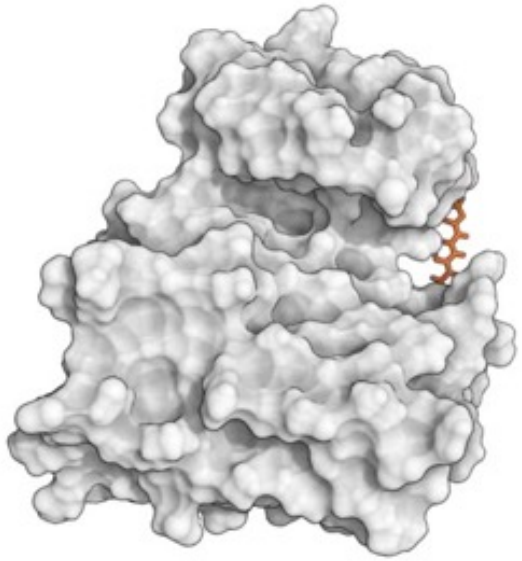
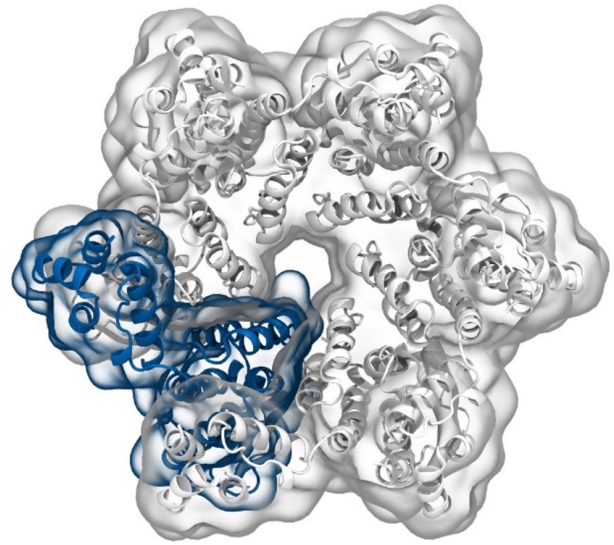
Simulation of Biomolecules



Docking

2024 CCP5 Summer School



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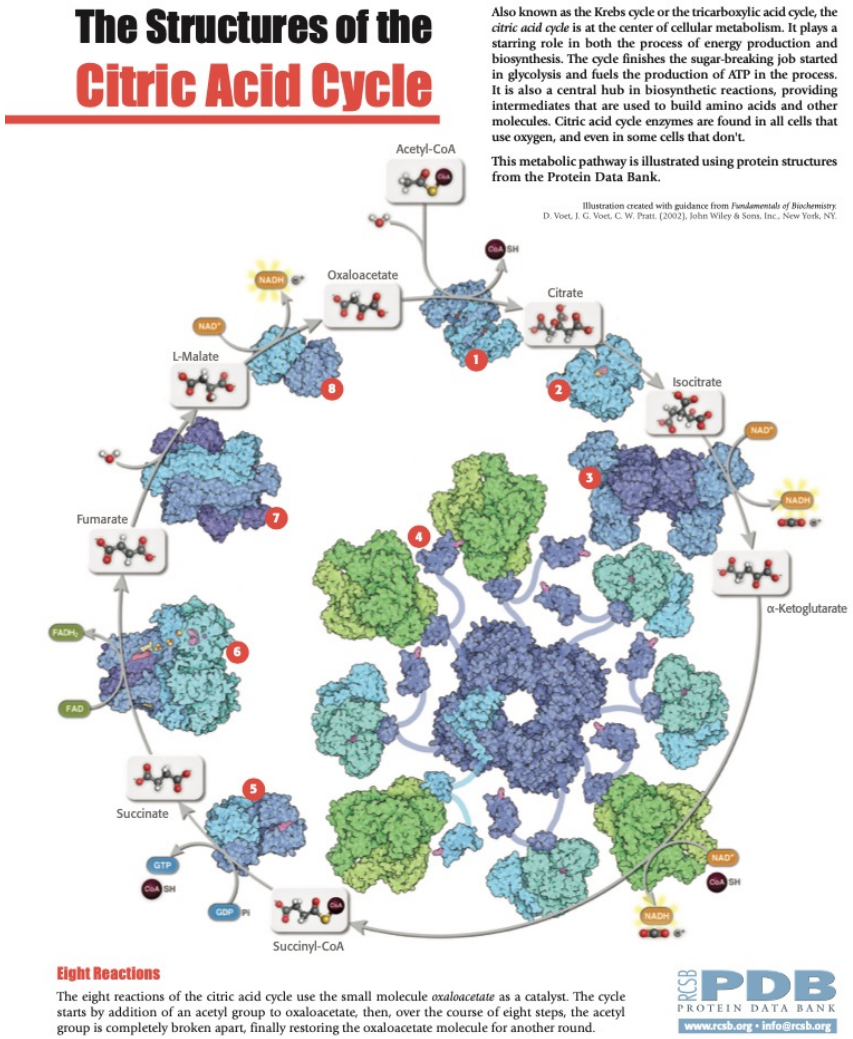
Life is built on protein and small molecule interactions



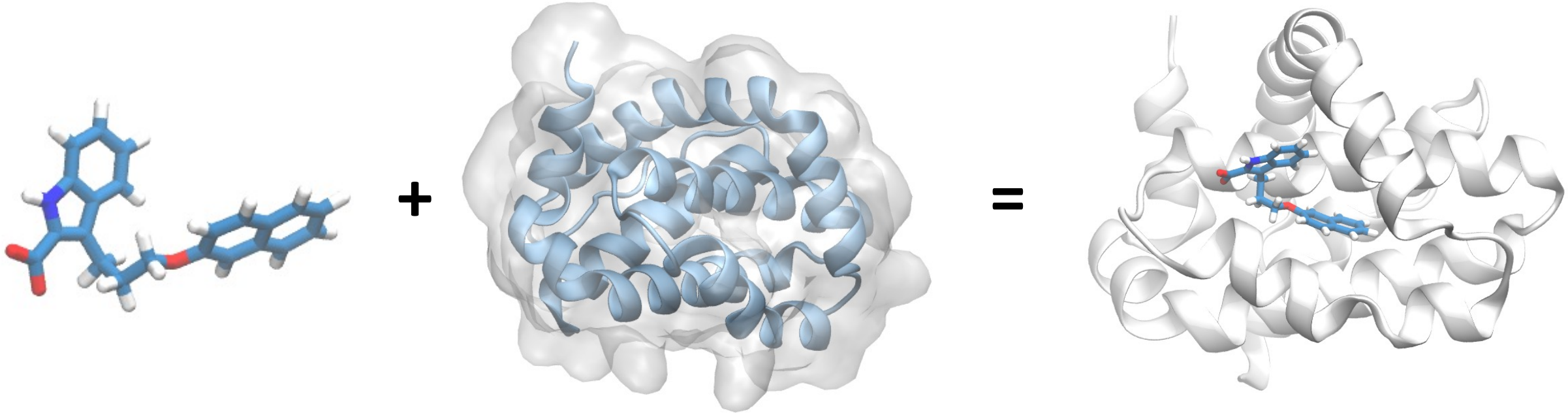
Small molecules are:

- 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.**



Nomenclature

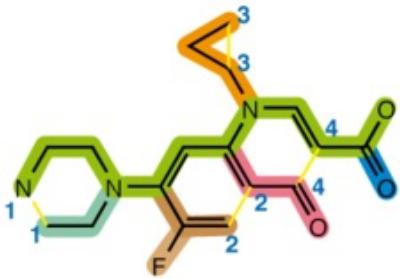
Ligand: Structure (usually a small molecule) that binds to the binding site.

