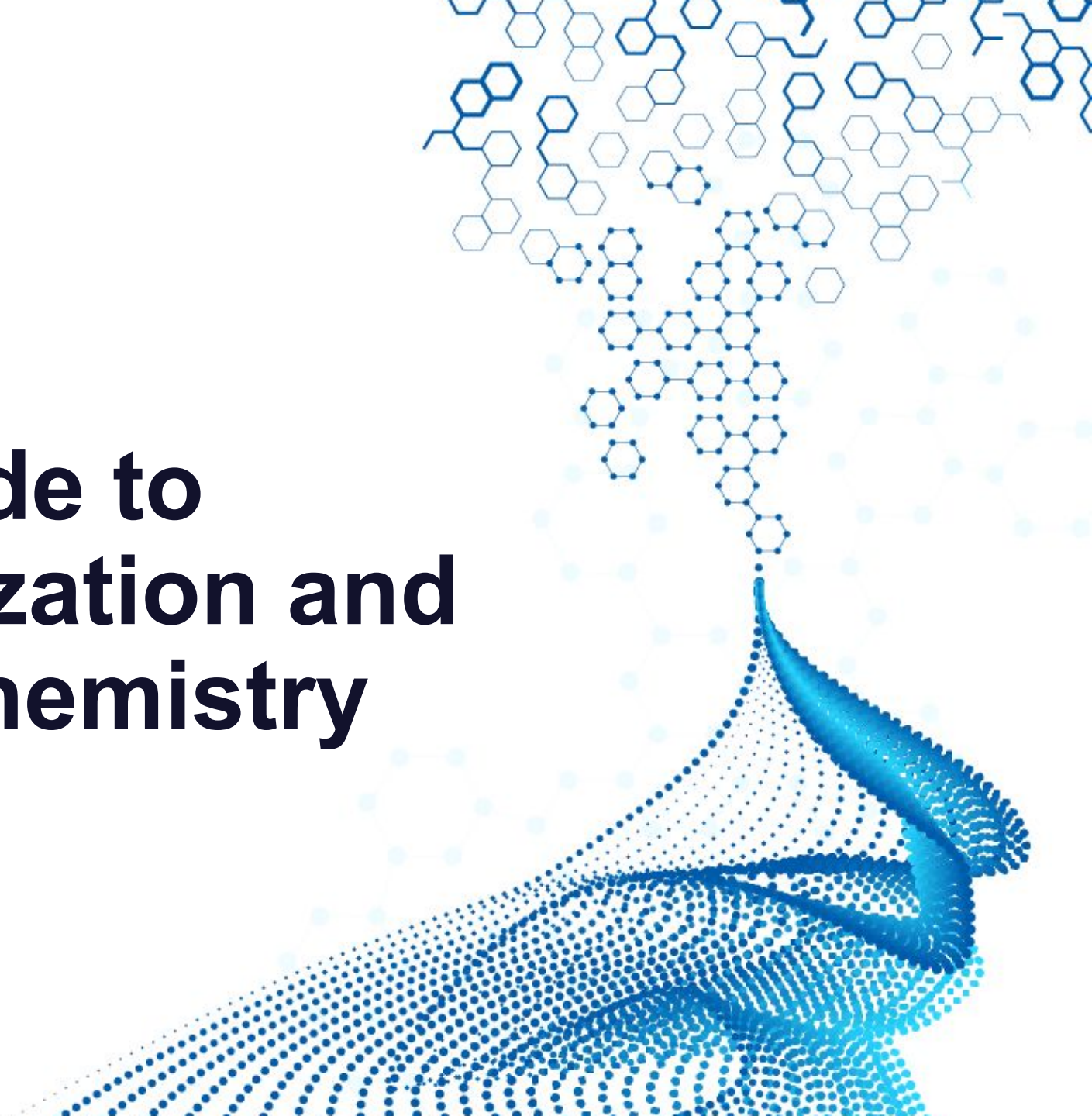




Schrödinger

A Beginner's Guide to Molecular Visualization and Computational Chemistry

Mila Krämer, Rita Podžuna
LRZ, 2022



Day 1 Agenda

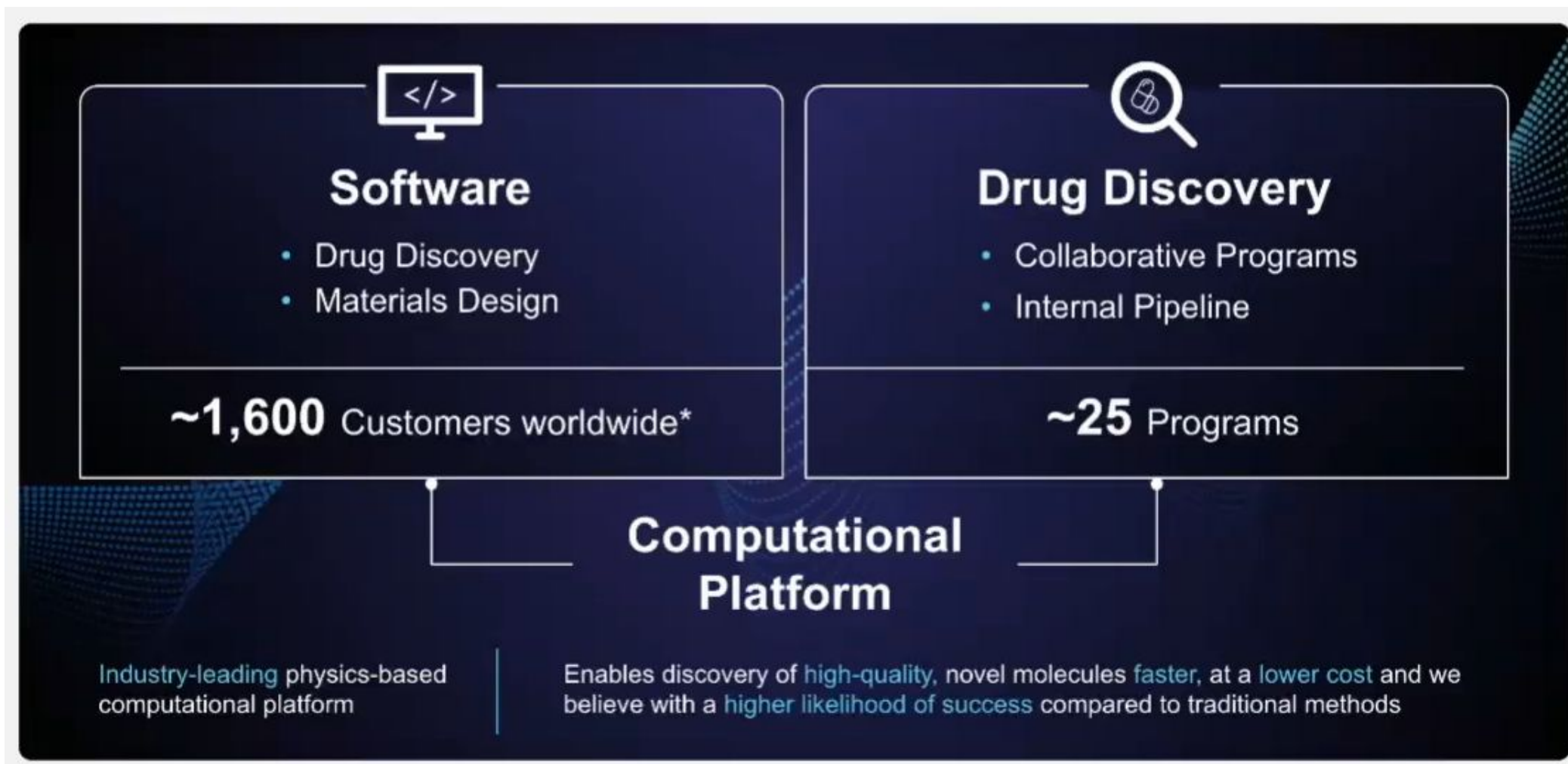
- A brief introduction to Schrödinger's design platform
- First steps in Maestro
- Preparing proteins
- Understanding the binding site
- Lunch (12:00 – 13:00)
- Designing new ligands: quick ideation
- Preparing ligands and docking with Glide
- Q&A and closing (15:00)

Downloading the workshop files

Download workshop files & slides from here: <https://bit.ly/3FnoSeM>

Link will remain active until Friday

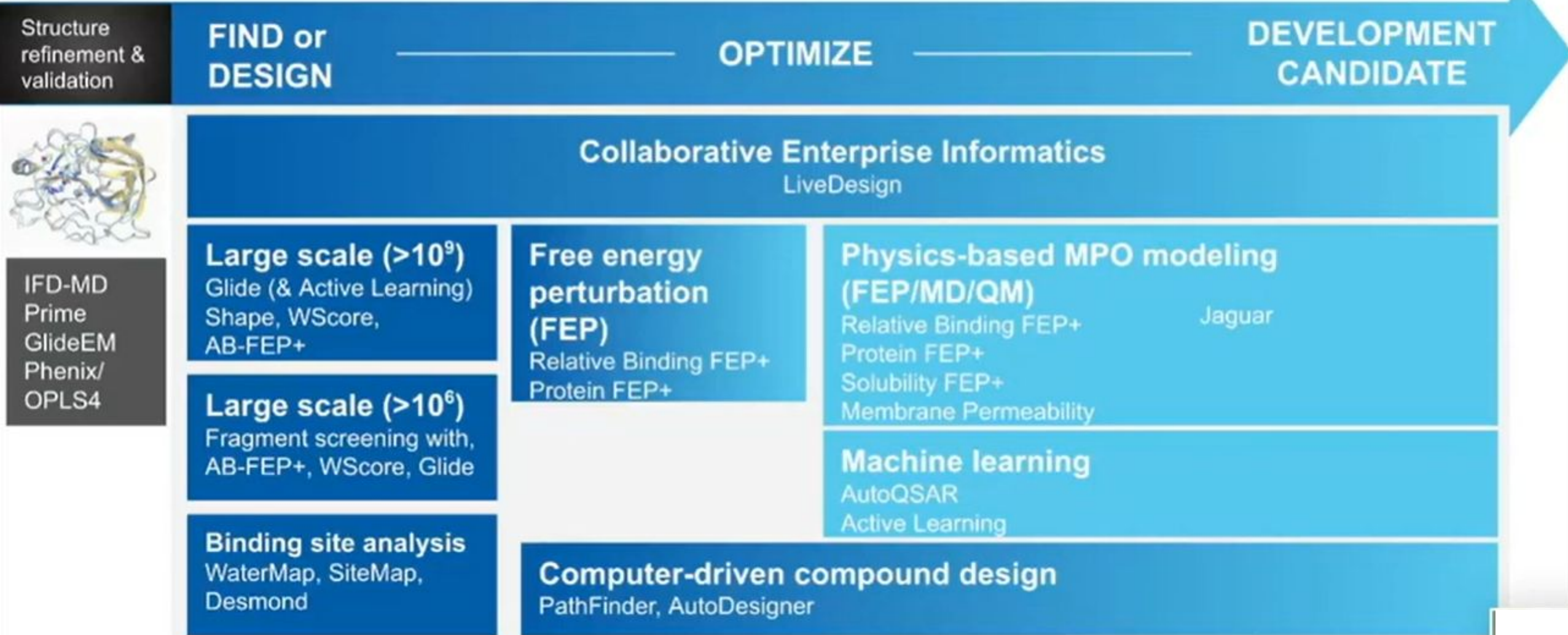
A few words about us



*Active customers as of Dec. 31, 2021. Active customers are defined as the number of customers who had an Annual Contract Value (ACV) of at least \$1,000 in a given fiscal year. See "Operating Metrics" for additional information regarding these metrics.

Schrödinger's digital chemistry toolbox

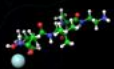
Breadth of solutions that can be applied across the drug discovery life cycle



Get to know complex workflows at your own pace

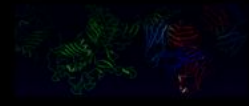
Small Molecule and Biologics Drug Discovery

Introduction to Molecular Modeling in Drug Discovery



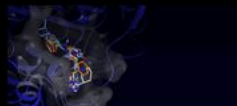
Learn how to apply molecular modeling in small-molecule drug discovery and design.

Introduction to Computational Antibody Engineering



Learn molecular modeling solutions for antibody discovery and design.

High-Throughput Virtual Screening for Hit Finding and Evaluation



Learn best practices for using virtual screening of large ligand libraries.

Free Energy Calculations for Drug Design with FEP+



Learn best practices for using relative binding FEP+

<https://www.schrodinger.com/learn/training/schrodinger-online-learning>

Organic Electronics

[Click for syllabus](#)

Pharmaceutical Formulations

[Click for syllabus](#)

Homogeneous Catalysis & Reactivity

[Click for syllabus](#)

Polymeric Materials

[Click for syllabus](#)

Surface Chemistry

[Click for syllabus](#)

Consumer Packaged Goods

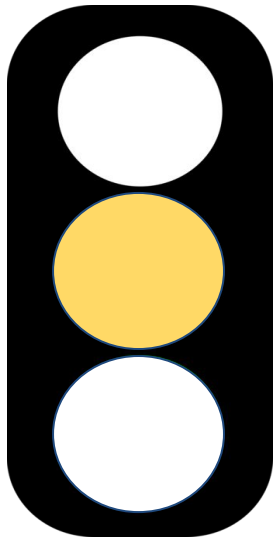
[Click for syllabus](#)

Getting Started

Visualization basics



Some tips and tricks: Getting unstuck



- **Hover** over it or **right-click** on it
 - Tooltips let you know what a button does
 - Almost everything gives more options for interactions via right-click
- **? Button** in the panels
 - Takes you to the appropriate part of the documentation
- **Search** the Documentation
 - Finds both technical documentation and tutorials
- **Search** the Tasks Tool
 - If you don't know what it is called or to see if it is available
 - Hit enter with a search term

Project Setup for Day 2

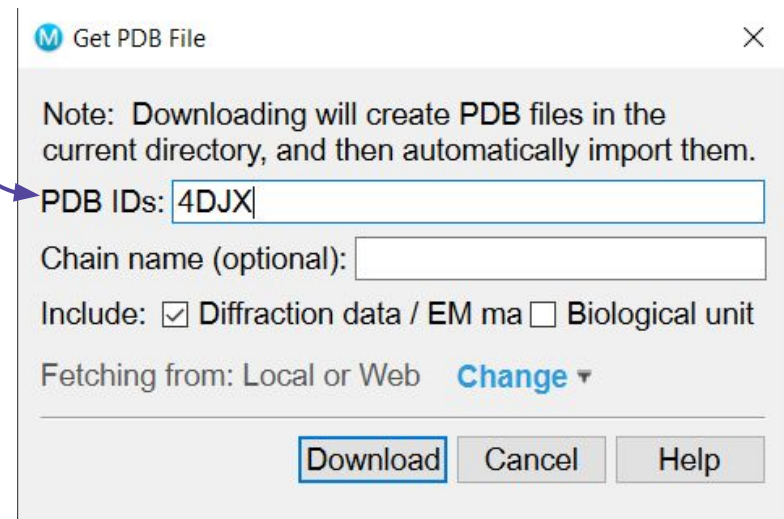
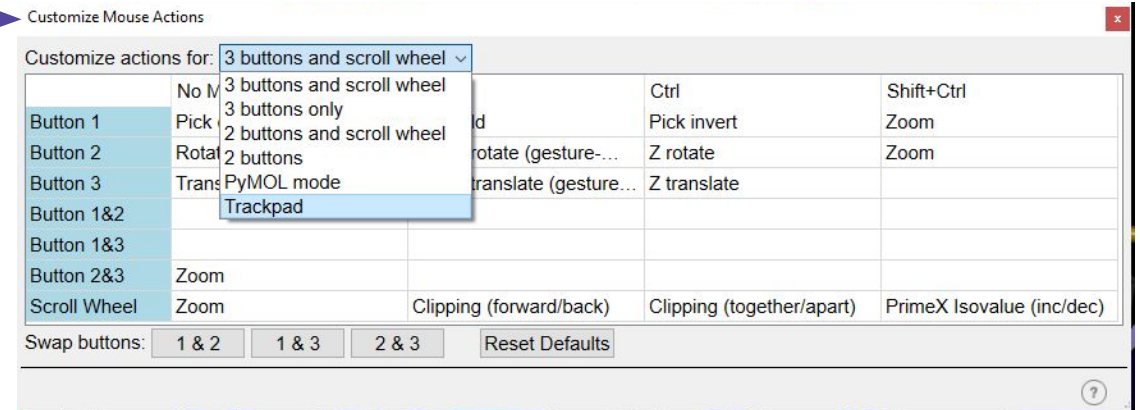


1. Choose where project data should be saved

3. Fetch BACE-1 structure from the PDB

2. Set to where Maestro should put results of calculations and other output
My recommendation: inside project folder

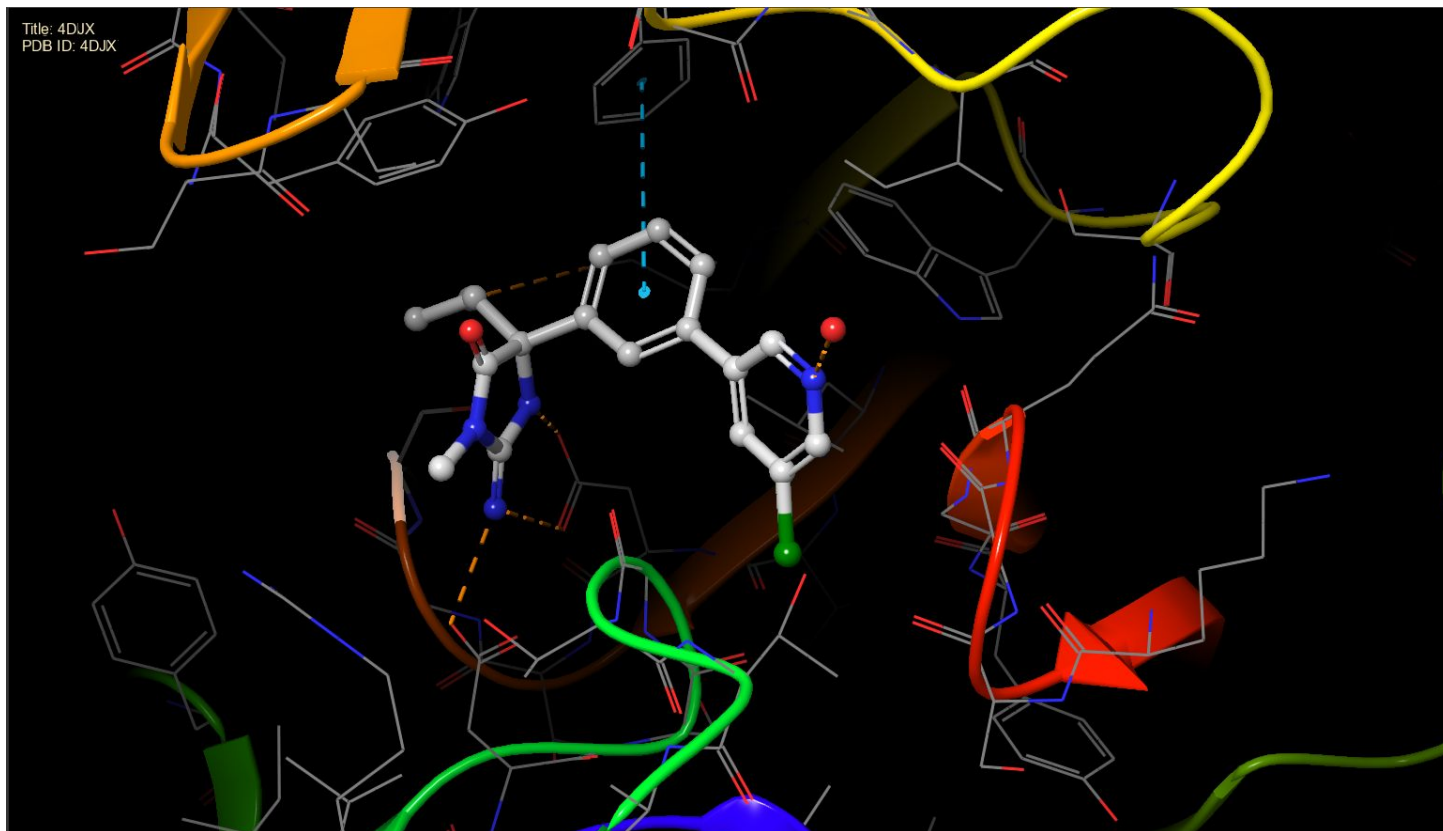
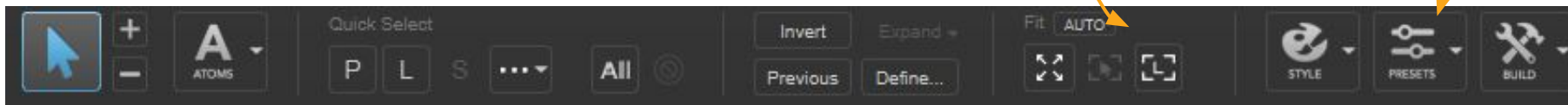
0. In case you're using a trackpad or are used to PyMOL:



