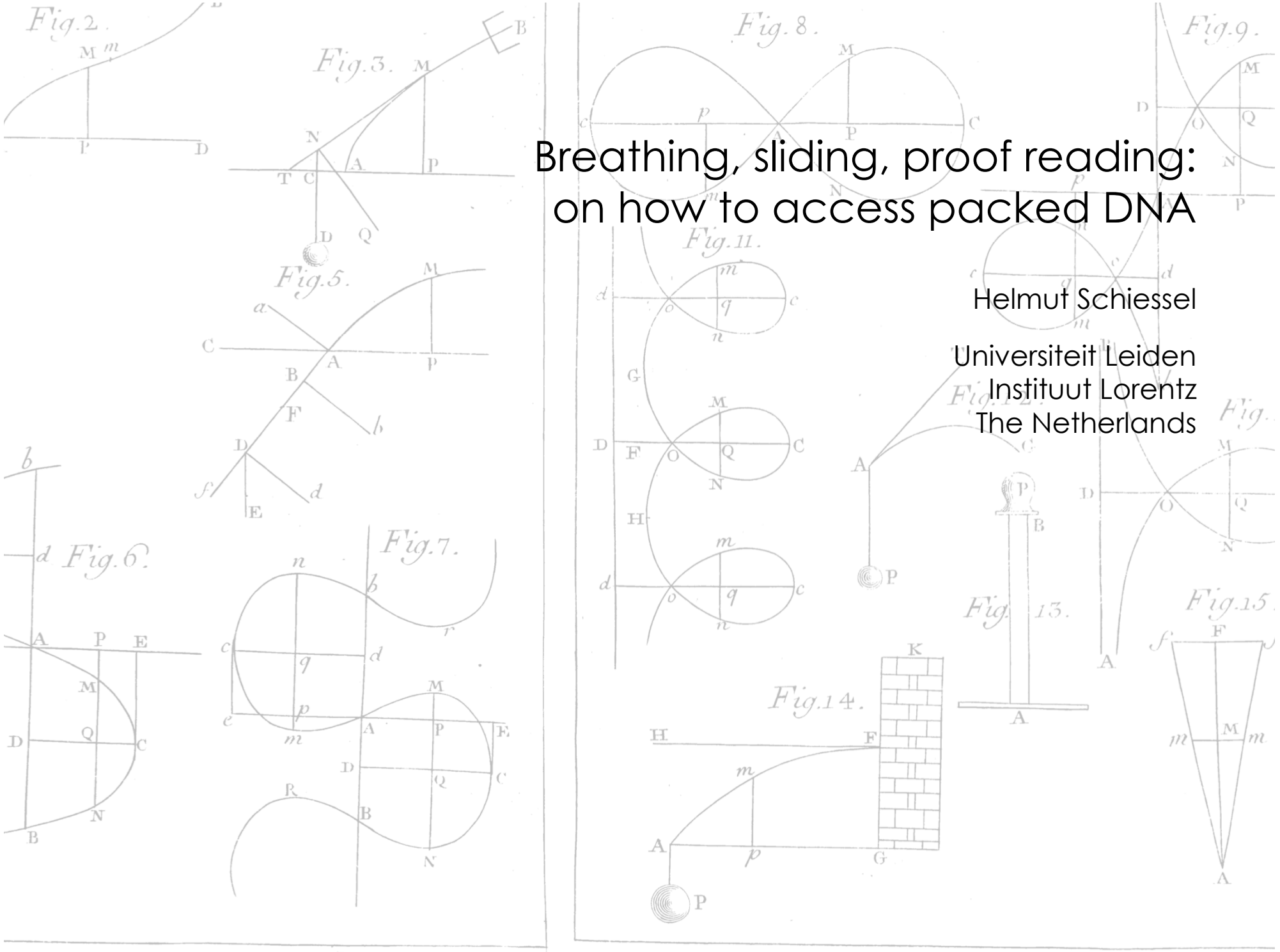


Breathing, sliding, proof reading: on how to access packed DNA

Helmut Schiessel

Universiteit Leiden
Instituut Lorentz
The Netherlands

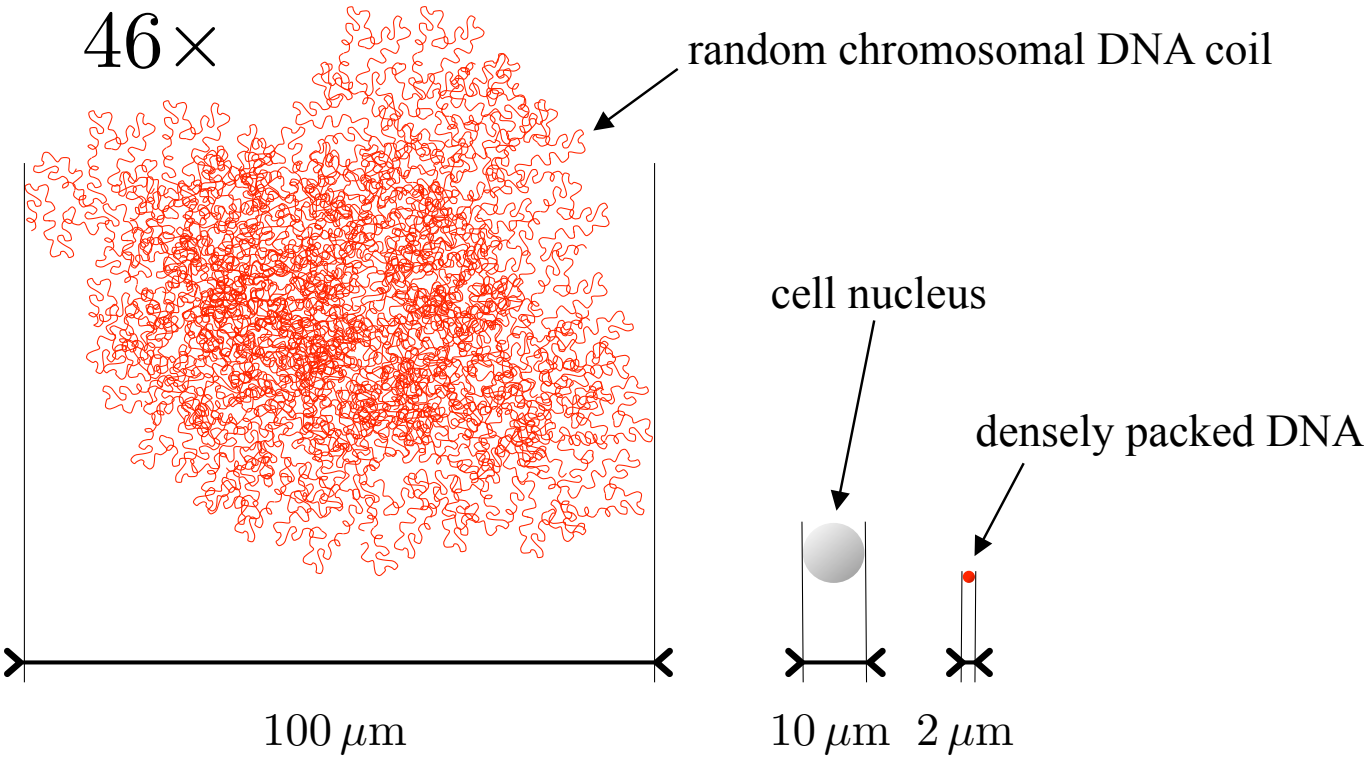
Numbers

human DNA per cell:

2 × human genome (2.9×10^9 bp)

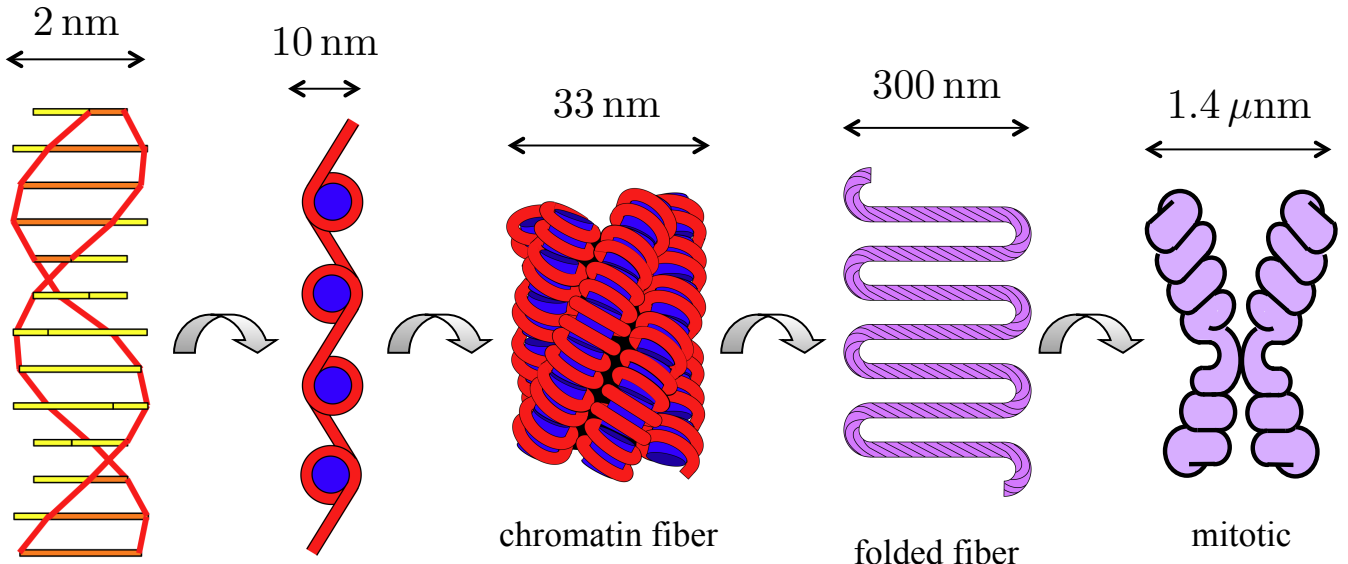
= 2 m DNA in total

= 46 chromosomes of length ≈ 4 cm

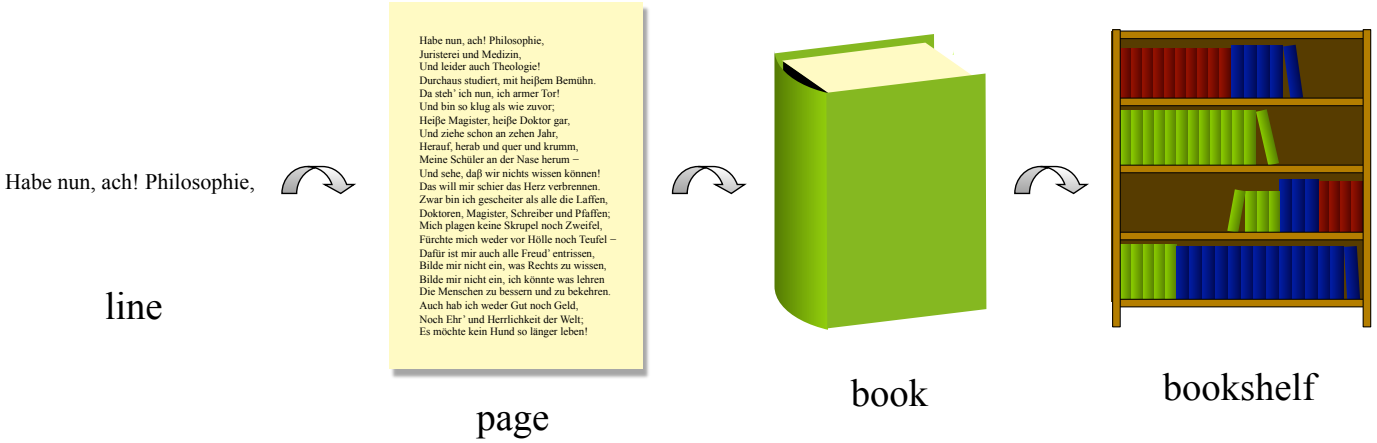


Hierarchical folding

chromatin:

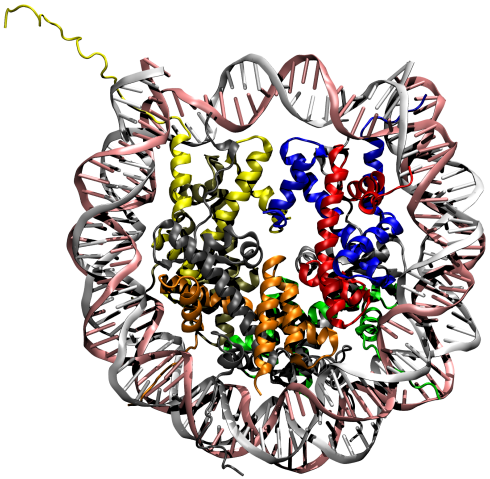


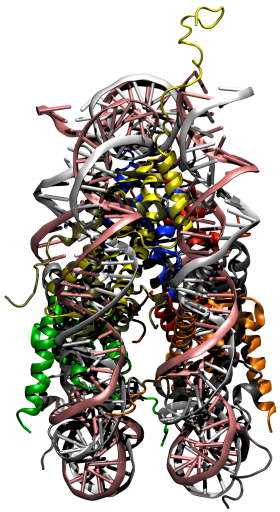
library:



Nucleosome

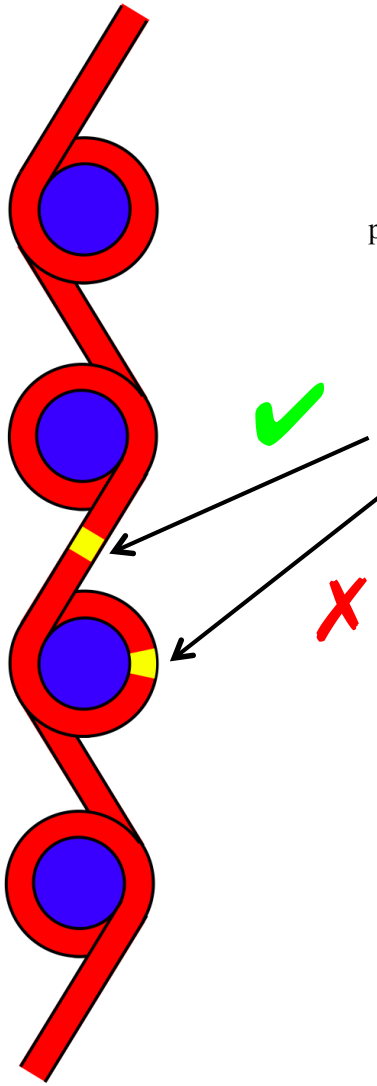
nucleosome core particle:

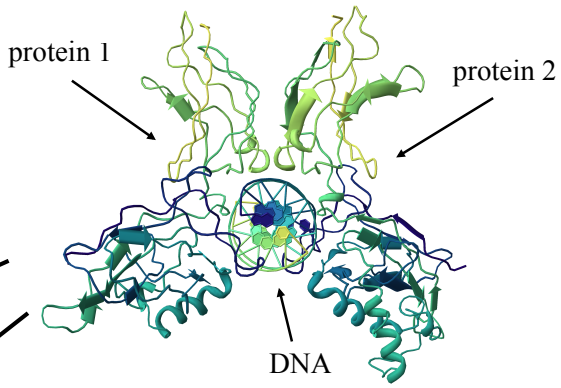




Luger et al., 97

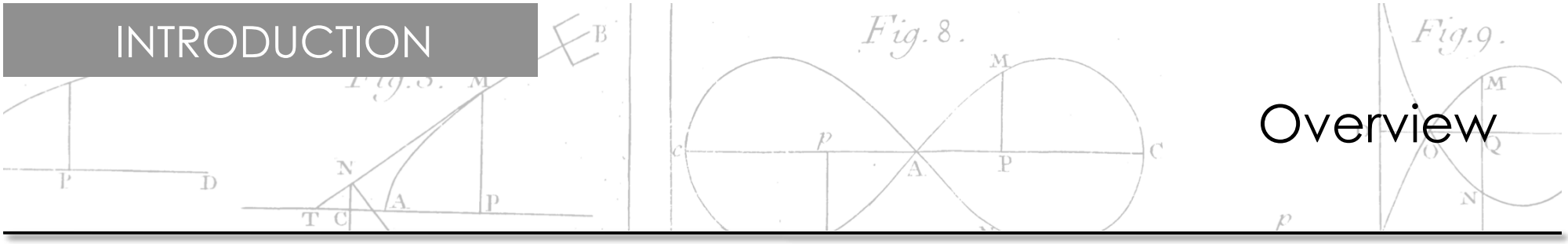
- 1 ¾ turns
- 147 bp, 50nm
- 14 binding sites





transcription factor

Chen et al., 98



Overview

BREATHING

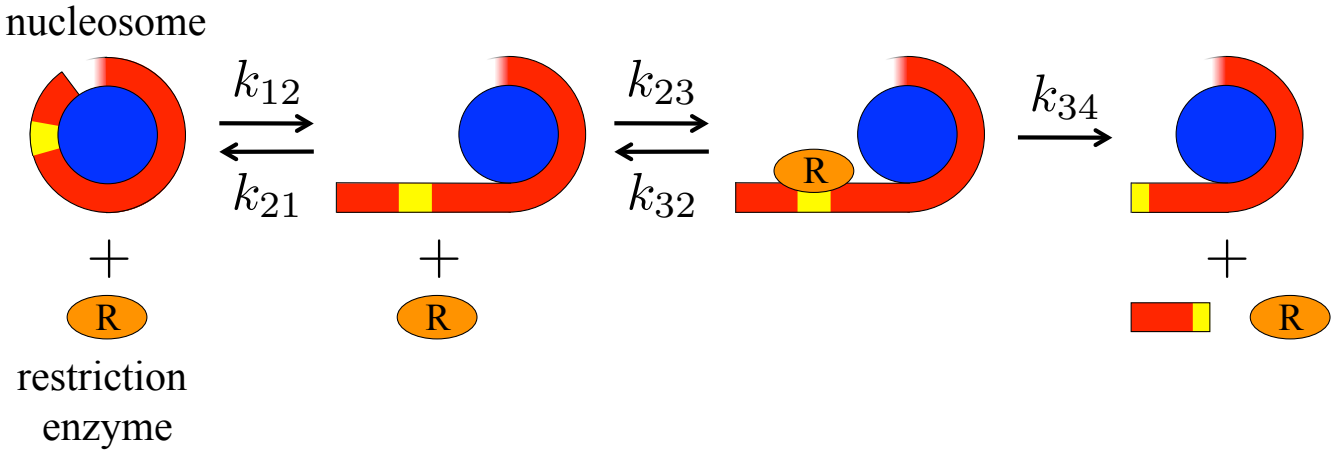
SLIDING

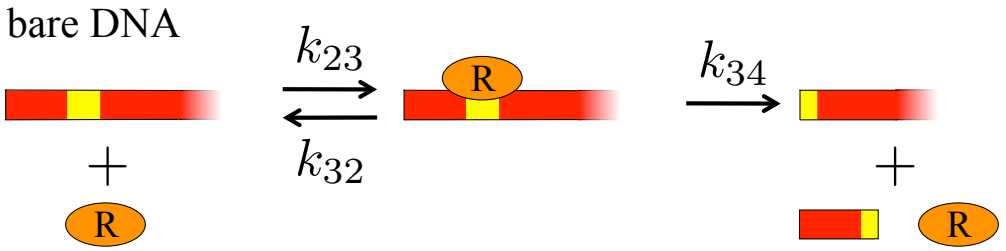
PROOFREADING

BREATHING

Site exposure mechanism

Polach & Widom, J. Mol. Biol. **254** (1995) 130





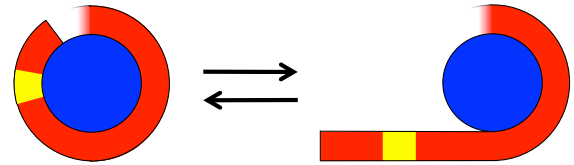
BREATHING

Probability for site open

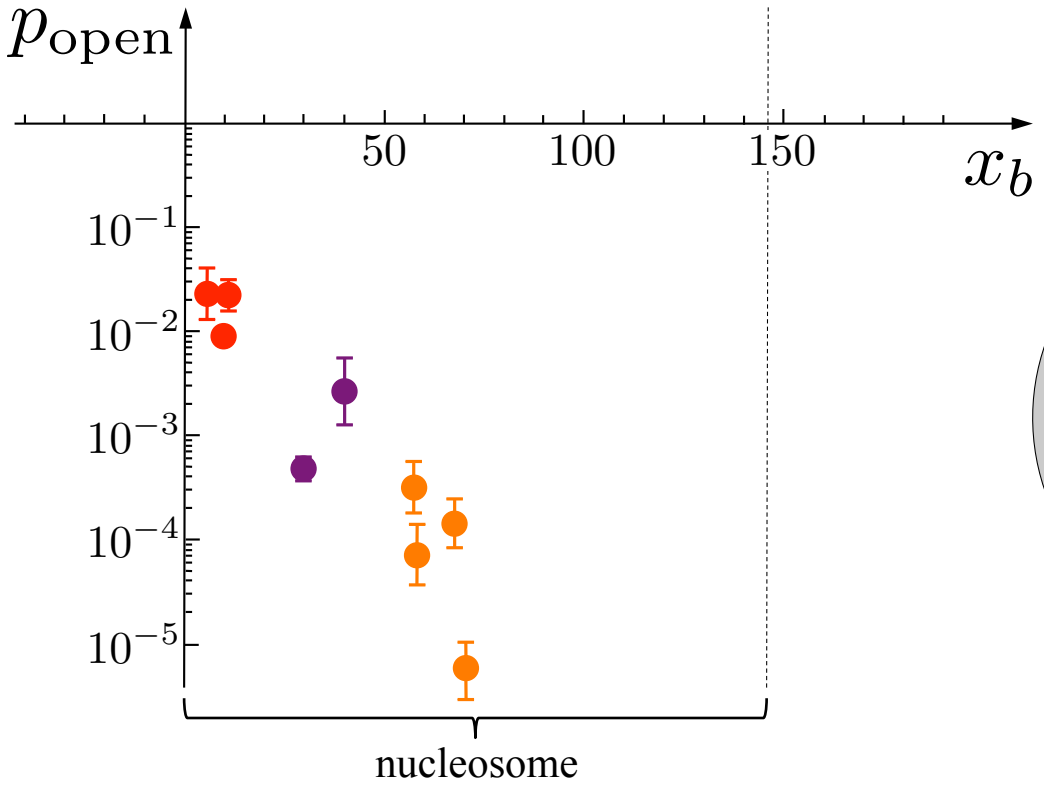
Polach & Widom, J. Mol. Biol. **254** (1995) 130

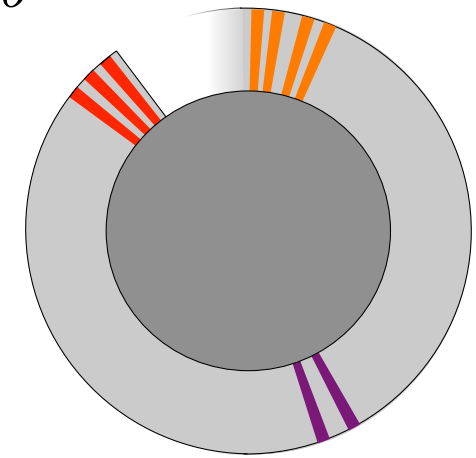
ratio of decay constants:

$$p_{\text{open}} \approx \frac{k_{\text{nucl}}}{k_{\text{bare}}}$$



$1 - p_{\text{open}}$ p_{open}

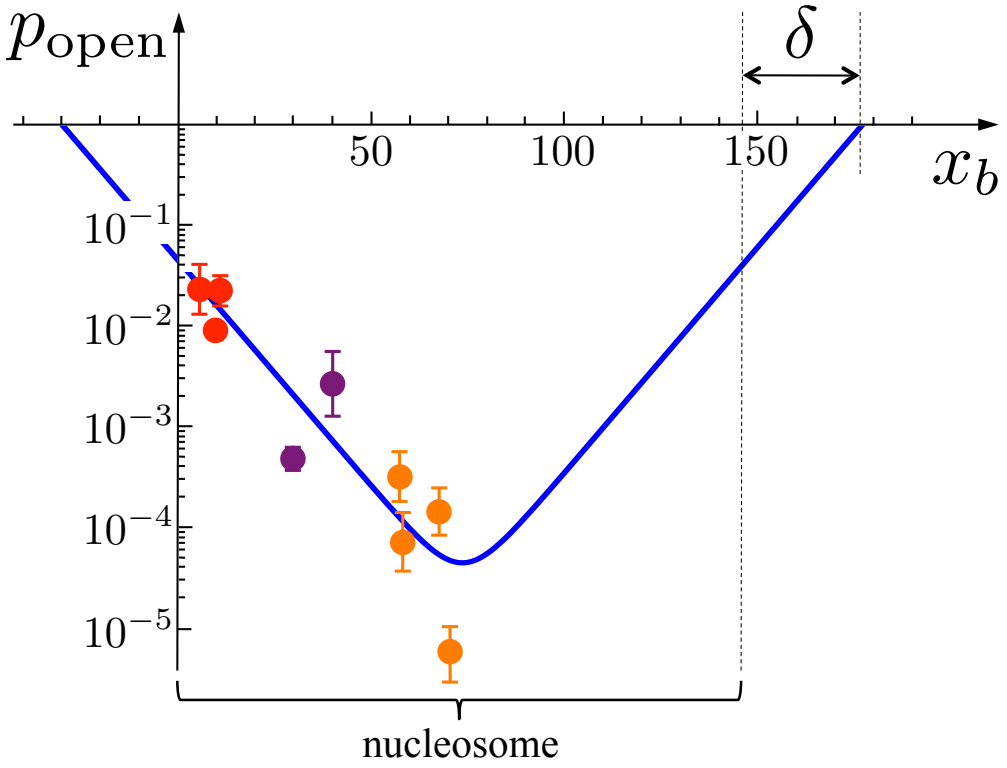




BREATHING

Critical force

Prinsen & HS, Biochimie **92** (2010) 1722

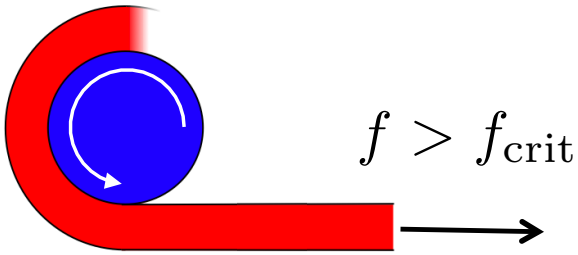


adsorption energy per length:

$$f_{\mathrm{crit}} \approx \frac{15 k_B T}{50\,\mathrm{nm}} = 1.2\,\mathrm{pN}$$

