Introduction to Maestro 11

Structure Visualization and Preparation

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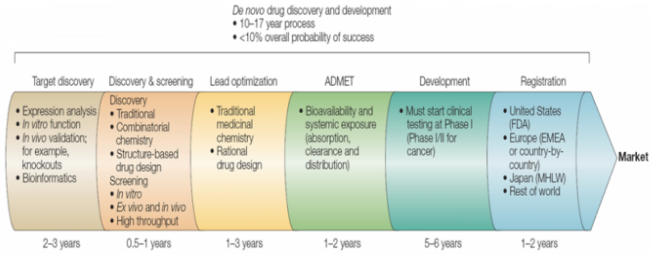
November 13th, 2017

Background on the drug discovery pipeline



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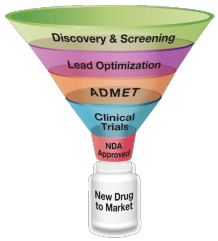
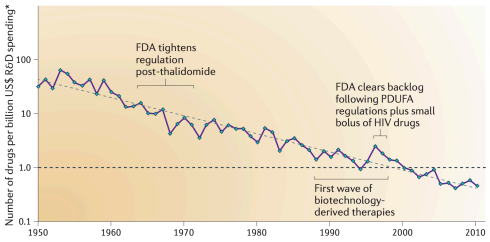
Drug Discovery is Expensive and Slow





Computer-aided drug design (CADD) can:

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

Scannell, J. W. et al. Nat. Rev. Drug Disc., **2012**, *11*, 191-200.
http://www.enzolifesciences.com/browse/drug-discovery/

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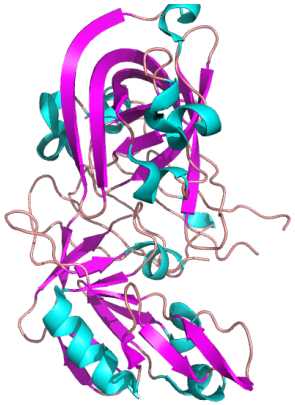
Structure-Based Drug Design is the Workhorse of CADD



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

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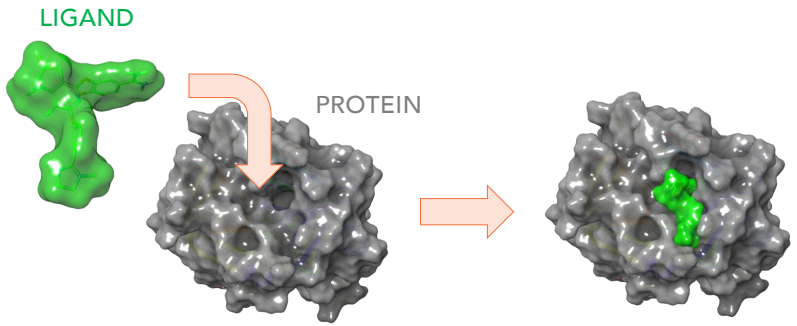
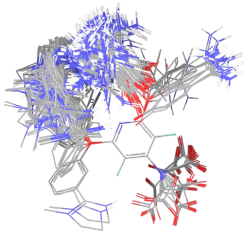
Docking at its core is a shape matching problem

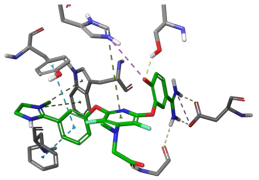


Ligands are flexible, an docking determines best fit based on interatomic interactions



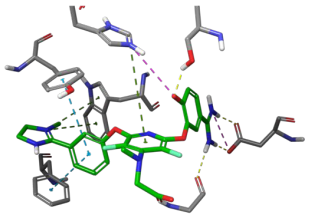
Bonding Interactions
- Bond length
- Bond angels
- Torsions

