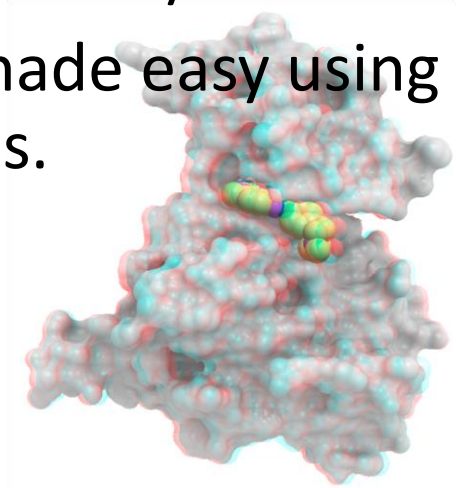
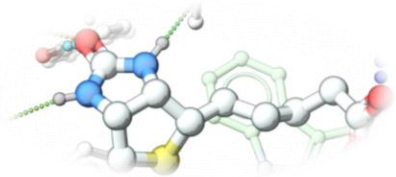
Molecular Graphics, Documents and Movies

Molecular Graphics

- 3D molecule annotation, coloring and representation
- Display binding pockets colored by binding properties
- Preparation of publication quality molecular images
- How to make fully interactive 3D slides including smooth and blending transitions
- How to import fully interactive 3D slides into Windows PowerPoint, web pages and iPad/Android devices
- Molecular movie making made easy using - movies from screenshots and slides.



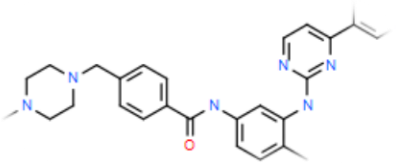
Browsing Molecular Data



Protein Structures

RCSB PDB PROTEIN DATA BANK

PocketTome

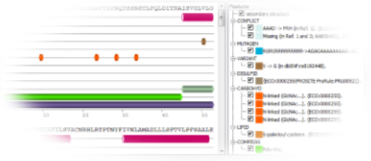


Chemical

DrugBank
Open Data Drug & Drug Target Database

ChEMBL

PubChem



Sequence

UniProt

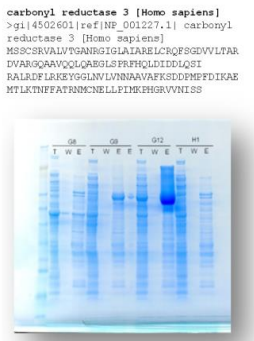
Pfam

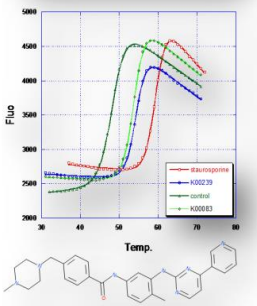
prosite

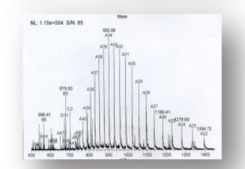
ActiveICM

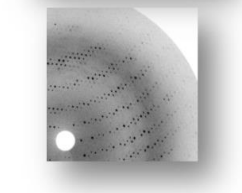
US Patent No:7,880,738

Gather Data





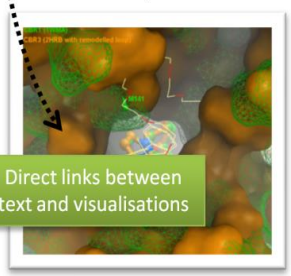




Interpret, Integrate and Annotate

Text annotation

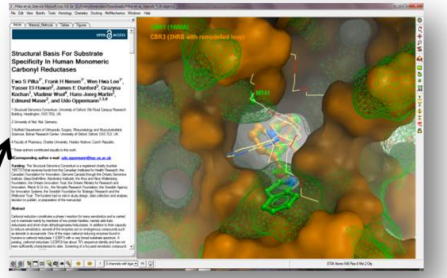
+



3D visualisations, annotations and animations

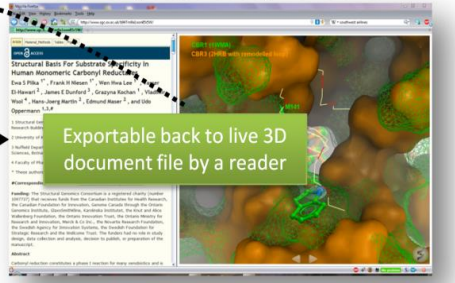
One File: 3D document: live data of various types

Publish and Share

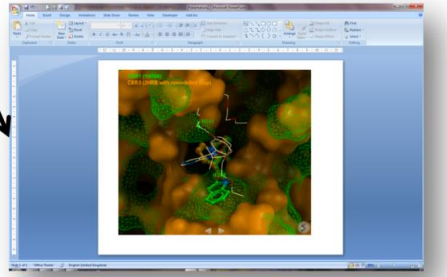


Standalone - ICM Browser

Live molecules, spreadsheets and plots, chemistry, sequence alignments e.t.c.



Web – activeICM



Office – activeICM

Microsoft PowerPoint, Word

SGC

Raush et al
Plos One 2009 (4) 10

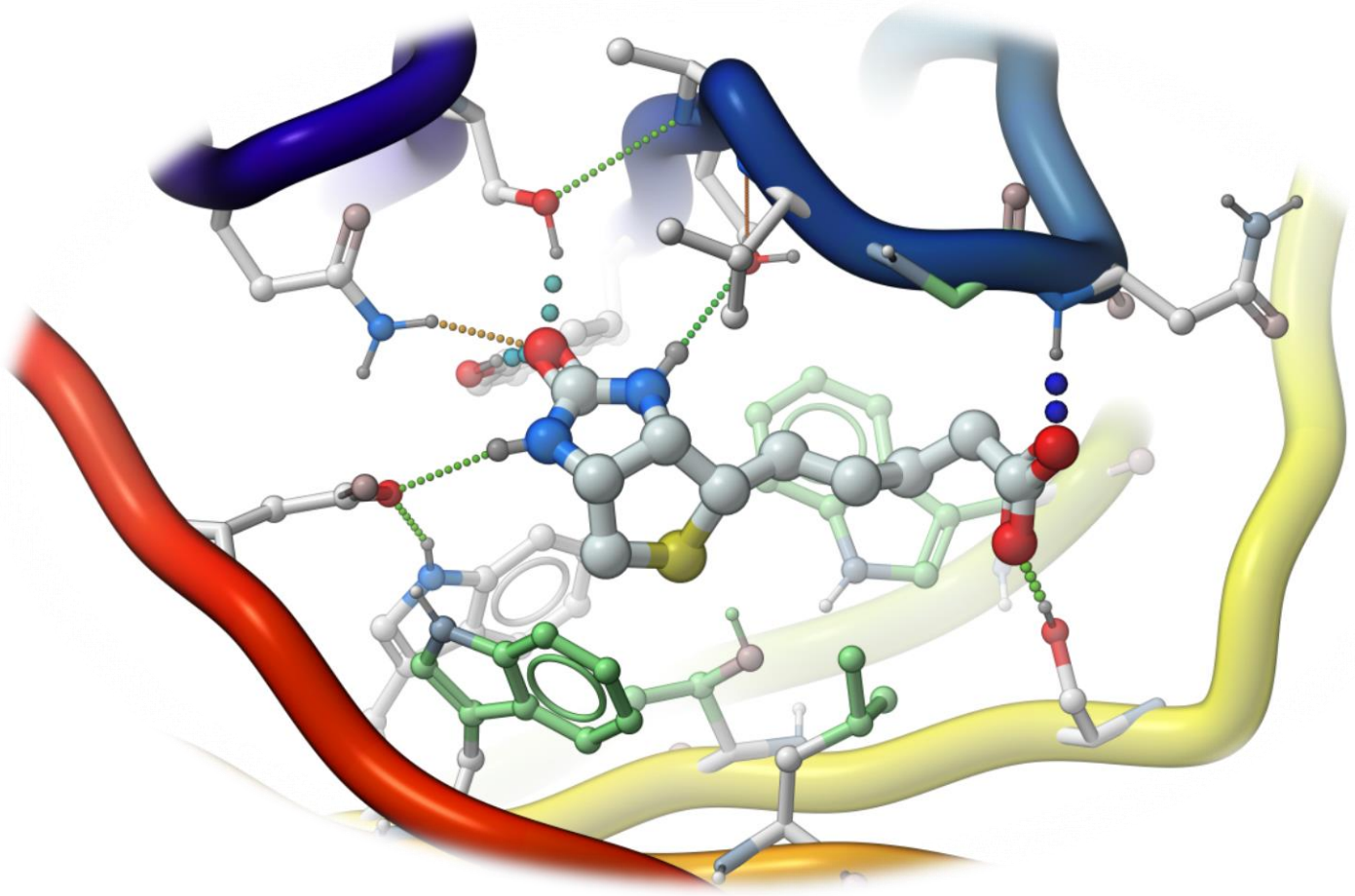
PLoS one
www.plosone.org

nature structural & molecular biology

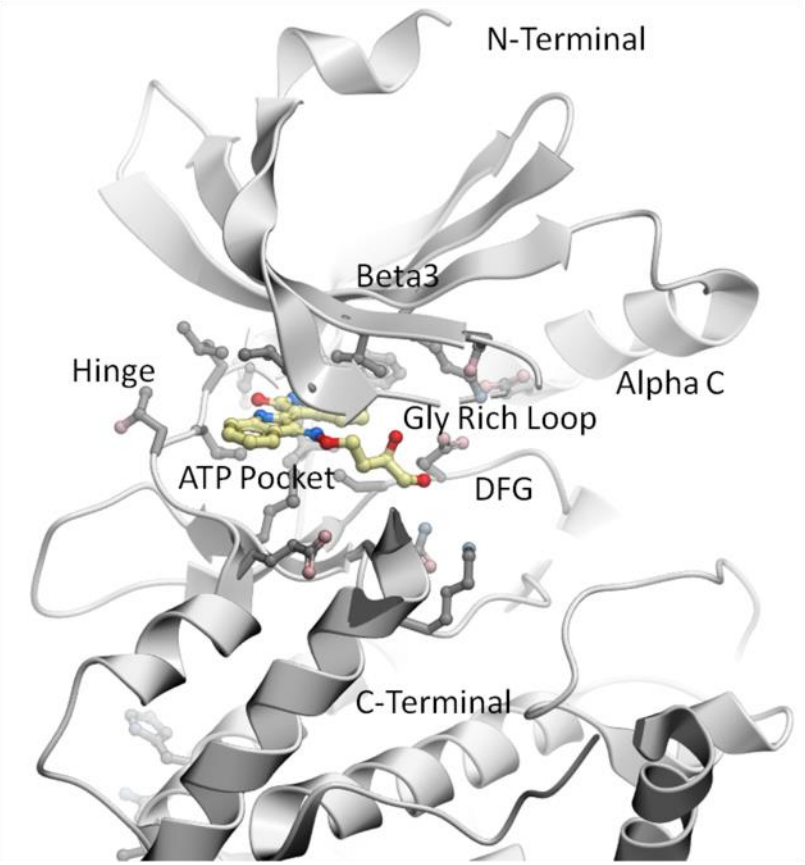
MCP

PLoS BIOLOGY

Coloring, Annotation, and Representation

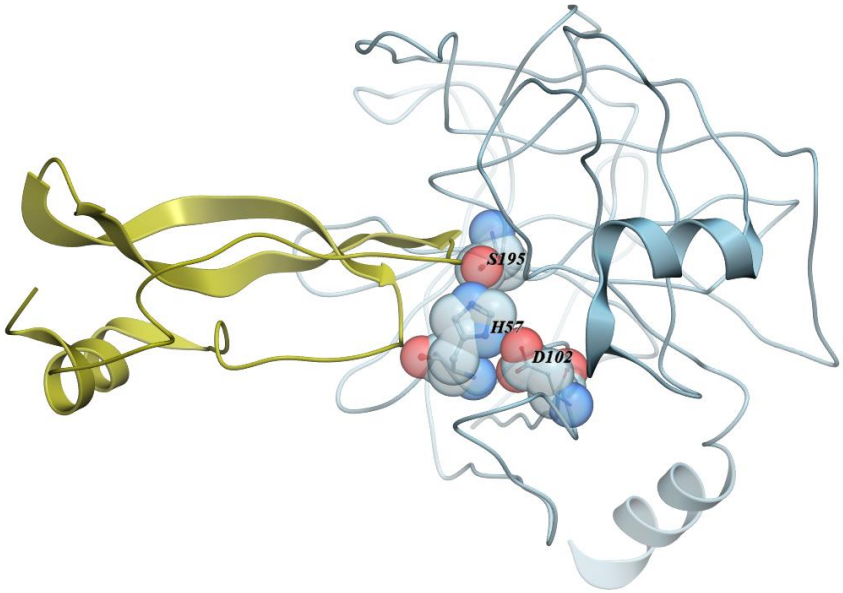


Kinase Example



- The catalytic domain is nestled between the N- and C- terminal and has high sequence conservation between kinase families.
- The adenine moiety of ATP interacts with the hinge region which links the N- and C-terminals of the catalytic domain.
- A flexible glycine-rich loop moves in and out of the pocket depending on the ligand bound state of the PK and is regulated to some extent by the movement in and out of the pocket by the Alpha C helix.
- A buried region at the "back" of the pocket is protected by a "gatekeeper residue" forming a variable hydrophobic cavity.
- The hydrophobic cavity along with the DFG region are of interest for drug design because it opens up regions of the pocket which are not conserved and do not bind regions of a protein kinase.

Example: Serine Protease



PDB: 2ptc

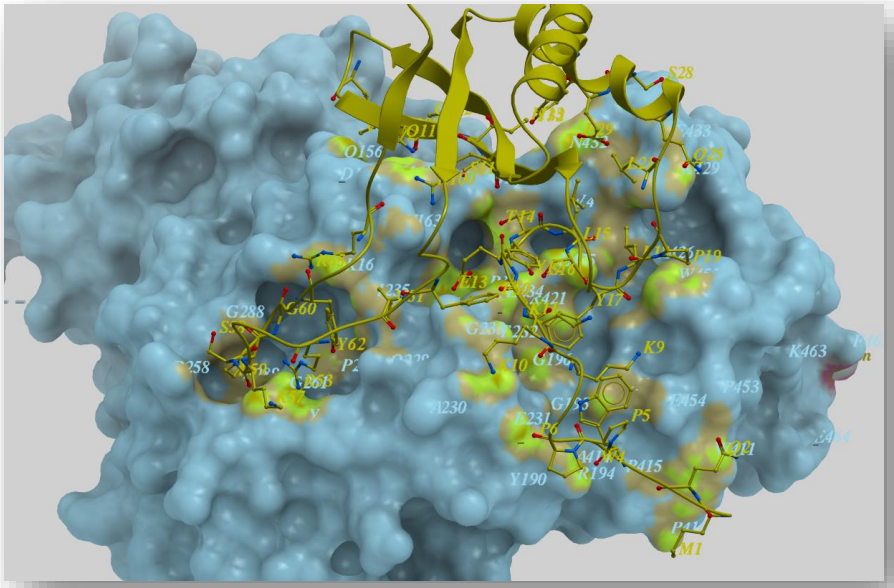
Serine proteases are involved in digestion, clotting, hormone activation, immune system activation.

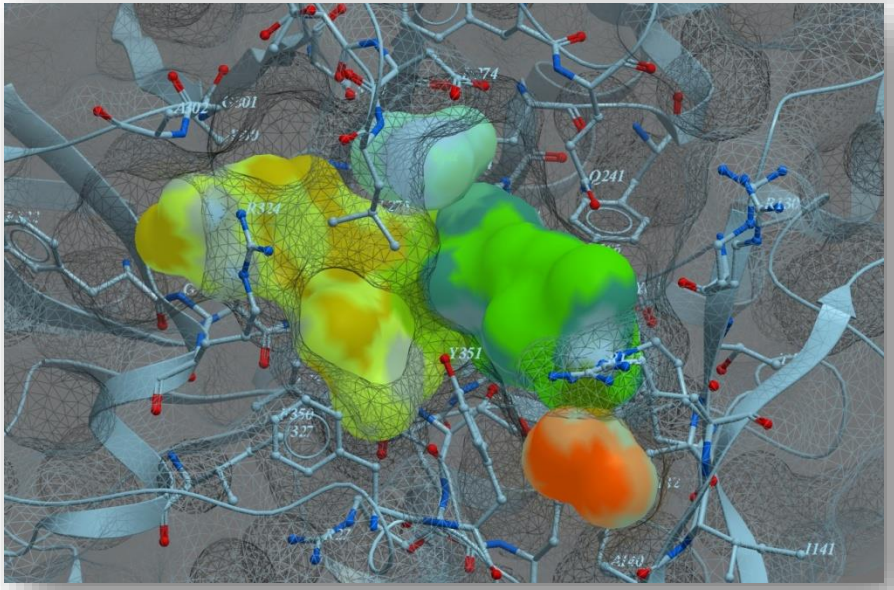
The key amino acid is a serine that is activated by a histidine and an aspartate forming a catalytic triad motif of an Acid-Base-Nucleophile (charge relay system).

The histidine and the aspartate assist in the removal of the hydrogen atom from the serine, which makes it more reactive when attacking the target protein chain.

Here we look at Trypsin **PDB: 2ptc** Trypsin cleaves peptide chains mainly at the carboxyl side of the amino acids lysine or arginine.

