XXIX International Colloquium on Group-Theoretical Methods in Physics, Nankai University, Tianjin, Chine.

Non-specific DNA-protein interaction: How proteins can diffuse along DNA

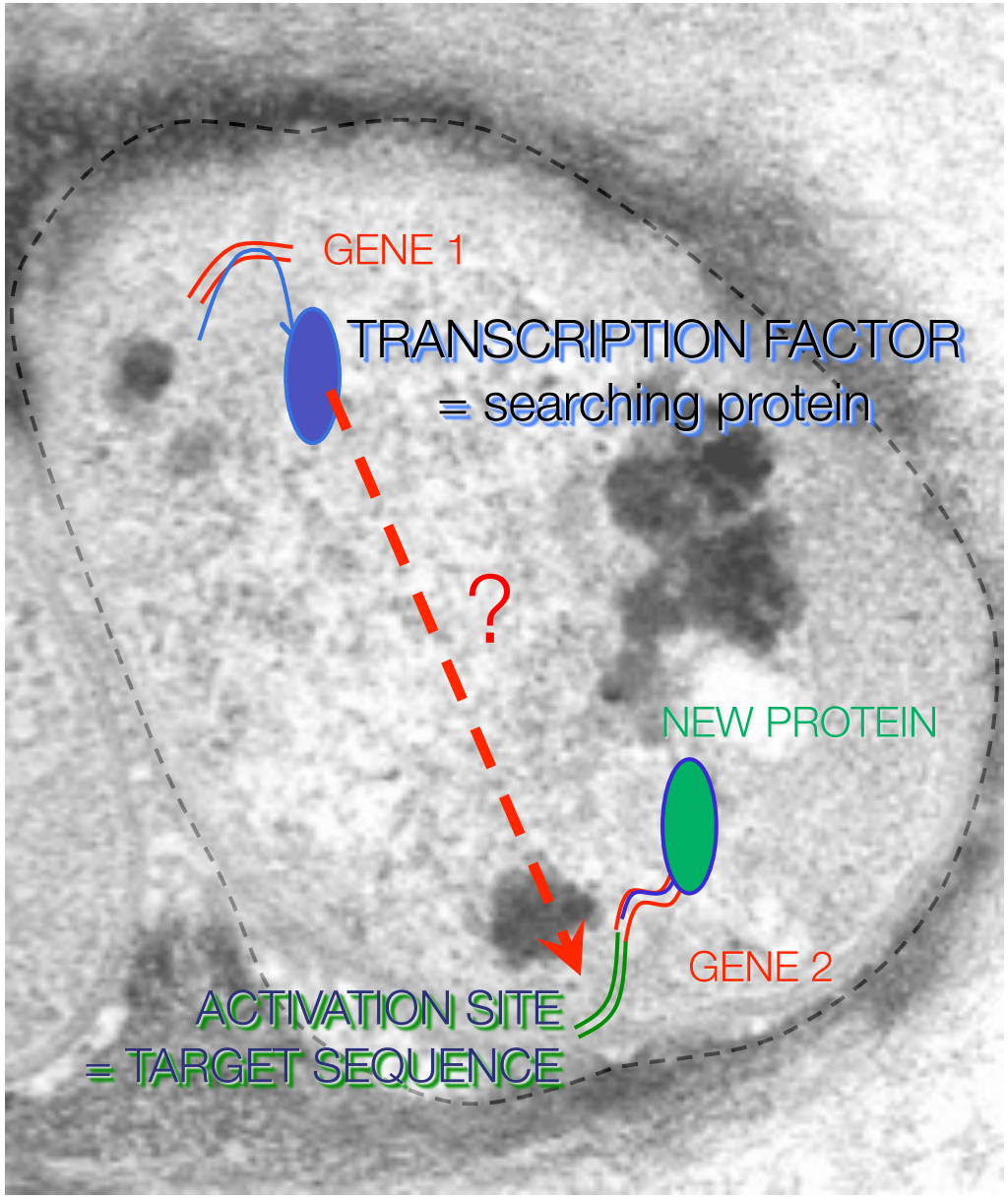
Fabien Paillusson, Maria Barbi, Jean-Marc Victor
LPTMC, UPMC - Paris VI

Aleksandra Nivina
Master student April-July 2012

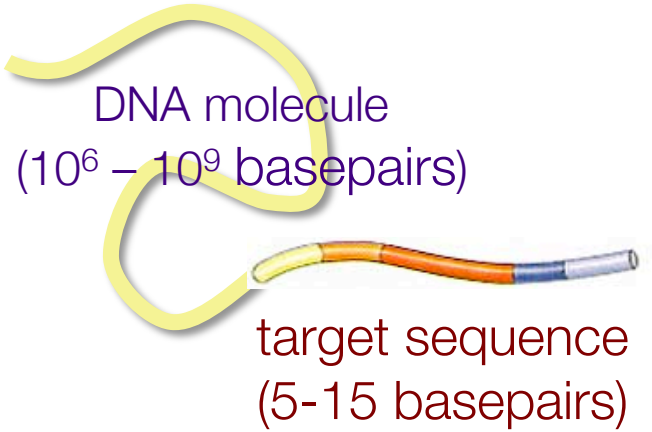
Marie Jardat, Vincent Dahirel
PECSA, UPMC - Paris VI

DNA-binding proteins

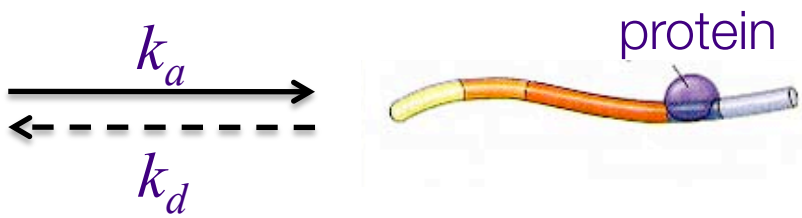
Example :



search of target sequences on DNA



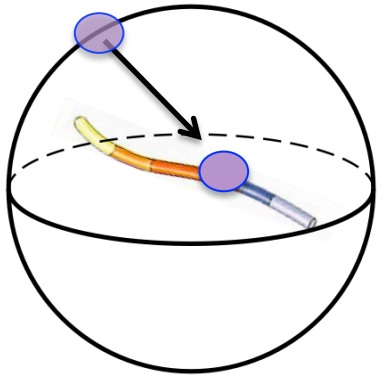
Reaction kinetics



Experimental

$$\frac{1}{\tau} = k_a \approx 10^{10}\ \mathrm{M}^{-1}\mathrm{s}^{-1}$$

Debye-Smoluchowski theory: 3D diffusion

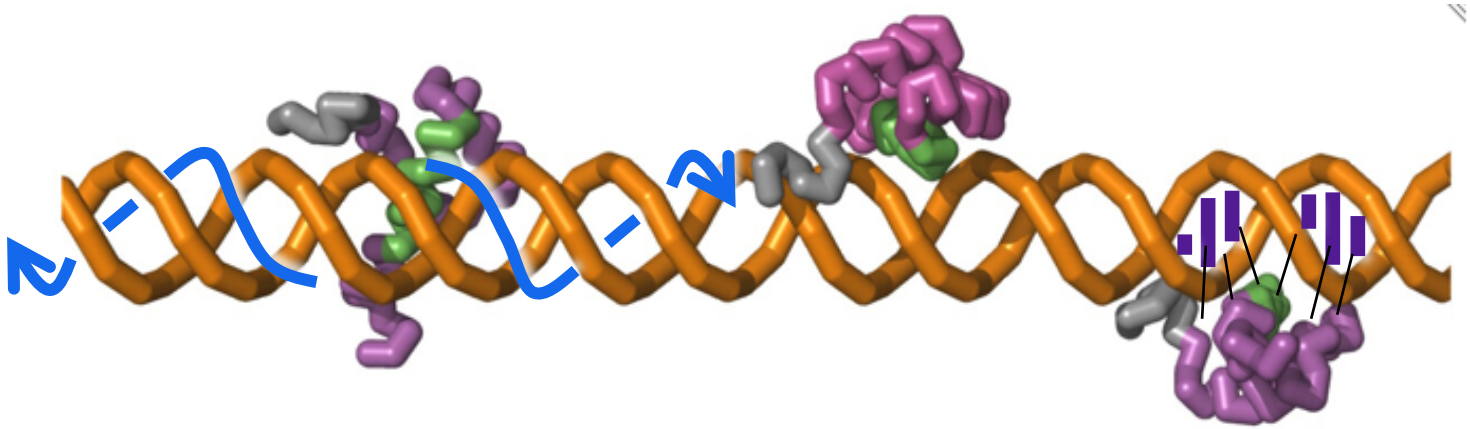


Calculated

$$\frac{1}{\tau_{th}} = k_a^{th} \approx 10^{8}\ \mathrm{M}^{-1}\mathrm{s}^{-1}$$

Riggs, JMB, 1970

search of target sequences on DNA



1. displacement along DNA

- 1D diffusion (sliding)
- 3D diffusion (jumps)

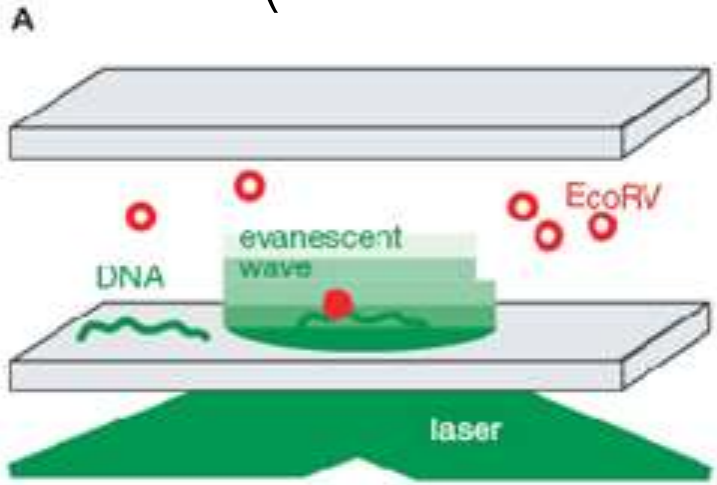
⇓

« intermittent process »

