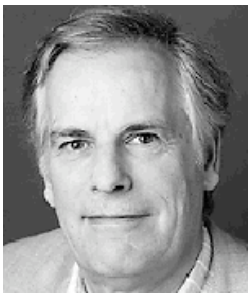
Biographics Laboratory 3R
Basel/Switzerland
E-Mail: admin@biograf.ch
Internet: http://www.biograf.ch

User Manual
Yeti^{X} 8.2

Protein molecular mechanics employing a directional force field

Yeti's realm: summit view from Shisha Pangma (8,046m, Himalaya/Tibet)

Authors



Max Dobler, PhD
Professor *emeritus*, ETH Zürich
and Biographics Laboratory 3R

Angelo Vedani, PhD
Associate Professor, University of Basel
and Biographics Laboratory 3R

Yeti^{X} — Protein molecular mechanics employing a directional force field

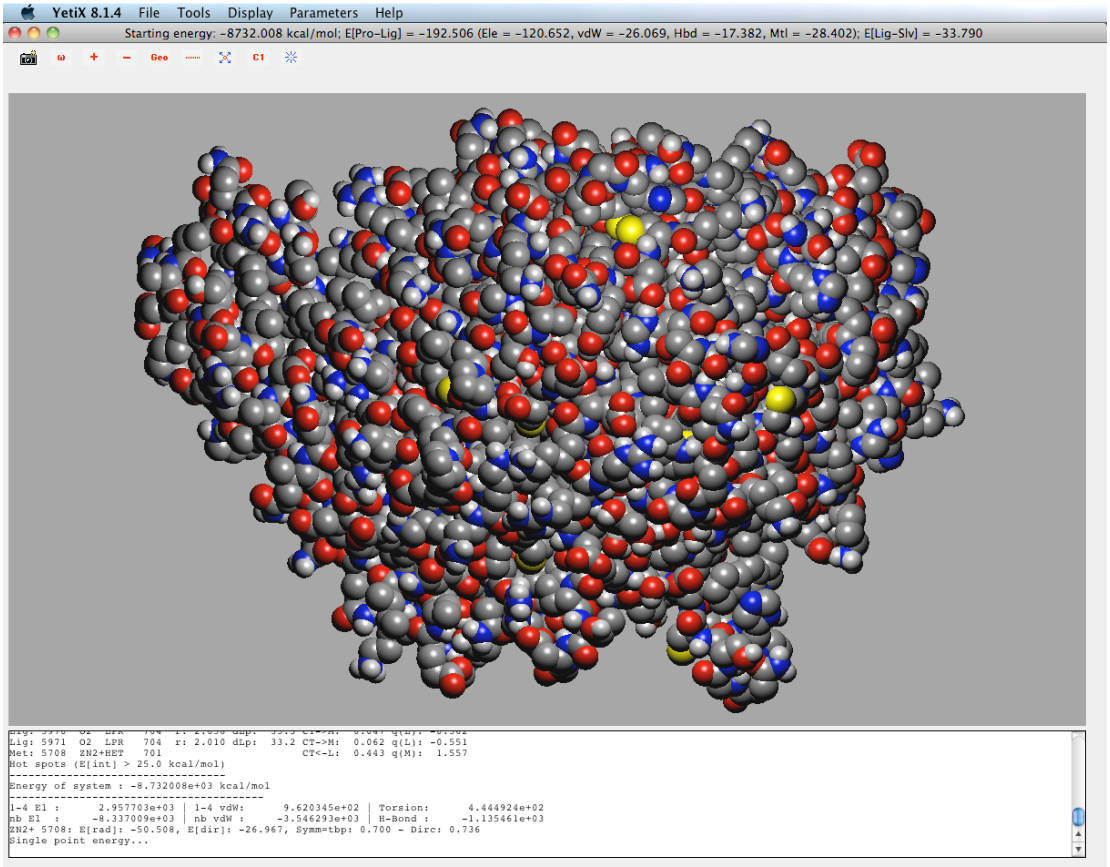


Figure 1: Appearance of *Yeti*^{X}

Special features of the *Yeti* technology

• Protein molecular mechanics based on a directional force field (hydrogen bonds, metals)
• Hydrogen bonds: linearity and directionality terms
• Metal centers: dynamic ligand–metal charge transfer; symmetry, LFSE
• Hydrogen-bond network orientation
• Protein solvation (structural and bulk waters)
• Interactive docking

References to the technology

1. Vedani, A. and Huhta, D.W. (1990). A new force field for modeling metalloproteins. *J. Am. Chem. Soc. 112*, 4759–4767.

2 Vedani, A. and Huhta, D.W. (1991). An algorithm for the systematic solvation of proteins based on the directionality of hydrogen bonds. *J. Am. Chem. Soc. 113*, 5860–5862.

3 Lill, M.A., Dobler, M. and Vedani, A. (2006). Prediction of small-molecule binding to Cytochrome P450 3A4: Flexible docking combined with multidimensional QSAR. *ChemMed Chem 1*, 73–81.

4 Vedani, A., Zumstein, M., Lill, M.A. and Ernst, B. (2007). Simulating α/β specificity at the thyroid receptor: Consensus scoring in multidimensional QSAR. *ChemMedChem 2*, 78–87.

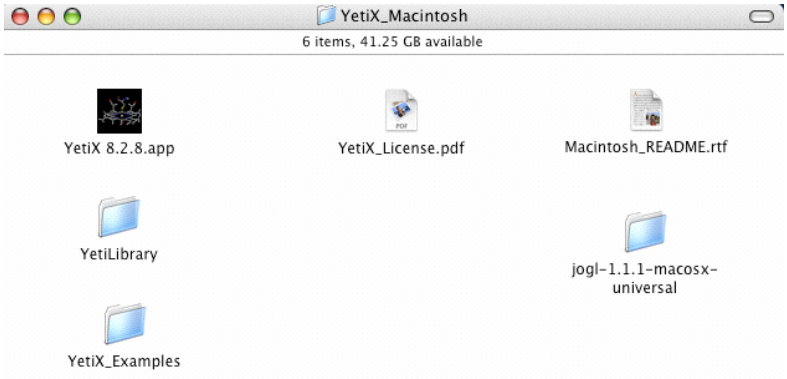
5 Spreafico, M., Smiesko, M. Lill, M.A., Ernst, B. and Vedani, A. (2009). Mixed-model QSAR at the glucocorticoid receptor: Predicting the binding mode and affinity of psychotropic drugs. *ChemMedChem 4*, 100–109.