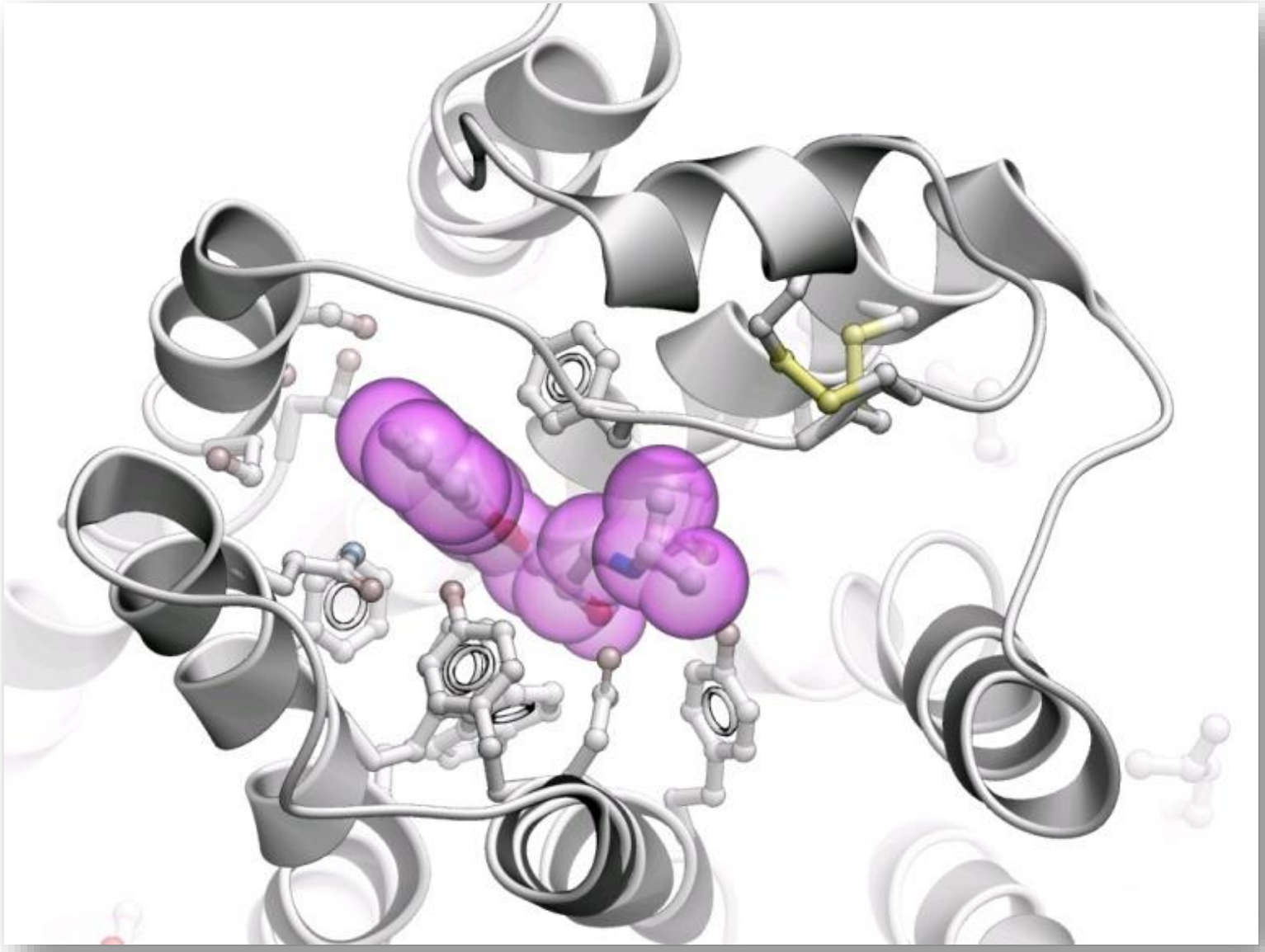
MolSkin



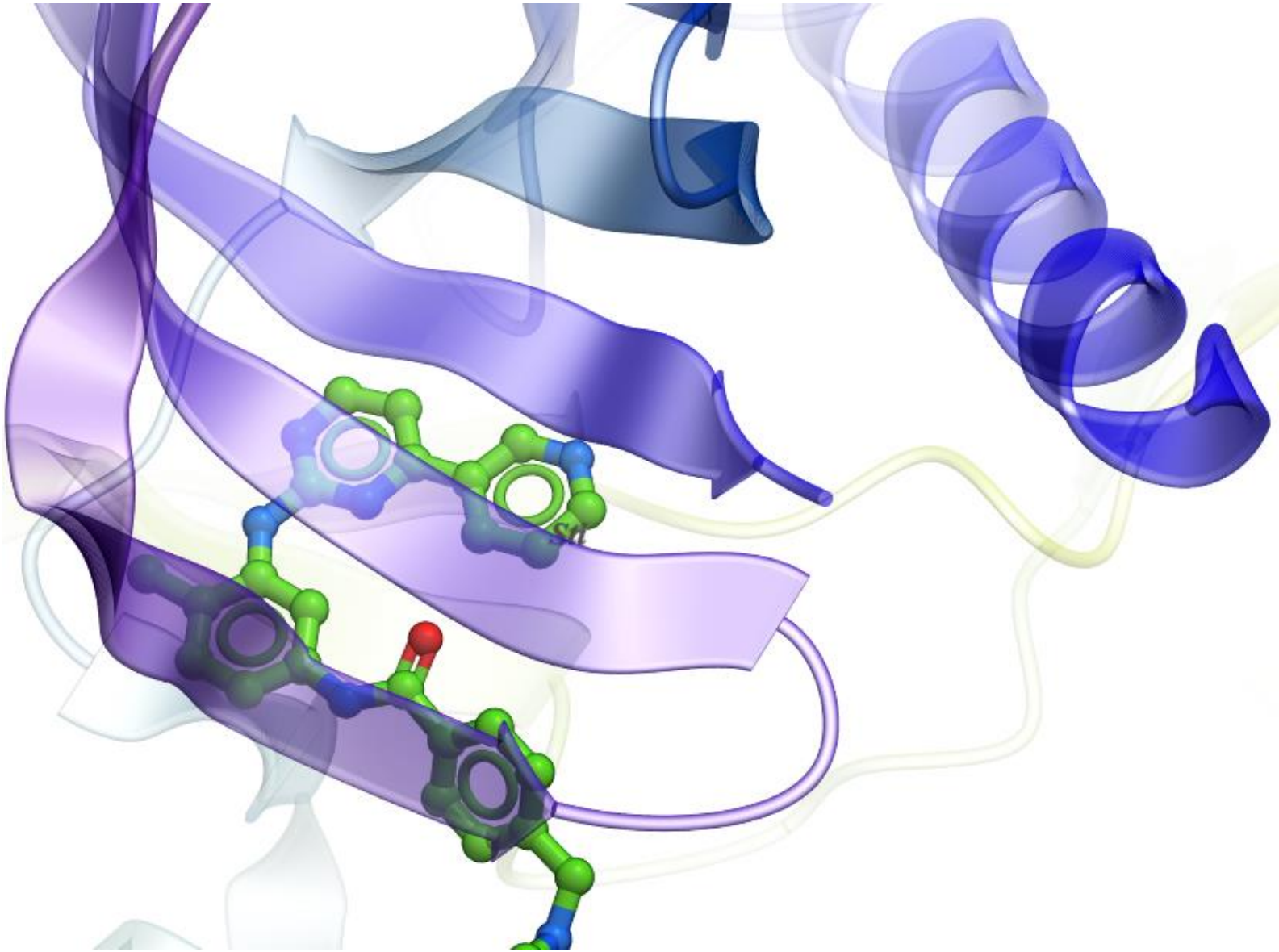


- Molecular surfaces are generated with assigned colors and occlusion shaded
- Carbons of each molecule are colored by its own consistent color
- Labels, ribbons, are colored accordingly
- Surfaces are gradually cross-colored by each other to mark the **contact patches**
- The labels are brought to the surfaces