« facilitated diffusion »

1. protein 1D diffusion (sliding)

experimental evidences (fluorescence microscopy)

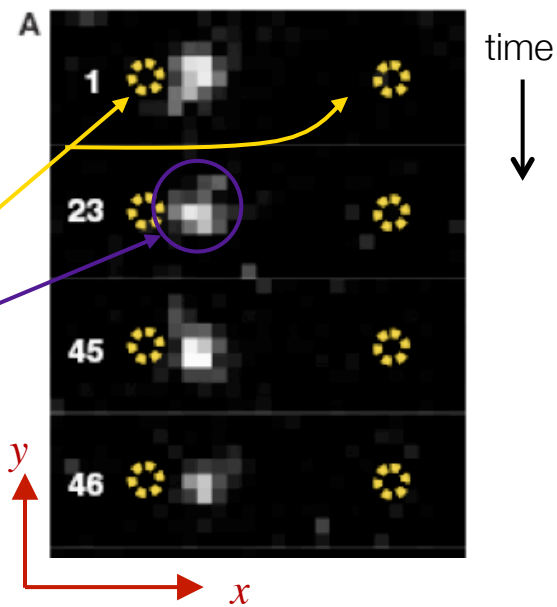


Bonnet et al NAR 2008

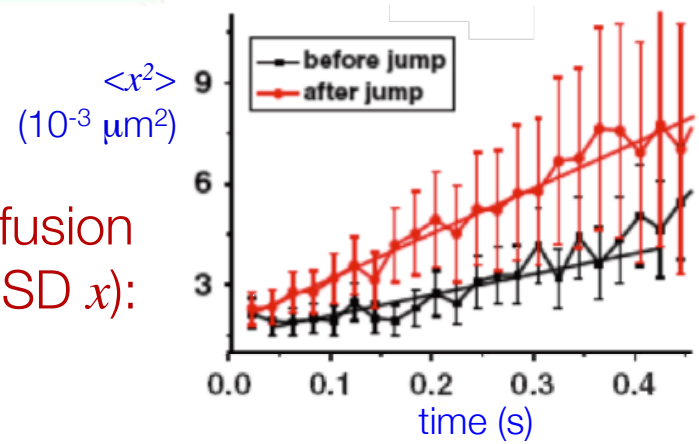
the protein diffusion « movie »:

DNA extremities

protein



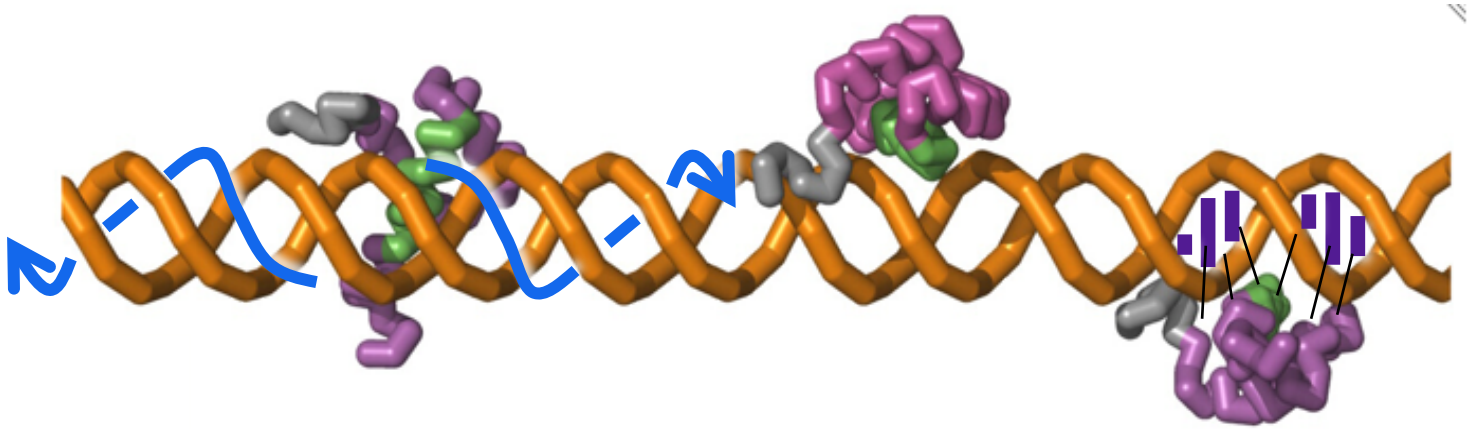
diffusion (MSD x):



diffusion coefficient: $D_1 \sim 10^{-2}$ μm^2/s

~ (300 pb)^2/s

search of target sequences on DNA



1. displacement along DNA

- 1D diffusion (sliding)
- 3D diffusion (jumps)

⇓

« intermittent process »

« facilitated diffusion »

2. sequence recognition

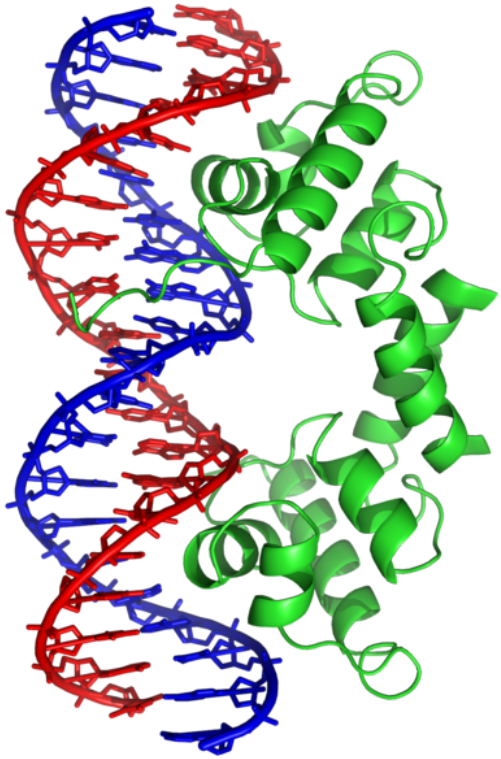
interaction (H bonds) with nucleotides

⇓

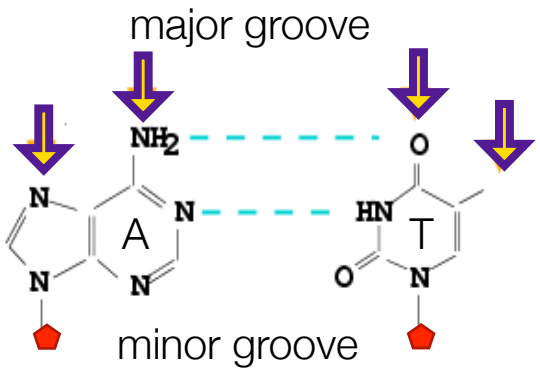
« reading »

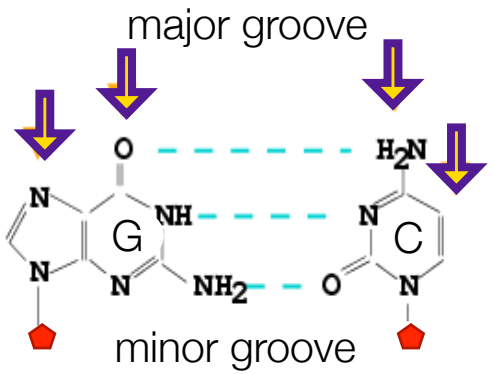
2. sequence recognition

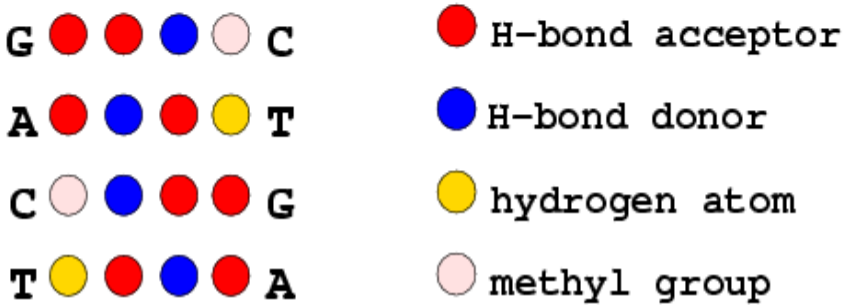
direct interaction:
hydrogen bonding to the bps sides



