The Abdus Salam
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Conference: From DNA-Inspired Physics to Physics-Inspired Biology

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The Homology Recognition Funnel

Alexei A. KORNYSHEV

Imperial College London
Dept of Chemistry, Faculty of Natural Sciences
London SW7 2AZ
UK

The homology recognition funnel

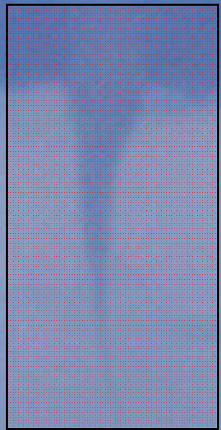
Alexei A. Kornyshev
Imperial College London

Dominic Lee

Max Planck Institute for the Physics of Complex Systems Dresden, Germany

Aaron Wynveen

Institut für Theoretische Physik II, Department of Physics Heinrich-Heine-University of Düsseldorf



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- ***Sergey Leikin***
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- ***Biophysics seminar in Max Planck Institute Dresden***

Imperial College London

A.A. Kornyshev and A.Wynveen
"The homology recognition well as an innate property of DNA structure"
PNAS, 1206, 4683 (2009)

D.J. Lee and A.A. Kornyshev
"The homology recognition funnel. Torsional adapatation: what role?"
(2009) to be submitted

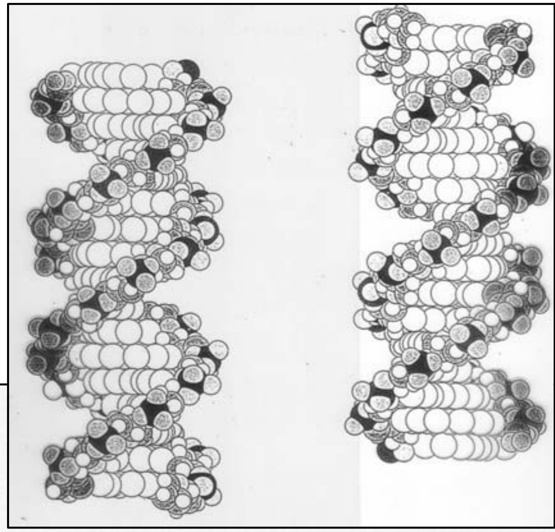
A. Barzel & M. Kupiec, Nature Reviews, 2008:

"Decades of research into homologous recombination have unraveled many of the details concerning the transfer of information between two homologous sequences. By contrast, the processes by which the interacting molecules initially co-localize are largely unknown. How can two homologous needles find each other in the genomic haystack?"

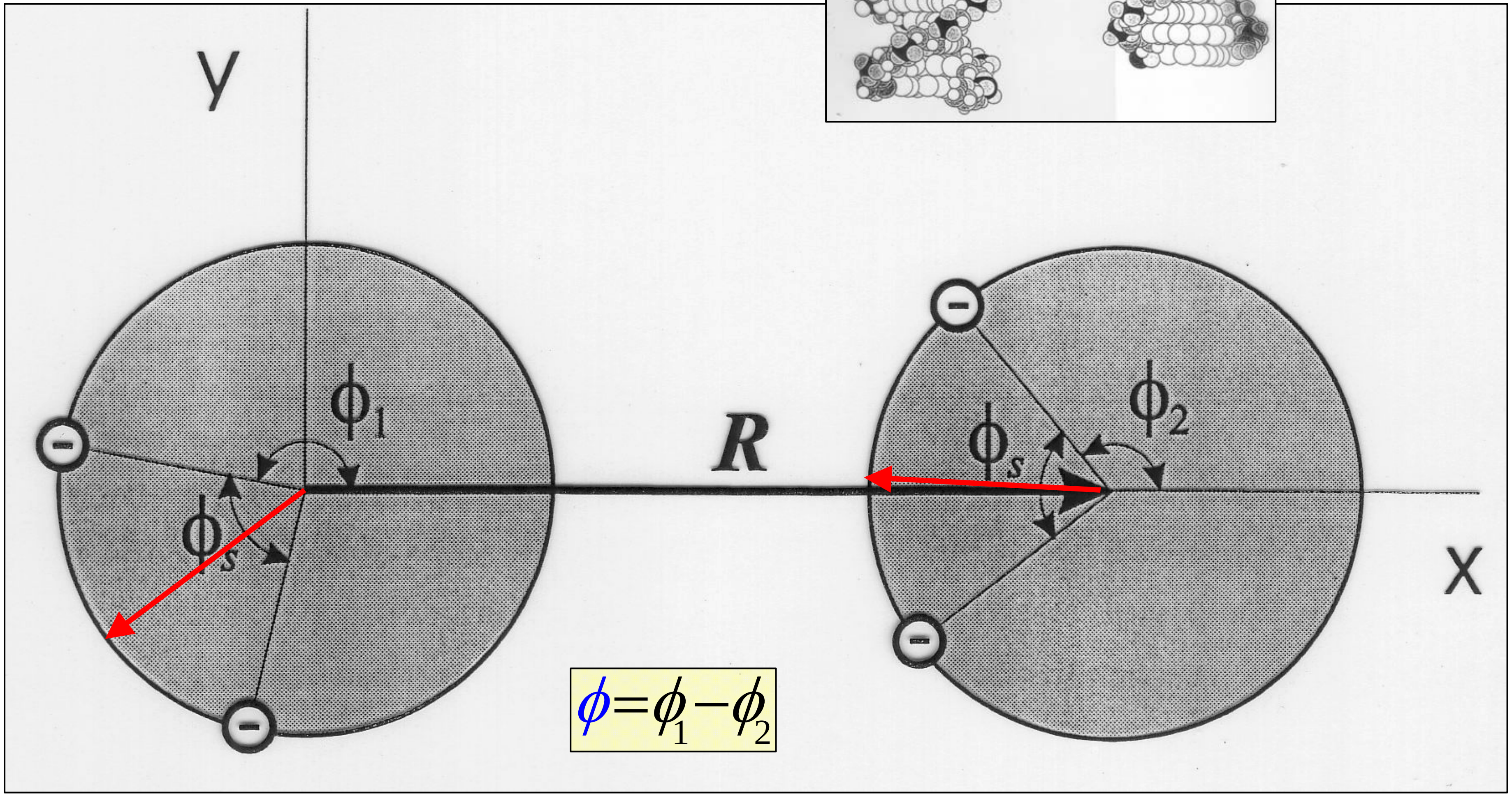
"Is homologous pairing an innate general charactersitic of the spatial organization of the genome?"

