Winter School AEBB

9 – 11 Février 2021

Apport de la modélisation moléculaire et des simulations numériques dans la compréhension des mécanismes d'actions de molécules biologiques

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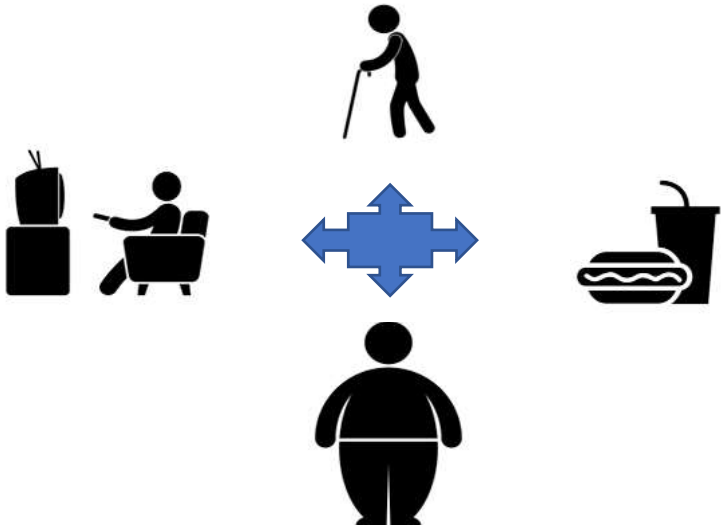
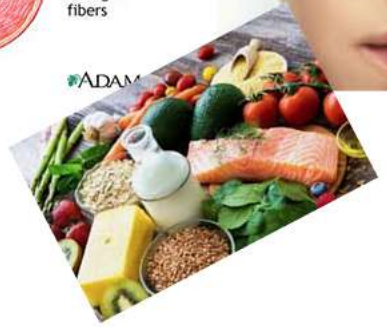
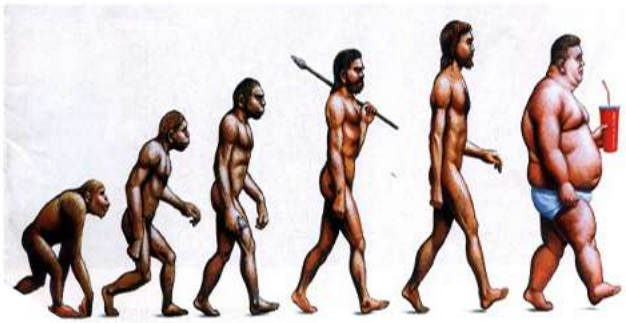
The biological context

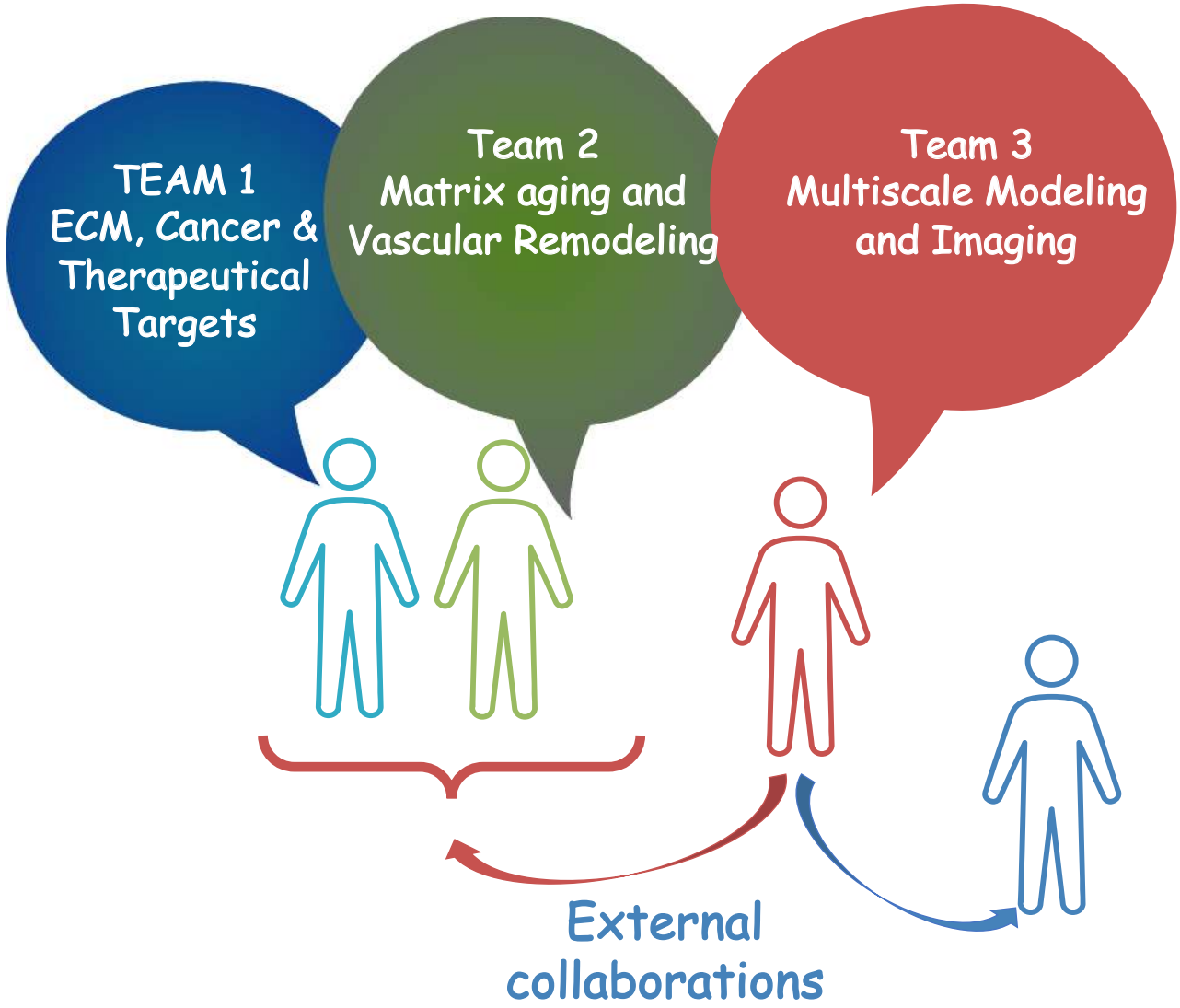
Extracellular Matrix and Cellular Dynamics







Extracellular Matrix and Cellular Dynamics



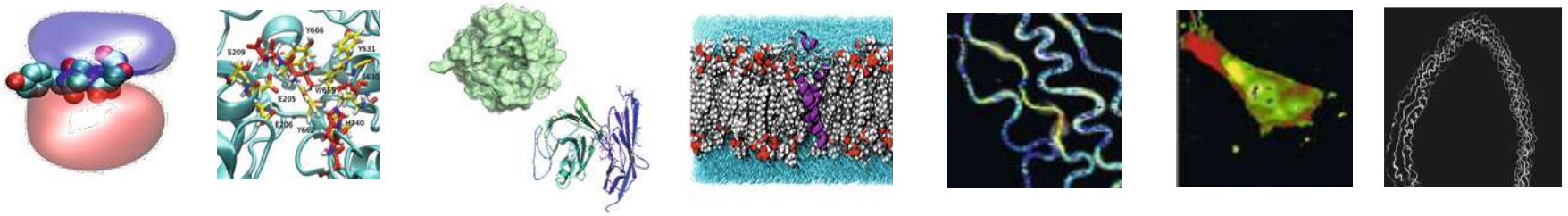
Multiscale Modeling and Imaging

« MIME »

"Bottom-up approach"

Nano — Multiscale — Macro

"Upside-down approach"



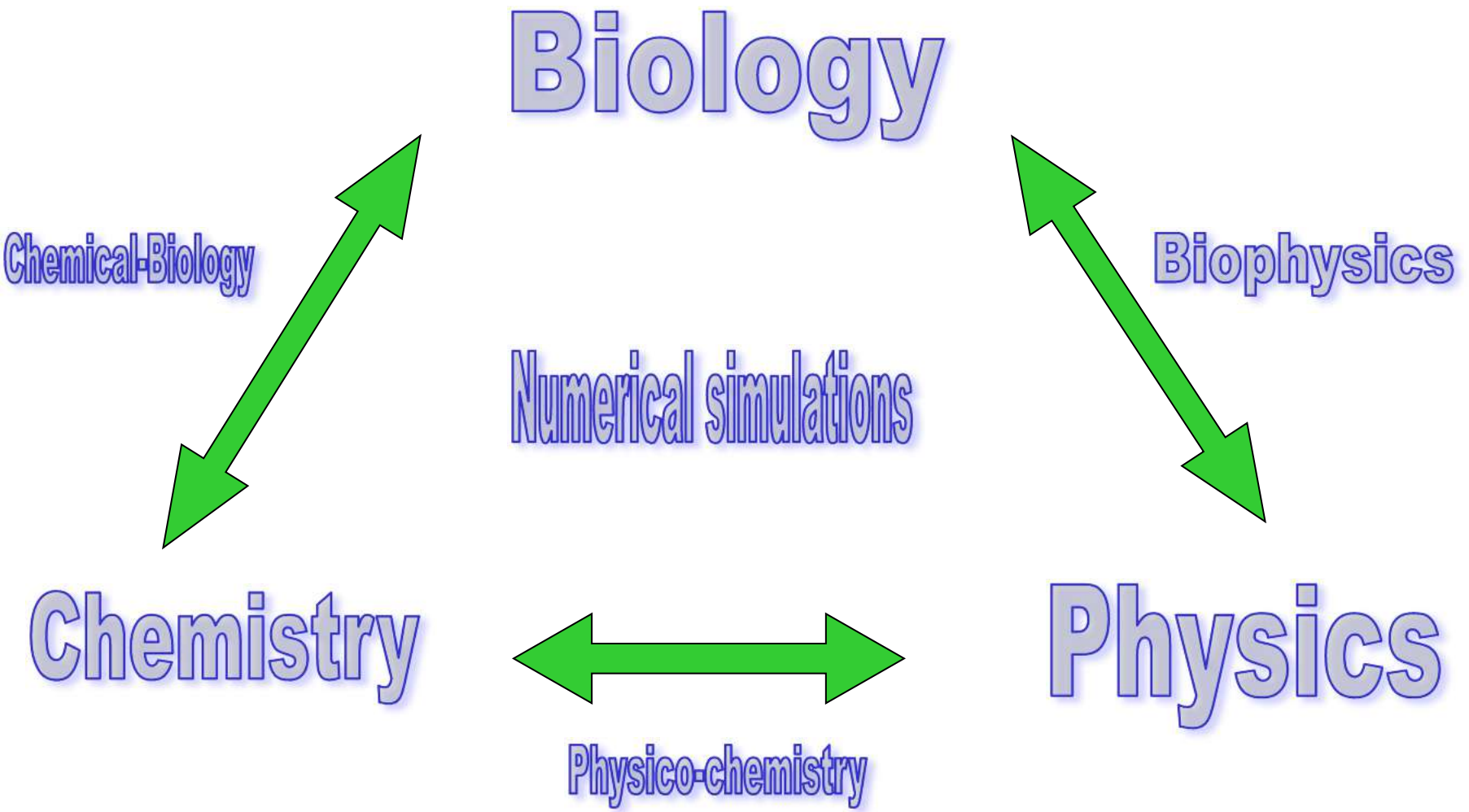
Observe ⇄ Understand

HPC as a computational microscope!

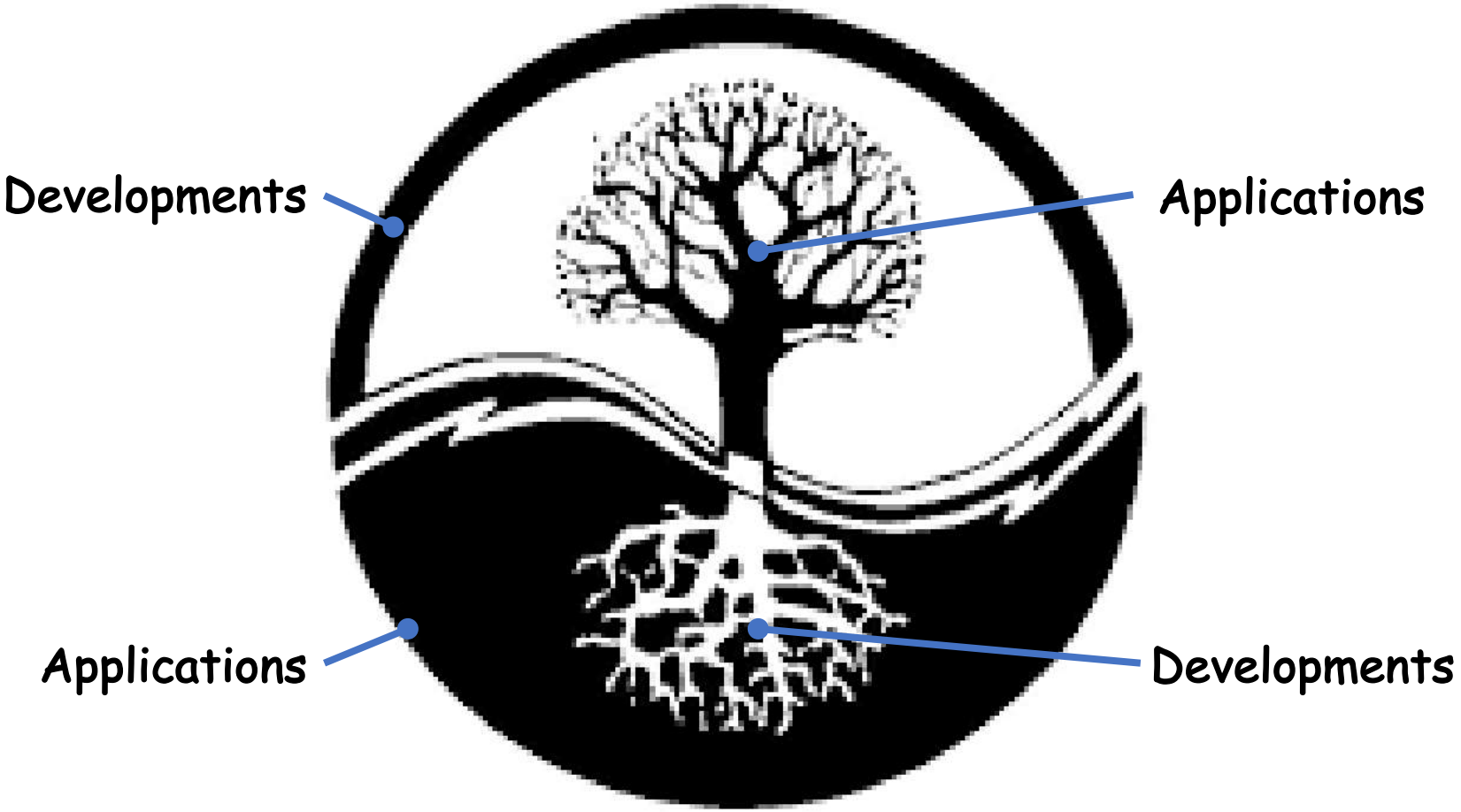
MAgICS

Université de Reims Champagne-Ardenne

Structural biochemistry *in silico*



MultiScale Modeling and Imaging - MSMI



Molecular Modelling: Why?

Numerical Simulations

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

«in silico veritas?»

