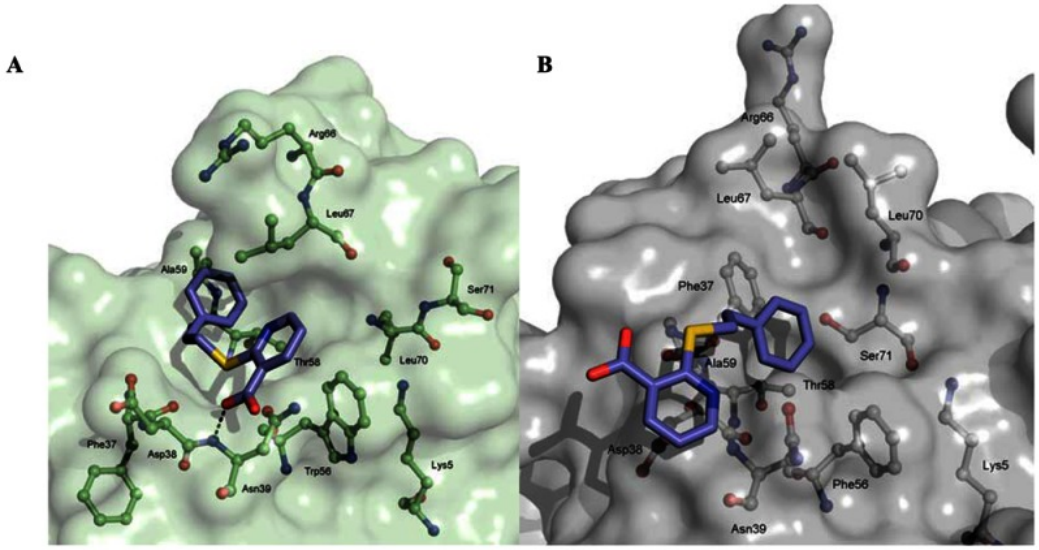
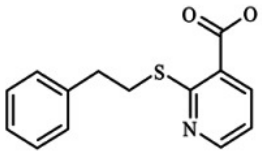
Molecular docking
and computation of protein-protein interactions

Molecular docking

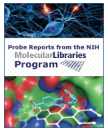
- Molecular docking strategies identify the orientations of molecules that are optimal for their interactions.
- In particular, applied for interactions between proteins and (small molecule) ligands that modulate protein functions.
- Proteins can have specific binding cavities and active sites.

An example of docking of a ligand to two related proteins:





From: Three small molecule pan activator families of Ras-related GTPases



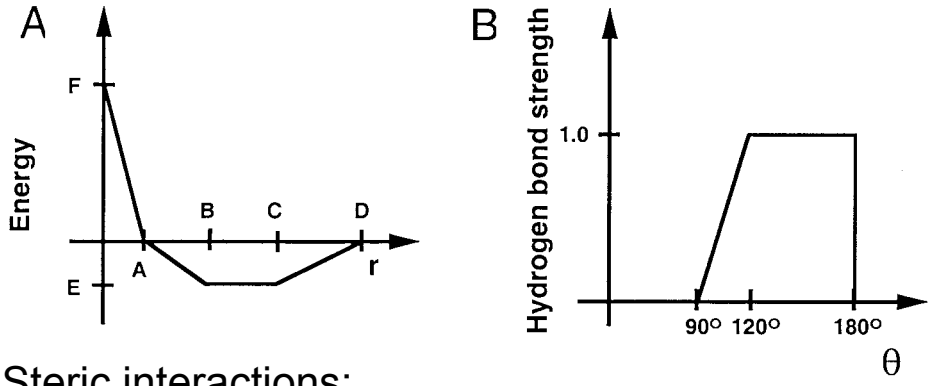
Probe Reports from the NIH Molecular Libraries Program [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2010-.

Molecular docking

The first approximation of protein-ligand interaction: lock-and-key model.

- Both protein and ligand are considered to be **rigid bodies**.
- The affinity is proportional to geometric fit.
- The fit is searched in 6-dimensional translational/rotational space.
- Binding free energy can be calculated as the sum of van der Waals, electrostatic and H-bonding interaction energies.

An example of approximated energy function for molecular docking:



(A) Steric interactions:
B = sum of van der Waals radii of two atoms
A = 0.93B; C = 1.25B; D = 1.5B;
E = −0.4; F = 15

(B) H-bond energy:
is multiplied by a strength term, which is a function of angle formed by proton donor and acceptor atoms

(Verkhivker et al., 2000)

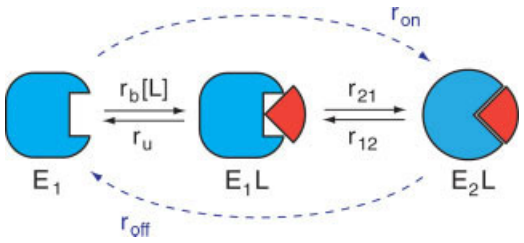
- More accurate energy functions can be used.
- Docking algorithms consider large numbers of conformations.
- Two main components of a docking protocol: scoring function (energy) and searching strategy, e.g. Molecular Dynamics, Monte Carlo algorithm etc.

