“Drug Design today … between myth and reality. ”

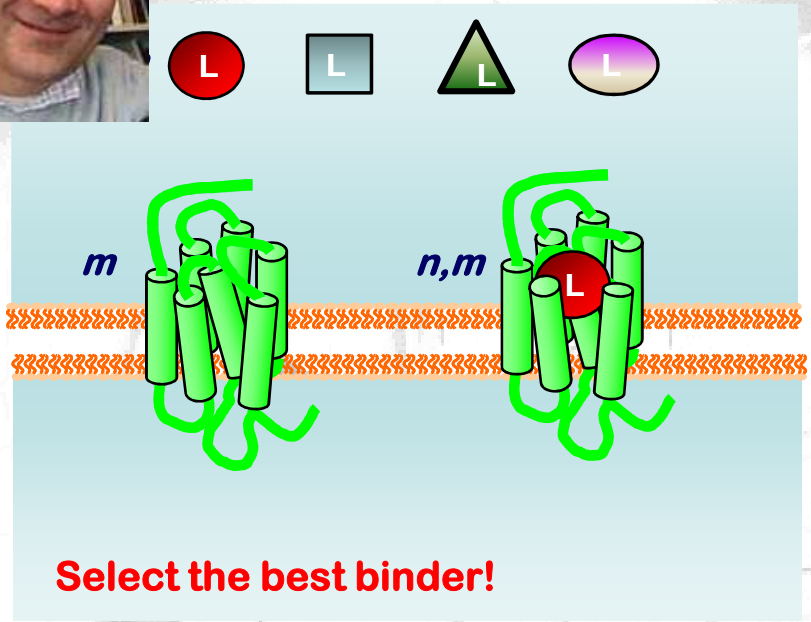
Stefano Moro

Molecular Modeling Section (MMS)

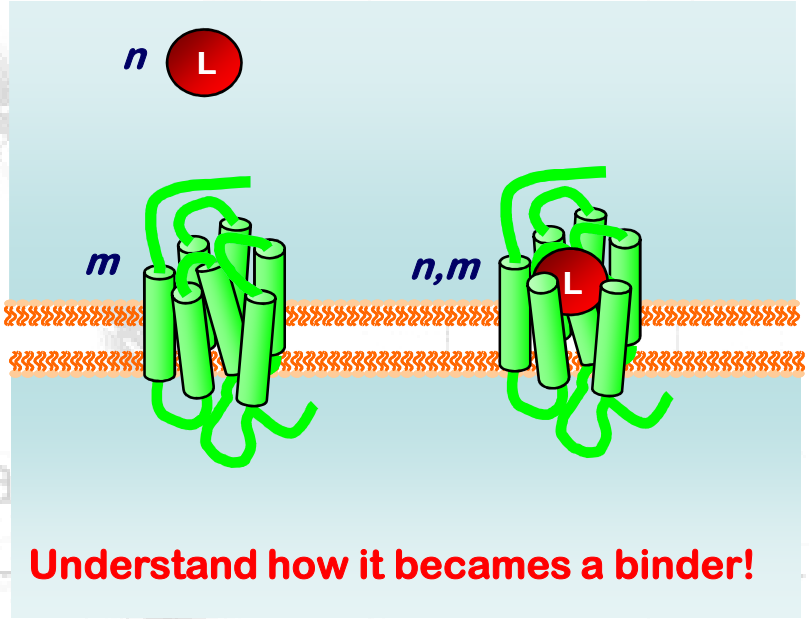
Department of Pharmaceutical and Pharmacological Sciences

University of Padova

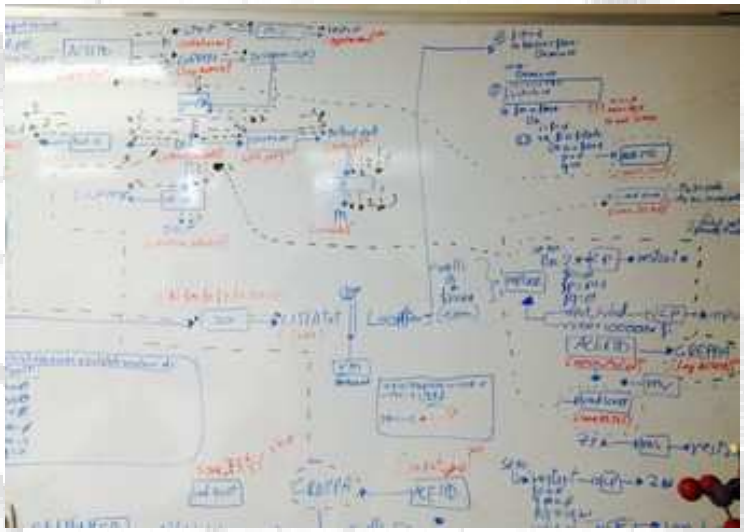
From a molecular point of view, of course!



Select the best binder!



Understand how it becames a binder!



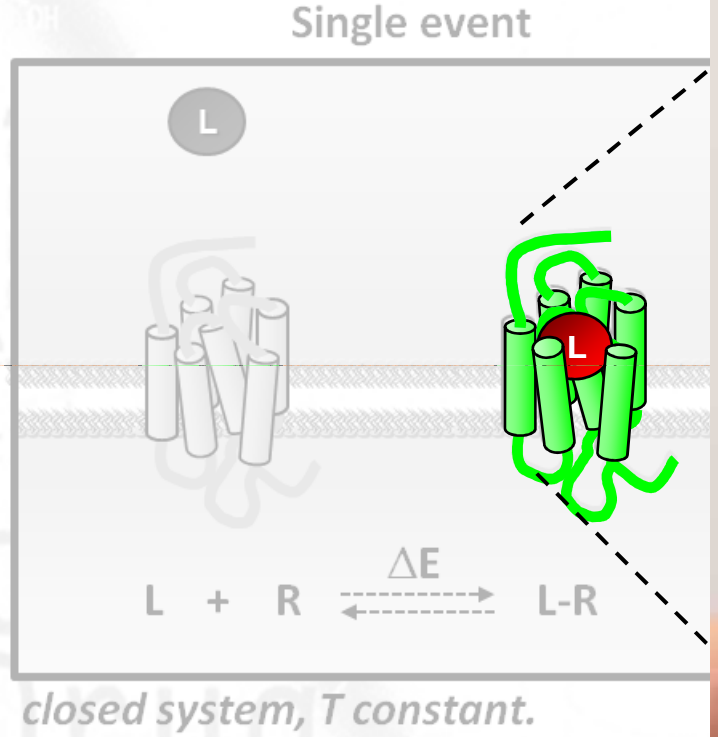
MMStools

Back when I was young:

"It is generally accepted that receptor and substrate molecules recognize each other at their molecular surfaces. Therefore, the binding strength of a receptor-drug complex depends on the shape of the substrate surface and on the distribution of certain properties on this surface. Any method attempting to model biological activity should take into account this information and try to correlate it to biological activity…"

by Johann Gasteiger *et al J.A.C.S.* 1995, 117, 7769-7775

Why X-ray structures are computationally exciting…



The natural link with

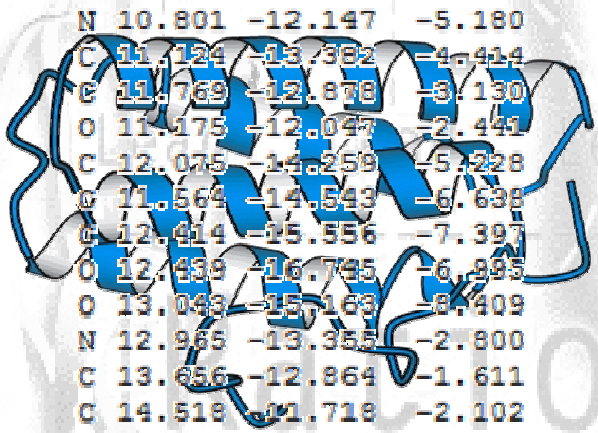
a ligand-receptor re

MMS Lab (2015): 3D printed model of the human A2A adenosine receptor co-crystallized its antagonist ZM 241385 (PDB entry: 4EIY)

I would like to start from here!

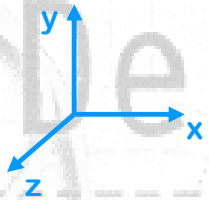
NMR
Spectroscopy

X-Ray
Crystallography



Comparative/Homology
Modeling

3D



… and this is our favorite hunting place!

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Search by PDB ID, author, macromolecule, sequence, or ligands

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A Structural View of Biology

This resource is powered by the Protein Data Bank archive-information about the 3D shapes of proteins, nucleic acids, and complex assemblies that helps students and researchers understand all aspects of biomedicine and agriculture, from protein synthesis to health and disease.

As a member of the wwPDB, the RCSB PDB curates and annotates PDB data.

The RCSB PDB builds upon the data by creating tools and resources for research and education in molecular biology, structural biology, computational biology, and beyond.

Structure and Health Focus: Ebola Virus Proteins

Video Tour

Molecule of the Month Article

March Molecule of the Month

Phototropin

PDB... in numbers:

Other Statistics

PDB Data Distribution by Experimental Method and Molecular Type

Copy | CSV

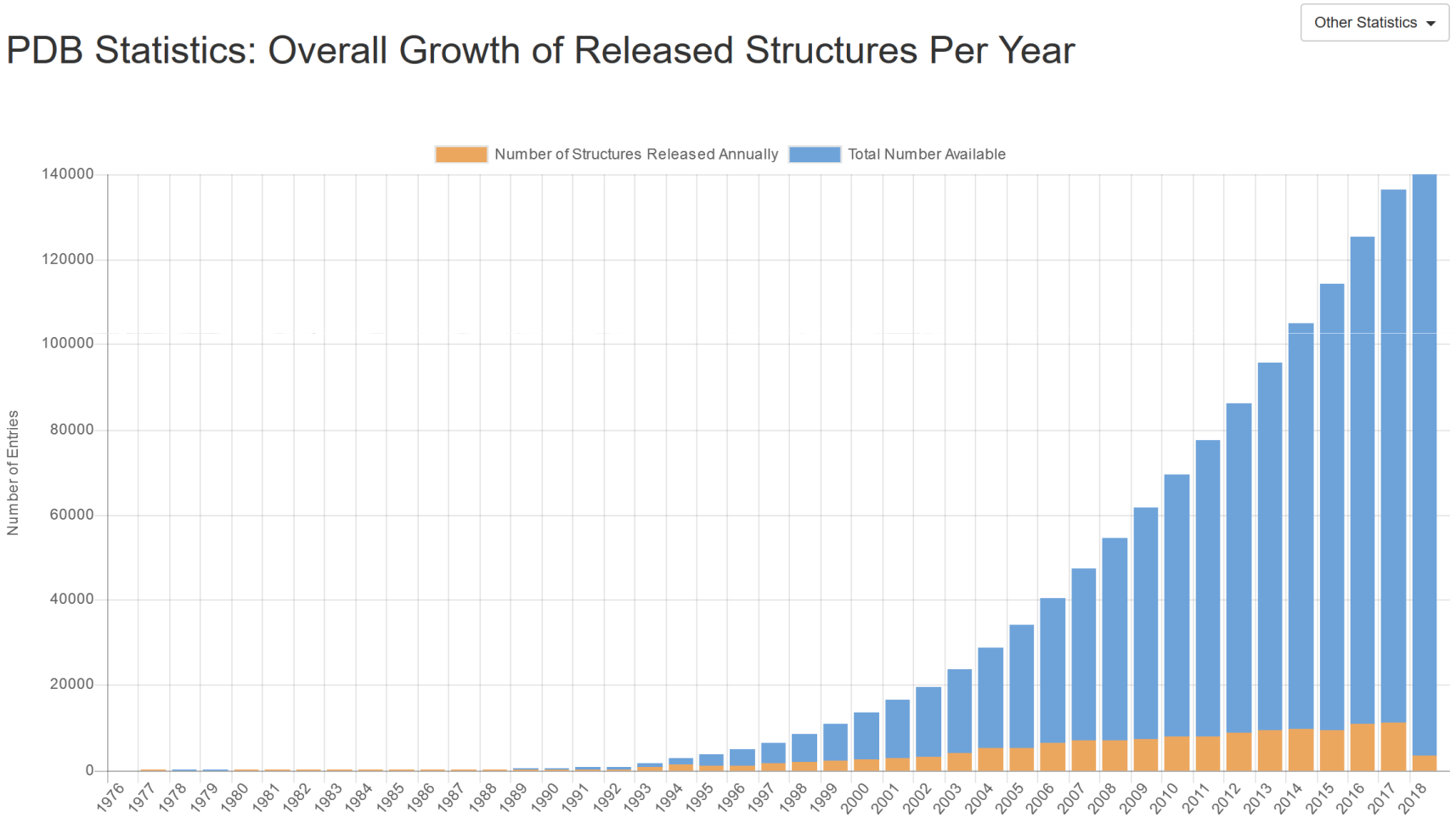
Experimental Method	Proteins	Nucleic Acids	Protein/NA Complex	Other	Total
X-Ray	117342	1919	6000	10	125271
NMR	10706	1243	249	8	12206
Electron Microscopy	1540	31	539	0	2110
Other	215	4	6	13	238
Multi Method	116	4	2	1	123
Total	129919	3201	6796	32	139948

