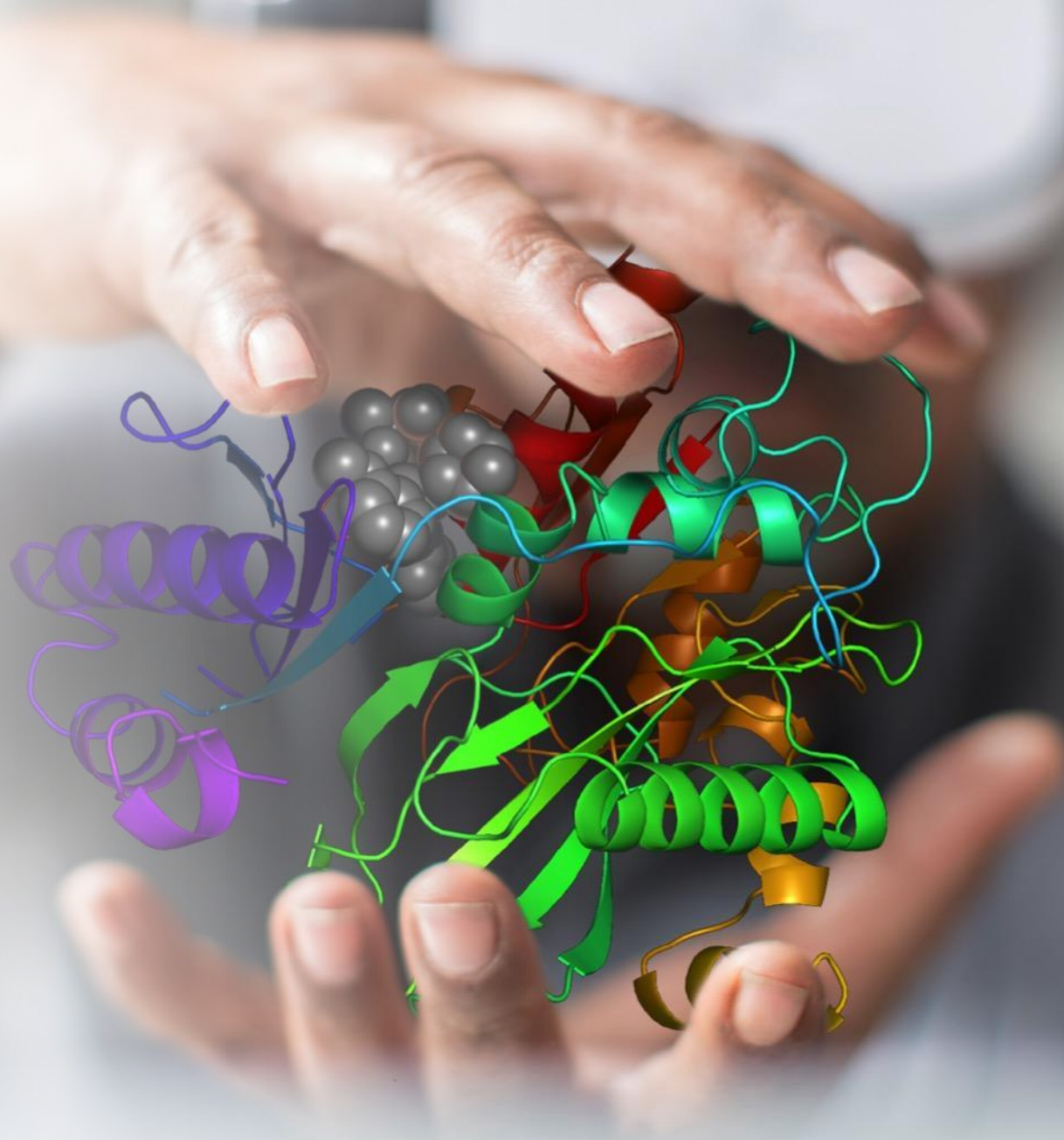
SCHRÖDINGER®

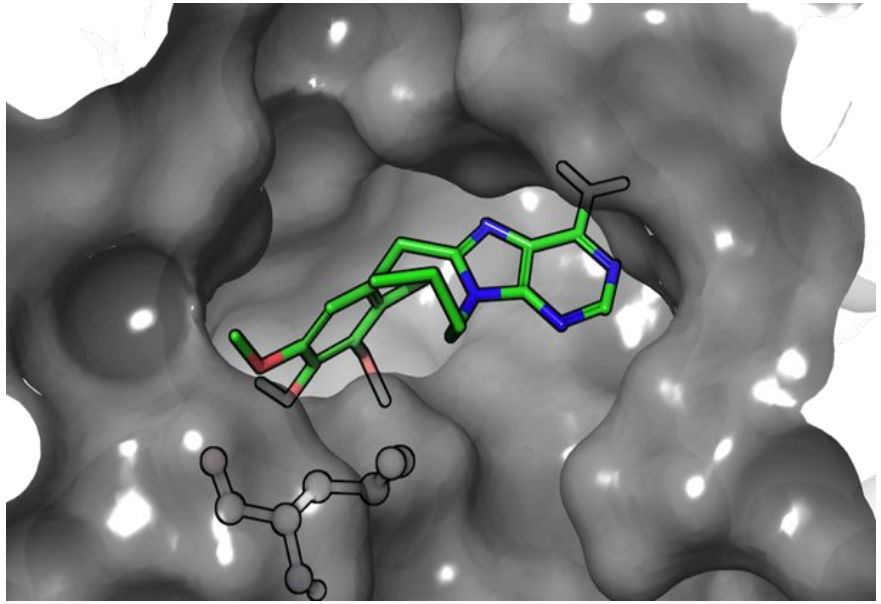
Modeling Protein-Ligand Poses for Hit Identification



By the end of this module, you should be able to...

- Compare and contrast structure-based and ligand-based virtual screening
- Describe how structure-based docking works
- Understand what docking scores can and cannot tell you
