ACS Chemistry for Life™

ACS Webinars

We will start momentarily at 2pm ET

Slides download at:
http://boilthisdown.org/?p=1486

ACS WEBINARS
Staying ahead of the game: Recent innovations in computational methods for drug discovery

Speaker: Woody Sherman
Schrodinger

Moderator: Karen Rossi
Bristol-Myers Squibb

Please submit your questions for the speaker via the Chat Panel in the GoToWebinar

Staying Ahead of the Game:

Recent Innovations in Computational Methods for Drug Discovery

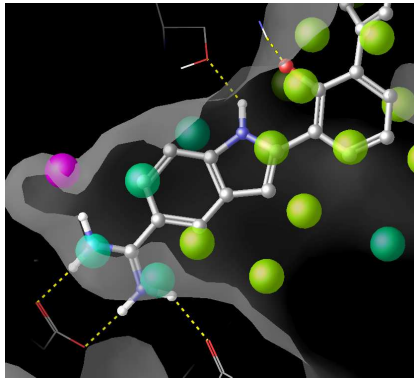
Woody Sherman
VP, Applications Science
Schrödinger

SCHRÖDINGER.

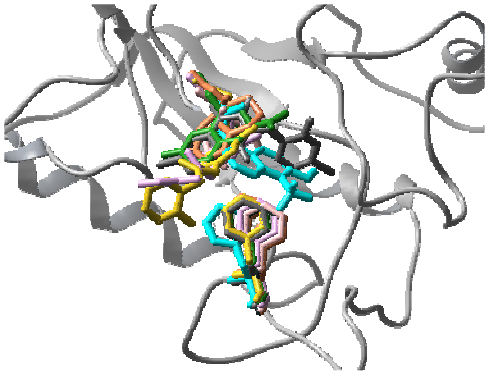
Overview

- Scope of the field
- What we can and cannot do
- Examples of successful applications
- Are computational tools right for you?
  - How to know when computational tools can be used
  - How to choose the right tools
  - Potential pitfalls
- Resources and references

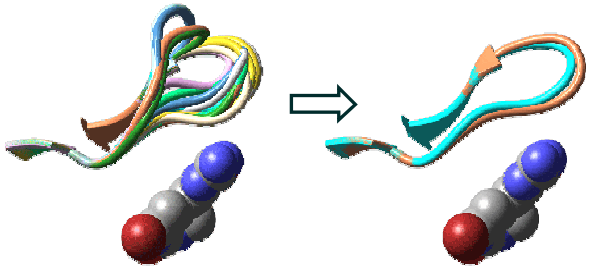
Visualization and Analysis



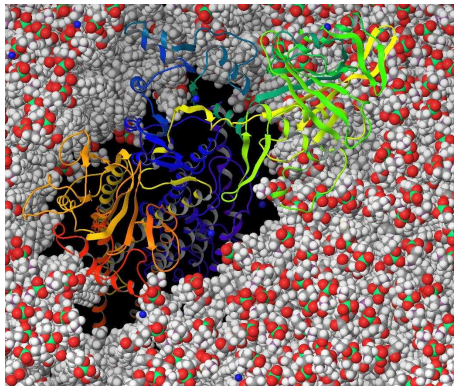
Docking



Protein Structure Prediction

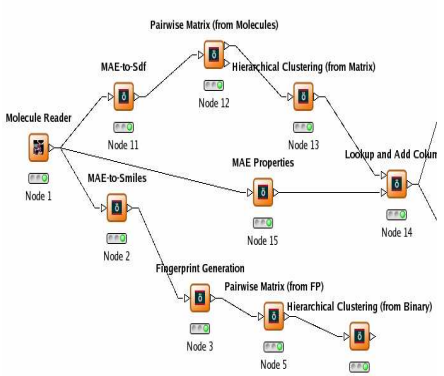


Molecular Dynamics

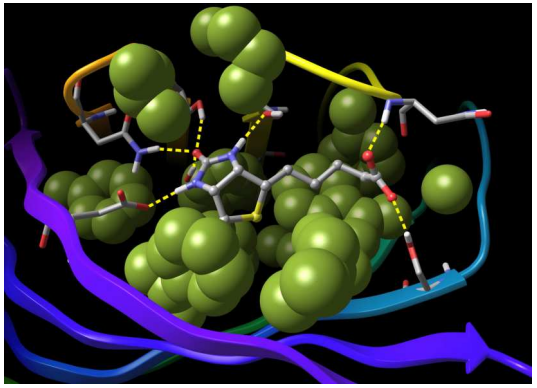


Core Technologies in Computer-Aided Drug Design

Workflows



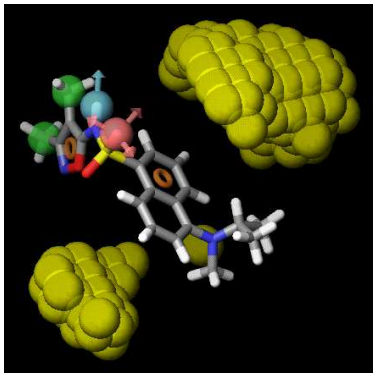
Scoring Functions



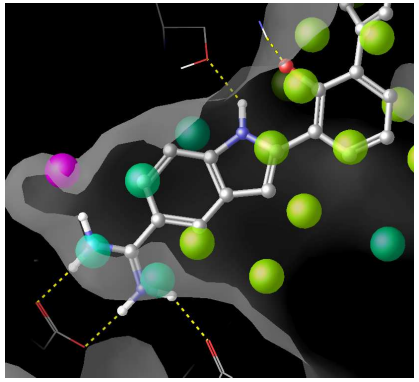
Cheminformatics

	2	4	7	8	1	3	5	6
4	0	0	0	0	1	1	1	1
6	0	0	0	0	1	1	1	1
9	0	0	0	0	1	1	1	1
5	0	0	1	0	0	1	1	1
3	0	0	0	0	1	1	0	0
7	1	1	1	1	0	0	0	0
8	1	1	1	1	0	0	0	0
2	1	1	1	1	0	0	1	0
10	1	1	1	1	1	0	1	0
1	1	1	1	0	0	0	0	1

