“Drug Design today … between myth and reality.”

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Molecular Dynamics (MD) Simulations

… the virtualization of the concept of time

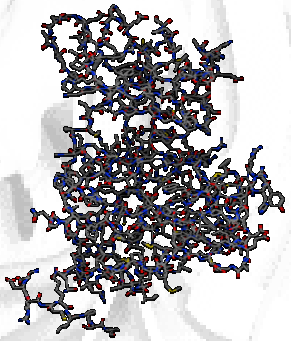
Why we need *time* virtualization?

1. Several molecular properties are time-dependent
2. Conformational space is naturally explored following time coordinate
3. Any recognition process is time-dependent
4. Dynamics controls equilibrium position
5. …

Back again to stability concept:

Molecular energy also fall under these categories:

POTENTIAL
stored energy



$Ep = f(x, y, z)$

KINETIC
energy of motion

$$E_k = \frac{1}{2} mv^2$$

$$E_i = \frac{1}{2} kT$$

How long we have followed MD simulation?

Bond vibrations: 1 fs

Collective vibrations: 1 ps

Conformational transitions: several ps or longer

Enzyme catalysis: microsecond/millisecond

Ligand Binding: micro/millisecond

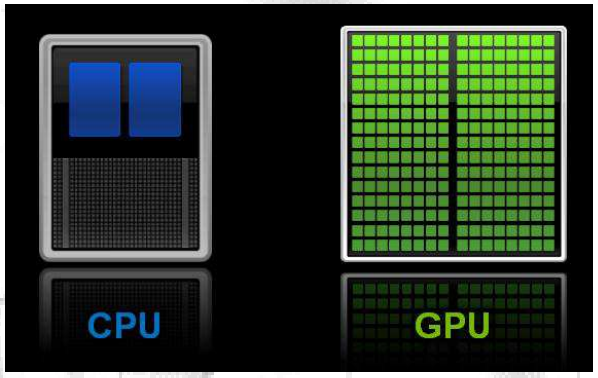
Protein Folding: millisecond/second

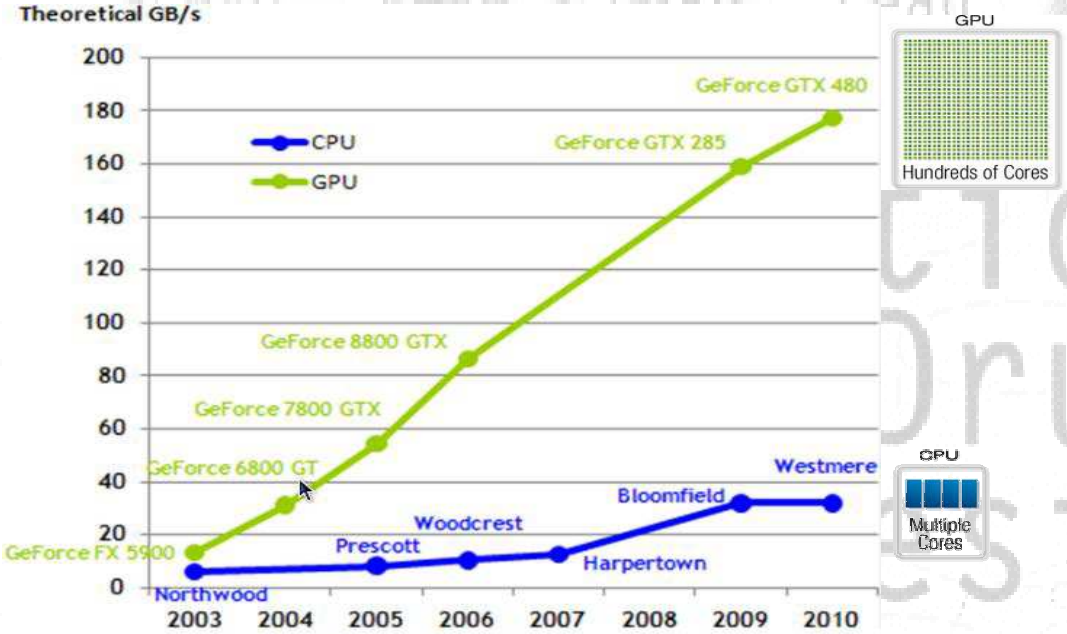
MD simulations: where theory needs technology.

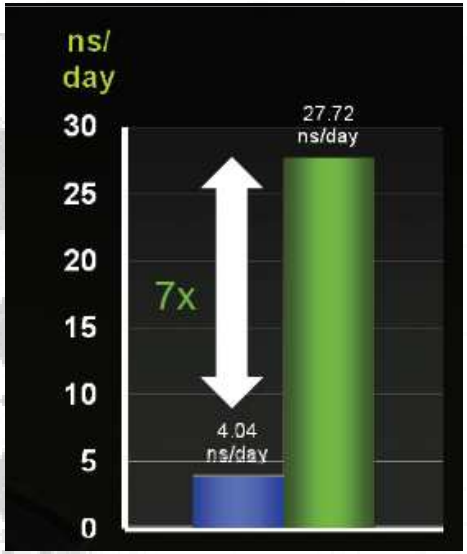
Remember: for the exploration of a very little *"molecular"* time we still need a huge amount of *"computational"* time!

