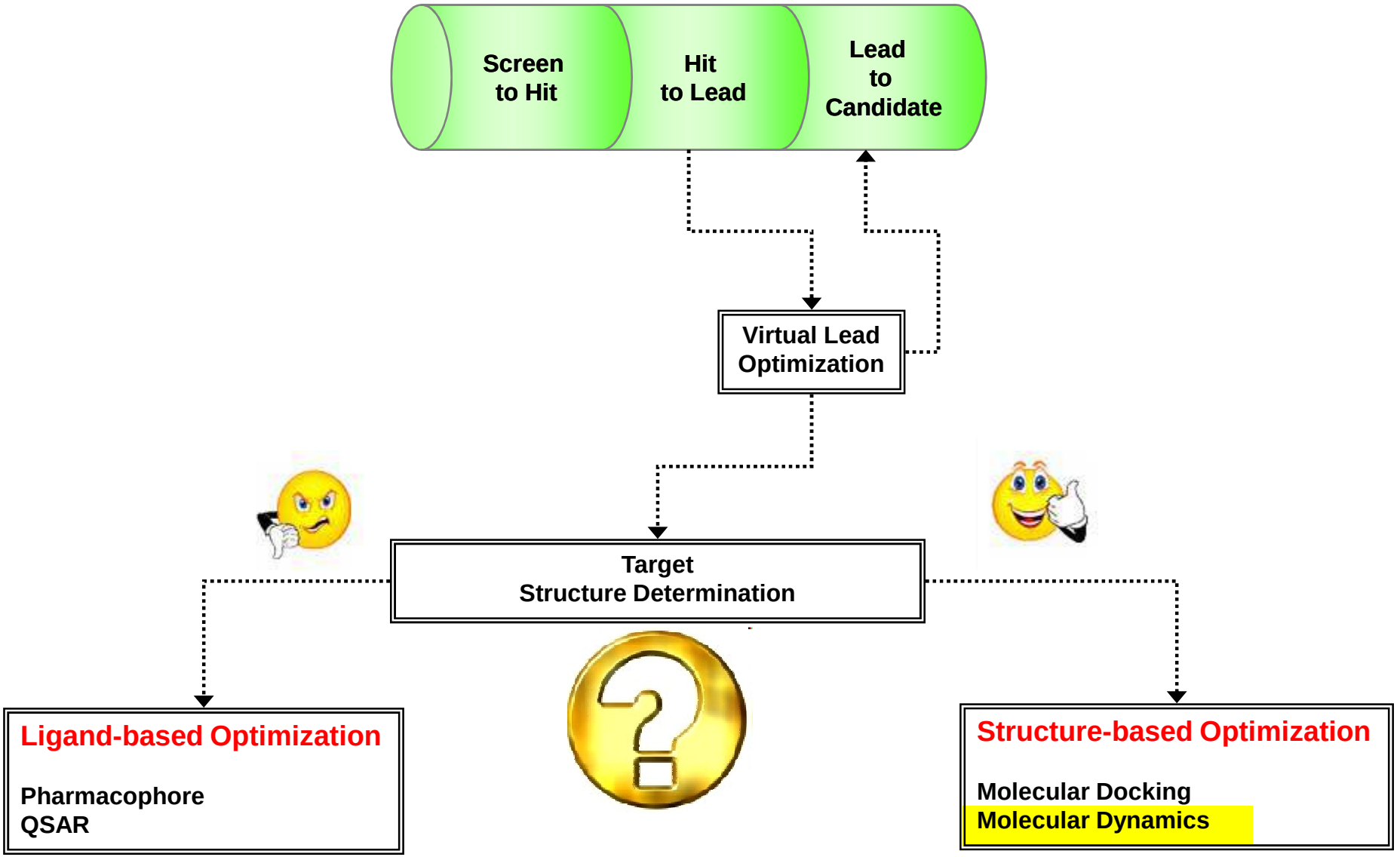
Time…

"Life would not exit without motion" by Martin Karplus


Screen to Hit
Hit to Lead
Lead to Candidate
Virtual Lead Optimization
Target Structure Determination
Ligand-based Optimization
Pharmacophore
QSAR
Structure-based Optimization
Molecular Docking
Molecular Dynamics

Why we need *time* virtualization?

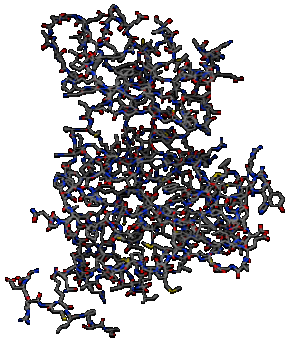
1. Several molecular properties are time-dependent
2. Conformational space is naturally explored following time coordinate
3. Any recognition process is time-dependent
4. Dynamics controls equilibrium position
5. …

Back again to stability concept:

Molecular energy also fall under these categories:

POTENTIAL
stored energy

KINETIC
energy of motion

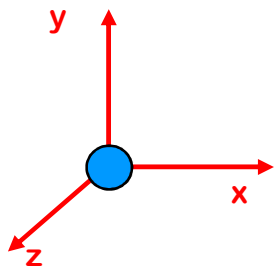


$Ep = f(x, y, z)$

Basic concepts:

1. Degrees of freedom of molecules

	Monatomic	Linear molecules	Non-linear molecules
Translation (*x*, *y*, and *z*)	**3**	**3**	**3**
Rotation (*x*, *y*, and *z*)	**0**	**2**	**3**
Vibration	**0**	**3*N* – 5**	**3*N* – 6**
Total	**3**	**3*N***	**3*N***

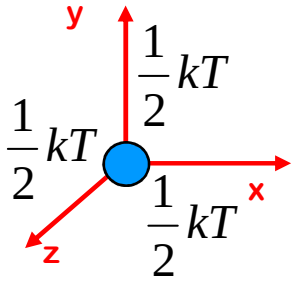


Basic concepts:

2. Equipartition theorem

Since the degrees of freedom are independent, the internal energy of the system is equal to the sum of the mean energy associated with each degree of freedom, which demonstrates the result:

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

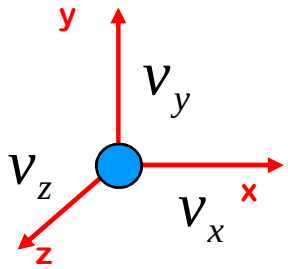


$$E_i = \frac{3}{2}kT$$

Boltzmann constant, $k = R/N_A = 1.38 \times 10^{-23}$ J/K

Basic concepts:

3. Kinetic energy

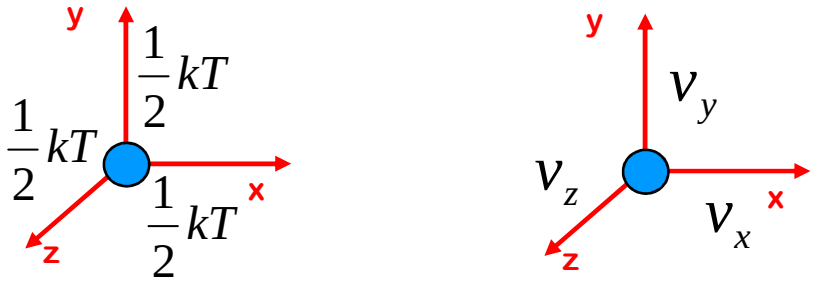


$$E_k = \frac{1}{2} m v^2$$

Velocity is a vectorial property

Basic concepts:

4. Combining the internal with kinetic energy



For a monoatomic gas (only 3 translation degrees of freedom) :

$$\frac{1}{2}mv^2 = \frac{3}{2}kT \qquad v = \sqrt{\frac{3kT}{m}} \qquad \frac{dx}{dt} = \sqrt{\frac{3kT}{m}}$$

For a non-linear molecule (with 3N degrees of freedom) :

$$\frac{1}{2}mv^2 = \frac{3N}{2}kT \qquad v = \sqrt{\frac{3NkT}{m}} \qquad \frac{dx}{dt} = \sqrt{\frac{3NkT}{m}}$$

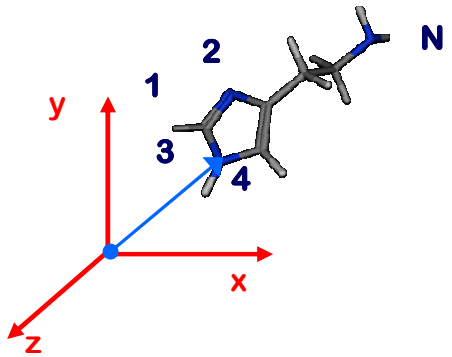
Molecular Dynamics basics:

A working definition of *molecular dynamics* (MD) simulation is technique by which one generates the atomic ***trajectories*** of a system of N particles by numerical integration of Newton's equation of motion, for a specific interatomic potential, with certain initial condition (IC) and boundary condition (BC).