Receptor: Structure (usually a protein) that contains the active binding site.

Binding site: Set of aminoacids (residues) that physically interact with the lingad (usually within 6 Ångstroms).

Typical workflow

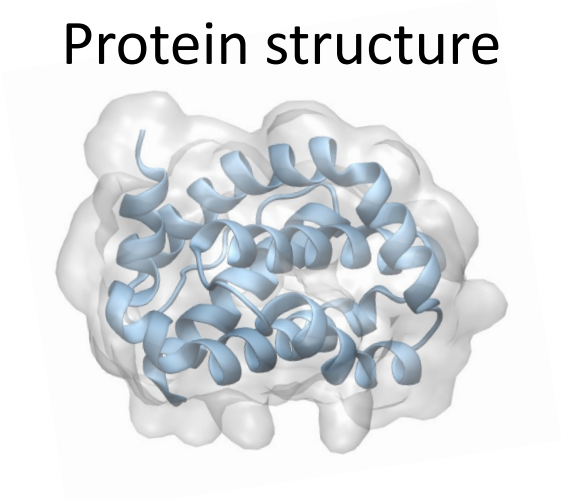
1-D or 2-D ligand structure

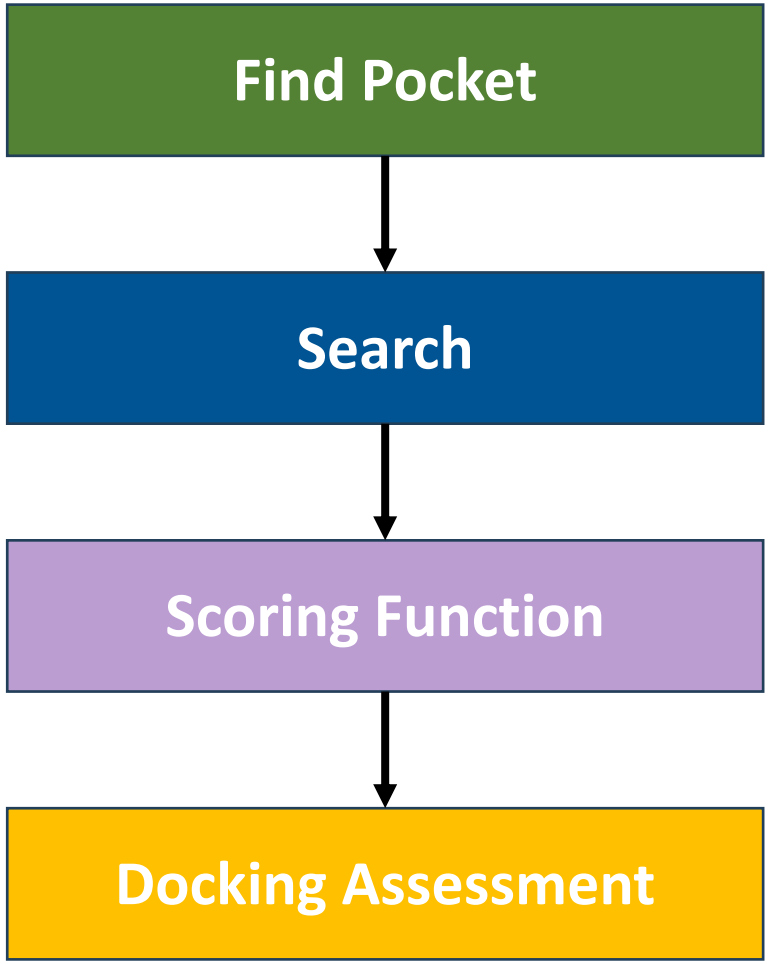