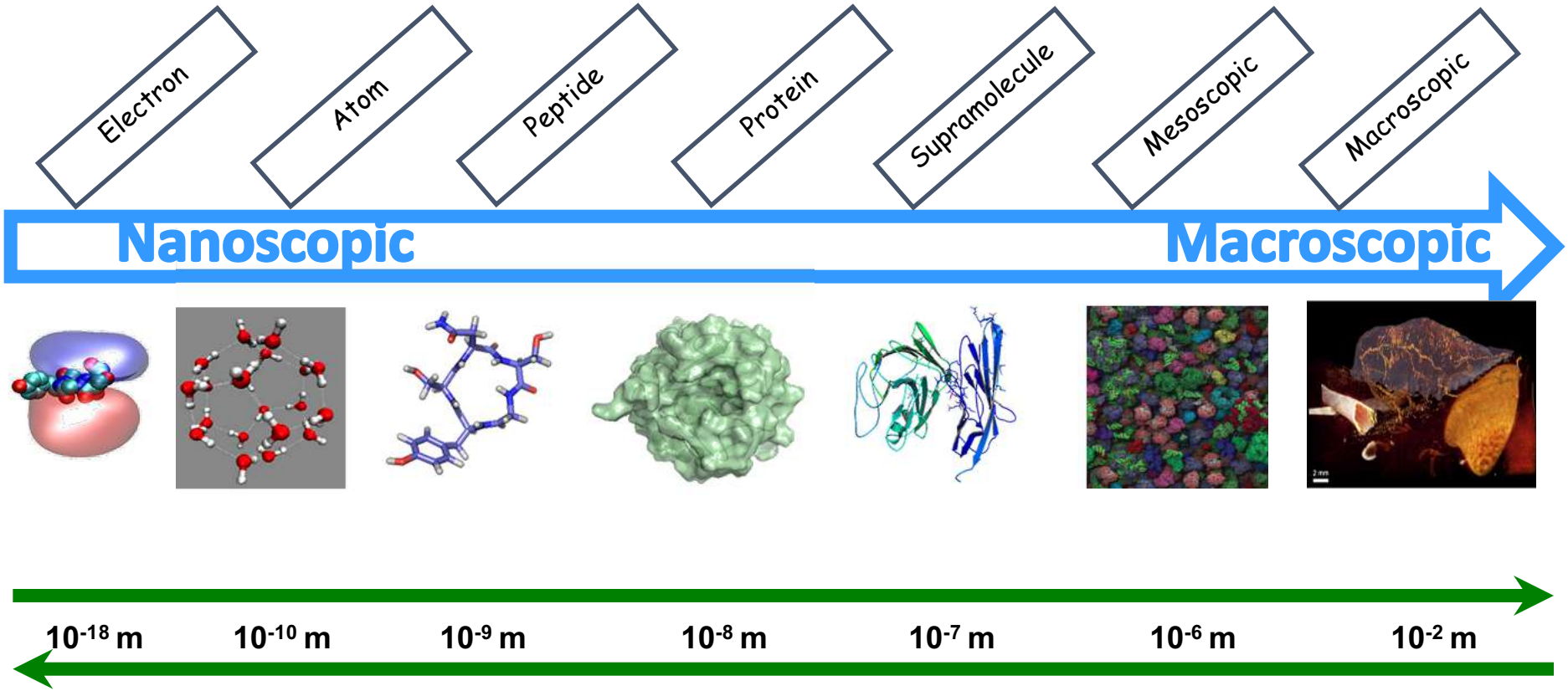
- Predictions, Homologies, Numerical Simulations,

  → **3D structures,**
- Determination of functionnal conformations,

  → **structural adapatability,**
- Determination of active sites, mutations, docking…

  → **functional prediction …**

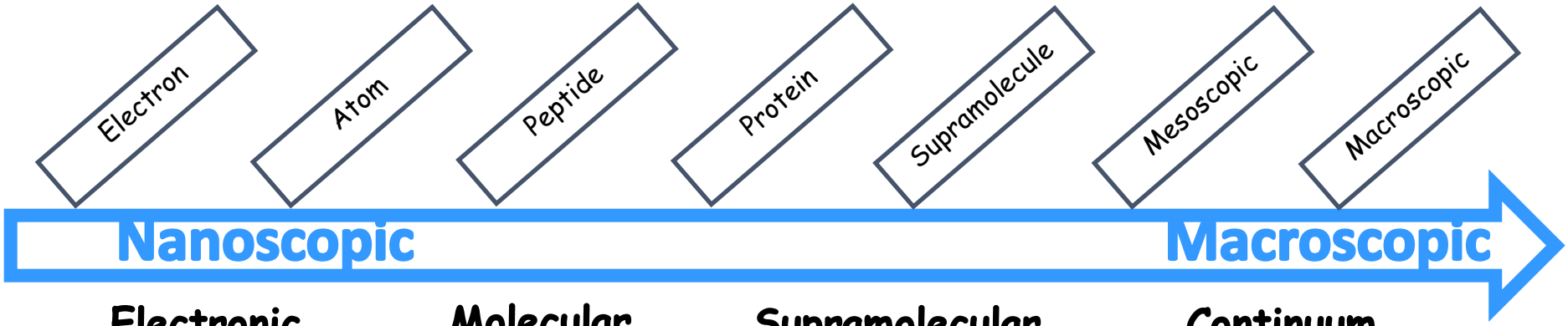
Multiscale problem



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

Multiscale problem

Multiscale problems ➔ Multiphysics



Electronic level
- 1-2 peptides
- 1 association
- $<10^2$ atoms
- « 50 ns »

Quantum Dynamics

Molecular level
- 2-10 proteins
- 1 complex
- 10^5 atoms
- 500 ns

Molecular Dynamics Normal Modes

Supramolecular level
- 5-20 proteins
- 10 complexes
- 10^6 atoms
- 5 μs

Coarse Grained or Langevin Dynamics

Continuum level
- >1000 proteins
- >100 complexes
- $>10^6$ atoms
- >1 ms

Mesoscopic Dynamics

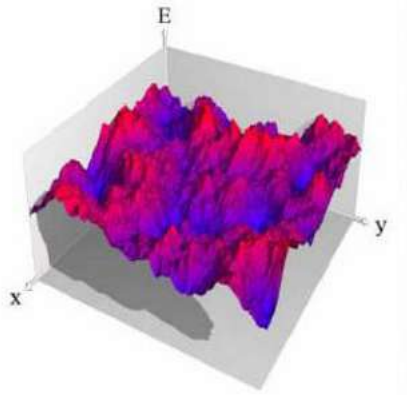
Molecular Modelling: How it works?

Molecular Dynamics

$E_T = E_c + V = cste$ $E_c = 3/2\ NkT = \frac{1}{2}\ mv^2$

Empirical Force Fields & programs

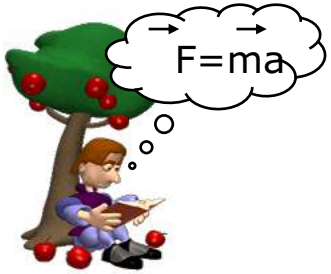
(Gromos, NAMD, Amber, Charmm…)



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

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

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

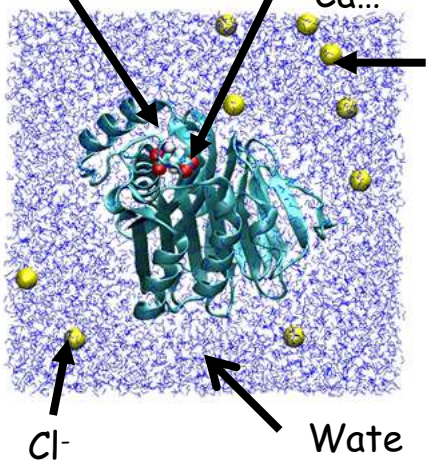


$\mathbf{r}_i(t) \rightarrow \mathbf{r}_i(t + \delta t)$

10^{-15}s ➔7-10 orders of magnitude

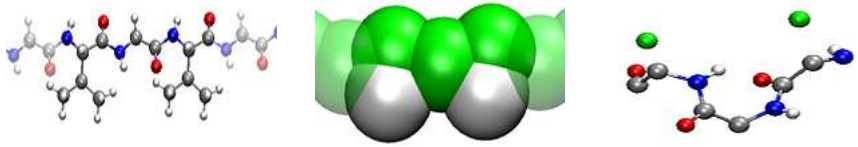
➔N atoms, N^2 Memory, N^3 time ➔ CPU & GPU

➢ **Local motion of peptides and proteins**



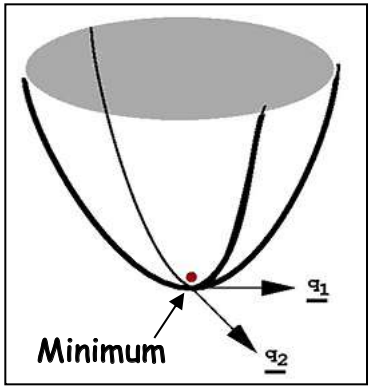
Coarse-grained

OPEP, Martini



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

Some other methodologies…



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

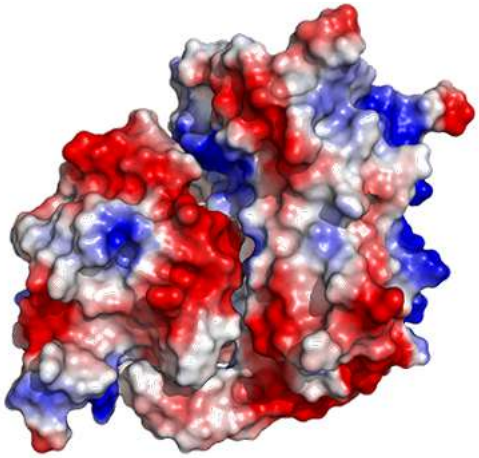
➔ CPU & GPU

Normal Modes Analysis

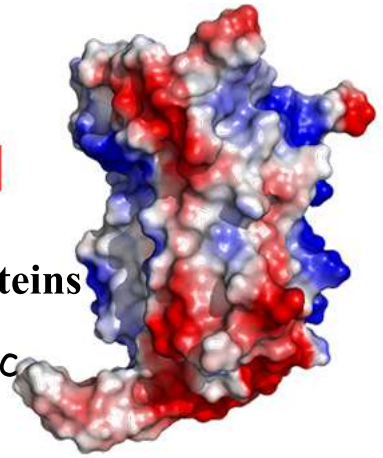
Analytical solving of
the equations of motion
eigenvalues = frequencies
eigenvectors = modes

Global motions of proteins

- **Functional motions**



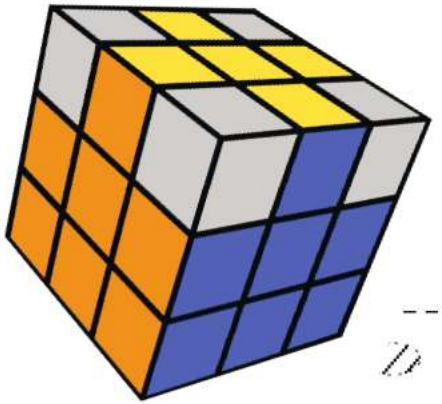
Docking



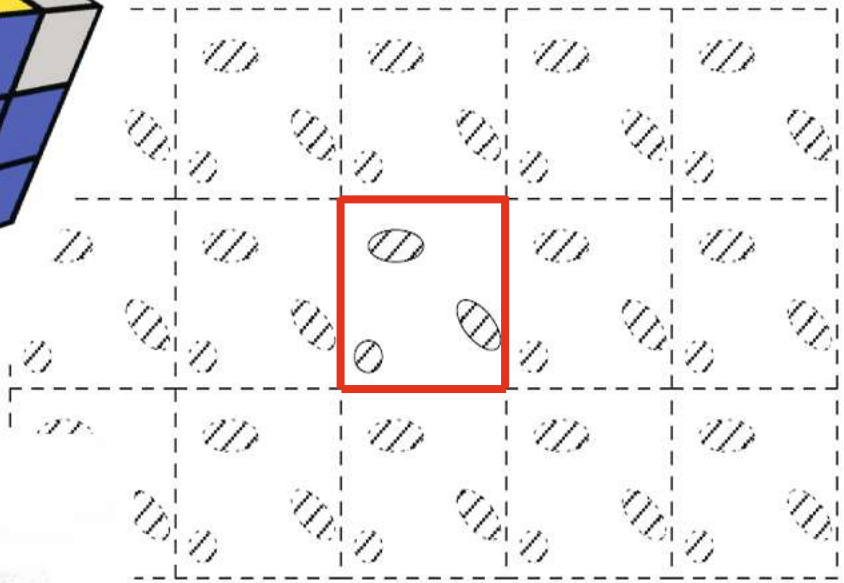
- **Interactions ligands/proteins & proteins/proteins**

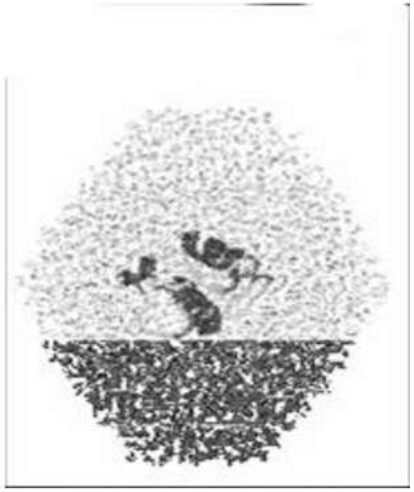
Surfaces + Electrostatic + Hydrophobic
Complementarities

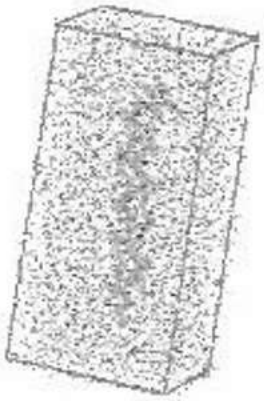
Molecular Modeling and Numerical Simulations

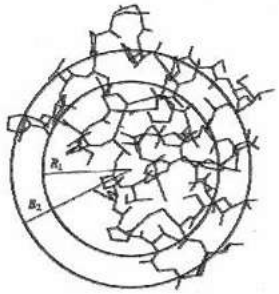


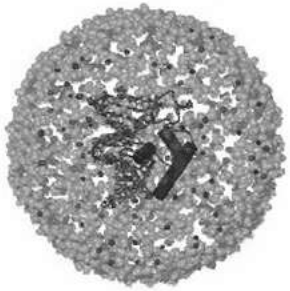
➔ Simulation of Avogadro number





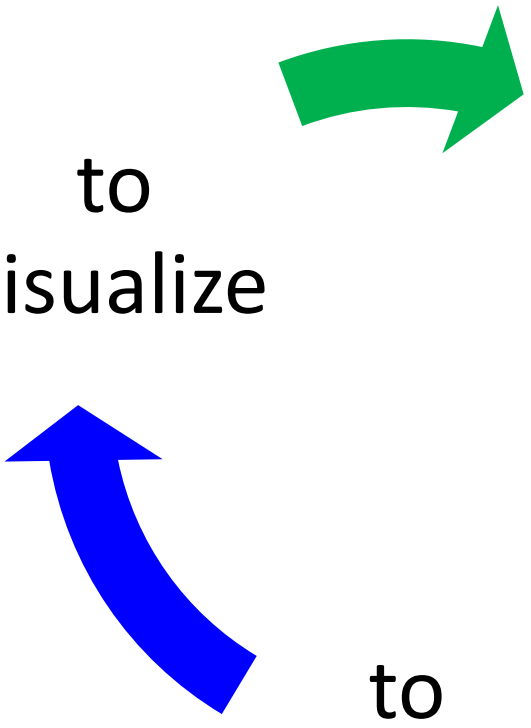






Tools to reach our goals…

- Pymol
- VMD
- Chimera
- Yasara…



- Schrödinger
- MOE
- OneAngströem
- Modeller
- iTasser…

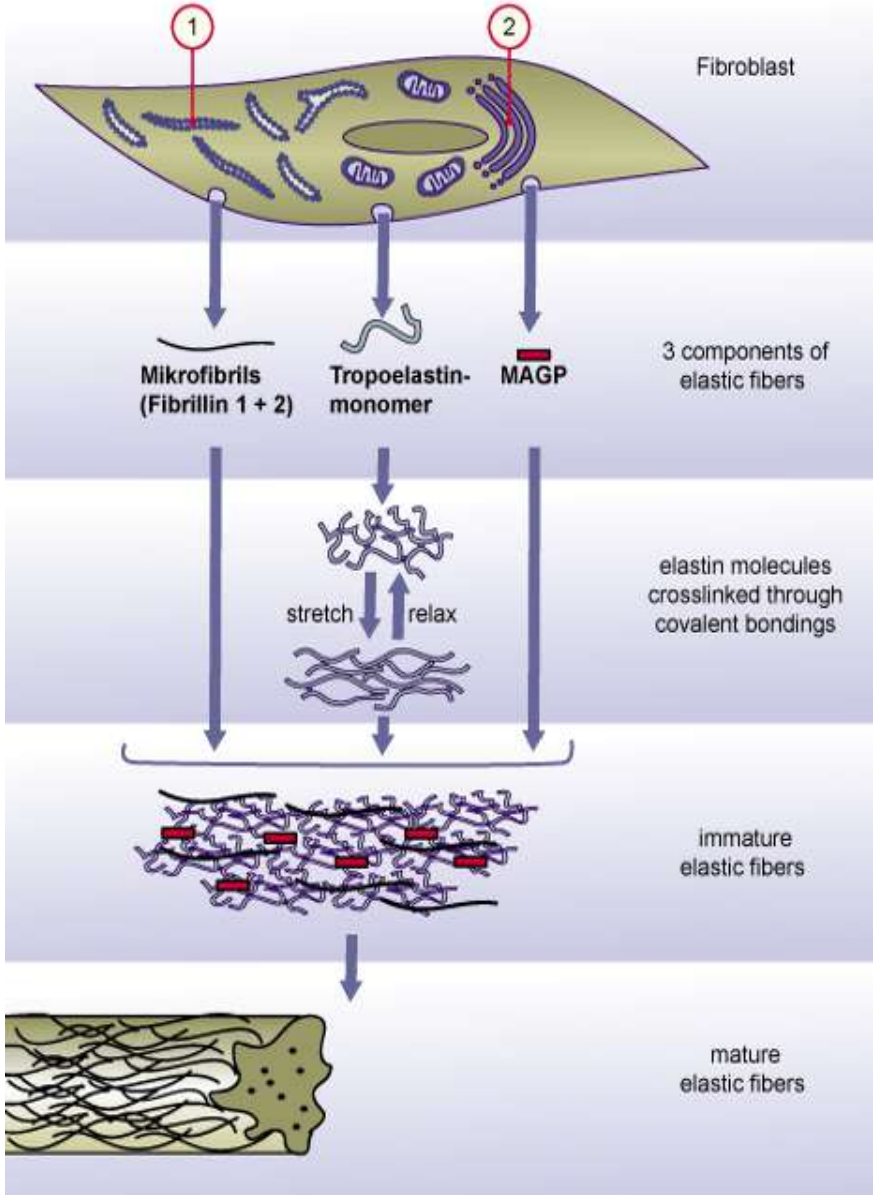
- NAMD
- CHARMm
- GROMOS
- AMBER
- Thinker…