Our unit of measurement is still... ns/day

My favorite C/G mutation

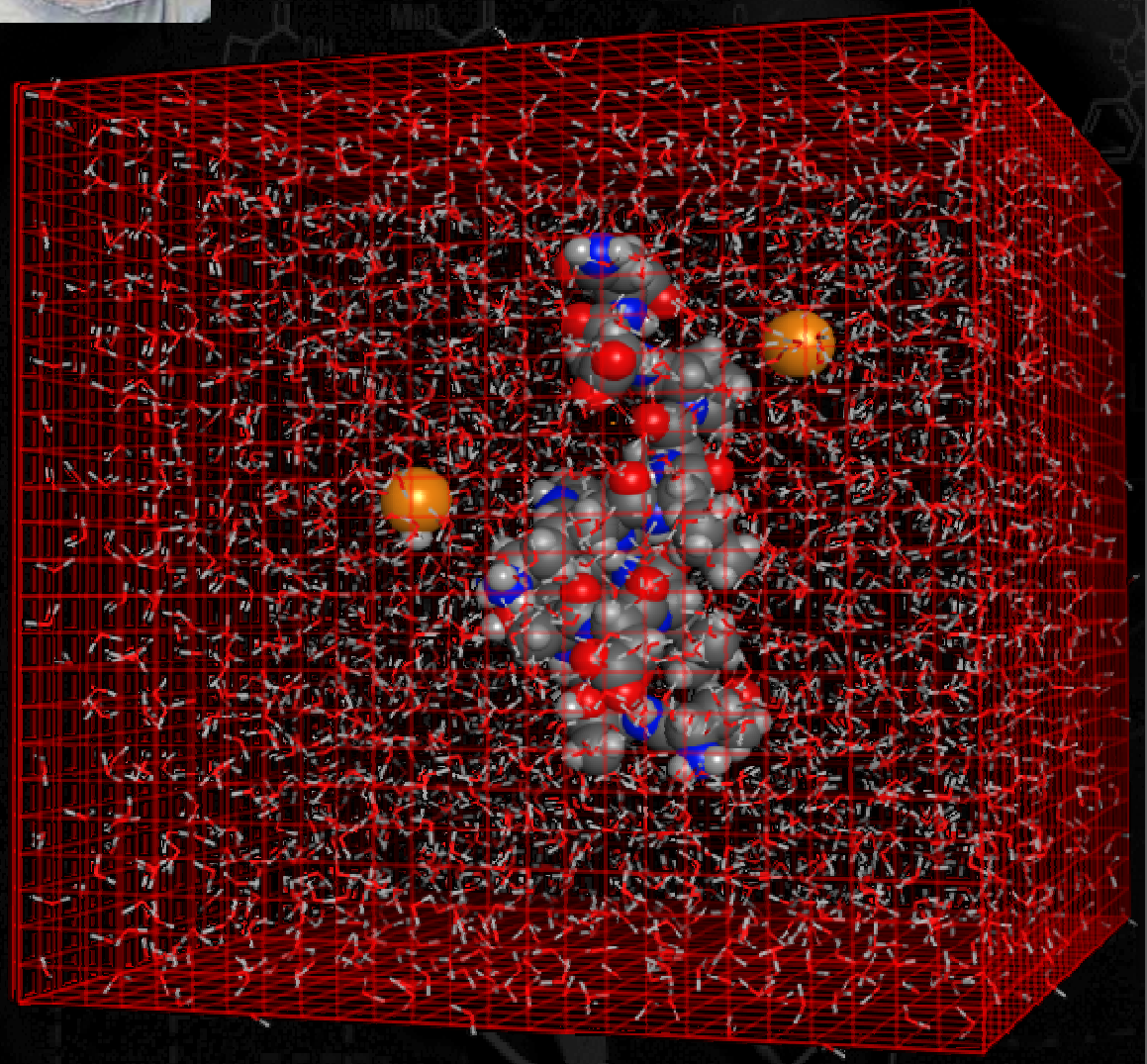






in collaboration with: acellera

MD simulations: how does it work?



