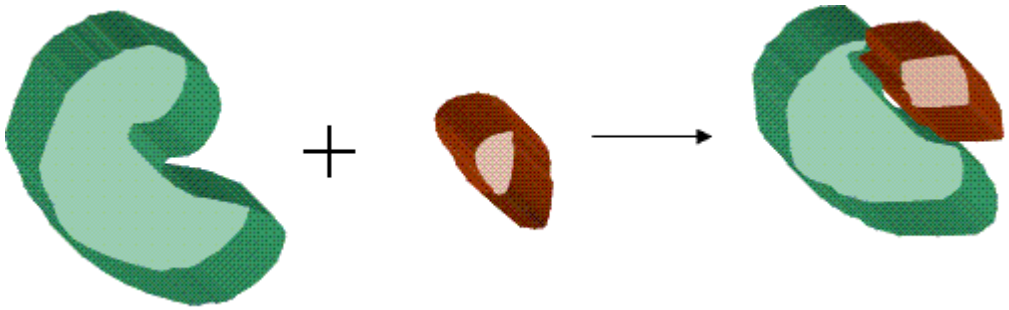
DOCKING
Program DOCK

What is docking

- Molecular docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex.
- Molecular docking is used for virtual screening of molecular libraries for prediction of possible bind molecules.

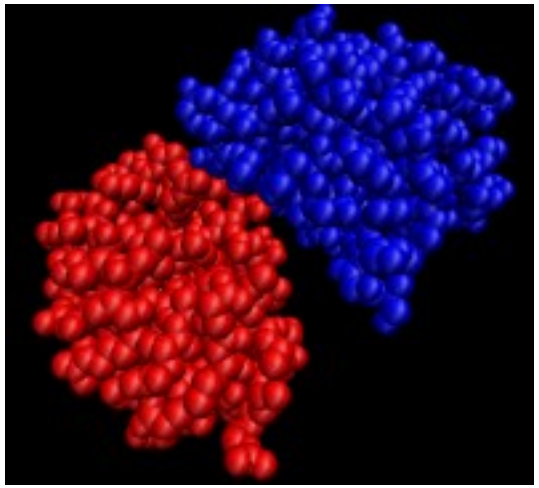
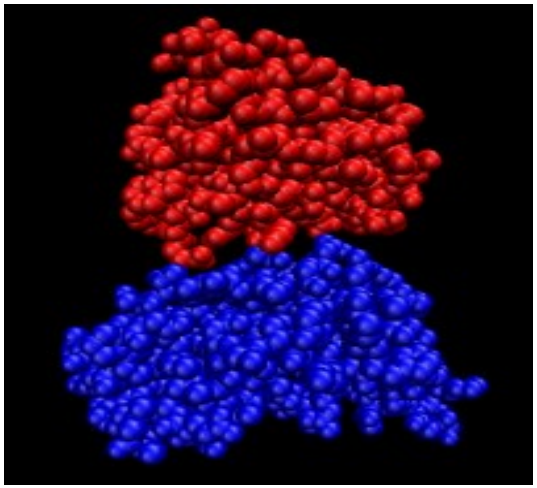
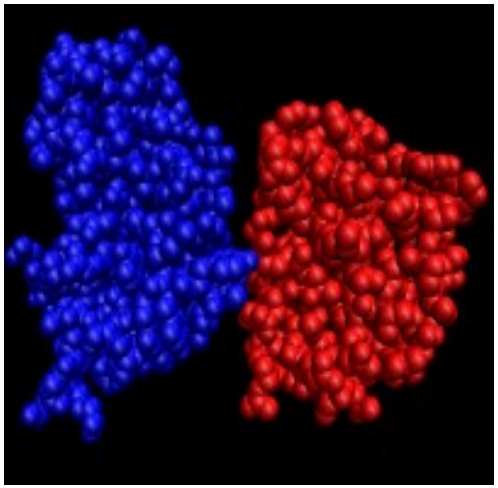


Why is docking important?

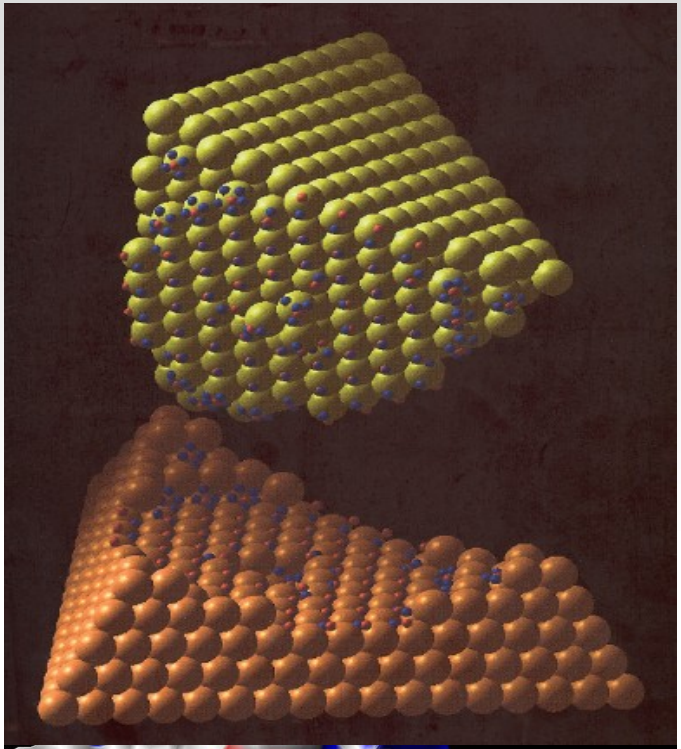
- It is of extreme relevance in **cellular biology**, where function is accomplished by proteins interacting with themselves and with other molecular components
- It is the key to rational **drug design**: The results of docking can be used to find inhibitors for specific target proteins and thus to design new drugs. It is gaining importance as the number of proteins whose structure is known increases

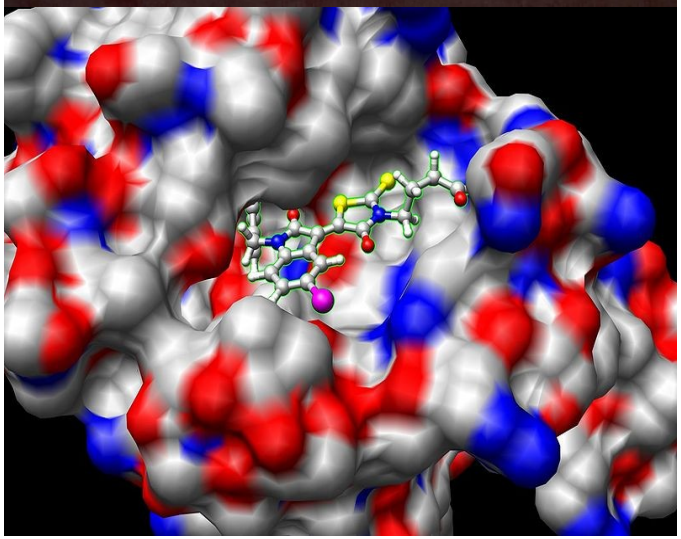
Why is the problem so complicated?

- Both molecules – receptor, ligand – are flexible
- Most complexes are not only designed by two molecules
- In many cases, we do not know the exact areas of molecules that are involved in the interactions

Docking approaches





- Matching technique that describes the protein and the ligand as complementary surfaces
- Simulation of the actual docking process in which the ligand-protein pairwise interaction energies are calculated

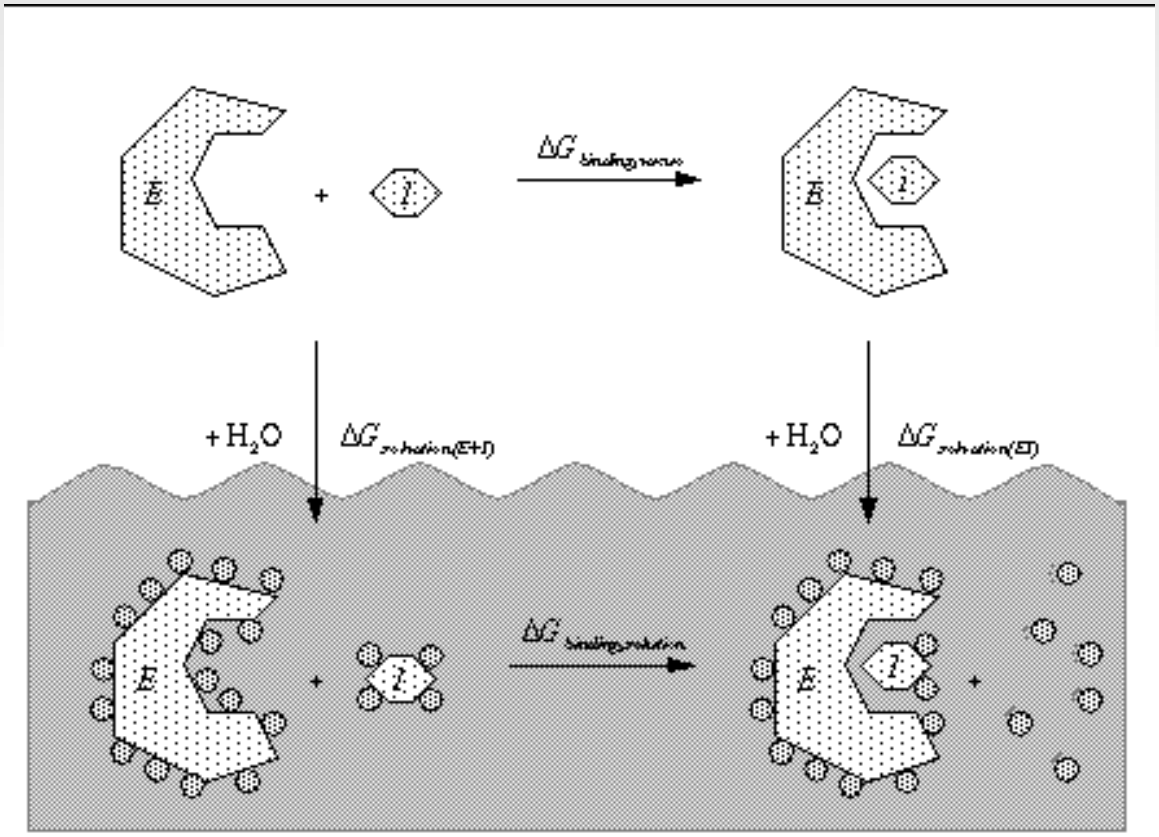
Docking methods

- Small ligand - large receptor
  - Rigid ligand into rigid receptor
  - Flexible ligand into rigid receptor
  - Flexible ligand into "flexible" receptor
- Protein – protein or protein – nucleic acid

Searching the conformational space for docking

- Molecular Dynamics
  - Simulated annealing
  - Dock,
- Genetic algorithm
  - AutoDock, GOLD
- Shape complementarity
  - Dock, GLIDE, FRED

