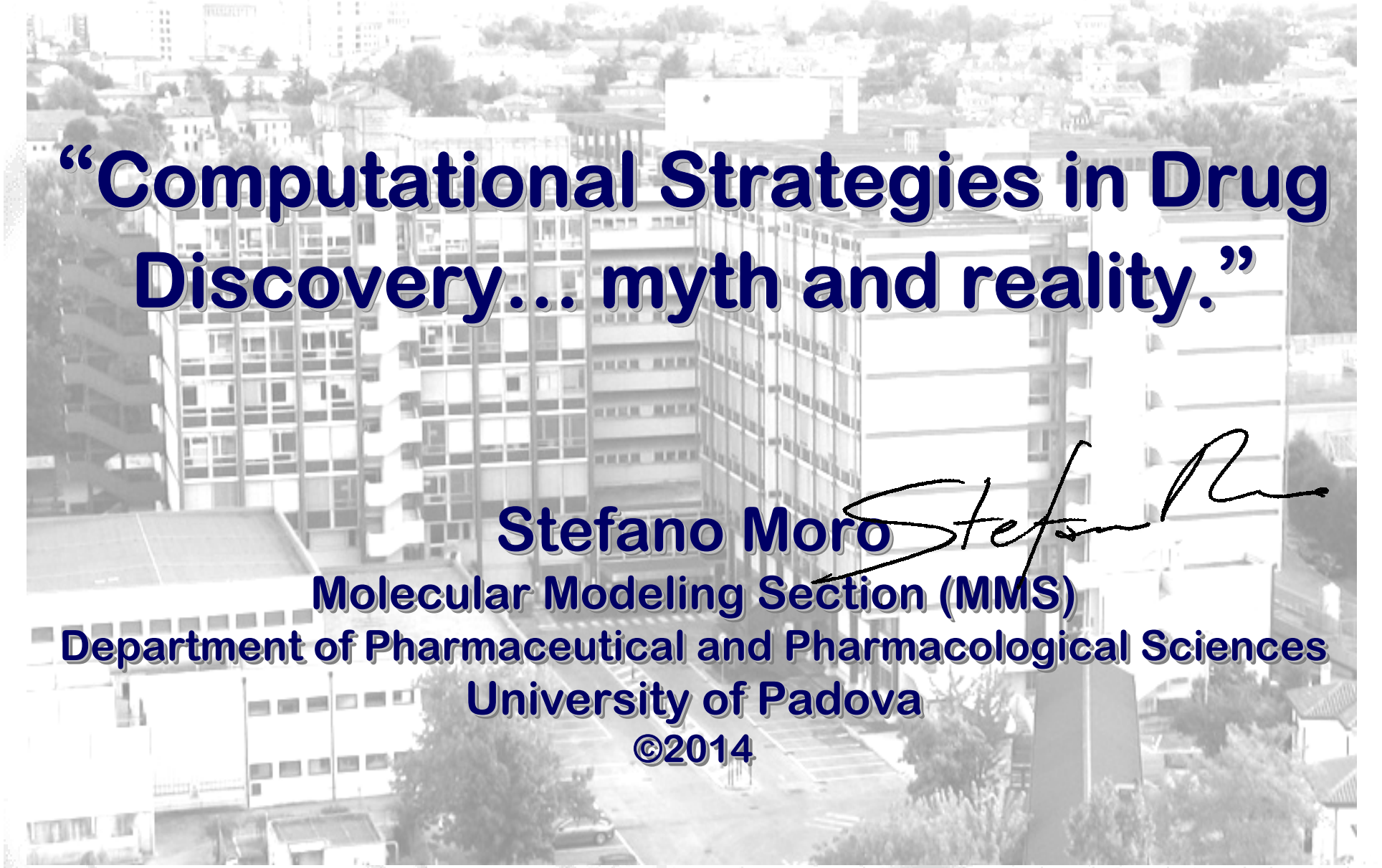


"Computational Strategies in Drug Discovery… myth and reality."

Stefano Moro

Molecular Modeling Section (MMS)

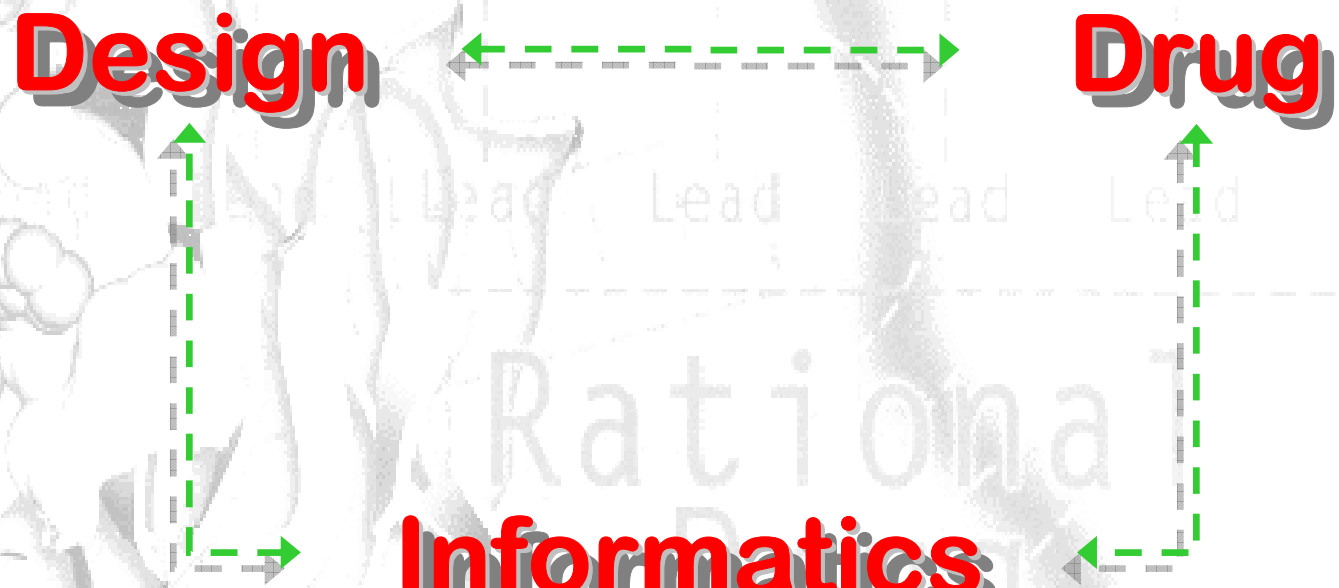
Department of Pharmaceutical and Pharmacological Sciences

University of Padova

The most insidious question that you can make me :

Is a drug designable?

Attending to answer this question... we try to find an intimate connection among these three concepts :



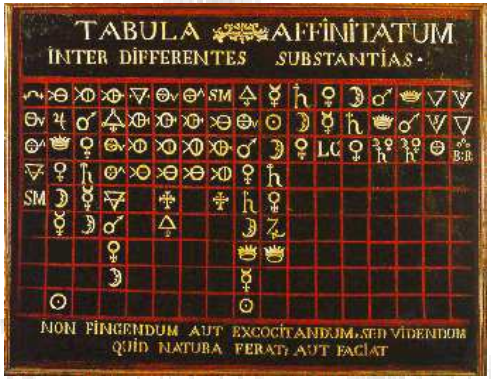
… a bit of:

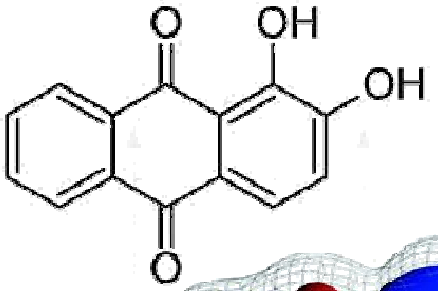
… be patient:

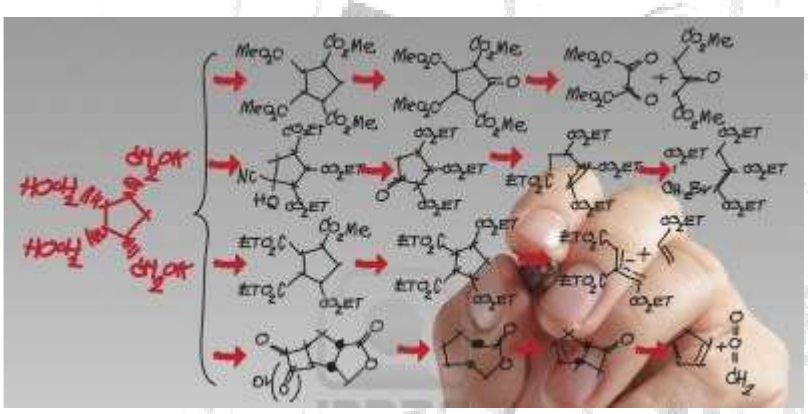
Design:

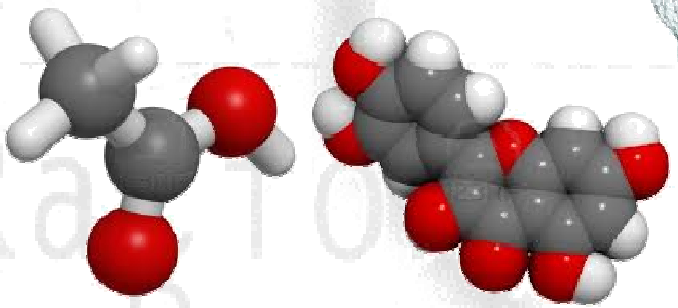
set up a project of a work by making **drawings** and **calculations** necessary for its realization.

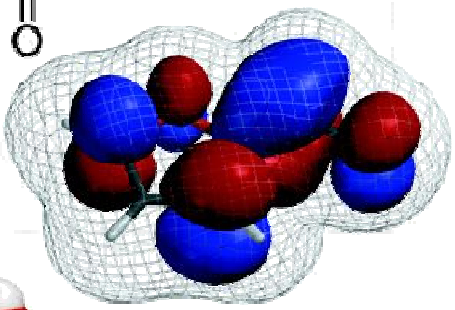
… there is no doubt that chemists (including medicinal chemists) are of great *drawers*:

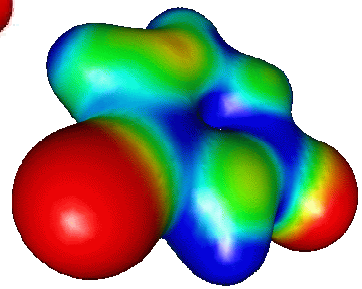












… but what *chemical drawings* can be subjected to *calculation procedures*?

… a bit of:

Design ⟷ Drug

Informatics

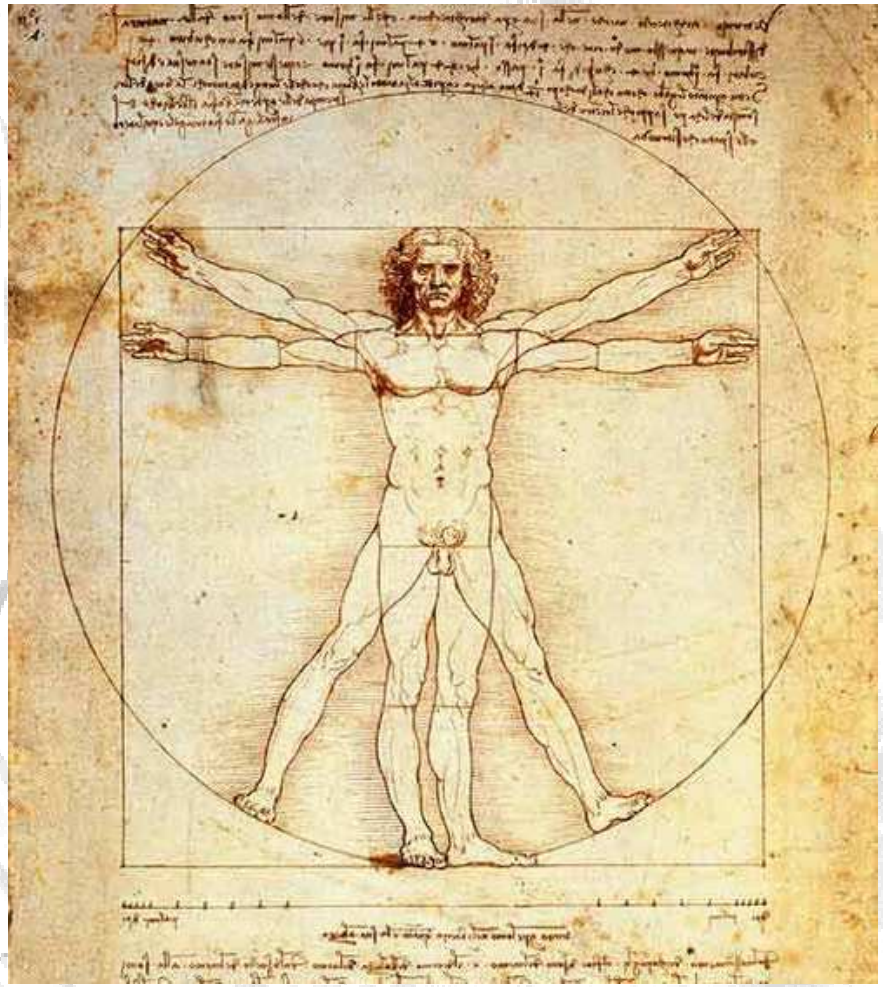
I know very well that you known what drug is... but reconsider its definition in this way:

Drug:

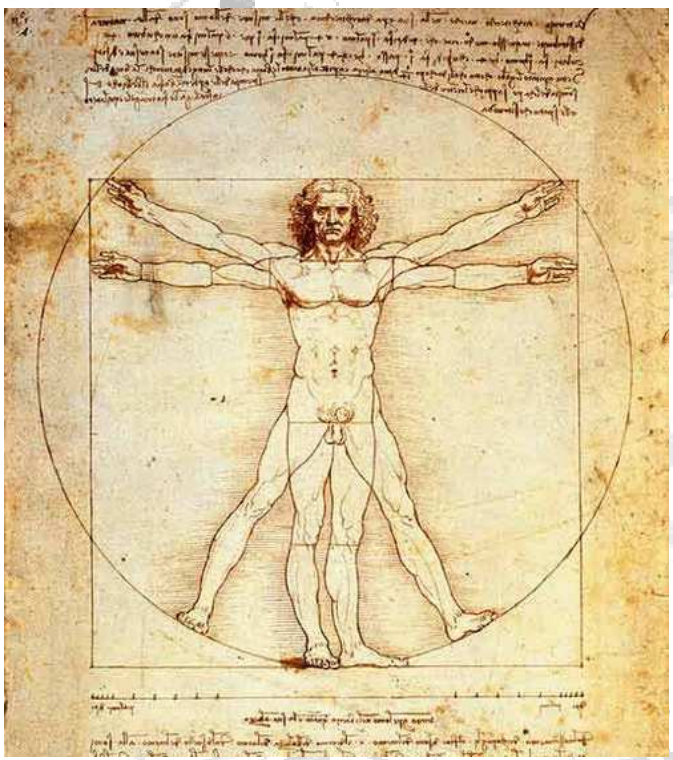
[from gr. φάρμακον] *Any substance, organic or inorganic, synthetic or natural, capable of producing in a* ***living organism*** *functional modifications, helpful or harmful, by chemical or physical action.*

Dizionario Treccani

... and a '*living organism*' is difficult to accommodate in a design process (drawing and calculations), though ...



… living organism is still too complex to *draw*



We will return later on this concept…

… couple of bits of:

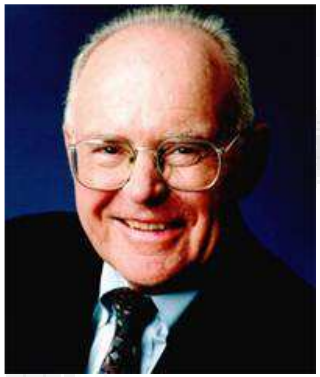
Design ⟷ Drug

Informatics

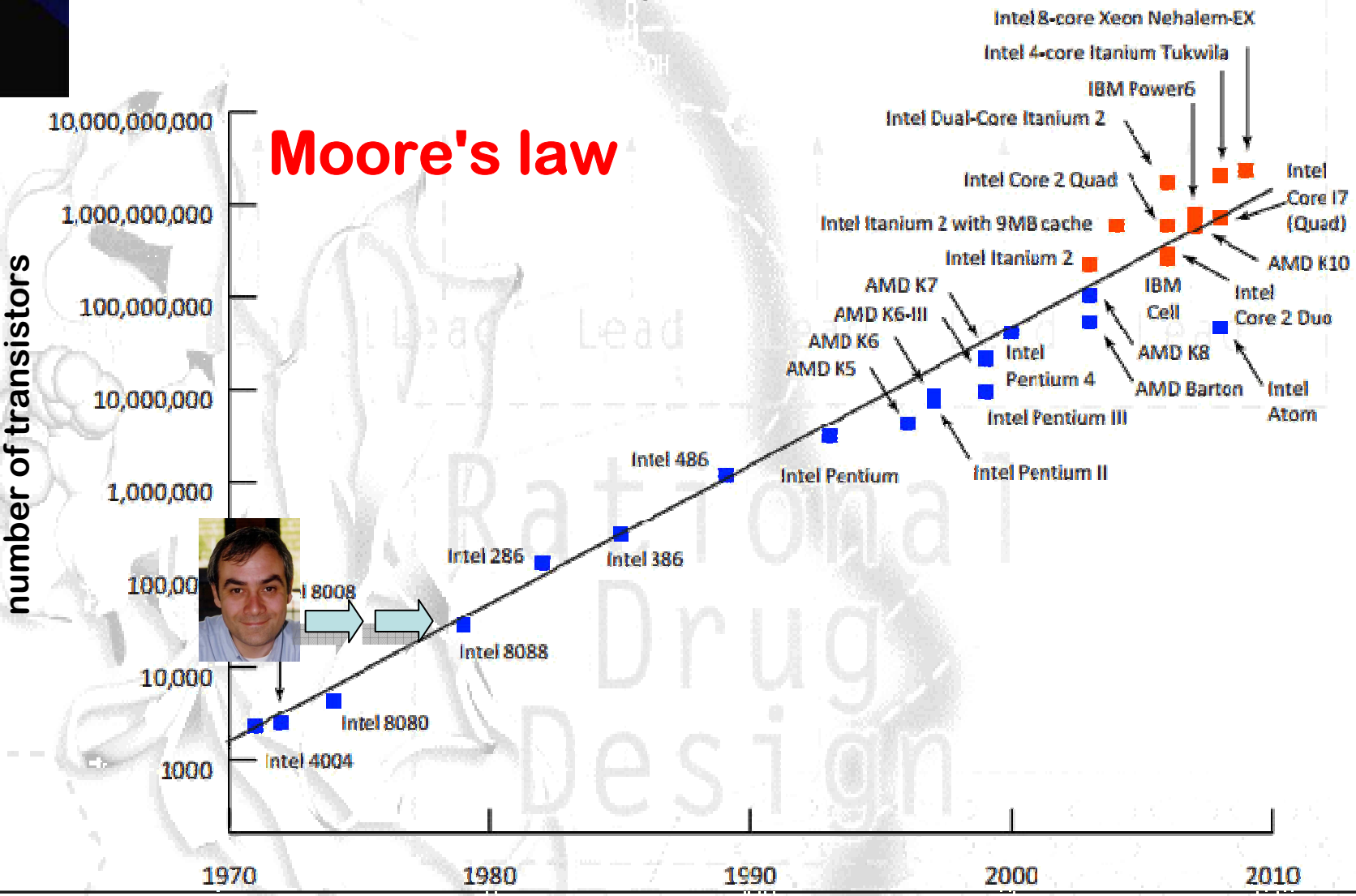
Now, in what informatics has influenced more in our daily life?

Well, we probably summarize the answer in only one word:

Time



Informatics as synonymous of speed?



couple of concrete example..

Informatics helps us to solve simple problems a number of times:

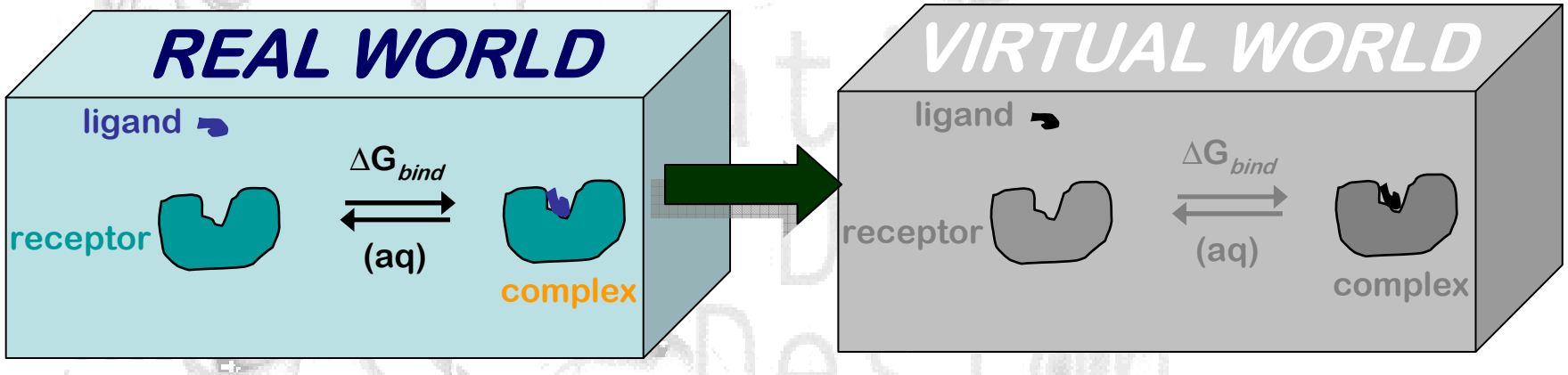
Calculate the molecular weight is trivial thing, calculate 4.5 million ... less!

or solve very complex problems:

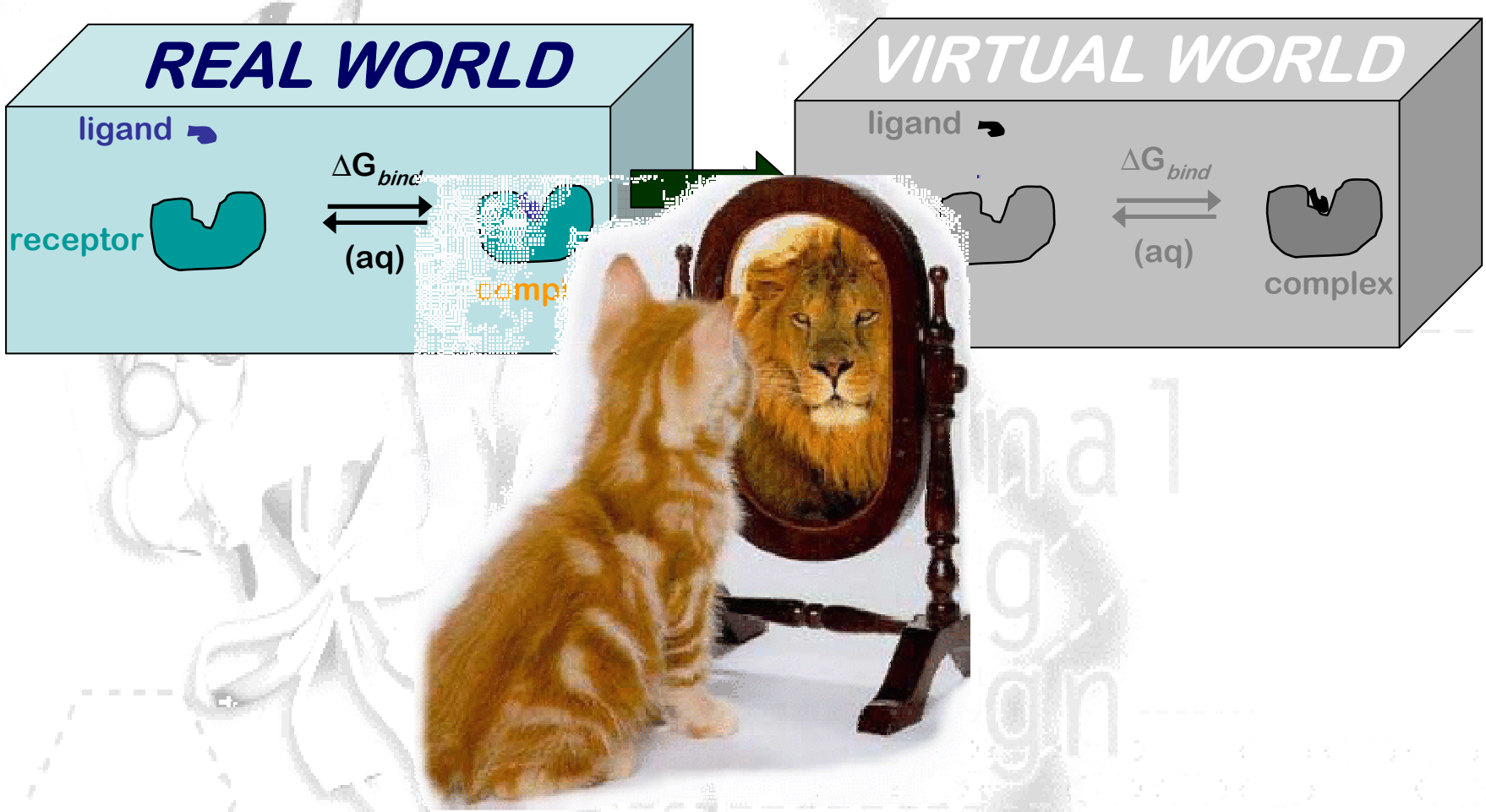
Calculate, for example, the binding energy (ΔG_{bind}, kcal x mol) between a ligand and its receptor!