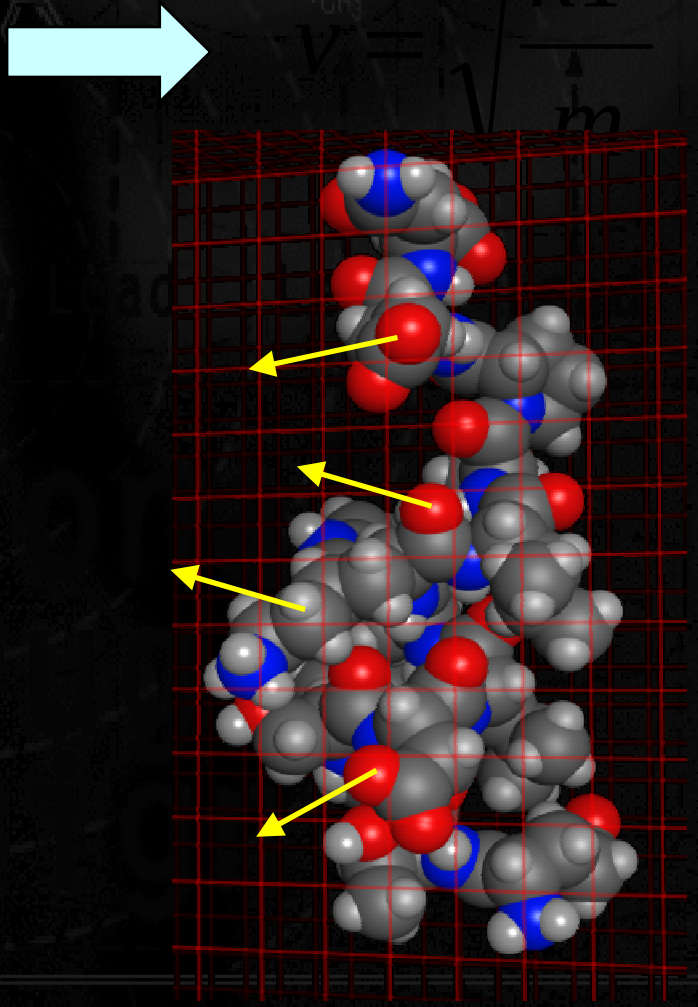
Atomic coordinates

Solvation

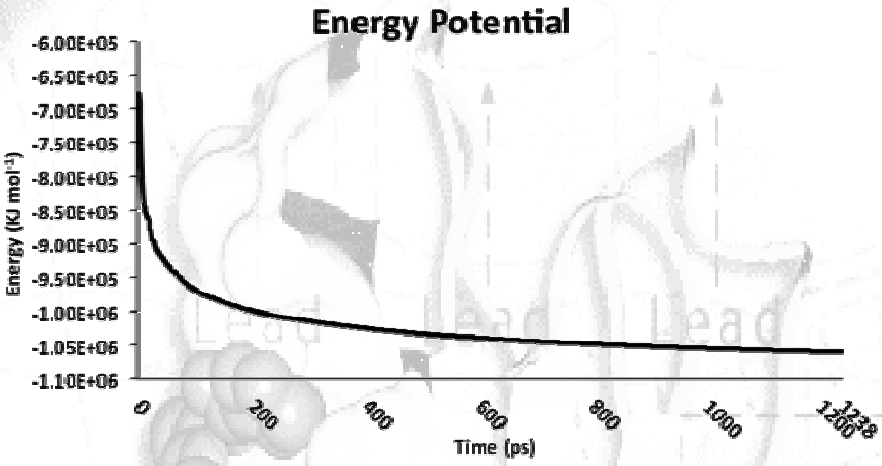
Adding ions

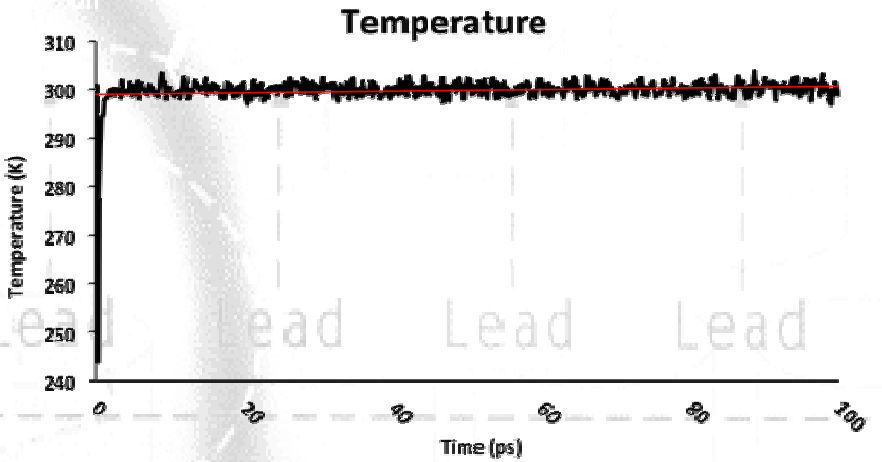
Equilibration

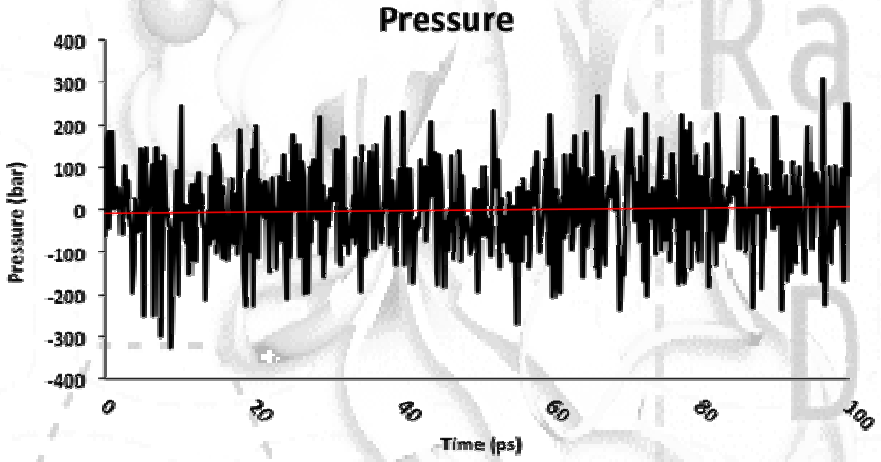
Equilibration…

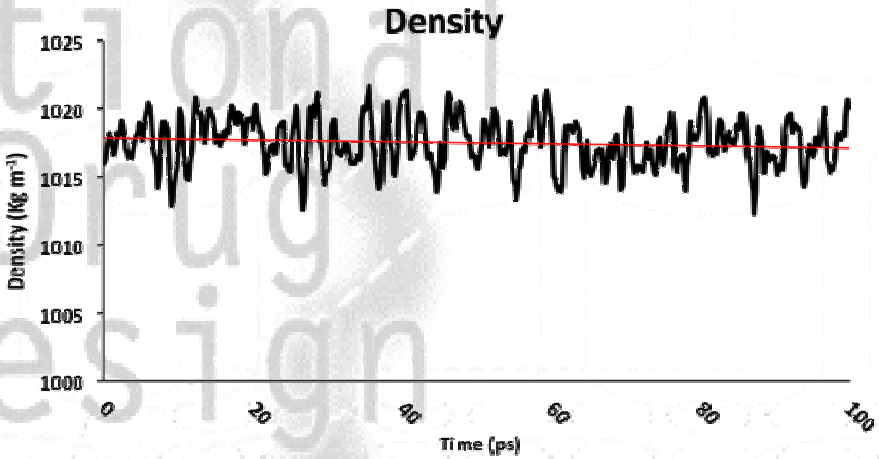


Equilibration…









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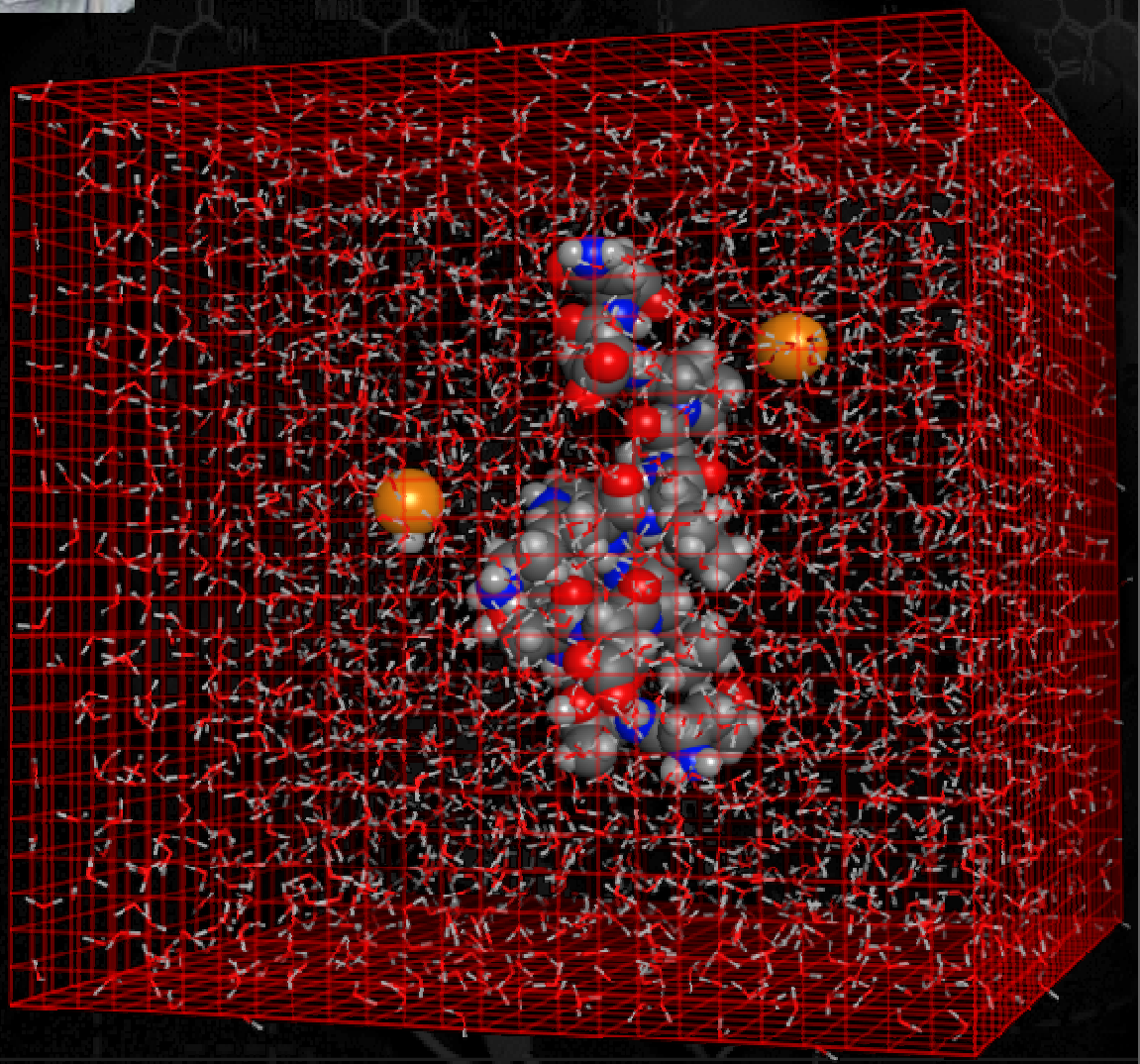