"After a long journey we are back at the starting position. The mechanism of homologous pairing has so far resisted our survey of possible explanations"

Two parallel DNA: **azimuthal alignment**



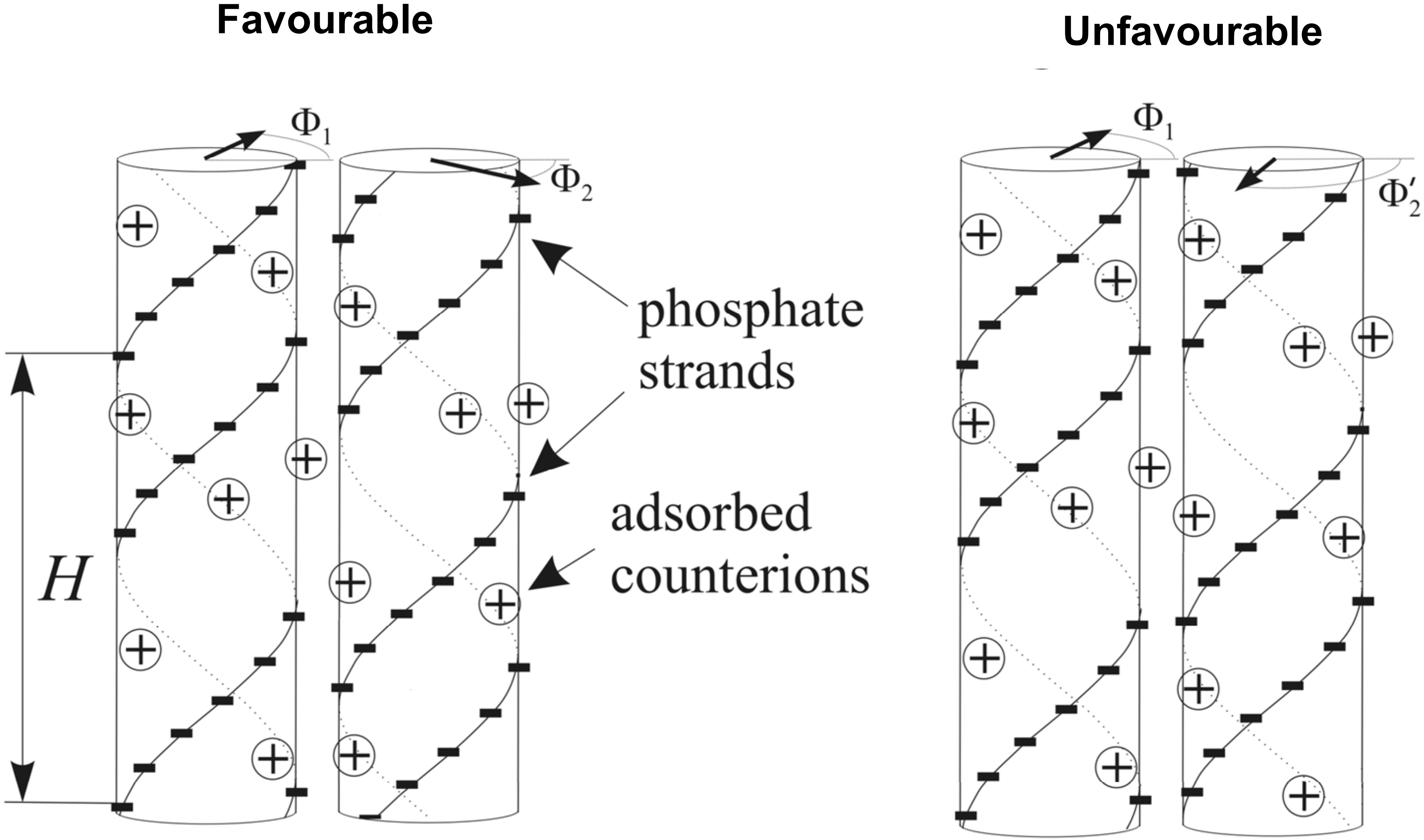
$$\Delta z = \frac{\phi}{2\pi} H$$



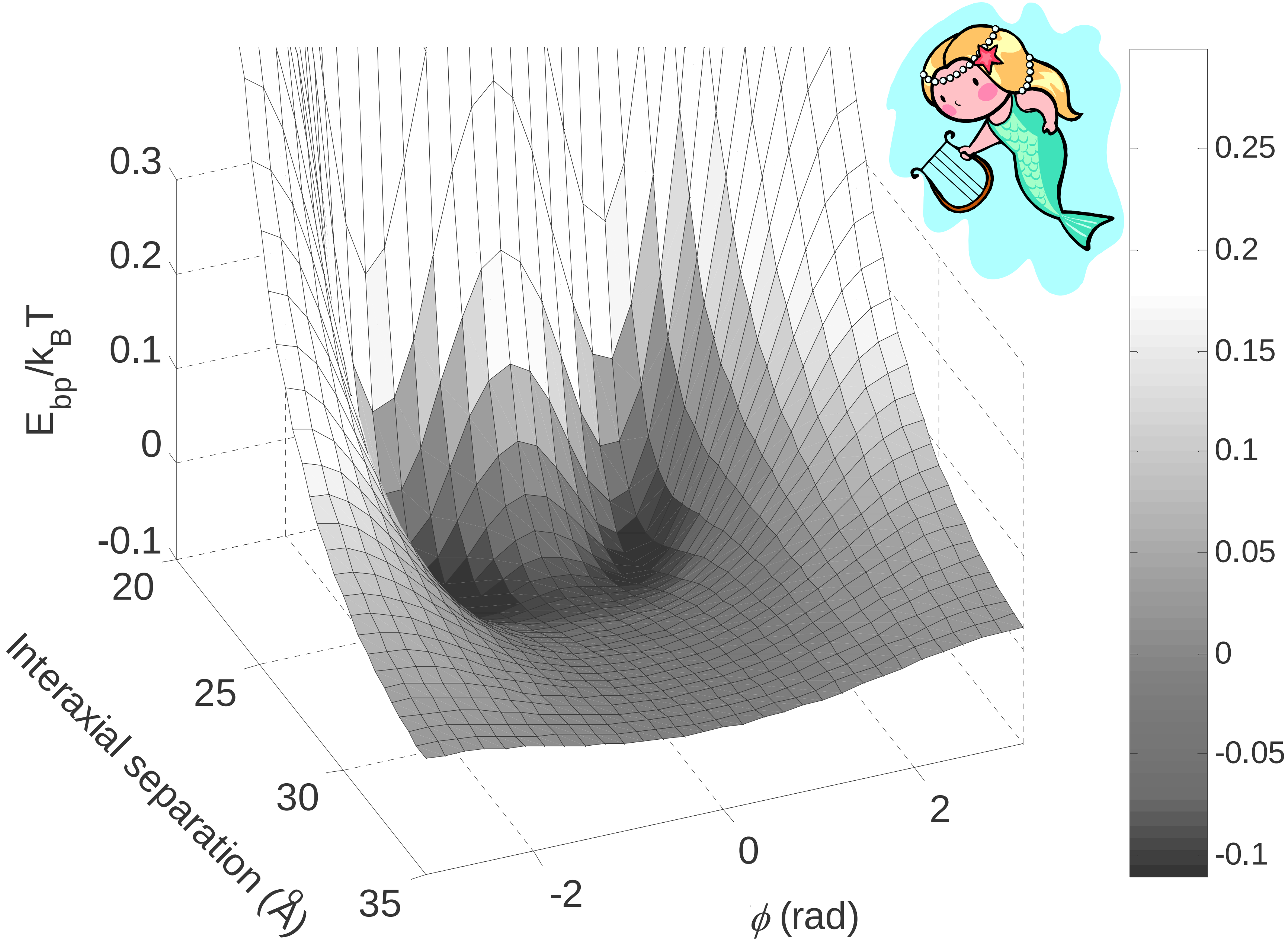
$$\phi = \phi_1 - \phi_2$$

B-DNA: $\phi_s = 0.8\pi$

DNA structure and azimuthal orientation



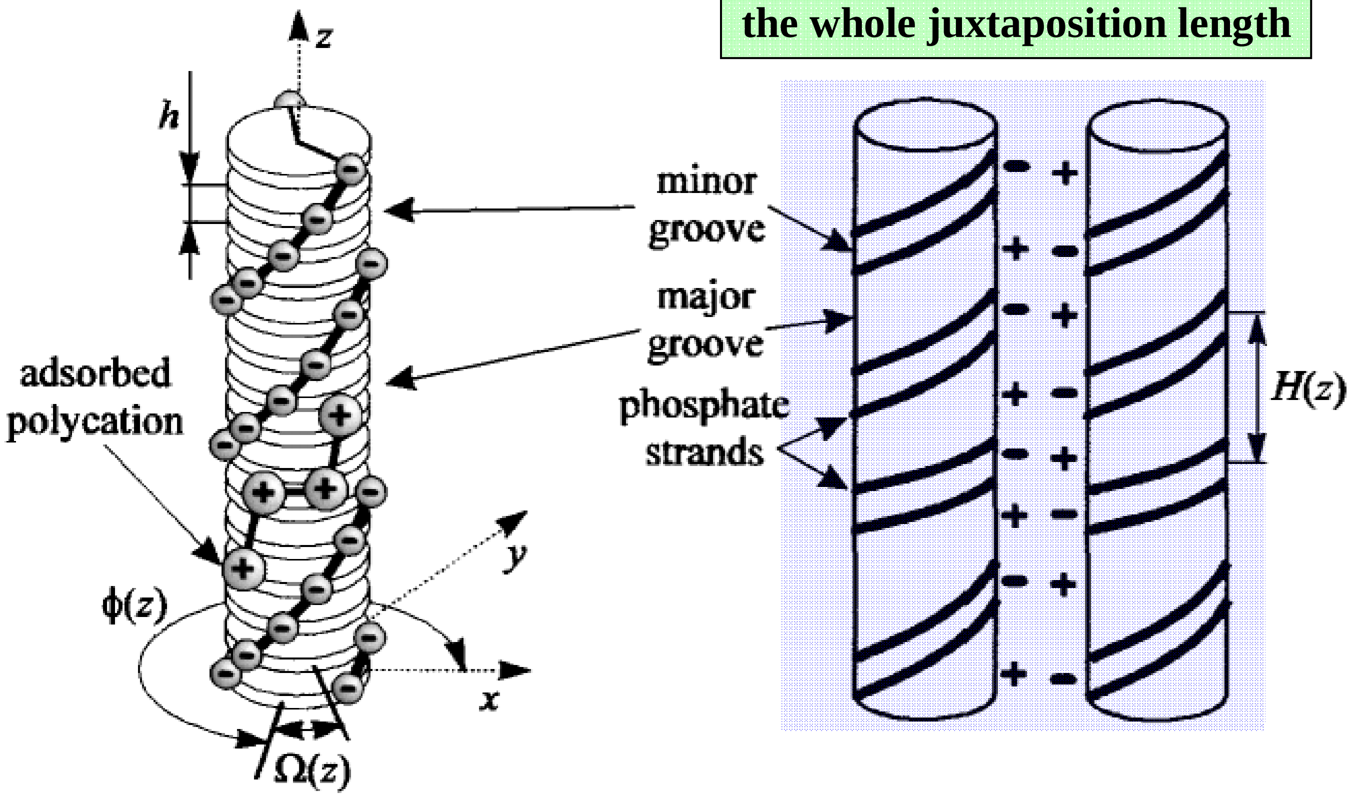
