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Amiens

GT MASIM - Paris, nov. 16-17, 2017

Biomolecular recognition from free energy simulations

Laboratoire de Glycochimie, des Antimicrobiens et des Agroressources

UNIVERSITÉ de Picardie Jules Verne

The lab

- Organic chemistry lab
- 4 tenured molecular modelers: molecular simulations, forcefield development

q4md-forcefieldtools.org

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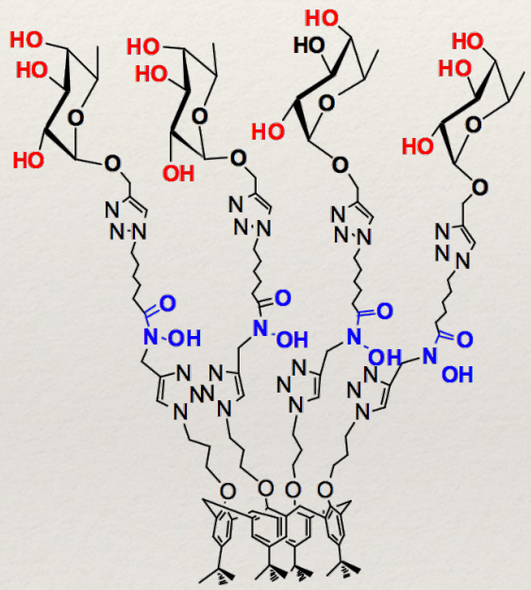
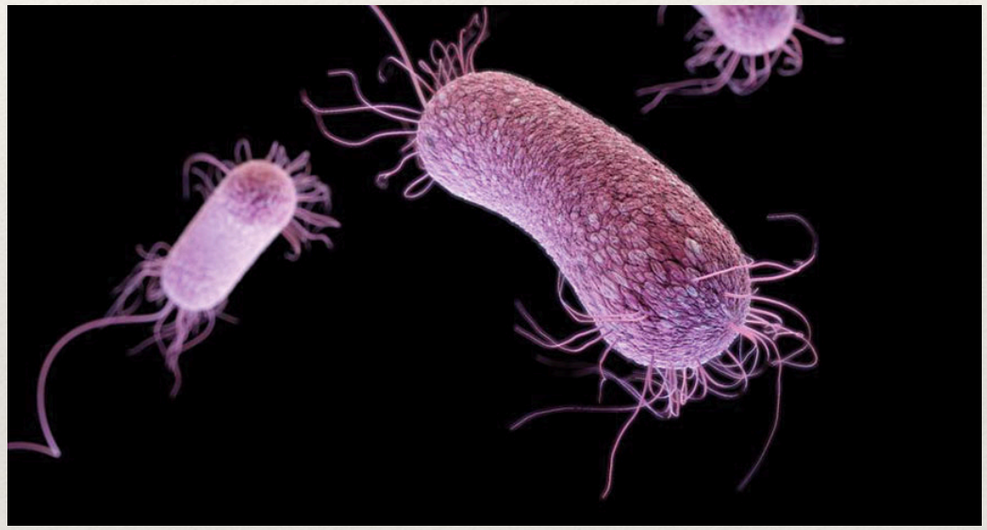
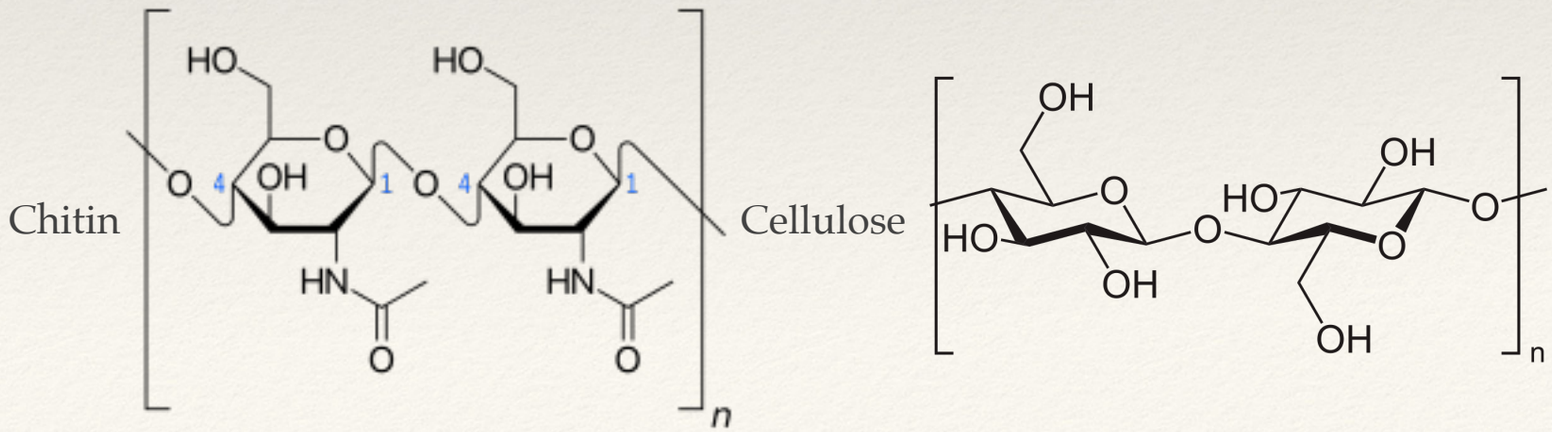
Glycochemistry applied to:

- Antibacterial agents
- Drug vectoring

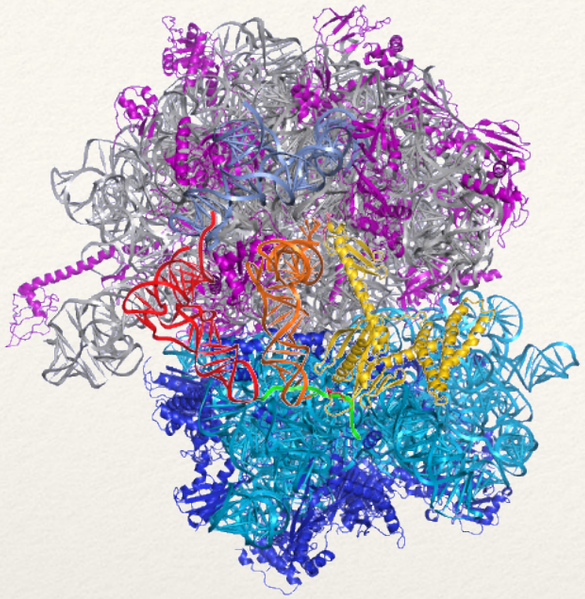




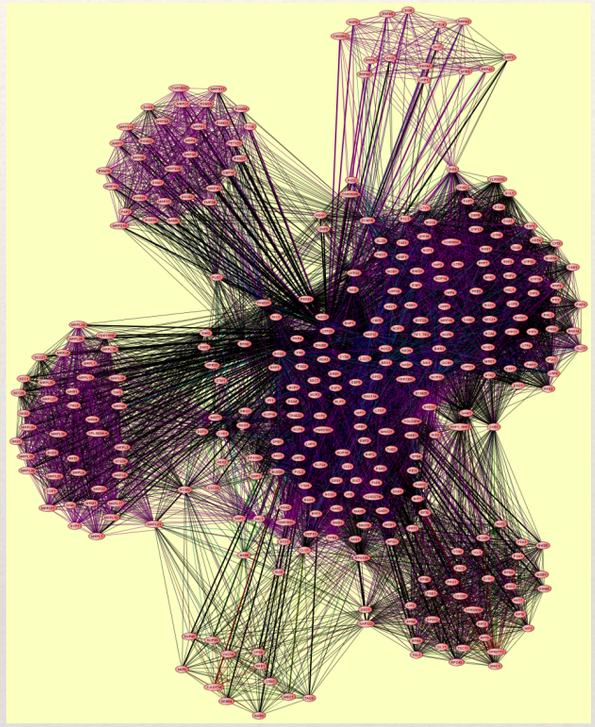
- Green chemistry from renewable bioresources (energy storage, liquid crystals, depolluting…)



