A Beginner's Guide to Molecular Visualization and Computational Chemistry

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LRZ, 2022

Day 1 Agenda

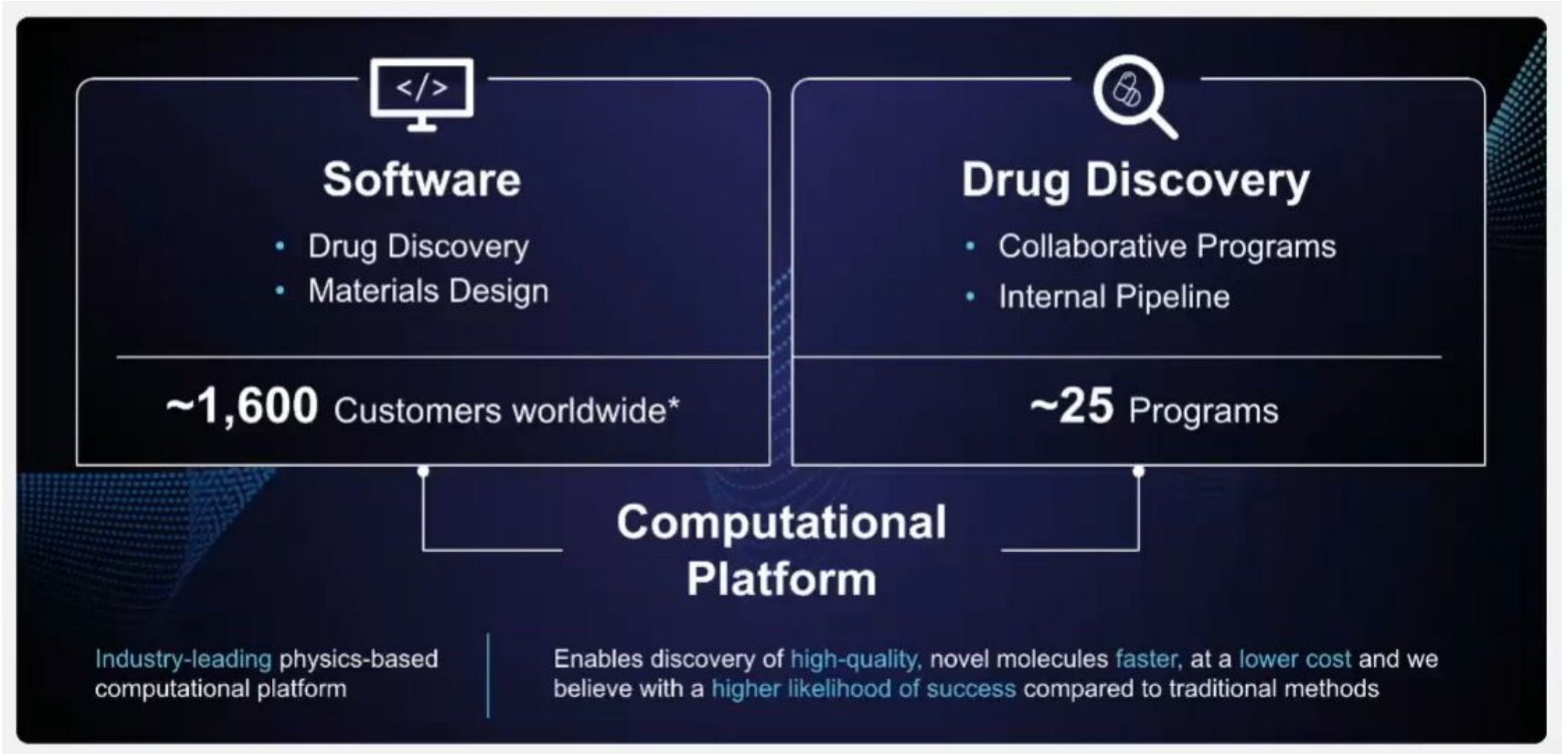
- A brief introduction to Schrödinger's design platform
- First steps in Maestro
- Preparing proteins
- Understanding the binding site
- Lunch (12:00 – 13:00)
- Designing new ligands: quick ideation
- Preparing ligands and docking with Glide
- Q&A and closing (15:00)

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



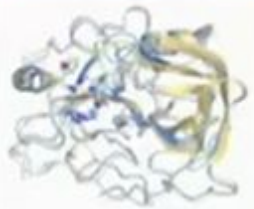
*Active customers as of Dec. 31, 2021. Active customers are defined as the number of customers who had an Annual Contract Value (ACV) of at least $1,000 in a given fiscal year. See "Operating Metrics" for additional information regarding these metrics.

Schrödinger's digital chemistry toolbox

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

Structure refinement & validation

FIND or DESIGN — OPTIMIZE — DEVELOPMENT CANDIDATE



IFD-MD
Prime
GlideEM
Phenix/
OPLS4

Collaborative Enterprise Informatics
LiveDesign

Large scale (>10^9)
Glide (& Active Learning)
Shape, WScore,
AB-FEP+

Large scale (>10^6)
Fragment screening with,
AB-FEP+, WScore, Glide

Binding site analysis
WaterMap, SiteMap,
Desmond

Free energy perturbation (FEP)
Relative Binding FEP+
Protein FEP+

Physics-based MPO modeling (FEP/MD/QM)
Relative Binding FEP+
Protein FEP+
Solubility FEP+
Membrane Permeability
Jaguar

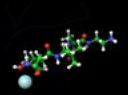
Machine learning
AutoQSAR
Active Learning

Computer-driven compound design
PathFinder, AutoDesigner

Get to know complex workflows at your own pace

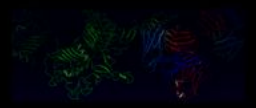
Small Molecule and Biologics Drug Discovery

Introduction to Molecular Modeling in Drug Discovery



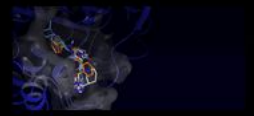
Learn how to apply molecular modeling in small-molecule drug discovery and design.

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

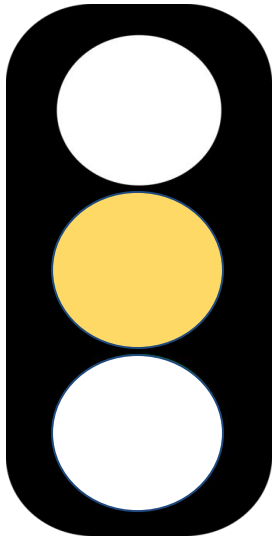
Surface Chemistry Click for syllabus

Consumer Packaged Goods Click for syllabus

Getting Started

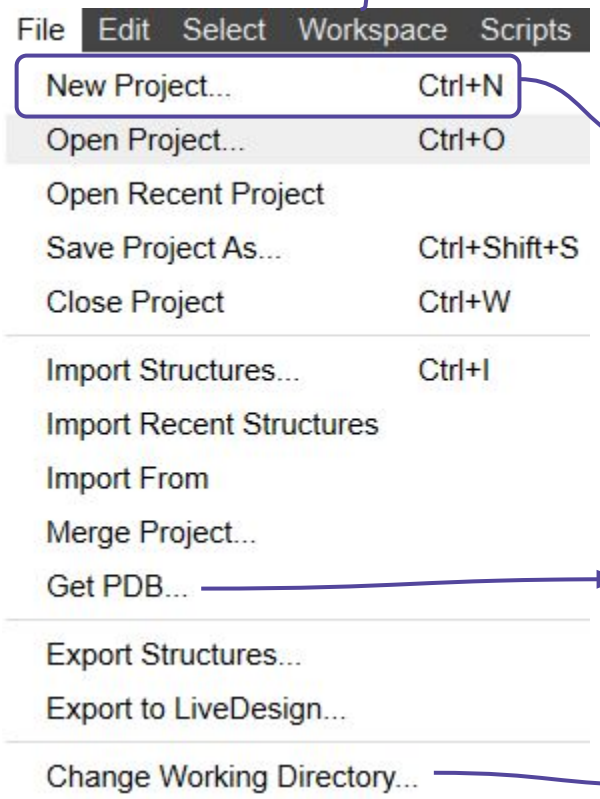
Visualization basics

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

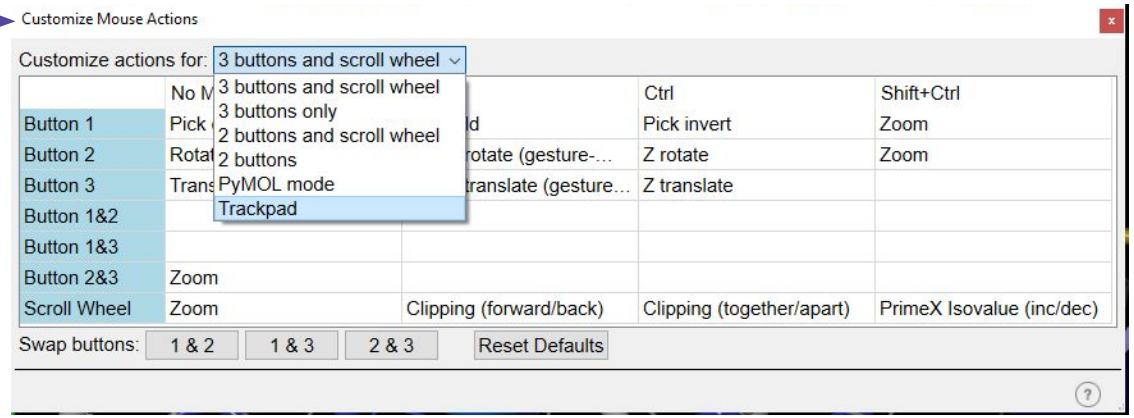


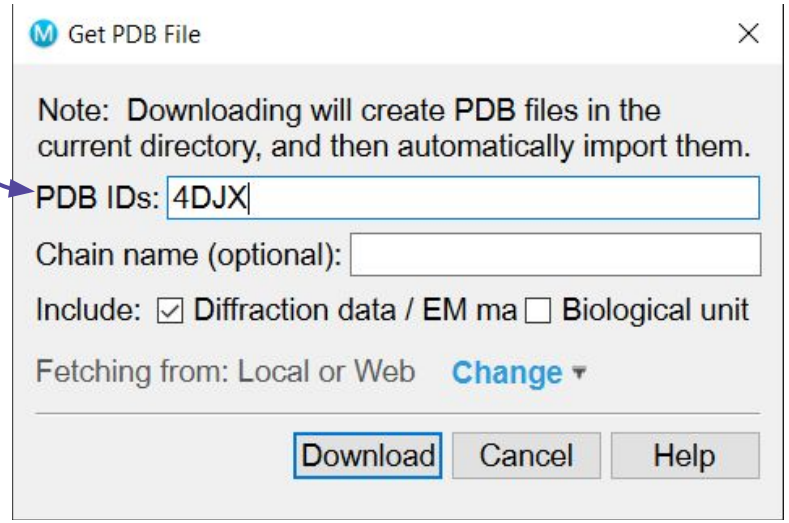
1. Choose where project data should be saved

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

3. Fetch BACE-1 structure from the PDB

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

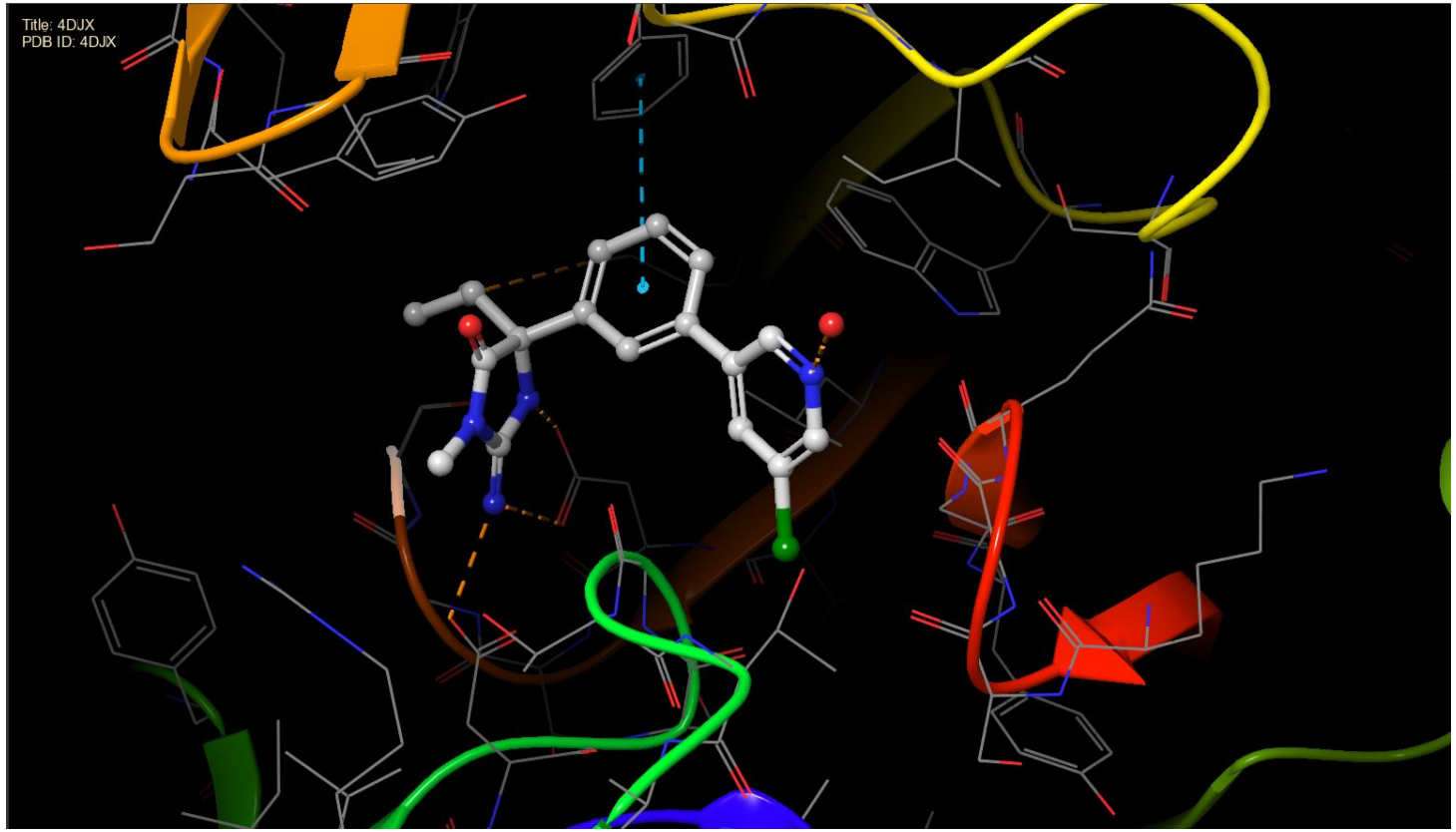




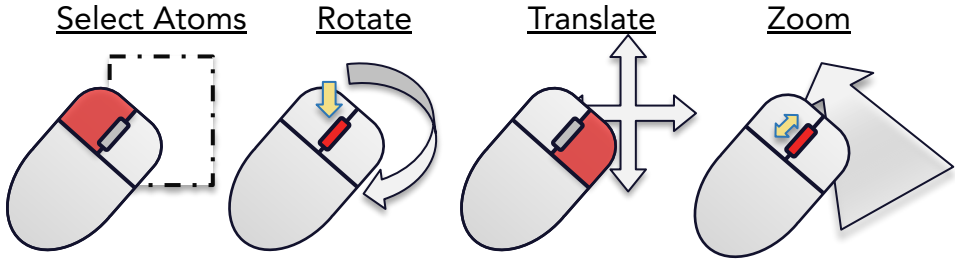
Getting familiar with BACE-1 (PDB id: 4DJX)

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

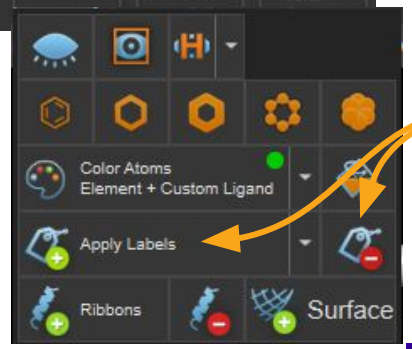
change display of selected entities

quickly switch between selection modes

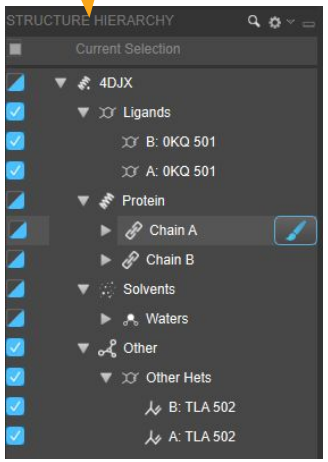
For labels, ribbons, surfaces:

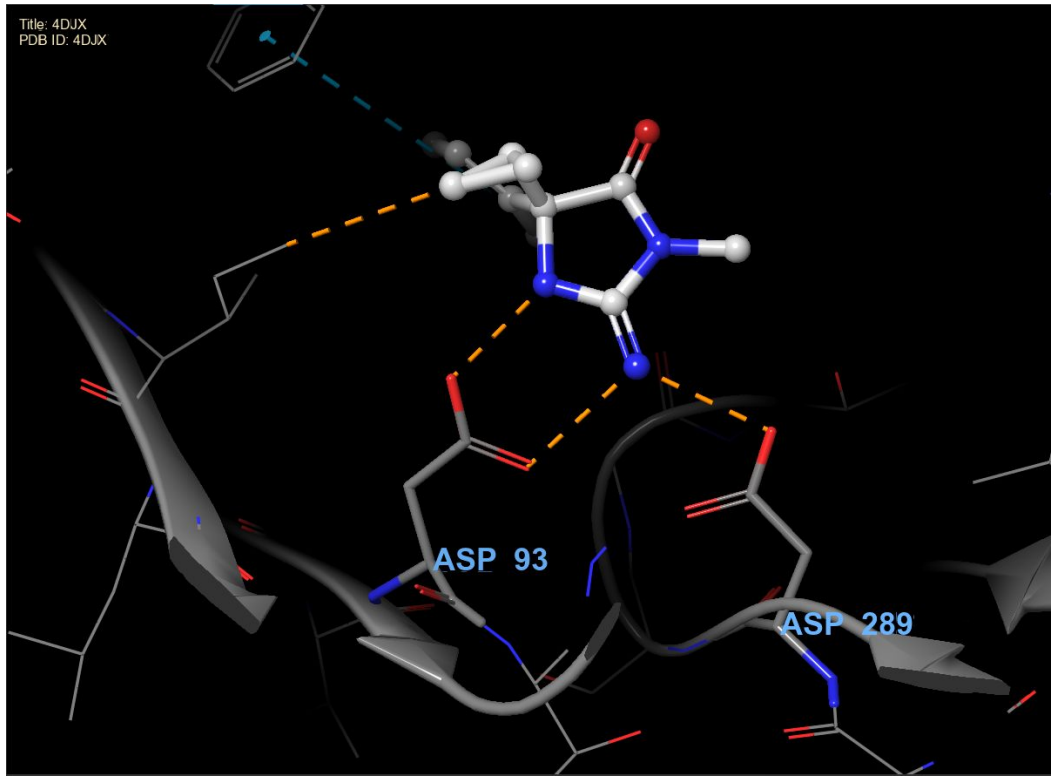
Add/Remove them here

Show/Hide them here:

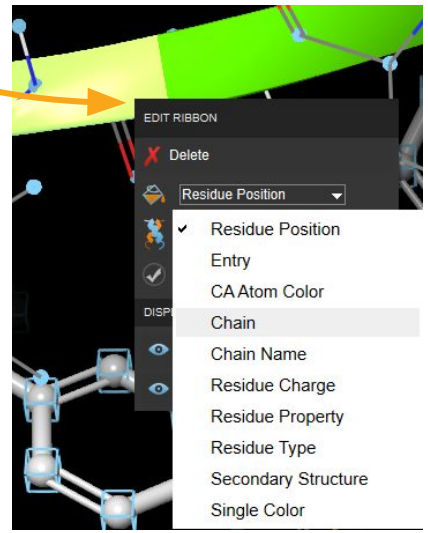


search and navigate semantically





right-click menus recognize context

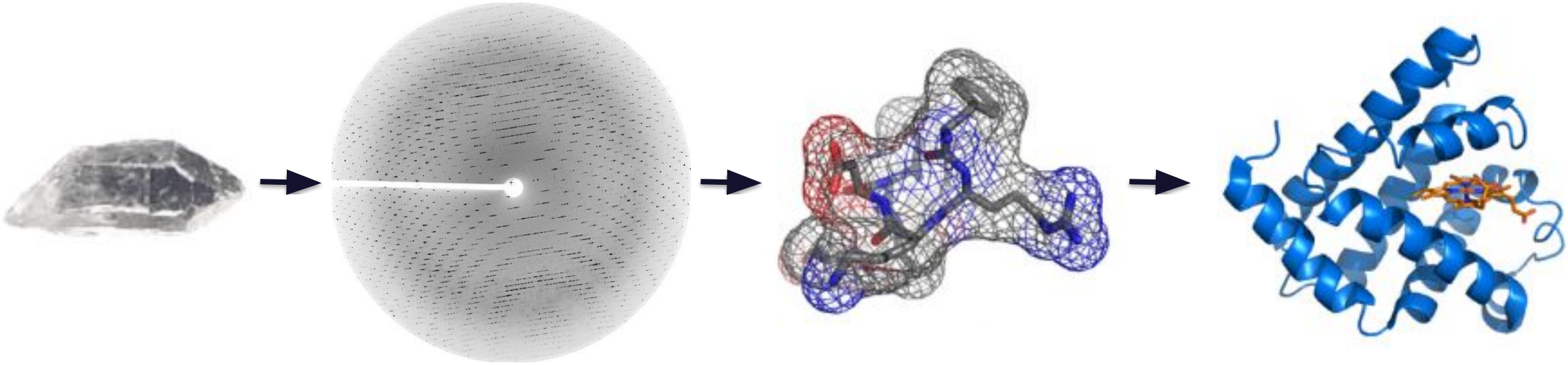


Try to reproduce this view:
color ribbons by CA Atom Color, remove all labels, find and select Asp pair, show as thin tubes, add labels for Asp pair only

Preparing Proteins

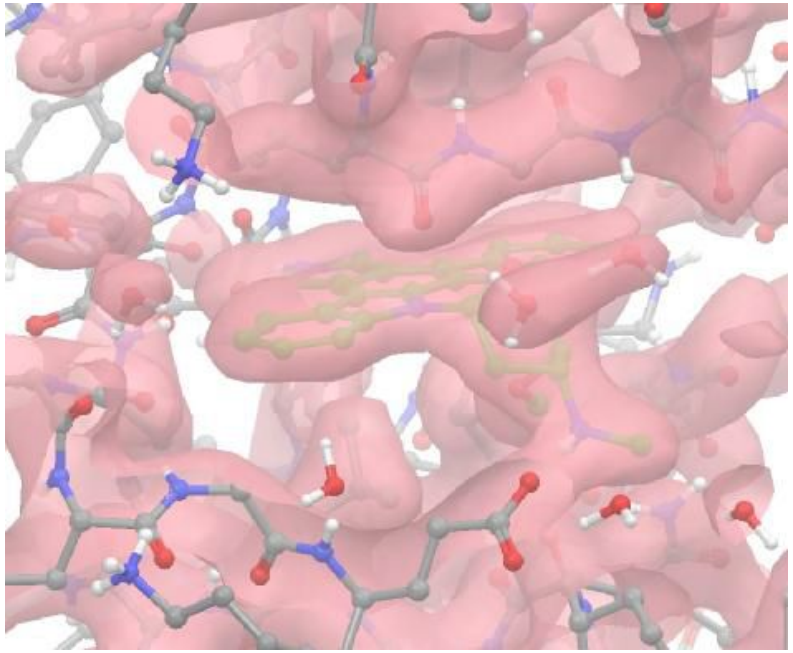
(the basics)

Where are my hydrogen atoms?

