

CHEM 498Q / 630Q

Molecular modelling of proteins

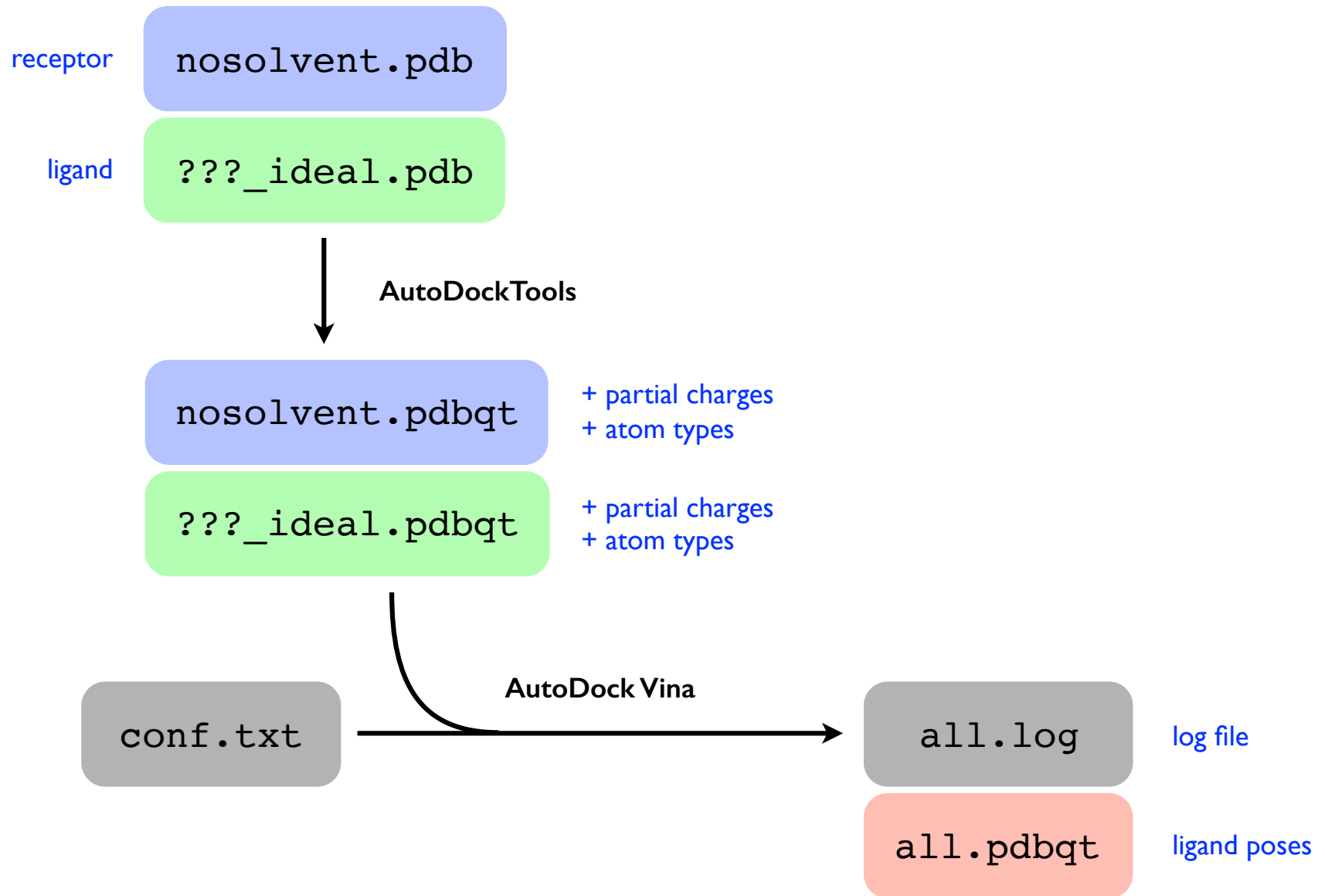
Fall 2015 Term

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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