Molecular Dynamics basics:

1. Physical system

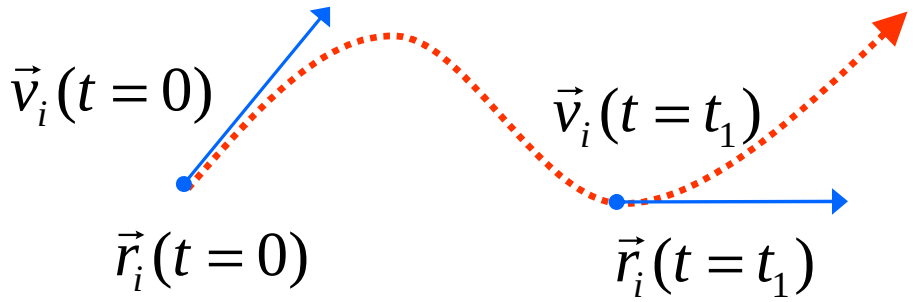
We can define as physical system a set of atomic coordinates using a vector notation:



$$\vec{r}_i = (x_i, y_i, z_i)$$

2. Trajectory

A mapping from time to a point in the 3-dimensional space:

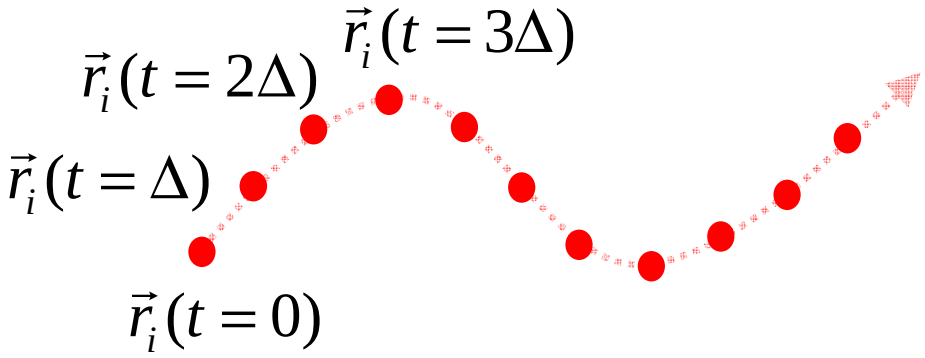


Molecular Dynamics basics:

for continuous time, we consider a sequence of states:

$$\left(\vec{r}_i(0), \vec{v}_i(0)\right) \mapsto \left(\vec{r}_i(\Delta), \vec{v}_i(\Delta)\right) \mapsto \left(\vec{r}_i(2\Delta), \vec{v}_i(2\Delta)\right)$$

time step



The question is: How to predict the next state from the current state?

Molecular Dynamics basics:

3. Velocity

Short time limit of an average speed (how fast and in which direction the particle is moving):

$$\vec{v}_i(t) = \frac{d\vec{r}_i}{dt} = \lim_{\Delta \to 0} \frac{\vec{r}_i(t+\Delta) - \vec{r}_i(t)}{\Delta}$$

Δ *time step*

Molecular Dynamics basics:

4. Random velocities

We generate random velocities of magnitude:

$$v_0 = \sqrt{\frac{3kT_i}{m}}$$

simulation temperature

For each atom, the velocity vector is then given by:

$$\vec{v}_0 = v_0(\xi_x, \xi_y, \xi_z) = v_0\vec{\xi}$$

where is a *randomly* oriented vector of unit length.

and finally:

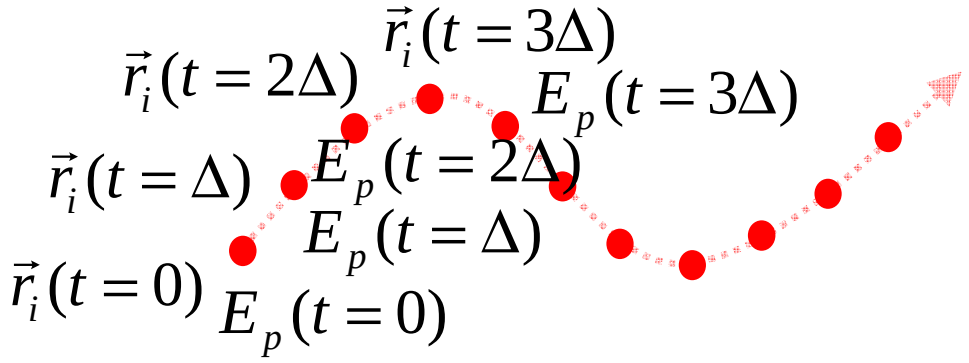
$$\vec{v}_i(t) = \frac{d\vec{r}_i}{dt} = \lim_{\Delta \to 0} \frac{\vec{r}_i(t+\Delta) - \vec{r}_i(t)}{\Delta}$$

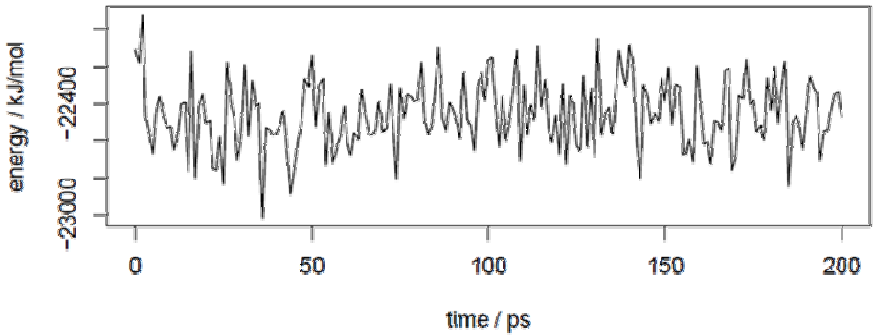
$$\vec{r}_i(t+\Delta) = \vec{r}_i(t) + \vec{v}_i(t)\Delta = \sqrt{\frac{3NkT}{m}}\bar{\zeta}\Delta$$

Back to the definition of *trajectory*:

$$\left(\vec{r}_i(0), \vec{v}_i(0)\right) \mapsto \left(\vec{r}_i(\Delta), \vec{v}_i(\Delta)\right) \mapsto \left(\vec{r}_i(2\Delta), \vec{v}_i(2\Delta)\right)$$

time step





using the appropriate *force field* is possible to calculate the potential energy of the system during all MD step.

How to select the appropriate Δt:

To ensure a correct numerical integration of the equations of motion, and therefore reduce the error in the calculation of the energy of the system, it is NECESSARY that the interval of integration is between 1/100 and 1/20 of the time associated with the fastest motion in our molecular system.

In classical molecular dynamics faster motions are associated with the bond vibrations (10-100 fs). In particular, all C-H, N-H and O-H stretching times are around 10 fs. An accepted compromise is to set as value interval of integration is equal to 1fs. Remember: 1 fs = 10^{-15} s

There are algorithms that provide the freezing of vibrational motions linked in particular to the C-H bonds, N-H and O-H (SHAKE ALGORITHM). This allows you to double the value of the integration time to 2fs.

How long we have followed MD simulation?