"Mermaid on a sand" potential



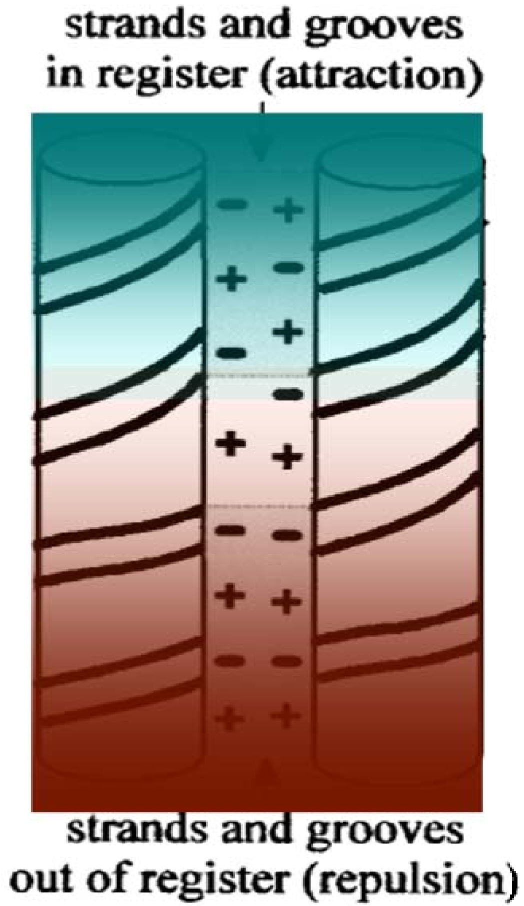
Electrostatic lock and key recognition between DNA duplexes

Homologous duplexes:

staying in register over
the whole juxtaposition length



Nonhomologous duplexes:



Recognition energy

$$\boxed{\Delta E \approx E_{\mathrm{int}}^{rand} - E_{\mathrm{int}}^{ident}}$$

A.A.Kornyshev and S.Leikin
Sequence recognition in pairing of DNA duplexes, *Phys.Rev.Lett.* **86**, 3666 (2001).

