MiniTAGp Annecy, 15-16 septembre 2011

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

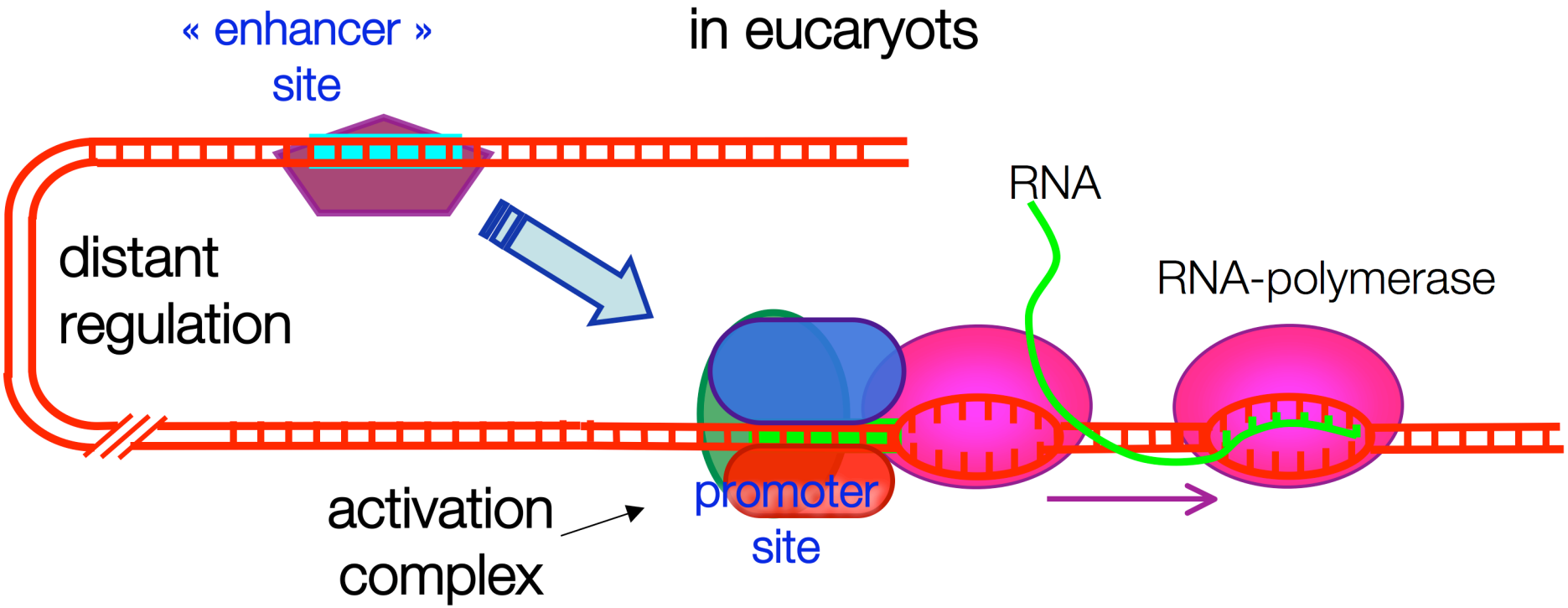
Fabien Paillusson, Maria Barbi, Jean-Marc Victor
LPTMC, UPMC - Paris VI

Marie Jardat, Vincent Dahirel
PECSA, UPMC - Paris VI

LPTMC

UPMC PARIS UNIVERSITAS

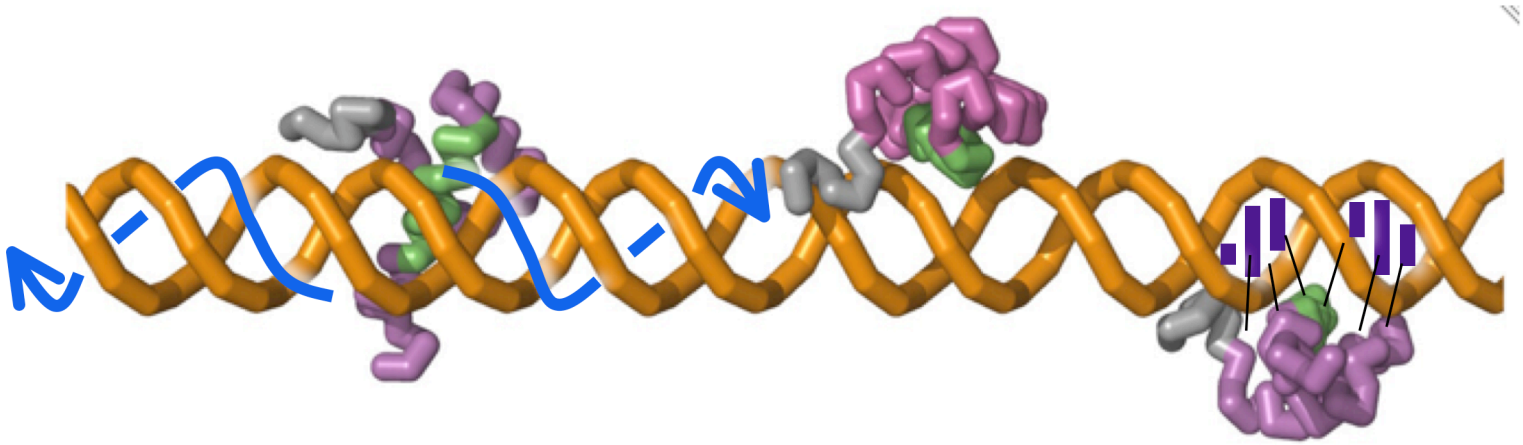
transcription



transcription initiation and regulation: search of target sequences

E. Coli: 5 10^6 pbs, 5000 genes
Human: 3 10^9 pbs, 2 10^6 genes

search of target sequences



1. displacement along DNA
   1D diffusion (sliding)
   + 3D jumps
   (= « facilitated diffusion »)

2. sequence reading
   interaction with bps

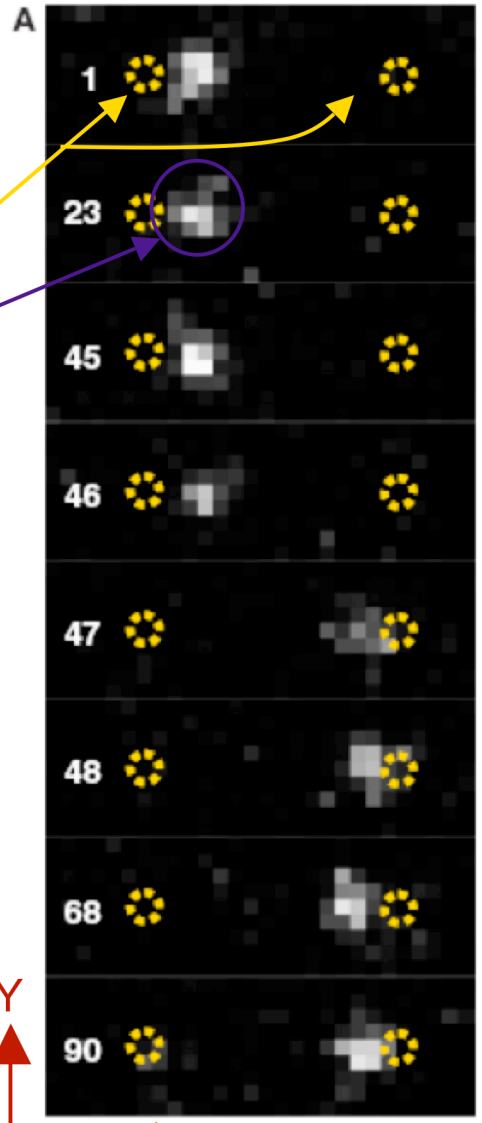
protein 1D diffusion (sliding)

experimental evidences (fluorescence microscopy)

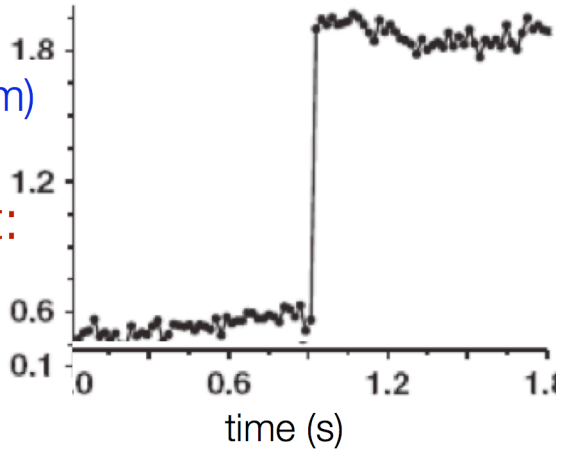
the protein diffusion « movie »:

DNA extremities

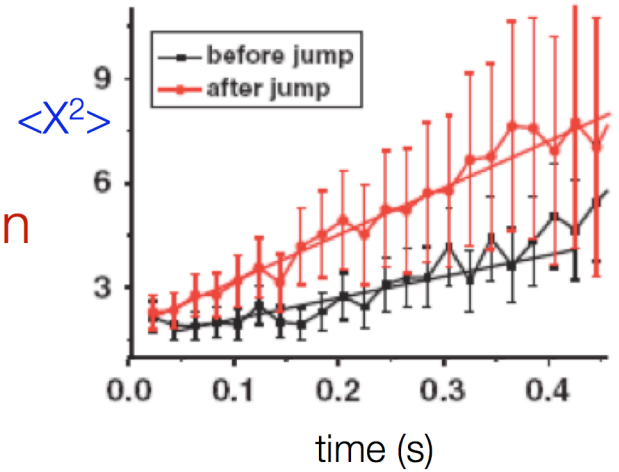
protein

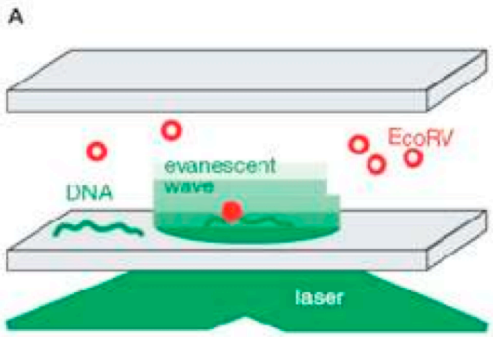


protein mouvement:



diffusion (MSD):



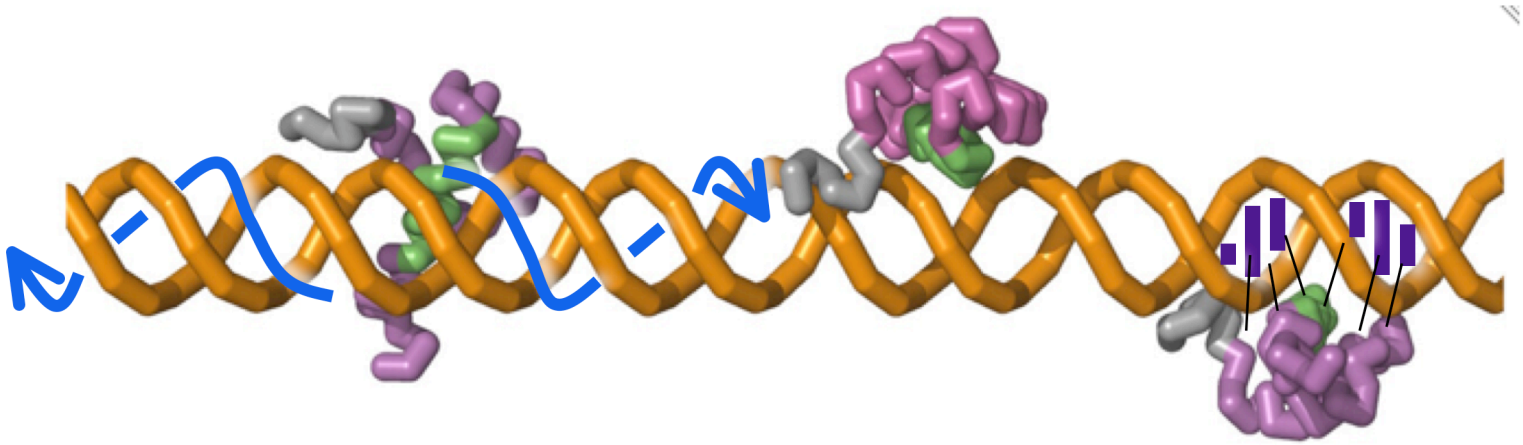


diffusion coefficient: $D_1 \sim 10^{-2}$ µm²/s

~(300 pb)²/s

Bonnet et al NAR 2008

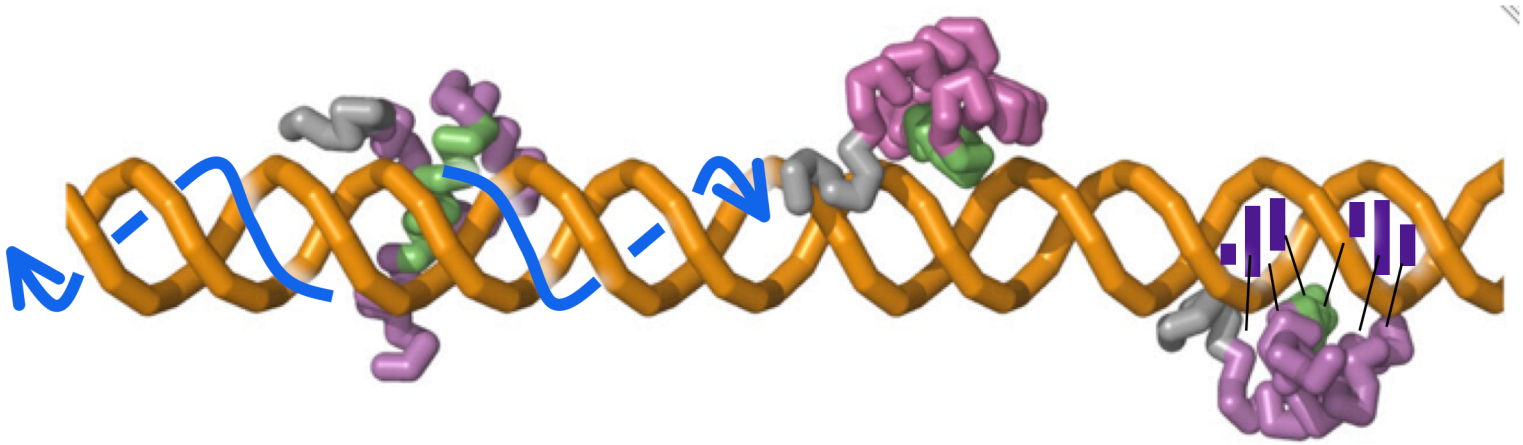
search of target sequences



1. displacement along DNA
1D diffusion (sliding)

2. sequence reading
interaction with bps

search of target sequences

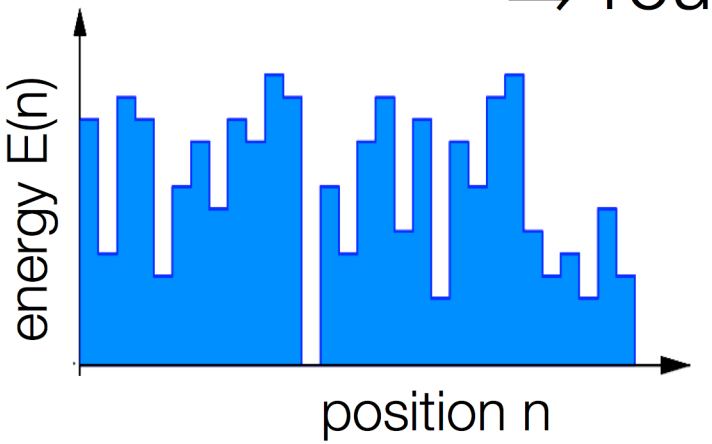


1. displacement along DNA
1D diffusion (sliding)

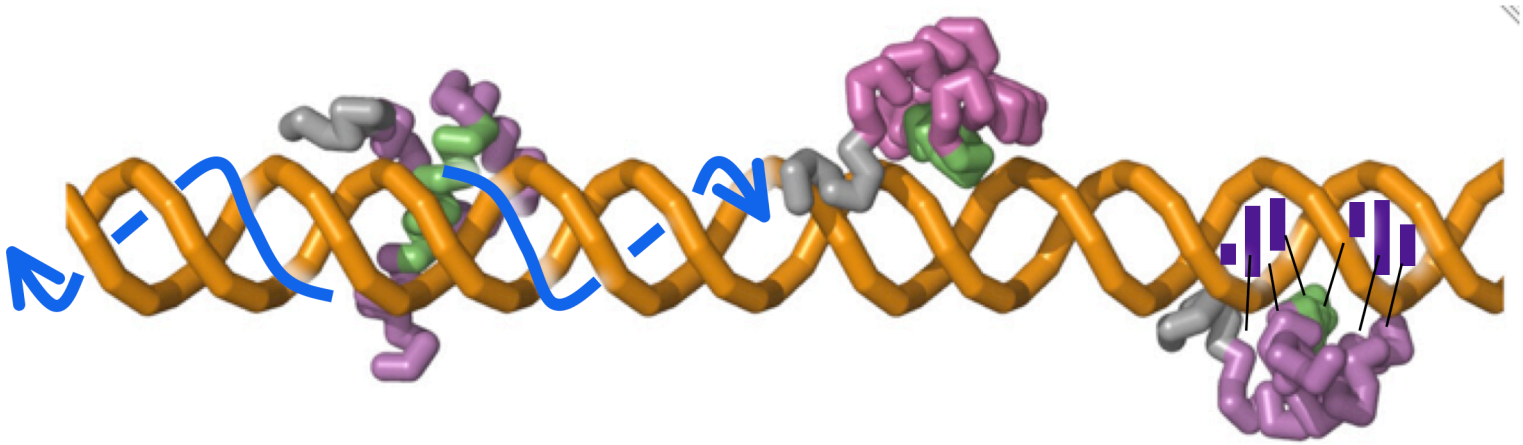
2. sequence reading
interaction with bps

recognition $\Rightarrow$ sequence dependent interaction

$\Rightarrow$ rough potential [J Biol Phys 04, PRE 04]



search of target sequences

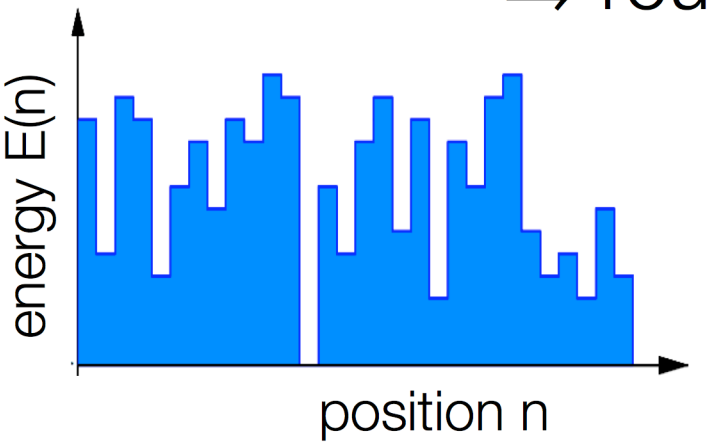


1. displacement along DNA
1D diffusion (sliding)

2. sequence reading
interaction with bps

recognition ⇒ sequence dependent interaction

⇒ rough potential [J Biol Phys 04, PRE 04]



↓

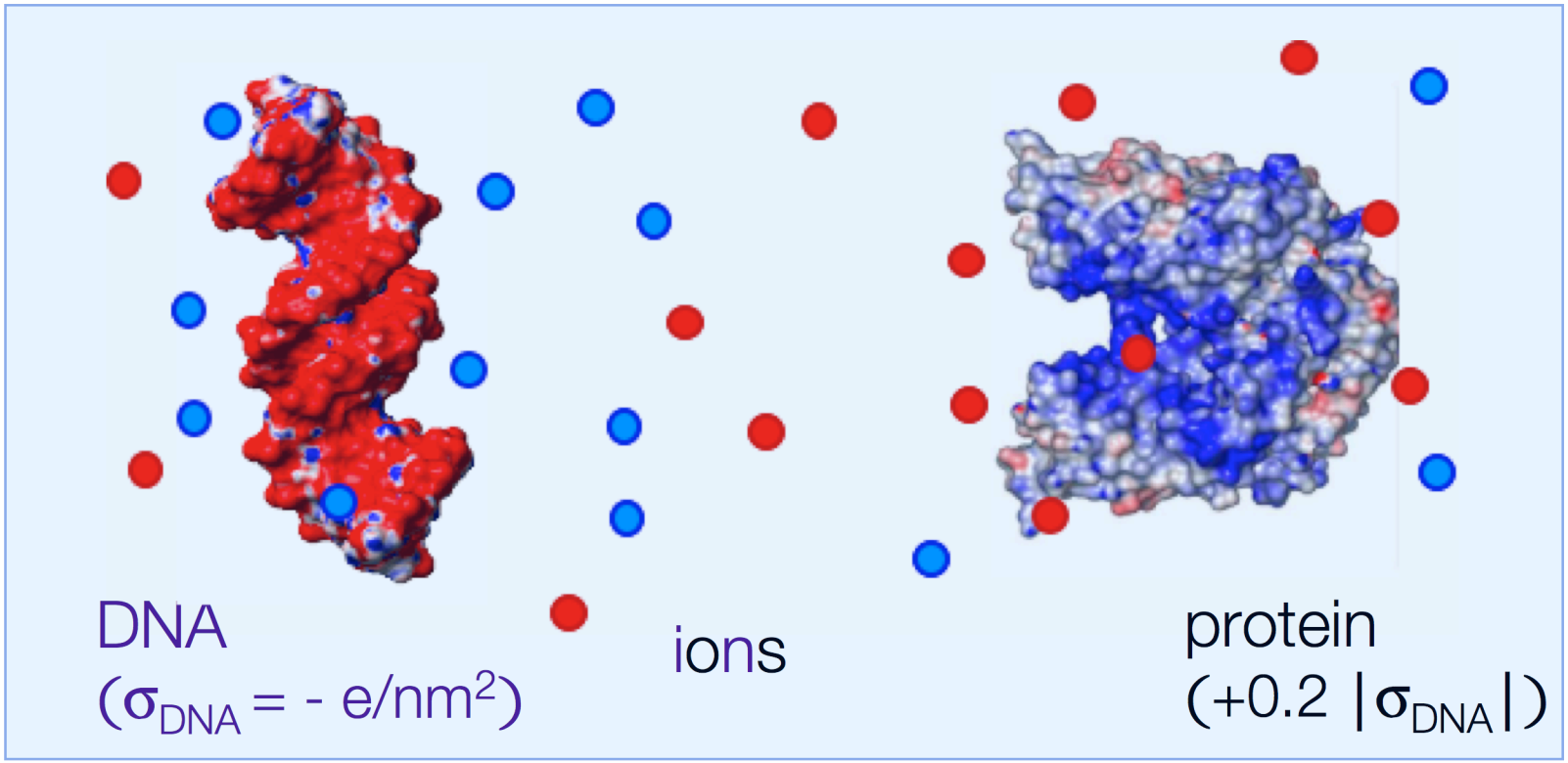
trapping, reduced mobility

→ mobility-specificity paradox

physics of the protein-DNA interaction

electrostatics in solution

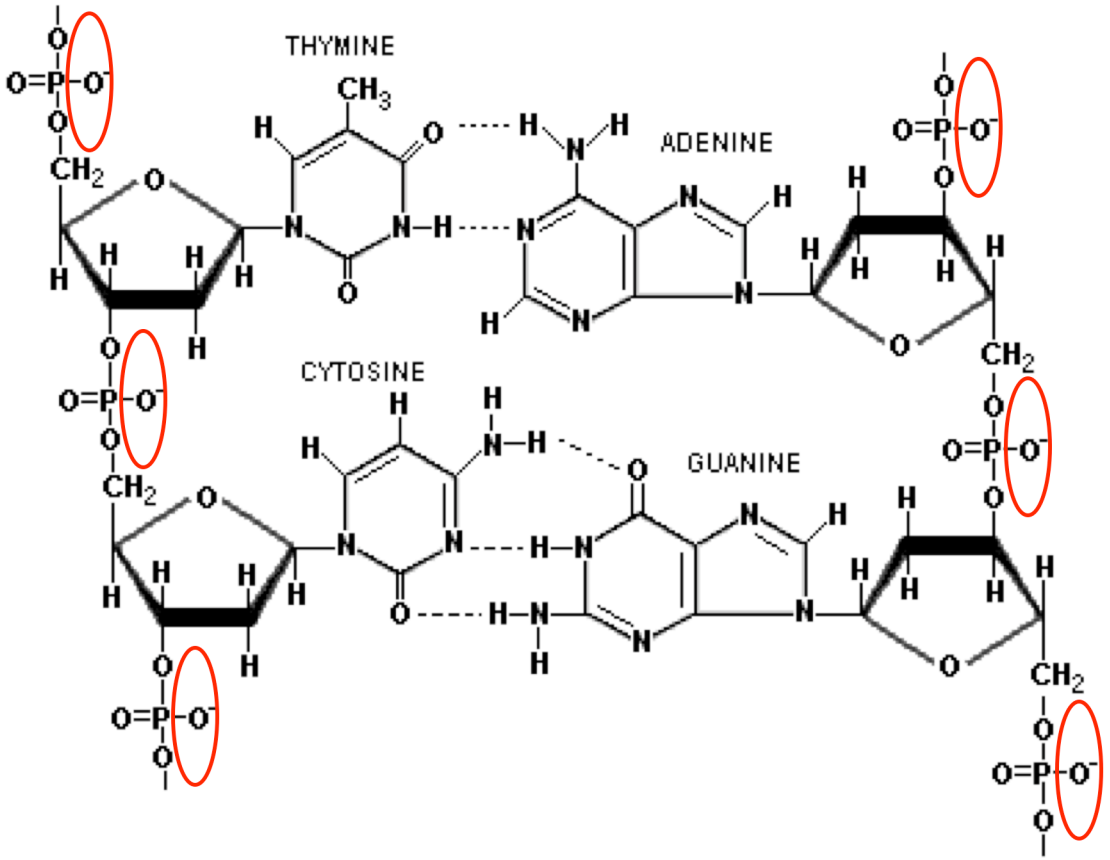
[Mol Phys 09, PRL 09, PCCP 11]



