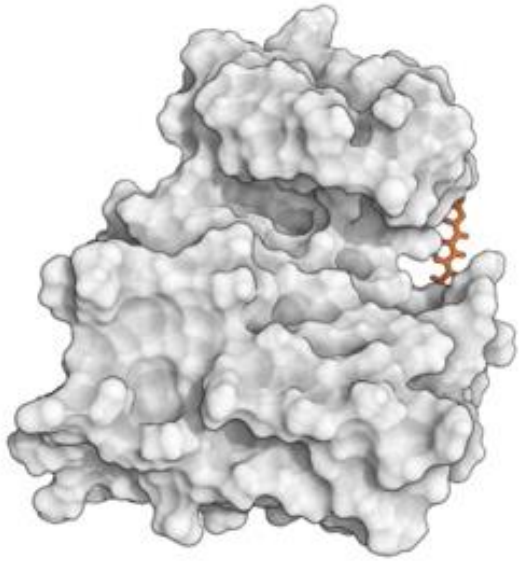
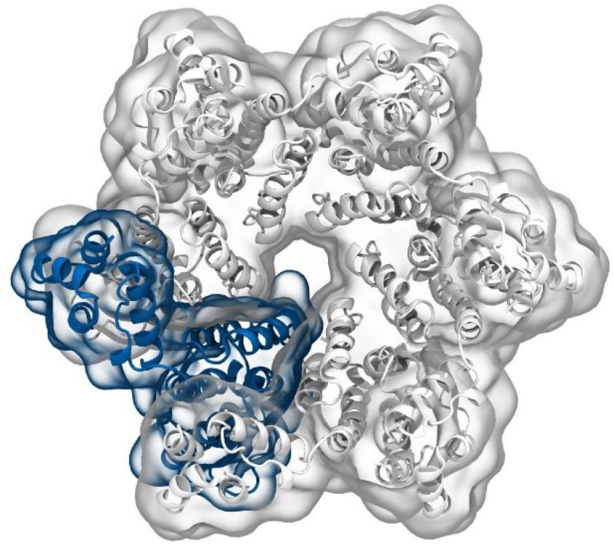
Simulation of Biomolecules



Docking



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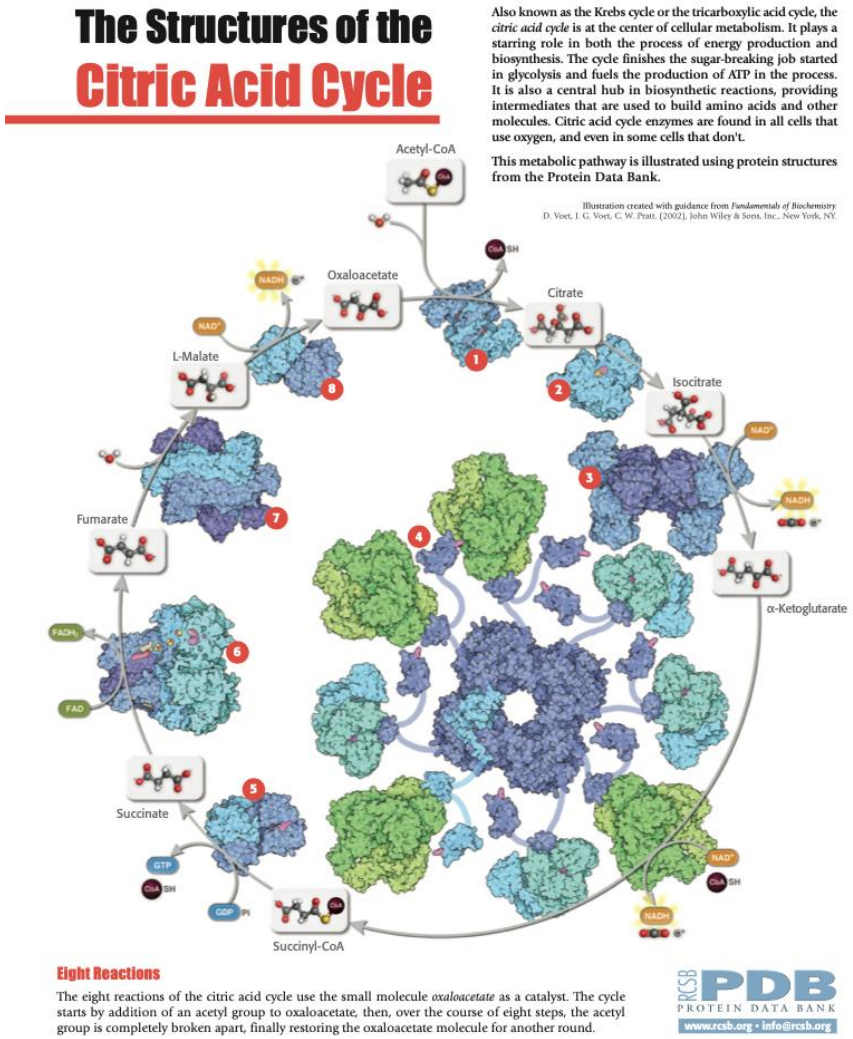
Life is built on protein and small molecule interactions



Small molecules are:

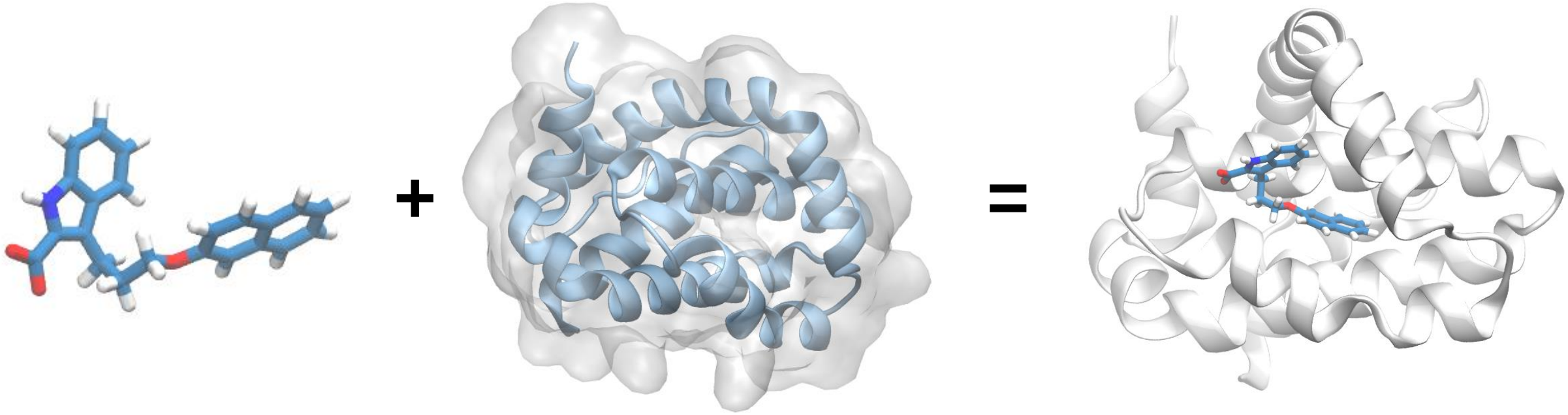
- substrates of enzymes
- Inhibitors or activators
- Co-factors

And play an important role in life. Accurate interaction prediction is essential.

What is docking?

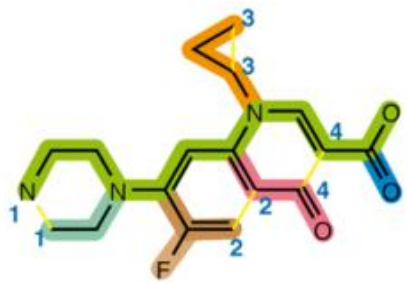
The process of predicting a stable 3D geometry of an interacting pair of molecules – **a binding mode/pose.**