6 Rossato, G., Ernst, B., Smiesko, M., Spreafico, M. and Vedani, A. (2010). Probing small-molecule binding to cytochrome P450 2D6 and 2C9: An in silico protocol for generating toxicity alerts. *ChemMedChem 5*, 2088–2101.

Installation of Yeti^X

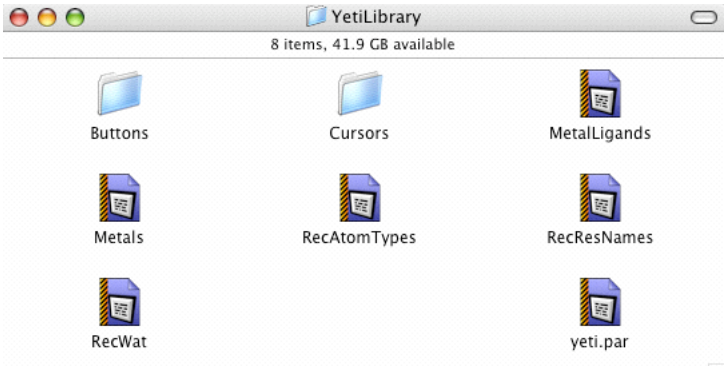
Important:
1. Yeti^X 8.2 requires Java 1.6 or higher. Type "java -version" on a terminal shell to obtain this information. If necessary, update your Java to version 1.6
2. Yeti^X 8.2 uses the OpenGL™ graphics libraries. In order to properly function, a series of jogl (java OpenGL) libraries must reside in /Library/Java/Extensions (Macintosh HD → Library→ Java→ Extensions). The libraries provided with the release should work — if not, download them from http://jogl.dev.java.net

The **Yeti^X** software is provided by electronic means as a single file *YetiX_version.zip* (2.7 or 3.6 MB in size; version = Macintosh or Linux). Save this file onto the Desktop of your computer (or any other location where you have write privilege). To generate and populate the folder *YetiX*, double-click its icon (Macintosh) or apply the appropriate procedure under Linux. The Yeti^X folder should then look as follows (Macintosh version):



Linux distribution: The executable carries the ending ".jar" instead of ".app", i.e. YetiX8.2.8.jar

YetiX 8.2.8.app (Macintosh) and *YetiX 8.2.8.jar* (Linux) are the executables (programs) themselves. The folder *YetiLibrary* includes the parameter files and two icon folders:



The Toolbar

Button	Description
	A picture file (TIFF format) of the graphical screen content is generated.
	Click a bond around which you want to change the torsion angle. The part of the molecule closest to the click point is rotated. To change the torsion angle you can use the + and – buttons, or press Ctrl/Shift and move the mouse left or right. **New**: by using the left or right arrow keys you can move the active torsion bond through a molecule, and the direction (affected atoms) can be changed with the down arrow key. For amino-acid residues, the torsions are restricted to the side chain and the direction cannot be changed.
	Click two atoms and <Esc> to calculate a bond distance, click three atoms and <Esc> to calculate a bond angle, click four atoms and <Esc> to calculate a torsion angle. Note that the atoms need not form actual bond or angles. The calculated values are written in the log window located at the bottom of the screen.
	Click any two atoms to define an interatomic distance, indicated by a violet dashed line. To remove an interatomic distance, click the two atoms again. To remove all interatomic distances, use *remove interatomic distances* from the **Tools** menu.
	Click an atom to define a new center of rotation. With the <A> key pressed, all rotations/translations affect only this residue (typically a small molecule to be docked).
	Label individual atoms.
	Center molecule on the screen.

File Formats

Yeti^{X} reads the following file formats:

- PDB (Protein Data Bank) in standard form:

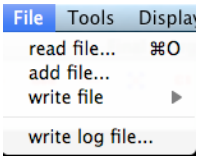
  ATOM 1 CT ALA 1 1.086 6.867 –2.071

- PDB extended format (Biographics software) that includes the partial atomic charge:

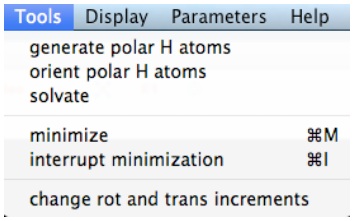
  ATOM 1 CT ALA 1 1.08628 6.86739 –2.07077 –0.24150

The Menus

1 The File Menu

Menu item	Description	Appearance
read file	read an existing coordinate file	
add file	add a new model to an existing one	
write file	save coordinates to output file	
write log file	write a log file of the session (can be activated at any time)	

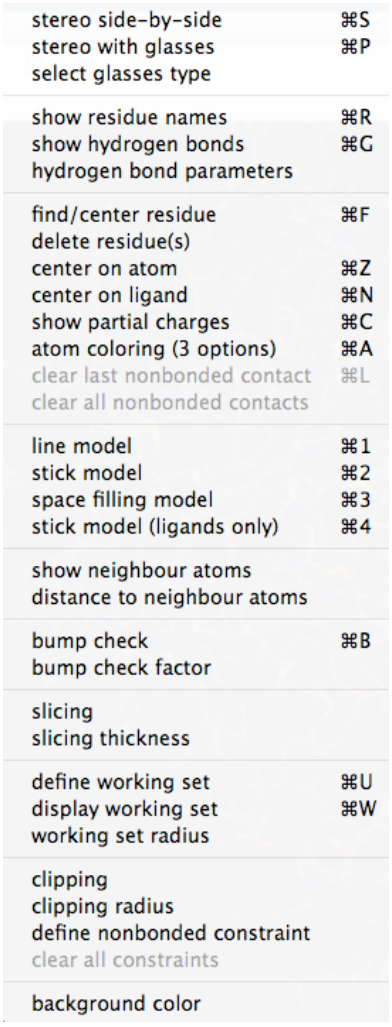
2 The Tools Menu

Menu item	Description	Appearance
generate polar H atoms	adds polar H atoms (OH, NH, SH) to a bare PDB structure (for details, cf. Yeti reference manual)	
orient polar H atoms	hydrogen-bond network orientation (for details, cf. Yeti reference manual)	
solvate	protein solvation (for details, cf. Yeti reference manual)	
minmize	start minimization	
interrupt minimizer	interrupt running minimization	
Change rot/trans increments	Torsional and translational movements upon a single mouse click.	

