



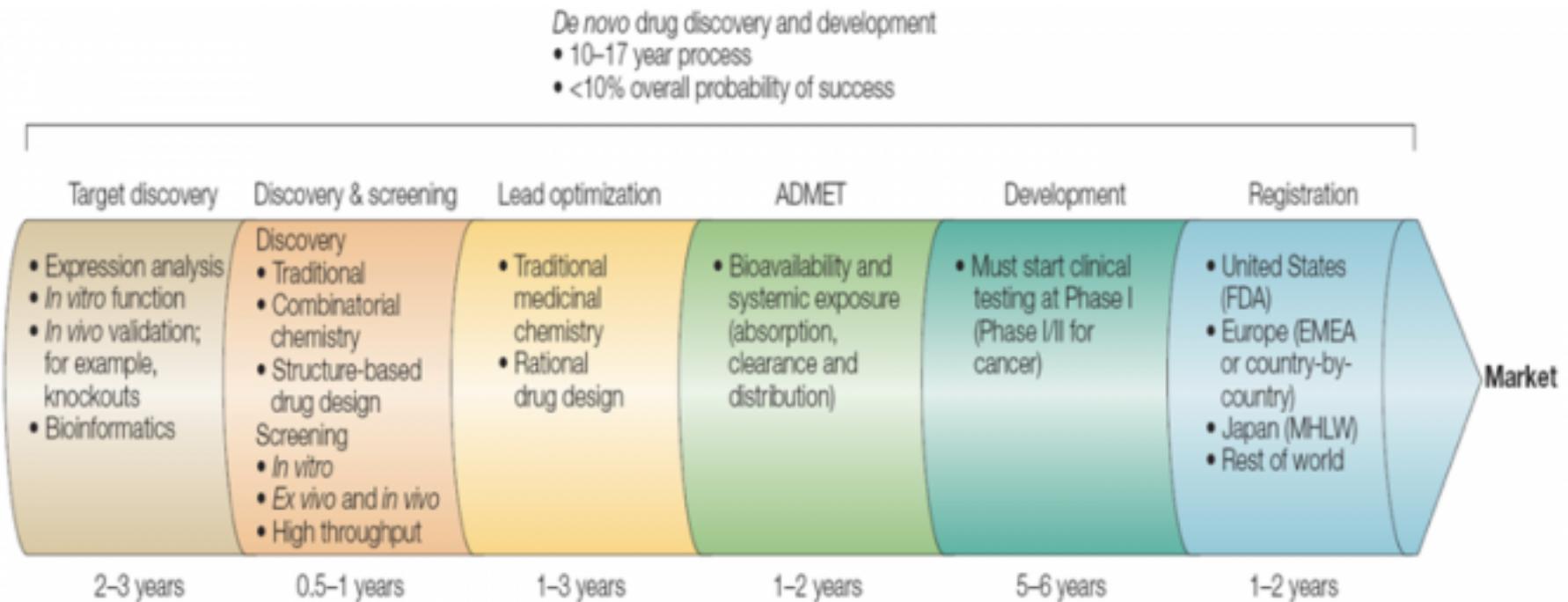
Introduction to Maestro 11

Structure Visualization and Preparation

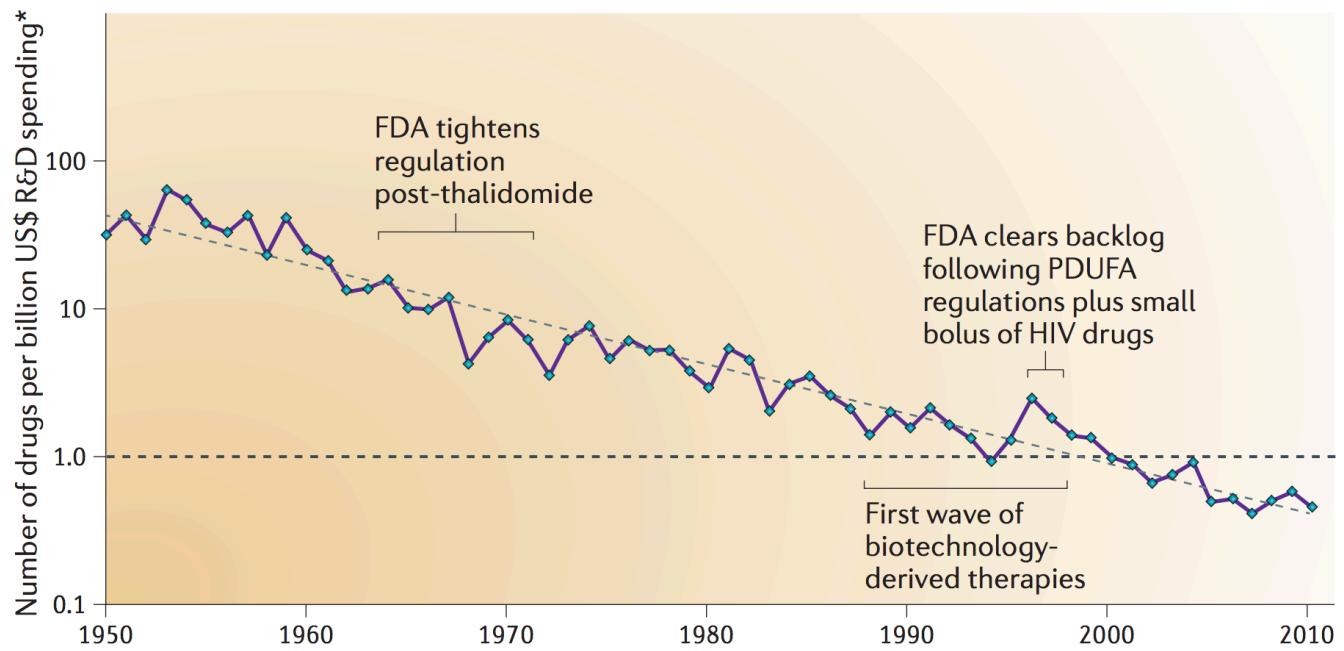
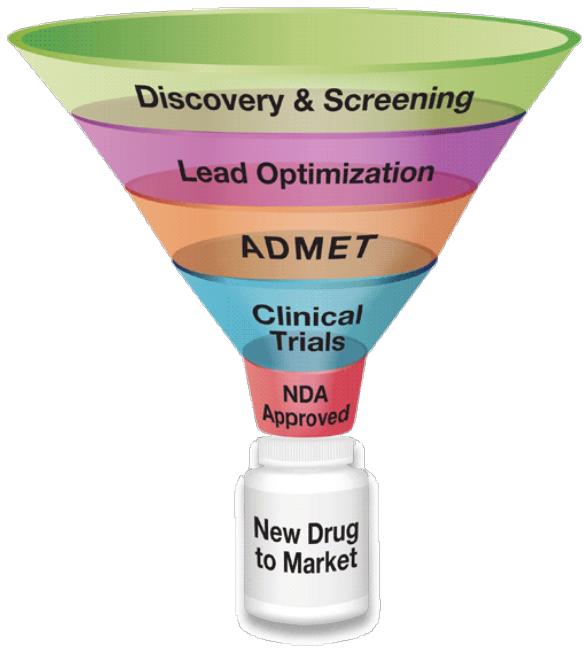
Jenny Chambers
Ana Rojas

November 13th, 2017

Background on the drug discovery pipeline



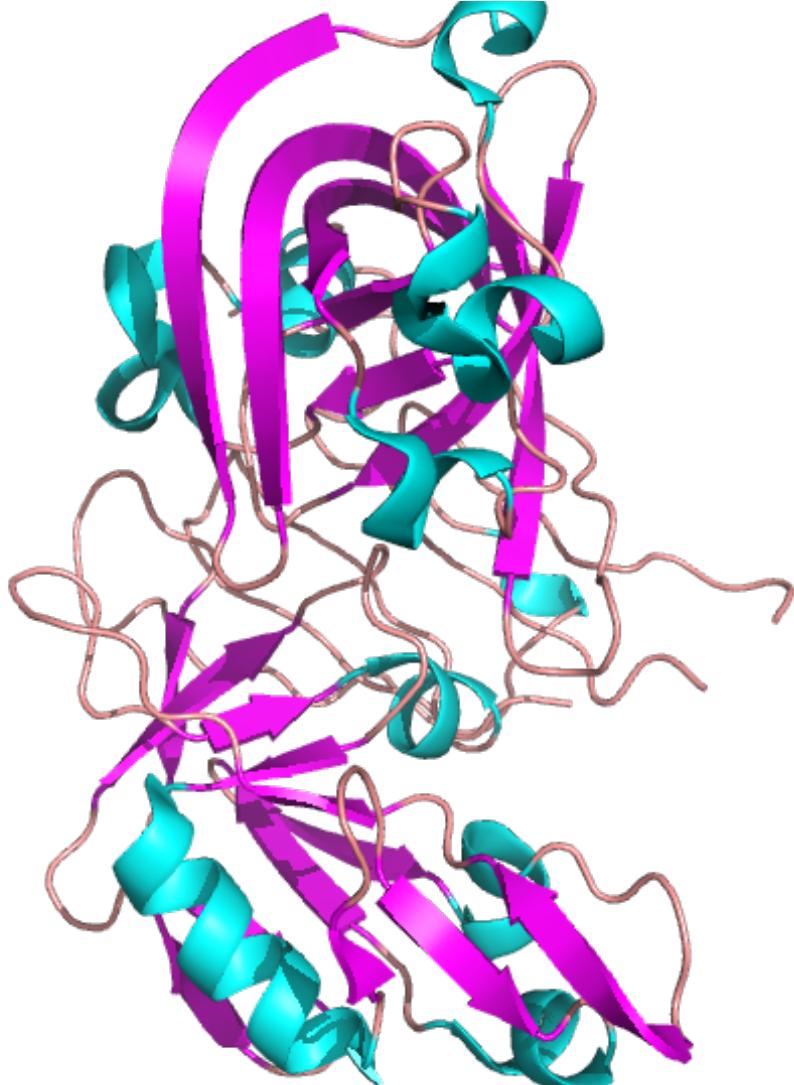
Drug Discovery is Expensive and Slow



Computer-aided drug design (CADD) can:

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

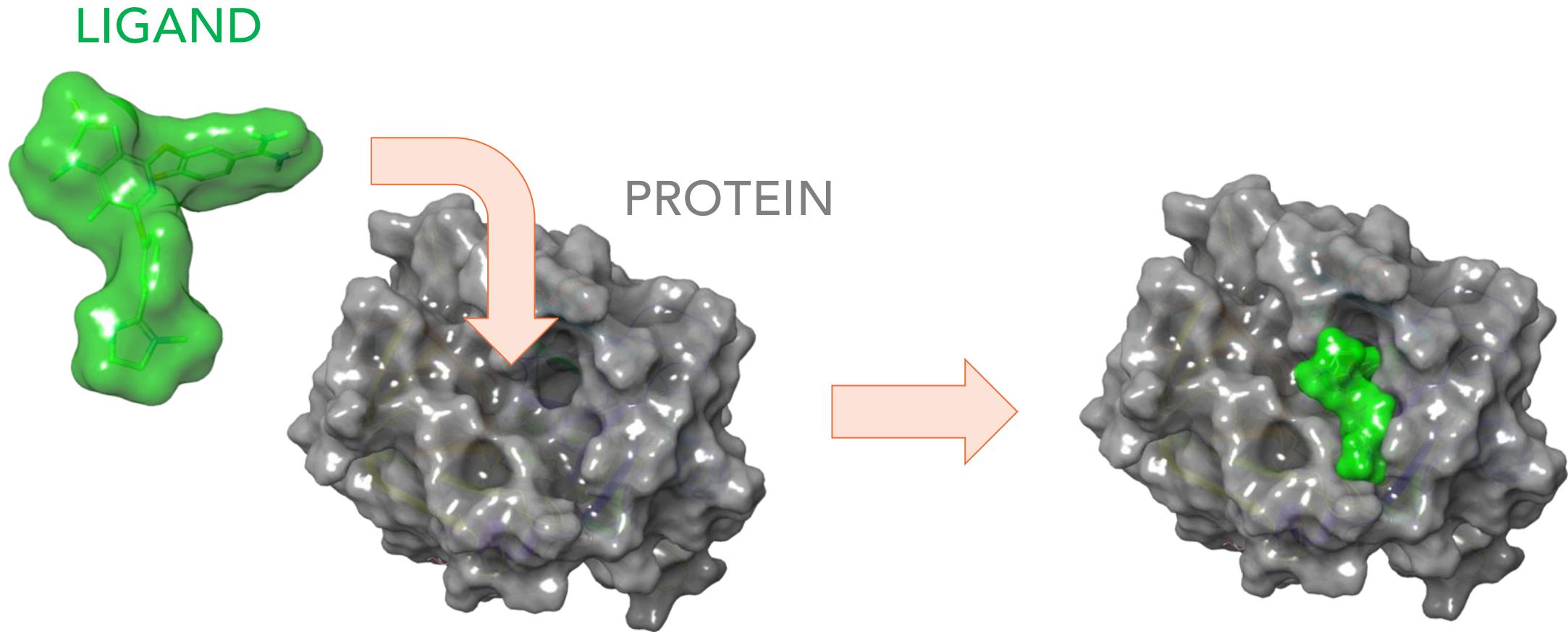
Structure-Based Drug Design is the Workhorse of CADD



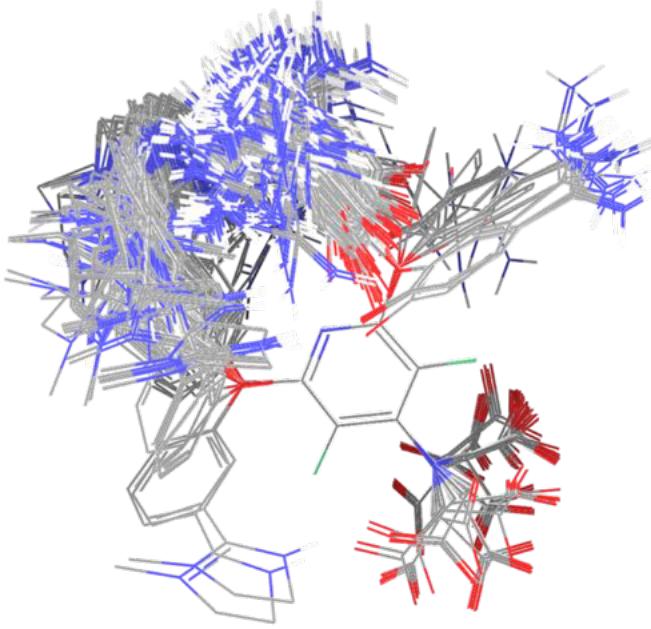
With a structure you can:

- 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, an docking determines best fit based on interatomic interactions

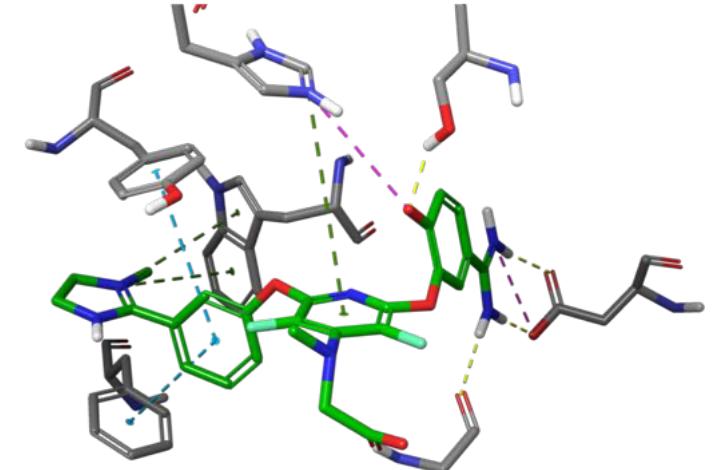


Bonding Interactions

- Bond length
- Bond angels
- Torsions

Non-Bonding Interactions

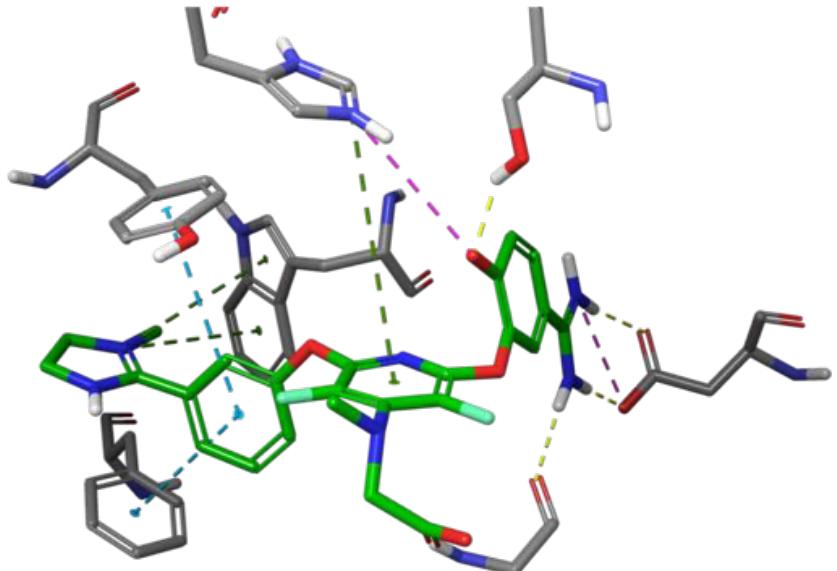
- van der Waal's interactions
- H-bonds
- Charge-Charge interactions
- pi-pi, pi-cation, etc.



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 ordination of the ligand in the binding site of the receptor.

