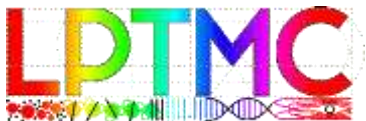


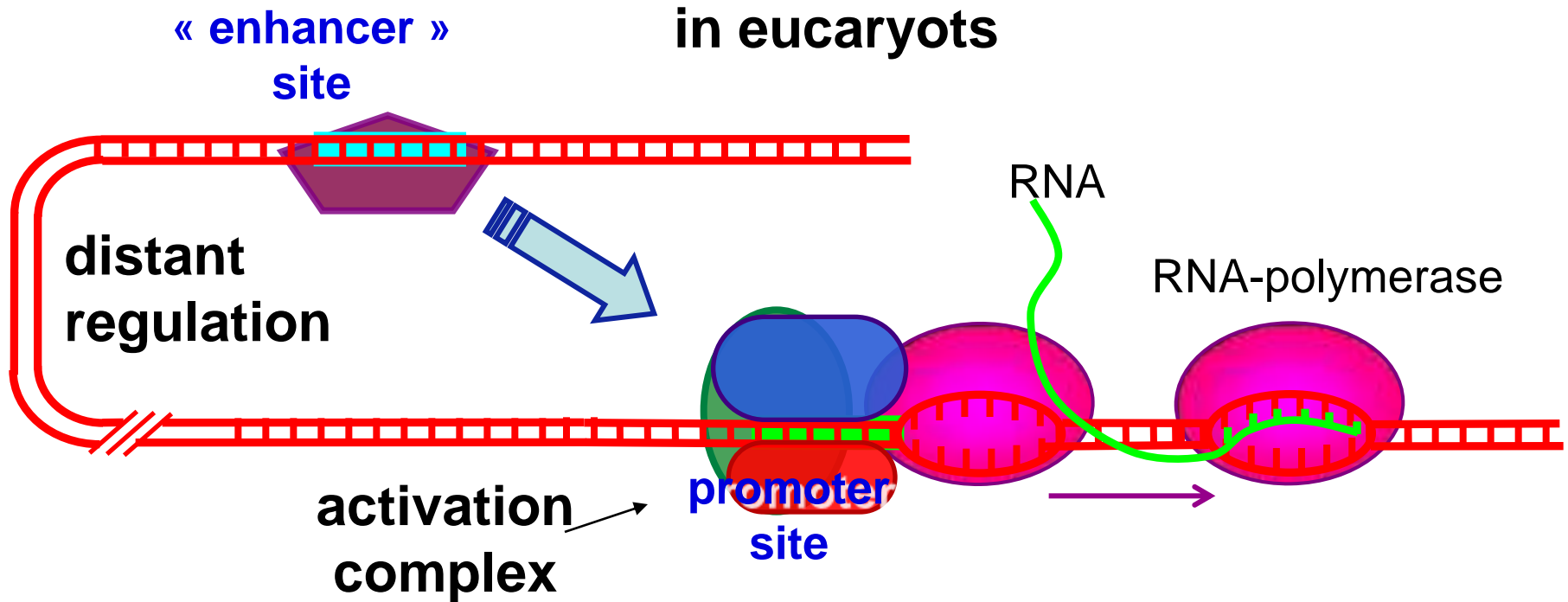
# Non-specific DNA-protein interaction: How proteins can diffuse along DNA

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

Marie Jardat, Vincent Dahirel  
PECSA, UPMC - Paris VI



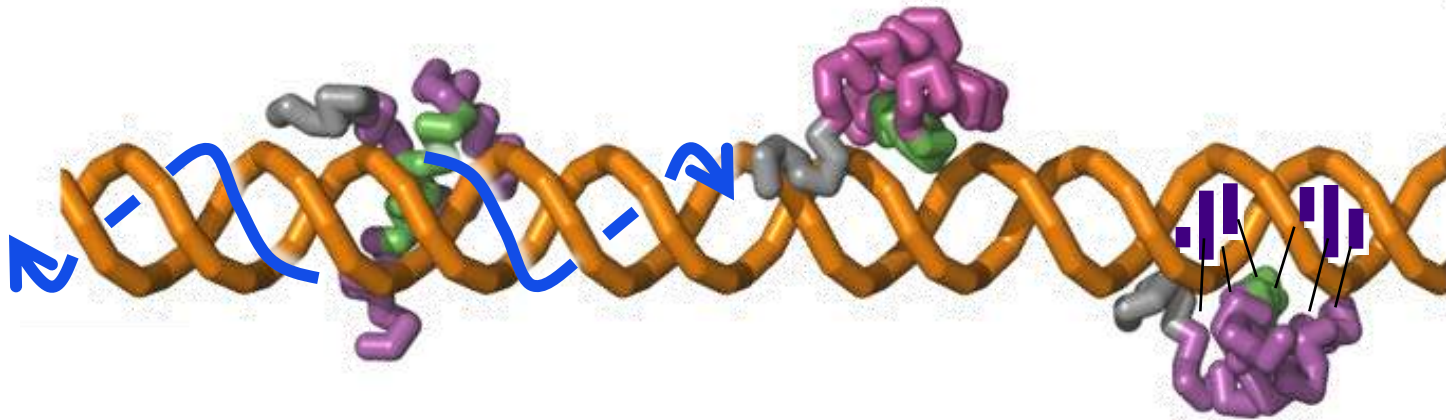
# transcription



transcription initiation and regulation:  
search of target sequences

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

# search of target sequences



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

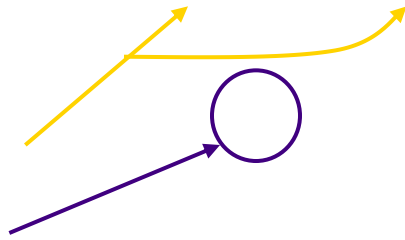
2. sequence reading  
interaction with bps

# protein 1D diffusion (sliding)

## experimental evidences (fluorescence microscopy)

the protein  
diffusion  
« movie »:

DNA extremities  
protein



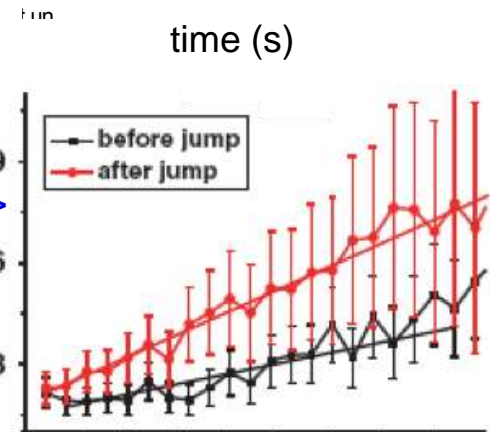
$X$  ( $\mu\text{m}$ )  
protein  
mouvement:

time  
↓

décc  
sont requis

diffusion  
(MSD):

$\langle X^2 \rangle$



QuickTime™ et un  
décompresseur TIFF (non compressé)  
sont requis pour visionner cette image.



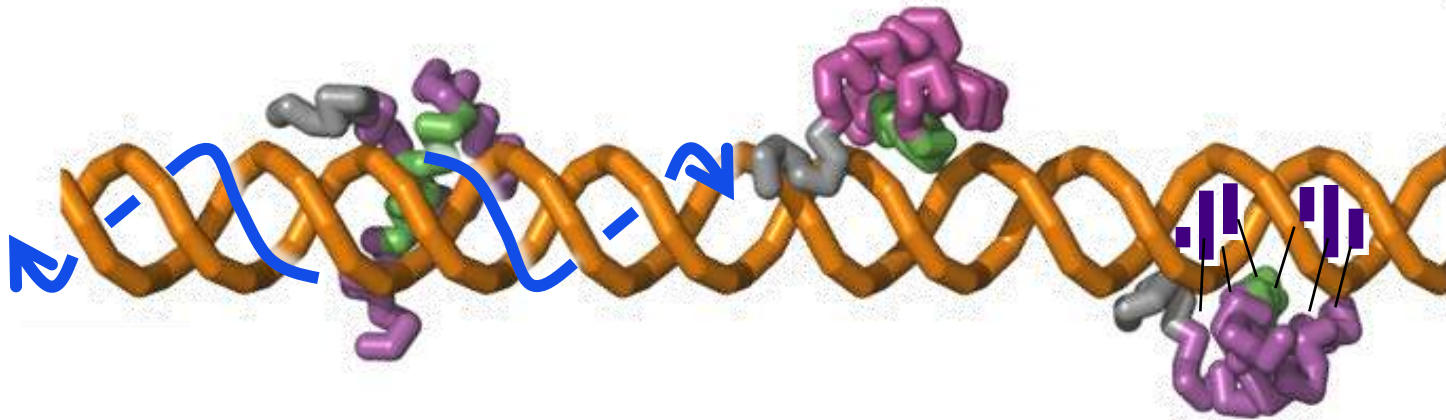
diffusion  
coefficient:

$$D_1 \approx 10^{-2} \mu\text{m}^2/\text{s}$$

$$\approx (300 \text{ pb})^2/\text{s}$$

Bonnet et al NAR 2008

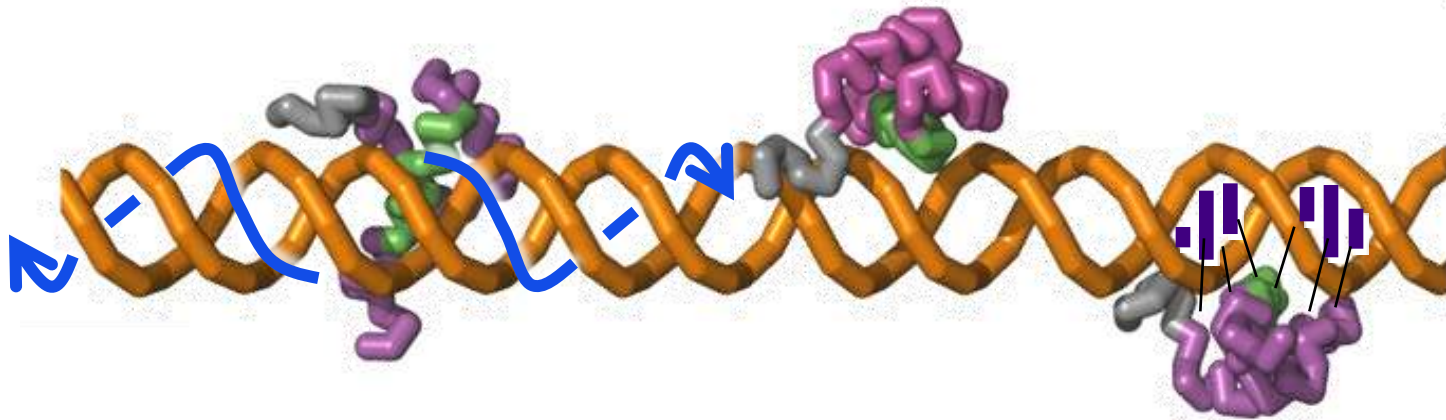
# search of target sequences



1. displacement along DNA  
1D diffusion (sliding)

2. sequence reading  
interaction with bps

# search of target sequences

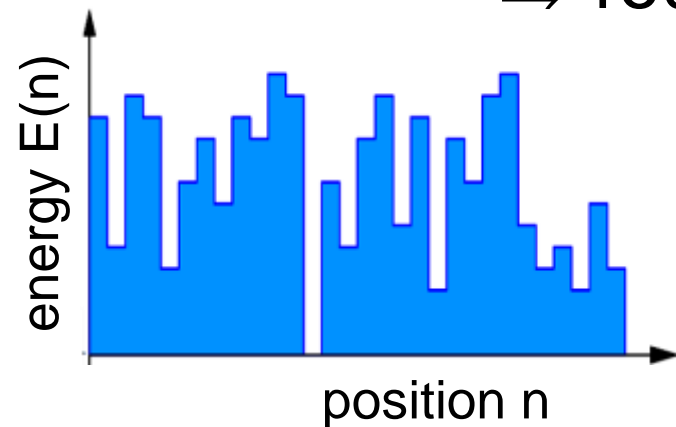


1. displacement along DNA  
1D diffusion (sliding)