Docking - approximations

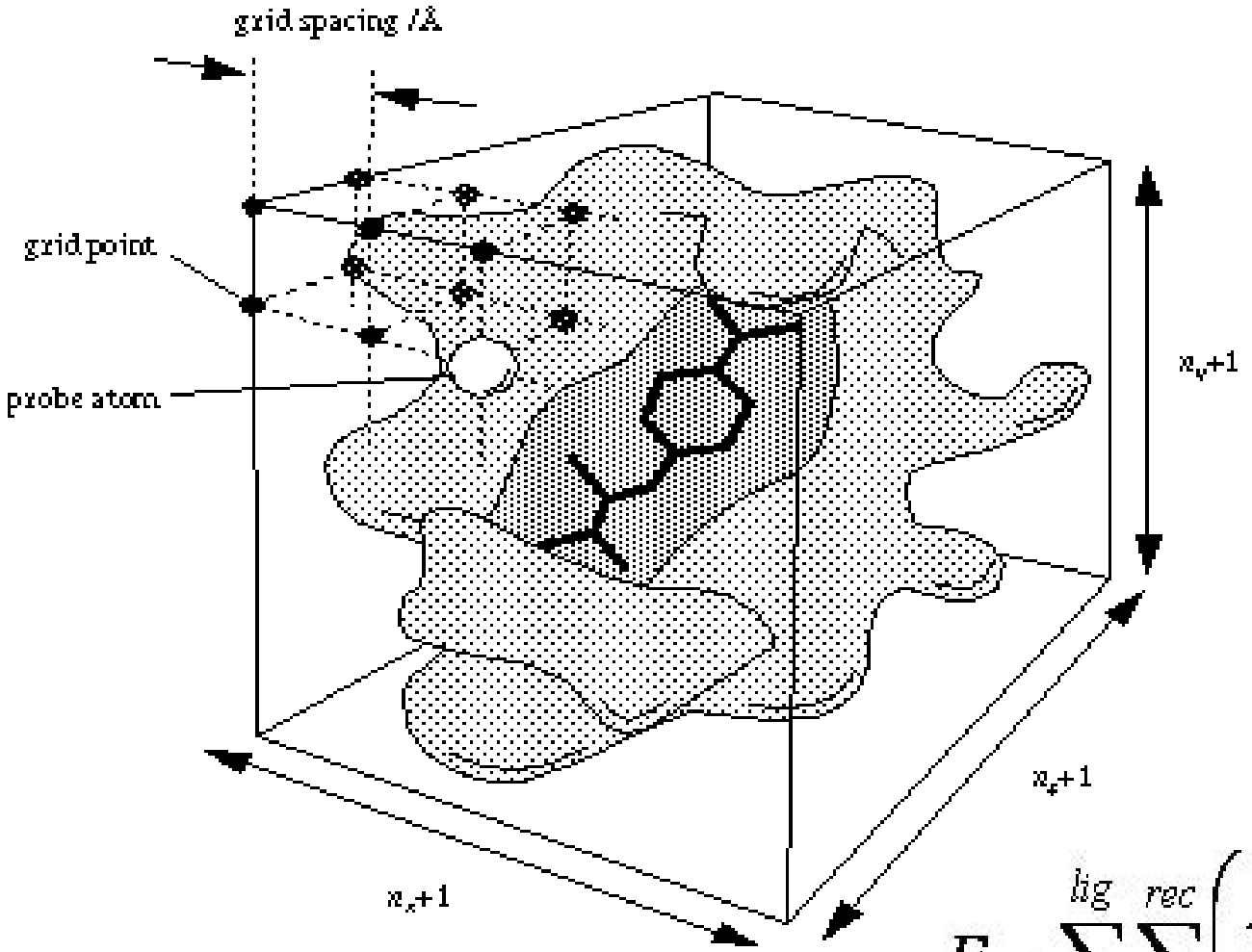


$$\Delta G_{binding/solution} = \Delta G_{binding/vakuo} + \Delta G_{solvation(E/I)} - \Delta G_{solvation(E+I)}$$

Docking - approximations

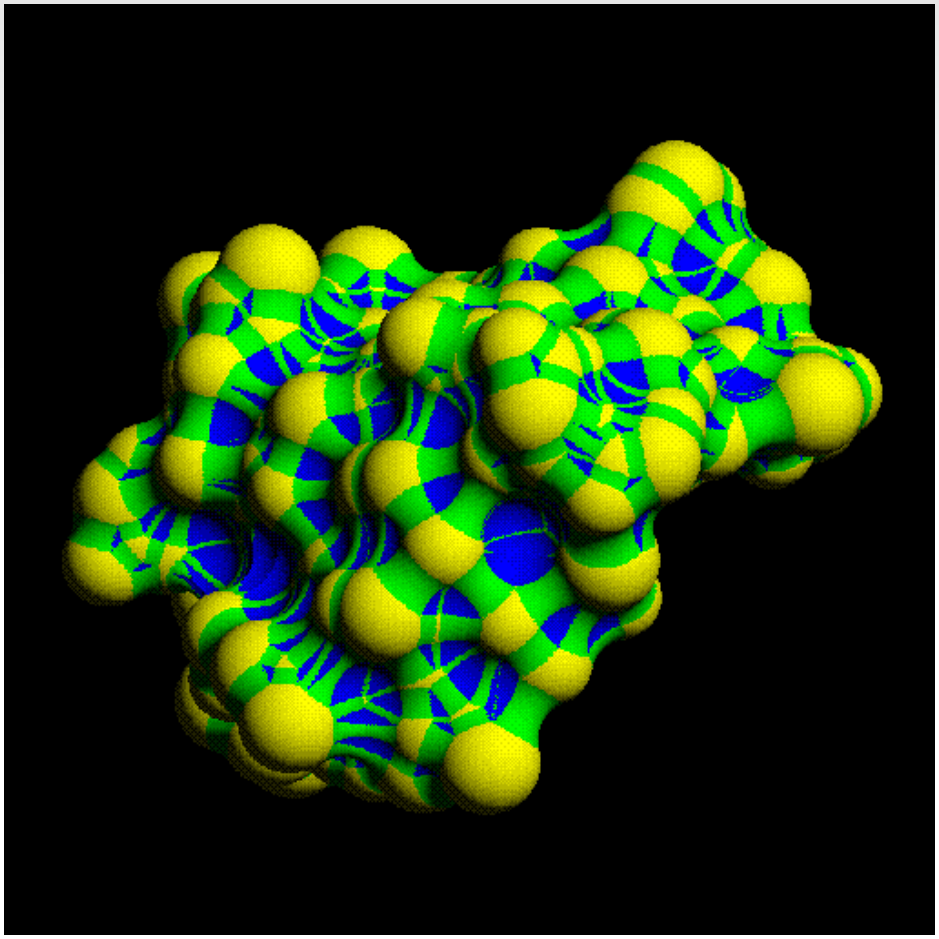
- First, interaction grids are calculated
- Focusing only on active site and not on the whole molecule
- Ligand is represented as the set of balls connected by springs
- Conformational space is described using non systematical methods
- First, chemical complementarity followed by energy calculations
- Solvent represented using implicit models

Docking – grid calculation



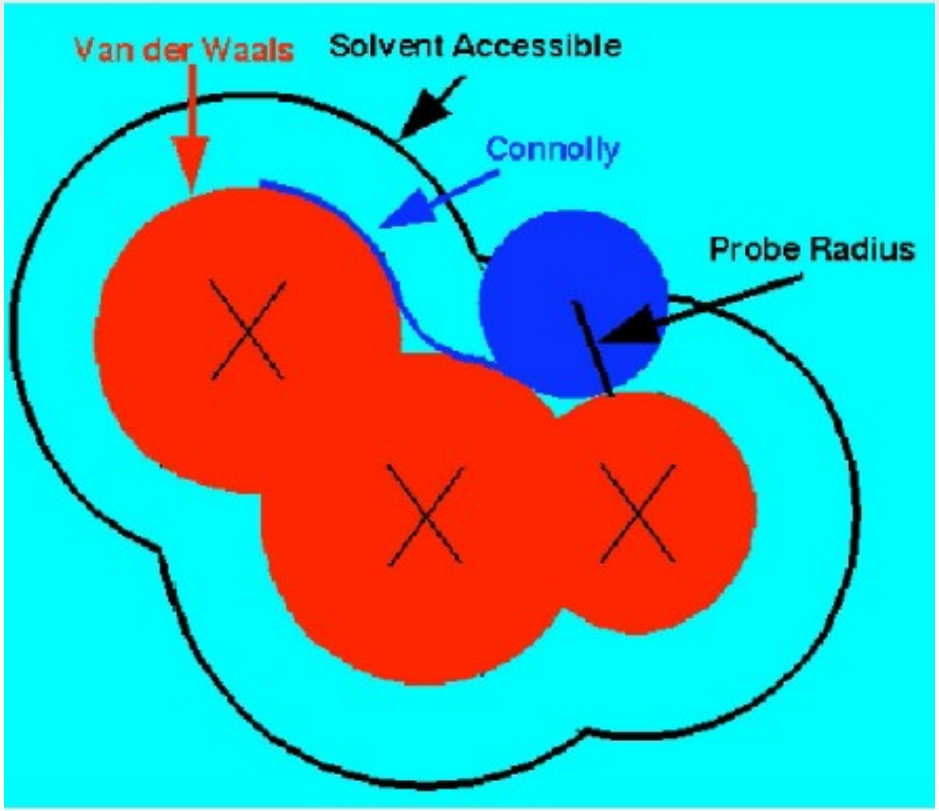
$$E = \sum_{i=1}^{lig} \sum_{j=1}^{rec} \left(\frac{A_{ij}}{r_{ij}^{a}} - \frac{B_{ij}}{r_{ij}^{b}} + 332 \frac{q_i q_j}{D r_{ij}} \right)$$

Docking – molecular surface



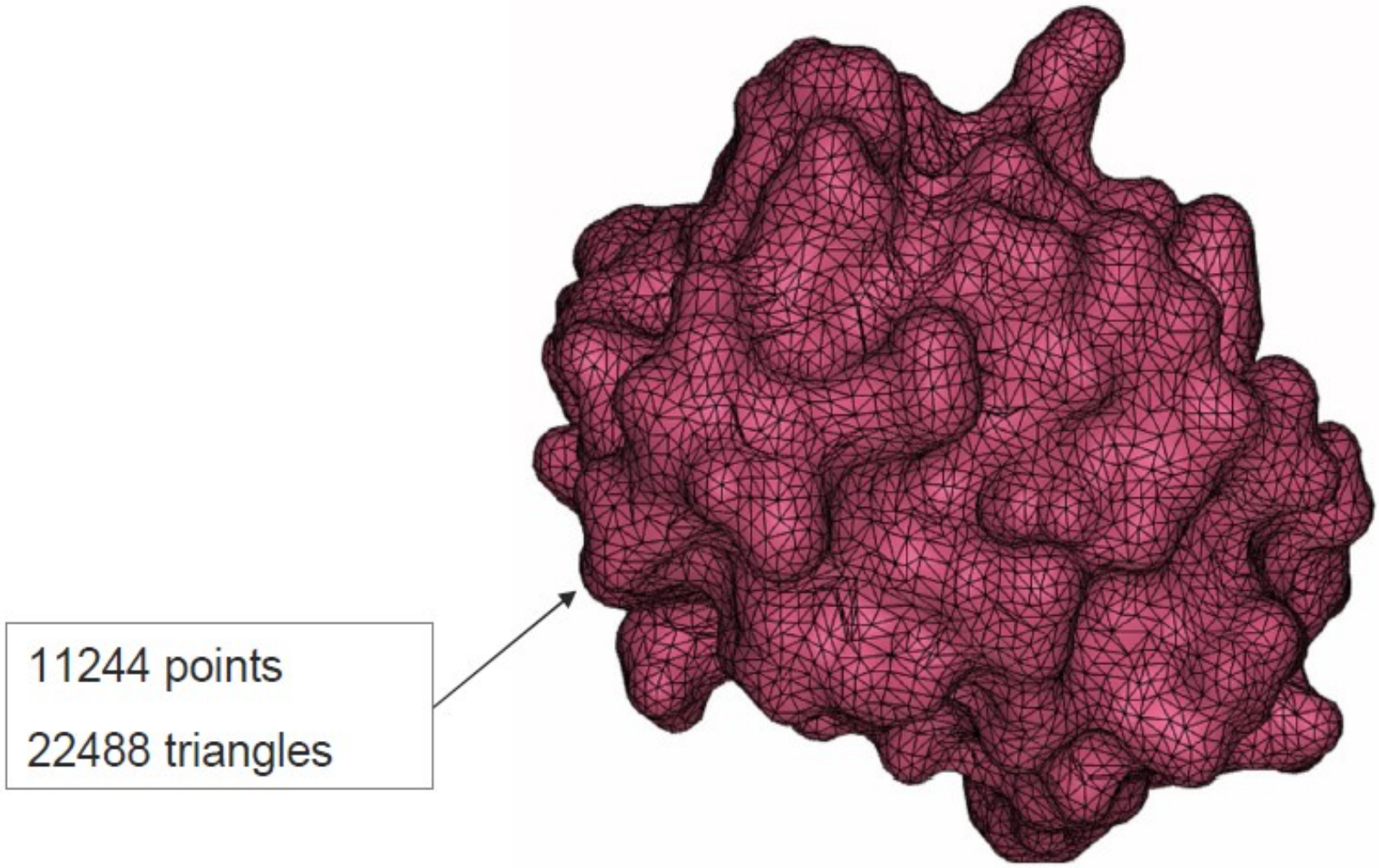
- Each atom is represented by the sphere with Vad der Waals radii. There are used Conolly surface, solvent accessible surface.