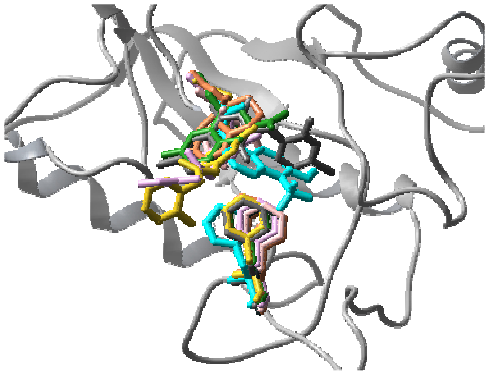
Pharmacophore Modeling



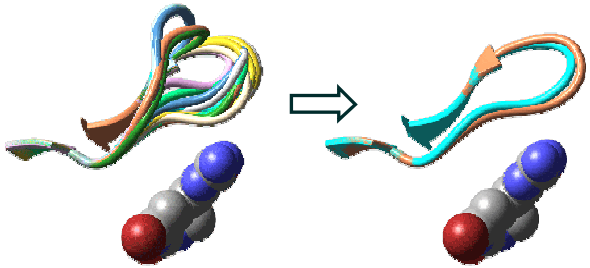
Visualization and Analysis



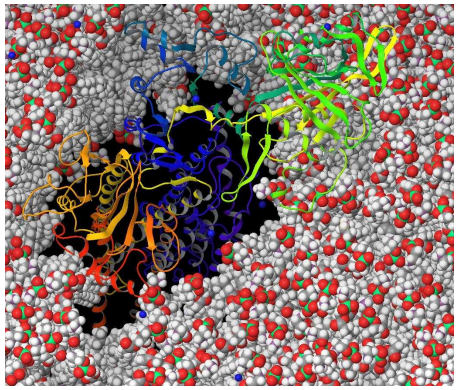
Docking



Protein Structure Prediction

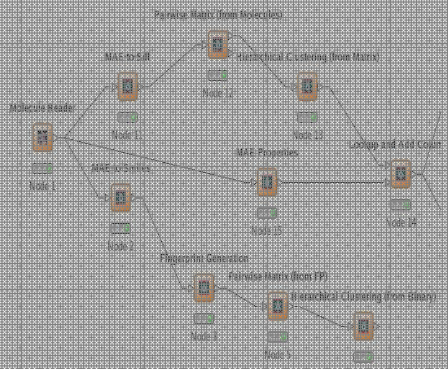


Molecular Dynamics

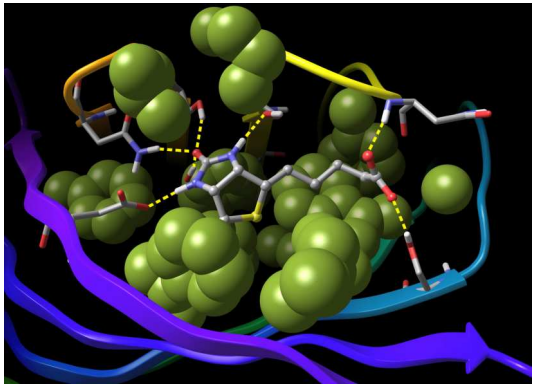


Core Technologies in Computer-Aided Drug Design

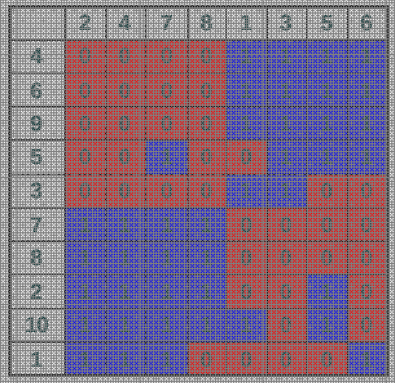
Workflows



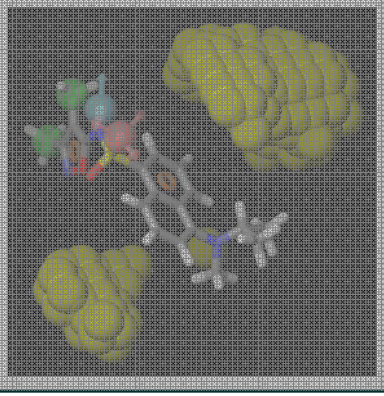
Scoring Functions

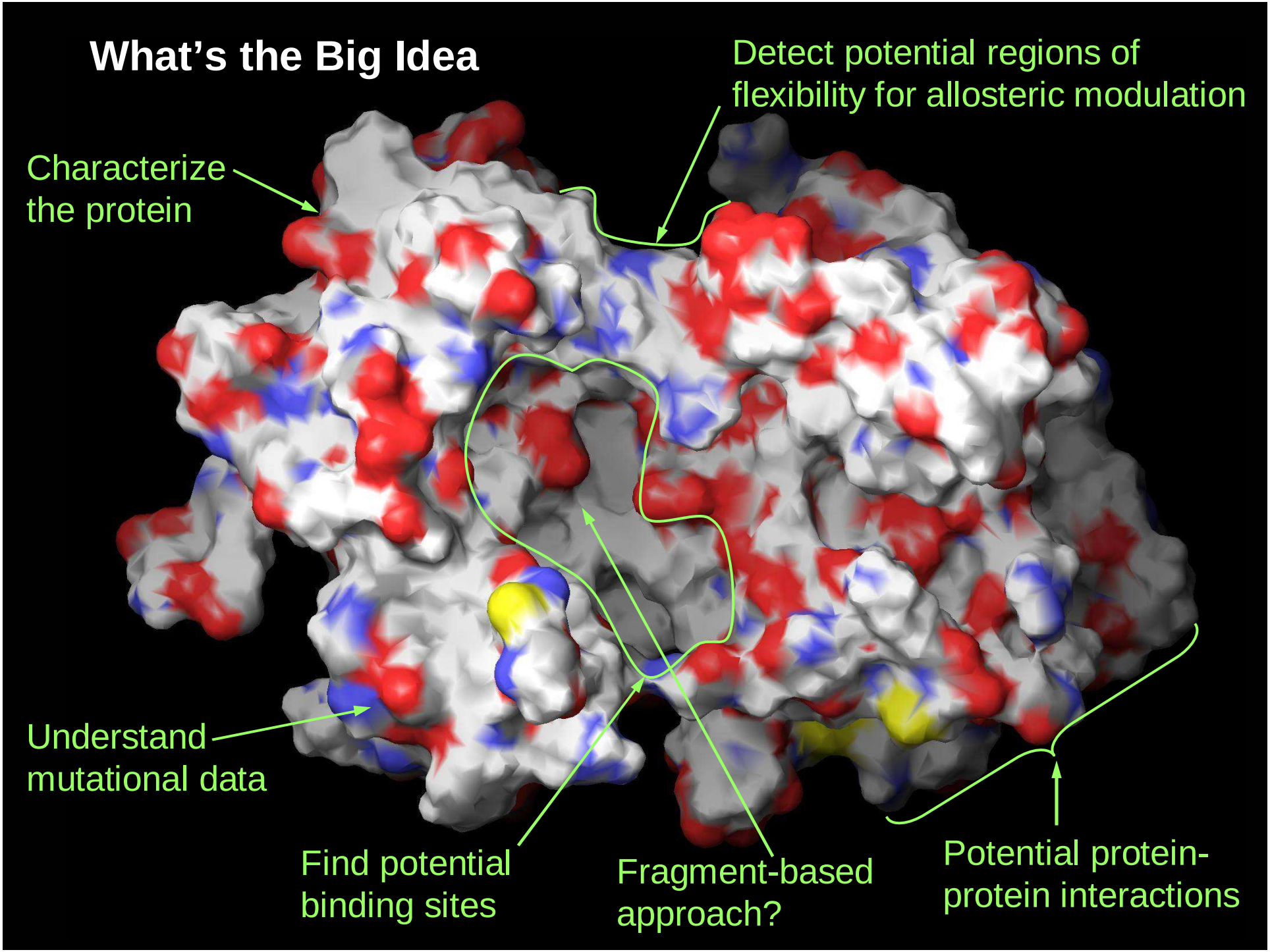


Cheminformatics

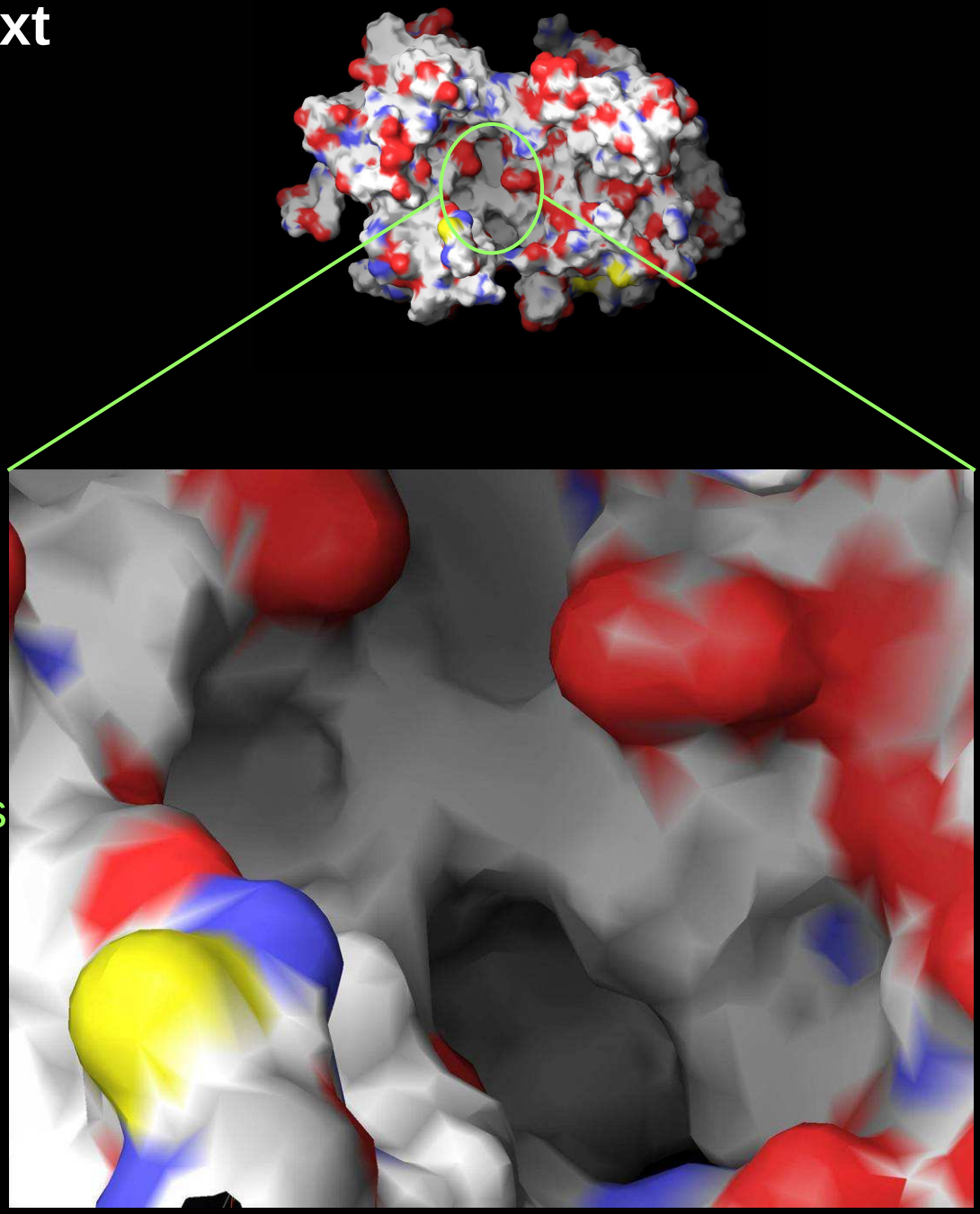


Pharmacophore Modeling




What's the Big Idea
Detect potential regions of flexibility for allosteric modulation
Characterize the protein
Understand mutational data
Find potential binding sites
Fragment-based approach?
Potential protein-protein interactions