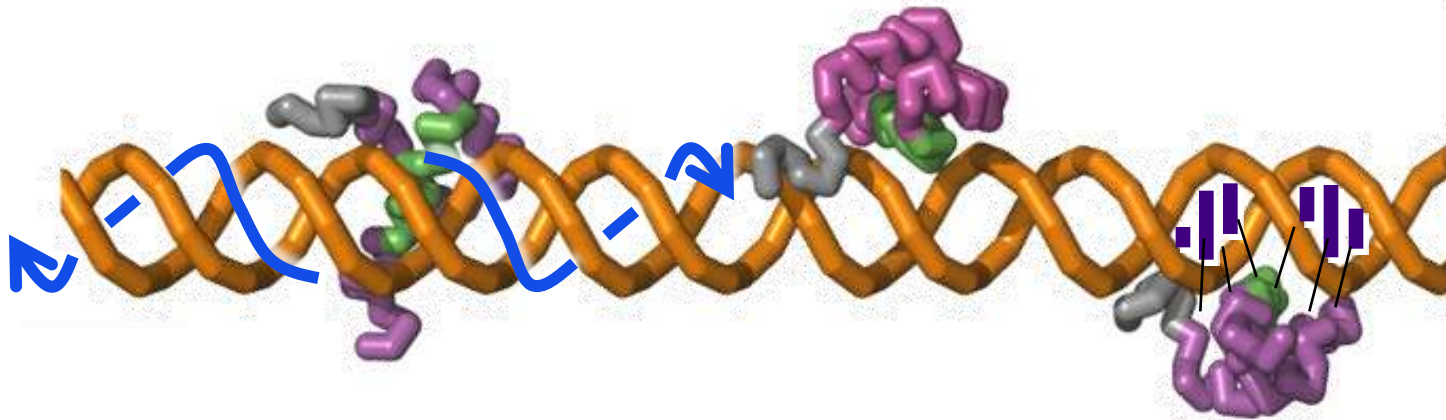
2. sequence reading  
interaction with bps

recognition  $\Rightarrow$  sequence dependent interaction

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



# search of target sequences

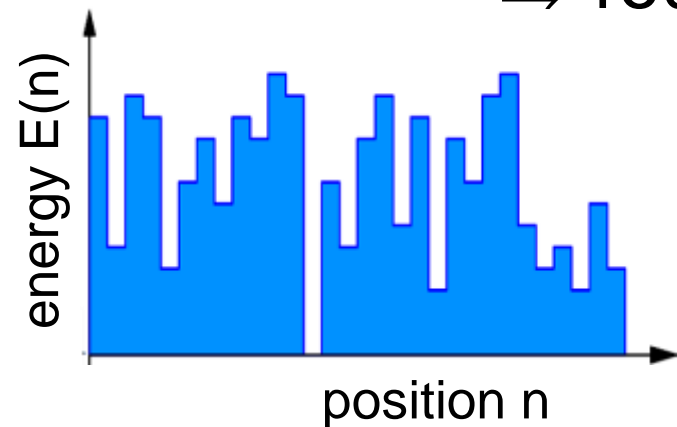


1. displacement along DNA  
1D diffusion (sliding)

2. sequence reading  
interaction with bps

recognition  $\Rightarrow$  sequence dependent interaction

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



trapping, reduced mobility

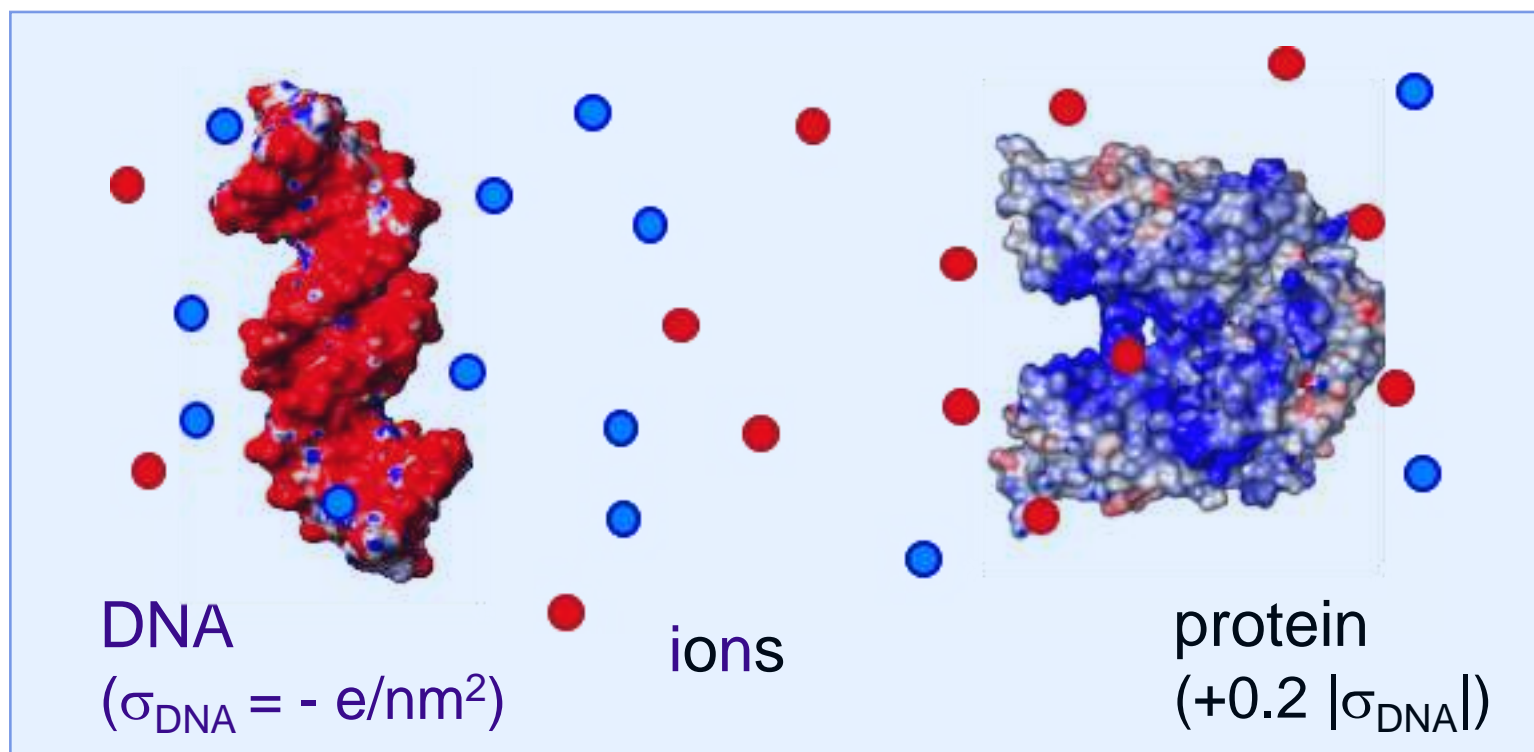
$\rightarrow$  **mobility-specificity paradox**



# physics of the protein-DNA interaction

## electrostatics in solution

[Mol Phys 09, PRL 09, PCCP 11]



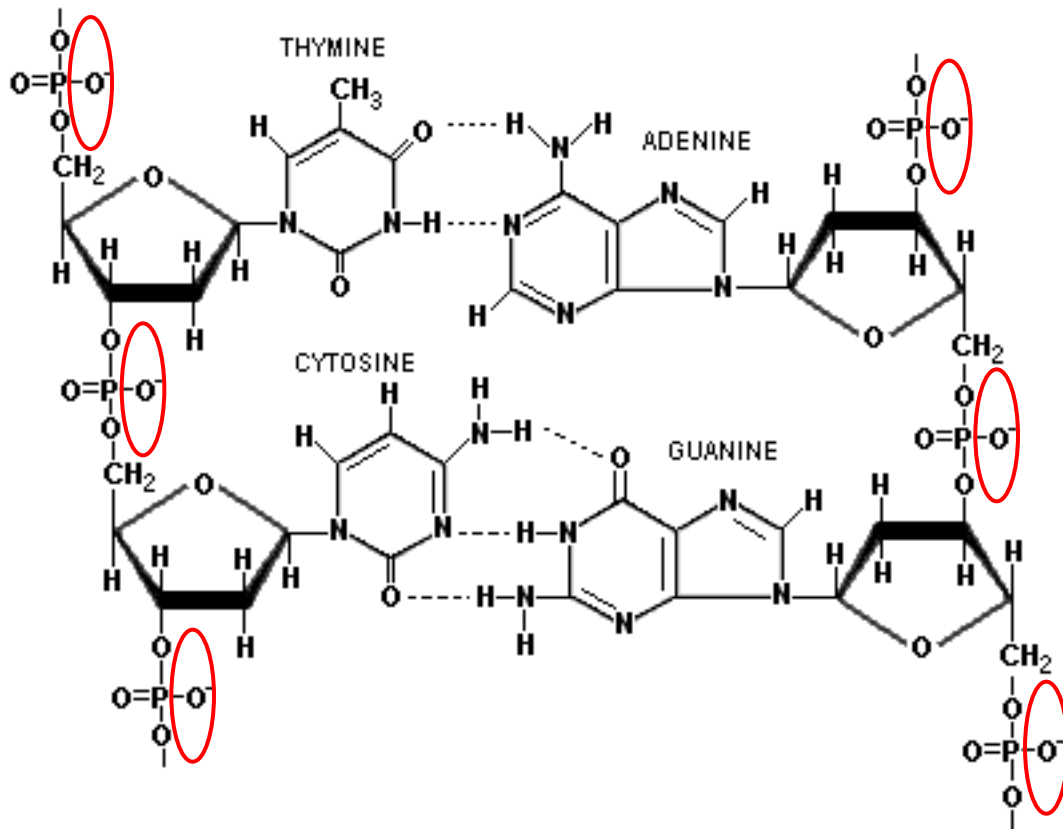
analytical approach: Poisson-Boltzmann (F. Paillusson PhD)