Docking – surface representation



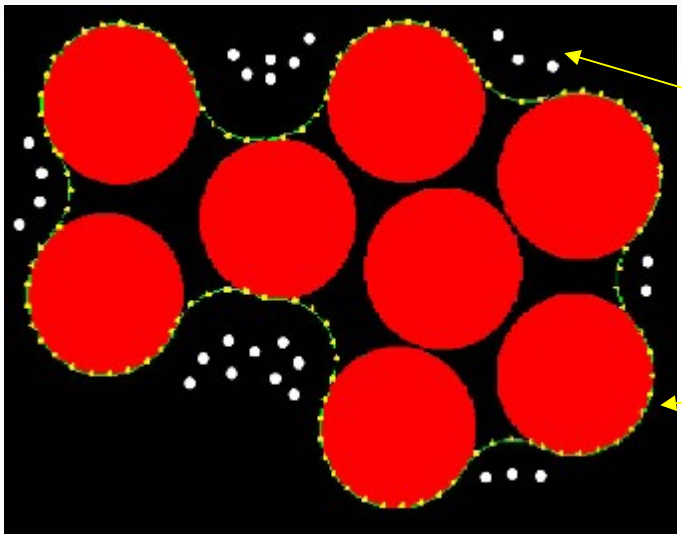
- Rolling a Probe Sphere over the molecule
- Everywhere the center of the sphere goes is the Solvent Accessible Surface (SAS)
- Everywhere the sphere touches (including empty space) is the Solvent Excluded (or "Connolly") Surface (SES)

MS Surface - Connolly



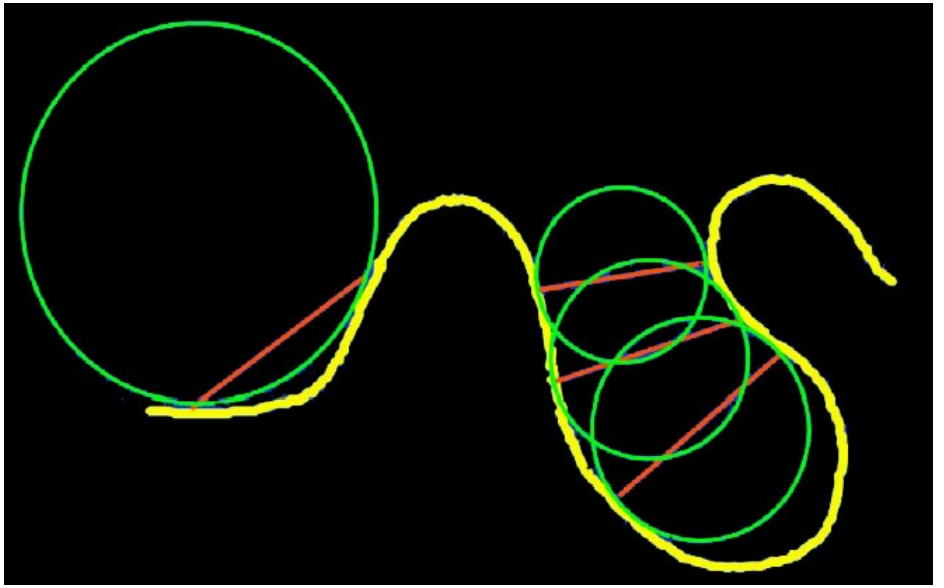
Lenhoff technique

- Computes a “complementary” surface for the receptor instead of the Connolly surface, i.e. computes possible positions for the atom centers of the ligand



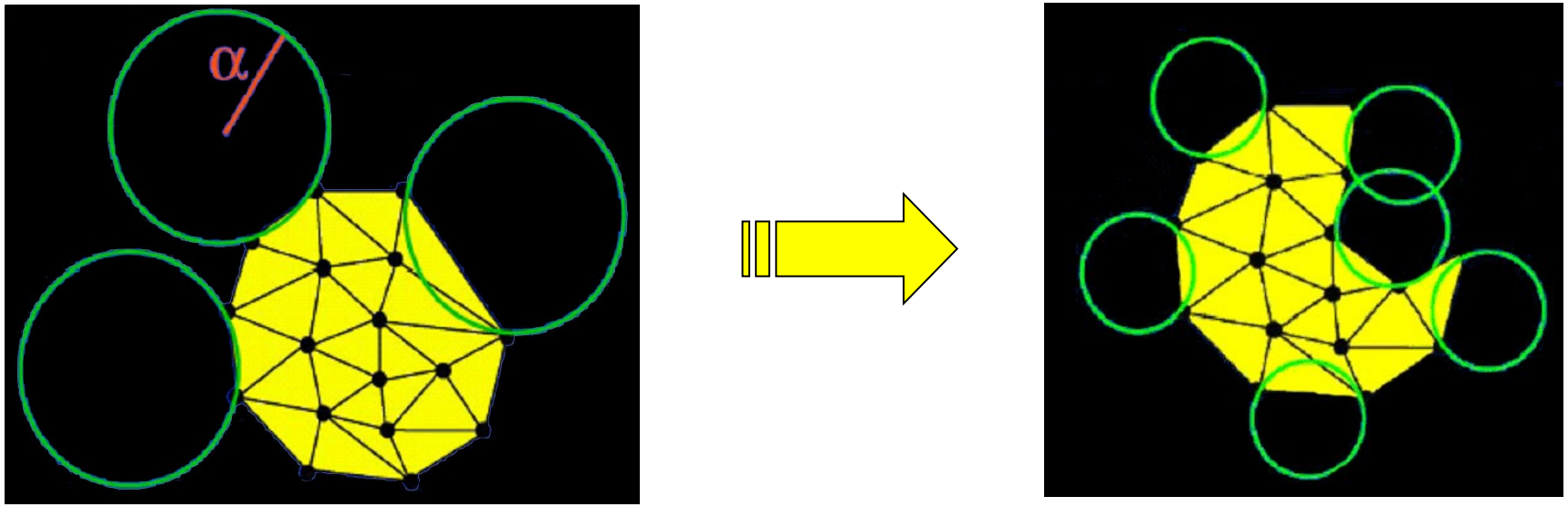
Kuntz et al. Clustered spheres

- Uses clustered-spheres to identify cavities on the receptor and protrusions on the ligand
- Compute a sphere for every pair of surface points, i and j, with the sphere center on the normal from point i
- Regions where many spheres overlap are either cavities (on the receptor) or protrusions (on the ligand)

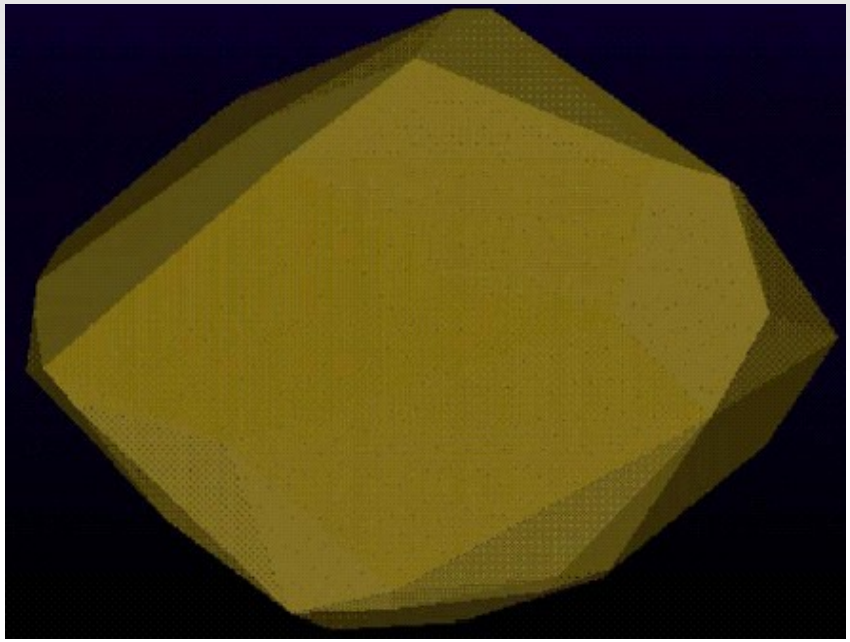


Alpha shapes

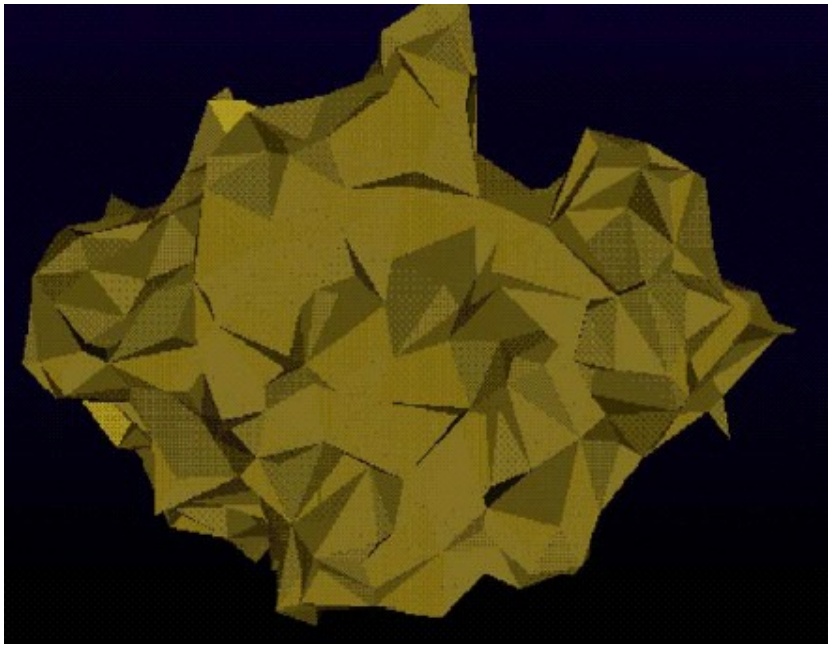
- Formalizes the idea of "shape"
- In 2D an "edge" between two points is "alpha-exposed" if there exists a circle of radius alpha such that the two points lie on the surface of the circle and the circle contains no other points from the point set



Alpha shapes



Alpha=infinity



Alpha=3.0 Å

Surface matching

- Find the transformation (rotation + translation) that will maximize the number of matching surface points from the receptor and the ligand

First satisfy steric constraints…

- Find the best fit of the receptor and ligand using only geometrical constraints

… then use energy calculations to refine the docking

- Selet the fit that has the minimum energy

Geometric hashing

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First satisfy steric constraints …

- Find the best fit of the receptor and ligand using only geometrical constraints

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- Selet the fit that has the minimum energy

Geometric hashing

- Determine those entries that received more than a threshold of votes, such entry corresponds to a potential match
- For each potential match recover the transformation T that results in the best least-squares match between all corresponding triplets
- Transform the features of the model according to the recovered transformation T and verify it. If the verification fails, choose a different receptor triplet and repeat the searching