What Next



Characterize binding site

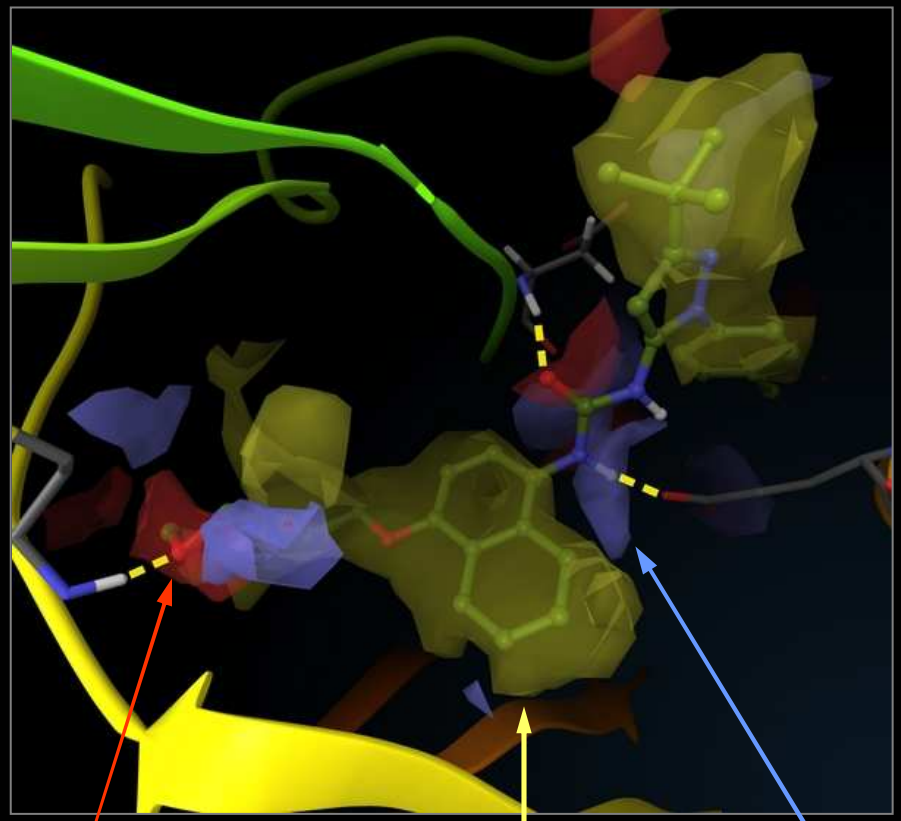
Dock molecules for validation

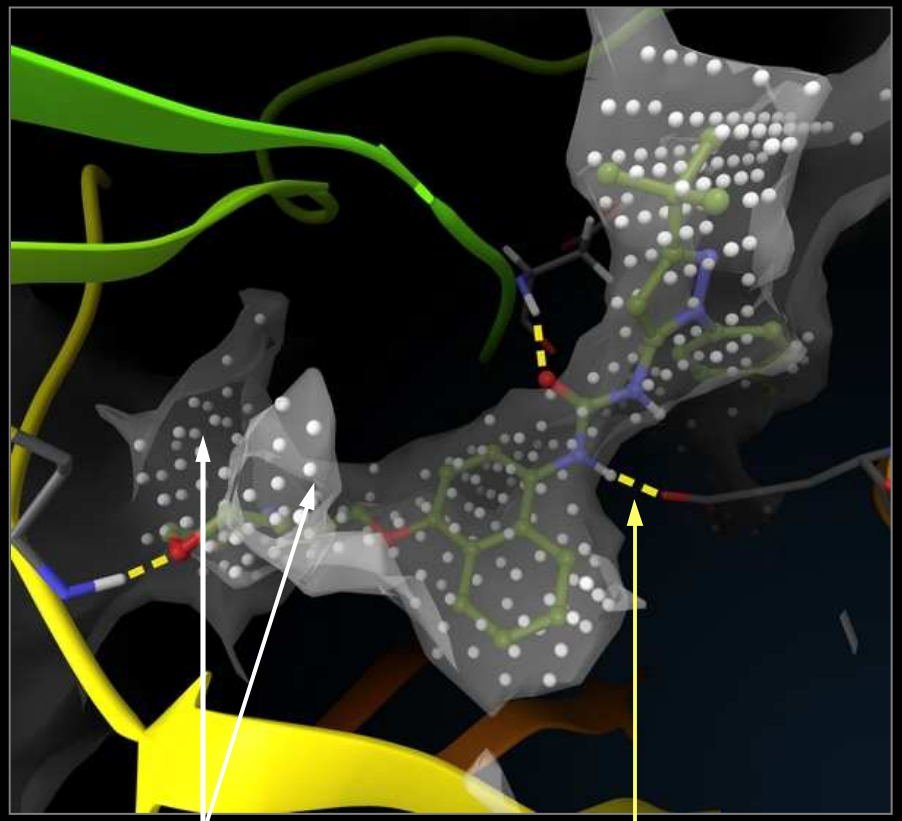
Compare with experimental data, if any

Use multiple receptor structures to account for flexibility

Accurate preparation of the binding site is essential

Binding Site Visualization and Complementarity Analysis





H-bond Acceptor Region

Hydrophobic

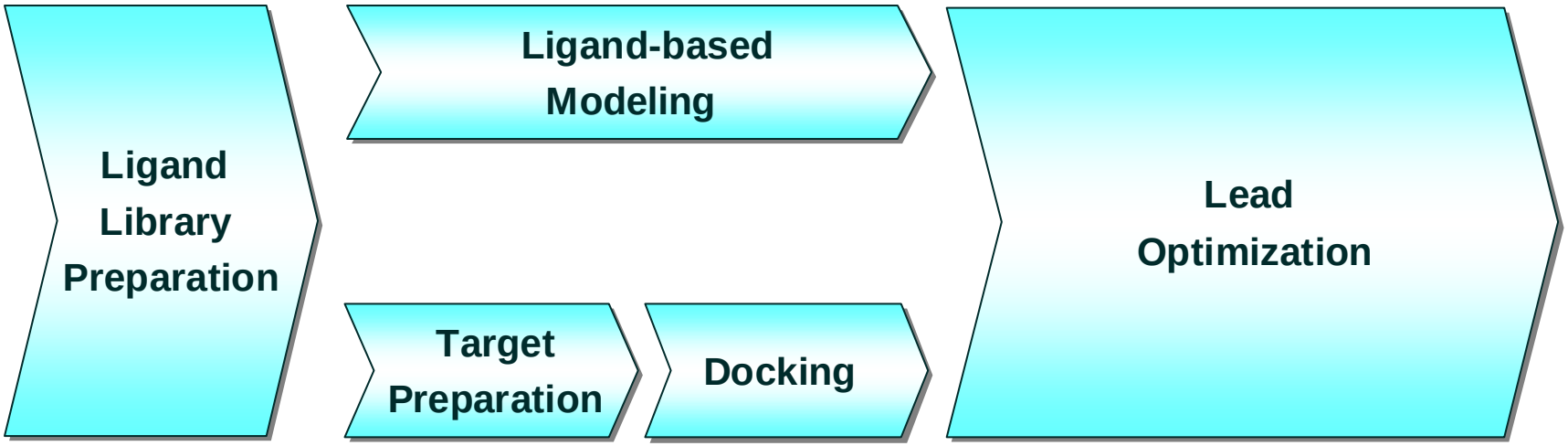
H-bond Donor Region

Cavity Detection

Existing H-bonds

SCHRÖDINGER.

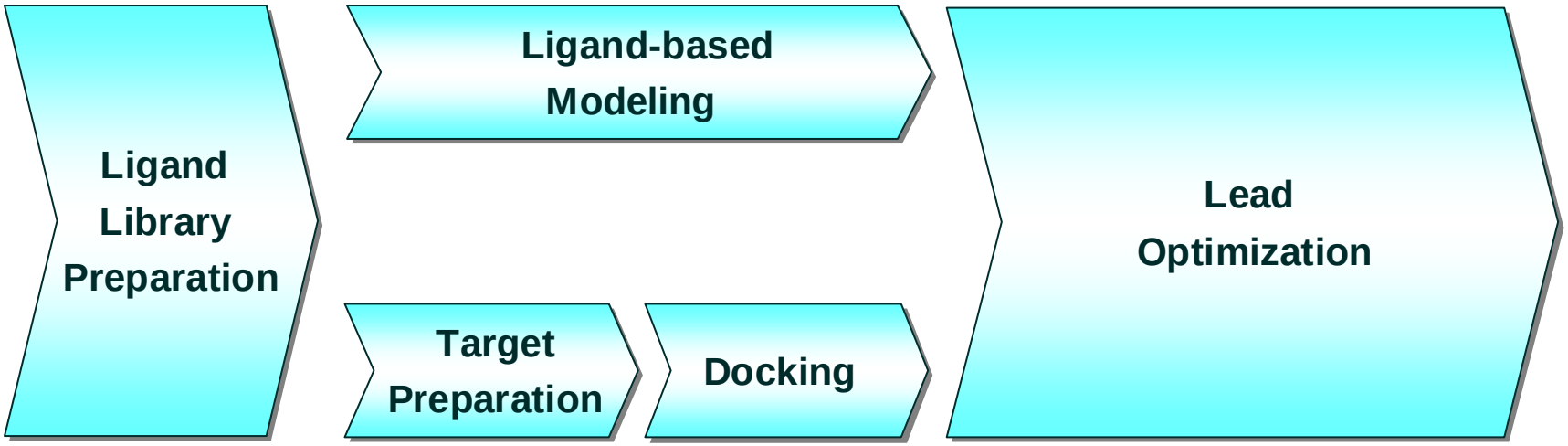
Computer-Aided Drug Discovery Workflow



Computer-aided drug design tools can be applied from the early discovery process through optimization.

SCHRÖDINGER.

Computer-Aided Drug Discovery Workflow



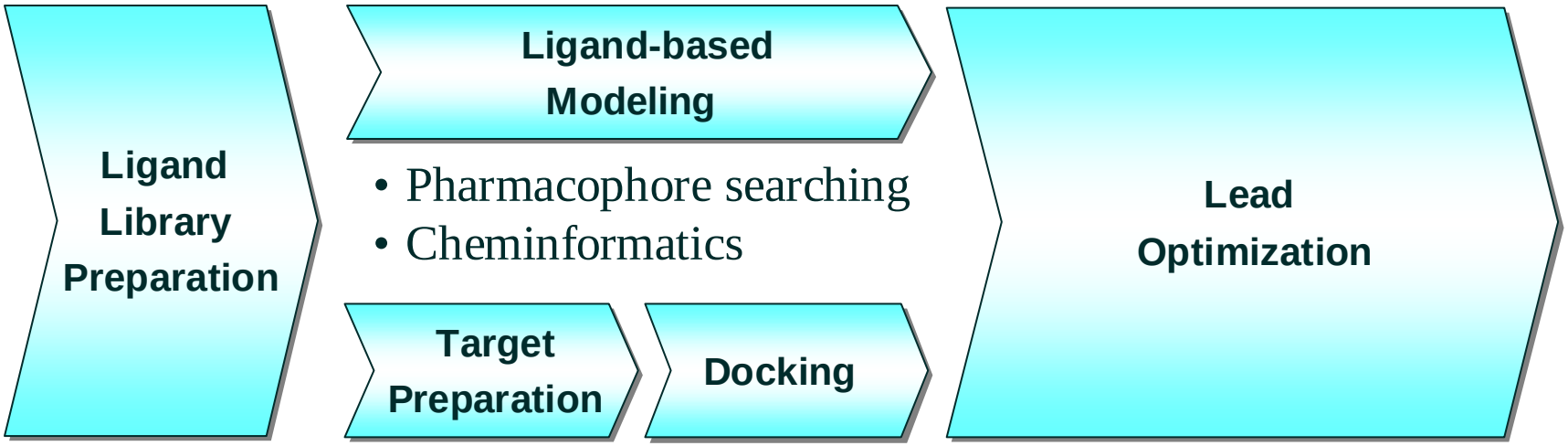
- 1D/2D→3D
  - Tautomers
  - Ionization states
  - Stereochemistry

Essential for physics-based methods

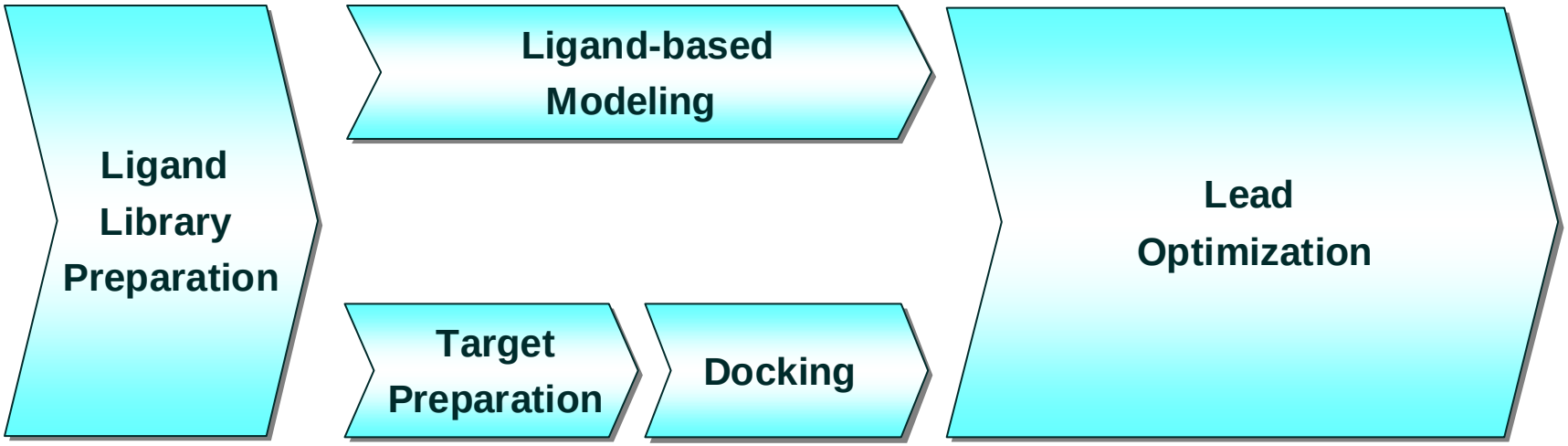
- Combinatorial libraries
- Target-specific libraries
- Conformation generation
- Energetic analysis

SCHRÖDINGER.

