



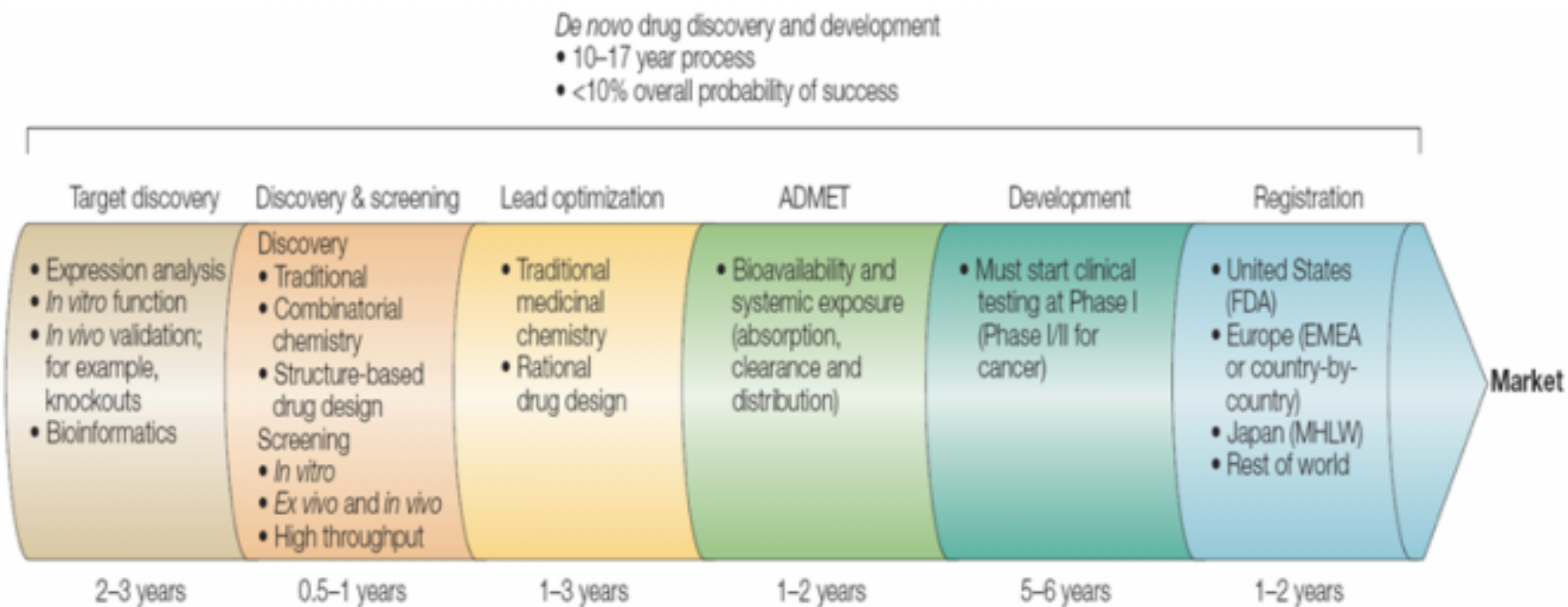
Introduction to Maestro 11

Structure Visualization and Preparation

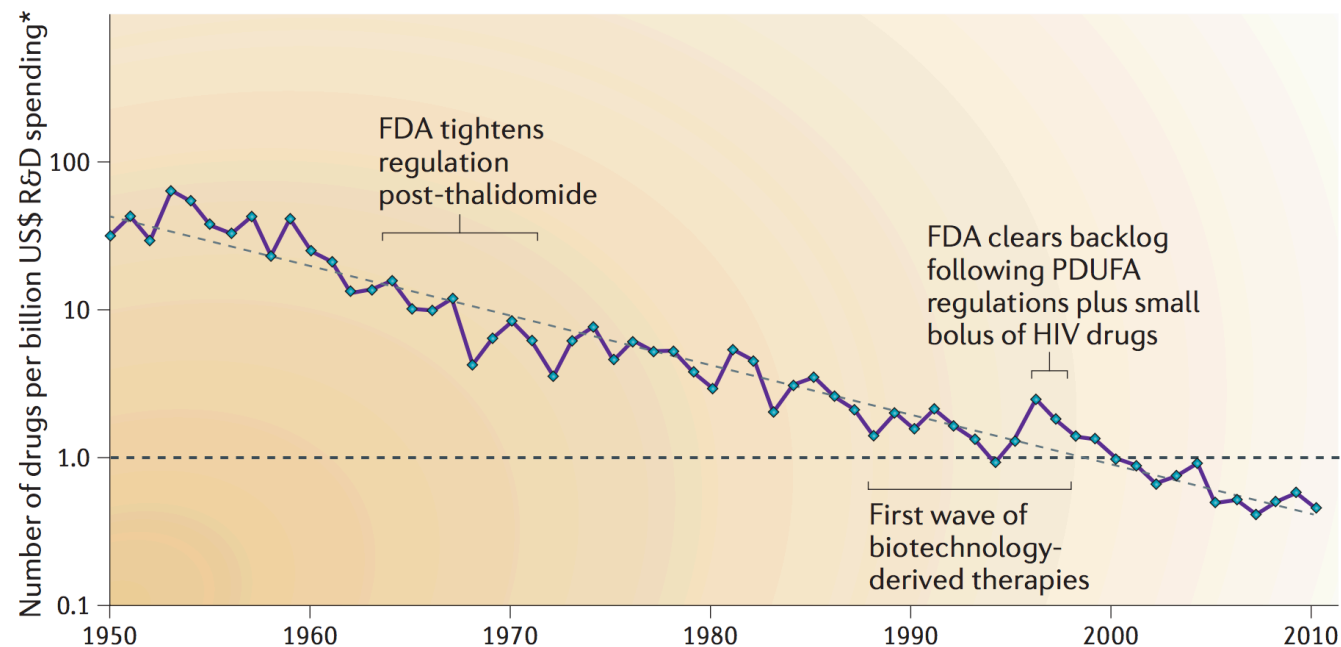
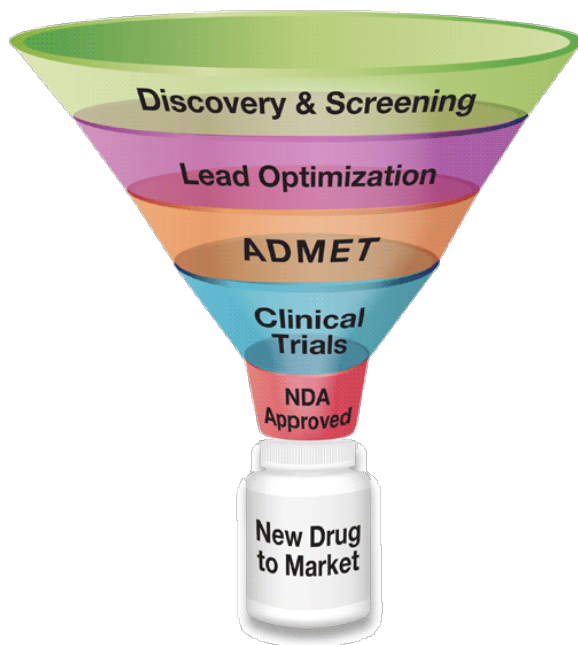
Jenny Chambers
Ana Rojas

November 13th, 2017

Background on the drug discovery pipeline



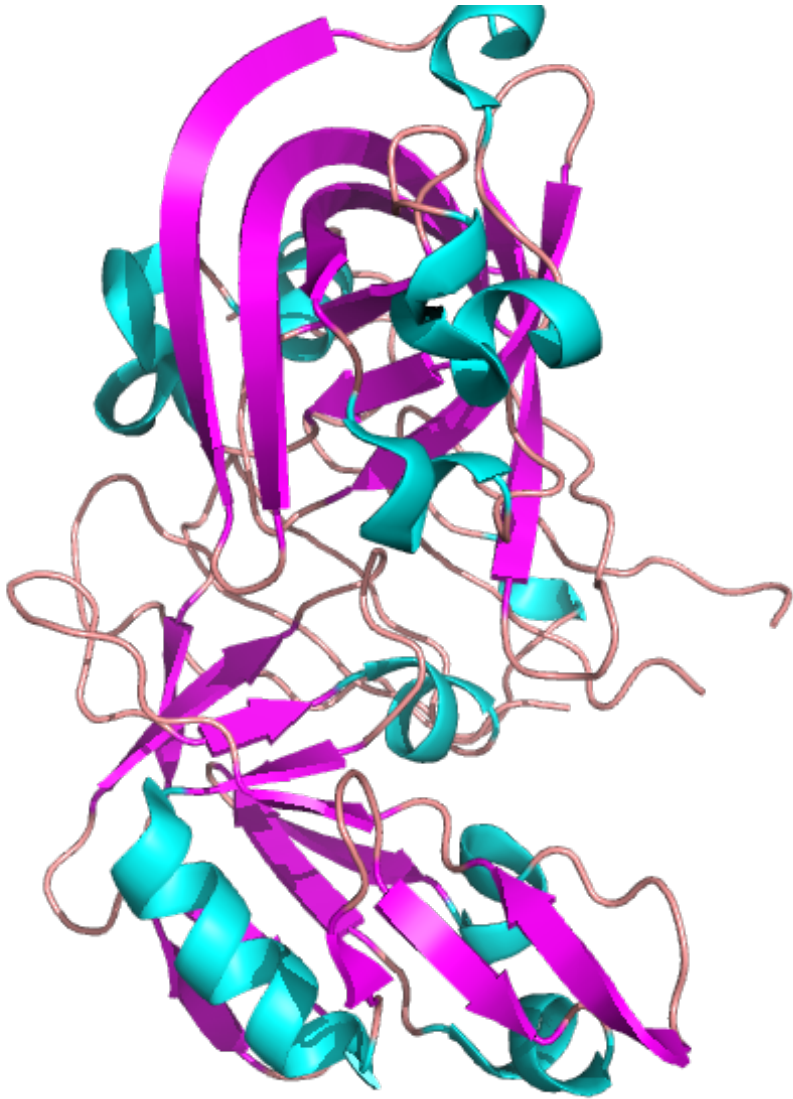
Drug Discovery is Expensive and Slow



Computer-aided drug design (CADD) can:

- Reduce the time and cost associated with preclinical development
- Inform the decision making process at each step

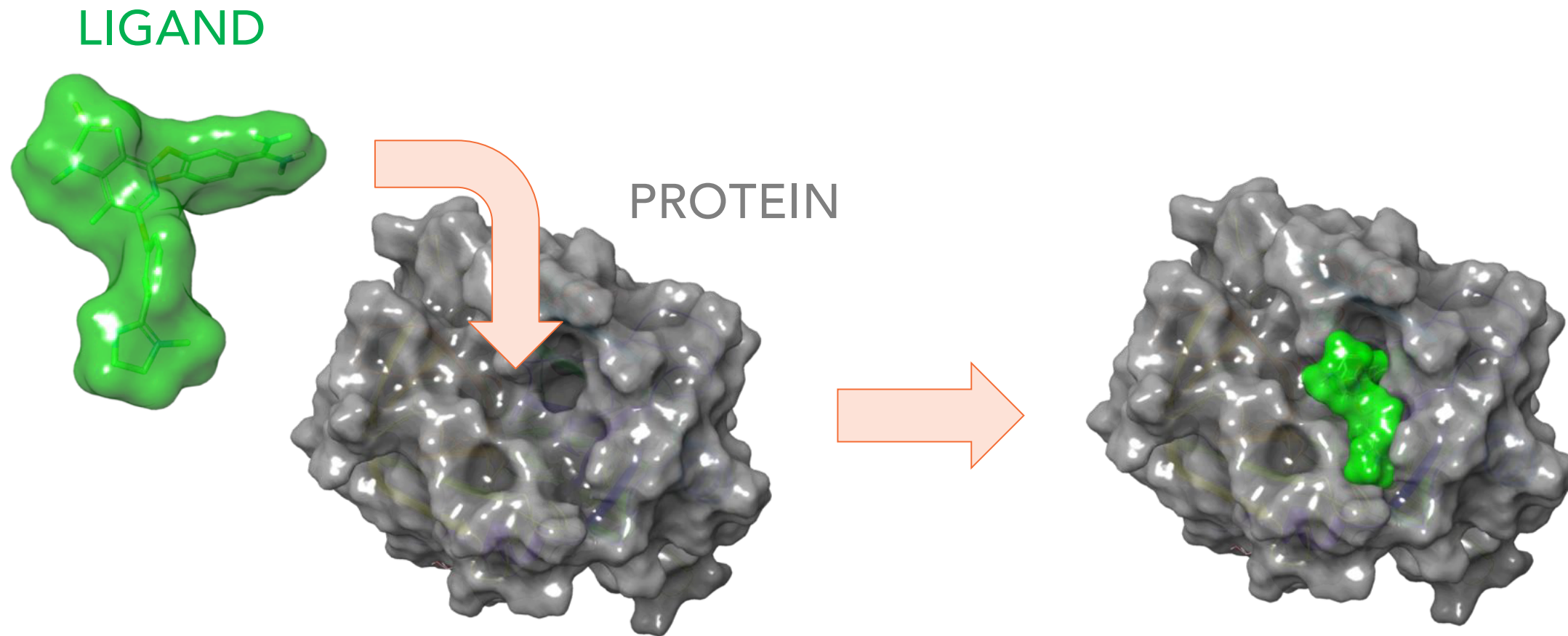
Structure-Based Drug Design is the Workhorse of CADD



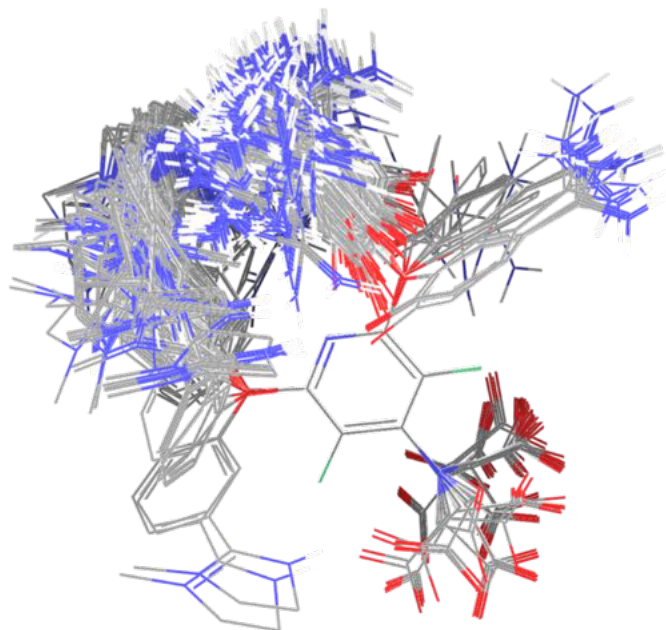
With a structure you can:

- Predict druggability
- Identify ligand binding sites and hot spots
- Virtually screen for novel chemical matter
- Optimize potency of leads
- Reduce off-target effects

Docking at its core is a shape matching problem



Ligands are flexible, and docking determines best fit based on interatomic interactions

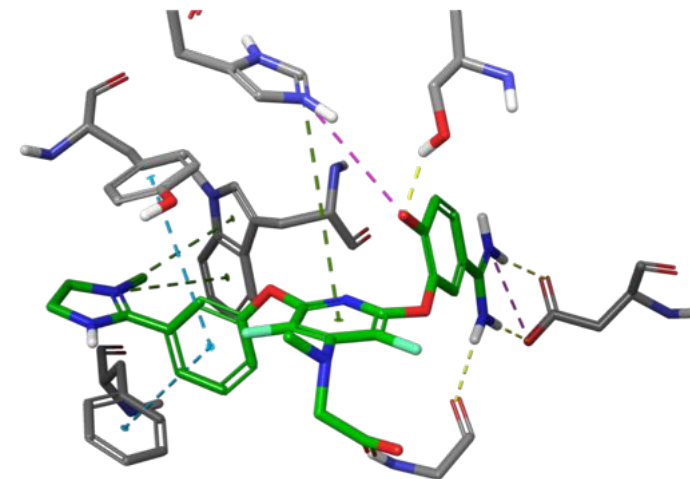


Bonding Interactions

- Bond length
- Bond angles
- Torsions

Non-Bonding Interactions

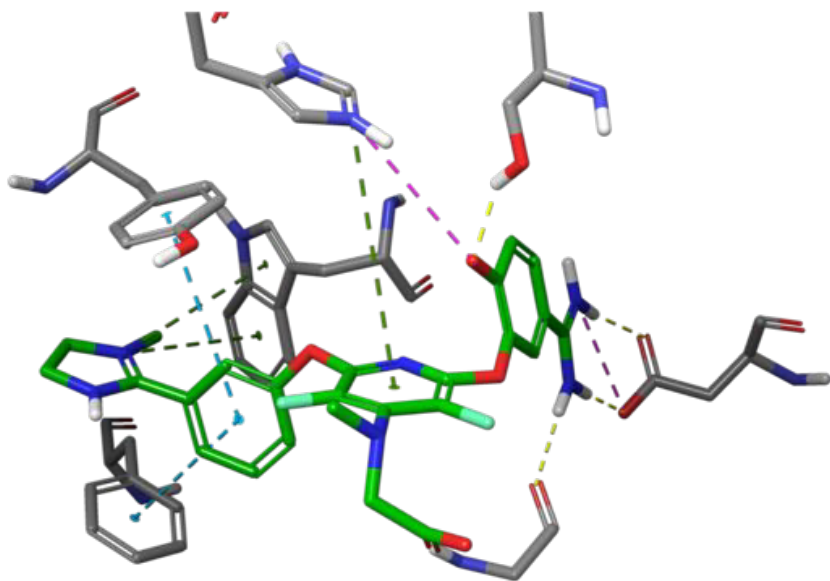
- van der Waal's interactions
- H-bonds
- Charge-Charge interactions
- pi-pi, pi-cation, etc.



