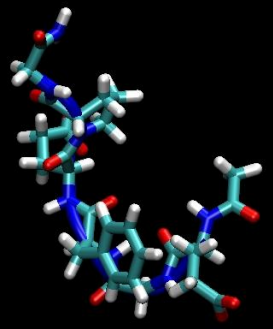
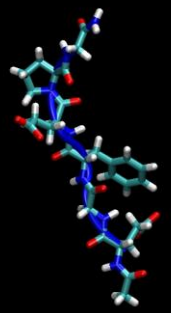
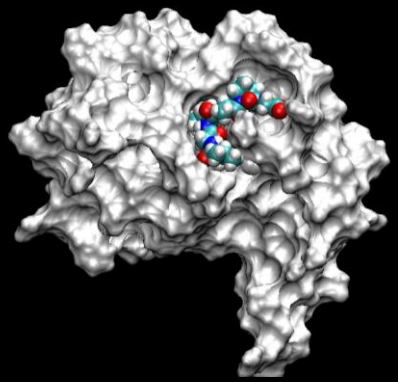


IX^{ème} journée Ter@tec

2 juillet 2014

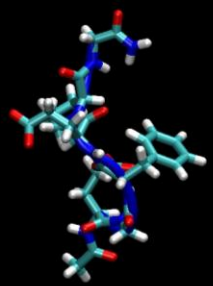


Deciphering molecular interactions using HPC simulations: getting new therapeutic targets

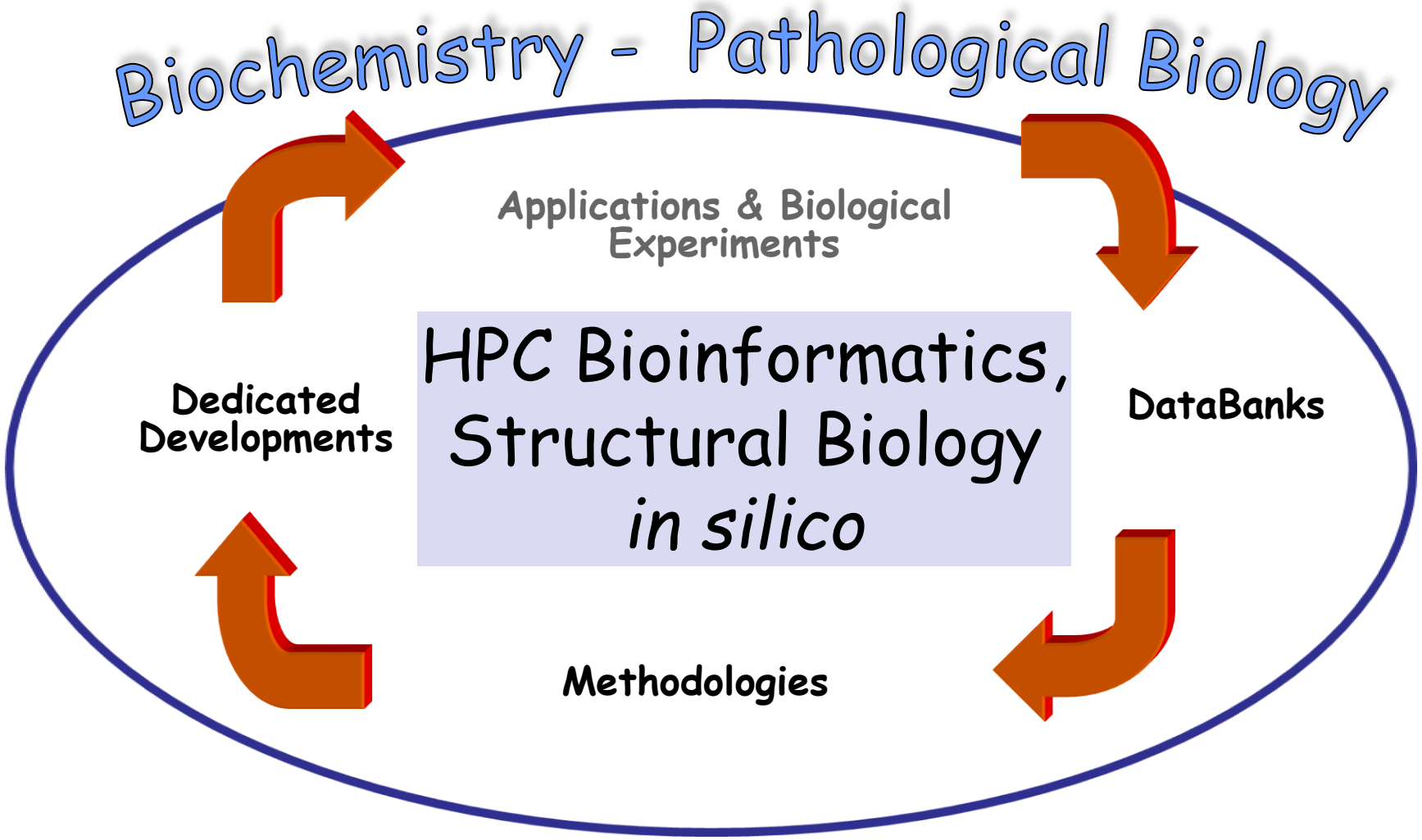


Pr Manuel Dauchez

Laboratoire SirMa
CNRS UMR 7369 MEDyC
Maison de la Simulation de Champagne-Ardenne
Université de Reims-Champagne-Ardenne



Biological context



Why to use simulations?

- ✓ explain experiment,
- ✓ provoke experiment,
- ✓ replace experiment,
- ✓ aid in establishing intellectual property…

→ **3D structures**

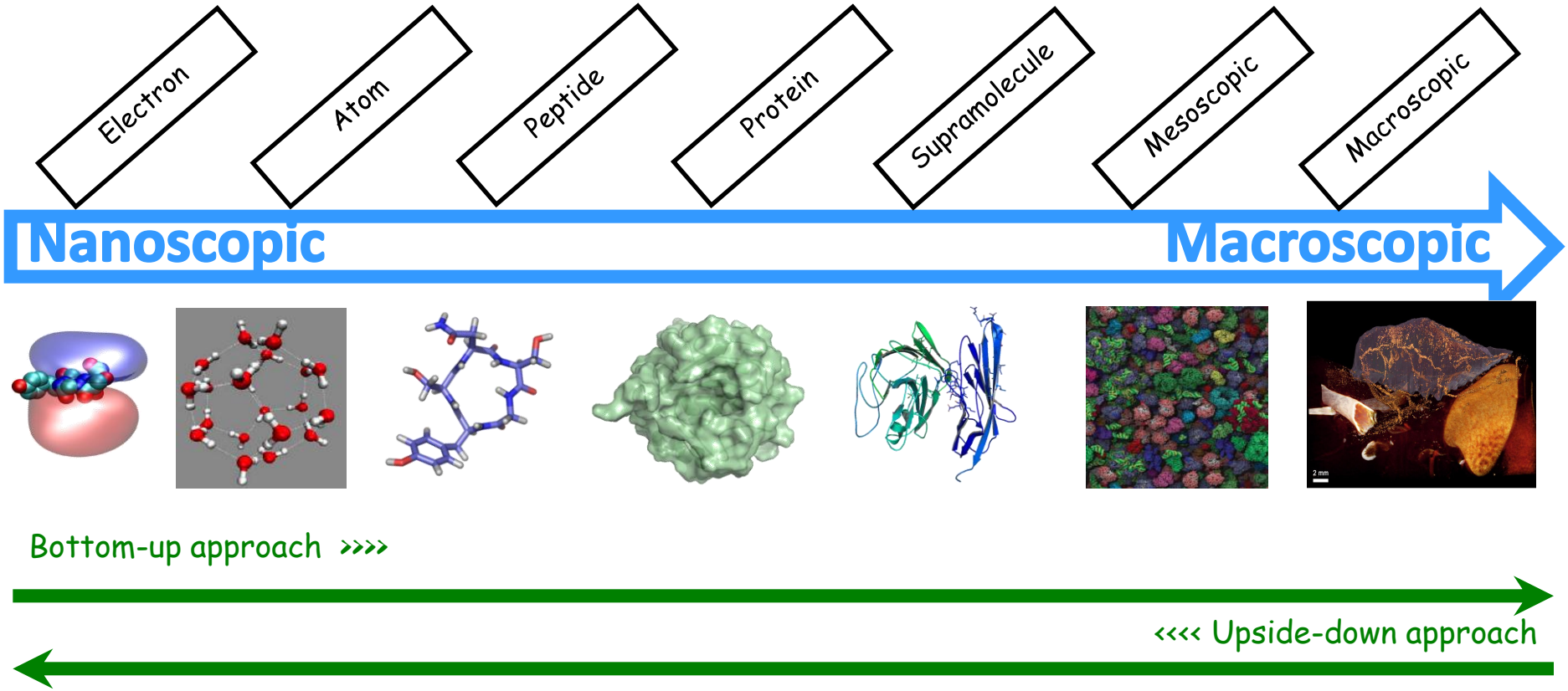
→ **structural adaptability**

→ **functional prediction**

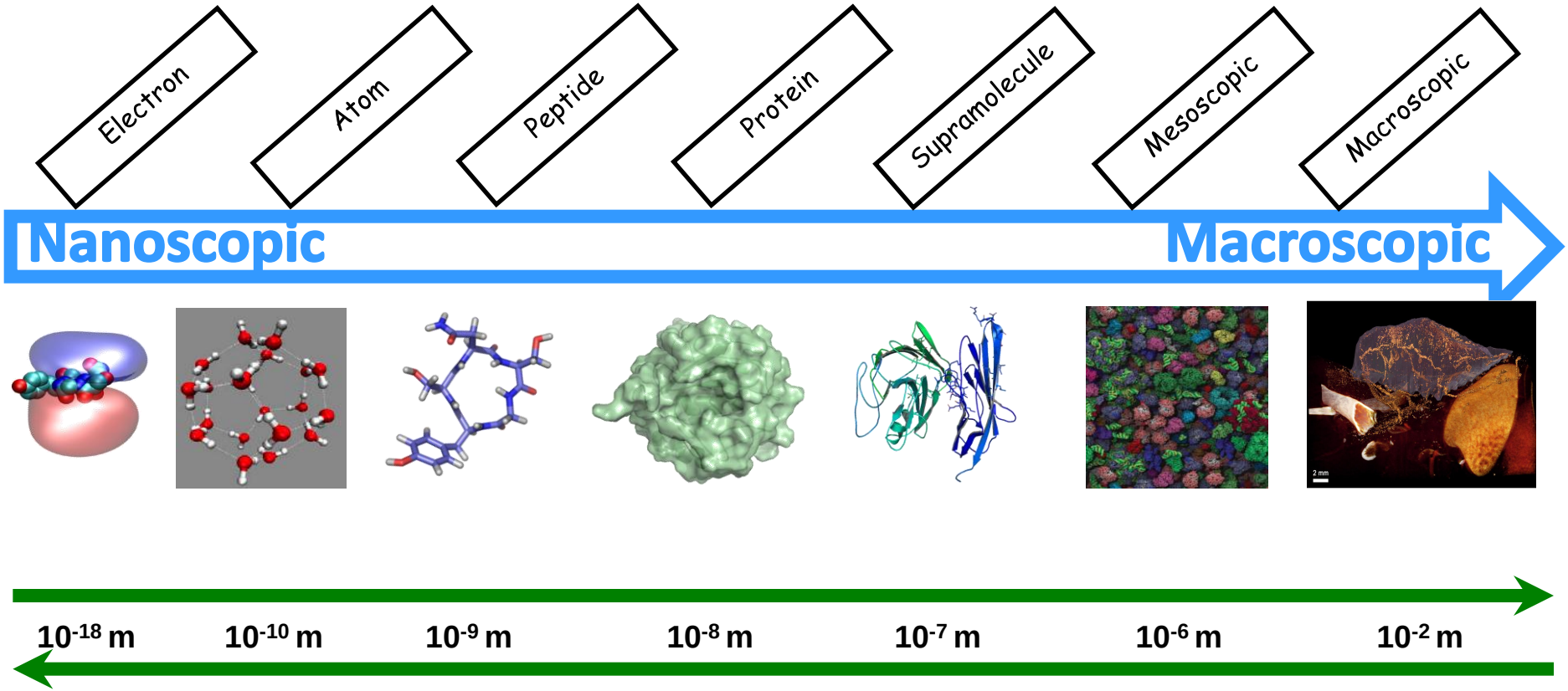
Structure/function/dynamics relationships

«in silico veritas ?»