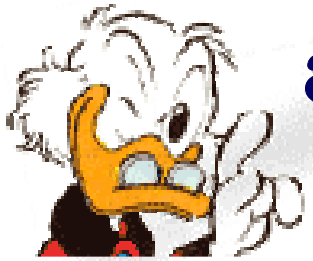
Informatics is the basic science of any *virtualization* process:

***virtualization process*: the creation of a abstraction version of the real process.**



The *accuracy* of this virtualization process is crucial:





and remember… "Time is money!"

Bringing a new drug to market can take 8-14 years and costs between $400 and $900 million

Some details about costs:

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

You understand why it is so attractive to the pharmaceutical industry!

Back to *"drug" design...*

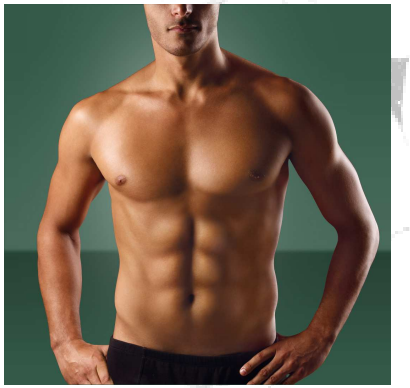
But unfortunately *"drug"* is not designable… yet!

Could we suggest a possible substitute of *"drug"* that is more easily designable?

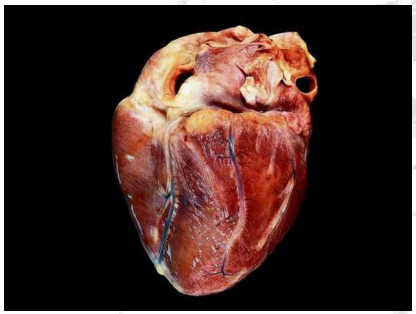
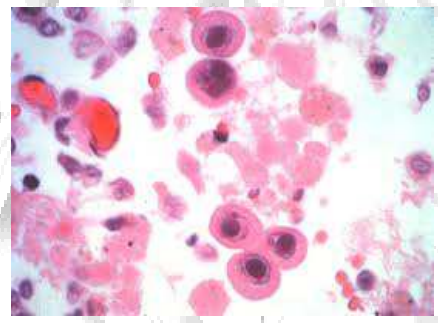
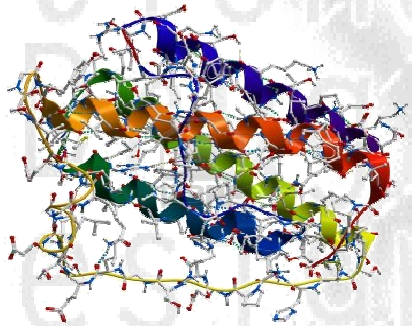
To do this we have to necessarily replace the concept of *living organism* !

An egoistic solution:

drug

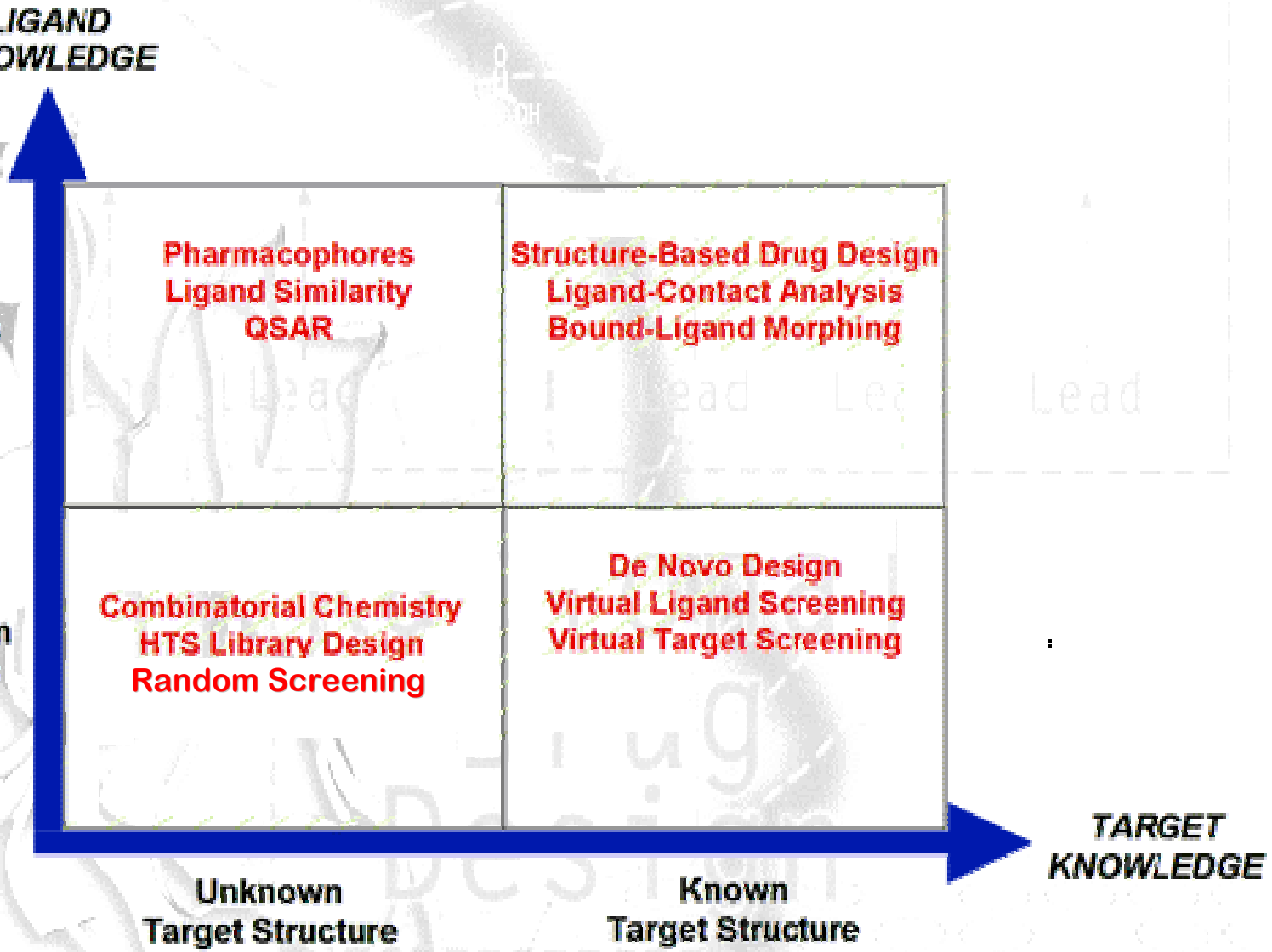




candidate

We surely need informatics but:

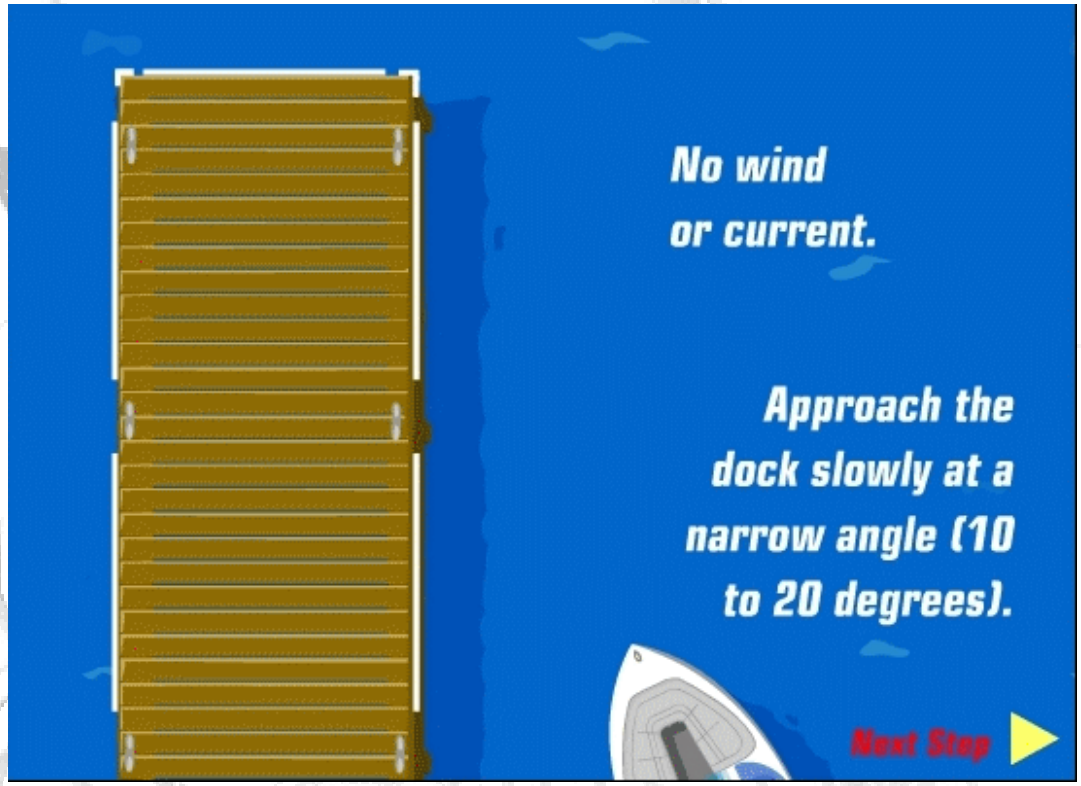


Back when I was young:

"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…"

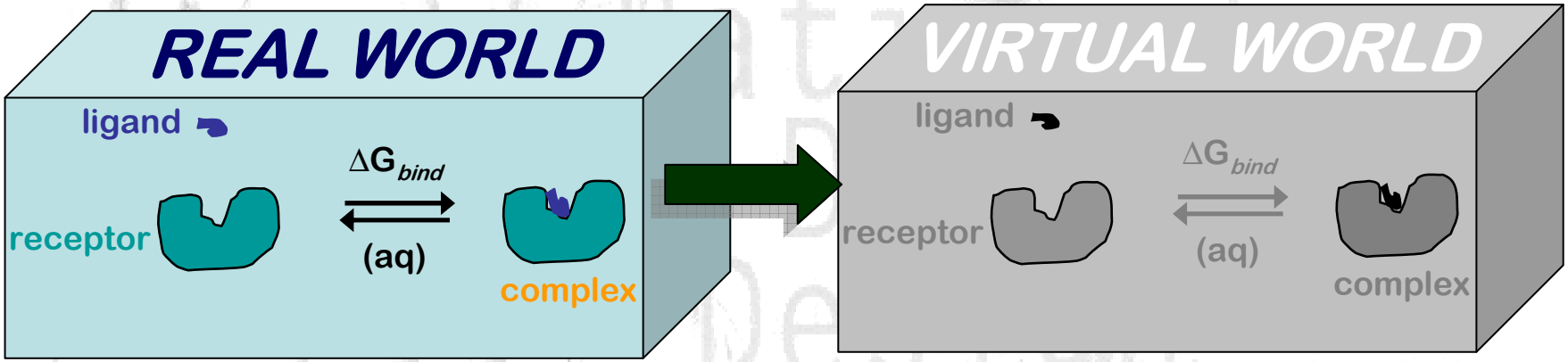
by Johann Gasteiger *et al J.A.C.S.* 1995, 117, 7769-7775

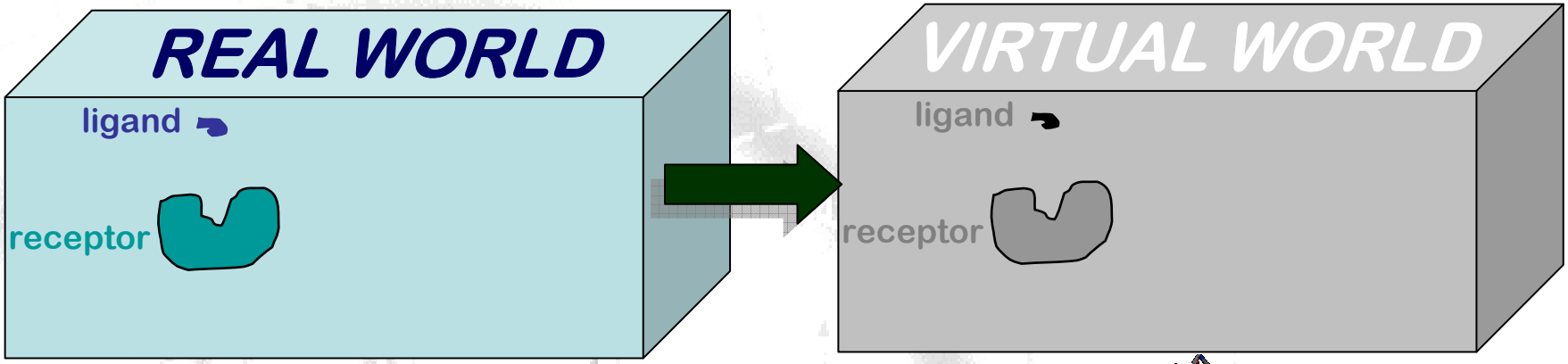
Docking and Scoring



What Docking really is?

