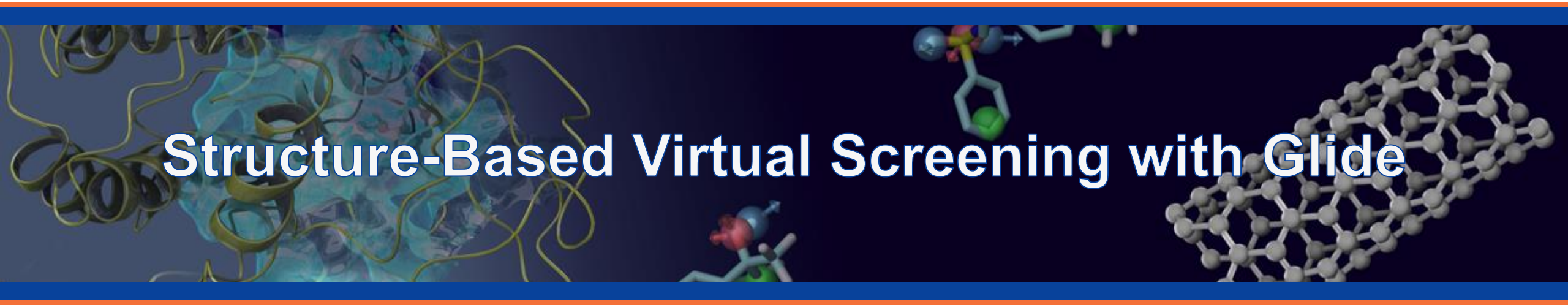
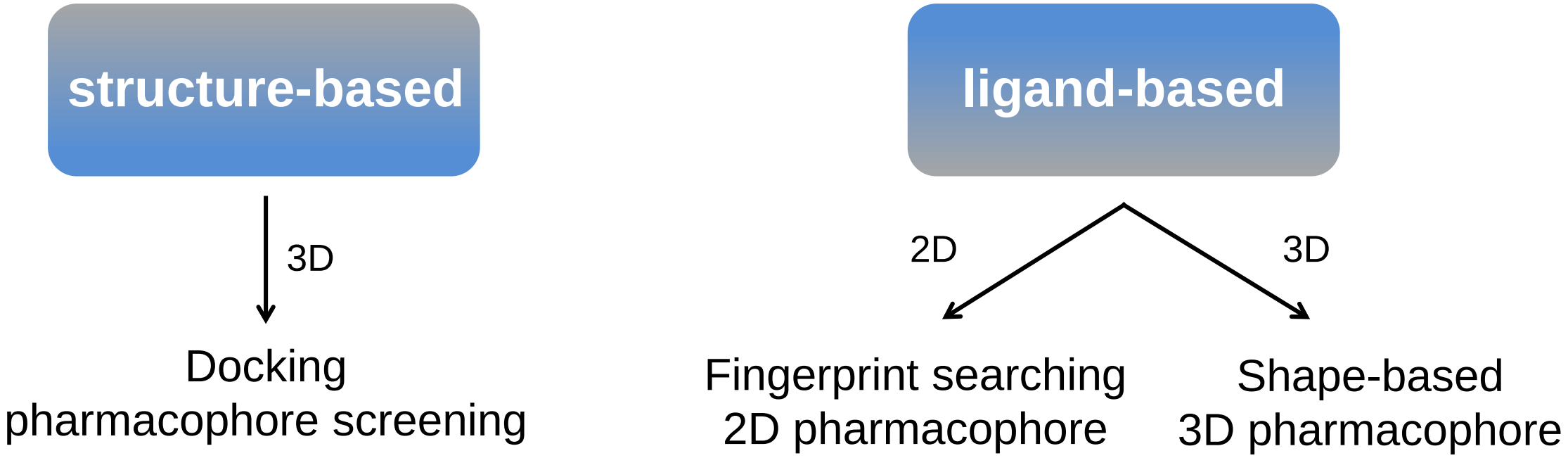
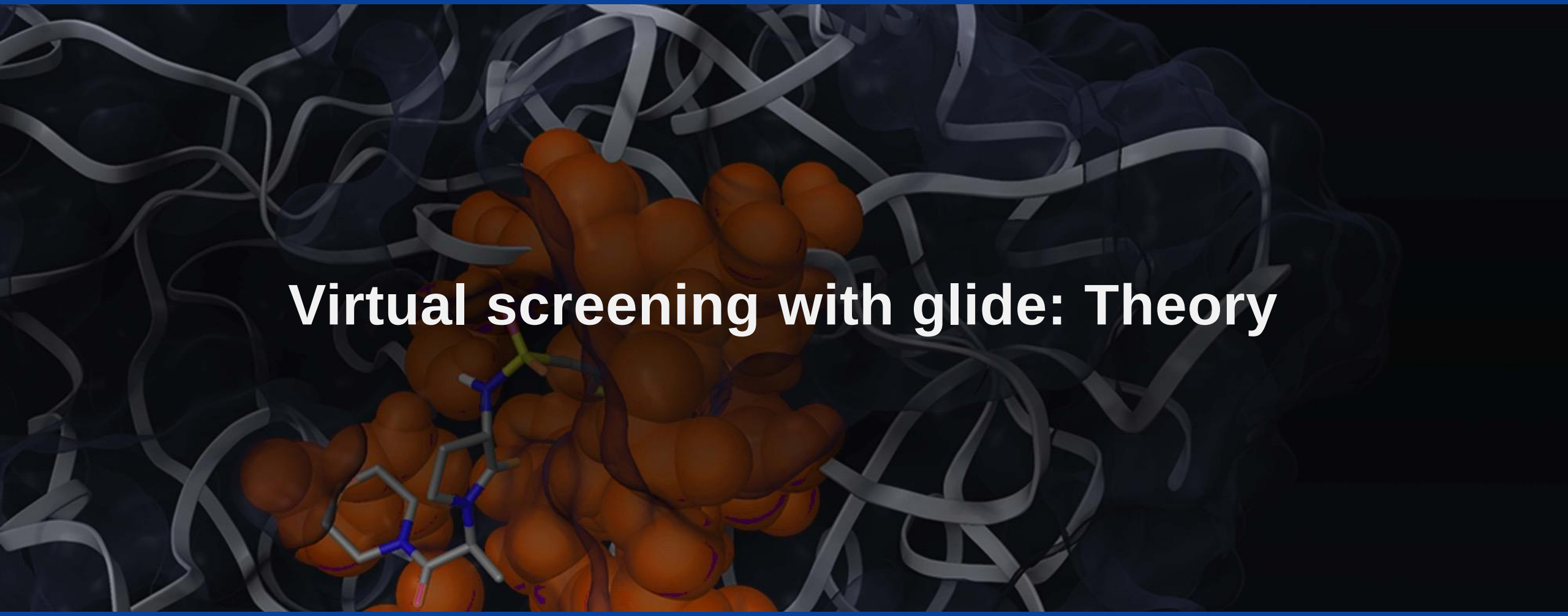