Limitations of Docking

- Entropy is not accounted for
- Protein flexibility is ignored
- Solvation is not accounted for

A Docking Program Generates a...



1) A Binding Pose

A model of the orientation of the ligand in the binding site of the receptor.

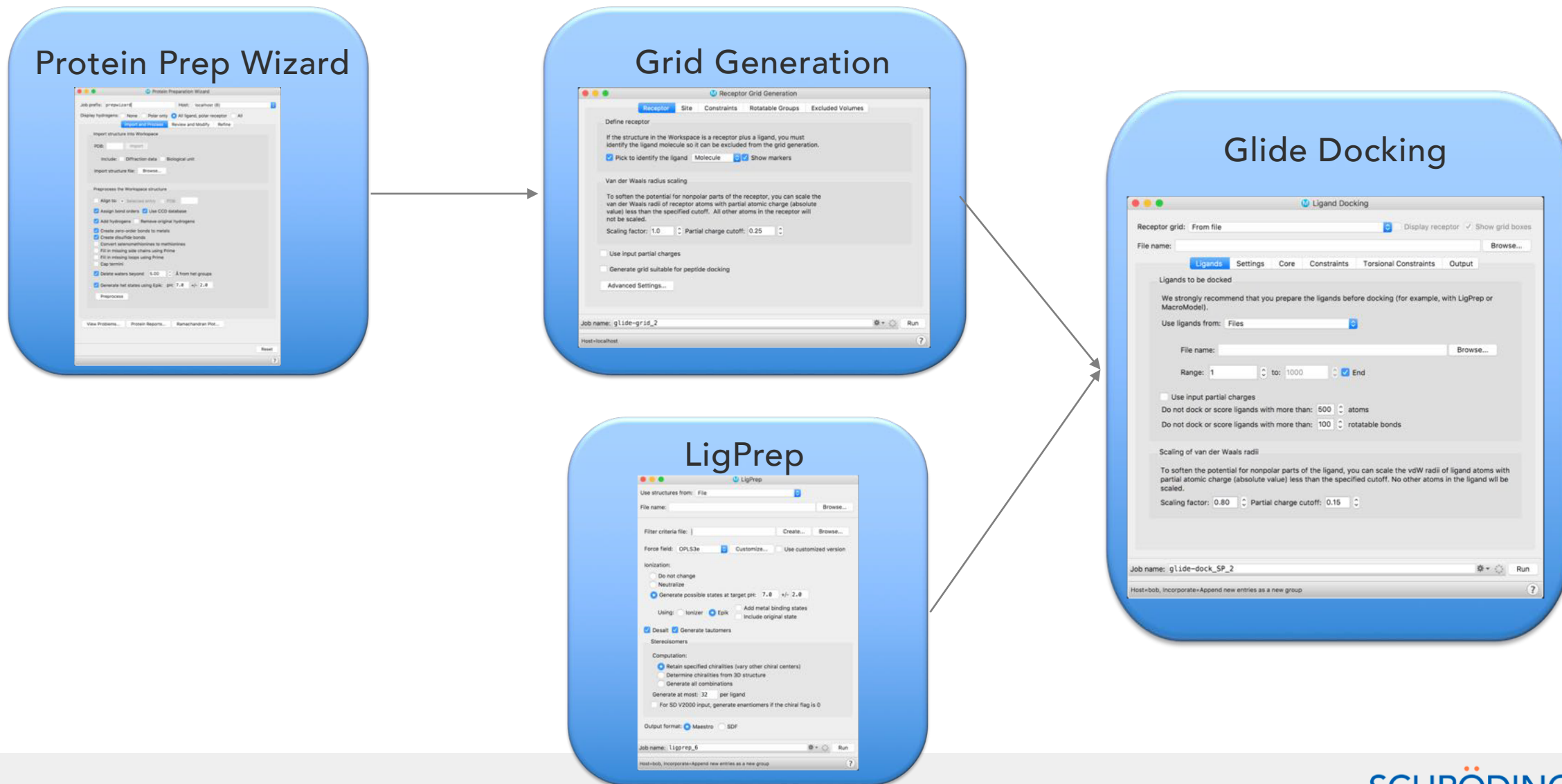
Accuracy: RMSD ~ 1 Å to Co-crystal Structures

2) Docking Score

A numerical value representing the quality of the pose. Often presented as binding energy.

Accuracy: Good for enrichment, High false positive rate, does not correlate with $\Delta G_{\text{binding}}$

How to create docking models with Glide:



Glide Docking Workflow:

Protein Prep Wizard



Grid Generation

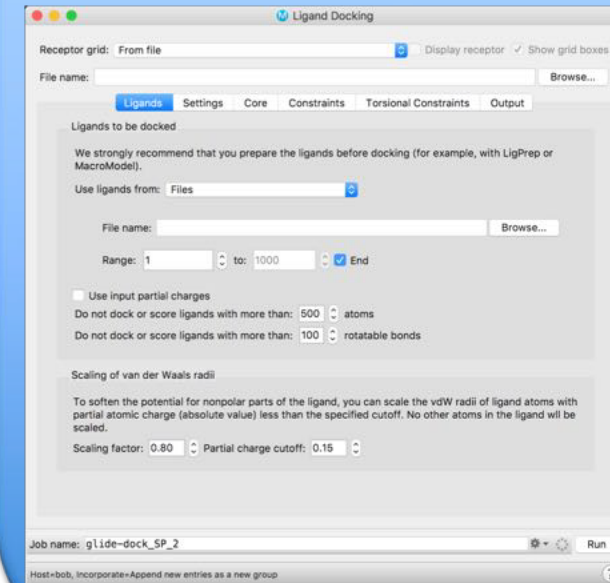


Dealing with
crystal model
limitations

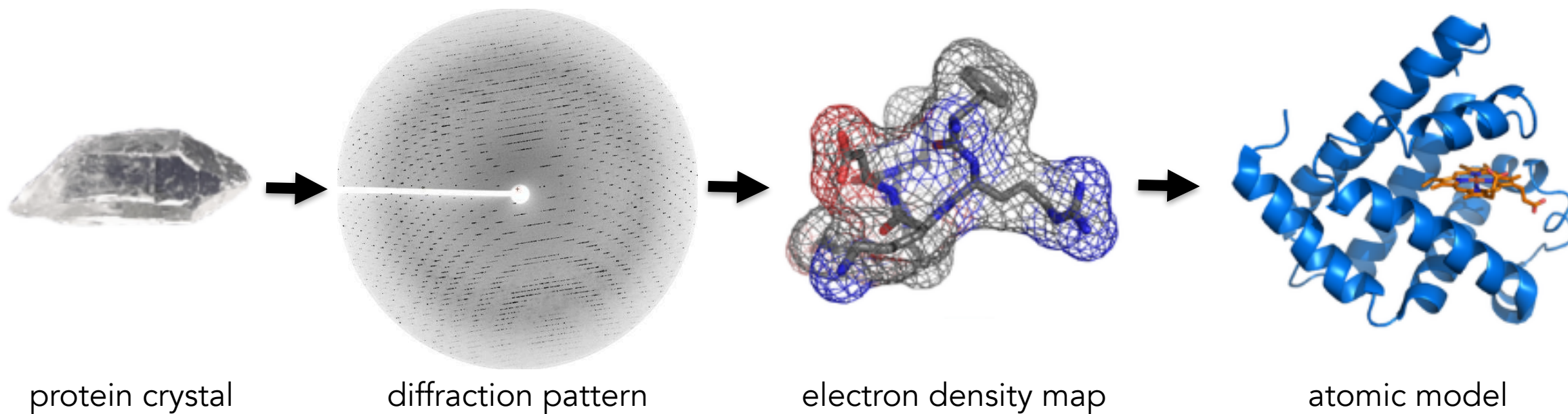
LigPrep



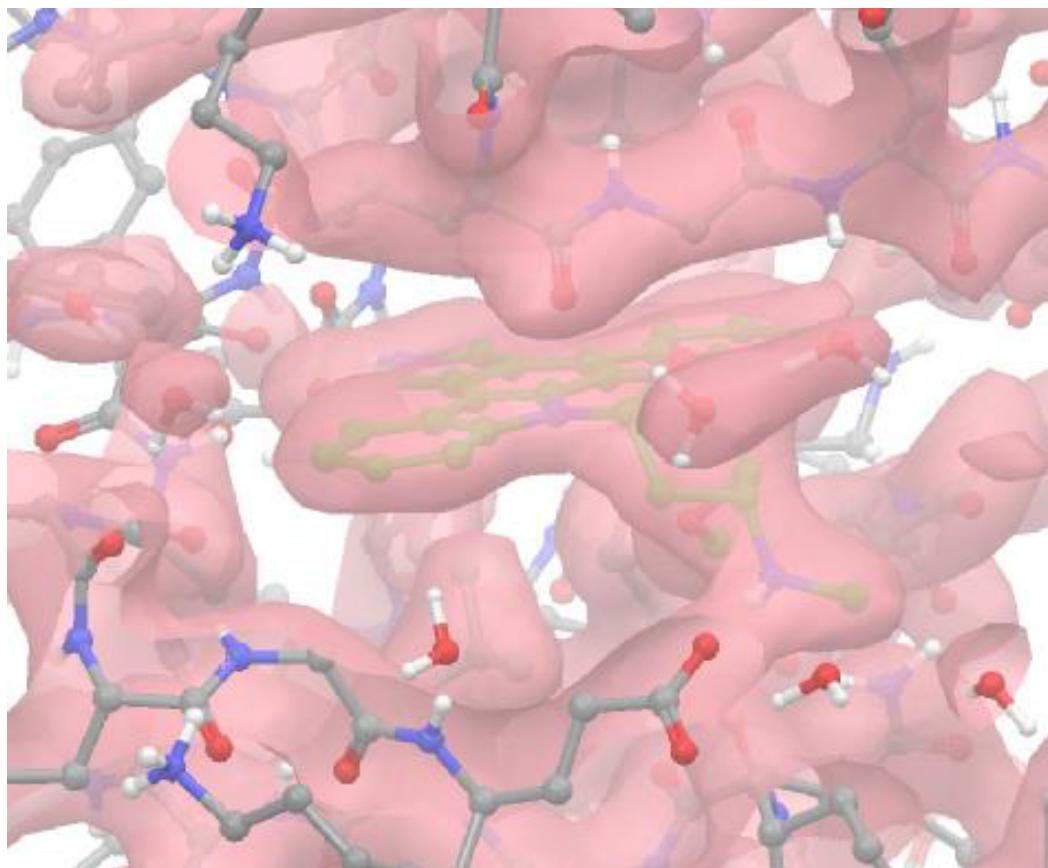
Glide Docking



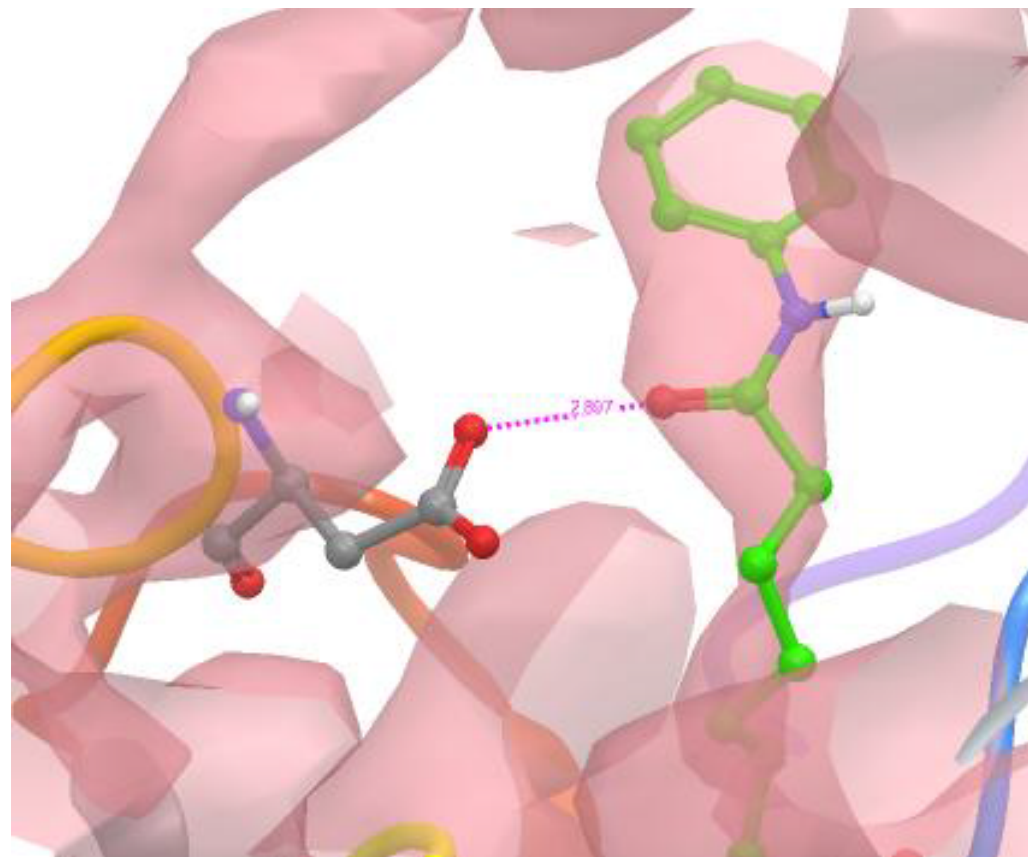
Most SBDD Projects Utilize Crystal Structures



Limitations to crystal structure models



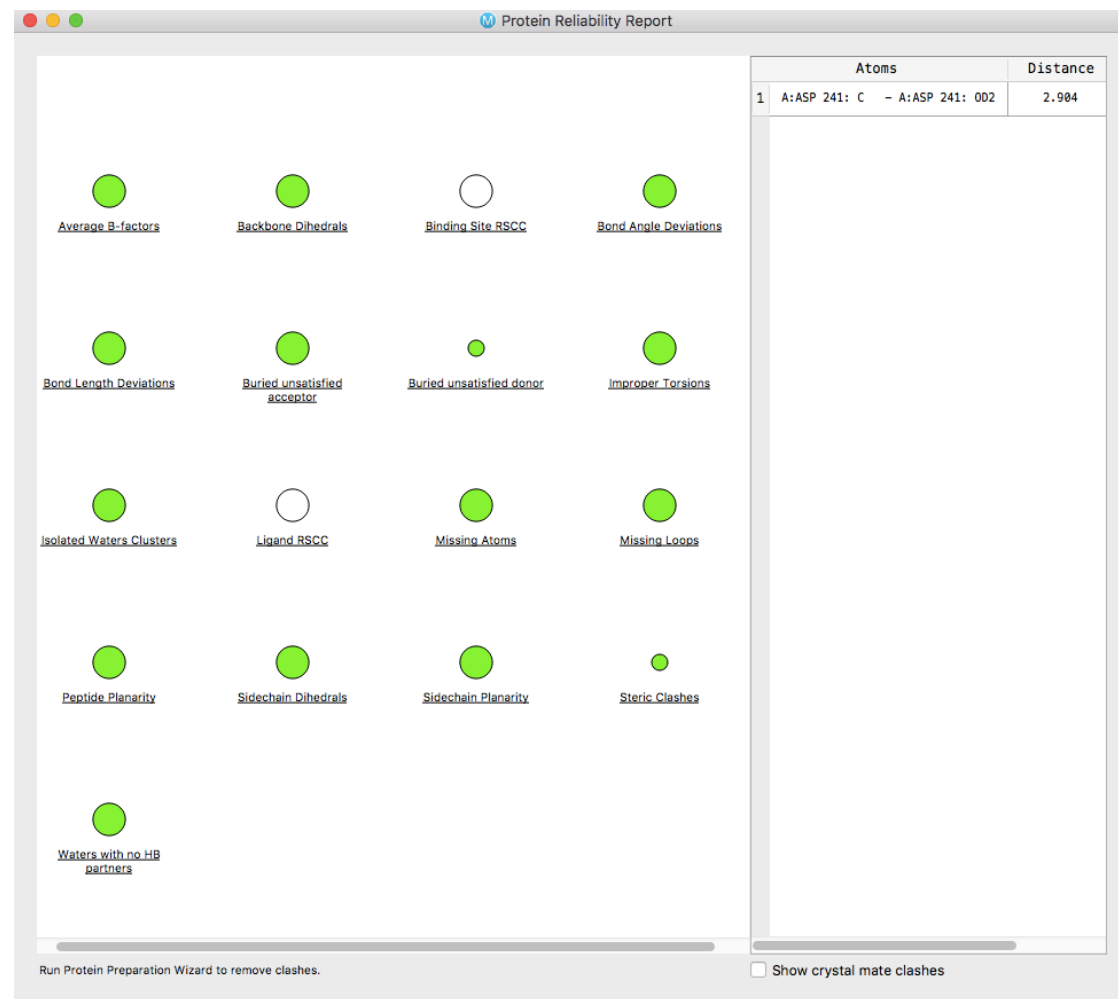
In this case, the ligand density is relatively unambiguous.