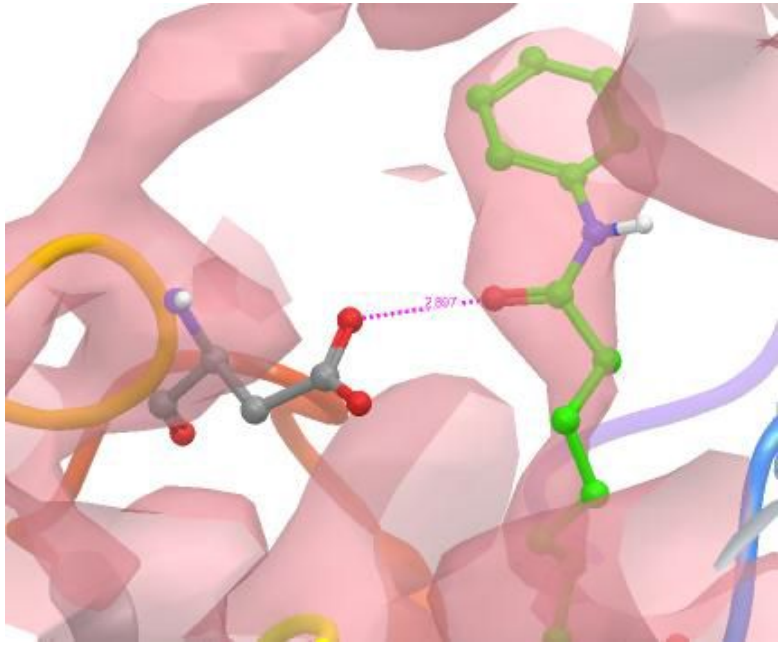


protein crystal | diffraction pattern | electron density map | atomic model

Not all Crystal Structures are Created Equal

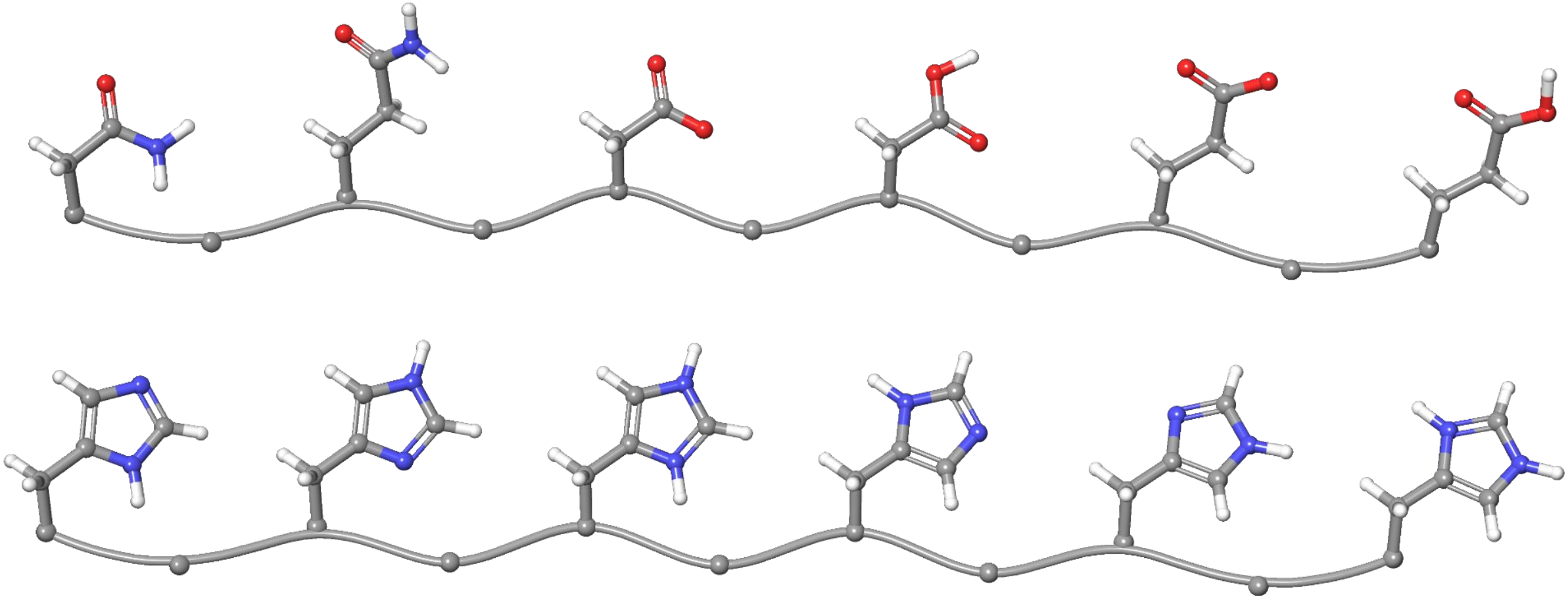


In this case, the ligand density is relatively unambiguous.



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

These all look very similar in X-Ray experiments!

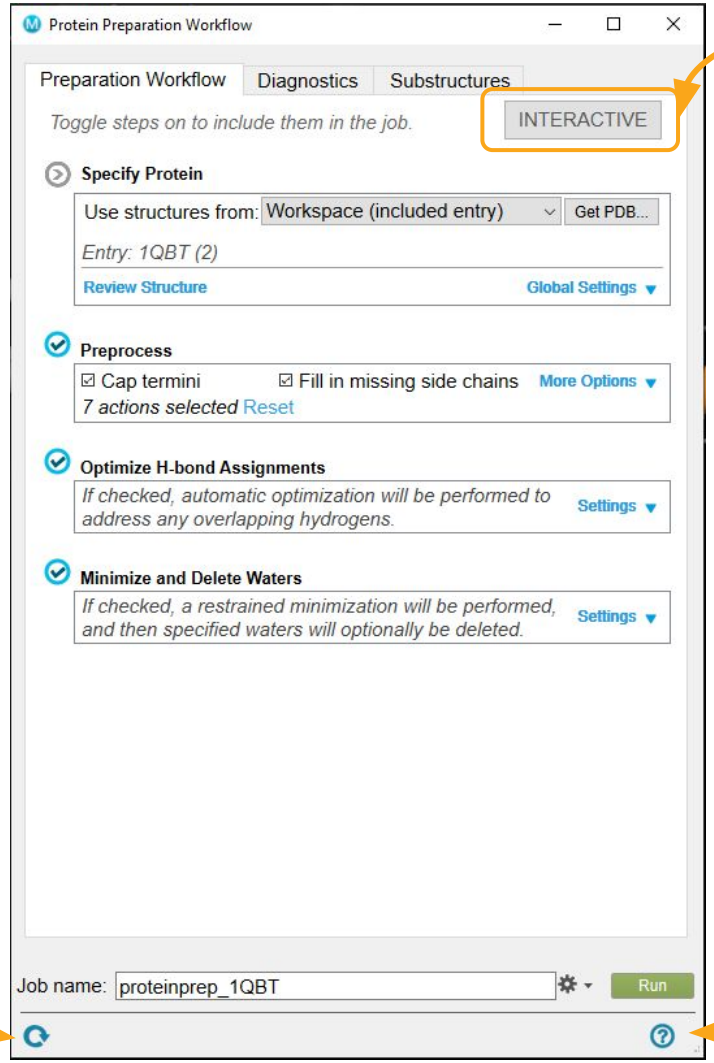


How do I prepare a protein?

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

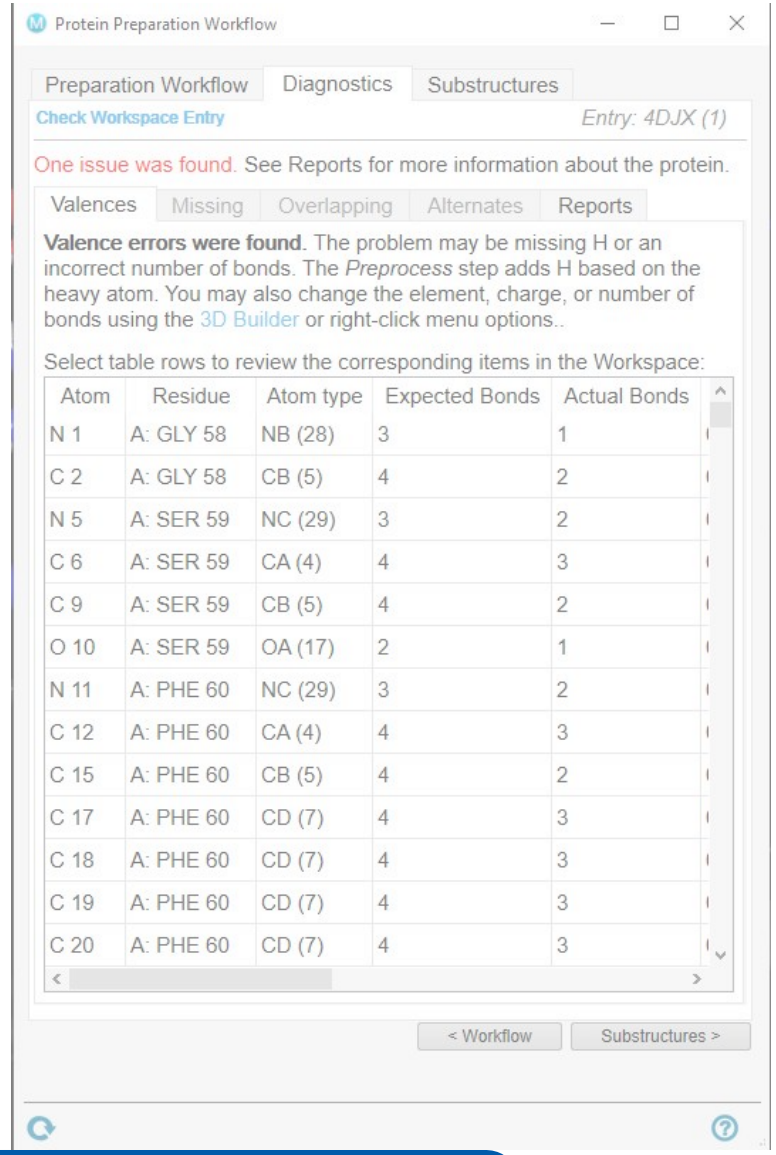


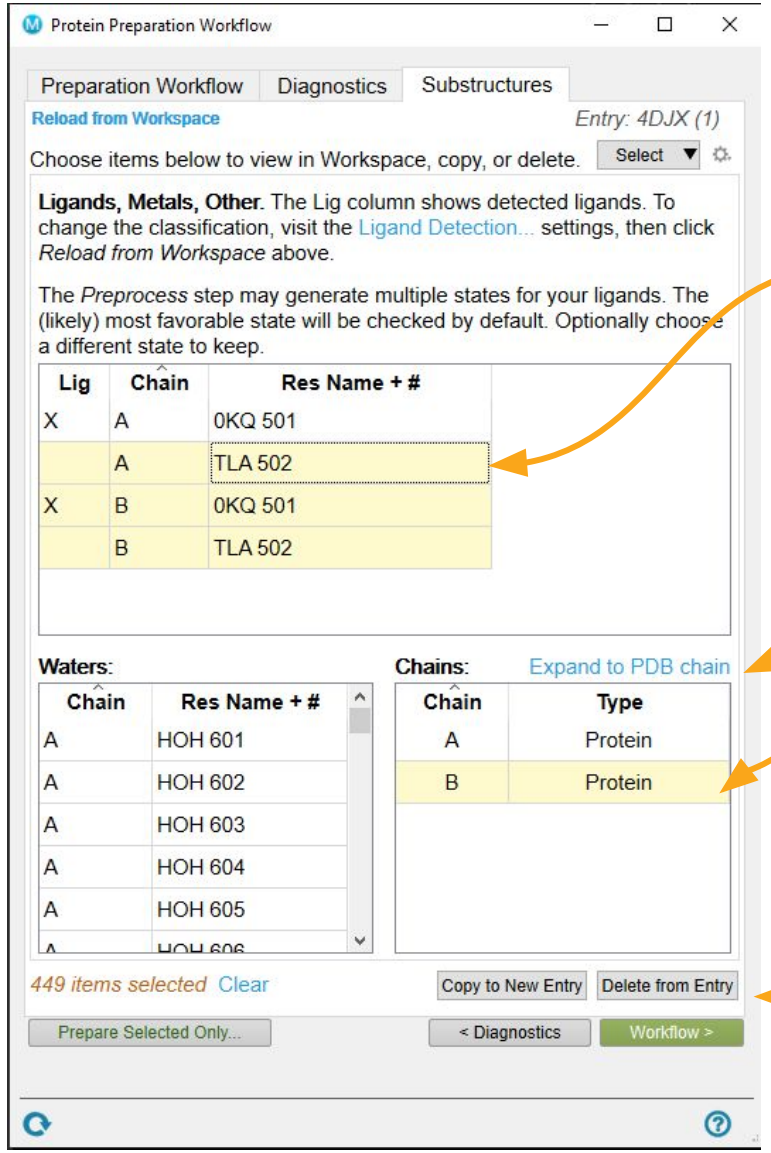
For more control you could switch to interactive mode

reset panel to defaults

Link to documentation

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



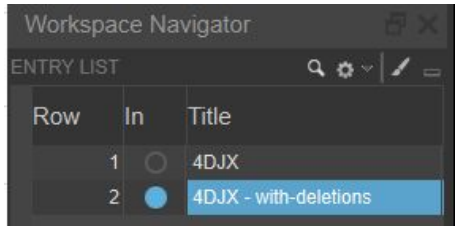


We prepare only chain A and delete TLA:

1. Select TLA from chain A

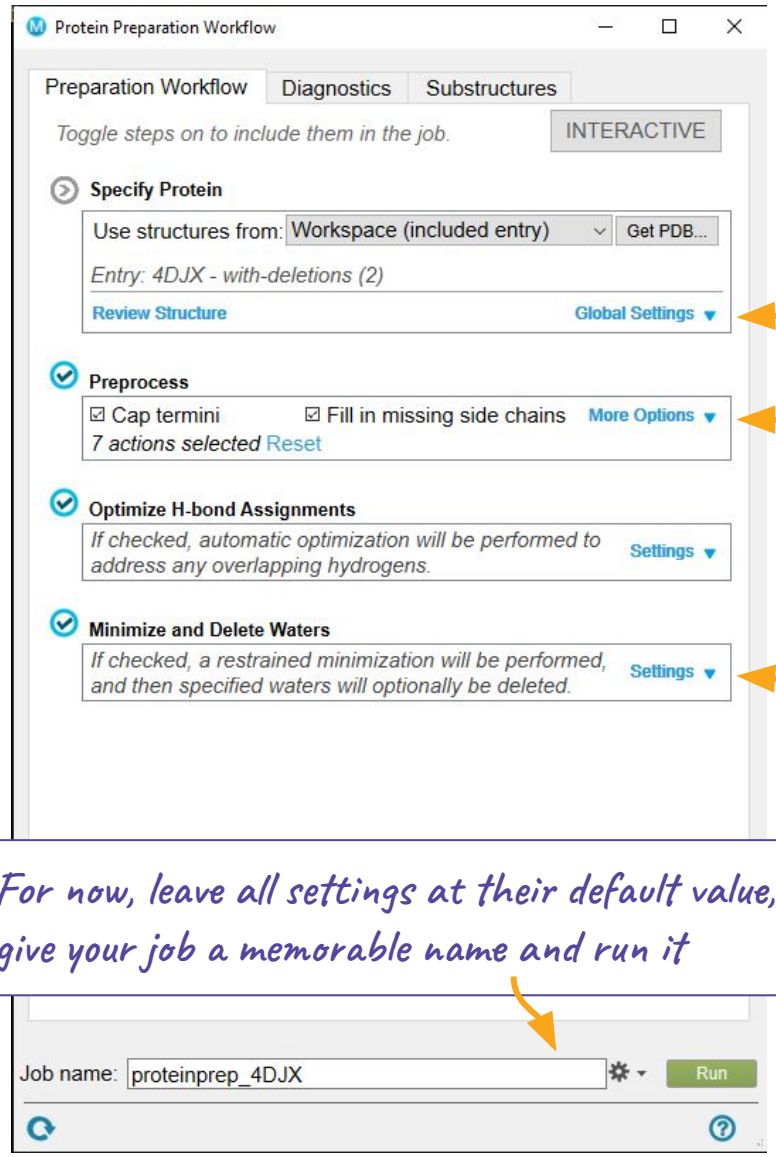
2. Ctrl+Click to also select Chain B
→ Expand selection to PDB Chain

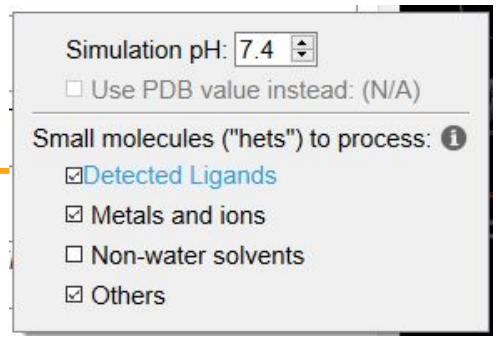
3. Create copy of the entry with deletions applied