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

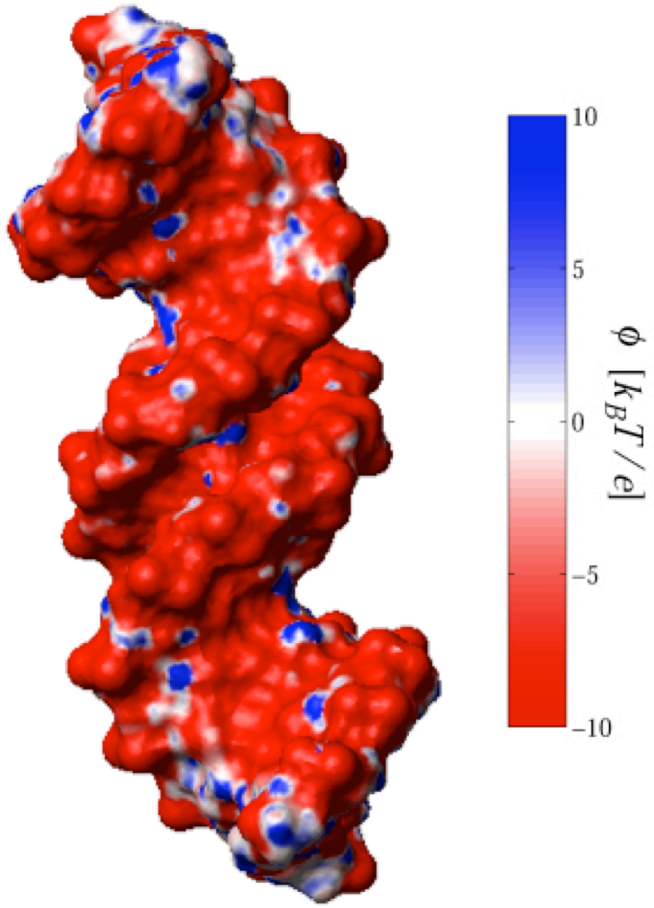
MC simulations: Marie Jardat et Vincent Dahirel PECSA-UPMC

DNA is a polyelectrolyte



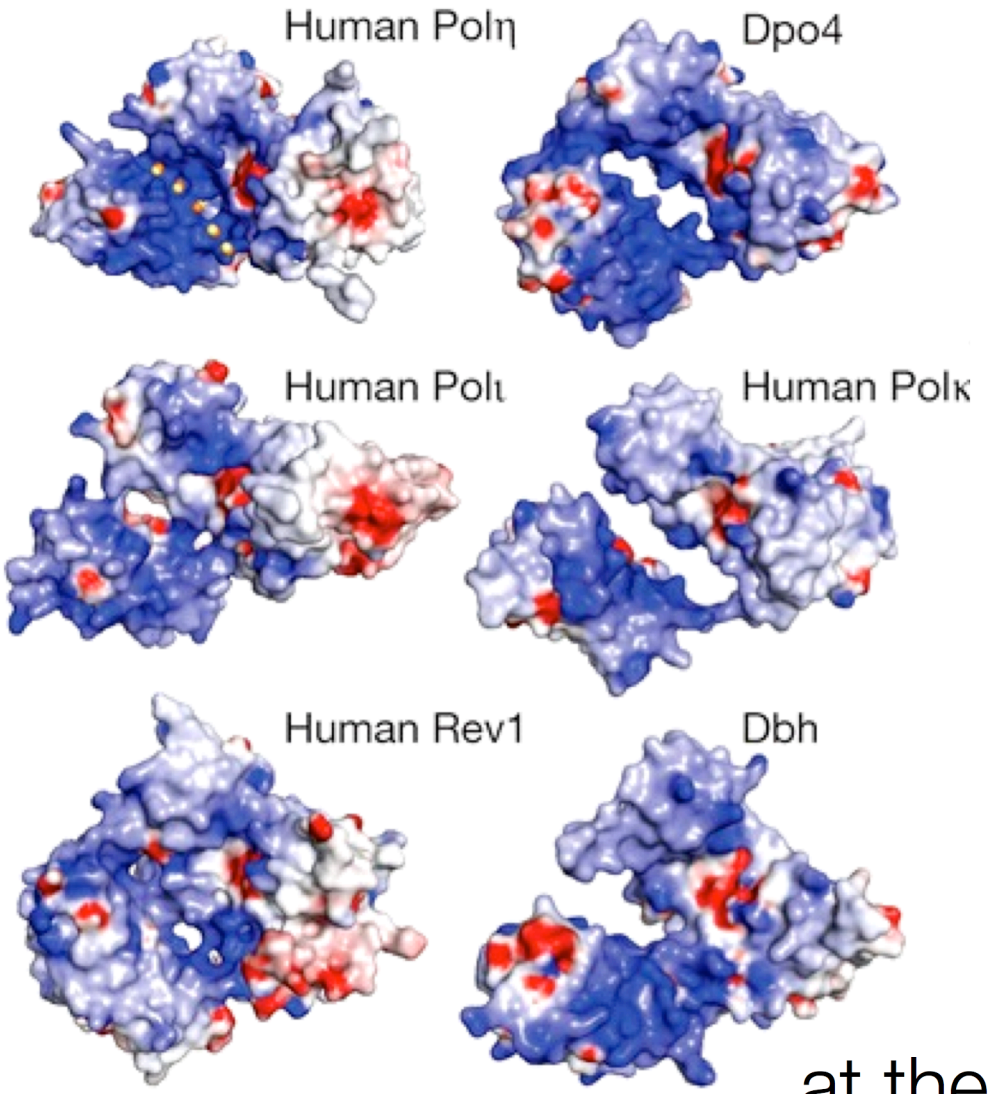
charge -2e/pb

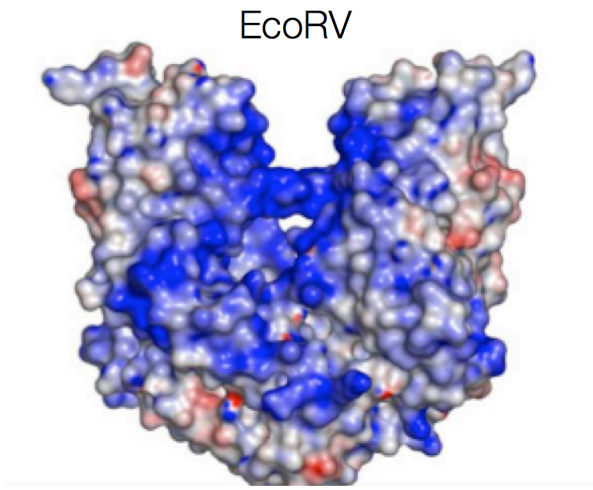
surface electrostatic potential

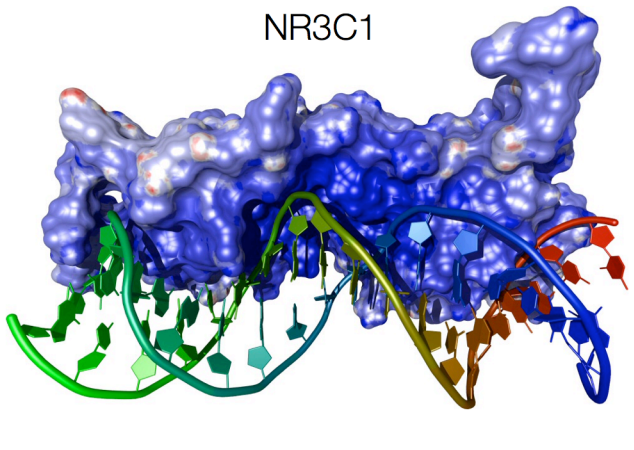


DNA-binding proteins

positively charged



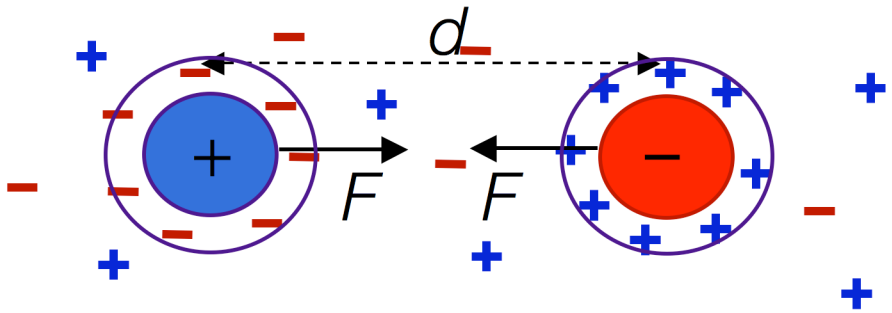




at the protein-DNA interface

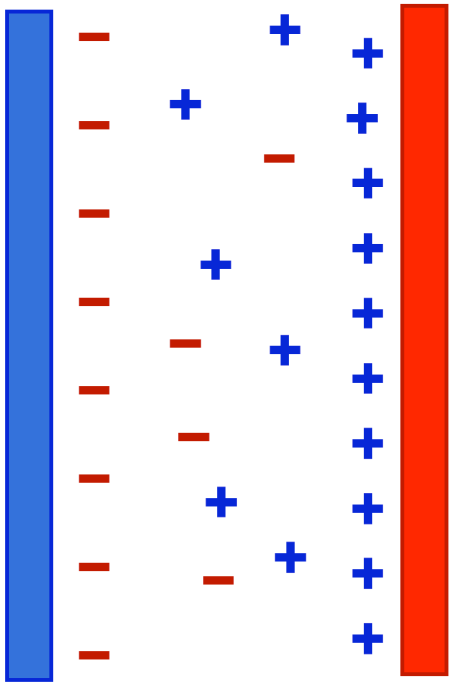
oppositely charged bodies in solution

2 charges in a solution: screened attraction (Debye)



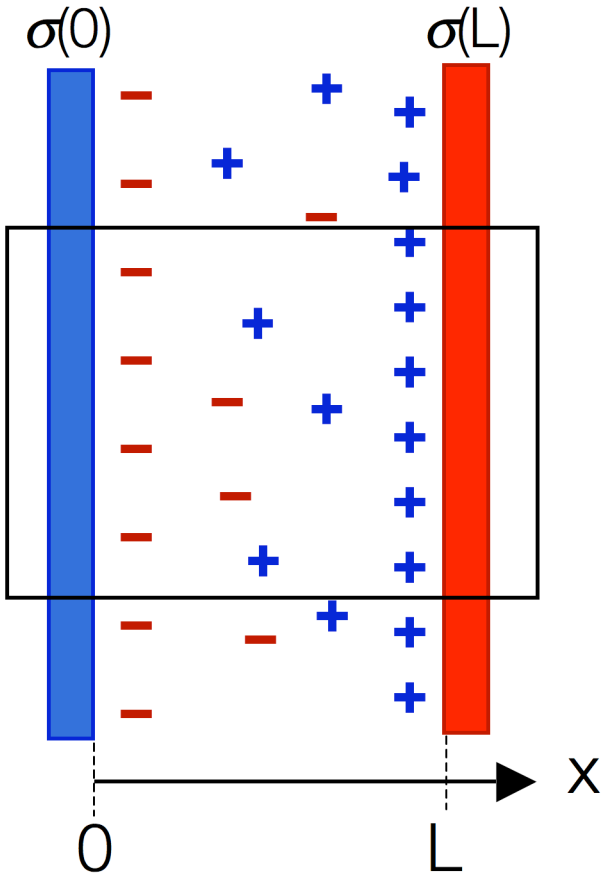
$$F = \frac{Q_1' Q_2'}{4\pi\varepsilon\, d^2}$$

…what about two facing surfaces ?



oppositely charged bodies in solution

Poisson-Boltzmann equation (1D) :



1. electrostatics potential $V(x)$:

   Poisson equation

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

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

with B.C.:

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

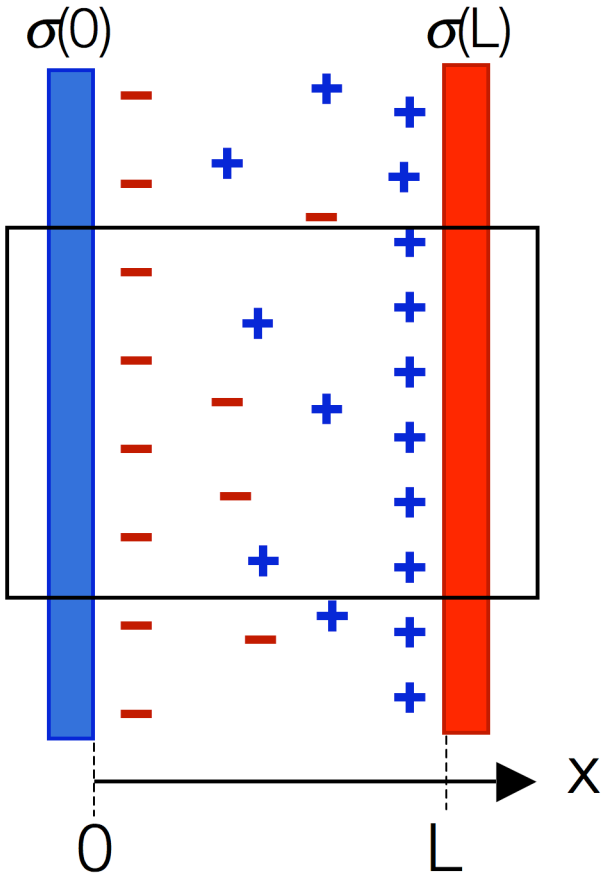
2. ions between plates:

   Boltzmann statistics

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

oppositely charged bodies in solution

Poisson-Boltzmann equation (1D) :



$\Rightarrow$ in monovalent salt (concentration c^0)

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

with B.C.:

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

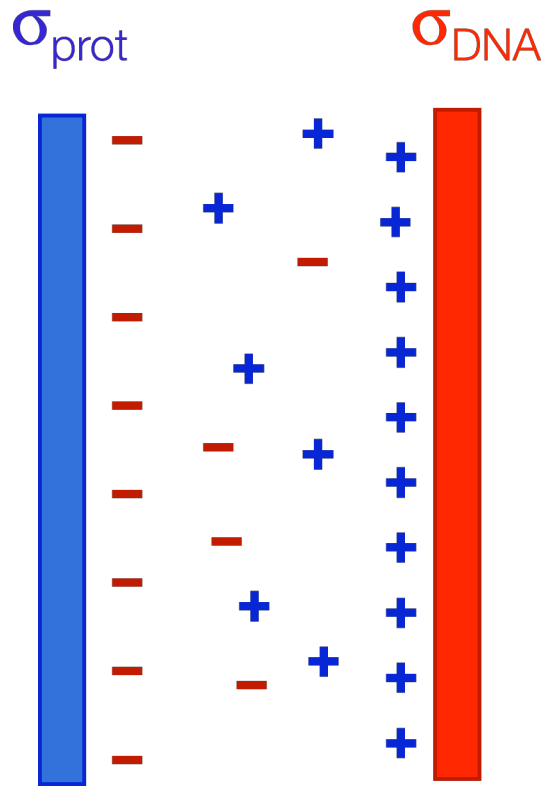
$\rightarrow$ numerical integration $\rightarrow$ pressure $\rightarrow$ interaction energy

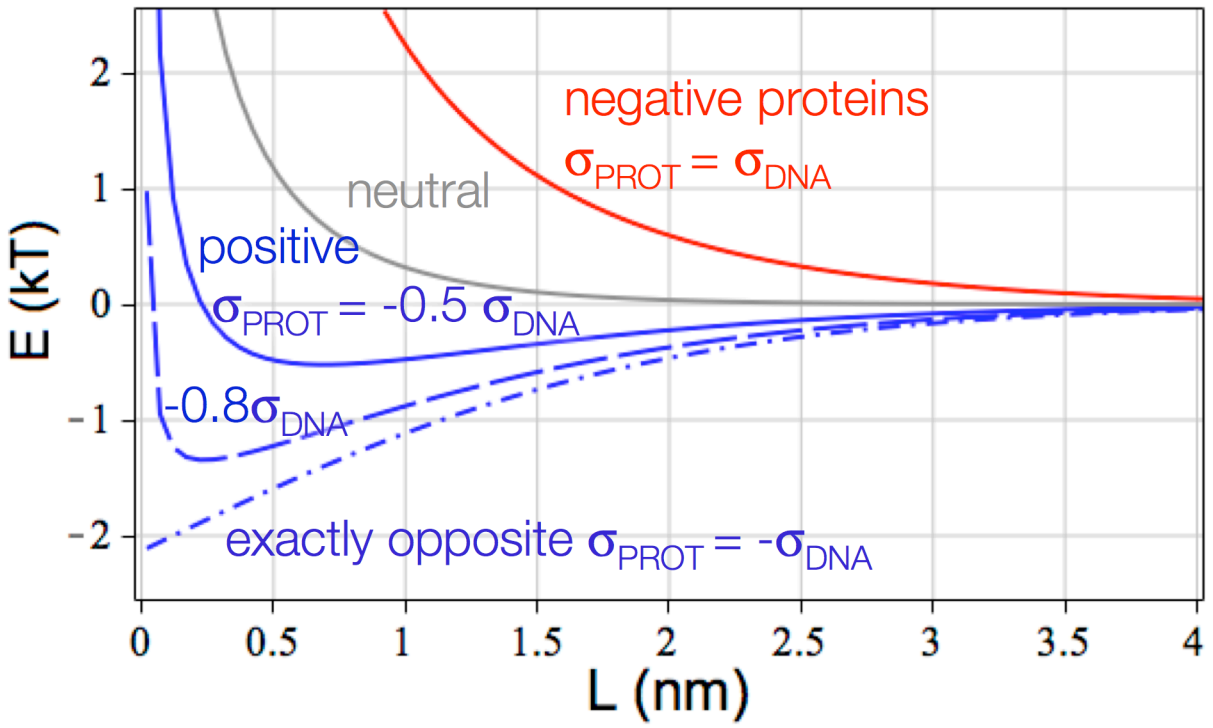
[Pailusson Mol Phys 09]

oppositely charged bodies in solution

Poisson-Boltzmann equation (1D) :

monovalent salt (+1/-1), numerical integration



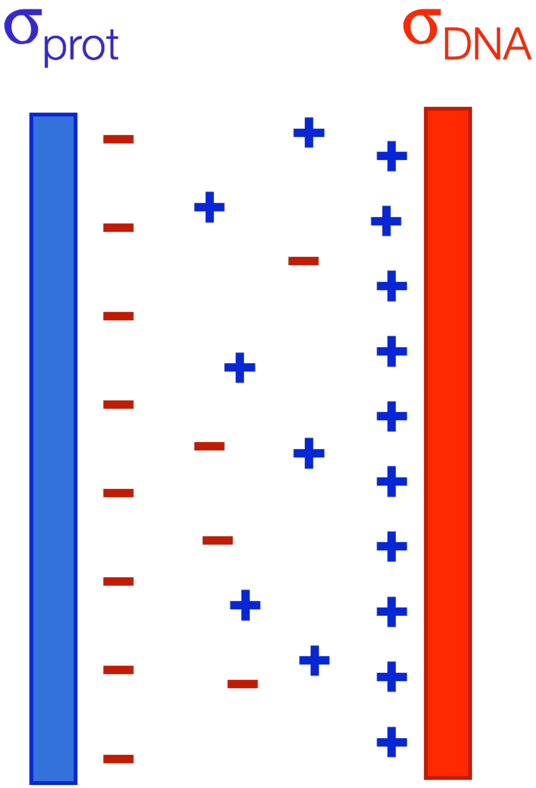


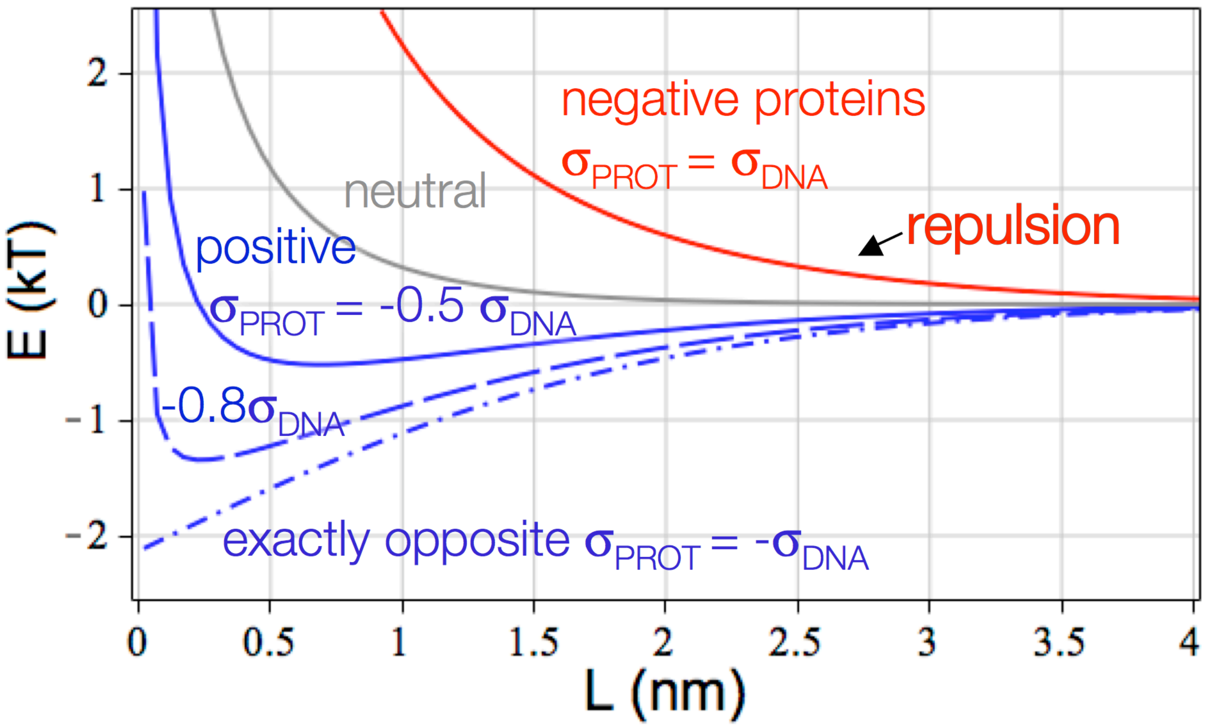
Antosiewicz et al. Mol. Phys. 2008

oppositely charged bodies in solution

Poisson-Boltzmann equation (1D) :

monovalent salt (+1/-1), numerical integration

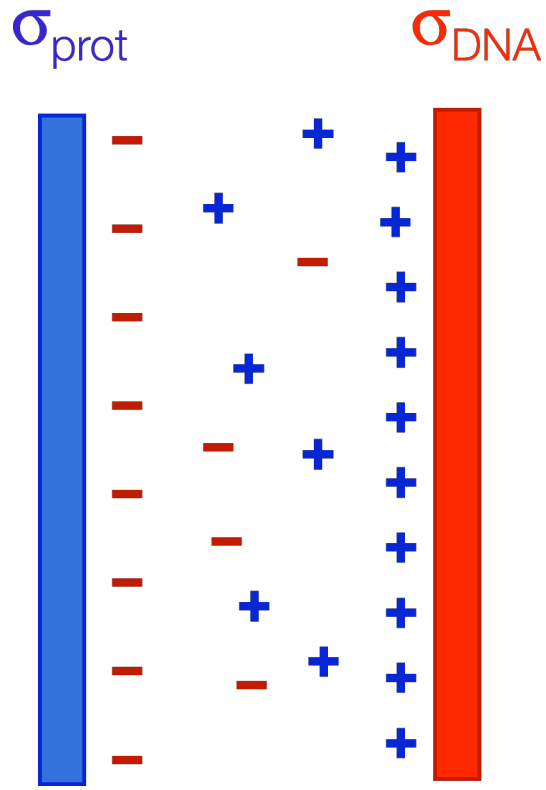


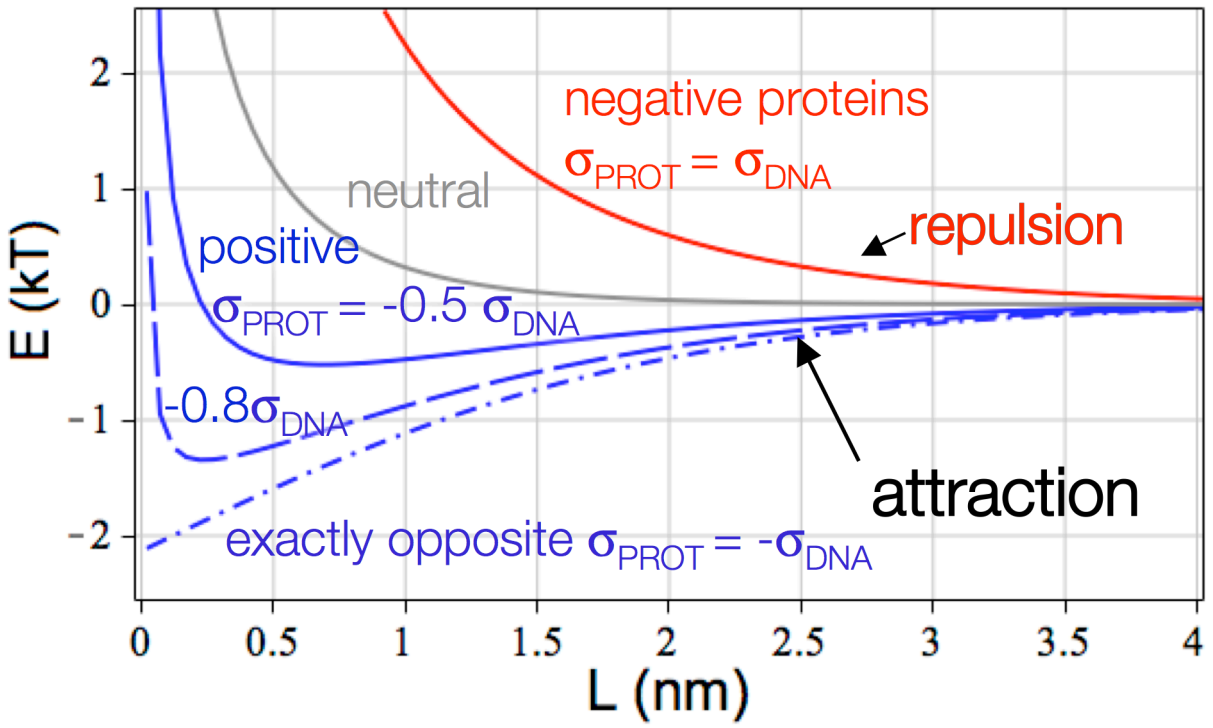


oppositely charged bodies in solution

Poisson-Boltzmann equation (1D) :