Ligand **Receptor** **Binding pose**



Typical workflow

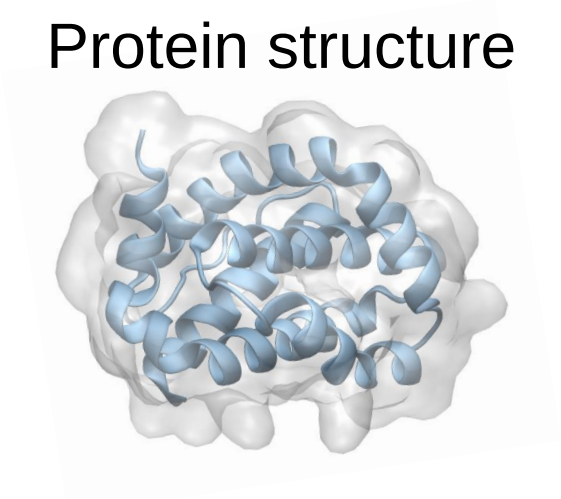
1-D or 2-D ligand structure

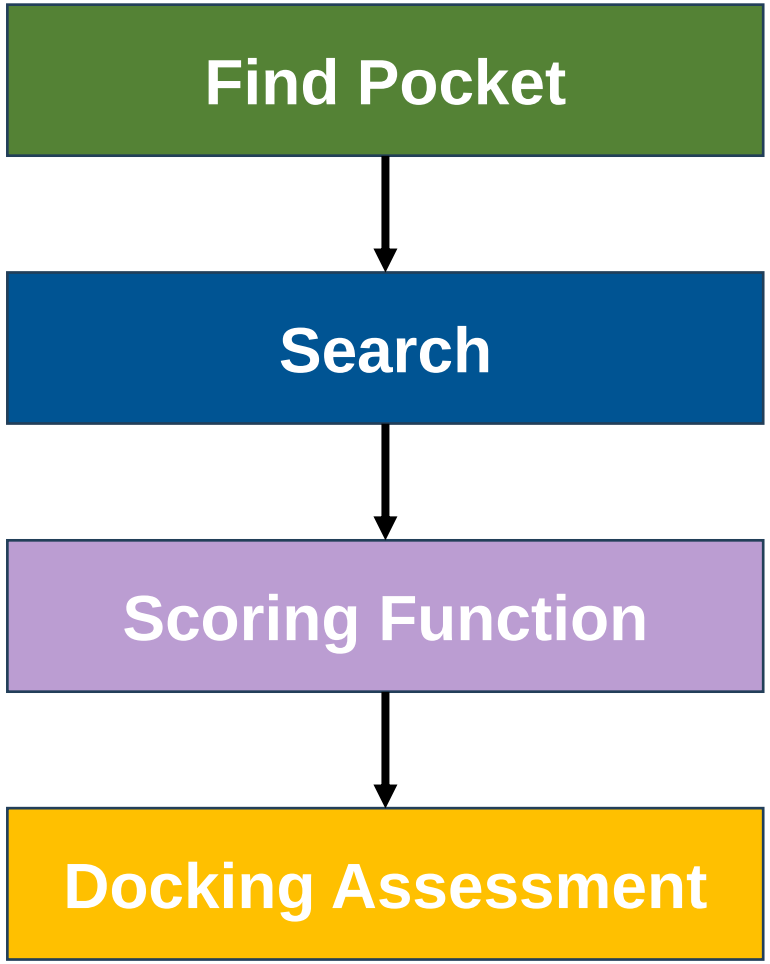


N1CCN(CC1)C(C(F)=C2)=CC(=C2C4=O)N(C3CC3)C=C4C(=O)O

+

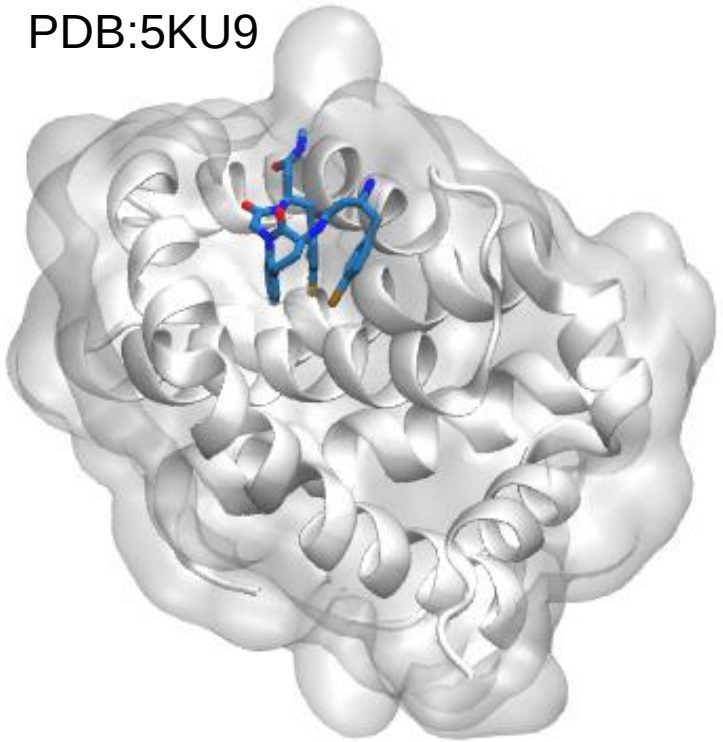
Protein structure



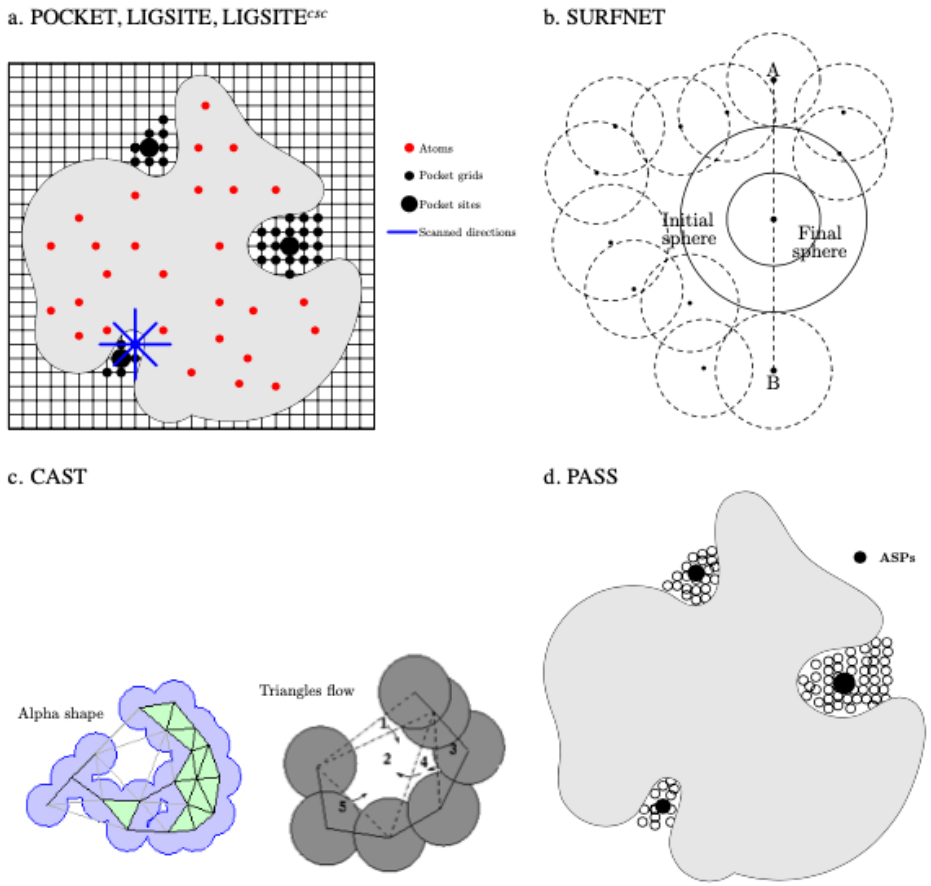


Finding a pocket

PDB:5KU9



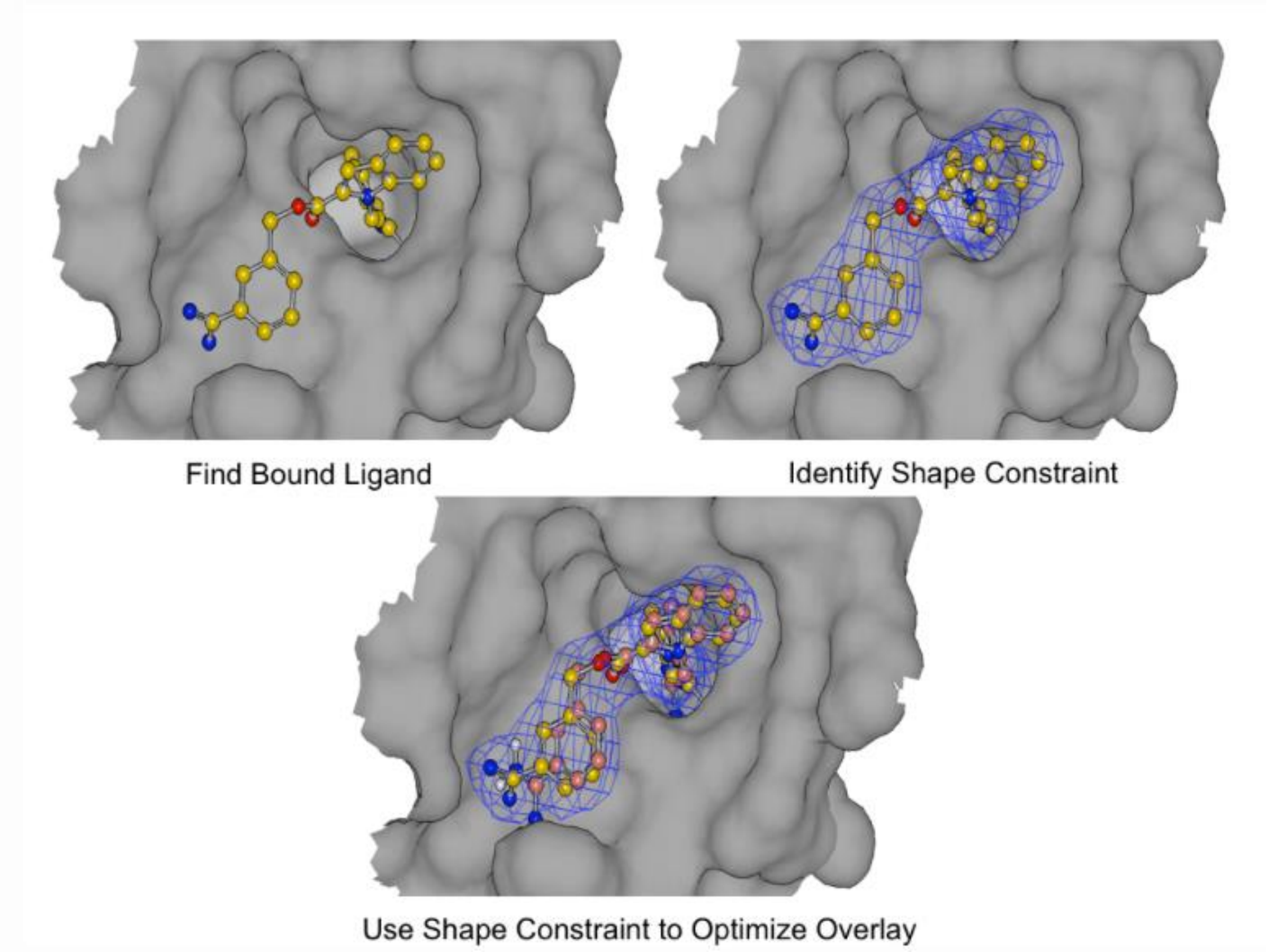
Using a reference atomic structure with an existing molecule bound



Using a pocket finding algorithm

BMC Structural Biology 2006, **6**:19 doi:10.1186/1472-6807-6-19

Shape based methods



With an existing ligand it is possible to match the shape and optimize the overlay

Fast and robust

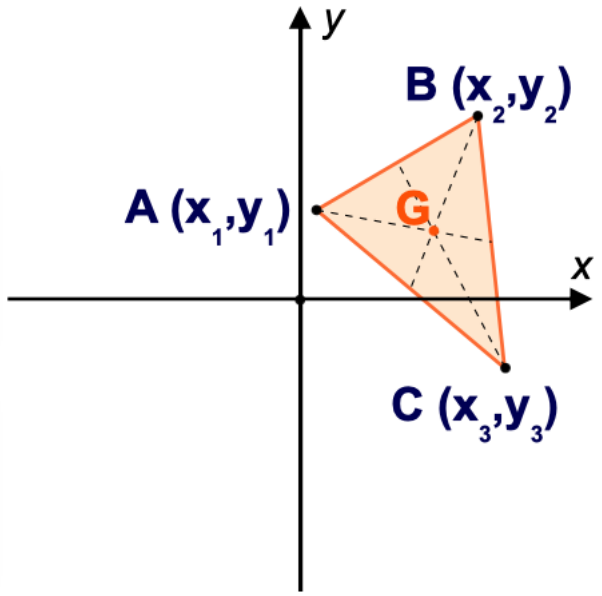
Ligand changes are not taken into account.