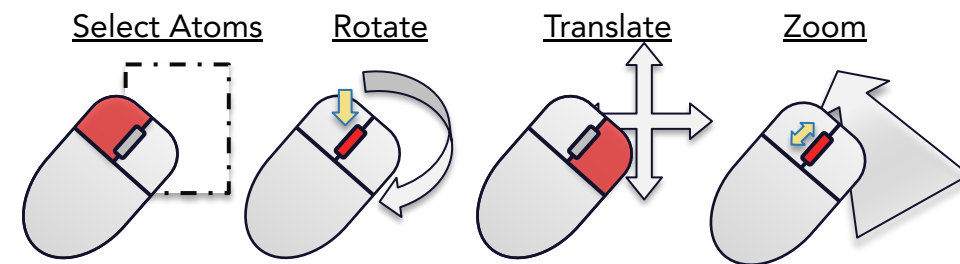
Getting familiar with BACE-1 (PDB id: 4DJX)

zoom and fit view (to all, selection, or ligand)

*apply visualization presets
(double-click to apply default preset)*



Default Maestro mouse/camera controls:



Toggle display of Labels and Interactions



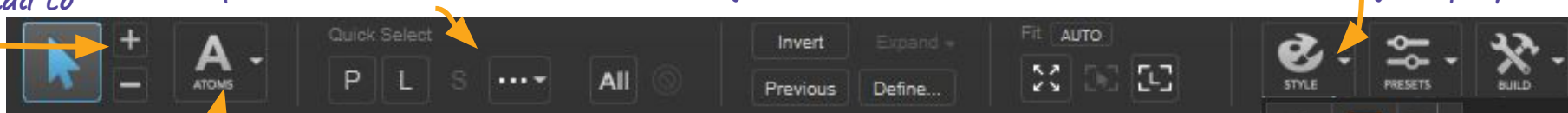
To reproduce: apply default preset, toggle labels off and interactions on, zoom to ligand, adjust camera

Getting familiar with BACE-1: Tweaking the style

“+” or Ctrl-Click to add to selection

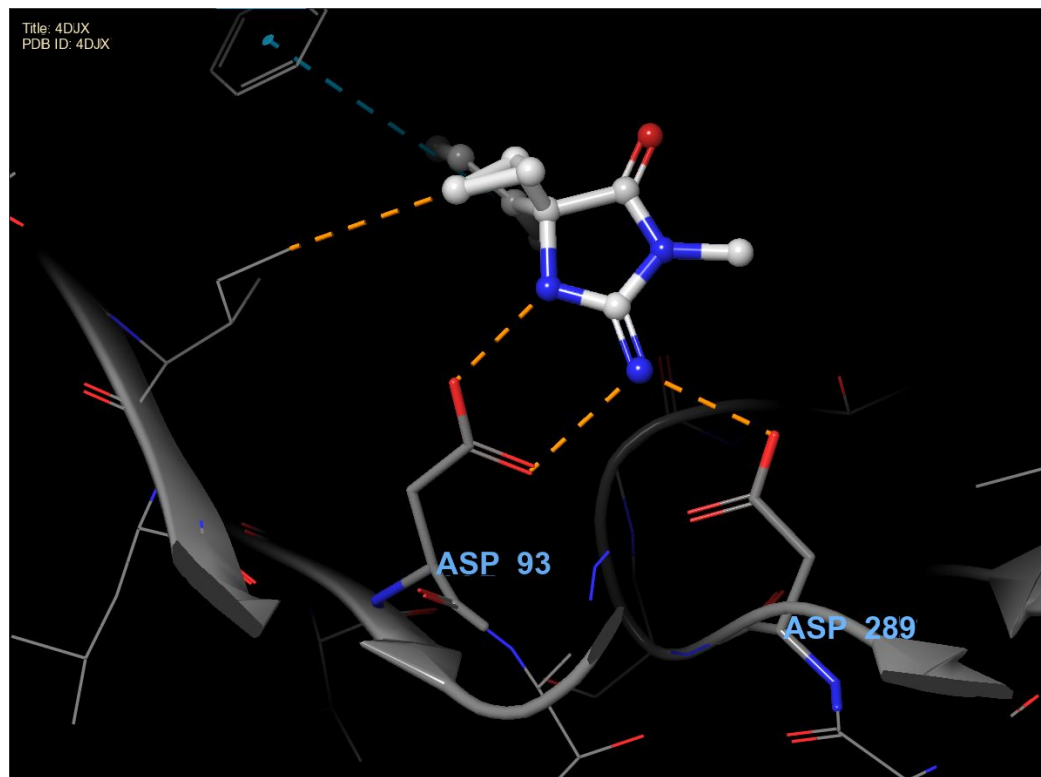
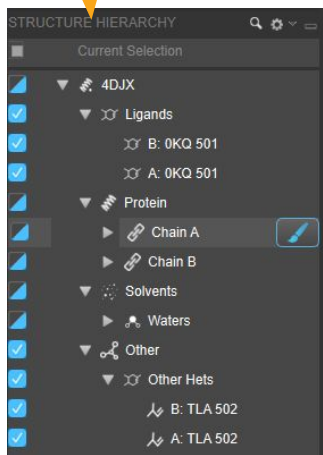
quick selection shortcuts: Protein, Ligand, Solvent, and more

change display of selected entities



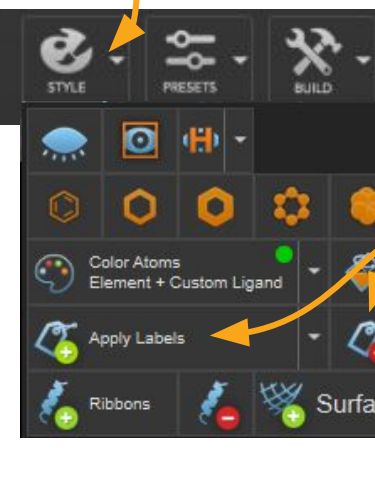
quickly switch between selection modes

search and navigate semantically

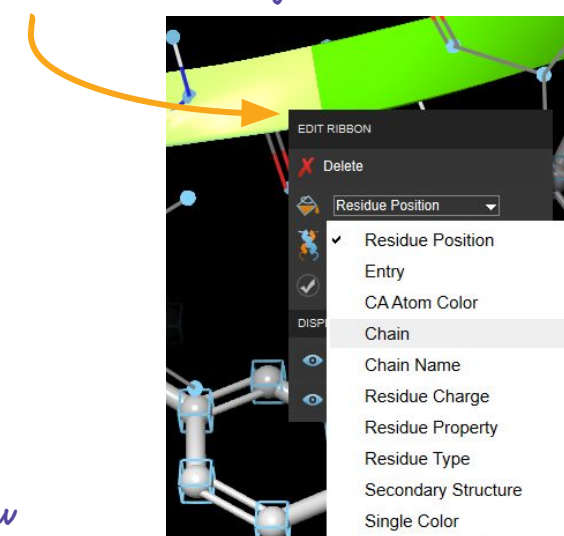


For labels, ribbons, surfaces:

Add/Remove them here
Show/Hide them here:



right-click menus recognize context



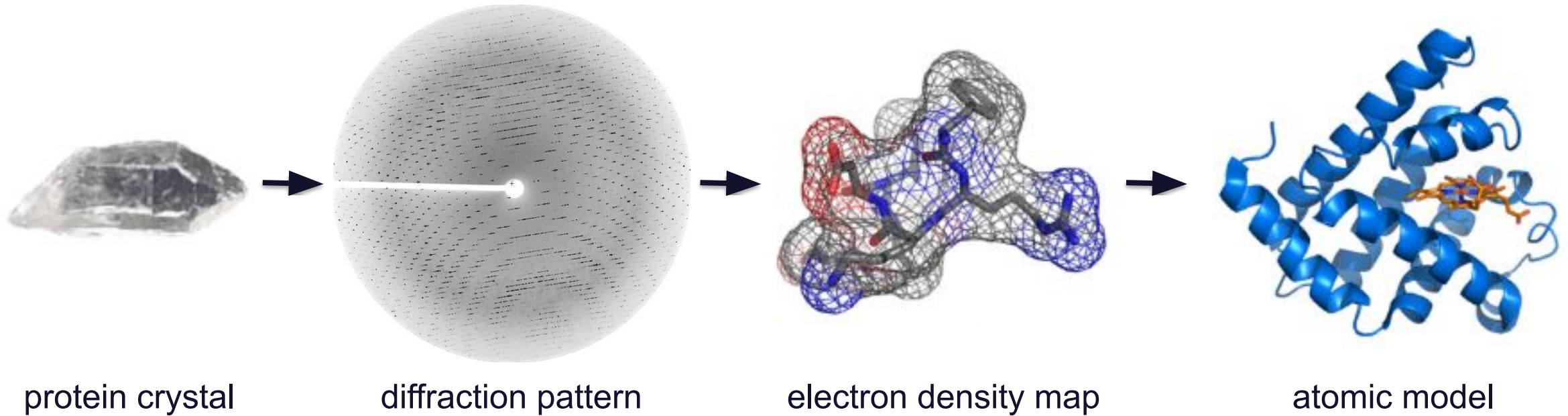
Try to reproduce this view:
color ribbons by CA Atom Color, remove all labels, find and select Asp pair, show as thin tubes, add labels for Asp pair only

Preparing Proteins

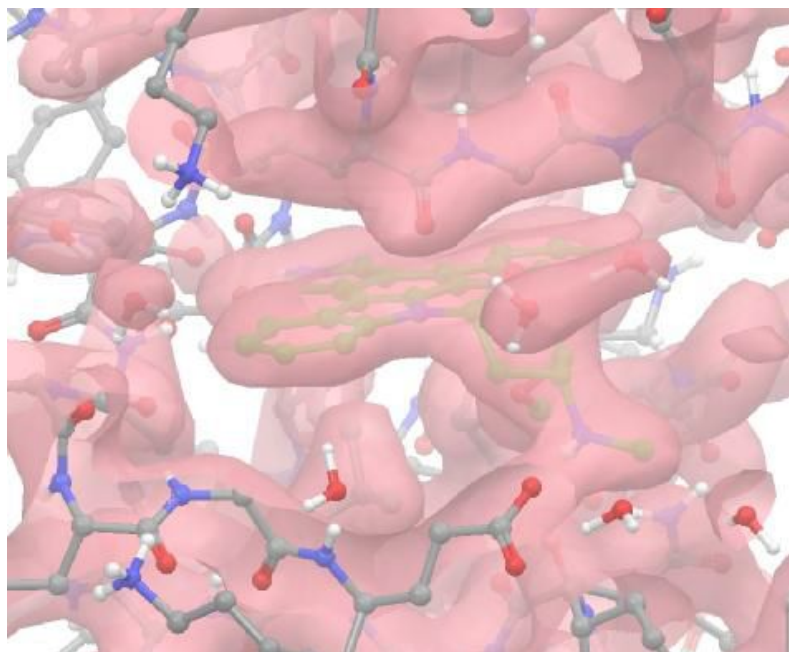
(the basics)



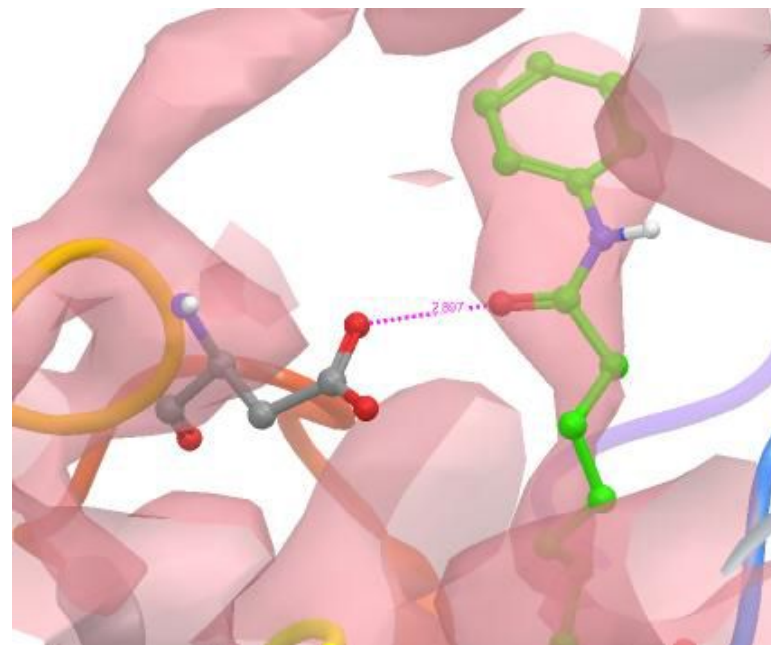
Where are my hydrogen atoms?



Not all Crystal Structures are Created Equal

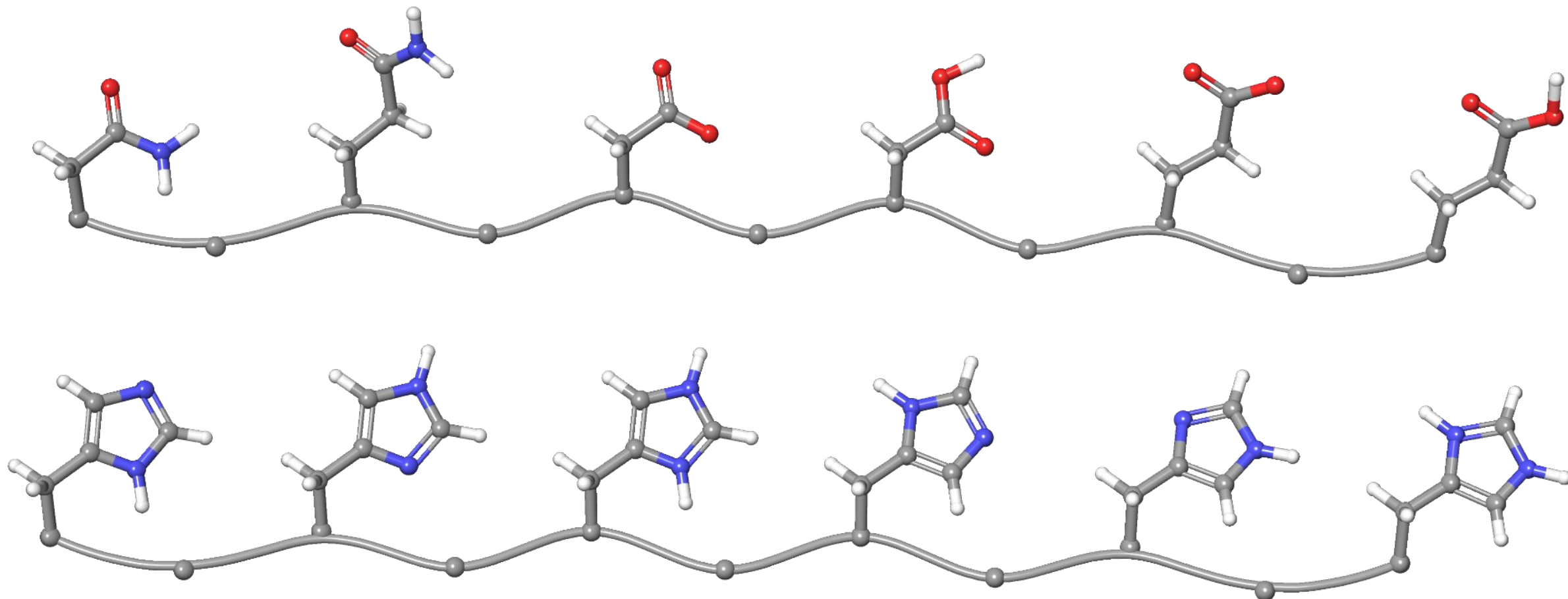


In this case, the ligand density is relatively unambiguous.



In this case the density is missing, which may result in misleading information.

These all look very similar in X-Ray experiments!



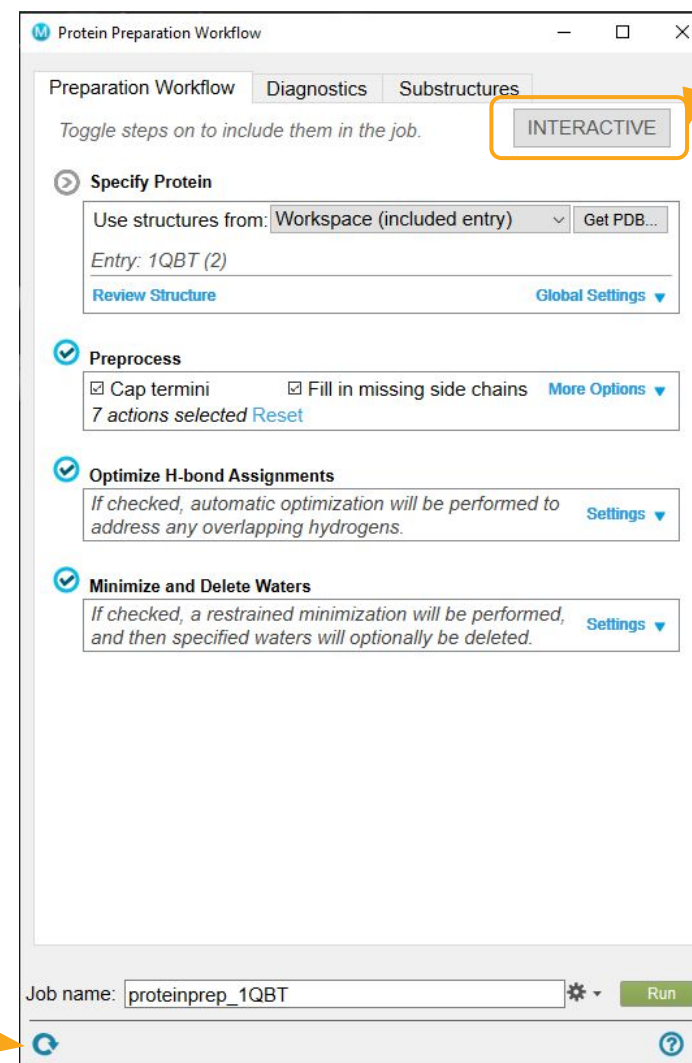
How do I prepare a protein?



Find "Protein Preparation Workflow" in Tasks

Protein Preparation Workflow takes care of:

- Alerting you to **potential issues** in the structure
- Adding in **missing atoms**, residues, and short loops
- Adding hydrogen atoms to achieve **sensible protonation states** for given pH
- Constructing a reasonable **hydrogen-bond network**
- Resolving **common issues and ambiguities** in the crystal structure



For more control you could switch to interactive mode

reset panel to defaults

Link to documentation

Preparing our Protein I: What's in the structure?

Protein Preparation Workflow

Preparation Workflow | Diagnostics | Substructures

Check Workspace Entry Entry: 4DJX (1)

One issue was found. See Reports for more information about the protein.

Valences | Missing | Overlapping | Alternates | Reports

Valence errors were found. The problem may be missing H or an incorrect number of bonds. The *Preprocess* step adds H based on the heavy atom. You may also change the element, charge, or number of bonds using the [3D Builder](#) or right-click menu options..

Select table rows to review the corresponding items in the Workspace:

Atom	Residue	Atom type	Expected Bonds	Actual Bonds
N 1	A: GLY 58	NB (28)	3	1
C 2	A: GLY 58	CB (5)	4	2
N 5	A: SER 59	NC (29)	3	2
C 6	A: SER 59	CA (4)	4	3
C 9	A: SER 59	CB (5)	4	2
O 10	A: SER 59	OA (17)	2	1
N 11	A: PHE 60	NC (29)	3	2
C 12	A: PHE 60	CA (4)	4	3
C 15	A: PHE 60	CB (5)	4	2
C 17	A: PHE 60	CD (7)	4	3
C 18	A: PHE 60	CD (7)	4	3
C 19	A: PHE 60	CD (7)	4	3
C 20	A: PHE 60	CD (7)	4	3

< Workflow | Substructures >

Protein Preparation Workflow

Preparation Workflow | Diagnostics | Substructures

Reload from Workspace Entry: 4DJX (1)

Choose items below to view in Workspace, copy, or delete. Select

Ligands, Metals, Other. The Lig column shows detected ligands. To change the classification, visit the [Ligand Detection...](#) settings, then click *Reload from Workspace* above.