Application to Elastin peptides: Elastokins

Elastin

- The elastic fibers
  - Endow elasticity to tissues
  - Insoluble elastin (> 90 %),
  - microfibrils (Fibrillins, MAGPs, …)

- **Elastogenesis**
  - Important during the development and growth of elastic tissues
  - Very limited otherwise
  - Lack of elastin repair



Human Tropoelastin

- 762 AA, 35 exons, 2.4 kb cDNA
- alternative splicing ⇒ various isoforms

82%

221 G	11 T
164 A	10 Q
98 V	10 R
96 P	5 E
45 L	3 D
35 K	2 C
16 I	1 H
16 F	0 W
15 Y	0 M
14 S	0 N

Repetitive sequences of elastin

XPG

VPG

VPGG

VPGVG

VGVAPG

PGVGVAPGV

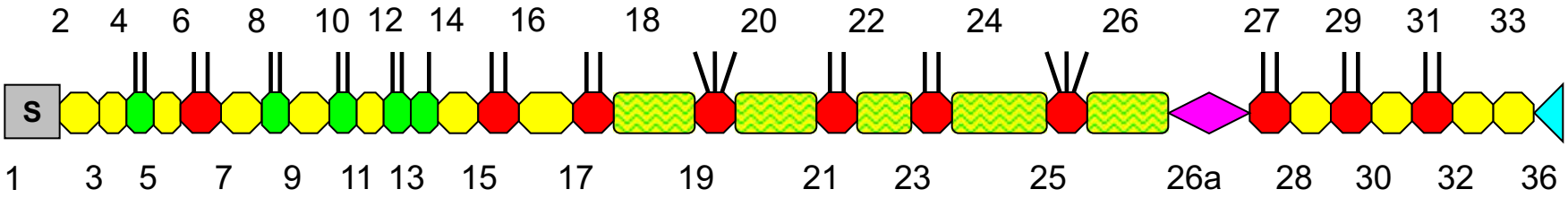
XGG

LGGVL

VGGLG

VGGVG

Structural Domains of Elastin



Hydrophobic Domain - Glycine rich

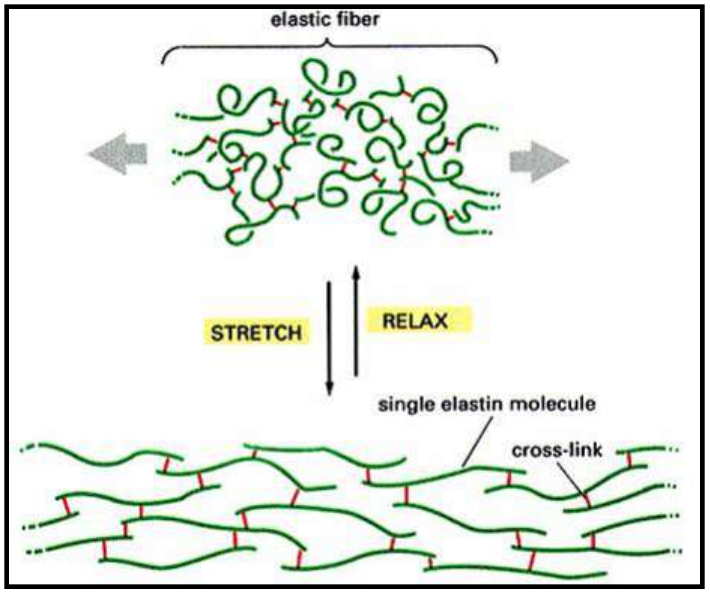
Hydrophobic Domain - Proline rich

Crossing Domain KA (Lys-Ala)

Crossing Domain KP (Lys-Pro)

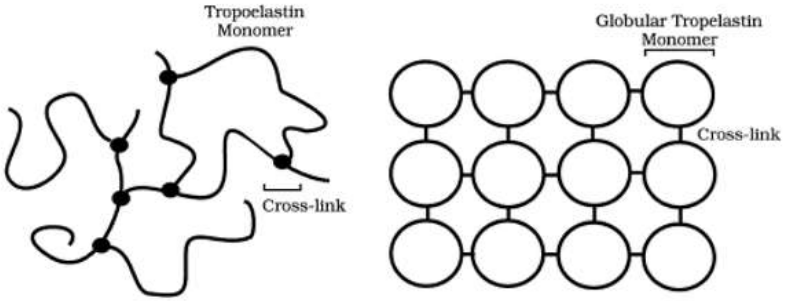
C-terminal Domain

How does elastin work ?

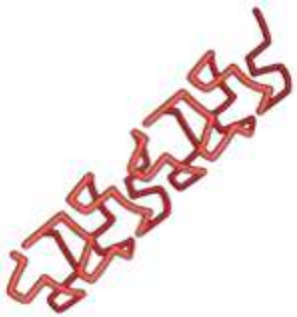


www.cella.cn/book/10/images/image011.jpg

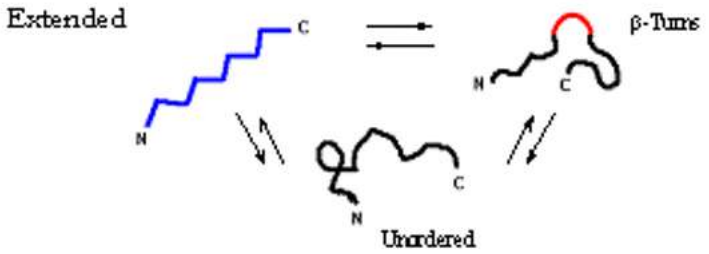
Proposed models of the structure



Vrovski et al 1998, Eur J Biochem 258. 1-18

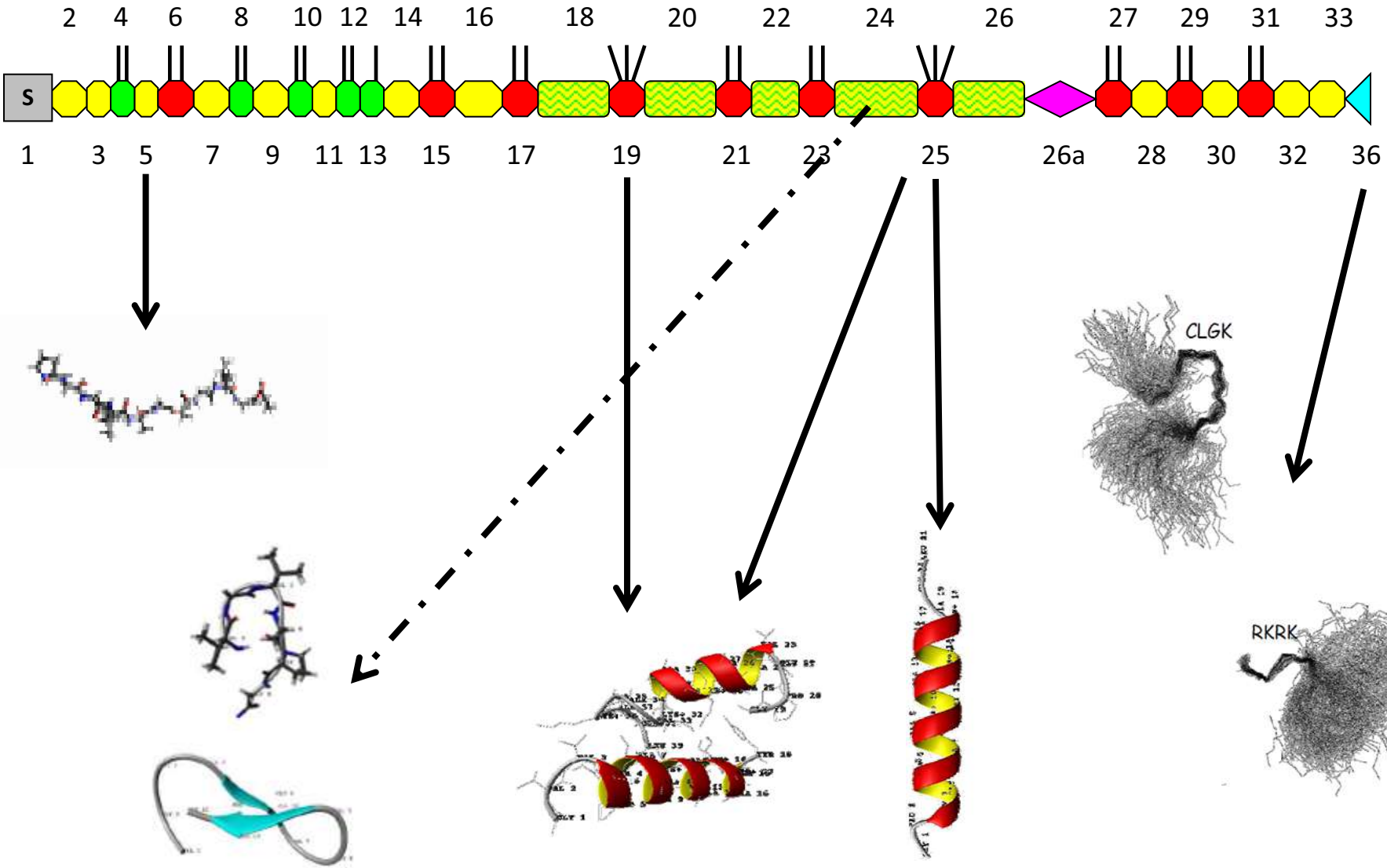


Pr D Urry's model



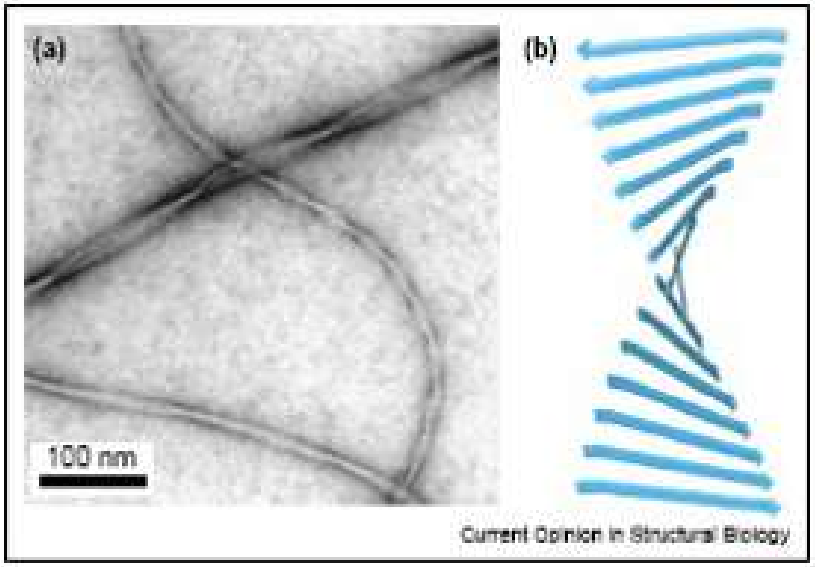
Tamburro, Bocchiccio, Pepe, Université de Potenza, Italie

Structural Domains of Elastin

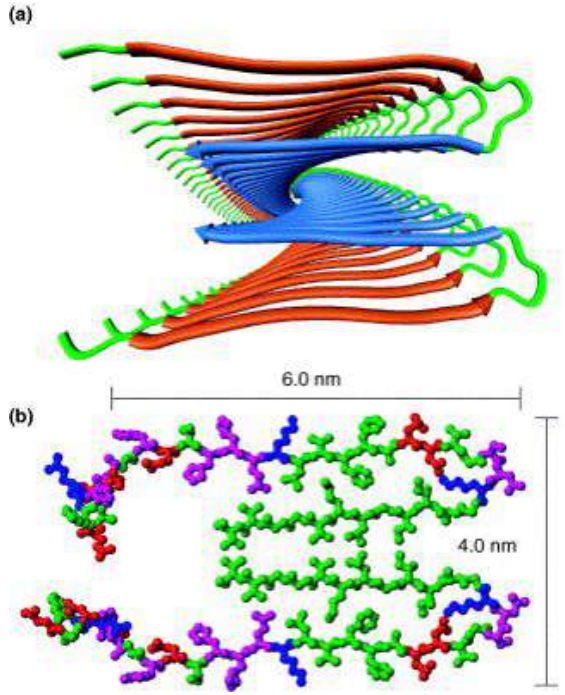


Amyloid

Amyloid fibrils are a pathogenic state of proteins associated with tissue degeneration in numerous debilitating diseases, including Alzheimer's disease, transmissible spongiform encephelopathies, and type II diabetes.