Atomic coordinates

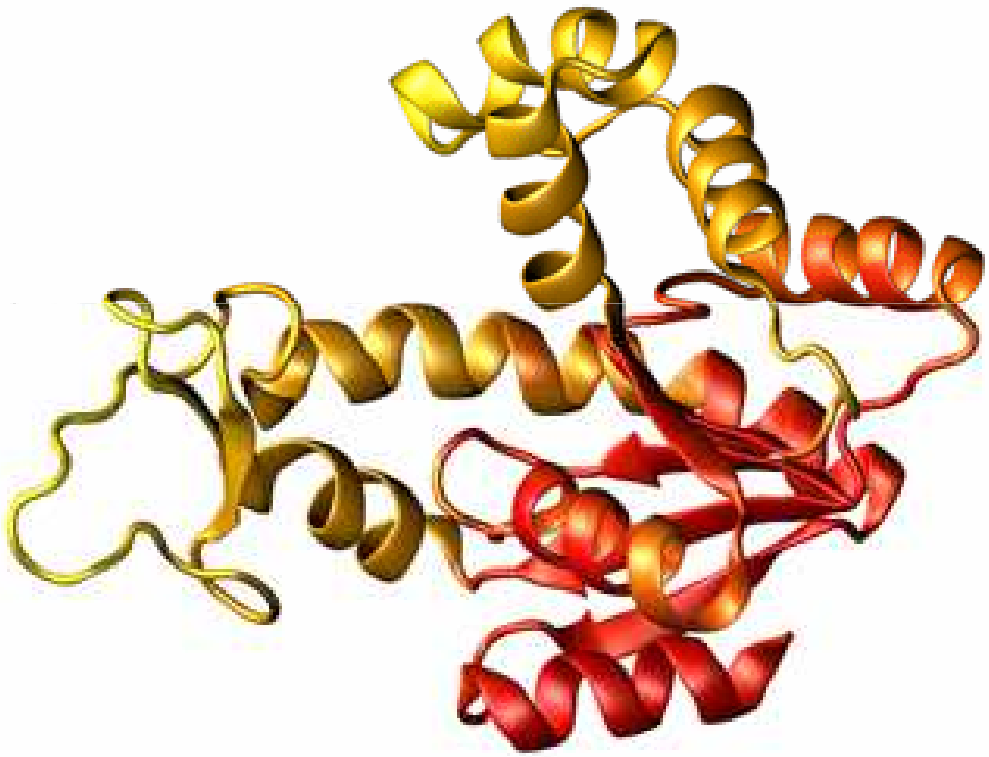
Solvation

Adding ions

Equilibration

MD trajectory

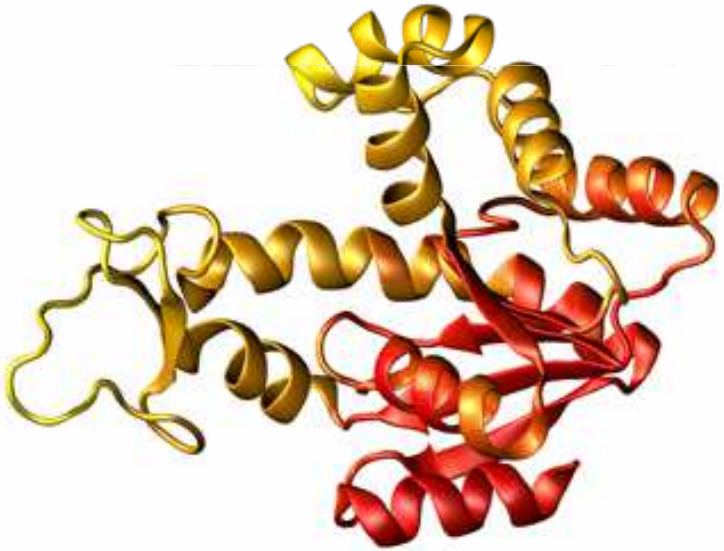
MD trajectory…

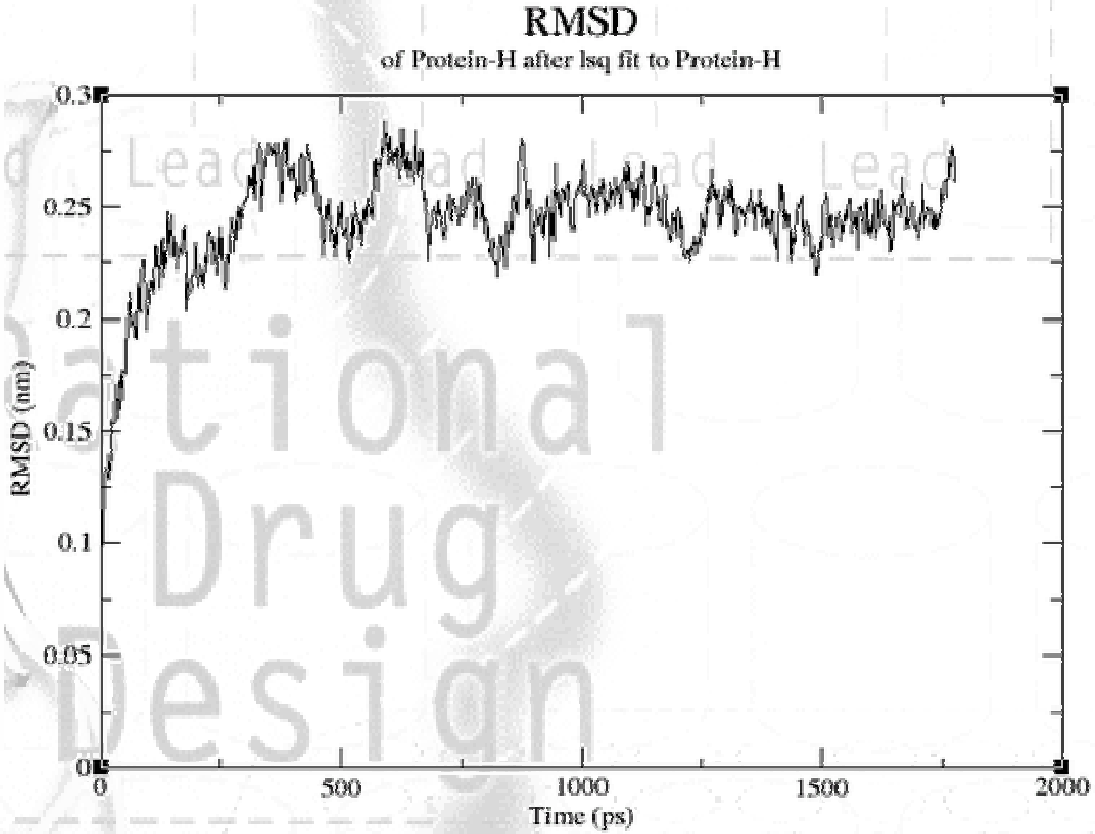


How to analyze a MD trajectory:

$$\mathrm{RMSD}(\mathbf{v},\mathbf{w}) = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\|v_i - w_i\|^2}$$