115093 structures in the PDB have a structure factor file.
9545 structures in the PDB have an NMR restraint file.
3297 structures in the PDB have a chemical shifts file.
2136 structures in the PDB have a 3DEM map file.

Sunburst Chart for Experimental Method and Molecular Type

Distribution by experimental method shown in yellow; molecular type in blue. Mouse over to view the statistical description of the particular section; click on a section to zoom in that particular section's statistical distribution, and then click on the center bullseye to zoom out back to the previous distribution.

PDB… in numbers:

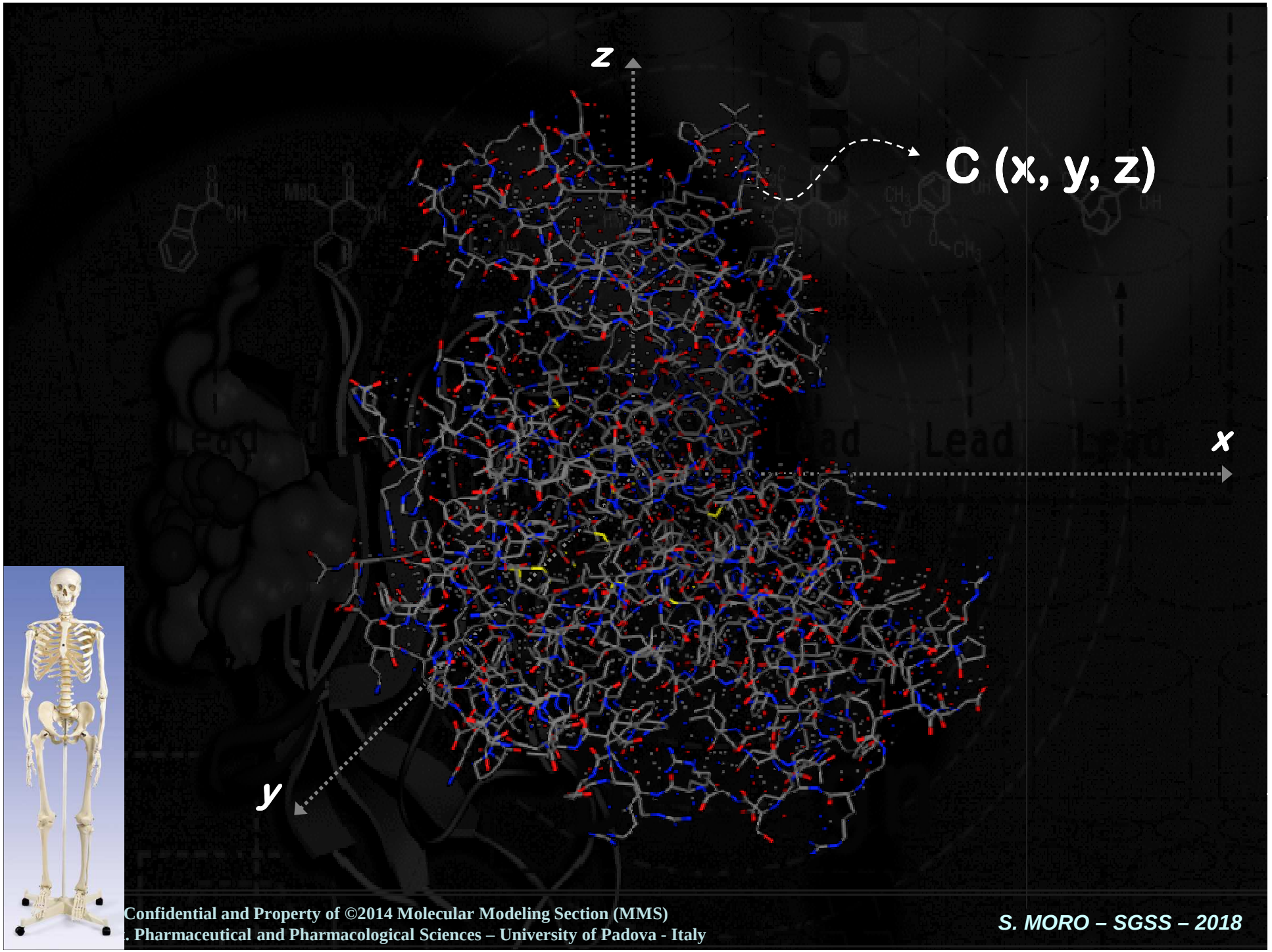


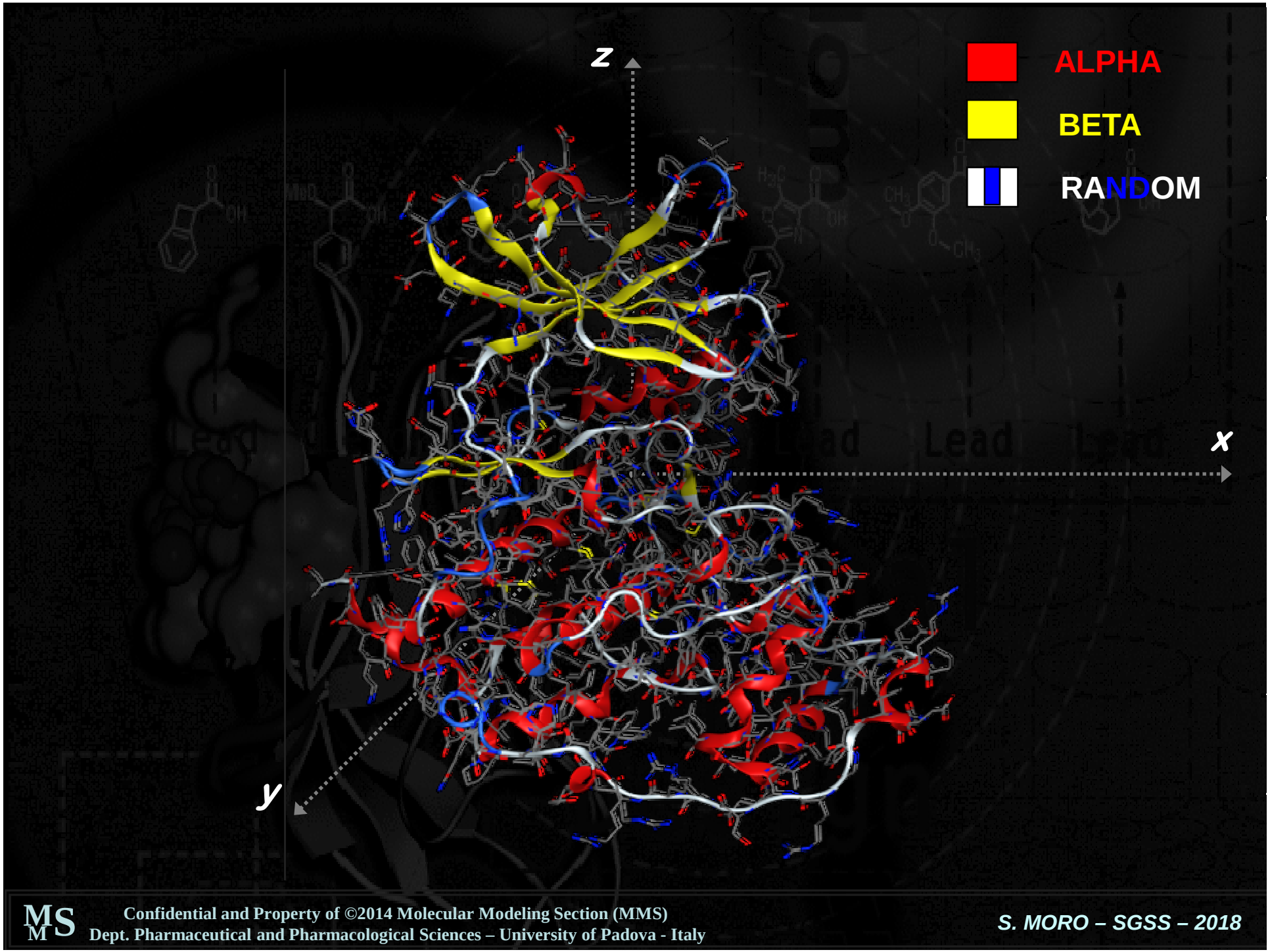
do you remember?