**MC simulations: Marie Jardat et Vincent Dahirel PECSA-  
LJBM**

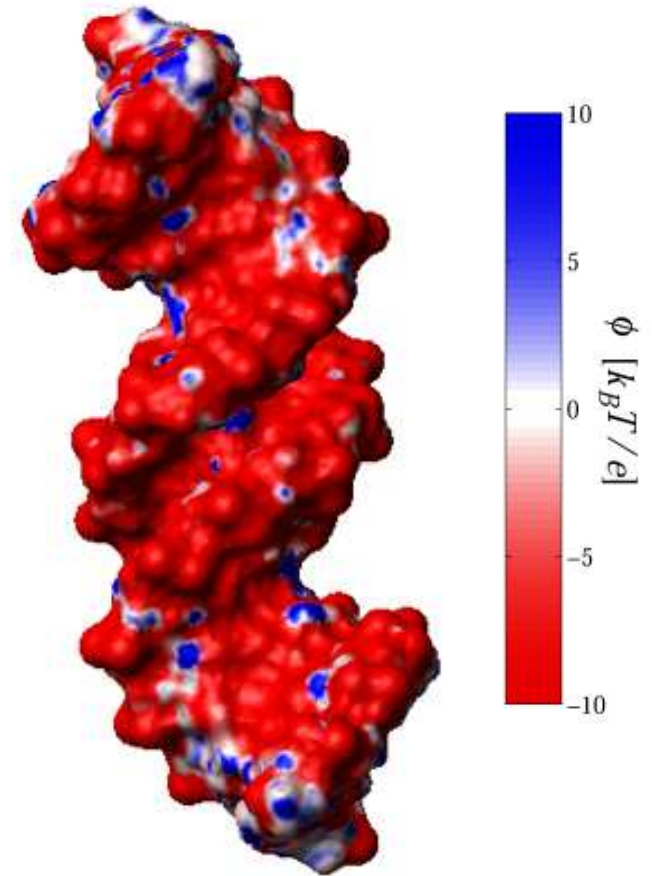


# DNA is a polyelectrolyte

surface electrostatic potential

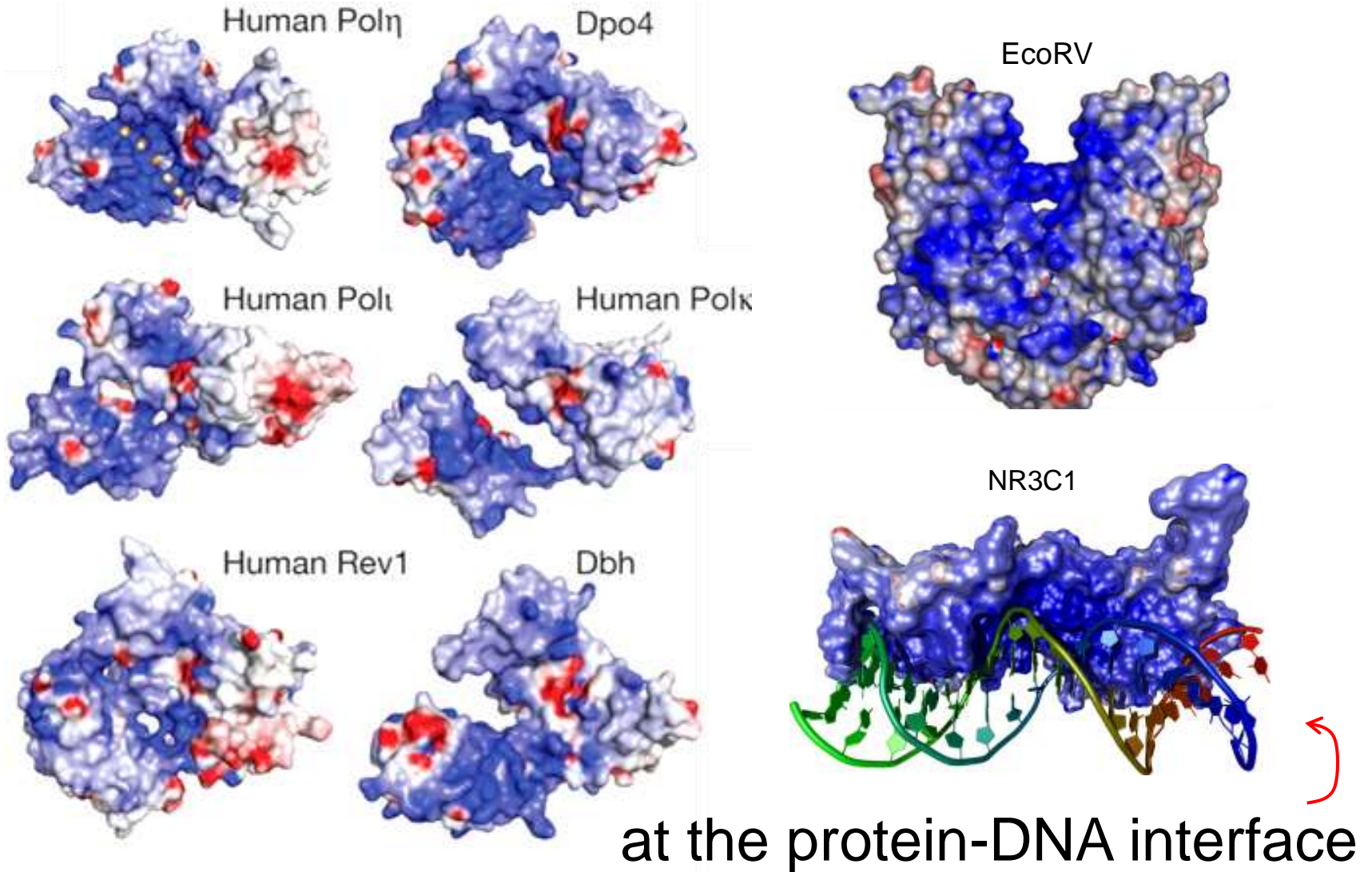


**charge  $-2e/\text{pb}$**



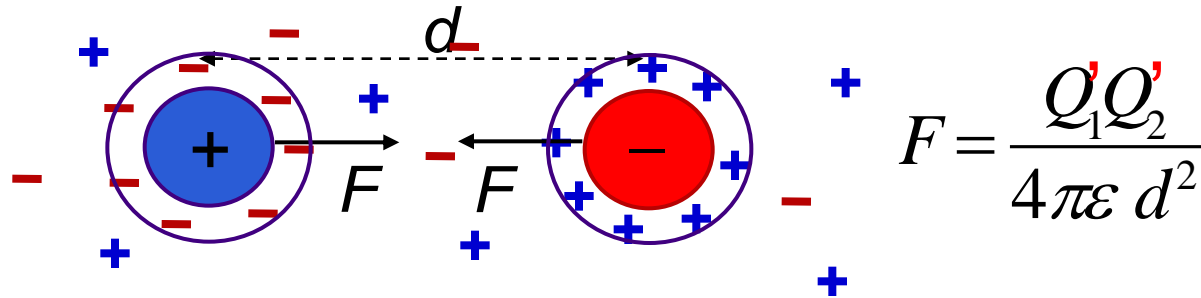
# DNA-binding proteins

positively charged

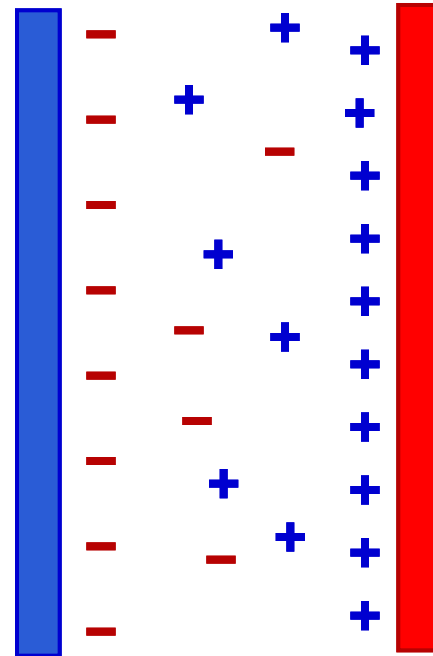


# oppositely charged bodies in solution

2 charges in a solution: screened attraction (Debye)

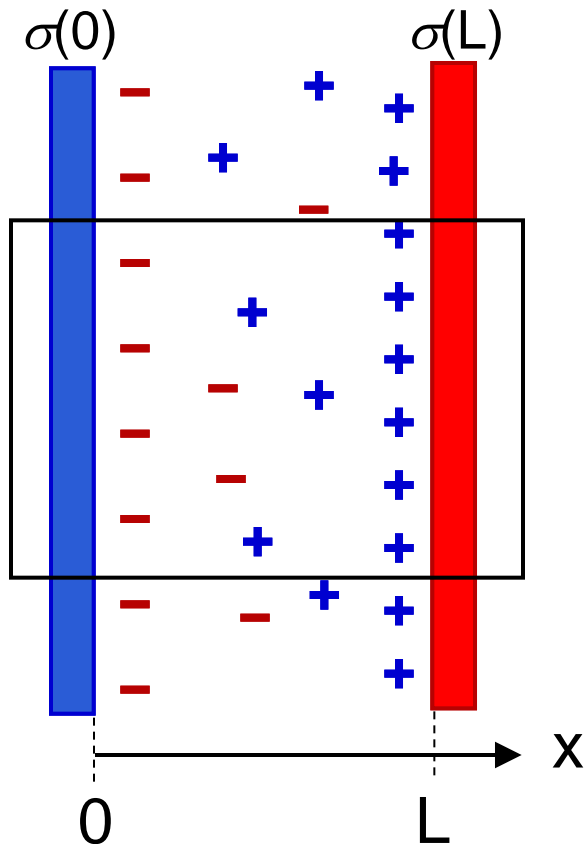


...what about two facing surfaces ?



# oppositely charged bodies in solution

Poisson-Boltzmann equation (1D) :



1. electrostatics potential  $V(x)$ :

**Poisson equation**

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

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

with B.C.:

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

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

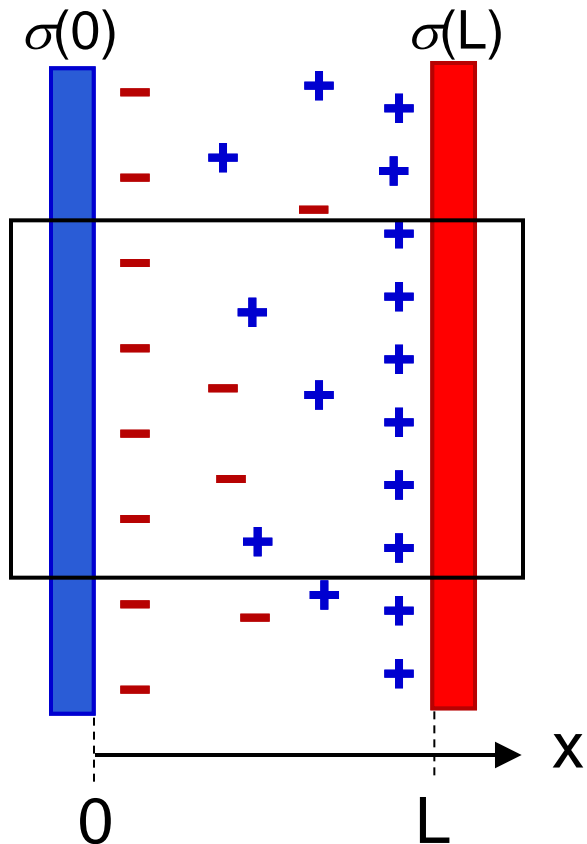
Poisson-Boltzmann equation (1D) :

⇒ in monovalent salt (concentration  $c^0$ )

$$\frac{dV(x)}{dx} = \frac{c^0}{\epsilon} \sinh(\beta q_i V(x))$$

with B.C.:

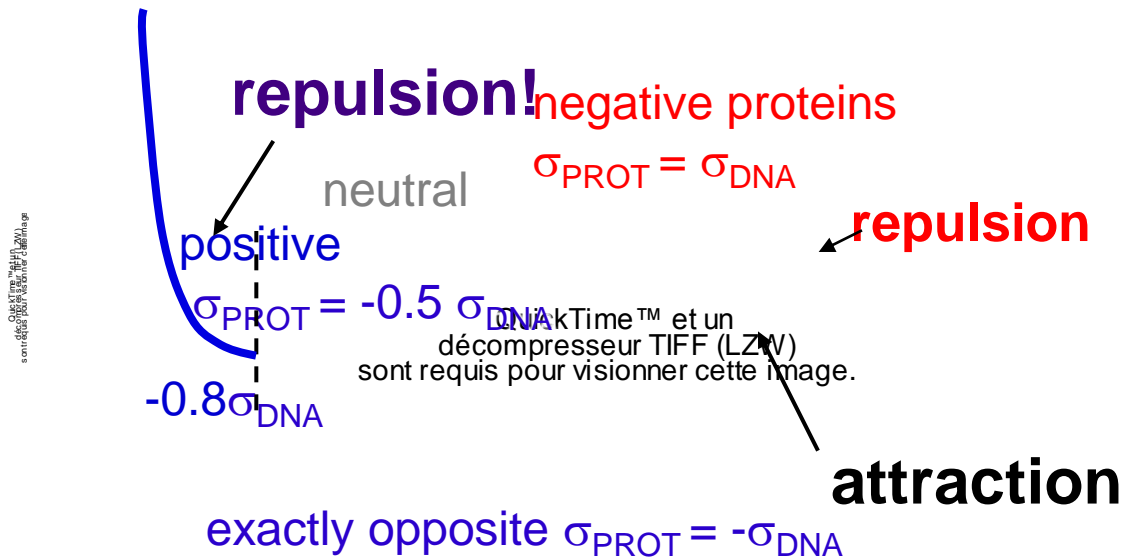
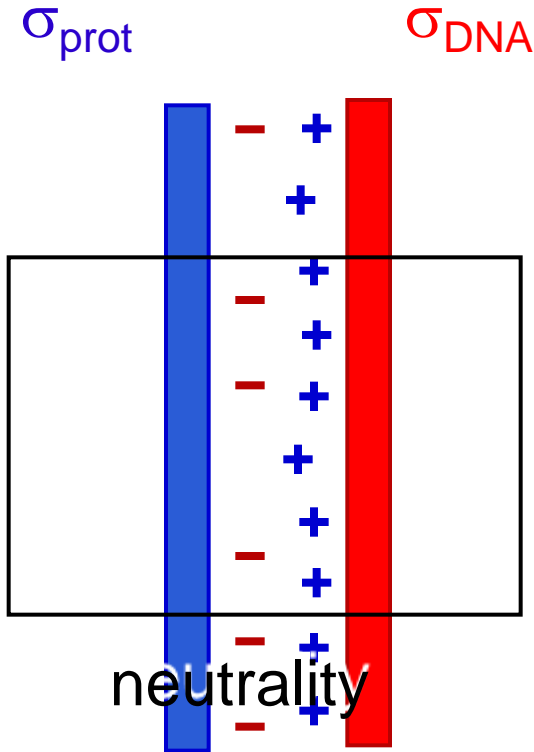
$$\begin{cases} \frac{dV}{dx}(0) = -\frac{\sigma(0)}{\epsilon} \\ \frac{dV}{dx}(L) = +\frac{\sigma(L)}{\epsilon} \end{cases}$$



