An Introduction to Molecular Docking

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What is Docking?

• *In silico* (computer-based) approach
• Identification of bound conformation
• Prediction of binding affinity
• Docking vs. (Virtual) Screening

• 2 “Modes”:
  – Respective: How does your molecule bind? What is its mode of action? What might be the reaction mechanism?
  – Prospective: What compounds might be good leads? What compound(s) should you make?
Docking Basics

- Initially – Receptor (protein) and ligand rigid
- Most current approaches – Receptor rigid, ligand flexible
- Advanced approaches – Receptor (to a degree) and ligand flexible
2 Stages of Docking

• Pose generation
  – Place the ligand in the binding site
  – Generally well solved

• Pose selection
  – Determine the proper pose
  – The hard part
Pose Generation

• Rigid docking with a series of conformers
  – Most techniques use this approach
  – Most techniques will generate the conformers internally rather than using conformers as inputs

• Incremental construction (FlexX)
  – Split ligand into base fragment and side-chains
  – Place base
  – Add side-chains to grow, scoring as you grow

• In general, use a very basic vdW shape function

• Often see variability with input conformers
Pose Selection/Scoring

• Where most of the current research focused
• More sophisticated scoring functions take longer
  – Balance need for speed vs. need for accuracy
  – Virtual screening needs to be very fast
  – Studies on single compounds can be much slower
  – Can do multi-stage studies
Example Multi-Stage Screening Workflow

2x10^6 Compounds

Glide HTVS – 10 seconds/compound = 2.3 days on 100 CPUs

2x10^5 Compounds

Glide SP – 120 seconds/compound = 2.7 days on 100 CPUs

2x10^4 Compounds

Glide XP – 10 minutes/compound = 1.4 days on 100 CPUs

2x10^3 Compounds

Visual Analysis, further refinement, synthetic considerations
Scoring Strategies

- Many tools use scoring grids to increase speed
  - AutoDock, UCSF DOCK, Glide

- Scoring function types
  - Force-field – electrostatic + vdW (+ solvation)
  - Empirical – many (LUDI, ChemScore), often combined with FFs
  - Knowledge-based – compare interactions to some reference set (DrugScore)

\[ S_{total} = \sum_{i \rightarrow \# f} w_i S_i \]

Weights from fitting to empirical binding data
Dealing with Protein Flexibility

• Reduce vdW radii
• Use flatter vdW function (e.g., 4-8 instead of 6-12)
• Alanine mutations
• Ensemble docking – use multiple input receptor structures
• Side-chain rotations – SLIDE
• Induced Fit Docking – far slower, Glide
What makes a good docking target?

• Deep, well defined pocket
  – Shallow pockets have too many options

• Sites for specific interactions
  + Many charge-charge or h-bonding sites
  – Mostly hydrophobic vdW interactions bad

• Well ordered side-chains
Receptor Preparation

- Dependent on docking program used
- Structure selection
- Site selection
- Add charges
- Often have to add hydrogens, some programs more sensitive to positions than other
- Remove/include waters, cofactors, metals
- Pre-docking refinement
- Remember to consider missing residues or atoms
Ligand preparation

• Input structures (extract from PDB, draw, convert from SMILES)
• Add bond orders
• Generate isomers if chiral centers
• Calculate charges
  – Predict pKa’s for each potential charged atom
  – Generate a structure for each charge combination for a given pH range (e.g., 5-9)
• Minimize structures
  – Generally using a molecular mechanics forcefield
• For Screening, can download public sets from ZINC (available compounds) or PubChem
How do we rate docking programs?

• Accuracy measures
  – Generally take average RMSD (comparing to crystal structures)
  – Better analyses consider interactions
  – Screening enrichment
    • Screen set of known actives + inactives
    • Do we see actives disproportionally represented in top x%?
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Docking Packages

• Free
  – AutoDock (Art Olsen, David Goodsell, Scripps)
  – UCSF DOCK (Kuntz Group)

• Commercial
  – Glide (Schroedinger)
  – GOLD (CCDC)
  – FlexX (BiosolveIT)
  – ICM (Molsoft)
  – Surflex (Tripos)
Autodock Demo

- p38 (PDB code 1w83)