Experiment Typical Cost per Compound (€)

Computer modeling	7
Biochemical assay	270
Cell culture assay	2.700
Rat acute toxicity	8.100
Protein crystal structure	68.000
Animal efficacy trial	200.000
Rat 2-year chronic oral toxicity	550.000
Human clinical trial	3.500.000

From small molecule to its biological target…





Back when I was young:

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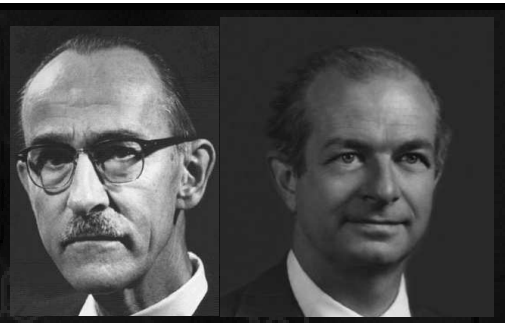
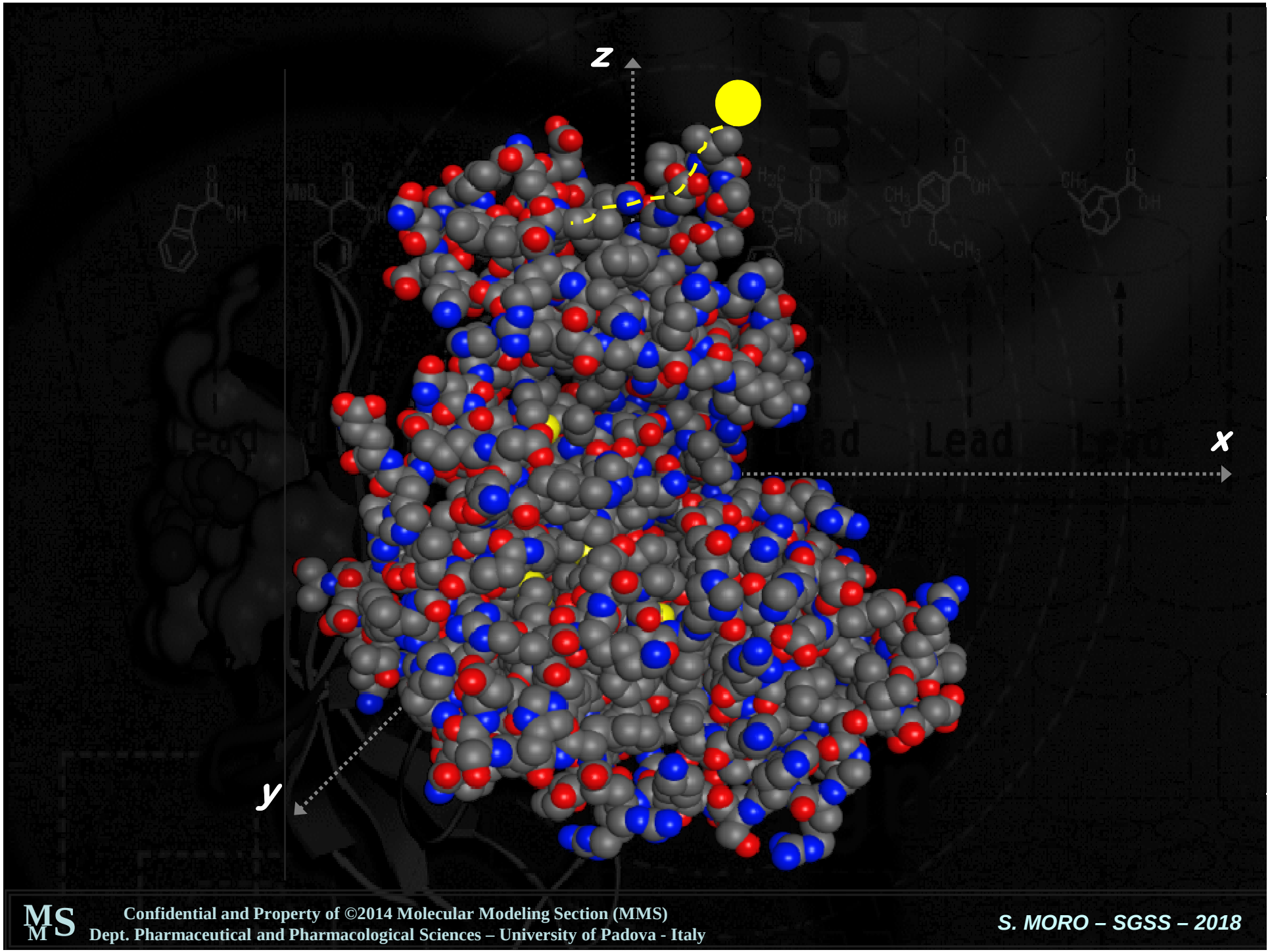
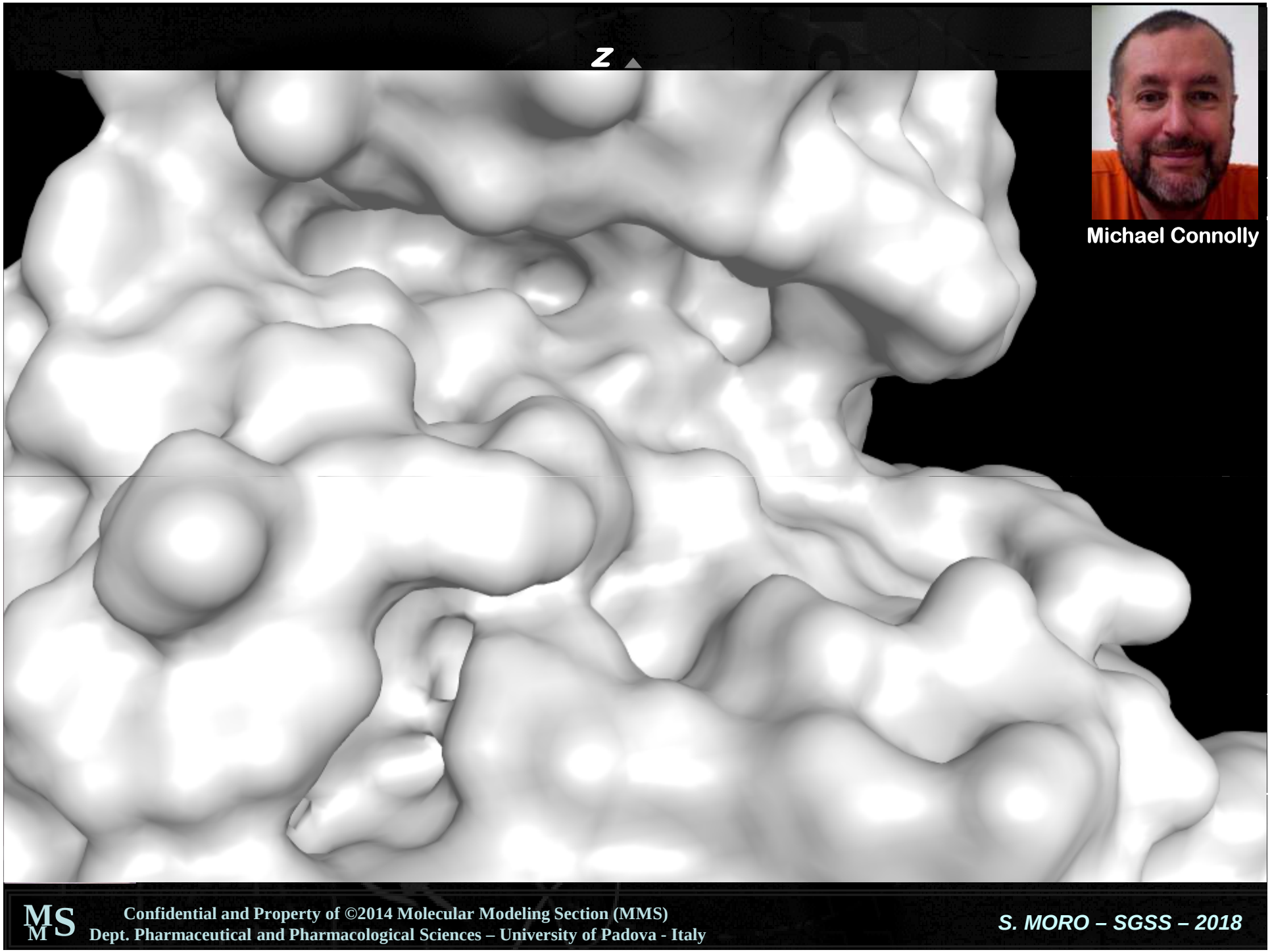
CPK model:



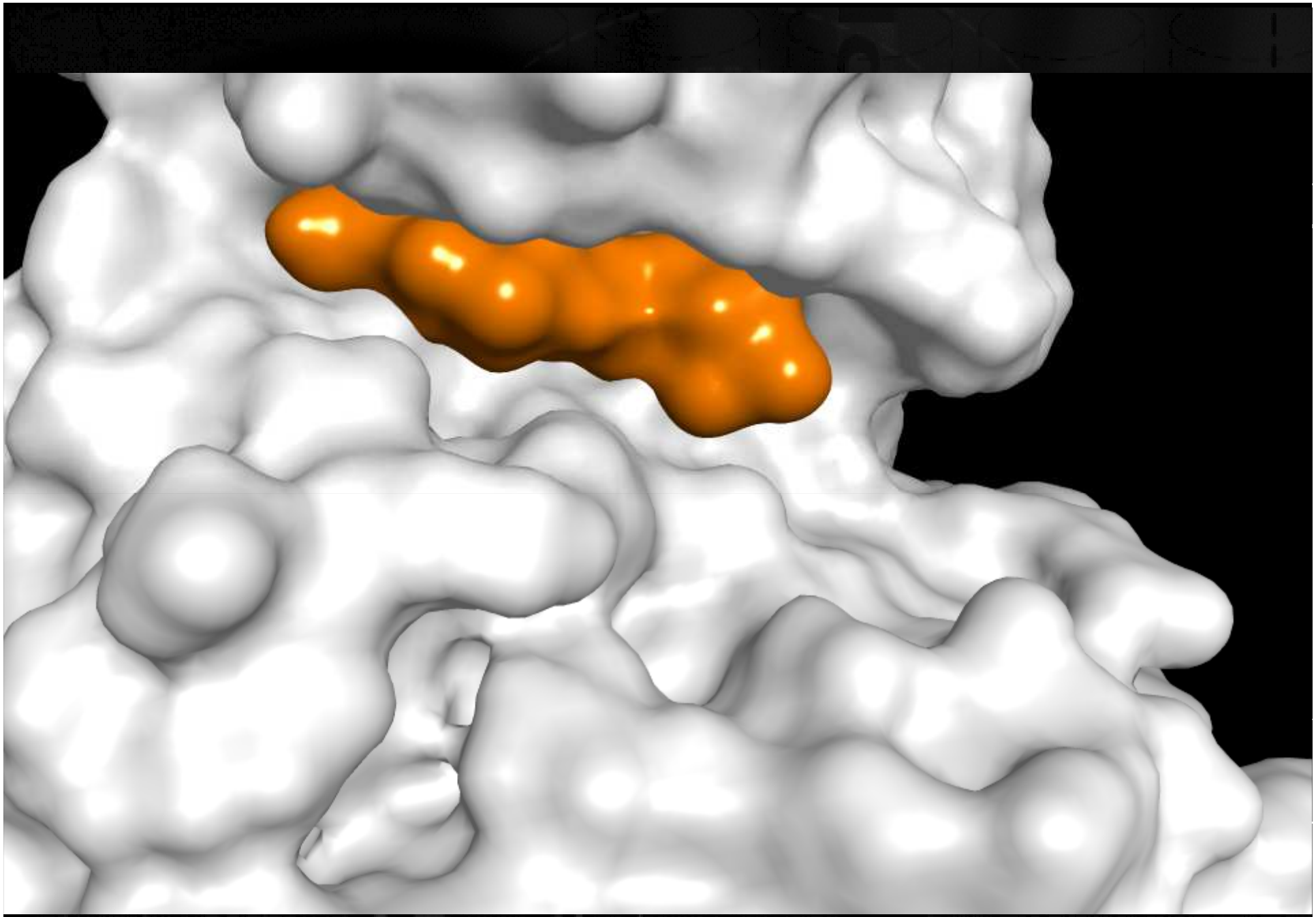
Robert Corey Linus Pauling

Walter Koltun

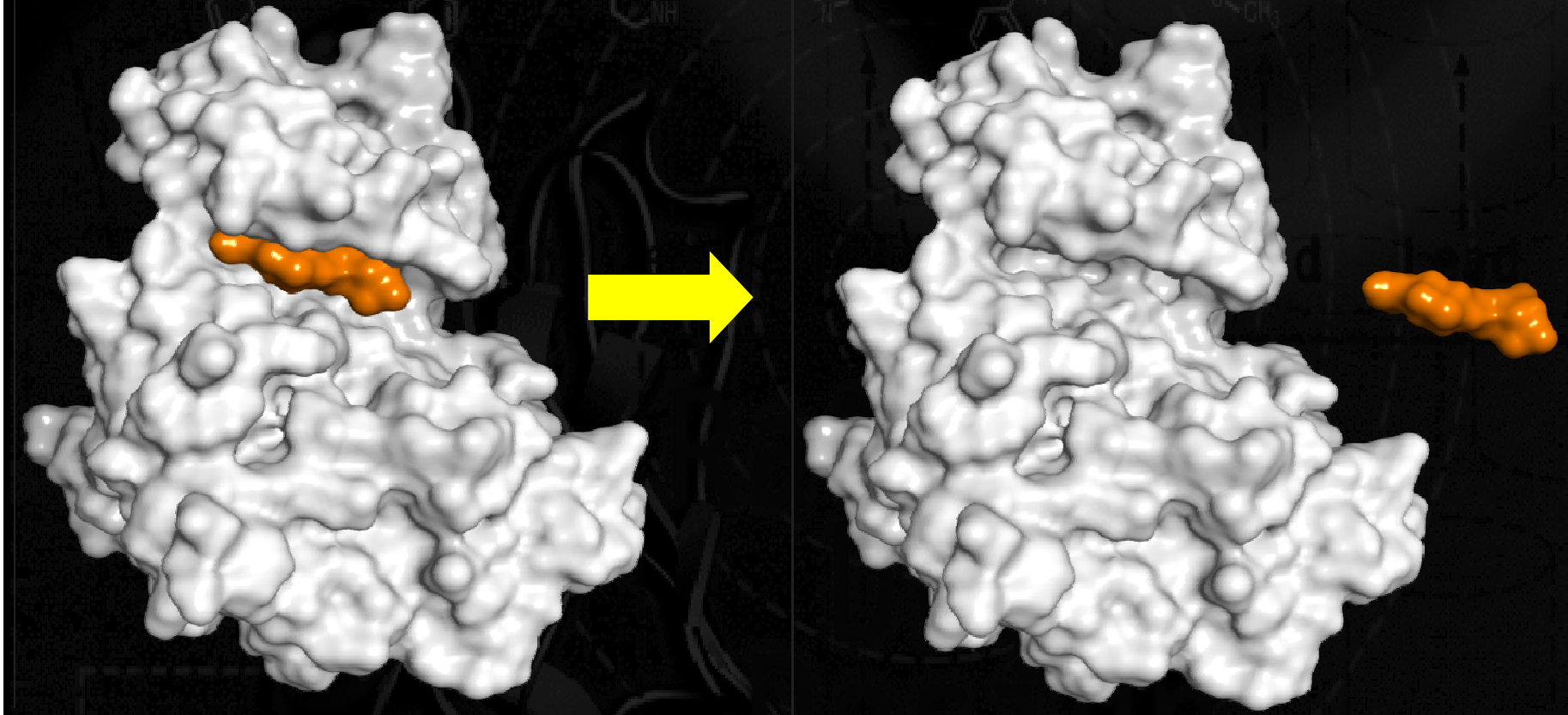




Michael Connolly



You have now a wonderful tool to estimate the topological complementarity between a cavity and its ligand:



$$\text{Complementarity} \propto \text{Vol}_{\text{cavity}} - \text{Vol}_{\text{ligand}}$$

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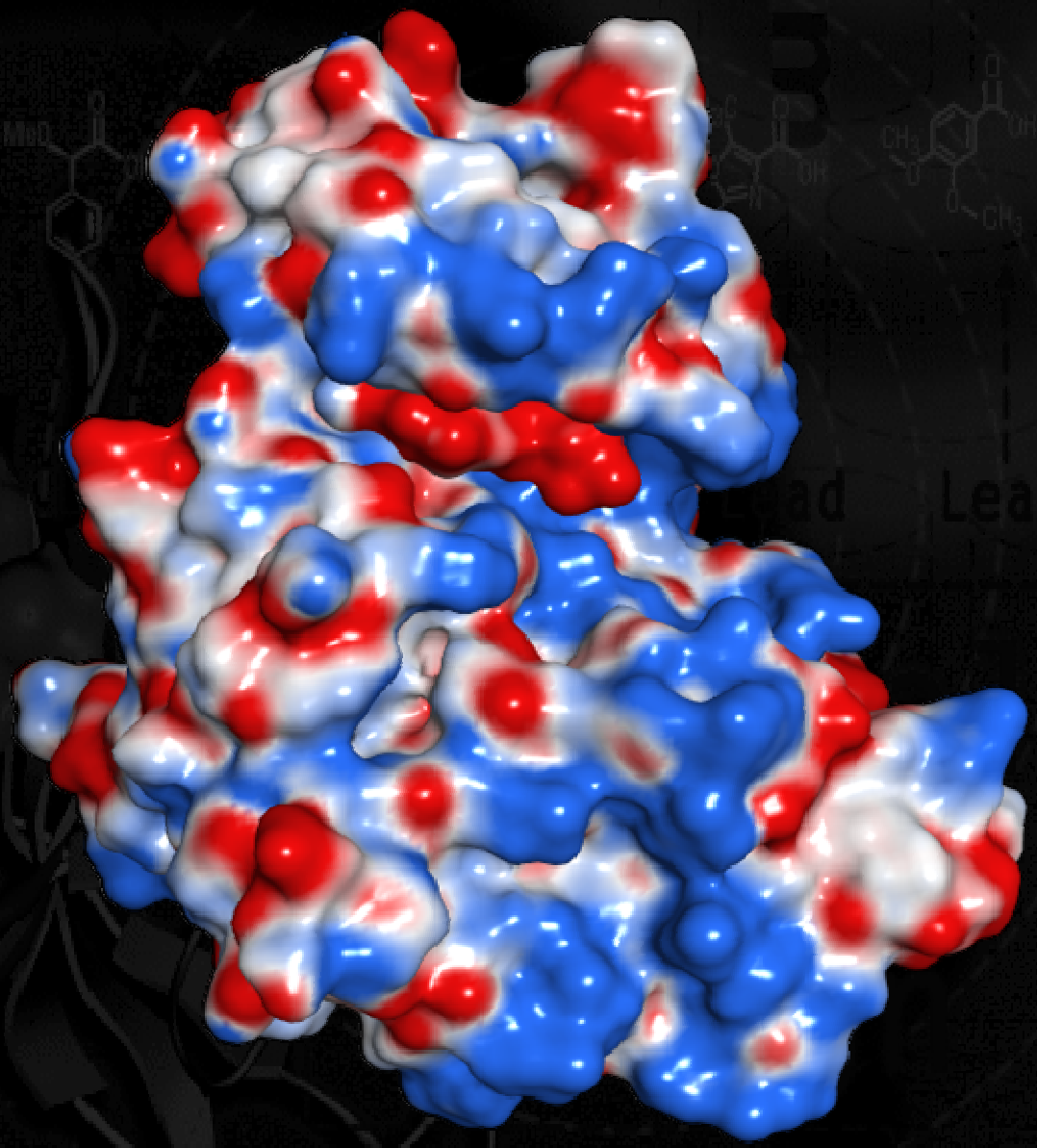
by Johann Gasteiger *et al J.A.C.S.* 1995, 117, 7769-7775

… very charming!

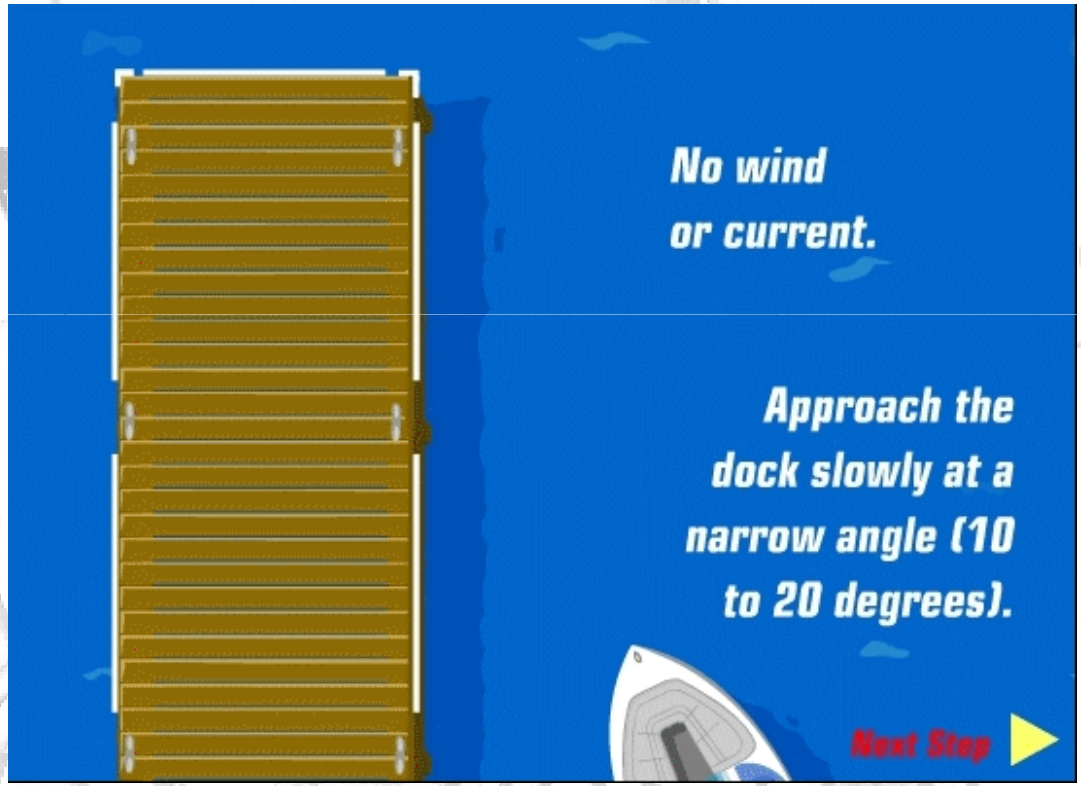


$V_{el} < 0$

$V_{el} = 0$

$V_{el} > 0$

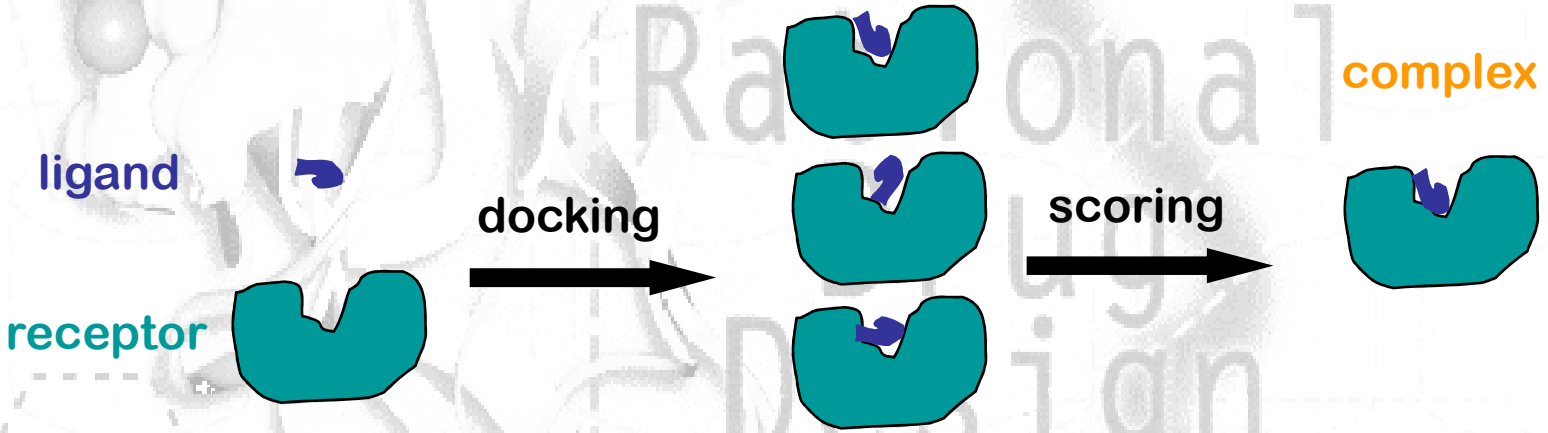
Docking and Scoring



The molecular docking problem:

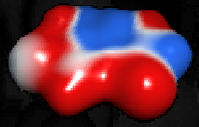
To place a ligand (small molecule) into the binding site of a receptor in the manners appropriate for optimal interactions with a receptor (DOCKING).