Multiscale problem

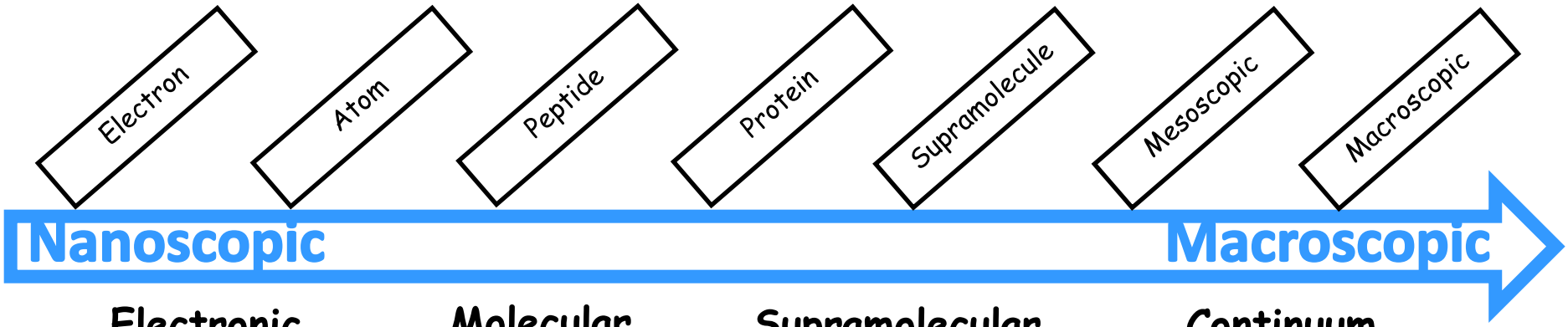


Multiscale problem



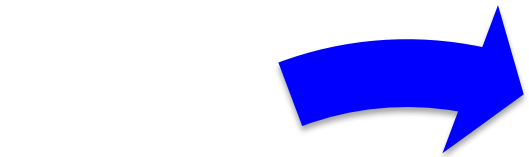
HPC, a Computational Microscope: a way to study molecular machines of living cell !

Multiphysics problem



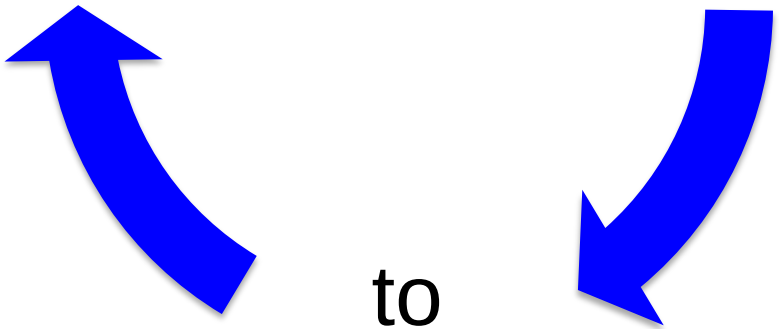
Electronic level	Molecular level	Supramolecular level	Continuum level
• 1-2 peptides	• 1-2 proteins	• 5-10 proteins	• >1000 proteins
• 1 association	• 1 complex	• 2-3 complex	• >100 complex
• $<10^2$ atoms	• 10^4 atoms	• 10^5 atoms	• $>10^6$ atoms
• « 10 ns »	• 100 ns	• 1 μs	• >1 ms
Quantum Dynamics	Molecular Dynamics Normal Modes	Coarse Grained or Langevin Dynamics	Mesoscopic Dynamics

Methodology



to visualise

to model



to simulate

CENTRE IMAGE

UNIVERSITÉ DE REIMS CHAMPAGNE-ARDENNE

Centre de Calcul ROMEO Champagne-Ardenne

« Maison de la Simulation de Champagne-Ardenne »

Empirical FF

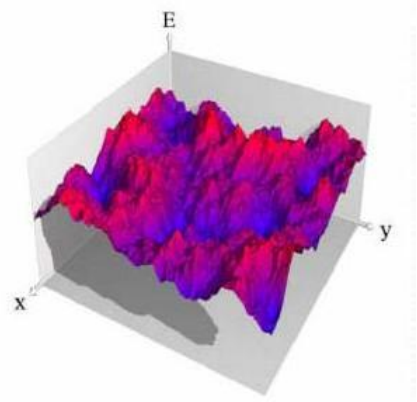
Empirical Force Fields & programs

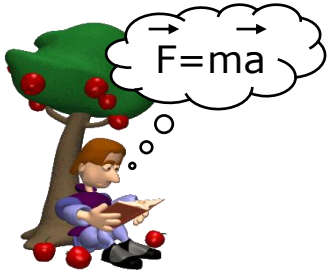
(Gromos, NAMD, Amber, Charmm…)

$$V = \sum_{\text{bonds}} k_b (b - b_0)^2 + \sum_{\text{angles}} k_\theta (\theta - \theta_0)^2 + \sum_{\text{dihedrals}} k_\phi [1 + \cos(n\phi - \delta)]$$

$$+ \sum_{\text{impropers}} k_\omega (\omega - \omega_0)^2 + \sum_{\text{Urey-Bradley}} k_u (u - u_0)^2$$

$$+ \sum_{\text{nonbonded}} \epsilon \left[\left(\frac{R_{\min_{ij}}}{r_{ij}} \right)^{12} - \left(\frac{R_{\min_{ij}}}{r_{ij}} \right)^{6} \right] + \frac{q_i q_j}{\epsilon r_{ij}}$$

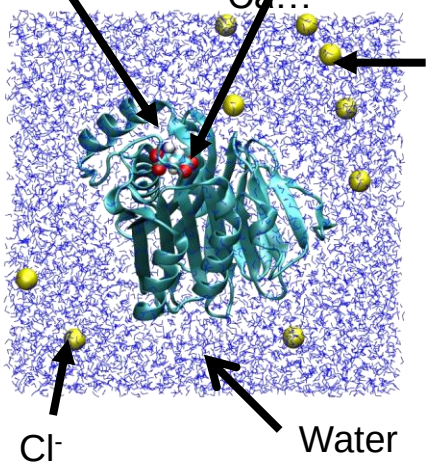




$\mathbf{r}_i(t) \rightarrow \mathbf{r}_i(t + \delta t)$

10^{-15}s ➔7-10 orders of magnitude

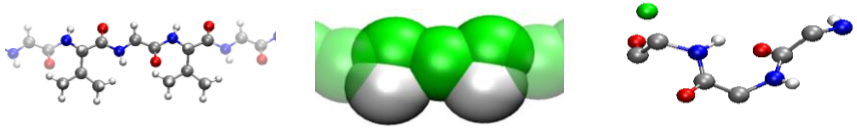
➔N atoms, N^2 Memory, N^3 time ➔ CPU & GPU



- **Local motion of peptides and proteins**

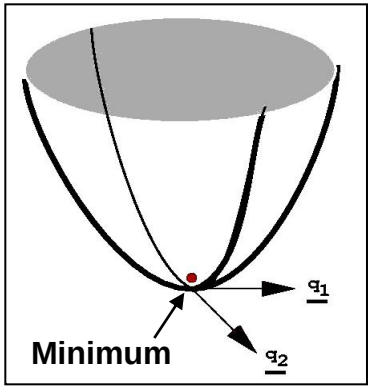
Coarse-grained

OPEP, Martini



- **Longer simulations and larger systems, but simplified !**

Others approaches



$$H = \begin{pmatrix} \frac{\partial^2 V}{\partial x_1 \partial x_1} & \frac{\partial^2 V}{\partial x_1 \partial x_2} & \cdots & \cdots & \frac{\partial^2 V}{\partial x_1 \partial x_n} \\ \frac{\partial^2 V}{\partial x_2 \partial x_1} & \frac{\partial^2 V}{\partial x_2 \partial x_2} & \cdots & \cdots & \frac{\partial^2 V}{\partial x_2 \partial x_n} \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ \frac{\partial^2 V}{\partial x_n \partial x_1} & \frac{\partial^2 V}{\partial x_n \partial x_2} & \cdots & \cdots & \frac{\partial^2 V}{\partial x_n \partial x_n} \end{pmatrix}$$

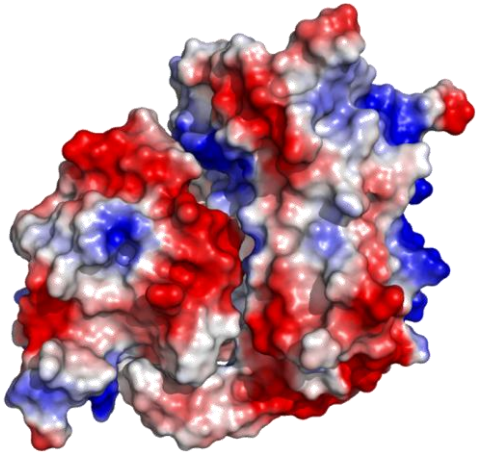
➔ CPU & GPU

Normal Modes Analysis

Analytical solving of
the equations of motion
eigenvalues = frequencies
eigenvectors = modes