$$\boxed{E_{\text{int}} \approx \int_0^L dz\left[a_0(R) - a_1(R)\cos\left(\phi(z)\right) + a_2(R)\cos\left(2\phi(z)\right)\right]}$$

Torsionally rigid molecules $\dfrac{d\phi(z)}{dz} = \dfrac{\delta\Omega(z)}{h} \longrightarrow \phi(z) = \dfrac{1}{h}\int_0^z dz'\,\delta\Omega(z')$

$$E_{\text{int}} = \int_0^L dz\left[a_0(R) - a_1(R)\cos\left(\frac{1}{h}\int_0^z dz'\,\delta\Omega(z')\right) + a_2(R)\cos\left(2\frac{1}{h}\int_0^z dz'\,\delta\Omega(z')\right)\right]$$

1. Identical (≈ homologous) molecules in correct juxtaposition

$$\delta\Omega(z') \equiv 0 \qquad E_{\text{int}}^{ident} \approx \int_0^L dz\left[a_0(R) - a_1(R) + a_2(R)\right] = \left[a_0(R) - a_1(R) + a_2(R)\right]\cdot L$$

2. Molecules the bp-texts of which are random to each (non-homologous).

$$E_{\text{int}}^{rand} = \int_0^L dz\left[a_0(R) - a_1(R)\left\langle \cos\left(\frac{1}{h}\int_0^z dz'\,\delta\widehat{\Omega}(z')\right)\right\rangle + a_2(R)\left\langle \cos\left(2\frac{1}{h}\int_0^z dz'\,\delta\widehat{\Omega}(z')\right)\right\rangle\right]$$

$$<\delta\widehat{\Omega}^2> = <\left[\widehat{\Omega}_1 - \widehat{\Omega}_2\right]^2> = <\widehat{\Omega}_1{}^2> + <\widehat{\Omega}_2{}^2> - 2<\widehat{\Omega}_1\widehat{\Omega}_2> = 2\overline{\Omega}^2$$

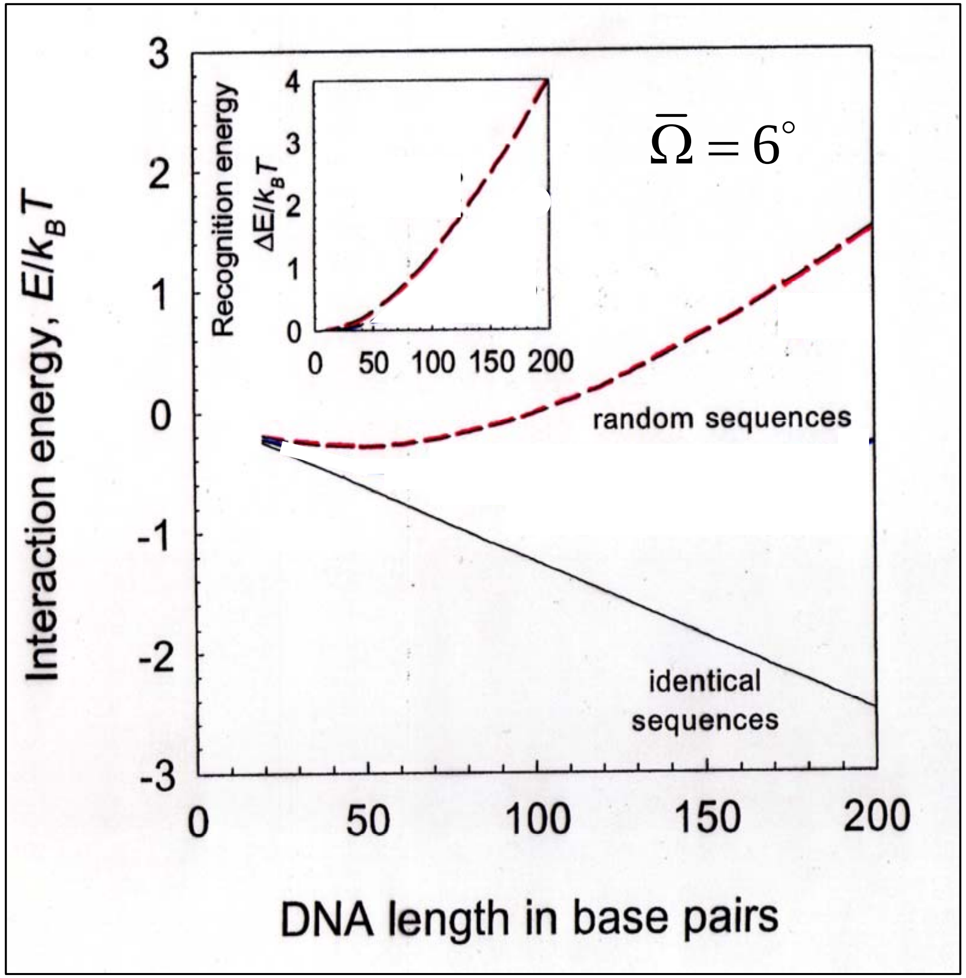
Recognition energy

$$\Delta E = \{\mu_1(L)a_1(R) - \mu_2(L)a_2(R)\} L$$

$$\mu_n(L) = 1 - \frac{1-\exp(-n^2 L/\lambda_c)}{n^2(L/\lambda_c)}$$

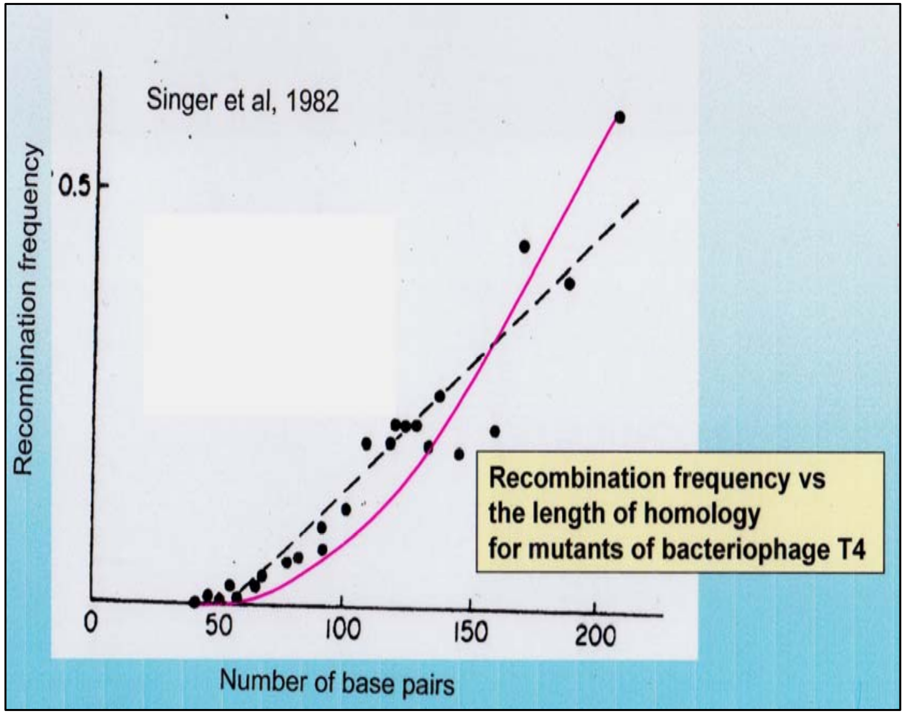
$$\lambda_c = \frac{h}{\bar{\Omega}^2}$$