3 The Display Menu

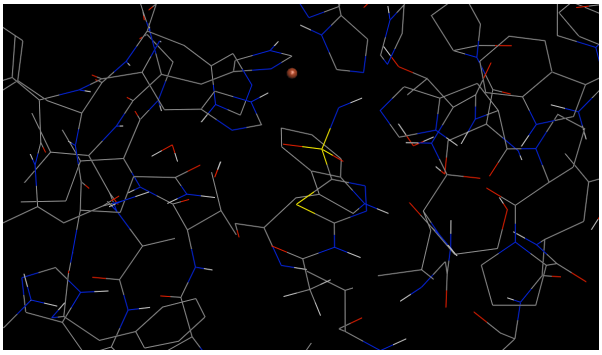
Menu item	Description
stereo side-by-side	toggle between mono/stereo modes (side-by-side)
stereo with glasses	toggle between sbs and anaglyph mode
select glass type	select glass type for anaglyph mode
show residue names	display residue names (ESC to clear)
show hydrogen bonds	show hydrogen bonds (ESC to clear)
hydrogen-bond parameters	define lower/upper display distances
find/center residue	enter residue number to find/center
delete residue	delete selected residue(s)
center on atom	click on atom to center display
center on ligand	automatically centers on ligand
show partial charges	display partial charges (ESC to clear)
atom coloring (3 options)	toggle between 3 options (cf. below)
clear last non-bonded contact	delete last displayed contact
clear all non-bonded contacts	delete all displayed contacts
line model	line representation (cf. below)
stick model	stick representation (cf. below)
space-filling model	space-filling representation (cf. below)
stick model (ligands only)	ligand(s): stick, others: line (cf. below)
show neighbour atoms	show non-bonded contacts
distance to neighbor atoms	radius of non-bonded contacts
bump check	bump-check during ligand docking: too close (van der Waals) contacts are indicated by green→yellow→red dashed lines
bump-check factor	define bump-check criteria
slicing	z-clipping

Appearance

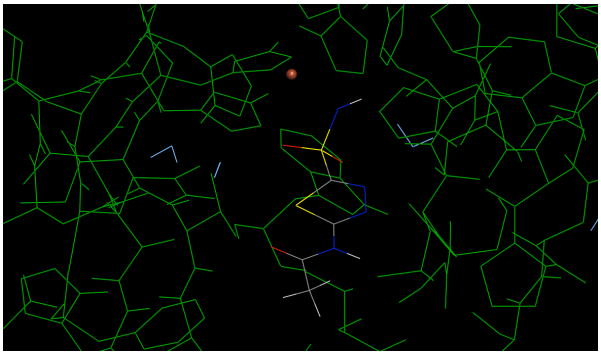


slicing thickness	z-clipping thisckness
define working set	select a working set
display working set	toggle: working set/complete structure
clipping	clipping (all directions)
clipping radius	define clipping radius
define non-bonded constraint	distance constraint(s) for minimization
clear all constraints	remove all constraints
background color	select background color (def = black)

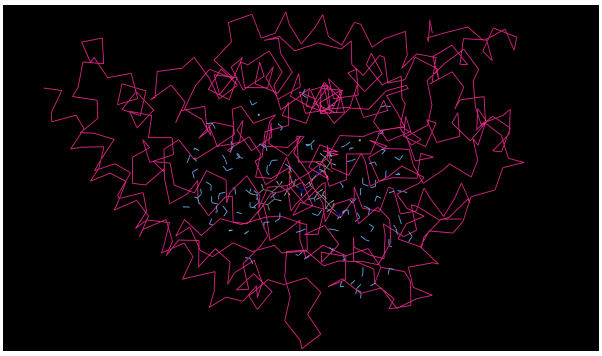
Atom-coloring options (toggle cmd+a or use cmd+*n*: *n*=1,2,3,4)



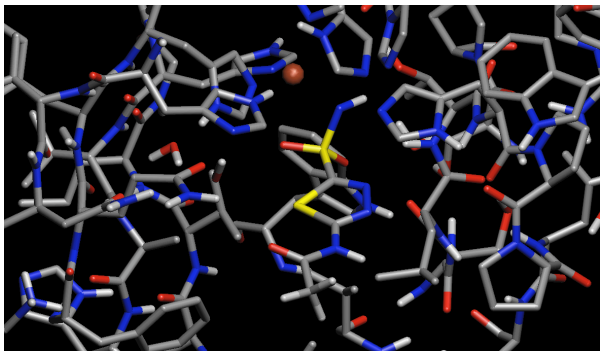
Mode A: colored by atom type (default display mode)



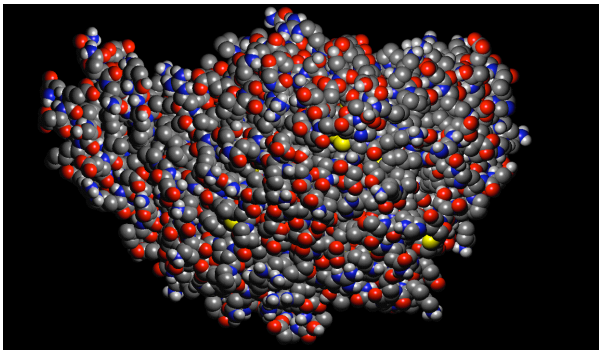
Mode B: protein = green, ligand = by atom (@ cmd+a)



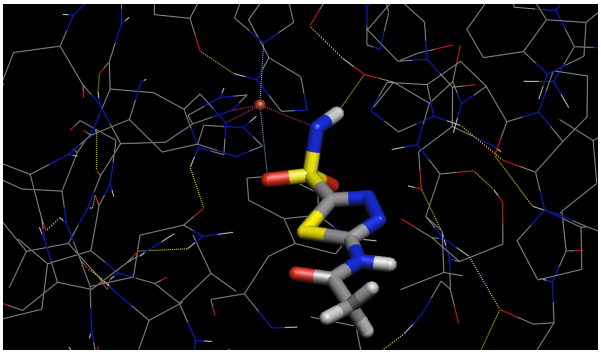
Mode C: protein backbone (@ cmd+a)



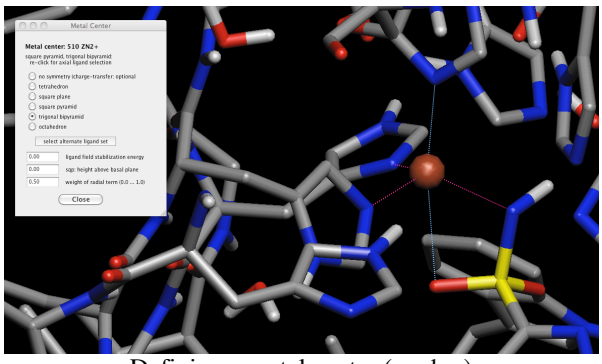
Mode 2: stick representation (cmd+2)



