CHEM 436 / 630

Molecular modelling of proteins

Winter 2018 Term

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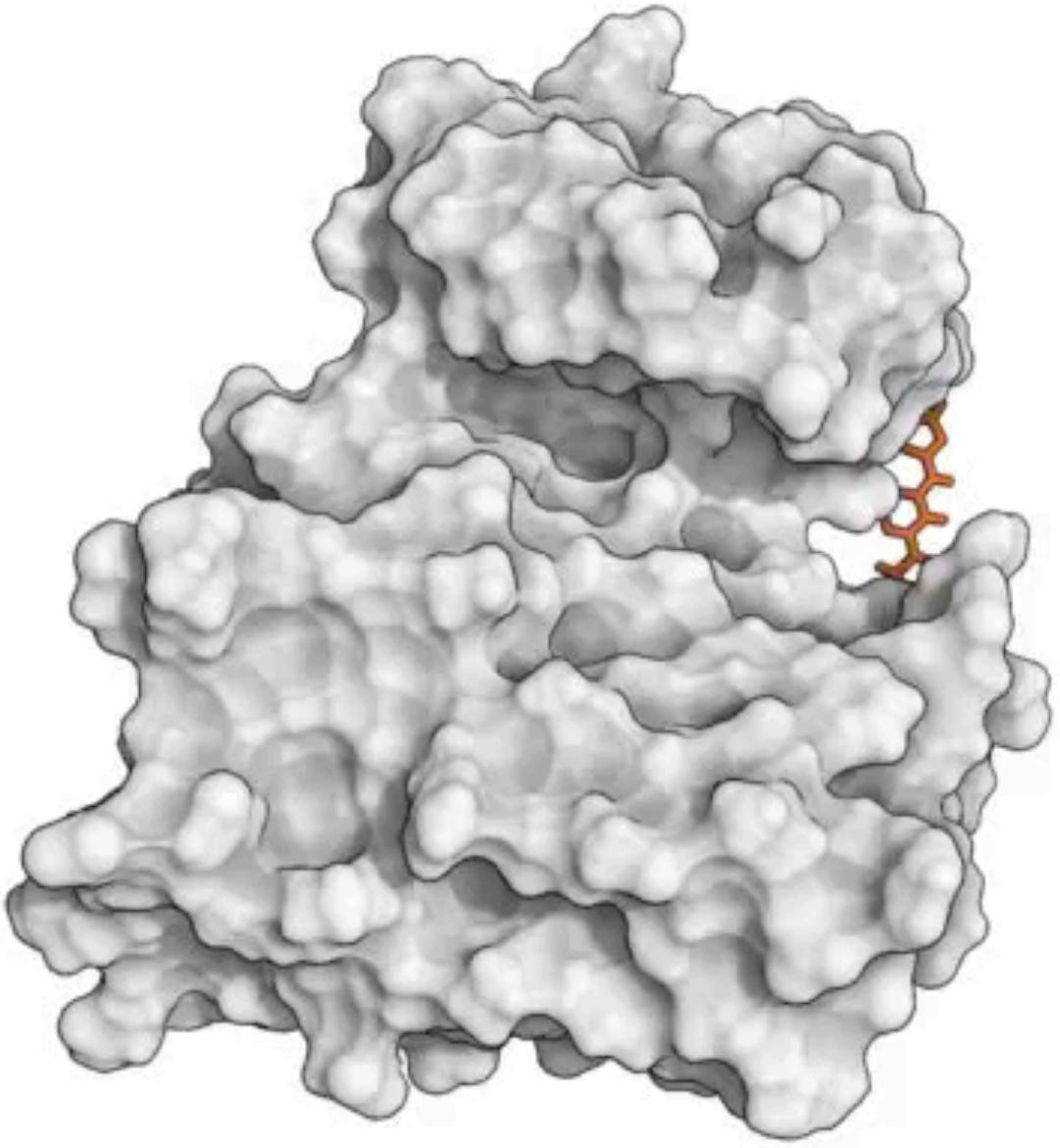
Dasatinib binding to Src kinase

- Molecular dynamics simulations (total of 35 μs)
- Ligand "finds" the known position (PDB: 3G5D)

- Amber99SB ff for the protein
- TIP3P ff for water
- GAFF ff with AM1-BCC for the ligand

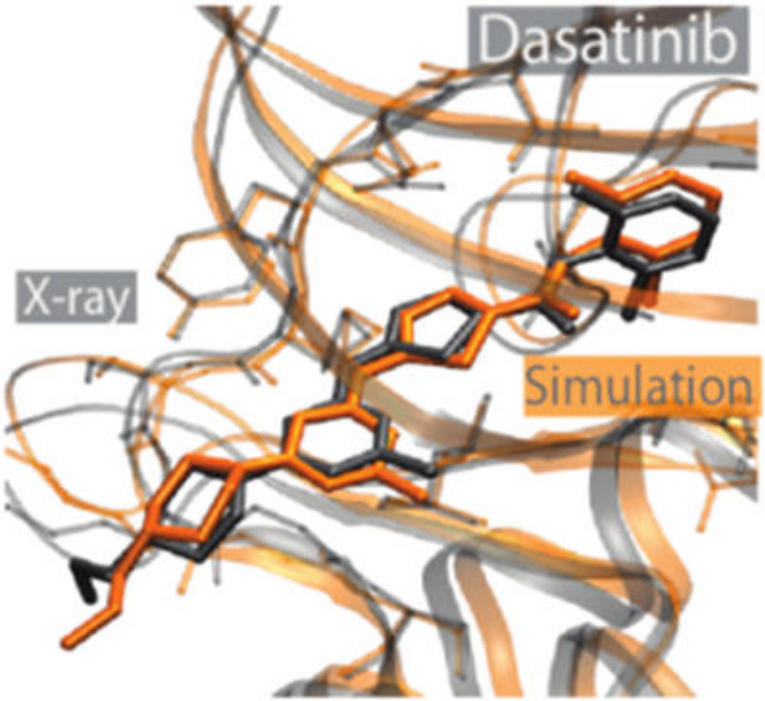
- k_{on} and k_{off} can be estimated from the simulation, and therefore K_A and ΔG