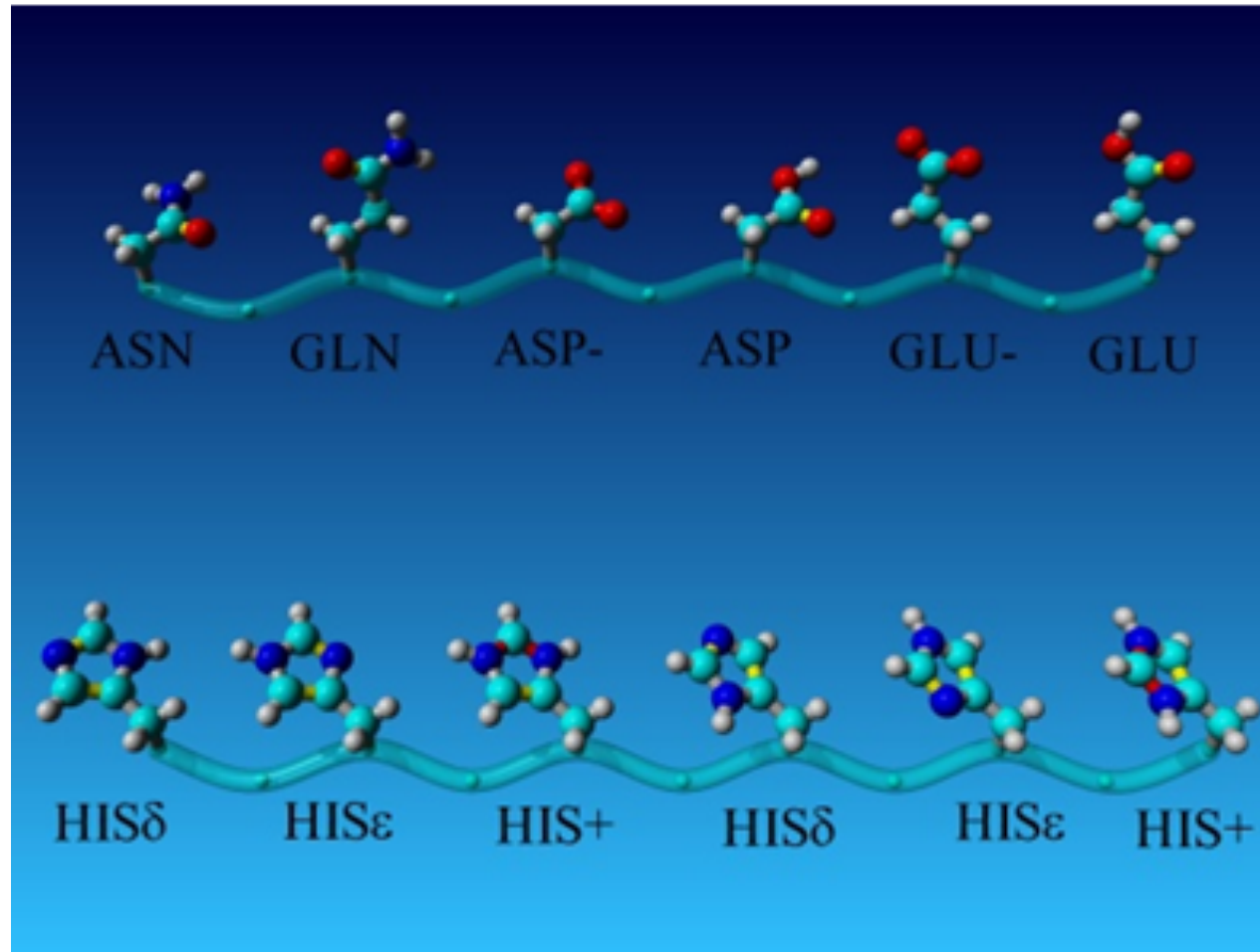
In this case the density is missing, which may result in misleading information.

Good CADD Starts with Good Science: Minimizing model limitations

1. The quality of your structure matters
2. The conformational state of your structure matters
3. The design of your experiment matters



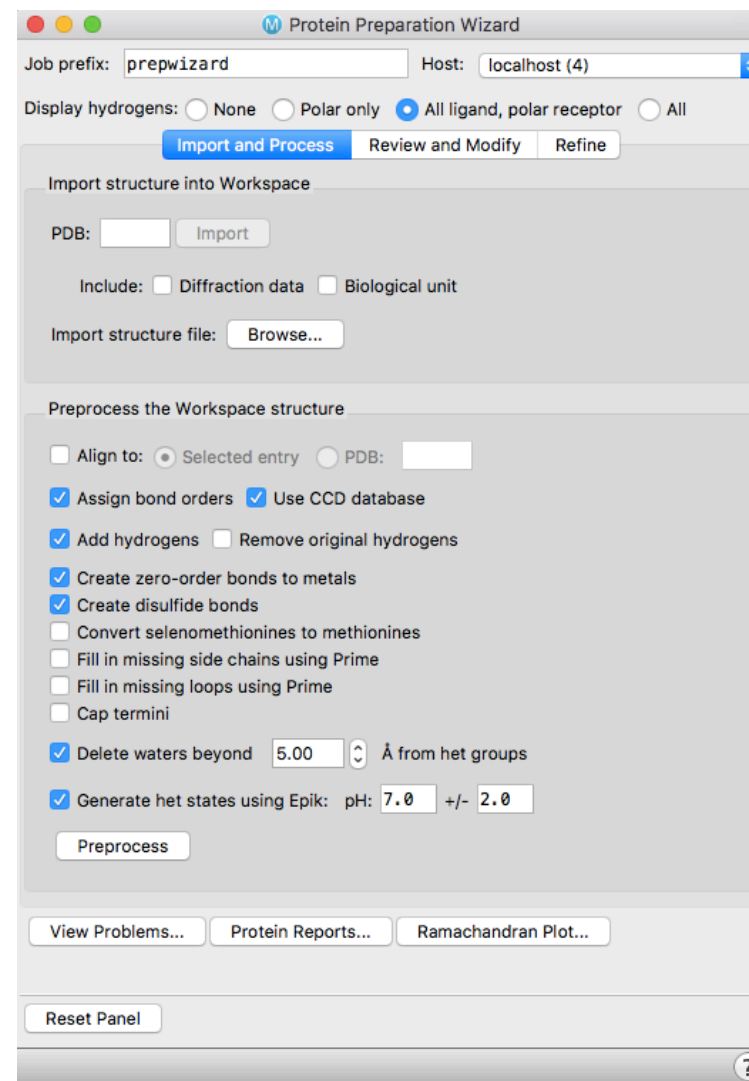
Limitations of crystal structure models continued: Tautomeric states.



pH-dependent tautomeric and protonation states for His, Glu, and Asp

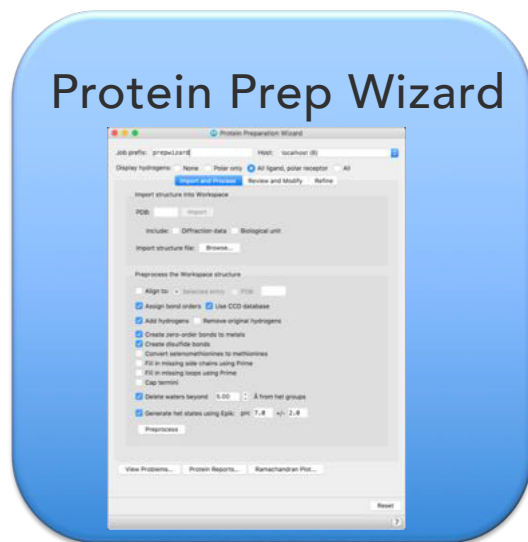
Protein Preparation Wizard Augments Crystal Data

- **Fix common problems**
 - Protonation
 - Missing side chains
 - Missing loops
- **Remove unwanted molecules**
 - Counterions, artifacts of crystallography, waters
 - Biologically relevant?
- **Optimize your model structure**
 - Hydrogen-bond optimization
 - Restrained minimization