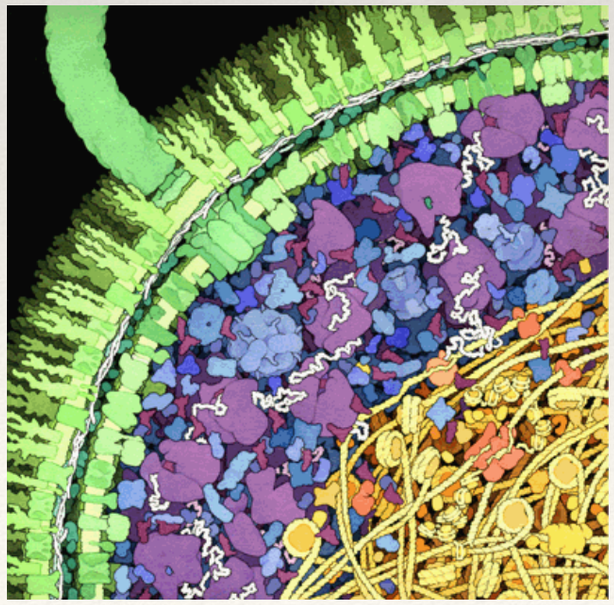
Biomacromolecular recognition



- Complex multipartner assemblies



- Regulatory networks

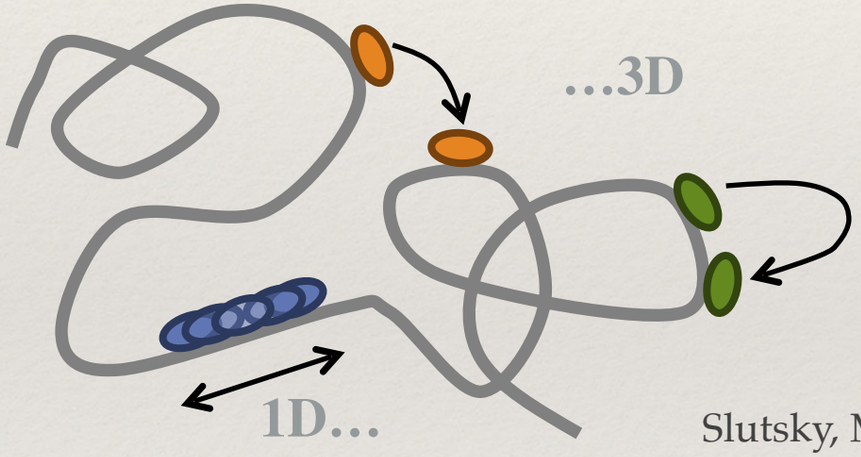


- Random encounters vs formation of biologically relevant complexes under conditions of crowding

Dynamic recognition: base mechanisms

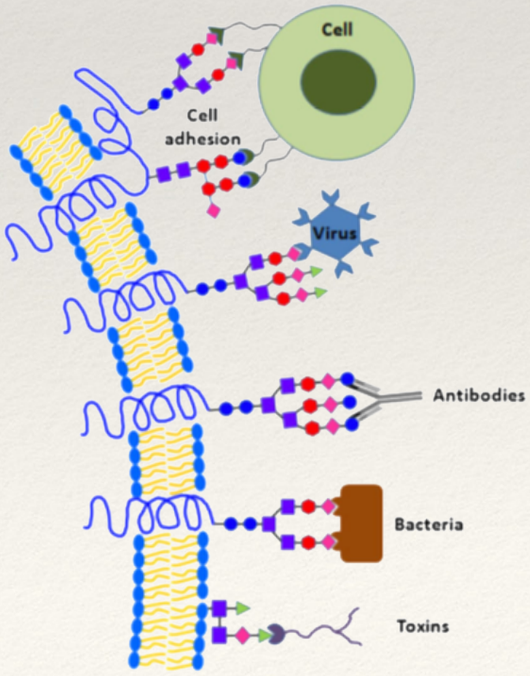
- **Indirect recognition:** recognizing a macromolecule through its (sequence-dependent) capacity to deform

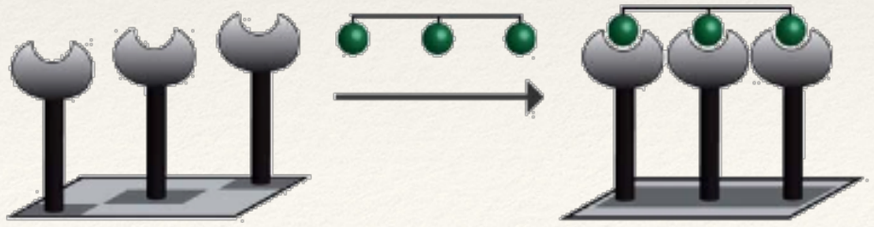
- **Accelerated diffusion:** forming transient complexes (with or without a third party molecule) to accelerate the search for the correct partner



Slutsky, Mirny, *Biophys. J.* 2004

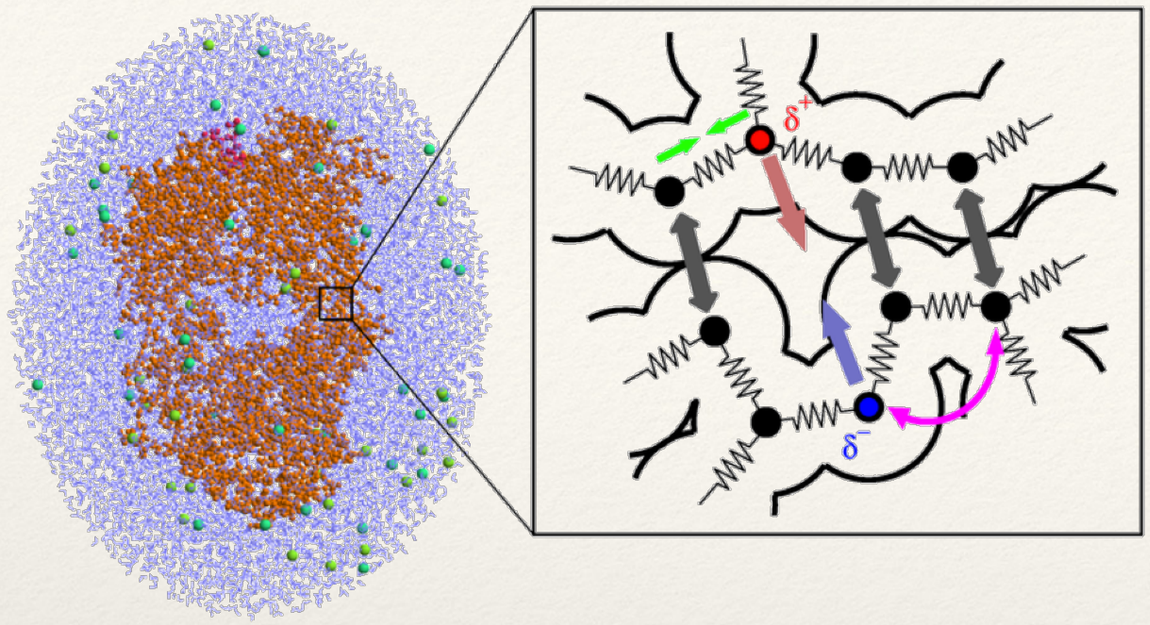
- **Multivalence:** strong, specific recognition achieved through a large number of simultaneous weak, nonspecific contacts ("sugar code")