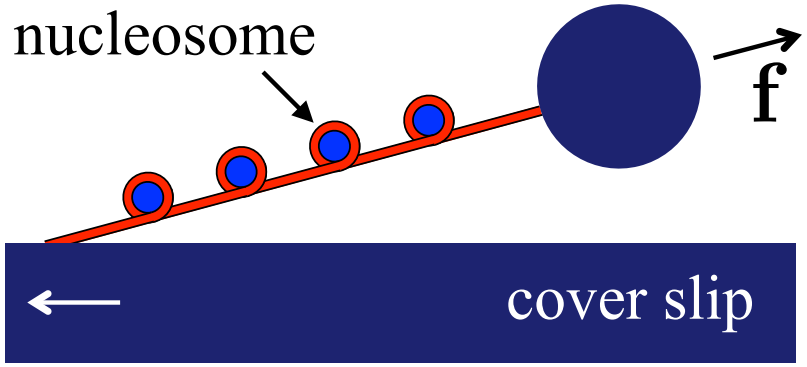
complexation energy:

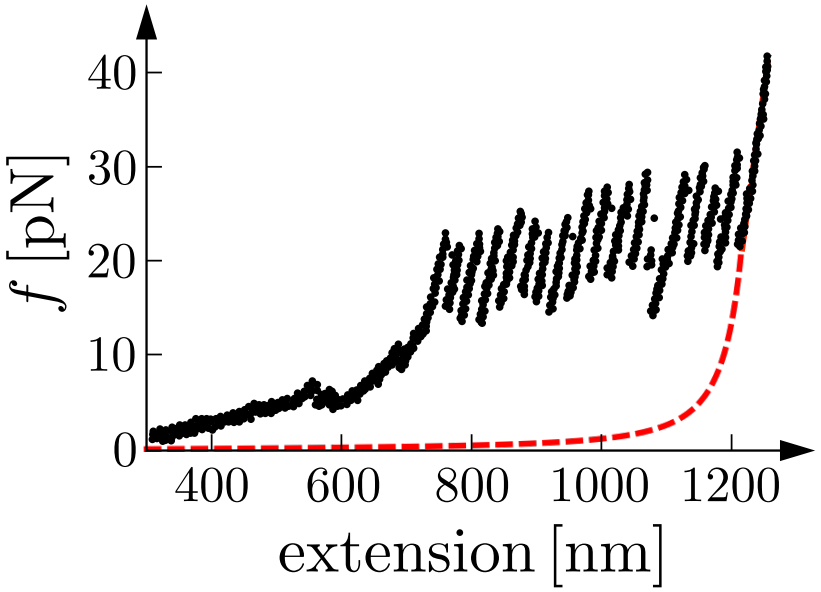
$$E_{\mathrm{complex}} \approx 15 k_B T$$



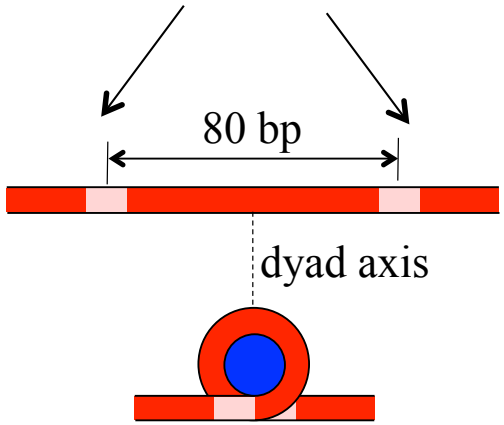
Force-induced unwrapping

Brower-Toland et al., PNAS **99** (2002) 1960





$E_b \approx 35 k_B T$



but:

$$f_{\text{crit}} \approx \frac{15\, k_B T}{50\,\text{nm}} = 1.2\,\text{pN}$$

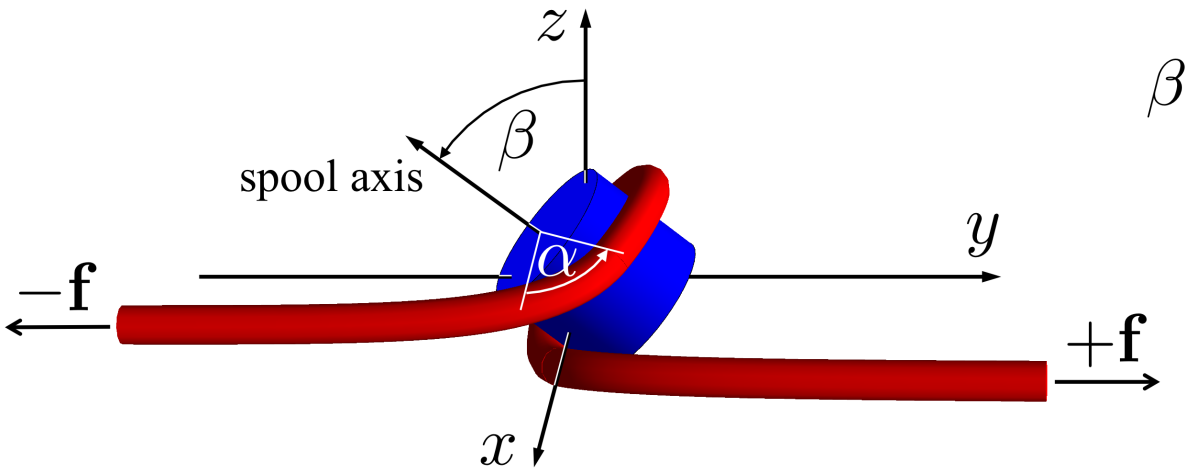
BREATHING

Force-induced unwrapping

Kulic & HS, Phys. Rev. Lett. **92** (2004) 228101

α : unwrapping angle

β : tilting angle

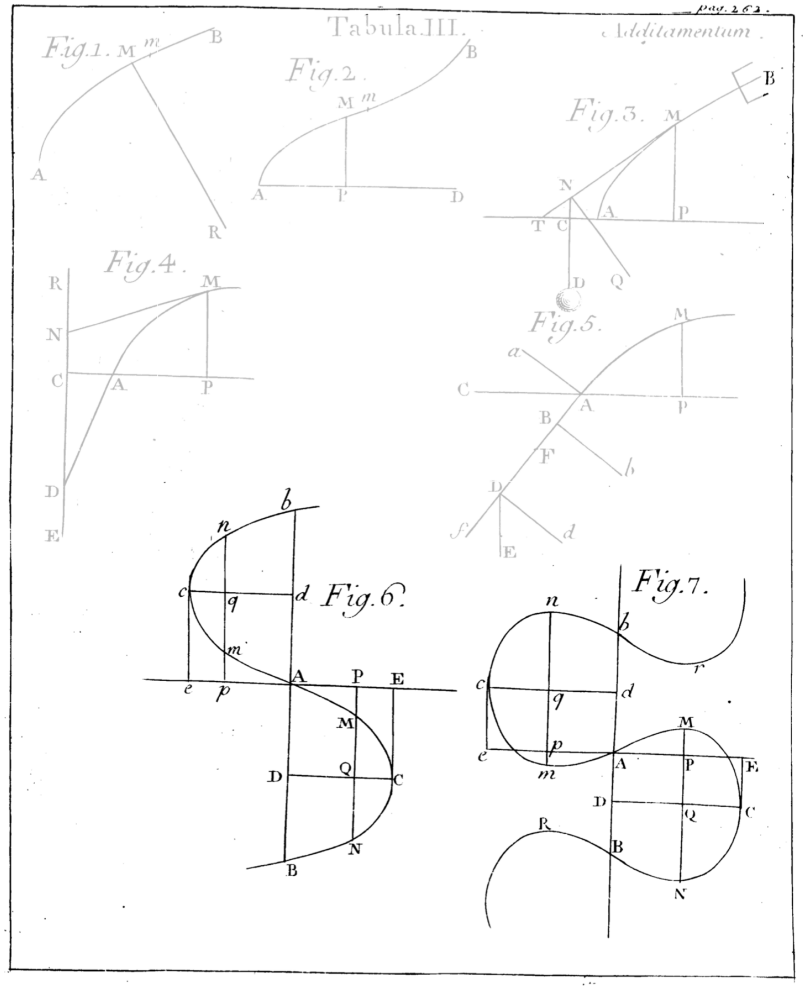


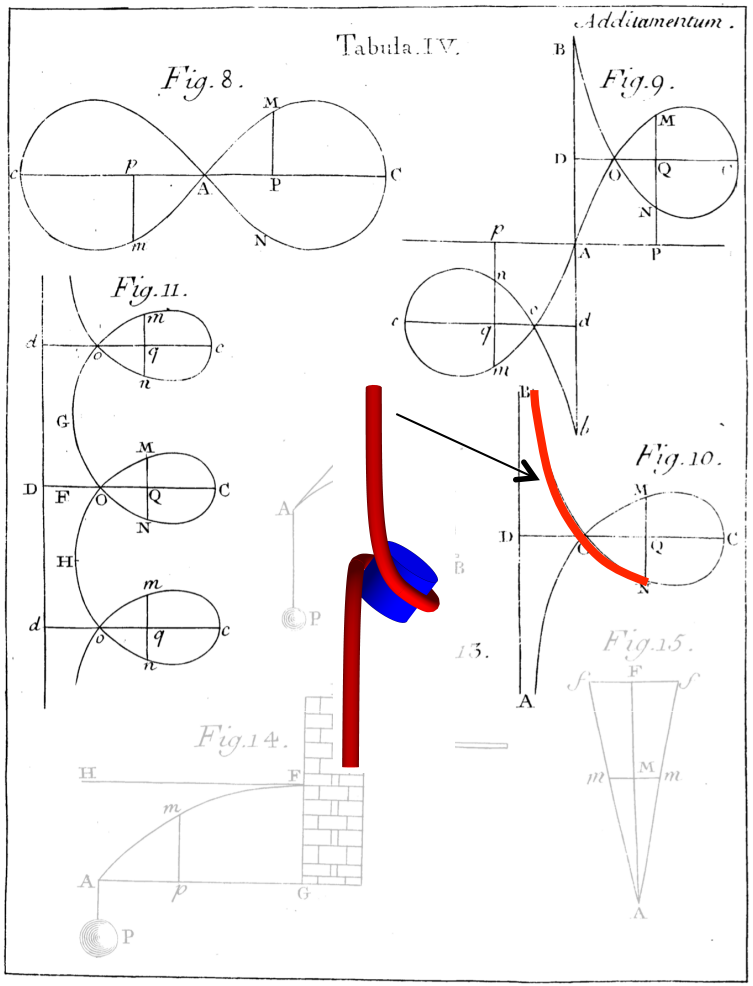
total energy:

$$E_{\mathrm{tot}} = \underbrace{\frac{A}{2}\int_0^L ds \left(\frac{1}{R(s)}\right)^2}_{\text{DNA bending}} \underbrace{- f L_{EE}}_{\text{external force}} \underbrace{+ 2R_0 f_{\mathrm{crit}} \alpha}_{\text{DNA adsorption}}$$

Euler elastica

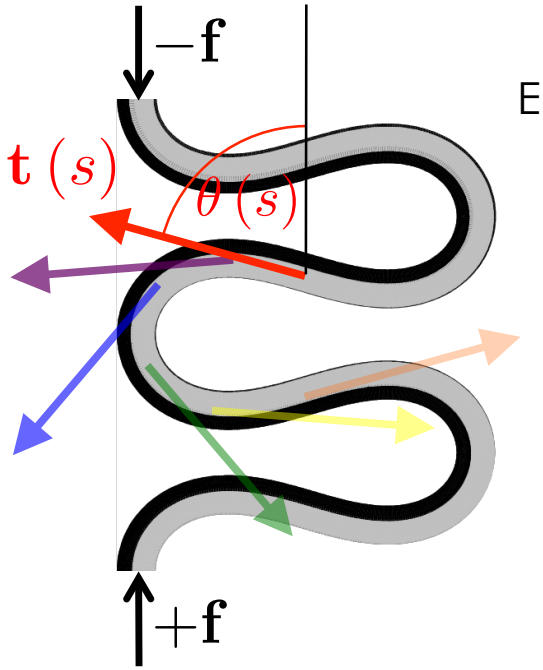
Leonard Euler, Methodus, 1744:





Kinetic analogy

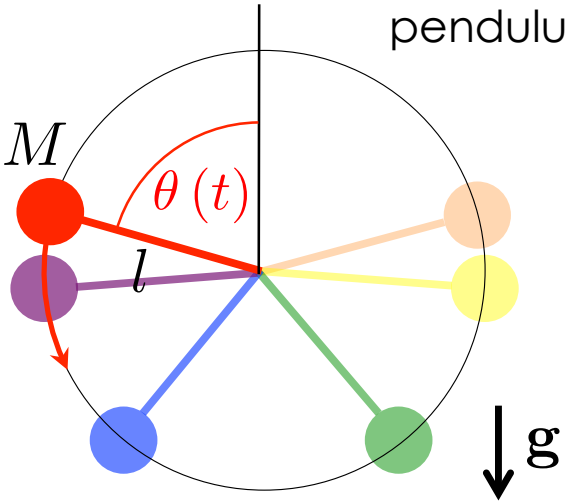
Gustav Kirchhoff, 1859



Euler elastica

1 : 1

pendulum



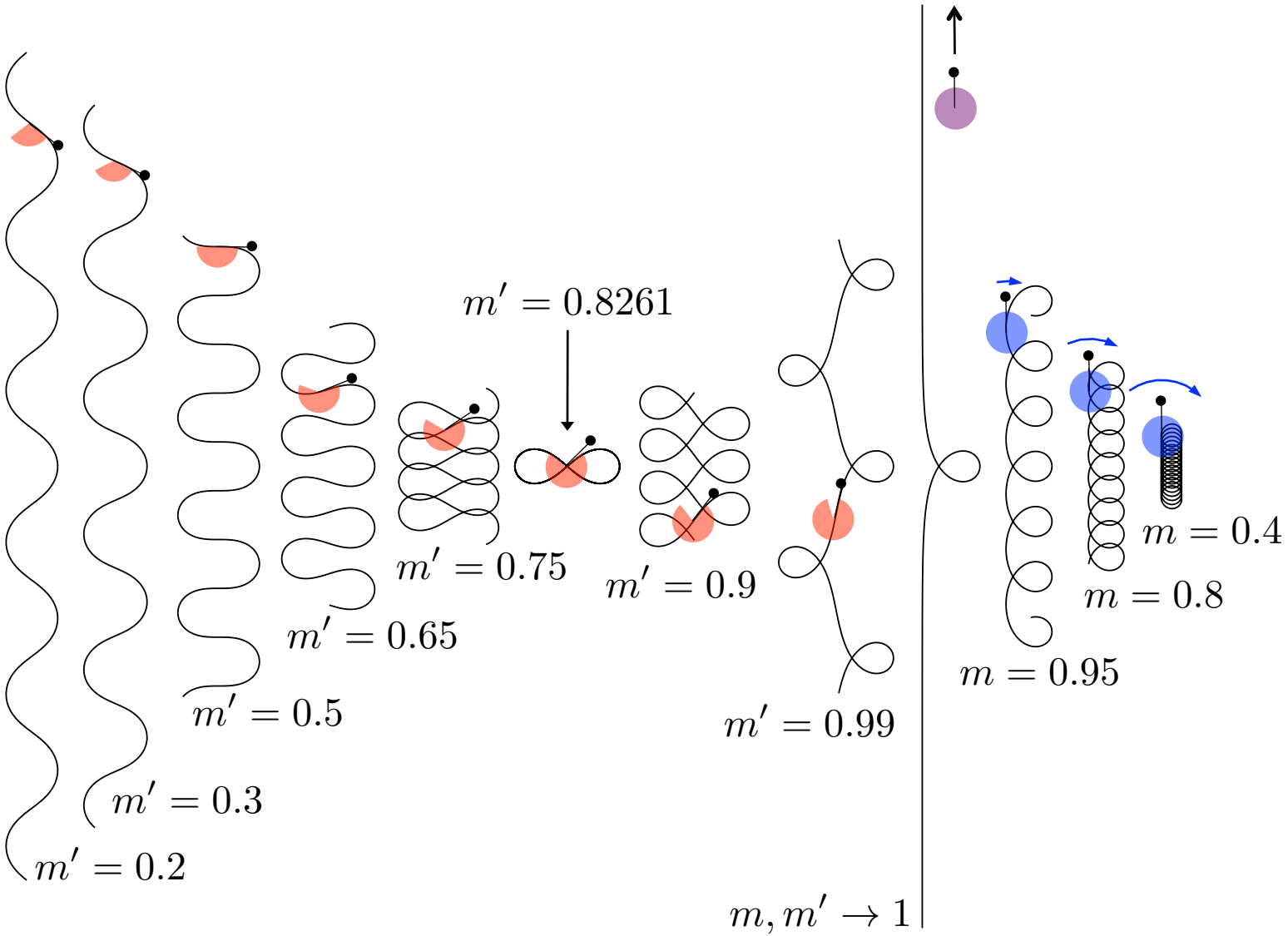
Hamiltonian (wormlike chain model):

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

Lagrangian action:

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

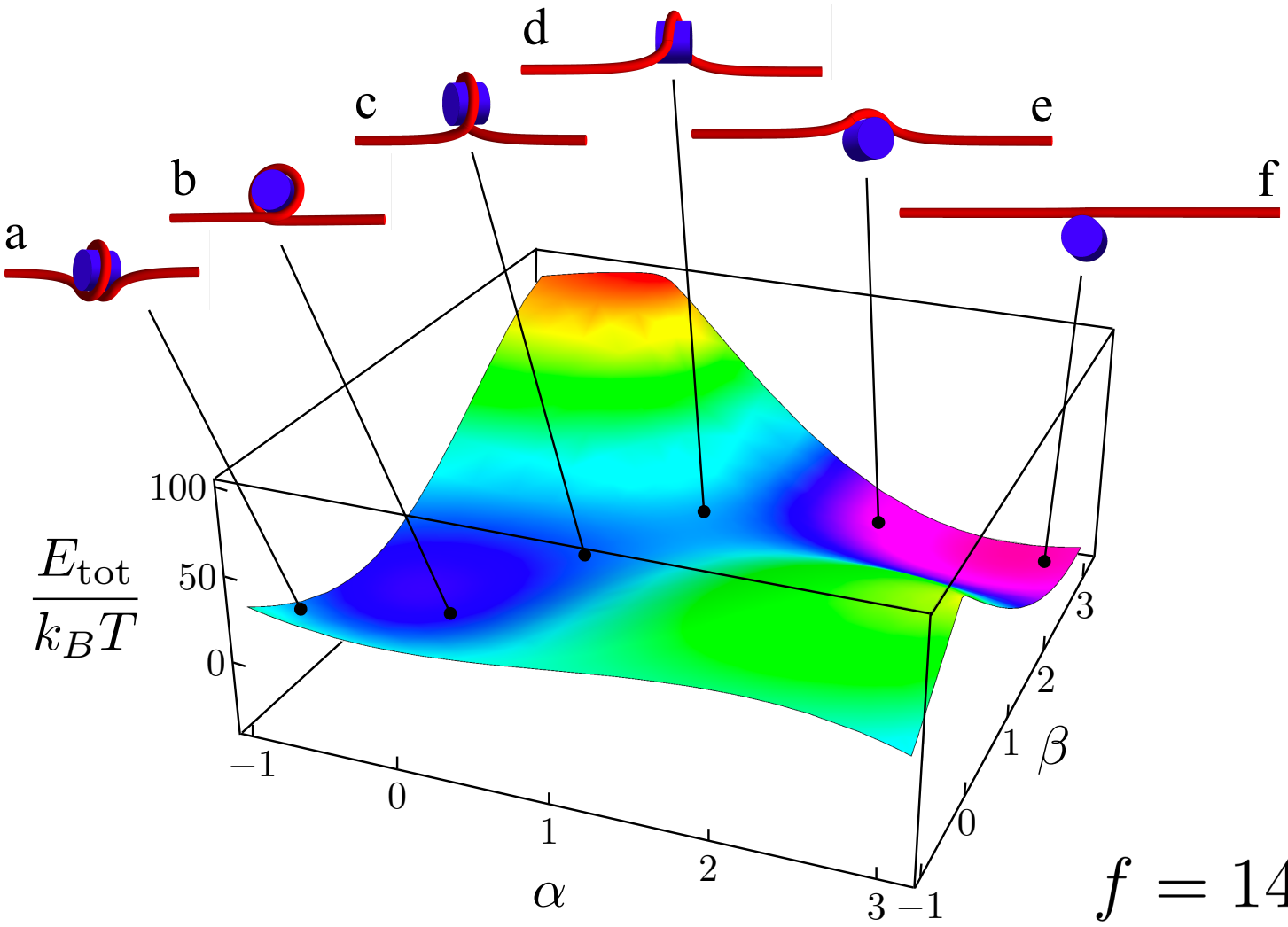
Kinetic analogy



BREATHING

Energy landscape

Kulic & HS, Phys. Rev. Lett. **92** (2004) 228101

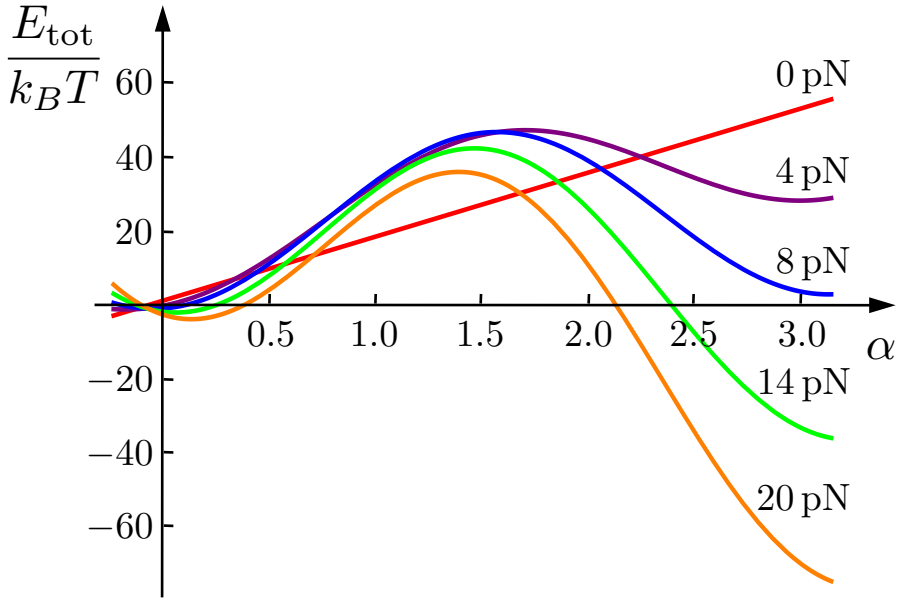


$f = 14pN$

Simplified landscape

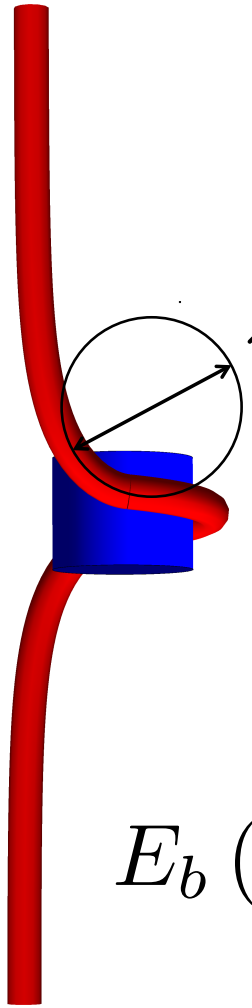
leading terms:

$$E_{\mathrm{tot}}(\alpha) \approx \underbrace{2R_0\,(f_{\mathrm{crit}} - f)\,\alpha}_{\text{tilting term}} \underbrace{- \frac{2}{\sqrt{3}}\sqrt{Af}\cos 2\alpha}_{\text{barrier term}}$$



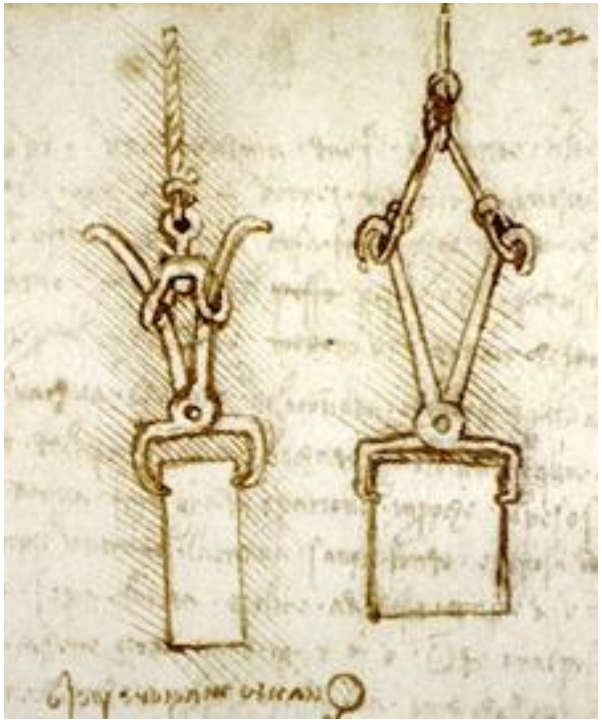
BREATHING

Force-induced strengthening



$$\lambda = \sqrt{A/f}$$

$$E_b(f) = \frac{4}{\sqrt{3}}\sqrt{Af}$$



Leonardo da Vinci:

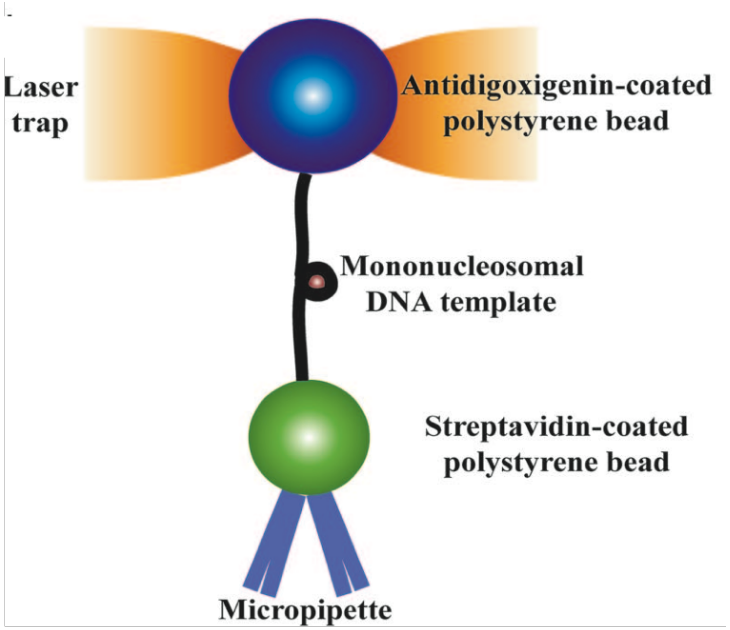
"The greater the weight held by this lifting tong, the better and stronger it will be supported."