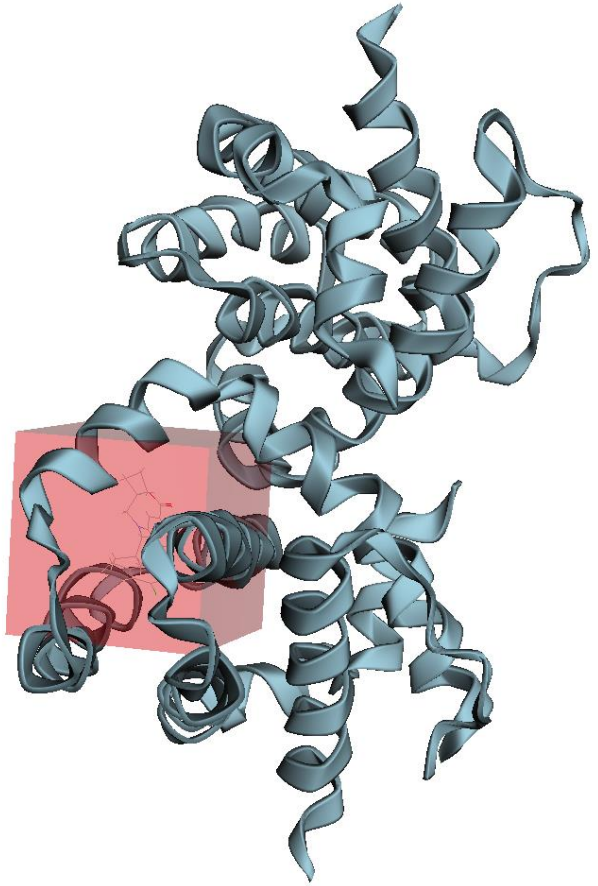
Ligands need to be of similar size.

https://docs.eyesopen.com/applications/oedocking/theory/posit_theory.html#posit-heat-map

Finding the docking grid area

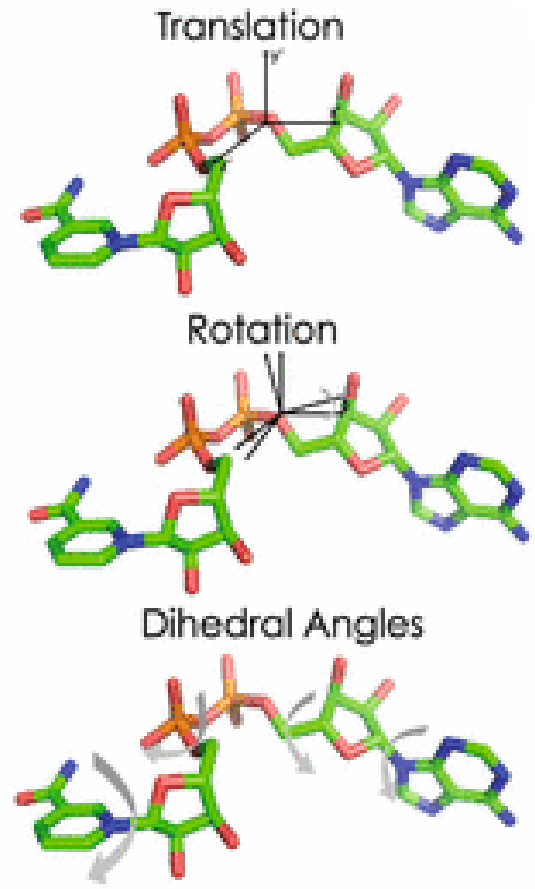
Often you have a ligand template or binding site residue to help with designing the docking grid



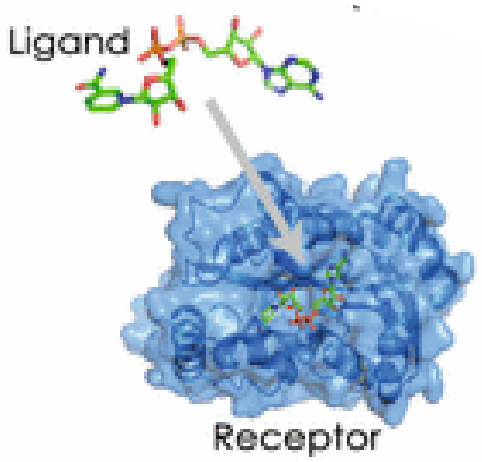


Use centre of geometry of a molecule from structure

Genetic algorithm for ligand conformers

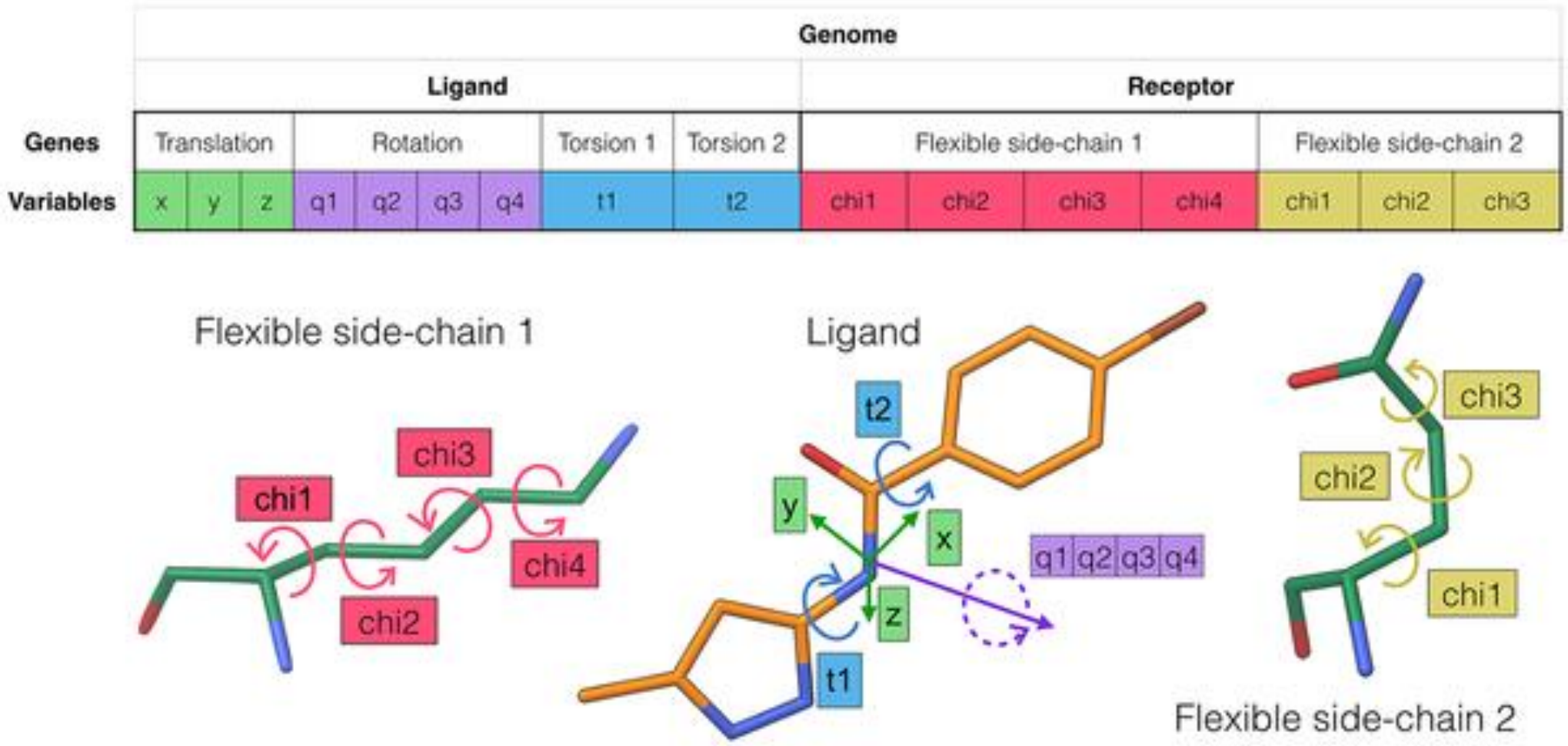


Testing different arrangements of the ligand in the rigid binding site of the protein