→ numerical integration → pressure → interaction energy

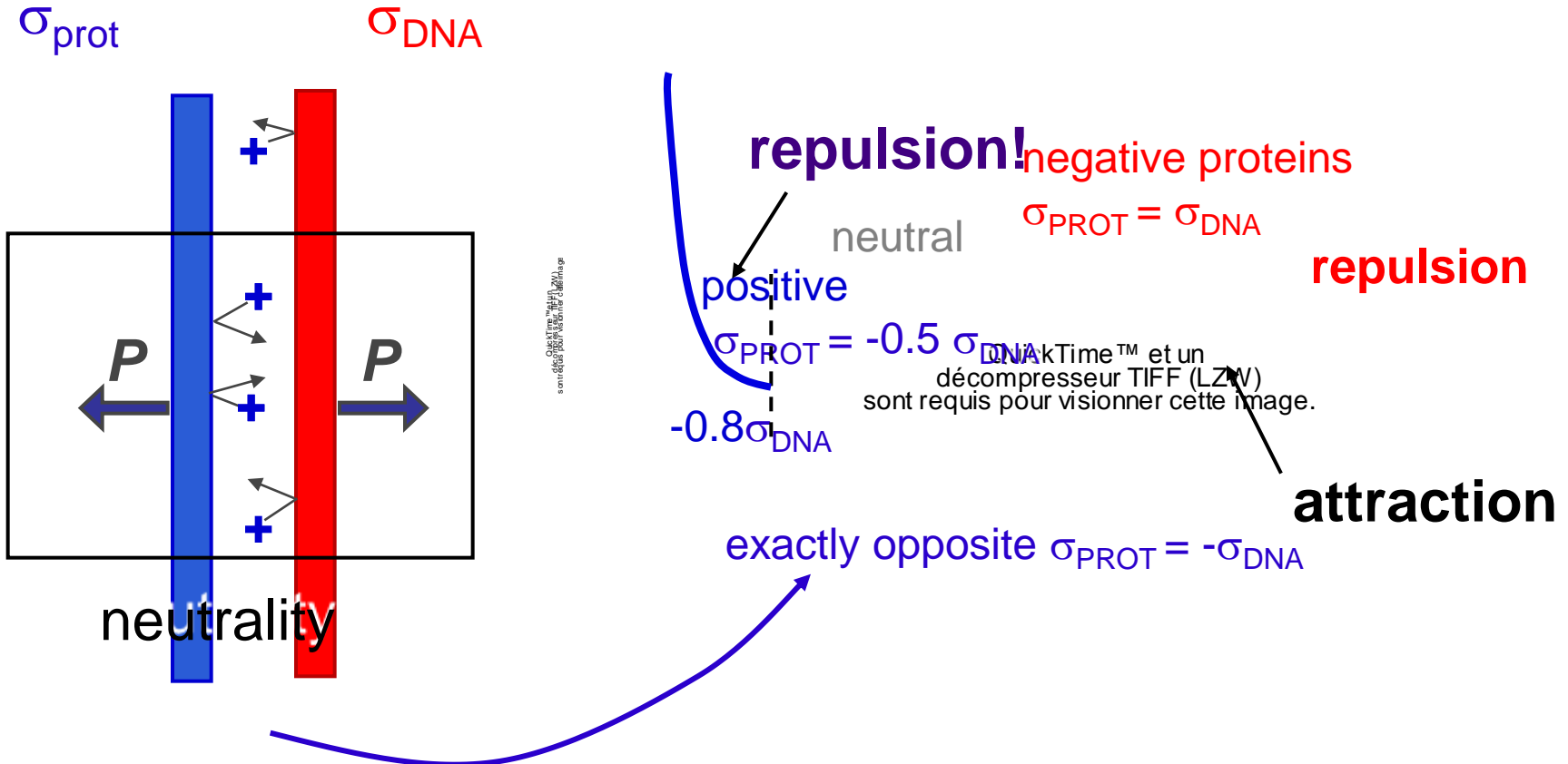
# oppositely charged bodies in solution

**Poisson-Boltzmann** equation (1D) :  
monovalent salt (+1/-1), numerical integration



# oppositely charged bodies in solution

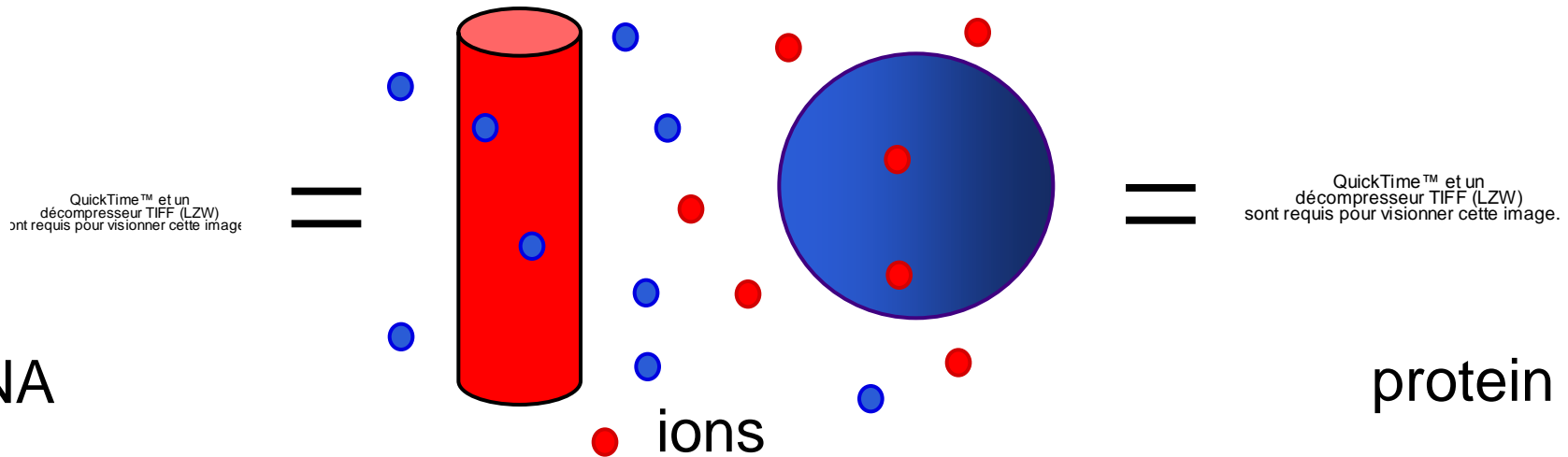
**Poisson-Boltzmann** equation (1D) :  
monovalent salt (+1/-1), numerical integration





# what about the DNA-protein system?

➡ Monte Carlo simulations



DNA

protein

ions

$E (k_B T)$

MC

**always attractive !**

QuickTime™ et un décompresseur TIFF (non compressé) sont requis pour visionner cette image.


PB + Derjaguin

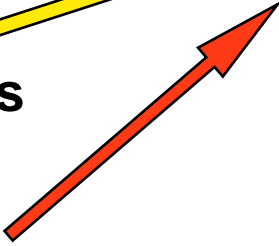
$L (nm)$

curvature effects can be accounted for by Derjaguin approximation.

**the protein shape matters!!**

# protein shape

**contacts  
with bases** 

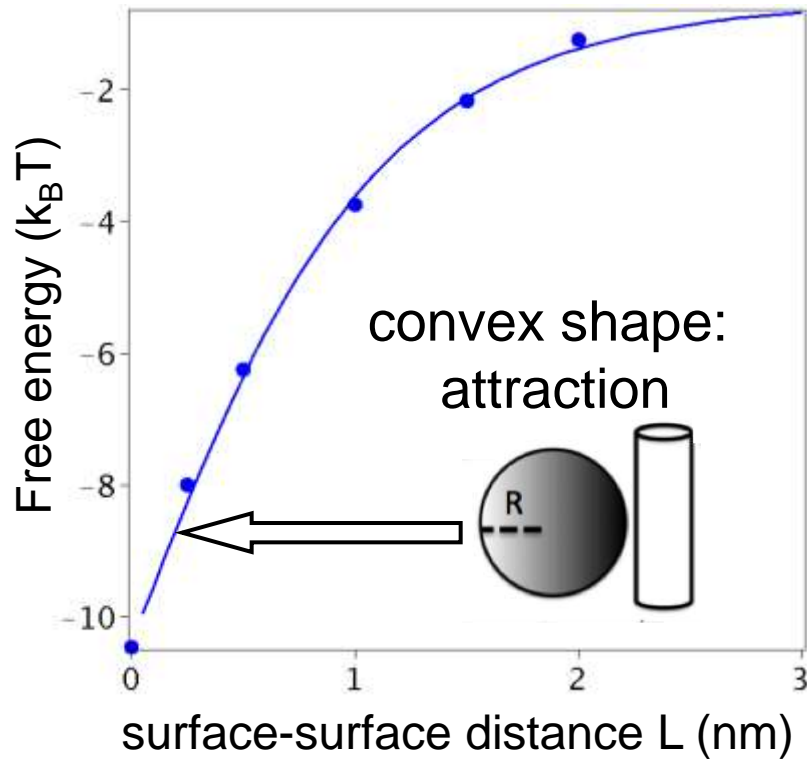
**contacts  
with  
backbone** 

QuickTime™ et un  
décompresseur TIFF (non compressé)  
sont requis pour visionner cette image.