Bond vibrations: 1 fs

Collective vibrations: 1 ps

Conformational transitions: ns or longer

Enzyme catalysis: microsecond/millisecond

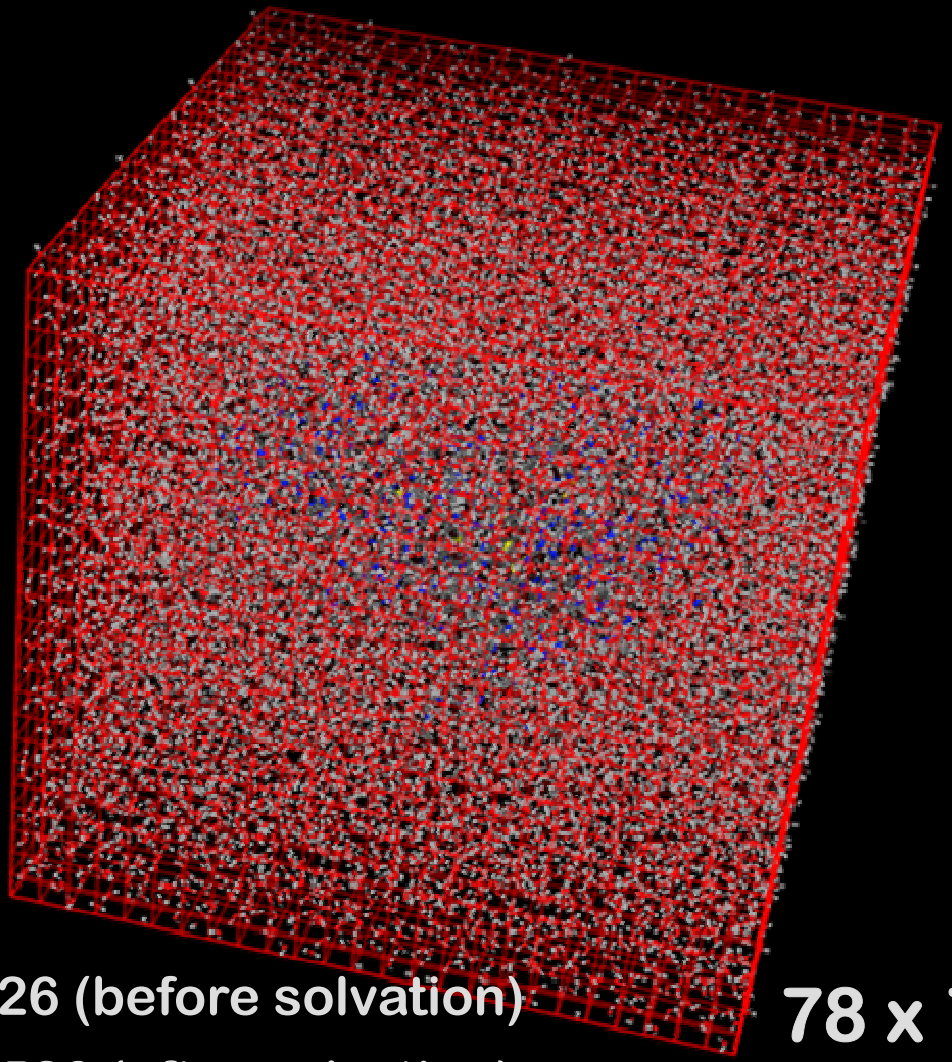
Ligand Binding: micro/millisecond

Protein Folding: millisecond/second

To depict realistic MD trajectories, it is crucial to guarantee realistic boundary conditions!!!

1. Solvent (water)
2. pH and ionic strength

Here is what I mean:



Number of atoms: 5526 (before solvation)

Number of atoms: 35523 (after solvation)

78 x 78 x 78 Å

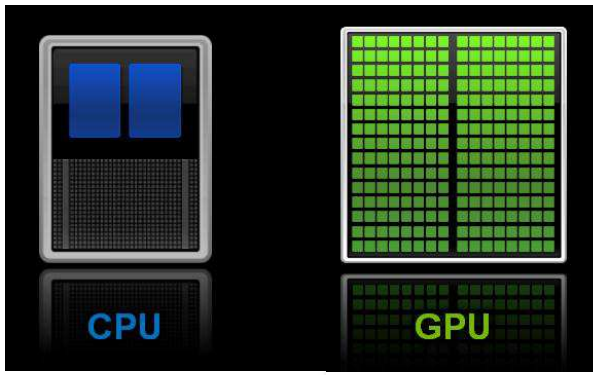
MD simulations: where theory needs technology.

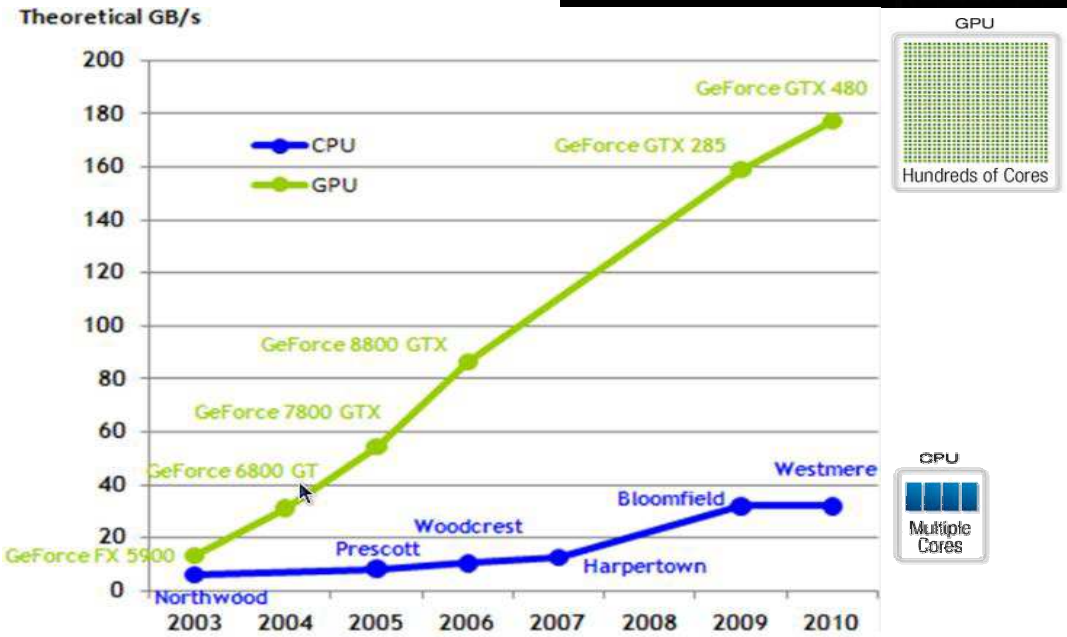
Remember: for the exploration of a very little *"molecular"* time we still need a huge amount of *"computational"* time!

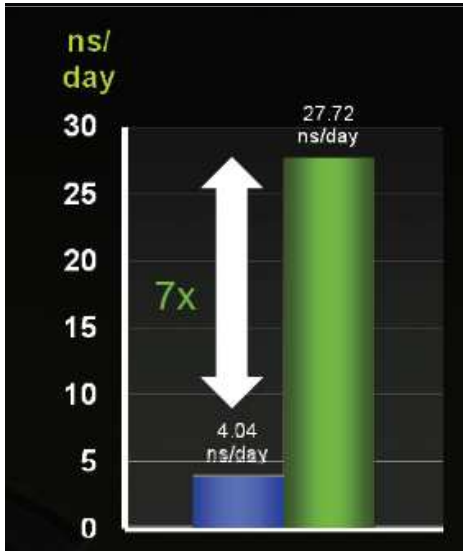
Our unit of measurement is still… ns/day

The GPU revolution!!!