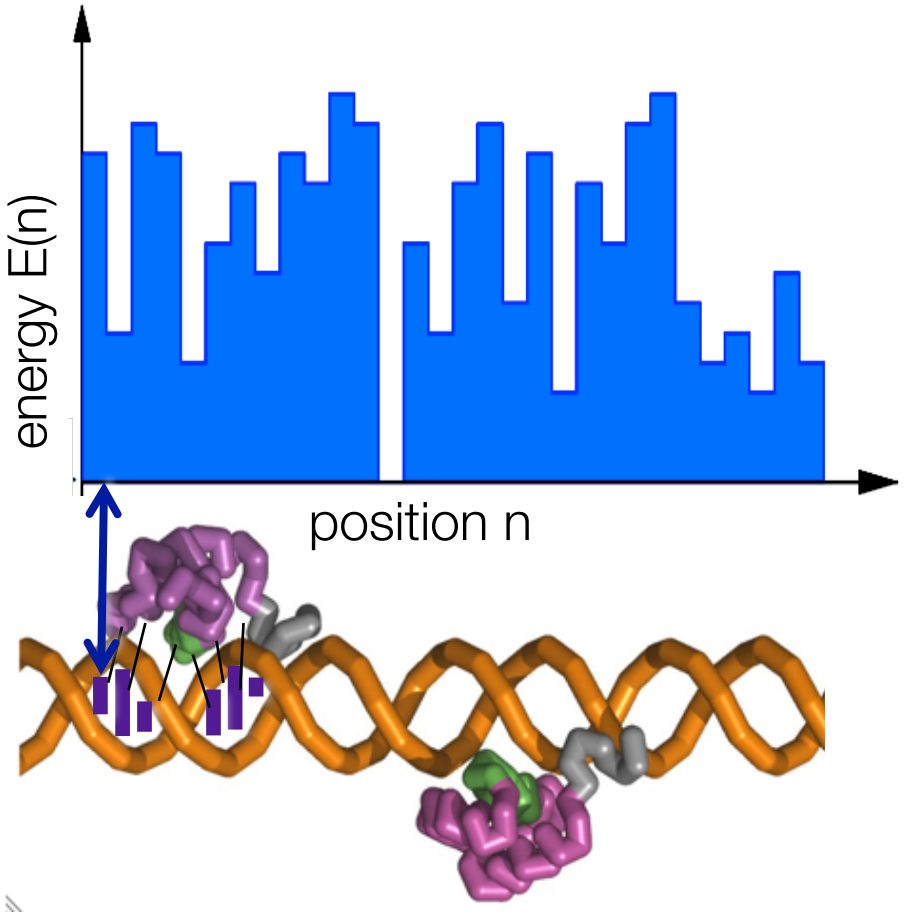
EcoRV and DNA







mobility-specificity paradox



sequence dependent interaction

(H bonds) $\Rightarrow$ rough potential

$\downarrow$

strongly reduced mobility,

trapping [J Biol Phys 04, PRE 04]

our starting point

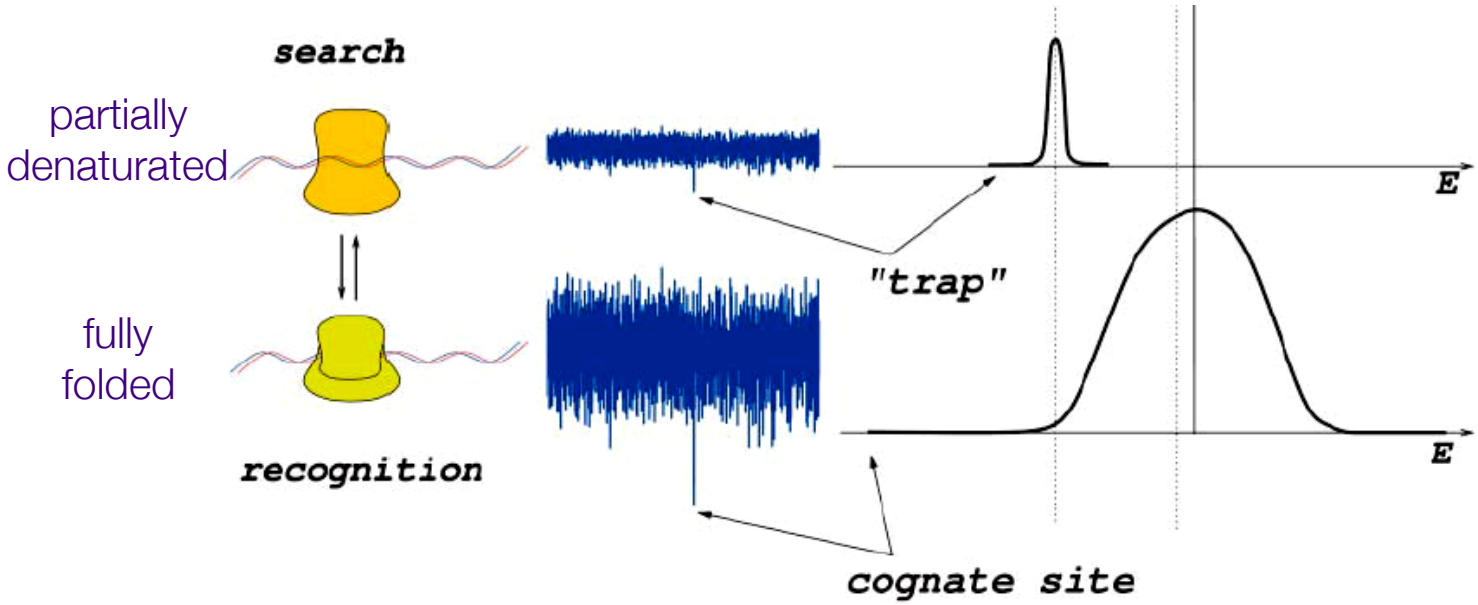
Two-state models

sliding state / reading state :

a possible solution for the paradox…

how ?

1. protein fluctuates between 2 conformations: hypothesis of Mirny lab



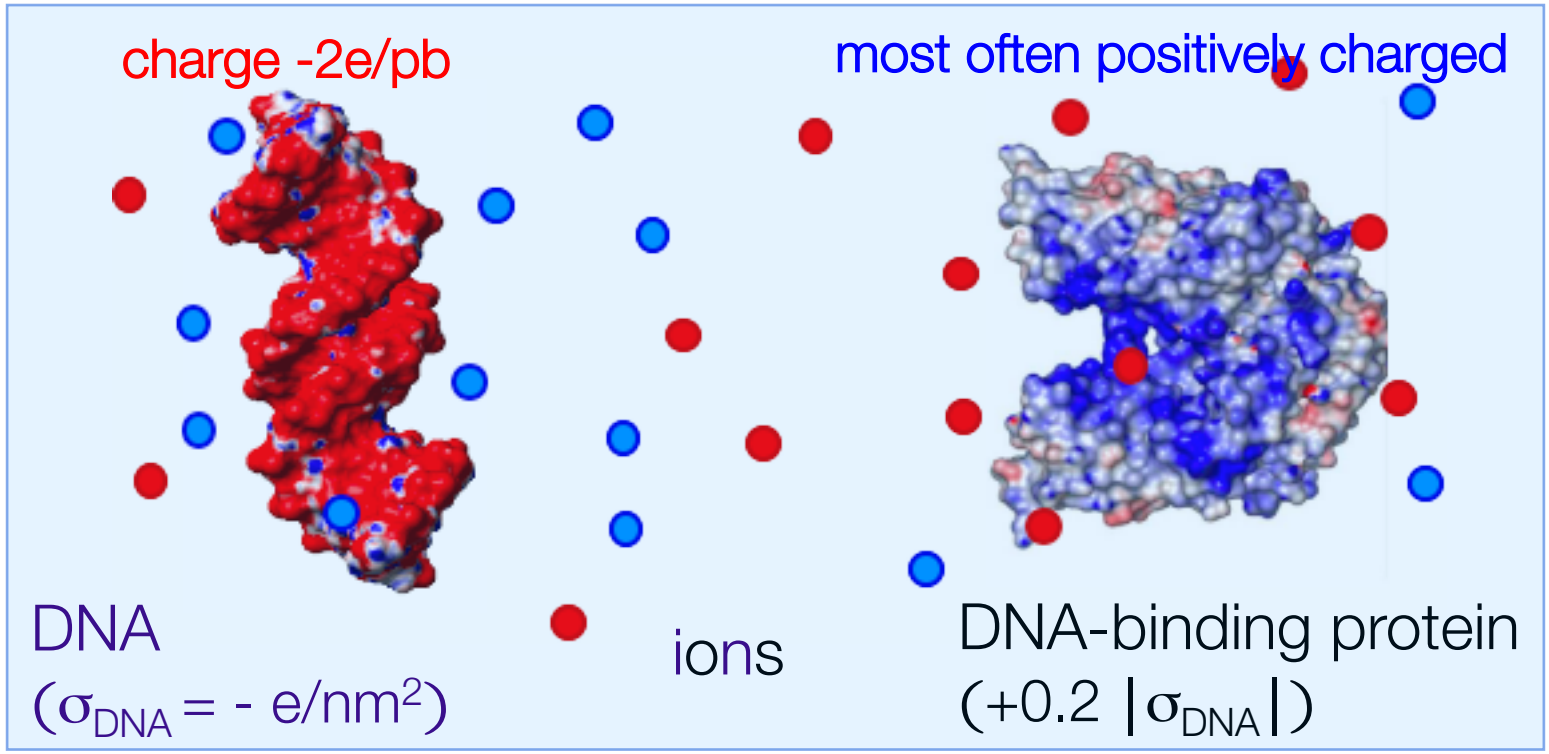
Slutsky and Mirny Biophys.J., 2004

2. we propose an alternative mechanism…
   where the distance between protein and DNA plays a role

physics of the protein-DNA interaction

electrostatics in solution

[Mol Phys 09, PRL 09, PCCP 11]