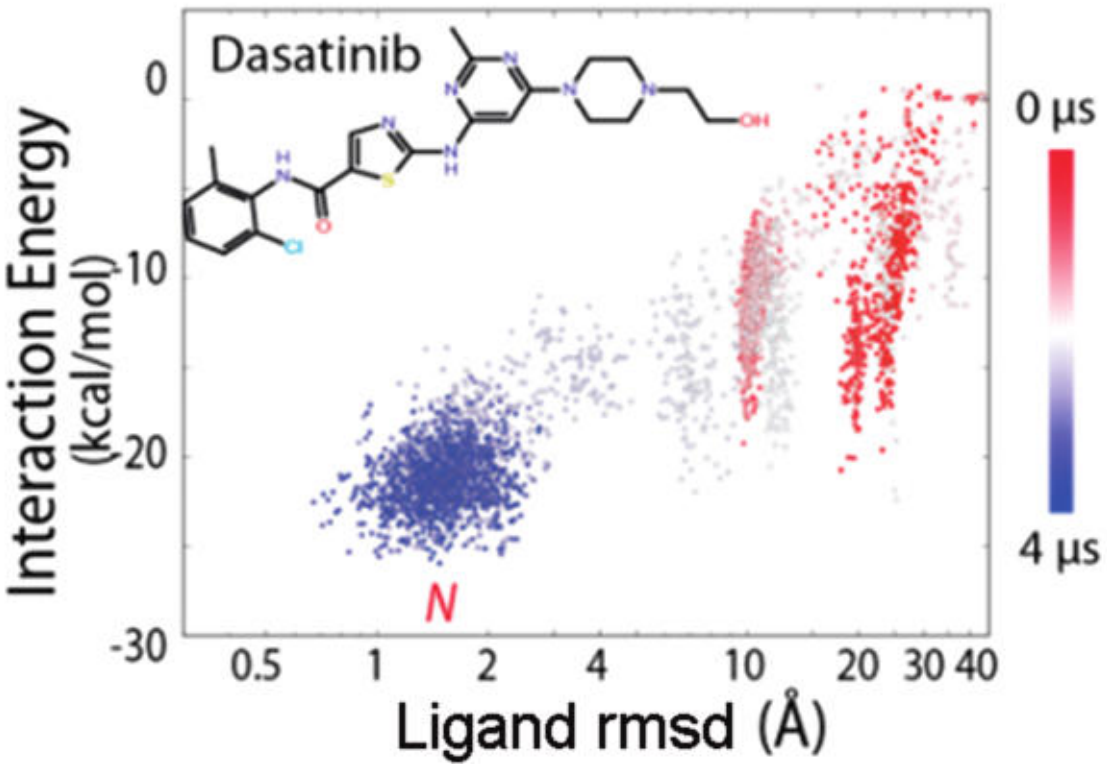


Movie from:

Y. Shan et al., *J. Am. Chem. Soc.* 2011, 133, 9181-9183.
http://dx.doi.org/10.1021/ja202726y

Dasatinib binding to Src kinase





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Dasatinib binding to Src kinase