Global motions of proteins

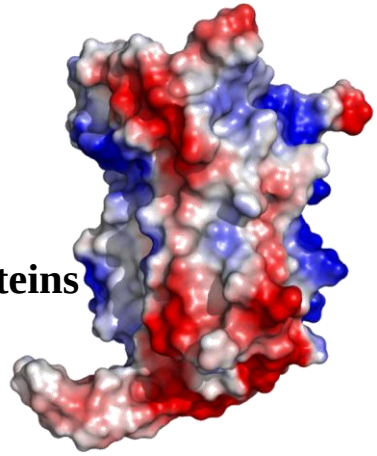
➢ **Functional motions**



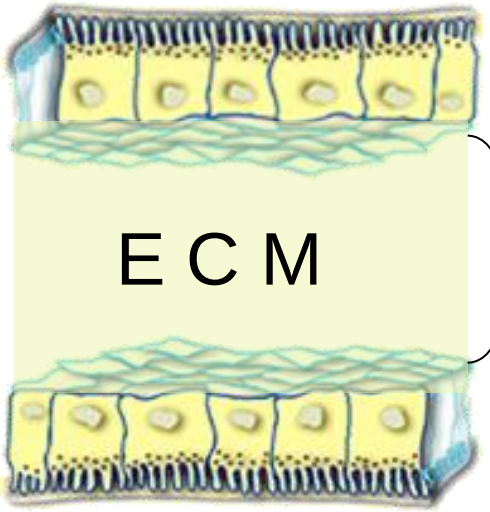
Docking

➢ **Interactions ligands/proteins & proteins/proteins**

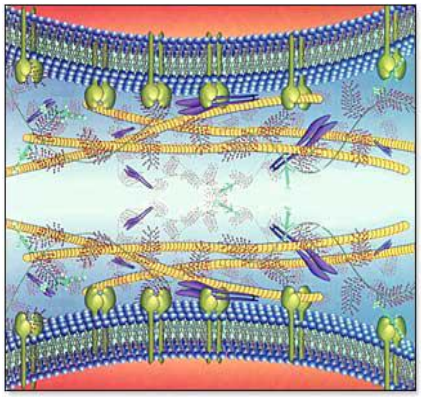
Surfaces + Electrostatic + Hydrophobic adjustements



Biological context



- Polysacharrides
- Glycosaminoglycannes
- Fibrous proteins (Elastin / collagen)
- Laminin, Fibronectin
- water…



Mecanical properties

[bones, elasticity of skin …]

Biological properties

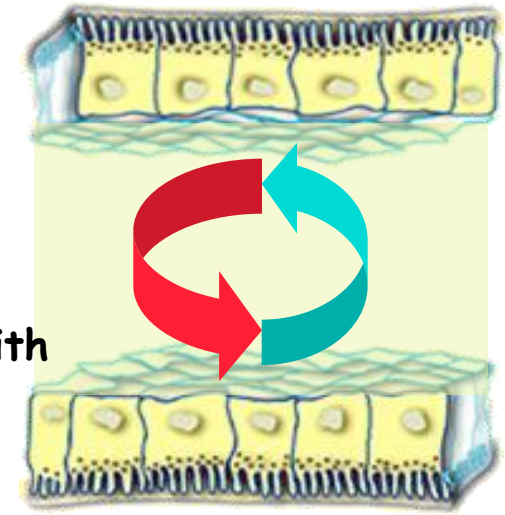
[**Cellular signals, inflammation**…]