Stephan Ehrlich

Virtual Screening is a Starting Point in CADD

- Uses *in silico* methods to identify molecules that could bind to a target
- These methods are classified as either **structure-based** or **ligand-based**:





Virtual screening with glide: Theory

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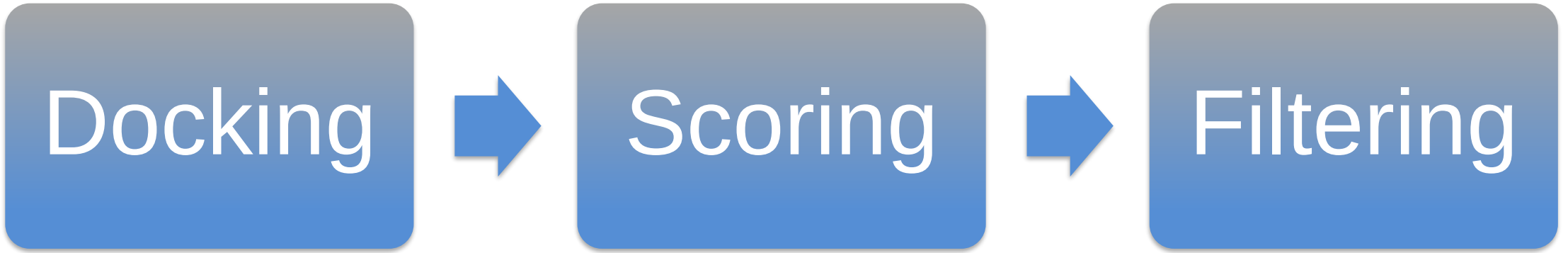
Ligands are Evaluated in Three Ways