- Be able to analyze a virtual screen

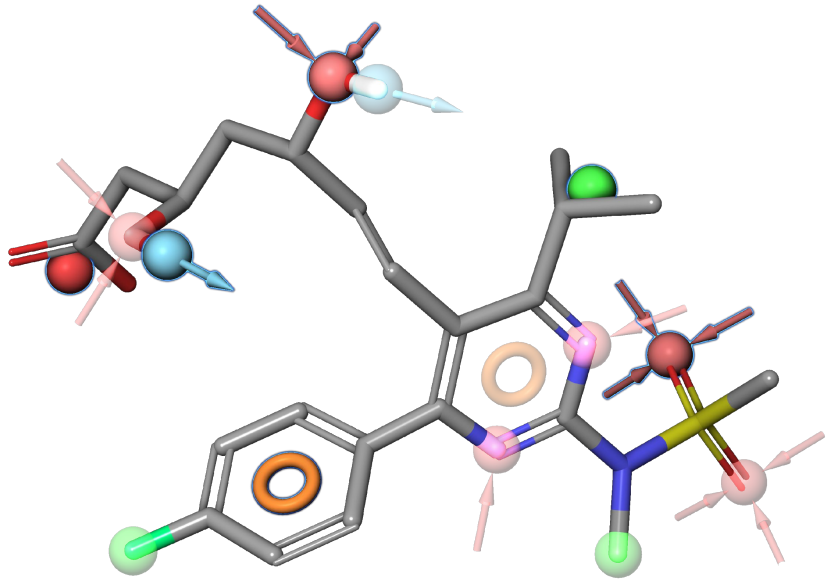
Ligand-based versus structure-based virtual screening



Structure-based Drug Design

3D

Docking
pharmacophore screening



Ligand-based Drug Design

2D

3D

Fingerprint searching
2D pharmacophore

Shape-based
3D pharmacophore

Steps of structure-based virtual screening

What possible poses can my ligand adopt in the binding site?

