Texas A&M HPRC Short Course Series

Drug Docking with Schrodinger

Xin Yang
Outline

10:00 - 10:20 Intro to Molecular Modeling in Drug Discovery
10:20 - 11:10 Hands-on Session 1 – Structure Preparation with Maestro

11:10-11:30 Basics of Structural Based Virtual Screening
11:30-12:15 Hand-on Session 2 – Docking with Glide

12:15-12:30 Covalent Docking with Covdock & Wrap-up
A Tough Road of Drug Discovery

Figure adapted from Paul SM et al., Nat. Rev. Drug Discov., 2010, 9, 203-214
Search larger and more diverse chemical space

- Chemical diversity (scaffolds) increases with large chemical space searching
- As screening decks expand there will be more tighter binders that could be found

Nature 2019, 566, 224–229
Methods for Hit Identification

**Hit**: A small molecule that is known to bind to a target in drug discovery.

High Throughput Screening (HTS)

High Throughput Virtual Screening (HTVS)

https://en.wikipedia.org/wiki/High-throughput_screening

Virtual Screening

Structure-based Drug Design

- known target structure
- known ligand binding site
- (optional) bound ligands/hits

Ligand-based Drug Design

- known hits
- (optional) active conformation

Figure from Joy Yang/Pfizer, C&EN, 2022, 100, 3

Figure from J. Chem. Inf. Model. 2007, 47, 3, 1097–1110
Protein Target

• Crystal structure
  RCSB Protein Data Bank (PDB)

• NMR
• Homology Model
• Cryoelectron Microscopy (cryo-EM)

Figure from https://www.schrodinger.com/webinars/archives/1248/virtual-screening/469153
Protein Preparation

• Typical PDB structure is not suitable for immediate use
  • it typically contains heavy atoms, co-crystalized ligand, water molecules, metal ions, cofactors, ...
  • may be multimeric, need to be reduced to a single unit
  • limited resolution, eg. it’s difficult to distinguish carbonyl oxygen and secondary amine nitrogen’s of amide
  • may have incorrect bond orders, assignment of charge state, orientation of groups

Color protein with PDB conversion Status
Gray: standard residue connect by standard
Red: standard residue with missing atoms
Orange: nonstandard residues, HET groups
Green: residue with an alternate conformation
Protein Preparation – Missing atoms

• Missing atoms
  • Hydrogens are not included
  • Entire side chains may be missing
  • There are a number of utilities to fill in missing atoms/sidechain

• Missing segments
  • More complicated to fix
  • Normally requires homology modeling to obtain reasonable results if more than a few residues are missing
Protein Preparation – Protonation states

• ASP, GLU and HIS

Adapted from https://commons.wikimedia.org/wiki/File:Amino_Acids.svg
Dancojocari / CC BY-SA (https://creativecommons.org/licenses/by-sa/3.0)

Protein Preparation Workflow

Preparation Workflow Tab

- **INTERACTIVE button:** switching between running the workflow interactively or as a batch job
Protein Preparation Workflow

Preparation Workflow Tab

- **Specify Protein step**
  - from local files
  - get PDB from RCSB website (need web access)

- **Review Structure link**
  - Links to the Substructures Tab

- **Global Settings link**
  - pH
  - small molecules to be included in the generation of ionization states (ligands, metal and ions, non-water solvents, other...)

![Protein Preparation Workflow interface](image)
Protein Preparation Workflow

Preparation Workflow Tab

- **Preprocess step**: fix structural defects and add necessary information
  - Cap protein termini with ACE and NMA residues
  - Align one protein to another protein
  - Assign bond order, replace hydrogens, and correct metal ionization states to ensure proper formal charge and force field treatment
  - Add sulfur bond between sulfur atoms that are within 3.2 Å of each other
  - Convert selenomethionines to methionine
  - Protein refinement with Prime
  - Remove water molecules at the user's discretion
  - generate ionization and tautomeric states for hets
Protein Preparation Workflow

Preparation Workflow Tab

- **Optimize H-bond Assignment step:** to optimize H-bonding network, to improve charge-charge interaction and hydrogen bonding
  - reorienting hydroxyl and thiol groups
  - flip terminal amide groups and histidines ring
  - predict protonation states of histadine, ASP and Glu
  - predict tautomeric states of histadine
  - iterative process, pass over all groups multiple times

- Sample water orientation
  - ensure water molecules are optimally placed
  - Delete unwanted water molecule before sampling
Protein Preparation Workflow

Preparation Workflow Tab

Optimize H-bond Assignment step:

- Use crystal symmetry: important when part of of structure is present in the asymmetric unit
- Minimize hydrogens of altered species (only)

- Two options for pH
  - PROPKA
  - simplified rules
    - very low: protonate ASU, GLU, HIS
    - low: protonate HIS
    - neutral: normal biological state
    - high: deprotonate cystines
Protein Preparation Workflow

Preparation Workflow Tab

• **Clean Up step:** Perform a restrained minimization on the structure and delete classes of water molecules. By default, all atoms are minimized, and only the waters near het groups are kept.