Docking algorithms

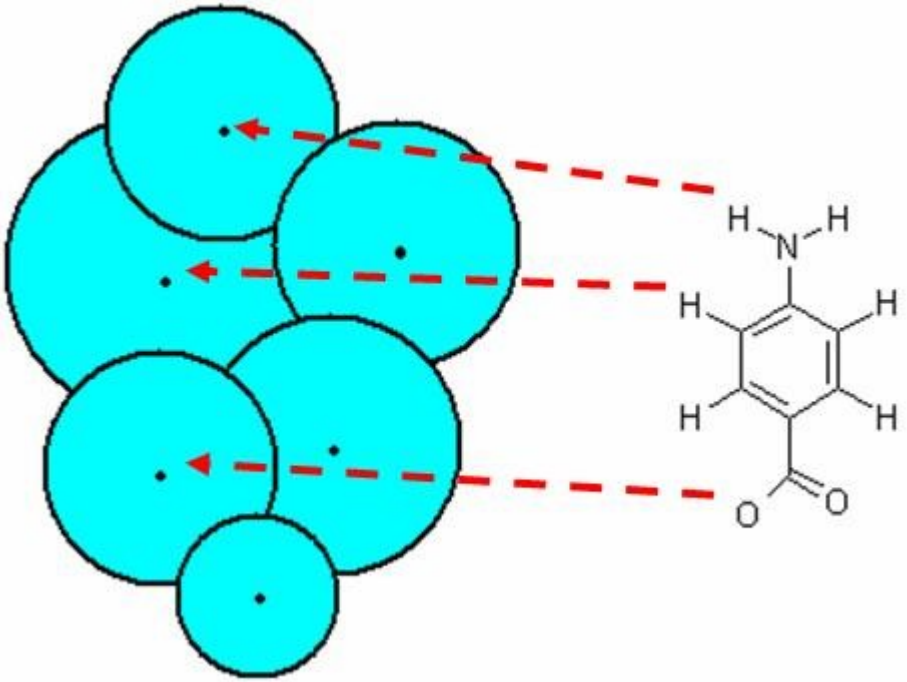
- Manual docking
- Rigid docking
- Flexible docking
  - Anchor and Growth algorithm
  - Monte Carlo
  - Genetic algorithm
- MD rescoring

Manual docking

- Precomputed vdw and electrostatic grid
- Use experience and knowledge of user
  - Is advantage and also lack of the method
- It is not automated
- Should be connected with haptic computer system and user can feel the attractions and repulsions during ligand movement
- Slow method in comparison with automated methods

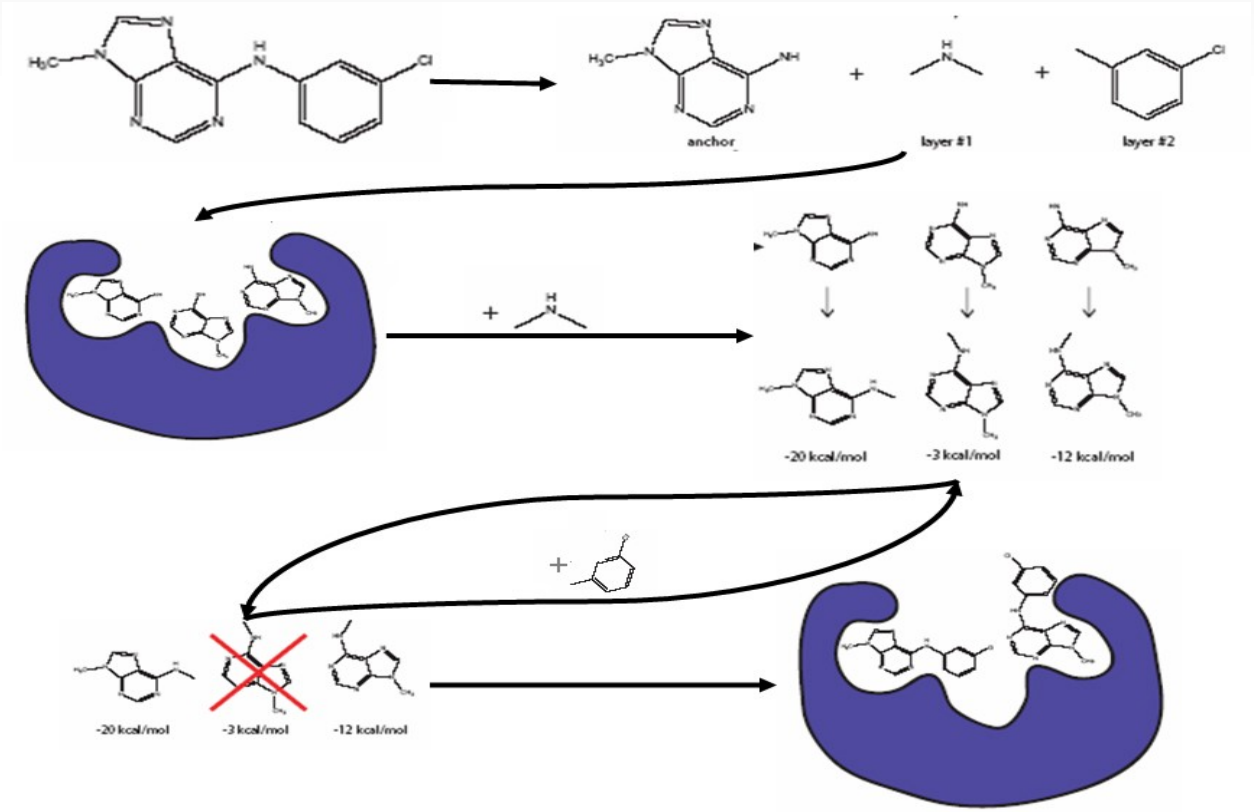
Rigid docking

- Only one conformation of ligand
- 6 degrees of freedom (3 rotations and 3 translations)
- The use is very limited on rigid ligands or on docking of different conformations of the ligand into receptor
- Relatively fast method



Flexible docking – Anchor and Growth algorithm

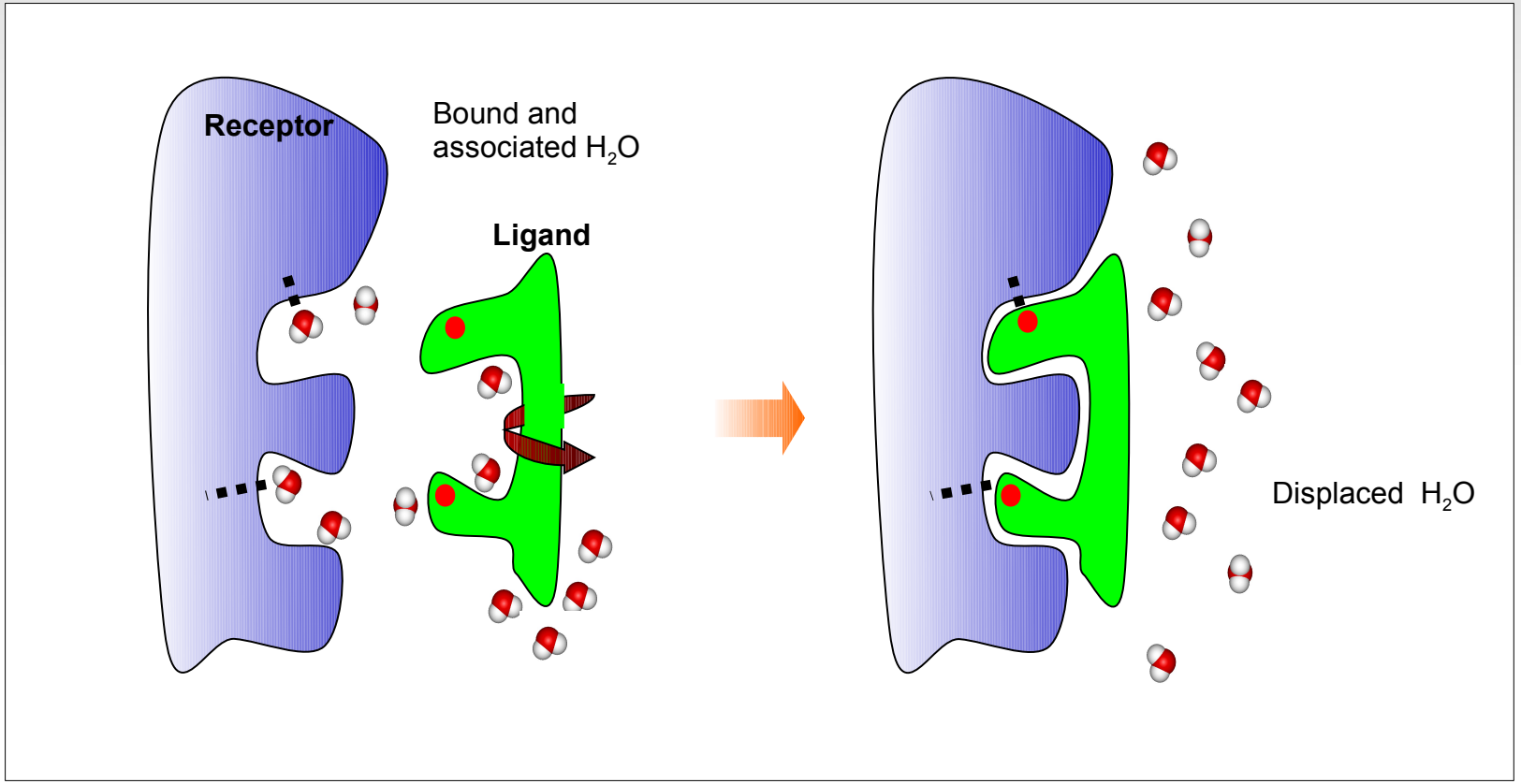
- Molecule is divided into rigid pieces that are docked separately
- The largest part of the ligand is docked firstly



Flexible docking

- Monte Carlo
  - Randomly generated conformations randomly placed into receptor
- Genetic algorithm
  - Conformations and orientation described as genetic code
  - Mutation or cross-over changes are used for generation of new conformations and orientations

What happens during complex association



MD - rescoring

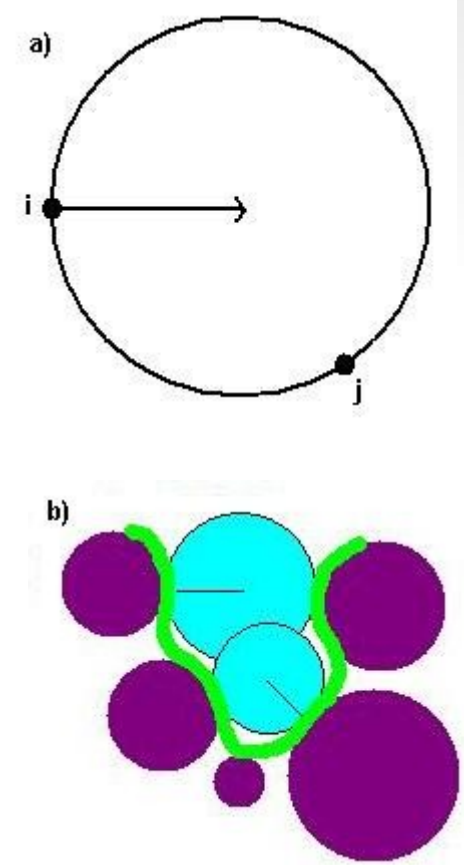
- Is postdock method
- The best docked structures are evaluated using classical MD simulations in implicit or explicit solvent.
- Slower than classical docking but in many cases more precise in energy or geometry point of view
- Very powerful for flexible systems