$$= \sqrt{\frac{1}{n}\sum_{i=1}^{n}(v_{ix} - w_{ix})^2 + (v_{iy} - w_{iy})^2 + (v_{iz} - w_{iz})^2}$$





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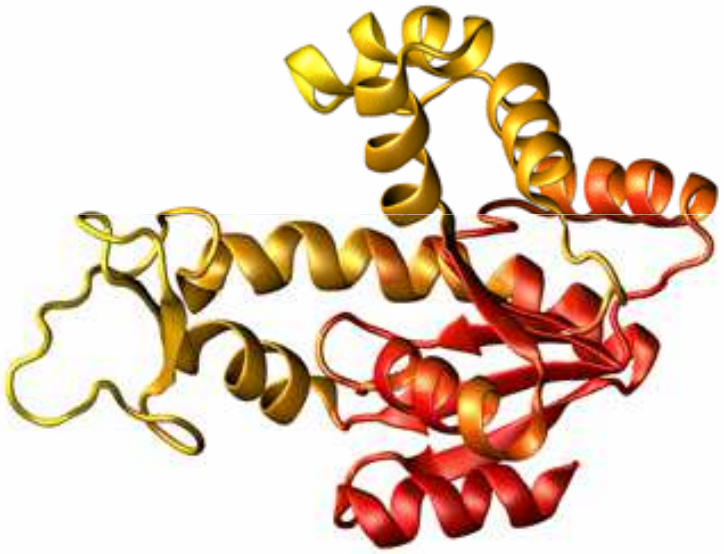
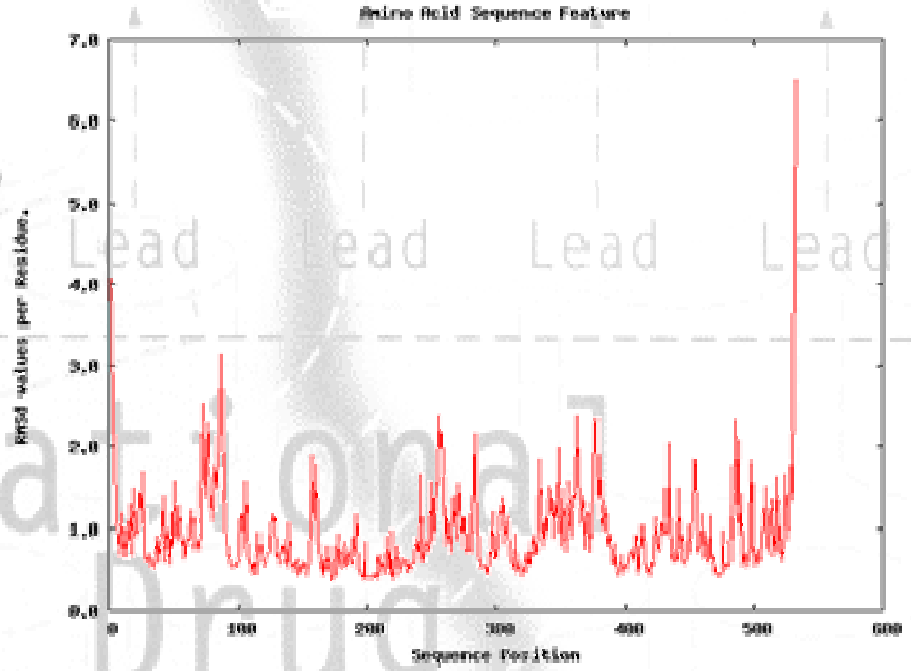
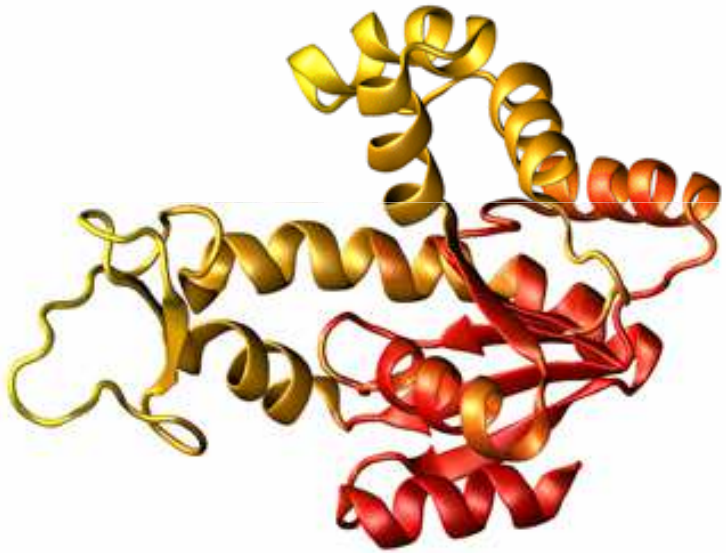
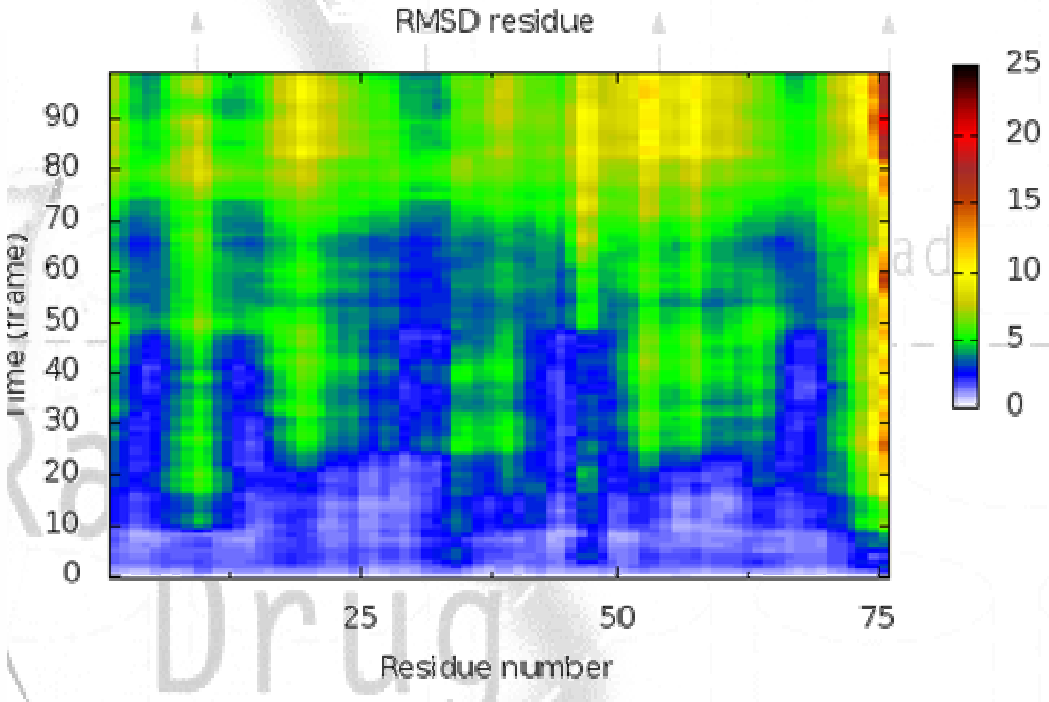