N1CCN(CC1)C(C(F)=C2)=CC(=C2C4=O)N(C3CC3)C=C4C(=O)O

+

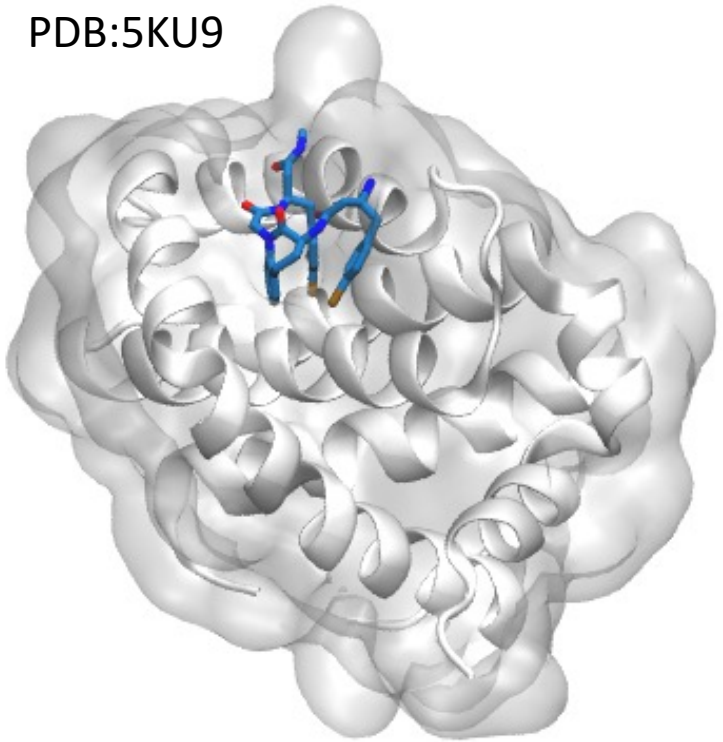
Protein structure



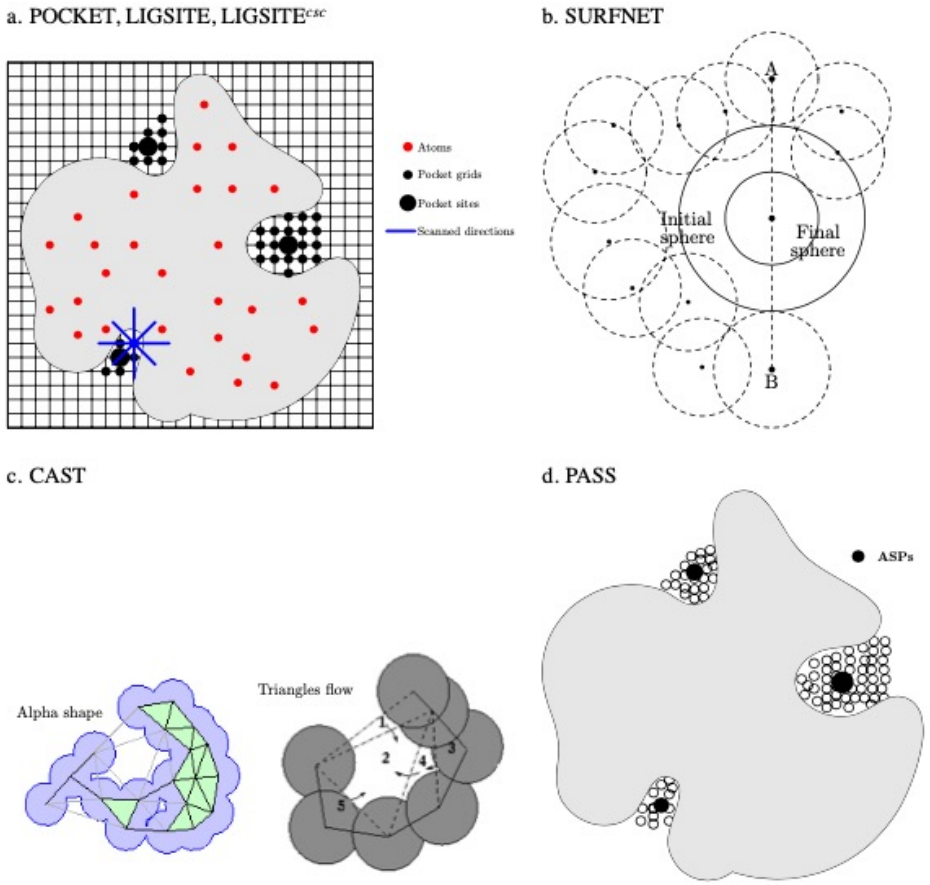


Finding a pocket

PDB:5KU9



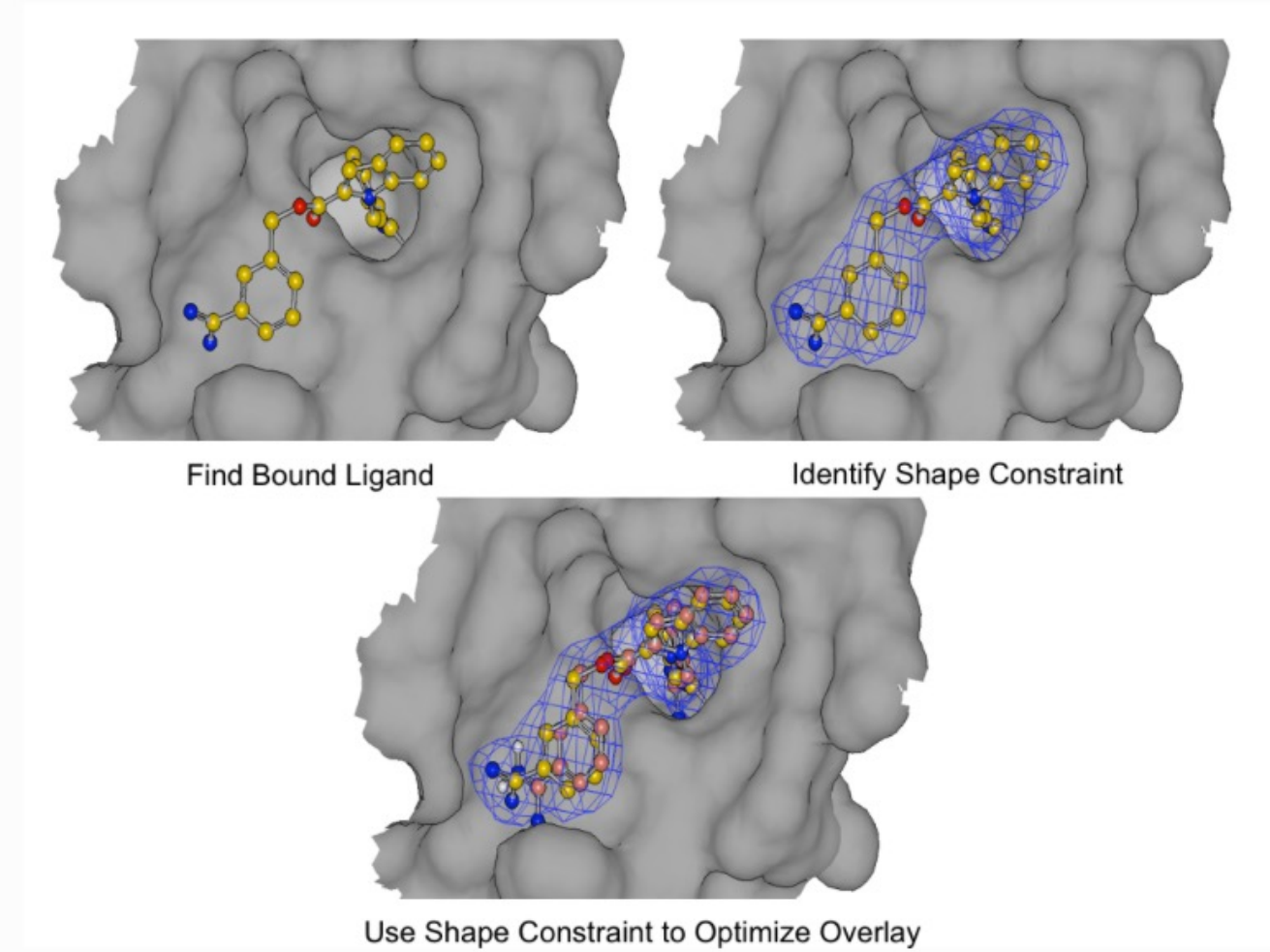
Using a reference atomic structure with an existing molecule bound