monovalent salt (+1/-1), numerical integration

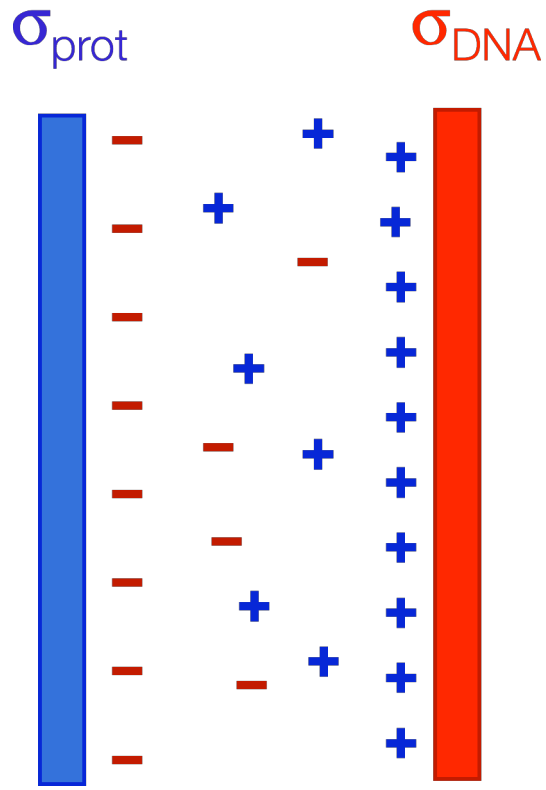


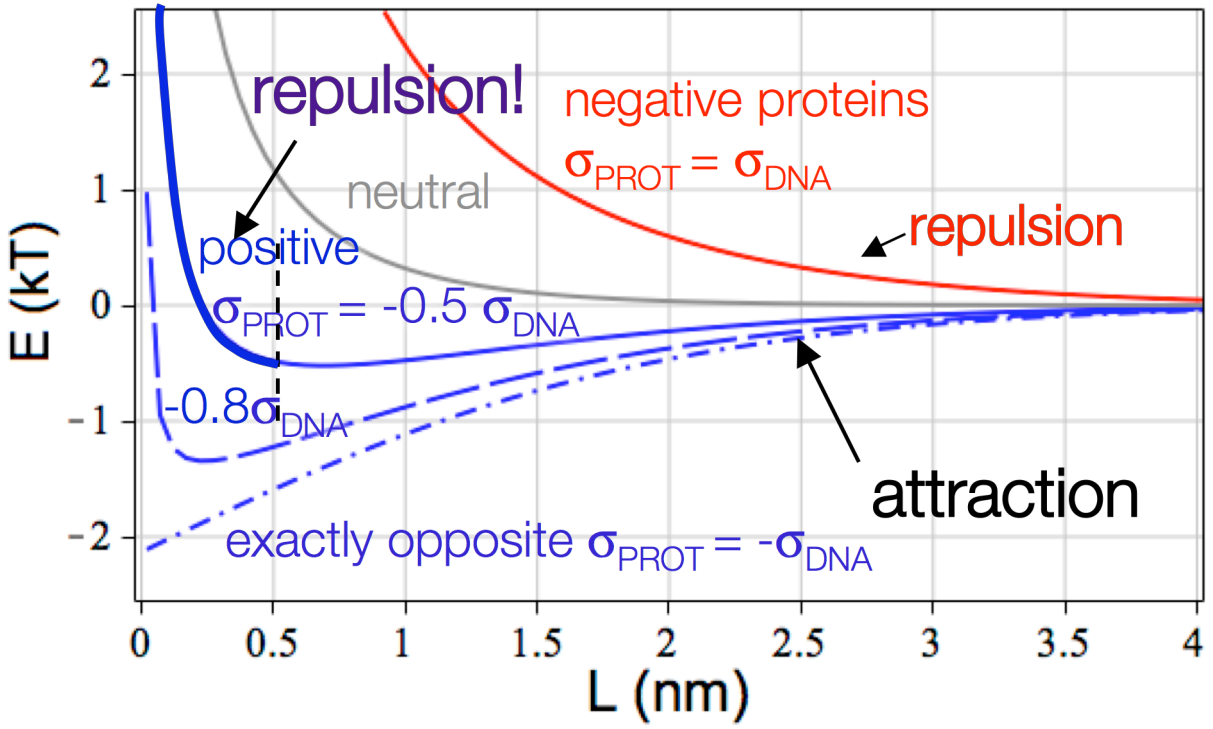


oppositely charged bodies in solution

Poisson-Boltzmann equation (1D) :

monovalent salt (+1/-1), numerical integration



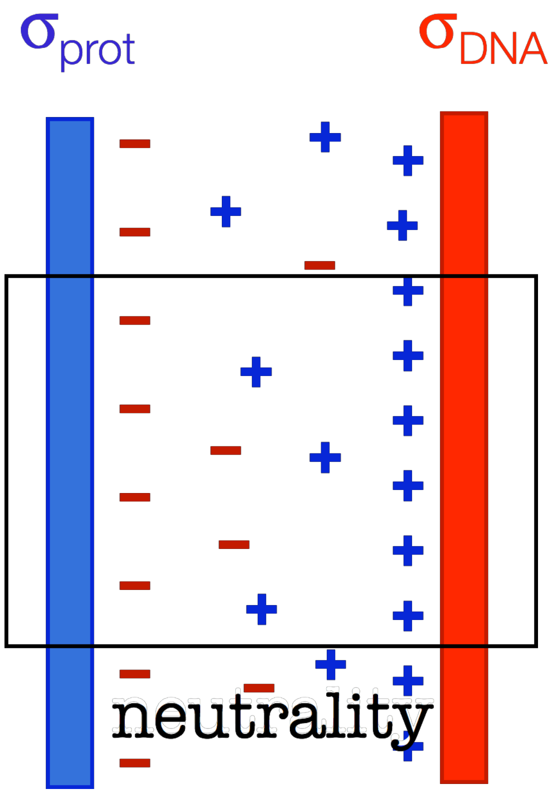


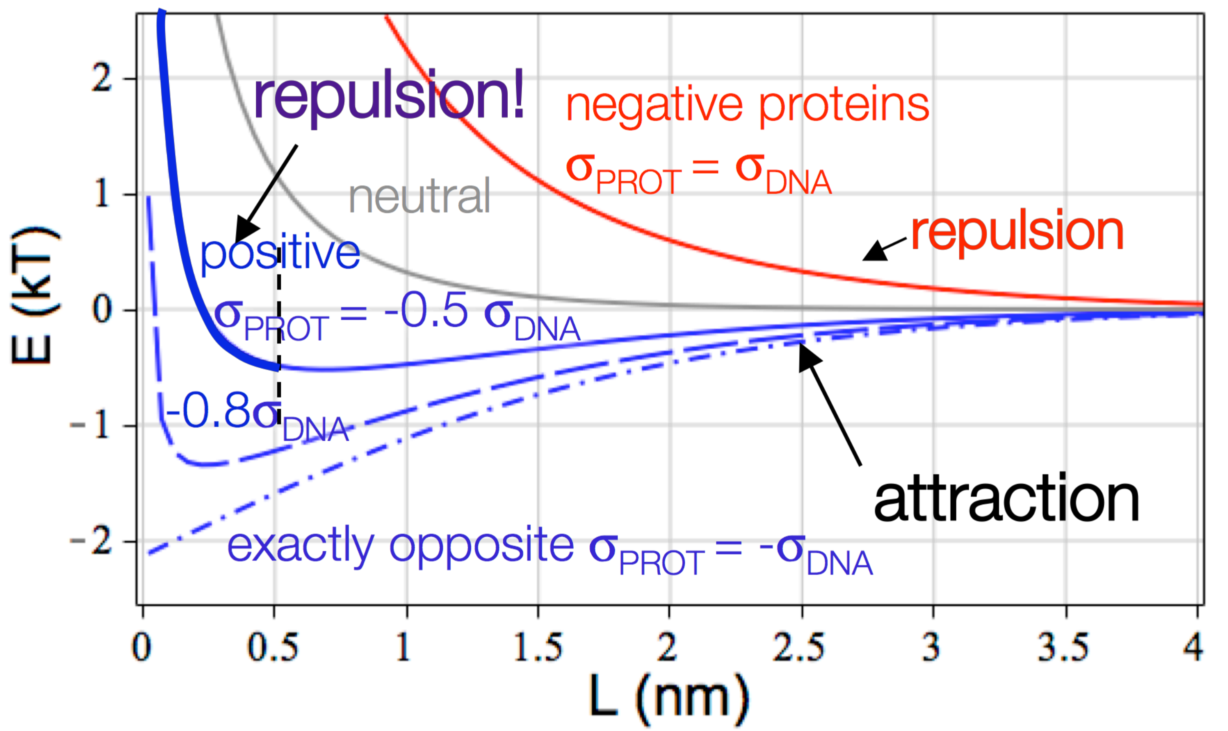
Antosiewicz et al. Mol. Phys. 2006

oppositely charged bodies in solution

Poisson-Boltzmann equation (1D) :

monovalent salt (+1/-1), numerical integration

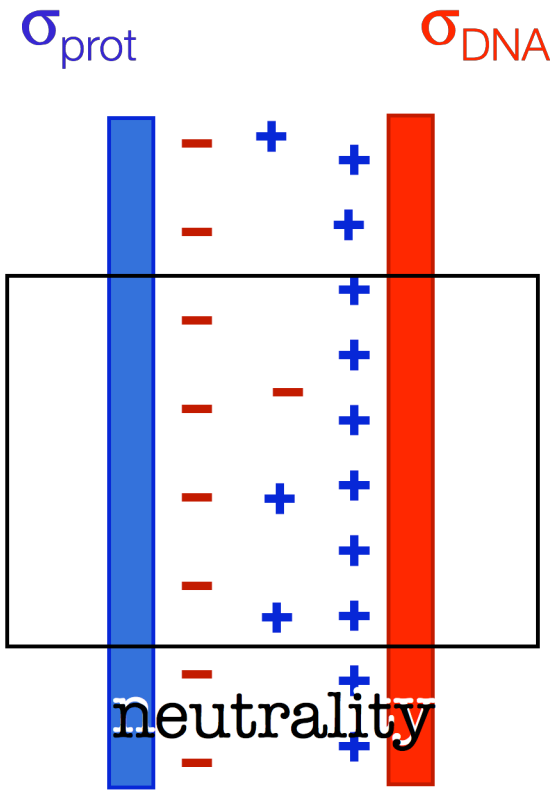


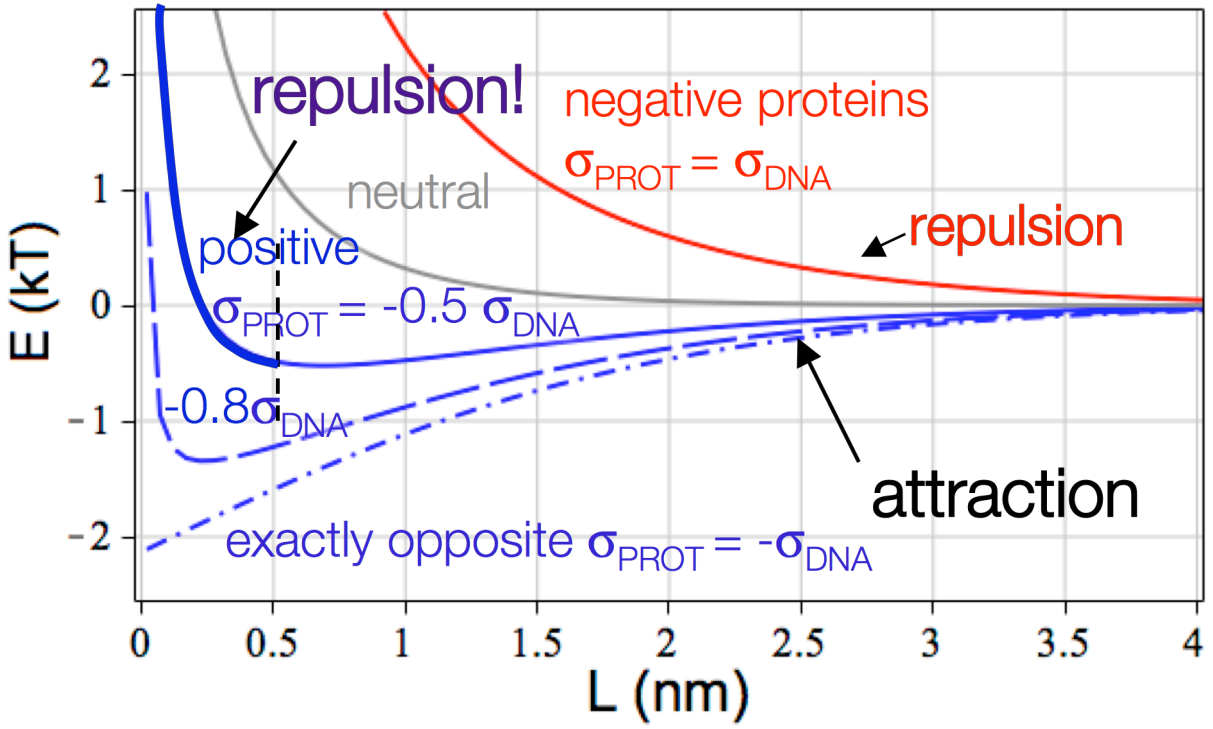


oppositely charged bodies in solution

Poisson-Boltzmann equation (1D) :

monovalent salt (+1/-1), numerical integration

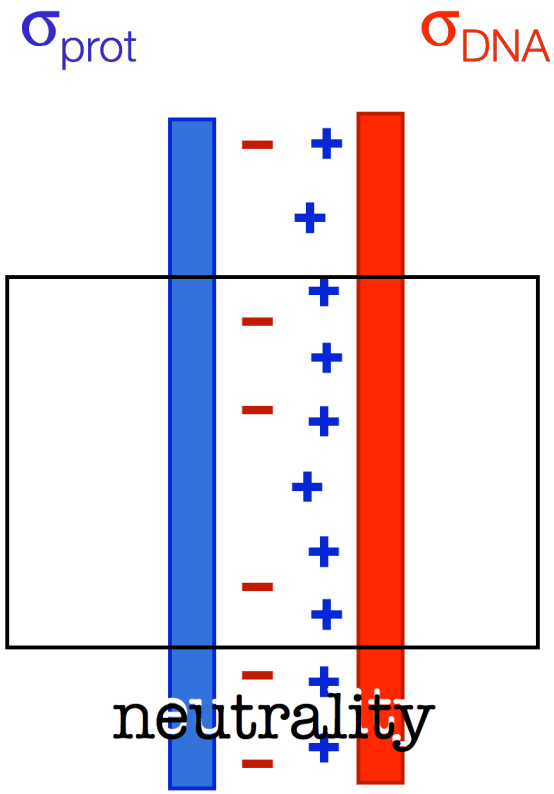


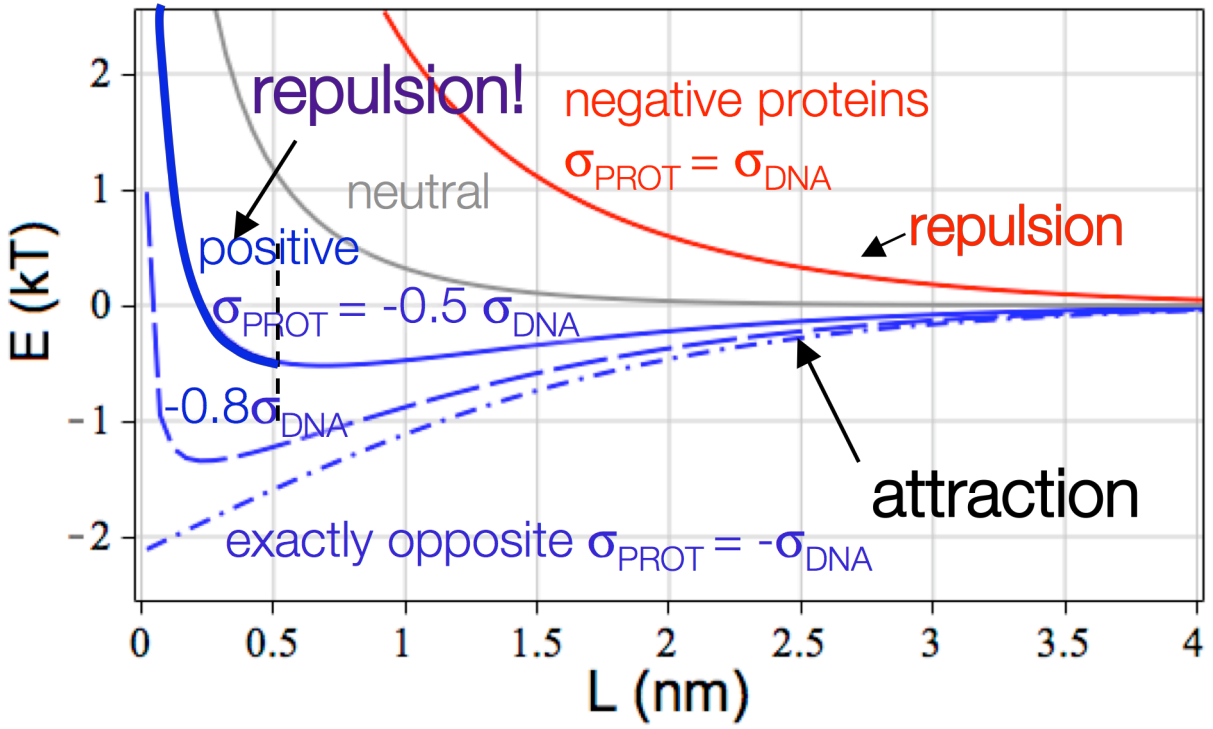


oppositely charged bodies in solution

Poisson-Boltzmann equation (1D) :

monovalent salt (+1/-1), numerical integration

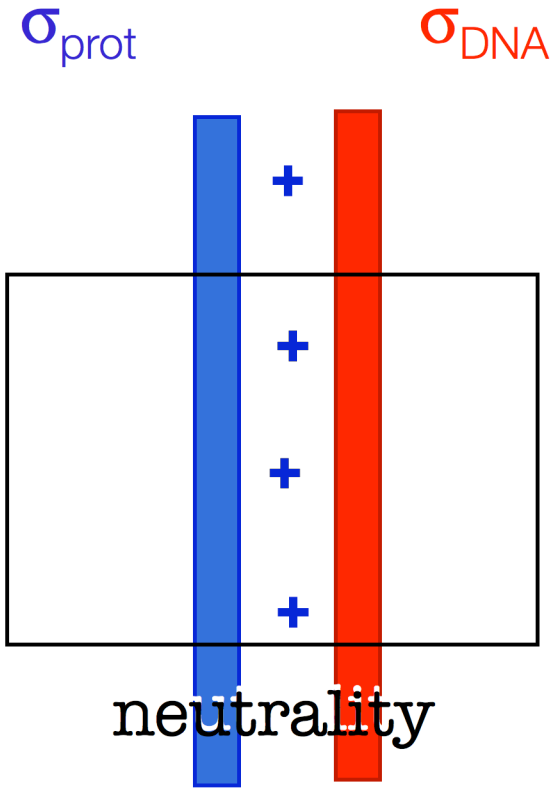


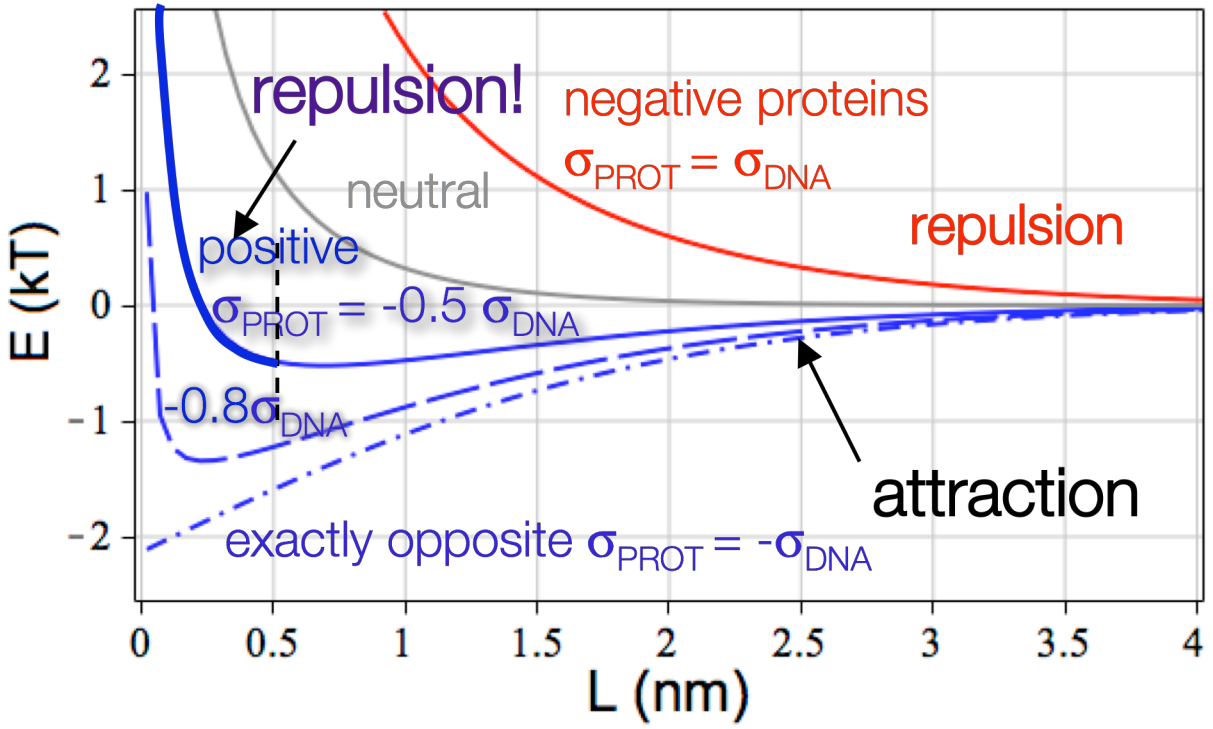


oppositely charged bodies in solution

Poisson-Boltzmann equation (1D) :

monovalent salt (+1/-1), numerical integration

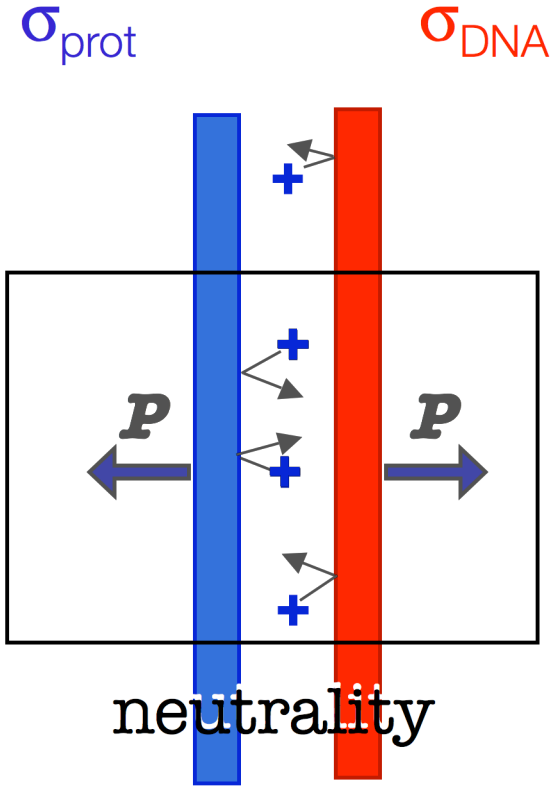


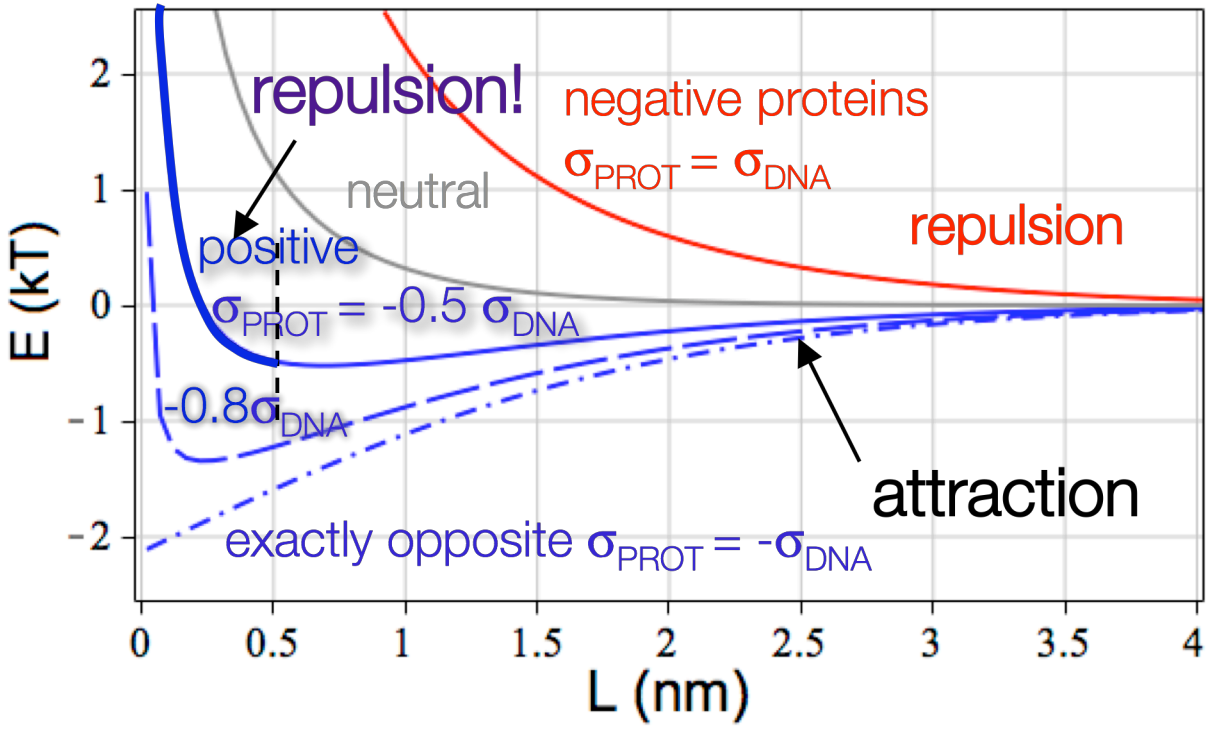


oppositely charged bodies in solution

Poisson-Boltzmann equation (1D) :