Tycko R. Current Opinion in Structural Biology 14, 2004, 96-103



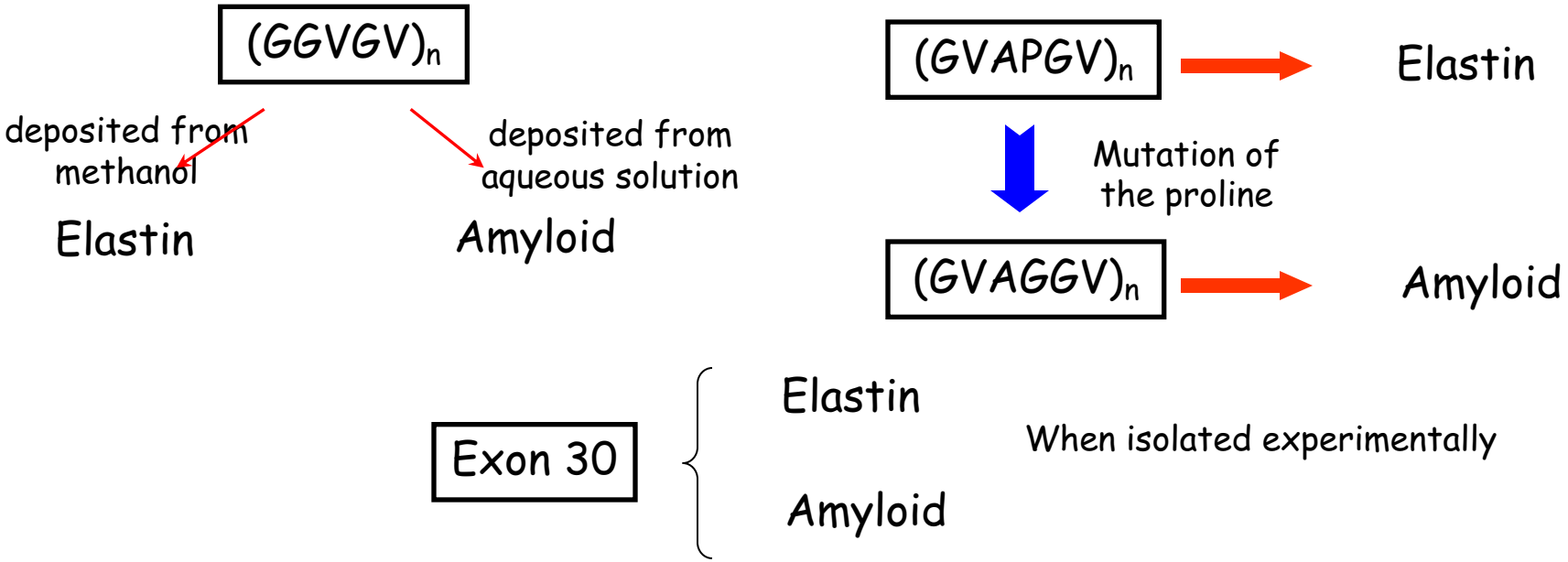
Proposed structure → Cross Beta Structure

- beta strands perpendicular to the long axis of the fiber
- hydrogen bond of the backbone parallel to the long axis.

Why Study Elastin and Amyloid ?

- Despite the importance of elastin as a structural biopolymer, the molecular basis underlying its distinct attributes remains poorly understood.

- The hydrophobic domain → give rise to self organization and to an intriguing high-temperature of coacervation.



- Where is the separation between elastin and amyloid ?

Single chain simulations

CONSENSUS SEQUENCES XGGZG
(X,Z = V,L)

LGGLG	**$(LGGLG)_2$**	**$(LGGLG)_3$**
LGGVG	**$(LGGVG)_2$**	**$(LGGVG)_3$**
VGGVG	**$(VGGVG)_2$**	**$(VGGVG)_3$**
VGGLG	**$(VGGLG)_2$**	**$(VGGLG)_3$**

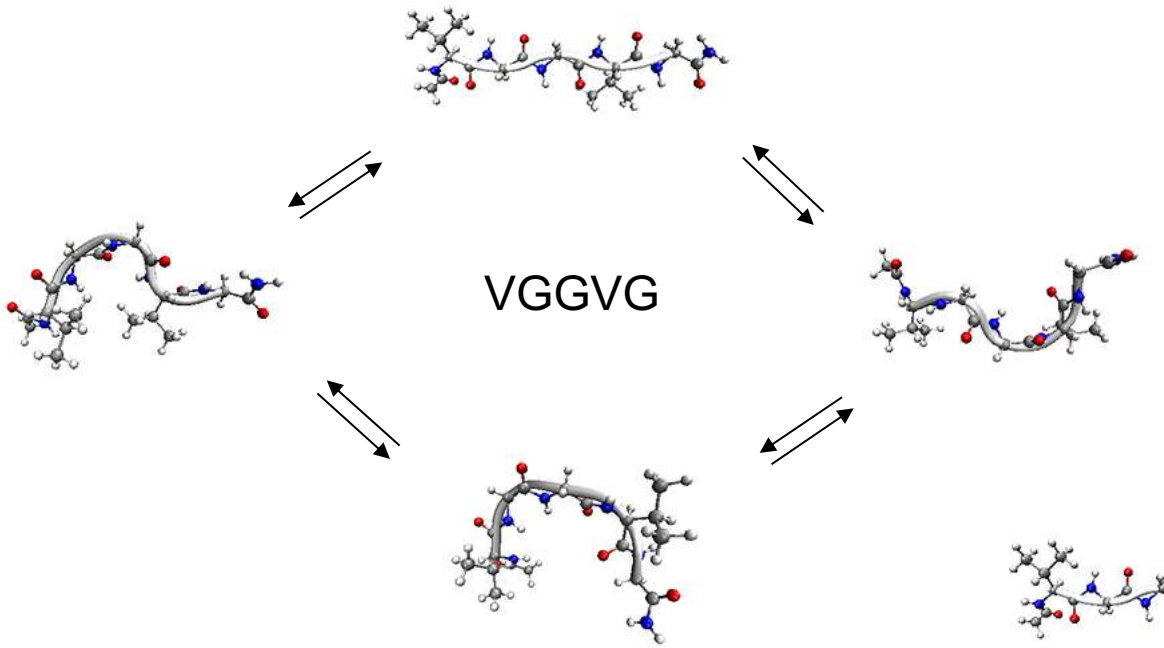
Solvatation de 13 Å (xyz) : 10000-50000 atomes,

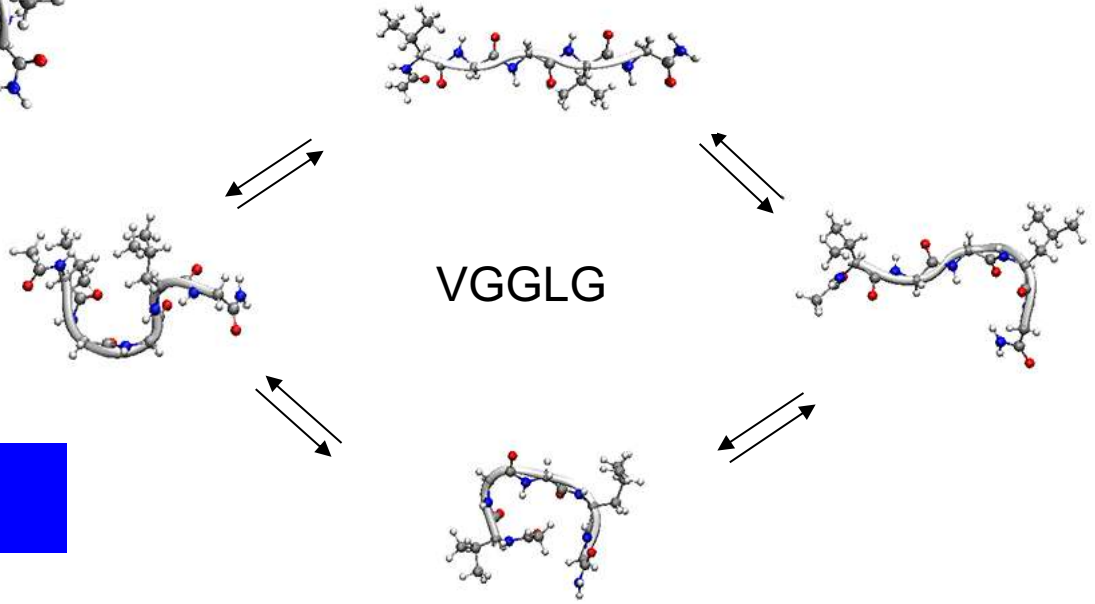
Conditions périodiques aux limites,

Simulations dans l' ensemble NPT à 298K,

50 ns de simulation – 10000 structures.

$(VGGVG)_1$



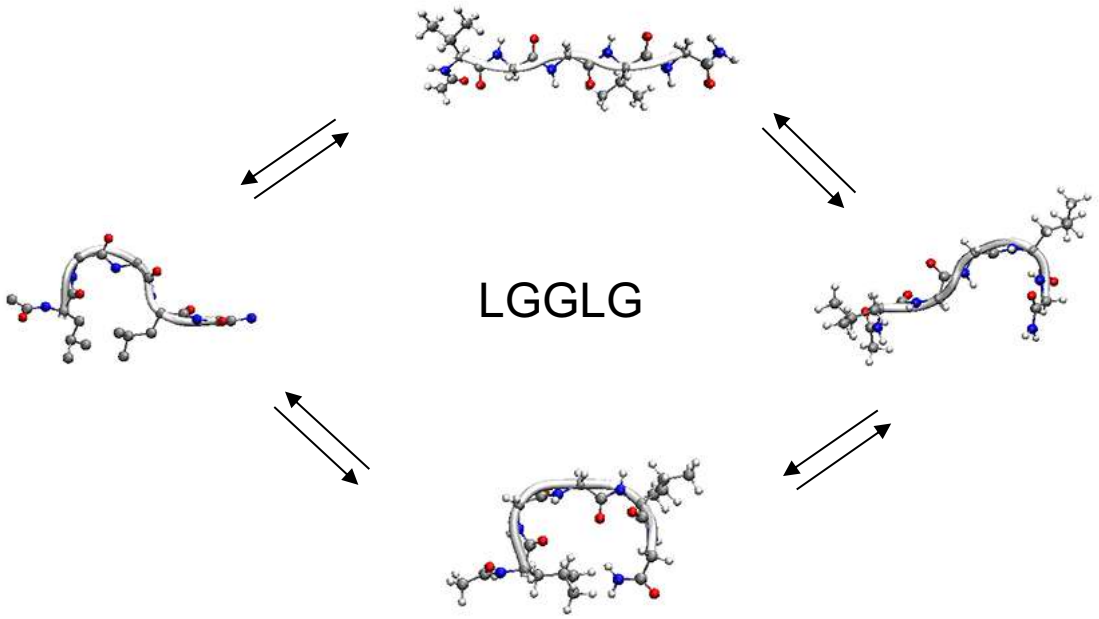


$(VGGLG)_1$

$(LGGLG)_1$

~25% of the structures display turns

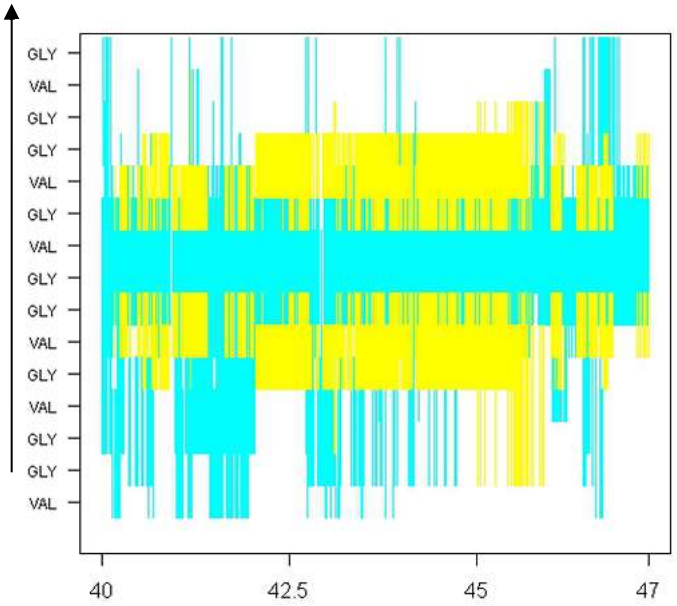
Evidence of sliding turns



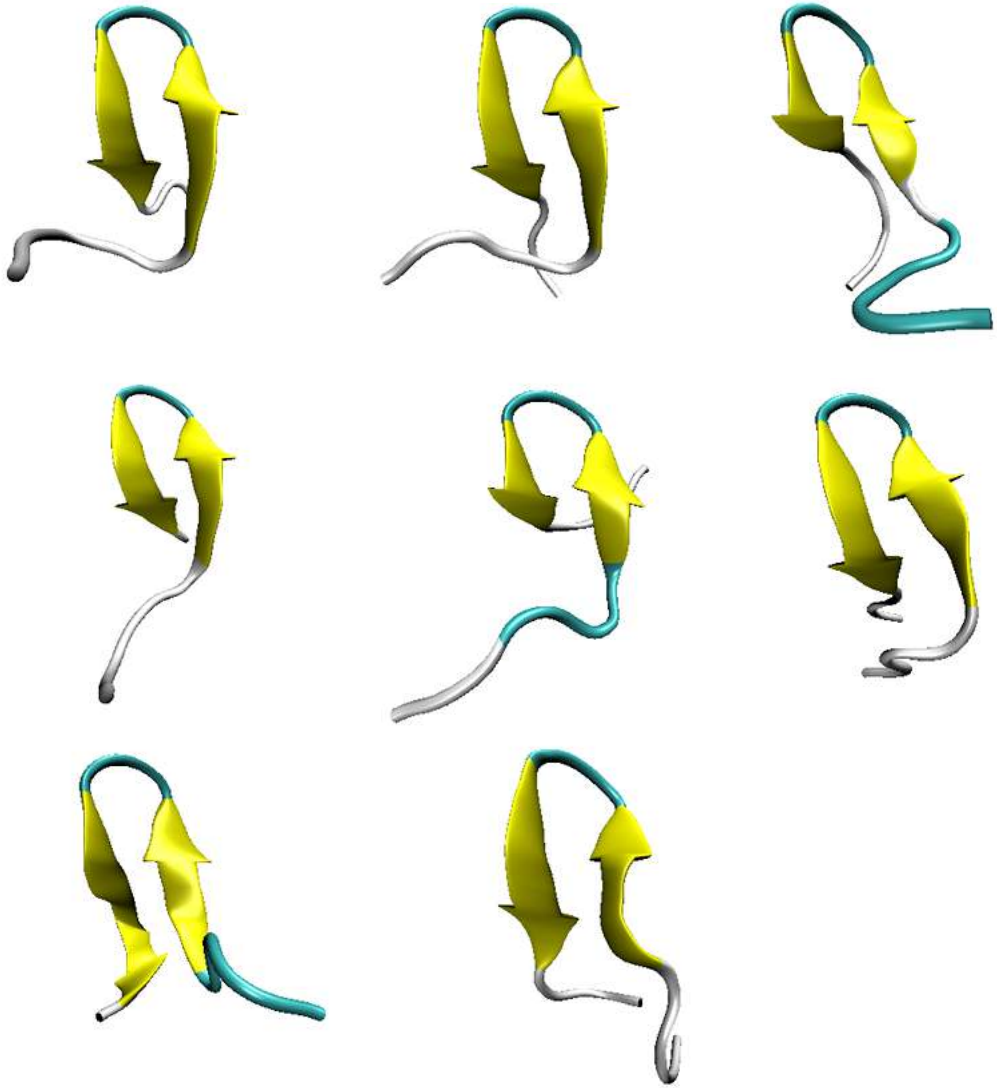
High flexibility due to the glycines

Equilibrium between extended and close conformations.