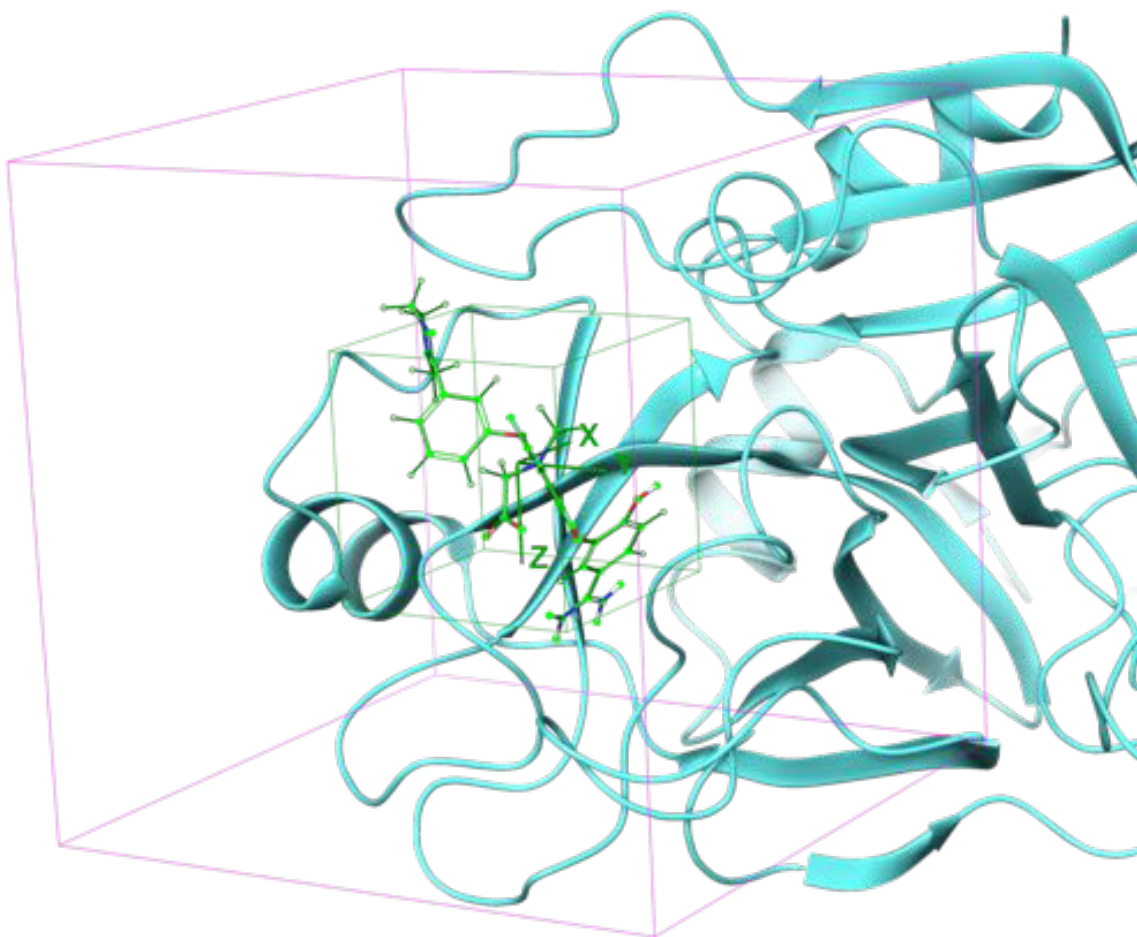


Glide Docking Workflow:

Model a protein for the computer
to interpret in docking



What is the role of the grid?



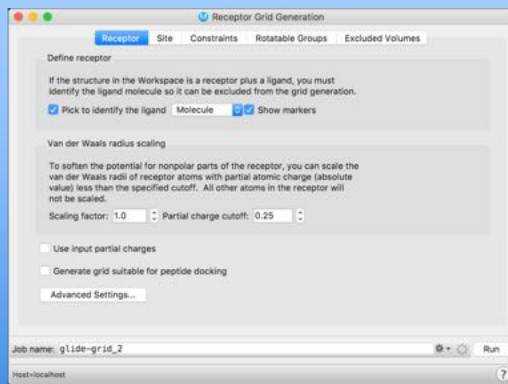
- Protein represented as a series of grids
 - Site point grid (10\AA^3 by default)
 - Chemscore grids
 - Adaptive Coulomb/vdW grids
- Grids precomputed once and applied for each ligand
- Ligand “center” must be found within inner box and all ligand atoms must be found within outer box
 - Inner box: 10\AA^3 by default
 - Outer box: $(12\text{\AA} + 0.8 * \text{ligand diameter})^3$ by default
- With energy-based grids ligand interaction energy for atom in a grid point evaluated using trilinear interpolation
- Want to use Goldilocks inner grid, i.e. smallest grid that will find desired poses

Glide Docking Workflow:

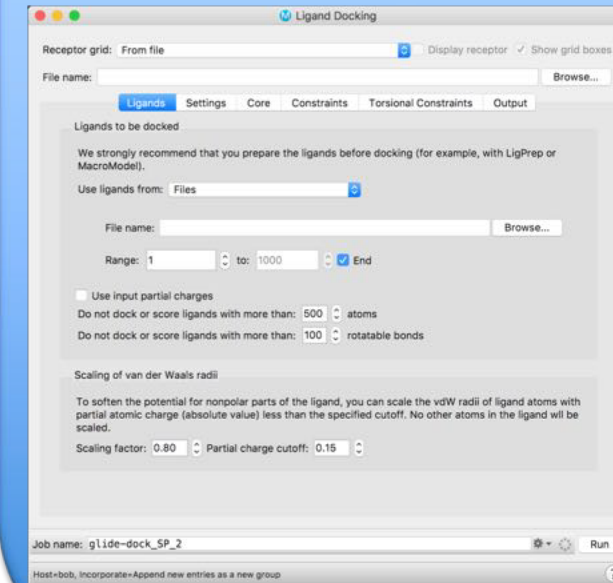
Protein Prep Wizard



Grid Generation



Glide Docking



LigPrep



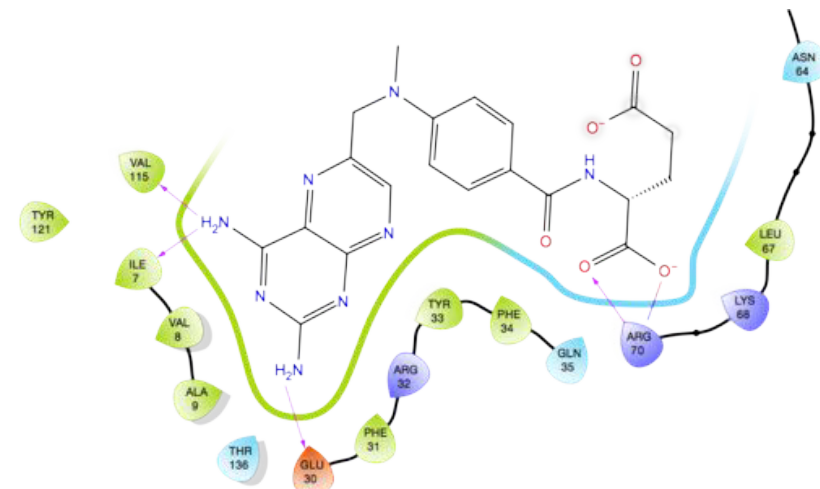
Ligand states are calculated in water, which may not adequately recapitulate active site

Required Inputs for Protein-Ligand Docking - Ligands

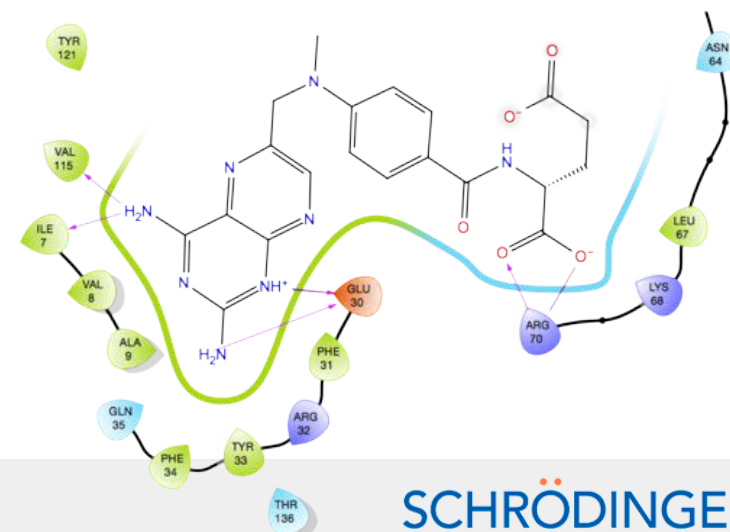
- Glide will only dock ligand states that are provided
- Recommendations for prepared ligand structures
 - Use LigPrep to generate low energy ionization/tautomeric states for ligands
 - Epik state penalties that estimate free energy required to generate ionization state in water with corrections for interaction with metal sites
 - 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)

State penalty=0.0 kcal/mol



State penalty=1.43 kcal/mol

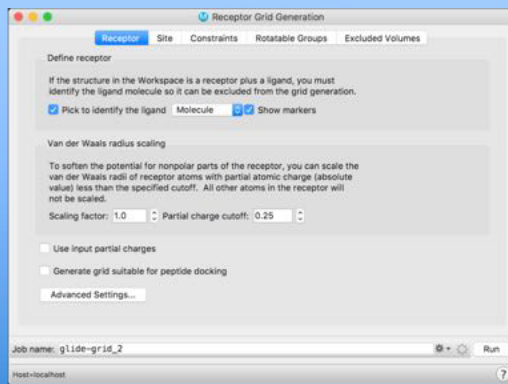


Glide Docking Workflow:

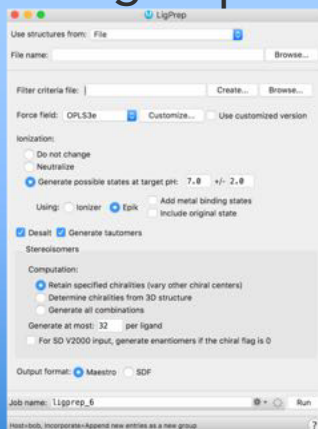
Protein Prep Wizard



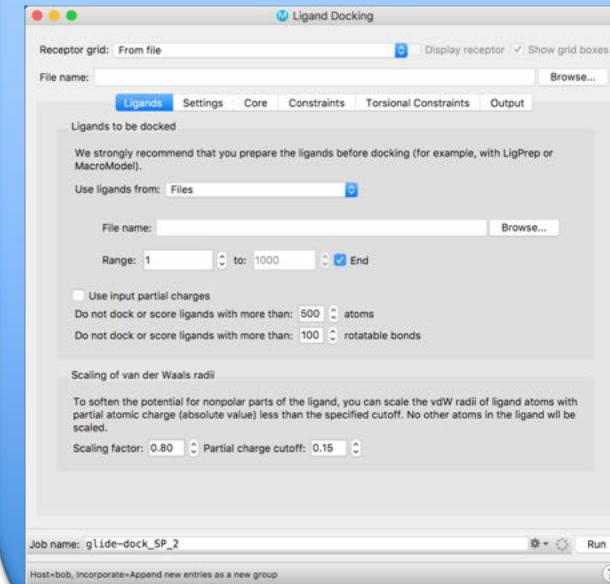
Grid Generation



LigPrep

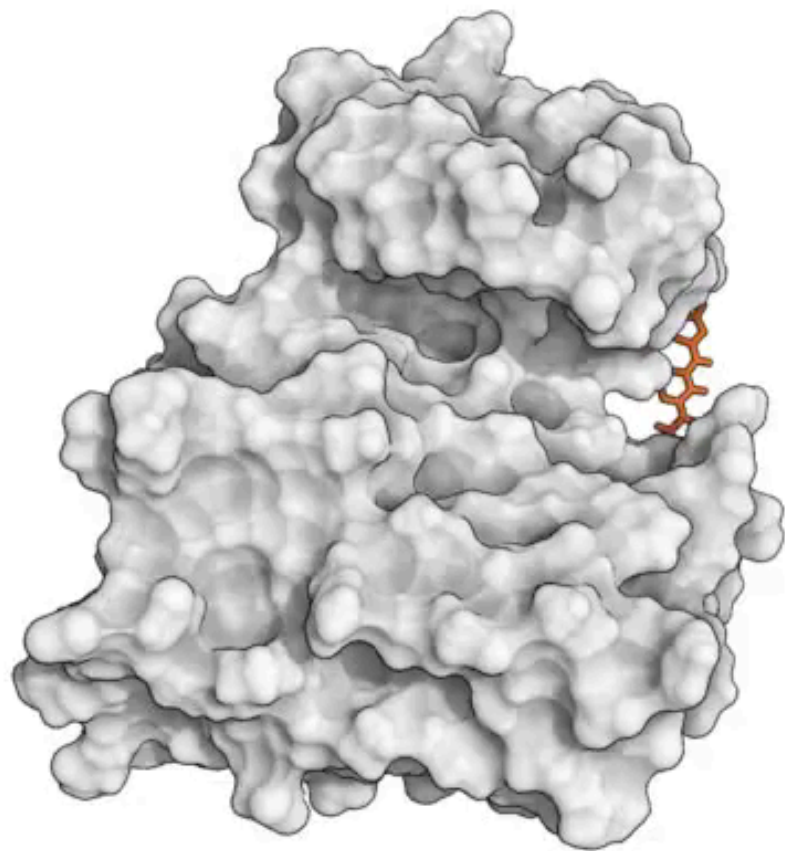


Glide Docking



Not necessarily accounting
for desolvation energies,
entropy or protein
dynamics

Proteins are flexible which is a limitation in Glide based docking on its own... but when combined with molecular dynamics can be a powerful tool!



A molecular simulation visualization showing a protein structure represented by grey ribbons and a large orange surface. A ligand molecule is shown in a stick representation, with atoms colored by element (carbon in grey, nitrogen in blue, oxygen in red, sulfur in yellow, phosphorus in green). The text "Maestro 11" is overlaid in white on the orange surface.

Maestro 11

The Maestro 11 Interface is User Friendly

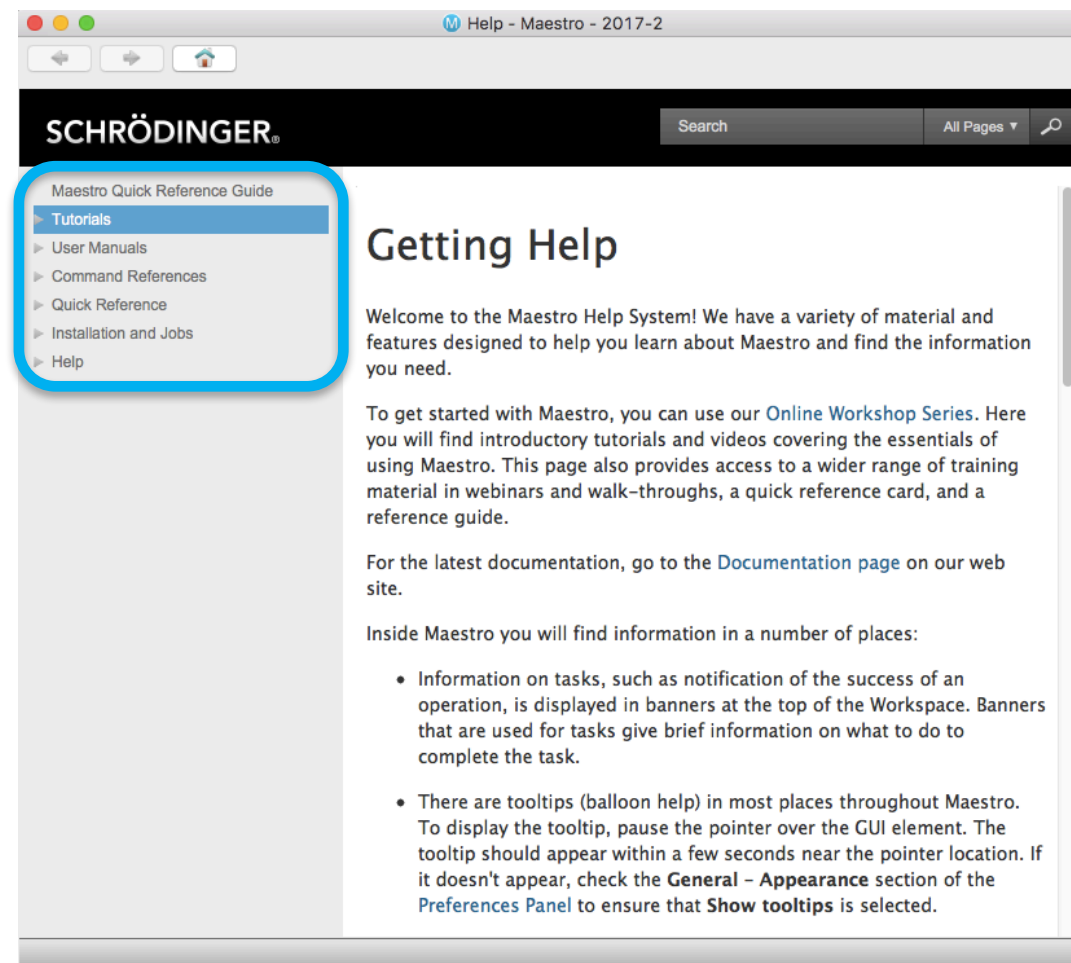
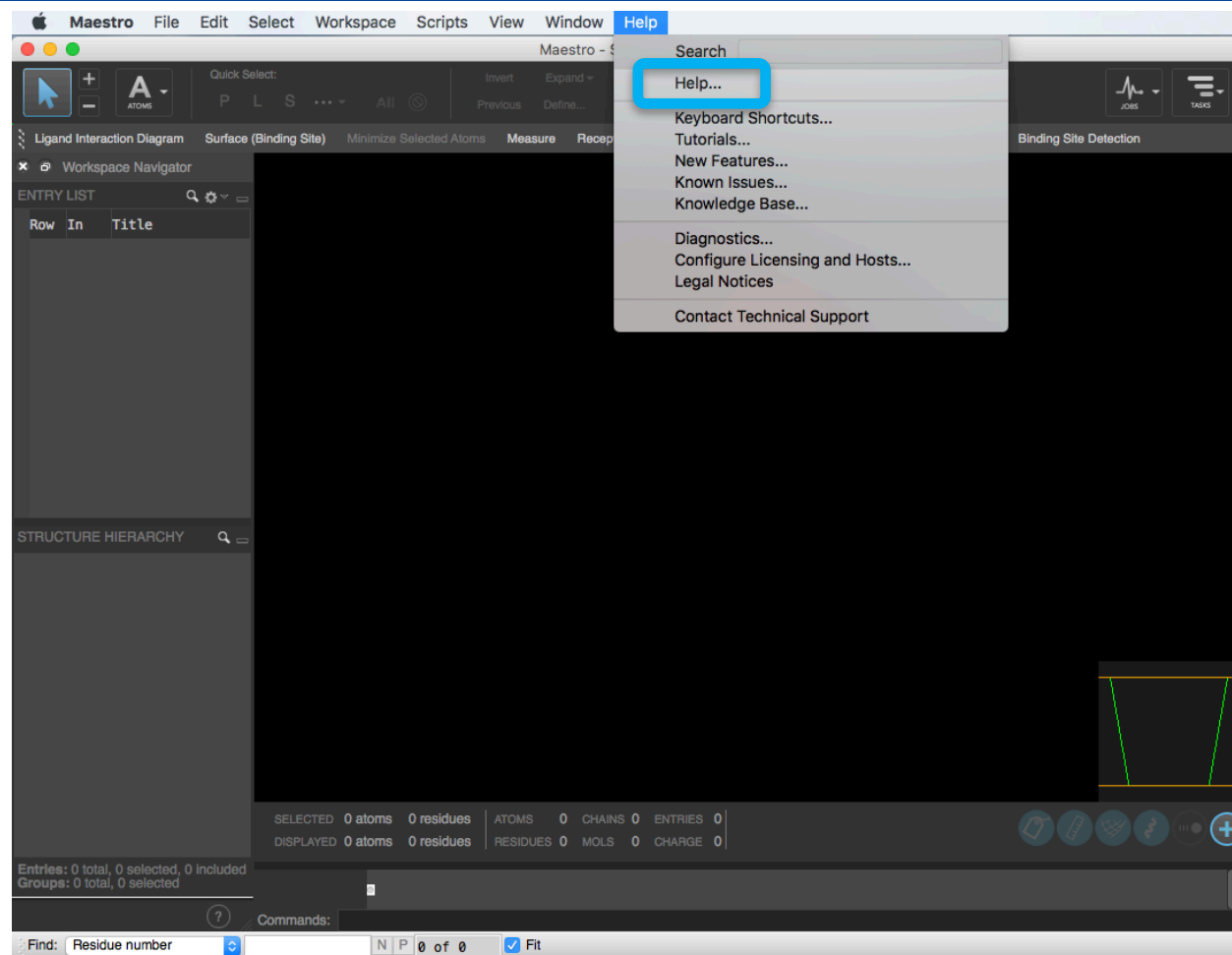
Selection Toolbar
Favorites Toolbar

