An Introduction to Molecular Docking

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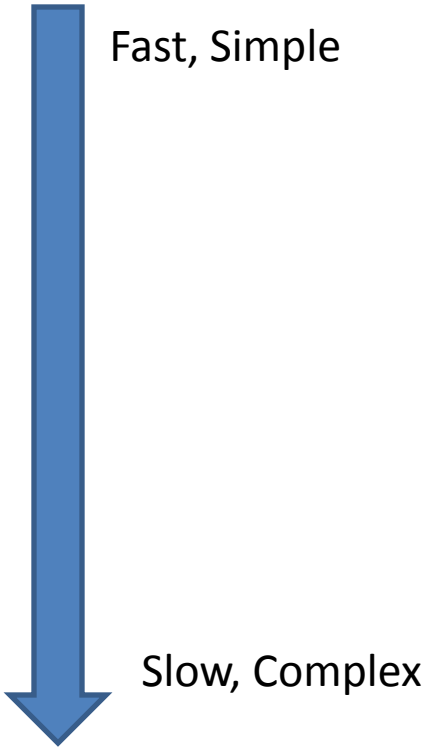
What is Docking?

- *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

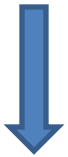
- Rigid docking with a series of conformers
  - Most techniques use this approach
  - Most techniques will generate the conformers internally rather than using conformers as inputs
- Incremental construction (FlexX)
  - Split ligand into base fragment and side-chains
  - Place base
  - Add side-chains 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

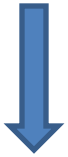
Example Multi-Stage Screening Workflow

$2x10^6$ Compounds



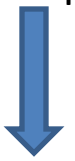
Glide HTVS – 10 seconds/compound = 2.3 days on 100 CPUs

$2x10^5$ Compounds



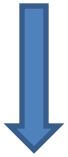
Glide SP – 120 seconds/compound = 2.7 days on 100 CPUs

$2x10^4$ Compounds



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

$2x10^3$ Compounds



Visual Analysis, further refinement, synthetic considerations

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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

$$S_{total} = \sum_{i \to \#f} w_i S_i$$

Weights from fitting to empirical binding data

  - Knowledge-based – compare interactions to some reference set (DrugScore)

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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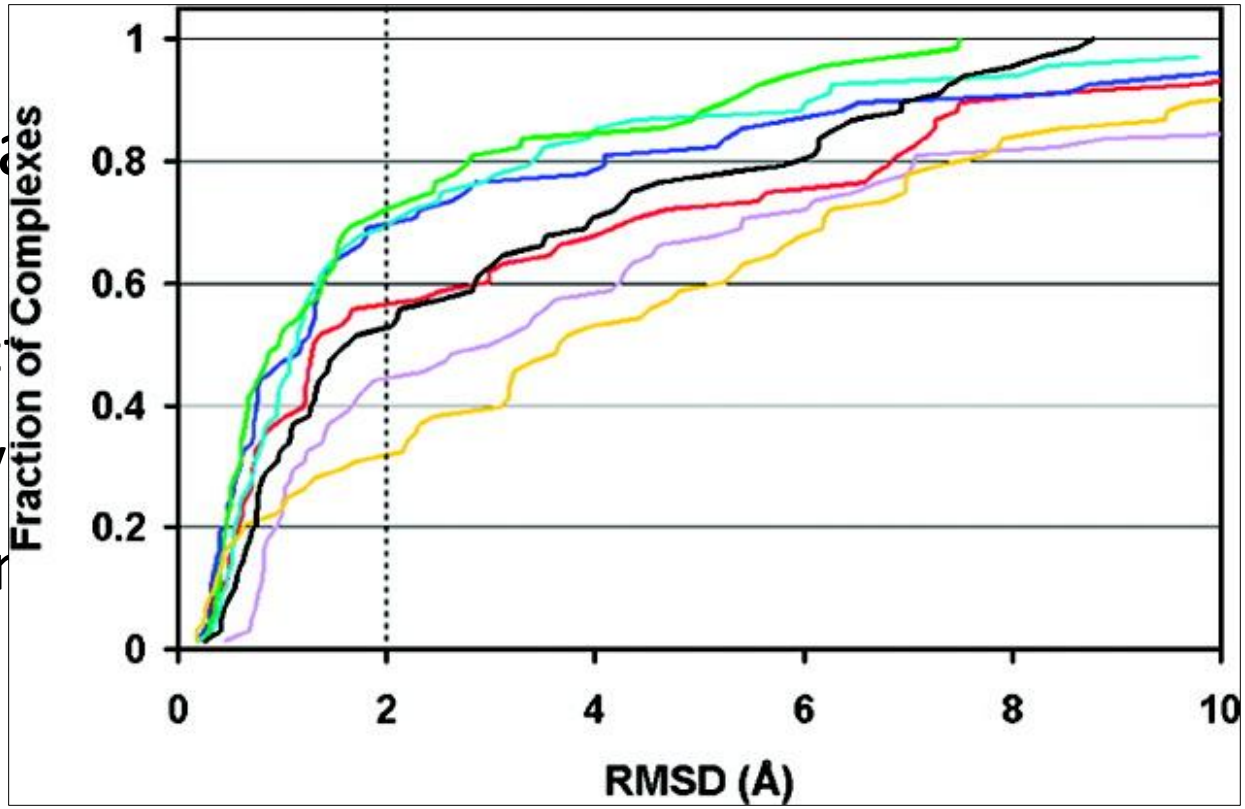