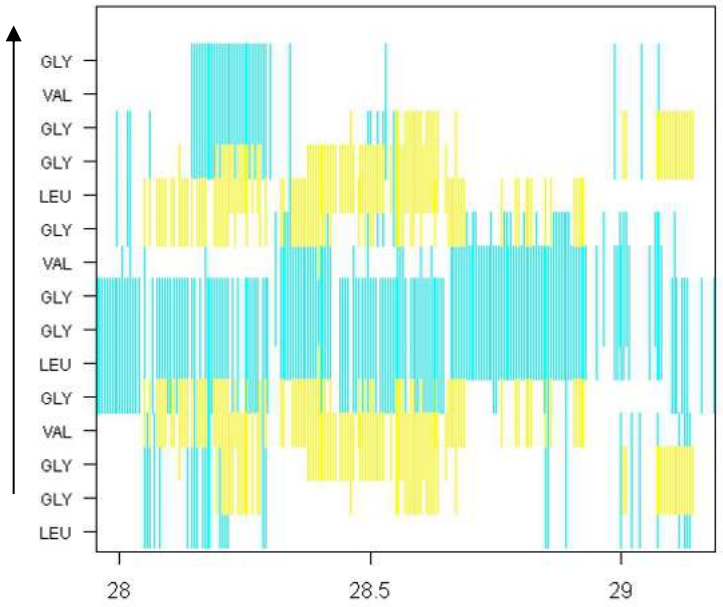
$(VGGVG)_3$



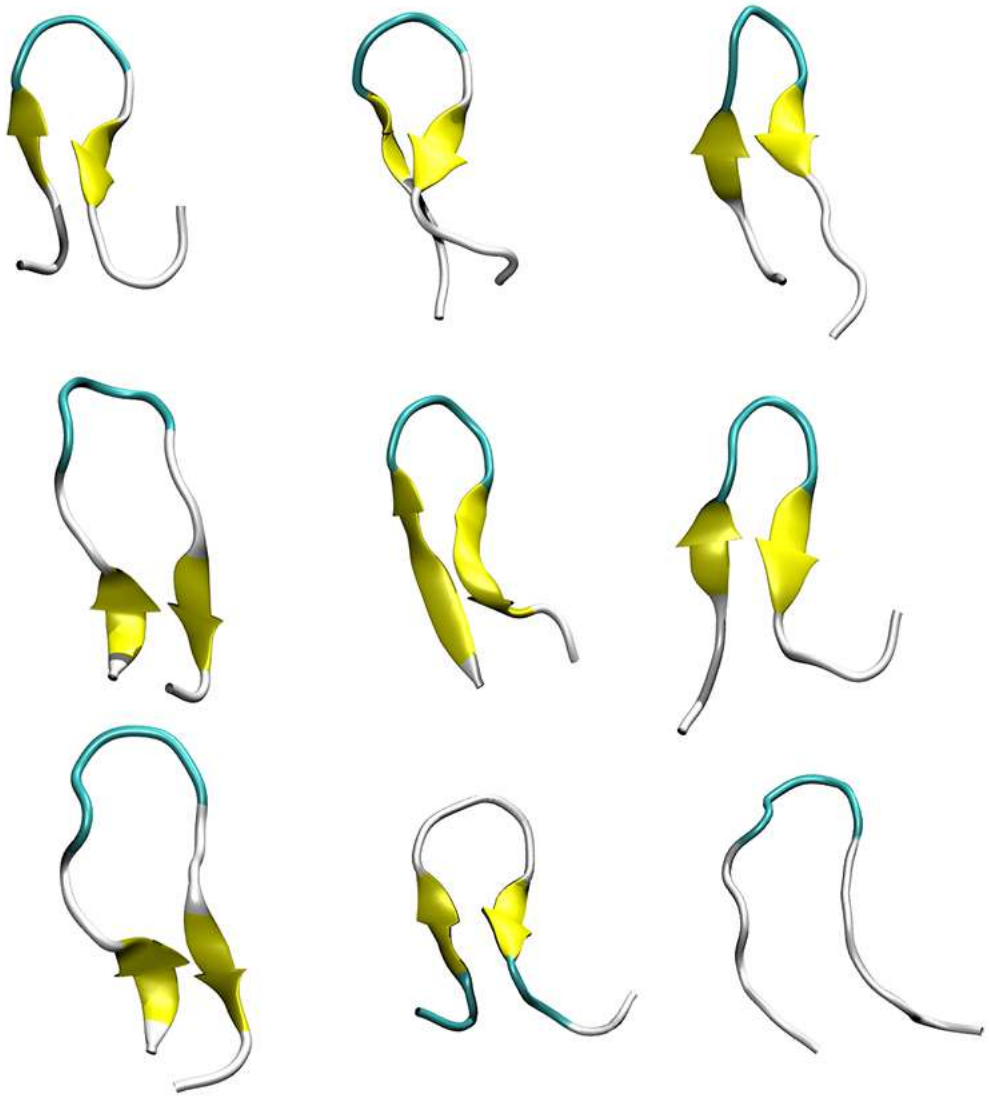
Temps en ns



$(LGGVG)_3$

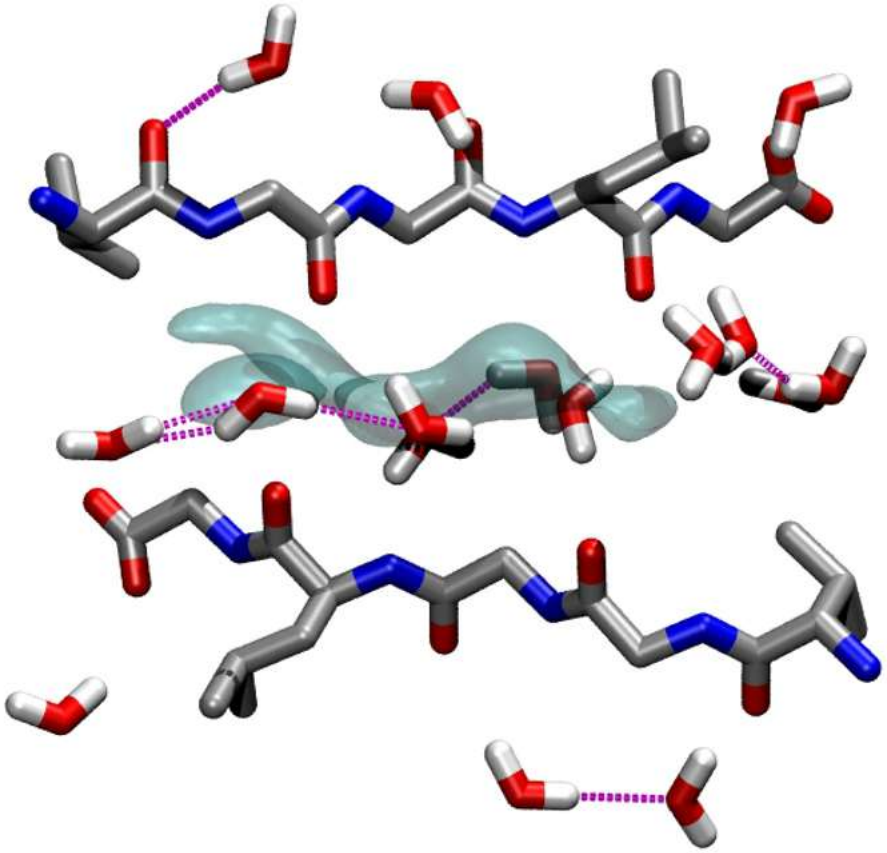


Temps en ns



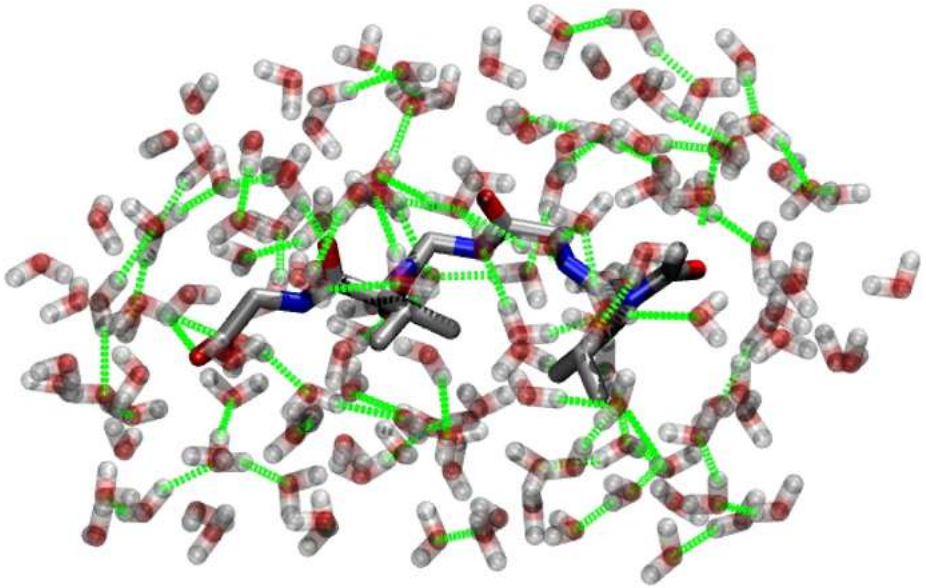
ELP Solvation

2 peptides VGGLG

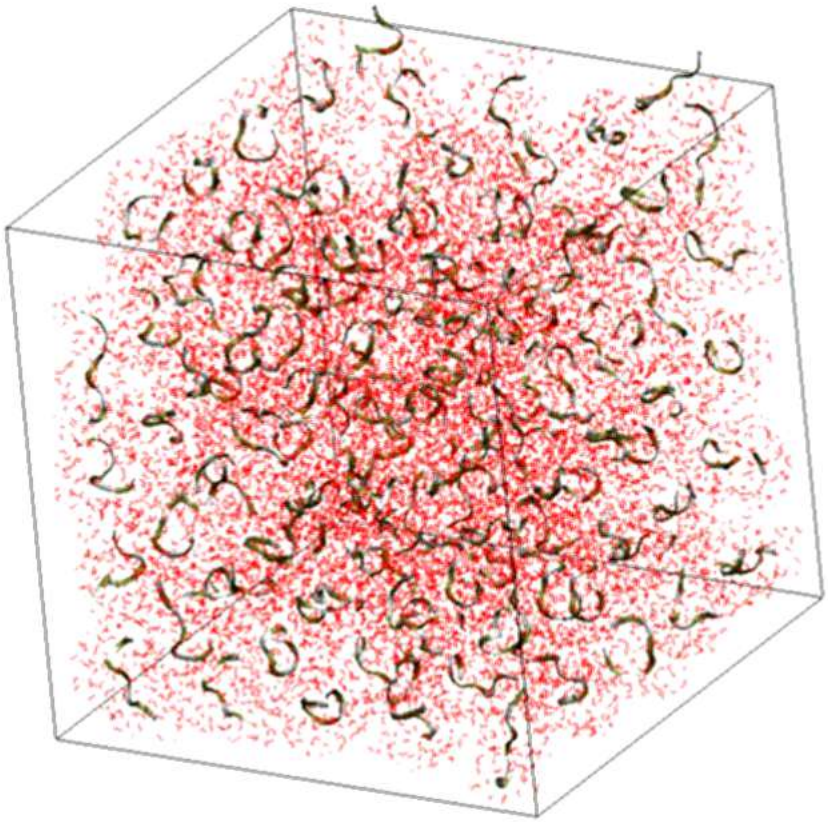


ELP Solvation

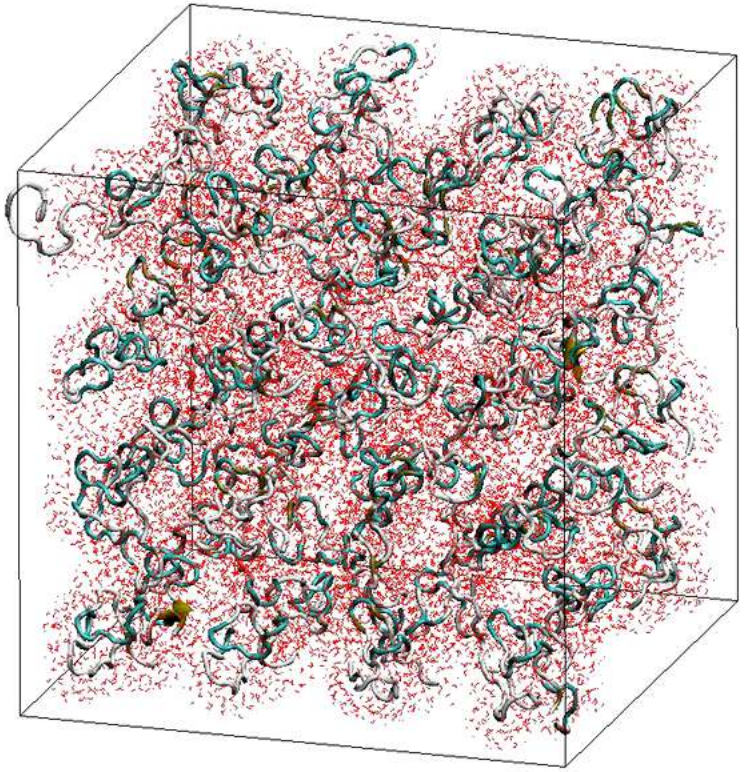
2 peptides VGGVG



Multichain simulations



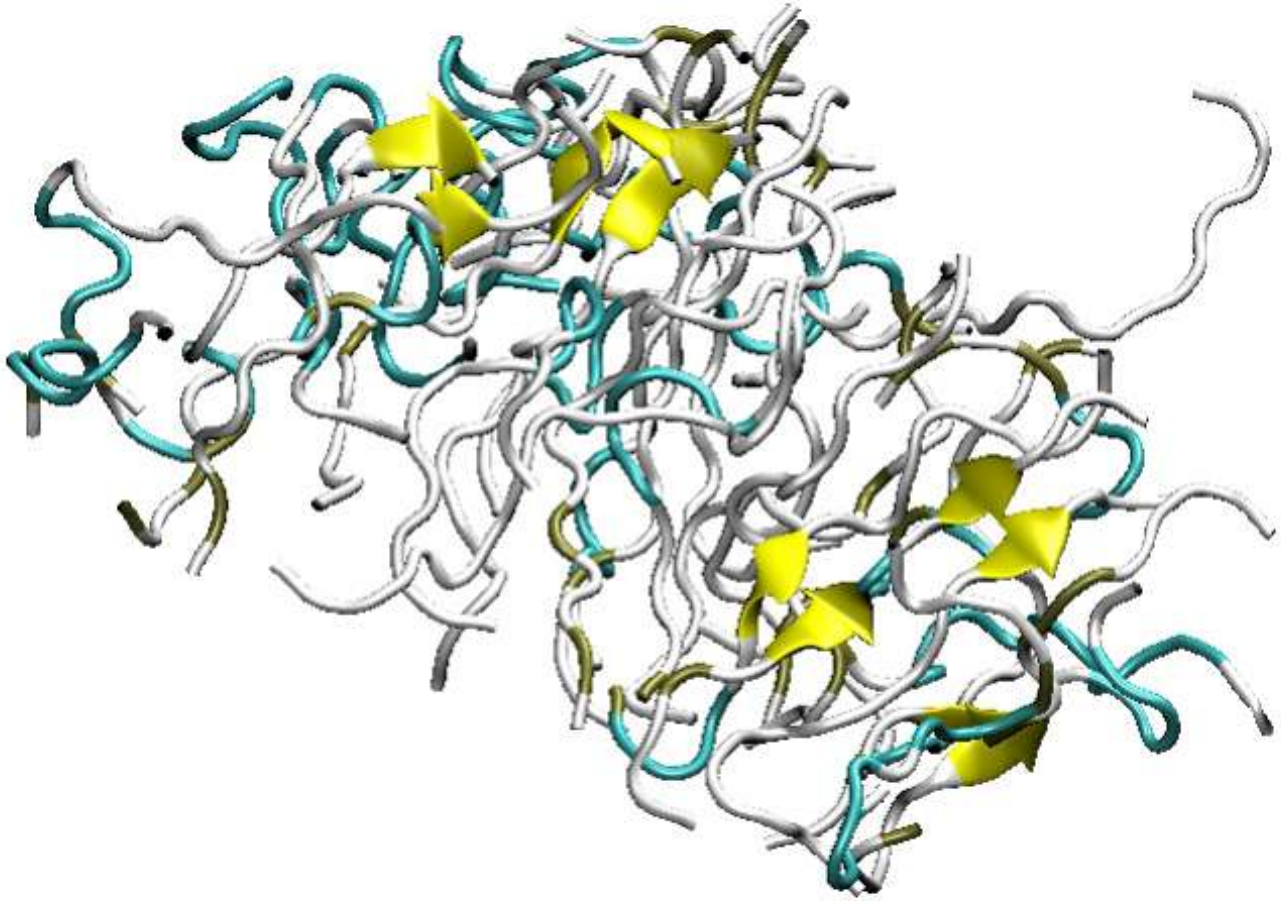
125 GVGVPGVG



64 $(GVPGV)_7$

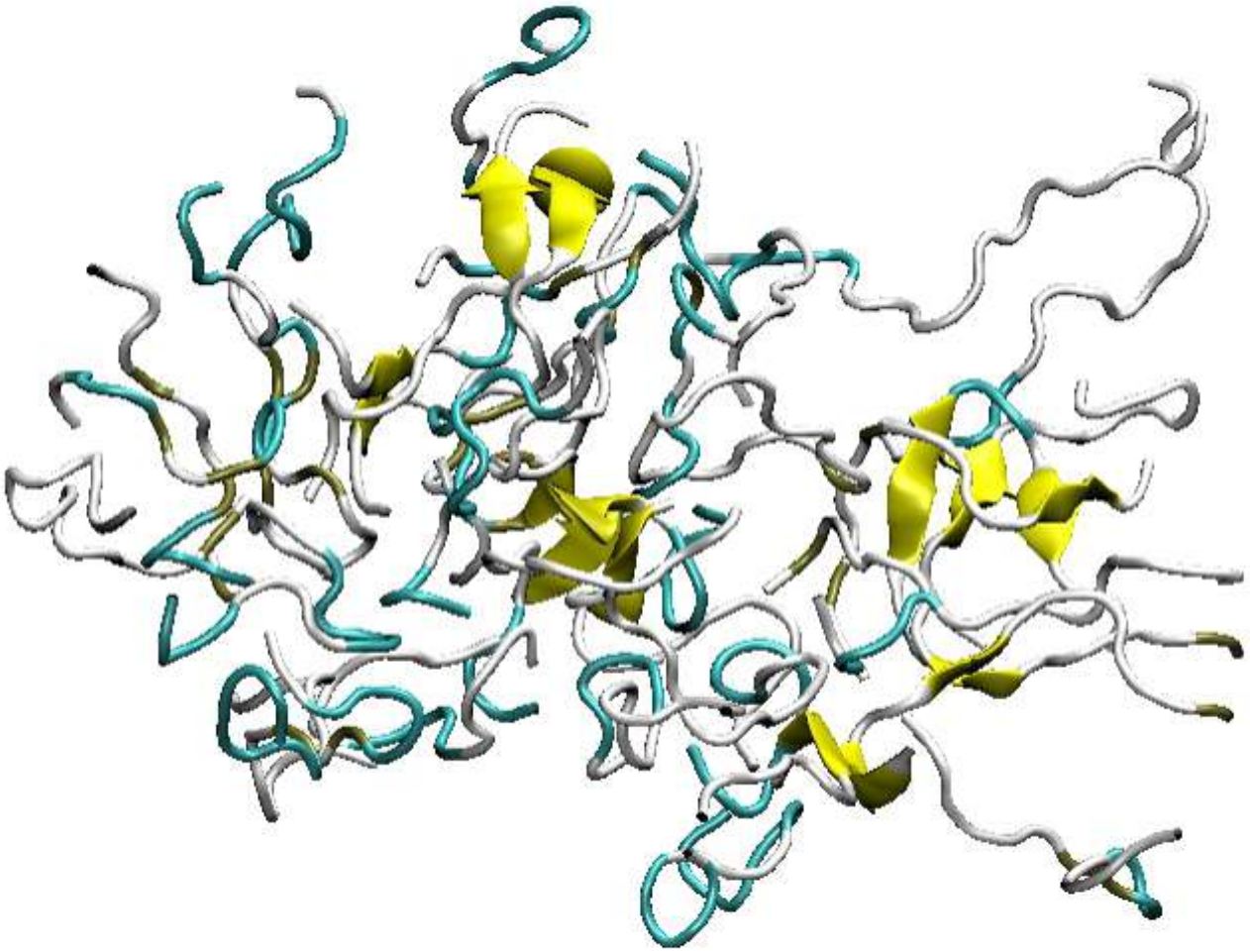
Multichain simulations

$(VGGLG)_3$



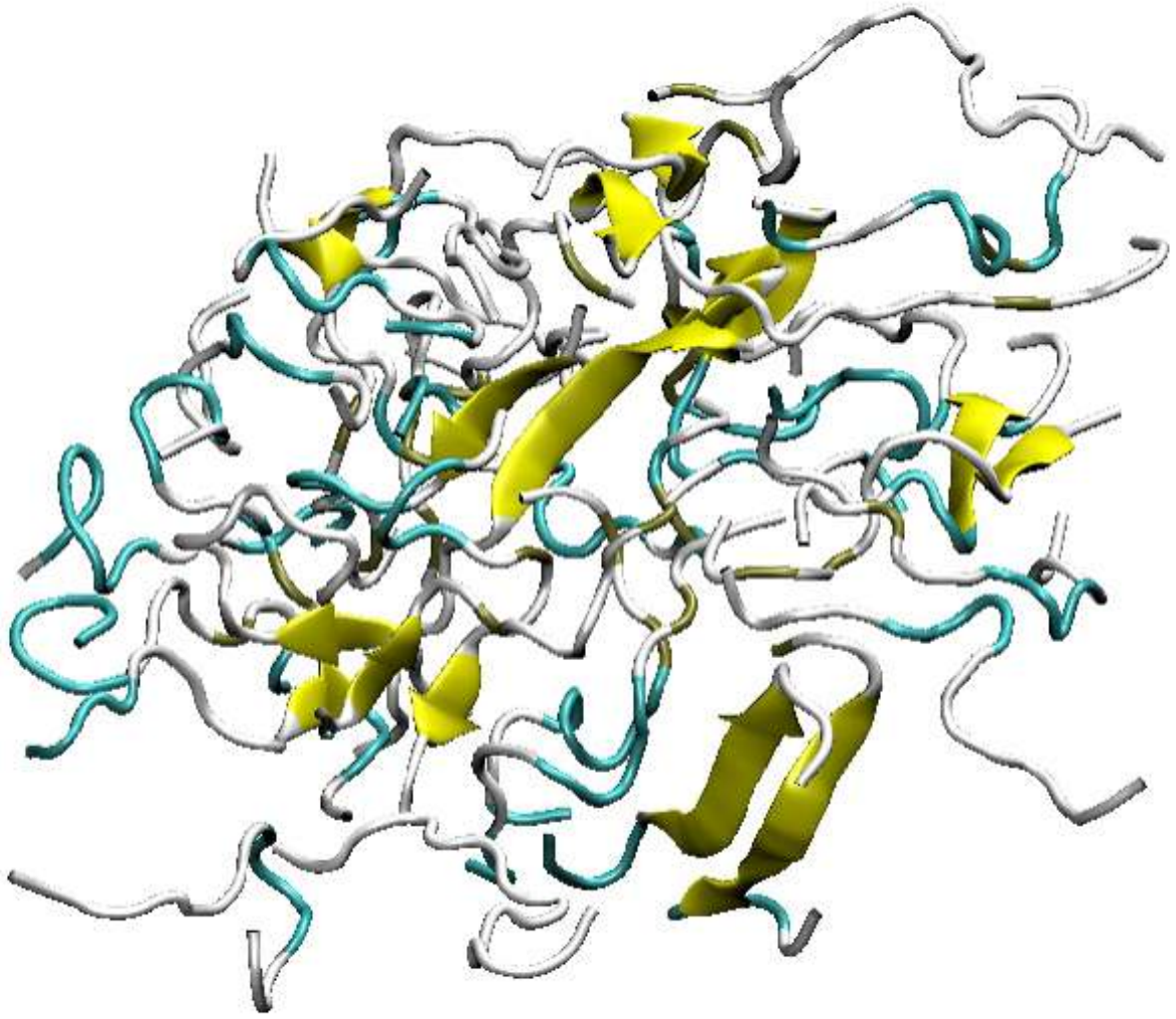
Multichain simulations

$(VGGVG)_3$



Multichain simulations

$(VGGVG)_3$ – antiparallel starting point



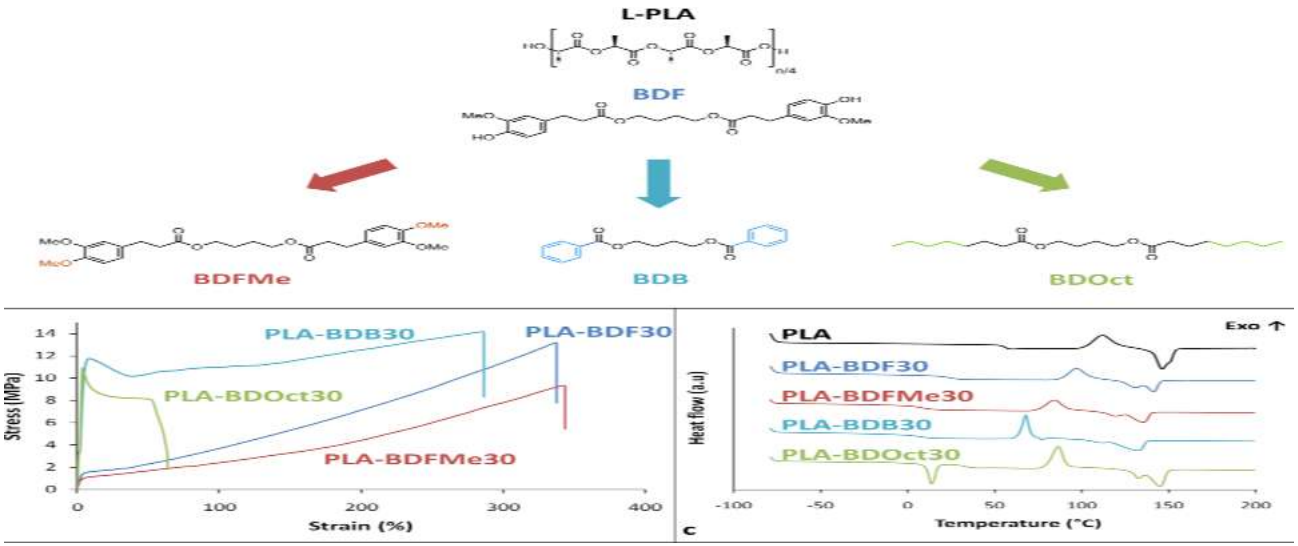