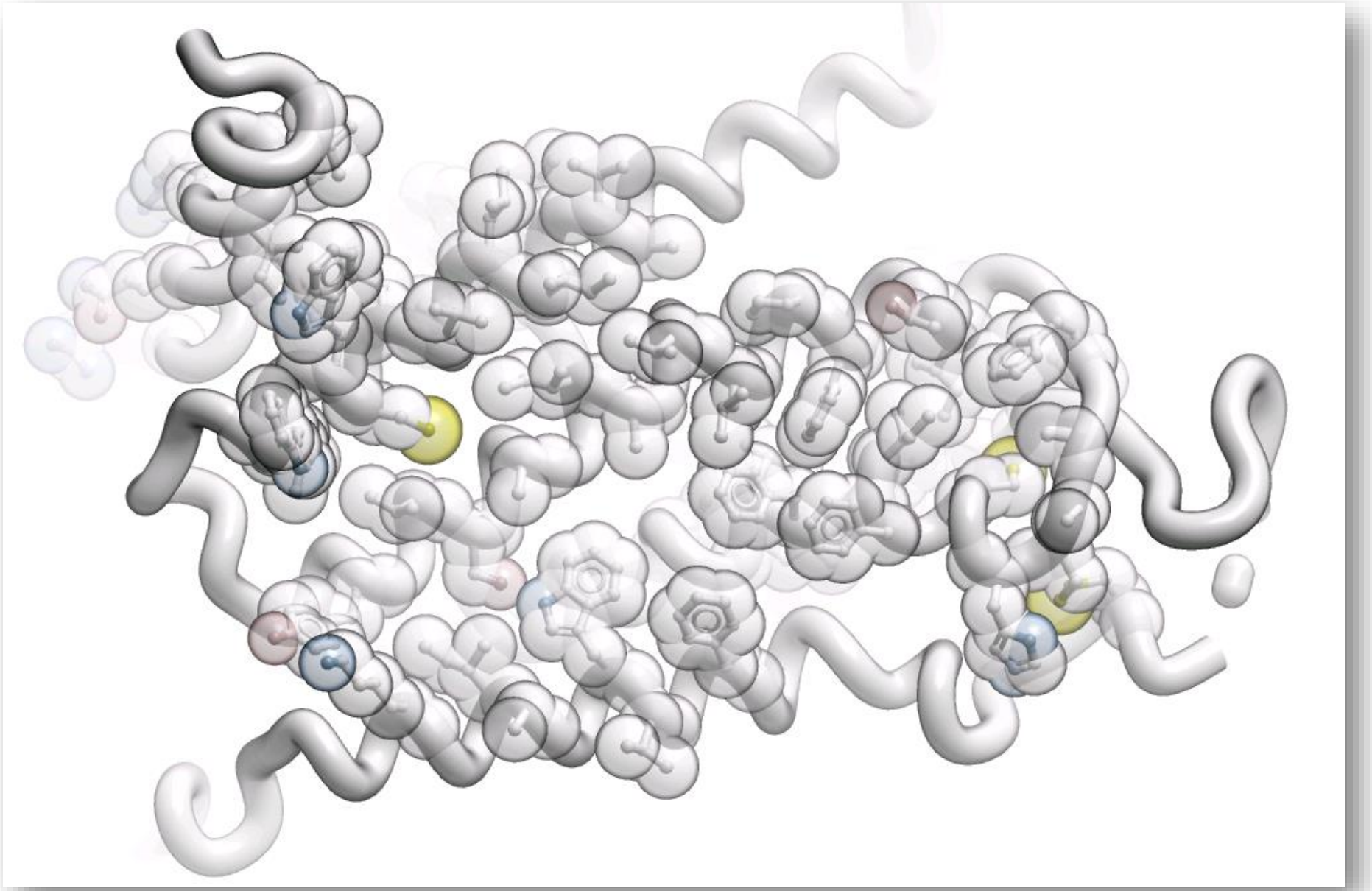
Fog Effect



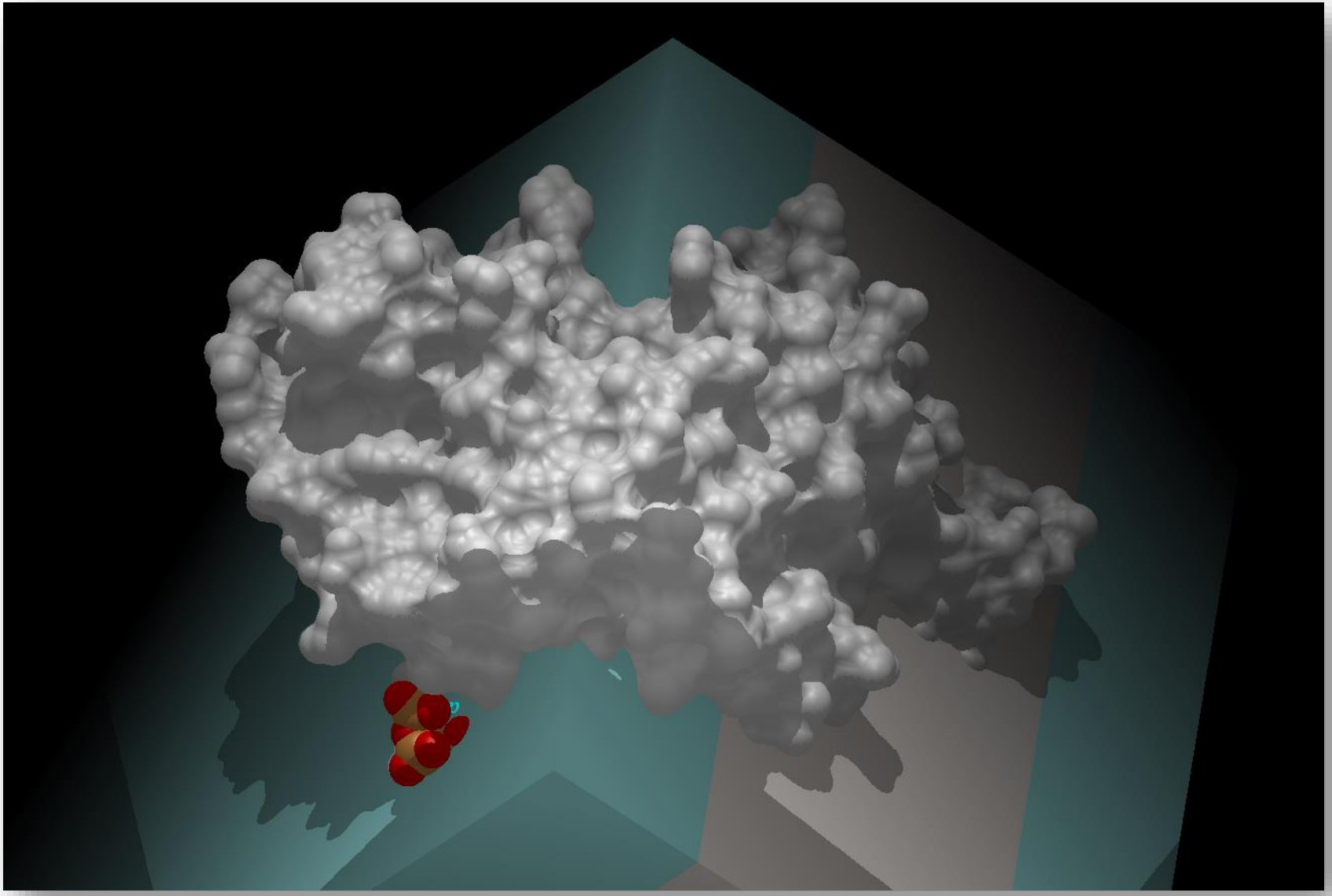
Transparency



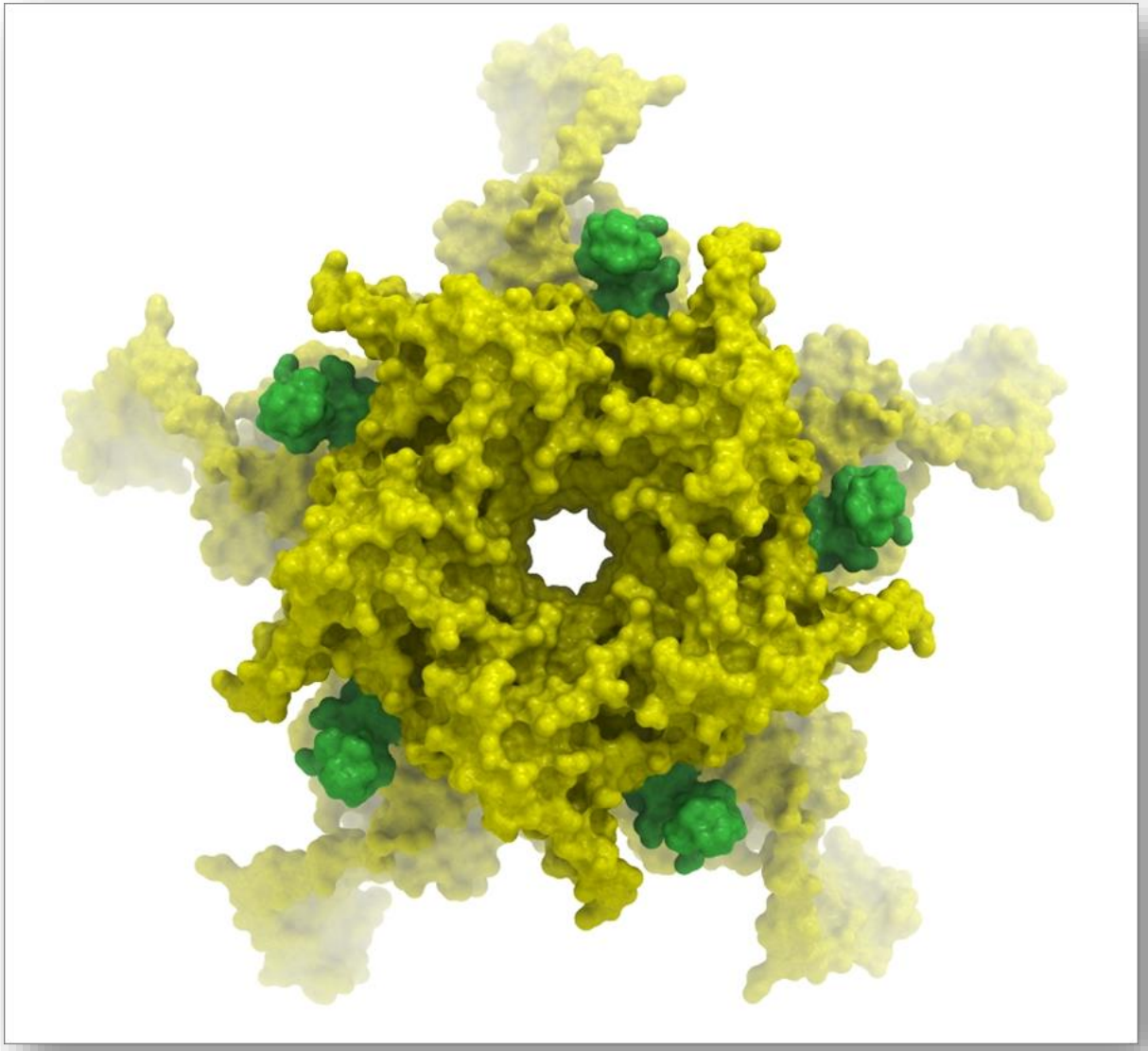
Sketch Accents



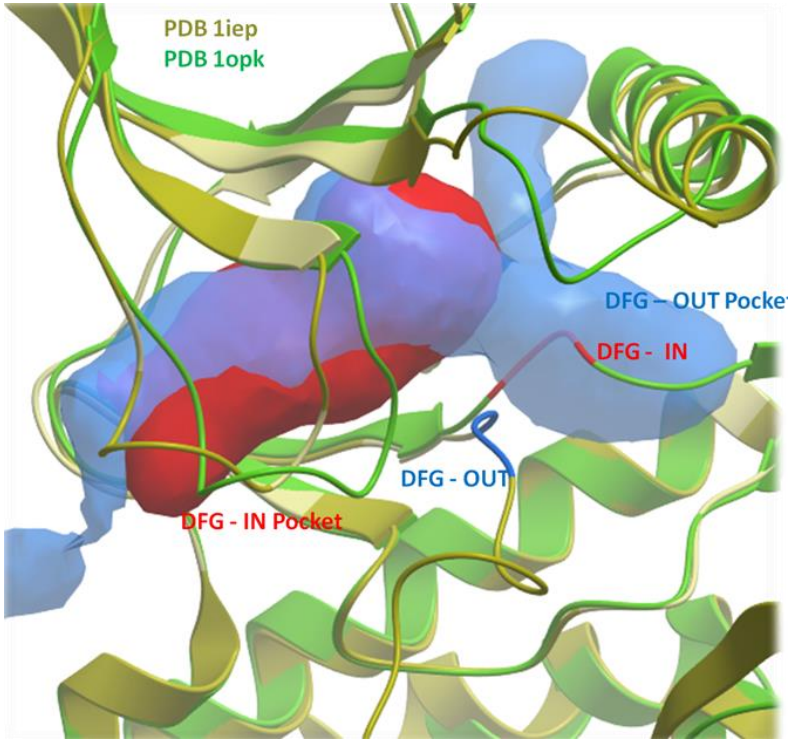
Graphics Effects - Shadows

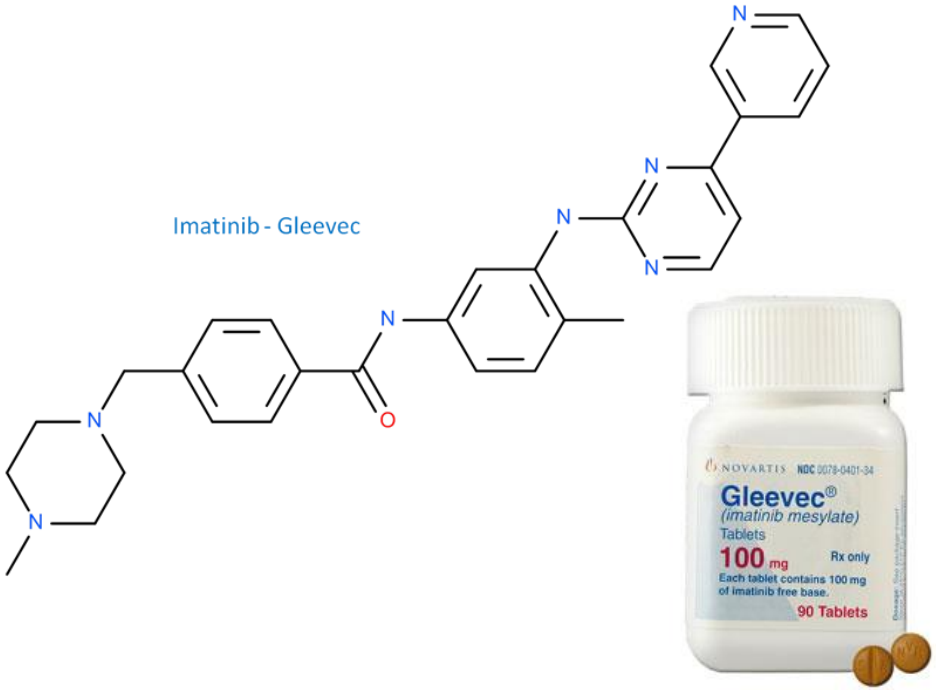


Occlusion Shading



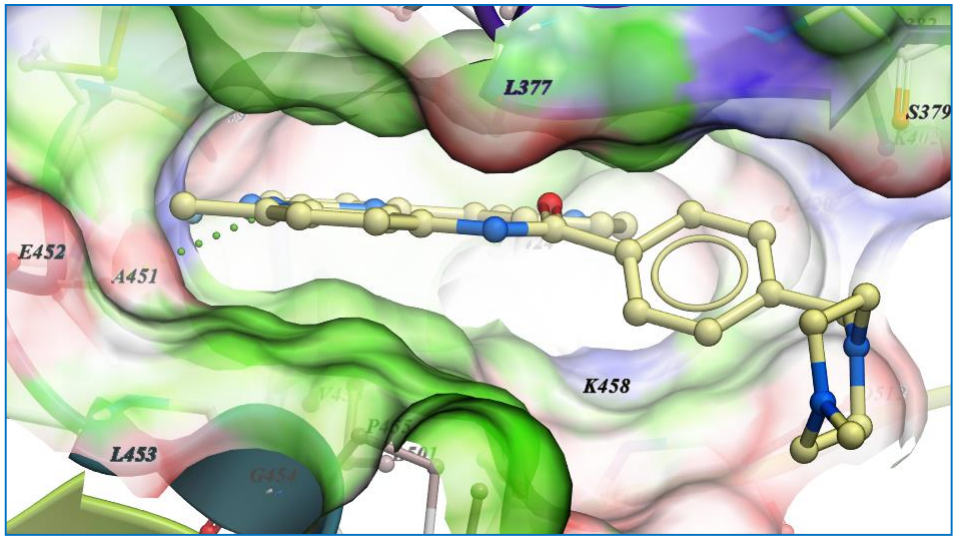
Type-I and II Kinase Example



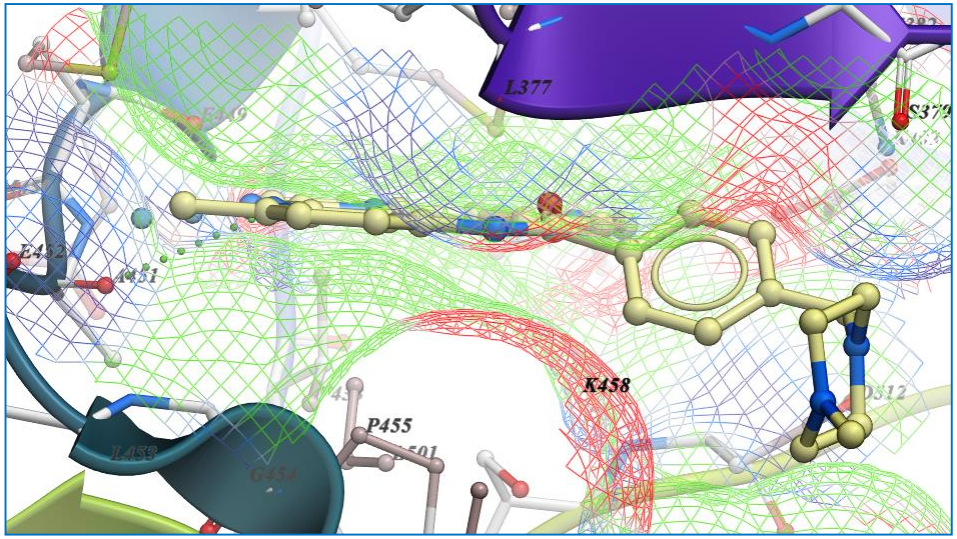


The positioning of the DFG motif in the activation loop of a protein kinase has an effect on the size and properties of the ATP binding pocket. Most kinase inhibitors target the kinase with the DFG inwards to the ATP binding site. Type-II inhibitors target the site where the DFG motif is in the out position which opens up the pocket and provides additional hydrophobic binding sites. Targeting DFG-out conformations can improve inhibitor specificity and slower-off rates.

Ligand Binding Pocket



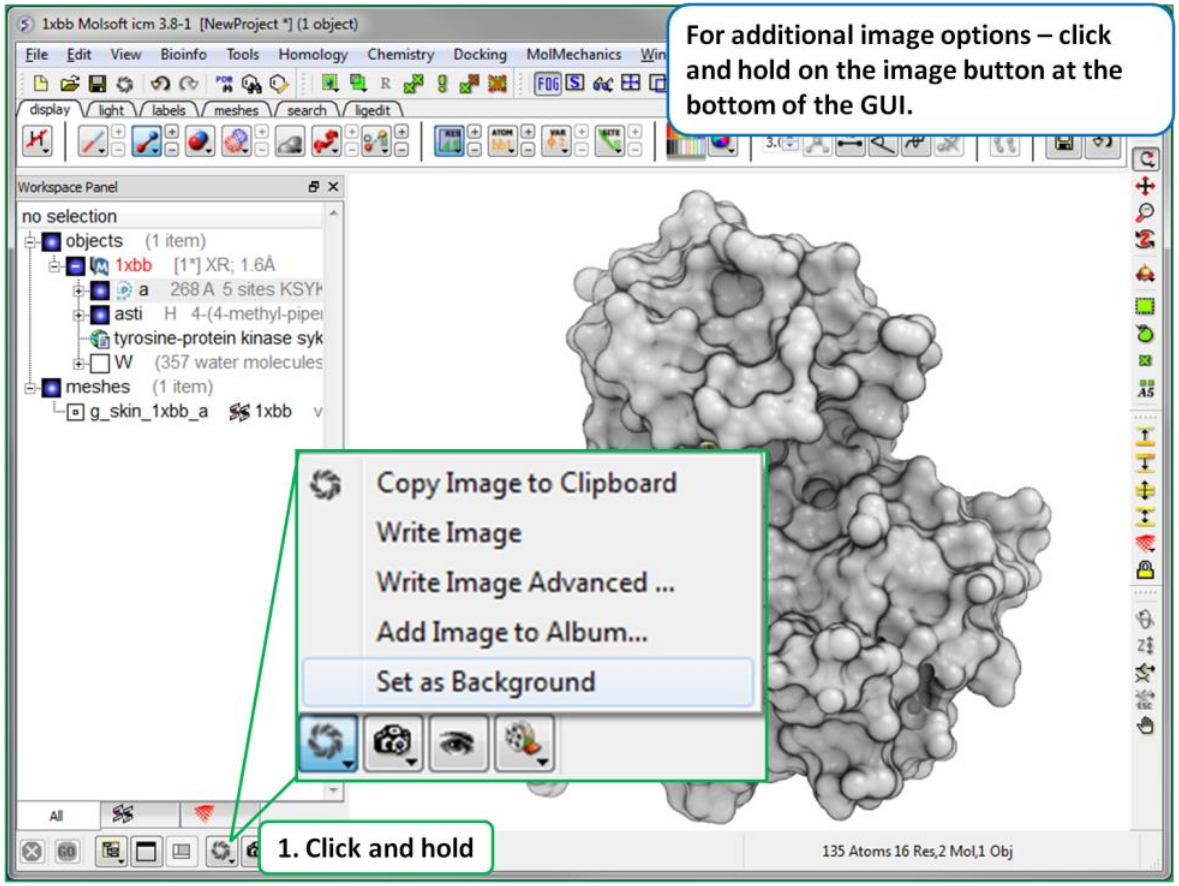
Receptor Surface



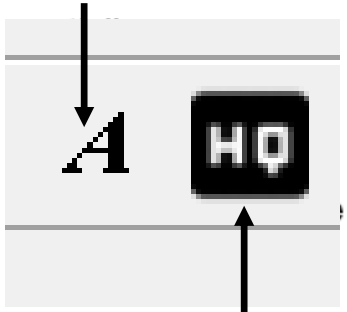
Ligand Surface

White = neutral, Green= hydrophobic, Red= HB acceptor, Blue= HB donor

Publication Quality Images



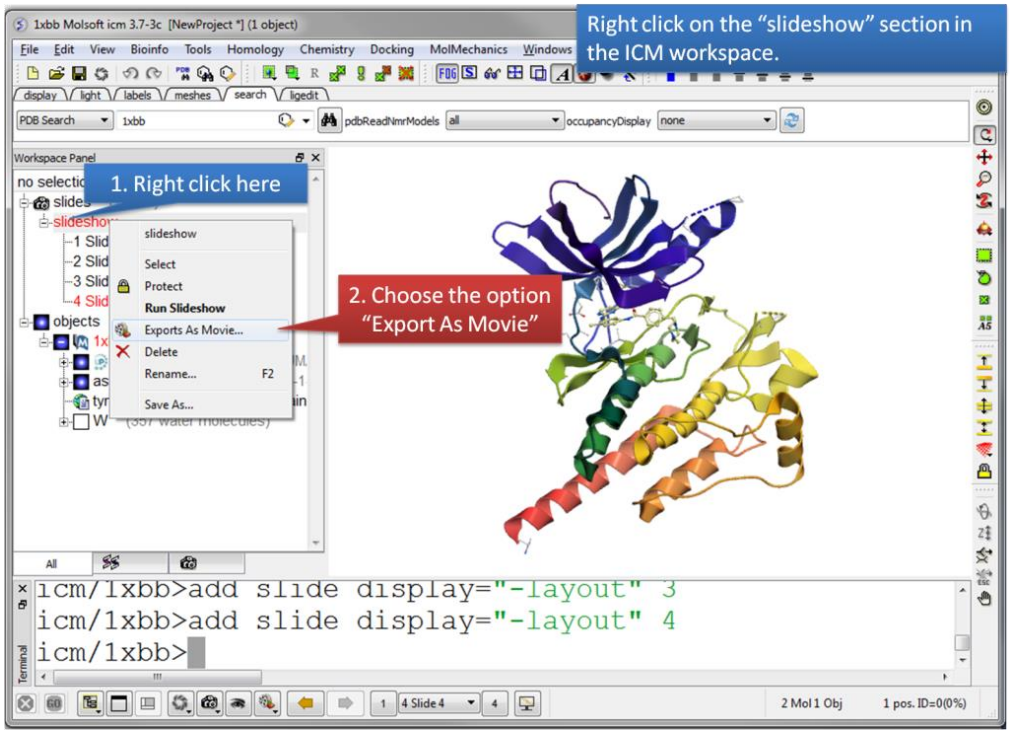
Antialias



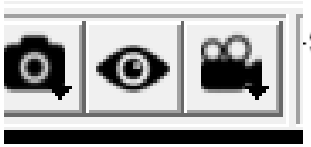
High Quality

Movies

By Slide:

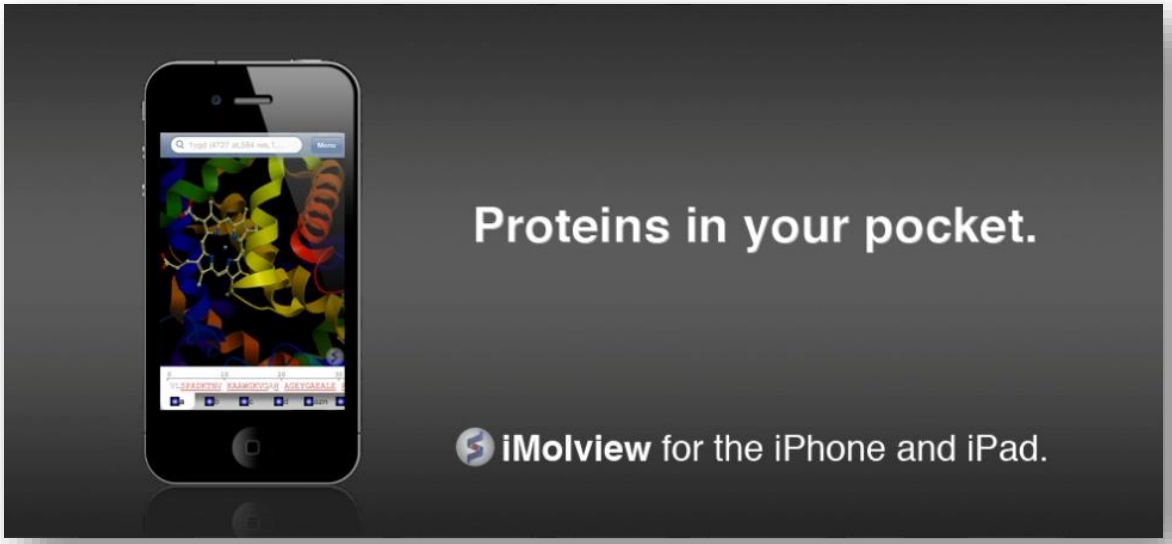


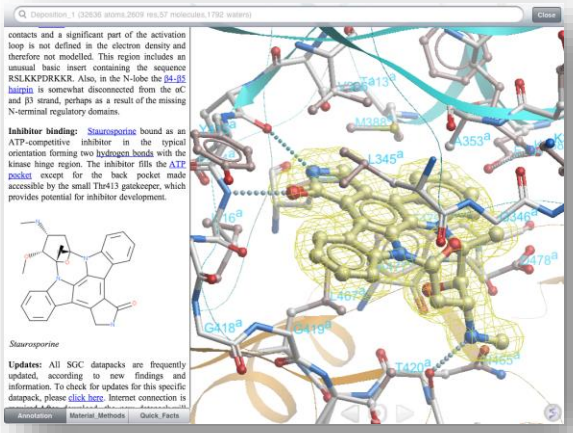
By Screenshot:

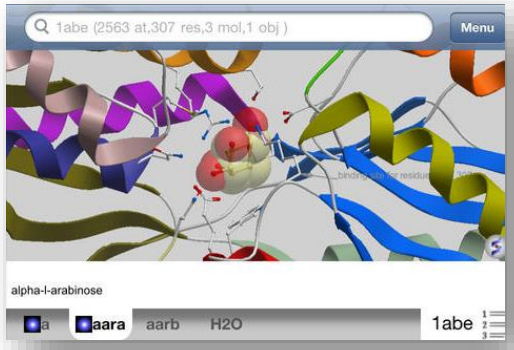


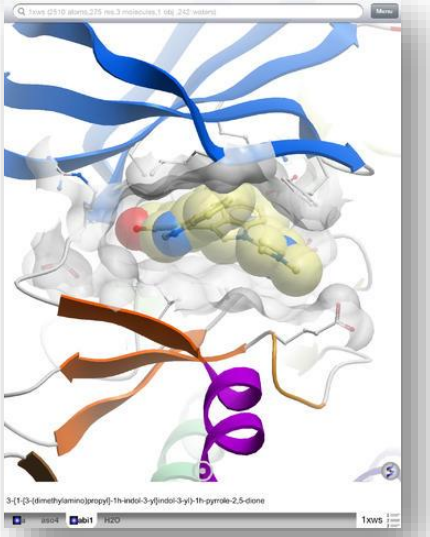
Screenshot movie making

iMolview App for Android and iPad

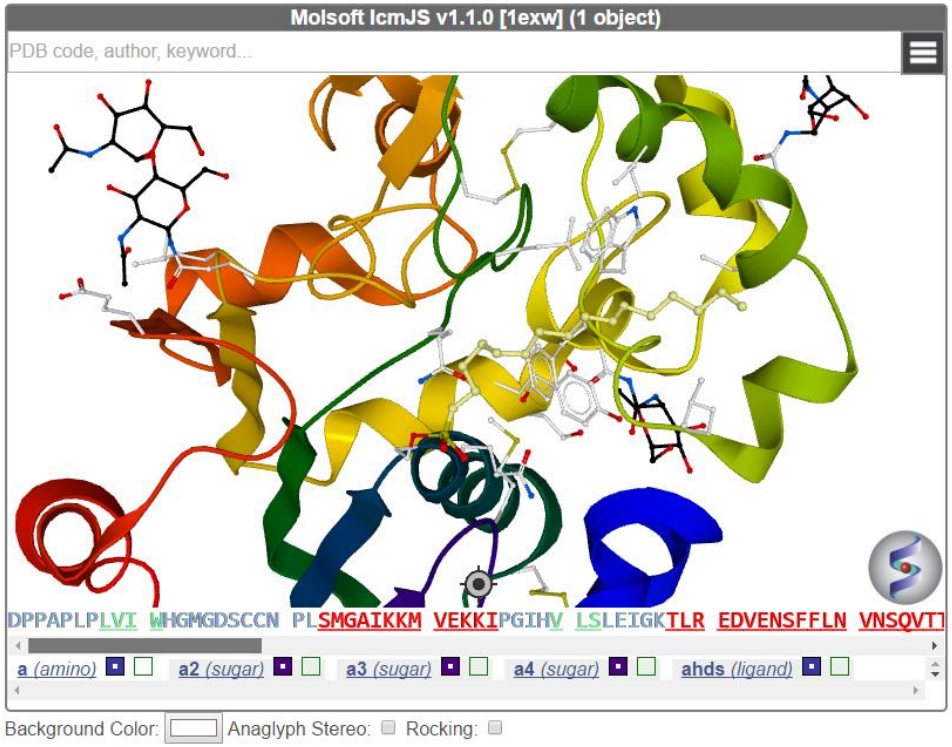








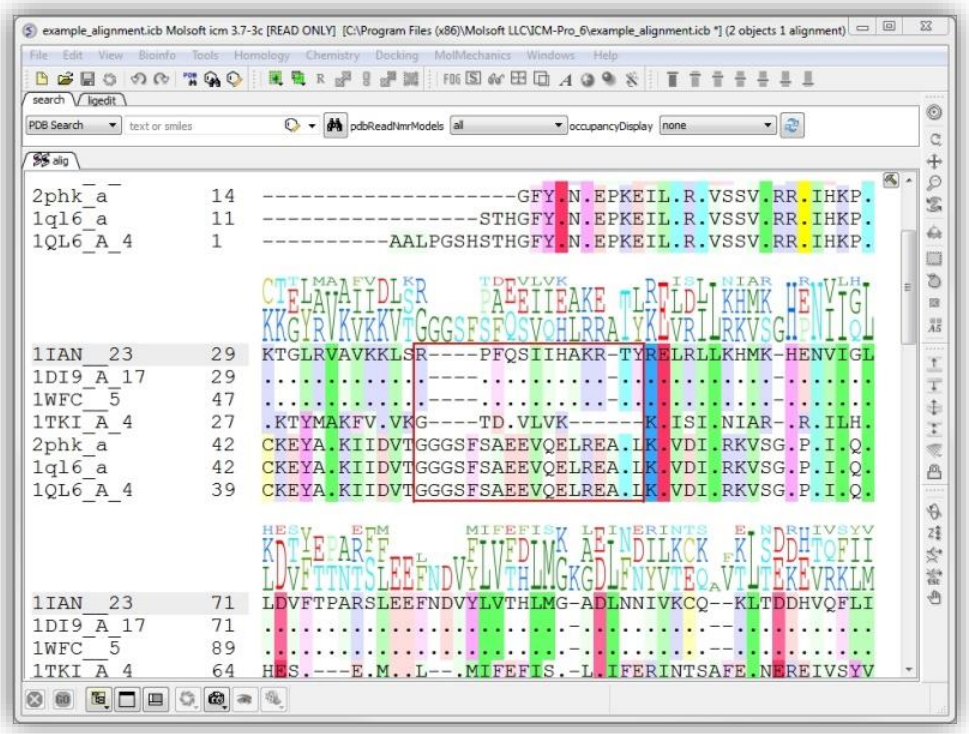
IcmJS – Fast High Quality Java Script Viewer



- ICMJS is a JavaScript/HTML5 viewer for 3D Molecular Graphics which does not require any plugin or installation.
- It runs on all modern browsers including Chrome, Firefox and Safari and is also mobile device friendly.
- IcmJS gives you full access to the ICM shell and graphics on a web browser. This means that commands available in the free ICM-Browser are also available on the web via IcmJS.