My favorite C/G mutation

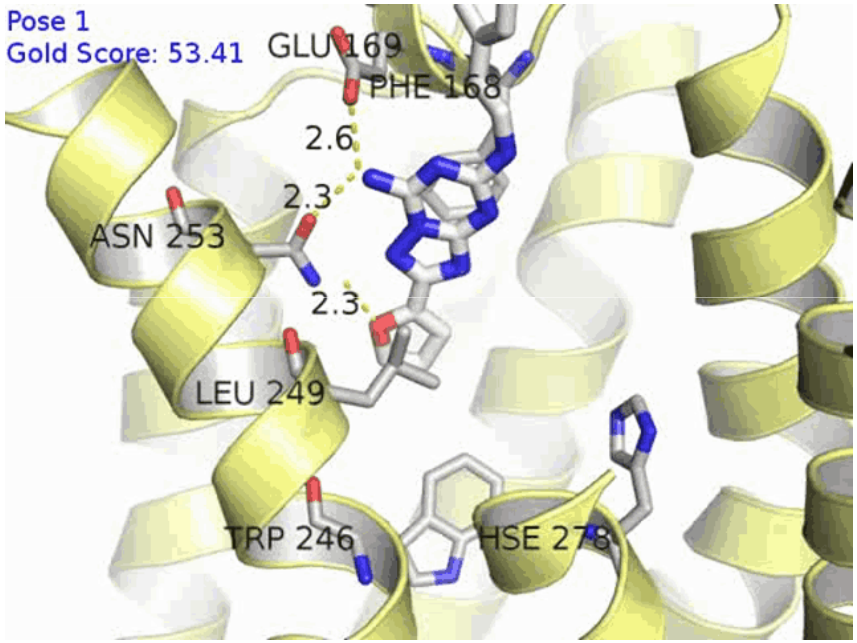


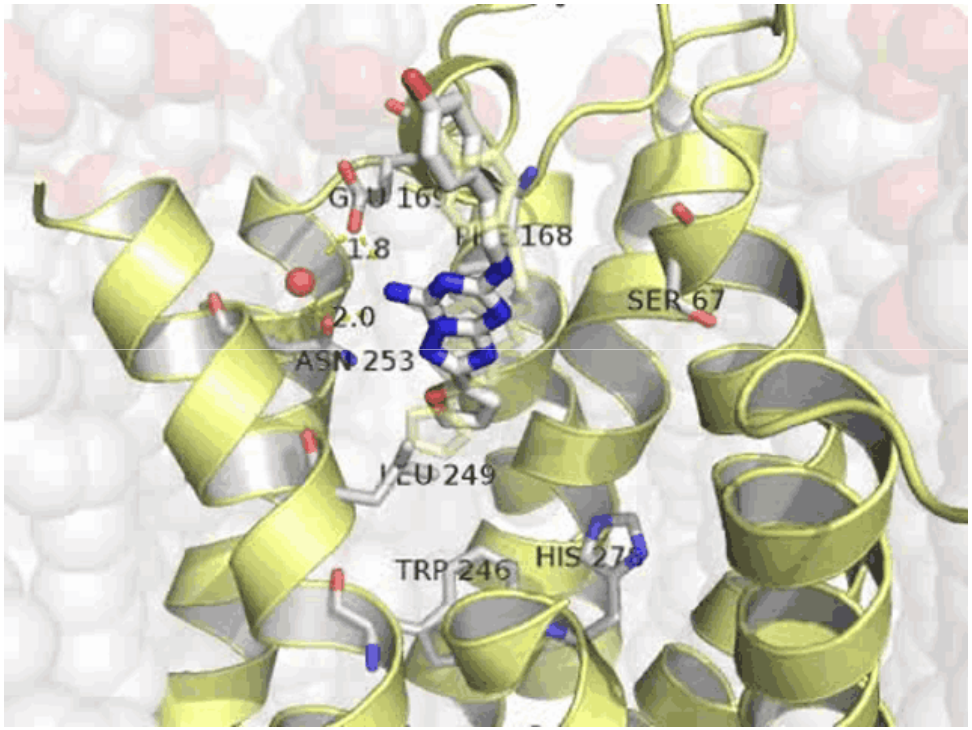




in collaboration with: acellera

Here is the big emotion:

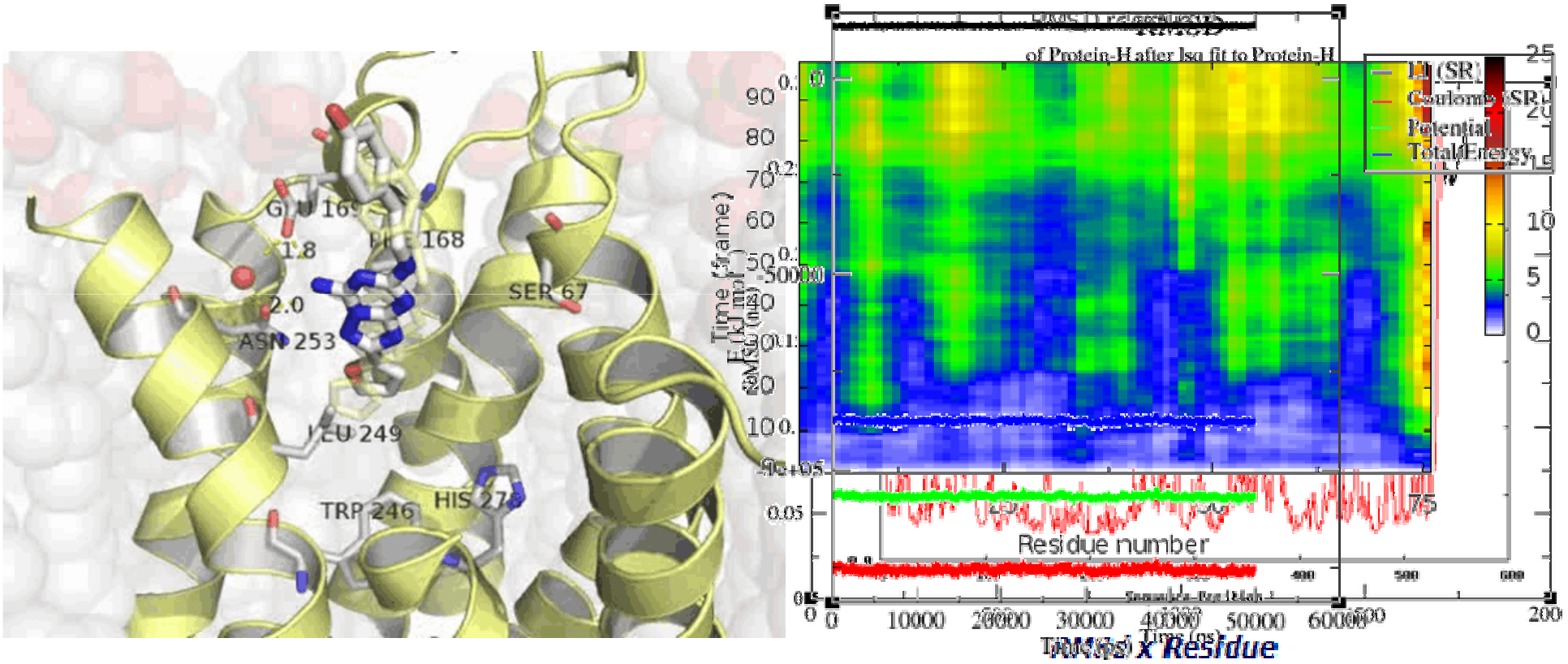




Molecular Docking

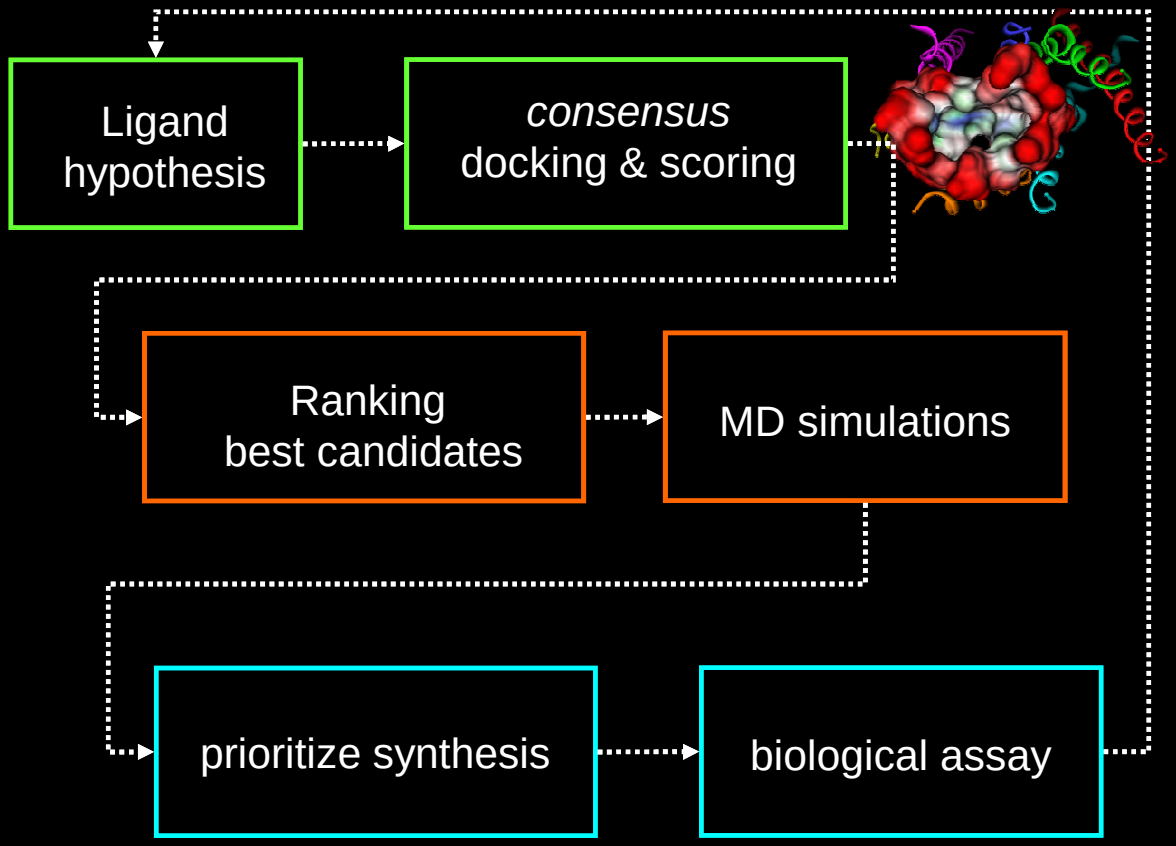
Molecular Dynamics

How to analyze a MD trajectory:

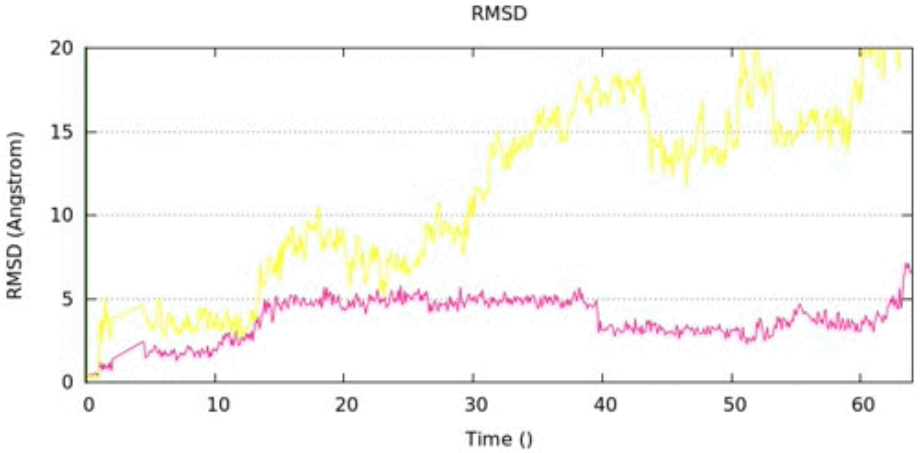


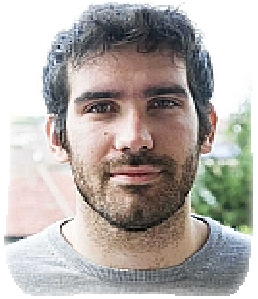
Molecular Dynamics

A possible workflow:

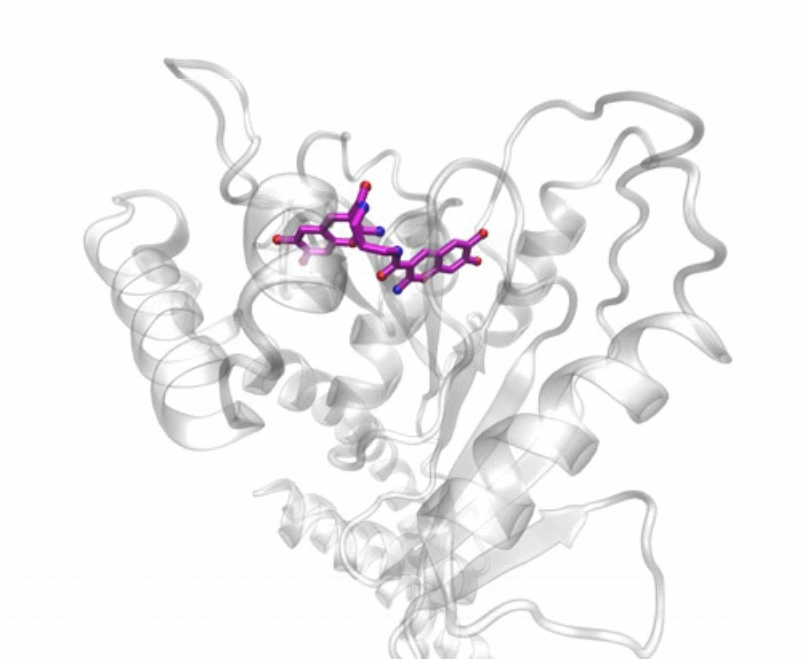


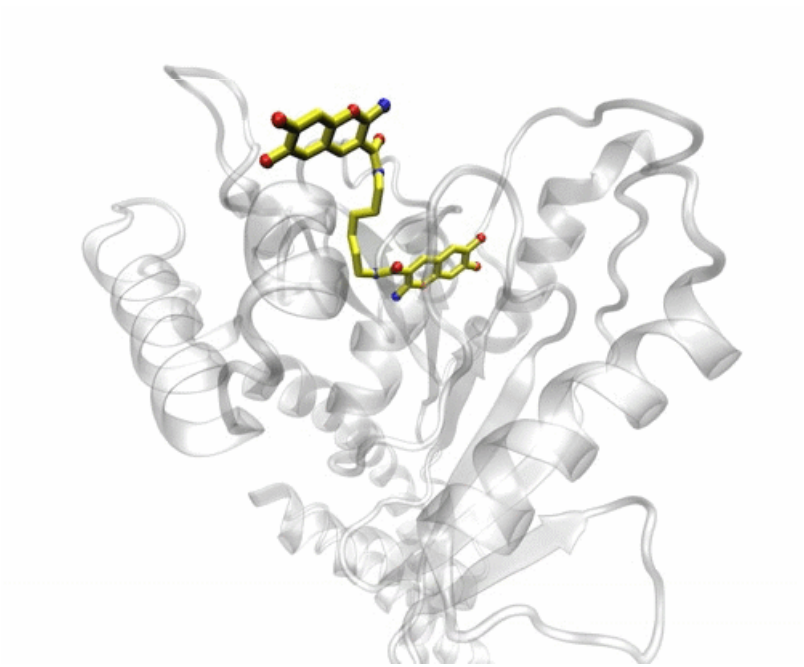
MMS dynamics:





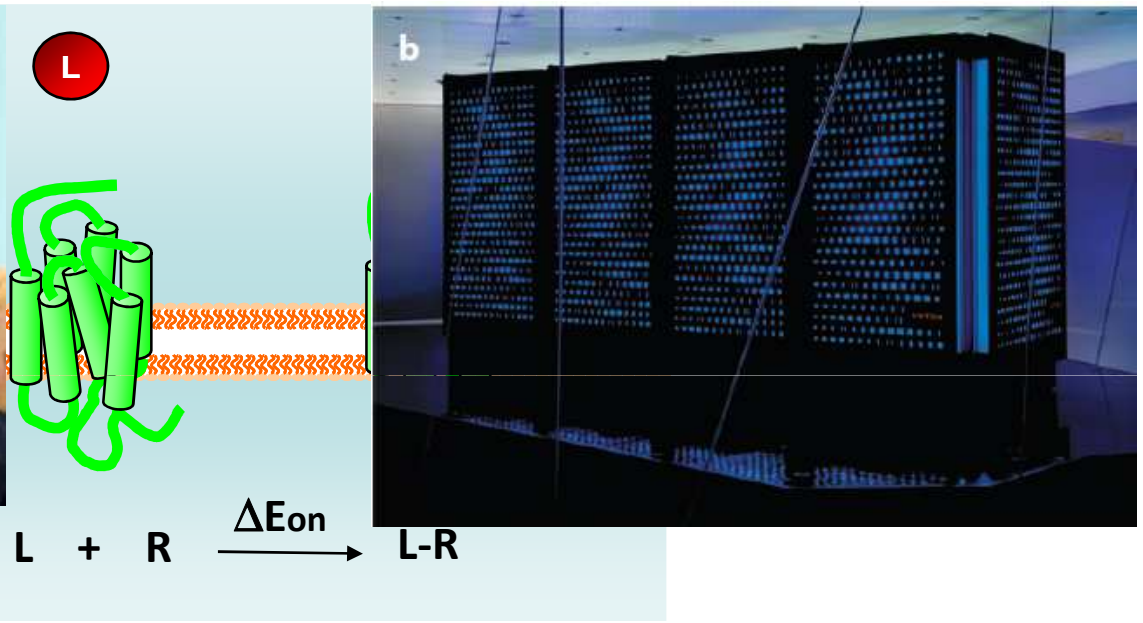
A. Cuzzolin



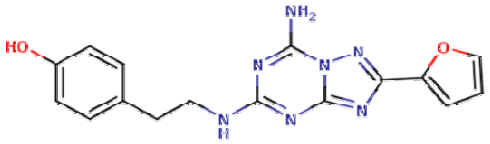


MMS dynamics:

what about ligand-receptor binding process?