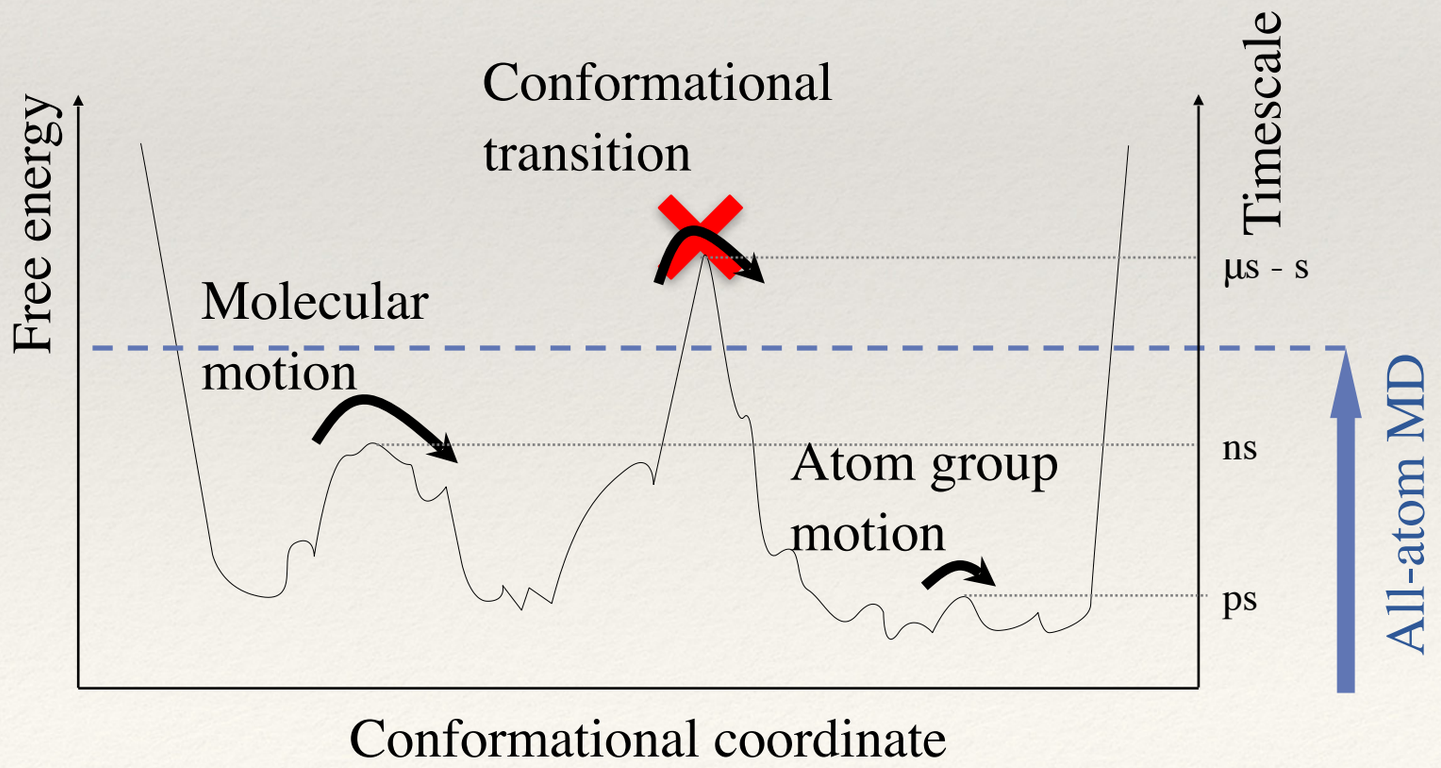
Gabius, *Biochem. Soc. Trans.* 2008

All-atom molecular dynamics



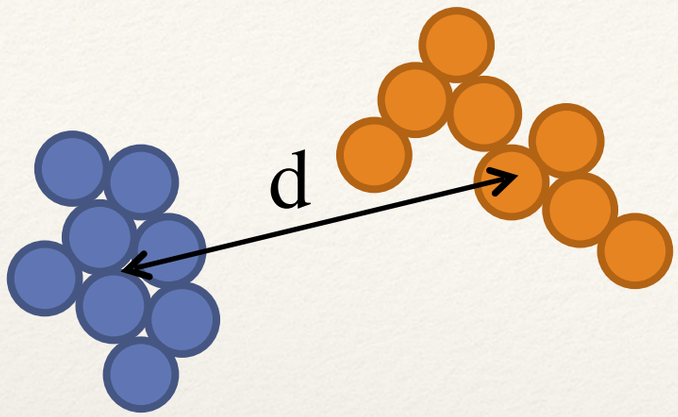
- Time-resolved molecular motion
- Thermodynamics (free energies…)

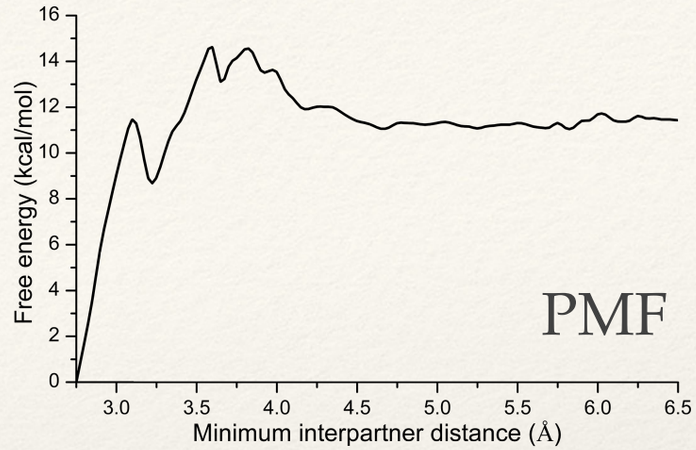
BUT simulations are limited to a few hundreds of nanoseconds, when collective motion/ complex formation and dissociation/partial unfolding last milliseconds or more…