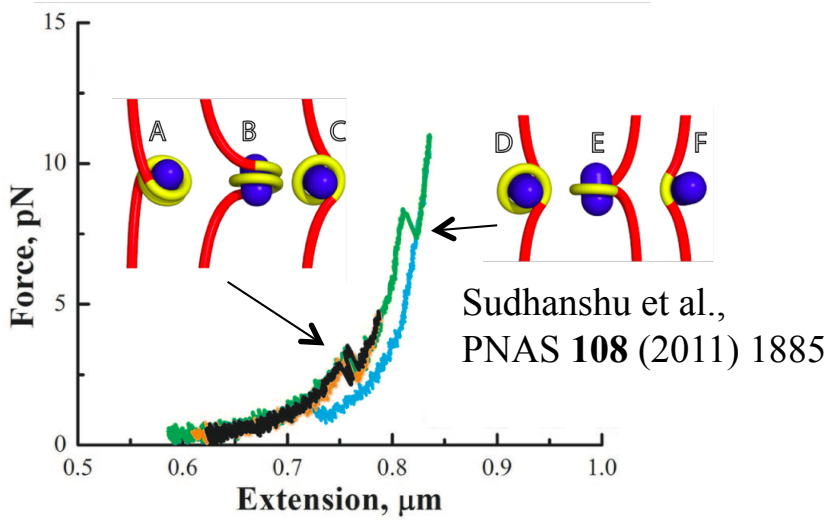
Madrid Ms. I (BNM), fol. 22r

BREATHING

Single nucleosome under tension

Mihardja, Spakowitz, Zhang & Bustamante, PNAS **103** (2006) 15871

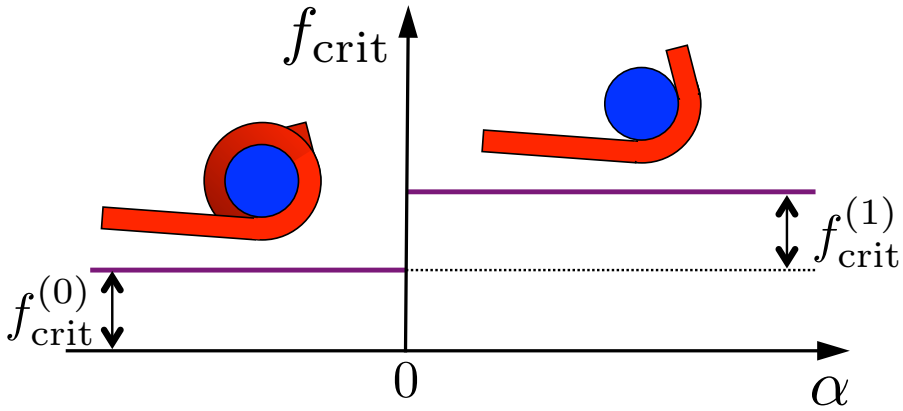


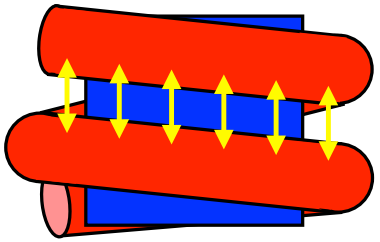


Sudhanshu et al., PNAS **108** (2011) 1885

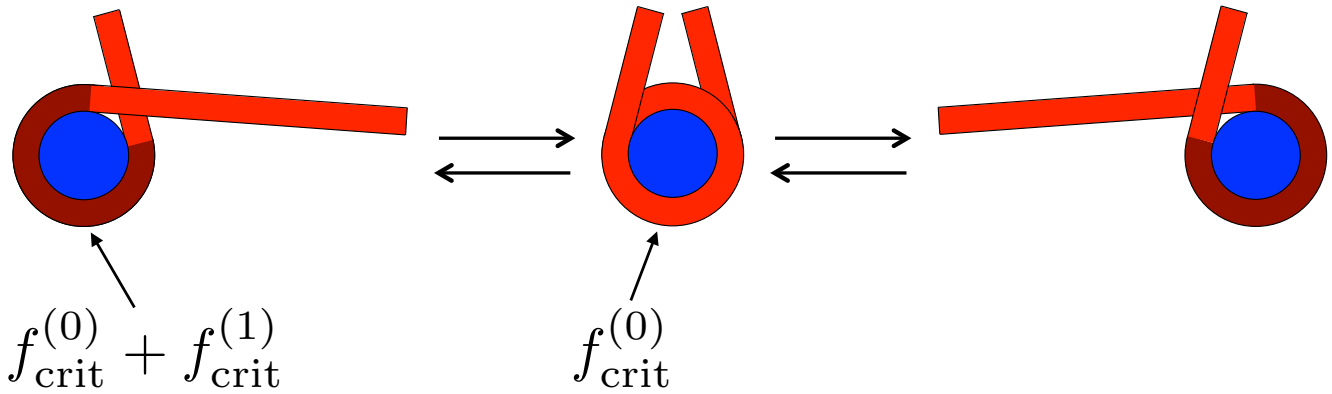
BREATHING

The first-second round difference



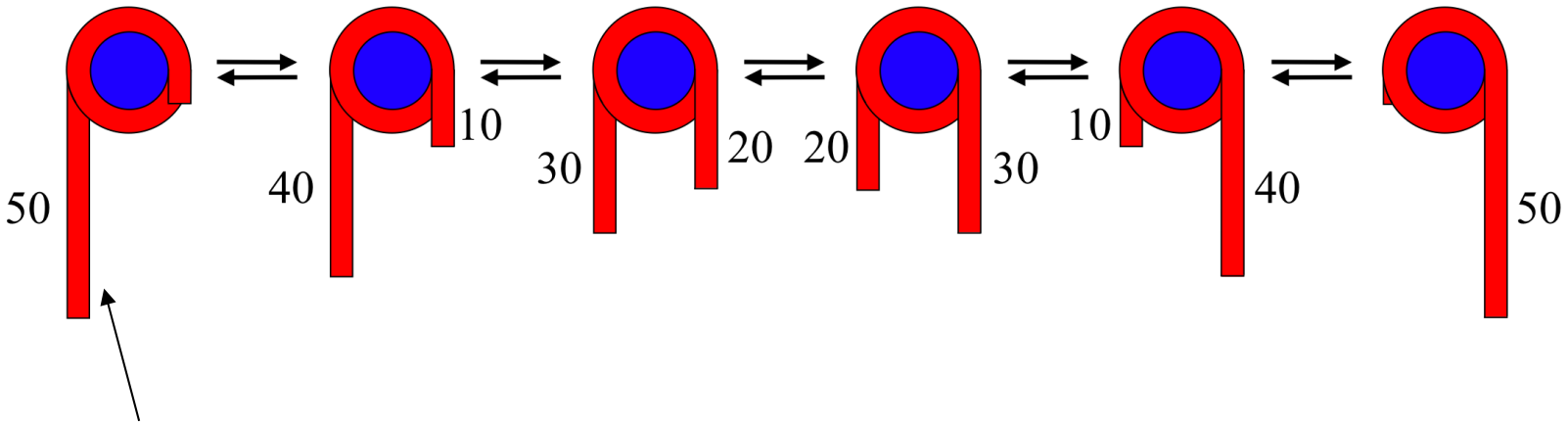


Two turn design combines accessibility and stability:



Nucleosome sliding

Pennings et al., J. Mol. Biol. **191** (1991) 220



≈ 205 bp DNA

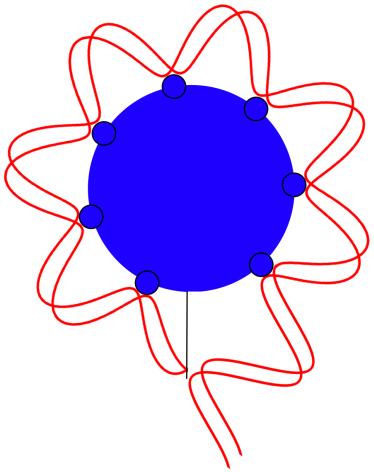
diffusion constant:

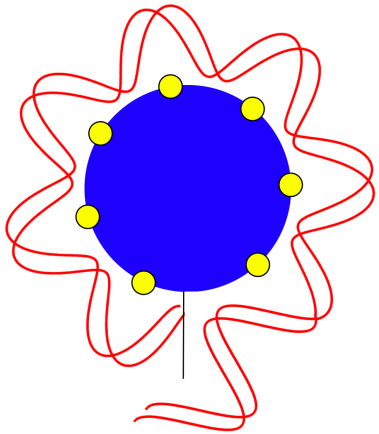
$$D \approx 1 bp^2/s$$

SLIDING

Possible mechanisms

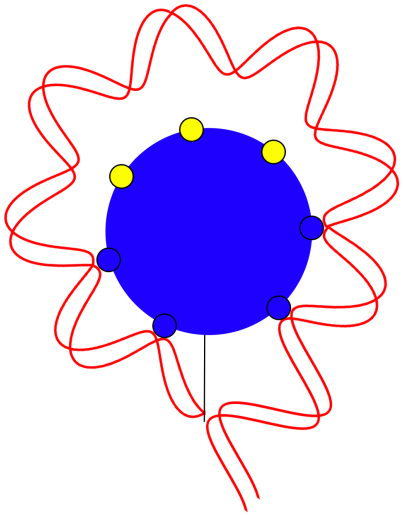
intact

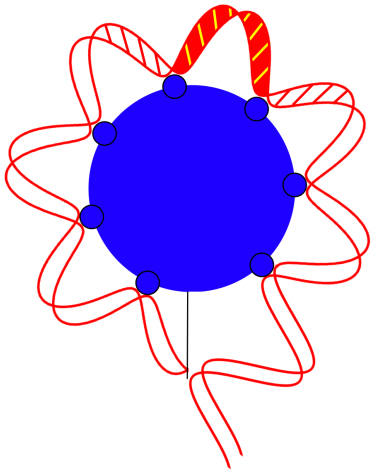




„sliding“

loop defect



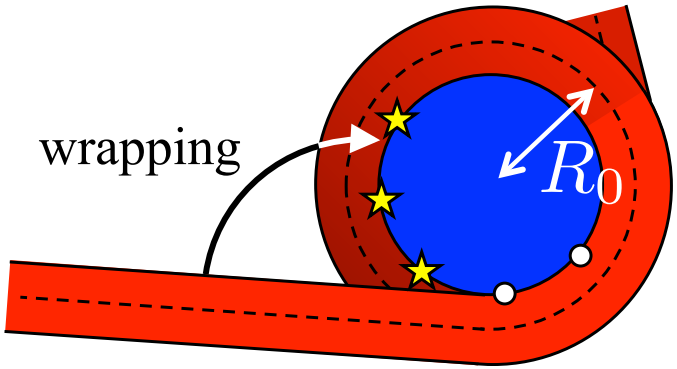


twist defect

Energetics

DNA wrapping:

adsorption energy per length > bending energy per length



„pure“ adsorption energy: $\approx -90 k_B T$

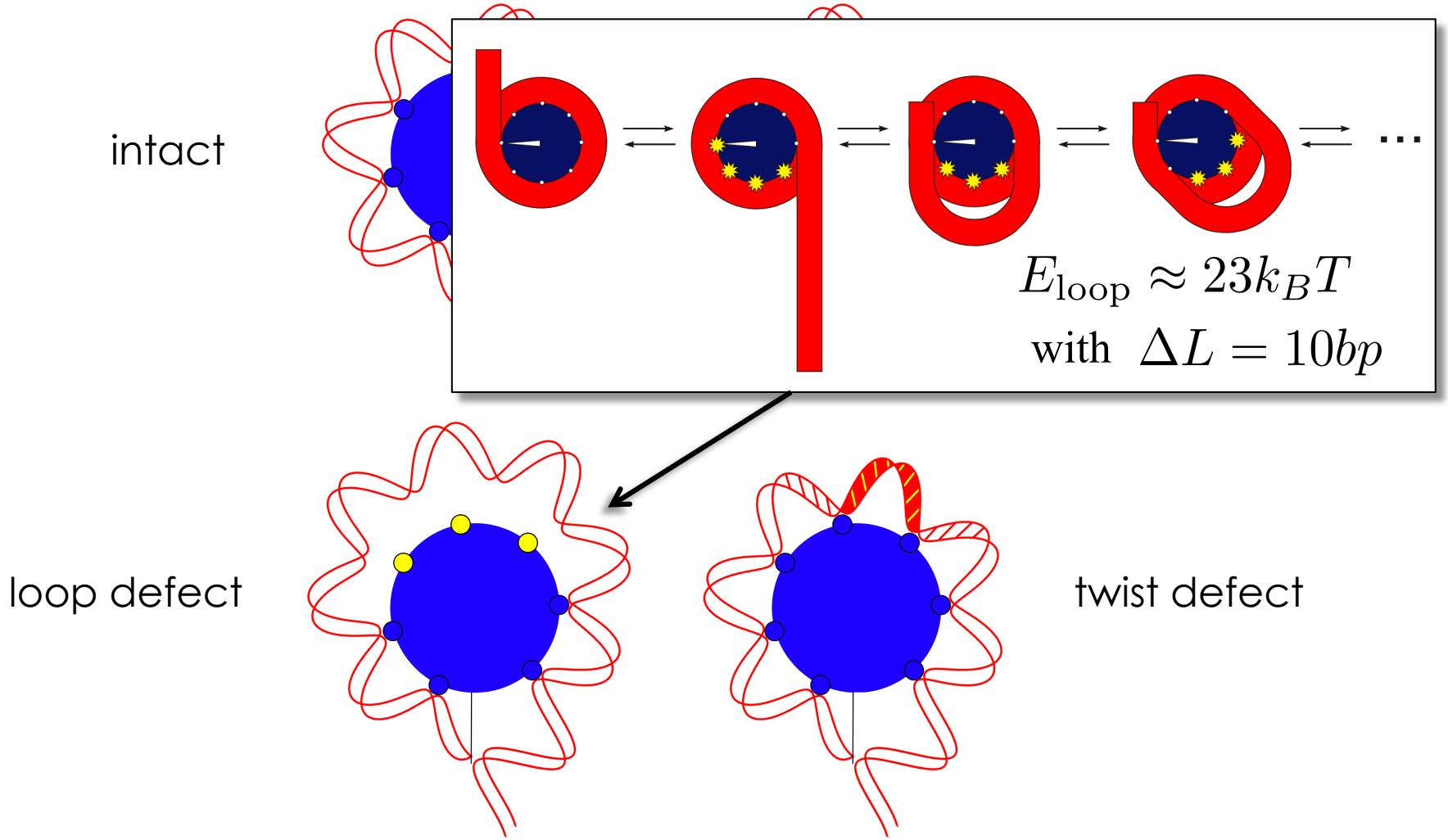
\+ bending energy: $l_P L_0 / 2R_0^2 \approx +80 k_B T$