➔ **Thrombospondin, LRP**

Degradation

➔ **MMPs**

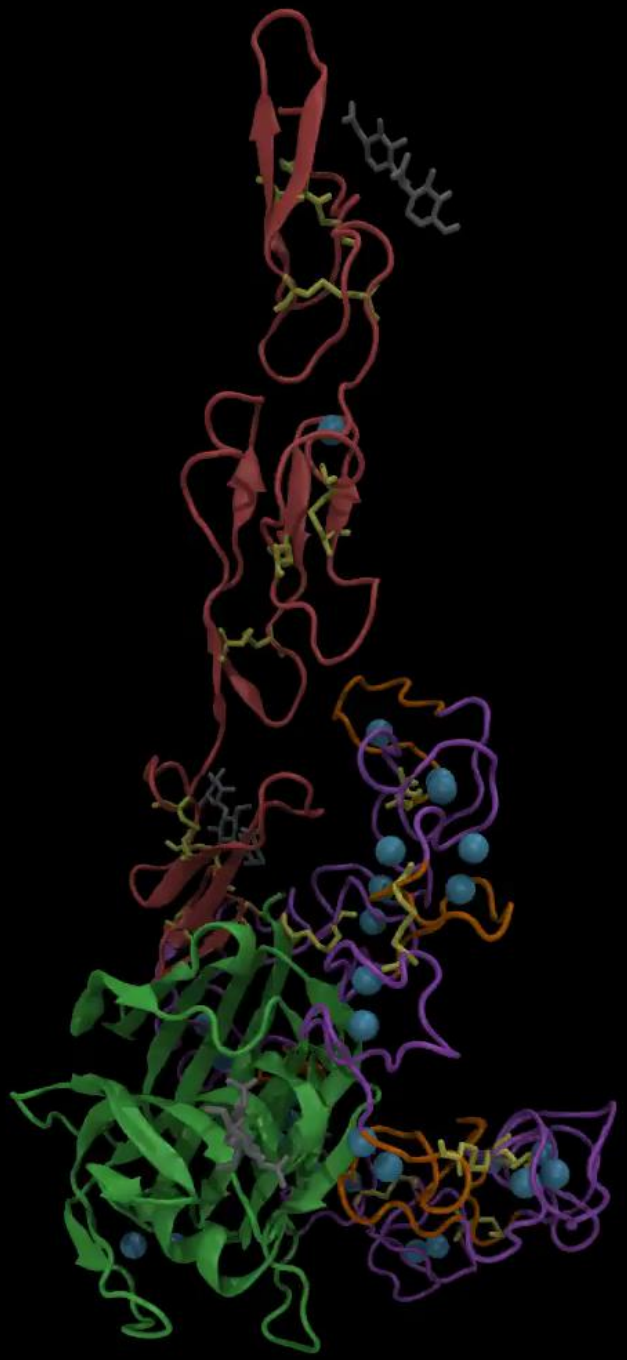
Regulation with
➔ **TIMPs**



➔ **Elastin peptides/EBP**

Extracellular Matrix ECM

Thrombospondin TSP1



EGF- like Repeats

Disulphide Bond

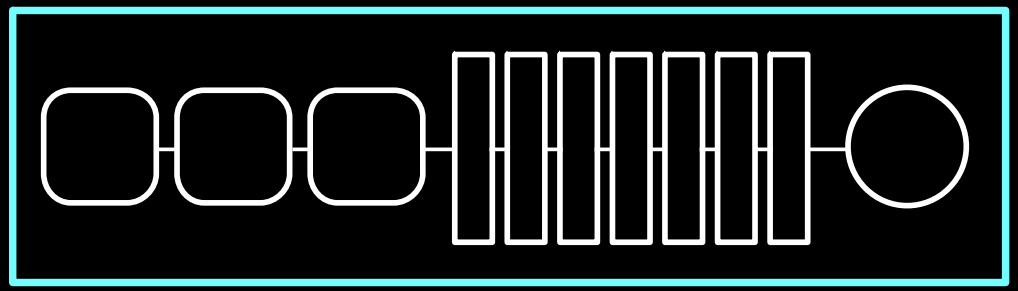
Calcium Ion

Mannose and Fucose

N- Type Stalk Repeat

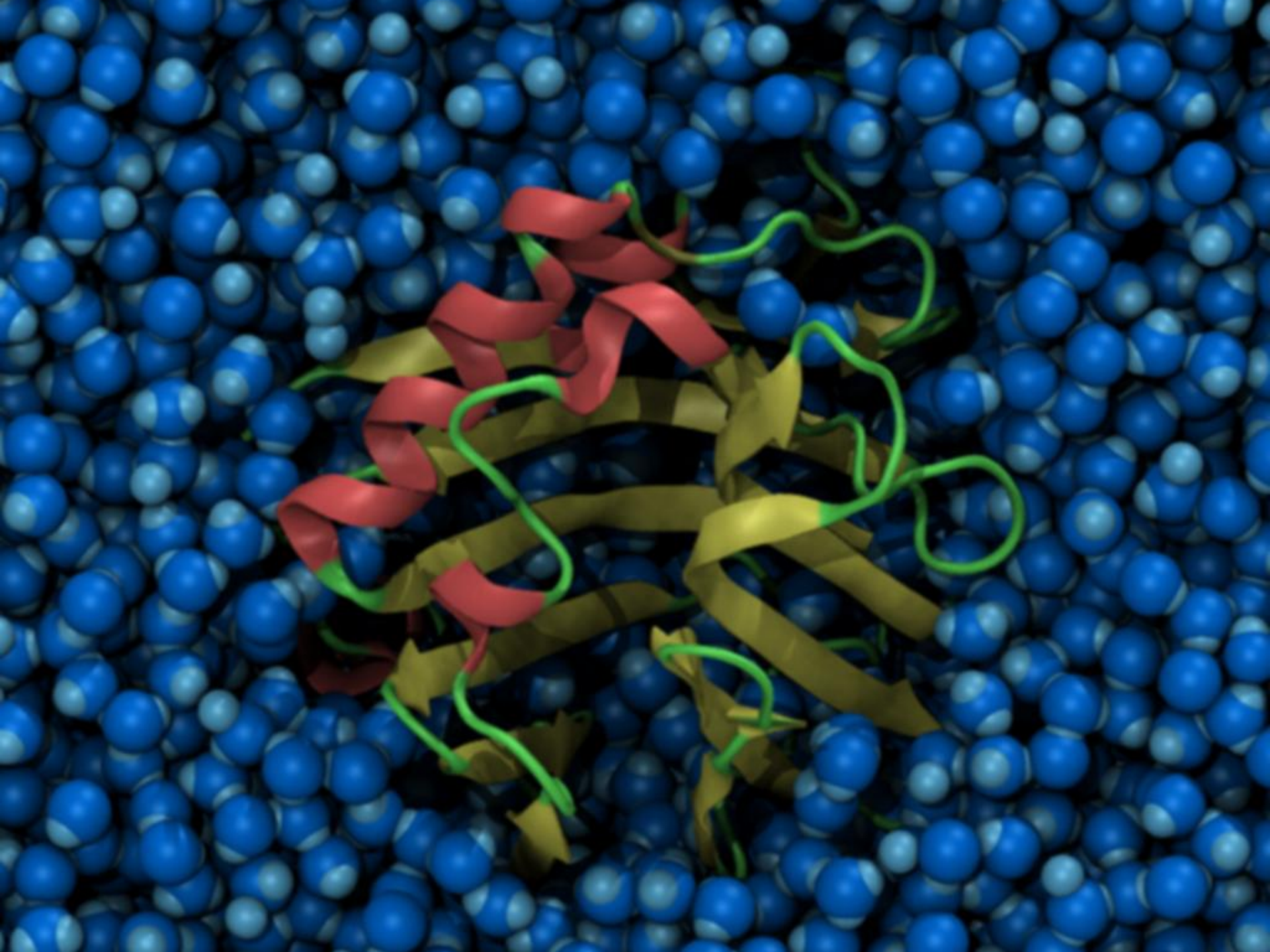
C- Type Stalk Repeat

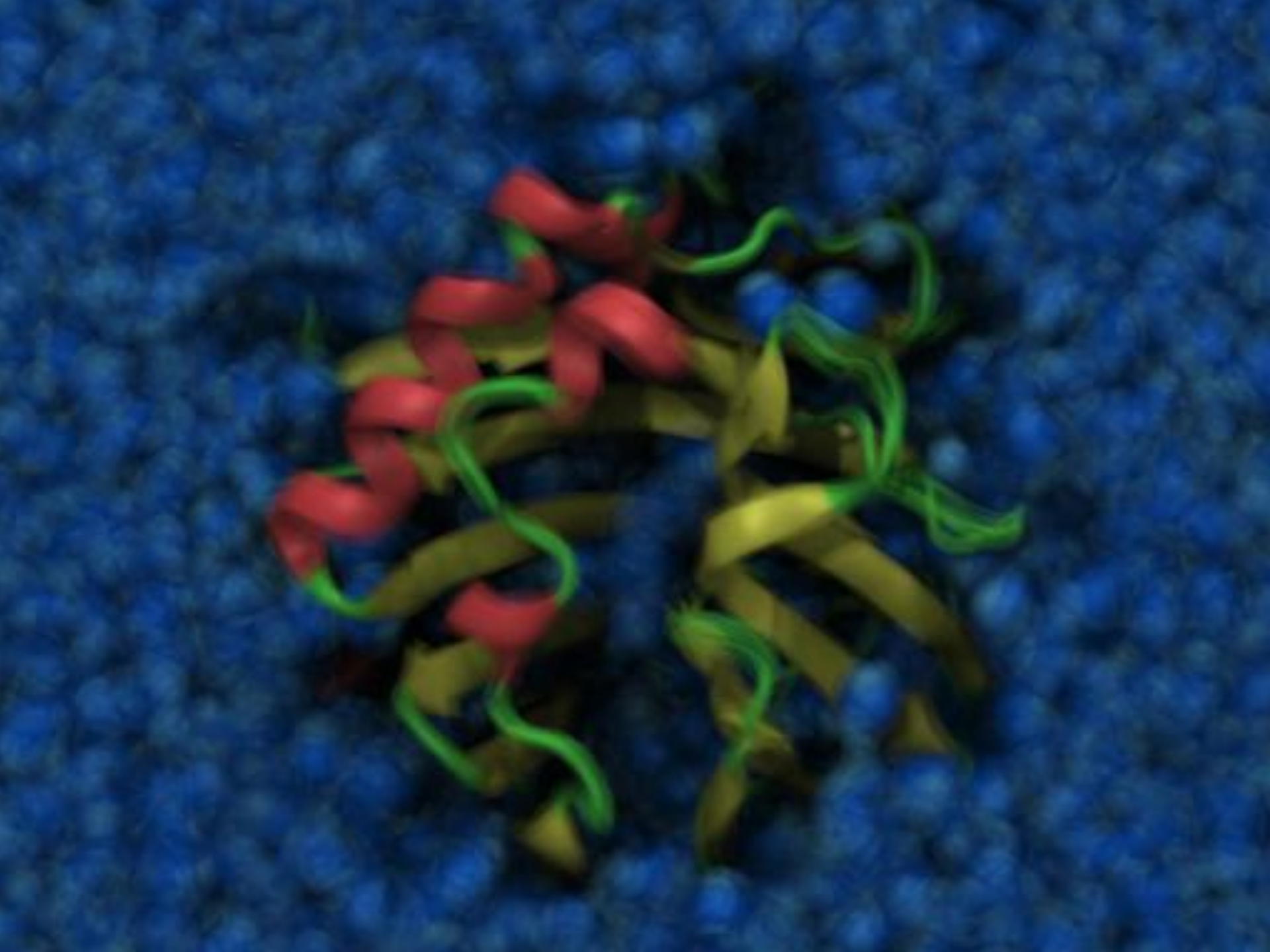
Globe



Simulation of TSP1

- Molecular Dynamics domain by domain
- Behaviour of « atomic parts »
- Normal Mode Analysis
- Detection of interactions using simulations
- New candidates
- Validation using HPC simulations
- Experimental validation…





Simulation of TSP1

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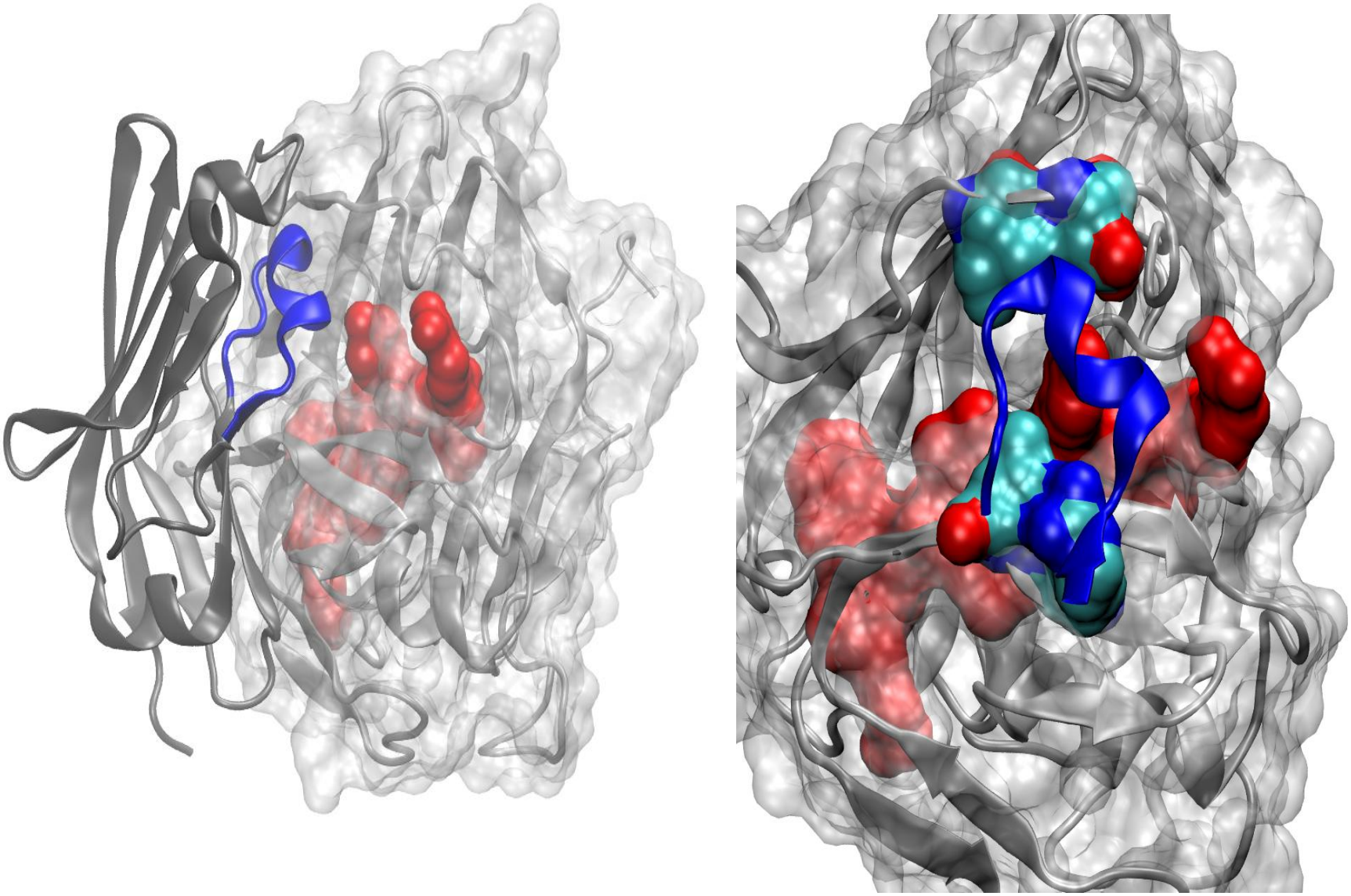
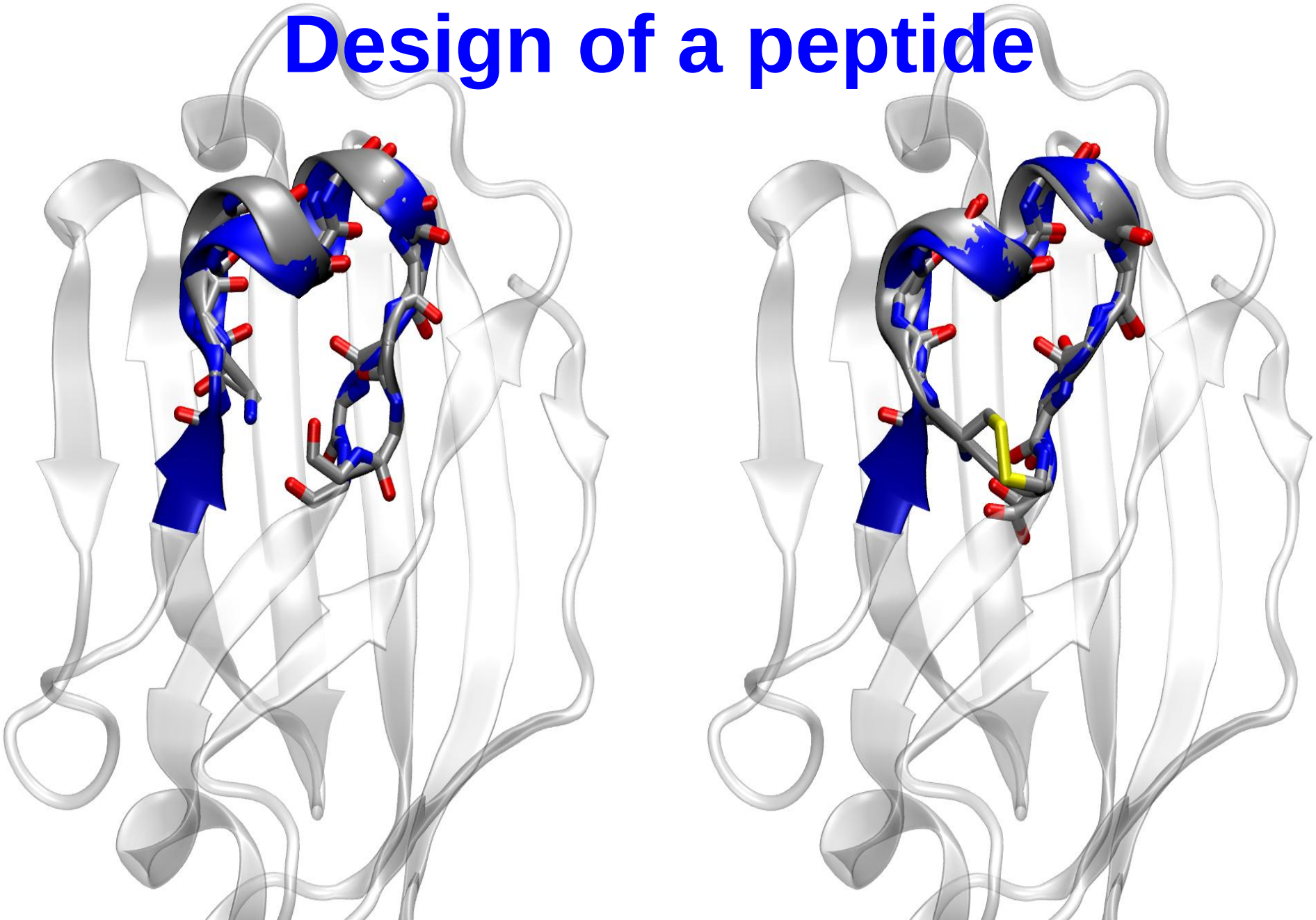
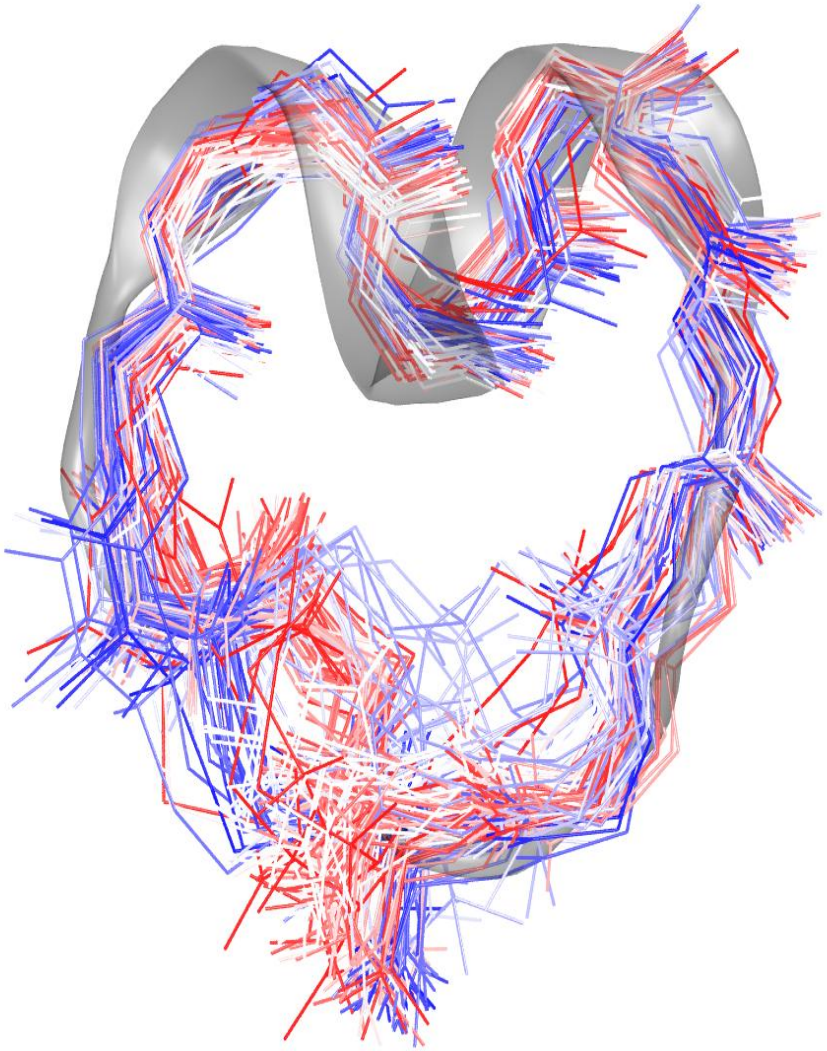
Interaction of TSP1/CD47