Molecular docking

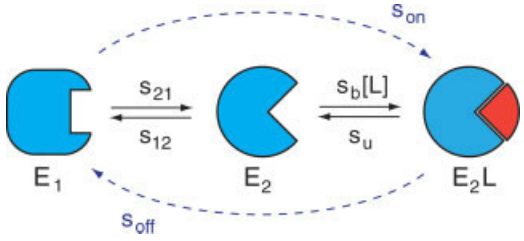
Conformations of interacting molecules change upon binding:
induced-fit or flexible docking.

- Computationally more demanding than lock-and-key docking.
- Various approximations, e.g. flexible ligand docking into rigid receptor, rigid backbone with flexible amino acid side chains etc.
- Conformational changes may be either induced by binding or caused by stabilizing ligand binding to one of suboptimal protein conformations (selected-fit).

Induced-fit vs. selected-fit



Induced-fit interaction model



Selected-fit interaction model

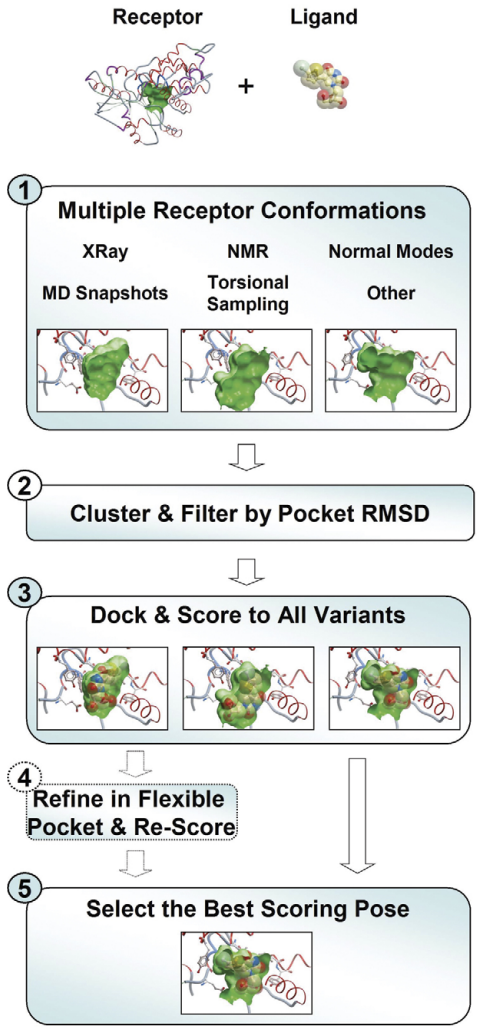
from Weikl & von Deuster (2000)

Molecular docking

Conformations of interacting molecules change upon binding:
induced-fit or flexible docking.

- Computationally more demanding than lock-and-key docking.
- Various docking protocols.

An example of docking flowchart:

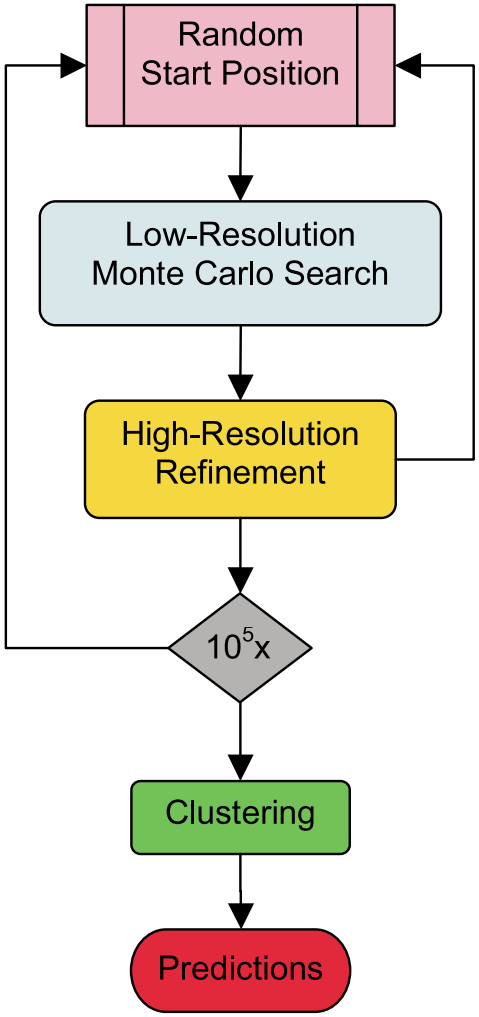


from Totrov & Abagyan (2008)

Protein-protein docking

Various approximations for optimization of interacting conformations.