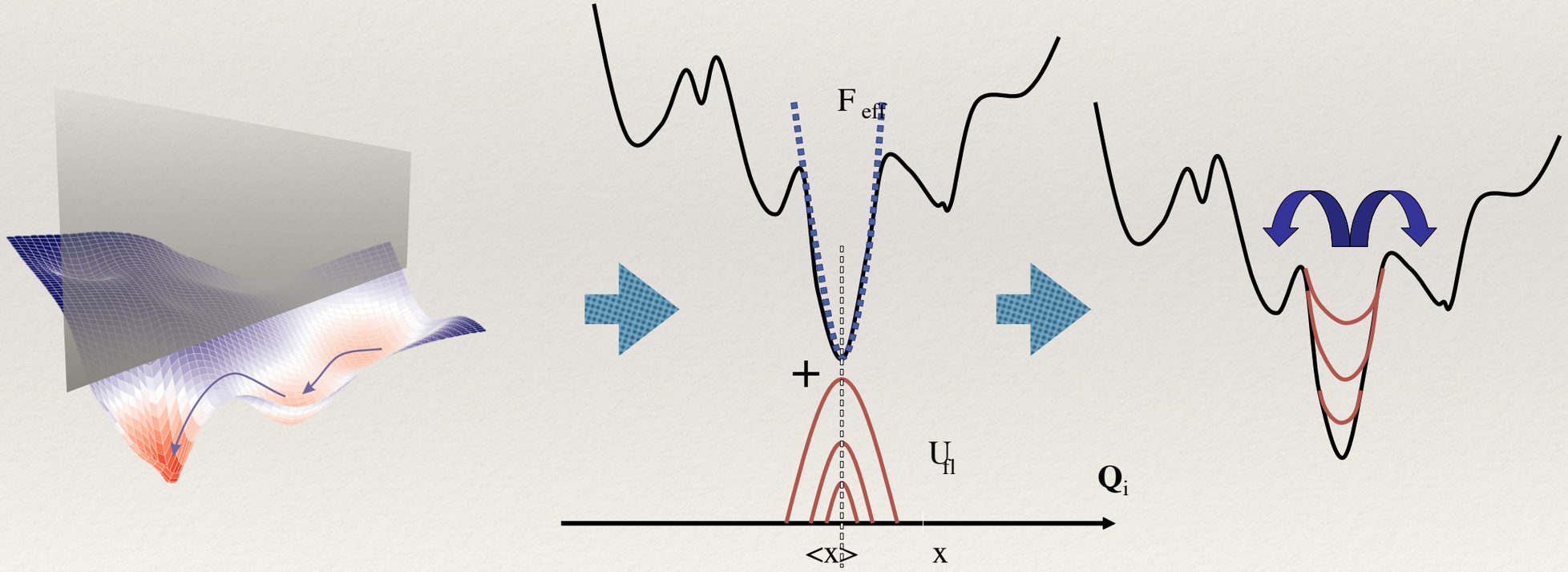
Accelerated sampling

1. Extract conformational coordinate(s) describing the transition under study;





2. Add biasing forces this coordinate to accelerate transitions over high free energy barriers;



Barducci, Bussi, Parrinello, *Phys. Rev. Lett.* 2009

3. Retrieve unbiased density of states from biased density and infer the PMF.

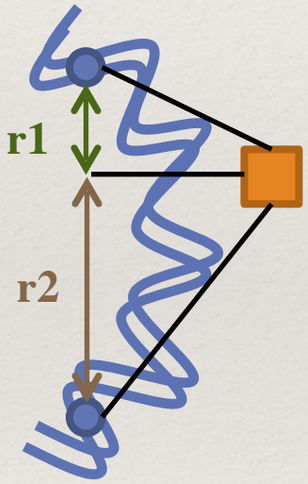
Defining collective variables

- Nearly any function of the position of the atoms can be used (as long as it is differentiable)
- Software is now available to use complex combinations of simple variables as biasing coordinates in most MD codes (PLUMED)

Bonomi et al, *Comp. Phys. Comm.* **180**, 1961, 2009.

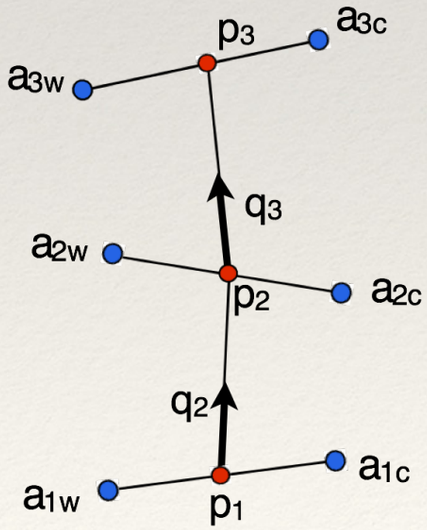
BUT: multiple definitions are possible in most nontrivial cases…

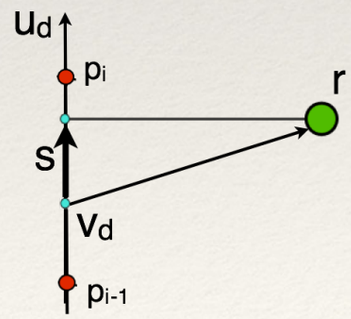
Example: sliding of transcription factors along DNA



Projection of ligand on segment defined by anchor points

→ DNA deformation ⚠



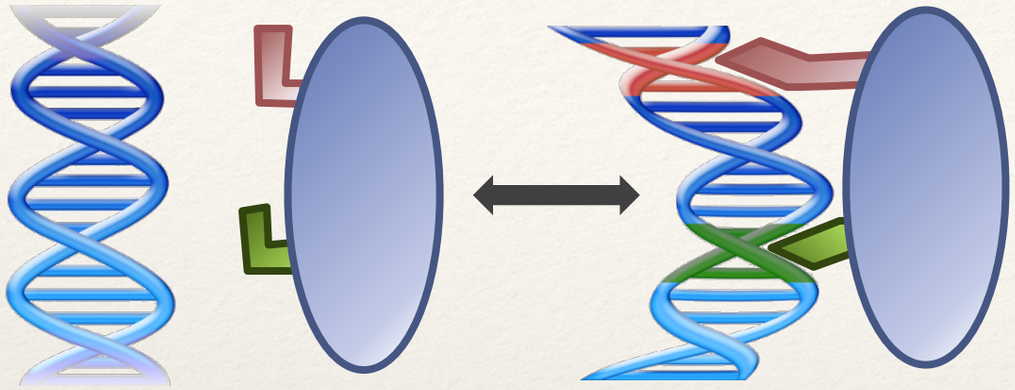


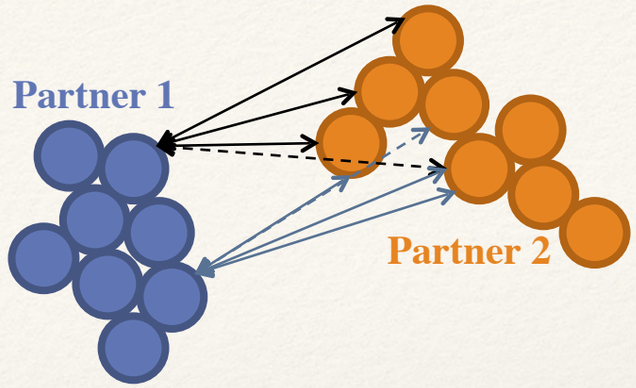
- Local interpolative approximation of local DNA axis
- Minimize projection of ligand-target position vector on local axis

Wilhelm, Mukherjee, Bouvier, Zakrzewska, Hynes, Lavery, *J. Am. Chem. Soc.* 2012

Defining collective variables

Example: complex formation/dissociation

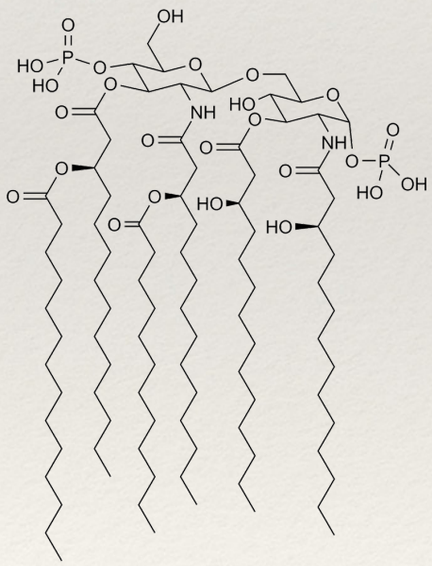


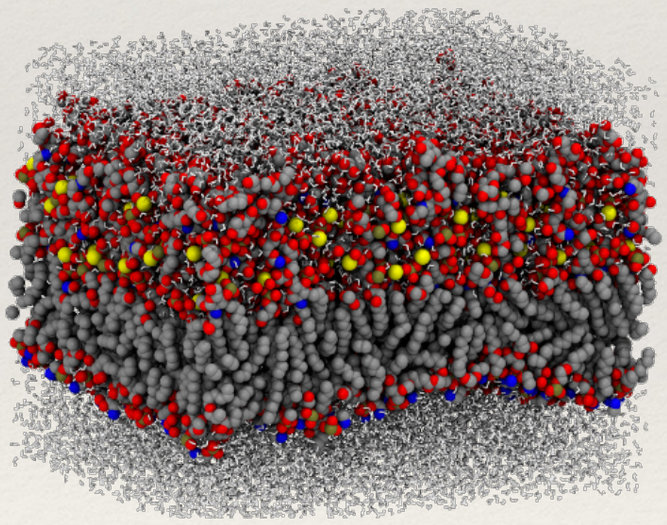


Mechanistic bias vs size of orthogonal conformational space…

Bouvier, Lavery, *J. Am. Chem. Soc.* 2009
Bouvier, *Phys. Chem. Chem. Phys.* 2014
Merino, Bouvier, Cojocaru, *Phys. Chem. Chem. Phys.* 2015

Example: membrane curvature





Jet fitting, Voronoi, Hough transform…

Local vs global, signal vs noise…

Derivatives, computational efficiency?