monovalent salt (+1/-1), numerical integration

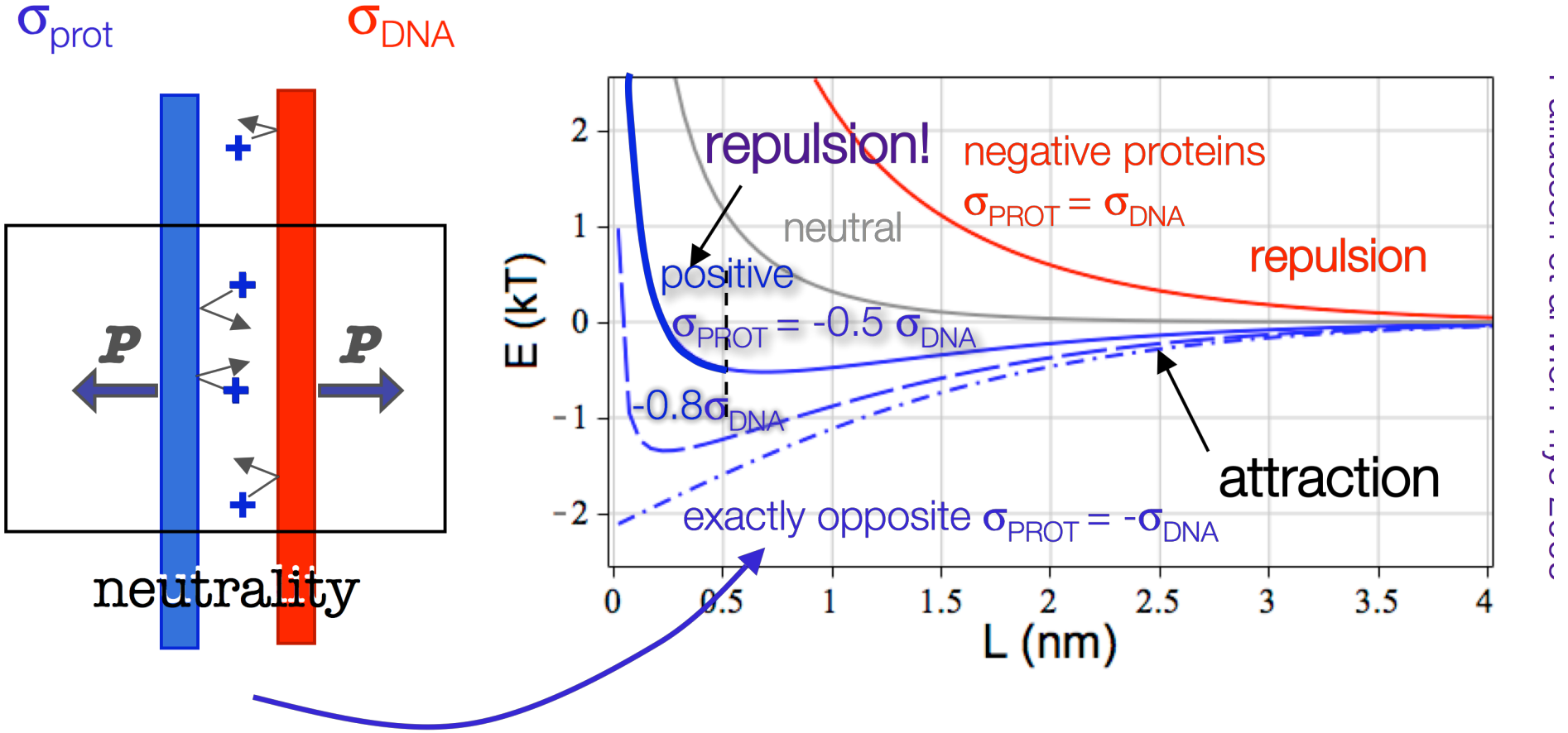




oppositely charged bodies in solution

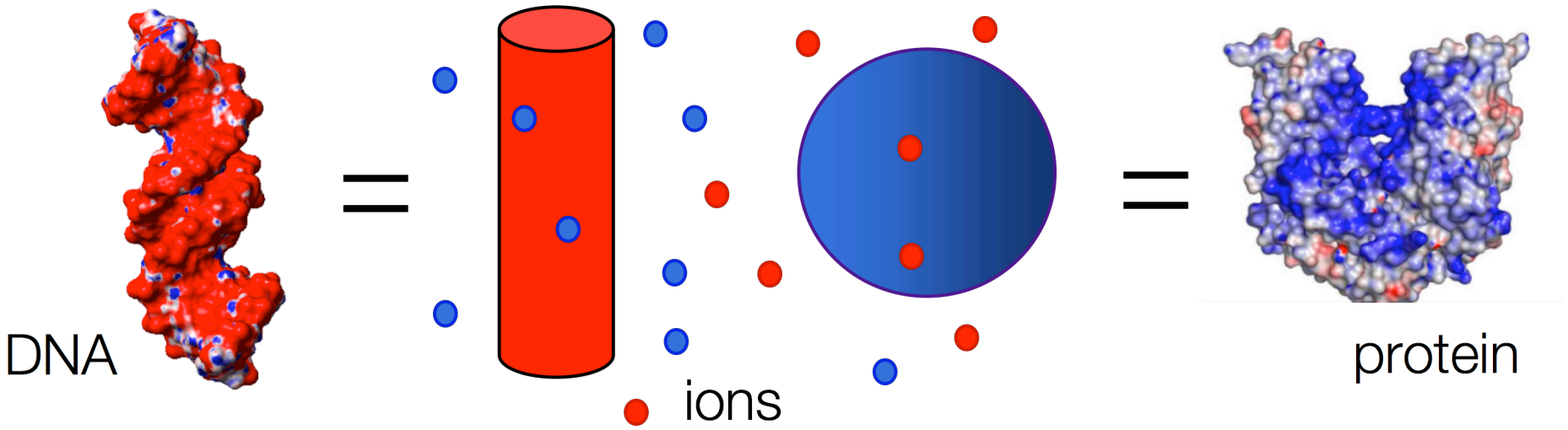
Poisson-Boltzmann equation (1D) :

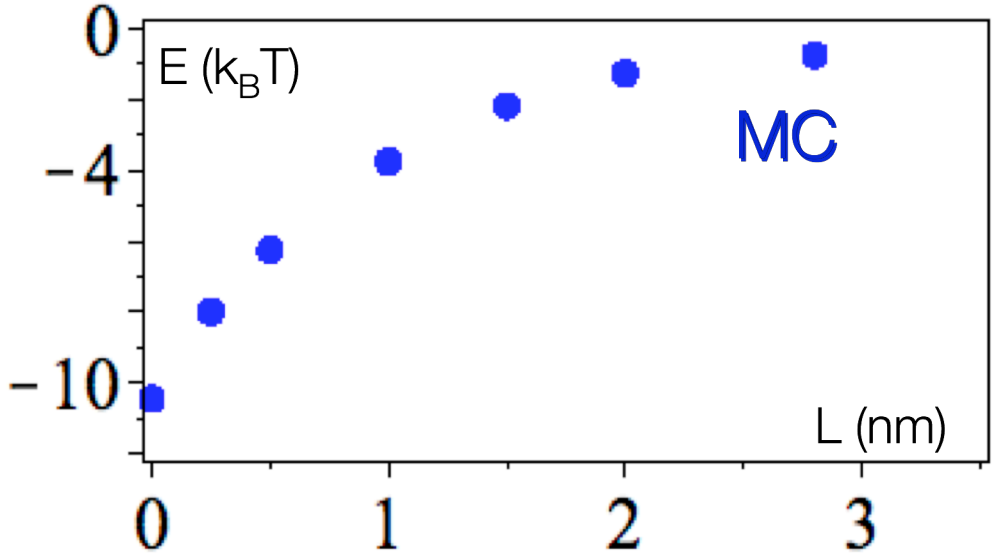
monovalent salt (+1/-1), numerical integration



what about the DNA-protein system?

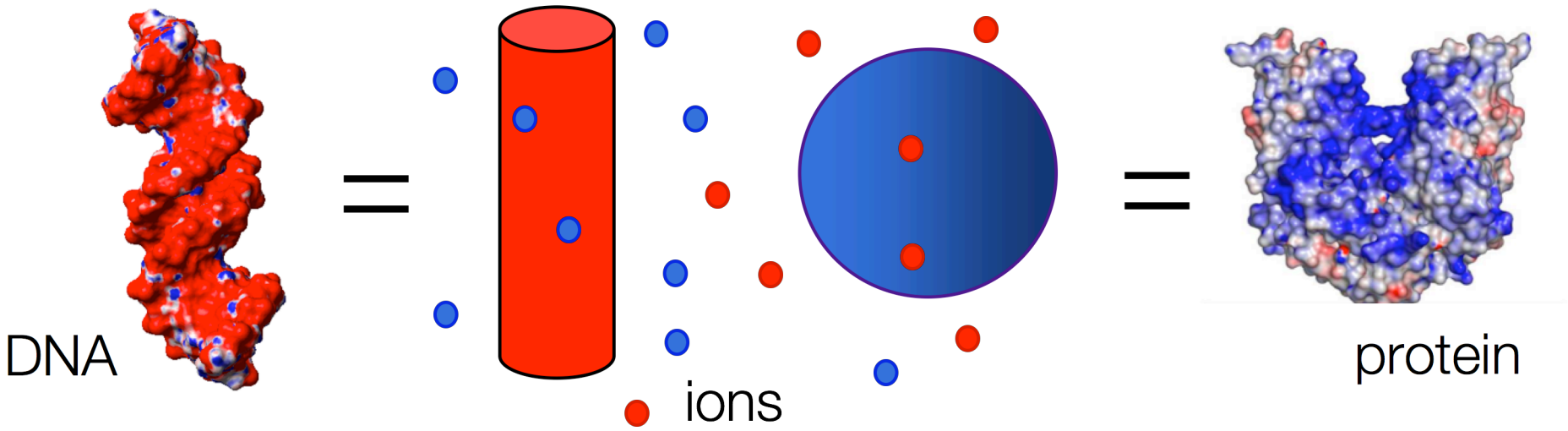
Monte Carlo simulations

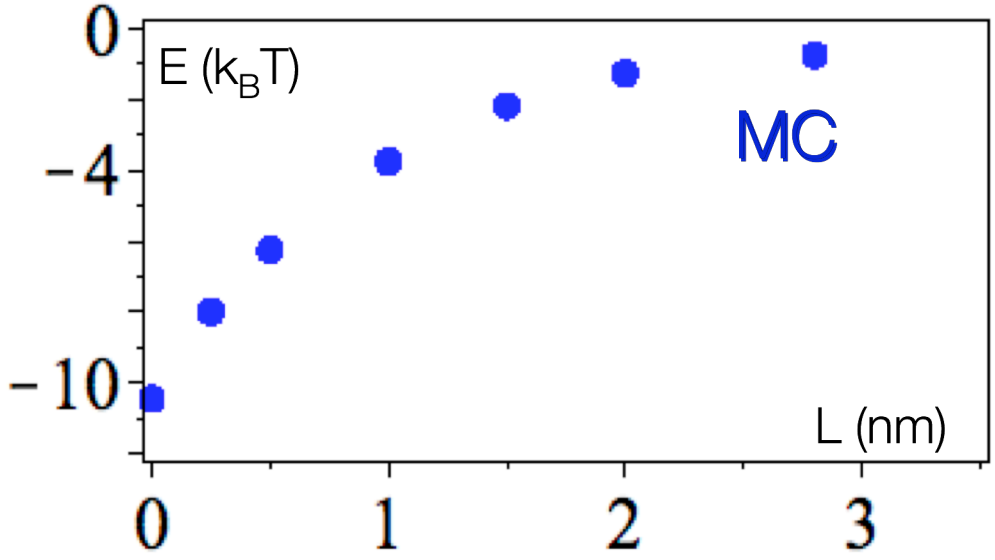




what about the DNA-protein system?

Monte Carlo simulations

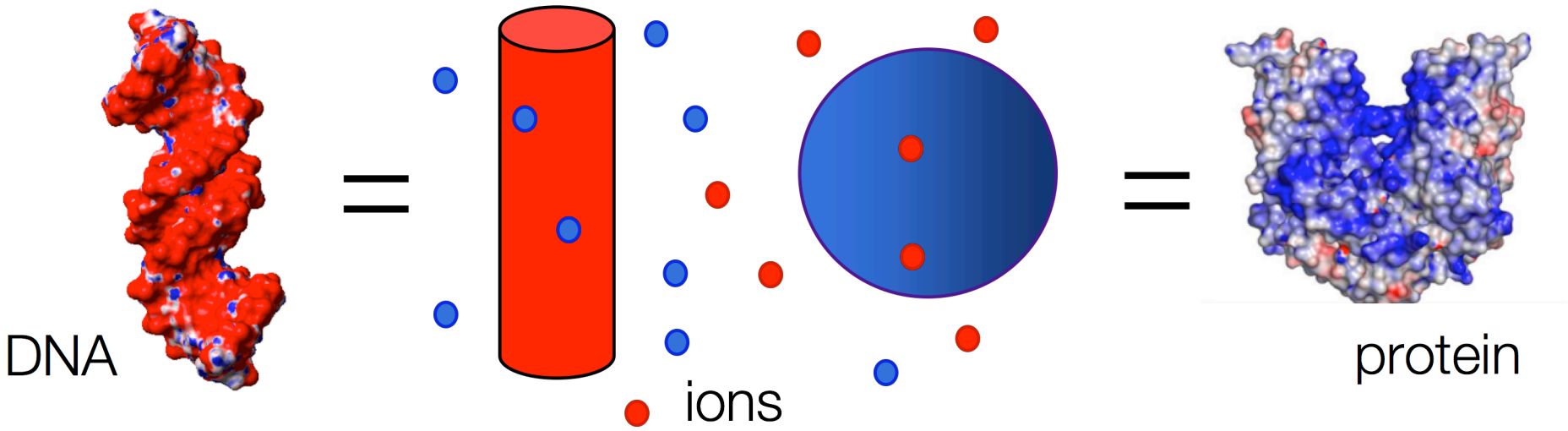


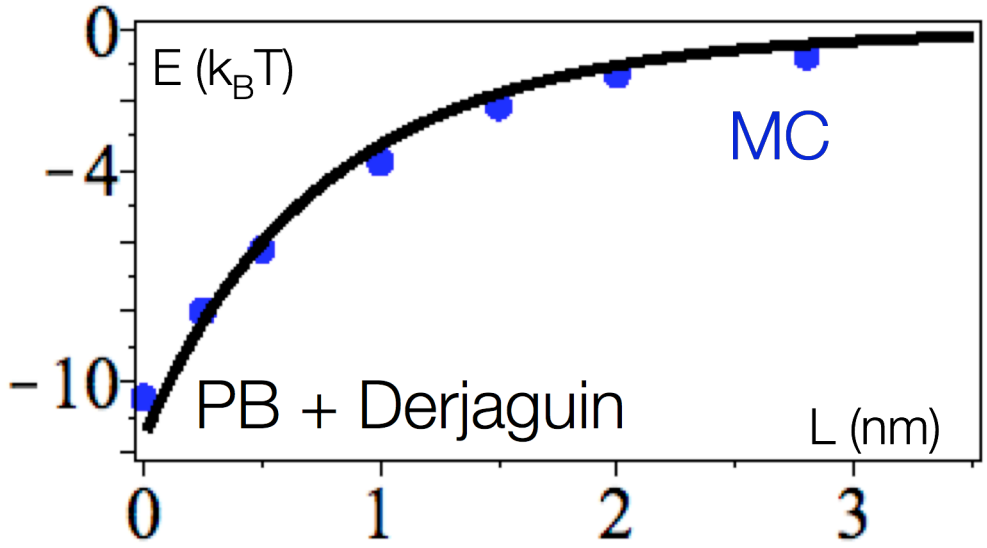


always attractive !

what about the DNA-protein system?

Monte Carlo simulations

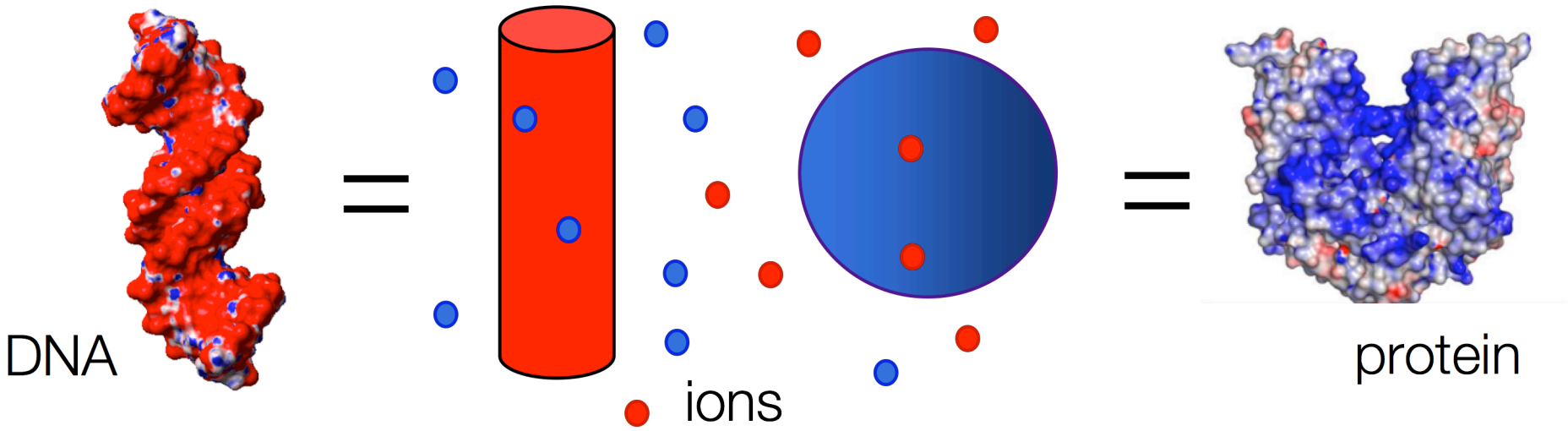


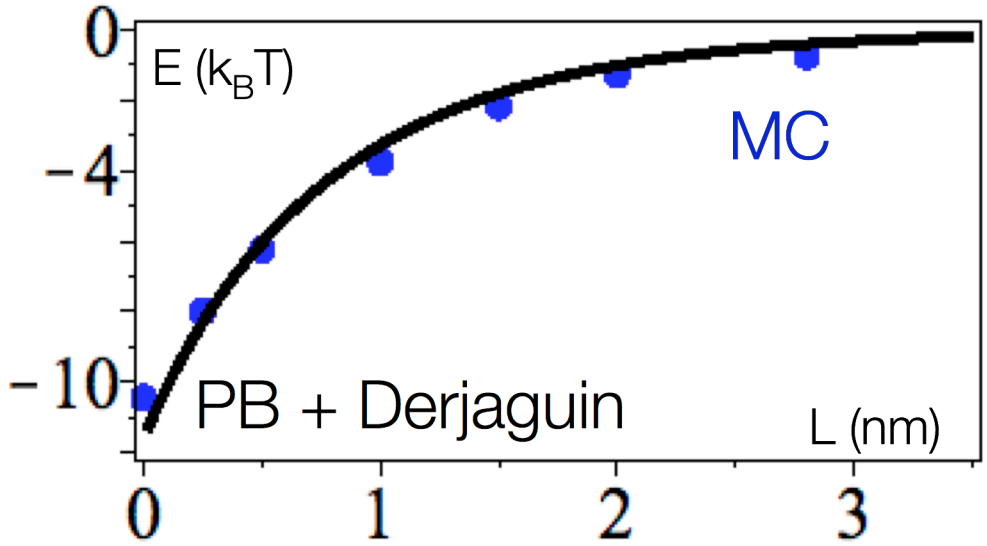


always attractive !

what about the DNA-protein system?

Monte Carlo simulations



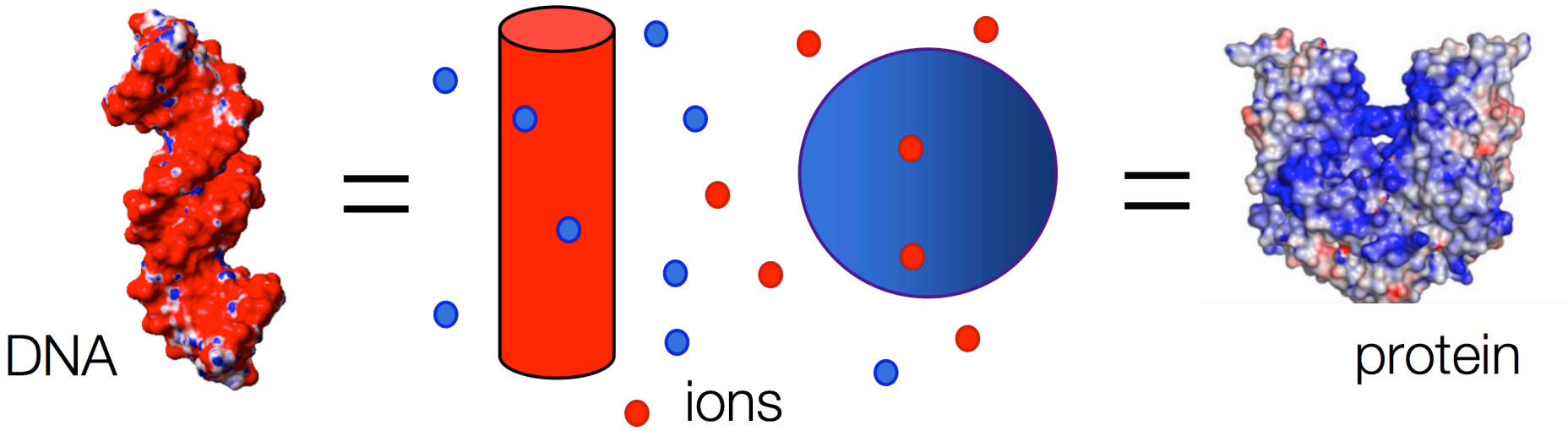


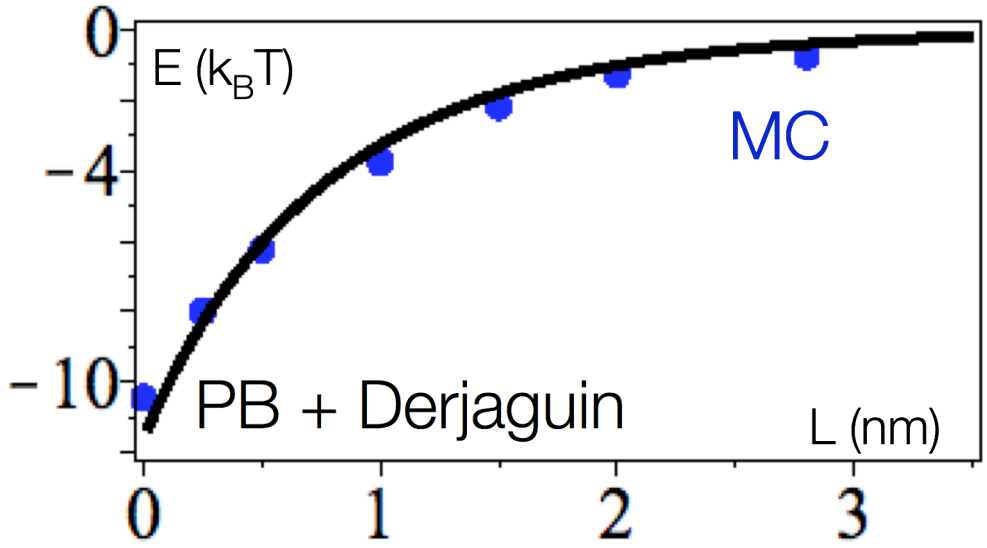
always attractive !

curvature effects can be accounted for by Derjaguin approximation.

what about the DNA-protein system?

