Molecular modeling in drug discovery

- ligand-based drug design

- similarity searching

- pharmacophore models (sometimes SBDD)

- structure-based drug design

- protein-ligand docking

- simulation-based methods

Structure-based drug design

	Targets	Ligands
Source	PDB (www.pdb.org)	ZINC (zinc.docking.org) ChEMBL, PubChem
Formats	PDB, mol2	mol2, sdf, smiles
Viewers	VMD, UCSF Chimera, Pymol and others	Chemaxon tools
Utilities	finding sites – fpocket conversion – OpenBabel	conversion – OpenBabel

Docking tasks

- prediction of binding mode(s)

- virtual screening

- other purposes

Docking essentials

- protein structure

- ligand structure

- algorithm:
  genetic algorithms, ant colony optimization, simulated annealing, incremental building

- scoring function:
  - potential energy
  - potential of mean force
  - empirical

Docking pitfalls

- protein heterogeneity
  dynamics/induced fit, protonation states, tautomers, water, cofactors ...

- ligand structure
  tautomers, protonation states, rings, cis/trans and other isomers, salts ...

- too much rotatable bonds

- metals

- poor scoring performance

- poorly druggable or difficult for docking sites

Caution

- docking is a compromise between speed and accuracy!

- error of ~2 kcal/mol for well established docking models

- it systematically over/under estimates affinities for some classes of targets or ligands

- predicted affinity tends to increase with ligand size

- be careful about removal of bound cofactors, proteins etc.

Virtual screening

1. chose and prepare target site
2. download a library of compounds
3. filter unwanted compounds
4. dock compounds
5. select the best compounds
6. purchase them and test them

Virtual screening

Retrospective vs. prospective

Receiver-operator curve (ROC)