net adsorption energy: $\approx -15 k_B T$

Polach & Widom, 1995

SLIDING

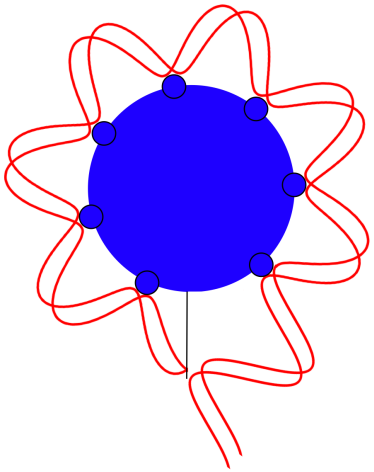
Possible mechanisms

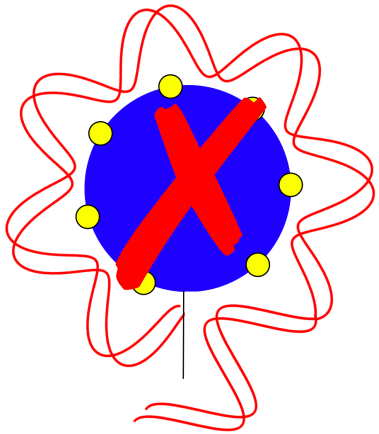


SLIDING

Possible mechanisms

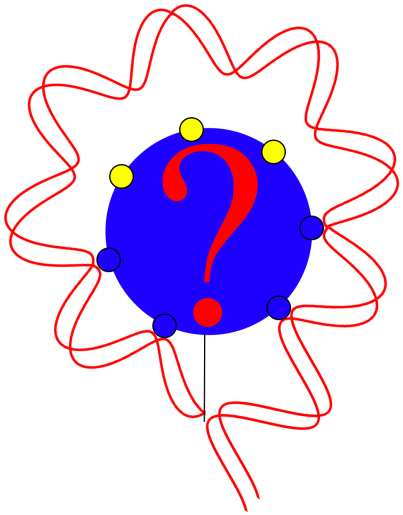
intact

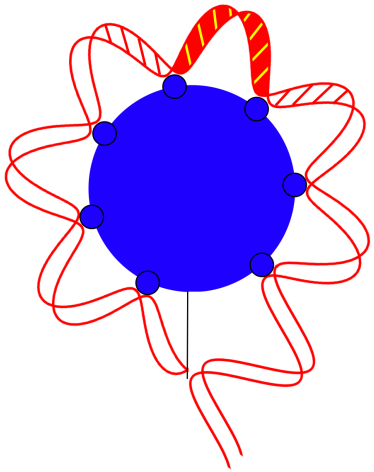




„sliding“

loop defect



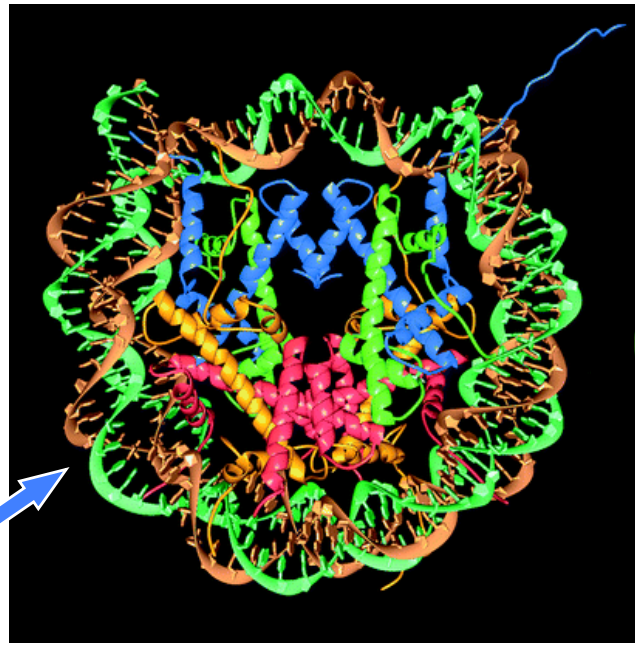


twist defect

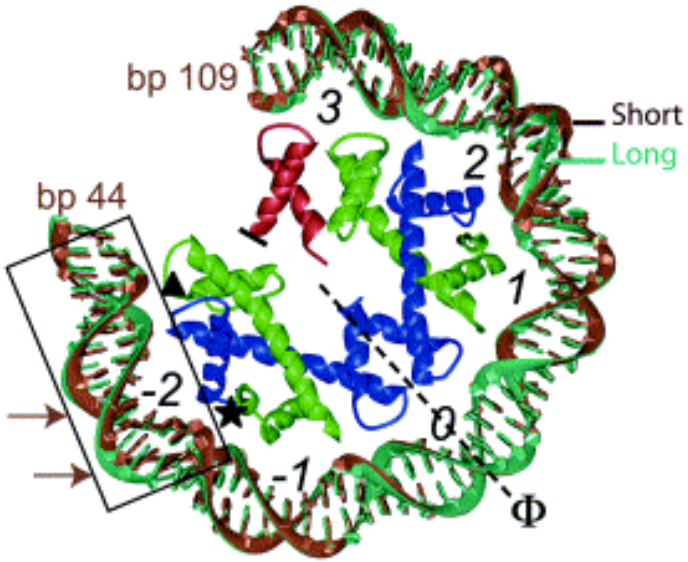
SLIDING

Twist defect in crystal structure

core particle reconstituted from histones and 146 bp DNA has twist defect, but with 147 bp DNA it has not (Davey et al. J. Mol. Biol. **319** (2002) 1097)



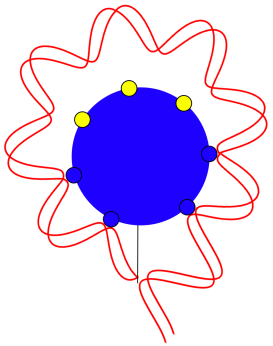
1bp missing!



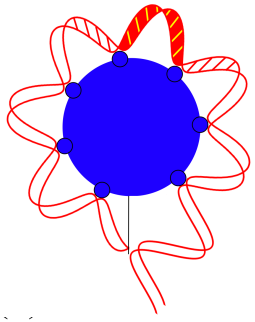
X-NCP

SLIDING

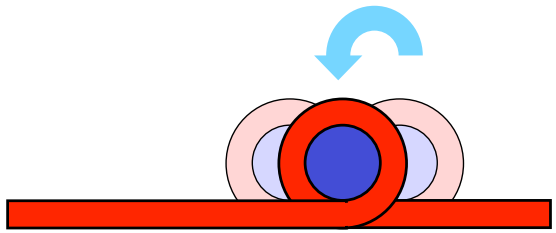
Loop vs. twist defect



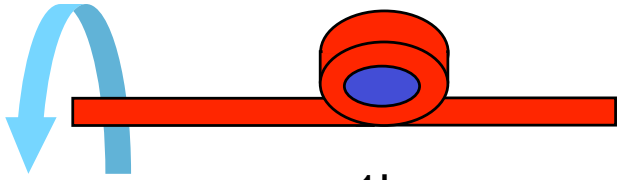
$\Delta L = 10\,\mathrm{bp}$



$\Delta L = 1\,\mathrm{bp}$



10bp

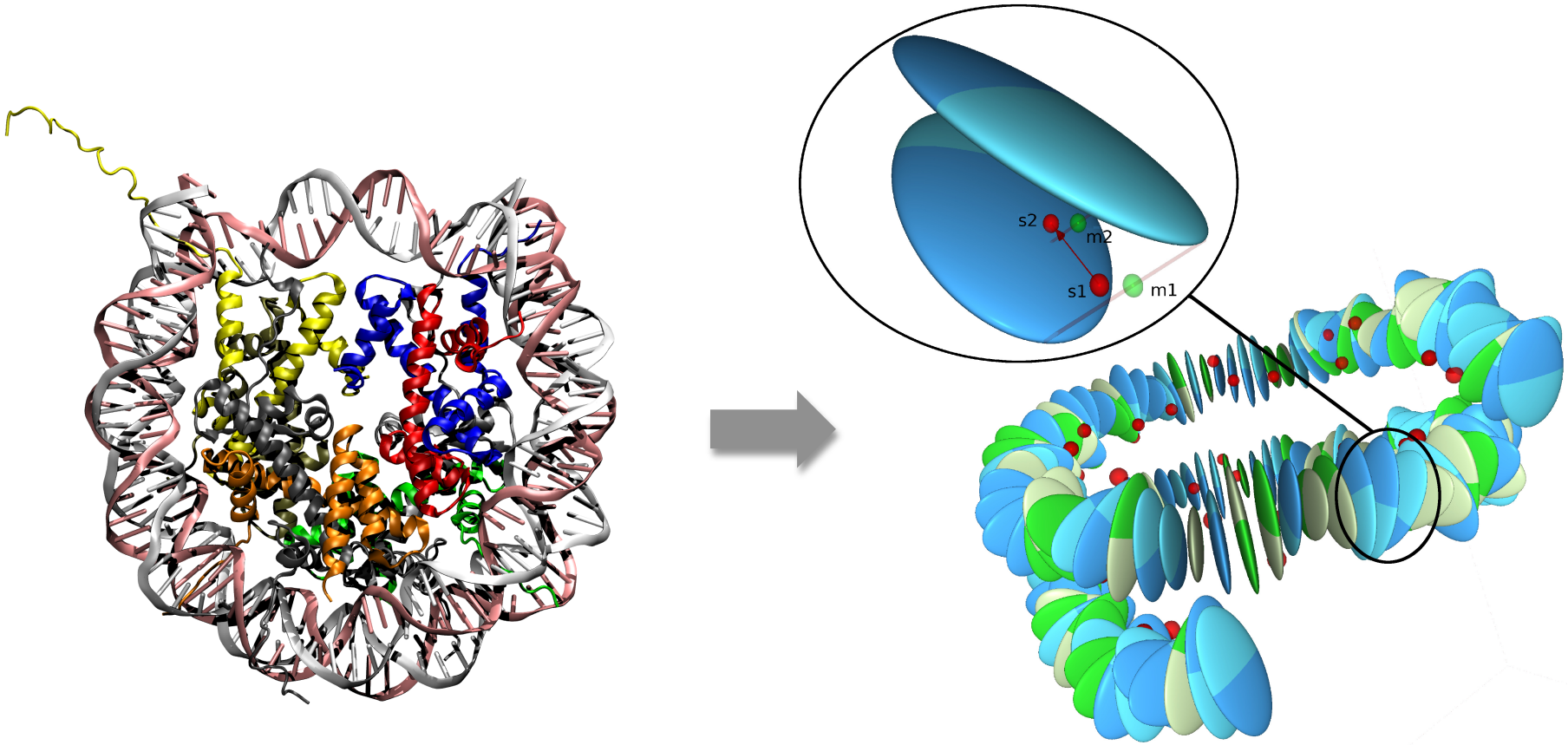


1bp

SLIDING

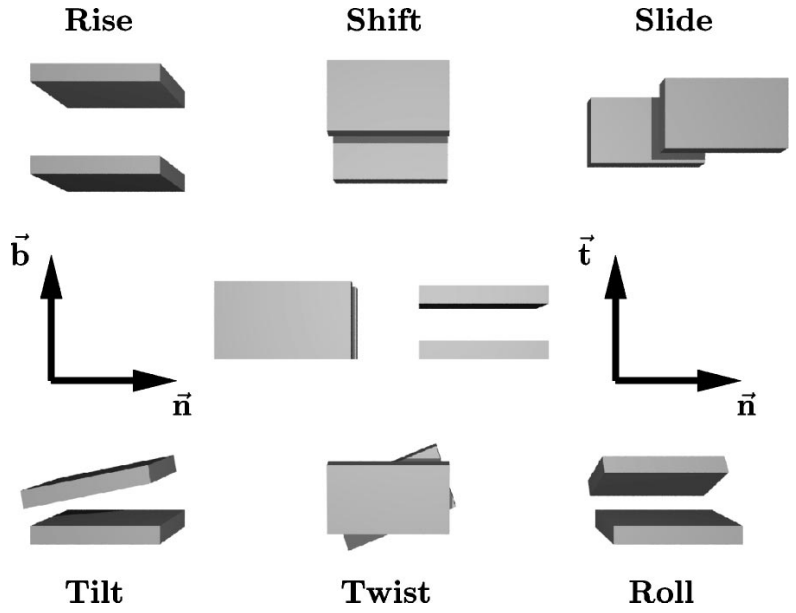
Rigid bp model for nucleosomal DNA

Fathizadeh, Besya, Ejtehadi & HS, EPJE **36** (2013) 21



SLIDING

Twist, Roll, Slide: The base pair ballet



Mergell, Ejtehadi & Everaers, Phys. Rev. E **68** (2003) 021911

Rigid base pair model:

$$U = \frac{1}{2}\left(\psi - \psi_0\right)^T \cdot \mathbf{K} \cdot \left(\psi - \psi_0\right)$$