• **Minimize:** to relieve any strain and fine-tune the placement of various groups
  - optimize hydrogens only: allows some movement of the heavy atoms and will result in some deviation from the input structure

• **Forcefield:**
  - OPLS4: latest forcefield since 2021-1 release

• **Delete waters:** For applications such as docking, where retaining the volume of the binding site can be important, you might want to remove waters after performing the restrained minimization, rather than before, as the minimization without waters can cause the binding site to shrink, and therefore not allow larger ligands to dock.
Protein Preparation Workflow

Substructures Tab: allow users to select, examine, and delete ligands, metals, waters and chains

- Table of het groups
  Het groups are everything that is not a water or a protein residue, and include ligands, metal ions, and cofactors.
- Table of water molecules
- Table of chains
  Chains are defined by the chain label, and can include waters and het groups.

- Before inspecting the structure, it is advisable to delete unwanted parts of the structure. If the protein is a multimer and you want to simplify it, you should delete the chains for the duplicate structural units. When you delete the chains, the waters and het groups that are labeled with that chain label are also deleted.
Protein Preparation Workflow

Substructures Tab:

- Delete waters (bulk water, water away from binding site, …)

- Correct the ionization and tautomeric states of listed HET groups
  - Generate States: run an epic job at the target pH range
  - Display state penalty
Protein Preparation Workflow

**Diagnostic Tab:** lists errors or issues found in the Workspace structure

- **Valences:**
  This tab lists atoms that have valence violations, such as missing hydrogens or the incorrect number of bonds.

- **Missing**
  This tab lists residues for which atoms are missing.

- **Overlapping**
  This tab lists pairs of atoms that are too close (bad contacts).

- **Alternates**
  This tab lists residues that have alternate positions in the input structure. Although these positions are legitimate, the protein preparation can only be done on a structure with a single set of coordinates, so you must choose one of the alternate positions for each residue.

- **Reports**
Ligand Preparation

• Take 2D or 3D structures and produce low energy 3D structures
• Generate reasonable atomic coordinates for a ligand dataset

  • tautomeric states
  • ionization states
  • ring conformations
  • stereoisomers
  • conformers

https://www.schrodinger.com/ligprep

Generation of multiple tautomeric forms of the ring system in a guanine ligand

Ligand Preparation with LigPrep

• **Import structures:** from project, SD, SMILES format …

• **Filter criteria:**
  - properties
  - general attributes: MW, number of atoms, …
  - functional group counts

• **Force field**

• **Generate ionization states:**
  - Ionizer
  - Epik (recommended)

• **Desalt:** removes extra water molecule or counter ions that are present in ligand files that are originate from some structure databases

• **Generate tautomers:** keto-enol, sulfur/nitrogen, histidine, DNA base tautomerization

• **Stereoisomers**

LigPrep takes about 1-2 seconds on average to process a ligand. Result in difference in Epik State penalty (kcal/mol)
Hands-on Session 1

Structure Visualization and Preparation with Maestro

1. Creating Projects and Importing Structures
2. Preparing Protein Structures *(Protein Preparation Workflow)*
3. Preparing Ligand Structures *(LigPrep)*
4. Visualizing Protein-Ligand Complexes (configuration bar, Ligand Interaction Diagram)

Download tutorial from /scratch/training/glide_docking/ on Grace
Steps of structure based virtual screening

**Docking**
- Rigid receptor docking
- Induced fit docking
- Covalent docking
- ...

**Scoring**
- Docking Score
- Glide Score
- Emodel
- ...

**Refining**
- RMSD
- Enrichment
- Receiver operator characteristic plots
- ...

Docking fits ligands to a rigid receptor in a pose

Search for the best-scoring binding pose for a given ligand
Rigid receptor docking with Glide HTVS, SP, XP
Receptor is rigid
Ligand is flexible


https://www.schrodinger.com/
Ligand Docking

• Procedure
  • Prepare the protein
    • Missing atoms/side chains
    • Protonation state
    • Flexible side chains
  • Prepare the ligand
    • Protonation state
  • Create a docking grid
    • Specify where to dock the ligand
  • Dock the ligand(s)
  • Scoring
  • Refinement

• Glide docking hierarchy

Glide docking “funnel”, showing the Glide docking hierarchy.