« enveloping »  
  
proteins

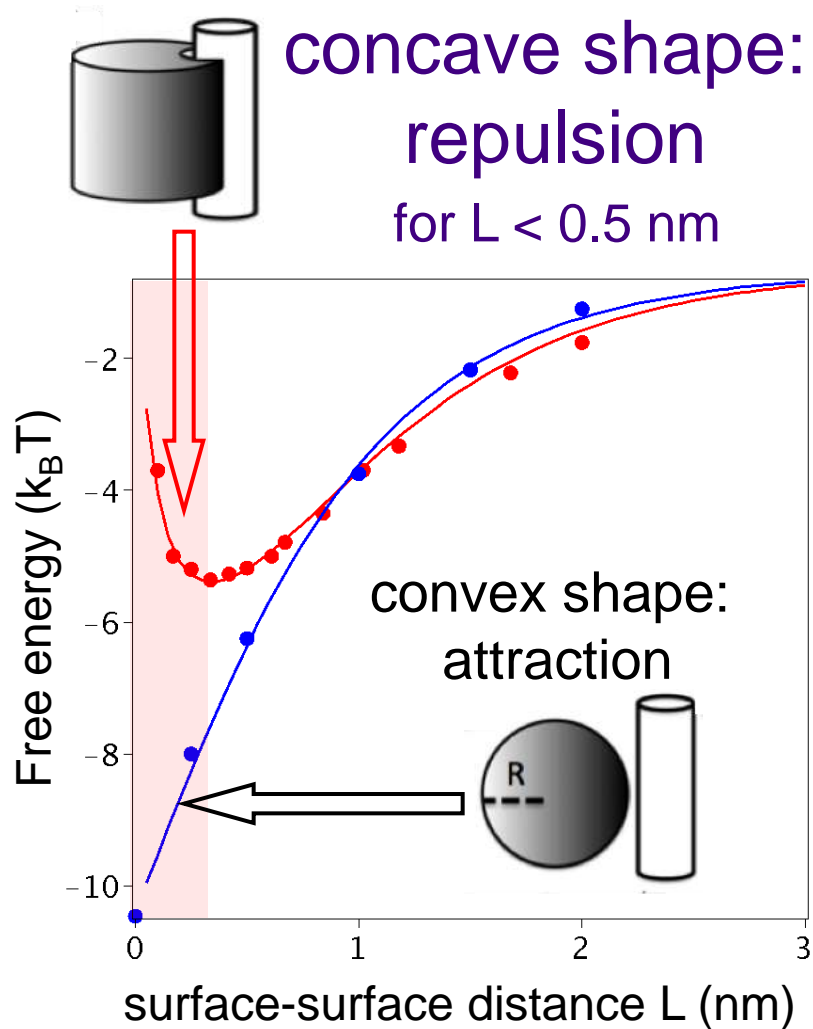
# protein shape

## MC simulations



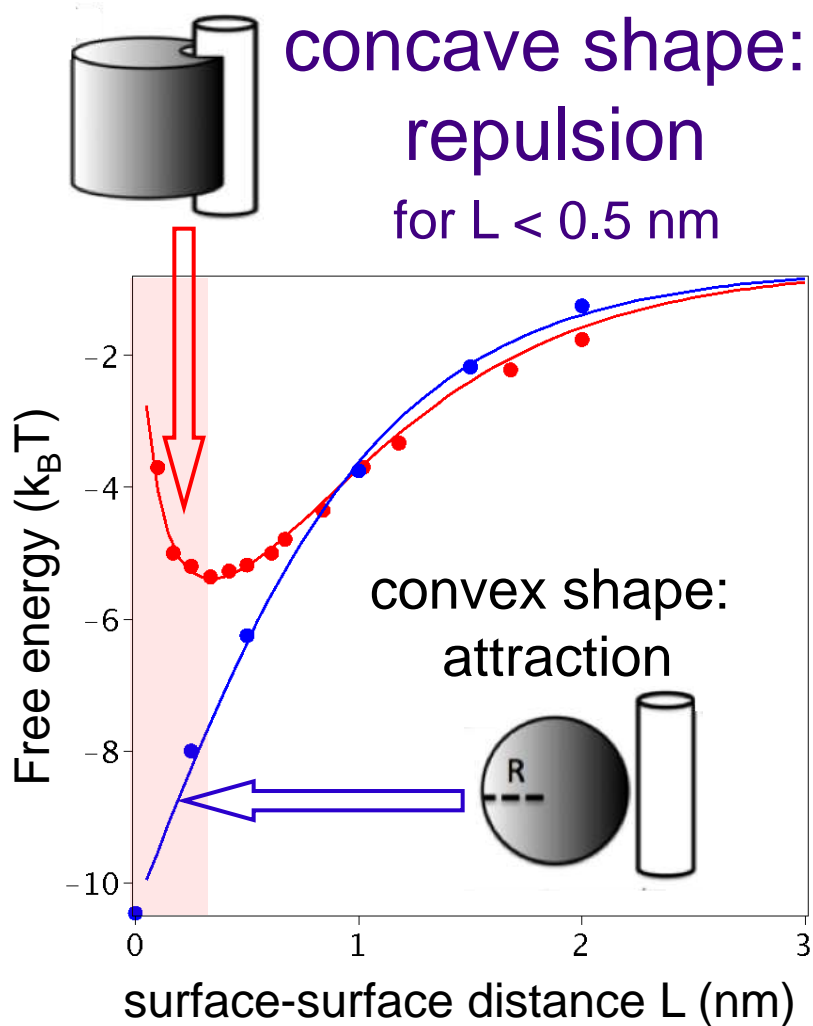
# protein shape

MC simulations

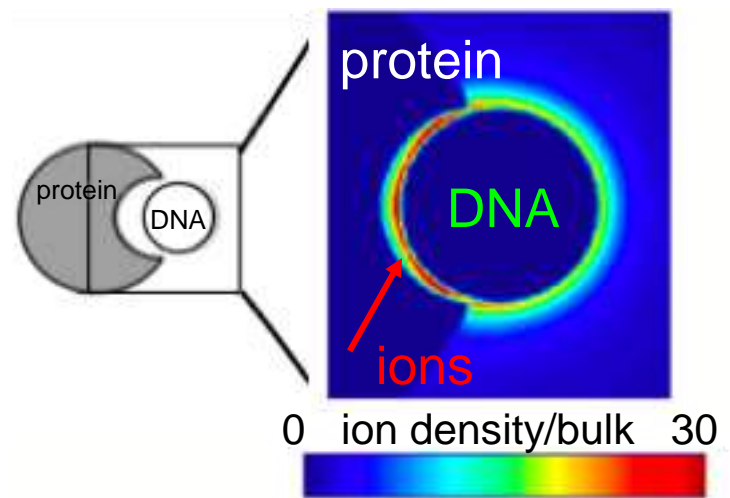


# protein shape

MC simulations



- osmotic origin : trapped ions



# protein shape

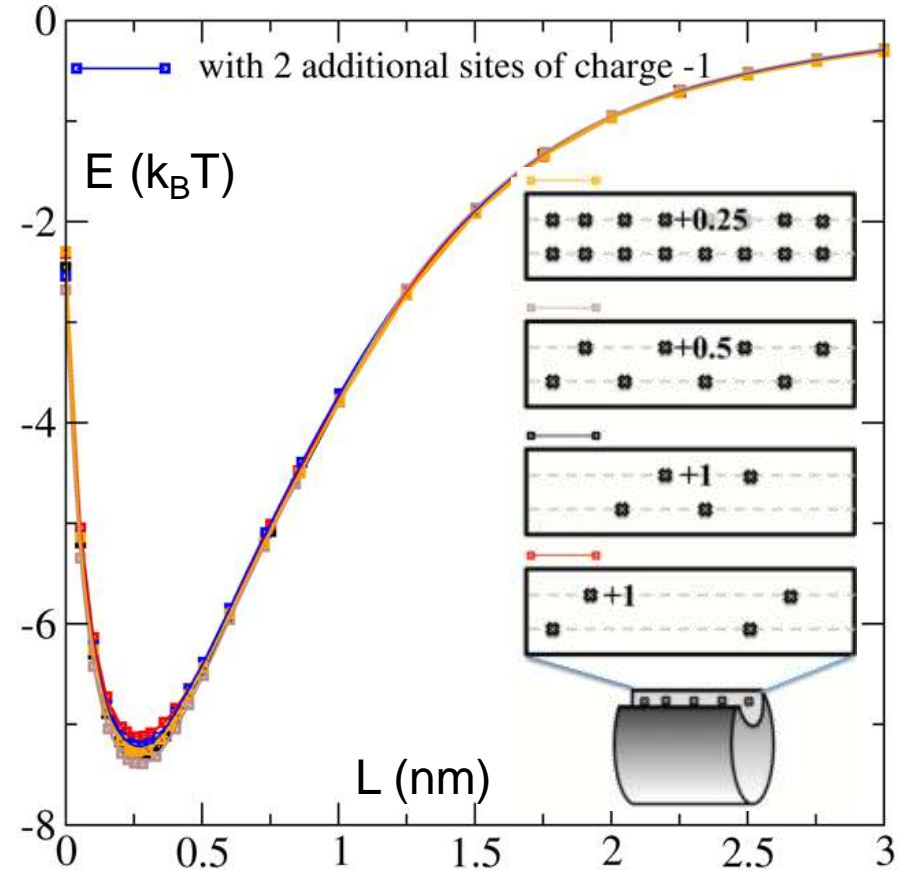
other concave shapes

different charge distributions

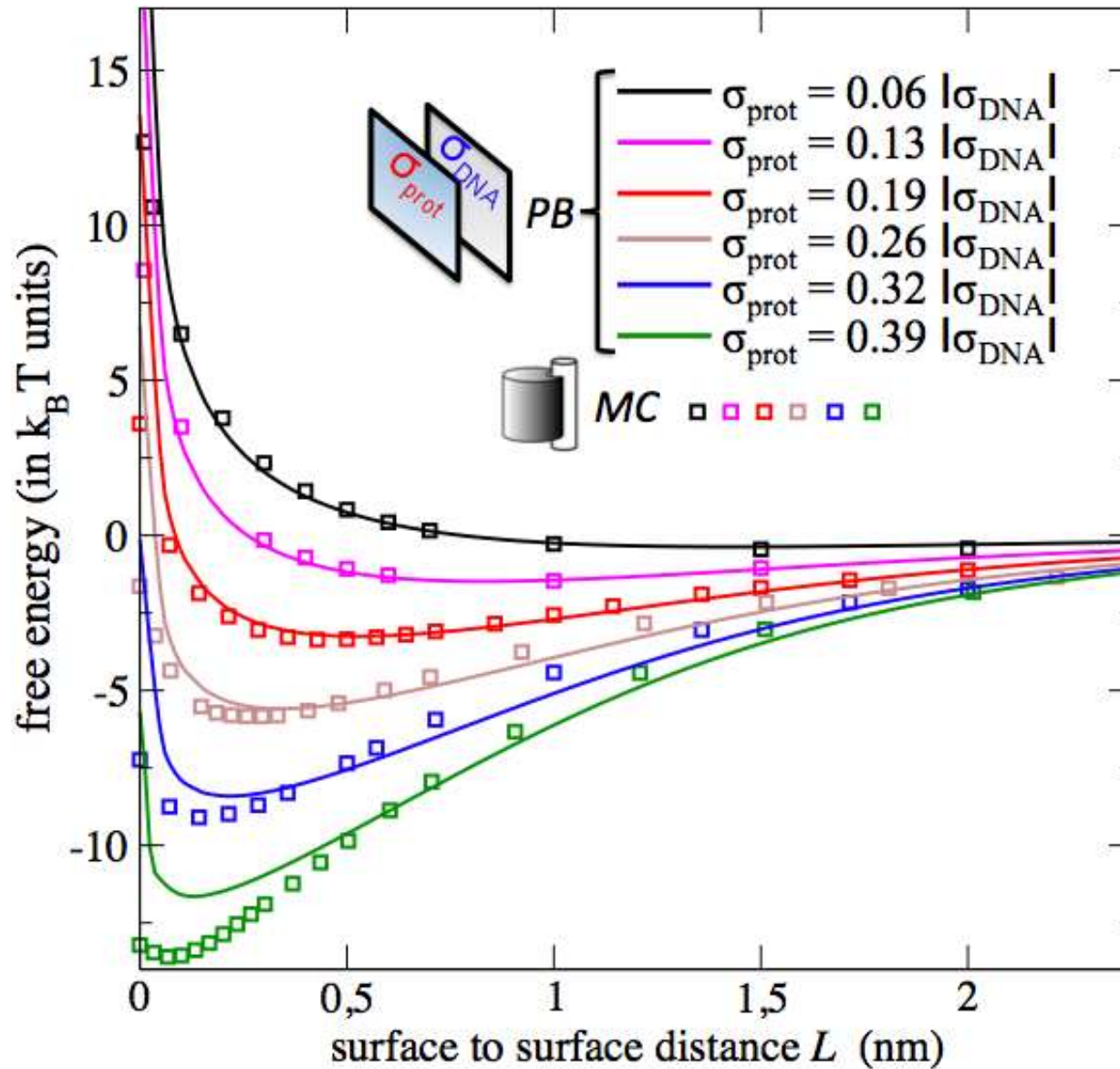
$E (k_B T)$

QuickTir  
décompresse  
sont requis pour visi

$L (nm)$



# role of the protein charge



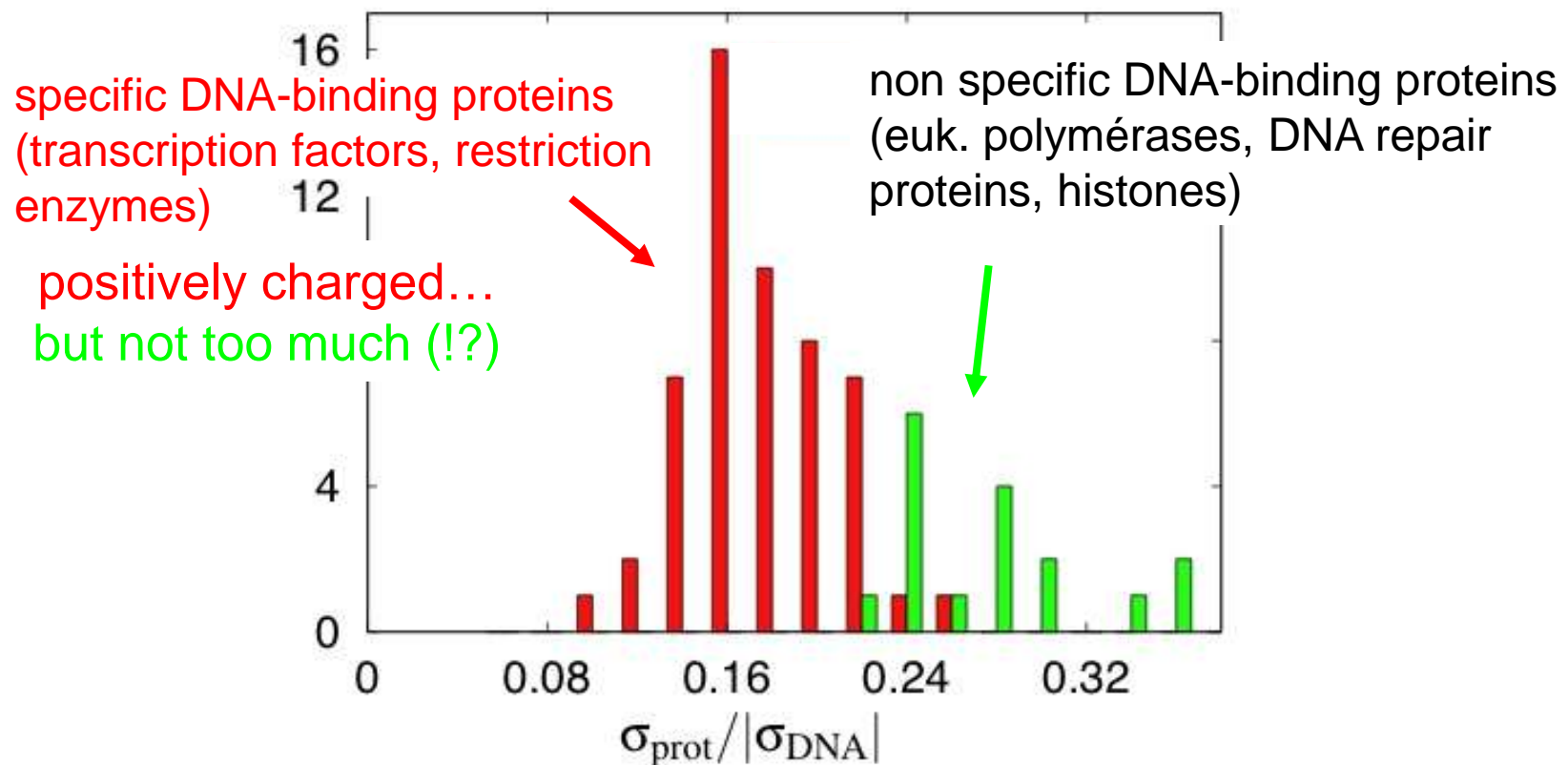


# DNA-binding proteins

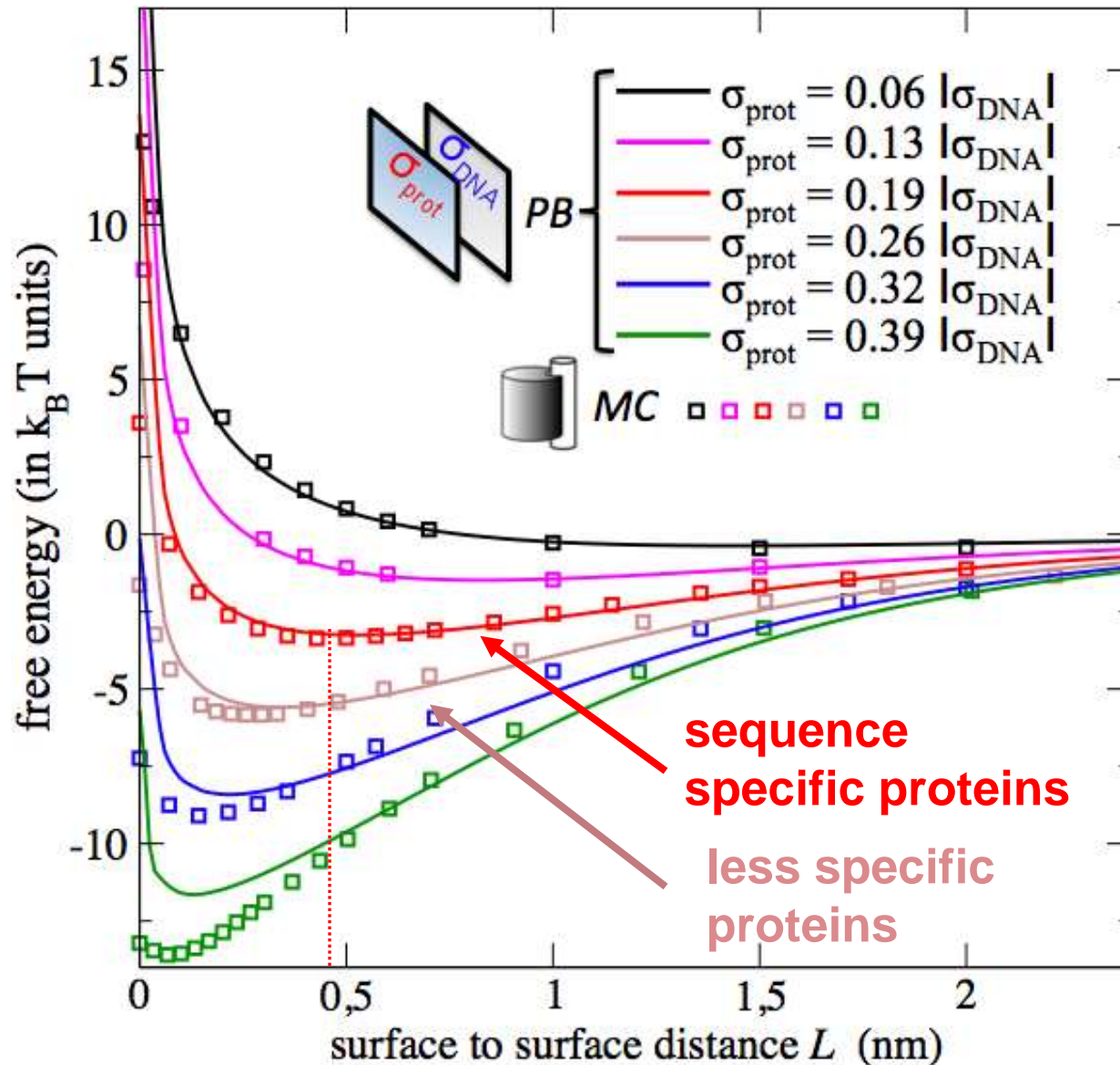