Helical coherence length
(B-DNA: 170Å)



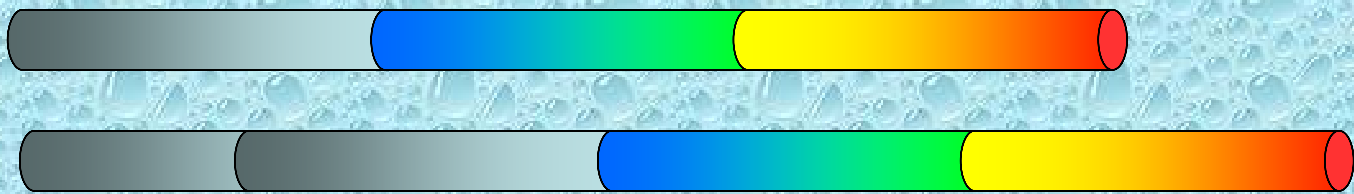
$$\frac{1}{\lambda_c^{(tot)}} = \sum_i \frac{1}{\lambda_c^{(i)}}$$

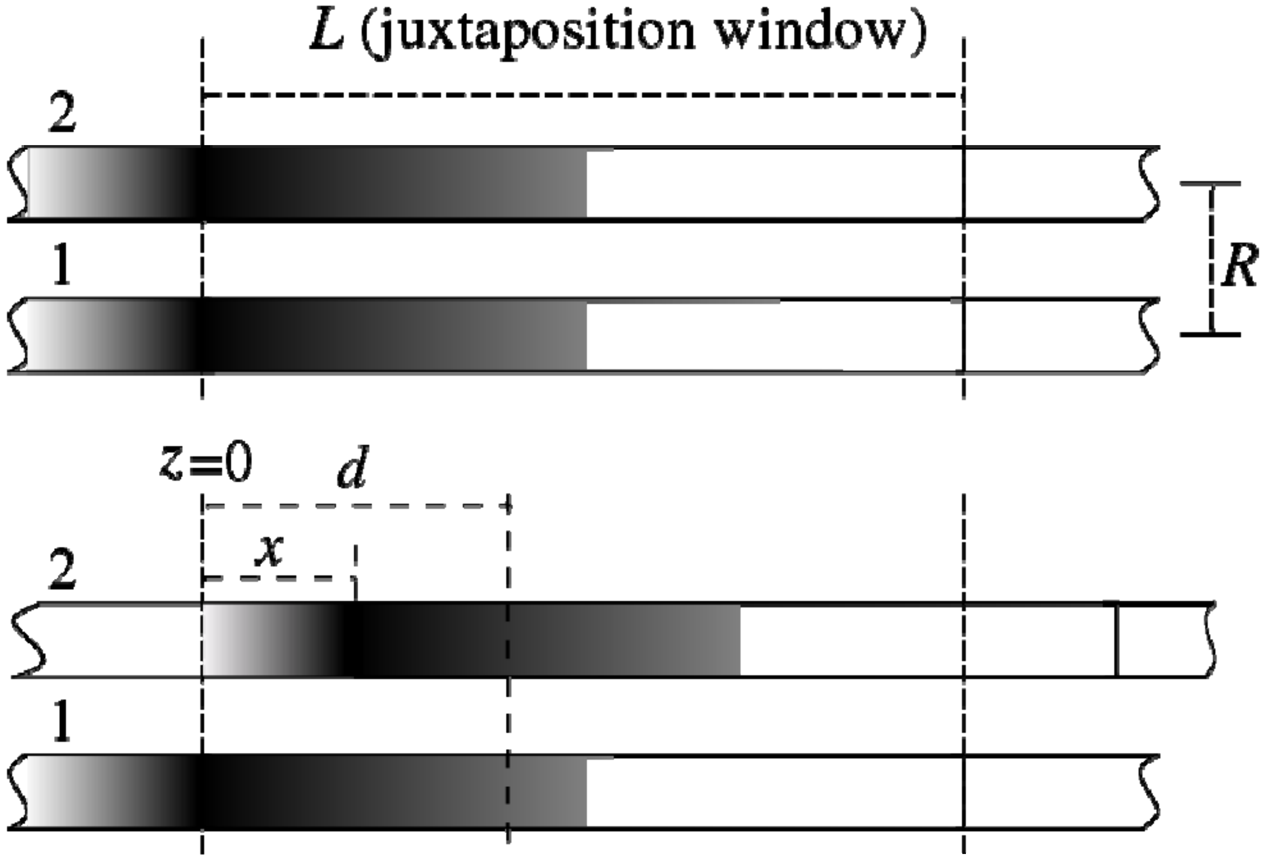
What length of DNA can be involved in recombination and how much is necessary?



Amplified recognition in juxtaposing series of genes?

What is the shape of the recognition well?