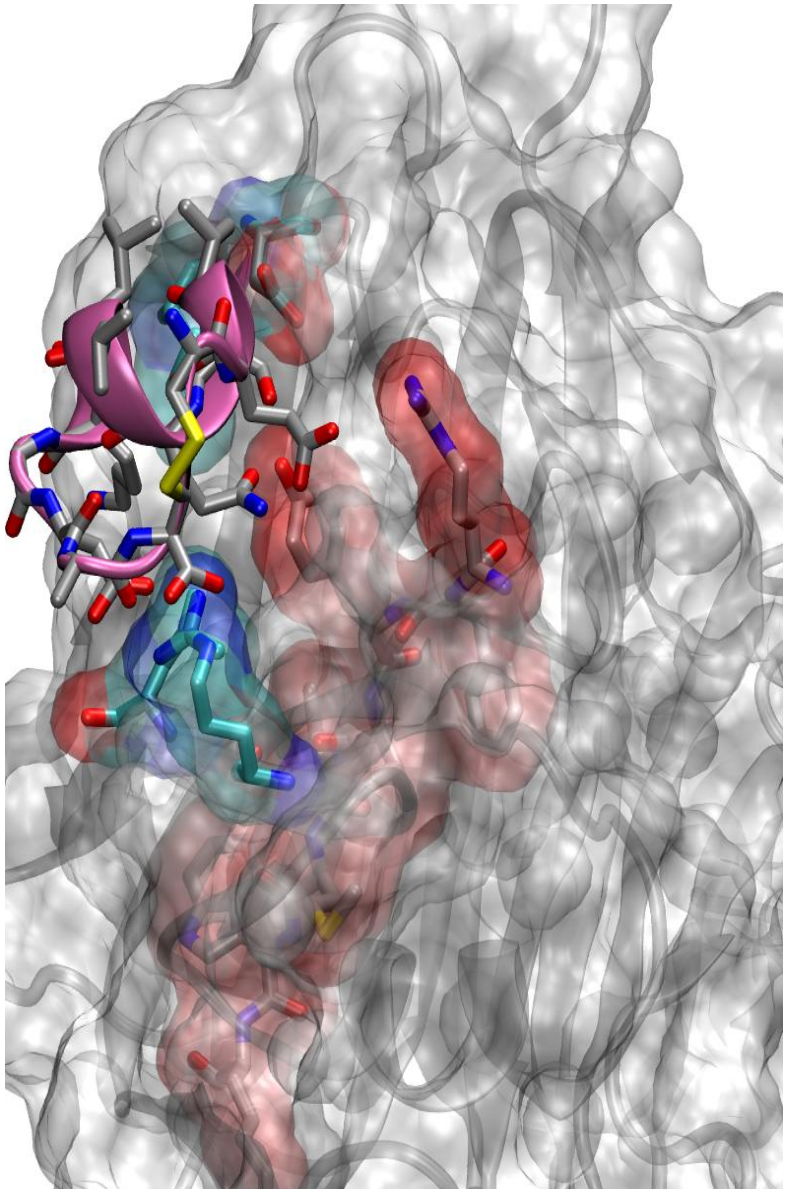


Design of a peptide



Simulation of the peptide





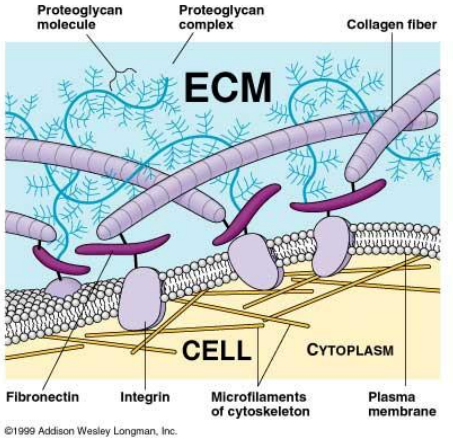
Biological effects

Biological effects

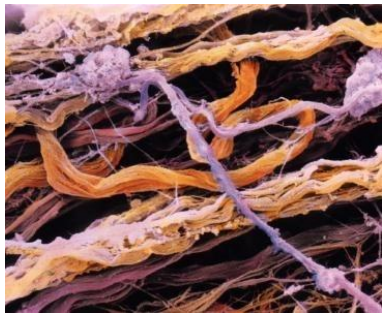
use of GPU : hours ➔ minutes

Inverse docking: how to get new molecules !

Problematic & scientific context

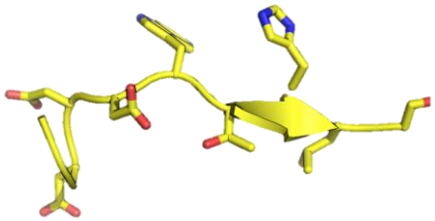


Fibrillar proteins



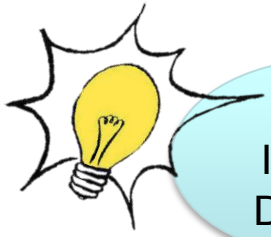
Elastin, collagen,…

Elastases
Collagenases
…



Active peptides
Matrikins
Matricryptins
…
Drugs
Chemical ligands

Which peptide/drug is able to interact with which ECM protein ???