Monte Carlo simulations



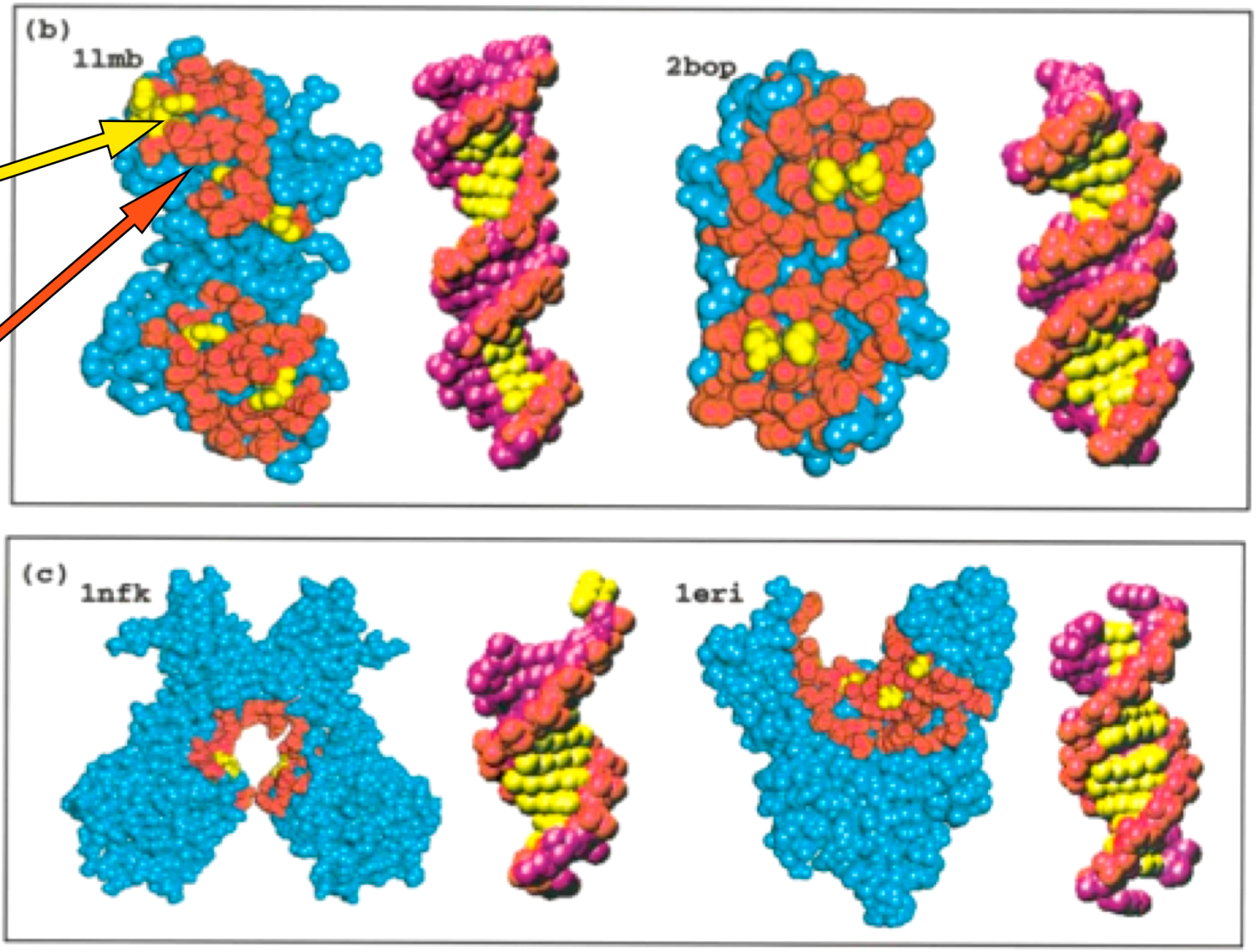


always attractive !

curvature effects can be accounted for by Derjaguin approximation.

the protein shape matters!!

protein shape



contacts with bases

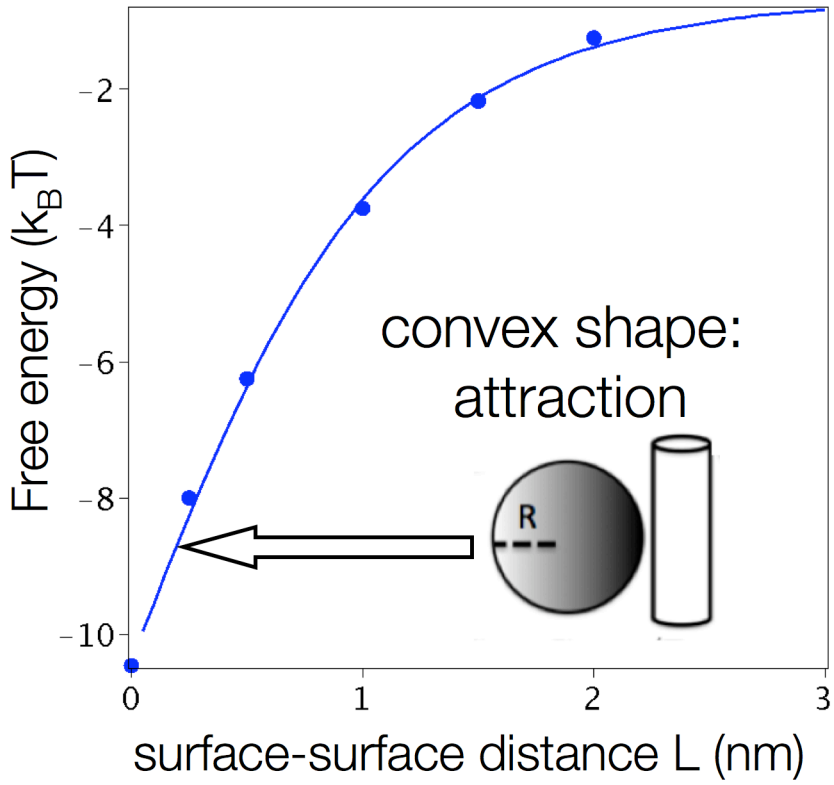
contacts with backbone

« enveloping » proteins

Jones et al J Mol Biol 1999

protein shape

MC simulations



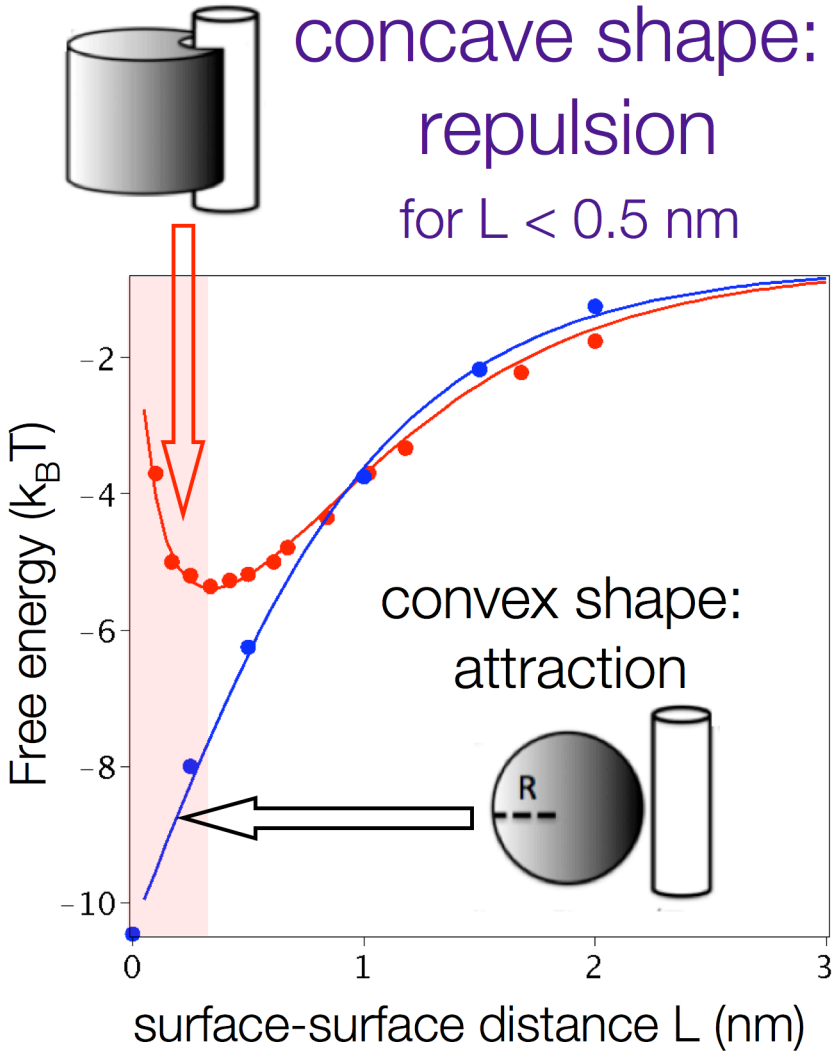
[Mol Phys 09, PRL 09, PCCP 11]

protein shape

MC simulations

concave shape:
repulsion

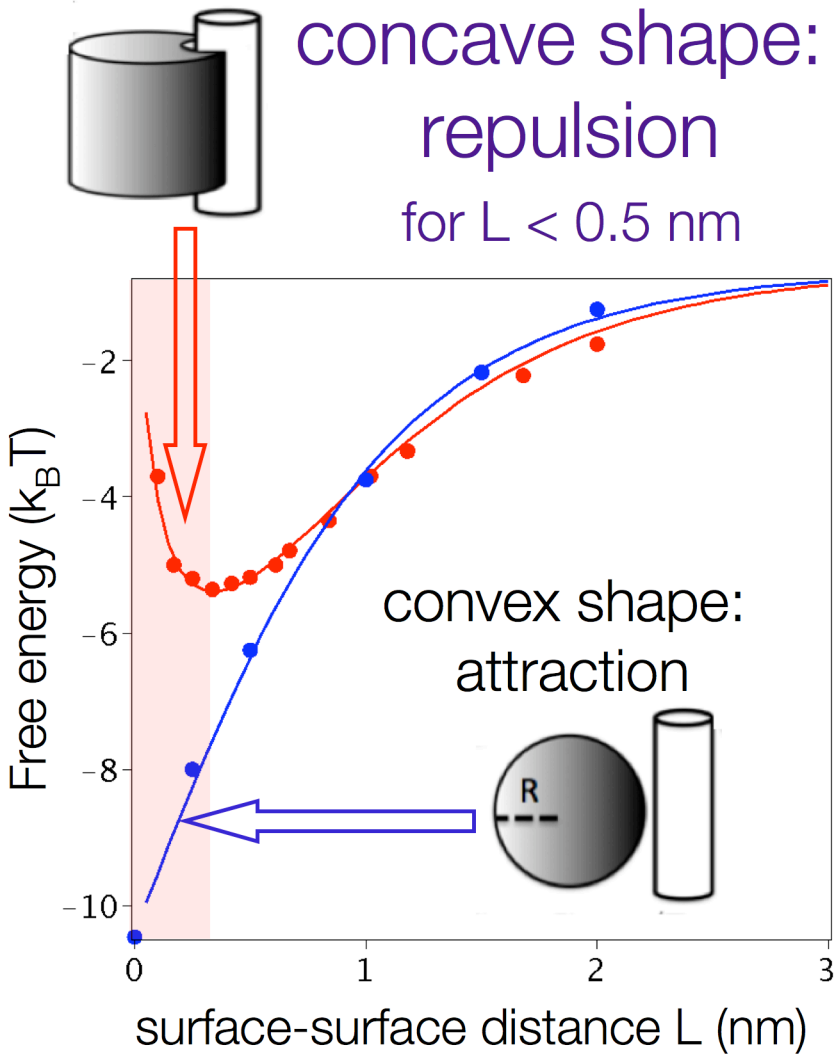
for L < 0.5 nm



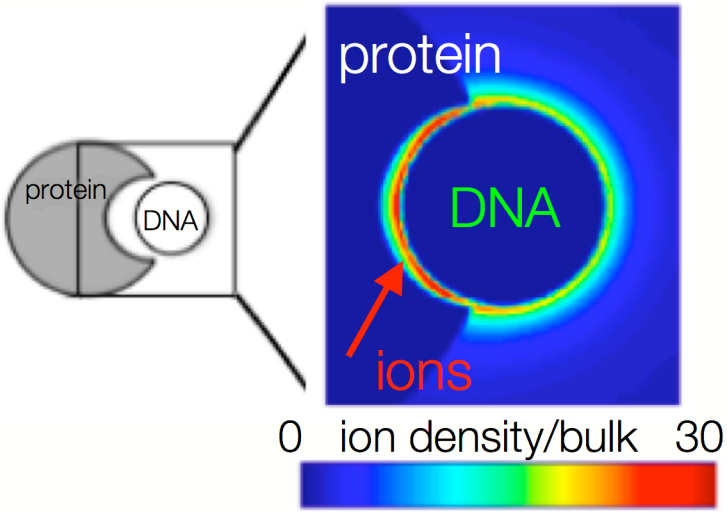
[Mol Phys 09, PRL 09, PCCP 11]

protein shape

MC simulations



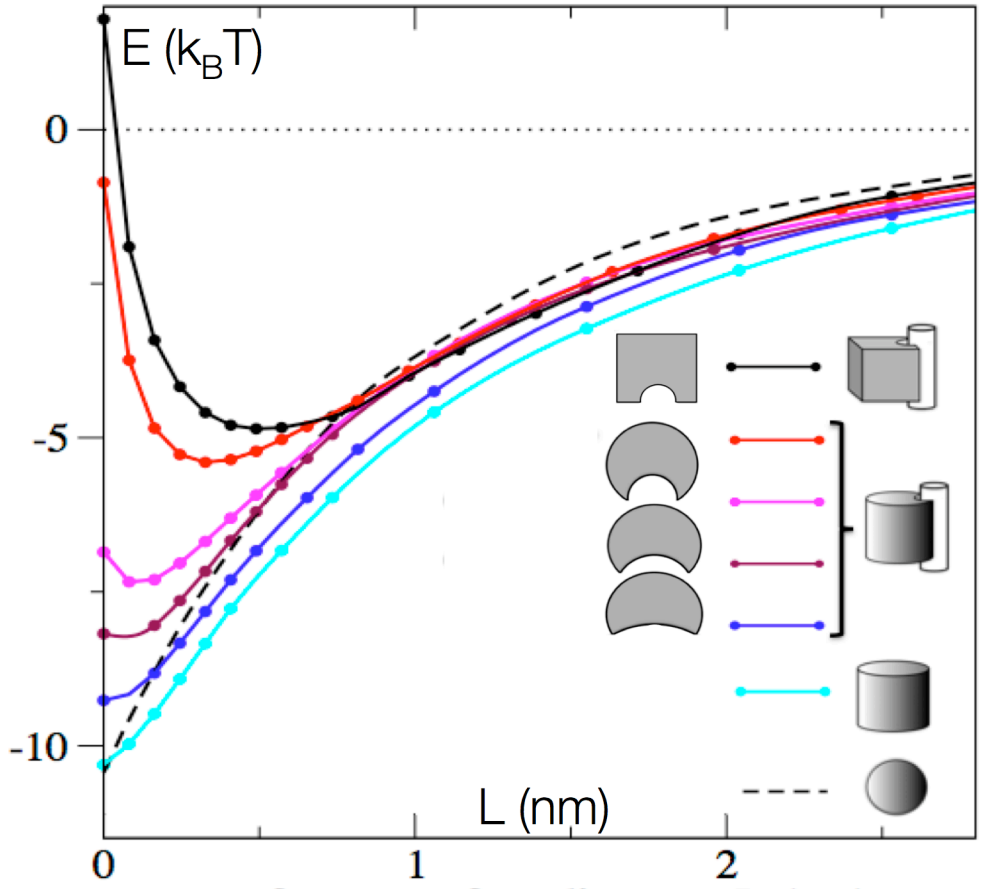
- osmotic origin : trapped ions



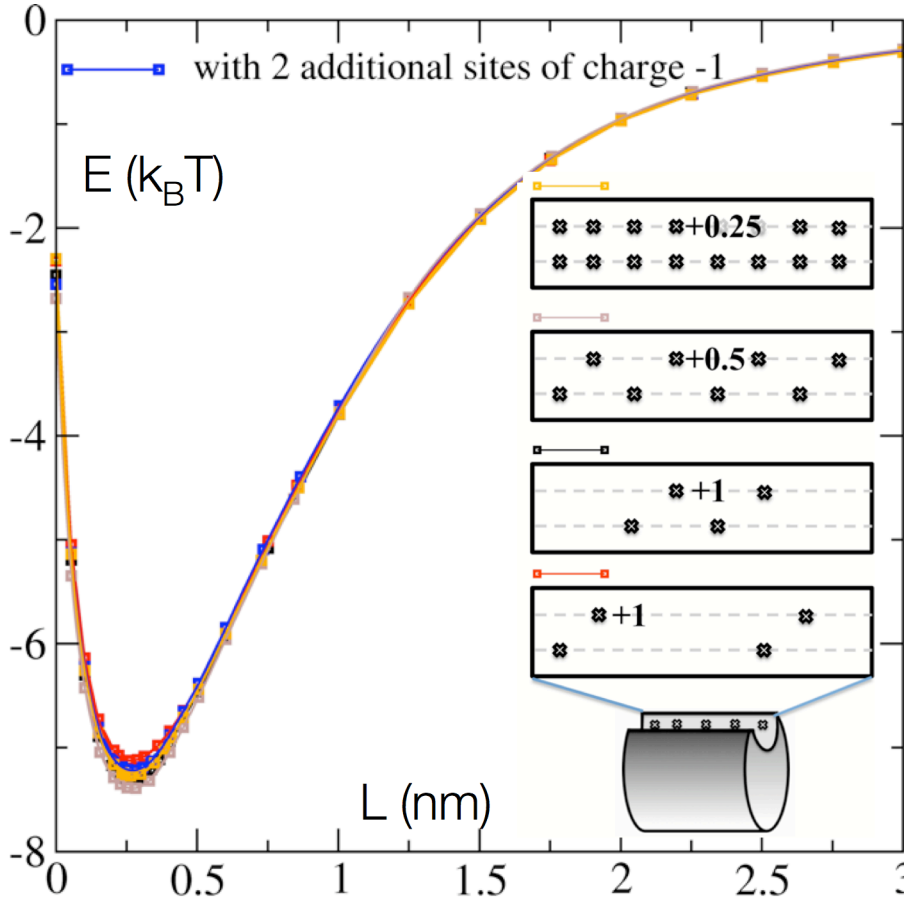
[Mol Phys 09, PRL 09, PCCP 11]

protein shape

other concave shapes

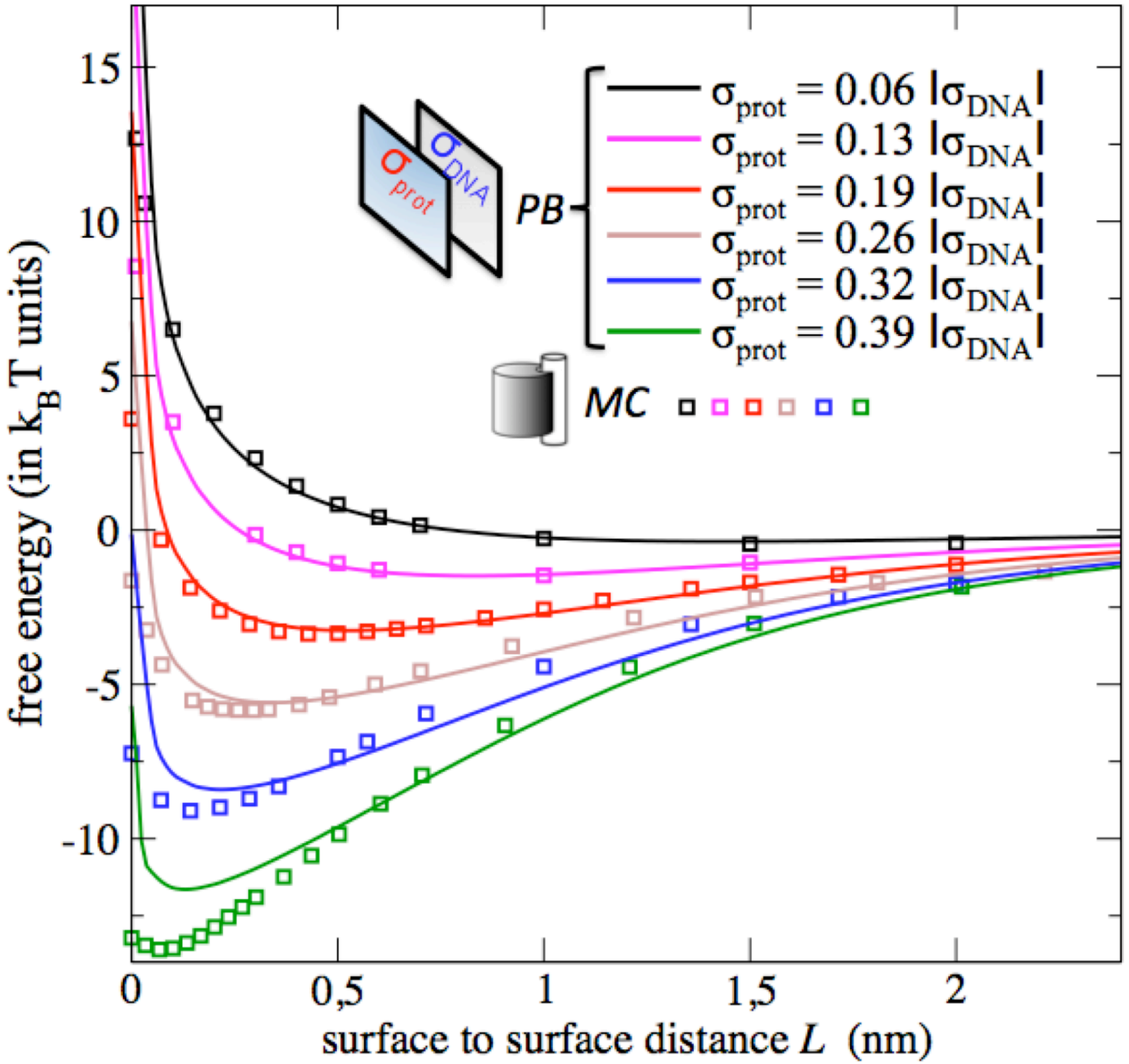


different charge distributions



Dahirel et al PRL 2009

role of the protein charge



DNA-binding proteins

estimation of the charge surface density over 77 proteins

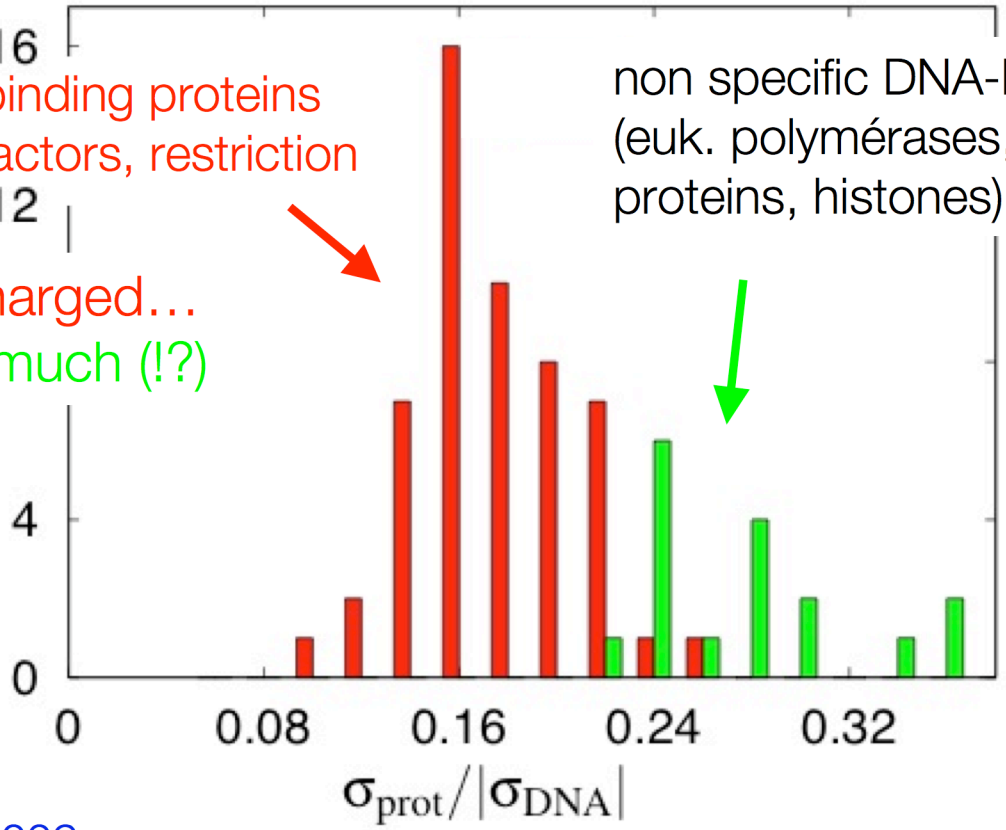
starting from structural data in Jones et al J Mol Biol 1999

charge surface density at the protein-DNA interface

specific DNA-binding proteins (transcription factors, restriction enzymes)

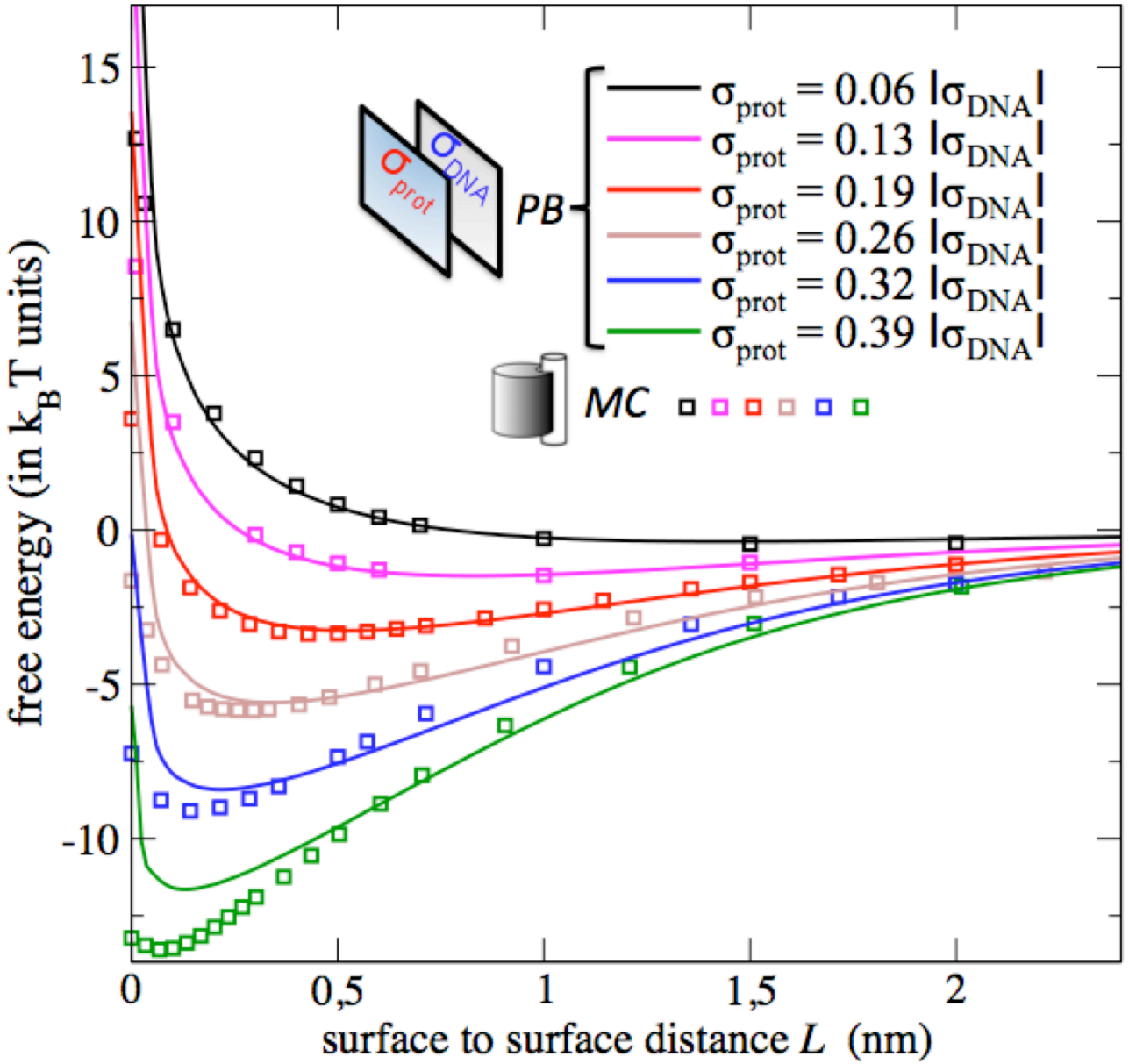
positively charged…
but not too much (!?)