Computer-Aided Drug Discovery Workflow



Computer-Aided Drug Discovery Workflow



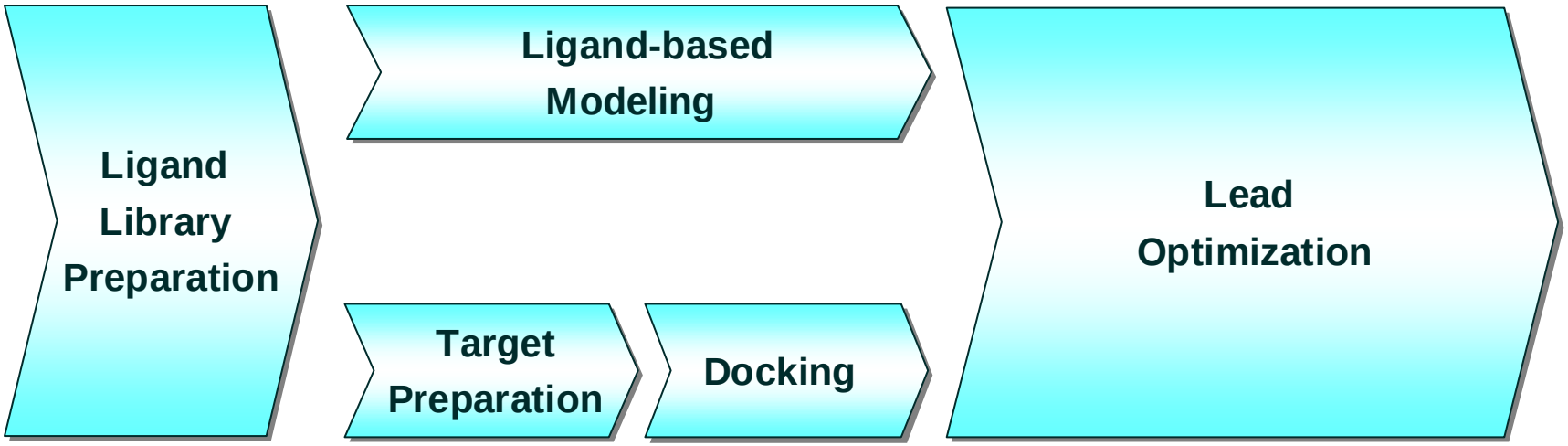
- Assignment of protein states
  - Ambiguous states (Asn, Gln, His)
    - May need multiple states
  - Addition of hydrogens
    - Hydroxyl orientations
- Treatment of waters

Essential for physics-based methods.
Garbage in, garbage out.

- Docking choices
  - Accuracy versus high throughput
  - Constraints
  - Rescoring and filtering
  - Multiple structures (ensembles)

SCHRÖDINGER.

Computer-Aided Drug Discovery Workflow



- Improved scoring functions
- More accurate solvent models
- Using experimental SAR data
- Accounting for off-targets
- ADME-Tox properties

SCHRÖDINGER.

What We Can and Cannot Do

- Routine
  - Small molecule conformation generation and energy profiling
  - Visualizing crystal structures
  - Binding site characterization
  - Virtual screening to enrich databases for actives
    - Cheminformatics, ligand-based, and structure-based
  - Predict binding modes when receptor can be treated rigidly
- Difficult
  - Separating highly from weakly active compounds
  - Predicting side chain rearrangements and backbone relaxation
- Very Challenging
  - Predicting binding free energies
  - Predicting large scale protein movements
  - Mapping free energy surfaces
  - Understanding off-target effects

What Makes the Difficult Things Difficult?

- Force field are approximate
  - Quantum mechanics would be better, but is too computationally expensive for most tasks
- Conformational sampling can be limiting
  - Typical drug like molecules can have many thousands of local minima that must be evaluated
  - Proteins have a significantly larger accessible conformational space
- The solution
  - Focus on specific problems
  - Know the limits of your method
  - Keep up with current methods
    - Methods are always improving
    - New resources can make problems accessible
      - Cloud Computing
  - Work closely with experts (i.e. the molecular modelers)
  - Ask questions
    - There are few black & white problems in this field

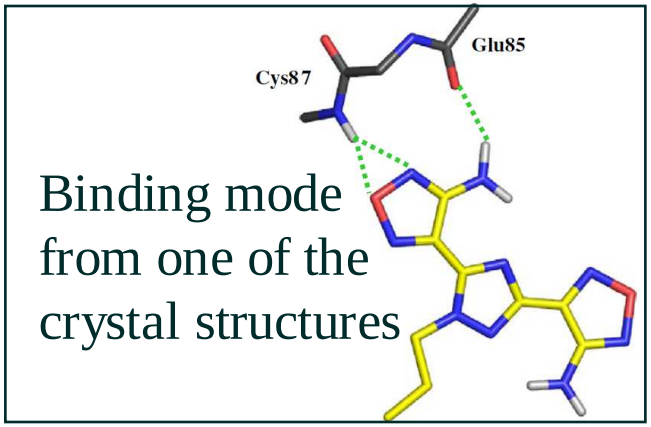
SCHRÖDINGER.

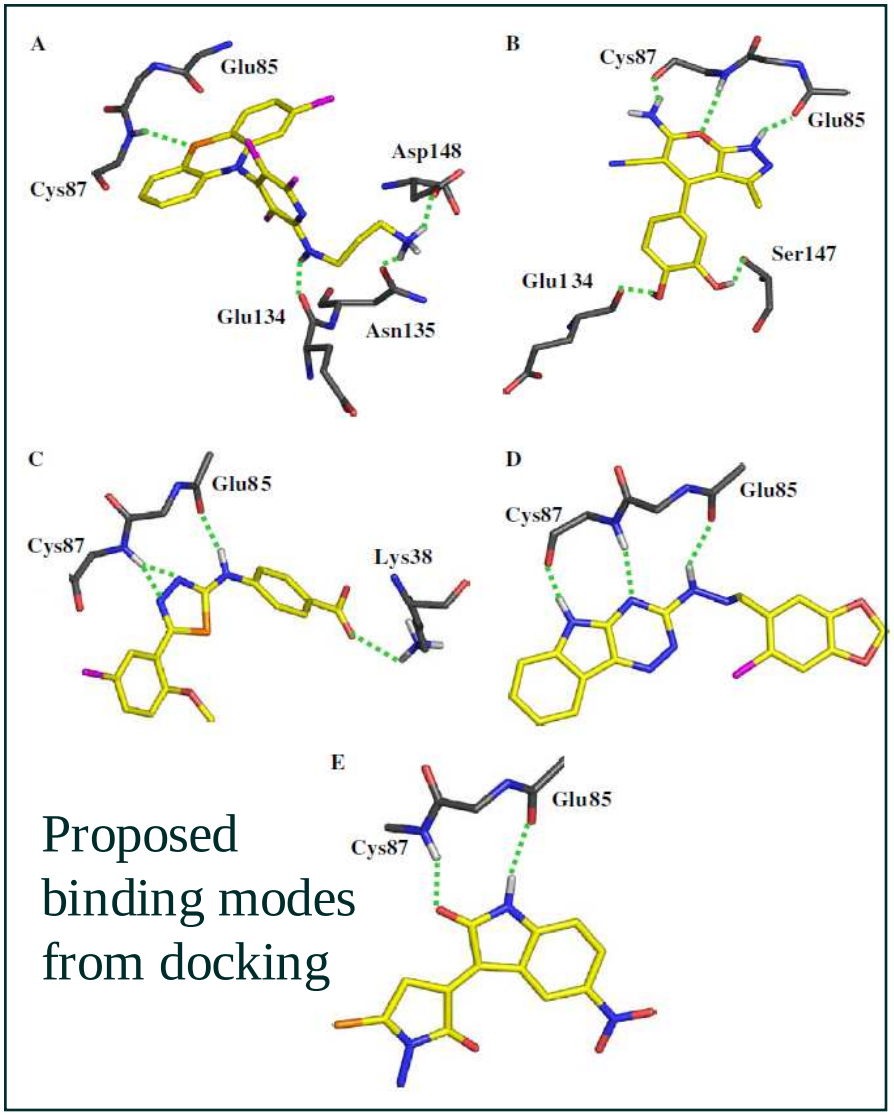
Examples of Published Applications

- Questions to think about
  - What approach was taken
  - What made these projects successful
  - What can be learned for other applications
  - How general is the method
  - Are the results statistically significant
- Small subset of applications to be presented here
  - Structure-based virtual screening
  - Treatment of water molecules
  - Molecular dynamics

Structure-based Virtual Screening Example 1

- Researchers at Vernalis used docking to screen commercially available compounds; found 10 novel inhibitors to Chk1 kinase
- Novel hinge interaction motifs were discovered
- Crystal structures were obtained for 4 inhibitors
  - The others were docked



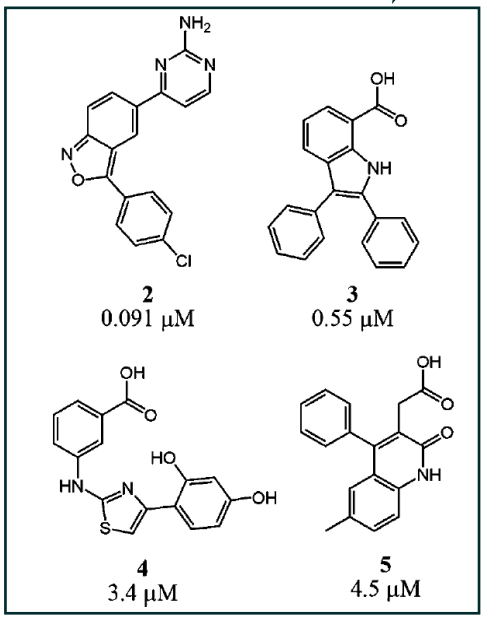


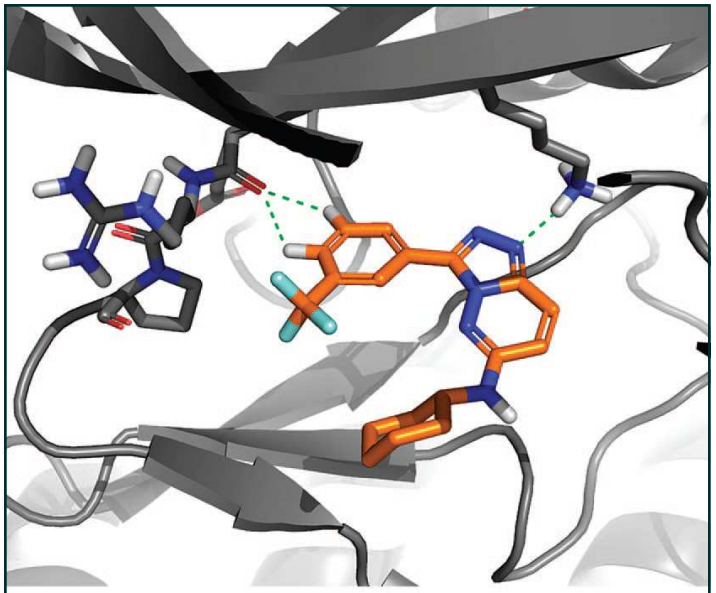
Foloppe, N., et al. Identification of chemically diverse Chk1 inhibitors by receptor-based virtual screening. *Bioorg Med Chem* **2006** (14) 4792–4802

SCHRÖDINGER.