The *Preprocess* step may generate multiple states for your ligands. The (likely) most favorable state will be checked by default. Optionally choose a different state to keep.

Lig	Chain	Res Name + #
X	A	0KQ 501
	A	TLA 502
X	B	0KQ 501
	B	TLA 502

Waters:

Chain	Res Name + #
A	HOH 601
A	HOH 602
A	HOH 603
A	HOH 604
A	HOH 605
A	HOH 606

Chains: Expand to PDB chain

Chain	Type
A	Protein
B	Protein

449 items selected Clear Copy to New Entry Delete from Entry

Prepare Selected Only... < Diagnostics Workflow >

We prepare only chain A and delete TLA:

1. Select TLA from chain A

2. Ctrl+Click to also select Chain B
→ Expand selection to PDB Chain

3. Create copy of the entry with deletions applied

Workspace Navigator

ENTRY LIST

Row	In	Title
1	<input type="radio"/>	4DJX
2	<input checked="" type="radio"/>	4DJX - with-deletions

Preparing our Protein II: Running the Preparation

Protein Preparation Workflow

Preparation Workflow Diagnostics Substructures

Toggle steps on to include them in the job. INTERACTIVE

Specify Protein

Use structures from: Workspace (included entry) Get PDB...

Entry: 4DJX - with-deletions (2)

Review Structure Global Settings

Preprocess

Cap termini Fill in missing side chains More Options

7 actions selected Reset

Optimize H-bond Assignments

If checked, automatic optimization will be performed to address any overlapping hydrogens. Settings

Minimize and Delete Waters

If checked, a restrained minimization will be performed, and then specified waters will optionally be deleted. Settings

Job name: proteinprep_4DJX Run

Simulation pH: 7.4

Use PDB value instead: (N/A)

Small molecules ("hets") to process:

- Detected Ligands
- Metals and ions
- Non-water solvents
- Others

Align to: First selected entry PDB: []

Assign bond orders: Using CCD database

Replace hydrogens

Create: Zero-order bonds to metals

Disulfide bonds

Antibody annotation scheme: Kabat

Renumber residues to match scheme

Add terminal oxygens to protein chains

Convert selenomethionines to methionines

Delete waters beyond hets: 8.00 Å

Fill in missing loops (using Prime)

Generate het states (with Epik): pH: 7.4 +/- 2.0

Max states to process automatically: 1

Don't delete the waters here unless your structure is too big otherwise

For now, leave all settings at their default value, give your job a memorable name and run it

Minimize:

Converge heavy atoms to RMSD: 0.30 Å

Optimize hydrogens only

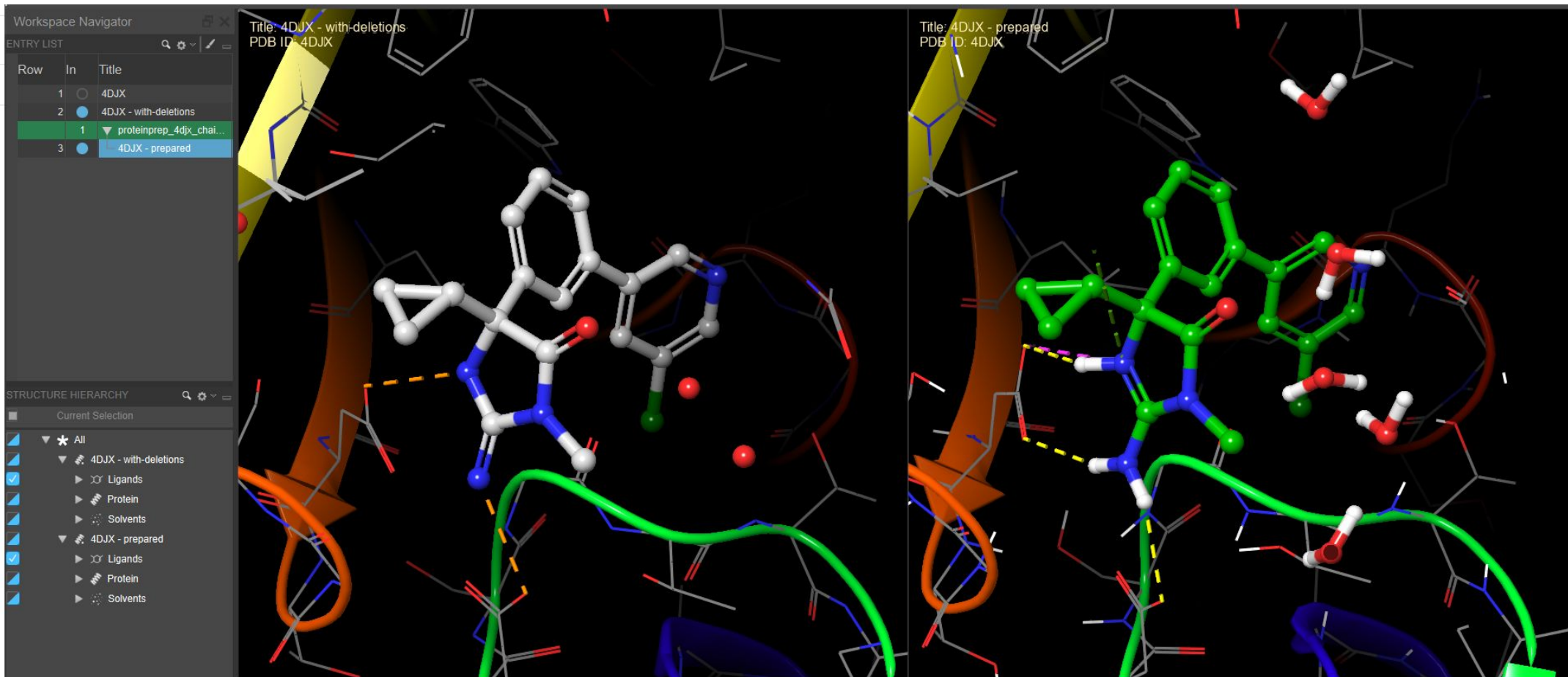
Force field: OPLS4 Use customized version

Delete waters:

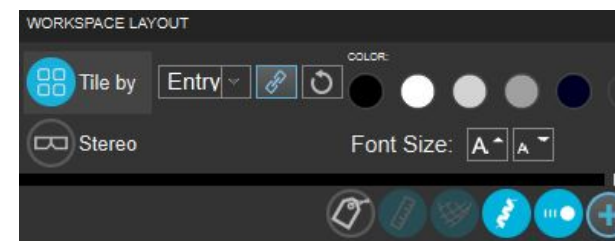
Distant from ligands (hets): 5 Å

With fewer than 3 bonds to non-waters

Before and after protein preparation



To reproduce: include both 4DJX-with-deletions and 4DJX-prepared, re-apply preset, tile the workspace (“+” workspace widget)



Visualizing the Pocket in 2D

Find "Ligand Interaction Diagram" in the tasks menu or the favorites bar

2D projection tied to 3D camera position

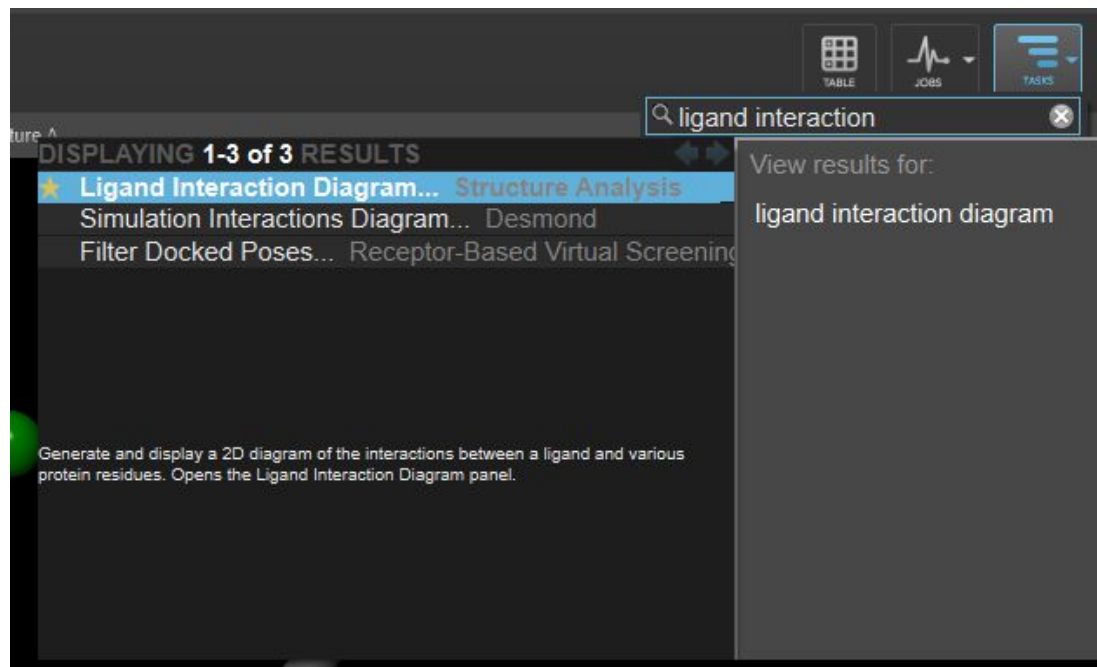


TABLE JOBS TASKS

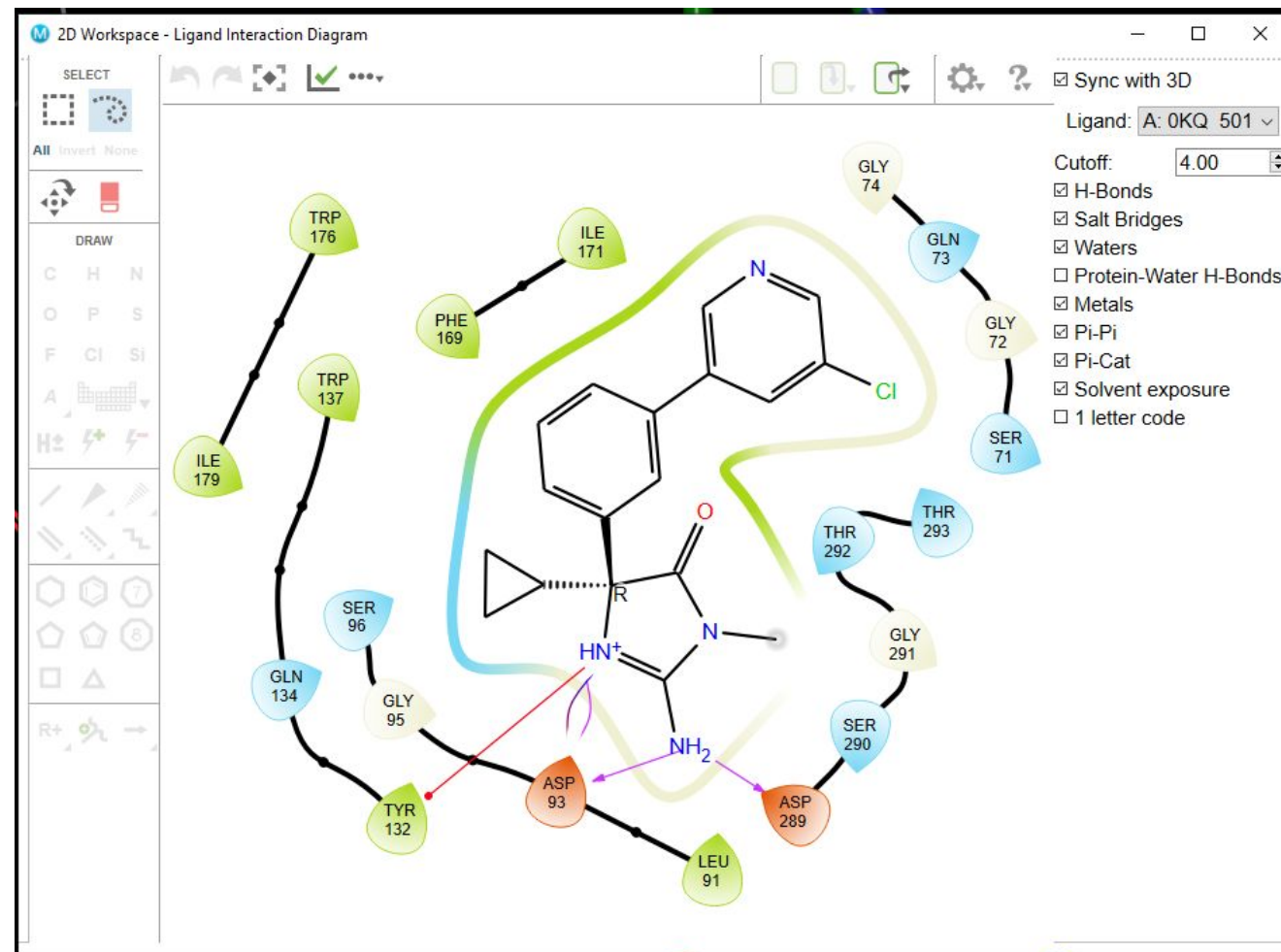
ligand interaction

DISPLAYING 1-3 of 3 RESULTS

- Ligand Interaction Diagram... Structure Analysis
- Simulation Interactions Diagram... Desmond
- Filter Docked Poses... Receptor-Based Virtual Screening

View results for:
ligand interaction diagram

Generate and display a 2D diagram of the interactions between a ligand and various protein residues. Opens the Ligand Interaction Diagram panel.

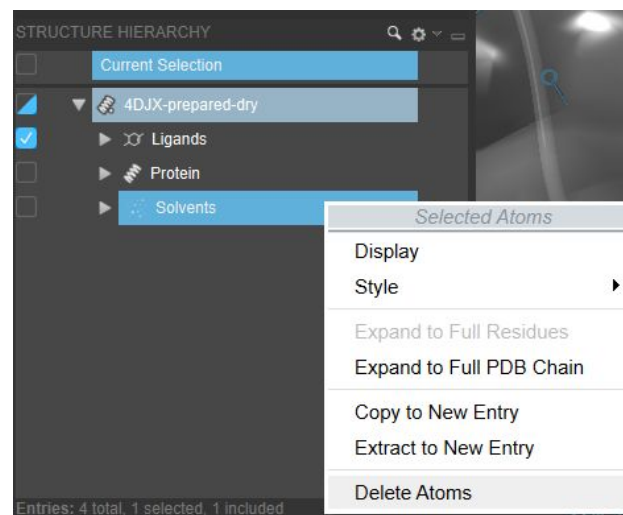
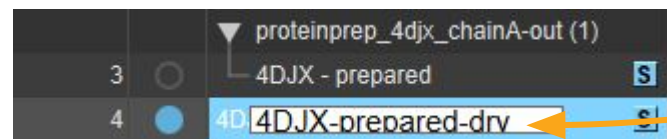
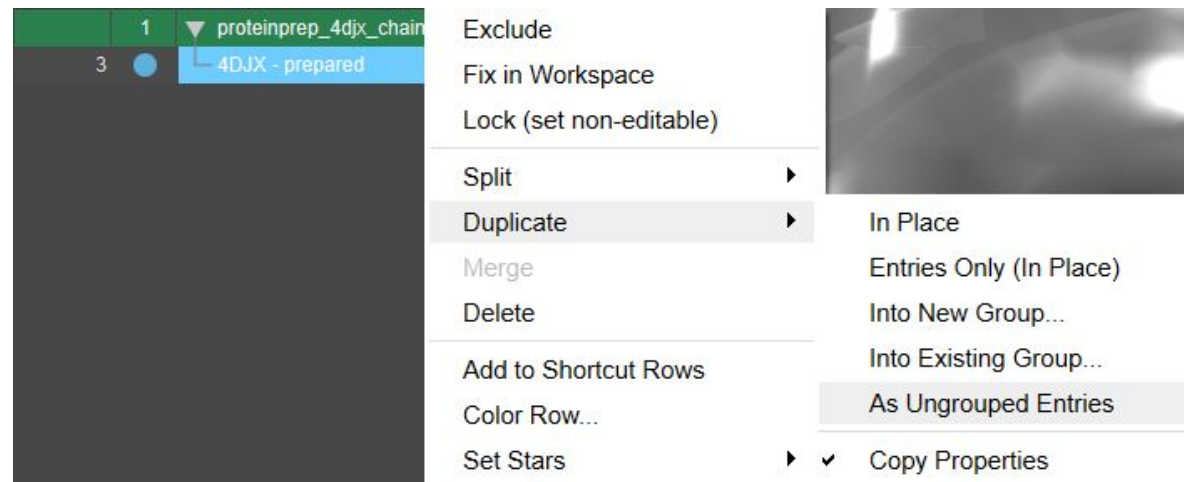


What to do with the crystal waters?

- Some workflows require a 'dry' structure, e.g. SiteMap, Glide docking
- For all MD based workflows, X-ray waters are helpful as the protein must be solvated

Best practice recommendations:

- Keep waters through to the end of the preparation workflow
- Duplicate your structure and rename it
- Select all water molecules and delete them
- Use 'wet' or 'dry' structure as appropriate



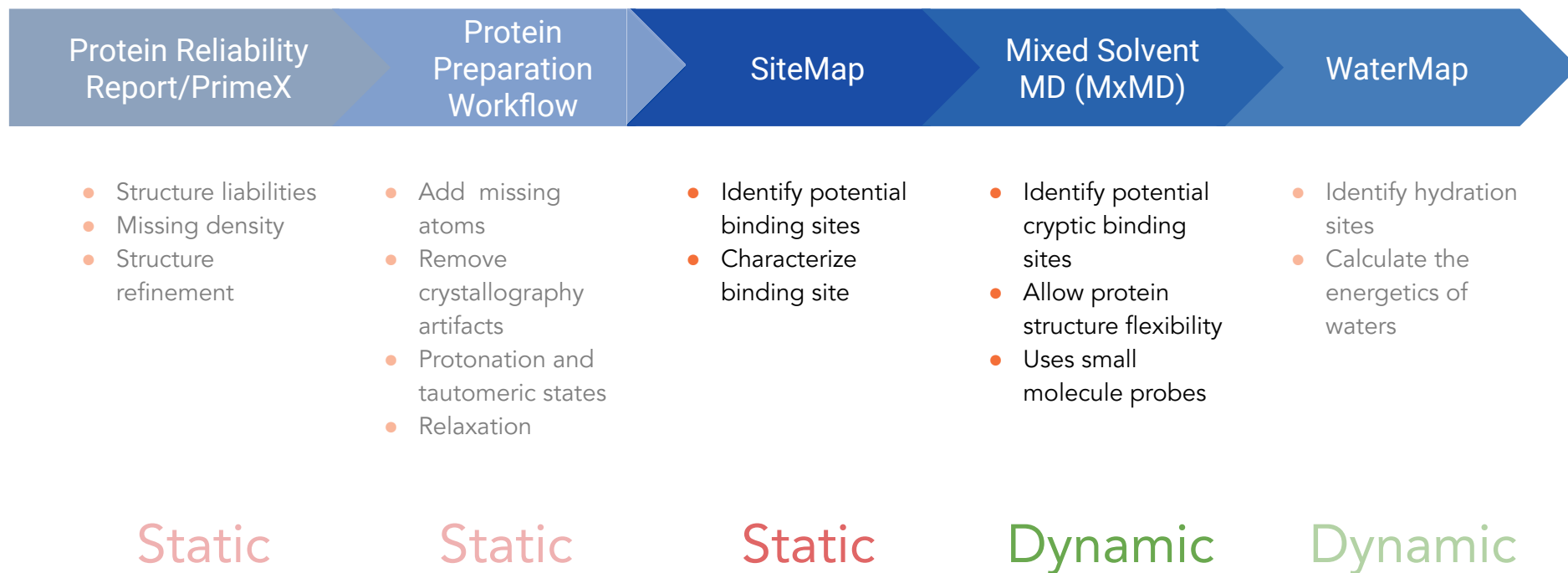
Make sure the "4DJX-prepared-dry" structure is included!