Using a pocket finding algorithm

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

Shape based methods



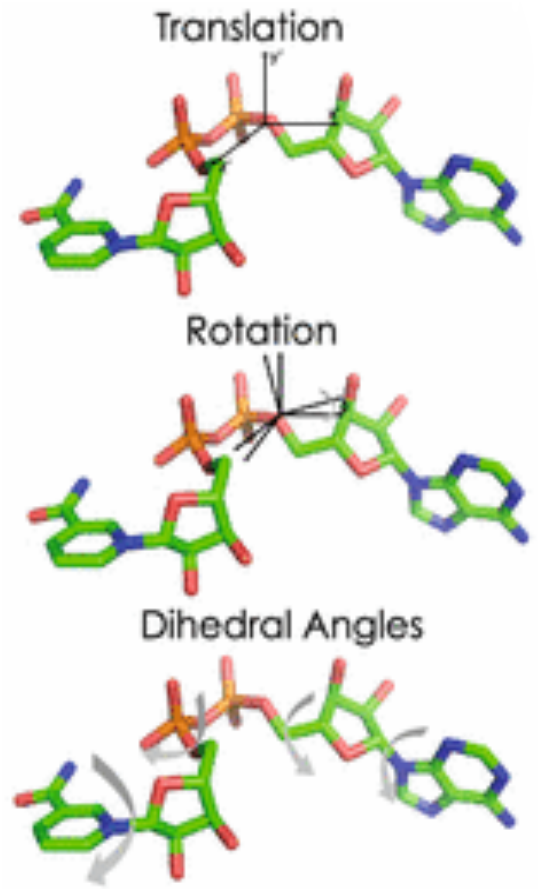
With an existing ligand it is possible to match the shape and optimize the overlay

Fast and robust

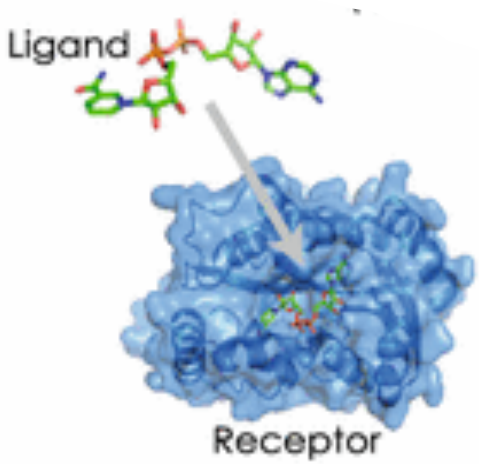
Ligand changes are not taken into account

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

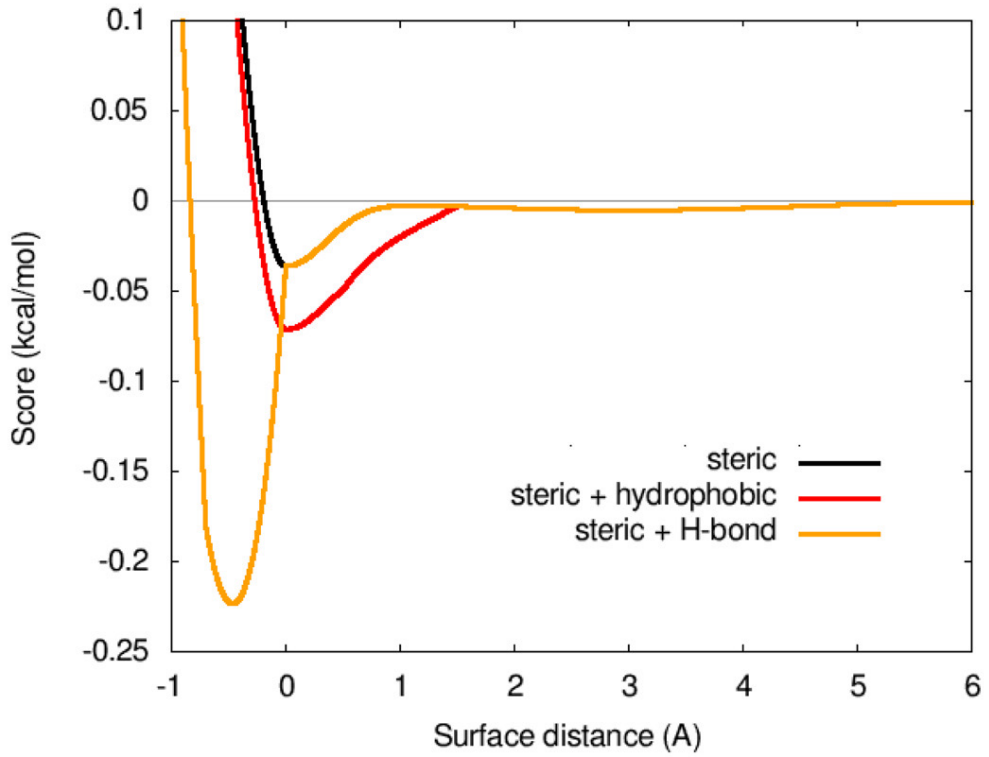
Genetic algorithm for ligand conformers



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



Scoring functions



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

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

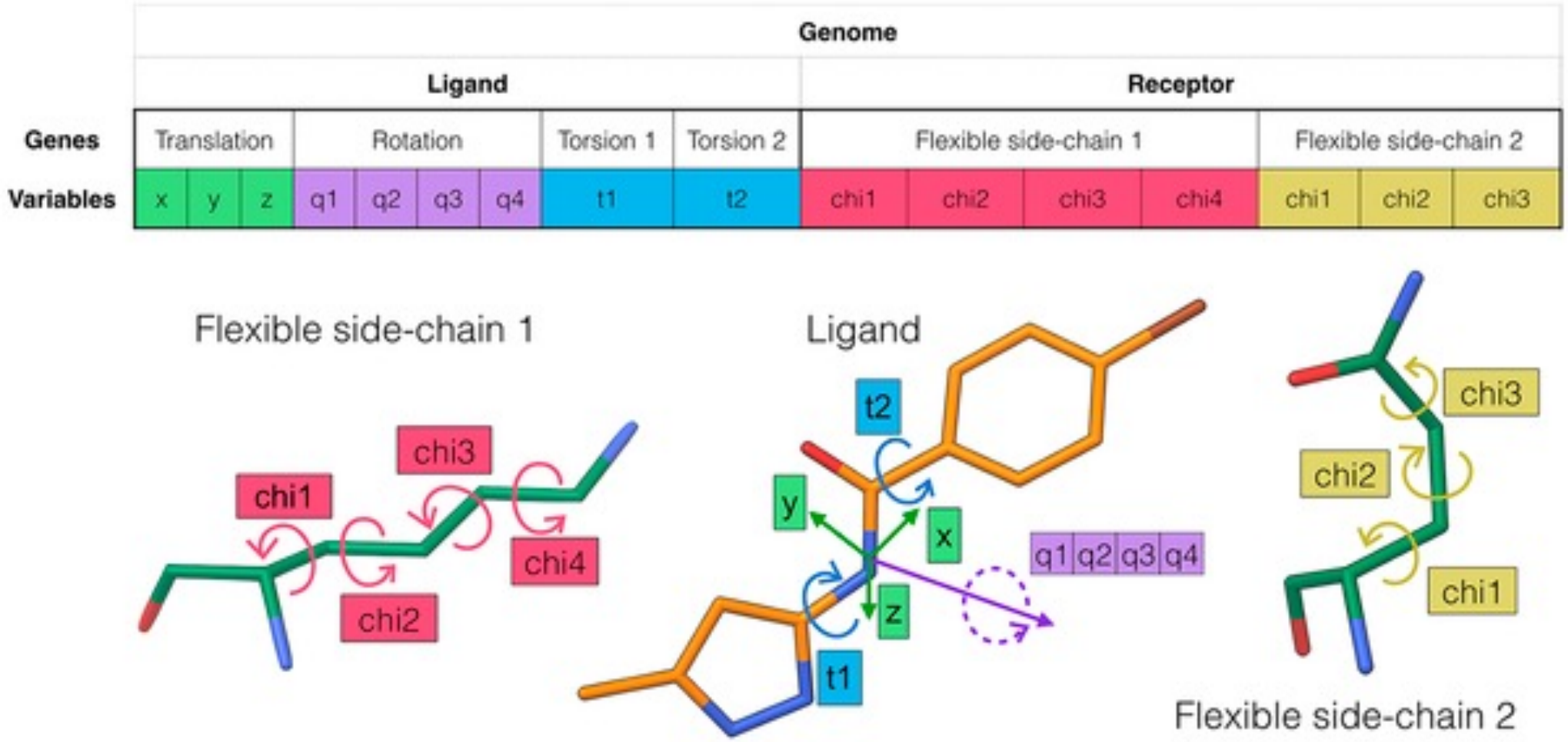
$$V = W_{vdw} \sum_{i,j} \left(\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^{6}}\right) + W_{hbond} \sum_{i,j} E(t) \left(\frac{C_{ij}}{r_{ij}^{12}} - \frac{D_{ij}}{r_{ij}^{10}}\right) + W_{elec} \sum_{i,j} \frac{q_i qj}{\epsilon(r_{ij}) r_{ij}} + W_{sol} \sum_{i,j} (S_i V_j + S_j V_i) e^{\frac{-r_{ij}^2}{2\sigma^2}}$$