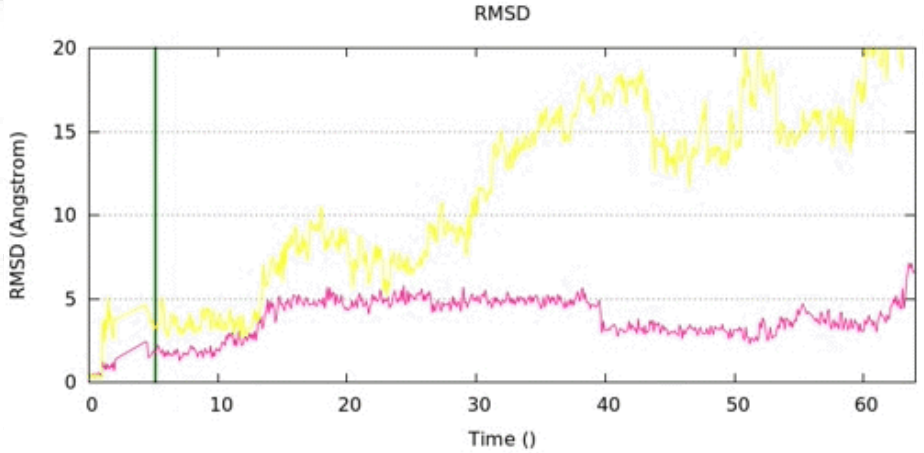
RMSd x Residue

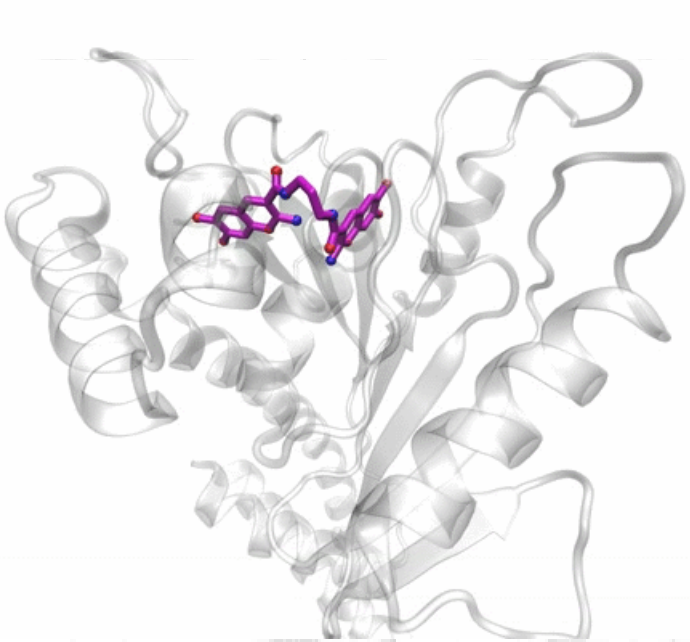
How to analyze a MD trajectory:

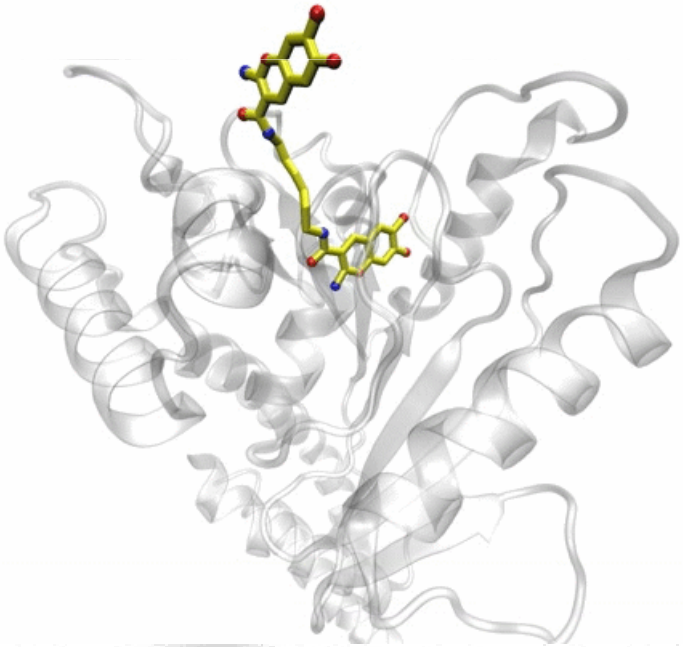


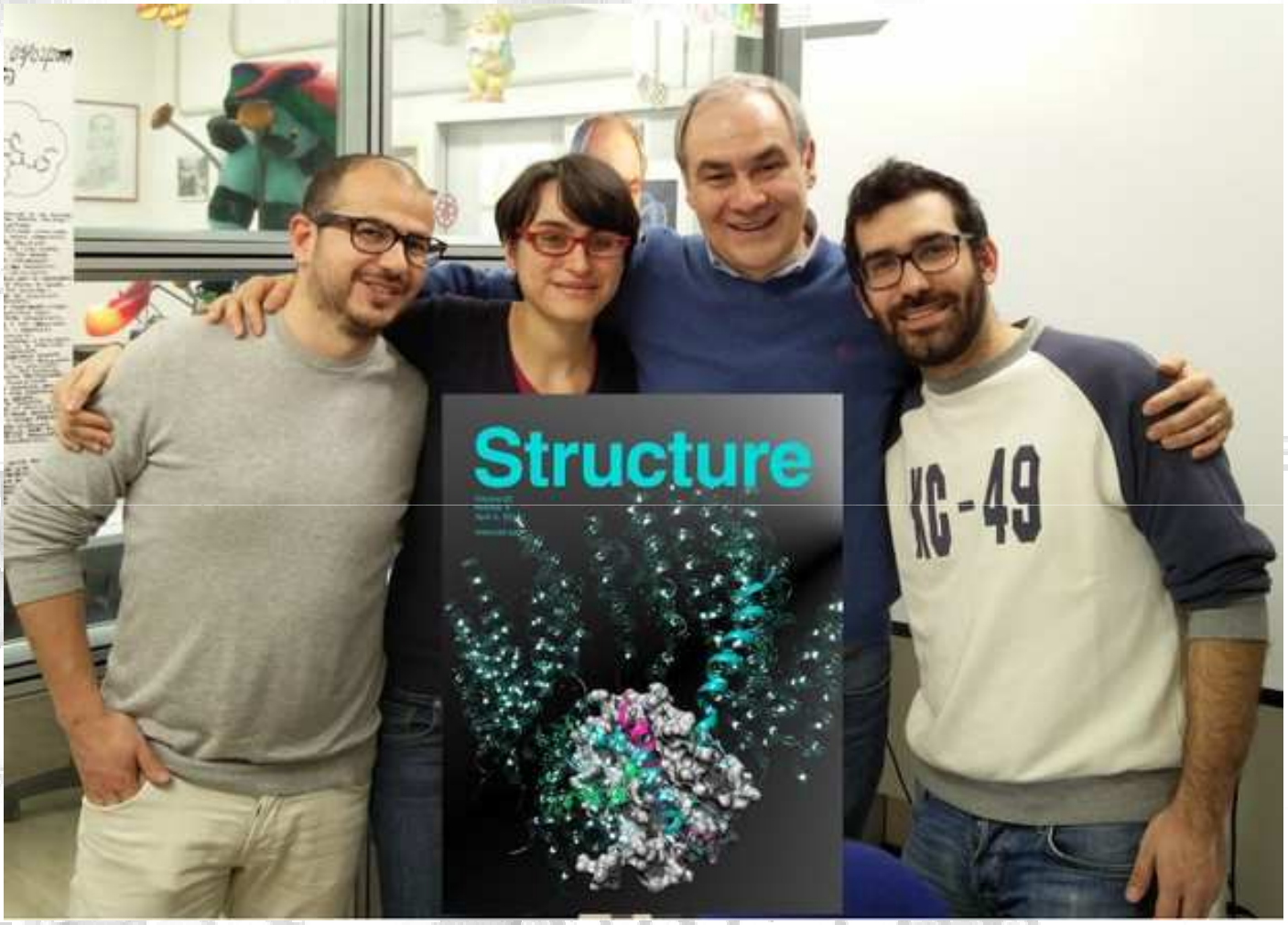


Bridging Docking and Molecular Dynamics





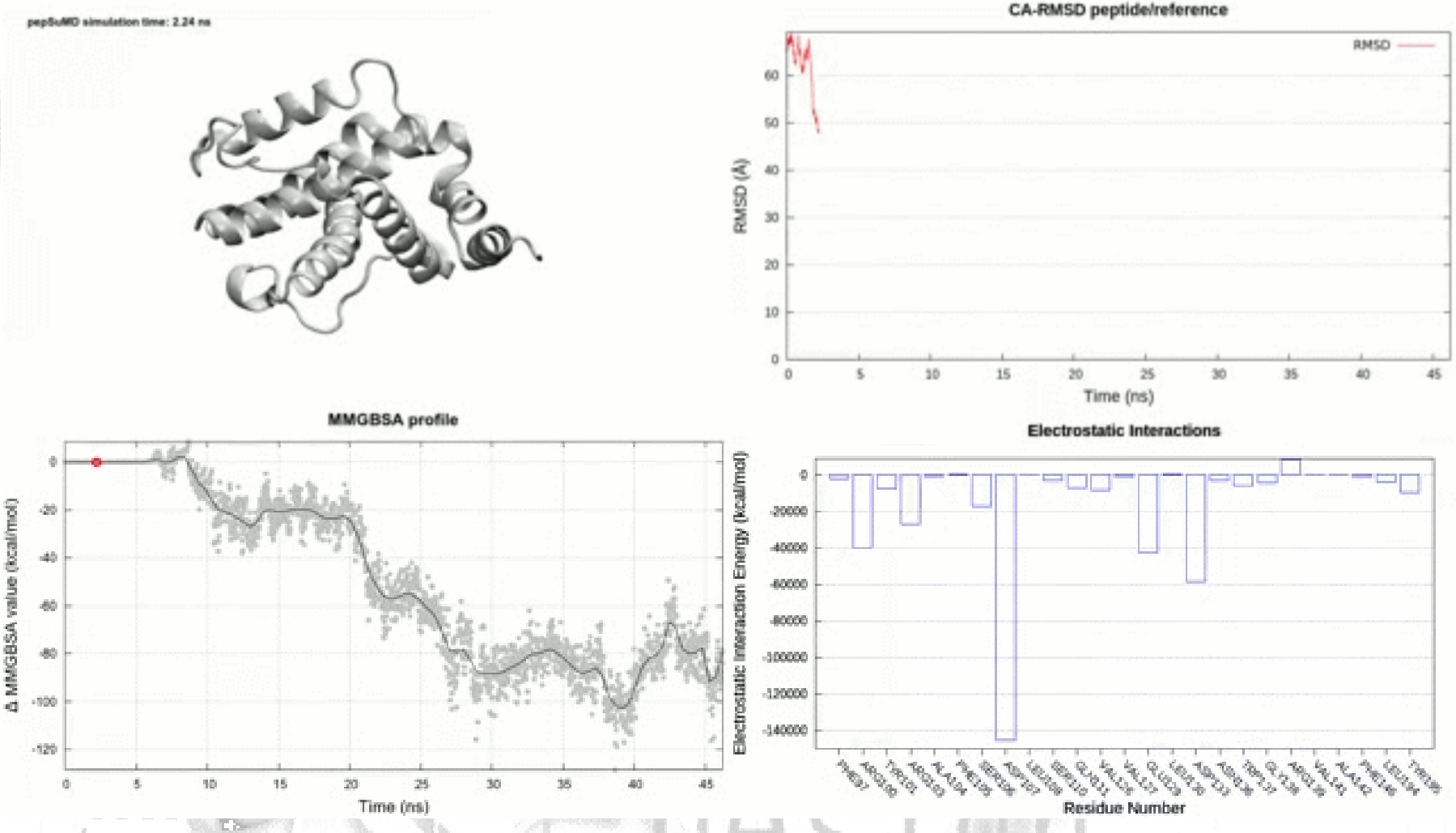




M. Sturlese **V. Salmaso** **A. Cuzzolin**

Salmaso V., Sturlese M.; Cuzzolin A.;Moro S. Structure 25, 655-662 (2017)