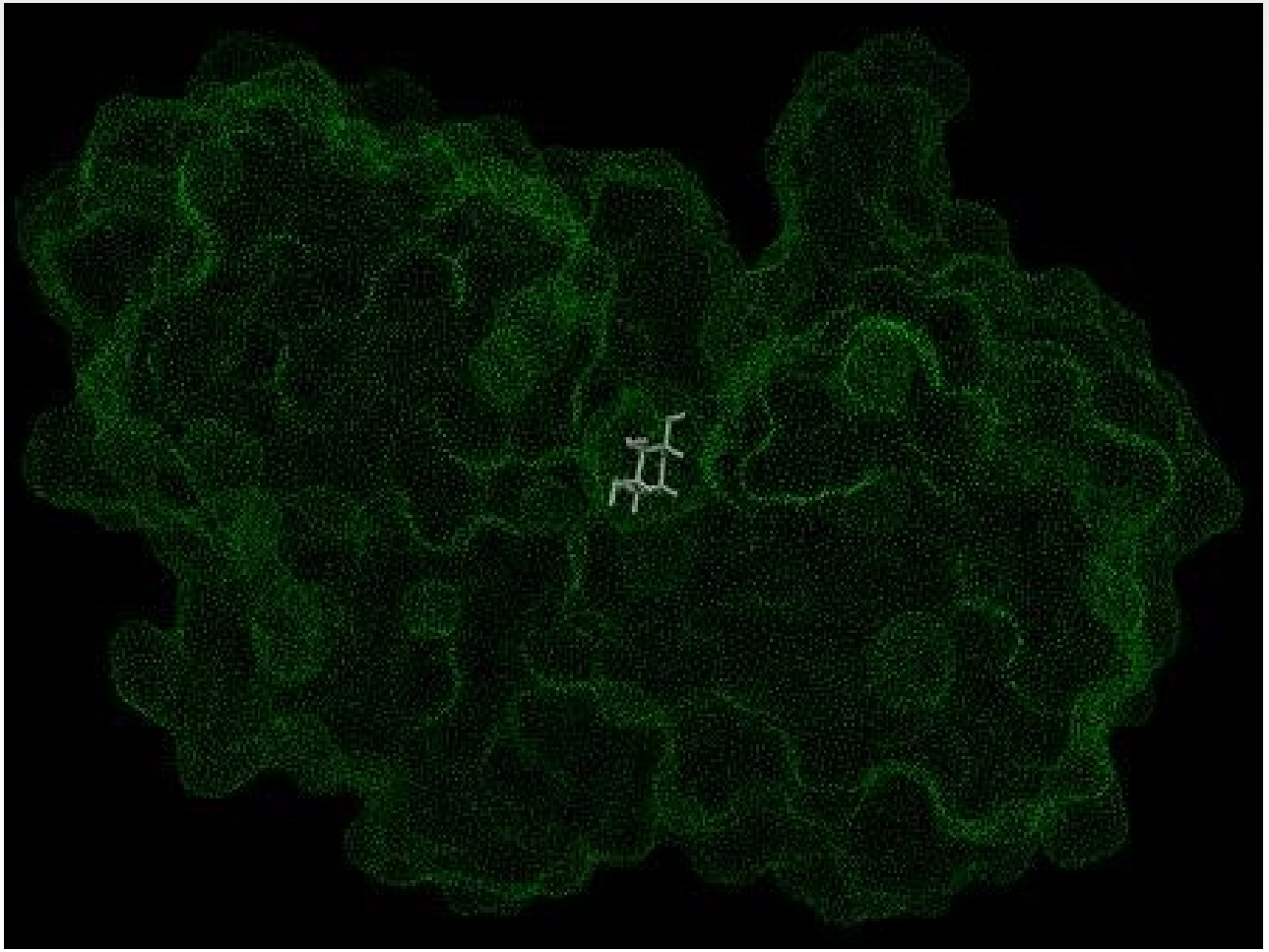
Program DOCK

- The first docking software
- Current version is 6.4
- Author I. D. Kuntz – UCSF
- Powerful for rigid or flexible docking, protein – protein docking also available
- Free for academic users
- Distributed in source code