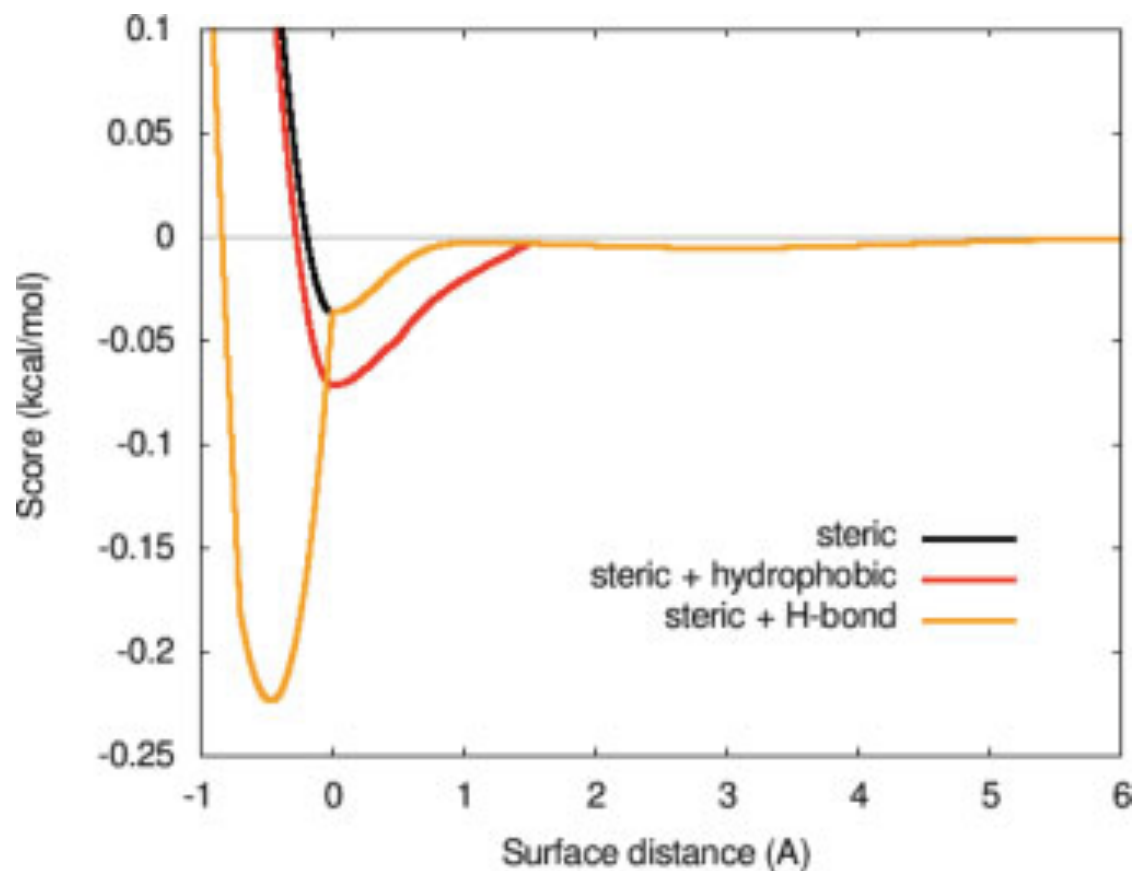


Figure from :
Trott & Olson. 2010. *J. Comput. Chem.*
31, 455–461.
<http://dx.doi.org/10.1002/jcc.21334>

Scoring function

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

scoring
function of
pose "p"

conformation-
dependent score
of pose "p"

intramolecular part of the
conformation-dependent
score of the best ranking
pose (#1)