An example:



Low-resolution rigid-body MC: translating and rotating one partner around the surface of the other (500 MC moves).
Energy functions for side-chain centroids.

Explicit side-chains are added ("packing" algorithm).
Rigid-body displacement is optimized.
Packing/displacement optimization is repeated 50 times.

Search procedure is repeated to create ~10^5 configurations.

The best 200 configurations are clustered.
The clusters with the most members are selected as the final predictions.

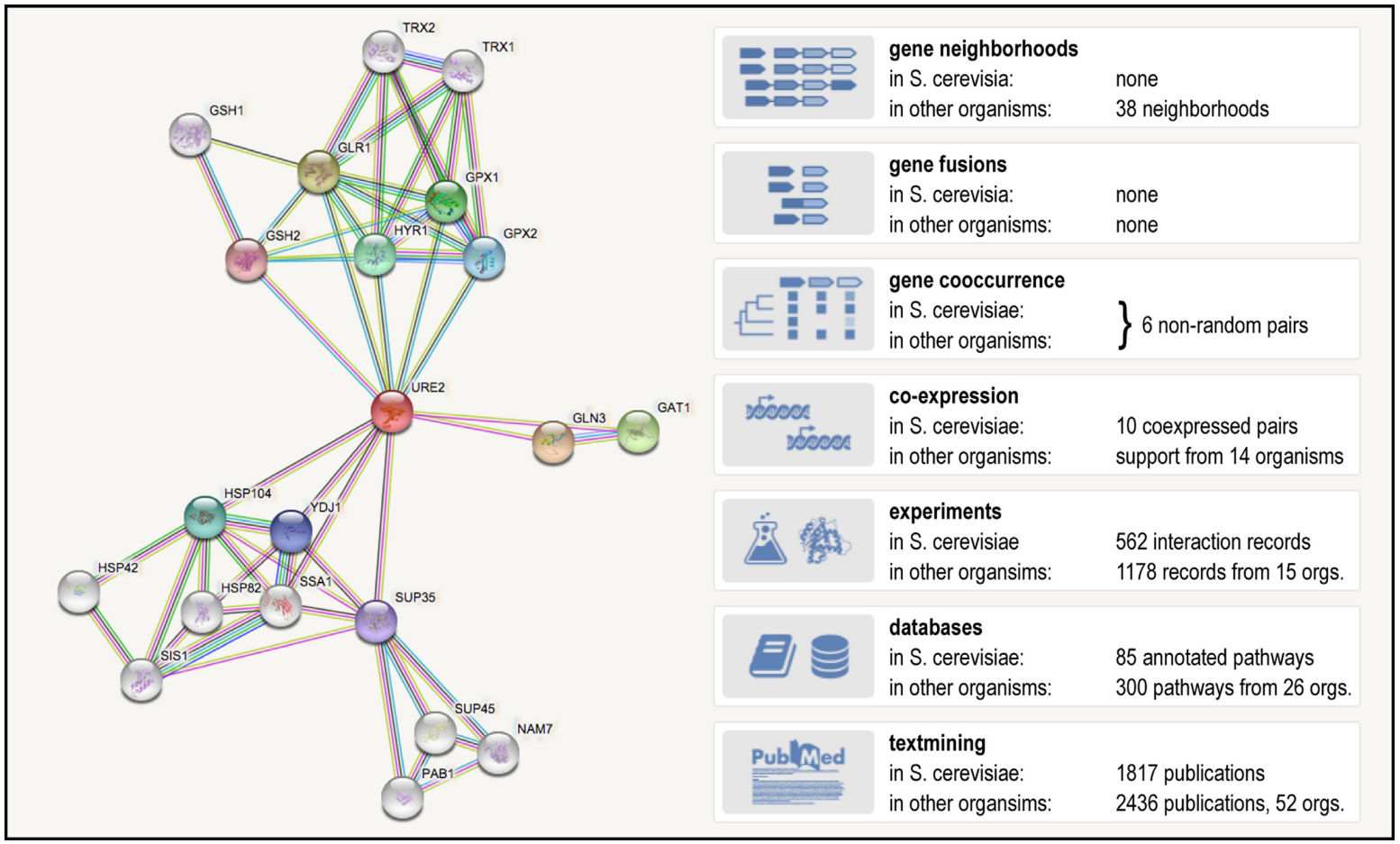
(Gray et al., 2003)

Protein-protein interactions

Direct (physical) and indirect (functional) associations

- Can be derived from various databases and used for the development of databases that integrate this information => computation of association networks.

An example of an association network in the STRING database (https://string-db.org):
(yeast prion-like protein URE2 was used as input)



from Szklarczyk et al. (2019)