"A common application of protein–ligand simulations is to compute the binding affinity of a ligand, often a drug candidate, to a known binding site. **Unbiased MD** simulations of ligand binding **are usually ill suited** for this purpose, as precise estimation of ligand affinity would typically require **seconds to hours of simulated time** in order to observe sufficiently many binding and unbinding events." *David E. Shaw Annu. Rev. Biophys. 2012. 41:429–52*



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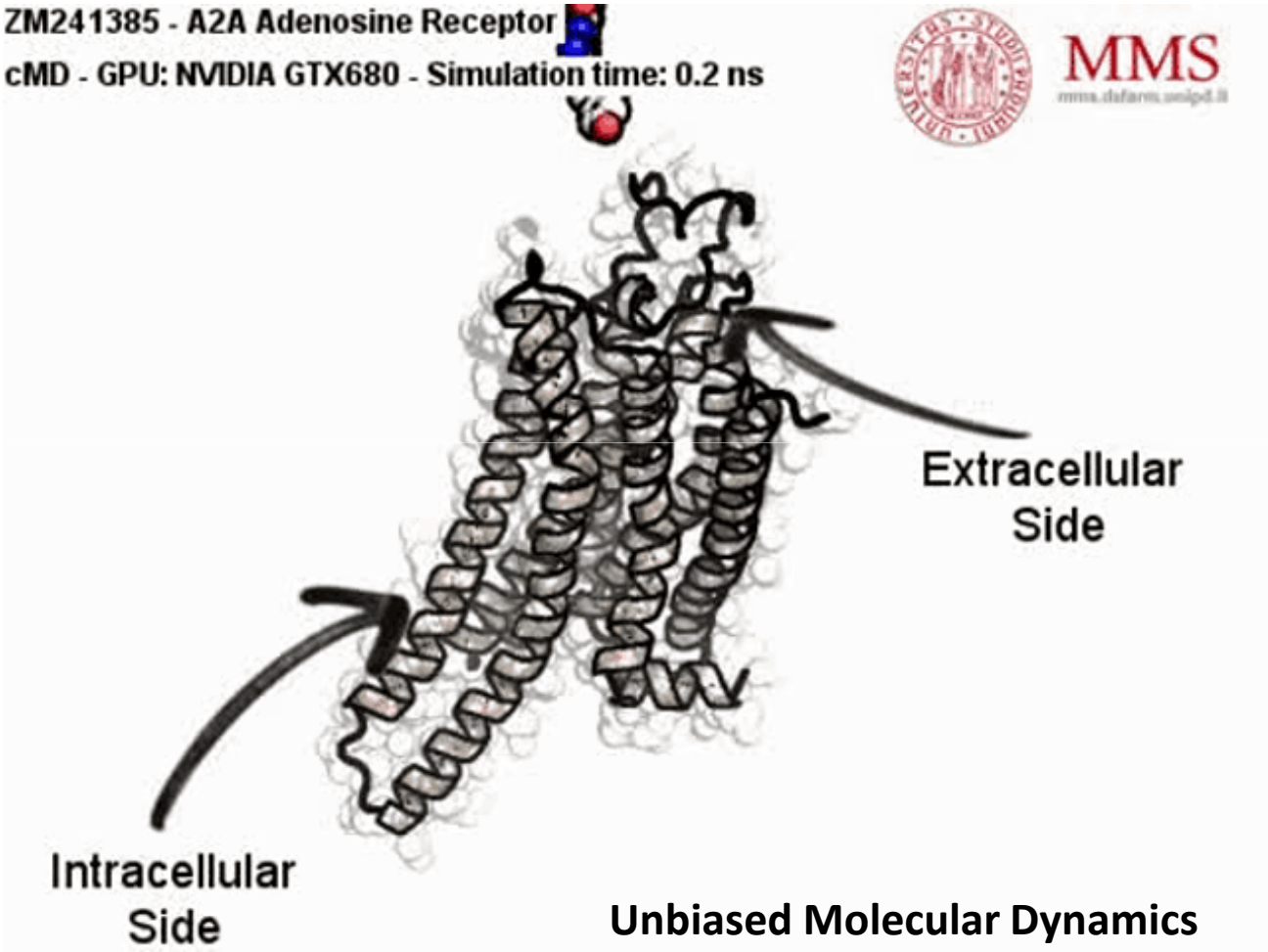
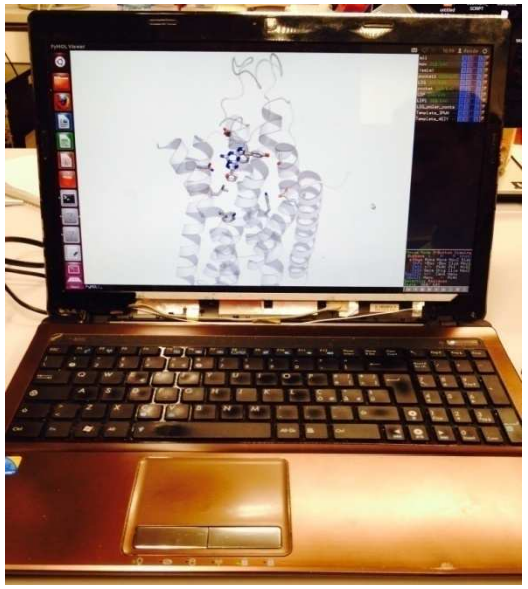


Unbiased Molecular Dynamics

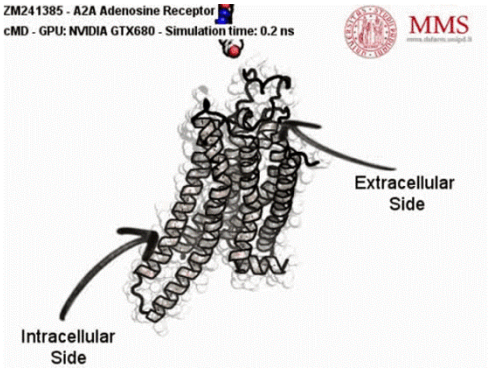
Sabbadin D.; Moro S. J Chem Inf Mod 54, 372-376, 2014)