From an informatics point of view, docking is a *virtualization process* dealing with the creation of a virtual (rather than real) version of the binding process.

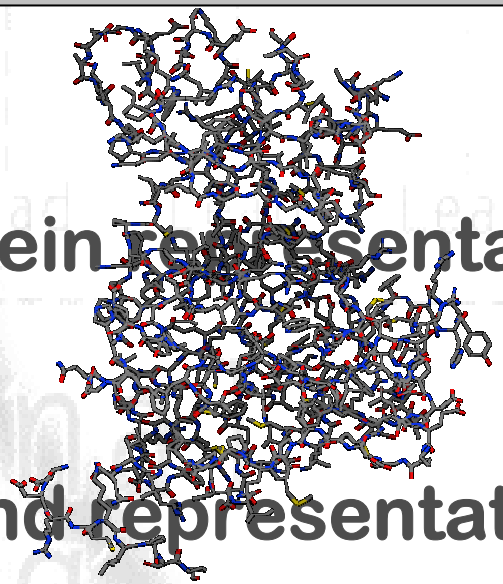




Real protein

Epithelial Grow Factor Receptor
(kinase domain)

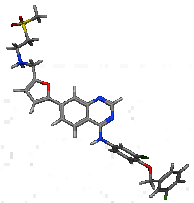
3D protein representation



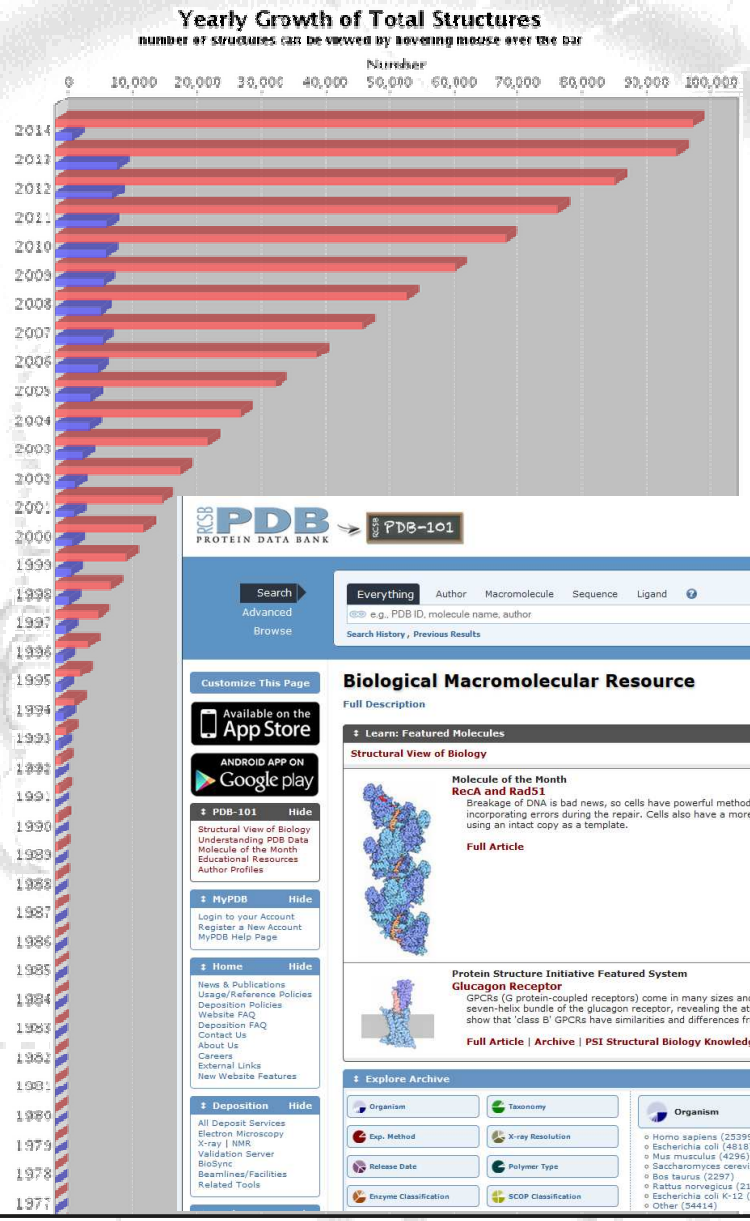
Real ligand

3D ligand representation

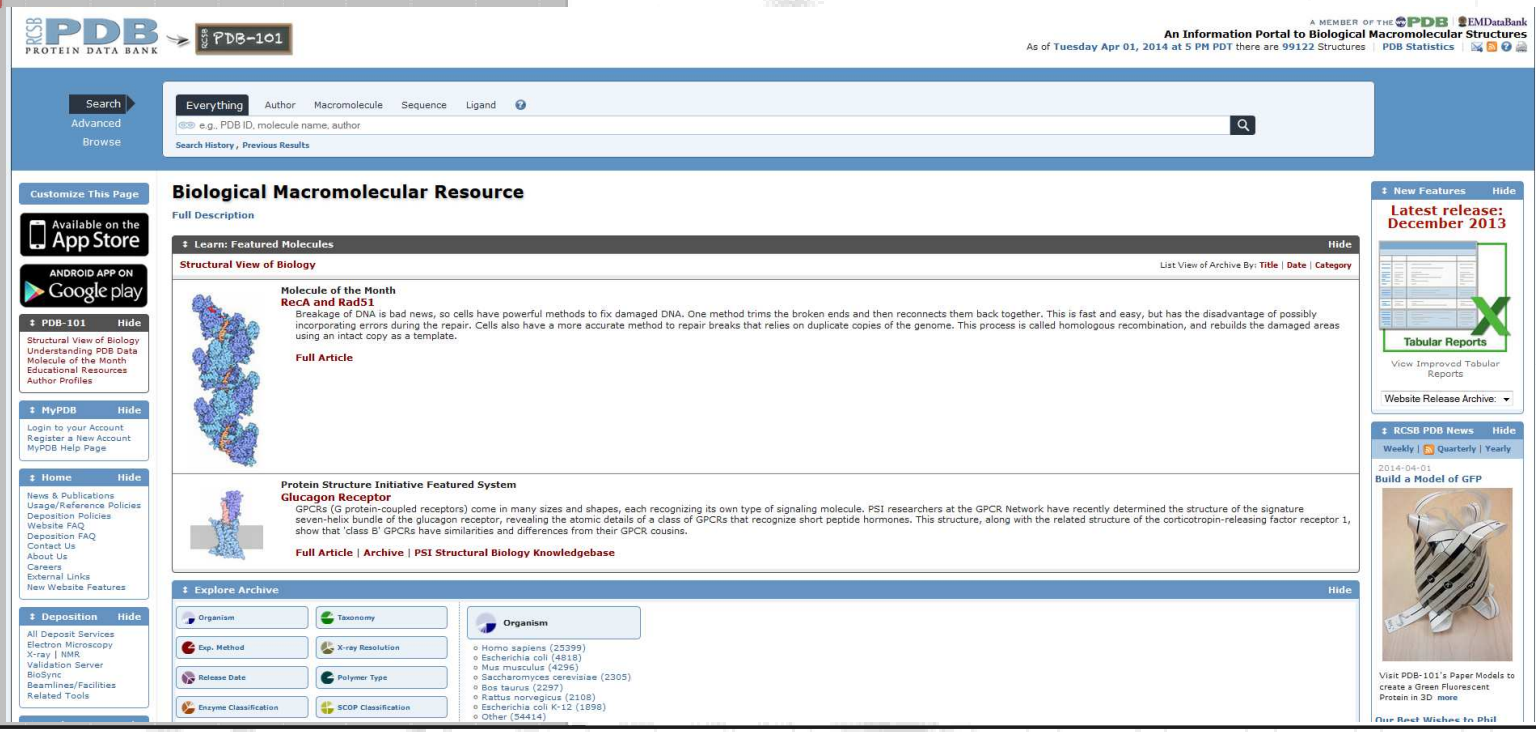
Lapatinib (Tykerb®, GSK)



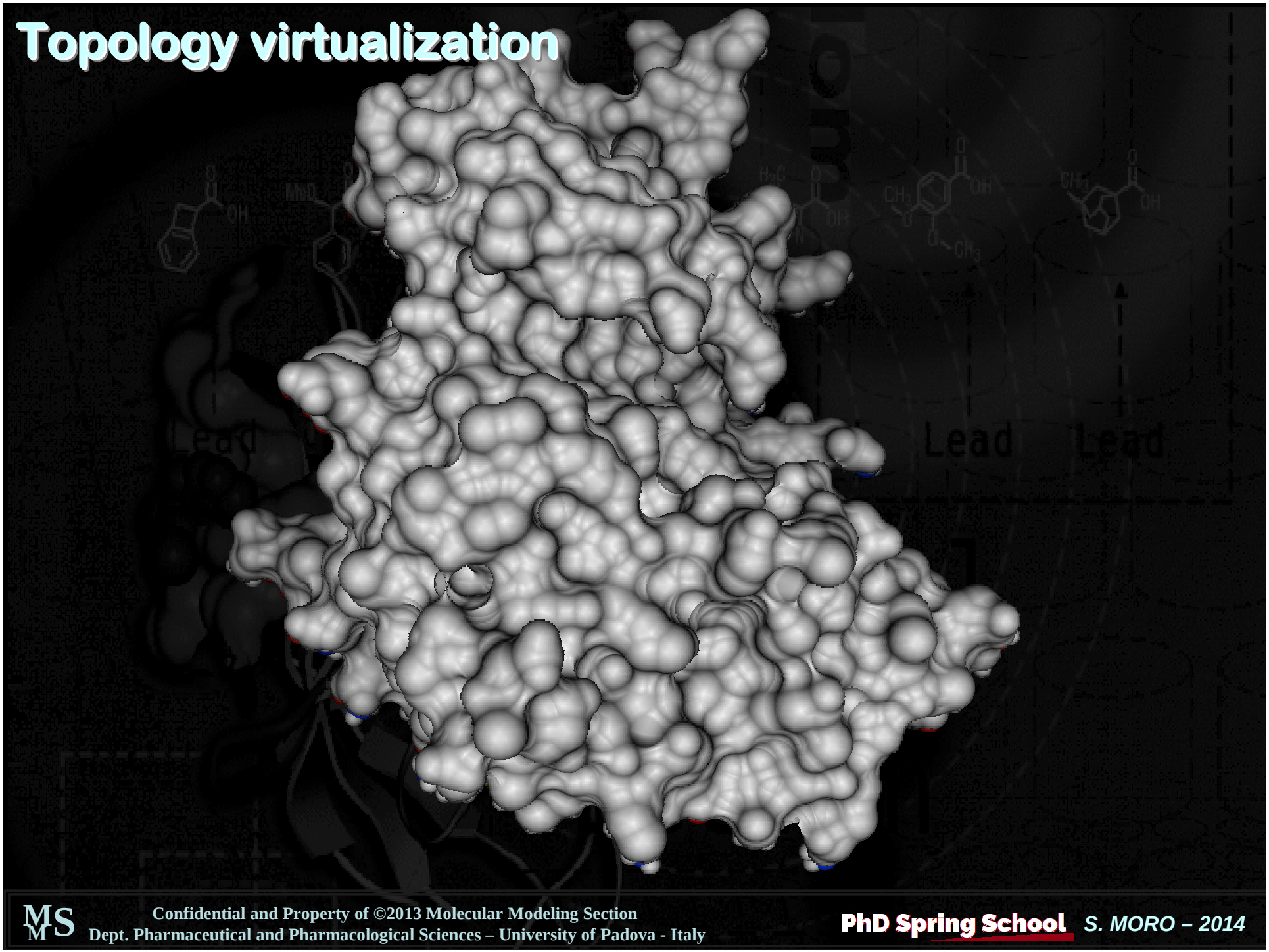
Dockers are coordinates hunters!