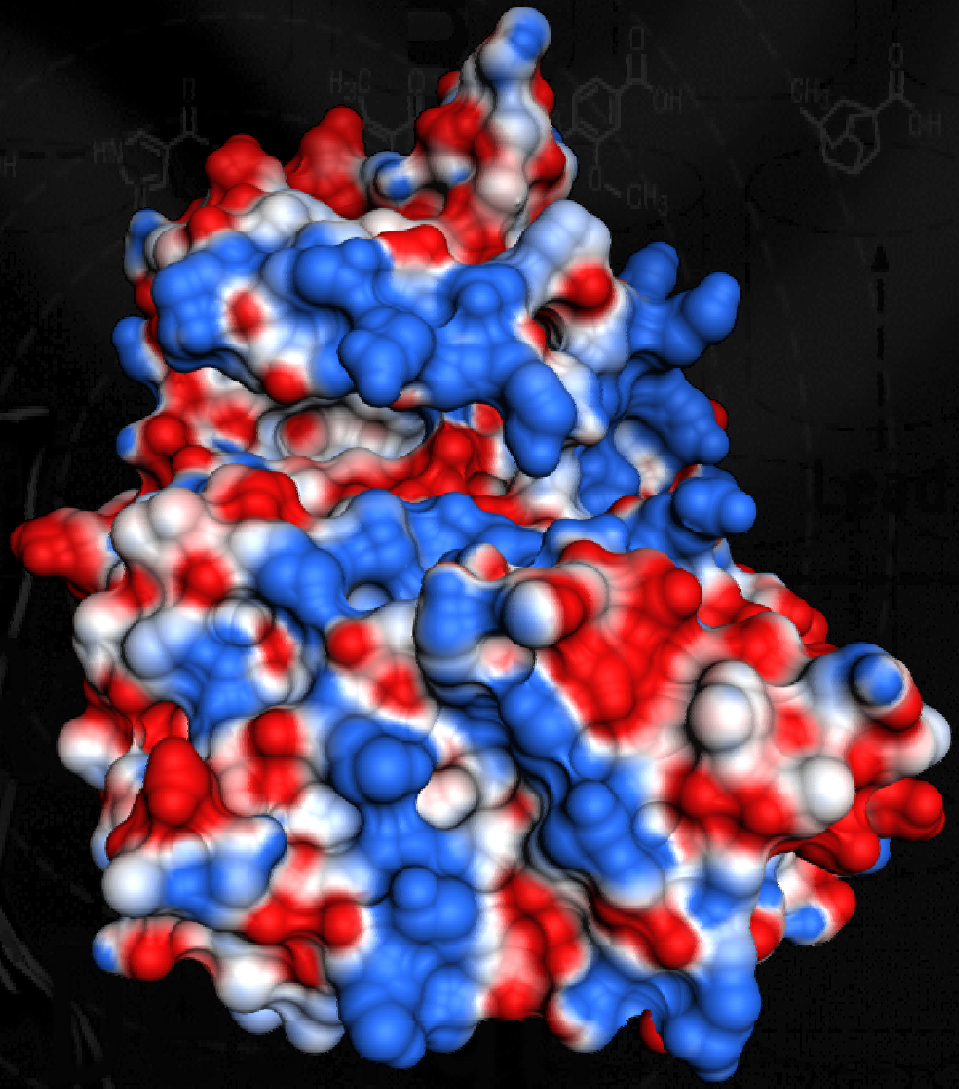
To evaluate the ligand-receptor interactions in a way that may discriminate the experimentally observed mode from others and estimate the binding affinity (SCORING).



predict (x,y,z) ... etc **predict "ΔG_{bind}"**

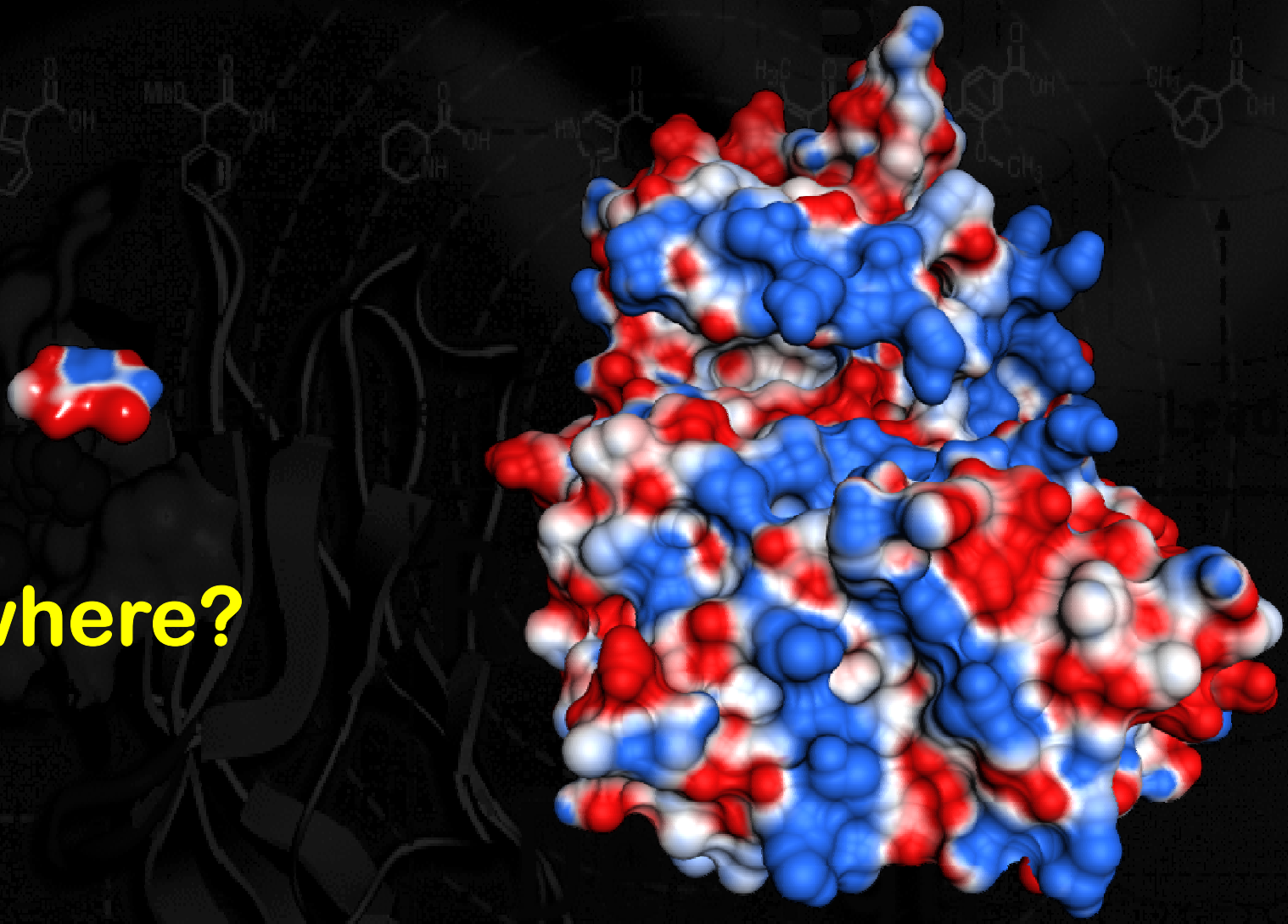
Here is the problem…



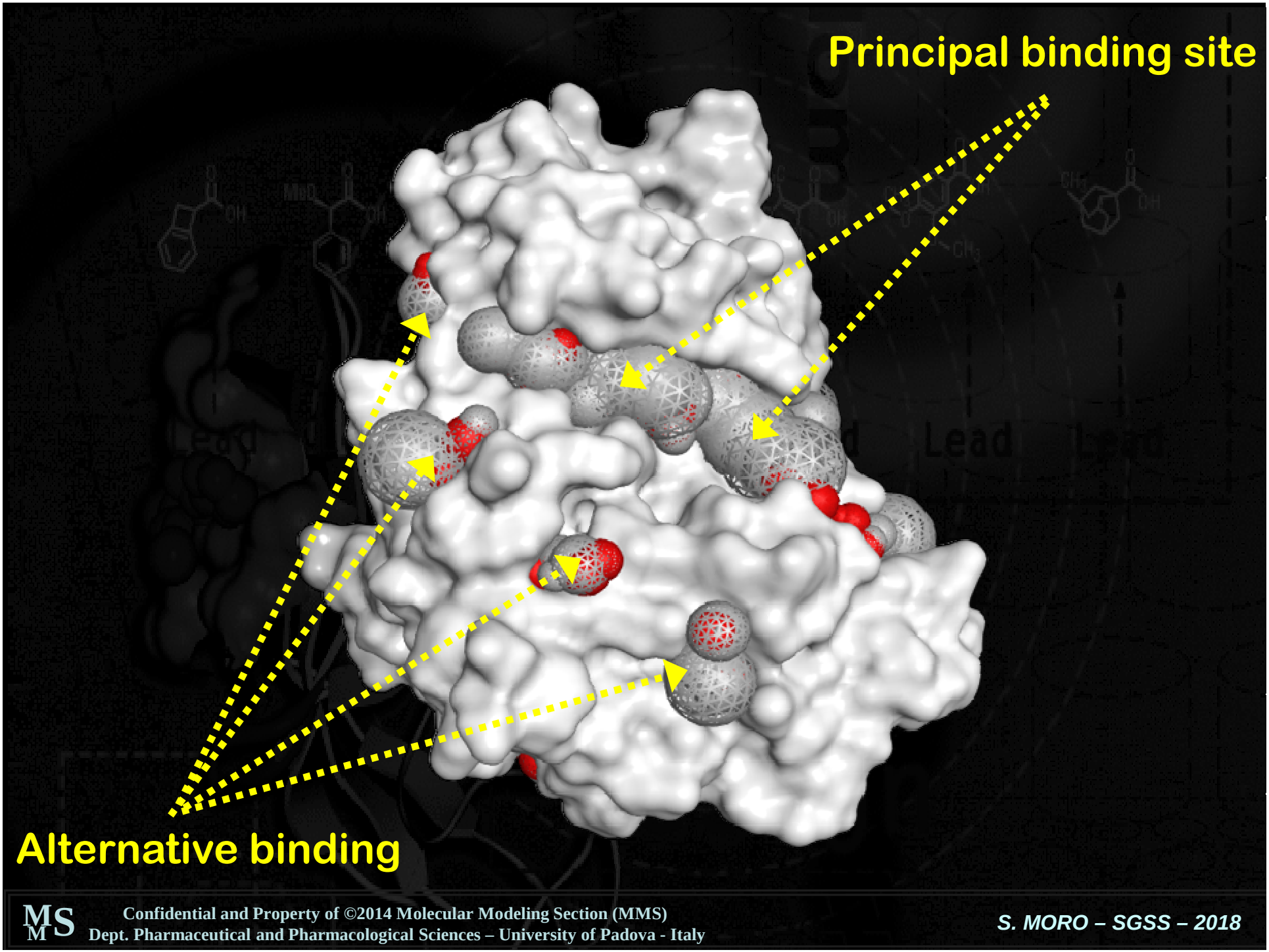


1. where?
2. how?
3. how long?