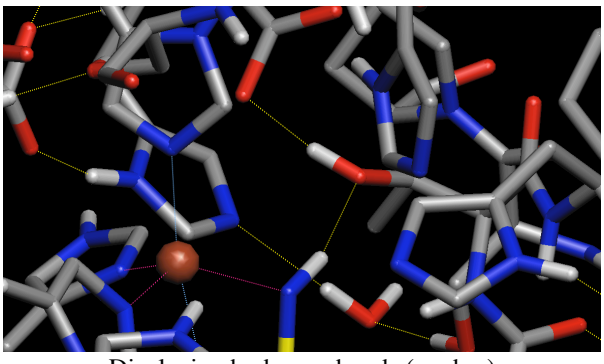
Mode 3: space-filling representation (cmd+3)



Mode 4: protein = lines, ligand = stick (cmd+4)

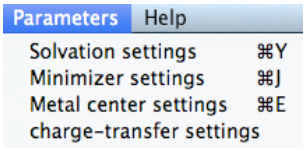


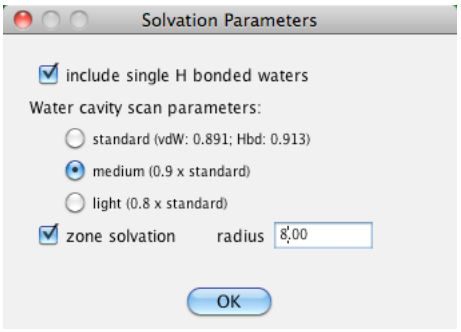
Defining a metal center (cmd+e)
(axial ligands are indicated by blue lines, equatorial ligands by red lines)

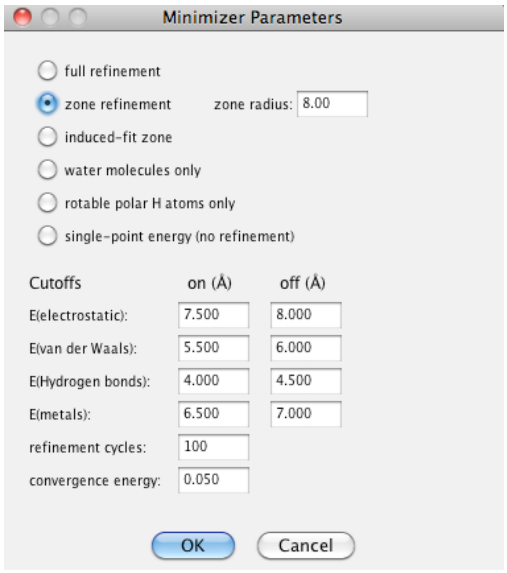


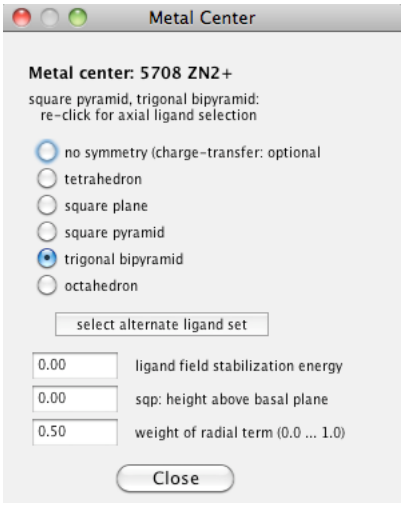
Displaying hydrogen bonds (cmd+g)
(yellow, dashed lines)

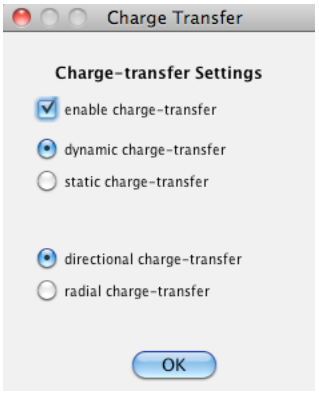
4 The Parameter Menu

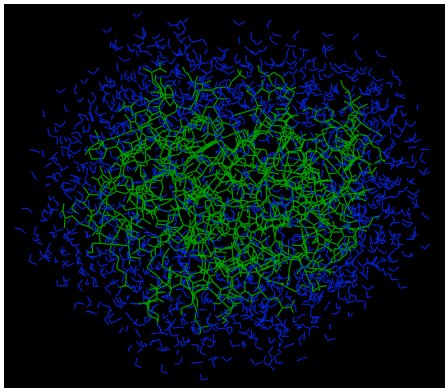
Menu item	Description	Appearance
Solvation settings	solvation options (cf. below)	
Minimizer settings	minimizer options (cf. below)	
Metal-center setting	metal-center options (cf. below)	
charge-transfer settings	charge-transfer options (cf. below)	



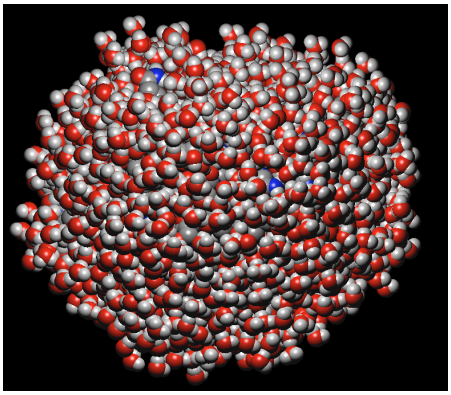




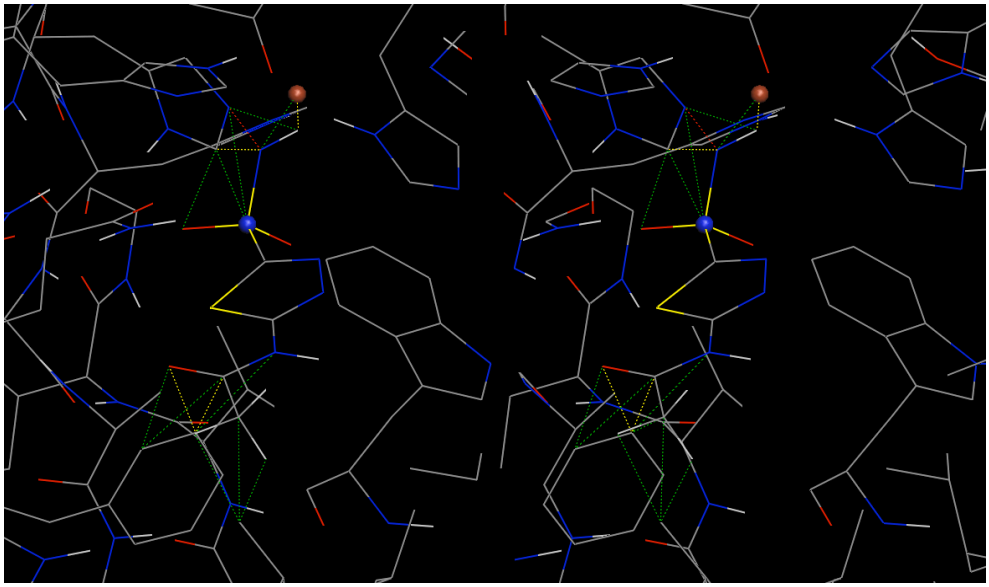




Solvated protein (display mode = B)