Structure-based Virtual Screening Example 2

- Researchers at Vertex used docking to supplement experimental HTS and found 4 novel hits for Pim-1 kinase
- Used special aromatic CH••O hydrogen-bond constraint to the hinge
- Enrichment of actives 14x over HTS





1

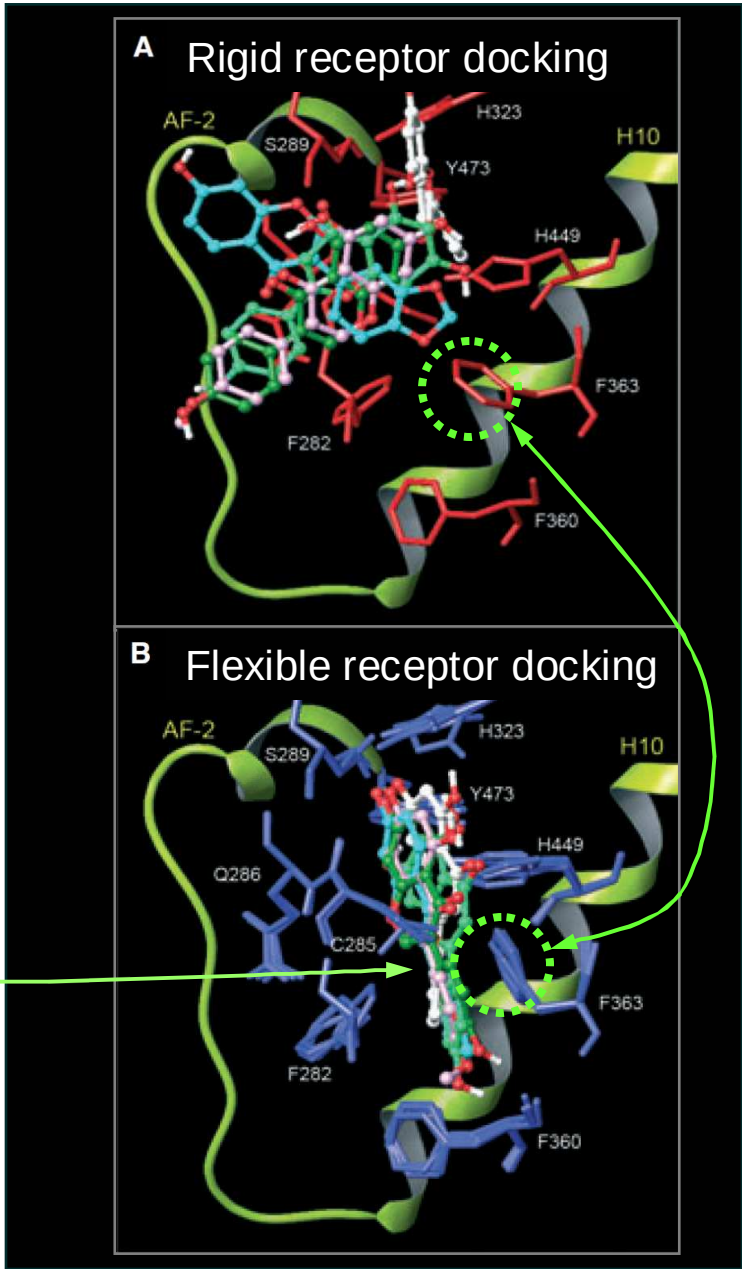
Crystal structure used for docking (PDB code 3BGQ)

Pierce, A.C., et al. Docking study yields four novel inhibitors of the protooncogene Pim-1 kinase. *J Med Chem* **2008** (51) 1972-1975

SCHRÖDINGER.

Accounting for Receptor Flexibility (Induced Fit)

- Many targets are known to be flexible, but the exact nature of the receptor movements are not always obvious
- Methods have been developed to treat some degree of receptor flexibility, usually involving side chain conformations and minor backbone rearrangement
- Researchers at the University of Sydney identified novel PPAR-γ agonists from a natural product library
  - Receptor flexibility was required to get good and consistent poses



Salam, N.K., et al. Novel PPAR-gamma agonists identified from a natural product library: A virtual screening, induced-fit docking and biological assay study. *Chem Biol Drug Des* **2008** (71) 51-70

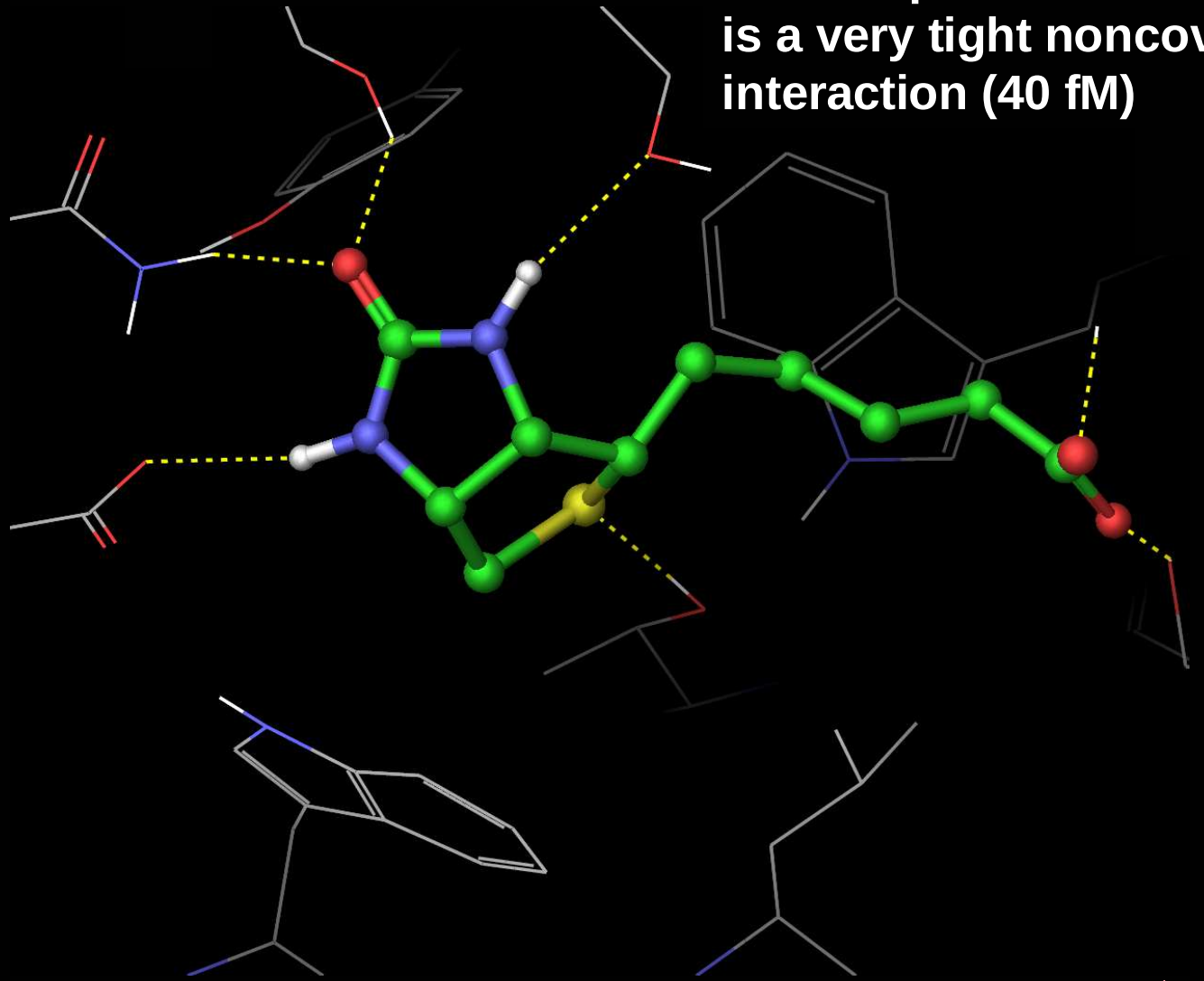
The Role of Waters in Drug Discovery

- "Hydrophobic effect" is driven by release of water molecules
- Explicit nature of water is essential to describe water behavior
- Water molecules have a great deal of mobility, making them ideal chemical probes with real physical implications
  - Water molecules are competing with ligands
  - We can learn from water locations and interactions
- Recent advances in methods and algorithms have allowed for the quantification of water molecule thermodynamics
    - Lazaridis, T. (1998) *J Phys Chem. B* 102:3531–3541
      - Inhomogeneous fluid approach to solvation thermodynamics
    - Young, T., et al. (2007) *PNAS* 104:808-813
      - Initial validation to describe hydrophobic enclosure motif
    - Abel, R., et al. (2008) *J Am Chem Soc* 130:2817-2831
      - Predicting affinity for congeneric pairs of factor Xa inhibitors
    - Beuming, T., et al. (2009) *Prot Sci* 18:1609-1619
      - Affinity and selectivity insights for PDZ domains
    - Robinson, D., et al. (2010) *ChemMedChem* (online Early View)
      - Kinase selectivity
    - Guimaraes, C., et al. (2010) *J Chem Inf Model (ASAP)*
      - Scoring of factor Xa and CDK2 ligands
    - Higgs, C., et al. (2010) *Med Chem Lett* (accepted)
      - Affinity predictions for a series of A2A GPCR inhibitors

SCHRÖDINGER.

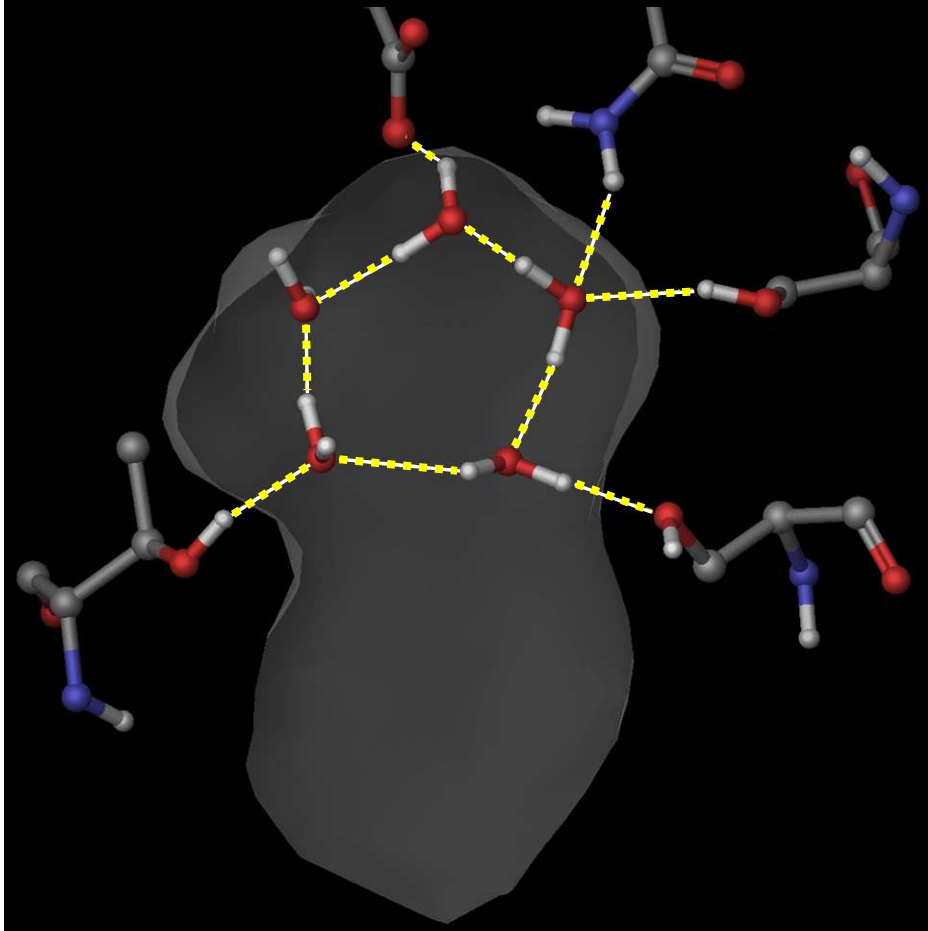
What Can we Learn from Waters?