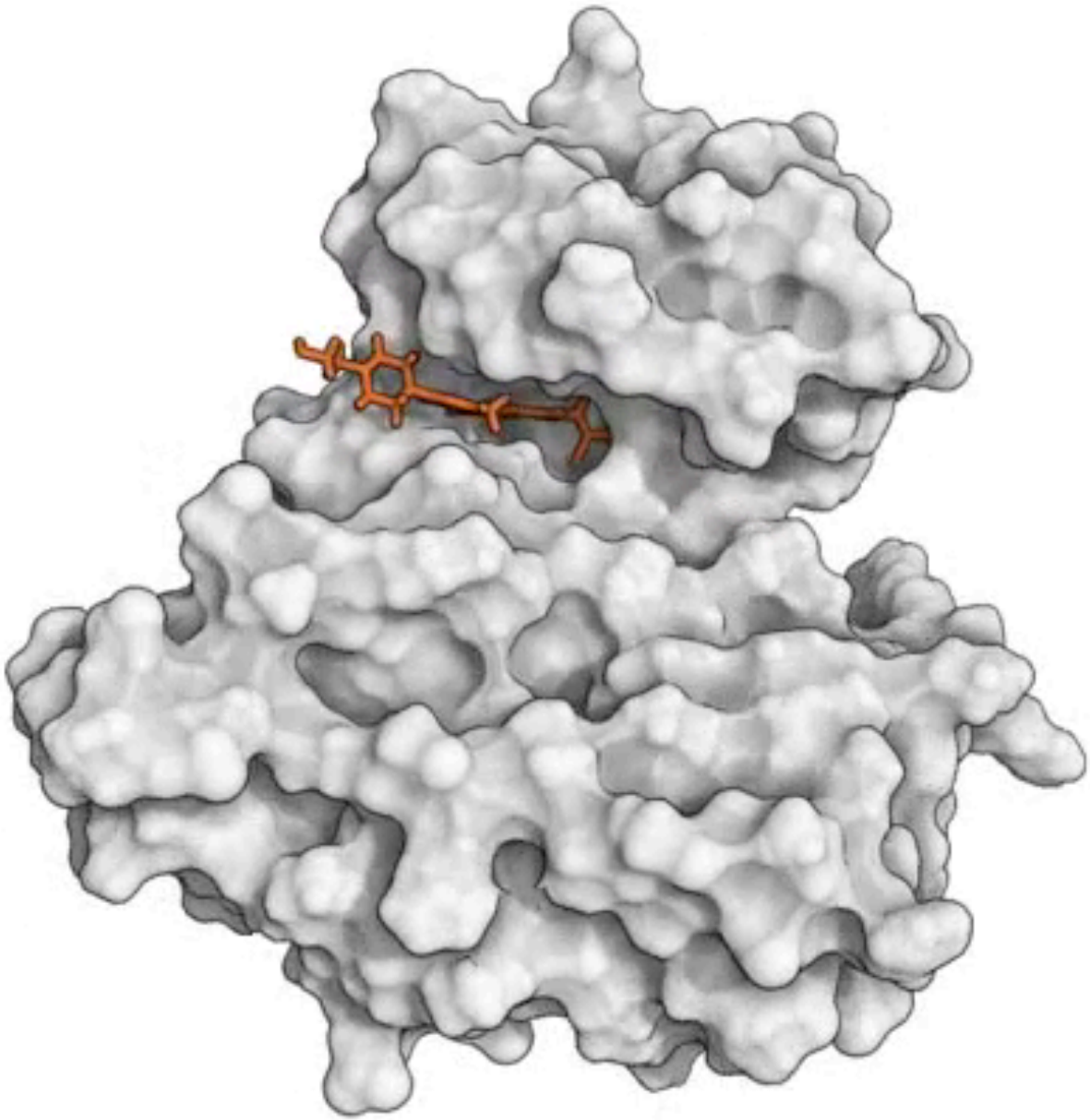
Do we need the full simulation to calculate ΔG ?

- Can we estimate ΔH from the number of H-bonds and nonpolar contacts formed upon binding?
- Can we estimate ΔS from the number of water molecules displaced and the conformational restriction created upon binding?

This is what molecular docking methods attempt to do:

- Finding the optimal pose for the ligand at the surface of the protein
- Estimating ΔH as the sum of all interactions formed (protein-ligand), minus the sum of all interactions broken (protein-solvent, protein-protein, ligand-solvent, ligand-ligand)
- Estimating ΔS from the number of rotatable bonds immobilized upon binding, and the number of water molecules "liberated".

Docking relies on a large number of approximations but is much faster than MD simulations.



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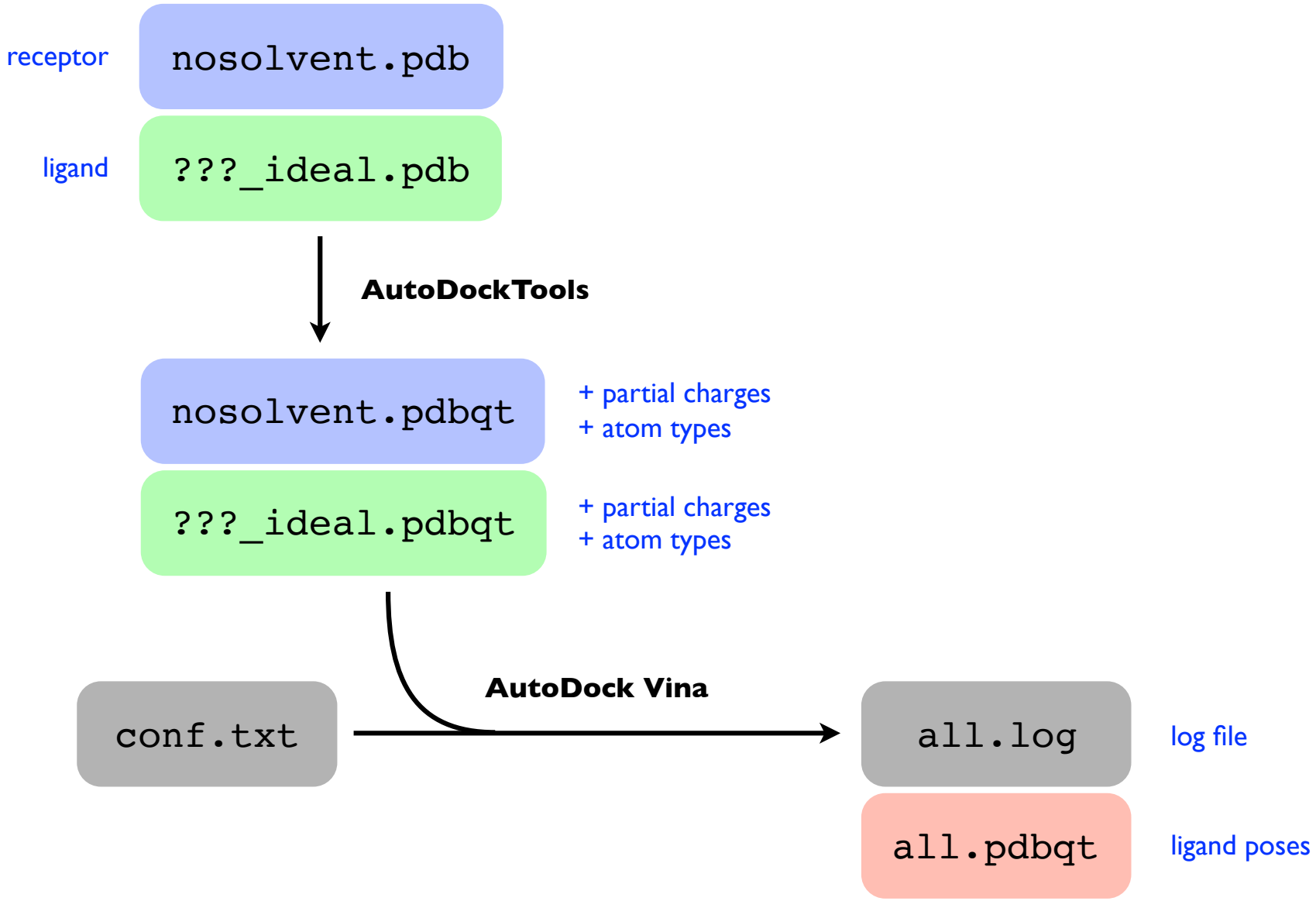
Molecular docking