Solvated protein (display mode = 3)

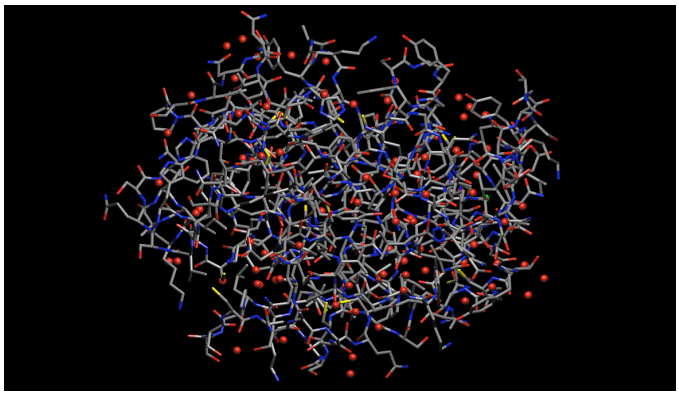


Bump check (green/yellow/red dashed lines) during interactive docking

Examples

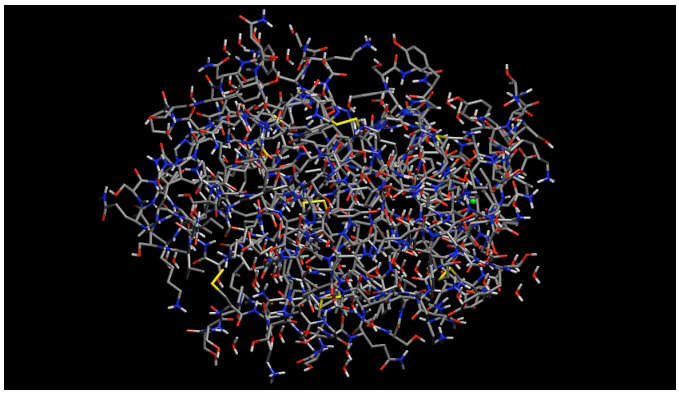
A. Processing a PDB file

1. Read PDB file: Trypsin.pdb (located in the folder YetiX_Examples). Please note that metals need a notation different from the standard PDB. Calcium for example, needs to be labeled as “CA2+ HET” (for details, see the Yeti reference manual).



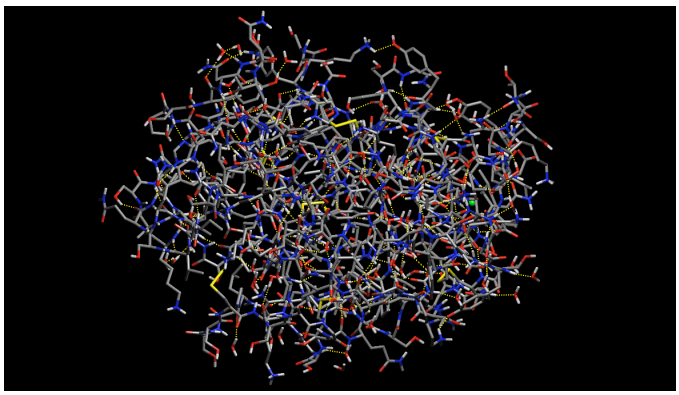
Starting structure from the PDB

2. Tools: generate polar H atoms



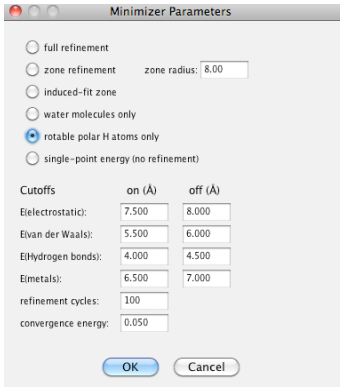
Structure with added polar H atoms (if you wish to add also apolar H atoms, use the Bio^{X} software instead)

3. Tools: orient polar H atoms

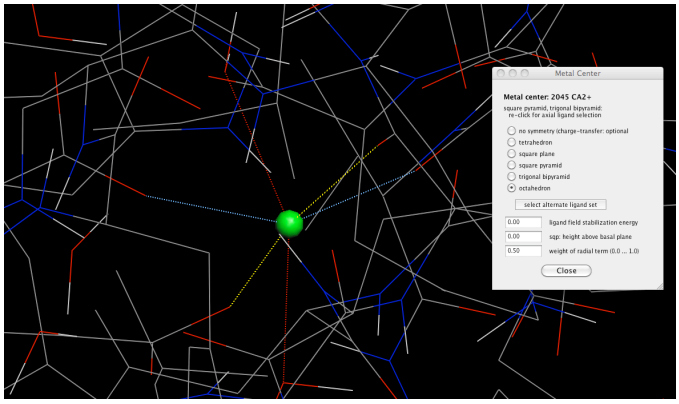


Structure with oriented polar H atoms (Thr, Ser, Thr, Cys, water)

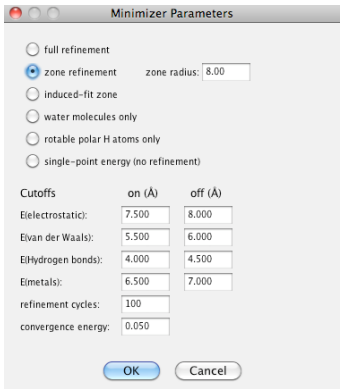
4. Minimizer settings (cmd+j): Select “rotable polar H atoms”, then click “OK” and start the minimizer (Tools: minimizer or cmd+m)