Bouvier, Cézard, Sonnet, *Phys. Chem. Chem. Phys.* 2015
Bouvier, Cézard *Phys. Chem. Chem. Phys.* 2017

Interest in GT-MASIM

Ideas / collaborations

on

Computational geometry

Machine learning

Etc…

methods for the

Identification from MD simulations

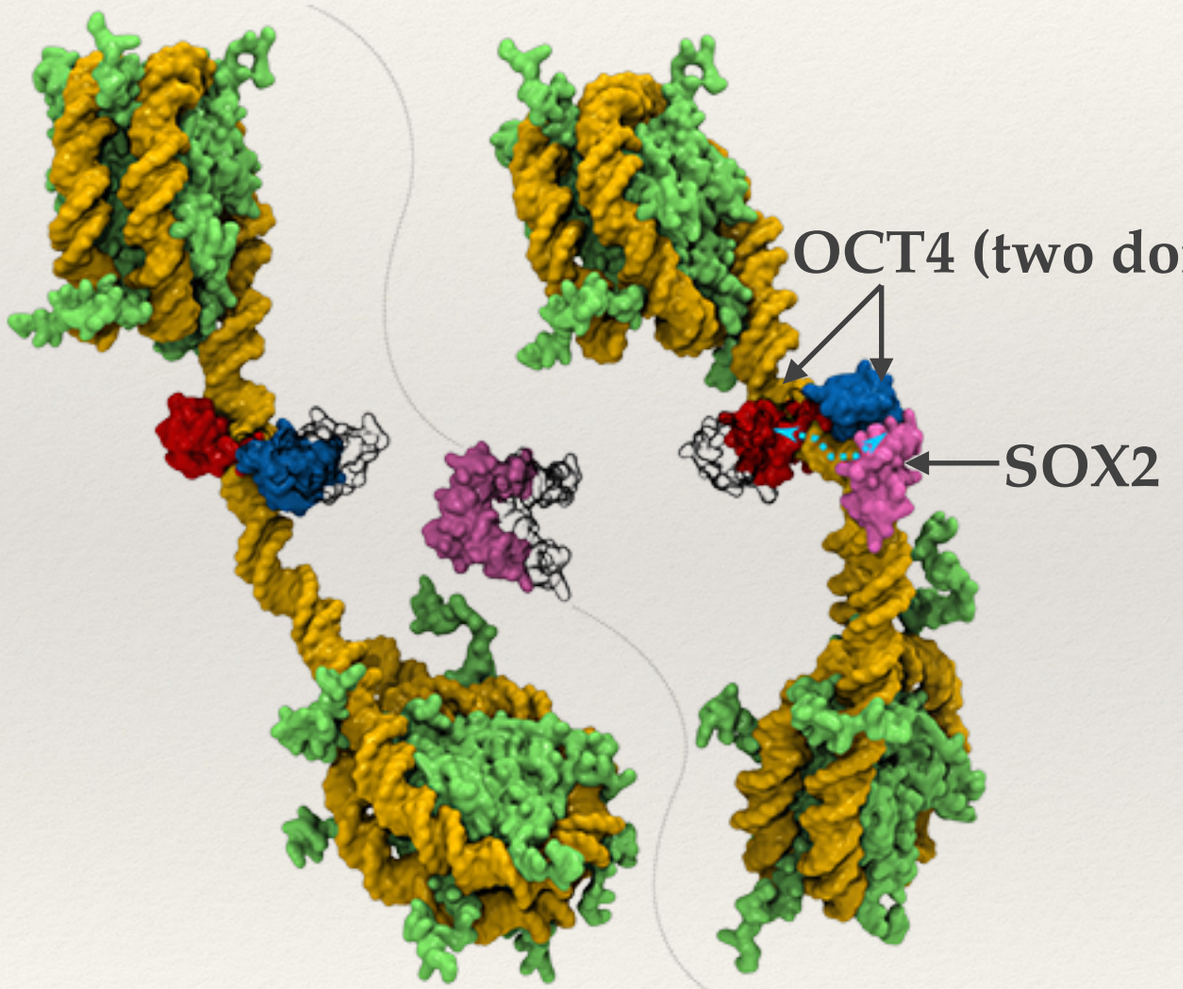
Use in enhanced sampling simulations

of collective variables…

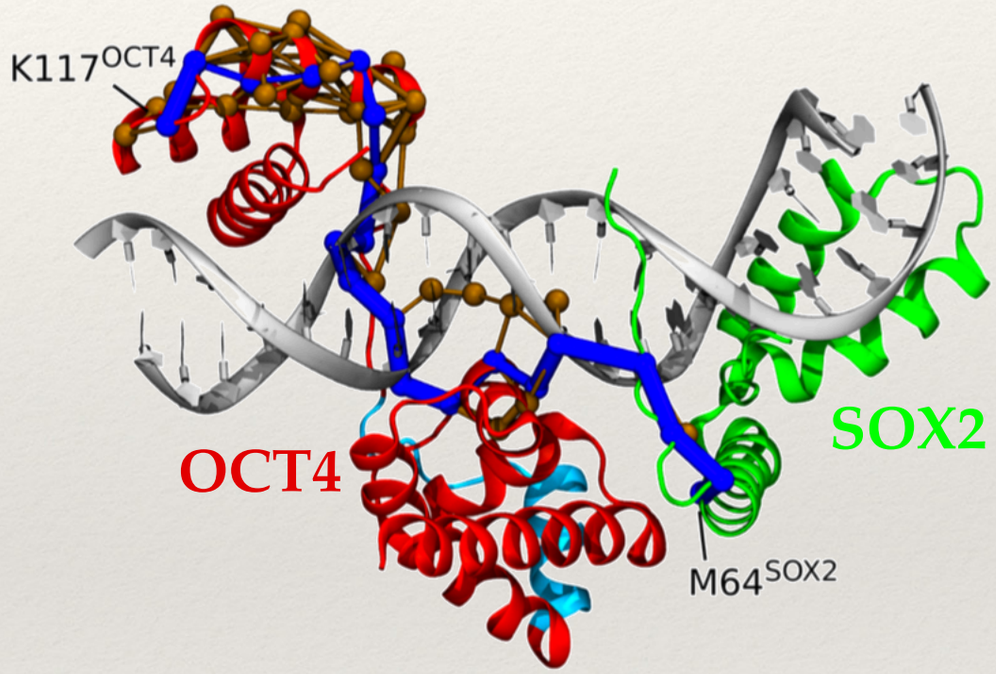
Enhanceosomes

- Multiple neighbouring ("tandem") transcription factor binding sites on DNA → enhance recognition specificity.
- Interactions between neighbouring transcription factors → facilitate binding (cooperativity)

Enhanceosomes in pluripotent stem cells: OCT4/SOX2 transcription factors:



Merino, Bouvier, Cojocaru, *PLoS Comp. Biol.* 2015



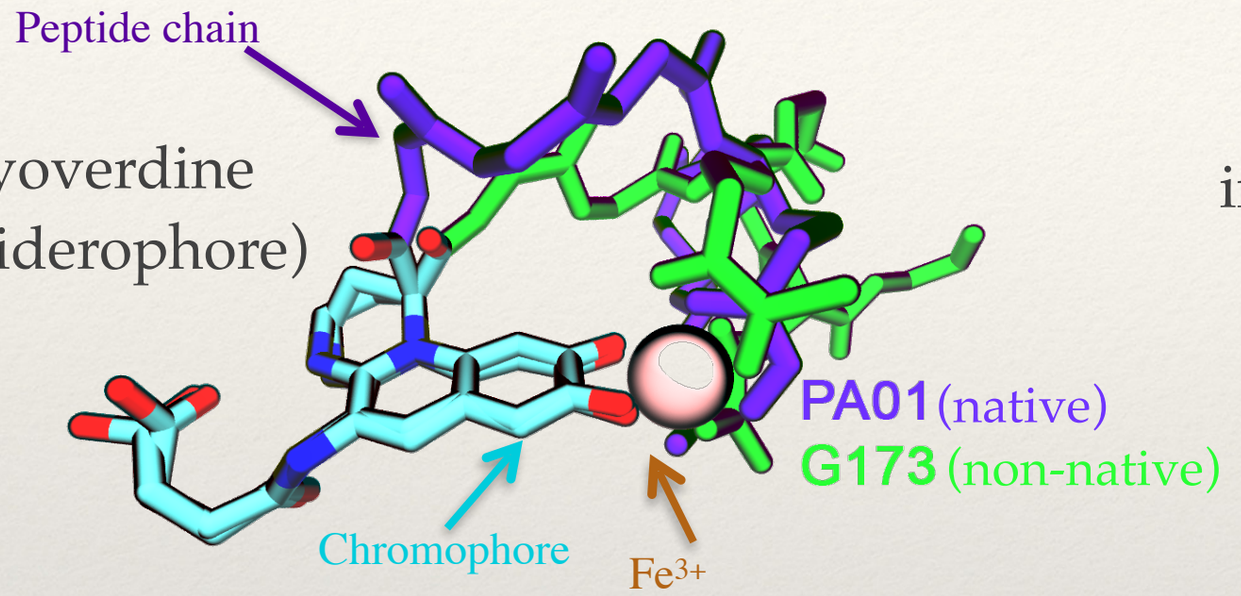
- SOX2 influences the conformation and dynamics of OCT4 bond to DNA
- SOX2 modifies the affinity of both domains of OCT4 for DNA (allostery)