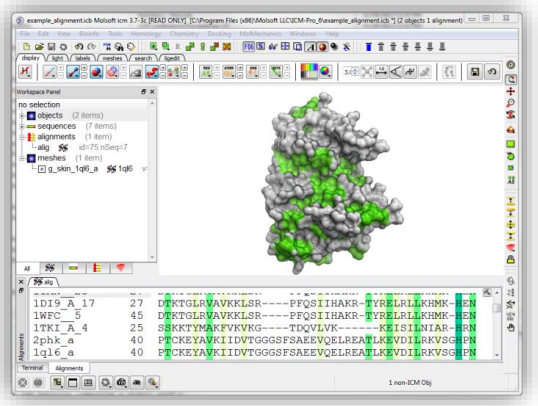
molsoft
molecules *in silico*

Linking Protein Structure to Sequence and Alignments



Key Topics

- How to read in sequence data into ICM and extract sequences from the PDB.
- How to create new sequences and edit them.
- Mapping UniProt and other annotation onto a sequence.
- How to build multiple sequence alignments.
- How to use the alignment editor:
  - How to edit an alignment
  - Coloring
  - Annotation
- Linking an alignment to protein 3D structure
- How to display sequence conservation in the ligand binding pocket and calculate sequence identity and similarity in an alignment.
- How to perform a BLAST search in ICM.



Sequence and Alignment DBs

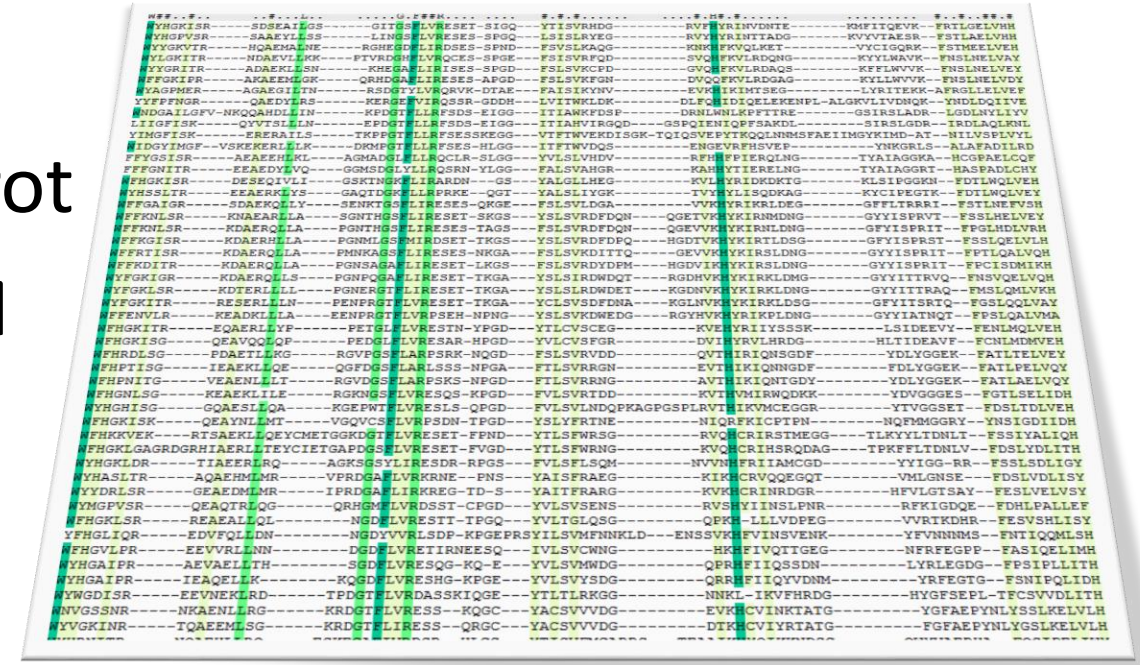
Central repository of protein sequence and function.

Protein domains, families and functional sites as well as associated patterns and profiles to identify them.

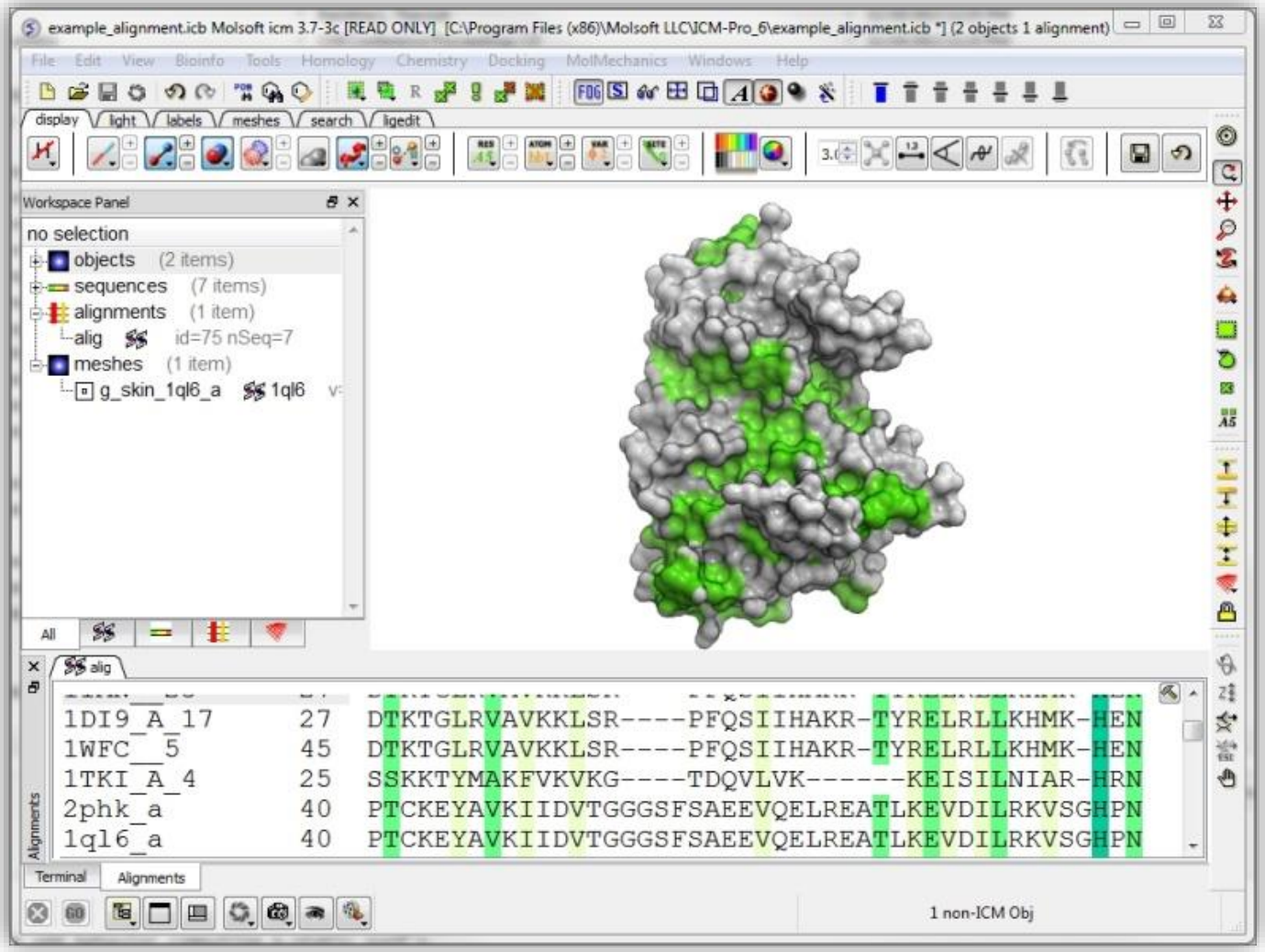
Pfam is a database of curated protein families, each of which is defined by two alignments and a profile hidden Markov model (HMM).

Example 1: Read Sequence Data

- SH2 Domain Example
- Read from UniProt
- Read from PFAM
- Read from PDB
- Create New Sequences



Example 2: Pocket Conservation

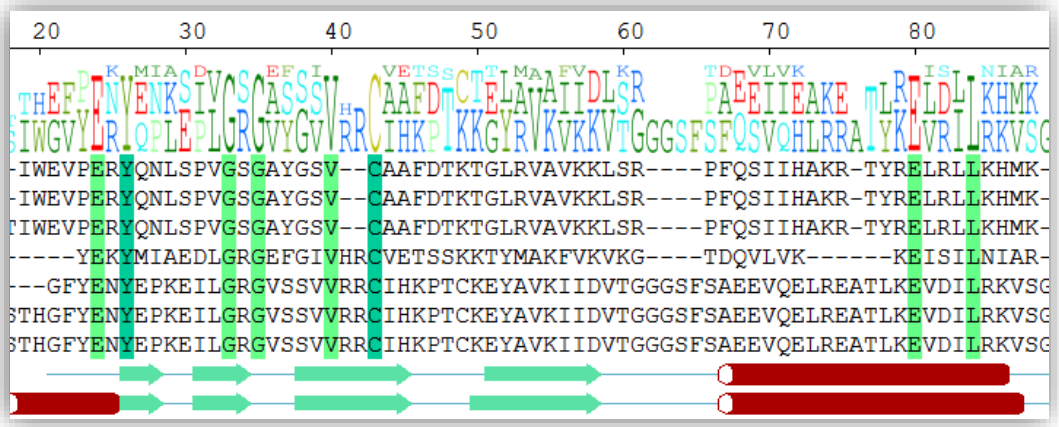


Example of Kinase Pocket Sequence Conservation

Alignment and Comparison Methods

Alignment

- Needleman-Wunsch/double-gap
- Smith-Waterman
- Wilbur-Lipman
- ZEGA



Comparison Matrices

- Gonnet
- Blosum
- Hssp

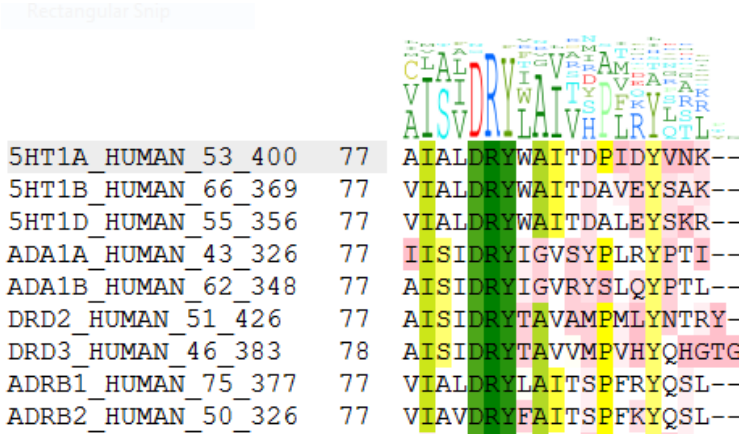
Secondary Structure Prediction

ICM modification of the DSSP algorithm of automatic secondary structure assignment (Kabsch and Sander, 1983) based on the observed pattern of hydrogen bonds in a three dimensional structure.

Example 3: Alignment Annotation

G-Protein Coupled Receptors (GPCRs) all share a common structural core of seven transmembrane helices but they lack significant sequence homology between subfamilies. When modeling GPCRs it is important to get a good alignment between the query and template structure. Each helix has one or more conserved motifs:

Helix 1: GX_3**N** or G**N**
Helix 2: N(S,H)LX_3**D**$X_{7,8,9}$P
Helix 3: SX_3LX_2IX_2D(E,H)**R**Y
Helix 4: **W**X_8,9P
Helix 5: FX_2**P**X_7Y
Helix 6: FX_2CW(Y,F)X**P**
Helix 7/Helix 8: LX_3NX_3N(D)**P**X_2Y$X_{5,6}$F



The ProSite class A alignment http://prosite.expasy.org/PDOC00210 can be used to guide GPCR alignments.

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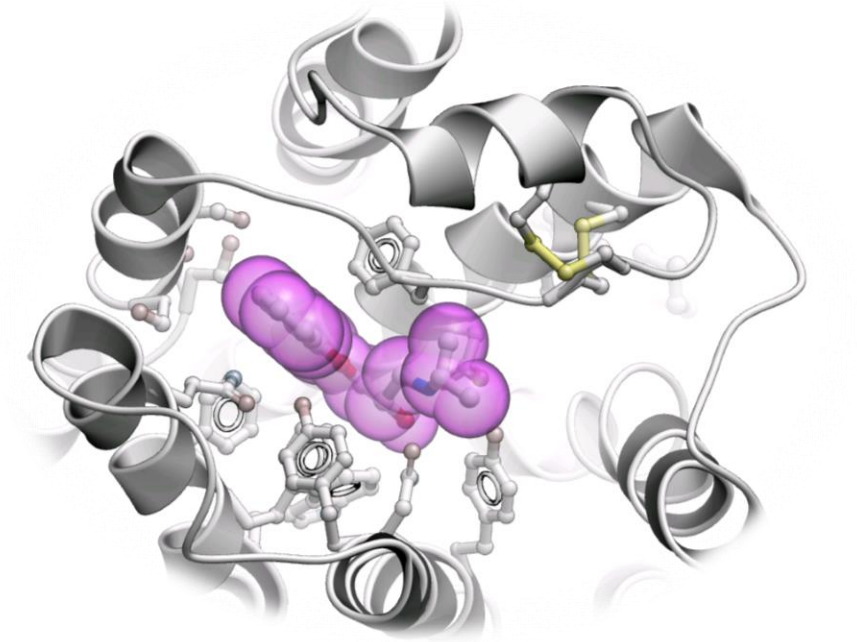
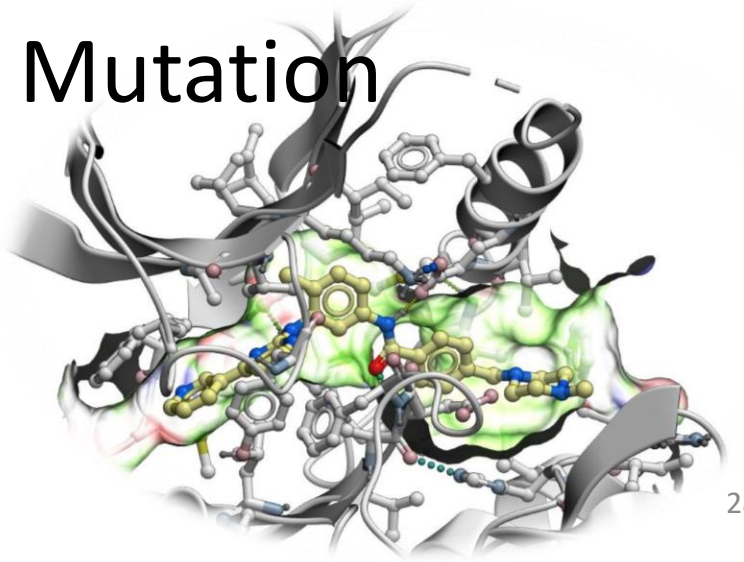
Protein Structure Modeling and Analysis

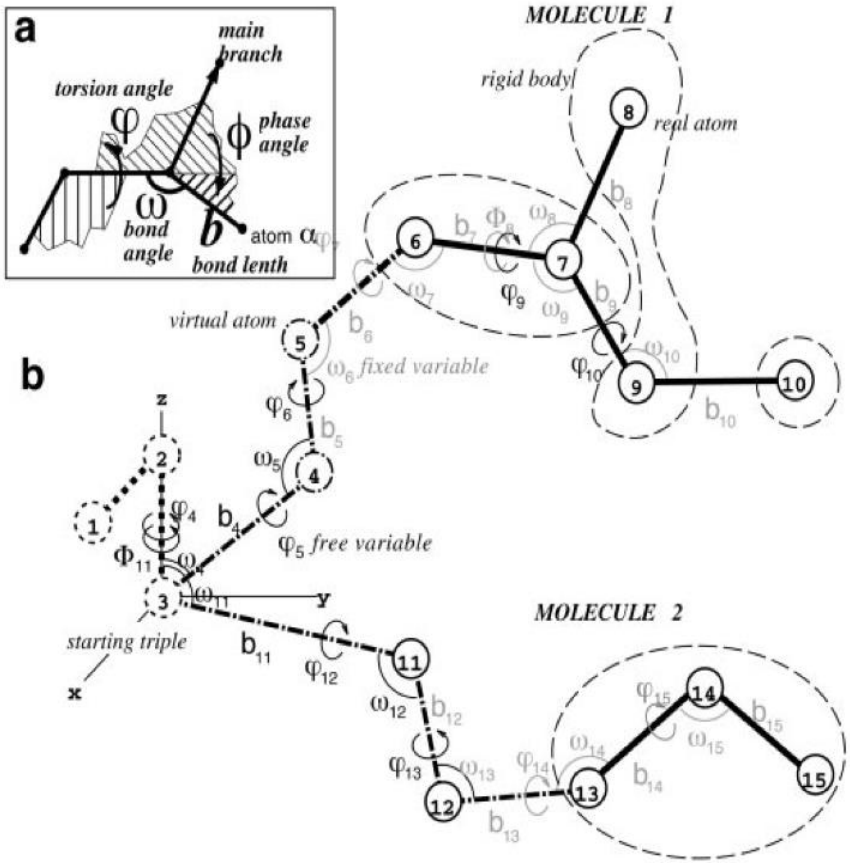


Key Topics

- Structure Analysis Tools
- Crystallographic Analysis Tools
- Homology Modeling
- Loop Modeling
- Predicting the Effect of Mutation



Method: Internal Coordinate Mechanics (ICM)

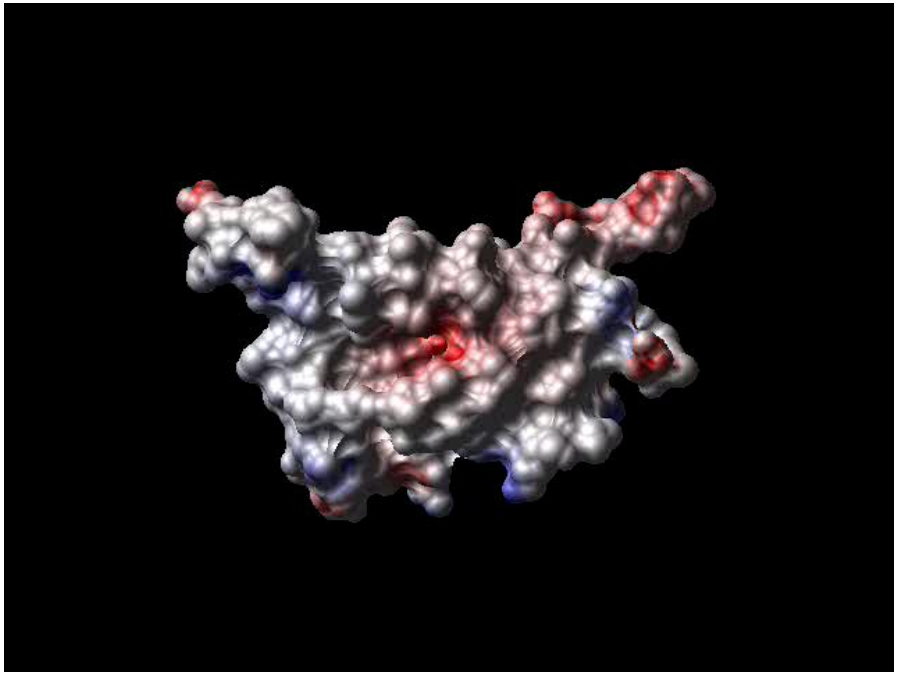


- One major problem is the size of the modeling system many thousands of atoms.
- IC substantially reduces the number of variables defining the system.
- A Cartesian description requires 3 variables per atom (x, y, and z).
- IC uses bond lengths, planar angles, and torsion angles instead.
- Bond lengths and planar angles are generally rigid in normal conditions – therefore **only allow torsion angle changes**.