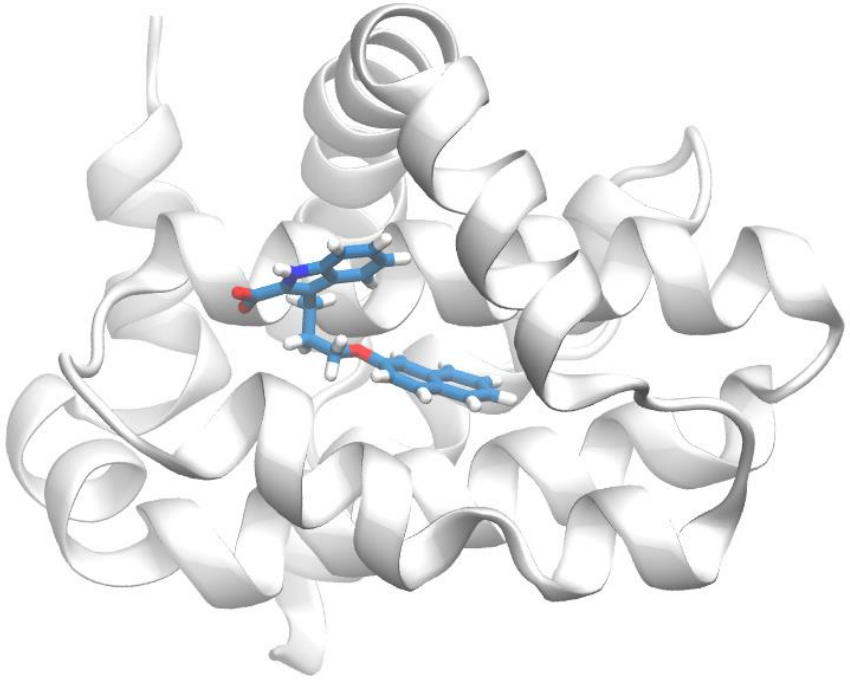


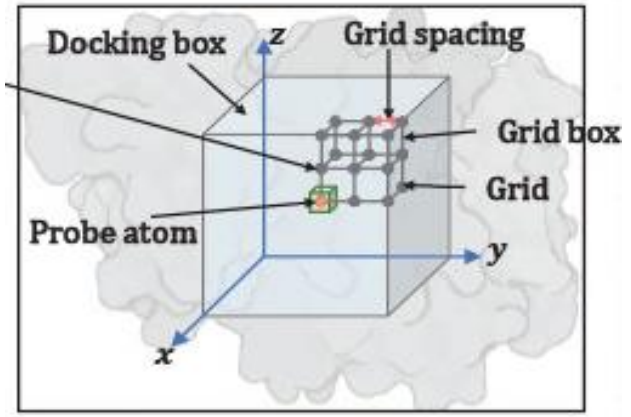
Soft Comput **23**, 4155–4176 (2019).

Allowing protein and ligand flexibility is often better

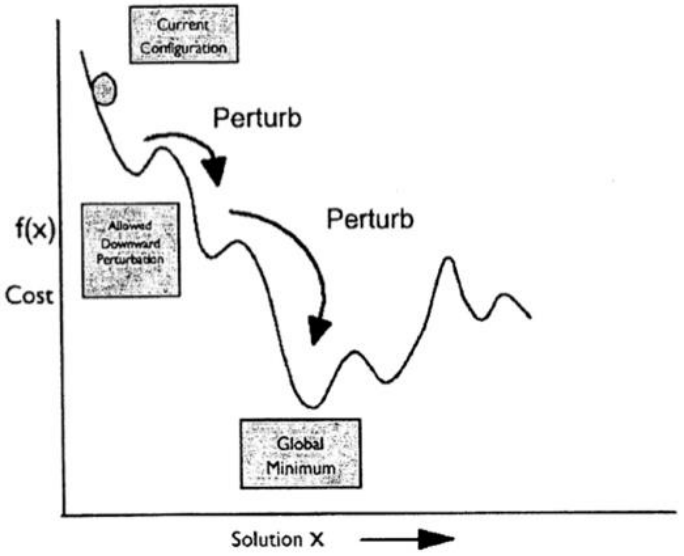


Flexibility increases compute time





Simulated annealing



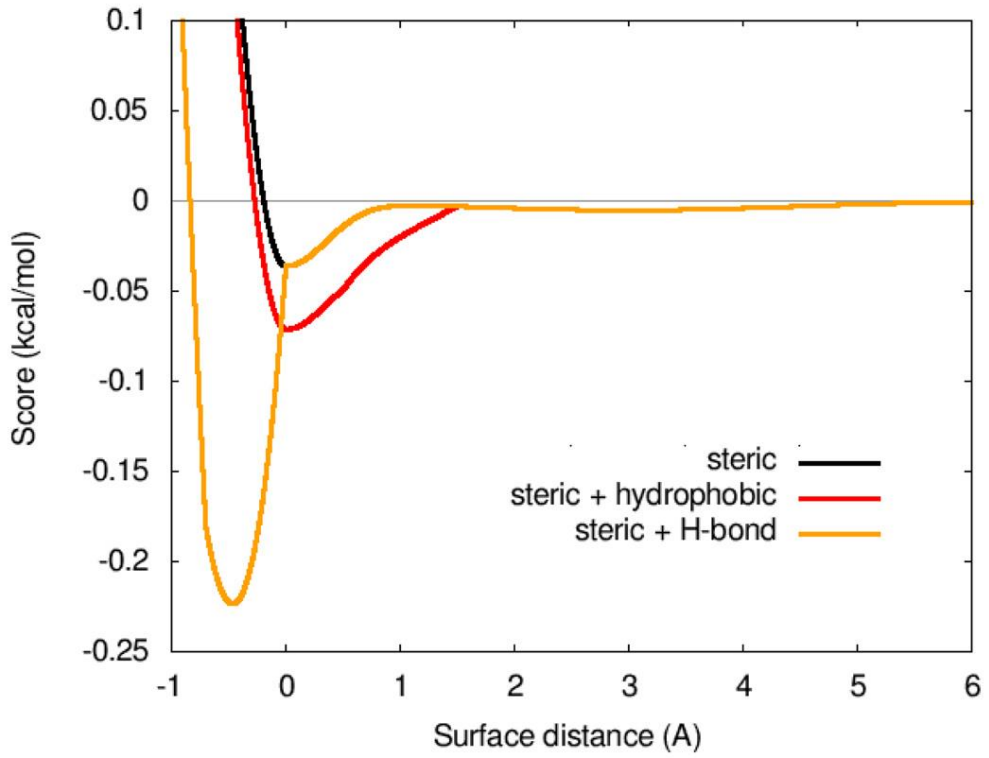
N=T360/i
N: number of conformations
T: number of rotable bonds
I: incremental degrees

Typical drug molecule
10 rotable bonds
30º increments (discrete)
10^{12} plausible conformations!

J. Chem. Inf. Model., **63**, 7, 1982–1998 (2023)

https://sgt.cnag.cat/www/presentations/files/slides/20110112_Docking.pdf

Scoring functions



Scoring functions can be used beyond shape optimization to optimize ligand and protein interactions

$$\Delta G = \left(V_{bonded}^{L-L} - V_{unbonded}^{L-L}\right) + \left(V_{bonded}^{R-R} - V_{unbonded}^{R-R}\right) + \left(V_{bonded}^{R-L} - V_{unbonded}^{R-L} + \Delta G_{conf}\right)$$

$$V = W_{vdw} \sum_{i,j} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}}\right) + W_{hbond} \sum_{i,j} E(t) \left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}}\right) + W_{elec} \sum_{i,j} \frac{q_i qj}{\epsilon(r_{ij}) r_{ij}} + W_{sol} \sum_{i,j} (S_i V_j + S_j V_i) e^{\frac{-r_{ij}^2}{2\sigma^2}}$$

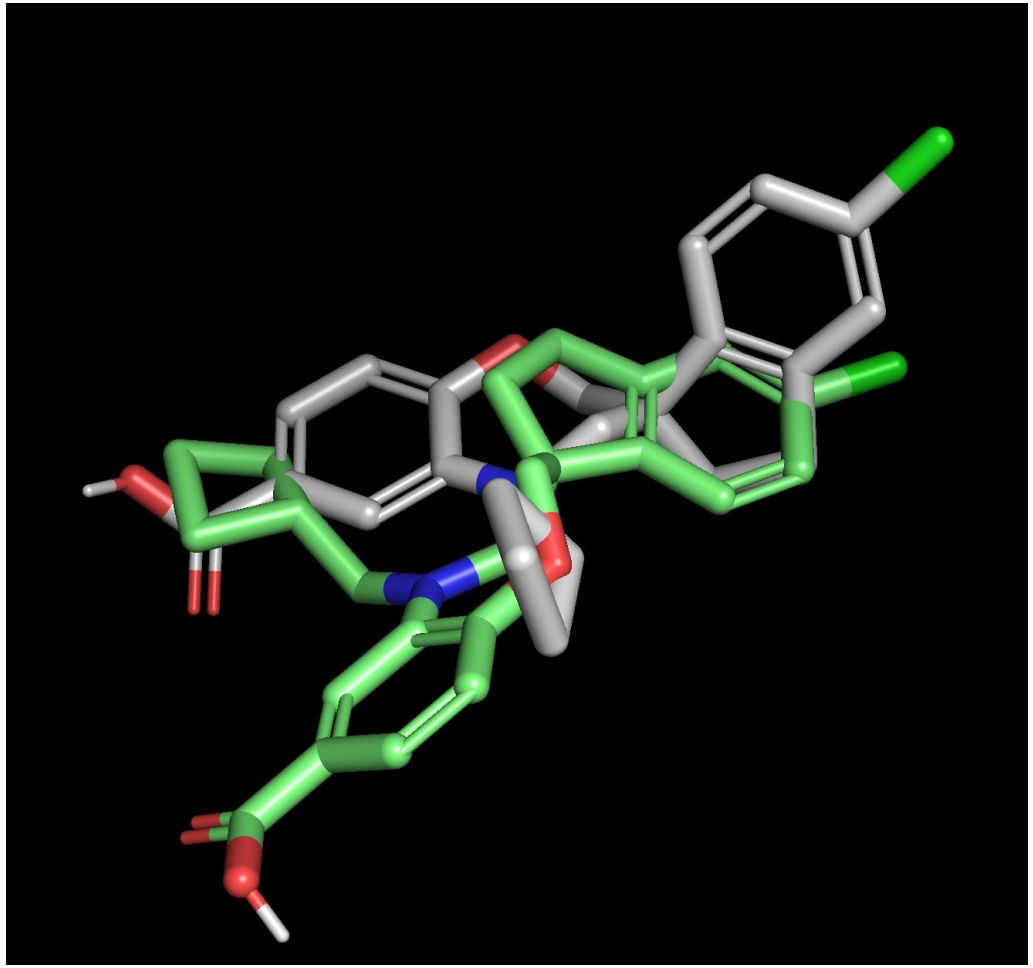
$$\Delta G_{conf} = W_{conf} N_{tors}$$

J. Comput Chem. **31(2)**: 455–461 (2010)

Soft Comput **23**, 4155–4176 (2019).