The streptavidin/biotin complex is a very tight noncovalent interaction (40 fM)

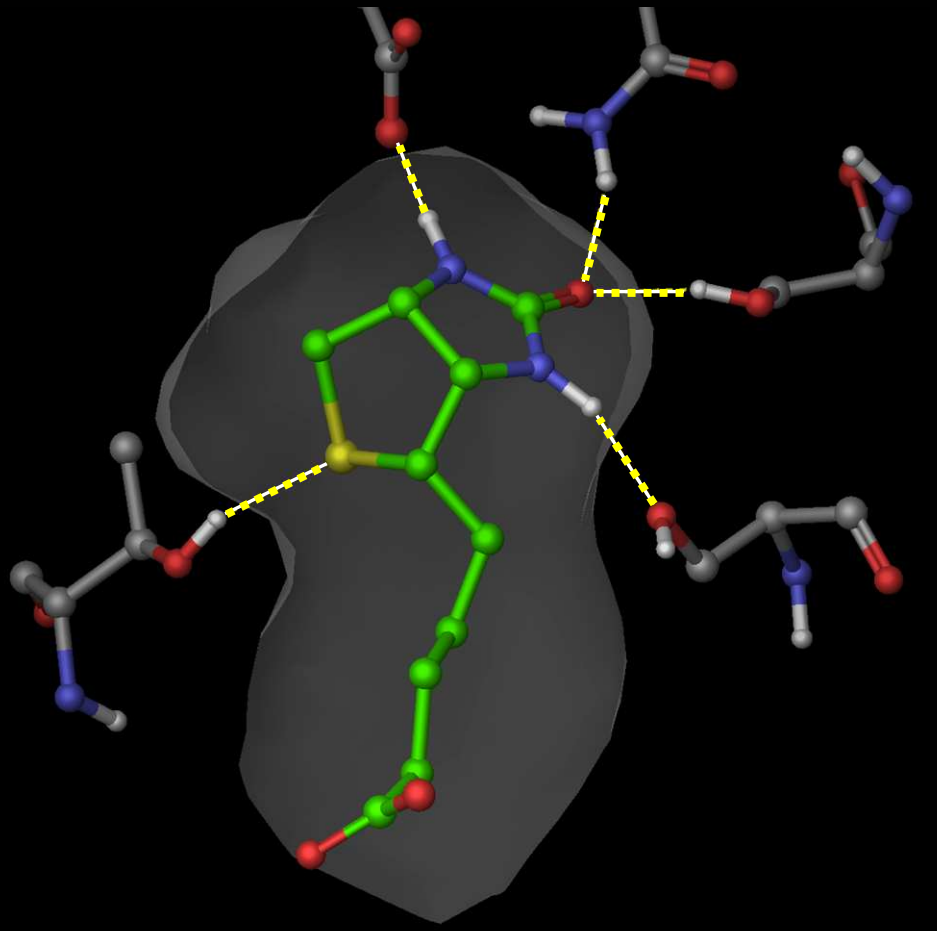


SCHRÖDINGER.

Streptavidin/biotin complex



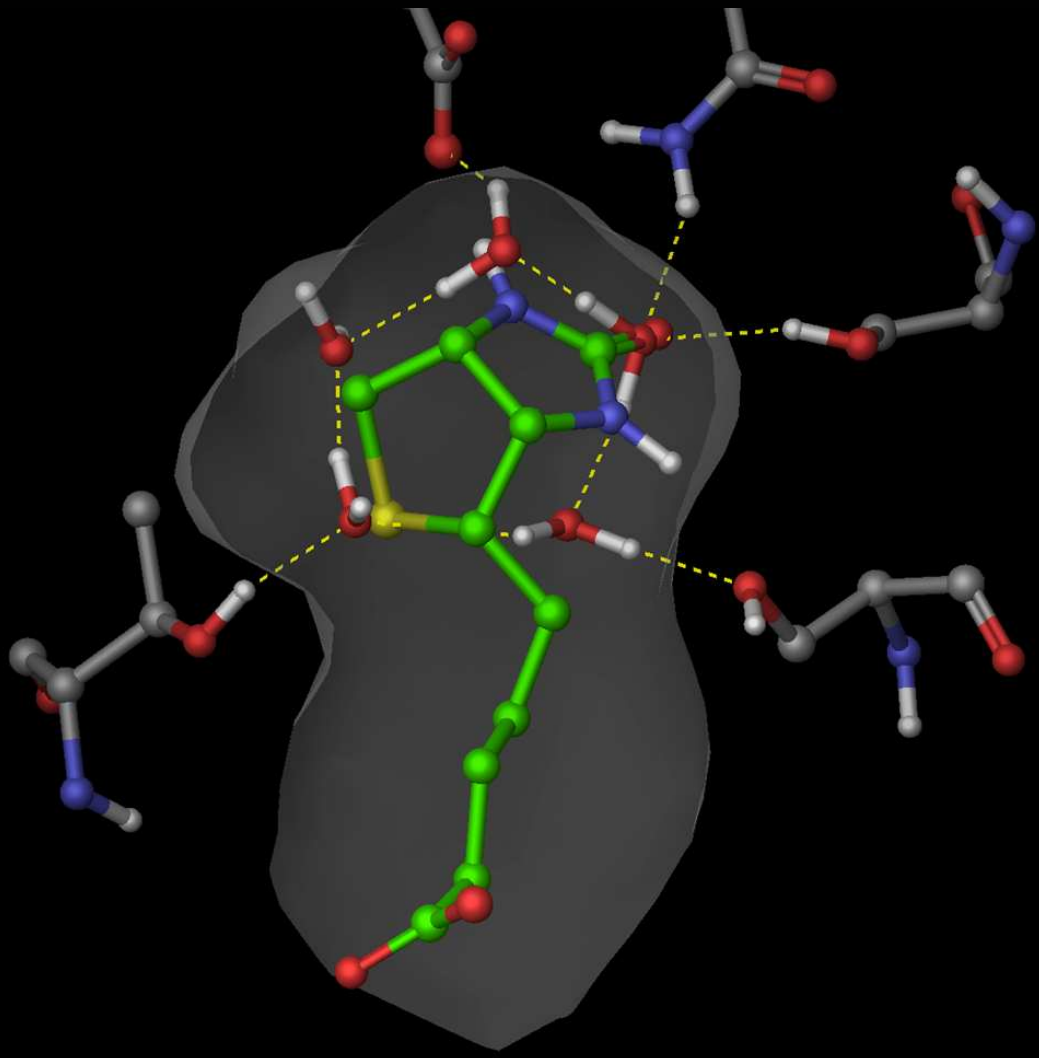
Clathrate ice-like water structure persists through an MD simulation



Biotin displaces these five waters and makes back the key H-bond interactions

SCHRÖDINGER.

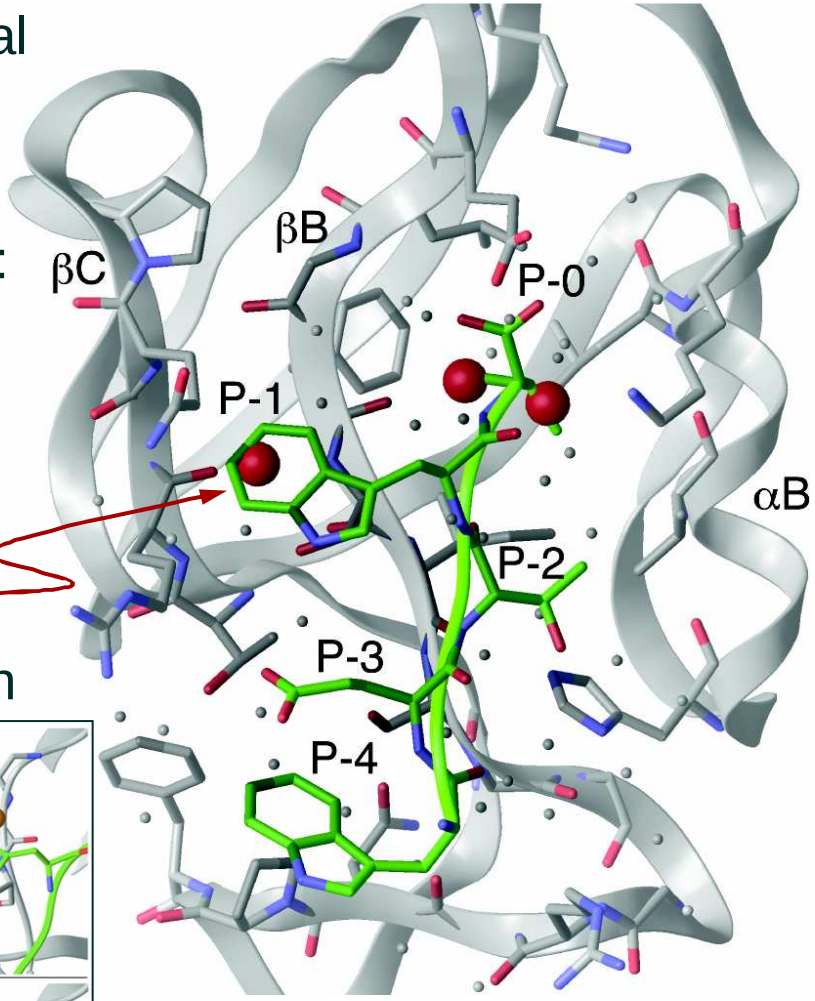
Streptavidin/biotin complex

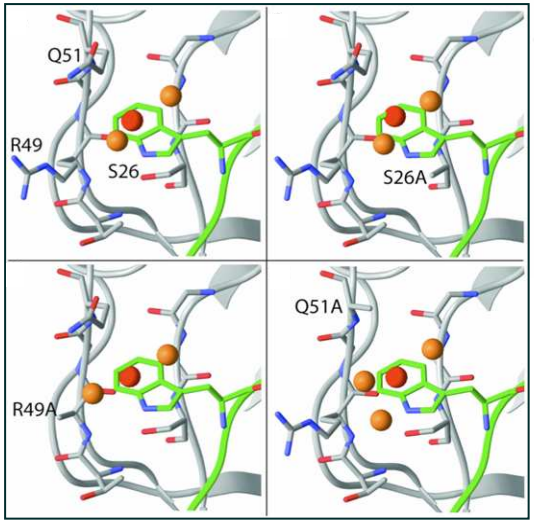


SCHRÖDINGER.