Dock

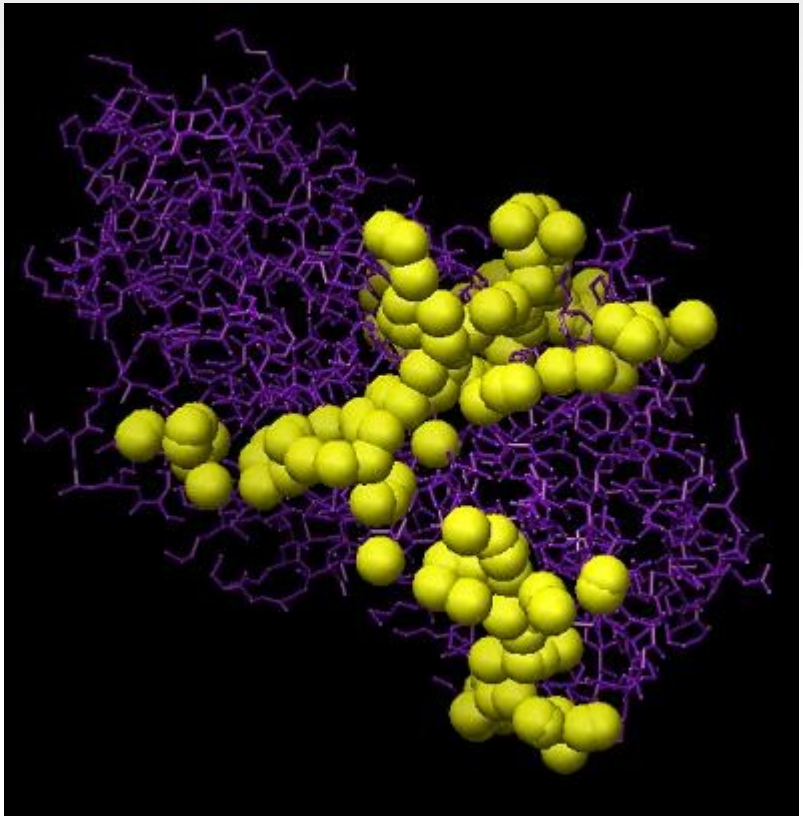
- Sphere generation

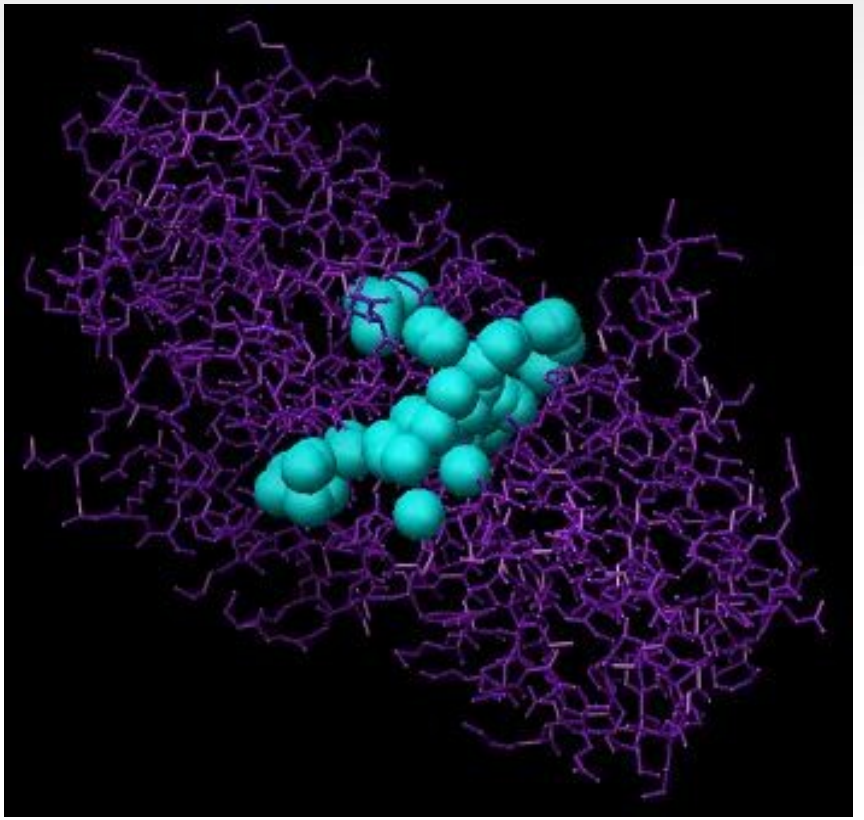




Dock

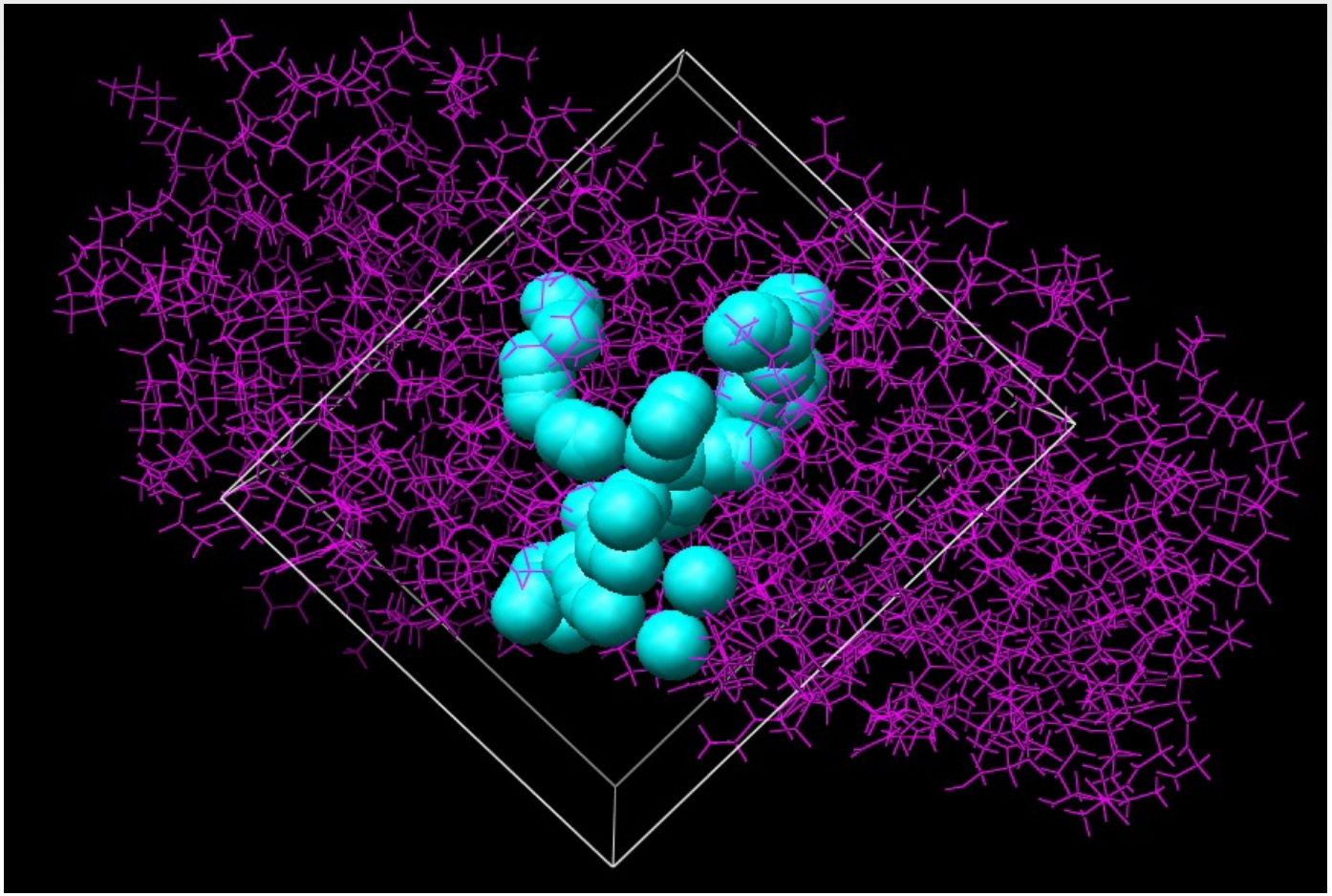
- Selection of spheres





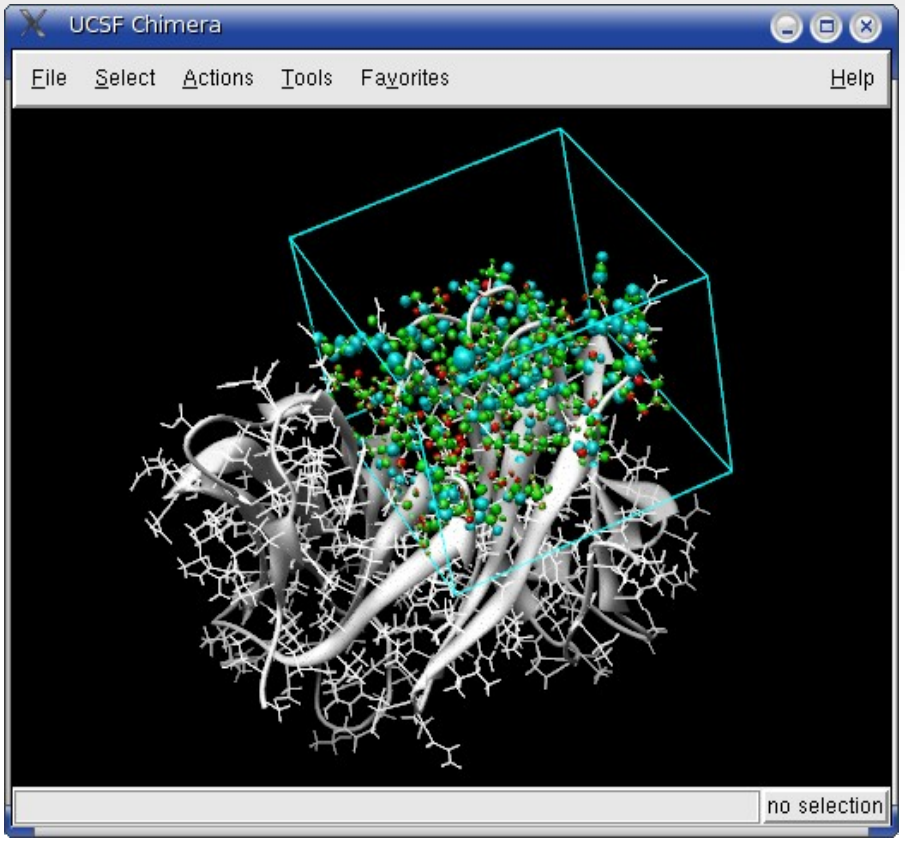
Dock

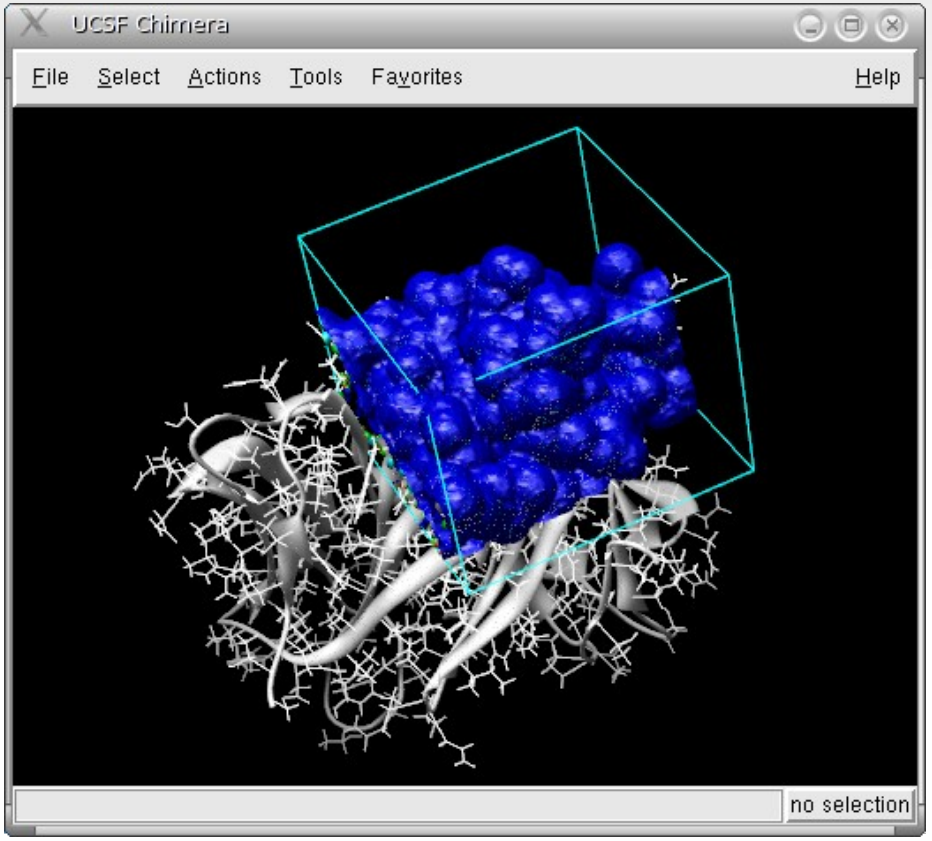
- Grid preparation



Dock

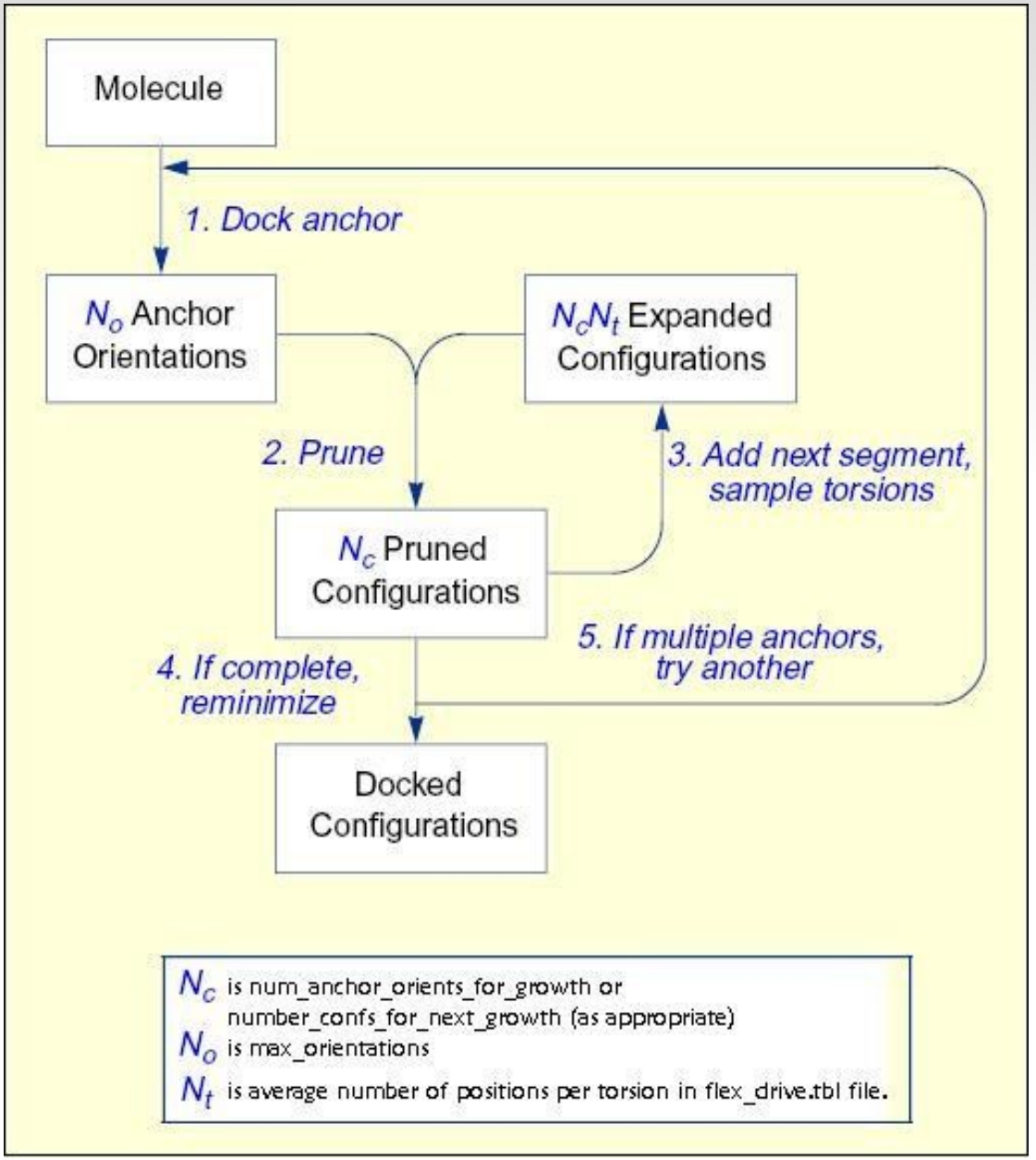
- Grid calculation



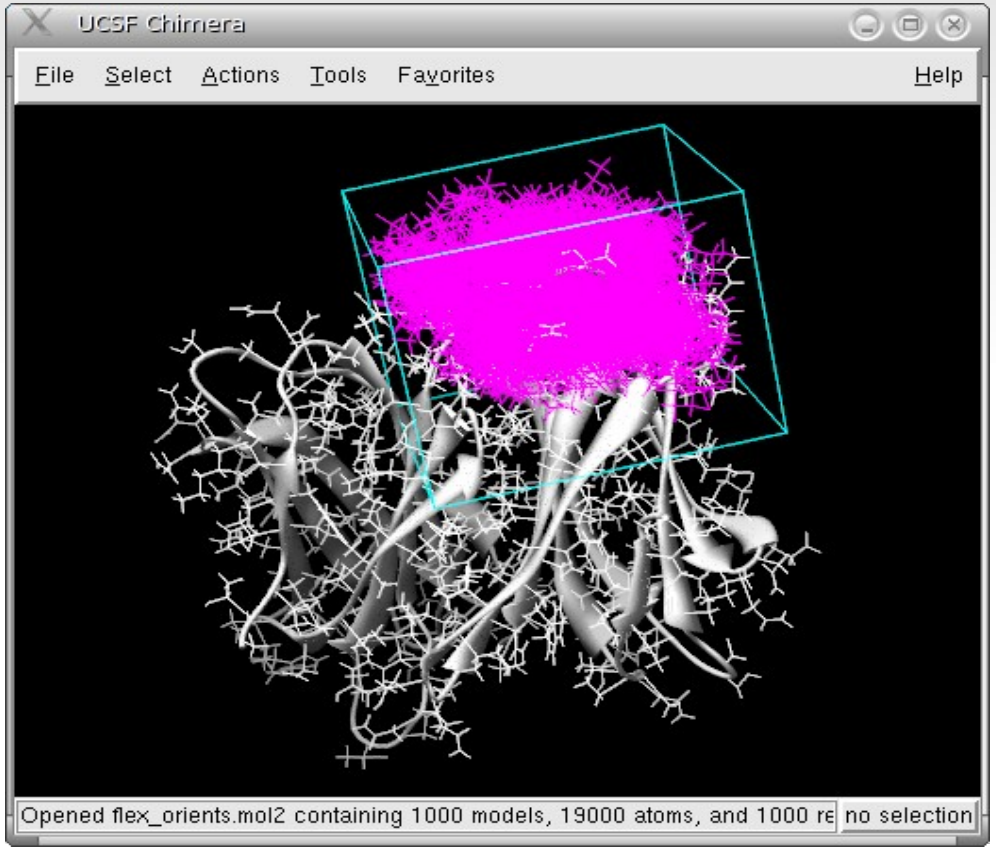


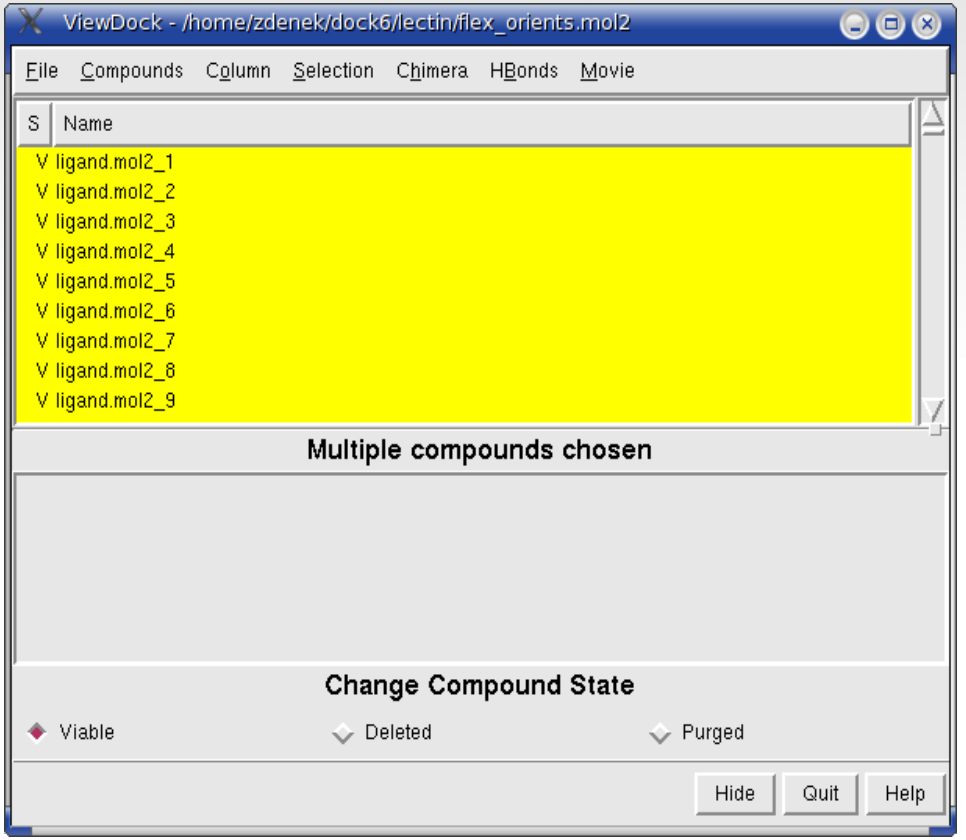