AutoDock Vina scoring function

Atom types

Chemical structure of ligand → Atom types & partial charges

Atom ***i*** is assigned type t_i and partial charge q_i.

Conformation-dependent score

$$c = \sum_{i<j} f_{t_i t_j}(r_{ij})$$

Sum over all ***(i,j)*** pairs that can move relative to one another

Interaction function (specific to the atom types of ***i*** and ***j***)

Distance between atoms ***i*** and ***j***

$$f_{t_i t_j}(r_{ij}) = h_{t_i t_j}(d_{ij})$$

Surface distance

$$d_{ij} = r_{ij} - R_{t_i} - R_{t_j}$$

Interaction function

$$h_{tt'}(d) = \text{steric}(d) + \text{Hphobic}_{tt'}(d) + \text{Hbond}_{tt'}(d)$$

same for all atom types

Attraction between nonpolar atom types

Attraction between polar (and oppositely charged) atom types

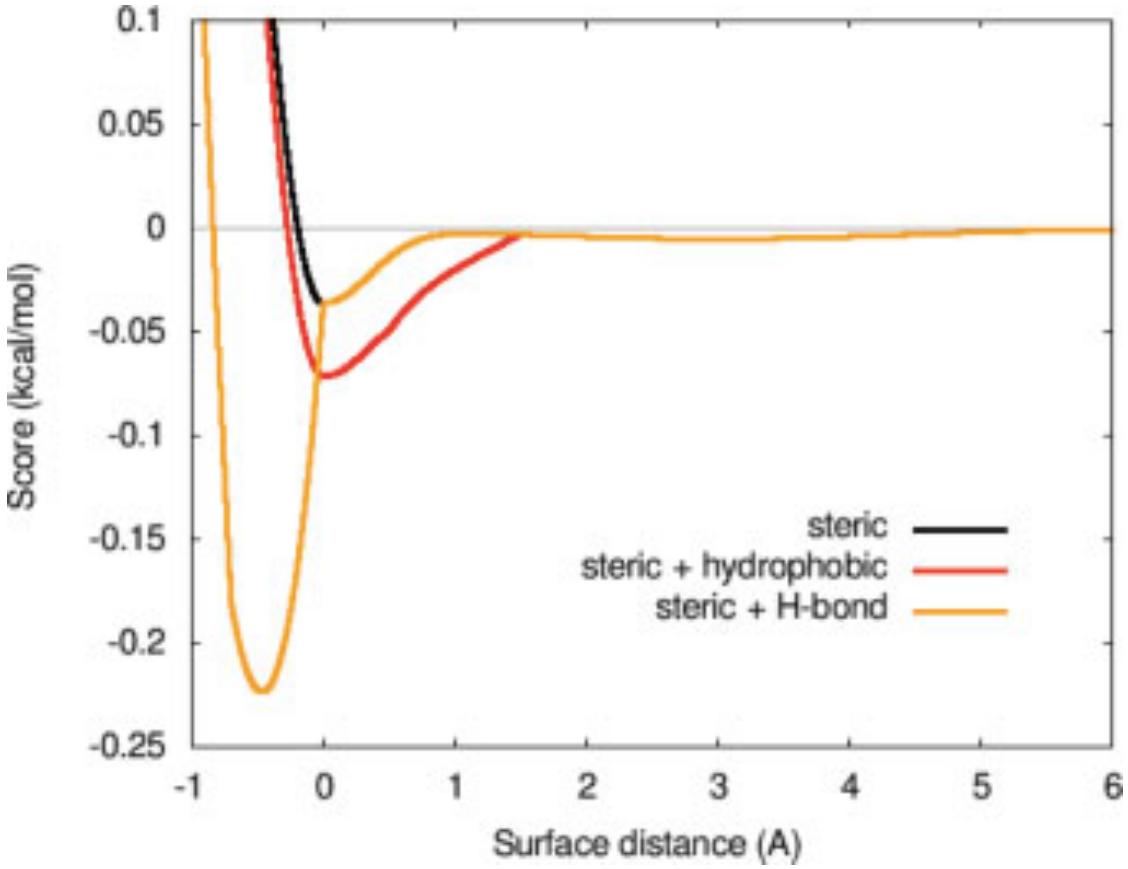