Interaction of PLA with a biosourced additive

Collaboration Pr Florent Allais & Antoine Gallois, ABI Chair

PLA + derivatives of Ferulic Acid

- Poly-L-L-lactic acid (PLA) is a recognized bioplastic but it has a low flexibility and a poor toughness, restricting its use
- A ferulic acid-based biosourced additive blended with polylactic acid leads to a transparent elastomeric material with shape-memory behavior, self-assembles during a simple and non-reactive hot-melt process
- BDF design allow weak interactions and molecular flexibility

BDF Bis-O-feruloyl-1,4-butanediol

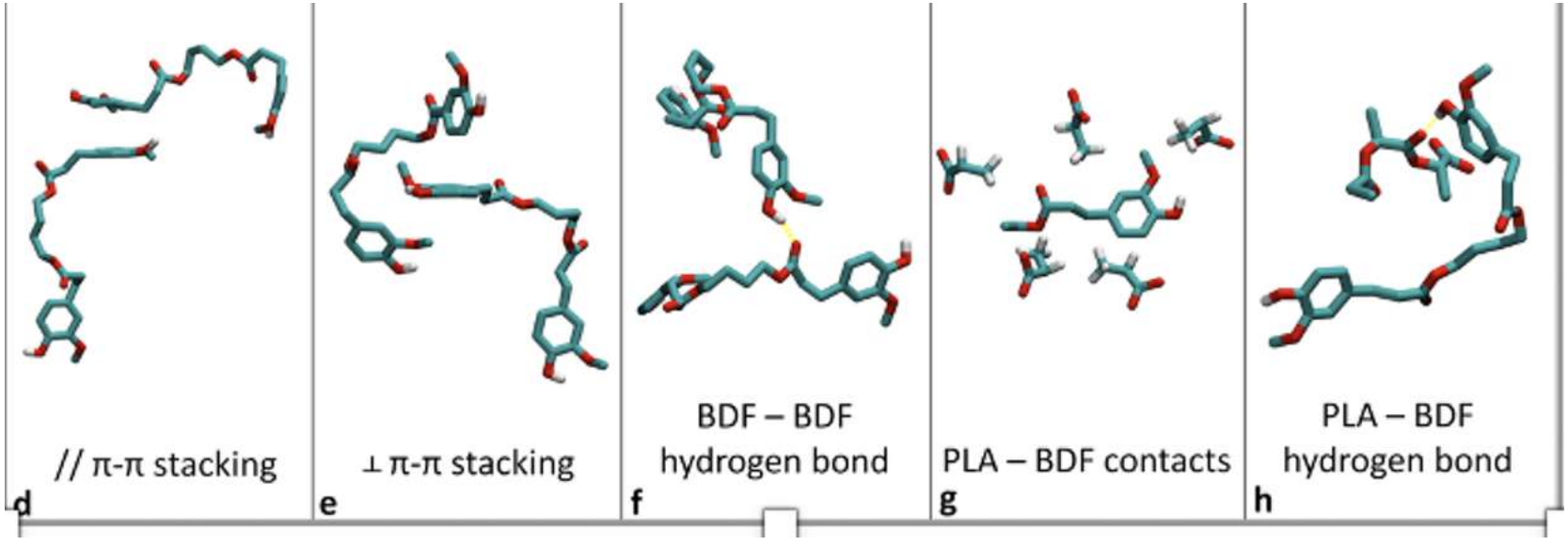


PLA + derivatives of Ferulic Acid

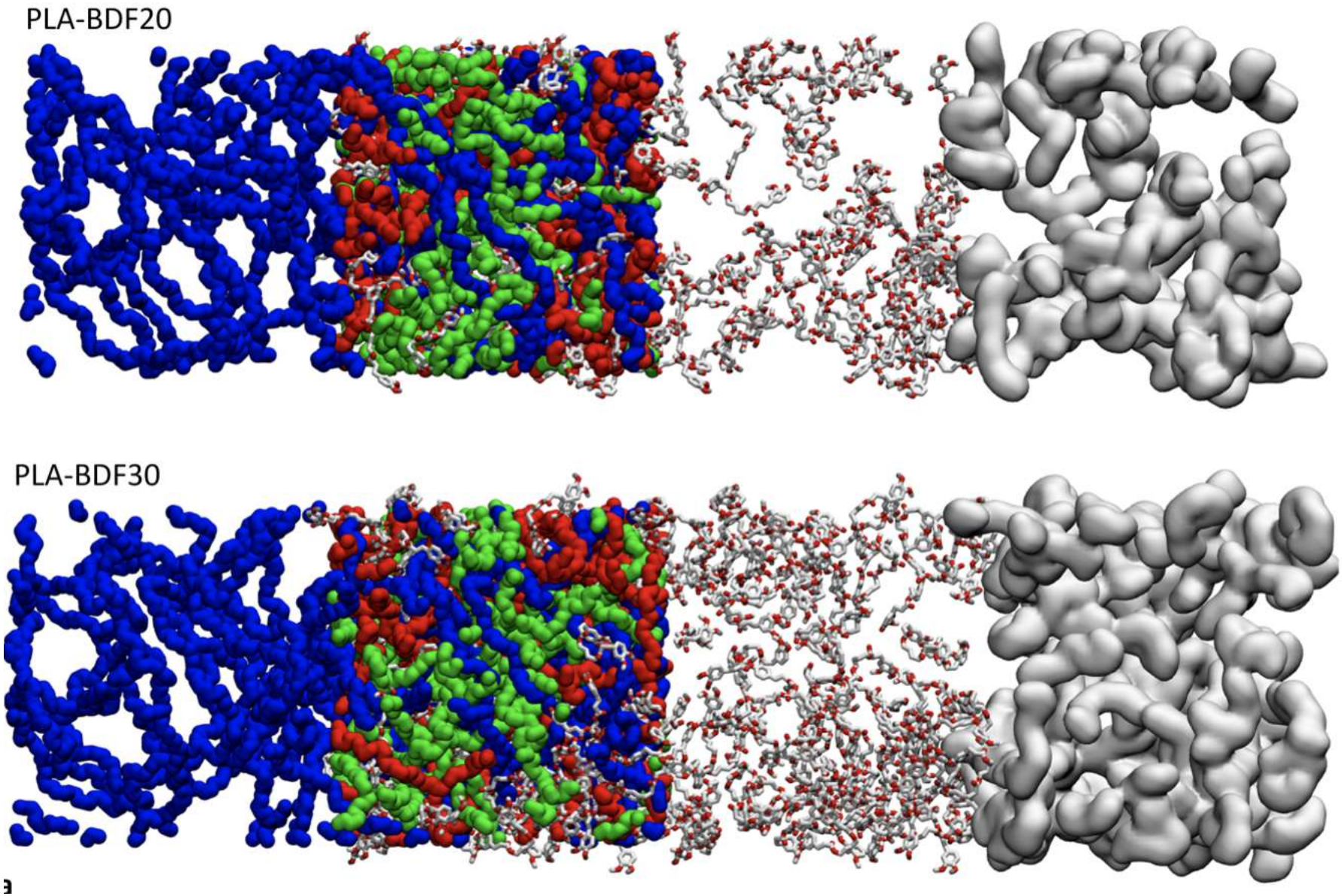
Elastomeric properties are reached when there is at least 30% of BDF