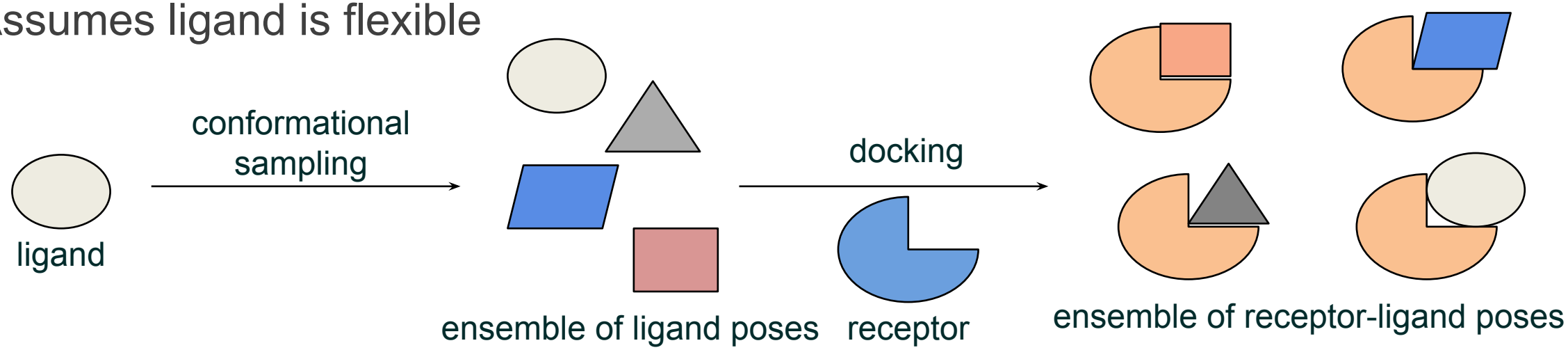
Which of those poses makes the best interactions with the receptor?

Which of those make the contacts I care about?