Interplay between protein-protein interactions and DNA-mediated allostery

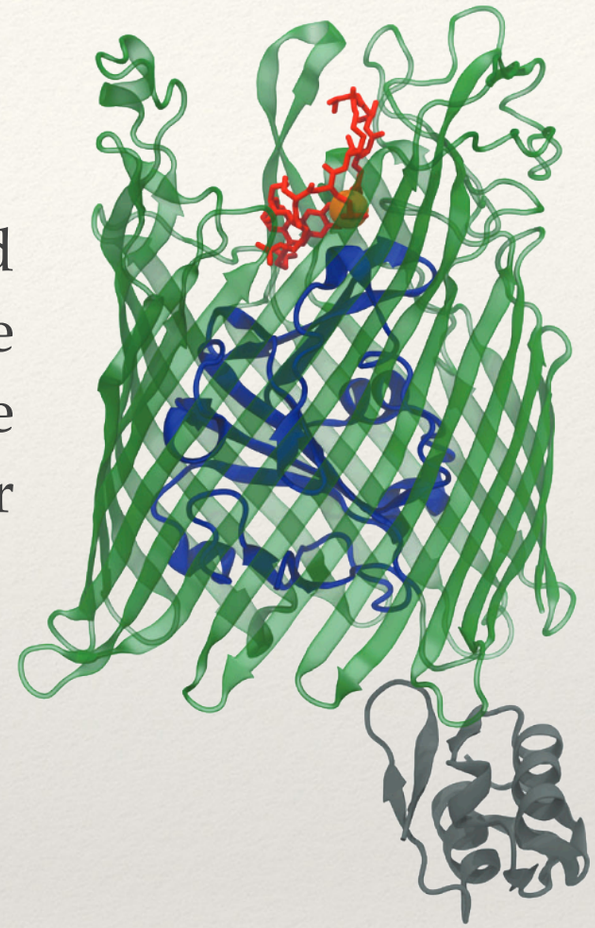
Fighting *Pseudomonas aeruginosa*

On ‘2017 WHO list of superbugs for which conceiving new antibiotics is of utmost importance