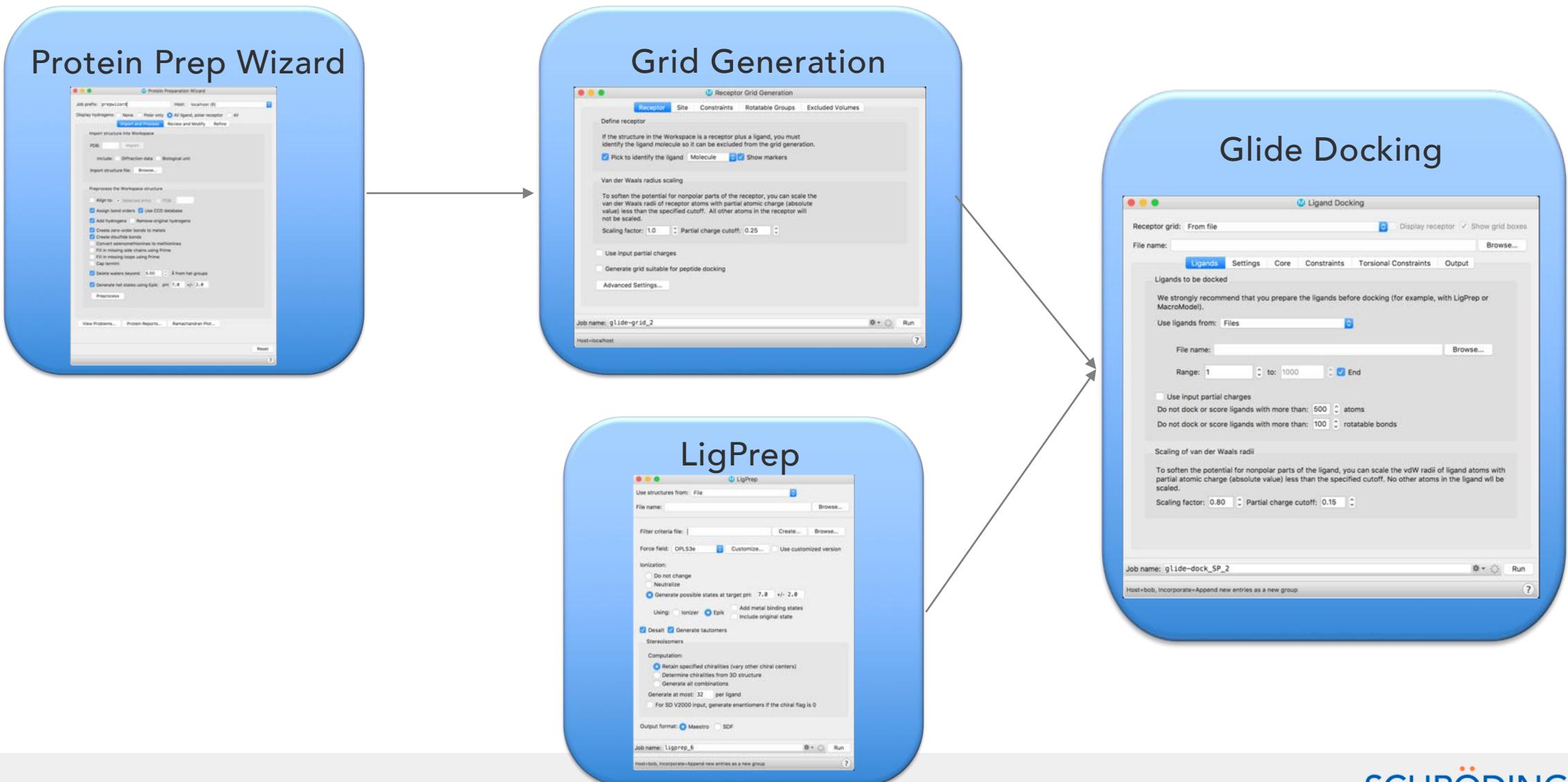
Accuracy: RMSD $\sim 1 \text{ \AA}$ to Co-crystal Structures

2) Docking Score

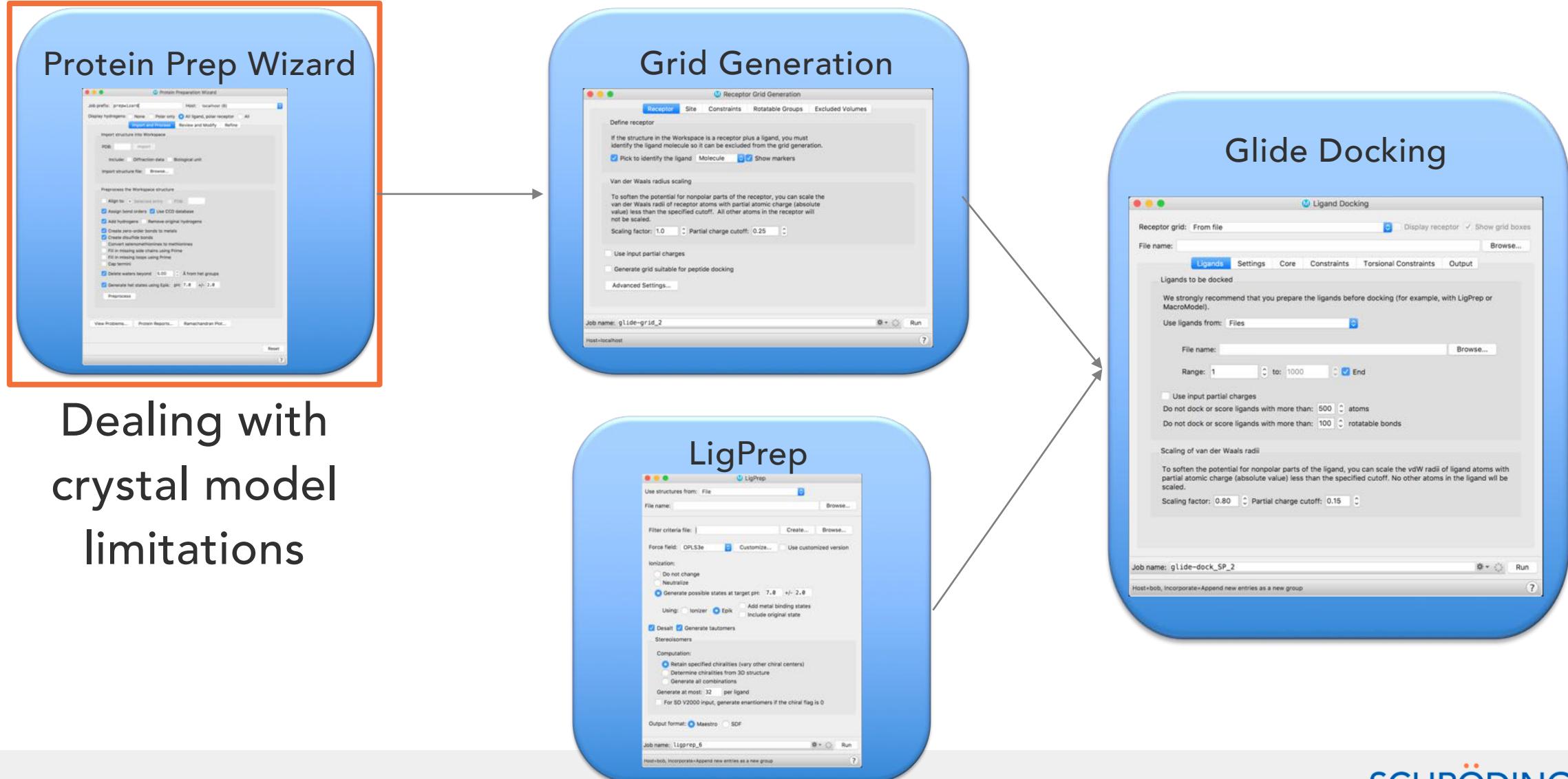
A numerical value of the representing the quality of the pose. Often presented as binding energy.

Accuracy: Good for enrichment, High false positive rate, does not correlate with $dG_{binding}$

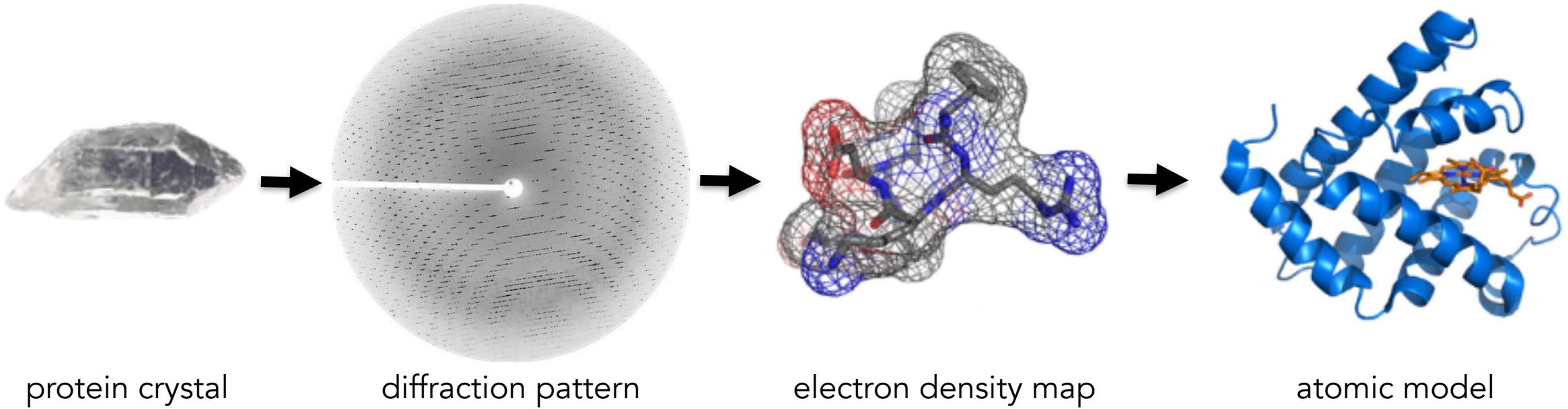
How to create docking models with Glide:



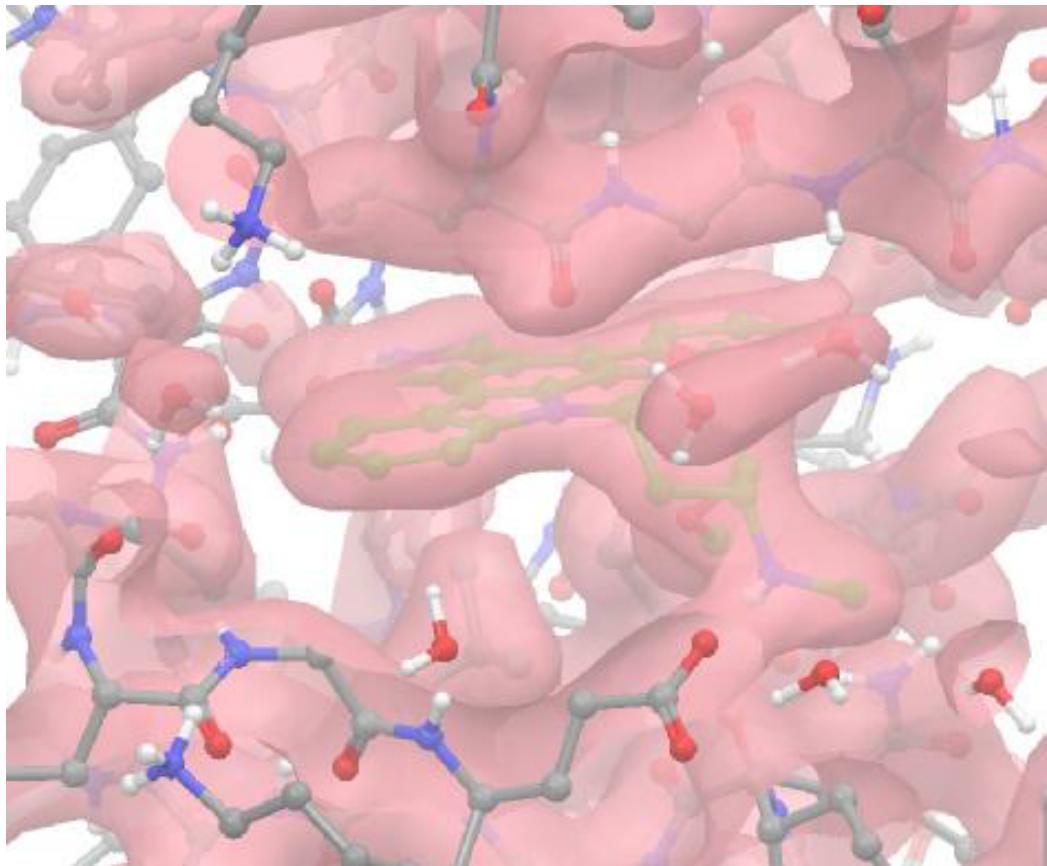
Glide Docking Workflow:



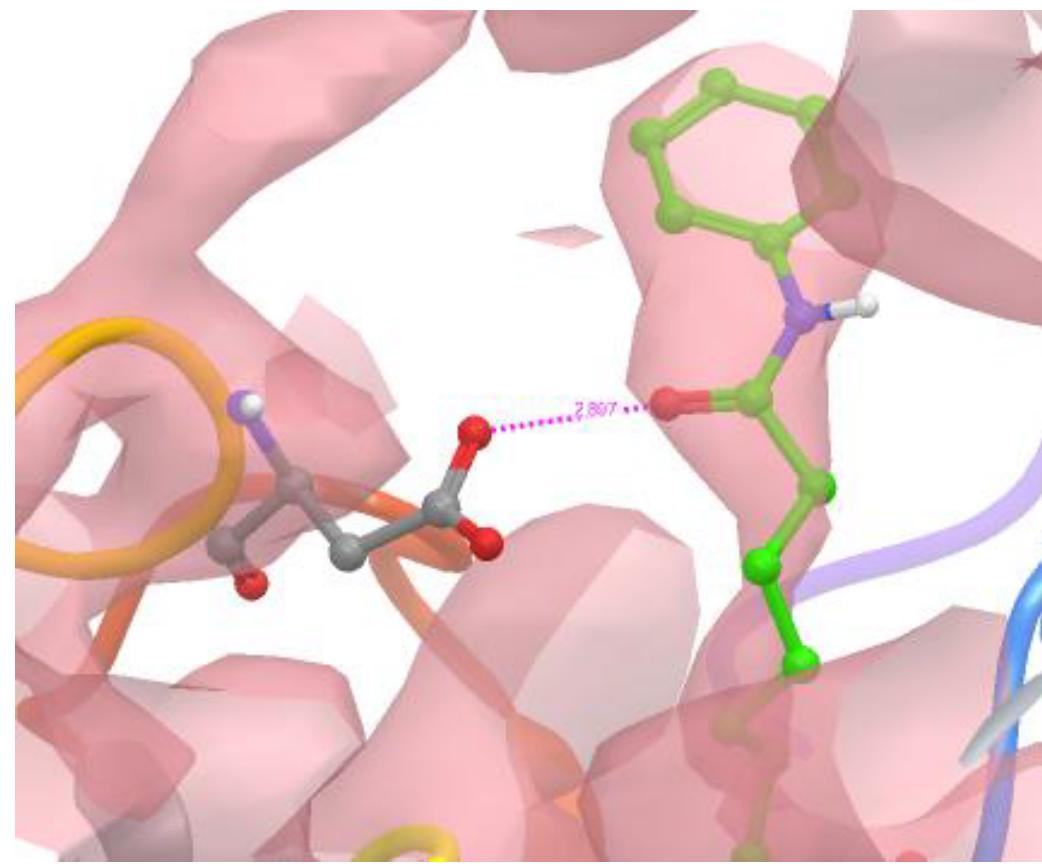
Most SBDD Projects Utilize Crystal Structures



Limitations to crystal structure models



In this case, the ligand density is relatively unambiguous.



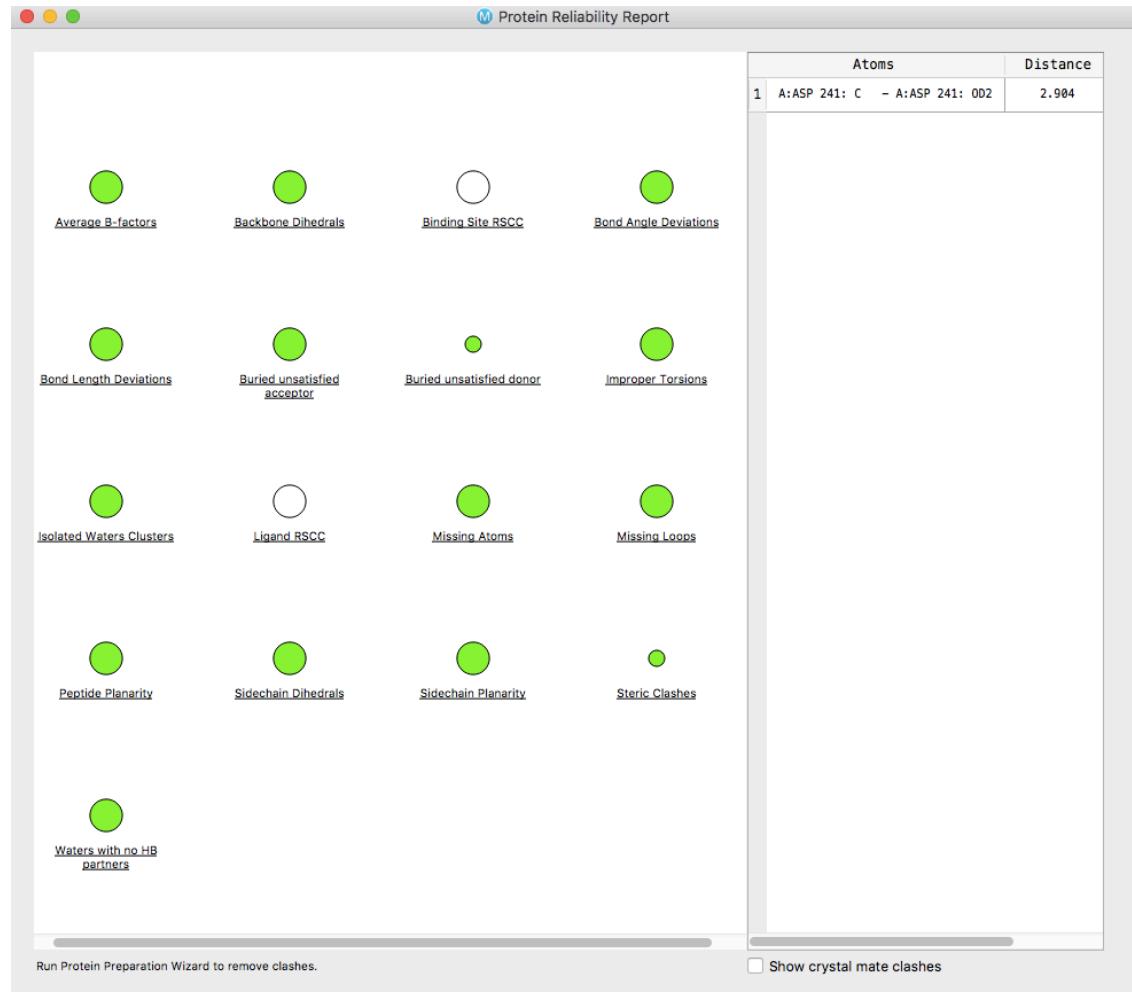
In this case the density is missing, which may result in misleading information.