non specific DNA-binding proteins (euk. polymérases, DNA repair proteins, histones)

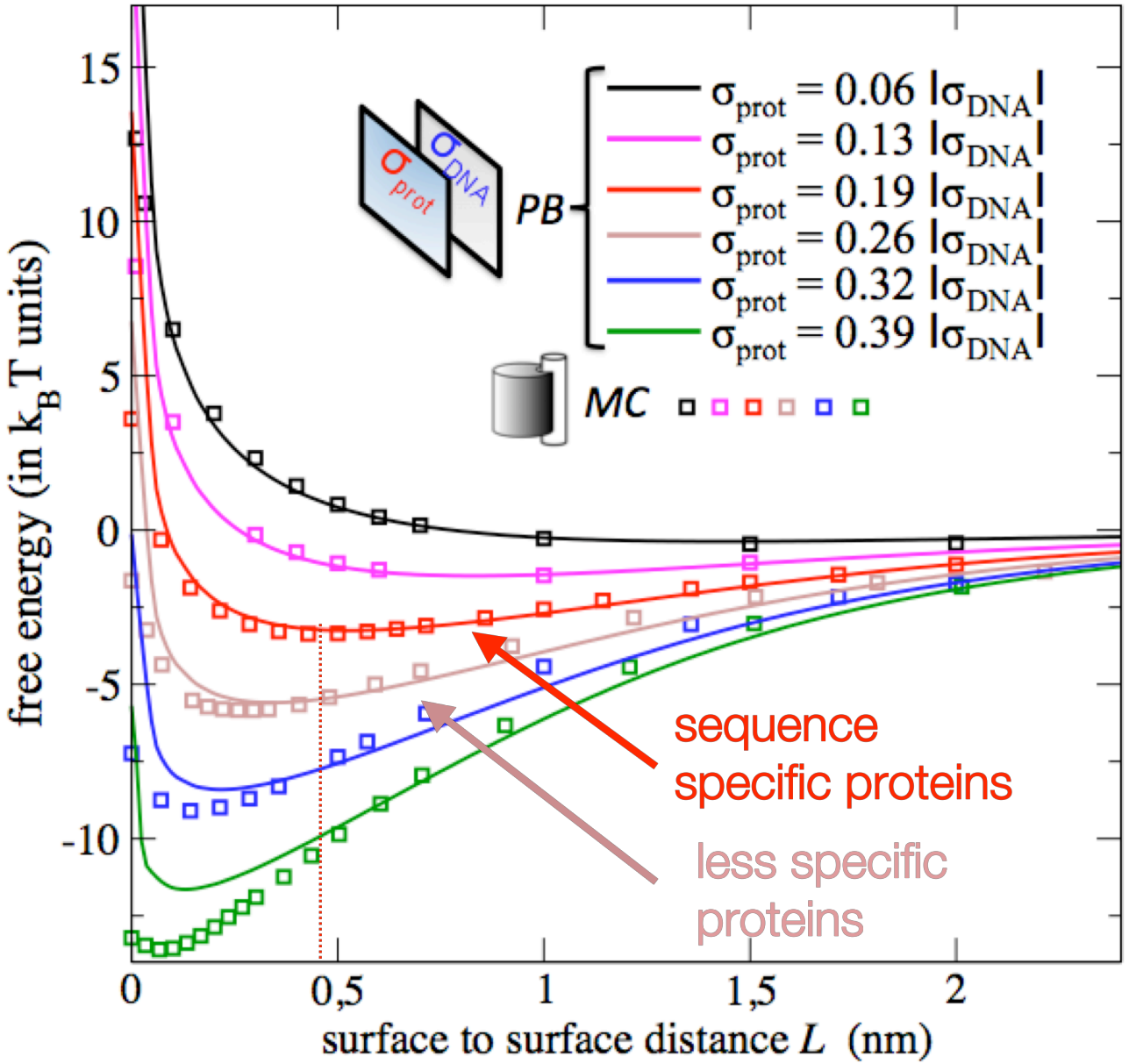


Dahirel et al PRL 2009

role of the protein charge

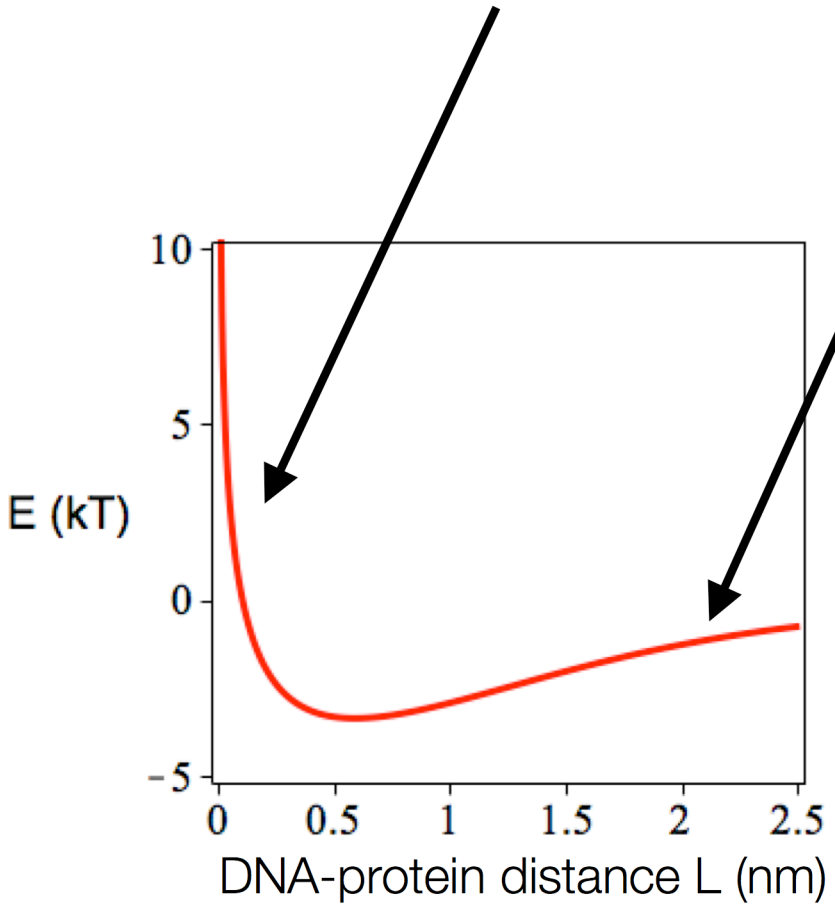


role of the protein charge



implications on sliding

osmotic repulsion + electrostatics

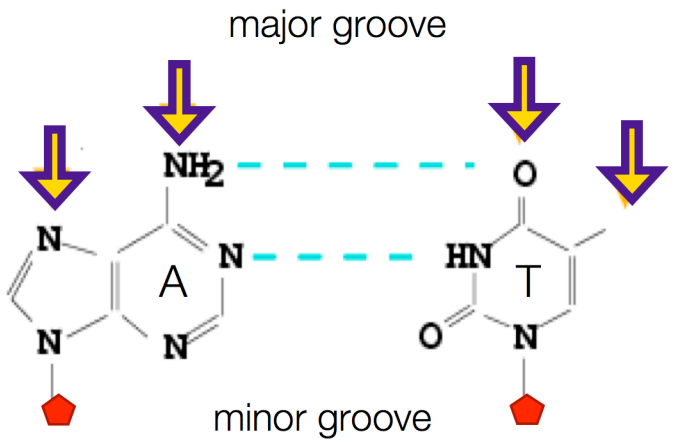


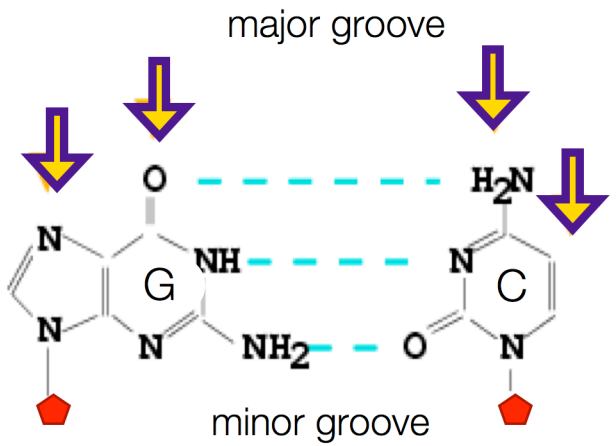
+ base-sensitive interaction (hydrogen bonds…)

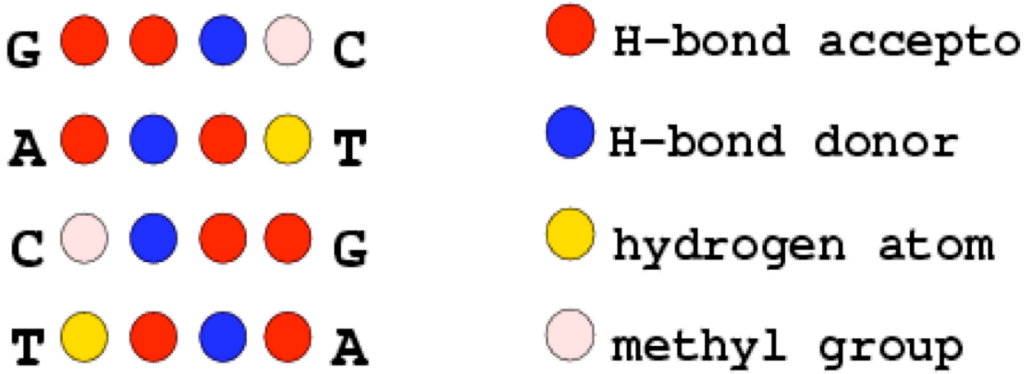
Dahirel et al PRL 2009

recognition

direct interaction:
hydrogen bonding to the bps sides







implications on sliding

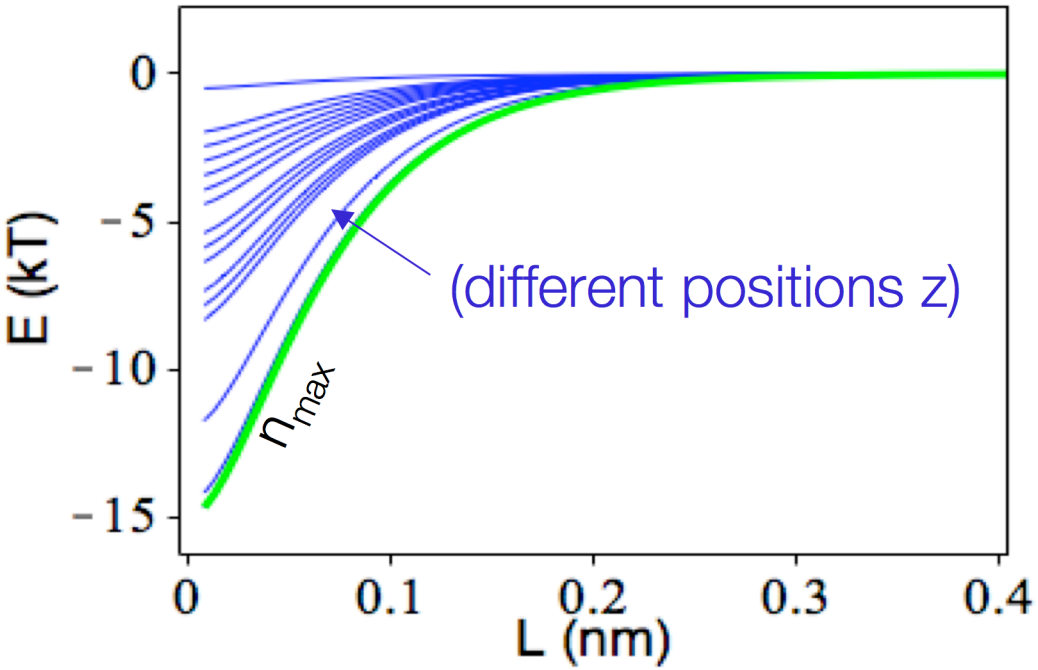
base-sensitive interaction (hydrogen bonds)

- number n of H-bonds dependent on the position z along DNA
- single H-bond = Morse potential $e_H(L) = \varepsilon \left[\left(1 - e^{-gL} \right) - 1 \right]$

$\varepsilon = 0.5\ k_B T \quad g = 2 \quad (L_0 = 0)$

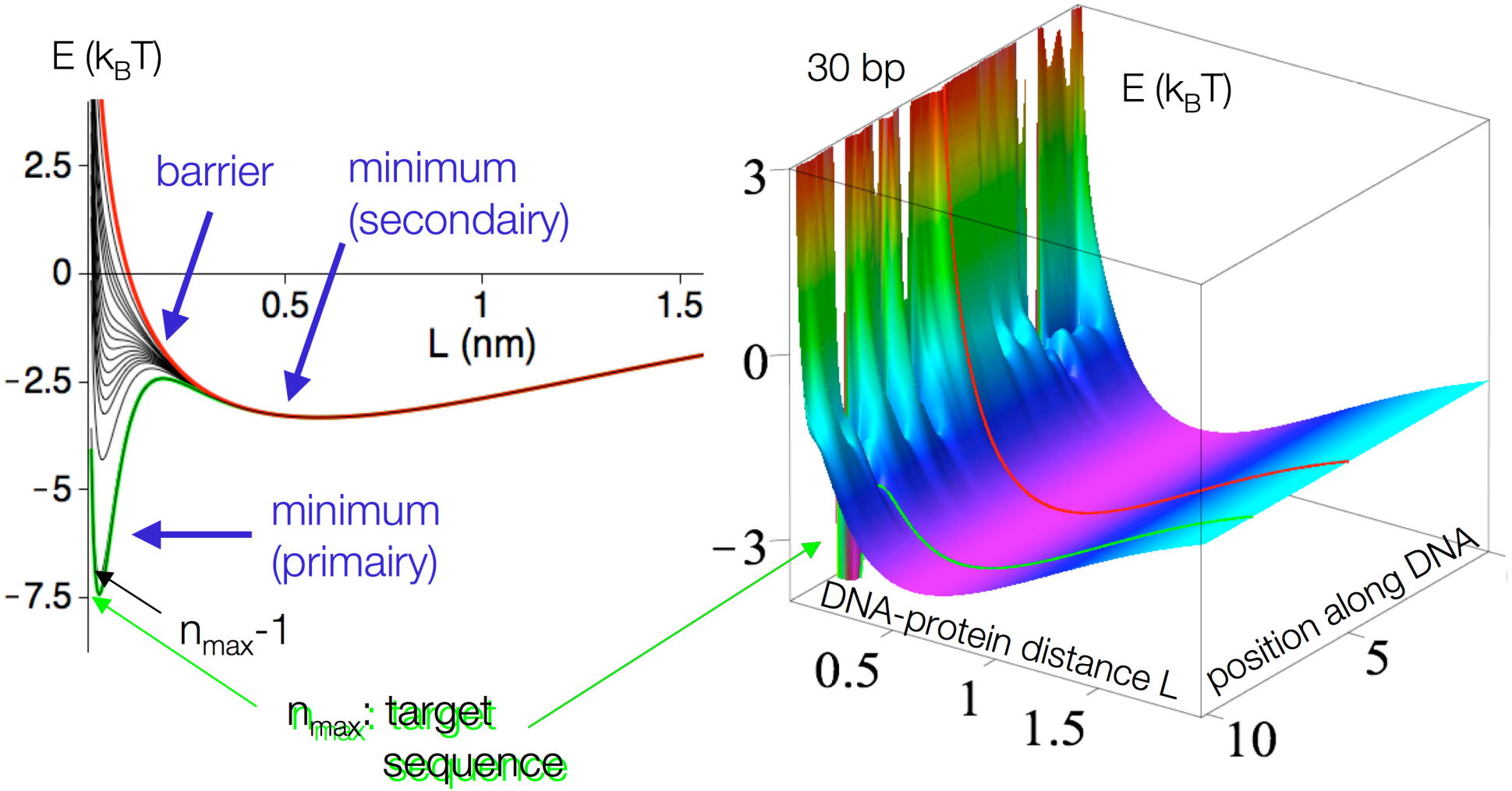
- $\Rightarrow$ sequence dependent energy profile

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



implications on sliding

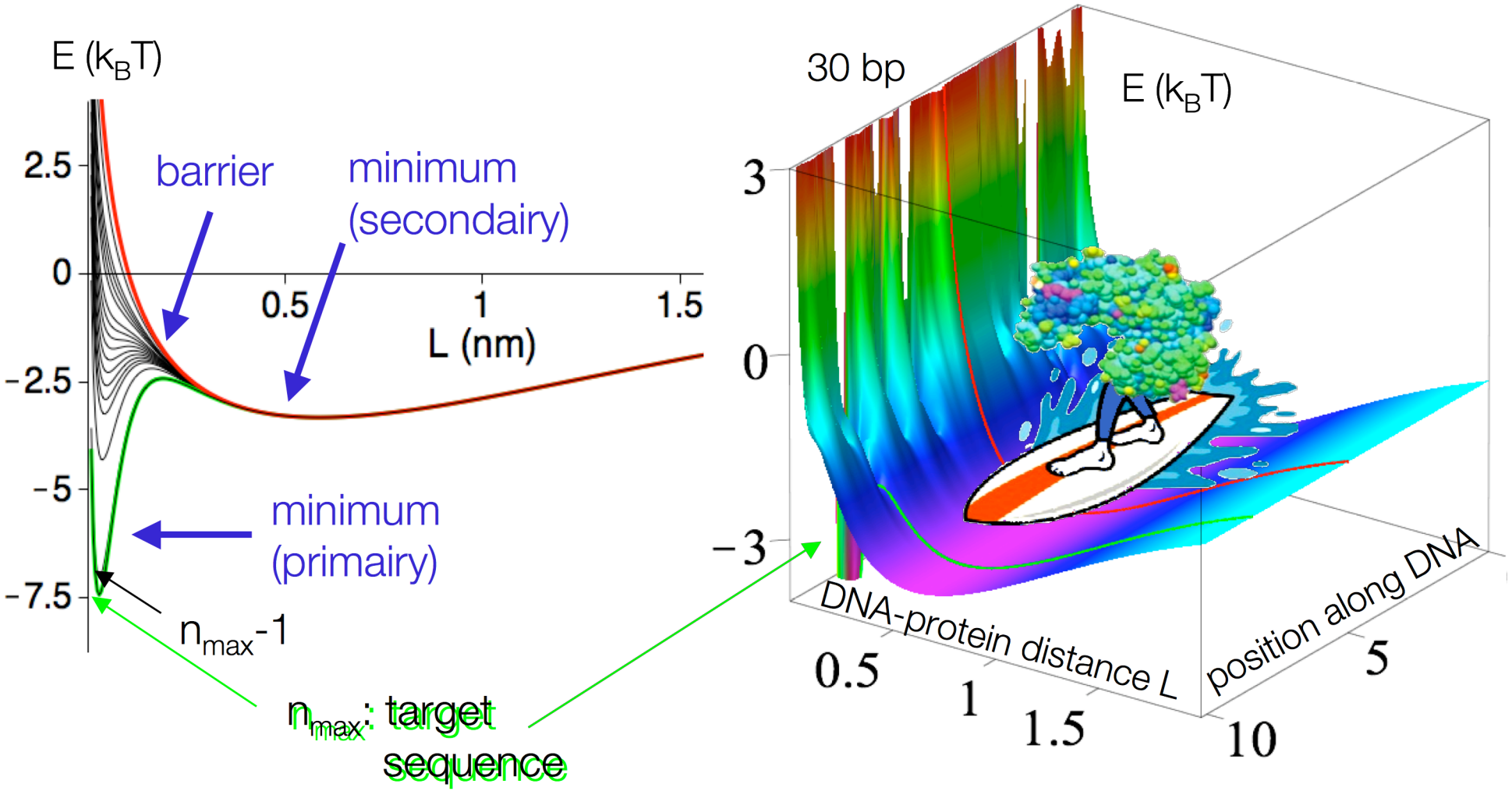
electrostatics + hydrogen bonds



Dahirel et al PRL 2009

implications on sliding

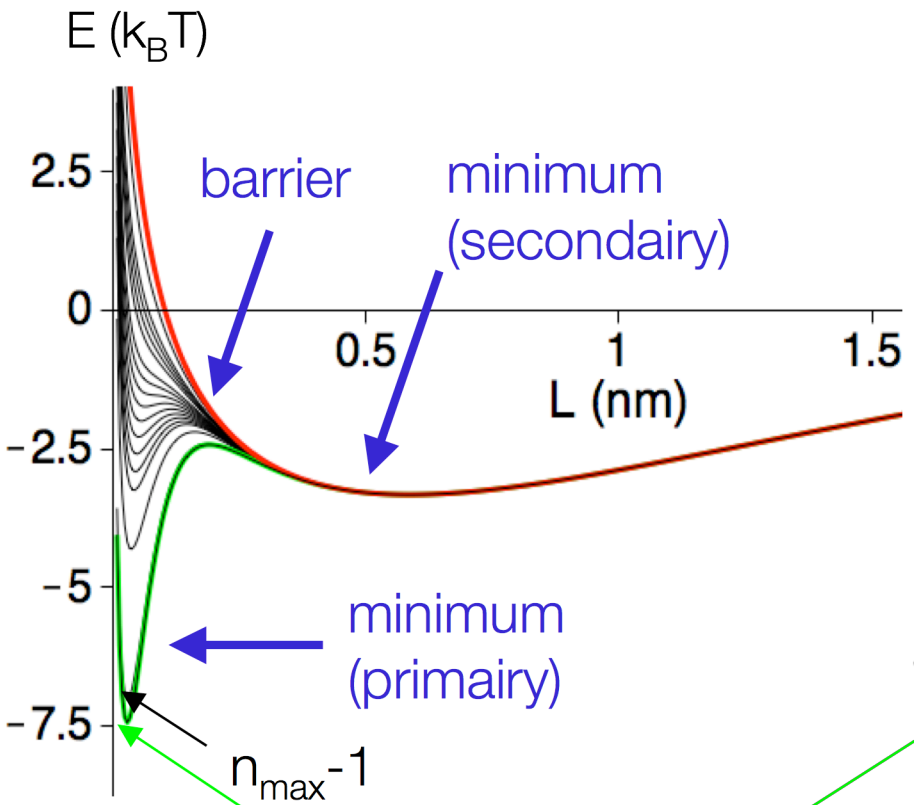
electrostatics + hydrogen bonds

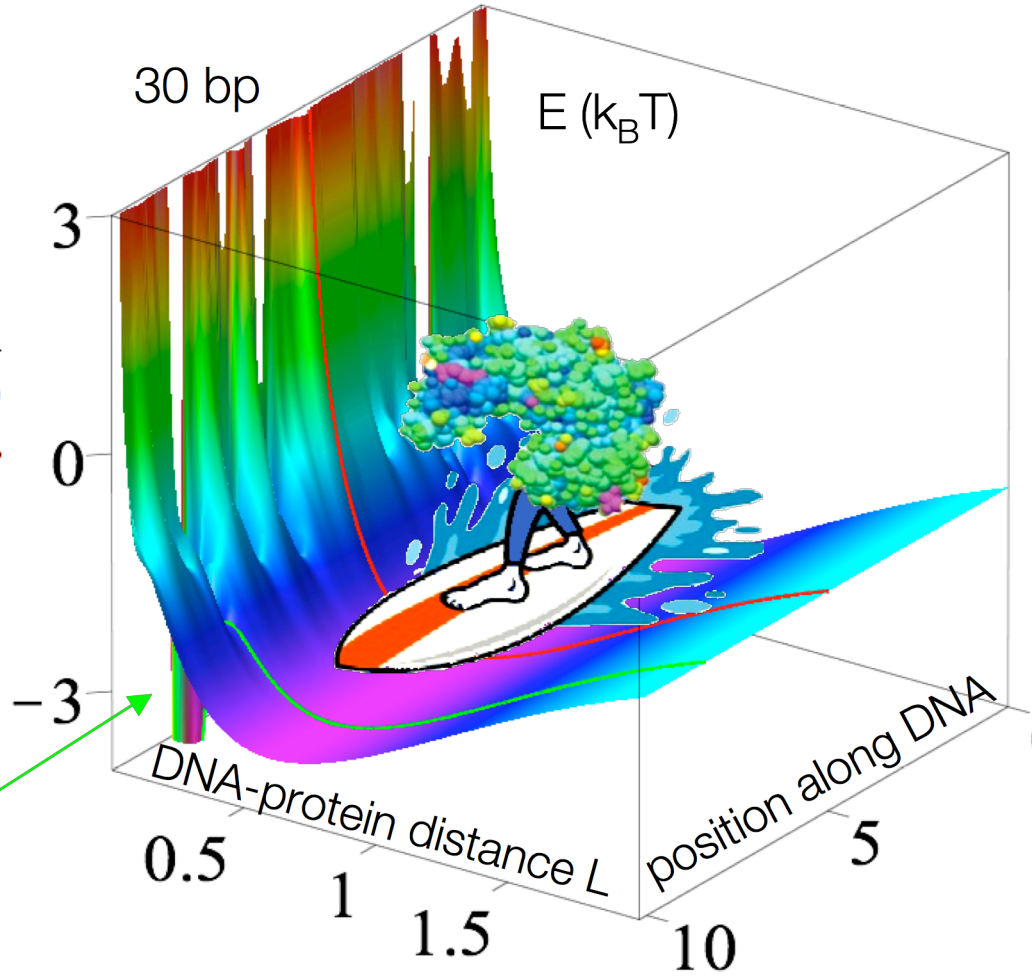


Dahirel et al PRL 2009

implications on sliding

electrostatics + hydrogen bonds





« facilitated sliding »!!