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

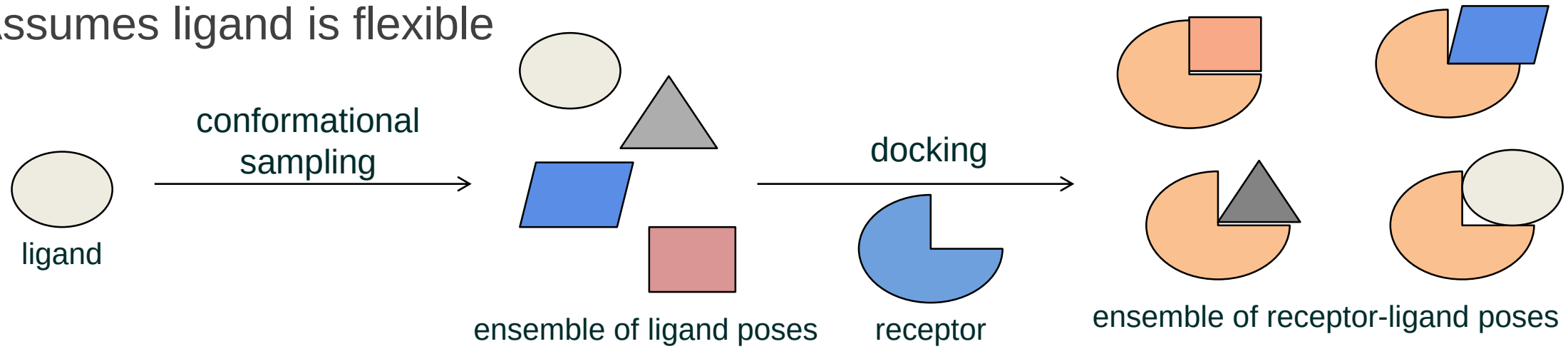
Which of those poses makes the best interactions with the receptor?

Which of those make the contacts I care about?