Docking fits ligands to a rigid receptor in a pose

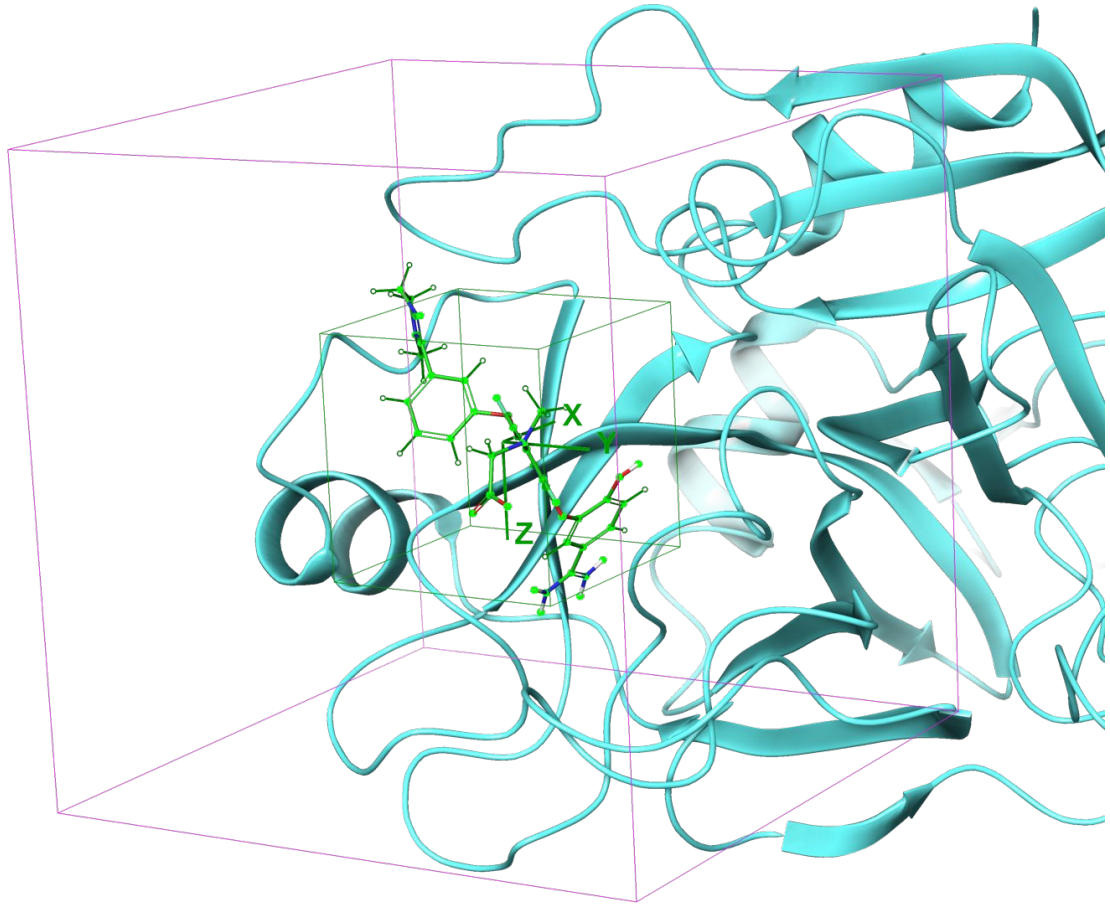
Docking → Scoring → Filtering

- Assumes receptor is rigid
- Assumes ligand is flexible



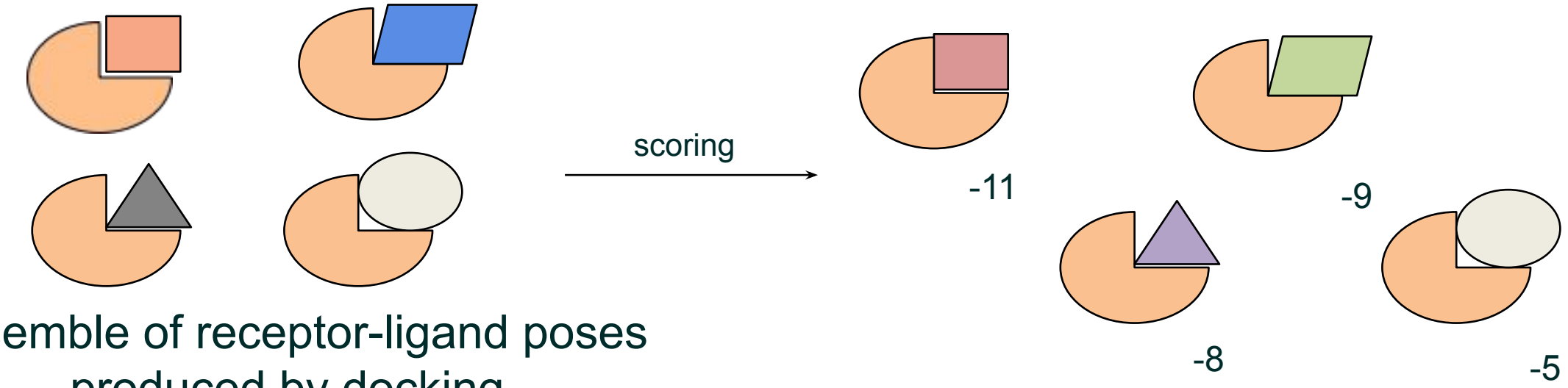
Glide uses a grid representation of binding site

- Protein represented as a series of grids
  - Site point grid (10Å^3 by default)
  - Chemscore grids
  - Adaptive Coulomb/vdW grids
- Grids precomputed once and applied for each ligand
- Ligand “center” must be found within inner box and all ligand atoms must be found within outer box
  - Inner box: 10Å^3 by default
  - Outer box: (12Å+0.8*ligand diameter)^3 by default
- Uses an optimized inner grid
  - not too small, not too big, just right
  - smallest grid that will find desired poses