Applications:
Folding, protein modeling, Docking, Virtual Screening

Abagyan et al. (1994) "ICM - a new method for protein modeling.." *J. Comp. Chem.* 15, 488-506

Structure Analysis and Prediction



icmPocketFinder

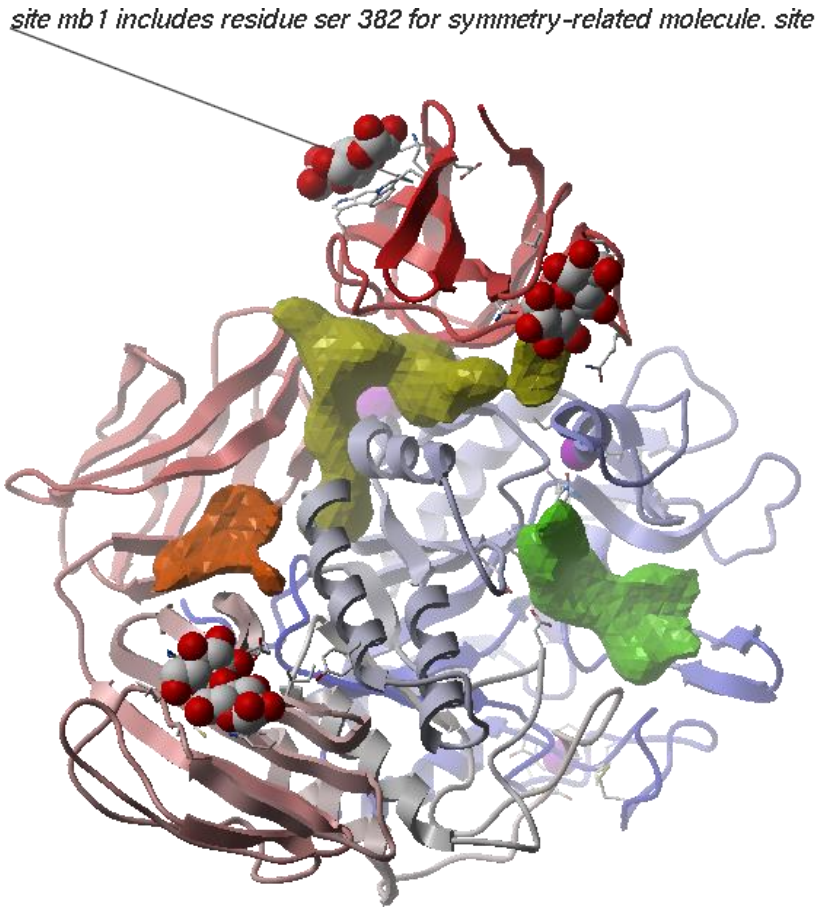
icmPocketfinder - An, et al Mol Cell Proteomics 2005.
Pocketome – Kufareva, et al Nucleic Acids Res. 2012
P-P prediction – Fernandez-Recio et al Proteins. 2005

- Calculate RMSD
- Contact Areas
- Surface
- Distances
- Angles
- Ramachandran plots
- Protein Superposition
- **icmPocketFinder**
- Protein-protein interaction sites

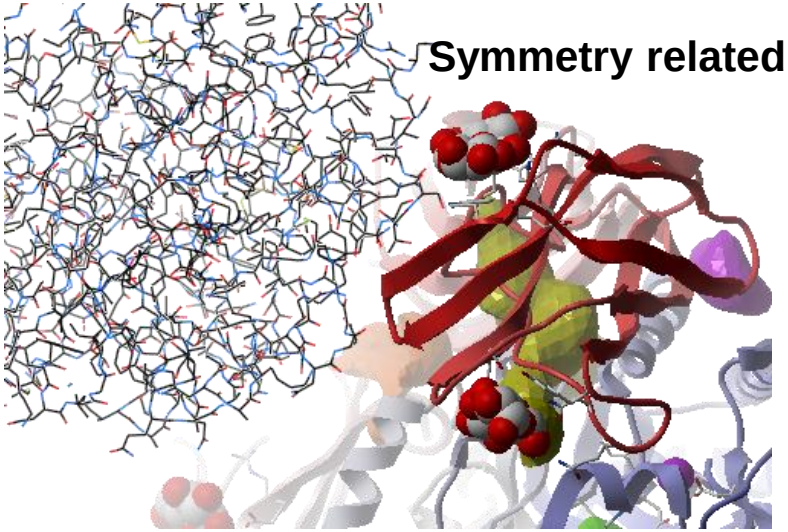
MERCK Be well

Drug-like density: a method for quantifying the "bindability" Sheridan et al JCIM 2010

Crystallographic **Symmetry**



Example: Cycloldextrin glycosyltransferase
Entry: 1cdg, Res. 2.0A (Docking Rmsd without symmetry: 9.76)
More examples: transthyretin 1f41 (thyroid hormone binds at the dimer



Symmetry related subuni

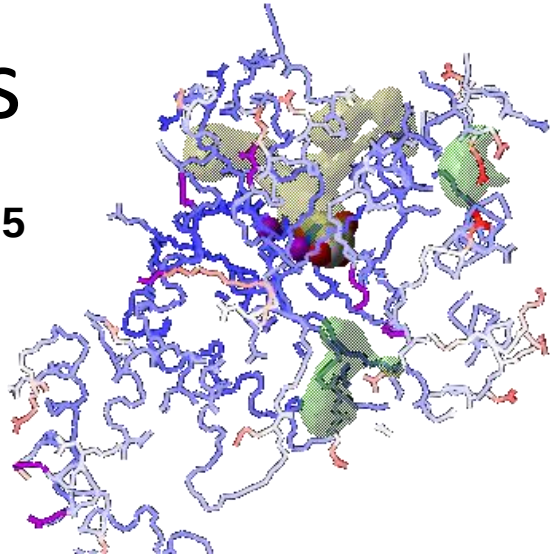
Problem: the true pocket is formed by chains which are not explicitly present in a pdb entry.

Goal: Find all molecules/subunits or chains involved in the interaction with the ligand.

Warning signs: ICM pocket finder does not show pocket density; Binding site is obviously exposed

Recovery: generate symmetry related

Occupancies, b-factors and alternatives



Occupancies <= 0.5 are shown in magenta
High b-factors are colored red

Glossary:
B-factor (or temperature factor): mean-square displacement of atom from its position in the model.
Bi = 79*<u^2> (B of 80 means 1A dev.)
Normal range: 5. – 50. A^2.

Occupancy:
A fraction of atomic density at a given center. It there are two equally occupied conformers, both will have occupancies of 0.5
Normal value: 1. Range: 0.-1.

Alternatives:
If two or more alternative conformations for the same atom or group are discernable in the density, several alternative sets of coordinates are deposited.

Problem: sometimes, when electron density is poor and/or ambiguous, crystallographers sometimes deposit an arbitrary conformation from a refinement program

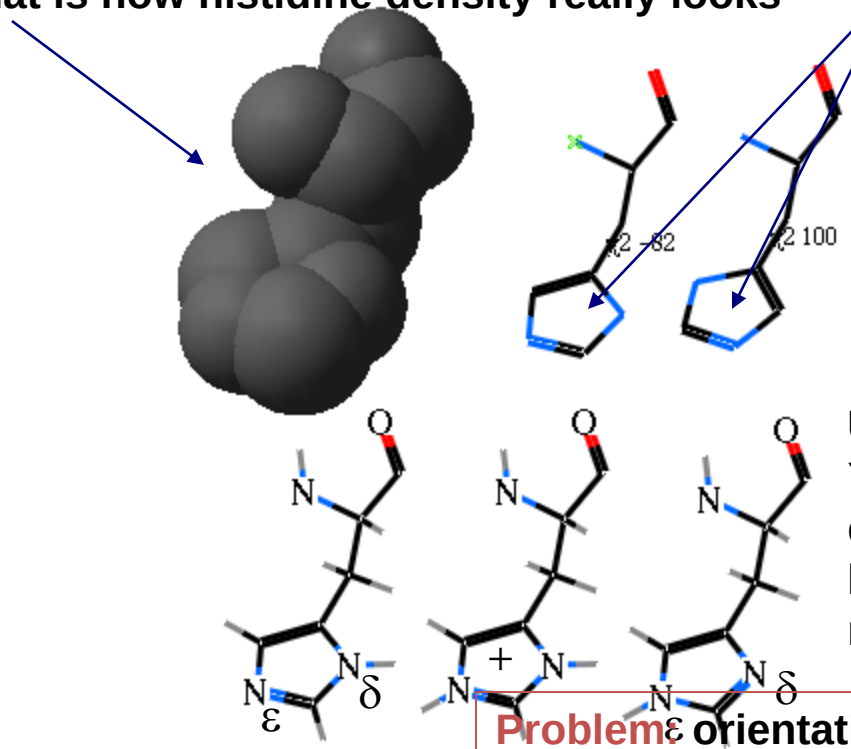
Goal: Identify fantasy atoms/groups

Warning signs: occupancies less than 0.5, b-factors larger than 60-80 A^2.
Tool: Color/label pocket atoms by occupancies/b-factors.

Recovery: Choose another entry, or refine with a ligand, or perform restrained minimization. Choose

Fixing Histidines

That is how histidine density really looks



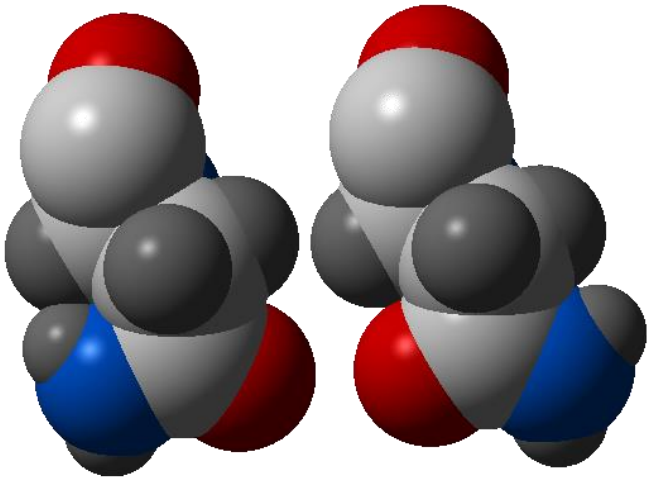
Orientation at the heavy atom level
We need to discriminate between
These two conformations

Often the xi2 angle needs to be
Corrected by 180 degrees.

Uncertainly at the protonation level
You need to decide which of the three conformations is correct for each important location. The charged conformation is rare.

Problem: orientations and protonation states of histidines are frequently wrong in pdb entries and need to be fixed to ensure correct docking results.
Placement principle: maximization of hydrogen bonds and other interactions with the rest of the protein and/or with the ligand.
Recovery: ICM procedure optimizeHisProAsnGln finds the best orientation and protonation state

Determining orientations of Gln, Asn, side chains



Orientation at the heavy atom level
The two conformations shown give similar electron density.
We need to discriminate between these two conformations of the **Asn** side chains. The same ambiguity needs to be resolved for the xi3 angle of **Gln**

Background: xi2 in asparagines and xi3 in glutamines are frequently wrong or undefined and need to be corrected ensure correct docking.

Placement principle: maximization of hydrogen bonds and other interactions with the rest of the protein and/or with the ligand.

Recovery: ICM optimizeHisProAsnGln procedure.

Homology Modeling

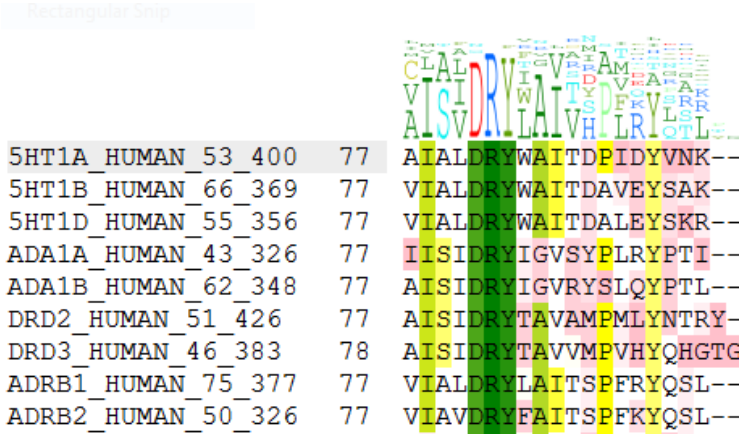
- Find closest template(s)
- Align sequence to template
- Copy the aligned backbone
- Predict side chains
- Predict loops
  - Best Db fragment
  - Explicit ICM-local SGO
  - Grid simulation
- Refine by ICM SGO
- Predict local reliability (B_i)

Monte Carlo – Abagyan et al JMB 1994

GPCR Modeling

G-Protein Coupled Receptors (GPCRs) all share a common structural core of seven transmembrane helices but they lack significant sequence homology between subfamilies. When modeling GPCRs it is important to get a good alignment between the query and template structure. Each helix has one or more conserved motifs:

Helix 1: GX_3**N** or G**N**
Helix 2: N(S,H)LX_3**D**$X_{7,8,9}$P
Helix 3: SX_3LX_2IX_2D(E,H)**R**Y
Helix 4: **W**X_8,9P
Helix 5: FX_2**P**X_7Y
Helix 6: FX_2CW(Y,F)X**P**
Helix 7/Helix 8: LX_3NX_3N(D)**P**X_2Y$X_{5,6}$F



The ProSite class A alignment http://prosite.expasy.org/PDOC00210 can be used to guide GPCR alignments.

Model - GPR120 Class A GPCR.

Loop Modeling

Algorithms:

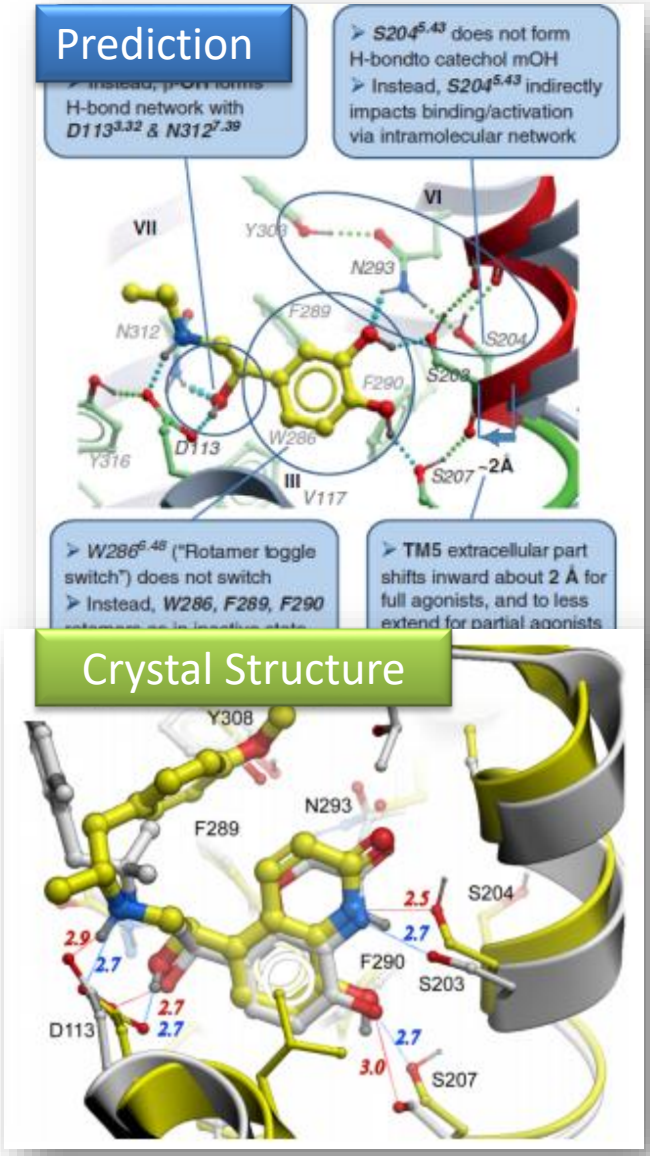
1. Search a database of loop conformations
2. Full atom ICM Stochastic Global Optimization

Applications:

Successful targeted backbone design of several loops in Triosephosphate Isomerase Collaboration with the Wierenga group (*Structure, PNAS, Prot. Eng. 1993-2002)*

Latest force-field and loop modeling benchmarking Arnautova et al Proteins 2011

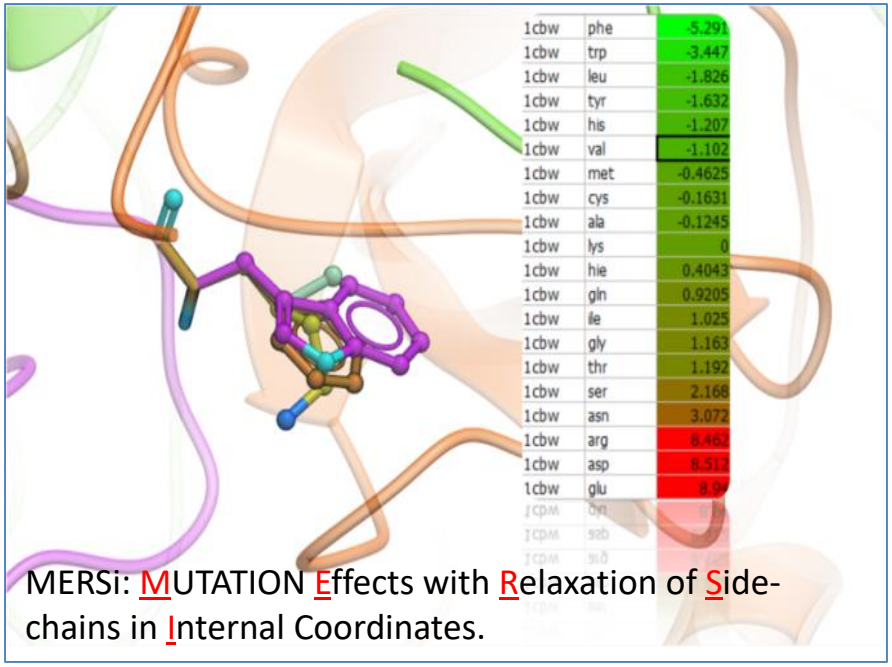
Protein Modeling Example



- Comparison of computational models published in 2009 and 2010 with X-Ray structure of agonist-bound structures of β-adrenergic and adenosine A2A receptors reveals high accuracy of the predicted agonist binding poses (0.8 A°and 1.7 A° respectively) and receptor interactions.
- In the case of the β2AR, energy-based models allowed characterization of side-chain rotations and a backbone shift in the pocket region as determinants of full, partial or inverse agonism.