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



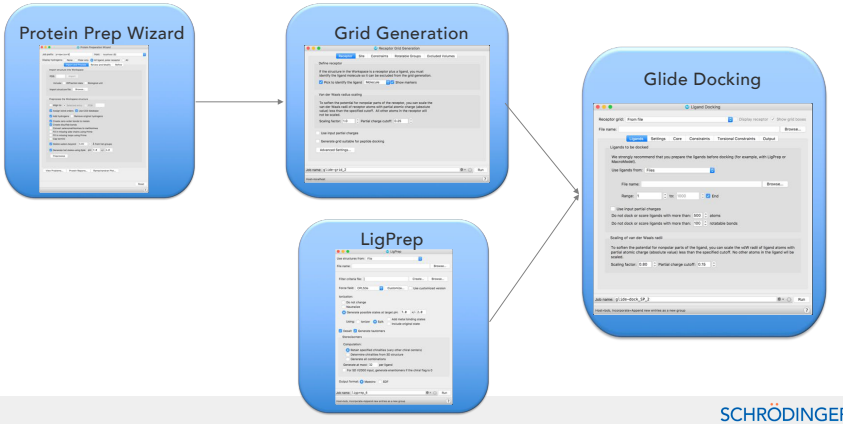
Limitations of Docking
- Entropy is not accounted for
- Protein flexibility is ignored
- Solvation is not accounted for

A Docking Program Generates a…

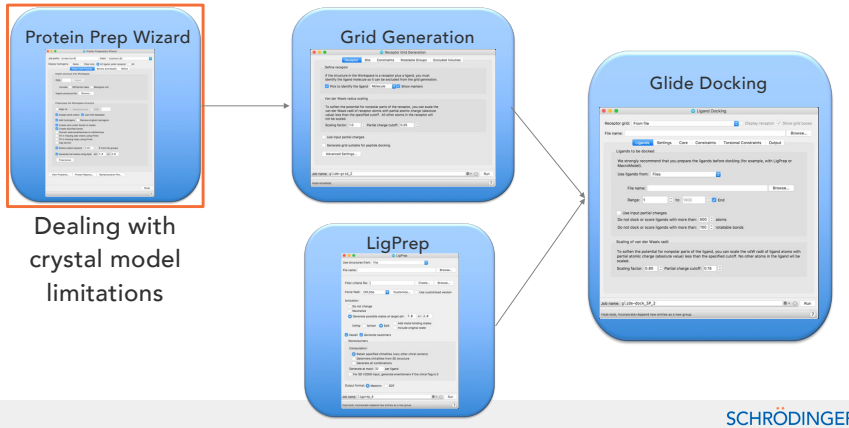


1) A Binding Pose
   A model of the ordination of the ligand in the binding site of the receptor.
   Accuracy: RMSD ~1 Å to Co-crystal Structures
2) Docking Score
   A numerical value of the representing the quality of the pose. Often presented as binding energy.
   Accuracy: Good for enrichment, High false positive rate, does not correlate with dGbinding

How to create docking models with Glide:



Glide Docking Workflow:



Dealing with crystal model limitations

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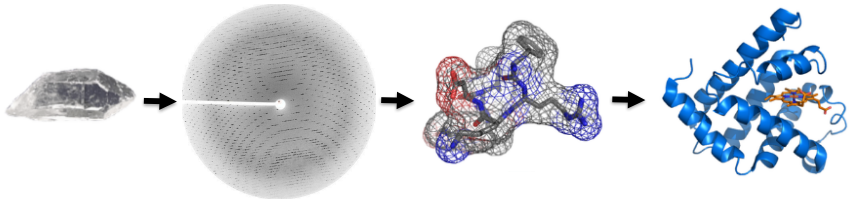
Most SBDD Projects Utilize Crystal Structures



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

Adapted from: http://www.scistyle.com/

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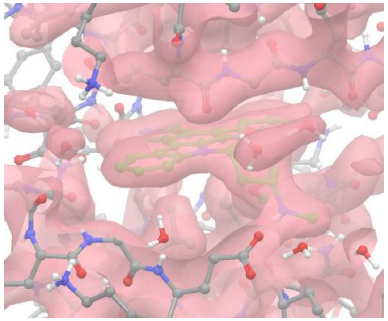
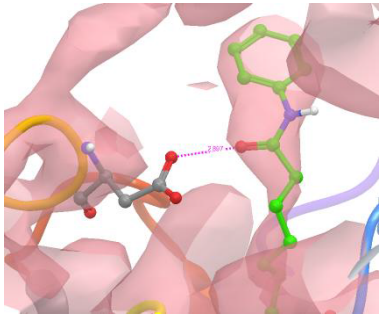
Limitations to crystal structure models



In this case, the ligand density is relatively unambiguous.