Dock

- Docking

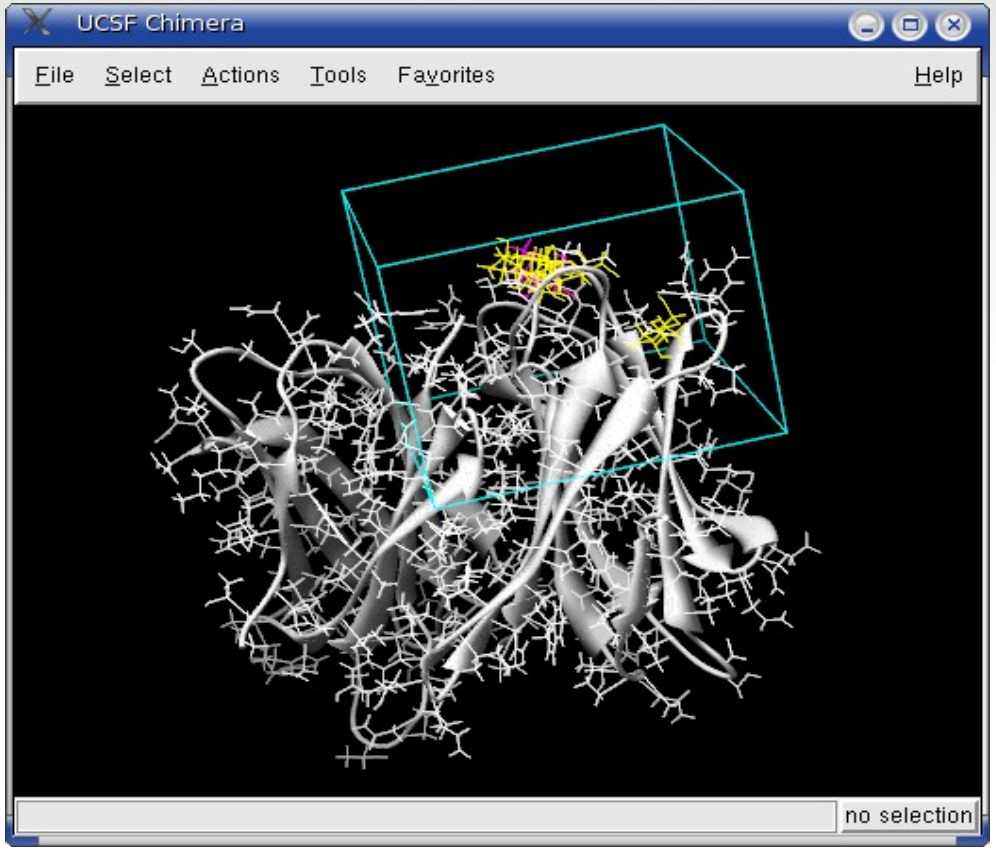


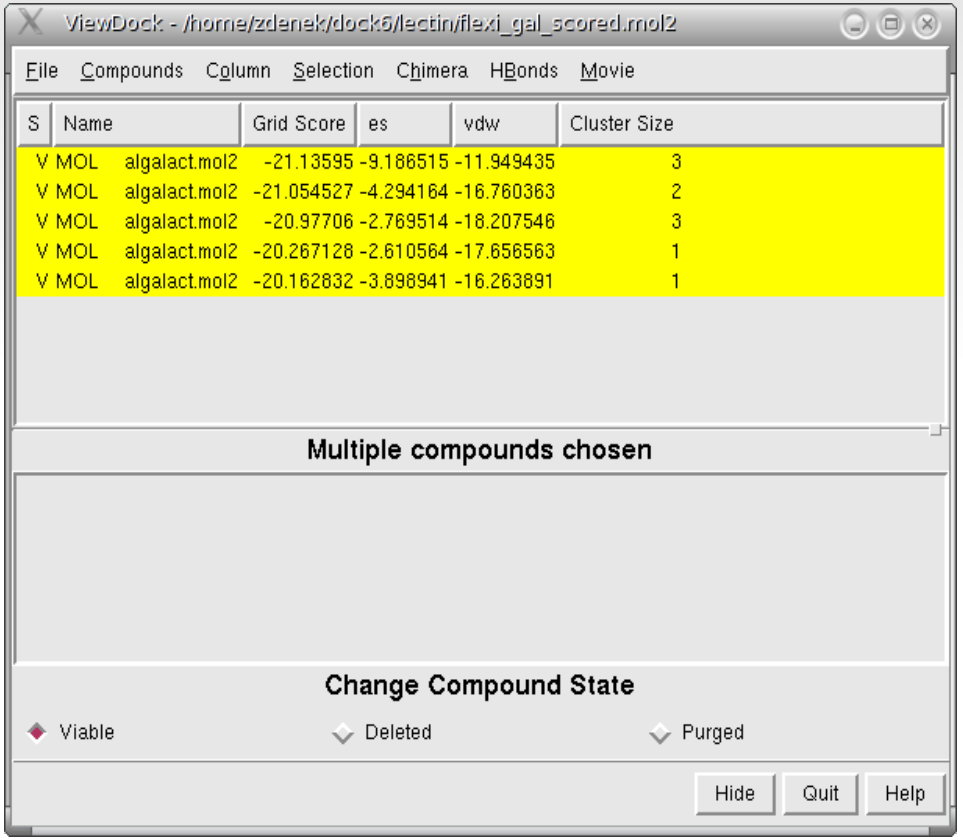
Docking results



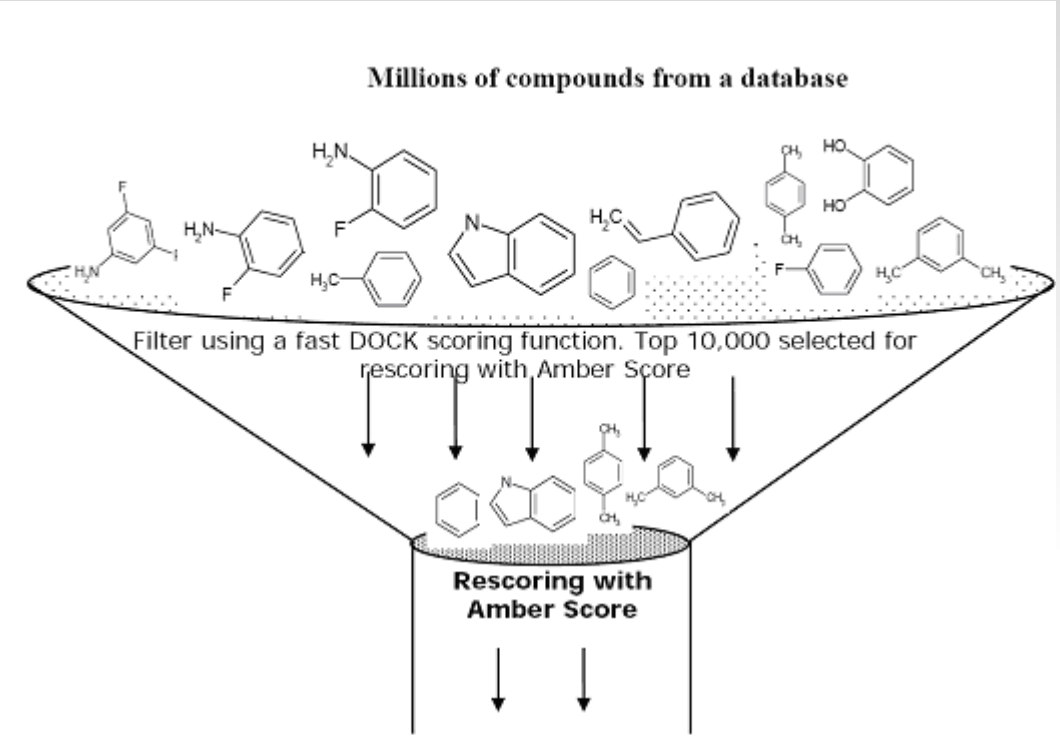


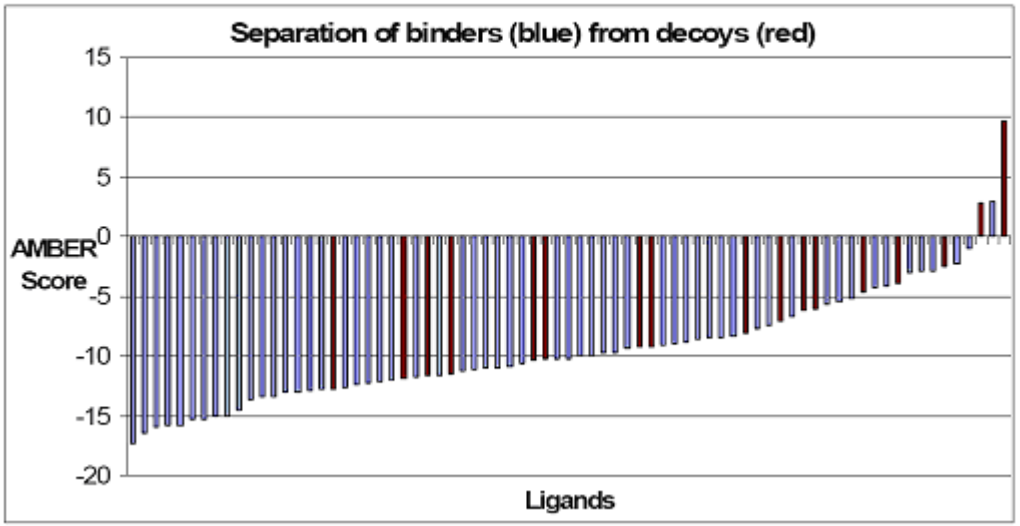
Docking results





Dock – AMBER rescoring

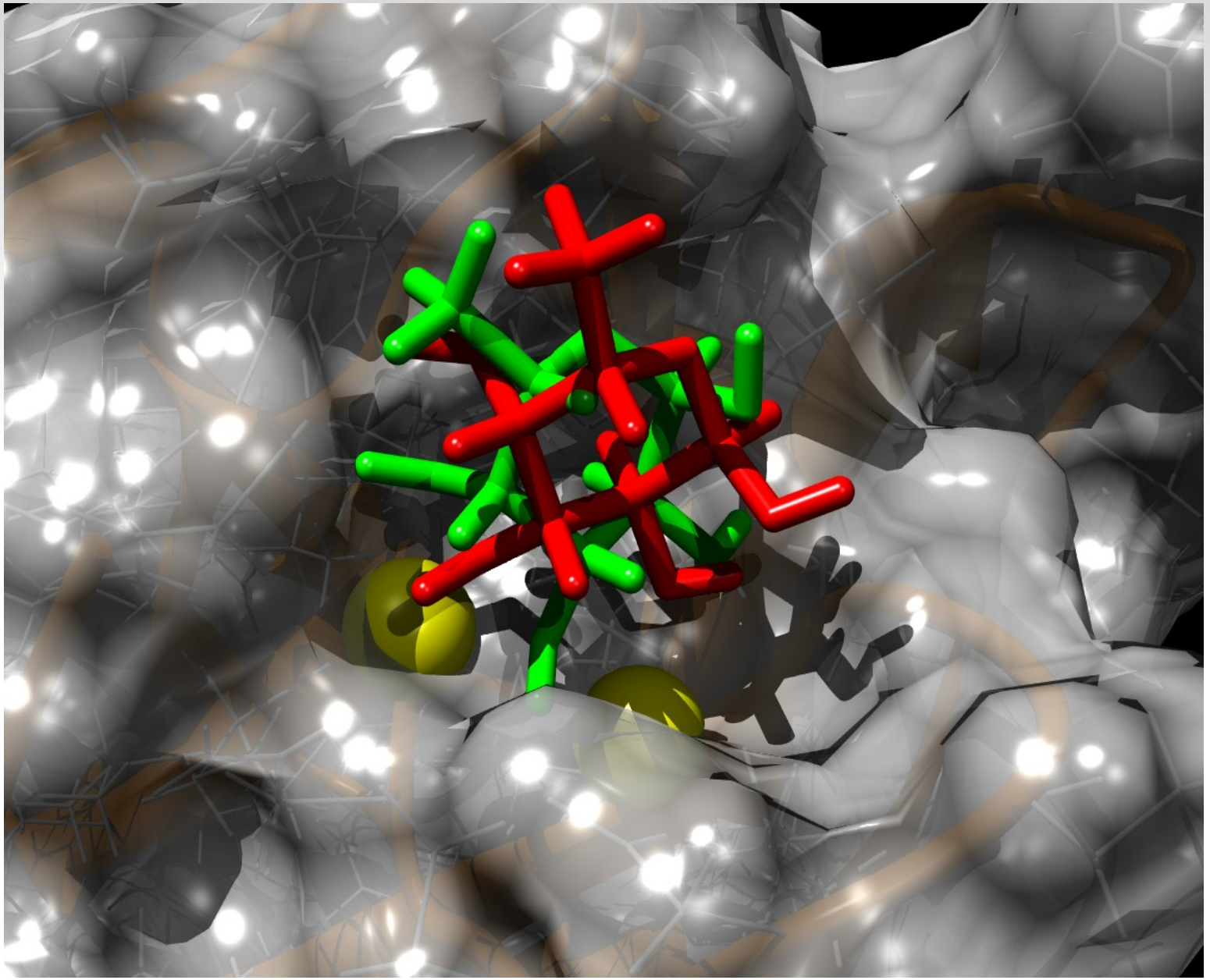




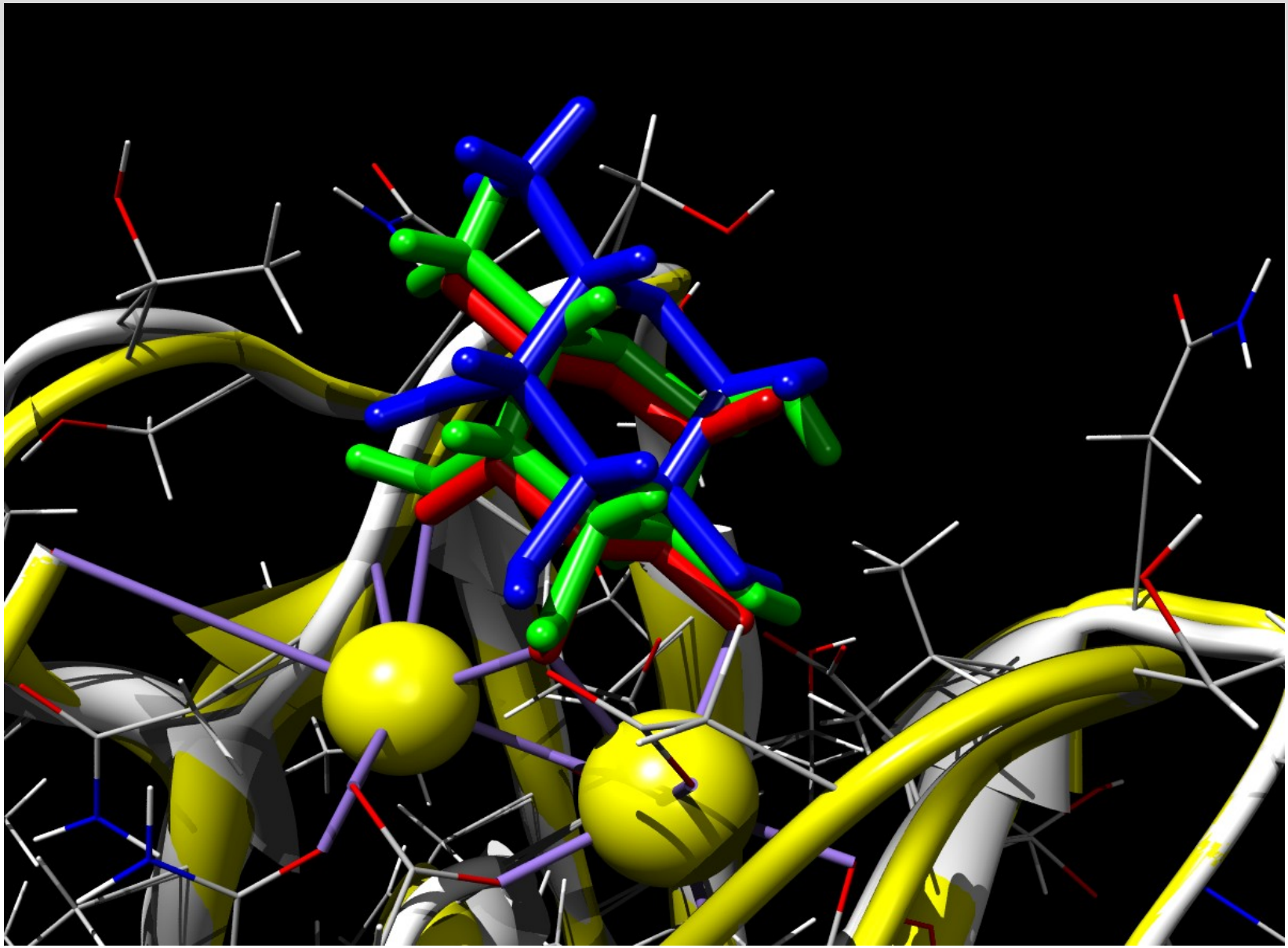
Dock – AMBER rescoring

- Movable ligand, ligand + active site, all