Katritch and Abagyan TIPS 2011

Predicting the Effect of Mutation on Binding



MERSi: MUTATION Effects with Relaxation of Side-chains in Internal Coordinates.

$$\Delta\Delta G_{bind} = \Delta G_{bind}^{mut} - \Delta G_{bind}^{wt}, \quad \text{where}$$

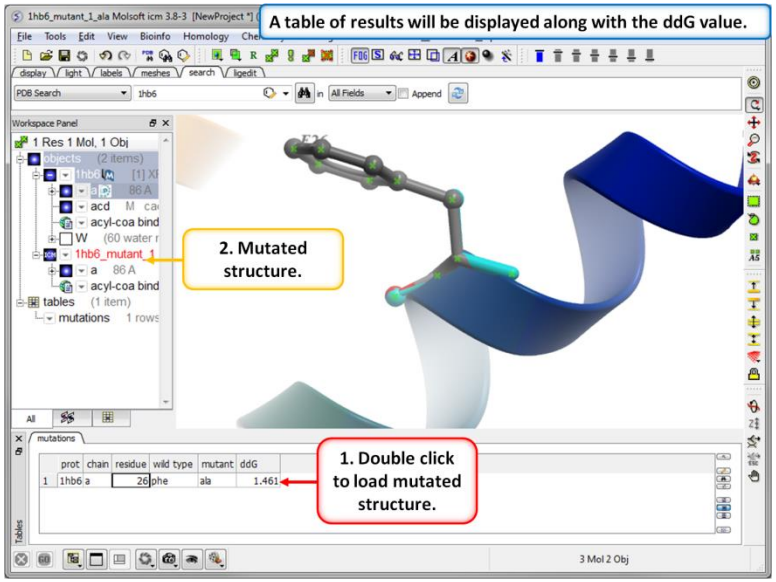
$$\Delta G_{bind} = (E_{intra}^{comp} - E_{intra}^{parts}) + (\Delta G_{solv}^{comp} - \Delta G_{solv}^{parts})$$

- Prediction of Protein-Protein, Protein-Peptide and Protein-Ligand affinity changes upon mutation

The binding free energy change, $\Delta\Delta G_{bind}$, is computed as a difference between the free energy of mutant and wild type.

The energy is calculated for fixed backbone and all the side chains except those in the vicinity of the mutatable residue. Monte Carlo simulations are carried out to relieve possible atomic clashes created as a result of mutations to larger amino acid residues.

Predicting the Effect of Mutation on Protein Stability



$\Delta\Delta G = \Delta G^{mutant} - \Delta G^{wt}$

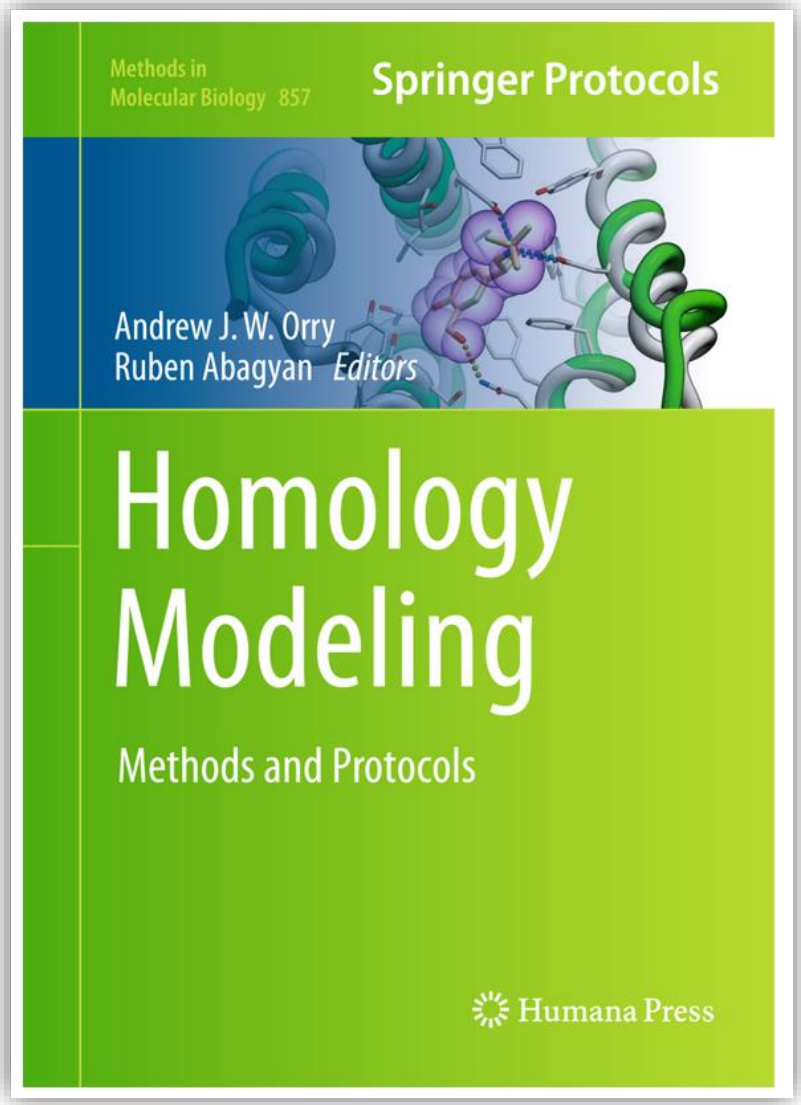
$\Delta G = \Delta G_{folded} - \Delta G_{unfolded}$

- Computes change in protein stability upon mutation of a single residue.
- The free energy change in protein stability is computed as shown.

The free energy of the unfolded and misfolded states is approximated by a sum of the residue-specific energies. The residue-specific energies were derived empirically using a large set of experimental data.

- Mutation of a given residue is followed by Monte Carlo simulations with flexible side chains for the mutated residue and its neighboring residues. The rest of the protein structure is considered rigid.

Recommended Reading!



Cheminformatics

Cheminformatics Data

Purchasable Compounds

ZINC > 35 M

eMolecules ~6 M

MolCart from MolSoft ~9 M

Activity Databases

PubChem

ChEMBL

SureChEMBL beta

Drugs

DrugBank

Open Data Drug & Drug Target Database

6.8K experimental and 1.8K approved

Known bio-metabolites (single molecules)

KEGG Kyoto Encyclopedia of Genes and Genomes

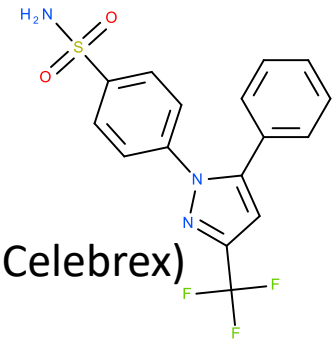
+ HMDB, Metlin

COX-2 Inhibitors

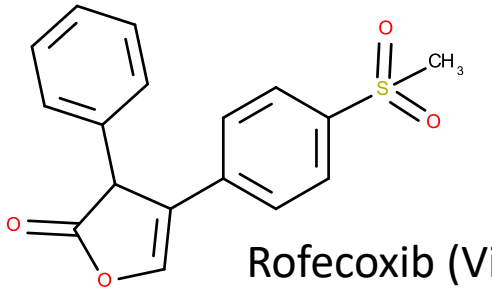
• Cycloxygenase-2 (COX-2) is responsible for formation of prostanoids, including prostaglandins such as prostacyclin and thromboxane. Inhibiting COX-2 can provide relief from inflammation and pain.

• Selective COX-2 inhibitors are members of the non-steroidal anti-inflammatory drug (NSAID) class.

• Targeting selectivity for COX-2 reduces the risk of peptic ulceration, and is the main feature of Celebrex, Vioxx and other members of this drug class.



Celecoxib (Celebrex)

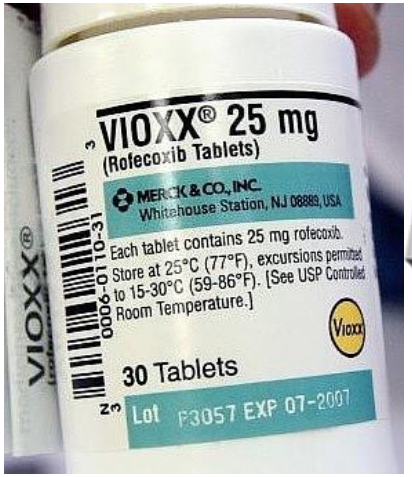


Rofecoxib (Vioxx)

Controversy

• After several COX-2 inhibiting drugs were approved for marketing, data from clinical trials revealed that some COX-2 inhibitors caused a significant increase in heart attacks and strokes, with some drugs in the class having worse risks than others.

•Rofecoxib (commonly known as Vioxx) was taken off the market in 2004 because of these concerns and celecoxib (Celebrex) and some other NSAIDS received boxed warnings on their labels.



CELEBREX®
celecoxib capsules

Cardiovascular Risk

- CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk (see **WARNINGS** and **CLINICAL TRIALS**).

- CELEBREX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see **WARNINGS**).

Gastrointestinal Risk

- NSAIDs, including CELEBREX, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see **WARNINGS**).

Chemical Input – SMILES 0D

- SMILES - is a specification in form of a line notation for describing the structure of chemical species using short ASCII strings.
  - Common atoms are represented by element symbols (e.g. C, N, O, Cl)
  - Other elements charges and isotopes are shown like this [Au], [H+]
  - Single bonds are not shown, = - double triple - #
  - Ring closure is shown by matching digits (C1CCCC1)
  - Full documentation here: www.daylight.com/smiles/index.html

O=S(=O)(N)c3ccc(c2c(onc2c1ccccc1)C)cc3 **COX-2 Inhibitor Valdecoxib (Bextra)**

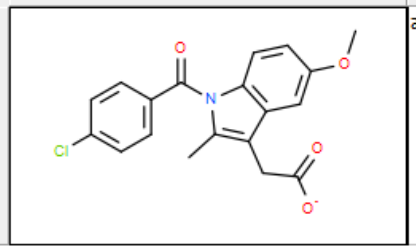
Chemical Input – InChI 0D

- IUPAC International Chemical Identifier (InChI)
- Textual identifier for chemical substances
- Provides a standard and human-readable way to encode molecular information
- Ideal for chemical search
- Initially developed by IUPAC and NIST during 2000–2005, the format and algorithms are non-proprietary.

InChI=1S/C18H15ClN2O2S/c1-12-3-4-14(10-20-12)18-17(9-15(19)11-21-18)13-5-7-16(8-6-13)24(2,22)23/h3-11H,1-2H3 COX-2 Inhibitor **Etoricoxib** (**Arcoxia**)

Chemical Input – 2D

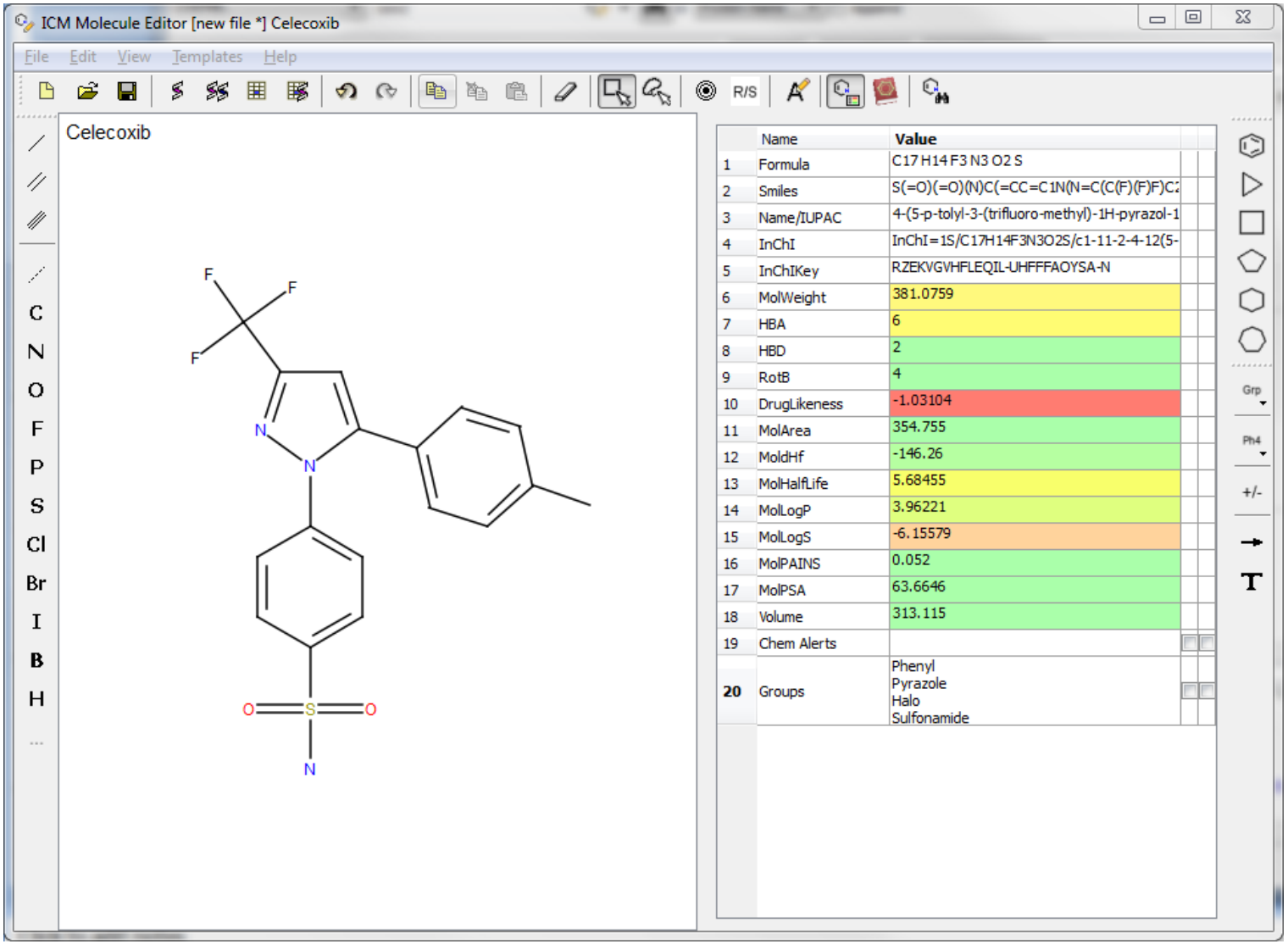
```
Benzene
  6  6  0  0  0  0  0  0  0  0  1 V2000
    1.9050   -0.7932    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
    1.9050   -2.1232    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
    0.7531   -0.1282    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
    0.7531   -2.7882    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   -0.3987   -0.7932    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
   -0.3987   -2.1232    0.0000 C   0  0  0  0  0  0  0  0  0  0  0  0
  2  1  1  0  0  0  0
  3  1  2  0  0  0  0
  4  2  2  0  0  0  0
  5  3  1  0  0  0  0
  6  4  1  0  0  0  0
  6  5  2  0  0  0  0
M  END
$$$$
```

	mol	name	comment	sel
1		aimn	indomethacin	a_4cox.aimn

- **Chemical table files**: .MOL file: example
- Multiple .molfiles form an .SDF
- .SDF file may have PROPERTY sections
- An .sdf file becomes an ICM table/spreadsheet

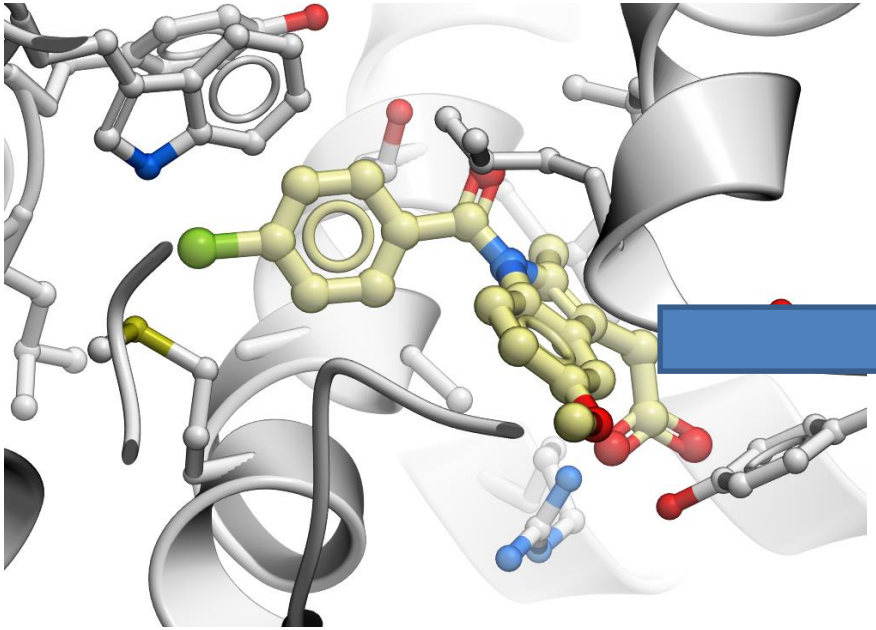
File/Open .sdf .mol

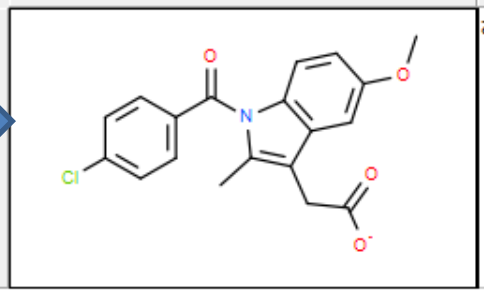
Chemical Sketching



	Name	Value
1	Formula	C17 H14 F3 N3 O2 S
2	Smiles	S(=O)(=O)(N)C(=CC=C1N(N=C(C(F)(F)F)C2
3	Name/IUPAC	4-(5-p-tolyl-3-(trifluoro-methyl)-1H-pyrazol-1
4	InChI	InChI=1S/C17H14F3N3O2S/c1-11-2-4-12(5-
5	InChIKey	RZEKVGVHFLEQIL-UHFFFAOYSA-N
6	MolWeight	381.0759
7	HBA	6
8	HBD	2
9	RotB	4
10	DrugLikeness	-1.03104
11	MolArea	354.755
12	MoldHf	-146.26
13	MolHalfLife	5.68455
14	MolLogP	3.96221
15	MolLogS	-6.15579
16	MolPAINS	0.052
17	MolPSA	63.6646
18	Volume	313.115
19	Chem Alerts	
20	Groups	Phenyl Pyrazole Halo Sulfonamide

Chemical Input - 3D

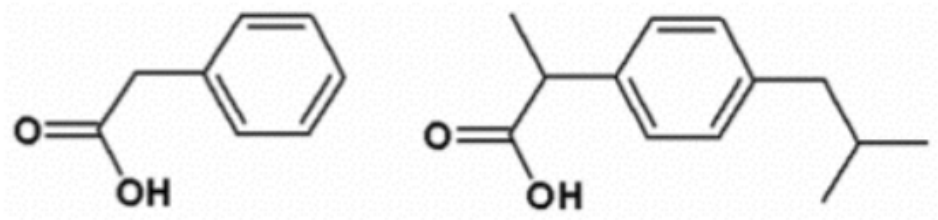


mol	name	comment	sel
	aimn	indomethacin	a_4cox.aimn

PDB 4COX – COX-2 Inhibitor Indomethacin

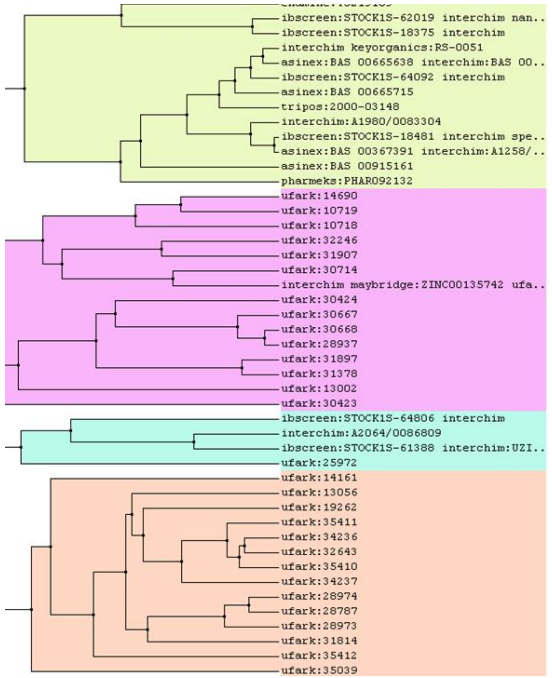
Chemical Search

- Exact Match
- Substructure Searching
- Pattern Searching
- Similarity Searching (Tanimoto of Fingerprints)

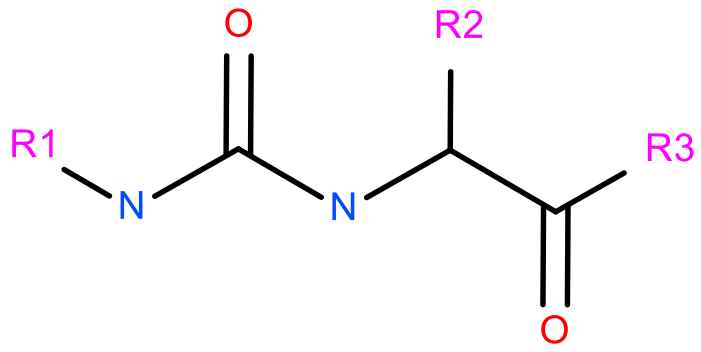


Chemical Similarity

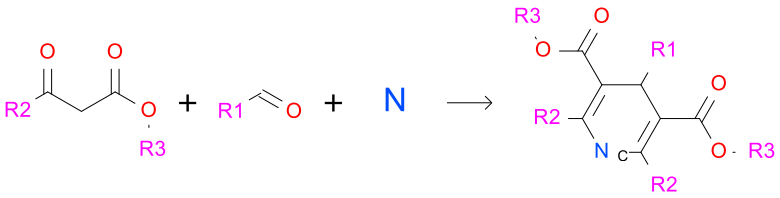
- Divide both structures (A and B) into small fragment
- Merge fragment lists and form two "bit-strings", e.g. 010001000111 and 101111011001
- Calculate a Tanimoto distance as nAB/nTotal
  nAB is the number of on-bits which are in common.
- Tanimoto distance is between 0.0 and 1.0



Combinatorial Library Design



Markush Based



Reaction Based

- Enumerate a library by scaffold (Markush) structure
- Decompose a library based on a scaffold
- Generate a SAR table
- Generate a library based on a reaction
- SALI Structure--activity landscape index: identifying and quantifying activity cliffs (Guha and Van Drie JCIM 2008).