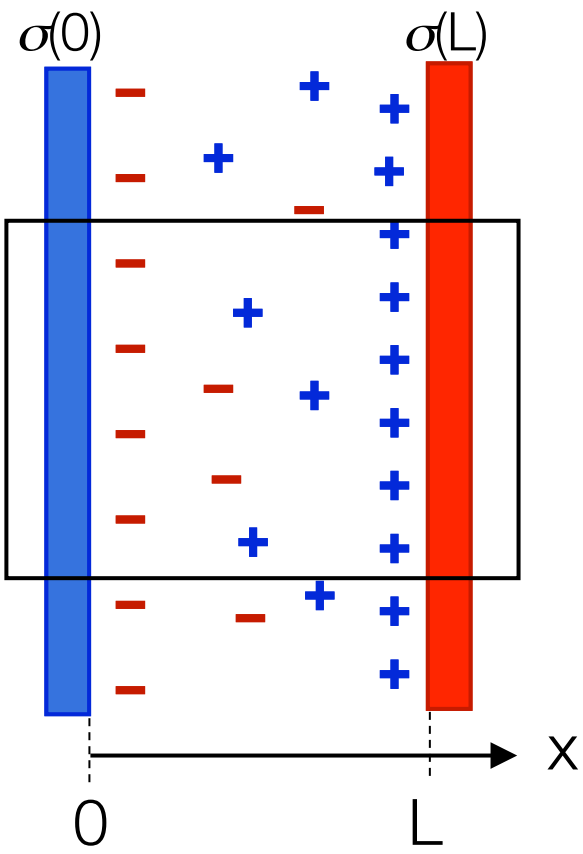


analytical approach: Poisson-Boltzmann (F. Paillusson PhD)

MC simulations: Marie Jardat et Vincent Dahirel PECSA-UPMC

oppositely charged surfaces in solution

Poisson-Boltzmann equation (1D) :



1. electrostatic potential $V(x)$:

   Poisson equation

   ($\rho(x)$ = local charge density between plates)

$$\boxed{\frac{dV(x)}{dx} = -\frac{\rho(x)}{\varepsilon}}$$

with B.C.:

$$\begin{cases} \frac{dV}{dx}(0) = -\frac{\sigma(0)}{\varepsilon} \\ \frac{dV}{dx}(L) = +\frac{\sigma(L)}{\varepsilon} \end{cases}$$

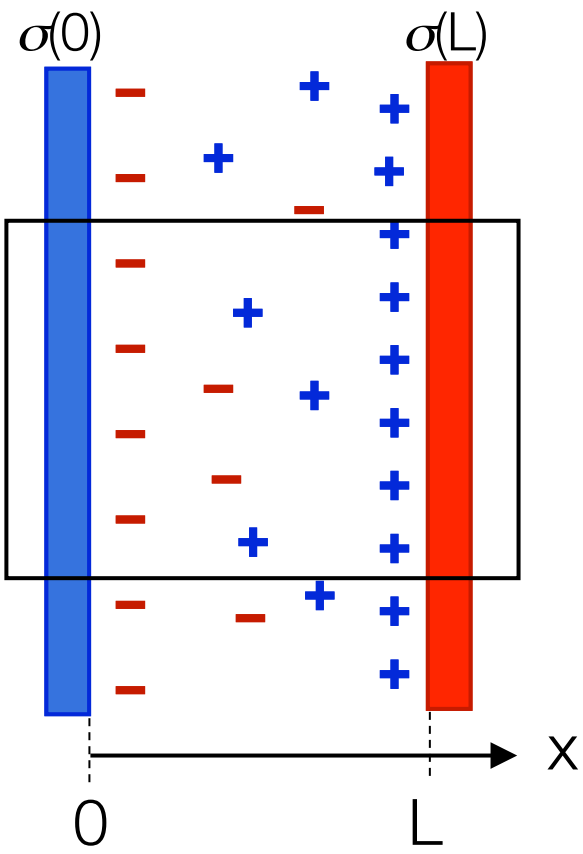
2. ions between plates:

   Boltzmann statistics

$$\boxed{\rho(x) = \sum q_i c_i^0 \, e^{-\beta q_i V(x)}}$$

oppositely charged surfaces in solution

Poisson-Boltzmann equation (1D) :



in monovalent salt

$$\frac{dV(x)}{dx} = \frac{c^0}{\varepsilon}\sinh\left(\beta\, q_i V(x)\right)$$

with B.C.:

$$\begin{cases} \frac{dV}{dx}(0) = -\frac{\sigma(0)}{\varepsilon} \\ \frac{dV}{dx}(L) = +\frac{\sigma(L)}{\varepsilon} \end{cases}$$

V(x) ⇒ pressure P(L) ⇒ free energy E(L)

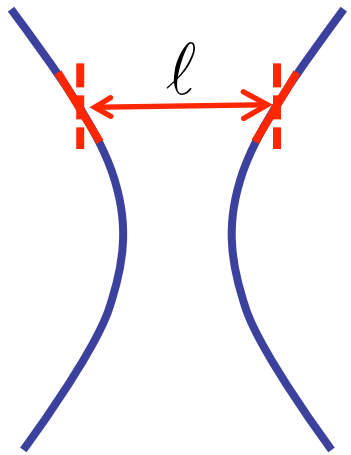
[Mol Phys 09]

protein shape

curvature effects can be accounted for by the Derjaguin approximation:

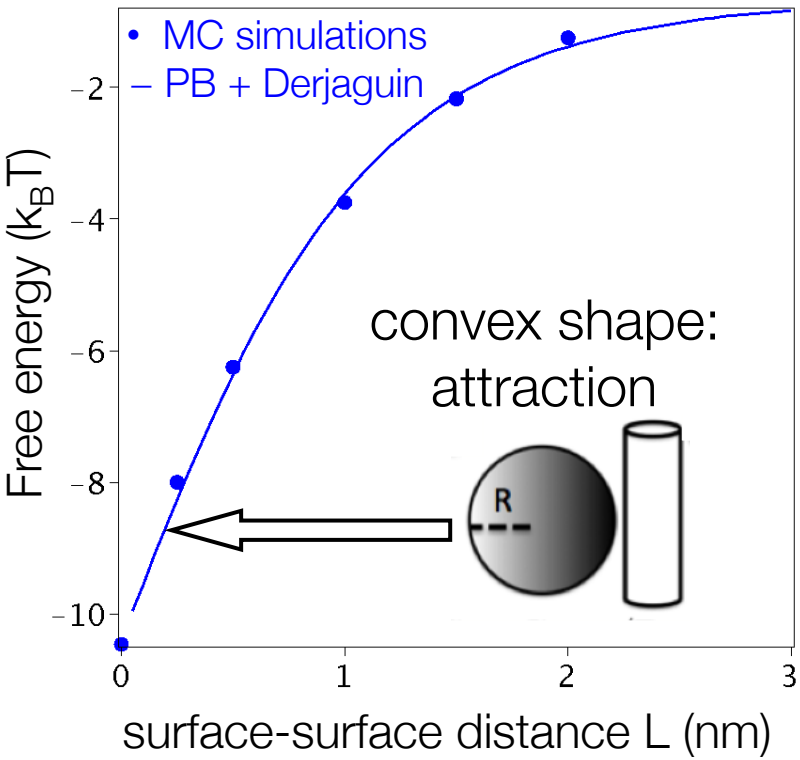
$$E(L) = \int_A dA \; E_{\parallel}(\ell)$$

plate-plate



protein shape

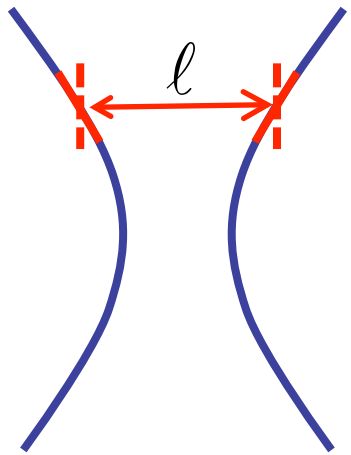
results:



curvature effects can be accounted for by the Derjaguin approximation:

$$E(L) = \int_A dA \; E_{\parallel}(\ell)$$

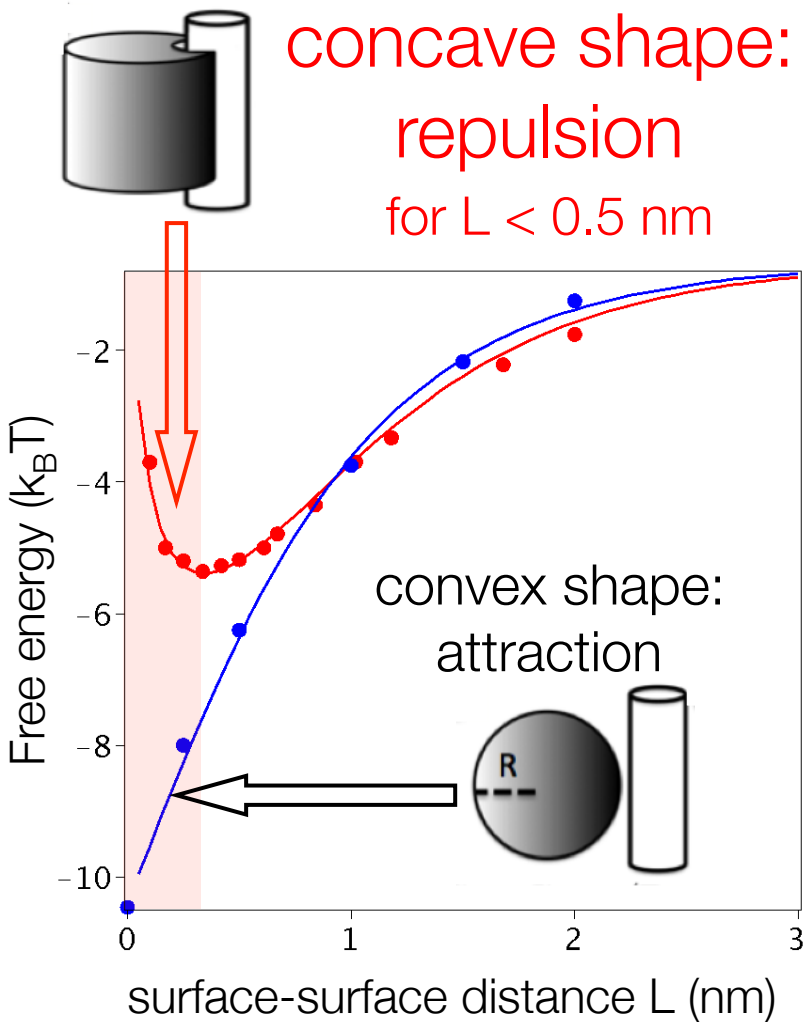
plate-plate



[Mol Phys 09, PRL 09, PCCP 11]

protein shape matters!