- Use AMBER MD simulations in implicit solvent
- Is used as secondary scoring function
- Should combine minimization with molecular dynamics simulation

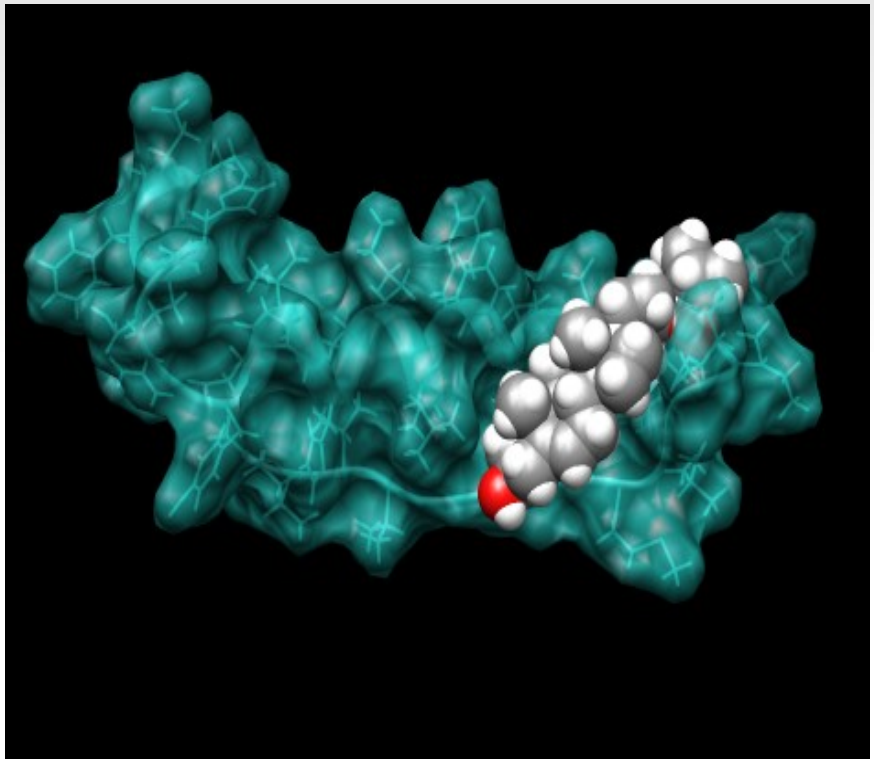
Dock – charge of atoms

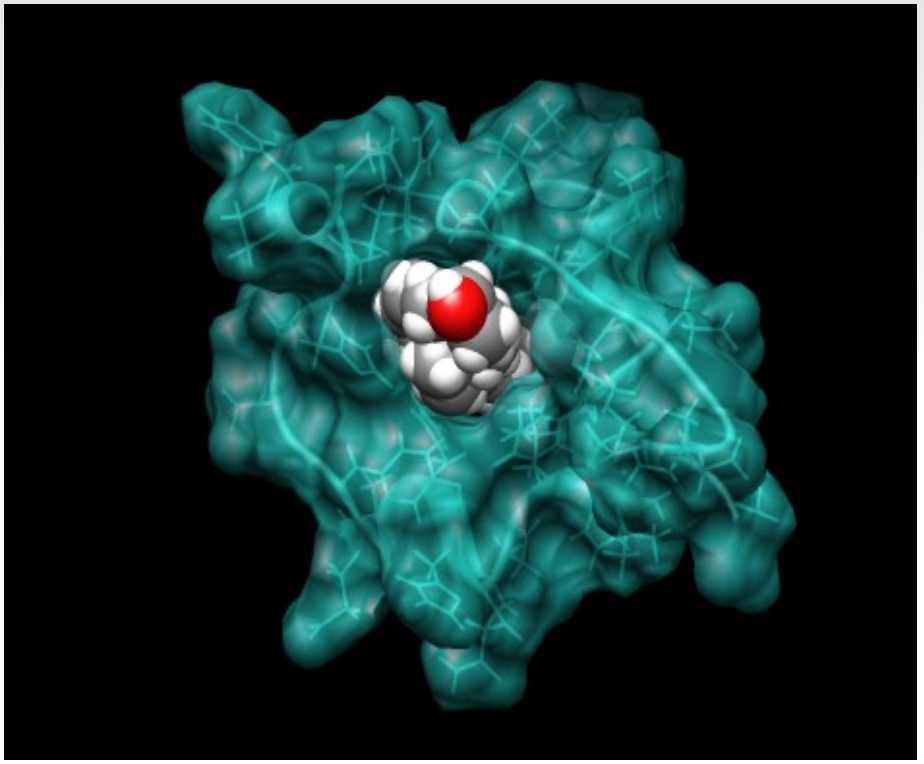


Dock – AMBER rescoring



Dock – AMBER rescoring + MD in explicit solvent





Other docking software

- AutoDock
- RosettaDock
- FlexX
- FTDock
- FlexiDock
- Gold
- ICM-Dock
- MolFit