Understanding the Binding Site

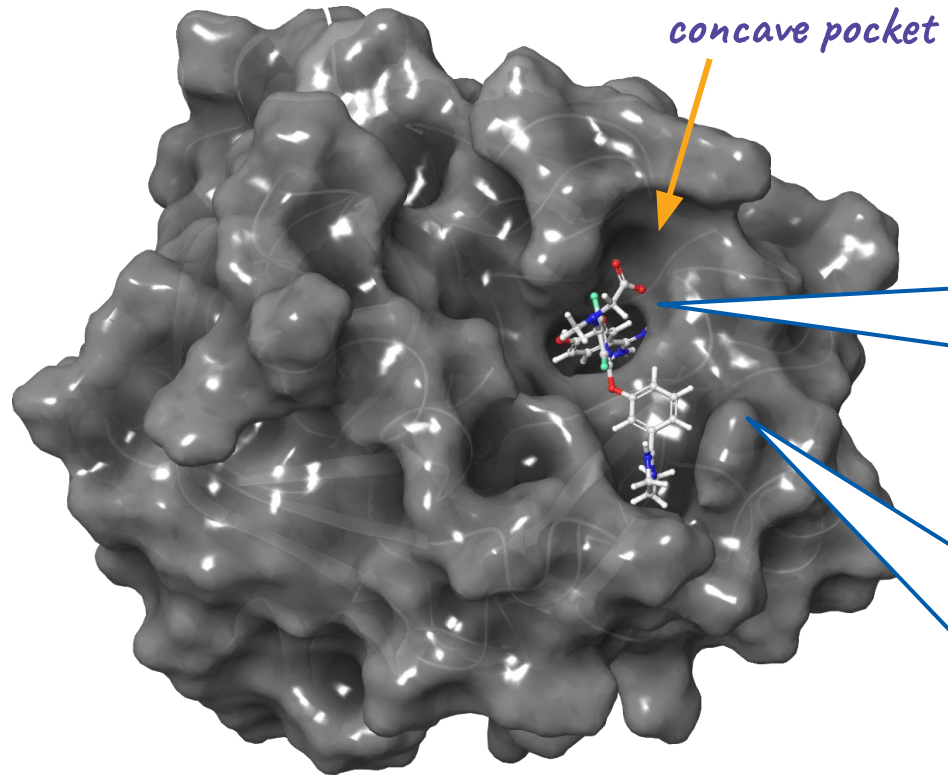
using SiteMap



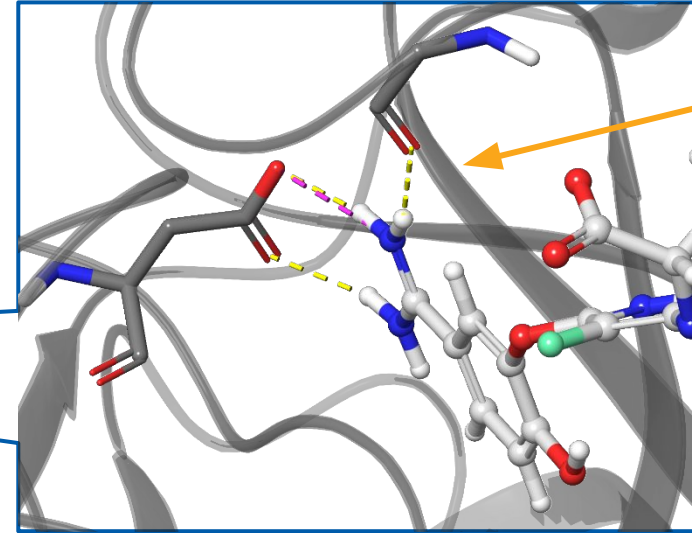
Many tools provide insight into the binding pocket



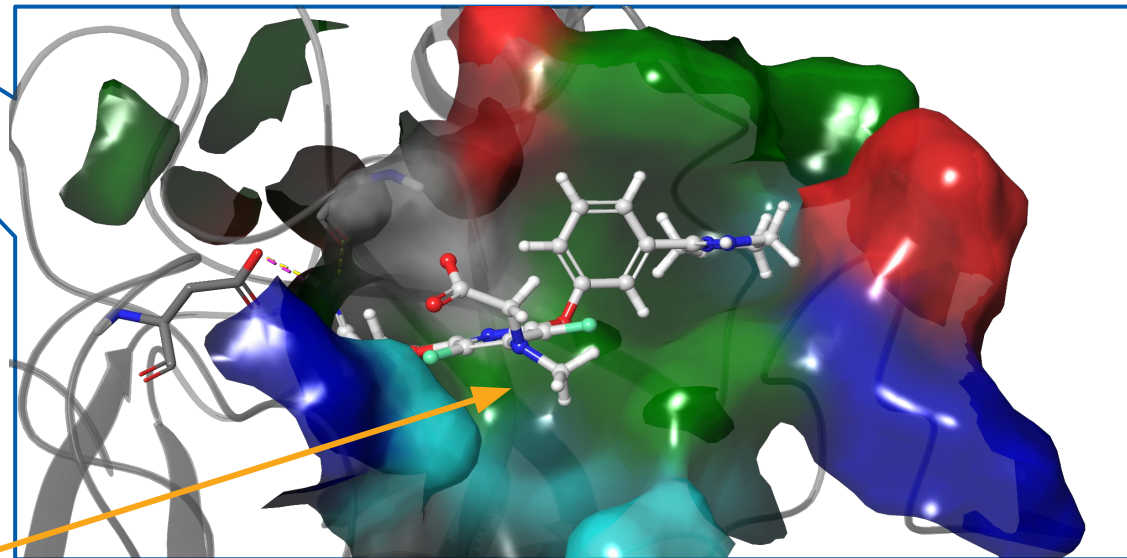
What does a binding site look like?



PDB: 1FJS (human Factor Xa)



specific interaction points for recognition or functionality

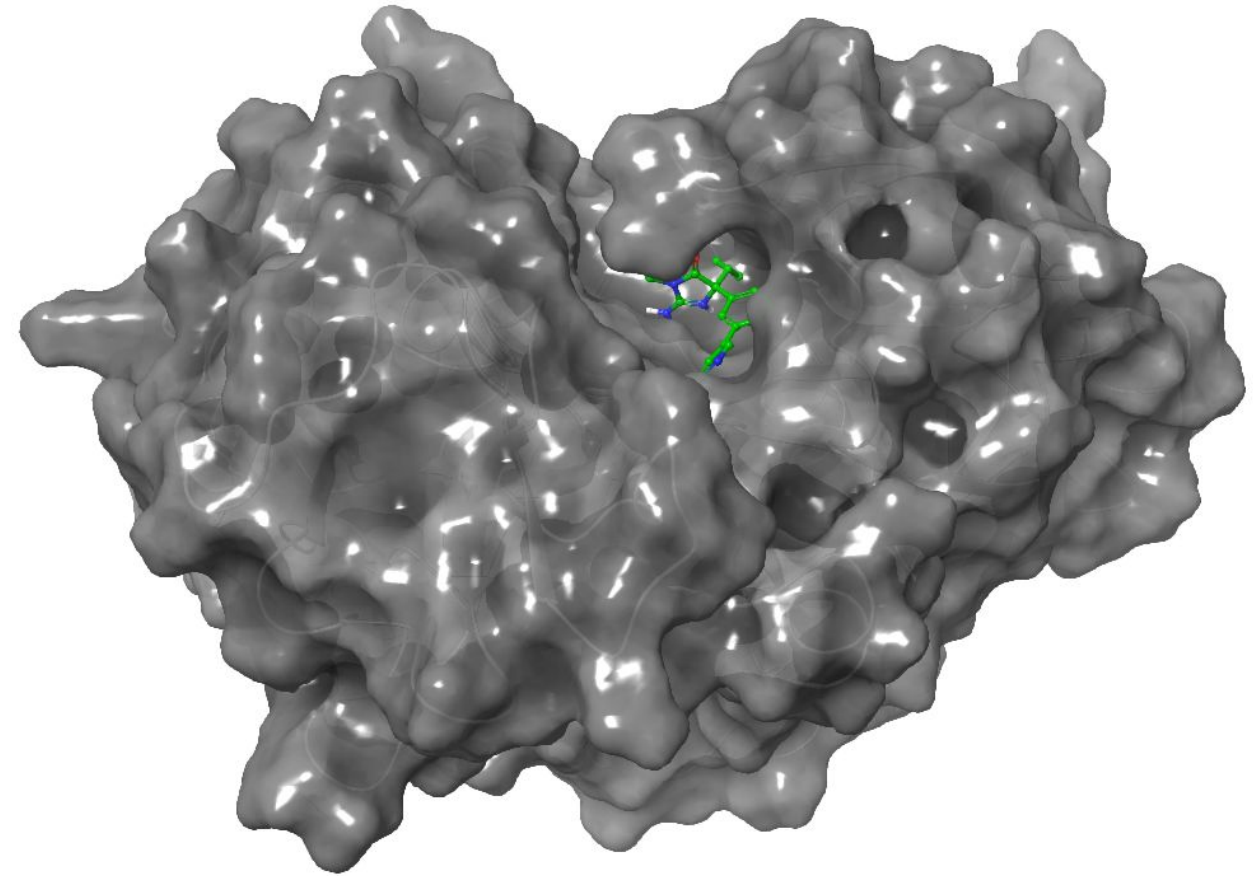
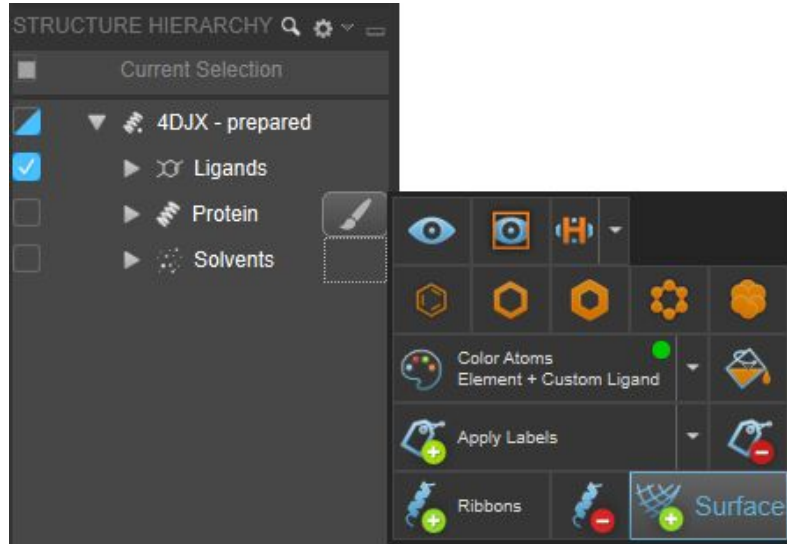


at least partially hydrophobic

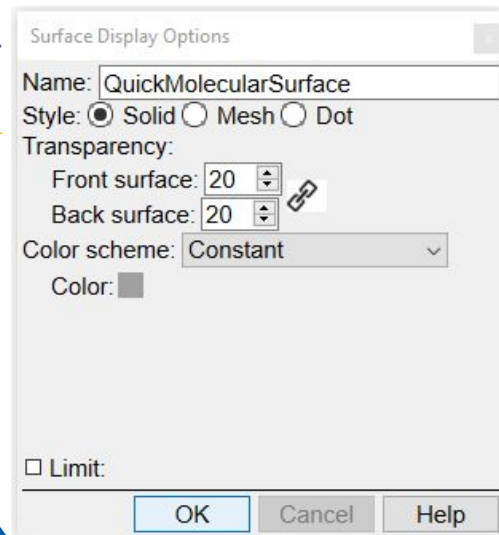
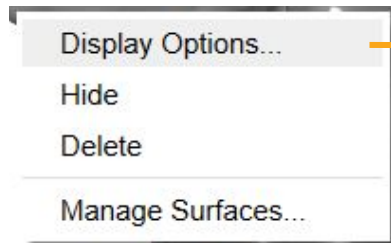
residue type: hydrophobic, polar uncharged, positives, negatives

A rough overview of the shape of BACE-1

One way to render the protein surface:



Right-click surface to configure:



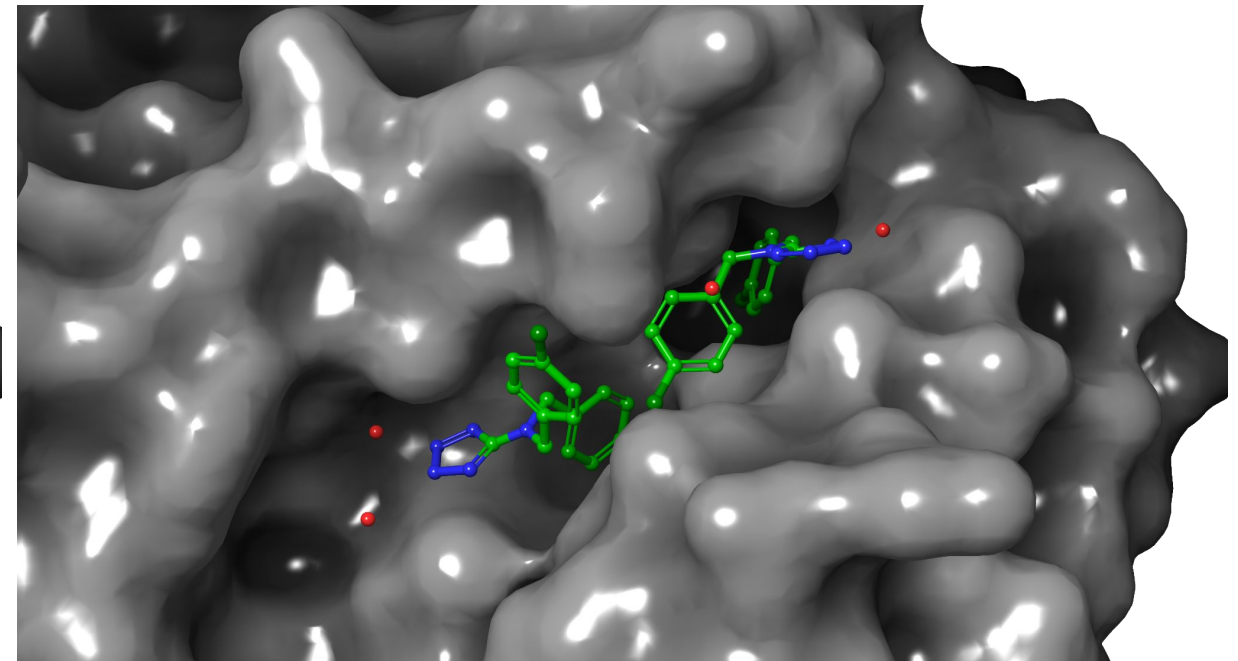
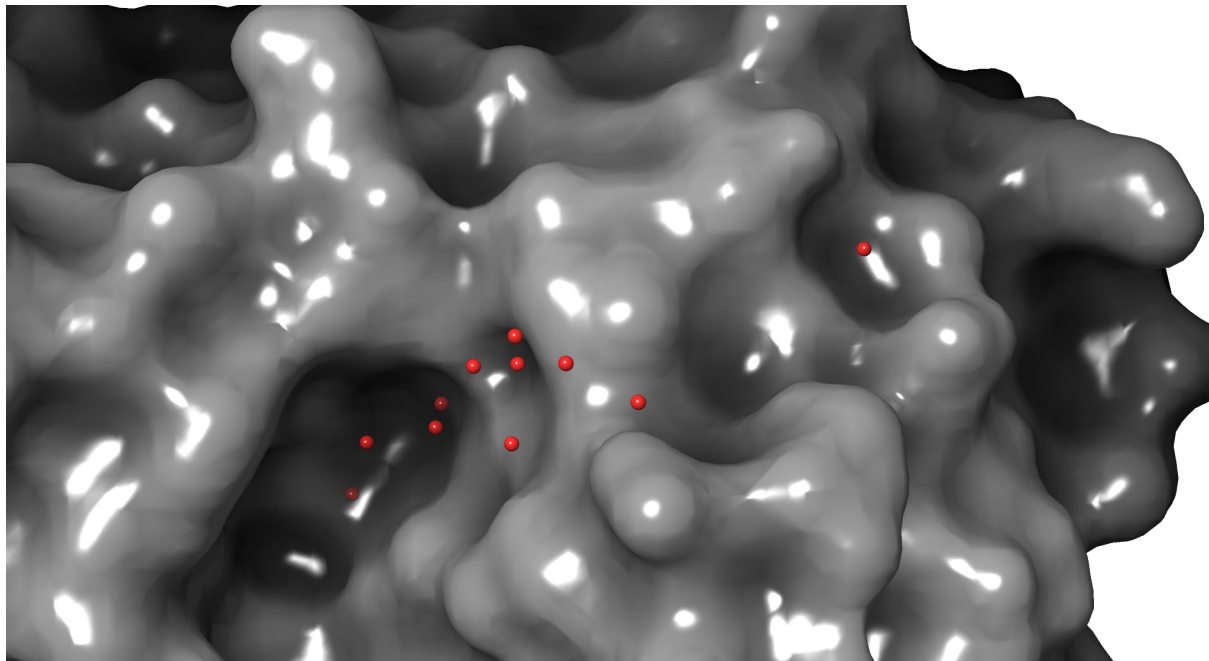
Toggle display of individual surfaces or all surfaces at once



What does an “empty” binding site look like?

An empty binding site is a high-energy state!

- apo and holo conformations can be very different
 - ↳ hand-in-glove, not key-in-lock
 - ↳ cryptic pockets are induced by ligand binding

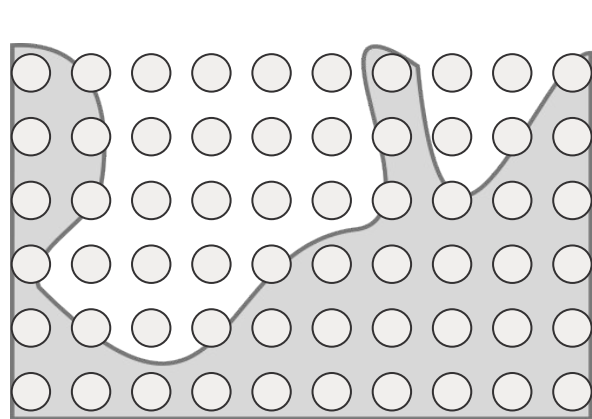


Structures of TEM1 cryptic pocket (left: 1JWP, right: 1PZO)

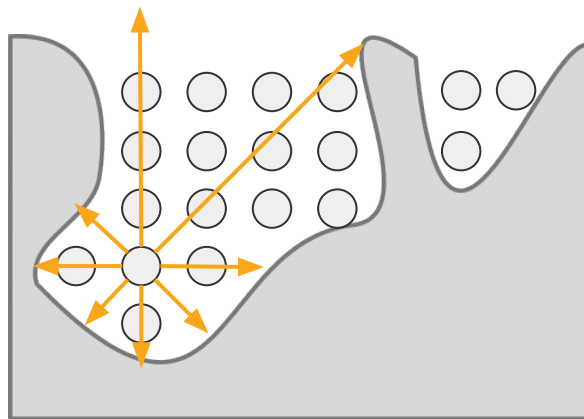
Sidenote: how do we find where binding sites are?

- experimentally: ligand-bound crystal structure, multiple-solvent crystal structures
- computationally:
 - compare with homologs to find binding-site-like sequence or structure patterns
 - can work well for representatives of a populous class of proteins (e.g. kinases)
→ homolog with validated binding site is very helpful here
 - scan surface topology to identify cavities likely to be pockets
 - can use a mix of geometry, energy, and other physchem properties
 - can work either on
 - static structure of target (quick, but cannot account for flexibility of protein)
 - or incorporate full dynamics (computationally expensive, but can find cryptic pockets)
 - variety of methods available, consensus methods (knowledge+physics) can help de-risk

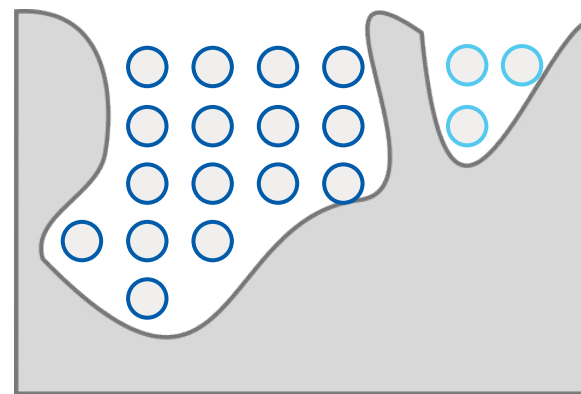
How SiteMap finds and scores sites:



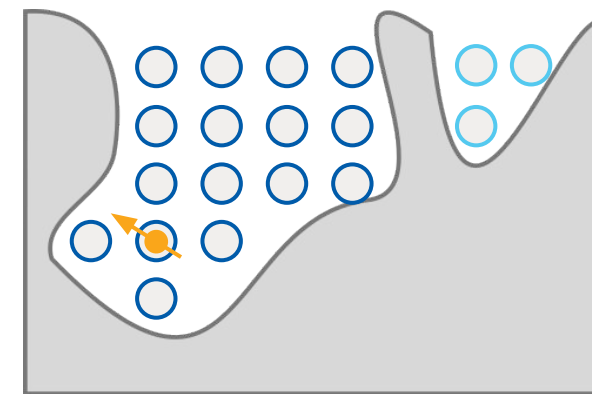
overlay grid,
discard internal points



determine enclosure



group points as sites,
bridge gaps



sample interactions with
water-like probe

calculate scores for each site based on:

- size of the site (larger sites are usually preferred)
- openness to solvent (deep sites have lots of functionality)
- hydrophobic vs philic character (hydrophobicity aids binding)
- donor vs acceptor character (good ligands tend to donate)

SiteScore: Can the site bind ligands tightly?