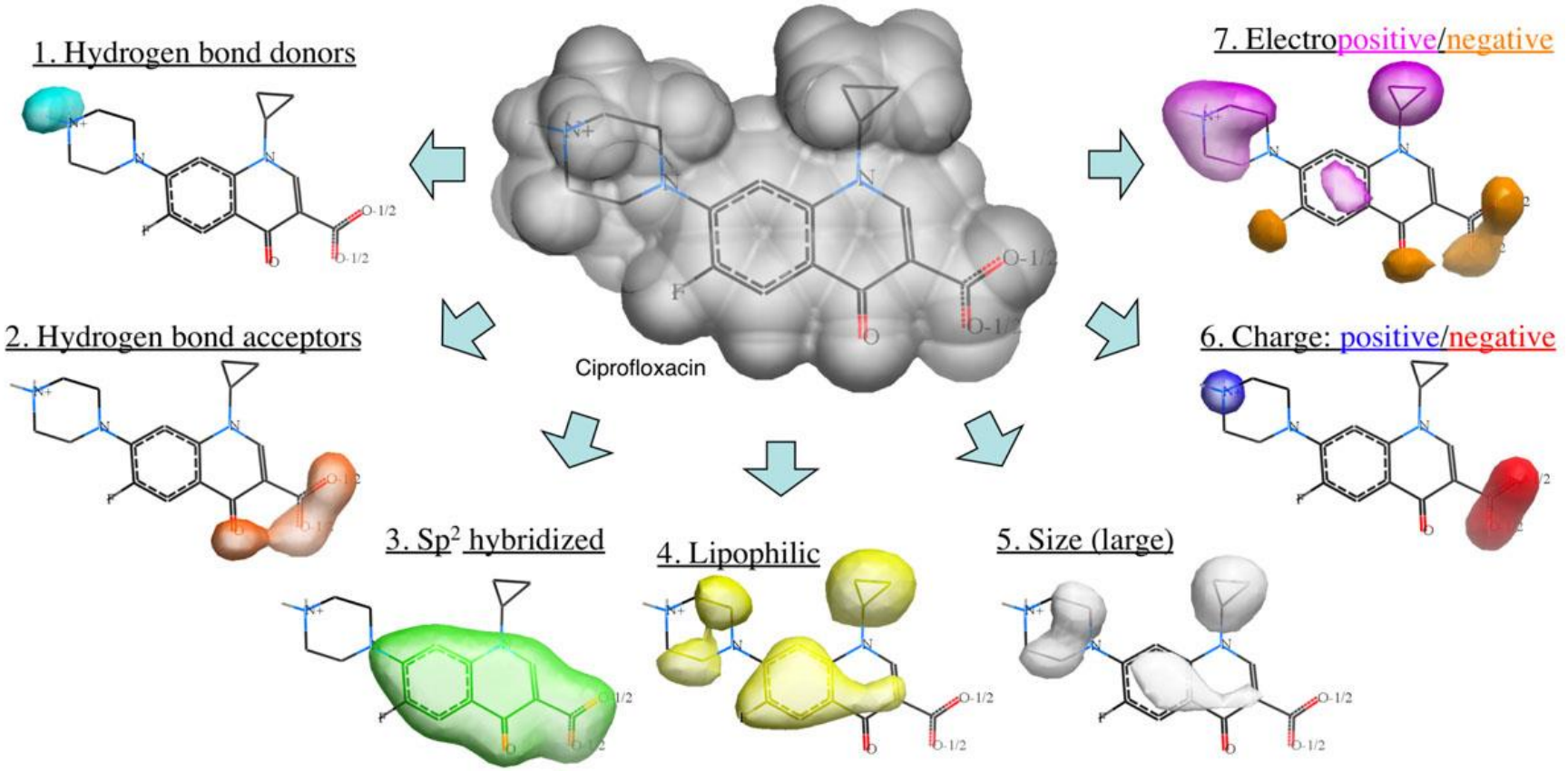
Atomic Property Fields (APF)

- APF is a 3D pharmacophore which replaces discrete points by continuous property distributions.

- APF replaces representation of chemical moieties with fixed pharmacophoric types by vectors of atomic properties that can be compared in a more flexible, quantitative manner rather than by binary matching.

Totrov M. Chem Biol Drug Des. 2008 Jan;71(1):15-27.

APF Potential Components

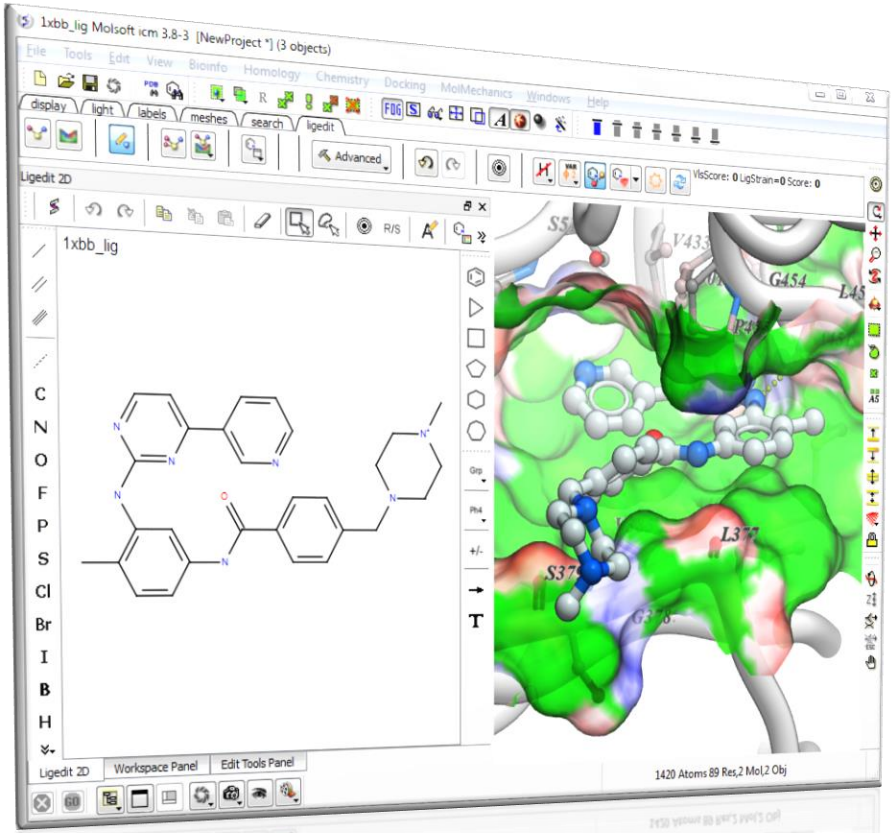


APF Utility

- APF pharmacophoric potential implemented on a continuously distributed grid can be used for:
  - ligand superposition
  - multiple compound alignment
  - virtual screening
  - 3D QSAR
  - ligand binding site superposition and comparison

3D Ligand Editor

About the Ligand Editor



- The editor is widely used throughout the pharmaceutical and biotech industry for ligand design and optimization
- The tool was built in close collaboration with Medicinal Chemists at Novartis
- It is a fully interactive tool whereby you can make changes to a ligand in **3D or 2D**
- Immediately see the effect of a modification on predicted binding affinity

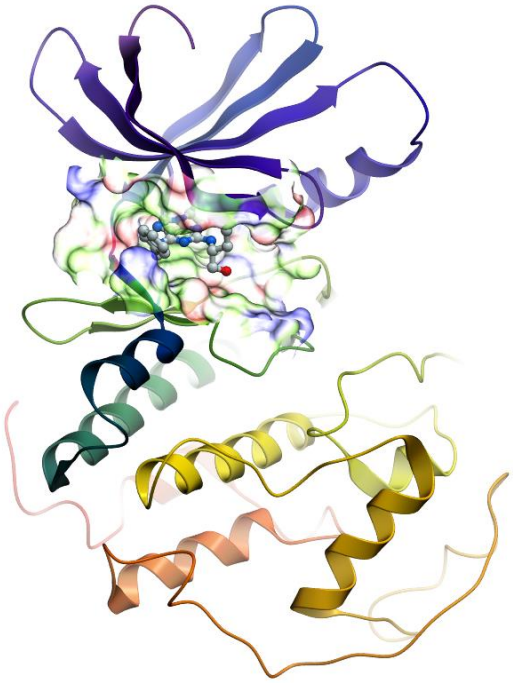
FOCUS — Development of a Global Communication and Modeling Platform for Applied and Computational Medicinal Chemists

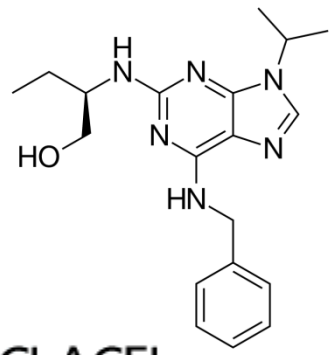
Nikolaus Stiefl[†], Peter Gedeck[‡], Donovan Chin[§], Peter Hunt[∥], Mika Lindvall[⊥], Katrin Spiegel[∥], Clayton Springer[§], Scott Biller[§], Christoph Buenemann[#], Takanori Kanazawa[∇], Mitsunori Kato[§∇], Richard Lewis[†], Eric Martin[⊥], Valery Polyakov[⊥], Ruben Tommasi[§], John van Drie[§], Brian Vash[§], Lewis Whitehead[§], Yongjin Xu[⊥], Ruben Abagyan[○], Eugene Raush[○], and Max Totrov[○]

Topics

- Ligand-Receptor visualization
- Ligand editing in 2D and 3D
- Evaluating the effect of a modification
- Undo/redo capabilities and save to spreadsheet
- Ligand docking, minimization and refinement
- Distance restraints and tethers during docking
- Substituent virtual screening
- Covalent and Fragment docking
- Methods to incorporate induced fit - MRC
- Ligand-based design to 3D pharmacophores

Seliciclib (Roscovitine)

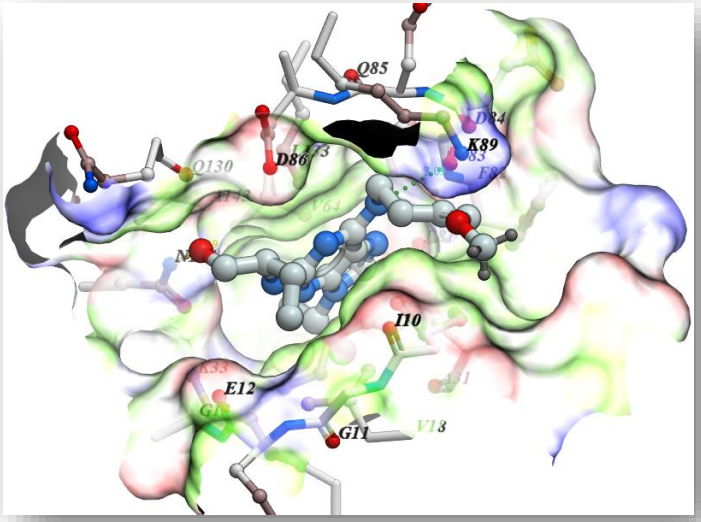


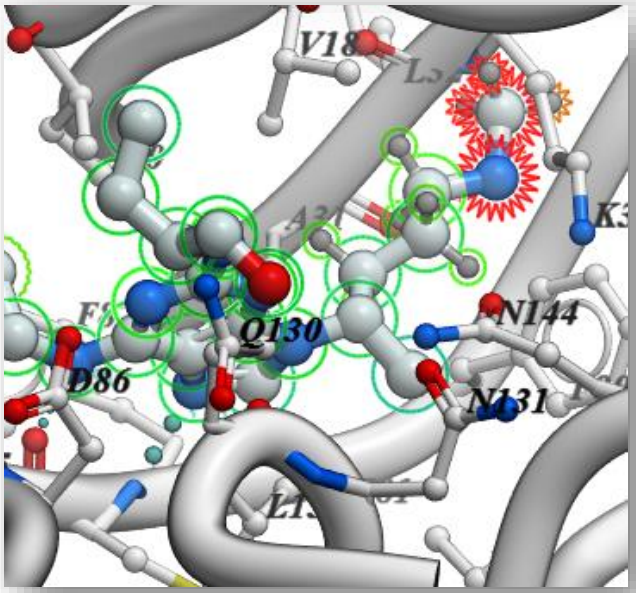


- It is an experimental drug candidate in the family of cyclin-dependent kinase (CDK)
- Preferentially inhibit multiple enzyme targets including CDK2, CDK7 and CDK9.
- Alters the growth phase or state within the cell cycle of treated cells.
- In clinical trials for treatment of non-small cell lung cancer (NSCLC), Cushing's Disease, leukemia, HIV infection, herpes simplex infection, cystic fibrosis