Figure from :
Trott & Olson. 2010. J. *Comput. Chem.* **31**, 455–461.
http://dx.doi.org/10.1002/jcc.21334

Scoring function

$$s_p = g(c_p - c_{\text{intra},1})$$

- s_p: scoring function of pose "*p*"
- c_p: conformation-dependent score of pose "*p*"
- $c_{\text{intra},1}$: intramolecular part of the conformation-dependent score of the best ranking pose (#1)

$$c = c_{\text{inter}} + c_{\text{intra}}$$

$$g(c_{\text{inter}}) = \frac{c_{\text{inter}}}{1 + wN_{\text{rot}}}$$

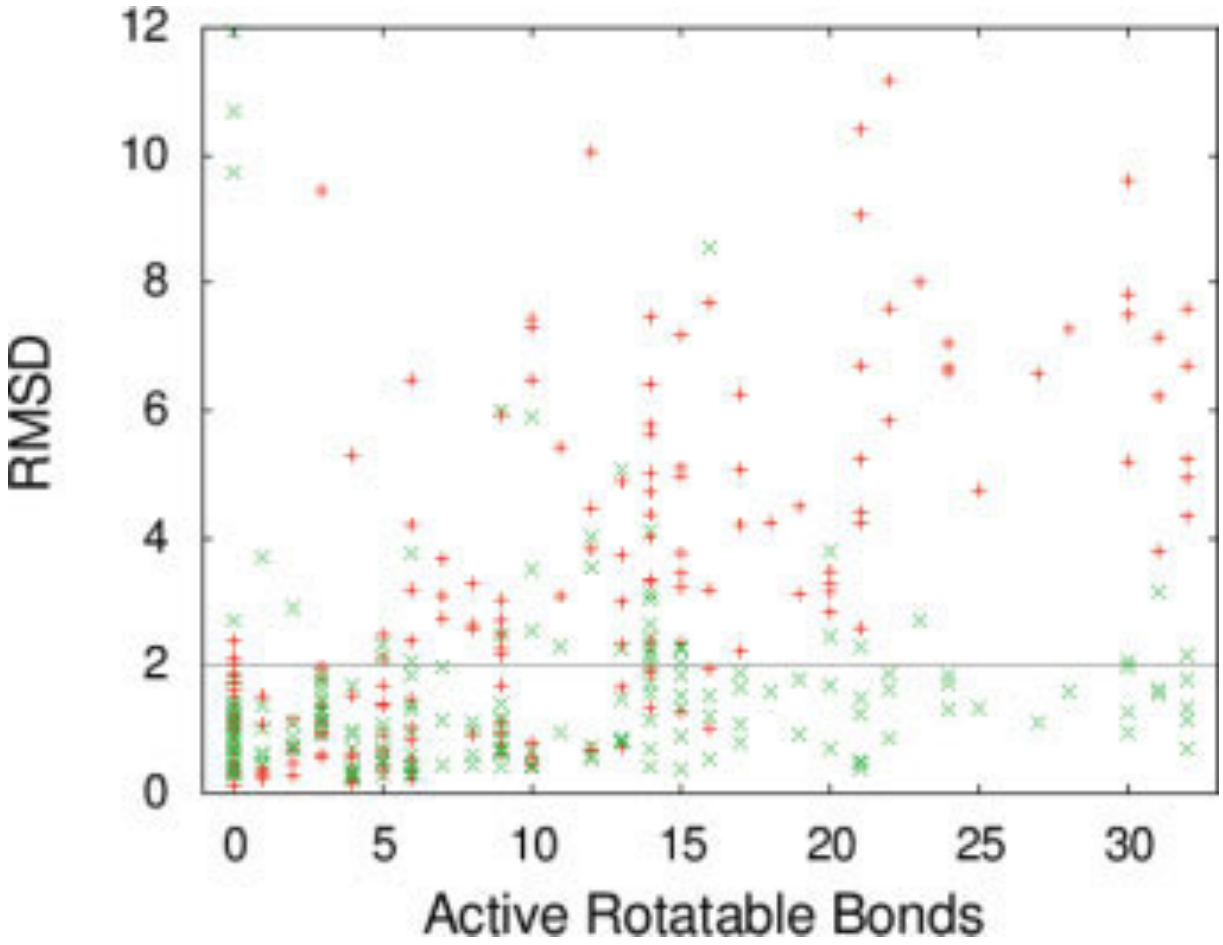
- w: empirical weight = 0.0585
- N_{rot}: number of rotatable bonds in the ligand

This score also corresponds to the binding affinity.

The function has 6 empirical parameters, that are adjusted to best reproduce a set of 190 known receptor-ligand structures.