estimation of the charge surface density over 77 proteins

starting from structural data in [Jones et al J Mol Biol 1999](#)

## charge surface density at the protein-DNA interface

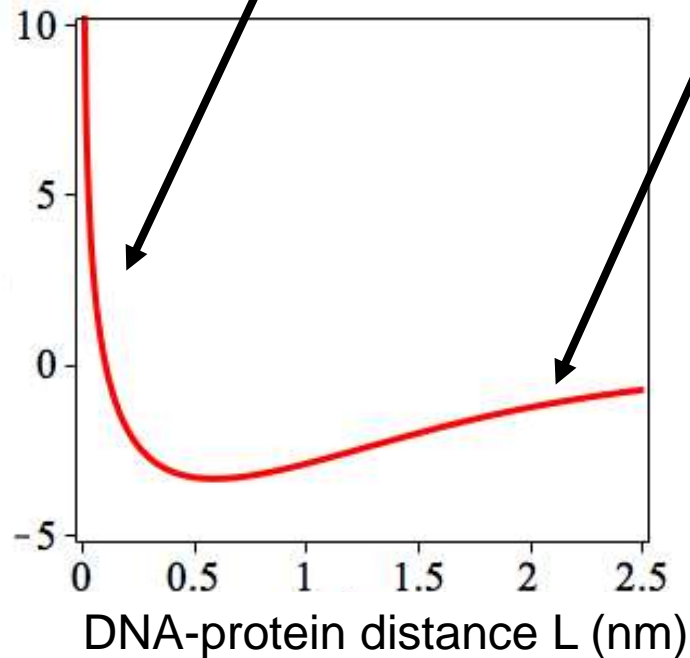


# role of the protein charge



# implications on sliding

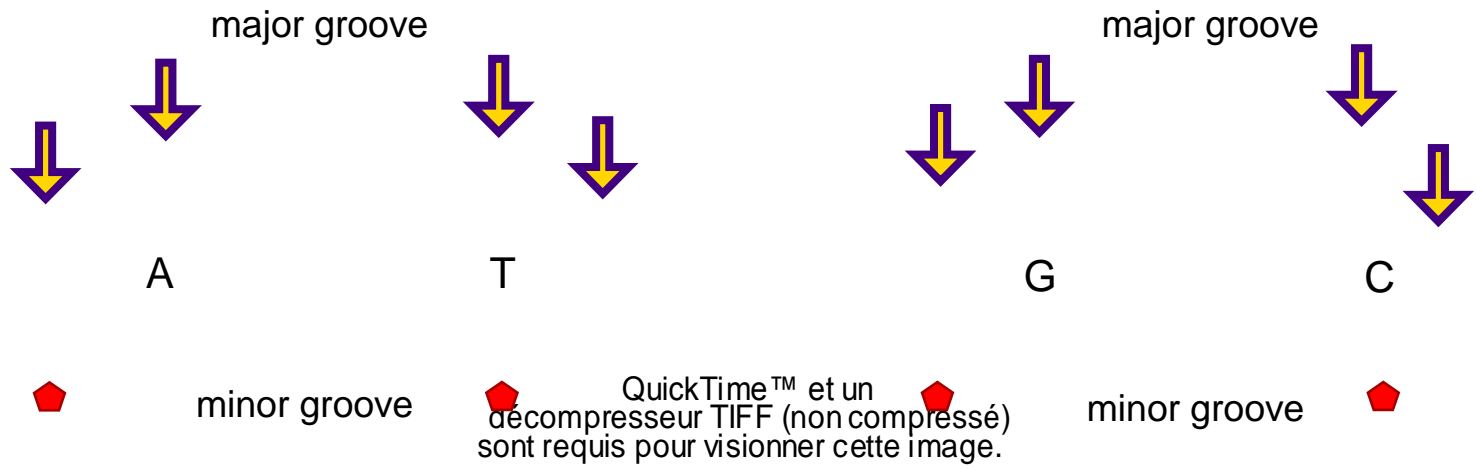
**osmotic repulsion + electrostatics**



**+ base-sensitive interaction  
(hydrogen bonds...)**

# recognition

direct interaction:  
hydrogen bonding to the bps sides



# implications on sliding

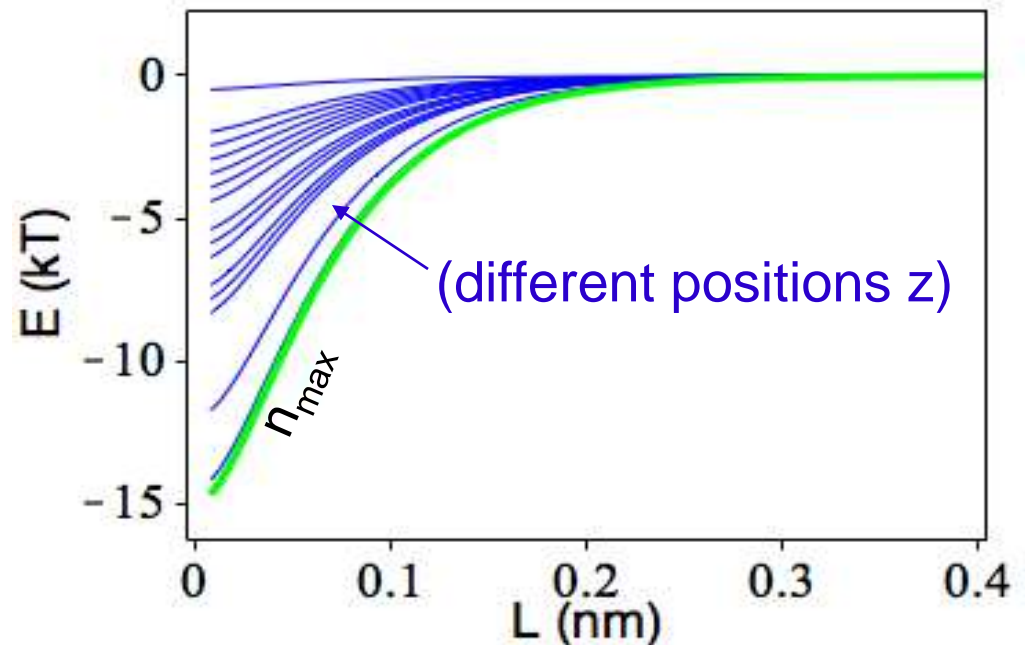
## base-sensitive interaction (hydrogen bonds)