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

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

empirical
weight = 0.0585

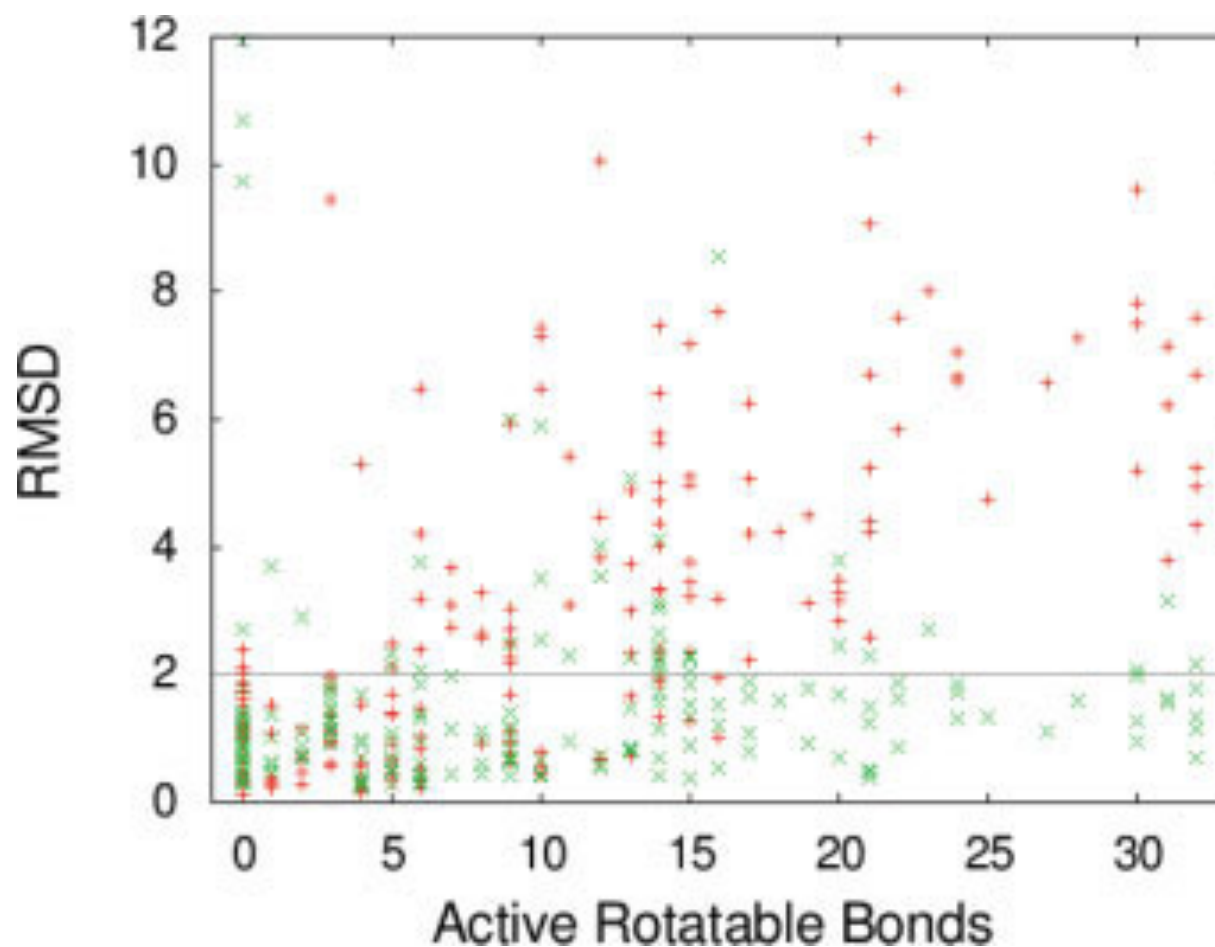
number of rotatable
bonds in the ligand

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

Performance: Free energies of binding

AutoDock 4.0.1

AutoDock Vina

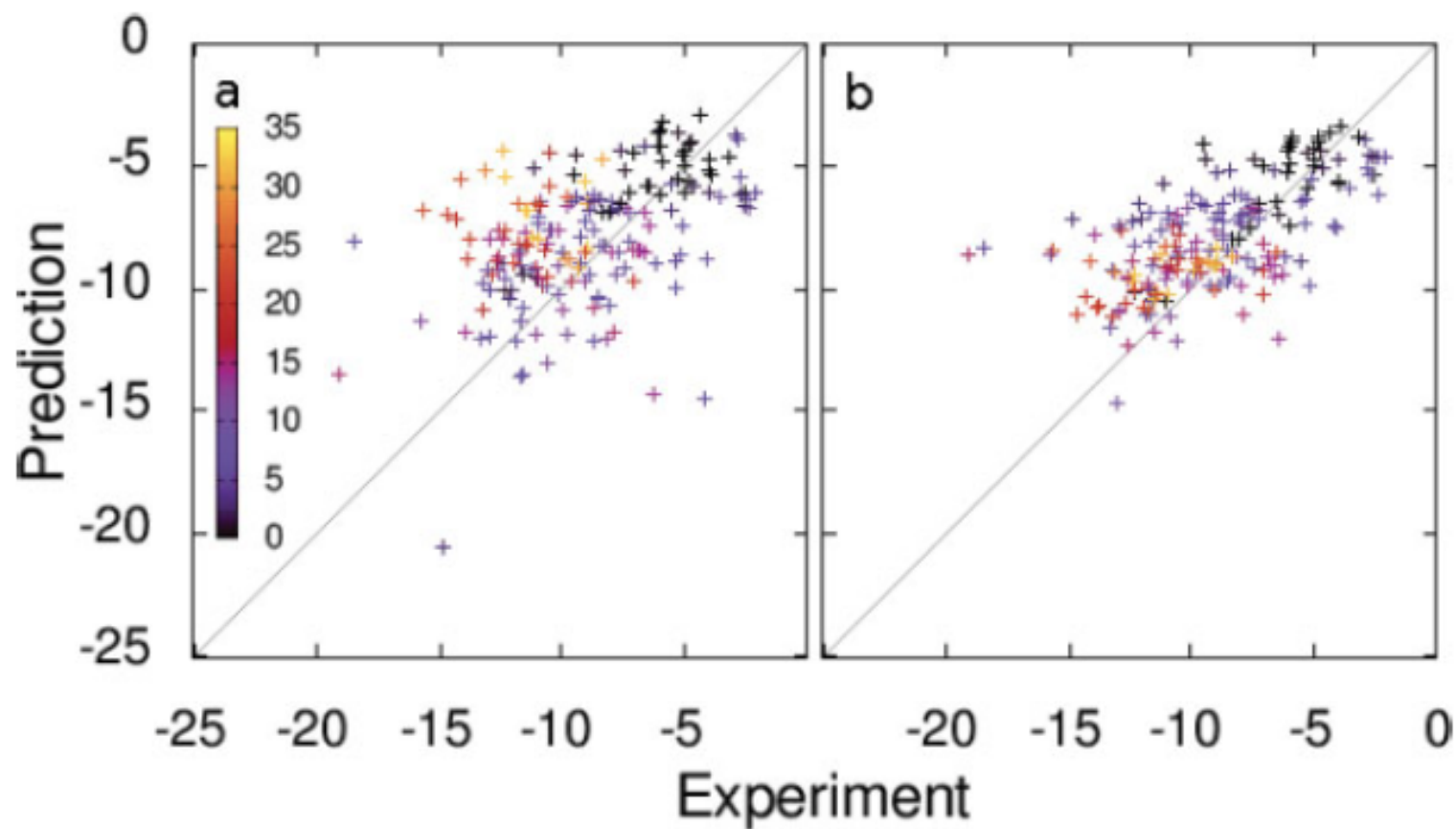


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What is missing?

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...

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

Molecular docking

receptor

nosolvent.pdb

ligand

???.ideal.pdb

Windows



AutoDockTools

nosolvent.pdbqt

+ partial charges
+ atom types

???.ideal.pdbqt

+ partial charges
+ atom types

Linux
VM

conf.txt

AutoDock Vina

all.log

log file

all.pdbqt

ligand poses