High-energy Water Determines P-1 Affinity/Specificity in PDZ Domains

- Phage display shows WETWV is the optimal Erbin binder (Skelton et al., JBC, 2003)
- However, mutagenesis of the PDZ domain cannot explain the crucial role of Trp at P-1:
  - *"curiously, alanine substitutions of residues that contact Trp-1 did not decrease peptide binding" (Skelton et al., JBC, 2003)*
- High-energy water at P-1 position explains preference for Trp
- Alanine mutations in P-1 have little effect on activity





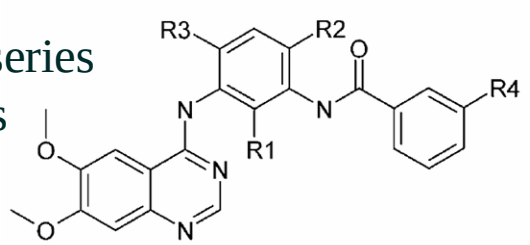
Beuming, T., et al. High-energy water sites determine peptide binding affinity and specificity of PDZ domains. *Prot Sci* **2009** 18:1609-1619

SCHRÖDINGER.

Scoring Congeneric Compounds for Lead Optimization

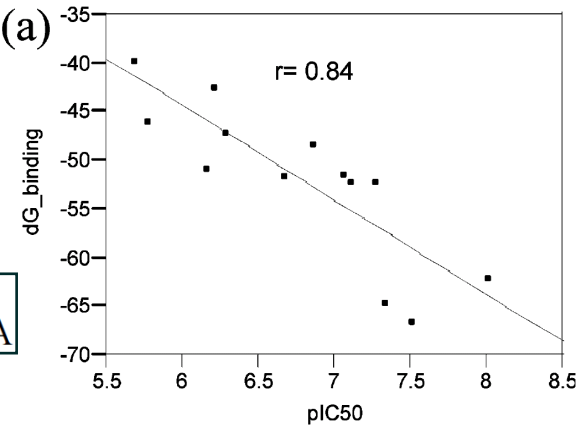
- For congeneric molecules, there has been success at predicting trends in binding activity
- Researchers at AstraZeneca made accurate predictions using MM-GBSA (an approximate free energy method) for 4 kinases
  - P38, aurora A, CDK2, and Jnk-3
- Note: This is challenging and there are a number of counter-examples (often not published) that show significantly less predictive ability
  - Validate your model

Activities for a series of P38 inhibitors



compd	R1	R2	R3	R4	IC_{50} (μM)
1a	H	H	H	H	0.141
1b	H	F	F	H	0.054
1c	H	H	Cl	H	0.088
1d	H	H	Me	H	0.078
1e	H	Cl	F	H	0.518
1f	H	Me	H	H	2.090
1g	F	H	H	H	0.690
1h	H	Cl	H	H	0.615
1i	H	H	H	NMe_2	0.212
1j	H	H	Cl	NMe_2	0.047
1k	H	H	Me	NMe_2	0.031
1l	H	Cl	H	NMe_2	1.690
1m	H	H	Me	*N*-morpholino	0.010

Predicted activities using MM-GBSA



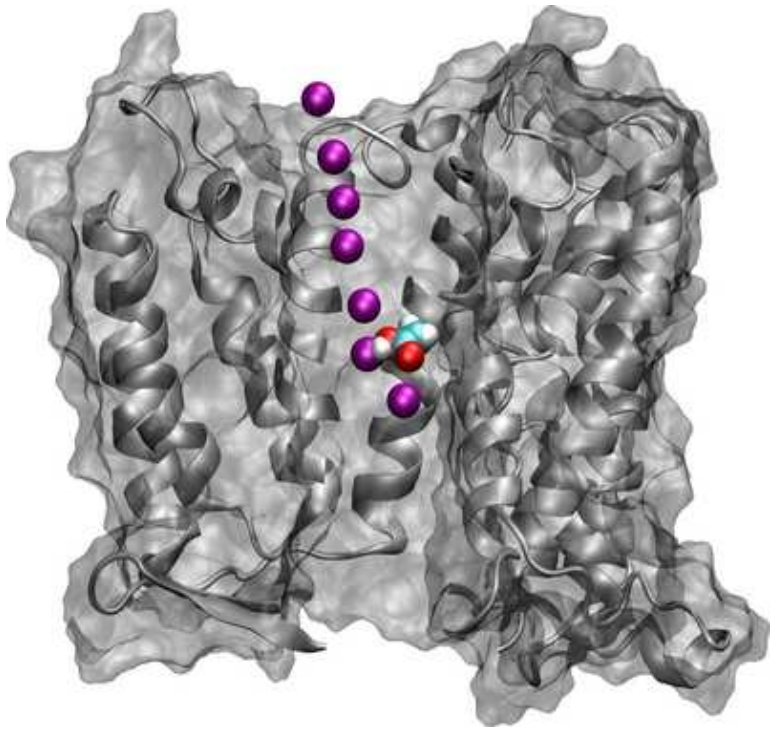
$$\Delta G_{\text{bind}} = \Delta E_{\text{MM}} + \Delta G_{\text{solv}} + \Delta G_{\text{SA}}$$

Lyne, P.D., et al. Accurate prediction of the relative potencies of members of a series of kinase inhibitors using molecular docking and MM-GBSA scoring. *J Med Chem* **2006** (49) 4805-4808

SCHRÖDINGER.

Molecular Dynamics

- Probing protein flexibility
- Generation of structural ensembles
- Visualization molecular processes
- Estimation binding energies
  - Solvation free energies
  - Binding free energies
  - Conformational free energies



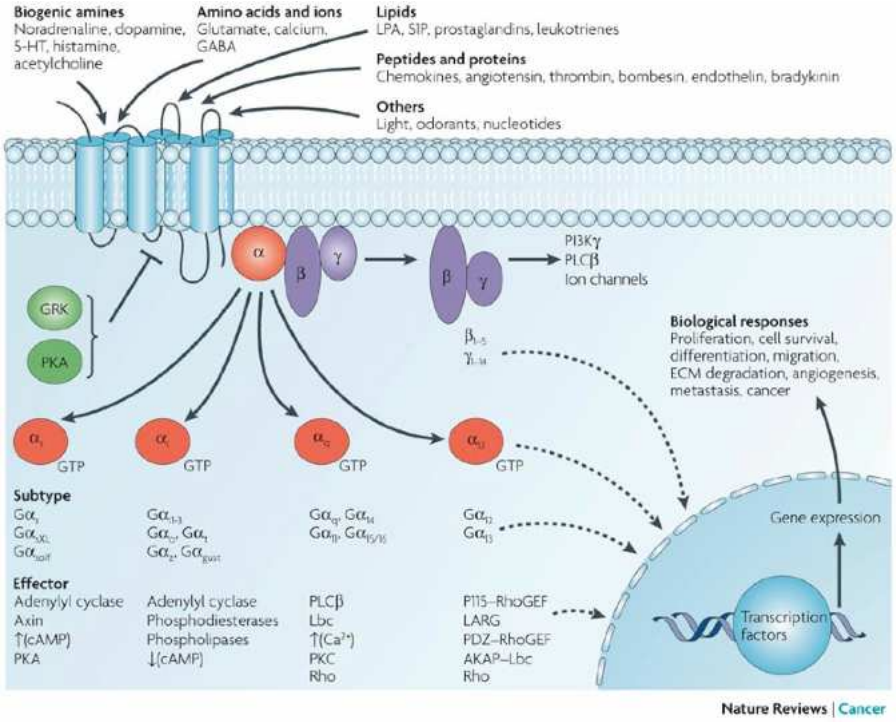
SCHRÖDINGER.

A Brief History of Biomolecular Simulations

- 1977
  - bovine pancreatic trypsin inhibitor (bPTI)
  - ~10 ps simulation of ~500 atoms
  - Nature paper
  - Karplus group (CHARMM)
- 1998
  - Partial protein folding (villin headpiece)
  - 200 ns simulation of ~20,000 atoms
  - Kollman group (Amber)
- 2006
  - Satelite tobacco mosaic virus (STMV)
  - 50 ns simulation of ~1 million atoms
  - Schulten group (NAMD)
- 2006
  - Protein folding (villin headpiece)
  - 500 μs simulation of ~20,000 atoms
  - Pande group (Folding@Home)

G-protein coupled receptors

- Largest gene family in the human genome
- Represent the target for >30% of drugs
- Structural data has historically been scarce



G-protein-coupled receptors and cancer. Robert T. Dorsam and J. Silvio Gutkind. Nature Reviews Cancer **2007** 7, 79-94

Table 2. Best-selling therapeutics targeted at GPCRs in 2000 [2]

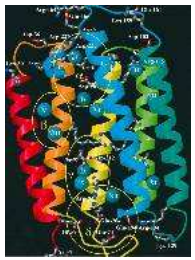
Product	Receptor(s)	Indication	Company
Zyprexa®	Serotonin 5-HT_2 and dopamine	Schizophrenia or antipsychotic	Eli Lilly, Indianapolis, IN, USA
Claritin®	Histamine H_1	Rhinitis or allergy	Schering-Plough, Kenilworth, NJ, USA
Risperdal™	Serotonin 5-HT_2	Schizophrenia	Johnson & Johnson, Titusville, NJ, USA
Imigran™	Serotonin 5-$HT_{1B/1D}$	Migraine	GlaxoSmithKline, Harlow, UK
Cozaar®	Angiotensin AT_2	Hypertension	Merck and Co., Whitehouse Station, NJ, USA
Serevent®	β2-adrenoceptor	Asthma	GlaxoSmithKline
Singulair®	BLT_1	Asthma	Merck and Co.
Gastridin™	Histamine H_2	Peptic ulcer	Merck and Co.
Zantac/Tagamet™	Histamine H_2	Peptic ulcer	GlaxoSmithKline
Zirtec™	Histamine H_1	Rhinitis or allergy	Pfizer, Sandwich, UK
BuSpar®	Serotonin 5-HT_{1a}	Anti-depressant	BMS, New York, NY, USA
Gaster®	Histamine H_2	Peptic ulcer	Yamanouchi, Tokyo, Japan

Target validation of G-protein coupled receptors. Wise A, Gearing K, Rees S. Drug Discov Today. **2002** Feb 15;7(4):235-46.

SCHRÖDINGER.