Glide Docking “Funnel”

1. Site-point search
2. Rough scoring
3. Grid minimization
4. Final scoring (GlideScore)

Top Hits

Binding Site

Figure from https://www.schrodinger.com
Binding Pocket – Grid Generation

• Binding Pocket Grid
  • Bounding box where docking is performed
  • Too small
    • ligands won’t dock
    • miss good ligands
  • Too big
    • increase computational cost substantially
    • miss good binding poses

• Is the binding pocket rigid or flexible?
  • Molecular dynamics simulations can be used to investigate the stability of the binding pocket
Steps of structure based virtual screening

Docking  |  Scoring  |  Refining

A scoring function very **roughly** approximates the **binding affinity** of a ligand to a protein given a binding pose.

Illustration of binding pose ensembles

Figure from *J. Chem. Inf. Model.* 2011, 51, 10, 2515–2527
Scoring evaluates the ligand pose

• Do not correlate with $IC_{50}$, $K_d$, $EC_{50}$, etc
• More negative the score, the better
• Are optimized to give good enrichment
  • Separate good from bad ligands
  • Limit the number of ligands that need to be investigated further

GlideScore and Emodel

- GlideScore
  rank-order compounds to separate compounds that bind strongly (actives) from those that don’t (inactives)

<table>
<thead>
<tr>
<th>Scoring Function</th>
<th>Computing Time</th>
<th>When to Use</th>
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<tbody>
<tr>
<td>SP</td>
<td>5 – 20 sec/molecule</td>
<td><strong>First pass virtual screening on large databases/hit generation</strong></td>
</tr>
<tr>
<td>XP</td>
<td>3-5 min/molecule</td>
<td><strong>Refinement of a smaller dataset for lead optimization</strong></td>
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</table>

- 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

- Emodel
  - primarily defined by protein-ligand coulomb-vdW energy with a small contribution from GlideScore
  - Choose the best-docked structure for each ligand

Glide Docking SP

GScore = 0.05*vdW + 0.15*Coul + Lipo + Hbond + Metal + Rewards + RotB + Site

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<th>Components</th>
<th>Description</th>
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<tr>
<td>VdW</td>
<td>Van der Waals energy. This term is calculated with reduced net ionic charges on groups with formal charges, such as metals, carboxylates, and guanidiniums.</td>
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<tr>
<td>Coul</td>
<td>Coulomb energy. This term is calculated with reduced net ionic charges on groups with formal charges, such as metals, carboxylates, and guanidiniums.</td>
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<td>Lipo</td>
<td>Lipophilic term, which is a pairwise term in SP but is derived from the hydrophobic grid potential for XP. Rewards favorable hydrophobic interactions.</td>
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<tr>
<td>HBond</td>
<td>Hydrogen-bonding term. This term is separated into differently weighted components that depend on whether the donor and acceptor are neutral, one is neutral and the other is charged, or both are charged.</td>
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<td>Metal</td>
<td>Metal-binding term. Only the interactions with anionic or highly polar acceptor atoms are included. If the net metal charge in the apo protein is positive, the preference for anionic or polar ligands is included; if the net charge is zero, the preference is suppressed.</td>
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<td>Rewards</td>
<td>Rewards and penalties for various features, such as buried polar groups, hydrophobic enclosure, correlated hydrogen bonds, amide twists, and so on. This category covers all terms other than those explicitly mentioned.</td>
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<tr>
<td>RotB</td>
<td>Penalty for freezing rotatable bonds.</td>
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<tr>
<td>Site</td>
<td>Polar interactions in the active site. Polar but non-hydrogen-bonding atoms in a hydrophobic region are rewarded.</td>
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Glide Docking XP (Extra Precision)

- Increase computational cost
- Glide SP with additional Extra Precision terms
- Locate regions where water molecules have unfavorable chemical potentials and occupy these regions with suitable ligand groups that provide exceptional gains in potency with a relatively small number of atoms
- Anchor fragments of the docked ligand, typically rings, are chosen from the set of SP poses and the molecule is re-grown bond by bond from these anchor positions
- Includes improvements to the scoring of hydrogen bonds as well as detection of buried polar groups, and detection of pi-cation and pi-pi stacking interactions
Glide Docking XP