Docking Fits Ligands to a Receptor

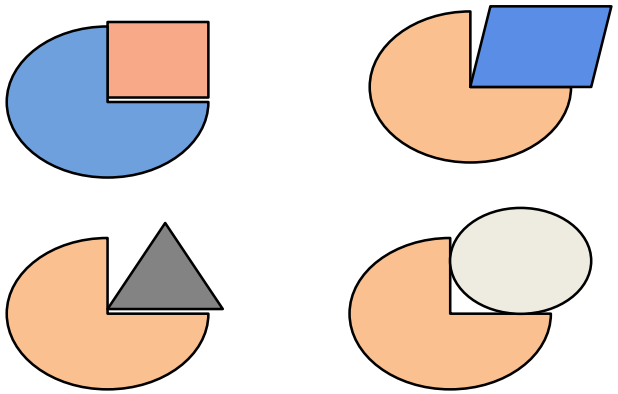
Docking → Scoring → Filtering

- Assumes receptor is rigid
- Assumes ligand is flexible

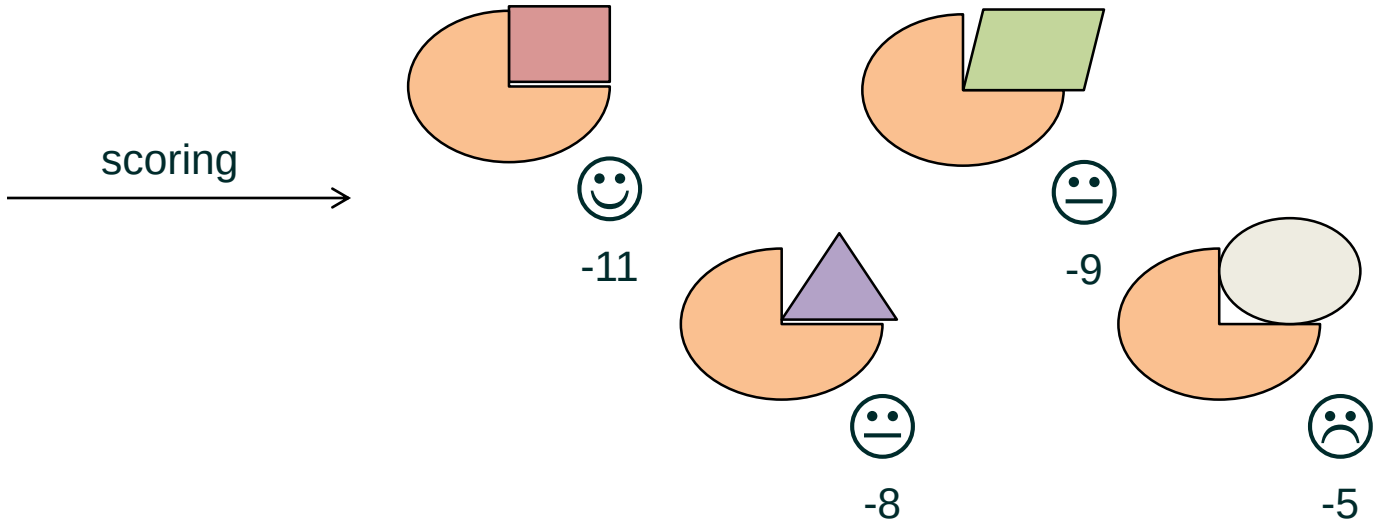


Scoring Evaluates the Ligand Fit

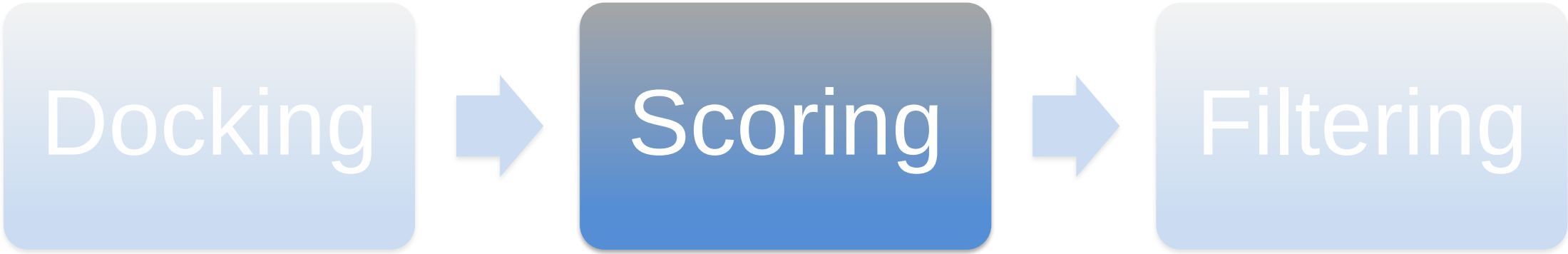
Docking → **Scoring** → Filtering



ensemble of receptor-ligand poses produced by docking



Scoring Evaluates the Ligand Fit



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

Glide has Different Scoring Functions

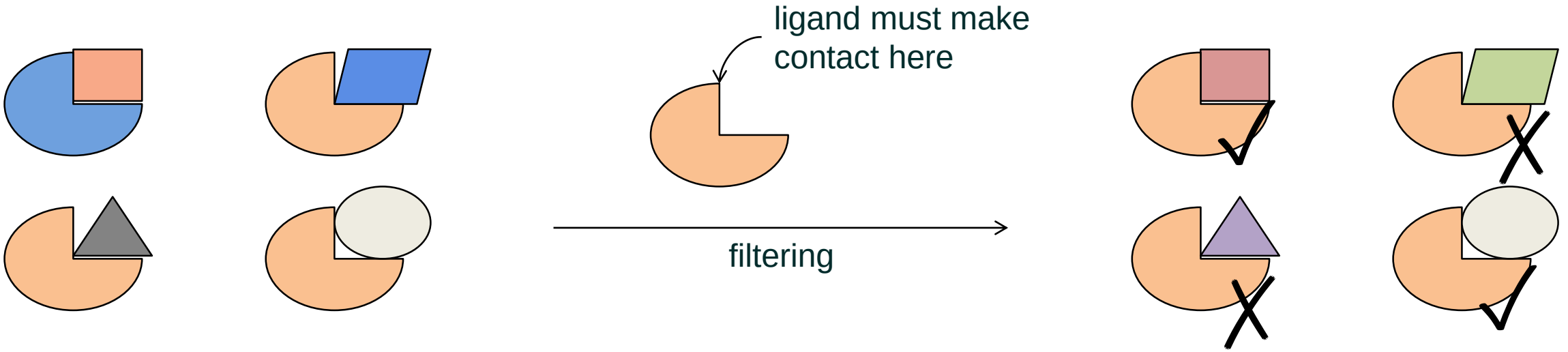
Scoring Function	Computing Time	When to Use
SP	10 – 30 sec/molecule	First pass virtual screening on large databases/hit generation
XP	3-5 min/molecule	Refinement of a smaller dataset /lead optimization