HPC
Inverse
Docking

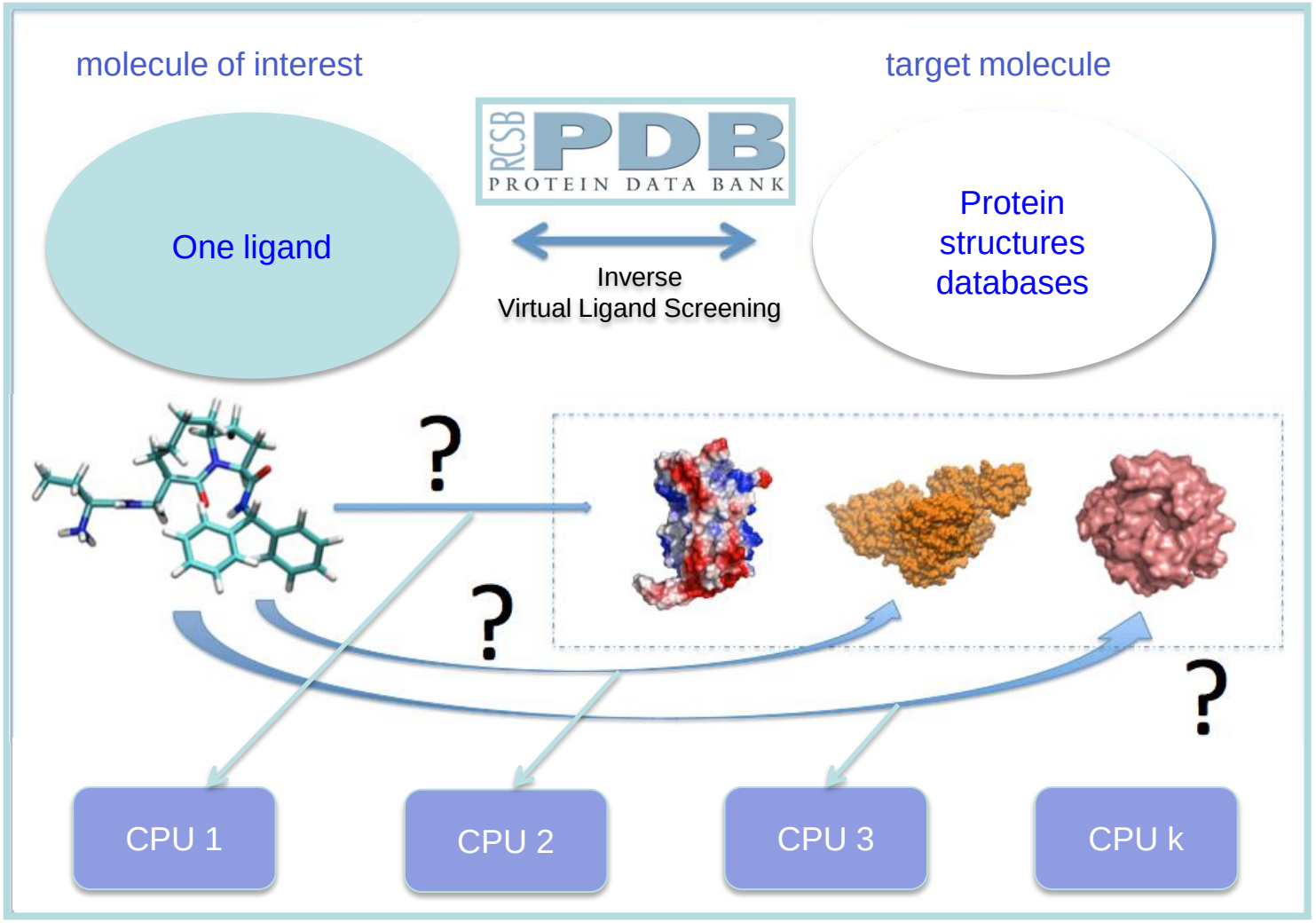
1

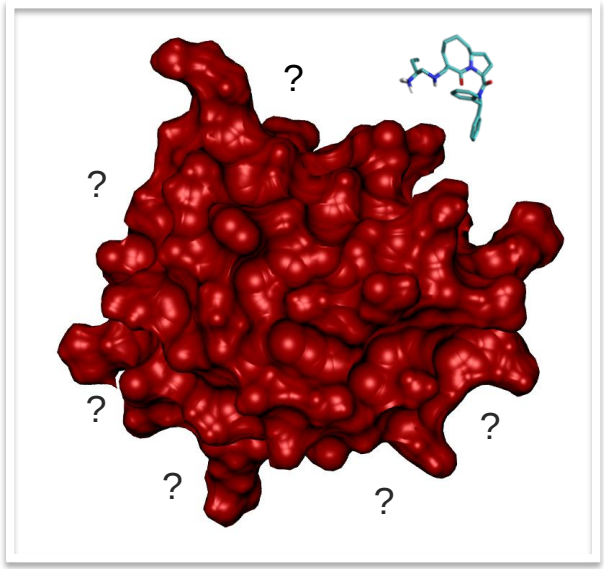
developments
for ligands

2

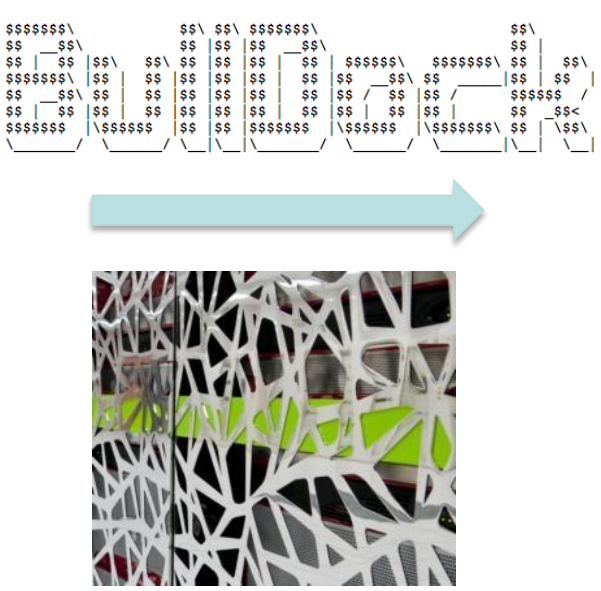
developments
for peptides

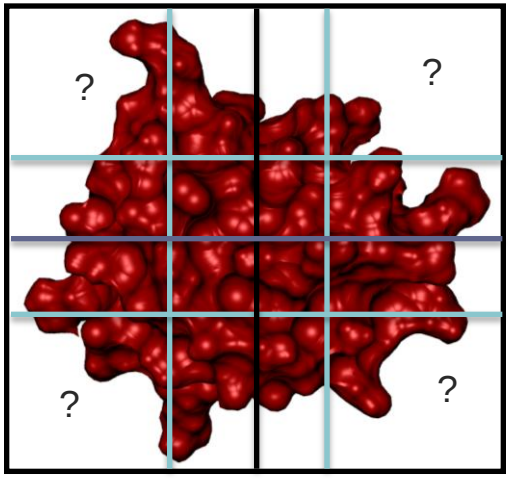
Inverse docking procedure



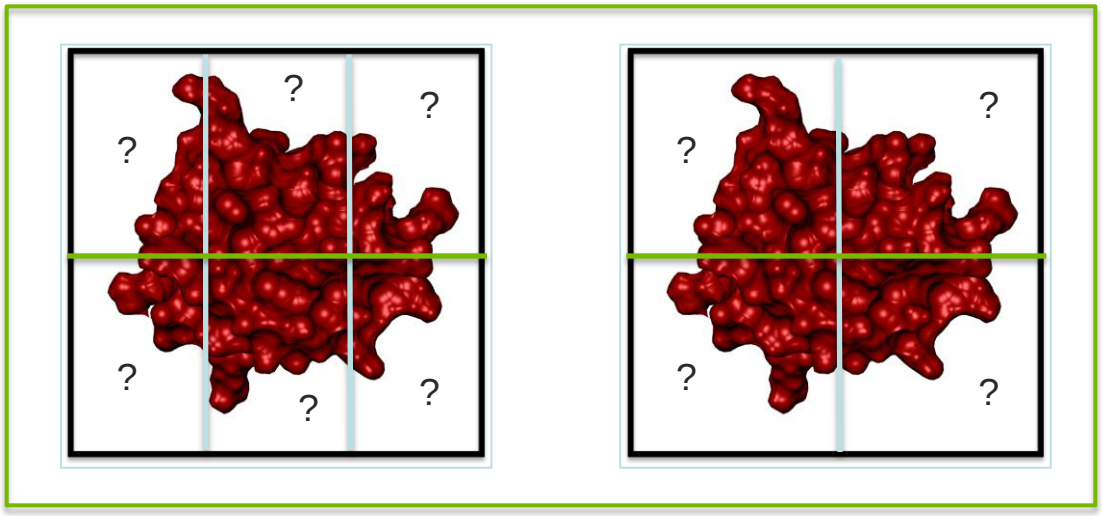


blind docking

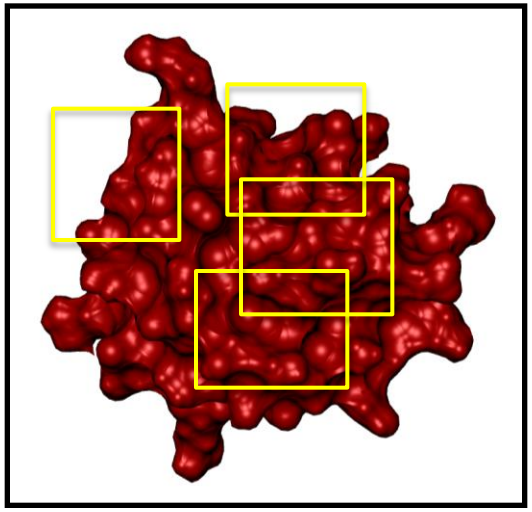




druggables cavities searchs
Fpocket[1]