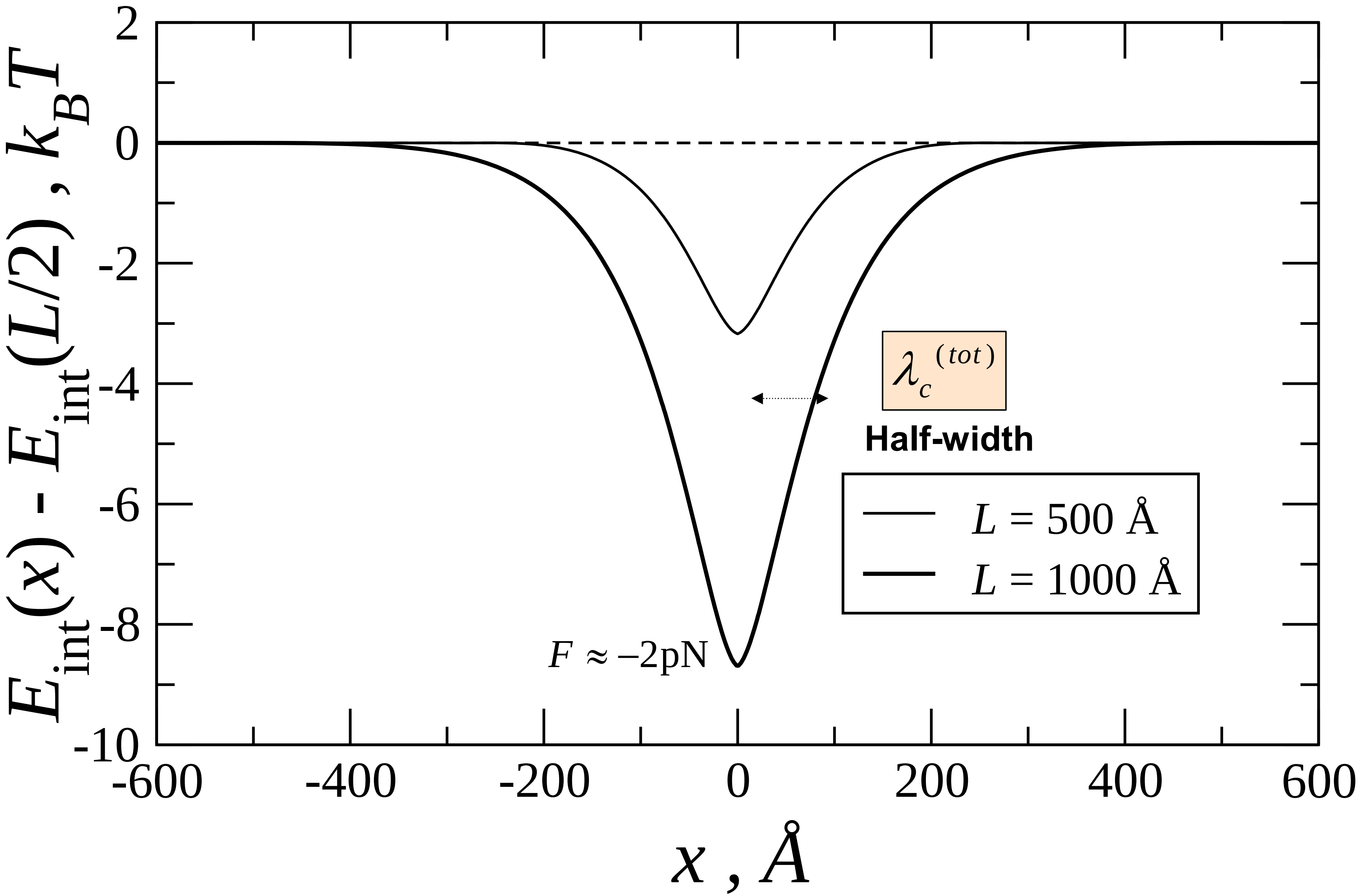


Rigid molecules:

$$E_{\text{int}}(x) = a_0 L - 2\lambda_c \begin{cases} a_1\left[\left(1-e^{-\frac{|x|}{\lambda_c}}\right) + \frac{L-2|x|}{2\lambda_c} e^{-\frac{|x|}{\lambda_c}}\right] - a_2\left[\frac{1}{4}\left(1-e^{-4\frac{|x|}{\lambda_c}}\right) + \frac{L-2|x|}{2\lambda_c} e^{-4\frac{|x|}{\lambda_c}}\right], & |x| \le L/2 \\ a_1\left(1-e^{-\frac{L}{2\lambda_c}}\right) - a_2\left[\frac{1}{4}\left(1-e^{-2\frac{L}{\lambda_c}}\right)\right] & , |x| > L/2 \end{cases}$$

Recognition well: rigid molecules

surface-to-surface separation: 10 Å



Adding torsional energy...

Torsionally elastic molecules in direct juxtaposition

$$E_t = \frac{C}{2}\sum_{i=1,2}\int_0^L dz\left[\frac{d\Phi_i}{dz} - \frac{\Omega_i(z)}{h}\right]^2$$

Eqution on twist angle difference -"**DNA - inspired physics**"

(sine-Gordon equation with frustration in random field):

$$\boxed{\frac{d^2\phi}{dz^2} - \sin(\phi)\left\{1 + B\sin^2\frac{\phi}{2}\right\} = \frac{\lambda_0^2}{h}\frac{d(\delta\Omega)}{dz}}$$

A.A.Kornyshev and S.Leikin
Phys.Rev.Lett. 86, 3666 (2001)

$$B \equiv 8a_2/(a_1 - 4a_2)$$

$$\lambda_0 \equiv \sqrt{C/2(a_1 - 4a_2)}$$

A.A.Kornyshev & A.Wynveen
Nonlinear effects in the torsional adjustment of interacting DNA, *Phys.Rev.E* 69,#041905 (2004)

A.G.Cherstvy, A.A.Kornyshev & S.Leikin
Torsional deformation of double helix in interaction and aggregation of DNA,
J.Phys.Chem. B 108, 6508 (2004)

Torsionally elastic molecules in shifted juxtaposition

$$H[\phi(z)] = \int_{-L/2}^{L/2} dz \left[\frac{C}{4}\left(\frac{d\phi(z)}{dz} - \frac{\Omega(z)}{h} + \frac{\Omega(z+\Delta z)}{h} \right)^2 - a_1(R)\cos\phi(z) + a_2(R)\cos 2\phi(z) \right]$$

$$\frac{C}{2}\frac{d^2\phi(z)}{d^2 z} - a_1 \sin\phi(z) + 2a_2 \sin 2\phi(z) = \frac{C}{2h}\left(\frac{d\Omega(z)}{dz} - \frac{d\Omega(z+\Delta z)}{dz} \right)$$

Variational approach

1. Linearize the equation:

$$\frac{d^2\Delta\Phi(z)}{d^2 z} - \frac{1}{\lambda_0^{\ 2}}\Delta\Phi(z) = \frac{1}{h}\frac{d\Omega(z)}{dz} - \frac{1}{h}\frac{d\Omega(z+\Delta z)}{dz} \qquad \lambda_0 \equiv \sqrt{\frac{C}{2\left(a_1\cos\phi_0 - 4a_2\cos 2\phi_0\right)}}$$

2. Find the linear response solution:

$$\Delta\Phi(z) = \phi_0 - \frac{\lambda_0}{2h}\int_{-\infty}^{\infty} dz' \left[\frac{d\Omega(z')}{dz'} - \frac{d\Omega(z'+\Delta z)}{dz'} \right] \exp\left(-\frac{|z-z'|}{\lambda_0} \right)$$

3. Build the trial function on this solution via replacing $\lambda_0 \Rightarrow \lambda$, the variational parameter.

4. Substitute this trial function into the Hamiltonian, minimize it to find λ and the free energy

Torsionally elastic, ‘adaptable’ molecules

Recognition force

$$F = -\operatorname{sgn}(\Delta z)\frac{CL}{4\lambda_c\lambda^2}\exp\left(-\frac{|\Delta z|}{\lambda}\right)$$