Virtualize docking and scoring…



1. where?



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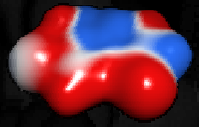
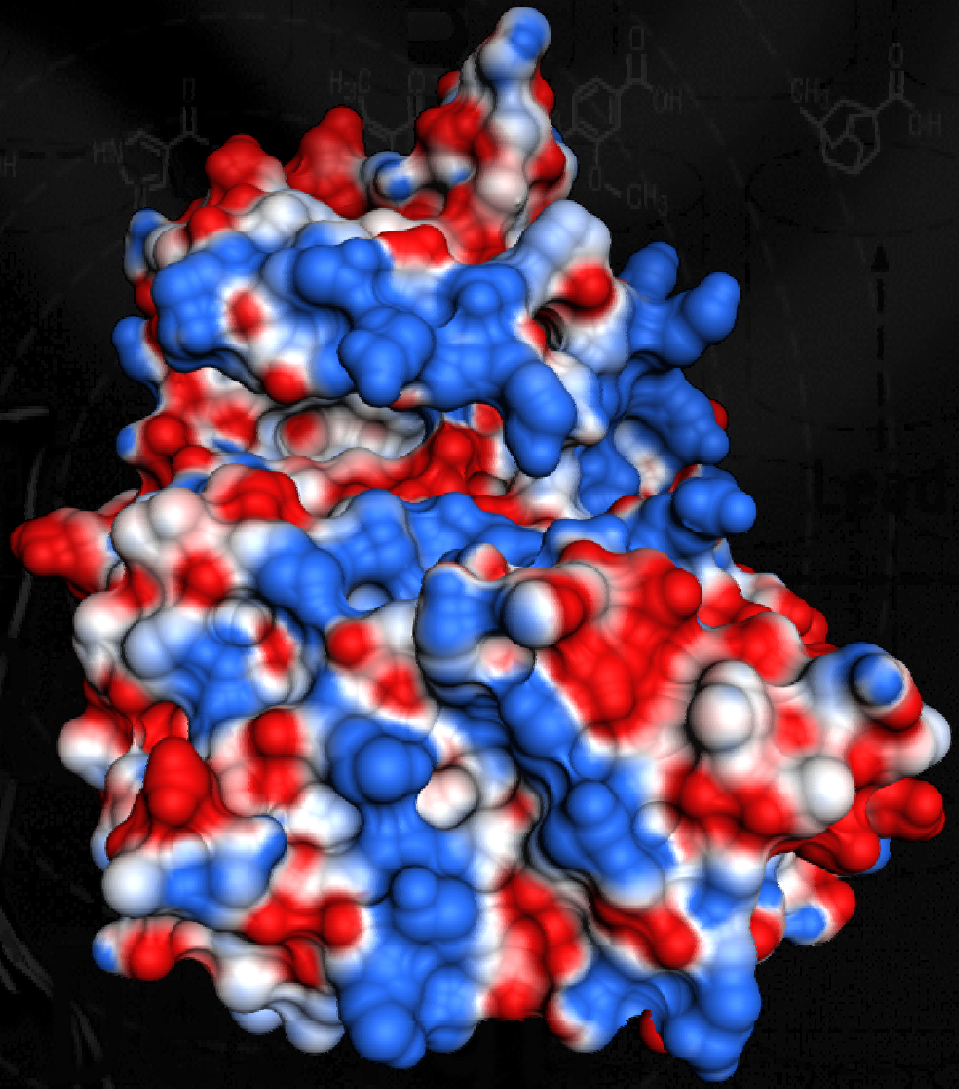
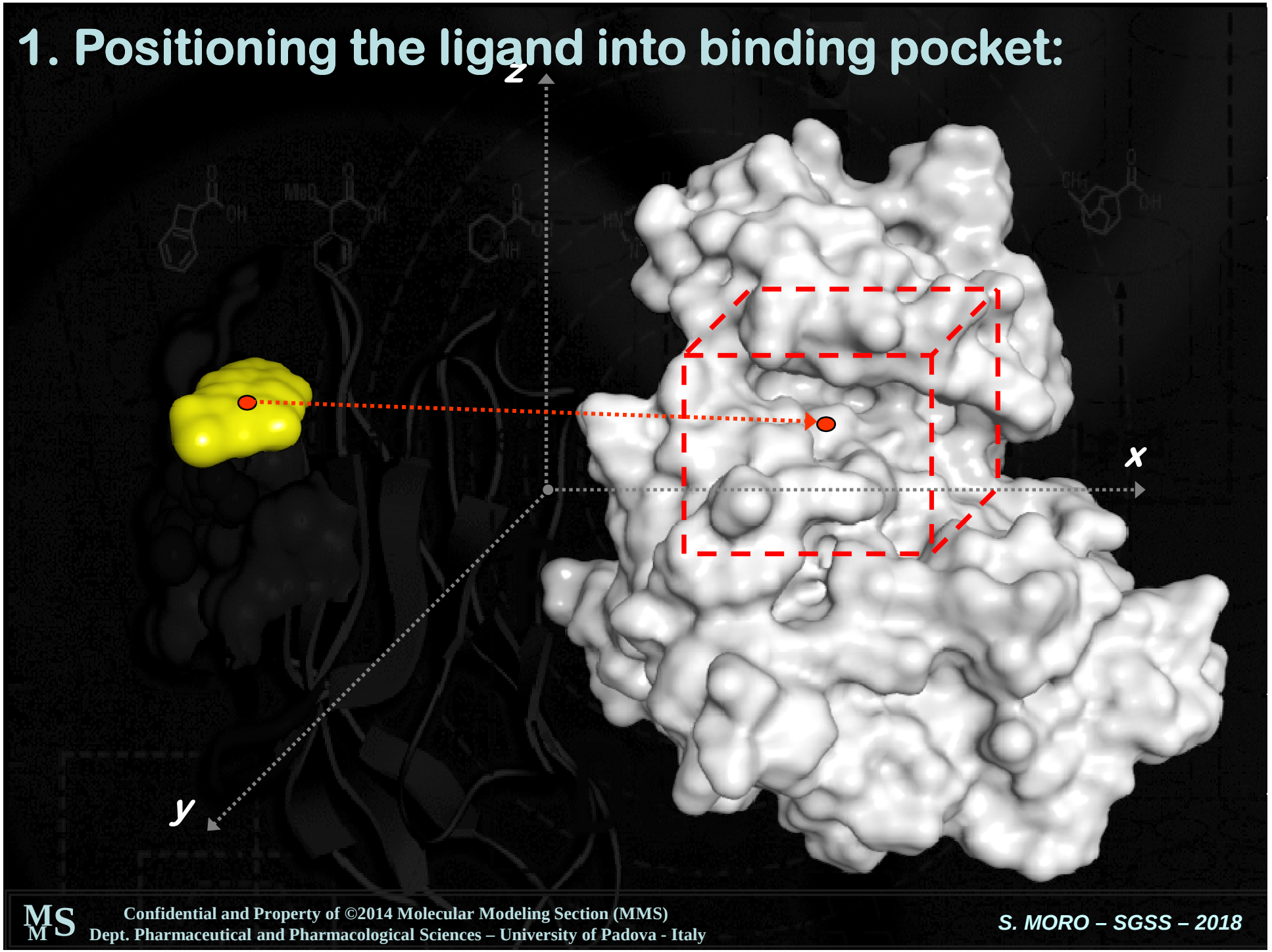