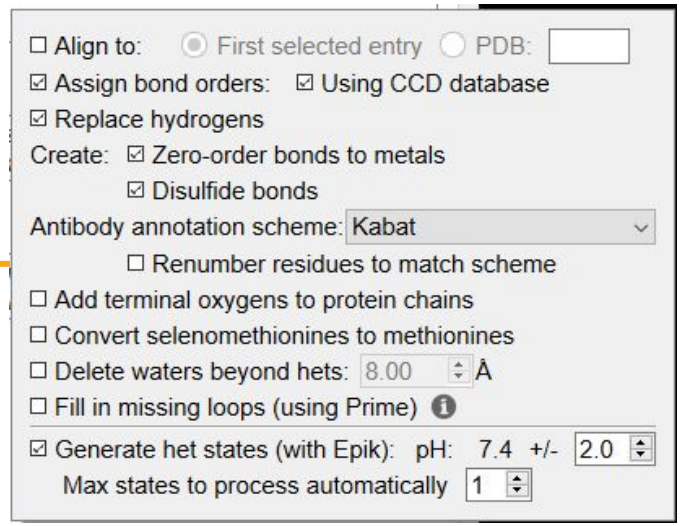


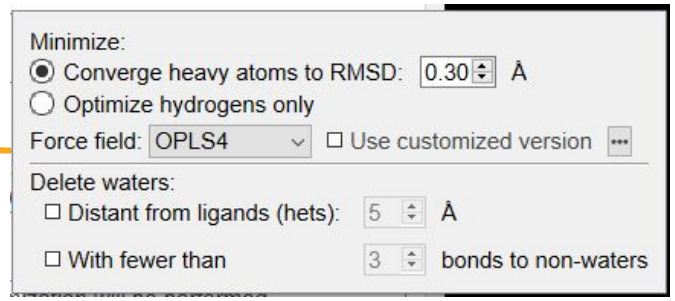
Schrödinger

Preparing our Protein II: Running the Preparation





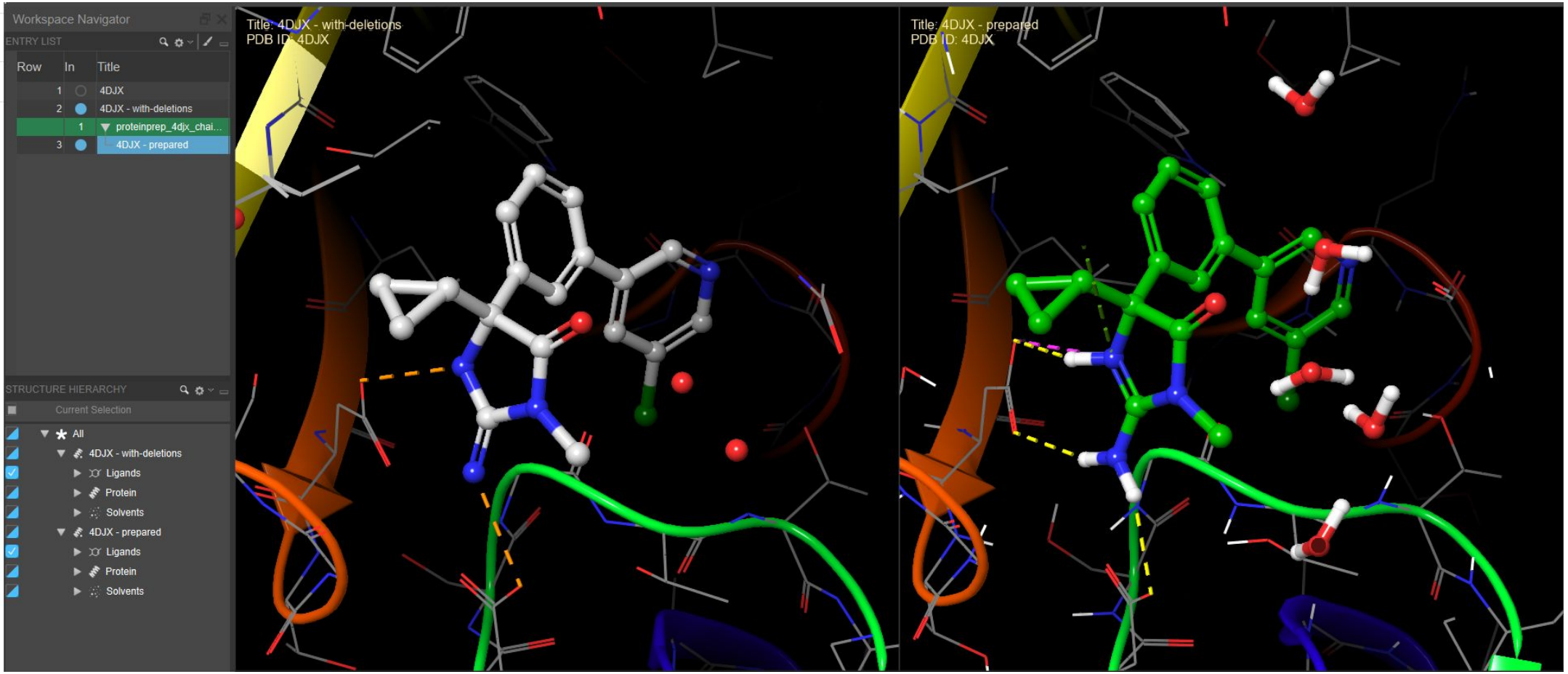




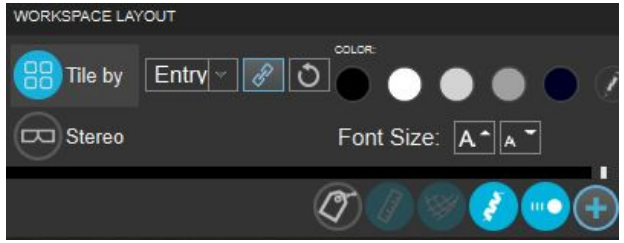
For now, leave all settings at their default value, give your job a memorable name and run it

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

Before and after protein preparation

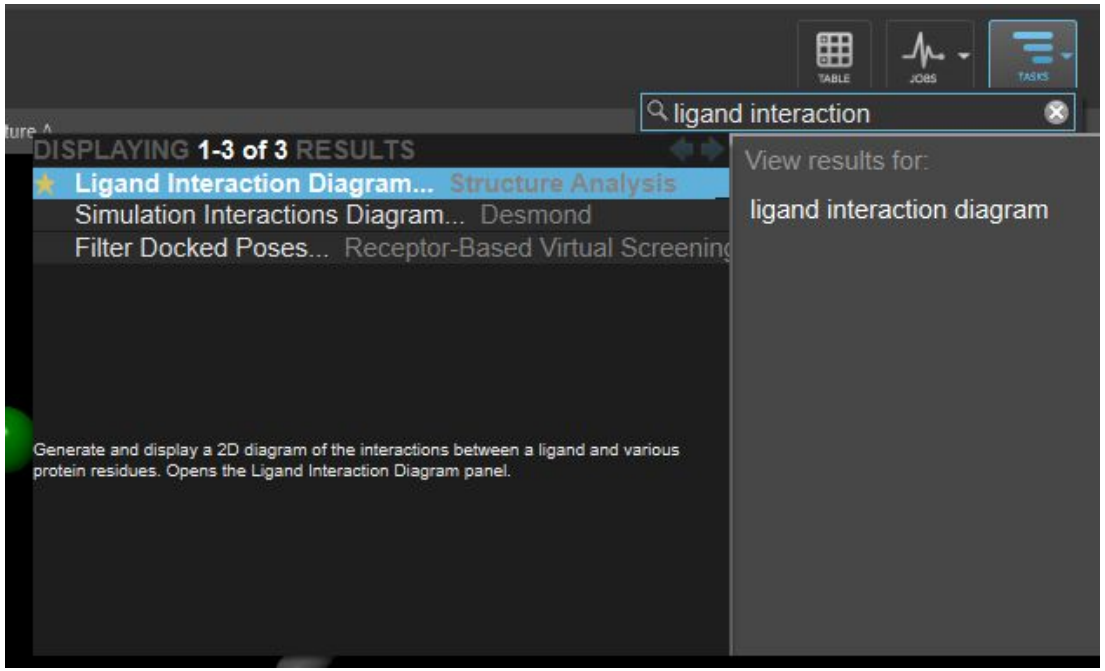


To reproduce: include both 4DJX-with-deletions and 4DJX-prepared, re-apply preset, tile the workspace ("+" workspace widget)

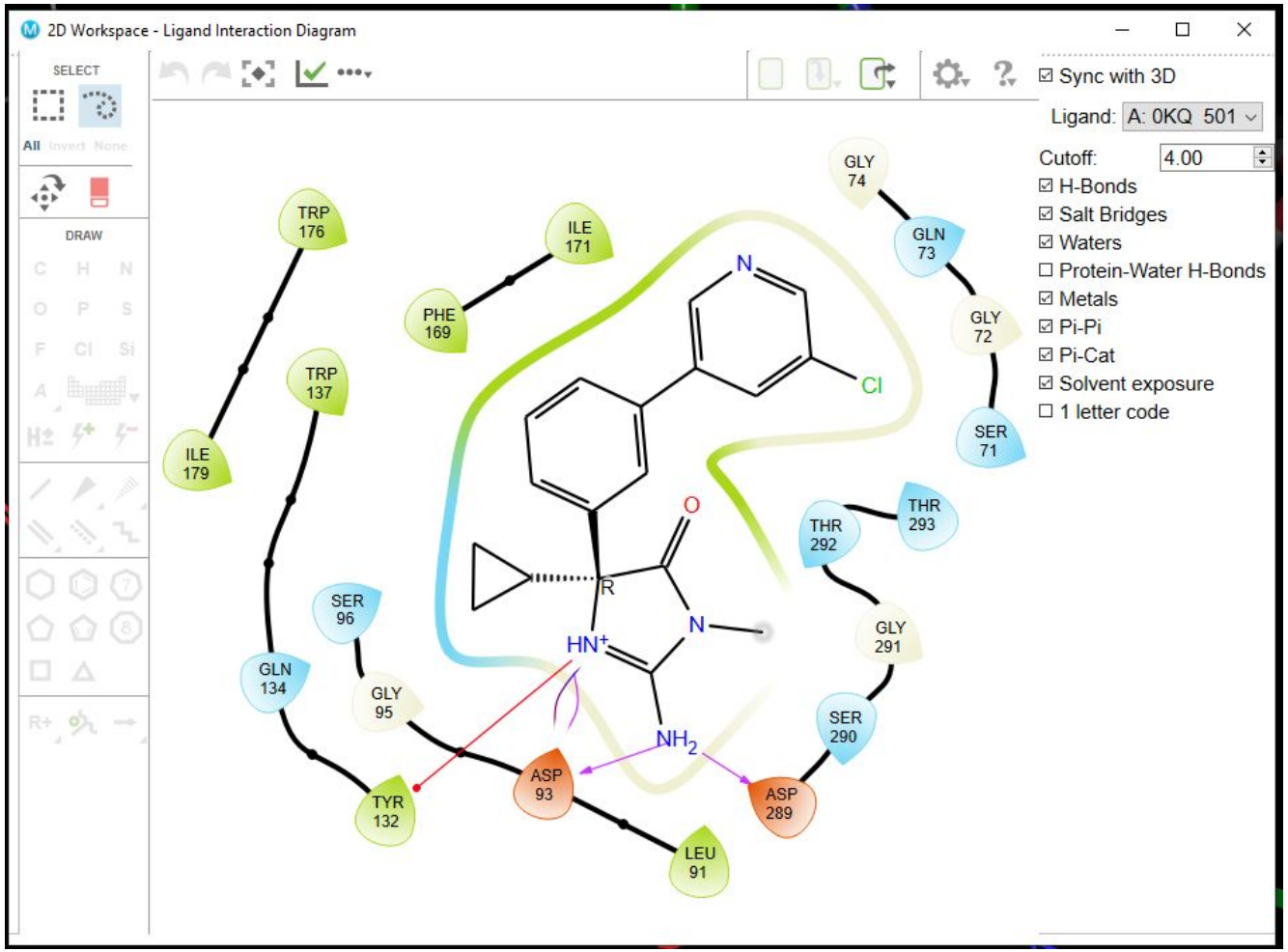


Visualizing the Pocket in 2D

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



2D projection tied to 3D camera position

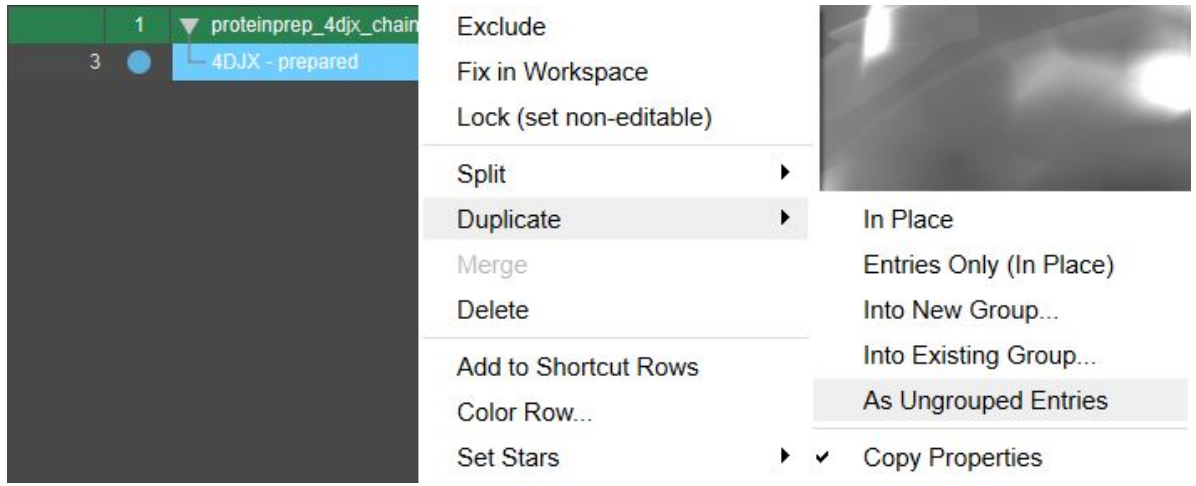


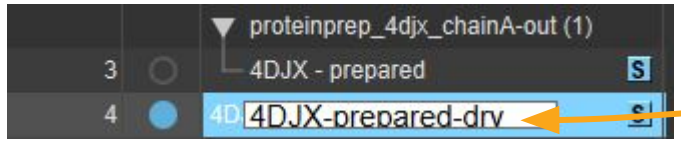
What to do with the crystal waters?

- 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

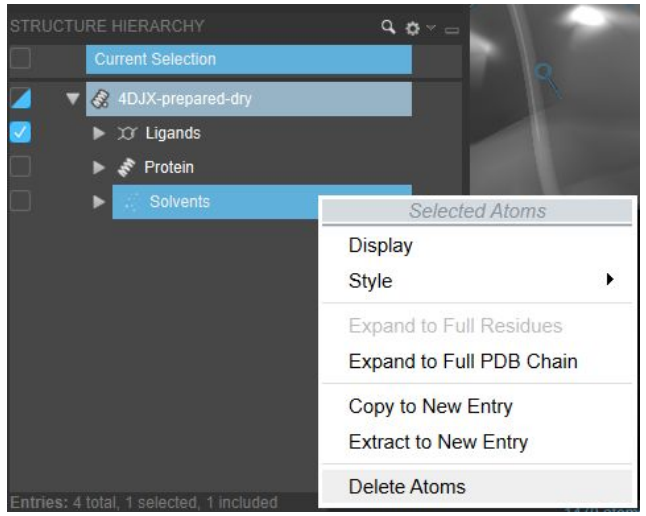
Best practice recommendations:

- 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





click selected entry to rename



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

Understanding the Binding Site

using SiteMap

Many tools provide insight into the binding pocket

- Structure liabilities
- Missing density
- Structure refinement

- Add missing atoms
- Remove crystallography artifacts
- Protonation and tautomeric states
- Relaxation

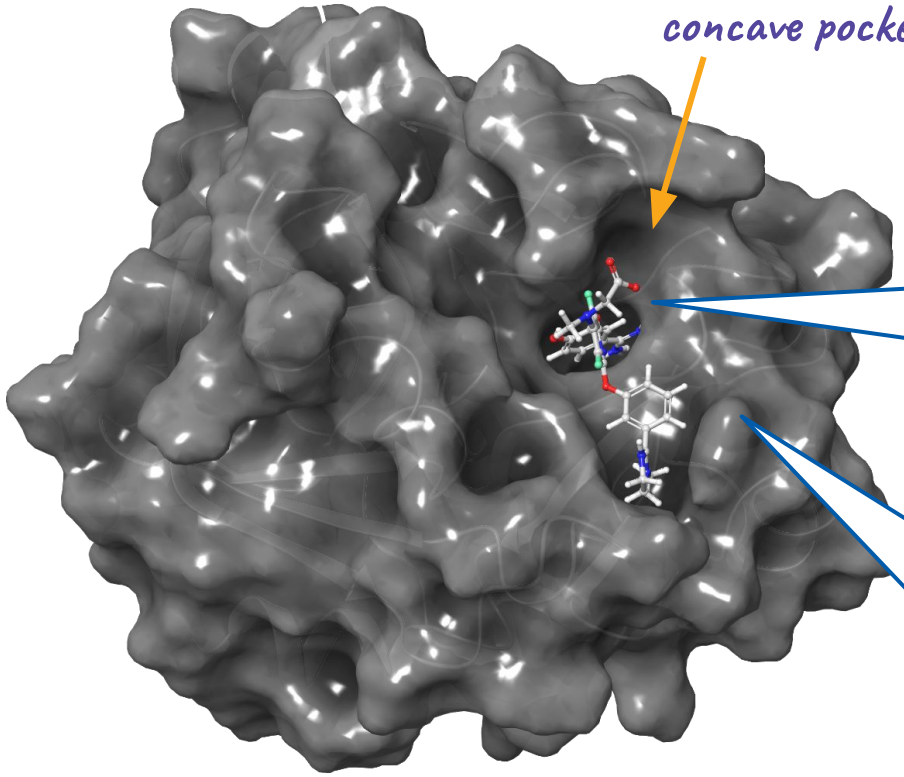
- Identify potential binding sites
- Characterize binding site

- Identify potential cryptic binding sites
- Allow protein structure flexibility
- Uses small molecule probes

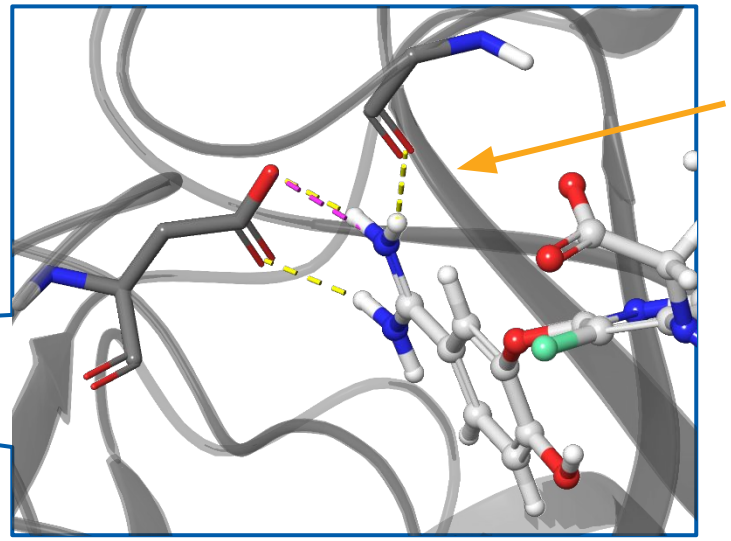
- Identify hydration sites
- Calculate the energetics of waters

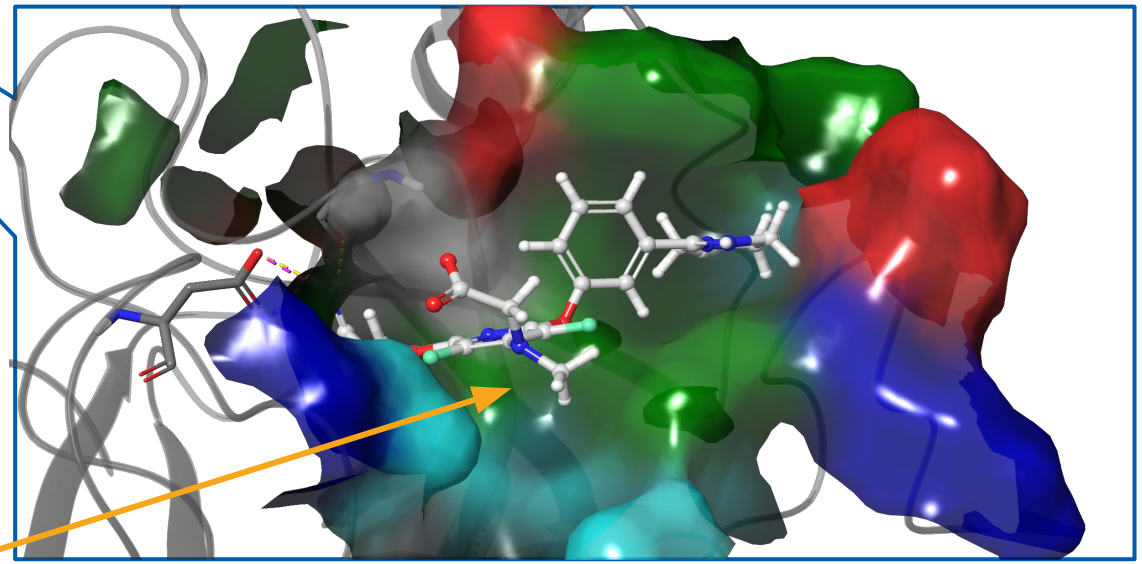
Static | Static | Static | Dynamic | Dynamic

What does a binding site look like?