Typical docking output generates multiple poses

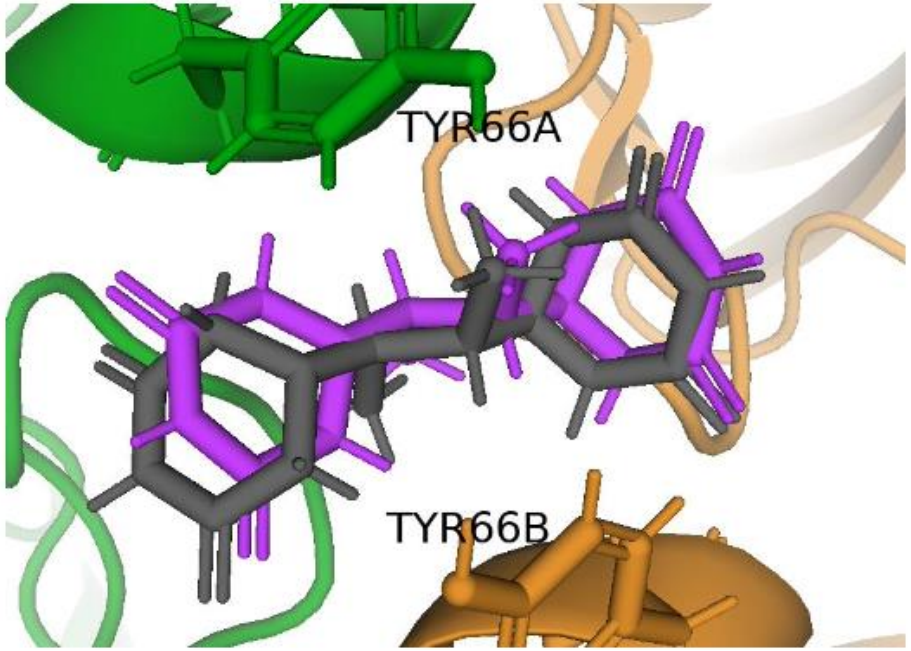
mode	affinity (kcal/mol)	dist from best mode rmsd l.b.	rmsd u.b.
1	-8.36	0	0
2	-8.08	2.899	6.789
3	-7.985	3.643	7.852
4	-7.914	3.415	5.21
5	-7.765	2.167	2.826



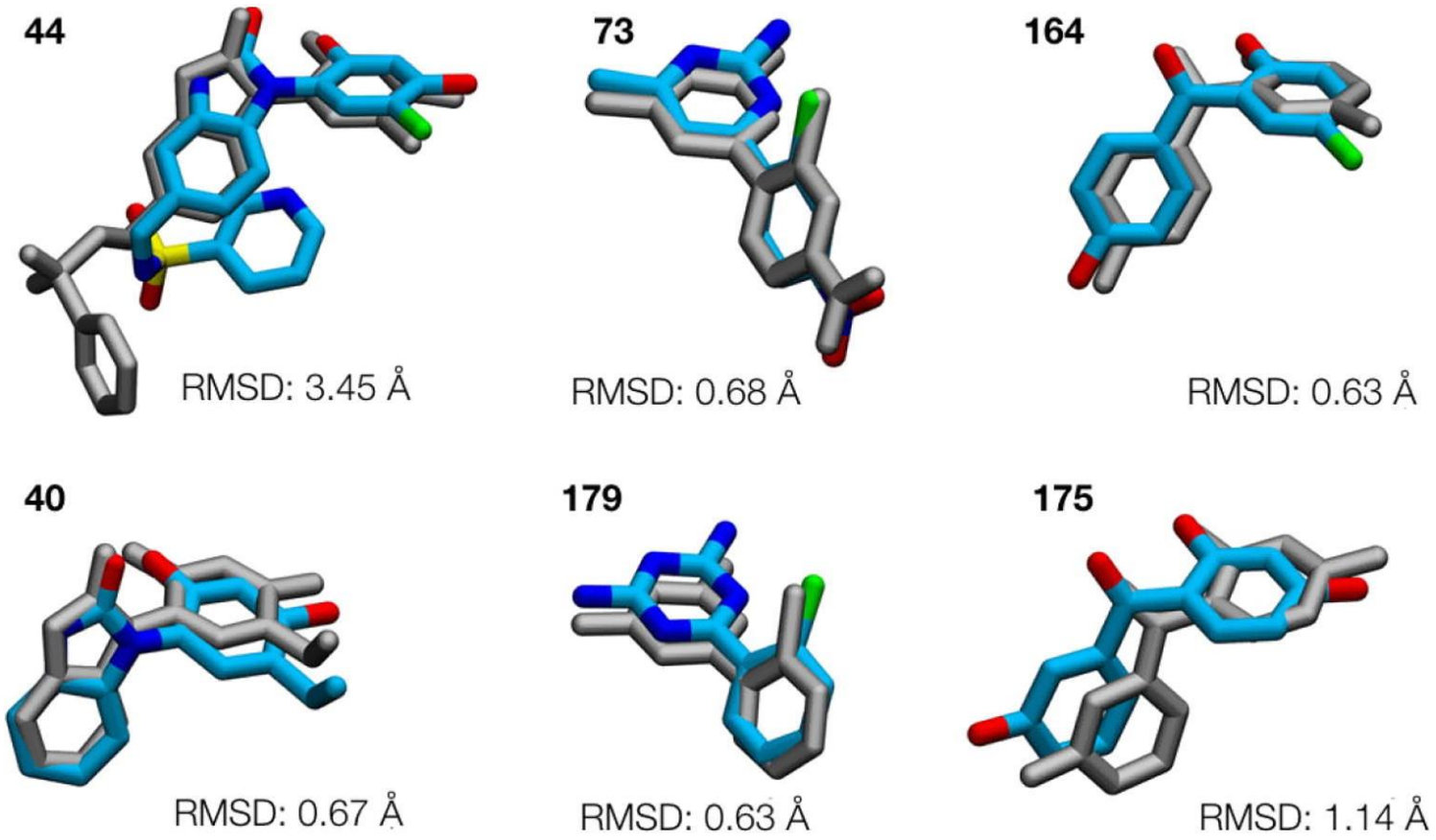
How good is my docking pose?

- Let a ligand with *N* atoms, an experimental reference structure x_o, and a predicted pose x_1.
- The *pose accuracy* is quantified with the Root Mean Square Deviation (RMSD):

$$RMSD = \sqrt{\frac{1}{N}\sum_{i=0}^{N}(x_1 - x_0)^2}$$

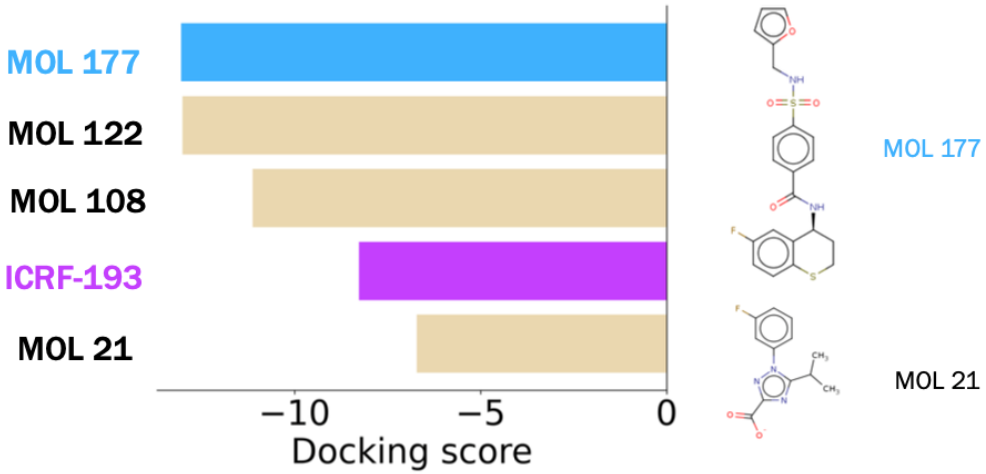


Examples of docking poses

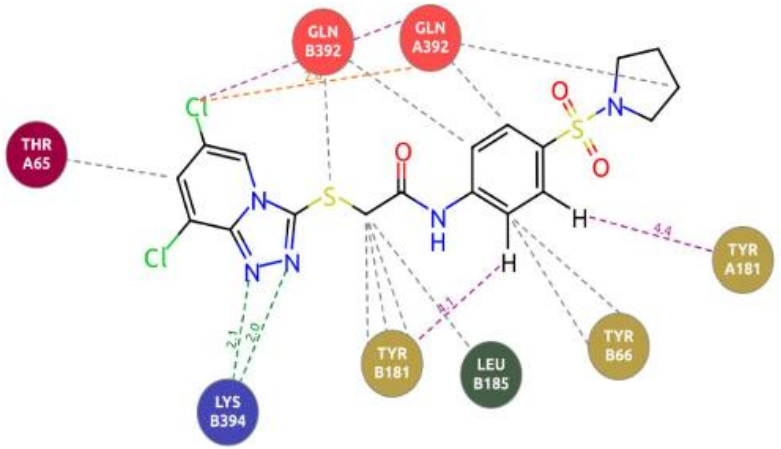


Bioorganic & Medicinal Chemistry Volume 24, Issue 20, 15 October 2016, Pages 4890-4899

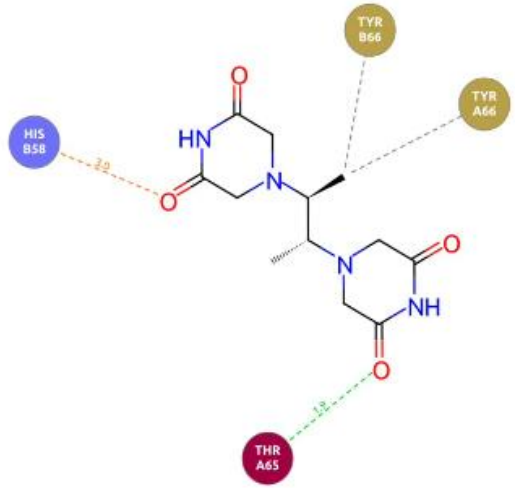
How good is my docking pose?