CYCLACEL

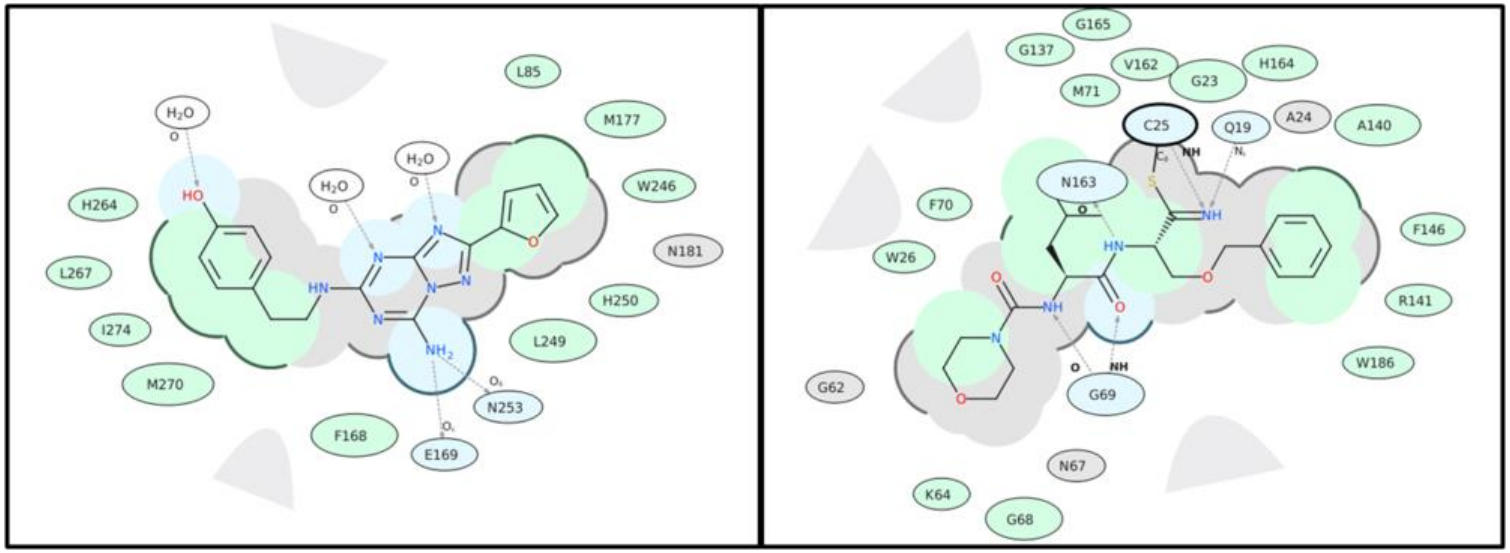
Ligand-Receptor Visualization



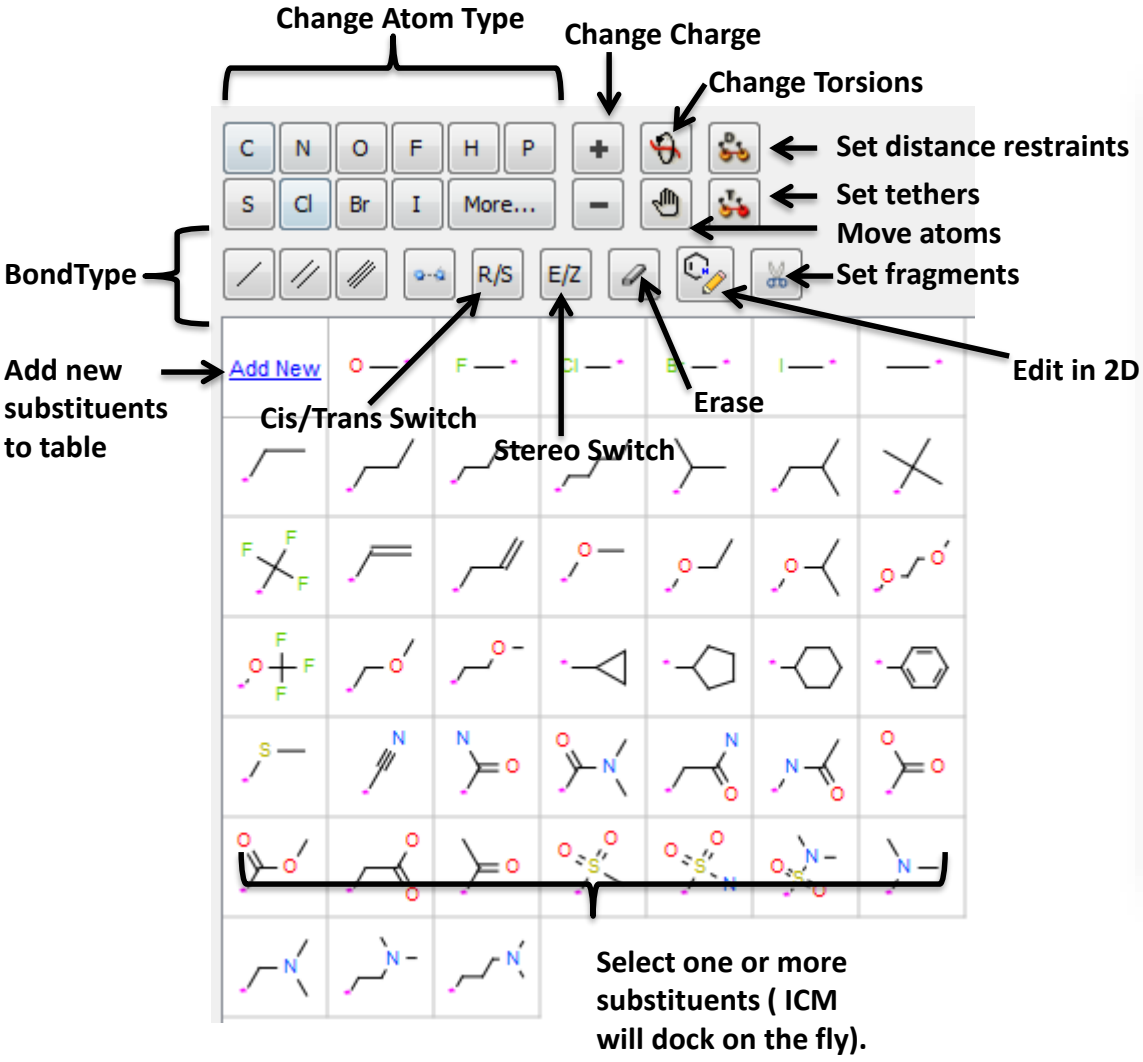


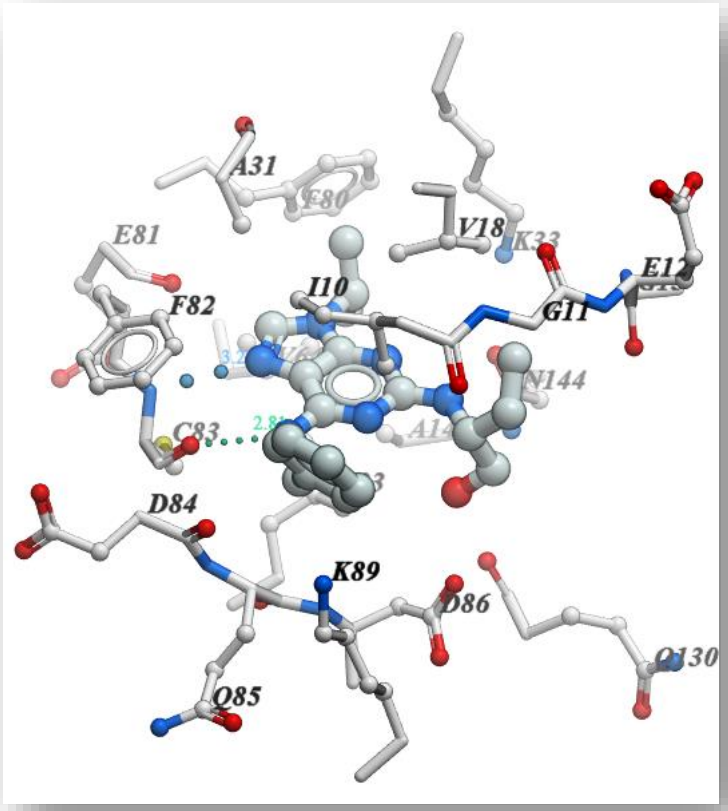
- Display receptor surface colored by binding property
- Display ligand pocket surface
- Display hydrogen bonds
- Display energy circles – easily highlight clashes
- Display relaxed ligand compared to docked ligand
- Display unsatisfied hydrogen bonds

2D Ligand Interaction Diagrams



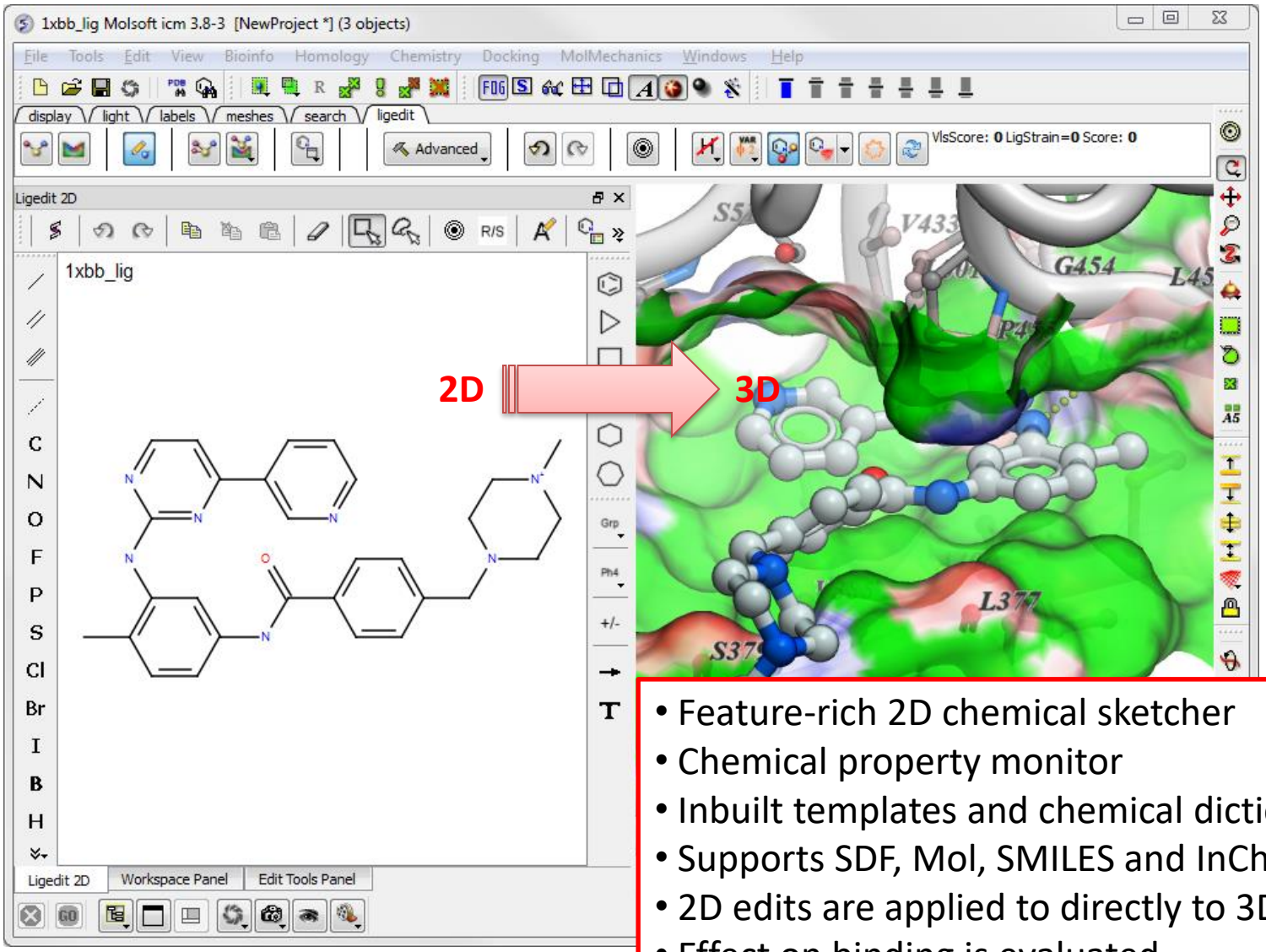
3D Ligand Editing





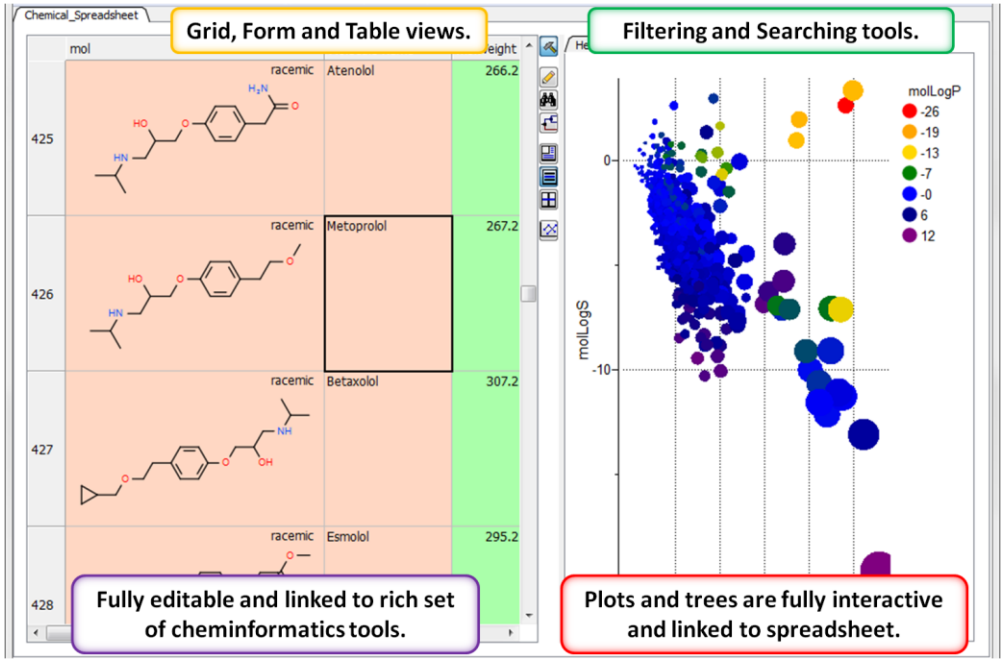
- Full undo/redo capability
- Screen multiple substituents

2D Editing



- Feature-rich 2D chemical sketcher
- Chemical property monitor
- Inbuilt templates and chemical dictionary
- Supports SDF, Mol, SMILES and InChI keys
- 2D edits are applied to directly to 3D
- Effect on binding is evaluated

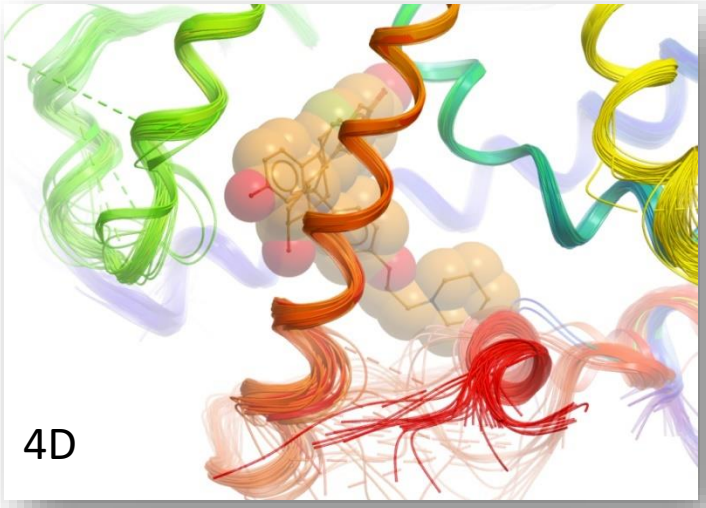
Save Modifications

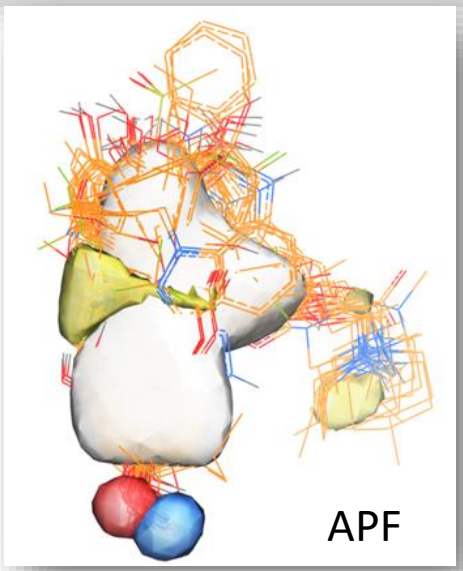


- Save your modifications in:
  - PDB format
  - Chemical Spreadsheet
  - SDF / Mol/ Mol2 format
- Export to:
  - Excel
  - HTML
- Save in ICM binary format:
  - Display in free ICM-Browser
  - Display on web using free Active ICM plugin.
  - Share on iPhone/iPad Android devices (iMolview)

Rich array of spreadsheet features:
- Chemical search
- Chemical edit
- Chemical clustering
- Plotting
- Compare, merge…

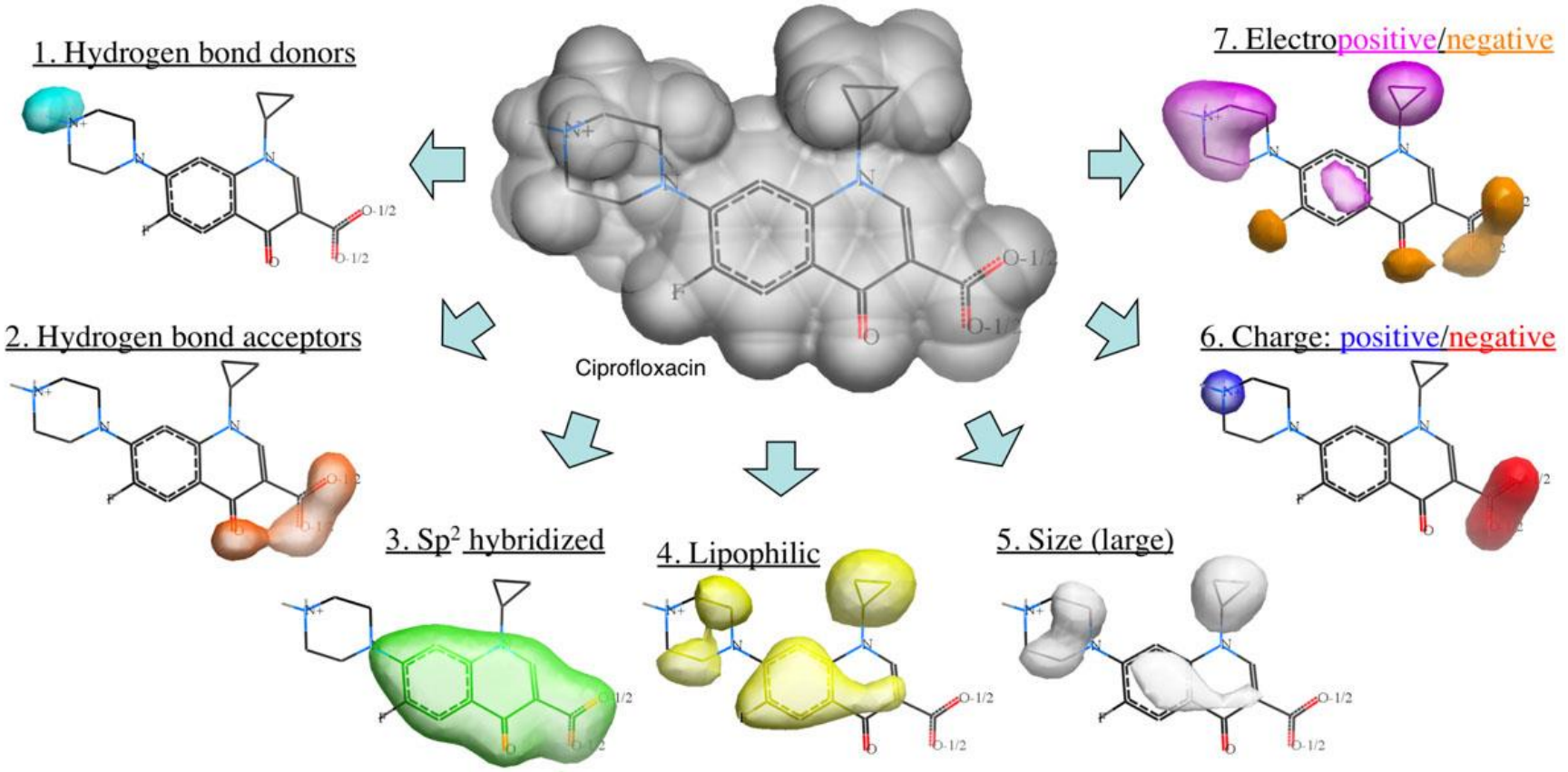
Ligand Docking / Minimization





- Uses MolSoft's ICM docking technology
- Dock a modified ligand
- Dock a chemical spreadsheet
- Screen a database of substituents
- Induced-fit docking using multiple receptor conformations (4D)
- Receptor side-chain refinement
- Ligand-based docking using 3D pharmacophoric properties fields (APF)
- Covalent docking
- Fragment docking and linking
- Docking using tethers and distance restraints

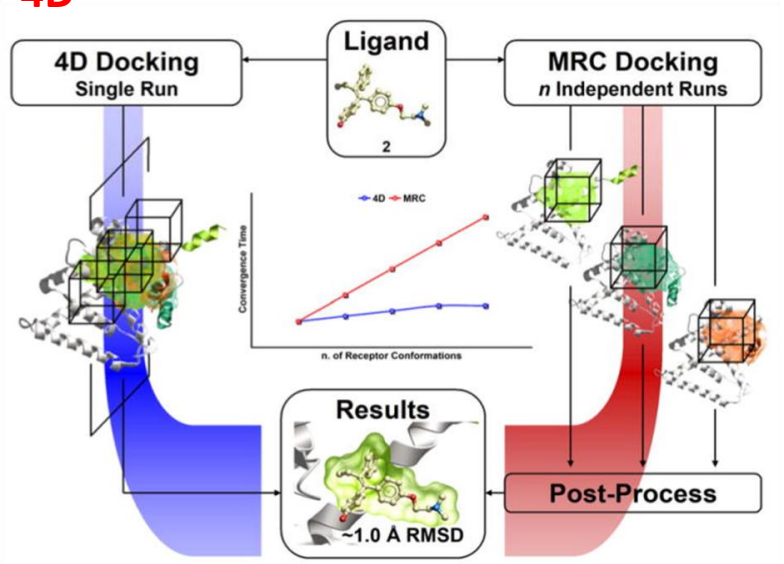
APF Potential Components



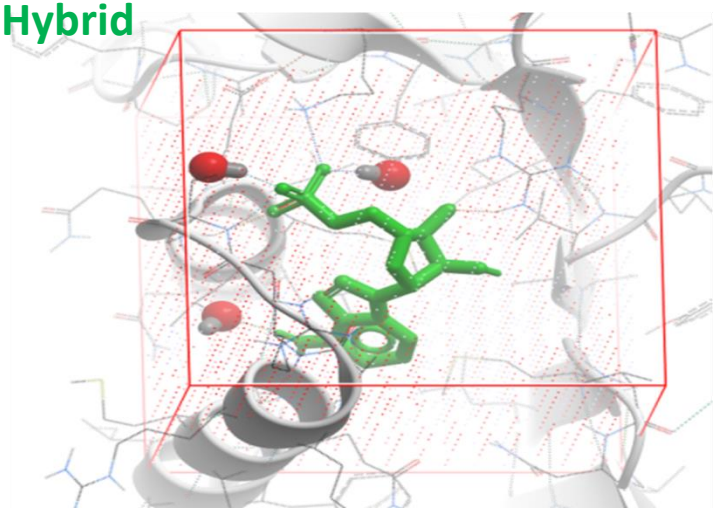
Totrov M. Chem Biol Drug Des. 2008 Jan;71(1):15-27.

Induced Fit Docking

4D



Hybrid



- 4D Docking The most efficient way to account for receptor flexibility is to use an ensemble of conformations of the receptor (Multiple Receptor Conformtion (MRC)). This method is referred to as 4D docking in ICM and in benchmark studies has been shown to reach convergence faster than conventional multiple receptor procedures
- Hybrid Partially Explicit Maps Selected explicit atoms can be used in hybrid partially explicit receptor maps whereby select residues can be defined as explicit inside the maps.
- Explicit Receptor Refinement Explicit receptor sampling can be used for side-chain refinement where minor adjustments are needed to optimize a ligand-receptor complex.

Reference:
Bottegoni *et al* (2009) Four-dimensional docking: a fast and accurate account of discrete receptor flexibility in ligand docking. J. Med. Chem. 52:397