PDB: 1FJS (human Factor Xa)

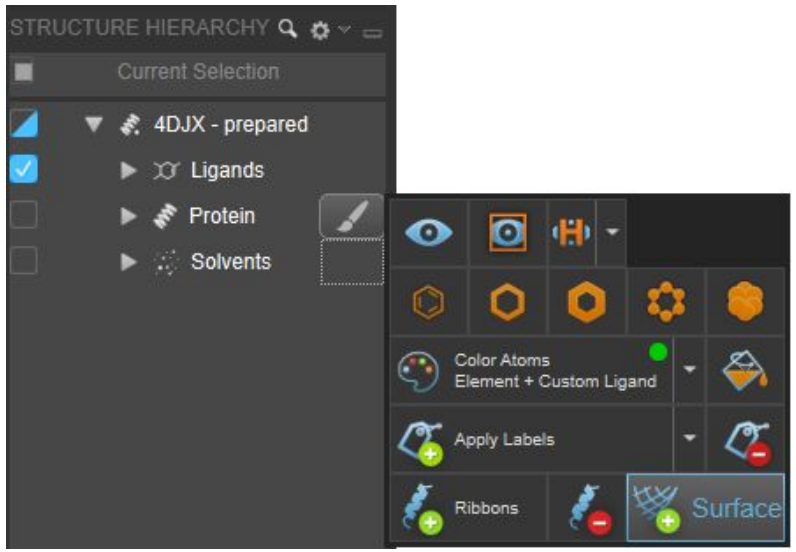


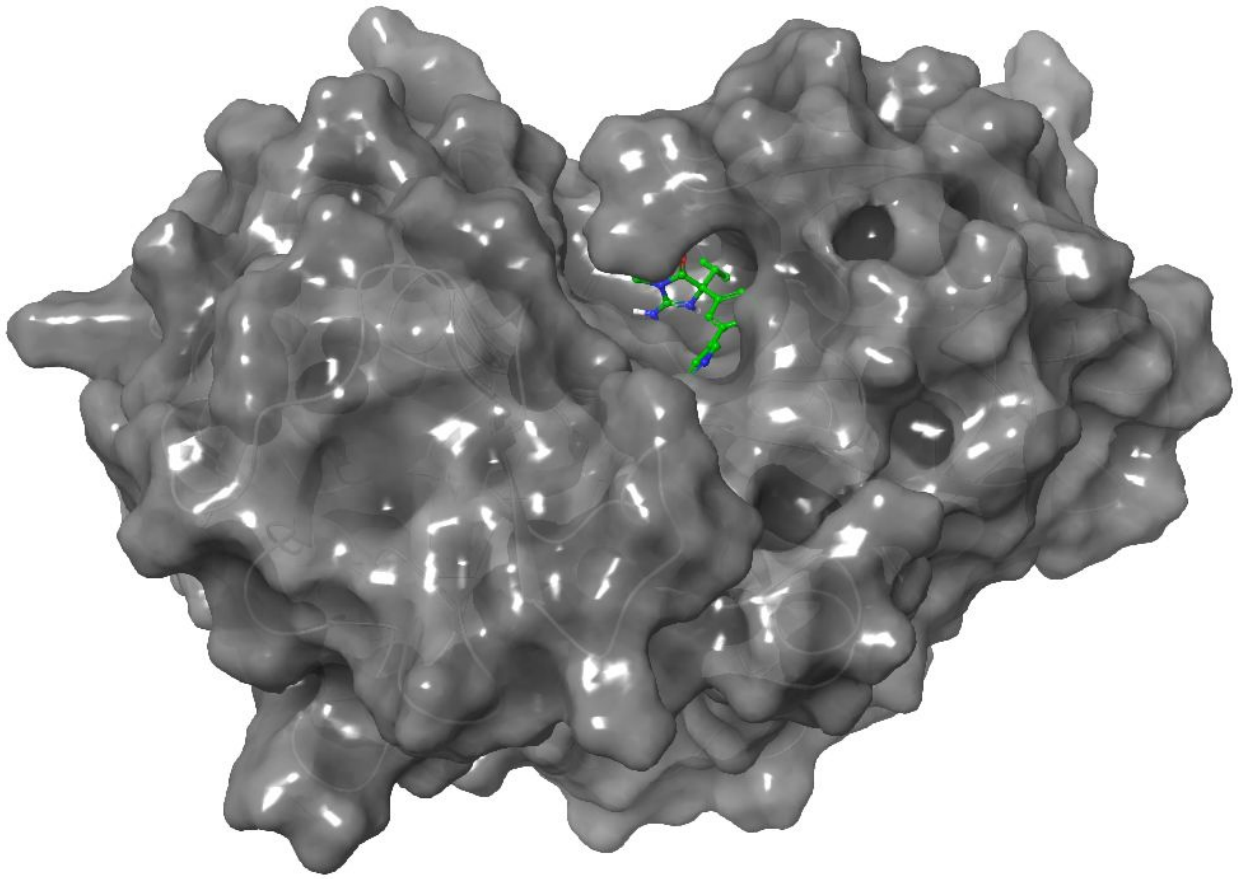


residue type: hydrophobic, polar uncharged, positives, negatives

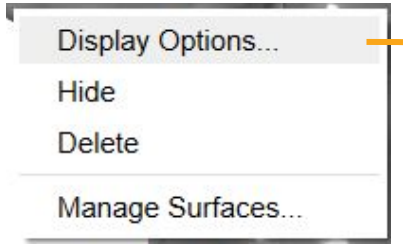
A rough overview of the shape of BACE-1

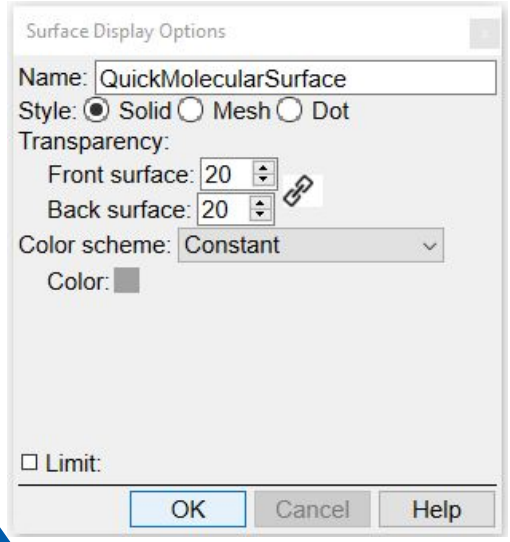
One way to render the protein surface:



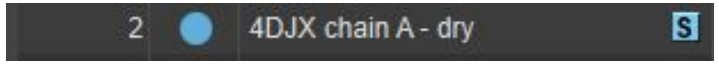


Right-click surface to configure:





Toggle display of individual surfaces or all surfaces at once

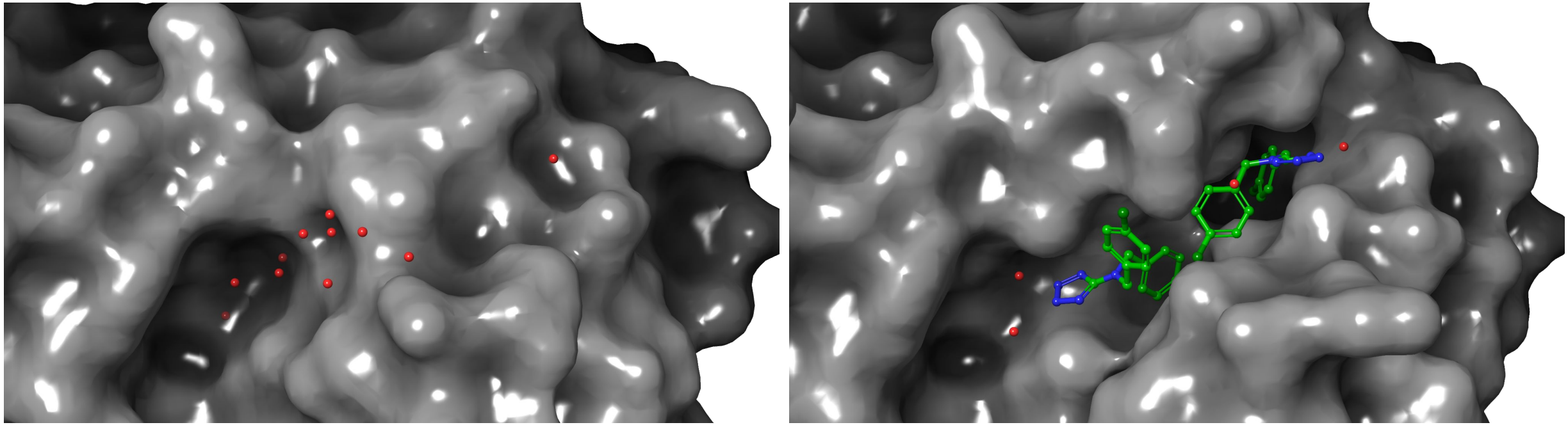


Schrödinger

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

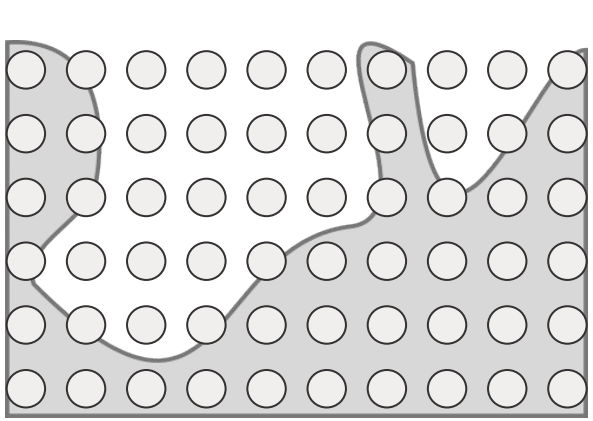


Structures of TEM1 cryptic pocket (left: 1JWP, right: 1PZO)

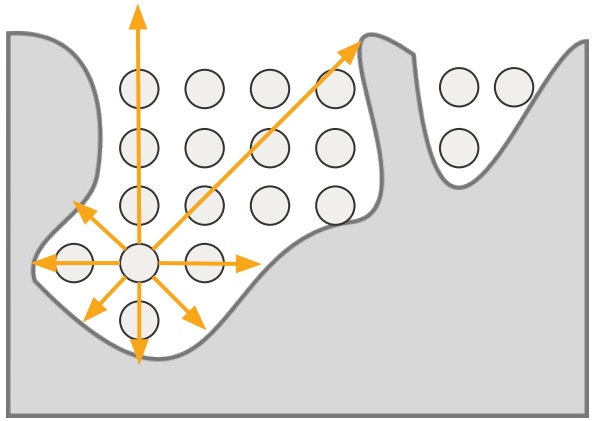
Sidenote: how do we find where binding sites are?

- 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

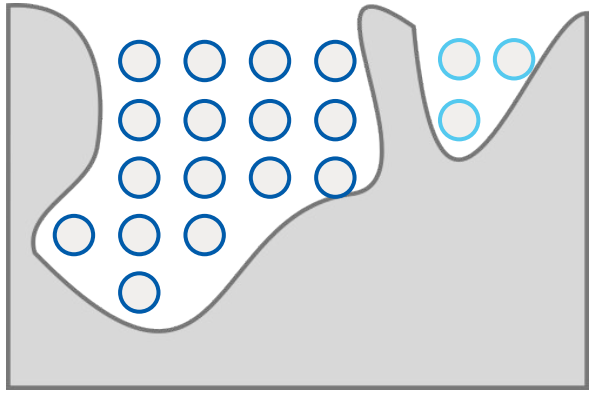
How SiteMap finds and scores sites:



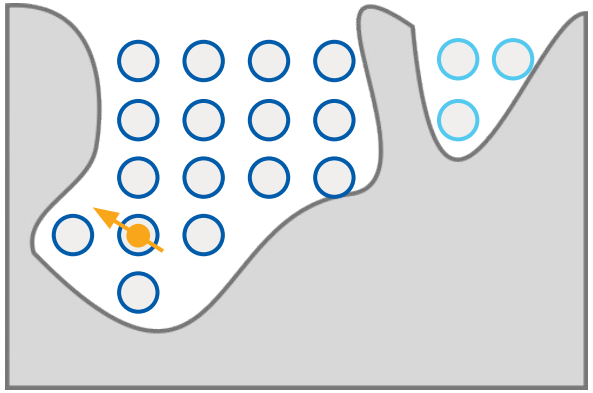
overlay grid,
discard internal points



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

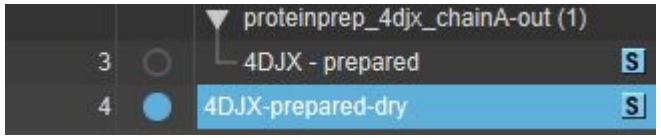
Volume, Balance, …: SiteMap User Manual

Halgren, T., *J. Chem. Inf. Model.*, **2009**, 49, 377–389.;

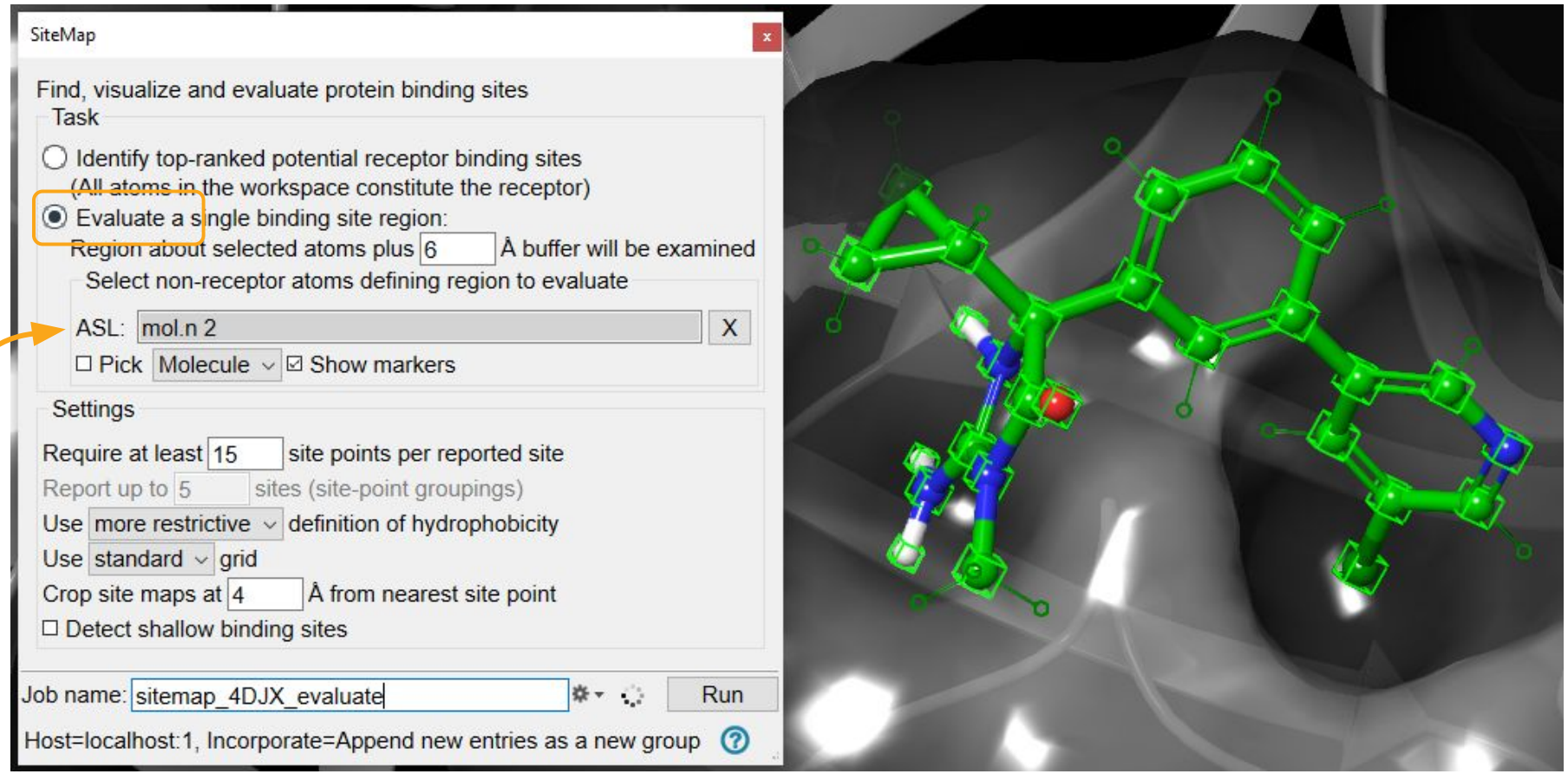
Using SiteMap: Evaluate

find SiteMap in the tasks menu

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

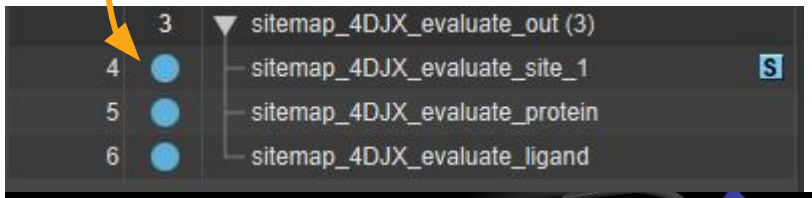


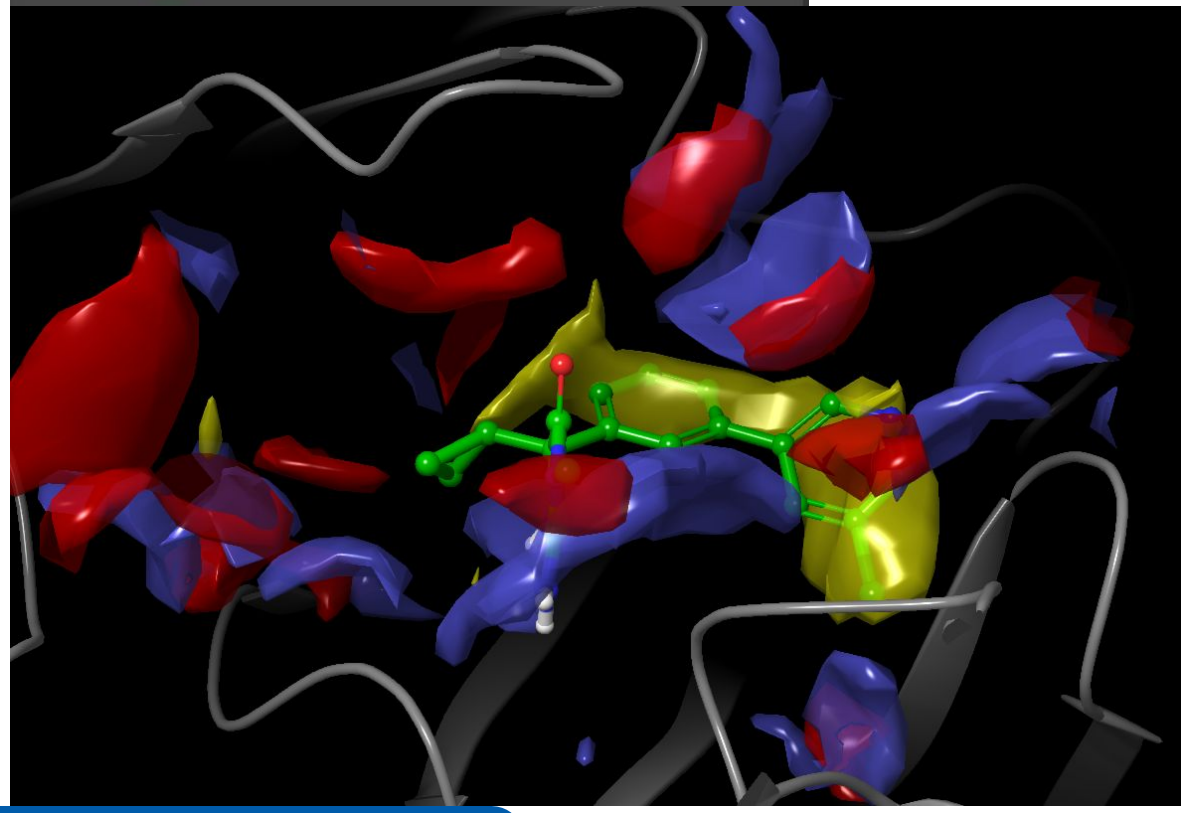
click ligand in workspace to select it



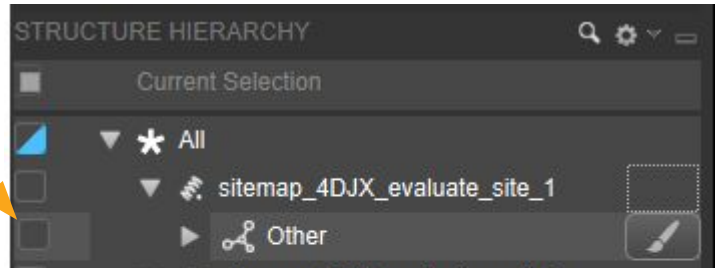
Interpreting SiteMap results

include all output entries by Ctrl+Clicking the empty circles

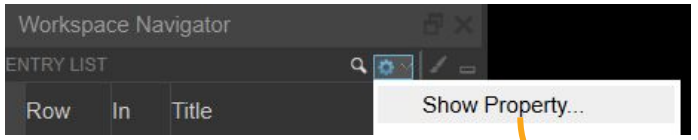


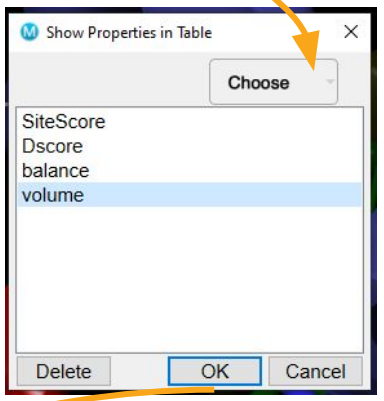


toggle white sphere display here



To view site metrics:





In	Title	SiteScore	Dscore	volume	balance
	4DJX chain A - prepared				
	4DJX chain A - dry S				
3	sitemap_4djx_evaluate_o...				
	sitemap_4djx_evaluat... S	1.055666	1.072768	602.308000	0.828940
	sitemap_4djx_evaluate_pr...				
	sitemap_4djx_evaluate_li...				