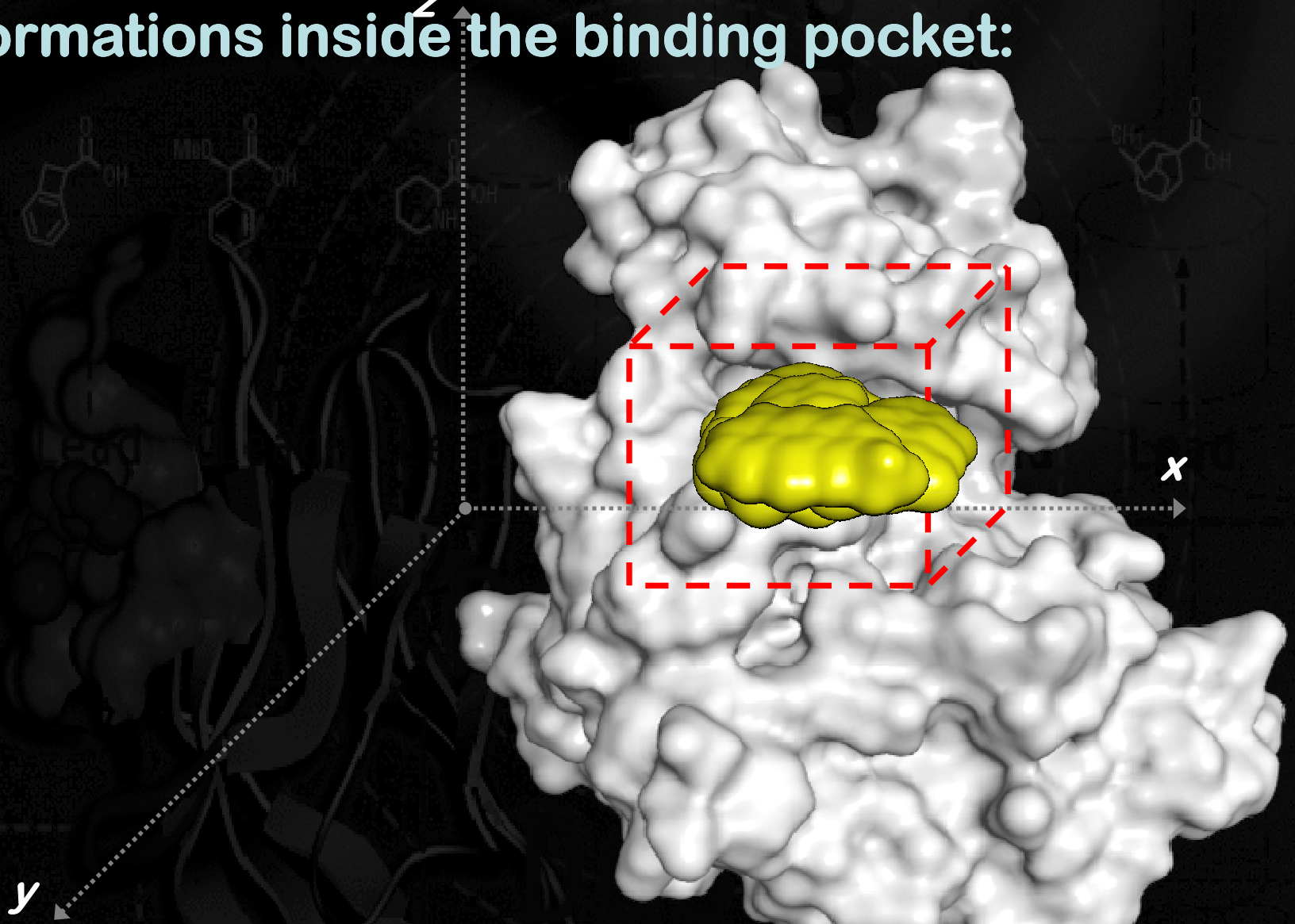


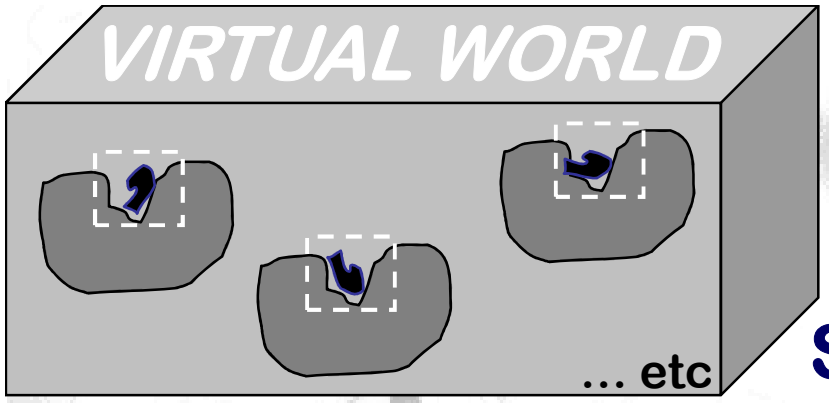
1. where?
2. how?

1. Positioning the ligand into binding pocket:



2. Docking: translate, rotate and exploring conformations inside the binding pocket:





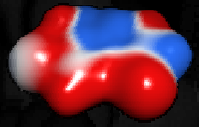
Some definitions:

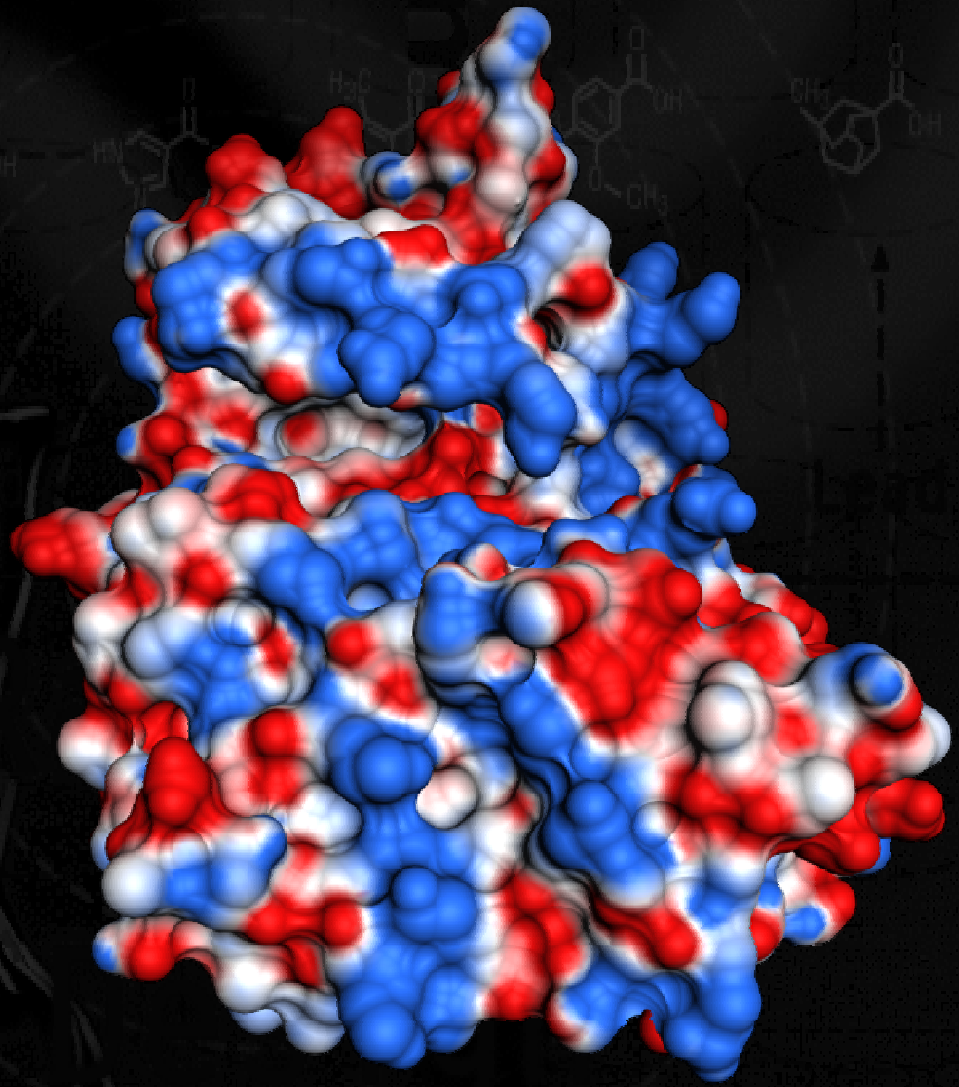
We define as POSE:

a. **the respective orientation of the ligand *vs* protein;**

b. **the bound conformation of the ligand.**

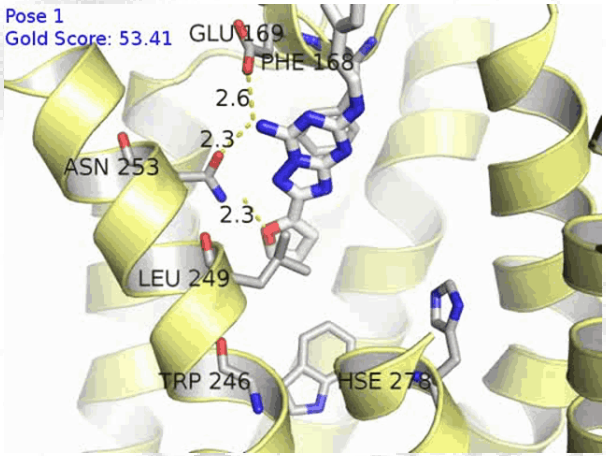
Virtualize docking and scoring…

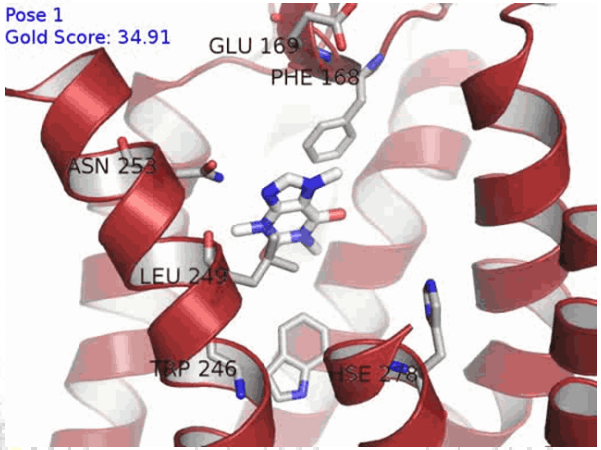


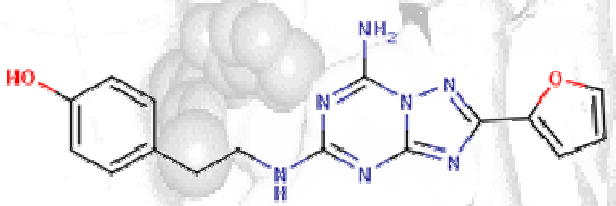


1. where?
2. how?
3. how long?

Docking performance: can we preliminary analyze the stability of the complex poses?

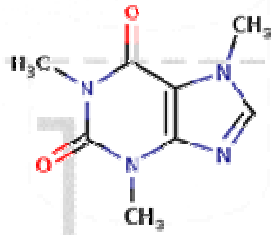






ZM 241385

strong binder

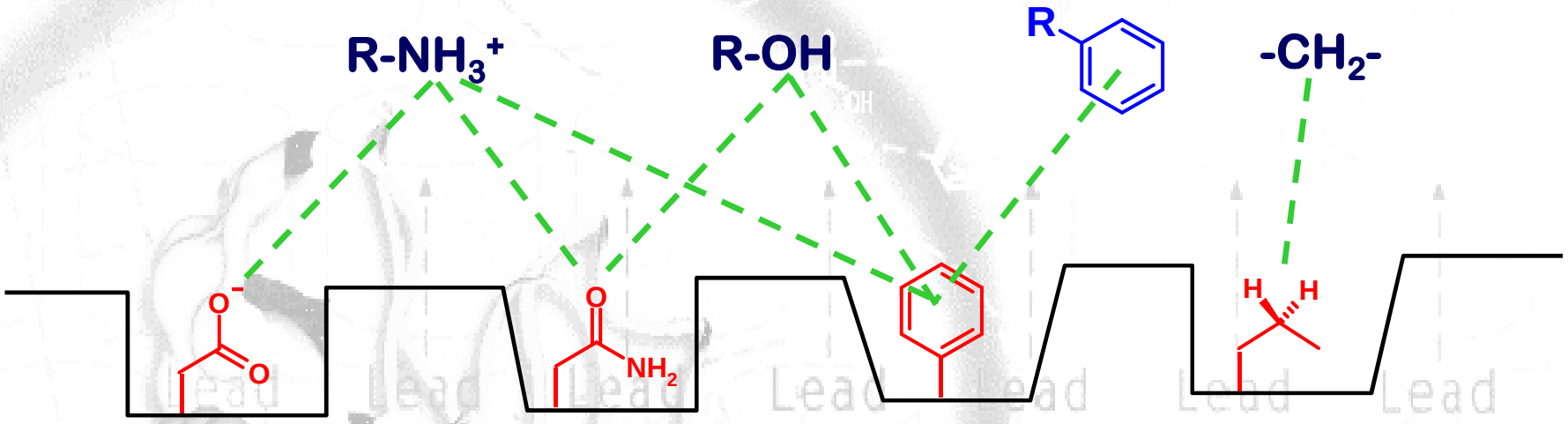


Caffeine

weak binder

… from a chemical point of view, how could we distinguish between strong and weak binders?