MD simulations 0, 20 and 30 % BDF

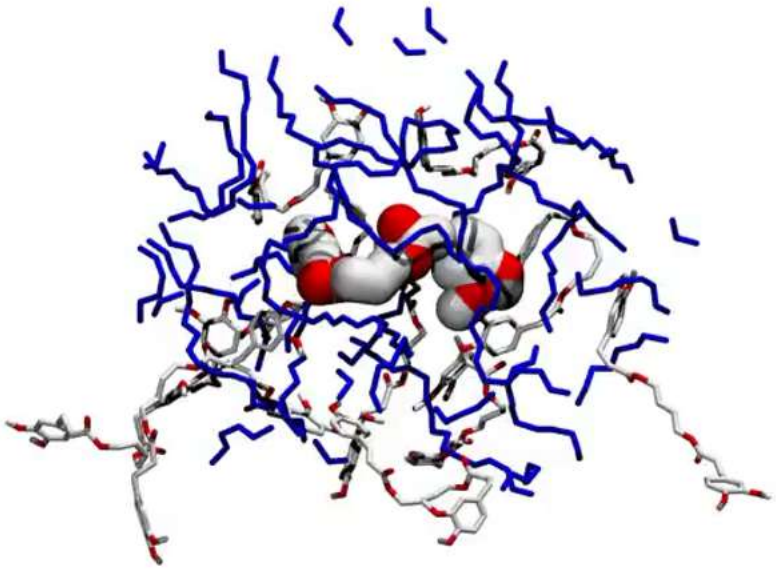
		PLA-BDF20	PLA-BDF30
Number of π-π stacking per BDF	//	0.19	0.27
	⊥	0.41	0.58
Number of hydrogen bonds in BDF – BDF interactions		0.14	0.19
Number of hydrogen bonds in BDF – PLA interactions		0.43	0.36
Average BDF – BDF contacts		3.2	4.7
Average PLA – BDF contacts		15.8	13.1
Average PLA – PLA contacts		3.4	3.0



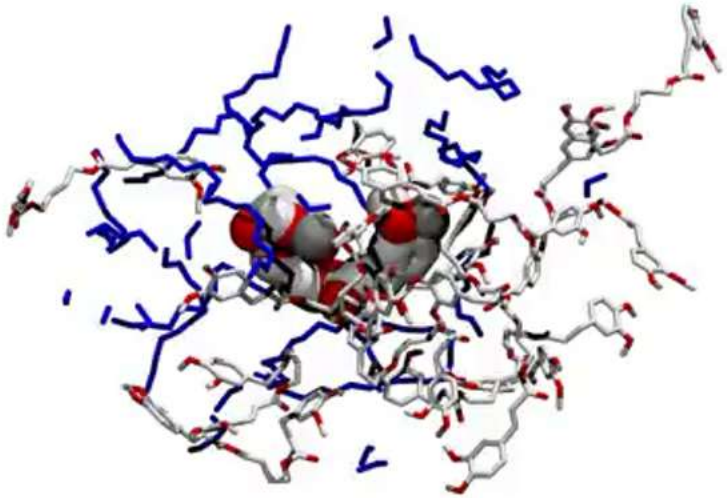
PLA + derivatives of Ferulic Acid



PLA + derivatives of Ferulic Acid

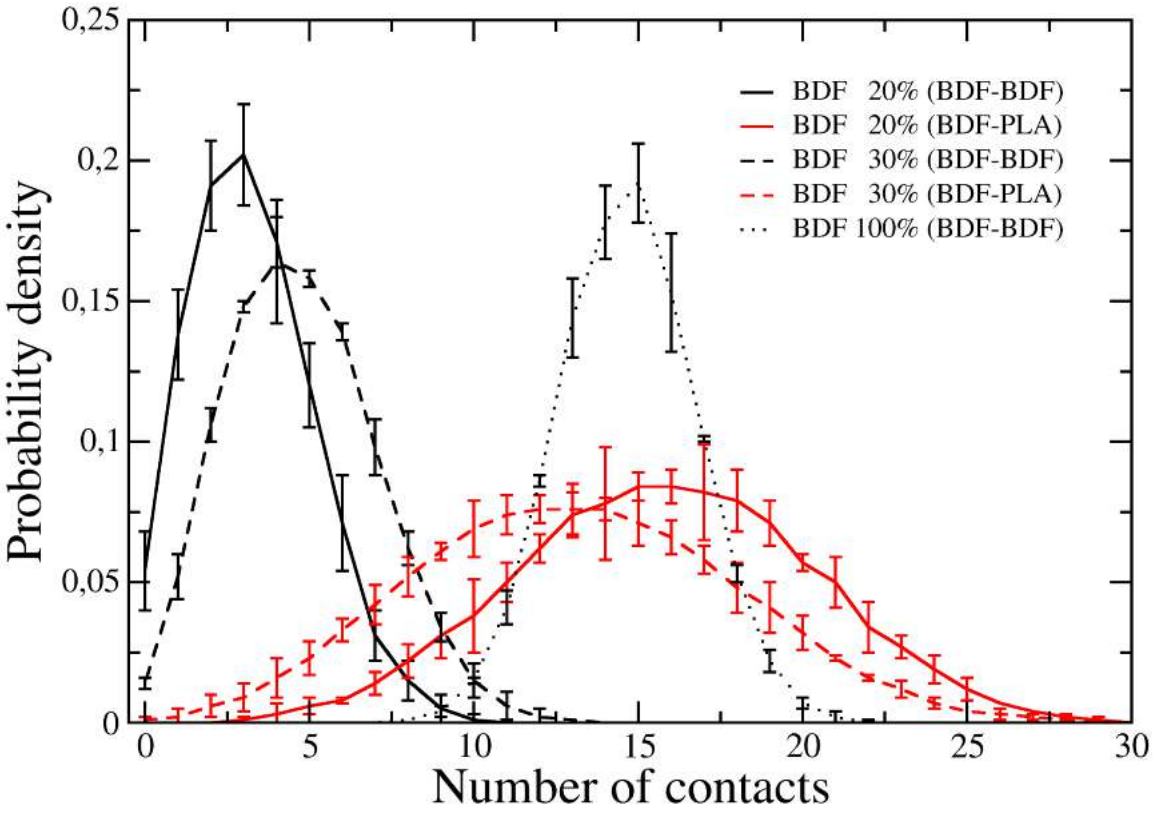


PLA-BDF20



PLA-BDF30

PLA + derivatives of Ferulic Acid



- BDF adopt a wide range of conformations, several BDF are isolated in PLA-BDF20
- while BDF clusters appears larger in PLA-BDF30

When the tension is released, the extended BDF molecules fold back to their original size and shape as well as PLA chains

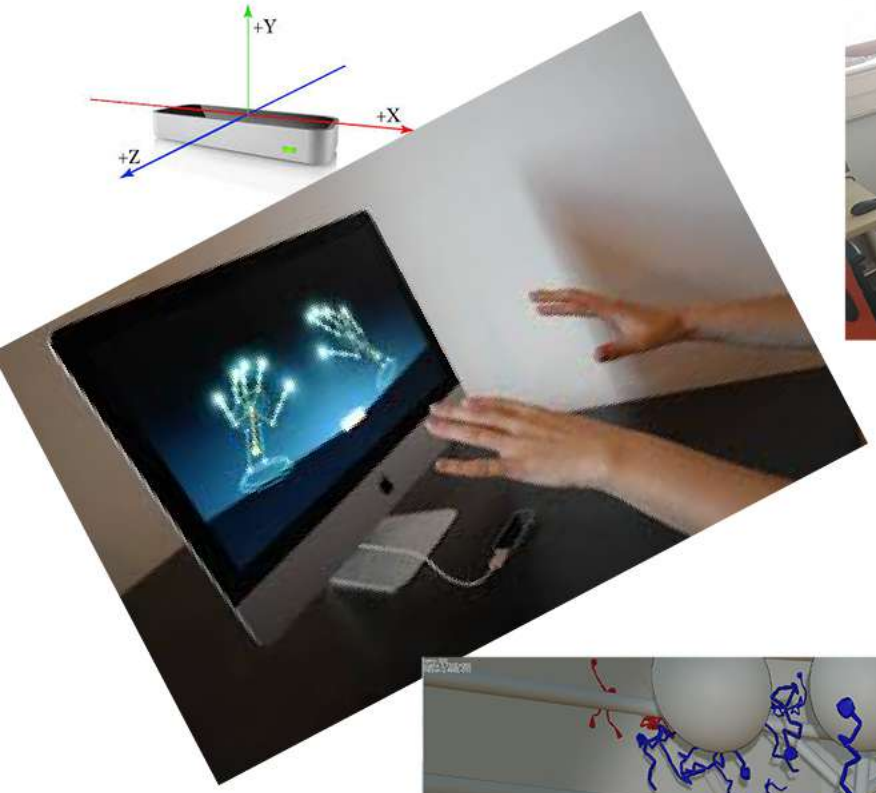
What about the future…

➔ Video games for the mesoscale?

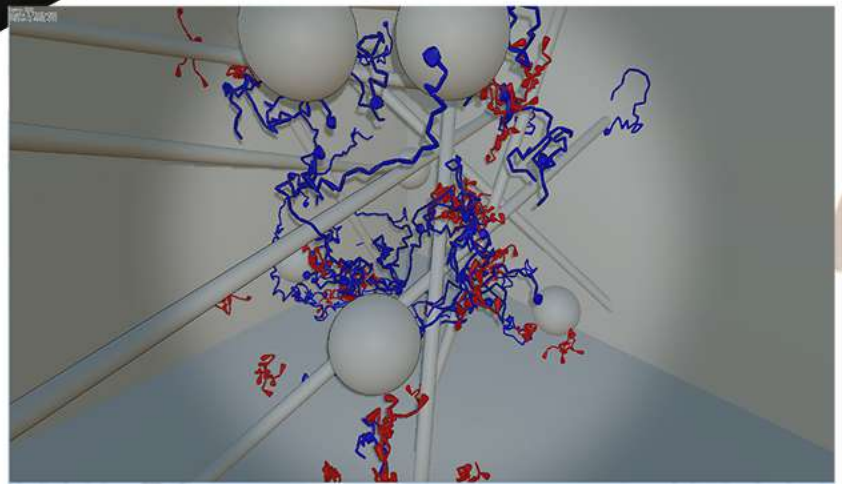
Now & Future

Now & Future

Augmented Reality



Virtual Reality



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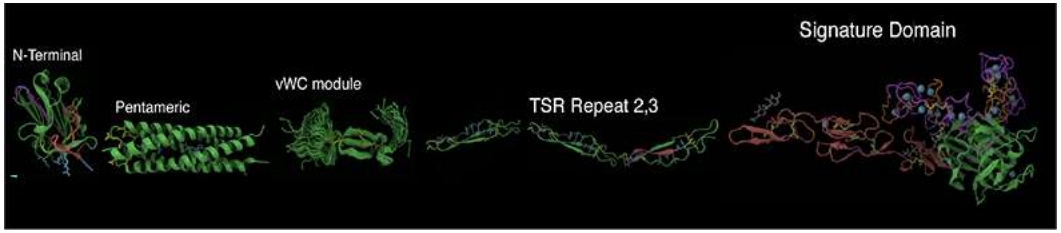
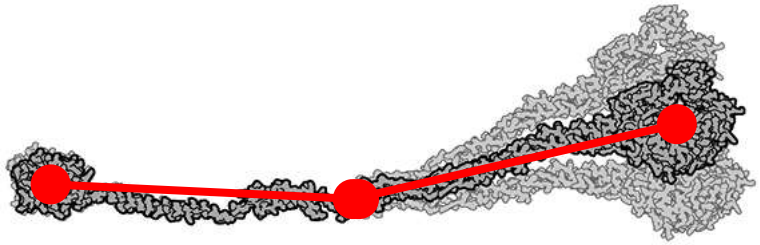
Project of « mesoscope's tool »

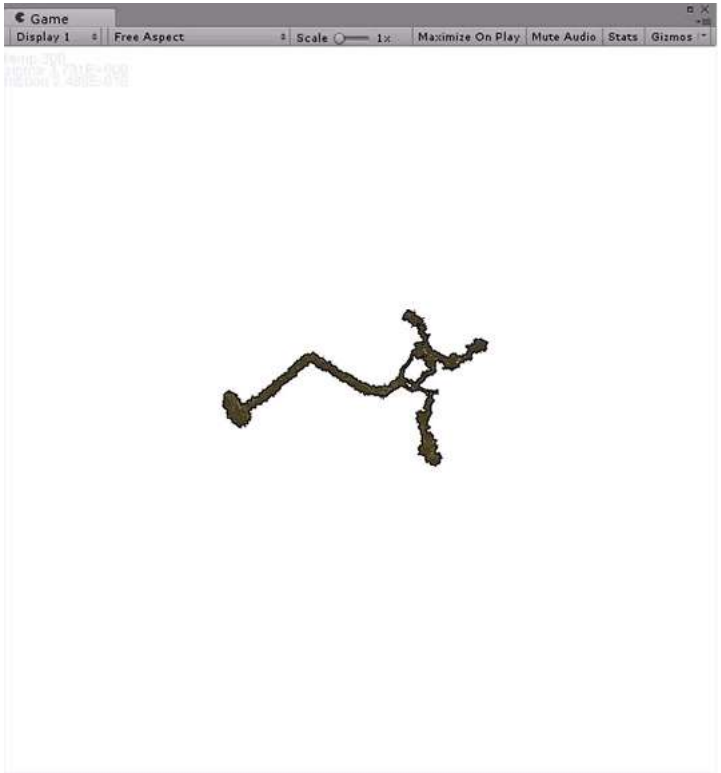
Re-Building in a very simple way

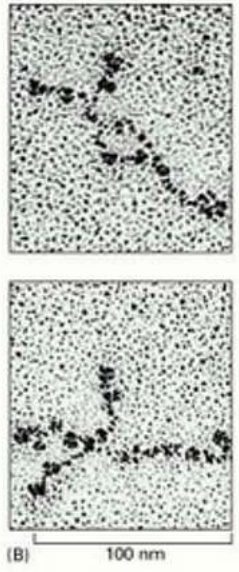
Thrombospondin

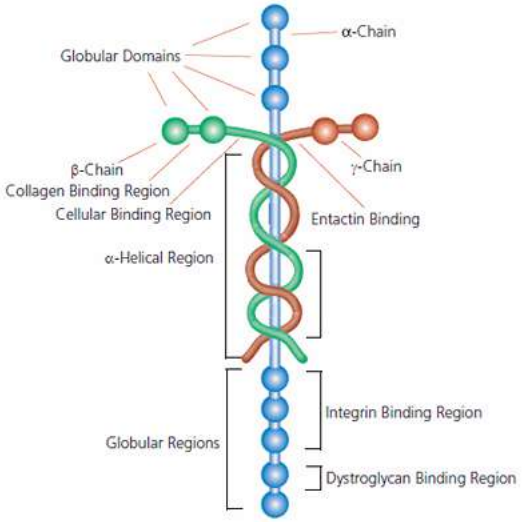




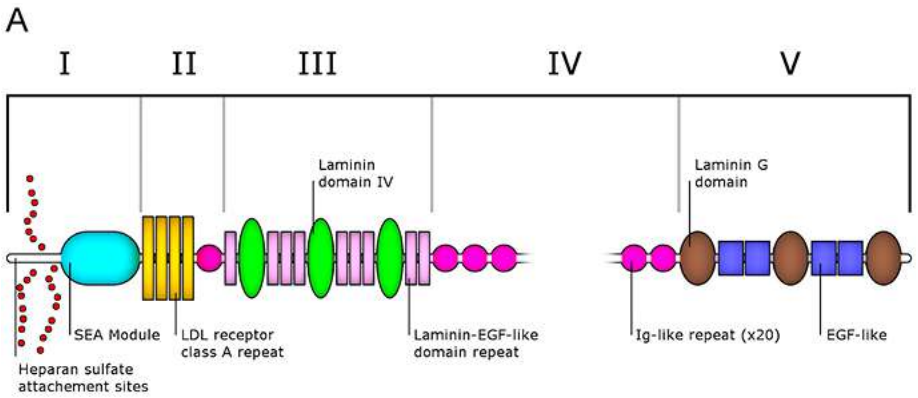
Laminin

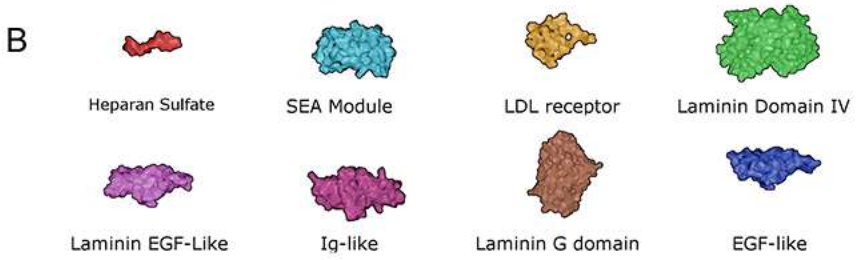


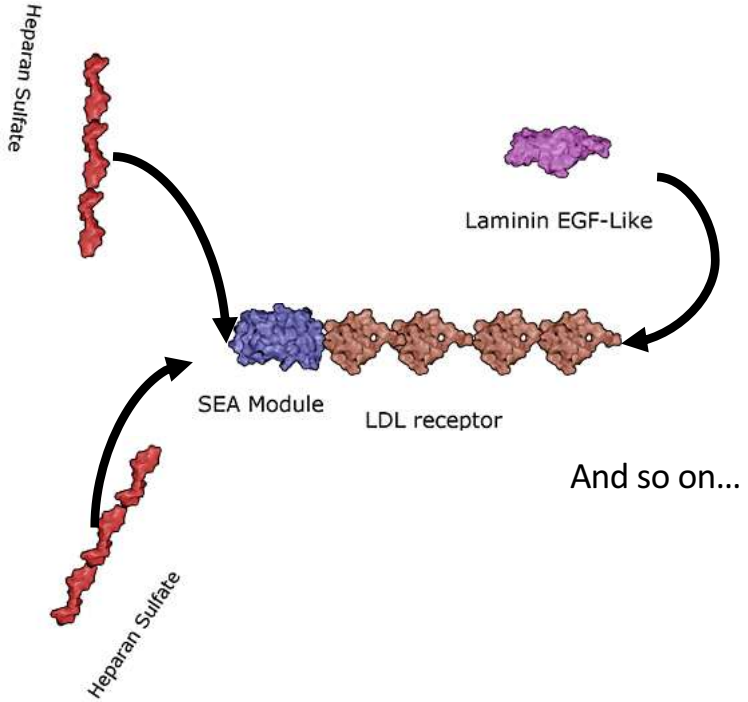




Project of « mesoscope's tool »