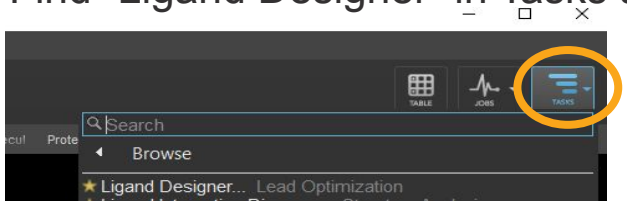
character of pocket: lipophilic, donor preferred, acceptor preferred

Designing Ligands

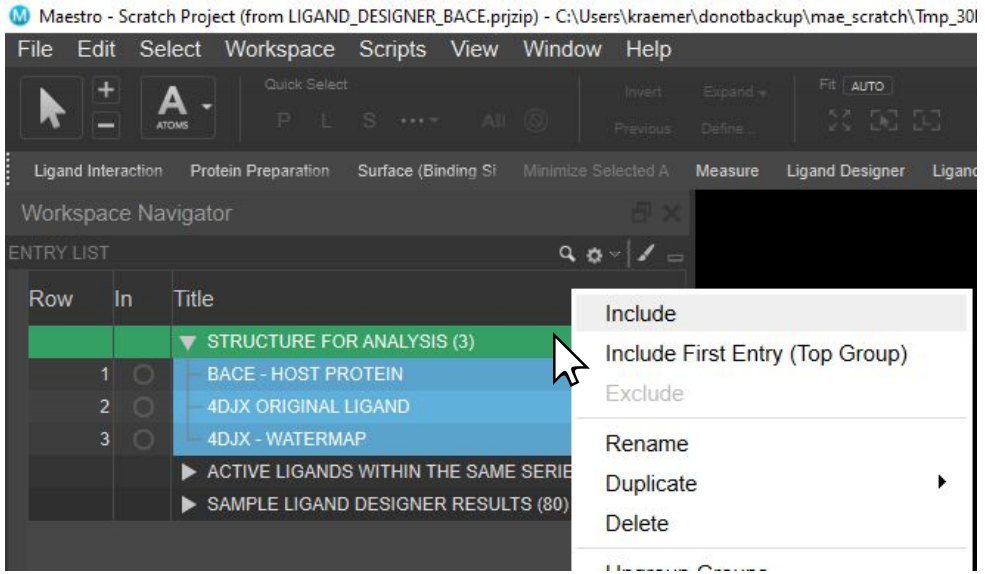
quick ideation with targeted enumeration and docking

Getting started with Designing Ligands

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



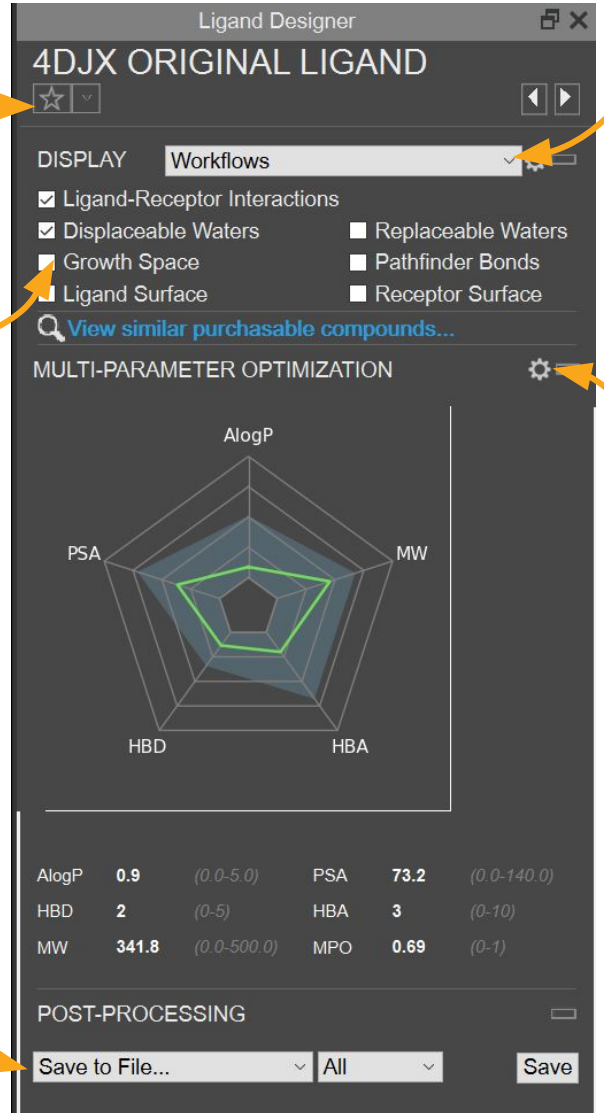
- Click “Analyze Workspace”



Now let's tweak our ligand!

mark ligand idea as favorite

customize what to show/highlight



choose a workflow:

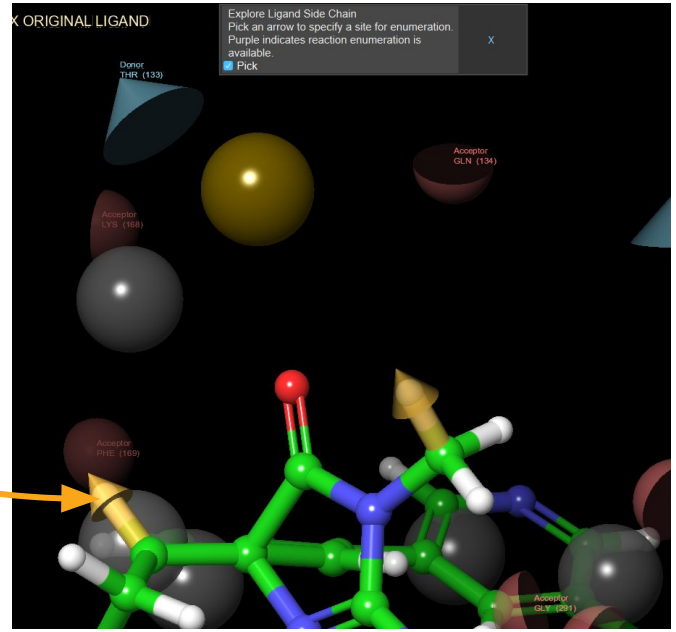
- Attach R-Group
- Fill Growth Space
- Bioisostere Replacement
- Isostere Scanning
- Displace Unstable Water
- Replace Stable Water
- Form Ligand-Receptor Interaction
- Cyclize Ligands
- Hybridize Ligands
- 2D/3D Editing...
- Dock Ligands from File...

Some Ideas:

- Remove Thiazole group

customize MPO function

follow the prompts in the banners



arrows highlight possible modification vectors

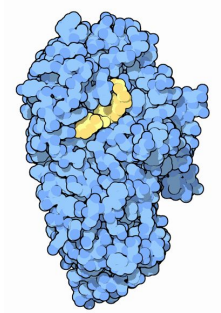
e.g.: sort selected ligands by MPO score

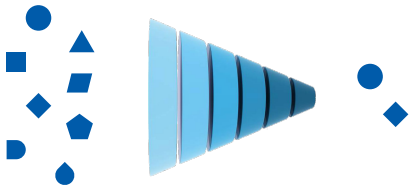
Ligand Preparation & Docking

setting up and validating a docking model

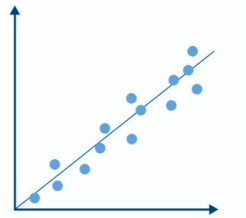
Different goals in HitID and LeadOpt require different tools

Target selection | Hit identification | Lead optimisation | Candidate selection | Clinical trials

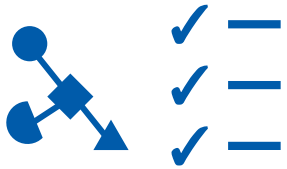




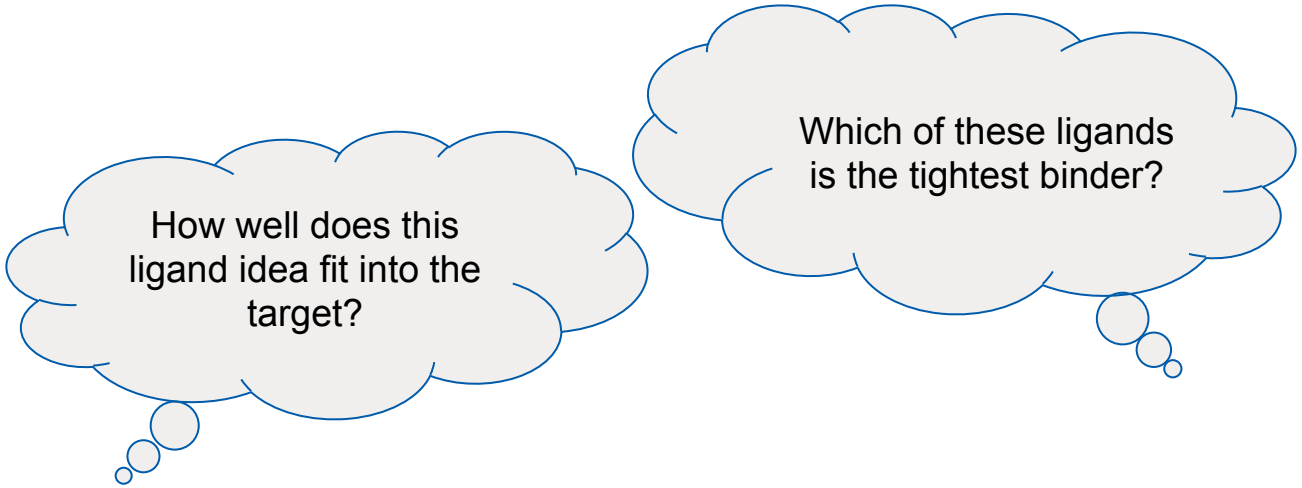
- Aim of virtual screening is to filter down large libraries of diverse compounds
- Requirement is enrichment wrt random screening, and to find diverse hits
- Additional properties are nice to have but less important at this stage



- 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



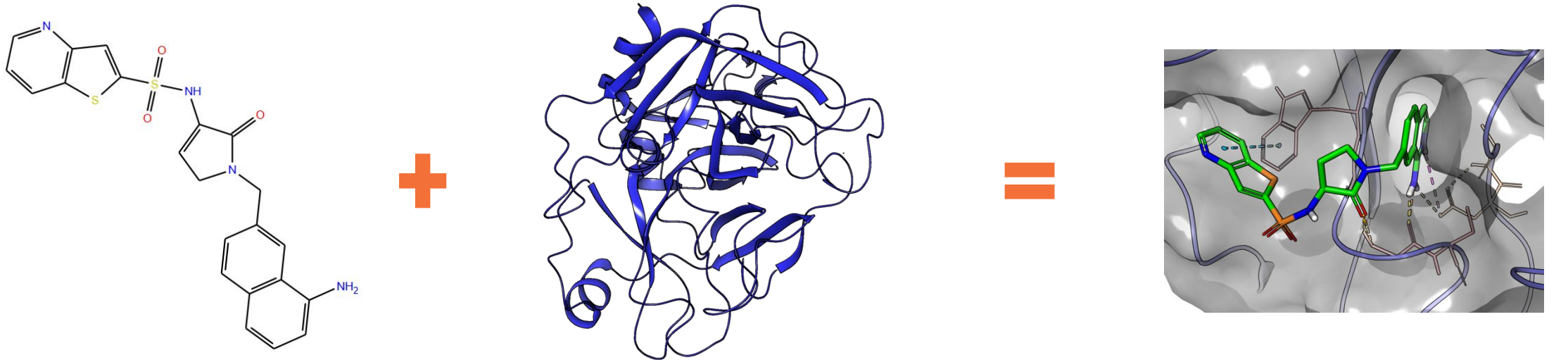
This afternoon's questions:



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?

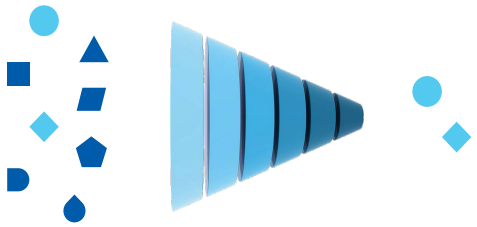


What do we hope to achieve?

- 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

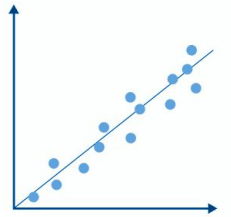
What's the point of scoring?

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

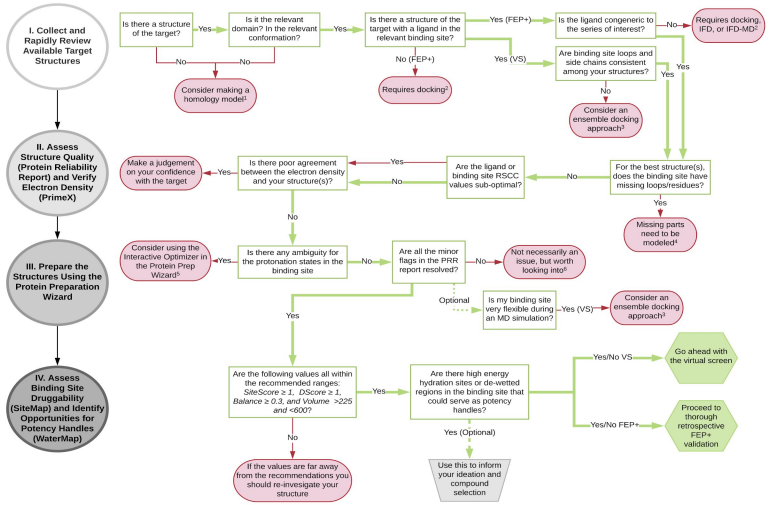
Friesner, R. A. et al, J. Med. Chem., 2004, 47, 1739-1749.
Halgren, T. A. et al, J. Med. Chem., 2004, 47, 1750-1759.
Friesner, R. A. et al, J. Med. Chem., 2006, 49, 6177-6196.
Repasky, M. P. et al, J. Comput. Aided Mol. Des., 2012, 26, 787-799.

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

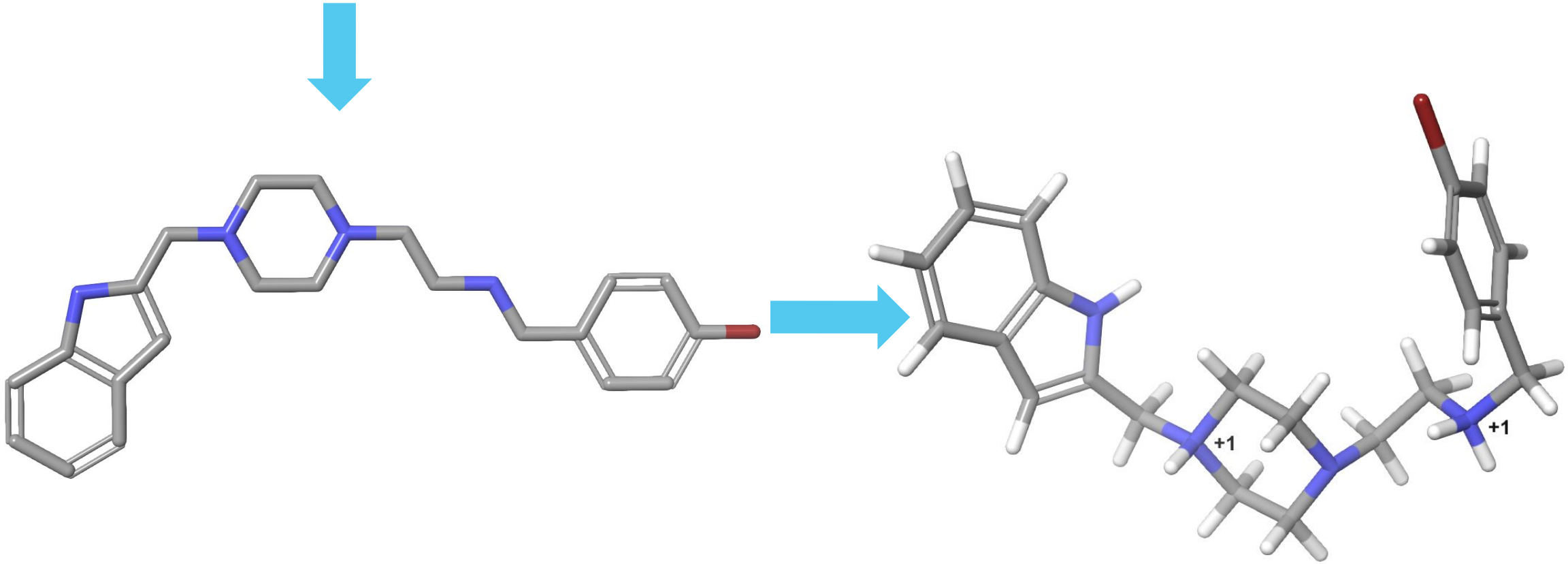
- ❑ Is the resolution high enough?
- ❑ Are the R and R_{free} factors low?
- ❑ What are the B-factors like?
- ❑ What about the RSCC values?
- ❑ Are there any geometric outliers or clashes?
- ❑ What were the experimental conditions like?
- ❑ Are there any parts of the structure that don't fit the electron density well?
- ❑ Any alternate conformations of protein residues or ligands?
- ❑ Were some parts of the protein modelled in (0-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?

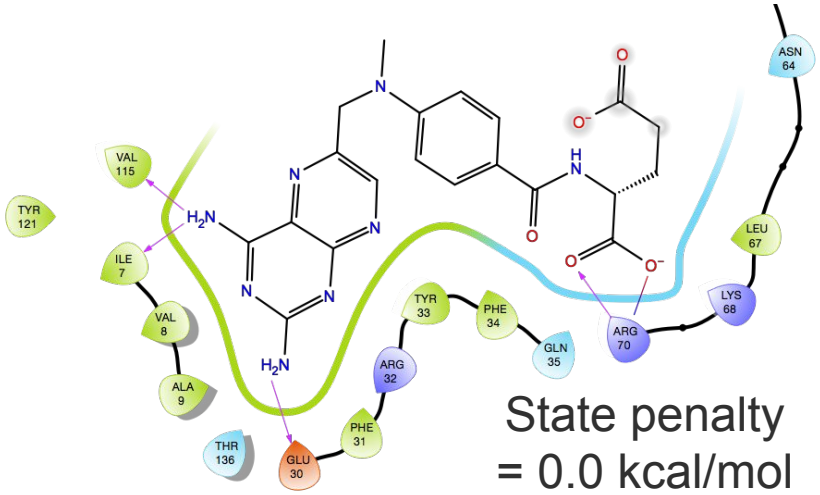
Ligand Preparation

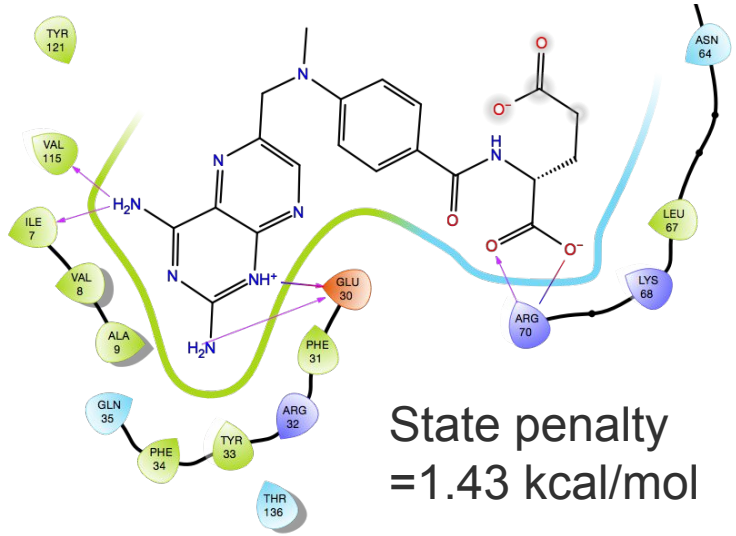
Brc1ccc(CNCCN2CCN(Cc3cc4ccccc4[nH]3)CC2)cc1