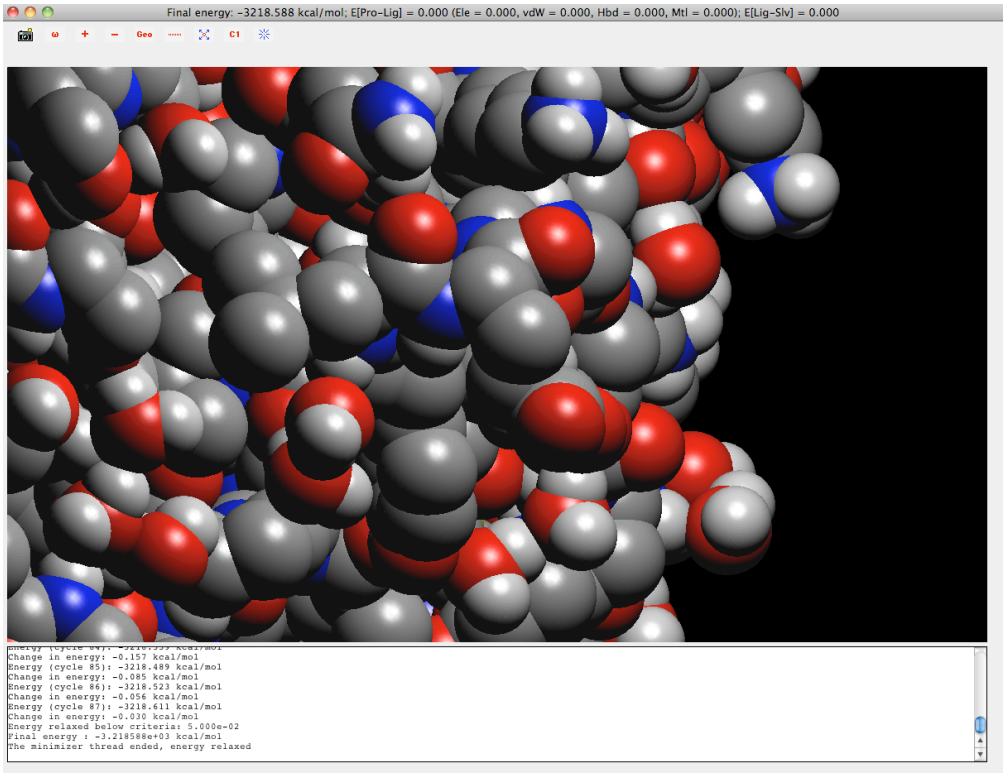
5. Define the metal center (cmd+e) and select “octahedron”, the click “Close”



6. Select the minimizer dialog (cmd+j) and select an 8Å refinement zone around the metal, then click “OK”



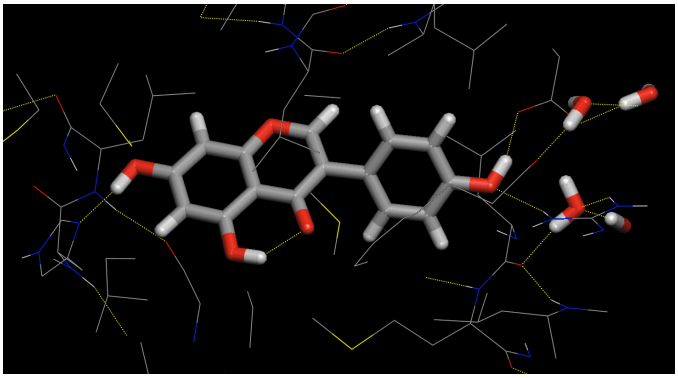
7. Minimize complete structure: proceed as for step #6 but select “full refinement” instead. During the minimization process, the first derivates are shown in color.



Fully minimized structure of native trypsin (detail of a surface region).

B. Optimizing a ligand–protein complex

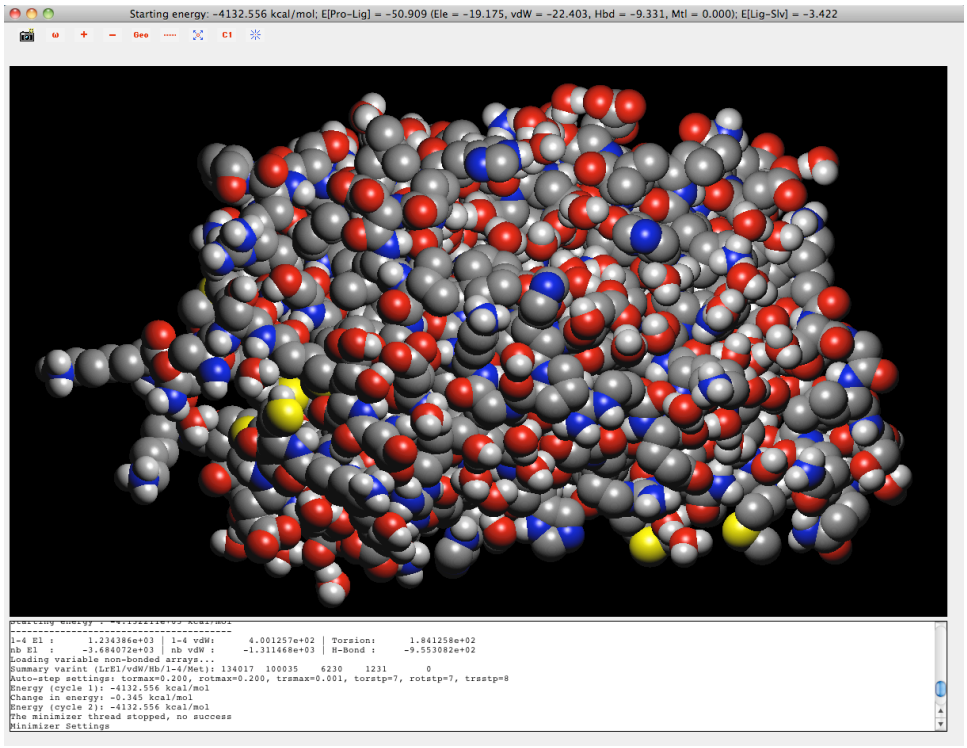
1. Read input file: ERb+Genistein.pdb_ext (located in the folder YetiX_Examples). The extension "pdb_ext" refers to an "extended PDB file format" including atomic partial charges and extended coordinates (5 decimal points). Such files can, for example, be generated using the Bio^X software.