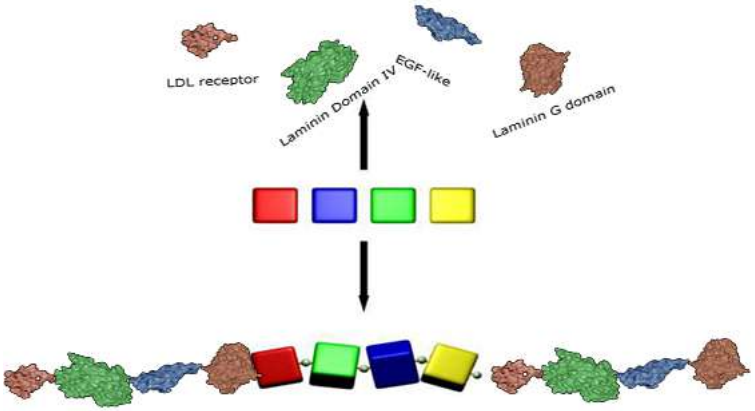




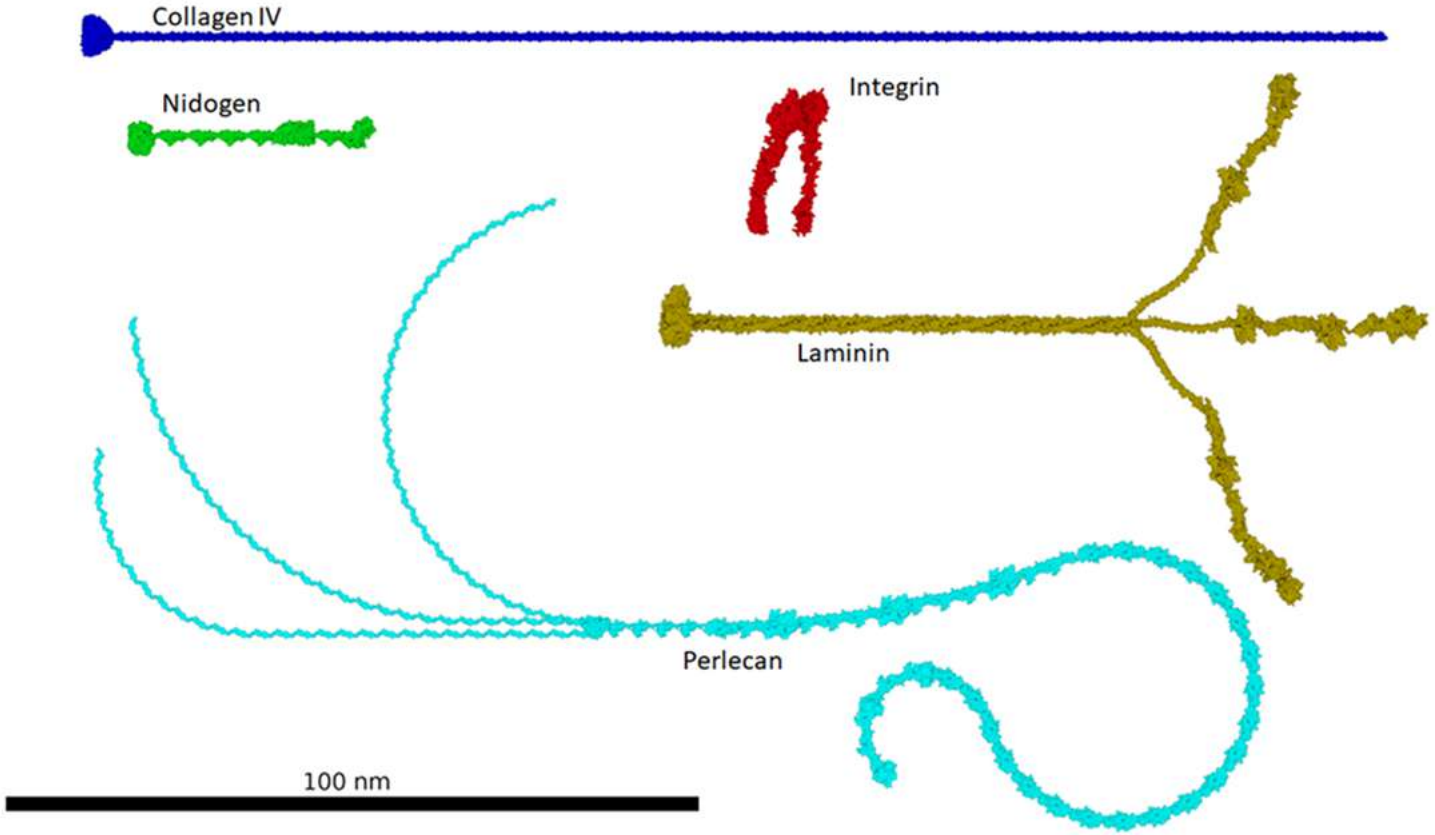


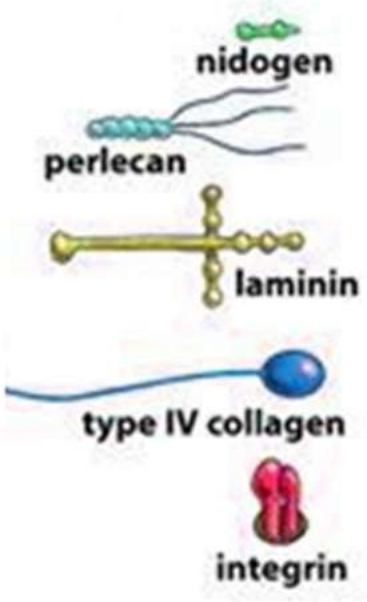
And so on…

A rigid body approach…



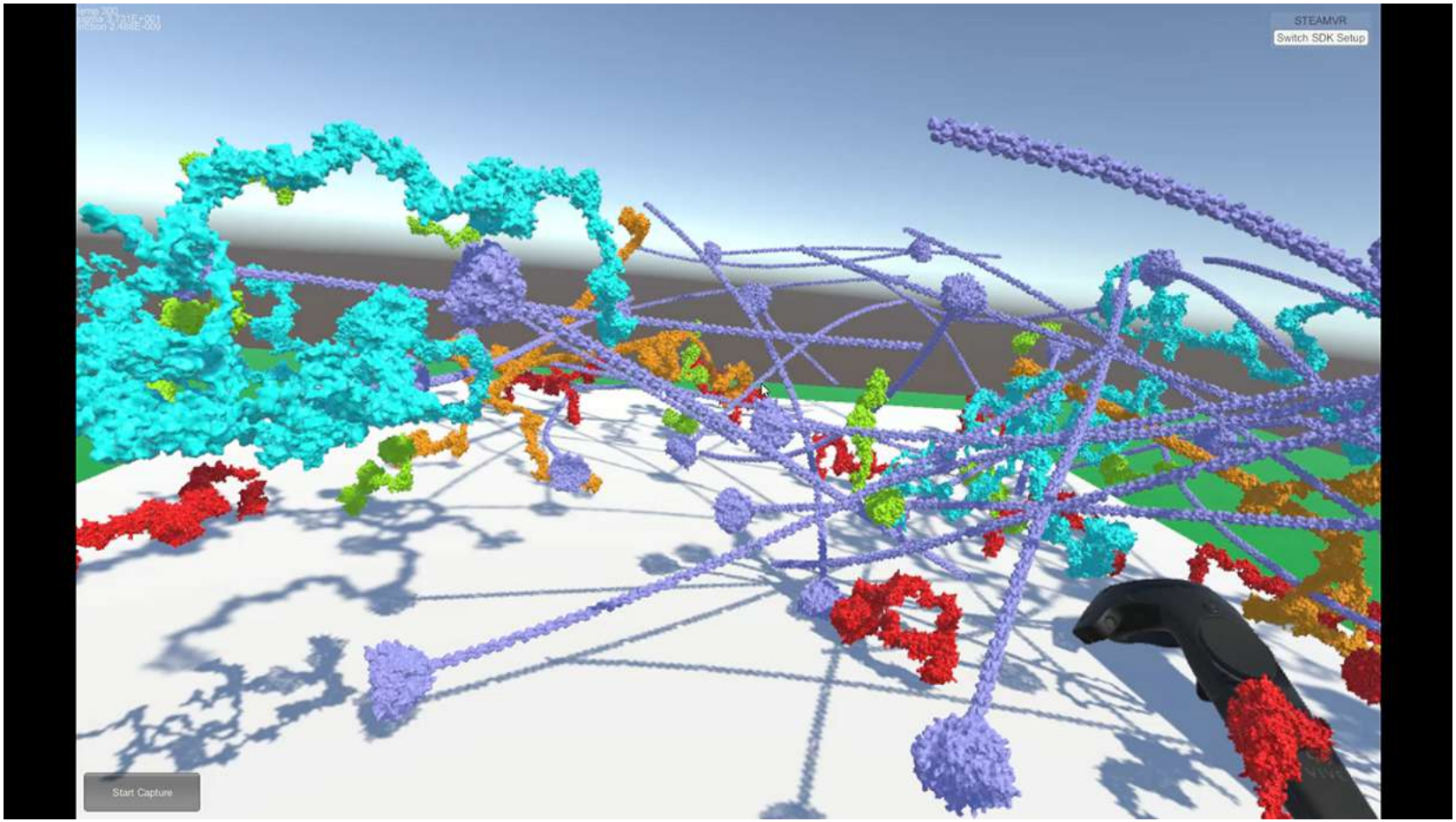
Project of « mesoscope's tool »



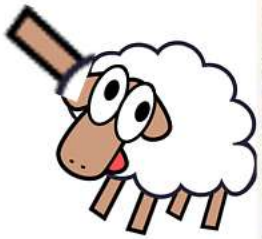


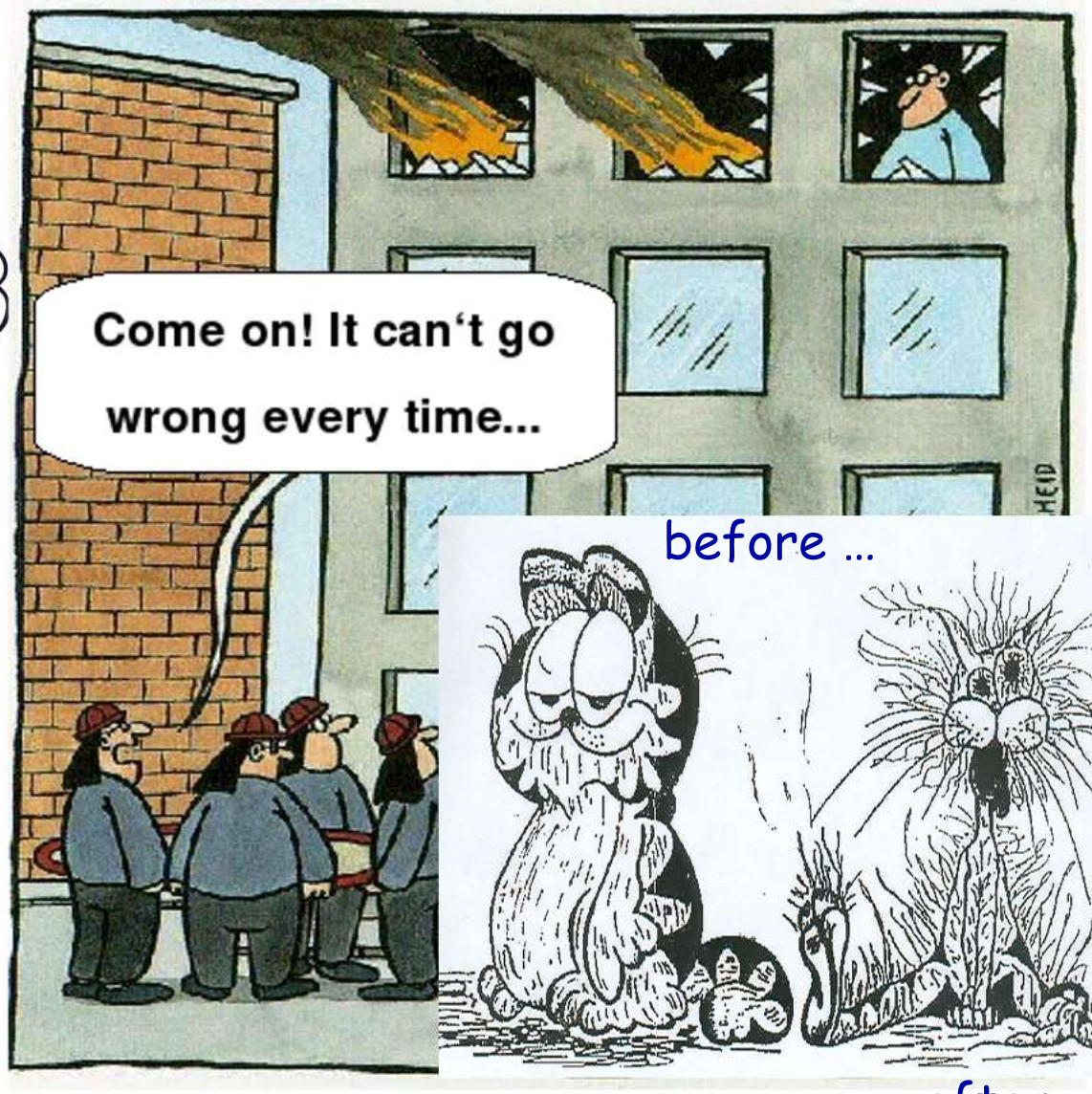
Project of « mesoscope's tool »

The ECM's context…



Some shortcuts!





Thanks to…

MIME's team

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SiRMa laboratory

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Centre de Calcul régional Roméo

https://romeo.univ-reims.fr/

HPC Center ROMEO Centre de Calcul Régional

Centre Image

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Plateforme de modélisation moléculaire

https://p3m.univ-reims.fr/

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