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



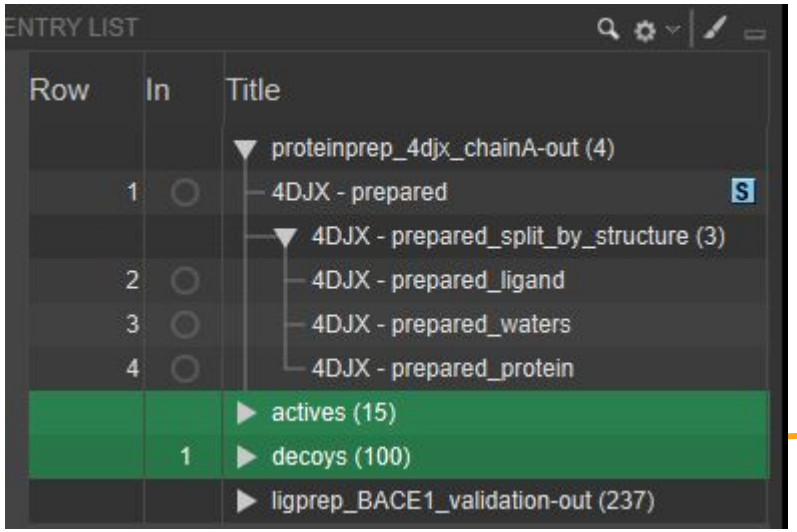


Methotrexate bound to DHFR (1U72)

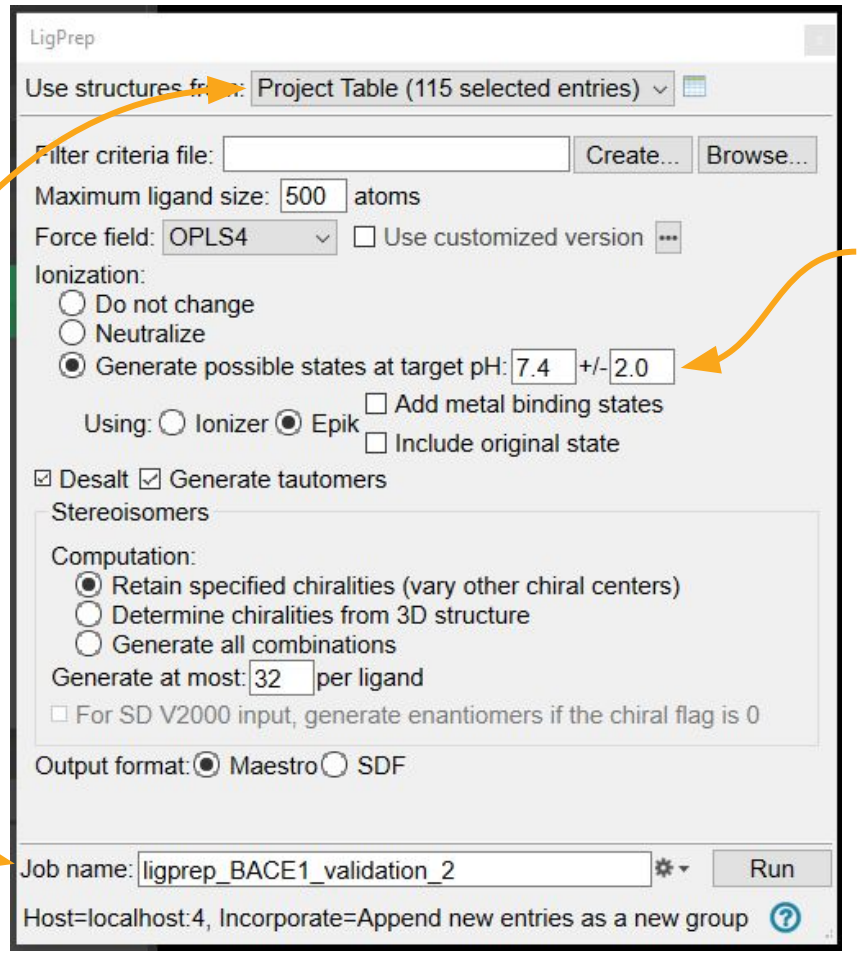
Setting up Ligand Preparation

find LigPrep in the tasks menu

- Open a new Maestro session
- File → Open Project…
  Find `BACE_docking_start.prjzip` in the provided files



Select both known actives and decoys



Adjust pH

Name your job and run it

Generating ionization/tautomer states

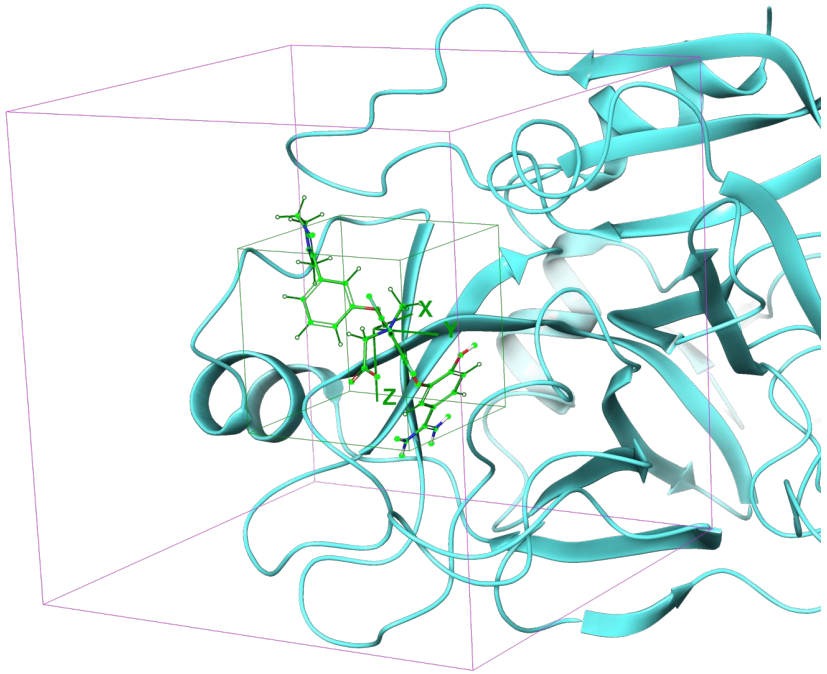
- Four options currently:
  - simple rule-based → very fast, but struggles with complex chemistry
  - Epik(-classic) → still fast, but should do well for most systems
  - Epik7 → ML-based, in beta in 22-3 release (not in LigPrep GUI yet), better than Epik-classic across the board
  - QM pKa prediction → 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:

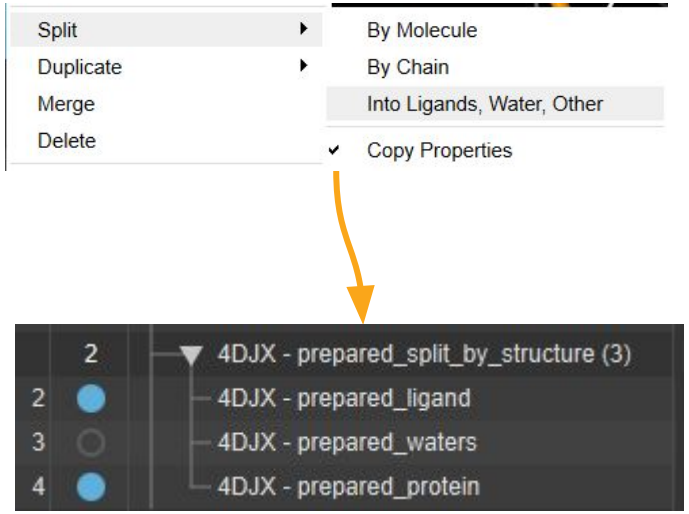
- uses “gridded” representation of the binding site to speed up calculations
  - ligands must fit within outer box,
    ligand centers must lie within inner box
- only scans rotational DOF of ligands
- employs a funnel to discard bad ligands and poses without calculating costly interactions
- focuses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



Setting up the Receptor Grid

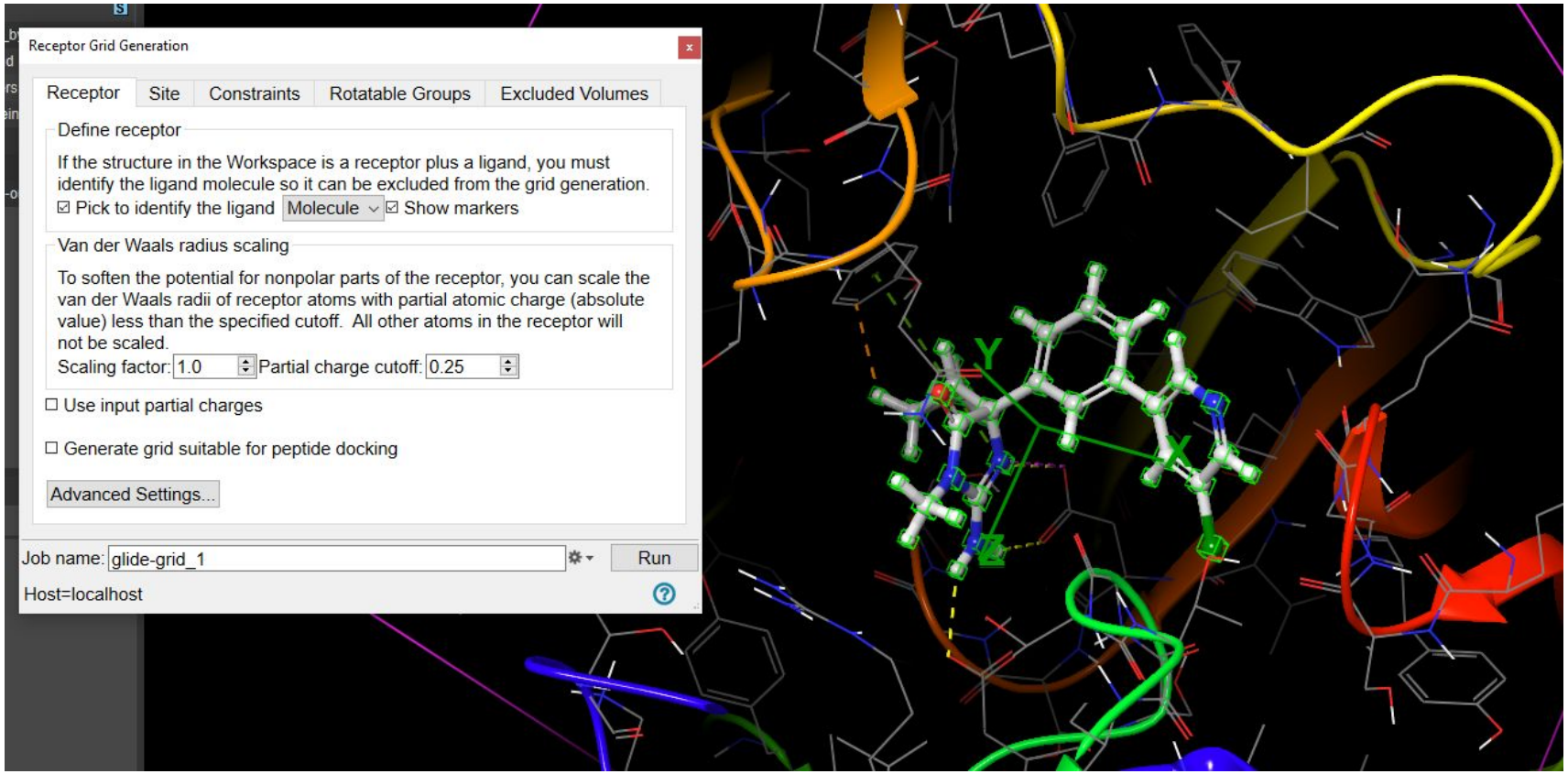
find Receptor Grid Generation in the tasks menu

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



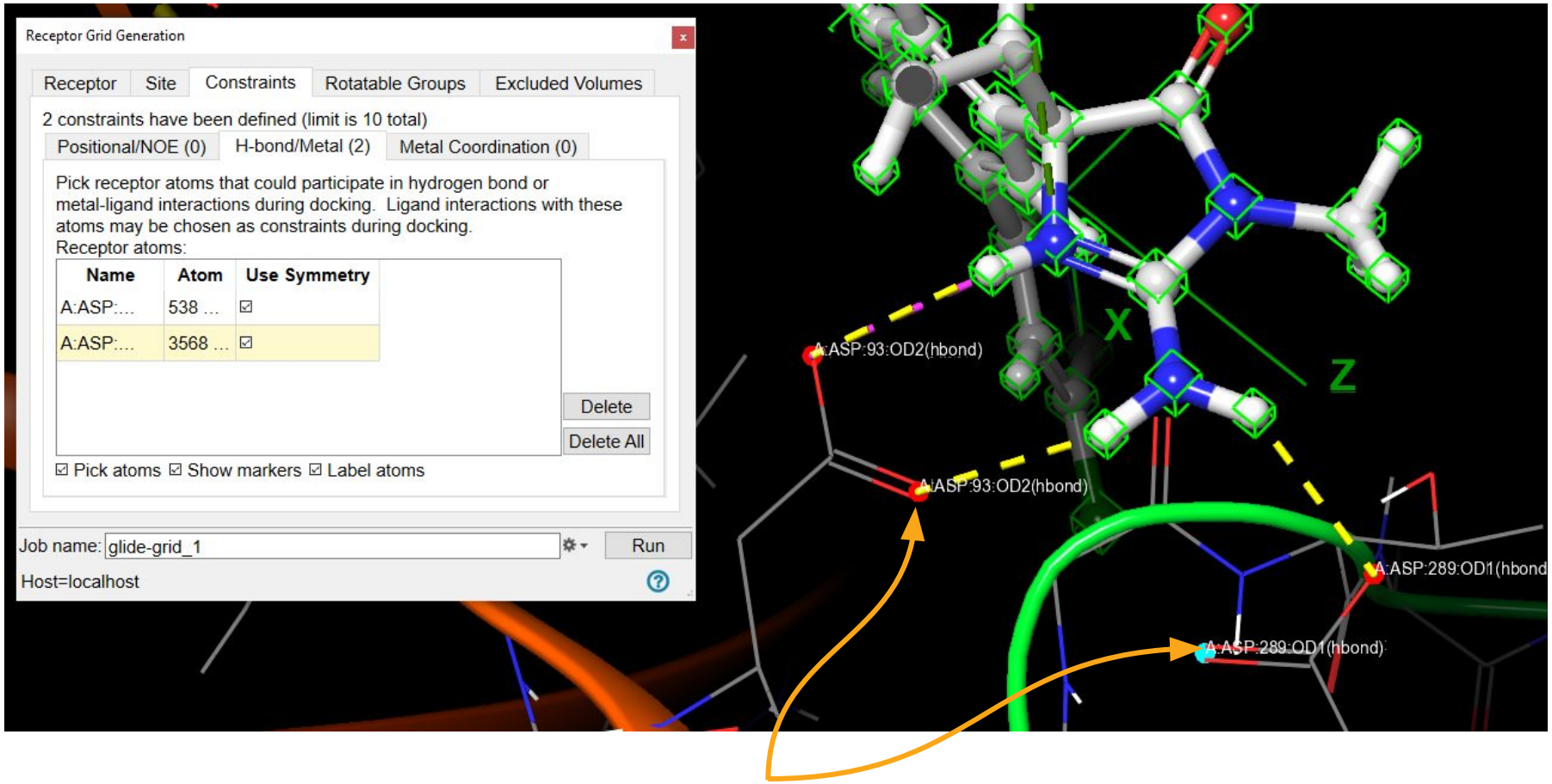
Include "4DJX - prepared_protein" and "4DJX - prepared_ligand"

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.



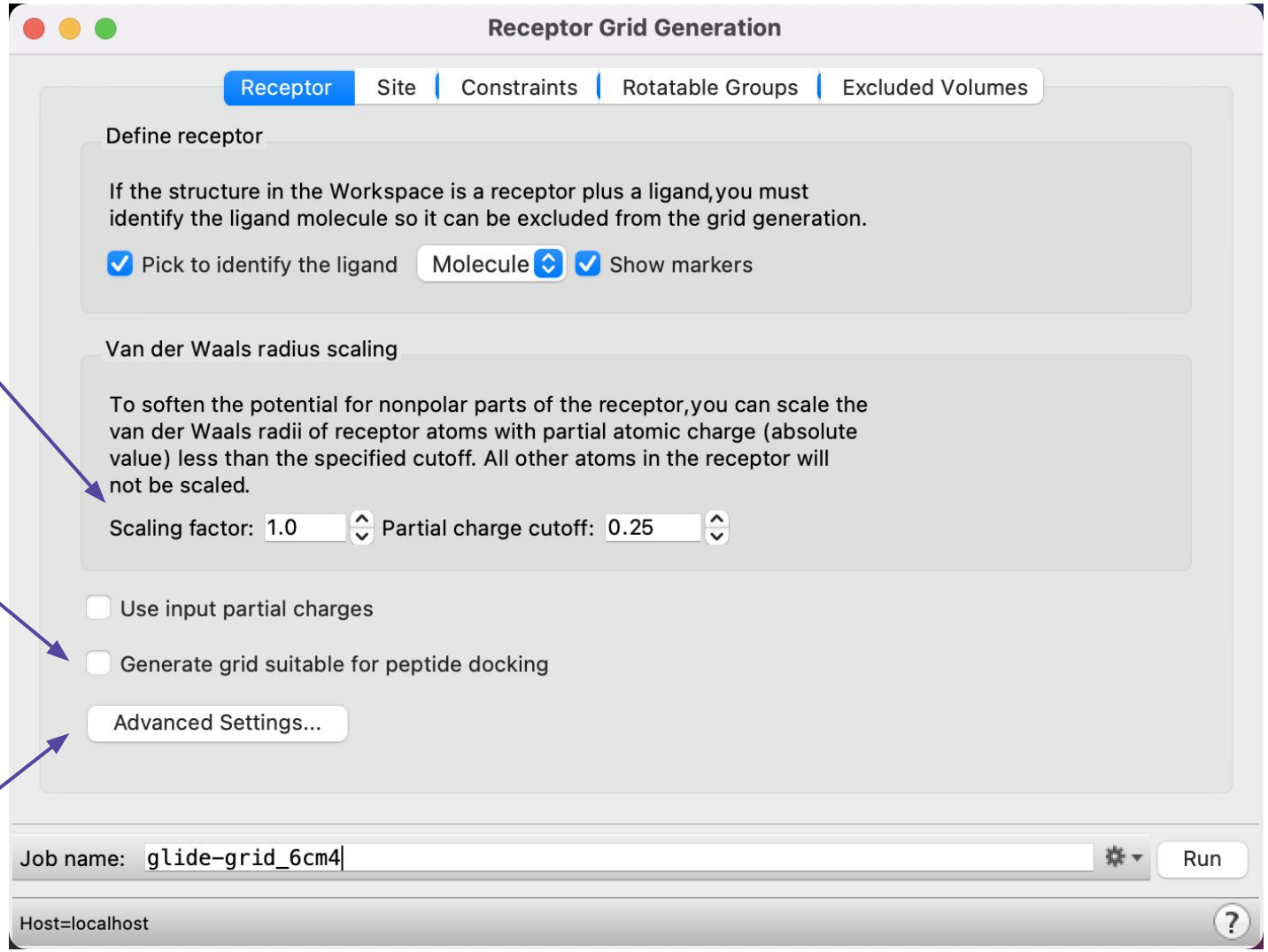
Find and click the Asp oxygens in the workspace

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.