Dahirel et al PRL 2009

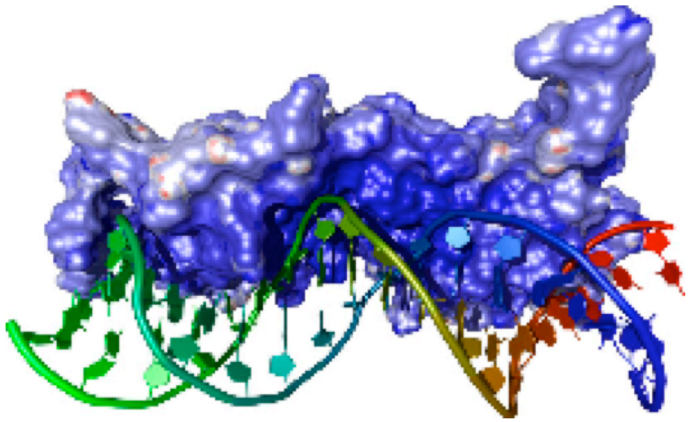
perspectives 1

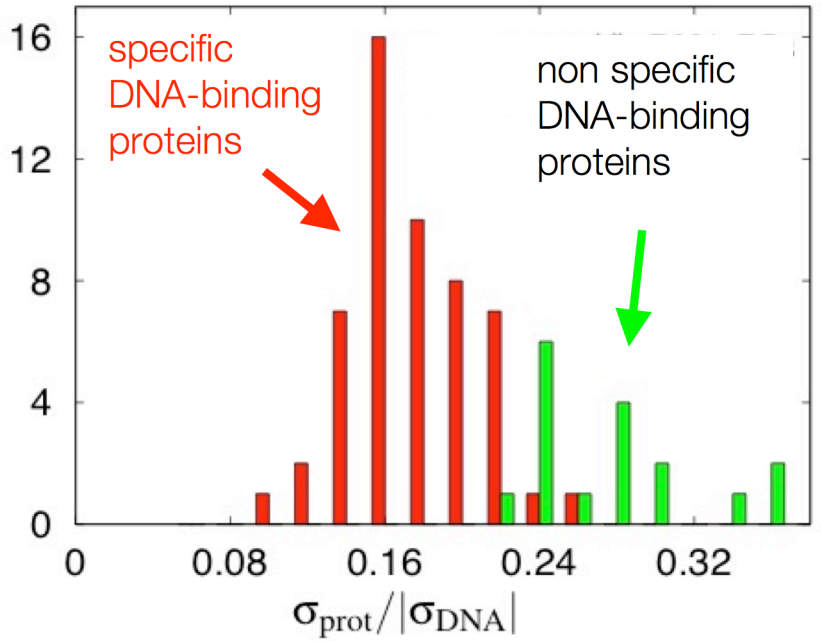
1. compare to structural data

systematic study of the physico chemical properties of proteins

(shape, charge distribution, pH dependence, details of the specific interaction)

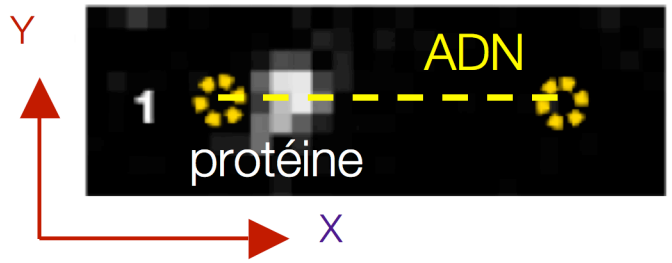
→ different protein classes for different functions?





perspectives 2

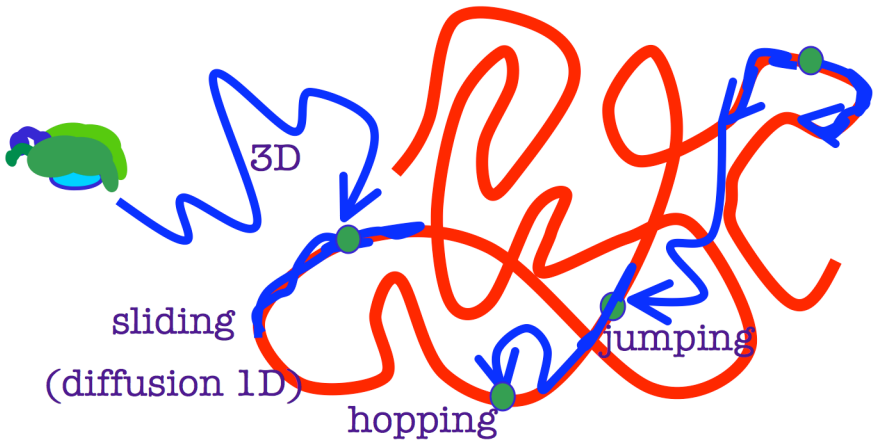
2. compare to diffusion experiments

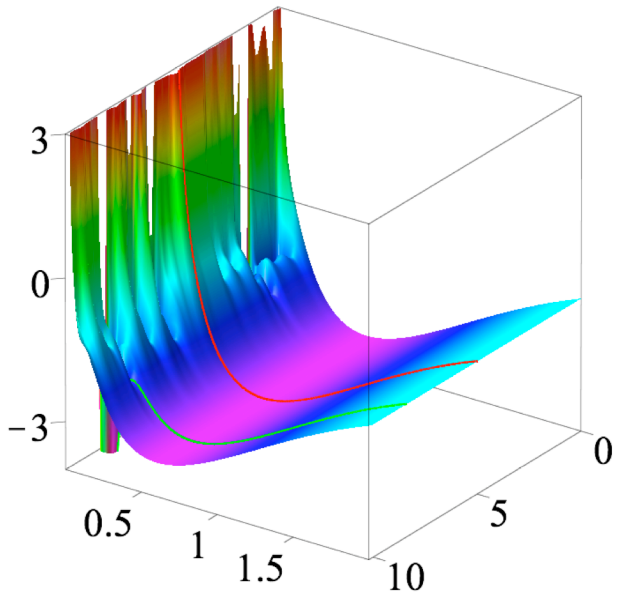


combine the existing kinetic models with the underlying physics

(diffusion on a physical energy profile)

→ can we reproduce the observed kinetic parameters ?





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

Julien MOZZICONACCI

Jean-Marc VICTOR

Maria BARBI

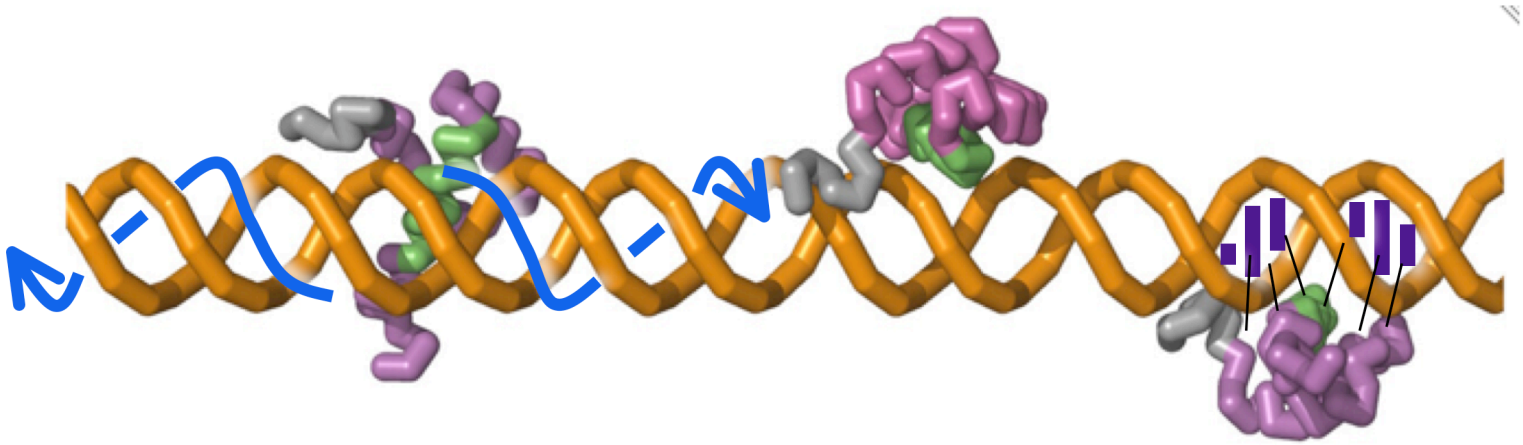
Fabien PAILLUSSON

Pascal CARRIVAIN

Christophe LAVELLE

Hua WONG

search of target sequences



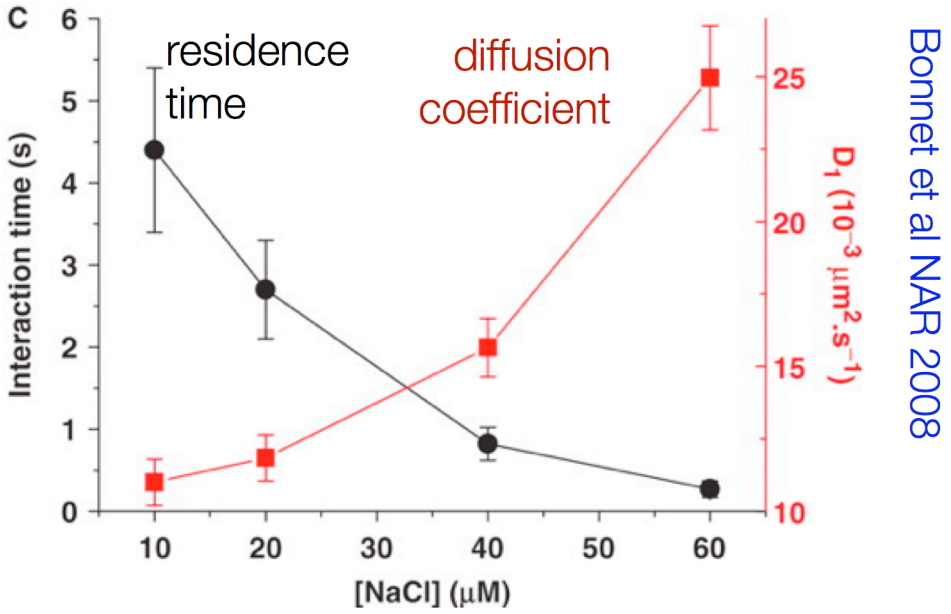
1. displacement along DNA
1D diffusion (sliding)

2. sequence reading
interaction with bps

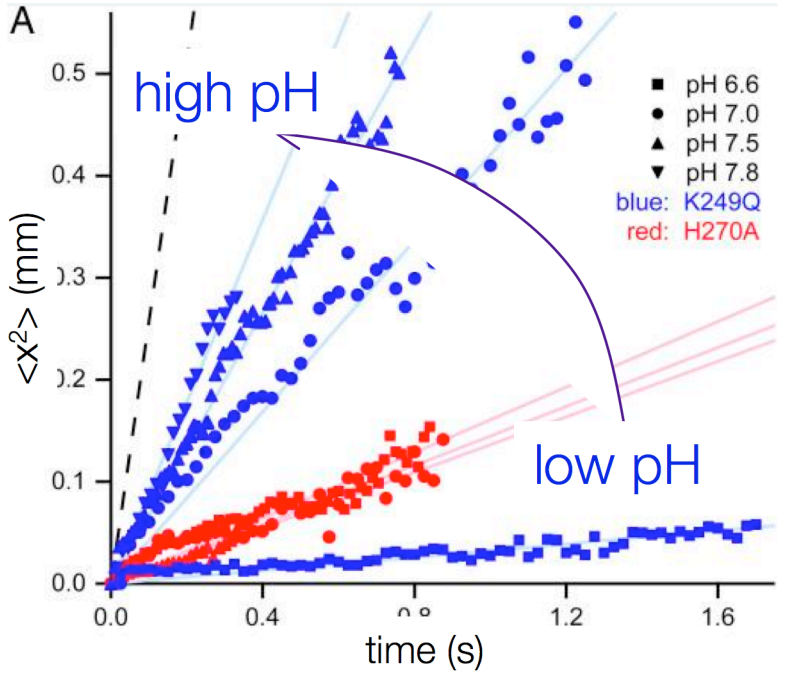
protein 1D diffusion (sliding)

remark : variability in quantitative results

(for different proteins or different conditions)



Bonnet et al NAR 2008

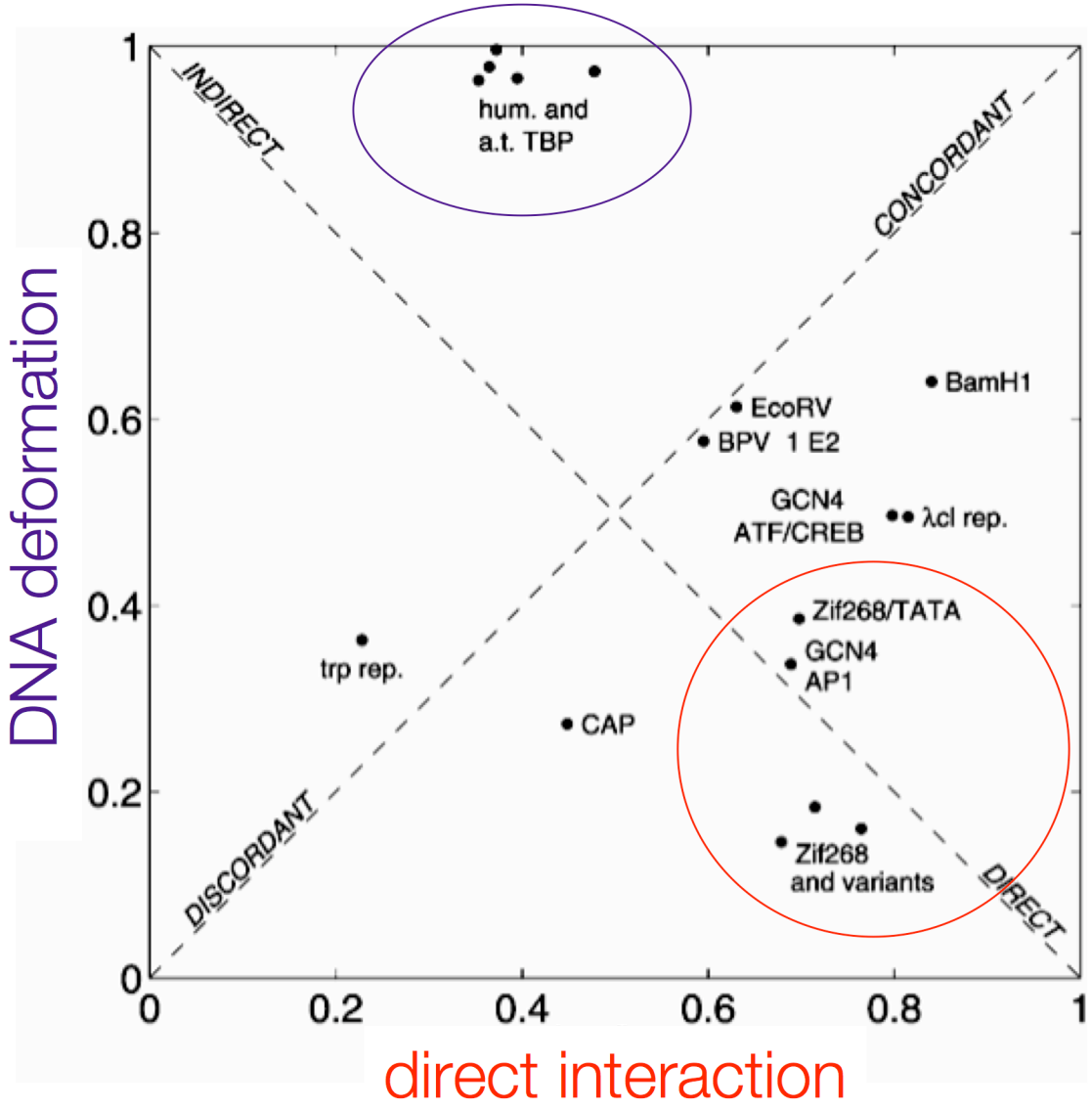


Blaney et al PNAS 2006

- diffusion coefficients D_1 from 0.01 to 0.5 µm^2/s
- residence times from 0.03 to 20 s ($\Rightarrow$ # visited pbs)

recognition

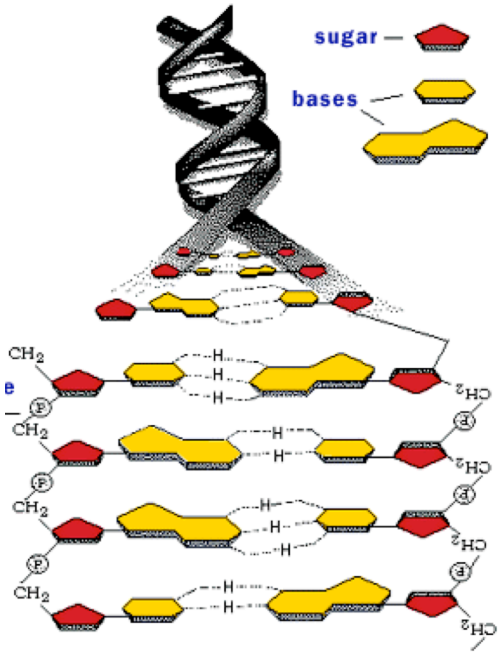
direct interaction / indirect interaction through DNA deformation

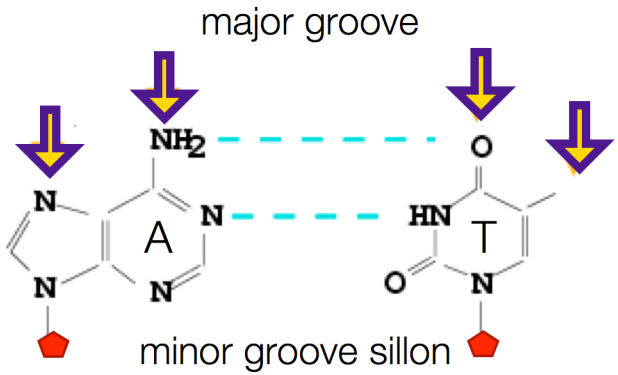


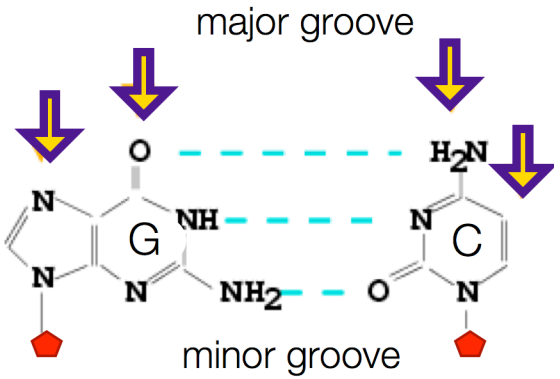
Paillard Lavery Structure 2004

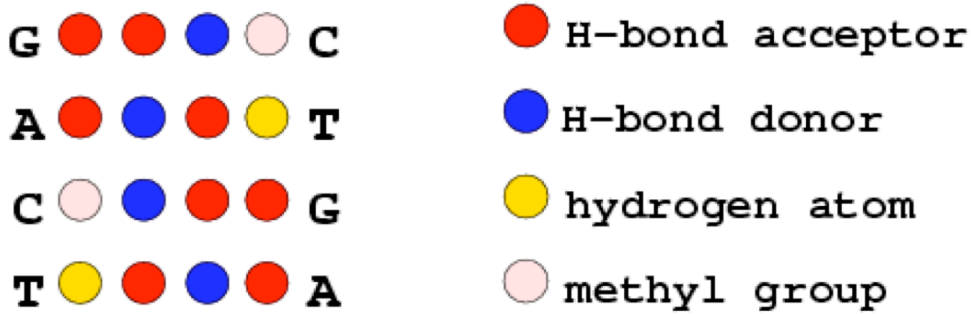
recognition

direct interaction:
hydrogen bonding to the bps sides









questions ouvertes

Q : comparer aux expériences

1. ingrédients :
    - charge protéine
    - sel monovalent
    - pH (fait !)
    - ions multivalent (en cours !)