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

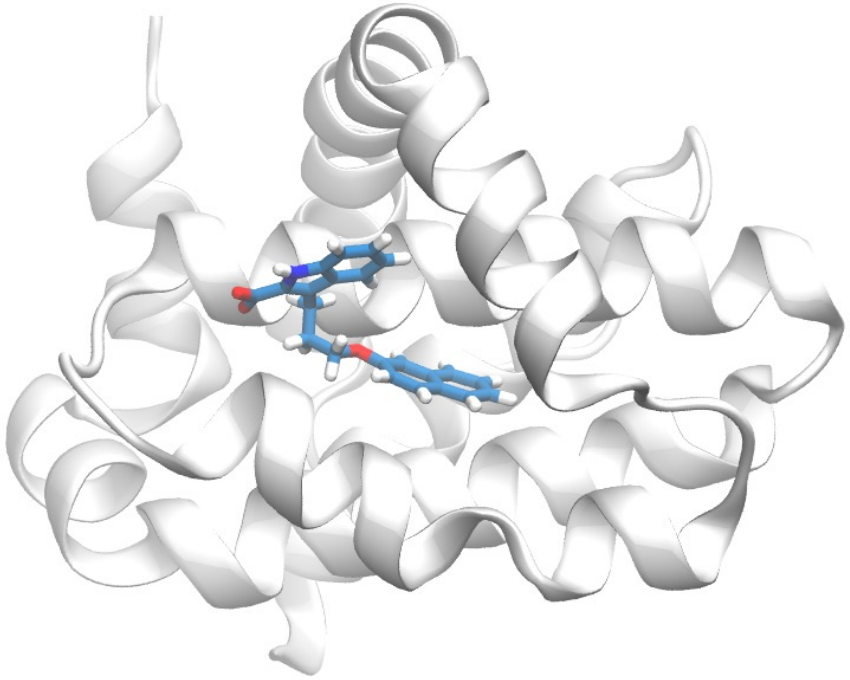
J Comput Chem. 2010 Jan 30; 31(2): 455–461.

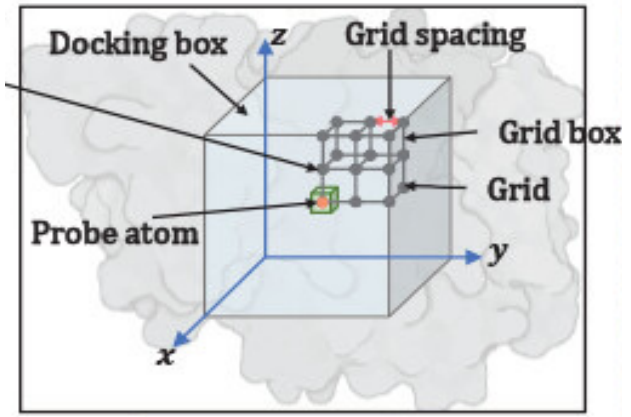
Soft Comput **23**, 4155–4176 (2019).

Allowing protein and ligand flexibility is often better

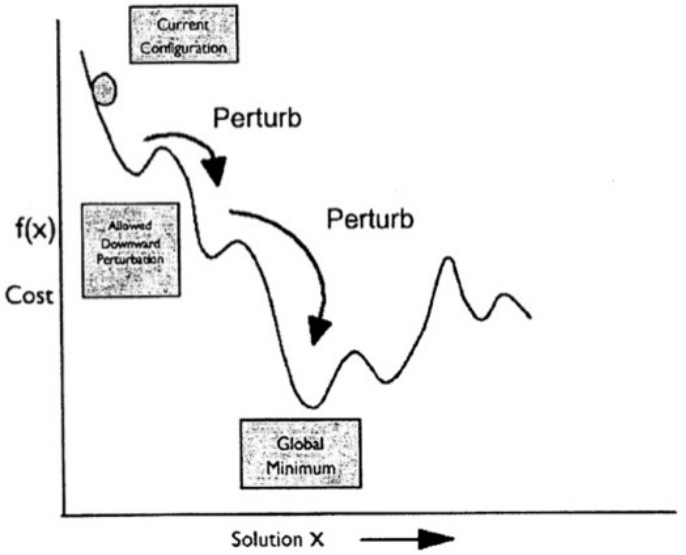


Flexibility increases compute time





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!

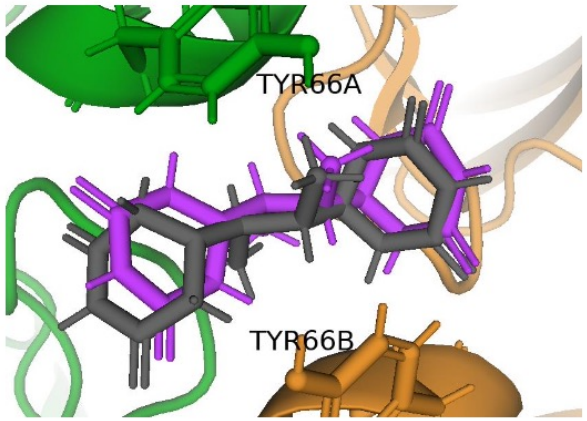
Typical docking output generates multiple poses

Example output, what does it mean?