- calibration:
> 0.8 reasonable, > 1 promising

DScore: Is the site druggable?

- calibration: > 1 promising

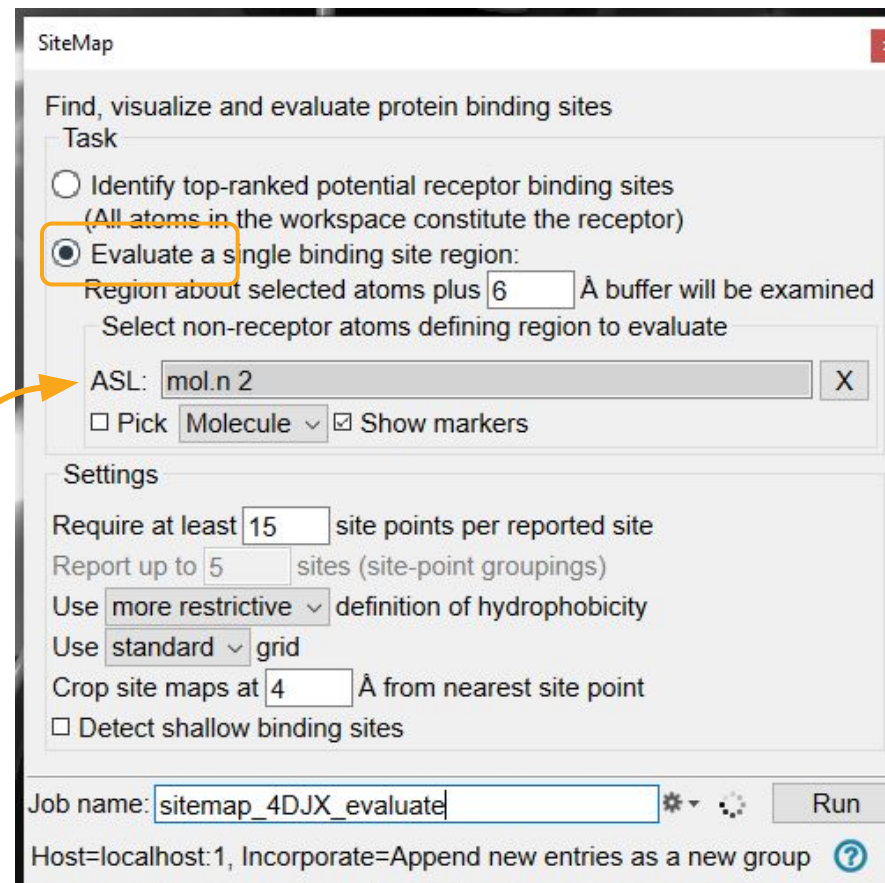
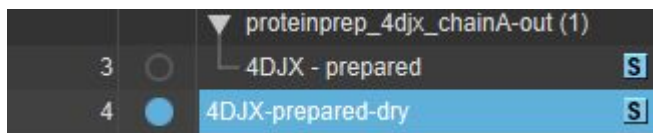
Volume, Balance, ...: [SiteMap User Manual](#)

Using SiteMap: Evaluate

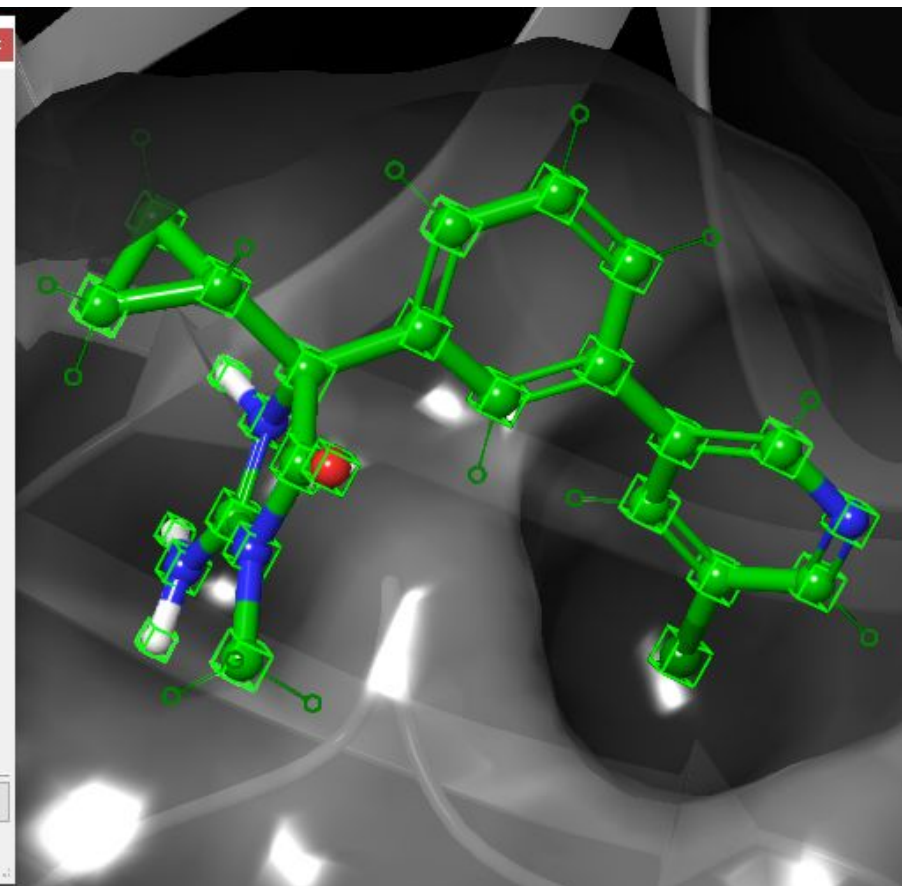


find SiteMap in the tasks menu

Make sure you've included the 'dry' structure without waters!



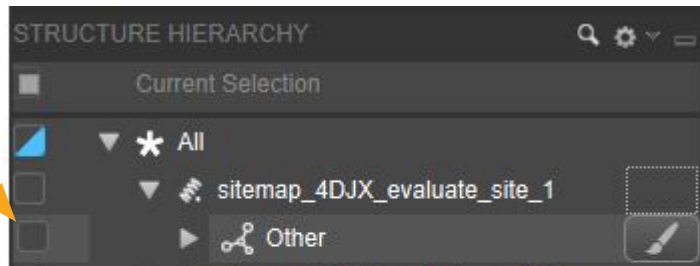
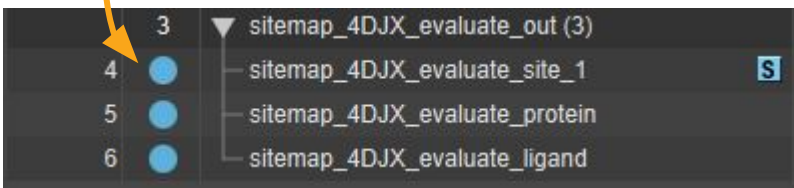
click ligand in workspace to select it



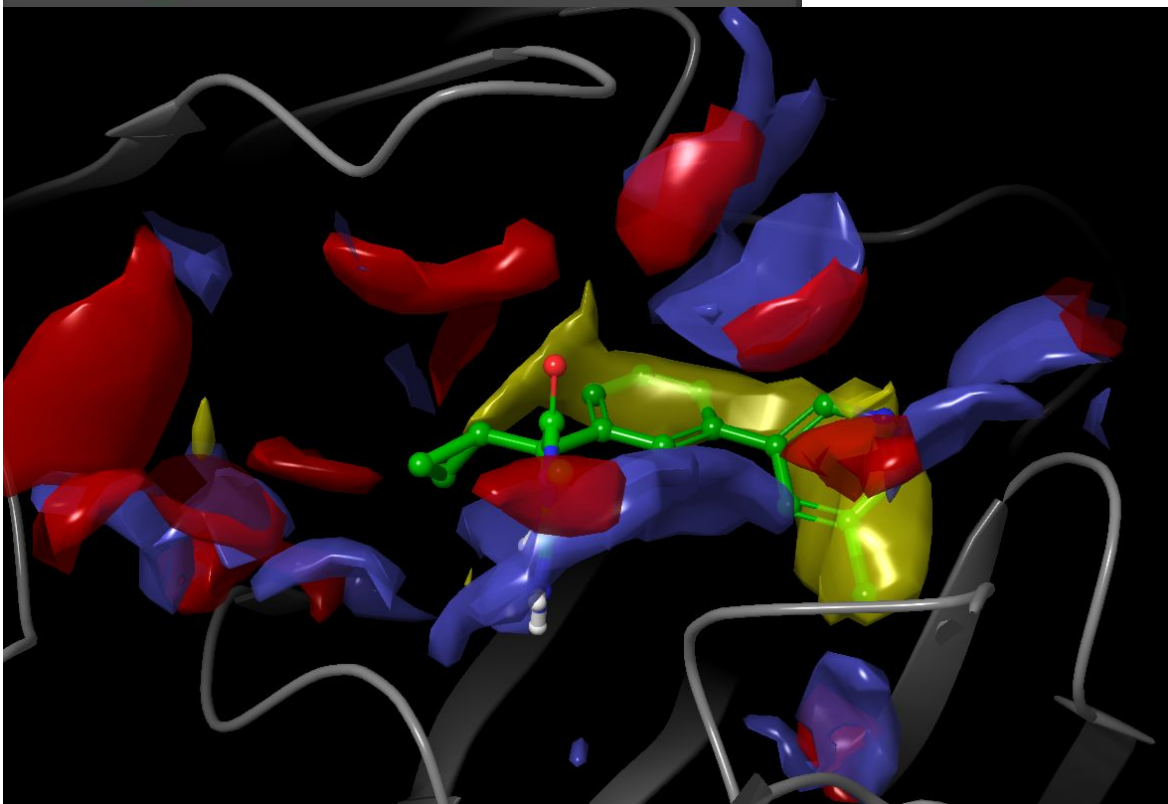
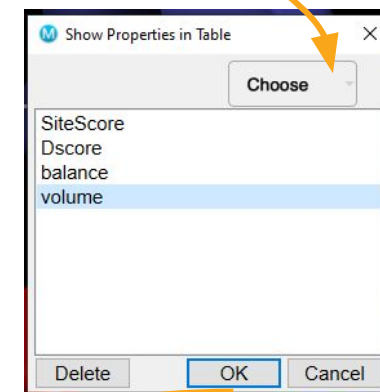
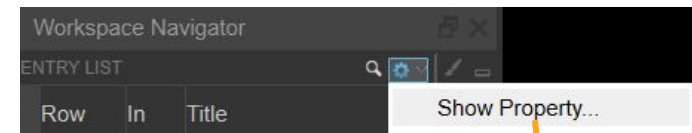
Interpreting SiteMap results

include all output entries by Ctrl+Clicking the empty circles

toggle white sphere display here



To view site metrics:



In	Title	SiteScore	Dscore	volume	balance
<input type="checkbox"/>	4DJX chain A - prepared				
<input type="checkbox"/>	4DJX chain A - dry				
3	sitemap_4djx_evaluate_o...				
<input checked="" type="checkbox"/>	sitemap_4djx_evaluat...	1.055666	1.072768	602.308000	0.828940
<input checked="" type="checkbox"/>	sitemap_4djx_evaluate_pr...				
<input checked="" type="checkbox"/>	sitemap_4djx_evaluate_li...				

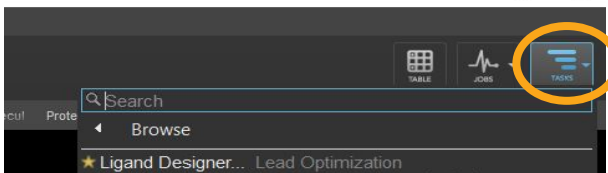
Designing Ligands

quick ideation with targeted enumeration and docking

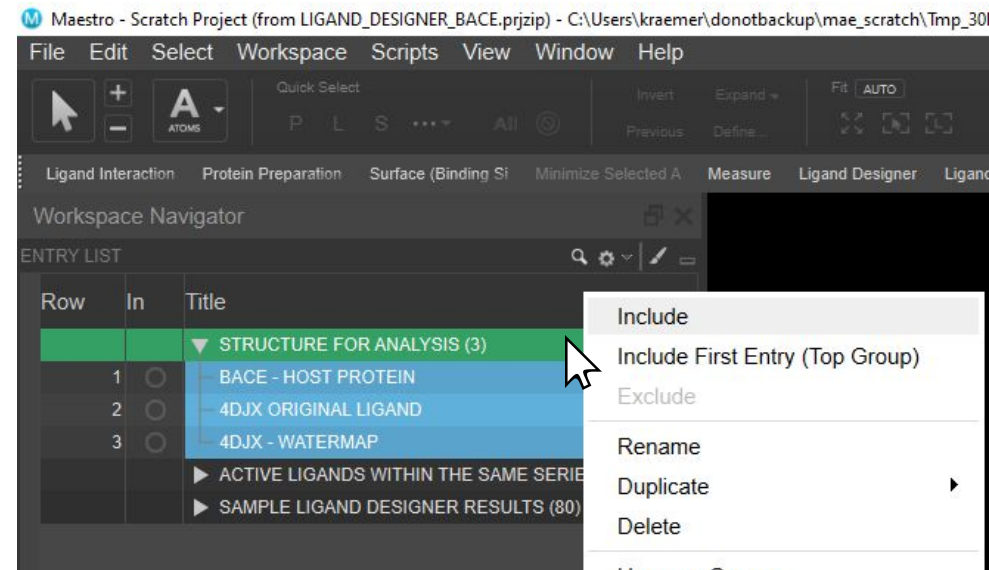


Getting started with Designing Ligands

- Open a new Maestro session
- File → Open Project...
Find `LIGAND_DESIGNER_BACE.prj.zip` in the provided files
- Include everything in the STRUCTURE FOR ANALYSIS group
- Find “Ligand Designer” in Tasks and open it:



- Click “Analyze Workspace”



Now let's tweak our ligand!

mark ligand idea as favorite

4DJX ORIGINAL LIGAND

DISPLAY Workflows

Ligand-Receptor Interactions
 Displaceable Waters
 Growth Space
 Ligand Surface

Replaceable Waters
 Pathfinder Bonds
 Receptor Surface

View similar purchasable compounds...

MULTI-PARAMETER OPTIMIZATION

AlogP PSA MW HBD HBA

AlogP	0.9	(0.0-5.0)	PSA	73.2	(0.0-140.0)
HBD	2	(0-5)	HBA	3	(0-10)
MW	341.8	(0.0-500.0)	MPO	0.69	(0-1)

POST-PROCESSING

Save to File... All Save

choose a workflow:

- Attach R-Group
- Fill Growth Space
- Bioisostere Replacement
- Isostere Scanning
- Displace Unstable Water
- Replace Stable Water
- Form Ligand-Receptor Interaction
- Cyclize Ligands
- Hybridize Ligands
- 2D/3D Editing...
- Dock Ligands from File...

Some Ideas:

- Remove Thiazole group

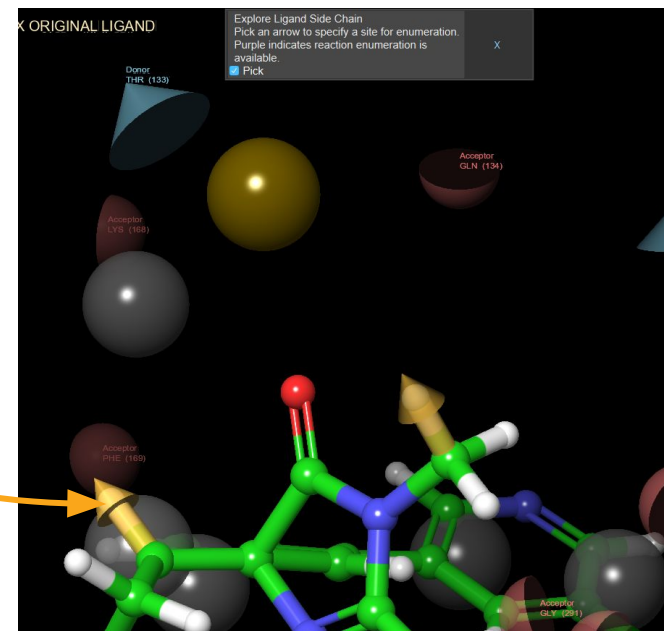
customize what to show/highlight

customize MPO function

e.g.: sort selected ligands by MPO score

arrows highlight possible modification vectors

follow the prompts in the banners



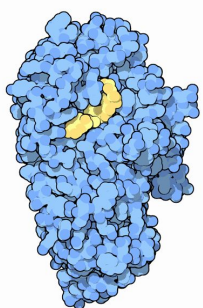
Ligand Preparation & Docking

setting up and validating a docking model

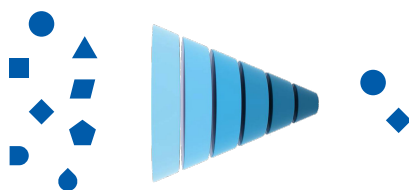


Different goals in HitID and LeadOpt require different tools

Target selection

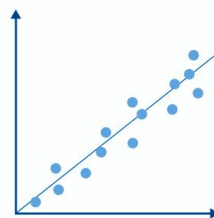


Hit identification



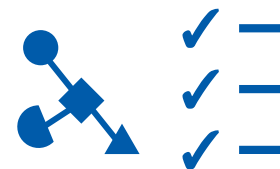
- Aim of virtual screening is to **filter down large libraries** of diverse compounds
- Requirement is **enrichment** wrt random screening, and to find **diverse hits**
- Additional properties are nice to have but less important at this stage

Lead optimisation



- Aim of virtual screening is to **rank order congeneric compound ideas**
- Requirement is to **accurately predict binding** and rank similar compounds
- Compounds have to optimally **balance activity and other properties**

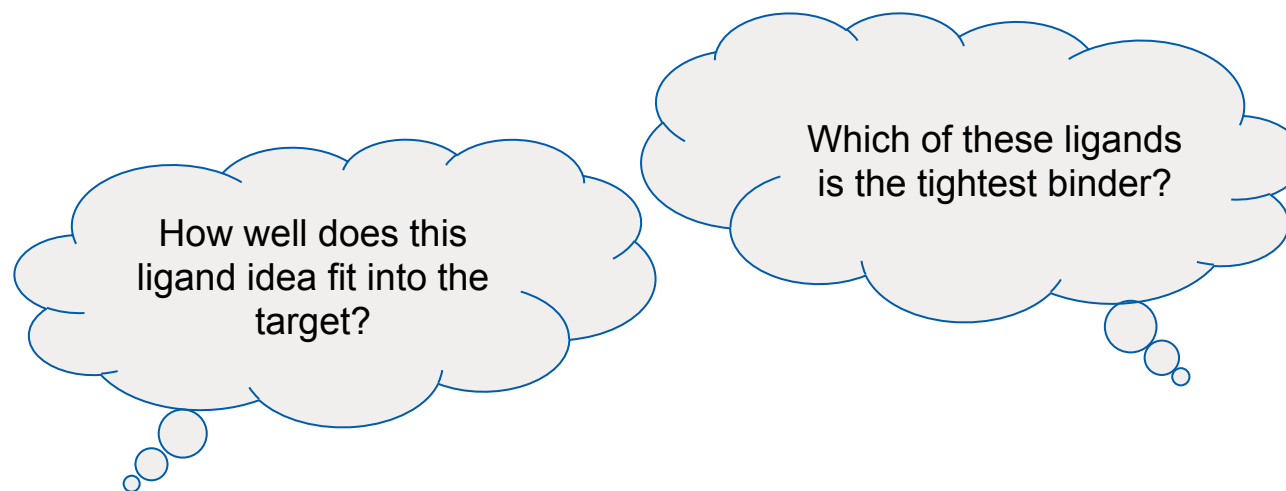
Candidate selection



Clinical trials



This afternoon's questions:



These questions are complex, and cannot be answered by individual tools
⇒ combine tools in concerted, **validated** workflows to get a rigorous answer!

What do we mean by docking?

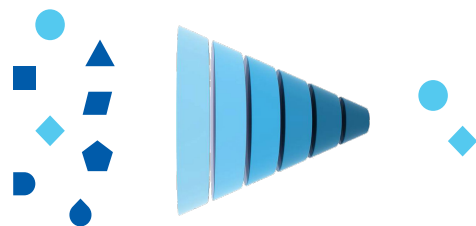


What do we hope to achieve?