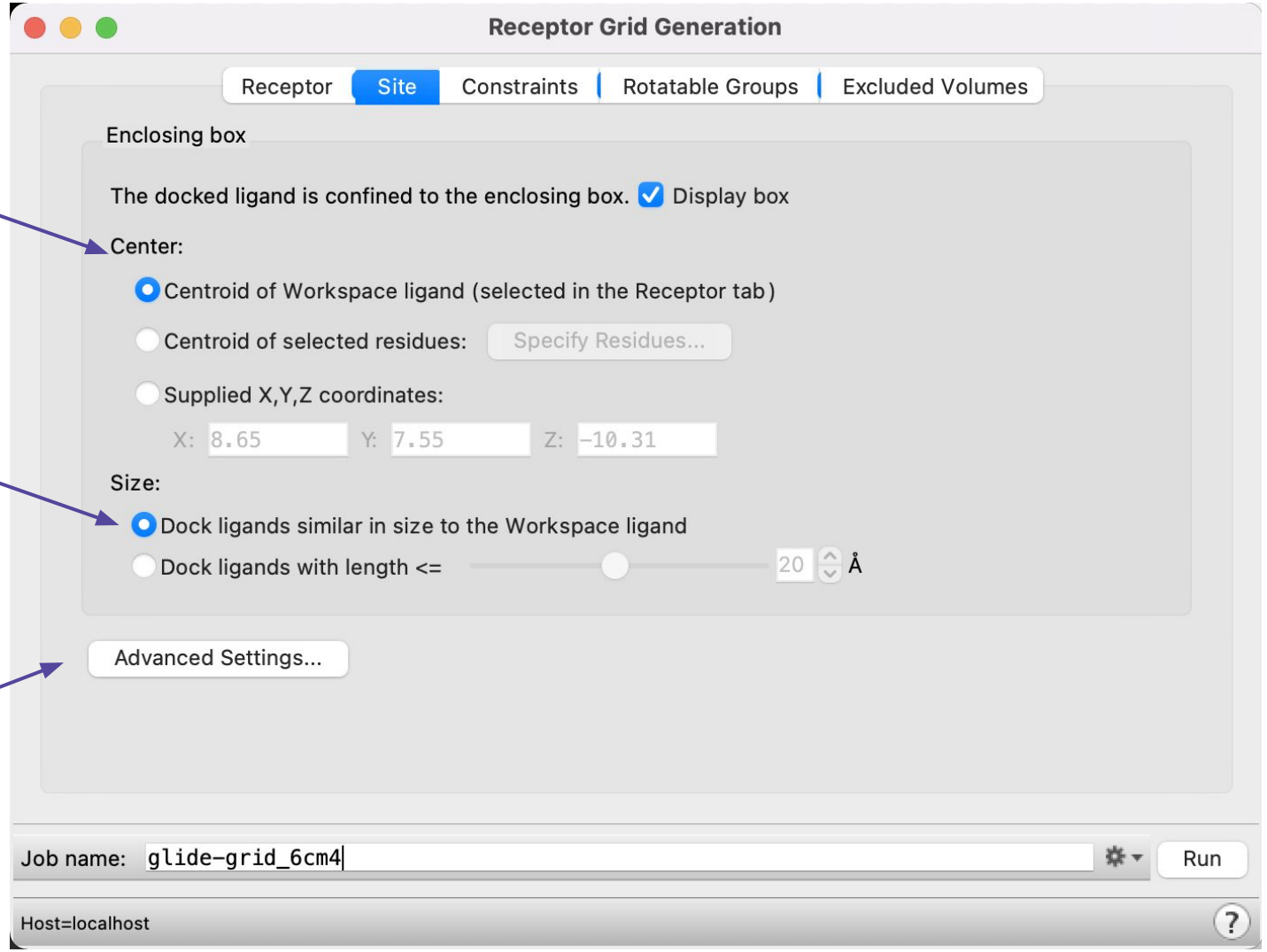


Grid generation

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

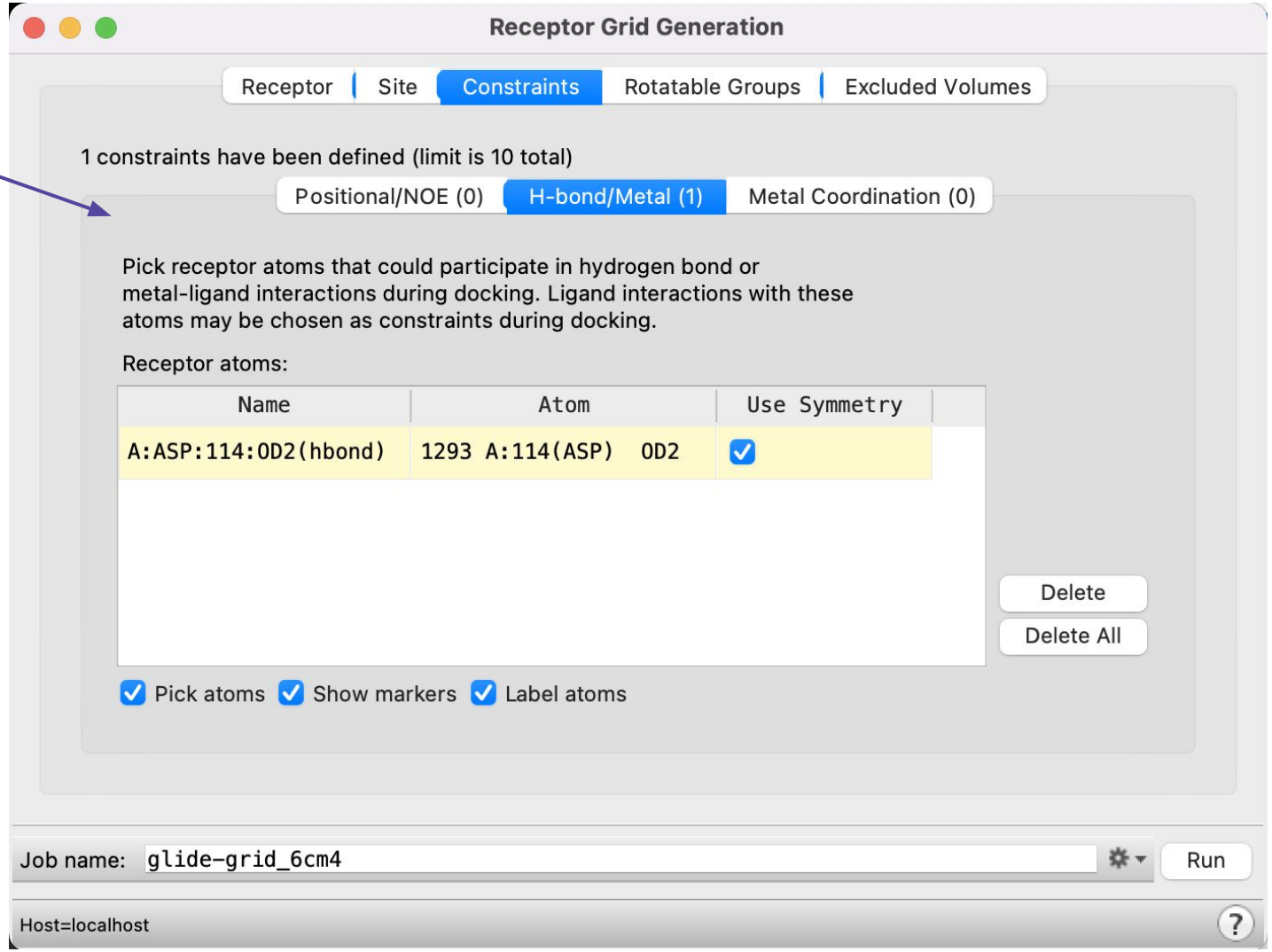
Specify ligand size to be docked (size of outer grid box). Increase if docked ligands are larger than the reference used to define the grid, but keep as small as possible.

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.



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.*



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.

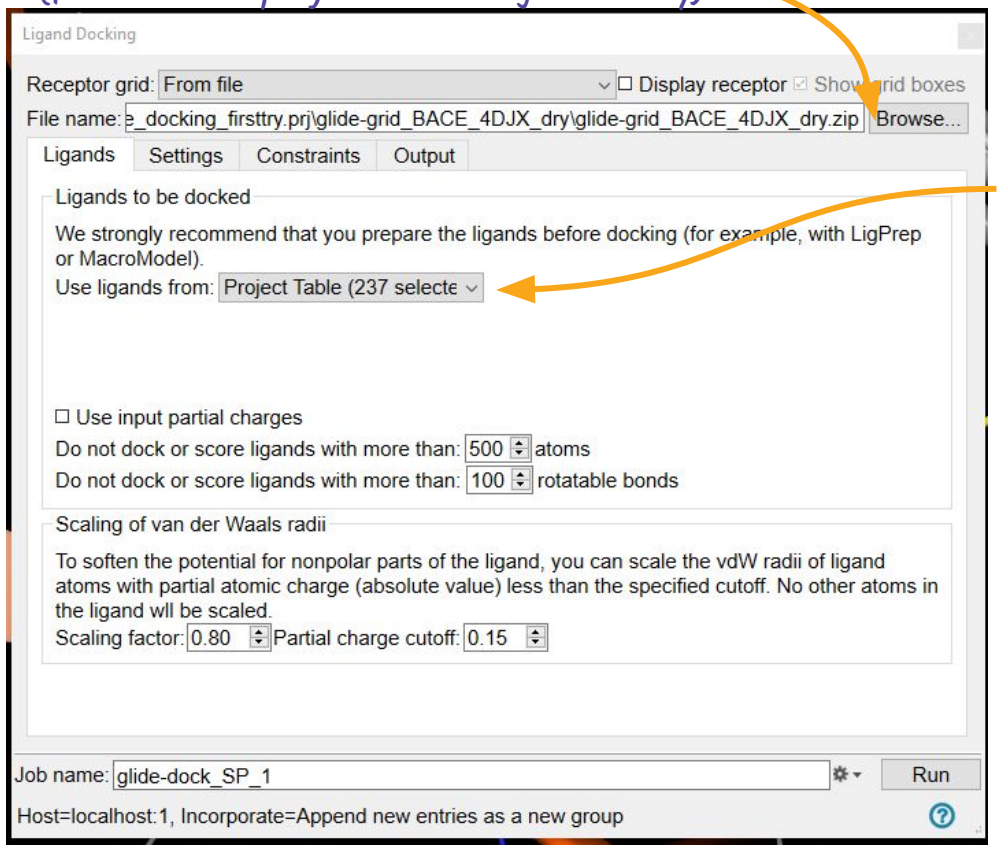
- There are three main scores from a Glide run:
  - GlideScore: Base score of a docked pose
  - docking score: GlideScore (+ Epik state penalty + strain penalty)
    - used to rank diverse ligands
  - emodel score: Reweighed GlideScore + interaction energy + ligand strain
    - used to rank poses of 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

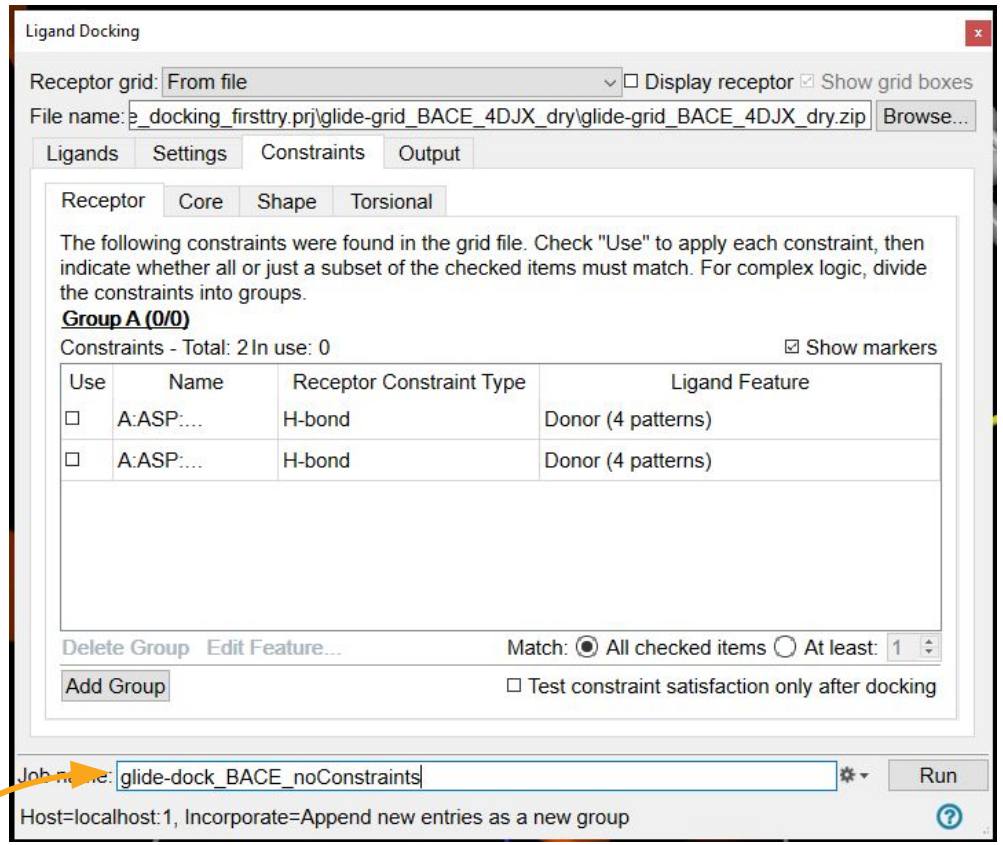
Navigate to your glide-grid_BACE_4DJX_dry.zip (found in the project's working directory)



select ligprep_BACE group in the entry list

we'll run docking twice:

1. no constraints on
2. both constrains on



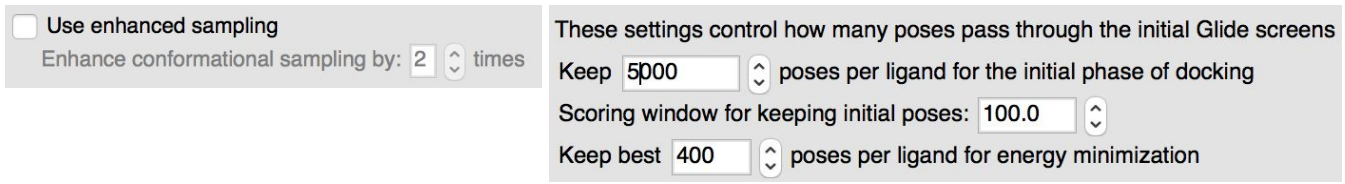
give your two jobs distinct names, e.g. "glide-dock_BACE_noConstraints" and "glide-dock_BACE_hbond"

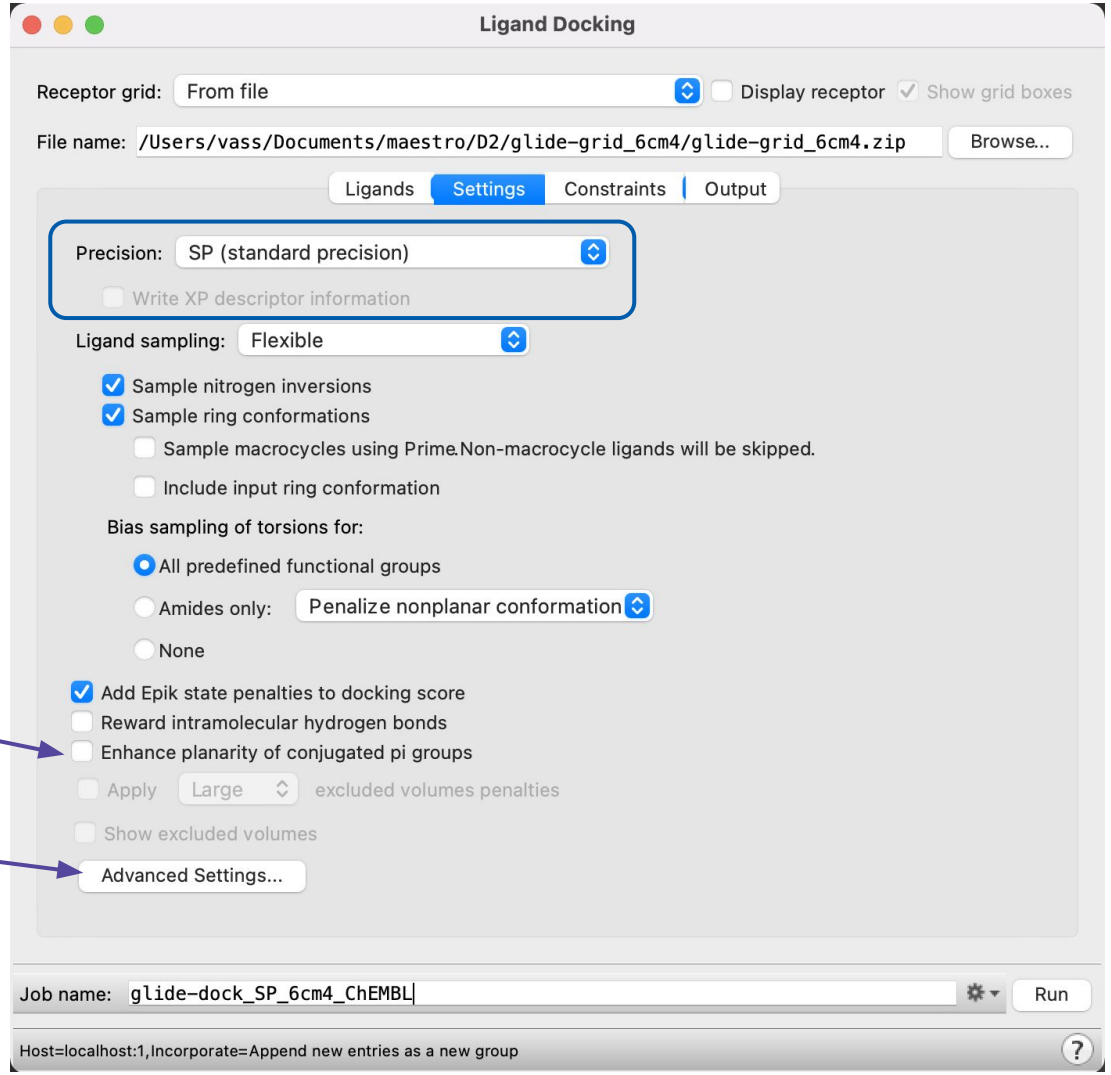
Docking Setup Settings – Glide Modes & Sampling

- 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:

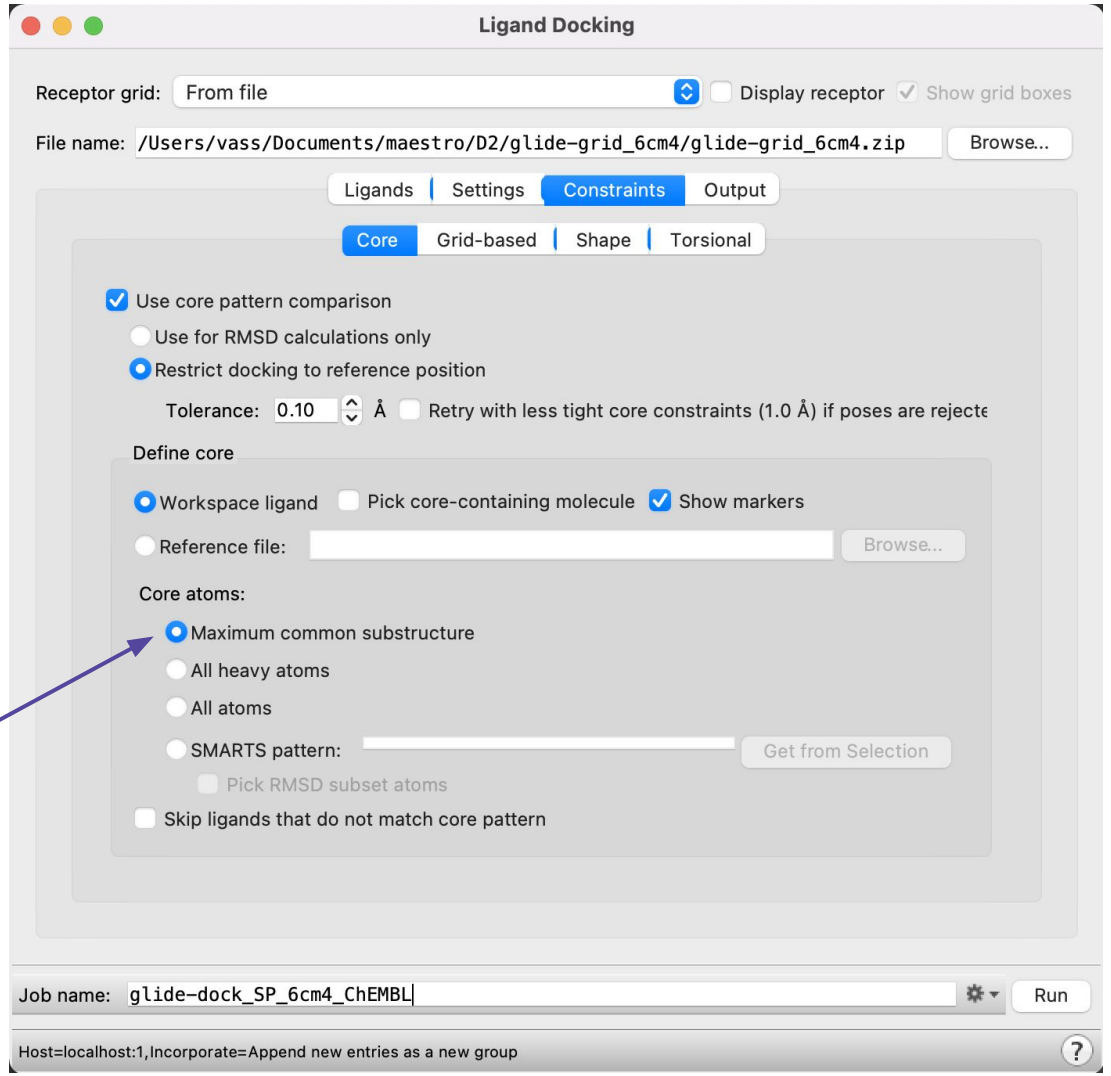




Docking Setup Settings – To Constrain or Not?