- number  $n$  of H-bonds dependent on the position  $z$  along DNA

- single H-bond = Morse potential 
$$e_H(L) = \varepsilon \left[ \left( 1 - e^{-gL} \right) - 1 \right]$$
$$\varepsilon = 0.5 k_B T \quad g = 2 \quad (L_0 = 0)$$

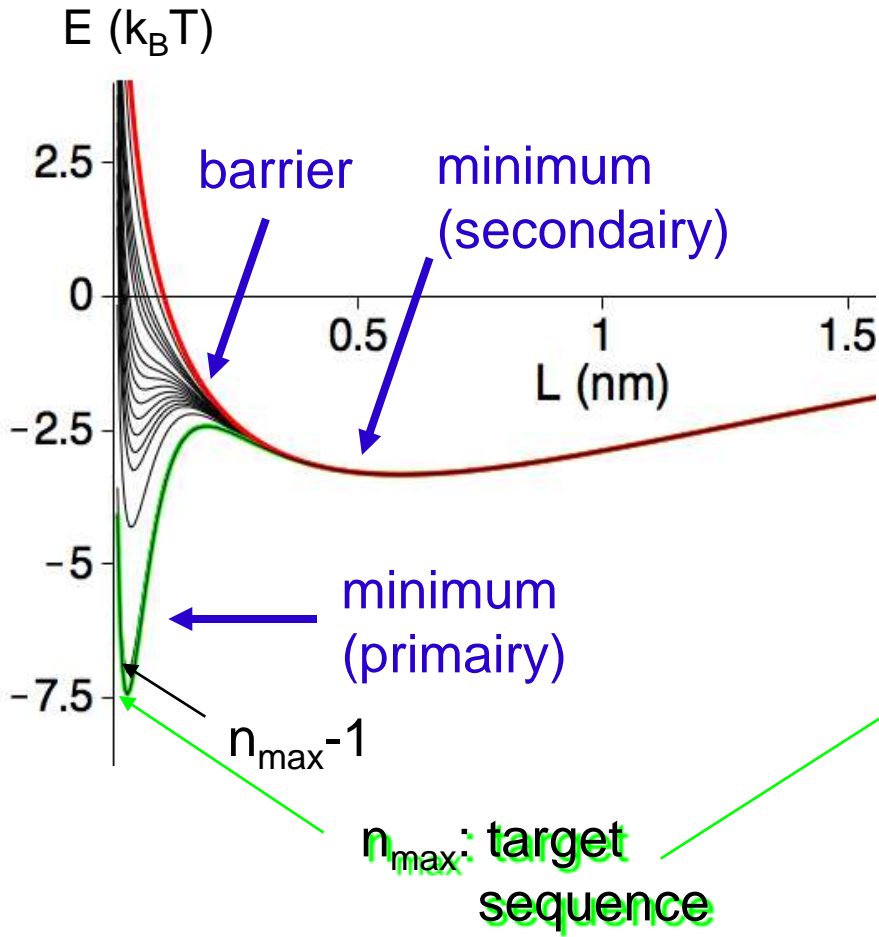
- $\Rightarrow$  sequence dependent energy profile

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

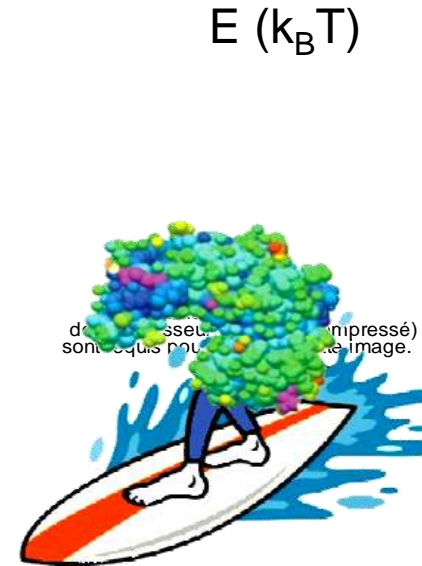


# implications on sliding

electrostatics + hydrogen bonds



30 bp



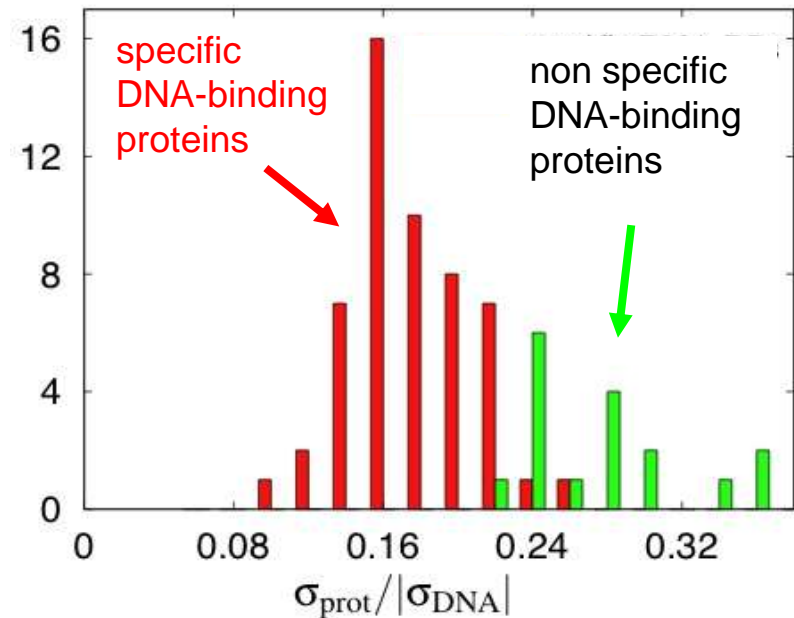
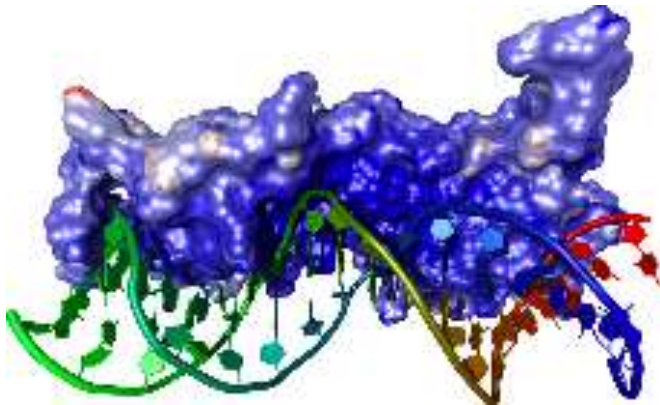
« facilitated sliding »!!

# 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)

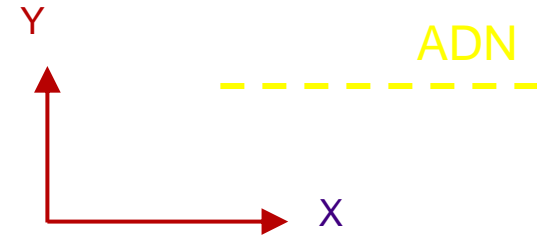
→ different protein classes for different functions?





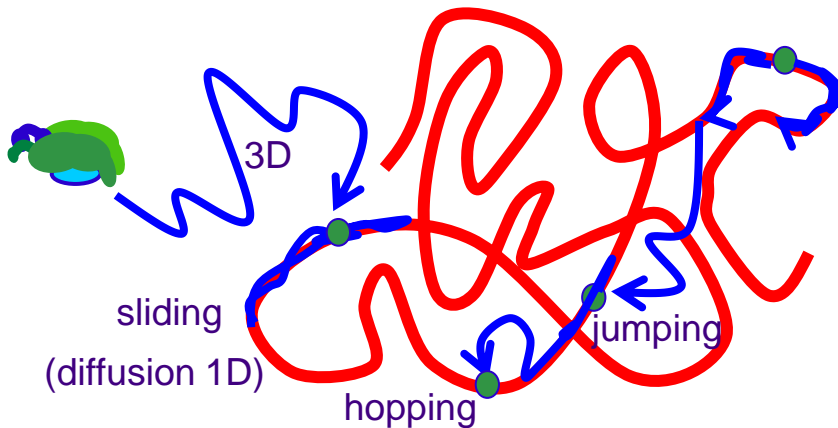
# perspectives 2

## 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 ?



QuickTime™ et un  
décompresseur TIFF (non compressé)  
sont requis pour visionner cette image.

# M3V group

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

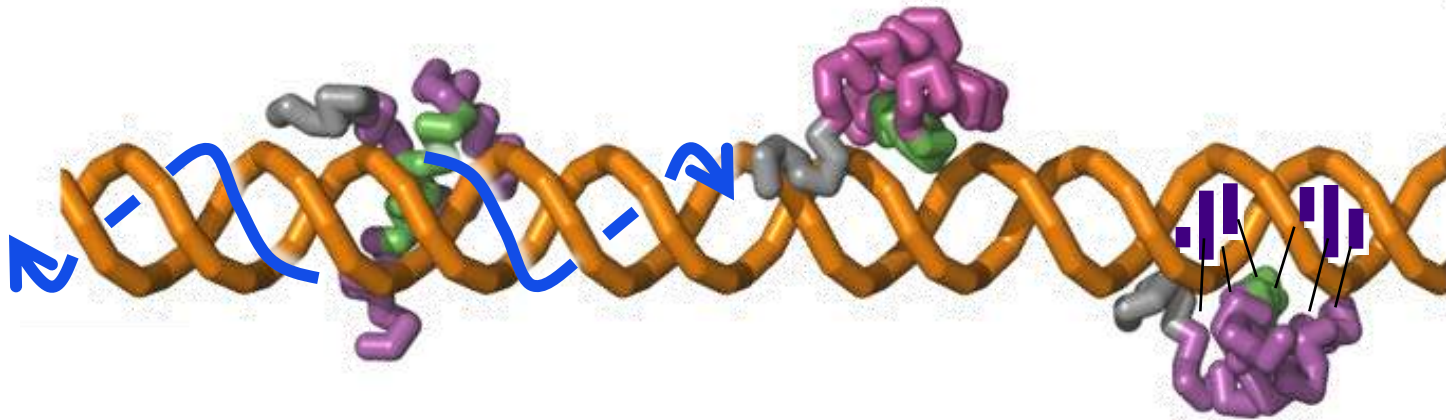
Laboratoire de Physique Théorique de la Matière Condensée  
Université Pierre et Marie Curie - Paris VI

Fabien PAILLUSSON

Jean-Marc VICTOR

Maria BARBI

# 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)

residence time      diffusion coefficient

QuickTime™ et un décompresseur TIFF (LZW) sont requis pour visionner cette image.