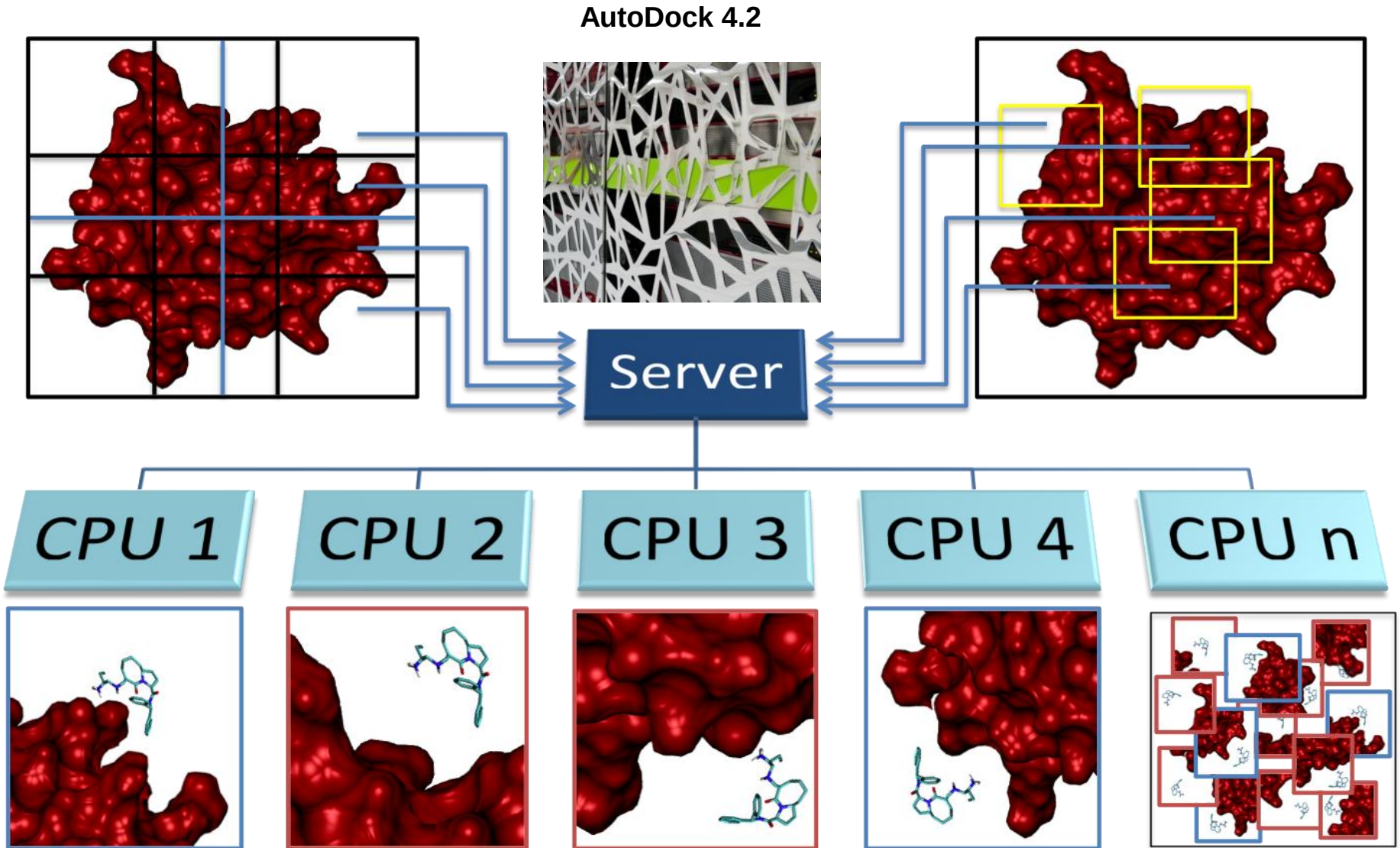


Arbitrary cutting in multiples boxes



1. Fpocket : V. Le Guilloux, P. Schmidtke,
and P. Tuffery, MTi, Paris.

Task scheduling and Distribution



center for
excellence in parallel
programming

User Needs

Faster Science, less power consumption, better results…

Application and Performance Experts

PhD in different scientific domains
Focussing on Performance

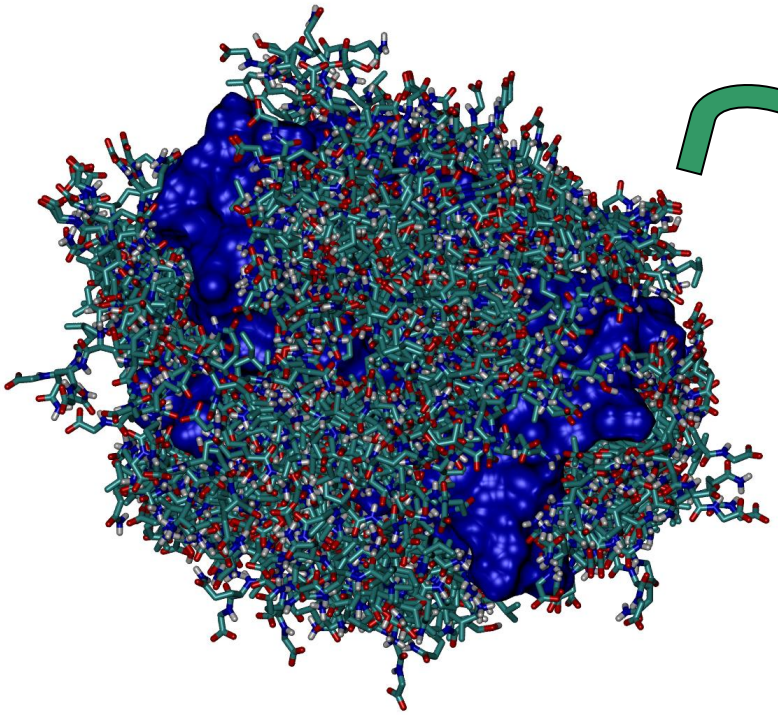
here
Soline LAFORET

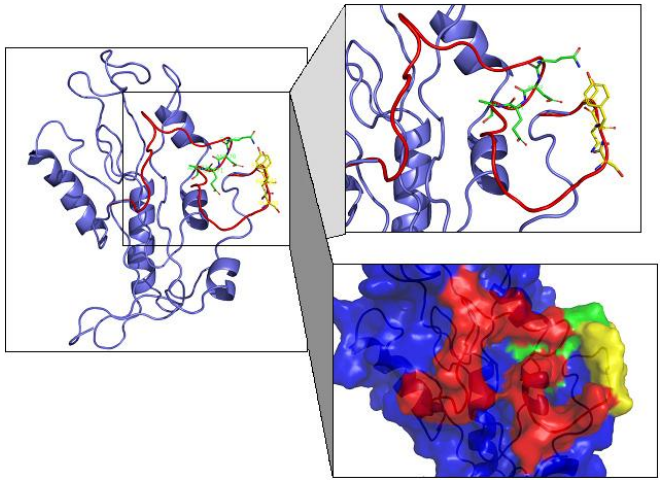
Bull Software Stack and Tools

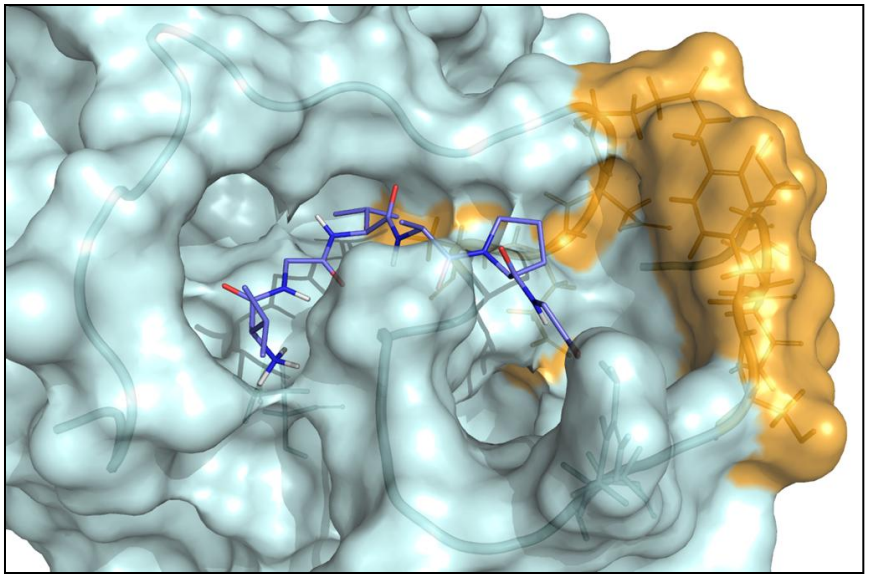
Dedicated Hardware

POC and Experiments
(CPU, Accelerators, …)

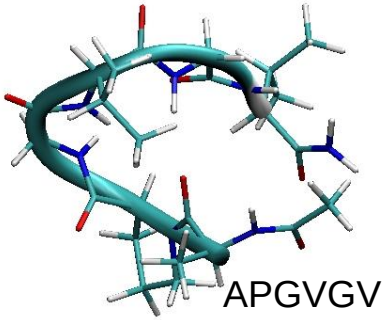
First application of « inverse docking »

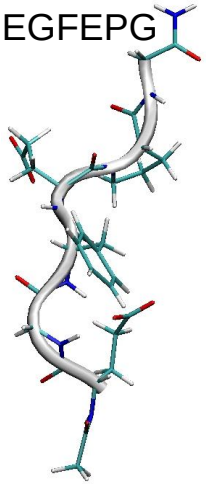


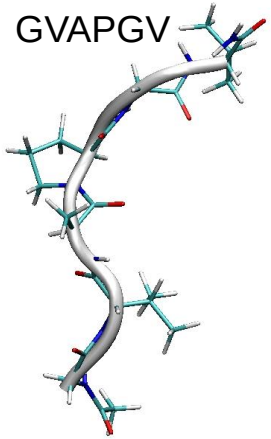


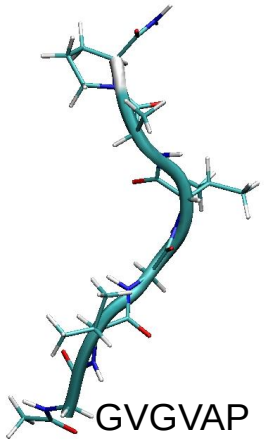


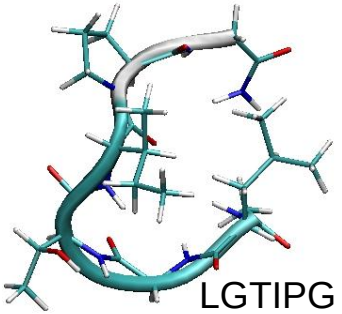
First application of « inverse docking »