Good CADD Starts with Good Science: Minimizing model limitations

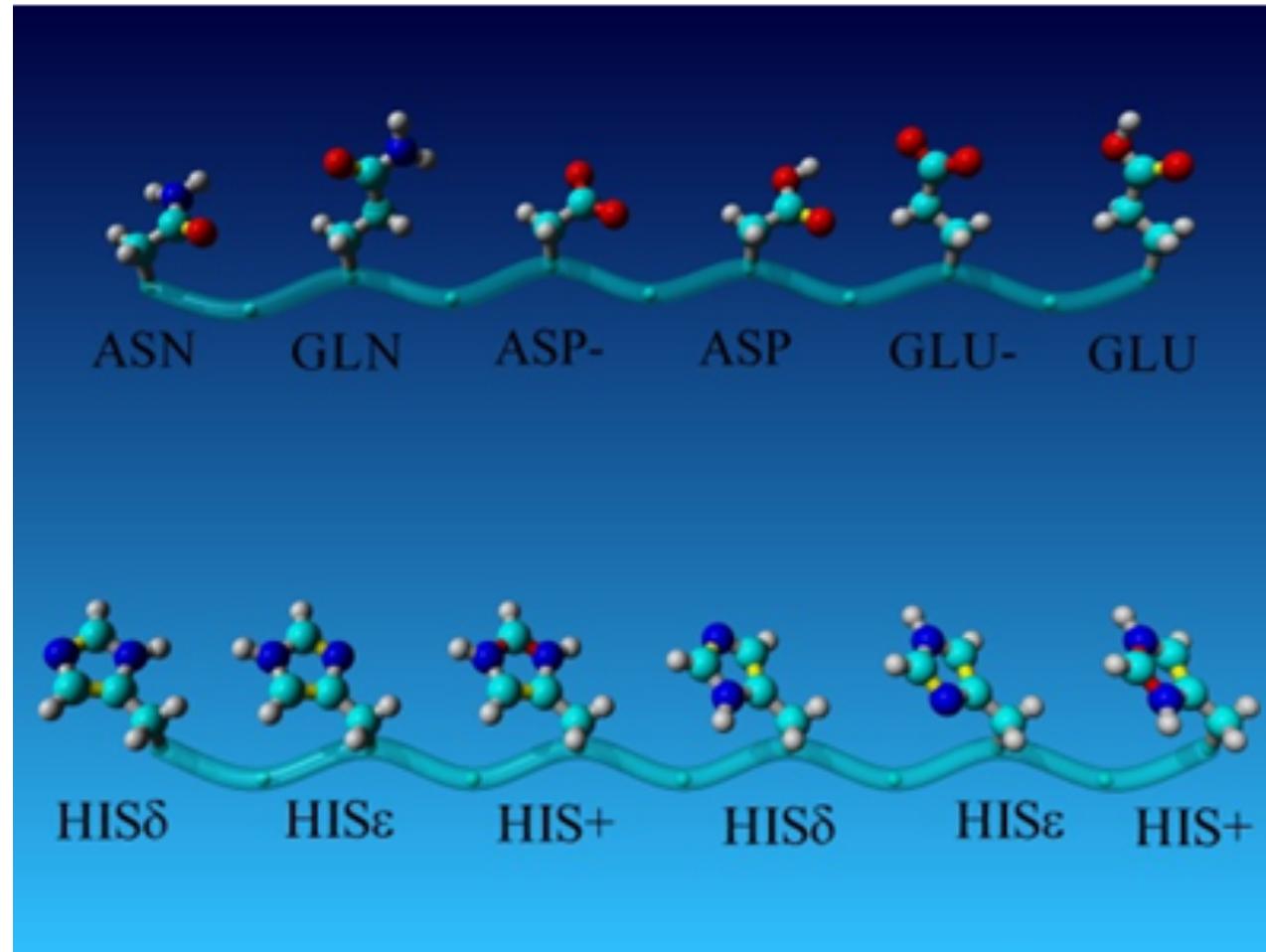
1. The quality of your structure matters

2. The conformational state of your structure matters

3. The design of your experiment matters



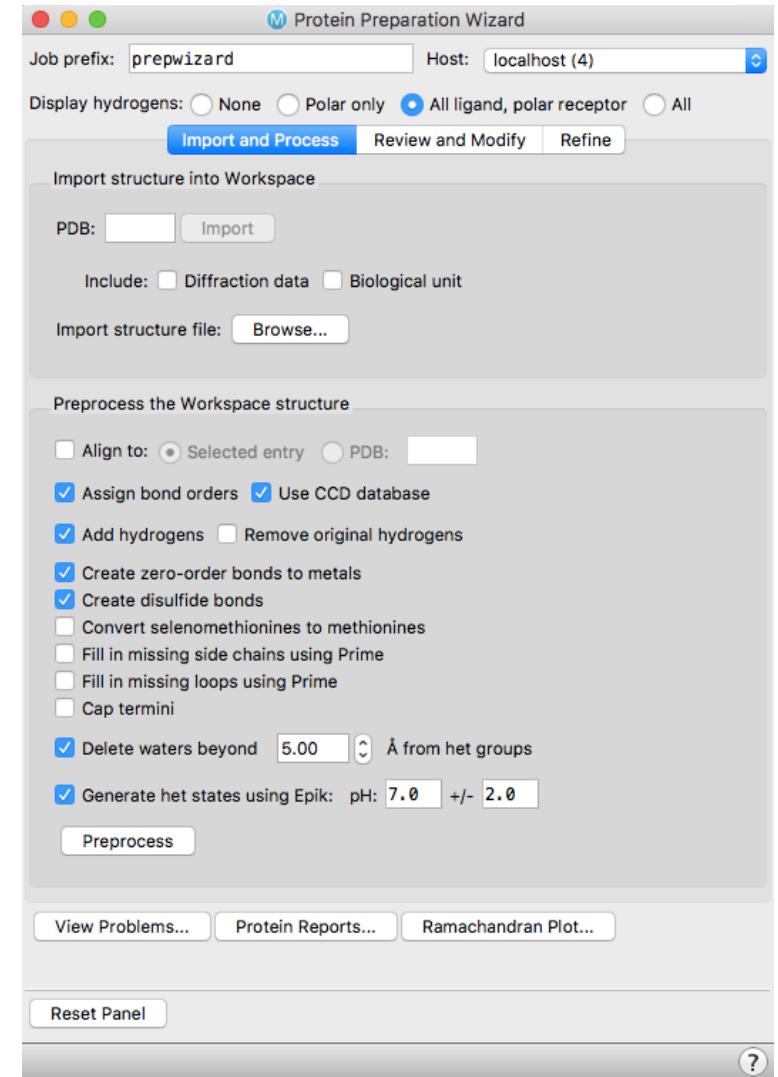
Limitations of crystal structure models continued: Tautomeric states.



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

Protein Preparation Wizard Augments Crystal Data

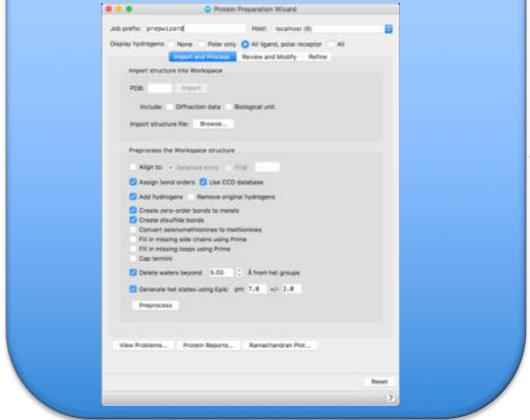
- **Fix common problems**
 - Protonation
 - Missing side chains
 - Missing loops
- **Remove unwanted molecules**
 - Counterions, artifacts of crystallography, waters
 - Biologically relevant?
- **Optimize your model structure**
 - Hydrogen-bond optimization
 - Restrained minimization



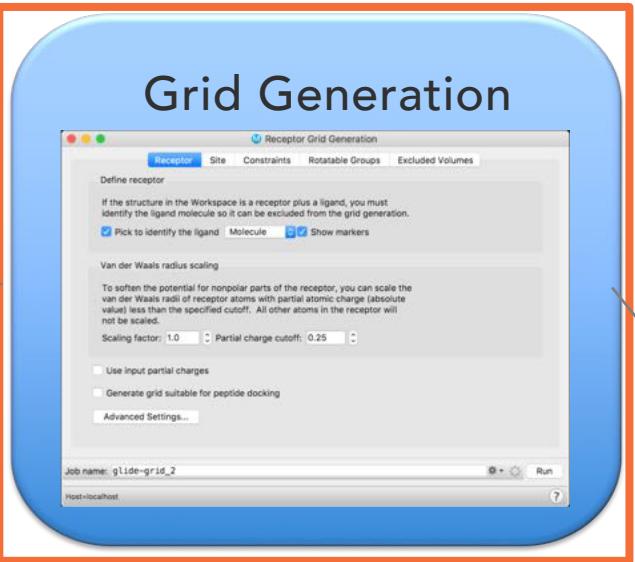
Glide Docking Workflow:

Model a protein for the computer
to interpret in docking

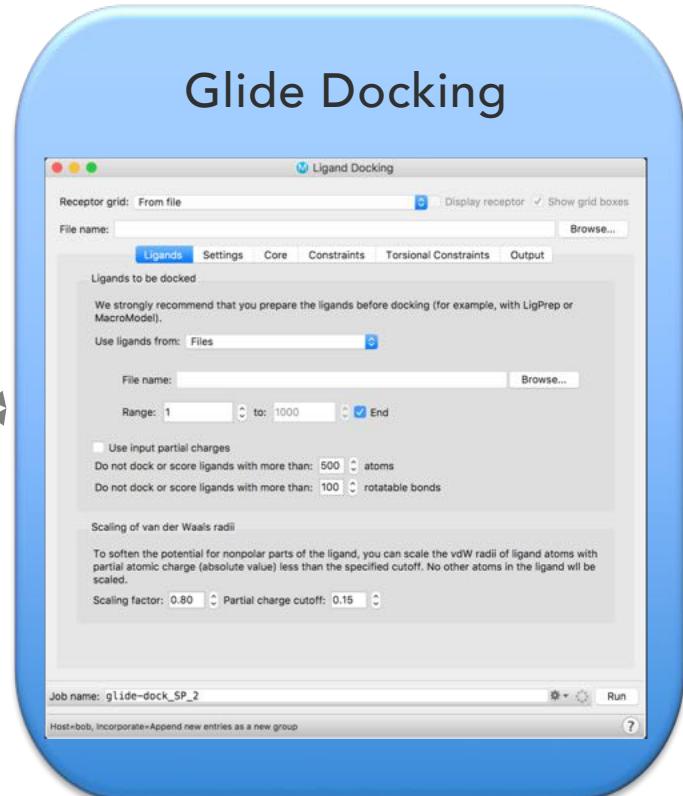
Protein Prep Wizard



Grid Generation



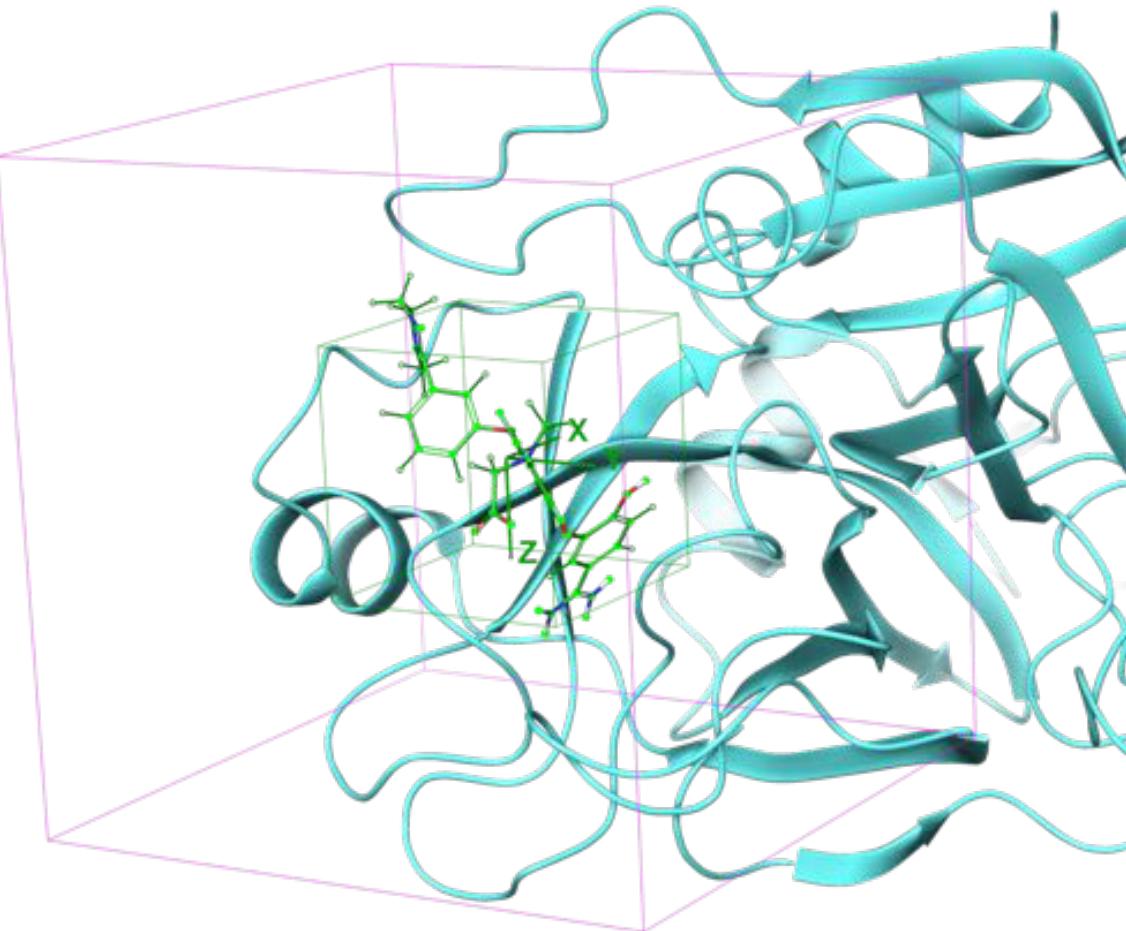
Glide Docking



LigPrep

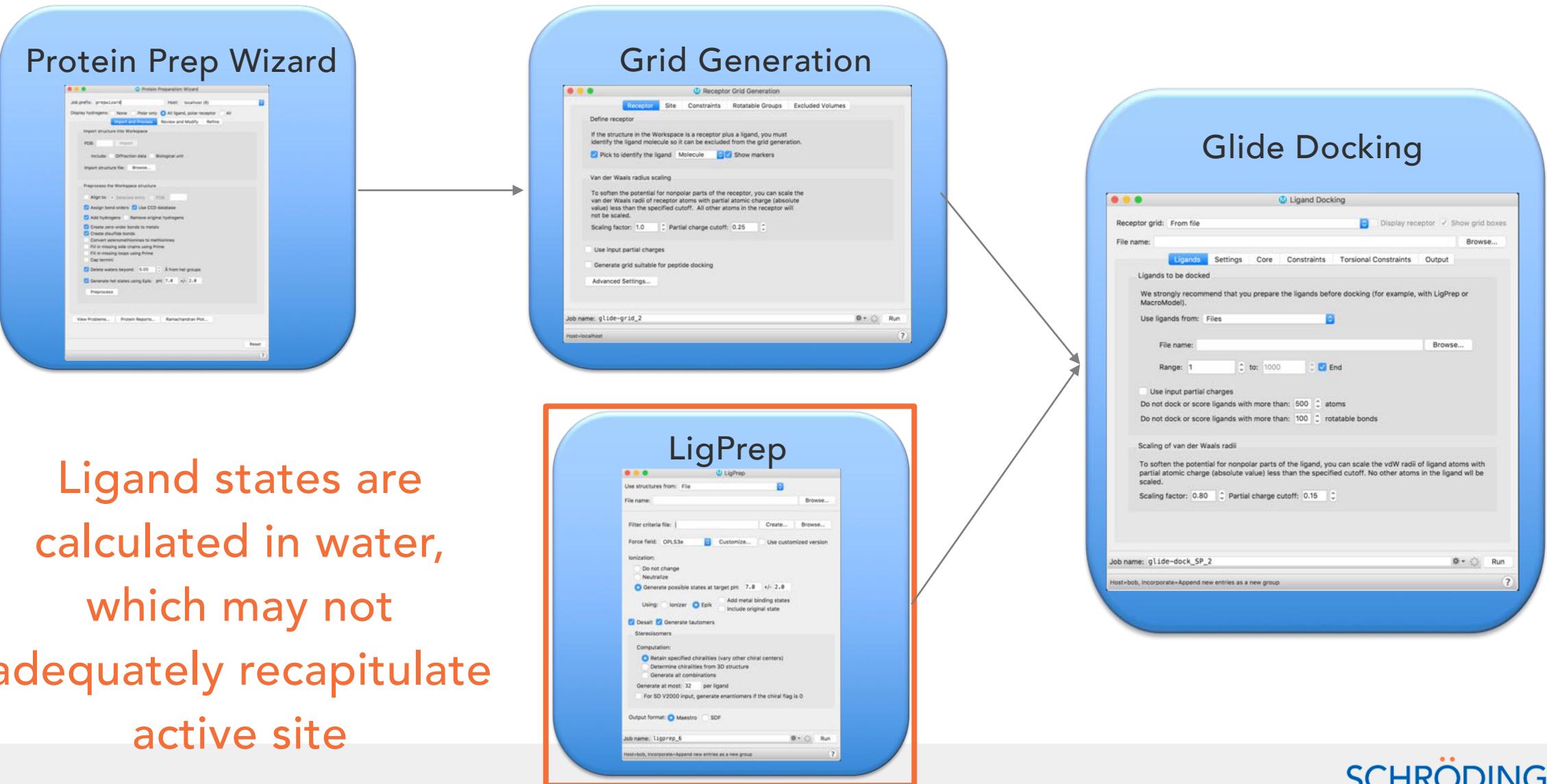


What is the role of the grid?



- 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

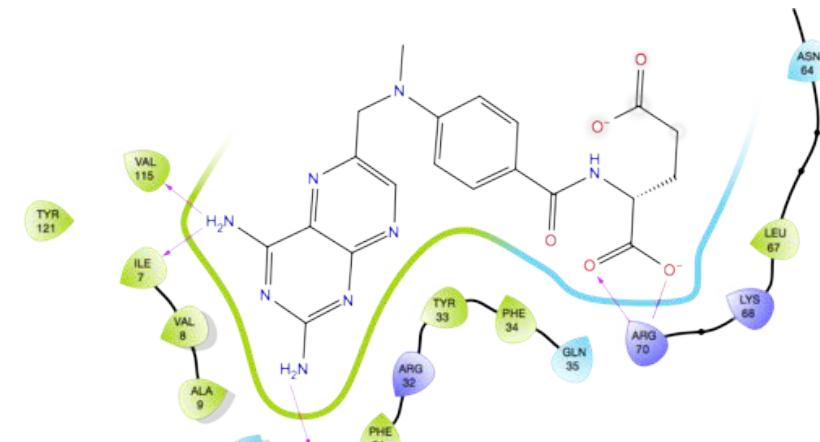
Glide Docking Workflow:



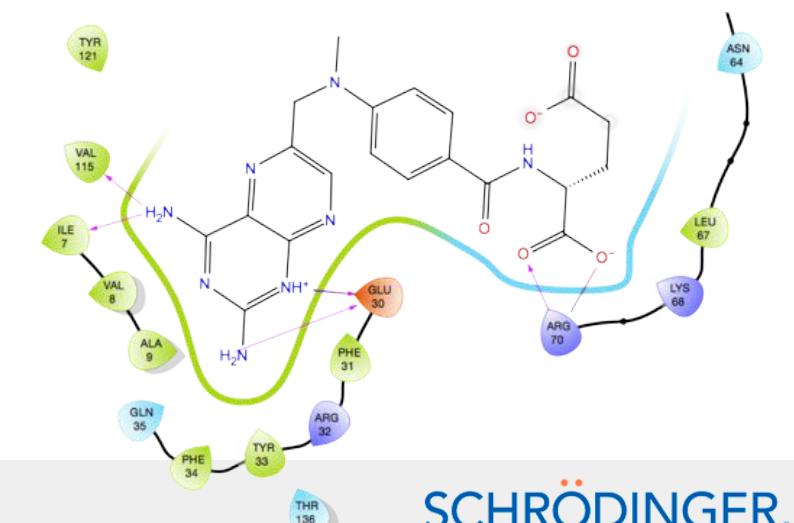
Required Inputs for Protein-Ligand Docking - Ligands

- 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

State penalty=0.0 kcal/mol

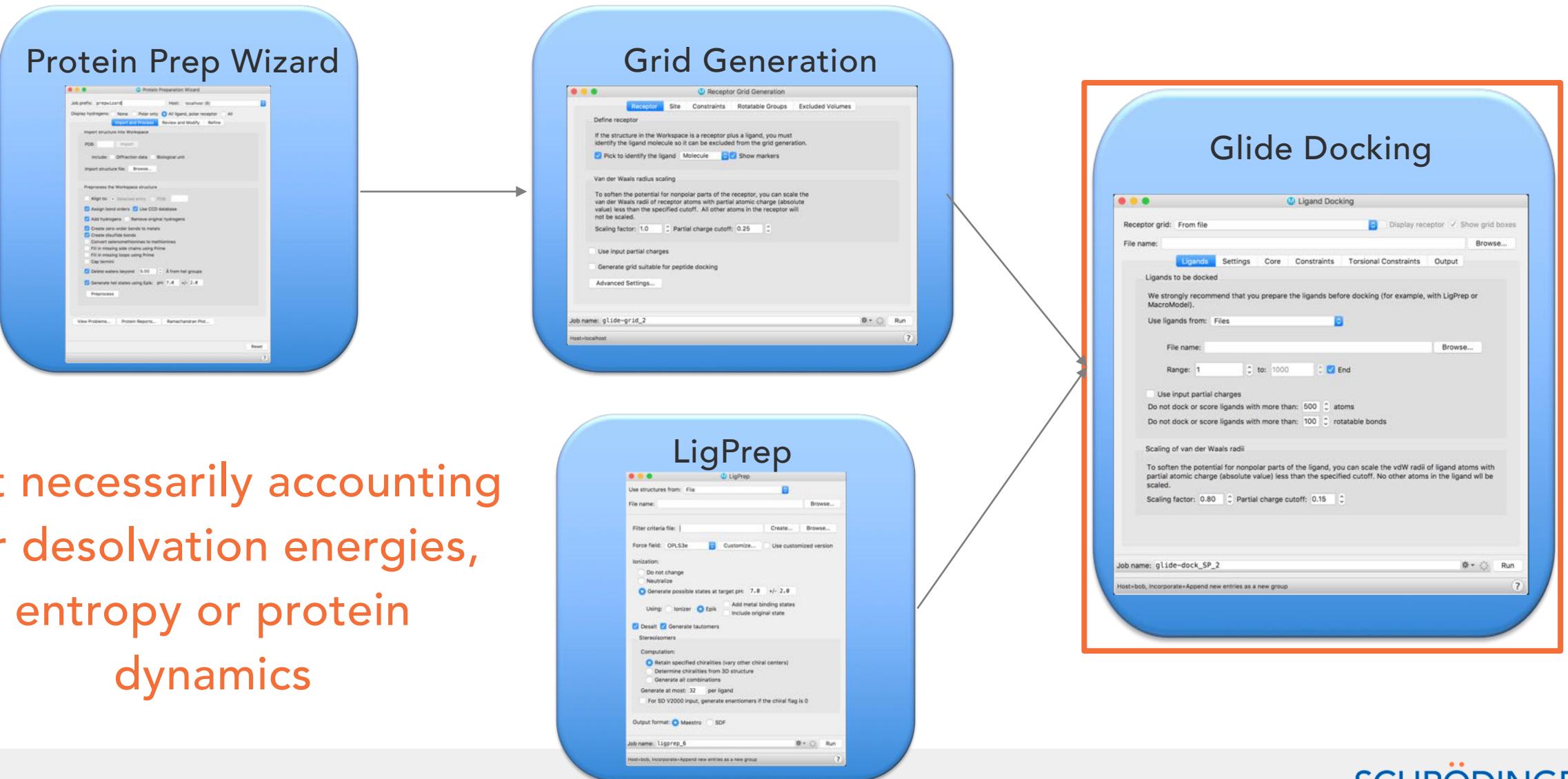


State penalty=1.43 kcal/mol

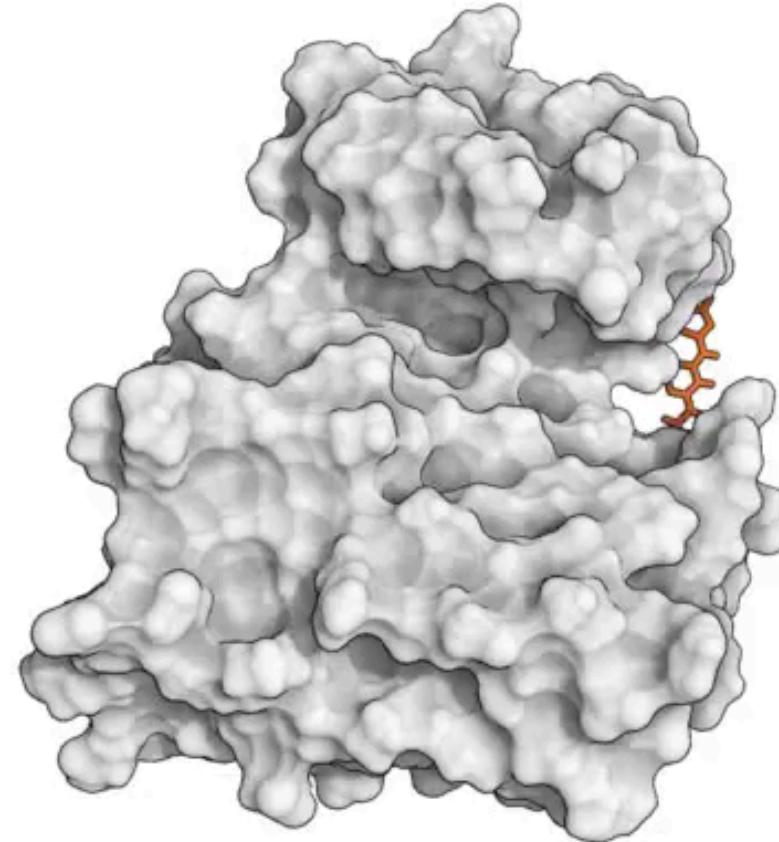


Methotrexate
bound to DHFR (1U72)

Glide Docking Workflow:



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!