Details of the binding of genistein to the estrogen receptor β

2. Optimize the ligand-binding pocket (8A zone)

3. Relax the entire protein

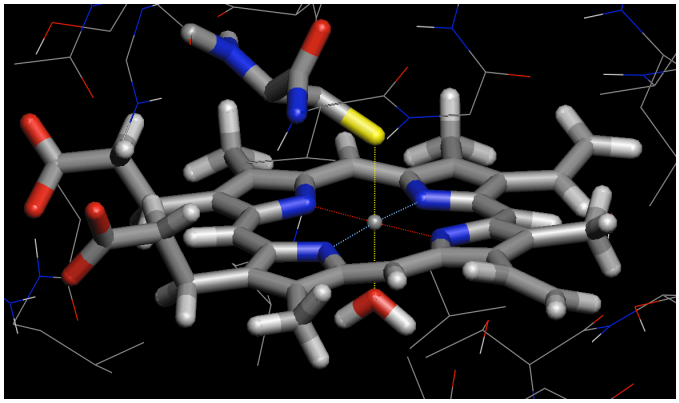


C. Optimizing a ligand–protein complex including a metal ion

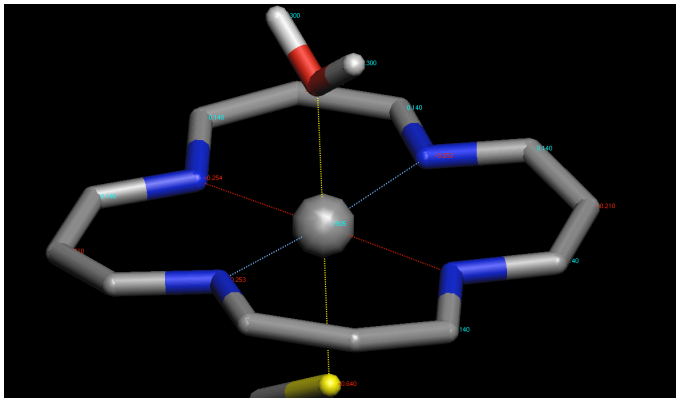
1. Read input file: CYP2C9+Warfarin.pdb_ext (located in the folder YetiX_Examples)

2. Define the metal center (cmd+e)

3. Proceed as in example 3



Octahedrally coordinated $Fe^{\cdots}$ in cytochrome P450 2C9

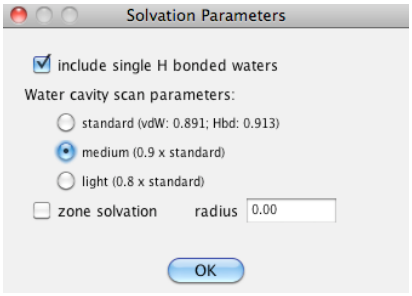


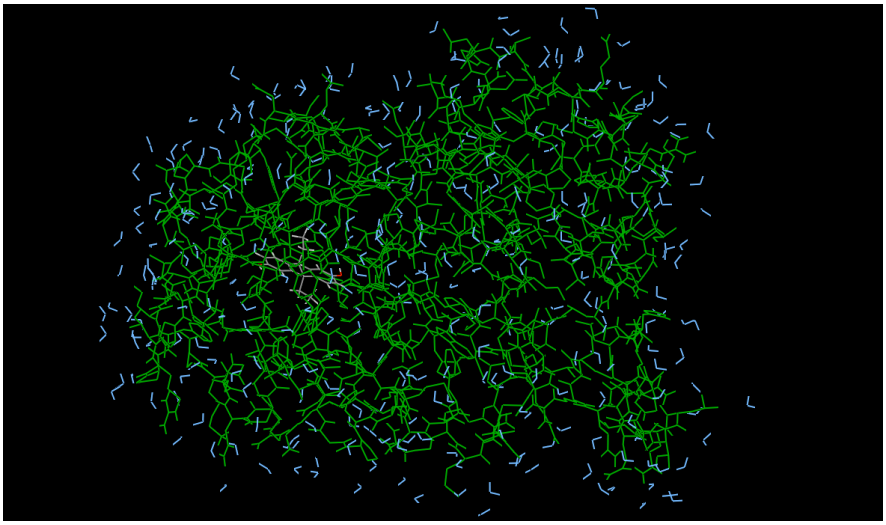
Display: charges (cmd+c) allows you to interactively inspect the ligand–metal charge transfer.

D. Solvating a ligand–protein complex

1. Read input file: ERa+Diethylstilbestrol.pdb_ext (located in the folder YetiX_Examples).

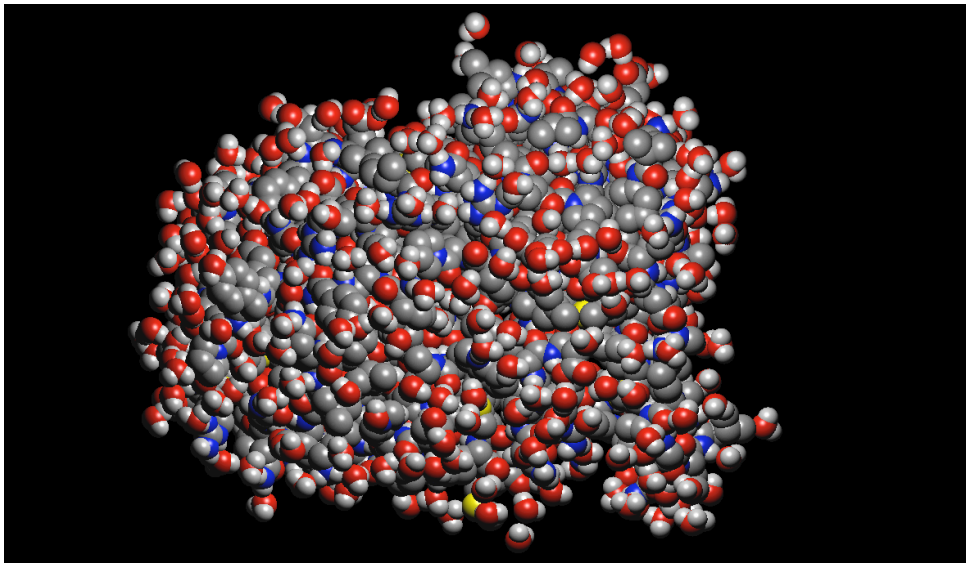
2. Solvate the entire protein (parameters: solvation settings or cmd+y): Select the setting shown below, click "OK" and launch the process (Tools: solvate)