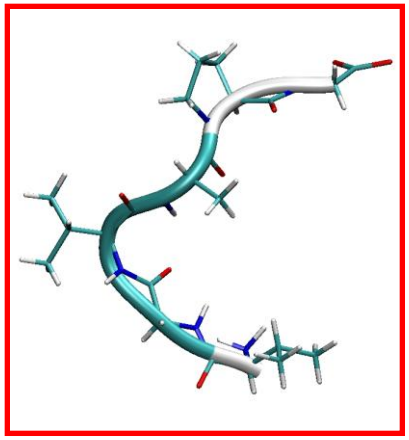


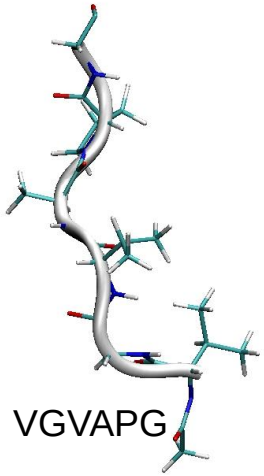


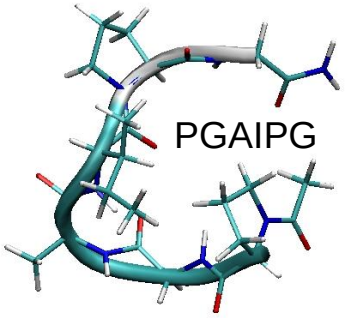


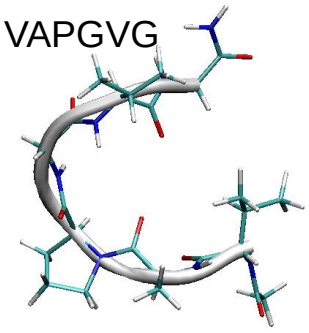


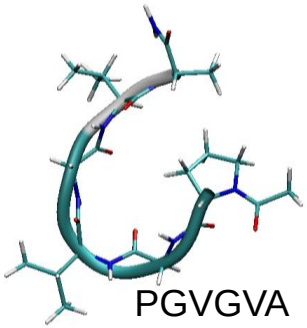


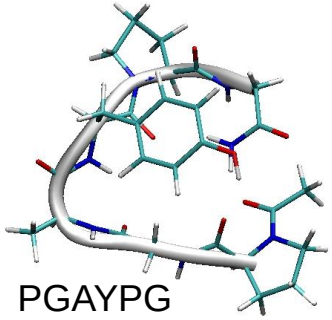




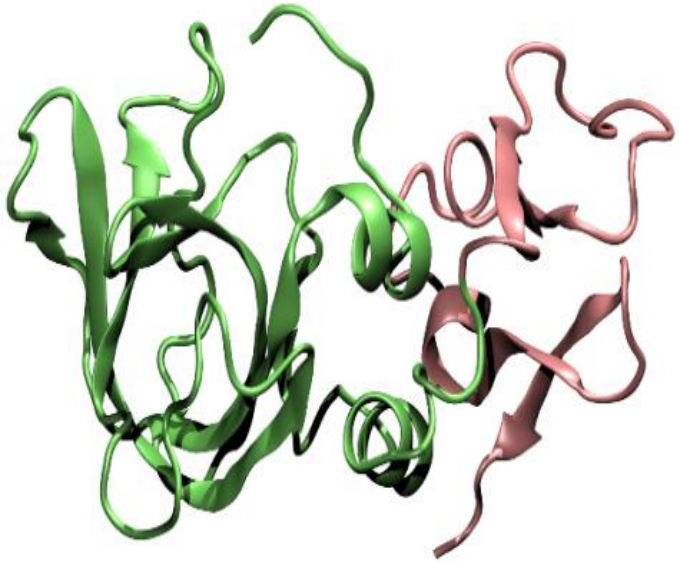


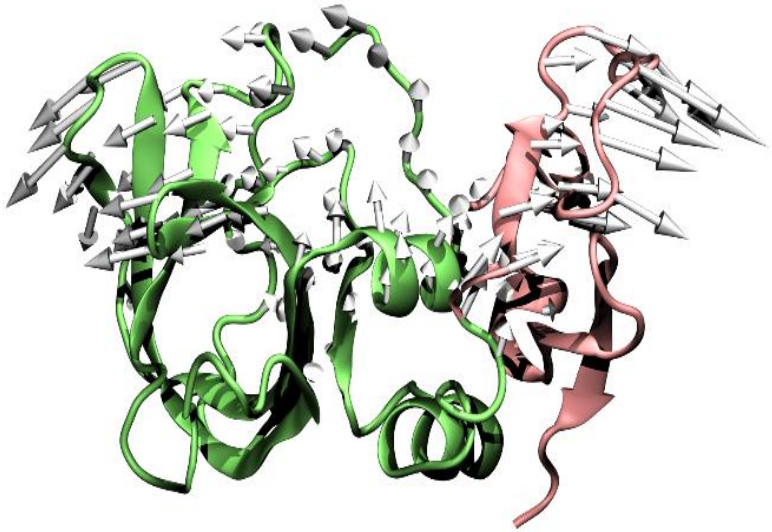


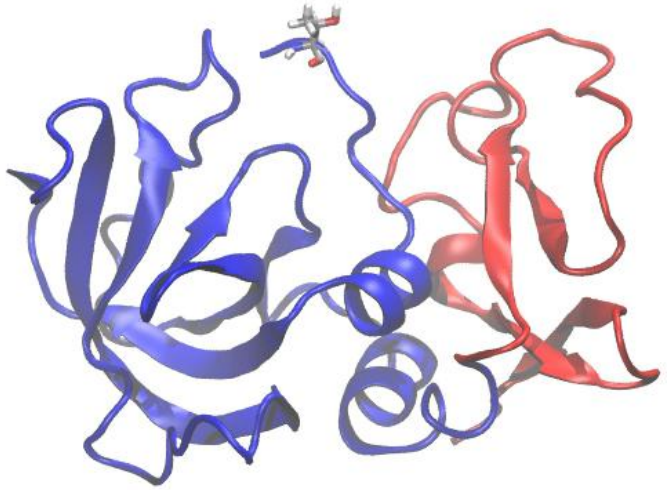




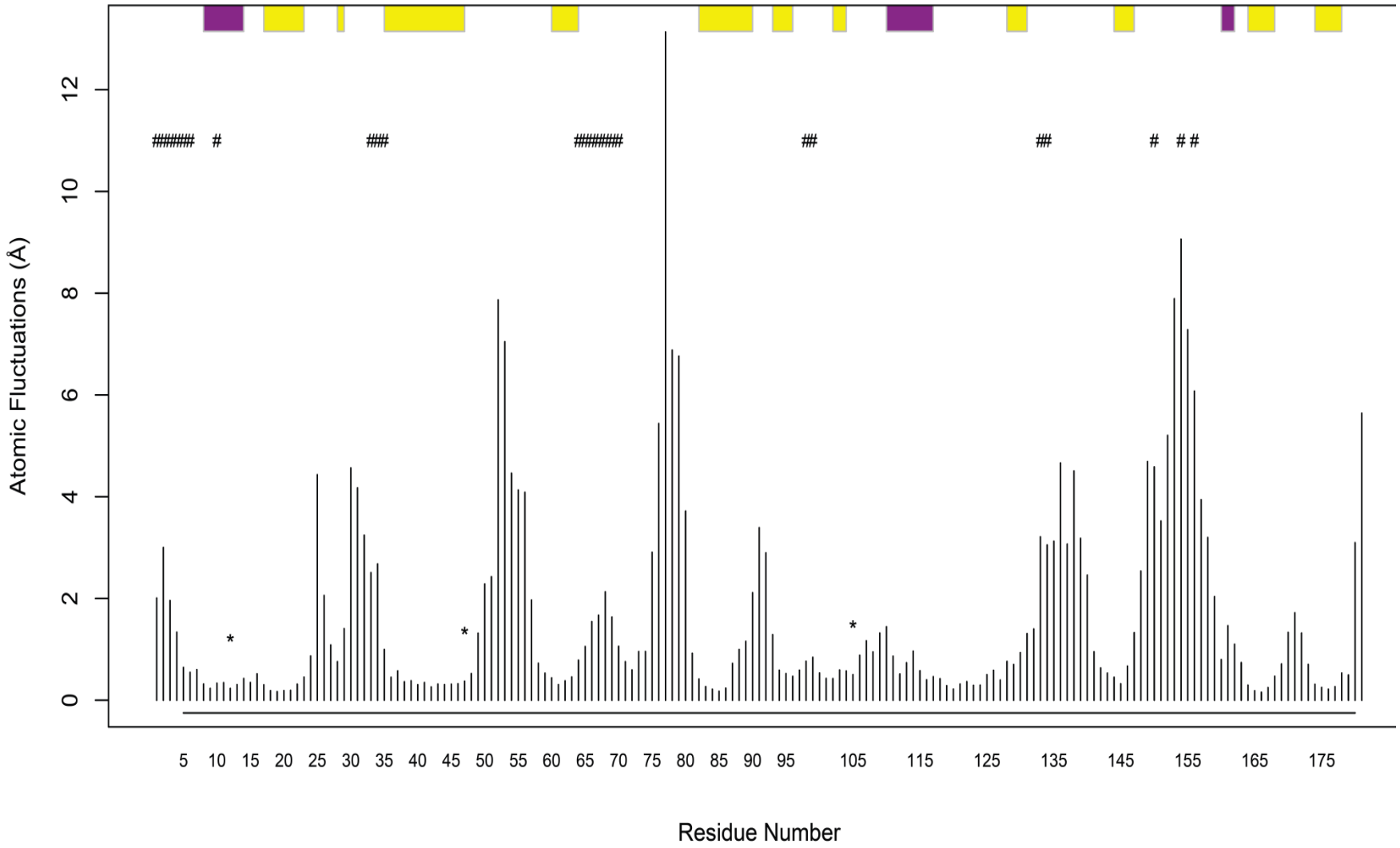
Second application of « inverse docking »



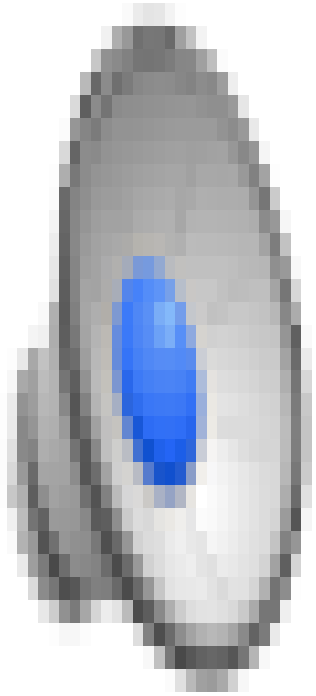




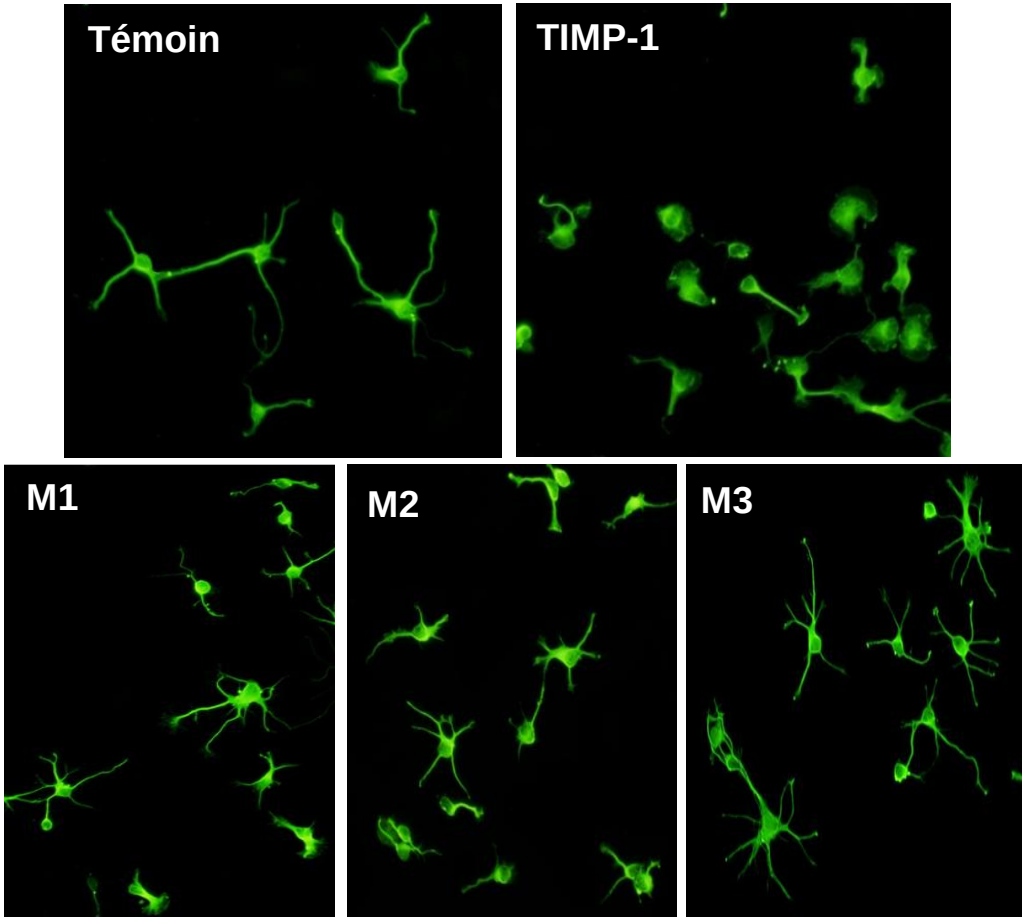
Second application of « inverse docking »



Second application of « inverse docking »



Biological associated effects

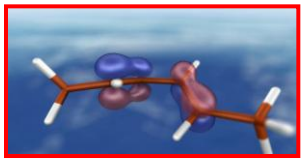


Quantum docking: how to get new interactions!

« Quantum Docking »

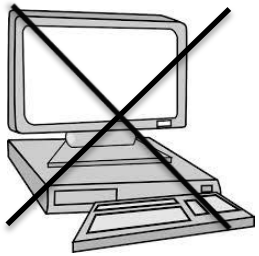
- Using Quantum Mechanics to evaluate affinity score between ligand and receptor.

$$H\Psi = E\Psi$$



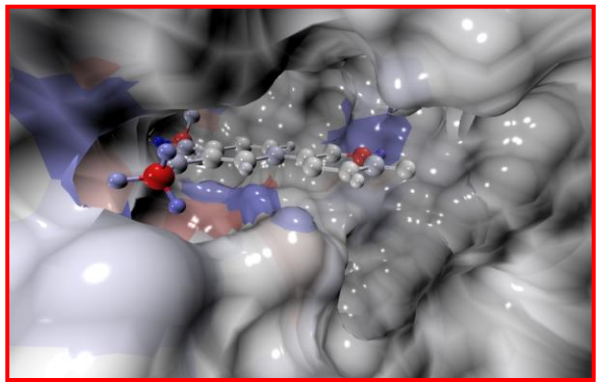
Very HUGE calculations

• New quantum methodologies called « linear » ➔ possibility to calculate very large systems at electronic levels for instance in active sites in Proteins…



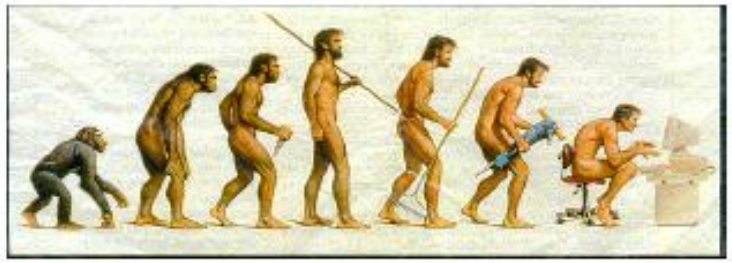
→ HPC NEEDED!

→ Access to polarization effects, water behaviour…



Some shortcuts!

FUTURE!



Age de pierre | Age de bronze | Age de fer | Prospectives

1980 | 1990 | 2000

➔ New TOOLS…
➔ Big Data…

to visualise

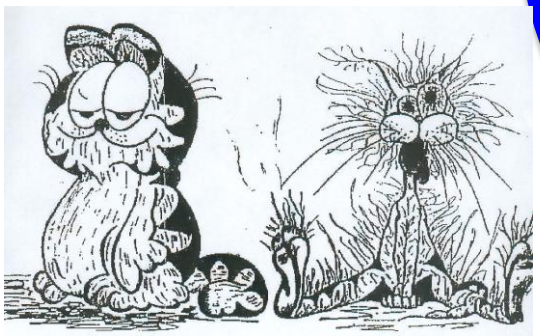
to model

➔ New TOOLS…
➔ Big Data…

to simulate

➔ Exascale ?? !!

before …



… after