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

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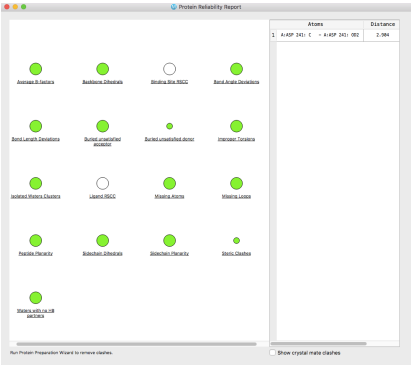
Good CADD Starts with Good Science: Minimizing model limitations

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



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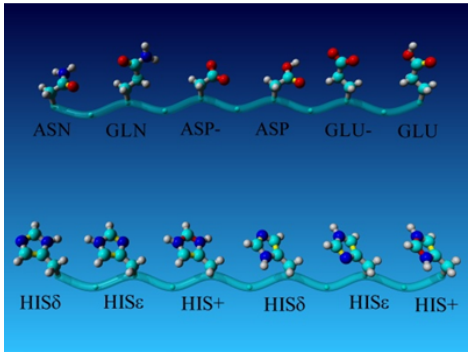
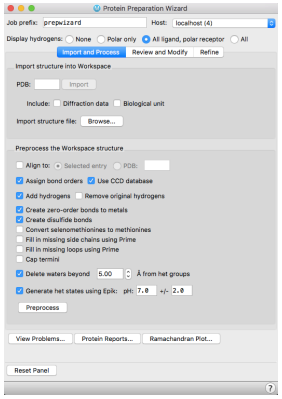
Limitations of crystal structure models continued: Tautomeric states.



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

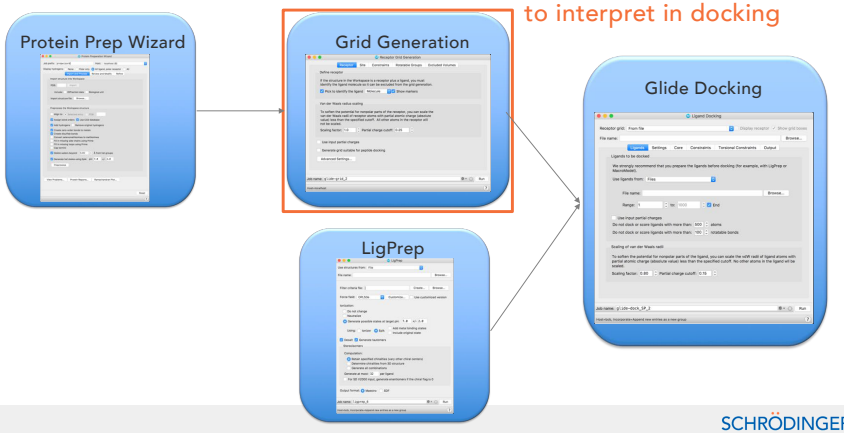
Protein Preparation Wizard Augments Crystal Data

- **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

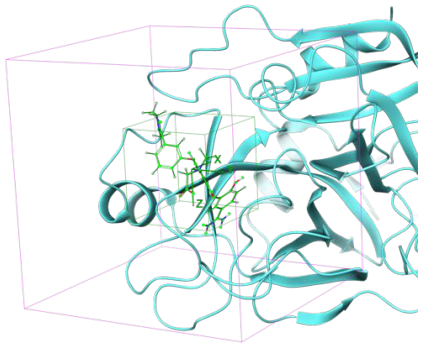


Glide Docking Workflow:

Model a protein for the computer to interpret in docking

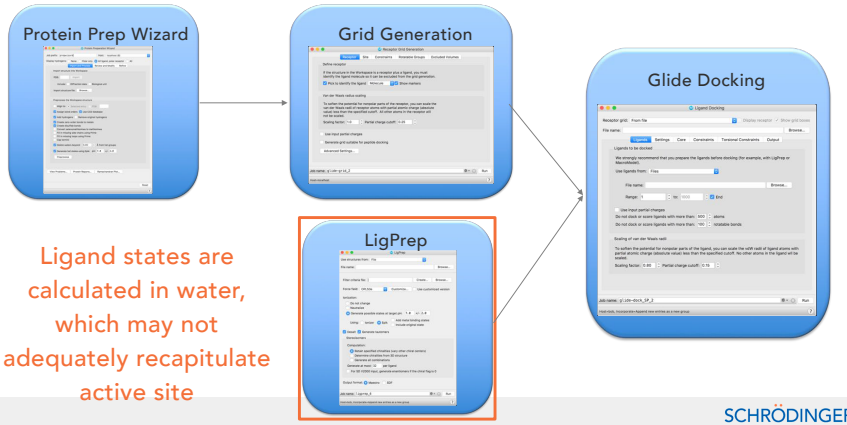


What is the role of the grid?



- Protein represented as a series of grids
  - Site point grid (10Å^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: 10Å3 by default
  - Outer box: (12Å+0.8*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:



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

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Required Inputs for Protein-Ligand Docking - Ligands

- Glide will only dock ligand states that are provided
- Recommendations for prepared ligand structures

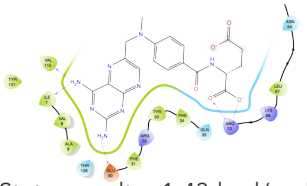
–Use LigPrep to generate low energy ionization/tautomeric states for ligands

•Epik state penalties that estimate free energy required to generate ionization state in water with corrections for interaction with metal sites

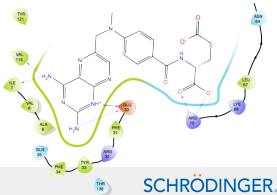
–Typical expansion of compounds by ionization/tautomeric/stereo expansion is 2.5x

– Increase or decrease pH value and +/- range depending on target physiological location and project goals

State penalty=0.0 kcal/mol

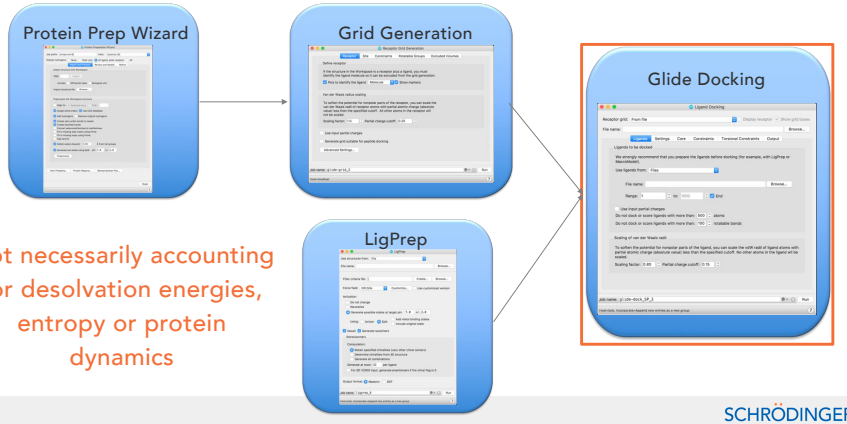


State penalty=1.43 kcal/mol



Methotrexate bound to DHFR (1U72)

Glide Docking Workflow:



Not necessarily accounting for desolvation energies, entropy or protein dynamics

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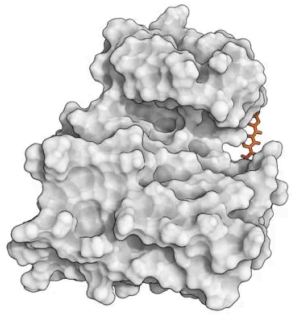
Proteins are flexible which is a limitation in Glide based docking on its own… but when combined with molecular dynamics can be a powerful tool!