Scoring evaluates the ligand pose

Docking → **Scoring** → Filtering



ensemble of receptor-ligand poses produced by docking

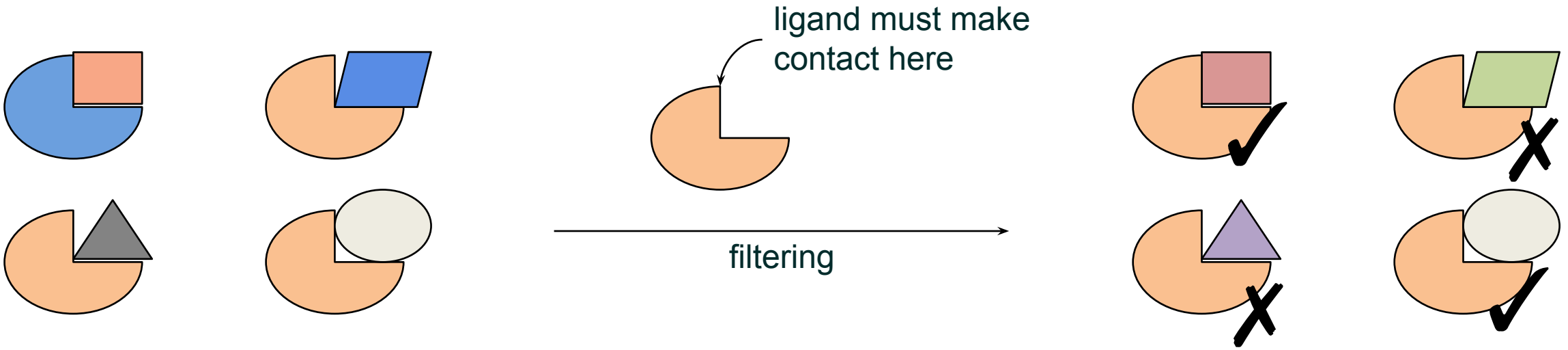
Scoring evaluates the ligand pose

Scoring functions:

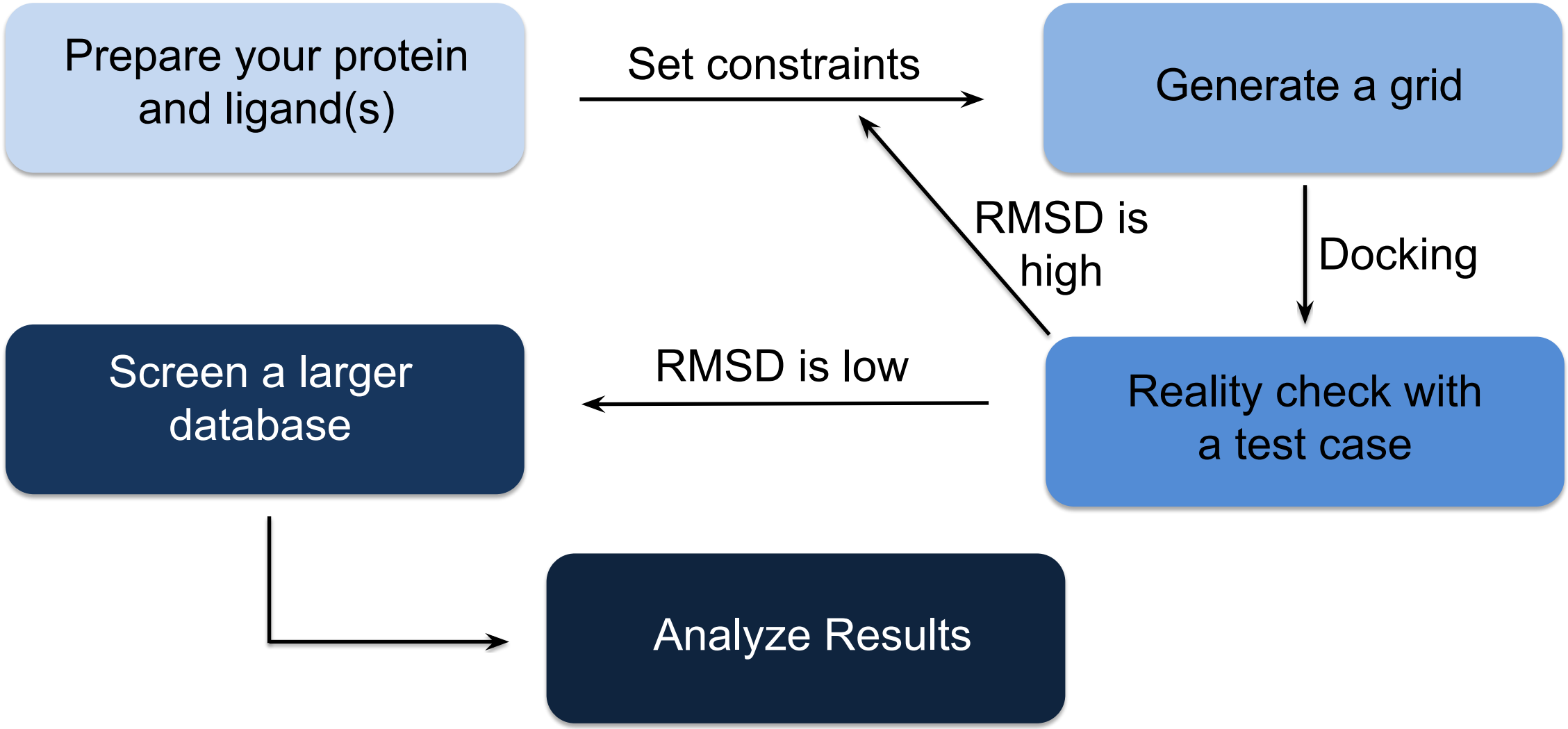
- ***Do not*** correlate with IC_{50}, K_d, EC_{50}, etc.
- ***Do not*** provide a rank-ordering of ligands
- Are optimized to ***give good enrichment***
  - Separates “good” ideas from “bad”
  - Limit the number of ligands to be investigated further