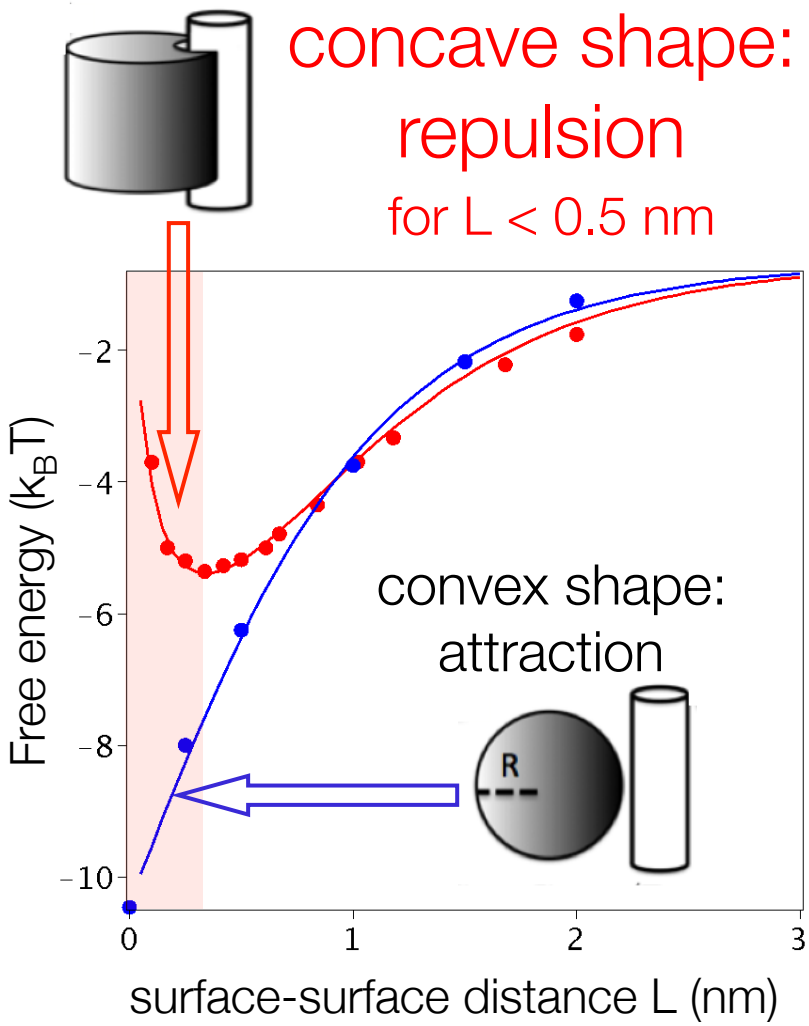
results:



[Mol Phys 09, PRL 09, PCCP 11]

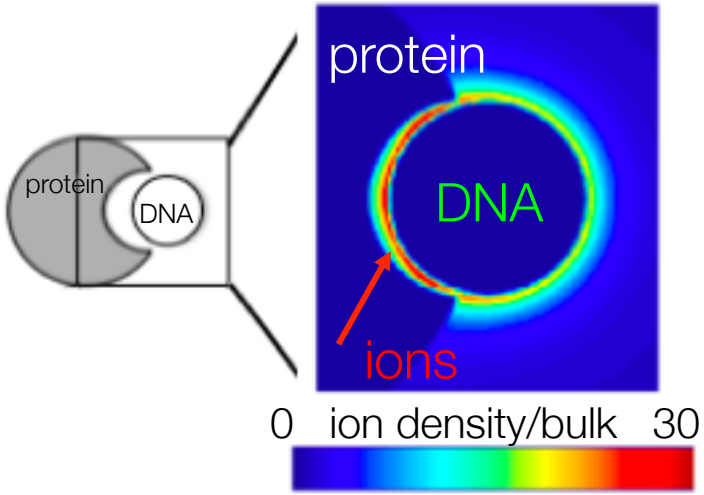
protein shape

results:

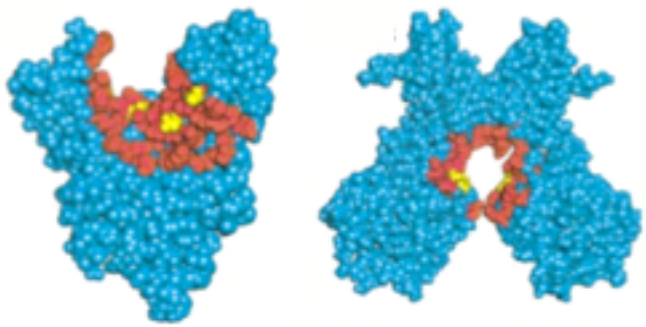


[Mol Phys 09, PRL 09, PCCP 11]

- osmotic origin : trapped ions

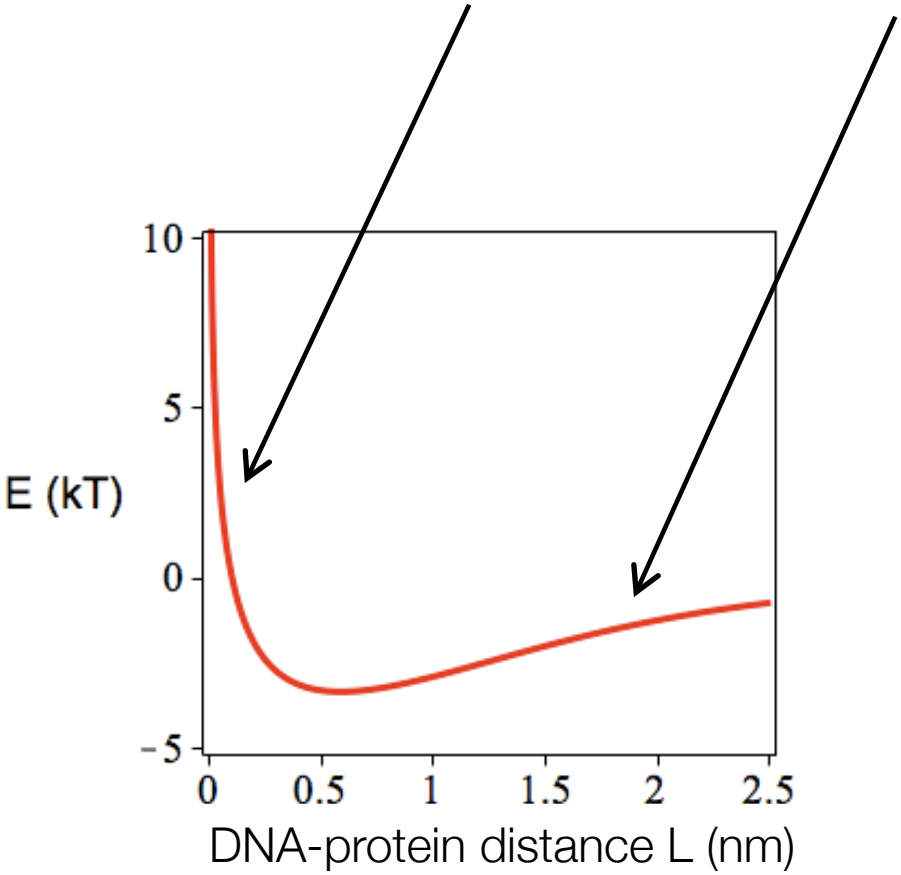


- pertinent for « DNA-binding proteins », concave



implications on sliding

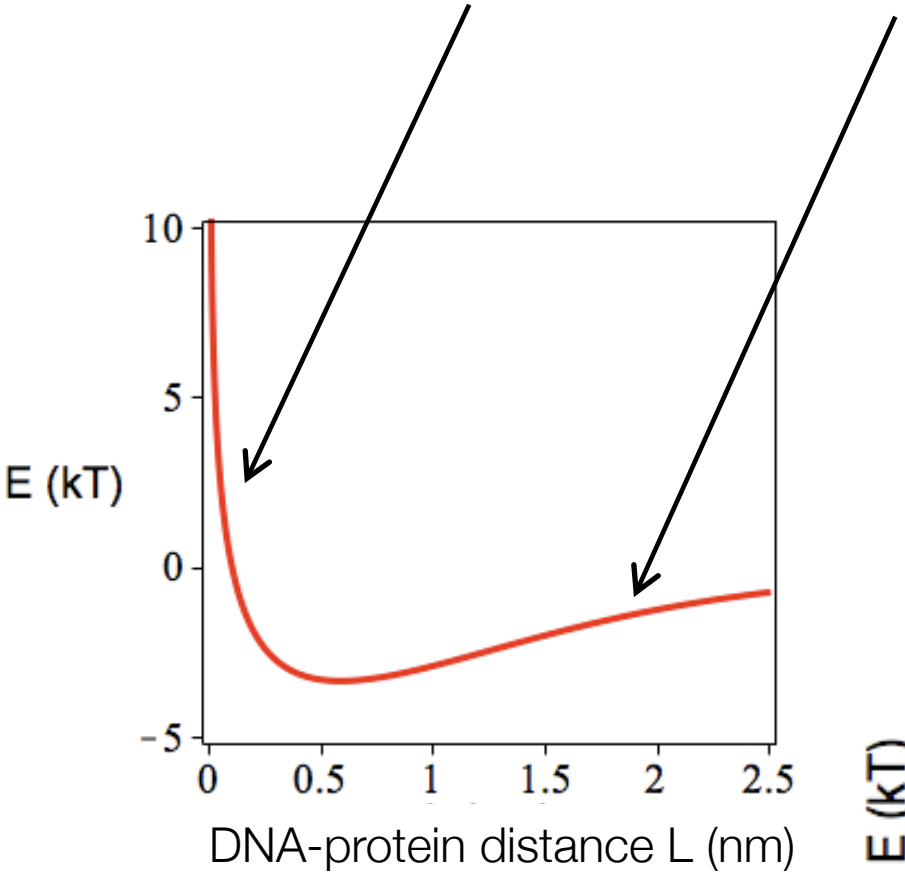
osmotic repulsion + electrostatics + hydrogen bonds