pepSupervised Molecular Dynamics (SuMD) – from small molecule to peptide…



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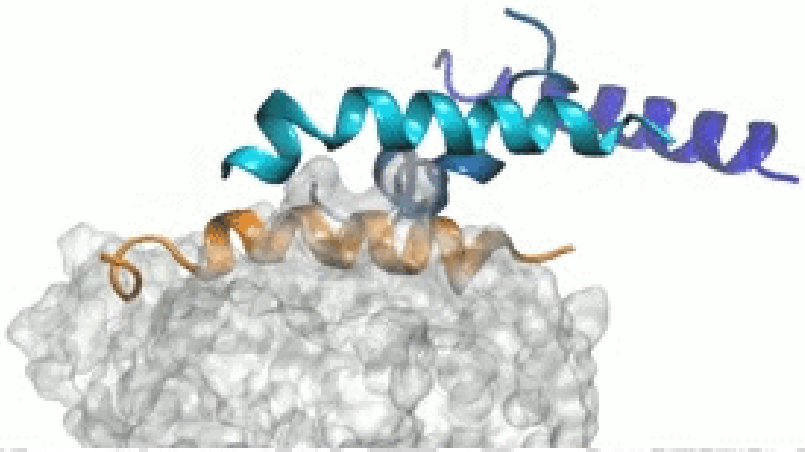
pepSupervised Molecular Dynamics (SuMD) – from small molecule to peptide…

pepSuMD simulation time: 5.86 ns



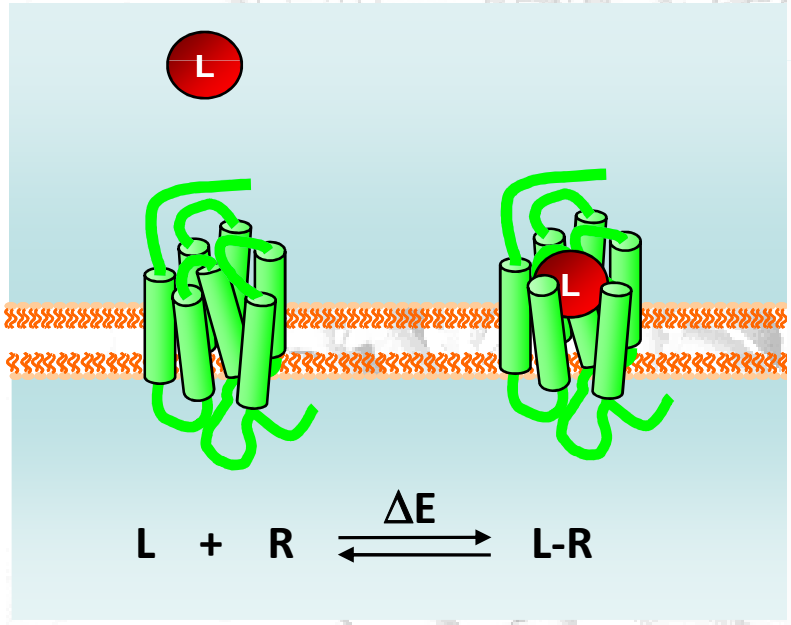
almaso V., Sturlese M.; Cuzzolin A.;Moro S. Structure 25, 655-662 (2017)

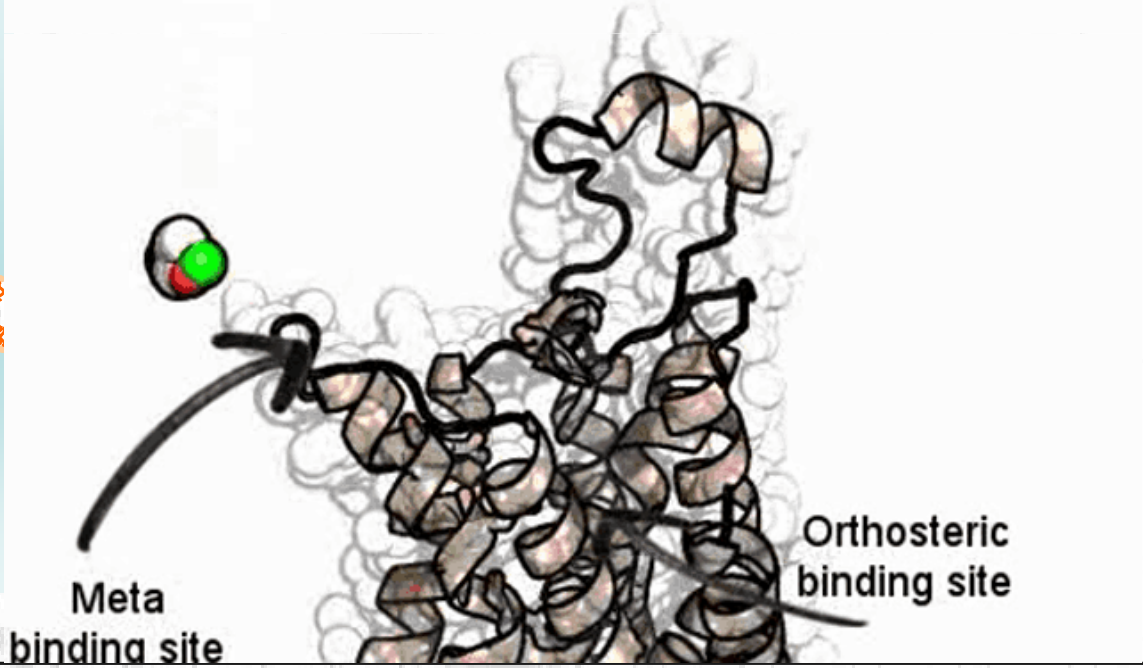
Supervised MD:

T4E - A2A Adenosine Receptor

suMD - GPU: NVIDIA GTX680 - Simulation time: 2.3 ns

MMS
mms.dsfarm.unipd.it





GRAZIE
PER LA PAZIENZA