6x6 stiffness matrix (bp-step dependent)

crystal structures:
Olson et al. (1998)

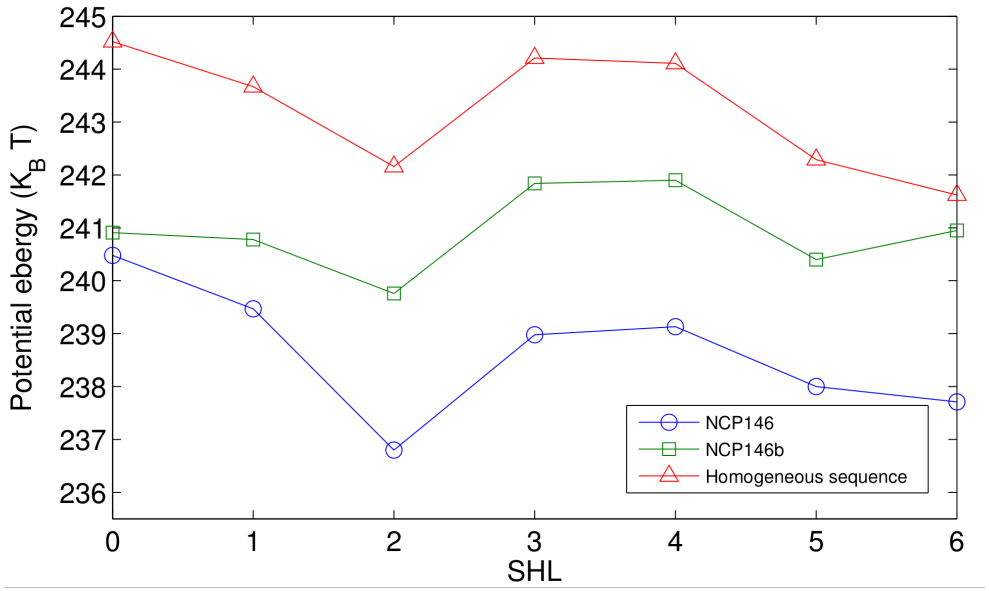
all atom MD simulation:
Lankas et al. (2003)

mixed parametrization:
Becker, Wolff, Everaers (2006)

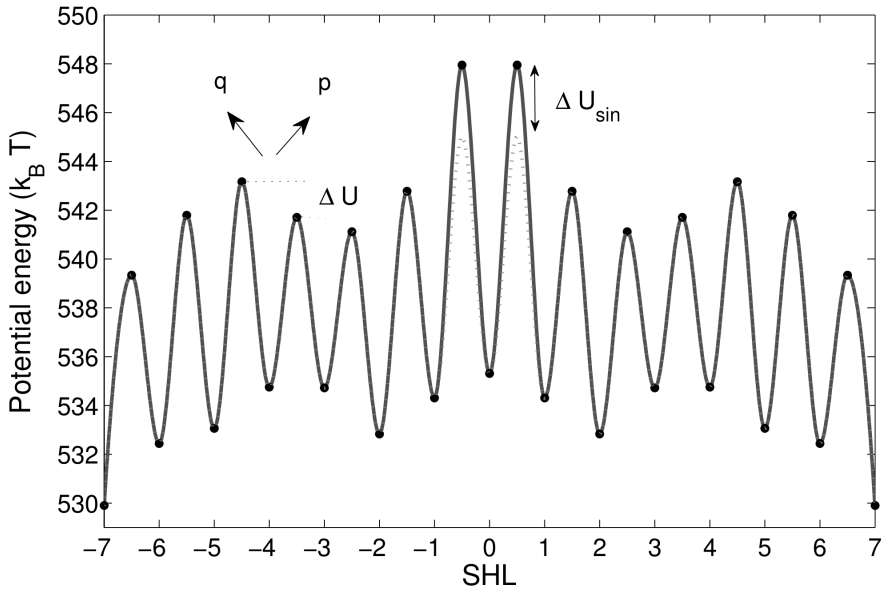
SLIDING

Twist defect energy landscape

Fathizadeh, Besya, Ejtehadi & HS, EPJE **36** (2013) 21



twist defect energy



energy landscape

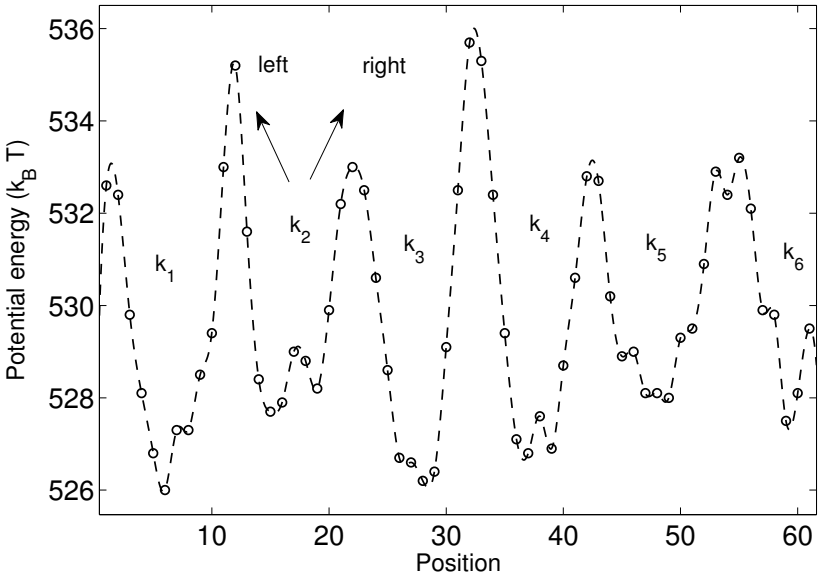
crossing probability $1/9000$

diffusion constant $D \approx 240\,\mathrm{bp/s}$

SLIDING

Effective diffusion constant

Fathizadeh, Besya, Ejtehadi & HS, EPJE **36** (2013) 21

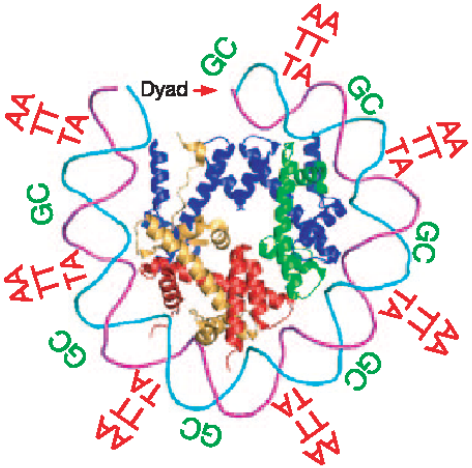


5S rDNA positioning sequence

$$D_{\text{eff}} \approx \frac{100\,\text{bp}^2}{2T_{\text{eff}}} \approx 8\text{bp}^2/\text{s}$$

$$T_{\text{eff}}^{-1} = \frac{\sqrt{U''(x_{\min})\,U''(x_{\max})}}{2\pi\zeta} e^{-A/k_BT}$$

