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 mo1 + mol2 <=> mol1:mol2

Pure/Complex Crystal Comparison

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

Quantitative Improvement

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Chimera</th>
<th>DM Chimera</th>
</tr>
</thead>
<tbody>
<tr>
<td>K5.38 - phosphate</td>
<td>4.07Å</td>
<td>2.92Å</td>
</tr>
<tr>
<td>K7.34 - phosphate</td>
<td>4.95Å</td>
<td>2.90Å</td>
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<tr>
<td>R3.28 - phosphate</td>
<td>2.87Å</td>
<td>2.64Å</td>
</tr>
<tr>
<td>E3.29 - ammonium</td>
<td>3.10Å</td>
<td>2.75Å</td>
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</tbody>
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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