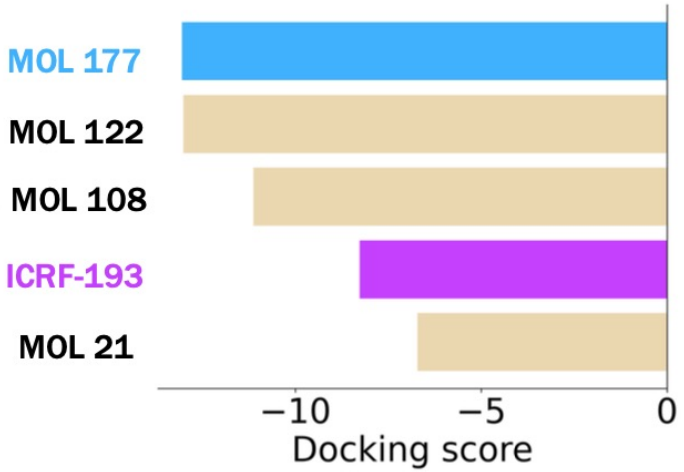
Template docking and cross docking

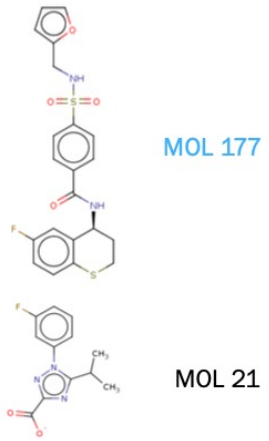
Example output, what does it mean?