- 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

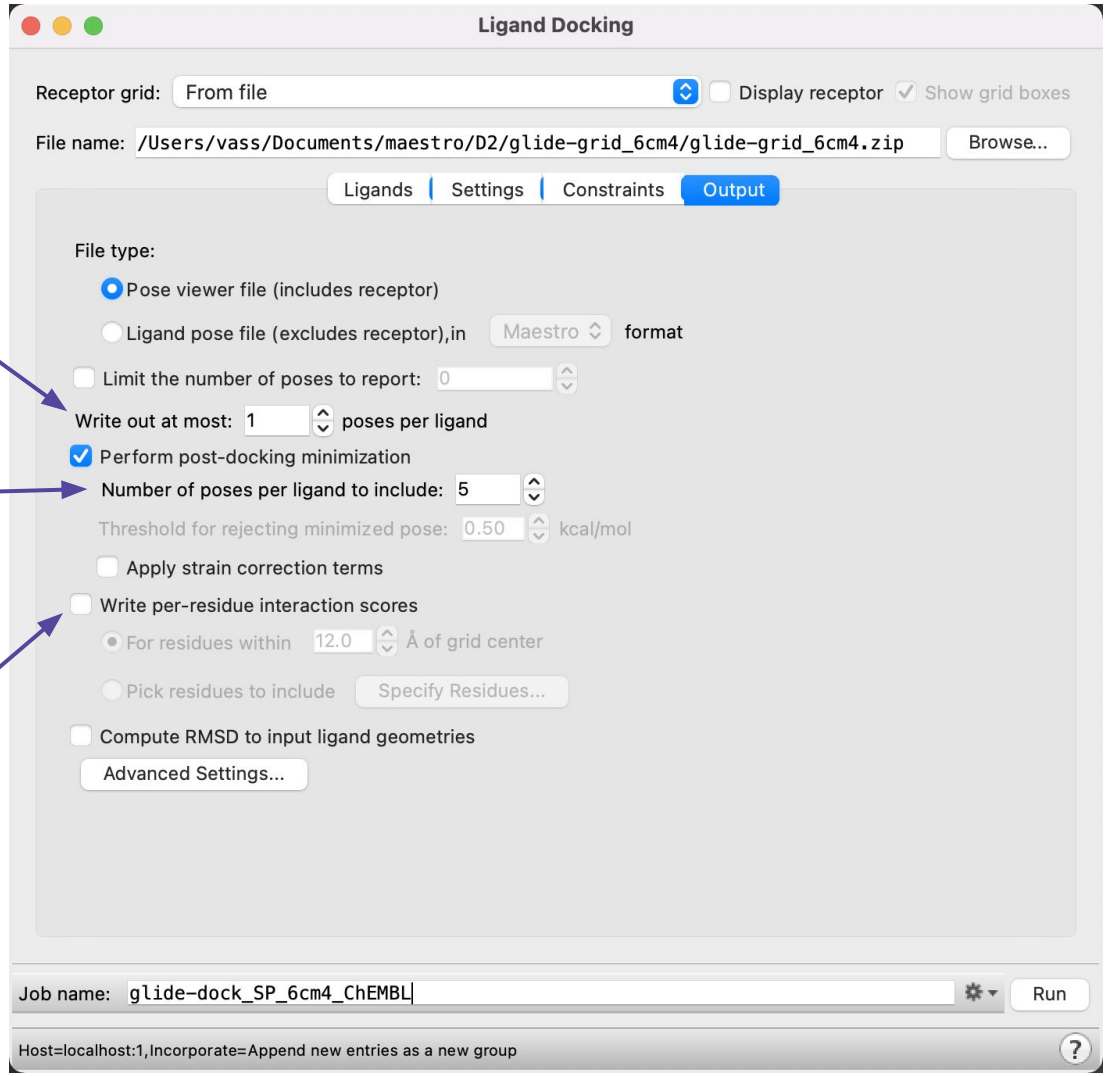


Docking Setup Settings – Reporting Options

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

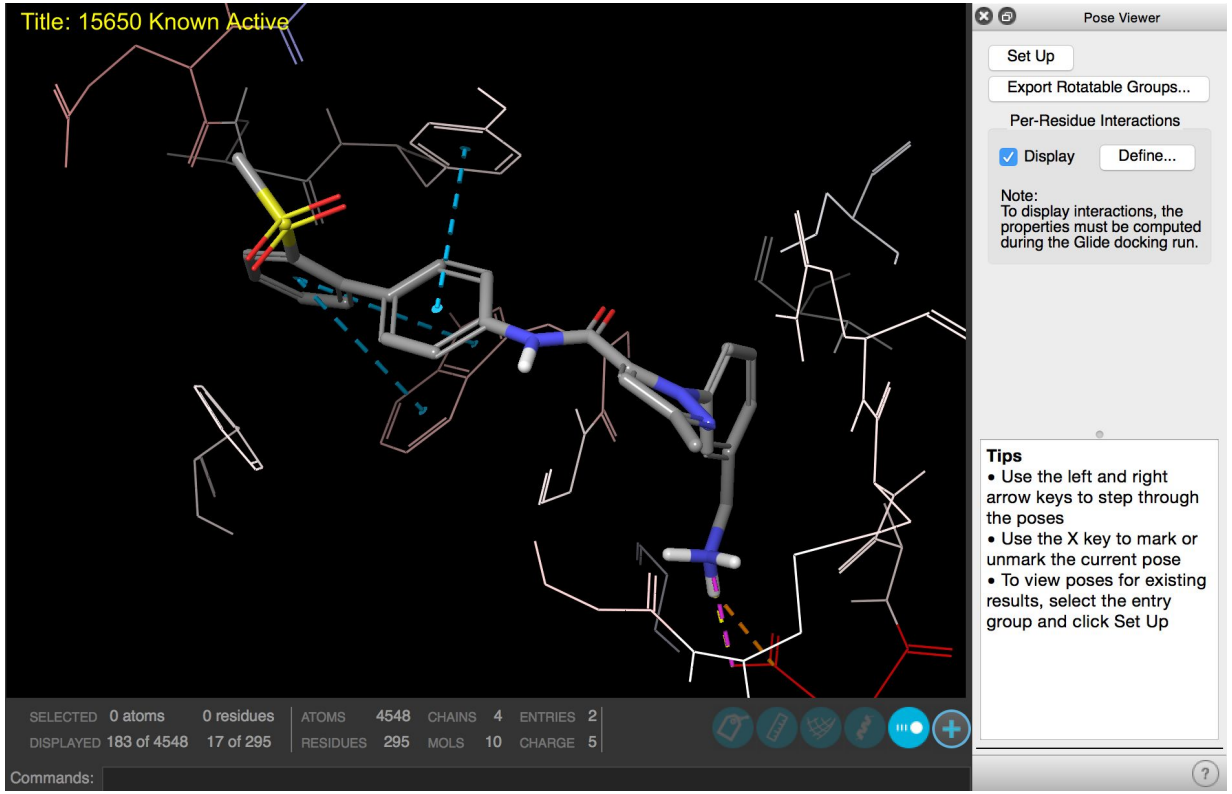
Allows visualizing contributions of each residue to final ligand score



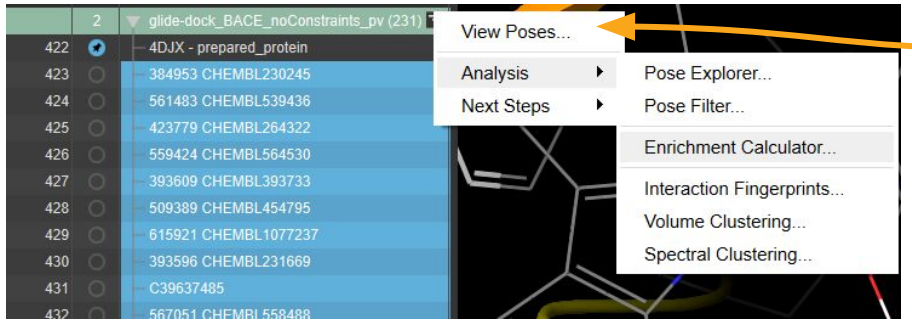
Rigid-Receptor Docking using Glide

Prepare Protein & Ligands | Setup Docking | Validate Model | Dock & Score | Analyze Results

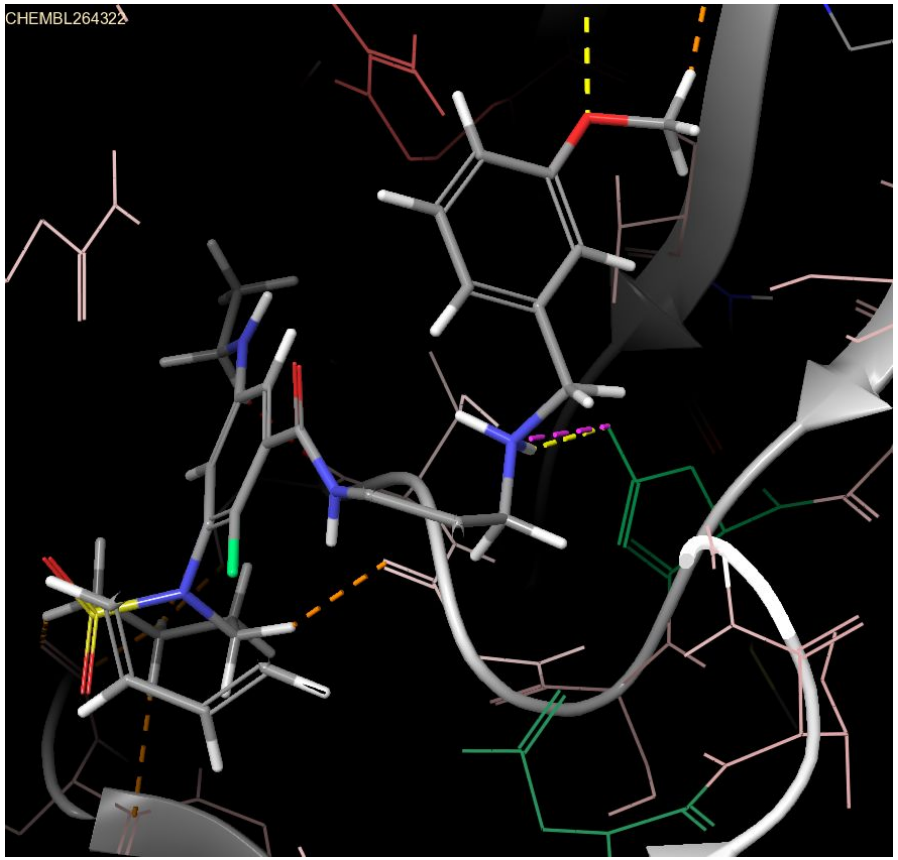
- Rank distinct compounds by GlideScore and multiple poses of the same compound by emodel score
- Visually inspect poses to recognize scoring function failures
- Some unfavorable torsions or interactions with the protein may be acceptable, as a small conformational shift in the receptor can resolve them

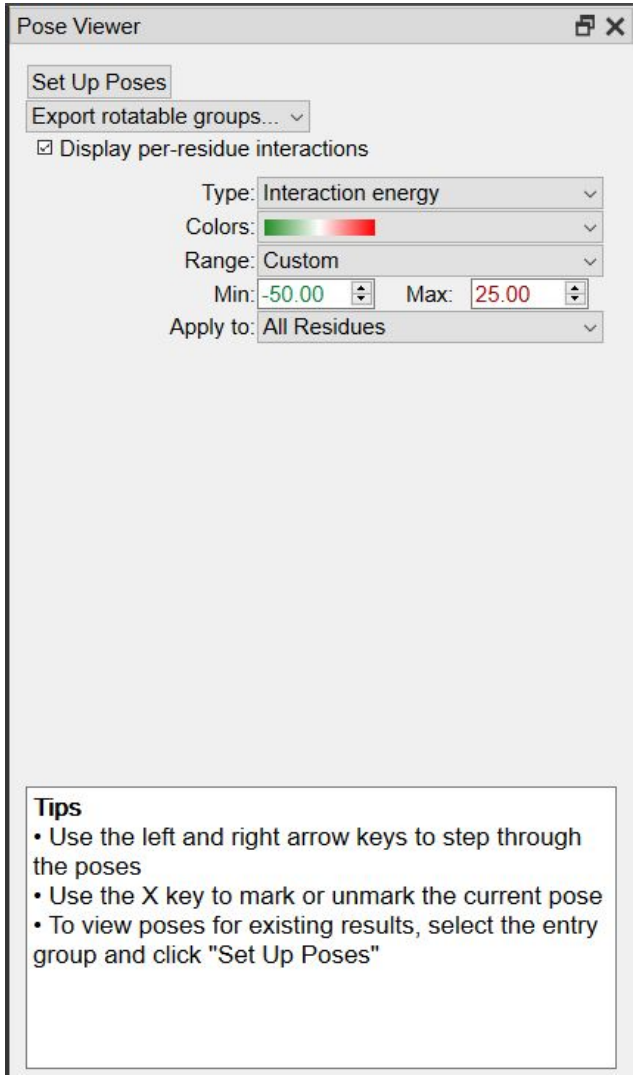


Analyzing Docking Results: Pose inspection



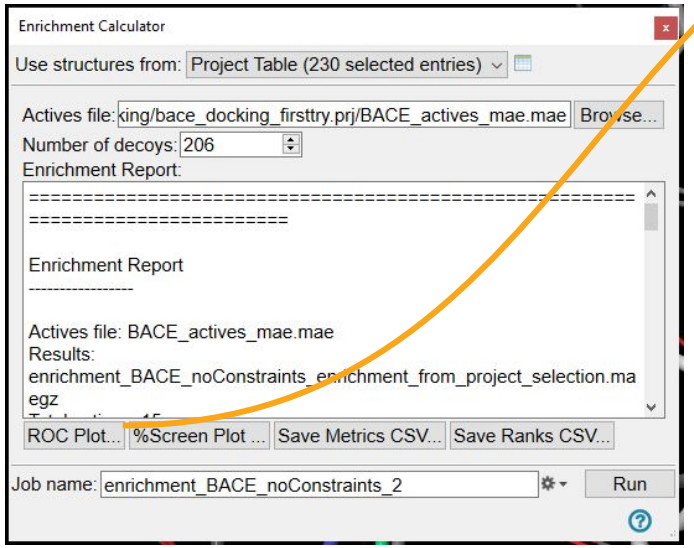
Visual inspection of poses



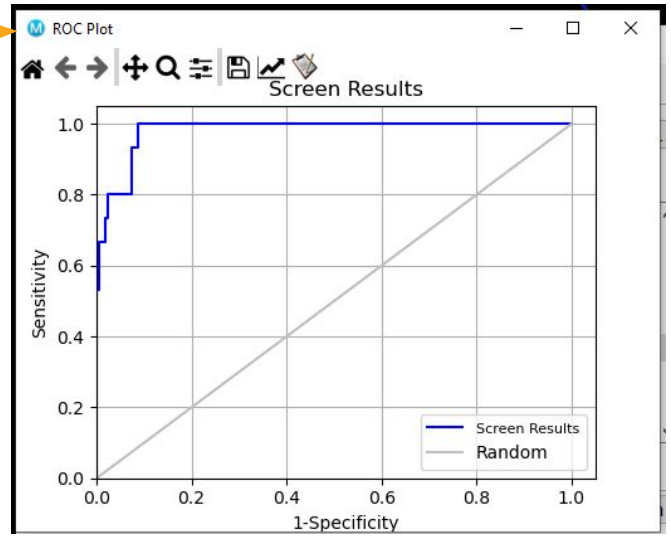


Comparing Docking Models for HTVS: Enrichment

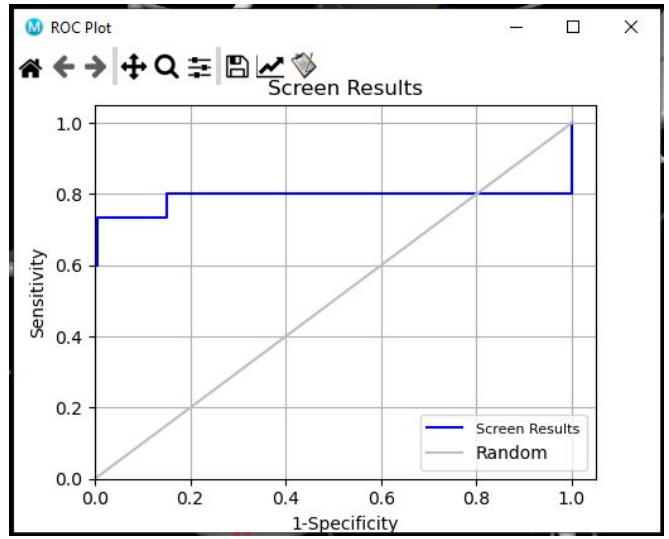
How well does the docking separate binders from non-binders?



without H-bond constraints:

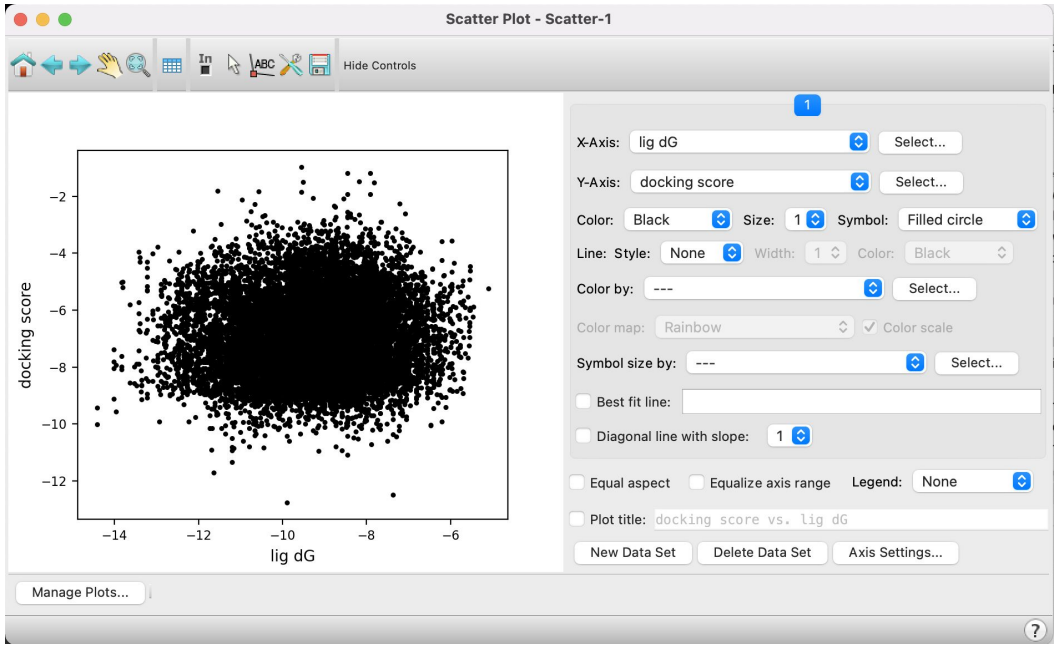


with active H-bond constraints:



Correlation of Docking Results to Binding Affinity

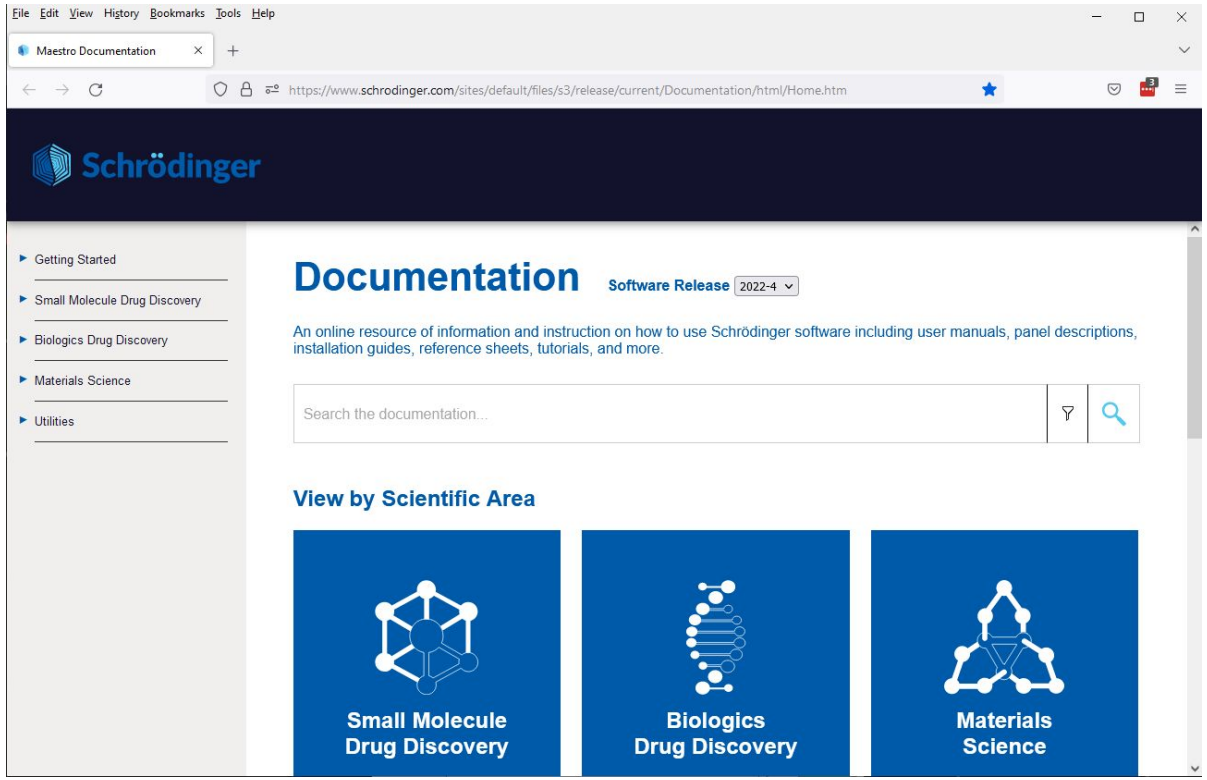
- In many compound sets, there is only a very weak correlation between docking score and experimental binding affinity or none at all.
- Generally docking score can not be used to distinguish between less and more active compounds



⇒ 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



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Thank You!

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