See Table 1 from :
Trott & Olson. 2010. J. *Comput. Chem.* **31**, 455–461.
http://dx.doi.org/10.1002/jcc.21334

Performance: Ligand pose and conformation



AutoDock 4.0.1

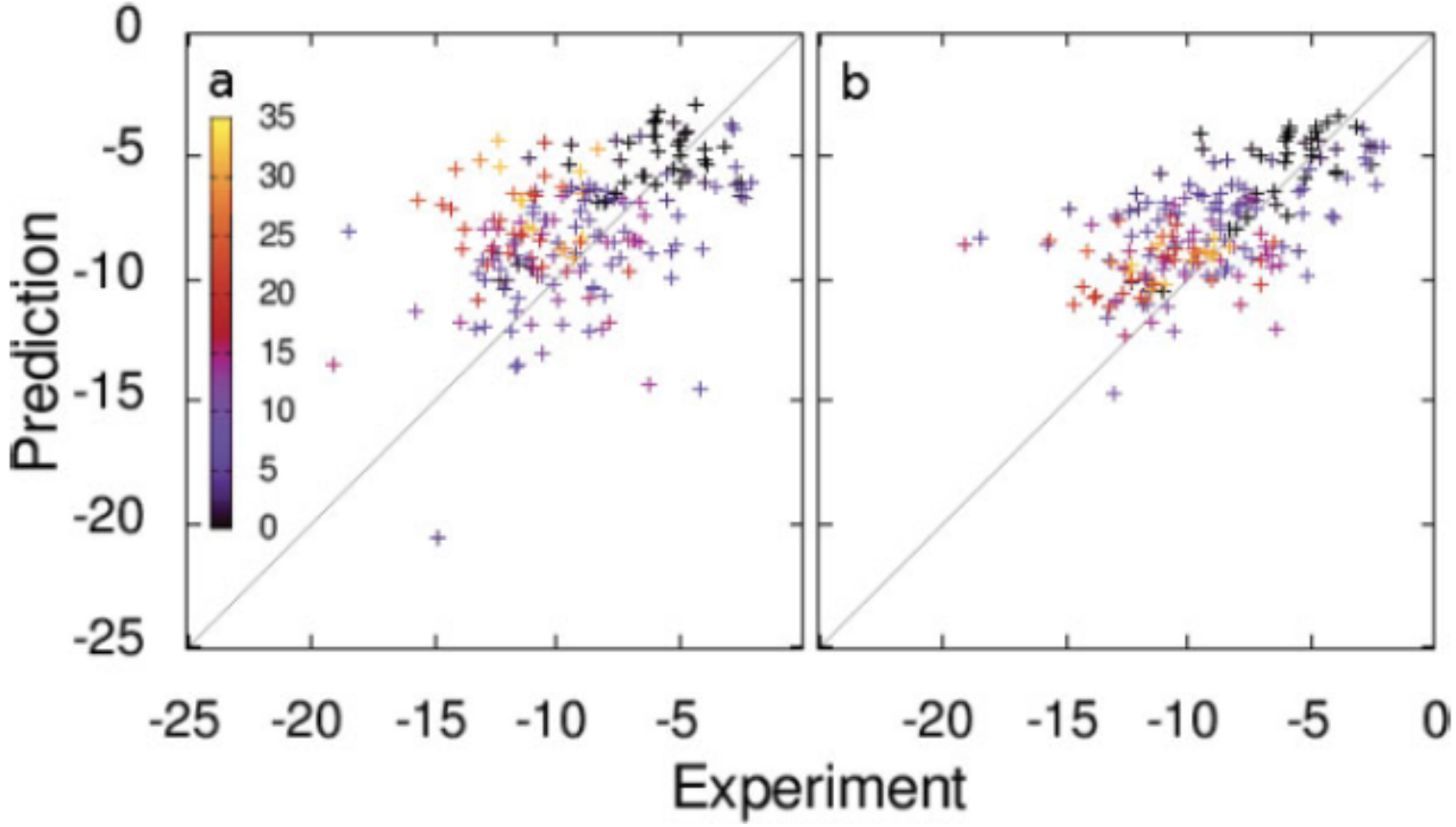
AutoDock Vina

Figure from :
Trott & Olson. 2010. J. *Comput. Chem.* **31**, 455–461.
http://dx.doi.org/10.1002/jcc.21334

Given its simplicity, the scoring function of AutoDock Vina works surprisingly well…

Performance: Free energies of binding

AutoDock 4.0.1 AutoDock Vina



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What is missing?

Protein is treated as a rigid molecule.

- AutoDock Vina can perform "flexible docking", with selected protein side chains allowed to flex. The protein backbone remains rigid, though.
- Newer docking methods allow for larger-scale deformations of the protein.

This is a serious limitation if we expect the binding to follow an *induced fit* model.

Water is described only implicitly.