- SP seeks to minimize **false negatives** while XP seeks to minimize **false positives**
- The XP scoring function includes more stringent terms for modeling desolvation, hydrophobic effects, and charged interactions

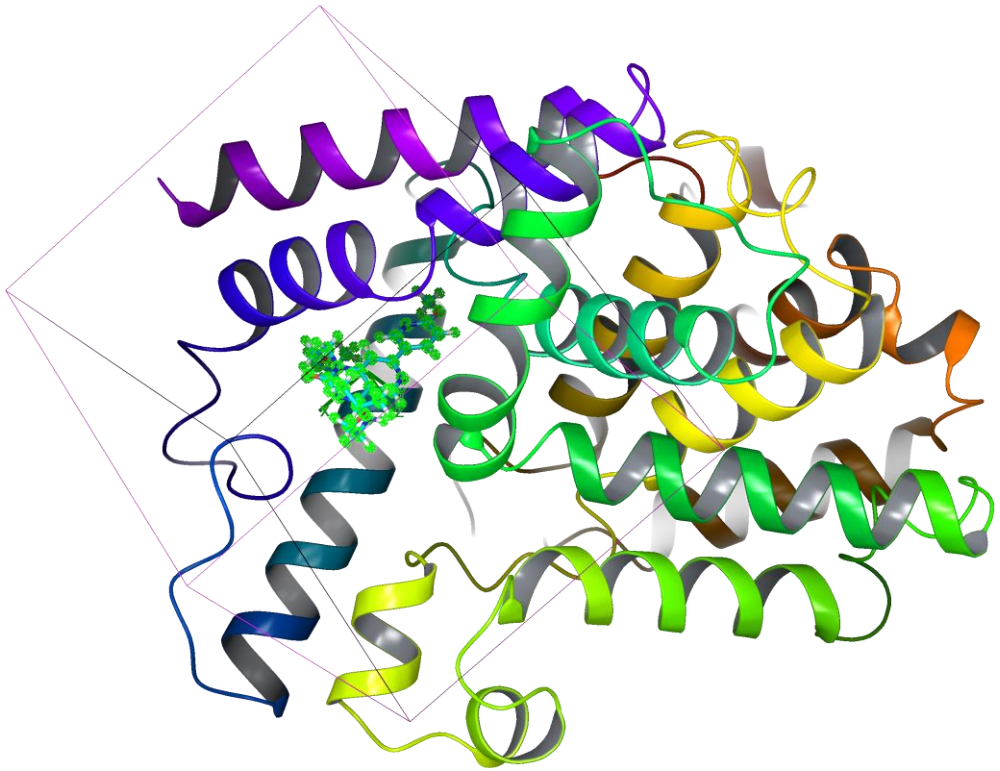
Friesner, R. A. et al. *J. Med. Chem*. **2004**, *47*, 1739-49.