Bonnet et al NAR 2008

(w) □  
<2>x>

high pH

QuickTime™ et un décompresseur TIFF (LZW) sont requis pour visionner cette image.

low pH

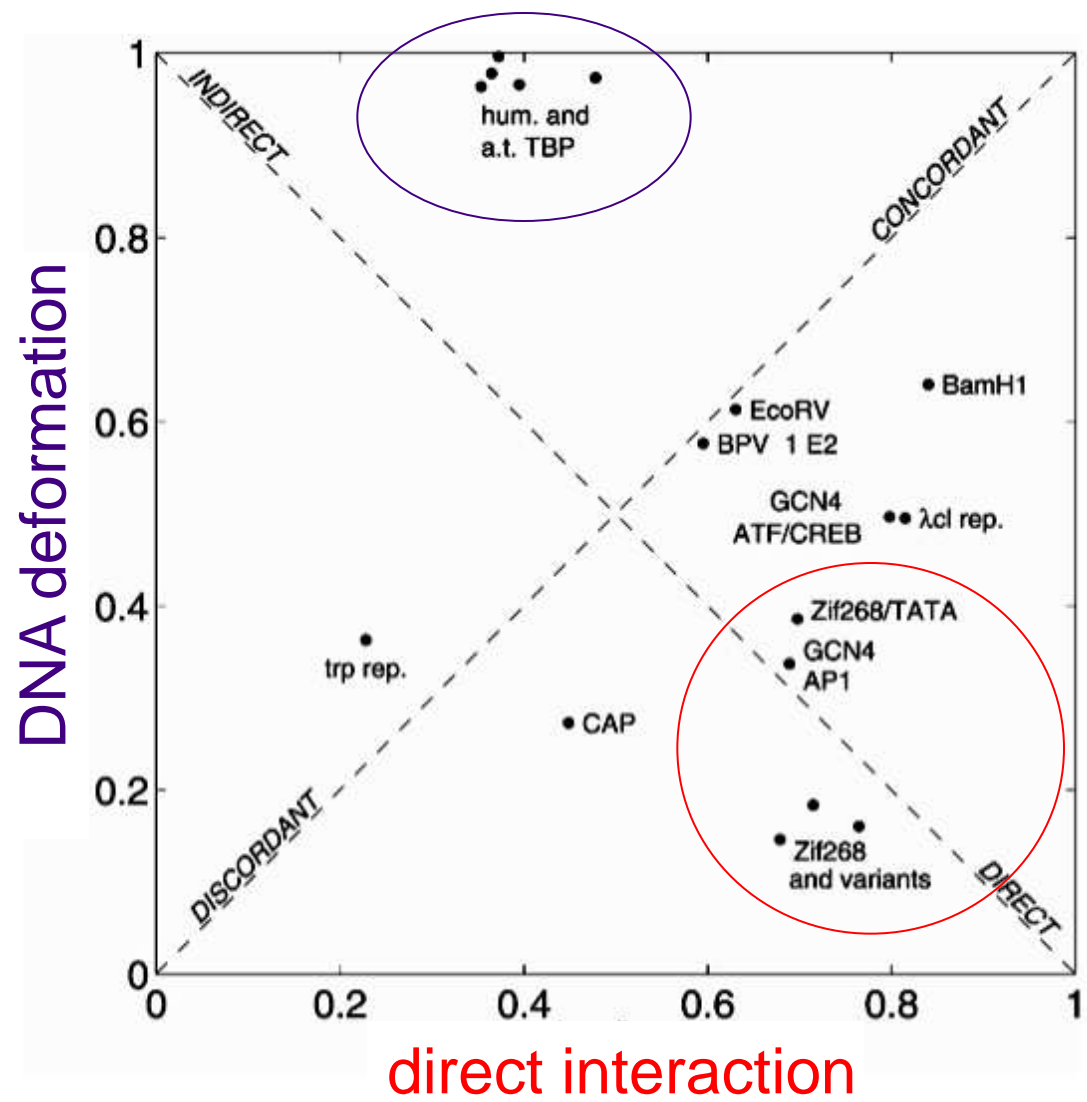
Blaney et al PNAS 2006

time (s)

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

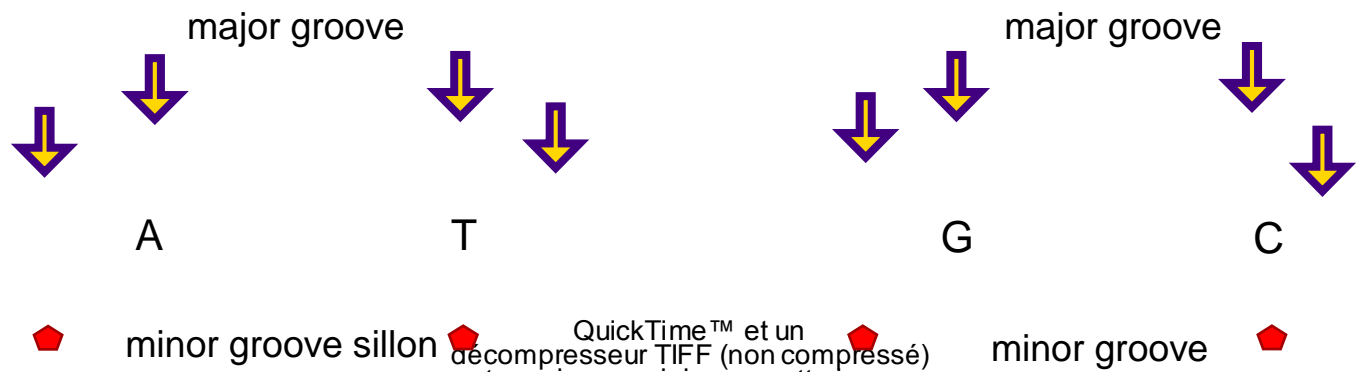
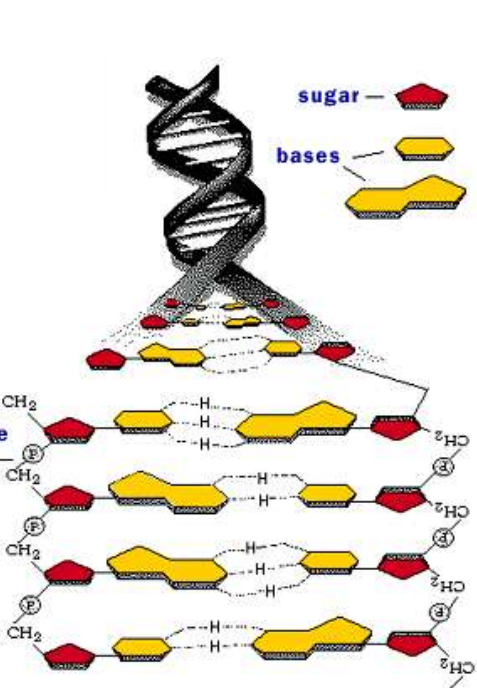
# recognition

direct interaction / indirect interaction through DNA deformation



# recognition

direct interaction:  
hydrogen bonding to the bps sides



QuickTime™ et un  
décompresseur TIFF (non compressé)  
sont requis pour visionner cette image.

# questions ouvertes

Q : comparer aux expériences

1. ingrédients :

- charge protéine
- sel monovalent
- pH (fait !)
- ions multivalent (en cours !)





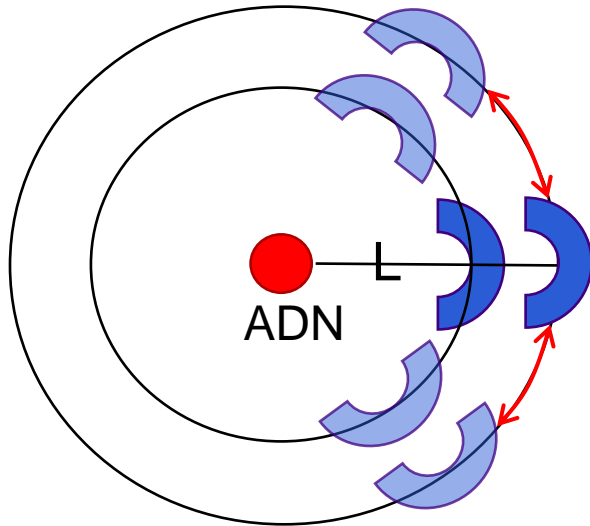
# questions ouvertes



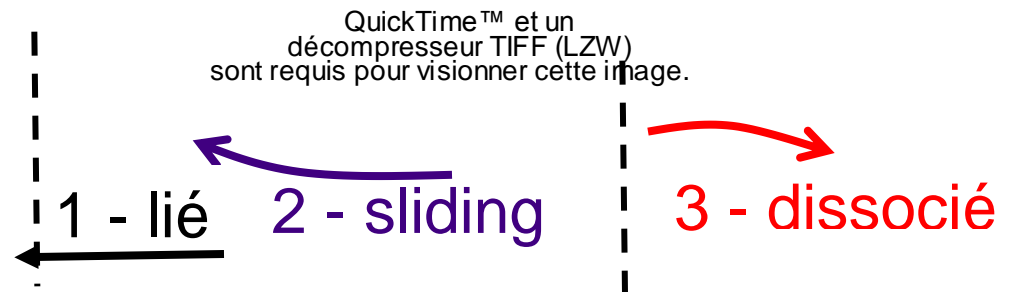
**Q** : comparer aux expériences

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

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



définition « naturelle » des états



**Q** : définition expérimentale ?

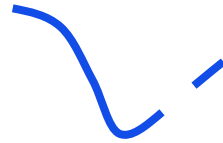
1 pixel  $\cong$  130 nm - champ  $\cong$  (4  $\mu$ m)<sup>2</sup> -  $\Delta t \cong$  20 ms

QuickTime™ et un décompresseur TIFF (LZW) sont requis pour visionner cette image.

# questions ouvertes

Q : comparer aux expériences

3. et la diffusion 1D ?



QuickTime™ et un  
décompresseur TIFF (LZW)  
sont requis pour visionner cette image.

Yaakov Levy

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

Q : charges sur 2 hélices  $\Rightarrow$  trajectoire hélicoïdale ?

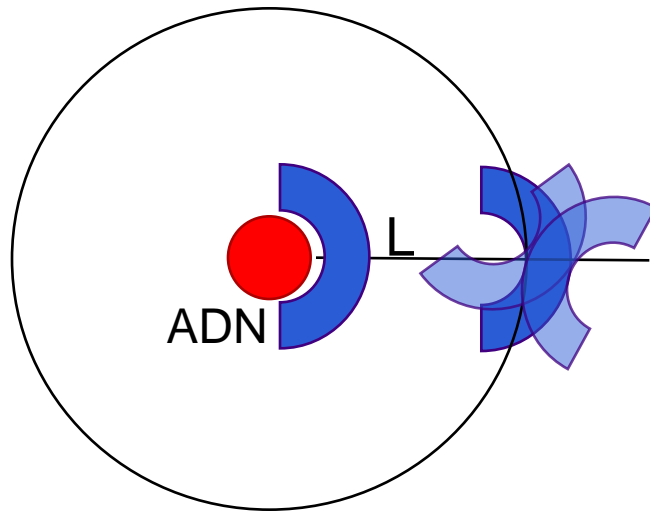
Q : effet vis-écrou ?

Q : hélicité = contrainte forte ?

QuickTime™ et un  
décompresseur TIFF (LZW)  
sont requis pour visionner cette image.

# questions ouvertes

Q : autres degrés de liberté :



Q : orientation protéine :

- entropie
- électrostatique  $\rightarrow 0$

Q : moment dipolaire ?

# questions ouvertes

Q : autres degrés de liberté :

Q : **flexibilité** ?

• de l'ADN :



distance ADN protéine (Å)

- déformation « à distance »

Bouvier Lavery JACS 2009

• de la protéine

- queues flexibles

énergie (kcal/mol)

QuickTime™ et un décompresseur TIFF (LZW) sont requis pour visionner cette image.



QuickTime™ et un décompresseur TIFF (LZW) sont requis pour visionner cette image.

Y. Levy

- dissipation d'énergie

Florescu Joyeux