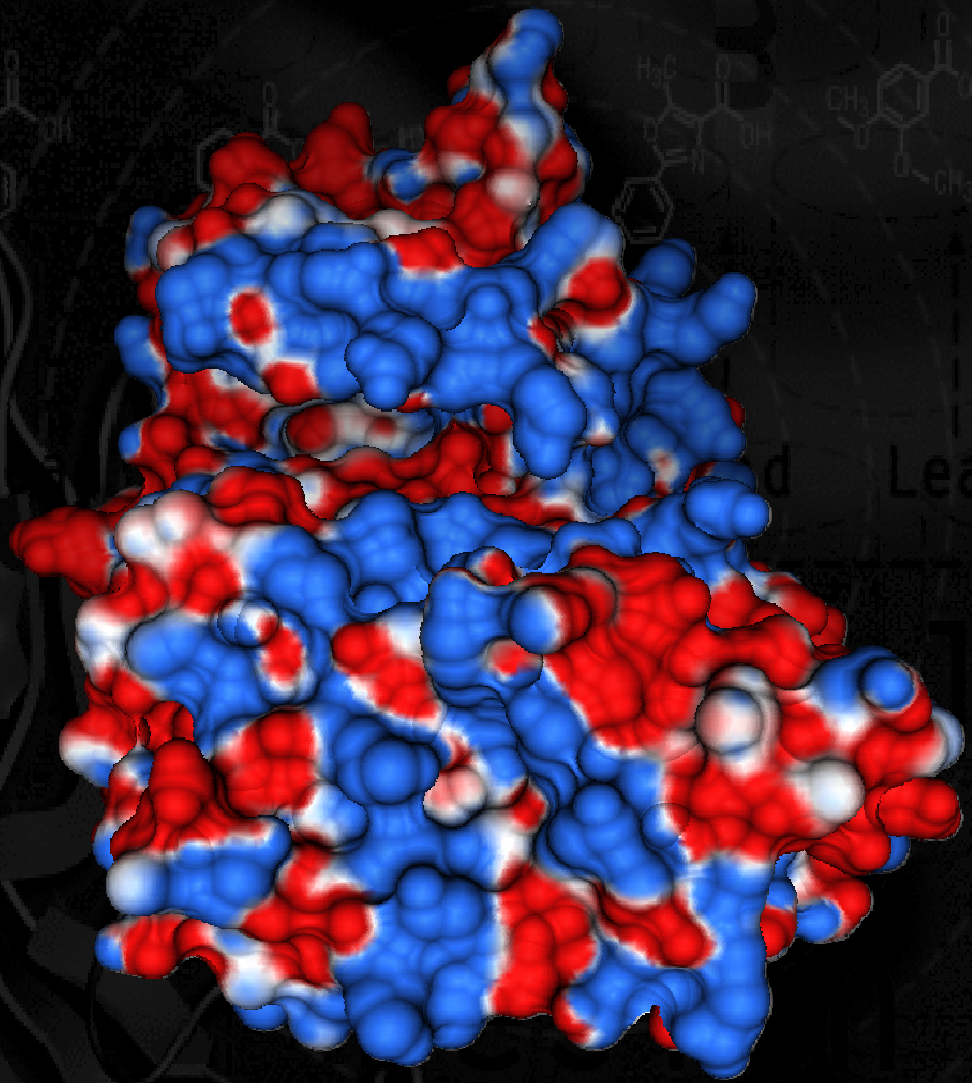
99122, yesterday.



Topology virtualization



Surface properties virtualization

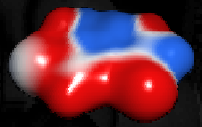


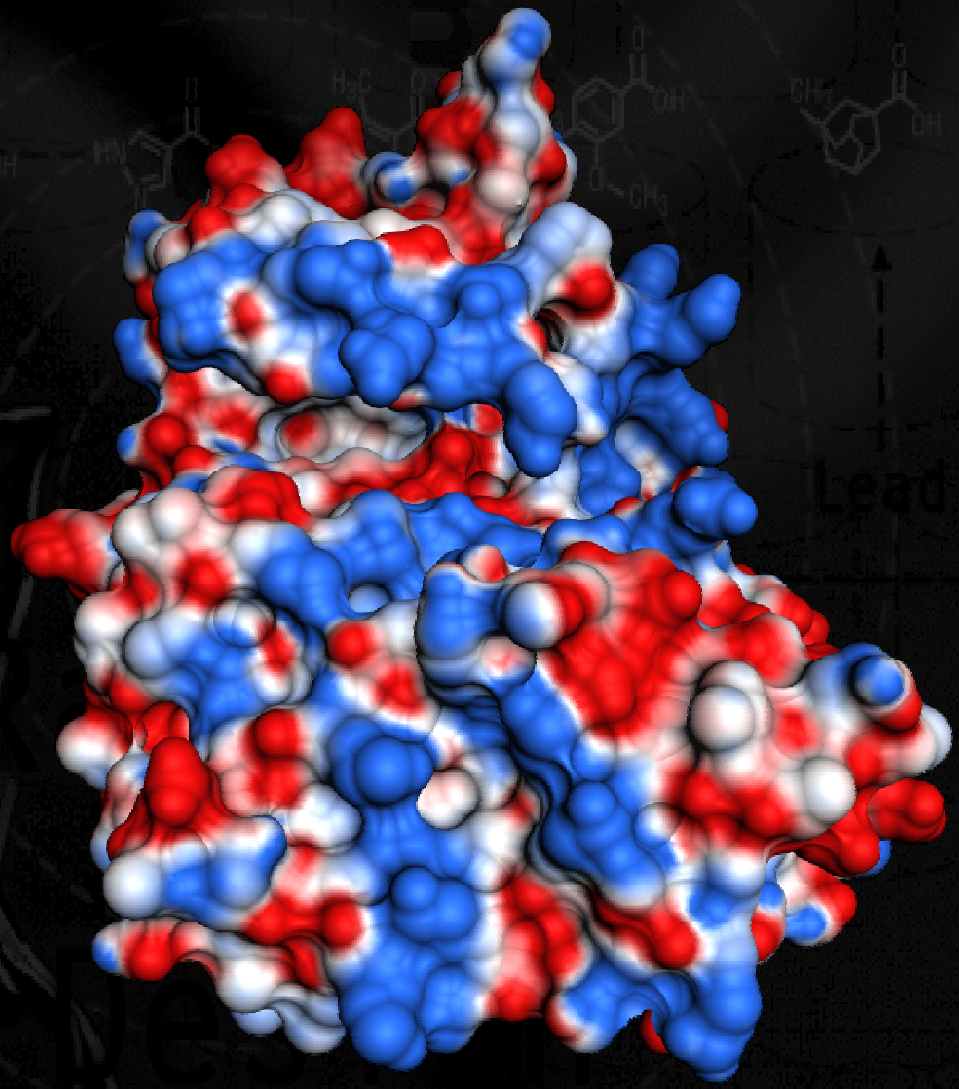
$V_{el} < 0$

$V_{el} = 0$

$V_{el} > 0$

Here is the problem…





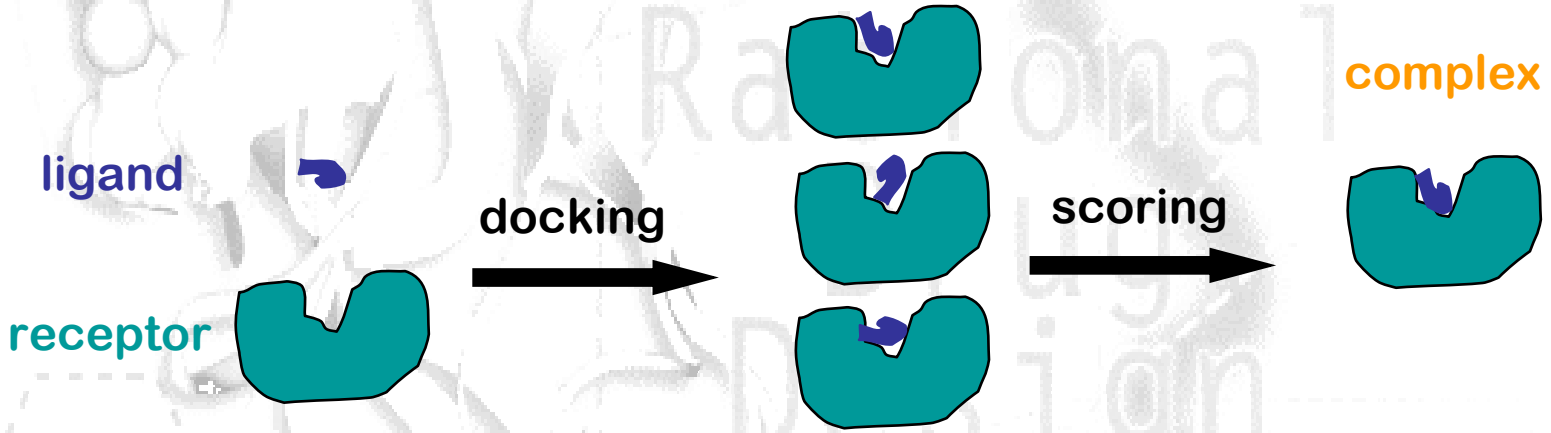
1. where?
2. how?
3. how long?

Stretching time!

The molecular docking problem:

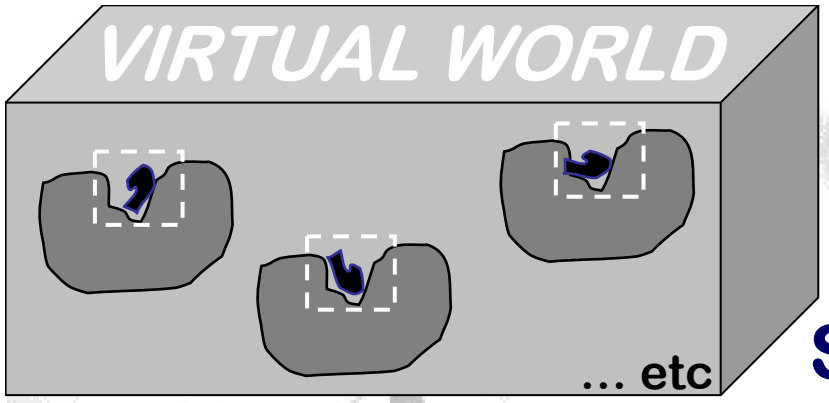
To place a ligand (small molecule) into the binding site of a receptor in the manners appropriate for optimal interactions with a receptor (DOCKING).

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}"



Some definitions:

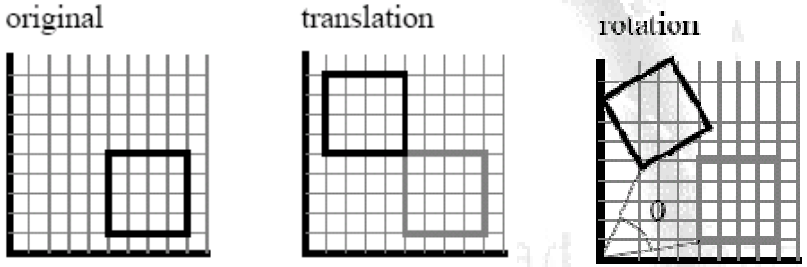
We define as POSE:

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

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

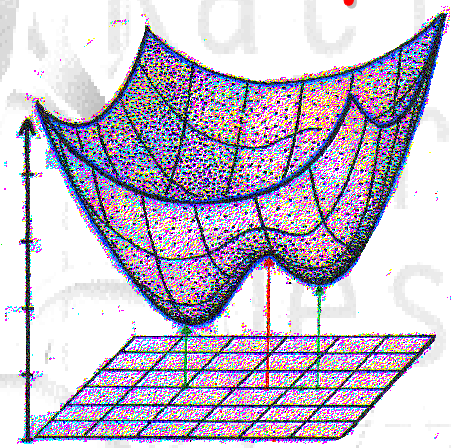
What we need…

1. Translate and rotate a molecular object:



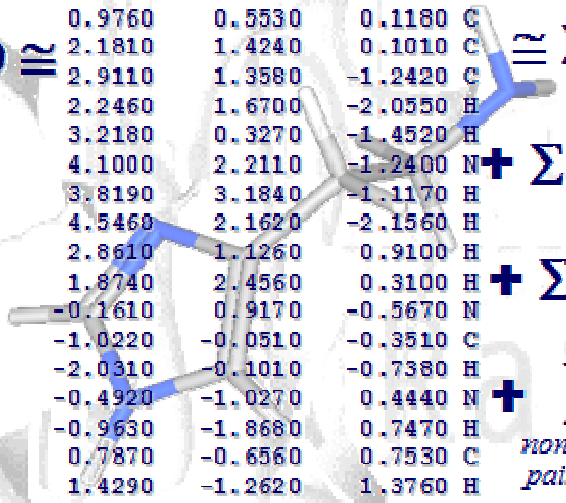
$$\begin{bmatrix} x' \\ y' \end{bmatrix} = \begin{bmatrix} d_x \\ d_y \end{bmatrix} + \begin{bmatrix} x \\ y \end{bmatrix} \qquad \begin{bmatrix} x' \\ y' \end{bmatrix} = \begin{bmatrix} \cos\theta & -\sin\theta \\ \sin\theta & \cos\theta \end{bmatrix} \cdot \begin{bmatrix} x \\ y \end{bmatrix}$$