- generate a realistic pose of the bound ligand
- distinguish between binders and non-binders
- get a (semi)quantitative measure of how strongly the ligand binds → **scoring**

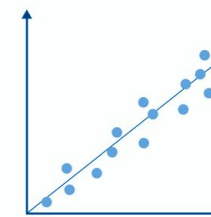
What's the point of scoring?

Hit
identification



- A useful scoring function...
 - provides enrichment
 - does well comparing diverse cpds
 - is very efficient to calculate

Lead
optimisation



- A useful scoring function...
 - is a proxy for the binding affinity
 - does well comparing similar cpds
 - prioritizes accuracy over speed

How to Approach Molecular Docking

Many docking algorithms and scoring functions:

- placement: systematic, MD-based, shape-based, genetic algorithms
- scoring: force field, empirical, knowledge-based, machine learning

Challenges:

- computational cost of treating the receptor flexibly is immense
→ most docking tools use rigid-receptor docking
- tricky to find both efficient to calculate and binding-affinity-like scoring functions
→ focus on distinguishing binders from non-binders



Friesner, R. A. et al, J. Med. Chem., 2004, 47, 1739-1749.

Halgren, T. A. et al, J. Med. Chem., 2004, 47, 1750-1759.

Friesner, R. A. et al, J. Med. Chem., 2006, 49, 6177-6196.

Repasky, M. P. et al, J. Comput. Aided Mol. Des., 2012, 26, 787-799.

Rigid-Receptor Docking using Glide

Prepare Protein & Ligands

Setup Docking

Validate Model

Dock & Score

Analyze Results

- Get to know your system

- find the binding site → SiteMap, MxMD, ...
- pay attention to protonation/tautomer states

- Use a ligand-bound structure

- lacking an experimental structure, use IFD-MD

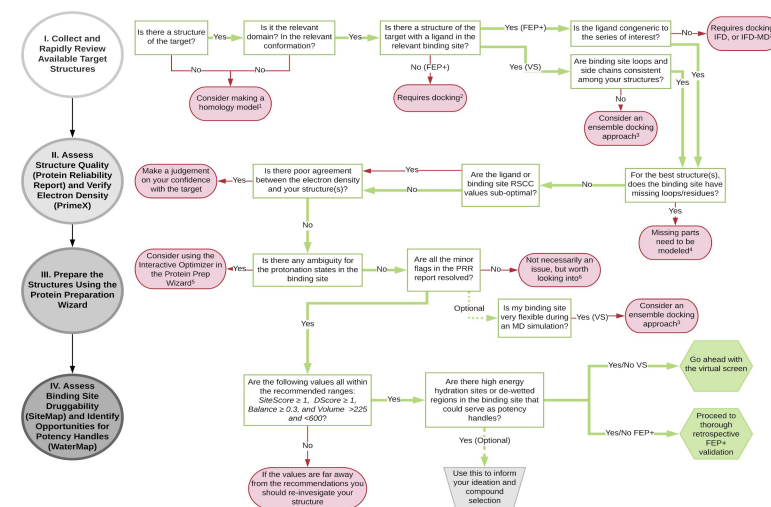
- Pay attention to flexibility of binding site

- compare to homologs, across ligands, run MD

- Decide which waters to keep (after PPrep)

- structural waters: check literature+WaterMap

⇒ if in doubt, use ensemble of structures



Function-related checks

- What's the subcellular location of the protein?
- Is the protein a monomer or a multimer? If a multimer, is it a homomer or a heteromer?
- Is the protein known for multiple conformational states?
- What about atypical chemical forms?
- Maybe there are some PTMs?
- Are any metals involved?
- Does the protein bind any other cofactors?

Sequence-related checks

- Is the whole protein there? Any missing (sub)domains?
- Are you working with the correct sequence?
- Are there any "extras", e.g. signalling peptides or expression tags?
- Are there any homologues?

X-ray related checks

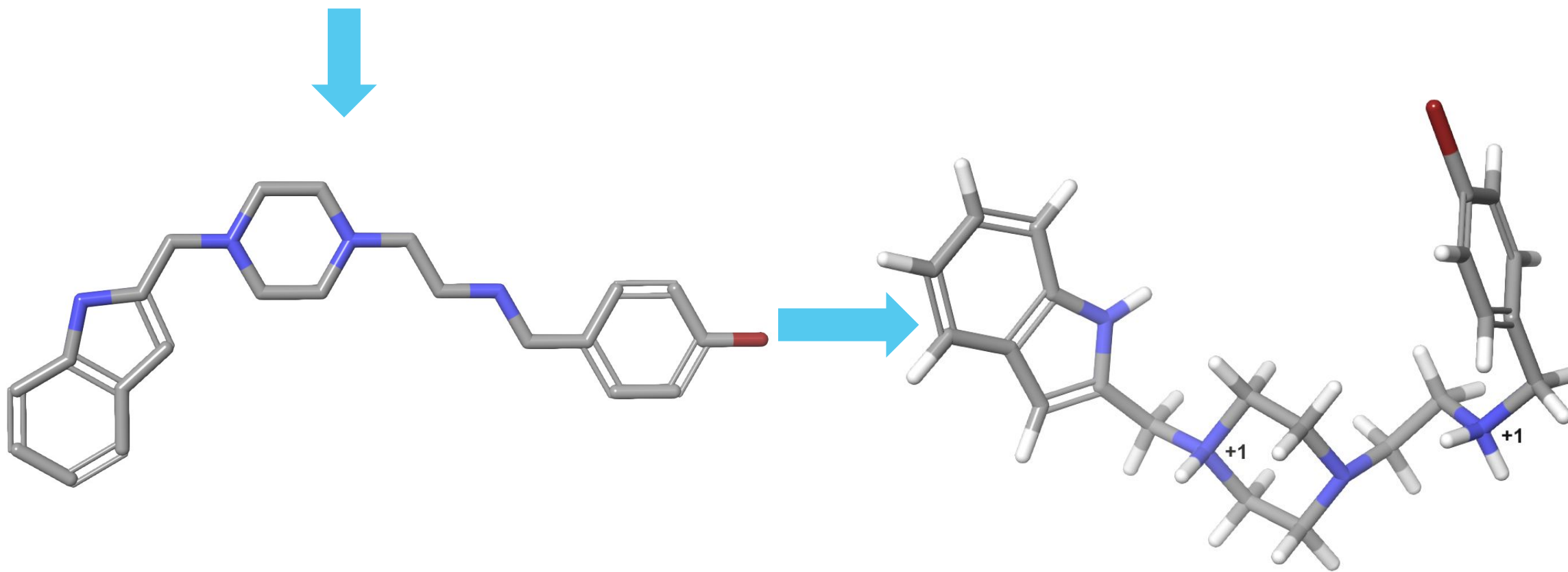
- Is the resolution high enough?
- Are the R and R_{free} factors low?
- What are the B-factors like?
- What about the RSCC values?
- Are there any geometric outliers or clashes?
- What were the experimental conditions like?
- Are there any parts of the structure that don't fit the electron density well?
- Any alternate conformations of protein residues or ligands?
- Were some parts of the protein modelled in (O-occupancy atoms)?
- What about the missing atoms/residues?
- Could the crystal contacts have caused some artifacts?

Preparation-related checks

- Are the bond orders assigned to HET groups correct?
- Are the protonation/tautomer states of HET groups reasonable?
- Any titratable residues of interest?
- Does the hydrogen bond network (incl waters) make sense?
- Have residues/loops been rebuilt correctly?
- Have non-standard residues or PTMs been treated correctly?
- Is the resulting structure stable?

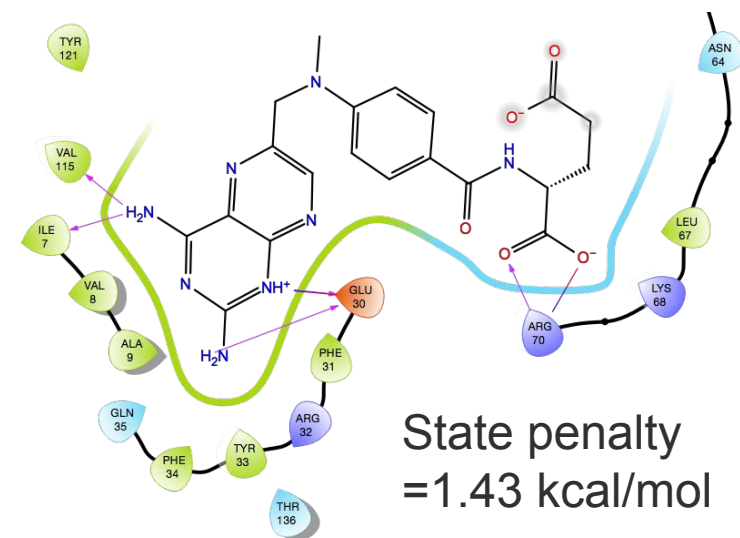
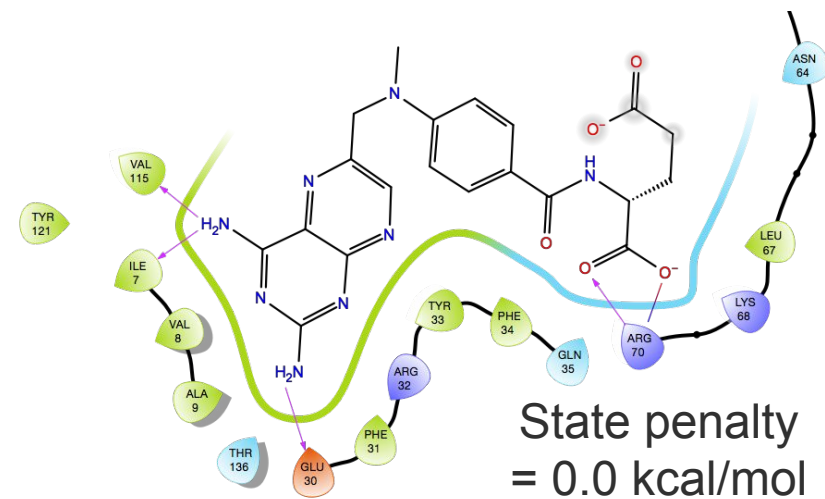
Ligand Preparation

Brc1ccc(CNCCN2CCN(Cc3cc4ccccc4[nH]3)CC2)cc1



Recommendations for Ligand Preparation

- Glide will only dock ligand states that are provided and only scans torsions
- Use LigPrep to generate low energy ionization/tautomeric states for ligands
- Typical expansion of compounds by ionization/tautomeric/stereo expansion is 2.5x
- Increase or decrease pH value and +/- range depending on target physiological location and project goals



Setting up Ligand Preparation



find LigPrep in the tasks menu

- Open a new Maestro session
- File → Open Project...
Find BACE_docking_start.prj.zip in the provided files

Row	In	Title
		proteinprep_4dix_chainA-out (4)
1	<input type="radio"/>	4DJX - prepared
		4DJX - prepared_split_by_structure (3)
2	<input type="radio"/>	4DJX - prepared_ligand
3	<input type="radio"/>	4DJX - prepared_waters
4	<input type="radio"/>	4DJX - prepared_protein
		actives (15)
1	<input type="radio"/>	decoys (100)
		ligprep_BACE1_validation-out (237)

Select both known actives and decoys

LigPrep

Use structures from: Project Table (115 selected entries)

Filter criteria file: Create... Browse...

Maximum ligand size: 500 atoms

Force field: OPLS4 Use customized version

Ionization:

Do not change

Neutralize

Generate possible states at target pH: 7.4 +/- 2.0

Using: Ionizer Epik Add metal binding states

Include original state

Desalt Generate tautomers

Stereoisomers

Computation:

Retain specified chiralities (vary other chiral centers)

Determine chiralities from 3D structure

Generate all combinations

Generate at most: 32 per ligand

For SD V2000 input, generate enantiomers if the chiral flag is 0

Output format: Maestro SDF

Job name: ligprep_BACE1_validation_2 Run

Host=localhost:4, Incorporate=Append new entries as a new group

Adjust pH

Name your job and run it

Generating ionization/tautomer states

- Four options currently:
 - simple rule-based → very fast, but struggles with complex chemistry
 - Epik(-classic) → still fast, but should do well for most systems
 - Epik7 → ML-based, in beta in 22-3 release (not in LigPrep GUI yet), better than Epik-classic across the board
 - QM pKa prediction → very costly, does not generate states for you, but gives you information to understand detailed acid-base behavior
- Epik state penalties estimate free energy required to generate ionization state in water with corrections for interaction with metal sites

Rigid-Receptor Docking using Glide

Prepare
Protein & Ligands

Setup Docking

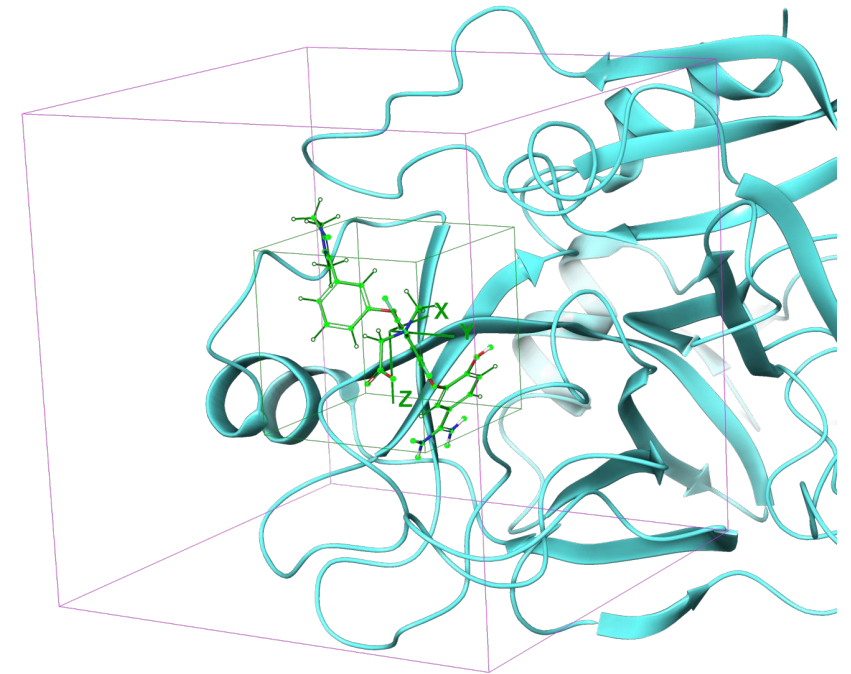
Validate Model

Dock & Score

Analyze
Results

Glide is optimized for speed:

- uses “gridded” representation of the binding site to speed up calculations
 - ligands must fit within outer box, ligand centers must lie within inner box
- only scans rotational DOF of ligands
- employs a funnel to discard bad ligands and poses without calculating costly interactions
- focuses on giving good poses and separating binders from non-binders

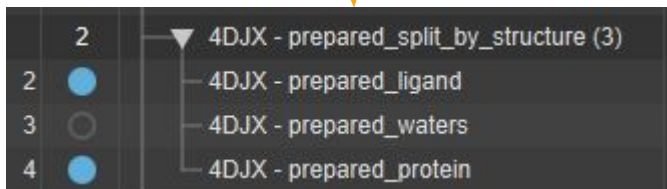


Setting up the Receptor Grid



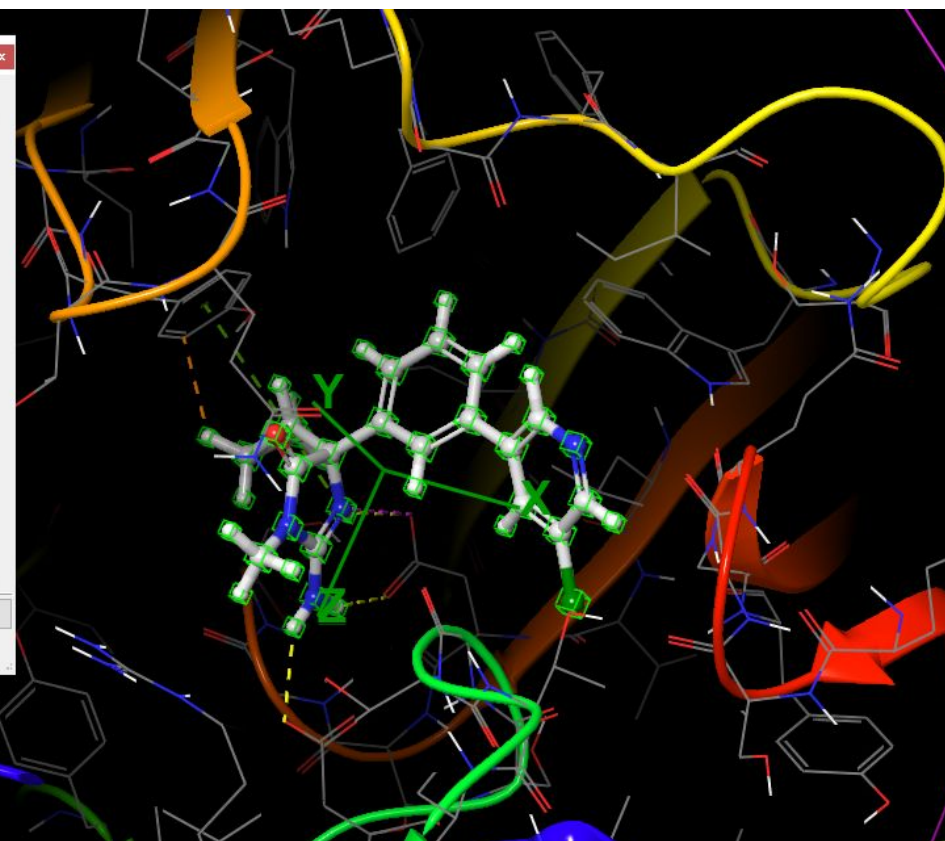
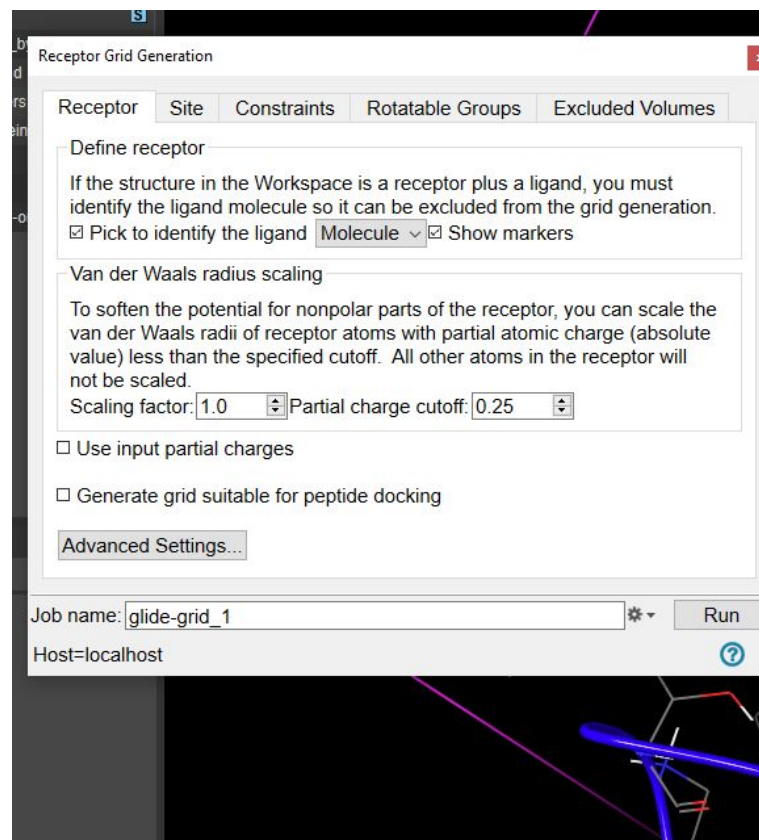
*find Receptor Grid Generation
in the tasks menu*

*Make sure you split your prepared
structure to extract ligand and solvent*



*Include "4DJX - prepared_protein" and
"4DJX - prepared_ligand"*

Click the ligand to define the binding site:



Setting up the Receptor Grid: Constraints

Define any constraints you consider using now, we can choose whether to actually use them later.