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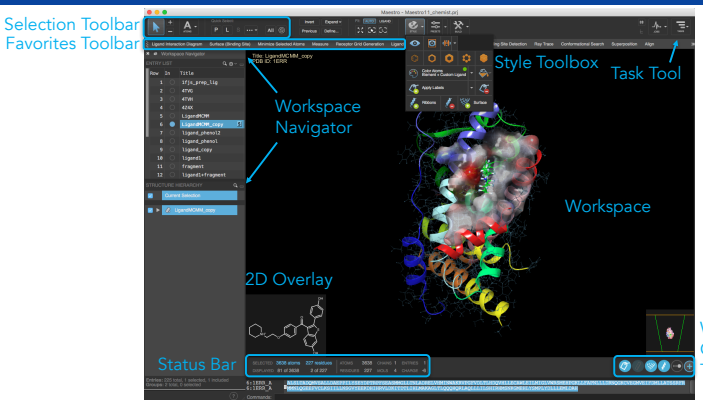
The Maestro 11 Interface is User Friendly



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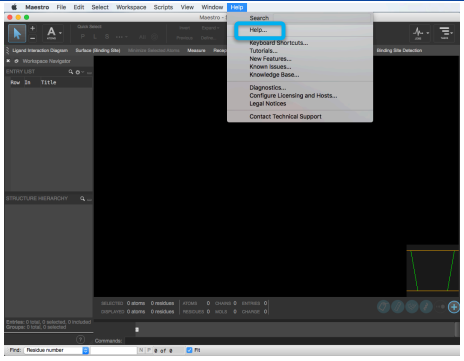
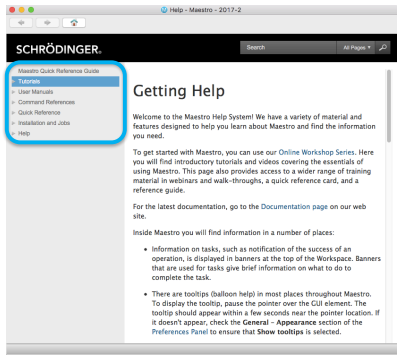
The Help Menu Contains More Detail





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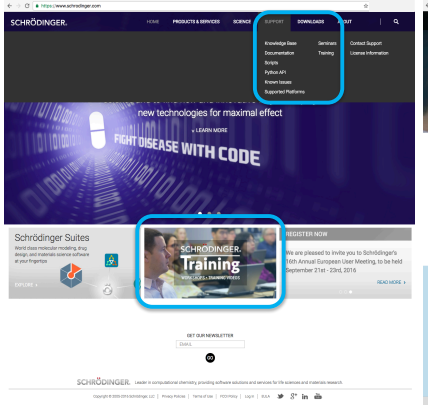
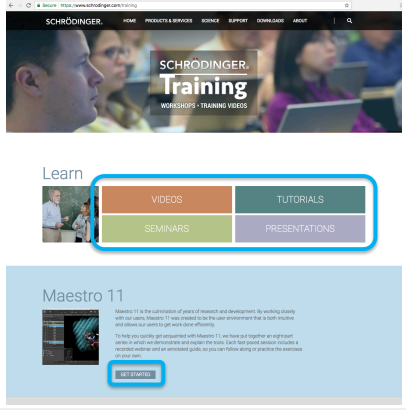
Learn More with the Training Portal





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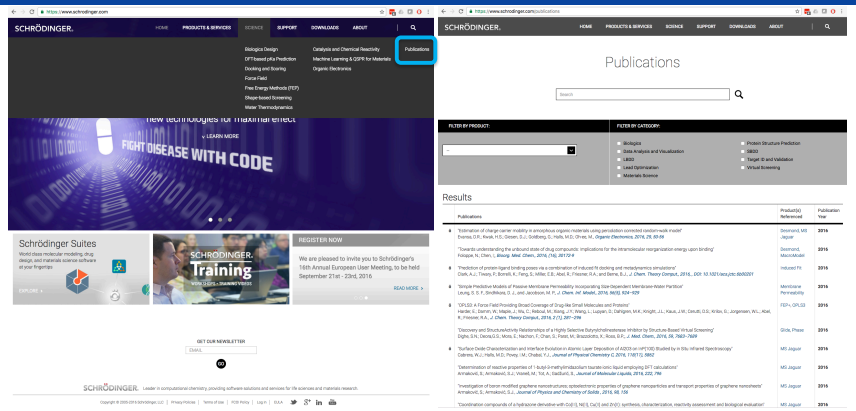
Use Our List of Publications to Generate Ideas



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
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