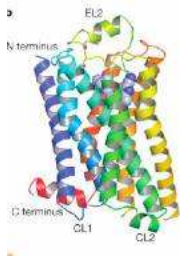
Milestones in structure determination

Henderson et al., Model for the structure of **bacteriorhodopsin** based on high-resolution **electron cryo-microscopy** (3.5Å). J Mol Biol. 1990

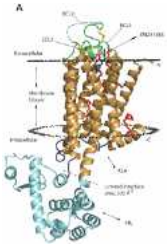


Grigorieff et al., Electron-crystallographic refinement of the structure of **bacteriorhodopsin**. J Mol Biol. 1996

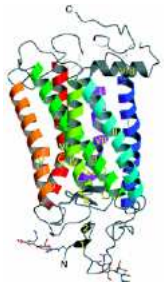
Cherezov et al., High-resolution **crystal structure** of an engineered human **beta2-adrenergic G protein-coupled receptor**. Science. 2007



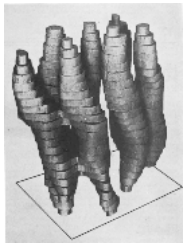
Warne et al., Structure of a **beta1-adrenergic** G-protein-coupled receptor. Nature. 2008



Jaakola et al., The 2.6 angstrom **crystal structure** of a human **A2A adenosine receptor** bound to an antagonist. Science. 2008

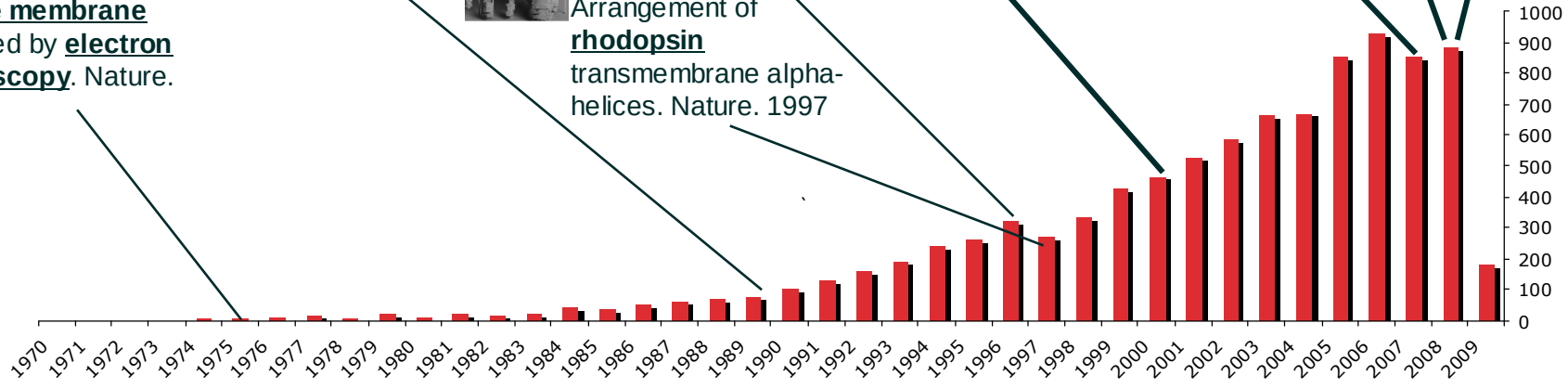


Palczewski et al., Crystal structure of **rhodopsin**: A G protein-coupled receptor. Science. 2000



Henderson et al., . Three-dimensional model of **purple membrane** obtained by **electron microscopy**. Nature. 1975.

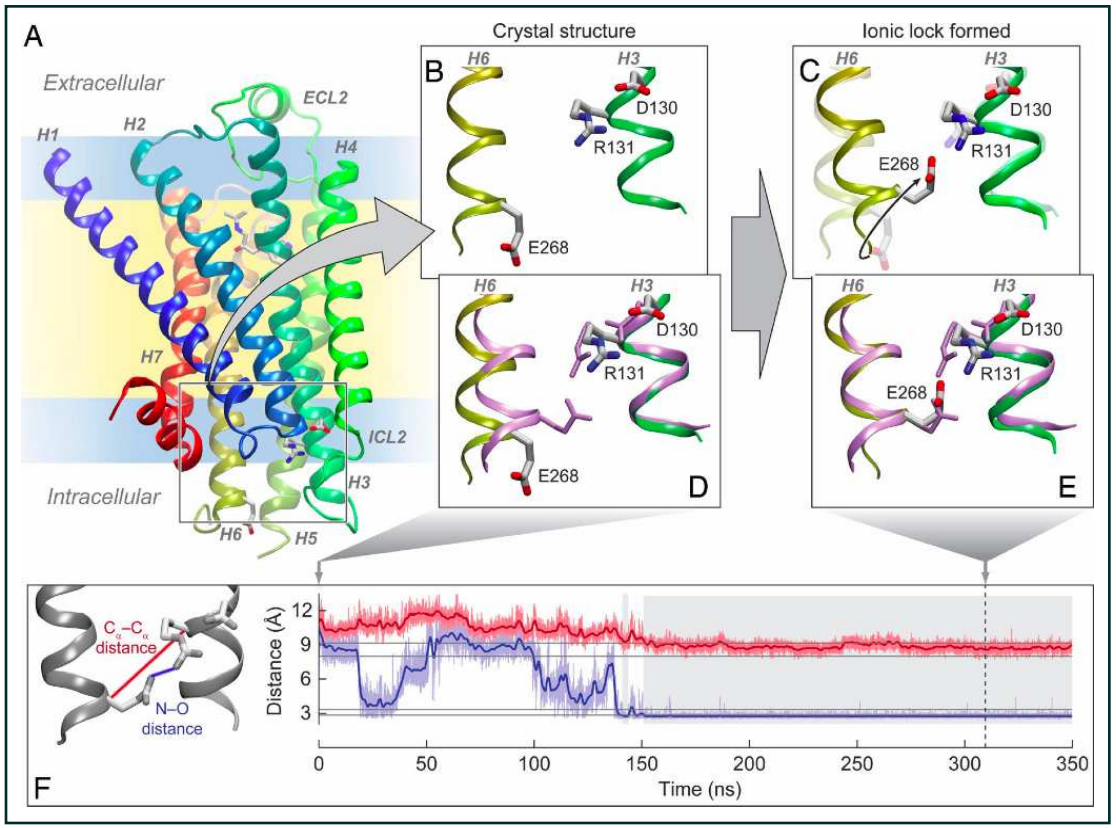
Unger et al., Arrangement of **rhodopsin** transmembrane alpha-helices. Nature. 1997



PubMed search: molecular model G-protein coupled receptor

Probing Flexibility in β_2 Adrenergic Receptor (B2AR) GPCR

- Scientists at D. E. Shaw Research ran a series of long simulations to understand the ionic lock between helices 3 & 6 in B2AR
- While these simulations were relatively long, it is possible to gain insights using shorter simulations or by taking advantage of enhanced sampling techniques
- Note: Simulations can be tricky and require some degree us user expertise



Dror, R.O., et al. Identification of two distinct inactive conformations of the beta2-adrenergic receptor reconciles structural and biochemical observations. *Proc Natl Acad Sci USA*, **2009** (106) 4689-4694

SCHRÖDINGER.

Are Molecular Modeling Tools Right for Your Project?

- Questions to ask
  - Is a crystal structure available?
    - Structural analysis
    - Docking
    - Binding energy prediction
    - Modification of existing molecules (scaffold hopping, combinatorial chemistry, lead optimization, etc.)
    - If no, cheminformatics and ligand-based tools can be very useful
  - Are there known active compounds?
    - Validate models based on known SAR
  - What are the project objectives?
    - Potency
    - Selectivity
    - Avoiding existing IP
    - Altering ADME-Tox profile
    - Other?

Where to Start

- What do you have accessible now?
  - Most companies have in-house modelers and software to help get things going
- Start working with software
  - Online training guides and video tutorials can be invaluable
    - http://www.schrodinger.com/supportcenter/
- Start a collaboration
  - Many academic modeling groups and software companies are looking for experimental validation or provide collaboration services

Software to Get Started

- Graphical user interfaces (GUIs)
  - Can be valuable for browsing PDB files, binding site analysis, etc.
  - Limited computation capabilities (no energies, docking, etc.)
  - Free GUIs are available:
    - Jmol, Maestro, PyMOL, RasMol, VMD
- Computational engines
  - A great deal of academic methods and algorithms
    - Many are focused on molecular dynamics
    - Limited graphical interface support
    - Free computational engines are available (for academics):
      - Amber, CHARMM, Desmond, Gromacs, NAMD, Plop, etc.
  - Commercial code typically offers a nice GUI plus computational engines
    - Be sure to ask for applications support
    - Most companies offer free evaluations (1-3 months)
    - There are a number of well-established companies:
      - Accelrys, CCG, Open Eye, MolSoft, Schrödinger, Tripos, etc.
  - There are many molecular modeling programs:
    - http://en.wikipedia.org/wiki/Molecular_modelling

Caveats

- Proper protein and ligand preparation
  - The underlying physics is only as good as the input structures
  - While ligand preparation can be mostly automated, protein preparation should be done carefully with interactive modeling tools
- Know the limitations of your method
  - For example, trying to predict binding energies for compounds having an activity range of 1 log unit is beyond the scope of today's methods
    - However, trends may still be possible to predict
- Know the experimental data
  - Crystal structure quality
    - Is there really good density around all atoms?
      - If density is missing around the binding site, it needs to be accurately modeled
    - How flexible is the protein?
    - Are the waters really there? Are there waters missing?

References

- Docking comparison studies
  - Vertex: Perola, E., et al. “A detailed comparison of current docking and scoring methods on systems of pharmaceutical relevance” *Proteins* **2004** 56:235-249
  - GSK: Warren, G.L., et al. “A critical assessment of docking programs and scoring functions” *J Med Chem* **2006** 49:5912-5931
  - Columbia U. & Rutgers U.: Zhou. Z., et al. “Comparative performance of several flexible docking programs and scoring functions: Enrichment studies for a diverse set of pharmaceutically relevant targets” *J Chem Inf Model* **2007** 47:1599-1608
- Flexible receptor docking studies
  - Murray, C.W., et al. “The sensitivity of the results of molecular docking to induced fit effects: Application to thrombin, thermolysin and neuraminidas” *J Comp Aided Mol Des* **1999** 13:547-562
  - Sherman, W., et al. “Novel procedure for modeling ligand/receptor induced fit effects” *J Med Chem* **2006** 49:534-553
  - Cornell, W. and Kiyean, N. “Steroid hormone binding receptors: Application of homology modeling, induced fit docking, and molecular dynamics to study structure-function relationships” *Curr Top Med Chem* **2009** 9:844-853
- Calculation of binding energies
  - Gilson, M.K. and Zhou, H.X. “Calculation of protein-ligand binding affinities” *Annu Rev Biophys Biomol Struct* **2007** 36:21-42

Conclusions

- Many methods exist that can be used to augment experiments
  - Cheminformatics
  - Ligand-based
  - Structure-based
- Idea generation is extremely valuable
  - Work in groups and look at structures
- We do not needed to get everything right
  - Just need to help design more efficient experiments
  - Eliminating bad ideas can provide substantial value
- As with any field in science, most tasks will require close collaboration with experts
- Get started
  - Visualization tools
  - Collaborations
  - Retrospective analysis on a system you know well

Thank you for your attention.
Now, time for questions.

Contact: Woody.Sherman@schrodinger.com

SCHRÖDINGER

Q&A SESSION
Staying ahead of the game: Recent innovations in computational methods for drug discovery

Speaker: Woody Sherman
Schrodinger

Moderator: Karen Rossi
Bristol-Myers Squibb

Please submit your questions for the speaker via the Chat Panel in the GoToWebinar

Upcoming Event:
March 25, 2010. 2-3pm ET

"*How to Grow Your Small Business into a Large Corporation – The Story of SAIC and the Secret Sauce of Employee Ownership*"

Join us to learn from speaker Martin Staubus, Director of Consulting at the Beyster Institute, University of California San Diego. Want to learn the secret to growing your business by empowering your employees? How does it actually work? Join us to learn how small and medium sized companies, and their employees, can create a system of employee ownership that is tailored expressly for their individual needs.

ACS Webinars: Small & Medium Business Series

Connecting you with subject experts and global thought leaders in chemical sciences, management, and business.

To Register:
http://boilthisdown.org/?page_id=385