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- **GScore**: Glide Score
- **DockS**: Dock Score
- **Lipopt**: Lipophilicity
- **PhobE**: Polar Subscore
- **HBonc**: Hydrophobicity
- **Electr**: Electrostatic Subscore
- **Sitem $i$**: Site Energy
- **$n$Cat**: Number of Contacts
- **CIBr**: Cation Dissociation Energy
- **LowM**: Low Molecular Weight
- **Pept**: Peptide Subscore
- **HBPer**: Hydrogen Bond Perthism
- **Expos**: Exposed Surface Area
- **RotPe**: Rotamer Probability
- **EpikSt**: Epitope Specificity
- **Zpotr**: Zwitterionic Potential
- **Similar**: Similarity Score
- **Activity**: Activity Score
Filtering refines the ligand evaluation

Docking

- Docking performance
  - Good performance on these target
  - Poor (near random) performance on these target

Scoring

- Screening compounds for further evaluation
  - Evaluate with more elaborate simulations, including properties such as entropy or explicit solvation

Refining
Hands-on Session 2

Structure-Based Virtual Screening Using Glide
1. Virtual Screening Prerequisites
2. Importing Structures
3. Generating a Receptor Grid
4. Docking the Cognate Ligand and Screening Compounds
5. Analyzing Results andBinding-Site Characterization
Covalent Docking

- Nearly 30% of the marketed drugs targeting enzymes known to act by covalent inhibition
- The inhibition can be either reversible or irreversible
- Covalent inhibitors derive their activity not only from the formation of a covalent bond between the target and the ligand but also from stabilizing non-covalent forces in the binding pocket

Examples of drug act through covalent mechanisms.

Examples of covalent complexes. A) Cathepsin K structure (PDB ID 1YT7) with the cocrystal ligand, B) HCV NS3 protease structure (PDB ID 2F9U) with the cocrystal ligand.

Covalent Docking

Custom Covalent Reactions

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<tr>
<th>Index</th>
<th>Reaction</th>
<th>Ligand SMARTS</th>
<th>Receptor SMARTS</th>
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https://www.schrodingers.com/newsletters/introducing-covdock-covalent-docking
CovDock Uses Glide & Prime

• Main steps
  • Conventional non-covalent docking of pre-reactive species (Glide)
  • Formation of covalent attachment (via a number of different mechanisms)
  • Structural refinement of the covalent complex (Prime)

• Output: cdock affinity, prime energy, ligand reaction site

• Speed
  • Pose selection (default) protocol: 1~2 hour per ligand
  • Virtual screening protocol: 10x faster than default protocol

• Challenges for covalent docking
  • Bond formation, bond cleavage and bond rearrangements all require an explicit treatment of electronic degrees of freedom and, hence, a quantum mechanics (QM) approach.
Drug Docking with Schrodinger: wrap-up

**Compound Library Preparation**
- Obtain Compound Library
- Filter Library
- LigPrep Library

**Receptor Grid Preparation**
- Prepare protein
- Generate Grids
- Test Grids

**Virtual Screening**

**Post Processing**
- Compile Virtual Screening Result
  - First Cut
  - Secondary Scoring
  - Second Cut
  - Visual Inspection
  - Final Cut
  - Generate Buy List
Running Schrodinger on HPRC

Schrödinger is a restricted software.
Usage of this software is restricted to subscribers of the Laboratory for Molecular Simulation (LMS).
Running Schrodinger on Grace and Terra, please refer to: https://hprc.tamu.edu/wiki/SW:Schrodinger.
More about the Schrodinger: documentation, training

The LMS also holds license for:

• Discovery Studio
• MOE
• Amber

• Material Studio
• Gaussian
• ADF

• Molpro
• Chemissian
• NBO
• AIMALL Professional
Need Help? Contact the HPRC Helpdesk

Website: hprc.tamu.edu
Email: help@hprc.tamu.edu
Telephone: (979) 845-0219

Help us, help you -- we need more info

• Which Cluster (Terra, Grace)
• NetID (NOT your UIN)
• Job id(s) if any
• Location of your jobfile, input/output files
• Application used if any
• Module(s) loaded if any
• Error messages
• Steps you have taken, so we can reproduce the problem