2. Explore conformational space of a molecule:



What we need…

3. Assign the potential energy of each molecules:



0.9760	0.5530	0.1180	C
2.1810	1.4240	0.1010	C
2.9110	1.3580	-1.2420	C
2.2460	1.6700	-2.0550	H
3.2180	0.3270	-1.4520	H
4.1000	2.2110	-1.2400	N
3.8190	3.1840	-1.1170	H
4.5460	2.1620	-2.1560	H
2.8610	1.1260	0.9100	H
1.8740	2.4560	0.3100	H
-0.1610	0.9170	-0.5670	N
-1.0220	-0.0510	-0.3510	C
-2.0310	-0.1010	-0.7380	H
-0.4920	-1.0270	0.4440	N
-0.9630	-1.8680	0.7470	H
0.7870	-0.6560	0.7530	C
1.4290	-1.2620	1.3760	H

$$Ep \cong \cong \sum \left[\tfrac{1}{2} k_{str} (r-r_e)^2 - D_e^{str}\right]$$

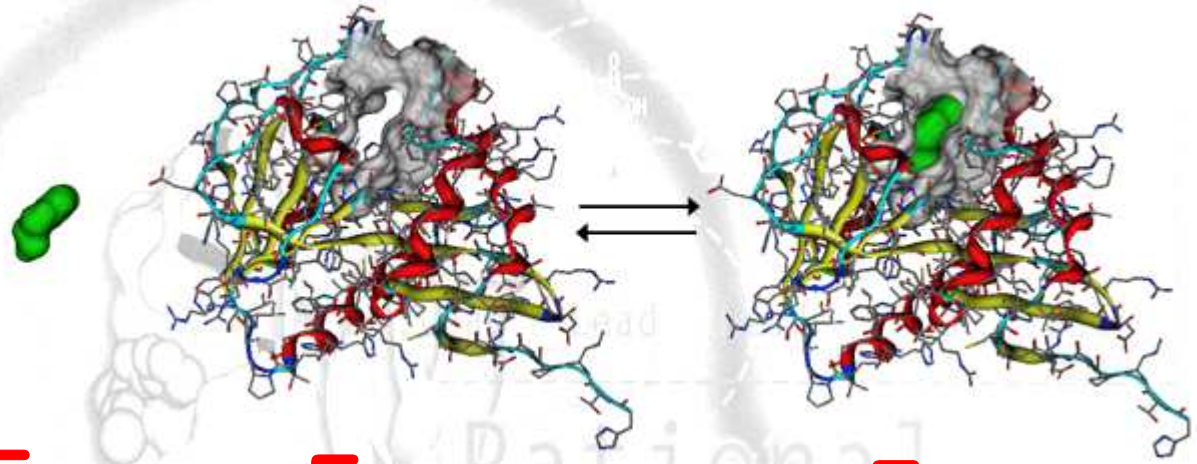
$$+ \sum \left[\tfrac{1}{2} k_{ben} (\tau-\tau_e)^2 - D_e^{ben}\right]$$

$$+ \sum \left[A\,(1 + \cos n\tau - \theta)\right]$$

$$+ \sum_{\substack{nonbonded \\ pairs}} \left(\frac{A_{ik}}{r_{ik}^{12}} - \frac{C_{ik}}{r_{ik}^{6}} \right)$$

$$+ \sum_{\substack{nonbonded \\ pairs}} \frac{q_i q_k}{4\pi\varepsilon_o r_{ik}}$$

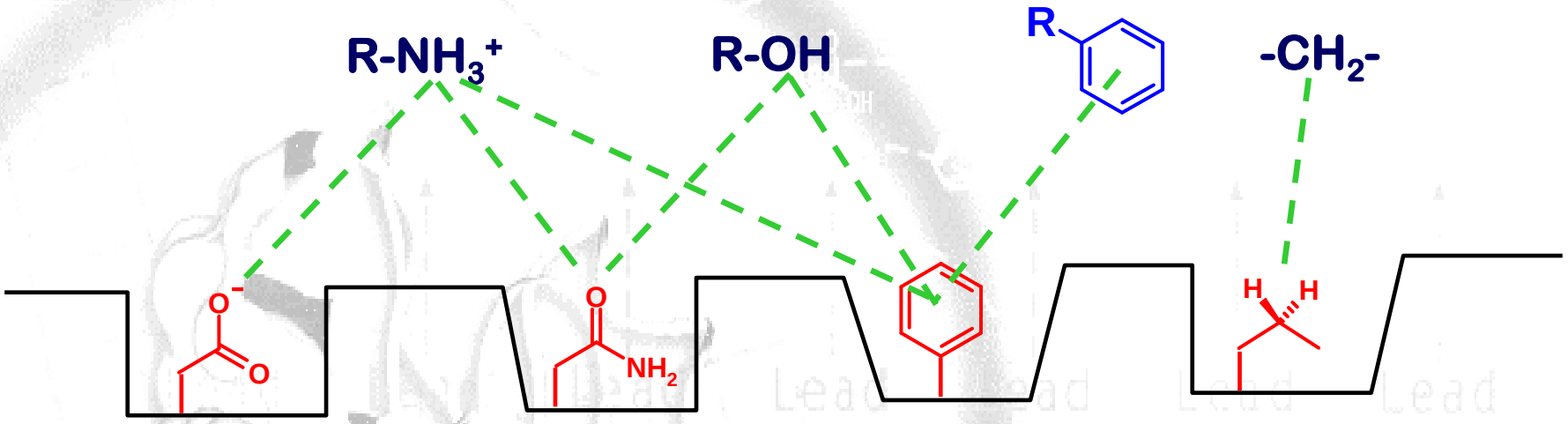
Force Field Based Scoring Functions



Ep_L Ep_R Ep_{RL}

$$\Delta Ep = \sum_{\substack{nonbonded \\ pairs}} \left(\frac{A_{ik}}{r_{ik}^{12}} - \frac{C_{ik}}{r_{ik}^{6}} \right) + \sum_{\substack{nonbonded \\ pairs}} \frac{q_i q_k}{4\pi\varepsilon_0 r_{ik}}$$

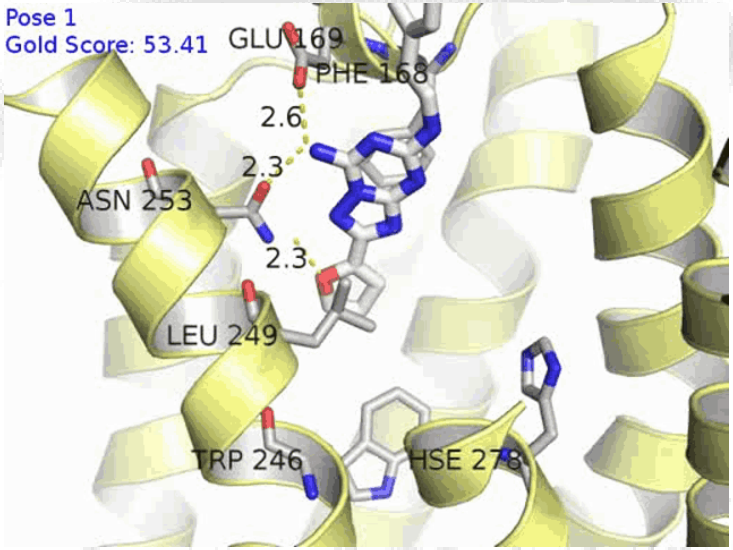
Empirical Scoring Functions

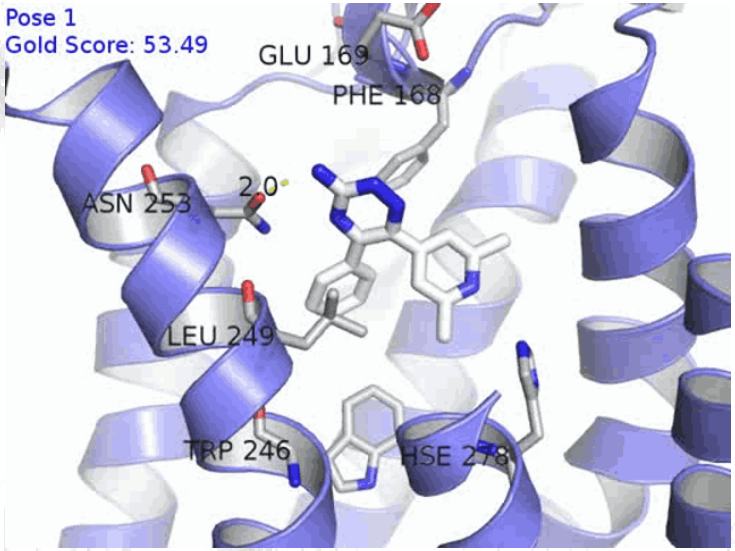


		(kcal/mol)
charge-charge interaction (*ionic bond*):	$-\Delta G^0 \cong$	5 ÷ 10
charge-dipole interaction:	$-\Delta G^0 \cong$	1 ÷ 7
charge-π interaction:	$-\Delta G^0 \cong$	8 ÷ 10
hydrogen bond:	$-\Delta G^0 \cong$	1 ÷ 7
charge transfer interaction:	$-\Delta G^0 \cong$	1 ÷ 6
π-π interaction:	$-\Delta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

Here is a real example:

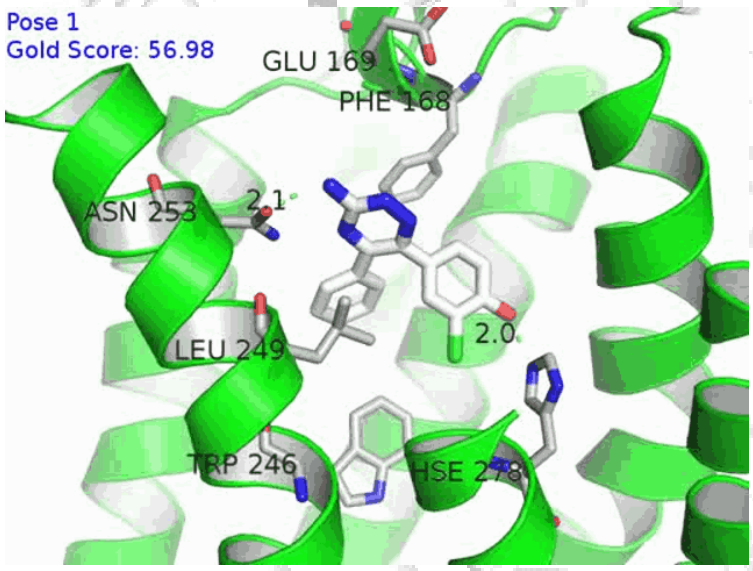
ZM

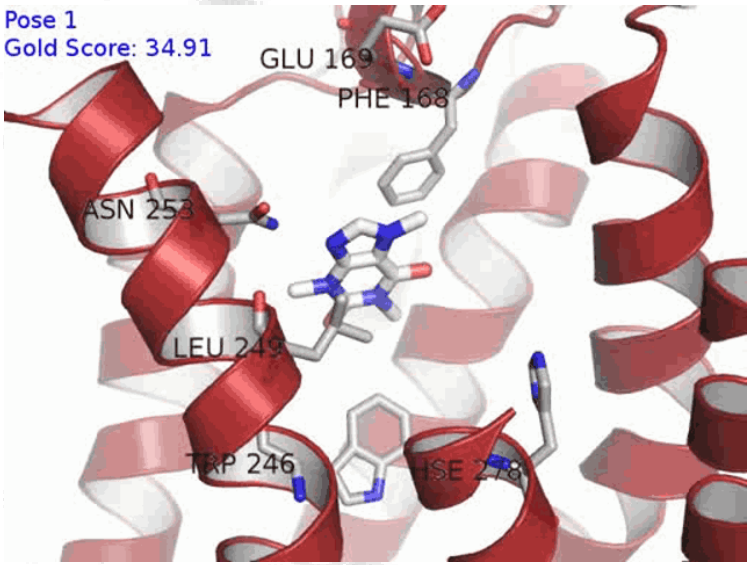




T4G

T4E

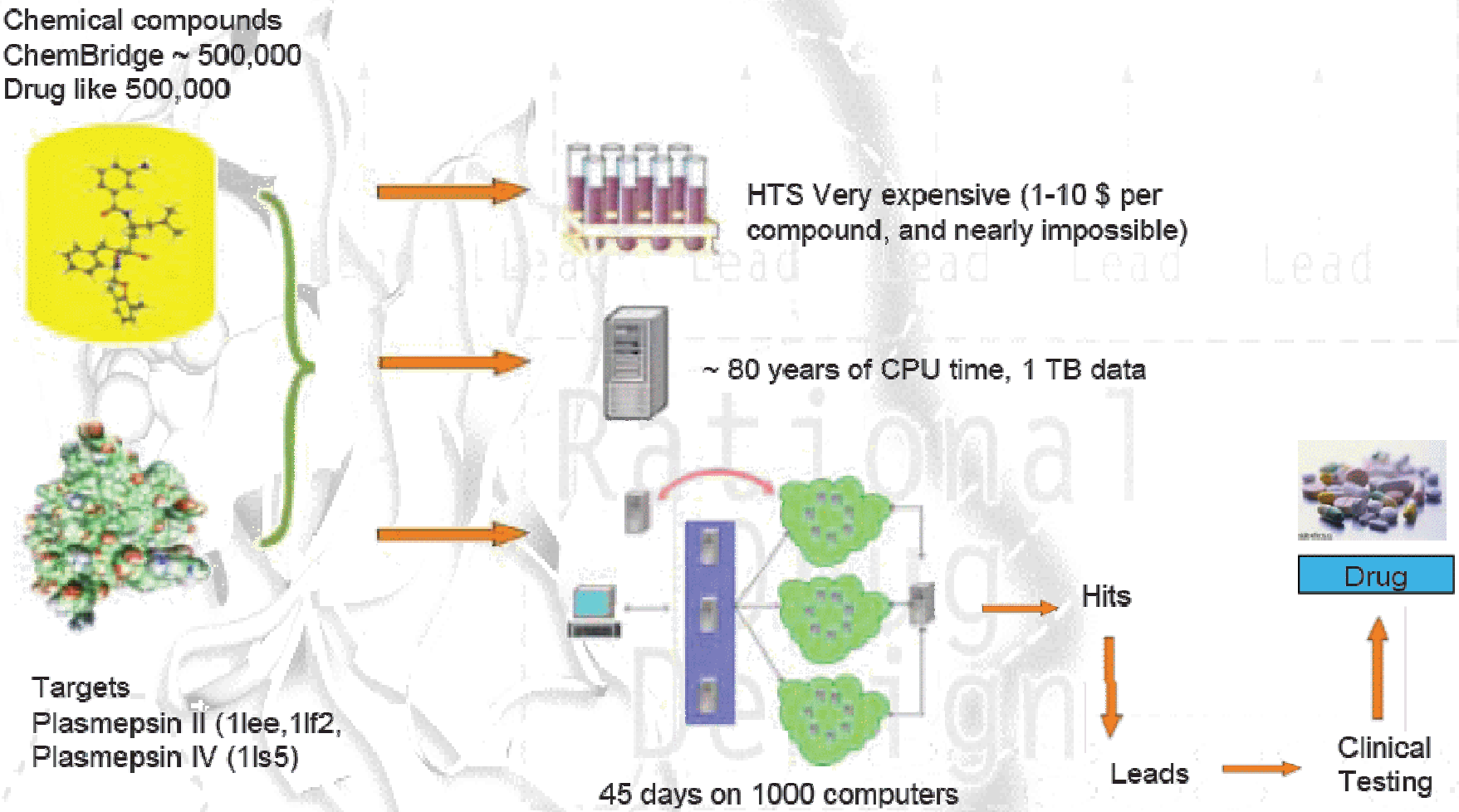




Caffeine

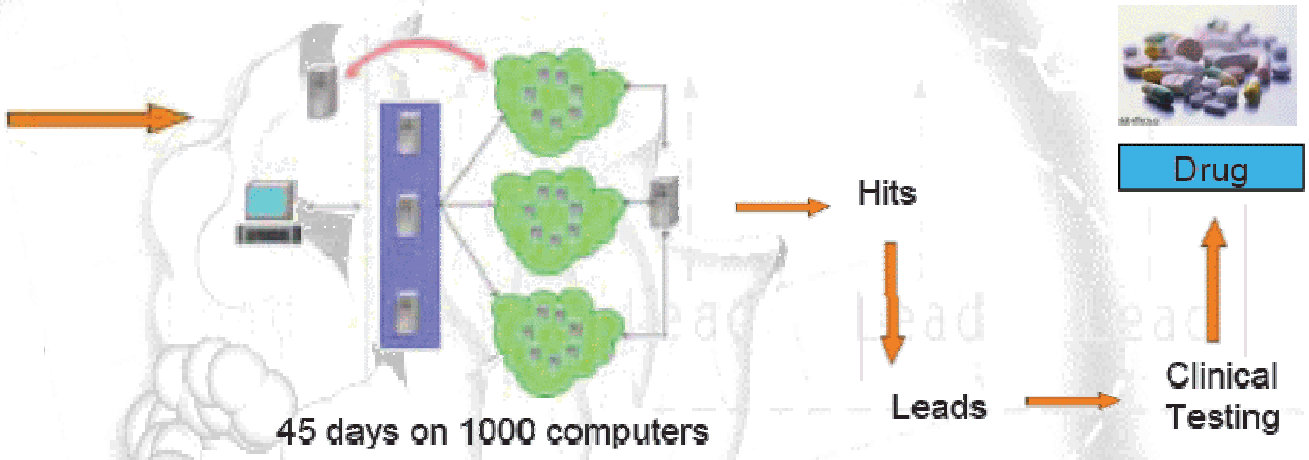
Docking Applications:

•*High-Throughput Virtual Screening (HTVS);*

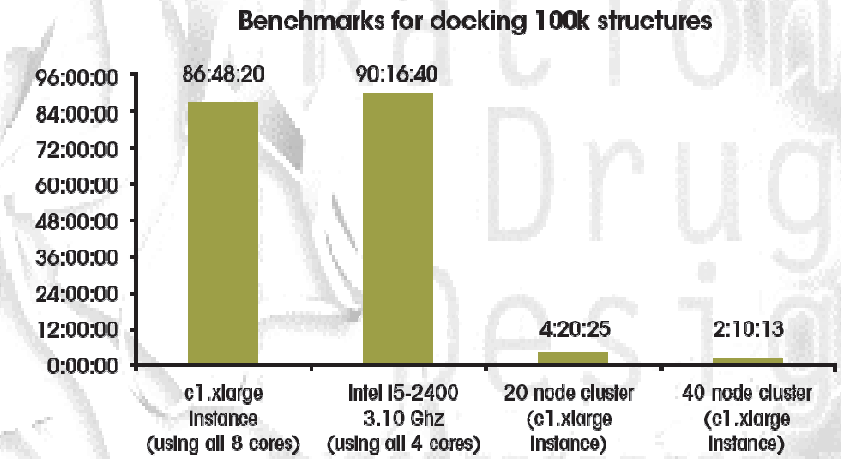


Docking Applications:

- *High-Throughput Virtual Screening (HTVS);*



2005



2013

Beyond docking…

SWOT analysis

Molecular Docking
Fast and scalable pose sampling
Rigid protein
Difficult solvent treatment
Serious scoring problems

Molecular Dynamics
Computational expensive
Investigate receptor full flexibility
Explicit solvent treatment
Accurate energy inspection

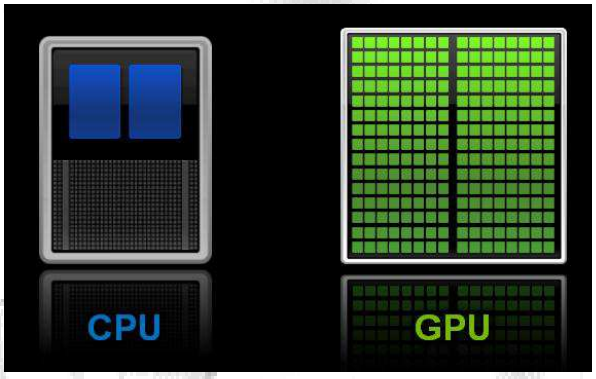
Dock&MD
Fast and scalable pose sampling
Investigate receptor full flexibility
Explicit solvent treatment
Accurate energy inspection

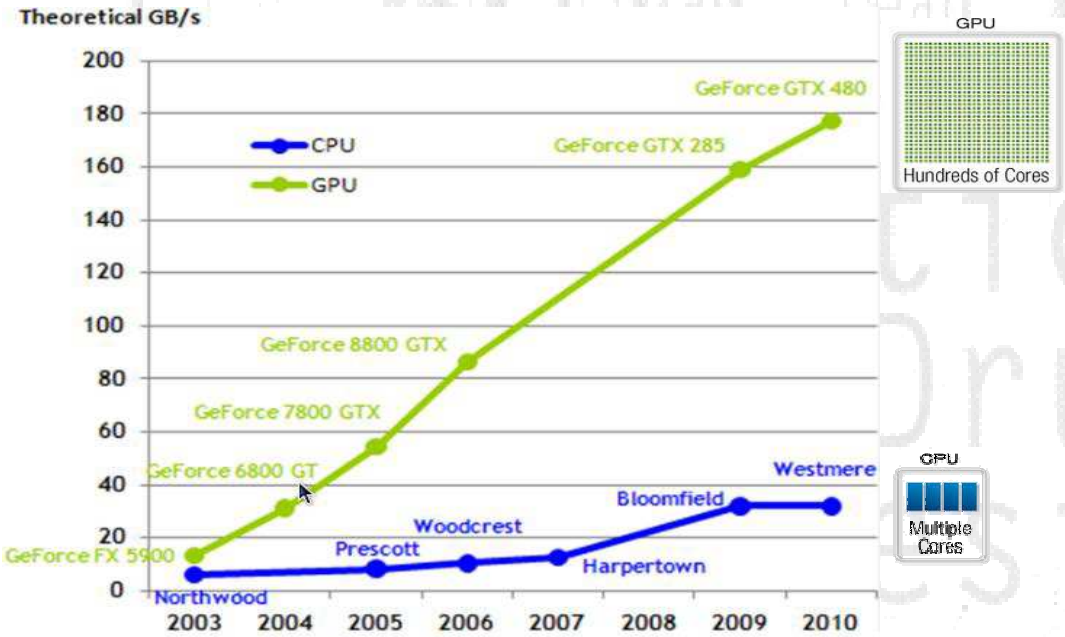
Is it possible to discriminate the bioactive (XRAY) conformation from an ensemble of docked poses taking advantage of MD versatility?

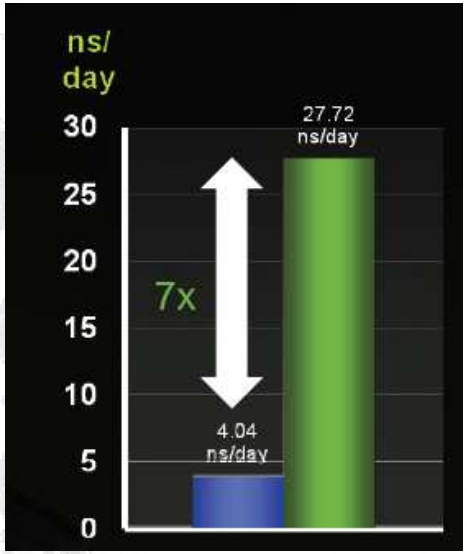
Why we need *time* virtualization?