Empirical Scoring Functions

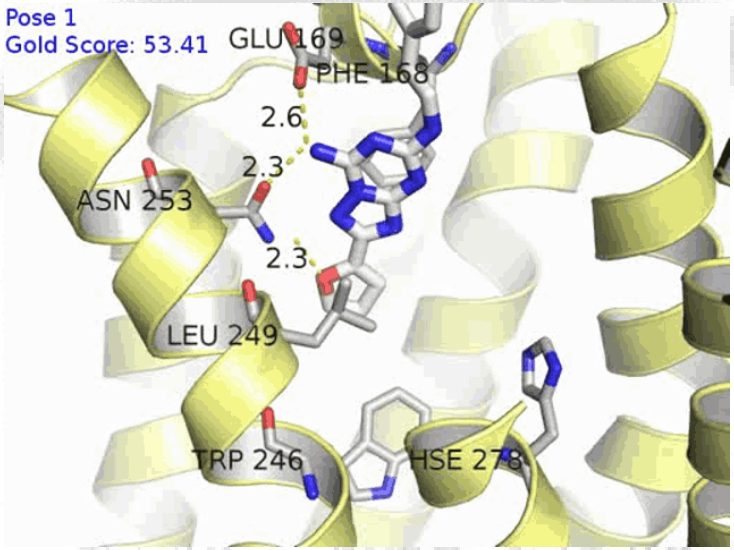


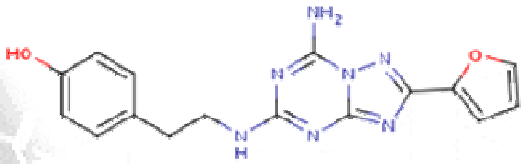
(kcal/mol)

charge-charge interaction (*ionic bond*):	$-\Delta G^0 \cong$	5 ÷ 10
charge-dipole interaction:	$-\Delta G^0 \cong$	1 ÷ 7
charge-π interaction:	$-\Delta G^0 \cong$	8 ÷ 10
hydrogen bond:	$-\Delta G^0 \cong$	1 ÷ 7
charge transfer interaction:	$-\Delta G^0 \cong$	1 ÷ 6
π-π interaction:	$-\Delta G^0 \cong$	1 ÷ 2
dipole-dipole interaction (van der Waals):	$-\Delta G^0 \cong$	0.5 ÷ 1

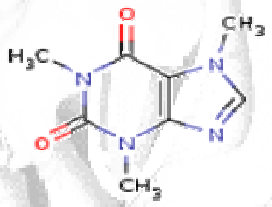
Here is a real example:

ZM

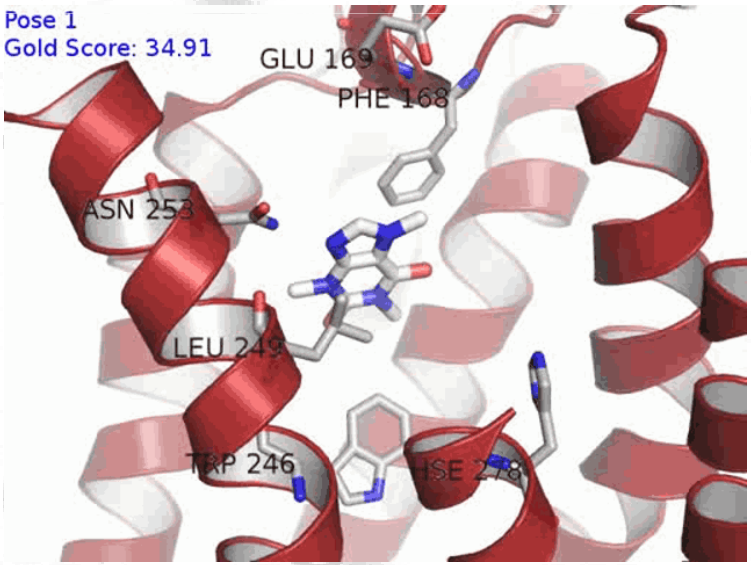




K_i = 1.6 nM (h_A_{2A})



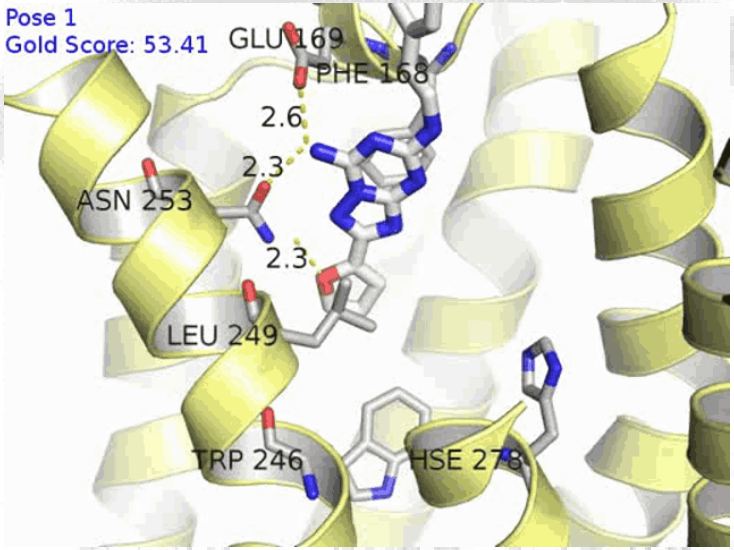
K_i = 23400 nM (h_A_{2A})

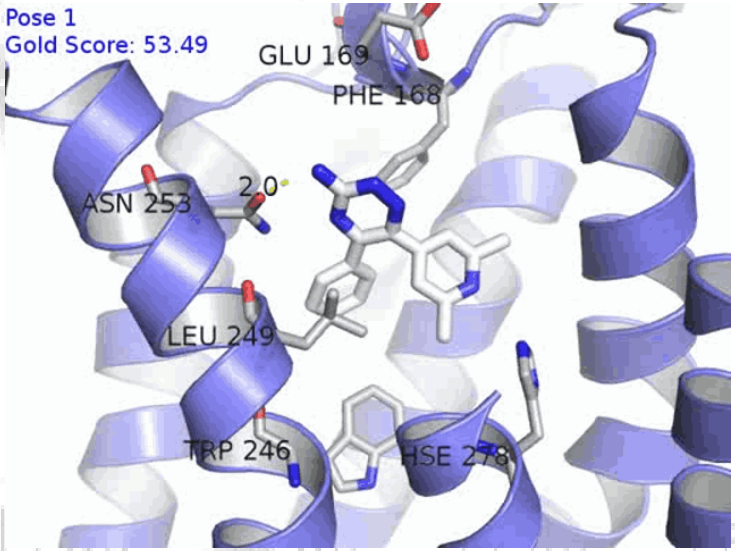


Caffeine

Here is a real example:

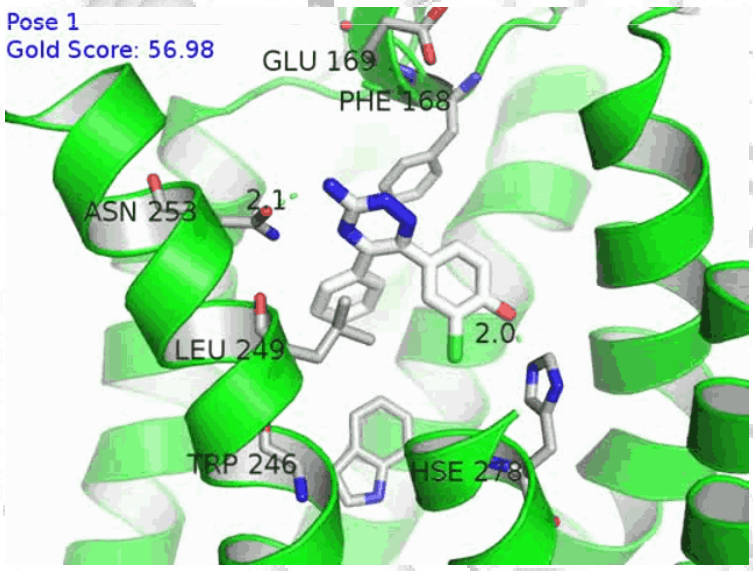
ZM

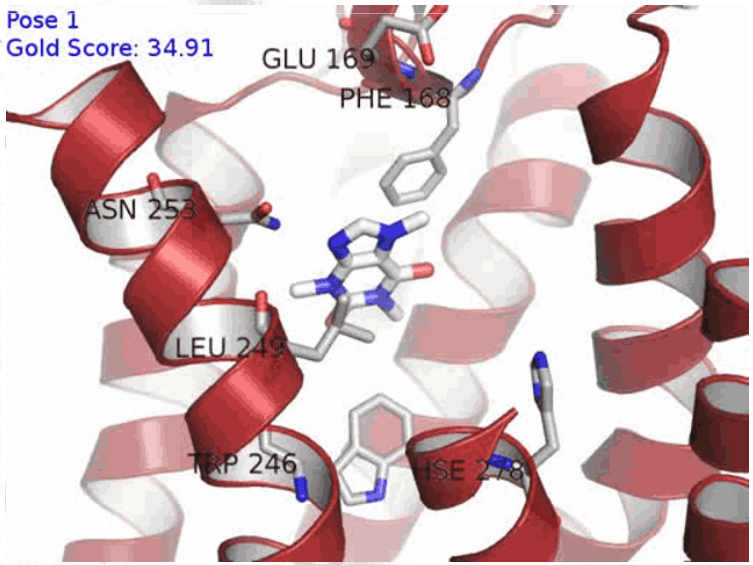




T4G

T4E

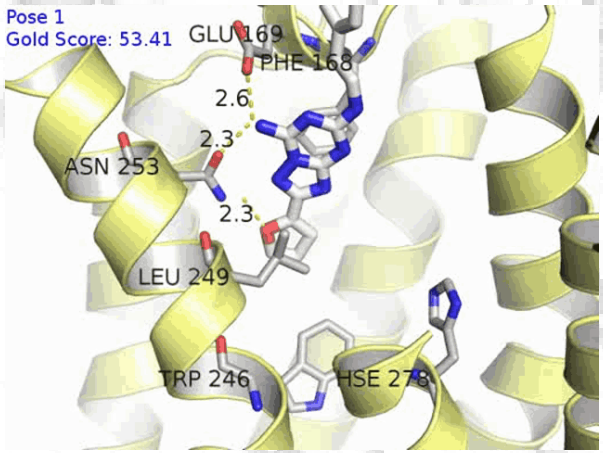


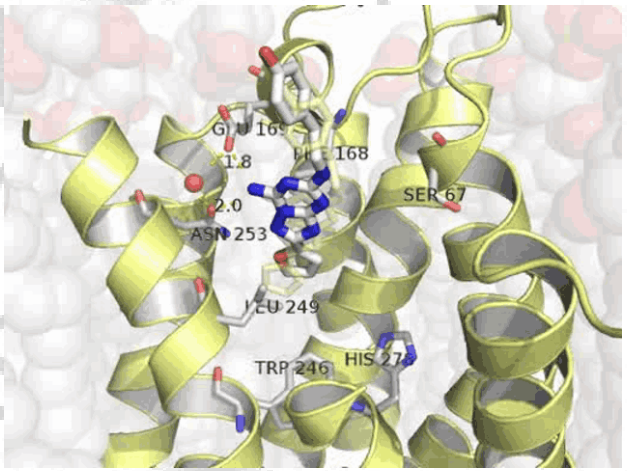


Caffeine

SWAT Analysis

Molecular Docking	Molecular Dynamics
Fast and scalable pose sampling	Computational expensive
Rigid protein	Investigate receptor full flexibility
Difficult solvent treatment	Explicit solvent treatment
Serious scoring problems	Accurate binding energy inspection (?)





Ciancetta A.; Moro S. TIPS 36, 878-890, (2015)

Stretching time!

GRAZIE
PER LA PAZIENZA