The image shows a software interface for setting up a receptor grid. On the left is a dialog box titled "Receptor Grid Generation" with tabs for "Receptor", "Site", "Constraints", "Rotatable Groups", and "Excluded Volumes". The "Constraints" tab is active, showing "2 constraints have been defined (limit is 10 total)". Below this are sub-tabs for "Positional/NOE (0)", "H-bond/Metal (2)", and "Metal Coordination (0)". A text box explains: "Pick receptor atoms that could participate in hydrogen bond or metal-ligand interactions during docking. Ligand interactions with these atoms may be chosen as constraints during docking. Receptor atoms:"

Name	Atom	Use Symmetry
A:ASP:...	538 ...	<input checked="" type="checkbox"/>
A:ASP:...	3568 ...	<input checked="" type="checkbox"/>

Buttons for "Delete" and "Delete All" are present. At the bottom, there are checkboxes for "Pick atoms", "Show markers", and "Label atoms". The "Job name" is "glide-grid_1" and "Host" is "localhost". A "Run" button is at the bottom right.

On the right is a 3D molecular model of a protein-ligand complex. The protein is shown in a stick representation with a green grid overlaid. Two specific oxygen atoms are highlighted with red spheres and labeled "A:ASP:93:OD2(hbond)" and "A:ASP:289:OD1(hbond)". Orange arrows point from these labels to the corresponding atoms in the 3D model.

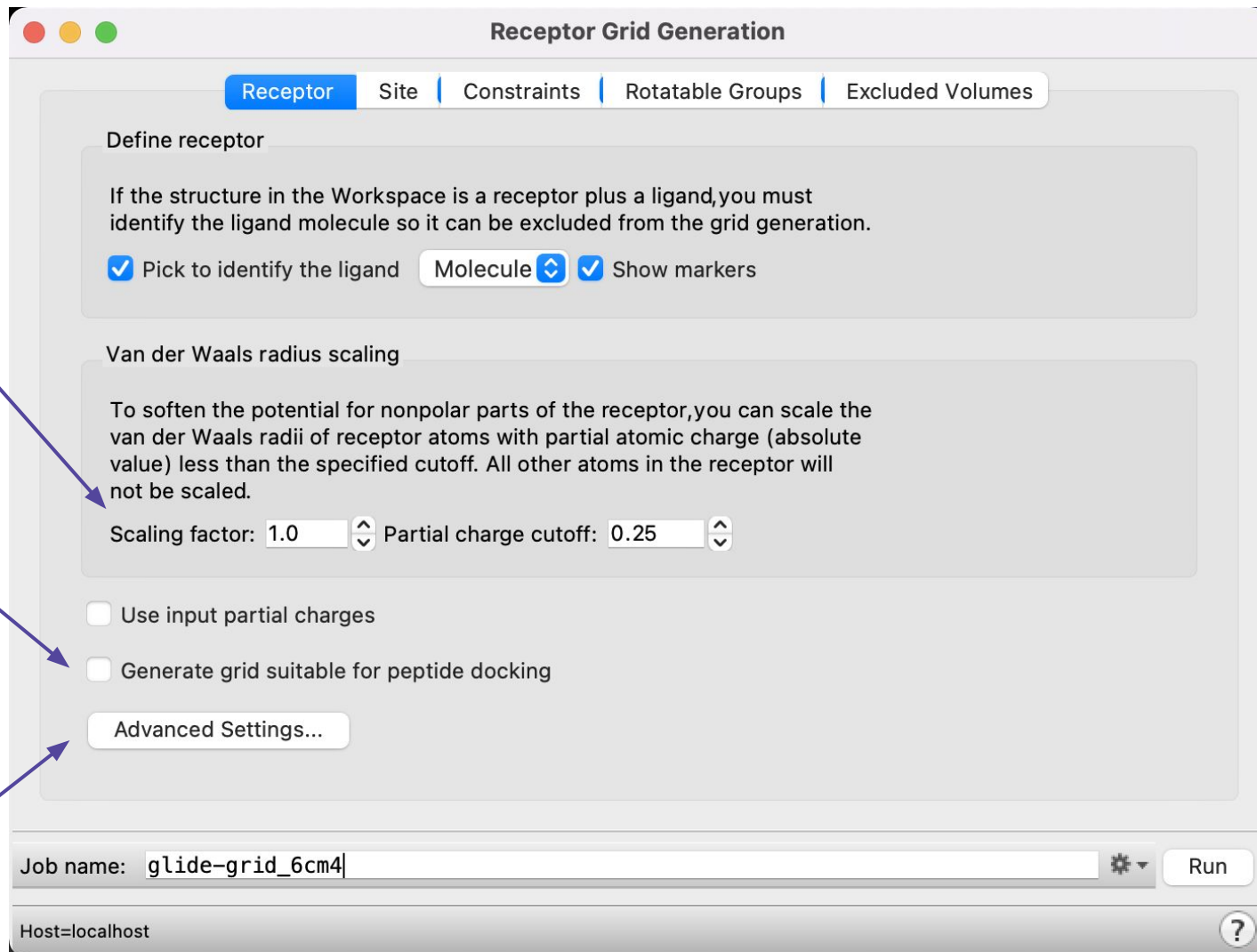
Find and click the Asp oxygens in the workspace

M Grid generation

Scaling of van der Waals radii of nonpolar atoms decreases penalties for close contacts and can be used to model a slight "give" in the receptor and the ligand.

Peptides are more flexible than small molecule ligands – Glide can dock short peptides, but for anything longer than ~15 residues, use dedicated peptide docking tools.

Aromatic H-bonds and halogen bonds are not scored the same as regular H-bonds by default. If they are essential in your system, you may want to change that here.

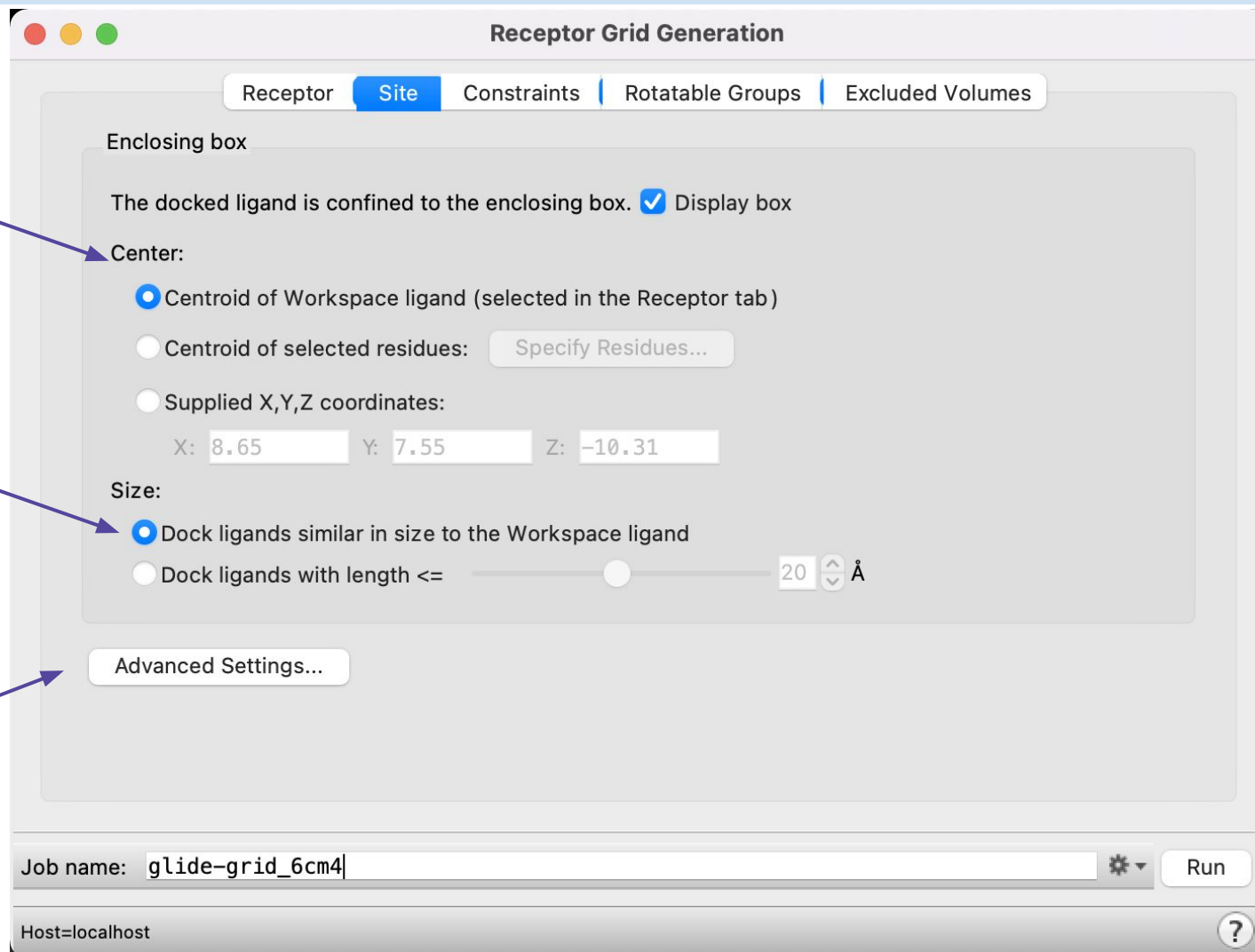


M Grid generation

May be useful if your reference ligand sits off-center in a larger pocket.

Specify ligand size to be docked (size of outer grid box). Increase if docked ligands are larger than the reference used to define the grid, but keep as small as possible.

In the advanced settings the inner grid box can be specified (where the ligand centroid will be placed during docking). Increase if ligands might occupy different parts of the binding pocket.



M Grid generation – Constraints

- Constraints are used to bias Glide if the docked poses do not match experimentally validated poses.
- You should define any constraints you consider using here, you can choose whether to actually use them later.
- Validate your model by docking known actives both with and without constraints.

Receptor Grid Generation

Receptor | Site | **Constraints** | Rotatable Groups | Excluded Volumes

1 constraints have been defined (limit is 10 total)

Positional/NOE (0) | **H-bond/Metal (1)** | Metal Coordination (0)

Pick receptor atoms that could participate in hydrogen bond or metal-ligand interactions during docking. Ligand interactions with these atoms may be chosen as constraints during docking.

Receptor atoms:

Name	Atom	Use Symmetry
A: ASP: 114: OD2 (hbond)	1293 A: 114 (ASP) OD2	<input checked="" type="checkbox"/>

Pick atoms Show markers Label atoms

Delete
Delete All

Job name: glide-grid_6cm4

Host=localhost

Rigid-Receptor Docking using Glide

Prepare
Protein & Ligands

Setup Docking

Validate Model

Dock & Score

Analyze
Results

Retrospective analysis is essential for model validation:

- evaluate how well methods work in general, whether they work on your specific target, whether they are configured correctly
 - use the most similar retrospective setting
 - usually done on a set of known active and inactive compounds (or decoys)
 - in HTVS, evaluation is done using metrics like enrichment or correlation
 - re-docking co-crystal ligands, known actives and inactives is good practice

⇒ The more data you have for your target, the more rigorously you can validate!

Rigid-Receptor Docking using Glide

Prepare
Protein & Ligands

Setup Docking

Validate Model

Dock & Score

Analyze
Results

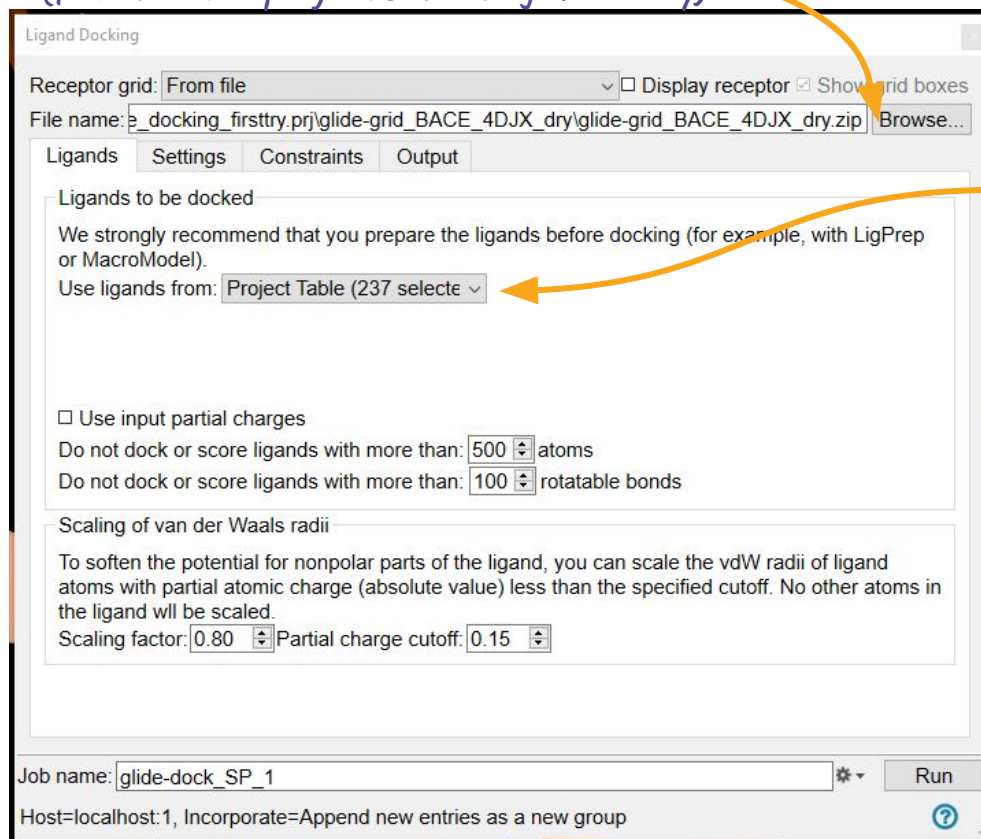
- Details on how Glide finds docked poses can be found in the [user manual](#).
 - There are three main scores from a Glide run:
 - GlideScore: Base score of a docked pose
 - docking score: GlideScore (+ Epik state penalty + strain penalty)
 - used to rank diverse ligands
 - emodel score: Reweighed GlideScore + interaction energy + ligand strain
 - used to rank poses of the same ligand
- ⇒ Remember: none of these scores used for rank-ordering of similar ligands

Docking our Set of Ligands



find Ligand Docking
in the tasks menu

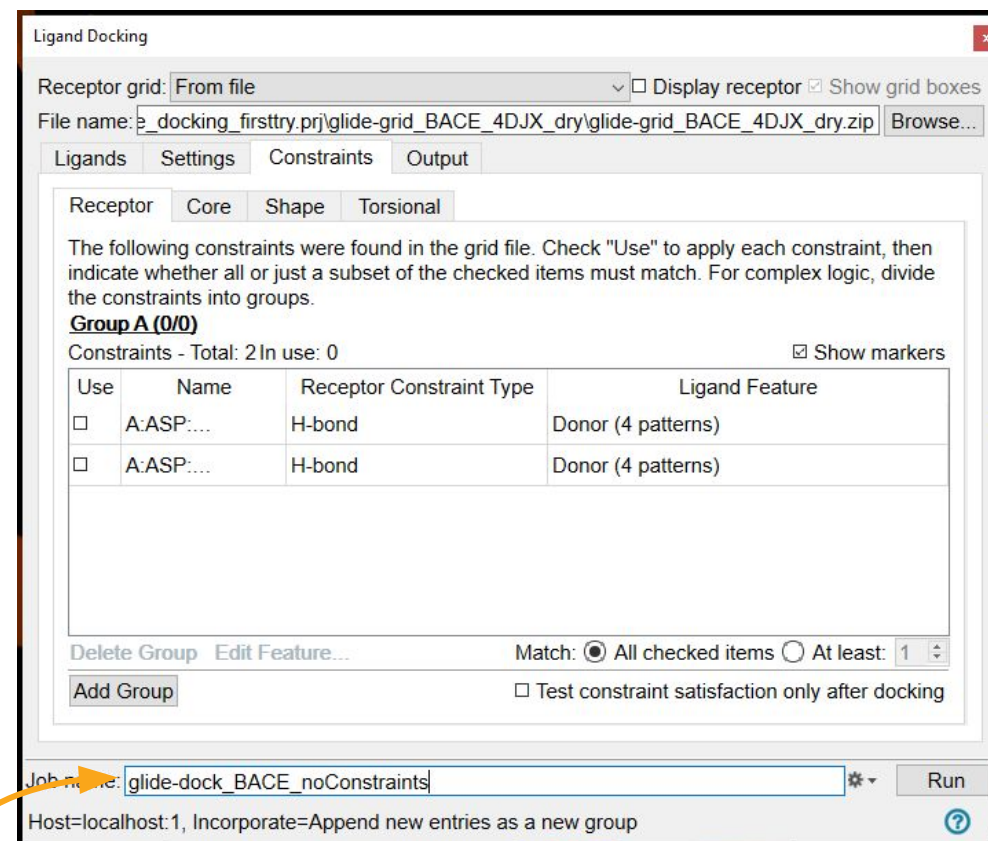
Navigate to your glide-grid_BACE_4DJX_dry.zip
(found in the project's working directory)



select ligprep_BACE
group in the entry list

we'll run docking twice:

1. no constraints on
2. both constrains on



give your two jobs distinct names, e.g.
"glide-dock_BACE_noConstraints" and
"glide-dock_BACE_hbond"

M Docking Setup Settings – Glide Modes & Sampling

- HTVS mode is for scanning through extremely large datasets.
- Standard-precision (SP) docking is appropriate for screening ligands of unknown quality in large numbers (general-purpose mode).
- Extra-precision (XP) docking and scoring is a more powerful and discriminating procedure, which takes longer to run than SP with additional scoring function terms. XP is designed to be used on ligand poses that have been determined to be high-scoring using SP docking.
- Peptide mode does not exhaustively sample ligand conformations and should be used with a grid generated for peptide docking

Useful to put additional emphasis on conjugated pi groups if docked poses do not match experimental results

Increasing the sampling can help if poses for known binders are not found:

Use enhanced sampling
Enhance conformational sampling by: 2 times

These settings control how many poses pass through the initial Glide screens

Keep 5000 poses per ligand for the initial phase of docking

Scoring window for keeping initial poses: 100.0

Keep best 400 poses per ligand for energy minimization

Ligand Docking

Receptor grid: From file Display receptor Show grid boxes

File name: /Users/vass/Documents/maestro/D2/glide-grid_6cm4/glide-grid_6cm4.zip

Ligands **Settings** Constraints Output

Precision: SP (standard precision)

Write XP descriptor information

Ligand sampling: Flexible

Sample nitrogen inversions

Sample ring conformations

Sample macrocycles using Prime. Non-macrocycle ligands will be skipped.

Include input ring conformation

Bias sampling of torsions for:

All predefined functional groups

Amides only: Penalize nonplanar conformation

None

Add Epik state penalties to docking score

Reward intramolecular hydrogen bonds

Enhance planarity of conjugated pi groups

Apply Large excluded volumes penalties

Show excluded volumes

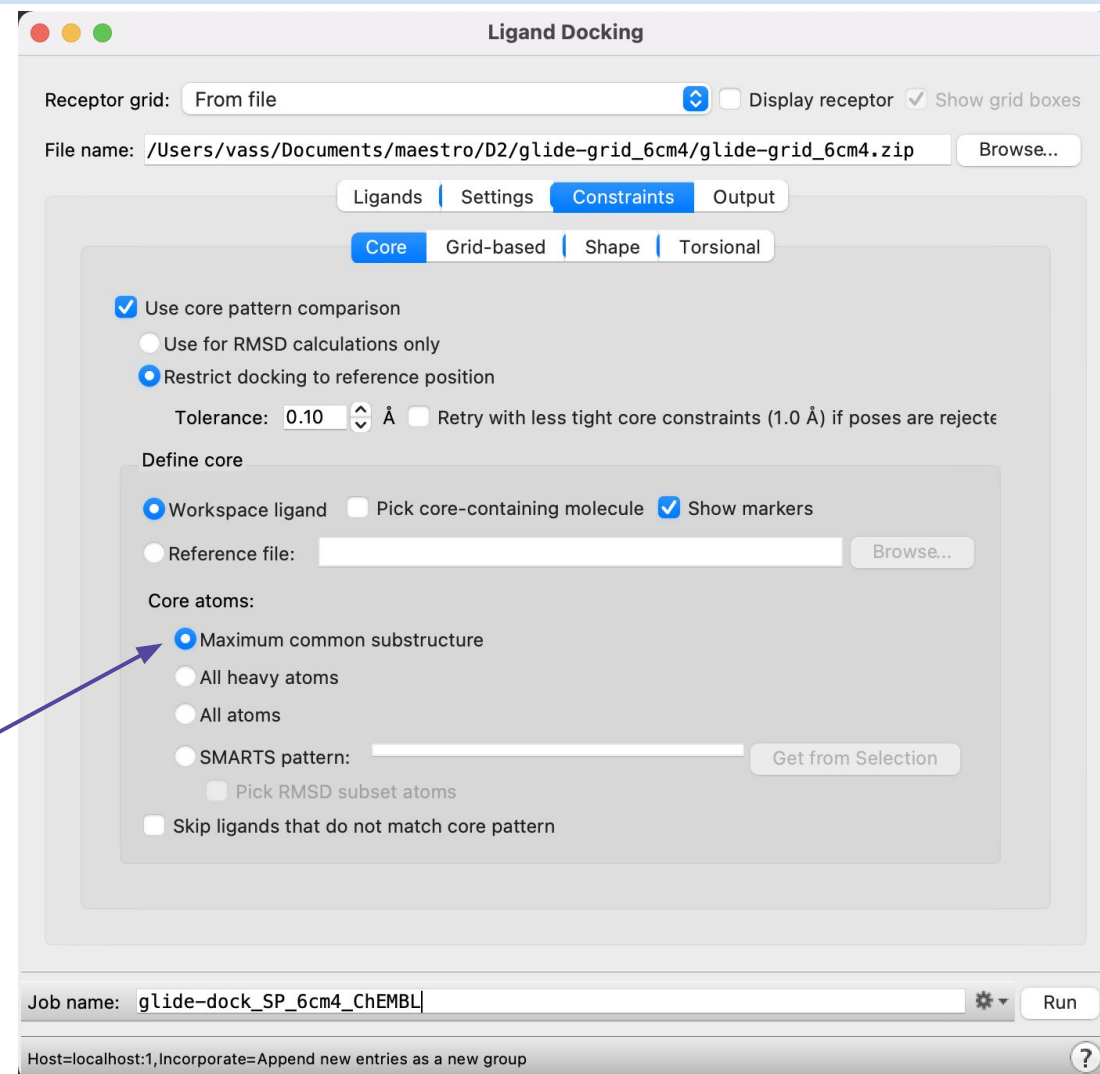
Job name: glide-dock_SP_6cm4_ChEMBL

Host=localhost:1, Incorporate=Append new entries as a new group

M Docking Setup Settings – To Constrain or Not?