[Mol Phys 09, PRL 09, PCCP 11]

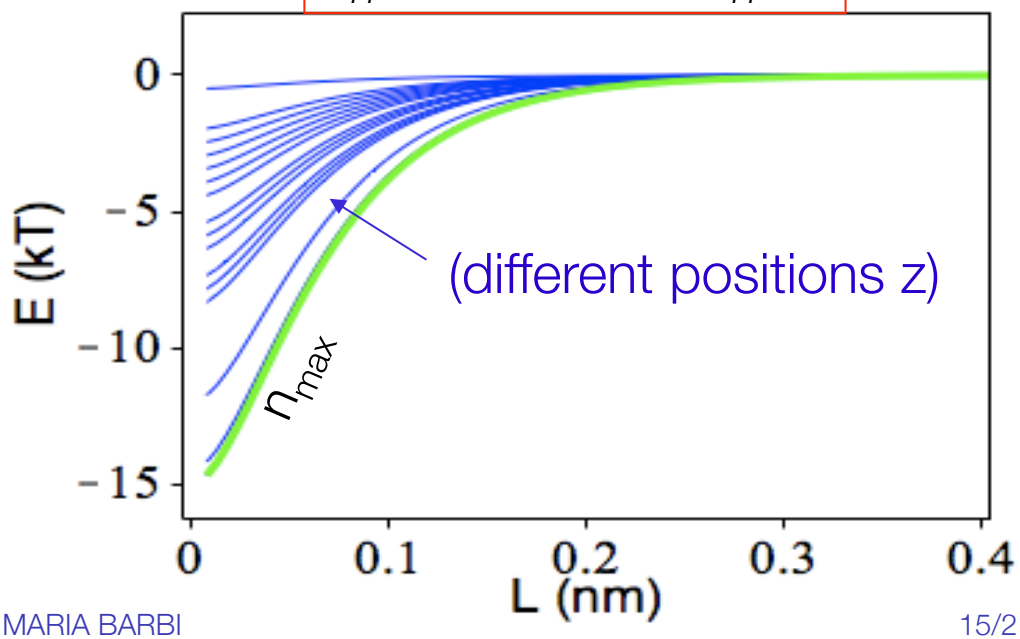
implications on sliding

osmotic repulsion + electrostatics + hydrogen bonds



- single H-bond = Morse potential
- number n of H-bonds dependent on the position z along DNA

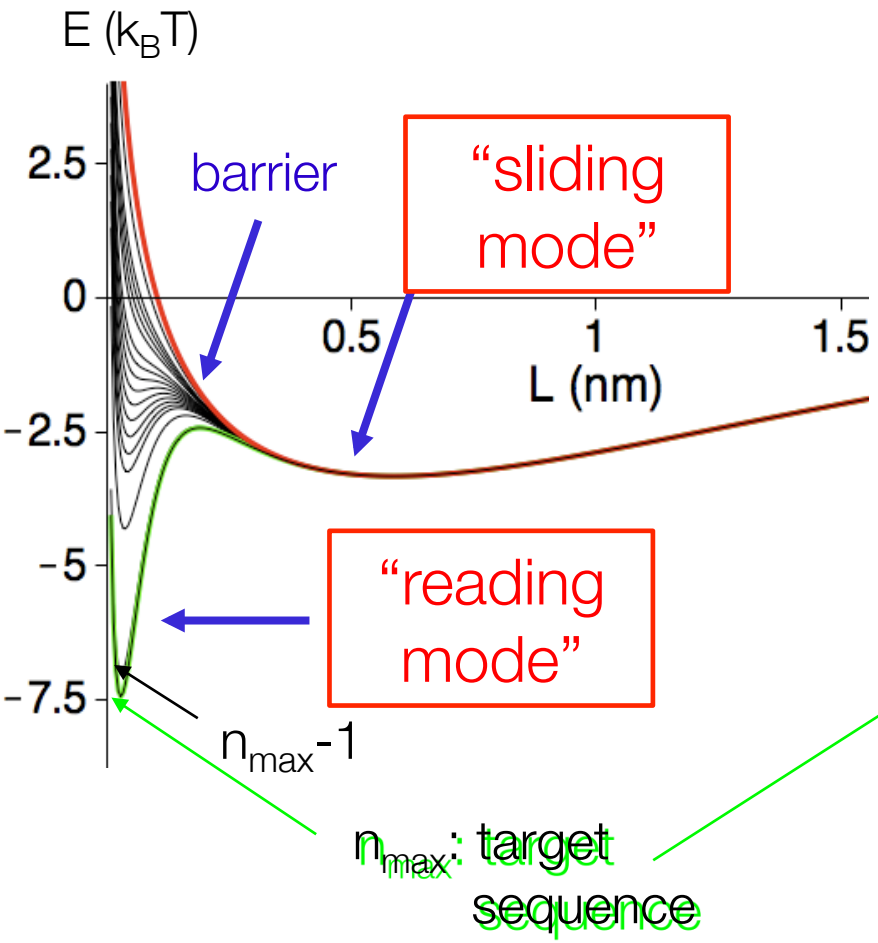
$$E_H(z,L) = n(z)\ e_H(L)$$

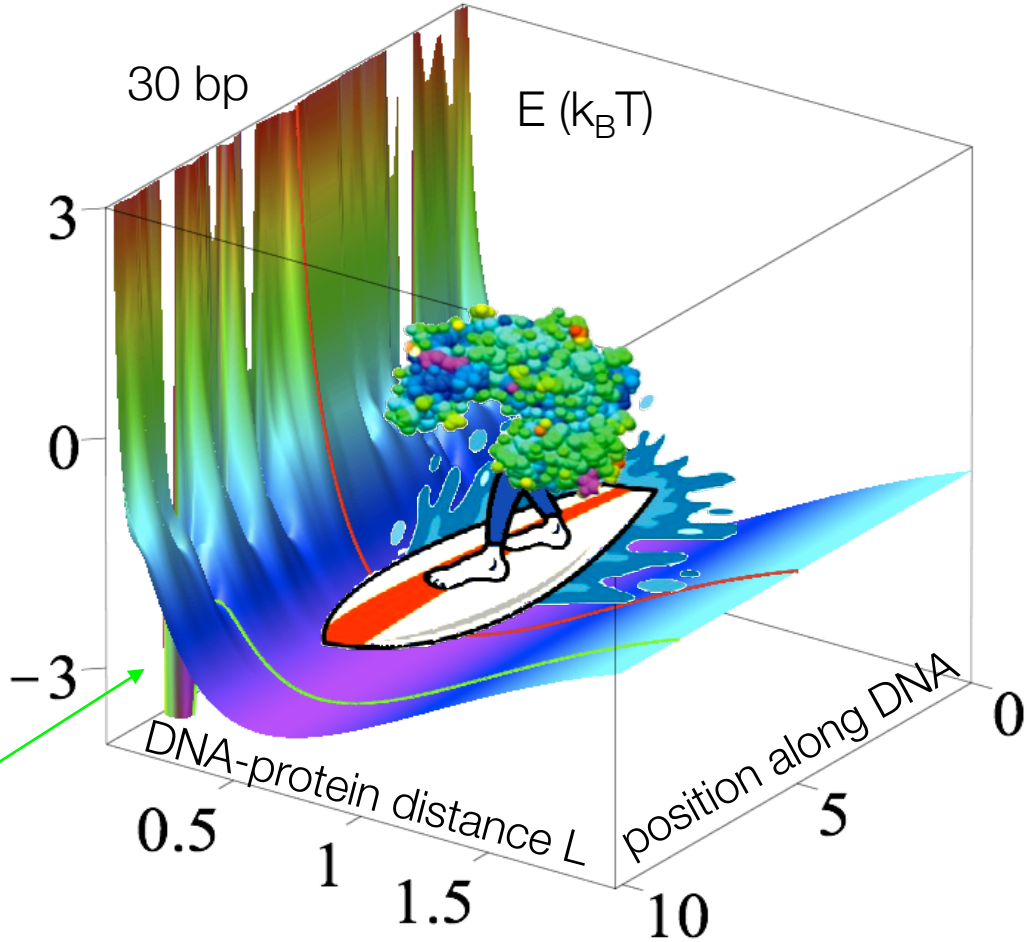


[Mol Phys 09, PRL 09, PCCP 11]