Filtering refines the ligand evaluation

Docking → Scoring → **Filtering**

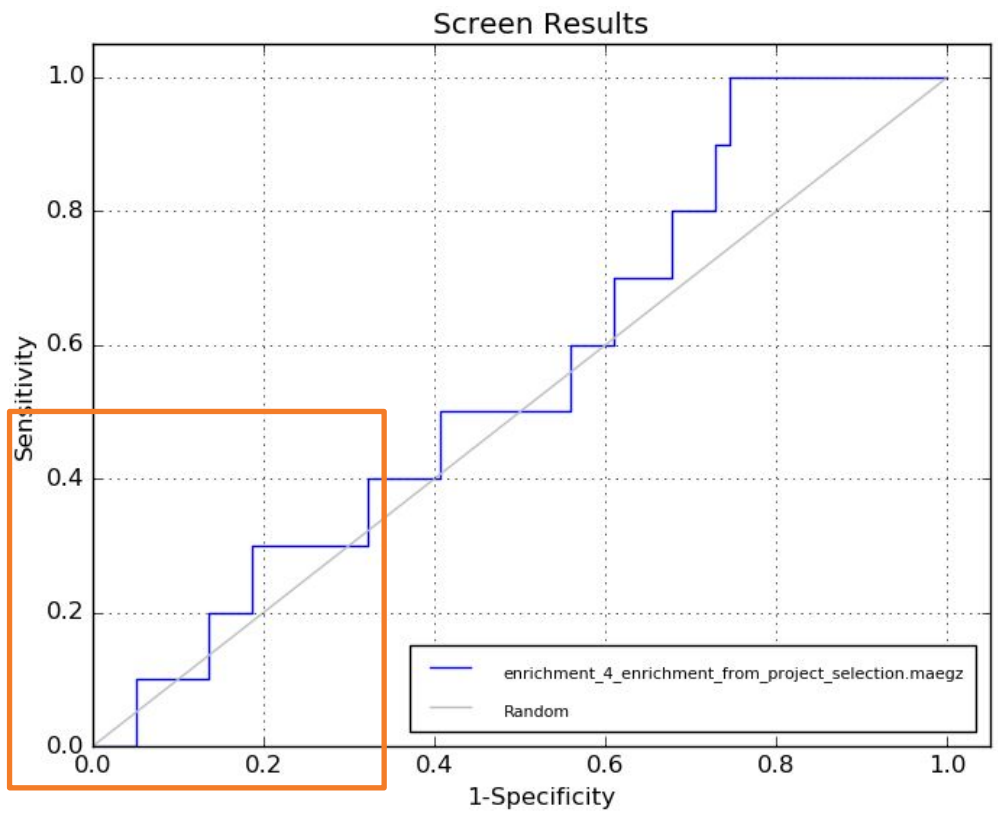


A simple workflow for a virtual screen

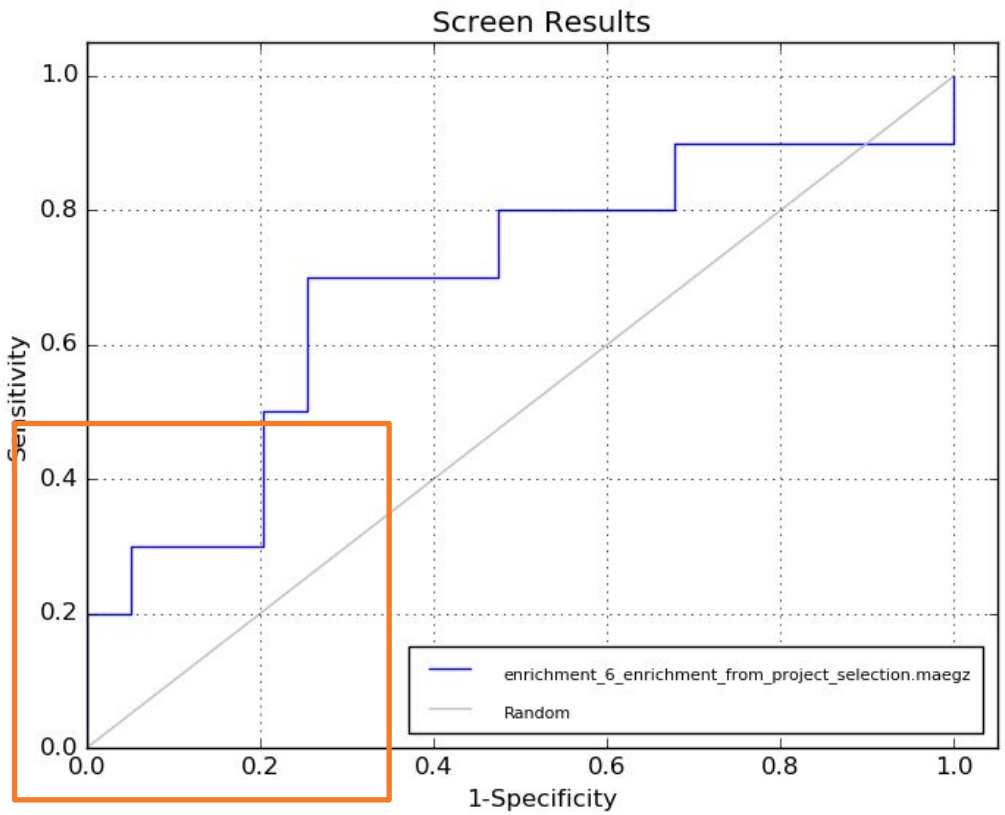


Good enrichment means you recover known actives earlier

No enrichment

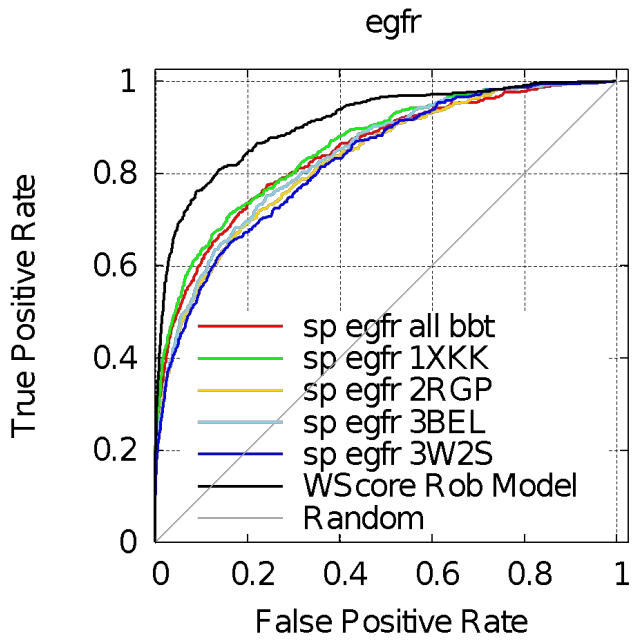


Enrichment



Computing hit rates and analyzing virtual screening results

- Hit rates
  - Prospective use in projects
  - Percent of compounds in fraction of ranked ligands tested that were found to satisfy affinity requirements of project
    - Typically ~1 - 20% for HTVS
- Retrospective metrics
  - Receiver operator characteristic (ROC) plots
  - Area under curve metric (AUC)



By the end of this module, you should be able to...

- Compare and contrast structure-based and ligand-based virtual screening
- Describe how structure-based docking works
- Understand what docking scores can and cannot tell you
- Be able to analyze a virtual screen

Now open web-based Maestro