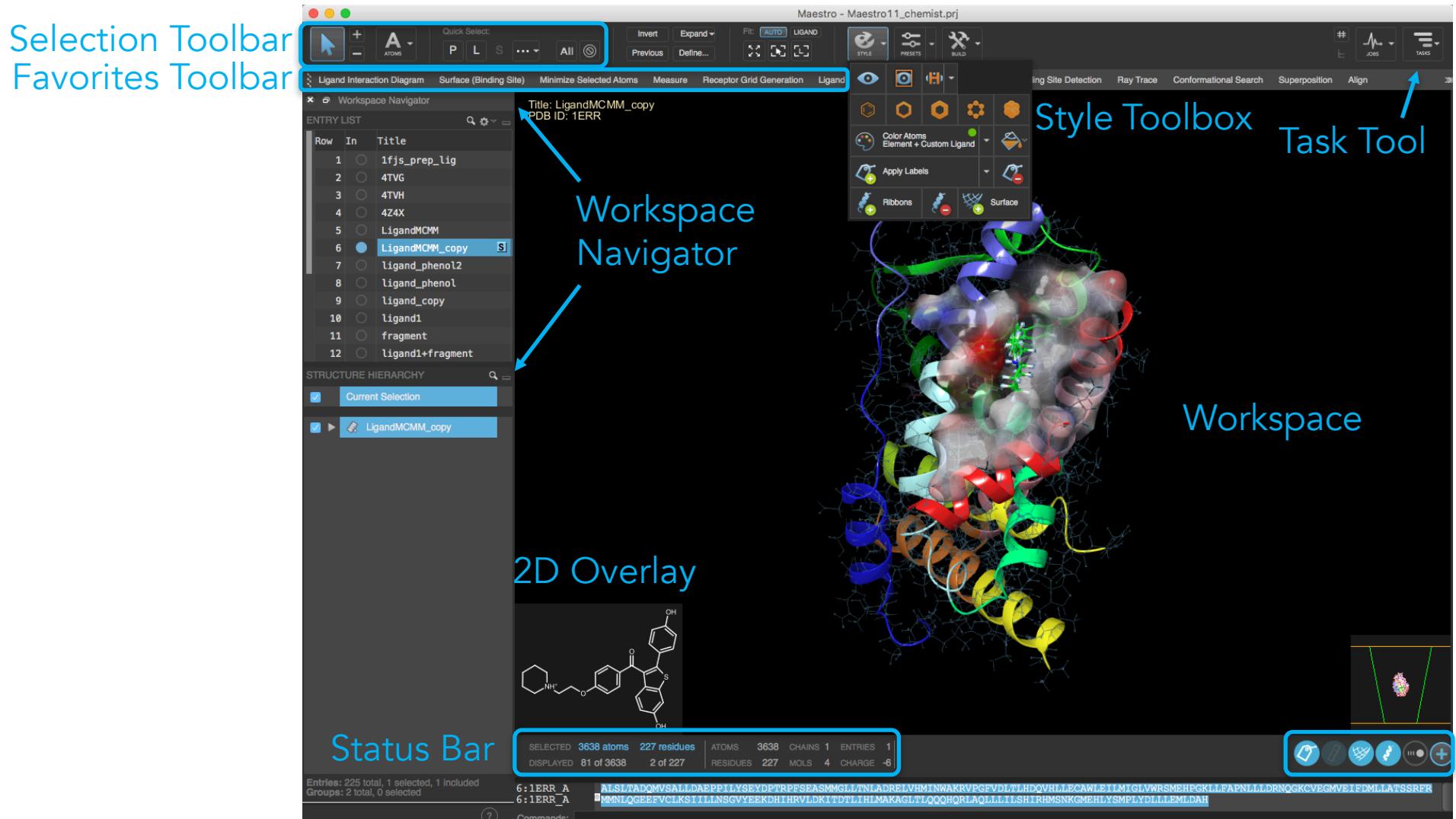




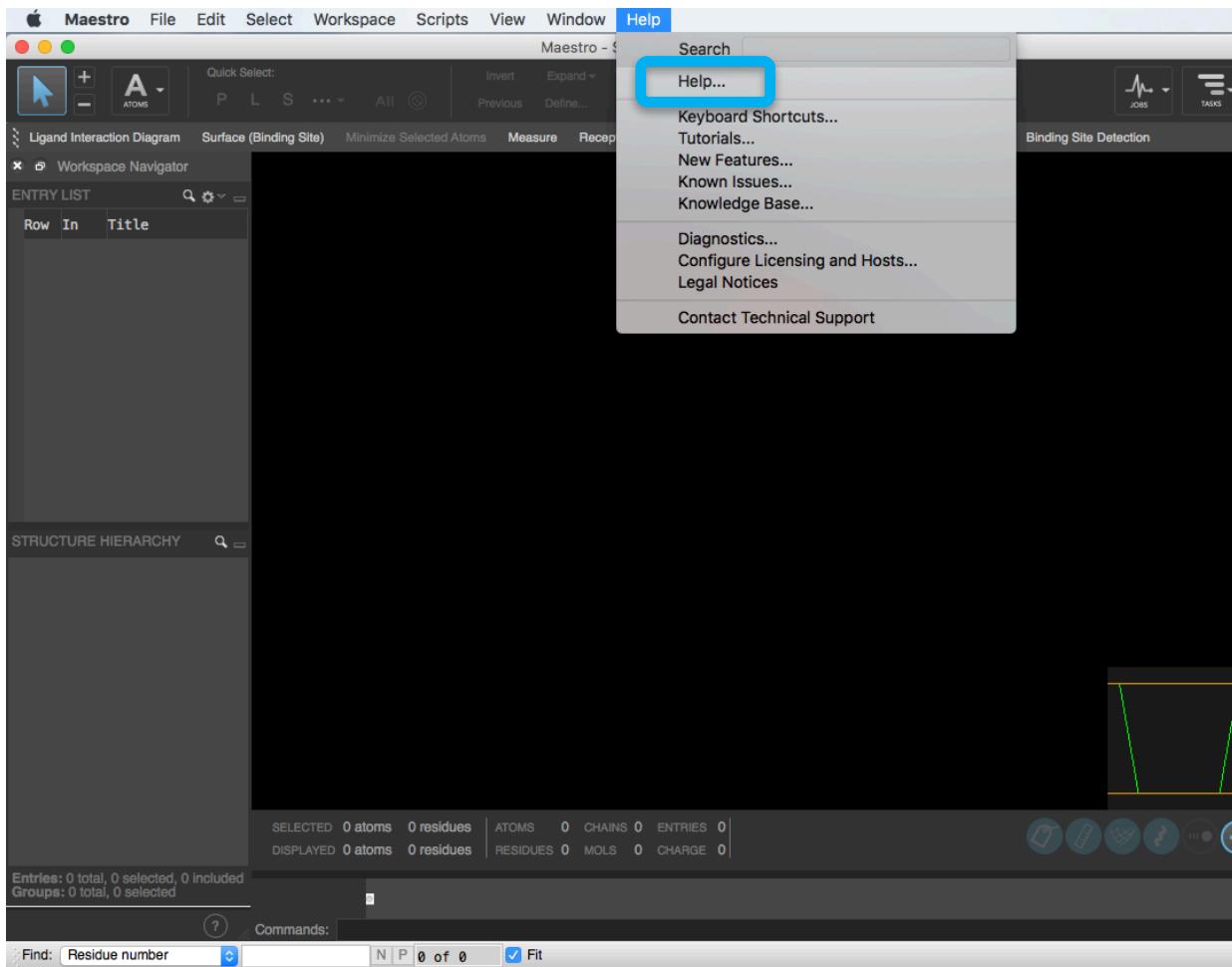
Maestro 11

SCHRÖDINGER®

The Maestro 11 Interface is User Friendly



The Help Menu Contains More Detail



A screenshot of the "Help - Maestro - 2017-2" window. The title bar says "SCHRÖDINGER®". The left sidebar has a "Maestro Quick Reference Guide" section with a blue box around the "Tutorials" item, which is also highlighted. Other items in the sidebar include "User Manuals", "Command References", "Quick Reference", "Installation and Jobs", and "Help". The main content area features a large heading "Getting Help" and a welcome message: "Welcome to the Maestro Help System! We have a variety of material and features designed to help you learn about Maestro and find the information you need." Below this, there's a section about getting started with Maestro, a link to the "Documentation page", and a list of places to find information inside Maestro.

Getting Help

Welcome to the Maestro Help System! We have a variety of material and features designed to help you learn about Maestro and find the information you need.

To get started with Maestro, you can use our [Online Workshop Series](#). Here you will find introductory tutorials and videos covering the essentials of using Maestro. This page also provides access to a wider range of training material in webinars and walk-throughs, a quick reference card, and a reference guide.

For the latest documentation, go to the [Documentation page](#) on our web site.

Inside Maestro you will find information in a number of places:

- Information on tasks, such as notification of the success of an operation, is displayed in banners at the top of the Workspace. Banners that are used for tasks give brief information on what to do to complete the task.
- There are tooltips (balloon help) in most places throughout Maestro. To display the tooltip, pause the pointer over the GUI element. The tooltip should appear within a few seconds near the pointer location. If it doesn't appear, check the [General - Appearance](#) section of the Preferences Panel to ensure that **Show tooltips** is selected.

Learn More with the Training Portal

The screenshot shows the Schrödinger website homepage. At the top, there's a navigation bar with links for HOME, PRODUCTS & SERVICES, SCIENCE, SUPPORT, DOWNLOADS (which is highlighted with a blue box), ABOUT, and a search icon. Below the navigation is a banner with the text "new technologies for maximal effect" and "FIGHT DISEASE WITH CODE". In the middle left, there's a section for "Schrödinger Suites" with a sub-section for "Training" featuring a video thumbnail of people in a classroom setting. A blue box highlights this "Training" section. At the bottom, there's a newsletter sign-up form with fields for "EMAIL" and a "GO" button, along with copyright and social media links.



The screenshot shows the "Maestro 11" page. The header includes the Schrödinger logo and navigation links for HOME, PRODUCTS & SERVICES, SCIENCE, SUPPORT, DOWNLOADS, ABOUT, and a search icon. The main content features a large image of a molecular model. To the right, there's a "Learn" section with four categories: "VIDEOS" (orange), "TUTORIALS" (teal), "SEMINARS" (green), and "PRESENTATIONS" (purple). A blue box highlights the "VIDEOS" category. Below this, there's a brief description of Maestro 11 and a "GET STARTED" button.

Use Our List of Publications to Generate Ideas

The image shows two screenshots of the Schrödinger website. The left screenshot shows the main homepage with various navigation links like Home, Products & Services, Science, Support, Downloads, and About. A blue box highlights the 'Publications' link in the Science menu. The right screenshot shows the 'Publications' page itself, which includes a search bar, filter options for 'Product' and 'Category', and a list of research papers with details like author names, journal, year, and product reference.

Left Screenshot (Main Website):

- HOME
- PRODUCTS & SERVICES
- SCIENCE
- SUPPORT
- DOWNLOADS
- ABOUT

Right Screenshot (Publications Page):

Publications

Search Search

FILTER BY PRODUCT:

FILTER BY CATEGORY:

- Biologics
- Data Analysis and Visualization
- LBDD
- Lead Optimization
- Materials Science
- Protein Structure Prediction
- SBDD
- Target ID and Validation
- Virtual Screening

Results

Product(s) Referenced	Publication Year
Desmond, MS Jaguar	2016
Desmond, MacroModel	2016
Induced Fit	2016
Membrane Permeability	2016
FEP+, OPLS3	2016
Glide, Phase	2016
MS Jaguar	2016

Left Screenshot (Main Website):

New Technologies for Maximum Effect

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We are pleased to invite you to Schrödinger's 16th Annual European User Meeting, to be held September 21st - 23rd, 2016

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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/>

Thanks for Joining Us!

Scientific and Technical Support
help@schrodinger.com

Email us for more info at
Training@schrodinger.com