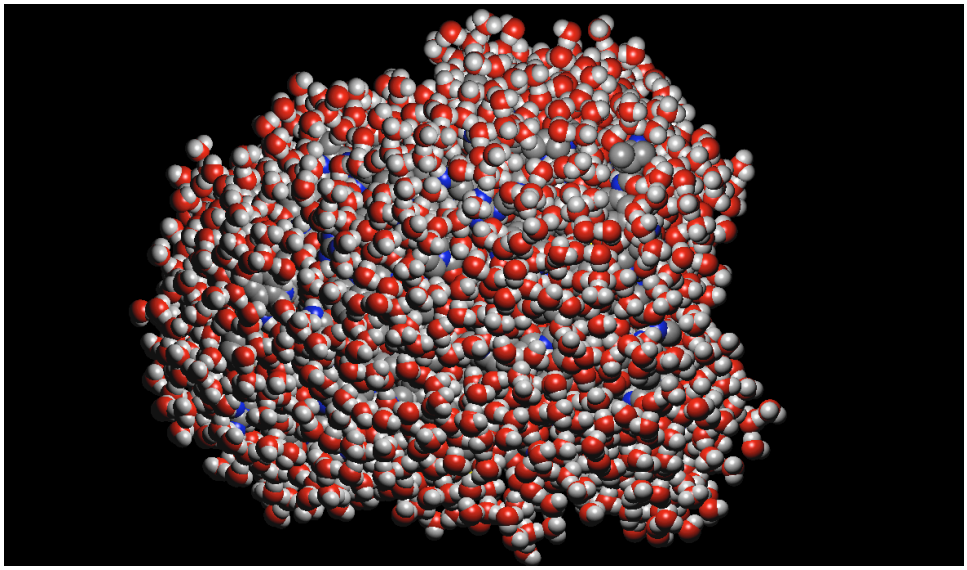
A total of 311 water molecules are generated

3. Relax the structure in four steps: water, zone (around ligand), full



Estrogen receptor α with a single solvent shell

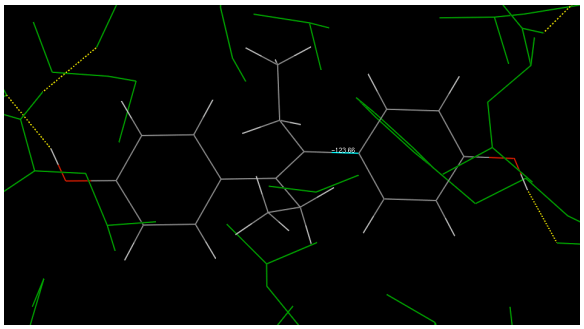
4. Repeat the solvation procedure to generate additional solvent shells (please note that the current dimensioning allows for a maximum of 12,000 atoms).



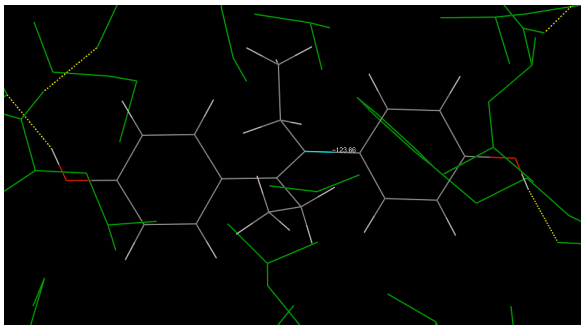
Estrogen receptor α with complete solvation (3 shells: 1,319 water molecules)

Docking small molecules

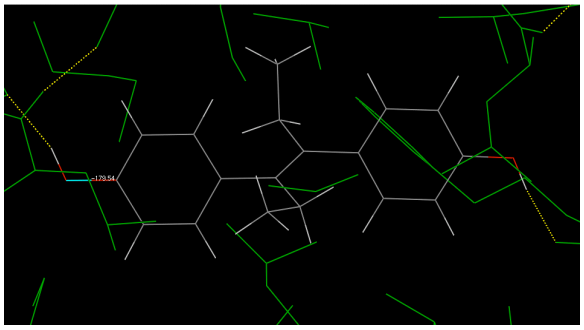
To dock small molecules into an existing protein structure, read the protein structure (read file) followed by the small molecule (add file). Then, you can change its position and orientation or conformation (for details, cf. Toolbar). Finally, use the various minimizer options (e.g. zone refinement).



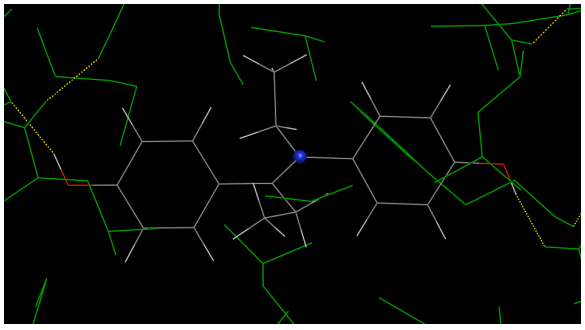
Activated torsion on ligand (ω button)



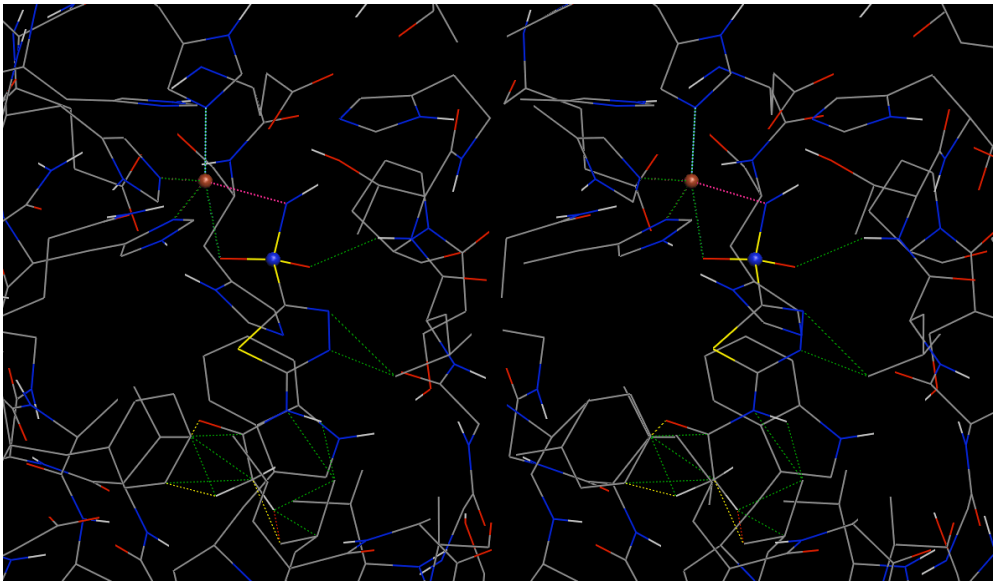
Change direction of atoms affected by torsion (↓)



Change affected torsion (→ or ←)



Activate translation/rotation ( )



Bump check option: unfavorable ligand–protein contacts of a poorly docked compound (green < yellow < red) [3D image]