implications on sliding

osmotic repulsion + electrostatics + hydrogen bonds





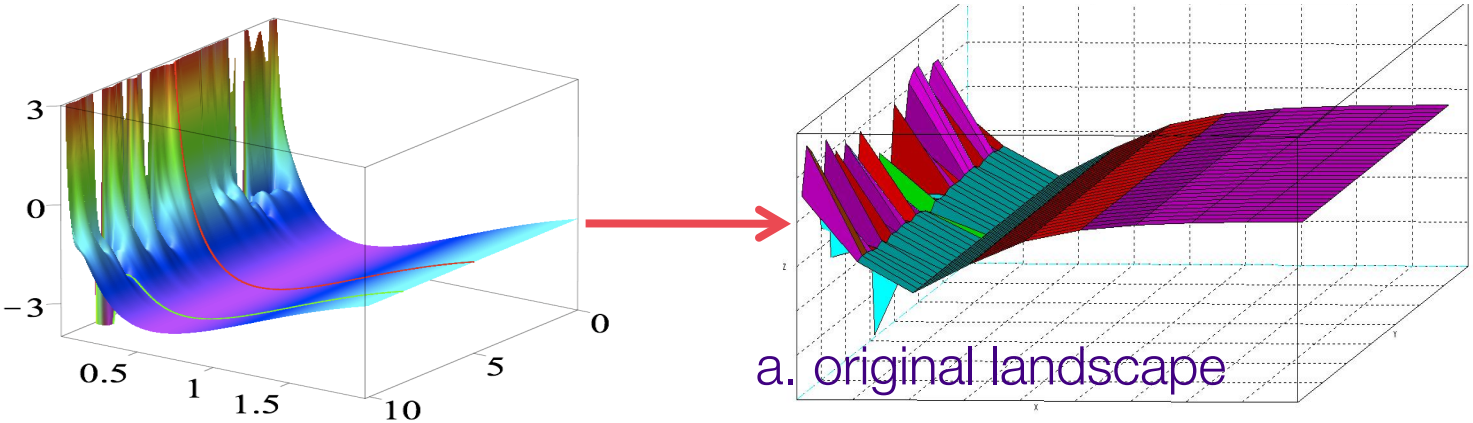
« facilitated sliding »!!

[Mol Phys 09, PRL 09, PCCP 11]

« facilitated sliding »: a proof of principle

Aleksandra Nivina master internship

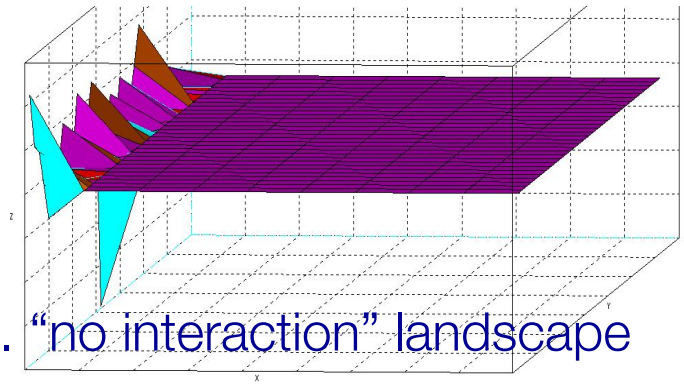
- original landscape (charged convex protein) : → discrete version



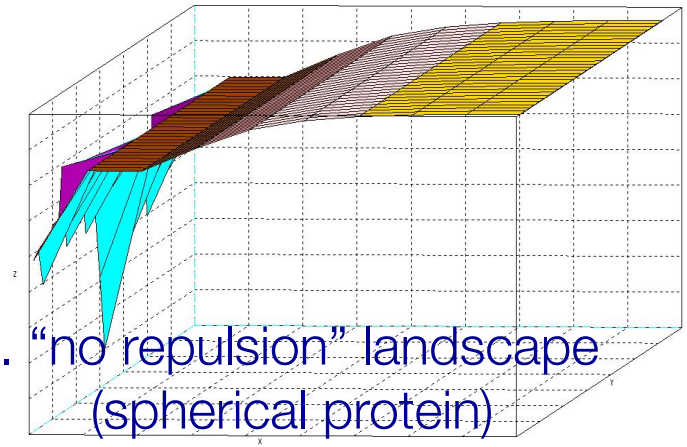
a. original landscape

- random walk on the energy profile (Arrhenius law)

- two « control » landscapes :



b. “no interaction” landscape

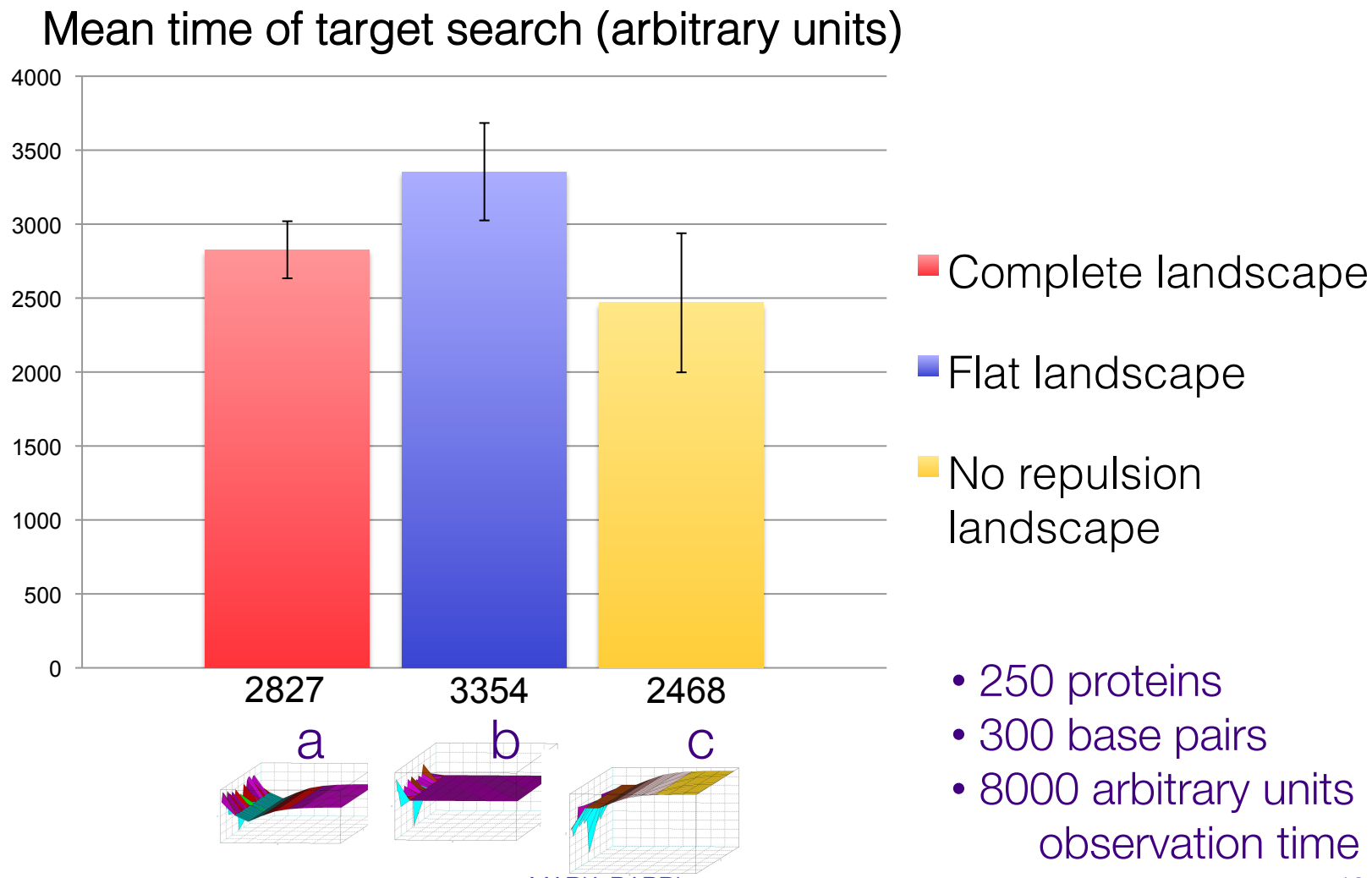


c. “no repulsion” landscape (spherical protein)

« facilitated sliding »: a proof of principle

very preliminary results:

no significant role on the time of target search

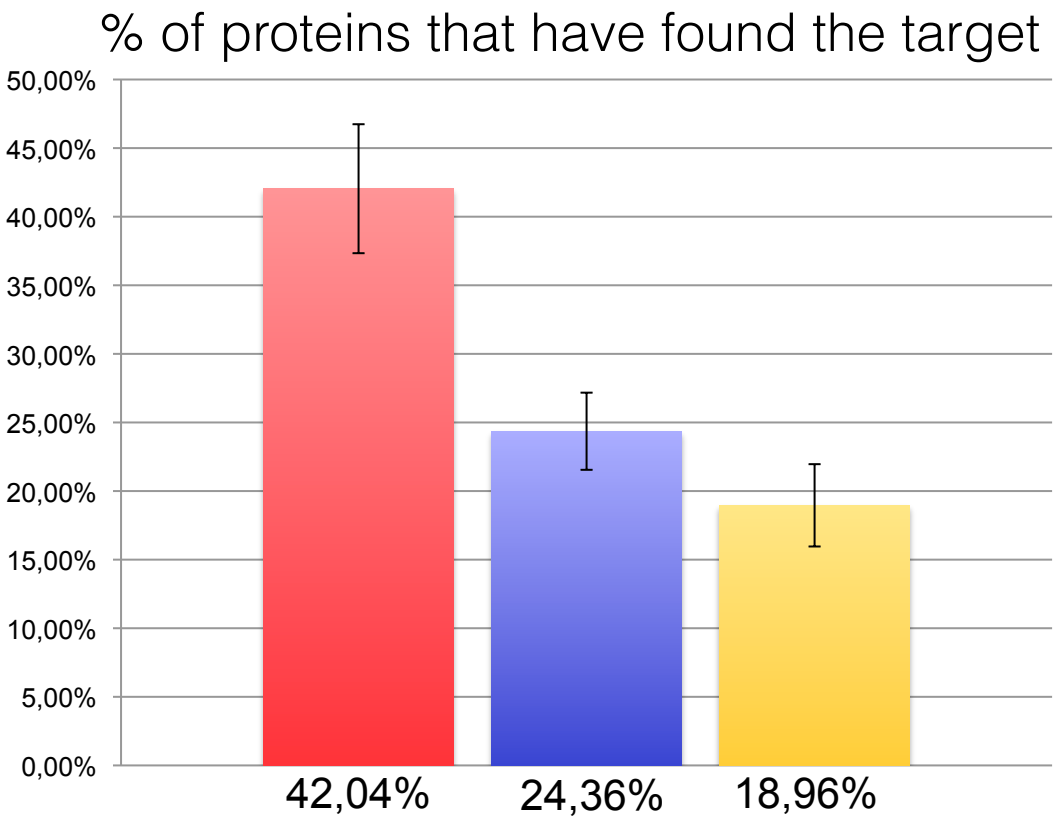


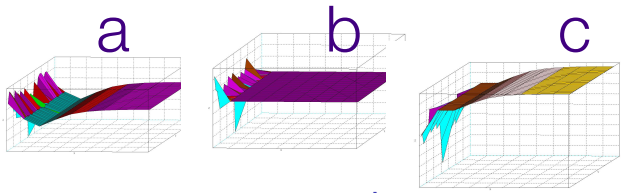
- 250 proteins
- 300 base pairs
- 8000 arbitrary units observation time

« facilitated sliding »: a proof of principle

very preliminary results:

increase the chances of finding the target within a fixed time





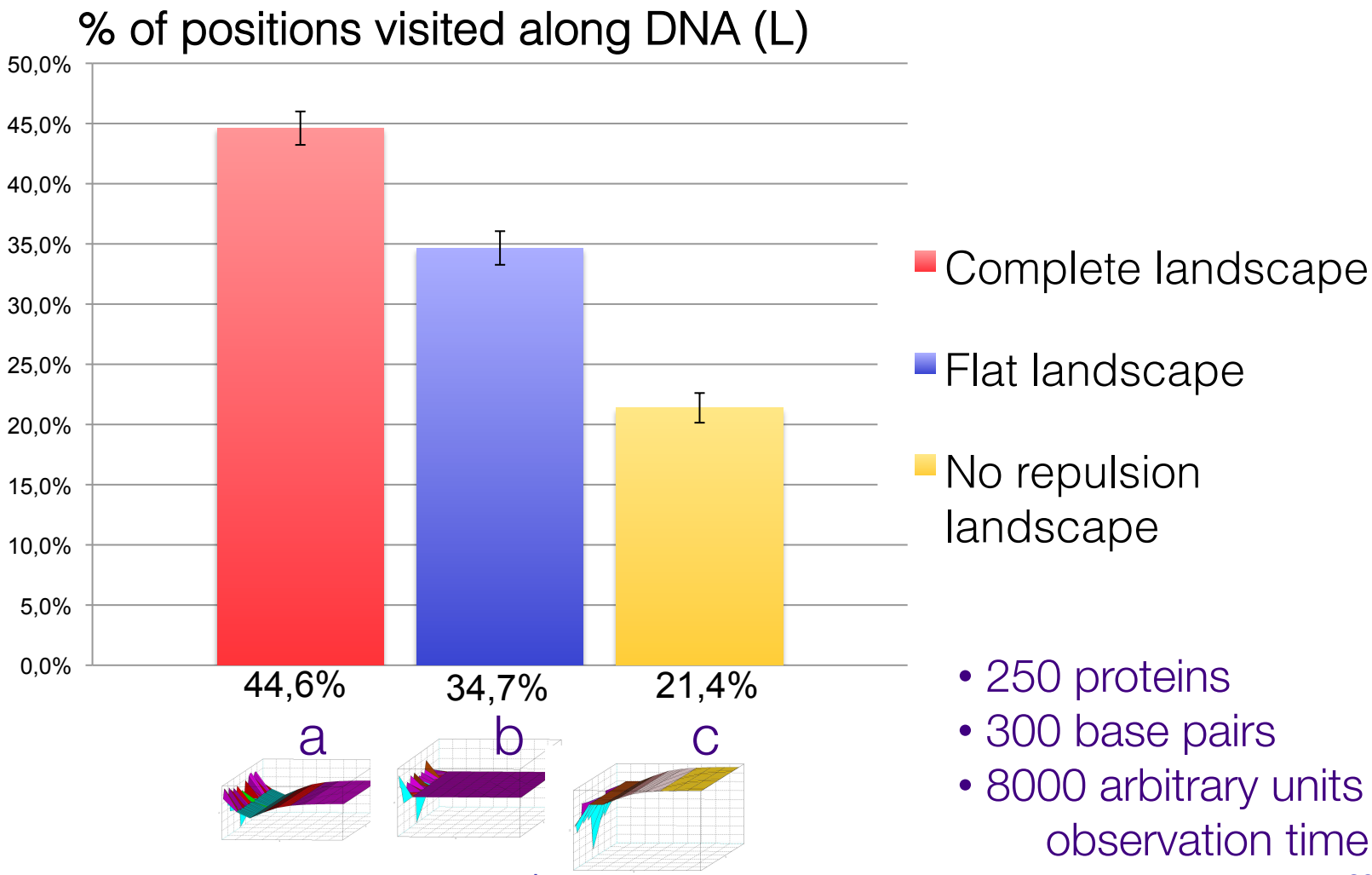
- Complete landscape
- Flat landscape
- No repulsion landscape

- 250 proteins
- 300 base pairs
- 8000 arbitrary units observation time

« facilitated sliding »: a proof of principle

very preliminary results:

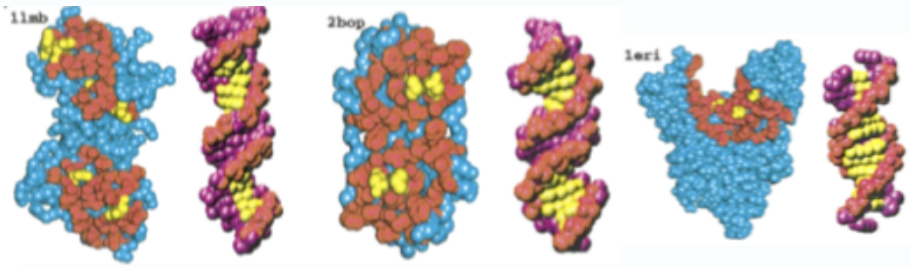
more DNA visited (regardless of distance L)



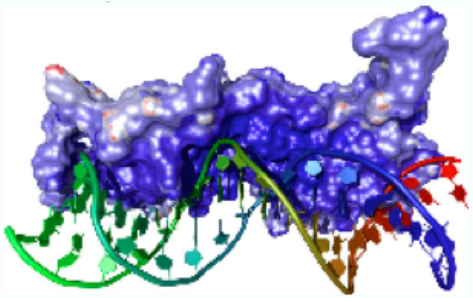
- 250 proteins
- 300 base pairs
- 8000 arbitrary units observation time

perspectives

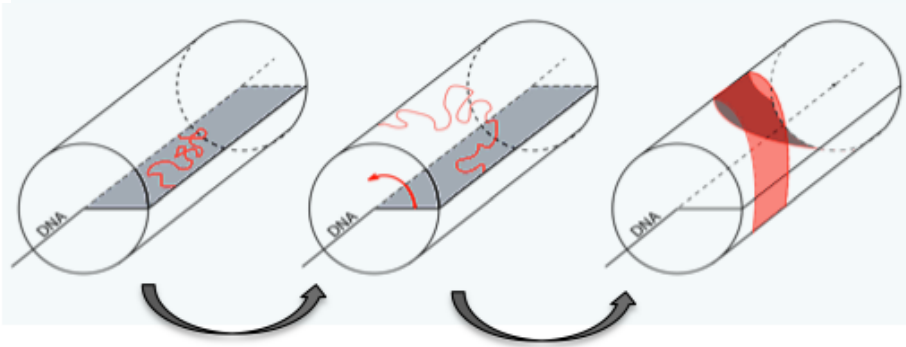
1. confirm these results with different parameters and/or different charges and shapes



2. compare to new structural data (different properties for different protein classes ?)



3. pass to a 3D model with helical path to obtain realistic quantitative results



4. compare to experimental data (association/dissociation constants, diffusion coeff…)

M3V group

modélisation multi-échelle de la matière vivante
multiscale modeling of living matter

Laboratoire de Physique Théorique de la Matière Condensée
Université Pierre et Marie Curie - Paris VI

Annick LESNE | Maria BARBI | Christophe LAVELLE
Julien MOZZICONACCI | Fabien PAILLUSSON | Hua WONG
Jean-Marc VICTOR | Pascal CARRIVAIN | Aleksandra NIVINA

Poisson-Boltzmann for oppositely charged bodies: an explicit derivation
Paillusson, Barbi, Victor, Molecular Physics, 107, 1419 (2009)

Non-specific DNA-protein interaction: Why proteins can diffuse along DNA
Dahirel, Paillusson, Jardat, Barbi, Victor, Phys. Rev. Lett, 102, 228101 (2009)

Effective interaction between charged nanoparticles and DNA
Paillusson, Dahirel, Jardat, Victor, Barbi, Phys. Chem. Chem. Phys. 13, 12603 (2011)