- The *score* gives a metric on how well the ligand can be expected to bind to the pocket
- Interaction diagrams show favourable interactions and clashes

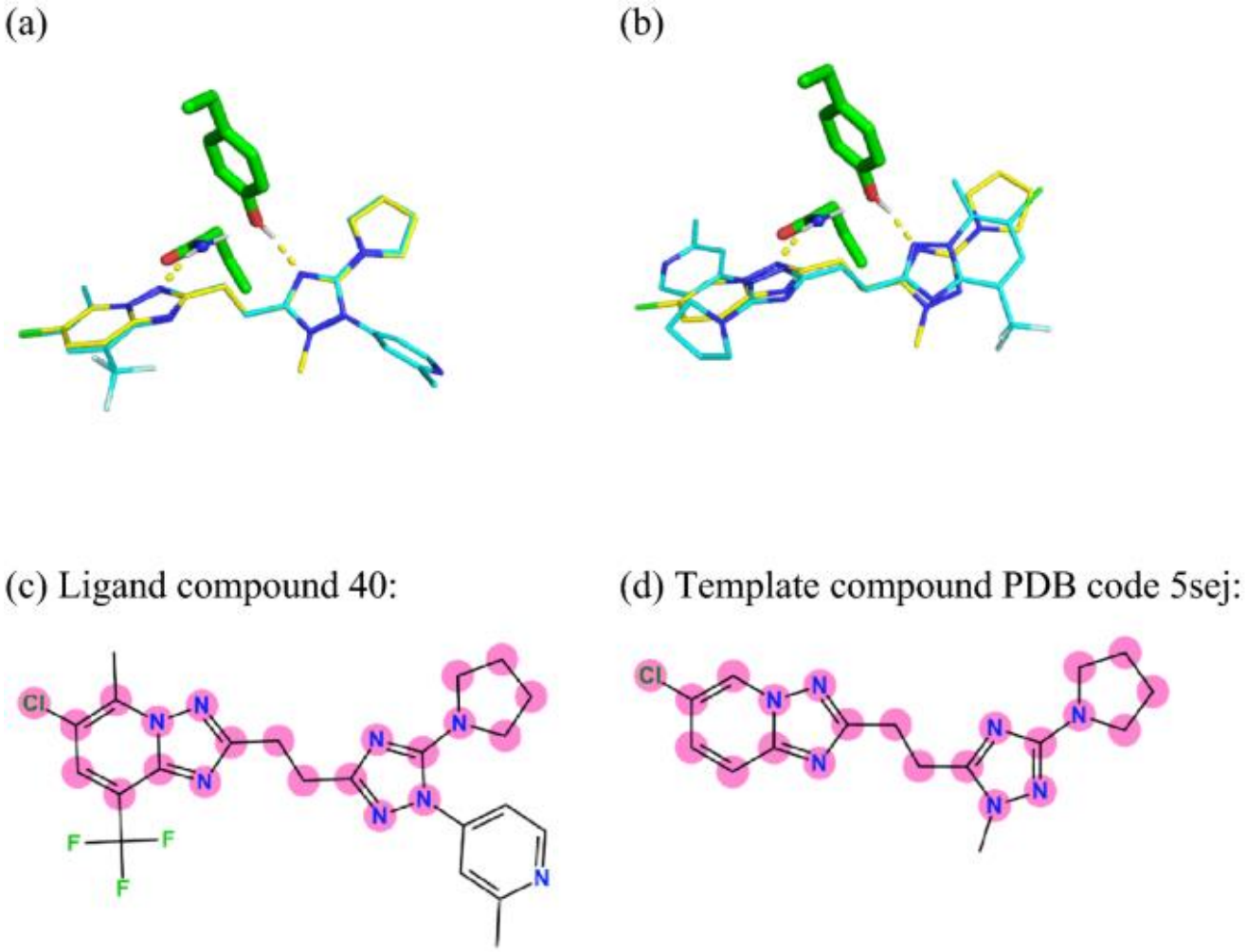


Contact map MOL-177



Contact map ICRF-193

Template docking and cross docking improves docking

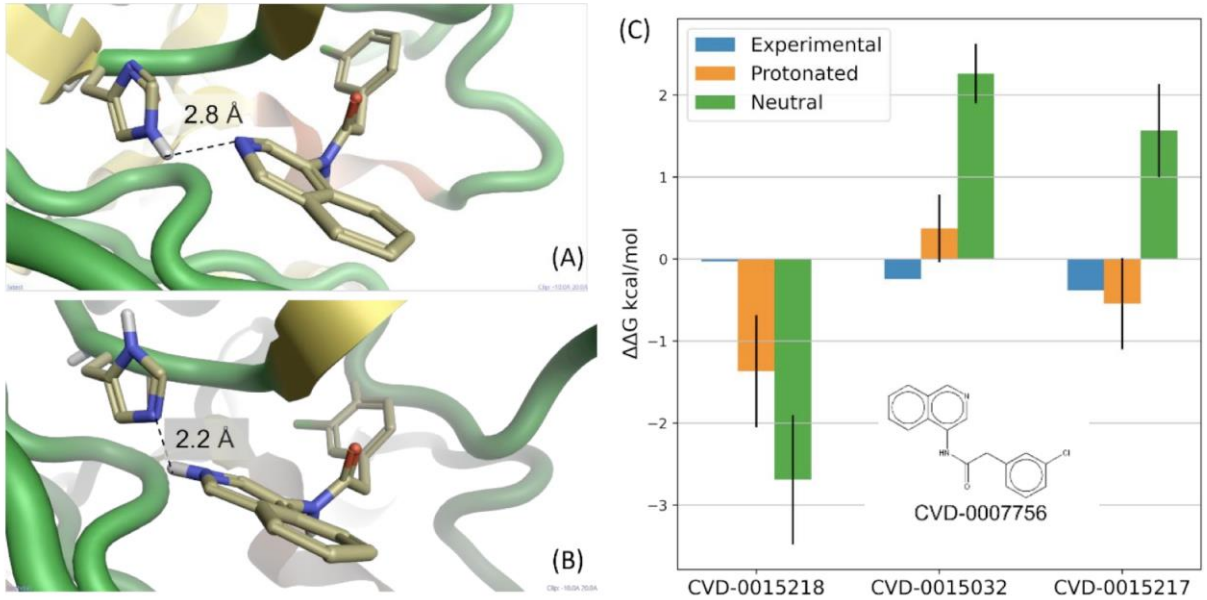


- Dock the same ligand into multiple protein structures (X-ray, MD)
- Generate multiple ligand conformers and dock into multiple structures
- Use existing ligand data as a template or guide e.g. through Maximum common substructure

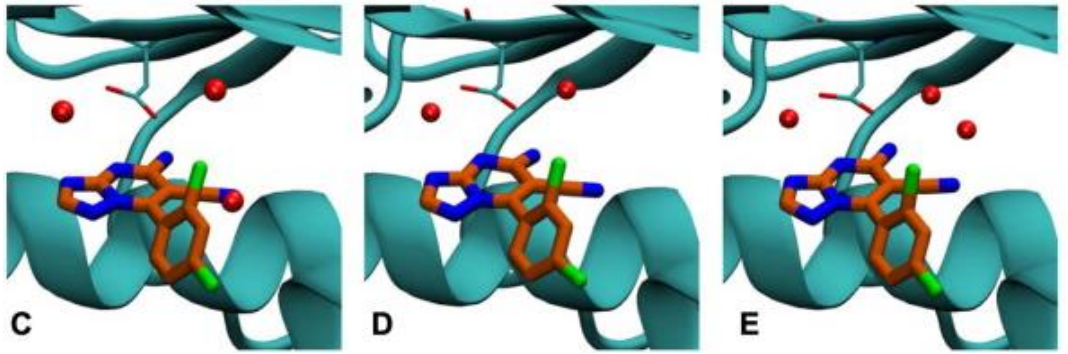
J Comput Aided Mol Des **36**, 753–765 (2022)