D. Sabbadin

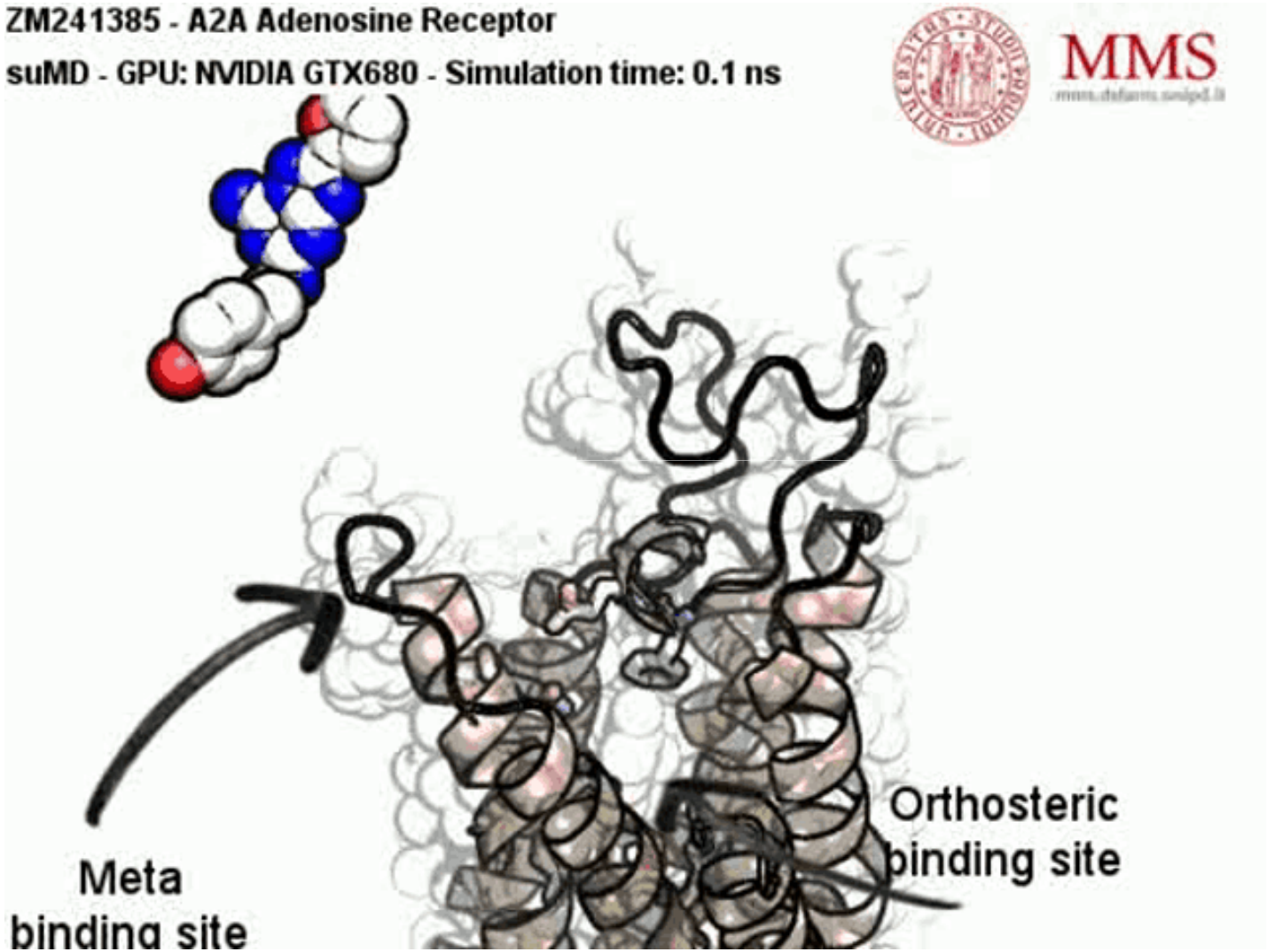


"I can run of protein–ligand simulations to compute the binding recognition in a **nanosecond** time scale on my laptop!" *Davide Sabbadin (J Chem Inf Mod 54, 372-376, 2014)*

Supervised Molecular Dynamics

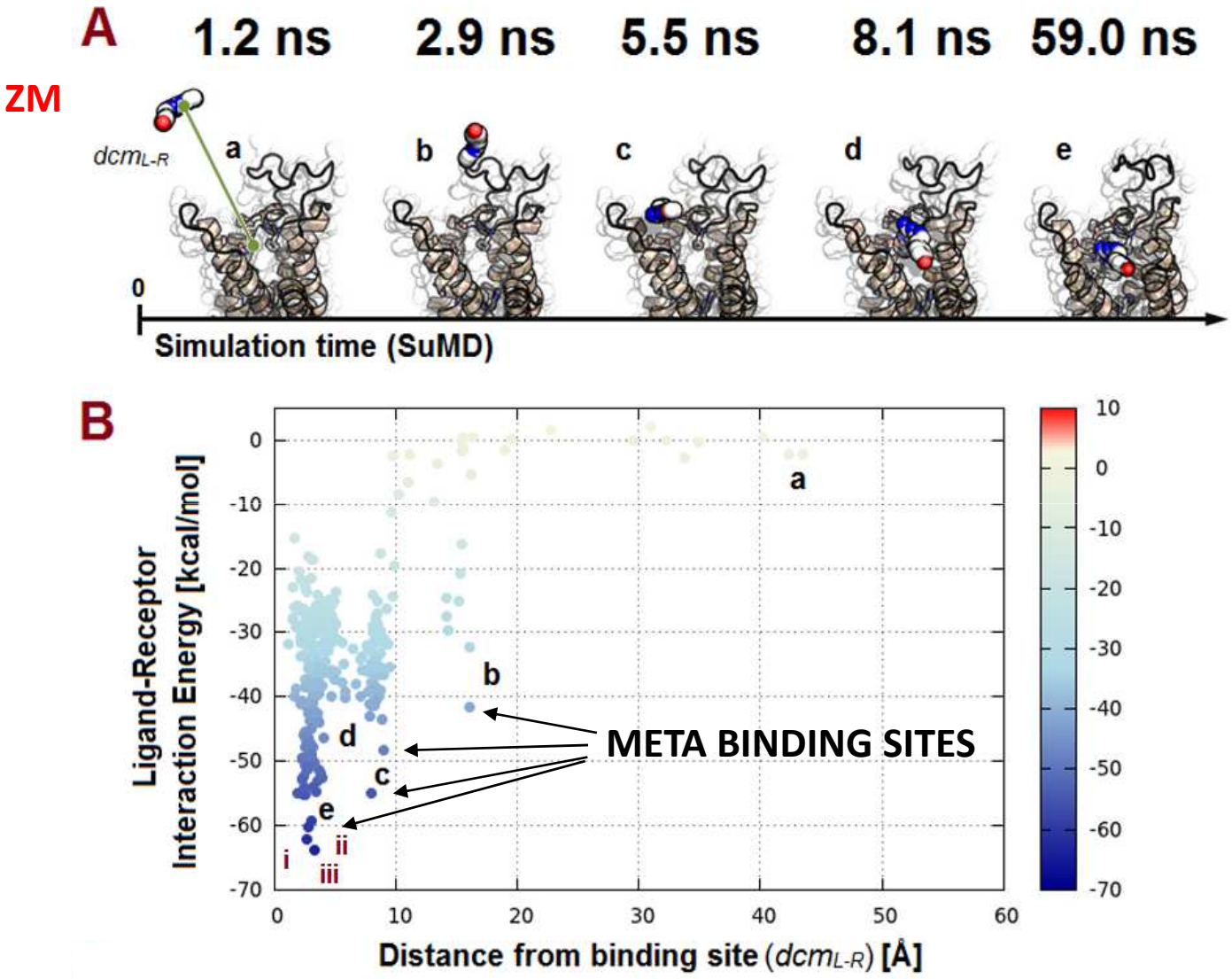


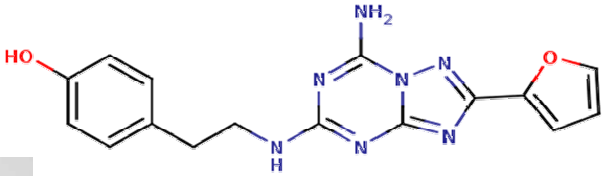
Unbiased Molecular Dynamics

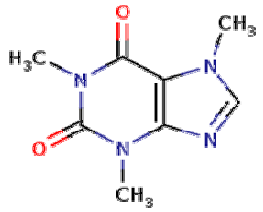


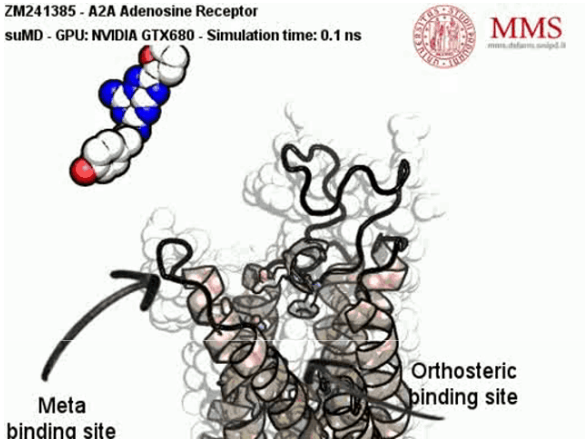
Sabbadin D.; Moro S. J Chem Inf Mod 54, 372-376 (2014)