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. …

My favorite C/G mutation





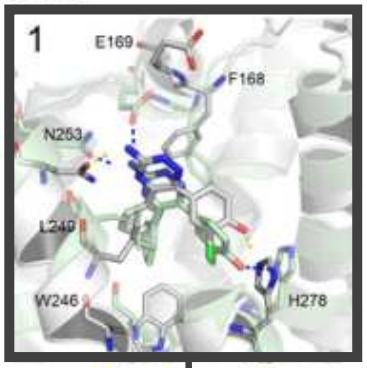


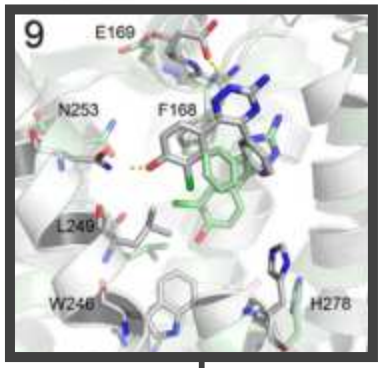
in collaboration with: acellera

Bridging Docking and Molecular Dynamics

Molecular Docking → Pose **1** ….. Pose **n**

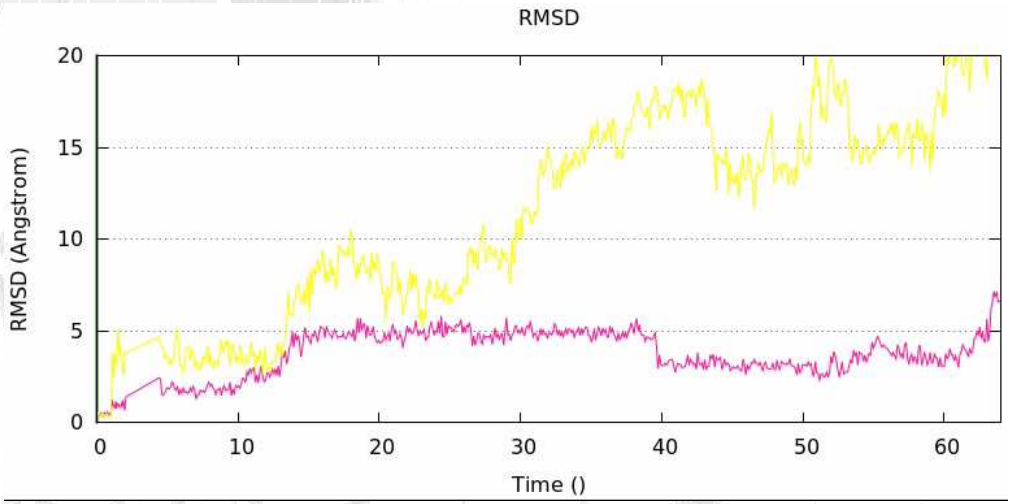
3UZC

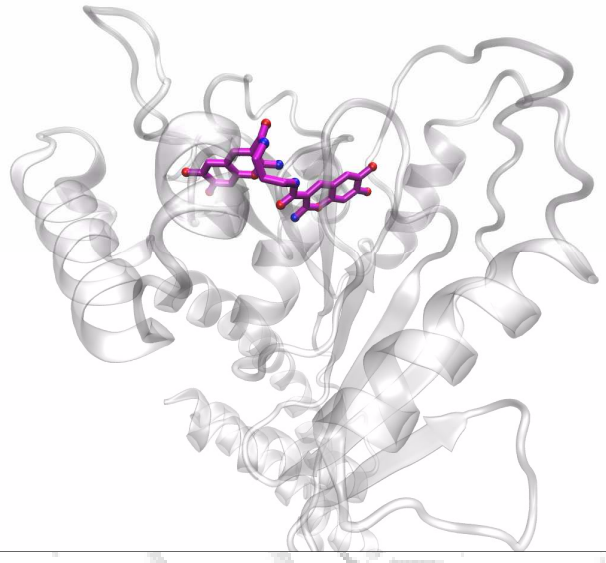


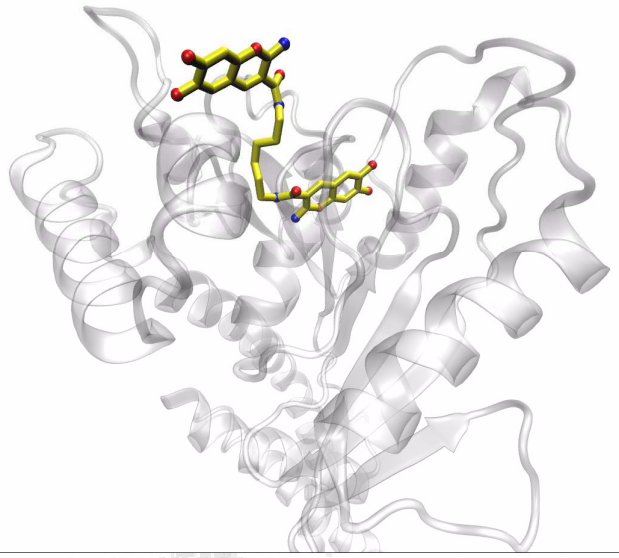


MD **MD**

Bridging Docking and Molecular Dynamics

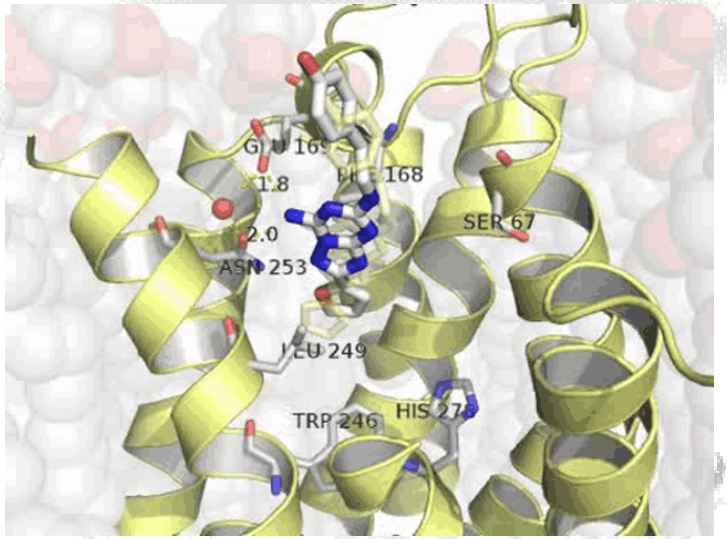


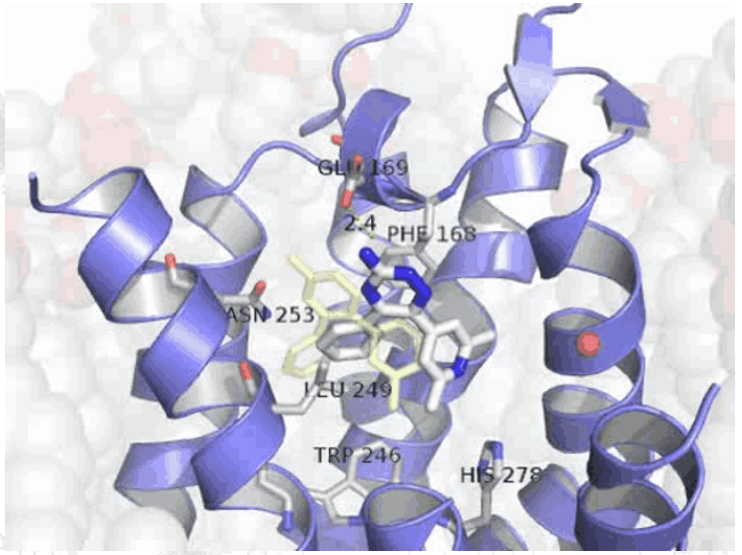




Bridging Docking and Molecular Dynamics - A_{2A} adenosine receptor

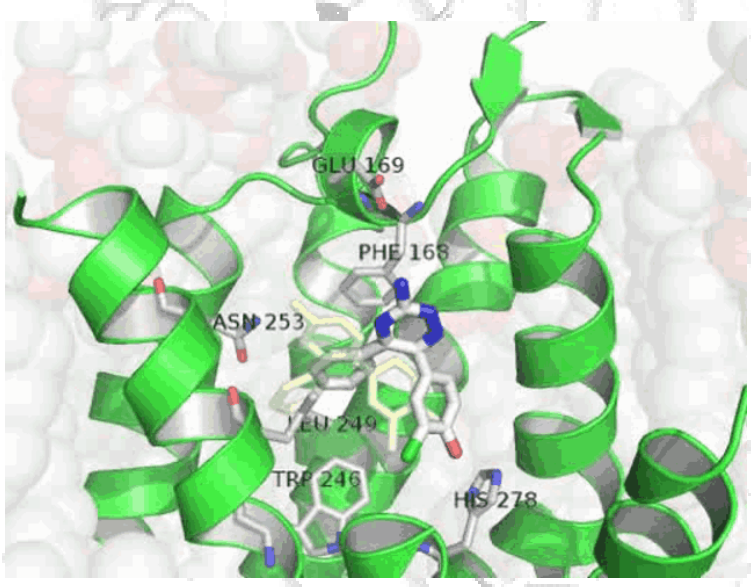
ZM

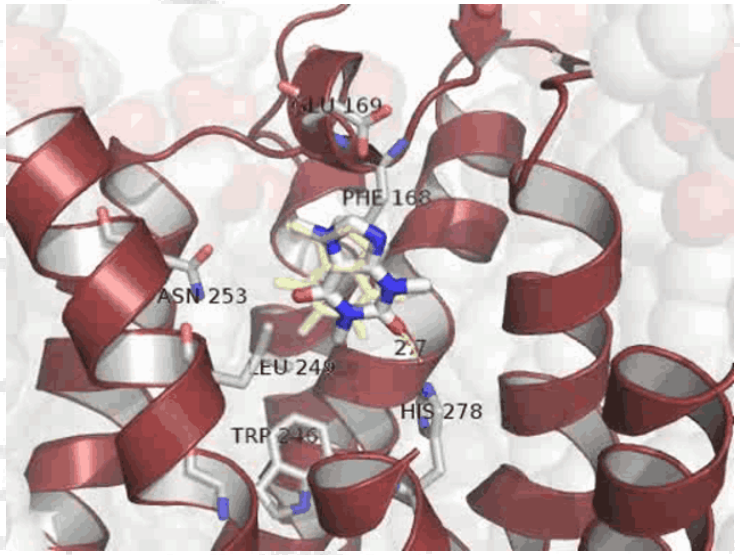




T4G

T4E



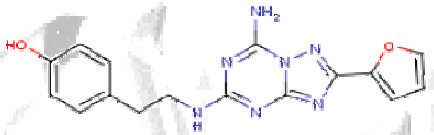


Caffeine

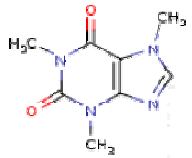
Sabbadin D., Ciancetta A., Moro S et al. J Chem Inf Mod (2014) in press

Bridging Docking and Molecular Dynamics - A_{2A} adenosine receptor

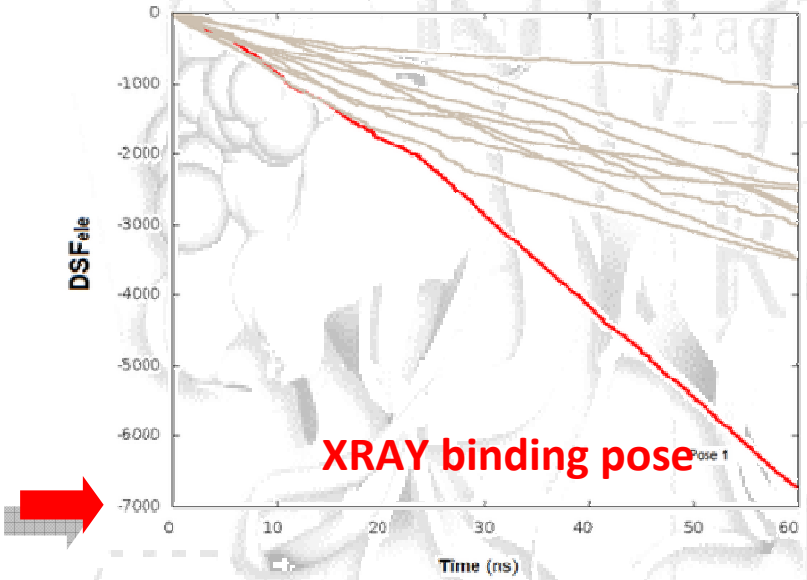
Comparison between a strong and a weak binders



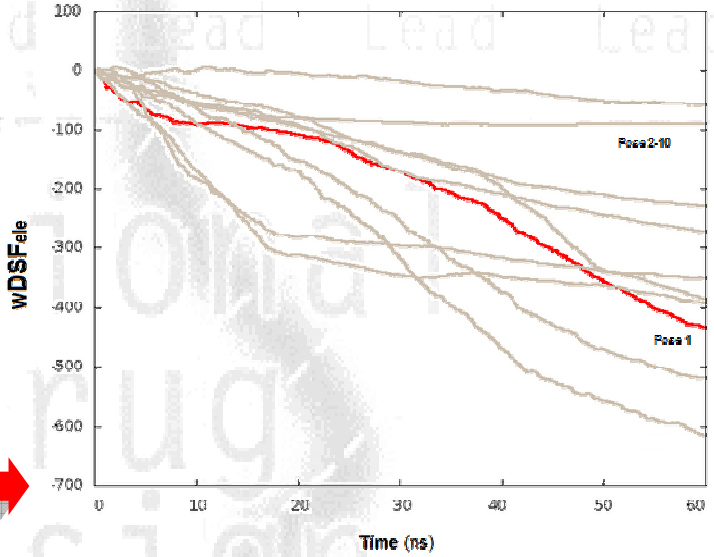
K_i = 1.6 nM (h_A_{2A})



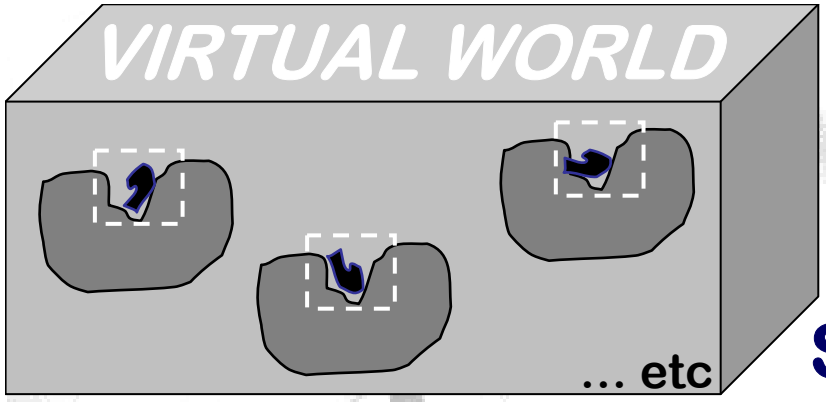
K_i = 23400 nM (h_A_{2A})



XRAY binding pose



GRAZIE
PER LA PAZIENZA



Some definitions:

	Translations (3N) Rotations (3N)	Conf. LIG	Conf. REC
RIGID			
SEMI-FLEXIBLE			
FLEXIBLE			

side-chains close to LIG