questions ouvertes

Q : comparer aux expériences

2. observables : potentiel radial

→ **cinétique d'association/dissociation**

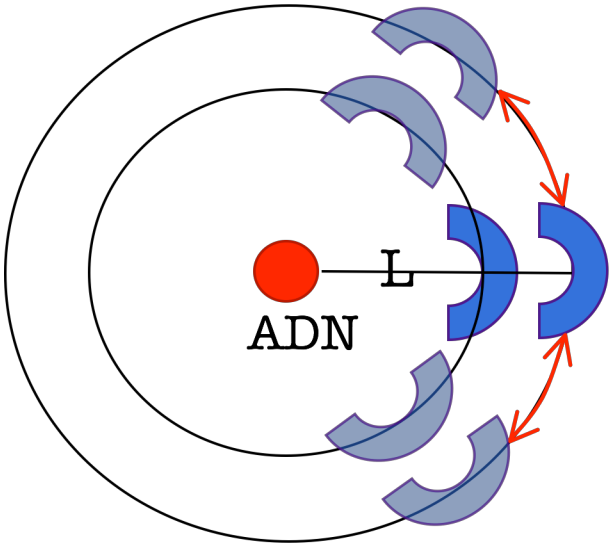
questions ouvertes

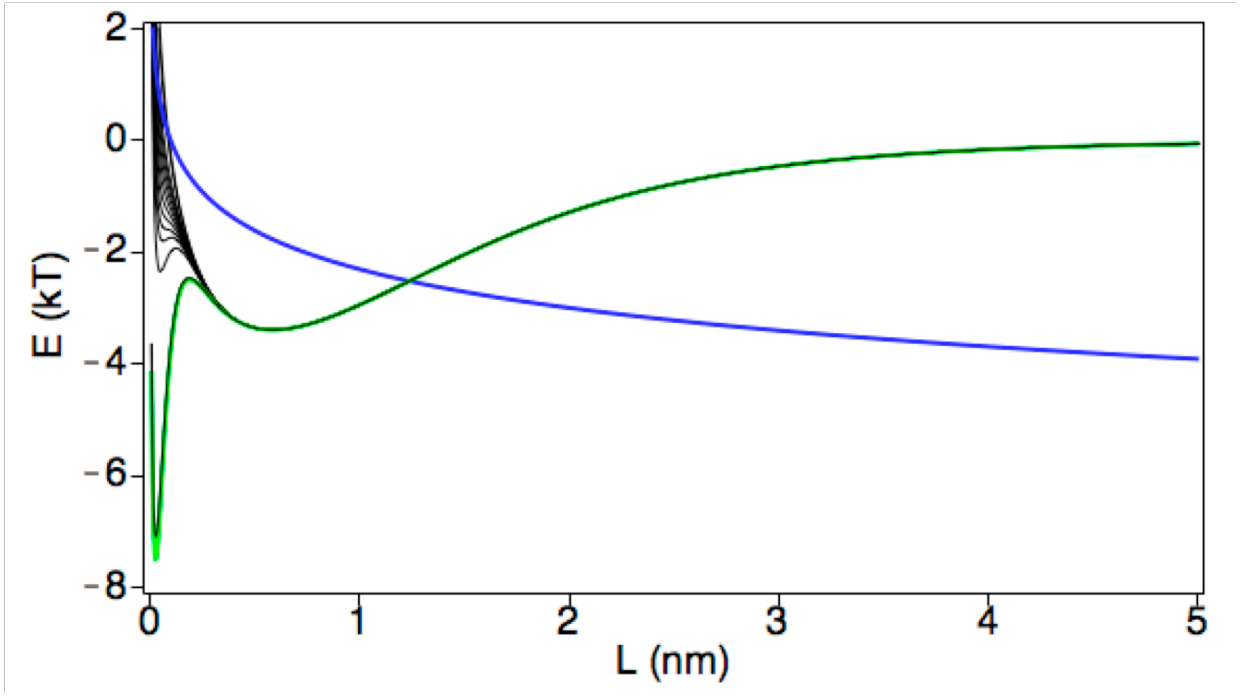
Q : comparer aux expériences

2. observables : potentiel radial

→ **cinétique d'association/dissociation**

symétrie cylindrique : contribution entropique $-\ln(L/L_0)$



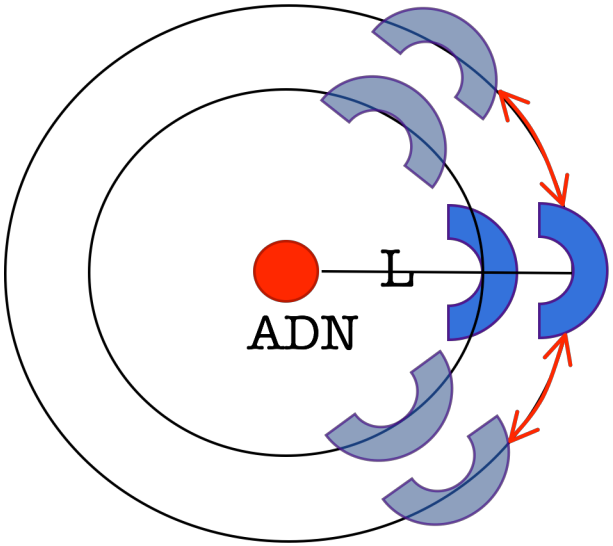


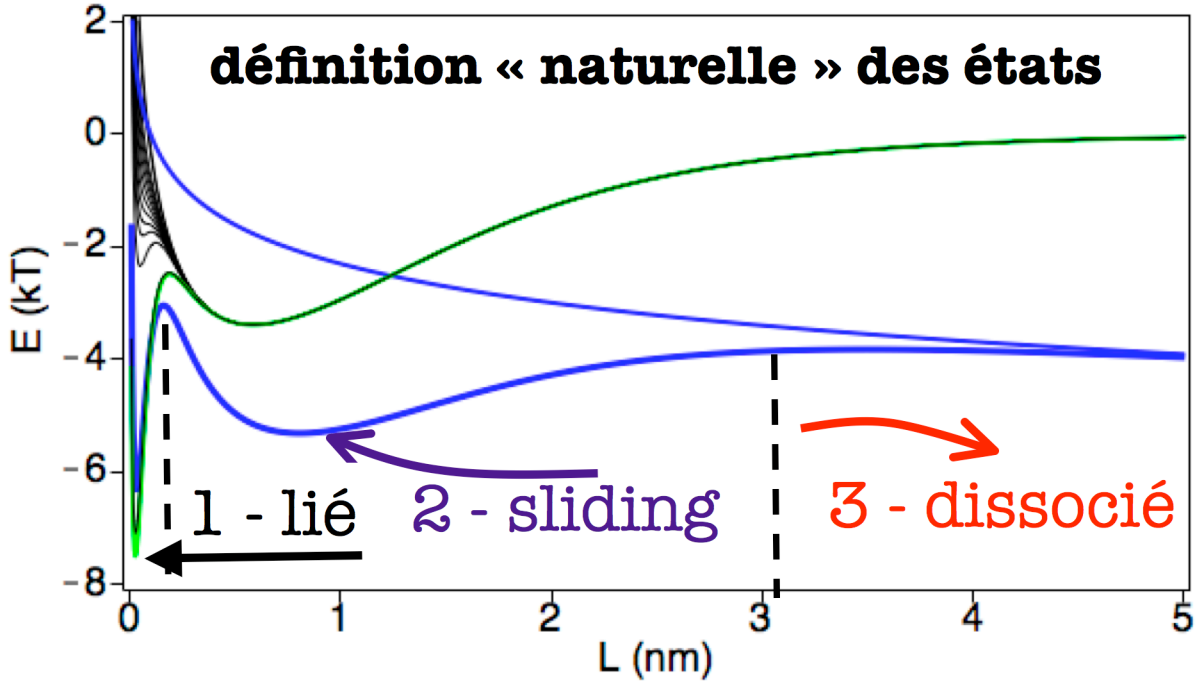
questions ouvertes

Q : comparer aux expériences

2. observables : potentiel radial
→ **cinétique d'association/dissociation**

symétrie cylindrique : contribution entropique $-\ln(L/L_0)$



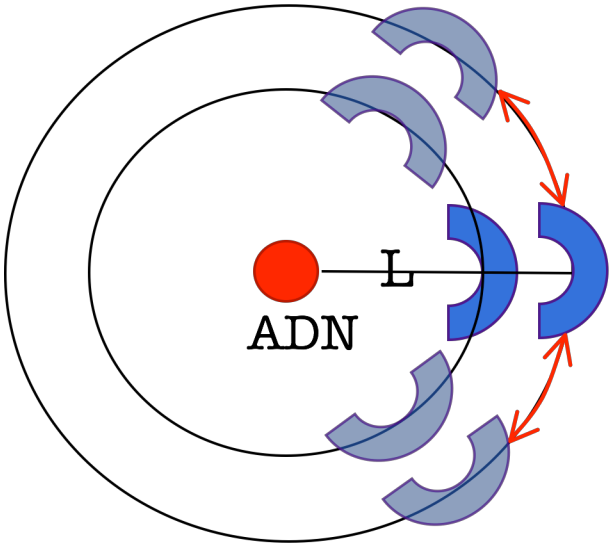


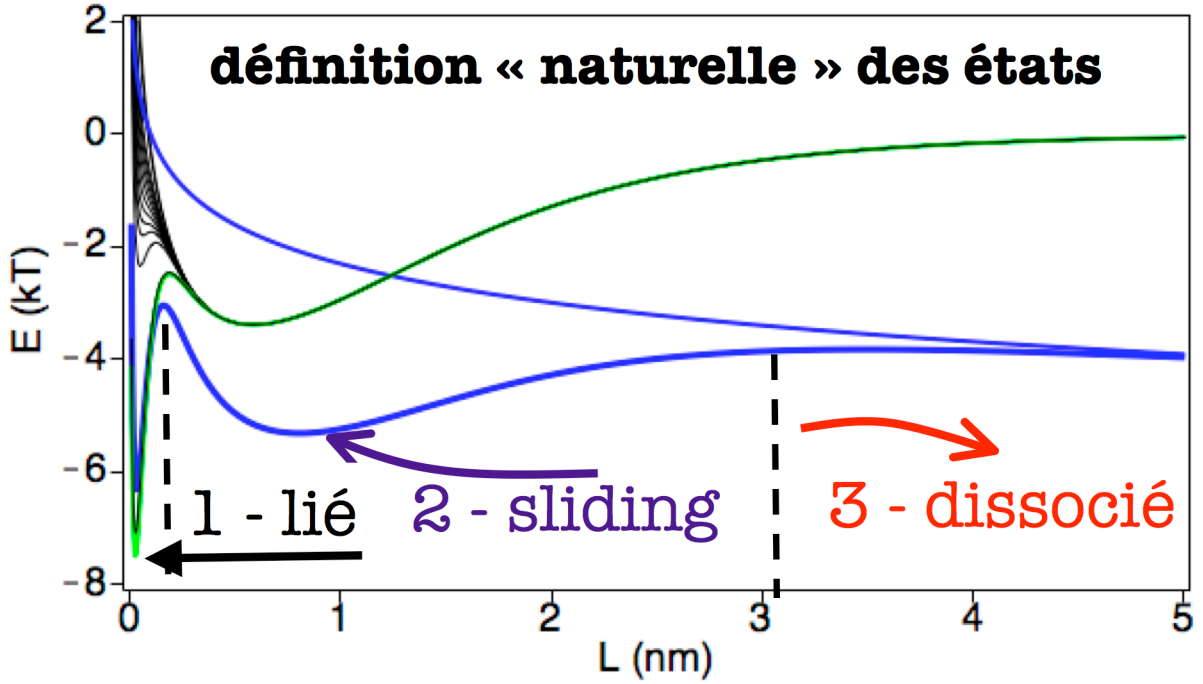
questions ouvertes

Q : comparer aux expériences

2. observables : potentiel radial
→ **cinétique d'association/dissociation**

symétrie cylindrique : contribution entropique $-\ln(L/L_0)$





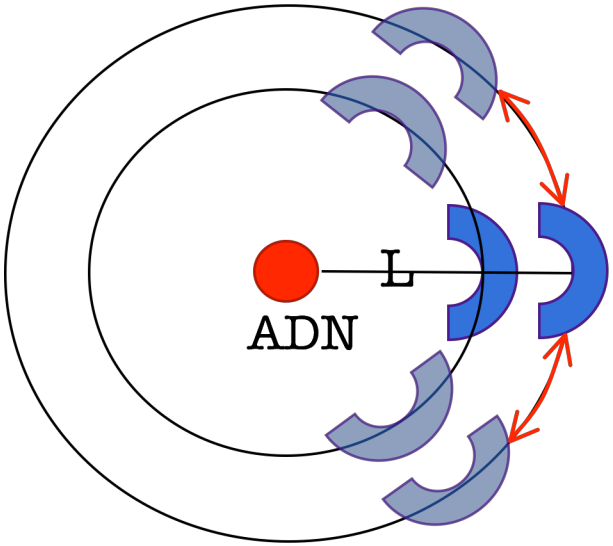
Q : quantitatif - dépendance des paramètres ?

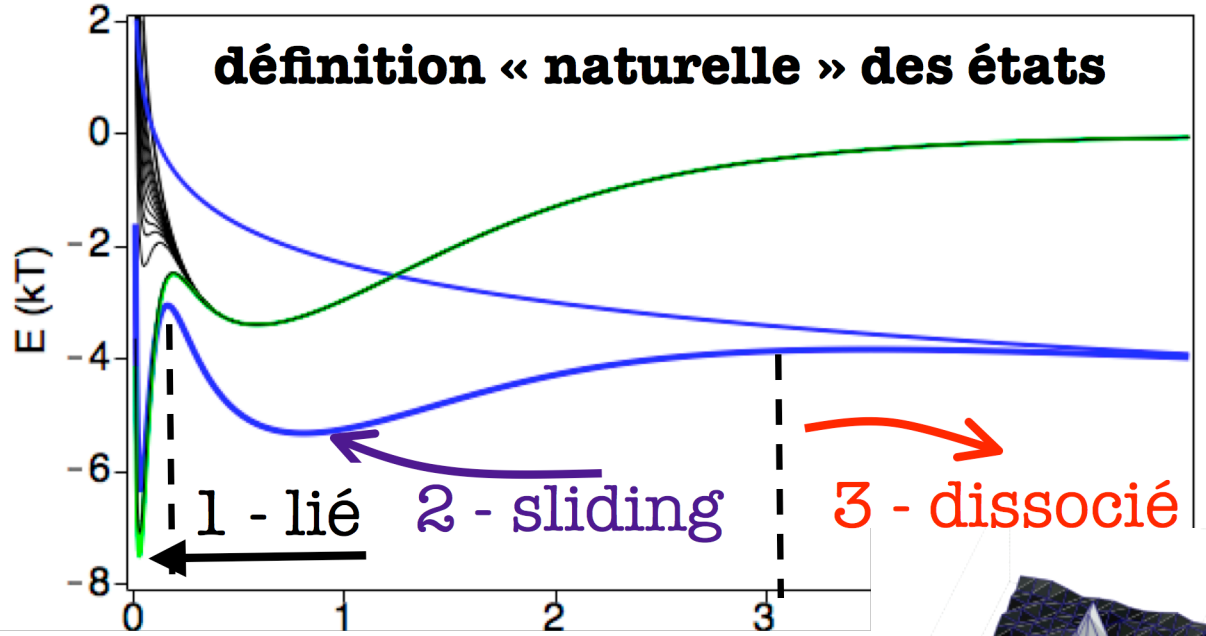
questions ouvertes

Q : comparer aux expériences

2. observables : potentiel radial
→ **cinétique d'association/dissociation**

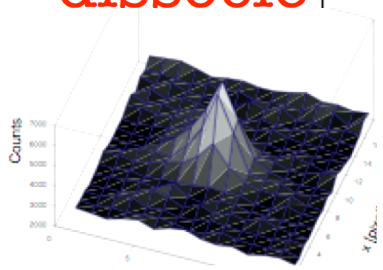
symétrie cylindrique : contribution entropique $-\ln(L/L_0)$





Q : définition expérimentale ?

1 pixel ≅ 130 nm - champ ≅ $(4\ \mu m)^2$ - $\Delta t \cong 20$ ms

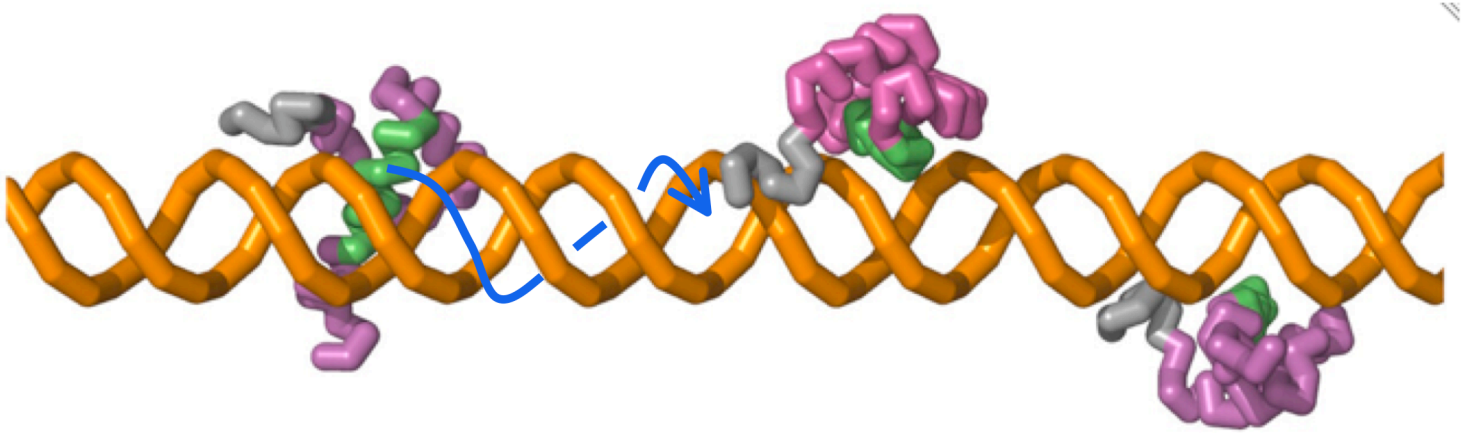


I. Bonnet - thès

questions ouvertes

Q : comparer aux expériences

3. et la diffusion 1D ?



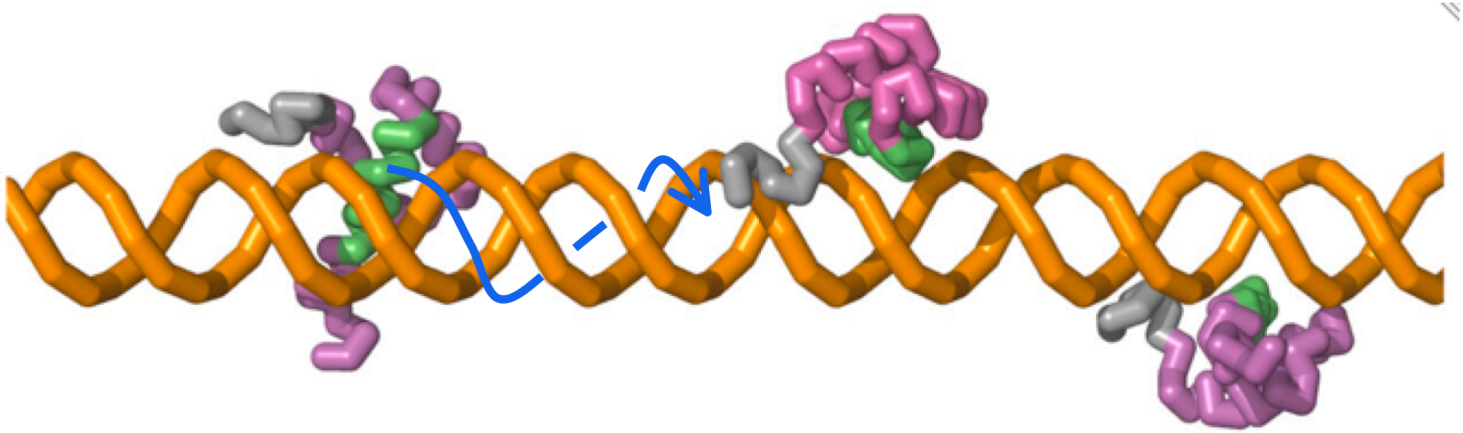
Yaakov Levy

la protéine suit le sillon $\Leftarrow$ on mesure $D_{1D} \ll D_{3D}$

questions ouvertes

Q : comparer aux expériences

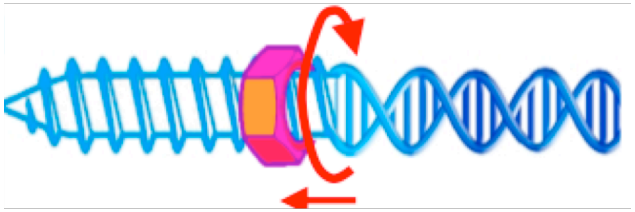
3. et la diffusion 1D ?



Yaakov Levy

la protéine suit le sillon ⇐ on mesure $D_{1D} << D_{3D}$

Q : charges sur 2 hélices ⇒ trajectoire hélicoïdale ?

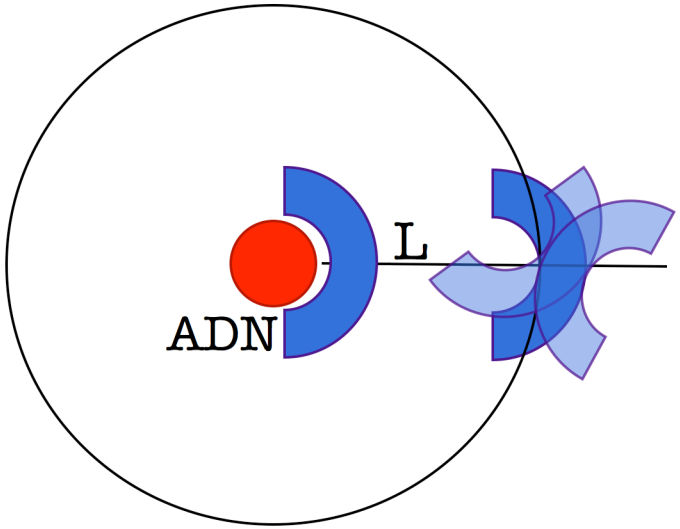


Q : effet vis-écrou ?

Q : hélicité = contrainte forte ?

questions ouvertes

Q : autres degrés de liberté :



Q : orientation protéine :

- entropie
- électrostatique → 0

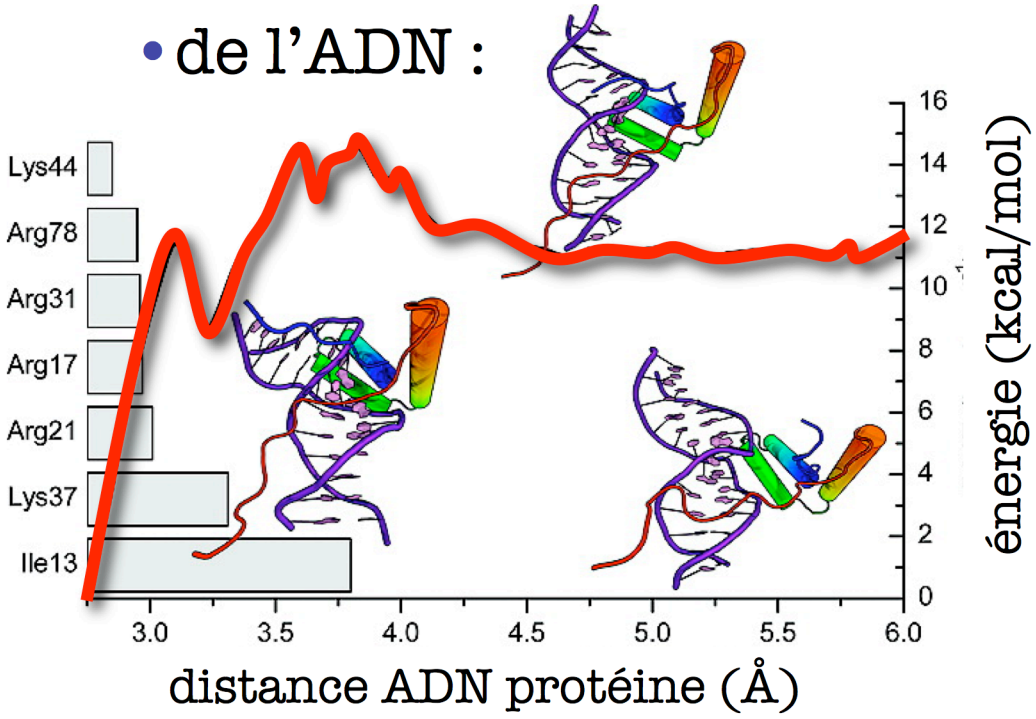
Q : moment dipolaire ?

questions ouvertes

Q : autres degrés de liberté :

Q : **flexibilité** ?

- de l'ADN :



- déformation « à distance »

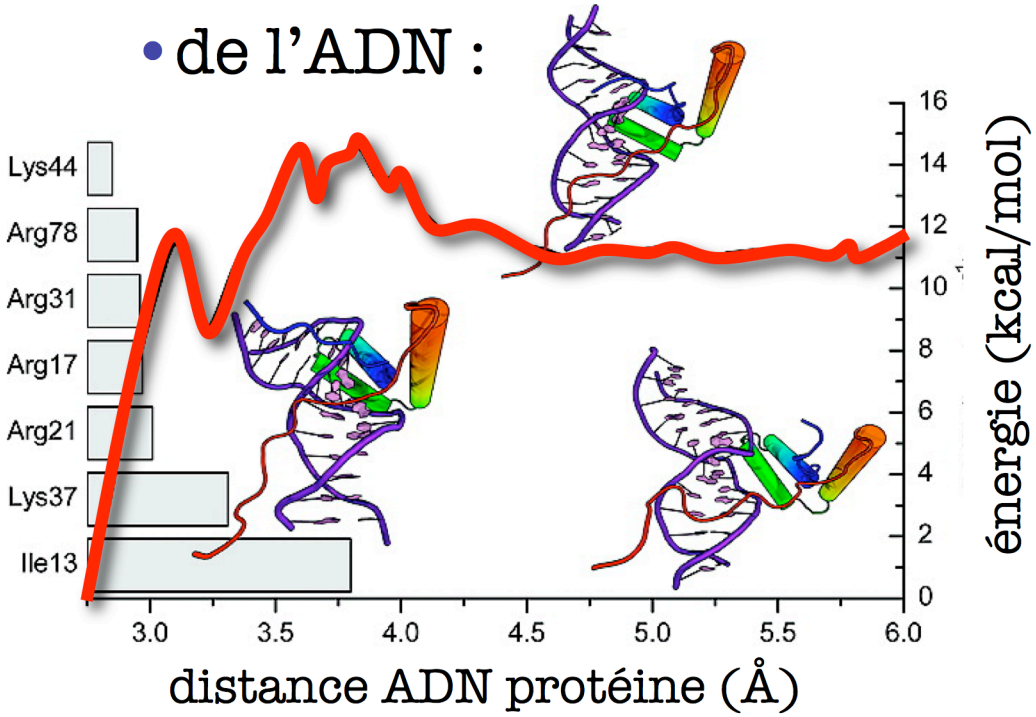
Bouvier Lavery JACS 2009

questions ouvertes

Q : autres degrés de liberté :

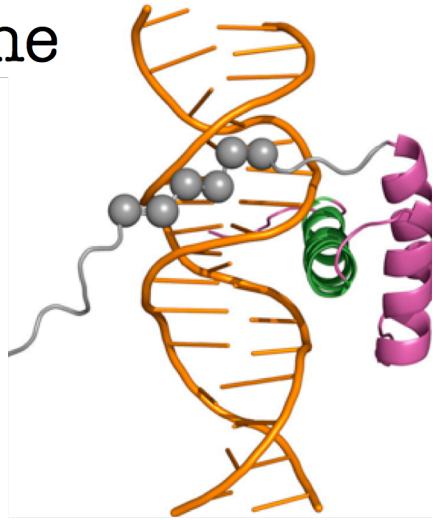
Q : **flexibilité** ?

- de l'ADN :



- de la protéine

  - queues flexibles



Y. Levy

- déformation « à distance »

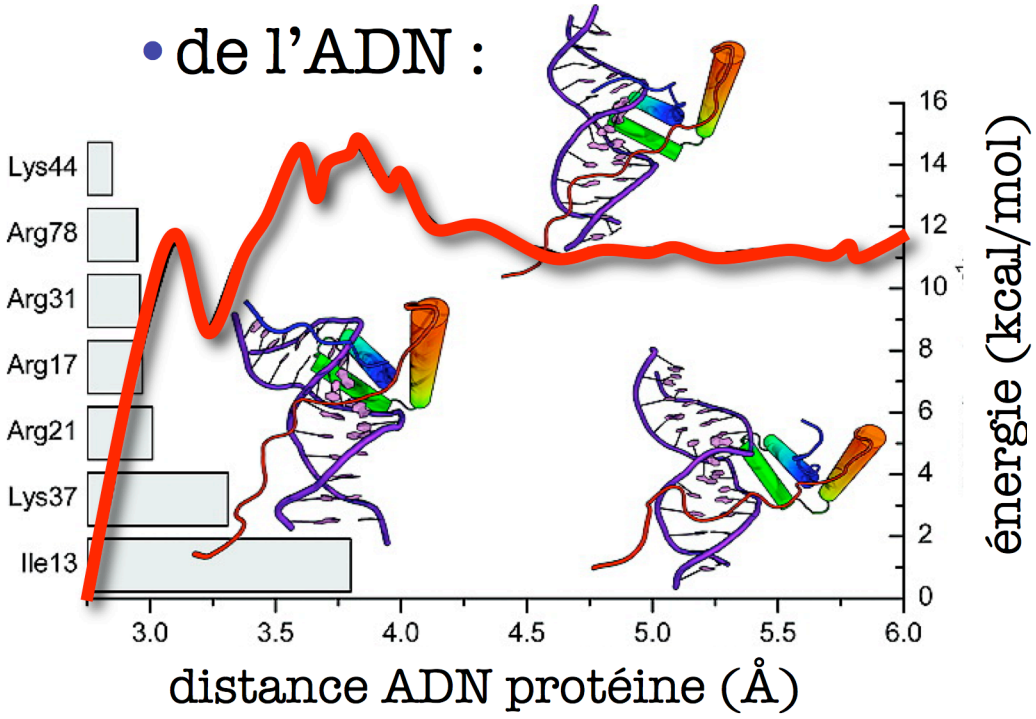
Bouvier Lavery JACS 2009

questions ouvertes

Q : autres degrés de liberté :

Q : **flexibilité** ?

- de l'ADN :

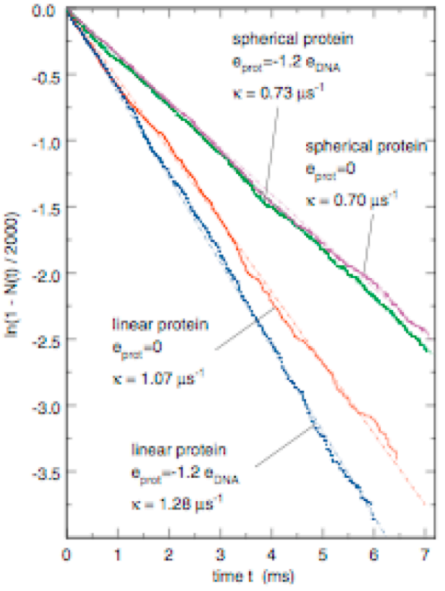


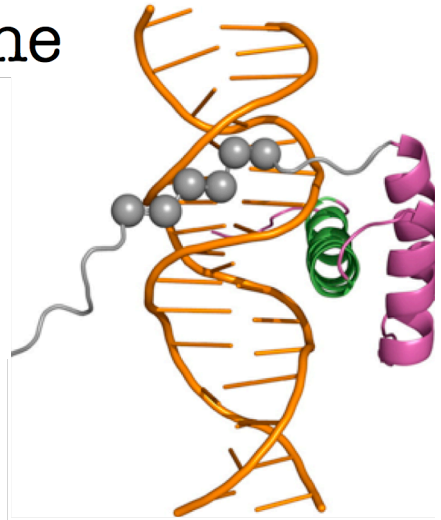
- déformation « à distance »

Bouvier Lavery JACS 2009

- de la protéine

- queues flexibles





Y. Levy

- dissipation d'énergie

Florescu Joyeux