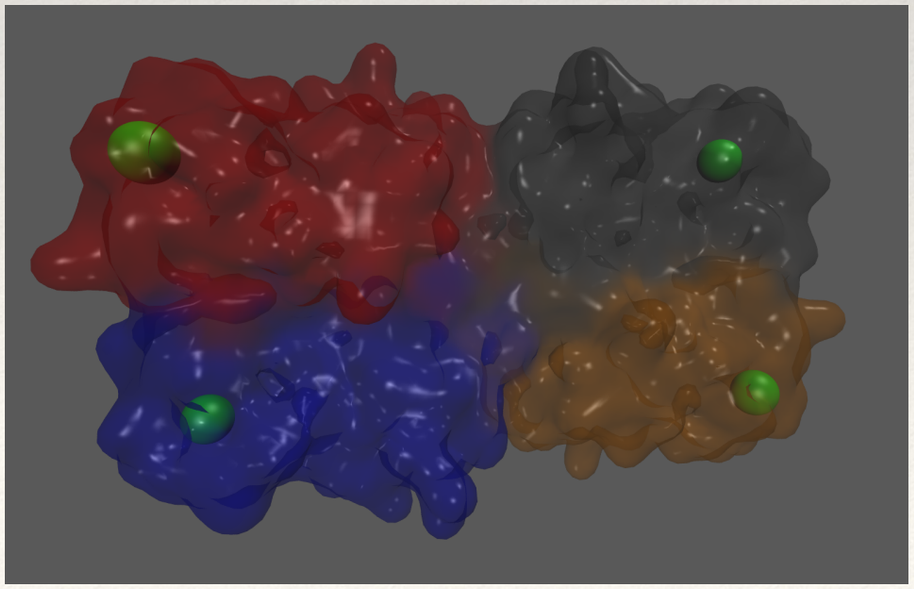
Iron scavenging mechanism



Recognition and internalization by the FpvA membrane transporter

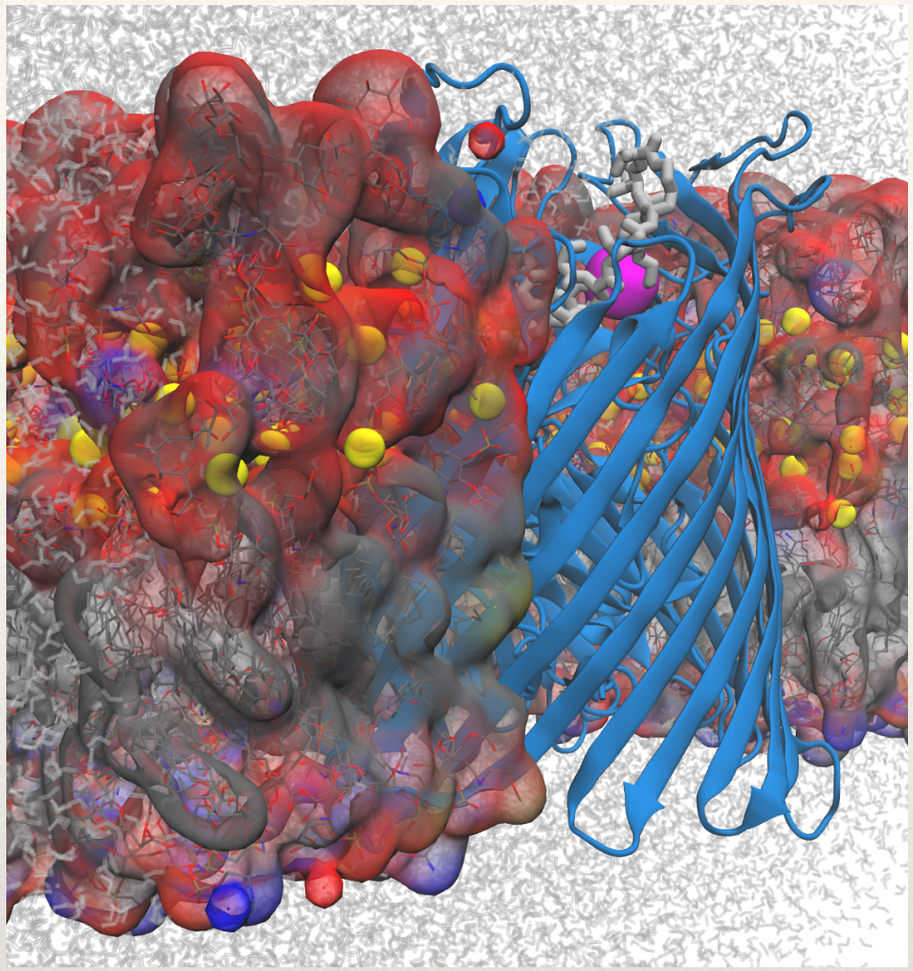


Lectin recognition



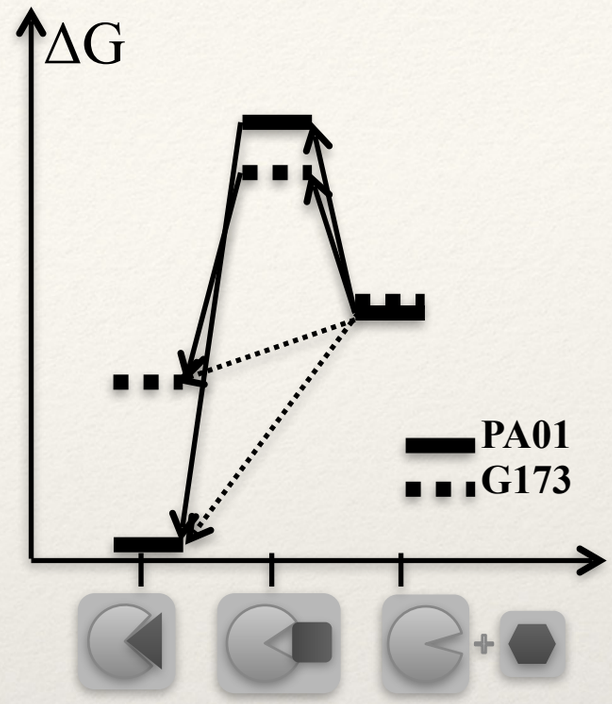
- Multivalent recognition of host cells via membrane-bound sugars (galactose, fucose)
- Triggering of virulence and infection

Iron acquisition in bacteria



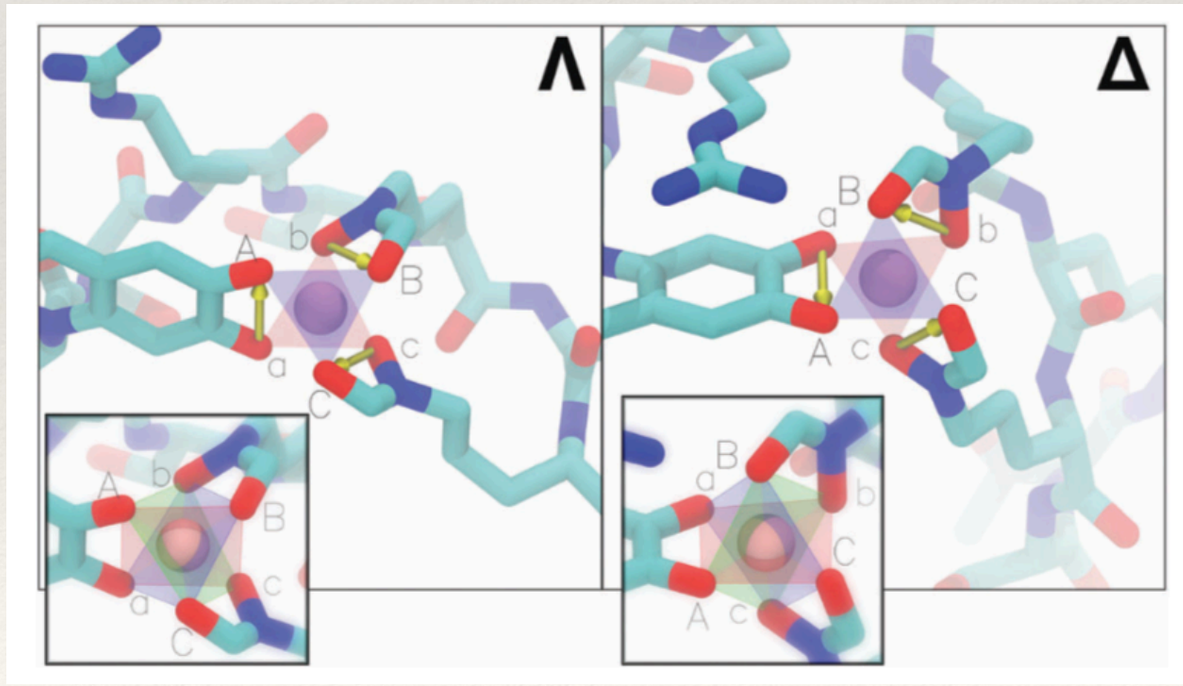
Combination of enhanced sampling binding/unbinding simulations and "alchemical" transformation of the pyoverdine sequence:

- Interaction with water has a dominant effect on recognition thermodynamics
- Recognition kinetics is linked to the pyoverdine peptide sequence



Enhanced sampling control of octahedral binding chirality:

- FpvA stabilizes both chiralities almost equally (unlike in solution)
- …but the conversion kinetics depend on the nature of the pyoverdine