- Unbiased docking is usually best to start with to see if the ligands can be docked without incorporating any additional constraints
- Biased docking can be useful when
 - unbiased docking fails but specific interactions are known to be important, or
 - the ligands are highly similar (e.g. for generating poses for FEP calculations)
- Validate your choices by re-docking known actives and inactives

Sidenote: LigandDesigner uses maximum common substructure docking to quickly find binding poses for ideas



M Docking Setup Settings – Reporting Options

*For virtual screening we usually only need the top pose, but for binding mode prediction we might be interested in more poses.
(Note: these should be ranked by emodel score, not GlideScore)*

Number of poses in post-docking minimization should be 3-5 times larger than the number of reported poses

Allows visualizing contributions of each residue to final ligand score

The screenshot shows the 'Ligand Docking' software interface. At the top, there are tabs for 'Ligands', 'Settings', 'Constraints', and 'Output'. The 'Settings' tab is active. Under 'File type', the 'Pose viewer file (includes receptor)' option is selected. Below this, there are several settings: 'Limit the number of poses to report' is set to 0; 'Write out at most' is set to 1 pose per ligand; 'Perform post-docking minimization' is checked; 'Number of poses per ligand to include' is set to 5; 'Threshold for rejecting minimized pose' is set to 0.50 kcal/mol; 'Apply strain correction terms' is unchecked; 'Write per-residue interaction scores' is unchecked, with a sub-option 'For residues within 12.0 Å of grid center' selected; 'Pick residues to include' has a 'Specify Residues...' button; and 'Compute RMSD to input ligand geometries' is unchecked. At the bottom, there is an 'Advanced Settings...' button. The 'Job name' field contains 'glide-dock_SP_6cm4_ChEMBL' and a 'Run' button is visible. The status bar at the bottom shows 'Host=localhost:1, Incorporate=Append new entries as a new group'.

Rigid-Receptor Docking using Glide

Prepare
Protein & Ligands

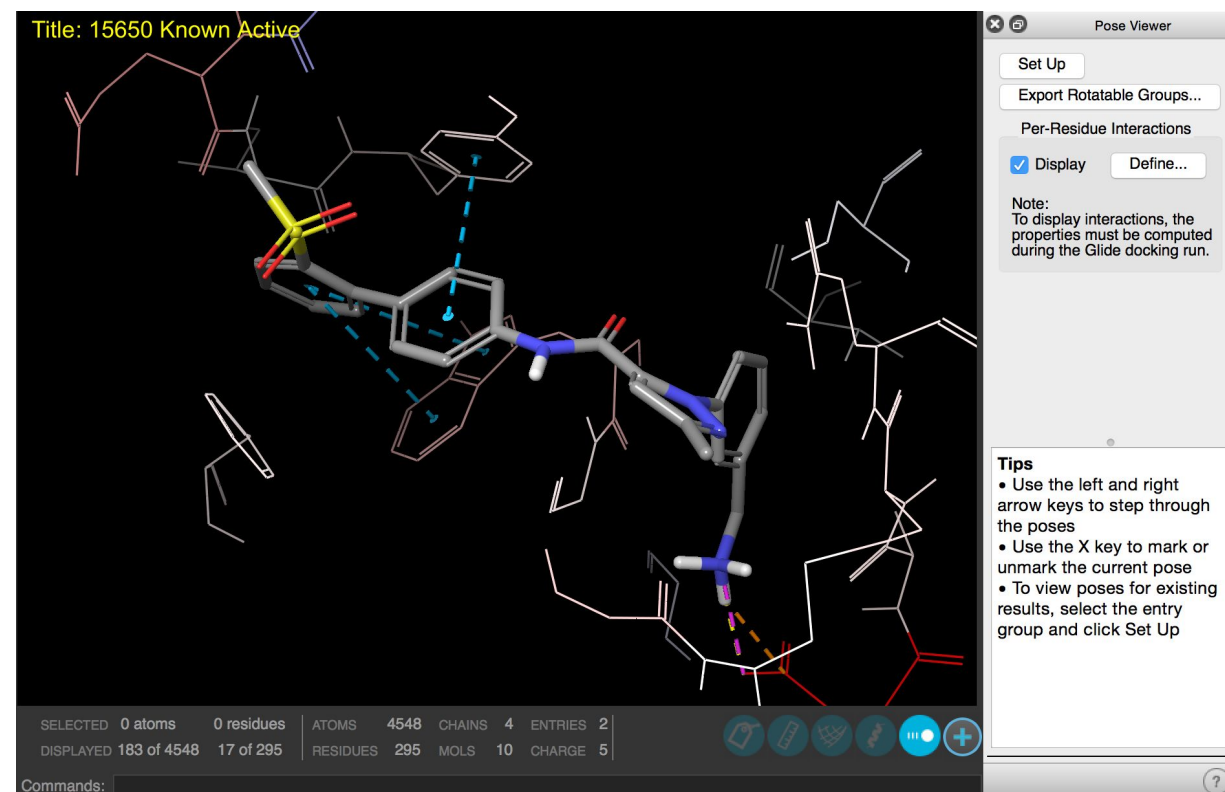
Setup Docking

Validate Model

Dock & Score

Analyze
Results

- Rank distinct compounds by GlideScore and multiple poses of the same compound by emodel score
- Visually inspect poses to recognize scoring function failures
- Some unfavorable torsions or interactions with the protein may be acceptable, as a small conformational shift in the receptor can resolve them

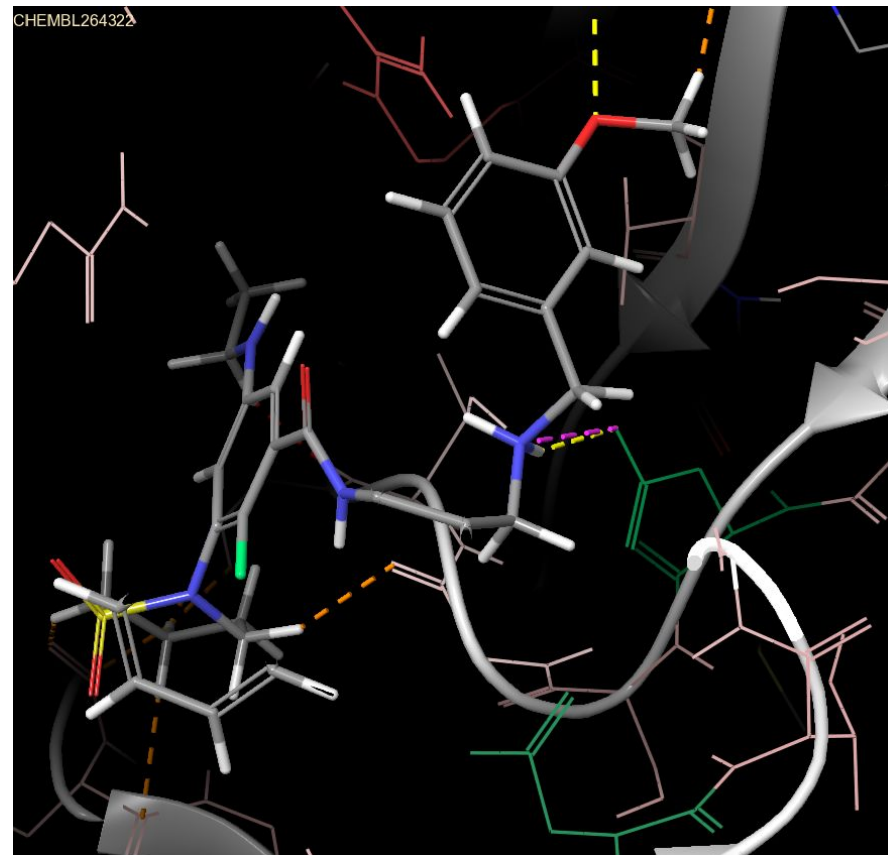


Analyzing Docking Results: Pose inspection

The screenshot shows a table of docking results with columns for rank, ID, and name. A context menu is open over the 'View Poses...' option. The menu items are:

- View Poses...
- Analysis
 - Pose Explorer...
- Next Steps
 - Pose Filter...
 - Enrichment Calculator...
 - Interaction Fingerprints...
 - Volume Clustering...
 - Spectral Clustering...

Visual inspection of poses



The Pose Viewer window shows the following settings:

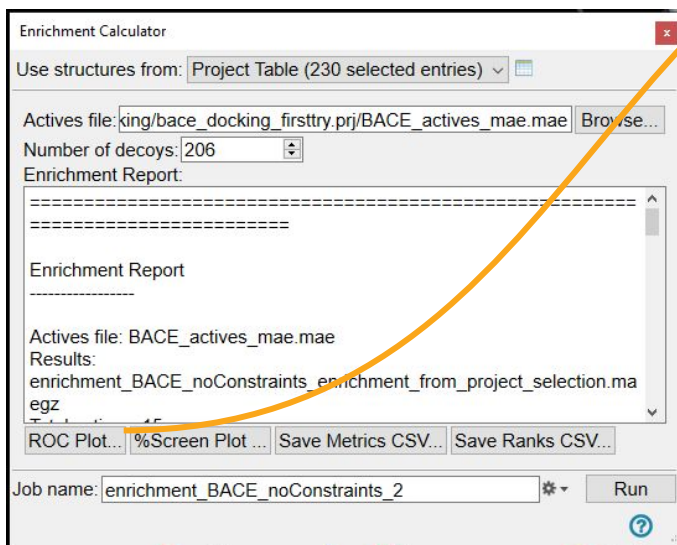
- Set Up Poses
- Export rotatable groups...
- Display per-residue interactions
- Type: Interaction energy
- Colors: [Color bar]
- Range: Custom
- Min: -50.00
- Max: 25.00
- Apply to: All Residues

Tips

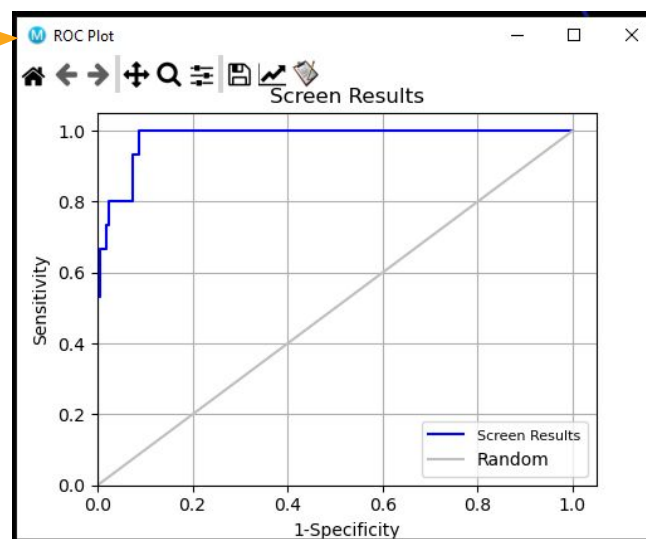
- Use the left and right arrow keys to step through the poses
- Use the X key to mark or unmark the current pose
- To view poses for existing results, select the entry group and click "Set Up Poses"

Comparing Docking Models for HTVS: Enrichment

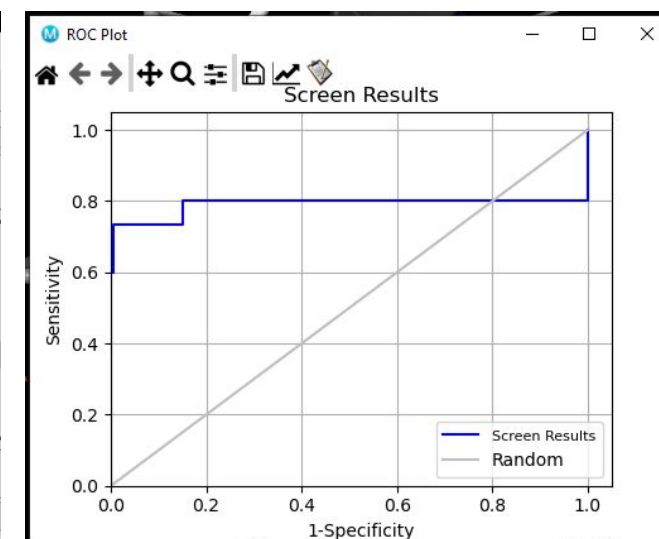
How well does the docking separate binders from non-binders?



without H-bond constraints:

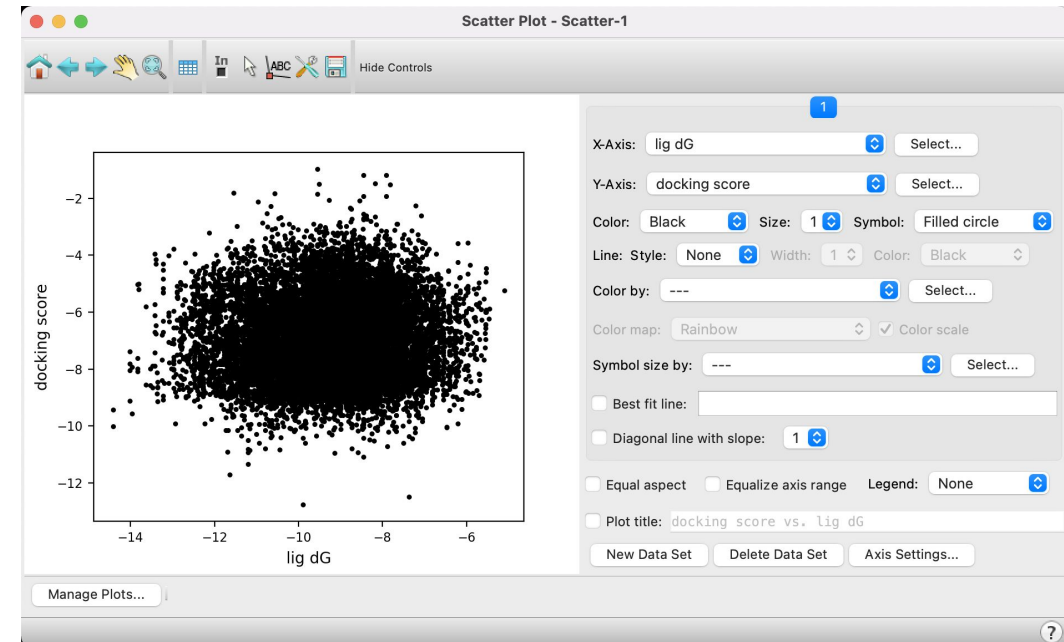


with active H-bond constraints:



Correlation of Docking Results to Binding Affinity

- In many compound sets, there is only a very weak correlation between docking score and experimental binding affinity or none at all.
- Generally docking score can not be used to distinguish between less and more active compounds

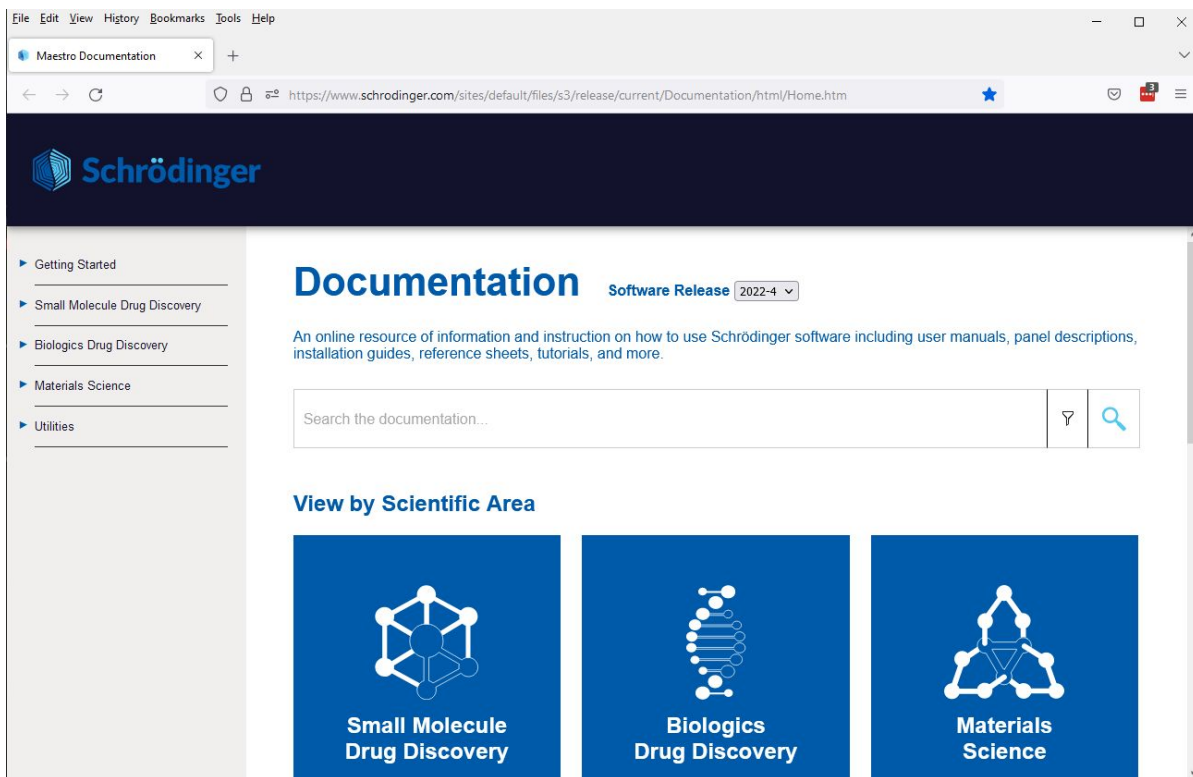


⇒ Reminder: the docking score is parametrized to efficiently distinguish binders from non-binders, not as a proxy for binding affinity

Closing and Q&A




Getting Help



The screenshot shows the Schrödinger Documentation website. The browser address bar indicates the URL: <https://www.schrodinger.com/sites/default/files/s3/release/current/Documentation/html/Home.htm>. The page has a dark blue header with the Schrödinger logo. A left sidebar contains a navigation menu with the following items: Getting Started, Small Molecule Drug Discovery, Biologics Drug Discovery, Materials Science, and Utilities. The main content area is titled 'Documentation' and includes a 'Software Release' dropdown menu set to '2022-4'. Below this is a search bar with the placeholder text 'Search the documentation...'. At the bottom, there is a section titled 'View by Scientific Area' with three blue buttons: 'Small Molecule Drug Discovery' (with a molecular structure icon), 'Biologics Drug Discovery' (with a DNA helix icon), and 'Materials Science' (with a molecular structure icon).

Documentation:

Click  in any panel, or go to Help > Help...

- 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/>
- Scientific & Technical Support:
help@schrodinger.com



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Thank You!



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