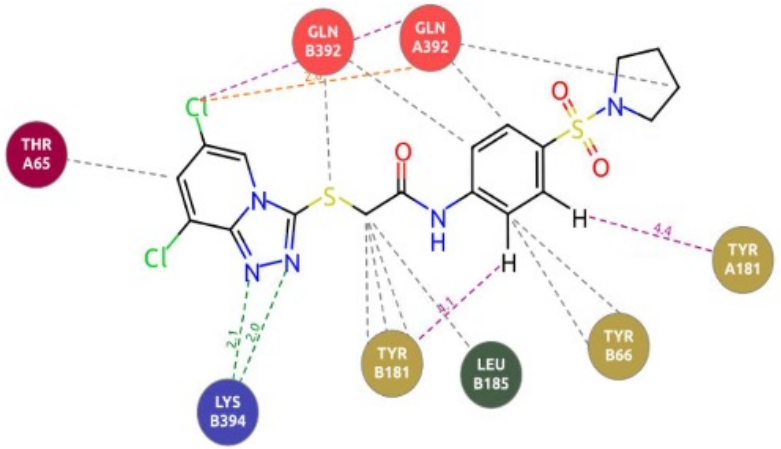
Evaluating Docked structures



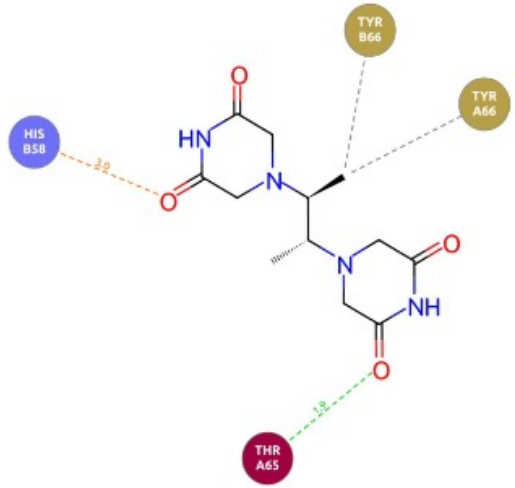
Crystal structure ICRF-193





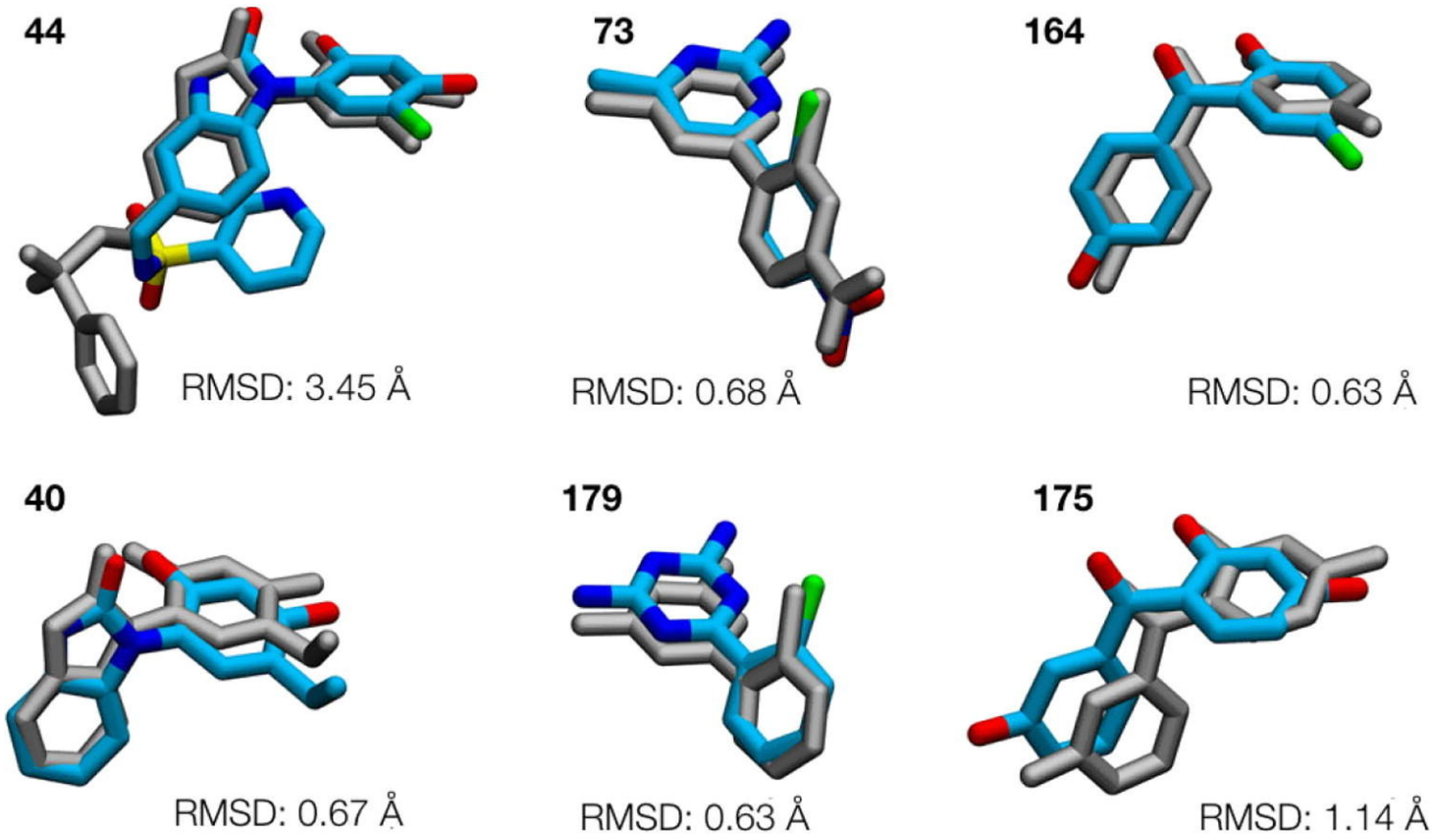


Contact map MOL-177



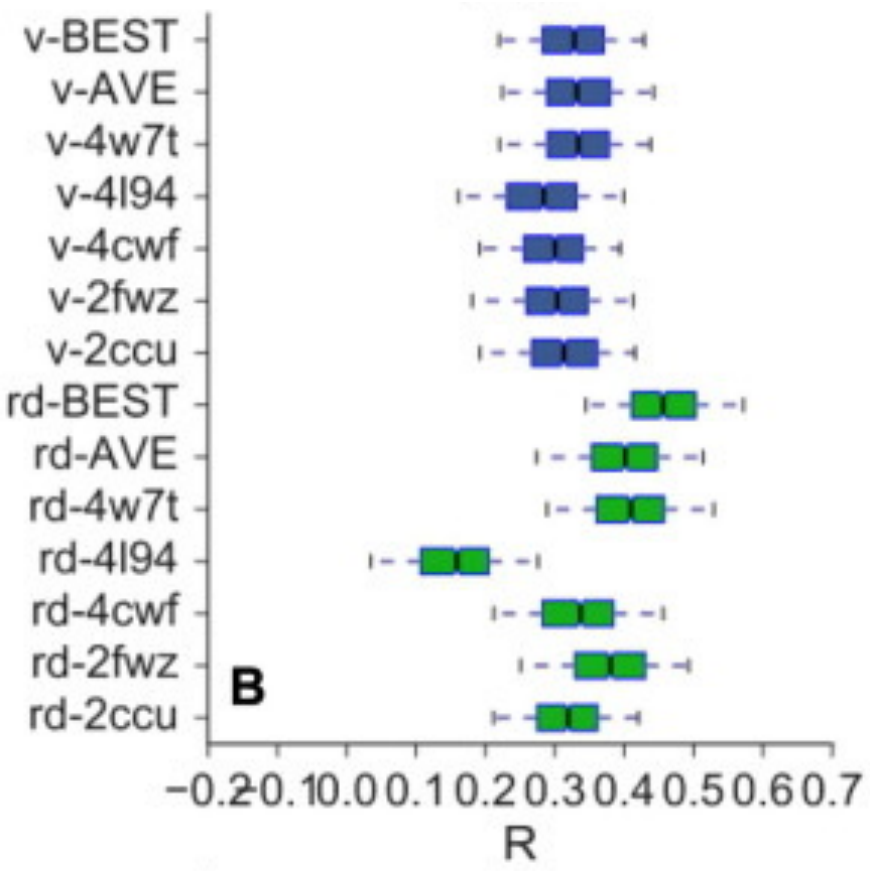
Contact map ICRF-193

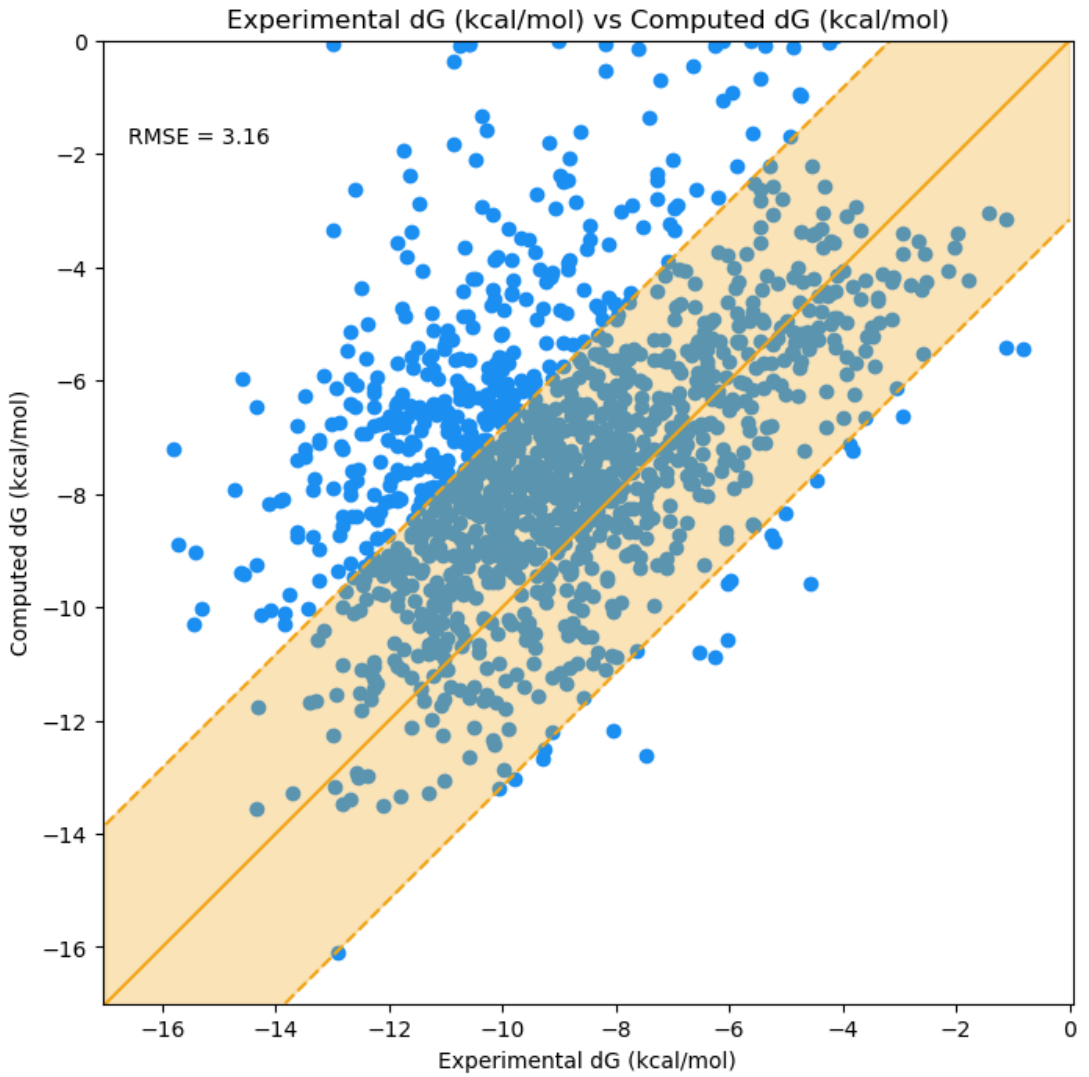
Evaluating the binding mode/pose



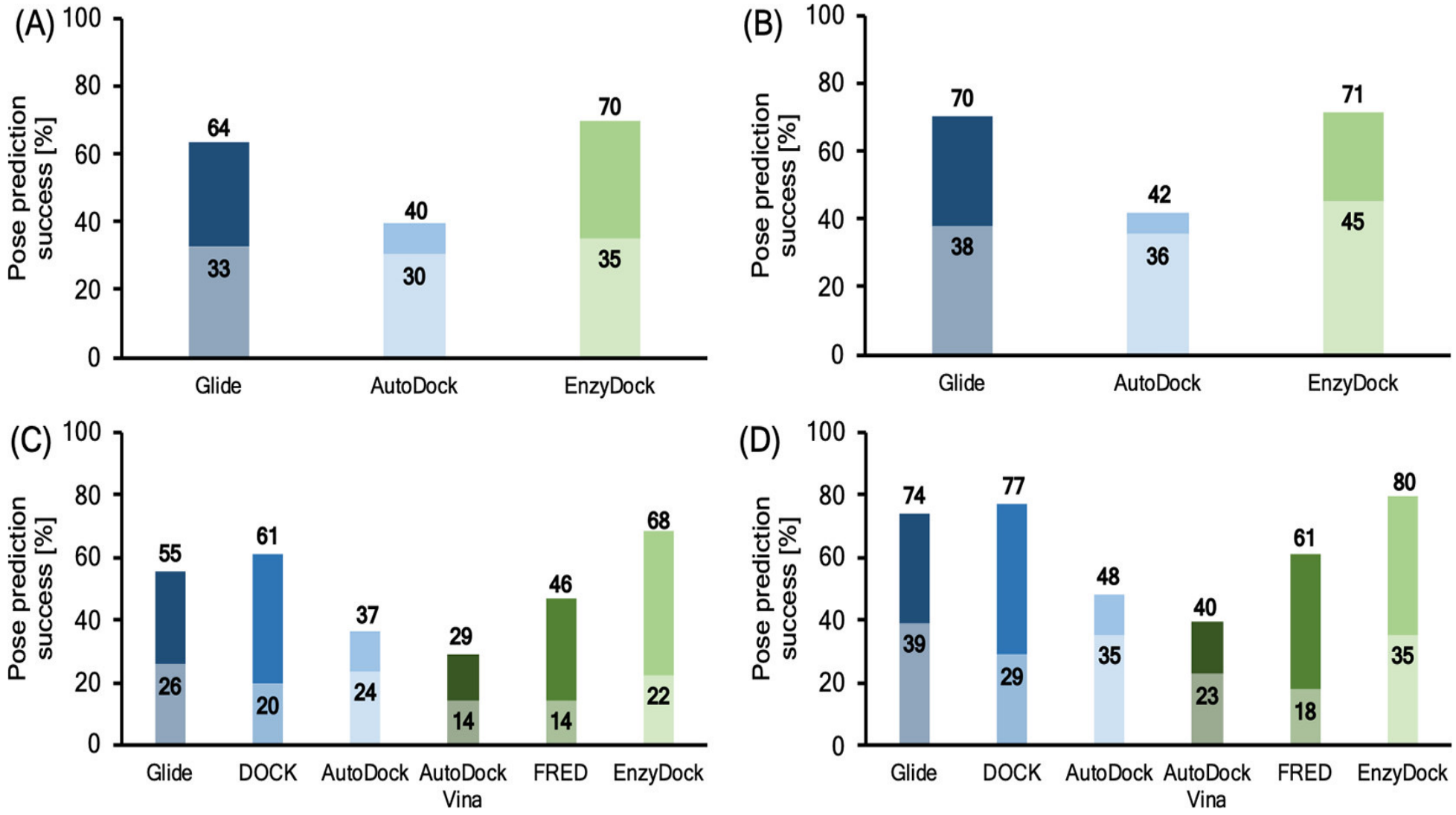
Bioorganic & Medicinal Chemistry
Volume 24, Issue 20, 15 October 2016, Pages 4890-4899

Comparing against experimental ΔG





Recent docking benchmark

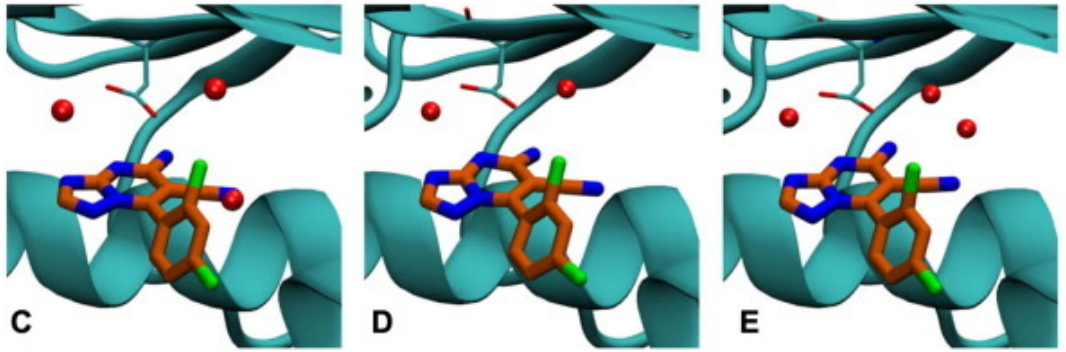


J. Chem. Inf. Model. 2021, 61, 6, 2957–2966

Things to worry about

pKa of ligands and
binding site protonation

structural waters are important



Scoring the pose with a scoring function

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

ligand

protein

Binding pose image

Evaluating the binding mode/pose

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

ligand

protein

Binding pose image

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

Finding the pocket in a protein

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

ligand

protein

Binding pose image

Predicting a binding mode/pose

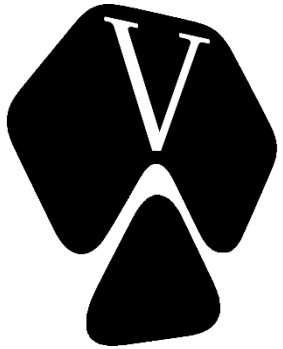
The process of predicting a stable 3D geometry of an interacting pair of molecules – **a binding mode/pose.**

ligand

protein

Binding pose image

What tools exist for molecular docking?



Autodock Vina

Glide

And others….

ML-based docking

Gnina

Deepdock

Diffdock

Equibind

TankBind

References

J. Chem. Inf. Model. 2010, 50, 8, 1432–1441


Break Time!