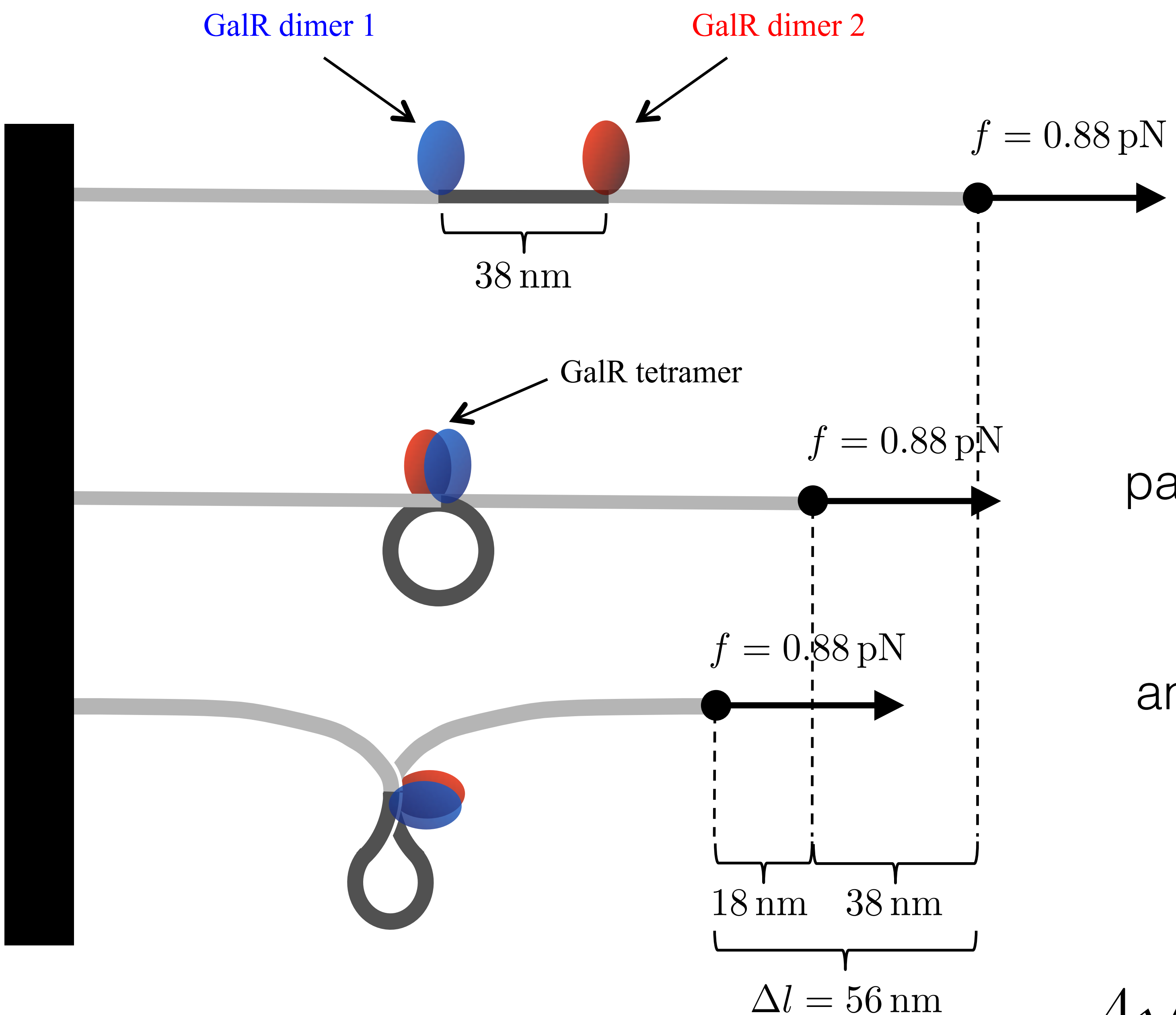
$$l_P^{\mathrm{app}} = \frac{l_P}{\left(1 + 8\frac{l_P}{L}\right)^2}$$



$$l_P^{\mathrm{app}} = \frac{l_P}{\left(1 + 8\frac{l_P}{L}\left(1 - \cos\left(\frac{\pi - \alpha}{4}\right)\right)\right)^2}$$

Example for kinked DNA: GalR repressor of E. coli

Lia et al., PNAS 100 (2003) 11373



experiment:

$$\Delta l = 55 \pm 5\mathrm{nm}$$

parallel loop configuration

$$\alpha = \pi$$

antiparallel loop configuration

$$\alpha = 0$$

$$4\sqrt{A/f}\left(1 - 1/\sqrt{2}\right) = 18\mathrm{nm}$$