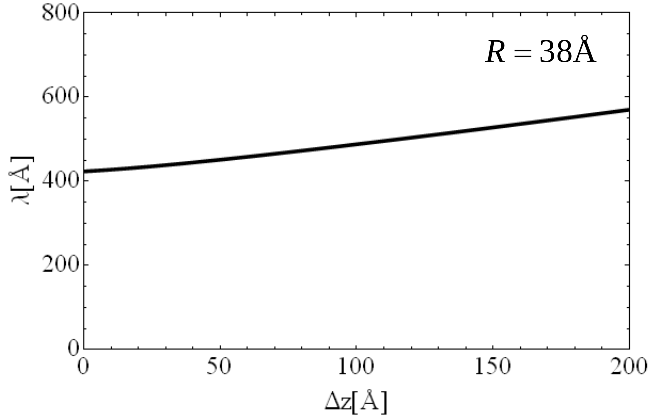
$$\lambda = \sqrt{\frac{C}{2\left(a_1(R)\exp\left(-\frac{\lambda}{4\lambda_c}\chi\left(\frac{|\Delta z|}{\lambda}\right)\right)\cos\bar{\phi} - 4a_2(R)\exp\left(-\frac{\lambda}{\lambda_c}\chi\left(\frac{|\Delta z|}{\lambda}\right)\right)\cos 2\bar{\phi}\right)}}$$

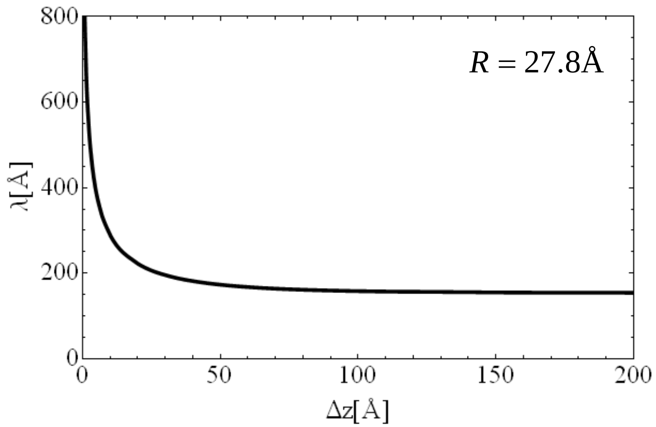
$$\bar{\phi} = 0 \qquad , \qquad R > R^*$$

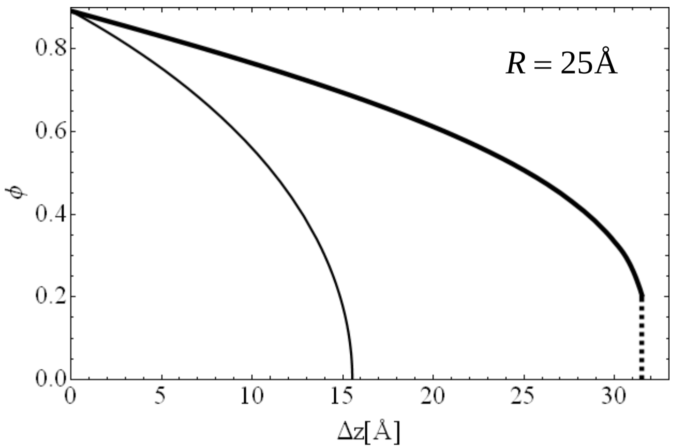
$$\bar{\phi} = \cos^{-1}\left(\frac{a_1(R)}{4a_2(R)}\exp\left(\frac{\lambda}{4\lambda_c}\chi\left(\frac{|\Delta z|}{\lambda}\right)\right)\right), \qquad R < R^*$$

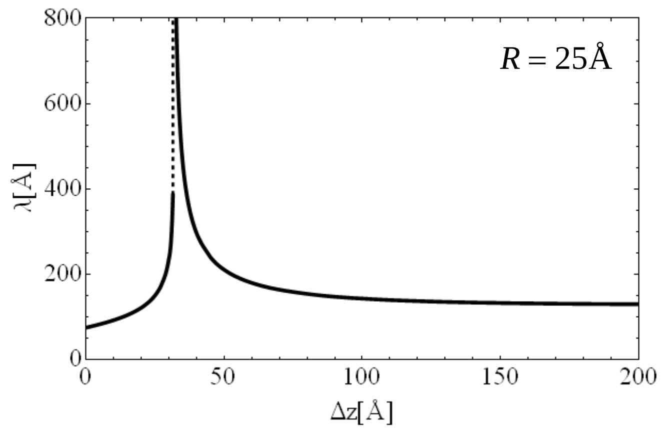
$$\chi(z) \equiv 1-(1-z)\exp(-z)$$

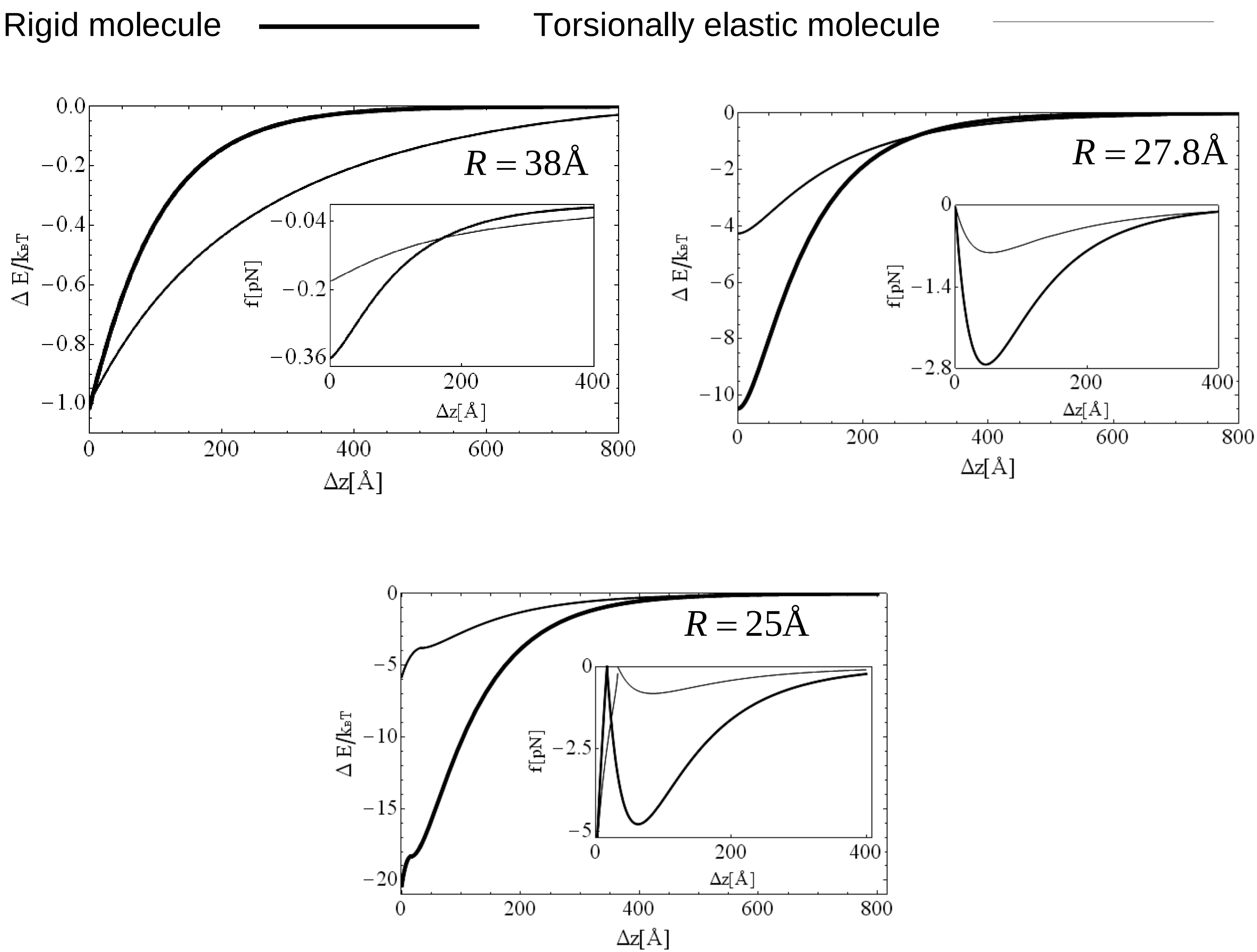
The meaning of λ :
cut-off length for accumulation of disorder,
i.e. force-induced **adaptation length**