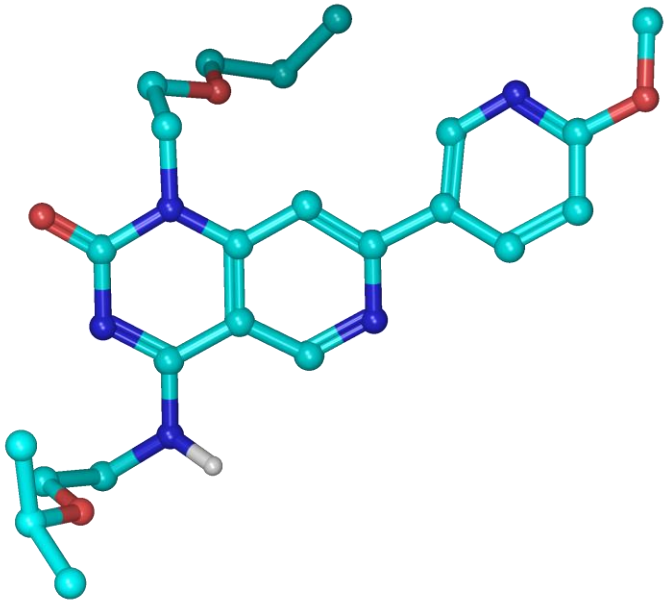
Filtering Refines the Ligand Evaluation

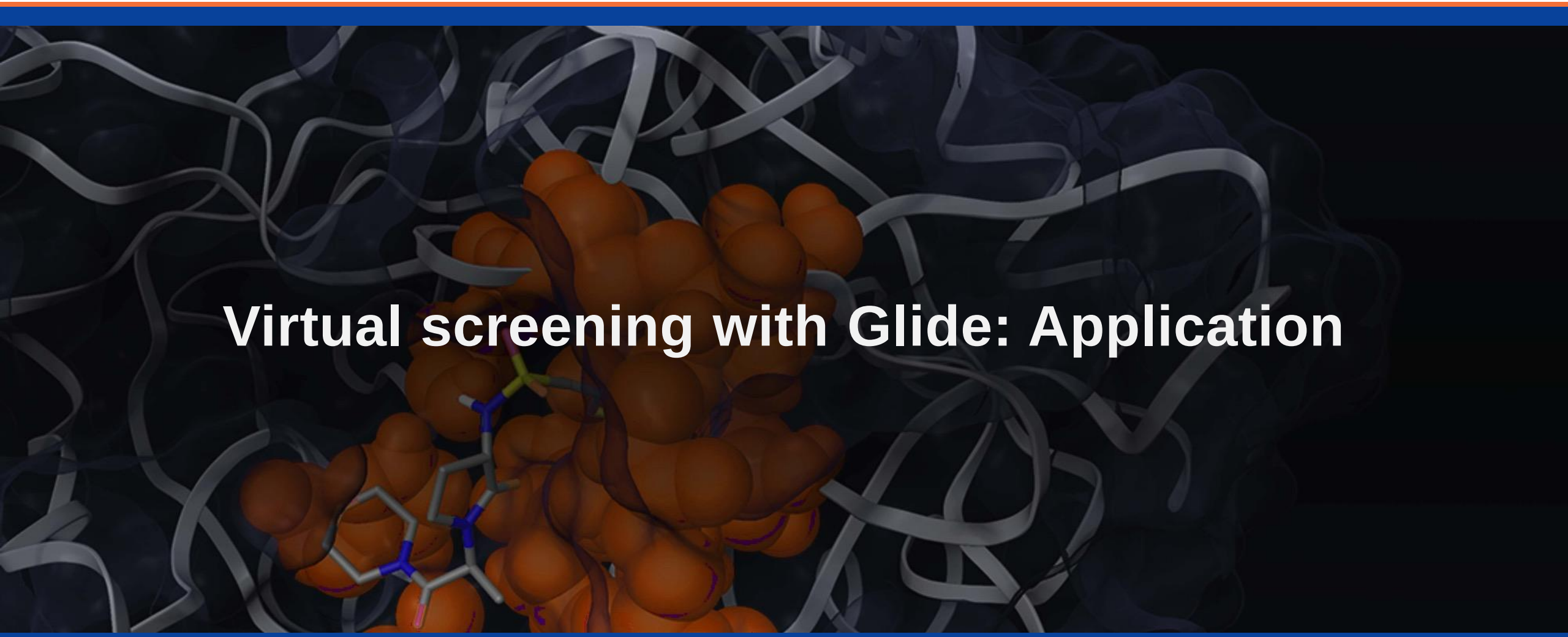
Docking → Scoring → **Filtering**



Glide Docking is Run in Two Steps







Virtual screening with Glide: Application

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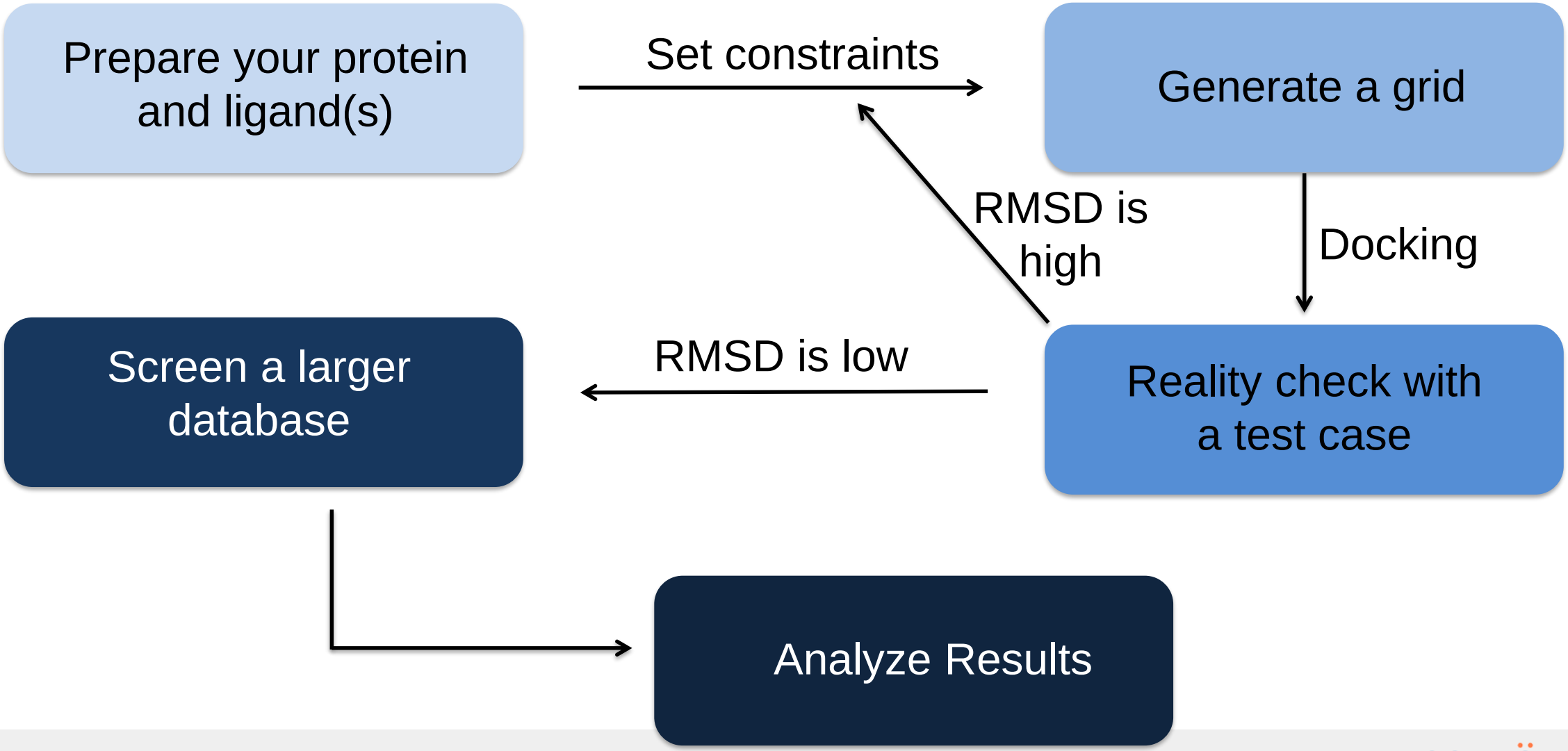
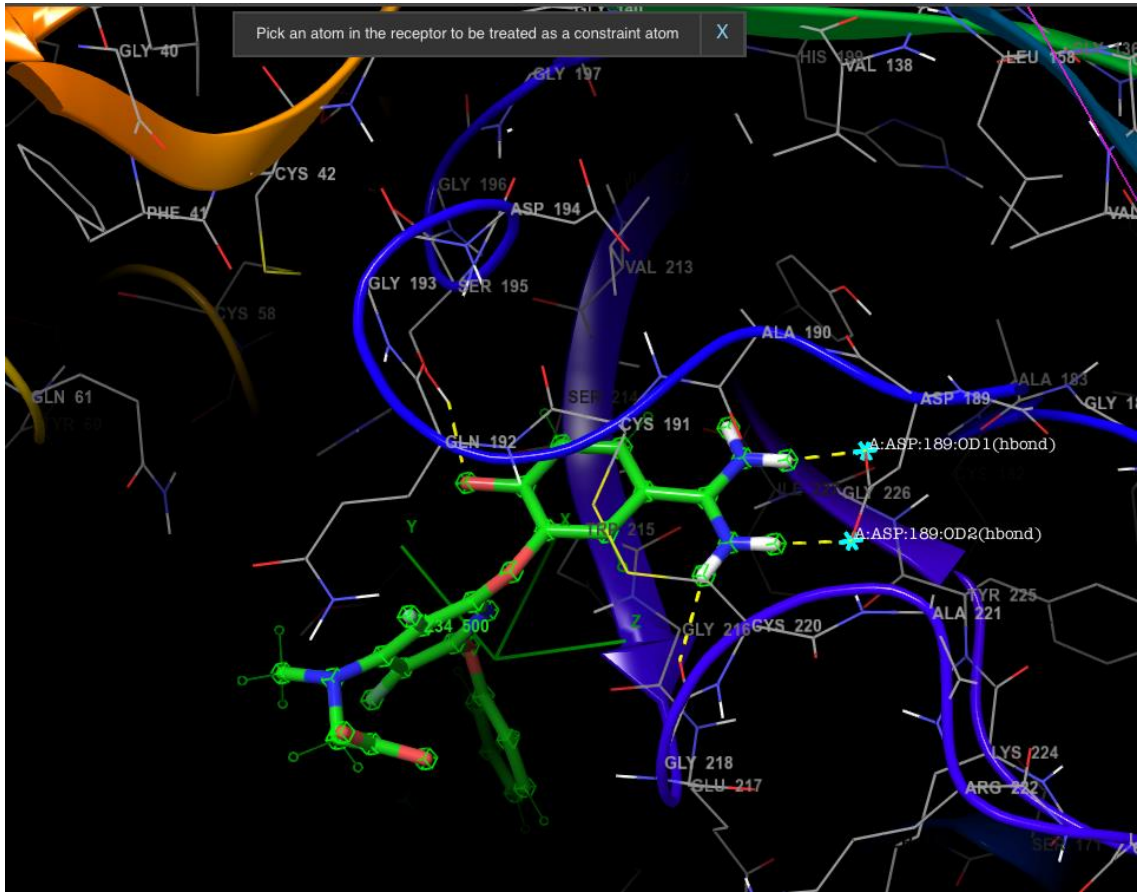
An Ideal Workflow for a Virtual Screen using Glide



Constraints Can Add Information

- Evaluate evidence that a ligand should bind in a specific area or make a particular contact
  - crystal structure data
  - site-directed mutagenesis data
  - biological data

- Types of constraints:
  - Positional and NOE
  - Hydrogen-bonding and metal
  - Metal coordination
  - Core



Useful Video Links Related to Today's Workshop

- Ligand Preparation

  https://www.schrodinger.com/training/videos/ligand-preparation
- Receptor Grid Generation

  https://www.schrodinger.com/training/videos/docking-receptor-grid-generation-docking-virtual-screening/glide-receptor-grid
- Docking

  https://www.schrodinger.com/training/videos/docking-ligand-docking
- Applying Constraints in Docking

  https://www.schrodinger.com/training/videos/docking-ligand-docking/using-h-bond-and-positional-constraints

Other Education Resources are Available Online

- Knowledge Base: https://www.schrodinger.com/kb/
- Support Center: https://www.schrodinger.com/supportcenter
- Training Center: https://www.schrodinger.com/training
- Schrödinger Seminar Series:
  https://www.schrodinger.com/seminars/current
  https://www.schrodinger.com/seminars/archives
- Script Center: https://www.schrodinger.com/scriptcenter/

Thanks for Joining Us!

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