Docking

The Big Picture

- Drug design made more efficient
- Docking vs QSAR
- Advantages and limitations of docking
  - Search method
  - Scoring function*******

Docking

- The study of multi-molecular complexes
- **"Structure-based drug design requires a detailed knowledge of three-dimensional molecular structure" –Garrett Morris**
- **Data available for individual conformation of ligand and protein, but not of ligand:protein complex**
- Common use: to study the interactions between proteins and small molecules (often inhibitors) in order to design improved ligands for that protein

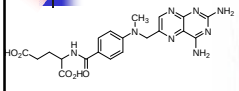
Challenges

- The lowest energy conformation of a molecule is dependent on its environment
  - The conformation of a small molecule may change when bound to a protein
  - The conformation of a protein may change when bound to a small molecule
  - Water molecules may mediate interactions
- The stability of the complex is best reflected by the Gibb's free energy for the process mol1 + mol2 <=> mol1:mol2

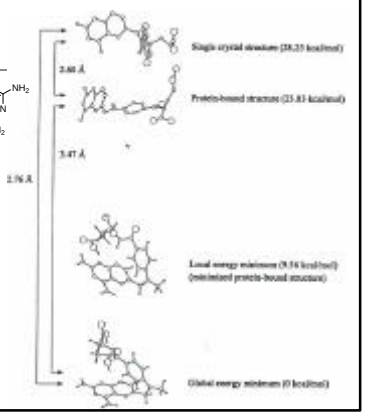
Pure/Complex Crystal Comparison

No.	Compound	RMS_{220} (Å)
Rigid Compounds		
1	Adamantane	0.08
2	β-L-Arabinose	0.043 ± 0.002
3	*trans*-Retinol	0.068 ± 0.015
4	DMSO	0.026 ± 0.011
5	Guanine	0.04
6	Imidazole	0.025 ± 0.002
Flexible Compounds		
7	ADP	1.62 ± 0.41
8	ATP	2.63 ± 0.51
9	Biotin	1.18
10	Chloramphenicol	0.584 ± 0.033
11	Citric acid	1.04 ± 0.25
12	Dimethylformamide	0.394 ± 0.033
13	Fructose-6-phosphate	0.41 ± 0.21
14	FK506	2.96
15	α-D-Galactose	0.485 ± 0.007
16	β-D-Galactose	0.129 ± 0.002
17	β-D-Glucose	0.554 ± 0.001
18	p-Hydroxybenzoic acid	0.963 ± 0.003
19	Isocitric acid	0.716 ± 0.050
20	D-Malic acid	0.294
21	L-Malic acid	0.84 ± 0.36
22	Maleic acid	0.501 ± 0.087
23	Maltose	0.579
24	Methotrexate	2.68 ± 0.16
25	Oxamic acid	0.188 ± 0.004
26	2-Phospho-D-glyceric acid	1.09
27	3-Phosphoglyceric acid	0.838
28	PALA	1.46 ± 0.18
29	Pyridoxamine-5-phosphate	0.569
30	Pyruvic acid	0.141
31	D-Sorbitol	1.01
32	Sucrose	1.72
33	Xylitol	0.915 ± 0.039

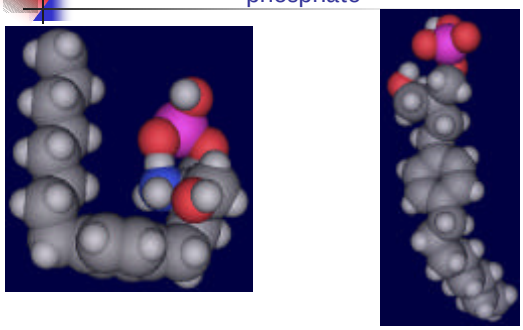
Nicklaus et al., "Conformational Changes of Small Molecules Binding to Proteins", Bioorg. Med. Chem., 1995, 3(4), 411-428



methotrexate



Conformational changes in FTY720 phosphate



Class Exercise I

- See handout

Common Docking Simplifications

- Protein Conformation
  - Rigid (MOE, DOCK, Autodock...)
  - Limited protein side chain flexibility (Flexi-dock)
- Ligand Conformation
  - Fully flexible
- Binding Free Energy
  - Grid-based interaction energy (MOE, Autodock)
  - Shape complementarity (DOCK)
  - Functional group complementarity (DOCK)
  - Empirical (SCORE ...)

General Docking Algorithms

1. Generate a relative orientation for the two molecules
   A. Randomly with subsequent optimization (MOE)
   B. Matched to protein surface (DOCK, Autodock)
2. Evaluate or score the orientation
   A. Grid-based
   B. Empirical
3. Repeat

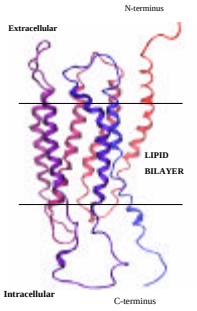
Grid-Based Dock Scoring

- Possible interactions with the protein are pre-computed
  - A grid of points that occupies the same volume as the protein is generated
  - Steric and electrostatic interactions with the protein at each point are computed
- The ligand orientation is scored by summing interactions at grid points contacting the ligand
- Neglected
  - Solvation changes upon binding
  - Entropy changes upon binding
  - Protein conformational changes

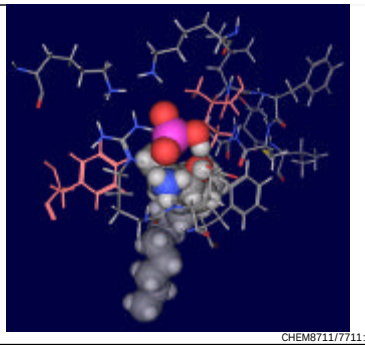
Class Exercise II

- See handout

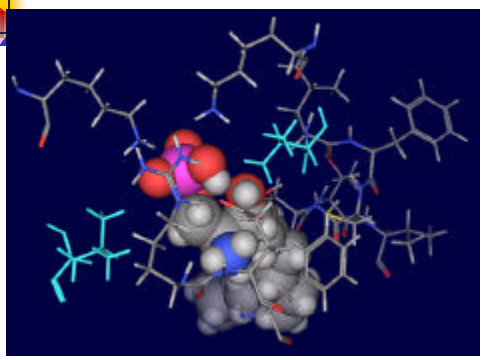
Receptor selectivity: a docking application to solve a stubborn problem



S1P_S1P2_TM5_CHIMERA



S1P_S1P2_TM5_CHIMERA_I5.41V/F7.39L



Quantitative Improvement

Interaction	Chimera	DM Chimera
K5.38 - phosphate	4.07Å	2.92Å
K7.34 - phosphate	4.95Å	2.90Å
R3.28 - phosphate	2.87Å	2.64Å
E3.29- ammonium	3.10Å	2.75Å

Docking in VHTS

- HTS: High Throughput Screening
  - Very rapid (and qualitative) means to screen libraries of chemical structures for biological activity
  - Represented a potential elimination of computational chemistry in the pharmaceutical industry
- VHTS: Virtual High Throughput Screening
  - Very rapid (and approximate) docking methods designed to evaluate libraries of compounds to enrich elaborated libraries with active compounds

Reading

- First Edition: Section 10.3
- Second Edition: Section 12.6