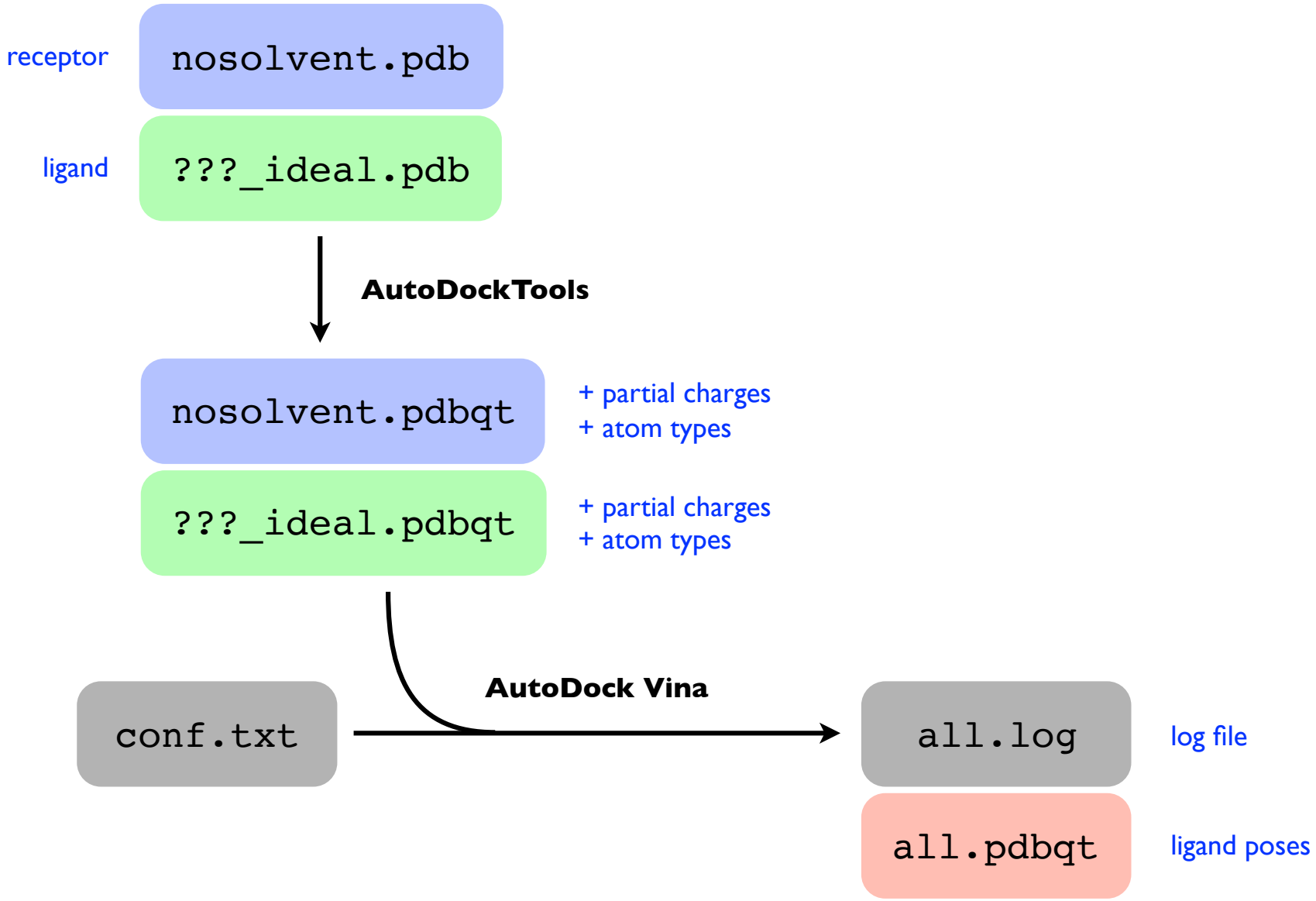
- Explicit water molecules can be added by hand, but this is not feasible for high-throughput studies.
- Newer docking methods allow for insertion of explicit water molecules around the ligand.

This is a problem if binding relies on *bridging* water molecules.

Many types of molecular interactions missing…

- Metal ligation, covalent bonds, cation–aromatic interactions, etc. (just to name some of the strongest ones)