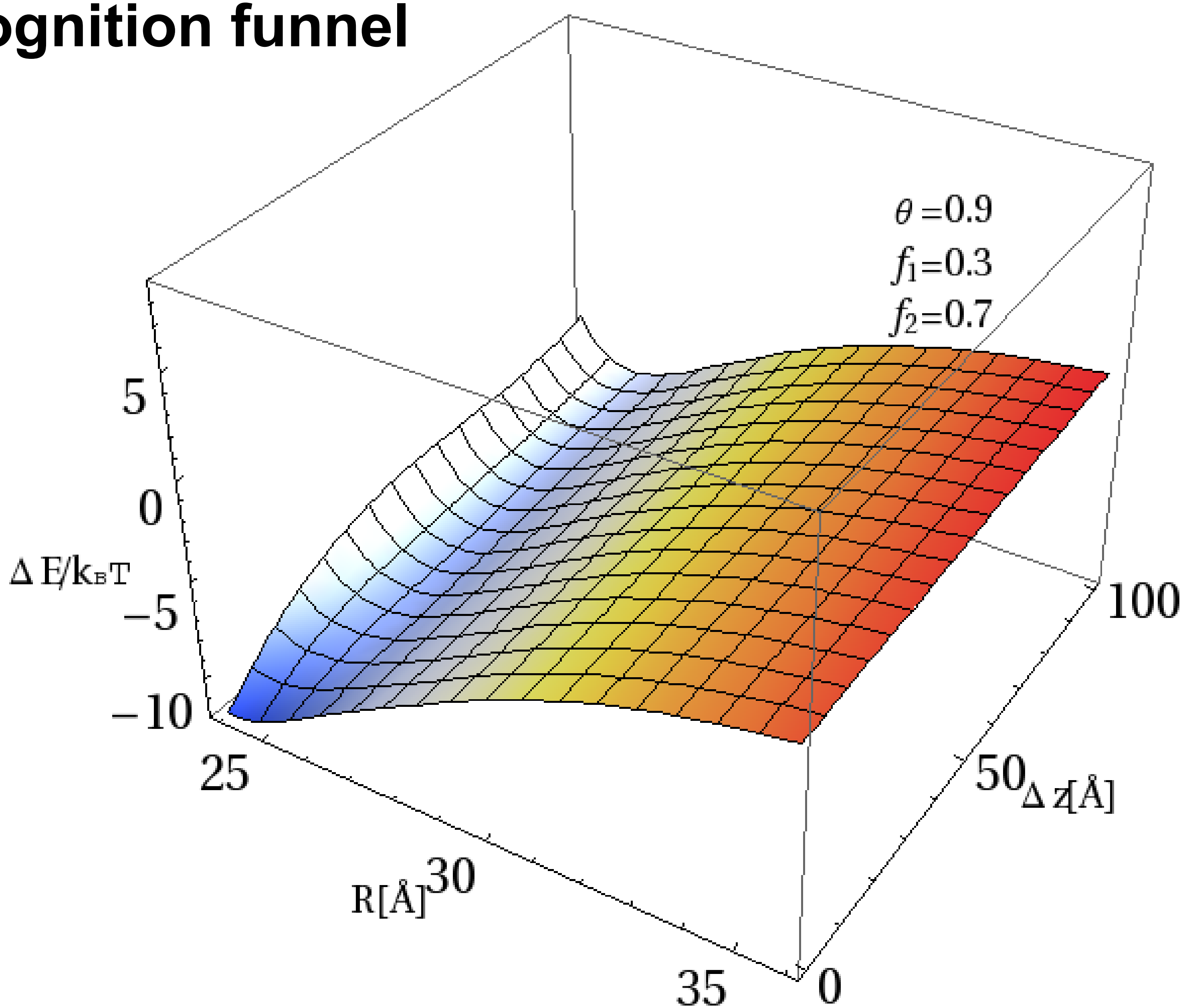






Rigid molecule
Torsionally elastic molecule
R = 38Å
ΔE/kBT
Δz[Å]
f[pN]
Δz[Å]
R = 27.8Å
ΔE/kBT
Δz[Å]
f[pN]
Δz[Å]
R = 25Å
ΔE/kBT
Δz[Å]
f[pN]
Δz[Å]

Recognition funnel



DNA double helices recognize mutual sequence homology in a protein-free environment
J.Baldwin, N.Brooks, R.Robson, A.Goldar, A.Wynveen, S.Leikin, J.M.Seddon, A.A.Kornyshev
J. Phys. Chem B, 112, 1060 (2008)

Genetic “telepathy”? A bizarre new property of DNA

ACS News Service Weekly PressPac: January 23, 2008

Paired Pairs

Nature Feb ‘08

Seeking Recognition

Biopolymers vol. 89

Spooky attraction of DNA from a distance

New Scientist Feb ‘08

Telepathic Genes

London Metro!

DNA's Self-Regard

Science Feb ‘08

Double-Helix Double Up

Scientific American Apr ‘08

WE NEED HOMOLOGY FORCE MEASUREMENTS!