From: Cross, et. al, *J Chem Inf Model*, **49**, 1455

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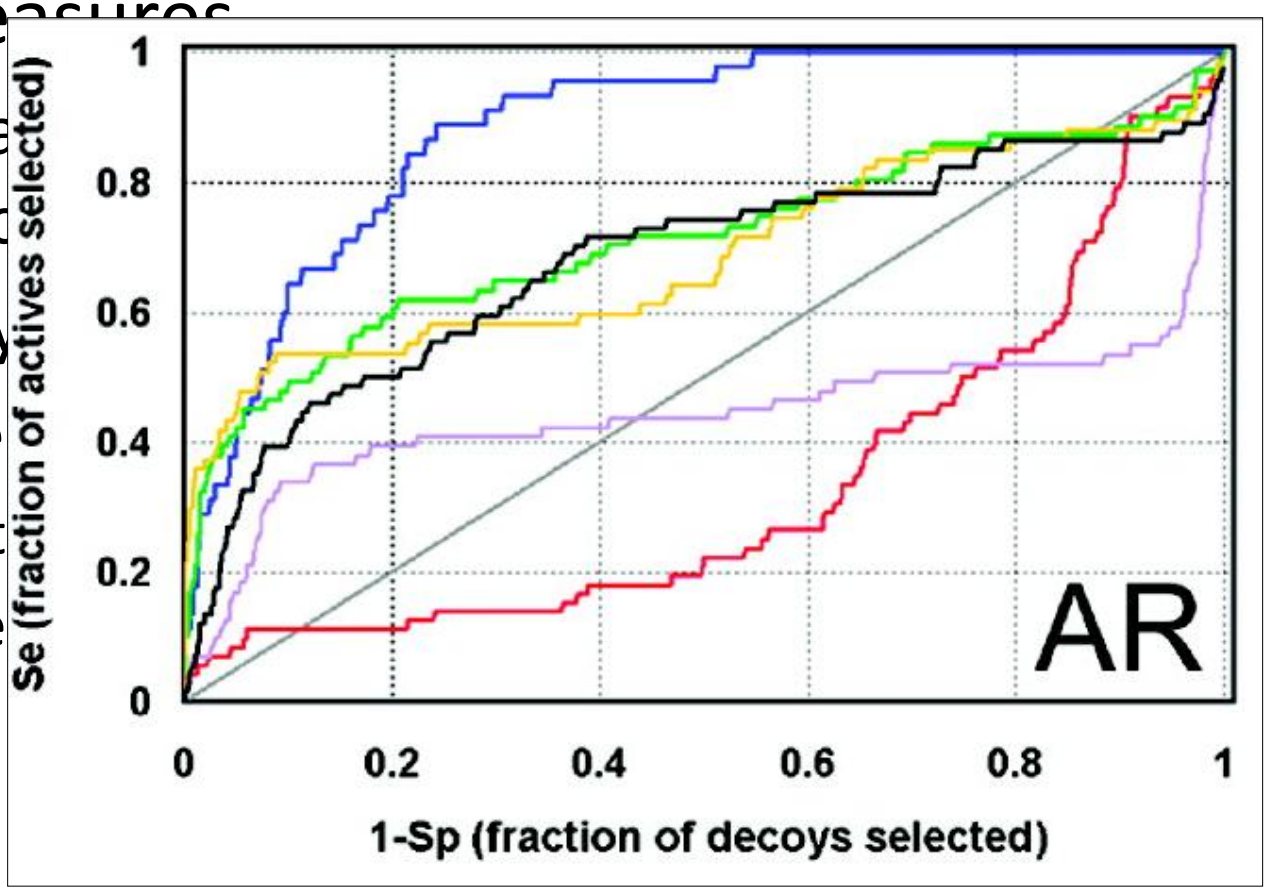

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Docking Packages

- Free
  - AutoDock (Art Olsen, David Goodsell, Scripps)
  - UCSF DOCK (Kuntz Group)
- Commercial
  - Glide (Schrodinger)
  - GOLD (CCDC)
  - FlexX (BiosolveIT)
  - ICM (Molsoft)
  - Surflex (Tripos)

Autodock Demo

- p38 (PDB code 1w83)