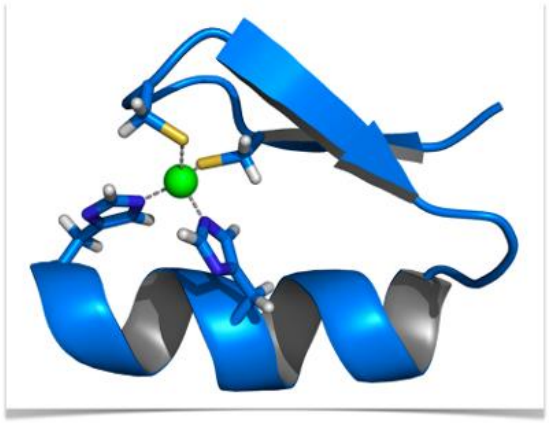
Things to worry about

pKa of ligands and binding site protonation need to be considered



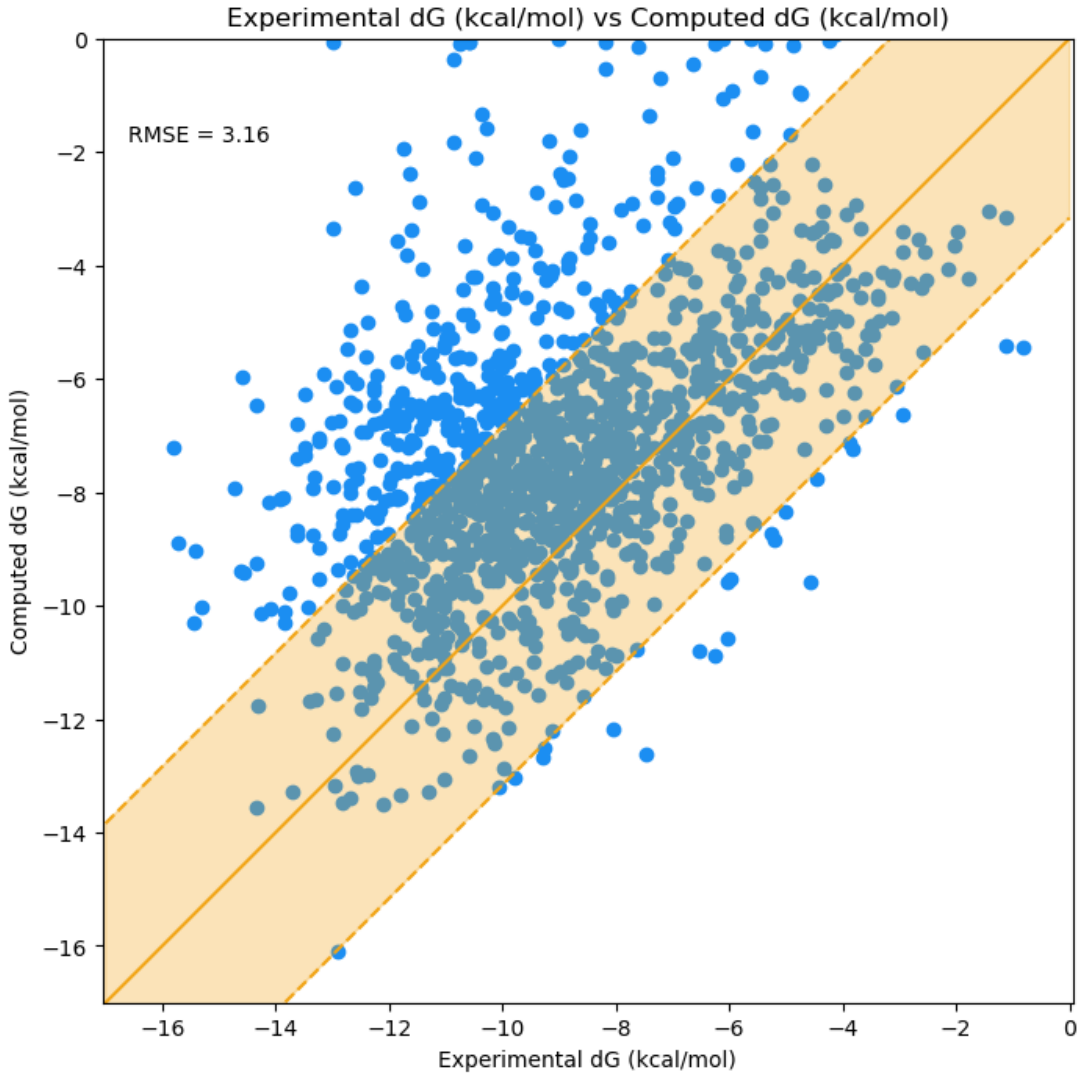
Structural waters are important



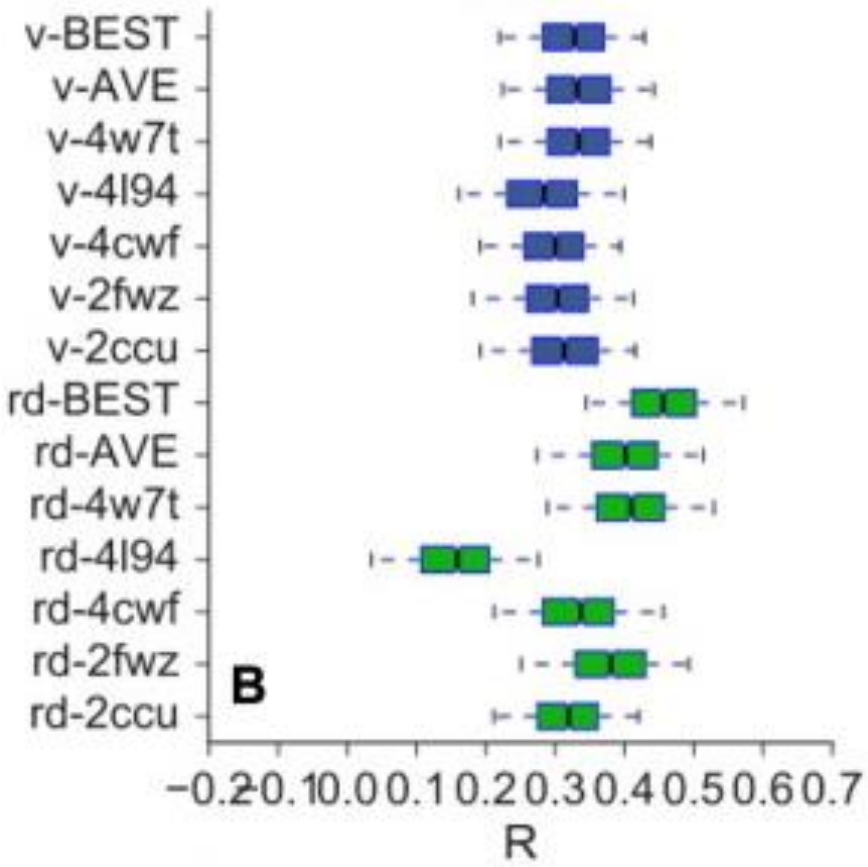


Co-factors such as ions and other molecules are important

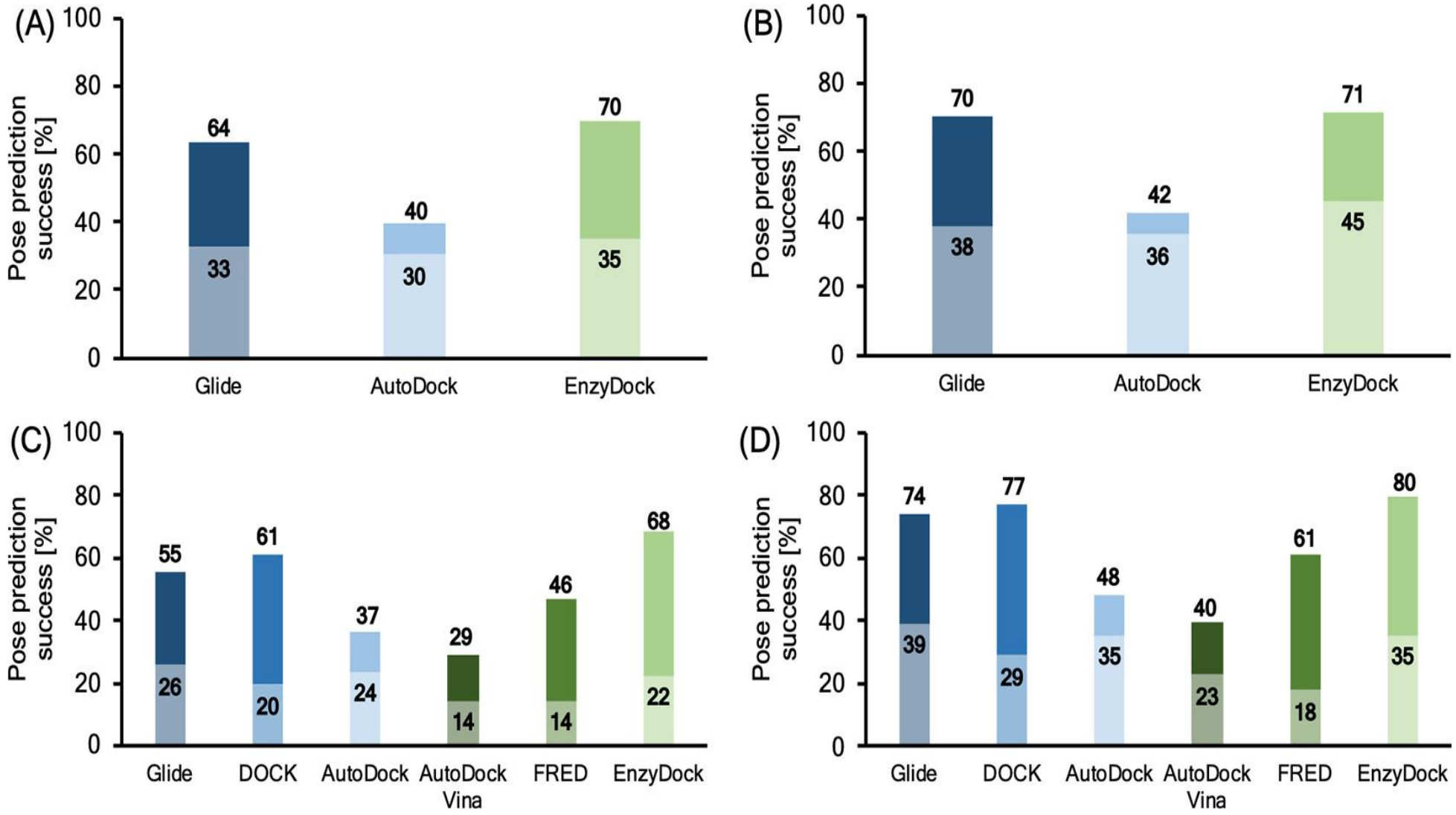
Comparing against experimental ΔG



Bulk assessment of correlation coefficient

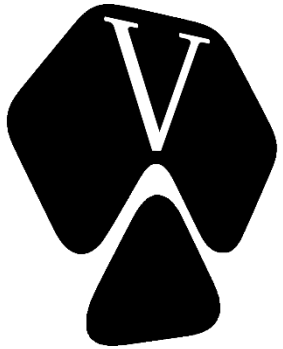


Recent docking benchmark



J. Chem. Inf. Model. 2021, 61, 6, 2957–2966

What tools exist for molecular docking?