Molecular docking



Nice ways to show a protein-ligand complex

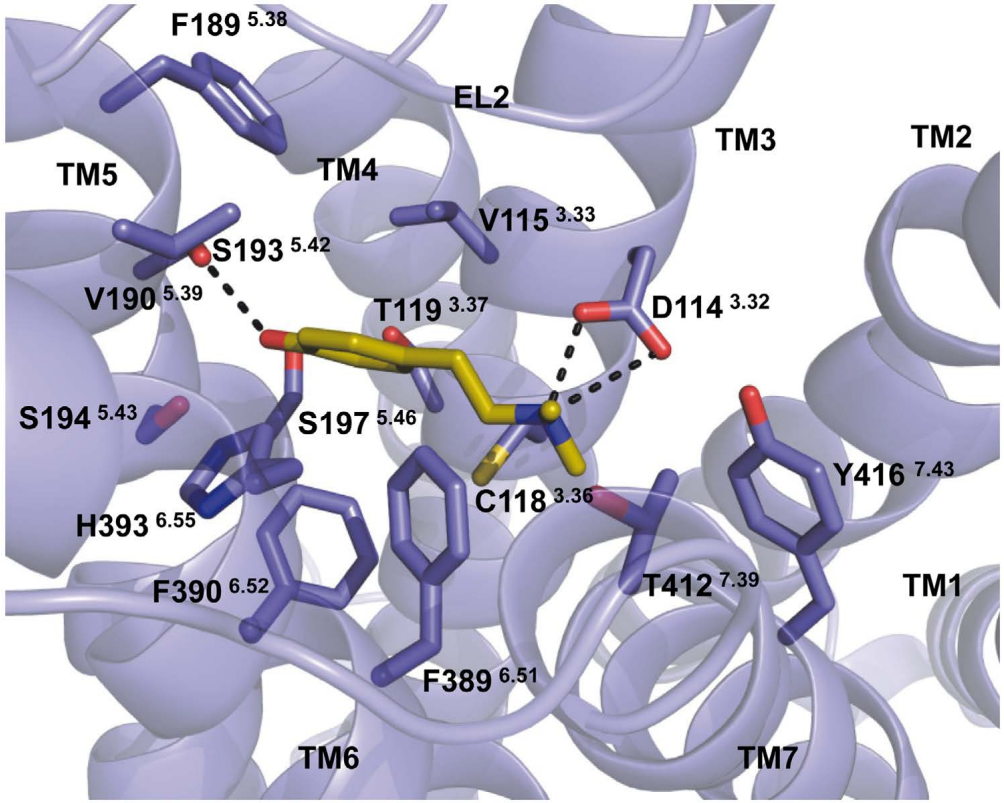


Figure 6. Conformation of hordenine and its receptor-ligand interactions obtained after docking and energy minimisation. We used an active-state homology model of D2R and performed MD simulations with the endogenous ligand dopamine[42]. Dopamine was removed from the model, hordenine was docked into the binding pocket and the resulting receptor-ligand complex was subjected to energy minimisation in a water box. Whereas dopamine is able to form two hydrogen bonds with both Ser193$^{5.42}$ and Ser197$^{5.46}$ in the D2^{Up}R model[42], our VS hit hordenine forms only a single hydrogen bond to Ser197$^{5.46}$ due to the lack of a second hydroxyl group.

Figure from :
Sommer et al. 2017. *Sci. Rep.* **7**, 44201.
http://dx.doi.org/10.1038/srep44201

Nice ways to show a protein-ligand complex

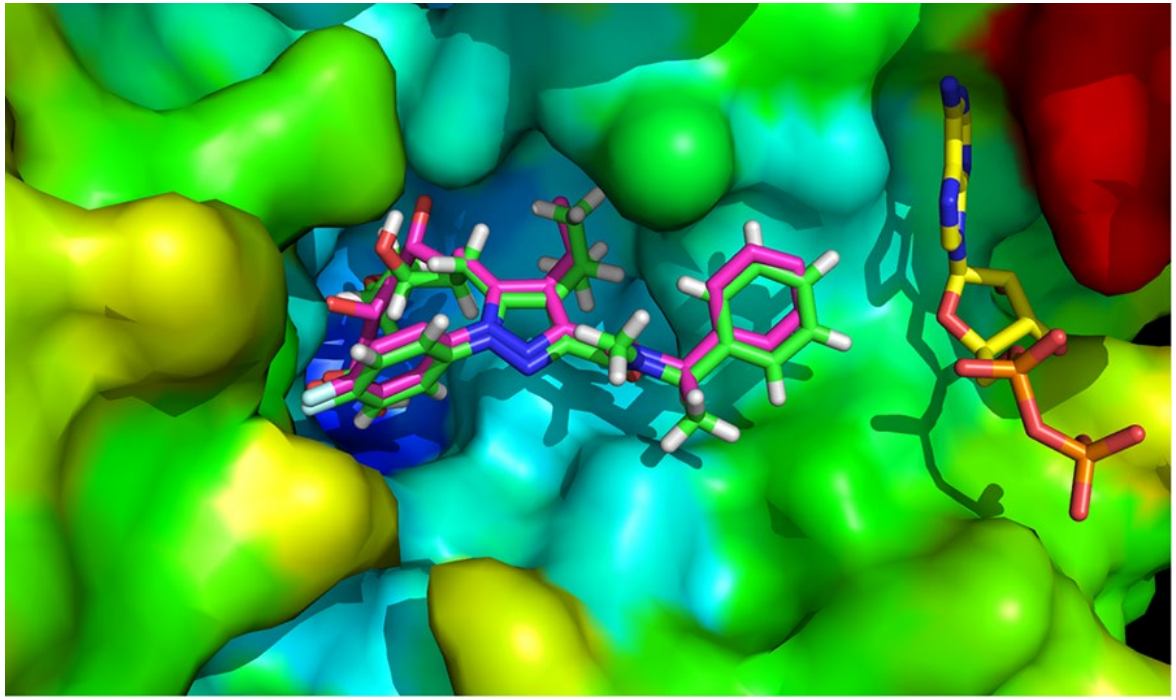


Fig. 2 Docked pose (*green*) of the ligand of 2R4F PDB code in the active site of HMG-CoA reductade structure with PDB code 1HWJ. The experimental pose of the ligand in PDB code 2R4F is shown in *magenta*. ADP is shown in *yellow* color. The calculated RMSD is 0.96 Å. The atoms in the 1HWJ active site were color coded by their B-factors. *Blue* is for low B-factor and *red* is for high B-factor value. Higher B-factor may indicate flexibility of the residues (inaccuracy in crystallography for some part of the protein also causes the higher B-factor)

Figure from :
Shamsara. 2016. *SpringerPlus* **5**, 334.
http://dx.doi.org/10.1186/s40064-016-1972-4