The screenshot displays the Maestro 11 interface with several key components labeled:

- Selection Toolbar** and **Favorites Toolbar**: Located at the top left, containing icons for selection and favorite management.
- Workspace Navigator**: A panel on the left showing a list of entries in the workspace, with 'LigandMCM_copy' selected.
- Style Toolbox**: A panel on the right containing various styling options for atoms, ribbons, and surfaces.
- Task Tool**: A panel on the right containing various task-oriented tools.
- Workspace**: The central 3D view showing a protein structure with a ligand bound to it.
- 2D Overlay**: A panel at the bottom left showing a 2D chemical structure overlay of the selected ligand.
- Status Bar**: A panel at the bottom showing system information such as 'SELECTED 3638 atoms 227 residues' and 'DISPLAYED 81 of 3638 2 of 227'.

Workspace
Configuration
Toolbar

The Help Menu Contains More Detail



Learn More with the Training Portal

The screenshot shows the Schrödinger website home page. The 'SUPPORT' menu is highlighted with a blue box, containing links for Knowledge Base, Documentation, Scripts, Python API, Known Issues, Supported Platforms, Seminars, Training, Contact Support, and License Information. A blue box also highlights a 'Training' banner featuring a person in a classroom setting, with the text 'SCHRÖDINGER Training WORKSHOPS • TRAINING VIDEOS'. Below the banner is a 'REGISTER NOW' button and a 'READ MORE >' link. At the bottom, there is a 'GET OUR NEWSLETTER' section with an email input field and a 'GO' button.

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The screenshot shows the Schrödinger Training portal page. The header includes the Schrödinger logo and navigation links: HOME, PRODUCTS & SERVICES, SCIENCE, SUPPORT, DOWNLOADS, ABOUT. The main content area features a large image of a person in a classroom setting with the text 'SCHRÖDINGER Training WORKSHOPS • TRAINING VIDEOS' overlaid.

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Learn



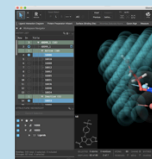
VIDEOS

TUTORIALS

SEMINARS

PRESENTATIONS

Maestro 11



Maestro 11 is the culmination of years of research and development. By working closely with our users, Maestro 11 was created to be the user environment that is both intuitive and allows our users to get work done efficiently.

To help you quickly get acquainted with Maestro 11, we have put together an eight-part series in which we demonstrate and explain the tools. Each fast-paced session includes a recorded webinar and an annotated guide, so you can follow along or practice the exercises on your own.

GET STARTED

Use Our List of Publications to Generate Ideas

The screenshot shows the Schrödinger website interface. The left sidebar contains a navigation menu with 'Publications' highlighted. The main content area features a search bar and filter options. The 'Results' section displays a list of publications with columns for 'Publications', 'Product(s) Referenced', and 'Publication Year'.

Publications	Product(s) Referenced	Publication Year
• "Estimation of charge carrier mobility in amorphous organic materials using percolation corrected random-walk model" Evansa, D.R.; Kwak, H.S.; Giesen, D.J.; Goldberg, G.; Halls, M.D.; Oh-ee, M., <i>Organic Electronics</i> , 2016, 29, 50-56	Desmond, MS Jaguar	2016
"Towards understanding the unbound state of drug compounds: implications for the intramolecular reorganization energy upon binding" Foloppe, N.; Chen, I., <i>Bioorg. Med. Chem.</i> , 2016, (16), 30172-9	Desmond, MacroModel	2016
• "Prediction of protein-ligand binding poses via a combination of induced fit docking and metadynamics simulations" Clark, A.J.; Tiwary, P.; Borrelli, K.; Feng, S.; Miller, E.B.; Abel, R.; Friesner, R.A.; and Berne, B.J., <i>J. Chem. Theory Comput.</i> , 2016, , DOI: 10.1021/acs.jctc.6b00201	Induced Fit	2016
• "Simple Predictive Models of Passive Membrane Permeability Incorporating Size-Dependent Membrane-Water Partition" Leung, S. S. F., Sindhikara, D. J., and Jacobson, M. P., <i>J. Chem. Inf. Model.</i> , 2016, 56(5), 924-929	Membrane Permeability	2016
• "OPLS3: A Force Field Providing Broad Coverage of Drug-like Small Molecules and Proteins" Harder, E.; Damm, W.; Maple, J.; Wu, C.; Reiboul, M.; Xiang, J.Y.; Wang, L.; Lupyan, D.; Dahlgren, M.K.; Knight, J.L.; Kaus, J.W.; Cerutti, D.S.; Krilov, G.; Jorgensen, W.L.; Abel, R.; Friesner, R.A., <i>J. Chem. Theory Comput.</i> , 2016, 2 (1), 281-296	FEP+, OPLS3	2016
"Discovery and StructureActivity Relationships of a Highly Selective Butyrylcholinesterase Inhibitor by Structure-Based Virtual Screening" Dighe, S.N.; Deora, G.S.; Mora, E.; Nachon, F.; Chan, S.; Parat, M.; Brazzolotto, X.; Ross, B.P., <i>J. Med. Chem.</i> , 2016, 59, 7683-7689	Glide, Phase	2016
• "Surface Oxide Characterization and Interface Evolution in Atomic Layer Deposition of Al2O3 on InP(100) Studied by In Situ Infrared Spectroscopy" Cabrera, W.J.; Halls, M.D.; Povey, I.M.; Chabal, Y.J., <i>Journal of Physical Chemistry C</i> , 2016, 118(11), 5862	MS Jaguar	2016
"Determination of reactive properties of 1-butyl-3-methylimidazolium taurate ionic liquid employing DFT calculations" Armaković, S.; Armaković, S.J.; Vraneš, M.; Tot, A.; Gadžurić, S., <i>Journal of Molecular Liquids</i> , 2016, 222, 796	MS Jaguar	2016
"Investigation of boron modified graphene nanostructures; optoelectronic properties of graphene nanoparticles and transport properties of graphene nanosheets" Armaković, S.; Armaković, S.J., <i>Journal of Physics and Chemistry of Solids</i> , 2016, 98, 156	MS Jaguar	2016
"Coordination compounds of a hydrazone derivative with Co(II), Ni(II), Cu(II) and Zn(II): synthesis, characterization, reactivity assessment and biological evaluation"	MS Jaguar	2016

Maestro 11 Useful Video Links

- **Maestro 11 Quick Start Guide**
 - <https://www.schrodinger.com/training/maestro11/home>
- **Maestro 11 Short Videos**
 - <https://www.schrodinger.com/training/videos/maestro-11>
- **Maestro 11 Introductory Webinar Series**
 - <https://www.schrodinger.com/seminars/archives/1238/introductory-series>
- **Maestro 11 Advanced Webinar Series**
 - <https://www.schrodinger.com/seminars/archives/1239/advanced>
- **Protein Preparation Wizard**
 - <https://www.schrodinger.com/training/videos/protein-preparation>
- **Other Small-Molecule Drug Discovery Tools**
 - <https://www.schrodinger.com/training/videos/small-molecule-drug-discovery>

Other Education Resources are Available Online

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

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