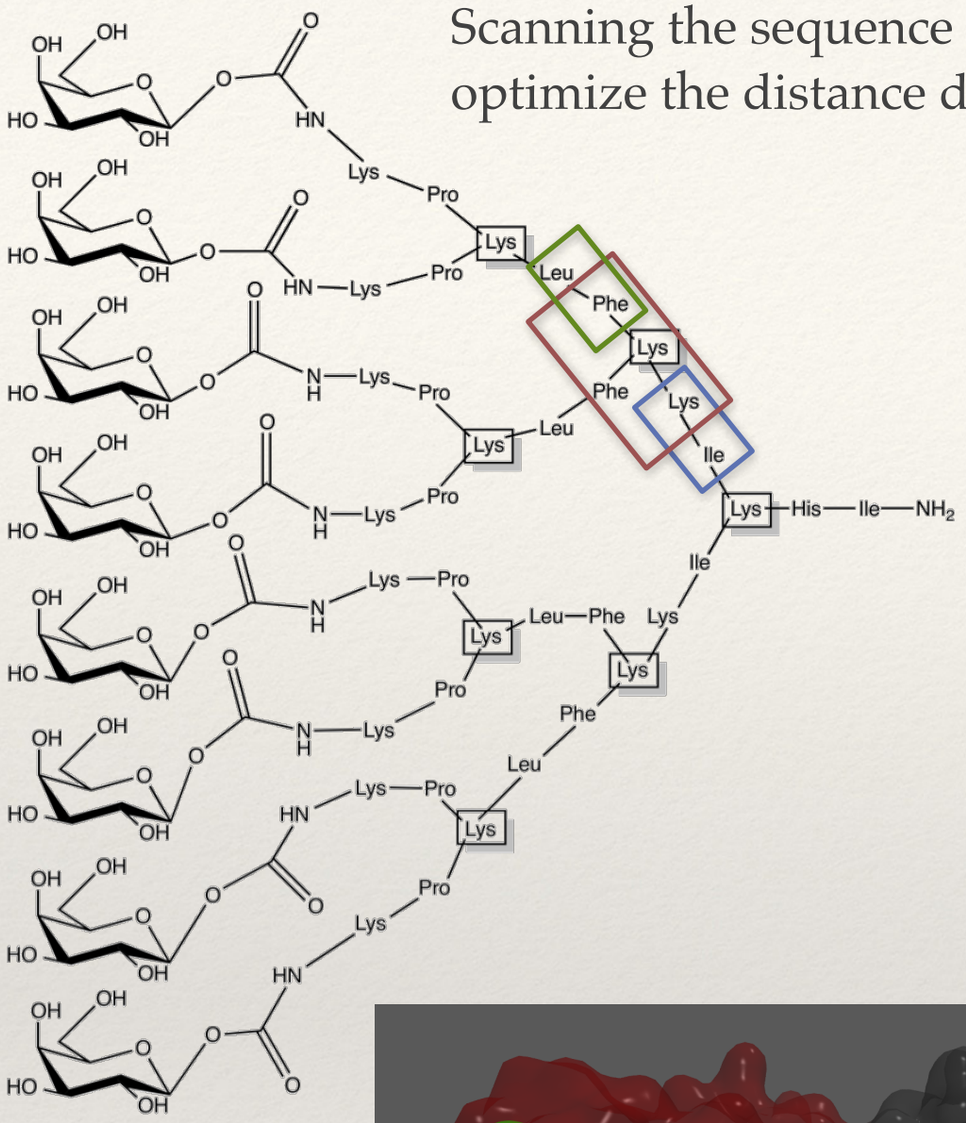


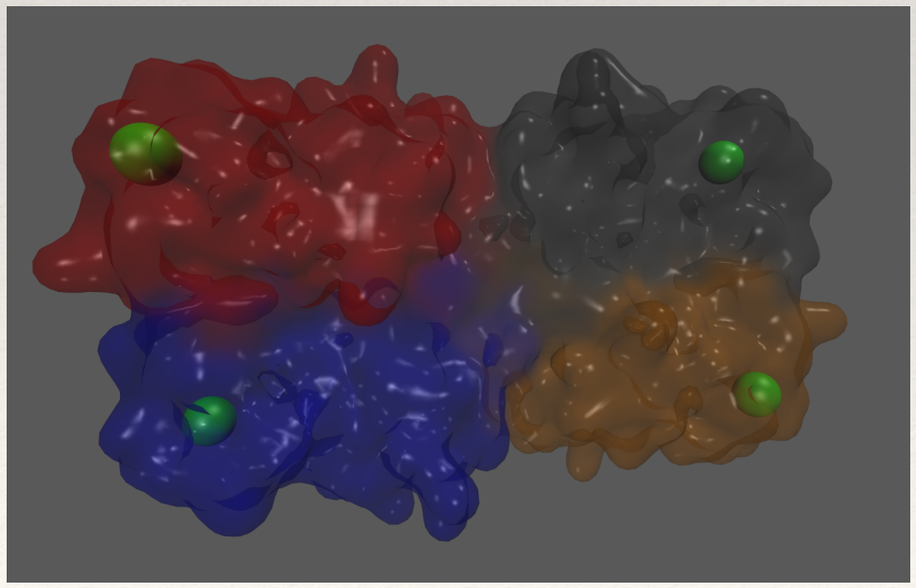
Exploit FpvA's "opportunism" to design novel antibiotics

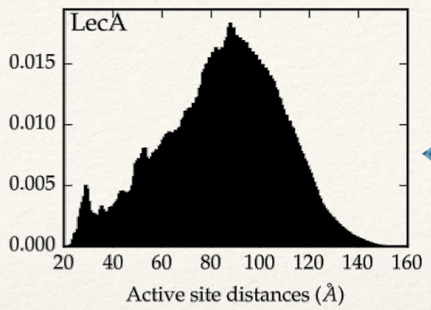
Bouvier, Cézard, Sonnet, *Phys. Chem. Chem. Phys.* 2015
Bouvier, Cézard, *Phys. Chem. Chem. Phys.* 2017

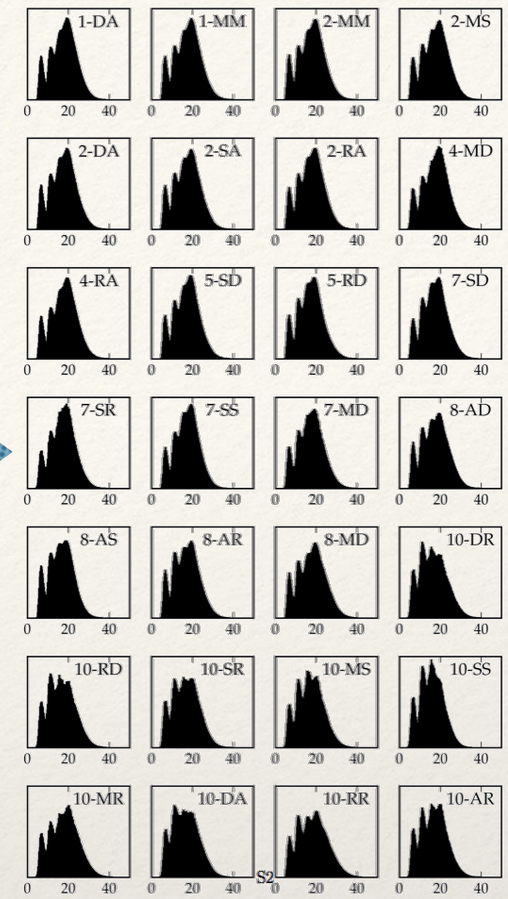
Optimizing the multivalent recognition of LecA

Scanning the sequence of glycopeptide dendrimers to optimize the distance distribution of galactoses…









Bouvier, *J. Chem. Inf. Model.* 2016

Co-workers

- Christine CÉZARD (Amiens)
- Pascal SONNET (Amiens)
- Vlad COJOCARU (Münster)
- Richard LAVERY (Lyon)
- Krystyna ZAKRZEWSKA (Lyon)

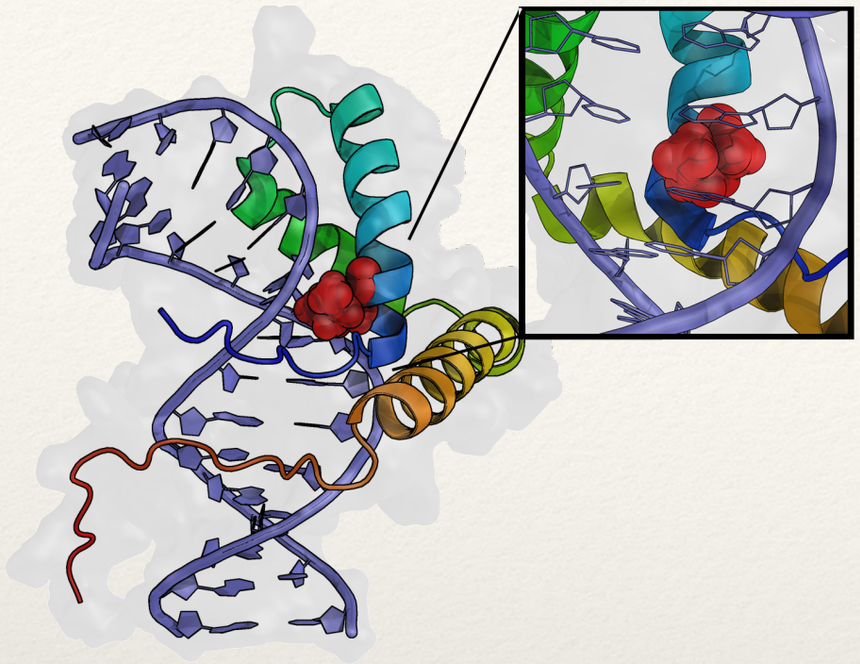
Funding

cnrs dépasser les frontières
UNIVERSITÉ de Picardie Jules Verne
Financé par ANR
PICARDIE LA RÉGION

High-performance computing resources

UNIVERSITÉ de Picardie Jules Verne Plateforme MeCS
GENCI

The SRY protein

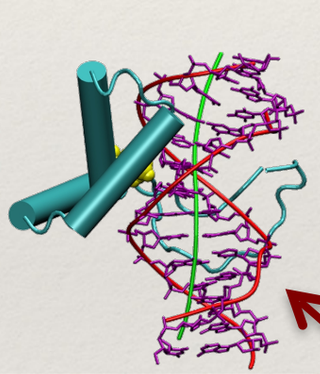


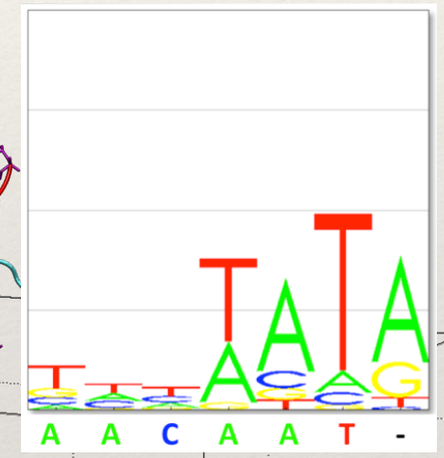
- Responsible for sexual differentiation in mammals (and related pathologies).
- Recognizes DNA sequence, but also shape and deformability.

- SRY/DNA recognition mechanisms
- Associated binding free energies

Specific binding pathway

Nonspecific readout pathway Compatible with facilitated diffusion





Bouvier, Lavery, *J. Am. Chem. Soc.* 2009
Bouvier, Zakrzewska, Lavery, *Angew. Chem.* 2011