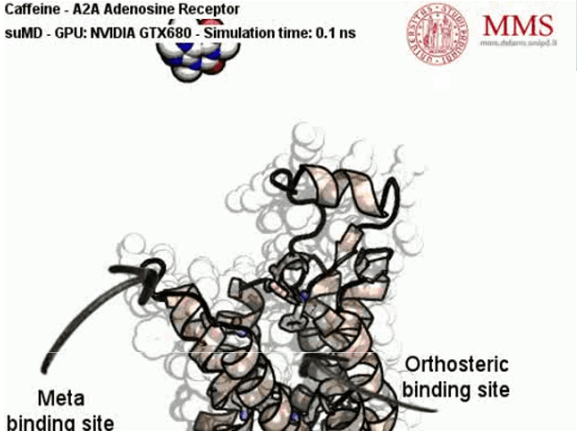
Supervised Molecular Dynamics (SuMD)

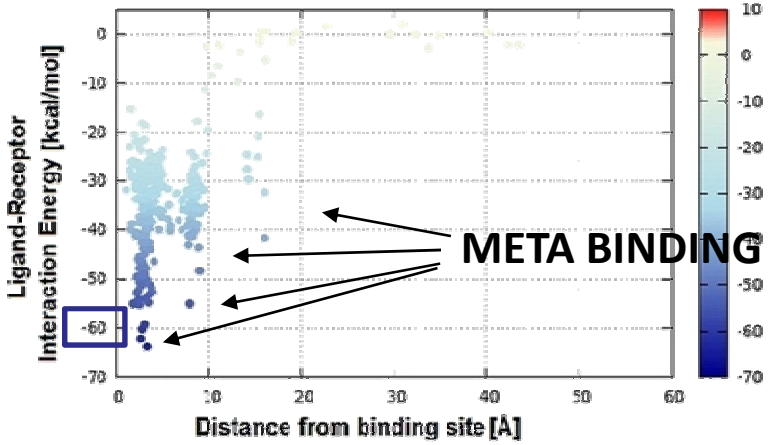




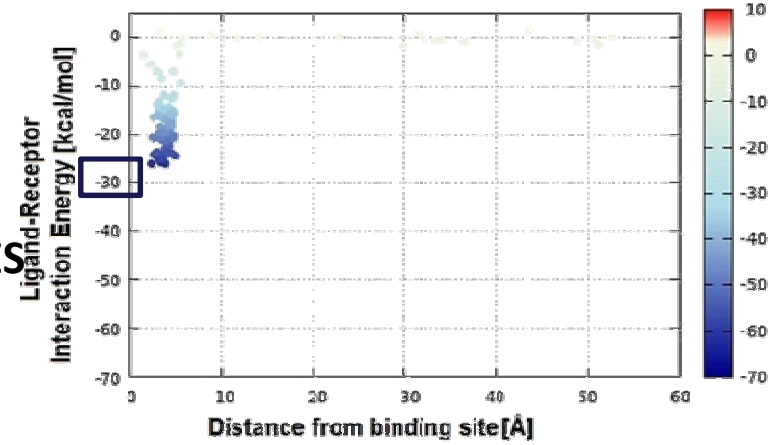






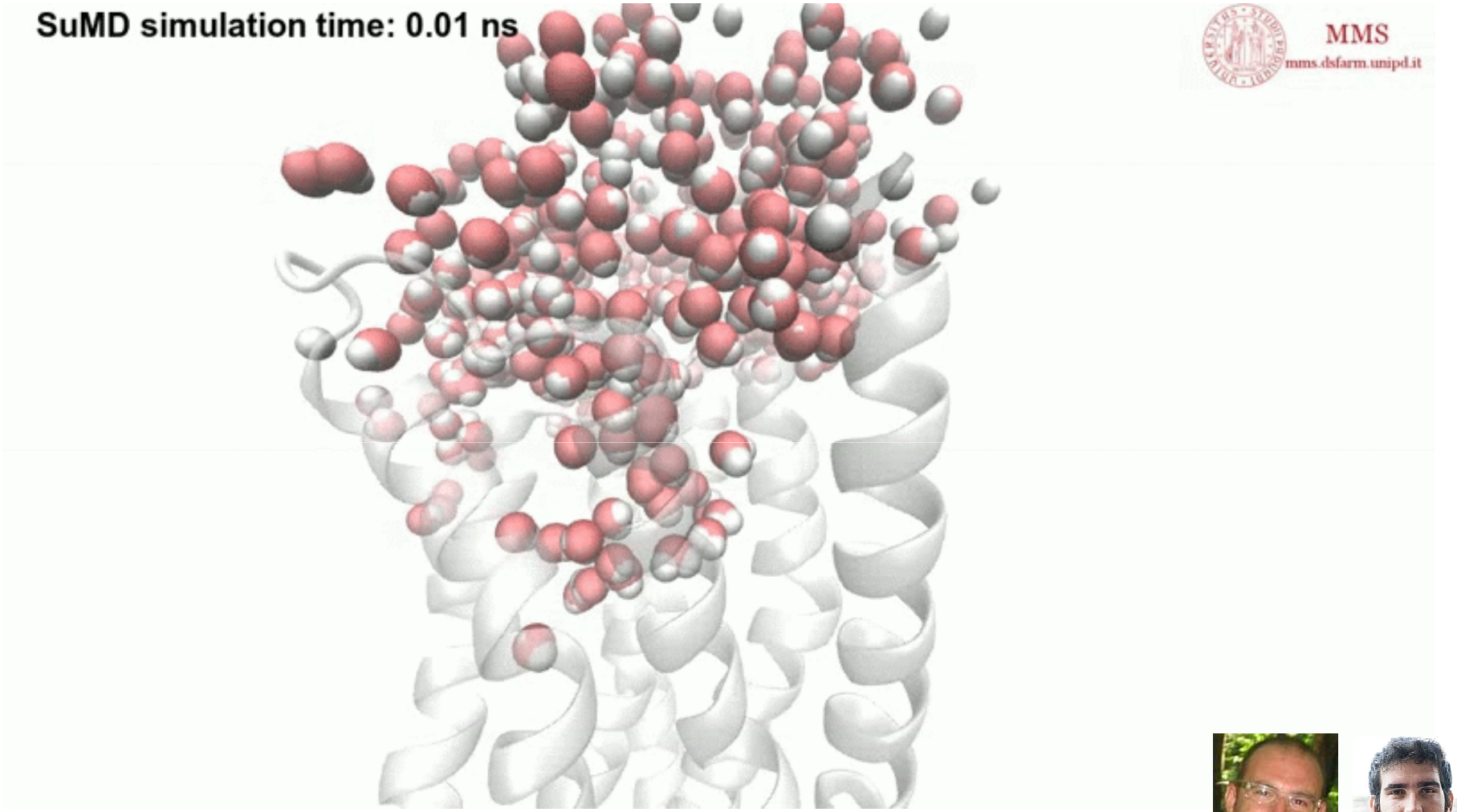


META BINDING SITES



Sabbadin D.; Moro S. J Chem Inf Mod 54, 372-376 (2014)

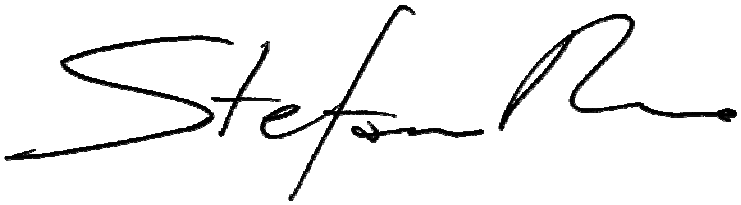
Supervised Molecular Dynamics (SuMD) – We love



G. Deganutti **A. Cuzzolin**

Cuzzolin A., Deganutti G., Moro S. (2016) manuscript in preparation

GRAZIE
PER LA PAZIENZA




TITLE
"Progettazione e Sviluppo di un Farmaco"
DIRECTOR
Stefano Moro
CAMERA
Chimica e Tecnologia Farmaceutiche
DATE
SCENE
TAKE