$$\zeta = k_BT/D$$



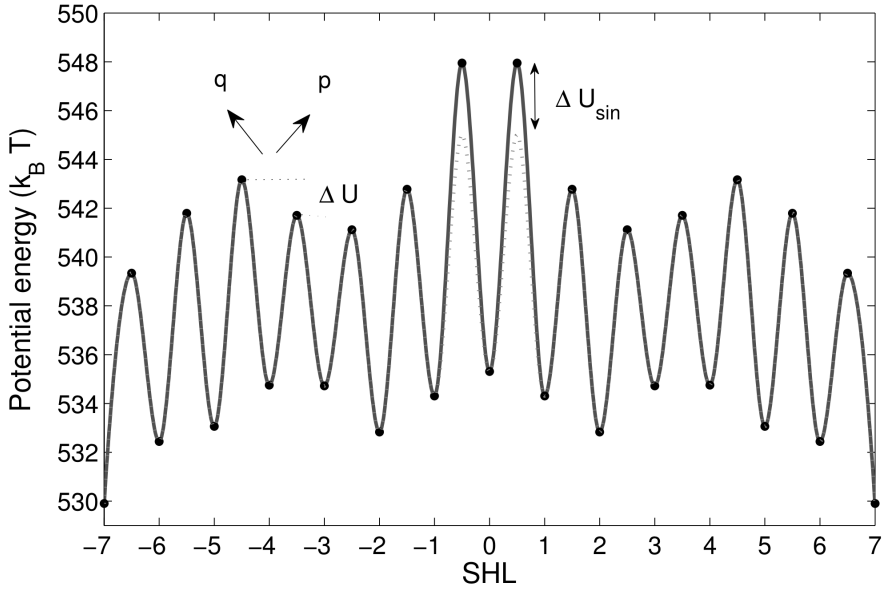
second genetic code

Segal et al., Nature 2006

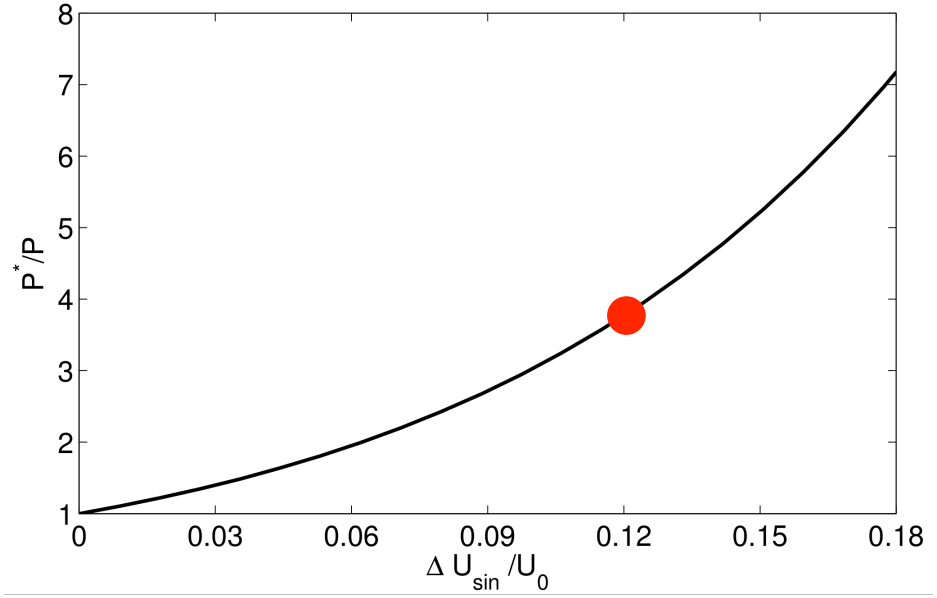
SLIDING

SIN mutations

Flaus et al., EPJE **36** (2013) 21



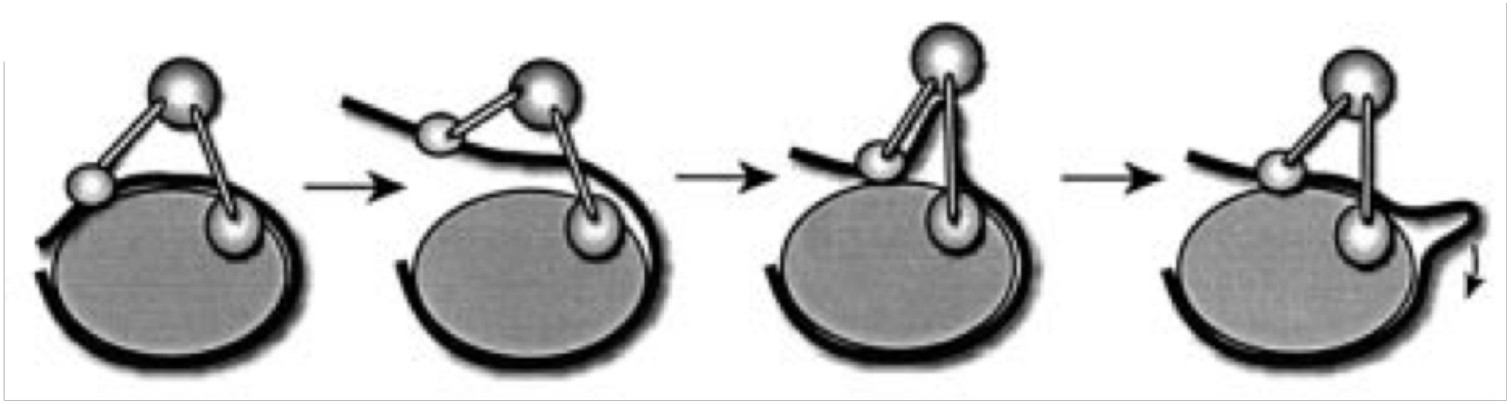
energy landscape



effect of point mutation
at SHL 0.5

Chromatin remodeller

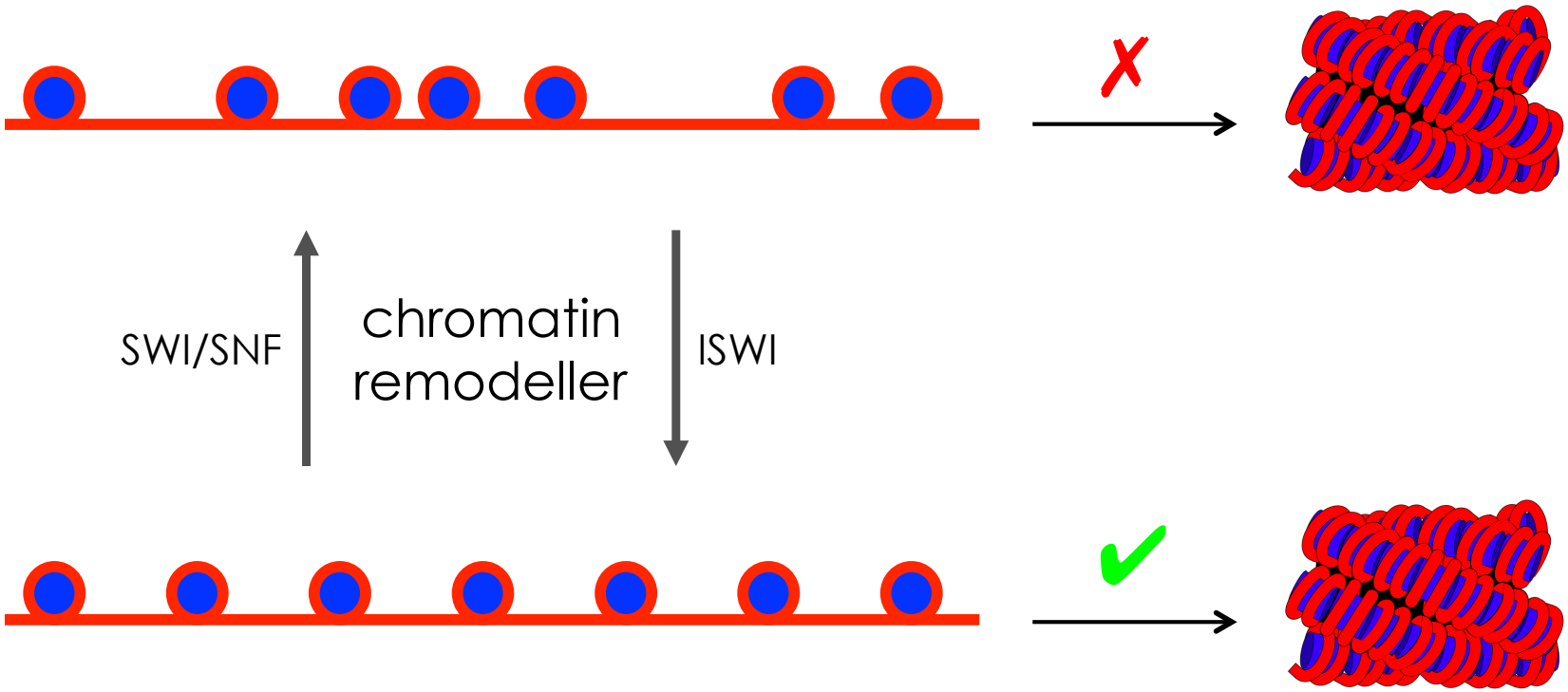
Actively pushing or pulling nucleosomes along DNA:



Becker(2002)

PROOFREADING

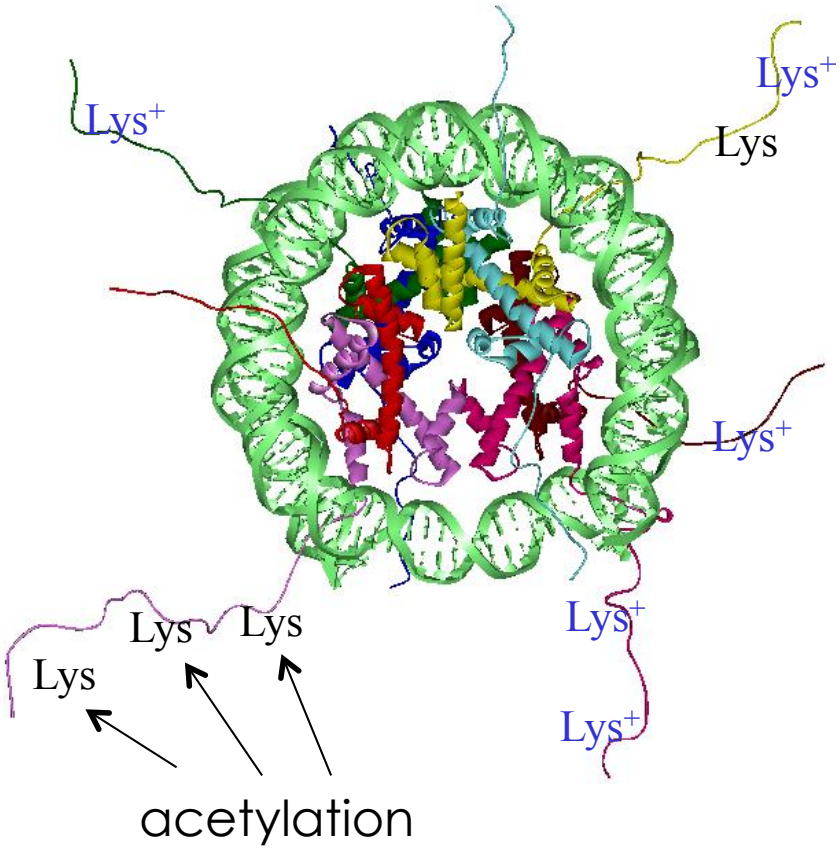
Antagonistic roles



Lanzani & HS, EPL **97** (2012) 38002

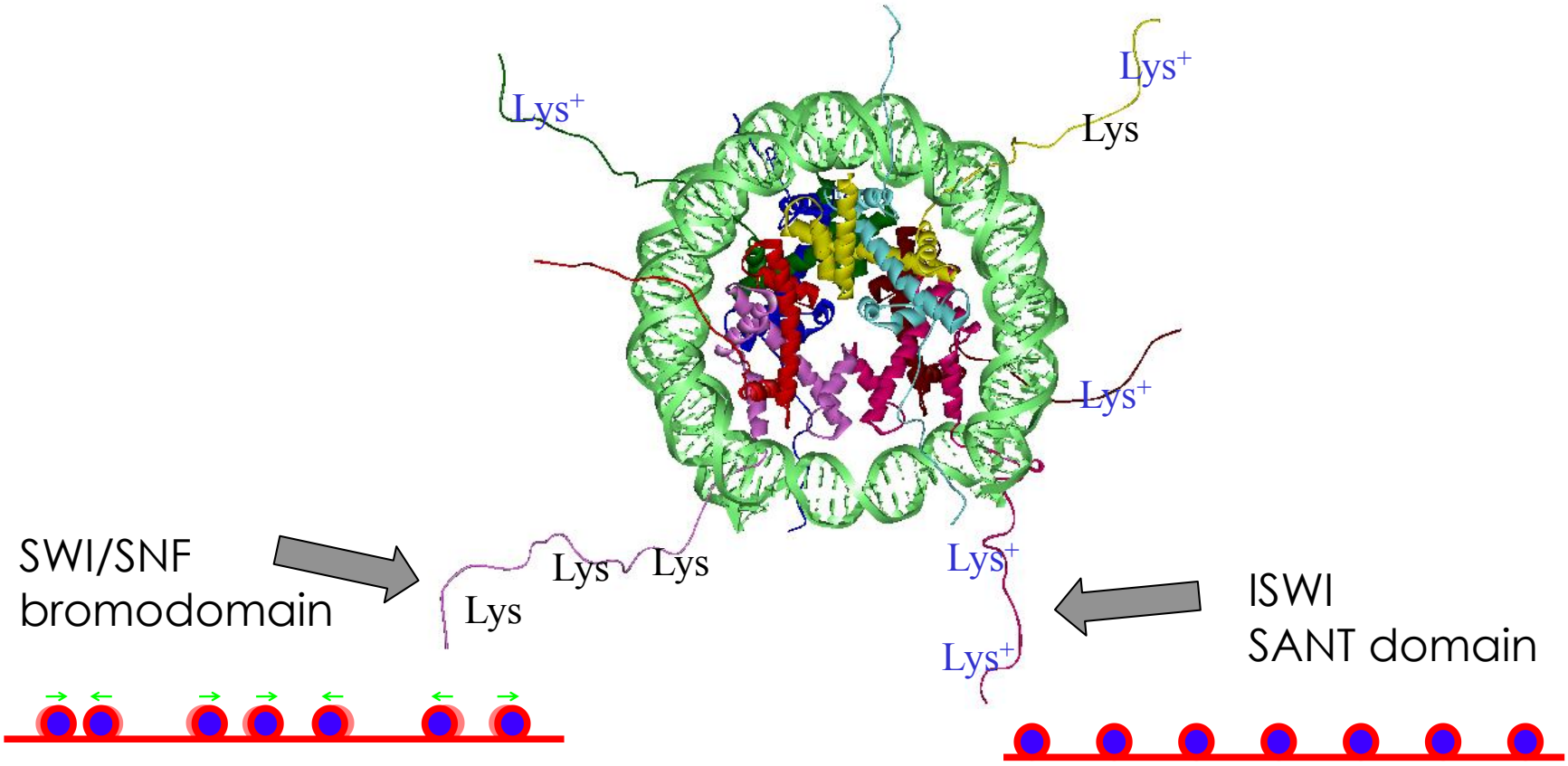
PROOFREADING

Histone tails



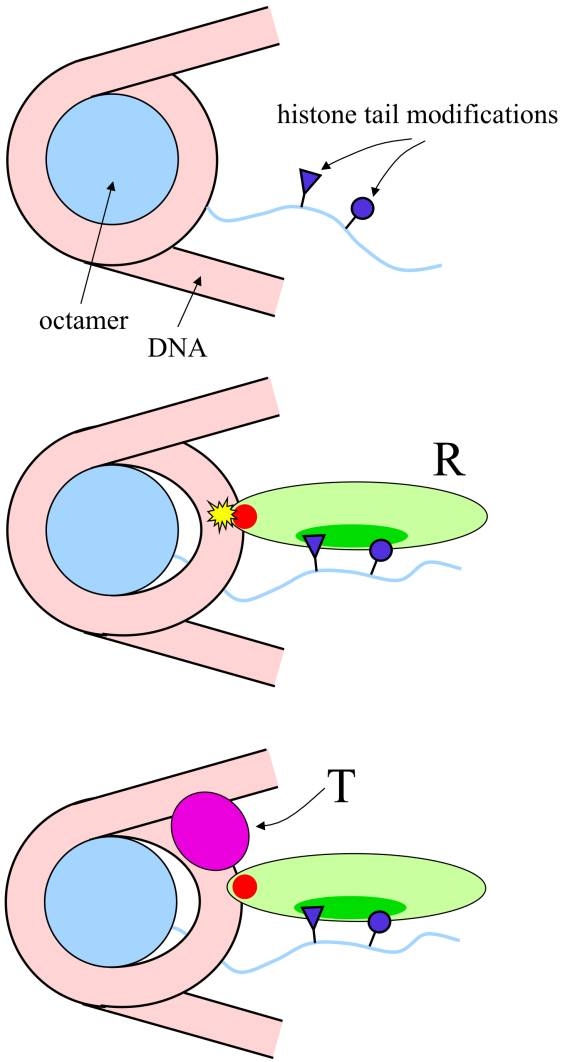
PROOFREADING

Histone tails



Chromatin kinetic proofreading

Blossey & HS, HFSP J. **2** (2008) 167



$$
\begin{array}{ccccccccc}
 & & & & AR^* & & & & \\
 & & \overset{a}{\nearrow} & & & & \overset{t_+}{\rightleftharpoons} & & \\
A+R & \overset{r_+}{\rightleftharpoons} & AR & & & +T & & AT & \xrightarrow{g} \\
 & \underset{r_-^A}{} & & & & & \underset{t_-^A}{} & & \\
 & & \underset{a}{\searrow} & & & & \underset{t_-^D}{\rightleftharpoons} & & \\
 & & & & DR^* & & & & \\
\end{array}
$$

$$
\begin{array}{ccccccccc}
 & & & & & & & & G \\
 & & & & & & & & \uparrow g \\
D+R & \overset{r_+}{\rightleftharpoons} & DR & \xrightarrow{a} & DR^* & +T & \overset{t_+}{\rightleftharpoons} & DT & \\
 & \underset{r_-^D}{} & & & & & \underset{t_-^D}{} & & \\
\end{array}
$$

$$
k^D \rightleftharpoons k^A
$$

$$
d^A \qquad d^D
$$

$2k_BT$ increases discrimination ratio by factor 50

Narlikar, Curr. Op. Chem. Biol. **14** (2010) 1
Blossey & HS, Biophys. J. **101** (2011) L30

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