Autodock Vina

rDock

OPEN-SOURCE

Glide

SCHRÖDINGER
Maestro

OpenEye
SCIENTIFIC

MOE
MOLECULAR OPERATING ENVIROMENT

flare

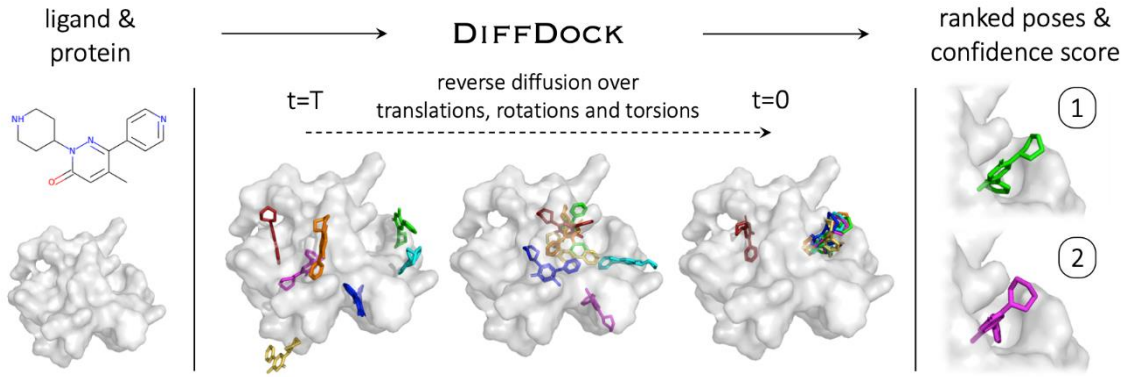
everyday drug design dashboard
SeeSAR

CCDC

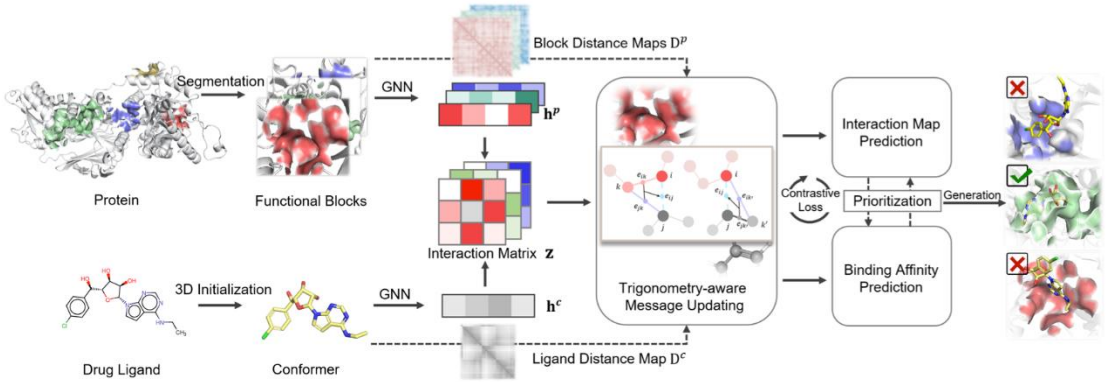
And others…

ML-based docking

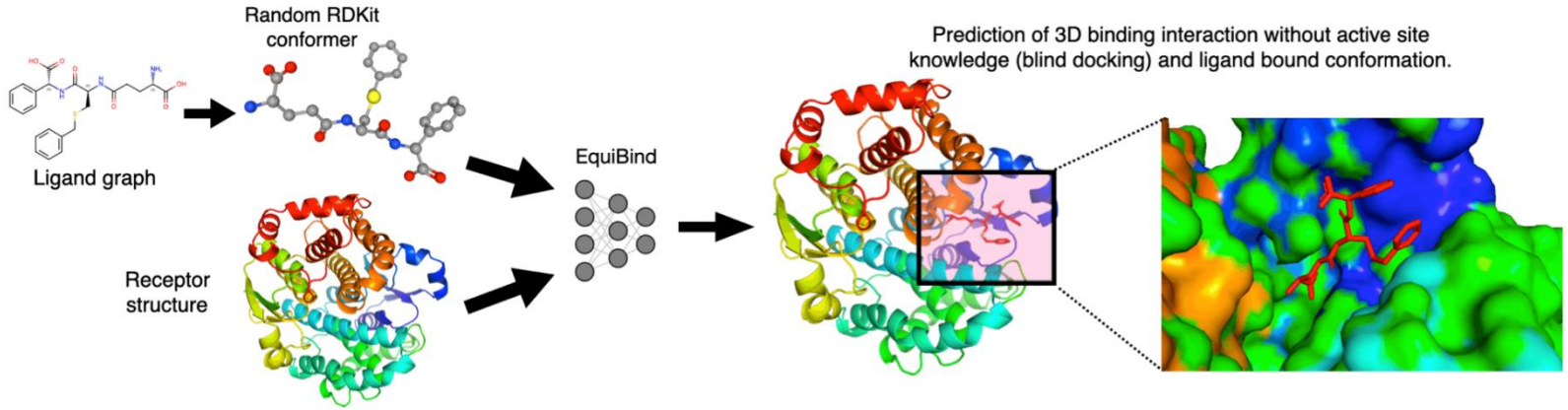
Diffdock



TankBind



Equibind



Gnina

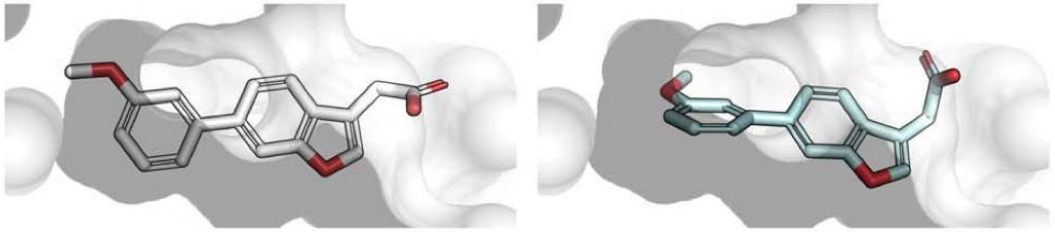
Deepdock

…

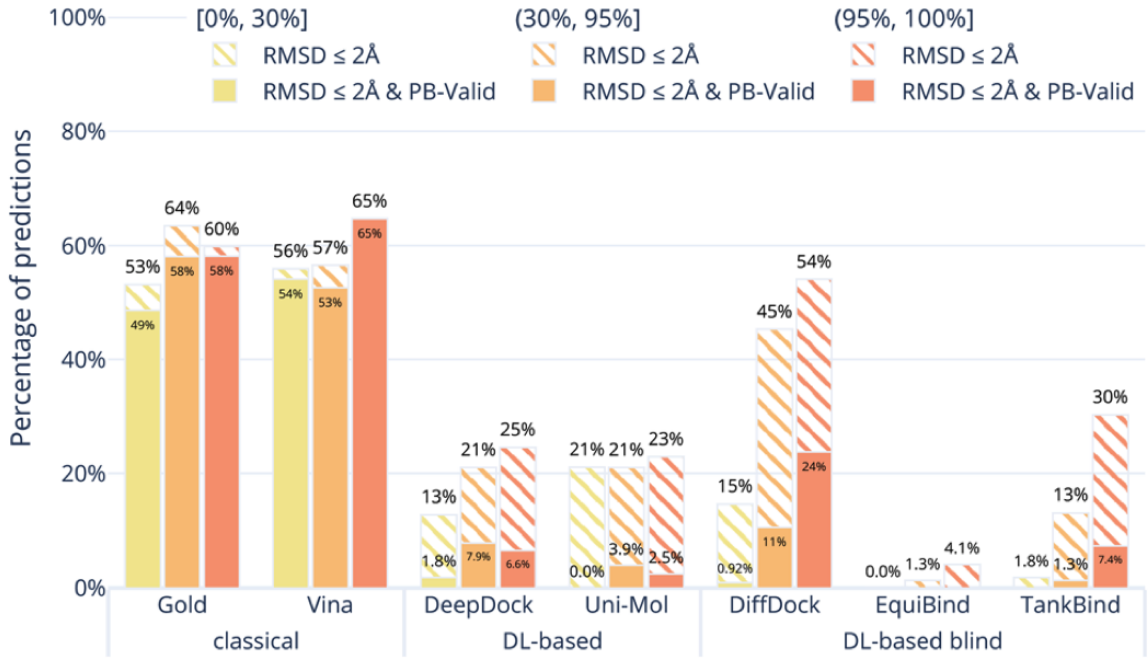
Evaluating the binding mode/pose of ML tools

(f) Double bond not flat. TankBind prediction for ligand DBQ of protein-ligand complex 1U4D. RMSD 1.7 Å.

(g) Energy ratio too high. AutoDock Vina prediction for ligand IFM of protein-ligand complex 7LOU. RMSD 1.9 Å.



(h) Clash with protein. DiffDock prediction for ligand XQ1 of protein-ligand complex 7L7C. RMSD 1.6 Å.



PoseBuster: *Chem. Sci.*,**15**, 3130-3139 (2024)